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Synthesis and Biological Evaluation of Novel GBR 12909 Tropane and Azetidine Hybrid Analogues

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Synthesis and Biological Evaluation of Novel GBR 12909 Tropane and Azetidine Hybrid Analogues

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Dedicated to:

Polly

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Abstract

The high affinity, selective dopamine transporter ligand GBR 12909 has served as a template for the design of two novel classes of dopamine transporter ligands. A series of 3-[2-(diarylmethoxyethyidenyl)]-N-substituted tropane derivatives were synthesized and the binding affinities of these compounds were determined at the dopamine (DAT), serotonin (SERT) and norepinephrine (NET) transporters in rat brain tissue preparations. The tropane derivatives were found to exhibit more potent affinity and selectivity for DAT than GBR 12909. From the SAR of the tropane analogues and GBR 12909, a novel series of 3-[2-(diarylmethoxyethylidenyl)]-N-substituted azetidine derivatives has been developed.

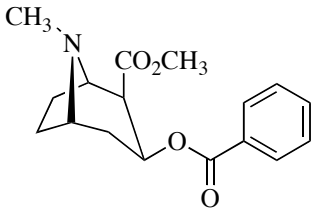
Keywords: Dopamine, serotonin, norepinephrine, tropane, GBR 12909, azetidine

Introduction

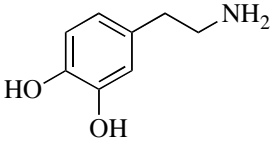
Cocaine

Cocaine (**1**) is a powerful stimulant that is isolated from the leaves of *Erythroxylum coca*, a plant found in South America.[1] The psychostimulant affects the central nervous system causing euphoria, an increase in heart rate and an increase in locomotor activity.[2] Cocaine is known to be highly addictive and a life-threatening problem.

Although cocaine inhibits the serotonin, norepinephrine, and dopamine reuptake systems, it is believed that cocaine binding to the dopamine transporter is responsible for the stimulant and reinforcing effects of the drug.[3] Cocaine is believed to block the reuptake of dopamine (**2**) at the dopamine transporter. This leads to an increased concentration of dopamine in the synapse and increased occupation of postsynaptic receptors by dopamine that causes the increased stimulation and up-regulation of dopamine receptors.[3, 4]



(-) Cocaine (**1**)



Dopamine (**2**)

Cocaine is a psycho stimulant that has historical significance. Its history includes enhancing the lifestyle of the ancient Incan empire, an anesthetic for optical surgery, prescribed by Sigmund Freud for depressed patients and finally as the worlds most addictive and exploited drug. Ancient Incans would chew the leaf of the coca plant, *Erythroxylum coca,* along with an alkaline mixture to extract the cocaine from the leaf when traveling on foot and were able to travel greater distances in less time and with less food. It was known that the effects of the coca

leaf without the alkali mixture were not produced. Cocaine in the free-base form is known today as the popular drug, "crack", or crack-cocaine.[5]

Sigmund Freud prescribed cocaine to his more depressed patients and eventually Freud became addicted to cocaine as well.[6, 7] Cocaine was demonized as being used by the poor, uneducated members of society, however, at the beginning of the 1900's, cocaine was more popular with the aristocrats and well-to-do people of society because of the high cost of cocaine. Many became addicted to the drug. Cocaine is the most addictive drug in the world and has been suggested to be more addictive in adolescence than in adults.[6, 7] Studies have shown that the addictive properties of cocaine are more pronounced in periadolescent rats than in adult rats.[7]

In South America, countries like Peru and Columbia were the major suppliers of cocaine to the United States and other parts of the world. Cocaine production was, and still is, a way of life and the sole means of income for many farmers to support their families. Because of the climate in these countries and the long life of the cocaine-producing plant, cocaine farming is more economical than some food production.[6]

In the late 1970's and early 1980's, cocaine had grown into a billion dollar industry and Reagan's War on Drugs campaign only added fuel to the fire. Drug lords in Columbia, like Pablo Escobar, started sending as many as 80 airplanes full of cocaine to the United States everyday with the idea that the Drug Enforcement Agency (DEA) could only catch a few planes on any given day. Pablo Escobar was the most notorious drug lord in South America making over a million dollars a day. In the 1980's it was estimated that children as young as 12 years old used cocaine. In 2001, approximately 15.9 million Americans aged 12 years or older used illicit drugs; 1.2 million are current cocaine users.[8] The National Drug Control Policy office estimates that number to be higher than 3.5 million chronic cocaine users.[9]

Cocaine Mode of Action

Cocaine binds to the monoamine transporters dopamine (DAT), serotonin (SERT) and norepinephrine (NET) blocking the reuptake of these neurotransmitters through the monoamine transporters.[10] Cocaine also binds to adrenergic, muscarinic, σ-receptors and sodium channels. Specifically, dopamine is normally released into the synapse and reuptake occurs across the dopamine transporter located on presynaptic nerve terminals.[8] Two Na^+ ions and one Cl^- ion bind at the transporter to allow for dopamine reuptake and finally the Na^+ and Cl^- ions cross the dopamine transporter as well. The mode of action of cocaine and subsequent addictive properties are caused by cocaine binding to the dopamine transporter and blocking the reuptake of dopamine in the synapse. Structure-activity relationship (SAR) studies have suggested that structurally diverse dopamine uptake inhibitors have binding affinities associated to two different binding sites on the dopamine transporter. [11-14] It was also mentioned by Izenwasser that cocaine competitively binds to a Na^+ ion binding site on the dopamine transporter suggesting cocaine binding at two binding sites in the nucleus accumbens.[15]

To be a potential cocaine therapeutic, a high binding affinity for the dopamine transporter, a long duration of action and slow onset of the drug would be desirable.[8] A slow onset of the drug should not cause the same effects as cocaine which has a fast onset; therefore, the "rush" is not induced by increasing the amount of dopamine in the synapse by the drug. A long duration of the drug would allow the drug to stay bound to the dopamine transporter and eventually be washed away.

Binding Constants

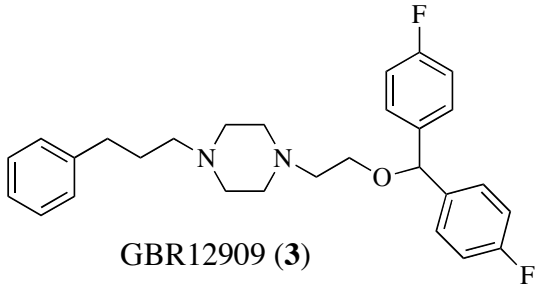
The concentration of drug needed to bind to the dopamine transporter can be measured by determining the concentration needed to produce 50% inhibition, (IC_{50}), of a radiolabeled ligand selective for dopamine transporter binding. When the drug displaces 50% of the radiolabeled ligand from the dopamine transporter, the concentration is determined as the IC_{50} value. The binding affinity is expressed as the inhibition constant K_i, which is calculated from the measured IC_{50} value by using the equation manifested by Cheng and Prusoff.[16] The substrate concentration, S, is the radio labeled ligand and K_M is the Michaelis constant for the substrate and is determined specifically for each substrate. Since these are inhibition constants, smaller K_i values correspond to increased potency (affinity) at the transporter.

$$K_i = IC_{50}/(1 + S/K_M)$$

Selectivity for the dopamine, serotonin and norepinephrine transporters is determined by the ability of the drug to displace the radio labeled ligands [^{3}H]WIN 35,428, [^{3}H]citalopram, and [^{3}H]nisoxetine, respectively, from the monoamine transporters.[7, 8]

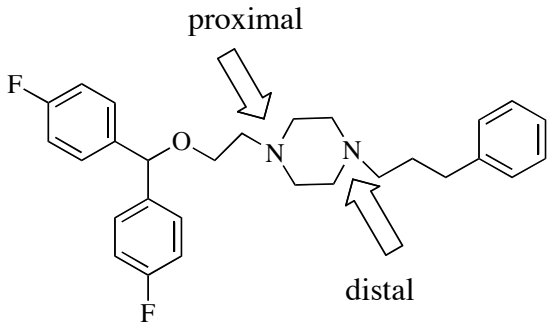
GBR 12909 Structure Activity Relationship

The piperazine compound, GBR 12909 (**3**) synthesized by van der Zee et al., was found to be a high affinity ligand (K_i = 12 nM) for the dopamine transporter.[17] GBR12909 is selective for the dopamine transporter over the serotonin transporter and is not self-administered in non-human primates; [18, 19] however, GBR 12909 also binds to σ-receptors, which is believed to be the source of dysphoria observed in humans.[20]



GBR12909 (**3**)

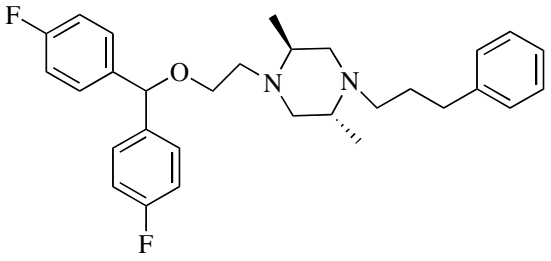
Based on the selectivity of GBR 12909 for the dopamine transporter over the serotonin transporter (SERT/ DAT = 35), GBR 12909 has been identified as a lead compound for the development of more selective analogues. Substitution around the rings of the benzhydryl moiety plays a vital role in dopamine transporter binding. Varying the size and shape of the ring and number of nitrogen atoms in the ring causes a variation in binding affinity. Furthermore, alkyl substitution on the nitrogen atom distal to the benzhydryl group has an effect on dopamine transporter binding. The distal and proximal positions are:



The benzhydryl moiety plays a vital role in dopamine transporter binding. Mono-substitution at the *para*-position of the phenyl rings with a halide increases affinity binding. High-affinity binding is displayed with dihalogen-substitution at the *para*-position with F > Cl > Br. Kulkarni et al. suggested that when there is a substituent, especially at the ortho-postion on the ring, this may interfere with the orientation of the phenyl rings by changing the torsion angle of the diphenylmethoxy moiety which causes a decrease in dopamine transporter binding affinity.[21] Small halogens at the para- and meta-positions of the diphenylmethoxy moiety can be

tolerated at the dopamine transporter, but high binding affinity requires 4,4'-difluoro phenyl substitution.[21] Many structure activity relationship studies have shown that while the difluoro benzhydryl moiety causes an increase in binding affinity at the dopamine transporter, it is the desfluoro benzhydryl moiety that exhibits the greatest selectivity for the dopamine transporter over the serotonin transporter.

Many structure-activity relationship studies have shown different binding affinities by varying the shape and size of the piperizine ring or by incorporating different functional groups into the piperazine skeleton of GBR 12909.[22-24] The piperazine analogue **4** showed dopamine transporter binding affinity equal to that of GBR 12909.[25] Winfield et al.[24] incorporated an imide functionality into the piperazine ring to give **5** which led to a decrease in binding affinity at the dopamine transporter. The expansion of the piperazine ring showed a limit to the size to which it can be expanded before the binding affinity starts to decrease. Eight-membered perhydro-diazocine rings **6** showed decreased selectivity and binding affinity for the dopamine transporter and were the limit to size the ring could be expanded. When the rings were opened (**7**), binding affinities increased but were not as potent and selective as GBR 12909.[26]



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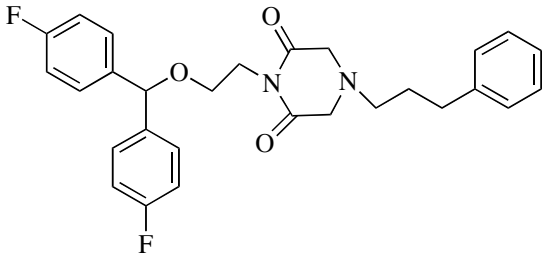

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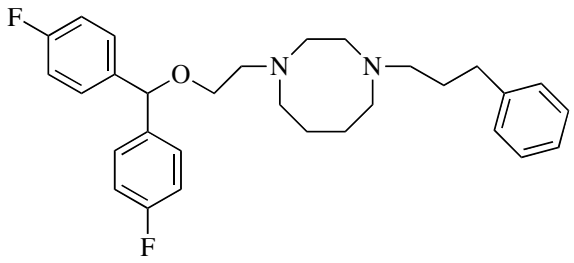
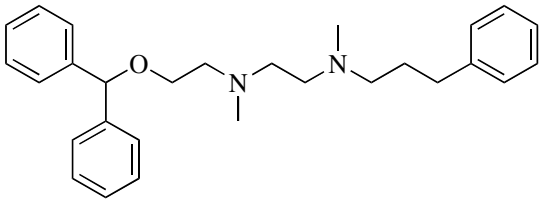
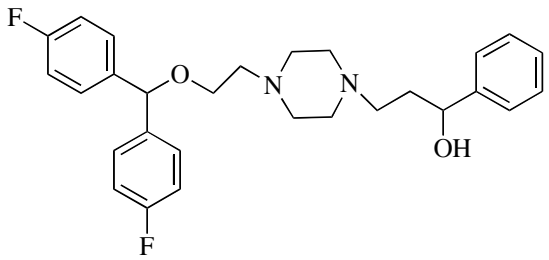
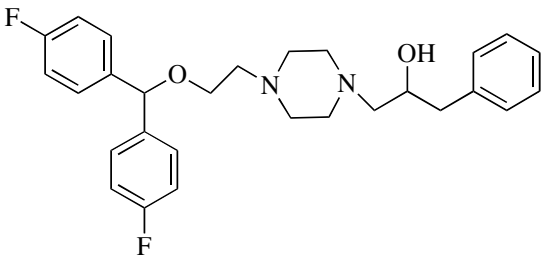




6 **7**

The *N*-alkyl chain length and substituent seem to enhance the potency and selectivity for the dopamine transporter if a phenylpropyl moiety is incorporated into the piperazine analogues.[27-30] Changing the substituents at the nitrogen atom of the piperazine analogues greatly affected dopamine transporter binding. It has also been demonstrated that a hydroxyl moiety incorporated onto the phenylpropyl moiety at the benzylic position of the GBR 12909 analogue **8** possessed binding affinity for the dopamine transporter.[31] The (S)-2-hydroxylated analogue **9** of GBR 12909 exhibited high binding affinity (DAT K_i = 0.75 nM) and was more selective than GBR 12909 or the (R)-2-hydroxylated for the dopamine transporter. The (S)-**9** analogue also increased extracellular dopamine levels in rats similar to GBR 12909 and was more potent than (R)-**9**.





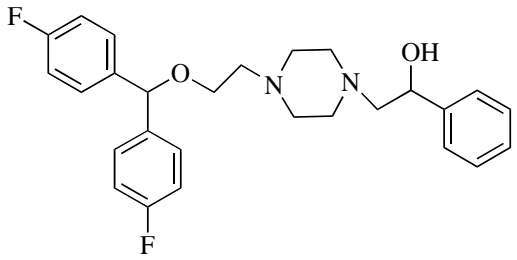
8 **9**

It has been proposed that high affinity dopamine transporter ligands reduce cocaine-maintained responding in rhesus monkeys.[31] During these behavioral studies, the rhesus monkey pushes a lever that administers a dose of cocaine, causing a positive correlation in

response to pushing the lever. When the rhesus monkey pushes the lever and the drug that produces no positive effects, the monkey stops pushing the lever because there is no reward associated with it. The (S)-**9** analogue was found to substitute for cocaine and was more potent than GBR 12909 and the R isomer. In this series of analogues, the (S)-2-hydroxyl unit was found to be vital for dopamine transporter binding *in vitro* and *in vivo* cocaine maintained responding.

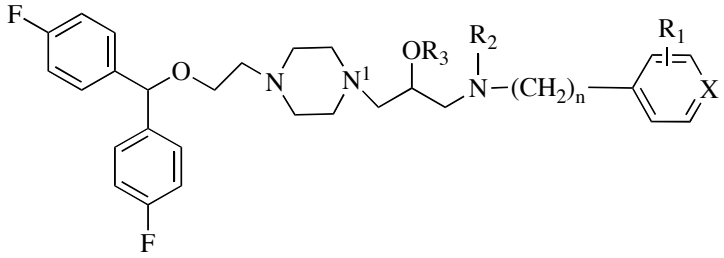
The bis-4-fluorophenyl substituted GBR 12909 compounds usually have higher binding affinities, but are less selective for the dopamine transporter than the unsubstituted diphenyl analogues. Following this trend, the unsubstituted diphenyl 2-hydroxylated analogues of **9** showed high affinity for the dopamine transporter, although not as high as the fluorine substituted analogues, and the selectivity for the dopamine transporter over the serotonin transporter was in fact higher than the fluorine substituted analogues. Interestingly, the unsubstituted (S)-2-hydroxylated analogue was 900-fold more selective for the dopamine transporter over the serotonin transporter.[31]

The phenylethyl 2-hydroxylated analogue **10** followed the trend that a phenylpropyl moiety is needed for more potent and selective dopamine transporter ligands. Following the trend of the analogues of **9**, the S isomer was more selective and more potent for the dopamine transporter than the R isomer. To increase the selectivity for the dopamine transporter, structure-activity relationship studies have shown that unsubstituted diphenyl rings and a phenylpropyl chain are needed. The R isomer of **10** incorporates the structure needed for the opposite effect for selective dopamine transporter binding and is one of the least selective dopamine transporter ligands (SERT/ DAT = 0.5). This suggests that the 2R-hydroxyl group is another factor causing the decrease in dopamine transporter selectivity over serotonin transporter selectivity.[31]



10

A series of analogues **11** were synthesized[32] that incorporate heteroaryl groups, chain elongation at N_1, derivatization of the heteroatom with chain elongation and substitution of the aryl ring. When R_3 and R_2 are hydrogen atoms and an unsubstituted aniline moiety is used, the binding affinity for the dopamine transporter was equipotent to that of GBR 12909. When the aniline analogue was changed to a benzyl amine, the binding affinity was equipotent with GBR 12909 but decreased as the number of methylene units was increased.



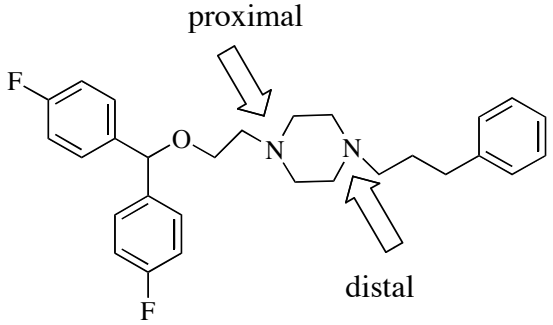
11

Para substitution (R_1) with -F, -OMe, -Me and -Cl showed no significant difference in binding affinity at the dopamine transporter. However, a bulkier and strongly electron-withdrawing 4-NO_2 moiety showed a slight decrease in binding affinity. When the bulkier substituents were incorporated onto the ring, binding affinities were significantly decreased. The 4-$N(CH_3)_2$ analogue had an IC_{50} = 109 that is much lower than GBR 12909 (IC_{50} = 12 nM) and may be caused by steric bulk and basicity of the nitrogen. The 4-pyridinyl analogue showed a decrease in binding affinity (IC_{50} = 32 nM) for the dopamine transporter which indicates that the

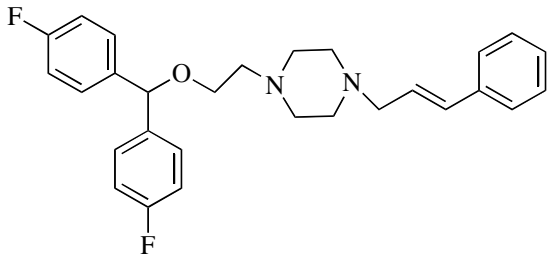
basicity of the pyridinyl nitrogen may cause some unfavorable interaction with the binding site of the dopamine transporter.[32]

Substitution of the 3-amino-2-propanol nitrogen with a methyl moiety showed no decrease in binding affinity. However, substitution with more electron-withdrawing acetyl and mesyl moieties elicited less potent binding affinities at the dopamine transporter. When the hydroxyl group was modified by replacing it with an acetoxy or methoxy moiety, the binding affinity decreased which suggests that the hydroxyl moiety is important in these compounds for hydrogen-bonding or hydrophilic interactions at the dopamine transporter.[32]

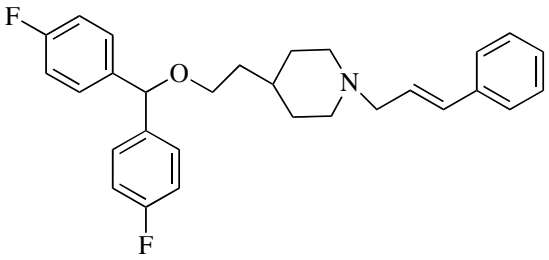
As previously mentioned, GBR 12909 possesses two nitrogen atoms in its structure although two nitrogen atoms are not necessary for binding to the dopamine transporter. Dutta et al.[33] proved which of the two nitrogen atoms was essential for dopamine transporter binding affinity and selectivity. By replacing the nitrogen atom proximal to the benzhydryl moiety with a carbon atom in the piperazine analogue, binding affinity for the dopamine transporter increased more so than by replacing the nitrogen atom distal from the benzhydryl group.



The cinnamyl derivative **12** of GBR 12909 demonstrated comparable potency (DAT IC_{50} = 1.9 nM) as a more rigid analogue of GBR 12909.[34] Interestingly, the piperidine analogue **13** showed higher affinity for the dopamine transporter than the piperazine analogue **12** and was more potent for the dopamine transporter over the serotonin transporter, (SERT/DAT = 104). [28]

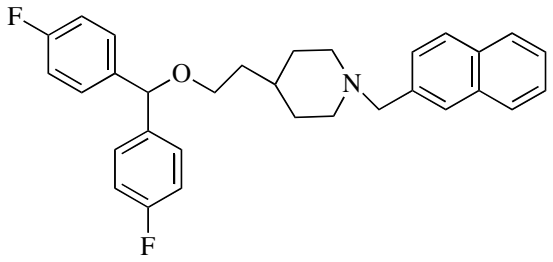


12



13

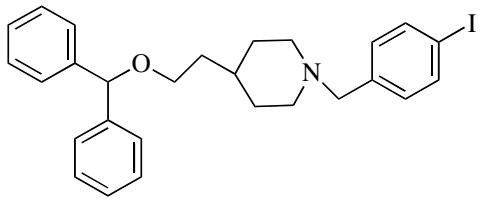
When the piperidine analogue **13** was incorporated with an alkyne moiety in place of the trans double bond, the affinity for the dopamine transporter decreased suggesting that a linear conformation was not favorable at the transporter. Further, the naphthylmethyl piperidine derivative **14** showed high affinity for the dopamine transporter (DAT K_i = 0.71 nM) and an increase in dopamine transporter selectivity over the serotonin transporter (SERT/ DAT = 323).[28] This suggests that the piperazine and piperidine analogues are not binding to the dopamine transporter in the same manner.



14

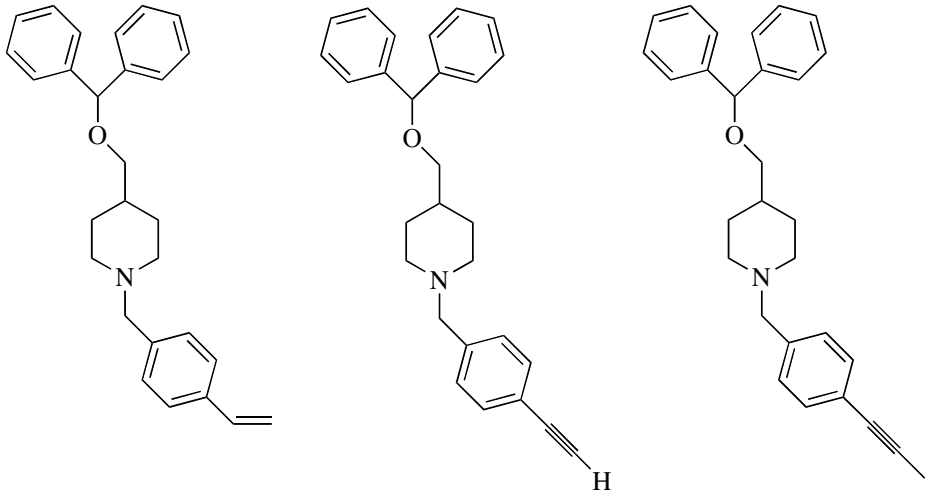
The piperidine analogues of GBR 12909 have been reported to show a preference for a one-carbon chain length between the nitrogen and the aryl derivative that is usually a benzyl moiety.[28-33] The iodo analogue **15** showed increased binding affinity for the dopamine transporter (DAT IC_{50} = 0.96 nM) and increased selectivity over the serotonin transporter (SERT/ DAT = 3041). [29] Interestingly, when the large iodine atom is in place of the naphthyl group, the binding affinity and selectivity for the dopamine transporter increases. This suggests that in these

piperidine compounds, a large halide atom at the para-position eliminates the need for such planar π-systems like the naphthyl-substituted analogues. It was also suggested that the large iodine atom might induce changes in the lipophilic and steric interactions at the dopamine transporter.[29]



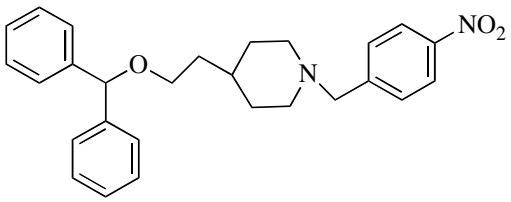
15

Introduction of a *para*-ethenyl benzyl **16** moiety or a *para*-ethynyl benzyl **17** moiety was tolerated by the dopamine transporter and showed selectivity for the transporter over the serotonin transporter but were not as potent or selective as the iodo analogue **15**. However, the *para*-ethenylbenzyl analogue **16** showed greater potency for dopamine uptake inhibition than **15**. It was also noted that in the 4-acetylenic substituted benzyl analogues, if the terminal H-atom was replaced with a methyl group to give **18**, the binding affinity decreased due to increased steric bulk.[29]



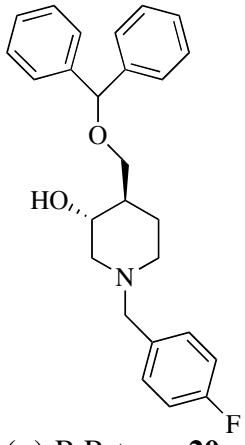
16 **17** **18**

Substitution around the benzyl ring of the piperidine analogues exhibited a significant difference in binding affinity. Typically, para-substitution led to higher affinities at the dopamine transporter whereas meta- or ortho- substitution decreased in binding affinity at the dopamine transporter. Electron-withdrawing groups on the *N*-benzyl ring were also favored for dopamine binding affinity over electron-donating groups. The desfluoro-piperidine analogues usually are not as potent as the fluorine substituted benzhydryl analogues, but do demonstrate better selectivity for the dopamine transporter over the serotonin transporter. It is noteworthy that the 4-NO_2 deslfuoro analogue **19** was highly selective for the dopamine transporter over the serotonin transporter (SERT/ DAT = 859) and in dopamine uptake inhibition studies (SERT/ DAT = 1310). [30]

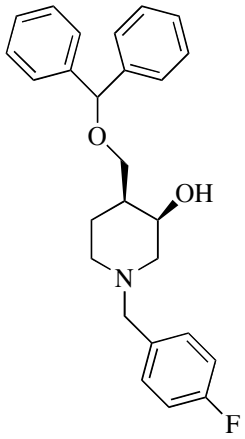


19

Many of the piperazine and piperidine analogues demonstrated high binding affinity and selectivity for the dopamine transporter by incorporating many different functional groups around the molecule. Hydroxy groups incorporated into the alkyl chains or substitution around the benzyl moiety has been shown to be important for high affinity binding. Introduction of a hydroxy group into the piperidine ring served to present compounds that were potent at the dopamine transporter.[34] The racemic cis and trans piperidine analogues **20** proved to be potent dopamine transporter ligands. However, the resolved trans (+)-R, R analogue (DAT IC_{50} = 0.46 nM) had a high binding affinity much greater than GBR 12909 and its unhydroxylated parent piperidine compound and was highly selective for the dopamine transporter over the serotonin transporter (SERT/ DAT = 7800). The cis analogue was approximately three times less potent than the racemic trans diastereomer. This illustrates the stereochemical importance of the hydroxyl moiety in these compounds for binding at the dopamine transporter. Interestingly, the (+)-R, R analogue had a lower dopamine uptake inhibition than what is normally expected for such a potent ligand. [25, 34]



(+)-R,R-trans-**20**



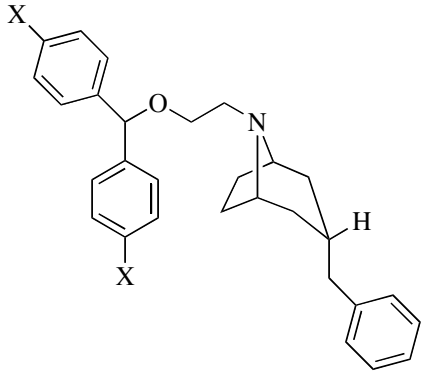
cis-**20**

In vivo studies for the racemic and resolved trans diastereomer produced substantial results when compared with cocaine. Cocaine produced maximum locomotor responses at 10 mg/kg within the first ten minutes and tapered off to that of the vehicle within three hours after the initial injection. It took 56 mg/kg of the racemic mixture to invoke maximum response between twenty to thirty minutes and continued to invoke a locomotor response for three hours. The (+)-trans isomer induced a response at 56 mg/kg at twenty minutes but locomotor activity decreased to that of the vehicle. Interestingly, the locomotor activity for a 30 mg/kg dose of trans-(+)-**20** remained elevated throughout the three-hour duration. Significantly, the (-)-trans isomer only showed locomotor response at doses of 100 mg/kg within twenty minutes but decreased almost immediately to that of the vehicle and remained constant throughout the rest of the three hours. In a cocaine discrimination response test in rats trained to discriminate cocaine, all three compounds tested produced a response in rats. This indicates that the compounds are not having a problem crossing the blood-brain barrier to reach the dopamine transporter in the central nervous system.[25, 34]

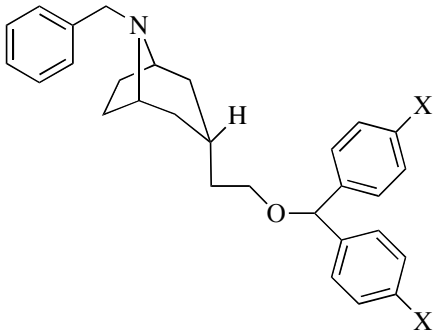
As has been previously reported, replacing the nitrogen atom distal to the benzhydryl moiety decreases binding affinity at the dopamine transporter.[29] A series of tropane-based analogues have been synthesized that show the same trend in binding as the piperidine analogues synthesized by Dutta. The fluorine-substituted analogue **21** (X = F) (DAT K_i = 144 nM) was shown to be more potent than cocaine but was significantly less potent than GBR 12909.[35] The chlorine, methyl and methoxy substituted analogues were shown to have binding affinities equipotent or less than that of the fluorine substituted analogue. Usually, the fluorine-substituted analogues of any series of dopamine transporter ligands follow a trend that binding affinities increase with fluorine-substitution. However, the unsubstituted analogue (X = H) was shown to

have the highest binding affinity at the dopamine transporter over the substituted analogues in the series (DAT K_i = 98 nM).[35] Interestingly, Bradley et al. reported the binding affinity for **21** to be equipotent with that observed with the unsubstituted analogue **22a** (DAT K_i = 99 nM).[36] The rigidity of the tropane ring system in **21** may cause a conformation suitable for binding at the dopamine transporter where the difference in which nitrogen is replaced is not a factor for high binding affinities in the tropane-class of compounds. Therefore, it was shown that a piperazine ring system was not needed for potent binding at the dopamine transporter and nitrogen replacement was no longer a factor.

The benzyl analogues **22** demonstrated decreased potency at the dopamine transporter. Interestingly, the 4, 4'-difluoro analogue of **22b** was shown to be the most potent (DAT K_i = 5.7 nM) and most selective dopamine transporter ligand (SERT/ DAT = 251) in the series. The 4, 4'-dichloro analogue **22c** was the least selective (SERT/ DAT = 9). These findings run counter to what is normally expected for GBR-based dopamine transporter ligands and is linked to the incorporation of the benzyl group.[36]

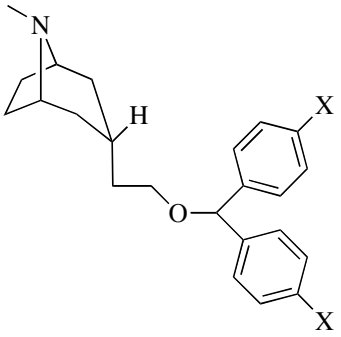


21

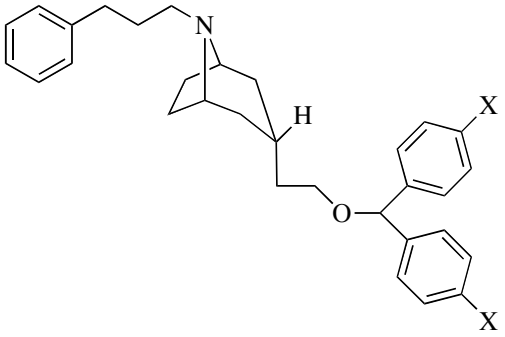


22a **X = H**
b **X = F**
c **X = Cl**

The *N*-methyl 3α-derivatives **23** were compared to the benzyl and phenylpropyl derivatives and were generally less potent than the phenylpropyl analogues **22** and slightly more potent than the benzyl analogues **21**. The desfluoro analogue of **23a** was the most selective (SERT/DAT = 243) analogue for the dopamine transporter over the serotonin transporter than its difluoro, dichloro or monochloro substituted analogues but the least potent (DAT K_i = 58 nM) of the series. Usually, the desfluoro analogues show greater selectivity for the dopamine transporter but tend to have diminished potency at the transporter.[36]



23a **X = H** **X = H, Cl**
b **X = F**
c **X = Cl**



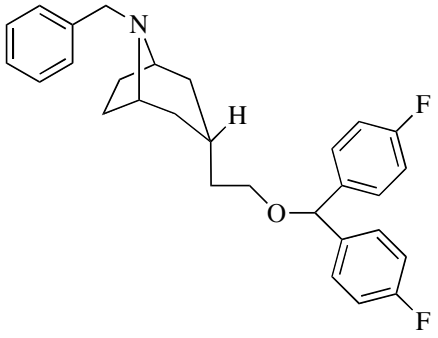
24

The phenylpropyl analogues **24** demonstrated high binding affinities for the dopamine transporter except for the dichloro analogue, which was the least selective of the series (SERT/ DAT = 4). The difluoro analogue was shown to be the most potent in the series (DAT K_i = 7.4 nM) but was not very selective for the dopamine transporter (SERT/ DAT = 24). The difluoro analogue showed a comparable affinity to that of ethylidene analogues **25** although it was not as selective for the dopamine transporter.[36]

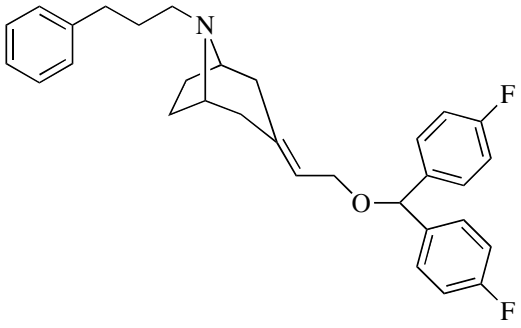
The ethylidene analogues **25** were synthesized as racemic compounds and designed to elucidate the stereochemical limits of the dopamine transporter. Constructing a more rigid compound proved to enhance the potency and selectivity at the dopamine transporter. The least

potent (DAT K_i = 48 nM) and least selective (SERT/ DAT = 113) of the series was the *N*-benzyl desfluoro benzhydryl analogue. Contrary to previous results, the difluoro substituted *N*-benzyl analogue was significantly more potent (DAT K_i = 7.9 nM) but was highly selective for the dopamine transporter (SERT/ DAT = 281). The *N*-phenylpropyl desfluoro analogue was more potent than its *N*-benzyl congener and was the most selective of the ethylidene analogues (SERT/ DAT = 327). Although less selective for the dopamine transporter than the desfluoro analogue, the *N*-phenylpropyl difluoro substituted analogue was slightly more potent (DAT K_i = 3.7 nM) than the other analogues in the series. The results proved that sp^2-hybridization of the C3-carbon atom increased binding affinity and selectivity for the dopamine transporter.[36]

During a recent biological study by the NIDA Medication Development Program[37], the α-tropane isomers were shown to be more potent than GBR 12909 at the dopamine transporter in HEK cells expressing cDNA for the human dopamine transporter (HEK-hDAT). Specifically, the tropane analogue, 8-benzyl-3α-bis(4-fluorophenyl) methoxyethyl-8-aza-bicyclo-[3.2.1]octane, [ALB-III-141 (**22b**), K_i = 147 nM][37] exhibited dopamine transporter (HEK-hDAT) affinity approximately twice that of cocaine. In addition, tropane derivative **25** proved to be even more potent than the α-tropane isomers, [ALB-IV-41 (**25**), K_i = 39 nM]. The alkylidene derivative **25** was found to be equipotent with GBR 12909.[37]



22b

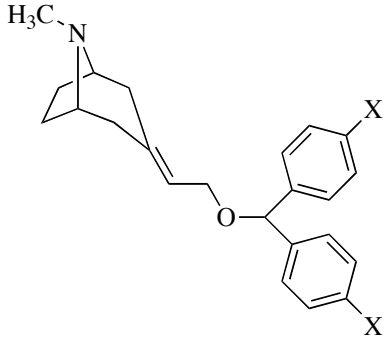


25

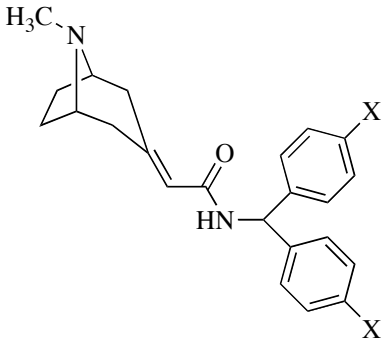
The compounds **22** and **25** differ from GBR 12909 by incorporation of the more rigid tropane skeleton and one nitrogen atom in the bicyclic system. The similarities of the tropane analogues to that of GBR 12909 include the N-alkyl chain, the benzhydryl moiety and the tether between the benzhydryloxy moiety and the parent skeleton. These compounds lack two nitrogens unlike that of GBR 12909 concluding that the second nitrogen is not necessary for potent dopamine transporter binding affinity.

Zhang et al.[38] synthesized a series of *N*-methyl alkylidenyl tropane analogues **26** and **27**. These compounds demonstrated comparable results to previous trends of other dopamine transporter ligands. The 4, 4'-difluoro substituted analogues showed increased binding affinity for the dopamine transporter and increased dopamine uptake inhibition over the desflouro analogues. This is consistent with previously reported GBR 12909 analogues. Usually, the desfluoro analogues show increased selectivity for the dopamine transporter when compared to the difluoro substituted analogues.

The 4, 4'-difluoro substituted analogue of **26** exhibited high binding affinity for the dopamine transporter (DAT K_i = 19 nM) and increased selectivity for the dopamine transporter over the serotonin transporter (SERT/ DAT = 189). The amide analogues **27** showed decreased binding affinity for the dopamine and serotonin transporters, decreased selectivity for the dopamine transporter and decreased dopamine uptake inhibition.[38]



26



27

Rationale for Design of Novel GBR-Related Analogues

GBR 12909 exhibits potency at the dopamine transporter but the piperazine ring allows for this compound to bind to σ-receptors in the brain. It is believed that by binding to these receptors GBR 12909 caused patients to experience dysphoria during human clinical trials and, therefore, GBR 12909 was abandoned as a potential medication. The tropane ring offers a more rigid bicyclic skeleton that decreases the flexibility of the molecule and subsequently could lead to a potential decrease in binding to σ-receptors in the brain. The structure-activity relationship studies of Dutta et al. proved that the distal nitrogen atom is the one needed for high affinity binding to the dopamine transporter.[29] Studies have suggested that increased pharmacokinetics may be due to increased lipophilicity of the analogues.[39-41]

GBR 12909 has a clogP value of 5.37. If a drug is too lipophilic, it will have difficulty crossing the blood-brain barrier and get stuck in the lipid bilayer.[48] Obviously with a clogP value of 5.37, GBR 12909 is very lipophilic and would not cross the blood-brain barrier very rapidly. Cocaine has a clogP value of 3.24 and is able to cross the blood-brain barrier very rapidly and occupy the dopamine transporter. Crack, the freebase form of cocaine has a very fast onset of

action and is subject to abuse because it is usually inhaled into the lungs where it can enter the blood stream rapidly where it is carried to the brain.

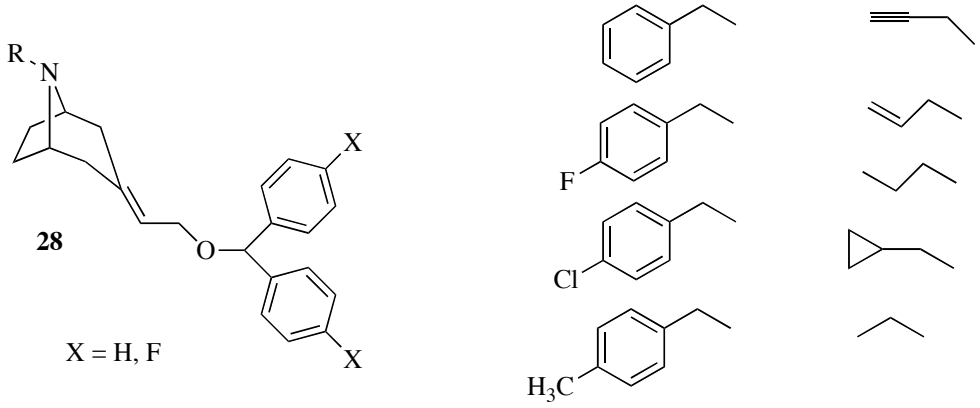
Objectives

As mentioned before, GBR 12909 has a high binding affinity and is selective for the dopamine transporter over the serotonin and norepinephrine transporters and is not self-administered in non-human primates.[18, 19] However, GBR 12909 does bind to σ-receptors, which is believed to be the cause of dysphoria in humans.[17-20] The goal of this research was to develop novel GBR 12909 tropane hybrid and azetidine analogues for potent dopamine transporter ligands as potential therapeutics for cocaine addiction. While utilizing the tropane skeleton, diminished σ-receptor activity and increased binding affinity and selectivity at the dopamine transporter is anticipated. The objective for the design of the azetidine analogues was to design compounds that were less lipophilic than the GBR 12909 tropane hybrid analogues. The azetidine compounds would keep the rigidity needed for binding to the dopamine transporter and would have lipophilicity less than or equal to GBR 12909.

Cocaine binds to the dopamine transporter stereoselectively.[38] In addition, Meltzer et al. found that methylphenidate binds to the dopamine transporter stereospecifically but did not exhibit addictive properties like that of cocaine.[43] It is interesting to note that the 3β-analogues of the tropane-based series of compounds have typically been less potent than their 3α-conformers. This indicates that, like cocaine, there is a stereoselective preference in binding affinity to the dopamine transporter as well as the other monoamine transporters. In other studies to synthesize potent dopamine uptake inhibitors, a 3β-diphenylmethoxyalkyl moiety of the tropane-based analogues have displayed low binding affinity for the dopamine transporter. Changing the stereochemistry and substituents around the tropane ring greatly affects the binding affinity.

Therefore, it was of interest to synthesize compounds that had a stereochemical preference for the dopamine transporter. It was envisioned that resolution of the racemic mixture of the alkyidenyl tropane compounds would enhance the binding affinity and selectivity at the dopamine transporter. Modifying the N-substitution could also enhance selectivity and potency. Benztropine and phenyltropane analogues substituted at the 2-position have shown to have high binding affinity to the dopamine transporter. Benztropine analogues incorporate a diphenly-methoxy moiety that is significantly bulkier and less water soluble than the phenyl moiety of the 3-phenyltropane analogues. Increasing the carbon chain length and steric bulk of the substituent on the nitrogen led to increased binding affinity to the dopamine transporter as well as increasing the lipophilicity of the compound.[43-49] To this end, a series of GBR-tropane hybrid analogues (Figure 1) and GBR-related azetidine analogues (Figure 2) were designed to further investigate the binding motifs of monoamine transporters in the hope of identifying new lead compounds for development of a cocaine medication.

Figure 1. Target GBR 12909 Tropane Hybrid Analogues



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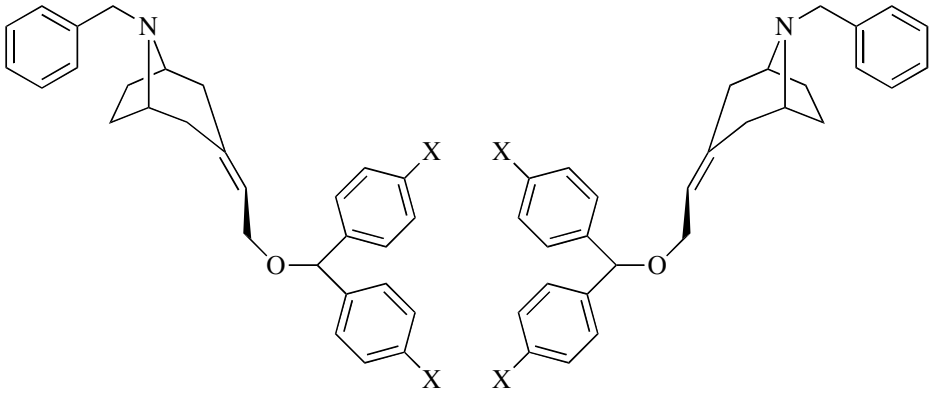
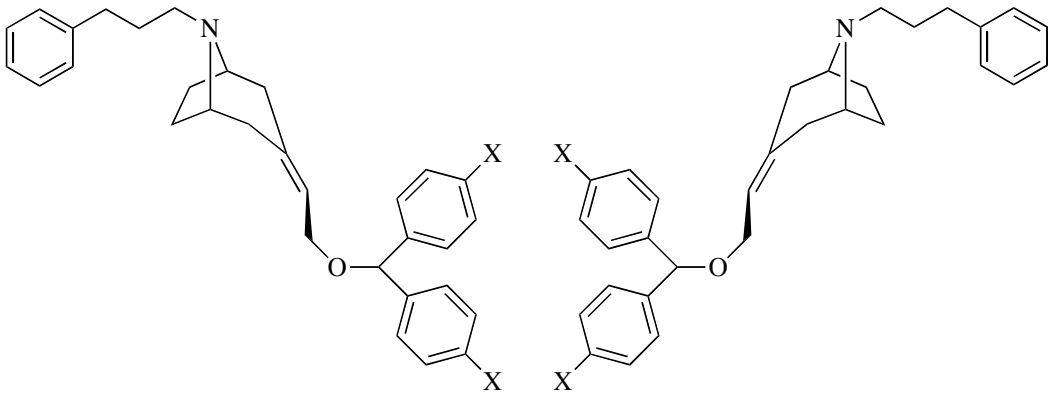
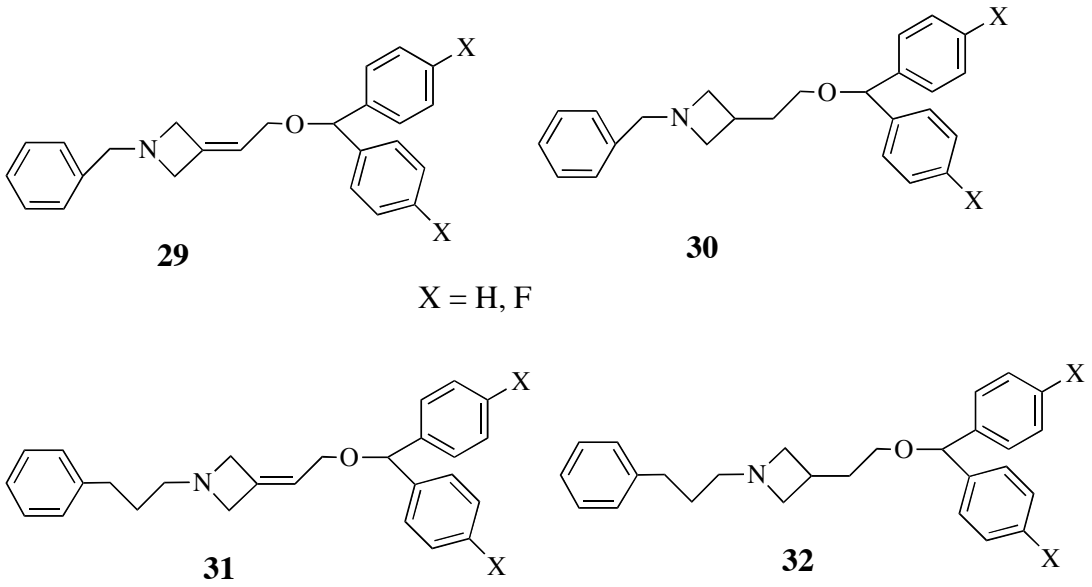


(±) 28a



(±) 25

Figure 2. Target Azetidine Analogues



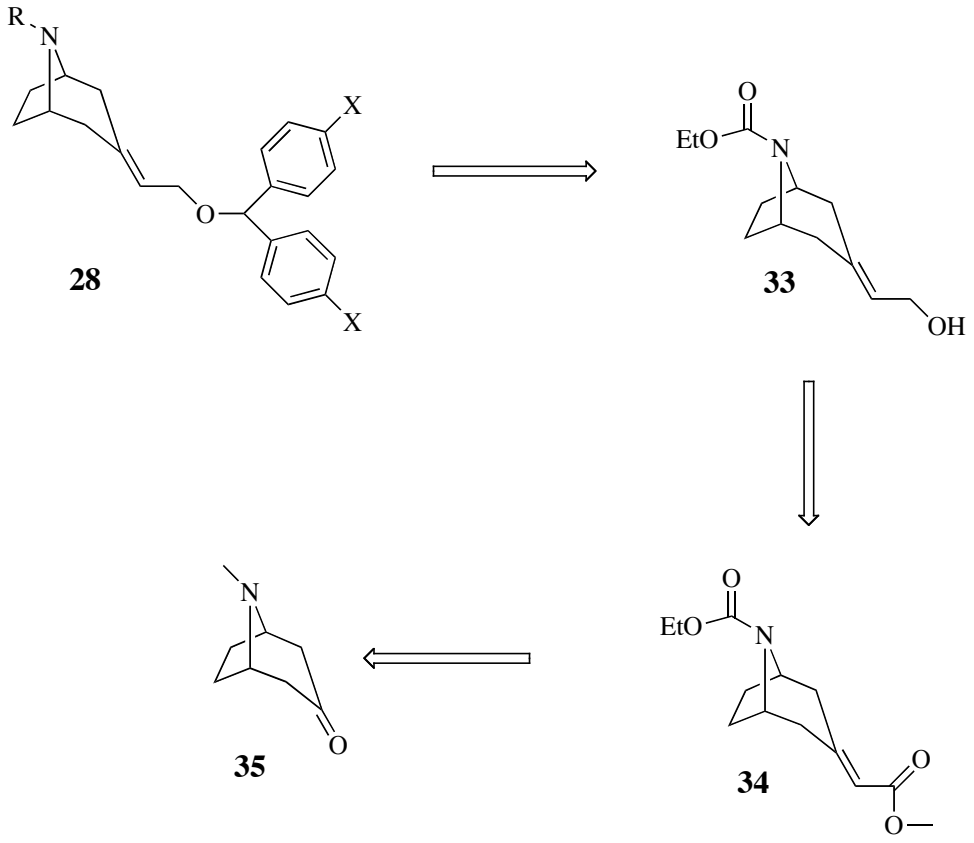
Synthesis of 8-alkyl-3-diarylmethoxyethylidenyl-8-azabicyclo[3.2.1]octane analogues

It was envisaged that the synthesis of these analogues would commence with the commercially available 3-tropinone (**35**). In the retrosynthetic analysis (Scheme 1), the olefination of the protected 3-tropinone would provide a scaffold (**34**) for incorporating stereochemistry into the molecule. Subsequent reduction of the conjugated ester **34** from the olefination would provide the allylic alcohol **33** and further ether synthesis would furnish the substituted diphenylmethoxyethylidene analogues. Deprotection of the secondary nitrogen atom would set the stage for the final derivatization to provide the final alkylidene analogues (**28**).

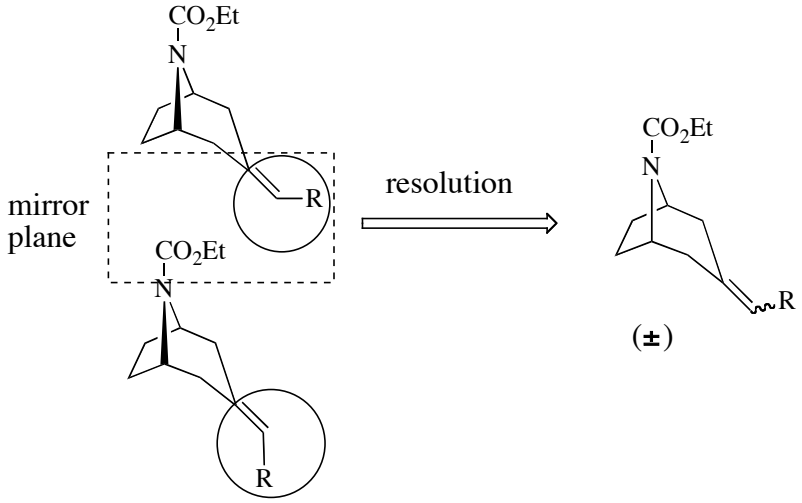
The 3-α tropane analogues **22** and **24** synthesized by Bradley et al.[37] were shown to be fairly potent dopamine transporter selective ligands. However, it was thought that bringing the stereochemistry at the 3-position into a more rigid planar conformation by incorporation of a double bond would lead to analogues that were more potent and more selective for the dopamine transporter. As illustrated in Scheme 2, it was concluded that the alkylidene could be resolved

into the enantiomeric forms of the molecule. Resolution could be carried out by various techniques that would set the stage early for further derivatization of the analogues and preparation of enantiomerically pure ligands.

Scheme 1. Retrosynthesis of Tropane Analogues



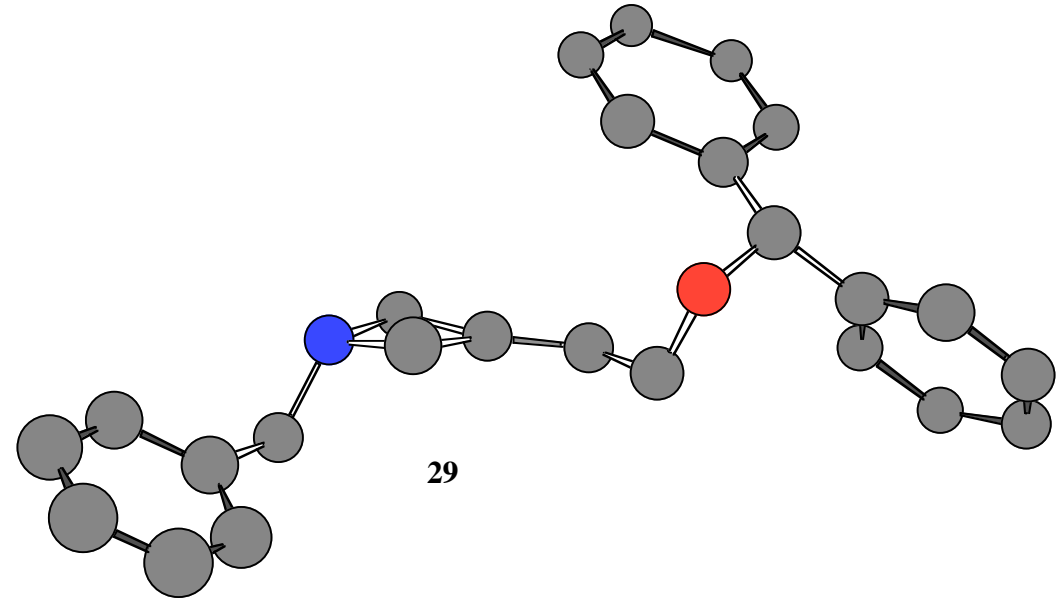
Scheme 2. Retrosynthesis of Resolved Enantiomers



Synthesis of 3-diphenylmethoxyalkyl-8-substituted-azetidine analogues

As mentioned previously, the rationale for synthesizing the novel azetidine analogues was to keep the rigidity of the tropane hybrid analogues but decrease the lipophilicity for better bioavailability. Compared to the tropane hybrid analogue (**28Ha**) (clogP = 6.29) the azetidine analogue (**29**) is significantly less lipophilic (clogP = 5.14) and would be expected to have better bioavailability. These four-membered nitrogen rings are highly strained molecules and the stability of these molecules during the synthesis was of great importance. Further, when subsequent incorporation of a double bond is introduced, the molecule adopts an almost planar conformation, Figure 3. These semi-planar azetidine analogues could be developed from a novel synthetic strategy that keeps these highly strained compounds intact throughout the process.

Figure 3. Conformation of 3-Alkylidenylazetidine **29** and 3-Alkylazetidine **30**.



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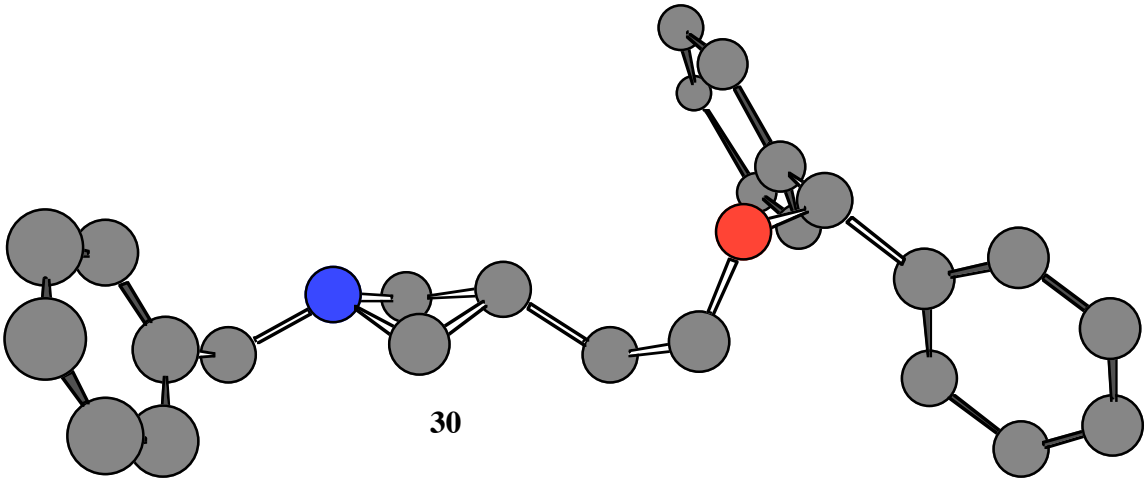
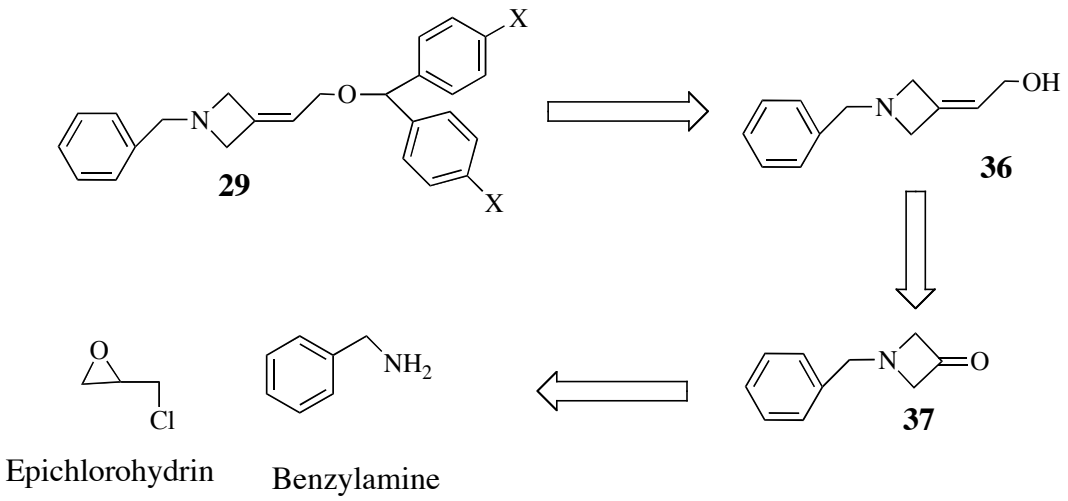


30

The synthetic approach for these novel azetidines can be seen in the retrosynthetic analysis depicted in Scheme 3. The synthesis would commence from the straightforward reaction of the commercially available starting materials epichlorohydrin and the appropriate alkylamine (i.e. benzylamine). Further oxidation of the alcohol formed from the ring-closed product would provide the key 3-azetidinone **37**. This would be subjected to Horner-Wadsworth-Emmons olefination and subsequent reduction to furnish the allylic alcohol **36**. To finish the synthesis and obtain the final product, a straightforward ether synthesis with the appropriately substituted benzhydryl derivative would provide the target diphenylmethoxy-alkylidenyl-*N*-substituted-azetidine analogues **29**.

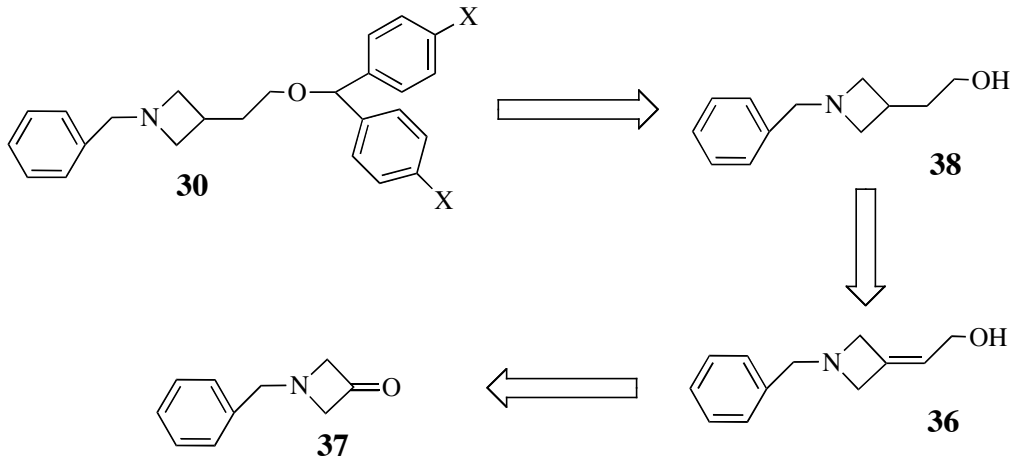
Scheme 3. Restrosynthesis of Unsaturated Azetidine Analogues



As illustrated in Scheme 4, the saturated azetidine analogues would be synthesized in similar fashion to the unsaturated highly strained congeners from the alkylidenyl alcohol **36**. Selective hydrogenation of the double bond of **36** would furnish the saturated azetidine analogues. This selective hydrogenation is predicted to occur in high yield due to the relief of

ring strain induced by saturation of the double bond. The saturated azetidine alcohol **38** will be furnished in a straightforward manner from **36**, which is readily obtained from azetidinone **37** (Scheme 3). The alcohol **38** in turn will be subjected to a straightforward ether synthesis with the appropriately substituted benzhydryl derivative, which will provide the target diphenylmethoxyalkyl-*N*-substituted-azetidine analogues **30**.

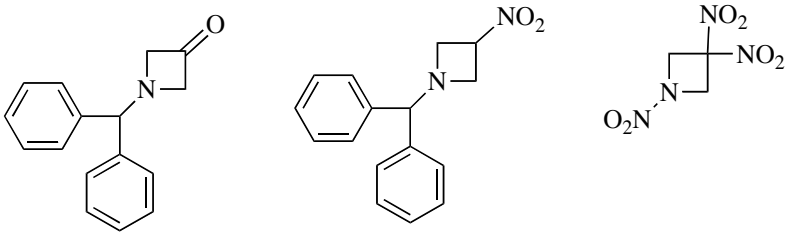
Scheme 4. Retrosynthesis of Saturated Azetidine Analouges



Construction of Azetidine Ring Systems

The challenge of synthesizing azetidine compounds has been attempted with some success by various other groups.[50-53] Figure 4 shows several of these azetidine derivatives that have been recently synthesized. Interestingly, the diphenylmethyl azetidine analogue **39** has been reported to be very stable when stored in the refrigerator for several weeks.[50] The stability is thought to be derived from the two phenyl moieties delocalizing the electron density from the nitrogen atom as well as steric interactions. This is believed to stabilize the strained ring system.

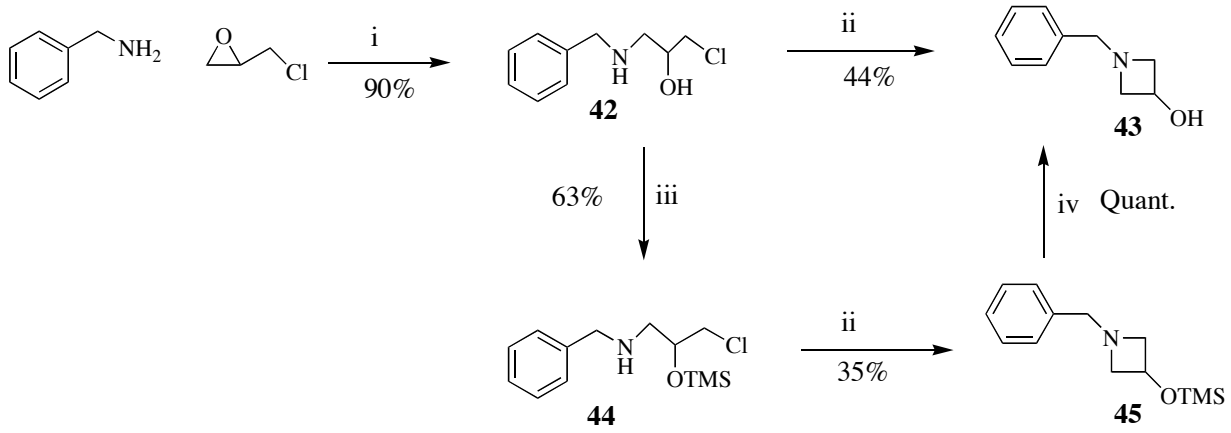
Figure 4. Important Azetidine Derivatives



39 **40** **41**

The few methods that are available for the synthesis of azetidines are somewhat tedious, limited in scope and low yielding. Of these methods, the procedure developed by Higgins et al[51]seemed to be one of the most versatile and highest yielding (Scheme 5). It was reported that starting with epichlorohydrin and benzylamine, epoxide ring opening occurred to give aminal **42** in moderate yield after two days at room temperature. Following the ring opening, the azetidinol **43** was formed in a modest yield by heating at reflux for three days. It was reported that the yield of the azetidinol **43** could be increased by protection of the alcohol as the trimethylsilyl ether **44**. Subsequent treatment of **44** in refluxing petroleum ether after three days furnished the protected azetidine **45** in 35% yield. The silyl ether **45** could then be deprotected with acid to give the azetidinol in a greater yield and higher purity.

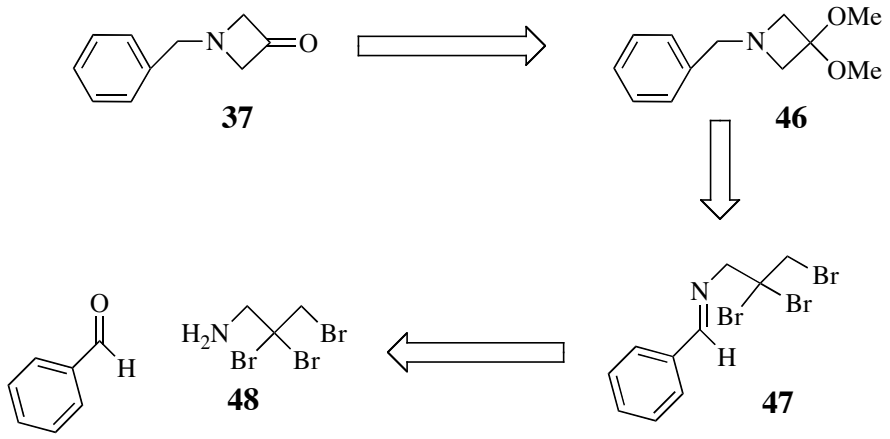
Scheme 5. Synthesis of Azetindinol **43**



Reagents: i) rt 2 days, pet ether. ii) reflux 3 days, CH_3CN, Et_3N. iii) N-(trimethylsilyl) acetamide, pet. ether, reflux 3 h. iv) aq HCl, 5 min.

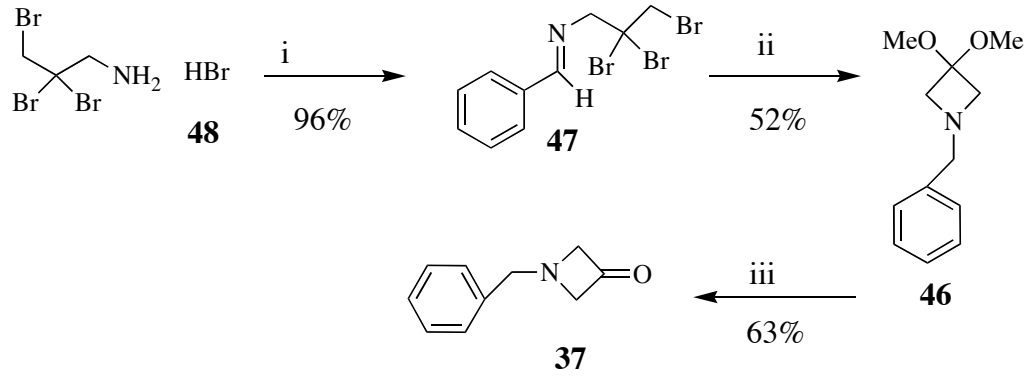
An elegant synthesis to obtain the key azetidine **37** was recently reported by De Kimpe et al.[54] The intermediate would set the stage for further reaction to obtain the target azetidine analogues. As illustrated in Scheme 6, the azetidinone **37** would be unmasked from the protected ketal **46**. The azetidine ring would be formed via a reductive condensation process that proceeds through imine **47** from reaction of the appropriate aldehyde and the tribromopropylamine **48**.

Scheme 6. Retrosynthesis of Azetidinone **37**



De Kimpe et al. initiated the synthesis of azetidinone **37** by condensation of readily available starting material **48** and benzaldehyde at room temperature under basic conditions (Scheme 7). Magnesium sulfate was used to scavenge the water that is produced and drive the reaction to completion. After purification, the imine **47** was reduced with sodium borohydride and subsequent ring-closure insued. Displacement of the bromines via methanolysis in refluxing methanol produced the protected ketal **46** in 52% yield over 3 steps. This set the stage for unmasking the ketone by methyl ether cleavage with 10 equivalents of concentrated sulfuric acid for three hours followed by a basic workup. De Kimpe reported the synthesis to afford the azetidinone **37** in 63% yield. It was also noted that the azetidinone **37** starts to decompose at room temperature after eight hours and electron-withdrawing or sterically demanding substituents on the nitrogen atom stabilize the azetidinone from self-condensation.[54]

Scheme 7. Synthesis of Azetidinone **37**



Reagents: i) Et_3N, benzaldehyde, $MgSO_4$, CH_2Cl_2, rt 1h. ii) $NaBH_4$, MeOH, reflux 14 h. iii) H_2SO_4, rt, 3h.

Based upon the rational described above and the chemistry outlined, the synthesis of the target GBR-related compounds—GBR-tropane hybrids (Figure 1) and GBR-related azetidines (Figure 2) were pursued.

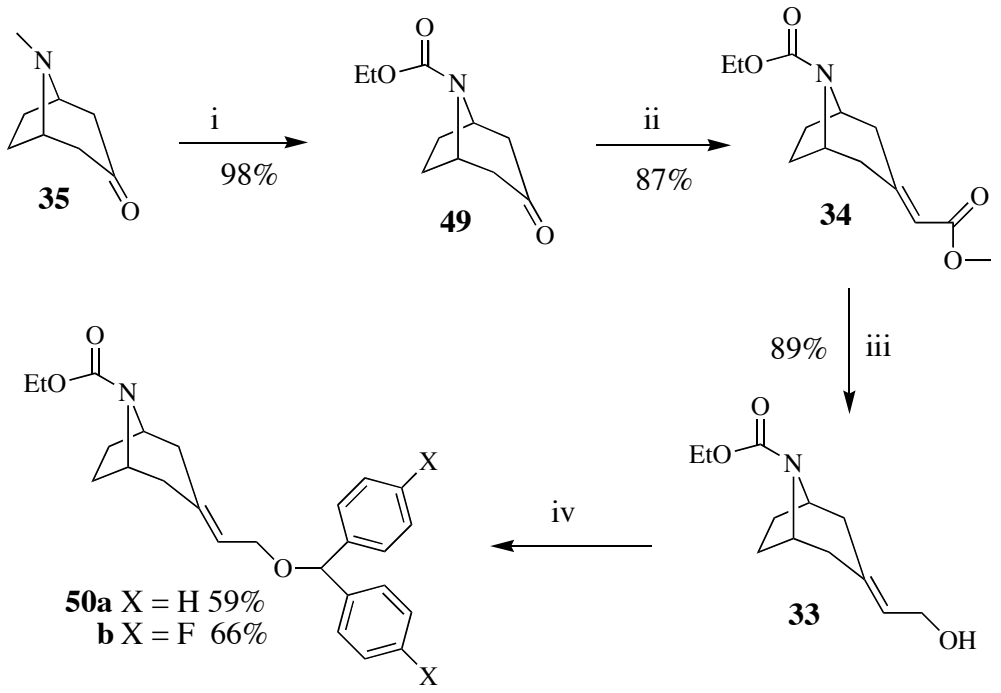
Results and Discussion

GBR 12909-Tropane Hybrids: Synthesis of 8-Alkyl-3-diarylmethoxyethylidenyl-8-azabicyclo[3.2.1]octane Analogues

The synthesis of the 8-alkyl-3-diarylmethoxyethylidenyl-8-azabicyclo[3.2.1]octane analogues commenced with the protection of the nitrogen atom of 3-tropinone (**35**). It was envisaged that the basicity of the nitrogen atom could cause complications with further base promoted reactions. As such, the carbamate **49** was prepared. Three equivalents of ethyl chloroformate were used to make the carbamate **49** by refluxing in toluene overnight with 3-tropinone under a nitrogen atmosphere. Three equivalents of potassium carbonate were used to keep the reaction media basic and to help scavenge any excess hydrochloric acid that would be generated during the reaction. After a standard workup and purification, the product **49** was obtained in 98% on a multigram scale (Scheme 8). The carbamate **49** was subjected to Masamune-Roush modification of the Horner-Wadsworth-Emmons reaction.[55] Normal olefination reactions usually undergo Wittig reaction conditions whereby an alkylphosphonate is treated with a strong base and added to the carbonyl compound. Wittig reagents are usually very reactive and require low temperatures to produce high yielding reactions. Under Masamune-Roush-Horner-Wadsworth-Emmons conditions, the reactions are much cleaner, can be performed at room temperature and yield the olefination products in high yields. Trimethyl-phosphonoacetate was added to a stirred solution of lithium chloride in acetonitrile at room temperature. The hindered base, 1, 8-diazabicylo[5.4.0]undec-7-ene (DBU), was added to the stirred solution followed by the carbamate **49** in acetonitrile. It was important to add the reagents in the proper order starting with lithium chloride coordination with the phosphonate to increase the acidity of the α-proton of the phosphonate and subsequently making the reagent

more reactive at room temperature. The reaction was allowed to stir at room temperature overnight under an atmosphere of nitrogen. After a standard workup and column chromatography, the alkene **34** was produced in 87% yield.

Scheme 8. Synthesis of Tropane Analogues



Reagents: i) EtOCOCl, K_2CO_3, toluene, Δ. ii) LiCl, $(CH_3O)_2POCH_2CO_2CH_3$, DBU, CH_3CN. iii) $LiAlH_4$, THF, 0° C. iv) $(Ph)_2CHCl$ or $(4\text{-F-Ph})_2CHCl$, neat, 145° C.

The reduction of the conjugated ester **34** had to be cautiously reacted with lithium aluminum hydride to yield the allyl alcohol **33**. Lithium aluminum hydride usually adds a hydride via 1,2-addition to reduce the ester to the alcohol. However, in the presence of a conjugated ester such as **34**, there is a potential for 1,4-addition of hydride to the double bond producing a mixture of side-products. The conjugated ester was carefully added to a solution of 1.2 equivalents of lithium aluminum hydride at 0° C via syringe over 30 minutes under a

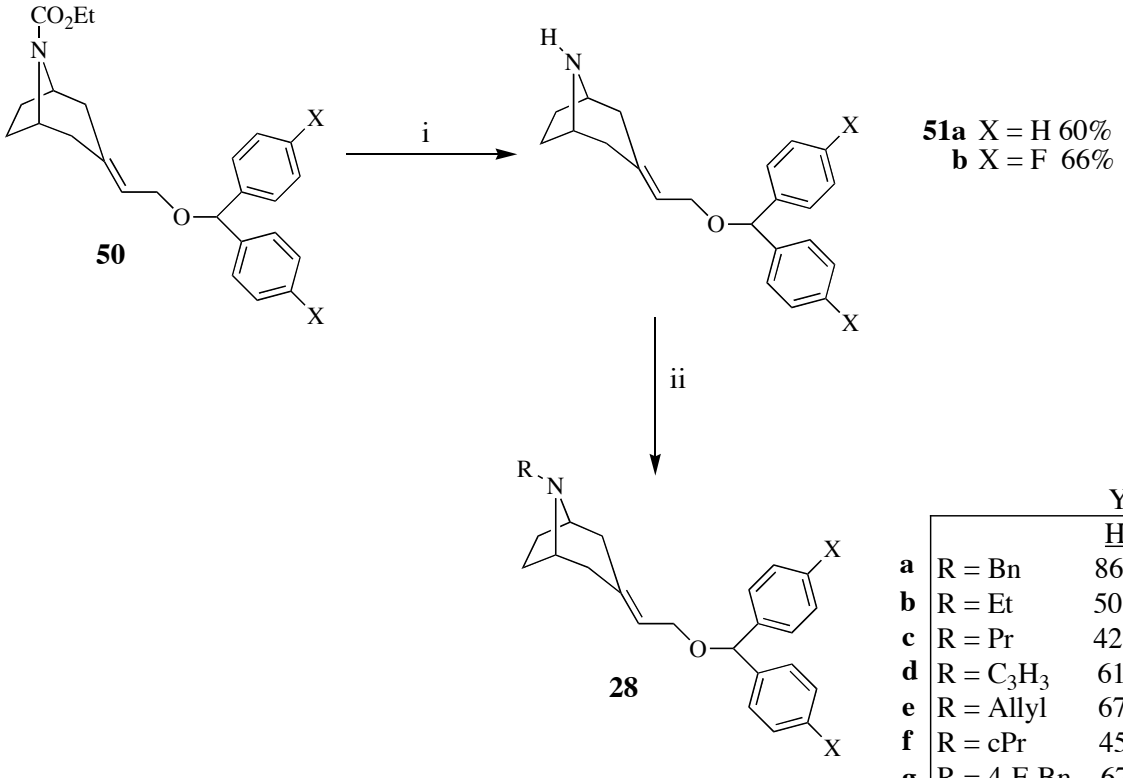
nitrogen atmosphere. After the addition of the ester was complete, the mixture continued to stir at 0° C. After monitoring the reaction via TLC, it was determined that the reaction was complete after two hours. The grey mixture was allowed to continue stirring at 0° C while a 10% KOH solution was very slowly added via syringe. After the first drop of the 10% KOH solution was added, the reaction mixture bubbled profusely. After the bubbles subsided, the reaction was slowly quenched and allowed to warm up to room temperature with stirring over one hour. The mixture was poured into a separatory funnel and the white solid left in the flask was washed with diethyl ether. The washings were added to the separatory funnel and phosphate buffer (pH = 7) was added. After workup and purification, the allylic alcohol **33** was obtained in 89% yield.

The allylic alcohol **33** was then reacted with 1.5 equivalents of either chlorodiphenyl-methane or bis(4-fluorophenyl)methylchloride to form the new benzhydryl ether derivative **50**. The ether synthesis was performed neat at 145° C for two hours and no workup was required. After the reaction cooled to room temperature, it was dissolved in a minimal amount of ethyl acetate and put directly onto a column for purification. The ether **50** was obtained in 59-66% yield.

The derivatized ether **50** was subjected to carbamate deprotection with refluxing hydrazine (Scheme 9). Hydrazine monohydrate was added to the protected ether **50** in ethylene glycol followed by 26 equivalents of potassium hydroxide. The mixture was stirred and brought to reflux for three hours. The stability of the ether under such harsh conditions was initially uncertain, but under these basic conditions the ether remained intact. After cooling to room temperature, the mixture was poured into a separatory funnel and washed with water. Upon addition of water, the mixture turned a milky white but returned to a clear yellow solution after mixing with ether. A standard workup and purification yielded the deprotected derivative **51** in

60-65% yield. Further derivatization of the nitrogen atom of **51** ensued by reaction with the appropriate alkylbromide. The reaction was carried out in DMF with 1.1 equivalents of the corresponding alkylbromide and 2.0 equivalents of potassium carbonate. The reaction was stirred under a nitrogen atmosphere at 80 °C overnight. The reaction was cooled to room temperature and a standard workup and purification yielded the various *N*-alkylated analogues **28** in 45%-94%.

Scheme 9. Synthesis of Tropane Analogues



		Yield H	Yield F
a	R = Bn	86%	80%
b	R = Et	50%	66%
c	R = Pr	42%	68%
d	R = C_3H_3	61%	63%
e	R = Allyl	67%	66%
f	R = cPr	45%	65%
g	R = 4-F-Bn	67%	87%
h	R = 4-Cl-Bn	93%	74%
i	R = 4-Me-Bn	60%	85%

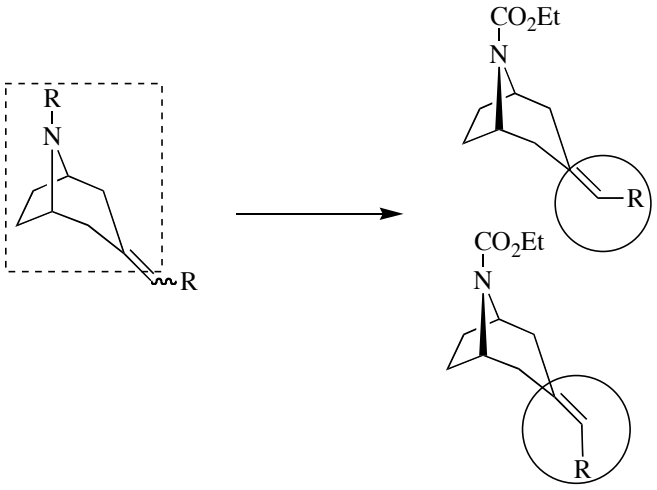
Reagents: i) H_2NNH_2 H_2O, KOH, ethylene glycol, Δ.
ii) RBr, K_2CO_3, DMF, 80 °C.

Resolution of 8-Alkyl-3-diarylmethoxyethylidenyl-8-azabicyclo[3.2.1]octane Analogues

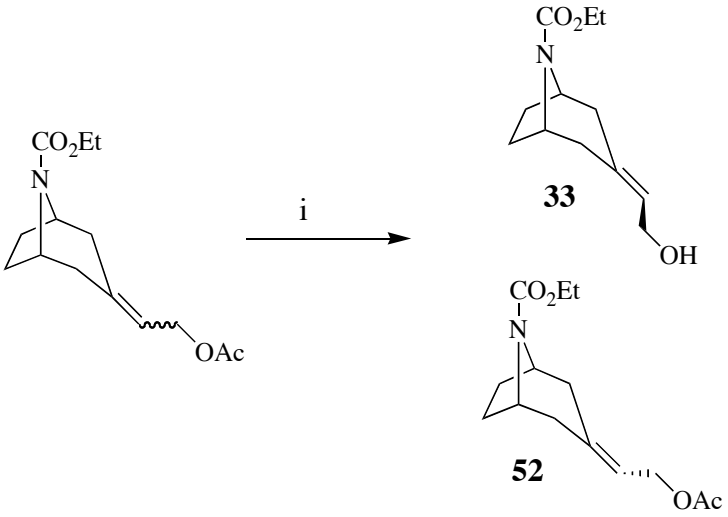
It was of great interest to determine the structure-activity relationships of the resolved 8-alkyl-3-diarylmethoxyethylidenyl-8-azabicyclo[3.2.1]octane analogues. It was envisaged that one enantiomer would potentially be more potent and more selective at the dopamine transporter than the racemic mixture or the other enantiomer. Enzymatic and kinetic resolutions were employed but yielded only starting material. Exhaustive attempts to try to resolve the enantiomers by way of enzymatic and kinetic resolutions failed to resolve the allylic alcohol **33**, vinylic ester **34**, allylic ether **50** and nortropane **51**.

The problem with trying to resolve these tropane analogues is the plane of symmetry that goes through the 8-azabicyclo[3.2.1.]octane ring system (Figure 5). This results in a very small enantiomeric differentiation. Initial attempts were made to resolve the allylic acetate ester **52** by enzymatic resolution with (PPL) porcine pancreatic lipase at 40° C to furnish the resolved ester $[\alpha]^{20}_{D} = -1.36$, c = 1.25 (Scheme 10).[56] Only a small amount of starting material was resolved and this approach was abandoned.

Figure 5. Plane of Symmetry Through the Tropane Skeleton



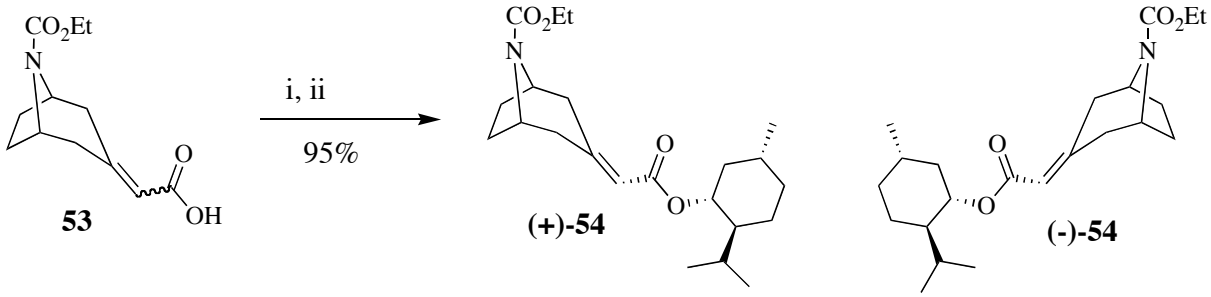
Scheme 10. Enzymatic Resolution with PPL



Reagents: i) PPL, Et_2O, EtOH, 40° C, overnight

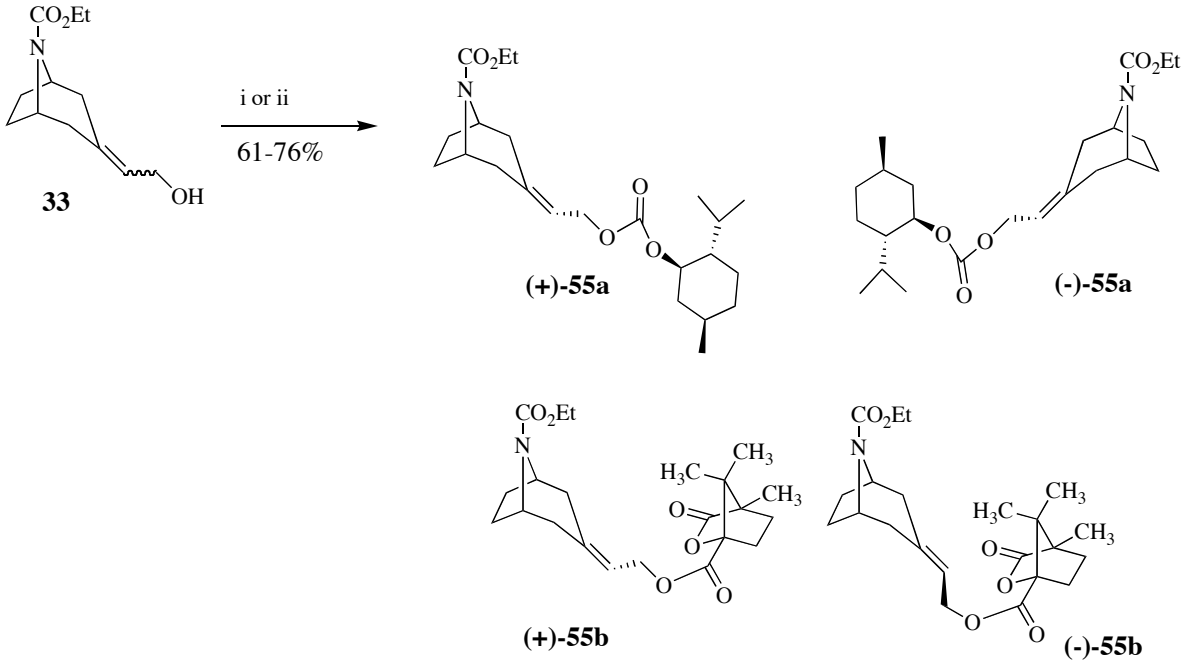
Derivatization of the vinylic carboxylic acid **53** with a menthol auxillary was attempted with the hope that the diastereomeric esters **54** could be separated by column chromatography or HPLC (Scheme 11). Although the reaction to make the diastereomeric esters ensued in high yield, 85-97%, the mixtures proved inseparable by column chromatography or HPLC. Derivatization of the allylic alcohol **33** with different menthol or camphor auxillaries was also attempted. The corresponding carbamates were obtained in 61-76% yield; however, these diastereomeric esters **55** were found to be inseparable as well (Scheme 12).

Scheme 11. Carboxylate Ester Derivatization



Reagents: i) $SOCl_2$, Δ. ii) Menthol, pyridine, rt overnight.

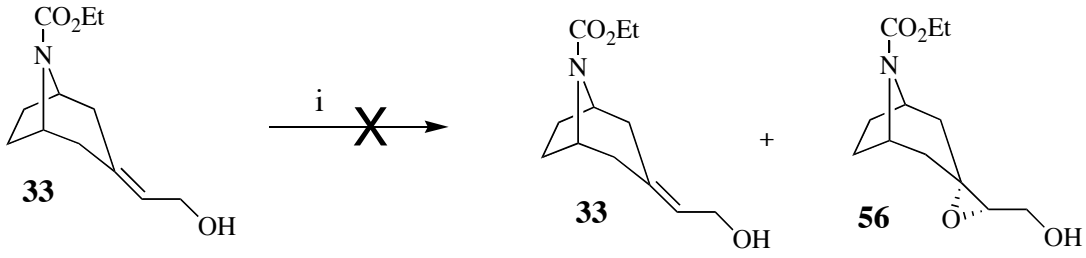
Scheme 12. Allylic Carbonate Ester Derivatization



Reagents: i) Mentholchloroformate, pyridine, rt overnight.
ii) Camphanic acid chloride, pyridine, rt overnight.

Another attempt to resolve the enantiomers employed the Sharpless epoxidation of the allylic alcohol **33**. It was envisaged that the Sharpless epoxidation would kinetically epoxidize one alcohol before the other (Scheme 13) giving the epoxide **56** and the resolved allylic alcohol **33**. All the attempts to resolve the alcohol by Sharpless epoxidation failed and only starting material was recovered.

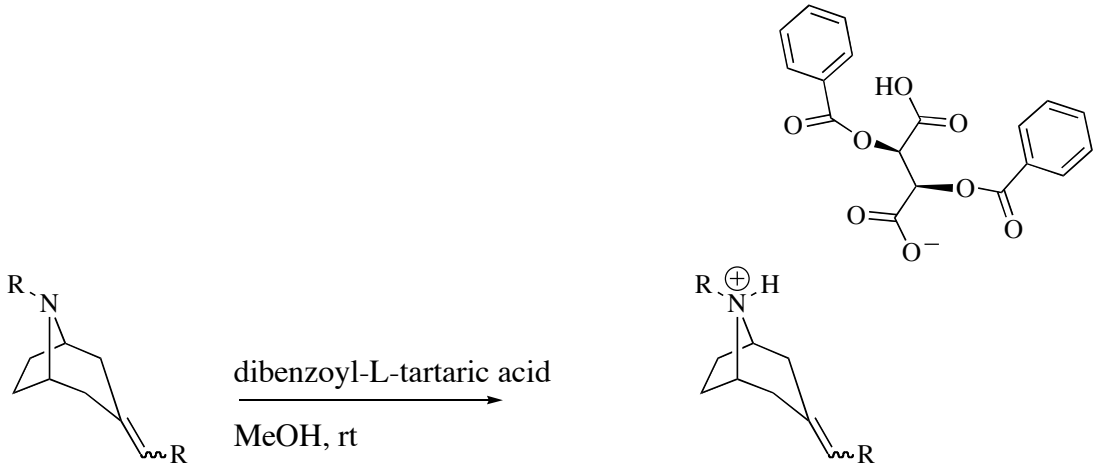
Scheme 13. Sharpless Epoxidation



Reagents: i) $Ti(OiPr)_4$, (+)-diethyl-tartrate, t-butyl hydrogen peroxide, molecular sieves, CH_2Cl_2, -20° C, overnight.

After all attempts to kinetically resolve the enantiomers failed, it was envisaged that resolution might be achieved by making a diastereomeric salt. Theoretically, one diasteromeric salt would crystallize better than the other, leaving the other diastereomeric salt in solution. Filtering the salt followed by freebasing the single diastereomeric salt would give the resolved alkylidenyltropane derivatives (Scheme 14). This approach, although potentially tedious since each final analogue would have to be resolved, did offer the advantage that the enantiomers could be resolved on a multigram scale without the need for column chromatography. In addition, the crystalline diastereomeric salt could be used to determine the absolute confirmation of the alkylidene by X-ray crystallography.

Scheme 14. Salt Formation

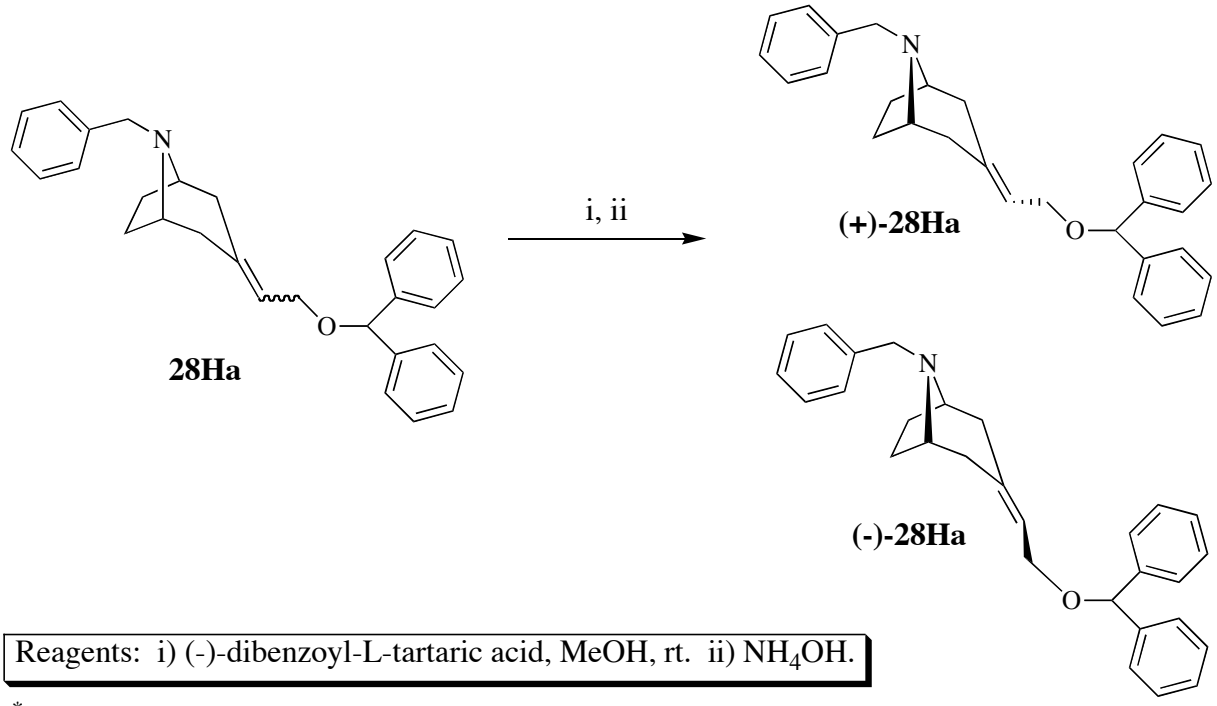


Many attempts to resolve any of the *N*-alkylidenyltropane analogues **28** by making a diastreomeric salt failed. Many chiral acids were used in attempts to make these salts. These included (+)-or (-)-mandelic acid and (+)-or (-)-tartaric acid. Finally, the *N*-benzyl desfluoro analogue **28a** was the only structure that was readily resolved (Scheme 15). The salt of (-)-L-dibenzoyl tartaric acid crystallized as the diastereomeric salt and resolved the tropane derivatives into the corresponding enantiomers.

The *N*-benzyl desfluoro analogue **28a** was dissolved in dry methanol and allowed to stir at room temperature. An equivalent of the L-or D-dibenzoyl tartaric acid was dissolved in dry methanol and added to the reaction flask. After stirring for several minutes at room temperature, a white precipitate persisted and the solution was allowed to stir at room temperature for an additional five hours. The precipitate was collected by vacuum filtration and the filtrate was concentrated under reduced pressure. The residue from the filtrate was freebased with ammonium hydroxide and extracted with chloroform. The organic layer concentrated and dissolved in dry methanol and subjected to resolution with the other chiral tartaric acid. The salts were combined in a flask and freebased with ammonium hydroxide. The freebase of the resolved analogue was separated from the aqueous layer with chloroform. The organic layer was

evaporated and optical rotations determined as $[\alpha]^{20}_{D} = -17.5$ and $[\alpha]^{20}_{D} = +17.0$. The enantiomers in Scheme 15 are ambiguously drawn for simplicity and do not represent the absolute stereochemistry of the resolved enantiomers. The absolute stereochemistry will be determined via X-ray crystallography.

Scheme 15. Resolution of Tropane Analogue **28Ha**



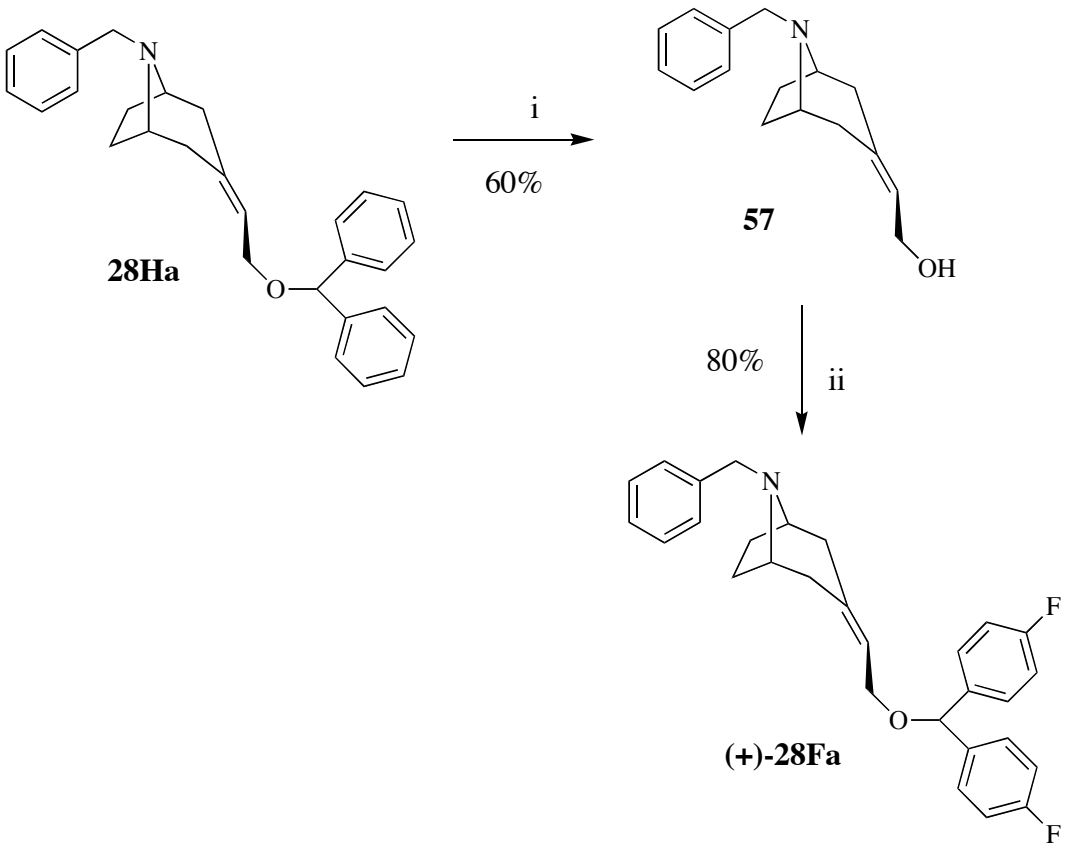
Reagents: i) (-)-dibenzoyl-L-tartaric acid, MeOH, rt. ii) NH_4OH.

*Compounds **(+)-28Ha** and **(-)-28Ha** are drawn for clarity but do not represent the absolute configurations of the enantiomers.

Now that the alkylidene analogues could be resolved, it was thought that simply cleaving the ether in refluxing hydrochloric acid would afford the allylic alcohol **48**. The alcohol could be derivatized with bis(4-fluorophenyl)methylchloride to produce the 4-fluoro substituted benzhydryl moiety (Scheme 16). Debenzylation of the nitrogen could have been carried out with

a simple hydrogenation using 10% Pd/C; however, the presence of the double bond eliminated use of that transformation. Other means of debenzylation would have to be found.

Scheme 16. Ether Derivatization



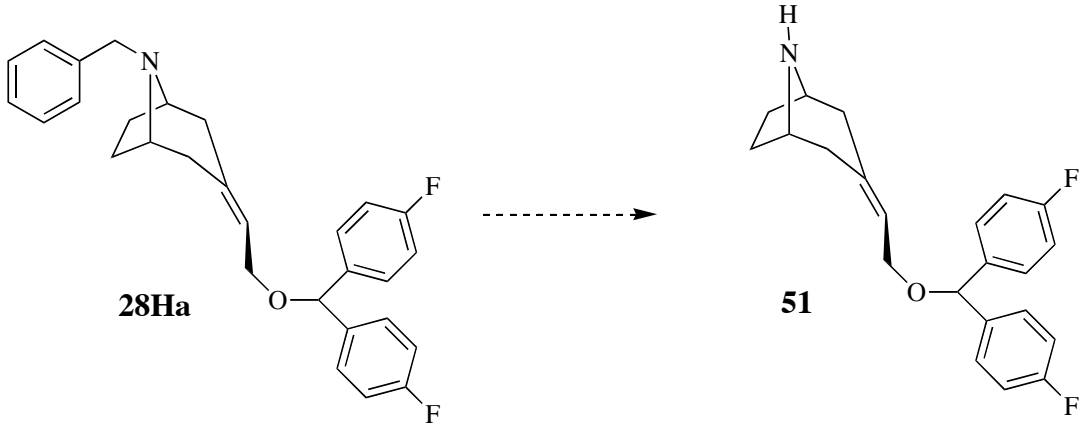
Reagents: i) HCl, MeOH, Δ. ii) bis(4-fluorophenyl)methylchloride, neat, 145 ºC

The resolved *N*-benzyl desfluoro **28Ha** compound was initially refluxed in 6M HCl, but the compound was not readily soluble in aqueous acid. Dissolving the compound in methanol followed by refluxing in 6M HCl only produced starting material after a basic workup. Finally, the resolved analogue **28Ha** was dissolved in methanol and refluxed with concentrated hydrochloric acid overnight. The solution was concentrated under reduced pressure and the

aqueous solution was chilled on an ice bath. The pH was adjusted to pH = 12 with the slow addition of ammonium hydroxide and extracted with CH_2Cl_2 to yield the allylic alcohol **57** in 60% yield. The alcohol **(57)** was derivatized with the appropriate benzhydryl moiety as mentioned previously to give **28Fa** to set the stage for debenzylation and further derivatization of the resolved analogues.

Attempts at nitrogen atom demethylation have been achieved with the addition of a carbamate in the initial nitrogen atom protection of 3-tropinone **35** described herein (Scheme 8). It was envisaged that debenzylation would work in the same fashion and deprotection would again produce the nortropane **51** (Figure 6).

Figure 6. Attempted Nitrogen Atom Debenzylation

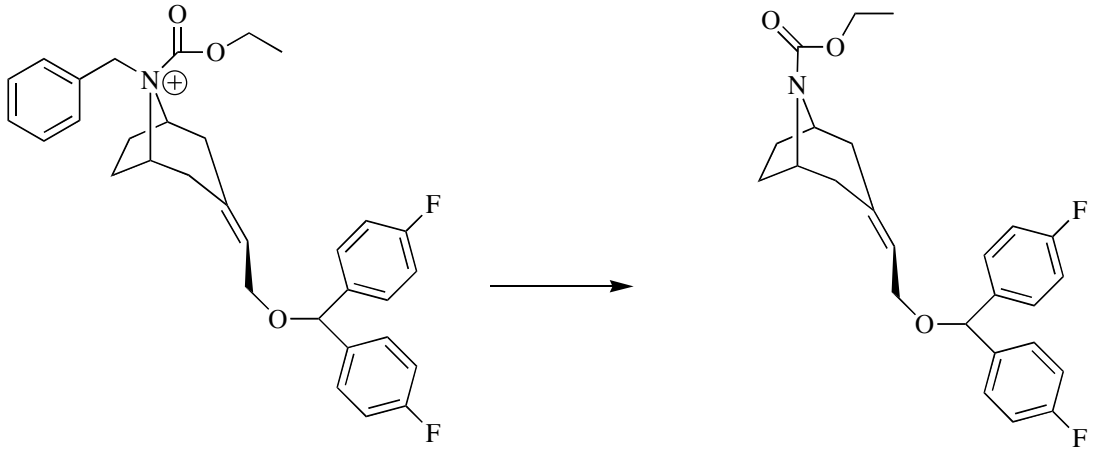


The *N*-benzyl difluoro analogue **28a** was subjected to debenzylation with three equivalents of ethylchloroformate and three equivalents K_2CO_3 in refluxing toluene overnight. After a standard workup, the reaction yielded only starting material. A stronger, more reactive carbamate might be more successful at debenzylation. After a thorough search of the literature, the very reactive α-chloroethylchloroformate, ACE-Cl, was identified as a potential reagent for

debenzylation of the nitrogen atom. However, after several attempts at room temperature and under refluxing conditions, only starting material was recovered or total decomposition of the resolved compound **28Fa** occurred.

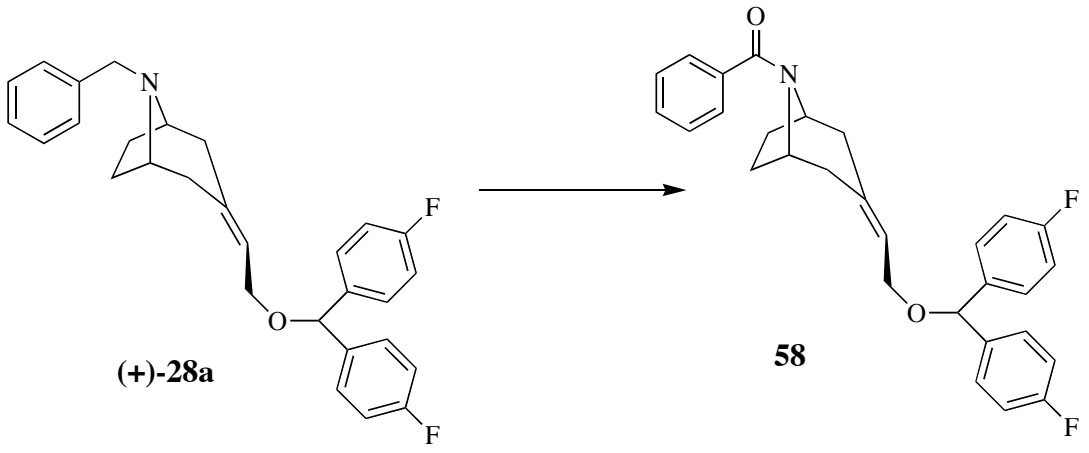
Although very reactive, ACE-Cl should have been able to debenzylate the nitrogen. However, there could be some steric interactions that keep the benzylic carbon atom from nucleophilic attack (Figure 7). Because the benzyl moiety is most likely oriented to the back of the tropane ring, subsequent nucleophilic attack of chloride to release the carbamate intermediate is hindered by the phenyl ring and the tropane skeleton. As a result, the reaction cannot proceed further and leads either to recovery of starting material after workup or decomposition.

Figure 7. Steric Interference from Tropane Ring and Substituents



Other attempts of debenzylation were investigated. It was thought that by selective oxidation at the benzyl position with potassium permanganate would install a carbonyl functionality **58**. The subsequent amide would be more reactive to deamidation with hydrazine in refluxing ethylene glycol.

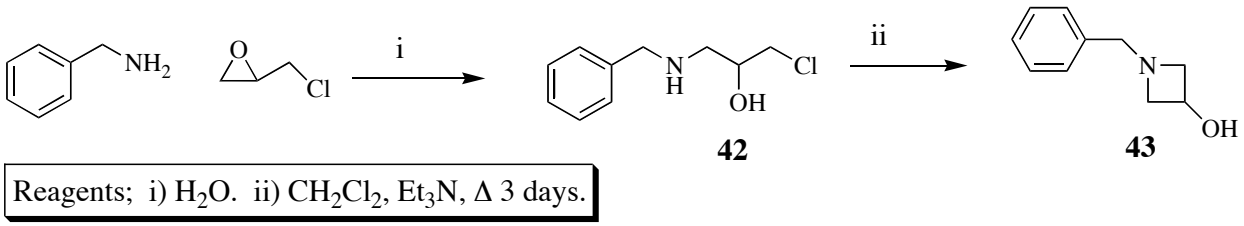
The *N*-benzyl difluoro analogue **28** was subjected to oxidation with three equivalents $KMnO_4$ overnight at room temperature. After workup, the amide **58** was refluxed with five equivalents hydrazine monohydrate, 25 equivalents KOH in ethylene glycol for three hours. However, NMR spectra showed only starting material **(+)-28Fa**. Attempts to debenzylate the nitrogen atom were abandoned at this point.



Attempted Synthesis of 3-Diphenylmethoxyalkyl-8-substituted-azetidine Analogues

The synthesis of the 3-diphenylmethoxyalkyl-8-substituted-azetidine analogues commenced with the readily available benzylamine and epichlorohydrin (Scheme 17). Benzylamine was added to a reaction flask and dissolved in water. Epichlorohydrine was added dropwise at 0 °C and the mixture was allowed to stir at room temperature for 3 hours. After adjusting the pH = 14, the mixture was subjected to a standard workup and the chlorohydrin **42** was isolated in 90% yield. The chlorohydrin **42** was dissolved in dichloromethane and brought to reflux for 3 days to generate the azetidine. However, after following the reaction via NMR, the azetidinol **43** was not being formed.

Scheme 17. Attempted Synthesis of Azetidinol **43**

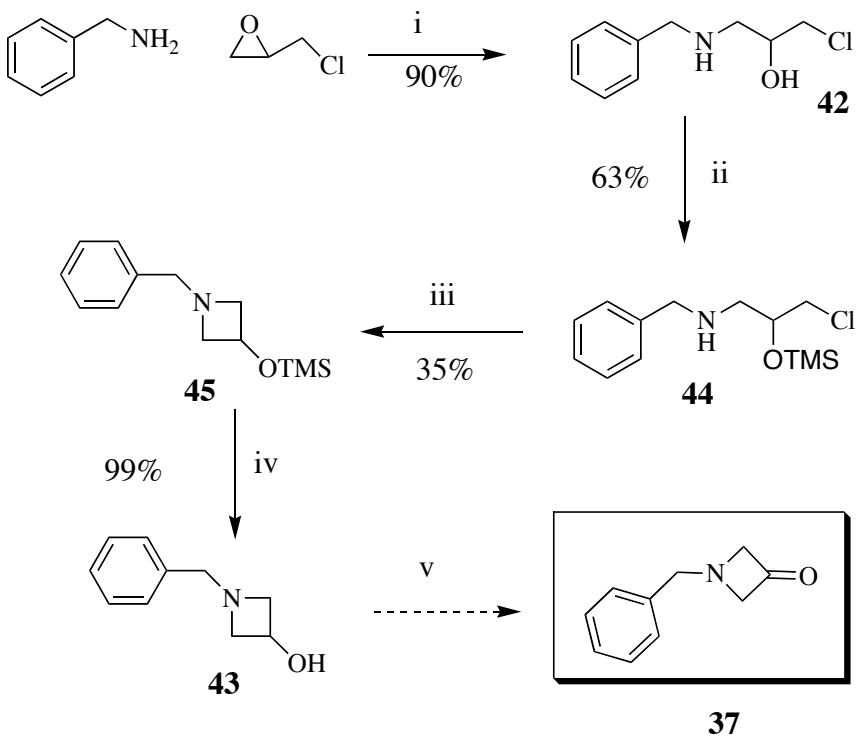


42 **43**

Reagents; i) H_2O. ii) CH_2Cl_2, Et_3N, Δ 3 days.

Another attempt to close the ring was made by reacting the alcohol **42** with trimethylsilylchloride (Scheme 18). This would protect the alcohol from any potential nucleophilic attack with the chloride causing unwanted side-products. The alcohol was dissolved in dichloromethane and two equivalents of triethylamine were added. The mixture was brought to 0 °C and trimethylsilylchloride was added dropwise via syringe. The mixture was allowed to stir at room temperature for three hours under an atmosphere of nitrogen. After a standard workup and purification via column chromatography, the silyl ether **44** was isolated in 63% yield. Refluxing for 48 hours in acetonitrile and triethylamine closed the ring giving the azetidinol ether **45** in 35% yield. The silyl ether was removed with concentrated hydrochloric acid at room temperature for five minutes to give the azetidinol **43** in quantitative yield. Many attempts were made to oxidize the alcohol to the azetidinone **37** with several oxidizing agents including Swern oxidation conditions and pyridinium dichromate. However, all attempts failed due to the instability of the azetidinone, workup conditions or purification techniques.

Scheme 18. Attempted Synthesis of Azetidinone **37**



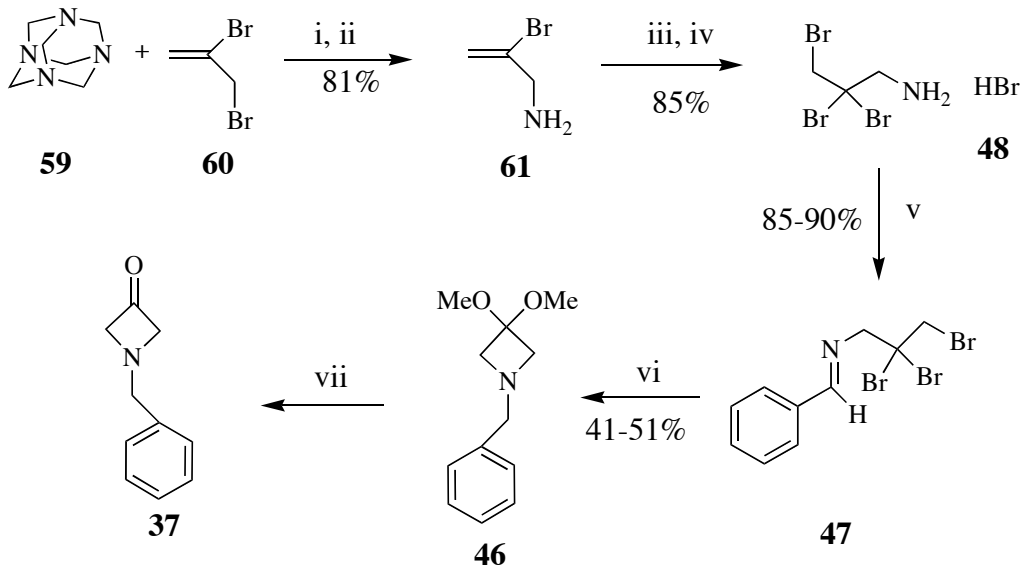
Reagents: i) H_2O, rt, 3 h. ii) TMSCl, Et_3N, CH_2Cl_2, rt, 3 h.
iii) CH_3CN, Et_3N, Δ, 48 h. iv) aq. HCl, rt, 5 min v)[oxidation]

Synthesis of 3-Diphenylmethoxyalkyl-8-substituted-azetidine Analogues

As illustrated in Scheme 19, the synthesis of the 3-diphenylmethoxyalkyl-8-substituted-azetidine analogues commenced with the synthesis of the amine **61** from the commercially available starting materials hexemethylenetetramine **59** and 2, 3-dibromopropene **60**. The reaction is known as the Delepine reaction.[56] To a three-neck flask fitted with an addition funnel and a condenser was added hexamethylentetramine in chloroform. The mixture was stirred using a Hershberg stirrer at reflux. The alkene **60** was added slowly via the addition funnel over one hour and the reaction was allowed to reflux an additional three hours. The reaction was then cooled to room temperature and allowed to stand overnight. The white precipitate was filtered

via vacuum filtration, collected and allowed to air dry. The product was acidified in ethanol, water and hydrochloric acid and allowed to stand at room temperature for 24 hours.

Scheme 19. Synthesis of Azetidinone **37**



Reagents: i) $CHCl_3$, Δ. ii) EtOH, 12N HCl. iii) aq. HBr . iv) Br_2. v) benzaldehyde, Et_3N, benzene, BF_3-Et_2O, H_2O, DST, Δ. vi) $NaBH_4$, MeOH, Δ. vii) H_2SO_4, NaOH.

The ammonium chloride salt was filtered via vacuum filtration and the mother liquor concentrated to dryness. This was dissolved in water and made basic to pH = 13. After extracting the aqueous layer with ether, the amine **61** was collected and distilled under reduced pressure in 81% yield. The amine **61** was dissolved in water and acidified to pH = 1 with 48% HBr. The amine was protected as the salt to keep it from reacting with itself or the bromine in the bromination step. Bromine was then added dropwise to the amine in water and allowed to stir at room temperature overnight. After concentrating the mixture under reduced pressure, the salt **48** was collected as an off-white solid in 85% yield.

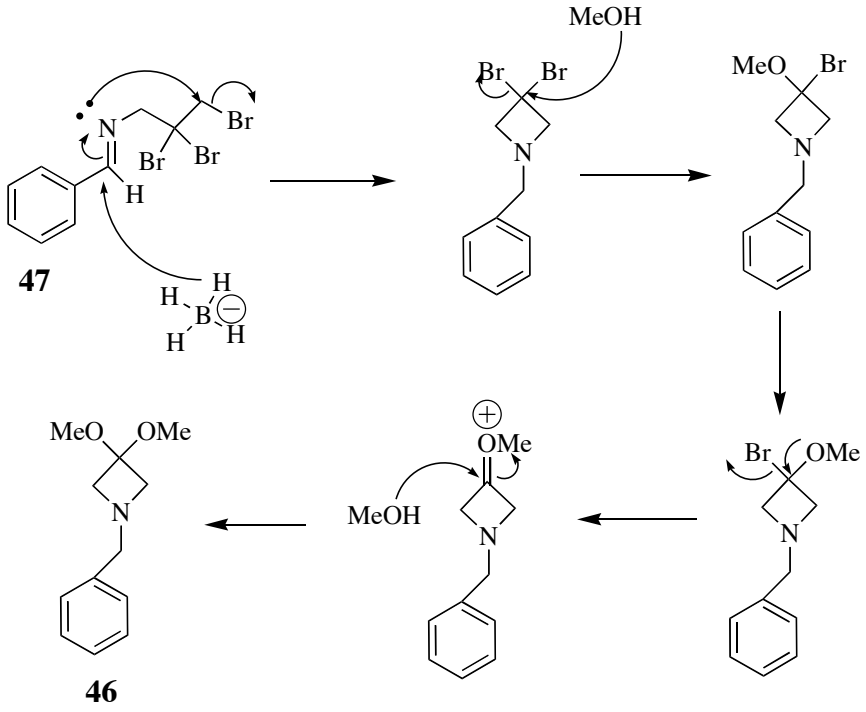
With the salt **48** in hand, this set the stage for derivatization and subsequent ring closure. Initially, the condensation of the amine **48** with the prospective aldehyde (i.e. benzaldehyde) was reacted at room temperature in dichloromethane. The reaction is an equilibrium reaction that generates water. The addition of magnesium sulfate was used to scavenge the water and drive the reaction to completion. However, attempts at accomplishing this transformation in any appreciable yield were unsuccessful even under refluxing conditions.

Because the reaction is an equilibrium reaction generating water, it was thought that azeotropic distillation with benzene would drive the reaction to completion forming the condensation product **47**. Benzene was added to the amine **48** then it was dissolved in water and triethylamine followed by the addition of benzaldehyde. Initial reactions involving the condensation and removal of water were not successful. Therefore, a catalytic amount of $BF_3 \bullet Et_2O$ was added to promote the reaction by acting as a Lewis acid, which would coordinate to the aldehyde to make it more reactive. After fitting the reaction flask with a Dean-Stark trap and condenser, the reaction was refluxed overnight. After cooling the reaction mixture to room temperature, diethyl ether was added to precipitate the ammonium chloride salt. The salt was filtered and the filtrate concentrated under reduced pressure to afford the crude imine **47**.

Initially, the imine was purified via column chromatography giving **47** in 85-90% yield. However, it was decided that the instability of the imine under purification conditions might give lower yields. Therefore, the imine was immediately dissolved in dry MeOH, placed under a nitrogen atmosphere and cooled to 0 °C. Sodium borohydride was added to the solution portion wise over one hour. With the addition of the reducing agent, the imine is reduced and subsequent ring closure of the amine occurs. Several attempts were tried in which the sodium borohydride was added at room temperature in one addition or in larger portions than previously

describe, however, these attempts produced lower yields. After the final addition of the reducing agent, the reaction was allowed to come to room temperature and then refluxed overnight. During the course of the reaction, there are three transformations occurring: (1) the imine reduction, (2) the ring closure and (3) the nucleophilic substitution with methanol (Figure 8). When the azetidine is formed, the ketal protecting group prevents the ring from decomposing or self-condensation.

Figure 8. Azetidine Ketal Formation



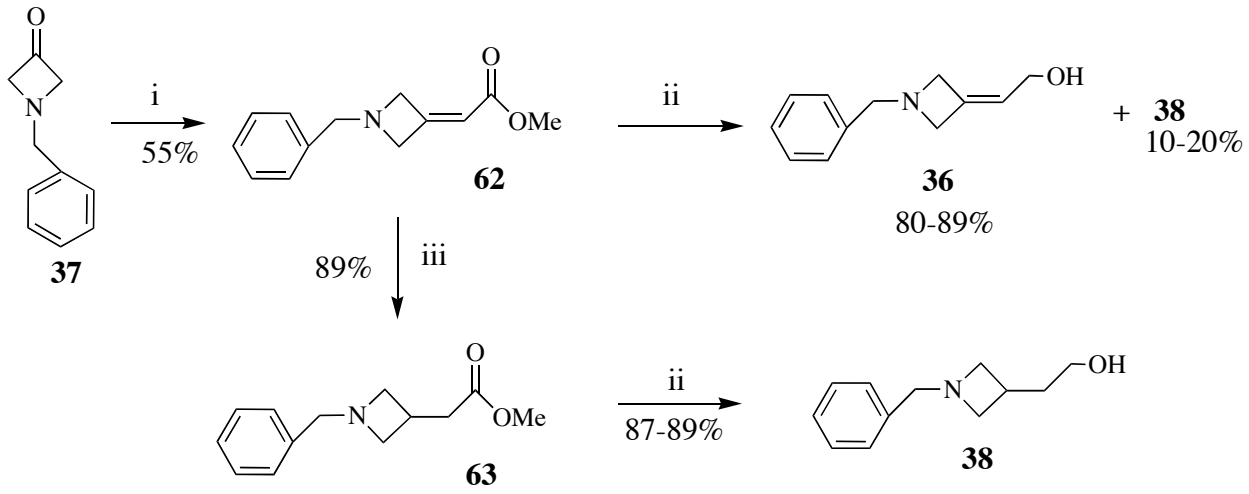
After all the water was collected and removed, the reaction was cooled to room temperature. The benzene was removed under reduced pressure and a standard workup ensued. The crude mixture was subjected to purification via column chromatography furnishing the azetidine **46** in 41-51% yield over four steps.

The azetidine was dried under vacuum to remove all traces of water. Initial attempts to deprotect the azetidine under aqueous conditions failed and only starting material was recovered. Standard acetal or ketal deprotection is performed in aqueous medium with a catalytic amount of the acid. The deprotection to aquire the azetidinone **37** was performed in water with a catalytic amount of concentrated sulfuric acid at room temperature overnight. After adjusting the pH = 12, the aqueous layer was extracted with dichloromethane to yield only starting material.

Treatment again of the ketal with water and 10 equivalents of concentrated sulfuric acid at room temperature overnight proved unreactive. The acidic solution was then refluxed for several hours but only starting material was acquired. As a last resort, the ketal was thoroughly dried under reduced pressure to remove all traces of water. The ketal was put on an ice water bath to lower the temperature to 0 °C. Concentrated sulfuric acid was added drop wise to the flask until all 10 equivalents were added. The reaction was allowed to stir at room temperature and the reaction was followed by NMR spectroscopy. After three hours, total transformation of the ketal to the azetidinone **37** was complete. The reaction was chilled again on an ice water bath and the temperature reduced to 0 °C. Saturated NaOH was added slowly to the reaction until a pH = 12 was reached. The mixture was taken up in water and extracted with dichloromethane.

The azetidinone **37** is highly unstable at room temperature and starts to decompose.[54, 58] Therefore, during the workup of the azetidinone, the solvent was concentrated under reduced pressure with no heat. Further, because of the instability of the newly formed ketone, column chromatography could not be used to purify the product. Fortunately, the azetidinone was pure enough by NMR spectroscopy to be carried forward to the next step as illustrated in Scheme 20.

Scheme 20. Synthesis of Alcohols **36** and **38**



Reagents: i) LiCl, $(CH_3O)_2POCH_2CO_2CH_3$, DBU, CH_3CN. ii) $LiAlH_4$, THF. iii) H_2, Pd/C, THF.

Following Masamune-Roush-Horner-Wadsworth-Emmons conditions, LiCl was stirred in acetonitrile. Trimethylphosphonoacetate was added followed by DBU. When the mixture is not performed in that order, the product of olefination is achieved in much lower yields. Following the addition, the azetidinone **37** was added as a solution in acetonitrile straight from the previous deprotection reaction. The olefination reaction is done under an atmosphere of nitrogen and in dry acetonitrile. Because the azetidinone from the previous reaction is worked up in water and is too unstable to leave on a drying pump for an extended amount of time, the absolute exclusion of water was unavoidable. Nevertheless, the reaction was stirred at room temperature overnight and the olefination product **62** was isolated after a standard workup and column chromatography in 55% yield over two steps from the ketal **46**.

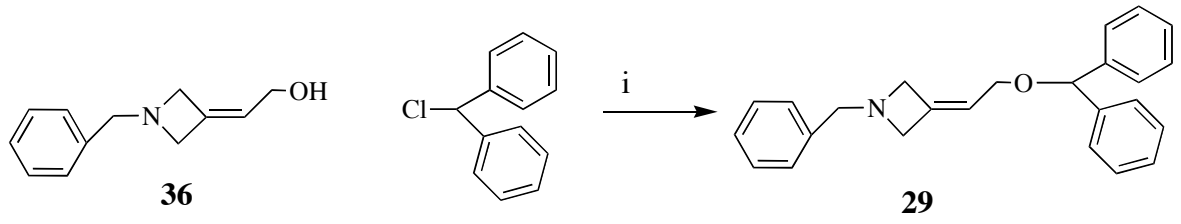
The conjugated ester **62** was taken up in THF and subjected to reduction to the allylic alcohol **36** with $LiAlH_4$ or reduced to the saturated ester **63** with 10% Pd/C under a hydrogen atmosphere. The ester **62** was reduced at 0 °C for two hours and quenched with 10% NaOH.

After workup, the crude allylic alcohol **36** in 89% was identified via NMR spectroscopy along with approximately 10% of a saturated side product. Because of the reactivity of the conjugated ester **62**, the reaction proceeds at low temperatures to prevent the formation of any side products. However, every attempt to reduce the ester to the allylic alcohol was contaminated with 10-20% of the saturated 1, 4-addition product. Further, attempts to purify the alcohol via column chromatography decreased the yield significantly. Therefore, after workup, the crude mixture was used in the next step without any further purification.

The ester **62** was also subjected to hydrogenation with 10% Pd/ C under 1atm H_2. The resulting saturated ester **63** was filtered through a layer of Celite® and collected. After concentrating under reduced pressure, the ester **63** was pure via NMR spectroscopy in 89%. The saturated ester was subjected to the same reduction conditions as the conjugated ester with $LiAlH_4$ to afford the saturated alcohol **38** in 89% yield.

The stability of the azetidine ring of the unsaturated analogues was of great importance when selecting the reaction to make the final product **29** and **30**. Several reactions were initially undertaken at lower temperatures to ensure the stability of the ring. The preparation of the ether **29** was initiated with the allylic alcohol and chlorodiphenylmethane in DMF at room temperature but was eventually heated to 80 °C overnight (Scheme 21). However, the reaction did not proceed at this temperature. Usually the reaction is performed at high temperatures (145-160° C).

Scheme 21. Synthesis of Azetidine **29**



36 **29**

Reagents: i) DMF, K_2CO_3, 80 °C, overnight.

Another attempt was employed to afford the product formed via Wittig olefination. Unfortunately, the starting Wittig reagent was not commercially available and had to be prepared from diphenylmethanol and bromoethanol (Scheme 22). This would then be reacted with triphenylphophine or a trialkylphosphonate to produce the Wittig reagent. This would in turn be reacted with the azetidinone to furnish the final product.

Diphenylmethanol was condensed with 2-bromoethanol using a Dean-Stark trap to furnish the ether **65**. However, all attempts to make the phosphine reagent failed because the affinity of the phosphorous atom for the oxygen atom of the ether produced an unwanted side reaction instead of the desired phosphine reagent (Figure 9). This route was abandoned and further investigations of reactions with the allylic alcohol were continued.

Scheme 22. Retrosynthesis of **29**

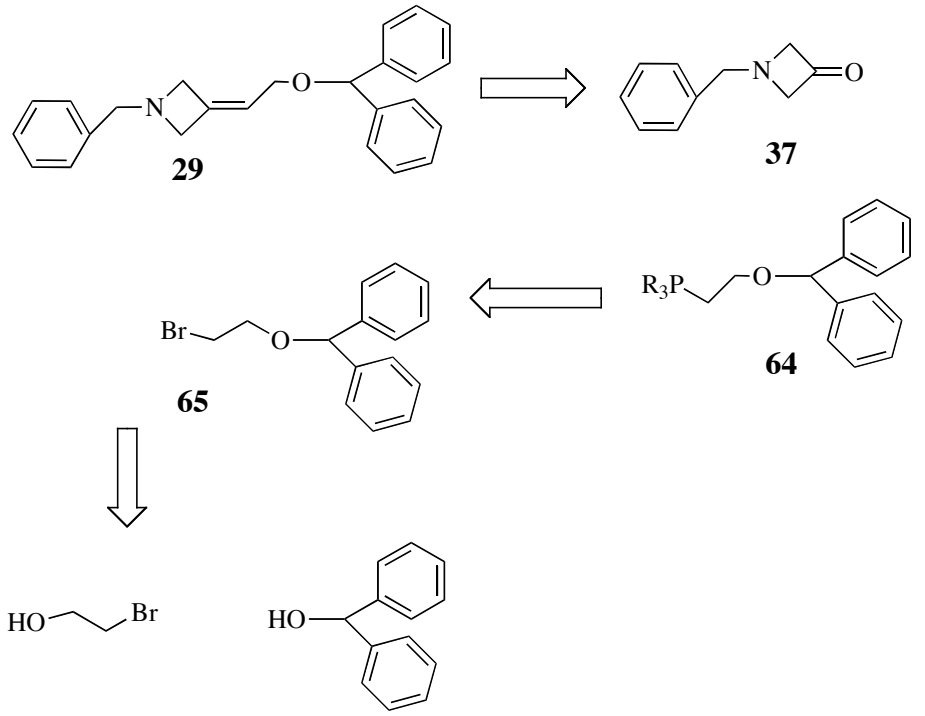
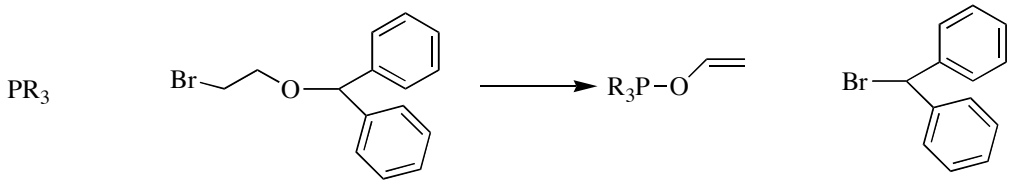


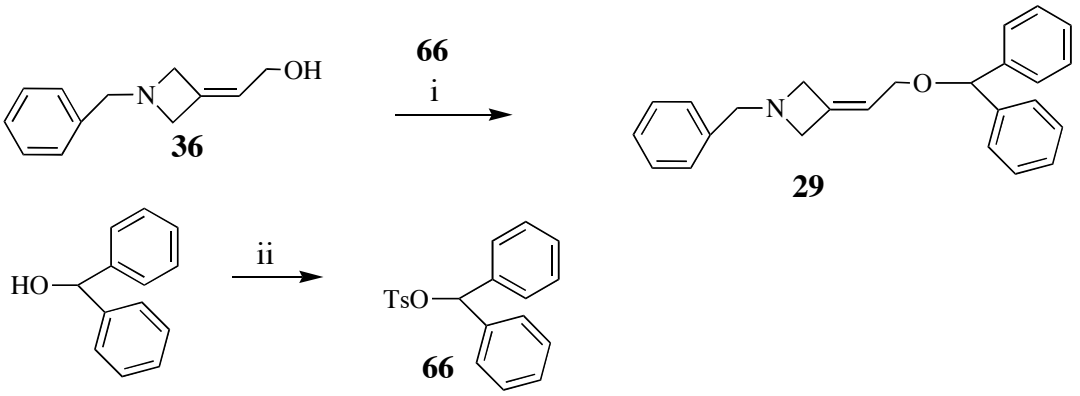
Figure 9. Side Reaction with Triphenylphosphine



To make the reaction more reactive so it would proceed at room temperature, diphenylmethanol was treated with NaH and reacted with half an equivalent of TsCl. The newly formed tosylate was added to a mixture of NaH and the allylic alcohol **36** and allowed to stir overnight. After following the reaction via NMR spectroscopy, it was observed that the reaction was not proceeding at room temperature. The reaction was slowly heated to 60 °C and the stability of the azetidine ring was observed via NMR spectroscopy to make sure it was still intact

at higher temperatures (Scheme 23). The reaction was allowed to react overnight at 60 °C. The mixture was then cooled to room temperature and quenched with water. After workup, the product was only obtained in 58% crude yield.

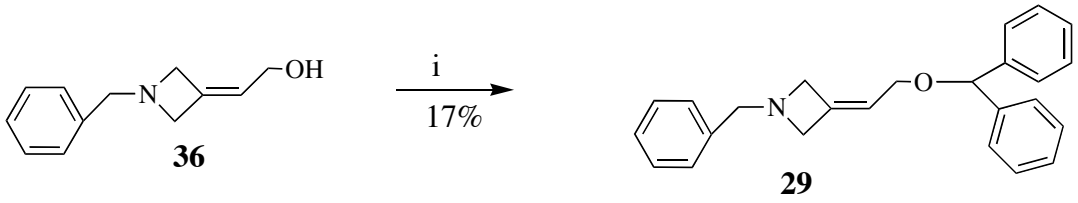
Scheme 23. Attempted Azetidine Synthesis



Reagents: i) NaH, DMF 60° C, overnight. ii) NaH, TsCl, Me_3NHCl, Et_3N, CH_3CN.

Because of the low yield produced from the previous procedure, other reaction conditions were investigated. Following the reduction of the conjugated ester **62**, the crude allylic alcohol **36** was dissolved in benzene (Scheme 24). To the solution was added *p*-toluenesulfonic acid (PTSA) and diphenylmethanol. The flask was fitted with a Dean-Stark trap and refluxed (80 °C) overnight. The reaction was concentrated under reduced pressure and following a standard workup and column chromatography, the product was obtained in 17% yield over two steps.

Scheme 24. Final Step to Azetidine Analogues



36 **29**

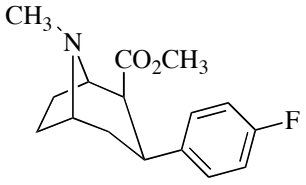
Reagents: i) diphenylmethanol, PTSA, benzene, Δ.

Biology: Dopamine, Serotonin and Norepinephrine Transporter Affinity of GBR 12909 Tropane Hybrid Analogues

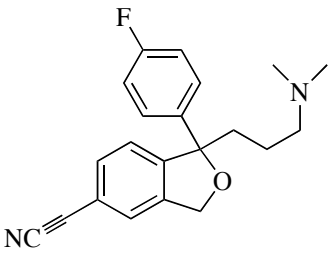
All final target compounds synthesized were tested as the oxalate salts. Binding affinities for the dopamine, serotonin and norepinephrine transporters were determined by the ability of the drug to displace the radiolabeled ligands [^{3}H]WIN 35,428 (**67**, [^{3}H]Citalopram (**68**), and [^{3}H]Nisoxetine (**69**), respectively, from the monoamine transporters found in rat caudate-putamen tissue.[7, 12, 59]

The binding affinities of all compounds listed in Table 1 were initially determined for the dopamine transporter. The compounds that exhibited dopamine transporter binding affinities with values K_i < 100 nM were evaluated at the serotonin and norepinephrine transporters to determine transporter selectivity. Those compounds that exhibited low binding affinity (K_i > 100 nM) at dopamine transporters were typically not evaluated further.

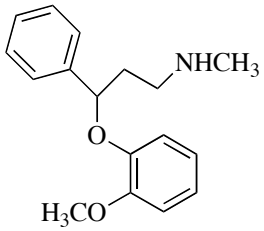
The racemic analogue **28Ha** was fairly potent (DAT K_i = 48 nM, SERT/ DAT = 113) and selective for the dopamine transporter over the serotonin transporter. However, the resolved analogues **(+)-28Ha** and **(-)-28Ha** varied, as expected, in the ability to displace the tritiated ligands from the appropriate monoamine transporters.



[^{3}H]WIN 35,428
67



[^{3}H]Citalopram
68



[^{3}H]Nisoxetine
69

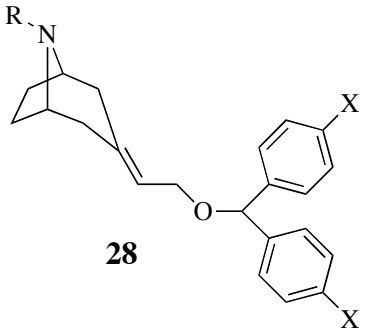
Interestingly, **(+)-28Ha** was 3-fold more potent and more selective than the racemic mixture (DAT K_i = 16 nM, SERT/ DAT = 316). Further, **(+)-28Ha** was 8-fold more potent and 7-fold more selective for the dopamine transporter over the serotonin transporter than its enantiomer **(-)-28Ha** (DAT K_i = 134 nM, SERT/ DAT = 46) and it was also equipotent with GBR 12909 (DAT K_i = 12 nM, SERT/ DAT = 35). The (-)-isomer **(-)-28Ha** was 3-fold less potent than the racemic mixture at the dopamine transporter and there was a 2.5-fold decrease in selectivity for the dopamine transporter over the serotonin transporter. Although the stereoselectivity of the dopamine transporter of the enantiomeric form of **28Ha** was not as dramatic as that observed for the stereoisomers of cocaine.[13, 19] These results further illustrate the sensitivity of the dopamine transporter to stereochemical differences in ligand topology.

Given the modest difference in binding affinity between the stereoisomers of **28a** the other analogues (**28b-i**) were tested as the unresolved mixture of racemates. The desfluoro analogues **28Hb**, **28Hc**, **28Hd**, **28He** and **28Hf** were found not to be very potent at the dopamine transporter. The propyl analogue **28Hc** (DAT K_i = 245 nM) was equipotent with the ethyl

analogue **28Hb** (DAT K_i = 286 nM). However, the allyl analogue **28He** was more potent (DAT K_i = 143 nM) than the propyl analogue **28Hc**. Interstingly, the propargyl analogue **28Hd** was less potent (DAT K_i = 536 nM) than either the propyl analogue **28Hc** or the allyl analogue **28He**. The cyclopropymethyl analogue **28Hf** (DAT K_i = 169 nM) was also not very potent at the dopamine transporter.

The 4-fluorophenyl analogues **28Fb-f** were tested at the monoamine transporters and proved to be more potent than the desfluoro analogues **28Hb-f**. The ethyl **28Fb** (DAT K_i = 40 nM) and propyl **28Fc** (DAT K_i = 41 nM) analogues proved to be equipotent but 6- to 7-fold more potent than their desfluoro analogues. This follows the trend that the 4-fluorophenyl analogues are more potent than the desfluoro analogues. Further, the allyl analogue **28Fe** (DAT K_i = 21 nM) was twice as potent as the ethyl and the propyl analogues **28Fb, c**. Interestingly, the cyclopropylmethyl analogue **28Ff** (DAT K_i = 4 nM, SERT/ DAT = 1060) was 3-fold more potent than GBR 12909 and greater than 30-fold more selective for the dopamine transporter over the serotonin transporter. This is the most selective dopamine transporter ligand synthesized to date from these laboratories.

Table 1. Inhibition of [^{3}H] WIN 35,428, [^{3}H] Citalopram and [^{3}H] Nisoxetine



28

Cmpd[a]	X	R	DAT[b] (K_i, nM)	SERT[b] (K_i, nM)	NET (K_i, nM)	SERT/DAT	NET/ DAT
GBR12909			12 ± 1.9			35	
28Ha	H	Bn	48 ± 5.0	5420 ± 74	1393 ± 147	113	29
28Ha-(+)	H	Bn	16 ± 3.0	5059 ±820	1200 ± 168	316	75
28Ha-(-)	H	Bn	134 ± 6.0	6143 ± 1529	2261 ± 463	46	17
28Fa	F	Bn	7.9 ± 0.5	2220 ± 740		281	
28Hb	H	Et	286 ± 25		2430 ± 560		8
28Fb	F	Et	40 ± 3.0	5958 ± 786	3577 ± 117	149	89
28Hc	H	Pr	245 ± 20		2087 ± 335		9
28Fc	F	Pr	41 ± 7.7	5463 ± 318	2847 ± 349	133	69
28He	H	$CH_2CH=CH_2$	143 ± 15		1740 ± 335		12
28Fe	F	$CH_2CH=CH_2$	21 ± 2	3461 ± 314	3120 ± 669	167	149
28Hd	H	$CH_2C\equiv CH$	536 ± 49				
28Fd	F	$CH_2C\equiv CH$	NA[c]				
28Hf	H	CH_2Cp	169 ± 44				
28Ff	F	CH_2Cp	4.0 ± 2.7	4239 ± 225		1060	
28Hg	H	4-F-Bn	7.0 ± 1.9	4094 ± 1528	2219 ± 543[d]	585	317
28Fg	F	4-F-Bn	4.9 ± 1.3	1145 ± 144	3270 ± 127[d]	234	654
28Hh	H	4-Cl-Bn	7.6 ± 1.0	544 ± 89	2827 ± 222[d]	72	372
28Fh	F	4-Cl-Bn	3.9 ± 2.0	656 ± 193	4974 ± 948[d]	168	1244
28Hi	H	4-CH_3-Bn	13 ± 2.0	746 ± 192	2132 ± 18[d]	57	164
28Fi	F	4-CH_3-Bn	6.1 ± 1.1	405 ± 98	3663[4]	68	611

a) All compounds were tested as the oxalate salts.
b) All values are the mean ± (SEM) of three experiments preformed in triplicate.
c) The compound decomposed and a reliable K_i value could not be obtained.
d) All values are the mean ± (SEM) of three experiments performed in duplicate.
e) All values are the mean ± (SEM) of three experiments.

The *N*-4-substituted-benzyl analogues **28Hh-i** and **28Fh-i** were tested at the monoamine transporters and were generally found to be more potent than GBR 12909. The *N*-(4-fluorobenzyl) analogue **28Hg** (DAT K_i = 7 nM, SERT/ DAT = 585) was more potent than GBR 12909 and more selective for the dopamine transporter over the serotonin transporter than the other analogues in this series. The *N*-(4-fluorobenzyl)-bis(4-fluorophenyl) analogue **28Fg** (DAT Ki = 4.9 nM, SERT/ DAT = 234) was equipotent with its conformer but was about 2-fold less selective for the dopamine transporter over the serotonin transporter. Further, the *N*-(4-fluorobenzyl) analogues **28Hg** and **28Fg** were more selective for the dopamine transporter over the norepinephrine transporter.

The *N*-(4-chlorobenzyl) analogues **28Hh** (DAT K_i = 7.6 nM, SERT/ DAT = 72) and **28Fh** (DAT K_i = 3.9 nM, SERT/ DAT = 168) were more potent than GBR 12909 (DAT K_i = 12 nM, SERT/ DAT = 35) and more selective for the dopamine transporter over the serotonin transporter. However, as the lipophilicity of the substituent on the *N*-benzyl group (Table 2) was increased, generally, there was a decrease in selectivity for the dopamine transporter over the serotonin transporter. This was due to increased serotonin transporter affinity. The *N*-(4-methylbenzyl) analogues **28Hi** (DAT K_i = 13 nM, SERT/ DAT = 57) and **28Fi** (DAT K_i = 6.1 nM, SERT/ DAT = 68) were the least potent in the series but were equipotent or more potent than GBR 12909. Further, the *N*-(4-chlorobenzyl) analogues **28Hh** and **28Fh** and the *N*-(4-methylbenzyl) analogues **28Hi** and **28Fi** were more selective for the dopamine transporter over the norepinephrine transporter. The *N*-(4-chlorobenzyl) analogue **28Fh** (NET/ DAT = 1244) was the most selective ligand for the dopamine transporter over the norepinephrine transporter in the series.

Table 2. clogP values of *N*-4-Substituted Benzyl Analogues **28g-i**

Cmpd	clogP
28Hg	6.44
28Fg	6.72
28Hh	7.01
28Fh	7.29
28Hi	6.79
28Fi	7.08

The tropane hybrid alkylidene analogues are more structurally rigid than GBR 12909. The bicyclic tropane ring system and the double bond decrease the flexability of the analogues unlike the piperazine ring system of GBR 12909. However, the similarities to GBR 12909 are the benzhydryl ether moiety and substitution of the distal nitrogen atom. The tropane hybrid analogues **28a-i** have, generally, been more selective than GBR 12909 for the dopamine transporter over the serotonin transporter.

Substitution of an *N*-benzyl or *N*-alkyl moiety at the nitrogen atom of the tropane hybrid analogues has demonstrated differences in binding at the dopamine transporter. Overall, the *N*-benzyl analogues were more potent than the *N*-alkyl analogues at the dopamine transporter. However, the *N*-cyclopropylmethyl analogue **28Ff** was equipotent with several of the *N*-benzyl analogues but was the most selective ligand in the series for the dopamine transporter over the serotonin transporter.

The structure-activity relationship of the *N*-4-substitutedbenzyl analogues demonstrated differences in potency at the dopamine transporter and selectivity for the dopamine transporter over the serotonin and norepinephrine transporters. The potency increased at the dopamine transporter as the lipophilicity of the *N-para*-substituted-benzyl analogue increased. The trend for increased potency at the dopamine transporter was $Cl > F > CH_3 > H$. The *N*-4-chlorobenzyl analogues **28Hh** (clogP = 7.01) and **28Fh** (clogP = 7.30) were the most lipophilic analogues of their class. The *N*-4-chlorobenzyl analogue **28Fh** (DAT K_i = 4.0 nM) was the most potent *N*-4-substitutedbenzyl analogue of the series.

Conclusions

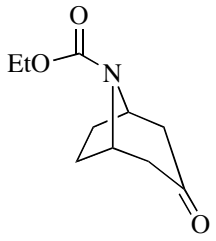
A series of GBR 12909-tropane analogues were synthesized and evaluated at the dopamine, serotonin and norepinephrine transporters. In general, the tropane hybrid analogues (**28Ha, 28Fb-i**) were potent at the dopamine transporter. Several of the GBR 12909-tropane hybrid analogues proved to be more potent at the dopamine transporter and more selective over the serotonin transporter than GBR 12909. An enantiomeric resolution of the tropane analogue **28Ha** has been developed on a multigram scale. The dopamine transporter binding affinity of the resolved *N*-benzyl tropane analogue **(+)-28Ha** further demonstrated a stereochemical sensitivity for ligand binding at the dopamine transporter. The resolved enantiomer **(+)-28Ha** was equipotent with GBR12909 and more than 3-fold more selective for the dopamine transporter over the serotonin transporter. Further, the fluoro-substituted analogues are more potent than the desfluoro analogues. The *N*-benzyl tropane analogues are more potent than the *N*-alkyl tropane analogues. However, the *N*-cyclopropylmethyl tropane analogue **28Ff** (DAT K_i = 4 nM, SERT/ DAT = 1060) proved to be the most selective dopamine transporter ligand that has been synthesized in these laboratories to date.

A novel synthesis of several GBR12909 azetidine hybrid analogues was developed. The rationale for the synthesis of these novel azetidine analogues was to decrease the lipophilicity of the compound while maintaining the structural rigidity. This will potentially increase the bioavailability of the compound without decreasing the potency at the dopamine transporter. These novel GBR 12909 azetidine hybrid analogues are currently being tested at the dopamine, serotonin and norepinephrine transporters and the biological data will be reported in due course.

Experimental

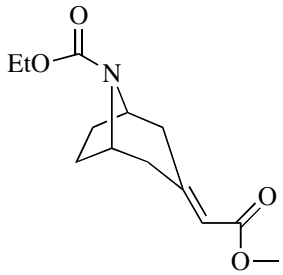
General Experimental Methods

All chemicals were purchased from Aldrich Chemical Company and used as received unless otherwise noted. Anhydrous toluene, dichloromethane (CH_2Cl_2), methanol (MeOH), chloroform ($CHCl_3$), tetrahydrofuran (THF) and acetonitrile (CH_3CN) were purchased from Mallinckrodt Baker, Inc. Thin layer chromatography (TLC) 20 × 20 cm glass plates precoated with 250 μm silica gel were purchased from Sorbent Technologies and used to monitor reactions via visualization with short-wave UV light, iodine, potassium permanganate, 2,4 dinitrophenyl hydrazine or Dragondorff's reagent. Chromatography was performed over Sorbent Technologies silica gel 60 angstrom (230-400 mesh). High-pressure hydrogenations were carried out on a Parr apparatus. Proton and carbon NMR were recorded on a Varian-400 MHz nuclear magnetic resonance spectrometer at ambient temperature in deuterated chloroform, acetone or water from Cambridge Isotope Laboratories, Inc. ^{1}H NMR chemical shifts are reported as δ values (ppm) relative to tetramethylsilane. Splitting patterns are designated as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. ^{13}C NMR chemical shifts are reported as δ values (ppm) relative to chloroform-*d* (77.0 ppm). Optical rotations were measured on Autopol III autopolarimeter at the sodium D line (2 mL sample cell). Melting points (m.p.) were measured with an Electrothermal ® Mel-Temp apparatus and are uncorrected.



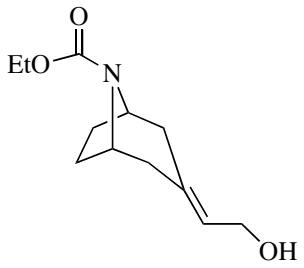
***N*-Ethoxycarbonyl-8-azabicyclo[3.2.1.]octan-3-one (49)**

In a clean, dry 500 mL round-bottom flask was added a stir-bar, 3-tropinone (10.0 g, 72 mmol) and K_2CO_3 (50 mg). Freshly distilled toluene (90 mL) was added followed by 3 equivalents of ethylchloroformate (21 mL, 220 mmol) via syringe, drop wise. The flask was fitted with a condenser, nitrogen bubbler and refluxed overnight with stirring. The reaction was concentrated under vacuum and the brown oil was dissolved in CH_2Cl_2 (100 mL) and washed with H_2O (100 mL). The layers were separated in a separatory funnel and the aqueous layer extracted with CH_2Cl_2 (3 × 50 mL). The organics were combined and dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by column chromatography (SiO_2, EtOAc/ hexane, 1:3) to produce 13.1 g, 92% of a light yellow oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 4.51 (bs, 2H), 4.16 (q, J = 7.2 Hz, 2H), 2.63 (bs, 2H), 2.31 (dd, J = 17.4, 1.6 Hz, 2H), 2.07-2.03 (m, 2H), 1.65 (d, J = 7.6 Hz, 2H), 1.25 (t, J = 7.2 Hz, 3H). ^{13}C NMR (400 MHz $CDCl_3$) δ 208.3, 154.1, 61.6, 53.2, 49.1, 29.5(2), 28.8(2), 14.9.[63]



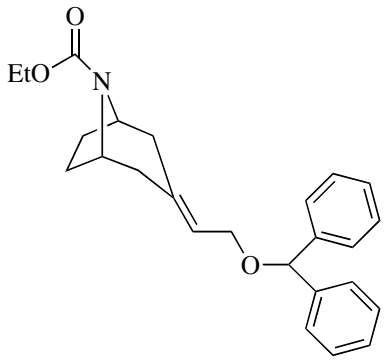
***N*-Ethoxycarbonyl-3-methoxycarboethylidenyl-8-azabicyclo[3.2.1.]octane (34)**

To a clean, dry 500 mL round-bottom flask was added 1.2 equivalents (3.4 g, 80 mmol) LiCl and a stir bar and sealed under a nitrogen balloon. Acetonitrile (180 mL) was added followed by 1.2 equivalents of trimethylphosphonoacetate (6.04 mL, 37 mmol). The mixture was allowed to stir at room temperature for 30 minutes to dissolve the LiCl. DBU (4.60 mL, 31 mmol) was added via syringe, drop wise, over 10 minutes. The protected tropinone **49** (13.1 g, 66 mmol) was dissolved in CH_3CN (60 mL) and syringed into the flask. The mixture was all allowed to stir at room temperature overnight under N_2. The reaction was concentrated under reduced pressure and the light brown oil was dissolved in CH_2Cl_2 (100 mL) and washed with H_2O (50 mL). The layers were separated in a separatory funnel and the aqeuous layer was extracted with CH_2Cl_2 (3 × 50 mL). The organics were combined and dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by column chromatography (SiO_2, EtOAc/ hexane, 1:4) to produce 14.5 g, 87% of a light yellow oil. ^{1}H NMR: δ 5.79 (s, 1H), 4.39 (brs, 2H), 4.19 (t, J = 6.8 Hz, 2H), 3.69 (s, 3H), 2.69 (brs, 1H), 2.36 (brs, 1H), 2.12 (d, J = 14.4 Hz, 1H), 1.94 (s, 2H), 1.59 (d, J = 7.2 Hz, 2H), 1.28 (t, J = 6.8 Hz, 4H). ^{13}C NMR: δ 165.6, 155.2, 153.2, 118.2, 60.4, 53.6, 53.4, 50.3, 42.1, 35.5, 27.9(2), 14.2. Anal. Calc. for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.46; H, 7.66; N, 5.48. NMR data is comparable to reference 64.



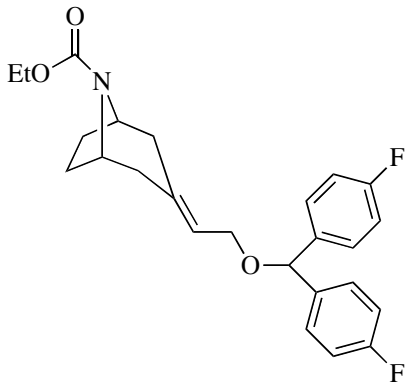
***N*-Ethoxycarbonyl-3-hydroxymethylethylidenyl-8-azabicyclo[3.2.1.]octane (33)**

Lithium aluminum hydride (1.2 equivalents, 870 mg, 23 mmol) and a stir bar were added to a clean, dry 250 mL round-bottom flask and sealed under a nitrogen balloon. THF (35 mL) was added via syringe and the solution brought to 0°C in an ice-water bath. The ester (3.85 g, 15 mmol) was dissolved in THF (15 mL) and added drop wise over 20 minutes via syringe. The reaction was stirred at 0 °C for 1.5 hours and quenched by the slow addition of 10% KOH (11 mL). Stirring was continued for an additional hour and the reaction mixture was decanted into a separatory funnel. The white solid was washed with diethyl ether (4 × 30 mL) and the organics added to the seperatory funnel. The organics were washed with phosphate buffer (75 mL) and the buffer extracted with diethyl ether (4 × 30 mL). The organics were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting alcohol was purified by column chromatography (SiO_2, EtOAc/ hexane, 1:1) to yield 3.0 g, 89% of a light yellow oil. ^{1}H NMR: δ 5.58 (m, 1H), 4.32 (s, 2H), 4.16 (m, 4H), 2.53 (d, J = 13.6 Hz, 2H), 2.41(d, J = 14 Hz, 2H), 2.23 (d, J = 14.4 Hz, 2H), 2.03 (d, J = 13.6 Hz, 2H), 1.89 (m, 3H), 1.61 (t, J = 7.6 Hz, 2H), 1.52 (t, J = 7.6 Hz, 2H). ^{13}C NMR: δ 153.7, 134.4, 127.7, 60.7, 57.7, 53.6, 41.6, 34.5(2), 27.8(2), 14.3. Anal. Calc. for $C_{12}H_{19}NO_3$: C, 63.97; H, 8.50; N, 6.22. Found: C, 63.76; H, 8.61; N, 6.43. NMR data is comparable to reference 64.



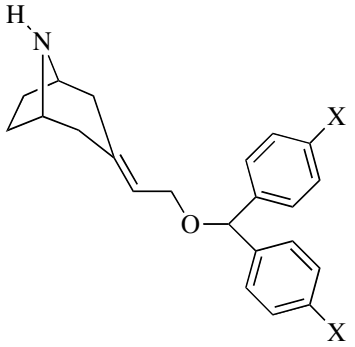
3-(2-Diarylmethoxy-ethylidene)- *N*-ethoxycarbonyl-8-azabicyclo[3.2.1]octane (50a)

In a clean, dry 10 mL round-bottom flask was added the alcohol (1.1 g, 5 mmol), bis-4-fluorophenylmethylchloride or chlorodiphenylmethane (1.5 equivalents, 1.30 mL, 7 mmol) and a stir bar. This was heated neat to 145 $^{\circ}$C for 2 hours under N_2. The reaction was cooled to room temperature, dissolved in pure ethyl acetate and purified immediately by column chromatography (60% w/w SiO_2, EtOAc/ hexane, 1:4) to afford 1.26g, 66% of **50a** as a clear light yellow oil. ^{1}H NMR: δ 7.3-7.22 (m, 10H), 5.63-5.61 (M, 1H), 5.39 (s, 1H), 4.36-4.20 (m, 2H), 4.18-4.10 (m, 2H), 4.04-3.98 (m, 2H), 2.55-2.45 (m, 1H) 2.27-2.07 (m, 1H) 1.95-1.86 (m, 2H), 1.64-1.59 (m, 2H), 1.30-1.21 (m, 3H).



3-(2-Diarylmethoxy-ethylidene)- *N*-ethoxycarbonyl-8-azabicyclo[3.2.1]octane (50b)

In a clean, dry 10 mL round-bottom flask was added the alcohol (1.4 g, 6.2 mmol), bis-4-fluorophenylmethylchloride or chlorodiphenylmethane (1.5 equivalents, 1.70 mL, 9 mmol) and a stir bar. This was heated neat to 145 $^{\circ}$C for 2 hours under N_2. The reaction was cooled to room temperature, dissolved in pure ethyl acetate and purified immediately by column chromatography (60% w/w SiO_2, EtOAc/ hexane, 1:4) to afford 2.0 g, 75% of **50b** as a clear light yellow oil. ^{1}H NMR: δ 7.3-7.26 (m, 4H), 7.03-6.98 (m, 4H), 5.63-5.61 (M, 1H), 5.39 (s, 1H), 4.36-4.20 (m, 2H), 4.18-4.10 (m, 2H), 4.04-3.98 (m, 2H), 2.55-2.45 (m, 1H) 2.27-2.07 (m, 1H) 1.95-1.86 (m, 2H), 1.64-1.59 (m, 2H), 1.30-1.21 (m, 3H).



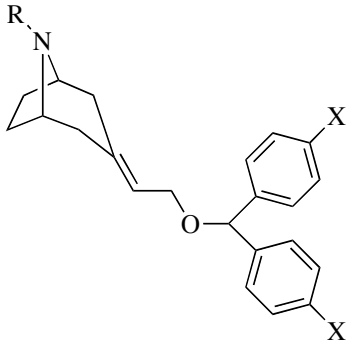
3-(2-Diarylmethoxy-ethylidene)-8-azabicyclo[3.2.1]octane (51)

In a clean 250 mL round-bottom flask was added ethylene glycol (88 mL), 26 equivalents KOH (4.42 g, 79 mmol), 5 equivalents $NH_2NH_2 \bullet H_2O$ (.75 mL, 15 mmol) and the corresponding protected tropane (1.26 g, 3 mmol). The reaction was heated to reflux for 3 hours. The reaction was then cooled to room temperature and poured into a separatory funnel and extracted with diethyl ether (6 × 75 mL). The combined ether layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting oil was purified by column chromatography (SiO_2, $CHCl_3$/MeOH/NH_4OH 90:9:1.) to afford the nortropane **51** as a light yellow oil.

51a 615 mg, 60% ^{1}H NMR: δ 7.36- 7.22 (m, 10H), 5.51-5.48 (M, 1H), 5.40 (s, 1H), 4.05-3.97 (m, 2H), 3.57-3.54 (m, 2H), 2.43-2.40 (d, J = 13.6 Hz, 1H), 2.28-2.25 (d, J = 14.0 Hz, 1H) 2.09-2.01 (t, J = 14.0 Hz, 2H) 1.84 (bs, 2H), 1.73-1.68 (m, 2H) 1.64-1.59 (m, 1H), 1.51-1.47 (m, 1H). ^{13}C NMR: δ 142.1(2), 138.0(4), 128.1(4), 126.8(2), 122.9, 82.3, 64.1, 55.1, 54.7, 43.8, 36.9, 29.1, 28.8(2). Anal. Calc. for $C_{22}H_{25}NO \bullet 0.25\ H_2O$: C, 81.75; H, 7.93; N, 4.33 Found: C, 81.57; H, 7.86; N, 4.35.[64]

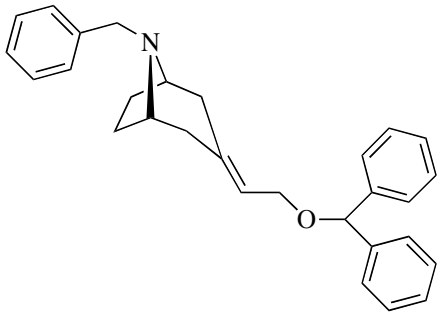
51b 577 mg, 66% ^{1}H NMR: δ 7.36- 7.22 (m, 4H), 7.02-6.97 (m, 4H) 5.51-5.48 (m, 1H), 5.40 (s, 1H), 4.05-3.97 (m, 2H), 3.57-3.54 (m, 2H), 2.43-2.40 (d, J = 13.6 Hz, 1H), 2.28-2.25 (d, J = 14.0 Hz, 1H) 2.09-2.01 (t, J = 14.0 Hz, 2H) 1.84 (bs, 2H), 1.73-1.68 (m, 2H) 1.64-1.59 (m, 1H), 1.51-1.47 (m, 1H). ^{13}C NMR: δ 158.14(2), 138.3, 138.1, 134.4(4), 128.5(2), 128.3(2), 123.1, 115.0,

81.2, 69.4, 64.1, 55.2, 54.8, 43.8, 36.9, 29.2. Anal. Calc. for $C_{22}H_{23}F_2NO \bullet 0.50\ H_2O$: C, 72.50; H, 6.63; N, 3.84 Found: C, 72.55; H, 6.50; N, 3.84.[64]



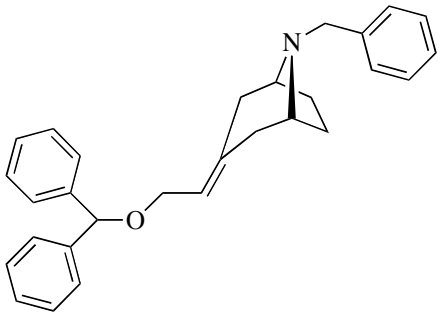
General procedure for *N*-alkylation of secondary amines (28a-i)

In a clean, dry 25 mL round-bottom flask was added 600 mg K_2CO_3, the nortropane **51** (2 mmol), DMF (15 mL) and the alkyl bromide (2 mmol) and a stir bar. The reaction was heated to 80 °C (oil bath) overnight under N_2. The reaction was cooled to room temperature and added to a separatory funnel followed by addition of H_2O (50 mL). The mixture was extracted with diethyl ether (4× 50 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The oil was purified by column chromatography and the pure free base was converted into the oxalate salt.



3-(2-Diphenylmethoxy-ethylidene)-8-alkyl-8-azabicyclo[3.2.1]octane (28Ha)

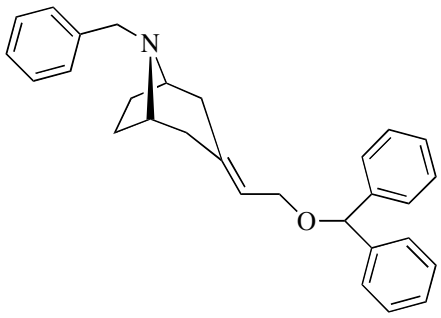
The oil was purified by column chromatography (SiO_2, EtOAc) to give **28a** as a thick yellow oil (642 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04-7.21 (m, 15H), 5.52-5.49 (t, J=8 Hz, 1H), 5.39 (s, 1H), 4.05-3.96 (m, 2H), 3.61 (s, 2H), 3.23-3.20 (d, J=12 Hz, 2H), 2.62-2.59 (d, J=12 Hz, 1H), 2.24-2.09 (dd, J=14 Hz, 2H), 1.95-1.92 (m, 3H), 1.59-1.54 (t, J=8 Hz, 1H), 1.47-1.42 (t, J=10 Hz, 1H). Anal. Calc. for $C_{29}H_{31}NO•C_2H_2O_4$: C 74.58; H 6.66; N 2.81. Found: C 74.62; H 6.71; N 2.79.



(+)-3-(2-Diphenylmethoxy-ethylidene)-8-benzyl-8-azabicyclo[3.2.1]octane (+)-(28Ha)

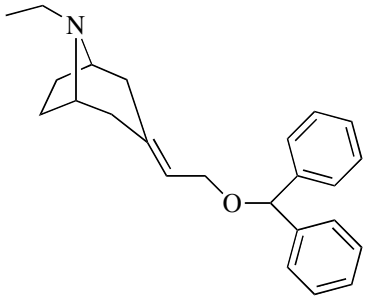
To a solution of the racemic **28a** (350 mg, 0.85 mmol) in MeOH (10 mL), was added a solution of dibenzoyl-L-tartaric acid (310 mg, 0.87 mmol) in MeOH (10 mL). This was allowed to stir at room temperature for 5 hours. A white precipitate formed after approximately 30 minutes. The precipitate was collected by filtration through a Buchner funnel and washed with MeOH (5 mL). The solid was added to a flask in addition to H_2O (20 mL). The chiral salt was

free-based with NH_4OH when a pH=12 was reached. The solution was extracted with $CHCl_3$ (4 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to produce a clear oil. The freebase was treated with a second equivalent of dibenzoyl-L-tartaric acid and the recrystallization process was repeated until a constant optical rotation was obtained. The resolved **28a** was obtained as a clear oil, 96 mg, $[\alpha]^{25}_D$ +17.0° (c 1.0, EtOH).



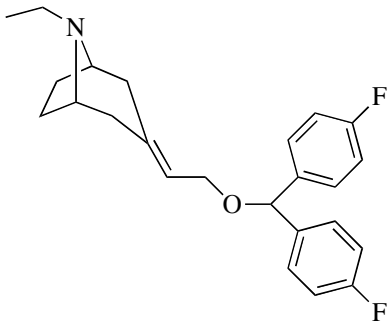
(-)-3-(2-Diphenylmethoxy-ethylidene)-8-benzyl-8-azabicyclo[3.2.1]octane (-)-(28Ha)

To a solution of the racemic **28Ha** (189 mg, 0.46 mmol) in MeOH (10 mL), was added a solution of dibenzoyl-D-tartaric acid (166 mg, 0.46 mmol) in MeOH (10 mL). The mixture was allowed to stir at room temperature for 5 hours. A white precipitate formed after approximately 30 minutes. The precipitate was collected by filtration through a Buchner funnel and washed with MeOH (5 mL). The solid was added to a flask in addition to H_2O (20 mL). The chiral salt was free-based with NH_4OH when a pH=12 was reached. This was extracted with $CHCl_3$ (4 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to produce a clear oil. The freebase was treated with a second equivalent of dibenzoyl-D-tartaric acid and the recrystallization process was repeated until a constant optical rotation was obtained. The resolved **28a** was obtained as a clear oil, 64 mg $[\alpha]^{25}_D$ -17.5° (c 1.25, EtOH).



3-(2-Diphenylmethoxy-ethylidene)-8-ethyl-8-azabicyclo[3.2.1]octane (28Hb)

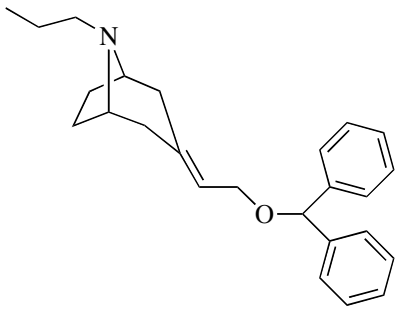
The oil was purified by column chromatography (SiO_2, EtOAc) to give **28Hb** as a thick oil (207 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.22 (m, 10H), 5.53-5.50 (t, J=6.6 Hz, 1H), 5.39 (s, 1H), 4.05-3.94 (m, 2H), 3.36-3.32 (d, J=16 Hz, 2H), 2.66-2.62 (d, J=16 Hz, 1H), 2.57-2.52 (q, J=7 Hz, 2H), 2.28-2.25 (d, J=13.2 Hz, 1H), 2.13-2.10 (d, J=14 Hz, 1H) 1.96-1.93 (d, J=14.4 Hz, 1H), 1.87 (s, 2H), 1.59-1.54 (t, J=9.2 Hz, 1H), 1.46-1.42 (t, J=8.8 Hz, 1H), 1.17-1.13 (t, J=7.2 Hz, 3H). Anal. Calc. for $C_{24}H_{29}NO•C_2H_2O_4$: C 70.58; H 7.47; N 3.17. Found: C 70.56; H 7.39; N 3.10.



3-{2-Bis(4-fluorophenyl)methoxy-ethylidene}-8-ethyl-8-azabicyclo[3.2.1.]octane (28Fb)

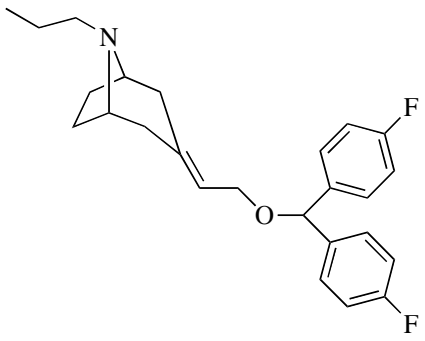
The oil was purified by column chromatography (SiO_2, EtOAc) to give **28Fb** as a thick yellow oil (140 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.26 (m, 4H), 7.03-6.98 (m, 4H), 5.49 (s, 1H), 5.33 (s, 1H), 4.01-3.91 (m, 2H), 3.31-3.28 (d, J=12 Hz, 2H), 2.58-2.47 (m, 3H),

2.21-2.17 (d, J=16 Hz, 1H), 2.09-2.05 (d, J=16 Hz, 1H), 1.13-1.09 (t, J=8 Hz, 3H). Anal. Calc. for $C_{24}H_{27}F_2NO \bullet C_2H_2O_4$: C 60.17; H 5.98; N 2.70. Found: C 60.10; H 5.88; N 2.45.



3-(2-Diphenylmethoxy-ethylidene)-8-propyl-8-azabicyclo[3.2.1]octane (28Hc)

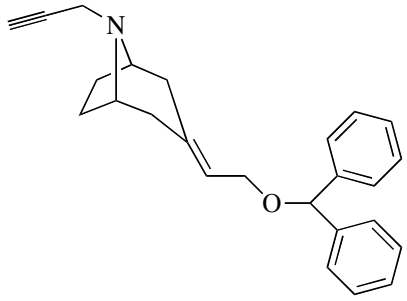
The oil was purified by column chromatography (SiO_2, EtOAc) to give **28Hc** as a thick yellow oil (72 mg, 42%). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.35-7.22 (m, 10H), 5.54 (s, 1H), 5.39 (s, 1H), 4.05-3.94 (m, 2H), 3.38 (bs, 2H), 2.49 (bs, 2H), 2.16 (d, J=13.2 Hz, 2H), 1.98-1.91 (m, 3H), 1.61 (bs, 5H), 0.95 (t, J=7.4 Hz, 3H). Anal. Calc. for $C_{27}H_{31}NO \bullet C_2H_2O_4$: C 69.06; H 7.51; N 2.98. Found: C 69.67; H 7.30; N 3.01.



3-{2-Bis(4-fluorophenyl)methoxy-ethylidene}-8-propyl-8-azabicyclo[3.2.1.]octane (28Fc)

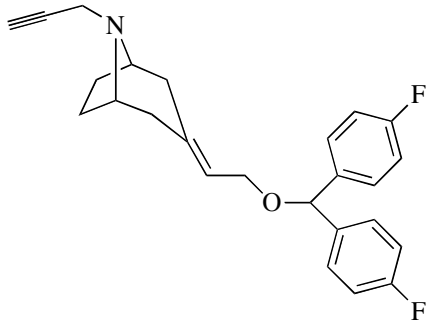
The oil was purified by column chromatography (SiO_2, EtOAc) to give **28Fc** as a thick yellow oil (64 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.26 (m, 4H), 7.03-6.98 (m, 4H), 5.45 (bs, 1H), 5.35 (s, 1H), 3.98-3.93 (m, 2H), 3.26 (bs, 2H), 2.57-2.54 (d, J=12 Hz, 1H), 2.40-

2.36 (t, J=8 Hz, 2H), 2.16-2.04 (m, 2H), 1.92-1.84 (m, 3H) 1.56-1.50 (m, 3H) 1.36 (s, 1H) 0.93-0.89 (t, J=7.2 Hz, 3H). Anal. Calc. for $C_{25}H_{29}F_2NO \bullet C_2H_2O_4$: C 62.97; H 6.41; N 2.72. Found: C 62.91; H 5.89; N 2.72.



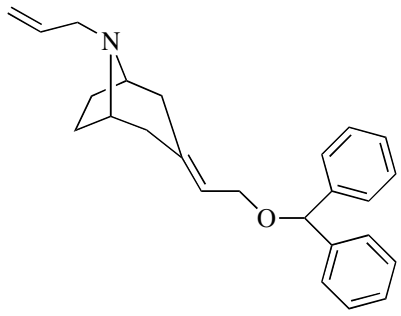
3-(2-Diphenylmethoxy-ethylidene)-8-(3-prop-2-ynyl)-8-azabicyclo[3.2.1]octane (28Hd)

The oil was purified by column chromatography (SiO_2, EtOAc) to give **28Hd** as a thick yellow oil (169 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.23 (m, 10H), 5.51 (t, J-6.4 Hz, 1H), 5.39 (s, 1H), 4.05-3.93 (m, 2H), 3.41-3.38 (d, J=12 Hz, 2H), 3.22 (s, 2H), 2.59-2.55 (d, J=16 Hz, 1H), 2.20-2.13 (m, 2H), 1.99-1.96 (d, J=12 Hz, 1H), 1.85 (bs, 2H) 1.59-1.56 (d, J=12 Hz, 2H) 1.46-1.42 (t, J=4.4 Hz, 1H). Anal. Calc. for $C_{25}H_{27}NO \bullet C_2H_2O_4$: C 68.98; H 6.60; N 2.98. Found: C 68.67; H 6.36; N 2.93.



3-{2-Bis(4-fluorophenyl)methoxy-ethylidene}-8-(3-prop-2-ynyl)-8-azabicyclo[3.2.1.]octane (28Fd)

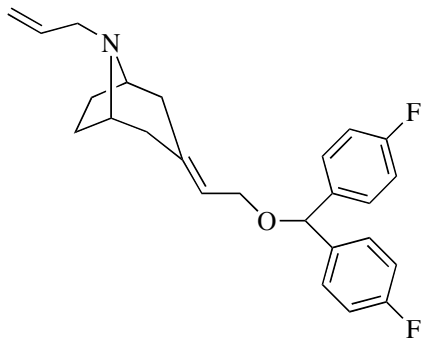
The oil was purified by column chromatography (SiO_2, EtOAc) to give **28Fd** as a thick yellow oil (130 mg, 63%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.26 (m, 4H), 7.03-6.98 (m, 4H), 5.50 (t, J=8 Hz, 1H), 5.34 (s, 1H), 4.01-3.90 (m, 2H), 3.41 (bs, 2H), 3.20 (s, 2H), 2.59-2.56 (d, J=14 Hz, 1H), 2.21-2.12 (m, 2H), 1.88-1.86 (m, 1H), 1.56 (s, 2H) 1.43-1.39 (m, 2H). Anal. Calc. for $C_{25}H_{25}F_2NO•C_2H_2O_4$: C 64.60; H 5.78; N 2.79. Found: C 63.80; H 5.50; N 2.59.



8-Allyl-3-(2-diphenylmethoxy-ethylidene)-8-azabicyclo[3.2.1]octane (28He)

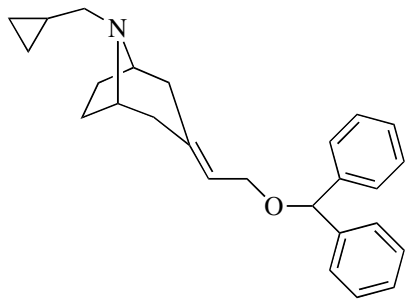
The oil was purified by column chromatography (SiO_2, EtOAc) to give **28He** as a thick yellow oil (132 mg, 67%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.21 (m, 10H), 5.96 (bs, 1H), 5.52 (bs, 1H), 5.39 (s, 1H), 5.21-5.14 (t, J=17.6 Hz, 2H) 4.05-3.93 (m, 2H) 3.32-3.29 (d, J=12 Hz, 2H), 3.12-3.10 (d, J=5.6 Hz, 2H), 2.63 (bs, 1H), 2.24 (bs, 1H), 2.16-2.12 (d, J=14 Hz, 1H), 1.98-

1.95 (d, J=12 Hz, 1H), 1.86 (bs, 2H), 1.60-1.43 (m, 2H). Anal. Calc. for $C_{25}H_{29}NO \bullet C_2H_2O_4$: C 68.64; H 6.99; N 2.97. Found: C 68.55; H 6.88; N 2.78.



8-Allyl-3-{2-bis(4-fluorophenyl)methoxy-ethylidene}-8-azabicyclo[3.2.1.]octane (28Fe)

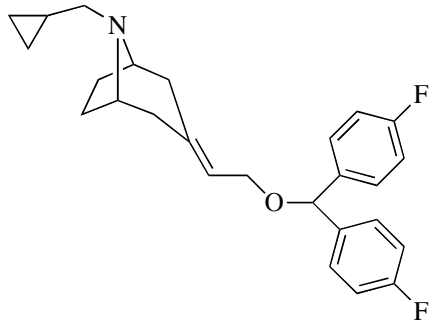
The oil was purified by column chromatography (SiO_2, EtOAc) to give **28Fe** as a thick yellow oil (158 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.26 (m, 4H), 7.03-6.98 (m, 4H), 5.94 (bs, 1H), 5.48 (bs, 1H), 5.34 (s, 1H), 5.20-5.15 (d, J=17.6 Hz, 2H), 4.01-3.90 (m, 2H), 3.28 (bs, 2H), 3.08 (bs, 2H), 2.56 (bs, 1H), 2.12 (m, 2H), 1.97-1.86 (m, 2H), 1.55 (s, 3H). Anal. Calc. for $C_{25}H_{27}F_2NO \bullet C_2H_2O_4$: C 64.35; H 6.16; N 2.78. Found: C 64.32; H 6.02; N 2.70.



3-(2-Diphenylmethoxy-ethylidene)-8-cyclopropylmethyl-8-azabicyclo[3.2.1]octane (28Hf)

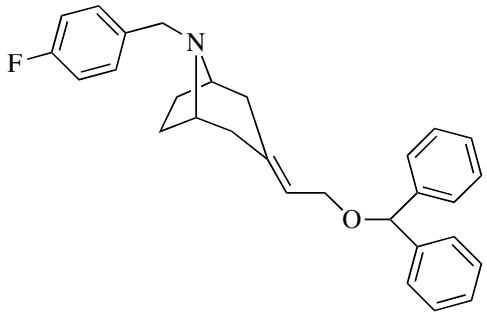
The oil was purified by column chromatography (SiO_2, EtOAc) to give **28Hf** as a thick yellow oil (227 mg, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.23 (m, 10H), 5.48 (t, J=6.8 Hz, 1H), 5.39 (s, 1H), 4.05-3.94 (m, 2H), 3.43-3.39 (d, J=16 Hz, 2H), 2.57-2.54 (d, J=12 Hz, 1H),

2.34-2.33 (d, J=4 Hz, 2H), 2.20-2.07 (m, 3H), 1.93-1.80 (m, 3H), 1.60-1.37 (m, 1H), 0.94 (m, 1H), 0.52 (m, 2H), 0.12 (m, 2H). Anal. Calc. for $C_{26}H_{31}NO \bullet C_2H_2O_4$: C 69.12; H 6.99; N 2.88. Found: C 69.00; H 6.97; N 2.83.



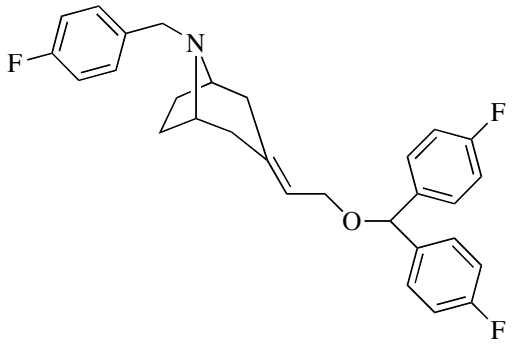
3-{2-Bis(4-fluorophenyl)methoxy-ethylidene}-8-cyclopropylmethyl-8-azabicyclo[3.2.1.]octane (28Ff)

The oil was purified by column chromatography (SiO_2, EtOAc) to give **28Ff** as a thick yellow oil (140 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.26 (m, 4H), 7.03-6.98 (m, 4H), 5.46 (bs, 1H), 5.35 (s, 1H), 4.01-3.90 (m, 2H), 3.42 (bs, 2H), 2.56 (bs, 1H), 2.17 (bs, 1H), 2.10-2.06 (d, J=14.8 Hz, 1H), 1.95-1.91 (d, J=14.4 Hz, 1H), 1.83 (bs, 2H), 1.58 (bs, 2H), 0.52-0.50 (d, J=7.2 Hz, 2H), 0.11-0.10 (d, J=4 Hz, 2H). Anal. Calc. for $C_{26}H_{29}F_2NO \bullet C_2H_2O_4$: C 65.00; H 6.40; N 2.70. Found: C 63.42; H 6.07; N 2.50.



3-(2-Diphenylmethoxy-ethylidene)-8-(4-fluorobenzyl)-8-azabicyclo[3.2.1]octane (28Hg)

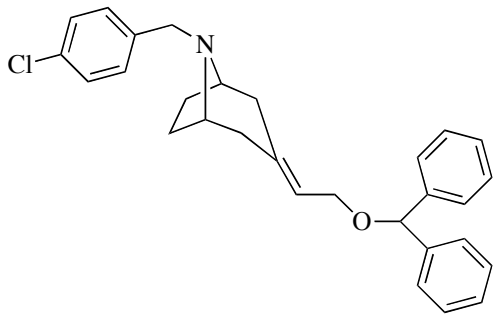
The oil was purified by column chromatography (SiO_2, EtOAc) to give **28Hg** as a thick yellow oil (77 mg, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.21 (m, 12H) 7.04-6.97 (m, 2H) 5.53-5.50 (t, J=6.4 Hz, 1H) 5.39 (s, 1H) 4.04-3.94 (m, 2H) 3.58 (s, 2H) 3.22 (s, 2H) 2.63-2.60 (d, J=13.2 Hz, 1H) 2.25-2.22 (d, J=14 Hz, 1H) 2.14-2.10 (d, J=14 Hz, 1H) 1.92 (bs, 3H) 1.60-1.53 (m, 2H). Anal. Calc. for $C_{29}H_{30}FNO \bullet C_2H_2O_4$: C 71.94; H 6.23; N 3.67. Found: C 66.30; H 5.98; N 2.44.



8-(4-Fluorobenzyl)-3-{2-bis(4-fluorophenyl)methoxy-ethylidene}-8-azabicyclo[3.2.1.]octane (28Fg)

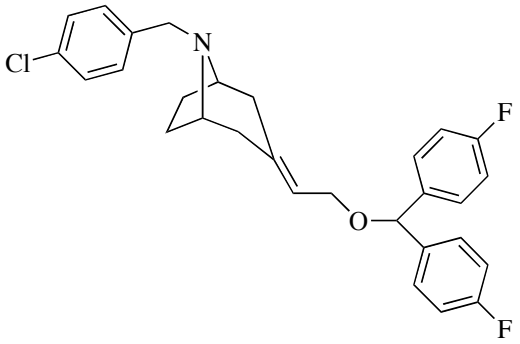
The oil was purified by column chromatography (SiO_2, EtOAc) to give **28Fg** as a thick yellow oil (73 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.25 (m, 6H) 7.06-6.98 (m, 6H) 5.50-5.47 (t, J=6.8 Hz, 1H) 5.35 (s, 1H) 4.01-3.92 (m, 2H) 3.56 (s, 2H) 3.21-3.20 (d, J=4 Hz,

2H) 2.60-2.57 (d, J=13.6 Hz, 1H) 2.19-1.90 (m, 5H) 1.56 (t, J=10 Hz, 1H) 1.42 (t, J=10 Hz, 1H). Anal. Calc. for $C_{29}H_{28}F_3NO \bullet C_2H_2O_4$: C 67.26; H 5.46; N 2.53. Found: C 66.44; H 5.45; N 2.56.



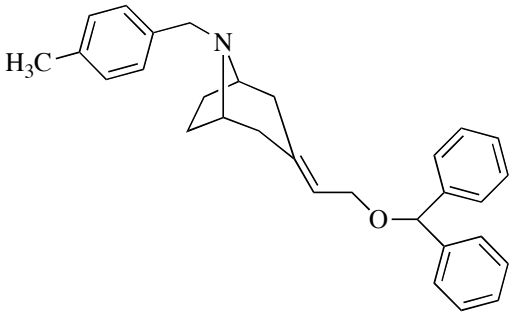
3-(2-Diphenylmethoxy-ethylidene)-8-(4-chlorobenzyl)-8-azabicyclo[3.2.1]octane (28Hh)

The oil was purified by column chromatography (SiO_2, EtOAc) to give **28Hh** as a thick yellow oil (95 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.21 (m, 14H) 5.51 (bs, 1H) 5.38 (s, 1H) 4.01-3.97 (m, 2H) 3.59-3.55 (d, J=16 Hz, 2H) 3.18-3.16 (d, J=6.8 Hz, 2H) 2.58-2.55 (d, J=12 Hz, 1H) 2.17-2.09 (m, 2H) 1.89 (bs, 3H) 1.58-1.44 (m, 2H). Anal. Calc. for $C_{32}H_{30}ClNO \bullet C_2H_2O_4$: C 69.72; H 6.04; N 2.62. Found: C 66.30; H 5.98; N 2.44.



8-(4-Chlorobenzyl)-3-{2-bis(4-fluorophenyl)methoxy-ethylidene}-8-azabicyclo[3.2.1.]octane (28Fh)

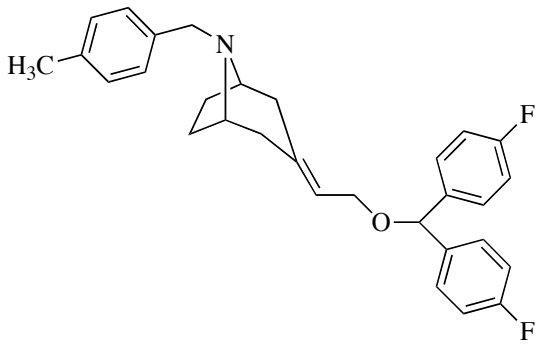
The oil was purified by column chromatography (SiO_2, EtOAc) to give **28Fh** as a thick yellow oil (56 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.23 (m, 8H) 7.04-6.97 (m, 4H) 5.48 (t, J=6.8 Hz, 1H) 5.35 (s, 1H) 4.01-3.91 (m, 2H) 3.56 (s, 2H) 3.19 (bs, 2H) 2.60-2.56 (d, J=14.4 Hz, 1H) 2.22-2.19 (d, J=14 Hz, 1H) 2.11-2.08 (d, J=14 Hz, 1H) 1.96-1.86 (m, 3H) 1.56 (t, J=9 Hz, 1H) 1.42 (t, J=8.8 Hz, 1H). Anal. Calc. for $C_{29}H_{28}F_2ClNO•C_2H_2O_4$: C 65.32; H 5.30; N 2.46. Found: C 63.74; H 5.26; N 2.63.



3-(2-Diphenylmethoxy-ethylidene)-8-(4-methylbenzyl)-8-aza-bicyclo[3.2.1]octane (28Hi)

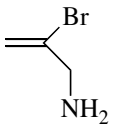
The oil was purified by column chromatography (SiO_2, EtOAc) to give **28Hi** as a thick yellow oil (74 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.11 (m, 14H) 5.51-5.48 (t, J=6.4 Hz, 1H) 5.39 (s, 1H) 4.04-3.97 (m, 2H) 3.56 (s, 2H) 3.22-3.19 (d, J=17.6 Hz, 2H) 2.61-2.57 (d,

J=13.6 Hz, 1H) 2.33 (s, 3H) 2.23-2.19 (d, J=14 Hz, 1H) 2.11-2.08 (d, J=14.4 Hz, 1H) 1.93 (bs, 3H) 1.57-1.43 (m, 2H). Anal. Calc. for $C_{30}H_{33}NO \bullet C_2H_2O_4$: C 74.83; H 6.87; N 2.73. Found: C 66.30; H 5.98; N 2.44.



3-{2-Bis(4-fluorophenyl)methoxy-ethylidene}-8-(4-methylbenzyl)-8-azabicyclo[3.2.1.]octane (28Fi)

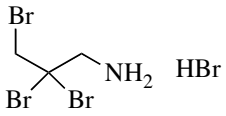
The oil was purified by column chromatography (SiO_2, EtOAc) to give **28Fi** as a thick yellow oil (153 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21-7.16 (m, 4H) 7.06-7.04 (d, J=8 Hz, 4H) 6.94-6.90 (m, 4H) 5.41-5.39 (t, J=8 Hz, 1H) 5.27 (s, 1H) 3.90-3.86 (m, 2H) 3.49 (s, 2H) 3.16-3.13 (m, 2H) 2.54-2.50 (d, J=16 Hz, 1H) 2.26 (s, 3H) 2.16-2.12 (d, J=14 Hz, 1H) 2.02-1.99 (d, J=14 Hz, 1H) 1.86-1.83 (m, 3H) 1.50-1.44 (t, J=8 Hz, 1H) 1.35-1.31 (t, J=8 Hz, 1H). Anal. Calc. for $C_{30}H_{31}F_2NO \bullet C_2H_2O_4 \bullet H_2O$: C 67.71; H 6.22; N 2.47. Found: C 66.30; H 5.98; N 2.44.



2-Bromopropenamine (61)

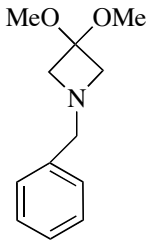
In a 1L 3-neck round bottom flask was added 2 equivalents of hexamethylenetetramine (126 g, 0.90 mol), $CHCl_3$ (800 mL) and fitted with a Hershberg stirrer. The mixture was brought to reflux with stirring while adding via an addition funnel 2, 3-dibromopropene, 80% (100 g, 0.40 mol) over one hour. The mixture was refluxed an additional 3 hours then cooled to room temperature overnight without stirring. The mixture was cooled in an ice bath and the salt filtered via vacuum filtration. The salt was allowed to air-dry overnight.

The salt was added to EtOH (2 L), 12N HCl (480 mL) and H_2O (400 mL). This was allowed to stir one hour then let stand at room temperature for 24 hours. The salt was removed by vacuum filtration and the filtrate concentrated to approximately 600 mL. The filtrate was filtered again and concentrated to dryness. The solid residue was dissolved in H_2O (300 mL) and the pH adjusted to pH = 13 with 6N NaOH (200 mL). The aqueous mixture was extracted with diethyl ether (3 × 100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was distilled under reduced pressure to afford **61** as an off-white solid (44g, 81%), which was immediately utilized in the next step. ^1H NMR (400 MHz, $CDCl_3$) δ 5.78 (s, 1H) 5.48 (s, 1H) 3.48 (s, 2H) 1.60 (bs, 2H).[65]



2, 3-Tribromopropylamine•HBr (48)

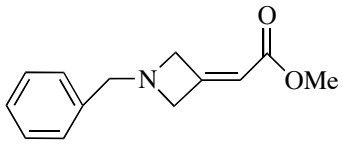
The amine from the previous step was dissolved in H_2O (70 mL) and brought to 0° C on an ice bath. HBr (48% solution, 40.5 mL, 0.36 mol) was added slowly with stirring followed by slow addition of Br_2 (25 mL, 0.49 mol). The mixture was allowed to stir at room temperature for 24 hours. The mixture was then concentrated under reduced pressure to afford **48** as an orange-white solid (104g, 85%). mp 196°-198° C [lit.[60] 196-198° C]. ^{1}H NMR (400 MHz, D_2O) δ 4.35 (s, 2H) 3.82 (s, 2H). Anal. Calc. for $C_3H_6NBr_3$•HBr: C 9.56; H 1.87; N 3.72. Found: C 9.66; H 1.81; N 3.70. NMR data is comparable to ref. 60.



1-Benzyl-3-dimethoxyazetidine (46)

In a 250 mL round bottom flask were added the amine (4.02g, .011 mol), benzaldehyde (1.2 mL, .011 mol), BF_3•Et_2O (3 drops), triethylamine (3 mL, .022 mol), H_2O (10 mL) and benzene (100 mL). This was fitted with a Dean-Stark trap and refluxed overnight. The mixture was cooled to room temperature and diethyl ether (100 mL) was added. The triethylammonium salts were filtered and the solvent evaporated under reduced pressure. The residue was dissolved in dry MeOH (50 mL) and flushed with N_2. The mixture was cooled to 0° C on an ice bath and $NaBH_4$ (1.01g, .022 mol) was added portionwise over 1 hour. The mixture was allowed to warm

to room temperature and then heated to reflux overnight. The mixture was concentrated under reduced pressure then dissolved in H_2O (50 mL) and extracted with CH_2Cl_2 (4 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The oil was purified by column chromatography (SiO_2, EtOAc/ hexanes 1:4) to give **46** as a thick yellow oil (957 mg, 43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.31 (m, 5H) 3.73 (s, 2H) 3.30 (s, 4H) 3.20 (s, 6H). NMR data is comparable to ref. 60.

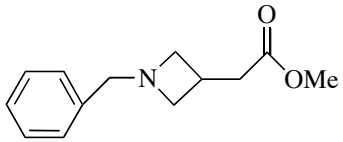


1-Benzyl-3-methoxycarbethylidenylazetidine (62)

In a 50 mL round bottom flask were added the protected azetidine **46** (.741g, 3.58 mmol) and 10 eq. 18 M H_2SO_4 (2 mL). The mixture was allowed to stir at room temperature for 3hours then cooled to 0° C on an ice bath. The reaction was quenched with sat. NaOH (12 mL) and the residue dissolved with H_2O (30 mL) and CH_2Cl_2 (30 mL). The mixture was poured into a separatory funnel and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (4 × 20 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduce pressure. The *N*-benzylazetidinone **37** was immediately carried on to the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.34 (m, 5H) 4.08 (s, 4H) 3.88 (s, 2H).[54]

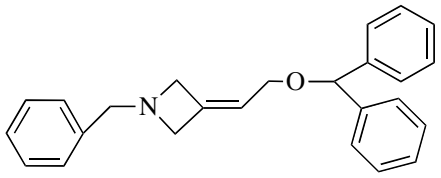
In a 100 mL round bottom flask were added LiCl (75 mg, 2.0 mmol), acetonitrile (25 mL) and a stir bar. Trimethylphosphonoacetate (0.22 mL, 2.0 mmol) was then added with stirring. DBU (0.20 mL, 1.3 mmol) was added followed by the azetidinone **37**. The mixture was allowed to stir at room temperature overnight. The mixture was concentrated under reduced pressure with minimal heat. The residue was partitioned over in H_2O (20 mL) and CH_2Cl_2 (30

mL) and added to a separatory funnel. The layers were separated and the aqueous extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The oil was purified by column chromatography (SiO_2, EtOAc/ hexanes 1:3) to give **62** as a yellow oil (158 mg, 55% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.33-7.26 (m, 5H) 5.68 (bs, 1H) 4.26-4.25 (d, J = 2.8 Hz, 2H) 4.01-4.00 (d, J = 2.4 Hz, 2H) 3.78 (s, 2H) 3.68 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$/ TMS) δ 166.1, 157.9, 138.3, 128.6(4), 127.4, 111.9, 64.1, 63.2, 62.2, 51.1. Anal. Calc. for $C_{13}H_{15}NO_2 \bullet C_2H_2O_4$: C 58.63; H 5.58; N 4.56. Found: C 57.76; H 5.57; N 4.51. M.p 147-150° C.



1-Benzyl-3-methoxycarbethylazetidine (63)

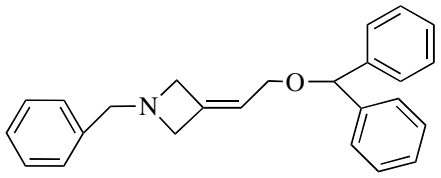
In a 100 ml round bottom flask were added the azetidine **62** (610 mg, 2.81 mmol), 10% Pd/C (65 mg) and dry THF (55 mL). The flask was evacuate of all gases and sealed under H_2 gas (1 atm). The mixture was allowed to stir at room temperature overnight. The mixture was then filtered through a pad of Celite, washed with EtOAc (50 mL) and concentrated under reduced pressure to afford **63** as a yellow oil (611 mg, quantitative) without any further purification.). ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.17-7.07 (m, 5H), 3.46 (bs, 5H), 3.36-3.32 (t, J = 7.2 Hz, 2H), 2.80-2.77 (t, J = 6.8 Hz, 2H), 2.69-2.66 (m, 1H), 2.45-2.43 (d, J = 7.6 Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$/ TMS) δ 172.6, 137.8, 128.7(2), 128.5(2), 127.3, 63.3, 59.8, 51.5(2), 38.3, 27.2. Anal. Calc. for $C_{13}H_{17}NO_2 \bullet C_2H_2O_4$: C 58.25; H 6.19; N 4.53. Found: C 57.96; H 6.21; N 4.56. M.p 156-157° C.



General Procedure for 1-Benzyl-3-diphenylmethoxyethylidenylazetidine (29a, b and 30a, b)

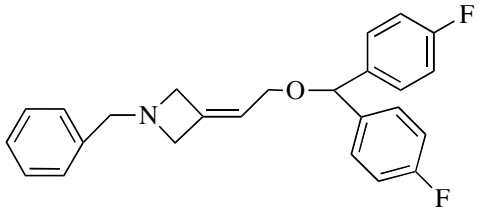
To a 100 mL round bottom flask was added $LiAlH_4$ (30 mg, 0.8 mmol) and dry THF (10 mL) then sealed under N_2. The reaction was cooled to 0° C on an ice bath and the azetidine ester **62** (123 mg, 0.6 mmol) in THF (3 mL) was added slowly via syringe. The reaction was stirred at 0° C for 2 hours and quenched with a 10% solution of KOH (0.5 mL). The mixture was allowed to come to room temperature with stirring for 1 hour and then poured into a separatory funnel. The white solid in the flask was washed with CH_2Cl_2 (3 × 10 mL) and the washings added to the separatory funnel. The organic layer was washed with phosphate buffer (30 mL) and the layers separated. The aqueous layer was then extracted with CH_2Cl_2 (4 × 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure with minimal heat. The crude alcohol was immediately added to a 100 mL round bottom flask and dissolved in benzene (70 mL). PTSA (750 mg, 4.0 mmol) and the corresponding benzhydrol (1.85 g, 10 mmol) were added to the flask and fitted with a Dean-Stark trap. The reaction was heated to reflux overnight.

The mixture was concentrated under reduced pressure and the residue was dissolved in CH_2Cl_2 (20 mL). The organic phase was washed with saturated $NaHCO_4$ (40 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (4 × 25 mL). The organics were combined and dried over Na_2SO_4, filtered and concentrated under reduced pressure.



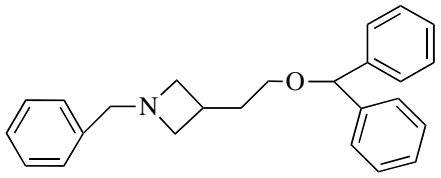
1-Benzyl-3-diphenylmethoxyethylidenylazetidine (29a)

The oil was purified by column chromatography (SiO_2, EtOAc) to give **29a** as a yellow oil (180 mg, 16% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.35-7.21 (m, 15H) 5.45-5.41 (m, 1H) 5.39 (s, 1H) 3.89-3.88 (d, J = 6.4 Hz, 4H) 3.82 (s, 2H) 3.71 (s, 2H). ^{13}C NMR (400 Mhz, $CDCl_3$/ TMS) δ 142.4(2), 138.6, 136.8, 128.7(12), 127.7(2), 127.3, 117.3, 87.8, 65.7, 63.8, 62.4, 61.5. Anal. Calc. for $C_{25}H_{25}NO•C_2H_2O_4$: C 72.79; H 6.11; N 3.14. Found: C 72.57; H 6.08; N 3.29. M.p 146.5-147° C.



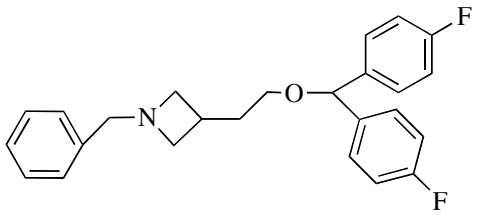
1-Benzyl-3-(bis-4-fluorophenyl)methoxyethylidenylazetidine (29b)

The oil was purified by column chromatography (SiO_2, EtOAc) to give **29b** as a yellow oil (80 mg, 16% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.36-7.26 (m, 10H), 7.04-7.00 (t, J = 8.4Hz, 4H), 5.45- 5.42 (m, 1H), 5.38 (s, 1H), 3.90-3.87 (t, J = 2.8Hz, 4H), 3.82 (s, 2H), 3.73 (s, 2H). ^{13}C NMR (400 MHz, $CDCl_3$/ TMS) δ 163.7, 161.2, 138.6, 138.1, 138.0, 137.3, 128.9(4), 128.8(2), 128.7(4), 127.4, 116.9(2), 115.7, 115.5, 81.3, 65.7, 63.8, 62.4, 61.4. Anal. Calc. for $C_{25}H_{25}NO•C_2H_2O_4$: C 67.35; H 5.23; N 2.91.



1-Benzyl-3-diphenylmethoxyethylazetidine (30a)

The oil was purified by column chromatography (SiO_2, EtOAc) to give **30a** as a yellow oil (142 mg, 30% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.38-7.25 (m, 15H), 5.33 (s, 1H), 3.62 (s, 2H), 3.55-3.51 (t, J = 6.8Hz, 2H), 3.46-3.43 (t, J = 8.0Hz, 2H), 2.89-2.85 (t, J = 6.8Hz, 2H), 2.75-2.71 (m, 1H), 1.94-1.90 (q, J = 6.8, 6.4Hz, 2H). ^{13}C NMR (400 Mhz, $CDCl_3$/ TMS) δ 142.7(2), 138.6, 128.8(4), 128.7(2), 128.6(4), 127.7(2), 127.2, 127.1(2), 84.0, 67.6, 64.3, 61.1(2), 34.9, 29.1. Anal. Calc. for $C_{25}H_{27}NO•C_2H_2O_4•0.25H_2O$: C 71.74; H 6.58; N 3.10. Found: C 71.72; H 6.53; N 3.11. M.p 146.5-147.5° C.



1-Benzyl-3-diphenylmethoxyethylazetidine (30b)

The oil was purified by column chromatography (SiO_2, EtOAc) to give **30b** as a yellow oil (223 mg, 49% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.35-7.24 (m, 8H), 7.04-7.00 (m, 4H), 5.26 (s, 1H), 3.69 (s, 2H), 3.51-3.47 (t, j = 6.4 Hz, 2H), 3.40-3.37 (t, 6.0Hz, 2H), 2.85-2.82 (t, J = 7.6 Hz, 2H), 2.70-2.66 (m, 1H), 1.91-1.86 (q, J = 6.0, 7.2 Hz, 2H). ^{13}C NMR (400 Mhz, $CDCl_3$/ TMS) δ 163.6, 161.2, 138.3(3), 128.7(8), 127.2, 115.6(2), 115.4(2), 82.6, 67.6, 64.2, 60.9(2), 34.7, 29.1. Anal. Calc. for $C_{25}H_{27}NO•C_2H_2O_4$: C 67.07; H 5.63; N 2.90. Found: C 66.93; H 5.55; N 2.92. M.p 162.5-163° C

Dopamine Transporter Binding Assay. Binding of [^{3}H]WIN 35,428 were done as described previously.[60,61] Male Sprague-Dawley rats (200-250 g, Taconic, Germantown, NY) were decapitated and their brains removed to an ice-cooled dish for dissection of the caudate putamen. The tissue was homogenized in 30 volumes ice-cold modified Krebs-HEPES buffer (15 mM HEPES, 127 mM NaCl, 5 mM KCl, 1.2 mM $MgSO_4$, 2.5 mM $CaCl_2$, 1.3 mM NaH_2PO_4, 10 mM D-glucose, pH adjusted to 7.4) using a Brinkman polytron and centrifuged at 20,000 x *g* for 10 min at 4°C. The resulting pellet was then washed two more times by resuspension in ice-cold buffer and centrifugation at 20,000 x *g* for 10 min at 4°C. Fresh homogenates were used in all experiments. Binding assays were conducted in modified Krebs-HEPES buffer on ice. The total volume in each tube was 0.5 mL and the final concentration of membrane after all additions was 0.5% (w/v) corresponding to 200-300 mg of protein/sample. [^{3}H]WIN 35,428 (2β-carbomethoxy-3β−(4-fluorophenyl)tropane 1,5-naphthalene disulfonate; specific activity 82.4 Ci/mmol, from New England Nuclear, Boston, MA) was added and the incubation was continued for 1 hr on ice. The incubation was terminated by the addition of 3 mL of ice-cold buffer and rapid filtration through Whatman GF/B glass fiber filter paper (presoaked in 0.1% BSA in water to reduce non-specific binding) using a Brandel Cell Harvester (Gaithersburg, MD). The filters were washed with three additional 3 mL washes and transferred to scintillation vials. Absolute ethanol (0.5 mL) and Beckman Ready Value Scintillation Cocktail (2.75 mL) was added to the vials, which was counted the next day at an efficiency of about 36%. For determination of K_i values, triplicate samples of membrane suspension was preincubated for 5 min in the presence or absence of the compound being tested. Each compound was tested with concentrations ranging from 0.01 nM to 100 μM for competition against binding of [^{3}H]WIN 35,428 (final concentration 1.5 nM), in three independent experiments. Under these assay conditions, an

average experiment yielded approximately 6,000 dpm total binding per sample and approximately 250 dpm non-specific binding, defined as binding in the presence of 100 μM cocaine. Each assay was replicated three times, and K_i values were determined using PRISM.

Serotonin transporter Binding Assay. Brains from male Sprague-Dawley rats weighing 200-225 g were removed, the midbrain was dissected and rapidly frozen. Membranes were prepared by homogenizing tissues in 20 volumes (w/v) of 50 mM Tris (120 mM NaCl, 5 mM KCl; pH 7.4 at 25º C) using a Brinkman polytron (setting 6 for 20 sec) and centrifuged (20,000 x *g*) for 10 min at 4º C. The resulting pellet was resuspended in buffer and recentrifuged (20,000 x *g* for 10 min at 4º C). The final pellet was resuspended in cold buffer to a concentration of 15 mg/ mL (original wet weight). Assays were conducted in the above Tris buffer at 25º C (room temperature). The total volume of each tube was 0.5 mL and contained 1.4 nM [^{3}H]citalopram (specific activity 80 Ci/mmol; New England Nuclear, Boston MA) and 1.5 mg midbrain tissue (original wet weight). [^{3}H]Citalopram was added and the incubation continued for 60 min at room temperature. Incubations were terminated by rapid filtration through Whatman GF/B filters (presoaked in 0.3% polyethylenimine in water to reduce non-specific binding) using a Brandel R48 filtering manifold (Brandel Instruments Gaithersburg, MD). The filters were washed twice with 5 mL cold buffer and transferred to scintillation vials. Beckman Ready Safe (3.0 mL) was added and the vials were counted the next day using a Beckman 6000 liquid scintillation counter (Beckman Coulter Instruments, Fullerton, CA) at an efficiency of 36%. Nonspecific binding is determined using 10 μM fluoxetine (RBI, Natick, MA). Each compound was tested at concentrations from 0.01 nM to 100 μM for competition against binding of [^{3}H]citalopram, in three independent experiments, each performed in triplicate. Each assay was replicated three times, and K_i values will be determined using PRISM.

Norepinephrine Transporter Binding Assay. Brains from male Sprague-Dawley rats weighing 200-225 g were removed, the frontal cortex was rapidly dissected and frozen. Membranes were prepared by homogenizing tissues in 20 volumes (w/v) of 50 mM Tris (120 mM NaCl, 5 mM KCl; pH 7.4 at 25° C), using a Brinkman polytron (setting 6 for 20 sec) and centrifuged (50,000 x *g*) for 10 min at 4°C. The resulting pellet was resuspended in buffer, recentrifuged (50,000 x *g*) for 10 min at 4°C and resuspended in buffer to a concentration of 80 mg/mL. Assays were conducted in the above Tris buffer on ice. The total volume of each tube was 0.5 mL and contained 0.5 nM [^{3}H]nisoxetine (specific activity 80 Ci/mmol, New England Nuclear, Boston, MA) and 8 mg frontal cortex tissue (original wet weight). Triplicate samples of the membrane suspension were preincubated for 5 min in the presence or absence of the test compound. [^{3}H]Nisoxetine was added and the incubation continued for 1 hr on ice. Incubations were terminated by rapid filtration through Whatman GF/B filters, presoaked in 0.05% polyethylenimine, using a Brandel R48 filtering manifold (Brandel Instruments Gaithersburg, MD). The filters were washed twice with 5 mL cold buffer and transferred to scintillation vials. Beckman Ready Safe (3.0 mL) was added to the vials, which were counted using a Beckman 6000 liquid scintillation counter (Beckman Coulter Instruments, Fullerton, CA) at an efficiency of 36%. Nonspecific binding is defined as binding in the presence of 1 μM desipramine. Each compound was tested at concentrations from 0.01 nM to 100 μM for competition against binding of [^{3}H]nisoxetine, in three independent experiments, each performed in triplicate. Each assay was replicated three times, and K_i values were determined using PRISM.

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