Pergamon

Bioorganic & Medicinal Chemistry 8 (2000) 2427–2432

BIOORGANIC & MEDICINAL CHEMISTRY

A Practical Synthesis of the Serotonin 5-HT_{2A} Receptor Antagonist MDL 100907, its Enantiomer and their 3-Phenolic Derivatives as Precursors for [^{11}C]Labeled PET Ligands

Thomas Ullrich and Kenner C. Rice*

Laboratory of Medicinal Chemistry, National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health, Building 8, Room B1-21, Bethesda, MD 20892-0815, USA

Received 18 April 2000; accepted 31 May 2000

Abstract—A practical synthesis of the 3-phenolic precursor of MDL 100907, a selective 5-HT_{2A} receptor antagonist, is described. The route was also applied to the enantiomeric series, thus affording the direct precursors of both 3-[^{11}C]MDL 100907 and its enantiomer as ligands for positron emission tomography. Similar methodology was developed for the direct synthesis of MDL 100907 and its enantiomer, MDL 100009. The routes utilized classical optical resolution of the *N*-nor intermediates in at least 98% enantiomeric excess and easily afforded multigram amounts of the chiral precursors of a variety of *N*- and 3-*O*-substituted enantiomers.

Introduction

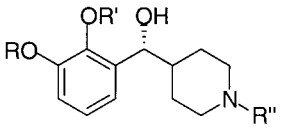
MDL 100907 (+)-**1a**, (*R*)-(+)-α-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-piperidinemethanol (Fig. 1), exhibits very high affinity and selectivity for serotonin 5-HT_{2A} receptors.[1] Its outstanding in vivo potency was documented in several pharmacological assays and led to application studies for a variety of disease states and conditions.[2] Positron emission tomography (PET) is an effective way to quantitatively measure receptor-related parameters in vivo. The availability of a high affinity and selective 5-HT_{2A} receptor ligand appropriately labeled would be of great interest as a tool to study the role of this receptor in several psychiatric disorders such as depression[3] and schizophrenia.[4] Although other radioligands have been used to study the 5-HT_{2A} receptor, including [^{11}C]*N*-methylspiperone,[5] [^{18}F]setoperone,[6] and [^{18}F]altanserin,[7] they either lack the necessary selectivity or have radio-metabolites which cross the blood–brain barrier. Carbon-11-labeled MDL 100907 has been synthesized and evaluated as a useful radioligand for 5-HT_{2A} receptor mapping in PET studies.[8] Radiolabeling by means of replacement of either of the *O*-methyl groups with an [^{11}C]methyl substituent has been reported.[8,9] The 3-labeled compound **3**, however, appears to be more useful for monkey and human PET studies, as MDL 100907 is partly metabolized to its 3-OH-analogue MDL 105725, (+)-**4**. Labeling in the 2-position [(+)-**2**] would therefore lead to extensive formation of labeled 3-OH-analogue, which may be expected to enter the brain and thus interfere with the interpretation of [^{11}C]MDL 100907 uptake.[9]

A useful route to (+)-**3** has recently been described by Huang et al.,[10] employing synthesis of the racemic phenolic precursor molecule (±)-**4**, followed by chiral derivatization with (*S*)-(+)-α-methoxyphenylacetic acid and flash chromatography separation. In an effort to improve practical aspects of the synthesis, we decided to modify this strategy in two respects:

(a) The optical resolution should be performed at an earlier stage of the synthesis, in particular before adding the *p*-fluorophenethyl substituent to the piperidine moiety. This would provide the possibility of introducing a variety of *N*-substituents, representing lipophilic domains of the compound, into the already optically resolved and protected material. Deprotection would then allow *O*-substitution.
(b) The method of optical resolution of (±)-**5b** should allow the preparation of both equally accessible enantiomers and convenient handling on a multigram scale, rather than being limited by the common disadvantages of silica gel chromatography.

*Corresponding author. Tel.: +1-301-496-1856; fax: +1-301-402-0589; e-mail: kr21f@nih.gov

0968-0896/00/$ - see front matter
PII: S0968-0896(00)00175-9



(+)-1a, R = R' = Me, R'' = p-fluorophenethyl, **MDL 100907**
(+)-1b, R = TBDPS, R' = Me, R'' = p-fluorophenethyl
(+)-2, R = Me, R' = [^{11}Me], R'' = p-fluorophenethyl
(+)-3, R = [^{11}Me], R' = Me, R'' = p-fluorophenethyl
(+)-4, R = H, R' = Me, R'' = p-fluorophenethyl, **MDL 105705**
(±)-5a, R = Me, R' = Me, R'' = H
(±)-5b, R = TBDPS, R' = Me, R'' = H

Figure 1.

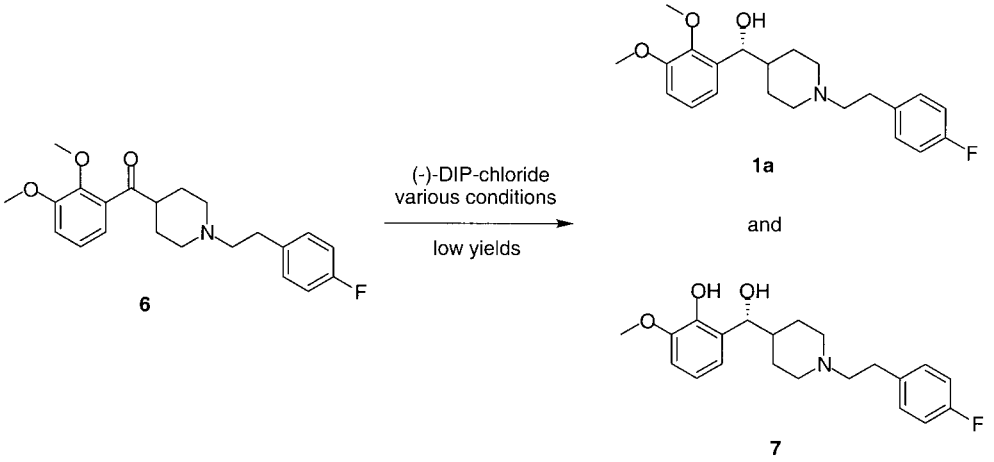
The radiolabeled enantiomer 2-*O*-[^{11}C]MDL 100009, (−)-**2**, was also investigated in PET studies and showed nonspecific, uniform brain distribution without regional localization, being consistent with the lower affinity of MDL 100009 for the 5-HT_{2A} receptor.[11] Availability of larger quantities of MDL 100009 and its labeled derivative was therefore considered desirable with respect to their use as potential controls in various biological studies.

Results and Discussion

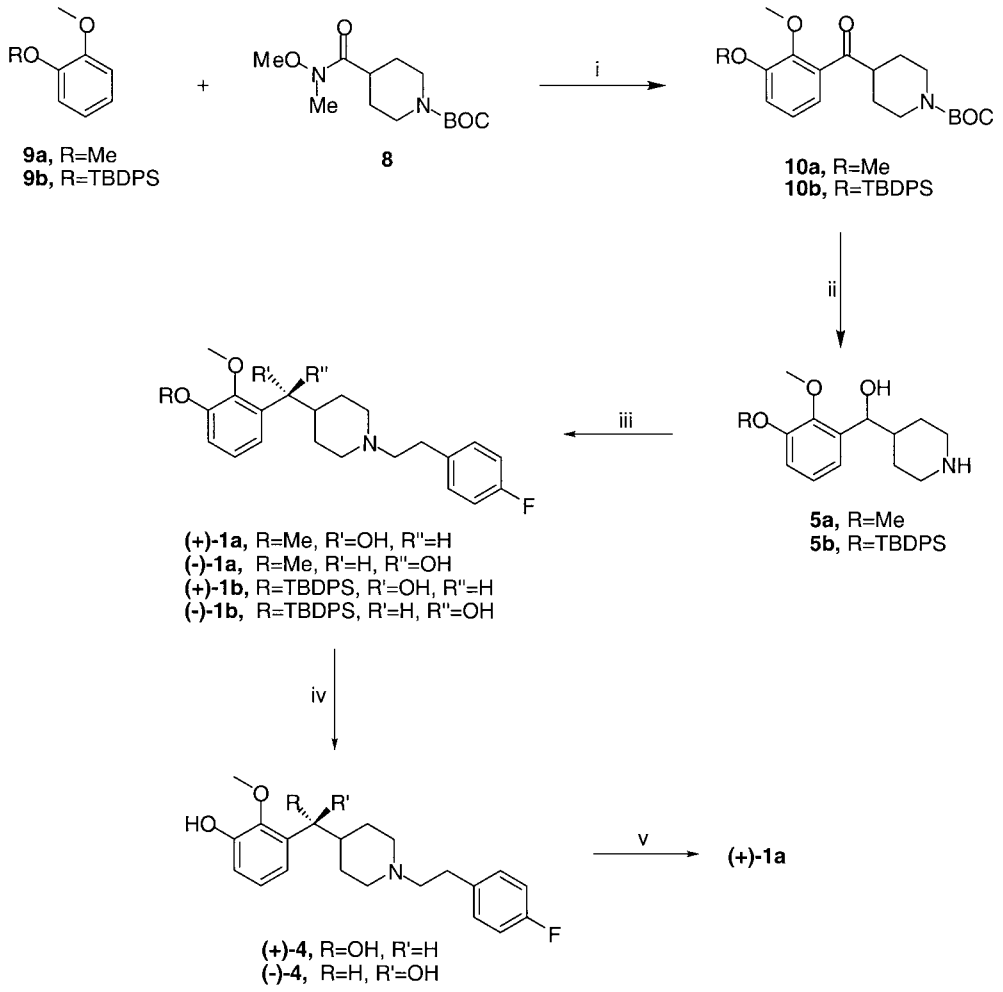
We initially examined asymmetric synthesis in order to overcome the drawbacks of chromatographic purification of diastereomers. This study involved the reduction of ketone **6** (Scheme 1), a precursor of MDL 100907, the preparation of which had been described in patent literature.[2] As a reagent of choice, *B*-chlorodiisopinocampheylborane (DIP-chloride) was considered for its high reactivity towards a variety of aralkyl ketones with predictable stereochemistry and high enantiomeric yields.[12] However, when ketone **6** was treated with commercial (−)-DIP-chloride in THF at between −25 and 0 °C—conditions reported to be most appropriate for this type of reaction[13]—no significant conversion could be observed. Using $CHCl_3$ instead of THF gave between 25 and 30% of desired product (+)-**1a**, but optical purity was found to be less than 70% ee. Elevation of temperature up to 60 °C led to higher yields (50–60%) but was detrimental to enantioselectivity and furthermore resulted in partial *O*-demethylation in the adjacent aromatic methoxy-substituent to give phenolic derivative **7**.[10] When (−)-DIP-chloride was prepared in situ, following a reported procedure,[14] no improvement was achieved. We decided then to focus our endeavors on optical resolution via formation of diastereomeric salts, as described in the following.

The t-Boc-protected *Weinreb* amide **8** and regioselectively *ortho*-lithiated TBDPS-guaiacol **9b** were prepared according to the literature[2,15] and reacted to afford ketone **10b** (Scheme 2). *N*-Deprotection with TFA and reduction of the carbonyl group with $NaBH_4$ gave racemic alcohol **5b**. The latter was successfully optically resolved by means of salt formation with (+)- and (−)-mandelic acid, respectively. The diastereomeric salts were isolated and recrystallized twice from methanol. Aqueous work up afforded the enantiomers in a purity of ee > 98% each, as evaluated with (*R*)-(−)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate (−)-BNP as an appropriate ^{1}H NMR-shift reagent for determining the enantiomeric ratio of amines.[16] The benzylic proton adjacent to the hydroxyl group was characterized by an isolated doublet (4.6 ppm) downfield from all other aliphatic signals. When 1.0 ± 0.3 equiv of weight of (−)-BNP was added to the racemic compound in $CDCl_3$, the peak multiplied to 2 doublets with a shift difference of approx. 0.1–0.2 ppm (Varian Gemini 300 FT-NMR spectrometer). Chemical shift changes of this signal were strictly linear with respect to the relative concentration of amine and (−)-BNP. Higher concentrations of (−)-BNP caused significant proton signal broadening, and were detrimental to the accuracy of spectrum interpretation, whereas lower concentrations led to insufficient peak splitting.

Resolved compounds (+)- and (−)-**5b** underwent *N*-alkylation with (2-bromoethyl)-4-fluorobenzene, which was obtained by treatment of commercial 4-fluorophenethyl alcohol with PBr_3.[17] Subsequent cleavage of the TBDPS-group was not performed by usual employment of strong bases[18] or TBAF.[19] Alternatively, the



Scheme 1.



Scheme 2. Reagents: (i) *n*-BuLi, THF, −50 °C, 61–84%; (ii) a. TFA, 25–30 °C; b. $NaBH_4$, MeOH, 25–30 °C, 71–74%; (iii) a. optical resolution; b. (4-F-Ph)C_2H_4Br, $NaHCO_3$, DMF, 80 °C, 72–80%; (iv) NH_4F (5 equiv), MeOH, 60 °C, 88%; (v) CH_2N_2, MeOH/Et_2O, rt, 79%.

inorganic nucleophile NH_4F afforded deprotected material selectively without the common work up problems caused by the phase-transfer properties of TBAF.[20] After chromatographic purification, (+)- and (−)-**4** were obtained as crystalline materials in multi-gram quantities.

As the described strategy of optical resolution proved to be very convenient and the enantiomers could be obtained in substantial overall yields, we applied a parallel methodology to the synthesis of MDL 100907 **1a** which we also needed for further biological studies. This synthetic route dispenses with the two steps of introduction and cleavage of the TBDPS group, veratrole **9a** (R = Me) being the starting material (Scheme 2). Ketone **10a** was synthesized as described in the literature,[2] while the deprotection/reduction step was carried out as mentioned above. Optical resolution of **5a** was achieved correspondingly. Whereas employment of mandelic acid did not afford crystalline salts, we succeeded using (+)- and (−)-di-*O,O′*-*p*-toluyltartaric acid, respectively. After we completed optical resolution of **5a**, a similar method using the same chiral acids was independently published in patent literature,[21] being in line with our findings. Three recrystallizations of the diastereomeric salts from MeOH, respectively, were found to be mandatory in order to reach purities >98% ee, resulting in slightly lower overall yields than in the case of (+)- and (−)-**5b**. Analysis of the optical purity was performed with the same ^{1}H NMR shift reagent as mentioned above.

Phenolic compound (+)-**4** could be easily transformed into (+)-**1a** under mild methylation conditions, using diazomethane in MeOH/Et_2O, a method successfully described for multifunctional aminoalkylphenols.[22] The (+)-**1a** thus obtained was identical with the sample prepared by *N*-alkylation of (+)-**5a**.

Absolute configurations for the enantiomers of **1a** and **4** are reported in the literature.[2,10] Since (+)-**4** is derived from (−)-**5b** via (−)-**1b** and afforded (*R*)-(+)-**1a** on methylation, the absolute configurations of these precursors are *R* and those of their enantiomers are *S*. These results are in agreement with the configuration previously stated[10] for (+)-**4**.

Conclusion

The present method represents a facile route to the [^{11}C]MDL 100907 precursor, MDL 105725, and its

enantiomer. Apart from few synthetic steps and high yields, its outstanding feature is the formation of salts for optical resolution, which affords either of the desired enantiomers and allows practical synthesis of the compound on a multi-gram scale. Furthermore, it offers the possibility to introduce various lipophilic domains by *N*-alkylation into an already resolved molecule, as well as 3-*O*-substituents. In addition, simplified methodology is described for the synthesis of multi-gram quantities of MDL 100907 and its enantiomer, MDL 100009. Both accomplishments contribute to a remarkable improvement of synthetic routes previously reported.

Experimental

General methods

Unless otherwise indicated, all reagents were purchased from commercial suppliers and used without further purification. TLC analyses were carried out on Analtech silica gel GHLF 0.25 mm plates, and spots were visualized with UV light and I_2. Chromatography refers to flash chromatography using Fluka silica gel 60, 220–240 mesh. Melting points were measured in open glass capillaries on a Thomas-Hoover melting point apparatus and are uncorrected. Optical analyses were carried out on a Perkin Elmer 341 polarimeter. ^{1}H NMR spectra were recorded at 300 MHz on a Varian Gemini spectrometer and are reported as ppm downfield from Me_4Si with multiplicity, number of protons, and coupling constant(s) in Hertz indicated parenthetically. The following abbreviations are used to indicate spin multiplicities: s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublets), t (triplet) or m (multiplet). Mass spectra (MS) were recorded on a VG 7070E spectrometer or a Finnigan 4600 spectrometer. Elemental analyses (C, H, and N) were performed by Atlantic Microlabs Inc., Norcross, GA, and the obtained results were within 0.4% of the theoretical values.

4-[2-Methoxy-3-[(1,1-dimethylethyl)diphenylsilyl]oxybenzoyl]-1-piperidinecarboxylic acid 1,1-dimethylethyl ester (10b). *n*-Butyllithium (64.5 mL of a 2.5 M solution in hexane, 161 mmol) was added to a stirred solution of (2-methoxyphenoxy)-(1,1-dimethylethyl)diphenylsilane[11] **9b** (58.4 g, 161 mmol) under nitrogen at 0 °C. The ice bath was removed and the solution was allowed to stir for 2 h. After cooling to −50 °C, 4-(*N*-methoxy-*N*-methyl-carboxamido)-1-piperidinecarboxylic acid 1,1-dimethyl ester[2] **8** (41.8 g, 153 mmol) was added dropwise to the stirred solution, followed by warming to room temperature and stirring for 2 h. Saturated aqueous NH_4Cl was added; the layers were separated and the aqueous layer was extracted 3× with ether. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and evaporated to afford a viscous oil. Filtration of the residue through silica gel 60 with 10:1 petroleum ether:EtOAc gave 53.5 g (61%) of **10b** as a colorless oil: R_f 0.4 (silica gel, 10:1 petroleum ether:EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.15 (s, 9H), 1.44 (s, 9H), 1.45–1.70 (m, 2H), 1.73–1.85 (m, 2H), 2.79–2.91 (m, 2H), 3.13–3.26 (m, 1H), 3.92 (s, 3H), 4.03–4.16 (m, 2H), 6.62 (dd, J = 8, 2 Hz, 1H), 6.70 (t, J = 8 Hz, 1H), 6.86 (dd, J = 8, 2 Hz, 1H), 7.33–7.48 (m, 6H), 7.73 (d, J = 8 Hz, 4H); MS (CI with NH_3) m/z 574 (M + 1). Anal. calcd for $C_{34}H_{43}NO_5Si$: C, 71.16; H, 7.55; N, 2.44; found: C, 70.92; H, 7.77; N, 2.34.

General procedure for Boc-deprotection and reduction of the carbonyl group

Ketone **10a** or **10b** (70 mmol) was carefully and gradually dissolved in trifluoroacetic acid (160 mL) with cooling at 25–30 °C. After 30 min of stirring at room temperature, the solution was diluted with 500 mL of ether and carefully neutralized with NH_4OH and ice bath cooling. The layers were separated and the aqueous layer was extracted 3× with ether. The combined organic extracts were washed with water, dried (Na_2SO_4), filtered and evaporated to afford a viscous oil that was dissolved in anhydrous MeOH (400 mL) and stirred under a nitrogen atmosphere. $NaBH_4$ (140 mmol) was added gradually at 25–30 °C, and the solution was stirred until no more gas evolved. After evaporation of the solvent, the residue was taken up in NH_4OH and extracted 3× with $CHCl_3$. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and evaporated to afford a viscous oil that crystallized when triturated with diisopropyl ether.

(±)-α-(2,3-Dimethoxyphenyl)-4-piperidinemethanol ((±)-5a). The compound was obtained as colorless crystals (71%); R_f 0.4 (silica gel, 5:1 MeOH:NH_4OH); mp 169–170 °C; ^{1}H NMR ($CDCl_3$) δ 1.18–1.40 (m, 3H), 1.65–1.85 (m, 1H), 1.86–2.14 (m, 2H), 2.43–2.67 (m, 2H), 2.97–3.09 (m, 1H), 3.11–3.19 (m, 1H), 3.89 (s, 6H), 4.62 (d, J = 8 Hz, 1H), 6.81–6.97 (m, 2H), 7.04 (t, J = 8 Hz, 1H); MS (CI with NH_3) m/z 252 (M + 1); anal. calcd for $C_{14}H_{21}NO_3$: C, 66.90; H, 8.42; N, 5.57; found: C, 66.66; H, 8.42; N, 5.58.

(±)-α-[2-Methoxy-3-[(1,1-dimethylethyl)diphenylsilyl]oxyphenyl]-4-piperidinemethanol ((±)-5b). The compound was obtained as colorless crystals (74%); R_f 0.35 (silica gel, 7:3:0.5 $CHCl_3$:MeOH:NH_4OH); mp 166–168 °C; ^{1}H NMR ($CDCl_3$): δ 1.14 (s, 9H), 1.18–1.37 (m, 3H), 1.75 (bs, 1H), 1.94–2.07 (m, 1H), 2.22–2.41 (m, 2H), 2.54 (m, 1H), 2.98–3.10 (m, 1H), 3.11–3.19 (m, 1H), 3.97 (s, 3H), 4.64 (d, J = 8 Hz, 1H), 6.44 (dd, J = 8, 2 Hz, 1H), 6.65 (t, J = 8 Hz, 1H), 6.80 (dd, J = 8, 2 Hz, 1H), 7.33–7.48 (m, 6H), 7.73 (d, J = 8 Hz, 4H); MS (CI with NH_3) m/z 476 (M + 1); anal. calcd for $C_{29}H_{37}NO_3Si$: C, 73.22; H, 7.84; N, 2.94; found: C, 72.96; H, 7.87; N, 2.81.

Optical resolution of 5a

(±)-**5a** (44.7 g, 178 mmol) and (+)-di-*O*,*O*′-*p*-toluyl-D-tartaric acid (68.7 g, 178 mmol) were taken up in hot MeOH (1L) and evaporated to dryness. The residue was recrystallized from *i*-PrOH (without refrigerating). After 2 h, the precipitated material was collected on a Buchner funnel, dried and recrystallized 3× from MeOH. The resolved diastereomeric salt (40.3 g) was then partitioned between NH_4OH and $CHCl_3$, and after separation of the organic layer, the aqueous phase was extracted 2× with $CHCl_3$. The combined organic extracts were washed

with brine, dried (Na_2SO_4), filtered and evaporated to afford 15.9 g (71%) of (*R*)-(+)-**5a** as colorless crystals: mp 194–195 °C; $[\alpha]_D^{20}$ +6.6° (*c* 0.1, MeOH); anal. calcd for $C_{14}H_{21}NO_3$: C, 66.90; H, 8.42; N, 5.57; found: C, 66.68; H, 8.37; N, 5.62.

The combined mother liquors from recrystallization were evaporated and free-based with $NH_4OH/CHCl_3$ in the same manner, to yield 28.8 g (115 mmol) of mixed base, which was treated with (−)-di-*O*,*O*′-*p*-toluyl-L-tartaric acid (44.4 g, 115 mmol) in MeOH (300 mL), as described above. 17.0 g (76%) of (*S*)-(−)-**5a** was obtained as colorless crystals: mp 194–195 °C; $[\alpha]_D^{20}$ −7.1° (*c* 0.1, MeOH); anal. calcd for $C_{14}H_{21}NO_3$: C, 66.90; H, 8.42; N, 5.57; found: C, 66.77; H, 8.41; N, 5.63.

NMR and mass spectral data for both enantiomers are identical with (±)-**5a**. Enantiomeric purity was determined after each step of recrystallization by combining 5 mg of the free-based sample with 5 mg of (*R*)-(−)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate in 0.6 mL of $CDCl_3$ and performing ^1H NMR. The limit of detection of enantiomeric impurity was found to be <2% ee. After two recrystallizations from MeOH no enantiomeric impurity was detected. The salt was then recrystallized a final time.

Optical resolution of 5b

(±)-**5b** (48.1 g, 101 mmol) and (−)-mandelic acid (15.4 g, 101 mmol) were taken up in hot MeOH (600 mL) and evaporated to dryness. The residue was recrystallized from MeOH (without refrigerating). After 2 h, the precipitated material was collected on a Buchner funnel, dried and recrystallized from MeOH again. The resolved diastereomeric salt (26.0 g) was then partitioned between NH_4OH and $CHCl_3$, and after separation of the organic layer, the aqueous phase was extracted 2× with $CHCl_3$. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and evaporated to afford 19.3 g (80%) of (*R*)-(−)-**5b** as colorless crystals: mp 187–189 °C; $[\alpha]_D^{20}$ −46.8° (*c* 0.1, MeOH); anal. calcd for $C_{29}H_{37}NO_3Si$: C, 73.22; H, 7.84; N, 2.94; found: C, 73.07; H, 7.80; N, 2.93.

The combined mother liquors from recrystallization were evaporated and free-based with $NH_4OH/CHCl_3$ in the same manner, to yield 37.8 g (79.5 mmol) of mixed base, which was treated with (+)-mandelic acid (12.1 g, 79.5 mmol) in MeOH (500 mL), as described above. 20.2 g (84%) of (*S*)-(+)-**5b** was obtained as colorless crystals: mp 187–189 °C ($CHCl_3$); $[\alpha]_D^{20}$ +45.5° (*c* 0.1, MeOH); anal. calcd for $C_{29}H_{37}NO_3Si$: C, 73.22; H, 7.84; N, 2.94; found: C, 72.95; H, 7.79; N, 2.90. NMR and mass spectral data for both enantiomers are identical with (±)-**5b**. Enantiomeric purity was determined as mentioned above.

General procedure for *N*-alkylation

A suspension of the appropriate, optically resolved amine **5a** or **5b** (21.4 mmol), $NaHCO_3$ (32.1 mmol), and (2-bromoethyl)-4-fluorobenzene (21.4 mmol) in anhydrous DMF (100 mL) was stirred for 90 min at 85 °C. After evaporation of the solvent, the residue was taken up in NH_4OH and extracted 3× with EtOAc. The combined organic extracts were washed 3× with brine, dried (Na_2SO_4), filtered and evaporated.

(*R*)-(+)-α-(2,3-Dimethoxyphenyl)-1-[2-(4-fluorophenyl) ethyl]-4-piperidinemethanol (+)-1a (MDL 100907). Alkylation of (*R*)-(+)-**5a** as above afforded (*R*)-(+)-**1a**. The compound crystallized when triturated with diisopropylether and gave colorless crystals (95%); mp 113–115 °C; R_f 0.7 (silica gel, 90:8:2 $CHCl_3$:MeOH:NH_4OH); $[\alpha]_D^{20}$ +14.2° (*c* 0.1, MeOH); lit.[2] $[\alpha]_D^{20}$ +13.9°; ^1H NMR ($CDCl_3$) δ 1.23–1.56 (m, 3H), 1.61–1.77 (m, 1H), 1.83–2.26 (m, 3H), 2.53 (t, *J* = 8 Hz, 2H), 2.77 (t, *J* = 8 Hz, 2H), 2.88–2.98 (m, 1H), 3.06–3.14 (m, 1H), 3.84 (s, 6H), 4.62 (d, *J* = 8 Hz, 1H), 6.81–6.99 (m, 4H), 7.05 (t, *J* = 8 Hz, 1H), 7.08–7.17 (m, 2H); MS (CI with NH_3) *m*/*z* 598 (M + 1); anal. calcd for $C_{22}H_{28}FNO_3$: C, 70.75; H, 7.56; N, 3.75; found: C, 70.68; H, 7.52; N, 3.79.

(*S*)-(−)-α-(2,3-Dimethoxyphenyl)-1-[2-(4-fluorophenyl) ethyl]-4-piperidinemethanol (−)-1a (MDL 100009). Alkylation of (*S*)-(−)-**5a** as above afforded (*S*)-(−)-**1a**. Yield: 96%. Analytical data are identical with (*R*)-(+)-**1a**, except for: $[\alpha]_D^{20}$ −14.3° (*c* 0.1, MeOH); anal. calcd for $C_{22}H_{28}FNO_3$: C, 70.75; H, 7.56; N, 3.75; found: C, 70.62; H, 7.49; N, 3.80.

(*S*)-(+)-α-[2-Methoxy-3-[(1,1-dimethylethyl)diphenylsilyl] oxyphenyl]-1-[2-(4-fluorophenyl)ethyl]-4-piperidinemethanol (+)-1b. Alkylation of (*S*)-(+)-**5b** as above afforded (*S*)-(+)-**1b**. The compound was obtained as a colorless oil (95%); R_f 0.3 (silica gel, 10:1 $CHCl_3$:MeOH); $[\alpha]_D^{20}$ +30.0° (*c* 0.1, MeOH); ^1H NMR ($CDCl_3$) δ 1.13 (s, 9H), 1.10–1.36 (m, 3H), 1.40 (m, 1H), 1.71–2.07 (m, 3H), 2.53 (t, *J* = 8 Hz, 2H), 2.79 (t, *J* = 8 Hz, 2H), 2.88–3.00 (m, 1H), 3.06–3.17 (m, 1H), 3.98 (s, 3H), 4.64 (d, *J* = 8 Hz, 1H), 6.43 (dd, *J* = 8, 2 Hz, 1H), 6.64 (t, *J* = 8 Hz, 1H), 6.80 (dd, *J* = 8, 2 Hz, 1H), 6.93–7.05 (m, 2H), 7.11–7.21 (m, 2H), 7.29–7.47 (m, 6H), 7.73 (d, *J* = 8 Hz, 4H); MS (CI with NH_3) *m*/*z* 598 (M + 1). Anal. calcd for $C_{37}H_{44}FNO_3Si \cdot 3/4H_2O$: C, 72.69; H, 7.50; N, 2.29; found: C, 72.31; H, 7.30; N, 2.27.

(*R*)-(−)-α-[2-Methoxy-3-[(1,1-dimethylethyl)diphenylsilyl] oxyphenyl]-1-[2-(4-fluorophenyl)ethyl]-4-piperidinemethanol (−)-1b. Alkylation of (*R*)-(−)-**5b** as above afforded (*R*)-(−)-**1b**. Yield: 95%. Analytical data are identical with (*S*)-(+)-**1b**, except for: $[\alpha]_D^{20}$ −30.8° (*c* 0.1, MeOH); anal. calcd for $C_{37}H_{44}FNO_3Si \cdot H_2O$: C, 72.16; H, 7.53; N, 2.27; found: C, 71.89; H, 7.49; N, 2.41.

α-(2-Hydroxy-3-methoxyphenyl)-1-[2-(4-fluorophenyl) ethyl]-4-piperidinemethanol (7) by chiral reduction. A solution of 1-[2-(4-fluorophenyl)ethyl]-4-[1-oxo-1-(2,3-dimethoxyphenyl)methyl]piperidine[2] **6** (500 mg, 1.35 mmol) in anhydrous $CHCl_3$ (5 mL) was treated with commercial (−)-Ipc-chloride (650 mg, 2.03 mmol) at −25 °C and stirred for 8 h at 0 °C and 48 h at ambient temperature. The mixture was quenched with 2 equiv of acetaldehyde, stirred overnight, and partitioned between NH_4OH and ether. The aqueous phase was extracted

2× with $CHCl_3$. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and evaporated to dryness. Chromatography of the residue with 90:10:1 $CHCl_3$:MeOH:NH_4OH gave fractions of unreacted starting material **7** (150 mg, 30%), partially resolved **1a** (210 mg, 42%, ee = 58% in favor of the (+)-isomer) and partially resolved **7** (76 mg, 16%, ee = 39% in favor of the (+)-isomer) as colorless crystals when triturated with diisopropyl ether: mp 147–149 °C (lit.[10] 147–149 °C); ^{1}H NMR ($CDCl_3$) δ 1.26–1.59 (m, 3H), 1.73–1.81 (m, 1H), 1.82–2.14 (m, 3H), 2.52 (t, J = 8 Hz, 2H), 2.73 (t, J = 8 Hz, 2H), 2.88–2.99 (m, 1H), 3.06–3.17 (m, 1H), 3.87 (s, 3H), 4.58 (d, J = 8 Hz, 1H), 6.72–6.86 (m, 3H), 6.93 (t, J = 8 Hz, 2H), 7.08–7.18 (m, 2H); MS (CI with NH_3) m/z 360 (M + 1); anal. calcd for $C_{21}H_{26}FNO_3 \cdot 1/4H_2O$: C, 69.30; H, 7.43; N, 3.85; found: C, 69.62; H, 7.29; N, 3.87.

(*R*)-(+)-α-(3-Hydroxy-2-methoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-piperidinemethanol (+)-4. A solution of (*R*)-(−)-**1b** (12.8 g, 21.4 mmol) and NH_4F (3.96 g, 107 mmol) in anhydrous MeOH (150 mL) was stirred for 15 min at 60 °C. After evaporation of the solvent, the residue was taken up in NH_4OH and extracted 3× with $CHCl_3$. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and evaporated to yield a viscous oil. Chromatography of the residue with 5:1 $CHCl_3$:MeOH gave 6.77 g (88%) of (*R*)-(+)-**4** as a colorless oil which crystallized from hexane: R_f 0.7 (silica gel, 5:1 $CHCl_3$:MeOH); mp 75–80 °C (decomp); $[\alpha]_D^{20}$ +21.9° (*c* 0.1, MeOH); lit.[10] $[\alpha]_D^{22}$ +22.2° (*c* 1.58, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.19–1.58 (m, 3H), 1.62–1.79 (m, 1H), 1.85–2.14 (m, 3H), 2.54 (t, J = 8 Hz, 2H), 2.76 (t, J = 8 Hz, 2H), 2.88–3.00 (m, 1H), 3.06–3.17 (m, 1H), 3.81 (s, 3H), 4.64 (d, J = 8 Hz, 1H), 6.81–7.07 (m, 5H), 7.08–7.18 (m, 2H); MS (CI with NH_3) m/z 360 (M + 1); anal. calcd for $C_{21}H_{26}FNO_3 \cdot 3/4H_2O$: C, 67.63; H, 7.43; N, 3.76; found: C, 67.28; H, 7.06; N, 3.58.

(*S*)-(−)-α-(3-Hydroxy-2-methoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-piperidinemethanol (−)-4. Deprotection of (*S*)-(+)-**1b** as above afforded (*S*)-(−)-**4**. Yield: 88%. Analytical data are identical with (+)-**4**, except for: $[\alpha]_D^{20}$ −22.2° (*c* 0.1, MeOH); anal. calcd for $C_{21}H_{26}FNO_3 \cdot 1/4H_2O$: C, 69.30; H, 7.34; N, 3.85; found: C, 69.57; H, 7.36; N, 3.81.

Methylation of (+)-4 to (+)-1a (MDL 100907). A freshly distilled, ethereal solution of diazomethane (4 mL) was gradually added to a stirred solution of (+)-**4** (50 mg, 0.14 mmol) in MeOH (0.5 mL) at room temperature. The completion of the reaction was monitored by TLC. After 8 h, the solution was evaporated to dryness, and the residue was filtered through silica gel 60 (10:1 $CHCl_3$:MeOH) to give 41 mg (79%) of (+)-**1a**. Analytical data are identical with those for (+)-**1a** obtained by *N*-alkylation, except for: $[\alpha]_D^{20}$ +14.3° (*c* 0.1, MeOH).

Acknowledgements

We acknowledge Dr. Michael A. Channing for very helpful discussions, and Noel Whittaker who provided all mass spectroscopy data reported.

References and Notes

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