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PCP receptor and dopamine uptake sites are discriminated by chiral TCP and BTCP derivatives of opposite configuration

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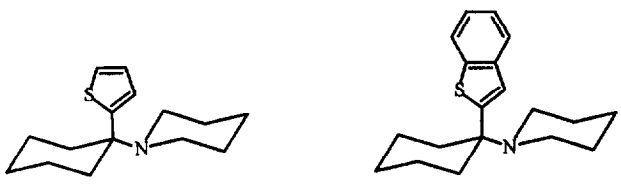
Summary — 3-Methylpiperidine derivatives of 1-[1-(2-thienyl)cyclohexyl]piperidine (TCP) and 1-[1-(2-benzo[*b*]thiophenyl)cyclohexyl]piperidine (BTCP) were obtained in their racemic and homochiral forms. They have been tested for their affinity for the PCP receptor labeled with [^{3}H]TCP and for the dopamine transporter labeled with [^{3}H]BTCP. The homochiral TCP derivative (+)-*R* displayed a very high affinity (5.2 nM) and selectivity for the PCP receptor. In contrast, the homochiral BTCP derivative (–)-*S*, therefore of opposite configuration, displayed a very high affinity (3.5 nM) and selectivity for the dopamine transporter.

TCP / BTCP / PCP receptor / dopamine transporter / chirality

Introduction

Interactions of 1-(1-phenylcyclohexyl)piperidine (phencyclidine or PCP) and its congeners with the dopaminergic system are well known. However, these interactions were difficult to clarify because PCP and ligands of the PCP receptor interact with the dopaminergic system by both direct and indirect mechanisms.

Behavioral pharmacological tests first indicated that PCP could be acting as an indirect dopaminergic agonist similar to dexamphetamine [1–3]. At the same time, it was also demonstrated that the drug could competitively inhibit the synaptosomal uptake of tritiated dopamine ([^{3}H]DA) [4, 5]. Vickroy and Johnson [6, 7] later demonstrated a DA–releasing effect of phencyclidine in striatal slices. Finally, the molecule was assessed to be a non-amphetaminic indirect DA agonist in the rat [8] inducing hyperlocomotion in rodents [9, 10]. A structure–activity study has shown that the inhibition of DA uptake by a series of analogues could be correlated with their affinity for the PCP receptor [11]. Nevertheless, more extended studies have demonstrated that this correlation was only valid for compounds with an unmodified phenyl ring [12, 13]. Such PCP-like structures could bind to the PCP receptor on one side and to the DA transporter on the other to inhibit the dopamine uptake. Substitution or replacement of the benzene ring yielded structures with various binding potencies for both systems. Interestingly, replacement of the phenyl ring by a 2-thienyl or a 2- benzo[*b*]thiophenyl ring yielded 1-[1-(2-thienyl)cyclohexyl]piperidine (TCP) and 1-[1-(2-benzo[*b*]thiophenyl)cyclohexyl]piperidine (BTCP) (scheme 1) displaying a high affinity for the PCP receptor [14] and a high affinity for the DA transporter [15], respectively. Other ligands of the PCP



TCP BTCP

Scheme 1.

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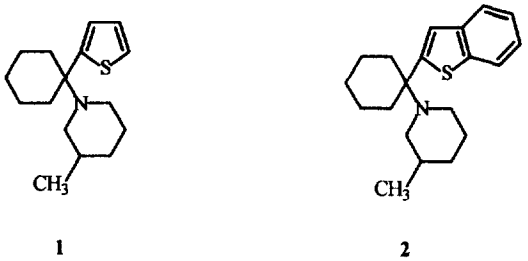
receptor, such as SKF 10047 or cyclazocine, appeared ineffective in inhibiting the DA reuptake [16]. A similar behavior was found for dizocilpine (MK-801), a high affinity ligand of the PCP receptor but a poor DA uptake blocker [17] with a very low affinity for the DA uptake sites labeled by [^{3}H]BTCP [14]. Interestingly enough, MK-801 demonstrated strong locomotor-stimulatory action in mice and rats [18] and displayed marked locomotor stimulation in monoamine-depleted mice [19].

These results strongly suggest two conclusions: (i) non-competitive antagonists of the NMDA receptor stimulate indirectly dopaminergic functions through various pathways as a result of their interaction with the PCP receptor; and (ii) PCP-like structures can interact directly with the dopaminergic system since their binding to the transporter inhibits the DA uptake. The first property appears to be intrinsically related to the glutamatergic transmission in the central nervous system. The second property appears to be intrinsically linked to the structure of PCP-like molecules. Consequently, TCP derivatives, which are known to provide potent protection of neurones against glutamate neurotoxicity [20, 21] by inhibiting Na^+ and Ca^{2+} influx through the NMDA-gated channel, may lead to an increased dopaminergic response *in vivo*.

Thus, the aim of the present study was to shed light on new structural features that prevent competitive NMDA antagonists derived from the TCP structure binding to the DA transporter. Previous works in our and other laboratories revealed that the 3-position of the piperidine ring may be important *in vitro* and *in vivo* to mediate activity in the BTCP [22] and PCP [26] (rotarod behavior) series, respectively. Considering that such structures are chiral, we decided to prepare racemic and pure enantiomeric (homochiral) forms of 1-[1-(2-thienyl)cyclohexyl]-3-methylpiperidine and 1-[1-(2-benzo[*b*]thiophenyl)cyclohexyl]-3-methylpiperidine (scheme 2) to test their affinity for the PCP receptor and the DA transporter labeled with [^{3}H]TCP or [^{3}H]BTCP, respectively.



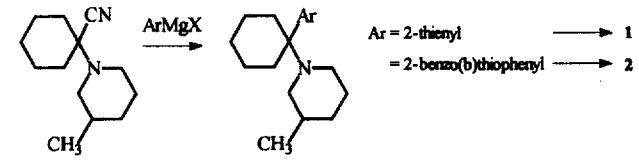
1 2

Scheme 2.

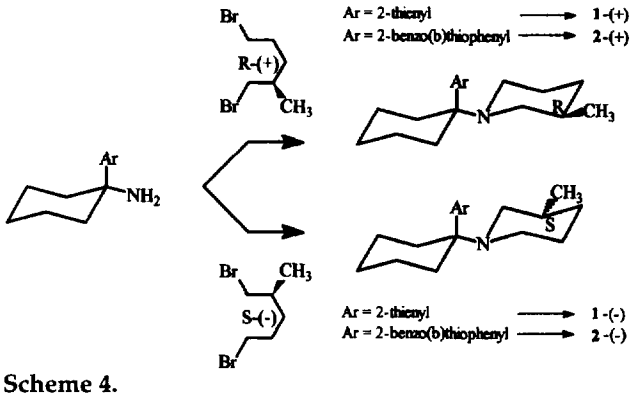
Chemistry

Racemic compounds (±)-1-[1-(2-thienyl)cyclohexyl]-3-methylpiperidine **1** and (±)-1-[1-(2-benzo[*b*]thiophenyl)cyclohexyl]-3-methylpiperidine **2** were easily obtained by the Bruylants reaction (scheme 3). This is the best known pathway from a suitable α-aminonitrile to the synthesis of arylcyclohexylamines unsubstituted at the cyclohexyl ring (see for example [22]).

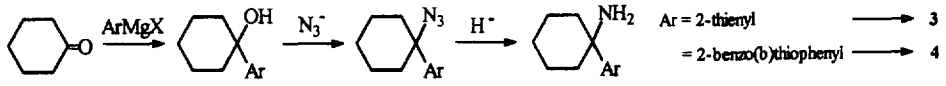
We chose the most general pathway (scheme 4) for the synthesis of homochiral 3-methylpiperidine structures with the asymmetric center introduced during the last step. Accordingly, various synthons were needed: 1-(2-thienyl)cyclohexylamine **3** or 1-(2-benzo[*b*]thiophenyl)cyclohexylamine **4** and (*S*)-(–)-2-methyl-1,5-dibromopentane or (*R*)-(+)-2-methyl-1,5-dibromopentane. The azide synthesis (scheme 5) is frequently used to prepare cyclohexyl-substituted congeners of PCP, TCP or BTCP (see for example [22, 23]) and is suitable for the preparation of unsubstituted primary amines derivatives, even if overall yields are rather low. The Von Braun degradation [24] of substituted piperidines is a general route to a variety of substituted primary and secondary 1,5-dibromopentanes [25]. Moreover, this degradation gives pure enantiomers from homochiral 3-methylpiperidines [27]. The optical resolution of 3-methylpiperidine racemate has



Scheme 3.

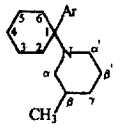


Scheme 4.



Scheme 5.

Table I. ^{13}C-NMR spectra of racemic and homochiral structures in $CDCl_3$ (or CD_3OD) at 50.323 MHz.



Carbon	*1*	*2*	*1-(+)*[a]	*1-(-)*[a]	*2-(+)*	*2-(-)*
1	69.65	69.70	70.36	70.40	69.97	69.48
2	33.19	33.10	*35.13*	*35.11*	*32.79*	*32.65*
3	22.88	23.10	24.35	24.37	22.87	22.56
4	*23.81*	*23.90*	*25.84*	*25.83*	*23.60*	*23.35*
5	22.88	23.10	24.35	24.37	22.87	22.56
6	33.06	33.10	*34.93*	*34.92*	*32.67*	*32.52*
α	52.56	53.00	54.41	54.41	52.82	52.27
α'	46.44	46.80	48.18	48.91	46.64	46.55
β	28.61	28.70	31.34	31.31	28.40	28.29
β'	*22.42*	*22.60*	*24.64*	*24.62*	*22.32*	*22.11*
γ	30.77	31.00	32.18	32.19	30.74	30.32
CH_3	19.13	19.30	19.48	19.49	18.98	18.72
C_{Ar}[b]	135.65	138.97	137.98	137.96	139.74	139.40
	to 127.85	to 122.22	to 129.07	to 129.09	to 121.93	to 121.64

Chemical shifts (δ ppm) from TMS (italicized chemical shifts may be exchanged). [a] Spectrum in CD_3OD. [b] Heteroaromatic carbons in 2-thienyl (1C, 3CH) and 2-benzo[*b*]thiophenyl (3C, 5CH) substitutions.

been achieved previously by means of (+)- and (–)-mandelic acid in ethyl acetate with optical purity up to 98–99% [26]. The *S*-(+)-3-methylpiperidine-(+)-mandelic acid salt was obtained from crystallization of (±)-3-methylpiperidine with (+)-mandelic acid and the *R*-(–)-3-methylpiperidine-(–)-mandelic acid salt from the evaporated filtrates treated with (–)-mandelic acid. Finally, application of scheme 4 yielded **1**-(+), **1**-(–) and **2**-(+), **2**-(–). ^{13}C-NMR spectra (table I) were used to control final structures by comparison with TCP and BTCP. Enantiomeric purities (eps) were determined on a chiral HPLC column able to discriminate **1**-(+) and **1**-(–). Both eps were found to be > 99% by comparative integrations of homochiral and racemic peaks. We could not obtain a sufficient separation of peaks corresponding to **2**-(+) and **2**-(–) to determine their eps. Nevertheless, their eps can be assessed to be the same as for enantiomers **1** if we consider they were obtained *via* the same reaction and using the same batches of chiral materials, *eg*, chiral 2-

Table II. TCP series: inhibition constants (IC_{50}, nM ± SEM), Hill's number (n_H), and selectivity (S)[a] of the binding of [^{3}H]TCP and [^{3}H]BTCP on rat brain and striatum, respectively.

Compound	*[^{3}H]TCP*	n_H	*[^{3}H]BTCP*	n_H	*S*
PCP	36.9	1.00	760	0.83	21
TCP	9.3	1.00	1330	0.82	143
1-(±)	5.5 ± 1.3	1.09	2900 ± 960	1.01	527
1-(-)	158 ± 20	1.08	9000 ± 900	0.94	57
1-(+)	5.2 ± 1.0	1.04	4800 ± 1000	1.04	923

[a]S = IC_{50} ([^{3}H]BTCP)/IC_{50} ([^{3}H]TCP). Since compounds were tested in similar conditions with radioligand concentrations lower than their respective K_d values, the IC_{50} values are close to the K_i values. Furthermore, because of close structural similarities, one can assume a competitive inhibition of both bindings like for TCP and BTCP [15]. Thus, S is assumed to reflect the *in vitro* selectivity.

Table III. BTCP series: inhibition constants (IC_{50}, nM ± SEM), Hill's number (n_H), and selectivity (S)[a] of the binding of [^{3}H]TCP and [^{3}H]BTCP on rat brain and striatum, respectively.

Compound	*[^{3}H]TCP*	n_H	*[^{3}H]BTCP*	n_H	*S*
PCP	36.9	1.00	760	0.83	0.049
TCP	6000	1.00	8.0	1.02	750
2-(±)	51800 ± 14600	0.91	3.3 ± 1.1	0.98	15700
2-(-)	133500 ± 30300	0.92	3.5 ± 0.3	0.82	38140
2-(+)	21300 ± 5400	1.07	9.7 ± 4.9	1.00	2200

[a]S = IC_{50} ([^{3}H]BTCP)/IC_{50} ([^{3}H]TCP). Since compounds were tested in similar conditions with radioligand concentrations lower than their respective K_d values, the IC_{50} values are close to the K_i values. Furthermore, because of close structural similarities, one can assume a competitive inhibition of both bindings like for TCP and BTCP [15]. Thus, S is assumed to reflect the *in vitro* selectivity.

methyl-1,5-dibromopentanes, than for the obtention of enantiomers **1**. The absolute configurations of the newly prepared homochiral derivatives of TCP and BTCP are easily derived from the known homochiral 3-methylpiperidine configurations [26] since the configuration does not change during the Von Braun degradation and the final cyclization [26, 27]. Thus, degradation of (+)-(*S*)-3-methylpiperidine yielded (–)-(*S*)-2-methyl-1,5-dibromopentane giving finally **1**-(–)-(*S*) and **2**-(–)-(*S*). Conversely, **1**-(+)-(*R*) and **2**-(+)-(*R*) were obtained from the degradation (–)-(*R*)-3-methylpiperidine.

Results and discussion

The affinities of the racemic and homochiral compounds for the PCP receptor and the DA uptake complex were determined in competition experiments with [^{3}H]TCP and [^{3}H]BTCP on rat brain homogenates and rat striatal membranes preparations, respectively. The results are summarized in tables II and III. In the PCP series (phenyl substitution instead of 2-thienyl), other workers have previously found [26] that the dextrorotatory isomer was 7–10 times more potent than the levorotatory. The results in table II show that **1**-(+) is more than 28-fold more potent than **1**-(–) and equipotent to the racemic **1**-(±), in binding to the PCP receptor. On the other hand (table III), **2**-(–) displays only a 2.7-fold better affinity than **2**-(+) and the same affinity as the racemic **2**-(+) for the DA transporter. It should be emphasized that **1**-(+) is one of the highest affinity ligands found in the TCP series and that **2**-(–) is one of the highest affinity ligands obtained in the BTCP series. Moreover, these compounds display the highest selectivity yet obtained for the PCP receptor and the DA transporter respectively. **1**-(+) displays a more than 900-fold better affinity for the PCP receptor than for the DA transporter, conversely, **2**-(–) displays nearly 38 000 times better affinity for the DA transporter than for the PCP receptor.

Therefore (+)-1-[1-(2-thienyl)cyclohexyl]-3(*R*)-methylpiperidine **1**-(+) and (–)-1-[1-(2-benzo[*b*]thiophenyl)cyclohexyl]-3(*S*)-methylpiperidine **2**-(–) of opposite configuration discriminate very strongly the PCP receptor and the DA transporter (tables II and III); a homochiral 3-methylpiperidine ring essentially enhances the selectivity generated by the heteroaromatic ring. Thus, a 2-thienyl ring associated with a *R* configuration at the 3-carbon of the piperidine ring yields a high affinity ligand for the PCP receptor with a 6.5 times selectivity enhancement compared with the achiral TCP structure. Conversely, a 2-benzo-[*b*]thiophenyl ring associated with a *S* configuration at the 3-carbon of the piperidine ring yields a high affinity ligand for the DA transporter with a 50 times selectivity enhancement compared with the achiral BTCP structure.

Thus, it could be hypothesized that the PCP receptor site in the NMDA-associated ionic channel and the BTCP site on the DA transporter differ not only by their ability to bind differently the heteroaromatic moieties of PCP-like structures but also by their respective configurations at the binding sites. Furthermore, the high selectivity of the ligands **1**-(+) and **2**-(–) demonstrate that (i) the direct activity of TCP-like molecules on the dopaminergic system can be almost completely prevented *in vitro*; and (ii) BTCP derivatives can be biochemically completely devoid of PCP-like activity. Finally, the suitable combination of chirality and heteroaromatic rings may give valuable tools to study interactions between the glutamatergic and dopaminergic systems and also to tentatively modelize ligand–receptor site interactions.

Experimental protocols

Generalities

Melting points were determined with a Büchi-Tottoli apparatus and are uncorrected. Elemental analysis was performed at the CNRS Microanalytical Section in Montpellier on the hydrochloride salts and were within ±0.4% of theoretical values. Optical rotations were obtained in methanol with a Perkin-Elmer 241 polarimeter in a 1 dm microcell at 20°C. GC/MS analysis were performed on a Hewlett-Packard 5890 instrument equipped with a 9825B computer through a 25 m OV-1 capillary column. Enantiomeric purities were determined on a Shimadzu HPLC equipment (LC-1O AD pump, SPD-6A UV spectrometer), computer-controlled by the Class LC-10 program. Analysis were made on a Chiralcel-OD column (10 µm, 4.6 x 250 mm) (Daicel Chemical Industries). UV detection was made at 240 nm. Typical injection volumes were 5 µl of a 30 µM solution of base compound in heptane. ^{13}C-NMR spectra were obtained on a Brucker AC 200 spectrometer at 50.323 MHz in 5 mm sample tubes in the FT mode. For signal assignments, a spin-echo sequence (Jmod) was used. Chemical shifts are reported in (δ) ppm downfield from TMS. All compounds were isolated as their hydrosoluble hydrochloride salts used for the *in vitro* experiments; salts were precipitated by bubbling a dry stream of HCl in an etheral solution of bases. After filtration, the solids collected were dried *in vacuo*.

Binding assays

[^{3}H]TCP binding to the PCP receptor was performed as previously described [28]. Briefly, the rat brain (minus the cerebellum) was removed and homogenized with an Ultraturax (Ika Werke, maximum setting) in 50 mM Tris/HCl, pH 7.7 buffer for 20 s at 4°C. The homogenate was then centrifuged at 49 000 *g* for 20 min. The pellet was resuspended in the same buffer and the homogenization-centrifugation steps performed a second time. The final pellet was resuspended in 10 volumes of a 50 mM Tris/Hepes, pH 7.7 buffer and used without further purification.

The homogenate (0.5–0.8 mg protein/ml) was incubated with [^{3}H]TCP (1 nM) (Amersham, 48 Ci/mmol) in a 5 mM Tris/Hepes, pH 7.7 buffer in the absence (total binding) and in the presence of the competing drug for 30 min at 25°C in a volume of 0.5 ml. The incubation was terminated by filtration over GF/B (Whatman) glass-fiber filters presoaked in 0.05% polyethyleneimine (PEI, Aldrich) with a MR24 Brandel cell harvester. The filters were rinsed twice with 5 ml of a 50 mM NaCl, Tris HCl 10 mM, pH 7.7 buffer and the radioactivity retained counted in 3.5 ml ACS (Aqueous Counting System Amersham) with an Excel 1410 (LKB) liquid scintillation spectrophotometer. The non-specific binding was determined in parallel experiments in the presence of 100 µM unlabeled TCP.

[^{3}H]BTCP binding to the DA uptake complex was performed using the method described by Vignon *et al* [15]. Rat striata were dissected on ice and homogenized with an Ultraturax in 320 mM sucrose, Tris 10 mM pH 7.4 buffer and

centrifuged at 1 000 *g* for 10 min. The supernatant was then centrifuged at 49 000 *g* for 20 min. The resulting pellet (synaptosomal homogenate) was resuspended in the same buffer (1 ml per striatum). The homogenate (0.01–0.05 mg protein/ml) was incubated with [^{3}H]BTCP (0.2–0.5 nM) (CEA, Service des Molécules Marquées, 55 Ci/mmol) in the absence or the presence of the competing drug in 50 mM Na_2HPO_4, pH 7.4 buffer in a volume of 2 ml for 90 min at 4°C. The incubation was terminated in the same manner as for the [^{3}H]TCP with the exception that the filters were presoaked in 0.5% PEI. The non-specific binding was determined in the presence of 10 μM unlabeled BTCP.

Chemistry

Preparation of 1-cyano-1-[1-(3-methyl)piperidino]cyclohexane
Acetone cyanhydrine (3.3 g, 39 mmol) was added with stirring to a mixture of cyclohexanone (3.8 g, 39 mmol), anhydrous $MgSO_4$ (23.4 g, 190 mmol), dimethylacetamide (5 g, 58 mmol), and 3-methylpiperidine (5.8 g, 58 mmol). The pasty mixture obtained was heated at 45°C for 48 h. After cooling to room temperature, the mixture was poured onto ice and vigorously stirred for 30 min. The aqueous mixture was extracted with ether and the organic phase washed to neutrality with water. Evaporation under reduced pressure of the ethereal solution, dried over Na_2SO_4, yielded 7 g (88%) of a yellow oily residue pure enough for use in the next step. GC/MS: 50–250°C (10°C/min) R_t= 16.9 min, *m/e* = 206.25.

(±)-1-[1-(2-Thienyl)cyclohexyl]-3-methylpiperidine 1-(±)
A Grignard reagent was prepared (under nitrogen) from Mg turnings (1.22 g, 50.5 mmol) and 50 ml anhydrous ether, and 2-bromothiophene (4.7 ml, 48.5 mmol) was added dropwise. After the addition was complete, the solution was refluxed for 4 h and then 1-cyano-1-[1-(3-methyl)piperidino]cyclohexane (4 g, 19.5 mmol) in 50 ml ether was added dropwise. After the addition was complete, the solution was refluxed for 20 h, cooled to room temperature, and poured onto an ice-cold saturated solution of NH_4Cl in water. The mixture was stirred for 30 min and treated as follows. Extraction with 3 x 50 ml ether, was followed by the washing of organic phases with 3 x 50 ml 10% HCl the neutralization of aqueous phases with 20% NH_4OH, the extraction with 3 x 50 ml ether, and the washing of organic layers with water until neutrality. The pooled organic layers, dried over Na_2SO_4, were evaporated under reduced pressure to yield an oil. The crude product obtained was purified on column chromatography (aluminoxide 2-3 Merck) in petroleum ether/ether (99:1 v/v) to yield pure oily **1**-(±) (4 g, 78.3%). The oily base was hydrochlorinated to give **1**-(±), HCl as a white solid (mp_{HCl} 178°C). GC/MS: 90–250°C (10°C/min), R_t = 16.40 min, *m/e* = 263. 15.

(±)-1-[1-(2-Benzo[b]thiophenyl)cyclohexyl]-3-methylpiperidine 2-(±)
The synthesis is essentially the same as above and has been published previously [22]. Thus, from 1-cyano-1-[1-(3-methyl)piperidino]cyclohexane (5 g, 24 mmol), 2-iodobenzo-[*b*]thiophene (9.4 g, 36 mmol) and Mg turnings (1.44 g, 60 mmol), a brownish solid residue (6 g) was obtained. Column chromatography (aluminoxide 2-3 Merck) in petroleum ether/ether (90:10 v/v) yielded pure **2**-(±) as a white solid (4.9 g, 65%, mp_{base} 85–86°C, mp_{HCl} 180–181°C).

(–)-(S)-2-Methyl-1,5-dibromopentane

(+)-(S)-3-Methylpiperidine mandelate. The procedure is essentially the same as in reference [26]. Thus, from (+)-mandelic acid (45.64 g, 300 mmol) and (±)-3-methylpiperidine (35.2 ml, 300 mmol) after three crystallizations from ethyl acetate, (+)-(*S*)-3-methylpiperidine mandelate (22.9 g, 60.7%) was obtained. Mp 120–124°C; $[\alpha_D^{20}]$ = +58.79° (*c* 0.995, MeOH) (lit [26]: mp 122–124°, $[\alpha_D^{23}]$ = +57.9° (*c* 1.04, MeOH)).

(+)-(S)-N-Benzoyl-3-methylpiperidine. The procedure is essentially the same as in reference [27]. Thus, the pure amide (14.93 g, 80.6%) was obtained from (+)-(*S*)-3-methylpiperidine mandelate (22.9 g, 91.15 mmol). Mp 72–73°C; $[\alpha_D^{20}]$ = +48° (*c* 1.125, MeOH) (lit [27]: mp 72°C, $[\alpha_D^{23}]$ = +49.5° (*c* 1, MeOH)); GC/MS: 90–250°C (10°C/min), R_t = 14.54 min, *m/e* = 202.1.

(–)-(S)-2-Methyl-1,5-dibromopentane. The procedure is essentially the same as in reference [27]. Thus, from powdered (+)-(*S*)-*N*-benzoyl-3-methylpiperidine (23.96 g, 117 mmol), phosphorus tribromide (11.2 ml, 117 mmol), and Br_2 (6.1 ml, 117 mmol) a yellow oil was obtained (11.21 g, 39%) $[\alpha_D^{20}]$ = –3.94° (neat) (lit [27]: $[\alpha_D^{23}]$ = –2.99° (neat)); GC/MS: 90–250°C (10°C/min), R_t = 9.38 min, *m/e* = 162.

(+)-(R)-2-Methyl-1,5-dibromopentane

(–)-(R)-3-Methylpiperidine mandelate. The procedure is essentially the same as in reference [26]. Thus, from (–)-mandelic acid (23 g) and the basic residue (14.86 g) yielded by combined filtrates and washings from crystallizations of the above (+)-(*S*)-3-methylpiperidine-(+)-mandelate, a white solid (12.78 g, 34%) was obtained after two crystallizations from ethyl acetate. Mp 120–125°C, $[\alpha_D^{20}]$ = –55.8° (*c* 1.015, MeOH) (lit [26]: mp 122–124.5°C, $[\alpha_D^{23}]$ = –57.5° (*c* 1.01, MeOH)).

(–)-(R)-N-benzoyl-3-methylpiperidine. (*R*)-(–)-3-Methylpiperidine mandelate (12.78 g) treated as described above for (+)-(*S*)-*N*-benzoyl-3-methylpiperidine gave 10.22 g (98%) of (–)-(*R*)-*N*-benzoyl-3-methylpiperidine. Mp 70–72°C, $[\alpha_D^{20}]$ = –51.9° (*c* 1.0, MeOH); GC/MS: 90–250°C (10°C/min), R_t = 14.42 min, *m/e* = 202.15.

(+)-(R)-2-Methyl-1,5-dibromopentane. (–)-(*R*)-*N*-benzoyl-3-methylpiperidine (32 g, 157 mmol) treated with phosphorus tribromide (15 ml) and Br_2 (8.2 ml) as described above for (+)-(*S*)-*N*-benzoyl-3-methylpiperidine gave 16 g (41.6%) of oily (+)-(*R*)-2-methyl-1,5-dibromopentane. $[\alpha_D^{20}]$ = +3.3° (neat); GC/MS: 70–250°C (10°C/min), R_t = 9.49 min, *m/e* = 163.95.

1-(2-Thienyl)cyclohexanol
A solution of 2-thienylmagnesium bromide was prepared from 2-bromothiophene (18.7 ml, 193 mmol), Mg turnings (5.15 g, 212 mmol and 150 ml anhydrous ether refluxed for 3 h. Cyclohexanone (10 ml, 96.5 mmol) in 150 ml ether was then added dropwise and the solution refluxed and stirred for 16 h. After cooling at room temperature and usual workup, the crude alcohol was purified on a chromatography column (silica gel chromagel ACC 60–200 μ (SDS)). A mixture of petroleum ether/ether (90:10 v/v) eluted the pure oily alcohol (15 g, 85.4%). GC/MS: 50–250°C (10°C/min), R_t = 15.09 min, *m/e* = 182.10).

1-Azido-1-(2-Thienyl)cyclohexane
The reaction was run under a hood and behind a protective screen due to risk of explosion of some azide derivatives. Sodium azide (5.37 g, 82.6 mmol) was added carefully at –15°C to a solution of trichloroacetic acid (20.25 g, 124 mmol) and chloroform (100 ml). The suspension was stirred vigo-

rously for 30 min, and then 1-(2-thienyl)cyclohexanol (7.52 g, 41.3 mmol) dissolved in 50 ml $CHCl_3$ was added dropwise. The suspension obtained was stirred at −15°C for 24 h and neutralized with cold NH_4OH 5%. The mixture was extracted with CH_2Cl_2, the combined organic layers washed with water to neutrality, dried over Na_2SO_4, and evaporated under reduced pressure to yield the crude azide.

1-(2-Thienyl)cyclohexylamine
The crude azide obtained above, without purification, was dissolved in isopropanol (100 ml) and heated to 60°C for 30 min. Raney Ni was added in portions until the gas evolution stopped. A vigorous stirring at 60°C was maintained for an additional period of 30 min. After cooling to room temperature, the mixture was filtered on celite, the precipitate rinsed with a solution of NH_4OH 5% (100 ml). The isopropanol was evaporated under reduced pressure. The remaining aqueous solution was then extracted successively with ether and CH_2Cl_2. The combined organic layers were washed with water until neutrality, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield the primary amine (4.83 g) as an oil. This oil was purified by hydrochlorination in ether to yield a pure hydrochloride (4.28 g, 47.6%). GC/MS: 80–250°C (10°C/min), R_t = 11.76 min, *m/e* = 181.10.

(−)-(S)-1-[1-(2-Thienyl)cyclohexyl]-3-methylpiperidine 1-(−)
(−)-(*S*)-2-Methyl-1,5-dibromopentane (1.5 g, 6.15 mmol) was added to a suspension of 1-(2-thienyl)cyclohexylamine (0.96 g, 5.3 mmol), K_2CO_3 (1.38 g, 9.9 mmol) and freshly distilled hexamethylphosphoramide (HMPA, Aldrich) (12.5 ml). The mixture was stirred for 48 h at 60°C. After cooling at room temperature the solution was poured onto water and yielded a crude oil after usual workup. Column chromatography (aluminium oxide 90 2-3 Merck) in petroleum ether/ether (99.5: 0.5, v/v) yielded a pure oily compound (0.92 g, 65.8%) which was hydrochlorinated (172–173°C). $[\alpha_D^{20}]_{base}$ = −20.77° (*c* 1.415, $CHCl_3$); $[\alpha_D^{20}]_{HCl}$ = −13.05° (*c* 0.82, MeOH); GC/MS: 90–250°C (10°C/min), R_t = 16.54 min, *m/e* = 263.15, chemical purity > 99%; HPLC: heptane/isopropanol (99:1) 0.5 ml/min, R_t = 671 s, ep > 99%.

(+)-(R)-1-[1-(2-Thienyl)cyclohexyl]-3-methylpiperidine 1-(+)
(+)-(*R*)-2-Methyl-1,5-dibromopentane (1.85 g, 7.6 mmol) was added to a suspension of 1-(2-thienyl)cyclohexylamine (1.06 g, 5.84 mmol), K_2CO_3 (1.6 g, 11.7 mmol), and freshly distilled hexamethylphosphoramide (HMPA, Aldrich) (17 ml). The mixture was stirred for 72 h at 60°C. After cooling to room temperature, the solution was poured onto water and yielded after usual workup a crude oil. Column chromatography (aluminium oxide 90 2-3 Merck) in petroleum ether/ether (99.5:0.5, v/v) yielded a pure oily compound (0.98 g, 63.6%) which was hydrochlorinated (173–174°C). $[\alpha_D^{20}]$ = +18.01° (*c* 1.36, $CHCl_3$); $[\alpha_{D\ HCl}^{20}]$ = +12.18° (*c* 0.78, MeOH); GC/MS: 90–250°C (10°C/min), R_t = 16.55 min, *m/e* = 263.15, chemical purity 99%; HPLC: heptane/isopropanol (99:1) 0.5 ml/min, R_t = 653 s, ep > 99%.

1-(2-Benzo[b]thiophenyl)cyclohexanol
A solution of *n*-BuLi (1.6 M in hexane) (47 ml, 75.2 mmol) was added dropwise, at −20°C and under a nitrogen atmosphere, to a solution of benzo[*b*]thiophene (10 g, 74.6 mmol) in anhydrous ether (100 ml). Once the addition was complete, the mixture was allowed to reach room temperature, and then refluxed for 2 h. Cyclohexanone (9.3 ml, 89 mmol) dissolved in ether (50 ml) was added dropwise to the 2-lithiobenzo[*b*]thiophene solution. After the completion of addition, the solution was stirred at room temperature for 16 h, poured onto a saturated solution of NH_4Cl. The combined organic layers from extractions with ether and CH_2Cl_2 were washed with water, dried on Na_2SO_4, and evaporated *in vacuo* to yield a yellow solid. Crystallization from petroleum ether gave the pure alcohol as a white solid (12 g, 70%). GC/MS: 90–250°C (10°C/min), R_t = 17.99 min; *m/e* = 232.10.

1-(2-Benzo[b]thiophenyl)cyclohexylamine
Treatment of 1-(2-benzo[*b*]thiophenyl)cyclohexanol (6 g, 25.8 mmol) by sodium azide (3.36 g, 51.7 mmol) in trichloroacetic acid (12.7 g, 71.6 mmol) and chloroform (100 ml) as described above for 1-(2-thienyl)cyclohexylamine yielded crude 1-(2-benzo[*b*]thiophenyl)cyclohexylamine (5.3 g) purified by hydrochlorination in ether to give the HCl salt of the primary amine (4 g, 58%). GC/MS: 80–250°C (10°C/min), R_t = 18.63 min, *m/e* = 231.15.

(−)-(S)-1-[1-(2-Benzo[b]thiophenyl)cyclohexyl]-3-methylpiperidine 2-(−)
(−)-(*S*)-2-Methyl-1,5-dibromopentane (1.55 g, 6.35 mmol) was added to a suspension of 1-(2-benzo[*b*]thiophenyl)cyclohexylamine (0.98 g, 4.24 mmol), K_2CO_3 (1.4 g, 10 mmol), and freshly distilled hexamethylphosphoramide (HMPA, Aldrich) (13 ml). The mixture was stirred for 48 h at 60°C. After cooling to room temperature, the solution was poured onto water and gave a crude oil after the usual workup. Purification on column chromatography (aluminium oxide 90, 2-3 Merck) in petroleum ether/ether (99.5:0.5 v/v) yielded pure **2**-(−) as an oil (0.59 g, 44.7%) which was hydrochlorinated (138–140°C). $[\alpha_D^{20}]_{base}$ = −31.66° (*c* 0.935, $CHCl_3$); $[\alpha_D^{20}]_{HCl}$ = −34.91° (*c* 0.57, MeOH); GC/MS: 80–250°C (10°C/min), R_t = 23.5 min, *m/e* = 313.20, chemical purity > 98.8%.

(+)-(R)-1-[1-(2-Benzo[b]thiophenyl)cyclohexyl]-3-methylpiperidine 2-(+)
The same protocol as for **2**-(−) was applied with (+)-(*R*)-2-methyl-1,5-dibromopentane (1.7 g, 6.97 mmol), 1-(2-benzo[*b*]-thiophenyl)cyclohexylamine (1.08 g, 4.67 mmol), K_2CO_3 (1.7 g, 12.3 mmol) and HMPA (14 ml). After a chromatographic purification (aluminium oxide 90, 2-3 Merck) in petroleum ether/ether (99.7:0.3 v/v), pure 2-(+) was obtained as an oil (0.84 g, 57%). Hydrochlorination gave a hemihydrate (+1/2H_2O) (145–148°C). $[\alpha_D^{20}]_{base}$ = +28.34° (*c* 0.635, $CHCl_3$); $[\alpha_D^{20}]_{HCl}$ = +30.17° (*c* 0.58, MeOH); GC/MS: 70–250°C (10°C/min), R_t = 24.75 min, *m/e* = 313.10, chemical purity = 98%.

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