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Synthesis and SAR exploration of dinapsoline analogues

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Abstract—Dinapsoline is a full D_1 dopamine receptor agonist that produces robust rotational activity in the unilateral 6-OHDA rat model. This compound is orally active, and shows a low tendency to cause tolerance in rat models. The active enantiomer was determined to have the *S*-(+) configuration, and the opposite enantiomer is essentially devoid of biological activity. Taken together, dinapsoline has significant metabolic and pharmacological advantages over previous D_1 agonists. In an attempt to define the structure–activity relationships (SARs) and to map out the key elements surrounding the unique structure of dinapsoline, *core* analogues and *substitution* analogues of the parent tetracyclic condensed ring structure were prepared. Based on a recently developed synthesis of dinapsoline and its enantiomers, both core and substitution analogues on all four rings (A, B′, C and D ring) of dinapsoline were synthesized. It was found that affinity for both $D_1$and D_2 receptors was decreased by most substituents on the A, B′, and C rings, whereas D ring substitutions preserved much of the dopamine receptor binding activity.
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1. Introduction[†]

Parkinson's disease (PD) is a slowly progressive disorder of the central nervous system. The disease affects several million people worldwide, and its prevalence rises sharply with age, and as many as 15% of PD patients are 50 years old or younger. Although current practice is to start most newly diagnosed PD patients on one of the available D_2 dopamine agonists (i.e., ropinirole or pramipexole), the combination of levodopa and a peripheral decarboxylase inhibitor (e.g., carbidopa or benserazide) remains unsurpassed in clinical efficacy, and is eventually used by almost all Parkinson's patients.[4] It is generally accepted that the therapeutic benefits of levodopa result from its conversion to dopamine in striatal terminals of residual dopaminergic neurons. Because the disease is progressive, however, and dopamine-producing cells continue to die, the effectiveness of such dopamine replacement therapy with levodopa decreases with time. For most patients, dose escalation, decreased efficacy, and the emergence of intolerable side effects such as nausea and dyskinesias are inevitable results. Thus, drugs that directly activate one or more dopamine receptors have been the target for rational PD drug design for three decades.

Dopamine receptors are known to fall into two pharmacological families (D_1 and D_2-like) that are coded by five genes.[5] It has been a subject of controversy about which receptor(s) needs to be activated to obtain therapeutic effects in PD that would equal levodopa. All of the dopamine agonists current available as anti-

Keywords: Dinapsoline; Dopamine agonist; Dopamine D_1 receptor; Parkinson's disease; SAR; Dihydrexidine.
[†] Due to an oversight, the biologically active enantiomer of dinapsoline formerly had been labeled as (*R*)-(+)-dinapsoline. The correct nomenclature should have been (*S*)-(+)-dinapsoline.[1] This change does not affect the results of the present work, nor the conclusions in prior publications.[2,3]*
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parkinson drugs have, in fact, targeted one or more receptors of the D_2-like family. These D_2 agonists, despite having a place in the treatment of PD,[4] have far lower efficacy than levodopa, and may also produce side effects such as nausea and psychotic symptoms that are associated with D_2 receptor activation. D_1 agonists received little attention for many years largely because early selective D_1 agonists had no antiparkinson efficacy, something that is now known to be due to the low intrinsic activity of compounds like SKF38393.[6–9] On the other hand, when the first full D_1 agonist was discovered, it was used to demonstrate that it was D_1, not D_2, agonism that was responsible for dramatic antiparkinson effects.[10] Since then, the unmatched antiparkinson efficacy of full D_1 agonists from different chemical families has not only been shown in non-human primates treated with MPTP,[11,12] but also in humans with PD.[13] Despite the promise of full D_1 agonists, a variety of issues has stymied the development of earlier compounds.[14]

Recently, dinapsoline (8,9-dihydroxy-2,3,7,11b-tetrahydro-1*H*-dibenz[*de*,*h*]isoquinoline) was discovered as the first member of a new class of full D_1 agonists, albeit one that was shown to also have significant D_2 affinity. In addition, dinapsoline was shown to desensitize D_1 receptors less than either dopamine[15] or A77636, a promising antiparkinson drug[11] that failed clinically because it produced rapid tolerance.[16] The promise of dinapsoline was further shown in studies where it had significant efficacy in a rat denervation model and unlike A77636, did not cause tolerance.[17] Dinapsoline,[3] like dihydrexidine,[18] has significant affinity for both D_1 and D_2 receptors, although the D_2 properties are not those of a typical agonist.[19,20] Of direct relevance to this work are findings that relatively subtle additions to dihydrexidine[21] or dinapsoline[1] can markedly alter both D_1 and D_2 affinity and functional characteristics in unexpected ways. These data suggest that compounds derived from these parent structures might have extremely interesting pharmacological properties. Thus, the present study provides new and detailed data on structure–activity relationships (SARs) of the dinapsoline backbone.

2. Results

We previously reported a highly convergent synthesis of dinapsoline, along with its resolution into a pair of enantiomers, and the pharmacological profile of *S*-(+)-dinapsoline.[2] The parent compound, dinapsoline, was synthesized by a newly developed seven-step procedure (Schemes 1 and 2). The improved synthesis offers better synthetic convergence and minimizes the use of protecting groups. More importantly, this new method does not rely on the late-stage, yield-limiting acid catalyzed ring closure step described in the original 14-step synthesis.[3]

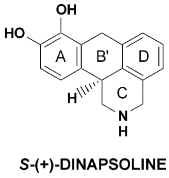
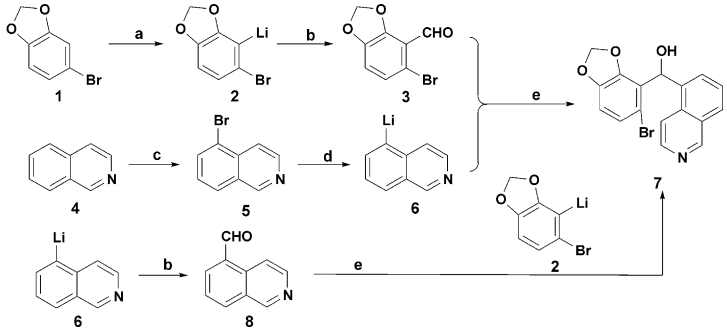


Figure 1.

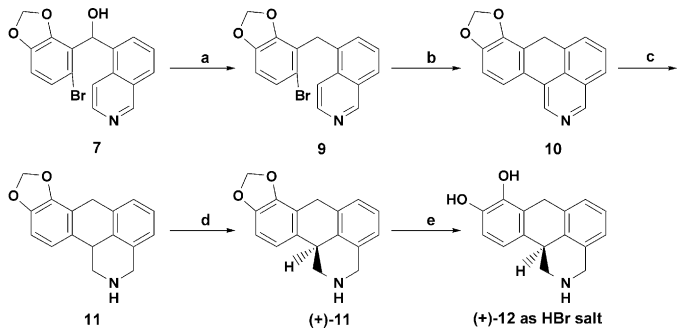
Using different substituted isoquinolines **4**, the improved synthesis served as the starting point for a number of dinapsoline analogues. Both dinapsoline core analogues and substitution analogues were prepared either through the improved synthesis or with appropriate modifications along the seven-step sequence (Fig. 1).

2.1. Core analogues of dinapsoline-7-thia analogue

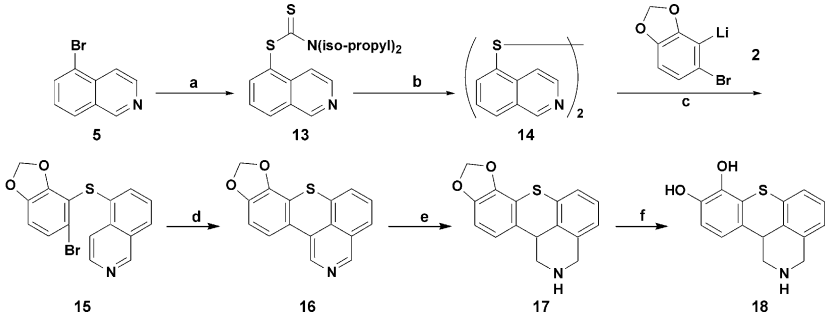
One of the main objectives of this project was to explore the SAR within the three-dimensional framework as provided for by the novel molecular structure of dinapsoline. The improved synthesis of dinapsoline described previously was designed with flexibility for modifying the 7-position in mind. The synthesis was readily adapted to the preparation of the 7-thia and the 7-aza analogues of dinapsoline (Schemes 3 and 4).



Scheme 1. Improved synthesis of the dinapsoline parent molecule. Reagents and reaction conditions: (a) LDA, THF at −78 °C; (b) DMF at −78 °C; (c) bromine, $AlCl_3$; (d) *n*-BuLi, THF at −78 °C; (e) the lithiated species **2**, THF at −78 °C.



Scheme 2. Improved synthesis of the dinapsoline parent molecule. Reagents and reaction conditions: (a) Et_3SiH, TFA at reflux; (b) Bu_3SnH, AIBN in degassed benzene at reflux; (c) $NaCNBH_3$, THF, HCl or PtO_2/H_2 in acetic acid at 110–120 psi (pound/in^2); (d) resolution by (+)-dibenzoyl-D-tartaric acid; (e) BBr_3 in methylene chloride at −78 °C.

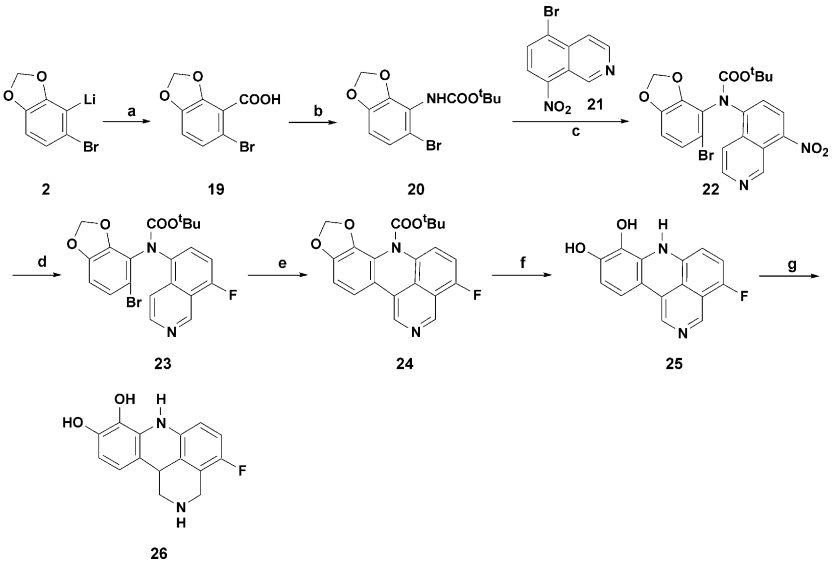


Scheme 3. Synthesis of 7-thia core analogue of dinapsoline. Reagents and reaction conditions: (a) *tert*-BuLi/THF at −78 °C, tetraisopropylthiuram disulfide; (b) NaOH, EtOH reflux, then HCl neutralization and iodine oxidation; (c) 3-lithio-4-bromo-1,2-(methylenedioxy)-benzene 2 at −78 °C; (d) Bu_3SnH, AIBN, benzene at 80 °C; (e) $NaBH_3CN$, THF, HCl; (f) BBr_3, CH_2Cl_2 at −78 °C.

5-Bromoisoquinoline **5** was converted (Scheme 3) into the disulfide of isoquinoline-5-thiol **14** by a three-step procedure from **13**.[22] The subsequent alkaline hydrolysis and iodine oxidation were carried out in one pot to give **14**. The *ortho* lithiated 4-bromo-1,2-(methylenedioxy)benzene **2** was thioalkylated with the disulfide **14** to furnish **15** in 62% yield. Compound **15** was reductively cyclized (AIBN, *n*-Bu_3SnH) in degassed benzene to give **16** as the major product (71%, mp 223–225 °C). A small amount of the uncyclized *des*-bromo-**15** was also formed, which was easily removed by trituration with a mixture of ethyl acetate and hexanes. Selective ring reduction of **16** using sodium cyanoborohydride in acidic medium gave **17** in 50% yield. The final deprotection was performed as before with boron tribromide.[2] The desired product **18** was isolated as its HBr salt.

2.2. Core analogues of dinapsoline-7-aza analogue

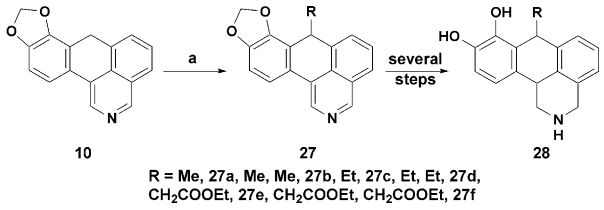
The carbanion **2** (Scheme 4) was quenched with carbon dioxide to give 81% of the expected carboxylic acid **19**. A Curtius rearrangement using diphenylphosphoryl azide (DPPA) in *tert*-butanol and triethylamine provided a 65% yield of the *tert*-butylcarbamate **20**. 5-Bromo-8-nitroisoquinoline **21**, prepared by nitration of 5-bromoisoquinoline,[23] was allowed to react with the carbamate in the presence of potassium carbonate in DMF to give the *ipso* product **22** in greater than 60% yield. In contrast to all of the other dinapsoline analogues, this adduct with a nitro group attached to the 8-position of the isoquinoline moiety defied all cyclization attempts using tin hydride/AIBN. Under forcing conditions, the nitro was reduced to the amino group, which was isolated in moderate yield. All further attempts to cyclize the 8-amino compound or the corresponding acetamide were unsuccessful. In view of this failure, an alternative approach was envisioned that allowed for the introduction of a fluorine atom into the molecule *prior* to the free-radical cyclization, which might alter the course of reaction. Indeed, a denitrofluorination in DMF using tetramethylammonium fluoride as the fluoride source gave good yields of the desired 8-fluoro product **23**.[24] The AIBN/tin-hydride free radical cyclization of the fluoro derivative **23** proceeded smoothly to afford the cyclized compound **24** in good yield. The usual reduction and deprotection sequence did not, however, work well with the 7-aza analogue. Instead of performing the deprotection step at the end, we found that it was more expedient to deprotect the methylenedioxy moiety and the *tert*-butyl carbamate of **24** all in one pot with boron tribromide. The final ring reduction to **25** was done without further purification other than the removal of solvents. The combined yield of the last two steps (deprotection and sodium cyanoborohydride reduction) was in excess of 58% (Scheme 4).



Scheme 4. Synthesis of the 7-aza core analogue of dinapsoline. Reagents and reaction conditions: (a) CO_2, THF; (b) DPPA, Et_3N, *tert*-BuOH at reflux; (c) K_2CO_3, DMF at 85 °C; (d) Me_4NF, DMF at 65 °C; (e) Bu_3SnH/AIBN, benzene at 80 °C; (f) BBr_3, CH_2Cl_2 at −78 °C; (g) $NaBH_3CN$, THF/HCl.

2.3. B′-Ring substitution analogues of dinapsoline

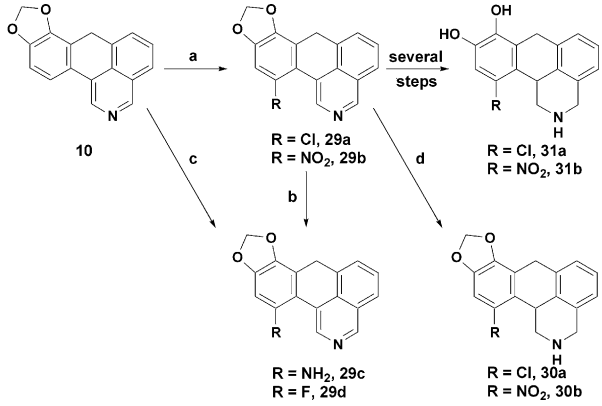
The 7-thia and 7-aza analogues of dinapsoline could affect catechol recognition by altering the overall electron density of the catechol ring. With regard to steric effects, substitution analogues at the 7-position on dinapsoline were prepared to study the steric influence at this position. The hydrogens attached to the 7-methylene, flanked by two adjacent phenyl rings, are sufficiently acidic to be deprotonated using strong base. Indeed, the carbanion of compound **10** was generated easily using sodium hydride in DMF. Alkylation of the resulting anion was carried out as usual to afford a wide range of 7-alkyl substituted derivatives as mixtures of diastereomers (Scheme 5).



Scheme 5. B′ ring modification. Reagents and reaction conditions: (a) NaH in DMF at 0 °C followed by the addition of alkyl bromide or iodide.

2.4. A-Ring substitution analogues of dinapsoline

Compound **10** is also a good starting point for a number of A-ring substituted dinapsoline analogues. The robust methylenedioxy moiety in compound **10** can withstand a variety of electrophilic aromatic substitution conditions. Nitration, fluorination, and chlorination of **10** all proceeded smoothly to give essentially a single product substituted at the 11-position (Scheme 6). The regiochemical assignment was performed by NMR spectroscopy, with results as expected.[25–27] The 11-nitro and 11-chloro derivatives **29** were carried to the end to afford 11-nitro and 11-chloro dinapsoline **31b** and **31a**. The nitro group in compound **29b** was also converted into the amino derivative **29c**. Unfortunately, this compound was not stable enough to be carried through to the end. The 11-fluoro was analogously prepared by an electrophilic aromatic substitution with the commercial fluorinating agent SelectFluoro™; however, the synthesis of this analogue was abandoned after 11-chlorodinapsoline was found to be inactive.

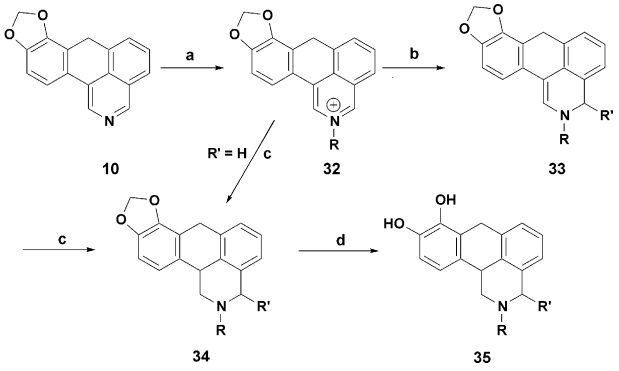


Scheme 6. A-ring modification. Reagents and reaction conditions: (a) nitration with HNO_3, HOAc; chlorination with SO_2Cl_2, methylene chloride; (b) $SnCl_2$, methanol at reflux temperature; (c) fluorination with SelectFluoro™ in MeCN and HOAc; (d) $NaCNBH_3$, THF, HCl at rt.

2.5. C-Ring substitution analogues of dinapsoline

Because the isoquinoline system allows for specific reactions on the nitrogen-bearing side of the heterocycle, access to C-ring derivatives was achieved in a straightforward manner. First, the C-ring nitrogen was quaternized using electrophiles such as methyl or ethyl iodide; the resulting isoquinolinium salt **32** (Scheme 7) was easily reduced with a hydride nucleophile to give

the 1,2,3,4-tetrahydroisoquinoline product **34**. Nucleophiles other than hydride added to the quaternary salt and led to **33**. Subsequent reduction gave substituted derivatives **34**.[28] The boron tribromide deprotection of **34** uneventfully furnished the final targets.



Scheme 7. C-Ring modification. Reagents and reaction conditions: (a) alkyl iodide, dichloroethane at room temperature; (b) alkyl lithium [R′Li] or alkyl Grignard reagent [R′MgBr]; (c) sodium triacetoxyborohydride, THF at −78 °C to rt; (d) BBr_3, methylene chloride at −78 °C.

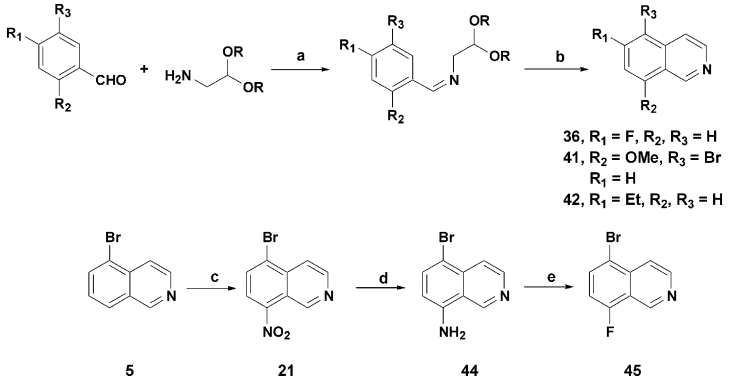
2.6. D-Ring substitution analogues of dinapsoline

As we have shown, intermediate **10** is a versatile starting point for dinapsoline derivatives. This utility is attributed partly to the robust methylenedioxy catechol protecting group, and more importantly to the secondary amine moiety disguised as part of an isoquinoline system. Chemical modifications on the A-, B′-, and C-rings are made possible through these unique qualities. D-ring analogues of dinapsoline are not readily derived from compound **10**, however, and these compounds must be prepared by the seven-step procedure developed for the dinapsoline parent compound. Substituted isoquinoline **4**, a nucleophilic **6** could be generated according to Scheme 1 to provide compounds that are otherwise unavailable by way of compound **10**. It is well known that substituted isoquinolines are difficult to obtain starting materials but synthetic approaches do exist to gain access to 6-, 7-, and 8-substituted isoquinolines. The 6-, 7-, and 8-positions of isoquinoline correspond to the 6-, 5-, and 4-positions of dinapsoline, respectively. These D-ring derivatives were therefore prepared through the appropriate isoquinoline derivatives substituted at the 6-, 7-, and 8-positions while the 5-position was kept as the connecting handle to form the bridging B-ring. With this synthetic strategy in mind, several important dinapsoline analogues were prepared.

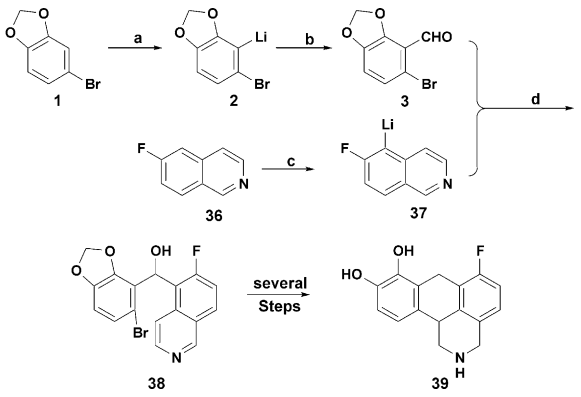
In order to carry out the reaction sequence depicted in Scheme 2, a suitably substituted isoquinoline with a nucleophilic handle at the 5-position (isoquinoline numbering) was required. Therefore, bromine was introduced (Scheme 2) at the 5-position of the isoquinoline congeners. Subsequent transmetalation furnished the 5-lithiated intermediate suitable for coupling with the aldehyde functionality on the catechol ring. This approach was used to prepare 4-hydroxydinapsoline **55**, 4-fluorodinapsoline **57**, and 6-ethyldinapsoline **56**. The starting substituted isoquinolines were prepared in accordance with known procedures (Pomeranz-Fritsch Synthesis, Scheme 8, and subsequently Scheme 10)[29–32] with minor modifications (see Experimental).

The 6-fluorodinapsoline **39** was a special case. The 6-fluoroisoquinoline was sufficiently reactive to be deprotonated directly at the 5-position (fluorine-directed deprotonation) without the need for a bromine handle (Scheme 9).[33] This fluorine atom-mediated regioselective deprotonation appeared to be specific to the isoquinoline system because evidence of benzyne generation through elimination of HF was never observed. The final target compound (±)-**39** was prepared in much the same way as dinapsoline (Schemes 1 and 2). The regiochemical outcome of this fluorine-directed metalation was later confirmed by comparing the end product with other dinapsoline derivatives (Scheme 9). Racemic **39** was further separated into a pair of enantiomers on a preparative HPLC equipped with a Chiralcel OD column using conditions as described previously (see Experimental).[2]

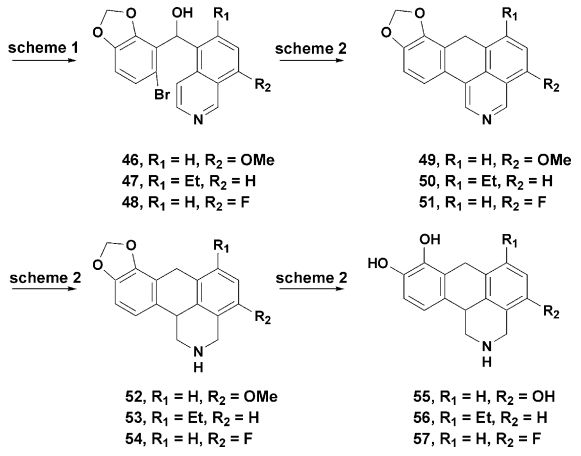
Once the suitable isoquinoline precursors, and the coupled products were prepared (Schemes 8, 9 and 10), the subsequent free-radical initiated ring closure, the reduction, and the BBr_3 deprotection were carried out in accordance with the general procedure described in Scheme 2.



Scheme 8. Synthesis of substituted isoquinolines for D-ring modifications. Reagents and reaction conditions: (a) reflux in benzene, azeotropic removal of water; (b) first step: ethyl chloroformate, trimethyl phosphite in THF, second step: titanium tetrachloride in chloroform; (c) concd H_2SO_4 and solid KNO_3; (d) Fe powder, NH_4Cl in H_2O; (e) $NaNO_2$, HBF_4 and water.



Scheme 9. Synthesis of 6-fluoro dinapsoline. Reagents and reaction conditions: (a) LDA in THF at −78 °C; (b) DMF at −78 °C; (c) LDA at −78 °C; (d) THF at −78 °C.



Scheme 10. Preparation of D-ring analogues.

3. Discussion

Earlier work had demonstrated that despite minor differences in structure, dinapsoline retained many of the pharmacological characteristics of dihydrexidine.[3,18] Structural comparison of dihydrexidine and dinapsoline reveals (Fig. 2) the molecular features shared by both chemotypes. Both molecules can be considered as a 'rigidified' form of 4-(3,4-dihydroxyphenyl)-tetrahydroisoquinoline[34] in which conformational constraint is introduced using either an ethyl tether to create an additional 'B-ring' as in the case of dihydrexidine, or a methylene tether to create the 'B′-ring' of dinapsoline.

Such modifications largely preserve all of the critical structural elements of a D_1 receptor agonist,[36] including the relative position and orientation of the basic nitrogen, catechol hydroxyls, and the accessory phenyl ring. These changes result in a novel dopamine D_1 receptor agonist that offers fresh opportunities for drug development. The introduction of the B′-ring and therefore the C-7 bridging methylene unit (absent in the dihydrexidine chemotype), served as a handle for designing both 'core' modifications and substitution analogues within the molecular framework of dinapsoline. Closer examination reveals that the rigidity imposed on the dinapsoline core structure by the 7-methylene unit also renders the molecule somewhat more planar relative to dihydrexidine.

There have been no full D_1 agonists synthesized that have not contained the catechol moiety,[37] and it was therefore of interest to explore the regions flanking the catechol moiety. To achieve this goal, core analogues were prepared where the C-7 atom in dinapsoline was modified by heteroatom replacement.

Changing the 7-carbon to a sulfur appeared to be detrimental (Table 1) to D_1 receptor affinity. This 7-thia analogue of dinapsoline (**18**) was about an order of magnitude less active at the D_1 site, whereas affinity at the D_2 receptor remained roughly the same. The sulfur replacement had an even greater impact on the intrinisic activity as determined by cAMP production. Replacing the 7-carbon with a larger sulfur atom transformed the 7-thia analogue into a partial agonist (70% of dopamine, Table 2). The diminished activity of the sulfur compound could partly be explained by the larger size of the sulfur atom, providing steric bulk adjacent to the catechol moiety that may hinder receptor interaction with the hydroxy groups. Furthermore, the introduction of a larger atom such as sulfur may push the accessory phenyl ring (D-ring) into a region less able to accommodate hydrophobic elements. On the other hand, the effect of substituting a sulfur atom adjacent to the catechol function in the prototypical dopamine D_1 agonist 7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (SKF-38393) is more subtle, where a shift from activity at peripheral receptors to central activity was reported.[38] It could be argued, however, that increased lipophilicity of the sulfur might account for that difference.

In the case of the 7-aza analogue (**26**), D_1 receptor affinity was lost, whereas D_2 affinity was decreased 3-fold. For the 7-aza analogue, the possibility of hydrogen bonding and lone pair delocalization may fundamentally change the nature of the molecule. The existence of a weakly basic NH may also allow for competition with respect to the catechol recognition site.[39] It is doubtful that steric factors alone could be the cause of the loss of

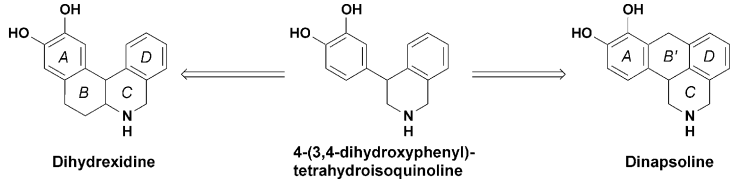
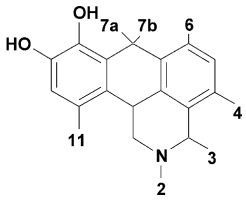


Figure 2. Dinapsoline created by Nichol's rigid β-phenyl dopamine model.[34,35]

Table 1. Results of D_1/D_2 binding assays[a]

Ring Substituted Analogs of *DINAPSOLINE* 12



Compd	Dinapsoline ring substitution						D_1 Affinity (rat striatum) ($K_{0.5}$, nM)	D_2 Affinity (rat striatum) ($K_{0.5}$, nM)	D_2 Affinity (hD_{2L}-HEK) ($K_{0.5}$, nM)
	R_2	R_3	R_4	R_6	$R_{7a,7b}$	R_{11}			
(±)-**12**	H	H	H	H	H,H	H	67±9 (35)	56±10 (17)	10.7±2.7 (3)
S-(−)-**12**	H	H	H	H	H,H	H	5300±1000 (4)	1500±500 (2)	N/A[b]
R-(+)-**12**	H	H	H	H	H,H	H	33±8 (11)	38±6 (7)	11.1±3.0 (9)
18	H	H	H	H	7-S	H	536±129 (2)	34.5±1.5 (2)	N/A
26	H	H	F	H	7-NH	H	>10000	160 (1)	N/A
28a	H	H	H	H	H,Me[c]	H	139±31 (3)	160±27 (2)	N/A
28b	H	H	H	H	Me,Me	H	870±120 (3)	390±8 (2)	N/A
28c	H	H	H	H	H,Et	H	430±64 (3)	440±30 (2)	N/A
28e	H	H	H	H	H,CH_2COOMe	H	2400±1000 (2)	990 (1)	N/A
31a	H	H	H	H	H,H	Cl	1500 (1)	16 (1)	N/A
31b	H	H	H	H	H,H	NO_2	>10000 (2)	1100 (1)	N/A
35a	Me	H	H	H	H,H	H	382±79 (2)	70±5 (2)	N/A
35b	n-Pr	H	H	H	H,H	H	>2000 (1)	N/A	15 (1)
35c	H	Me	H	H	H,H	H	>3000 (1)	N/A	190 (1)
35d	H	n-Bu	H	H	H,H	H	>2000 (1)	N/A	40 (1)
35e	Me	Me	H	H	H,H	H	299±35 (2)	93±6 (2)	N/A
35f	Me	Et	H	H	H,H	H	410±90 (2)	220±8 (2)	N/A
35g	H	C_4F_9	H	H	H,H	H	9500±500 (2)	N/A	>10000 (1)
35h	Me	n-Bu	H	H	H,H	H	340±70 (2)	78±1 (2)	N/A
(−)-**39**	H	H	H	F	H,H	H	>3000 (2)	170 (1)	N/A
(+)-**39**	H	H	H	F	H,H	H	71±13 (2)	7 (1)	N/A
55	H	H	OH	H	H,H	H	72±7 (2)	15 (1)	N/A
56	H	H	H	Et	H,H	H	14±4 (2)	N/A	27 (1)
57	H	H	F	H	H,H	H	69 (1)	28 (1)	N/A

[a] See experimental for details.
[b] N/A stands for data not available
[c] Mixture of diastereomers.

Table 2. Adenylate cyclase (AC) response (in vitro functionality)

Compd	D_1 (SK-N-MC)[a]	
	I.A.±SE[b]	EC_{50}±SE(n), nM[c]
(±)-**12**	1.2±0.06	190±60 (3)
(−)-**12**	0[d]	>10,000 (3)
(+)-**12**	1.0±0.04	220±40 (5)
18	0.69±0.17	5600±2,200 (3)
28a	1.26	110 (1)
28b	0	>10,000 (1)
(±)-**39**	1.29±0.06	300±80 (3)
(−)-**39**	0	>10,000
(+)-**39**	0.97±0.01	200±90 (2)
55	0.98±0.2	670±200 (3)
56	1.40±0.06	350±90 (3)
57	1.30±0.00	240±100 (2)

[a] Neuroblastoma cell preparation.
[b] Intrinsic activity±Standard error.
[c] SE (number of repeat).
[d] No detectable cylase activity at the maximum concentration.

D_1/D_2 affinity. Although D_1 affinity and intrinsic activity were dramtically attenuated by replacing the 7-carbon with a sulfur or nitrogen, D_2 activity was affected to a lesser extent. This finding is consistent with the idea that the ligand binding site of the D_2 receptor has less stringent requirements than does the D_1.

Introduction of substitutions on the 7-carbon also diminished D_1 receptor affinity with the magnitude of the effect being related to the size of the substituent. Compound **28a** (mixture of two diastereomers) had about one-half the D_1, and one-third the D_2, receptor affinity of the unsubstituted parent dinapsoline, yet at the maximal dose **28a** showed full intrinsic activity in activating adenylate cyclase (AC) (Table 2) and robust rotational activity (Table 3) comparable to that of dinapsoline. The halved D_1 receptor affinity of **28a** might further suggest that only one of the two diastereomers is active. Conceivably the active isomer has the 7-methyl positioned so that it does not interfere with catechol recognition. Taken together, these results demonstrate that the region surrounding the 7-atom is sensitive to substitution, and has low tolerance for bulky substituents. Smaller alkyl groups such as methyl may be tolerated, however, if they do not interfere with catechol recognition. This result strongly suggests that molecular recognition of the catechol moiety may require an open access space that cannot be occluded by substituents at the 7-position. One of the initial objectives

Table 3. In vivo pharmacology[4]

Comp	Dose (mg/kg s.c.)	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
A-86929	0.2	1100 ± 200	8
A-86929	2	4200 ± 1000	7
(±)-**28a**	0.2	180 ± 100	5
(±)-**28a**	2	3700 ± 800	6
(±)-**39**	0.2	1100 ± 200	8

of our efforts was to develop compounds with enhanced metabolic stability. Catechol compounds, in general, are metabolized rapidly through sulfation and glucuronidation, processes that are affected by the lipophilicity of the substance and the steric environment proximal to the hydroxy groups.[40–44] Introduction of steric bulk near the catechol moiety could conceivably slow down this degradation. Unfortunately, steric elements that may retard metabolism also appear to prevent efficient recognition of the catechol by the receptor.

Likewise, introducing substitution on the A-ring (catechol ring) offered no advantages in augmenting D_1 receptor affinity. In fact, the negative effects of either a chlorine or a nitro group substitution were substantial. Both 11-chlorodinapsoline (**31a**) and 11-nitrodinapsoline (**31b**) were more than 100-fold less active than the parent dinapsoline at the D_1 site, whereas 11-chlorodinapsoline unexpectedly showed *enhanced* D_2 receptor affinity (3-fold greater). The prototypical dopamine *partial* D_1 receptor agonist SKF-38393, on the other hand, tolerates some substitutions on its catechol ring while preserving substantial D_1 receptor affinity and in vivo activity.[45]

We next turned our attention to the C-ring, where the basic nitrogen is positioned. This region had not been previously investigated in dinapsoline due mainly to the difficulty in synthesizing these analogues. *N*-Substituted dihydrexidine analogues are known, but substitutions on either side of the basic nitrogen are not. Using the versatile chemical synthesis reported here, series of 2-substituted, 3-substituted, and 2,3-disubstituted dinapsoline derivatives were prepared. Generally speaking, D_1 receptor affinity was negatively affected when either the 2- or 3-position was substituted, and similar results were observed if both the 2- and 3-positions were simultaneously substituted. Surprisingly, substitutions appeared to affect binding affinity equally among the *smaller* alkyl groups such as methyl and ethyl groups. These smaller groups attached to either, or both of the 2- and 3-positions, produced compounds with an order of magnitude lower affinity at the D_1 receptor than the dinapsoline parent. This result strongly indicates that a free secondary basic amine moiety is a prerequisite for D_1 activity, a conclusion consistent with earlier findings.[1,21,34] The lack of activity of long alkyls at the 3-position also appeared to be independent of chain polarity because the perfluorinated *n*-butyl chain gave results comparable to that of the *n*-butyl group. Mottola et al.[36] suggested previously that the piperidine (C-ring, 5-position) in dihydrexidine was a potentially fertile site for generation of active analogues. From these results with substituted dinapsoline, however, it seems less likely that any substantial gain in activity can be achieved by modification at the corresponding C-5 region in dihydrexidine, which corresponds to the 3-position of dinapsoline.

Finally, substitutions on the D-ring were investigated. Based on studies of dihydroxybenzopyrans, dihydrexidine, and ABT-431, it was expected that D_1 receptor affinity could be at least maintained or even improved by attaching hydrophobic groups to the D-ring (4-, 5-, and 6-positions).[46] Our early hypothesis about a D_1 pharmacophore[34] included the existence of an accessory hydrophobic binding pocket, as defined by the region surrounding the D-ring in both dihydrexidine and dinapsoline.[3,47,48] Both the orientation of the basic nitrogen and the co-planarity of the accessory ring with respect to the catechol moiety are essential to achieving high levels of in vitro and functional D_1 receptor activity.[36]

All D-ring analogues of dinapsoline synthesized showed D_1/D_2 receptor activity in the same range as the parent compounds, consistent with a recent report.[1] Substitutions at the 6-position were distinguished as the most potent analogues tested in vitro at D_1/D_2 binding while analogues substituted at the 4-position were equipotent to dinapsoline. It is also remarkable to see very little dependence on the nature of the substituent at these positions with respect to in vitro binding affinity. Within the series 4-OH, 4-F, 6-F, and 6-Et substituted dinapsoline, 4-hydroxy and 4-fluoro dinapsoline had almost identical D_1/D_2 affinity despite the vastly different nature of the attached groups. Evidently, the presence of a hydroxy group at the 4-position did not have any significant influence on in vitro binding, in spite of the expectation that this general region of the receptor would be fairly hydrophobic. On the other hand, fluoro and ethyl substitutions at the 6-position yielded compounds with improved D_1/D_2 receptor affinities over dinapsoline, although the gains were not substantial. The 6-fluoro dinapsoline had enhanced activity at both the D_1 and D_2 receptors whereas an increase in subtype-selective binding was detected at the D_1 site only for the 6-ethyl analogue. It is possible that both steric and electrostatic recognition elements operate in this region of the molecule. Further useful improvements in this series may be achieved by optimizing the nature of substituents attached to these positions.

In the unilateral 6-OHDA rat rotation model the activity of most compounds correlated well with their in vitro D_1 receptor binding affinities and intrinsic activities. When tested at a single dose (1 mg/kg) administered subcutaneously (sc), all but one compound that had a D_1 receptor affinity of 50 nM or better produced rotational activity (Table 3). The single exception to this trend was 6-ethyl dinapsoline that was only marginally active in vivo despite its high in vitro affinity and full

intrinsic activity (Table 2) at the D_1 receptor. This observation may indicate that the 6-ethyl substitution affects the pharmacokinetic profile of the dinapsoline chemotype, modulates brain absorption, or possibly suggests that the compound may be functionally selective at the D_1 receptor.[49]

4. Conclusions

Systematic SAR studies were performed on the core structure of dinapsoline. With the exception of the 7-position, which tolerated limited modifications, substitutions on the A-, B′-, and C-rings generally produced compounds with decreased dopamine D_1 receptor activity relative to the parent unsubstituted dinapsoline. Although affinity at the D_2 receptor subtype is not affected to the same extent as observed at the D_1 receptor, it is generally decreased. Substitutions on the D-ring retained much of the in vitro D_1/D_2 activity of the parent. Relative intrinsic activity, as measured by accumulation of cAMP, remained about comparable to dopamine or slightly better among the D-ring congeners. The active D-ring analogue, 6-fluorodinapsoline (**39**) was prepared in enantiomeric pure form by resolution of a precursor. The (+)-enantiomer was determined to be the biologically active compound, a result that was consistent with the activity of (+)-dinapsoline. Although the absolute configuration of (+)-**39** was not independently determined, it is predicted to have the 11b(*S*) configuration as required by the dinapsoline core structure and its shared pharmacological similarity to other potent and selective D_1 agonists such as dihydrexidine and A-86929.[2,36,50,51]

5. Experimental

5.1. In vitro and in vivo assays: materials

[^{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, USA). Rat striata were purchased from ABS Inc. (Wilmington, DE, USA). 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 20,000*g* for 10 min. Pellets were re-suspended in homogenization buffer, incubated for 30 min at 37 °C and centrifuged again. The final pellets were re-suspended 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 in buffer consisting of 50 mM Tris (pH 7.7 at 25 °C) and 2 mM $MgCl_2$ for use in [^{125}I]-7-OH-PIPAT binding assays.

5.2. 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 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 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. Non-specific 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 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 addition of ice-cold wash buffer (20 mM Tris). Filtration over glass fiber filters (Whatman GF/B) was performed using a Brandel cell harvester. Non-specific binding was defined with 2 μM (+)-butaclamol. Binding of [^{125}I]-7-OH-PIPAT to D_2 receptors was also performed using HEK-293 cells that stably express recombinant human dopamine D_{2L} receptors. HEK-D_{2L} cells were grown at 37 °C in 5% CO_2 as a monolayer in medium consisting of MEM supplemented with 10% fetal bovine serum and G418 sulfate (500 μg/mL). To prepare membranes for radioligand binding experiments, cells were rinsed twice with phosphate-buffered saline (9 g/L NaCl, 0.795 g/L $Na_2HPO_4{\cdot}7H_2O$, 0.144 g/L KH_2PO_4, pH 7.4), and incubated for 5–10 min at 4 °C in hypotonic lysis buffer consisting of 10 mM Tris (pH 7.4) and 5 mM EDTA. Cells were transferred from plates to polypropylene tubes (16×100 mm), homogenized and centrifuged at 32,000*g* for 20 min. Following centrifugation, pellets were resuspended by homogenization in buffer consisting of 50 mM Tris (pH 7.7 at 25 °C) and 1 mM EDTA. Homogenates were stored at −80 °C until needed. On the day of the experiment frozen homogenates were thawed, homogenized then centrifuged at 32,000*g* for 20 min. Following centrifugation, supernatants were discarded and remaining pellets were re-suspended in buffer consisting of 50 mM Tris (pH 7.7 at 25 °C) and 2 mM $MgCl_2$. Homogenates (10 μg protein/well) were assayed for [^{125}I]-7-OH-PIPAT binding as described above for rat striatal homogenate.[52]

5.3. cAMP accumulation

cAMP production in SK-N-MC cells endogenously expressing D_1 receptor was measured by using 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, 5% CO_2 1 day before the assay. Assays were initiated by the addition of 700 μL assay buffer containing 1 mM 3-isobutyl-1-methyl-xanthine in the presence of varying concentration of compounds. After incubation for 10 min at 37 °C, he supernatant was removed, and 1 mL 0.1 N HCl was added to terminate the reaction. The cAMP production was quantified using the Amersham protocol. Non-linear regression curve-fitting (Prism 3.0, GraphPad Inc., San Diego, CA, USA) was used to fit dose-response curves. The reported intrinsic activity is based on the response (E_{max}) relative to dopamine.

5.4. In vivo pharmacology

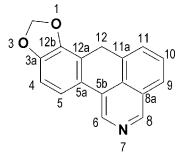
Rotation experiments were performed in Sprague–Dawley rats with unilateral 6-OHDA lesions of the medial forebrain bundle as described previously.[17] Only animals that met pre-screening criteria for rotational response to amphetamine (5 mg/kg giving 800 ipsilateral rotations/3 h) and apomorphine (0.2 mg/kg: 100 contralateral 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.

5.5. General chemical procedures

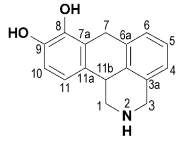
Melting points were recorded on a Thomas-Hoover capillary apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer System 2000 FT-IR spectrometer, or performed by Robertson Microlit Lab. Optical rotations were measured on a Perkin–Elmer 241 polarimeter with a 10-cm standard cell; results are reported as $[\alpha]_D$. Proton NMR (^{1}H NMR) and carbon NMR (^{13}C NMR) spectra were obtained on a Bruker ACP 300 spectrometer and are reported relative to a tetramethylsilane (TMS) reference. NMR coupling constants (J) are reported in hertz (Hz). Analytical and preparative HPLC were performed on YMC columns (A-302, S-5, 120A ODS, 4.6×150 mm; S5 ODS, 30×100 mm) with methanol:water gradients containing 0.1% trifluoroacetic acid. LC–MS were obtained with a Shimadzu-MicromassLC 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.

5.6. Compounds 3, 5, and 7–12

The synthetic procedure for compounds **3**, **5**, and **7–12** has been described recently.[2] It should be noted that the numbering system on polycyclic condensed system often changes with additional rings attached. Here we include the CAS nomenclature and numbering for the following systems. For clarity in discussing SAR, dinapsoline core numbering was used throughout.



12H-benzo[*de*]-1,3-benzo dioxolo[4,5-*h*]isoquinoline



8,9-Dihydroxy-2,3,7,11*b*-tetrahydro-1H-dibenz[*de,h*]isoquinoline

5.7. Synthesis of 1,2,3,11b-tetrahydro[1]benzothiopyrano[4,3,2-de]isoquinolin-8,9-diol (18)

5.7.1. [Bis(1-methylethyl)amino]carbodithioic acid, 5-isoquinolinyl ester (13). To a chilled (−78 °C) solution of 5-bromoisoquinoline (**1**, 8.0 g, 39 mmol) in 250 mL THF was added *tert*-butyl lithium (1.7 M in pentane, 45 mL, 77 mmol) over a period of 15 min. Metalation was allowed to proceed at −78 °C for 30 min before it was treated with a solution of tetraisopropylthiuram disulfide (13.6 g, 39 mmol) in 55 mL THF. TLC showed complete reaction after 45 min. The reaction mixture was quenched with 30 mL of a saturated solution of NH_4Cl and the organic residues were extracted with ethyl acetate to give the crude product (7.5 g, 63%), mp 143–145 °C: ^{1}H NMR ($CDCl_3$) δ 9.29 (d, 1H, J=0.7), 8.59 (d, 1H, J=6.0), 8.11 (d, 1H, J=8.2), 7.95 (t, 2H, J=7.5), 7.67 (t, 1H, J=7.7), 3.6–3.5 (br, 12H); LC/MS m/z 305.18 (MH^+). Anal. calcd for $C_{16}H_{20}N_2S_2{\cdot}0.2H_2O$: C, 62.38; H, 6.68; N, 9.09. Found: C, 62.13; H, 6.44; N, 8.89.

5.7.2. 5,5′-Dithiobisisoquinoline (14). The crude *N,N*-diisopropyl dithiocarbamate (**13**, 7.5 g, 24.7 mmol) was taken up into 300 mL of 95% EtOH containing 10 mL of 10 M aqueous NaOH solution. The hydrolysis was conducted at reflux temperature for 36 h. The final disulfide formation was accomplished by the addition of iodine solution in EtOH and the progress was monitored by LC/MS. The desired product was isolated by crystallization to give 1.8 g (21%), mp 143–146 °C: ^{1}H NMR ($CDCl_3$) δ 9.25 (d, 2H, J=0.8), 8.54 (d, 2H, J=5.0), 7.9 (m, 4H), 7.74 (d, 2H, J=7.0), 7.43 (t, 2H, J=7.5); LC/MS m/z 321.12 (MH^+). Anal. calcd for $C_{18}H_{12}N_2S_2{\cdot}0.2H_2O$: C, 66.72; H, 3.86; N, 8.65. Found: C, 66.54; H, 4.17; N, 8.35.

5.7.3. 5-[(5-Bromo-1,3-benzodioxol-4-yl)thio]isoquinoline (15). To a solution of 4-bromo-1,2-(methylenedioxy)-benzene (**1**, 1.2 g, 6.0 mmol) in 38 mL THF at −78 °C was added lithium diisopropyl amide (LDA) solution in THF (Aldrich, 1.5 M, 4.7 mL, 7.1 mmol) over a period of 10 min. Deprotonation was allowed to proceed at −78 °C for 30 min before adding a solution of disulfide **14** (1.8 g, 5.6 mmol) in 9.2 mL THF. The mixture was stirred at −78 °C for 45 min, and at room temperature for a further 30 min and was then quenched with a saturated solution of NH_4Cl. The crude product was extracted with ethyl acetate. The final pure material was obtained by flash chromatography on silica gel type-H (Merck) eluted with mixtures of ethyl acetate and hexanes. The yield of the desired product was 1.3 g (62%), mp 140–141 °C : ^{1}H NMR ($CDCl_3$) δ 9.24 (d, 1H, J=0.9), 8.59 (d, 1H, J=6.0), 8.17 (d, 1H, J=6.5), 7.82 (dd, 1H, J=6.5, 2.0), 7.45–7.41 (m, 2H), 7.20 (d, 1H, J=8.3), 6.73 (d, 1H, J=8.3), 5.91 (s, 2H); LC/MS m/z 362.03 (MH^+). Anal. calcd for $C_{16}H_{10}BrNO_2S{\cdot}0.2H_2O$: C, 52.82; H, 2.88; N, 3.85. Found: C, 52.60; H, 2.96; N, 3.81.

5.7.4. 8,9-(1,3-Dioxolyl)[1]benzothiopyrano[4,3,2-*de*]isoquinoline (16). To a solution of bromide **15** (1.0 g, 2.6 mmol) in benzene (107 mL), acetic acid (0.9 mL) and 2,2′-azobisisobutyronitrile (AIBN, 0.45 g) were added. The reaction mixture was cooled to −78 °C and degassed (four times) followed by purging with argon gas. After warming to room temperature, the solution was slowly warmed to 80 °C and tributyltin hydride (2.8 mL) in degassed benzene (29 mL) was added

dropwise through a dropping funnel over a period of 3.5 h. Starting material was consumed after stirring overnight at 80 °C. Triethylamine (0.22 mL) was added to the solution and the mixture was stirred for 5 min. The solvent was removed and purification was performed by precipitation of the product with EtOAc/CH_2Cl_2/hexanes to obtain compound **16** (0.56 g, 71%), mp 223–225 °C: ^{1}H NMR ($CDCl_3$) δ 8.91 (s, 1H), 8.83 (s, 1H), 7.57–7.52 (m, 2H), 7.40–7.35 (m, 2H), 7.10 (d, 1H, J = 8.29), 6.07 (s, 2H); MS (ESI) m/z 280.07 (MH^+). Anal. calcd for $C_{16}H_9NO_2S{\cdot}0.5H_2O$: C, 66.65; H, 3.50; N, 4.86. Found: C, 66.82; H, 3.65; N, 4.85.

5.7.5. 1,2,3,11*b*-Tetrahydro-8,9-(1,3-dioxolyl)[1]benzothiopyrano[4,3,2-*de*]isoquinoline, (17). The cyclized compound **16** (0.06 g) was dissolved in warm THF (15 mL) followed by hydrochloric acid (2 N, 1.1 mL). Sodium cyanoborohydride (0.19 g) was added after the temperature returned to ambient (25 °C). Stirring proceeded for an h and then saturated sodium bicarbonate was added to neutralize the mixture. The organic layer was separated and concentrated. Purification was performed by column filtration to obtain **17** as a gum in 50% yield: ^{1}H NMR ($CDCl_3$) δ 7.36 (d, 1H, J = 7.56), 7.13 (t, 1H, J = 7.62), 6.98 (d, 1H, J = 7.44), 6.73 (q, 2H, J = 8.13 and 13.62), 6.03 (dd, 2H, J = 1.05 and 9.87), 4.16–4.03 (m, 2H), 3.98–3.88 (m, 1H), 3.59–3.50 (m, 2H); LC/MS m/z 284.00 (MH^+).

5.7.6. 1,2,3,11*b*-Tetrahydro.[1]benzothiopyrano[4,3,2-*de*]isoquinolin-8,9-diol (18) To a solution of the tetrahydroisoquinoline **17** (0.03 g, 0.11 mmol) in dichloromethane (2 mL) cooled to −78 °C was added boron tribromide (1 M solution in dichloromethane, 0.5 mL). The reaction solution was stirred at −78 °C for 2 h and was then warmed to room temperature and stirring continued overnight. The solution was cooled to −78 °C and dry methanol was added to quench the reaction. After stirring for 10 min, the solution was gradually warmed to reflux at 70 °C for 30 min. The solvents were evaporated and purification was performed by precipitation with CH_2Cl_2 to obtain solid product **18** (0.031 g, 84%): ^{1}H NMR (CD_3OD) δ 7.50 (d, 1H, J = 7.77), 7.28 (t, 1H, J = 7.71), 7.18 (d, 1H, J = 7.65), 6.79 (d, 1H, J = 8.28), 6.66 (d, 1H, J = 8.52), 4.52–4.40 (m, 2H), 4.34–4.27 (m, 1H), 3.93 (t, 1H, J = 11.13), 3.83–3.77 (m, 1H); LC/MS m/z 272.12 (MH^+). Anal. calcd for $C_{15}H_{13}NO_2S$: C, 47.04; H, 3.78; N, 3.66. Found: C, 47.07; H, 4.07; N, 3.53.

5.7.7. 5-Bromo-1,3-benzodioxole-4-carboxylic acid (19). To a cooled (−78 °C) solution of 4-bromo-1,2-(methylenedioxy)benzene (**1**, 3.2 g, 15.9 mmol) in THF (100 mL) was added dropwise LDA (Aldrich, 11.2 mL of 1.5 M solution in cyclohexane, 16.8 mmol). The resulting mixture was stirred at −78 °C under nitrogen for an hour. Dry CO_2 was introduced by bubbling through a needle over a period of an hour. The reaction mixture was then allowed to warm to room temperature and H_2O was added. The mixture was neutralized to pH 10–11 by dropwise addition of 10 N aqueous NaOH. The remaining organic residues were extracted with a mixture (2:1 v/v) of EtOAc and hexanes. The aqueous layer was acidified to pH 1–2 with 6 N HCl. The precipitates were collected, washed with water, and dried under vacuum to furnish the desired product as a white solid (3.14 g, 12.8 mmol, 81%): mp 166–168 °C; MS m/z 243 (M−H); ^{1}H NMR (DMSO-d_6) δ 13.75 (br s, 1H), 7.12 (d, 1H, J = 8.4), 6.95 (d, 1H, J = 8.4), and 6.13 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 164.7, 147.4, 146.3, 125.6, 117.9, 110.7, 119.3, and 102.6. Anal. calcd for $C_8H_5BrO_4$: C, 39.21; H, 2.06; N, 0.00. Found: C, 39.34; H, 2.11; N, 0.00.

***5.7.8.N*-(5-Bromo-1,3-benzodioxol-4-yl)carbamic acid, 1,1-dimethylethyl ester (20).** To a solution of acid **19** (0.50 g, 2.0 mmol) in *tert*-BuOH (15 mL) was added Et_3N (0.45 g, 4.5 mmol) followed by diphenylphosphoryl azide (DPPA, 0.62 g, 2.2 mmol). The resulting mixture was stirred at room temperature for 15 min. The stirring continued while the temperature was raised to reflux for 1 h. All the volatile solvents were removed by evaporation in vacuo. The residue was purified by flash chromatography on silica gel (Type-H, Merck), eluted with 1:1 v/v mixture of EtOAc in hexanes, final recrystalization from hexanes furnished the desired product as white flakes (4.2 g, 1.3 mmol, 65%): mp 87–88 °C; MS m/z 314 (M−H); ^{1}H NMR (DMSO-d_6) δ 8.68 (s, 1H), 7.09 (d, 1H, J = 8.4), 6.80 (d, 1H, J = 8.4), 6.07 (s, 2H), and 1.42 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 153.0, 147.6, 144.9, 124.3, 119.9, 114.1, 107.8, 102.1, 79.0, and 28.0. Anal. calcd for $C_{12}H_{14}BrNO_4$: C, 45.59; H, 4.46; N, 4.43. Found: C, 45.43; H, 4.51; N, 4.44.

5.7.9. 5-Bromo-8-nitroisoquinoline (21). This preparation followed literature procedures, with minor modifications described herein: to a mixture of KNO_3 (5.1 g, 50.5 mmol) and concentrated H_2SO_4 (42 mL) was slowly added 5-bromoisoquinoline (**5**). Once the addition was complete, the reaction mixture was stirred at 0 °C for an h and was then poured into 400 g of crushed ice. The solution phase was neutralized to pH 8–9 using concentrated aqueous NH_3 solution. The precipitates were filtered off and purified by recrystallization (MeOH) to provide product as a grayish solid (4.1 g, 16.2 mmol, 84.4%): ^{1}H NMR ($CDCl_3$) δ 10.06 (s, 1H), 8.86 (d, 1H, J = 5.7), 8.23 (d, 1H, J = 8.1), 8.20 (d, 1H, J = 5.7), 8.14 (d, 1H, J = 8.1).

5.7.10. *N*-(5-Bromo-1,3-benzodioxol-4-yl)-*N*-(8-nitroisoquinolin-5-yl)carbamic acid, 1,1-dimethylethyl ester (22). To a solution of 5-bromo-8-nitro-isoquinoline (0.67 g, 2.6 mmol) in dimethylformamide (DMF) was added **20** (0.83 g, 2.6 mmol) followed by KNO_3 (1.0 g, 9.9 mmol). The resultant mixture was stirred at 85 °C under N_2 for 11 h and then poured into H_2O. The product was extracted with EtOAc and dried over Na_2SO_4. Chromatography (silica gel, 25% v/v ethyl acetate in hexanes) provided product as a dry foam (0.78 g, 1.6 mmol, 61.5%): MS m/z 488 (MH^+). Anal. calcd for $C_{21}H_{18}BrN_3O_6{\cdot}0.27C_6H_{14}{\cdot}0.37H_2O$: C, 52.44; H, 4.38; N, 8.11. Found: C, 52.45; H, 4.06; N, 8.29.

5.7.11. *N*-(5-Bromo-1,3-benzodioxol-4-yl)-*N*-(8-fluoroisoquinolin-5-yl)carbamic acid, 1,1-dimethylethyl ester (23).

Me_4NF (0.80 g, 7.9 mmol) was added to a solution of **22** (0.94 g, 1.9 mmol) in DMF (120 mL). The reaction mixture was stirred at 65 °C under N_2 for 25 min and then poured into H_2O. The product was extracted with EtOAc and dried over Na_2SO_4. Chromatography (silica gel, 25% v/v EtOAc in hexanes) gave product as a yellow foam (0.40 g, 0.9 mmol, 47.3%): MS *m*/*z* 461 (MH^+). Anal. calcd for $C_{21}H_{18}BrFN_2O_4 \cdot 0.2H_2O$: C, 54.26; H, 3.99; N, 6.03. Found: C, 54.49; H, 4.20; N, 5.95.

5.7.12. 8,9-(1,3-Dioxolyl)-4-fluoro-7H-pyrido[3,4,5-*k*]acridine-7-carboxylic acid, 1,1-dimethylethyl ester (24). To a solution of **23** (0.38 g, 1.0 mmol) in benzene (40 mL) was added glacial acetic acid (0.34 g, 5.6 mmol) followed by AIBN (0.18 g, 1.1 mmol). The resultant mixture was cooled to −78 °C, degassed, purged with N_2, and heated to 80 °C. A solution of tributyltin hydride (1.0 g, 3.4 mmol) in benzene (10 mL) was added dropwise in the course of 80 min. The stirring continued at 80 °C under N_2 for 16 h. The mixture was neutralized by adding Et3N (0.80 mL) and the solvent was removed. Chromatography (silica gel, 25% v/v EtOAc in hexanes) gave the desired product as a yellow solid (0.20 g, 0.7 mmol, 67%): mp 171–173 °C; MS *m*/*z* 381 (MH^+); ^{1}H NMR ($CDCl_3$) δ 9.13 (s, 1H), 8.82 (s, 1H), 7.87 (dd, 1H, *J* = 8.7 and 4.5), 7.31 (d, 2H, *J* = 8.4), 7.11 (dd, 1H, *J* = 9.9 and 9.0), 6.74 (d, 2H, *J* = 8.1), 5.99 (s, 2H), and 1.38 (s, 9H).

5.7.13. 4-Fluoro-7H-pyrido[3,4,5-*k*]acridin-8,9-diol (25) and 4-fluoro-2,3,7,11b-tetrahydro-1H-pyrido[3,4,5-*k*]acridin-8,9-diol (26). BBr_3 (2.6 mL of 1.0 M in CH_2Cl_2 2.6 mmol) was added to a chilled solution (−78 °C) of **24** (0.13 g, 0.5 mmol) in CH_2Cl_2 (26 mL). The resulting mixture was stirred at room temperature for 3 h and then was cooled to −78 °C. Methanol (10 mL) was added dropwise at −78 °C while stirring. Stirring was continued at room temperature for 16 h. The dry residue (**25**) remaining after solvent removal was dissolved in THF (50 mL) and cooled to 0 °C. HCl (2.6 mL of 2.0 N in H_2O) was added followed by $NaCNBH_3$ (0.52 g, 8.3 mmol). The reaction mixture was stirred at room temperature for 3 h. The precipitates were filtered off. Chromatography (silica gel type-H, 10% MeOH in CH_2Cl_2) of the filtrate provided product **26** as a pink solid (0.070 g, 0.29 mmol, 58%): mp > 280 °C; MS *m*/*z* 273 (MH^+); ^{1}H NMR (DMSO-d_6) δ 7.01 (dd, 1H, *J* = 9.0 and 5.7), 6.93 (d, 1H, *J* = 9.3), 6.69 (d, 1H, *J* = 11.7), 6.53 (br. s, 2H), 6.31 (br. s, 2H), 6.10 (dd, 1H, *J* = 36.9 and 8.1), and 4.23–3.90 (m, 5H).

5.8. 12-Alkyl-12H-benzo[*de*]-1,3-benzodioxol[4,5-*h*]isoquinoline (27a to 27i)

5.8.1. General procedure. To a mixture of starting materials 12*H*-benzo[*de*]-1,3-benzodioxol[4,5-*h*]-isoquinoline (**10**, 0.77 mmol) and sodium hydride (5.0 mmol) was added 30 mL of DMF. The resulting suspension was stirred at room temperature under argon for an h before addition of the alkylating agent. Stirring was continued for 5 min after addition of the electrophile, and the reaction mixture was then quenched by the addition of 5 mL of satd aqueous NH_4Cl solution. The product was extracted with ethyl acetate and the combined organic layers were washed with water, brine, and dried over $MgSO_4$. After filtration and concentration in vacuo, the residue was purified by flash chromatography (SiO_2, type-H eluted with mixtures of EtOAc/hexanes).

5.8.2. 12-Methyl-12*H*-benzo[*de*]-1,3-benzodioxol[4,5-*h*]-isoquinoline (27a). This compound was obtained as a yellowish dry foam (yield 57%): MS *m*/*z* 276.1 (MH^+). ^{1}H NMR (DMSO-d_6) δ 1.43 (d, *J* = 7.14, 3H), 4.6 (q, 1H), 6.1 (s, 1H), 6.2 (s, 1H), 7.05 (d, *J* = 9.03, 1H), 7.7 (t, 1H), 7.8 (m, 1H), 7.9 (d, *J* = 8.34, 1H), 9.16 (d, *J* = 11.4, 1H). ^{13}C NMR (DMSO-d_6) δ 27.34, 32.16, 101.57, 107.62, 117.50, 122.15, 122.86, 122.93, 125.25, 127.62, 127.75, 127.94, 129.06, 135.92, 136.95, 145.07, 147.17, 150.65. Anal. calcd for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.38; H, 4.94; N, 5.05.

5.8.3. 12,12′-Dimethyl-12*H*-benzo[*de*]-1,3-benzodioxol[4,5-*h*]isoquinoline (27b). This compound was obtained as a dry yellow foam (65% yield): MS *m*/*z* 290.1 (MH^+). ^{1}H NMR (DMSO-d_6) δ 1.75 (s, 6H), 6.15 (s, 2H), 7.04 (d, *J* = 8.4, 1H), 7.76 (t, 1H), 8.02 (m, 1H), 9.17 (d, *J* = 1.62, 2H). ^{13}C NMR (DMSO-d_6) δ 8.48, 32.67, 37.74, 101.49, 107.58, 117.36, 120.41, 123.39, 124.30, 125.28, 127.28, 127.56, 129.05, 129.37, 134.81, 135.91, 144.97, 147.10, 150.61. Anal. calcd for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.23; N, 4.84. Found: C, 78.55; H, 5.47; N, 4.72.

5.8.4. 12-Ethyl-12*H*-benzo[*de*]-1,3-benzodioxol[4,5-*h*]isoquinoline (27c). This compound was obtained as a pale-yellow dry foam (57% yield): MS *m*/*z* 290.1 (MH^+). ^{1}H NMR (DMSO-d_6) δ 0.395 (t, 3H), 1.75 (m, 1H), 1.96 (m, 1H), 4.6 (t, 1H), 6.1 (s, 1H), 6.20 (s, 1H), 7.01 (d, *J* = 8.34, 1H), 7.77 (m, 3H), 7.85 (d, *J* = 8.4, 1H), 9.15 (d, *J* = 13.4, 2H). ^{13}C NMR (DMSO-d_6) δ 31.34, 36.66, 100.99, 107.95, 117.30, 122.14, 122.54, 125.27, 126.62, 126.83, 127.27, 127.50, 127.88, 136.00, 142.07, 145.15, 147.89, 150.55. Anal. calcd for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.23; N, 4.84, Found: C, 78.67; H, 5.29; N, 4.80.

5.8.5. 12,12′-Diethyl-12*H*-benzo[*de*]-1,3-benzodioxol[4,5-*h*]isoquinoline (27d). This compound was obtained as a pale gray dry foam (8% yield): MS *m*/*z* 318.13 (MH^+). ^{1}H NMR (DMSO-d_6) δ 0.25 (t, 6H), 1.98 (m, 2H), 2.7 (m, 2H), 6.11 (s, 2H), 7.11 (d, *J* = 8.34, 1H), 7.8 (t, 1H), 8.05 (m, 3H), 8.95 (d, *J* = 3.06, 2H).

5.8.6. 12-Ethoxycarbonylmethyl-12*H*-benzo[*de*]-1,3-benzodioxol[4,5-*h*]isoquinoline (27e). This compound was obtained as a brown gum (24% yield): MS *m*/*z* 348 (MH^+). ^{1}H NMR (DMSO-d_6) δ 0.82 (t, 3H), 2.7 (q, 1H), 2.9 (q, 1H), 3.7 (q, 2H) 6.1 (s, 1H), 6.2 (s, 1H), 7.05 (d, *J* = 9.8, 1H), 7.7 (m, 2H), 7.8 (d, *J* = 9.8, 1H), 7.9 (d, *J* = 8.3, 1H), 9.16 (d, *J* = 10.3, 2H).

5.8.7. 12-Cyanomethyl-12H-benzo[*de*]-1,3-benzodioxol[4,5-*h*]isoquinoline (27f). This compound was obtained as a yellow solid (19% yield): MS *m*/*z* 301.1 (MH^+). ^{1}H NMR (DMSO-d_6) δ 3.15 (d, *J* = 5.0, 2H), 4.9 (t, 1H), 6.1 (dd, *J* = 0.87, 1H), 6.22 (dd, = 0.87, 1H), 7.09 (d, *J* = 8.4, 1H), 7.8 (t, 1H), 7.95 (m, 2H), 8.1 (d, *J* = 8.4, 1H), 9.17 (d, *J* = 9.9, 2H).

5.9. (±)-7-Alkyl-8,9-methylenedioxy-2,3,7,11b-tetrahydro-1H-dibenz[de,h]isoquinoline and (±)-7-alkyldinapsoline (28a–28f)

Products from alkylation were reduced as described previously using sodium cyanoborohydride in acidified THF. Products from the reduction step were deprotected using BBr_3 in CH_2Cl_2 at −78 °C. The desired products were isolated in accordance with the procedures described previously. Some of the 7-substituted intermediates (**27d**, **27f**) could not withstand the BBr_3 deprotection conditions; only four compounds from this series survived to the end.

5.9.1. (±)-7-Methyl-8,9-methylenedioxy-2,3,7,11b-tetrahydro-1*H*-dibenz[de,h]isoquinoline and (±)-7-methyldinapsoline hydrobromide (28a). The reduction product was obtained as a dry yellow foam (57% yield): MS *m*/*z* 280.2 (MH^+). ^1H NMR (DMSO-d_6) δ 1.31 (d, *J* = 7.2, 3H), 3.09 (t, 1H), 4.28 (m, 5H), 6.02 (s, 1H), 6.1 (s, 1H), 6.87 (m, 2H), 7.06 (d, *J* = 6.7, 1H), 7.24 (t, 1H), 7.30 (d, *J* = 7.4, 1H). The deprotected final product was obtained as a yellow foam (57% yield): MS *m*/*z* 268.18 (MH^+). ^1H NMR (DMSO-d_6) δ 1.24 (d, *J* = 7.1, 3H), 3.33 (m, 5H), 6.56 (d, *J* = 8.3, 1H), 6.70 (d, *J* = 8.2, 1H), 7.12 (d, *J* = 7.1, 1H), 7.33 (m, 2H), 8.5 (s, 1H), 9.31 (s, 1H).

5.9.2. (±)-7,7′-Dimethyl-8,9-methylenedioxy-2,3,7,11b-tetrahydro-1*H*-dibenz[de,h]isoquinoline and (±)-7,7′-dimethyldinapsoline hydrobromide (28b). The reduction product was obtained as a yellow foam (65% yield): MS *m*/*z* 294.2 (MH^+). ^1H NMR (DMSO-d_6) δ 1.43 (d, *J* = 18.0, 3H), 1.98 (d, *J* = 21.4, 3H), 2.94 (t, 1H), 4.19 (m, 4H), 6.10 (t, 2H), 6.82 (m, 2H), 7.17 (m, 1H), 7.22 (m, 1H), 7.5 (m, 1H). The deprotected final product was obtained as a yellow foam (65% yield): MS *m*/*z* 282.2 (MH^+). ^1H NMR (DMSO-d_6) δ 1.69 (s, 3H), 1.81 (s, 3H), 4.31 (m, 5H), 6.70 (d, *J* = 8.4, 1H), 6.81 (d, *J* = 8.4, 1H), 7.25 (d, *J* = 7.4, 1H), 7.39 (t, 1H), 7.66 (d, *J* = 7.8, 1H), 8.34 (s, 1H), 9.55 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 29.22, 29.62, 31.81, 37.35, 43.31, 45.82, 113.48, 116.66, 122.30, 124.39, 126.37, 127.02, 128.90, 129.02, 129.66, 143.71, 144.38, 144.72. Anal. calcd for $C_{18}H_{19}NO_2 \cdot 1.6HBr \cdot 0.6H_2O$: C, 51.28; H, 5.21; N, 3.33; Br, 30.32. Found: C, 50.89; H, 5.11; N, 3.94; Br, 29.44.

5.9.3. (±)-7-Ethyl-8,9-methylenedioxy-2,3,7,11b-tetrahydro-1*H*-dibenz[*de*,*h*]isoquinoline and (±)-7-ethyldinapsoline hydrobromide (28c). The reduction product was obtained as a dry pale yellow foam (57% yield): MS *m*/*z* 294.2 (MH^+). ^1H NMR (DMSO-d_6) δ 0.90 (t, 3H), 1.61 (m, 2H), 2.79 (t, 1H), 3.9 (m, 4H), 5.96 (s, 1H), 6.05 (s, 1H), 6.79 (m, 2H), 6.96 (m, 1H), 7.14 (m, 2H). This final compound was obtained as a pale yellow dry foam (57% yield): MS *m*/*z* 282.4 (MH^+); 280.3 (M−H). ^1H NMR (DMSO-d_6) δ 0.868 (t, 3H), 1.17 (m, 2H), 4.37 (m, 5H), 6.55 (d, *J* = 8.2, 1H), 6.7 (d, *J* = 8.2, 1H), 7.17 (t, 1H), 7.27 (t, 2H), 8.45 (s, 1H), 9.3 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 12.33, 27.25, 31.97, 40.85, 43.86, 44.21, 112.82, 114.04, 124.09, 126.38, 126.49, 127.56, 127.70, 131.66, 140.15, 142.21, 143.80. Anal. calcd for $C_{18}H_{19}NO_2 \cdot 1.0HBr$: C, 53.25; H, 5.67; N, 3.45. Found: C, 53.26; H, 5.58; N, 3.44.

5.9.4. (±)-7,7′-Diethyl-8,9-methylenedioxy-2,3,7,11b-tetrahydro-1*H*-dibenz[*de*,*h*]isoquinoline and (±)-7,7′-diethyldinapsoline hydrobromide (28d). This compound was obtained as a pale gray dry foam (8% yield): MS *m*/*z* 352.11 (MH^+). ^1H NMR (DMSO-d_6) δ 1.14 (t, 3H), 2.6 (m, 2H), 3.08 (t, 1H), 4.11 (m, 6H), 4.58 (t, 1H), 6.01 (s, 1H), 6.08 (s, 1H), 6.77 (d, *J* = 8.0, 1H), 6.85 (d, *J* = 8.0, 1H), 7.1 (t, 1H), 7.21 (d, *J* = 4.3, 2H). Attempted BBr_3 deprotection led to extensive decomposition of the starting material.

5.9.5. (±)-7-Ethoxycarbonylmethyl-8,9-methylenedioxy-2,3,7,11b-tetrahydro-1*H*-dibenz[*de*,*h*]isoquinoline and (±)-7-methoxycarbonylmethyldinapsoline (28e). The reduced compound was obtained as a brown gum (24% yield): MS *m*/*z* 284.15 (MH^+). ^1H NMR (DMSO-d_6) δ 2.87 (t, 1H), 3.47 (dd, *J* = 17.8, 3.5, 1H), 3.7 (bt, 1H), 3.9 (d, *J* = 11.4, 3H), 4.2 (d, *J* = 17.9, 1H), 6.01 (s, 1H), 6.07 (s, 1H), 6.82 (q, 2H), 7.01 (d, *J* = 7.6, 2H). Evidently the ethyl ester group was also trans-esterified into the methyl ester upon methanol workup. This compound was obtained as a pale gray dry foam (8% yield): MS *m*/*z* 326.19 (MH^+). 324.14 (M−H). ^1H NMR (DMSO-d_6) δ 2.482 (m, 2H), 2.62 (dd, *J* = 13. 9, 4.7, 1H), 3.53 (s, 3H), 4.31 (m, 2H), 4.37 (s, 2H), 4.83 (q, 1H), 6.57 (d, *J* = 8.2, 1H), 6.73 (d, *J* = 8.2, 1H), 7.15 (t, 1H), 7.27 (m, 2H), 8.67 (s, 1H), 9.42 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 14.08, 20.70, 31.88, 35.11, 43.73, 44.18, 51.32, 59.75, 113.38, 114.1, 124.69, 125.71, 126.67, 126.73, 127.06, 127.99, 131.95, 138.45, 142.10, 143.88, 171.17. Anal. calcd for $C_{19}H_{19}NO_4 \cdot 1.0HBr$: C, 54.12; H, 5.60; N, 3.32. Found: C, 54.06; H, 5.51; N, 3.29.

5.9.6. (±)-7-Cyanomethyl-8,9-methylenedioxy-2,3,7,11b-tetrahydro-1*H*-dibenz[*de*,*h*]isoquinoline and (±)-7-cyanomethyldinapsoline (28f). This compound was obtained as a yellow solid (19% yield): MS *m*/*z* 292.08 (MH^+). ^1H NMR (DMSO-d_6) δ 0.71 (m, 1H), 1.01 (m, 1H), 1.98 (m, 1H), 2.29 (m, 1H), 4.22 (m, 4H), 5.94 (s, 1H), 5.98 (s, 1H), 6.73 (d, *J* = 8.2, 1H), 6.80 (d, *J* = 8.0, 1H), 7.22 (m, 3H). Attempted deprotection with BBr_3 in methylene chloride at −78 °C caused extensive decomposition of the starting material.

5.9.7. 5-Chloro-12*H*-benzo[*de*]-1,3-benzodioxol[4,5-*h*]isoquinoline (29a). To a solution of starting material **10** (0.36 g, 1.38 mmol) in CH_2Cl_2 (15 mL) was slowly added SO_2Cl_2 (0.276 mL) at 0 °C. The mixture was stirred at 0 °C for 3 h, and was then quenched with saturated $NaHCO_3$ solution. The product was extracted with CH_2Cl_2, dried over Na_2SO_4, and purified by chromatography (silica gel, EtOAc in hexanes). This compound was obtained as a yellow dry foam (57% yield): ^1H NMR (DMSO-d_6) δ 4.35 (s, 2H), 6.21 (s, 2H), 7.18 (s, 1H), 7.66 (t, 1H), 7.73 (d, *J* = 7.6, 1H), 7.98 (d, *J* = 7.8, 1H), 9.19 (s, 1H), 9.72 (s, 1H).

5.9.8. 5-Nitro-12*H*-benzo[*de*]-1,3-benzodioxol[4,5-*h*]isoquinoline (29b). To a solution of starting material **10** (0.10 g, 0.38 mmol) in acetic acid (4 mL) was added HNO_3 (70%, 0.4 mL). The mixture was stirred at 45 °C until starting material disappeared (about 35 min) and was then poured into ice-water. The resulting mixture

was neutralized by adding saturated $NaHCO_3$ solution and organic materials were extracted into EtOAc. The desired product was purified by chromatography (silica gel, EtOAc in hexanes). This compound **29b** was obtained as a yellow dry foam (65% yield): MS *m*/*z* 306.31 (MH^+). ^1H NMR (DMSO-d_6) δ 4.42 (s, 2H), 6.31 (s, 2H), 7.54 (s, 1H), 7.73 (q, 1H), 7.79 (d, $J=8.0$, 1H), 8.02 (d, $J=8.0$, 1H), 8.31 (s, 1H), 9.2 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 26.93, 103.65, 104.61, 116.44, 118.12, 119.34, 125.27, 127.57, 127.79, 129.14, 129.27, 130.02, 137.46, 143.30, 146.58, 147.23, 152.15. Anal. calcd for $C_{17}H_{10}N_2O_4{\cdot}0.35H_20$: C, 65.34; H, 3.45; N, 8.97. Found: C, 65.39; H, 3.67; N, 8.60.

5.9.9. 5-Amino-12*H*-benzo[*de*]-1,3-benzodioxol[4,5-*h*]isoquinoline (29c). To a solution of starting material **29b** (0.26 g, 0.85 mmol) in MeOH (50 mL) was added $SnCl_2{\cdot}2H_2O$ (0.77 g, 3.4 mmol). The mixture was held at reflux for two h, and then quenched with saturated $NaHCO_3$ solution. The product was extracted into EtOAc, dried over Na_2SO_4, and purified by chromatography (silica gel, EtOAc in hexanes). This compound was obtained as a pale yellow dry foam (57% yield): MS *m*/*z* 277.03 (MH^+). ^1H NMR (CD_3OD) δ 4.26 (s, 2H), 5.94 (s, 2H), 6.42 (s, 1H), 7.61 (d, $J=7.08$, 2H), 7.86 (d, $J=7.2$, 1H), 8.9 (s, 1H), 9.29 (s, 1H).

5.9.10. 5-Fluoro-12*H*-benzo[*de*]-1,3-benzodioxol[4,5-*h*]-isoquinoline (29d). To a solution of starting material **10** (0.10 g, 0.38 mmol) in a mixture of MeCN (20 mL) and CH_3COOH (2 mL) was added SelectFluoro™ (0.35 g, 0.87 mmol). The mixture was stirred at 70 °C for 25 min, and was then quenched with saturated $NaHCO_3$ solution and extracted into EtOAc. The desired product was purified by chromatography (silica gel, EtOAc in hexanes). This compound was obtained as a pale gray dry foam (8% yield): MS *m*/*z* 280.01 (MH^+). ^1H NMR (DMSO-d_6) δ 4.42 (s, 2H), 6.19 (s, 2H), 7.2 (d, $J=10.2$, 1H), 7.74 (m, 2H), 7.95 (d, $J=8.0$, 1H), 9.16 (d, $J=6.2$, 2H).

5.9.11. (±)-11-Chloro-8,9-methylenedioxy-2,3,7,11*b*-tetrahydro-1*H*-dibenz[*de*,*h*]isoquinoline (30a). Using the $NaCNBH_3$ procedure as described, this compound was obtained as a yellow solid (24% yield): MS *m*/*z* 299.97 (MH^+). ^1H NMR (DMSO-d_6) δ 3.48 (dd, $J=17.3$, 5.3, 2H), 4.15 (m, 5H), 6.11 (s, 1H), 6.16 (s, 1H), 7.31 (m, 4H).

5.9.12. (±)-11-Nitro-8,9-methylenedioxy-2,3,7,11*b*-tetrahydro-1*H*-dibenz[*de*,*h*]isoquinoline (30b). Similarly, the nitro derivative was converted into the desired tetrahydroisoquinoline product. This compound was obtained as a yellow solid (57% yield): MS *m*/*z* 311.06 (MH^+). ^1H NMR (DMSO-d_6) δ 1.99 (s, 1H), 4.20 (m, 4H), 4.6 (b, 1H), 4.8 (bd, 1H), 6.27 (s, 1H), 6.32 (s, 1H), 7.37 (m, 3H), 7.60 (s, 1H).

5.9.13. (±)-11-Chlorodinapsoline hydrobromide (31a). This compound was obtained through BBr3 deprotection and was isolated as a brown gum (24% yield): MS *m*/*z* 288.15 (MH^+). 286.23 (M−H). ^1H NMR (DMSO-d_6) δ 3.16 (s, 1H), 4.0 (s, 2H), 4.32 (m, 4H), 6.86 (s, 1H), 7.39 (m, 3H), 8.94 (s, 1H), 9.89 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 32.43, 42.79, 48.60, 114.84, 119.22, 121.84, 124.06, 125.21, 127.04, 128.29, 130.89, 131.06, 132.25, 141.94, 144.61. Anal. calcd for $C_{16}H_{14}ClNO_2{\cdot}HBr$: C, 40.02; H, 4.25; N, 3.72. Found: C, 39.720; H, 4.270; N, 3.870.

5.9.14. (±)-11-Nitrodinapsoline hydrobromide (31b). This compound was likewise obtained as a brown gum (18% yield): MS *m*/*z* 299.04 (MH^+). ^1H NMR (DMSO-d_6) δ 2.61 (t, 1H), 3.63 (m, 1H), 4.10 (bs, 2H), 4.36 (bs, 2H), 5.03 (m, 1H), 7.41 (m, 3H), 7.61 (bs, 1H).

5.9.15. (±)-2-Methyl-8,9-methylenedioxy-2,3,7,11*b*-tetrahydro-1*H*-dibenz[*de*,*h*]isoquinoline (34a). To a solution of 12H-benzo[*de*]-1,3-benzodioxol[4,5-*h*]-isoquinoline **10** (0.38 mmol) in warm dichloroethane (4 mL), methyl iodide (12.8 mmol) was added and a yellow suspension formed after a few minutes. The mixture was warmed to 40 °C with stirring for 20 min. After all the starting material was gone, nitrogen was passed into the reaction vessel to remove both the solvent and the excess MeI and the residue was further dried under high vacuum. The resulting yellow solids were resuspended in dry THF, followed by the sequential addition of sodium triacetoxyborohydride (0.4 g) and sodium cyanoborohydride (0.12 g). After a few minutes, the suspension turned orange and stirring was continued for 20 min. Saturated NH_4Cl and HCl (2.0 N) were added to the suspension to form two layers, which were separated. The organic layer was evaporated and dried under vacuum. Partial isolation and purification of product was achieved by recrystallization to give the title compound (0.047 g). The mother liquor was further purified by filtration over a bed of silica gel type-H to afford a second portion of the desired product (0.04 g, totaling 82% yield): ^1H NMR (DMSO-d_6) δ 7.39 (d, 1H, $J=7.4$), 7.28 (t, 1H, $J=7.5$), 7.13 (d, 1H, $J=7.3$), 6.86 (d, 1H, $J=8.0$), 6.72 (d, 1H, $J=8.0$), 6.09 (s, 1), 6.02 (s, 1H), 4.60–4.25 (m, 3H), 4.20–4.03 (m, 2H), 3.75–3.68 (m, 1H), 3.60–3.40 (m, 1H), 3.02 (s, 3H); LC/MS *m*/*z* 280.13 (MH^+) as a single homogeneous peak.

5.9.16. (±)-2-Methyl-8,9-dihydroxy-2,3,7,11b-tetrahydro-1*H*-dibenz[*de*,*h*]isoquinoline, (±)-2-methyldinapsoline hydrobromide (35a). To a solution of **34a** (0.16 mmol) in dichloromethane (4 mL) cooled to −78 °C, boron tribromide (1 M in dichloromethane, 0.77 mmol) was added. The reaction solution was stirred at −78 °C for 2 h and then warmed to room temperature overnight. The solution was cooled to −l78 °C and dry methanol was added to quench the reaction. After stirring for 10 min, the solvent was removed and dry methanol was added again. The process was repeated three times. Purification was performed by recrystallization from MeOH/CH_2Cl_2 to obtain the title compound (0.035 g): ^1H NMR (CD_3OD) δ 7.37 (d, 1H, $J=7.3$), 7.29 (t, 1H, $J=7.4$), 7.11 (d, 1H, $J=7.3$), 6.72 (d, 1H, $J=8.2$), 6.59 (d, 1H, $J=8.5$), 4.7–4.39 (m, 3H), 4.20–4.05 (m, 1H) 3.70–3.40 (m, 2H), 3.20 (s, 3H); LC/MS *m*/*z* 268.16 (MH^+) as a single homogeneous peak.

5.9.17. (±)-2-Propyl-8,9-methylenedioxy-2,3,7,11*b*-tetrahydro-1*H*-dibenz[*de*,*h*]isoquinoline (34b). Likewise **34b** was prepared from **10** and *n*-propyl iodide in 40% yield: ^1H NMR ($CDCl_3$) δ 7.18-7.10 (m, 2H), 6.97 (d, 1H,

$J=6.9$), 6.72 (s, 2H), 5.97 (dd, 2H, $J=1.4$, 25.4), 4.05 (t, 2H, $J=17.5$), 3.94–3.80 (m, 1H), 3.84–3.77 (m, 1H), 3.62 (dd, 1H, $J=3.5$, 17.4), 3.43 (d, 1H, $J=14.8$), 2.67–2.54 (m, 3H), 1.79–1.69 (m, 2H), 1.02 (t, 3H, $J=7.4$); LC/MS m/z 308.15 (MH^+) as a single homogeneous peak.

5.9.18. (±)-2-Propyl-8,9-dihydroxy-2,3,7,11b-tetrahydro-1*H*-dibenz[*de*,*h*]isoquinoline, (±)-2-Propyldinapsoline hydrobromide (35b). Simiarly, **35b** was prepared from **34b** in 88% yield: ^1H NMR (CD_3OD) δ 7.36 (d, 1H, $J=7.1$), 7.29 (t, 1H, $J=7.$ 6), 7.13 (d, 1H, $J=7.4$), 6.72 (d, 1H, $J=8.2$), 6.62 (d, 1H, $J=8.2$), 4.69 (d, 1H, $J=14.7$), 4.55–4.49 (m, 1H), 4.42 (d, 1H, $J=18.0$), 4.20–4.10 (m, 1H), 3.58–3.38 (m, 5H), 1.98 (q, 2H, $J=7.53$, 15.4), 1.13 (t, 3H, $J=7.4$); LC/MS m/z 296.15 (MH^+) as a single homogeneous peak.

5.9.19. 8-Methyl-12*H*-benzo[*de*]-1,3-benzodioxol[4,5-*h*]-isoquinoline (33d). To a solution of **10** (0.15 g) in a 1:1 (v/v) mixture of diethyl ether/THF (7 mL) was added boron trifluoride etherate (0.11 mL). The mixture was cooled to −78 °C, and methyllithium (0.61 mL, 1.4 M in ether) was added dropwise. Stirring was continued for an hour at −78 °C, then saturated NH_4Cl solution was added to quench the reaction. The mixture was allowed to warm to room temperature, the aqueous layer was extracted (2×10 mL) with ethyl acetate, and the combined organic layers were washed with saturated NaCl solution, dried over sodium sulfate, filtered, and concentrated. Purification was performed by silica column chromatography to obtain the *fully aromatized* form of **33d** in 37% yield: ^1H NMR ($CDCl_3$) δ 8.83 (s, IH), 7.94–7.91 (m, 1H), 7.61–7.52 (m, 3H), 6.84 (d, 1H, $J=8.4$), 6.06 (s, 2H), 4.39 (s, 2H), 2.91 (s, 3H); LC/MS m/z 276.15 (MH^+) as a single homogeneous peak.

5.9.20. (±)-3-Methyl-8,9-dihydroxy-2,3,7,11b-tetrahydro-1*H*-dibenz[*de*,*h*]isoquinoline, (±)-3-methyldinapsoline hydrobromide (35d). The reduction and the subsequent deprotection were carried out as previously described to give **35d** in 75% yield: ^1H NMR (CD_3OD) δ 7.37–7.24 (m, 3H), 6.71 (d, 1H, $J=8.0$), 6.58 (d, 1H, $J=8.0$), 4.72–4.65 (m, 1H), 4.45–4.34 (m, 2H), 4.12–4.03 (m, 1H), 3.55–3.43 (m, 2H), 1.78 (d, 3H, $J=6.7$); LC/MS m/z 268.16 (MH^+) as a single homogeneous peak.

5.9.21. 8-Butyl-12*H*-benzo[*de*]-1,3-benzodioxol[4,5-*h*]isoquinoline (33e). Likewise **10** was treated with *n*-butyl lithium to give 33e in 46% yield: ^1H NMR ($CDCl_3$) δ 8.86 (s, 1H), 8.03 (d, 1H, $J=6.8$), 7.63–7.59 (m, 3H), 6.87 (d, 1H, $J=8.3$), 6.08 (s, 2H), 4.44 (s, 2H), 3.33 (t, 2H, $J=7.6$), 1.89–1.82 (m, 2H), 1.58–1.46 (m, 2H), 1.00 (t, 3H, $J=7.3$); LC/MS m/z 318.15 (MH^+) as a single homogeneous peak.

5.9.22. (±)-3-Butyl-8,9-dihydroxy-2,3,7,11b-tetrahydro-1*H*-dibenz[*de*,*h*]isoquinoline (34e) and (±)-3-*n*-butyldinapsoline hydrobromide (35e). The reduction and the subsequent deprotection were performed as previously described to give **34e** in 95% yield: ^1H NMR ($CDCl_3$) δ 7.33–7.31 (m, 2H), 7.15–7.13 (m, 1H), 6.74 (d, 1H, $J=8.0$), 6.63 (d, 1H, $J=8.0$), 5.99 (dd, 2H, $J=1.1$, 20.9), 4.56–4.50 (m, 1H), 4.29–4.10 (m, 3H), 3.68 (dd, 1H, $J=2.9$, 17.2), 3.28 (t, 1H, $J=11.8$), 2.24–2.02 (m, 2H), 1.50–1.37 (m, 4H), 1.02–0.86 (m, 3H); LC/MS calcd for $C_{21}H_{23}NO_2$ (M^+): 321.17. Found: (MH^+) 322.14; and **35e** in 82% yield: ^1H NMR (CD_3OD) δ 7.36–7.25 (m, 3H), 6.72 (d, 1H, $J=8.2$), 6.60 (d, 1H, $J=8.25$), 4.68–4.65 (m, 1H), 4.38–4.30 (m, 2H), 4.10–4.04 (m, 1H), 3.53–3.41 (m, 2H), 2.40–2.22 (m, 1H), 2.08–1.92 (m, 1H), 1.60–1.40 (m, 4H), 1.15–0.90 (m, 3H); LC/MS m/z 310.14 (MH^+) as a single homogeneous peak.

5.9.23. (±)-2,3-Dimethyl-8,9-methylenedioxy-2,3,7,11*b*-tetrahydro-1H-dibenz[*de*,*h*]isoquinoline (34g). To a solution of **10** (0.3 g) in warm dichloroethane (10 mL), was added CH_3I (2.4 mL). The reaction was warmed to 40 °C for 30 min and a yellow-orange suspension was formed. All the volatile solvents were removed by a stream of nitrogen and the residue was dried under high vacuum. The residue was resuspended in THF, cooled to −78 °C and methyllithium (2.5 mL, 1.4 M in diethyl ether) was added. The solution was stirred for 20 min at −78 °C, then slowly warmed to 0 °C for an hour. Saturated NH_4Cl (10 mL) and hydrochloric acid (2 N, 10 mL) were added to the solution followed by sodium cyanoborohydride (0.72 g). The organic layer was separated and concentrated, the desired product was obtained after a flash silica gel (type-H) column eluted with mixtures of hexanes and ethyl acetate to give **34g** in 71%: ^1H NMR ($CDCl_3$) δ 7.20–7.11 (m, 3H), 6.73 (q, 2H, $J=8.2$, 13.1), 5.97 (dd, 2H, $J=1.2$, 23.2), 4.09 (d, 1H, $J=17.3$), 3.99-3.94 (m, 1H), 3.74 (dd, 1H, $J=5.4$, 11.2), 3.66 (dd, 1H, $J=3.6$, 17.3), 3.52–3.47 (m, 1H), 2.73 (t, 1H, $J=11.0$), 2.64 (s, 3H), 1.56 (d, 3H, $J=6.4$); LC/MS m/z 294.15 (MH^+) as a single homogeneous peak.

5.9.24. (±)-2,3-Dimethyl-8,9-dihydroxy-2,3,7,11*b*-tetrahydro-1H-dibenz[*de*,*h*]isoquinoline, (±)-2,3-dimethyldinapsoline hydrobromide (35g). Likewise the desired product was obtained as described above in 95% yield: ^1H NMR (CD_3OD) δ 7.35–7.24 (m, 3H), 6.72 (d, 1H, $J=8.2$), 6.63 (d, 1H, $J=7.$ 6), 5.67–5.55 (m, 1H), 4.42 (d, 1H, $J=17.6$), 4.15–4.05 (m, 1H), 3.65–3.46 (m, 2H), 3.35–3.20 (m, 4H), 1.84 (d, 3H, $J=6.4$); LC/MS m/z 282.23 (MH^+) as a single homogeneous peak.

5.9.25. 8-Perfluorobutyl-12H-benzo[*de*]-1,3-benzodioxol[4,5-*h*]isoquinoline (33h). To a suspension of **10** (0.2 g) in ether (8 mL) was added boron trifluoride etherate (0.19 mL). The reaction was cooled to −78 °C, then perfluorobutyl iodide (0.26 mL) was added, followed by methyllithium (1.1 mL, 1.4 M in diethyl ether) dropwise. Stirring was continued for an hour at −78 °C before quenching with saturated NH_4Cl solution. Extractive workup and concentration gave a gummy crude product that was further purified by a silica gel (Type-H) column to give 9% of the desired product, with the remaining mass being mostly unreacted starting material: ^1H NMR ($CDCl_3$) δ 9.08 (s, 1H), 6.96 (d, 1H, $J=8.2$), 7.69–7.64 (m, 3H), 6.89 (d, 1H, $J=8.3$), 6.11 (s, 2H), 4.56 (s, 2H); LC/MS m/z 480.07 (MH^+) as a single homogeneous peak.

5.9.26. (±)-3-Perfluorobutyl-8,9-methylenedioxy-2,3,7,11*b*-tetrahydro-1H-dibenz[*de*,*h*]isoquinoline (34h). Using the catalytic hydrogenation procedure (PtO_2/

HOAc/H_2, Method B) described for compound (±)-**11**,[2] **34h** was obtained in 74% yield: ^{1}H NMR ($CDCl_3$) δ 7.36–7.31 (m, 1H), 7.27–7.17 (m, 2H), 6.71 (q, 2H, J = 8.2, 15.3), 5.99 (dd, 2H, J = 1.4, 27.3), 4.68 (dd, 1H, J = 6.2, 24.5), 4.16 (d, 1H, J = 17.2), 3.86–3.44 (m, 4H); LC/MS m/z 484.05 (MH^+) as a single homogeneous peak.

5.9.27. (±)-3-Perfluorobutyl-8,9-dihydroxy-2,3,7,11*b*-tetrahydro-1H-dibenz[*de*,*h*]isoquinoline, ((±)-3-perfluorobutyldinapsoline hydrobromide, 35h). Likewise **35h** was obtained in 70% yield: ^{1}H NMR (CD_3OD) δ 7.32–7.28 (m, 1H), 7.19–7.12 (m, 2H), 6.67 (d, 1H, J = 8.2), 6.56 (d, 1H, J = 8.2), 4.71 (dd, 1H, J = 7.5, 25.5), 4.36 (d, 1H, J = 17.8), 3.78–3.71 (m, 1H), 3.58–3.53 (m, 1H), 3.41 (dd, 1H, J = 3.6, 17.7), 3.28–3.24 (m, 1H); LC/MS m/z 472.17 (MH^+) as a single homogeneous peak.

5.9.28. (±)-2-Methyl-3-butyl-8,9-methylenedioxy-2,3,7,11*b*-tetrahydro-1H-dibenz[*de*,*h*]isoquinoline (34i). The experimental procedure was identical to that for **34g** except that *n*-butyllithium (2.5 M in hexanes) was used instead of methyllithium. Purification was performed by column filtration to obtain **34i** in 39% yield: ^{1}H NMR ($CDCl_3$) δ 7.21–7.11 (m, 3H), 6.73 (q, 2H, J = 8.0, 18.8), 5.97 (dd, 2H, J = 1.2, 23.3), 4.08 (d, 1H, J = 17.3), 3.95–3.85 (m, 1H), 3.75–3.69 (m, 2H), 3.59–3.51 (m, 1H), 2.72–2.60 (m, 1H), 2.57 (s, 3H), 2.05–1.85 (m, 2H), 1.41–1.25 (m, 4H), 0.88 (t, 3H, J = 7.1); LC/MS m/z 336.27 (MH^+) as a single homogeneous peak.

5.9.29. (±)-2-Methyl-3-butyl-8,9-dihydroxy-2,3,7,11*b*-tetrahydro-1H-dibenz[*de*,*h*]isoquinoline (35i). Purification was achieved by precipitation of product with EtOH/CH_2Cl_2 to obtain **35i** in 54% yield: ^{1}H NMR (CD_3OD) δ 7.39–7.30 (m, 2H), 7.22 (d, 1H, J = 7.3), 6.70 (q, 2H, J = 8.2, 17.6), 4.62–4.69 (m, 1H), 4.43–4.36 (m, 2H), 4.20–4.09 (m, 1H), 3.56 (dd, 2H, J = 3.7, 17.9), 3.15 (s, 3H), 2.30–2.15 (m, 2H), 1.50–1.10 (m, 4H), 0.98–0.85 (m, 3H); LC/MS m/z 324.20 (MH^+) as a single homogeneous peak.

5.9.30. 6-Fluoroisoquinoline (36). Aminoacetaldehyde diethyl acetal (21.0 g, 158 mmol) was added to a solution of 4-fluorobenzaldehyde (19.2 g, 155 mmol) in $CHCl_3$ (400 mL). The solvents in the mixture were removed by distillation, and azeotropic removal of water. The residue was dissolved in chlorobenzene (250 mL) and the solution was cooled to −10 °C. After addition of ethyl chloroformate (15.0 mL, 157 mmol), stirring was continued at −10 °C under N_2 for 10 min. Trimethyl phosphite (22.0 mL, 186 mmol) was added, and the resulting mixture was warmed to room temperature and stirred under N_2 for 40 h. After the solution was cooled to 0 °C, $TiCl_4$ (100.0 g, 527 mmol) was added slowly. The reaction mixture was stirred at 100 °C under N_2 for 24 h (precipitates were formed in about 7 h). After cooling to room temperature, the mixture was diluted with ethyl acetate and was basified in an ice bath using 5 N NaOH. The product was extracted with a mixture of ethyl acetate and hexanes (1:2, v/v). The organic layers were re-extracted with 1 N HCl. The aqueous layer was basified to pH > 10 by 5 N NaOH and was extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried over Na_2SO_4. Evaporation of solvent yielded **36** as a pale yellow solid (7.70 g, 52.4 mmol, 34% yield): mp 48–50 °C; MS (ESI) m/z 148 (MH^+); ^{1}H NMR (DMSO-d_6) δ 9.33 (s, 1H), 8.51 (d, 1H, J = 6.0), 8.25 (dd, 1H, J = 9.0, 6.0), 7.83 (d, 1H, J = 5.7), 7.77 (dd, 1H, J = 10.0, 2.4), 7.60 (td, 1H, J = 9.0, 2.4). Anal. calcd for C_9H_6FN: C, 73.46; H, 4.11; N, 9.52. Found: C, 73.19; H, 3.95, N, 9.49.

5.9.31. α-(5-Bromo-1,3-benzodioxol-4-yl)-6-fluoro-5-isoquinolinemethanol (38). A solution of lithium diisopropylamide (103.0 mL of 1.5 M in cyclohexane, 155.0 mmol) was added dropwise to a cooled (−78 °C) solution of 6-fluoroisoquinoline in THF (500 mL). The resulting mixture was stirred at −78 °C under nitrogen for 150 min followed by addition of 2-bromo-5,6-methylenedioxybenzaldehyde **3**[2] (37.75 g, 165.0 mmol). Stirring was continued at −78 °C for 45 min and then at room temperature for 75 min. The reaction was quenched by adding saturated aqueous NH_4Cl solution. The product was extracted with ethyl acetate. The organic layers were combined and dried over Na_2SO_4. Chromatography (silica gel, 50% EtOAc in hexanes) provided **38** as a pale yellow solid (23.0 g, 61.2 mmol, 98% yield): mp 149–152 °C; MS (ESI) m/z 377 (MH^+); ^{1}H NMR (DMSO-d_6) δ 9.30 (s, 1H), 8.52 (d, 1H, J = 6.0), 8.40 (d, 1H, J = 6.0), 8.18 (dd, 1H, J = 9.0, 5.4), 7.50 (dd, 1H, J = 10.8, 9.0), 7.06 (d, 1H, J = 8.3), 6.83 (dd, 1H, J = 8.1, 3.0), 6.62 (d, 1H, J = 5.1), 6.32 (d, 1H, J = 5.1), 5.99 (s, 1H), 5.94 (s, 1H). Anal. calcd for $C_{17}H_{11}BrFNO_3$: C, 54.28; H, 2.95; N, 3.72. Found: C, 53.90; H, 2.76, N, 3.45.

5.9.32. 6-Fluorodinapsoline hydrobromide (39). Product **38** from the previous step was reduced using the exact procedure as described for compound **7** to give 6-fluoro-5-[(5-bromo-1,3-benzodioxol-4-yl)methyl]isoquinoline as a white solid (84% yield): mp 139–142 °C; MS (ESI) m/z 361 (MH^+); ^{1}H NMR (DMSO-d_6) δ 9.31 (s, 1H), 8.51 (d, 1H, J = 6.0), 8.18 (dd, 1H, J = 9.0, 5.4), 7.90 (d, 1H, J = 6.0), 7.56 (t, 1H, J = 8.4), 7.10 (d, 1H, J = 8.1), 6.79 (d, 1H, J = 8.4), 5.92 (s, 2H), 4.42 (s, 2H). Anal. calcd for $C_{17}H_{11}BrFNO_2 \cdot 1.1CH_2Cl_2$: C, 47.93; H, 2.93; N, 3.09. Found: C, 48.12; H, 2.66, N, 2.90. Likewise the free radical initiated cyclization of **39** was carried out as described for 6-fluoro-5-[(5-bromo-1,3-benzodioxol-4-yl)methyl]isoquinoline to give 6-fluoro-12H-benzo[*de*]-1,3-benzodioxol[4,5-*h*]isoquinoline in 51% yield): mp 233–235 °C; MS (ESI) m/z 280 (MH^+); ^{1}H NMR (DMSO-d_6) δ 9.13 (d, 2H, J = 9.6), 8.09 (dd, 1H, J = 9.0, 5.4), 7.87 (d, 1H, J = 8.7), 7.63 (t, 1H, J = 9.0), 7.00 (d, 1H, J = 9.0), 6.16 (s, 2H), 4.31 (s, 2H). Anal. calcd for $C_{17}H_{10}FNO_2 \cdot 0.073HBr$: C, 71.59; H, 3.56; N, 4.91. Found: C, 71.63; H, 3.95, N, 4.78. The $NaCNBH_3$ reduction was carried out as described for **11** to give (±)-8,9-methylenedioxy-2,3,7,11*b*-tetrahydro-1H-6-fluoro-dibenz[*de*,*h*]isoquinoline in 72% yield: mp 125–127 °C; MS (ESI) m/z 284 (MH^+); ^{1}H NMR (DMSO-d_6) δ 6.99 (d, 2H, J = 7.5), 6.80 (d, 1H, J = 8.1), 6.75 (d, 1H, J = 8.1), 6.07 (s, 1H), 6.00 (s, 1H), 4.15 (d, 1H, J = 18), 3.96–3.81 (m, 3H), 3.67 (m, 1H), 3.43 (dd, 1H, J = 18, 3.6), 2.82 (dd, 1H, J = 12.0, 10.8). Finally, the methylenedioxy protecting group was removed by BBr_3

deprotection to furnish the desired product as a pale white solid in 84% yield: mp > 275 °C; MS (ESI) *m/z* 272 (MH^+); ^1H NMR (DMSO-d_6) δ 9.33 (br. s, 3H), 8.64 (s, 1H), 7.17 (m, 2H), 6.73 (d, 1H, *J* = 8.1), 6.57 (d, 1H, *J* = 8.1), 4.48 (d, 1H, *J* = 19.2), 4.35–4.25 (m, 3H), 4.00 (m, 1H), 3.32–3.17 (m, 2H). Anal. calcd for $C_{16}H_{14}FNO_2 \cdot 0.95HBr \cdot 0.40H_2O$: C, 54.08; H, 4.47; N, 3.94. Found: C, 53.78; H, 4.30, N, 3.68.

5.9.33. Chiral separation of (±)-8,9-methylenedioxy-2,3,7,11*b*-tetrahydro-1H-6-fluoro-dibenz[*de*,*h*]isoquinoline, (±)-39. The following HPLC chiral separation procedure is essentially identical to the one described previously. Preparative HPLC on a Chiralcel OD column using 5% EtOH/hexanes + 0.1% diethylamine at a flow rate of 65 mL/min was employed with a loading per run up to 1 g/10 mL EtOH per injection. Baseline separation was achieved under these conditions. (−)-8,9-methylenedioxy - 2,3,7,11*b* - tetrahydro - 1*H* - 6 - fluorodibenz[*de,h*]isoquinoline was obtained as a white solid (89% recovery): mp 163–165 °C; $[\alpha]_D$ −83.5° (*c* 0.010, MeOH); chiral analytical HPLC was performed on an analytical Chiralcel OD column at a reduced flow rate; enantiomeric purity was estimated to be in excess of 99%, with no discernible signal from the other enantiomer. Anal. calcd for $C_{17}H_{14}FNO_2$: C, 72.07; H, 4.98; N, 4.94. Found: C, 71.80; H, 5.00, N, 4.71; MS and ^1H NMR (identical to the racemate). Likewise (+)-8,9-methylenedioxy - 2,3,7,11*b* - tetrahydro - 1*H* - 6 - fluorodibenz[*de,h*]isoquinoline was resolved with 90% recovery: $[\alpha]_D$ +82.8° (*c* 0.010, MeOH); chiral analytical HPLC (single peak); mp, elemental analysis, MS and ^1H NMR were identical to that of the (−)-enantiomer.

5.9.34. Chiral 6-fluorodinapsoline hydrobromide. The resolved (−) and (+)-isomers from above were deprotected as usual to give (−)-6-fluorodinapsoline hydrobromide as a pale solid (84% yield): $[\alpha]_D$ −43.5° (*c* 0.010, MeOH) and (+)-6-fluorodinapsoline in 68% yield: $[\alpha]_D$ +42.8° (*c* 0.010, MeOH). NMR, MS and CHN of these compounds were identical to that of racemate.

5.10. Preparation of 4-hydroxydinapsoline hydrobromide (55)

5.10.1. 5-Bromo-8-methoxy isoquinoline (41). A solution of 3-bromo-6-methoxybenzaldehyde (25.0 g, 116 mmol) and aminoacetaldehyde diethyl acetal (15.5 g, 117 mmol) in benzene (200 mL) was heated to reflux in a Dean-Stark apparatus. Approximately 1 equivalent of water was collected after 2 h. The reaction was cooled to room temperature, and the solvent removed in vacuo. The resulting material was dissolved in THF (100 mL) and cooled to −10 °C. Ethyl chloroformate (11.8 mL, 123 mmol) was added over 5 min. After 10 min of additional stirring, the ice bath was removed. Trimethylphosphite (17.5 mL, 148 mmol) was then added, the reaction was allowed to stir for another 16 h, and the solvents were removed in vacuo. Toluene was added and removed in vacuo, and the process was repeated twice to remove residual trimethylphosphite. The residue was redissolved in chloroform (220 mL) followed by the *SLOW* addition of titanium (IV) chloride (38.3 mL, 349 mmol). After addition was complete, the reaction was brought to reflux for 36 h. After cooling to room temperature, the reaction was poured into 4 equiv of 10 M NaOH, with cooling as necessary. The thick residue was filtered over sand, and washed with methanol and then CH_2Cl_2. The filtrate was concentrated; the resulting aqueous suspension was extracted three times with methylene chloride and the combined organic extracts were dried over $MgSO_4$. The extracts were concentrated in vacuo, and finally purified by silica gel chromatography eluted with mixtures of hexanes/ethyl acetate to provide 9.65 g (35%) of pure product. ^1H ($CDCl_3$) δ 9.64 (s, 1H), 8.65 (d, 1H, *J* = 6.2), 7.97 (d, 1H, *J* = 6.2), 7.90 (d, 1H, *J* = 8.4), 6.83 (d, 1H, *J* = 8.4), 4.05 (s, 3H).

5.10.2. 8-Methoxyisoquinoline-5-carboxaldehyde. The formylation was done essentially as described in Scheme 2 to give 75% yield of the desired product: ^1H ($CDCl_3$) δ 10.22 (s, 1H), 9.71 (s, 1H), 9.07 (d, 1H, *J* = 6.0), 8.73 (d, 1H, *J* = 6.0), 8.16 (d, 1H, *J* = 8.2), 7.04 (d, 1H, *J* = 8.2), 4.16 (s, 3H).

5.10.3. α-(5-Bromo-1,3-benzodioxol-4-yl)-8-methoxy-5-isoquinolinemethanol (46). The condensation was performed in accordance with the procedure described in Scheme 2, and the desired product was isolated in 68% yield: ^1H ($CDCl_3$) δ 9.62 (s, 1H), 8.59 (d, 1H, *J* = 6.2), 8.06 (d, 1H, *J* = 6.2), 7.34 (d, 1H, *J* = 8.3), 7.10 (d, 1H, *J* = 8.3), 6.76 (d, 1H, *J* = 8.2), 6.72 (d, 1H, *J* = 8.3), 6.66 (br s, 1H), 5.98 (d, 1H, *J* = 1.3), 5.94 (d, 1H, *J* = 1.3), 4.00 (s, 3H), 3.5 (br s, 1H).

5.10.4. 5-[(5-Bromo-1,3-benzodioxol-4-yl)methyl]-8-methoxyisoquinoline. The silane reduction was done as described in Scheme 3; the desired product was obtained in 79% yield: ^1H ($CDCl_3$) δ 9.67 (s, 1H), 8.61 (d, 1H, *J* = 6.1), 7.94 (d, 1H, *J* = 6.1), 7.14 (d, 1H, *J* = 8.1), 7.12 (d, 1H, *J* = 8.3), 6.79 (d, 1H, *J* = 8.1), 6.69 (d, 1H, *J* = 8.3), 5.94 (s, 2H), 4.37 (s, 2H), 4.00 (s, 3H).

5.10.5. 9-Methoxy-12H-benzo[*de*]-1,3-benzodioxolo[4,5-*h*]isoquinoline (49). The free radical initiated cyclization was carried out in exactly the same way as described for compound **10** in Scheme 3; the desired product was isolated in about 15% yield along with uncyclized starting material and some *des*-bromo byproduct: ^1H ($CDCl_3$) δ 9.41 (s, 1H), 8.95 (s, 1H), 7.61 (d, 1H, *J* = 8.4), 7.50 (dt, 1H, *J* = 1.5, 7.9), 6.90 (d, 1H, *J* = 8.0), 6.84 (d, 1H, *J* = 8.3), 6.06 (br s, 2H), 4.33 (s, 2H), 4.02 (s, 3H).

5.10.6. (±)-4-Methoxy-8,9-methylenedioxy-2,3,7,11*b*-tetrahydro-1H-dibenz[*de*,*h*]isoquinoline (52). The selective ring reduction was done in essentially the same way as described for compound **11** in Scheme 3; the desired product was isolated in 52% yield: ^1H ($CDCl_3$) δ 7.14 (d, 1H, *J* = 8.2), 6.73–6.67 (m, 3H), 6.00 (d, 1H, *J* = 1.4), 5.92 (d, 1H, *J* = 1.4), 4.27–3.05 (m, 7H), 3.80 (s, 3H), 2.24 (br s, 1H).

5.10.7. 4-Hydroxydinapsoline hydrobromide (55). To a solution of **52** (40.9 mg, 139 μmol) in 2 mL CH_2Cl_2 at −78 °C was added a 1 M solution of boron tribromide

(665 μL, 665 μmol) dropwise. The solution was stirred at this temperature for 4 h, and was then allowed to warm to room temperature. After 16 h, the reaction was chilled to −78 °C, followed by the slow addition of dry methanol (2 mL). The solvents were removed in vacuo. More methanol was added, and the mixture was brought to reflux for an h. The solvents were removed in vacuo. Chromatography on C_{18} media using water as eluent provided the desired pure compound, 25.0 mg (42%): ^{1}H (CD_3OD) δ 7.17 (d, 1H, J = 8.2), 6.73 (d, 1H, J = 8.2), 6.72 (d, 1H, J = 8.1), 6.60 (d, 1H, J = 8.3), 5.1–4.7 (m, solvent, 4H), 4.51–4.04 (m, 6H), 3.45–3.32 (m, solvent, 1H); ^{13}C (CD_3OD) δ 151.97, 143.63, 141.87, 132.47, 127.21, 127.01, 126.90, 124.19, 113.58, 113.35, 112.21, 112.05, 48.35–46.65 (solvent), 44.32, 33.25, 27.29.

5.11. Preparation of 6-ethyldinapsoline hydrobromide (56)

5.11.1. 6-Ethylisoquinoline (42). This compound was obtained as an orange oil (57% yield): MS (ESI) m/z 158 (MH^+); ^{1}H NMR (DMSO-d_6) δ 9.22 (d, 1H, J = 4.0), 8.44 (d, 1H, J = 6.0), 8.00 (dd, 1H, J = 9.0, 6.0), 7.70 (m, 2H), 7.53 (dd, 1H, J = 10.0, 2.4), 2.76 (q, 2H, J = 7.5), 1.22 (t, 3H, J = 7.5).

5.11.2. 5-Bromo-6-ethylisoquinoline (43). This compound was prepared in accordance with the bromination procedure as described previously.[2] The brominated desired product was obtained as an orange solid (70% yield): ^{1}H NMR (DMSO-d_6) δ 9.26 (s, 1H), 8.57 (d, 1H, J = 6.0), 8.06 (d, 1H, J = 8.4), 7.90 (d, 1H, J = 6.0), 7.62 (d, 1H, J = 8.4), 2.91 (q, 2H, J = 7.5), 1.22 (t, 3H, J = 7.5).

5.11.3. α-(5-Bromo-1,3-benzodioxol-4-yl)-6-ethyl-5-isoquinolinemethanol (47). This compound was obtained as a brown gum (24% yield): MS m/z 386.05 (MH^+). ^{1}H NMR (DMSO-d_6) δ 1.10 (t, 3H), 2.90 (q, 2H), 5.75 (s, 1H), 5.79 (s, 1H), 6.23 (d, J = 5.13, 1H), 6.63 (d, J = 5.13, 1H), 6.82 (d, J = 8.25, 1H), 7.13 (d, J = 8.28, 1H), 7.49 (d, J = 8.43, 1H), 7.97 (d, J = 8.34, 1H), 8.33 (d, J = 6.21, 1H), 8.39 (d, J = 6.18, 1H), 9.18 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 15.42, 27.09, 70.24, 101.45, 109.11, 115.13, 119.05, 125.30, 126.04, 127.74, 133.87, 135.14, 142.33, 143.63, 145.24, 146.82, 147.78, 152.77.

5.11.4. 11-Ethyl-12H-benzo[*de*]-1,3-benzodioxolo[4,5-*h*]-isoquinoline (50). Silane deoxygenation of **47** (precursor of **50**). This compound was obtained as a yellow solid (19% yield): MS m/z 372.08 (MH^+). ^{1}H NMR (DMSO-d_6) δ 1.12 (t, 3H), 2.88 (q, 2H), 4.46 (s, 2H), 5.65 (s, 2H), 6.76 (d, J = 8.3, 1H), 7.15 (d, J = 8.3, 1H), 7.54 (d, J = 8.4, 1H), 7.78 (d, J = 6, 1H), 7.96 (d, J = 8.4, 1H), 8.41 (d, J = 6.1, 1H), 9.2 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 15.22, 27.02, 29.48, 101.48, 108.43, 115.50, 117.32, 121.92, 125.74, 126.95, 127.51, 129.32, 130.36, 135.40, 143.12, 145.60, 147.09, 147.18, 152.90. Anal. calcd for $C_{19}H_{16}BrNO_2$: C, 61.64; H, 4.36; N, 3.78. Found: C, 61.65; H, 4.54; N, 3.65. Compound **50** was obtained as a brown gum (18% yield): MS m/z 290.13 (MH^+). ^{1}H NMR (DMSO-d_6) δ 1.27 (t, 3H), 2.76 (q, 2H), 4.23 (s, 2H), 6.13 (s, 2H), 6.95 (d, J = 8.3, 1H), 7.57 (d, J = 8.34, 1H), 7.81 (d, J = 8.4, 1H), 7.91 (d, J = 8.4, 1H), 9.03 (d, J = 6.9, 2H). ^{13}C NMR (DMSO-d_6) δ 13.51, 24.55, 25.61, 101.89, 107.74, 116.42, 117.03, 123.38, 123.73, 125.50, 126.72, 128.56, 129.580, 136.02, 142.88, 145.52, 147.01, 150.72. Anal. calcd for $C_{19}H_{15}NO_2 \cdot 0.073H_20 \cdot 0.049C_6H_{16}NBr$: C, 77.355; H, 5.361; N, 4.905. Found: C, 77.41; H, 5.52; N, 5.12.

5.11.5. 6-Ethyldinapsoline hydrobromide (56). $NaCNBH_3$ reduction of **50** was conducted as usual to give **53**. This compound was obtained as yellow crystals (57% yield): MS m/z 294.17 (MH^+). ^{1}H NMR (DMSO-d_6) δ 1.17 (t, 3H), 2.71 (q, 2H), 2.91 (t, 1H), 3.92 (m, 4H), 4.17 (d, J = 17.4, 1H), 6.01 (s, 1H), 6.04 (s, 1H), 6.76 (t, 2H), 6.87 (d, J = 7.7, 1H), 6.995 (d, J = 7.7, 1H). The 6-ethyldinapsoline was obtained by the standard BBr_3 deprotection procedure. Compound **56** was obtained as a yellow solid (24% yield): MS m/z 282.16 (MH^+). ^{1}H NMR (DMSO-d_6) δ 1.19 (t, 3H), 2.75 (q, 2H), 3.47 (t, 1H), 4.11 (m, 1H), 4.39 (m, 3H), 4.68 (d, J = 18.15, 1H), 6.61 (d, J = 7.83, 1H), 6.73 (d, J = 8.28, 1H), 7.07 (d, J = 7.95, 1H), 7.17 (d, J = 7.86, 1H), 8.57 (s, 1H), 9.26 (s, 1H). ^{13}C NMR (CD_3OD) δ 14.62, 15.69, 25.53, 27.46, 35.11, 46.44, 46.69, 114.05, 115.27, 124.99, 125.42, 125.75, 128.51, 128.69, 133.43, 136.26, 142.54, 145.25, 145.27, 145.33. Anal. calcd for $C_{18}H_{19}NO_2 \cdot 1.1HBr$: C, 58.38; H, 5.47; N, 3.78. Found: C, 58.50; H, 5.63; N, 3.78.

5.12. Preparation of 4-fluorodinapsoline hydrobromide (57)

5.12.1. 8-Amino-5-bromoisoquinoline (44). To a solution of **21** (29 g, 0.115 mol) in methanol (380 mL) heated to reflux, a solution of NH_4Cl (30 g, 0.578 mol) in H_2O (130 mL) was added followed by Fe° (iron powder, 21.8 g, 0.391 mol). The mixture was allowed to stir for 3 h, after which the hot reaction mixture was filtered over Celite. The filtrate was evaporated and the residue was triturated in methanol to give a brown solid **44** (15.4 g, 62%): ^{1}H NMR: δ 9.27 (1H, s), 8.61 (1H, d, J = 6.0), 7.92 (1H, d, J = 6.0), 7.72 (1H, d, J = 8.1), 6.71 (1H, d, J = 8.1); LC/MS m/z 222.92 (MH^+) as a single homogeneous peak.

5.12.2. 5-Bromo-8-fluoroisoquinoline (45). To a solution of **44** (15.4 g, 69.4 mmol) in HBF_4 (74.4 mL) at −5 °C was added dropwise a solution of $NaNO_2$ in 20 mL H_2O. The reaction was stirred for 2 h, filtered, and washed with cold Et_2O, ethanol, and Et_2O. The residue was dried overnight under vacuum followed by a pyrolysis of the neat material under vacuum at about 120 °C. The tarry residue was then taken up in 2 N HCl and extracted with CH_2Cl_2. The aqueous layer was adjusted to pH 8 followed by extraction with CH_2Cl_2; the extract was dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography on silica gel eluted with 10% EtOAc in hexane to give a white solid **45** (500 mg, 3%): ^{1}H NMR: δ 9.54 (1H, s), 8.74 (1H, d, J = 6.0), 8.00–7.89 (2H, m), 7.17 (1H, dd, J = 8.5, 9.7); LC/MS m/z 207.86 (MH^+) as a single homogeneous peak.

5.12.3. α-(5-Bromo-1,3-benzodioxol-4-yl)-8-fluoro-5-isoquinolinemethanol (48). Step 1: Preparation of 8-Fluoro-

isoquinoline-5-carboxaldehyde. The formylation was done in essentially the same way as compound **8** in Scheme 2 to give 57% yield of the desired product: ^{1}H NMR: δ 10.32 (1H, s), 9.64 (1H, s), 9.09 (1H, d, J = 6.0), 8.82 (1H, d, J = 6.0), 8.22 (2H, dd, J = 5.4, 8.1), 7.41 (1H, dd, J = 8.1, 9.5). (Step 2) The condensation was performed in accordance with the preparation of compound **7** in Scheme 2, the desired product was isolated in 47% yield: ^{1}H NMR ($CDCl_3$) δ 9.57 (1H, s), 8.67 (1H, d, J = 6.1), 8.09 (1H, d, J = 4.4), 7.49–7.44 (1H, m), 7.15–7.12 (2H, m), 6.77–6.70 (2H, m), 6.0 (1H, s), 5.92 (1H, s); LC/MS m/z 375.96 (MH^+) as a single homogeneous peak.

5.12.4. 9-Fluoro-12H-benzo[*de*]-1,3-benzodioxolo[4,5-h]-isoquinoline (51). Step 1: 5-[(5-Bromo-1,3-benzodioxol-4-yl)methyl]-8-fluoroisoquinoline. The silane reduction was done in a procedure essentially identical to that described for compound **9** in Scheme 3; the desired product was obtained in 61% yield: ^{1}H ($CDCl_3$) δ 9.57 (1H, s), 8.69 (1H, d, J = 6.1), 7.97 (1H, d, J = 6.1), 7.15–7.11 (3H, m), 6.71 (1H, d, J = 8.3), 5.95 (2H, s), 4.42 (2H, s); LC/MS m/z 360.04 (MH^+). Step 2: The free radical-initiated cyclization was carried out in exactly the same way as described for compound **10** in Scheme 3; the desired product was isolated in about 15% yield along with uncyclized, *des*-bromo byproduct: ^{1}H ($CDCl_3$) δ 9.33 (1H, s), 9.02 (1H, s), 7.65 (1H, d, J = 8.4), 7.57–7.53 (1H, m), 7.27–7.21 (1H, m), 6.88, (1H, d, J = 8.4), 6.09 (2H, s), 4.40 (2H, s); LC/MS m/z 280.14 (MH^+) as a single homogeneous peak.

5.12.5. (±)-4-Fluoro-8,9-methylenedioxy-2,3,7,11*b*-tetrahydro-1H-dibenz[*de*,*h*]isoquinoline (54). The selective ring reduction was done in essentially the same way as described for compound **11** in Scheme 3; the desired product was isolated in 52% yield: ^{1}H ($CDCl_3$) δ 7.15–7.11 (1H, m), 6.86 (1H, dd, J = 9.0, 8.1), 6.72 (2H, s), 6.02 (1H, s), 5.94 (1H, s), 4.08–4.00 (3H, m), 3.75–3.71 (1H,m), 3.61–3.55 (1H, m), 3.10 (1H, dd, J = 10.7, 12.0), 2.24 (1H, bs); LC/MS m/z 283.99 (MH^+) as a single homogeneous peak.

5.12.6. 4-Fluorodinapsoline hydrobromide (57). The BBr_3 deprotection was performed in essentially the same way as described for compound **55**, the desired product was obtained in 45% yield: ^{1}H (CD_3OD) δ 7.37 (1H, dd, J = 5.6, 8.1), 7.06 (1H, dd, J = 9.0, 8.2), 6.72 (1H, d, J = 8.2), 6.01 (1H, d, J = 8.2), 4.56 (1H, d, J = 16), 4.43–4.35 (3H, m), 4.08–4.05 (1H, m), 3.50–3.42 (2H, m). Anal. calcd for $C_{16}H_{14}FNO_2$·HBr: C, 54.56; H, 4.29; N, 3.98; Br, 22.69. Found: C, 54.32; H, 4.36; N, 3.94; Br, 22.71; IR (KBr, cm^{-1}) 3408, 3295; LC/MS m/z 272.12 (MH^+) as a single homogeneous peak.

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References and notes

1. Qandil, A. M.; Lewis, M. M.; Jassen, A.; Leonard, S. K.; Mailman, R. B.; Nichols, D. E. *Bioorg. Med. Chem.* **2003**, *11*, 1451.
2. Sit, S. Y.; Xie, K.; Jacutin-Porte, S.; Taber, M. T.; Gulwadi, A. G.; Korpinen, C. D.; Burris, K. D.; Molski, T. F.; Ryan, E.; Xu, C.; Wong, H.; Zhu, J.; Krishnananthan, S.; Gao, Q.; Verdoorn, T.; Johnson, G. *J. Med. Chem.* **2002**, *45*, 3660.
3. Ghosh, D.; Snyder, S. E.; Watts, V. J.; Mailman, R. B.; Nichols, D. E. *J. Med. Chem.* **1996**, *39*, 549.
4. Siderowf, A.; Stern, M. *Ann. Intern. Med.* **2003**, *138*, 651.
5. Neve, K. A.; Neve, K. A. *The Dopamine Receptors*; Humana: Totowa, NJ, 1997.
6. Setler, P. E.; Sarau, H. M.; Zirkle, C. L.; Saunders, H. L. *Eur. J. Pharmacol.* **1978**, *50*, 419.
7. Gilmore, J. H.; Watts, V. J.; Lawler, C. P.; Noll, E. P.; Nichols, D. E.; Mailman, R. B. *Neuropharmacology* **1995**, *34*, 481.
8. Watts, V. J.; Lawler, C. P.; Gonzales, A. J.; Zhou, Q. Y.; Civelli, O.; Nichols, D. E.; Mailman, R. B. *Synapse* **1995**, *21*, 177.
9. Watts, V. J.; Lawler, C. P.; Gilmore, J. H.; Southerland, S. B.; Nichols, D. E.; Mailman, R. B. *Eur. J. Pharmacol.* **1993**, *242*, 165.
10. Taylor, J. R.; Lawrence, M. S.; Redmond, D. E.; Elsworth, J. D.; Roth, R. H.; Nichols, D. E.; Mailman, R. B. *Eur. J. Pharmacol.* **1991**, *199*, 389.
11. Kebabian, J. W.; Britton, D. R.; DeNinno, M. P.; Perner, R.; Smith, L.; Jenner, P.; Schoenleber, R.; Williams, M. *Eur. J. Pharmacol.* **1992**, *229*, 203.
12. Shiosaki, K.; Jenner, P.; Asin, K. E.; Britton, D. R.; Lin, C. W.; Michaelides, M.; Smith, L.; Bianchi, B.; Didomenico, S.; Hodges, L.; Hong, Y.; Mahan, L.; Mikusa, J.; Miller, T.; Nikkel, A.; Stashko, M.; Witte, D.; Williams, M. *J. Pharmacol. Exp. Ther.* **1996**, *276*, 150.
13. Rascol, O.; Blin, O.; Thalamas, C.; Descombes, S.; Soubrouillard, C.; Azulay, P.; Fabre, N.; Viallet, F.; Lafnitzegger, K.; Wright, S.; Carter, J. H.; Nutt, J. G. *Ann. Neurol.* **1999**, *45*, 736.
14. Mailman, R. B.; Huang, X.; Nichols, D. E. *Current Opinion in Investigational Drugs* **2001**, *2* (11), 1582.
15. Lewis, M. M.; Watts, V. J.; Lawler, C. P.; Nichols, D. E.; Mailman, R. B. *J. Pharmacol. Exp. Ther.* **1998**, *286*, 345.
16. Asin, K. E.; Wirtshafter, D. *Eur. J. Pharmacol.* **1993**, *235*, 167.
17. Gulwadi, A. G.; Korpinen, C. D.; Mailman, R. B.; Nichols, D. E.; Sit, S. Y.; Taber, M. T. *J. Pharmacol. Exp. Ther.* **2001**, *296*, 338.
18. Brewster, W. K.; Nichols, D. E.; Riggs, R. M.; Mottola, D. M.; Lovenberg, T. W.; Lewis, M. H.; Mailman, R. B. *J. Med. Chem.* **1990**, *33*, 1756.
19. Mailman, R. B.; Gay, E. A. *Med. Chem. Res.* In press.
20. Kilts, J. D.; Connery, H. S.; Arrington, E. G.; Lewis, M. M.; Lawler, C. P.; Oxford, G. S.; O'Malley, K. L.; Todd, R. D.; Blake, B. L.; Nichols, D. E.; Mailman, R. B. *J. Pharmacol. Exp. Ther.* **2002**, *301*, 1179.
21. Knoerzer, T. A.; Watts, V. J.; Nichols, D. E.; Mailman, R. B. *J. Med. Chem.* **1995**, *38*, 3062.
22. Gronowitz, S.; Hoernfeldt, A.-B.; Temciuc, M. *Synthesis* **1993**, *5*, 483.
23. Mathison, I. W.; Morgant, P. H. *J. Org. Chem.* **2003**, *39*, 3211.
24. Clark, J. H.; Wails, D.; Jones, C. W.; Smith, H.; Boechat, N.; Mayer, L. U.; Mendonca, J. S. *J. Chem. Res.* **1994**, 478 Synop. 1994.
25. Majetich, G.; Hicks, R.; Reister, S. *J. Org. Chem.* **1997**, *62*, 4321.

26. White, J. D.; Hrnciar, P.; Stappenbeck, F. *J. Org. Chem.* **1997**, *62*, 5250.
27. Takakis, I.; Hadjimihalakis, P. M.; Tsantali, G. G.; Pilini, H. *J. Heterocycl. Chem.* **1992**, *29*, 123.
28. Iqbal, N.; Wei, Z.-Y.; Baker, G. B.; Knaus, E. E. *Canadian J. Chem.* **1997**, *75*, 601.
29. Bellas, S. *J. Chem. Soc.* **1964**, 4561.
30. Schlosser, M.; Simig, G.; Geneste, H. *Tetrahedron* **1998**, *54*, 9023.
31. Kucznierz, R.; Dickhaut, J.; Leinert, H.; Von Der Saal, W. *Synth. Commun.* **1999**, *29*, 1617.
32. Pomerantz, C. *Monatsh. Chem.* **1893**, *14*, 116.
33. Cram, D. J.; Brown, S. B.; Taguchi, T.; Feigel, M.; Maverick, E.; Trueblood, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 695.
34. Nichols, D. E. The Development of Novel Dopamine Agonists. In *Dopamine Receptors*; Kaiser, C., Kebabian, J. W., Eds.; American Chemical Society: Washington, DC, 1983; p 201–218.
35. Mailman, R. B.; Nichols, D. E.; Tropsha, A. Molecular Drug Design and Dopamine Receptors. In *The Dopamine Receptors*; Neve, K. A., Neve, R. L., Eds.; Humana Press: Totowa, NJ, 1997; pp 105–133.
36. Mottola, D. M.; Laiter, S.; Watts, V. J.; Tropsha, A.; Wyrick, S. D.; Nichols, D. E.; Mailman, R. B. *J. Med. Chem.* **1996**, *39*, 285.
37. Seiler, M. P.; Markstein, R. *Mol. Pharmacol.* **1984**, *26*, 452.
38. Holden, K. G., Alkylthio-7,8-dihdroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepines having dopaminergic activity. Patent US 4206210, 1980.
39. Wei, C.-C.; Teitel, S. *Heterocycles* **1977**, *8*, 97.
40. Hansch, C.; Hoekman, D.; Leo, A.; Zhang, L.; Li, P. *Toxicol. Lett.* **1995**, *79*, 45.
41. Kim, K. H. *J. Pharm. Sci.* **1991**, *80*, 966.
42. Holmes, E.; Sweatman, B. C.; Bollard, M. E.; Blackledge, C. A.; Beddell, C. R.; Wilson, I. D.; Lindon, J. C.; Nicholson, J. K. *Xenobiotica* **1995**, *25*, 1269.
43. Schaefer, M.; Okulicz-Kozaryn, I.; Batt, A. M.; Siest, G.; Loppinet, V. *J. Med. Chem. Chim. Ther.* **1981**, *16*, 461.
44. Campbell, N. R.; Van Loon, J. A.; Sundaram, R. S.; Ames, M. M.; Hansch, C.; Weinshilboum, R. *Mol. Pharmacol.* **1987**, *32*, 813.
45. Gnanalingham, K. K.; Erol, D. D.; Hunter, A. J.; Smith, L. A.; Jenner, P.; Marsden, C. D. *Psychopharmacology (Berl.)* **1995**, *117*, 275.
46. DeNinno, M. P.; Schoenleber, R.; Perner, R. J.; Lijewski, L.; Asin, K. E.; Britton, D. R.; MacKenzie, R.; Kebabian, J. W. *J. Med. Chem.* **1991**, *34*, 2561.
47. Noerzer, T. A.; Nichols, D. E.; Brewster, W. K.; Watts, V. J.; Mottola, D.; Mailman, R. B. *J. Med. Chem.* **1994**, *37*, 2453.
48. Brewster, W. K.; Nichols, D. E.; Watts, V. J.; Riggs, R. M.; Mottola, D.; Mailman, R. B. *J. Med. Chem.* **1995**, *38*, 318.
49. Mailman, R. B.; Gay, E. A. *Med. Chem. Res.* In press.
50. Asano, Y.; Yamashita, M.; Nagai, K.; Kuriyama, M.; Yamada, K.; Tomioka, K. *Tetrahedron Lett.* **2001**, *42*, 8493.
51. Michaelides, M. R.; Hong, Y.; Didomenico, S.; Bayburt, E. K.; Asin, K. E.; Britton, D. R.; Lin, C. W.; Shiosaki, K. *J. Med. Chem.* **1997**, *40*, 1585.
52. Burris, K. D.; Pacheco, M. A.; Filtz, T. M.; Kung, M-P.; Kung, H. F.; Molinoff, P. B. *Neuropsychopharmacology* **1995**, *12*, 335.