(+)-Dinapsoline: An Efficient Synthesis and Pharmacological Profile of a Novel Dopamine Agonist

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A highly convergent synthesis was developed for the novel dopamine agonist dinapsoline (**12**) (Ghosh, D.; Snyder, S. E.; Watts, V. J.; Mailman, R. B.; Nichols, D. E. 8,9-Dihydroxy-2,3,7, 11b-tetrahydro-1*H*-naph[1,2,3-*de*]isoquinoline: A Potent Full Dopamine D_1 Agonist Containing a Rigid β-Phenyldopamine Pharmacophore. *J. Med. Chem.* **1996**, *39* (2), 549−555). The crucial step in the new synthesis was a free radical-initiated cyclization to give the complete dinapsoline framework. The improved synthesis required *half* as many steps as the original procedure (Nichols, D. E.; Mailman, R.; Ghosh, D. Preparation of novel naphtho[1,2,3-*de*]isoquinolines as dopamine receptor ligands. PCT Int. Appl. WO 9706799 A1, Feb 27, 1997). One of the late-stage intermediates (**11**) was resolved into a pair of enantiomers. From there, the (*R*)-(+)-**12** (absolute configuration by X-ray) of dinapsoline was identified as the active enantiomer. In unilateral 6-hydroxydopamine (6-OHDA)-lesioned rats, (+)-dinapsoline showed robust rotational behavior comparable to that of an external benchmark, *trans*-4,5,5a,6,7,11b-hexahydro-2-propyl-benzo[*f*]thieno[2,3-*c*]quinoline-9,10-diol, hydrochloride **18** (Michaelides, M. R.; Hong, Y. Preparation of heterotetracyclic compounds as dopamine agonists. PCT Int. Appl. WO 9422858 A1, Oct 13, 1994).

Introduction

Dinapsoline, 8,9-dihydroxy-2,3,7,11b-tetrahydro-1*H*-naphth[1,2,3-*de*]isoquinoline ((±)-**12**), was first synthesized and characterized as a full-efficacy dopamine receptor agonist with some selectivity for D_1 over D_2 receptors by Nichols, Mailman, and co-workers in 1996. Subsequently, (±)-**12** was shown to produce robust rotational behavior in unilateral 6-hydroxydopamine (6-OHDA)-lesioned rats.[4] The study found that (±)-**12** was active after oral and subcutaneous dosing. It was D_1 selective in vivo, and it did not produce tolerance when dosed *intermittently* for up to 14 days.[4] Such a profile suggests that dinapsoline has potential as a novel anti-Parkinsonian agent. In an attempt to identify a superior compound, one that is more suitable for clinical development, and a synthetic route to analogues of dinapsoline, including its enantiomers, we reexamined the synthesis of dinapsoline with the aim of identifying a more practical preparation of the parent compound and its analogues. The development of dinapsoline represented a novel approach in the design of rigid β-phenyl dopamine as an anti-Parkinsonian drug.[7] It effectively extended the concept underlying an earlier discovery of *trans*-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine-10,11-diol (dihydrexidine, **17**) as a rigid dopamine surrogate. Analogous to this structurally rigid β-phenyl dopamine model, the bioisostere thiophene[8] was employed in another attempt to mimic the phenyl D-ring in dihydrexidine to give *trans*-4,5,5a,6,7,11b-hexahydro-2-propyl-benzo[*f*]thieno[2,3-*c*]quinoline-9,10-diol, hydrochloride (**18**).[9] The presence of a rigid β-phenyl dopamine, such as in **17** and **12**, or a rigid β-thiophene dopamine (**18**) is deemed essential for attaining high D_1 receptor subtype specificity, a critical property for high intrinsic dopamine activity and in vivo efficacy (Figure 1).[10] Both dihydrexidine (**17**) and **18** have shown anti-Parkinsonian efficacy in clinical studies.[11] In the case of dihydrexidine given intravenously (iv), anti-Parkinsonian effects were observed when the drug reached a high plasma level. Motor improvement was accompanied by choreic dyskinesias similar to those generated by levodopa, the current "gold standard" in the pharmacotherapy of Parkinson's disease (PD). More recently, positive clinical results on patients intravenously given **19**, the diacetoxy ester derivative of **18**, strongly support the role of the dopamine receptor agonist as a treatment of PD. Equally significant is that dyskinesia was reduced in several patients after they received **19**.[11b]

Although efficacious, the latest crops of dopamine receptor agonists are not metabolically stable, nor are they orally bioavailable. Stability issues aside, dihydrexidine (**17**) showed anti-Parkinsonian efficacy only at dosages approaching the upper tolerable dose, thus limiting its useful therapeutic window. Toxicity, stability, and tolerability are critical factors for any drugs that are to be used chronically, even when patients are individually titrated. The ability to develop practical

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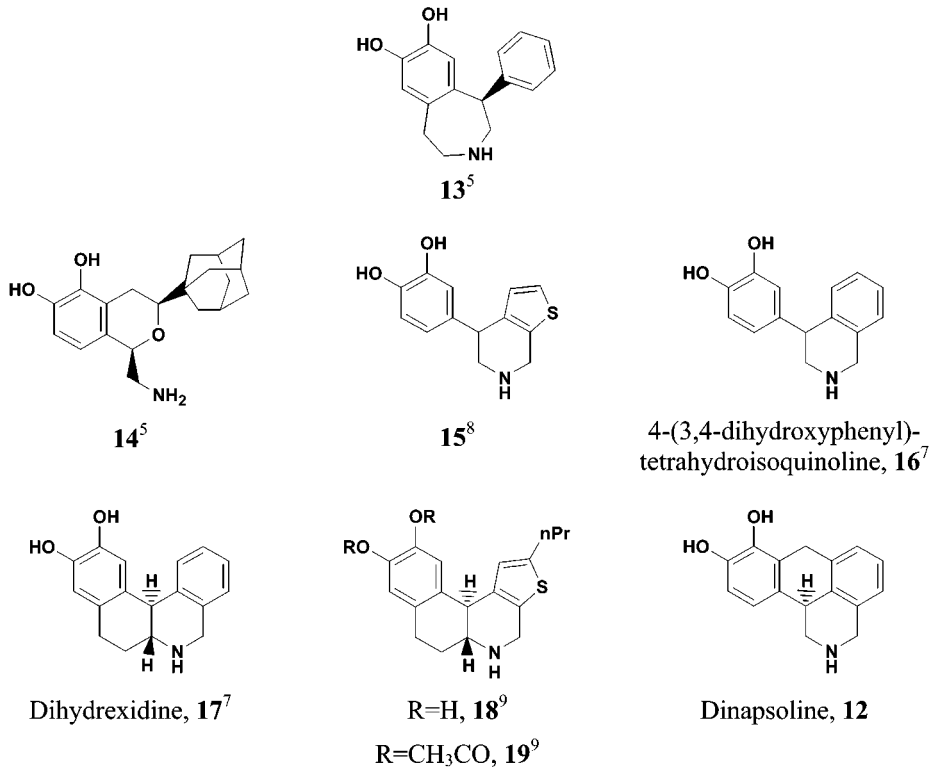


Figure 1. Dopamine agonists.

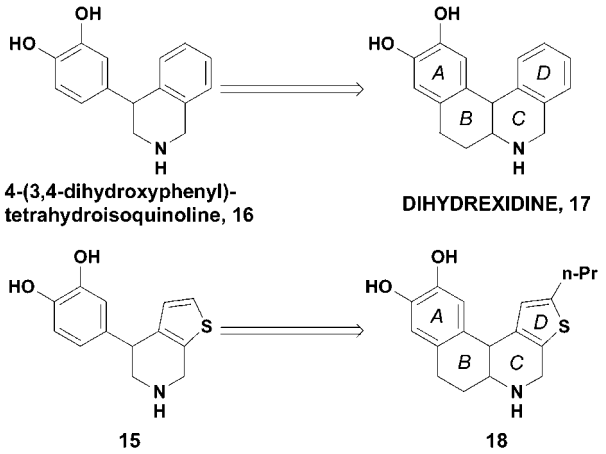


Figure 2. Structural comparison of dihydrexidine (**17**) and **18**.

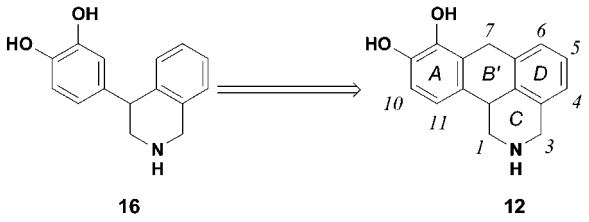
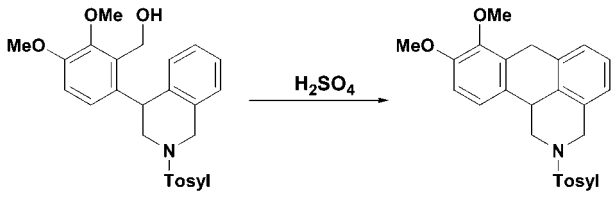


Figure 3. Introducing molecular rigidity through the B′-ring in dinapsoline.

Scheme 1. Original Ring-Closure Procedure



synthesis thereby allowing access to the dinapsoline core molecule for further studies is central to this project.

Structural analysis of **17** and **18** revealed (Figure 2) the molecular features shared by both chemotypes. These molecules can be considered as the rigid form of 4-(3,4-dihydroxyphenyl)tetrahydroisoquinoline (**16**) and **15**. Rigidity is introduced into these molecules by incorporating an additional "B-ring" in the precursor molecules, and this is essentially the concept "rigid *β*-phenyl dopamine model" previously proposed by Nichols.[5]

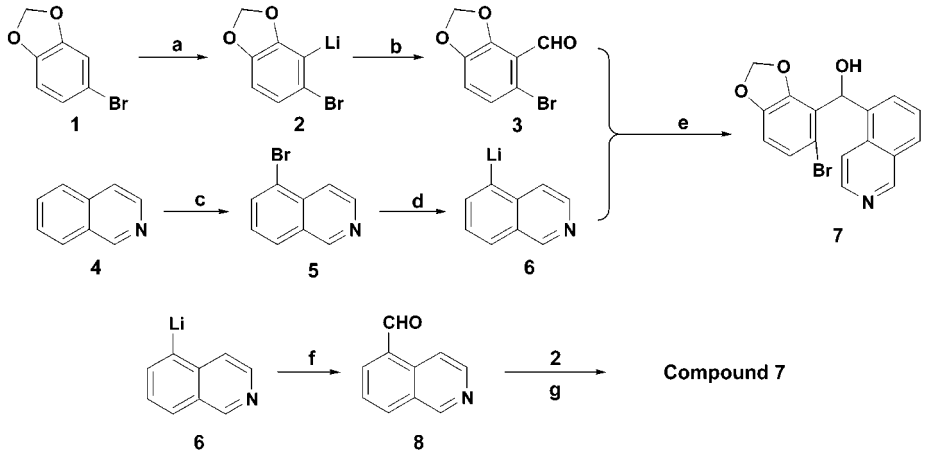
The design of dinapsoline represented another approach to the structurally rigid 4-(3,4-dihydroxyphenyl)-tetrahydroisoquinoline core (**16**) by linking the A-ring and D-ring (Figure 3) through a methylene unit forming the B′-ring. Such modification could offer fresh opportunities for drug development while keeping all the essential elements needed for dopaminergic activity.

Efficient synthesis was unavailable when the molecule was first disclosed. Indeed, the original chemical synthesis as described in the patent literature required as many as 11−14 steps to complete.[7] Furthermore, the problem with the original preparation was aggravated by a difficult ring-closure step occurring *near the end* stage of the synthesis! To gain a better understanding of the properties and the potential of dinapsoline, we developed an improved synthesis together with a chiral resolution into a pair of enantiomers.

Chemistry

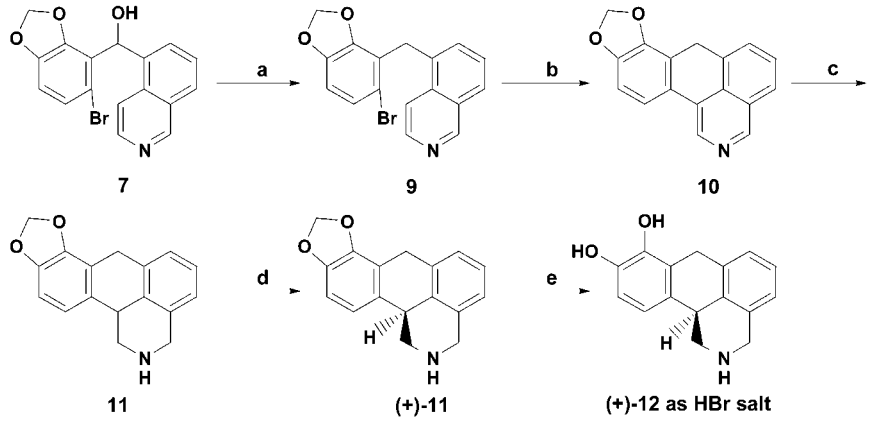
The original synthesis of dinapsoline required a late-stage cyclization step (Scheme 1). Unfortunately, the cyclization gave erratic results, especially when it was scaled up to more than just a few grams of the starting

Scheme 2. Improved Procedure[a]



[a] Reagents and reaction conditions: (a) LDA/THF at −78 °C; (b) DMF at −78 °C; (c) bromine and $AlCl_3$; (d) *t*-BuLi/THF at −78 °C; (e) **3** and **6** in THF at −78 °C; (f) *n*-BuLi/THF at −78 °C; (g) **8** and **2** in THF at −78 °C.

Scheme 3. Improved Synthesis of Dinapsoline[a]



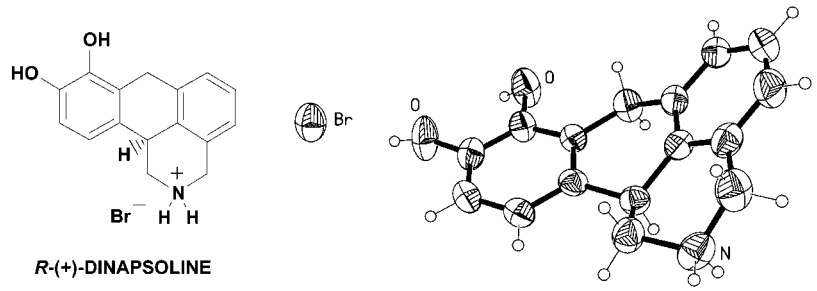
[a] Reagents and reaction conditions: (a) Et_3SiH/TFA at reflux; (b) Bu_3SnH/AIBN in degassed benzene at reflux; (c) $NaCNBH_3$/HCl or PtO_2/H_2 in acetic acid at 140−190 psi; (d) resolution by (+)-dibenzoyl-D-tartaric acid; (e) BBr_3 in methylene chloride at −78 °C.

material. The preferred pathway appeared to be a dimerization.

An alternative approach using the commercially available 4-bromo-1,2-(methylenedioxy)benzene to circumvent the problematic electrophilic aromatic cyclization was developed (Scheme 2).

Selective metalation of compound **1** by lithium diisopropylamide (LDA) gave 3-lithio-4-bromo-1,2-(methylenedioxy)benzene **2**.[12] Formylation of **2** using dimethylformamide (DMF) at −78 °C furnished 4-bromo-1,2-(methylenedioxy)-3-benzaldehyde **3** in good yields. Compound **3** was allowed to couple with the 5-lithio isoquinoline **6**, generated in situ by treatment of 5-bromoisoquinoline[13] **5** with *tert*-butyllithium (*t*-BuLi), to give the benzhydrol **7**. Alternatively, compound **7** was prepared by reversing the reactive functional groups on the isoquinoline fragment and the methylenedioxy component. Formylation of **6** with DMF gave **8** in 64% yield. This 5-isoquinolincarboxaldehyde **8** was coupled with **2** to furnish **7** in 65% yield. The yield of the reverse reaction sequence was better than the yield of the other method. More importantly, the alternate route enhances the utility of the present synthetic approach. Benzhydrol **7** was deoxygenated by refluxing in trifluoroacetic acid in the presence of triethylsilane. The key cyclization step in assembling the dinapsoline core was accomplished by a radical-initiated ring-closure reaction.[14] The tri-*n*-butyltin hydride (TBTH) and 2,2′-azobisisobutyronitrile (AIBN) combination was by far the most efficient reductive system for generating the free radical species for cyclization.[15] A small amount of uncyclized *des*-bromo-**9** was also formed due to a competing hydride abstraction. The side product was removed either by trituration with mixtures of ethyl acetate and hexanes or by silica gel column chromatography (Experimental Section). The TBTH−AIBN pair gave the most consistent results, and the cyclization could be scaled up to 100 g of starting material at a time (Scheme 3).

Once cyclized, the isoquinoline moiety in compound **10** was reduced to the corresponding 1,2,3,4-tetrahydroisoquinoline system **11** using sodium cyanoborohydride in acidic medium. The same reduction could also be effected by a catalytic hydrogenation using Adam's catalyst in glacial acetic acid at elevated pressure and temperature. However, the borohydride reduction gave more consistent results due to its greater tolerance to minor variations in reaction conditions and reagent impurities. The racemic product, (±)-**11**, could be deprotected with boron tribromide in methylene chloride at −78 °C to give the racemic (±)-**12** or be resolved into (+)-**11** and (−)-**11** by chiral HPLC separation on a Chiralcel OD column. Preparative scales of (+)-**11** and



R-(+)-DINAPSOLINE

Figure 4. Absolute configuration of (*R*)-(+)-dinapsoline.

(−)-**11** were achieved by chemical resolution using the unnatural form of tartaric acid (D-form) or its dibenzoyl ester. In general, the dibenzoyl ester of tartaric acid gave results superior to those of the simple tartaric acid for such resolution. Chemical resolution was by far the most practical way to produce multigram quantities of (+)-**11** (Experimental Section); from there, (+)-**12** was obtained after the removal of the methylenedioxy protecting group. The absolute configuration of (+)-dinapsoline ((+)-**12**, HBr salt) was determined by a single-crystal X-ray analysis (Figure 4).

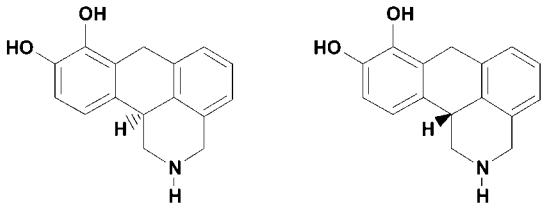
Results and Discussion

Early work by Nichols and Mailman demonstrated that, despite the structural deviation from their original D_1 agonist pharmacophore, dinapsoline retained many of the original characteristics of dihydrexidine (**17**). Dinapsoline was created by joining the A-ring and D-ring of **17** through a methylene bridge forming the B′-ring while the original B-ring in dihydrexidine was deleted.[1] Such modifications effectively preserved all the critical structural elements of a D_1 receptor agonist which include the relative position and orientation of the basic nitrogen, catechol hydroxyl groups, and the accessory phenyl ring. These changes resulted in a novel dopamine D_1 receptor agonist which offers new opportunities for drug development. The introduction of the B′-ring and, therefore, the 7-carbon bridging methylene unit, which was previously absent in the dihydrexidine (**17**) chemotype, provided further opportunities for designing "core" modifications in addition to the substitution of analogues within the molecular framework of dinapsoline.

In the early reports,[1,4] racemates were screened in all in vitro and in vivo assays; no distinction was made as to which enantiomer was responsible for the biological activities. On the basis of the results reported by Nichols and co-workers on dihydrexidine and dinapsoline as well as the work by Michaelides on **18** and **19**, we predicted that dopamine binding activity should reside largely or even entirely on one of the enantiomers.[9,10] From the use of the active pharmacophore model developed by Nichols and others, it was predicted that both the affinity and intrinsic activity of racemic (±)-**12** reside in only one of its enantiomers, that with the 11b*R* absolute configuration. Data from in vitro and in vivo pharmacological assays (Tables 1−3) indicated that this prediction was indeed correct. The potencies of (+)-**12** and (±)-**12** for inhibition of radioligand binding to D_1 and D_2 receptors were determined. In rat striatal membranes, (+)-**12** inhibited binding of [^{125}I]SCH-23982 to D_1 receptors with potency 2-fold higher than that of racemic dinapsoline. Likewise, (+)-**12** was more potent then the racemic dinapsoline in inhibiting the binding of [^{125}I]-7-OH-PIPAT to D_2 receptors. Furthermore, the D_1 activity of racemic (±)-**12** could be attributed primarily to the active enantiomer (+)-**12** by the fact that (−)-**12** showed no sign of adenylate cyclase stimulation. The intrinsic activity (defined as the ratio of the cyclase response of an agonist relative to that of dopamine) for (+)-**12** was nearly 1, indicating a full dopamine D_1 agonist (Table 2). Finally, when the pair of enantiomers was assayed in whole animals, the opposite enantiomer (−)-**12** induced no rotational behavior at 0.2 and 2.0 mg/kg dosed subcutaneously (Table 3). On the contrary, (+)-**12** is the most active compound tested in vivo as part of the present study (Table 3). The assignment is consistent with the corresponding chiral centers of the biologically active **17** and **18** when these molecules are compared with (+)-**12**. This result further affirmed that dihydrexidine (**17**), **18**, and dinapsoline (**12**) share a set of common pharmacophoric descriptors.

The absolute configuration of (+)-dinapsoline was established from single-crystal analysis of an HBr salt of the compound using the anomalous scattering effect of bromine atoms. Light-brown plate-like crystals were

Table 1. Results of D_1/D_2 Binding Assays[a]



(+)-12 (-)-12

	IC_{50} (nM)	
compound	D_1[b]	D_2
(±)-**12**	67 ± 9 (35)	56 ± 10 (17)
(−)-**12**	5300 ± 1000 (4)	1500 ± 500 (2)
(+)-**12**	33 ± 8 (11)	38 ± 6 (7)

[a] Experimental Section for details. [b] SE (number of repeats).

Table 2. Adenylate Cyclase (AC) Response (in Vitro Functionality)

	D_1 (SK-N-MC)[a]	
compound	intrinsic activity	EC_{50} ± SE(*n*), nM[b]
(±)-**12**	1.2	190 ± 60 (3)
(−)-**12**	ND[c]	>10000 (3)[d]
(+)-**12**	1.0	220 ± 40 (5)

[a] Neuroblastoma cell preparation. [b] SE (number of repeats). [c] Not able to determine. [d] Estimated value.

Table 3. In Vivo Pharmacology[4]

compound	dose (mg/kg sc)	rotations/ 10 h (mean ± sem)	n
(±)-**12**	0.2	1900 ± 200	10
(±)-**12**	2	4800 ± 500	10
(+)-**12**	0.2	4100 ± 400	5
(+)-**12**	2	7000 ± 1000	5
(−)-**12**	0.2	8 ± 2	5
(−)-**12**	2	7 ± 2	5
18	0.2	1100 ± 200	8
18	2	4200 ± 1000	7

grown from MeOH. A crystal of 0.05 × 0.14 × 0.22 mm was used for X-ray diffraction data collection at room temperature using a Nonius CAD4 single-crystal diffractometer with Cu Kα radiation. The crystal data are as follows: space group $P2_12_12_1$, $a = 5.8440(2)$ Å, $b = 10.9602(7)$ Å, $c = 22.190(1)$ Å, $Z = 4$, $V = 1421.3(1)$ Å^3, $d_x = 1.561$ g cm^{-3}; 1721 independent reflections ($\theta_{max} = 75°$) were obtained. The structure was solved and refined using SHELXTL with 181 variables and 1408 observed ($I \geq 4\sigma$) reflections. The final agreement factors are as follows: $R(F) = 0.032$, $wR(F^2) = 0.082$ where $w = 1/[\sigma^2(F) + 0.03F^2]$, $S = 1.044$, $-0.39 \leq \Delta\rho \leq 0.24$ e/Å^3. The hydroxy hydrogens were located in the final difference Fourier maps, while the positions of all the other hydrogen atoms were calculated from an idealized geometry with standard bond lengths and angles. They were assigned isotropic temperature factors and were included in structure factor calculations with fixed parameters. The crystal coordinates are available from Cambridge Crystallographic Database (deposition number 183552).

Conclusions

The synthetic challenge with the original 14-step procedure was largely overcome. The new synthetic protocol allowed for the practical preparation of dinapsoline (**12**). The biologically active enantiomeric (+)-dinapsoline was efficiently prepared by a resolution procedure through the formation of tartrate salt. The newly developed synthesis could also be used to gain access of many substituted derivatives of dinapsoline. Preliminary results have suggested that in vitro dopamine (D_1/D_2) binding activities were negatively affected by *most* substituents on the A-, B′-, and C-rings while D-ring substitutions preserved much of the dopamine receptor binding activities. Also confirmed in this study was the absolute chirality of the active enantiomer of dinapsoline; (+)-**12** was determined to have an *R* absolute configuration. The synthetic tools developed in the present study will allow further optimization of the dinapsoline core with regard to in vivo potency, absorption, metabolism, and pharmacokinetic and safety characteristics.

Experimental Section

In Vitro and in Vivo Assays. [^{125}I]-7-OH-PIPAT (2200 Ci/mmol) and [^{125}I]-(+)-SCH-23982 (2200 Ci/mmol) were purchased from NEN Life Sciences Products (Boston, MA). Rat striata were purchased from ABS Inc. (Wilmington, DE). The frozen striata were thawed rapidly in homogenization buffer (20 mM HEPES, 154 mM NaCl, 5 mM EDTA, pH 7.5 at 4 °C), homogenized, and centrifuged at 20000*g* for 10 min. The pellets were resuspended in homogenization buffer, incubated for 30 min at 37 °C, and centrifuged again. The final pellets were resuspended in buffer consisting of either 50 mM Tris (pH 7.5 at 37 °C), 10 mM $MgSO_4$, 2 mM EDTA, 154 mM NaCl, and 20 μg/mL BSA for use in [^{125}I]-(+)-SCH-23982 binding assays or 50 mM Tris (pH 7.7 at 25 °C) and 2 mM $MgCl_2$ for use in [^{125}I]-7-OH-PIPAT binding assays.

Radioligand Binding Assays. Binding of [^{125}I]-(+)-SCH-23982 to D_1 receptors was performed using crude membrane homogenates from rat striatal tissue. Homogenates (6 μg of protein/well) were incubated with [^{125}I]-(+)-SCH-23982 (500 pM) for 30 min at 37 °C in buffer (100 μL) consisting of 50 mM Tris (pH 7.5 at 37 °C), 10 mM $MgSO_4$, 2 mM EDTA, 154 mM NaCl, 20 μg/mL BSA, and 1% DMSO. Assays were stopped by the addition of ice-cold wash buffer (20 mM Tris containing 0.9% NaCl). Filtration over glass fiber filters (Whatman GF/B) was performed using a Brandel cell harvester. Nonspecific binding was defined with 2 μM (+)-butaclamol. Binding of [^{125}I]-7-OH-PIPAT to D_2 receptors was performed using crude membrane homogenates from rat striatal tissue. Homogenates (10 μg of protein/well) from rat striatum were incubated with [^{125}I]-7-OH-PIPAT (200 pM) for 60 min at 37 °C in buffer (100 μL) consisting of 50 mM Tris (pH 7.7 at 25 °C), 2 mM $MgCl_2$, 0.1% BSA, 0.025 mN HCl, and 1% DMSO. Assays were stopped by the addition of ice-cold wash buffer (20 mM Tris). Filtration over glass fiber filters was performed using a Brandel cell harvester. Nonspecific binding was defined with 2 μM (+)-butaclamol.

cAMP Accumulation. cAMP production in SK-N-MC cells endogenously expressing the D_1 receptor was measured by using a cAMP radioimmunoassay system from Amersham (code RPA 509). Briefly, cells were seeded at a concentration of 10^5 cells/mL on 48-well plates and were incubated at 37 °C, with 5% CO_2 1 day before the assay. Assays were initiated by the addition of 700 μL of assay buffer containing 1 mM 3-isobutyl-1-methylxanthine in the presence of varying concentrations of compounds to the cells and were incubated for 10 min at 37 °C. Assay mix was then removed, and 1 mL of 0.1 N HCl was added to terminate the reaction. The cAMP production was detected by the kit following the protocol. The nonlinear regression curve-fitting method was used to fit dose−response curves with GraphPad Prism 3.0. Relative efficacy (intrinsic activity) is the ratio of the maximum response (E_{max}) between the test compound and dopamine.

In Vivo Pharmacology. Rotation experiments were performed in Sprague-Dawley rats with unilateral 6-OHDA lesions of the medial forebrain bundle as described previously.[4] Only animals that met prescreening criteria for rotational response to amphetamine (5 mg/kg: 800 rotations/3 h) and the dopamine agonist apomorphine (0.2 mg/kg: 100 rotations/1 h) were used in these studies. Four groups of rats were used, and each rat received four treatments, once per week, in a counterbalanced order.[4]

General Chemical Procedures. Melting points were recorded on a Thomas-Hoover capillary apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer System 2000 FT-IR spectrometer or performed by Robertson Microlit Lab. Optical rotations were measured on a Perkin-Elmer 241 polarimeter on a 10 cm standard cell, and results are reported as $[\alpha]_D$. Proton NMR (^{1}H NMR) and carbon NMR (^{13}C NMR) spectra were obtained on Brucker ACP 300 spectrometers and are reported relative to a tetramethylsilane (TMS) reference. NMR coupling constants (*J*) were reported in hertz (Hz). Analytical and preparative HPLC were performed on YMC columns (A-302, S5, 120A ODS, 4.6 × 150 mm; S5 ODS, 30 × 100 mm) with methanol/water gradients containing 0.1% trifluoroacetic acid. LC−MS measurements were taken on a Shimadzu-Micromass LC unit using the same mobile phase. TLC and medium-pressure chromatography were performed under flash conditions using EM silica type H. THF was used as supplied by Aldrich. Solutions were dried with magnesium sulfate unless otherwise noted.

4-Bromo-1,2-(methylenedioxy)-3-benzaldehyde (3). To a solution of 4-bromo-1,2-(methylenedioxy)benzene (5.0 g, 24.9 mmol) in THF (52 mL) at −78 °C was added lithium diisopropylamide in cyclohexane (1.5 M, 18.2 mL, 27.3 mmol), and

the resulting solution was stirred for 15 min. *N*,*N*-Dimethylformamide (DMF, 4.2 mL, 54.2 mmol) was added dropwise, and the solution was allowed to warm to room temperature for 1 h. The reaction mixture was washed with saturated aqueous NH_4Cl, and the organic layer was concentrated and dried. The solid yellow product was recrystallized using isopropyl acetate to afford the desired product as yellow needles (3.9 g, 69% yield): mp 158−159 °C; ^{1}H NMR ($CDCl_3$) δ 10.29 (s, 1H), 7.08 (d, 1H, J = 8.25 Hz), 6.83 (d, 1H, J = 8.22 Hz), 6.17 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 190.8, 149.8, 149.1, 126.5, 117.7, 115.9, 113.9, 103.8. Anal. ($C_8H_5BrO_3$) C, H, Br.

5-Bromoisoquinoline (5). The apparatus consisted of a 500 mL three-necked flask equipped with a large bore condenser, a dropping funnel, and a stirrer terminating in a stiff, crescent-shaped Teflon paddle. To neat isoquinoline (57.6 g, 447 mmol) in the flask was added $AlCl_3$ (123 g, 920 mmol). The mixture was heated to 75−85 °C, and bromine (48.0 g, 300 mmol) was added over a period of 4 h using a dropping funnel. The resulting mixture was stirred for another hour at 75 °C. The nearly black mixture was poured into vigorously hand-stirred crushed ice in water (about 1.5 kg). The cold mixture was treated with sodium hydroxide solution (10 N) to dissolve all the aluminum salts, and the oily layer was extracted with ether. The organic extract was dried over Na_2SO_4 and concentrated, and the oily crude product was distilled at 0.3 mmHg. The desired product was collected as a white solid (16.3 g, 78 mmol, 26% yield) from a fraction at about 125 °C: mp (pentane) 80−81 °C; ^{1}H NMR (DMSO-d_6) δ 9.34 (s, 1H), 8.63 (d, 1H, J = 9.0 Hz), 8.17 (d, 1H, J = 7.5 Hz), 8.11 (d, 1H, J = 6.6 Hz), 7.90 (d, 1H, J = 6.0 Hz), 7.60 (t, 1H, J = 7.5 Hz); ^{13}C NMR (DMSO-d_6) δ 153.0, 144.7, 134.3, 134.0, 129.3, 128.5, 128.0, 120.3, 118.6. Anal. (C_9H_6BrN) C, H, N.

α-(5-Bromo-1,3-benzodioxol-4-yl)-5-isoquinolinemethanol (7). Method A. To a solution of 5-bromoisoquinoline (0.50 g, 2.4 mmol) in ether (8 mL) at −78 °C was added dropwise *tert*-butyllithium (3.6 mL of a 1.7 M solution in pentane, 6.1 mmol) under argon. The mixture was stirred at −78 °C under argon for 30 min, and then it was stirred for 15 min at −45 to −55 °C before it was cooled to −78 °C. 4-Bromo-1,2-(methylenedioxy)-3-benzaldehyde **3** (0.524 g, 2.3 mmol) was added in one portion under argon. The mixture was stirred at −78 °C for 5 min, and then warmed to room temperature. The mixture was stirred for 20 min at room temperature before the reaction was quenched with saturated NH_4Cl aqueous solution. The organic residues were extracted with EtOAc and dried over Na_2SO_4. Chromatography (SiO_2, 35% EtOAc in hexanes) yielded the desired product as a yellow solid (0.18 g, 0.50 mmol, 21% yield): mp 173−175 °C; ^{1}H NMR (DMSO-d_6) δ 9.32 (s, 1H), 8.47 (d, 1H, J = 6.0 Hz), 8.05 (d, 1H, J = 8.1 Hz), 7.96 (d, 1H, J = 7.2 Hz), 7.76 (d, 1H, J = 6.0 Hz), 7.66 (t, 1H, J = 7.8 Hz), 7.14 (d, 1H, J = 8.1 Hz), 6.84 (d, 1H, J = 8.1 Hz), 6.58 (d, 1H, J = 8.1 Hz), 6.28 (d, 1H, J = 5.4 Hz), 5.95 (s, 1H), 5.80 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 153.1, 147.6, 147.0, 142.9, 136.9, 132.7, 128.9, 128.3, 127.3, 126.7, 125.6, 124.4, 116.3, 114.0, 109.3, 101.6, 69.0. Anal. ($C_{17}H_{12}BrNO_3$) C, H, N.

5-Isoquinolinecarboxaldehyde (8). To a solution of *n*-butyllithium (19.3 mL of 2.5 M in hexanes, 48 mmol) in a mixture of ether (80 mL) and THF (80 mL) at −78 °C was added dropwise a solution of 5-bromoisoquinoline (5.0 g, 24 mmol) in THF (10 mL). The reaction mixture was stirred at −78 °C under argon for 30 min. Prior to mixing, a DMF solution (3.3 g, 45 mmol) in THF (10 mL) was chilled to −78 °C, and it was quickly added into the isoquinolyllithium solution. The resulting mixture was stirred at −78 °C for 15 min. Ethanol (20 mL) was added followed by saturated NH_4Cl solution. The suspension was warmed to room temperature. The organic residue was extracted twice with ether, and the ether layers were combined and dried over Na_2SO_4. A pale yellow solid (2.4 g, 15 mmol, 64% yield) was obtained after chromatographic purification (SiO_2 type H, 50% EtOAc in hexanes) and recrystallization (ethanol): mp 114−116 °C; ^{1}H NMR (DMSO-d_6) δ 10.40 (s, 1H), 9.44 (s, 1H), 8.85 (d, 1H, J = 6.0 Hz), 8.69 (d, 1H, J = 6.0 Hz), 8.45 (m, 2H), 7.90 (t, 1H, J = 7.2 Hz); ^{13}C NMR (DMSO-d_6) δ 194.23, 153.5, 146.2, 140.2, 135.2, 132.6, 130.2, 128.6, 127.5, 117.2. Anal. ($C_{10}H_7NO$) C, H, N.

α-(5-Bromo-1,3-benzodioxol-4-yl)-5-isoquinolinemethanol (7). Method B. To a solution of 4-bromo-1,2-(methylenedioxy)benzene (3.01 g, 15 mmol) in THF (20 mL) at −78 °C was added dropwise lithium diisopropylamide (10.6 mL of a 1.5 M solution in cyclohexane, 16 mmol). The reaction mixture was stirred at −78 °C under argon for 20 min, forming a brownish solution. The lithiated species was treated with a solution of 5-isoquinolinecarboxaldehyde (**8**, 1.9 g, 12 mmol) in THF (4 mL). The resulting mixture was stirred at −78 °C for 10 min, and then warmed to room temperature. The mixture was stirred for 30 min at room temperature before the reaction was quenched with saturated NH_4Cl solution. The addition product was extracted with EtOAc (3 × 20 mL), and the organic layers were combined, dried, and evaporated under reduced pressure. Chromatography (SiO_2 type H, 35% EtOAc in hexanes) of the crude product yielded the title compound as a yellow solid (2.8 g, 7.8 mmol, 65% yield): mp 173−175 °C. Anal. ($C_{17}H_{12}BrNO_3$) C, H, N.

5-[(5-Bromo-1,3-benzodioxol-4-yl)methyl]isoquinoline (9). To a solution of the secondary alcohol α-(5-bromo-1,3-benzodioxol-4-yl)-5-isoquinolinemethanol (**7**, 3.0 g, 8.4 mmol) in trifluoroacetic acid (100 mL) was added triethylsilane (13.4 mL, 83.7 mmol), and the resulting mixture was refluxed at 70−75 °C for 1 h. The reaction mixture was then stirred overnight at room temperature. The mixture was concentrated under vacuum, and the residue was redissolved in ethyl acetate, washed with saturated NH_4Cl, dried over Na_2SO_4, filtered, and concentrated. Purification was performed by column chromatography (silica gel, type H, eluted with mixtures of ethyl acetate and hexanes) to give the trifluoroacetate salt form of the title compound as a white crystalline solid (1.9 g, 67% yield): mp 138−140 °C; ^{1}H NMR ($CDCl_3$) δ 9.64 (s, 1H), 8.63 (d, 1H, J = 6.59 Hz), 8.45 (d, 1H, J = 6.62 Hz), 8.14 (d, 1H, J = 8.22 Hz), 7.77 (t, 1H, J = 7.39 Hz), 7.64 (d, 1H, J = 7.29 Hz), 7.13 (d, 1H, J = 8.33 Hz), 6.71 (d, 1H, J = 8.31 Hz), 5.94 (s, 2H), 4.53 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 147.8, 147.7, 147.1, 137.2, 135.1, 134.7, 133.4, 130.3, 128.6, 128.3, 125.9, 120.7, 119.4, 116.3, 109.1, 101.9, 31.7. Anal. ($C_{17}H_{12}BrNO_2 \cdot C_2HF_3O_2$) C, H, N, Br.

12*H*-Benzo[*d*,*e*][1,3]benzodioxol[4,5-*h*]isoquinoline (10). Method A, Small Scale. A solution of 5-[(5-bromo-1,3-benzodioxol-4-yl)methyl]isoquinoline (**9**, 0.357 g, 1.0 mmol) and 2,2′-azobisisobutylronitrile (AIBN, 0.064 g, 0.39 mmol) in benzene (10 mL) was cooled to −78 °C, degassed 4 times (purged with N_2), and then heated to 80 °C under argon. A solution of tributyltin hydride (TBTH, 1.14 g, 3.9 mmol) in 10 mL of degassed benzene was added over a period of 2 h. Trifluoroacetic acid (TFA, 0.185 g, 1.6 mmol) was added in 4 equal portions ($^1/_4$ each half-hour) over the next 2 h. The reaction mixture was stirred at 80 °C under argon for another 6 hours after the addition of TFA. At this point, TLC analysis indicated an incomplete reaction. More tributyltin hydride (1.14 g, 3.9 mmol) in 10 mL of degassed benzene was added dropwise over 2 h followed by TFA (0.185 g, 1.6 mmol) in 4 equal portions ($^1/_4$ each half-hour). The reaction mixture was stirred overnight (16 h). Most of the solvent was removed under reduced pressure. Pentane (100 mL) was added to the residue, and the mixture was cooled to −78 °C, causing a brown gummy solid to precipitate out. The pentane layer was extracted with MeCN (20 mL), and the MeCN layer was combined with the brown gum. The crude product from evaporation of MeCN was purified by chromatography (SiO_2 type H, 15% EtOAc in hexanes). The purified compound was redissolved in CH_2Cl_2 and extracted with HCl (1 N). The aqueous layer was made basic to pH ∼10 using 10 N NaOH solution, and the free base was reextracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4. Evaporation of the solvent yielded the desired compound as an orange solid (0.068 g, 0.26 mmol, 25% yield): mp 194−197 °C; ^{1}H NMR (DMSO-d_6) δ 9.12 (s, 1H), 9.06 (s, 1H), 7.93 (d, 1H, J = 6.9 Hz), 7.83 (d, 1H, J = 8.1 Hz), 7.73 (dd, 1H, J = 7.2, 1.5 Hz), 7.66 (t, 1H, J = 7.8 Hz), 6.96 (d, 1H, J =

8.4 Hz), 6.14 (s, 2H), 4.44 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 150.6, 147.0, 145.2, 135.6, 130.6, 129.3, 129.1, 127.7, 127.5, 125.0, 123.6, 117.2, 116.1, 107.5, 101.6, 26.6. Anal. ($C_{17}H_{11}NO_2$) C, H, N.

12*H*-Benzo[*d*,*e*][1,3]benzodioxol[4,5-*h*]isoquinoline (10). Method B, Large Scale. A solution of 5-[(5-bromo-1,3-benzodioxol-4-yl)methyl]isoquinoline (**9**, 12.6 g, 36.8 mmol) and 2,2′-azobisisobutylronitrile (5.92 g, 36.0 mmol) in degassed benzene (1500 mL) was heated to 80 °C under argon. To this solution was added glacial acetic acid (12.6 g, 210 mmol), followed by a solution of tributyltin hydride (39.9 g, 137 mmol) in 30 mL of degassed benzene over a period of 3 h. The reaction mixture was stirred at 80 °C under argon for an additional 16 h. Excess triethylamine was added to neutralize the remaining acetic acid, and the mixture was concentrated into a semisolid. Methylene chloride (250 mL) was added to dissolve the semisolid. This was followed by the addition of hexanes to a point just before the mixture turned cloudy. This solution was poured over a short bed of silica gel, and the byproduct tri-*n*-butyltin acetate was removed by washing it with hexanes until it was no longer detected by TLC. The product was then eluted with mixtures of hexanes and ethyl acetate to give the uncyclized *des*-bromo **9** (20.6%) followed by the desired cyclized compound **10** (6.1 g, 23.4 mmol, 63.5% yield). The main desired product was analyzed and found to be identical to the product prepared by method A. The main side product from the cyclization was the *des*-bromo **9** (2.0 g, 7.6 mmol, 20.6% yield): mp 109−111 °C; MS *m*/*e* 264.2 (MH^+); ^{1}H NMR (DMSO-d_6) δ 4.33 (s, 2H), 6.04 (s, 2H), 6.57 (dd, J = 1.2, 8.4 Hz, 1H), 6.72 (m, 2H), 7.62 (m, 2H), 7.93 (d, J = 6.0 Hz, 1H), 8.02 (m, 1H), 8.51 (d, J = 6.0 Hz, 1H), 9.31 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 30.8, 100.7, 106.9, 116.8, 121.1, 121.7, 122.6, 126.5, 127.2, 128.6, 130.9, 133.9, 135.0, 143.2, 145.1, 146.9, 153.0. Anal. ($C_{17}H_{13}NO_2$) C, H, N.

(±)-8,9-Methylenedioxy-2,3,7,11b-tetrahydro-1*H*-naphth[1,2,3-*de*]isoquinoline ((±)-11). Method A. To a solution of 12*H*-benzo[*d*,*e*][1,3]benzodioxol[4,5-*h*]isoquinoline (**10**, 0.085 g, 0.33 mmol) in THF (43 mL) was added 2 N HCl (1.7 mL, 3.4 mmol), and an orange precipitate was formed. Sodium cyanoborohydride (0.274 g, 4.4 mmol) was added in one portion. The resulting suspension was stirred at room temperature for 2 h. HCl (2 N, 10 mL) was added, and the mixture was stirred for 5 min. Saturated $NaHCO_3$ solution was added to neutralize the excess HCl (pH 7−8). The resulting mixture was extracted with EtOAc and dried over Na_2SO_4, and the solvent was removed under reduced pressure. Chromatography (SiO_2 type H, 5% MeOH in CH_2Cl_2) of the residue yielded the title compound as a yellow gum (0.066 g, 0.25 mmol, 75% yield): ^{1}H NMR ($CDCl_3$) δ 7.15 (m, 2H), 6.97 (d, 1H, J = 6.9 Hz), 6.83 (br s, 1H), 6.68 (d, 1H, J = 8.1 Hz), 6.59 (d, 1H, J = 8.1 Hz), 6.01 (d, 1H, J = 1.4 Hz), 5.91 (d, 1H, J = 1.4 Hz), 4.40−4.00 (m, 5H), 3.55 (dd, 1H, J = 17.7, 3.0 Hz), 3.10 (t, 1H, J = 12.0 Hz); ^{13}C NMR ($CDCl_3$) δ 146.1, 144.8, 136.0, 132.2, 130.4, 128.6, 127.1, 127.0, 124.5, 118.5, 116.2, 106.2, 101.2, 45.8, 35.1, 34.3, 28.9. Anal. ($C_{17}H_{15}NO_2$) C, H, N.

(±)-8,9-Methylenedioxy-2,3,7,11b-tetrahydro-1*H*-naphth[1,2,3-*de*]isoquinoline ((±)-11). Method B. 12*H*-Benzo[*d*,*e*][1,3]benzodioxol[4,5-*h*]isoquinoline (**10**, 11.26 g) was dissolved into 500 mL of glacial acetic acid in a suitable glass liner that fitted into a 1 L Parr "bomb reactor". To this dark-amber solution were added 480 mg of PtO_2 and a magnetic stirring bar. The usual freeze−thaw cycles were repeated 3 times at −78 °C. Finally, hydrogen gas was charged into the steel bomb at 140 psi (pounds/inch^2) while the content was *still* at −78 °C. The reactor was allowed to warm to room temperature over a period of 2 h while the internal pressure reached 195 psi. Gas absorption was faster after about 4 h at room temperature. After 24 h, the internal pressure returned to 165 psi, indicating roughly stoichiometric uptake of hydrogen gas. The black suspension was removed from the Parr reactor after the internal pressure was relieved. The suspension was filtered over silica gel, rinsed with acetic acid, and concentrated under reduced pressure to give about 19 g of a brownish gummy substance. The crude product was neutralized with sodium bicarbonate solution followed by extraction with methylene chloride to give 11.6 g of the crude title compound; ^{1}H NMR was indistinguishable from that of the purified material prepared above by method A.

(±)-8,9-Dihydroxy-2,3,7,11b-tetrahydro-1*H*-naphth[1,2,3-*de*]isoquinoline ((±)-12). BBr_3 (25.0 mL of a 1 M solution in CH_2Cl_2, 25.0 mmol) was added to a cooled solution (−78 °C) of (±)-8,9-methylenedioxy-2,3,7,11b-tetrahydro-1*H*-naphth-[1,2,3-*de*]isoquinoline (1.4 g, 5.3 mmol) in CH_2Cl_2. The mixture was stirred at −78 °C under nitrogen for 3 h and at room temperature overnight. After the mixture was cooled to −78 °C, anhydrous methanol (50 mL) was added dropwise, and the solvent was removed under reduced pressure. The residue was dissolved in methanol (100 mL), and the solution was refluxed under nitrogen for 2 h. After removal of the solvent, chromatography (SiO_2 type H, eluted with 10% MeOH in CH_2Cl_2) of the residue yielded the title compound as a dark-brown solid (1.65 g, 4.94 mmol, 93% yield): MS (ESI) *m*/*z* 254 (MH^+); ^{1}H NMR (DMSO-d_6) δ 9.50 (br s, 2H), 9.28 (s, 1H), 8.54 (s, 1H), 7.32 (d, 1H, J = 8.3 Hz), 7.23 (t, 1H, J = 8.3 Hz), 7.12 (d, 1H, J = 8.5 Hz), 6.70 (d, 1H, J = 9.3 Hz), 6.54 (d, 1H, J = 6.7 Hz), 4.37 (s, 2H), 4.30−4.23 (m, 2H), 3.97 (m, 1H), 3.45−3.31 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 143.8, 142.0, 136.9, 132.1, 127.6, 127.0, 126.6, 124.1, 123.7, 114.0, 112.7, 44.0, 43.6, 32.9, 28.5. Anal. ($C_{16}H_{15}NO_2$) C, H, N.

(+)-8,9-Methylenedioxy-2,3,7,11b-tetrahydro-1*H*-naphth-[1,2,3-*de*]isoquinoline ((+)-11). Racemic **(±)-11** was injected into a preparative HPLC instrument (Dynamax Rainin model SD-1) equipped with a Chiralcel OD column (5 cm × 50 cm, 20 μm, lot 738-60328c, Chiral Technologies, Inc.) coupled in series with a UV detector (Dynamax Absorbance Detector model UV-D II) set at λ = 220 nm. Using an isocratic method, a solvent system composed of 5% ethanol in hexanes plus 0.1% (by volume) TFA at a flow rate of 50 mL/min was found to separate the enantiomers. As much as 150 mg/5 mL of ethanol can be injected into the column per run. A total of 425 mg of racemic **(±)-11** was injected which produced about 200 mg of each enantiomer. The analytical chiral separation was performed using an identical setup as previously described but with an analytical Chiralcel OD column (0.46 cm × 25 cm, 10 μm) at a reduced solvent flow rate of 1 mL/min at sampling intervals of 0.1 s. The preparative column and the analytical column could be switched by a flow selector. Optical rotation was taken for each of the enantiomers: first peak (R_f = 19.6 min), $[\alpha]_D$ −88.9° (*c* 0.03, $CHCl_3$); second peak (R_f = 23.6 min), $[\alpha]_D$ +90.3° (*c* 0.03, $CHCl_3$).

Larger quantities of (+)-**11** could also be prepared by a conventional resolution using tartaric acid dibenzoyl ester as the resolving agent. A solution of racemic **(±)-11** (3.0 g, 11.3 mmol) in 100 mL of 95% ethyl alcohol at room temperature was mixed with a warm solution of (+)-dibenzoyl-D-tartaric acid in 40 mL of 95% ethyl alcohol. The mixture was allowed to stand at room temperature for 4 h, and the grayish off-white crystals were collected by filtration and subsequently dried in a vacuum oven at 35 °C to give 1.3 g (mp 175−176 °C, 35.7%). The salt was neutralized with a 2 M potasium hydroxide solution, and the organic material was extracted with methylene chloride. The organic layers were combined and concentrated under reduced pressure to give a white solid. The enantiomeric purity was determined by the same chiral HPLC conditions on an analytical Chiralcel OD column as described above. The ratio of the second peak to the first was determined to be greater than 40:1. The identical resolution could also be carried out using the unnatural, free D-tartaric acid, but the use of (+)-dibenzoyl-D-tartaric acid ester appeared to be more consistent. (*R*)-(+)-8,9-Methylenedioxy-2,3,7,11b-tetrahydro-1*H*-naphth[1,2,3-*de*]isoquinoline·(+)-dibenzoyl-D-tartaric acid salt: mp 175−176 °C. (*R*)-(+)-8,9-Methylenedioxy-2,3,7,11b-tetrahydro-1*H*-naphth[1,2,3-*de*]isoquinoline·D-tartaric acid salt: mp 186−188 °C.

(*R*)-(+)-8,9-Dihydroxy-2,3,7,11b-tetrahydro-1*H*-naphth-[1,2,3-*de*]isoquinoline ((+)-12). The identical deprotection procedure described for the racemic compound was used, and each of the two resolved compounds of **11** was treated with

BBr_3 deprotection to give chiral (+)-**12**: [α] +75.0° (*c* 0.03, MeOH); MS (ESI) *m*/*z* 254.12 (MH^+); ^1H NMR (DMSO-d_6) δ 9.50 (br s, 2H), 9.28 (s, 1H), 8.54 (s, 1H), 7.32 (d, 1H, $J = 8.3$ Hz), 7.23 (t, 1H, $J = 8.3$ Hz), 7.12 (d, 1H, $J = 8.5$ Hz), 6.70 (d, 1H, $J = 9.3$ Hz), 6.54 (d, 1H, $J = 6.7$ Hz), 4.37 (s, 2H), 4.30−4.23 (m, 2H), 3.97 (m, 1H), 3.45−3.31 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 143.8, 141.9, 136.9, 132.1, 127.6, 126.9, 126.5, 126.4, 124.0, 123.5, 114.0, 112.6, 44.0, 43.6, 32.9, 28.5. (−)-**12**: [α] −70.7° (*c* 0.03, MeOH). Anal. ($C_{16}H_{15}NO_2$·HBr) C, H, N.

Scale-Up Resolution Processes of Racemic 11 and the Preparation of (+)-12 via Enrichment Procedures. To a solution of (±)-**11** (8.7 g, 33 mmol) in warm 95% ethanol (300 mL) was added dibenzoyl-L-tartaric acid (DB-L-TA, 33 mmol) in warm 95% ethanol (90 mL). The solution under argon was allowed to cool slowly to room temperature over a period of 12 h which resulted in the appearance of a flaky, off-white crystalline material. The crystals were filtered and dried to give 3.3 g of the adduct of (−)-**11** (mp 174−175 °C). The "enriched" mother liquor was concentrated and neutralized with 2 M NaOH, and the free base was isolated as usual, readying for the second resolution. The same protocol was used as described above, and the recovered material (20 mmol) in 95% ethanol (200 mL) was resolved with dibenzoyl-D-tartaric acid (DB-D-TA, 20 mmol) in 95% ethanol (50 mL). Almost instantly, a white fluffy solid was observed which extended through the entire solution phase. The suspension was then reheated to reflux for 15 min, forming a somewhat thinner suspension; the solid remained there and was never dissolved, despite the brief reflux. The contents were allowed to cool slowly to about 40−45 °C, and the precipitate was collected and dried to give 3.8 g of the adduct of (+)-**11** (mp 175−176 °C). While the enrichment procedure did not greatly improve the overall resolution efficiency, the quality of the resolved material showed superior purity with respect to enantiomeric separation. Analysis of the neutralized samples by the HPLC instrument equipped with a Chiralcel OD analytical column showed >99.9% ee.

(+)-Dinapsoline ((+)-12). The (+)-**11** adduct obtained above was neutralized with NaOH, and the free base ((+)-**11**) was extracted with CH_2Cl_2. Boron tribromide (BBr_3, 1 M in CH_2Cl_2, 99 mL) was added dropwise to a cold solution (−78 °C) of (+)-**11** (5.5 g, 20.8 mmol) in CH_2Cl_2 (500 mL). The mixture was stirred at −78 °C under N_2 for 15 min before the reaction mixture was allowed to warm to room temperature. After the mixture was stirred at RT for an additional 3 h, it was cooled to −78 °C. Absolute methanol (100 mL) was added slowly. The dry ice/acetone bath was removed, and the stirring was continued at 25 °C for 12 h. The reaction mixture was evaporated, and the crude product was purified by chromatography (SiO_2 type H, 10% MeOH in CH_2Cl_2). The column-purified greenish solid was recrystallized from MeOH to furnish a light-greenish crystalline material (5.5 g, 16.5 mmol, 79%). With the exception of the optical rotations, these samples were analyzed in a manner identical to that of (±)-**12**.

sample	$[\alpha]_D$ of HBr salt form	mp (°C)	HBr salt form
(+)-**12**	+80.4° (*c* 0.0083 g/mL, MeOH)	>265	1 HBr/molecule
(−)-**12**	−70.0° (*c* 0.0083 g/mL, MeOH)	>265	1 HBr/molecule

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Supporting Information Available: Detailed analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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