Asymmetric Synthesis and Absolute Configuration of (+)- and
(−)-Perhexiline

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This work is dedicated to Professor Iwao Ojima on the occasion of  
his 70th birthday.

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Abstract  
Racemic perhexiline has been used (or is currently undergoing  
clinical trials) for the treatment of a variety of cardiovascular  
disorders. Increasing evidence suggests that the (−)-enantiomer should be  
used, as opposed to the racemic mixture. Here, we report the first  
asymmetric synthesis of both enantiomers of perhexiline in high enan-  
tiometric excess and the assignment of their (−)-S/(+)−R absolute stereo-  
chemistry by X-ray crystallography.

Key words  
perhexiline, asymmetric synthesis, stereochemistry, me-  
dicinal chemistry, crystal structure

Cardiovascular diseases are the leading cause of death  
in the developed world and they are now also one of the  
leading causes of death in the developing world. Among  
cases of heart failure (HF), systolic HF can be treated phar-  
macologically by a number of therapeutic agents, such as  
loop diuretics, β-blockers, and inhibitors of angiotensin-  
converting enzyme. In contrast, diastolic HF currently has  
no effective treatments, and its prognosis is comparable to  
that of systolic HF.1a Clinical trials of perhexiline in systolic  
HF1a and hypertrophic cardiomyopathy1c have shown excellent  
efficacy, and perhexiline is currently in Phase II clinical  
trials for the treatment of diastolic HF (NCT00839228).  

Perhexiline was originally designed as an antianginal  
drug, and was launched on the UK market in 1975 under  
the trade name Pexid, as a racemic mixture of the maleate  
salt; however, it was withdrawn in 1985, owing to serious  
side-effects, including neuro- and hepatotoxicity. Currently,  
racemic perhexiline maleate is still used as an antianginal  
drug in Australia and New Zealand, where it is adminis-  
tered under strict medical surveillance. The drug is highly  
efficacious in many cardiac contexts in which alternative  
treatments have failed.2 However, the primary route of me-  
tabolism for perhexiline is via CYP2D6,2a a member of the  
cytochrome P450 oxidase system for which many polymor-  
phisms exist. The rate of perhexiline clearance can vary  
100-fold between patients; consequently, it is unlikely that  
racemic perhexiline could ever be reintroduced for clinical  
use outside a controlled and carefully monitored patient  
population. Perhexiline is believed to be an inhibitor of car-  
nitine palmitoyltransferase-1 (CPT-1), and probably also of  
carnitine palmitoyltransferase-2 (CPT-2).2 These enzymes  
are responsible for the transport of free mid- and long-  
chain fatty acids across mitochondrial cell membranes. Re-  
cent research has revealed the ability of perhexiline to alter  
myocardial metabolism from fatty acid to carbohydrate  
consumption, which improves substrate-utilization effi-  
ciency.2a As an effective CPT-1 inhibitor, perhexiline might  
also represent a potential candidate for use as an anticancer  
drug.5–7

It has long been known that the pharmacokinetic prop-  
erties of the two enantiomers of perhexiline differ, and that  
(−)-perhexiline is more rapidly metabolized than (+)-per-  
hexiline.3 In addition, the two enantiomers have different  
metabolic fates and produce different metabolites.8 It has  
recently been shown that (+)- and (−)-perhexiline also have  
different pharmacodynamic profiles, and it has been sug-  
ggested that the (−)-enantiomer is primarily responsible for  
the therapeutic effects, whereas the (+)-enantiomer is pri-  
marily responsible for the toxic effects.3 It has been pro-  
posed that the use of (−)-perhexiline, as opposed to the ra-  
cemic mixture, might represent an important therapeutic  
strategy for the treatment of a number of cardiovascular  
conditions, which would not be restricted to limited patient  
populations or to use in clinical environments, thereby  
benefitting a wider patient population for a range of cardio-  
vascular diseases (e.g., HF).
To the best of our knowledge, however, the absolute configuration of the (+)- and (-)-perhexiline enantiomers is unknown and no stereoselective synthesis of perhexiline has yet been reported.

In terms of its structure, perhexiline consists of a piperidine framework with a 2,2-dicyclohexylethyl substituent at the 2-position (Scheme 1). The known synthesis of racemic perhexiline ([rac]-1) is based on nucleophilic addition of lithiated 2-picoline to dicyclohexyl ketone to give the corresponding tertiary lithium alkoxide, which undergoes thioyl chloride mediated elimination and subsequent full reduction catalyzed by a transition metal in an acidic reaction medium under a hydrogen atmosphere.9

Optically enriched perhexiline has been hitherto obtained by resolution of the 1,1’-binaphthyl-2,2’-diyl[(hydrogen]phosphate (BNPA) diastereomeric salts of perhexiline by a series of fractional crystallization processes.9 ([S]-(-)-Perhexiline ([S]-1) can be obtained by treatment of rac-perhexiline ([rac]-1) with ([S]-(+)-BNPA, followed by crystallization from a methanol–acetone mixture, whereas the (+)-enantiomer ([R]-1) is prepared by resolution with ([R]-(-)-BNPA. Although the two enantiomers are obtained with high optical purity by chiral resolution of rac-perhexiline, this process requires tedious iterative crystallization operations from the diastereomeric salts, which limits the availability of both enantiomers.

Here, we report an efficient and scalable synthesis of both enantiomers of perhexiline in high enantiomeric excess through a stereoselective catalytic hydrogenation of the 2-(oxazolidin-2-one)-substituted-pyridine 2 (Scheme 2) as a key precursor;10–13 we also report the elucidation of the absolute configurations of the two enantiomers of perhexiline.

By addition of lithiated 6-chloro-2-picoline to dicyclohexylmethane, followed by a one-pot elimination using thionyl chloride, we obtained the intermediate 3 (Scheme 2) as a 2:1 mixture of noninterconverting double-bond regioisomers, not separable by silica gel chromatography. In the sequence leading to ([S]-perhexiline ([S]-1), the ([R]-oxazolidinone was employed for Ullmann–Goldberg coupling14,15 to afford the chiral pyridines ([R]-2 as a 2:1 ratio of regioisomers. Full reduction of the pyridine-oxazolidinone adducts ([R]-2 in acetic acid with one atmosphere of hydrogen in the presence of Pearlman’s catalyst [Pd(OH)2] gave the desired hydrogenation product 1. We hypothesize that the stereocontrol stems from a rigid six-membered-ring intermediate 1 (Scheme 2), in which the orientation of the chiral auxiliary is rigidly defined by hydrogen bonding between its carbonyl group and the adjacent pyridinium nitrogen, leading to efficient shielding of one n-face. As a result, hydrogen atoms absorbed onto heterogeneous catalysts can be predominantly delivered from the face of the
isopropyl group opposite to the aromatic system. Based on a conformational analysis of the intermediate 1, the (R)-auxiliary should result in a piperidine skeleton with an (S)-configuration. Polarimetric analysis showed levorotation indicating that the stereochemical assignment of this product is (S)-(−)-perhexiline [(S)-1] (70% overall yield, 93% ee).16 (R)-(−)-perhexiline [(R)-1] (68% overall yield, 88% ee) was then synthesized by using the corresponding (S)-chiral auxiliary, following the same protocol (Scheme 2).

A range of heterogeneous catalysts was evaluated for asymmetric hydrogenation of (R)-2 as a model system to give enantiomerically enriched (S)-(−)-perhexiline 1 [(S)-1] (Table 1). Conventional palladium-, platinum- and rhodium-based heterogeneous catalysts were screened, and the progress of the hydrogenation was monitored by electro-spray ionization mass spectrometry. Palladium and platinum catalysts were found to be effective, affording (S)-(−)-perhexiline [(S)-1] in good to excellent enantiomeric excess (Table 1, entries 1–4). Conversely, the rhodium/alumina-catalyzed hydrogenation (entry 5) was sluggish (>168 hours), and showed no improvement at a higher temperature. Note that (R)-2 was reduced to the intermediate aminal 4 after 24 hours under one atmosphere of hydrogen at 23 °C in acetic acid, but the dissociation of the auxiliary from aminal 4 to give the iminium ion 5 and the subsequent hydrogenation of the C=N bond to give the desired product and the oxazolidinone required longer reaction times under these conditions.

Palladium(II) hydroxide/carbon was found to be the optimal catalytic system for hydrogenation of the regioisomeric pyridine–oxazolidinone adducts 2, giving perhexiline with high optical purity and yield. Treatment of (R)-2 with palladium(II) hydroxide/carbon under one atmosphere of hydrogen in acetic acid at 23 °C for 24 h, followed by increasing the temperature to 65 °C, facilitated the formation of (S)-(−)-perhexiline [(S)-1] with no loss of stereoselectivity (Table 1, entry 4).

Having established the asymmetric hydrogenation profiles of the pyridine–oxazolidinone adducts 2, we turned our attention to the synthesis of enantiomerically pure (R)-(−)-perhexiline [(R)-1] on a preparative scale by using catalyst (S)-2 (2.16 mmol) under the optimal conditions, namely 20 mol% palladium(II) hydroxide in acetic acid at 23 °C. Upon completion of the hydrogenation, hydrochloric acid was added to form the perhexiline hydrochloride, salt which was purified to afford (−)-perhexiline hydrochloride [(+)-6; 91% yield, 88% ee], with 85% recovery of the chiral auxiliary. Further crystallization of (−)-6 from 1:1 dichloromethane–ethyl acetate gave 420 mg of (+)-perhexiline hydrochloride [(+)-6] (68% yield, 98% ee) as crystals suitable for X-ray structural analysis, which confirmed the (R)-absolute configuration of the (+)-enantiomer (Figure 1).17

The six-membered rings in the C$_7$H$_8$N$^{+}$ cation adopt chair conformations, with the linking bond in an equatorial orientation in each case. The C5–C6–C7–C8 link has an anti-orientation [torsion angle = 165.8 (3)°], whereas the C5–C6–C7–C14 link is gauche [−67.0 (3)°]. The C8–C13 ring is disordered over two orientations in a 0.814(5):0.186(5) ratio. In the extended structure, the chloride ions bridge the cations into [010] chains through N–H···Cl hydrogen bonds.

In conclusion, we have developed a practical and scalable asymmetric synthesis of both enantiomers perhexiline with excellent optical purities. The method involves a late-stage asymmetric hydrogenation of the 2-oxazolidinone-

### Table 1  Screening of Heterogeneous Catalysts for Stereoselective Hydrogenation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst*</th>
<th>Time (h)</th>
<th>Yieldb (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OH)$_2$/C</td>
<td>96</td>
<td>92</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>PtO$_2$</td>
<td>72</td>
<td>85</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>Pd/C</td>
<td>60</td>
<td>62</td>
<td>90</td>
</tr>
<tr>
<td>4d</td>
<td>Pd(OH)$_2$/C</td>
<td>48</td>
<td>88</td>
<td>92</td>
</tr>
<tr>
<td>5e</td>
<td>Rh/Al$_2$O$_3$</td>
<td>&gt;168</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

* Reaction conditions: catalyst loading: 2% metal-to-substrate ratio, AcOH, 23 °C, H$_2$ (1 atm).

b Isolated yield.

d Determined by chiral HPLC analysis of the N-benzoyl derivative 7; HPLC conditions: ChiralPak IA, 4.6 × 250 mm, 5 μm, mobile phase: 2-propanol–hexane (3:97); flow rate: 0.6 mL/min; UV/vis detection: 220 nm.

e Reaction carried out at 23 °C for 24 h and then at 65 °C.

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substituted pyridines 2 catalyzed by active charcoal-supported palladium(II) hydroxide in acetic acid under one atmosphere of hydrogen, and traceless cleavage of the chiral auxiliary, which can be recycled. Furthermore, the (−)-(S) and (+)-(R) absolute configurations of the perhexiline enantiomers have been unambiguously assigned by X-ray crystallography.

All reactions were carried out under N2 or argon in dry solvents under anhydrous conditions, unless otherwise mentioned. Solvents and reagents: Anhyd THF, Et2O, CH2Cl2, and toluene were purchased from commercial suppliers. Reagents were purchased at the highest commercial purity, according to the method described by Still. 18

The mixture was then cooled to –78 °C, and a solution of Cy2CO (2.56 mmol, 11 mmol, 1.2 mL) in THF (15 mL) at –78 °C. The resulting red solution was stirred at –78 °C for 10 min then warmed to –10 °C for 20 min. The mixture was then cooled to –78 °C, and a solution of Cy2CO (2.56 g, 13.2 mmol, 2.6 mL) in THF (2 mL) was added. The mixture was stirred at –78 °C for 30 min, then SOCl2 (2.12 g, 17.8 mmol, 1.3 mL) was added. The milky mixture was warmed to 0 °C for 30 min and then the reaction was quenched with sat. aq NH4Cl (10 mL). The mixture was diluted with EtOAc (20 mL), and the layers were separated. The organic layer was washed with brine (20 mL), dried (Na2SO4), and concentrated in vacuo. Flash column chromatography [silica gel, hexanes–EtOAc (5:1)] gave a mixture of pyridines 3 as a white amorphous solid; yield: 2.87 g (85%, –2:1 mixture of regioisomers by 1H NMR).

IR (film): 2926, 2851, 1632, 1578, 1436, 1134, 188 cm−1.

1H NMR (400 MHz, CDCl3): δ = 7.59–7.43 (m, 1 H), 7.15–6.88 (m, 2 H), 6.21 (s, 0.6 H), 3.58 (s, 0.6 H), 3.17 (tt, J = 11.7, 3.1 Hz, 0.6 H), 2.68–2.55 (m, 0.3 H), 2.32–2.39 (m, 0.1 H), 2.35–2.23 (m, 0.6 H), 2.16–2.05 (m, 0.6 H), 2.05–1.99 (m, 0.6 H), 1.88–1.51 (m, 9 H), 1.50–0.99 (m, 10 H).

13C NMR (100.6 MHz, CDCl3): δ = 163.4, 160.2, 158.4, 150.3, 150.2, 138.5, 138.2, 136.6, 129.9, 121.9, 121.6, 120.9, 120.5, 120.2, 49.1, 40.8, 40.7, 40.3, 36.4, 34.8, 31.7, 31.6, 30.5, 30.1, 28.6, 28.5, 28.0, 27.0, 26.9, 26.6, 26.24, 26.21, 26.1, 26.0, 25.8, 25.7.


HRMS (ESI): m/z [M + H]+ calcld for C19H27NCl: 304.1827; found: 304.1825 (∆ = 0.5 ppm).

(3)-R-3-[6-(2,2-Dicyclohexylvinyl)pyridin-2-yl]-4-isopropyl-1,3-oxazolidin-2-one [(R)-3](751 mg, 2.47 mmol) in toluene (10 mL). (+)-3-[6-(2-Cyclohexyl-2-cyclohexylideneethane-1,2-diamine (99 mg, 1.13 mmol, 99% ee), CuI (141 mg, 0.74 mmol), N,N′-dimethylhex-1,2-diamine (99 mg, 1.13 mmol, 121 μL), and K2CO3 (683 mg, 4.95 mmol) were added to the stirred solution at 23 °C, and the tube was sealed. The resulting mixture was stirred and heated at 140 °C for 60 h, then cooled to 23 °C. The reaction was quenched with sat. aq NH4Cl (10 mL), and the mixture was diluted with EtOAc (10 mL). The layers were separated and the organic layer was washed with brine (20 mL), dried (Na2SO4), and concentrated in vacuo. Flash column chromatography [silica gel, hexanes–EtOAc (2:1)] gave the regioisomeric adducts (R)-2 as a white amorphous solid; yield: 878 mg (90%, –2:1 mixture of regioisomers by 1H NMR).

IR (film): 2923, 2850, 1758, 1578, 1484, 1437, 1392, 1207, 1156, 796 cm−1.

1H NMR (400 MHz, CDCl3): δ = 7.95–7.78 (m, 1 H), 7.70–7.58 (m, 0.66 H), 7.58–7.53 (m, 0.35 H), 6.95–6.77 (m, 1 H), 6.15 (s, 0.66 H), 5.01–4.84 (m, 1 H), 4.45–4.31 (m, 1 H), 4.31–4.20 (m, 1 H), 3.55–3.39 (m, 1.33 H), 2.63–2.38 (m, 1.4 H), 2.28 (s, 0.66 H), 2.15–2.04 (m, 1.34 H), 1.85–1.51 (m, 9 H), 1.48–1.08 (m, 9.6 H), 0.97–0.86 (m, 3 H), 0.81 (d, J = 6.8 Hz, 3 H).

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Table 1, Entry 4

(R)-2 (85 mg, 0.214 mmol) and wet 20% Pd(OH)\textsubscript{2}/active charcoal (18 mg) were employed, following the procedure of entry 1, modified as follows. The suspension was stirred at 23 °C for 24 h under an atmosphere of H\textsubscript{2} before it was heated to 65 °C for 24 h. Purification by flash column chromatography [silica gel, MeOH–CH\textsubscript{2}Cl\textsubscript{2} (0:100 to 10:90)] gave (S)-1: yield: 52.3 mg (88%, 92% ee).

Table 1, Entry 5

(R)-2 (60 mg, 0.151 mmol) and 5% Rh/Al\textsubscript{2}O\textsubscript{3} (24 mg) were employed, following the procedure of entry 1, modified as follows. The suspension was stirred at 23 °C for 24 h under an atmosphere of H\textsubscript{2} then heated to 80 °C (ESI-MS monitoring). The majority of products were found to be partially hydrogenated, and no further progress was made after stirring at 80 °C for over 144 h.

(R)-(+)-Perhexiline [(R)-1]  
This was prepared by the same method as described above for preparing (S)-1, but using (S)-2 (55 mg, 0.139 mmol) and wet 20% Pd(OH)\textsubscript{2} on active charcoal (11 mg). Purification by flash column chromatography [silica gel, MeOH–CH\textsubscript{2}Cl\textsubscript{2} (0:100 to 10:90)] gave a pale-yellow oil; yield: 34.6 mg (90%, 88% ee); [\(\alpha\textsubscript{D}\)]\textsubscript{28} +5.3 (c 3.4, CH\textsubscript{2}Cl\textsubscript{2}). The analytical and spectroscopic data were identical to those for (S)-1.

(2S)-(–)-2-(2,2-Dicyclohexylethyl)piperidine hydrochloride [(R)-(+)-Perhexiline Hydrochloride] (6)  
This was prepared by the same method as described previously for preparing (S)-1, using (S)-2 (857 mg, 2.16 mmol) and wet 20% Pd(OH)\textsubscript{2}/active charcoal (172 mg) in AcOH (25 mL). The reaction was monitored by ESI-MS analysis until hydrogenation was complete. The mixture was filtered through a plug of Celite and flushed with MeOH (5 mL) and EtOAc (10 mL). The collected filtrates were combined and neutralized with sat. aq NaHCO\textsubscript{3} until effervescence ceased. The layers were separated and the organic layer was washed with brine (20 mL), dried (Na\textsubscript{2}SO\textsubscript{4}), and concentrated in vacuo. Flash column chromatography [silica gel, hexanes–EtOH (20:80)] gave (S)-1: yield: 26.8 mg (62%, 90% ee).

δ (857 mg, 2.16 mmol) and wet 20% Pd(OH)\textsubscript{2}/active charcoal (11 mg). Purification by flash column chromatography [silica gel, MeOH–CH\textsubscript{2}Cl\textsubscript{2} (0:100 to 10:90)] gave a pale-yellow oil; yield: 34.6 mg (90%, 88% ee); [\(\alpha\textsubscript{D}\)]\textsubscript{28} +5.3 (c 3.4, CH\textsubscript{2}Cl\textsubscript{2}). The analytical and spectroscopic data were identical to those for (S)-1.

(2S)-(–)-2-(2,2-Dicyclohexylethyl)piperidine hydrochloride [(R)-(+)-Perhexiline Hydrochloride] (6)  
This was prepared by the same method as described previously for preparing (S)-1, using (S)-2 (857 mg, 2.16 mmol) and wet 20% Pd(OH)\textsubscript{2}/active charcoal (172 mg) in AcOH (25 mL). The reaction was monitored by ESI-MS analysis until hydrogenation was complete. The mixture was filtered through a plug of Celite and flushed with MeOH (3 × 10 mL). The collected filtrates were combined, mixed with 12 N aq HCl (0.36 mL), and concentrated in vacuo until no AcOH remained. Flash column chromatography [silica gel, hexanes–EtOAc (50:50 to 1:00)] gave (S)-1: yield: 617 mg (91%, 88% ee). This was crystallized from 1:1 CH\textsubscript{2}Cl\textsubscript{2}–EtOAc to give white needle crystals; yield: 420 mg (68%, 98% ee); mp 233–235 °C; [\(\alpha\textsubscript{D}\)]\textsubscript{20} +17.6 (c 2.4, EtOH); IR (film): 3391 (br), 2922, 2850, 2709, 2499, 1447, 1268, 732, 700 cm\textsuperscript{-1}.

**Table 1, Entry 1**

(2S)-(–)-2-(2,2-Dicyclohexylethyl)piperidine [(S)-(–)-Perhexiline] (S)-1: Hydrogenation Procedure (Table 1, Entry 1)  
This procedure is a modified version of the method reported by Glori. This to a stirred solution of the pyridine–oxazolidinone adducts (R)-2 (72 mg, 0.182 mmol) in AcOH (10 mL) was added 20% Pd(OH)\textsubscript{2}/active charcoal (15 mg, 50% H\textsubscript{2}O; 2% catalyst–substrate by weight). The reaction vessel was charged with H\textsubscript{2} (1 atm), evacuated, and back-filled with H\textsubscript{2}, and the mixture was stirred at 23 °C under an atmosphere of H\textsubscript{2}. When the hydrogenation was complete (ESI-MS analysis), the mixture was filtered through a plug of Celite and flushed with MeOH (5 mL) and EtOAc (10 mL). The combined filtrates were neutralized with sat. aq NaHCO\textsubscript{3} until effervescence ceased. The layers were separated and the organic layer was washed with brine (20 mL), dried (Na\textsubscript{2}SO\textsubscript{4}), and concentrated in vacuo. Flash column chromatography [silica gel, MeOH–CH\textsubscript{2}Cl\textsubscript{2} (0:100 to 10:90)] gave a pale-yellow oil; yield: 46.4 mg (92%, 93% ee); [\(\alpha\textsubscript{D}\)]\textsubscript{25} = 397 [M + H]+. HRMS (ESI): m/z ccalcd for C\textsubscript{25}H\textsubscript{37}N\textsubscript{2}O\textsubscript{2}: 397.2838; found: 397.2834 (\(\Delta = 1.8\) ppm).

**Table 1, Entry 2**

(R)-2 (60 mg, 0.151 mmol) and PtO\textsubscript{2} (1.2 mg, 2% w/w) were employed, following the procedure of entry 1 above, to give (S)-1: yield: 35.6 mg (85%, 87% ee).

**Table 1, Entry 3**

(R)-2 (62 mg, 0.156 mmol) and dry 10% Pd/active charcoal (12 mg) were employed, following the procedure of entry 1 above, to give (S)-1: yield: 26.8 mg (62%, 90% ee).
with brine (5 mL), dried (Na2SO4), and concentrated in vacuo. Flash column chromatography [silica gel, hexanes–EtOAc (3:1)] gave a colorless oil; yield: 39 mg (95%).

IR (film): 2921, 2850, 1627, 1578, 1445, 1423, 1272, 1011, 784, 732, 700 cm–1.

1H NMR (400 MHz, CDCl3): δ = 7.56–7.27 (m, 5 H), 4.97 (br s, 0.5 H), 4.58 (br s, 0.5 H), 3.89 (br s, 0.5 H), 3.50 (br s, 0.5 H), 3.14 (br s, 0.5 H), 2.90 (br s, 0.5 H), 1.86–0.66 (m, 31 H); rotamers were present at 298 K.

MS (ESI): m/z (%) = 382 [M + H]+.

HRMS (ESI): m/z [M + H] + calcd for C26H40NO+: 382.3104; found: 382.3106 (Δ+0.4 ppm).

(2S)-(–)-1-Benzoyl-2-(2,2-dicyclohexylethyl)piperidine [(S)-(–)-7]

This was prepared by the same method as described above for preparing rac-7, using (S)-perhexiline (42 mg, 0.151 mmol), BzCl (32 mg, 0.23 mmol, 27 μL), DMAP (1 mg, 0.01 mmol), and Et3N (51 mg, 0.504 mmol, 70 μL) to give a colorless oil; yield: 55 mg (95%); [α]D23 +34.7 (c 2.6, CH2Cl2). Spectroscopic data were identical to those for rac-7.

(2R)-(+)1-Benzoyl-2-(2,2-dicyclohexylethyl)piperidine [(R)-(+)7]

This was prepared by the same method as described above for preparing rac-7, using (R)-perhexiline (30 mg, 0.108 mmol), BzCl (23 mg, 0.164 mmol, 19 μL), DMAP (1 mg, 0.01 mmol), and Et3N (36 mg, 0.359 mmol, 50 μL) to give a colorless oil; yield: 38 mg (92%); [α]D23 +31.3 (c 1.5, CH2Cl2). Spectroscopic data were identical to those for rac-7.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560708.

References


(16) Because perhexiline 1 is not UV-detectable, the enantiomeric excesses of perhexiline samples were determined by chiral HPLC analysis of the corresponding UV-detectable benzamide derivatives 7. See the experimental section for details on the preparation of 7 from perhexiline.

(17) Crystallographic data for compound 6 have been deposited with the accession number CCDC 1057017, and can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)366033; E-mail: deposit@ccdc.cam.ac.uk; Web site: www.ccdc.cam.ac.uk/conts/retrieving.html.