Enantioselective Syntheses of Dopaminergic (*R*)- and (*S*)-Benzyltetrahydroisoquinolines

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Optically pure (1*S*,*R*)- and (1*R*,*S*)-benzyltetrahydroisoquinolines (BTHIQs), **12a**,**b** as the major diastereomers, were prepared by stereoselective reduction of the isoquinolinium salt possessing (*R*)- and (*S*)-phenylglycinol as the chiral auxiliary, respectively. The absolute configurations of (1*S*,*R*)-**13a** hydrochloride (*O*-debenzoylated derivative from **12a**) and (1*R*,*S*)-**12b** diastereomers were unambiguously determined by single-crystal X-ray analysis. Reductive removal of the chiral auxiliary group, subsequent *N*-propylation, and cleavage of the methylenedioxy group furnished the optically active catecholamines (1*S*)-**16a** and (1*R*)-**16b** in good overall yield. We have separately prepared for the first time pairs of dopaminergic 1-BTHIQs enantiomers through a classical methodology in asymmetric synthesis. The (1*S*)-enantiomers (**14a**−**16a**) bind to D_1 and D_2 dopamine receptors with affinities 5−15 times higher than those of the corresponding (1*R*)-enantiomers (**14b**−**16b**). Moreover, (1*S*)-**14a** inhibits [^{3}H]dopamine uptake with high affinity. It appears that synthesis and testing of (*S*)-enantiomers of BTHIQ are very important for the search for new active drugs at dopamine receptors.

Introduction

Several important asymmetric approaches have been reported for the stereoselective synthesis of tetrahydroisoquinoline and benzyltetrahydroisoquinoline skeletons.[1−3] Many of the synthetic methods are based on the procedures employing chiral building blocks, auxiliaries, or reagents, via, for example, Pictet−Spengler condensation,[4] asymmetric alkylation[5,6] into the 1-position, or asymmetric reduction of dihydroisoquinolines.[7] Some natural and synthetic 1-benzyl-1,2,3,4-tetrahydroisoquinoline (BTHIQ) alkaloids bind to dopamine receptors from striatal membranes[8] and in some cases inhibit dopamine uptake by striatal synaptosomes.[9] The application of gene cloning techniques has allowed the identification of five dopamine receptors subtypes which can be classified into two classes: D_1-like dopamine receptors (D_1 and D_5) and D_2-like dopamine receptors (D_2, D_3, and D_4).[10,11] The D_2-like dopamine receptors show high affinities for drugs (antagonists) used for the treatment of schizophrenia (antipsychotics) and those (agonists) used in the treatment of Parkinson's disease.[10] A natural catecholic BTHIQ (the 4′-glycoside of 1-benzyl-6,7,4′-trihydroxy-1,2,3,4-tetrahydroisoquinoline) exhibits a better selectivity for D_2 and D_4 dopamine receptors than standard dopaminergic antagonists including the clinically useful compound clozapine.[12] Other racemic catecholic BTHIQs show significant in vivo or in vitro dopaminergic activities. It is proposed that 6,7-dihydroxy-BTHIQs can act as dopaminergic antagonists.[13] The study of the dopaminergic efficiency of isoquinoline enantiomers was scarcely reported in the literature. The D_1 and D_2 dopaminergic affinities of a pair of enantiomers with a structure related to the BTHIQs, the (*R*)- and (*S*)-tertiary *N*-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinolines, have been compared.[14] The (*S*)-enantiomer showed the best affinity and selectivity for D_1 receptors.

Recently we have described the synthesis of (*R*)-*nor*roefractine,[8] a monophenolic unmethylated BTHIQ, and have also accomplished the synthesis of racemic monophenolic *N*-alkyl-BTHIQs by a new method incorporating a 'one-pot' cyclization−reduction−alkylation sequence.[15] All those compounds were reported to bind to D_1 and/or D_2 dopamine receptors.[8,15]

To further explore the comparative affinity of BTHIQs for dopamine receptors, we decided to prepare BTHIQs which included two important structural factors: a catecholic moiety (6,7-diphenolic) and a well-defined configuration at C-1 (pair of (*S*)- and (*R*)-enantiomers). Thus, we describe here the enantioselective syntheses of (*S*)- and (*R*)-1-benzyl-6,7-dioxygenated-1,2,3,4-tetrahydroisoquinolines **14a**−**16a** and **14b**−**16b**. Our strategy was based on the enantioselective construction of these pairs of enantiomers by Polniaszek's method[16,17] using as chiral source (*R*)- and (*S*)-phenylglycinol,[18,19] respectively, in two different routes. These compounds were tested for their ability to displace [^{3}H]raclopride (a D_2 dopamine receptor-selective ligand) and [^{3}H]SCH 23390 (a D_1 dopamine receptor-selective ligand) from their specific binding sites in rat striatum and to inhibit [^{3}H]dopamine uptake by rat striatal synaptosomes.[9]

Results and Discussion

Our synthetic route involves *N*-acylation of an optically pure *β*-amino-*O*-protected alcohol **7a** (obtained

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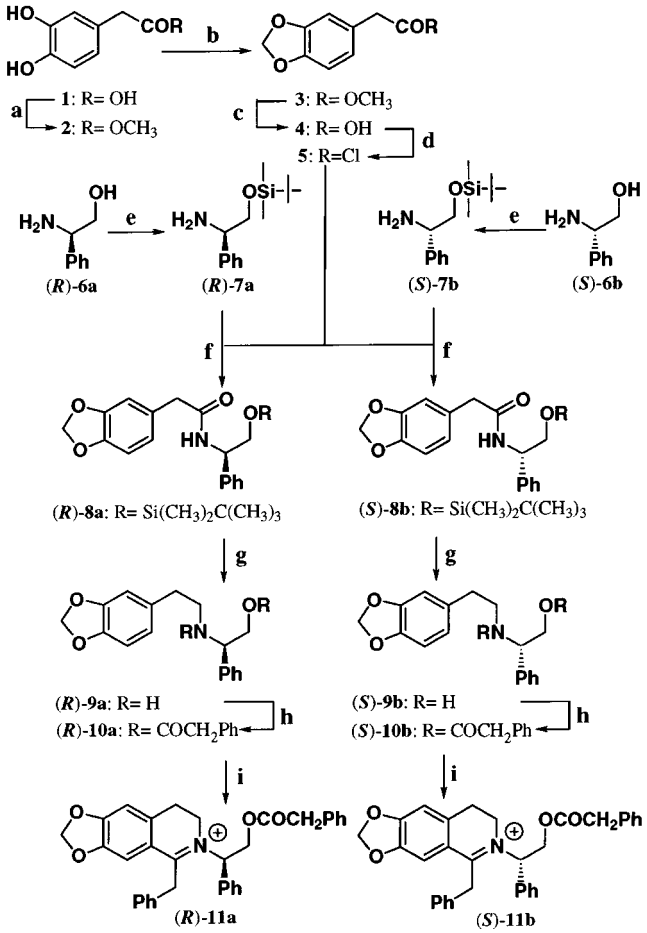
Scheme 1. Preparation of Iminiums **11**[a]



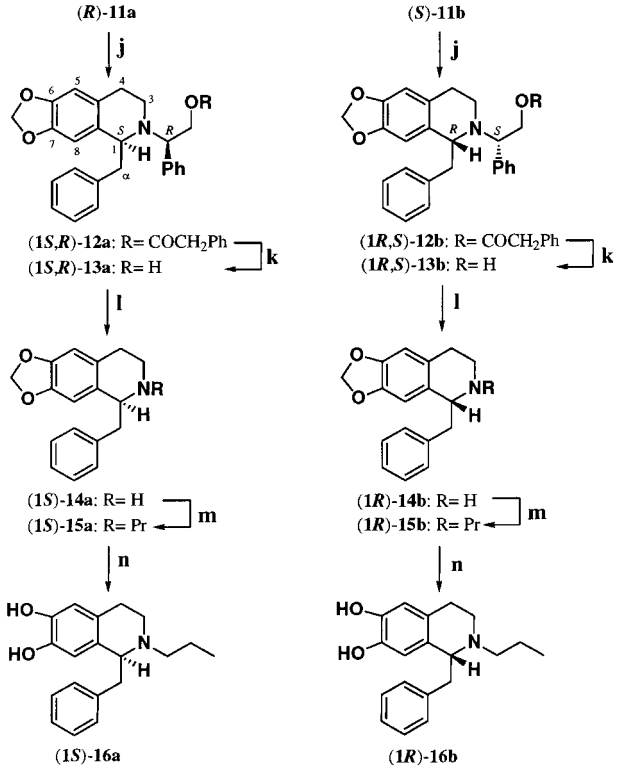
[a] Reagents: (a) H_2SO_4/MeOH; (b) CH_2Cl_2/CsF/DMF; (c) 20% aq KOH/MeOH; (d) $SOCl_2/CH_2Cl_2$; (e) *t*-BDMS chloride/DMF/imidazole; (f) 4-DMAP/Et_3N/CH_2Cl_2; (g) BF_3−etherate/BH_3−THF/THF; (h) $PhCH_2COCl$/4-DMAP/Et_3N/CH_2Cl_2; (i) $POCl_3/CH_2Cl_2$.

from (*R*)-(−)-phenylglycinol, **6a**) with the acid chloride **5**, which was prepared from 3,4-dihydroxyphenylacetic acid (**1**), as starting material. To avoid side reaction due to the presence of the catechol group on the phenylacetic acid **1** and the free hydroxyl on the chiral appendage **6a**, we decided to protect both groups with *O*,*O*-acetal and *O*-TBDMS to give **3** and **7a**, respectively. Then esterification of **5** with **7a** allows us to afford (*R*)-*N*-(1-phenyl-2-*tert*-butyldimethylsilylethoxy)-2-(3,4-methylenedioxyphenyl)-acetamide (**8a**) (Scheme 1).

The amide **8a** was reduced by borane affording a 90% yield of desilylated (*R*)-*N*-[2-(3,4-methylenedioxyphenyl)ethyl]-1-phenylethanol amine (**9a**). A second *N*-acylation[17] with 2 equiv of phenylacetyl chloride attained the *N*,*O*-diacylated amide **10a** as an inseparable mixture of *cis*,*trans* rotamers. A Bischler−Napieralski cyclization, refluxing with excess of $POCl_3$ in dry CH_2Cl_2, allowed us to obtain the iminium ion **11a** possessing the corresponding chiral auxiliary.[16−19] The unpurified iminium ion was reduced with sodium borohydride under controlled conditions, furnished the 1-BTHIQ (1*S*,*R*)-**12a** as a major diastereomer (Scheme 2), in addition to the (1*R*,*R*)-epimer obtained in small amounts.

The optical purity was determined by ^{1}H NMR, affording an 89:11 ratio (1*S*,*R*)/(1*R*,*R*) corresponding to 78% ed. These two compounds were readily purified by silica gel column chromatography. The slower eluting

Scheme 2. Preparation of BTHIQs **16**[a]



[a] Reagents: (j) $NaBH_4$/MeOH; (k) 5% HCl concd−MeOH; (l) H_2/10% C−Pd/5% HCl−EtOH; (m) PrBr/K_2CO_3/DMF; (n) BBr_3/CH_2Cl_2.

diastereomer (1*S*)-1-benzyl-(*R*)-*N*-(1-phenyl-2-phenylacetylethoxy)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (**12a**) was converted into its *O*-deprotected **13a** hydrochloride salt, whose absolute stereochemistry was confirmed by single-crystal X-ray analysis [**13a** base, $[\alpha]_D$ +29° (*c* 0.8, EtOH)].

Removal of the chiral auxiliary of (1*S*,*R*)-**12a** (or (1*S*,*R*)-**13a**) was accomplished by catalytic hydrogenation over Pd/C to give the optically active secondary amine (1*S*)-**14a** [base, $[\alpha]_D$ −33° (*c* 0.7, EtOH)]. When the chiral inductor of the epimer of **12a**, (1*R*,*R*), was removed, the corresponding (1*R*)-enantiomer was obtained. This compound is identical to that prepared from the major diastereoisomer of the series "**b**", (1*R*)-**14b** (see later).

To prepare the amine (*R*)-**14b**, we carried out a synthetic strategy as above using the optically pure *β*-amino alcohol, (*S*)-phenylglycinol (**6b**). In this case, the stereoselective reduction of (*S*)-**11b** led us to obtain (1*R*,*S*)-**12b** and the corresponding (1*S*,*S*)-epimer as a mixture (87:13 ratio, 74% ed, determined by ^{1}H NMR), which was also purified by silica gel chromatography. The absolute configuration of (1*R*,*S*)-**12b** was confirmed by single-crystal X-ray analysis. Reductive removal of the chiral auxiliary group of the major diastereomer (1*R*,*S*)-**12b** (or (1*R*,*S*)-**13b**) gave the optically active (1*R*)-**14b** [base, $[\alpha]_D$ +29° (*c* 0.3, EtOH)].

X-ray crystal structures of the compounds (1*S*,*R*)-**13a**·HCl and (1*R*,*S*)-**12b** are shown in Figures 1 and 2. Both molecular structures show the *N* and C(3) atoms out of the isoquinoline main plane on a half-chair conformation. For both compounds the C(1) atom in the benzyl group is in a pseudoaxial position *trans* to the pseudo-

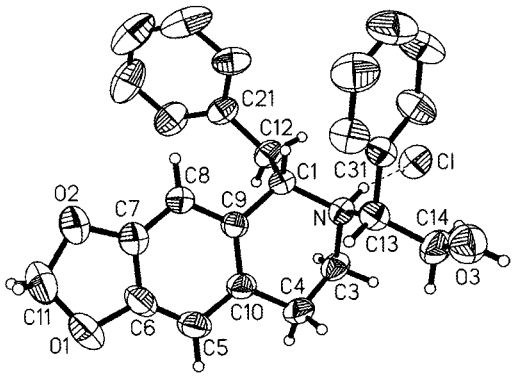


Figure 1. Thermal ellipsoid plot of compound **13a** hydrochloride with the molecular labeling. Phenyl hydrogen atoms have been omitted for clarity.

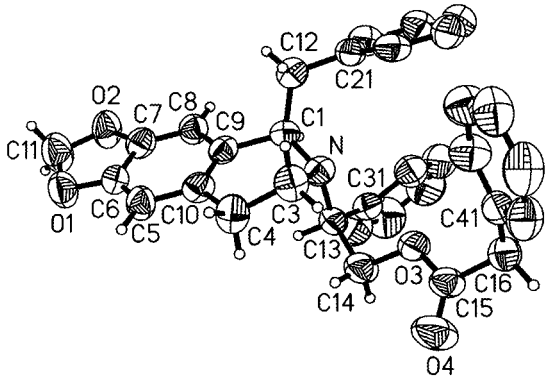


Figure 2. Thermal ellipsoid plot of compound **12b** with the molecular labeling. Phenyl hydrogen atoms have been omitted for clarity.

axial *N*-substituent. In the crystal structure of **13a**·HCl an *anti* conformation of the phenyl ring C(21)−C(26) and the *N* atom respect the C(1)−C(12) bond has been observed. However, for compound **12b** the crystal structure shows the phenyl ring C(21)−C(26) *anti* to C(9) with respect to the C(1)−C(12) bond, due to sterically unfavorable conformation. However, in solution an *anti* conformation of the phenyl ring and the *N*-substituted atom has been observed by ^{1}H NMR for **13a**·HCl and **12b** and similar described compounds.[8,15] In **12b** crystal, weak C−H···O intermolecular interactions form infinite linear chains (C(16)−H(16)···O(2#)) perpendicular to zigzag chains (C(23)−H(23)···O(4*)) thus producing molecular layers (see Figure 3). The shortest contacts between layers correspond to weak C−H···π and C−H···O interactions. In **13a**·HCl crystal an N−H···Cl hydrogen bond has been observed.

N-Propyl derivatives, (1*S*)-**15a** and (1*R*)-**15b**, were prepared with corresponding halide under reflux in alkaline conditions,[20] from both enantiomers (1*S*)-**14a** and (1*R*)-**14b**, respectively. Finally, the expected catecholamines (1*S*)-**16a** and (1*R*)-**16b** were prepared in good yield from (1*S*)-**15a** and (1*R*)-**15b** by cleavage of the methylenedioxy group with boron tribromide.[21]

The (1*R*)-BTHIQs **14b**−**16b** were poorly effective at dopamine receptors. None of them were able to displace [^{3}H]SCH 23390 from its D_1 binding sites in striatum at concentrations up to 0.1 μM. However, **14b** and **16b**, but not **15b**, were able to displace [^{3}H]raclopride from its D_2 binding sites at high concentrations. In contrast,

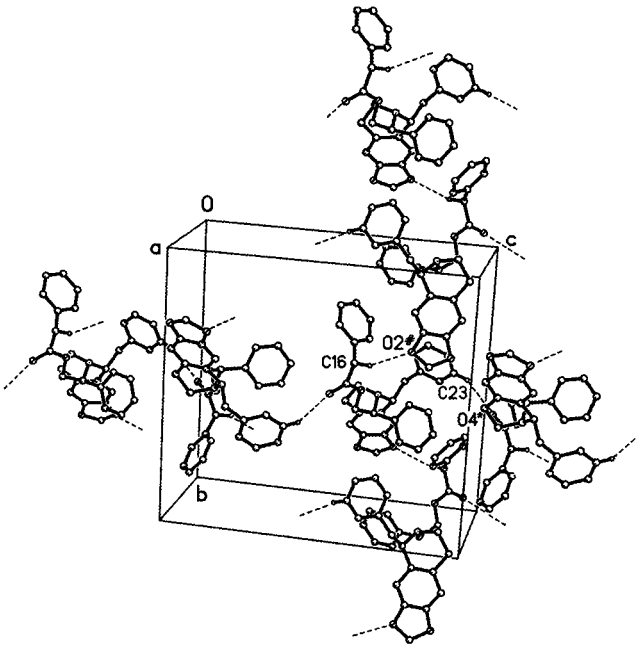


Figure 3. Packing diagram of compound **12b**.

Table 1. IC_{50} Values[a] of BTHIQ Enantiomers on [^{3}H]SCH 23390 and [^{3}H]Raclopride Binding to Rat Striatal Membranes and on [^{3}H]Dopamine Uptake by Rat Striatal Synaptosomes

compd	IC_{50} (μM) on [^{3}H]SCH 23390 binding	IC_{50} (μM) on [^{3}H]raclopride binding	IC_{50} (μM) on [^{3}H]dopamine uptake
14a	23.9 ± 2.5	4.0 ± 0.5	3.6 ± 0.6
14b	>100	53.1 ± 4.2	6.8 ± 0.5
15a	51.9 ± 4.7	21.9 ± 3.1	20.3 ± 9.1
15b	>100	>100	43.6 ± 8.4
16a	16.6 ± 0.4	14.7 ± 0.6	64.8 ± 3.6
16b	>100	61.2 ± 1.5	91.5 ± 13.2

[a] IC_{50} values were calculated from concentration−effect curves with 4−11 concentrations and 4−6 determinations for each concentration.

all the (1*S*)-BTHIQs **14a**−**16a** were able to displace [^{3}H]-SCH 23390 and [^{3}H]raclopride from their respective binding sites. Therefore, it appears clearly that in this series of BTHIQs, the (1*S*)-enantiomers are 5−15 time more effective at D_1-like and D_2-like dopamine receptors than the (1*R*)-enantiomers. In addition to this difference between enantiomers, it appears that the 6,7-methylenedioxy derivative (1*S*)-**14a** is slightly more effective at dopamine receptors and more selective for D_2-like dopamine receptors than the corresponding *N*-propyl derivative (1*S*)-**15a**. This result seems to indicate that introduction of a propyl chain on the *N* atom is not favorable for activity of BTHIQs. This could account for the low increase of affinity of the catecholic compound (1*S*)-**16a**, as compared to its methylenedioxy homologue (1*S*)-**15a**.

Contrary to what occurred at dopamine receptors, the efficiency of the enantiomers of each compound appeared relatively similar on [^{3}H]dopamine uptake (the ratios of the IC_{50} of (1*R*)/(1*S*)-enantiomers were less than 2), even if differences were observed between the IC_{50} measured for the different compounds: **14a**,**b** were more effective than **15a**,**b** which were more effective than **16a**,**b** (Table 1). As was previously described for anonaine in the case of aporphine derivatives,[9] the BTHIQs with a methylenedioxy group were more effective on [^{3}H]-

dopamine uptake than the catecholic one. Again, an *N*-propyl chain appears to not be favorable.

In conclusion, this is the first report on the comparative efficiency of pairs of enantiomers (1*S*)- and (1*R*)-BTHIQs at dopamine receptors and on [^{3}H]dopamine uptake. It appears that synthesis and testing of (*S*)-enantiomers of BTHIQs are very important in the search for new active drugs at dopamine receptors, but not at the dopamine uptake site.

Experimental Section

General Instrumentation. Optical rotations were determined with a Perkin-Elmer 241 polarimeter. IR spectra (film) were run on a Perkin-Elmer 1750 FTIR spectrometer. EIMS, LSIMS, and HREIMS were determined on a VG Auto Spec Fisons instrument, and electrospray ionization (LC−MSD, API-electrospray positive) was determined on a Hewlett-Packard (HP-1100). NMR spectra were recorded on a Bruker AC-250, Varian Unity-300, or Varian Unity-400 spectrometer at 250, 300, or 400 MHz for ^{1}H and 75 or 100 MHz for ^{13}C. Multiplicities of ^{13}C NMR signals were assigned by DEPT experiments. NOEDIFF irradiations, COSY 45, and HMQC correlations were recorded at 400 MHz. All reactions were monitored by analytical TLC with silica gel 60 F_{254} (Merck 5554). The residues were purified through 60 H silica gel column (5−40 μm, Merck 7736) and by flash chromatography (230−400 μm, Merck 9385).

Bioassays. Binding experiments were performed on striatal membranes. Each striatum was homogenized in 2 mL ice-cold Tris-HCl buffer (50 mM, pH = 7.4 at 22 °C) with a Polytron (4 s, maximal scale) and immediately diluted with Tris buffer. The homogenate was centrifuged either twice ([^{3}H]SCH 23390 binding experiments) or four times ([^{3}H]raclopride binding experiments) at 20000*g* for 10 min at 4 °C with resuspension in the same volume of Tris buffer between centrifugations. For [^{3}H]SCH 23390 binding experiments, the final pellet was resuspended in Tris buffer containing 5 mM $MgSO_4$, 0.5 mM EDTA and 0.02% ascorbic acid (Tris-Mg buffer) and the suspension was briefly sonicated and diluted to a protein concentration of 1 mg/mL. A 100 μL aliquot of freshly prepared membrane suspension (100 μg of striatal protein) was incubated for 1 h at 25 °C with 100 μL Tris buffer containing [^{3}H]-SCH 23390 (0.25 nM final concentration) and 800 μL of Tris-Mg buffer containing the required drugs. Non-specific binding was determined in the presence of 30 μM SK&F 38393 and represented around 2−3% of total binding. For [^{3}H]raclopride binding experiments, the final pellet was resuspended in Tris buffer containing 120 mM NaCl, 5 mM KCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$ and 0.1% ascorbic acid (Tris-ions buffer), and the suspension was treated as described above. A 200 μL aliquot of freshly prepared membrane suspension (200 μg of striatal protein) was incubated for 1 h at 25 °C with 200 μL of Tris buffer containing [^{3}H]raclopride (0.5 nM final concentration) and 400 μL of Tris-ions buffer containing the drug being investigated. Non specific binding was determined in the presence of 50 μM apomorphine and represented around 5−7% of total binding. In both cases, incubations were stopped by addition of 3 mL of ice-cold buffer (Tris-Mg buffer or Tris-ions buffer, as appropriate) followed by rapid filtration through Whatman GF/B filters. Tubes were rinsed with 3 mL ice-cold buffer, and filters were washed with 3 × 3 mL ice-cold buffer. After the filters had been dried, radioactivity was counted in 4 mL BCS scintillation liquid at an efficiency of 45%. Filter blanks corresponded to approximately 0.5% of total binding and were not modified by drugs.

[^{3}H]Dopamine uptake was studied using a preparation of rat striatal synaptosomes. For the preparation of synaptosomes, rats (male Wistar rats, 150−250 g; Charles River, France) were killed by decapitation and the striatum was dissected (temperature = 0−4 °C) and homogenized in 10 volumes (w/v) of 0.32 M sucrose using 10 up-and-down strokes of a Teflon glass homogenizer (800 rpm). Nuclear material was removed by centrifugation at 1000*g* for 10 min (4 °C). The supernatant was centrifuged at 15000*g* for 30 min (4 °C). The resultant pellet was resuspended in 20 volumes of ice-cold Krebs-Ringer medium previously oxygenated (95% O_2−5% CO_2). The medium contained (mM): NaCl = 109, KCl = 3.6, KH_2PO_4 = 1.1, $CaCl_2$ = 2.4, $MgSO_4$ = 0.6, $NaHCO_3$ = 25, glucose = 5.5, pH = 7.6. [^{3}H]Dopamine uptake was evaluated on aliquots of the synaptosomal preparation. After a 5 min preincubation in Krebs-Ringer buffer containg 10 μM pargyline, [^{3}H]dopamine (47 Ci/mmol; Amersham, France) was added to a final 2 nM concentration. Five-minute incubations were stopped by dilution into ice-cold Krebs-Ringer medium followed by filtration in vacuo on Whatman GF/B filters. Filters were washed twice with 3 mL cold Krebs-Ringer medium and dried. Tissue radioactivity retained by synaptosomes was determined by liquid scintillation spectrometry. Blank values, obtained by incubating parallel samples at 0 °C, were subtracted.

3,4-Methylenedioxyphenylacetyl Methyl Ester, 3. 3,4-Dihydroxyphenylacetic acid (**1**; 2.0 g, 11.9 mmol) was treated by MeOH (40 mL) in acid medium with concentrated H_2SO_4 (0.5 mL), stirred and refluxed for 3 h. Then, the MeOH was evaporated off under reduced pressure to afford a residue of 3,4-dihydroxyphenylacetyl methyl ester (**2**; 2.1 g): 97% yield; IR (film) ν_{max} 3370, 1714 (CO), 1608, 1523, 1445, 1350, 1285, 1197, 1150, 1115, 1012, 964, 797, 726 cm^{-1}.

Dichloromethane (3 mL, 46.7 mmol) and CsF (8.4 g, 55.3 mmol) were added to a solution of this compound **2** (2.1 g, 11.5 mmol) in anhydrous DMF (40 mL), and the mixture was refluxed for 3 h with stirring. After cooling, the reaction mixture was extracted with CH_2Cl_2 and the organic layer was washed with 5% aq $NaHCO_3$ and water, dried over Na_2SO_4 and concentrated in vacuo to dryness. The residue was purified by flash chromatography (CH_2Cl_2/hexane 6:4) furnishing 1.23 g (55%) of 3,4-methylenedioxyphenylacetyl methyl ester (**3**) as a pale yellow oil; IR (film) ν_{max} 1737 (CO), 1504, 1492, 1445, 1248, 1161, 1039, 929, 810 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.72 (d, J = 1.4 Hz, 1H), 6.69 (d, J = 7.5 Hz, 1H), 6.64 (dd, J = 7.5, 1.4 Hz, 1H), 5.83 (s, 2H), 3.61 (s, 3H), 3.46 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7 (CO), 147.7, 146.6, 127.7, 122.2, 109.6, 108.0, 101.0, 51.5, 40.3; EIMS *m*/*z* (%) 194 [M]$^+$ (100), 136 (91), 135 [M − $COOCH_3$]$^+$ (91), 105 (78), 77 (87).

3,4-Methylenedioxyphenylacetyl Chloride, 5. Hydrolysis of ester was carried out dissolving 3,4-methylenedioxyphenylacetyl methyl ester (**3**; 1.0 g, 5.15 mmol) in MeOH (2 mL) and 20% aq KOH solution (10 mL), stirred and refluxed for 3 h. Methanol was evaporated and the aqueous solution was made acid with 5% aq HCl and extracted with AcOEt. The organic layer was washed with brine and water, dried over Na_2SO_4 and concentrated to dryness to yield a white solid which was recrystallized from AcOEt/CH_2Cl_2, to give **4**: 0.9 g (97%) as colorless needles; mp 129−131 °C; IR (film) ν_{max} 3200, 2911, 1698 (CO), 1504, 1448, 1408, 1339, 1254, 1184, 1038, 925, 785, 692 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (d, J = 1.1 Hz, 1H), 6.76 (d, J = 7.9 Hz, 1H), 6.71 (dd, J = 7.9, 1.1 Hz, 1H), 5.93 (s, 2H), 3.55 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178 (CO), 147.8, 146.9, 126.7, 122.5, 109.7, 108.3, 101.0, 40.6; LSIMS *m*/*z* 180 [M]$^+$, 135 [M − COOH]$^+$.[22]

A mixture of 3,4-methylenedioxyphenylacetic acid (**4**; 0.5 g, 2.78 mmol) and $SOCl_2$ (1.5 mL, 20.6 mmol) in anhydrous CH_2Cl_2 was refluxed for 3 h. Then, the solvent was removed to obtain compound **5** as a pale yellow oil which was used in the next step without further purification.

Synthesis of (*S*)-BTHIQs Using (*R*)-(−)-Phenylglycinol (6a). (*R*)-*N*-(1-Phenyl-2-*tert*-butyldimethylsilylethoxy)-2-(3,4-methylenedioxyphenyl)acetamide, 8a. The hydroxyl group of the chiral auxiliary was protected treating a solution of (*R*)-1-phenylethanolamine (**6a**; 1.0 g, 7.3 mmol) in anhydrous DMF (4 mL) with *tert*-butyldimethylsilane chloride (1.3 g, 8.62 mmol), imidazol (1.3 g, 19.1 mmol) under N_2 atmosphere, at room temperature and stirring for 7 h. The reaction mixture was extracted with CH_2Cl_2, washed with 5% aq $NaHCO_3$ and water, dried, and concentrated. This residue was purified through flash chromatography (CH_2Cl_2/MeOH/DEA 9.9:0.1:0.1) to afford a colorless oil of (*R*)-*N*-(1-phenyl-2-*tert*-butyldimeth-

ylsilylethoxy)amine (**7a**; 1.3 g, 71%): $[\alpha]_D$ −16.6° (*c* 0.6, EtOH); IR (film) ν_{max} 3385, 2954, 2929, 2856, 1690, 1471, 1256, 1089, 837, 777, 700 cm^{-1}; ^1H NMR* (300 MHz, $CDCl_3$) δ 7.40−7.23 (m, 5H), 4.07 (dd, J = 8.4, 3.9 Hz, 1H, C*H*Ph), 3.72 (dd, J = 9.6, 3.9 Hz, 1H, CH_2O), 3.52 (dd, J = 9.6, 8.4 Hz, 1H, CH_2O), 1.85 (br s, exchange with D_2O), 0.90 (s, 9H), 0.04 (s, 6H); ^{13}C NMR* (75 MHz, $CDCl_3$) δ 142.6, 128.2, 127.2, 126.9, 69.5 (CH_2O), 57.6 (*C*HPh), 25.9, 18.2, −5.5; LSIMS *m/z* 252 $[MH]^+$, 235 $[M - NH_2]^+$, 194 $[M - t\text{-BDMS}]^+$. *The assignments were made by COSY 45, DEPT, and HMQC.

The crude of 3,4-methylenedioxyphenylacetyl chloride (**5**) obtained as described above from 0.5 g of **4** (2.78 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise to a solution of (*R*)-*N*-(1-phenyl-2-*tert*-butyldimethylsilylethoxy)amine (**7a**; 680 mg, 2.71 mmol), 4-DMAP (50 mg, 0.41 mmol) and Et_3N (0.4 mL, 2.88 mmol) in dry CH_2Cl_2 (10 mL) under N_2 atmosphere and in a cooling ice bath. After stirring at room temperature for 1 h, 5% aq HCl (15 mL) solution was added and extracted with CH_2Cl_2. The organic layer was washed with 5% aq $NaHCO_3$ solution, brine, water, dried and the solvent was removed under reduced pressure to give 1.03 g of compound **8a** (92%): $[\alpha]_D$ − 8.2° (*c* 0.6, EtOH); IR (film) ν_{max} 3289, 2953, 2857, 1645 (CO), 1546, 1503, 1444, 1247, 1119, 1041, 837, 779, 700 cm^{-1}; ^1H NMR* (300 MHz, $CDCl_3$) δ 7.30−7.13 (m, 5H), 6.79 (d, J = 7.8 Hz, 1H), 6.75 (d, J = 1.7 Hz, 1H), 6.71 (dd, J = 7.8, 1.7 Hz, 1H), 6.33 (d, J = 7.5 Hz, 1H, NHCO), 5.95 (s, 2H), 4.97 (m, 1H, C*H*Ph), 3.78 (dd, J = 10.0, 4.0 Hz, 1H, CH_2O), 3.65 (dd, J = 10.0, 3.8 Hz, 1H, CH_2O), 3.51 (s, 2H), 0.74 (s, 9H), −0.15 (s, 3H), −0.26 (s, 3H); ^{13}C NMR* (75 MHz, $CDCl_3$) δ 170.4 (CO), 148.2, 147.0, 140.2, 128.4, 128.2, 127.2, 126.6, 122.7, 109.8, 108.8, 101.1, 66.0 (CH_2O), 54.2 (*C*HPh), 43.5, 25.6, 17.9, −5.9; EIMS *m/z* (%) 413 $[M]^+$ (1.2), 398 (14), 356 $[M - t\text{Bu}]^+$ (100), 268 (62), 236 (90), 177 (71), 135 (88), 106 (94). *The assignments were made by COSY 45, DEPT and HMQC.

(*R*)-*N*-[2-(3,4-Methylenedioxyphenyl)ethyl]-1-phenylethanolamine, 9a. (*R*)-*N*-(1-Phenyl-2-*tert*-butyldimethylsilylethoxy)-2-(3,4-methylenedioxyphenyl)acetamide (**8a**; 0.5 g, 1.21 mmol) in anhydrous THF (25 mL) was reduced by BF_3−etherate (ca. 47%, 0.3 mL, 1.14 mmol) and 1 M BH_3−THF solution (4.0 mL, 4.0 mmol) carefully added dropwise, at room temperature and then, the mixture was refluxed for 2.5 h, under N_2 atmosphere. Excess reagent was destroyed with 5 N aq HCl solution. The organic solvent was evaporated off and the aqueous solution was made basic with 15% aq NH_4OH, then extracted with AcOEt. The combined organic phases were washed with brine, water, dried over Na_2SO_4 and concentrated to dryness. Compound **9a**, (310 mg, 90%) was obtained as a white solid: $[\alpha]_D$ −55.9° (*c* 0.8, EtOH); IR (film) ν_{max} 3300, 2923, 1608, 1502, 1443, 1366, 1246, 1191, 1039, 938, 891, 809, 760, 702 cm^{-1}; ^1H NMR* (400 MHz, $CDCl_3$) δ 7.35−7.20 (m, 5H), 6.71 (d, J = 8.0 Hz, 1H), 6.62 (d, J = 1.2 Hz, 1H), 6.59 (dd, J = 8.0, 1.2 Hz, 1H), 5.91 (s, 2H), 3.78 (dd, J = 8.4, 4.4 Hz, 1H, C*H*Ph), 3.69 (dd, J = 10.5, 4.4 Hz, 1H, CH_2O), 3.53 (dd, J = 10.5, 8.4 Hz, 1H, CH_2O), 2.80−2.66 (m, 4H), 2.21 (br s, exchange with D_2O); ^{13}C NMR* (100 MHz, $CDCl_3$) δ 147.6, 145.8, 140.3, 133.4, 128.6, 127.6, 127.1, 121.4, 109.0, 108.1, 100.7, 66.5 (CH_2O), 64.5 (*C*HPh), 48.5, 36.0; LSIMS *m/z* 286 $[MH]^+$; EIMS *m/z* (%) 254 $[M - CH_2OH]^+$ (93), 150 (100), 135 (72), 121 (95). *The assignments were made by COSY 45, DEPT and HMQC.

(*R*)-*N*-(1-Phenyl-2-phenylacetylethoxy)-*N*-[2-(3,4-methylenedioxyphenyl)ethyl]-2-phenylacetamide, 10a. Commercially available phenylacetyl chloride (0.53 mL, 4.0 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise to a solution of (*R*)-*N*-[2-(3,4-methylenedioxyphenyl)ethyl]-1-phenylethanolamine (**9a**; 560 mg, 1.96 mmol), 4-DMAP (60 mg, 0.49 mmol) and Et_3N (0.6 mL, 4.31 mmol) in dry CH_2Cl_2 (20 mL) under N_2 atmosphere, in an ice bath, then stirred at room temperature for 2.5 h. The mixture reaction was washed with 5% aq HCl and 5% aq $NaHCO_3$ solutions, brine, water, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel 60H column chromatography (toluene/CH_2Cl_2/AcOEt 7.2:2.2:0.6) to afford 613 mg of a colorless oily compound **10a** (60%): LSIMS *m/z* 522 $[MH]^+$, 386 $[MH - OCOCH_2Ph]^+$; EIMS *m/z* (%) 521 $[M]^+$ (5), 385 (62), 268 (20), 238 (54), 148 (100), 136 (49), 91 (79).

(1*S*)-1-Benzyl-(*R*)-*N*-(1-phenyl-2-phenylacetylethoxy)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline, 12a, and (1*R*,*R*)-Epimer. A mixture of amide **10a** (200 mg, 0.38 mmol) as inseparable *cis* and *trans* rotamers, and $POCl_3$ (1.5 mL, 16.1 mmol) in dry CH_2Cl_2 (4.0 mL) was refluxed overnight with stirring. Excess reagent and solvent were removed in vacuo to give yellow residue of iminium **11a** (LC−MSD, API-electrospray positive: *m/z* 386 $[M - COCH_2Ph]^+$; LISMS *m/z* 504 $[M]^+$). This compound was used for the following reaction without purification.

A solution of this chiral isoquinolinium salt (**11a**) in dry MeOH (15 mL) was reduced by means of $NaBH_4$ (420 mg, 11.1 mmol) at −78 °C and in stirring for 2 h. Excess $NaBH_4$ was decomposed with 5% aq HCl solution. The mixture was concentrated, made basic with 5% aq NH_4OH solution, extracted with CH_2Cl_2, washed with brine, water, dried and the solvent was evaporated off to dryness. The crude was purified by silica gel 60H column chromatography (hexane/AcOEt 9.2:0.8) to attain 159 mg of (1*S*,*R*)-**12a** (83%) and 8 mg of (1*R*,*R*)-epimer (4.2%).

(1*S*,*R*)-12a: $[\alpha]_D$ +32° (*c* 0.4, EtOH); IR (film) ν_{max} 2920, 1729 (CO), 1496, 1378, 1261, 1226, 1149, 1043, 925, 850 cm^{-1}; ^1H NMR* (300 MHz, $CDCl_3$) δ 7.25−6.94 (m, 13H), 6.79 (d, J = 8.4 Hz, 2H), 6.52 (s, 1H, H-5), 6.11 (s, 1H, H-8), 5.81 (s, 2H, OCH_2O), 4.39 (dd, J = 11.2, 5.6 Hz, 1H, CH_2O), 4.21 (dd, J = 11.2, 5.6 Hz, 1H, CH_2O), 3.84 (t, J = 5.6 Hz, 1H, C*H*Ph), 3.59 (dd, J = 8.7, 5.4 Hz, 1H, H-1), 3.44 (m, 2H, OCOC*H*$_2$Ph), 3.38 (m, 1H, H-3a), 3.11 (dd, J = 14.4, 5.4 Hz, 1H, H-3b), 2.98 (dd, J = 13.6, 8.7 Hz, 1H, H-α1), 2.86 (m, 1H, H-4a), 2.68 (dd, J = 13.6, 5.4 Hz, 1H, H-α2), 2.32 (dd, J = 17.1, 3.3 Hz, 1H, H-4b); ^{13}C NMR* (100 MHz, $CDCl_3$) δ 171.2 (CO), 145.8 and 145.3 (C-6 and C-7), 140.3−125.8 (CH, C), 108.5 (C-5), 107.9 (C-8), 100.4 (OCH_2O), 67.1 (CH_2O), 62.3 (*C*HPh), 61.1 (C-1), 43.2 (C-α), 41.3 (OCO*C*H$_2$Ph), 39.6 (C-3), 23.6 (C-4); LSIMS *m/z* 506 $[MH]^+$, 414 $[M - CH_2Ph]^+$. *The assignments were made by COSY 45, DEPT, NOESY and HMQC.

(1*R*,*R*)-Epimer: $[\alpha]_D$ −46° (*c* 0.3, EtOH); IR (film) ν_{max} 2921, 1735 (CO), 1482, 1379, 1228, 1152, 1049 cm^{-1}; ^1H NMR* (400 MHz, $CDCl_3$) δ 7.31−7.05 (m, 15H), 6.53 (s, 1H, H-5), 6.29 (s, 1H, H-8), 5.88 and 5.86 (2d, J = 1.4 Hz, 2H, OCH_2O), 4.12−4.02 (m, 3H, H-1 and CH_2O), 3.90 (t, J = 5.4 Hz, 1H, C*H*Ph), 3.38 (s, 2H, OCOC*H*$_2$Ph), 3.16 (m, 1H, H-3a), 3.05 (dd, J = 13.6, 8.4 Hz, 1H, H-α1), 2.86 (dd, J = 13.6, 5.2 Hz, 1H, H-α2), 2.70 (m, 2H, H-4a and H-3b), 2.25 (m, 1H, H-4b); ^{13}C NMR* (75 MHz, $CDCl_3$) δ 171.1 (CO), 146.0 and 145.4 (C-6 and C-7), 140.1−126.0 (CH, C), 108.5 (C-5), 107.8 (C-8), 100.5 (OCH_2O), 67.5 (CH_2O), 62.6 (*C*HPh), 60.6 (C-1), 42.7 (C-α), 41.2 (OCO*C*H$_2$Ph), 40.1 (C-3), 24.3 (C-4); LSIMS *m/z* 506 $[MH]^+$, 414 $[M\text{-}CH_2Ph]^+$. *The assignments were made by COSY 45, DEPT and HMQC.

(1*S*)-1-Benzyl-(*R*)-*N*-(1-phenyl-2-hydroxyethyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline, 13a. Compound (1*S*,*R*)-**12a** (10 mg, 0.02 mmol) was dissolved in 5% methanol/HCl concentrated (2 mL) and then this solution was evaporated under reduced pressure. The residue was crystallized from a mixture of CH_2Cl_2/MeOH affording 7 mg (91%) of **13a**·HCl: colorless needles; mp 164−166 °C; $[\alpha]_D$ +29° (*c* 0.8, EtOH); IR (film) ν_{max} 3435, 2918, 1481, 1379, 1227, 1038, 937 cm^{-1}; ^1H NMR* (400 MHz, $CDCl_3$) δ 7.35−7.09 (m, 13H), 6.90 (d, J = 7.2 Hz, 2H), 6.53 (s, 1H, H-5), 6.20 (s, 1H, H-8), 5.86 (s, 2H, OCH_2O), 3.78 (m, 2H, CH_2OH), 3.72 (dd, J = 9.4, 5.3 Hz, 1H, H-1), 3.65 (dd, J = 9.8, 3.0 Hz, 1H, C*H*Ph), 3.55 (td, J = 14.0, 4.9 Hz, 1H, H-3a), 3.26 (dd, J = 14.0, 6 Hz, 1H, H-3b), 3.05 (dd, J = 13.7, 9.4 Hz, 1H, H-α1), 2.96 (m, 1H, H-4a), 2.80 (dd, J = 13.7, 5.3 Hz, 1H, H-α2), 2.48 (dd, J = 16.8, 4.9 Hz, 1H, H-4b); ^{13}C NMR* (100 MHz, $CDCl_3$) δ 145.8 and 145.3 (C-6 and C-7), 140.2−126.2 (CH, C), 108.4 (C-5), 107.5 (C-8), 100.4 (OCH_2O), 65.4 (*C*HPh), 63.5 (CH_2OH), 60.1 (C-1), 43.0 (C-α), 40.3 (C-3), 23.9 (C-4); LSIMS *m/z* 388 $[MH]^+$; EIMS *m/z* (%) 386 $[M - 1]^+$, 296 $[M - CH_2Ph]^+$, 280, 176. *The assignments were made by COSY 45 and DEPT.

(1*S*)-1-Benzyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline, 14a. A solution of (1*S*,*R*)-**12a** (21 mg, 0.04 mmol) in ethanol (2.5 mL) and 5% HCl (0.34 mL) was shaken under hydrogen atmosphere (1 atm) in the presence of 10% palladium on charcoal (8 mg) for 29 h at rt. To remove the catalyst, the mixture was filtered through Celite and then, the solution was evaporated off in vacuo. The residue was basified with 5% aq NH_4OH and extracted with CH_2Cl_2. The organic layer was washed with brine, water and dried over anhydrous Na_2SO_4. The filtrate was concentrated and the residue purified by silica gel 60H column chromatography (toluene/AcOEt/methanol/DEA 3:6.8:0.2:0.1) to give 9 mg of (1*S*)-1-benzyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (**14a**; 84%): $[\alpha]_D$ −33° (*c* 0.7, EtOH); IR (film) ν_{max} 3391, 2923, 2853, 1618, 1484, 1381, 1247, 1038, 934 cm^{-1}; ^1H NMR* (400 MHz, $CDCl_3$) δ 7.35−7.25 (m, 5H), 6.72 (s, 1H, H-8), 6.57 (s, 1H, H-5), 5.91 (s, 2H, OCH_2O), 4.11 (dd, J = 10.0, 3.6 Hz, 1H, H-1), 3.18 (m, 2H, H-3a and H-α1), 2.87 (m, 2H, H-3b and H-α2), 2.72 (m, 2H, H-4), 1.73 (br s, exchange with D_2O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.8 and 145.7 (C-6 and C-7), 138.8−126.5 (CH, C), 108.8 (C-5), 106.2 (C-8), 100.6 (OCH_2O), 57.2 (C-1), 42.5 (C-3), 40.4 (C-α), 29.9 (C-4); LSIMS *m*/*z* 268 $[MH]^+$, 176 $[M - CH_2Ph]^+$; HRLISMS *m*/*z* 268.13267 $[MH]^+$ (268.13375 calcd for $C_{17}H_{18}NO_2$); HREIMS *m*/*z* 176.07121 (176.07115 calcd for $C_{10}H_{10}NO_2$). *The assignments were made by COSY 45 and NOEDIFF.

(1*S*)-*N*-Propyl-1-benzyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline, 15a. A suspension of secondary amine **14a** (6 mg, 0.023 mmol) in dry DMF (2 mL) and anhydrous K_2CO_3 (6 mg) was treated with 1-bromopropane (9 μL, 0.1 mmol) in stirring overnight at 70 °C, under N_2 atmosphere. The mixture reaction was diluted with water (5 mL) and extracted with CH_2Cl_2. The combined organic layers were washed with brine, water, dried over Na_2SO_4 and evaporated off under reduced pressure. The residue was purified through flash chromatography (CH_2Cl_2/AcOEt 6:4) to obtain 5 mg of **15a** (70%): $[\alpha]_D$ +24° (*c* 1, EtOH); IR (film) ν_{max} 2964, 2928, 1619, 1486, 1390, 1342, 1254, 1036, 937, 863 cm^{-1}; ^1H NMR* (400 MHz, $CDCl_3$) δ 7.28−7.14 (m, 5H), 6.54 (s, 1H, H-5), 6.19 (s, 1H, H-8), 5.87 and 5.84 (2d, J = 1.2 Hz, 2H, OCH_2O), 3.78 (t, J = 6.8 Hz, 1H, H-1), 3.26 (m, 1H, H-3a), 3.09 (m, 1H, H-α1), 2.83 (m, 3H, H-3b, H-4a and H-α2), 2.48 (m, 3H, H-4b and NCH_2-), 1.41 (m, 2H, CH_2-), 0.78 (t, J = 7.4 Hz, 3H, CH_3); ^{13}C NMR* (75 MHz, $CDCl_3$) δ 148.1 and 146.4 (C-6 and C-7), 135.6−122.5 (CH, C), 108.6 (C-5), 108.3 (C-8), 101.4 (OCH_2O), 64.6 (C-1), 54.5 (NCH_2-), 42.1 (C-3), 41.6 (C-α), 22.0 (CH_2-), 18.0 (C-4), 11.2 (CH_3); LSIMS *m*/*z* 310 $[MH]^+$, 218 $[M - CH_2Ph]^+$; HREIMS *m*/*z* 308.16614 $[M - 1]^+$ (308.16505 calcd for $C_{20}H_{22}NO_2$), 218.11900 (218.11810 calcd for $C_{13}H_{16}NO_2$). *The assignments were made by COSY 45, DEPT and HMQC.

(1*S*)-*N*-Propyl-1-benzyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline, 16a. Boron tribromide (5 μL, 0.053 mmol) was added to a solution of (1*S*)-*N*-propyl-BTHIQ (**15a**; 5.6 mg, 0.018 mmol) in anhydrous CH_2Cl_2 (1.4 mL) at −78 °C under N_2 atmosphere, and then the mixture was stirred for 4h at room temperature. Water was added dropwise to decompose the excess of BBr_3. The mixture was made basic with 5% aq NH_4OH and extracted with CH_2Cl_2. The organic layer was washed with brine, water and dried over Na_2SO_4. The organic solvent was partially removed and diluted with 5% methanolic HCl solution to obtain a residue which was purified through Sephadex column chromatography affording 3.5 mg of (1*S*)-*N*-propyl-1-benzyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (**16a**·HCl; 58%): $[\alpha]_D$ +50° (*c* 0.5, EtOH); IR (film) ν_{max} 3370, 2925, 2854, 1602, 1453, 1370, 1267, 1109, 1030 cm^{-1}; ^1H NMR* (300 MHz, D_2O) δ 7.28−7.08 (m, 5H), 6.65 (s, 1H, H-5), 6.09 (s, 1H, H-8), 4.54 (t, J = 7.6 Hz, 1H, H-1), 3.65 and 3.46 (2m, 2H, H-3a and H-α1), 3.27 and 3.14 (2m, 3H, H-3b, H-4a and H-α2), 2.92 (m, 3H, H-4b and NCH_2-), 1.60 (m, 2H, CH_2-), 0.70 (t, J = 7.4 Hz, 3H, CH_3); LSIMS *m*/*z* 298 $[MH]^+$, 206 $[M\text{-}CH_2Ph]^+$; HREIMS *m*/*z* 296.16317 $[M - 1]^+$ (296.16505 calcd for $C_{19}H_{22}NO_2$), 206.11801 (206.11810 calcd for $C_{12}H_{16}NO_2$). *The assignments were made by COSY 45.

Synthesis of (*R*)-BTHIQs Using (*S*)-(+)-Phenylglycinol (6b). Our purpose to approach the major (*R*)-enantiomer should be feasible following this same route, by means of (*S*)-(+)-phenylglycinol and subjected to the above conditions.

***(S)*-*N*-(1-Phenyl-2-*tert*-butyldimethylsilylethoxy)-2-(3,4-methylenedioxyphenyl)acetamide, 8b.** (*S*)-1-Phenylethanolamine (**6b**; 1.0 g, 7.3 mmol) was also protected by *tert*-butyldimethylsilyl group as noted above, giving a colorless oil of (*S*)-*N*-(1-phenyl-2-*tert*-butyldimethylsilylethoxy)amine (**7b**; 1.15 g, 63%): $[\alpha]_D$ +16.9° (*c* 2.6, EtOH); IR (film) ν_{max} 3387, 2954, 2929, 2857, 1696, 1462, 1256, 1088, 837, 777, 700 cm^{-1}; ^1H NMR* (300 MHz, $CDCl_3$) δ 7.40−7.22 (m, 5H), 4.08 (dd, J = 8.2, 3.9 Hz, 1H, C*H*Ph), 3.73 (dd, J = 9.8, 3.9 Hz, 1H, CH_2O), 3.52 (dd, J = 9.8, 8.2 Hz, 1H, CH_2O), 1.79 (br s, exchange with D_2O), 0.91 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$)* identical chemical shifts to **7a**; LSIMS *m*/*z* 252 $[MH]^+$, 235 $[M - NH_2]^+$, 194 $[M - t\text{-BDMS}]^+$. *The assignments were made by COSY 45, DEPT and HMQC.

The crude of 3,4-methylenedioxyphenylacetyl chloride (**5**) obtained as described above from 0.5 g of **4** (2.78 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise to a solution of (*S*)-*N*-(1-phenyl-2-*tert*-butyldimethylsilylethoxy)amine (**7b**; 680 mg, 2.71 mmol), in the presence of 4-DMAP (50 mg, 0.41 mmol) and Et_3N (0.4 mL, 2.88 mmol) in dry CH_2Cl_2 (10 mL), under N_2 atmosphere, and in an ice bath. After stirring at room temperature for 1 h, classical workup gave 1.0 g (89%) of **8b**: $[\alpha]_D$ + 10.0° (*c* 2.4, EtOH); IR (film) ν_{max} 3289, 2929, 2857, 1646 (CO), 1543, 1490, 1444, 1361, 1248, 1118, 1041, 932, 837, 779, 700 cm^{-1}; ^1H NMR* (400 MHz, $CDCl_3$) δ 7.28−7.13 (m, 5H), 6.79 (d, J = 7.4 Hz, 1H), 6.75 (d, J = 1.6 Hz, 1H), 6.73 (dd, J = 7.4, 1.7 Hz, 1H), 6.32 (d, J = 7.6 Hz, 1H, NHCO), 5.95 (s, 2H), 4.97 (m, 1H, C*H*Ph), 3.78 (dd, J = 10.0, 4.0 Hz, 1H, CH_2O), 3.65 (dd, J = 10.0, 3.6 Hz, 1H, CH_2O), 3.52 (s, 2H), 0.72 (s, 9H), −0.16 (s, 3H), −0.27 (s, 3H); ^{13}C NMR* (100 MHz, $CDCl_3$) δ identical chemical shifts to **8a**; EIMS *m*/*z* (%) 413 $[M]^+$ (11), 398 (50), 357 (92), 268 (82), 236 (82), 177 (83), 135 (100), 106 (96). *The assignments were made by COSY 45, DEPT and HMQC.

(*S*)-*N*-[2-(3,4-Methylenedioxyphenyl)ethyl](1-phenyl)-ethanolamine, 9b. A mixture of **8b** (0.67 g, 1.62 mmol) in anhydrous THF (25 mL), BF_3−etherate (ca. 47%, 0.3 mL, 1.14 mmol) and 1 M BH_3−THF solution (4.0 mL, 4.0 mmol) were carefully added dropwise, at room temperature. Afterward, it was refluxed for 2.5 h, under N_2 atmosphere to yield a solid **9b** (430 mg, 93%) in white crystals from CH_2Cl_2/EtOH: mp 96−98 °C; $[\alpha]_D$ +52° (*c* 0.7, EtOH); IR (film) ν_{max} 3321, 2924, 1606, 1489, 1443, 1363, 1246, 1189, 1099, 1039, 934, 809, 759, 702 cm^{-1}; ^1H NMR* (300 MHz, $CDCl_3$) δ 7.34−7.19 (m, 5H), 6.70 (d, J = 7.8 Hz, 1H), 6.61 (d, J = 1.5 Hz, 1H), 6.58 (dd, J = 7.8, 1.5 Hz, 1H), 5.89 (s, 2H), 3.75 (dd, J = 8.7, 4.4 Hz, 1H, C*H*Ph), 3.67 (dd, J = 10.7, 4.4 Hz, 1H, CH_2O), 3.49 (dd, J = 10.7, 8.7 Hz, 1H, CH_2O), 2.78−2.62 (m, 4H), 2.36 (br s, exchange with D_2O); ^{13}C NMR* (75 MHz, $CDCl_3$) δ identical chemical shifts to **9a**; LSIMS *m*/*z* 286 $[MH]^+$.*The assignments were made by COSY 45, DEPT and HMQC.

(*S*)-*N*-(1-Phenyl-2-phenylacetylethoxy)-*N*-[2-(3,4-methylenedioxyphenyl)ethyl]-2-phenylacetamide, 10b. Phenylacetyl chloride (0.50 mL, 3.78 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise to a solution of (*S*)-*N*-[2-(3,4-methylenedioxyphenyl)ethyl]-1-phenylethanolamine (**9b**; 440 mg, 1.54 mmol), 4-DMAP (40 mg, 0.33 mmol) and Et_3N (0.5 mL, 3.60 mmol) in dry CH_2Cl_2 (15 mL) in a cooling ice bath, then stirred at room temperature for 2.5 h. After classical workup and 60H column chromatography purification, 530 mg of compound **10b** were afforded as a colorless oil (66%): EIMS *m*/*z* (%) 521 $[M]^+$ (9), 385 (57), 374 (58), 268 (66), 239 (59), 148 (100), 136 (49), 118 (56), 91 (90).

(1*R*)-1-Benzyl-(*S*)-*N*-(1-phenyl-2-phenylacetylethoxy)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline, 12b, and (1*S*,*S*)-Epimer. Compound **10b** (312 mg, 0.6 mmol) was refluxed overnight with $POCl_3$ (1.5 mL, 16.1 mmol) in dry CH_2Cl_2 (2.5 mL) to obtain **11b** in the same conditions as above for **11a**. Then, **11b** was reduced with $NaBH_4$ (240 mg, 6.34 mmol) in dry MeOH (10 mL) at −78 °C with stirring for 2 h.

Workup attained 175 mg of (1*R*,*S*)-**12b** (58%) and 12 mg of (1*S*,*S*)-epimer (4%).

(1*R*,*S*)-12b: mp 106−108 °C; $[\alpha]_D$ −34° (*c* 0.3, EtOH); IR (film) ν_{max} 2912, 1953, 1734 (CO), 1602, 1482, 1454, 1380, 1229, 1147, 1038, 938, 860, 753, 700 cm^{-1}; ^1H NMR* (300 MHz, $CDCl_3$) δ 7.25−6.94 (m, 13H), 6.79 (d, J = 6.9 Hz, 2H), 6.52 (s, 1H, H-5), 6.11 (s, 1H, H-8), 5.81 (s, 2H, OCH_2O), 4.39 (dd, J = 11.0, 5.6 Hz, 1H, CH_2O), 4.21 (dd, J = 11.0, 5.6 Hz, 1H, CH_2O), 3.84 (t, J = 5.6 Hz, 1H, C*H*Ph), 3.59 (dd, J = 8.7, 5.4 Hz, 1H, H-1), 3.44 (m, 2H, OCOC*H*$_2$Ph), 3.38 (m, 1H, H-3a), 3.11 (dd, J = 14.4, 5.7 Hz, 1H, H-3b), 2.98 (dd, J = 13.7, 8.7 Hz, 1H, H-α1), 2.86 (m, 1H, H-4a), 2.68 (dd, J = 13.7, 5.4 Hz, 1H, H-α2), 2.32 (dd, J = 17.1, 3.6 Hz, 1H, H-4b); ^{13}C NMR* (75 MHz, $CDCl_3$) δ identical chemical shifts to (1*S*,*R*)-**12a**; LSIMS *m*/*z* 506 $[MH]^+$, 414 $[M - CH_2Ph]^+$. *The assignments were made by COSY 45, DEPT and HMQC.

(1*S*,*S*)-Epimer: $[\alpha]_D$ +41° (*c* 0.5, EtOH); IR (film) ν_{max} 2920, 1735 (CO), 1601, 1482, 1380, 1229, 1145, 1038, 937, 863, 754, 700 cm^{-1}; ^1H NMR* (400 MHz, $CDCl_3$) δ 7.31−7.05 (m, 15H), 6.53 (s, 1H, H-5), 6.29 (s, 1H, H-8), 5.88 and 5.86 (2d, J = 1.4 Hz, 2H, OCH_2O), 4.11−4.02 (m, 3H, H-1 and CH_2O), 3.90 (t, J = 5.6 Hz, 1H, C*H*Ph), 3.38 (s, 2H, OCOC*H*$_2$Ph), 3.16 (m, 1H, H-3a), 3.05 (dd, J = 13.6, 8.4 Hz, 1H, H-α1), 2.86 (dd, J = 13.6, 5.6 Hz, 1H, H-α2), 2.70 (m, 2H, H-4a and H-3b), 2.25 (m, 1H, H-4b); ^{13}C NMR* (100 MHz, $CDCl_3$) δ identical chemical shifts to (1*R*,*R*)-epimer; LSIMS *m*/*z* 506 $[MH]^+$, 414 $[M - CH_2Ph]^+$, 370 $[M - OCOCH_2Ph]^+$. *The assignments were made by COSY 45, DEPT and HMQC.

(1*R*)-1-Benzyl-(*S*)-*N*-(1-phenyl-2-hydroxyethyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline, 13b. Compound **13b** was prepared from (1*R*,*S*)-**12b** as above for **13a**: $[\alpha]_D$ −24° (*c* 1.2, EtOH); all its spectroscopic data were identical to those reported for **13a**.

(1*R*)-1-Benzyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline, 14b. A solution of (1*R*,*S*)-**12b** (19 mg, 0.038 mmol) in ethanol (2.5 mL), 5% HCl (0.34 mL) and 10% palladium on charcoal (7 mg) was shaken under hydrogen atmosphere (1 atm) for 29 h at room temperature. The mixture was filtered through Celite and then, the solution was evaporated off in vacuo. After classical workup we obtained the secondary amine **14b** (8.3 mg, 82%): $[\alpha]_D$ +29° (*c* 0.3, EtOH); IR (film) ν_{max} 3365, 2922, 2852, 1484, 1380, 1265, 1241, 1038, 936, 862 cm^{-1}; ^1H NMR* (400 MHz, $CDCl_3$) δ 7.35−7.25 (m, 5H), 6.71 (s, 1H, H-8), 6.57 (s, 1H, H-5), 5.91 (s, 2H, OCH_2O), 4.12 (dd, J = 9.8, 3.8 Hz, 1H, H-1), 3.18 (m, 2H, H-3a and H-α1), 2.88 (m, 2H, H-3b and H-α2), 2.72 (m, 2H, H-4), 1.80 (br s, exchange with D_2O); LSIMS *m*/*z* 268 $[MH]^+$, 176 $[M - CH_2Ph]^+$; HREIMS *m*/*z* 266.11558 $[M - 1]^+$ (266.11810 calcd for $C_{17}H_{16}NO_2$), 176.07109 (176.07115 calcd for $C_{10}H_{10}NO_2$). *The assignments were made by COSY 45 and NOEDIFF.

(1*R*)-*N*-Propyl-1-benzyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline, 15b. 1-Bromopropane (8 μL, 0.09 mmol) was added to the amine **14b** (5.1 mg, 0.019 mmol) in dry DMF (2 mL) and K_2CO_3 (5 mg) under N_2 atmosphere and in stirring overnight at 70 °C. The mixture reaction was treated as described above for preparing **15a** and purified through flash chromatography (CH_2Cl_2/AcOEt 6:4) to obtain 4.5 mg of **15b** (77%): $[\alpha]_D$ −21° (*c* 0.8, EtOH); IR (film) ν_{max} 2964, 2928, 1605, 1460, 1390, 1312 cm^{-1}; ^1H NMR* (300 MHz, $CDCl_3$) δ 7.27−7.16 (m, 5H), 6.55 (s, 1H, H-5), 6.17 (s, 1H, H-8), 5.88 and 5.85 (2d, J = 1.3 Hz, 2H, OCH_2O), 3.80 (t, J = 6.6 Hz, 1H, H-1), 3.25 (m, 1H, H-3a), 3.12 (m, 1H, H-α1), 2.85 (m, 3H, H-3b, H-4a and H-α2), 2.54 (m, 3H, H-4b and NCH_2-), 1.44 (m, 2H, CH_2-), 0.78 (t, J = 7.4 Hz, 3H, CH_3); LSIMS *m*/*z* 310 $[MH]^+$, 218 $[M - CH_2Ph]^+$.*The assignments were made by COSY 45.

(1*R*)-*N*-Propyl-1-benzyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline, 16b. Boron tribromide (4 μL, 0.04 mmol) was added to a solution of (1*R*)-*N*-propyl-BTHIQ (**15b**; 4 mg, 0.013 mmol) in anhydrous CH_2Cl_2 (1 mL) at −78 °C, under N_2 atmosphere and then, the mixture was stirred for 4 h at room temperature. A classical workup gave 3 mg of (1*S*)-*N*-propyl-1-benzyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (**16b**·HCl; 69%): $[\alpha]_D$ −55° (*c* 0.6, EtOH); IR (film) ν_{max} 3391, 2923, 2854,1602, 1464, 1375, 1350, 1267, 1114, 941, 868 cm^{-1}; ^1H NMR* (400 MHz, D_2O) δ 7.28−7.11 (m, 5H), 6.67 (s, 1H, H-5), 6.11 (s, 1H, H-8), 4.56 (t, J = 7.6 Hz, 1H, H-1), 3.55−3.15 (m, 5H, H-3, H-α and H-4a), 2.90 (m, 3H, H-4b and NCH_2-), 1.45 (m, 2H, CH_2-), 0.75 (t, J = 7.4 Hz, 3H, CH_3); LSIMS *m*/*z* 298 $[MH]^+$, 206 $[M - CH_2Ph]^+$.

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Supporting Information Available: X-ray data of compounds (1*S*,*R*)-**13a**·HCl and (1*R*,*S*)-**12b**; crystal data, final atomic positional parameters, atomic thermal parameters, full bond lengths and angles, torsion angles, and hydrogen bond tables for both compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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