Journal of Medicinal Chemistry

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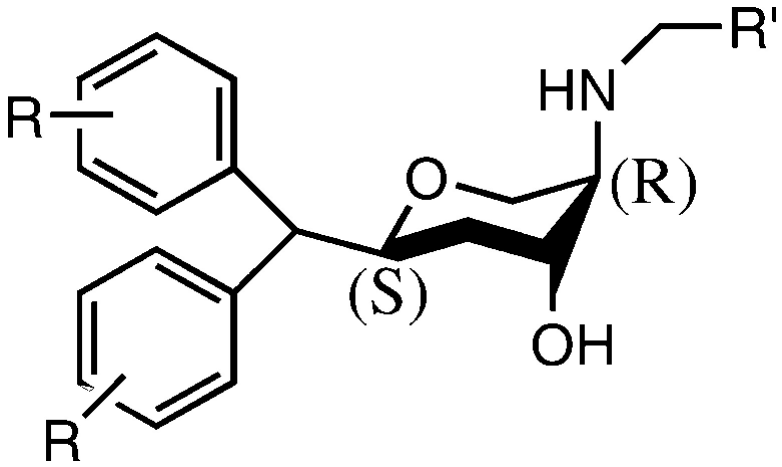
J. Med. Chem., **2005**, 48 (15), 4962-4971• DOI: 10.1021/jm049021k • Publication Date (Web): 22 June 2005



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Discovery of Novel Trisubstituted Asymmetric Derivatives of (2*S*,4*R*,5*R*)-2-benzhydryl-5-benzylaminotetrahydropyran-4-ol, Exhibiting High Affinity for Serotonin and Norepinephrine Transporters in a Stereospecific Manner

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Received December 1, 2004

In our structure−activity relationship study on 3,6-disubstituted pyran derivatives, we have carried out asymmetric synthesis and biological characterization of trisubstituted (2*S*,4*R*,5*R*)-2-benzhydryl-5-benzylaminotetrahydropyran-4-ol and (3*S*,4*R*,6*S*)-6-benzhydryl-4-benzylaminotetrahydropyran-3-ol derivatives and their enantiomers. All synthesized derivatives were tested for their affinities for the dopamine transporter (DAT), serotonin transporter (SERT), and norepinephrine transporter (NET) in the brain by measuring their potency in inhibiting the uptake of [^{3}H]DA, [^{3}H]-5-HT, and [^{3}H]NE, respectively. Compounds were also tested for their binding affinity at the DAT by their inhibition of [^{3}H]WIN 35,428. Biological results indicated that regioselectivity and stereoselectivity played important roles in determining activity for monoamine transporters as only (−)-isomers of 2-benzhydryl-5-benzylaminotetrahydropyran-4-ol derivatives exhibited appreciable potency for the monoamine transporters, in particular for the SERT and NET. Among the active analogues, (−)-**9d** exhibited potent and selective affinity at the NET (K_i, [^{3}H]NE = 4.92 nM; DAT/NET = 91 and SERT/NET = 140). One of the derivatives with *p*-methoxybenzyl substitution, (−)-**9a**, was potent at both SERT and NET (K_i, [^{3}H]-5-HT = 25.9 and [^{3}H]NE = 15.8 nM, respectively). In the active analogue series ((−)-**9a**−(−)-**9e**), a cis-relationship between the biphenyl and the amino moiety was maintained for the SERT and NET interactions, as was observed with our earlier 3,6-disubstituted pyran compounds for the DAT interaction. To the best of our knowledge, this current series of compounds represents a novel class of pyran derivatives as blockers for monoamine transporters.

Introduction

The monoamine transporters terminate the action of released biogenic amines such as dopamine (DA), norepinephrine (NE), and serotonin (5-HT) in the central nervous system (CNS) and are known as DAT, NET, and SERT, respectively.[1] These transporters play a vital role in maintaining the extracellular concentration of biogenic amine neurotransmitters.[2] Drugs binding to the DAT are typically regarded as stimulants. Cocaine- and amphetamine-related compounds are known to produce their action by binding to both DAT and SERT with cocaine acting as a blocker and amphetamine as a substrate.[3−7] On the other hand, drugs binding to the SERT and NET are known to produce, among other effects, antidepressant activity.[8−10]

There is much evidence that the strong reinforcing effects of cocaine originate from its binding to the DAT.[5−7,11−14] However, the serotonergic system also has been implicated in some of cocaine's effects.[15,16] For the past 15 years DAT has been a target for development of medications for cocaine addiction. Compounds with diverse structures have been developed for DAT and have been extensively reviewed in recent articles.[17−19] These compounds can be classified in the following categories: 3-phenyltropane, benztropine, and GBR-12909 (1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine) analogues and methylphenidate, mazindol, and phencyclidine analogues.

In our effort to design and discover novel nontropane-based molecules for developing pharmacotherapies for cocaine addiction, we recently have embarked on development of 3,6-disubstituted pyran derivatives targeting monoamine transporter systems. These pyran analogues are the bioisosteric versions of our earlier structurally constrained *cis*-3,6-disubstituted piperidine derivatives that exhibited potent and selective affinities toward DAT in a stereoselective manner (see compound **1b** in Figure 1).[20,21] In general, we have noted a slight reduction of affinity in these pyran derivatives for the DAT compared to their piperidine counterparts.[22] This loss of affinity could be due to the replacement of the basic N-atom in the piperidine derivative by a less basic O-atom, resulting in an altered mode of interaction. In this regard, we have also demonstrated that the *cis*-3,6-disubstituted pyran derivatives, as shown in structure **1b** in Figure 1, actually represent pharmacophoric structures for DAT interaction as *cis*- or *trans*-2,4-

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10.1021/jm049021k CCC: $30.25
Published on Web 06/22/2005

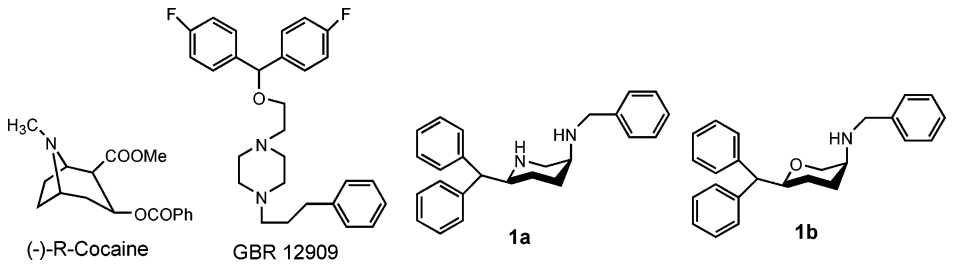


Figure 1.

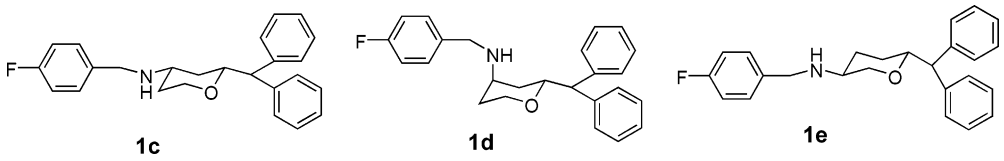


Figure 2.

disubstituted and *trans*-3,6-disubstituted compounds, shown as **1c**, **1d**, **1e** in Figure 2, and were much weaker at DAT.[23] Interestingly, one of the notable features we observed in pyran derivatives bearing a potential H-bonding hydroxyl or amino functionality in the aromatic ring was their significant increase in activity toward NET, which we did not observe for the corresponding piperidine counterparts.[21,23] This affinity for NET was attributed to H-bonding between the functional groups in the benzyl moiety of the pyran molecules and the NET. Support for this came from the design of a molecule in which the original potential H-bonding-bearing functional hydroxyl group connected to a phenyl moiety was modified into a bioisosteric equivalent indole substituent where an indole amino moiety effectively replaced the hydroxyl group. The resulting indole derivative was also potent at NET, thus confirming the potential involvement of an H-bond interaction. Similar approaches for DA receptor compounds in the past produced potent DA agonist activity by replacing catechol groups by indole at appropriate positions.[24,25]

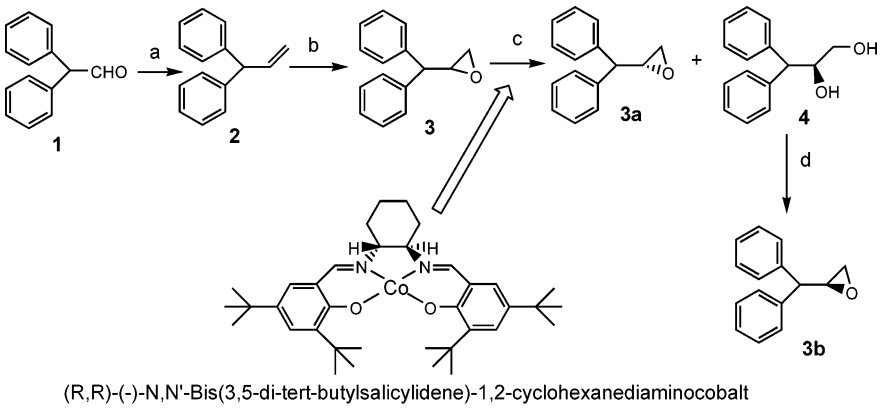
In the present study, we wanted to take this observation further by exploring the effect of the presence of an additional hydroxyl group, as a third substituent, on the pyran ring. Evidence for the influence of such a hydroxyl group on binding activity at DAT was shown by us recently.[26] In one of our piperidine analogues of GBR 12909, the presence of a hydroxyl group in the piperidine ring introduced significant DAT potency in the molecule compared to the parent compound. DAT binding affinity was 20-fold higher compared to the parent non-hydroxylated molecule, which was attributed to the formation of a H-bond between the hydroxyl moiety in the compound and the DAT. This was recently confirmed in our site-directed mutagenesis study, which demonstrated selective involvement of the aspartate residue in the 68 position in the first transmembrane domain of DAT in such H-bonding interaction.[27] Consequently, it was reasoned that introduction of a hydroxyl group as a third substituent in our newly developed 3,6-disubstituted pyran template could allow additional interaction with the monoamine transporter potentially, resulting in compounds with interesting potency and selectivity. While introducing such a hydroxy group in the pyran ring, we also wanted to explore the additional influence of stereospecificity and regioselectivity in the interaction of the pyran compounds with monoamine transporters. For this purpose we used a novel asymmetric synthesis method via isomeric epoxide ring opening to introduce all three substituents in a stereo- and regiospecific manner which was followed by their biological evaluation at all three monoamine transporters.

Chemistry

Design of Asymmetric Synthesis. In our design of regio- and stereospecific synthesis, the recent resolution of chiral epoxide by hydrolytic kinetic resolution (HKR) reaction, as developed by Jacobsen et al., was incoporated in the design of the initial asymmetric synthetic building block.[28] Thus, in Scheme 1, the synthesis of the two enantiomers of 2-benzhydryloxirane is described. Starting from diphenylacetaldehyde **1**, Wittig reaction gave olefin **2** in moderate yield. Epoxidation of **2** with mCPBA delivered the racemic 2-benzhydryloxirane **3** in 80% yield. The racemate **3** was resolved by HKR reaction with (*R*,*R*)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt catalyst efficiently to give (2*R*)-2-benzhydryloxirane **3a** and (2*S*)-3,3-diphenylpropane-1,2-diol **4** in high enantiomeric excess ratio. Mitsunobu reaction of diol (2*S*)-3,3-diphenylpropane-1,2-diol **4** with DEAD and TPP in benzene furnished (2*S*)-2-benzhydryloxirane **3b** in 78% yield.[29] The absolute stereochemistry of the epoxides was determined by converting the ring-opened product **5a** into a Mosher's ester.[30−32] The ^{1}H NMR analysis of the Mosher ester demonstrated *S*-stereochemistry in the asymmetric center in **5a**. This implied that the epoxides **3a** and **3b** possess *R*- and *S*-configuration, respectively. The optical purity and the detailed determination of absolute stereochemistry of the epoxides are included in the Supporting Information.

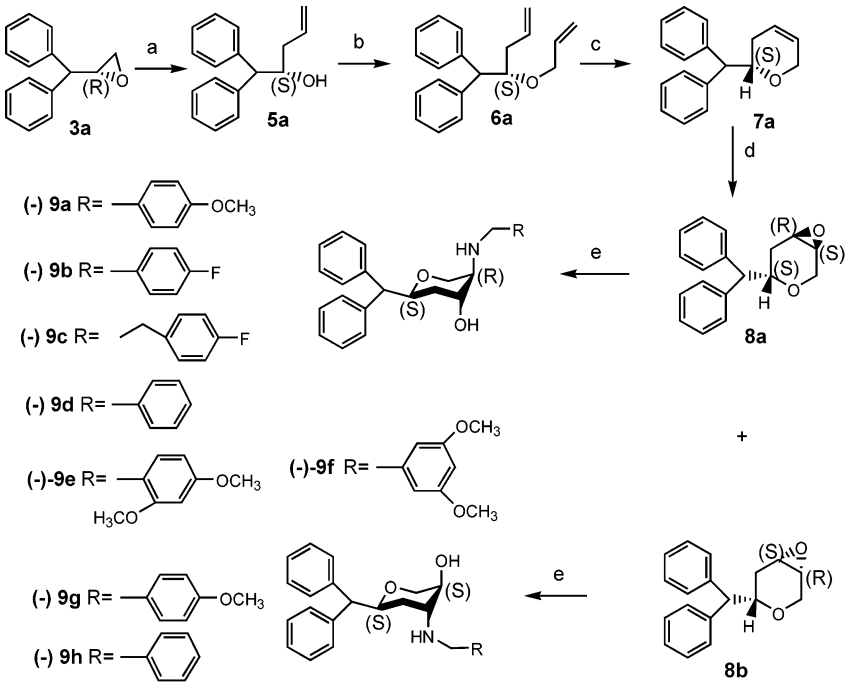
The synthesis of optically active compounds (−)-**9a**−**h** is described in Scheme 2. Opening of (2*R*)-2-benzhydryloxirane **3a** with a copper reagent, produced in situ from vinylmagnesium bromide and copper(I) iodide, gave (2*S*)-1,1-diphenylpent-4-en-2-ol **5a** in 70% yield. *O*-Alkylation of **5a** with allyl bromide under basic conditions delivered (2*S*)-1,1-diphenyl-2-allyloxypent-4-ene **6a** in 85% yield. Ring-closing metathesis (RCM) reaction in the presence of Grubb's catalyst, benzylidenebis-

Scheme 1[a]



[a] (a) Methyldiphenylphosphonium bromide/BuLi/THF. (b) mCPBA/CH_2Cl_2. (c) Jacobsen's catalyst/H_2O. (d) TPP/DEAD/benzene.

Scheme 2[a]

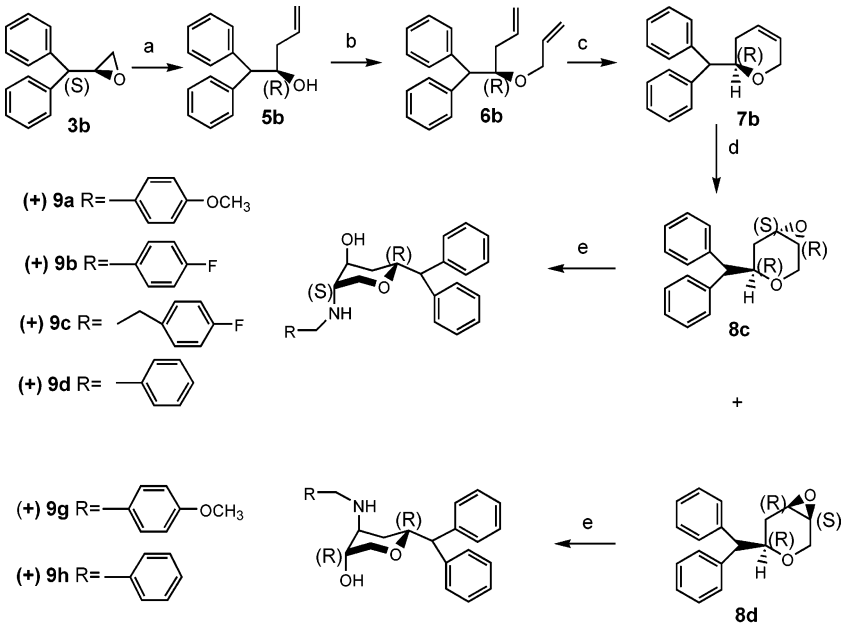


[a] (a) Vinylmagnesium bromide/CuI/THF. (b) NaH/allyl bromide/DMF. (c) Grubbs' catalyst/benzene. (d) mCPBA/CH_2Cl_2. (e) Amine/ethanol.

(tricyclohexylphosphine)dichloro ruthenium, produced cyclic (2*S*)-2-benzhydryl-3,6-dihydro-2*H*-pyran **7a** in 88% yield.[33] Epoxidation of **7a** with mCPBA gave two diastereomers: *trans*-epoxide (1*S*,4*S*,6*R*)-4-benzhydryl-3,7-dioxabicyclo[4,10]heptane **8a** and the *cis*-epoxide (1*R*,4*S*,6*S*)-4-benzhydryl-3,7-dioxabicyclo[4,10]hep-tane **8b** in 50% and 41% yields, respectively, which were separated by column chromatography. Opening of the *trans*-**8a** with different benzylamines in ethanol under refluxing conditions furnished the final products (−)-**9a**−**f** in optically pure form. On the other hand, different regioselective opening of *cis*-**8b** by *p*-methoxybenzylamine and benzylamine produced optically pure products **(−)-9 g** and **(−)-9h**, in 63% and 86% yield, respectively.

The present synthetic strategy takes advantage of regioselective ring opening of cis and trans epoxide rings in asymmetric 2-substituted pyran derivatives by nucleophilic amines.[34,35] It was expected, from work by previous authors, that a trans diaxial epoxide ring opening will take place if a pyran ring exist in a semirigid configuration.[34] ^{1}H NMR data indicated that the diphenyl group in our pyran derivatives was oriented in an equatorial position. Regioselectivity in pyran epoxide ring opening, as found in cis and trans epoxides **8a** and **8b**, was observed earlier.[34,35] These ring openings produced regioselectively two different trans-diaxial products. In our case, we wanted to observe the influence of the benzhydryl substituent at the 2-position on the pyran ring in regio- and stereoselective opening of

Scheme 3[a]



[a] (a) Vinylmagnesium bromide/CuI/THF. (b) NaH/allyl bromide/DMF. (c) Grubbs' catalyst/benzene. (d) mCPBA/CH_2Cl_2. (e) Amine/ethanol.

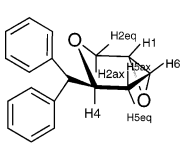
cis- and *trans*-epoxide rings. It is evident from our results that epoxide ring opening took place with complete regioselectivity, depending upon the stereochemistry of the epoxide molecule. Thus, *trans*-epoxide **8a** underwent trans diaxial opening with nucleophilic amines at position 1 and from the same phase as the biphenyl moiety in the pyran ring, giving rise to compounds **9a**. On the other hand, *cis*-epoxide **8b** underwent ring opening by amine at position 6 in a trans diaxial mode in an opposite regioselective manner and from a different phase as the biphenyl moiety, as is evident in compounds (−)-**9g** and (−)-**9h**.[34] The detailed structural assignments for *trans*- and *cis*-epoxide **8a** and **8b**, along with their ring-opened products, are described in the Supporting Information.

Scheme 3 describes the synthesis of compounds (+)-**9a**−**d** and (+)-**9g**−**h** starting from *trans*-(1*R*,4*R*,6*S*)-4-benzhydryl-3,7-dioxabicyclo[4,10]heptane **8c** and *cis*-(1*S*,4*R*,6*R*)-4-benzhydryl-3,7-dioxabicyclo[4,10]heptane **8d** in the same way as described in Scheme 2.

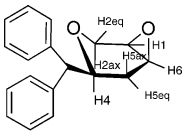
The assignment of the relative stereochemistry in compounds **8a** and **8b** was based on the ^{1}H NMR spectrum data (normal proton NMR and 2-D COSY NMR). The protons were assigned by the 2-D COSY NMR method. In compound **8a**, the splitting of H-1 at 3.27 ppm (assigned from ^{1}H NMR and COSY NMR) is a triplet (J = 4.00 Hz). This triplet is from the couplings with H-6 and H-2eq. No coupling between H-2ax and H-1 was observed. Furthermore, the data from 2-D COSY NMR also supported this observation. All these observations have demonstrated that H-1 is in the same phase as H-2eq. This confirmed the trans-stereochemistry of compound **8a** relative to the benzhydryl moiety.

In compound **8b**, the splitting of H-6 at 3.29 ppm (assigned from ^{1}H NMR and 2D COSY NMR) is a triplet (J = 4.00 Hz). In the cis-isomer no coupling exists between H-5ax and H-6. This triplet splitting of H-6 is from the couplings with H-5eq and H-1, respectively. Furthermore, 2-D COSY NMR study demonstrated the coupling between H-6 and H-5eq and no coupling between H-6 and H-5ax. Because of the same phase location of benzhydryl moiety and H-5ax, the cis-stereochemistry of compound **8b** relative to benzhydryl moiety was confirmed. These findings were further confirmed by ^{1}H homo decoupling (HMDC) and nuclear Overhauser experiments (NOE) in a 500-MHz FT NMR machine and is described in detail in the Supporting Information. The results from our above experiments conclusively established the conformational structures of the *cis*- and *trans*-epoxides. The proton signals with the coupling data are summarized in Table 1.

Table 1. ^{1}H NMR Signals of Respective Protons in *cis*- and *trans*-Epoxides 8a and 8b



8a



8b

	compound **8a** (ppm)	compound **8b** (ppm)
H-1	3.27 (t, J = 4.0 Hz)	3.06 (d, J = 4.0 Hz)
H-2ax	3.95 (d, J = 13.6 Hz)	3.82 (d, J = 13.6 Hz)
H-2eq	4.22 (dd, J = 4.0 Hz, 13.6 Hz)	4.19 (d, J = 13.6 Hz)
H-4	4.14 (dt, J = 2.4 Hz, 10.2 Hz)	3.93 (dt, J = 4.0 Hz, 10.0 Hz)
H-5ax	1.71 (m)	1.82 (dd, J = 10.40 Hz, 15.20 Hz)
H-5eq	1.89 (m)	1.71 (td, J = 4.0 Hz, 15.6 Hz)
H-6	3.34 (m)	3.29 (t, J = 4.0 Hz)
Ph_2CH	3.82 (d, J = 10.0 Hz)	3.86 (d, J = 10.0 Hz)

Table 2. Affinity of Drugs at DAT, SERT, and NET in Rat Brain

	IC_{50}, nM				K_i, nM		
compound	DAT binding, [^{3}H]WIN 35,428[a]	DAT uptake, [^{3}H]DA[a]	SERT uptake, [^{3}H]-5-HT[a]	NET uptake, [^{3}H]NE[a]	DAT uptake, [^{3}H]DA[a]	SERT uptake, [^{3}H]-5-HT[a]	NET uptake, [^{3}H]NE[a]
GBR 12909[b]	10.6 ± 1.9	14.2 ± 2.9	101.4 ± 14.2	114 ± 36	10.6 ± 2.2	91.1 ± 12.8	102 ± 32
(+)-**9a** (D-151)	182 ± 11	148 ± 22	745 ± 30	445 ± 39	110 ± 16	669 ± 26	412 ± 36
(+)-**9b** (D-1 59)	1030 ± 120	440 ± 30	5560 ± 640	1130 ± 580	327 ± 22	5000 ± 570	1050 ± 50
(+)-**9c** (D-157)	443 ± 52	218 ± 20	2950 ± 380	77.3 ± 3.0	162 ± 15	2650 ± 340	71 ± 2.7
(+)-**9d** (D-1 40)	596 ± 84	341 ± 43	6120 ± 730	770 ± 33	253 ± 32	5500 ± 650	691 ± 29
(+)-**9g** (D-160)	3750 ± 620	2670 ± 260	3810 ± 460	1840 ± 580	1980 ± 190	3420 ± 410	1700 ± 50
(+)-**9h** (D-1 43)	1250 ± 100	962 ± 97	4420 ± 410	3220 ± 570	716 ± 72	3970 ± 370	2890 ± 510
(-)-**9a** (D-142)	226 ± 40	155 ± 16	28.9 ± 4.1	17.7 ± 5.9	115 ± 12	25.9 ± 3.6	15.8 ± 5.3
(-)-**9b** (D-153)	308 ± 25	169 ± 20	676 ± 33	13.3 ± 1.0	125 ± 20	607 ± 30	12.2 ± 1
(-)-**9c** (D-154)	1050 ± 40	427 ± 67	3570 ± 140	439 ± 14	317 ± 50	3210 ± 130	406 ± 13
(-)-**9d** (D-165)	1860 ± 710	600 ± 79	862 ± 36	5.59 ± 1.05	446 ± 59	707 ± 30	4.92 ± 0.92
(-)-**9e** (D-180)	1,060 ± 100	710 ± 130	24.0 ± 4.0	115 ± 14	528 ± 95	20.8 ± 2.0	95.0 ± 9.7
(-)-**9f** (D-179)	298 ± 29	135 ± 3	25.4 ± 2.0	108 ± 11	100 ± 2	19.7 ± 3.0	101 ± 12
(-)-**9g** (D-141)	771 ± 86	822 ± 120	1070 ± 100	765 ± 34	611 ± 93	793 ± 84	686 ± 30
(-)-**9h** (D-166)	4640 ± 1030	2610 ± 140	10,600 ± 1400	336 ± 33	1940 ± 100	9560 ± 1250	296 ± 29

[a] For binding, the DAT was labeled with [^{3}H]WIN 35,428. For uptake by DAT, SERT, and NET, [^{3}H]DA, [^{3}H]-5-HT, and [^{3}H]NE accumulation were measured. Results are average ± SEM of three to eight independent experiments assayed in triplicate. [b] Results from Zhen et al.[27]

Results and Discussion

Our effort to develop unique molecular templates for interaction with monoamine transporters led to the pyran template. Interestingly, some of our previous pyran derivatives displayed a unique activity profile with high affinity for the NET.[23] This interaction with NET was especially pronounced when an H-bond-forming moiety, e.g. OH or NH_2 group, was incorporated in the para-position of the phenyl moiety of the *N*-benzyl group.[23] The results strongly supported the formation of a preferential H-bond with the NET. Building upon this observation, we decided to incorporate another element of complexity into the basic pyran template by introducing a hydroxyl group in a stereospecific manner. In this regard, as mentioned above, our previous study with piperidine analogues of GBR derivatives uncovered the strong influence of such a group in the piperidine moiety, resulting in one of the most selective and potent molecules at DAT known to date.[26,27] In the present study we used asymmetric synthesis to synthesize the target molecules as described in the Chemistry section and assessed whether the introduction of a hydroxyl group in stereo- and regiospecific manners results in potency and selectivity for monoamine transporters.

It is evident that *cis*- and *trans*-epoxides, derived from the S-pyran intermediate **7a**, produced (−)-isomers upon epoxide ring opening whereas the R-pyran intermediate **7b** provided the (+)-isomers upon ring opening. Epoxidation of **7a** resulted in formation of *trans*- and *cis*-epoxides **8a** and **8b**, which were characterized thoroughly by ^{1}H NMR analysis. Opening of trans **8a** by various substituted benzylamines produced the final targets, where the benzhydryl moiety at the 2-position and the amino substitution at the 5-position maintained the desirable cis-pharmacophoric structural requirement for activity as established earlier by us for pyran derivatives.[23] Thus, ring-opened products from **8a** were expected to exhibit activity unless the presence of the hydroxyl functionality at the 4-position imparts a detrimental effect. On the other hand, *cis*-epoxide opening, as in case of **8b**, resulted in production of substitutions at different locations in the target molecules, and the activity of these derivatives could not be predicted. In addition, enantiomeric preference for activity could also not be predicted at this point.

The (+)-isomeric derivatives (+)-**9a**−**d** were derived from the *trans*-epoxide **8c** and were in the correct pharmacophoric cis configuration with respect to the benzhydryl and amino moieties on the pyran ring. As shown in Table 2, these compounds exhibited moderately weak to potent activity either at DAT or NET. Compound (+)-**9c** was the most active at the NET with a K_i value of 71 nM, whereas compound (+)-**9a** exhibited maximal potency at DAT (K_i = 110 nM). As expected, (+)-**9g** and (+)-**9h** were almost inactive at all three transporters (see Table 2). This was not entirely unexpected, as these derivatives assumed a nonfavorable pharmacophoric structure with the amino substitution located in the 4- instead of the 5-position with respect to the 2-benzhydryl substitution in the molecule, as described above.

The (−)-isomers of **9a**−**h** were synthesized from the *trans*- and *cis*-epoxides **8a** and **8b**. As was the case for (+)-**9g** and (+)-**9h**, the enantiomers (−)-**9g** and (−)-**9h** were almost inactive at all three transporters, consonant with their nonpharmacophoric configuration. Interestingly, the other optically active (−)-isomers displayed a different pattern as compared with their (+)-counterparts by exhibiting potent activity either at the NET, SERT, or both. Among these, (−)-**9d** exhibited maximal potency at NET (K_i = 4.92 nM) and selectivity for the NET (Table 3, DAT/NET = 91 and SERT/NET = 140). The −OH group at the 4-position contributed appreciably to the binding interaction between (−)-**9d** and NET, as evidenced by comparison with the corresponding less potent 3,6-disubstituted derivative **1b** (Figure 1) without the hydroxyl group, which we published earlier.[23] Thus, the presence of the −OH group resulted in a significantly higher potency at the NET and selectivity for the NET.[23] In addition to (−)-**9d** compound, (−)-**9b**, with 4-fluoro substitution, also exhibited potent activity at the NET but it exhibited less selectivity than (−)-**9d** for the NET (Table 3). However, compound (−)-**9c**, where 4-fluorobenzyl was replaced by 4-fluorophenethyl, was much less potent, indicating low tolerance for this particular N-substitution.

Table 3. Selectivity of Drugs (ratio of K_i) in Inhibiting Uptake by Monoamine Transporters

compound	DAT uptake/ SERT uptake[a]	DAT uptake/ NET uptake[a]	SERT uptake/ NET uptake[a]
GBR 12909[b]	0.12	0.10	0.89
(+)-9a	0.16	0.27	1.6
(+)-9b	0.065	0.31	4.8
(+)-9c	0.061	2.3	37
(+)-9d	0.046	0.37	8.0
(+)-9g	0.58	1.2	2.0
(+)-9h	0.18	0.25	1.4
(-)-9a	4.4	7.3	1.6
(-)-9b	0.21	10.2	50
(-)-9c	0.099	0.78	7.9
(-)-9d	0.63	91	140
(-)-9e	25	5.6	0.22
(-)-9f	5.1	0.99	0.20
(-)-9g	0.77	0.89	1.2
(-)-9h	0.20	6.6	32

[a] Ratio of K_i values. [b] Results from Zhen et al.[27]

Interestingly, compound (−)-**9a** with 4-methoxybenzyl substitution was found to be active at both SERT and NET. It is obvious that either the electron-donating or steric effect of the methoxy substitution impacted the profile of activity for monoamine transporters. Thus, 4-methoxy substitution, while producing activity at NET similar to that of (−)-**9b** and (−)-**9d**, displayed an additional high affinity for SERT. Thus, (−)-**9a** exhibited a dual-action profile. Similarly, the corresponding methoxy analogue in the non-hydroxylated 3,6-disubstituted **1b** family of compounds (Figure 1), was almost inactive at the SERT and NET while exhibiting moderate affinity for the DAT.[23] Once again, these results indicate the profound influence of stereoselective introduction of a hydroxyl functionality in the pyran ring on the binding interaction.

Furthermore, as an extension of our results on monomethoxylated (−)-**9a**, we wanted to explore the effect of dimethoxy substitutions on the aromatic ring of the *N*-benzyl moiety to assess whether such disubstitutions produce an additive effect. Interestingly, results indicated that instead of dual activity for both SERT and NET, as exhibited by (−)-**9a**, compounds (−)-**9e** and (−)-**9f** exhibited selective and high potency at the SERT (K_i of 20.8 and 19.7 nM, respectively). In this regard, compound (−)-**9e** was more selective than (−)-**9f** for NET and SERT compared with DAT (Table 3).

From these results, it is evident that an unsubstituted or fluorosubstituted phenyl ring as in compounds (−)-**9d** and (−)-**9b** favors interaction with the NET, perhaps reflecting a role for both steric and electronic interactions in activity. On the other hand, the presence of an electron-donating methoxy substituent in (−)-**9a** generated dual potency at both SERT and NET. In an extension of our study on (−)-**9a**, the two dimethoxy compounds, (−)-**9e** and (−)-**9f**, also exhibited potency for SERT with retention of appreciable affinity for NET. This might indicate a possible role of H-bonding in addition to steric and electronic effects in potency and selectivity for these molecules.

Conclusion

In conclusion, we have generated a novel trisubstituted pyran template based on our recent work on 3,6-disubstituted pyran derivatives. To the best of our knowledge, these derivatives represent a unique molecular template with a pyranal backbone structure as blockers for monoamine transporters. We have successfully designed and carried out asymmetric synthesis of these analogues. The results indicated a clear separation of activity between enantiomers and have demonstrated the presence of (2*S*,4*R*,5*R*) absolute configuration in the most active enantiomer for interaction with NET and SERT. Furthermore, we have demonstrated that regiospecific ring opening is an absolute requirement for activity for NET and SERT. Thus, the opening of *trans*-epoxide **8a** yielded active molecules with the desired cis-relationship between the benzhydryl and amino substitutions, whereas the opening of *cis*-epoxide **8b** produced a different positional substitution pattern between the benzhydryl and amino moieties and were not potent at monoamine transporters. We have observed interesting differences in activity profile in this limited set of compounds depending on the nature of substitution on the phenyl ring of the *N*-benzyl moiety.

Furthermore, analysis of activity of pyran derivatives in comparison to their piperidine versions requires some comments. In general, pyran molecules have shown higher affinity for NET compared to DAT. Additionally, some trisubstituted pyran derivatives have exhibited high affinity for SERT. The overall tendency of pyran molecules to exhibit higher affinity for NET and SERT compared to DAT may lie in the capacity of pyran derivatives to form efficient H-bond interactions with the former two transporters in addition to other favorable interactions that are not clear at this point. Evidence for such H-bond formation was observed in our earlier studies[23] and is further demonstrated with the current derivatives containing a hydroxyl group in the pyran ring. We are currently exploring this in more detail. Our ongoing studies are directed toward developing a reliable model that will enable us to predict the nature of the binding interaction.

Experiment Section

Reagents and solvents were obtained from commercial suppliers and used as received unless otherwise indicated. Dry solvent was obtained according to the standard procedure as described in Vogel's book.[36] All reactions were performed under inert atmosphere (N_2) unless otherwise noted. Analytical silica gel-coated TLC plates (Si 250F) were purchased from Baker, Inc. and were visualized with UV light or by treatment with phosphomolybdic acid (PMA). Flash chromatography was carried out on Baker silica gel 40 M. ^{1}H NMR spectra were routinely obtained with a Varian 400 MHz FT NMR. The NMR solvent used was $CDCl_3$ as indicated. TMS was used as an internal standard. Elemental analyses were performed by Atlantic Microlab, Inc. and were within 0.4% of the theoretical value.

[^{3}H]WIN 35,428 (86.0 Ci/mmol), [^{3}H]nisoxetine (80.0 Ci/mmol), and [^{3}H]dopamine (48.2 Ci/mmol), [^{3}H]serotonin (23.7 Ci/mmol), and [^{3}H]norepinephrine (49.7 Ci/mmol) were obtained from Dupont-New England Nuclear (Boston, MA). Cocaine hydrochloride was purchased from Mallinckrodt Chemical Corp. (St. Louis, MO). WIN 35,428 naphthalene sulfonate was purchased from Research Biochemicals, Inc. (Natick, MA). (−)-Cocaine HCl was obtained from the National Institute on Drug Abuse. GBR 12909 dihydrochloride (1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-[3-phenylpropyl]piperazine) was purchased from Sigma-Aldrich (#D-052; St. Louis, MO).

Synthesis of 3,3-Diphenylpropene (2). Solid methyltriphenyl phosphonium bromide (4.00 g, 11.12 mmol) was added over a 15-min period into a solution of butyllithium (7.30 mL of 1.60 M solution in THF, 11.76 mmol) in dry THF (50 mL)

with stirring under nitrogen atmosphere at 0 °C. The reaction mixture was stirred for 2 h at room temperature followed by recooling back to 0 °C. A solution of diphenylacetaldehyde (2.20 g, 11.12 mmol) in dry THF (10 mL) was added to the above mixture over a 15-min period. The reaction mixture was stirred for 24 h at room temperature, which was followed by addition of ethyl ether (200 mL), and finally, the reaction mixture was filtered. The ether extracts were combined, washed with water (3 × 50 mL) and brine (100 mL), and dried over anhydrous sodium sulfate. The crude material was purified by flash chromatography over a silical gel column (hexane/ethyl ether = 9:1) to give pure **2** (0.46 g, 46%). ^{1}H NMR ($CDCl_3$, 400 MHz): 4.82 (d, J = 6.4 Hz, 1H, H-3), 5.08 (d, J = 17.2 Hz, 1H, H-1), 5.31 (d, J = 12.0 Hz, 1H, H-1), 6.39 (m, 1H, H-2), 7.20−7.40 (m, 10H, aromatic-H).

Synthesis of 2-Benzhydryloxirane (3). A flask was charged with **2** (5.10 g, 26.30 mmol) in 100 mL of CH_2Cl_2, which was followed by portionwise addition of *m*-chloroperbenzoic acid (9.10 g, 70% purity, 52.60 mmol) at 0 °C. The mixture was stirred at room temperature for 24 h and the reaction was then quenched with 30 mL of 1 M Na_2SO_3. The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phase was washed in turn with saturated $NaHCO_3$ and brine and then dried over anhydrous Na_2SO_4. Purification by flash chromatography (hexane/ether = 9:1) gave pure **3** (4.70 g, 85%). ^{1}H NMR ($CDCl_3$, 400 MHz): 2.54 (m, 1H, H-1), 2.87 (t, J = 4.8 Hz, 1H, H-1), 3.54 (m, 1H, H-2), 3.86 (d, J = 7.6 Hz, 1H, Ph_2CH), 7.20−7.40 (m, 10H, aromatic-H).

Resolution of Racemic 2-Benzhydryloxirane (3) by HKR Reaction. A mixture of (*R*,*R*)-(−)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexane diaminocobalt (II) (0.22 g, 0.37 mmol, 0.8%), toluene (5 mL), and acetic acid (0.04 g, 0.74 mmol) was stirred for 1 h at room temperature. The solvent was removed in vacuo and the residue was dried. Compound **2** (9.60 g, 45.7 mmol) was added in one portion with stirring and the mixture was then cooled under an ice bath. H_2O (0.58 g, 32 mmol) was slowly added over a 30-min period. Following addition of water, the ice bath was removed and the reaction mixture was stirred at room temperature for 72 h. Compounds were separated via flash chromatography over a slica gel column to give (2*R*)-2-benzhydryloxirane **3a** (4.50 g, 93%) ($[\alpha]_D$ = (+)-9.58, c = 1, MeOH) and (2*S*)-3,3-diphenylpropane-1,2-diol **4** (3.53 g) ($[\alpha]_D$ = (+)-48, c = 1, MeOH, ee = 97%). The ^{1}H NMR of **3a** was identical to that of the racemate **2**; ^{1}H NMR ($CDCl_3$, 400 MHz): 2.56 (m, 1H, H-1), 2.89 (t, J = 4.0 Hz, 1H, H-1), 3.56 (m, 1H, H-2), 3.89 (d, J = 6.4 Hz, 1H, Ph_2CH), 7.20−7.40 (m, 10H, aromatic-H). For (2*S*)-3,3-diphenylpropane-1,2-diol (**4**), ^{1}H NMR ($CDCl_3$, 400 MHz): 2.39 (bs, 2H, OH), 3.45 (m, 1H, H-1), 3.62 (dd, J = 2.8 Hz, 11.6 Hz, 1H, H-1), 4.02 (d, J = 9.6 Hz, 1H, Ph_2CH), 4.45 (m, 1H, H-2), 7.16−7.22 (m, 10H, aromatic-H).

Synthesis of (2*S*)-2-Benzhydryloxirane (3b). A solution of **4** (3.50 g, 15.35 mmol), Ph_3P (8.05 g, 30.7 mmol), and DEAD (5.40 g, 30.70 mmol) in benzene (50 mL) was refluxed for 24 h. Solvent was removed under vacuo and the residue was diluted with ethyl ether (200 mL) to precipitate Ph_2PO. The filtrate was concentrated and the residue was chromatographed over a silical gel column (hexane/ether = 9:1) to give **3b** (2.50 g, 78%) ($[\alpha]_D$ = (−)-9.6, c = 1, MeOH). The ^{1}H NMR was identical with that of the (*R*)-isomer; ^{1}H NMR ($CDCl_3$, 400 MHz): 2.54 (m, 1H, H-1), 2.87 (m, 1H, H-1), 3.54 (m, 1H, H-2), 3.86 (d, J = 7.6 Hz, 1H, Ph_2CH), 7.20−7.40 (m, 10H, aromatic-H).

Procedure A. Synthesis of (2*S*)-1,1-Diphenylpent-4-en-2-ol (5a). Compound **3a** (0.50 g, 2.38 mmol) was dissolved in dry THF (5 mL) and was added into a dry THF solution at −78 °C containing CuI (0.05 g, 0.24 mmol) and vinylmagnesium bromide (5.95 mL of 1.0 M solution in THF, 5.95 mmol). The reaction mixture was stirred and was allowed to reach room temperature over a period of 2 h, followed by quenching with saturated NH_4Cl solution. The aqueous phase was extracted with ethyl acetate (3 × 30 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed and the residue was purified by flash chromatography over a silica gel column (hexane/ethyl ether = 4:1) to give **5a** (0.40 g, 70%) ($[\alpha]_D$ = (−)-25, c = 1, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz): 2.14 (m, 1H, H-3), 2.33 (m, 1H, H-3), 3.93 (d, J = 8.8 Hz, 1H, H-1), 4.44 (m, 1H, H-2), 5.10 (m, 2H, H-5), 5.90 (m, 1H, H-4), 7.16−7.24 (m, 10H, aromatic-H).

Synthesis of (2*R*)-1,1-Diphenylpent-4-en-2-ol (5b). Compound **3b** (0.61 g, 2.91 mmol) was reacted with vinylmagnesium bromide (7.26 mL of 1.0 M solution in THF, 7.26 mmol) in the presence of CuI (0.06 g, 0.29 mmol) (procedure A) to yield **5b** (0.48 g, 70%) ($[\alpha]_D$ = (+)26, c = 1, MeOH). The ^{1}H NMR was identical with that of (2*S*)-1,1-diphenyl-pent-4-en-2-ol. ^{1}H NMR ($CDCl_3$, 400 MHz): 2.14 (m, 1H, H-3), 2.33 (m, 1H, H-3), 3.93 (d, J = 8.8 Hz, 1H, H-1), 4.44 (m, 1H, H-2), 5.10 (m, 2H, H-5), 5.90 (m, 1H, H-4), 7.16−7.24 (m, 10H, aromatic-H).

Procedure B. Synthesis of (2*S*)-1,1-Diphenyl-2-allyloxypent-4-ene (6a). Compound **5a** (0.37 g, 1.57 mmol) was dissolved in dry DMF (2 mL) and was added to a suspension of NaH (60% in mineral oil, 0.13 g, 3.14 mmol) in dry DMF (20 mL) at 0 °C. The reaction mixture was allowed to reach room temperature for over a period of 1 h. The reaction mixture was cooled back to 0 °C in an ice bath. Neat allyl bromide (0.57 g, 4.71 mmol) was then added slowly. The reaction mixture was removed from the ice bath and stirred overnight at room temperature. The reaction was cooled again to 0 °C and was quenched by slowly adding H_2O (20 mL). The resulting mixture was extracted with Et_2O (3 × 50 mL), and the combined organic phase was washed in turn with H_2O, brine, and finally dried over anhydrous Na_2SO_4. Filtration of the solution followed by concentration gave crude product as a light orange oil. Purification by chromatography (hexane/ethyl ether = 10:1) gave **6a** (0.37 g, 85%) ($[\alpha]_D$ = (+)19.7, c = 1, MeOH). ^{1}H NMR ($CDCl_3$, 500 MHz): 2.26 (m, 1H, H-3), 2.38 (m, 1H, H-3), 3.74 (m, 1H, H-3′), 3.96 (m, 1H, H-3′), 4.10 (m, 2H, H-1, H-2), 5.00−5.16 (m, 4H, H-5, H-1′), 5.71 (m, 1H, H-2′), 5.93 (m,1H, H-4), 7.20−7.46 (m, 10H, aromatic-H).

Synthesis of (2*R*)-1,1-Diphenyl-2-allyloxypent-4-ene (6b). Compound **5b** (0.42 g, 1.75 mmol) was reacted with allyl bromide (0.63 g, 5.25 mmol) (procedure B) to yield **6b** (0.43 g, 87%) ($[\alpha]_D$ = (−)20, c = 1, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz): 2.22 (m, 1H, H-3), 2.34 (m, 1H, H-3), 3.70 (m, 1H, H-3′), 3.94 (m, 1H, H-3′), 4.08 (m, 2H, H-1, H-2), 4.96−5.12 (m, 4H, H-5, H-1′), 5.69 (m, 1H, H-2′), 5.89 (m,1H, H-4), 7.10−7.50 (m, 10H, aromatic-H).

Procedure C. Synthesis of (2*S*)-2-Benzhydryl-3,6-dihydro-2H-pyran (7a). Into a solution of **6a** (0.19 g, 0.68 mmol) in dry benzene was added Grubb's catalyst (0.03 g, 0.03 mmol, 5%), and the solution was refluxed under N_2 for 20 h. The solvent was removed, and the residue was purified by flash chromatography (hexane/ether = 9:1) to give **7a** (0.15 g, 88%) ($[\alpha]_D$ = (−)79.3, c = 1, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz): 1.82 (m, 1H, H-3), 2.09 (m, 1H, H-3), 4.00 (d, J = 8.8 Hz, 1H, Ph_2CH), 4.23 (m, 2H, H-6), 4.32 (dt, J = 2.4 Hz, 9.6 Hz, H-2), 5.77 (m, 2H, H-4, H-5), 7.16−7.26(m, 10H, aromatic-H).

Synthesis of (2*R*)-2-Benzhydryl-3,6-dihydro-2H-pyran (7b). Compound **6b** (0.25 g, 0.90 mmol) was cyclized in the presence of Grubb's catalyst (0.04 g, 0.05 mmol) (procedure C) to produce **7b** (0.20 g, 89%) ($[\alpha]_D$ = (+)80.8, c = 1, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz): 1.82 (m, 1H, H-3), 2.09 (m, 1H, H-3), 4.00 (d, J = 8.8 Hz, 1H, Ph_2CH), 4.23 (m, 2H, H-6), 4.32 (dt, J = 2.4 Hz, 9.6 Hz, H-2), 5.77 (m, 2H, H-4, H-5), 7.16−7.26 (m, 10H, aromatic-H).

Procedure D. Synthesis of (1*S*,4*S*,6*R*)-4-Benzhydryl-3,7-dioxa-bicyclo[4.1.0]heptane (8a) and (1*R*,4*S*,6*S*)-4-Benzhydryl-3,7-dioxa-bicyclo[4.1.0]heptane (8b). Into a solution of **7a** (0.15 g, 0.6 mmol) in CH_2Cl_2 (20 mL) was added mCPBA (0.3 g, 70%, 1.2 mmol) in a portionwise manner at 0 °C. The reaction mixture was brought to room temperature and was stirred for 20 h under N_2. Na_2SO_3 (20 mL 1.0 M solution) was added to the reaction mixture at 0 °C to quench the reaction. The aqueous phase was extracted with CH_2Cl_2 (20 mL × 2). The combined organic phase was washed in turn

with saturated $NaHCO_3$ and brine and then dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a light brown solid residue. The crude products were purified by flash chromatography on silica gel (hexane/ethyl ether = 9:1) to give **8a** (0.08 g, 50%) ($[\alpha]_D = (-)60$, $c = 1$, MeOH) and **8b** (0.065 g, 41%) ($[\alpha]_D = (-)76$, $c = 1$, MeOH). For (1*S*,4*S*,6*R*)-4-benzhydryl-3,7-dioxa-bicyclo[4.1.0]heptane **8a**, ^{1}H NMR ($CDCl_3$, 400 MHz): 1.71 (m, 1H, H-5), 1.89 (m, 1H, H-5), 3.27 (t, $J = 4.0$ Hz, 1H, H-1), 3.34 (m,1H, H-6), 3.82 (d, $J = 9.6$ Hz, 1H, Ph_2-CH), 3.95 (d, $J = 13.6$ Hz, 1H, H-2ax), 4.14 (dt, $J = 2.4$ Hz, 10.0 Hz, H-4), 4.22 (dd, $J = 4.0$ Hz, 13.6 Hz, 1H, H-2eq), 7.16−7.36 (m, 10H, aromatic-CH). For (1*R*,4*S*,6*S*)-4-benzhydryl-3,7-dioxabicyclo[4.1.0]heptane **8b**, ^{1}H NMR ($CDCl_3$, 400 MHz): 1.71 (td, $J = 4.0$ Hz, 15.6 Hz, 1H, H-5eq), 1.82 (dd, $J = 10.4$ Hz, 15.2 Hz, 1H, H-5ax), 3.06 (d, $J = 4.0$ Hz, 1H, H-1), 3.29 (t, $J = 4.0$ Hz, 1H, H-6), 3.82 (d, $J = 13.6$ Hz, 1H, H-2), 3.86 (d, $J = 9.2$ Hz, 1H, Ph_2CH), 3.93 (dt, $J = 4.0$ Hz, 9.2 Hz, 1H, H-4), 4.19 (d, $J = 13.6$ Hz, 1H, H-2), 7.16−7.36 (m, 10H, aromatic-CH).

Synthesis of (1*R*,4*R*,6*S*)-4-Benzhydryl-3,7-dioxabicyclo-[4.1.0]heptane (8c) and (1*S*,4*R*,6*R*)-4-Benzhydryl-3,7-dioxabicyclo[4.1.0]heptane (8d). Compound **7b** (0.20 g, 0.79 mmol) was reacted with mCPBA (0.27 g, 70%, 1.58 mmol) (procedure D) to yield the corresponding **8c** (0.11 g, 52%) ($[\alpha]_D = (+)60.4$, $c = 1$, MeOH) and **8d** (0.086 g, 41%) ($[\alpha]_D = (+)78$, $c = 1$, MeOH). For (1*R*,4*R*,6*S*)-4-benzhydryl-3,7-dioxa-bicyclo-[4.1.0]heptane **8c**, ^{1}H NMR ($CDCl_3$, 400 MHz): 1.71 (m, 1H, H-5eq), 1.89 (m, 1H, H-5qx), 3.27 (t, $J = 4.0$ Hz, 1H, H-1), 3.34 (m,1H, H-6), 3.82 (d, $J = 9.6$ Hz, 1H, Ph_2CH), 3.95 (d, $J = 14.0$ Hz, 1H, H-2ax), 4.14 (dt, $J = 2.4$ Hz, 10.2 Hz, H-4), 4.22 (dd, $J = 4.0$ Hz, 12.8 Hz, 1H, H-2eq), 7.16−7.36 (m, 10H, aromatic-CH). For (1*S*,4*R*,6*R*)-4-benzhydryl-3,7-dioxabicyclo-[4.1.0]heptane **8d**, ^{1}H NMR ($CDCl_3$, 400 MHz): 1.71 (td, $J = 4.0$ Hz, 15.6 Hz, 1H, H-5eq), 1.82 (dd, $J = 10.4$ Hz, 15.2 Hz, 1H, H-5ax), 3.06 (d, $J = 4.0$ Hz, 1H, H-1), 3.28 (t, $J = 4.0$ Hz, 1H, H-6), 3.82 (d, $J = 12.8$ Hz, 1H, H-2), 3.86 (d, $J = 10.0$ Hz, 1H, Ph_2CH), 3.93 (dt, $J = 3.6$ Hz, 10.0 Hz, 1H, H-4), 4.19 (d, $J = 12.8$ Hz, 1H, H-2), 7.16−7.36 (m, 10H, aromatic-CH).

Procedure E. Synthesis of (2*S*,4*R*,5*R*)-2-Benzhydryl-5-(4-methoxybenzylamino)tetrahydropyran-4-ol (−)-9a. A mixture of **8a** (0.03 g, 0.10 mmol) and *p*-methoxybenzylamine (0.28 g, 2.03 mmol) in ethanol (1 mL) was refluxed under N_2 overnight. The solvent was removed and the residue was purified by flash chromatography on silica gel (hexane/ethyl acetate/Et_3N = 6:4:0.2) to give (−)-**9a** (0.03 g, 73%) ($[\alpha]_D = (-)71.9$, $c = 1$, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz): 1.42 (m, 1H, H-3eq) 1.70 (dt, $J = 3.2$ Hz, 12.0 Hz, 1H, H-3ax), 1.72 (s, 2H, NH, OH), 2.44 (m, 1H, H-5), 3.66 (d, $J = 12.8$ Hz, Ph-CH_2), 3.74−3.84 (m, 5H, H-6, $-OCH_3$, Ph-CH_2), 3.90 (dd, $J = 2.4$ Hz, 12.0 Hz, 1H, H-6), 3.92−3.98 (m, 2H, H-4, Ph_2CH), 4.50 (dt, $J = 2.4$ Hz, 9.6 Hz, 1H, H-2), 6.80−7.40 (m, 14H, aromatic-CH). The free base was converted into the oxalate: mp 230−232 °C. Anal. [$C_{26}H_{29}NO_3 \cdot (COOH)_2$] C, H, N.

Synthesis of (2*R*,4*S*,5*S*)-2-Benzhydryl-5-(4-methoxybenzylamino)tetrahydropyran-4-ol (+)-9a. Compound **8c** (0.02 g, 0.075 mmol) was reacted with *p*-methoxybenzylamine (0.21 g, 1.50 mmol) in ethanol (procedure E) to yield (+)-**9a** (0.02 g, 80%) ($[\alpha]_D = (+)72.8$, $c = 1$, MeOH). The ^{1}H NMR was identical to that of (−)-**9a**; ^{1}H NMR (CD_3OD, 400 MHz): 1.43 (td, $J = 2.8$ Hz, 14.4 Hz, 1H, H-3eq), 1.67 (dt, $J = 2.8$ Hz, 12.0 Hz, 1H, H-3ax), 2.44 (m, 1H, H-5), 3.65 (d, $J = 12.8$ Hz, Ph-CH_2), 3.70−3.80 (m, 5H, H-6, $-OCH_3$, Ph-CH_2), 3.87 (dd, $J = 2.4$ Hz, 12 Hz, 1H, H-6), 3.91 (m, 1H, H-4), 3.95 (d, $J = 9.2$ Hz, Ph_2CH), 4.51 (dt, $J = 2.4$ Hz, 9.6 Hz, 1H, H-2), 6.80−7.40 (m, 14H, aromatic-CH). The free base was converted into the oxalate: mp 230−232 °C. Anal. [$C_{26}H_{29}NO_3 \cdot (COOH)_2 \cdot 0.5H_2O$] C, H, N.

Synthesis of (2*S*,4*R*,5*R*)-2-Benzhydryl-5-(4-fluorobenzylamino)tetrahydropyran-4-ol (−)-9b. Compound **8a** (0.03 g, 0.09 mmol) was reacted with *p*-fluorobenzylamine (0.24 g, 1.88 mmol) in ethanol (procedure E) to yield (−)-**9b** (0.03 g, 86%) ($[\alpha]_D = (-)77.2$, $c = 1$, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz): 1.40 (m, 1H, H-3eq), 1.71 (dt, $J = 3.2$ Hz, 12.0 Hz, 1H, H-3ax), 1.78 (bs, 2H, NH, OH), 2.41 (m, 1H, H-5), 3.66 (d, $J = 13.2$ Hz, 1H, $PhCH_2$), 3.72−3.96 (m, 5H, H-4, 2H-6, Ph_2CH, $PhCH_2$), 4.49 (dt, $J = 2.4$ Hz, 10.0 Hz, 1H, H-2), 6.80−7.40 (m, 14H, aromatic-CH). The free base was converted into the oxalate: mp 222−223 °C. Anal. [$C_{25}H_{26}NFO_2 \cdot (COOH)_2$] C, H, N.

Synthesis of (2*R*,4*S*,5*S*)-2-Benzhydryl-5-(4-fluorobenzylamino)tetrahydropyran-4-ol (+)-9b. Compound **8c** (0.02 g, 0.08 mmol) was reacted with *p*-fluorobenzylamine (0.19 g, 1.50 mmol) in ethanol (procedure E) to yield (+)-**9b** (0.03 g, 94%) ($[\alpha]_D = (+)77.6$, $c = 1$, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz): 1.43 (td, $J = 3.2$ Hz, 14.4 Hz, 1H, H-3eq), 1.68−1.78 (m, 3H, H-3ax, NH, OH), 2.43 (m, 1H, H-5), 3.68 (d, $J = 13.2$ Hz, 1H, $PhCH_2$), 3.74−4.00 (m, 5H, H-4, 2H-6, Ph_2CH, $PhCH_2$), 4.50 (dt, $J = 2.4$ Hz, 10.4 Hz, 1H, H-2), 6.80−7.40 (m, 14H, aromatic-CH). The free base was converted into the oxalate: mp 223−225 °C. Anal. [$C_{25}H_{26}NFO_2 \cdot (COOH)_2 \cdot 0.25H_2O$] C, H, N.

Synthesis of (2*S*,4*R*,5*R*)-2-Benzhydryl-5-[2-(4-fluorophenyl)ethylamino]tetrahydropyran-4-ol (−)9c. Compound **8a** (0.03 g, 0.09 mmol) was reacted with 2-(4-fluorophenyl)ethylamine (0.26 g, 1.88 mmol) in ethanol (procedure E) to yield (−)-**9c** (0.04 g, 98%) ($[\alpha]_D = (-)62.9$, $c = 1$, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz): 1.40 (td, $J = 3.2$ Hz, 14.0 Hz, 1H, H-3eq), 1.63 (dt, $J = 3.2$ Hz, 12.0 Hz, 1H, H-3ax), 1.84 (s, 2H, NH, OH), 2.43 (m, 1H, H-5), 2.73−2.92 (m, 4H, (F)$PhCH_2CH_2$), 3.70 (dd, $J = 2.0$ Hz, 11.6 Hz, 1H, H-6), 3.86−3.98 (m, 3H, H-4, H-6, Ph_2CH), 4.49 (dt, $J = 2.4$ Hz, 10.0 Hz, 1H, H-2), 6.80−7.40 (m, 14H, aromatic-CH). The free base was converted into the oxalate: mp 205−207 °C. Anal. [$C_{26}H_{28}NFO_2 \cdot (COOH)_2$ $0.25H_2O$] C, H, N.

Synthesis of (2*R*,4*S*,5*S*)-2-Benzhydryl-5-[2-(4-fluorophenyl)ethylamino]tetrahydropyran-4-ol (+)-9c. Compound **8c** (0.02 g, 0.08 mmol) was reacted with 2-(4-fluorophenyl)ethylamine (0.21 g, 1.50 mmol) in ethanol (procedure E) to yield (+)-**9c** (0.03 g, 98%) ($[\alpha]_D = (+)63.4$, $c = 1$, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz): 1.40 (td, $J = 3.2$ Hz, 14.4 Hz, 1H, H-3eq), 1.63 (dt, $J = 3.2$ Hz, 12.0 Hz, 1H, H-3ax), 1.70 (s, 2H, NH, OH), 2.43 (m, 1H, H-5), 2.73−2.92 (m, 4H, (F)$PhCH_2CH_2$), 3.70 (dd, $J = 2.0$ Hz, 11.6 Hz, 1H, H-6), 3.86−3.98 (m, 3H, H-4, H-6, Ph_2CH), 4.49 (dt, $J = 2.4$ Hz, 10.0 Hz, 1H, H-2), 6.80−7.40 (m, 14H, aromatic-CH). The free base was converted into the oxalate: mp 203−205 °C. Anal. [$C_{26}H_{28}NFO_2 \cdot (COOH)_2 \cdot$ $0.5H_2O$] C, H, N.

Synthesis of (2*S*,4*R*,5*R*)-2-Benzhydryl-5-benzylaminotetrahydropyran-4-ol (−)-9d. Compound **8a** (0.03 g, 0.09 mmol) was reacted with benzylamine (0.20 g, 1.88 mmol) in ethanol (procedure E) to yield (−)-**9d** (0.03 g, 86%) ($[\alpha]_D = (-)54.0$, $c = 1$, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz): 1.43 (m,1H, H-3eq), 1.69 (s, 2H, NH, OH), 1.74 (dt, $J = 2.8$ Hz, 10.8 Hz, 1H, H-3ax), 2.45 (m, 1H, H-5), 3.73 (d, $J = 13.2$ Hz, 1H, Ph-CH_2), 3.79 (dd, $J = 2.0$ Hz, 12.0 Hz, 1H, H-6), 3.86−4.02 (m, 4H, H-4, H-6, Ph_2CH, Ph-CH_2), 4.50 (dt, $J = 2.4$ Hz, 10.0 Hz, 1H, H-2), 7.00−7.40 (m, 15H, aromatic-CH). The free base was converted into the oxalate: mp 250−252 °C. Anal. [$C_{25}H_{27}NO_2 \cdot$ $(COOH)_2 \cdot 0.5H_2O$] C, H, N.

Synthesis of (2*R*,4*S*,5*S*)-2-Benzhydryl-5-benzylaminotetrahydropyran-4-ol (+)-9d. Compound **8c** (0.02 g, 0.08 mmol) was reacted with benzylamine (0.18 g, 1.64 mmol) in ethanol (procedure E) to yield (+)-**9d** (0.03 g, 81%) ($[\alpha]_D = (+)53.7$, $c = 1$, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz): 1.43 (m, 1H, H-3eq), 1.68 (s, 2H, NH, OH), 1.74 (dt, $J = 2.4$ Hz, 12.0 Hz, 1H, H-3ax), 2.54 (m, 1H, H-5), 3.73 (d, $J = 13.6$ Hz, 1H, Ph-CH_2), 3.79 (m, 1H, H-6), 3.86−4.02 (m, 4H, H-4, H-6, Ph_2CH, Ph-CH_2), 4.50 (dt, $J = 2.4$ Hz, 9.6 Hz, 1H, H-2), 7.00−7.40 (m, 15H, aromatic-CH). The free base was converted into the oxalate: mp 249−251 °C. Anal. [$C_{25}H_{27}NO_2 \cdot (COOH)_2$ $0.25H_2O$] C, H, N.

Synthesis of (3*S*,4*R*,6*S*)-6-Benzhydryl-4-(4-methoxybenzylamino)tetrahydropyran-3-ol (−)-9g. Compound **8b** (0.02 g, 0.08 mmol) was reacted with *p*-methoxybenzylamine (0.22 g, 1.58 mmol) (procedure E) to yield (−)-**9g** (0.02 g, 63%) ($[\alpha]_D = (-)63.75$, $c = 1$, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz): 1.37 (m, 1H, H-5eq), 1.81 (dt, $J = 4.0$ Hz, 12.0 Hz, 1H, H-5ax), 2.95 (m, 1H, H-4), 3.46 (m, 1H, H-3), 3.63 (m, 2H, $PhCH_2$),

3.69 (dd, J = 2.8 Hz, 12.0 Hz, 1H, H-2), 3.81 (s, 3H, $-OCH_3$), 3.96 (d, J = 9.6 Hz, 1H, Ph_2CH), 4.04 (dd, J = 1.6 Hz, 12.0 Hz, 1H, H-2), 4.53 (dt, J = 2.4 Hz, 9.6 Hz, 1H, H-6), 6.8−7.4 (m, 14H, aromatic-CH). The free base was converted into the oxalate: mp 234−235 °C. Anal. [$C_{26}H_{29}NO_3 \cdot (COOH)_2 \cdot 0.25H_2O$] C, H, N.

Synthesis of (3*R*,4*S*,6*R*)-6-Benzhydryl-4-(4-methoxybenzylamino)tetrahydropyran-3-ol (+)-9g. Compound **8d** (0.02 g, 0.08 mmol) was reacted with *p*-methoxybenzylamine (0.21 g, 1.50 mmol) (procedure E) to yield (+)-**9g** (0.03, 94%) ([α]$_D$ = (+)65, c = 1, MeOH). ^{1}H NMR (CD_3OD, 400 MHz): 1.40 (m, 1H, H-5eq), 1.78 (m, 1H, H-5ax), 2.86 (m, 1H, H-4), 3.45 (m, 1H, H-3), 3.48−3.66 (m, 3H, H-2, $PhCH_2$), 3.76 (s, 3H, $-OCH_3$), 3.80 (dd, J = 3.2 Hz, 12.0 Hz, 1H, H-2), 4.04 (d, J = 9.6 Hz, 1H, Ph_2CH), 4.59 (dt, J = 2.8 Hz, 9.2 Hz, 1H, H-6), 6.80−7.40 (m, 14H, aromatic-CH). The free base was converted into the oxalate: mp 235−237 °C. Anal. [$C_{26}H_{29}NO_3 \cdot (COOH)_2 \cdot 0.25H_2O$] C, H, N.

Synthesis of (3*S*,4*R*,6*S*)-6-Benzhydryl-4-benzylaminotetrahydropyran-3-ol (−)-9h. Compound **8b** (0.03 g, 0.09 mmol) was reacted with benzylamine (0.20 g, 1.88 mmol) (procedure E) to yield (−)-**9h** (0.03 g, 86%) ([α]$_D$ = (−)70.6, c = 1, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz): 1.30 (td, J = 3.2 Hz, 14 Hz, 1H, H-5eq), 1.68−1.80 (m, 3H, H-5ax, NH, OH), 2.88 (m, 1H, H-4), 3.40 (m, 1H, H-3), 3.54−3.70 (m, 3H, H-2, $PhCH_2$), 3.88 (d, J = 9.6 Hz, 1H, Ph_2CH), 3.96 (dd, J = 1.6 Hz, 12.00 Hz, 1H, H-2), 4.46 (dt, J = 2.4 Hz, 10.0 Hz, 1H, H-6) 7.00−7.40 (m, 15H, aromatic-CH). The free base was converted into the oxalate: mp 259−260 °C. Anal. [$C_{25}H_{27}NO_2 \cdot (COOH)_2 \cdot 0.25H_2O$] C, H, N.

Synthesis of (3*R*,4*S*,6*R*)-6-Benzhydryl-4-benzylaminotetrahydropyran-3-ol (+)-9h. Compound **8d** (0.02 g, 0.07 mmol) was reacted with benzylamine (0.15 g, 1.43 mmol) (procedure E) to yield (+)-**9h** (0.02 g, 85%) ([α]$_D$ = (+)70.1, c = 1, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz): 1.38 (m, 1H, H-5eq), 1.81 (dt, J = 3.20 Hz, 12.00 Hz, 1H, H-5ax), 2.96 (m, 1H, H-4), 3.48 (m, 1H, H-3), 3.62−3.78 (m, 3H, H-2, $PhCH_2$), 3.96 (d, J = 9.6 Hz, 1H, Ph_2CH), 4.05 (m, 1H, H-2), 4.54 (dt, J = 2.4 Hz, 9.6 Hz, 1H, H-6), 7.00−7.40 (m, 15H, aromatic-CH). The free base was converted into the oxalate: mp 259−260 °C. Anal. [$C_{25}H_{27}NO_2 \cdot (COOH)_2 \cdot 0.25H_2O$] C, H, N.

Synthesis of (2*S*,4*R*,5*R*)-2-Benzhydryl-5-(3,5-dimethoxybenzylamino)tetrahydropyran-4-ol (−)-9f. Compound **8a** (0.02 g, 0.07 mmol) was reacted with 3,5-dimethoxybenzylamine (0.25 g, 1.50 mmol) (procedure E) to yield (−)-**9f** (0.03 g, 95%) ([α]$_D$ = (−)58.60, c = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): 1.40 (m, 1H, H-3), 1.72 (m, 1H, H-3), 2.42 (m, 1H, H-5), 3.62−4.00 (m, 12H, H-4, H-6, $PhCH_2$, $-OCH_3$, Ph_2CH), 4.49 (dt, J = 2.0 Hz, 10.0 Hz, 1H, H-2), 6.34, 6.48, 7.10−7.40 (m, 13H, aromatic-CH). The free base was converted into the oxalate: mp 245−247 °C. Anal. [$C_{27}H_{31}NO_4 \cdot (COOH)_2 \cdot 0.2H_2O$] C, H, N.

Synthesis of (2*S*,4*R*,5*R*)-2-Benzhydryl-5-(2,4-dimethoxybenzylamino)tetrahydropyran-4-ol (−)-9e. Compound **8a** (0.02 g, 0.07 mmol) was reacted with 2,4-dimethoxybenzylamine (0.25 g, 1.50 mmol) (procedure E) to yield (−)-**9e** (0.03 g, 70%) ([α]$_D$ = (−)3.70, c = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): 1.42 (m, 1H, H-3), 1.77 (m, 1H, H-3), 2.10 (bs, 2H, OH, NH), 2.47 (m, 1H, H-5), 3.66−4.06 (m, 12H, H-4, H-6, $PhCH_2$, $-OCH_3$, Ph_2CH), 4.50 (dt, J = 2.8 Hz, 9.6 Hz, 1H, H-2), 6.40, 7.10−7.40 (m, 13H, aromatic-CH). The free base was converted into the oxalate: mp 208−210 °C. Anal. [$C_{27}H_{31}NO_4 \cdot (COOH)_2$] C, H, N.

Biology. The affinity of test compounds in binding to rat DAT was assessed by measuring inhibition of binding of [^{3}H]-WIN 35,428 exactly as described by us previously.[21,23] Briefly, rat striatum was the source for DAT. Final [Na^+] was 30 mM; all binding assays were conducted at 0−4 °C for a period of 2 h, and nonspecific binding of [^{3}H]WIN 35,428 was defined with 100 μM cocaine. Test compounds were dissolved in dimethyl sulfoxide (DMSO) and diluted out in 10% (v/v) DMSO. Additions from the latter stocks resulted in a final concentration of DMSO of 0.5%, which by itself did not interfere with radioligand binding. At lease five triplicate concentrations of each test compound were studied, spaced evenly around the IC_{50} value. For DAT uptake assays, uptake of [^{3}H]DA into rat striatal synaptosomes was measured exactly as described by us previously.[27] Briefly, rat striatal P_2 membrane fractions were incubated with test compounds for 5 min followed by the additional presence of [^{3}H]DA for 4 min at 25 °C. Nonspecific uptake was defined with 100 μM cocaine. Construction of inhibition curves and dissolvement of test compounds were as described above. The same general protocol was used for the measurement of uptake of [^{3}H]serotonin and [^{3}H]NE into synaptosomes prepared from rat cerebral cortex, with nonspecific uptake defined by 10 μM citalopram and 10 μM desipramine, respectively.[27] After initial range-finding experiments, at least five concentrations of the test compound were studied spaced evenly around its IC_{50} value. The latter was estimated by nonlinear computer curve-fitting procedures as described by us previously[27] and converted to K_i with the Cheng−Prusoff equation.[37] In this conversion, the K_m values for uptake of [^{3}H]DA, [^{3}H]serotonin, and [^{3}H]norepinephrine determined in parallel experiments were 145, 129, and 80 nM; the respective radiolabeled substrate concentrations used in many drug-screening experiments were 50, 21, and 11 nM. Slightly different concentrations were used in other experiments, and these were taken into account in the K_i conversions.

Acknowledgment. This work was supported by the National Institute on Drug Abuse, Grant No. DA 12449 (A.K.D.). We acknowledge Dr. Bashar Ksebati for his help with the 500 MHz NMR study. We also like to thank Dr. Hanley Abramson for reviewing this paper.

Supporting Information Available: Details of the determination of the structural assignment of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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JM049021K