



## Synthesis of Chiral Alcohols by Asymmetric Reductions of Various Ketones including $\alpha$ -Aminophenones

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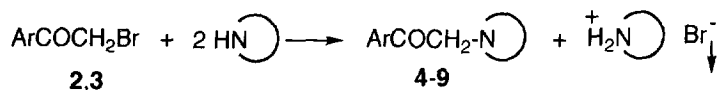
**Abstract** :  $\text{LiAlH}_4$  previously treated with 2.5 equiv. of (S)-(+)- or (R)-(-)-2-(2-iso-indoliny)butan-1-ol **1** reduced the six  $\alpha$ -aminophenones **4-9** into the corresponding optically active  $\beta$ -aminoalcohols **10-15** whose ee's were in the range 40-97% after chromatography and recrystallization. The asymmetric reduction of the ortho-dimethylaminobenzophenone **18**, using the same reducing agents afforded the enantiomerically pure benzhydrols (R)-(-)-**19** and (S)-(+)-**19**, respectively, and in 86-100% yields. The ortho-aminobenzhydrol (S)-(+)-**20** and  $\alpha$ -fluorenyl ethanol (R)-(+)-**23** and (S)-(-)-**23** were similarly obtained from the corresponding ketones **17** and **25**, respectively. The latter carbinols were obtained in an enantiomerically pure state after recrystallization. Copyright © 1996 Elsevier Science Ltd

In a previous paper,<sup>1</sup> we described the preparation of various enantiomerically pure benzhydrols by asymmetric reductions of prochiral ortho-substituted benzophenones using ethereal solutions of  $\text{LiAlH}_4$  partially decomposed with 2.5 equivalents of (S)-(+)- or (R)-(-)-2-(2-iso-indoliny)butan-1-ol **1** (see Scheme). In the search of new optically active chiral aminoalcohols, we considered reducing various aminoketones with the above reagent.

### Preparations and asymmetric reduction of $\alpha$ -aminophenones

1-Bromoacetyl-2,5-dichlorobenzene **3**<sup>2</sup> was obtained upon treatment of p-dichlorobenzene with one equiv. of bromoacetyl chloride in the presence of  $\text{AlCl}_3$  (1.2 equiv.), without any solvent and at 75°C for 3 h 30 min.

Reaction of commercial bromoacetylbenzene **2** with 2 equiv. of piperidine, morpholine or 1,2,3,4-tetrahydroquinoline in dry ether afforded the corresponding  $\alpha$ -aminoketones **4-6**, respectively. Their dichloro analogues **7-9** were similarly obtained from bromoacetyl-2,5-dichlorobenzene **3**. At the end of each reaction, the precipitated ammonium salt was removed by filtration, the solvent was evaporated and the crude aminoketone was purified as shown in Table 1. The aminoketones **6-9** are new compounds.

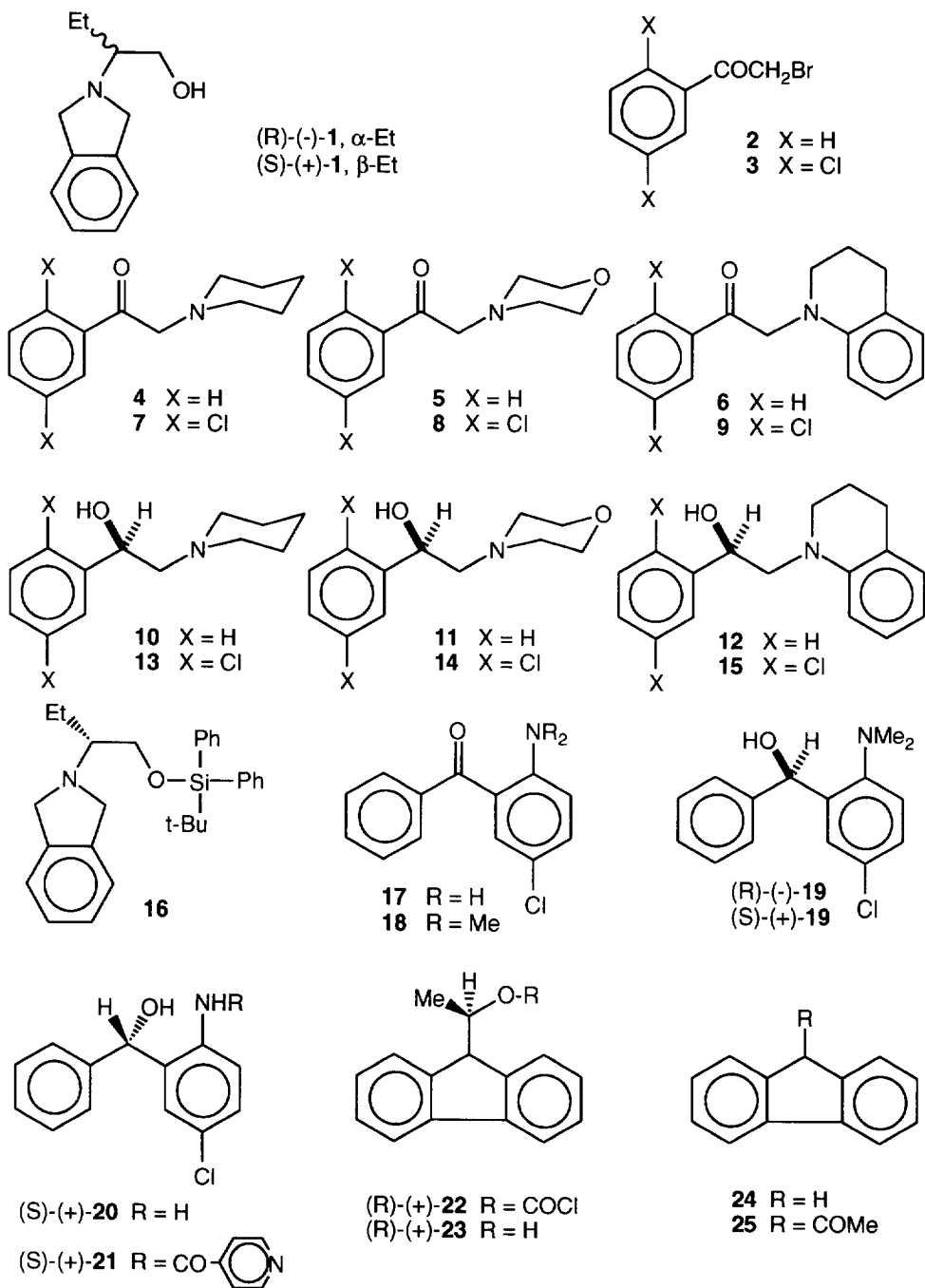


	Experimental conditions	Purification method
<b>4</b>	0°C/3h	Distillation
<b>5</b>	0°C/15h	Recrystall. from petroleum ether
<b>6</b>	20°C/88h	Recrystall. from EtOH
<b>7</b>	0°C/3h	Recrystall. of the hydrochloride from EtOH
<b>8</b>	0°C/15h	Recrystall. from petroleum ether
<b>9</b>	20°C/48h	Column chromatography

**Table 1.** Synthesis of the aminoketones **4-9**

Approximately molar, commercial, LiAlH<sub>4</sub> solutions in ether were used.<sup>2</sup> Their LiAlH<sub>4</sub> content was estimated by means of fluorenone as we previously described.<sup>3</sup> The aminoketones **4-9** were next reduced at -15°C or -78°C with LiAlH<sub>4</sub> in ether, previously treated with 2 or 2.5 equiv. of the aminoalcohol (R)-(-)-**1**, and this afforded the optically active β-aminoalcohols **10-15**, respectively. At the end of each reaction, and after hydrolysis, the resulting mixture contained the desired β-aminoalcohols **10-15**, together with the chiral auxiliary (R)-(-)-**1**. The tetrahydroquinoline aminoalcohols **12** and **15** were readily separated from (R)-(-)-**1** by column chromatography. But since this could not be achieved in the case of the other β-aminoalcohols (**10**, **11**, **13** and **14**), a separation method was developed which involved selective O-silylation of the primary alcohol (R)-(-)-**1**. Three silyl chlorides were examined for this purpose, namely trimethylsilyl chloride, t-butyl dimethylsilyl chloride and t-butyl diphenylsilylchloride (TBDPSCl).<sup>4</sup> The latter reagent gave the best results, using Et<sub>3</sub>N as a base and DMAP as a catalyst. Under these conditions, selective O-silylation of (R)-(-)-**1** took place in dichloromethane and within one hour at room temperature, and the O-silyl derivative **16** was next readily separated from the secondary alcohol (**10**, **11**, **13** and **14**), by column chromatography over silica gel. Both the β-aminoalcohols **10** and **11** are known in optically active form.<sup>5</sup> The enantiomeric excesses (ee, %) of the optically active β-aminoalcohols **12** and **15** were determined by examination of the signal of the carbinolic proton, in the <sup>1</sup>H NMR spectrum (400 MHz) run in the presence of the chiral shift reagent Eu (hfc)<sub>3</sub>. The ee's of the β-aminoalcohols **10**, **11**, **13** and **14** were determined using enantiomerically pure O-acetyl-mandelic acid as a chiral shift reagent, according to Parker and Taylor's method.<sup>6</sup>

The results we obtained are displayed in Table 2. These results show that the presence of both chlorine atoms in the starting ketones **7-9** play a negative part in the enantioselectivity of the reduction. Recrystallization of the aminoalcohols **10-13** and **15** (**14** is a liquid) substantially increased their ee's (in the case of **12** and **15**, enrichment of the major dextrorotary enantiomer occurred in the mother-liquor). The alcohol (+)-**12** was obtained in an enantiomerically pure state by a further recrystallization.



Scheme

$\beta$ -Aminoalcohol	Method A				Method B		
	Yield (%) <sup>a</sup>	$[\alpha]_D$ (c, MeOH) <sup>a</sup>	ee (%) <sup>a</sup>	ee (%) <sup>b</sup>	Yield (%) <sup>a</sup>	$[\alpha]_D$ (c, MeOH)	ee (%) <sup>a</sup>
<b>10<sup>c</sup></b> )	70	- 24.8 (2.1)	51	60	50	- 26.7 (2.9)	55
<b>11<sup>c</sup></b> )	90	- 23.3 (3.0)	45	54	33.5	- 27.1 (3.5)	63
<b>12<sup>d</sup></b> )	95.5	+ 41.7 (2.1)	42	88	83	+ 71.0 (2.0)	75
<b>13<sup>c</sup></b> )	66.5	- 15.6 (2.1)	29	40			
<b>14<sup>c</sup></b> )	86	- 9.5 (3.1)	12	(liquid)			
<b>15<sup>d</sup></b> )	100	+ 1.9 (2.7)	10	51			

Method A : using  $\text{LiAlH}_4$  and 2 equiv. of (R)-(-)-**1** at  $-15^\circ\text{C}$  for 10 min.

Method B : using  $\text{LiAlH}_4$  and 2.5 equiv. of (R)-(-)-**1** at  $-78^\circ\text{C}$  for 4h.

a) After chromatography ; b) after chromatography and one recrystallization from cyclohexane or petrol ether ; c) ee's were determined using O-acetylmandelic acid ; d) ee's were determined using  $\text{Eu}(\text{hfc})_3$ .

**Table 2.** Enantiomeric excesses of  $\beta$ -aminoalcohols **10-15**, according to the reduction method used.

The reduction time was much longer at  $-78^\circ\text{C}$  (2-4h) than at  $-15^\circ\text{C}$  (10 min), but in the former case, the ee's were higher, and particularly so for (+)-**12**.

Since the  $\beta$ -aminoalcohols (-)-**10** and (-)-**11** are known to have the R configuration,<sup>5b,c</sup> it can be assumed that it is also the case for the other four analogues **12-15**.

### Asymmetric reductions of ortho-aminobenzophenones

Treatment of commercial 2-amino-5-chlorobenzophenone **17** with excess formic acid and formaldehyde in water, afforded the crystalline o-dimethylamino benzophenone **18**. This ketone was reduced with  $\text{LiAlH}_4$  previously treated with 2.5 equiv. of (S)-(+)- or (R)-(-)-**1** at  $-15^\circ\text{C}$  for 30 min. The resulting benzhydrol (+)-**19** or (-)-**19** was thus obtained in 86-100% yields after chromatography and in the enantiomerically pure state, as evidenced by means of  $\text{Eu}(\text{hfc})_3$  as a chiral shift reagent. The absolute configurations of both enantiomers of **19** were determined using Horeau's method.<sup>7</sup> Thus, the chiral auxiliary (R)-(-)-**1** led to (R)-(-)-**19** and (S)-(+)-**1** led to (S)-(+)-**19**.

(S)-(+)-N-Isonicotinoyl-2-amino-5-chlorobenzhydrol (S)-(+)-**21** is a powerful rice-growth regulator. Kato and his coworkers<sup>8</sup> obtained the corresponding free aminoalcohol (S)-(+)-**20** in twenty-milligram quantities after seven days by microbiological reduction (using *Rhodospiridium toruloides*) of the commercially available aminobenzophenone **17**. We reduced the ketone **17** by means of the chiral complex deriving from  $\text{LiAlH}_4$  and (R)-(-)-**1**. Since the amino group of **17** can react with the complex hydride, a slight excess (1.5 molar equivalent) of the latter was used. The reduction came to completion in 5 min at  $-15^\circ\text{C}$ . The resulting benzhydrol (S)-(+)-**20** had ee = 70%. One recrystallization from ethyl acetate/pentane afforded enantiomerically pure (S)-(+)-**20** on the gram scale and in 54% overall yield. This carbinol was acylated into the isonicotinamide (S)-(+)-**21** in agreement with the literature.<sup>8</sup>

### Asymmetric reduction of 9-acetylfluorene

The resolution of chiral aminoacids, amines and alcohols can be performed by derivatization with (+)-1-(9-fluorenyl)ethyl chloroformate (FLEC) (R)-(+)-**22**, followed by inverse phase liquid chromatography.<sup>9</sup> Trace amounts of D-aminoacids in a mixture can be detected by this method. Einarsson and his coworkers<sup>9</sup> prepared the racemic alcohol **23** by treating fluorene **24** with *n*-butyllithium and acetaldehyde. The resolution of (±)-**23** was achieved by esterification with D-camphor-10-sulphonyl chloride. The diastereomerically pure ester thus obtained was split with LiAlH<sub>4</sub> and the resulting dextrorotary carbinol (+)-**23** was subsequently treated with phosgen in order to form the chloroformate (+)-**22**. The above authors reported neither the yields of the different steps of their synthesis, nor the absolute configuration and specific optical rotation of the carbinol **23**.

We found that our reduction method of ketones provides an alternative access to *both* enantiomers of the carbinol **23**. Thus, condensation of fluorene **24** with ethyl acetate, using potassium *t*-butoxide as a base, afforded 9-acetylfluorene **25** in good yields. The latter was asymmetrically reduced using the above reagent deriving from LiAlH<sub>4</sub> and 2.5 equiv. of (R)-(-)-**1**. The resulting carbinol (+)-**23** was obtained in moderate yields, presumably because the carbonyl group of the starting ketone **25** is sterically hindered. The alcohol (+)-**23** was next isolated in an enantiomerically pure state by recrystallization from petrol ether. The levorotary enantiomer of **23** was subsequently obtained in a similar fashion using the reagent deriving from LiAlH<sub>4</sub> and (S)-(+)-**1**. The absolute configurations of the dextrorotary and levorotary enantiomers of **23** were determined using Horeau's method<sup>7</sup> and were found to be R and S, respectively. Since it was prepared from the dextrorotary alcohol (+)-**23**,<sup>9</sup> the FLEC reagent **22** must have the same R absolute configuration.

### Conclusion

There are reports on the asymmetric reductions of α-aminoketones by means of LiBH<sub>4</sub> modified with N,N'-dibenzoylcystine,<sup>5b</sup> or by means of chiral organoboranes such as K glucoride<sup>5c</sup> and B-chlorodiisopinocampheylborane.<sup>5d</sup> The ee's of the resulting β-aminoalcohols were in the ranges 58-73%, 81-92% and 75-99%, respectively. In our present case, the asymmetric reduction of the α-aminophenones **4-9**, by means of ethereal LiAlH<sub>4</sub> partially decomposed with 2 or 2.5 equiv. of (R)-(-)-**1**, gave the corresponding β-aminoalcohols **10-15** whose ee's were generally in the range 40-97% after chromatography and recrystallization. As a matter of comparison, the asymmetric reduction of the *o*-dimethylaminobenzophenone **18**, using the above reducing species deriving from (R)-(-)-**1** or (S)-(+)-**1**, afforded the enantiomerically pure benzhydrols (R)-(-)-**19** and (S)-(+)-**19**, respectively, and in 86-100% yields. This again shows that our reduction method is very well suited for the asymmetric synthesis of enantiomerically pure, chiral benzhydrols.<sup>1</sup> Our method was also applied to the syntheses of two useful carbinols, namely (S)-(+)-**20** and (R)-(+)-**23**. Both compounds were isolated in an enantiomerically pure state and in appreciable amounts after recrystallization. As exemplified in the case of 1-(9-fluorenyl)ethanol **23**, using both enantiomers of the chirality vector **1** can give access to both enantiomers of any of the chiral carbinols described above. Finally, it must be emphasized that the chirality vector **1** can be readily recovered after use, and recycled after purification.

### Experimental section

**General** : IR spectra were recorded with Nicolet 5DX and Genesis (Matteson) spectrophotometers. <sup>1</sup>H NMR (400 MHz) and <sup>13</sup>C NMR (100 MHz) spectra were recorded with a Bruker AC 400 spectrometer, using Me<sub>4</sub>Si

as an internal standard. Melting points were determined with a Reichert microscope. Optical rotations were measured at 20°C with a Perkin-Elmer 241 micropolarimeter. Elemental analyses were carried out at the I.C.S.N. (C.N.R.S., Gif sur Yvette).

**Abbreviations** : THF, tetrahydrofuran ; TBDPSCl, t-butyl diphenylsilyl chloride ; DMAP, p-dimethylaminopyridine ; RP, reduced pressure ; RT, room temperature.

*(R)-(-)-2-(2-Iso-indolinyl)butan-1-ol (R)-(-)-1*

The following procedure is an improvement of that previously described.<sup>1b</sup> Commercial (R)-(-)-2-aminobutan-1-ol (15.0 g ; 168 mmol),  $[\alpha]_D$ -10 (neat),  $\alpha,\alpha'$ -dichloro-o-xylene (29.5 g ; 168,5 mmol) and sodium carbonate (35.7 g ; 337 mmol) in dry THF (200 mL) were refluxed under nitrogen for 13 h. The mixture was filtered, the solid was triturated with THF and the combined filtrates were evaporated under RP, thus giving a yellow solid. The latter was dissolved in ether (400 mL) and the resulting solution was partially evaporated in the cold in order to induce crystallization. The aminoalcohol (R)-(-)-1 (26.0 g ; 81%) was thus obtained as white crystals, m.p. 59-60°C and  $[\alpha]_D$ -19.8 to -20.0 (3.5, EtOH). Anal. Calc. for C<sub>12</sub>H<sub>17</sub>NO : C, 75.35 ; H 8.95 ; N, 7.32 ; O, 8.36. Found : C, 75.09 ; H, 8.97 ; N, 7.20 ; O, 8.48 ; IR (KBr) : 3187 (OH) and 1459 (aryl) cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  : 7.26 (4H, s) ; 4.05 (4H, s) ; 3.75 (1H, dd, J = 10.8 and 6.9 Hz) ; 3.50 (1H, dd, J = 10.8 and 4.4 Hz) ; 2.74 (1H, m) ; 1.71 (1H, m) ; 1.50 (1H, m) ; 0.98 (3H, t, J = 7.4 Hz).

The enantiomer (S)-(+)-1, m.p. 60-61°C and  $[\alpha]_D$ + 19.8 (c 1.0, EtOH) was similarly prepared from (S)-(+)-2-aminobutan-1-ol.

*2-[1-(1,2,3,4-Tetrahydro)quinolino]acetophenone 6*

A solution of bromoacetyl benzene **2** (10.0 g ; 50.2 mmol) in dry ether (50 mL) was added under nitrogen to a stirred solution of 1,2,3,4-tetrahydroquinoline (12.6 mL ; 100.4 mmol) in dry ether (50 mL) at RT. After 88 h at RT, the mixture was filtered and the solvent was evaporated. Recrystallization of the residue from absolute ethanol gave the  $\alpha$ -aminoketone **6** (11.6 g ; 92%) as yellow crystals, m.p. 102-103°C. Anal. Calc. for C<sub>17</sub>H<sub>17</sub>NO : C, 81.24 ; H, 6.82 ; N, 5.57. Found : C, 80.93 ; H, 7.07 ; N, 5.55. IR (CH<sub>2</sub>Cl<sub>2</sub>) : 1693 (CO) and 1600 (aryl) cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  : 8.02 (2H, m) ; 7.63 (1H, tt, J = 7.4 and 1.4 Hz) ; 7.52 (2H, m) ; 6.98 (2H, m) ; 6.61 (1H, dt, J = 7.4 and 0.8 Hz) ; 6.33 (1H, d, J = 8.1 Hz) ; 4.72 (2H, s) ; 3.42 (2H, t, J = 5.7 Hz) ; 2.85 (2H, t, J = 6.3 Hz) ; 2.05 (2H, m).

*2',5'-Dichloro-2-(1-piperidino)acetophenone 7*

A solution of 2-bromo-2',5'-dichloroacetophenone **3**<sup>10</sup> (4.9 g ; 18.2 mmol) in dry ether (20 mL) was added to piperidine (3.8 mL ; 38.4 mmol) in dry ether (15 mL) at 0°C. After 3h at 0°C, the mixture was filtered and the filtrate was treated at 0°C with a solution of dry HCl in ethanol. The precipitated hydrochloride was filtered and recrystallized from absolute ethanol. The hydrochloride (2.91 g ; 52%) of the base **7** was obtained as white crystals, m.p. 185-187°C. Anal. Calc. for C<sub>13</sub>H<sub>16</sub>NOC<sub>2</sub>Cl<sub>2</sub> : C, 50.59 ; H 5.23 ; N, 4.54 ; Cl, 34.46. Found : C, 50.58 ; H, 5.25 ; N, 4.43 ; Cl, 34.24. IR (KBr) : 1705 (CO) cm<sup>-1</sup>. <sup>1</sup>H NMR (DMSO)  $\delta$  : 10.29 (1H, s) ; 8.10 (1H, d, J = 2.4 Hz) ; 7.76 (1H, dd, J = 8.6 and 2.5 Hz) ; 7.69 (1H, d, J = 8.6 Hz) ; 4.99 (2H, s) ; 3.45 (2H, s) ; 3.07 (2H, s) ; 1.83 (4H, s) ; 1.68 (1H, s) ; 1.44 (1H, s).

The above hydrochloride (0.40 g ; 1.30 mmol) in a mixture of ether (10 mL) and water (5 mL) was cooled to 0°C and treated dropwise with a solution of 1N NaOH (4 mL) until pH = 10. the organic phase was

separated, dried (MgSO<sub>4</sub>), filtered and evaporated under RP, thus giving the free base **7** (0.35 g ; 98%) as an unstable yellow oil which was used straight away.

*2',5'-Dichloro-2-(4-morpholino)acetophenone 8*

This compound was obtained by reaction of 2-bromo-2',5'-dichloroacetophenone **3**<sup>10</sup> (1.54 g ; 5.75 mmol) in dry ether (7 mL) with morpholine (1.0 mL ; 11.4 mmol) in dry ether (5 mL) at 0°C for 15 h. The crude reaction product was isolated and recrystallized for petroleum ether, thus affording yellow crystals (1.1 g ; 72%), m.p. 67-68°C. Anal. Calc. for C<sub>12</sub>H<sub>13</sub>NO<sub>2</sub>Cl<sub>2</sub> : C, 52.58 ; H, 4.78 ; N, 5.11 ; Cl, 25.86. Found : C, 52.47 ; H, 4.68 ; N, 4.99 ; Cl, 26.12. IR (CH<sub>2</sub>Cl<sub>2</sub>) : 1724 (CO) cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 7.44 (1H, m) ; 7.37 (2H, m) ; 3.73 (6H, m) ; 2.59 (4H, m).

*2',5'-Dichloro-2-[1-(1,2,3,4-tetrahydroquinolino)acetophenone 9*

This compound was prepared by reaction of 2-bromo-2',5'-dichloroacetophenone **3**<sup>10</sup> (3.8 g ; 14.2 mmol) in dry ether (30 mL) with 1,2,3,4-tetrahydroquinoline (3.80 mL ; 30.3 mmol) in dry ether (20 mL) at RT for 48 h. The reaction mixture was diluted with THF (50 mL), followed by filtration and evaporation under RP. This gave a brown oil which was chromatographed over silica gel (200 g ; petrol ether/ether from 0 to 10%), thus affording the α-aminoketone **9** (4.0 g ; 88%) as an unstable yellow oil which was characterized by its spectral and chemical properties. IR (film) : 1708 (CO) and 1602 (C=C arom.) cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 7.38 (3H, m) ; 7.02 (1H, t, J = 7.9 Hz) ; 6.98 (1H, d, J = 7.3 Hz) ; 6.63 (1H, t, J = 7.3 Hz) ; 6.36 (1H, d, J = 8.2 Hz) ; 4.56 (2H, s) ; 3.39 (2H, t, J = 5.6 Hz) ; 2.78 (2H, t, J = 6.3 Hz) ; 1.97 (2H, m). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ : 199.9 (s), 144.5 (s), 139.3 (s), 133.2 (s), 131.8 (d), 131.5 (d), 129.3 (d), 128.9 (s), 128.8 (d), 127.1 (d), 122.7 (s), 116.9 (d), 110.3 (d), 61.2 (t), 50.7 (t), 27.8 (t), 22.2 (t).

*(R)-(-)-2-(1-Piperidino)-1-phenylethanol 10*

A solution of (R)-(-)-2-(2-iso-indolyl)butan-1-ol (R)-(-)-**1** (1.85 g ; 9.7 mmol), [α]<sub>D</sub> -20.0 (4.1, EtOH), in dry THF (25 mL) was added dropwise in 1 h to an ethereal solution of LiAlH<sub>4</sub> (3.80 mL ; 3.9 mmol), the mixture was stirred at RT for 30 min and was cooled to -78°C. 2-(1-Piperidino)acetophenone **4**<sup>11</sup> (0.79 g ; 3.9 mmol) in dry THF (8 mL) was treated at -78°C for 4 h with the chiral reducing complex thus prepared. The reaction product (a white solid) was isolated in the usual way<sup>1</sup>. It was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and treated dropwise with TBDPSCl (2.80 mL ; 10.8 mmol ; 1.1 equiv.) in the presence of Et<sub>3</sub>N (1.65 mL ; 11.84 mmol) and DMAP (47 mg ; 0.4 mmol). After stirring at RT for 1 h, the reaction mixture was washed with water (15 mL) then with brine (15 mL), the organic phase was dried (MgSO<sub>4</sub>), filtered and evaporated under RP. the brown oily residue was filtered through silica gel (50 g , petrol ether ; elution with ether then with AcOEt) and this afforded the unstable (R)-(-)-2-(1-piperidino)-1-phenylethanol (R)-(-)-**10** (0.40 g ; 50%) as pale yellow crystals, m.p. 68-70°C, [α]<sub>D</sub> -26.7 (2.9, MeOH). Lit.<sup>5b</sup> +39.54 (1.43, MeOH) and ee = 82%. The <sup>1</sup>H NMR spectrum of (R)-(-)-**10** was run in the presence of enantiomerically pure O-acetylmandelic acid<sup>6</sup> (1.2 equiv.) an revealed an ee = 55%. IR (CH<sub>2</sub>Cl<sub>2</sub>) : 3231 (OH) and 1450 (aryl) cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 7.35 (4H, m) ; 7.26 (1H, m) ; 4.71 (1H, dd, J = 10.6 and 3.6 Hz) ; 3.66 (1H, s) ; 2.69 (2H, s) ; 2.42 (1H, dd, J = 12.4 and 3.6 Hz) ; 2.39 (3H, m) ; 1.61 (4H, m) ; 1.47 (2H, m).

*(R)-(-)-2-(4-Morpholino)-1-phenylethanol (R)-(-)-11*

2-(4-Morpholino)acetophenone **5**<sup>11</sup> (0.92 g ; 4.47 mmol) in dry THF (10 mL) was partially reduced at -78°C for 2h with the chiral reagent prepared as previously described, from ethereal LiAlH<sub>4</sub> (3.88 mmol) and the chiral auxiliary (R)-(-)-**1** (1.85 g ; 9.7 mmol ; 2.5 equiv.), [α]<sub>D</sub> -20.0 (4.1, EtOH), in dry THF (25 mL). The crude reaction product was isolated in the usual way<sup>1</sup> and was treated with TBDPSCI (10.8 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (50 mL), and in the presence of Et<sub>3</sub>N (11.5 mmol) and DMAP (47 mg ; 0.4 mmol).

After standing for 1 h at room temperature, the reaction mixture was worked up and the resulting orange oil was chromatographed over silica gel using petrol ether/ether (5:5) as an eluent, and this afforded the β-aminoalcohol (R)-(-)-**11** (0.31 g ; 33.5%) as pale yellow crystals, m.p. 75-80°C, [α]<sub>D</sub> -27.1 (3.5, MeOH) and ee = 63%, as evidenced from the <sup>1</sup>H NMR spectrum (400 MHz) run in the presence of O-acetylmandelic acid.<sup>6</sup> Lit.<sup>5b</sup> [α]<sub>D</sub> +41.83 (5.1, MeOH) and ee = 89%. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ(ppm) : 7.37 (4H, m) ; 7.29 (1H, m) ; 4.70 (1H, dd, J = 10.4 Hz and 3.6 Hz) ; 3.77 (4H, m) ; 3.30 (1H, s) ; 2.76 (2H, m) ; 2.56 (1H, dd, J = 12.5 Hz and 3.6 Hz) ; 2.49 (3H, m).

*(+)-2-[1-(1,2,3,4-Tetrahydroquinolino)-1-phenylethanol (+)-12*

2-[1-(1,2,3,4-Tetrahydroquinolino)acetophenone **6** (0.29 g ; 1.15 mmol) in dry THF (2 mL) was reduced at -78°C for 4 h with the chiral reagent prepared from ethereal LiAlH<sub>4</sub> (1.0 mmol) and (R)-(-)-**1** (0.48 g ; 2.5 mmol ; 2.5 equiv.) in THF (7 mL).<sup>1</sup> The crude reaction product was isolated in the usual way<sup>1</sup> and was chromatographed over silica gel (40 g) using petrol ether/ether (5:5) as an eluent. The β-aminoalcohol (+)-**12** (0.24 g ; 83%) was thus obtained as white crystals, m.p. 50-55°C, [α]<sub>D</sub> +71.0 (2.0, MeOH) and ee = 75%, as evidenced from the <sup>1</sup>H NMR spectrum (400 MHz) run in the presence of 0.2 equiv. of Eu(hfc)<sub>3</sub>. Recrystallization of a sample of (+)-**12** (0.20 g) from a mixture of pentane and hexane afforded pure (+)-**12** (0.15 g ; 63% overall yield), m.p. 68-69°C, [α]<sub>D</sub> +94.5 (1.0, MeOH) and ee = 97%. Anal. Calc. for C<sub>17</sub>H<sub>19</sub>NO : C, 80.60 ; H, 7.56 ; N, 5.53. Found : C, 80.29 ; H, 7.64 ; N, 5.49. IR (CH<sub>2</sub>Cl<sub>2</sub>) : 3415 (OH) and 1602 (aryl) cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ(ppm) : 7.44 (2H, d, J = 7.0 Hz) ; 7.39 (2H, td, J = 7.4 Hz and 1.7 Hz) ; 7.32 (1H, tt, J = 7.1 Hz and 1.4 Hz) ; 7.09 (1H, t, J = 6.8 Hz) ; 6.98 (1H, d, J = 6.9 Hz) ; 6.78 (1H, d, J = 8.2 Hz) ; 6.65 (1H, t, J = 7.1 Hz) ; 5.03 (1H, m) ; 3.44 (2H, m) ; 3.31 (1H, m) ; 3.23 (1H, m) ; 2.78 (2H, m) ; 2.46 (1H, d, J = 2.2 Hz) ; 1.93 (2H, m). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ(ppm) : 145.7 (s) ; 142.1 (s) ; 129.4 (d) ; 128.5 (d) ; 127.8 (d) ; 127.1 (d) ; 125.9 (d) ; 123.0 (s) ; 116.6 (d) ; 111.5 (d) ; 71.5 (d) ; 60.8 (t) ; 50.8 (t) ; 28.3 (t) ; 22.1 (t).

*(-)-2',5'-Dichloro-2-(1-piperidino)-1-phenyl ethanol (-)-13*

A solution of 2',5'-dichloro-2-(1-piperidino)acetophenone **7** (1.0 g ; 3.7 mmol) in dry ether (5 mL) was totally reduced at -15°C in 10 min by the chiral reagent prepared from ethereal LiAlH<sub>4</sub> (5.0 mL ; 4.65 mmol) and a solution of (R)-(-)-**1** (1.78 g ; 9.3 mmol) in dry ether (20 mL). The crude reaction product was isolated using TBDPSCI, as described above and was chromatographed over silica gel (35 g, petrol ether ; elution with petrol ether and with ether). This gave the β-aminoalcohol (-)-**13** in 66.5% yield, as pale yellow crystals, m.p. 54-60°C, [α]<sub>D</sub> -15.6 (2.1, MeOH) and ee = 29% (<sup>1</sup>H NMR with O-acetylmandelic acid).<sup>6</sup> This compound was recrystallized from cyclohexane. Evaporation of the mother-liquor yielded about 60% of the β-aminoalcohol (-)-**13** having an ee = 40%. Anal. Calc. for C<sub>13</sub>H<sub>17</sub>NOC<sub>2</sub>Cl<sub>2</sub> : C, 56.95 ; H, 6.25 ; N, 5.11 ; Cl, 25.86. Found : C, 57.01 ; H, 6.31 ; N, 5.00 ; Cl, 26.07. IR (CH<sub>2</sub>Cl<sub>2</sub>) : 3355 (OH) cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 7.67 (1H, d, J = 2.5 Hz) ; 7.23 (1H, d, J = 8.4 Hz) ; 7.16 (1H, dd, J = 8.5 and 2.5 Hz) ; 5.06



(1H, dd,  $J = 10.3$  and  $3.1$  Hz) ; 4.34 (1H, s) ; 2.70 (3H, dd,  $J = 12.4$  and  $3.2$  Hz) ; 2.38 (2H, s) ; 2.18 (1H, dd,  $J = 12.4$  and  $10.4$  Hz) ; 1.62 (4H, m) ; 1.47 (2H, m).

**(-)-2',5'-Dichloro-2-(4-morpholino)-1-phenylethanol (-)-14**

A solution of 2',5'-dichloro-2-(1-morpholino)acetophenone **8** (0.82 g ; 3 mmol) in dry ether (10 mL) was totally reduced at  $-15^{\circ}\text{C}$  in 10 min by the chiral reagent prepared from ethereal  $\text{LiAlH}_4$  (2.0 mL ; 1.94 mmol) and a solution of (R)-(-)-**1** (0.74 g ; 3.9 mmol) in dry ether (10 mL). The crude reaction product was isolated using  $\text{TBDPSCl}$  as described above and was chromatographed over silica gel (20 g ; elution with petrol ether/ether 5/5 then with ether). This gave the  $\beta$ -aminoalcohol (-)-**14** (0.70 g ; 86%) as a yellow oil,  $[\alpha]_{\text{D}} -9.5$  (3.1, MeOH) and  $ee = 12\%$  ( $^1\text{H}$  NMR with O-acetylmandelic acid).<sup>6</sup> Anal. Calc. for  $\text{C}_{12}\text{H}_{15}\text{NO}_2\text{Cl}_2$  : C, 52.19 ; H, 5.47 ; N, 5.07 ; Cl, 25.68. Found : C, 52.11 ; H 5.22 ; N, 5.01 ; Cl, 25.78. IR ( $\text{CH}_2\text{Cl}_2$ ) : 3421 (OH)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  : 7.68 (1H, d,  $J = 2.5$  Hz) ; 7.26 (1H, d,  $J = 4.6$  Hz) ; 7.19 (1H, dd,  $J = 8.5$  and  $2.5$  Hz) ; 5.11 (1H, dd,  $J = 10.4$  and  $2.9$  Hz) ; 3.77 (5H, m) ; 2.78 (2H, m) ; 2.76 (1H, dd,  $J = 12.4$  and  $3.0$  Hz) ; 2.48 (m, 2H) ; 2.28 (1H, dd,  $J = 12.4$  and  $10.4$  Hz).

**(+)-2',5'-Dichloro-2-[1-(1,2,3,4-tetrahydro)quinolino]-1-phenylethanol (+)-15**

A solution of 2',5'-dichloro-2-[1-(1,2,3,4-tetrahydro)quinolino]acetophenone **9** (0.99 g ; 3.1 mmol) in dry THF (3 mL) was totally reduced at  $-15^{\circ}\text{C}$  in 10 min by the chiral reagent prepared from ethereal  $\text{LiAlH}_4$  (2.0 mL ; 2.0 mmol) and a solution of (R)-(-)-**1** (0.77 g ; 4.0 mmol) in dry ether (11 mL). The crude reaction product was isolated in the usual way<sup>1</sup> (*without* using  $\text{TBDPSCl}$ ) and was chromatographed over silica gel (30 g ; petrol ether/ether 5/5). The  $\beta$ -aminoalcohol (+)-**15** (0.99 g ; *ca.* 100%) was obtained as a yellow oil which crystallized on cooling, having m.p.  $90\text{--}94^{\circ}\text{C}$ ,  $[\alpha]_{\text{D}} + 1.9$  (2.7, MeOH) and  $ee = 10\%$  [ $^1\text{H}$  NMR using  $\text{Eu}(\text{hfc})_3$ ]. This compound was recrystallized from cyclohexane. Evaporation of the mother-liquor yielded about 15% of the  $\beta$ -aminoalcohol (+)-**15**, m.p.  $92\text{--}95^{\circ}\text{C}$  and  $[\alpha]_{\text{D}} +10.3$  (2.8, MeOH), having an  $ee = 51\%$ . Anal. Calc. for  $\text{C}_{17}\text{H}_{17}\text{NOCl}_2$  : C, 63.37 ; H, 5.32 ; N, 4.35 ; Cl 22.00. Found : C, 63.35 ; H, 5.15 ; N, 4.56 ; Cl, 21.99. IR ( $\text{CH}_2\text{Cl}_2$ ) : 3509 (OH)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) : 7.74 (1H, s) ; 7.27 (2H, m) ; 7.11 (1H, t,  $J = 7.2$  Hz) ; 7.01 (1H, d,  $J = 7.0$  Hz) ; 6.93 (1H, d,  $J = 8.2$  Hz) ; 6.69 (1H, t,  $J = 7.2$  Hz) ; 5.38 (1H, d,  $J = 9.0$  Hz) ; 3.59 (1H, d,  $J = 14.7$  Hz) ; 3.38 (2H, m) ; 3.23 (1H, dd,  $J = 14.4$  and  $9.8$  Hz) ; 2.82 (2H, s) ; 2.72 (1H, s) ; 2.00 (2H, s).

**5-Chloro-2-(dimethylamino)benzophenone 18**

A 35% aqueous solution of formaldehyde (7.55 mL ; 95.0 mmol) was added dropwise to a cooled (*ca.*  $0^{\circ}\text{C}$ ) mixture of commercial 2-amino-5-chlorobenzophenone **17** (10.0 g ; 43.2 mmol) and formic acid (8.30 mL ; 0.22 mol). The resulting mixture was refluxed for 6 h, then cooled and treated with aqueous 6N HCl. Excess formic acid and formaldehyde were removed under RP, and the cooled aqueous solution was treated with KOH pellets and extracted with ether (3 x 50 mL). The organic phase was dried ( $\text{MgSO}_4$ ), filtered and evaporated and the final residue was recrystallized from absolute ethanol, thus affording the dimethylamino benzophenone **18** (9.8 g ; 87%) as yellow crystals, m.p.  $91\text{--}92^{\circ}\text{C}$ . Lit.<sup>12</sup> yield 59% and m.p.  $91\text{--}92^{\circ}\text{C}$ . IR ( $\text{CH}_2\text{Cl}_2$ ) : 1656 (CO) and 1590 (aryl)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  : 7.82 (2H, d,  $J = 7.3$  Hz) ; 7.57 (1H, t,  $J = 7.4$  Hz) ; 7.44 (2H, t,  $J = 7.7$  Hz) ; 7.33 (1H, dd,  $J = 8.8$  and  $2.5$  Hz) ; 7.27 (1H, s) ; 6.91 (1H, d,  $J = 8.8$  Hz) ; 2.69 (6H, s).

*(R)-(-) And (S)-(+)-5-chloro-2-(dimethylamino)benzhydrol 19*

5-Chloro-2-(dimethylamino)benzophenone **18** (7.0 g ; 27.0 mmol) in dry ether (70 mL) was reduced at -15°C for 30 min with the chiral reagent prepared from ethereal LiAlH<sub>4</sub> (32.4 mmol) and (R)-(-)-**1** (15.5 g ; 81 mmol ; 2.5 equiv.) in dry ether (250 mL).<sup>1</sup> The crude solid reaction product was isolated in the usual way<sup>1</sup> and was chromatographed over silica gel (250 g) using cyclohexane/AcOEt (9 : 1) as an eluent. The benzhydrol (R)-(-)-**19** (6.1 g ; 86%) was thus obtained as a pale yellow oil, [α]<sub>D</sub> -22.0 (2.9, Me<sub>2</sub>CO) and ee > 99%, as evidenced from the <sup>1</sup>H NMR spectrum (400 MHz) run in the presence of 1.5 equiv. of Eu(hfc)<sub>3</sub>.

The benzophenone **18** (0.65 g ; 2.50 mmol) in dry ether (3 mL) was reduced at -15°C for 3 h 10 min with the chiral reagent prepared from ethereal LiAlH<sub>4</sub> (3.0 mmol) and (S)-(+)-**1**<sup>1</sup> (1.43 g ; 7.50 mmol), [α]<sub>D</sub> +19.8 (2.9, EtOH), in dry ether (20 mL). The reaction product was isolated in the usual way and was chromatographed over silica gel (40 g) as above. The enantiomeric benzhydrol (S)-(+)-**19** (0.65 g ; 100%) was thus obtained as a yellow oil, [α]<sub>D</sub> +21.6 (3.2, Me<sub>2</sub>CO) and ee > 99% [<sup>1</sup>H NMR using Eu(hfc)<sub>3</sub>]. Racemic (±)-**19** is a known compound.<sup>13</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ(ppm) : 7.37-7.29 (4H, m) ; 7.26-7.16 (2H, m) ; 7.02 (1H, s) ; 6.96 (1H, s) ; 5.91 (1H, s) ; 2.53 (6H, s) ; 2.14 (1H, s). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ (ppm) : 150.5 (s) ; 143.5 (s) ; 140.7 (s) ; 130.6 (s) ; 128.9 (d) ; 128.3 (d) ; 128.2 (d) ; 127.3 (d) ; 126.5 (d) ; 123.5 (d) ; 75.0 (d) ; 45.6 (q).

The absolute configurations of (R)-(-)-**19** and (S)-(+)-**19** were separately determined using Horeau's method.<sup>7</sup>

*(S)-(+)-2-Amino-5-chlorobenzhydrol (S)-(+)-20*

A solution of 2-amino-5-chlorobenzophenone **17** (2.0 g ; 8.6 mmol) in dry ether (25 mL) was totally reduced at -15°C in 5 min by the chiral reagent prepared from ethereal LiAlH<sub>4</sub> (13.0 mL ; 12.6 mmol) and a solution of (R)-(-)-**1** (6.0 g ; 31.5 mmol) in dry ether (85 mL). The crude reaction product was isolated in the usual way and was chromatographed over silica gel (150 g ; petrol ether/ether 7/3 then 5/5). The aminoalcohol (S)-(+)-**20** (2.0 g ; 18%) was thus obtained as white crystals, [α]<sub>D</sub> +6.4 (3.0, EtOH). A recrystallization from AcOEt/pentane afforded the purified aminoalcohol (S)-(+)-**20** (1.11 g ; 55%) as white crystals, m.p. 130-132°C (Lit.<sup>8</sup> m.p. 131-132°C), [α]<sub>D</sub> +10.9 (3.1, EtOH) and ee > 99% as evidenced from the <sup>1</sup>H NMR spectrum run in the presence of 1.0 molar equiv. of Eu(hfc)<sub>3</sub>. IR (KBr) : 3384 (NH<sub>2</sub>), 3220 (OH) and 1602 (aryl) cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 7.38 (4H, m) ; 7.35-7.30 (1H, m) ; 7.06 (2H, m) ; 6.58 (1H, d, J = 8.8 Hz) ; 5.79 (1H, s) ; 3.94 (2H, s) (NH<sub>2</sub>) ; 2.57 (1H, s) (OH).

*(S)-(+)-N-Isonicotinoyl-2-amino-5 chlorobenzhydrol (S)-(+)-21*

A mixture of the aminoalcohol (S)-(+)-**20** (117 mg ; 0.50 mmol) and the hydrochloride of isonicotinoyl chloride (107 mg ; 0.60 mmol) in dry AcOEt (2 mL) was stirred at RT for 16 h. The mixture was then filtered and the precipitate was washed with ether. The pale yellow solid thus obtained was dissolved in a mixture of water (1.5 mL) and AcOEt (1.5 mL), and a saturated aqueous NaHCO<sub>3</sub> solution was then added. The organic phase was separated, dried (MgSO<sub>4</sub>), filtered and evaporated under RP, thus leaving a white solid (122 mg ; 72%), m.p. 166-167°C and [α]<sub>D</sub> +14.0 (1.0, MeOH). A recrystallization from a mixture of AcOEt and pentane afforded (S)-(+)-**21** (100 mg ; 59%) as white crystals, m.p. 168-169°C and [α] +14.1 (1.1, MeOH). Lit.<sup>8</sup> m.p. 163-165°C and [α]<sub>D</sub> +16.4 (1.0, MeOH). IR (KBr) : 3056 (OH), 2809, 1681 (NHCO) and 1602 (aryl) cm<sup>-1</sup>. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ : 10.42 (1H, s) ; 8.80 (2H, d, J = 5.7 Hz) ; 7.74 (1H, d, J = 8.6 Hz) ; 7.70

(2H, d,  $J = 5.3$  Hz) ; 7.58 (1H, d,  $J = 2.4$  Hz) ; 7.41 (1H, dd,  $J = 8.5$  and  $2.5$  Hz) ; 7.28-7.17 (5H, m) ; 6.66 (1H, d,  $J = 4.3$  Hz) ; 6.02 (1H, d,  $J = 4.3$  Hz).

#### 9-Acetylfluorene **25**

Fluorene **24** (1.70 g ; 10.2 mmol ; recrystallized from ethanol) was thoroughly mixed with freshly sublimed potassium *t*-butoxide (1.72 g ; 15.3 mmol). Dry ethyl acetate (1.5 mL ; 15.3 mmol) in dry ether (20 mL) was added dropwise to the above powdered solids. The resulting mixture was refluxed for 4 h, then cooled and treated with a saturated aqueous solution of  $\text{NH}_4\text{Cl}$  (9 mL). The aqueous phase was extracted with ether (2 x 15 mL). The combined organic phases were dried ( $\text{MgSO}_4$ ), filtered and evaporated under RP, thus leaving a pale yellow solid which was chromatographed over silica gel (80 g ; elution with cyclohexane and then with cyclohexane/ether from 99/1 to 80/20). 9-Acetylfluorene **25** (1.58 g ; 74%) was thus obtained as pale yellow crystals, m.p. 70-72°C. Lit.<sup>14</sup> m.p. 72.5-73.5°C. IR (KBr) : 1702 (CO) and 1446  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  : 7.84 (2H, d,  $J = 7.6$  Hz) ; 7.52 (2H, d,  $J = 7.6$  Hz) ; 7.48 (2H, t,  $J = 7.5$  Hz) ; 7.37 (2H, dt,  $J = 7.4$  and  $0.8$  Hz) ; 4.81 (1H, s) ; 1.63 (3H, s).

#### (*R*)-(+)-And (*S*)-(-)-1-(9-fluorenyl) ethanol **23**

A solution of 9-acetylfluorene **25** (0.4 g ; 1.9 mmol) in dry ether (4 mL) was partially reduced at -15°C in 24 h, by the chiral reagent prepared from ethereal  $\text{LiAlH}_4$  (2.20 mL ; 2.3 mmol) and a solution of (*R*)-(-)-**1** (1.1 g ; 5.8 mmol) in dry ether (16 mL). The crude reaction product was isolated in the usual way and was chromatographed over silica gel (4 g ; elution with cyclohexane/ether from 100/0 to 70/30), thus affording white crystals (93 mg ; 23%), m.p. 78-81°C and  $[\alpha]_D +46.4$  (0.8,  $\text{Me}_2\text{CO}$ ). After two recrystallizations from petrol ether, enantiomerically pure (*R*)-(+)-1-(9-fluorenyl)ethanol (*R*)-(+)-**23** was obtained, m.p. 100-102°C,  $[\alpha]_D +64.2$  (1.1,  $\text{Me}_2\text{CO}$ ) and  $ee > 99\%$  [ $^1\text{H}$  NMR using  $\text{Eu}(\text{hfc})_3$ ]. Lit.<sup>9</sup> m.p. 91-93°C.

Similarly 9-acetylfluorene **25** (920 mg ; 4.41 mmol) in ether (7 mL) was partially reduced at -18°C in 19 h by the reagent prepared from ethereal  $\text{LiAlH}_4$  (4.9 mL ; 5.0 mmol) and (*S*)-(+)-**1** (2.4 g ; 12.5 mmol),  $[\alpha]_D +20.0$  (4.2, EtOH), in ether (35 mL). A pale yellow oil was isolated in the usual manner and was chromatographed as above, thus affording white crystals (418 mg ; 45%),  $[\alpha]_D -54.9$  (1.6,  $\text{Me}_2\text{CO}$ ). After a single recrystallization from petrol ether, (*S*)-(-)-1-(9-fluorenyl)ethanol (*S*)-(-)-**23** (308 mg ; 36%) was obtained, m.p. 107°C,  $[\alpha]_D -65.5$  (1.3,  $\text{Me}_2\text{CO}$ ) and  $ee > 99\%$  [ $^1\text{H}$  NMR using  $\text{Eu}(\text{hfc})_3$ ]. Lit.<sup>9</sup> m.p. 91-93°C. IR ( $\text{CH}_2\text{Cl}_2$ ) : 3367 (OH)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  : 7.78 (2H, d,  $J = 7.6$  Hz) ; 7.73 (1H, d,  $J = 7.6$  Hz) ; 7.56 (1H, d,  $J = 7.8$  Hz) ; 7.41 (2H, tt,  $J = 6.5$  Hz) ; 7.32 (2H, dtd,  $J = 7.4$  and  $1.2$  Hz) ; 4.54 (1H, m) ; 4.15 (1H, d,  $J = 4.3$  Hz) ; 1.69 (1H, d,  $J = 4.7$  Hz) ; 0.92 (3H, d,  $J = 6.4$  Hz). The absolute configurations of (*R*)-(+)-**23** and (*S*)-(-)-**23** were determined using Horeau's method.<sup>7</sup>

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