# SYNTHESIS AND PHARMACOLOGY OF POTENTIAL SITE-DIRECTED THERAPEUTIC AGENTS FOR COCAINE ABUSE

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SYNTHESIS AND PHARMACOLOGY OF POTENTIAL SITE-DIRECTED THERAPEUTIC AGENTS FOR COCAINE ABUSE

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## DEDICATION

This thesis is dedicated to my daughter, Serina,
for her compassionate and understanding heart,
for her comfort during the most trying and difficult times in our lives,
and for her willingness to endure this struggle by my side.

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## ABBREVIATIONS AND SYMBOLS

| | |
|---|---|
| DA | Dopamine |
| DAT | Dopamine transporter |
| NE | Norepinephrine |
| NET | Norepinephrine transporter |
| 5-HT | Serotonin |
| 5-HTT | Serotonin transporter |
| N-$Ph_c$ | Nitrogen-centroid phenyl distance |
| $IC_{50}$ | Inhibition concentration at 50% |
| [$^3$H] WIN 35,428 | Radioligand used to measure binding to the dopamine transporter |
| [$^3$H] DA | Radiolabeled dopamine used to measure dopamine uptake |
| [$^3$H] Nisoxetine | Radioligand used to measure binding to the norepinephrine transporter |
| [$^3$H] Citalopram | Radioligand used to measure binding to the serotonin transporter |
| COSY | Correlated spectroscopy |
| NOESY | Nuclear Overhauser Effect spectroscopy |
| HMQC | Heteronuclear Multiple Quantum Coherence |

| | |
|---|---|
| HMBC | Heteronuclear Multiple Bond Correlation |
| NMR | Nuclear magnetic resonance spectroscopy |
| ppm | parts per million |
| THF | Tetrahydrofuran |
| LDA | Lithium diisopropyl amide |
| DEAD | Diethyl azodicarboxylate |
| mp | melt point (˚C) |
| SARs | Structure-activity relationships |
| DMSO | Dimethyl sulfoxide |
| DMAP | Dimethylamino pyridine |

## SUMMARY

Stimulants such as cocaine continue to dominate the nation's illicit drug problem. An effective medication for any aspect of cocaine addiction has not been developed. Cocaine binds, although not selectively, to the dopamine transporter (DAT) and disrupts normal dopamine (DA) neurotransmission between neurons. While the "dopamine hypothesis" for the mechanism of action of cocaine has been widely accepted, cocaine also possesses the ability to block the uptake of serotonin at the serotonin transporter (5-HTT) and norepinephrine at the norepinephrine transporter (NET). The purpose of the work described herein is directed towards synthesizing and testing compounds selective for the DAT, leading to the identification of candidates as potential pharmacotherapies for cocaine dependence.

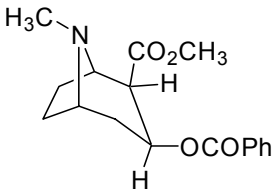
A series of disubstituted and trisubstituted [2.2.2] and [2.2.1]bicycles were synthesized and tested for inhibitor potency in [$^3$H]WIN 35,428 (WIN) binding at the DAT and for inhibition of [$^3$H]DA uptake. Based on results from some of the pharmacology data new regio- and stereochemical isomers of bicyclic [2.2.1]heptanes and [2.2.2]octanes were synthesized. This will lead to further structure-activity-relationships, which will provide a better understanding of the structural requirements needed to bind at the DAT.

# CHAPTER I

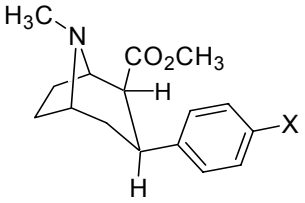
# AN INTRODUCTION TO THE DEVELOPMENT OF POTENTIAL PHARMACOTHERAPIES FOR COCAINE ADDICTION

## Background

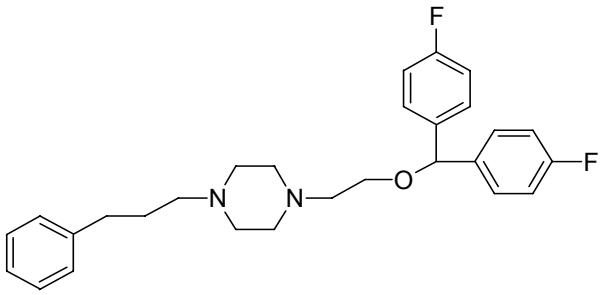
First isolated from the coco leaves (*erythroxylon coca*) as a naturally occurring local anesthetic, (-) cocaine (**1**, Figure 1.1) has become problematic and a safety hazard due to its powerful reinforcing effects on individuals and society.[1] Cocaine is a widely abused drug with strong addiction liabilities that need to be further understood. To date, an effective medication for any aspect of cocaine addiction does not exist. Our work is directed towards combining medicinal chemistry and preclinical pharmacology to design, synthesize, and test site-directed compounds leading to the identification of candidates as potential pharmacotherapies for cocaine dependence.[2] While considerable effort has been expended in the study of the mechanism of action of cocaine, the details are still under investigation. Studies show cocaine binds, although not selectively, to the DAT[3,4,5,6] and disrupts normal DA neurotransmission between neurons (Figure 1.2[7]). Vesicles in the presynaptic



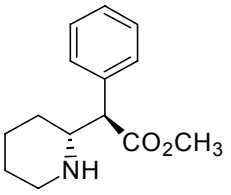

**1**, Cocaine



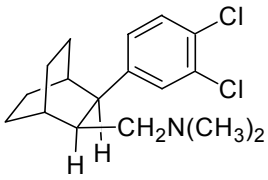

**2a**, x= F, WIN 35,428
**2b**, x= H, WIN 35,065-2




**3**, GBR 12909




**4**, Methylphenidate




**5**, LR5182

**Figure 1.1.** Potent DA Uptake Inhibitors.

neuron release DA into the synaptic cleft between neurons when an electrical impulse is transduced through the neuron. The DA released into the synapse binds to a receptor protein on the postsynaptic neuron. Upon binding to the receptor, DA activates the neuron and the electrical impulse is transduced through the receiving neuron. Once the receiving neuron has been activated, the DA is released by the receptor protein and taken back up into the presynaptic neuron via the DAT. When cocaine is present it blocks reuptake of DA back into the presynaptic neuron due to competitive binding between DA and cocaine at the DAT. Excess amounts of DA accumulate in the synapse, which prolongs neurotransmission and, in turn, produces a reinforcing effect or the characteristic cocaine "high".[8] Activation of postsynaptic receptors alone does not appear to be sufficient to lead to addiction. Rather, it is the rapid onset and short duration of action of cocaine and concomitant surge in available DA that presumably accounts for the rapid cycles observed clinically and the high addiction potential of cocaine. While the "dopamine hypothesis" for the mechanism of action of cocaine has been widely accepted, cocaine also possesses the ability to block the uptake of serotonin at the serotonin transporter (5-HTT) and norepinephrine at the norepinephrine transporter (NET).[9,10]

Evidence exists for two distinct binding sites for dopamine and cocaine on the DAT, which may, or may not, overlap.[11,12,13] This creates the possibility of producing a therapeutic agent that will block the binding of cocaine to the DAT, but will allow the reuptake of DA into the transmitting neuron (*i.e.*, a cocaine antagonist). An alternate candidate would elicit some of the same effects in the user as cocaine itself,

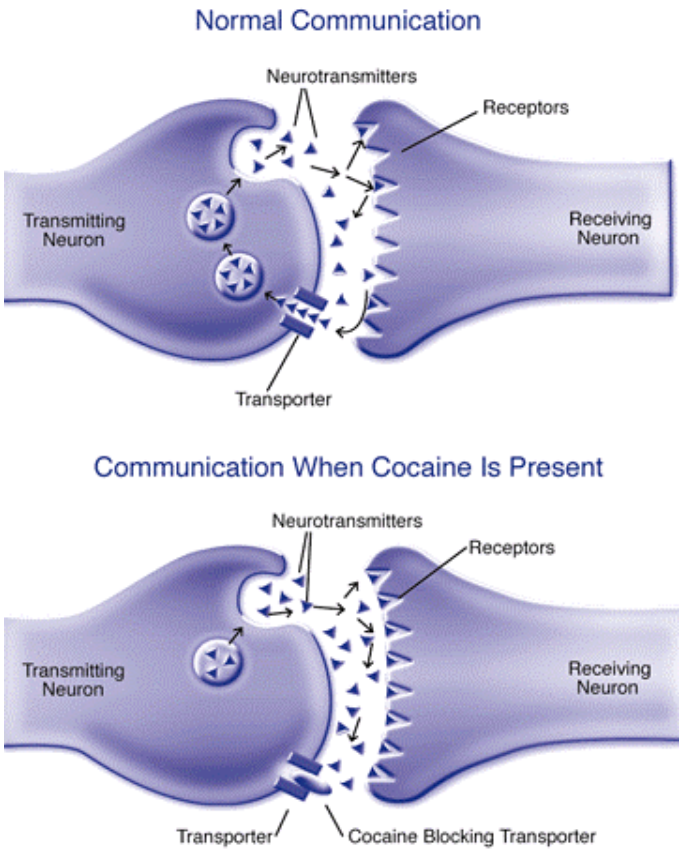



**Figure 1.2.** Dopamine neurotransmission with/without cocaine present.[7]

but not cause the same degree of euphoria. The most promising of these drugs would be a long lasting, slow onset, cocaine agonist.

To date, the search for compounds to be used in the development of safe and effective treatment agents for cocaine addiction has led to the synthesis of a number of tropane and non-tropane compounds. Among these compounds are WIN 35,428 and 35,065-2 (**2a** and **2b**, respectively),[14] GBR 12909 (**3**),[15] methylphenidate (**4**),[16] and LR 5182 (**5**)[17] (Figure 1.1), which have all been reported to demonstrate potential as cocaine abuse therapeutic agents. The structural analogy of the WIN analogues to cocaine is obvious. The binding affinity of WIN 35,065-2 to the DAT is 8 times greater than that of cocaine. One of the main structural differences between cocaine and GBR 12909 is the non-tropane, disubstituted, piperazine ring. GBR 12909 binds potently to the DAT and produces a relatively modest and long lasting increase in the DA concentration in the synapse, which does not cause the same degree of euphoria as cocaine. LR 5182, a potent stimulant, also does not contain the tropane core of cocaine, but molecular modeling suggests a high degree of analogy between the three-dimensional spatial arrangement of structural features (the phenyl ring and nitrogen) of cocaine and LR 5182. The stimulant properties of methylphenidate are also believed to arise from its structural homology with cocaine, and a common mode of binding the phenyl rings and the basic nitrogen at the DAT.

The $IC_{50}$ values for inhibition of [$^3$H]DA uptake[18] and the inhibition of ligand binding to the DA,[19] norepinephrine (NE),[20] and 5-hydroxytryptamine (5-HT, serotonin) transporters have been used as comparative measures to determine the extent of binding and the selectivity for the different biogenic amine transporters.[21]

**Table 1.1**. Binding Data for reference compounds.

| | $IC_{50}(\mu M)$ | |
|---|---|---|
| Compound | [$^3$H]WIN 35,428 | [$^3$H] DA uptake |
| (-)-cocaine (**1**) | 0.160 ± 0.015 | 0.404 ± 0.026 |
| WIN 35,428 (**2a**) | 0.0199 ± 0.001 | 0.0512 ± 0.00025 |
| WIN 35,065-2 (**2b**)[28] | 0.023 ± 0.005[28] | 0.0498 ± 0.0023*[28] |
| Methylphenidate (**4**) | 0.083 ± 0.0079 | 0.24 ± 0.0.19 |
| LR 5182 (**5**) | 0.0142 ± 0.0016 | 0.0293 ± 0.0017 |
| GBR 12909 (**3**) | 0.0140 ± 0.0006 | 0.0073 ± 0.0002 |

*Reported as the $K_i$.
The experiments were performed under the supervision of Dr. Margaret M. Schweri at Mercer School of Medicine.

The bicyclic LR5182 is potent for inhibition of both WIN binding and DA uptake (Table 1.1), leading to our interest in derivatives of LR 5182. A number of LR 5182 analogs show potential as therapeutic agents[17] by combining the potency and selectivity of GBR derivatives in a conformationally restricted structure bearing more

similarity to cocaine. Modification of the rigid framework (stereochemistry, substituents on the framework and phenyl ring, type of amine, etc.) allow the determination of structure-activity relationships, which will aid in the development of therapeutic agents.

The DAT has been cloned and the binding site for DA described.[22] The human DAT (hDAT) is comprised of 620 amino acids, putatively arranged in 12 interconnected helices to form transmembrane channels (Figure 1.3). Each helical domain presents its polar amide linkages toward the core of the helix. This places the amino acid side chain on the outside of the helix facing the internal structure of the channel. Site-mutagenesis studies show that the aspartic acid residue lying within the putative hydrophobic transmembrane domain 1 (TMD 1) is crucial for DAT function (Figure 1.4). An explanation for this observation is that the carboxylic acid of aspartic acid 79 interacts with the amine of DA to play a crucial role in DA transport.[11] This amino acid may also recognize the tropane nitrogen of cocaine to participate in cocaine binding. These studies also show two serines in TMD 7 (359 and 354) play an important role by hydrogen bonding to the two hydroxyl groups of DA. It is still uncertain whether cocaine interacts with the same amino acids of the DAT in the same manner. As of yet, no crystallographic data is available that clearly defines how the DAT is actually configured in membranes in its functional state.

The development of structure-activity relationships has led to a proposed pharmacophore for cocaine (Figure 1.5). The model, proposed by Carroll *et al.*,[23] consists of an electrostatic or hydrogen bond site on the DAT to interact with the basic amino group of cocaine. It is speculated that one or two additional hydrogen bonding sites in the pharmacophore binds to the two oxygen atoms of the ester group of cocaine.

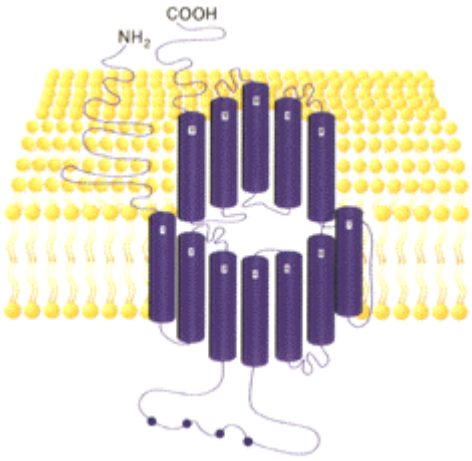



**Figure 1.3**. Proposed model for the DAT as a transmembrane channel.[24]

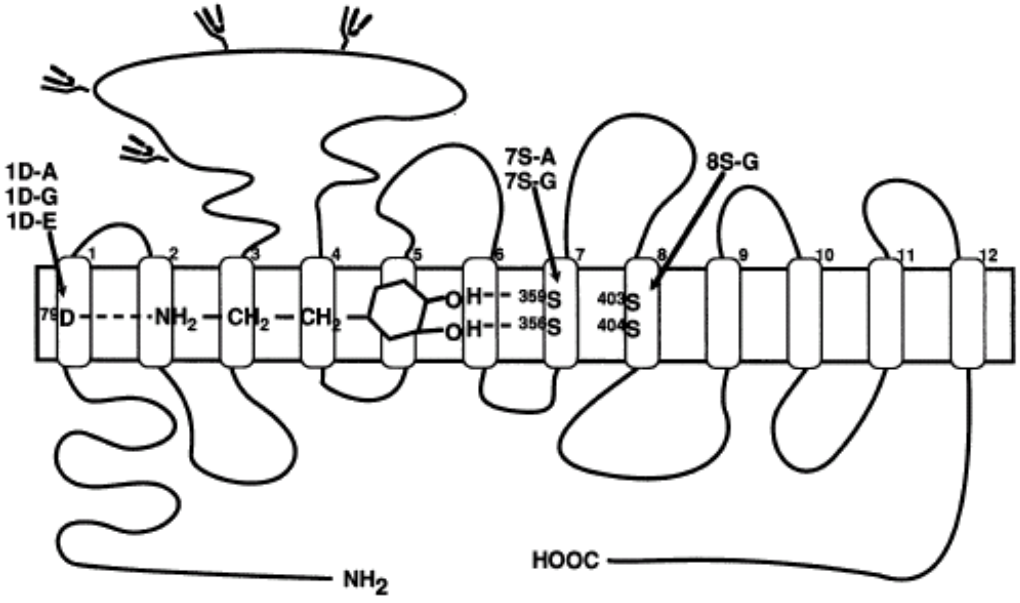



**Figure 1.4**. Depiction of the interactions of DA at the DAT.[25]

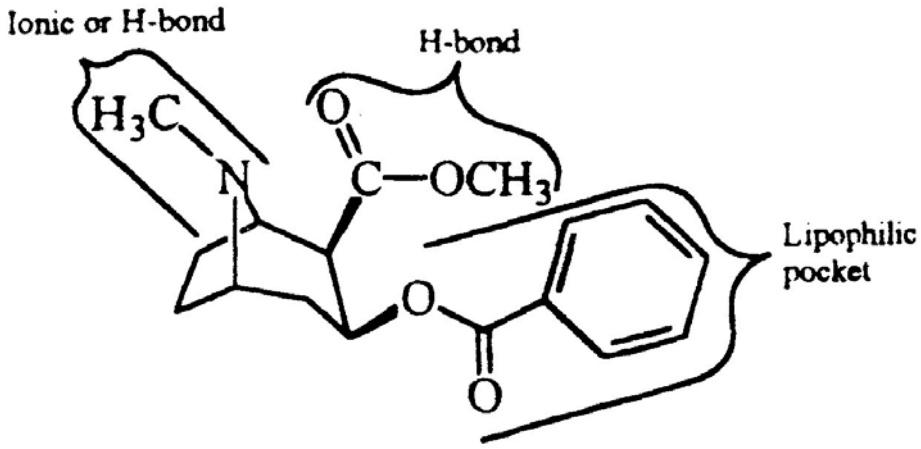



**Figure 1.5**. Proposed pharmacophore by Carroll *et al*.[23]

Recent studies have shown the replacement of the methyl ester group by ketones,[26] heterocycles,[27] amides,[28] alkyl groups,[29] and olefins[30] did not decrease the potency at the DAT. A hydrophobic pocket, which is believed to accommodate the benzoate group, has also been suggested. An important structural feature of all uptake inhibitors is an aromatic ring situated in such a way that it may interact with this "aromatic ring binding site" of the transporter protein. Structure-activity studies have also

shown that halogens in the 3- or 4-position on this aromatic ring often increase the binding potency. A more elaborate pharmacophore, Figure 1.6[31], has been proposed which suggests: i) the tropane nitrogen and the phenyl ring should be in the same plane for optimal binding; ii) the distance from the nitrogen to the centroid of the phenyl should be 5 to 7 Ångstroms; iii) the distance from the nitrogen to the carbonyl should be 2.2 to 4.5 Ångstroms; and iv) the distance from the centroid of the phenyl ring to the carbonyl should be 3.4 to 6.1 Ångstroms.

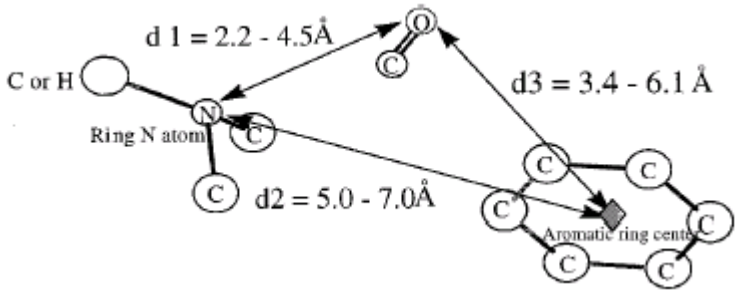
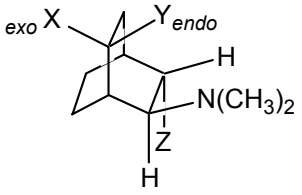



**Figure 1.6.** A 3-D pharmacophore model derived from cocaine by Johnson *et al*.[31]

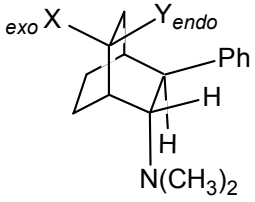
Recently, a series of 2-substituted-6-amino-5-phenylbicyclo[2.2.2]octanes were synthesized and tested for inhibitor potency in [$^3$H]WIN 35,428 (WIN) binding at the DAT and for inhibition of [$^3$H]DA uptake (Table 1.2).[32] The [$^3$H]DA uptake data is not shown in Table 1.2 but shows the same trends as that for [$^3$H]WIN 35,428 binding. Data presented in Table 1.2 indicates the *endo*-amines are more potent than the corresponding *exo*-amines and the ketones are similar in potency to the corresponding *exo*-acetates. The benzoate esters inhibited the uptake of [$^3$H]DA better than the corresponding alcohols and the stereochemistry at C-2 has little effect on the potency. The *endo*-amino-*endo*-benzoate **6** and the *endo*-amino-*endo*-4-chlorobenzoate **7** were the two most potent derivatives made from this series with an $IC_{50}$= 270 nM and $IC_{50}$=295 nM, respectively. Moving the halogen from the *para* position on the benzoate phenyl ring to the *meta* position did not affect the potency (**7** vs **8**). These values are comparable to that of (-) cocaine ($IC_{50}$= 160 nM). Clearly, the second phenyl group present in benzoate **6**, enhances the potency of these compounds.

Preliminary research to extend this study focused on this secondary effect on binding to the DAT to determine the relative importance of the two phenyl rings (the benzoate at C-2 and the phenyl at C-5) and to further explore structure-activity relationships.[33] One approach we took was to prepare esters **8** and **9**,[34] as analogs of **6**. A second approach to determine structure-activity-relationships of substituted bicycloalkane analogs of **6** was to prepare the analog without the phenyl ring at C-5, i.e. **10.**[34] Derivative **9** is the most potent compound with an $IC_{50}$=33 nM (Table 1.2) for [$^3$H]WIN binding and an $IC_{50}$=137 nM for the DA uptake. Congener **9** shows high

**Table 1.2.** Binding Data for 2-Substituted-6-(*N*,*N*-dimethylamino)-5-phenylbicyclo[2.2.2]octanes.




**6n**




**6x**

| | *endo*-amine | | | | | *exo*-amine | | |
|---|---|---|---|---|---|---|---|---|
| | $IC_{50}(\mu M)$ | | | | | | | |
| | X | Y | Z | [$^3$H]WIN 35,428 | | X | Y | [$^3$H]WIN 35,428 |
| | C=O | | Ph | 4.01 ± 0.40 | | C=O | | 10.3 ± 0.40 |
| | OH | H | Ph | 1.77 ± 0.13 | | OH | H | 7.04 ± 0.29 |
| | H | OH | Ph | 2.04 ± 0.24 | | H | OH | 9.92± 0.94 |
| | $OCOCH_3$ | H | Ph | 5.33 ± 0.36 | | $OCOCH_3$ | H | 13.6 ± 1.43 |
| | H | $OCOCH_3$ | Ph | 12.2 ± 0.69 | | H | $OCOCH_3$ | 45.6 ± 6.24 |
| | OCOPh | H | Ph | 0.358 ± 0.067 | | OCOPh | H | 2.20 ± 0.31 |
| **6** | H | OCOPh | Ph | 0.270 ± 0.029 | | H | OCOPh | 2.27 ± 0.066 |
| **7** | H | OCOAr | Ph | 0.295 ± 0.036 | | | | |
| **8** | H | OCOAr' | Ph | 0.576 ± 0.056 | | | | |
| **9** | H | OCOPh | Ar | 0.033 ± 0.0005 | | | | |
| **10** | H | OCOPh | H | 21.7 ± 2.3 | | | | |

Ar = 4-chlorophenyl
Ar' = 3-chlorophenyl

binding affinity at the dopamine transporter, with about an 8-fold increase in potency over *endo*-amino-*endo*-benzoate **6**. Derivative **10**, with an $IC_{50}$= 21700 nM, is 8 times less potent than *endo*-amino-*endo*-benzoate **7**. Removal of the phenyl ring at C-5 clearly demonstrates a decreased interaction between the des-phenyl **10** and the "aromatic ring binding site" on the DAT.

## Scope of Thesis

In Chapter 1 of this thesis, the effect of removing the phenyl at the C-5 position of the bicycle is further evaluated by isolating the other three desphenyl diastereomers of bicycloalkane analog **10,** structure **11** (Figure 1.7). Extensive analysis of the structural changes allow for the development of SARs, which may be related to the fit of these compounds with the proposed active site. These compounds will provide guidance in the design of new derivatives with cocaine agonist and antagonist activity.

To further evaluate the role of the phenyl substituent on the *endo*-amino 2,6-disubstituted [2.2.2]bicycle **10** mentioned above, the ester functionality was excised[35] (Chapter 2). An arene was attached directly to the bicyclic framework or by a one or two carbon linker, *e.g.* arenes **12**, Figure 1.7. These homologues will help determine the distance between the nitrogen and the phenyl ring for optimal binding. Increasing the number of carbons between the bicycle and the phenyl ring increases the flexibility, which may be needed to allow the phenyl ring to adopt a low energy conformation to bind to the active site. Lengthening the distance between the nitrogen and phenyl ring could render the distance too long, and as a result, decrease the potency of the

compounds. The excision of the ester is also expected to increase the half-life of the molecule in vivo, since it will not be subject to hydrolysis by esterases.

Chapter 3 discusses another approach taken to further understand the role of the phenyl ring, the transposition of the benzoate from the C-2 position on the bicycle to the C-3 position, *e.g.* structure **13**. Thus, extensive analysis of the structural changes allows for the development of SARs related to the fit of these compounds at the active site of the DAT.

An additional challenge has been to construct compounds which fill the gap between carbons 2 and 3 on the disubstituted [2.2.2]octanes discussed above. In Chapter 4, an approach is described which is based on disubstituted [2.2.1]heptanes, structures **14** and **15** (Figure 1.7). One can imagine the one-carbon bridge occupying a position so as to orient the phenyl substituent in an orientation between that occupied in the 2,5 and 2,6 disubstituted [2.2.2]octanes. The benzoate is placed on the one-carbon bridge for a direct comparison with the compounds already made. The substituents on the bicycle are exchanged so as to place the benzoate on the two-carbon bridge and the dimethylamine on the one-carbon bridge, benzoates **15**. By exchanging the substituents, a direct comparison of compounds containing an unsubstituted carbon adjacent to the amine or benzoate can be made with those compounds where the substituent is placed on the one carbon bridge. Placing the amine on the one-carbon bridge will also allow for a comparison with cocaine due to the resemblance in structure.

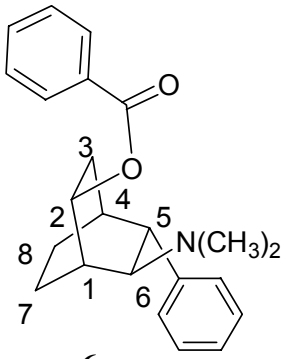
Since the most potent compounds of the trifunctional [2.2.2]bicyclic series synthesized previously in the our group were benzoate esters,[32] a challenge was to introduce a benzoate ester on the bicyclic [2.2.1]heptane skeleton to allow for comparison

to previously synthesized 2-(*N*,*N*-dimethylamino)methyl-3-phenyl bicyclo[2.2.1]heptanes (Chapter 5). Compounds **16** and **17**,[2] Figure 1.7, were of interest because of the difference in the inhibitor potency in [$^3$H]WIN 35,428 (WIN) binding at the DAT. The only difference between compounds **16** and **17** is the trans stereochemistry at the C-2 and C-3 position on the bicycle. This variation in the structures leads to a difference in potency of 515 nM for the *trans endo*-amine **16** versus 2510 nM for the *trans exo*-amine **17**, a 5-fold increase. Based on the trends seen with the series of 2-substituted-6-amino-5-phenylbicyclo[2.2.2]octanes (Table 1.2), a benzoate ester of **18** may increase the potency of these amines. The placement of the 4-chloro substituent on the phenyl ring may also increase the potency of these compounds.

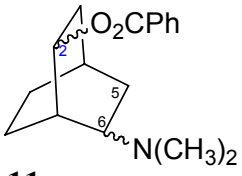
The series of [2.2.1] and [2.2.2]bicycloalkane analogs already synthesized provide a guide in the design of new derivatives with cocaine agonist and antagonist activity. The synthetic work described will provide further insight into the development of SARs for inhibition of cocaine binding.

**Specific Goals**

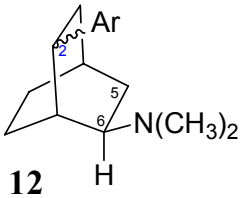
The goals of this thesis are to design, synthesize, characterize and pharmacologically investigate new regio- and stereochemical isomers of bicyclic [2.2.1]heptanes and [2.2.2]octanes. This will lead to further structure-activity relationships, which will provide a better understanding of the structural requirements needed to bind at the DAT. This will in turn help identify potential pharmacotherapies for cocaine dependence.



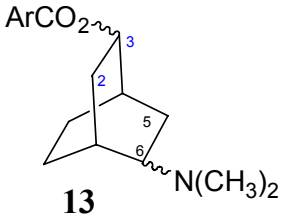

**6**




**11**




**12**

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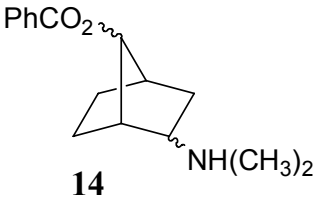
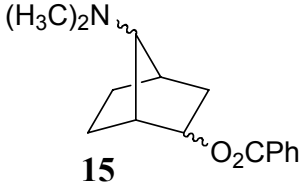
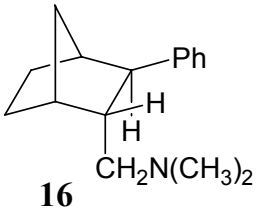


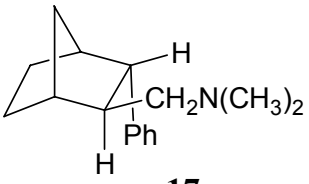

**14**



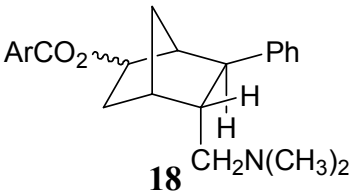

**15**




**16**
trans endo
WIN $IC_{50}$= 515 nM




**17**
trans exo
WIN $IC_{50}$= 2510 nM




**18**
Ar= Ph, 4-ClPh
trans endo

**Figure 1.7.** Di- and trisubstituted [2.2.1] and [2.2.2]bicycles.

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# CHAPTER II

# SYNTHESIS AND PHARMACOLOGY OF 2-BENZOYL-6-AMINO[2.2.2]BICYCLOOCTANES

## Introduction

Previous work in our group incorporated an oxygen functionality at the C-2 position of 6-amino-5-phenylbicyclo[2.2.2]octanes.[1] The more potent of these esters are the benzoates, containing two phenyl groups (the ester phenyl ring and the phenyl ring at C-5 of the bicyclic moiety). Based on the binding data shown in Table 1.2, the second phenyl group present in benzoate **6** enhances the potency of these compounds (Figure 2.1). Since two phenyl rings are present, an uncertainty exists as to which phenyl ring binds to the hydrophobic pocket (aromatic binding region) of the various monoamine transporters. While attempting to determine with more certainty the influence of the phenyl rings (the benzoate at C-2 or the phenyl ring at C-5) on benzoate **6**, three other stereoisomers of the desphenyl analog **10**, congeners **26-28**, were synthesized (Figure 2.1). Using MM2 energy-minimized conformations[2] the distances between the nitrogen and the centroid of the phenyl ring were calculated for each of these compounds. The

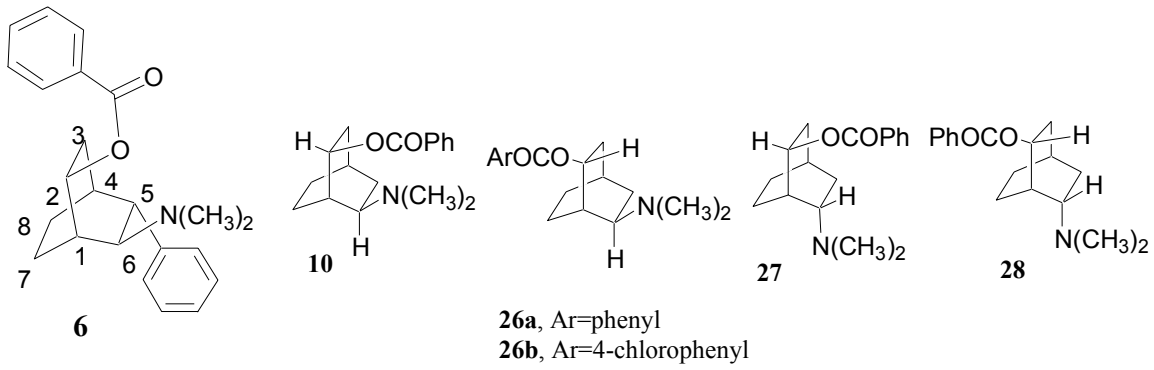
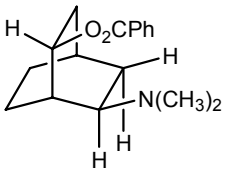
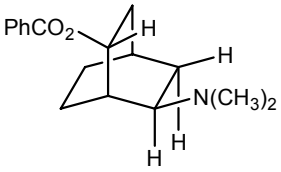
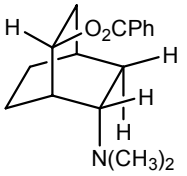
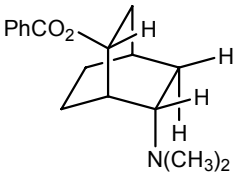



**Figure 2.1.** Benzoates **6**, **10**, and **26-28**.

distance varied between 5.4 and 8.69 Ångstroms for benzoates **10**, **26-28**. The distance from the nitrogen to the plane of the phenyl ring was also calculated for each of these compounds, with the distance varying between 0.004 and 0.281 Ångstroms. Based on the pharmacophore suggested by Johnson *et al*,[3] the distance from the nitrogen to the centroid of the phenyl ring should be 5 to 7 Å to provide a good fit with the binding site. All benzoates met this criteria, except benzoate **28**. Figure 2.2 shows an overlay of cocaine and benzoates **26a** and **28**. Comparison of the [$^3$H]WIN 35,428 binding and the inhibition of [$^3$H]DA uptake data will help to further characterize the binding affinity at the active site of the DAT.

**Table 2.1.** Measured distances between the nitrogen and the centroid of the phenyl ring and the nitrogen and the plane of the phenyl ring for benzoates **10**, **26-28**.[4]

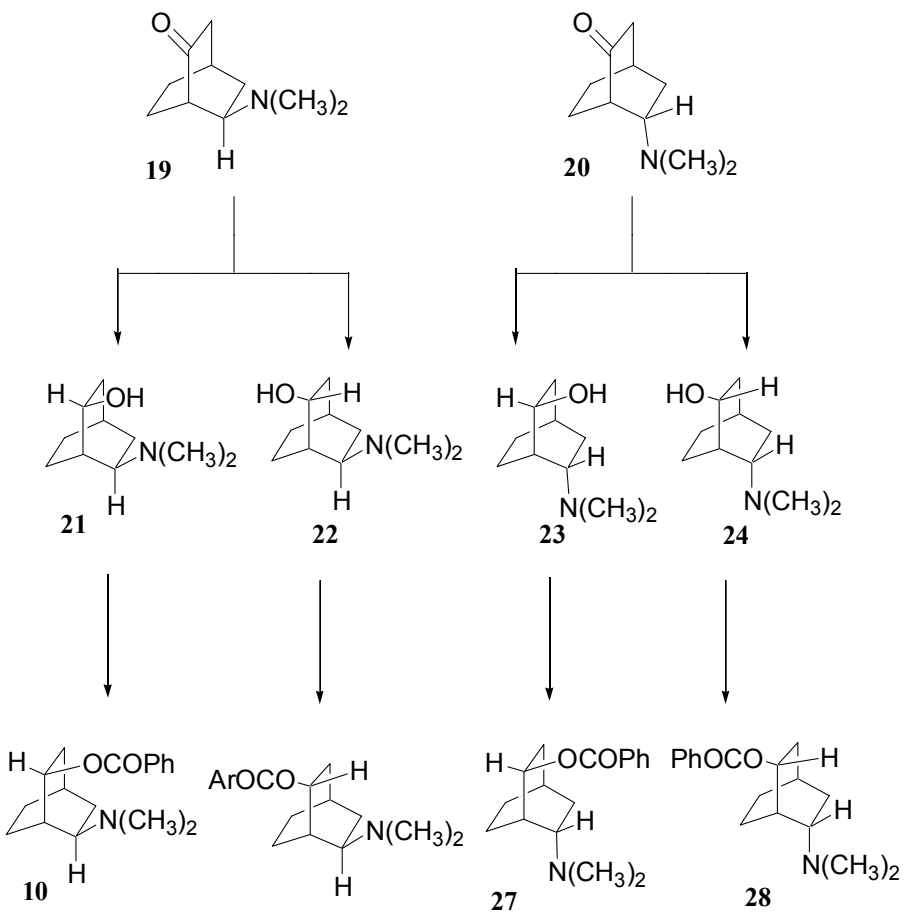
.

| Distance (Ångstroms) | | |
|---|---|---|
| **Compound** | **N-Ph$_c$** | **N-Ph$_p$** |
| Cocaine (**1**) | 7.89 | 0.707 |
| WIN (**2a**) | 5.67 | 0.110 |
|  **10** | 5.40 | 0.249 |
|  **26a** | 7.55 | 0.281 |
|  **27** | 7.44 | 0.004 |
|  **28** | 8.69 | 0.033 |

[a]N-Ph$_c$ = the distance between the nitrogen and the centroid of the phenyl ring
[b]N-Ph$_p$ = the distance between the nitrogen and the plane of the phenyl ring

## Chemistry

The syntheses of benzoate stereoisomers **26a**, **26b**, **27**, and **28** are shown in Figure 2.3. The mixture of *endo*- and *exo*-amino ketones **19** and **20** was previously synthesized.[5] The 4:1 diastereomeric mixture (determined by $^1$H NMR spectroscopy, based on ratio of signals δ 2.60 and δ 2.57 ppm) of *endo*-keto amine **19** and *exo*-keto amine **20** were separated by flash column chromatography. The relative stereochemistry of *endo*-amino ketone **19** was assigned using $^1$H NMR spectroscopy (Appendix A). The $^1$H NMR spectrum shows a peak at δ 2.18 ppm, which was assigned to the *exo* proton on C-3. This peak is coupled to the *exo* proton on C-5 by an in-plane W coupling, and shows *cis* coupling with the *exo* proton on C-6. Reduction of amino ketone **19** with $NaBH_4$ in absolute EtOH provided a 2:3 mixture (determined by $^1$H NMR spectroscopy, based on ratio of signals δ 3.90 and δ 4.20 ppm) of diastereomeric *endo*- and *exo*-alcohols **21** and **22**. The reduction of ketone **20** with $NaBH_4$ in absolute EtOH provided a 1:1 mixture (determined by $^1$H NMR spectroscopy, based on ratio of signals δ 4.02 and δ 3.89 ppm) of diastereomeric *endo*- and *exo*-alcohols **23** and **24**. The diastereomers were separated using column chromatography. The assignment of the relative stereochemistry of *exo*-amino alcohol **24** was done using $^1$H NMR spectroscopy (Appendix B). The carbinol proton at C-2 of *exo*-amino alcohol **24** shows a *doublet of doublet of doublet of doublets* at δ 3.89 ppm due to *cis* coupling (9.6 Hz) with the *endo* proton on C-3, *trans* coupling (3.3 Hz) with the *exo* proton on C-3, coupling to the bridgehead at C-1 (3.3 Hz), and an in- plane "W-coupling" (0.9 Hz) to the *exo* proton on C-7. This is the only arrangement of atoms on the bicycle which would allow the in-plane "W-coupling". The relative stereochemical assignment was confirmed by x-ray diffraction. Treatment of the




**26a**, Ar=phenyl
**26b**, Ar=4-chlorophenyl

Reagents: a) $NaBH_4$, EtOH, reflux; and b) ArCOCl, $Et_3N$, DMAP, benzene.

**Figure 2.3.** Synthesis of Derivatives **10, 26-28.**

appropriate alcohol with benzoyl chloride gave the corresponding benzoate esters **26-28**. The stereochemistry assignment for benzoate **10** was published previously.[6] Benzoate **26a** must have the ester functionality *exo* at C-2 while maintaining the *endo* stereochemistry of the amino ketone at C-6. The stereochemistry assignment of *exo*-amino-*endo*-benzoate **28** was established using single crystal x-ray crystallography (Appendix C). By process of elimination, compound **27** must contain the benzoate *exo* at C-2 and the *exo* stereochemistry at C-6.

## Pharmacology

The benzoate amines, **26-28**, were tested to determine the $IC_{50}$ values for the inhibition of [$^3$H]WIN 35,428 binding to the DAT and the inhibition of [$^3$H]DA uptake into synaptosomes according to established protocols.[6] The inhibition of [$^3$H]5-hydroxytryptamine(5-HT, serotonin) was also tested using citalopram or paroxetine to determine the selectivity for the DAT.

### In Vitro Testing

#### Inhibition of WIN Binding, Citalopram Binding, and [$^3$H]DA Uptake

Previous work provided congener **6**[1] which shows inhibition of [$^3$H]WIN 35,428 binding comparable to that of cocaine ($IC_{50}$= 270 nM vs 160 nM, respectively, Table 2.2). Additional experiments,[7] show that derivative **9** is the most potent trisubstituted [2.2.2]bicyclooctane with an $IC_{50}$ of 33 nM for [$^3$H]WIN binding and an $IC_{50}$=137 nM for

DA uptake. Derivative **9 (**which contains a 4-chloro substituent on the C-5 phenyl ring) is eight times more potent than cocaine for [$^3$H]WIN binding. We proposed that this increase in potency is due to a greater interaction between the "aromatic ring binding region" on the DAT and the 4-chlorophenyl ring at C-5 on the bicyclic framework. Desphenyl analogue **10** shows a low binding affinity at the dopamine transporter with about an 80-fold decrease in potency than *endo*-amino-*endo*-benzoate **6** ($IC_{50}$= 21700 nM vs 270 nM, respectively).

The *exo*-amino diastereomeric analogs of **10**, benzoates **27** and **28**, were tested for inhibition of [$^3$H]WIN 35,428 binding ($IC_{50}$ = 6460 nM and 9410 nM, respectively) and DA uptake ($IC_{50}$ = 21800 nM and 30700 nM, respectively). Both analogs are less potent than *exo*-benzoate-*endo*-amine **26a**, which is equipotent with cocaine for WIN binding ($IC_{50}$ of 193 nM versus 160 nM, respectively). Analogue **26a** is slightly selective for the DAT over the 5-HTT (1.60/.192= 8.4-fold). Thus, congener **26a** constitutes a new lead compound for further exploration.

Preliminary test results shows potency was lost by the inclusion of a 4-chloro substituent on the phenyl ring, benzoate **26b** versus **26a** ($IC_{50}$ = 6500 nM versus 192 nM, respectively). This can be understood in terms of the *para*- chloro substituent increasing the size of the aryl substituent beyond the requirements needed for a good fit at the DAT. However, this is unusual since it has been demonstrated in the literature that substitution of the phenyl group with a halogen tends to increase the potency with which a drug binds to the DAT. A second sample of benzoate **26b** was submitted to verify these results.

## In Vivo Testing

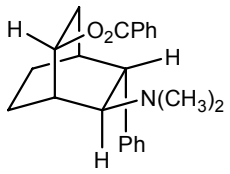
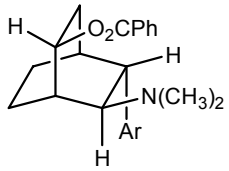
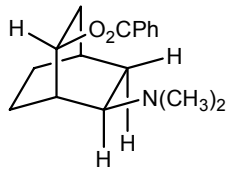
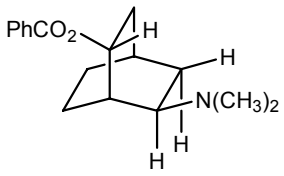
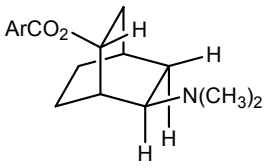
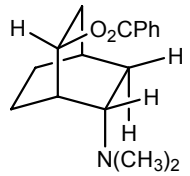
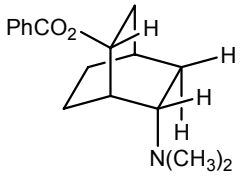
### Drug Discrimination

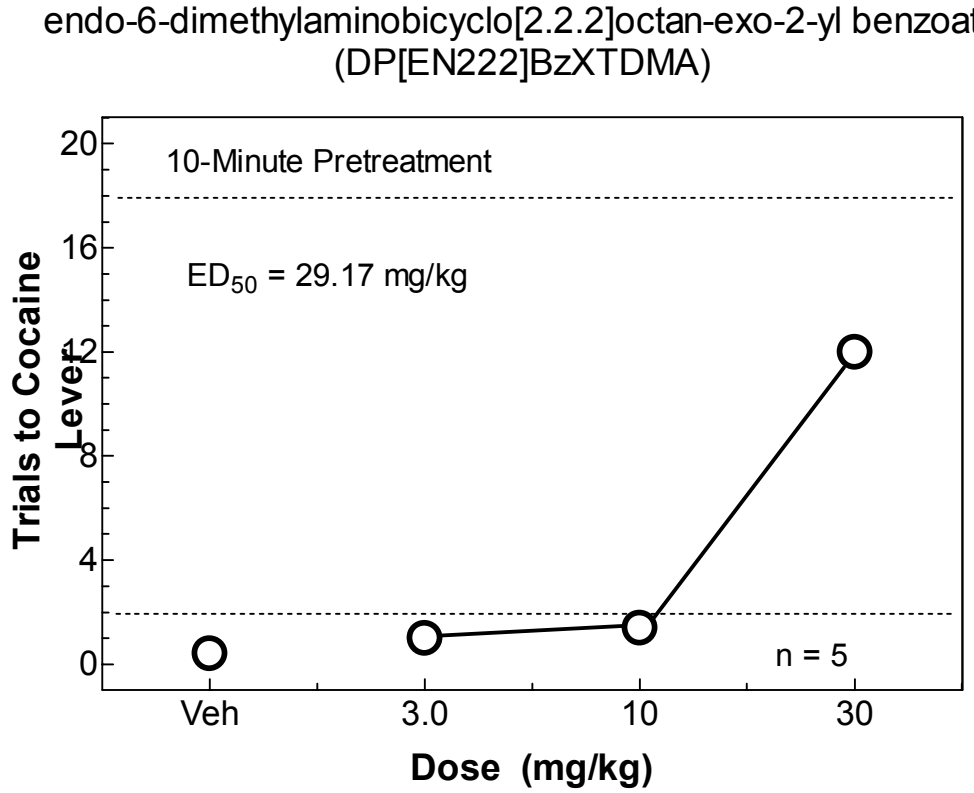
In drug discrimination experiments with rats[8], benzoate **26a** shows very little activity at the 3 and 10 mg/kg dosage (Figure 2.4) compared with cocaine, which shows a slight increase in activity at 1mg/kg and 0.3 mg/kg, respectively (Figure 2.5). More than half of the rats tested at 30 mg/kg were able to discriminate the test drug injection from the saline injection of benzoate **26a** ($ED_{50}$= 29.17). Although benzoate **26a** was equipotent as cocaine by comparing WIN binding ($IC_{50}$= 192 nM vs $IC_{50}$= 160 nM, respectively) the drug discrimination experiment shows a difference of 11-fold in potency ($ED_{50}$ = 93.9 uM versus $ED_{50}$ = 8.45 uM, respectively) when comparing benzoate **26a** and cocaine. This difference could be due to cocaine getting to the brain faster than congener **26a**.

### Locomotor Stimulation

The locomotor activity reported for analogue **26a** is shown in Figure 2.6. Some unusual activity peaks in the control are seen at 90 and 200 minutes. Since these peaks are not common it is believed the activity is due to some outside aggravation in the environment affecting the rats. Analogue **26a** was tested at 3, 10, and 30 mg/kg over 240 minutes. The normal spike in activity is seen with all three concentrations, with the 10 and 30 mg/kg reaching a maximum at almost 3,000 counts. Cocaine shows counts of 7,000 for a dose of 30 mg/kg, and 9,000 with a dose of 56 mg/kg, and a more gradual decrease in the locomotor stimulation (Figure 2.7). The decrease in locomotor activity compared to that of cocaine, maybe an indicator that congener **26a** is consumed quicker by the body than cocaine.

T**able 2.2.** Data for [$^3$H]WIN 35,428 binding, [$^3$H]DA Uptake, and 5-HT[$^3$H]CIT binding.[9]

| | **$IC_{50}$ (uM) or % Inhibition** | | |
|---|---|---|---|
| **Compound** | **[$^3$H]WIN 35,428** | **[$^3$H]DA Uptake** | **[$^3$H]CIT** |
| Cocaine (**1**) | 0.160 ± 0.015 | 0.404 ± 0.026 | 0.389 ± 0.020 |
| LR5182 (**2**) | 0.0142 ± 0.0016 | 0.0255 ± 0.0004 | 91% @ 10 uM |
|  **6** | 0.270 ± 0.029 | 0.687 ± 0.015 | 0.085 ± 0.008 |
|  Ar= 4-chlorophenyl **9** | 0.033 ± 0.0005 | 0.137 | 96% @ 10 uM |
|  **10** | 21.7 ± 2.3 | 58.3 ± 0.7 | 2.42 ± 0.92 |
|  **26a** | 0.192 ± 0.024 | 1.31 ± 0.091 | 1.61 ± 0.18 |
|  Ar= 4-chlorophenyl **26b** | 6.50 | * | 99% @ 10 uM |
|  **27** | 6.46 | 21.8 ± 1.54 | 52% ± 4% @ 10 uM |
|  **28** | 9.41 ± 0.57 | 30.7 ± 1.6 | 2.9 ± 0.2 |




| Dose (mg/kg) | R23 | R27 | R28 | R30 | R31 | Mean |
|---|---|---|---|---|---|---|
| **veh** | 0 | 0 | 1 | 1 | 0 | **0.4** |
| **3.0** | 0 | 1 | 1 | 3 | 0 | **1.0** |
| **10** | 0 | 2 | 1 | 4 | 0 | **1.4** |
| **30** | 3 | 18 | 0 | 19 | 20 | **12.0** |

**Figure 2.4**. Drug discrimination data for benzoate **26a**.

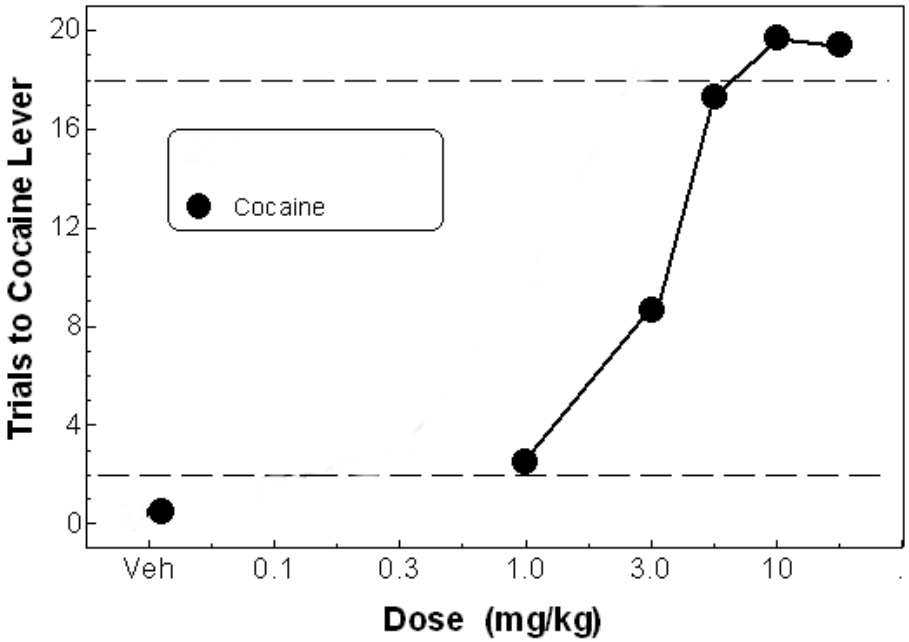



**Figure 2.5.** Drug discrimination data for cocaine.

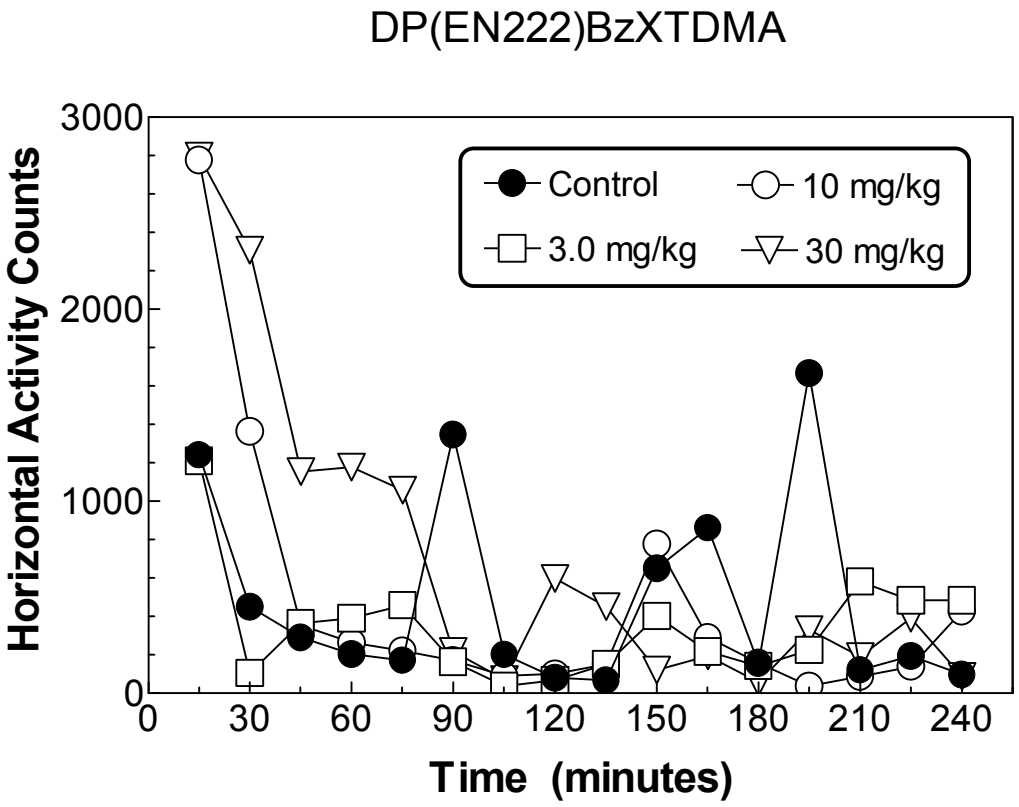



**Figure 2.6**. Locomotor stimulation data for benzoate **26a**.

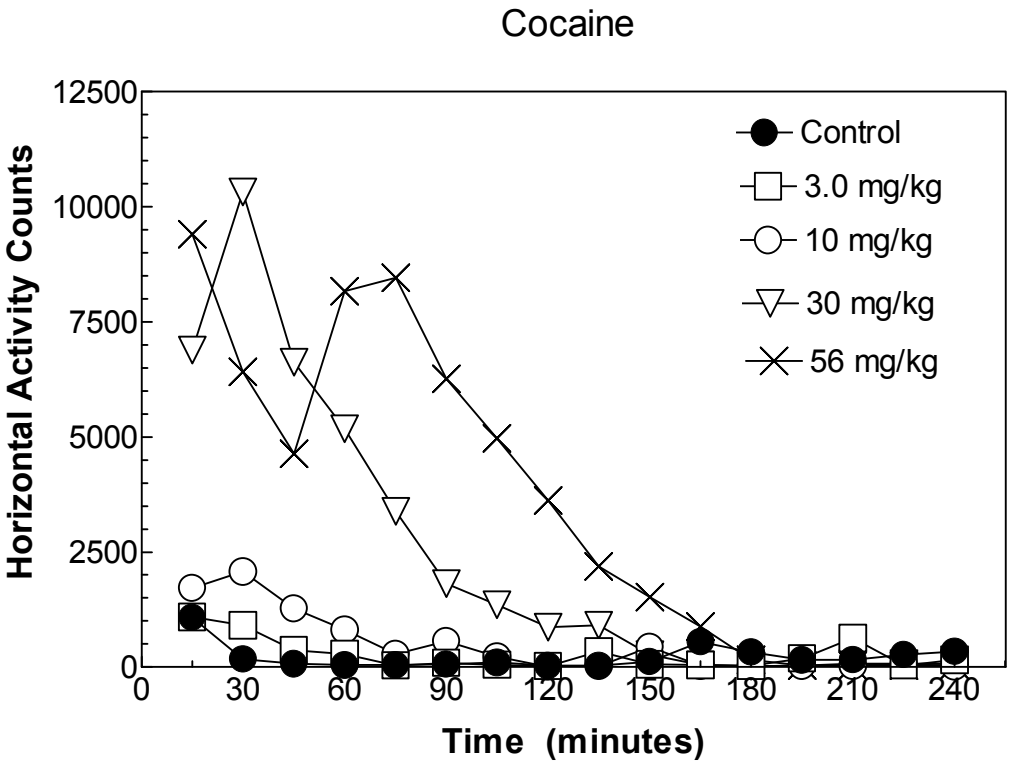



**Figure 2.7.** Locomotor stimulation data for cocaine.

## Conclusions

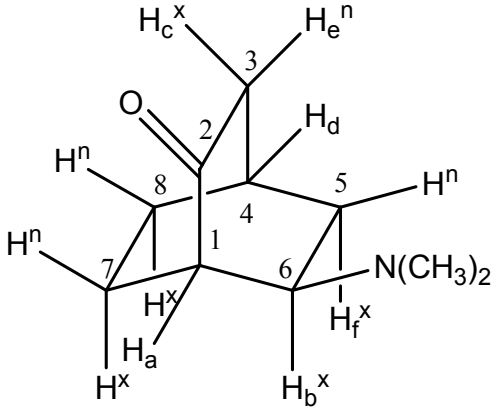
A series of 6-(*N*,*N*-dimethylamino)-2-benzylbicyclo[2.2.2]octanes was prepared by reduction of amino ketones **19** and **20**, followed by benzoylation of the corresponding alcohols. No clear trends could be ascertained from the data in Table 2.1. The *exo*-benzoate-*endo*-amine **26a** is equipotent with cocaine for WIN binding ($IC_{50}$ = 193 nM vs 160 nM) and is 8-fold more selective for the DAT over the 5-HTT. The *in vivo* pharmacology indicates that congener **26a** is 8-fold less potent than cocaine by drug discrimination ($ED_{50}$ = 6.47 uM versus $ED_{50}$ = 0.855 uM, respectively) and the locomotor activity is not as high as that for cocaine (3,000 counts versus 7,000 counts, respectively). The data obtained from the *in vivo* pharmacology testing can be interpreted in the following manner: 1) the drug discrimination results may be the result of a slower on-set, and 2) the locomotor activity may be the result of the drug being metabolized faster than cocaine. Further structure-activity relationships will be developed based on this new lead compound.

## Experimental Section

**General Methods.** All starting materials were used as received from Aldrich Chemical Company. Melting points were determined on a Mel-Temp apparatus and are uncorrected. $^{1}H$ and $^{13}C$ NMR spectra were obtained on a Varian Gemini spectrometer at 300 MHz and 75 MHz, respectively, unless otherwise noted. COSY and HMQC spectra were recorded on a Bruker AMX 500 MHz. Fourier transform infrared spectra were obtained using a Nicolet 520 FTIR spectrometer. Gas chromatography-mass spectroscopy was performed on a HP 5890 gas chromatogram coupled to a VG 70SE mass spectrometer. Elemental analyses were obtained from Atlantic Microlabs, Norcross, Georgia. Tetrahydrofuran (THF) was dried over sodium benzophenone ketyl prior to distillation under nitrogen. Benzene was dried over 4 Å molecular sieves. Amines were dissolved in minimum amount of MeOH and were converted to HCl salts by the addition of 1.5 equivalents of concentrated 1 M HCl in diethyl ether. MeOH was added and the HCl was removed under reduced pressure. The resulting solid was recrystallized from MeOH/EtOAc or EtOAc/hexane.

The synthesis of a mixture *endo*- and *exo*-6-(*N*,*N*-dimethylamino)bicyclo[2.2.2] octan-2-ones, **19** and **20** was reported previously.[10] The *exo*-amino ketone isomer **20** (0.424 g, 16.2% yield) was eluted from the silica column first (silica gel, 1:1:30 ethyl acetate:methanol:chloroform) and isolated as a brown liquid, followed by the *endo*-amino ketone isomer **19** (2.03 g, 77.7% yield), which was isolated as a brown solid**.**

***endo* 6-(*N*,*N*-Dimethylamino)bicyclo[2.2.2]octan-2-ones, 19**. mp: 194-198 °C.$^{1}$H NMR ($CDCl_3$): δ 1.53-1.63 (m, 3H), 1.73-1.83 (m, 2H), 1.93 (qt, *J*=13.2, 9.3, 3 Hz 1H, C-5*exo*), 2.18 (dt, *J*=18, 2.4 Hz, 1H, C-3*endo*), 2.21-2.23 (m, 7H, C-4, $N(CH_3)_2$), 2.30 (dt, *J*=18, 2.1 Hz, 1H, C-3*exo*), 2.40 (ddd, *J*=9.3, 4.5, 3 Hz, 1H, C-6*exo*) 2.60 (q, *J*=3 Hz, 1H, C-1). $^{13}$C ($CDCl_3$): δ 22.09, 23.52, 27.98, 32.87, 42.96, 44.53, 45.45, 64.59 (C-6), 216 (C-2).




**19**
n= endo
x=exo

***exo* 6-(*N*,*N*-Dimethylamino)bicyclo[2.2.2]octan-2-ones, 20**. $^{1}$H NMR ($CDCl_3$): δ 1.51-1.65 (m, 4H), 1.72-1.82 (m, 1H), 1.92 (tm, 1H, *J*=13.2 Hz), 2.06-2.22(m, 4H), 2.22 (s, 6H, $N(CH_3)_2$), 2.57 (q, *J*=2.4 Hz, 1H, C-1). $^{13}$C ($CDCl_3$): δ 16.51, 25.02, 27.83, 3.52, 43.33, 43.89, 46.11, 60.13, 172.58 (C-2).

**6-(*N*,*N*-Dimethylamino)bicyclo[2.2.2]octan-2-ols (21-24).** The conversion of **20** to **23** and **24** is illustrated. A mixture of $NaBH_4$ (196.3 mg, 5.19 mmol) in ethanol (15 mL) was added to *exo*-amino ketone **20** (436 mg, 2.6 mmol) in 5 mL of ethanol. The

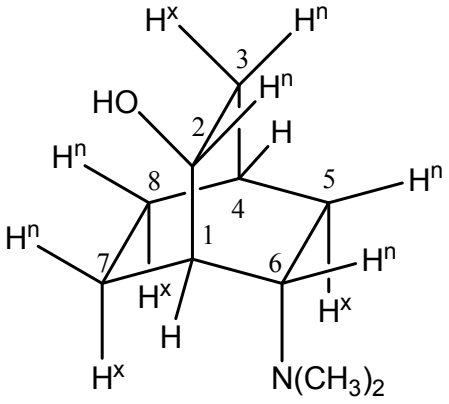
mixture was heated to reflux for 3 h, cooled to rat., and $H_2O$ (20 mL) was added. The ethanol was removed under reduced pressure. The mixture was extracted with $CH_2Cl_2$ (3 × 10 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure to obtain 320 mg (73% yield) of crude product. Flash column chromatography (silica gel; $CH_3OH$ eluant) provided alcohol **23** ($R_f$=0.32, , 40 mg, 18% yield) as a colorless oil and alcohol **24** ($R_f$=0.35, 68 mg, 31% yield) as a colorless oil.

*endo- 6-(N,N-Dimethylamino)bicyclo[2.2.2]octan-endo-2-ol and the HCl salt (21, 21HCl).* The spectroscopic data was previously reported.[10]

*endo- 6-(N,N-Dimethylamino)bicyclo[2.2.2]octan-exo-2-ol,* ***22.*** 26.6% yield, white crystalline solid, mp 53-56 ˚C, Rf= 0.38 ($CH_3OH$ eluant). $^1$H NMR ($CDCl_3$): δ 1.16-1.41 (m, 3H), 1.47-1.58 (tm, *J*=12.3, 5.7, 3 Hz, 1H), 1.69-1.88 (m, 4H), 1.91 (sept, 1H, *J*=2.7 Hz, C-4), 1.94-2.14 (m, 3H, C-1, C-6), 2.21 (s, 6H, $N(CH_3)_2$), 4.20 (dddd, *J*=9.3, 4.5, 2.7, 1.8 Hz, 1H, C-2). $^{13}$C ($CDCl_3$): δ 18.30, 24.40, 25.83, 33.61, 34.59, 37.55, 43.97 ($N(CH_3)_2$), 64.52 (C-6), 69.94 (C-2).

*exo-6-(N,N-Dimethylamino)bicyclo[2.2.2]octan-endo-2-ol,* ***23.*** $^1$H NMR ($CDCl_3$) δ 1.21-1.36 (m, 4H), 1.48 (ddddd, *J*=13.8, 9.6, 6.3, 2.7, 1.2 Hz, 1H), 1.72 (sept, *J*=2.1 Hz, 1H, C-4), 1.82-1.90 (m, 2H), 1.90 (p, *J*=1.8 Hz, 1H, C-1), 2.01 (dddd, *J*=13.5, 9.6, 3.9, 2.4 Hz, 1H), 2.35 (s, 6H, $N(CH_3)_2$), 2.34 (tm, *J*=7.5 Hz, 1H, C-6), 4.02 (ddd, *J*=9.6, 5.1, 3 Hz, 1H, C-2). $^{13}$C ($CDCl_3$): δ 17.96, 24.42, 25.77, 34.22, 34.81, 36.18, 43.68 ($N(CH_3)_2$), 57.55 (C-6), 69.07 (C-2).

*exo-6-(N,N-Dimethylamino)bicyclo[2.2.2]-octan-exo-2-ol,* ***24.*** $^{1}$H NMR ($CDCl_3$) δ 1.28-1.38 (m, 2H, C-5, C-3), 1.48-1.56 (m, 2H, C-7), 1.60-1.76 (m, 4H, C-8, C-4, C-5), 1.80-2.00 (m, 3H, C-1, C-3, C-6), 2.22 (s, 6H, $N(CH_3)_2$), 3.89 (dtd, *J*=9.6, 3.3, 0.9Hz, 1H, C-2). $^{13}$C ($CDCl_3$): δ 13.00, 25.11, 25.52, 33.11, 34.62, 36.54, 44.06 ($N(CH_3)_2$), 63.08 (C-6), 69.38 (C-2).




**24**
n= endo
x=exo

**6-(*N*,*N*-Dimethylamino)bicyclo[2.2.2]octan-2-yl benzoates (10-28).** The conversion from **24** to **28** is illustrated. A solution of benzoyl chloride (103 μL, 0.888 mmol) in 2 mL of benzene was added to a mixture of **24** (100 mg, 0.591 mmol), DMAP (1mg, mmol), and $Et_3N$ (412 μL, 0.2.96 mmol) in 3 mL of benzene. The mixture was stirred for 24 h at room temperature. The mixture was washed with 5% $NaHCO_3$ (3 × 5 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Flash

column chromatography (silica gel; THF) provided benzoate **28** ($R_f$=0.50, 100 mg, 62% yield) as a yellow oil.

*endo-6-(N,N-Dimethylamino)bicyclo[2.2.2]octan-endo-2-yl benzoate and the HCl salt,**(10, 10·HCl).*** The spectroscopic data was previously reported.[10]

*endo-6-(N,N-Dimethylamino)bicyclo[2.2.2]oct-exo-2-yl benzoate, **26a***. 41.2% yield, pale yellow oil, $R_f$= 0.55 (THF eluant). $^1$H NMR ($CDCl_3$) δ 1.25-1.39 (m, 1H), 1.40-1.51 (m, 2H), 1.53-1.69 (m, 2H), 1.76-1.88 (m, 2H, C-4, C-3), 2.00 (dddd, *J*=15.9, 10.8, 4.5, 3.6 Hz, 1H, C-7), 2.12-2.33 (m, 3H, C-1, C-3, C-6), 2.35 (s, 6H, $N(CH_3)_2$), 5.38-5.45 (m, 1H, C-2), 7.43 (tm, *J*=7.2 Hz, 2H, $Ar_{3,5}$), 7.55 (tt, *J*=7.2, 2.4 Hz, 1H, $Ar_4$), 8.04 (dm, *J*=6.6 Hz, 2H, $Ar_{2,4}$). $^{13}$C ($CDCl_3$) δ 18.94, 24.17, 25.37, 31.08, 33.28, 34.02, 43.80, 64.17 (aliphatic); 128.27, 129.45, 132.67 (aryl); 166.23 (C=O).

***26a·HCl***. 51% yield. mp 223-226 $^o$C. $^1$H NMR ($D_2O$) δ 1.31-1.45 (m, 2H), 1.51-1.67 (m, 2H), 1.88 (m, 1H, C-4), 1.97-2.19 (m, 3H), 2.40 (p, *J*=2.7 Hz, 1H, C-1), 2.84 (s, 6H, N(CH3)2), 3.27-3.36 (m, 1H, C-6), 5.08-5.16 (m, 1H, C-2), 7.42 (t, *J*=7.2 Hz, 2H, $Ar_{3,5}$), 7.57 (tt, *J*=7.5, 1.2 Hz, 1H, $Ar_4$), 7.94 (dt, *J*=7.2, 1.2 Hz, 2H, $Ar_{4,6}$). IR (neat): 2953, 2710, 1716, 1650, 1288, 715 cm$^{-1}$. MS (EI) M+ 273. Anal Elem Anal cald for $C_{17}H_{23}O_2NCl·0.33\ H_2O$: C, 64.66; H, 7.87; N, 4.44; O, 11.81; Cl, 11.23. Found: C, 64.54; H, 7.74; N, 4.40; Cl, 11.42.

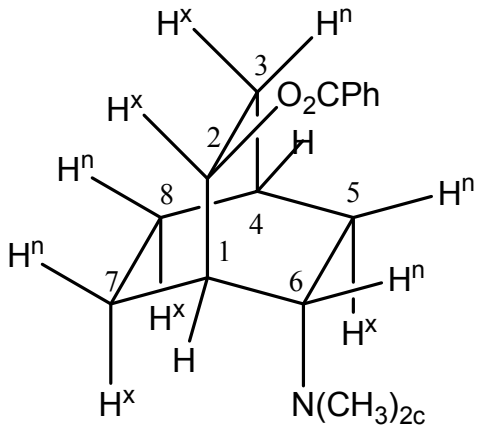
*endo-6-(N,N-Dimethylamino)-4-clorophenylbicyclo[2.2.2]oct-exo-2-yl benzoate,*

***26b***. 96% yield, colorless oil, Rf= 0.35 ($CH_3OH$:$CH_2Cl_2$ eluant). $^1$H NMR ($CDCl_3$): δ 1.29–1.39 (m, 2H), 1.45 (dddd, J=16.5, 11.0, 5.0, 2.5 Hz, 1H), 1.55 (ddd, J=14.5, 6.5, 3.0 Hz, 1H, C-3 exo), 1.57-1.64 (m, 1H), 1.78 (dt, *J*=12.5, 3.0 Hz, 1H, C-5 endo), 1.80 (sept, *J*=2.5 Hz, 1H, C-4), 1.96 (dddd, J=16.5, 8.5, 5.0, 3.0 Hz, 1H, C-8 endo), 2.07 (ddd, J=9.0, 5.0, 3.0 Hz, 1H, C-6), 2.21 (qt, *J*=13.5, 10.0, 3.0 Hz, 1H, C-3 endo), 2.25 (p, J=3.0 Hz, C-1), 2.26 (s, 6H, $N(CH_3)_2$), 5.35-5.42 (m, 1H, C-2), 7.83 (dt, *J*=7.5, 1.5 Hz, 2H, $Ar_{2,6}$), 7.95 (dt, *J*=7.5, 1.5 Hz, 2H, $Ar_{3,5}$). $^{13}$C NMR ($CDCl_3$): δ 18.94, 24.17, 25.37, 31.20, 33.61, 34.12, 43.97, 64.07, 70.14 (aliphatic), 128.57, 130.82, 139.03, 165.31 (aryl).

***26b·HCl***. 60% yield. mp 220-225 $^o$C. $^1$H NMR ($D_2O$) δ 1.31-1.45 (m, 2H), 1.51-1.67 (m, 2H), 1.88 (m, 1H, C-4), 1.97-2.19 (m, 3H), 2.40 (p, *J*=2.7 Hz, 1H, C-1), 2.84 (s, 6H, N(CH3)2), 3.27-3.36 (m, 1H, C-6), 5.08-5.16 (m, 1H, C-2), 7.42 (t, *J*=7.2 Hz, 2H, $Ar_{3,5}$), 7.57 (tt, *J*=7.5, 1.2 Hz, 1H, $Ar_4$), 7.94 (dt, *J*=7.2, 1.2 Hz, 2H, $Ar_{4,6}$). IR (neat): 2947, 2683, 2479, 2354, 1716, 1300, 1018, 762 $cm^{-1}$. MS (EI) M+ 307. Elem Anal cald for $C_{17}H_{24}O_2NCl_2$: C, 59.48; H, 6.71; N, 4.08; O, 8.32; Cl, 20.41. Found: C, 59.09; H, 6.83; N, 4.05; Cl, 20.37.

*exo-6-(N,N-Dimethylamino)bicyclo[2.2.2]oct-endo-2-yl benzoate,* ***27***. 68% yield, yellow oil, $R_f$=0.45 (THF eluant). $^1$H NMR ($CDCl_3$) δ 1.35-1.45 (qt, *J*=13.8, 6.9, 3 Hz, 1H), 1.51-1.67 (m, 3H), 1.70-1.82 (m, 4H), 1.95-2.13 (m, 2H), 2.20 (p, *J*=3 Hz, 1H, C-4),

2.25 (s, 6H, $N(CH_3)_2$), 5.10 (dt, *J*=9.6, 2.4 Hz, 1H), 7.45 (td, *J*=7.5, 1.5 Hz, 2H, $Ar_{3,5}$), 7.56 (tt, *J*=7.5, 1.5 Hz, 1H, $Ar_4$), 8.05 (dt, *J*=6.9, 1.2 Hz, 2H, $Ar_{3,5}$). $^{13}C$ NMR ($CDCl_3$) δ 13.90, 24.79, 25.39, 31.42, 33.30, 33.76, 44.05 ($N(CH_3)_{2)}$, 62.28 (C-6), 72.86 (C-2) (aliphatic); 128.32, 129.49, 130.78, 132.80 (aryl); 166.18 (C=O).




**27**
n= endo
x=exo

***27·HCl***. 75.8% yield. mp 233-236 °C. $^1H$ NMR ($D_2O$) δ 1.38-1.52 (m, 2H), 1.52-1.70 (m, 3H), 1.84-1.91 (m, 1H), 1.91-2.10 (m, 1H), 2.10-2.16 (m, 1H), 2.41-2.47(m, 1H) 2.80 (s, 3H, $NCH_3$), 2.86 (s, 3H, $NCH_3$), 3.21-3.30 (m, 1H), 5.03-5.10 (m, 1H, C-2), 7.45 (td, *J*=7.5, 1.5 Hz, 2H, $Ar_{3,5}$), 7.60 (tt, *J*=7.5, 1.2 Hz, 1H, $Ar_4$), 7.97 (dt, J=7.2, 1.5 Hz, 2H, $Ar_{2,6}$). IR: 2940, 2670, 1729, 1281, 1110, 715 $cm^{-1}$. MS (EI) M+ 273. Elem Anal cald for $C_{17}H_{24}O_2NCl·0.30\ H_2O$: C, 64.77; H, 7.87; N, 4.44; O, 11.67; Cl, 11.25. Found: C, 64.29; H, 7.68; N, 4.36; Cl, 11.86

*exo-6-(N,N-Dimethylamino)bicyclo[2.2.2]oct-exo-2-yl benzoate,* ***28***. 61.9% yield, pale yellow oil, $R_f$= 0.50 (THF eluant). $^1$H NMR ($CDCl_3$) δ 1.34-1.62 (m, 5H), 1.87-2.01 (m, 3H), 2.14-2.26 (m, 2H), 2.22 (s, 6H, $N(CH_3)_2$ ), 2.40 (dddd, *J*=9, 6, 2.1, 1.5 Hz, 1H, C-6), 5.20 (ddd, *J*=9.9, 4.8, 3 Hz, 1H, C-2), 7.45 (td, *J*=7.5, 1.5 Hz, 2H, $Ar_{3,5}$), 7.57 (tt, *J*=7.5, 1.5 Hz, 1H, $C_4$), 8.04 (dt, *J*=6.9, 1.5 Hz, 2H, $Ar_{2,6}$). $^{13}$C NMR ($CDCl_3$) δ 17.51, 24.53, 25.60, 31.75, 33.59, 34.23, 43.96 ($N(CH_3)_2$), 58.42 (C-6), 72.90 (C-2)(aliphatic); 128.34, 129.49, 130.76, 132.80 (aryl); 166.15 (C=O).

***28·HCl***. 57.6% yield. mp 220-225 $^o$C. $^1$H NMR ($D_2O$) δ 1.40-1.54 (m, 4H), 1.56-1.59 (m, 2H), 1.85-1.93 (m, 1H), 2.10-2.30 (m, 2H), 2.38-2.44 (m, 1H), 2.76 (s, 3H, $N(CH_3)_2$), 2.84 (s, 3H, $N(CH_3)_2$), 3.48-3.56 (tm, *J*=7.5 Hz, 1H, C-6), 5.16 (dt, *J*=9.6, 4.2 Hz,1H, C-2), 7.45 (t, *J*=7.5 Hz, 2H, $Ar_{3,5}$), 7.60 (tt, *J*=7.5, 1.8 Hz, 1H, $Ar_4$), 7.94 (dt, *J*=6.9, 1.8 Hz, 2H, $Ar_{2,6}$). IR (neat): 2947, 2611, 2479, 1722, 1275, 715 $cm^{-1}$. MS (EI) M+ 273. Elem Anal cald for $C_{17}H_{24}O_2NCl·0.85\ H_2O$: C, 62.80; H, 7.97; N, 4.31; O, 14.02; Cl, 10.90. Found: C, 62.32; H, 7.55; N, 4.27; Cl, 11.53.

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9 . All compounds were tested as the HCl salt at Mercer School of Medicine under the supervision of Dr. Margaret M. Schweri.

# CHAPTER III

# SYNTHESIS AND PHARMACOLGY OF 2-AMINO-6-ARYLBICYCLO[2.2.2]OCTANES

## Introduction

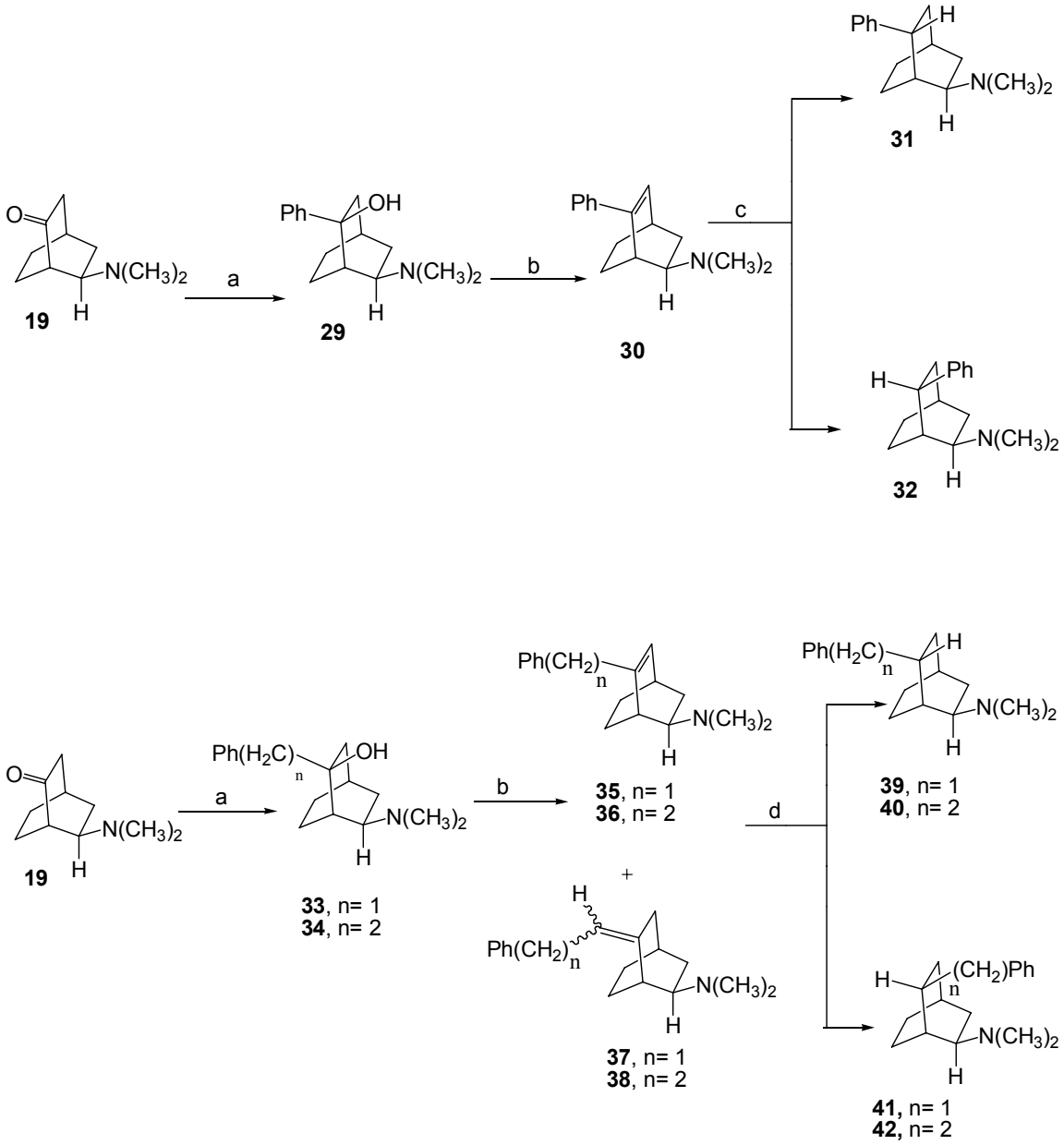
The work in this chapter is a continuation of the work described in Chapter 2. In Chapter 2, a series of 6-amino-[2.2.2]bicyclo-2-benzoates (**26-28**) was synthesized and pharmacologically assessed. The phenyl substituent was introduced through a benzoate ester linkage at the C-2 position of the bicycle. *endo*-Amino-*exo*-benzoate **26** is equipotent with cocaine for WIN binding ($IC_{50}$ of 193 nM versus 160 nM, respectively) and provided a new lead compound. To further elucidate the structure-activity relationships for binding to the DAT, the synthesis of compounds in which a phenyl ring is directly attached to the bicycle at C-2 or is linked by one or two carbons was undertaken. These homologues will help determine the optimal distance between the nitrogen and the phenyl ring, while allowing us to investigate the effect of removing the ester functionality. All of the molecules synthesized will be tested *in vitro* for their ability to inhibit the binding of [$^3$H]WIN 35,428 to rat striatal tissue membrane preparations and the uptake of [$^3$H]dopamine (DA) into rat striatal synaptosomes. *In vitro* inhibition of

[$^3$H]citalopram binding to the serotonin transporter (5-HT) will also be measured to establish the relative selectivity of the congeners for the various transporters. Results of the SARs will allow for fine tuning of future compounds.

## Chemistry

### 2-Amino-6-phenylbicyclo[2.2.2]octanes

Phenylmagnesium bromide was added to *endo*-amino ketone **19** at –20 °C in ether. GC/MS of crude product showed that only one diastereomer was formed during the reaction. The phenyl reagent was delivered to the least sterically hindered face of the bicycle to give solely the *endo*-amino-*exo*-phenyl compound **29**. Purification by column chromatography afforded *endo*-amino-*exo*-phenyl compound **29**. The assignment of the relative stereochemistry was done using 1-D and 2-D nuclear magnetic resonance spectroscopy (Appendix D). Dehydration of **29** with p-TSA gave the unsaturated amine **30**, which gave a *doublet of doublets* at δ 6.64 ppm in the $^1$H NMR spectrum with coupling constants of 6.9 Hz and 1.8 Hz. This is consistent for the vinylic proton at the C-3 position on the bicycle, which couples to the bridgehead proton at C-4 with a small dihedral angle and the bridgehead proton at C-1 (*i.e.*, via long-range allylic coupling). Alkene **30** was hydrogenated to afford a 1:3 mixture of *endo*- and *exo*-phenyl amines **32** and **31**, which were separated by column chromatography. The stereochemical assignment of amine **31** was established using nuclear magnetic spectroscopy and confirmed by x-ray analysis (Appendix E).




Reagents: a) aryl magnesium bromide, ether, - 20 C; b) p-TSA, toluene, reflux; c) $H_2$, Pd/C, 40 psi; and d) 50 % w/w Rainey Ni/$H_2O$, $H_2$, $CH_3OH$, 60 psi.

**Scheme 3.1.** Synthesis of 2,6-disubsttuted compounds **30-32** and **39-42**.

**2-Amino-6-benzylbicyclo[2.2.2]octanes**

Amino ketone **19** was treated with benzyl magnesium chloride to give a single product by GC/MS, which was assigned as the *endo*-amino-*exo*-phenyl alcohol **33**. Just like the phenyl grignard mentioned in the paragraph above, the benzyl reagent was delivered to the least sterically hindered face of the bicycle. Since the two benzylic protons are adjacent to a stereocenter, the benzylic protons are diastereotopic and appear as a pair of doublets at δ 2.89 ppm and δ 2.65 ppm with a coupling constant of 13.8 Hz. The *endo*-amino-*exo*-phenyl alcohol **33** was dehydrated by treatment with p-TSA to give a 9:1 ratio (determined by $^1$H NMR spectroscopy) of endocyclic unsaturated amine **35** and a mixture of *cis* and *trans* exocyclic alkenes, **37**. Without any further purification, this mixture of alkenes was hydrogenated over Pd/C to obtain a 10:1 mixture of exo-benzyl-*endo*-amine **39** and *endo*-benzyl-*endo*-amine **41**. Since the hydrogenation conditions gave mostly *exo*- benzyl diastereomer **39**, alternate routes were explored to obtain the *endo*-benzyl amine **41**. Some of the methods attempted were: 1) a Barton reductive deoxygenation[1] of alcohol **33**, 2) hydroboration of the mixture of **35** and **37** with borane[2], and 3) hydrogenations of the mixture of **35** and **37** with either Pd/C or Rainey nickel and different solvents (methanol, ethyl acetate, $H_2O$, hexane). The hydrogenation with 50% w/w of Rainey nickel in $H_2O$ and methanol provided a 50:50 mixture of the *endo*-benzyl amine **39** and the *exo*-benzyl amine **41** (determined by $^1$H NMR spectroscopy, based on the dimethylamine singlet at δ 2.10 ppm and δ 1.99 ppm, respectively). The diastereomers were separated using column chromatography to obtain the two pure diastereomers **39** and **41**. The structural assignment of benzyl **39** was done by 1- and 2-dimensional NMR spectroscopy (Appendix F) and based on the differences

in chemical shifts of the benzyl protons in the free amine. (Appendix F). The benzylic protons directly above the dimethylamine, as is the case for *endo*-benzyl-*endo*-amine **41**, should be shifted further downfield than the corresponding diastereomer, *exo*-benzyl-*endo*-amine **39**, due to the electrochemical environment being influenced by the electronegative nitrogen.

**2-Amino-6-phenethylbicyclo[2.2.2]octanes**

Addition of phenethylmagnesium bromide to amino ketone **19** in the same manner as the benzyl Grignard, gave the *exo*-phenethyl-*endo* amino **34** (determined by GC/MS) and 30% of the reduced *endo*-alcohol **21** (determined by GC/MS and $^1$H NMR spectroscopy). The mixture was dehydrated with p-TSA to give a 3:1 mixture (based on the $^1$H NMR spectrum) of *cis* and *trans* exocyclic alkenes **38** and endocyclic alkene **36**. The mixture was hydrogenated to obtain a 20:1 *exo*:*endo* mixture (determined by the $^1$H NMR spectrum, based on the 6 proton singlet for the dimethylamine at δ 2.20 ppm and δ 2.17 ppm) of diastereomers *exo*-phenethyl amine **40** and *endo*-phenethyl amine **42**. Hydrogenation with 50% w/w Rainey nickel in $H_2O$ and methanol provided a 60:40 mixture of the *exo*-phenethyl amine **40** and the *endo*-benzyl amine 42. The hydrogenation of the phenethyl diastereomers required harsher conditions than the benzyl or phenyl analogs (40 psi overnight vs 60 psi for 3 days). The mixture of **40** and **42** was separated using column chromatography to obtain the two pure diastereomers. The structure of *endo*-phenethyl-*endo*-amine **42** was determined by single crystal x-ray diffraction (Appendix G). The two benzylic protons appear at different chemical shifts in the $^1$H NMR spectrum (δ 2.70 ppm and δ 2.58 ppm), which may be due to the dimethylamine

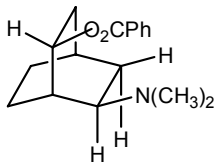
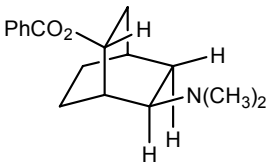
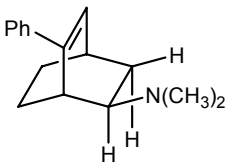
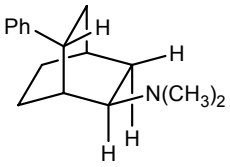
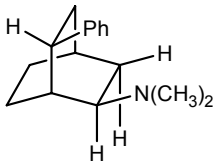
functionality inhibiting rotation of the benzylic group. In contrast, the two benzylic protons for the *exo*-phenethyl amino **40** are identical and appear as a *doublet of doublets* (10.5 Hz) at δ 2.80 ppm in the $^{1}$H NMR spectrum.

## Pharmacology

### Inhibition of WIN Binding and [$^{3}$H]DA Uptake.

The phenyl amines, **30-32**, were tested to determine the $IC_{50}$ values for the inhibition of ligand binding to the DAT according to established protocols (Table 3.1).[3,4,5] The potency of the phenyl amines was increased with excision of the ester when comparing *endo*-benzoate**10** with *endo*-arene-*endo*-amine **32 (**$IC_{50}$= 21700 nM versus $IC_{50}$= 1300 nM, respectively). e*xo*-Arene-*endo*-amine **31** has an $IC_{50}$= 20900 nM versus $IC_{50}$= 192 nM for compound **26a**, which suggests potency was lost by the excision of the ester functionality when the phenyl ring is *exo* on the bicycle. Preliminary data shows *exo*-arene-*endo*-amine **31** to be over 20-fold selective for the 5-HT over the DAT. The *endo*-arene-*endo*-amine **32** has an $IC_{50}$ of 1300 nM, which is more potent by 16-fold than the *exo*-arene-*endo*-amine **31**, which has an $IC_{50}$ of 20900 nM. An unexpected result was the potency of the unsaturated *endo*-amine **30** with an $IC_{50}$ of 740 nM, which is similar in potency as the *endo*-amino-*exo*-benzoate **26a** ($IC_{50}$= 192 nM) and *exo*-arene-*endo*-amine **32** (1300 nM). The potency increases by placing the arene moiety *exo* or by the increased nitrogen to phenyl distance seen with benzoate **26a**. The phenyl ring of the

**Table 3.1.** Binding Data for the Phenyl Amines **30-32**.[6]

| | $IC_{50}$ (uM) | | |
|---|---|---|---|
| **Compound** | **[$^3$H]WIN 35,428** | **[$^3$H]DA Uptake** | **5-HT[$^3$H]CIT** |
| Cocaine (1) | 0.160 ± 0.015 | 0.404 ± 0.026 | 0.389 ± 0.020 |
| LR5182 (5) | 0.0142 ± 0.0016 | 0.0255 ± 0.0004 | 91% @ 10 uM |
|  **10** | 21.7 ± 2.3 | 58.3 ± 0.7 | 2.42 ± 0.92 |
|  **26a** | 0.192 ± 0.024 | 1.31 ± 0.091 | 1.61 ± 0.18 |
|  **30** | 0.740 | * | 60% @ 10 uM |
|  **31** | 20.9 | * | 0.797<br>94% @ 10 uM |
|  **32** | 1.3 | * | 85% @ 10 uM |

All compounds tested as the HCl salt. *The DA Uptake results are pending.

benzoate may occupy a space similar to the phenyl ring on the unsaturated compound **30** and arene **32**. It will be interesting to determine the pharmacological data on the benzyl and phenethyl analogs of **31**, to investigate the increased length between the nitrogen and the phenyl ring.

## Conclusions

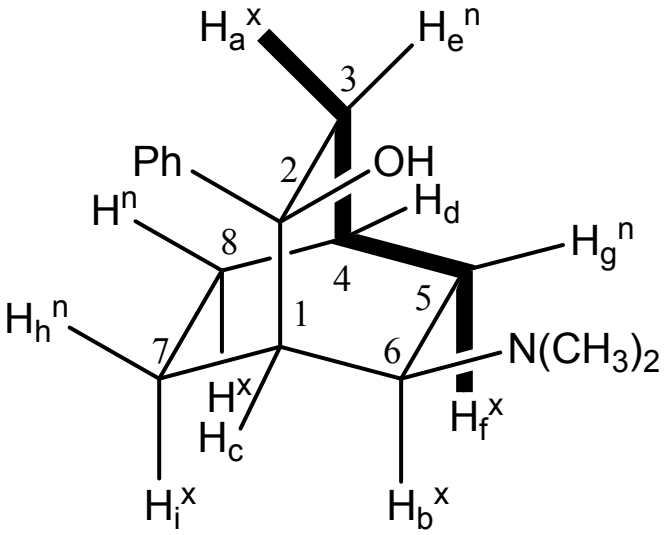
A series of 6-(*N*,*N*-dimethylamino)-2-benzylbicyclo[2.2.2]octanes was prepared by Grignard addition to amino ketone **19**. Comparison of the WIN binding of benzoate ester **26a**, with an $IC_{50}$ of 192 nM vs phenyl analog **31**, with an $IC_{50}$ of 1300 nM, shows the potency was lost by the excision of the ester. Preliminary data shows *exo*-arene-*endo*-amine **31** to be over 20-fold selective for the 5-HT over the DAT. The *endo*-arene-*endo*-amine **32** is more potent by 16-fold at the DAT than the *exo*-arene-*endo*-amine **31** ($IC_{50}$= 1300 nM vs $IC_{50}$= 20900 nM, respectively) and more potent by 16-fold than the *endo*-amino-*endo*-benzoate **10** ($IC_{50}$= 1300 nM vs $IC_{50}$= 21700 nM). The potency of unsaturated *endo*-amine **30**, with an $IC_{50}$ of 740 nM, is similar to that of the *endo*-amino-*exo*-benzoate **26a** ($IC_{50}$= 192 nM) and *endo*-amine-*endo*-arene **32** ($IC_{50}$= 1300 nM). The tether of the benzoate ester may allow the phenyl ring to fit in a similar binding space as the phenyl ring on the unsaturated compound **30**. It will be interesting to obtain the pharmacological data on the benzyl and phenethyl analogs of **31**, as these arenes have an increased length between the nitrogen and the phenyl ring. These homologues will help determine the optimal distance needed between the nitrogen and the phenyl ring.

## Experimental Section

**General Methods.** The general methods can be found in the experimental section of Chapter 2.

**6-*endo*-(*N*,*N*,-Dimethylamino-2-*exo*-phenylbicyclo[2.2.2]octan-endo-2-ol (29).** A solution of 3 M phenylmagnesium bromide in ether (4.08 mL, 11.98 mmol) at -20 °C was added dropwise a solution of amino ketone **19** (500 mg, 2.99 mmol) in ether (100 mL). The mixture was stirred for 4 h, $H_2O$ (50 mL) was added, and solvent was removed by reduced pressure. The aqueous layer was made acidic with 1 M HCl, washed with $CH_2Cl_2$ (3 x 50 mL), and then made basic with NaOH pellets, and extracted with $CH_2Cl_2$ (3 x 100 mL). The organic extracts were combined, dried over $MgSO_4$, and the solvent was removed under reduced pressure to afford 550 mg of crude *endo*-amino alcohol **29**. Purification by column chromatography (5:1 methanol:chloroform as the eluant) afforded *endo*-alcohol-*endo*-amine **29** ($R_f$=0.40, 400 mg, 54 % yield) as a white crystalline solid. mp 53-56 ˚C. $^1$H NMR ($CDCl_3$): δ 1.25–1.29 (m, 1H, C-7exo), 1.37–1.42 (m, 1H, C-8), 1.43-1.55 (m, 2H, C-7 endo, C-8), 1.81 (qt, J=13.2, 7.5, 1.8, 1.8 Hz, 1H, C-5 endo), 1.92 (dddd, *J*=13.2, 9.3, 3.9, 2.4 Hz, 1H, C-5 exo), 2.00 (dt, *J*=14, 2.1 Hz, 1H, C-3endo), 2.02-2.06 (m, 1H, C-4) 2.12-2.15 (m 1H, C-1), 2.28 (ddd, *J*=9.0, 7.2, 1.5 Hz, 1H, C-6), 2.31-2.41 (m, 7H, C-3 exo, $N(CH_3)_2$), 7.24 (tt, *J*=7.5, 1.5 Hz, 1H, $Ar_4$), 7.36 (tt, *J*=7.5, 1.5 Hz, 2H, $Ar_{2,6}$), 7.60 (dt, *J*=8.0, 1.5 Hz, 2H, $Ar_{3,5}$). $^{13}$C NMR ($CDCl_3$): δ 21.07, 23.10, 26.11,

32.88, 36.55, 42.91, 43.09, 65.24, 75.43 (aliphatic), 126.25, 126.29, 127.77, 148.02 (aryl).




n= endo
x=exo

**29·HCl**. mp 125-127°C, white solid. $^1$H NMR ($CDCl_3$): δ 1.25-2.20 (m, 9H), 2.45-3.2 (m, 7H), 3.35 (br s, 1H, C-6), 4.35 (br s, 1H, OH), 7.10-7.45 (m, 5H, aromatic), 9.05 (br s, 1H, HCl). IR (neat): 3407, 2953, 2874, 2578, 2440, 2295, 1472, 1446, 1031, 755 cm$^{-1}$. Elem Anal cald for $C_{16}H_{24}NOCl·0.8\ H_2O$: C, 64.87; H,8.71; N, 4.73; O, 9.72; Cl, 11.97. Found C, 64.59; H, 8.62; N, 4.61; Cl, 12.22.

**6-*endo*-(*N*,*N*,-Dimethylamino)-2-phenylbicyclo[2.2.2]octan-2-ene (30).** p-Toluene sulfonic acid (620 mg, 3.26 mmol)was added to a solution of *endo*-amino alcohol **29** (400 mg, 1.63 mmol) in toluene (100 mL). The mixture was heated at reflux with a Dean-Stark trap overnight. The flask was cooled, 5% NaOH was added (50 mL),

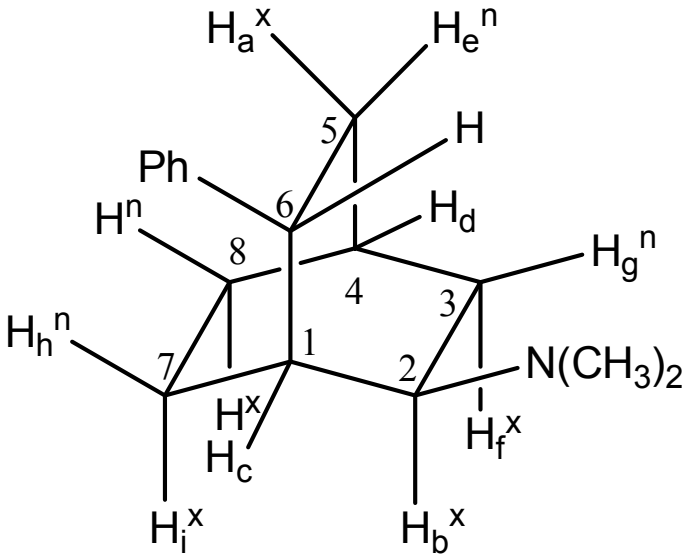
and the mixture was stirred for 2h. The organic layer was dried over Mg $SO_4$, and the solvent removed under reduced pressure to afford crude product (375 mg, quant yield). Purification by column chromatography (5:1 chloroform:methanol) afforded **30** as a white solid (290 mg, 78% yield, $R_f$= 0.25). $^1$H NMR ($CDCl_3$): δ 1.26–1.33 (m, 2H, C-5 endo, C-8 endo), 1.41 (dddd, 1H, J=16.0, 11.5, 4.5, 3.5 Hz, 1H, C-7 endo), 1.51 (dddd, J=16.5, 11.5, 4.5, 2.0 Hz, 1H, C-8 exo), 1.67 (dddd, J=15.5, 9.5, 3.0, 2.5 Hz, 1H, C-7 exo), 1.85 (ddd, *J*=12.5, 9.0, 3.0 Hz, 1H, C-5 exo), 2.12 (s, 6H, $N(CH_3)_2$), 2.73-2.76 (m, 2H, C-4, C-6) 3.38 (p, J=2.5 Hz, 1H, C-1), 6.64 (dd, *J*=6.5, 1.5 Hz, 1H, C-3), 7.21 (tt, *J*=7.0, 1.5 Hz, 1H, $Ar_4$), 7.32 (tt, *J*=7.5, 1.5 Hz, 2H, $Ar_{2,6}$), 7.47 (dt, *J*=7.0, 1.5 Hz, 2H, $Ar_{3,5}$). $^{13}$C NMR ($CDCl_3$): δ 24.48, 25.96, 30.68, 31.84, 33.88, 42.26, 65.28 (aliphatic), 124.61, 126.79, 128.54, 129.06, 138.66, 141.14 (aryl).

**30·HCl.** mp: 191-194 ºC, white solid. $^1$H NMR ($D_2O$): δ 1.09-1.29 (m, 2H), 1.35-1.53 (m, 2H), 1.58 (d, *J*=11.1 Hz, 1H), 2.04 (t, J=11.7 Hz, 1H), 2.46 (s, 3H, $N(CH_3)_2$), 2.56 (s, 3H, $N(CH_3)_2$), 2.78 (br s, 1H), 3.44 (br s, 1H) 3.55 (br s, 1H), 6.77 (d, J=6.6 Hz, 1H, C-3), 7.22 (d, J=6.6 Hz, 1H, $Ar_4$), 7.30 (t, J=8.1 Hz, 2H, $Ar_{2,6}$), 7.43 (d, J=7.5 Hz, 2H, $Ar_{3,5}$). IR (neat): 2953, 2868, 2657, 2479, 2354, 1722, 1466, 762, 702 $cm^{-1}$. MS (EI) M+ 227. Elem Anal cald for $C_{16}H_{22}NCl·0.29\ H_2O$: C, 71.43; H, 8.46; N, 5.21; O, 1.72; Cl, 13.18. Found: C, 71.43; H, 8.34; N, 5.27; Cl, 13.42.

**2-*endo*-(*N*,*N*-Dimethylamino)-6-phenylbicyclo[2.2.2]octanes (31 and 32).** A mixture of unsaturated amine **30** (200 mg, 0.88 mmol) and carbon on palladium (25 mg) in 20 mL of ethyl acetate was shaken under $H_2$ (40 psi) overnight. The reaction mixture

was filtered through celite 503 and the solvent was removed under reduced pressure to afford 195 mg of a mixture of *endo*- and *exo*-phenyl amines. The mixture was separated by column chromatography (5:1 chloroform:methanol) to afford *exo*-phenyl-*endo*-amine **31** as a colorless liquid (100 mg, 50% yield, $R_f$= 0.55) and *endo*-phenyl-*endo*-amine **32** as a colorless liquid (30 mg, 15% yield, $R_f$= 0.35).

*2-endo-(N,N-Dimethyl)amino-6-exo-phenylbicyclo[2.2.2]octane* ***(31).*** $^1$H NMR ($CDCl_3$): δ 1.23 (ddddd, *J*=16.5, 11.0, 5.0, 3.0, 2.0 Hz, 1H, C-8 exo), 1.39-1.45 (m, 2H, C-3 endo, C-7 exo), 1.54 (dddd, *J*=14.5, 9.5, 6.0, 3.0 Hz, 1H, C-8 endo), 1.72 (ddd, *J*=13.0, 8.0, 2.5 Hz, 1H, C-5 exo), 1.75-1.83 (m, 3H, C-1, C-4, C-8 endo), 1.87 (dddd, *J*=15.5, 9.0, 4.5, 2.5 Hz, 1H, C-3 exo), 1.96 (dddd, *J*=15.5, 9.0, 4.5, 2.5 Hz, 1H, C-5 endo), 2.00 (ddd, *J*=9.0, 6.0, 2.0 Hz, 1H, C-2), 2.29 (s, 6H, $N(CH_3)_2$), 3.31 (qt, *J*=10.5, 8.0, 1.5 Hz, 1H, C-6), 7.15-7.19 (m, 1H, $Ar_4$), 7.28-7.32 (m, 4H, $Ar_{2,3,5,6}$). $^{13}$C NMR ($CDCl_3$): δ 20.15, 24.88, 25.66, 31.98, 33.87, 34.36, 34.73, 43.82, 65.71 (aliphatic), 125.52, 127.89, 128.16, 146.26 (aryl).




n= endo
x=exo

***31·HCl.*** mp: 211-214 ºC, white solid. $^1$H NMR ($CDCl_3$): δ 1.24-152 (m, 2H), 1.61-1.84 (m,2H), 1.89-2.16 (m, 5H), 2.28 (t, J= 13.8 Hz, 1H, C-5), 2.84 (s, 3H, $N(CH_3)_2$), 2.89 (s, 3H, $N(CH_3)_2$), 3.09 (br s, 1H, C-2), 3.87 (t, *J*= 8.8 Hz, 1H, C-6), 7.15-7.40 (m, 5H, aromatic), 12.05 (br s, 1H, HCl). IR (neat): 2953, 2874, 2683, 2486, 2124, 1643, 1485, 702 $cm^{-1}$. MS (EI) M+ 229. Elem Anal cald for $C_{16}H_{24}NCl·0.9\ H_2O·0.2$ HCl: C, 66.61; H, 8.80; N, 4.85; O, 4.99; Cl, 14.75. Found: C, 66.04; H, 8.44; N, 4.78; Cl, 14.75.

*2-endo-(N,N-Dimethyl)amino-6-endo-phenylbicyclo[2.2.2]octane* ***(32).*** $^1$H NMR ($CDCl_3$): δ 1.41-1.55 (m, 2H), 1.56-1.64 (m, 2H), 1.70 (s, 6H, $N(CH_3)_2$), 1.73-1.84 (m, 2H), 1.85-1.91 (m, 3H, C-2, C-4), 2.01 (sept, *J*=2.0 Hz, 1H, C-1), 2.06 (dddd, *J*=14.0, 11.0, 3.5, 2.0 Hz, 1H, C-5 endo), 2.98 (t, *J*=10.0 Hz, 1H, C-6), 7.11 (tt, *J*=7.0, 1.5 Hz, 1H, $Ar_4$), 7.22 (tt, *J*=8.0, 2.0 Hz, 2H, $Ar_{2,4}$), 7.44 (d, *J*=7.5 Hz, 2H, $Ar_{3,5}$). $^{13}$C NMR ($CDCl_3$): δ 23.70, 25.57, 29.44, 31.54, 34.52, 35.25, 42.12, 43.91, 66.71 (aliphatic), 125.22, 127.25, 129.13, 145.83 (aryl).

***32·HCl.*** mp: 124-127 °C, white solid. $^1$H NMR ($D_2O$): δ 1.36-1.60 (m, 4H), 1.78-1.90 (m, 1H), 1.95-2.00 (m, 1H), 2.05-2.20 (m, 3H), 2.22-2.36 (6H, $N(CH_3)_2$), 2.39 (br s, 1H), 3.05-3.25 (m, 1H), 7.19 (t, J=7.2 Hz, 1H, $Ar_4$), 7.32 (t, J=7.5 Hz, 2H, $Ar_{2,6}$), 7.40 (d, J=7.5 Hz, 2H, $Ar_{3,5}$). IR (neat): 2960, 2868, 2683, 1729, 1650, 1466, 1262, 1077, 1025, 808, 709 $cm^{-1}$. MS (EI) M+ 229. Elem Anal cald for $C_{16}H_{24}NCl$: C, 72.29; H, 9.10; N, 5.27; Cl, 13.34. Found: C, 72.14; H, 8.97; N, 5.17; Cl, 13.47.

**6-*endo*-Amino-2-*exo*-benzylbicyclo[2.2.2]octan-endo-2-ol (33).** A solution of 1 M benzylmagnesium chloride in THF (6.32 mL, 6.32 mmol) at -20 °C was added dropwise to a solution of amino ketone **19** (500 mg, 2.99 mmol) in ether (100 mL). The mixture was stirred for 4 h, $H_2O$ (50 mL) was added, and the solvent was removed by reduced pressure. The aqueous layer was made acidic with 1 M HCl, washed with $CH_2Cl_2$ (3 x 50 mL), the aqueous layer was then made basic with NaOH pellets, and extracted with $CH_2Cl_2$ (3 x 100 mL). The organic extracts were combined, dried over $MgSO_4$, and the solvent was removed under reduced pressure to afford 568 mg of *endo*-alcohol-*endo*-amine **33** as a yellow liquid (73.3 % yield). $^1$H NMR ($CDCl_3$): δ 1.27–1.48 (m, 3H) 1.54 (dt, *J*=13.8, 2.1 Hz, 1H, C-3), 1.58-1.90 (m, 6H), 2.03-2.10 (m, 7H, $N(CH_3)_2$), 2.65 (d, *J*=13.8 Hz, 1H, C-9), 2.89 (d, *J*=13.8 Hz, 1H, C-9), 7.15-7.37 (m, 5H, aromatic). $^{13}$C NMR ($CDCl_3$): δ 21.49, 23.59, 25.98, 32.13, 32.86, 42.81, 45.12, 47.18, 64.82, 73.99 (aliphatic), 125.73, 127.50, 130.58, 138.71 (aryl).

**33·HCl.** (very hygroscopic). $^1$H NMR ($D_2O$): δ 1.23-1.55 (m, 5H), 1.59 (dt, *J*= 14.7, 2.1 Hz, 1H, C-3), 1.68-1.80 (m, 1H), 1.81-1.87 (m, 1H, C-4), 1.97 (br s, 1H, C-1), 2.00-2.12 (m, 1H), 2.41 (s, 3H, $N(CH_3)_2$), 2.61 (s, 3H, $N(CH_3)_2$), 2.77 (s, 2H, C-9), 3.01 (t, *J*= 7.8 Hz, 1H, C-6), 7.12-7.26 (m, 5H, aromatic). MS (EI) M+ 259. Elem Anal cald for $C_{17}H_{26}NCl$: C, 62.37; H, 9.08; N, 4.28; Cl, 10.83. Found: C, 62.21; H, 8.69; N, 4.12.; Cl, 11.63.

**2-*endo*-(*N*,*N*-Dimethylamino)-6-benzylbicyclo[2.2.2]octanes (39 and 41).** p-Toluene sulfonic acid (739 mg, 3.88 mmol)was added to a solution of *endo*-amino

alcohol **33** (503 mg, 1.94 mmol) in toluene (100 mL). The mixture was heated at reflux with a Dean-Stark trap overnight. The flask was cooled, 5% NaOH was added (50 mL), and the mixture was stirred for 2h. The organic layer was dried over Mg $SO_4$, and the solvent removed under reduced pressure to afford crude product (403 mg, 86 % yield). The crude mixture was used without further purification.

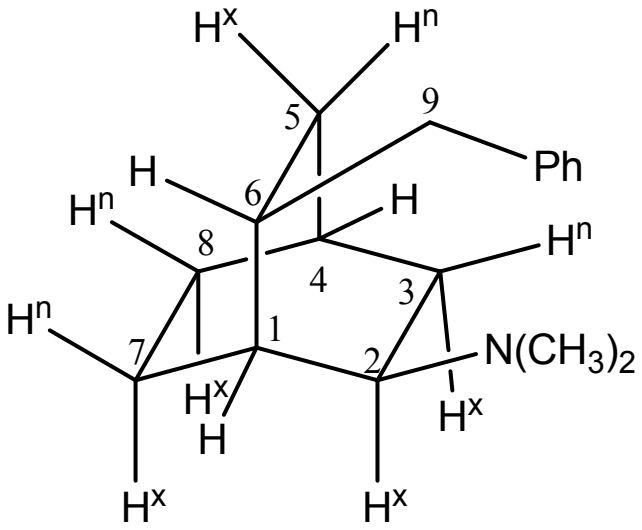
A mixture of unsaturated amines **35** and **37** (200 mg, 0.88 mmol) in methanol (20 mL) and 50 % w/w Rainey Nickel in $H_2O$ (40 mg) was shaken under $H_2$ (40 psi) overnight. The reaction mixture was filtered through celite 503 and the solvent was removed under reduced pressure to afford 200 mg (quant yield) of a mixture of 1:1 *endo*:*exo* benzyl amines. The mixture was separated by column chromatography (1:1:1 acetone:chloroform:methanol) to afford *exo-be*nzyl-endo-mine **39** (30 mg, 15% yield, $R_f$= 0.45) as a pale yellow oil and *endo-b*enzyl-*endo*-amine **41** (20 mg, 10% yield, $R_f$= 0.35) as a pale yellow oil.

*2-endo-(N,N-Dimethyl)amino- 6-exo-benzylbicyclo[2.2.2]octane **(39)**.* $^1$H NMR ($CDCl_3$): δ 1.23 (dm, *J*=13.2 Hz, 1H, C-3), 1.35-1.60 (m, 6H, C-3, C-5, C-7, C-8), 1.65 (sept, *J*=2.7 Hz, 1H, C-4), 1.77 (tt, *J*=12.9, 3.9 Hz, 1H, C-5), 1.85-1.93 (m, 2H, C-1, C-2), 1.95-2.10 (p, *J*= Hz, 1H, C-6), 2.10 (s, 6H, $N(CH_3)_2$), 2.95 (d, *J*= 7.8 Hz, 1H, C-9), 7.09-7.26 (m, 5H, aromatic).

***39·HCl.*** mp: 218 ºC, decomposed, white solid. $^1$H NMR ($D_2O$): δ 1.03-1.16 (m, 1H), 1.30-1.76 (m, 8H), 2.05-2.20 (m, 3H), 2.48 (t, J= 12 Hz, 1H, C-9), 2.70 (s, 6H,

$N(CH_3)_2$), 3.16 (t, J= 9 Hz, 1H, C-2), 7.12-7.27 (m, 5H, aromatic). MS (EI) M+ 243. IR (neat): 2917, 2580, 2472, 1449, 707 $cm^{-1}$.

*2-endo-(N,N-Dimethyl)amino-6-endo-benzylbicyclo[2.2.2]octane (**41**)*. $^1$H NMR ($CDCl_3$): δ 1.01 (qt, *J*= 12.0, 7.2 Hz, 1H, C- endo), 1.24-1.38 (m, 3H, C-3 exo, C-5 exo, C-8), 1.42-1.48 (m, 1H, C-8), 1.45 (ddd, *J*=11.0, 9.6, 2.1 Hz, 1H, C-8), 1.50 (br sm, 1H, C-1), 1.64 (decet, *J*=1.2 Hz, 1H, C-4), 1.73-1.81 (m, 2H, C-7), 1.83-1.91 (m, 2H, C-2, C-5), 1.99 (s, 6H, $N(CH_3)_2$), 2.20 (p, *J*=8.4, 1H, C-6), 2.49 (dd, *J*= 13.2, 9.3 Hz, 1H, C-9), 2.67 (dd, *J*= 13.2, 6.6 Hz, 1H, C-9), 7.14 (t, *J*= 4.5 Hz, 1H, $Ar_4$), 7.18 (d, *J*= 3.9 Hz, 2H, $Ar_{2,6}$) 7.23 (t, J=4.5 Hz, 2H, $Ar_{3,5}$). $^{13}$C NMR ($CDCl_3$): δ 19.97, 25.00, 25.54, 29.04, 30.61, 33.98, 34.28, 40.69, 43.46, 65.53 (aliphatic), 125.44, 127.92, 128.89, 141.22 (aryl).




n= endo
x=exo

***41·HCl.*** mp 212-215°C, white solid. $^1$H NMR ($D_2O$): δ 1.35-1.90 (m, 9H), 1.98-2.30 (m, 3H), 2.65-3.15 (m, 7H), 3.45 (m, 1H, C-2), 7.05-7.60 (m, 5H, aromatic), 11.50 (br s, 1H, HCl). MS (EI) M+ 243. IR (neat): 2940, 2868, 2664, 2585, 2479, 1663, 1466, 709 $cm^{-1}$.

**6-*endo*-Amino-2-*exo*-phenethylbicyclo[2.2.2]octan-endo-2-ol (34).** A solution of 3 M phenethylmagnesium bromide in THF (17.9 mL, 17.9 mmol) was added dropwise to amino ketone **19** (1.50 g, 8.98 mmol) in ether (100 mL) at -20 °C. The mixture was stirred for 4 h, $H_2O$ (50 mL) was added, and the solvent was removed by reduced pressure. The mixture was stirred for 4 h, $H_2O$ (50 mL) added, and solvent was removed by reduced pressure. The aqueous layer was made acidic with 1 M HCl, washed with $CH_2Cl_2$ (3 x 50 mL), the aqueous layer was then made basic with NaOH pellets, and extracted with $CH_2Cl_2$ (3 x 100 mL). The organic extracts were combined, dried over $MgSO_4$, and the solvent was removed under reduced pressure to afford 1.09 g of *endo*-alcohol-*endo*-amine **34** as a pale yellow liquid with 30 % of the reduced *endo*-amino-*endo*-alcohol **21**. The *endo*-alcohol-*endo*-amine **34** was purified by column chromatography (silica gel, 5:3:1 methanol:acetone:chloroform eluant) to obtain 253 mg of pure product (10 % yield). $^1$H NMR ($CDCl_3$): δ 1.28–1.40 (m, 3H) 1.51 (dt, *J*=13.5, 2.1 Hz, 1H, C-3), 1.57-1.90 (m, 6H), 2.01 (br s, 1H, C-1), 2.13-2.25 (m, 2H), 2.27 (s, 6H, $N(CH_3)_2$), 2.77 (t, *J*=8.4 Hz, 2H, C-10), 7.13-7.32 (m, 5H, aromatic). $^{13}$C NMR ($CDCl_3$): δ 21.50, 23.29, 25.98, 29.29, 32.78, 33.86, 43.15, 44.57, 65.14, 73.26 (aliphatic), 125.42, 128.25, 128.48, 143.65 (aryl).

**34·HCl.** (very hygroscopic). $^1$H NMR ($CDCl_3$): δ 0.70-1.00 (m, 1H), 1.23-2.44 (m, 14H), 2.60-3.40 (m 8H), 4.55(br s, 1H, OH), 7.05-7.40 (m, 5H, aromatic), 9.70 (br s, 1H, HCl). Elem Anal cald for $C_{18}H_{28}NOCl \cdot 0.3\ H_2O$: C, 67.39; H, 8.89; N, 4.37; O, 4.99; Cl, 14.37. Found: C, 67.01; H, 9.05; N, 4.27; Cl, 14.51.

**2-*endo*-2-(*N*,*N*-Dimethyl)amino-6-phenethylbicyclo[2.2.2]octanes (40 and 42).** p-Toluene sulfonic acid (1.8 g, 9.52 mmol) was added to a mixture of *endo*-alcohol-*endo*-amine **34** (1.3 g, 4.76 mmol) in toluene (100 mL). The mixture was heated at reflux with a Dean-Stark trap overnight. The flask was cooled, 5% NaOH (25 mL) was added, and the mixture was stirred for 2h. The organic layer was separated, dried over Mg $SO_4$, and the solvent removed under reduced pressure to afford the crude product mixture of unsaturated products **40** and **42** (1.2 g, quant yield). The crude mixture was used without further purification.

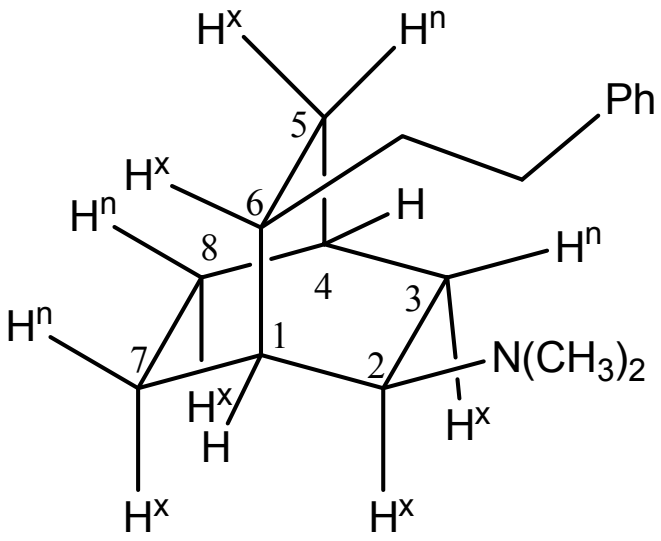
A mixture of unsaturated amines **40** and **42** (600 mg, 2.35 mmol) in methanol (20 mL) and 50 % w/w Rainey Nickel in $H_2O$ (100 mg) was shaken under $H_2$ (65 psi) for 3 d. The mixture was filtered through celite 503 and the solvent was removed under reduced pressure to afford 400 mg (66% yield) of a mixture of 3:2 *exo*:*endo* phenethyl amines. The mixture was separated by column chromatography (1:1:1 acetone:$CHCl_3$:$CH_3OH$) to afford *exo*-phenethyl-*endo*-amine **40** (57 mg, 9% yield, $R_f$= 0.33) and *endo*-phenethyl-*endo*-amine **42** (60 mg, 10% yield, $R_f$= 0.42).

*2-endo-(N,N-Dimethyl)amino-6-exo-phenethylbicyclo[2.2.2]octane **(40).*** $^1$H NMR ($CDCl_3$): δ 0.97 (qt, *J*= 12, 6.9, 1.8 Hz, 1H, C-5), 1.21-1.46 (m, 4H), 1.56-1.69 (m, 4H),

1.70-1.88 (m, 3H), 1.88-2.00 (m, 2H), 2.20 (s, 6H, $N(CH_3)_2$), 2.58 (dd, *J*= 10.5, 6.3 Hz, 1H, C-10), 7.13-7.30 (m, 5H, aromatic). $^{13}C$ NMR ($CDCl_3$): δ 20.53, 25.07, 25.71, 29.29, 31.35, 34.16, 34.28, 34.36, 37.85, 43.91, 65.79 (aliphatic), 125.42, 128.13, (overlap) 143.11 (aryl).

***40·HCl.*** mp: 219-222 ˚C, white solid. $^1H$ NMR ($D_2O$): δ 0.65-1.40 (m, 1H), 1.16-1.85 (m, 12H), 1.980 (t, *J*= 9.6 Hz, 1H), 2.52 (s, 3H, $N(CH_3)_2$), 2.67 (s, 3H, $N(CH_3)_2$), 3.07 (t, *J*= 6.3 Hz, 1H), 7.05-7.25 (m, 5H, aromatic). IR (neat): 2933, 2861, 2578, 2466, 1453, 709 $cm^{-1}$. MS (EI) M+ 257. Elem Anal cald for $C_{18}H_{28}NCl·0.65\ H_2O$: C, 70.75; H, 9.66; N, 4.58; O, 3.40; Cl, 11.60. Found: C, 70.47; H, 9.29; N, 4.47; Cl, 11.64.

*2-endo-(N,N-Dimethyl)amino-6-endo-phenethylbicyclo[2.2.2]octane* ***(42).*** $^1H$ NMR ($CDCl_3$): δ 1.23-1.33 (m, 1H, C-5), 1.46-1.57 (m, 5H, C-8, C-7, C-5), 1.59-1.67 (m, 1H, C-6), 1.73 (br s, 1H, C-4), 1.77-1.83 (m, 2H, C-3), 1.87 (br s, 1H, C-1), 1.93-2.01 (m, 3H, C-2, C-9), 2.17 (s, 6H, $N(CH_3)_2$), 2.58 (dt, *J*= 15, 10 Hz, 1H, C-10), 2.70 (dd, *J*= 15, 5 Hz, 1H, C-10), 7.18-7.34 (m, 5H, aromatic). $^{13}C$ NMR ($CDCl_3$): δ 23.52, 25.61, 28.84, 30.62, 34.35, 35.09, 35.97, 38.09, 44.35, 67.08 (aliphatic), 125.35, 128.11, 128.55, 143.58 (aryl).




n= endo
x=exo

***42·HCl.*** mp: 220-223˚C, white crystalline solid. $^1$H NMR ($CDCl_3$): δ 1.26-1.54 (m, 4H), 1.58-1.72 (m, 3H), 1.72-1.82 (m, 2H), 1.82-1.90 (m, 2H), 1.90-2.02 (m, 1H), 2.06-2.19 (m, 1H), 2.36-2.48 (m, 1H), 2.50-2.62 (m, 1H), 2.71 (s, 3H, $N(CH_3)_2$), 2.76-2.94 (m, 4H, $N(CH_3)_2$), 7.05-7.30 (m, 5H, aromatic), 11.37 (br s, 1H, HCl). MS (EI) M+ 257. IR (neat): 2940, 2861, 2670, 2637, 2591, 2512, 2460, 1485, 1453, 1420, 1005, 702 $cm^{-1}$.

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6. The experiments were conducted at Mercer School of Medicine under the supervision of Dr. Margaret M. Schweri.

# CHAPTER IV

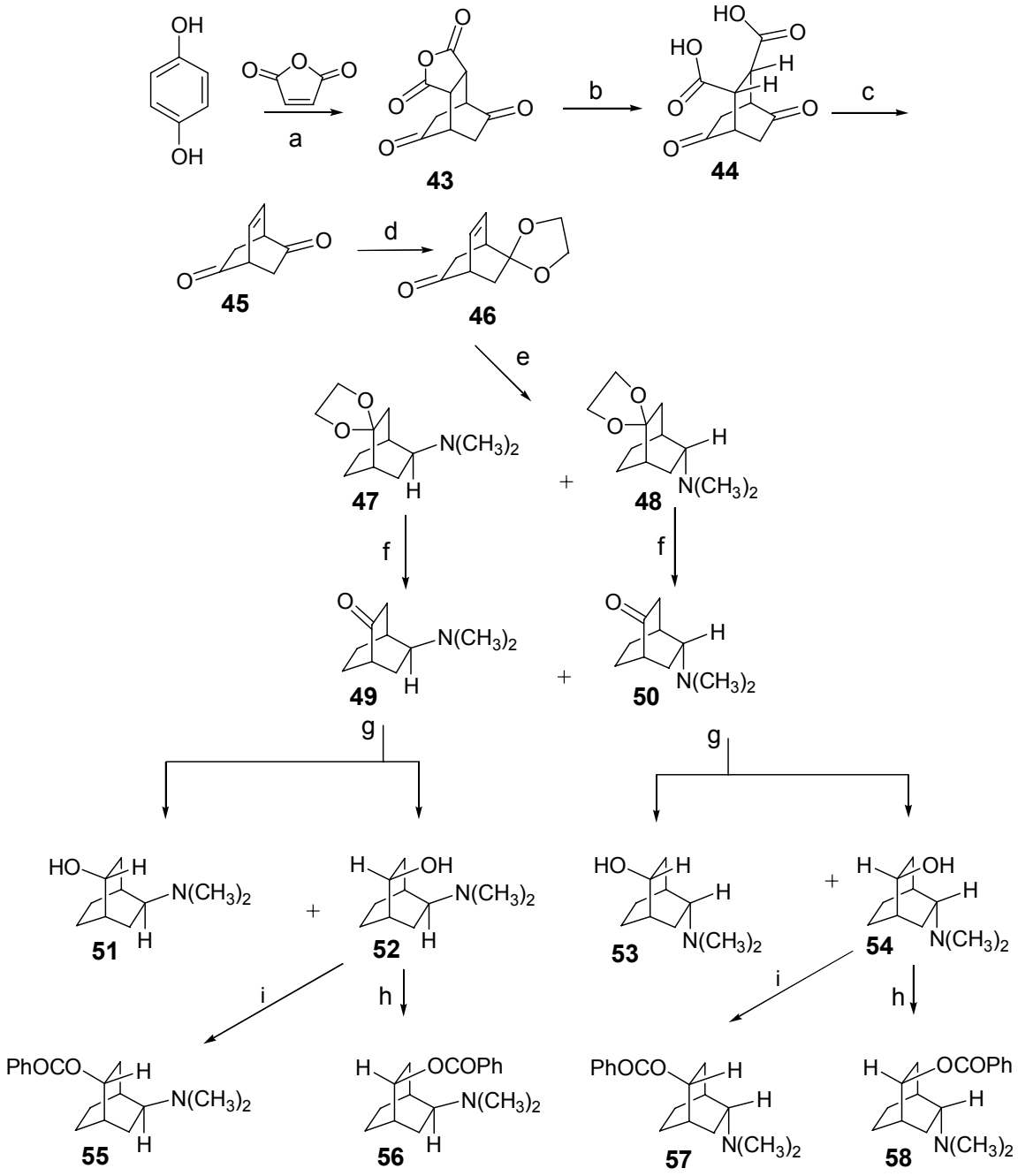
# SYNTHESIS OF 5-AMINO-2-BENZOYLBICYCLO[2.2.2]OCTANES

## Introduction

Another approach taken to further understand the role of the phenyl ring on the 6-amino-[2.2.2]bicyclo -2-benzoates (**10-28**, Chapter 3) was to transpose the benzoate from the C-2 position on the bicycle to the C-3 position. This places the benzoate one carbon over on the same bridge, *e.g.* compounds **55-58**. The transposition of the benzoate one carbon over increases the length between the nitrogen and the phenyl ring, which should influence the binding of the inhibitor at the DAT. Thus, extensive analysis of the structural changes will allow for the development of SARs related to the fit of these compounds at the active site of the DAT.

## Chemistry

The transposition of the ester functionality from the C-2 position to the C-3 position was achieved employing a new synthetic strategy shown in Scheme 4.1. Diels-Alder reaction between hydroquinone and maleic anhydride provided the cycloaddition




Reagents: a) 170-190 °C melt, 6 h; b) $H_2O$, heat; c) $Pb(OAc)_4$, dioxane, pyridine; d) $HOCH_2CH_2OH$, p-TSA·$H_2O$, $C_6H_6$, reflux, 1h; e) 1) $NH(CH_3)_2 \cdot H_2O$, $Et_3N$, $CH_3OH$, 4 Å molecular sieves, 2) $H_2$, Pd/C, 40 psi; f) HCl, $CH_2Cl_2$; g) $NaBH_4$, EtOH, reflux; h) PhCOCl, $Et_3N$, DMAP, $C_6H_6$, 50 °C; and i) TTP, DEAD, benzoic acid, THF.

**Scheme 4.1.** Synthesis of 2-Amino-5-benzylbicyclo[2.2.2]octanes **55-58**.

adduct **43** in low yield (5-11%).[1] The product was purified by triturating the crude product with a 3:7 mixture of boiling ethyl acetate and diethyl ether. Although the reaction proceeded in low yield, the starting materials are cheap and the purification is trivial. The anhydride **43** was hydrolyzed to the *cis* diacid **44** by heating in $H_2O$. The diacid **44** was oxidatively decarboxylated with lead tetraacetate to form the enedione **44**. The $^1$H NMR spectrum of enedione **45** shows a peak at δ 6.56, which integrates to 2Hs which can be assigned to the two vinylic protons. Enedione **45** was ketalized with an equimolar quantity of ethylene glycol to give a mixture of diacetal, acetal, and starting material.[2] Hydrogenation of the mixture gave a 6:71:23 ratio of diacetal, acetal **46**, and starting material (determined by $^1$H NMR). The mixture was purified by column chromatography using a 1:1 hexane:ether eluant. The starting material could be recovered directly from the column and by hydrolysis of the diacetal. The monoacetal **46** was reductively aminated with dimethylamine hydrochloride to afford a 5:1 mixture of the *endo*:*exo* diastereomeric amino acetals **47** and **48** (determined by $^1$H NMR, based on the appearance of the 6H proton singlet for the dimethylamino group at δ 2.19 ppm and δ 2.20 ppm), which were separated by column chromatography on alumina with chloroform as the eluant. The separate amino acetals were deprotected with 1 M HCl and $CH_2Cl_2$ to give the corresponding amino ketones **49** and **50**. The amino ketones were then reduced to afford a 3:2 ratio of *endo*-amino alcohols **51** and **52** and a 1:1 ratio of *exo*-amino alcohols **53** and **54**, respectively. The structure of *endo*-amino alcohol **52** was determined by x-ray diffraction (Appendix H). The amino alcohols **51-54** were purified by column chromatography. The hydroxy amines **52** and **54** were benzoylated to afford the corresponding benzoates **56** and **58**, and benzoates **55** and **57** were obtained by

Mitsunobu chemistry of hydroxy amines **52** and **54**. The structure of benzoate **57** was confirmed by x-ray analysis (Appendix I).

## Pharmacology

Benzoates **55-58** were submitted for pharmacological testing and the results are pending.

## Conclusions

A series of new regioisomers, benzoates **55-58**, were synthesized using Diels-Alder chemistry to construct the bicycle. The bicycle was formed by reacting hydroquinone with maleic anhydride. This strategically places ketones at the C-2 and C-5 position of the bicyclooctane skeleton. This was used to introduce a benzoate and an amine moiety. The transposition of the benzoate relative to the 6-amino-[2.2.2]bicyclo-2-benzoates (**10-28**) lengthens the distance between the nitrogen and phenyl, and as a result, will provide more insight into the active site of the DAT. While the pharmacology data is still pending for benzoates **55-58**, the new substitution pattern on the bicycle, with the amine at C-2 and the benzoate at C-5, will allow for a direct comparison with regioisomers **10-28**, whose synthesis is described in Chapter 2.

## Experimental Section

**General Methods.** The general methods can be found in the experimental section of Chapter 2.

**5,7-Dioxo bicyclo[2.2.2]octane-2,3-dicarboxylic anhydride (43).** Maleic anhydride (500 g, 5.1 mol) was heated to 130˚C and hydroquinone (321 g, 2.9 mol) was added to the flask. The mixture was then heated to 190 ˚C for 6 h, cooled to 60 ˚C, and a mixture of ethyl acetate (300 mL) and diethyl ether (700 mL) was added to the flask. The mixture was heated at reflux for 30 min and 57 g of the insoluble anhydride **43** was isolated by filtration (11.5% yield, mp 252-256 ˚C, lit mp 265-270 ˚C). $^{1}$H NMR (DMSO-$d_6$): δ 2.35 (dd, *J*=20.1, 3.0 Hz, 1H, C-6 endo), 2.68 (dd, *J*=19.2, 2.7 Hz, 1H, C-8), 2.77 (dd, *J*=19.2, 3 Hz, 1H, C-8), 2.80 (dt, *J*= 20.4, 2.7 Hz, 1H, C-6 exo), 2.98 (q, *J*= 3 Hz, 1H, C-1), 3.01 (q, *J*=3.6 Hz, 1H, C-4), 3.80 (ddd, *J*=10.2, 3.6, 2.1 Hz, 1H, C-2), 3.96 (dd, *J*=10.2, 3.6 Hz, 1H, C-3). $^{13}$C (DMSO-$d_6$): δ 36.90, 37.54, 40.72, 42.97, 44.98, 46.92, 171.40, 171.48, 206.11, 207.02.

**5,7-Dioxo bicyclo[2.2.2]octane-2,3-dicarboxylic acid (44)**. The *cis* diacid **44** was obtained by recrystallizing the anhydride (58 g) from $H_2O$ (100% yield). mp: 262-265 ºC, lit mp 264-266˚. $^{1}$H NMR (DMSO-$d_6$): δ 2.35-2.49 (m, 2H), 2.66-2.87 (m, 4H), 3.34 (dd, *J*=11.1, 1.8 Hz, 1H, C-2), 3.45 (dd, *J*= 11.1, 2.7 Hz, 1H, C-3). $^{13}$C (DMSO-$d_6$): δ 36.11, 38.11, 39.77, 43.76, 45.98, 47.98, 172.08, 173.98, 208.40, 208.94.

**Bicyclo[2.2.2]oct-7-ene-2,5-dione (45)**. Pyridine (568 mL, 7.0 mol) was added dropwise to a mixture of diacid **44** (63.2 g, 0.280 mol) and lead tetraacetate (282.2 g, 0.636 mol) in dioxane ( mL) at 0 ˚C. The mixture was then heated to 60 ˚C for min, cooled, and 2 M $HNO_3$ (2000 mL) was added. The mixture was extracted with chloroform (2000 mL x 3), the organic extracts were combined and washed with saturated NaHCO3 (500 mL x 1), dried over $MgSO_4$, and the solvent was removed under reduced pressure to obtain 8 g of crude product. Pure product (4.3 g, 11.2% yield) was obtained by flash column chromatography (20% ethyl acetate/ PET ether, $R_f$= 0.55) as a pale brown solid. mp 101-105 ˚C lit mp 95-99 ˚C[1]. $^1$H NMR ($CDCl_3$): δ 2.33 (dd, *J*=18.6, 2.7 Hz, 2H, C-3, C-5), 2.43 (dd, *J*=18.6, 2.1 Hz, 2H, C-3, C-5), 3.43-3.47 (m, 2H, C-1, C-4), 6.50-6.56 (m, 2H, C-7, C-8). $^{13}$C ($CDCl_3$): δ 34.89, 49.76, 132.06, 207.50.

**5-(Ethylenedioxy)bicyclo[2.2.2]octan-2-one (46)**. A mixture of dione **45** (4.28 g, 31 mmol), p-toluene sulfonic acid (300 mg, 1.58 mmol), and ethylene glycol (1.12 g, 31 mmol) in 70 mL of benzene was heated to reflux for 1 h. The mixture was cooled and 5% NaOH was added to the mixture. The solution was stirred for 4 hours and the solvent removed under reduced pressure. The aqueous layer was extracted with $CH_2Cl_2$ (3 x 100 mL), the organic extracts were collected, dried over $MgSO_4$, and the solvent was removed by reduced pressure to obtain 5.4 g of crude product. The crude acetal was dissolved in methanol (50 mL), Pd/C catalyst was added, and the mixture was stirred overnight, under 40 psi. The mixture was filtered through celite, and the solvent removed under reduced pressure to obtain 5.3 g of crude product. The acetal **46** (3.65 g, 63% yield, Rf= 0.40)) was obtained by flash column chromatography (1:1 hexane:ether) as a

colorless oil. $^{1}$H NMR ($CDCl_3$): δ 1.43-1.55 (m, 1H), 1.65-1.84 (m, 2H), 1.93- 2.14 (m, 5H), 2.34 (p, *J*= 3 Hz, 1H), 2.51 (dt, *J*= 19.5, 3 Hz, 1H, C-3), 3.80-3.97 (m, 4H). $^{13}$C ($CDCl_3$): δ 20.35, 20.99, 36.27, 38.64, 40.31, 44.27, 64.02, 64.35, 109.02 (OCO), 215.14 (C=O).

**2-(*N*,*N*-Dimethylamino)-5-(ethylenedioxy)bicyclo[2.2.2]octanes (47 and 48)**. A mixture of ketone 6**5** (3.4 g, 18.6 mmol), dimethylamine hydrochloride (9.1 g, 112 mmol), triethylamine (22.6 g, 223 mmol), and 4 Å molecular sieves (70 g) in 200 mL of methanol was stirred overnight, followed by the addition of Pd/C catalyst and $H_2$ (40 psi). The mixture was stirred for 3 d, filtered through celite, and the solvent removed under reduced pressure to obtain 3.7 g of crude product (89% yield). The diastereomers were separated by flash column chromatography (alumina, chloroform) to obtain 1.68 g of *endo*-amine **47** (41.1% yield, Rf= 0.40) as a colorless oil and 0.367 g of *exo*-amine **48** (9% yield, Rf= 0.45) as a pale yellow solid.

*2-endo-(N,N-Dimethylamino)-5-(ethylenedioxy)bicyclo[2.2.2]octane **(47)***. $^{1}$H NMR ($CDCl_3$): δ 1.36 (dddd, *J*= 12.3, 8.7, 5.1, 1.5 Hz, 1H), 1.43 (dq, *J*= 11.1, 3 Hz, 1H, C-3endo), 1.55-1.86 (m, 7H), 1.99 (sextet, *J*= 2.4 Hz, 1H, C-1), 2.12 (dt, *J*= 14.4, 2.1 Hz, 1H, C-6), 2.19 (s, 6H, $N(CH_3)_2$), 3.79-3.99 (m, 4H, C-9, C-10). $^{13}$C ($CDCl_3$): δ 20.50, 24.02, 28.79, 30.47, 33.34, 35.07, 43.78, 63.49, 63.79, 63.91, 110.10 (C-5).

*2-exo-(N,N-Dimethylamino)-5-(ethylenedioxy)bicyclo[2.2.2]octane **(48)***. $^{1}$H NMR ($CDCl_3$): δ 1.27 (ddd, *J*= 12.3, 4.8, 2.7 Hz, 1H, C-3exo), 1.31-1.40 (m, 1H), 1.52 (dddd,

*J*= 13.8, 9.3, 5.4, 1.2 Hz, 1H), 1.65-1-83 (m, 4H), 1.89 (dd, *J*= 14.4, 3 Hz, 1H, C-6), 1.92-2.08 (m, 3H), 2.20 (s, 6H, $N(CH_3)_2$), 3.81-4.00 (m, 4H, C-9, C-10). $^{13}C$ ($CDCl_3$): δ 18.03, 21.46, 29.06, 30.32, 32.84, 40.43, 44.07, 63.59, 63.84, 63.91, 99.81 (C-5).

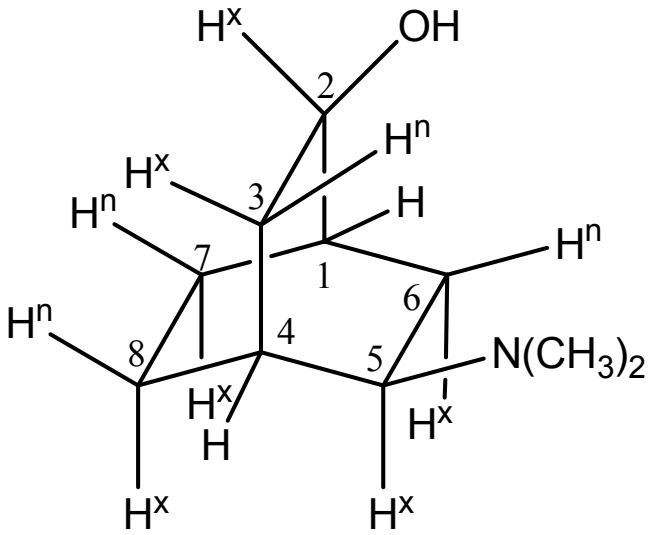
**5-(*N*,*N*-Dimethylamino)bicyclo[2.2.2]octan-2-ones (49 and 50)**. The transformation from **47** to **49** is illustrated. Acetal **47** (1.8 g, 8.53 mmol) was hydrolyzed in $CH_2Cl_2$ (50 mL) with 1M HCl (20 mL) overnight. The organic layer was separated, dried over $MgSO_4$, and the solvent removed under reduced pressure to obtain ketone **49** (1.5 g, 100% yield) as a pale yellow oil.

*5-endo-(N,N-Dimethylamino)bicyclo[2.2.2]octan-2-one **(49)***. $^1H$ NMR ($CDCl_3$): δ 1.58-1.83 (m, 5H), 1.96-2.12 (m, 3H), 2.21 (s, 6H, $N(CH_3)_2$), 2.28 (p, *J*=3 Hz, 1H, C-1), 2.34 (sextet, *J*=2.7 Hz, 1H, C-4), 2.57 (dt, *J*=18.9, 2.4 Hz, 1H, C-3). $^{13}C$ ($CDCl_3$): δ 22.75, 24.20, 30.46, 31.63, 38.81, 42.95, 43.63, 63.00, 217.50.

*5-exo-(N,N-Dimethylamino)bicyclo[2.2.2]octan-2-one **(50)***. (240 mg, 100% yield, pale yellow oil). $^1H$ NMR ($CDCl_3$): δ 1.46 (ttd, *J*=12.3, 3, 0.9 Hz, 1H), 1.64 (qd, *J*=17.1, 9.6, 2.1 Hz, 1H, C-6), 1.76 (dddd, *J*=15.6, 10.2, 4.2, 2.4 Hz, 1H), 1.89 (tt, *J*=13.5, 3.3 Hz, 1H) 1.96-2.11 (m, 4H), 2.12 (p, *J*=3 Hz, 1H, C-1), 2.22-2.34 (m, 2H), 2.26 (s, $N(CH_3)_2$, 6H). $^{13}C$ ($CDCl_3$): δ 18.03, 21.46, 29.06, 30.32, 32.84, 40.43, 44.07, 63.59, 63.84, 63.91, 217.50.

**5-(*N*,*N*-Dimethylamino)bicyclo[2.2.2]octan-2-ols (51-54)**. The transformation from **49** to **51** and **52** is illustrated. $NaBH_4$ (0.600 mg, 15.8 mmol) was added to a mixture of ketone **49** (1.32 g, 7.90 mmol) in 100 mL of ethanol. The mixture was heated to reflux for 4 h, $H_20$ (50 mL) was added, and the solvent removed under reduced pressure. The mixture was extracted with $CH_2Cl_2$ (3 x 50 ml), the organic layers combined, dried over $MgSO_4$, and the solvent removed under reduced pressure to obtain 1.1 g of crude product (82% yield). The two diastereomers were separated by flash column chromatography (silica, 10:5:1: methanol:acetone:chloroform) to afford 380 mg (29% yield, $R_f$= 0.32) of *endo*-alcohol **52** as a colorless oil and 290 mg (22% yield, $R_f$= 0.44) of *exo*-alcohol **51** as a white solid.

*5-endo-(N,N-Dimethylamino)bicyclo[2.2.2]octan-endo-2-ol* ***(52)***. $^1$H NMR ($CDCl_3$): δ 1.25-1.57 (m, 6H), 1.60-1.78 (m, 2H), 1.81-2.00 (m, 4H), 2.27 (s, 6H, $N(CH_3)_2$), 3.73-3.77 (m, 1H). $^{13}$C ($CDCl_3$): δ 22.25, 23.46, 25.55, 27.50, 30.96, 31.93, 43.72, 62.91, 67.49.




n= endo
x=exo

*5-endo-(N,N-Dimethylamino)bicyclo[2.2.2]octan-exo-2-ol* ***(51)***. mp 35- 40 ˚C. $^{1}$H NMR ($CDCl_3$): δ 1.15-1.43 (m, 3H), 1.61-1.72 (m, 2H), 1.79-1.92 (m, 4H), 2.00-2.25 (m, 9H, $N(CH_3)_2$), 3.90 (ddd, *J*= 9, 3.6, 1.5 Hz, 1H, C-2). $^{13}$C ($CDCl_3$): δ 17.21, 25.01, 27.28, 31.57, 32.13, 32.48, 43.74, 63.52, 68.51.

*5-exo-(N,N-Dimethylamino)bicyclo[2.2.2]octan-endo-2-ol* ***(54)***. colorless oil, $R_f$= 0.0.40). $^{1}$H NMR ($CDCl_3$): δ 1.16 (dtd, *J*=12.6, 3.3, 1.2 Hz, 1H), 1.22-1.35 (m, 3H), 1.52-1.79 (m, 3H), 1.85 (sextet, *J*= 2.7 Hz, 1H), 1.99-2.15 (m, 3H), 2.23 (s, $N(CH_3)_2$, 6H), 2.45 (br s, 1H, OH), 3.89 (dt, *J*=9.3, 2.7 Hz, C-2) $^{13}$C ($CDCl_3$): δ 17.72, 23.36, 27.28, 27.36, 32.22, 37.41, 43.56, 64.09, 68.48.

*5-exo-(N,N-Dimethylamino)bicyclo[2.2.2]octan-exo-2-ol* ***(53)***. colorless oil, $R_f$= 0.25. $^{1}$H NMR ($CDCl_3$): δ 1.31-1.42 (m, 3H), 1.58 (sextet, *J*=3 Hz, 1H), 1.65-1.86 (m, 6H), 1.93 (qt, *J*= 15.9, 10.5, 3 Hz, 1H), 2.15 (s, $N(CH_3)_2$, 6H), 3.89 (dddd, *J*=9, 4.2, 2.7, 1.5 Hz, C-2) $^{13}$C ($CDCl_3$): δ 18.19, 19.12, 27.59, 32.31, 32.96, 36.57, 44.16, 63.71, 68.43.

**5-(*N*,*N*-Dimethylamino)bicyclo[2.2.2]oct-2-yl benzoate (56 and 58)**. The transformation from **52** to **56** is illustrated. Triethylamine (126 μL, 0.659 mmol) and benzoyl chloride (126 μL, 1.39 mmol) were added to a solution of alcohol **52** (0.189 g, 1.12 mmol) in benzene (20 mL). DMAP (3 mg, 0.02 mmol) was added and the mixture was heated to 50 °C for 24 h. Saturated $NaHCO_3$ (5 mL) was added to the solution and the mixture was stirred for 2 h. The aqueous layer was removed and the organic layer was dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure to

afford a **56** as a yellow oil (180 mg). The pure product (60 mg, 20% yield) was obtained by column chromatography (1:1 methanol:chloroform, Rf= 0.41) pale yellow oil.

*5-endo-(N,N-Dimethylamino)bicyclo[2.2.2]oct-endo-2-yl benzoate* ***(56)***. pale yellow oil. $^{1}$H NMR ($CDCl_3$): δ 1.46-1.60 (m, 3H), 1.61-1.83 (m, 3H), 1.85-1.97 (m, 4H), 2.04 (dddd, *J*= 13.5, 8.1, 3.9, 1.5 Hz, 1H, C-3), 2.24 (s, $N(CH_3)_2$, 6H), 5.03 (qt, *J*=9.6, 5.7, 1.8 Hz, 1H, C-2), 7.42 (tt, *J*= 7.2, 1.5 Hz, 2H, $Ar_{3,5}$), 7.54 (tt, *J*= 7.5, 1.2 Hz, 1H, $Ar_4$), 8.08 (dt, *J*= 7.2, 1.8 Hz, 2H, $Ar_{2,6}$). $^{13}$C ($CDCl_3$): δ 22.67, 24.43, 27.15, 28.15, 28.27, 30.27, 43.86, 64.58, 73.29 (aliphatic), 128.07, 129.54, 130.71, 132.53 (aryl), 166.28 (C=O).

***56·HCl***. mp 220 ºC, decomposed, pale yellow solid. $^{1}$H NMR ($D_2O$): δ 1.42-1.60 (m, 5H), 1.78 (qm, *J*= 6.7 Hz, 1H), 1.94-2.20 (m, 4H), 2.72 (s, $N(CH_3)_2$, 3H), 2.72 (s, $N(CH_3)_2$, 3H), 3.14 (t, *J*= 7.2 Hz, 1H, C-5), 4.93 (br s, 1H, C-2), 7.39 (t, *J*= 7.8 Hz, 2H, $Ar_{3,5}$), 7.54 (t, *J*= 7.5 Hz, 1H, $Ar_4$), 7.91 (d, *J*= 7.2 Hz, 2H, $Ar_{2,6}$). IR (neat): 2954, 2877, 2610, 2483, 1712, 1452, 1275, 1122, 996 $cm^{-1}$. MS (EI) M+ 273. Elem Anal cald for $C_{17}H_{24}NO_2Cl·0.13\ H_2O$: C, 65.41; H, 7.83; N, 4.49; O, 10.92; Cl, 11.36. Found: C, 65.07; H, 7.75; N, 4.52; Cl, 11.44.

*5-exo-(N,N-Dimethylamino)bicyclo[2.2.2]oct-exo-2-yl benzoate* ***(58)***. $^{1}$H NMR ($CDCl_3$): δ 1.28-1.55 (m, 4H), 1.75 (dddd, *J*=18, 12.6, 5.1, 3 Hz, 1H), 1.82-1.94 (m, 4H), 2.03 (sextet, *J*= 3.3 Hz, 1H), 2.21 (s, $N(CH_3)_2$, 6H), 2.36 (dddd, *J*=14.7, 9.3, 2.7, 2.4 Hz,

1H), 5.15 (ddd, *J*=9.3, 4.2, 2.7, 1.5 Hz, 1H, C-2). $^{13}$C ($CDCl_3$): δ 18.28, 24.80, 27.00, 28.76, 29.03, 32.01, 43.80, 63.33, 72.55, 128.16, 129.35, 130.80, 132.55, 165.90.

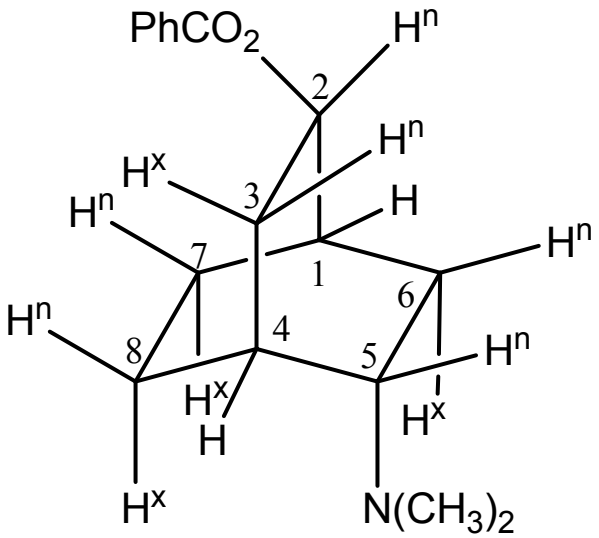
***58·HCl***. mp 165 ºC, decomposed, white solid. $^1$H NMR ($D_2O$): δ 1.20-1.80 (m, 6H), 1.80-2.15 (m, 4H), 2.70 (s, $N(CH_3)_2$, 3H), 2.74 (s, $N(CH_3)_2$, 3H), 3.11 (br s, 1H, C-5), 4.88 (br s, 1H, C-2), 7.32 (br s, 2H, $Ar_{3,5}$), 7.49 (br s, 1H, $Ar_4$), 7.81 (br s, 2H, $Ar_{2,6}$). IR (neat): 2947, 2868, 2585, 2479, 1703, 1453, 1275, 1117 $cm^{-1}$. MS (EI) M+ 273.

**5-(*N*,*N*-Dimethylamino)bicyclo[2.2.2]oct-2-yl benzoate (55 and 57).** The transformation of amino alcohol **52** to benzoate **55** is illustrated. Diethylazodicarboxylate (711 uL, 4.52 mmol) was added to a mixture of amino alcohol **52** (382 mg, 2.26 mmol), triphenylphosphine (1.19 g, 4.54 mmol), benzoic acid (607 mg, 4.97 mmol) in 20 mL of THF at room temperature. The mixture was stirred overnight and the solvent was removed by reduced pressure. The triphenylphosphine was removed by recrystallization twice from chloroform. The pure product (45 mg, 7.3 % yield) was isolated by flash column chromatography (silica, 10:5:1 methanol:acetone:chloroform) as a yellow oil.

*5-endo-(N,N-Dimethylamino)bicyclo[2.2.2]oct-2-exo-yl benzoate **(55)***. $^1$H NMR ($CDCl_3$): δ 1.41-1.57 (m, 2H), 1.63 (dt, *J*=14.1, 3.3 Hz, 1H), 1.80-2.00 (m, 7H), 2.14 (qt, *J*= 14.1, 9.9, 3 Hz, 1H), 2.23 (s, $N(CH_3)_2$, 6H), 5.08 (dddd, *J*=9.6, 4.2, 2.7, 1.8 Hz, 1H, C-2), 7.44 (tt, *J*= 7.8, 1.8 Hz, 2H, $Ar_{3,5}$), 7.56 (tt, *J*= 7.2, 1.5 Hz, 1H, $Ar_4$), 8.05 (dt, *J*= 6.9, 1.8 Hz, 2H, $Ar_{2,6}$). $^{13}$C ($CDCl_3$): δ 18.95, 19.24, 27.32, 29.61, 31.87, 33.96, 44.18, 63.64, 72.24 (aliphatic), 128.19, 129.39, 130.68, 132.66 (aryl), 166.16 (C=O).

***55·HCl***. mp 185-188 ºC, yellow solid. $^1$H NMR ($D_2O$): δ 1.35-1.72 (m, 5H), 1.87-2.22 (m, 5H), 2.71 (s, $N(CH_3)_2$, 3H), 2.77 (s, $N(CH_3)_2$, 3H), 3.13 (br s, 1H, C-5), 4.91 (br s, 1H, C-2), 7.37 (t, *J*= 7.8 Hz, 2H, $Ar_{3,5}$), 7.52 (t, *J*= 7.5 Hz, 1H, $Ar_4$), 7.90 (d, *J*= 6.9 Hz, 2H, $Ar_{2,6}$). IR (neat): 2953, 2874, 2683, 2479, 1716, 1459, 1281, 1117 $cm^{-1}$. MS (EI) M+ 273. Elem Anal cald for $C_{17}H_{24}NO_2Cl·0.5\ H_2O·0.25$ HCl: C, 62.23; H, 7.76; N, 4.27; O, 12.19; Cl, 13.55. Found: C, 62.08; H, 7.39; N, 3.92; Cl, 13.42.

*5-exo-(N,N-Dimethylamino)bicyclo[2.2.2]oct-exo-2-yl benzoate* ***(57)***. yellow oil. $^1$H NMR ($CDCl_3$): δ 1.22-1.37 (m, 2H), 1.42-1.55 (m, 2H), 1.59-1.87 (m, 2H), 1.89-2.07 (m, 4H), 2.14 (dt, *J*= 12.9, 3.3 Hz, 1H), 2.23 (s, $N(CH_3)_2$, 6H), 5.10 (dt, *J*=9.3, 3.0 Hz, 1H, C-2), 7.42-7.47 (m, 2H, $Ar_{3,5}$), 7.53-7.58 (m, 1H, $Ar_4$), 8.02-8.06 (m, 2H, $Ar_{2,6}$). $^{13}$C ($CDCl_3$): δ 18.94, 23.08, 27.12, 28.70, 29.09, 34.77, 43.89, 63.99, 72.38, 128.21, 129.35, 130.70, 132.64, 165.96.




n= endo
x=exo

***57·HCl***. mp 243 ºC, decomposed, pale yellow solid. $^{1}$H NMR ($D_2O$): δ 1.25-1.65 (m, 6H), 2.04 (br s, 1H), 2.10-2.30 (m, 2H), 2.39 (t, *J*= 11 Hz, 2H), 2.72 (s, $N(CH_3)_2$, 3H), 2.77 (s, $N(CH_3)_2$, 3H), 3.23 (t, *J*= 8 Hz, 1H, C-5), 4.96 (dm, *J*= 9.3 Hz, 1H, C-2), 7.38 (t, *J*= 7.8 Hz, 2H, $Ar_{3,5}$), 7.53 (t, *J*= 7.2 Hz, 1H, $Ar_4$), 7.87 (d, J= 7.5 Hz, 2H, $Ar_{2,6}$). IR (neat): 2954, 2877, 2680, 2470, 1719, 1452, 1270, 1115 $cm^{-1}$. MS (EI) M+ 273. Elem Anal cald for $C_{17}H_{24}NO_2Cl·1.0\ H_2O·0.15$ HCl: C, 61.26; H, 7.91; N, 4.20; O, 14.40; Cl, 12.23. Found: C, 61.57; H, 7.38; N, 3.92; Cl, 11.86.

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# CHAPTER V

# SYNTHESIS OF AMINO BENZOYLBICYCLO[2.2.1]HEPTANES

## Introduction

In contrast to the previous chapters which describe synthesis for [2.2.2]bicyclooctanes, the work described in Chapter V involves the synthesis of disubstituted bicyclo[2.2.1]heptanes that are substituted at the C-2 and C-7 position of the bicycle (amino benzoates **66-67**, Figure 5.2). The substitution at the C-7 position provides compounds which places substituents at a position which is between carbon atom 2 and 3 in the [2.2.2]octanes, discussed in Chapters 2 and 4 (Figure 5.1). One can imagine the one-carbon bridge occupying a position so as to orient the phenyl substituent in an orientation between that occupied in the 2,5 and 2,6 disubstituted [2.2.2]octanes. By placing the benzoate on the one-carbon bridge and the dimethyl amine at the C-2 position of the bicycle, a direct comparison can be completed by comparing the pharmacology data with the compounds previously synthesized. The positions of the benzoate can be reversed to give benzoate **67**, which provides an arrangement of substituents that closely resembles the relative position of the nitrogen and arene cocaine. Exploring these analogs

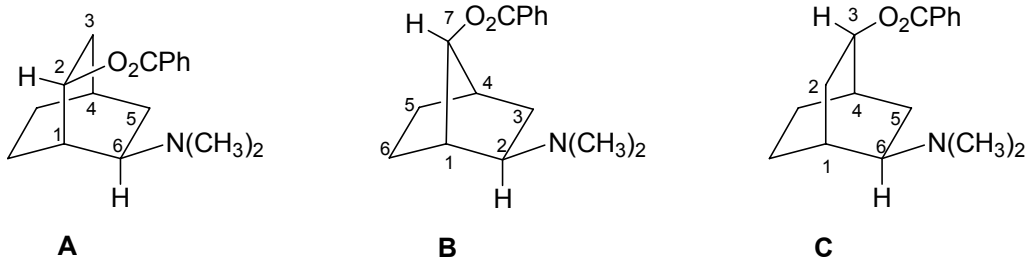



**Figure 5.1.** Regiochemistry comparison of C-2 substituted [2.2.2]bicyclooctanes (**A**), C-3 substituted [2.2.2]bicyclooctanes (**C**), and C-7 substituted [2.2.1]bicycloheptanes (**B**).

will provide us a better understanding of the necessary spatial arrangement, which the active site of the DAT can accommodate.

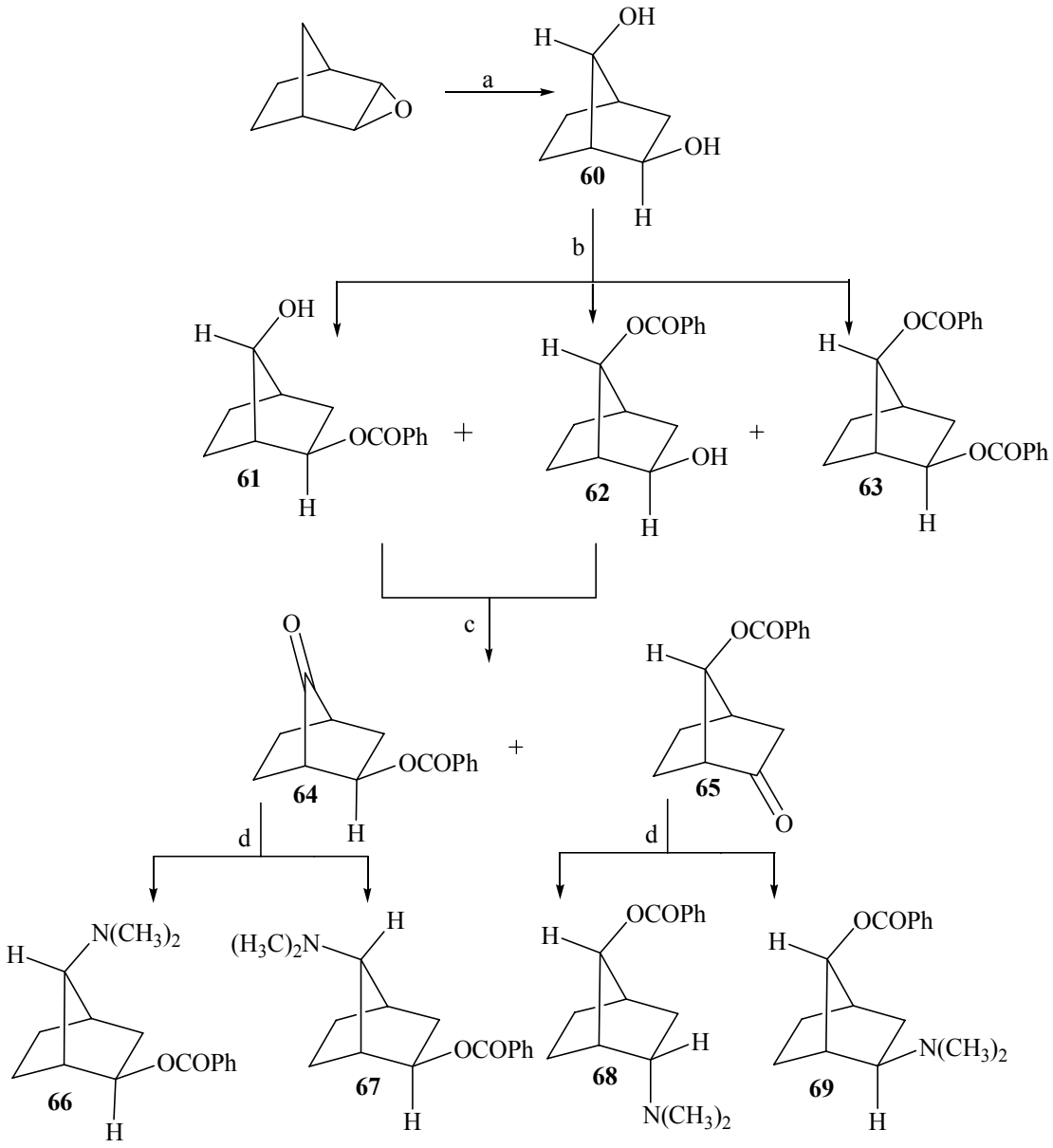
## Chemistry

A synthetic route, which strategically placed alcohol groups on the one- and two-carbon bridges of the disubstituted bicyclo[2.2.1]heptanes is shown in Figure 6.2. Epoxynorbornane was subjected to an acid-catalyzed Wagner-Meerwein rearrangement using perchloric acid to obtain the *syn* diol product **60**, which was purified by column chromatography.[1] The $^1$H NMR spectrum ($D_2O$) shows two peaks at δ 3.84 and 3.70 ppm

for the protons at C-7 and C-2. The stereochemistry of diol **60** was determined using 2-D $^1$H NMR spectroscopy and is consistent with the syn diol **60** (Appendix J). The *syn* diol **60** was benzoylated using an equimolar amount of benzoyl chloride to afford a mixture of benzoate **61**, benzoate **62**, and dibenzoylated **63** product in a 1:1:1 ratio (determined by $^1$H NMR spectroscopy). The $^1$H NMR spectrum shows a *singlet* at δ 5.08 ppm for the proton alpha to the benzoate for **62** and a *multiplet* at δ 5.03 ppm for benzoate **61**. A *doublet of doublets* at δ 3.92 ppm was assigned to the carbinol proton of alcohol **62** and a singlet at δ 4.05 ppm was assigned to the carbinol proton of alcohol **61**. The crude mixture was treated with DMSO and oxalyl chloride in a Swern oxidation to give a 1:1 mixture of keto esters **64** and **65**, which were separated by column chromatography. The structure assignment of keto ester **64** was completed by $^1$H NMR spectroscopy (Appendix K). Keto ester **64** was reductively aminated with dimethylamine (using $H_2$ and Pd over carbon as the catalyst) to obtain amino benzoate **66**. The benzoate at the C-2 position of **64** sterically hinders the *syn* addition of hydrogen to the *endo* face of the bicycle, thereby only allowing hydrogenation of the *exo* face. When sodium cyanoborohydride was used as the reducing agent a 3:2 mixture of keto esters **66** and **67** was obtained. Keto benzoate **65** was reductively aminated under these conditions to give a 10:1 mixture of keto esters **68** and **69**. Analytically pure samples of keto esters **66-69** were obtained by column chromatography. The structure assignments of amino benzoates **66** and **68** were completed by x-ray analysis (Appendix L and M).

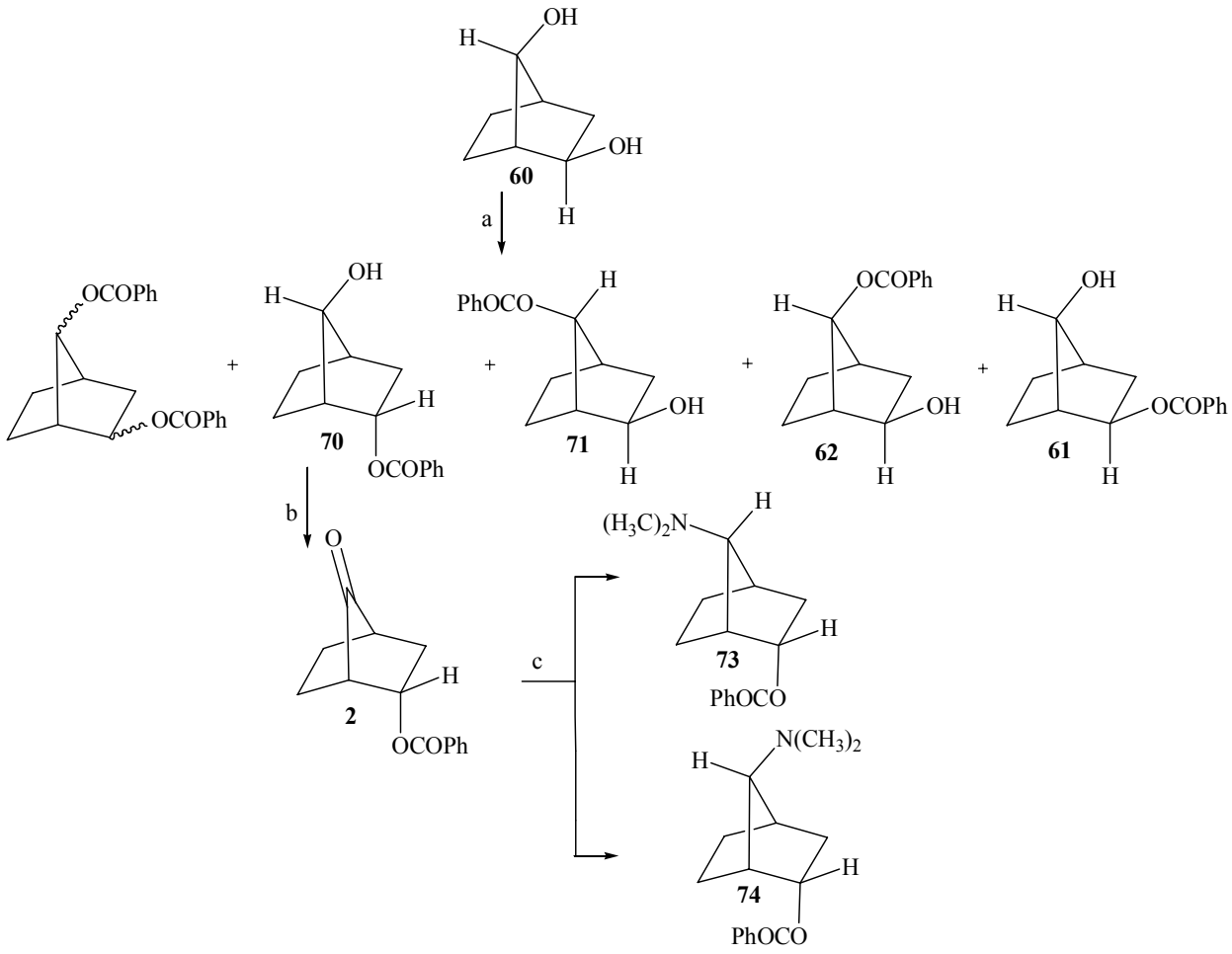
The approach used to synthesize amino norboranyl benzoates (**73** and **74**) is shown in Figure 6.3. Diol **60** was treated with triphenyl phosphine, benzoic acid, and diethylazodicarboxylate (DEAD) in a Mitsunobu reaction in an effort to invert the

stereochemistry at the C-2 and C-7 positions while placing a benzoate directly on the bicycle. A 2:1:1:2 mixture (determined by $^1$H NMR spectroscopy) of benzoates **70**, **71**, **61**, **62**, and dibenzoates was obtained and separated by column chromatography. For benzoate **70**, a *doublet of triplets* at δ 5.63 ppm and a *doublet* at δ 4.25 were assigned to the proton α to the benzoate and to the carbinol proton, respectively. Benzoate **70** was treated with DMSO and oxalyl chloride in a Swern oxidation to give keto ester **72**. The $^1$H NMR spectrum of **72** has a doublet for the carbinol proton at δ 4.25 and a *doublet of doublet of doublet of doublets* for the proton α to the benzoate to δ 5.40 ppm. Keto ester **72** was reductively aminated using sodium cyanoborohydride to obtain amino benzoates **73** and **74**, which were separated by column chromatography. The relative stereochemical assignment of benzoates **73** and **74** was completed (Appendix P)




Reagents: a) $HClO_4$, $H_2O$; b) benzoyl chloride, DMAP, pyridine, $CH_2Cl_2$; c) DMSO, oxalyl chloride, $Et_3N$, $CH_2Cl_2$; and d) $NH(CH_3)_2 \cdot HCl$, $Et_3N$, $NaCNBH_3$, $CH_2Cl_2$.

**Figure 5.2.** Synthesis of amino[2.2.1]benzoates **66-69**.




Reagents: a) TPP, DEAD, benzoic acid, THF; b) DMSO, oxalyl chloride, $Et_3N$, $CH_2Cl_2$; and c) $NH(CH_3)_2 \cdot HCl$, $Et_3N$, $NaCNBH_3$, $CH_2Cl_2$.

**Figure 5.3.** Synthesis of Amino[2.2.1]benzoates **73** and **74**.

## Pharmacology

Benzoates **66-69** and **73-74** were submitted for pharmacological testing and the results are pending.

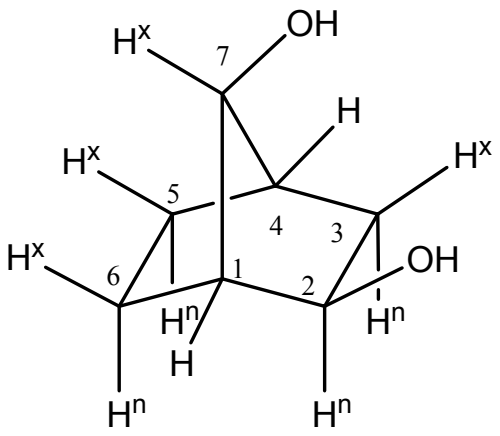
## Conclusions

A series of new [2.2.1]bicycloheptanes, benzoates **66-69** and **73-74**, were synthesized using epoxynorbornane as the scaffold. The bicycle undergoes a non-classical carbocation rearrangement to form a *syn* diol. This strategically places an oxygen substituent at the C-2 and C-7 position of the bicycloheptane skeleton. This was used to introduce a benzoate and an amine moiety. The benzoate and amine substituents were exchanged so as to place the nitrogen on the one-carbon bridge in one set of regioisomers with the benzoate at the C-2 position. In the other set of regioisomers the nitrogen is placed at the C-2 position and the benzoate on the one-carbon bridge. The pharmacology data is still pending for benzoates **66-69** and **73-74**. The new substitution pattern on the bicycle, with the amine at C-2 or C-7 and the benzoate at C-2 or C-7, will allow for a direct comparison with other benzoates synthesized.

## Experimental Section

**General Methods.** The general methods can be found in the experimental section of Chapter 2.

**2-*endo*-7-*exo*-bicyclo[2.2.1]heptane diol (60)**. A catalytic amount of perchloric acid (2 drops) was added to a stirred solution of *exo* epoxy norbornane (25 g, 0.227 mol) in $H_2O$ (150 mL). The mixture was heated to 60 °C for 20 min, cooled to room temperature, and extracted with $CH_2Cl_2$ (3 x 150 mL). The combined extracts were dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure to afford the crude product (22 g). The final product was obtained by column chromatography (silica, 1:1 ethyl acetate:hexane, $R_f$= 0.44) as a white solid (15 g, 53% yield) mp 168.5-170.5 °C, lit. 179.5-181 °C[2]. $^1$H NMR ($D_2O$): δ 0.79-0.91 (m, 2H, C-6endo, C-7endo), 1.23-1.46 (m, 2H, C-6exo, C-7exo), 1.59-1.64 (dm, *J*= 13.8 Hz, 1H, C-3exo), 1.71-1.78 (dd, *J*= 13.8, 7.5 Hz, 1H, C-3endo), 1.90 (d, *J*= 3.3 Hz, 1H, C-1), 1.99 (br s, 1H, C-4), 3.70 (br d, *J*= 6.6 Hz, 1H, C-2endo), 3.84 (s, 1H, C-5). $^{13}$C NMR ($D_2O$): δ 21.72, 24.84, 38.77, 40.29, 46.23, 75.76, 79.89.



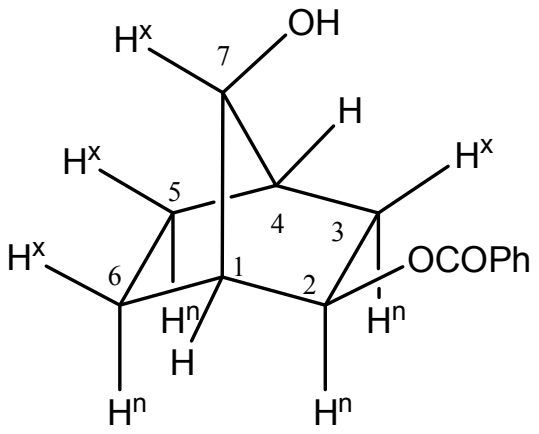

n= endo
x=exo

**Benzoylbicyclo[2.2.1]heptanol (61** and **62).** Diol **60** (5.9 g, 46 mmol) was added to a stirred solution of benzoyl chloride (5.35 mL, 46.1 mmol), pyridine (11.52 mL, 92.2 mmol), and DMAP (60 mg, 0.49 mmol) in $CH_2Cl_2$ (100 mL). The mixture was stirred overnight at room temperature and $H_2O$ (mL) was added. The mixture was extracted with $CH_2Cl_2$ (3 x 100 mL), the organic extracts were combined, dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to afford 9.9 g of a mixture of benzoates **61** and **62**, dibenzoate **63**, and diol **60** in a 25:51:23:1 ratio. Recrystallization of the mixture from ethyl acetate:hexane gave benzoate **62** as colorless solid (1.2 g, 34% yield).The solvent was removed from the mother liquor and chromatographed (silica gel, 1:1 ethyl acetate:hexane eluant) to obtain dibenzoate (2.5 g), benzoate **61** (3.3 g, 46% yield, $R_f$= 0.55) as a yellow oil and benzoate **62** (0.520 g, 14% yield, $R_f$= 0.52) as a white solid. The crude mixture of benzoates and dibenzoate can be used without further purification.

*7-endo-Benzoylbicyclo[2.2.1]hepta-2-exo-ol* (**62**). mp 106-107 °C, lit. 102-104 °C[1]. $^1$H NMR ($CDCl_3$): δ 1.25-1.09 (m, 2H, C-6endo, C-5endo) 1.75-1.63 (m, 2H, C-

6exo, C-5exo), 1.87 (dm, *J*= 14.1 Hz, 1H, C-3exo), 2.05 (dd, *J*= 14.1, 7.5 Hz, 1H, C-3endo), 2.41 (d, *J*= 3 Hz, 1H, C-4), 2.49 (br s, 1H, C-1), 3.92 (dd, *J*= 6.6, 1.5 Hz, 1H, C-7endo), 5.08 (s, 1H, C-2), 7.45 (t, *J*= 7.5 Hz, 2H, $Ar_{3,5}$), 7.57 (t, *J*= 7.5 Hz, 1H, $Ar_4$), 7.99 (d, *J*= 7.2 Hz, 2H, $Ar_{2,6}$). $^{13}C$ NMR ($CDCl_3$): δ 21.98, 24.75, 38.73, 40.99, 45.59, 75.75, 82.19 (aliphatic), 128.47, 129.32, 129.88, 133.04 (aromatic), 165.85 (OC=O).

*2-exo-Benzoylbicyclo[2.2.1]hepta-7-endo-ol* (**61**). $^1H$ NMR ($CDCl_3$): δ 1.08-1.27 (m, 2H, C-6endo, C-5endo) 1.55-1.95 (m, 4H, C-6exo, C-5exo, C-3, OH), 2.10 (m, 1H, C-3), 2.27 (s, 1H, C-1/C-4), 2.38 (d, *J*= 4.5 Hz, 1H, C-1/C-4), 4.05 (s, 1H, C-7), 5.03 (m, 1H, C-2), 7.42 (t, *J*= 7.5 Hz, 2H, $Ar_{3,5}$), 7.58 (t, *J*= 7.5 Hz, 1H, $Ar_4$), 7.97 (d, *J*= 7.2 Hz, 2H, $Ar_{2,6}$). $^{13}C$ NMR ($CDCl_3$): δ 22.18, 24.96, 36.89, 40.76, 44.88, 78.76, 80.47 (aliphatic), 128.36, 129.35, 130.03, 132.98 (aromatic), 166.05 (OC=O).




n= endo
x=exo

**Benzoylbicyclo[2.2.1]heptanones (64 and 65)**. Dimethylsulfoxide (15.6 mL, 0.22 mol) was added dropwise to a stirred solution of oxalyl chloride (8.0 mL, 91.6 mmol) in $CH_2Cl_2$ (80 mL) at –78 °C. The solution was stirred for 20 min and a solution of crude benzoates **60** and **61** and dibenzoate (8.50 g, 36.7 mmol) in 20 mL of $CH_2Cl_2$ was added dropwise to the mixture. Stirring was continued for another 20 min at –78 °C, after which triethylamine (51 mL, 0.37 mmol) was added slowly and the mixture was allowed to warm to room temperature. The mixture was diluted with $H_2O$ (50 mL) and extracted with $CH_2Cl_2$ (3 x 150 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo to obtain a 1:1:1 ratio of ketone **64** to ketone **65** to benzoate as a yellow oil (15 g). Silica gel chromatography using 4:1 hexane:ethyl acetate eluant furnished pure samples of keto benzoate **64** (1.7 g, 40% yield, $R_f$= 0.53) as a pale yellow oil and keto benzoate **65** (318 mg, 15% yield, $R_f$= 0.47) as a pale yellow solid.

*2-exo-Benzoylbicyclo[2.2.1]hepta-7-one (**64**)*. $^1$H NMR ($CDCl_3$): δ 1.34-1.54 (m, 2H, C-6endo, C-5endo), 1.68-1.91 (m, 2H, C-6exo, C-5exo), 1.91-1.95 (m, 2H, C-3exo, C-1 or C-4), 2.03 (d, *J*= 5.4 Hz, 1H, C-1 or C-4), 2.09 (ddd, *J*= 15, 8, 1.98 Hz, 1H, C-3endo), 5.17 (ddd, *J*= 8, 2.1, 0.9 Hz, 1H, C-2), 7.24 (t, *J*= 8.1 Hz, 2H, $Ar_{3,5}$), 7.37 (tt, *J*= 7.2, 1.2 Hz, 1H, $Ar_4$), 7.82 (dt, *J*= 7.2, 1.8 Hz, 2H, $Ar_{2,6}$). $^{13}$C NMR ($CDCl_3$): δ 18.63, 22.96, 35.25, 43.28, 72.11 (aliphatic), 128.24, 129.51, 129.61, 133.07 (aromatic), 165.64 (OC=O), 213.88 (C=O).

*7-endo-Benzoyl [2.2.1]bicycloheptan-2-one (**65**)*. mp 106-107 °C. $^1$H NMR ($CDCl_3$): δ 1.51-1.65 (m, 2H, C-6endo, C-5endo) 1.95-2.19 (m, 3H, C-6exo, C-5exo, C-3endo), 2.56 (dd, *J*= 17.7, 4.5 Hz, 1H, C-3exo), 2.77 (br s, 1H, C-1), 2.81-2.90 (m, 1H, C-4), 5.25 (q, *J*= 1.5 Hz, 1H, C-7), 7.43 (tt, *J*= 7.5, 1.5 Hz, 2H, $Ar_{3,5}$), 7.57 (tt, *J*= 7.8, 1.5 Hz, 1H, $Ar_4$), 7.99 (dd, *J*= 8.4, 1.5 Hz, 2H, $Ar_{2,6}$). $^{13}$C NMR ($CDCl_3$): δ 20.55, 22.93, 24.78, 38.03, 41.25, 52.10, 80.37 (aliphatic), 128.32, 129.33, 129.45, 133.19 (aromatic), 165.79 (OC=O), 214.83 (C=O).

**7-(*N*,*N*-Dimethylamino)bicyclo[2.2.1]hepta-7-*exo*-yl benzoates (66** and **67).** Ketone **64** (0.638 g, 2.77 mol) was added to a stirred solution of dimethylamine (1.36 g, 16.6 mmol), triethylamine (4.6 mL, 33.3 mmol), sodium cyanoborohydride(1.22 g, 19.4 mmol), and 4 Å molecular sieves (3g) in methanol (50 mL). The mixture was stirred for 3 d, filtered through celite, and the solvent was removed under reduced pressure. $CH_2Cl_2$ (150 mL) was added to the residue and the solution was washed with $K_2CO_3$ (3 x 50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo to obtain a 3:2 ratio of amine **66** and amine **67** as a pale yellow oil (0.60 g). Silica gel chromatography using 9:1 ethyl acetate:methanol eluant furnished amino benzoate **66** (181 mg, 38% yield, $R_f$= 0.68) as a colorless oil and amino benzoate **67** (60 mg, 25% yield, $R_f$= 0.61) as a pale yellow oil.

*7-endo-(N,N-Dimethylamino) [2.2.1]bicyclohepta-2-exo-yl benzoate (**66**)*. $^1$H NMR ($CDCl_3$): δ 1.13-1.30 (m, 2H, C-6endo, C-5endo) 1.52-1.71 (m, 2H, C-6exo, C-5exo), 1.90 (dd, *J*= 12.9, 7.8 Hz, 1H, C-3endo), 2.11 (dq, *J*= 12.6, 3.6 Hz, 1H, C-3exo),

2.24 (br s, 6H, ($N(CH_3)_2$), 2.45 (br d, *J*= 4.5 Hz, 1H, C-1/C-4), 2.58 (d, *J*= 5.7 Hz, 1H, C-1/C-4), 4.88 (dd, *J*= 7.2, 3.3 Hz, 1H, C-2), 7.41 (tt, *J*= 7.5, 1.5 Hz, 2H, $Ar_{3,5}$), 7.52 (tt, *J*= 7.2, 1.2 Hz, 1H, $Ar_4$), 8.03 (dt, *J*= 7.2, 1.2 Hz, 2H, $Ar_{2,6}$). $^{13}C$ NMR ($CDCl_3$): δ 24.86, 26.40, 37.32, 38.61, 42.84, 43.21, 45.23, 76.10, 78.18 (aliphatic), 128.07, 129.44, 130.94, 132.40 (aromatic), 166.41 (OC=O).

***66·HCl.*** mp 153-163 ˚C, decomposed, yellow crystalline solid. $^1H$ NMR ($D_2O$): δ 1.30-1.33 (m, 2H, C-6endo, C-5endo) 1.55-1.78 (m, 2H, C-6exo, C-5exo), 1.90 (dddd, *J*= 15.2, 6.9, 4.2, 3 Hz, 1H, C-3exo), 2.16 (dd, *J*= 15.6, 7.8 Hz, 1H, C-3endo), 2.57 (t, *J*= 3.6 Hz, 1H, C-4), 2.81 (d, *J*= 4.2 Hz, 1H, C-1), 2.86 (s, 6H, ($N(CH_3)_2$), 3.27 (s, 1H, C-5), 4.96 (dd, *J*= 7.8, 3 Hz, 1H, C-2), 7.40 (tt, *J*= 8.1, 1.5 Hz, 2H, $Ar_{3,5}$), 7.55 (tt, *J*= 7.5, 1.5 Hz, 1H, $Ar_4$), 7.84 (dt, *J*= 7.2, 1.2 Hz, 2H, $Ar_{2,6}$). IR (neat): 2960, 2683, 1729, 1281, 1123, 762 $cm^{-1}$. MS (EI) M+ 259.

*7-exo-(N,N-Dimethylamino) [2.2.1]bicyclohepta-2-exo-yl benzoate (**67**)*. $^1H$ NMR ($CDCl_3$): δ 1.09-1.25 (m, 2H, C-6endo, C-5endo) 1.73 (ddd, *J*= 12, 4, 3 Hz, 1H, C-3exo), 1.76-1.95 (m, 2H, C-6exo, C-5exo), 1.91 (dd, *J*= 14.1, 7.8 Hz, 1H, C-3endo), 2.26 (br s, 6H, ($N(CH_3)_2$, C-4), 2.38 (br d, *J*= 4.5 Hz, 1H, C-1), 2.41 (s, 1H, C-5), 4.84 (dd, *J*= 7.5, 2.7 Hz, 1H, C-2), 7.44 (tt, *J*= 7.8, 1.5 Hz, 2H, $Ar_{3,5}$), 7.55 (tt, *J*= 7.5, 1.5 Hz, 1H, $Ar_4$), 8.03 (dt, *J*= 7.2, 1.5 Hz, 2H, $Ar_{2,6}$). $^{13}C$ NMR ($CDCl_3$): δ 22.61, 25.69, 37.44, 38.62, 44.04, 44.74, 73.64, 77.34 (aliphatic), 128.19, 129.38, 130.59, 132.67 (aromatic), 165.91 (OC=O).

***67·HCl.*** mp 230-240 ˚C; 210 ˚C decomposed, pale yellow crystalline solid. $^1$H NMR ($D_2O$): δ 1.40-1.55 (m, 2H, C-6endo, C-5endo), 1.56-1.74(m, 2H, C-6exo, C-5exo), 1.74-1.85 (dm, *J*= 15 Hz, 1H, C-3endo), 2.00 (dd, *J*= 14.1, 7.5 Hz, 1H, C-3exo), 2.57 (s, 1H, C-1/C-4), 2.70 (br d, *J*= 3.9 Hz, 1H, C-1/C-4), 2.82 (s, 6H, ($N(CH_3)_2$), 3.50 (br s, 1H, C-7), 4.82 (dddd, *J*= 7.8, 2.4, 0.6, 0.3 Hz, 1H, C-2), 7.44 (tt, *J*= 7.2, 1.2 Hz, 2H, $Ar_{3,5}$), 7.59 (tt, *J*= 7.5, 1.2 Hz, 1H, $Ar_4$), 7.94 (dt, *J*= 7.2, 2.1 Hz, 2H, $Ar_{2,6}$). IR (neat): 2966, 2881, 2683, 1722, 1274, 1116, 721 $cm^{-1}$. MS (EI) M+ 259.

**2-(*N*,*N*-Dimethylamino)bicyclo[2.2.1]hepta-7-*endo*-yl benzoates (68** and **69).** The same procedure provided above to make 7-amino-2-*endo*-norboranyl benzoates **66** and **67** was used to obtain a 10:1 ratio of amino benzoate **68** and amino benzoate **69** as a yellow oil. Silica gel chromatography using 1:1:1 chloroform:methanol:ethyl acetate eluant furnished amino benzoate **68** (400 mg, 60% yield, $R_f$= 0.043) as a colorless oil and amino benzoate **69** (60 mg, 10% yield, Rf= 0.36) as a pale yellow oil.

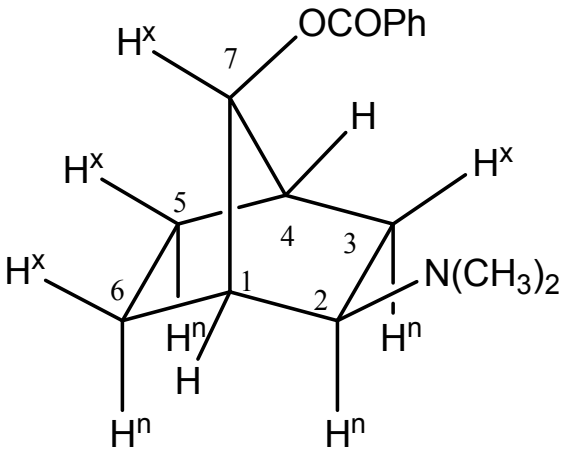
*2-endo-(N,N-Dimethylaminobicyclo[2.2.1]hepta-7-exo-yl benzoate (**68**)*. $^1$H NMR ($CDCl_3$): δ 1.27 (ddd, *J*= 12.6, 4.5, 1.2 Hz, 1H, C-3endo) 1.45 (ddd, *J*= 11.7, 10.2, 4.8 Hz, 1H, C-5endo), 1.56 (dtd, *J*= 12, 4.5, 1.2 Hz, 1H, C-6endo), 1.76 (dddd, *J*= 15.9, 11.4, 5.2, 4 Hz, 1H, C-5exo), 1.94 (ddd, *J*= 12.3, 10.5, 4.8 Hz, 1H, C-6exo), 2.15 (dddd, *J*= 15.3, 9.9, 5.1, 3 Hz, 1H, C-3exo), 2.24 (s, 6H, ($N(CH_3)_2$), 2.32 (t, *J*= 4.8 Hz, 1H, C-4), 2.45 (t, *J*= 3 Hz, 1H, C-1), 2.65 (dt, *J*= 8.7, 4.5 Hz, 1H, C-2), 5.09 (br d, *J*= 1.8, 1H, C-7), 7.45 (tt, *J*= 8.1, 1.8 Hz, 2H, $Ar_{3,5}$), 7.57 (tt, *J*= 7.2, 1.5 Hz, 1H, $Ar_4$), 8.04 (dt, *J*= 7.5, 1.5

Hz, 2H, $Ar_{2,6}$). $^{13}C$ NMR ($CDCl_3$): δ 18.45, 26.69, 34.56, 38.97, 41.92, 45.06, 66.58, 82.84 (aliphatic), 128.22, 129.38, 130.29, 132.78 (aromatic), 166.05 (OC=O).

***68·HCl***. mp 260-268 ˚C; 237 ˚C decomposed, white solid. $^1H$ NMR ($D_2O$): δ 1.34-1.50 (m, 3H), 1.75-1.95 (m, 2H), 2.35-2.45 (m, 2H), 2.60-3.00 (m, 7H), 3.75 (br s, 1H, C-2), 5.06 (s, 1H, C-7), 7.43 (t, J= 6.3 Hz, 2H, $Ar_{3,5}$), 7.59 (t, J= 7.5 Hz, 1H, $Ar_4$), 7.91 (d, J= 6.9 Hz, 2H, $Ar_{2,6}$). IR (neat): 2956, 2871, 2825, 2779, 1712, 1467, 1305, 1282, 1113, 714 $cm^{-1}$. MS (EI) M+259.

*2-exo-(N,N-Dimethylamino)bicyclo[2.2.1]hepta-7-exo-yl benzoate (**69**)*. $^1H$ NMR ($CDCl_3$): δ 1.10-1.25 (m, 2H, C-5endo, C-6endo), 1.59-1.78 (m, 3H, C-5exo, C-6exo, C-3endo), 1.96 (ddd, *J*= 14.1, 4.2, 2.4 Hz, 1H, C-3exo), 2.02 (dd, *J*= 12.3, 5.1 Hz, 1H, C-2endo), 2.09 (s, 6H, $(N(CH_3)_2)$, 2.35 (t, *J*= 3.9 Hz, 1H, C-1 or C-4), 2.63 (dd, *J*= 3.9, 1.5 Hz, 1H, C-1 or C-4), 4.83 (br s, 1H, C-7), 7.38 (tt, *J*= 7.8, 1.8 Hz, 2H, $Ar_{3,5}$), 7.50 (tt, *J*= 7.2, 1.2 Hz, 1H, $Ar_4$), 8.05 (dt, *J*= 6.9, 1.2 Hz, 2H, $Ar_{2,6}$). $^{13}C$ NMR ($CDCl_3$): δ 24.78, 25.39, 36.19, 39.08, 40.48, 44.22, 71.23, 81.05 (aliphatic), 128.01, 129.71, 131.08, 132.32 (aromatic), 166.85 (OC=O).

***69·HCl***. mp 208-211˚C. $^1H$ NMR ($CDCl_3$): δ 1.20-1.70 (m, 4H0, 1.70-2.00 (m, 2H), 2.00-2.45 (m, 2H), 2.45-3.00 (m, 7H), 4.93 (s, 1H, C-7), 7.47 (br s, 2H, $Ar_{3,5}$), 7.58 (br s, 1H, $Ar_4$), 7.99 (br s, 2H, $Ar_{2,6}$), 12.12 (br s, 1H, HCl). IR (neat): 29730, 2664, 2624, 1716, 1275, 1110, 722 $cm^{-1}$. MS (EI) M+259.




n= endo
x=exo

**2-*endo*-Benzoylbicyclo[2.2.1]hepta-7-one (72).** Benzoic acid (0.954 g, 7.81 mmol) was added to a stirred solution of diol **60** (1.0 g, 7.81 mmol), diethylazodicarboxylate (2.72 g, 15.6 mmol), and triphenylphosphine (4.10 g, 15.6 mmol) in THF (50 mL). The mixture was stirred for 24 h and the solvent was removed under reduced pressure to obtain a dark red oil (9 g). Silica gel chromatography using 4:1 hexane:ethyl acetate eluant furnished crude alcohol **70** (1.5 g, $R_f$= 0.25)which was used without further purification.

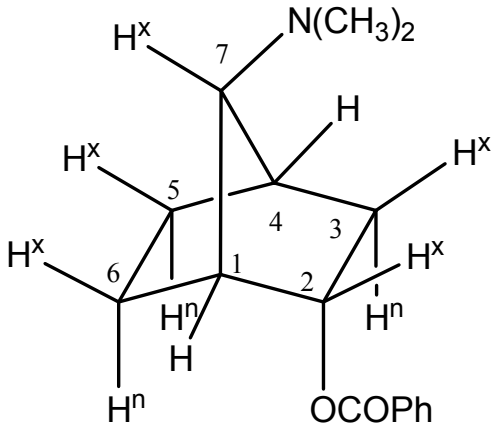
The same procedure provided above to make benzoyl norboranones **64** and **65** was used to obtain crude ketone **72** as a yellow oil. Silica gel chromatography using chloroform provided keto benzoate **72** (100% yield) as a white solid. $^1$H NMR ($CDCl_3$): δ 1.60-1.85 (m, 3H), 1.90-2.25 (m, 2H), 2.45-2.60 (m, 2), 5.40 (dddd, *J*= 8.4, 6.3, 3.3, 2.1 Hz, 1H, C-2exo), 7.41 (t, *J*= 7.5 Hz, 2H, $Ar_{3,5}$), 7.52 (t, *J*= 7.2 Hz, 1H, $Ar_4$), 8.03 (d, *J*= 7.2 Hz, 2H, $Ar_{2,6}$). $^{13}$C NMR ($CDCl_3$): δ 15.60, 23.76, 34.63, 40.14, 43.95, 68.48 (aliphatic), 128.36, 129.41, 129.68, 133.13 (aromatic), 165.78 (OC=O), 212.01 (C=O).

**7-(N,N-Dimethylamino)bicyclo[2.2.1]hepta-7-*endo*-yl benzoates** (**73** and **74**). The same procedure described above to make benzoates **66** and **67** was used to obtain a

1:1 ratio of amino benzoate **73** and amino benzoate **74** as a yellow oil. Silica gel chromatography using 10:1 ethyl acetate:methanol eluant furnished amino benzoate **73** (25 mg, 25% yield, $R_f$= 0.60) as a colorless oil and crude amino benzoate **74** (20 mg, 20% yield, $R_f$= 0.72) as a pale yellow oil. Amino benzoate **74** (20 mg, 2.90 mmol) was converted to the HCl salt and recrystallized from ethyl acetate:$CH_2Cl_2$ to obtain pure product (10 mg, 50% yield).

*7-exo-(N,N-Dimethylamino) [2.2.1]bicyclohepta-2-endo-yl benzoate* (**73**). $^1$H NMR ($CDCl_3$): δ 1.23 (dd, J= 13.2, 3.9 Hz, 1H, C-3endo) 1.33 (ddd, J= 15.6, 9.0, 3.6 Hz, 1H), 1.70 (tt, *J*= 12.9, 3.9 Hz, 1H, C-53exo or C-6exo), 1.79-190 (m, 2H), 2.13 (s, 1H, C-1 or C-4), 2.16-2.22 (m, 1H0, 2.20 (s, 6H, ($N(CH_3)_2$), 2.62 (t, *J*= 4.2 Hz, 1H, C-7endo), 5.16 (ddd, *J*= 8.1, 6.3, 3.3 Hz, 1H, C-2), 7.41 (t, *J*= 7.8 Hz, 2H, $Ar_{3,5}$), 7.53 (tt, *J*= 7.8, 2.1 Hz, 1H, $Ar_4$), 8.02 (d, *J*= 7.2 Hz, 2H, $Ar_{2,6}$). $^{13}$C NMR ($CDCl_3$): δ 18.97, 26.98, 36.50, 38.91, 43.19, 44.36, 74.28, 74.32 (aliphatic), 128.24, 129.39, 130.38, 132.75 (aromatic), 166.25 (OC=O).

***73·HCl***. mp 190-196 ˚C, decomposed. $^1$H NMR ($CDCl_3$): δ 1.40-1.80 (m, 2H), 2.04-2.08 (m, 1H), 2.22-2.40 (m, 2H), 2.41-2.59 (m, 2H), 2.80-3.10 (m, 8H), 5.21 (br s, 1H, C-2), 7.44 (t, *J*= 8.1 Hz, 2H, $Ar_{3,5}$), 7.57 (t, *J*= 7.5 Hz, 1H, $Ar_4$), 8.00 (d, *J*= 7.2 Hz, 2H, $Ar_{2,6}$), 11.23 (br s, 1H, HCl). IR (neat): 2968, 2659, 2624, 1712, 1284, 1115, 722 $cm^{-1}$. MS (EI) M+259.




n= endo
x=exo

*7-endo-(N,N-Dimethylamino) [2.2.1]bicyclohepta-2-endo-yl benzoate (**74·HCl**).*

mp 215-218 ˚C. $^{1}$H NMR ($CDCl_3$): δ 1.45-1.96 (m, 6H), 2.49 (t, J= 3 Hz, 1H), 2.88 (d, *J*= 4.2 Hz, 3H, N(CH3), 2.94 (d, *J*= 4.5 Hz, 3H, $N(CH_3)$), 3.02-3.20 (m, 2H, C-7), 5.70-5.80 (m, 1H, C-2), 7.40 (t, *J*= 7.5 Hz, 2H, $Ar_{3,5}$), 7.53 (t, *J*= 7.2 Hz, 1H, $Ar_4$), 7.96 (d, *J*= 7.8 Hz, 2H, $Ar_{2,6}$), 11.27 (br s, 1H). IR (neat): 2966, 2710, 2453, 1722, 1657, 1281, 1117, 722 $cm^{-1}$. MS (EI) M+259.

## References

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2. Crandall, Jack.K. Rearrangements of Norbornene Oxide, JOC, 1964, 29, 2830-2833.

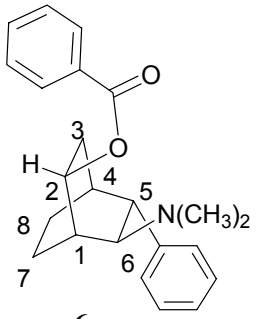
# CHAPTER VI

## SYNTHESIS OF 2-BENZOYL-5-((*N*,*N*-DIMETHYLAMINO)METHYL)-6-PHENYL[2.2.1]BICYCLOHEPTANES

### Introduction

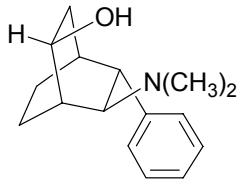
Work previously pursued in our group on 2-substituted-6-amino-5-phenylbicyclo[2.2.2]octanes[1] showed that the incorporation of an oxygen functionality at the C-2 position of the bicycle has the following trends: *endo*-benzoate-*endo*-amine **6** was more potent than the *endo*-alcohol-*endo*-amine, which was more potent than the C-2 ketone (Figure 6.1). The incorporation of the benzoyl ester enhanced the potency of these compounds. In another set of experiments previously completed in our group,[2] amines **16** and **17** were synthesized. Both compounds contain a *trans* stereochemical arrangement at C-2 and C-3 with the only difference being the amino methyl substituent is *endo* in amine **16** and *exo* in amine **17**. Amines **16** and **17** were of interest because of the difference in the inhibitor potency in [$^3$H]WIN 35,428 (WIN) binding at the DAT. This relatively minor variation in structure leads to a large difference in potency. The $IC_{50}$ for the *trans endo*-amine **16** is 515 nM, whereas the *trans exo*-amine **17** is 2510 nM, a 5-fold increase. The work described in this chapter allows for the determination of the effect of incorporating a benzoate onto the [2.2.1]bicyclic scaffold of amines **16** and **17**. In

addition, the 4-chlorobenzoate analogs were synthesized since it is known that the incorporation of a halogen on the phenyl ring generally increases the potency relative to the unsubstituted phenyl compound.[2] The [$^3$H]WIN 35,428 binding and DA uptake will indicate the importance of each benzoate and the 4-chlorophenyl at the C-2 position of the [2.2.1]bicycloheptane.

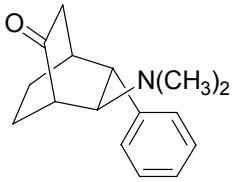



**6**

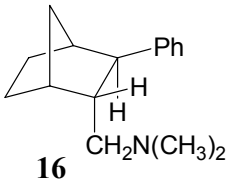
$IC_{50}$= 270 nM



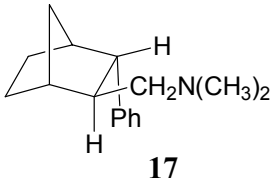

$IC_{50}$= 2040 nM




$IC_{50}$= 4010 nM




**16**
trans endo
WIN $IC_{50}$= 515 nM

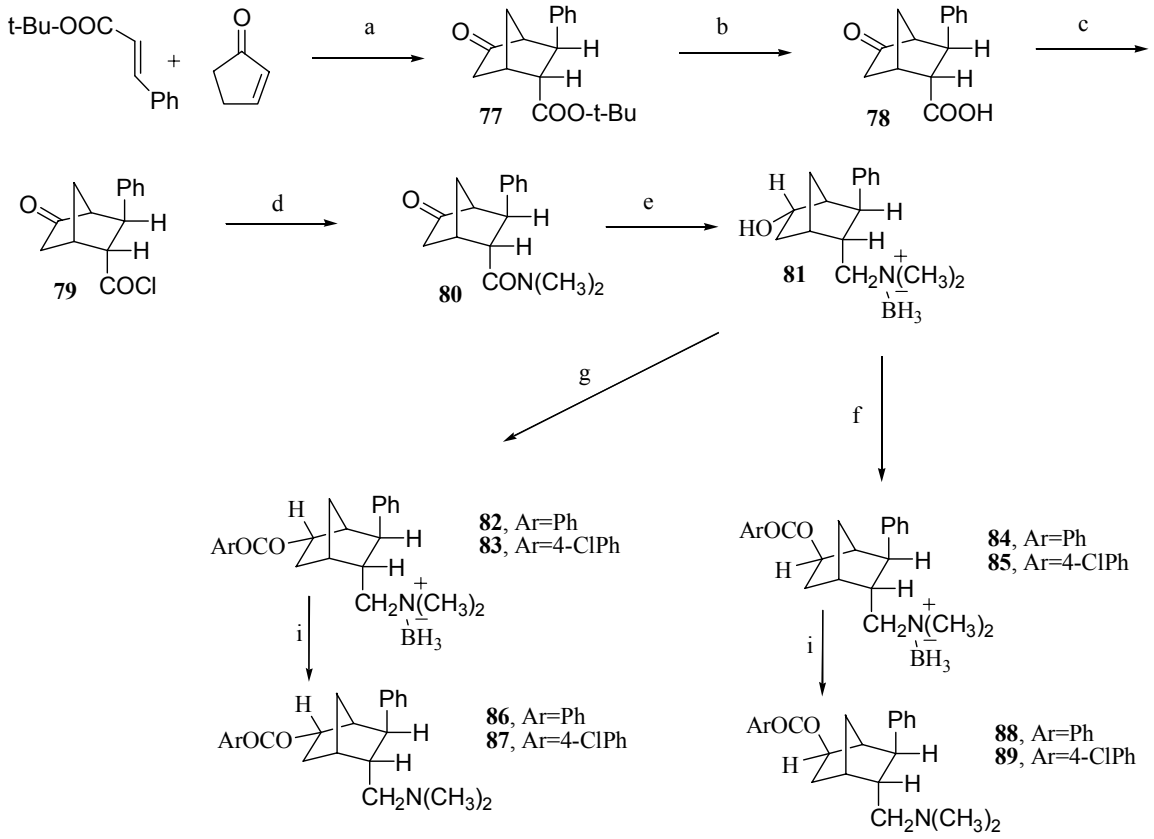



**17**
trans exo
WIN $IC_{50}$= 2510 nM

**Figure 6.1.** Structures and [$^3$H]WIN 35,428 binding data.[1,2]

## Chemistry

An attractive route which places a ketone on the unsubstituted two-carbon bridge of 2-amino-3-phenylbicyclo[2.2.1]heptanes is shown in Figure 6.2. A double-Michael addition of *tert*-butyl acrylate to 2-cyclopentenone provides the *trans* bicyclic ketone **77**.[3] The appearance of a *doublet* at δ 3.51 ppm in the $^1$H NMR spectrum of **77** with a coupling constant of 5.1 Hz for the proton α to the phenyl is consistent with retention of the *trans* stereochemical arrangement. The *t*-butyl ester **77** was hydrolyzed to the carboxylic acid by treatment with trifluoroacetic acid. A complete structure assignment of acid **78** was completed (Appendix N). Acid **78** was converted to an acid chloride with oxalyl chloride (**79**, monitored by the appearance of peaks in the IR at 1796 and 1757 cm$^{-1}$), aminated with dimethylamine, and recrystallized from ethyl acetate to give amide **80**. The $^1$H NMR spectrum shows two singlets at δ 3.06 ppm and δ 2.97 ppm that integrate to 3 protons each for the dimethyl amide moiety. Amide **80** was reduced with borane to provide exclusively the *endo*-hydroxy amine **81**. The hydride was delivered to the least sterically hindered face of the bicycle to provide only the *endo*- alcohol **81**. The $^1$H NMR spectrum has a peak at δ 4.32 ppm which we assign to the carbinol proton at C-2. The multiplicity, a *doublet of triplets*, is consistent with a proton in an *exo* position which couples with the *exo* proton at C-3 with a large coupling constant (10.5 Hz), couples to the *endo* proton at C-3 (4.2 Hz), and couples to the bridgehead proton at C-1 (4.2 Hz). The borate salt of the amine was formed during the reduction of amide **80** to amine **81** but was not cleaved during the acidic work-up. The synthesis was continued with the borate salt. Treatment of the *endo*-hydroxy amine **81** with the appropriate benzoyl




Reagents: a) LDA, THF, - 78 °C; b) TFA; c) oxalyl chloride, DMF, $CH_2Cl_2$; d) $NH(CH_3)_2$, $CH_2Cl_2$, e) $BH_3$, THF, -78 °C; f) benzoic acid, DEAD, $PPh_3$, THF; and g) BnCl, $Et_3N$, DMAP, $C_6H_6$.

**Figure 6.1**. Synthesis of Trisubstitituted [2.2.1]bicycles **86-89**.

chloride gave the corresponding benzoates (**82** and **83**). The structure of benzoate **82** was resolved by x-ray analysis (Appendix O). Hydrolysis of the borate salts with a 3:1 acetone:1M HCl mixture gave the corresponding free amines (**86-87**). The *exo*-benzoate **84** and 4-chlorobenzoate **85** were obtained by Mitsunobu chemistry, using triphenylphosphine, diethylazodicarboxylate (DEAD), and benzoic acid or 4-chlorobenzoic acid. The final products, benzoates **88** and **89**, were purified by flash column chromatography.

## Pharmacology

Benzoates **86-89** were submitted for pharmacological testing. Results are still pending.

## Conclusions

Preliminary investigations in our group on 2-substituted-6-amino-5-phenylbicyclo[2.2.2]octanes[1] showed that the incorporation of a benzoate onto the [2.2.2]bicyclooctane increased the binding interaction at the DAT (Figure 6.1). Exploration on 2,3-disubstituted [2.2.1]bicycloheptanes pursued previously in our group[2] provided amines **16** and **17**, which were synthesized in an effort to further evaluate structure-activity relationships that probe the active site of the DAT. In pursuit of the most potent of these two amines, **16**, and utilizing the trend seen with the [2.2.2]bicyclooctanes, we incorporated a benzoyl ester onto the [2.2.1]bicycloheptane core. The approach we took involved synthesizing a series of trisubstituted [2.2.1]bicycloheptanes by double-Michael addition of *tert*-butyl acrylate and cyclopentenone. Based on the mechanism of the addition, only one product is obtained,

the *trans* ketone **77**. This gave the same stereochemistry as in amine **16** at the C-5 and C-6 stereocenters. Through a series of simple functional group interconversions, the *endo* and *exo* benzoates and 4-chlorobenzoates were obtained. The pharmacology results for benzoates **86-89** are still pending.

## Experimental Section

**General Methods.** The general methods can be found in the experimental section of Chapter 2.

***5-endo-tert*-Butoxycarbonyl- 6-*exo*-phenyl[2.2.1]bicyclohept-2-one (77).** 2-cyclopentenone (4.08 mL, 48.8 mmol) was added to a cooled (-78 ºC) stirred solution of lithium diisopropyl amide (1.8 M, 36.6 mL, 65.9 mmol) in 150 mL of anhydrous THF. The solution was stirred at –78 ºC for 1.5 h, and *tert*-butyl phenyl acrylate (4.98 mL, 24.4 mmol) was added. The reaction mixture was warmed to room temperature and stirred overnight. Distilled water (50 mL) was added to the reaction mixture and the THF was removed under reduced pressure. The residual aqueous layer was extracted with $CH_2Cl_2$ (3 x 75 mL), the organic extracts were combined and dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to afford crude product (8.84 g, 100% yield). The crude product was dissolved in 50 mL of $CH_2Cl_2$ and the solution was passed through a plug of silica gel to obtain 6.52 g of a light brown solid (94% yield). $^1$H NMR ($CDCl_3$): δ 1.45 (s, 9H, *t*-butyl), 1.86 (dd, *J*=10.5, 1.2 Hz, 1H, C-7), 2.10-2.21 (m, 3H, C-3, C-7), 2.84 (s, 1H, C-4), 3.02-3.11 (m, 2H, C-1, C-6), 3.51 (d, *J*=5.1, 1H, C-5), 7.20–7.35 (m, 5H, Ar). $^{13}$C NMR ($CDCl_3$): δ 28.07, 36.91, 39.82, 40.01, 43.50. 54.55, 56.53, 81.20 (aliphatic), 126.63, 126.92, 128.73, 142.43, 172.05, 214.90 (C=O).

***5-endo*-Carboxyl- 6-*exo*-phenyl[2.2.1]bicyclohept-2-one (78).** A mixture of keto ester **77** (6.52 g, 22.8 mmol) and trifluoroacetic acid ( 17 mL, 220 mmol) was stirred

for 2 d. The TFA was removed under reduced pressure to obtain crude product (6.35 g, 100% yield). The brown crude product was recrystallized from a 9:1 mixture of hexane:benzene to obtain **78** as a white crystalline solid. $^{1}$H NMR ($CDCl_3$): δ1.92 (d, *J*=10.5 Hz, 1H, C-7), 2.14–2.32 (m, 3H, C-3, C-7), 2.90 (s, 1H, C-4), 3.16 (s, 1H, C-1), 3.25 (t, *J*= 4.8 Hz, 1H, C-6), 3.53 (d, *J*=5.7, 1H, C-5), 7.20-7.37 (m, 5H, Ar). $^{13}$C NMR ($CDCl_3$): δ 37.04, 39.79, 40.25, 43.65, 53.33, 56.43 (aliphatic), 126.81, 126.99, 128.89, 141.46, 178.88, 215.56 (C=O). IR cm$^{-1}$ (neat): 3434, 1749, 1709.

***5-endo*-Carbonyl chloride- 6-*exo*-phenyl[2.2.1]bicyclohept-2-one (79)**. **O**xalyl chloride (4.83 mL, 55.2 mmol) and two drops of dimethylformamide was added to a mixture of acid **78** (6.35 g, 27.6 mmol) in $CH_2Cl_2$ (150 mL) at 0 °C. To was added. The reaction mixture was stirred for 4 h and the solvent was removed under reduced pressure to give 5.72 g of crude product (84% yield) which was used without further purification. $^{1}$H NMR ($CDCl_3$): δ 1.11 (dddd, *J*=15.9, 11.4, 4.8, 2 Hz, 1H, C-8endo), 1.25-1.38 (m, 2H, C-7endo, C-5exo) 1.49 (dddd, *J*=15.9, 9.9, 5.4, 3 Hz, 1H, C-8exo), 1.61 (septet, *J*=3 Hz, 1H, C-4), 1.66 (ddd, *J*=13.8, 9.6, 3 Hz, 1H, C-5endo) 1.71-1.87 (m, 2H, C-3) 2.17 (dddd, *J*=13.8, 11.4, 5.1, 3 Hz, 1H, C-7exo), 2.37 (q, *J*=3 Hz, 1H, C-1), 2.43 (br s, 1H, OH), 3.81-03.92 (m, 1H, C-6). $^{13}$C NMR ($C_6D_6$): δ 15.88, 24.52, 27.85, 36.30, 43.36, 51.63, 65.37 (aliphatic), 214.68 (C=O). IR (neat): 2982, 1796, 1757, 1169, 756, 707 cm$^{-1}$.

***5-endo*-Amido- 6-*exo*-phenyl[2.2.1]bicyclohept-2-one (80).** Dimethyl amine was added subsurface for 30 min to a mixture of acid chloride **79** (5.72 g, 23.1 mmol) in dry $CH_2Cl_2$ (200 mL) at 0 ºC. The reaction mixture was stirred overnight, followed by the

removal of the excess dimethyl amine under reduced pressure. $CH_2Cl_2$ (50 mL) was added to the mixture, and the solution was washed with $H_2O$ (3 x 20 mL), dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give 6.5 g of crude product (100% yield). The product was recrystallized from ethyl acetate to obtain a light brown solid, mp 110-113 ˚C. $^1$H NMR ($CDCl_3$): δ 1.89-2.01 (m, 2H), 2.22-2.33 (m, 2H), 2.85 (s, 1H), 2.97 (s, 3H, $N(CH_3)$), 2.99 (s, 1H), 3.06 (s, 3H, $N(CH_3)$) 3.29 (ddd, *J*=5.7, 4.2, 1.5 Hz, 1H ), 3.86 (d, *J*=6.0 Hz, 1H), 7.17-7.31 (m, 5H, Ar). $^{13}$C NMR ($CDCl_3$): δ 35.75, 36.94, 37.56, 38.88, 39.08, 43.77, 51.75, 55.82 (aliphatic), 126.28, 126.58, 128.53, 142.84, 171.13 ($C=ON(CH_3)_2$), 214.41 (C=O).

***5-endo*-((*N*,*N*-Dimethylamino)methyl)-6-*exo*-phenyl[2.2.1]bicycloheptan-*endo*-2-ol borate salt (81).** 1M borane in THF (98 mL, 101 mmol) was added to a mixture of amide **80** (6.5 g, 25.3 mmol) in THF (100 mL). The reaction was heated to reflux for 2 d, followed by the addition of 6 M HCl until the mixture was acidic (pH<2). The mixture was then made basic by addition of NaOH pellets and the solvent was removed under reduced pressure. Brine (30 mL) was added and the mixture was extracted with $CH_2Cl_2$ (3 x 75 mL), the organic extracts combined, dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to obtain 6 g of crude product. The crude product was dissolved in ethyl acetate (50 mL) and the solution was passed through a plug of silica gel. The solvent was removed to give **81** as a white solid (4.90 g, 73% yield). $^1$H NMR ($CDCl_3$): δ 1.2-1.32 (m, 1H, C-7), 1.45 (dd, *J*=11.7, 1.5 Hz, 1H, C-3), 1.80-1.96 (m, 2H, C-3, C-7), 2.04 (s, 1H, C-1), 2.40 (s, 3H, $N(CH_3)_2$), 2.47 (s, 3H, $N(CH_3)_2$), 2.49 (s, 1H, C-4 ), 2.64-2.78 (m, 1H, C-5), 2.97 (dd, *J*=13.5, 5.1 Hz, 1H, C-8),

3.08 (dd, *J*=6.9, 1.2 Hz, 1H, C-6), 3.15 (dd, *J*=13.2, 6.9 Hz, 1H, C-8), 4.32 (dt, *J*=10.5, 4.2 Hz, 1H, C-2), 7.16-7.31 (m, 5H, ar). $^{13}$C NMR ($CDCl_3$): δ 31.46, 36.97, 41.98, 43.79, 43.80, 51.24, 51.39, 52.36, 65.79, 72.27 (aliphatic), 126.11, 127.57, 128.56, 144.80.

***5-endo*-((*N*,*N*-Dimethylamino)methyl)-6-*exo*-phenyl[2.2.1]bicycloheptan-2-benzoylborate salts, (82 and 83)**. The transformation from alcohol **81** to benzoate **82** and **83** is illustrated. Alcohol **81** (333 mg, 1.29 mmol) in benzene (1 mL) was added to a solution of benzoyl chloride (237 μL, 2.04 mmol), triethylamine (948 μL, 6.8 mmol), dimethylaminopyridine (2 mg) in benzene (2 mL). The reaction mixture was heated to 50 °C for 2 d. The solvent was removed by reduced pressure, $CH_2Cl_2$ ( 40 mL) was added and the mixture was washed with saturated $NaHCO_3$ (3 x 30 mL). The organic layer was dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure to obtain 566 mg (100% yield) of crude product. The product was purified by column chromatography using $CH_2Cl_2$ as the eluant, followed by recrystallization from 7:2:1 hexane:$CH_2Cl_2$:ethyl acetate to give benzoate **83** (200 mg, 36% yield) as a white solid.

*5-endo-((N,N-Dimethylamino)methyl)-6-exo-phenylbicyclo[2.2.1]heptan-2-endo-benzoyl borate salt, (**82**)*. (125 mg, 30% yield, white solid). $^1$H NMR ($CDCl_3$): δ 1.53-1.60 (m, 2H, C-3, C-7endo), 1.96 (dt, *J*=10.8, 1.8 Hz, 1H, C-7), 2.17 (dddd, *J*=14.4, 10.2, 4.5, 1.8 Hz, 1H, C-7exo), 2.47 (s, 3H, $N(CH_3)_2$), 2.49 (s, 3H, $N(CH_3)_2$), 2.63 (s, 1H), 2.65 (s, 1H), 2.80 (m, 1H, C-5), 2.98 (d, *J*=6.9 Hz, 1H, C-6), 3.02 (dd, *J*=13.8, 4.5 Hz, 1H, C-8), 3.16 (dd, *J*=13.8, 6.9 Hz, 1H, C-8), 5.27 (dt, *J*=10.8, 4.5 Hz, 1H, C-2), 7.18-7.34 (m, 5H, Ar), 7.50 (tt, *J*=7.5, 1.5 Hz, 2H, Ar'$_{3,5}$), 7.61 (tt, J=7.2, 1.5 Hz, 1H,

Ar'$_4$), 8.1 (dd, *J*=7.2, 1.5 Hz, 2H, Ar'$_{2,6}$). $^{13}$C NMR ($CDCl_3$): δ 29.44, 36.53, 41.40, 43.04, 45.27, 49.07, 51.37, 52.09, 65.72, 75.49 (aliphatic), 126.45, 127.47, 128.54, 129.42, 130.15, 133.14, 143.66, 166.28 (C=O). MS (EI) M+ 349. Elem Anal cald for $C_{23}H_{30}NO_2B$: C, 76.04; H, 8.32; N, 3.86; O, 8.81; B, 2.98. Found: C, 76.24; H, 8.24; N, 3.85.

*5-endo-((N,N-Dimethylamino)methyl)-6-exo-phenylbicyclo[2.2.1]heptan-2-endo- 4-chlorobenzoyl borate salt,(**83**)*. $^1$H NMR ($CDCl_3$): δ 1.52-1.61 (m, 2H, C-3, C-7endo), 1.96 (dt, *J*=10.8, 1.5 Hz, 1H, C-7), 2.17 (ddd, *J*=13.8, 9.9, 4.2 Hz, 1H, C-7exo), 2.47 (s, 3H, N($CH_3$)$_2$), 2.48 (s, 3H, N($CH_3$)$_2$), 2.64 (s, 1H, C-1/C-4), 2.65 (s, 1H, C-1/C-4), 2.74-2.84 (m, 1H, C-5), 2.92 (d, *J*=6.6 Hz, 1H, C-6), 3.01 (dd, *J*=13.8, 4.5 Hz, 1H, C-8), 3.16 (dd, *J*=13.5, 7.2 Hz, 1H, C-8), 5.25 (dt, *J*=10.5, 4.5 Hz, 1H, C-2), 7.19-7.35 (m, 5H, Ar), 7.47 (dt, *J*=8.7, 2.1 Hz, 2H, Ar'$_{2,6}$), 8.01 (dt, *J*=8.4, 2.1 Hz, 2H, Ar'$_{3,5}$) . $^{13}$C NMR ($CDCl_3$): δ 29.35, 36.57, 41.37, 43.21, 45.27, 48.93, 51.31, 52.09, 65.64, 75.84 (aliphatic), 126.54, 127.42, 128.57, 128.76, 128.92, 130.82, 139.62, 143.55, 165.46 (C=O).

***5-endo*-((*N,N*-Dimethylamino)methyl)-6-*exo*-phenyl[2.2.1]bicycloheptan-2-benzoate, (86** and **87)**. The free amine was obtained by stirring 180 mg of the borate salt in 4 mL of a 3:1 mixture of acetone and 1M HCl for 10 min. The solvent was removed under reduced pressure and saturated $NaHCO_3$ (30 mL) was added. The aqueous layer was extracted with $CH_2Cl_2$ (3 x 50 mL), the organic extracts were combined, dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure to obtain 170 mg

of crude product. The product was purified by flash column chromatography using a 5:1 ethyl acetate:methanol eluant to give **86** (169 mg, 98% yield) as a colorless oil.

*5-endo-((N,N-Dimethylamino)methyl)-6-exo-phenyl[2.2.1]bicycloheptan-2-endo-benzoate, (**86**).* $^{1}$H NMR ($CDCl_3$): δ 1.58 (dd, *J*=10.8, 3.0 Hz, 1H, C-7), 1.61 (dt, *J*=14.1, 3.6 Hz, 1H, C-3endo), 1.87 (dp, *J*=10.8, 1.8 Hz, 1H, C-7), 2.11 (dddd, *J*=14.4, 10.5, 4.8, 1.2 Hz, 1H, C-7exo), 2.22 (s, 6H, $N(CH_3)_2$), 2.30-2.40 (m, 1H, C-5), 2.41 (dd, J=11.7, 5.1 Hz, 1H, C-8), 2.49 (d, *J*=3.0 Hz, 1H, C-4), 2.68 (dd, *J*=11.7, 1.8 Hz, 1H, C-8), 2.76 (dd, *J*=4.2, 1.2 Hz, 1H, C-1), 2.94 (d, *J*=5.1 Hz, 1H, C-6), 5.29 (dt, *J*=10.5, 4.5 Hz, 1H, C-2), 7.14-7.34 (m, 5H, Ar), 7.47 (tt, *J*=7.2, 1.2 Hz, 2H, Ar'$_{3,5}$), 7.58 (tt, *J*=7.2, 1.2 Hz, 1H, Ar'$_4$), 8.07 (dm, *J*=8.1 Hz, 2H, Ar'$_{2,6}$). $^{13}$C NMR ($CDCl_3$): δ 29.26, 36.67, 39.44, 43.06, 45.77, 46.76, 47.72, 60.42, 75.82 (aliphatic), 125.8, 127.2, 128.4, 129.4, 130.4, 132.9, 145.3, 166.3 (C=O).

***86·HCl.*** (157 mg, 93 % yield). mp 240-244 ˚C, . $^{1}$H NMR ($D_2O$): δ 1.41 (d, *J*=14.4 Hz, 1H), 1.53 (br s, 1H), 1.84 (br s, 1H), 2.03 (br s, 1H), 2.39-2.46 (m, 3H), 2.63 (s, 3H, $N(CH_3)_2$), 2.70 (s, 3H, $N(CH_3)_2$), 2.84 (br s, 1H), 3.18 (br s , 1H), 3.32 (d, *J*=10.5 Hz, 1H), 5.03 (br s, 1H, C-2), 7.21 (br s, 5H, Ar), 7.41 (d, *J*=5.4 Hz, 2H, Ar'$_{3,5}$), 7.54 (br s, 1H, Ar'$_4$), 7.91 (br s, 2H, Ar'$_{2,6}$). IR (neat): 2954, 2659, 1726, 1277, 1115, 722 $cm^{-1}$. MS (EI) M+ 349. Elem Anal cald for $C_{23}H_{28}NO_2Cl$·0.29 H2O·0.1 HCl: C, 69.97; H, 7.30; N, 3.55; O, 9.30; Cl, 9.88. Found: C, 69.97; H, 7.18; N, 3.54; Cl, 9.75.

*5-endo-((N,N-Dimethylamino)methyl)-6-exo-phenylbicyclo[2.2.1]heptan-2-*

*endo-(4-chlorophenyl) benzoate, (**87**)*. (59 mg, 36% yield). pale yellow oil. $^1$H NMR ($CDCl_3$): δ 1.58 (dd, *J*=9.6, 1.8 Hz, 1H, C-7), 1.61 (dt, *J*=14.1, 3.6 Hz, 1H, C-3endo), 1.88 (dp, *J*=10.8, 2.1 Hz, 1H, C-7), 2.11 (dddd, *J*=15.0, 10.2, 4.5, 1.2 Hz, 1H, C-7exo), 2.22 (s, 6H, $N(CH_3)_2$), 2.27-2.38 (m, 1H, C-5), 2.39 (dd, *J*=11.7, 5.4 Hz, 1H, C-8), 2.49 (d, *J*=3.0 Hz, 1H, C-4), 2.64 (dd, *J*=11.7, 1.8 Hz, 1H, C-8), 2.76 (dd, *J*= 4.2, 1.2 Hz, 1H, C-1), 2.88 (d, *J*=5.4 Hz, 1H, C-6), 5.28 (dt, *J*=10.8, 4.2 Hz, 1H, C-2), 7.16-7.33 (m, 5H, Ar), 7.45 (dt, *J*=9.0, 2.1 Hz, 2H, Ar'$_{2,6}$), 8.00 (dt, *J*=8.7, 2.1 Hz, 2H, Ar'$_{2,6}$) . $^{13}$C NMR ($CDCl_3$): δ 29.23, 36.70, 39.44, 43.09, 45.86, 46.91, 47.64, 60.50, 76.21 (aliphatic), 125.93, 127.21, 128.45, 128.80, 128.89, 130.85, 139.38, 145.33, 165.53 (C=O).

***87·HCl.*** (55 mg, 93 % yield). mp193-196 ˚C. $^1$H NMR ($D_2O$): δ 1.43 (dm, *J*=15.0 Hz, 1H, C-3), 1.56 (dm, *J*=11.1 Hz, 1H, C-7), 1.87 (dm, *J*=11.1 Hz, 1H, C-7), 2.00-2.12 (m, 1H, C-3), 2.41 (br s, 1H), 2.46-2.56 (m, 2H, C-5), 2.65 (s, 3H, $N(CH_3)_2$), 2.71 (s, 3H, $N(CH_3)_2$), 2.85 (d, *J*=6.3 Hz, 1H, C-6), 3.19 (dd, *J*=13.2, 5.4 Hz, 1H, C-8), 3.34 (dd, *J*=13.5, 9.6 Hz, 1H, C-8), 5.15-5.30 (m, 1H, C-2), 7.15-7.30 (m, 5H, Ar), 7.41 (d, *J*=8.4 Hz, 2H, Ar'$_{2,6}$), 7.88 (d, *J*=8.4 Hz, 2H, Ar'$_{3,5}$). IR (neat): 2961, 2645, 1726, 1270, 1129, 722 cm$^{-1}$. MS (EI) M+ 383. Elem Anal cald for $C_{23}H_{27}NO_2Cl_2$·0.1HCl ·0.74$H_2O$: C, 63.17; H, 6.57; N, 3.20; O, 10.04; Cl, 17.02. Found: C, 63.17; H, 6.20; N, 3.22; Cl, 17.12.

***5-endo*-((*N*,*N*-Dimethylamino)methyl)-6-*exo*-phenyl[2.2.1]bicycloheptan-2-*exo*-benzoyl borate salt, (84** and **85)**. The transformation from **81** to **84** is illustrated. DEAD (.658 mL, 4.18 mmol) was added to a mixture of benzoic acid (562 mg, 4.6

mmol), triphenylphosphine (1.15 g, 4.39 mmol), and borane alcohol **81** (513 mg, 1.98 mmol) in THF (2 mL). The mixture was stirred at room temperature overnight and the solvent was removed by reduced pressure. The product was purified by flash column chromatography using 7:2:1 hexane:$CH_2Cl_2$:ethyl acetate as the eluant, followed by recrystallization from 7:2:1 hexane:$CH_2Cl_2$:ethyl acetate to give 153 mg of benzoate **84** (150 mg, 21% yield) as a colorless oil.

*5-endo-(N,N-Dimethylaminomethyl)-6-exo-phenylbicyclo[2.2.1]heptan-2-endo-benzoyl borate salt, (**84**).* $^1$H NMR ($CDCl_3$): δ 1.65 (dm, *J*=14.7 Hz, 1H, C-3endo), 1.80 (dd, *J*=10.5, 1.5 Hz, 1H, C-7), 1.89 (dm, *J*=10.5 Hz, 1H, C-7), 2.13 (d, *J*=6.3 Hz, 1H, C-1/C-4), 2.24 (ddd, *J*=14.4, 6.9, 2.1 Hz, 1H, C-3 exo), 2.43 (s, 3H, $N(CH_3)_2$), 2.48 (s, 1H, C-1/C-4), 2.49 (s, 3H, $N(CH_3)_2$), 2.59-2.74 (m, 2H, C-5, C-6), 2.84 (dd, *J*=13.5, 4.8 Hz, 1H, C-8), 3.02 (dd, *J*=13.8, 6.6 Hz, 1H, C-8), 5.00 (dd, *J*=6.9, 1.2 Hz, 1H, C-2), 7.19-7.36 (m, 5H, Ar), 7.42 (tt, *J*=7.8, 1.8 Hz, 2H, Ar'$_{3,5}$), 7.54 (tt, *J*=7.5z, 1.8 Hz, 1H, Ar'$_4$), 8.00 (dt, *J*=6.6, 1.5 Hz, 2H, Ar'$_{2,6}$). $^{13}$C NMR ($CDCl_3$): 32.46, 35.22, 40.29, 42.71, 50.13, 50.86, 51.34, 52.51, 66.16, 77.28 (aliphatic), 126.60, 127.27, 128.30, 128.73, 129.42, 130.32, 132.91, 143.21, 166.02 (C=O). Elem Anal cald for $C_{23}H_{29}NO_2BCl$: C, 69.45; H, 7.35; N, 3.52; O, 8.04; B, 2.72; Cl, 8.91. Found: C, 69.36; H, 7.29; N, 3.48; Cl, 8.97.

*5-endo-(N,N-Dimethylaminomethyl)-6-exo-phenylbicyclo[2.2.1]heptan-2-endo-(4-chlorophenyl)benzoyl borate salt, (**85**).*(45 mg, 21% yield) pale yellow oil. $^1$H NMR ($CDCl_3$): δ 1.64 (dm, 1H, C-3), 1.79 (dd, *J*=10.5, 1.5 Hz, 1H, C-7), 1.90 (dm,

*J*=10.5 Hz, C-7), 2.12 (d, *J*=6.6 Hz, 1H) 2.24 (ddd, *J*=14.4, 6.6, 2.1, 1Hz, C-3) 2.43 (s, 3H, $N(CH_3)_2$), 2.46 (s, 1H), 2.50 (s, 3H, $N(CH_3)_2$), 2.60-2.72 (m, 2H, C-5, C-6), 2.83 (dd, *J*=13.5, 4.5 Hz, 1H, C-8), 3.02 (dd, *J*=13.5, 6.9 Hz, 1H, C-8), 4.98 (dm, *J*=6.9 Hz, 1H, C-2), 7.20-7.36 (m, 5H, Ar), 7.40 (dt, *J*=8.4, 2.1 Hz, 2H, $Ar'_{2,6}$), 7.93 (dt, *J*=8.7, 2.4 Hz, 2H, $Ar'_{3,5}$) . $^{13}C$ NMR ($CDCl_3$): δ 32.45, 35.22, 40.28, 42.69, 50.11, 50.84, 51.33, 52.51, 66.16, 77.6 (aliphatic), 126.66, 127.27, 128.66, 128.77, 130.83, 139.37, 143.13, 165.17 (C=O). Elem Anal cald for $C_{23}H_{30}NO_2B$: C, 76.04; H,8.32; N, 3.86; O, 8.81; B, 2.98. Found: C, 76.23; H, 8.33; N, 3.87.

***5-endo*-((*N,N*-Dimethylamino)methyl)-6-*exo*-phenyl[2.2.1]bicycloheptan-2-benzoates (88 and 89)**. The same procedure as is shown for benzoate **86** was used for the conversion of benzoates **84** and **85** to free amines **88** and **89**.

*5-endo-((N,N-Dimethylamino)methyl)-6-exo-phenyl[2.2.1]bicycloheptan-2-endo-benzoate (**88**)*. (60 mg, 56% yield). pale yellow oil.$^1H$ NMR ($CDCl_3$): δ 1.60 (dt, *J*=14.1, 2.4 Hz, 1H, C-3endo), 1.79 (d, *J*= 11.4 Hz, 1H, C-7), 1.81 (d, *J*=11.4 Hz, 1H, C-7), 2.08 (d, *J*=6.3 Hz), 2.10-2.20 (m, 1H, C-7exo), 2.19 (s, 6H, $N(CH_3)_2$), 2.25 (d, *J*=5.7 Hz, 1H), 2.28 (dd, *J*=12.7, 5.1 Hz, 1H, C-8), 2.44 (dd, *J*=12.0, 1.8 Hz, 1H, C-8), 2.50-2.56 (m, 1H, C-5), 2.57 (s, 1H), 4.98 (dd, *J*=6.9, 2.1 Hz, 1H, C-2), 7.16-7.34 (m, 5H, Ar), 7.41 (tt, *J*=8.1, 1.5 Hz, 2H, $Ar'_{3,5}$), 7.53 (tt, *J*=7.8, 1.2 Hz, 1H, $Ar'_4$), 8.02 (dt, *J*=7.5, 1.5 Hz, 2H, $Ar'_{2,6}$) . $^{13}C$ NMR ($CDCl_3$): δ 32.46, 35.19, 38.09, 45.77, 46.29, 48.49, 48.85, 60.89, 77.82 (aliphatic), 125.96, 127.04, 128.22, 128.39, 129.44, 130.53, 132.76, 144.78, 166.02 (C=O).

***88·HCl.*** (55 mg, 92% yield). mp 241-243 ˚C, pale yellow solid. $^1$H NMR ($D_2O$): δ 1.55 (dm, *J*=14.1 Hz, 1H, C-3), 1.72 (d, *J*=12 Hz, 1H, C-7), 1.77 (d, *J*=12 Hz, 1H, C-7), 2.06 (dd, *J*=14.1, 6.9 Hz, 1H, C-3), 2.13 (d, *J*=6.9 Hz, 1H), 2.21-2.36 (m, 1H), 2.33 (s, 6H, $N(CH_3)_2$), 2.44 (s, 1H), 2.67 (s, 1H), 3.09 (dd, *J*=13.5, 5.4 Hz, 1H, C-8), 3.22 (dd, *J*=13.2, 9.9 Hz, 1H, C-8), 4.79 (dm, *J*=4.8 Hz, 1H, C-2), 7.16-7.30 (m, 5H, Ar), 7.36 (t, J=7.5 Hz, 2H, $Ar'_{3,5}$), 7.52 (t, J=7.5 Hz, 1H, $Ar'_4$), 7.84 (d, J=7.5 Hz, 2H, $Ar'_{2,6}$). IR (neat): 2973, 2696, 1716, 1275, 762 cm$^{-1}$. MS (EI) M+ 349. Elem Anal cald for $C_{23}H_{28}NO_2Cl$: C, 71.58; H, 7.31; N, 3.63; O, 8.29; Cl, 9.19. Found: C, 71.16; H, 7.29; N, 3.62; Cl, 9.46.

*5-endo-((N,N-Dimethylamino)methyl)-6-exo-phenyl[2.2.1]bicycloheptan-2-endo-(4-chlorophenyl) benzoate (**89**)*. (130 mg, 96% yield). pale yellow oil. $^1$H NMR ($CDCl_3$): δ 1.58 (dm, *J*=14.4 Hz, 1H, C-3), 1.78 (s, 2H), 2.07 (d, *J*=6.3 Hz, 1H), 2.10-2.19 (s, 6H, $N(CH_3)_2$), 2.24-2.31 (m, 2H), 2.44 (dd, *J*=10.2, 2.1 Hz, 1H, C-8), 2.51-2.56 (m, 1H), 2.56 (s, 1H, C-8), 4.96 (dd, *J*=6.9, 2.4 Hz, 1H, C-2), 7.16-7.32 (m, 5H, ar), 7.39 (dt, *J*=8.7, 2.7 Hz, 2H, $Ar'_{2,6}$), 7.95 (dt, *J*=8.7, 2.4 Hz, 2H, $Ar'_{2,6}$). $^{13}$C NMR ($CDCl_3$): δ 32.46, 35.21, 38.09, 45.79, 46.29, 48.47, 48.84, 60.91, 78.13 (aliphatic), 126.01, 127.04, 128.42, 128.59, 128.92, 130.87, 139.2, 144.72, 165.23 (C=O).

***89·HCl.*** (60 mg, 46% yield). mp 244-247 ˚C, pale yellow solid. $^1$H NMR ($D_2O$): δ 1.59 (m, 1H), 1.72-1.86 (m, 1H), 2.04-2.14 (m, 1H), 2.17 (d, *J*=6.9 Hz, 1H), 2.26-2.36 (m, 1H), 2.39 (s, 1H), 2.46 (s, 1H) 2.69 (s, 3H, $N(CH_3)_2$), 3.08-3.16 (m, 1H), 3.20-3.30

(m, 1H), 4.81-4.87 (m, 1H, C-2), 7.16-7.31 (m, 5H, Ar), 7.38 (d, *J*=8.7 Hz, 2H, Ar'$_{2,6}$), 7.83 (d, *J*=8.7 Hz, 2H, Ar'$_{3,5}$). IR (neat): 2960, 2683, 1629, 1123, 762 cm$^{-1}$. MS (EI) M+ 383. Elem Anal cald for $C_{23}H_{27}NO_2Cl_2$: C, 65.72; H, 6.47; N, 3.33; O, 7.61; Cl, 16.87. Found: C, 65.30; H, 6.40; N, 3.30; Cl, 16.98.

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# CHAPTER VII

# FUTURE WORK

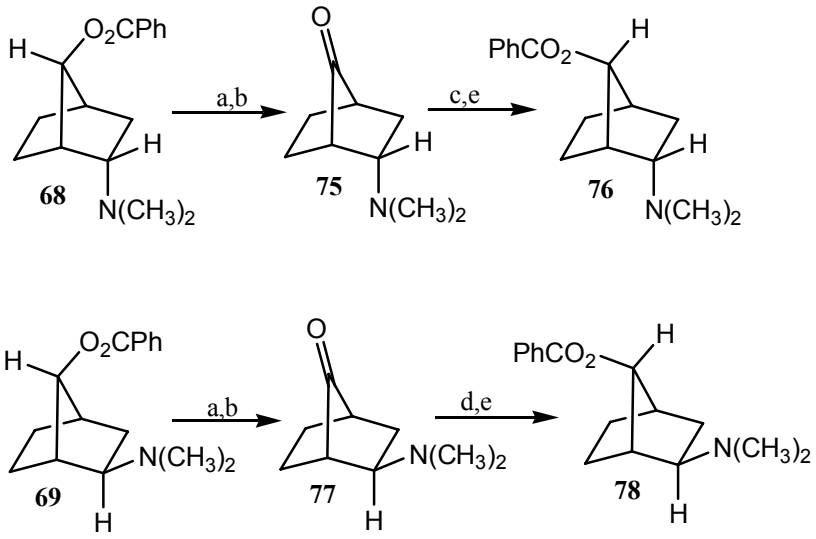
## Introduction

To continue probing the constraints of binding at the DAT, additional analogs are proposed in this chapter for synthesis and pharmacological evaluation. The proposed compounds take into consideration the importance of the relative stereochemistry and the regiochemistry of the amine and phenyl group. Also, the optimal length between the nitrogen and the phenyl ring is explored by varying the number of carbons in a tether. This will allow for the construction of further SARs which, in turn, provides an insight into the binding at the DAT.

## Chemistry

### Synthesis of 2-amino-7-*exo*-norboranyl benzoate (76 and 78).

Since the other regioisomer of **71** (i.e. the *exo*-alcohol-*exo*-benzoate) was not obtained in pure from the mixture (Figure 5.3), an alternate pathway is suggested




Reagents: a) 15% KOH, THF; b) DMSO, oxalyl chloride, $Et_3N$, $CH_2Cl_2$; c)$NaBH_4$, EtOH, reflux; d) $BH_3$, THF, -78 ºC; and e) benzoyl chloride, DMAP, pyridine, $CH_2Cl_2$.

**Figure 7.1.** Proposed synthesis of amino[2.2.1]benzoates **76** and **78**.

to synthesize benzoates **76** and **78** (Figure 7.1). Amino benzoate **76** can be made by the hydrolysis of benzoate **68** to the corresponding alcohol, the alcohol subjected to Swern oxidation conditions, reduced with $NaBH_4$ to obtain a mixture of *endo* and *exo* alcohols, followed by benzoylation and separation. Amino benzoate **78** can be made by similar chemistry; hydrolysis of benzoate **69**, Swern oxidation of the corresponding alcohol, a

borane reduction to obtain solely the *exo*-alcohol, followed by benzoylation to obtain the final product.

**Prospective Synthesis of 2-amino-3-phenyl-7-norboranyl benzoates (79).**

The work described in this section takes advantage of the oxygen functionality on the C-7 carbon on the [2.2.1] skeleton, *i.e.* in Chapter 6 (Figure 6.2), and places an arene (phenyl, 4-chlorophenyl, benzyl, phenethyl, etc.) substituent at the C-5 position of the bicycle. Placing an oxygen functionality at the C-7 position of the [2.2.1]bicyclic scaffold and the introduction of an arene at the C-5 position allows for comparison to previously synthesized 6-(*N*,*N*-dimethylamino)-5-phenyl bicyclo[2.2.2]octanes.[1] The substitution at the C-7 position in compound **B** (Figure 7.1) provides compounds which fill the space

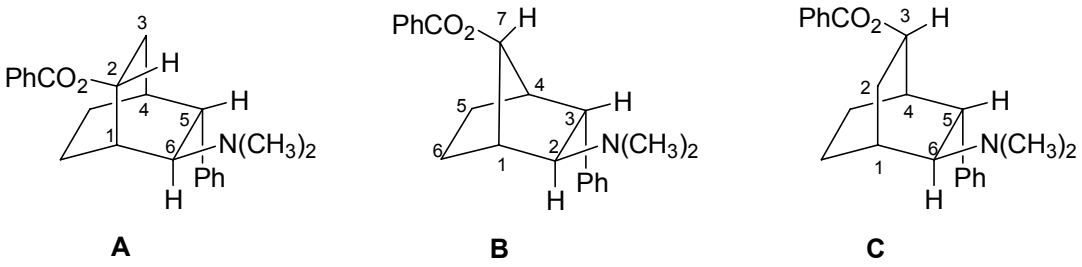
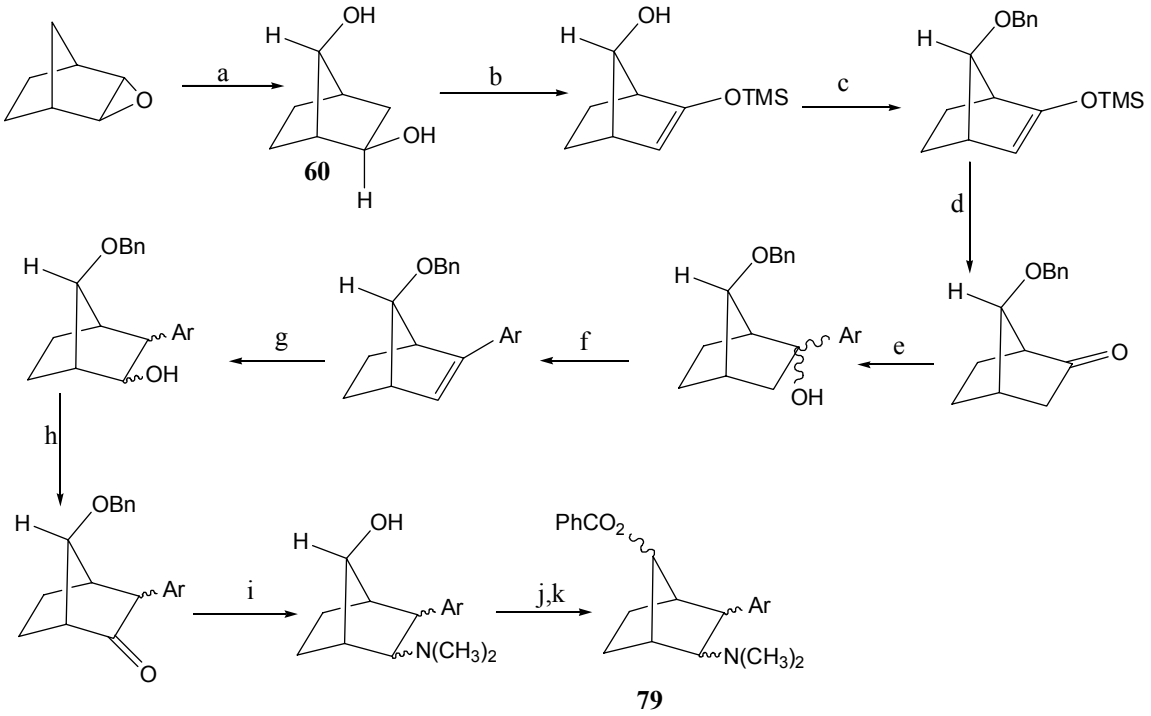



**Figure 7.2.** Regiochemistry comparison of C-2 substituted [2.2.2]octanes (**A**), C-3 substituted [2.2.2]octanes (**C**), and C-7 substituted [2.2.1]heptanes (**B**).

between carbons 2 and 3 on the triisubstituted [2.2.2]octanes **A** and **C** (Figure 7.2). This chemistry can be achieved by selectively protecting diol **60** on the two-carbon bridge using TMSCl (Figure 7.3). The alcohol on the C-7 carbon can then be protected using benzyl chloride, followed by the hydrolysis of the TMS protecting group at the C-2 position. The alcohol is then exposed to Swern oxidation conditions, followed by addition of a phenyl or 4-chlorophenyl Grignard reagent to the ketone. Dehydration of the Grignard adduct, hydroboration of the resulting alkene, and exposing the alcohol to Swern oxidation conditions will provide a ketone at the C-6 position on the bicycle. Reductive amination of the ketone and concomitant deprotection of the benzyl group gives diastereomeric amino alcohols, which will be separated by column chromatography. The amino alcohol will then be exposed to Swern oxidation conditions, reduced with sodium borohydride, and followed by benzoylation to obtain the corresponding amino benzoates **79**.




**Reagents:** a) $HClO_4$, $H_2O$; b) LDA, TMSCl, -78 ˚C; c) NaH, benzyl chloride, $CH_2Cl_2$; d) 1) HCl, THF; 2) Swern oxidation conditions; e) phenyl or 4-chlorophenyl magnesium bromide, ether, -20 ˚C, f) p-TSA, toluene, heat; g) $BH_3$, $H_2O_2$, THF; h) Swern oxidations conditions, i) 1) $NH(CH_3)_2$·HCl, $Et_3N$; and 2) $H_2$, Pd/C, $CH_2Cl_2$; j) 1) Swern oxidation conditions; 2) $NaBH_4$, EtOH; 3) benzoyl chloride, DMAP, pyridine, $CH_2Cl_2$.

**Figure 7.3.** Proposed synthesis for amino benzoates **79**.

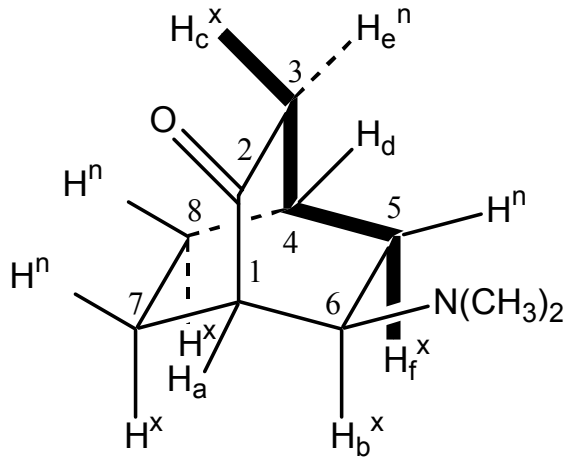
## References

1. Javanmard, S. Synthesis and pharmacology of site-specific cocaine abuse treatment agents. Ph.D. Thesis (2002), Georgia Institute of Technology.

# APPENDICES

## APPENDIX A

### Structural Assignment of 19.




n= endo
x=exo

Signal **a** at δ 2.60 ppm in the $^1$H NMR (Figure A.1) appears as a quartet with a coupling constant of 3 Hz, which can be assigned to the bridgehead carbon on C-1. This bridgehead carbon is coupled to one proton on C-6 and two protons on C-7, apparently with similar coupling constants. Signal **b** at δ 2.40 ppm, was assigned to the *exo* proton on C-6 since this is the only proton that couples to protons in *cis* (9.3 Hz, C-5) and *trans* (4.5 Hz, C-5) methinine positions on the bicycle, and is coupled to a bridgehead proton (3.0 Hz, C-1). Signal **d** at δ 2.21-2.23 ppm was assigned to the bridgehead proton at C-4

and the dimethylamine protons (7H). The signals **c** (δ 2.30 ppm) and **e** (δ 2.18 ppm) were assigned to the *endo* and *exo* protons on C-3, respectively. These two signals both contain geminal coupling (18 Hz), coupling to the bridgehead proton at C-4 (2.1 Hz), and a long range in-plane "W-coupling" to the *exo* protons on C-5 and C-8 (2.1 Hz) as illustrated in the above structure with the highlighted bonds. The peak at δ 1.93 (quartet of triplets), signal **f**, was assigned to the *exo* proton on C-5. The *exo* proton on C-5 is the only proton on the bicycle, which has geminal coupling (13.2 Hz, C-5 *endo*), *cis* coupling (9.3 Hz, C-6 *exo*), coupled to the bridgehead proton at C-4 (3.0 Hz), and a long range in-plane "W-coupling" with the *exo* proton on C-2. It is this long range "W-coupling" between the *exo* proton on C-2 and the *exo* proton on C-5 and the *cis* coupling between the *exo* proton on C-5 and the *exo* proton on C-6 which establishes the stereochemistry at the C-6 stereocenter.

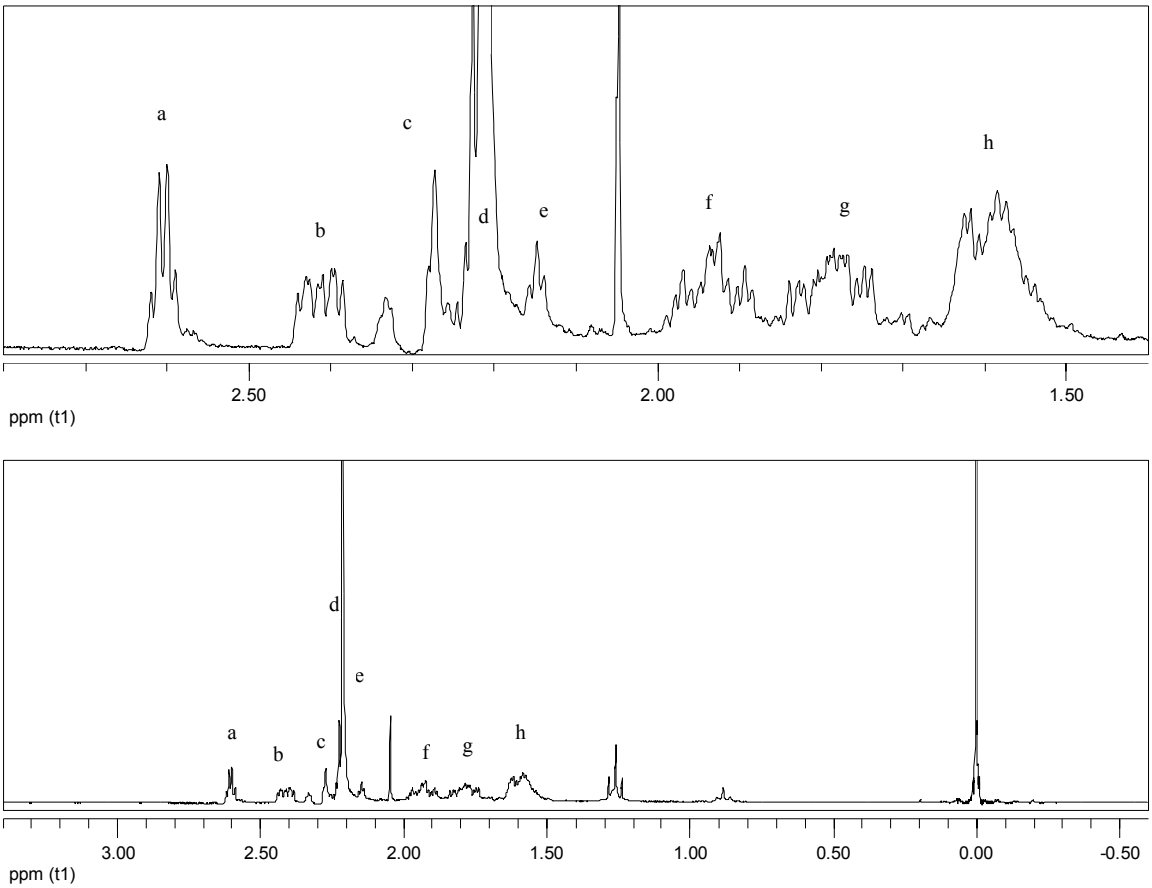
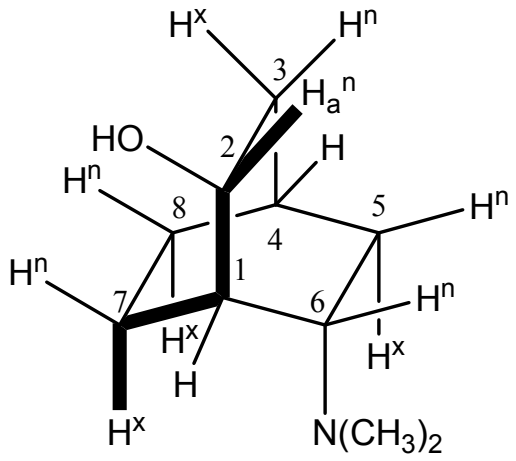



**Figure A.1**. $^{1}H$ NMR spectrum (Gemini 300MHz, $CDCl_3$) of amino ketone **19**.

## APPENDIX B

### Structural Assignment of 24




n= endo
x=exo

The stereochemistry at the C-6 stereocenter is the opposite of that assigned to amino ketone **19** (Appendix A). Signal **a** (δ 3.89 ppm) was assigned to the *endo* proton of the hydroxy substituted methine, C-2. The multiplicity of this peak, *dddd*, arises from a *cis* coupling with the *endo* proton on C-3 (9.6 Hz), a *trans* coupling with the *exo* proton on C-3 (6.6 Hz), coupling to the bridgehead proton on C-1 (3.3 Hz), and a long range in-plane "W-coupling" with the *exo* proton on C-7 (0.9 Hz) as illustrated by the highlighted bonds in the structure above. Since this is the only arrangement on the bicycle, which

would allow “W-coupling” of the proton on C-2, this piece of evidence establishes the stereochemistry at the C-2 stereocenter. The relative stereochemical assignment was confirmed by x-ray analysis (Figure B.2).

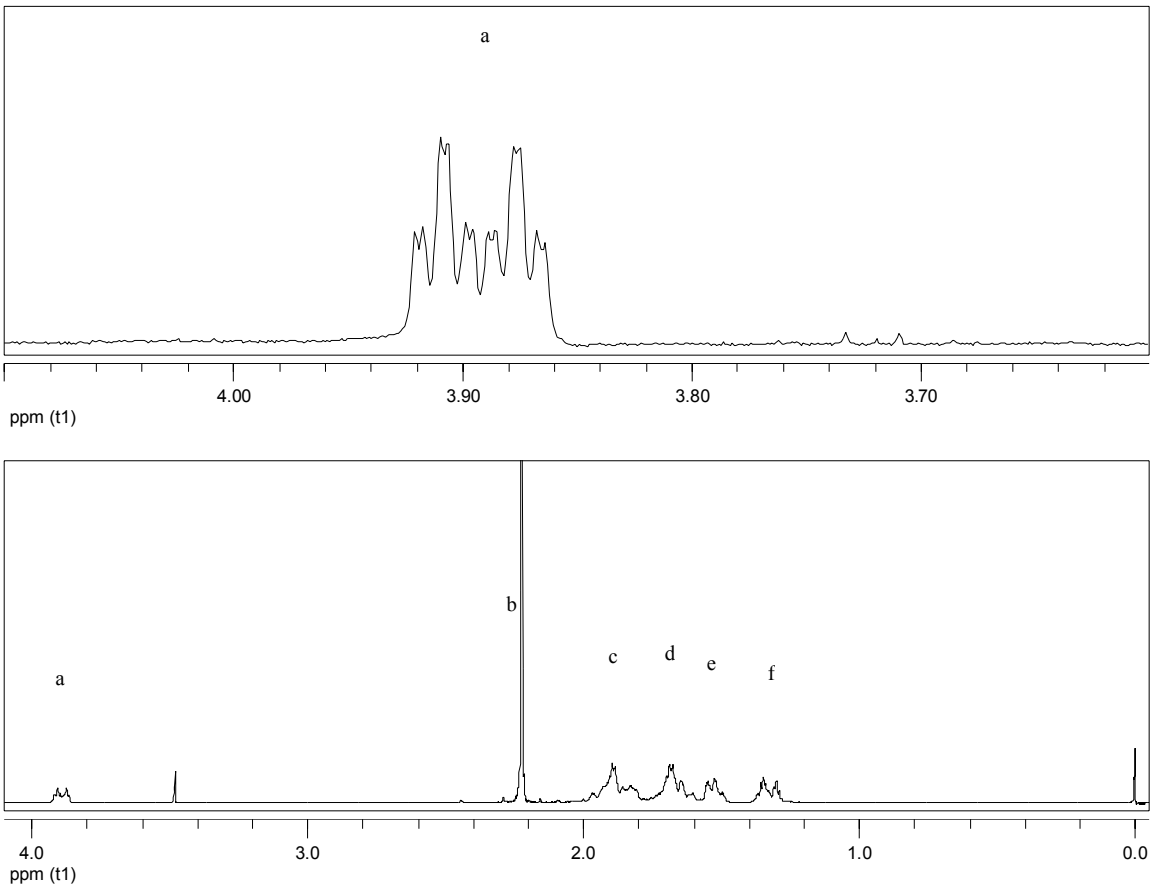



**Figure B.1**. $^{1}H$ NMR spectrum (Gemini 300MHz, $CDCl_3$) of amino alcohol **24**.

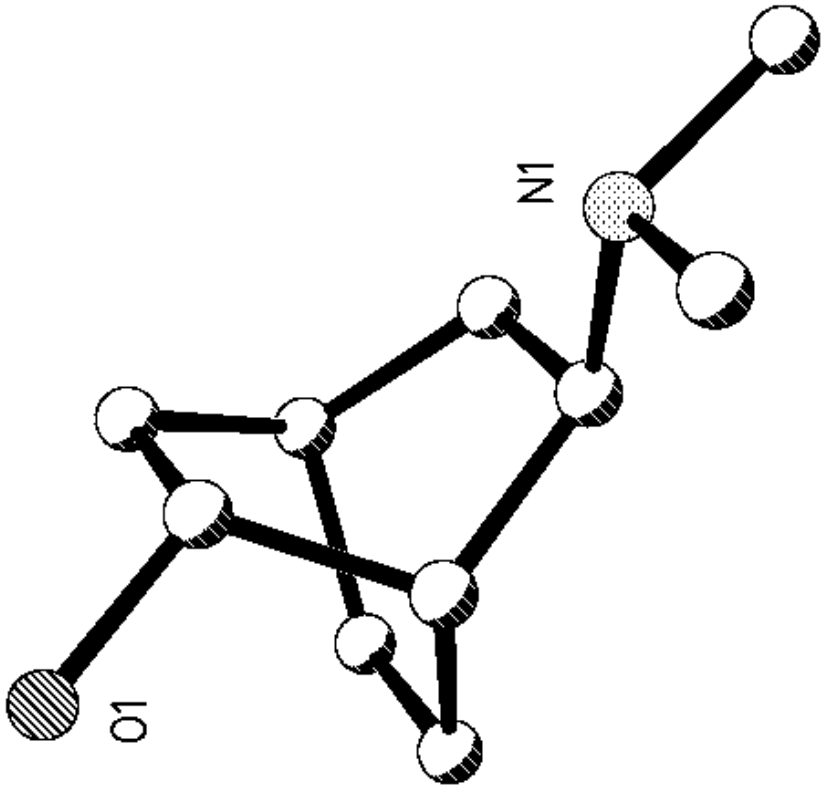



**Figure B.2**. The ORTEP drawing of amino alcohol **24**.

**Table B.1.** Crystal data and structure refinement for amino alcohol **24**.

| | |
|---|---|
| Identification code | coons3 |
| Empirical formula | C10 H21 N O2 |
| Formula weight | 187.28 |
| Temperature | 203(2) K |
| Wavelength | 0.71073 A |
| Crystal system, space group | Monoclinic, P2(1)/c |
| Unit cell dimensions | a = 8.4903(6) A alpha = 90 deg.<br>b = 11.7029(9) A beta = 98.055(2) deg.<br>c = 21.9146(16) A gamma = 90 deg. |
| Volume | 2156.0(3) A^3 |
| Z, Calculated density | 8, 1.154 Mg/m^3 |
| Absorption coefficient | 0.079 mm^-1 |
| F(000) | 832 |
| Crystal size | 0.65 x 0.54 x 0.15 mm |
| Theta range for data collection | 1.88 to 25.05 deg. |
| Limiting indices | -10<=h<=7, -13<=k<=13, -26<=l<=20 |
| Reflections collected / unique | 11043 / 3810 [R(int) = 0.0381] |
| Completeness to theta = 25.05 | 99.9 % |
| Absorption correction | None |
| Max. and min. transmission | 0.9880 and 0.9508 |
| Refinement method | Full-matrix least-squares on F^2 |
| Data / restraints / parameters | 3810 / 0 / 266 |
| Goodness-of-fit on F^2 | 0.857 |

| | |
|---|---|
| Final R indices [I>2sigma(I)] | R1 = 0.0380, wR2 = 0.0859 |
| R indices (all data) | R1 = 0.0727, wR2 = 0.0921 |
| Extinction coefficient | 0.0017(6) |
| Largest diff. peak and hole | 0.179 and -0.156 e.A^-3 |

**Table B.2.** Atomic coordinates ( x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for amino alcohol **24**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O(1) | 7581(1) | 8615(1) | 2041(1) | 37(1) |
| N(1) | 11034(2) | 10938(1) | 1449(1) | 29(1) |
| C(1) | 9163(2) | 9258(1) | 1258(1) | 25(1) |
| C(2) | 8218(2) | 9600(1) | 1772(1) | 28(1) |
| C(3) | 6840(2) | 10381(1) | 1507(1) | 37(1) |
| C(4) | 6891(2) | 10600(1) | 828(1) | 34(1) |
| C(5) | 8477(2) | 11128(1) | 747(1) | 39(1) |
| C(6) | 9871(2) | 10334(1) | 999(1) | 27(1) |
| C(7) | 8080(2) | 8673(1) | 737(1) | 33(1) |
| C(8) | 6701(2) | 9469(1) | 482(1) | 45(1) |
| C(9) | 12290(2) | 10183(2) | 740(1) | 44(1) |
| C(10) | 11800(2) | 11864(1) | 1142(1) | 47(1) |
| O(1') | 2557(1) | 7235(1) | 2070(1) | 33(1) |
| N(1') | 5766(2) | 4821(1) | 1373(1) | 34(1) |
| C(1') | 3954(2) | 6540(1) | 1240(1) | 26(1) |
| C(2') | 3086(2) | 6228(1) | 1782(1) | 28(1) |
| C(3') | 1635(2) | 5499(2) | 1550(1) | 41(1) |
| C(4') | 1557(2) | 5268(1) | 866(1) | 37(1) |
| C(5') | 3086(2) | 4677(1) | 753(1) | 41(1) |
| C(6') | 4540(2) | 5447(1) | 955(1) | 30(1) |
| C(7') | 2822(2) | 7155(1) | 739(1) | 33(1) |
| C(8') | 1387(2) | 6396(1) | 514(1) | 45(1) |
| C(9') | 6359(2) | 3837(2) | 1052(1) | 59(1) |
| C(10') | 7127(2) | 5544(2) | 1591(1) | 55(1) |
| O(2) | -38(1) | 2547(1) | 2283(1) | 48(1) |
| O(3) | 4923(1) | 3323(1) | 2310(1) | 43(1) |

**Table B.3.** Bond lengths [A] and angles [deg] for amino alcohol **24**.

| | |
|---|---|
| O(1)-C(2) | 1.4348(17) |
| N(1)-C(9) | 1.460(2) |
| N(1)-C(10) | 1.4740(18) |
| N(1)-C(6) | 1.4752(19) |
| C(1)-C(7) | 1.524(2) |
| C(1)-C(2) | 1.525(2) |
| C(1)-C(6) | 1.5377(19) |
| C(2)-C(3) | 1.534(2) |
| C(3)-C(4) | 1.516(2) |
| C(4)-C(5) | 1.514(2) |
| C(4)-C(8) | 1.523(2) |
| C(5)-C(6) | 1.545(2) |
| C(7)-C(8) | 1.539(2) |
| O(1')-C(2') | 1.4370(17) |
| N(1')-C(10') | 1.458(2) |
| N(1')-C(9') | 1.474(2) |
| N(1')-C(6') | 1.4813(19) |
| C(1')-C(2') | 1.5280(19) |
| C(1')-C(7') | 1.533(2) |
| C(1')-C(6') | 1.5364(19) |
| C(2')-C(3') | 1.525(2) |
| C(3')-C(4') | 1.516(2) |
| C(4')-C(5') | 1.521(2) |
| C(4')-C(8') | 1.526(2) |
| C(5')-C(6') | 1.542(2) |
| C(7')-C(8') | 1.532(2) |
| | |
| C(9)-N(1)-C(10) | 107.59(13) |
| C(9)-N(1)-C(6) | 112.43(11) |
| C(10)-N(1)-C(6) | 110.13(12) |
| C(7)-C(1)-C(2) | 110.27(12) |
| C(7)-C(1)-C(6) | 108.47(13) |
| C(2)-C(1)-C(6) | 109.35(12) |
| O(1)-C(2)-C(1) | 111.12(12) |
| O(1)-C(2)-C(3) | 108.87(12) |
| C(1)-C(2)-C(3) | 109.19(13) |
| C(4)-C(3)-C(2) | 110.35(13) |
| C(5)-C(4)-C(3) | 109.40(13) |
| C(5)-C(4)-C(8) | 109.27(13) |
| C(3)-C(4)-C(8) | 109.06(14) |
| C(4)-C(5)-C(6) | 111.22(13) |
| N(1)-C(6)-C(1) | 113.89(12) |
| N(1)-C(6)-C(5) | 110.99(12) |

| | |
|---|---|
| C(1)-C(6)-C(5) | 107.78(13) |
| C(1)-C(7)-C(8) | 110.40(12) |
| C(4)-C(8)-C(7) | 108.83(13) |
| C(10')-N(1')-C(9') | 107.61(14) |
| C(10')-N(1')-C(6') | 111.81(12) |
| C(9')-N(1')-C(6') | 110.34(14) |
| C(2')-C(1')-C(7') | 110.27(13) |
| C(2')-C(1')-C(6') | 109.64(12) |
| C(7')-C(1')-C(6') | 107.88(13) |
| O(1')-C(2')-C(3') | 108.50(12) |
| O(1')-C(2')-C(1') | 111.08(11) |
| C(3')-C(2')-C(1') | 109.22(12) |
| C(4')-C(3')-C(2') | 110.53(13) |
| C(3')-C(4')-C(5') | 108.78(14) |
| C(3')-C(4')-C(8') | 109.49(14) |
| C(5')-C(4')-C(8') | 109.48(14) |
| C(4')-C(5')-C(6') | 110.80(13) |
| N(1')-C(6')-C(1') | 113.58(13) |
| N(1')-C(6')-C(5') | 110.72(12) |
| C(1')-C(6')-C(5') | 108.12(12) |
| C(8')-C(7')-C(1') | 110.39(13) |
| C(4')-C(8')-C(7') | 108.91(14) |

---

Symmetry transformations used to generate equivalent atoms:

**Table B.4.** Anisotropic displacement parameters (A^2 x 10^3) for amino alcohol **24**. The anisotropic displacement factor exponent takes the form:
-2 pi^2 [ h^2 a*^2 U11 + ... + 2 h k a* b* U12 ]

| | U11 | U22 | U33 | U23 | U13 | U12 |
|---|---|---|---|---|---|---|
| O(1) | 35(1) | 29(1) | 48(1) | 9(1) | 13(1) | -3(1) |
| N(1) | 33(1) | 21(1) | 34(1) | -2(1) | 8(1) | -4(1) |
| C(1) | 26(1) | 17(1) | 31(1) | 2(1) | 3(1) | 4(1) |
| C(2) | 29(1) | 22(1) | 32(1) | 1(1) | 6(1) | -4(1) |
| C(3) | 36(1) | 31(1) | 46(1) | -4(1) | 10(1) | 7(1) |
| C(4) | 34(1) | 27(1) | 40(1) | -1(1) | -3(1) | 12(1) |
| C(5) | 48(1) | 27(1) | 40(1) | 7(1) | 5(1) | 7(1) |
| C(6) | 35(1) | 20(1) | 28(1) | 1(1) | 10(1) | 3(1) |
| C(7) | 35(1) | 22(1) | 39(1) | -5(1) | 2(1) | 2(1) |
| C(8) | 42(1) | 40(1) | 48(1) | -12(1) | -9(1) | 7(1) |
| C(9) | 33(1) | 40(1) | 57(1) | -5(1) | 0(1) | -5(1) |
| C(10) | 58(1) | 34(1) | 53(1) | -2(1) | 21(1) | -17(1) |
| O(1') | 32(1) | 27(1) | 42(1) | -9(1) | 10(1) | 2(1) |
| N(1') | 36(1) | 26(1) | 41(1) | 7(1) | 13(1) | 10(1) |
| C(1') | 27(1) | 17(1) | 34(1) | 0(1) | 5(1) | -1(1) |
| C(2') | 33(1) | 20(1) | 30(1) | -2(1) | 6(1) | 2(1) |
| C(3') | 46(1) | 37(1) | 43(1) | -5(1) | 15(1) | -15(1) |
| C(4') | 38(1) | 30(1) | 42(1) | -8(1) | 2(1) | -9(1) |
| C(5') | 54(1) | 24(1) | 44(1) | -6(1) | 7(1) | -3(1) |
| C(6') | 38(1) | 23(1) | 31(1) | 4(1) | 11(1) | 4(1) |
| C(7') | 43(1) | 23(1) | 36(1) | 6(1) | 8(1) | 7(1) |
| C(8') | 44(1) | 40(1) | 48(1) | 1(1) | -5(1) | 5(1) |
| C(9') | 78(2) | 43(1) | 61(1) | 12(1) | 34(1) | 31(1) |
| C(10') | 34(1) | 59(1) | 71(1) | 21(1) | 7(1) | 8(1) |
| O(2) | 50(1) | 38(1) | 62(1) | -23(1) | 26(1) | -18(1) |
| O(3) | 43(1) | 39(1) | 50(1) | 17(1) | 20(1) | 15(1) |

**Table B.5.** Hydrogen coordinates ( x 10^4) and isotropic displacement parameters (A^2 x 10^3) for amino alcohol **24**.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(1A) | 8500 | 8172 | 2245 | 66(6) |
| H(1) | 10006 | 8748 | 1419 | 25(4) |
| H(2) | 8902 | 10006 | 2085 | 22(4) |
| H(3A) | 5847 | 10029 | 1559 | 49(4) |
| H(3B) | 6914 | 11094 | 1726 | 49(4) |
| H(4) | 6045 | 11109 | 670 | 34(4) |
| H(5A) | 8592 | 11846 | 961 | 50(4) |
| H(5B) | 8506 | 11272 | 318 | 50(4) |
| H(6) | 10400 | 10106 | 659 | 20(4) |
| H(7A) | 7661 | 7982 | 888 | 38(3) |
| H(7B) | 8683 | 8473 | 413 | 38(3) |
| H(8A) | 6714 | 9598 | 50 | 64(4) |
| H(8B) | 5703 | 9124 | 533 | 64(4) |
| H(9A) | 11840 | 9625 | 1986 | 54(3) |
| H(9B) | 13072 | 10625 | 1997 | 54(3) |
| H(9C) | 12782 | 9803 | 1427 | 54(3) |
| H(10A) | 12337 | 11548 | 823 | 58(3) |
| H(10B) | 12556 | 12250 | 1438 | 58(3) |
| H(10C) | 11006 | 12397 | 964 | 58(3) |
| H(1A) | 3515 | 7649 | 2270 | 75(6) |
| H(1') | 4843 | 7025 | 1379 | 22(4) |
| H(2') | 3788 | 5801 | 2080 | 26(4) |
| H(3'1) | 1695 | 4788 | 1770 | 64(4) |
| H(3'2) | 687 | 5888 | 1626 | 64(4) |
| H(4') | 664 | 4785 | 729 | 40(5) |
| H(5'1) | 3033 | 4500 | 323 | 53(4) |
| H(5'2) | 3201 | 3973 | 980 | 53(4) |
| H(6') | 4992 | 5658 | 593 | 27(4) |
| H(7'1) | 2463 | 7855 | 902 | 47(3) |
| H(7'2) | 3376 | 7341 | 399 | 47(3) |
| H(8'1) | 423 | 6772 | 582 | 60(4) |
| H(8'2) | 1339 | 6255 | 80 | 60(4) |
| H(9'1) | 5486 | 3343 | 903 | 67(3) |
| H(9'2) | 7122 | 3423 | 1332 | 67(3) |
| H(9'3) | 6853 | 4104 | 710 | 67(3) |
| H(10D) | 7937 | 5094 | 1829 | 63(3) |
| H(10E) | 6799 | 6145 | 1844 | 63(3) |
| H(10F) | 7541 | 5871 | 1245 | 63(3) |

| | | | | |
|---|---|---|---|---|
| H(2A) | -1013 | 2350 | 2420 | 86(7) |
| H(2B) | 173 | 1940 | 2047 | 104(8) |
| H(3C) | 4090 | 3561 | 2525 | 69(6) |
| H(3D) | 5111 | 3884 | 1997 | 106(8) |

## APPENDIX C

**Structural Assignment of 27.**

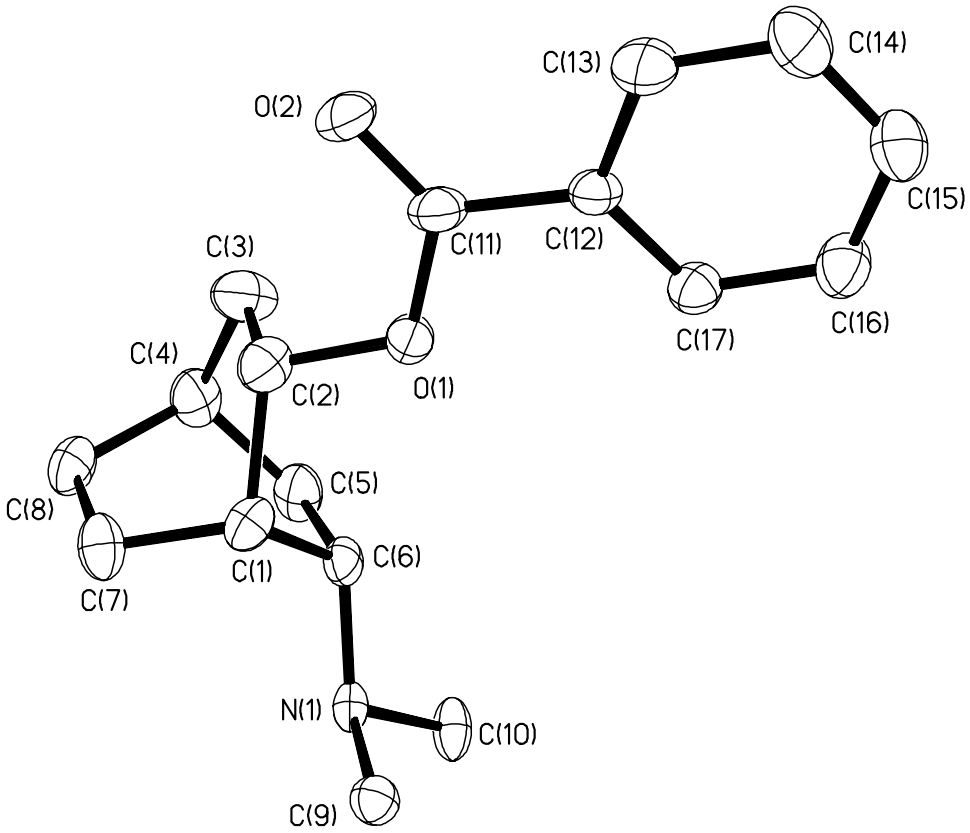



**Figure C.1.** The ORTEP Diagram of Benzoate **27**.

**Table C.1.** Crystal data and structure refinement for benzoate **27**.

| | |
|---|---|
| Identification code | coons4 |
| Empirical formula | C17 H24 Cl N O2 |
| Formula weight | 309.82 |
| Temperature | 198(2) K |
| Wavelength | 0.71073 A |
| Crystal system, space group | Monoclinic, P2(1)/c |
| Unit cell dimensions | a = 6.3245(9) A alpha = 90 deg.<br>b = 10.8229(15) A beta = 96.448(2) deg.<br>c = 24.494(3) A gamma = 90 deg. |
| Volume | 1666.0(4) A^3 |
| Z, Calculated density | 4, 1.235 Mg/m^3 |
| Absorption coefficient | 0.234 mm^-1 |
| F(000) | 664 |
| Crystal size | 0.24 x 0.22 x 0.04 mm |
| Theta range for data collection | 1.67 to 25.00 deg. |
| Limiting indices | -7<=h<=4, -11<=k<=12, -29<=l<=27 |
| Reflections collected / unique | 8320 / 2925 [R(int) = 0.0664] |
| Completeness to theta = 25.00 | 99.8 % |
| Absorption correction | None |
| Max. and min. transmission | 0.9907 and 0.9465 |
| Refinement method | Full-matrix least-squares on F^2 |
| Data / restraints / parameters | 2925 / 0 / 208 |
| Goodness-of-fit on F^2 | 1.061 |

| | |
|---|---|
| Final R indices [I>2sigma(I)] | R1 = 0.0754, wR2 = 0.1543 |
| R indices (all data) | R1 = 0.1277, wR2 = 0.1875 |
| Largest diff. peak and hole | 0.466 and -0.478 e.A^-3 |

**Table C.2.** Atomic coordinates ( x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for benzoate **27**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| N(1) | -889(6) | -1525(3) | 2283(2) | 33(1) |
| Cl(1) | -3655(2) | 6216(1) | 2438(1) | 41(1) |
| O(1) | -736(5) | 1111(3) | 1024(1) | 49(1) |
| O(2) | -1860(6) | 2068(4) | 225(2) | 64(1) |
| C(1) | -2882(8) | -281(5) | 1512(2) | 43(1) |
| C(2) | -2562(9) | 269(5) | 939(2) | 49(1) |
| C(3) | -2084(11) | -737(5) | 544(2) | 66(2) |
| C(4) | -2400(9) | -2031(5) | 811(2) | 56(2) |
| C(5) | -783(9) | -2153(5) | 1302(2) | 54(1) |
| C(6) | -933(7) | -1036(4) | 1703(2) | 39(1) |
| C(7) | -4875(8) | -1066(5) | 1424(2) | 52(1) |
| C(8) | -4646(9) | -2092(5) | 991(2) | 54(2) |
| C(9) | -1373(8) | -576(4) | 2696(2) | 41(1) |
| C(10) | 1227(7) | -2080(4) | 2470(2) | 48(1) |
| C(11) | -596(9) | 1984(5) | 631(2) | 47(1) |
| C(12) | 1302(8) | 2784(4) | 760(2) | 38(1) |
| C(13) | 1447(10) | 3860(5) | 452(2) | 64(2) |
| C(14) | 3170(11) | 4646(6) | 557(3) | 73(2) |
| C(15) | 4761(10) | 4362(5) | 961(3) | 60(2) |
| C(16) | 4652(9) | 3295(5) | 1263(2) | 56(2) |
| C(17) | 2913(8) | 2508(5) | 1168(2) | 43(1) |

**Table C.3.** Bond lengths [A] and angles [deg] for benzoate **27**.

| | |
|---|---|
| N(1)-C(10) | 1.491(6) |
| N(1)-C(9) | 1.499(6) |
| N(1)-C(6) | 1.514(6) |
| O(1)-C(11) | 1.358(6) |
| O(1)-C(2) | 1.467(6) |
| O(2)-C(11) | 1.209(6) |
| C(1)-C(6) | 1.508(7) |
| C(1)-C(7) | 1.515(7) |
| C(1)-C(2) | 1.561(7) |
| C(2)-C(3) | 1.510(8) |
| C(3)-C(4) | 1.567(8) |
| C(4)-C(5) | 1.494(7) |
| C(4)-C(8) | 1.536(7) |
| C(5)-C(6) | 1.568(7) |
| C(7)-C(8) | 1.553(7) |
| C(11)-C(12) | 1.485(7) |
| C(12)-C(17) | 1.378(6) |
| C(12)-C(13) | 1.395(7) |
| C(13)-C(14) | 1.383(8) |
| C(14)-C(15) | 1.365(8) |
| C(15)-C(16) | 1.378(8) |
| C(16)-C(17) | 1.390(7) |
| | |
| C(10)-N(1)-C(9) | 108.2(4) |
| C(10)-N(1)-C(6) | 110.6(4) |
| C(9)-N(1)-C(6) | 114.2(3) |
| C(11)-O(1)-C(2) | 116.4(4) |
| C(6)-C(1)-C(7) | 112.2(4) |
| C(6)-C(1)-C(2) | 107.5(4) |
| C(7)-C(1)-C(2) | 106.0(4) |
| O(1)-C(2)-C(3) | 109.1(5) |
| O(1)-C(2)-C(1) | 106.8(4) |
| C(3)-C(2)-C(1) | 110.9(4) |
| C(2)-C(3)-C(4) | 109.4(5) |
| C(5)-C(4)-C(8) | 109.6(5) |
| C(5)-C(4)-C(3) | 107.9(5) |
| C(8)-C(4)-C(3) | 108.9(5) |
| C(4)-C(5)-C(6) | 110.6(5) |
| C(1)-C(6)-N(1) | 114.1(4) |
| C(1)-C(6)-C(5) | 109.2(4) |
| N(1)-C(6)-C(5) | 108.8(4) |
| C(1)-C(7)-C(8) | 111.0(5) |
| C(4)-C(8)-C(7) | 109.0(4) |

| | |
|---|---|
| O(2)-C(11)-O(1) | 123.1(5) |
| O(2)-C(11)-C(12) | 125.0(5) |
| O(1)-C(11)-C(12) | 111.8(4) |
| C(17)-C(12)-C(13) | 119.0(5) |
| C(17)-C(12)-C(11) | 122.8(4) |
| C(13)-C(12)-C(11) | 118.2(4) |
| C(14)-C(13)-C(12) | 120.8(6) |
| C(15)-C(14)-C(13) | 119.8(6) |
| C(14)-C(15)-C(16) | 120.0(6) |
| C(15)-C(16)-C(17) | 120.7(5) |
| C(12)-C(17)-C(16) | 119.7(5) |

Symmetry transformations used to generate equivalent atoms:

**Table C.4.** Anisotropic displacement parameters (A^2 x 10^3) for benzoate **27**. The anisotropic displacement factor exponent takes the form: -2 pi^2 [ h^2 a*^2 U11 + ... + 2 h k a* b* U12 ]

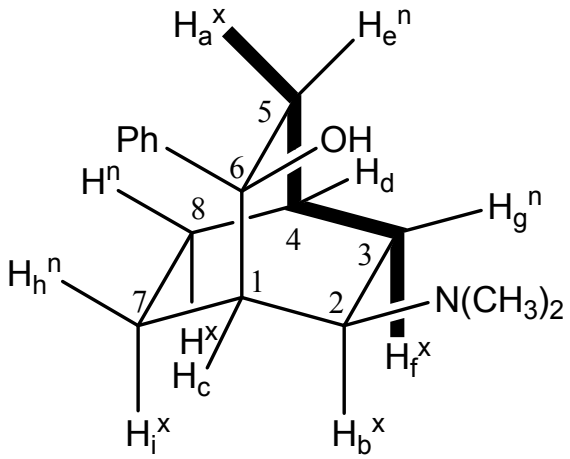
| | U11 | U22 | U33 | U23 | U13 | U12 |
|---|---|---|---|---|---|---|
| N(1) | 25(2) | 28(2) | 46(2) | 1(2) | -3(2) | -3(2) |
| Cl(1) | 33(1) | 30(1) | 59(1) | 0(1) | 3(1) | -6(1) |
| O(1) | 48(2) | 51(2) | 46(2) | 18(2) | -8(2) | -16(2) |
| O(2) | 71(3) | 70(3) | 44(2) | 22(2) | -17(2) | -18(2) |
| C(1) | 45(3) | 38(3) | 44(3) | -4(2) | -6(2) | 1(2) |
| C(2) | 54(4) | 42(3) | 49(3) | 0(3) | -1(3) | -1(3) |
| C(3) | 84(5) | 66(4) | 50(4) | 3(3) | 16(3) | -5(4) |
| C(4) | 56(4) | 52(3) | 60(4) | -19(3) | 10(3) | -9(3) |
| C(5) | 42(3) | 59(3) | 62(4) | -15(3) | 9(3) | 3(3) |
| C(6) | 36(3) | 35(2) | 46(3) | 6(2) | -2(2) | -10(2) |
| C(7) | 34(3) | 46(3) | 76(4) | -2(3) | 3(3) | 3(3) |
| C(8) | 52(3) | 49(3) | 58(3) | -7(3) | -9(3) | -10(3) |
| C(9) | 43(3) | 40(3) | 42(3) | -2(2) | 7(2) | -4(2) |
| C(10) | 30(3) | 32(2) | 78(4) | 7(3) | -8(3) | 1(2) |
| C(11) | 60(4) | 46(3) | 34(3) | 9(3) | 1(3) | -4(3) |
| C(12) | 47(3) | 35(2) | 32(3) | 3(2) | 4(2) | -1(2) |
| C(13) | 75(4) | 55(3) | 58(4) | 24(3) | -10(3) | -10(3) |
| C(14) | 85(5) | 49(3) | 83(5) | 16(3) | -3(4) | -24(4) |
| C(15) | 61(4) | 46(3) | 72(4) | -5(3) | 5(3) | -12(3) |
| C(16) | 49(3) | 52(3) | 63(4) | 5(3) | -9(3) | -1(3) |
| C(17) | 46(3) | 40(3) | 43(3) | 3(2) | 2(2) | 1(2) |

**Table C.5.** Hydrogen coordinates ( x 10^4) and isotropic displacement parameters (A^2 x 10^3) for benzoate **27**.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(1) | -1884 | -2133 | 2280 | 57(16) |
| H(1A) | -3062 | 370 | 1769 | 56(16) |
| H(2) | -3811 | 716 | 793 | 15(10) |
| H(3A) | -646 | -659 | 458 | 94(16) |
| H(3B) | -3018 | -662 | 208 | 94(16) |
| H(4) | -2215 | -2677 | 552 | 72(18) |
| H(5A) | 616 | -2183 | 1185 | 106(18) |
| H(5B) | -1016 | -2911 | 1490 | 106(18) |
| H(6) | 297 | -523 | 1686 | 52(15) |
| H(7A) | -6071 | -551 | 1301 | 91(16) |
| H(7B) | -5136 | -1439 | 1766 | 91(16) |
| H(8A) | -4876 | -2888 | 1147 | 82(14) |
| H(8B) | -5689 | -1975 | 679 | 82(14) |
| H(9A) | -380 | 95 | 2695 | 48(8) |
| H(9B) | -1256 | -944 | 3055 | 48(8) |
| H(9C) | -2793 | -270 | 2604 | 48(8) |
| H(10A) | 2268 | -1436 | 2534 | 66(10) |
| H(10B) | 1632 | -2630 | 2192 | 66(10) |
| H(10C) | 1142 | -2532 | 2804 | 66(10) |
| H(13) | 337 | 4058 | 165 | 68(18) |
| H(14) | 3247 | 5389 | 345 | 130(30) |
| H(15) | 5958 | 4907 | 1034 | 75(19) |
| H(16) | 5790 | 3093 | 1542 | 69(18) |
| H(17) | 2834 | 1776 | 1386 | 54(15) |

## APPENDIX D

### Structural Assignment of 29.




n= endo
x=exo

The stereochemistry at the C-6 stereocenter was previously assigned for amino ketone **19** (Appendix A). Signal **a** at δ 2.31-2.41 ppm in the $^1$H NMR spectrum appears as a multiplet and is assigned to the six protons of dimethyl amine and the *exo* proton on C-3 (Figure D.1). The 2-D NOESY spectrum shows cross-coupling between the *meta* protons on the phenyl ring and signal **a**, since the *exo* proton on C-3 is *cis* to the phenyl ring (Figure D.2). The HMQC spectrum indicates that one of the protons assigned to signal **a** (the *exo* proton on C-3) and the proton assigned to signal **e** apparently are on the

same carbon, C-3 (Figure D.3). Signal **e** appears as a *dt* at δ 2.00 with couplings of 14 Hz (geminal coupling with the *exo* proton on C-3), and 2.1 Hz with the bridgehead proton at C-4 and the *exo* proton at C-8. The NOESY spectrum also shows a cross-coupling peak between signal **e** and signal **g**, assigned as the *endo* proton on C-5. Signal **g** appears as a *qt* at δ 1.81 ppm due to geminal coupling (13.2 Hz with the *exo* proton on C-5), *trans* coupling (7.5 Hz with the *exo* proton on C-6), coupling to the C-4 bridgehead proton (1.8 Hz), and an in-plane "W-coupling" with the *endo* proton on C-8 (2.4 Hz). This peak was assigned to the *endo* proton on C-5 because this is the only proton on the bicycle with these neighboring protons.

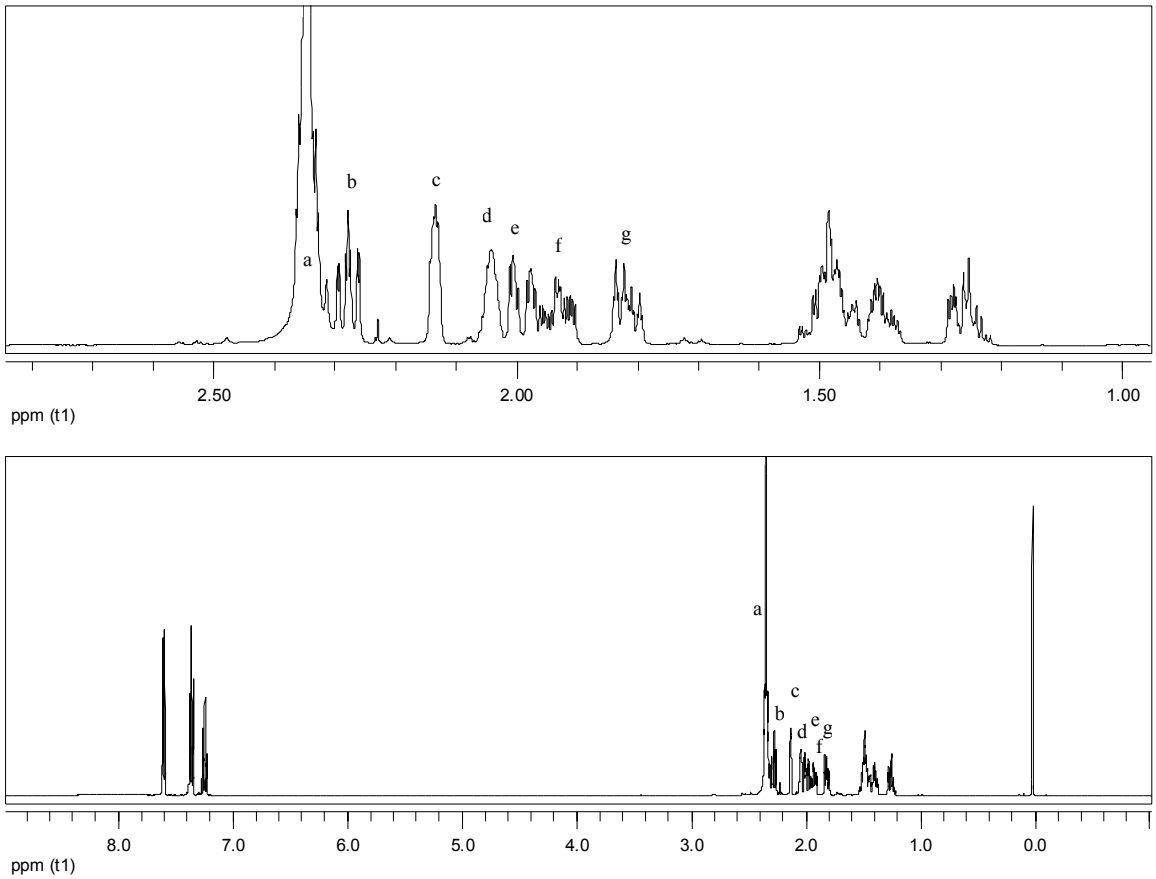



**Figure D.1**. The $^{1}$H NMR spectrum (Bruker AMX 500 MHz, $CDCl_3$) of *endo*-amino-*exo*-phenyl alcohol **29**.

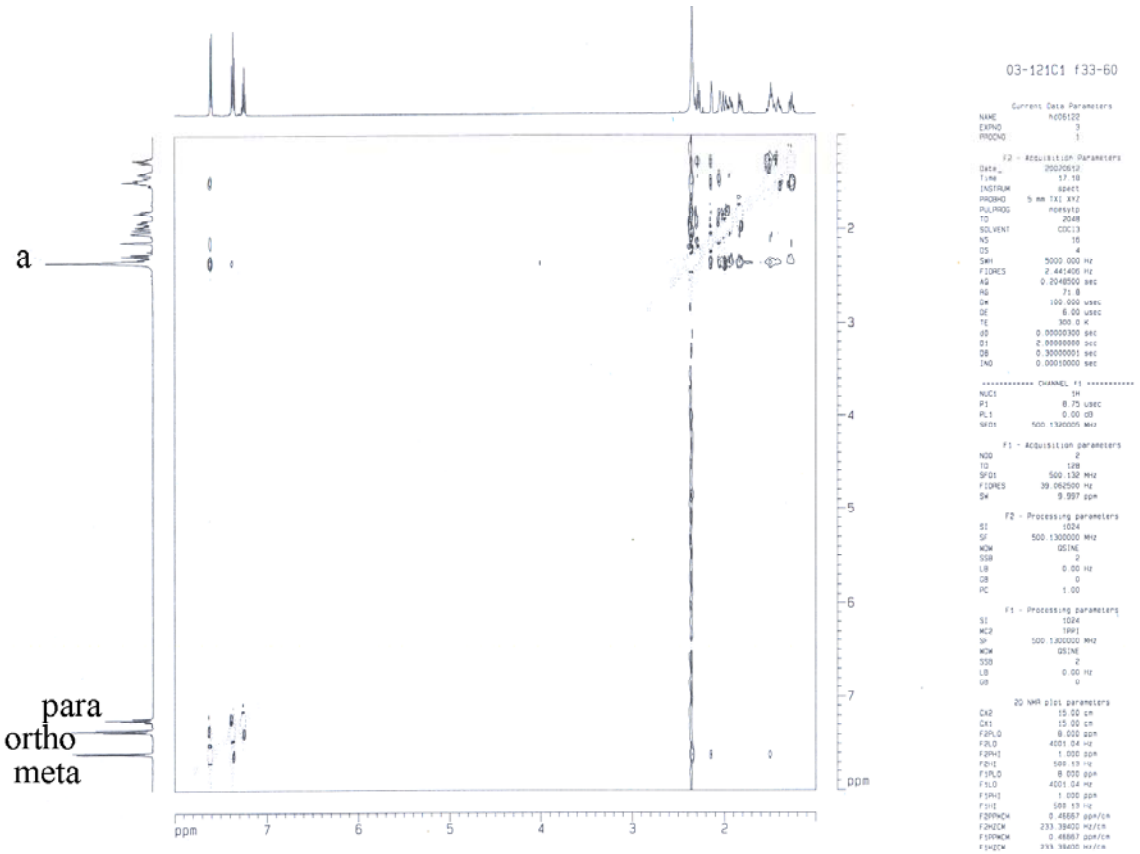



**Figure D.2.** The NOESY spectrum (Bruker AMX 500 MHz, $CDCl_3$) of *endo*-amino-*exo*-phenyl alcohol **29.**

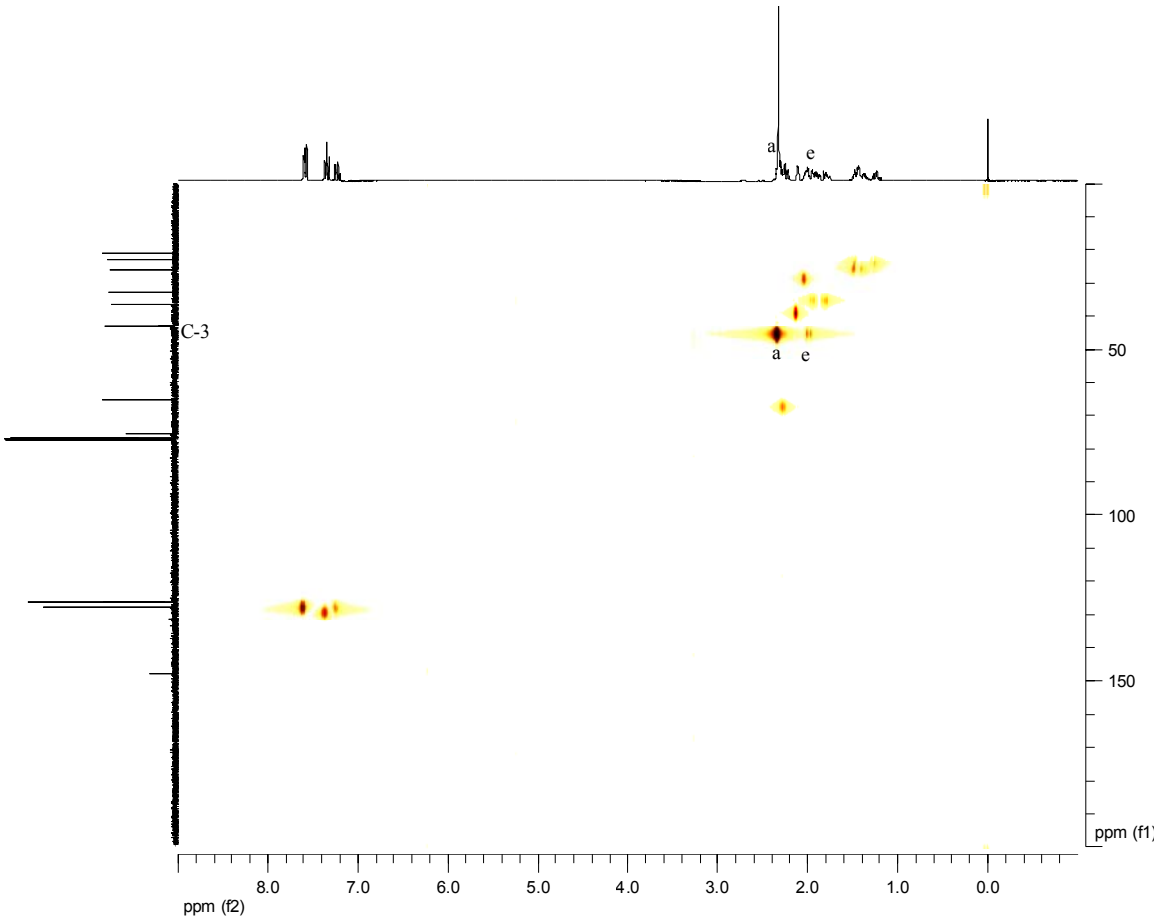
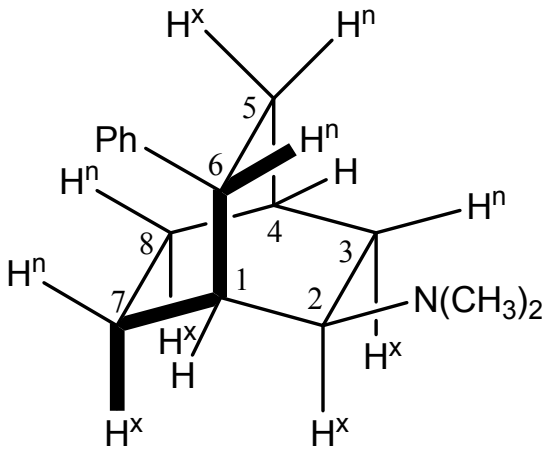



**Figure D.3**. The HMQC NMR (Bruker AMX 500 MHz, $CDCl_3$) of *endo*-amino-*exo*-phenyl alcohol **29**.

## APPENDIX E

### Structural Assignment of 31.




n= endo
x=exo

The stereochemistry at the C-6 stereocenter was previously assigned for amino ketone **19** (Appendix A). The signal at δ 3.31 ppm (signal **a**) in the $^{1}$H NMR spectrum (Figure E.1) of **31** was assigned to the *endo* proton on C-6 based on cross-coupling seen in the HMBC spectrum between the ipso carbon of the *exo* phenyl ring and the benzylic proton on C-6 (Figure E.2). The $^{1}$H NMR spectrum shows a *qt* for signal **a**, which is consistent with *cis* coupling (with the *endo* proton on C-3, 10.5 Hz), *trans* coupling (with the *exo* proton on C-3, 8 Hz), coupling with the bridgehead proton on C-1 (1.5 Hz), and

an in-plane W-coupling with the *exo* proton on C-7 (1.5 Hz). A cross-coupling exists in the NOESY spectrum between the *endo* proton on C-6, signal **a**, and the *endo* dimethyl amine six proton singlet, signal **b** (Figure E.3.). This is the only arrangement on the bicycle, which will give rise to a NOESY between the *endo* proton on C-6 and the *endo* dimethyl amine moiety. The assignment was verified by singly crystal X-ray crystallography.

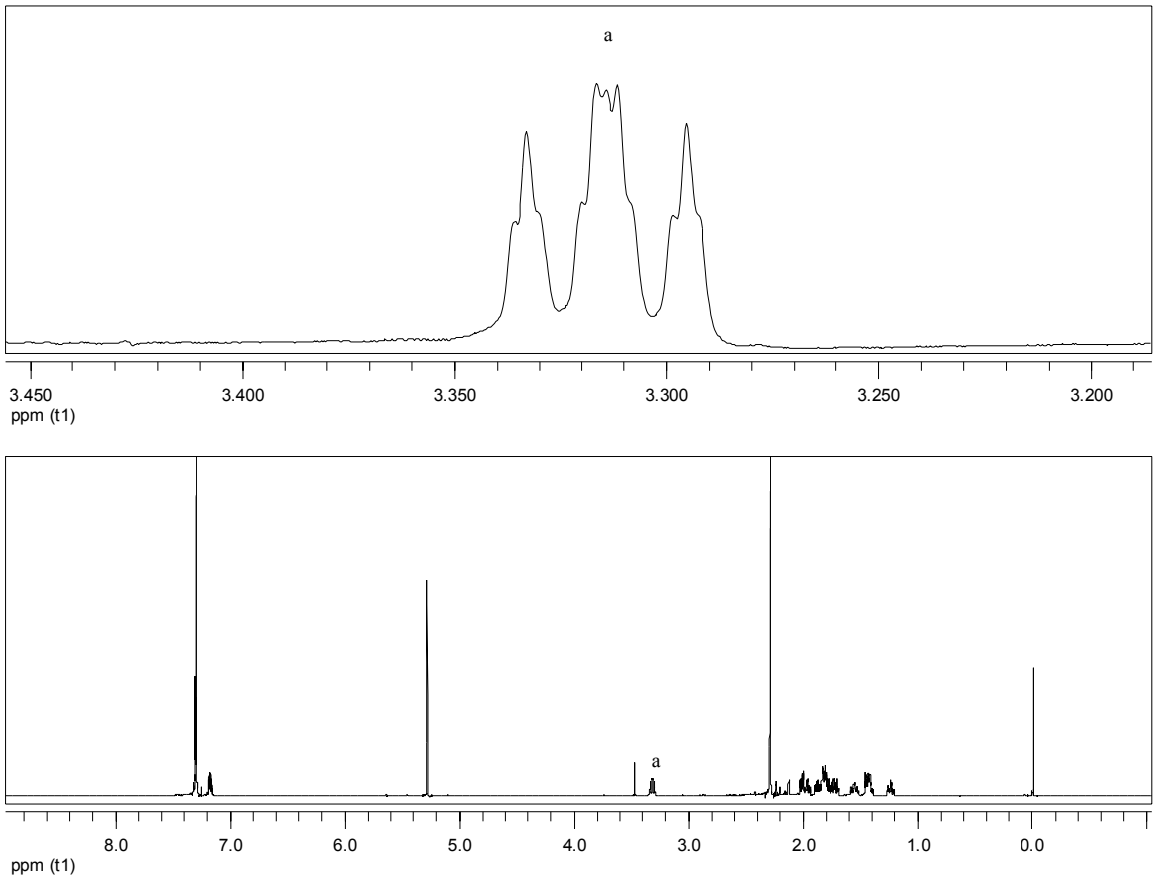



**Figure E.1.** The $^{1}H$ NMR spectrum (Bruker AMX 500 MHz, $CDCl_3$) of arene **31**.

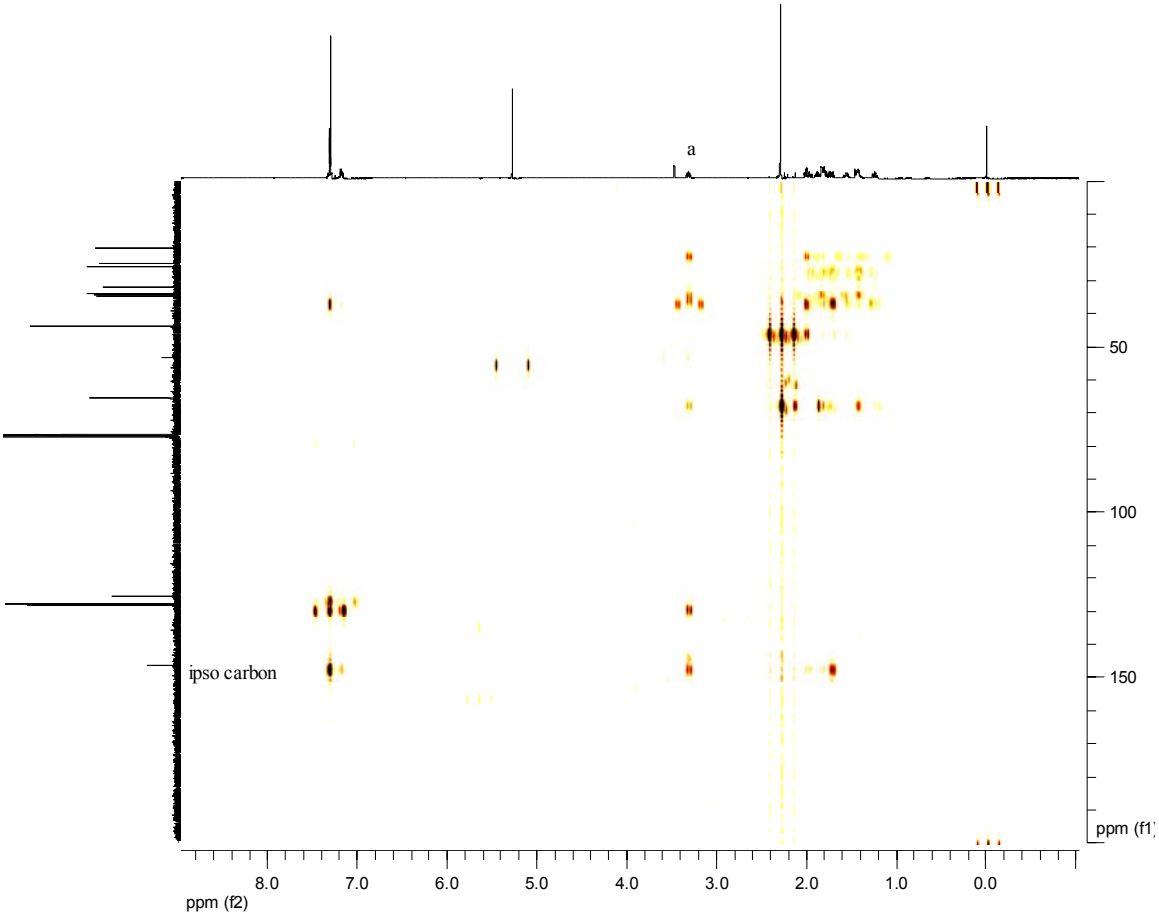



**Figure E.2.** The HMBC spectrum (Bruker AMX 500 MHz, $CDCl_3$) of arene **31**.

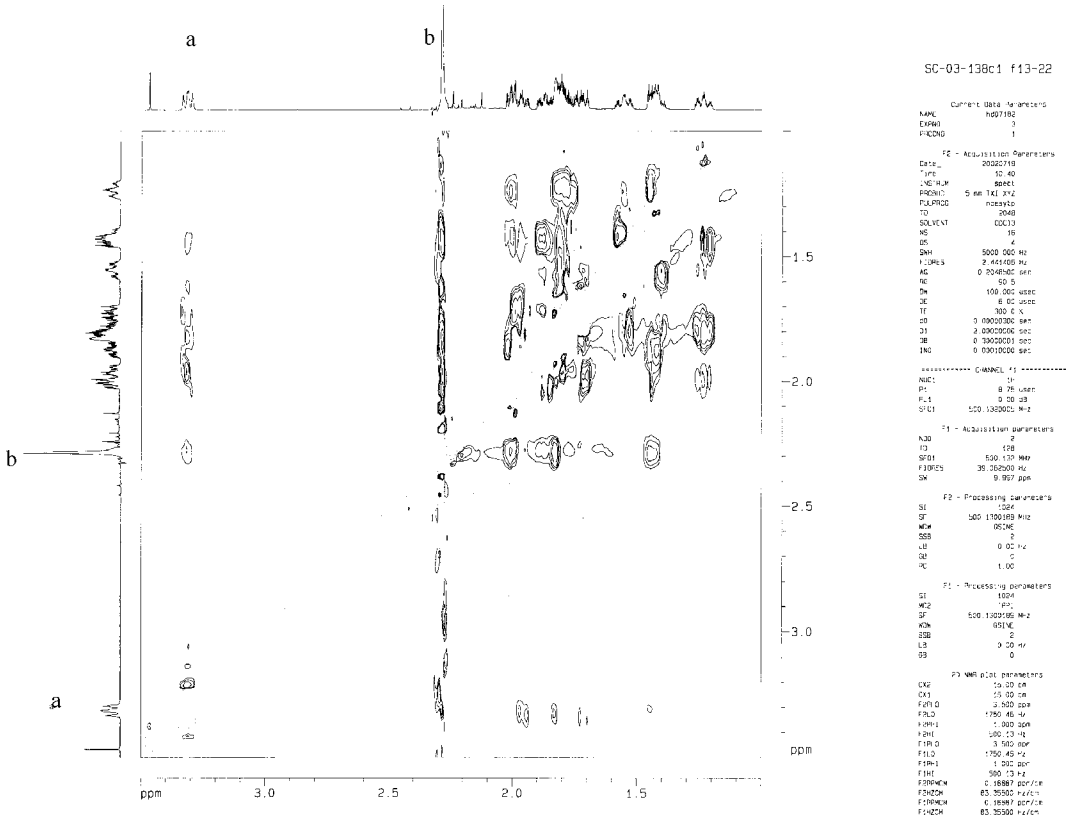



**Figure E.3.** The NOESY spectrum (Bruker AMX 500 MHz, $CDCl_3$) of arene **31**.

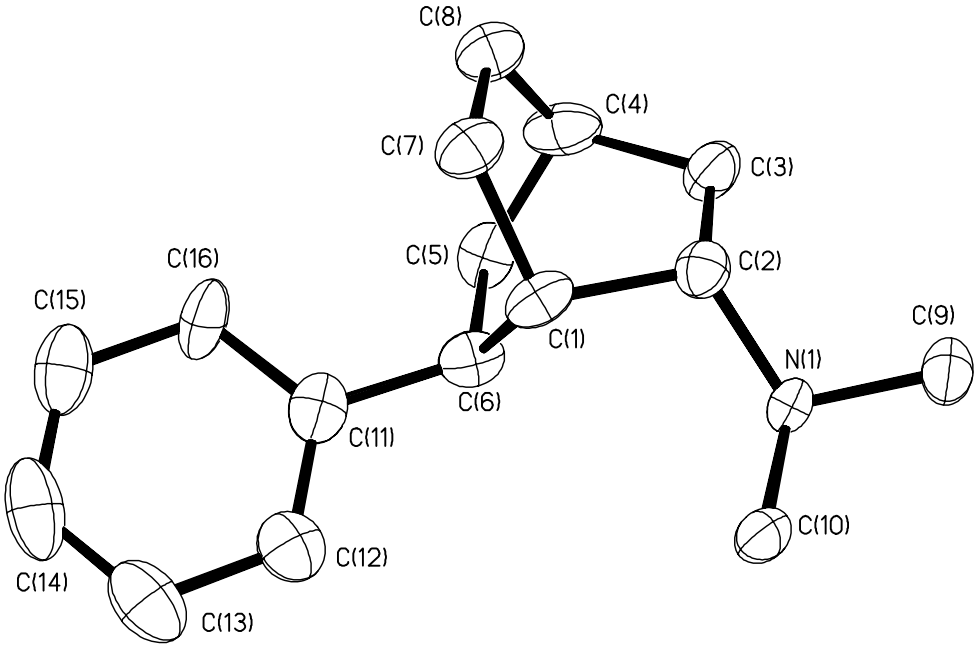



**Figure E.4.** The ORTEP drawing of arene **31**.

**Table E.1.** Crystal data and structure refinement for arene **31**.

| | |
|---|---|
| Identification code | coons6 |
| Empirical formula | C16 H24 Cl N |
| Formula weight | 265.81 |
| Temperature | 301(2) K |
| Wavelength | 0.71073 A |
| Crystal system, space group | Orthorhombic, Pca2(1) |
| Unit cell dimensions | a = 25.700(19) A alpha = 90 deg.<br>b = 7.189(5) A beta = 90 deg.<br>c = 16.001(12) A gamma = 90 deg. |
| Volume | 2956(4) A^3 |
| Z, Calculated density | 8, 1.194 Mg/m^3 |
| Absorption coefficient | 0.243 mm^-1 |
| F(000) | 1152 |
| Crystal size | 0.37 x 0.27 x 0.20 mm |
| Theta range for data collection | 1.58 to 25.10 deg. |
| Limiting indices | -30<=h<=22, -6<=k<=8, -19<=l<=16 |
| Reflections collected / unique | 12554 / 4719 [R(int) = 0.1068] |
| Completeness to theta = 25.10 | 99.4 % |
| Absorption correction | None |
| Max. and min. transmission | 0.9522 and 0.9147 |
| Refinement method | Full-matrix least-squares on F^2 |
| Data / restraints / parameters | 4719 / 1 / 369 |
| Goodness-of-fit on F^2 | 1.039 |

| | |
|---|---|
| Final R indices [I>2sigma(I)] | R1 = 0.0980, wR2 = 0.2242 |
| R indices (all data) | R1 = 0.1570, wR2 = 0.2775 |
| Absolute structure parameter | 0.13(16) |
| Largest diff. peak and hole | 0.788 and -0.454 e.A^-3 |

**Table E.2.** Atomic coordinates ( x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for arene **31**.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| Cl(1) | 1808(1) | 5517(3) | 2747(2) | 55(1) |
| Cl(1') | 5701(1) | -9266(3) | 729(2) | 55(1) |
| Cl(1A) | 1806(9) | 4290(30) | 2761(18) | 23(7) |
| Cl(1B) | 5707(8) | -10700(20) | 708(18) | 14(6) |
| N(1) | 1784(3) | -167(7) | 2765(5) | 40(2) |
| C(1) | 2691(3) | 927(10) | 3225(5) | 53(2) |
| C(2) | 2111(3) | 689(11) | 3459(5) | 47(2) |
| C(3) | 2056(4) | -425(13) | 4279(7) | 59(3) |
| C(4) | 2623(5) | -863(12) | 4629(6) | 71(3) |
| C(5) | 2921(4) | -2026(11) | 3977(6) | 59(2) |
| C(6) | 2952(4) | -973(10) | 3135(5) | 55(2) |
| C(7) | 2940(4) | 2045(10) | 3941(6) | 55(2) |
| C(8) | 2891(4) | 968(12) | 4761(6) | 65(3) |
| C(9) | 1226(4) | 74(11) | 2952(9) | 60(3) |
| C(10) | 1904(4) | 493(13) | 1921(6) | 58(2) |
| C(11) | 3511(3) | -685(9) | 2772(7) | 60(2) |
| C(12) | 3580(5) | -611(12) | 1921(7) | 67(3) |
| C(13) | 4074(6) | -339(13) | 1557(10) | 84(4) |
| C(14) | 4493(6) | -127(14) | 2065(13) | 88(5) |
| C(15) | 4439(5) | -196(13) | 2919(13) | 81(4) |
| C(16) | 3947(4) | -449(14) | 3285(9) | 73(3) |
| N(1') | 5709(3) | -4987(7) | 710(6) | 41(2) |
| C(1') | 4797(3) | -3893(10) | 242(6) | 50(2) |
| C(2') | 5379(3) | -4089(11) | 29(5) | 47(2) |
| C(3') | 5432(4) | -5173(12) | -786(6) | 59(3) |
| C(4') | 4904(4) | -5595(10) | -1170(6) | 54(2) |
| C(5') | 4599(4) | -6810(11) | -542(6) | 60(2) |
| C(6') | 4544(4) | -5800(11) | 300(5) | 56(2) |
| C(7') | 4560(4) | -2748(11) | -464(6) | 55(2) |
| C(8') | 4624(5) | -3774(14) | -1295(7) | 81(3) |
| C(9') | 6279(4) | -4758(11) | 534(8) | 53(3) |
| C(10') | 5586(4) | -4302(12) | 1583(6) | 59(2) |
| C(11') | 3997(3) | -5617(10) | 655(6) | 53(2) |
| C(12') | 3914(4) | -5596(13) | 1523(7) | 67(3) |
| C(13') | 3428(6) | -5340(15) | 1874(10) | 87(4) |
| C(14') | 3001(6) | -5182(13) | 1377(14) | 88(5) |
| C(15') | 3056(5) | -5180(14) | 526(15) | 94(5) |
| C(16') | 3546(5) | -5408(12) | 156(9) | 73(3) |

**Table E.3.** Bond lengths [A] and angles [deg] for arene **31**.

| | |
|---|---|
| Cl(1)-Cl(1A) | 0.88(2) |
| Cl(1')-Cl(1B) | 1.034(17) |
| N(1)-C(10) | 1.464(13) |
| N(1)-C(9) | 1.476(12) |
| N(1)-C(2) | 1.523(11) |
| C(1)-C(6) | 1.528(11) |
| C(1)-C(7) | 1.539(11) |
| C(1)-C(2) | 1.547(12) |
| C(2)-C(3) | 1.544(12) |
| C(3)-C(4) | 1.592(16) |
| C(4)-C(8) | 1.501(13) |
| C(4)-C(5) | 1.540(13) |
| C(5)-C(6) | 1.547(12) |
| C(6)-C(11) | 1.563(13) |
| C(7)-C(8) | 1.529(12) |
| C(11)-C(12) | 1.374(15) |
| C(11)-C(16) | 1.401(14) |
| C(12)-C(13) | 1.410(18) |
| C(13)-C(14) | 1.36(2) |
| C(14)-C(15) | 1.37(2) |
| C(15)-C(16) | 1.405(17) |
| N(1')-C(9') | 1.501(11) |
| N(1')-C(10') | 1.514(13) |
| N(1')-C(2') | 1.525(11) |
| C(1')-C(6') | 1.520(12) |
| C(1')-C(7') | 1.524(12) |
| C(1')-C(2') | 1.541(11) |
| C(2')-C(3') | 1.526(12) |
| C(3')-C(4') | 1.520(14) |
| C(4')-C(8') | 1.507(14) |
| C(4')-C(5') | 1.546(13) |
| C(5')-C(6') | 1.537(13) |
| C(6')-C(11') | 1.521(13) |
| C(7')-C(8') | 1.530(14) |
| C(11')-C(12') | 1.406(15) |
| C(11')-C(16') | 1.415(15) |
| C(12')-C(13') | 1.380(16) |
| C(13')-C(14') | 1.36(2) |
| C(14')-C(15') | 1.37(2) |
| C(15')-C(16') | 1.402(19) |
| C(10)-N(1)-C(9) | 110.7(8) |
| C(10)-N(1)-C(2) | 115.2(6) |

| | |
|---|---|
| C(9)-N(1)-C(2) | 109.9(8) |
| C(6)-C(1)-C(7) | 110.8(7) |
| C(6)-C(1)-C(2) | 110.2(7) |
| C(7)-C(1)-C(2) | 106.1(7) |
| N(1)-C(2)-C(3) | 111.1(6) |
| N(1)-C(2)-C(1) | 113.6(7) |
| C(3)-C(2)-C(1) | 110.6(7) |
| C(2)-C(3)-C(4) | 108.5(7) |
| C(8)-C(4)-C(5) | 110.1(9) |
| C(8)-C(4)-C(3) | 107.3(8) |
| C(5)-C(4)-C(3) | 108.9(8) |
| C(4)-C(5)-C(6) | 110.5(7) |
| C(1)-C(6)-C(5) | 109.5(7) |
| C(1)-C(6)-C(11) | 108.6(6) |
| C(5)-C(6)-C(11) | 115.8(8) |
| C(8)-C(7)-C(1) | 109.9(7) |
| C(4)-C(8)-C(7) | 111.1(7) |
| C(12)-C(11)-C(16) | 118.2(11) |
| C(12)-C(11)-C(6) | 119.5(9) |
| C(16)-C(11)-C(6) | 122.3(10) |
| C(11)-C(12)-C(13) | 122.1(12) |
| C(14)-C(13)-C(12) | 118.8(14) |
| C(13)-C(14)-C(15) | 120.8(14) |
| C(14)-C(15)-C(16) | 120.6(14) |
| C(11)-C(16)-C(15) | 119.5(13) |
| C(9')-N(1')-C(10') | 110.0(8) |
| C(9')-N(1')-C(2') | 111.3(7) |
| C(10')-N(1')-C(2') | 113.9(6) |
| C(6')-C(1')-C(7') | 111.2(7) |
| C(6')-C(1')-C(2') | 110.2(7) |
| C(7')-C(1')-C(2') | 105.8(7) |
| N(1')-C(2')-C(3') | 110.1(7) |
| N(1')-C(2')-C(1') | 114.9(7) |
| C(3')-C(2')-C(1') | 108.9(7) |
| C(4')-C(3')-C(2') | 111.5(8) |
| C(8')-C(4')-C(3') | 107.9(7) |
| C(8')-C(4')-C(5') | 109.6(8) |
| C(3')-C(4')-C(5') | 107.7(8) |
| C(6')-C(5')-C(4') | 110.4(7) |
| C(11')-C(6')-C(1') | 109.8(7) |
| C(11')-C(6')-C(5') | 117.0(8) |
| C(1')-C(6')-C(5') | 109.5(7) |
| C(1')-C(7')-C(8') | 110.0(7) |
| C(4')-C(8')-C(7') | 110.8(8) |
| C(12')-C(11')-C(16') | 115.6(9) |
| C(12')-C(11')-C(6') | 120.8(8) |

| | |
|---|---|
| C(16')-C(11')-C(6') | 123.6(10) |
| C(13')-C(12')-C(11') | 122.8(11) |
| C(14')-C(13')-C(12') | 120.2(14) |
| C(13')-C(14')-C(15') | 119.8(14) |
| C(14')-C(15')-C(16') | 120.9(15) |
| C(15')-C(16')-C(11') | 120.6(13) |

Symmetry transformations used to generate equivalent atoms:

**Table E.4.** Anisotropic displacement parameters (A^2 x 10^3) for arene **31**.
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [ h^2 a*^2 U11 + ... + 2 h k a* b* U12 ].

| | U11 | U22 | U33 | U23 | U13 | U12 |
|---|---|---|---|---|---|---|
| Cl(1) | 45(1) | 43(2) | 76(2) | -2(1) | -3(1) | -1(1) |
| Cl(1') | 46(1) | 45(1) | 74(2) | 3(1) | -7(1) | 2(1) |
| N(1) | 32(4) | 43(3) | 45(4) | 1(3) | -8(4) | -3(2) |
| C(1) | 67(7) | 44(4) | 46(5) | 3(3) | -19(5) | -4(4) |
| C(2) | 45(5) | 42(5) | 53(5) | -2(3) | -3(4) | -3(3) |
| C(3) | 52(7) | 75(6) | 51(6) | 7(4) | -11(5) | -9(4) |
| C(4) | 107(10) | 65(6) | 42(5) | 4(4) | -1(5) | -22(5) |
| C(5) | 58(6) | 46(4) | 72(6) | 17(4) | -6(5) | -6(4) |
| C(6) | 71(7) | 43(4) | 50(5) | 4(4) | -8(5) | 5(4) |
| C(7) | 65(6) | 39(4) | 60(6) | -5(4) | -10(5) | -3(4) |
| C(8) | 72(7) | 72(6) | 51(5) | 3(4) | -12(5) | 1(5) |
| C(9) | 39(6) | 74(6) | 67(9) | 2(4) | -4(6) | 3(4) |
| C(10) | 43(5) | 92(7) | 38(5) | 6(4) | -7(4) | -8(4) |
| C(11) | 55(6) | 42(4) | 83(7) | -2(5) | -6(5) | 4(3) |
| C(12) | 70(8) | 55(6) | 77(7) | -3(4) | 7(6) | 7(4) |
| C(13) | 90(11) | 62(6) | 99(10) | -1(6) | 34(9) | 17(6) |
| C(14) | 51(10) | 55(6) | 156(18) | 12(6) | 26(11) | 15(5) |
| C(15) | 50(9) | 63(6) | 131(14) | 9(6) | -8(9) | 4(4) |
| C(16) | 39(7) | 84(7) | 97(10) | 16(6) | -22(6) | -4(5) |
| N(1') | 26(4) | 46(3) | 50(4) | 7(3) | 3(4) | -2(2) |
| C(1') | 51(6) | 46(4) | 53(5) | -3(4) | 5(4) | 7(4) |
| C(2') | 53(5) | 46(4) | 43(4) | -2(3) | -4(4) | 1(3) |
| C(3') | 55(7) | 81(6) | 42(6) | -5(4) | 14(5) | 12(4) |
| C(4') | 52(6) | 59(5) | 50(5) | -6(4) | -14(4) | 2(4) |
| C(5') | 52(6) | 52(5) | 75(7) | -15(4) | 0(5) | 0(4) |
| C(6') | 70(7) | 47(5) | 52(5) | 4(4) | -16(5) | -1(4) |
| C(7') | 54(6) | 51(5) | 59(6) | 6(4) | -11(5) | 3(4) |
| C(8') | 91(9) | 72(6) | 80(7) | -4(5) | -13(6) | 8(6) |
| C(9') | 30(6) | 72(5) | 57(7) | 0(4) | 1(5) | -8(3) |
| C(10') | 49(5) | 70(6) | 58(6) | -2(4) | -3(5) | 1(4) |
| C(11') | 39(5) | 55(5) | 64(6) | 1(4) | -1(4) | -1(3) |
| C(12') | 53(7) | 70(6) | 78(7) | 6(5) | -4(6) | 0(5) |
| C(13') | 75(10) | 79(7) | 106(11) | -5(6) | 50(9) | -9(6) |
| C(14') | 52(10) | 63(7) | 149(16) | 2(7) | 37(11) | -10(5) |
| C(15') | 33(8) | 78(7) | 172(19) | 15(7) | -12(9) | -1(4) |
| C(16') | 55(8) | 74(7) | 91(9) | 14(6) | -10(6) | -5(5) |

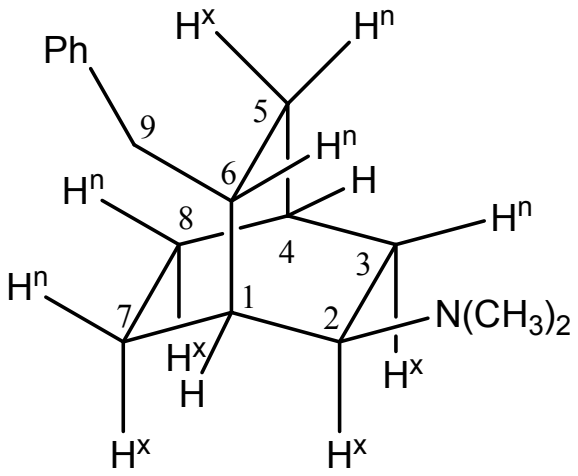
**Table E.5.** Hydrogen coordinates ( x 10^4) and isotropic displacement parameters (A^2 x 10^3) for arene **31**.

| | X | y | z | U(eq) |
|---|---|---|---|---|
| H(1) | 1850 | -1439 | 2771 | 26(14) |
| H(1) | 2721 | 1606 | 2710 | 60(20) |
| H(2) | 1974 | 1910 | 3563 | 80(30) |
| H(3A) | 1872 | -1564 | 4176 | 100(20) |
| H(3B) | 1863 | 286 | 4682 | 100(20) |
| H(4) | 2600 | -1530 | 5147 | 60(20) |
| H(5A) | 2746 | -3194 | 3896 | 62(16) |
| H(5B) | 3266 | -2277 | 4177 | 62(16) |
| H(6) | 2756 | -1672 | 2732 | 60(20) |
| H(7A) | 3300 | 2268 | 3820 | 80(20) |
| H(7B) | 2769 | 3227 | 3993 | 80(20) |
| H(8A) | 3232 | 755 | 4989 | 120(30) |
| H(8B) | 2698 | 1695 | 5157 | 120(30) |
| H(9A) | 1160 | -276 | 3522 | 50(12) |
| H(9B) | 1024 | -697 | 2586 | 50(12) |
| H(9C) | 1131 | 1353 | 2872 | 50(12) |
| H(10D) | 1640 | 72 | 1541 | 130(30) |
| H(10E) | 2236 | 14 | 1750 | 130(30) |
| H(10F) | 1914 | 1828 | 1919 | 130(30) |
| H(12) | 3283 | -750 | 1563 | 70(30) |
| H(13) | 4113 | -304 | 961 | 80(30) |
| H(14) | 4830 | 73 | 1825 | 120(50) |
| H(15) | 4741 | -69 | 3268 | 150(70) |
| H(16) | 3911 | -460 | 3882 | 70(30) |
| H(1') | 5639 | -6255 | 700 | 80(30) |
| H(1') | 4757 | -3245 | 763 | 37(17) |
| H(2') | 5513 | -2862 | -66 | 100 |
| H(3'A) | 5636 | -4463 | -1175 | 66(18) |
| H(3'B) | 5612 | -6319 | -680 | 66(18) |
| H(4') | 4944 | -6233 | -1693 | 50(20) |
| H(5'A) | 4260 | -7078 | -763 | 90(20) |
| H(5'B) | 4777 | -7968 | -461 | 90(20) |
| H(6') | 4742 | -6501 | 699 | 38(17) |
| H(7'1) | 4730 | -1560 | -494 | 71(19) |
| H(7'2) | 4198 | -2540 | -355 | 71(19) |
| H(8'1) | 4288 | -4003 | -1535 | 80(20) |
| H(8'2) | 4818 | -3011 | -1677 | 80(20) |

| | | | | |
|---|---|---|---|---|
| H(9'1) | 6363 | -3458 | 511 | 73(16) |
| H(9'2) | 6362 | -5330 | 8 | 73(16) |
| H(9'3) | 6477 | -5341 | 970 | 73(16) |
| H(10A) | 5855 | -4691 | 1959 | 56(14) |
| H(10B) | 5259 | -4812 | 1761 | 56(14) |
| H(10C) | 5565 | -2969 | 1581 | 56(14) |
| H(12') | 4207 | -5766 | 1887 | 100(40) |
| H(13') | 3392 | -5274 | 2470 | 100 |
| H(14') | 2661 | -5073 | 1623 | 130(50) |
| H(15') | 2755 | -5019 | 178 | 90(40) |
| H(16') | 3577 | -5423 | -442 | 40(20) |

## APPENDIX F

**Structural Assignment of 39.**




n= endo
x=exo

The stereochemistry at the C-6 stereocenter was previously assigned for the amino ketone **19** (Appendix A). The HMQC spectrum of benzyl amine **39**, indicates the peaks at δ 2.67 ppm (*dd*, 13.2 and 6.6 Hz, signal **a**) and δ 2.49 ppm (*dd*, 13.2 and 9.3 Hz, signal **b**) in the $^1$H NMR spectrum are on the same carbon (Figure F.1). Signals **a** and **b** were assigned to the two benzylic protons at C-9. The COSY spectrum shows cross-

coupling between signals **a** and **b** and signal **c** (Figure F.2). The peak at δ 2.20 ppm (1H, signal **c**) was assigned to the proton at C-6. The COSY spectrum also shows cross-coupling between signal **c** and the peaks labeled **f** and **l**. Signal **l**, a *quartet of triplets*, was assigned to the *exo* proton on C-5 based on the $^{1}$H NMR spectrum (Figure F.3) coupling constants (J= $12_{geminal}$, $7_{trans}$, $2_{bridgehead\ and\ W}$ Hz). Also, the NOESY spectrum shows a cross-coupling between signals **a** and **l**, which indicates the close proximity of the protons on C-5 to the benzyl proton on C-9 (Figure F.4). The HMQC spectrum indicates the multiplet labeled **f** at δ 1.81-1.73 ppm has two protons on the same carbon. Signal **f** was assigned to the protons at C-7. The COSY spectrum indicates a long-range coupling between the *endo* proton at C-6, signal **f** and signal **e**, the *exo* proton on C-2. This piece of evidence provides the correct relative stereochemistry at C-6.

Further analysis of compounds that contain protons on the same face of the bicycle and whose chemical shifts are affected by the dimethylamine moiety can be found in Appendix P. This provides additional evidence with the relative stereochemical assignment.

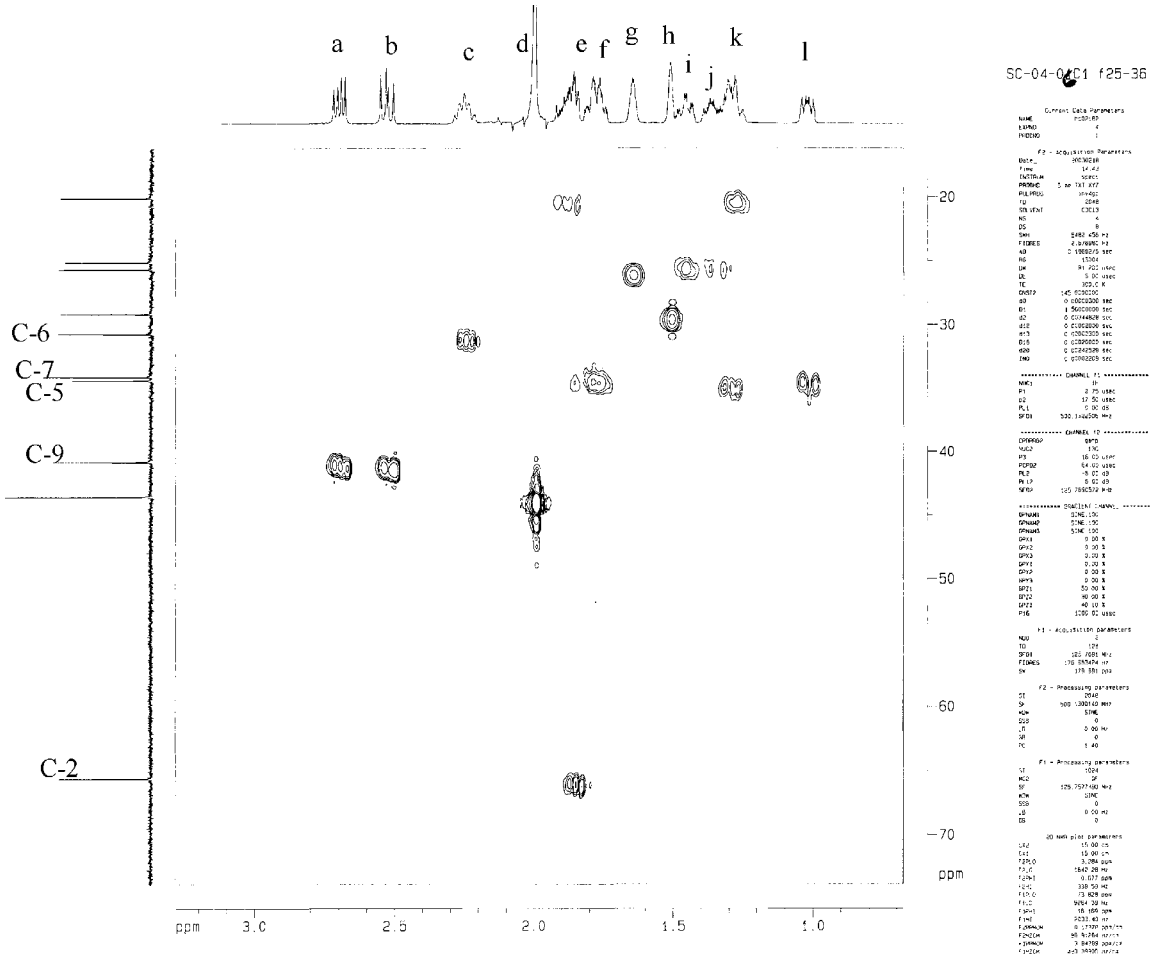



**Figure F.1.** The HMQC spectrum (Bruker AMX 500 MHz, $CDCl_3$) of benzyl arene **39**.

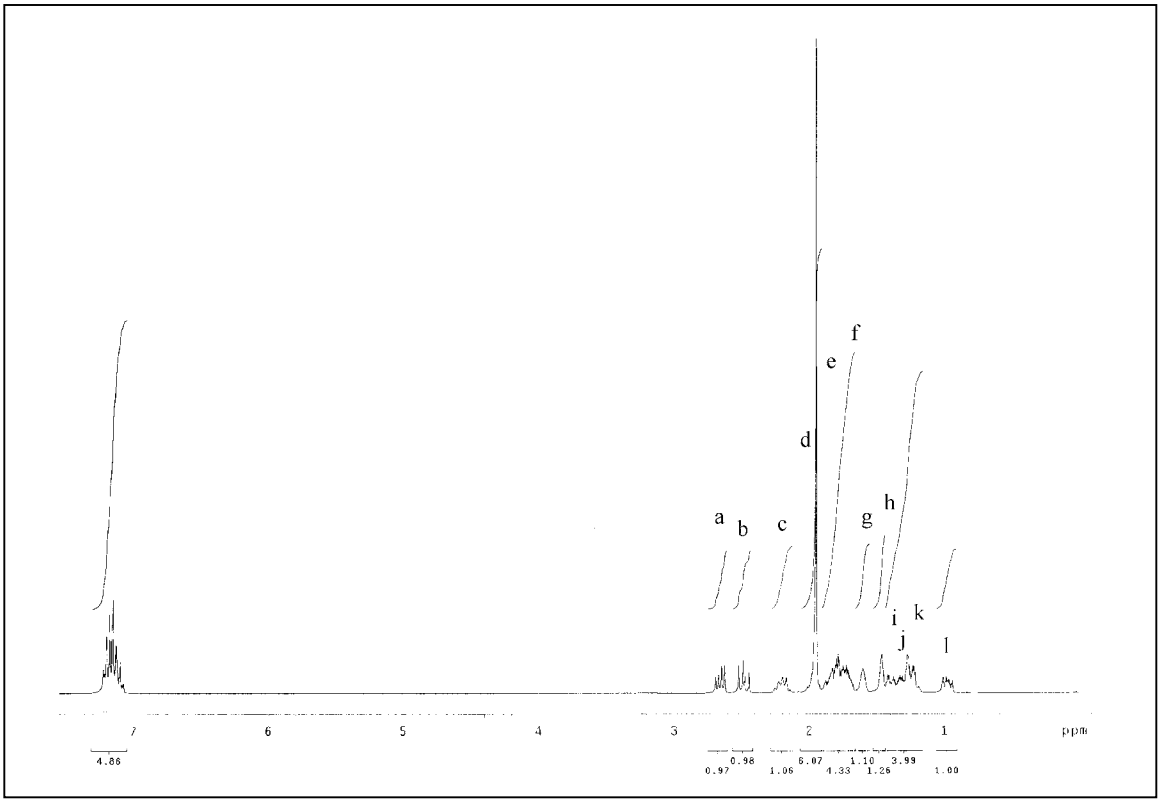



**Figure F.1.** The $^{1}H$ NMR spectrum (Mercury Varian 300 MHz, $CDCl_3$) of benzyl **39**.

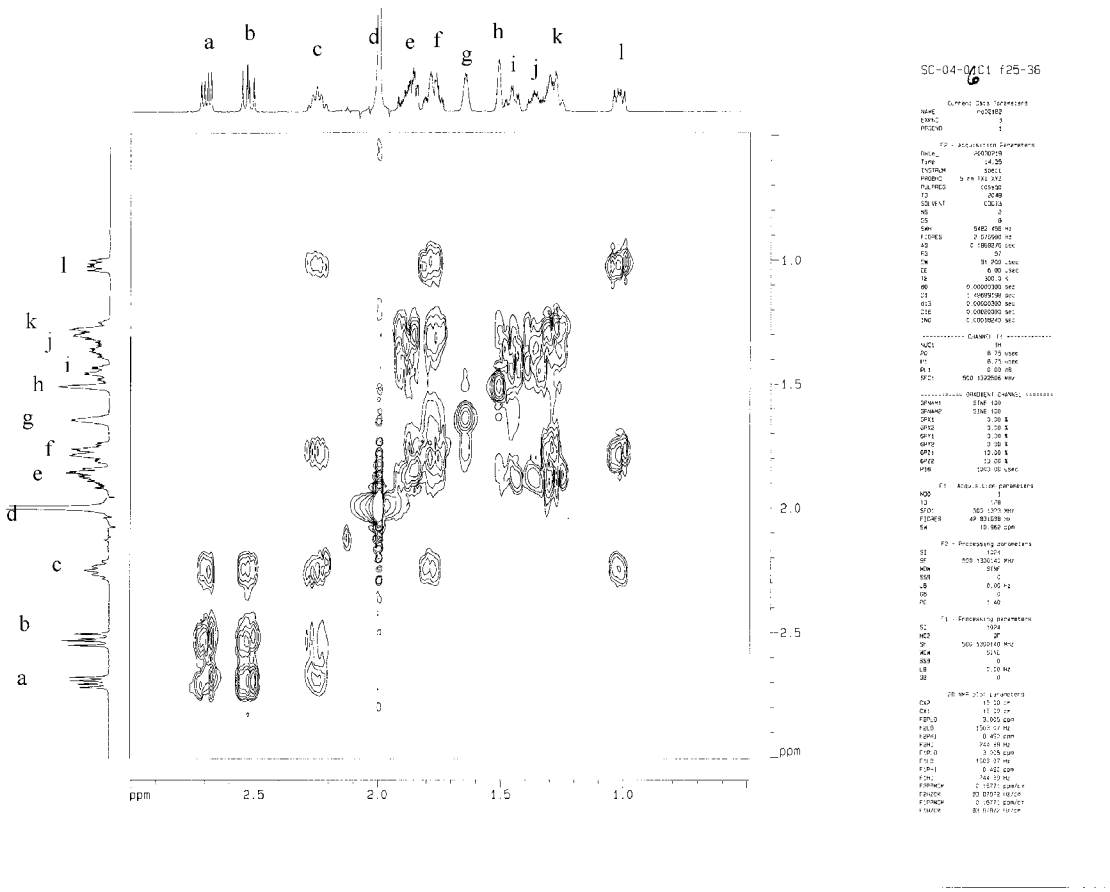



**Figure F.3.** The COSY spectrum (Bruker AMX 500 MHz, $CDCl_3$) of benzyl arene **39**.

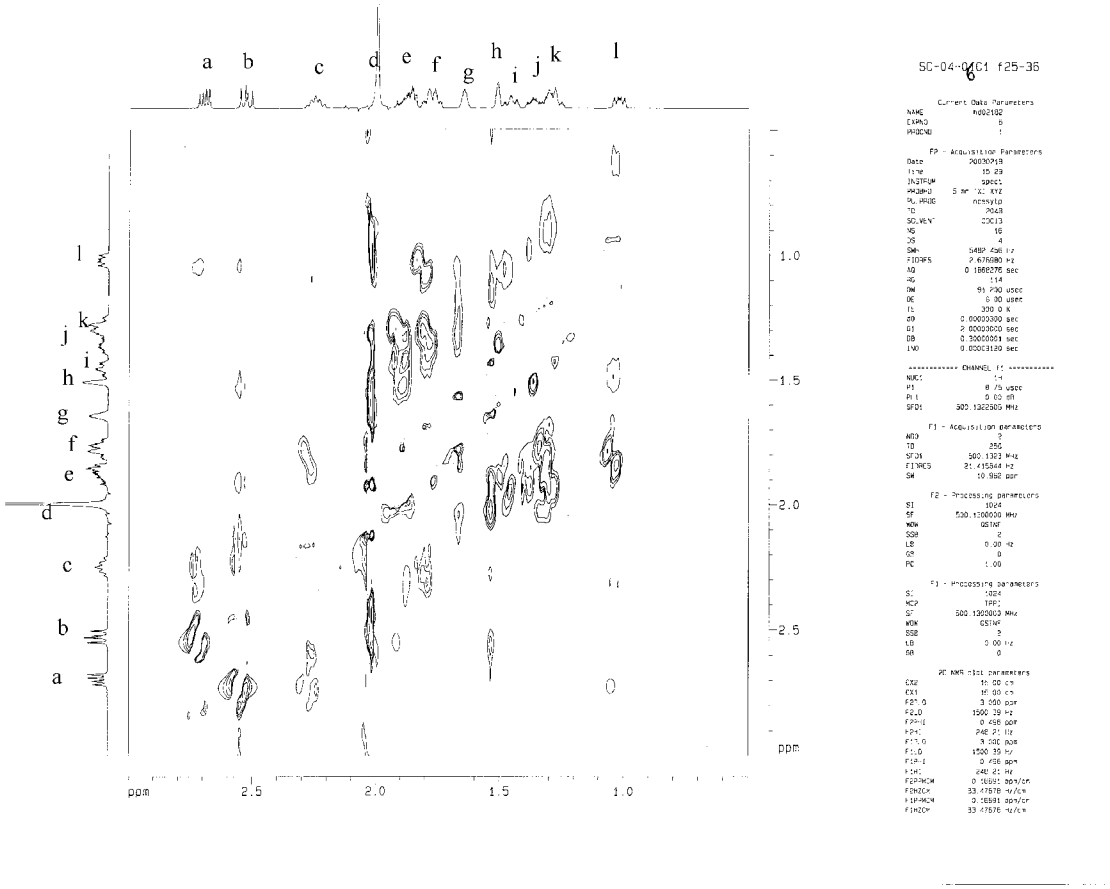
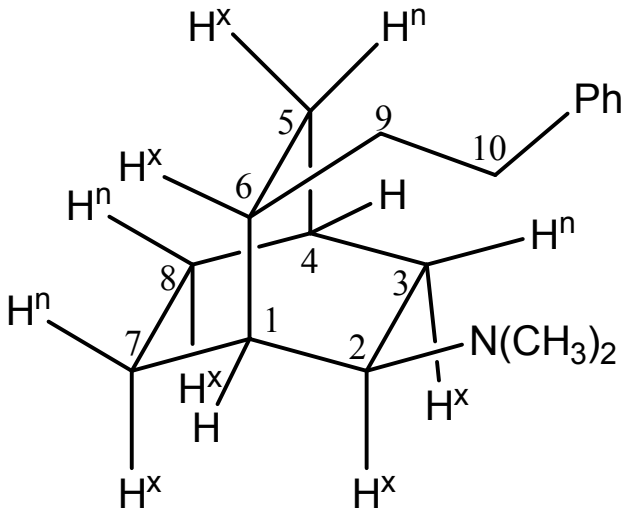



**Figure F.4.** The NOESY spectrum (Bruker AMX 500 MHz, $CDCl_3$) of benzyl arene **39**.

## APPENDIX G

**Structural Assignment of 42.**




n= endo
x=exo

The relative stereochemical assignment of the *endo*-phenethyl arene **42** was determined by single crystal x-ray crystallography.

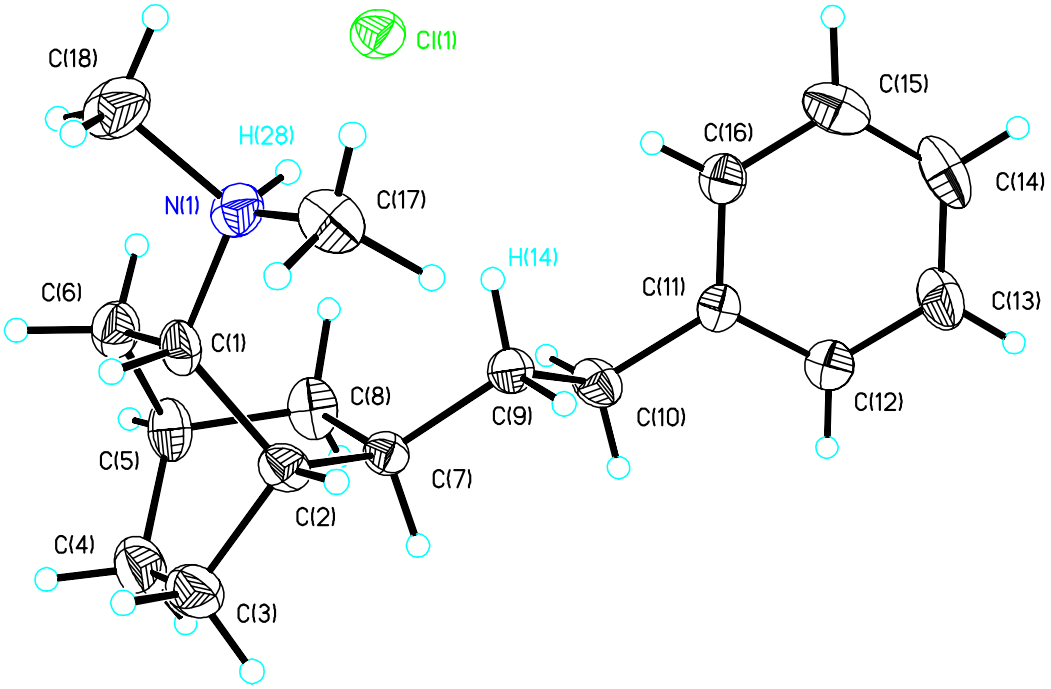



**Figure G.1.** The Ellipsoid Drawing of *endo*-phenethyl arene **42**.

**Table G.1.** Crystal data and structure refinement for *endo*-phenethyl arene **42**.

| | | |
|---|---|---|
| Identification code | sc0520s | |
| Empirical formula | C18 H28 Cl N | |
| Formula weight | 293.86 | |
| Temperature | 173(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/c | |
| Unit cell dimensions | a = 13.157(4) Å | α= 90°. |
| | b = 17.972(5) Å | β= 105.466(7)°. |
| | c = 7.271(2) Å | γ = 90°. |
| Volume | 1657.0(9) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.178 $Mg/m^3$ | |
| Absorption coefficient | 0.223 $mm^{-1}$ | |
| F(000) | 640 | |
| Crystal size | 0.22 x 0.06 x 0.02 $mm^3$ | |
| Theta range for data collection | 1.61 to 24.71°. | |
| Index ranges | -15<=h<=15, -21<=k<=21, -8<=l<=8 | |
| Reflections collected | 17186 | |
| Independent reflections | 2836 [R(int) = 0.1100] | |
| Completeness to theta = 24.71° | 100.0 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 0.9956 and 0.9527 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 2836 / 0 / 292 | |
| Goodness-of-fit on $F^2$ | 1.159 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0895, wR2 = 0.1666 | |
| R indices (all data) | R1 = 0.1140, wR2 = 0.1780 | |
| Largest diff. peak and hole | 0.264 and -0.241 $e.Å^{-3}$ | |

**Table G.2.** Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for *endo*-phenethyl arene **42**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| C(1) | 7802(4) | 1305(2) | 6385(6) | 24(1) |
| C(2) | 7092(4) | 618(3) | 6322(6) | 24(1) |
| C(3) | 6224(4) | 893(3) | 7204(7) | 35(1) |
| C(4) | 5521(5) | 1468(3) | 5875(8) | 41(1) |
| C(5) | 6033(4) | 1675(3) | 4281(7) | 30(1) |
| C(6) | 7171(4) | 1930(3) | 5156(7) | 30(1) |
| C(7) | 6525(3) | 331(2) | 4303(6) | 21(1) |
| C(8) | 6064(4) | 1005(3) | 3017(7) | 33(1) |
| C(9) | 7157(3) | -189(3) | 3358(6) | 23(1) |
| C(10) | 6457(4) | -503(3) | 1477(7) | 27(1) |
| C(11) | 6996(3) | -1025(2) | 405(6) | 21(1) |
| C(12) | 6533(4) | -1699(3) | -271(7) | 28(1) |
| C(13) | 6997(4) | -2180(3) | -1296(7) | 37(1) |
| C(14) | 7927(4) | -1986(3) | -1674(7) | 42(1) |
| C(15) | 8405(4) | -1316(3) | -1049(7) | 38(1) |
| C(16) | 7932(4) | -841(3) | 1(6) | 26(1) |
| C(17) | 9394(4) | 490(3) | 6820(7) | 34(1) |
| C(18) | 9532(5) | 1830(3) | 6423(9) | 40(1) |
| Cl(1) | 8873(1) | 1163(1) | 1687(2) | 31(1) |
| N(1) | 8830(3) | 1167(2) | 5891(5) | 26(1) |

**Table G.3.** Bond lengths [Å] and angles [°] for *endo*-phenethyl arene **42**.

| | |
|---|---|
| C(1)-N(1) | 1.509(6) |
| C(1)-C(6) | 1.535(6) |
| C(1)-C(2) | 1.541(6) |
| C(1)-H(1) | 0.98(5) |
| C(2)-C(3) | 1.534(6) |
| C(2)-C(7) | 1.547(6) |
| C(2)-H(2) | 0.93(4) |
| C(3)-C(4) | 1.542(7) |
| C(3)-H(3) | 0.96(5) |
| C(3)-H(4) | 0.97(5) |
| C(4)-C(5) | 1.533(7) |
| C(4)-H(5) | 0.96(6) |
| C(4)-H(6) | 1.01(6) |
| C(5)-C(8) | 1.523(6) |
| C(5)-C(6) | 1.532(7) |
| C(5)-H(7) | 0.96(5) |
| C(6)-H(8) | 0.97(5) |
| C(6)-H(9) | 0.99(5) |
| C(7)-C(9) | 1.530(6) |
| C(7)-C(8) | 1.552(6) |
| C(7)-H(10) | 1.02(4) |
| C(8)-H(11) | 0.91(4) |
| C(8)-H(12) | 1.08(5) |
| C(9)-C(10) | 1.538(6) |
| C(9)-H(13) | 1.01(5) |
| C(9)-H(14) | 0.95(5) |
| C(10)-C(11) | 1.511(6) |
| C(10)-H(15) | 0.96(5) |
| C(10)-H(16) | 1.03(5) |
| C(11)-C(16) | 1.381(6) |
| C(11)-C(12) | 1.386(6) |
| C(12)-C(13) | 1.384(7) |
| C(12)-H(17) | 0.90(4) |
| C(13)-C(14) | 1.370(8) |
| C(13)-H(18) | 0.95(5) |
| C(14)-C(15) | 1.378(8) |
| C(14)-H(19) | 0.91(5) |
| C(15)-C(16) | 1.397(7) |
| C(15)-H(20) | 0.96(5) |
| C(16)-H(21) | 0.84(5) |
| C(17)-N(1) | 1.490(6) |
| C(17)-H(22) | 1.09(5) |
| C(17)-H(23) | 0.97(5) |
| C(17)-H(24) | 0.85(4) |

| | |
|---|---|
| C(18)-N(1) | 1.494(6) |
| C(18)-H(25) | 0.87(4) |
| C(18)-H(26) | 0.93(4) |
| C(18)-H(27) | 1.01(6) |
| N(1)-H(28) | 0.91(5) |

| | |
|---|---|
| N(1)-C(1)-C(6) | 111.2(4) |
| N(1)-C(1)-C(2) | 115.9(3) |
| C(6)-C(1)-C(2) | 109.9(4) |
| N(1)-C(1)-H(1) | 100(3) |
| C(6)-C(1)-H(1) | 113(3) |
| C(2)-C(1)-H(1) | 106(3) |
| C(3)-C(2)-C(1) | 104.0(4) |
| C(3)-C(2)-C(7) | 106.3(4) |
| C(1)-C(2)-C(7) | 115.5(4) |
| C(3)-C(2)-H(2) | 112(2) |
| C(1)-C(2)-H(2) | 112(2) |
| C(7)-C(2)-H(2) | 107(2) |
| C(2)-C(3)-C(4) | 110.0(4) |
| C(2)-C(3)-H(3) | 107(3) |
| C(4)-C(3)-H(3) | 114(3) |
| C(2)-C(3)-H(4) | 107(3) |
| C(4)-C(3)-H(4) | 111(3) |
| H(3)-C(3)-H(4) | 107(4) |
| C(5)-C(4)-C(3) | 109.0(4) |
| C(5)-C(4)-H(5) | 108(3) |
| C(3)-C(4)-H(5) | 109(3) |
| C(5)-C(4)-H(6) | 106(3) |
| C(3)-C(4)-H(6) | 112(3) |
| H(5)-C(4)-H(6) | 114(5) |
| C(8)-C(5)-C(6) | 107.9(4) |
| C(8)-C(5)-C(4) | 110.6(4) |
| C(6)-C(5)-C(4) | 109.6(4) |
| C(8)-C(5)-H(7) | 111(3) |
| C(6)-C(5)-H(7) | 110(3) |
| C(4)-C(5)-H(7) | 108(3) |
| C(5)-C(6)-C(1) | 109.8(4) |
| C(5)-C(6)-H(8) | 107(3) |
| C(1)-C(6)-H(8) | 111(3) |
| C(5)-C(6)-H(9) | 112(3) |
| C(1)-C(6)-H(9) | 112(3) |
| H(8)-C(6)-H(9) | 104(4) |
| C(9)-C(7)-C(2) | 116.6(4) |
| C(9)-C(7)-C(8) | 112.3(4) |
| C(2)-C(7)-C(8) | 108.9(4) |
| C(9)-C(7)-H(10) | 106(2) |

| | |
|---|---|
| C(2)-C(7)-H(10) | 106(2) |
| C(8)-C(7)-H(10) | 106(2) |
| C(5)-C(8)-C(7) | 108.9(4) |
| C(5)-C(8)-H(11) | 109(3) |
| C(7)-C(8)-H(11) | 108(3) |
| C(5)-C(8)-H(12) | 108(2) |
| C(7)-C(8)-H(12) | 105(2) |
| H(11)-C(8)-H(12) | 117(4) |
| C(7)-C(9)-C(10) | 110.8(4) |
| C(7)-C(9)-H(13) | 110(2) |
| C(10)-C(9)-H(13) | 108(2) |
| C(7)-C(9)-H(14) | 113(3) |
| C(10)-C(9)-H(14) | 108(3) |
| H(13)-C(9)-H(14) | 107(4) |
| C(11)-C(10)-C(9) | 115.7(4) |
| C(11)-C(10)-H(15) | 107(3) |
| C(9)-C(10)-H(15) | 114(3) |
| C(11)-C(10)-H(16) | 108(3) |
| C(9)-C(10)-H(16) | 109(3) |
| H(15)-C(10)-H(16) | 102(4) |
| C(16)-C(11)-C(12) | 117.8(4) |
| C(16)-C(11)-C(10) | 121.9(4) |
| C(12)-C(11)-C(10) | 120.2(4) |
| C(13)-C(12)-C(11) | 121.4(5) |
| C(13)-C(12)-H(17) | 121(3) |
| C(11)-C(12)-H(17) | 118(3) |
| C(14)-C(13)-C(12) | 119.6(5) |
| C(14)-C(13)-H(18) | 121(3) |
| C(12)-C(13)-H(18) | 119(3) |
| C(13)-C(14)-C(15) | 120.7(5) |
| C(13)-C(14)-H(19) | 120(3) |
| C(15)-C(14)-H(19) | 119(3) |
| C(14)-C(15)-C(16) | 118.9(5) |
| C(14)-C(15)-H(20) | 124(3) |
| C(16)-C(15)-H(20) | 117(3) |
| C(11)-C(16)-C(15) | 121.5(5) |
| C(11)-C(16)-H(21) | 116(3) |
| C(15)-C(16)-H(21) | 122(3) |
| N(1)-C(17)-H(22) | 110(3) |
| N(1)-C(17)-H(23) | 108(3) |
| H(22)-C(17)-H(23) | 110(4) |
| N(1)-C(17)-H(24) | 110(3) |
| H(22)-C(17)-H(24) | 109(4) |
| H(23)-C(17)-H(24) | 108(4) |
| N(1)-C(18)-H(25) | 105(3) |
| N(1)-C(18)-H(26) | 108(3) |

| | |
|---|---|
| H(25)-C(18)-H(26) | 106(4) |
| N(1)-C(18)-H(27) | 105(3) |
| H(25)-C(18)-H(27) | 116(5) |
| H(26)-C(18)-H(27) | 117(4) |
| C(17)-N(1)-C(18) | 109.6(4) |
| C(17)-N(1)-C(1) | 113.3(4) |
| C(18)-N(1)-C(1) | 109.8(4) |
| C(17)-N(1)-H(28) | 108(3) |
| C(18)-N(1)-H(28) | 106(3) |
| C(1)-N(1)-H(28) | 110(3) |

Symmetry transformations used to generate equivalent atoms:

**Table G.4.** Anisotropic displacement parameters ($Å^2 x\ 10^3$) for *endo*-phenethyl arene **42**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| C(1) | 32(2) | 22(2) | 19(2) | -5(2) | 6(2) | 1(2) |
| C(2) | 28(2) | 26(2) | 19(2) | 5(2) | 8(2) | 4(2) |
| C(3) | 36(3) | 42(3) | 28(3) | -6(2) | 13(2) | -5(2) |
| C(4) | 40(3) | 38(3) | 47(3) | -10(3) | 16(3) | 6(3) |
| C(5) | 33(3) | 25(3) | 29(3) | -2(2) | 0(2) | 9(2) |
| C(6) | 39(3) | 24(3) | 28(3) | 0(2) | 9(2) | 0(2) |
| C(7) | 19(2) | 23(2) | 22(2) | 1(2) | 6(2) | 2(2) |
| C(8) | 35(3) | 32(3) | 26(3) | -1(2) | 0(2) | 6(2) |
| C(9) | 22(2) | 22(2) | 25(2) | 2(2) | 7(2) | 2(2) |
| C(10) | 18(2) | 34(3) | 29(3) | -3(2) | 4(2) | 4(2) |
| C(11) | 24(2) | 20(2) | 15(2) | 3(2) | 0(2) | 2(2) |
| C(12) | 28(3) | 29(3) | 26(2) | 0(2) | 5(2) | 0(2) |
| C(13) | 38(3) | 36(3) | 37(3) | -13(2) | 9(2) | 4(3) |
| C(14) | 43(3) | 50(3) | 29(3) | -12(3) | 5(2) | 20(3) |
| C(15) | 30(3) | 55(4) | 29(3) | 6(2) | 11(2) | 7(3) |
| C(16) | 27(3) | 27(3) | 22(2) | -3(2) | 4(2) | -2(2) |
| C(17) | 29(3) | 43(3) | 28(3) | 0(2) | 5(2) | 5(3) |
| C(18) | 36(3) | 48(4) | 34(3) | -7(3) | 5(3) | -16(3) |
| Cl(1) | 37(1) | 34(1) | 25(1) | 0(1) | 13(1) | -6(1) |
| N(1) | 27(2) | 29(2) | 21(2) | -4(2) | 4(2) | -6(2) |

**Table G.5.** Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters (Å$^2$x $10^3$) for *endo*-phenethyl arene **42**.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(1) | 8070(30) | 1440(20) | 7740(70) | 30 |
| H(2) | 7460(30) | 210(20) | 6990(50) | 9(10) |
| H(3) | 6570(30) | 1080(20) | 8440(70) | 26(12) |
| H(4) | 5820(40) | 460(30) | 7390(70) | 49(16) |
| H(5) | 5490(40) | 1910(30) | 6590(80) | 61(18) |
| H(6) | 4810(50) | 1260(30) | 5220(90) | 70(20) |
| H(7) | 5630(40) | 2070(30) | 3550(70) | 39(14) |
| H(8) | 7460(40) | 2060(30) | 4100(70) | 35(13) |
| H(9) | 7210(40) | 2400(30) | 5870(70) | 39(14) |
| H(10) | 5890(30) | 30(20) | 4440(50) | 11(10) |
| H(11) | 5390(40) | 880(20) | 2350(60) | 22(12) |
| H(12) | 6620(40) | 1120(20) | 2210(60) | 33(12) |
| H(13) | 7430(30) | -620(20) | 4220(60) | 26(12) |
| H(14) | 7750(40) | 50(30) | 3100(70) | 45(15) |
| H(15) | 5840(40) | -750(30) | 1600(60) | 33(13) |
| H(16) | 6140(40) | -70(30) | 580(70) | 38(13) |
| H(17) | 5930(30) | -1830(20) | 20(60) | 15(11) |
| H(18) | 6690(30) | -2650(30) | -1640(60) | 29(13) |
| H(19) | 8230(40) | -2300(30) | -2370(70) | 40(14) |
| H(20) | 9060(40) | -1150(30) | -1270(70) | 51(16) |
| H(21) | 8170(30) | -420(30) | 340(60) | 26(13) |
| H(22) | 8960(40) | -10(30) | 6220(70) | 45(14) |
| H(23) | 9450(30) | 520(20) | 8180(70) | 30(12) |
| H(24) | 10010(30) | 470(20) | 6660(60) | 15(11) |
| H(25) | 9760(30) | 1810(20) | 7660(70) | 13(11) |
| H(26) | 10120(40) | 1750(20) | 5960(60) | 19(12) |
| H(27) | 9070(50) | 2270(30) | 5890(90) | 70(20) |
| H(28) | 8710(30) | 1120(30) | 4610(70) | 32(13) |

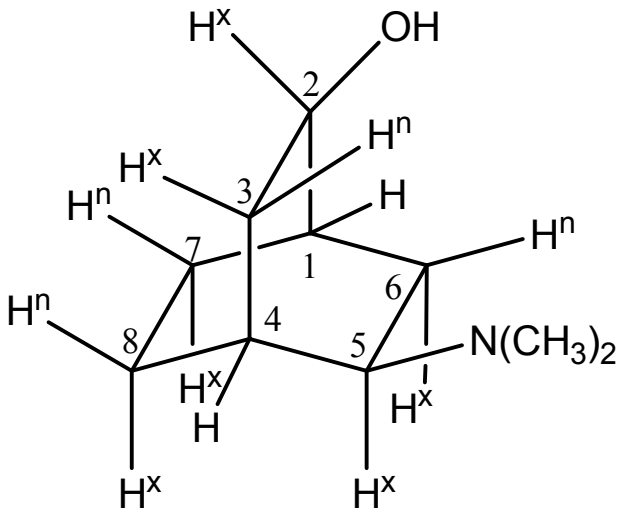
**Table G.6.** Hydrogen bonds for *endo*-phenethyl arene **42** [Å and °].

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|
| N(1)-H(28)...Cl(1) | 0.91(5) | 2.19(5) | 3.072(4) | 163(4) |

Symmetry transformations used to generate equivalent atoms:

## APPENDIX H

**Structural Assignment of 52**.




n= endo
x=exo

The assignment of *endo* amino *endo* alcohol **52** was elucidated by single crystal X-ray diffraction.

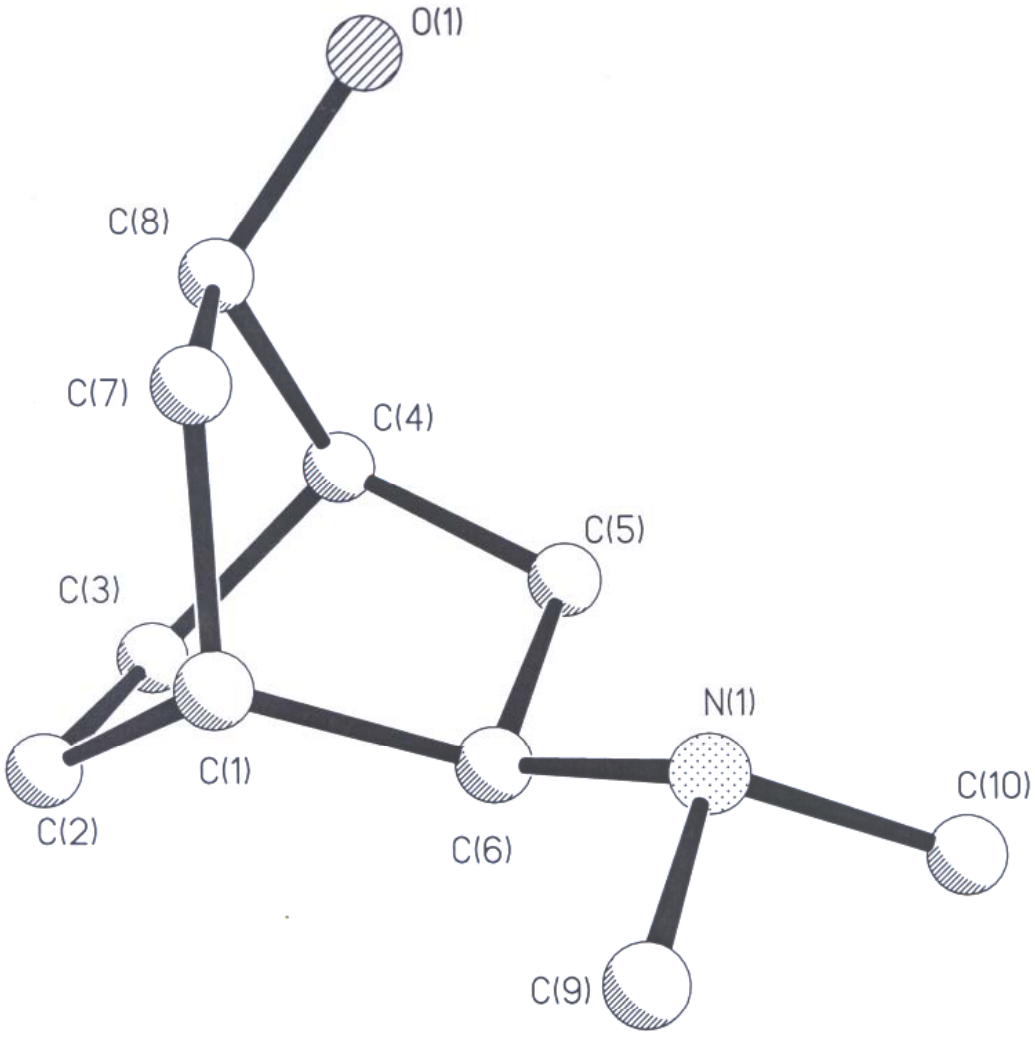
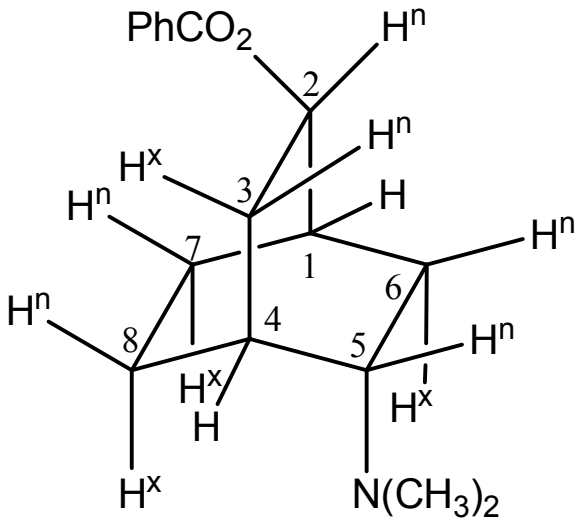



**Figure H.1.** The ORTEP drawing of *endo*-amino-*endo*-alcohol **52**.

## APPENDIX I

**Structural Assignment of 57**.




n= endo
x=exo

The assignment of *exo*-amino-*exo*-benzoate **57** was elucidated by single crystal X-ray diffraction.

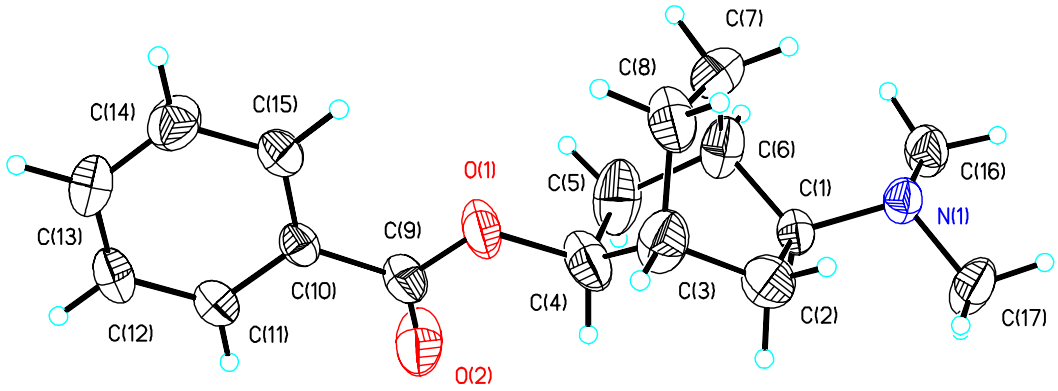



**Figure I.1.** The ORTEP drawing of *exo*-amino- *exo*-benzoate **57**.

**Table I.1.** Crystal data and structure refinement for *exo*-amino-*exo*-benzoate **57**.

| | | |
|---|---|---|
| Identification code | sc04_109 | |
| Empirical formula | C17 H23 N O2 | |
| Formula weight | 273.36 | |
| Temperature | 173(2) K | |
| Wavelength | 1.54178 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/n | |
| Unit cell dimensions | a = 9.0507(8) Å | α= 90°. |
| | b = 11.2442(9) Å | β= 97.826(5)°. |
| | c = 14.8498(14) Å | γ = 90°. |
| Volume | 1497.2(2) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.213 $Mg/m^3$ | |
| Absorption coefficient | 0.621 $mm^{-1}$ | |
| F(000) | 592 | |
| Crystal size | 0.48 x 0.34 x 0.23 $mm^3$ | |
| Theta range for data collection | 4.95 to 66.68°. | |
| Index ranges | -10<=h<=9, -12<=k<=12, -15<=l<=17 | |
| Reflections collected | 7017 | |
| Independent reflections | 2485 [R(int) = 0.1101] | |
| Completeness to theta = 66.68° | 93.7 % | |
| Absorption correction | None | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 2485 / 0 / 183 | |
| Goodness-of-fit on $F^2$ | 1.104 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0823, wR2 = 0.2242 | |
| R indices (all data) | R1 = 0.1097, wR2 = 0.2374 | |
| Largest diff. peak and hole | 0.736 and -0.379 $e.Å^{-3}$ | |

**Table I.2.** Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters (Å$^2$x $10^3$) for *exo*-amino-*exo*-benzoate **57**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| C(1) | -2444(3) | 3613(3) | 2433(2) | 33(1) |
| C(2) | -1093(4) | 4090(4) | 2016(3) | 52(1) |
| C(3) | 266(4) | 4248(4) | 2714(3) | 54(1) |
| C(4) | 548(4) | 3058(3) | 3167(3) | 56(1) |
| C(5) | -705(5) | 2758(4) | 3697(3) | 70(1) |
| C(6) | -2049(4) | 3648(4) | 3462(3) | 49(1) |
| C(7) | -1497(5) | 4868(5) | 3758(3) | 74(2) |
| C(8) | -71(4) | 5172(3) | 3420(3) | 56(1) |
| C(9) | 2752(4) | 2167(3) | 3977(2) | 38(1) |
| C(10) | 4160(3) | 2362(3) | 4611(2) | 29(1) |
| C(11) | 5220(3) | 1468(3) | 4693(2) | 36(1) |
| C(12) | 6533(4) | 1595(3) | 5274(3) | 41(1) |
| C(13) | 6801(4) | 2612(3) | 5776(3) | 45(1) |
| C(14) | 5764(4) | 3509(3) | 5702(3) | 49(1) |
| C(15) | 4432(4) | 3392(3) | 5124(2) | 40(1) |
| C(16) | -5079(4) | 3958(3) | 2513(3) | 46(1) |
| C(17) | -4158(4) | 4182(4) | 1116(3) | 54(1) |
| N(1) | -3775(3) | 4307(2) | 2095(2) | 34(1) |
| O(1) | 1947(3) | 3150(2) | 3820(2) | 55(1) |
| O(2) | 2398(3) | 1228(2) | 3636(2) | 68(1) |

**Table I.3.** Bond lengths [Å] and angles [°] for *exo*-amino-*exo*-benzoate **57**.

| | | | |
|---|---|---|---|
| C(1)-N(1) | 1.466(4) | C(14)-C(15) | 1.388(5) |
| C(1)-C(6) | 1.522(5) | C(14)-H(14) | 0.9500 |
| C(1)-C(2) | 1.540(5) | C(15)-H(15) | 0.9500 |
| C(1)-H(1) | 1.0000 | C(16)-N(1) | 1.461(4) |
| C(2)-C(3) | 1.506(5) | C(16)-H(16A) | 0.9800 |
| C(2)-H(2A) | 0.9900 | C(16)-H(16B) | 0.9800 |
| C(2)-H(2B) | 0.9900 | C(16)-H(16C) | 0.9800 |
| C(3)-C(4) | 1.504(5) | C(17)-N(1) | 1.454(4) |
| C(3)-C(8) | 1.535(6) | C(17)-H(17A) | 0.9800 |
| C(3)-H(3) | 1.0000 | C(17)-H(17B) | 0.9800 |
| C(4)-O(1) | 1.490(4) | C(17)-H(17C) | 0.9800 |
| C(4)-C(5) | 1.505(6) | | |
| C(4)-H(4) | 1.0000 | N(1)-C(1)-C(6) | 113.6(3) |
| C(5)-C(6) | 1.577(6) | N(1)-C(1)-C(2) | 109.7(3) |
| C(5)-H(5A) | 0.9900 | C(6)-C(1)-C(2) | 107.7(3) |
| C(5)-H(5B) | 0.9900 | N(1)-C(1)-H(1) | 108.6 |
| C(6)-C(7) | 1.505(6) | C(6)-C(1)-H(1) | 108.6 |
| C(6)-H(6) | 1.0000 | C(2)-C(1)-H(1) | 108.6 |
| C(7)-C(8) | 1.487(6) | C(3)-C(2)-C(1) | 112.6(3) |
| C(7)-H(7A) | 0.9900 | C(3)-C(2)-H(2A) | 109.1 |
| C(7)-H(7B) | 0.9900 | C(1)-C(2)-H(2A) | 109.1 |
| C(8)-H(8A) | 0.9900 | C(3)-C(2)-H(2B) | 109.1 |
| C(8)-H(8B) | 0.9900 | C(1)-C(2)-H(2B) | 109.1 |
| C(9)-O(2) | 1.196(4) | H(2A)-C(2)-H(2B) | 107.8 |
| C(9)-O(1) | 1.328(4) | C(4)-C(3)-C(2) | 106.0(3) |
| C(9)-C(10) | 1.494(4) | C(4)-C(3)-C(8) | 109.5(3) |
| C(10)-C(11) | 1.384(4) | C(2)-C(3)-C(8) | 109.2(3) |
| C(10)-C(15) | 1.390(4) | C(4)-C(3)-H(3) | 110.7 |
| C(11)-C(12) | 1.378(4) | C(2)-C(3)-H(3) | 110.7 |
| C(11)-H(11) | 0.9500 | C(8)-C(3)-H(3) | 110.7 |
| C(12)-C(13) | 1.369(5) | O(1)-C(4)-C(3) | 107.9(3) |
| C(12)-H(12) | 0.9500 | O(1)-C(4)-C(5) | 108.0(4) |
| C(13)-C(14) | 1.372(5) | C(3)-C(4)-C(5) | 109.9(3) |
| C(13)-H(13) | 0.9500 | O(1)-C(4)-H(4) | 110.4 |

| | | | |
|---|---|---|---|
| C(3)-C(4)-H(4) | 110.4 | C(10)-C(11)-H(11) | 119.7 |
| C(5)-C(4)-H(4) | 110.4 | C(13)-C(12)-C(11) | 120.1(3) |
| C(4)-C(5)-C(6) | 110.8(3) | C(13)-C(12)-H(12) | 120.0 |
| C(4)-C(5)-H(5A) | 109.5 | C(11)-C(12)-H(12) | 120.0 |
| C(6)-C(5)-H(5A) | 109.5 | C(12)-C(13)-C(14) | 120.2(3) |
| C(4)-C(5)-H(5B) | 109.5 | C(12)-C(13)-H(13) | 119.9 |
| C(6)-C(5)-H(5B) | 109.5 | C(14)-C(13)-H(13) | 119.9 |
| H(5A)-C(5)-H(5B) | 108.1 | C(13)-C(14)-C(15) | 120.5(3) |
| C(7)-C(6)-C(1) | 109.8(3) | C(13)-C(14)-H(14) | 119.8 |
| C(7)-C(6)-C(5) | 107.4(3) | C(15)-C(14)-H(14) | 119.8 |
| C(1)-C(6)-C(5) | 105.9(3) | C(14)-C(15)-C(10) | 119.5(3) |
| C(7)-C(6)-H(6) | 111.2 | C(14)-C(15)-H(15) | 120.3 |
| C(1)-C(6)-H(6) | 111.2 | C(10)-C(15)-H(15) | 120.3 |
| C(5)-C(6)-H(6) | 111.2 | N(1)-C(16)-H(16A) | 109.5 |
| C(8)-C(7)-C(6) | 112.3(3) | N(1)-C(16)-H(16B) | 109.5 |
| C(8)-C(7)-H(7A) | 109.1 | H(16A)-C(16)-H(16B) | 109.5 |
| C(6)-C(7)-H(7A) | 109.1 | N(1)-C(16)-H(16C) | 109.5 |
| C(8)-C(7)-H(7B) | 109.1 | H(16A)-C(16)-H(16C) | 109.5 |
| C(6)-C(7)-H(7B) | 109.1 | H(16B)-C(16)-H(16C) | 109.5 |
| H(7A)-C(7)-H(7B) | 107.9 | N(1)-C(17)-H(17A) | 109.5 |
| C(7)-C(8)-C(3) | 109.7(3) | N(1)-C(17)-H(17B) | 109.5 |
| C(7)-C(8)-H(8A) | 109.7 | H(17A)-C(17)-H(17B) | 109.5 |
| C(3)-C(8)-H(8A) | 109.7 | N(1)-C(17)-H(17C) | 109.5 |
| C(7)-C(8)-H(8B) | 109.7 | H(17A)-C(17)-H(17C) | 109.5 |
| C(3)-C(8)-H(8B) | 109.7 | H(17B)-C(17)-H(17C) | 109.5 |
| H(8A)-C(8)-H(8B) | 108.2 | C(17)-N(1)-C(16) | 107.6(3) |
| O(2)-C(9)-O(1) | 123.5(3) | C(17)-N(1)-C(1) | 111.3(3) |
| O(2)-C(9)-C(10) | 123.6(3) | C(16)-N(1)-C(1) | 112.6(3) |
| O(1)-C(9)-C(10) | 112.9(3) | C(9)-O(1)-C(4) | 117.0(3) |
| C(11)-C(10)-C(15) | 119.2(3) | | |
| C(11)-C(10)-C(9) | 118.0(3) | | |
| C(15)-C(10)-C(9) | 122.7(3) | Symmetry transformations used to generate equivalent atoms: | |
| C(12)-C(11)-C(10) | 120.6(3) | | |
| C(12)-C(11)-H(11) | 119.7 | | |

**Table I.4.** Anisotropic displacement parameters ($Å^2 x\ 10^3$) for *exo*-amino-*exo*-benzoate **57**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

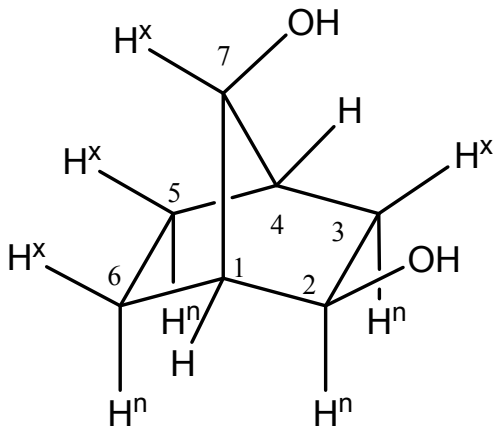
| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| C(1) | 28(2) | 35(2) | 35(2) | 2(1) | 1(1) | 4(1) |
| C(2) | 31(2) | 81(3) | 47(3) | 0(2) | 13(2) | 2(2) |
| C(3) | 38(2) | 78(3) | 47(3) | 13(2) | 7(2) | -5(2) |
| C(4) | 35(2) | 46(2) | 83(3) | -6(2) | -1(2) | 9(2) |
| C(5) | 64(3) | 73(3) | 70(3) | 38(2) | -4(2) | 2(2) |
| C(6) | 33(2) | 72(3) | 42(2) | 20(2) | 3(2) | -5(2) |
| C(7) | 65(3) | 106(4) | 47(3) | -23(2) | -9(2) | 23(3) |
| C(8) | 42(2) | 39(2) | 81(3) | -2(2) | -10(2) | 3(2) |
| C(9) | 32(2) | 31(2) | 51(2) | 0(2) | 5(2) | 4(1) |
| C(10) | 25(2) | 30(2) | 34(2) | 4(1) | 8(1) | 2(1) |
| C(11) | 34(2) | 32(2) | 43(2) | 2(1) | 9(2) | 4(1) |
| C(12) | 29(2) | 44(2) | 51(2) | 12(2) | 6(2) | 9(1) |
| C(13) | 36(2) | 49(2) | 46(2) | 9(2) | -8(2) | -6(2) |
| C(14) | 53(2) | 39(2) | 50(2) | -6(2) | -7(2) | -1(2) |
| C(15) | 41(2) | 34(2) | 45(2) | -2(2) | 1(2) | 10(1) |
| C(16) | 31(2) | 59(2) | 47(2) | 5(2) | 3(2) | 3(2) |
| C(17) | 48(2) | 76(3) | 33(2) | 5(2) | -7(2) | -1(2) |
| N(1) | 28(1) | 39(2) | 32(2) | 5(1) | 0(1) | 2(1) |
| O(1) | 35(1) | 44(1) | 79(2) | -15(1) | -18(1) | 14(1) |
| O(2) | 58(2) | 36(2) | 97(2) | -13(1) | -30(2) | 5(1) |

**Table I.5.** Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for *exo*-amino-*exo*-benzoate **57**.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(1) | -2617 | 2766 | 2240 | 39 |
| H(2A) | -854 | 3532 | 1542 | 62 |
| H(2B) | -1358 | 4865 | 1721 | 62 |
| H(3) | 1143 | 4501 | 2417 | 65 |
| H(4) | 650 | 2429 | 2703 | 67 |
| H(5A) | -340 | 2797 | 4356 | 84 |
| H(5B) | -1050 | 1935 | 3552 | 84 |
| H(6) | -2919 | 3410 | 3771 | 59 |
| H(7A) | -2263 | 5464 | 3529 | 89 |
| H(7B) | -1352 | 4907 | 4430 | 89 |
| H(8A) | 749 | 5183 | 3934 | 67 |
| H(8B) | -146 | 5973 | 3140 | 67 |
| H(11) | 5041 | 760 | 4346 | 43 |
| H(12) | 7254 | 975 | 5327 | 49 |
| H(13) | 7707 | 2698 | 6177 | 54 |
| H(14) | 5959 | 4216 | 6049 | 59 |
| H(15) | 3711 | 4012 | 5080 | 48 |
| H(16A) | -5267 | 3106 | 2416 | 69 |
| H(16B) | -5950 | 4411 | 2238 | 69 |
| H(16C) | -4896 | 4123 | 3167 | 69 |
| H(17A) | -3316 | 4444 | 815 | 81 |
| H(17B) | -5034 | 4671 | 908 | 81 |
| H(17C) | -4381 | 3347 | 966 | 81 |

## APPENDIX J

**Structural Assignment of 60.**




n= endo
x=exo

Signal **a** at δ 3.84 ppm (singlet) in the $^1$H NMR spectrum (Figure J.1) was assigned to the proton on C-7. Signal **b** at δ 3.70 appears as a broad doublet and can be assigned to the *endo* proton on C-2 due to the 6.6 Hz coupling with the *endo* proton on C-3. The exo position of the hydroxyl group on C-2 can be discerned from the lack of coupling between the *endo* proton on C-2 and the proton on C-1. Also, a signal in the

COSY spectrum (Figure J.2) for coupling between signal **a** and signal **b** suggests the proton on C-7 is *exo* and the proton on C-2 is *endo*. This is the only arrangement, which would give rise to a COSY between these two protons. A COSY exists between signal **b** and the peak assigned as signal **c** at δ 1.99 ppm. Signal **c** was assigned to the proton on C-4. Signal **d** at δ 1.90 ppm appears as a *doublet* and can be assigned to the bridgehead proton on C-1. The peak at δ 1.75 ppm, which appears as a *doublet of doublets* (13.8 and 7.5 Hz), was assigned to the *endo* proton on C-3 (signal **e**). Signal **f** at δ 1.60 ppm (doublet) was assigned to the *exo* proton on C-3. The multiplet at δ 1.46-1.23 ppm was assigned to the *endo* protons on C-6 and C-5, signal **g**. The HMQC spectrum (Figure J.3) shows the two protons are on different carbons. A COSY between signal **g** and signal **d**, and signal **g** and signal **c** suggests the two protons in signal **g** are the *endo* protons on C-6 and C-5. The multiplet at δ 0.91-0.79 ppm was assigned to the *exo* protons on C-6 and C-5, signal **h**.

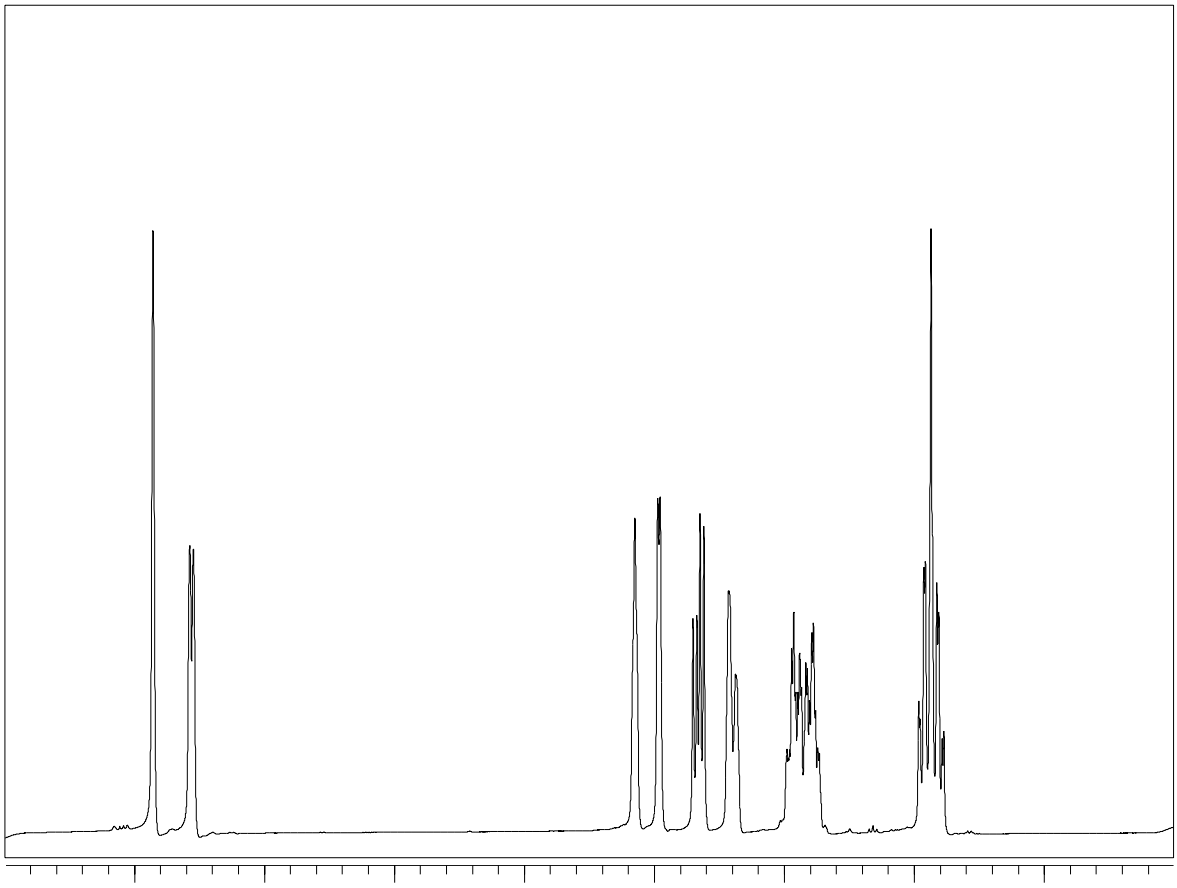


**Figure J.1.** The $^{1}$H NMR spectrum of syn diol **60**.

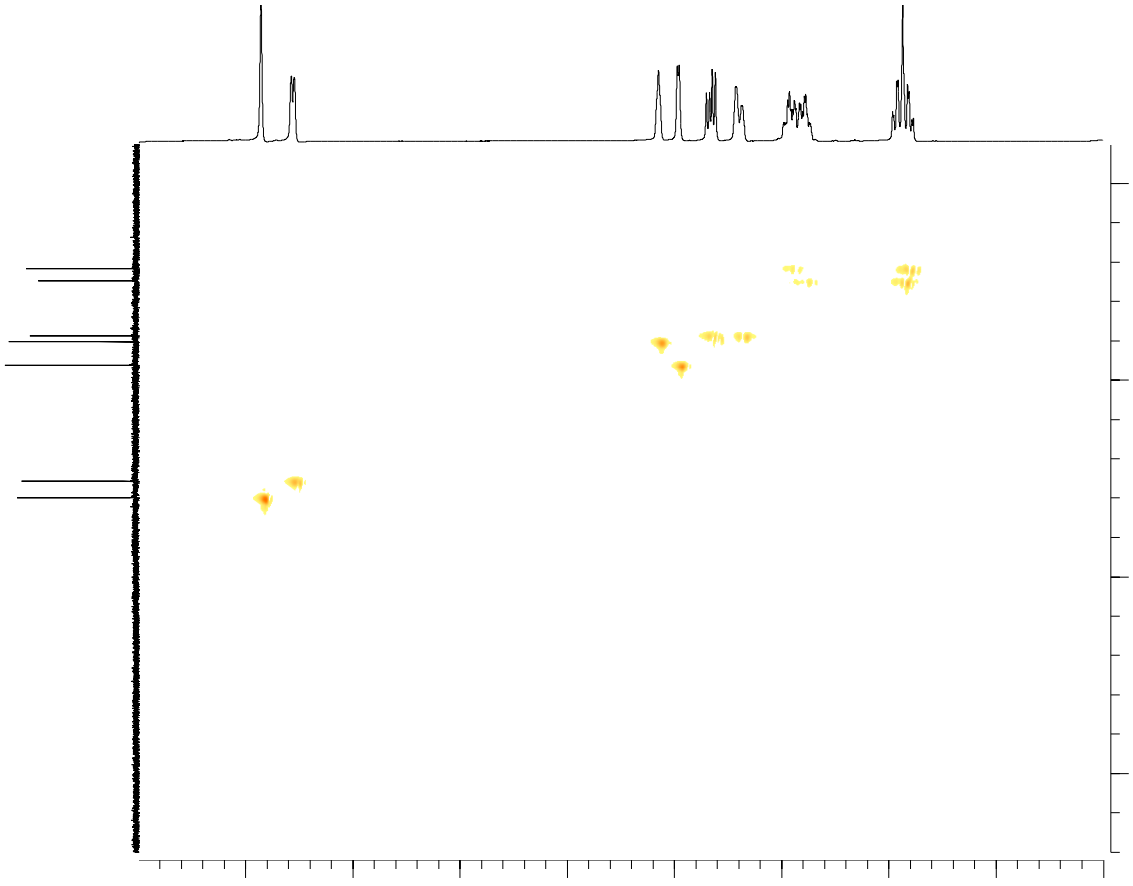


**Figure J.2.** The HMQC NMR spectrum of syn diol **60**.

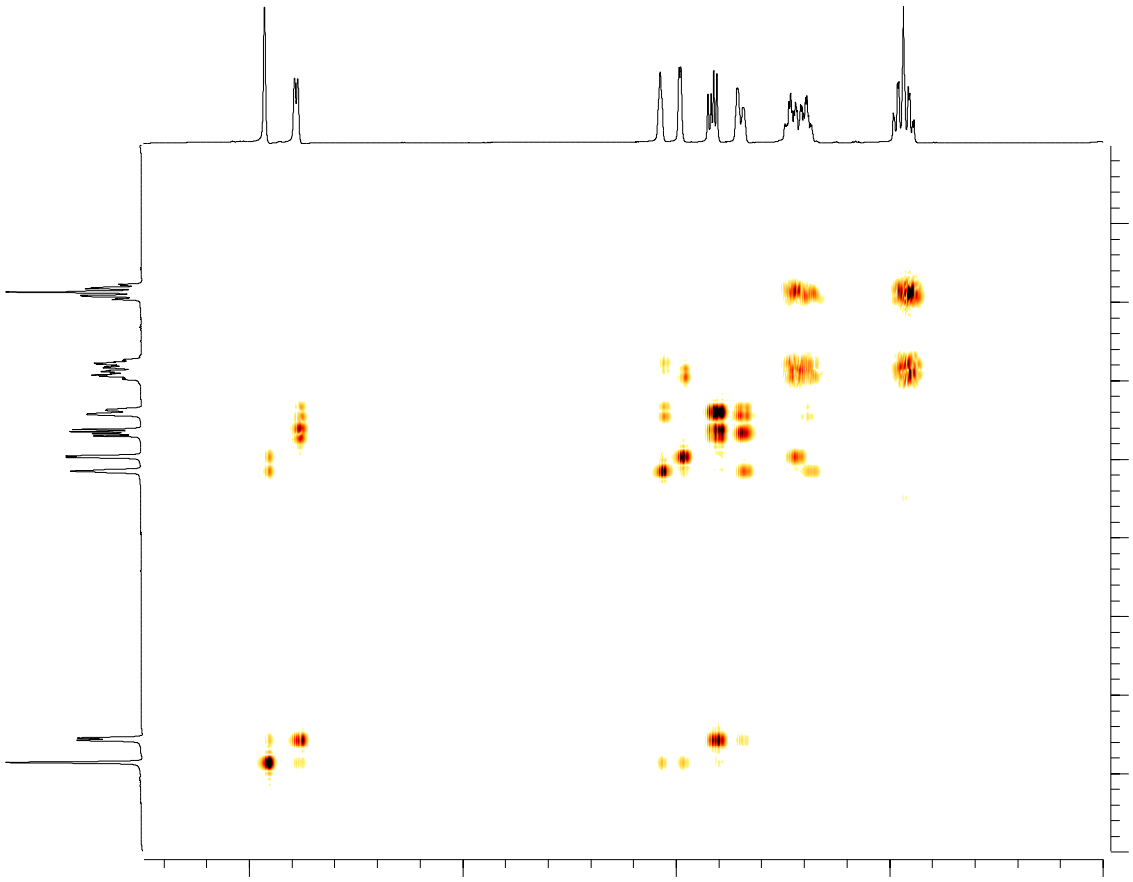
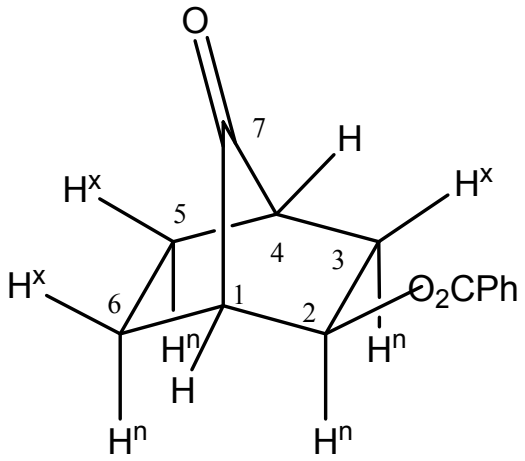


**Figure J.3.** The COSY NMR spectrum of syn diol **60**.

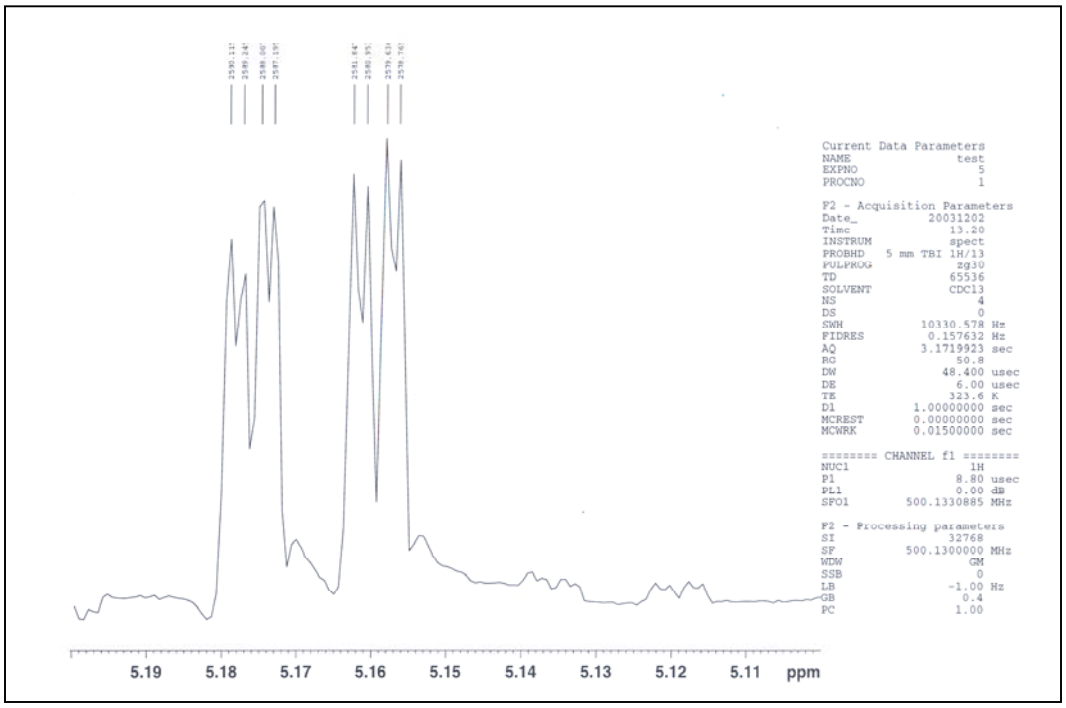
# APPENDIX K

**Structural Assignment of 64.**




n= endo
x=exo

Signals **a**, **b**, **c** between δ 7.24-7.82 ppm in the $^{1}$H NMR spectrum (Figure K.1) were assigned to the aromatic protons of the benzoate. Signal **d** at δ 5.17 appears as a ddd and can be assigned to the *endo* proton on C-2 due to the *cis* coupling (8 Hz) with the *endo* proton on C-3, *trans* coupling (2.1 Hz) with the *exo* proton on C-3, and coupling to the bridgehead proton on C-1 (0.9 Hz). This peak alone provides the correct regioisomer and stereochemistry at the C-2 stereocenter and is consistent with the structure shown above.



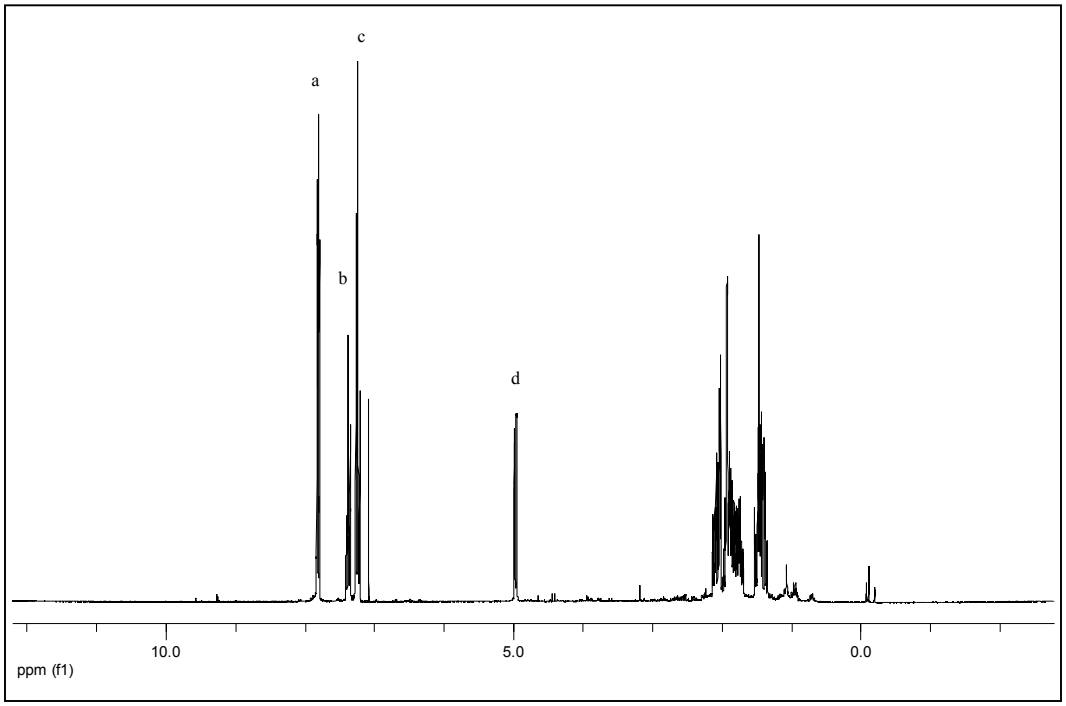
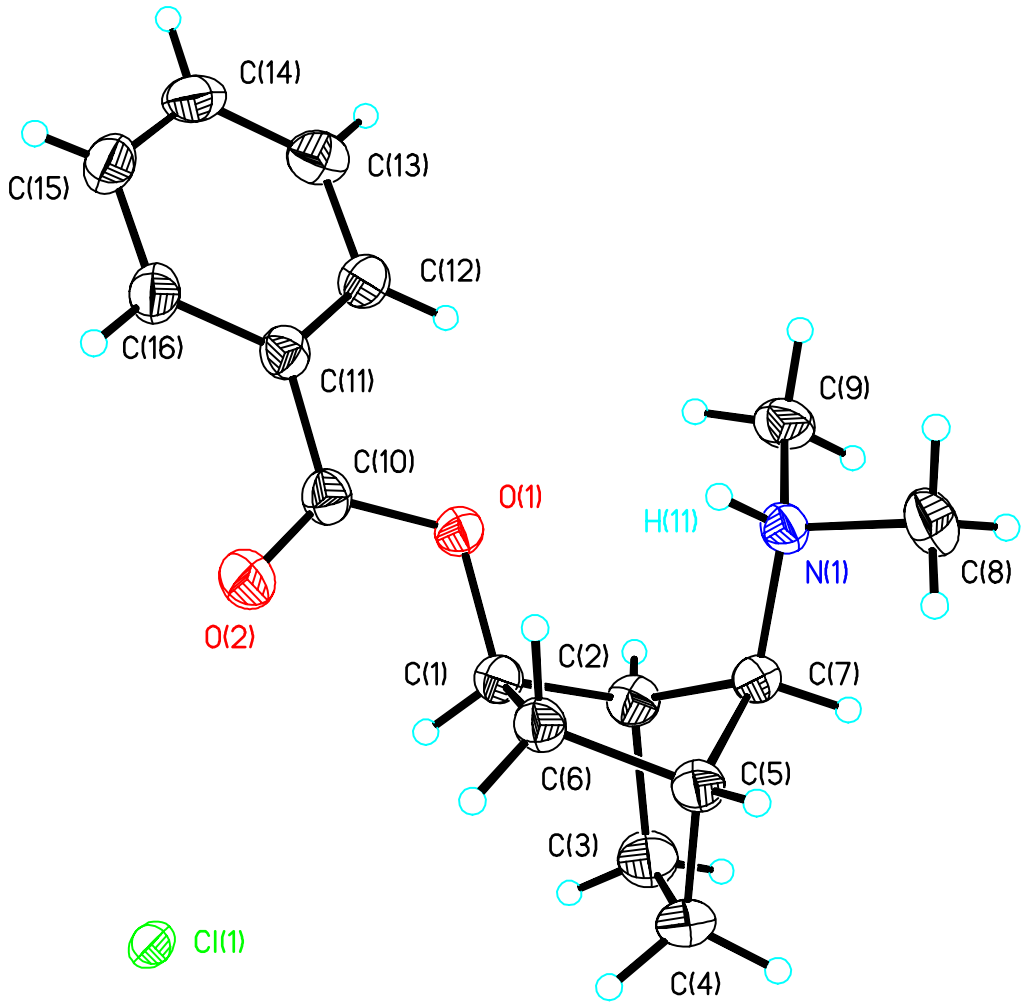




**Figure K.1.** The $^{1}$H NMR spectrum of keto benzoate **64**.

## APPENDIX L

**Structural Assignment of 66.**




**L1.** The Elllipsoid Diagram of amino benzoate **66**.

**Table 1.** Crystal data and structure refinement for benzoate **66**.

| | | |
|---|---|---|
| Identification code | sc0533s | |
| Empirical formula | C16 H22 Cl N O2 | |
| Formula weight | 295.80 | |
| Temperature | 173(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1) | |
| Unit cell dimensions | a = 5.8976(6) Å | α= 90°. |
| | b = 11.3060(12) Å | β= 103.544(2)°. |
| | c = 11.6317(12) Å | γ = 90°. |
| Volume | 754.01(14) $Å^3$ | |
| Z | 2 | |
| Density (calculated) | 1.303 $Mg/m^3$ | |
| Absorption coefficient | 0.255 $mm^{-1}$ | |
| F(000) | 316 | |
| Crystal size | 0.33 x 0.14 x 0.08 $mm^3$ | |
| Theta range for data collection | 1.80 to 28.36°. | |
| Index ranges | -7<=h<=7, -15<=k<=15, -15<=l<=15 | |
| Reflections collected | 10540 | |
| Independent reflections | 3739 [R(int) = 0.0249] | |
| Completeness to theta = 28.36° | 99.8 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 0.9811 and 0.9207 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 3739 / 1 / 269 | |
| Goodness-of-fit on $F^2$ | 1.058 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0363, wR2 = 0.0882 | |
| R indices (all data) | R1 = 0.0376, wR2 = 0.0891 | |
| Absolute structure parameter | 0.01(4) | |
| Largest diff. peak and hole | 0.344 and -0.154 e.$Å^{-3}$ | |

**Table L.2.** Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters (Å$^2$x $10^3$) for benzoate **66**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| C(1) | 7402(3) | 7852(1) | 3214(1) | 23(1) |
| C(2) | 5716(3) | 6949(1) | 2507(1) | 25(1) |
| C(3) | 6639(4) | 5725(2) | 2973(2) | 38(1) |
| C(4) | 8917(3) | 5595(2) | 2543(2) | 38(1) |
| C(5) | 8973(3) | 6727(2) | 1815(1) | 27(1) |
| C(6) | 9561(2) | 7773(1) | 2679(1) | 25(1) |
| C(7) | 6351(2) | 6906(1) | 1299(1) | 23(1) |
| C(8) | 6195(3) | 7662(2) | -683(1) | 34(1) |
| C(9) | 3353(3) | 8402(2) | 374(2) | 31(1) |
| C(10) | 7370(3) | 9852(1) | 3768(1) | 25(1) |
| C(11) | 5931(3) | 10943(1) | 3708(1) | 25(1) |
| C(12) | 3581(3) | 10969(1) | 3142(1) | 27(1) |
| C(13) | 2304(3) | 11993(2) | 3163(1) | 32(1) |
| C(14) | 3377(3) | 12991(2) | 3735(2) | 34(1) |
| C(15) | 5730(4) | 12973(2) | 4296(2) | 36(1) |
| C(16) | 6999(3) | 11950(2) | 4286(1) | 30(1) |
| Cl(1) | 1507(1) | 5299(1) | 9388(1) | 34(1) |
| N(1) | 5797(2) | 7965(1) | 508(1) | 23(1) |
| O(1) | 6273(2) | 8997(1) | 3053(1) | 24(1) |
| O(2) | 9285(2) | 9731(1) | 4411(1) | 34(1) |

**Table L.3.** Bond lengths [Å] and angles [°] for benzoate **66**.

| | | | |
|---|---|---|---|
| C(1)-O(1) | 1.4478(18) | C(12)-H(18) | 0.92(2) |
| C(1)-C(2) | 1.525(2) | C(13)-C(14) | 1.385(3) |
| C(1)-C(6) | 1.5454(19) | C(13)-H(19) | 0.92(3) |
| C(1)-H(1) | 0.937(17) | C(14)-C(15) | 1.388(3) |
| C(2)-C(7) | 1.537(2) | C(14)-H(20) | 0.88(2) |
| C(2)-C(3) | 1.539(2) | C(15)-C(16) | 1.380(3) |
| C(2)-H(2) | 0.931(18) | C(15)-H(21) | 0.78(3) |
| C(3)-C(4) | 1.547(3) | C(16)-H(22) | 1.00(2) |
| C(3)-H(3) | 0.94(3) | N(1)-H(11) | 0.84(2) |
| C(3)-H(4) | 0.92(2) | | |
| C(4)-C(5) | 1.539(2) | O(1)-C(1)-C(2) | 107.85(12) |
| C(4)-H(5) | 0.97(2) | O(1)-C(1)-C(6) | 113.37(12) |
| C(4)-H(6) | 0.95(3) | C(2)-C(1)-C(6) | 103.80(12) |
| C(5)-C(7) | 1.535(2) | O(1)-C(1)-H(1) | 106.8(10) |
| C(5)-C(6) | 1.538(2) | C(2)-C(1)-H(1) | 109.8(10) |
| C(5)-H(7) | 0.966(19) | C(6)-C(1)-H(1) | 115.1(10) |
| C(6)-H(8) | 0.977(18) | C(1)-C(2)-C(7) | 104.29(11) |
| C(6)-H(9) | 1.00(2) | C(1)-C(2)-C(3) | 106.23(13) |
| C(7)-N(1) | 1.4990(19) | C(7)-C(2)-C(3) | 98.75(13) |
| C(7)-H(10) | 0.996(19) | C(1)-C(2)-H(2) | 114.2(11) |
| C(8)-N(1) | 1.498(2) | C(7)-C(2)-H(2) | 118.7(11) |
| C(8)-H(12) | 1.00(3) | C(3)-C(2)-H(2) | 112.9(12) |
| C(8)-H(13) | 0.93(3) | C(2)-C(3)-C(4) | 103.50(14) |
| C(8)-H(14) | 0.92(2) | C(2)-C(3)-H(3) | 107.9(16) |
| C(9)-N(1) | 1.497(2) | C(4)-C(3)-H(3) | 110.3(16) |
| C(9)-H(15) | 0.95(2) | C(2)-C(3)-H(4) | 110.7(15) |
| C(9)-H(16) | 0.96(2) | C(4)-C(3)-H(4) | 115.1(15) |
| C(9)-H(17) | 0.95(2) | H(3)-C(3)-H(4) | 109(2) |
| C(10)-O(2) | 1.2076(19) | C(5)-C(4)-C(3) | 103.37(13) |
| C(10)-O(1) | 1.3390(19) | C(5)-C(4)-H(5) | 109.5(12) |
| C(10)-C(11) | 1.489(2) | C(3)-C(4)-H(5) | 111.4(12) |
| C(11)-C(12) | 1.389(2) | C(5)-C(4)-H(6) | 107.7(15) |
| C(11)-C(16) | 1.395(2) | C(3)-C(4)-H(6) | 112.3(15) |
| C(12)-C(13) | 1.384(2) | H(5)-C(4)-H(6) | 112.1(19) |

| | | | |
|---|---|---|---|
| C(7)-C(5)-C(6) | 101.90(11) | C(13)-C(12)-C(11) | 119.78(15) |
| C(7)-C(5)-C(4) | 100.08(13) | C(13)-C(12)-H(18) | 120.8(14) |
| C(6)-C(5)-C(4) | 108.10(12) | C(11)-C(12)-H(18) | 119.4(14) |
| C(7)-C(5)-H(7) | 118.1(11) | C(12)-C(13)-C(14) | 120.03(16) |
| C(6)-C(5)-H(7) | 114.3(12) | C(12)-C(13)-H(19) | 120.7(17) |
| C(4)-C(5)-H(7) | 112.8(12) | C(14)-C(13)-H(19) | 119.2(17) |
| C(5)-C(6)-C(1) | 103.10(12) | C(13)-C(14)-C(15) | 120.51(16) |
| C(5)-C(6)-H(8) | 111.6(11) | C(13)-C(14)-H(20) | 119.7(15) |
| C(1)-C(6)-H(8) | 113.2(11) | C(15)-C(14)-H(20) | 119.8(15) |
| C(5)-C(6)-H(9) | 113.9(11) | C(16)-C(15)-C(14) | 119.51(17) |
| C(1)-C(6)-H(9) | 103.7(12) | C(16)-C(15)-H(21) | 116.8(19) |
| H(8)-C(6)-H(9) | 110.9(17) | C(14)-C(15)-H(21) | 123.7(19) |
| N(1)-C(7)-C(5) | 113.57(12) | C(15)-C(16)-C(11) | 120.25(16) |
| N(1)-C(7)-C(2) | 118.13(12) | C(15)-C(16)-H(22) | 119.4(17) |
| C(5)-C(7)-C(2) | 94.93(11) | C(11)-C(16)-H(22) | 120.3(16) |
| N(1)-C(7)-H(10) | 105.1(11) | C(9)-N(1)-C(8) | 109.58(12) |
| C(5)-C(7)-H(10) | 113.8(10) | C(9)-N(1)-C(7) | 113.16(12) |
| C(2)-C(7)-H(10) | 111.5(11) | C(8)-N(1)-C(7) | 109.08(13) |
| N(1)-C(8)-H(12) | 107.4(13) | C(9)-N(1)-H(11) | 104.6(14) |
| N(1)-C(8)-H(13) | 110.5(16) | C(8)-N(1)-H(11) | 107.6(14) |
| H(12)-C(8)-H(13) | 114(2) | C(7)-N(1)-H(11) | 112.6(14) |
| N(1)-C(8)-H(14) | 105.0(14) | C(10)-O(1)-C(1) | 115.12(1) |
| H(12)-C(8)-H(14) | 112(2) | | |
| H(13)-C(8)-H(14) | 108(2) | | |
| N(1)-C(9)-H(15) | 105.3(14) | | |
| N(1)-C(9)-H(16) | 106.9(13) | | |
| H(15)-C(9)-H(16) | 116.9(18) | | |
| N(1)-C(9)-H(17) | 113.3(14) | | |
| H(15)-C(9)-H(17) | 114.0(19) | | |
| H(16)-C(9)-H(17) | 100.5(19) | | |
| O(2)-C(10)-O(1) | 123.27(15) | | |
| O(2)-C(10)-C(11) | 124.26(14) | | |
| O(1)-C(10)-C(11) | 112.44(12) | | |
| C(12)-C(11)-C(16) | 119.91(15) | | |
| C(12)-C(11)-C(10) | 122.34(13) | | |
| C(16)-C(11)-C(10) | 117.71(13) | | |

Symmetry transformations used to generate equivalent atoms:

**Table L.4.** Anisotropic displacement parameters ($Å^2 x\ 10^3$) for benzoate 6**3**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| C(1) | 25(1) | 23(1) | 21(1) | 0(1) | 6(1) | 3(1) |
| C(2) | 25(1) | 24(1) | 27(1) | 2(1) | 7(1) | -2(1) |
| C(3) | 53(1) | 25(1) | 33(1) | 5(1) | 6(1) | -3(1) |
| C(4) | 48(1) | 25(1) | 35(1) | 0(1) | -2(1) | 12(1) |
| C(5) | 25(1) | 30(1) | 25(1) | -2(1) | 3(1) | 8(1) |
| C(6) | 20(1) | 29(1) | 23(1) | -2(1) | 4(1) | 3(1) |
| C(7) | 24(1) | 21(1) | 23(1) | -1(1) | 3(1) | 2(1) |
| C(8) | 38(1) | 43(1) | 20(1) | 1(1) | 5(1) | 0(1) |
| C(9) | 24(1) | 31(1) | 34(1) | 4(1) | 0(1) | 4(1) |
| C(10) | 25(1) | 28(1) | 22(1) | -2(1) | 6(1) | 0(1) |
| C(11) | 28(1) | 27(1) | 21(1) | -1(1) | 8(1) | -1(1) |
| C(12) | 27(1) | 26(1) | 28(1) | -2(1) | 8(1) | 0(1) |
| C(13) | 30(1) | 36(1) | 33(1) | 4(1) | 12(1) | 7(1) |
| C(14) | 50(1) | 26(1) | 31(1) | 6(1) | 17(1) | 12(1) |
| C(15) | 54(1) | 26(1) | 28(1) | -4(1) | 9(1) | -4(1) |
| C(16) | 35(1) | 29(1) | 25(1) | -3(1) | 6(1) | -4(1) |
| Cl(1) | 29(1) | 28(1) | 43(1) | -9(1) | 3(1) | 2(1) |
| N(1) | 22(1) | 24(1) | 20(1) | 0(1) | 2(1) | -1(1) |
| O(1) | 24(1) | 25(1) | 24(1) | -3(1) | 4(1) | 4(1) |
| O(2) | 28(1) | 36(1) | 32(1) | -4(1) | -2(1) | 4(1) |

**Table L.5.** Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for benzoate **66**.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(1) | 7680(30) | 7675(14) | 4023(15) | 10(3) |
| H(2) | 4160(30) | 7069(17) | 2528(15) | 22(4) |
| H(3) | 5540(50) | 5150(30) | 2610(20) | 56(7) |
| H(4) | 6820(40) | 5680(20) | 3780(20) | 43(6) |
| H(5) | 10270(40) | 5574(18) | 3199(18) | 33(5) |
| H(6) | 8870(40) | 4940(20) | 2030(20) | 47(7) |
| H(7) | 9980(30) | 6658(18) | 1271(17) | 27(5) |
| H(8) | 11010(30) | 7640(17) | 3270(16) | 21(4) |
| H(9) | 9590(40) | 8556(19) | 2283(17) | 28(5) |
| H(10) | 5580(30) | 6229(17) | 813(16) | 22(4) |
| H(11) | 6640(40) | 8550(20) | 766(18) | 29(5) |
| H(12) | 7780(40) | 7300(20) | -555(19) | 42(6) |
| H(13) | 5000(50) | 7190(30) | -1100(20) | 53(7) |
| H(14) | 6110(40) | 8380(20) | -1080(20) | 37(5) |
| H(15) | 2380(40) | 7740(20) | 90(19) | 34(5) |
| H(16) | 3180(40) | 9090(20) | -126(19) | 31(5) |
| H(17) | 3080(40) | 8740(20) | 1080(20) | 41(6) |
| H(18) | 2900(40) | 10310(20) | 2745(18) | 38(5) |
| H(19) | 720(50) | 12010(30) | 2820(20) | 48(6) |
| H(20) | 2570(40) | 13650(20) | 3718(19) | 36(5) |
| H(21) | 6390(40) | 13510(30) | 4630(20) | 45(7) |
| H(22) | 8710(40) | 11950(30) | 4650(20) | 50(6) |

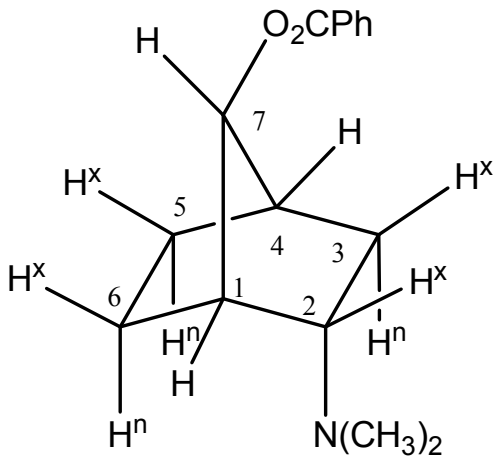
**Table L.6.** Hydrogen bonds for benzoate **66** [Å and °].

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|
| N(1)-H(11)...Cl(1)#1 | 0.84(2) | 2.28(2) | 3.0684(14) | 155.1(18) |

Symmetry transformations used to generate equivalent atoms:
#1 -x+1,y+1/2,-z+1

## APPENDIX M

**Structural Assignment of 68.**




n= endo
x=exo

The stereochemistry at the C-7 stereocenter was established in the formation of 2,7-syn diol **58** (Appendix J). The stereochemistry does not change upon benzoylation. Signals **a**, **b**, **c** between δ 7.45-8.04 ppm in the $^{1}$H NMR spectrum (Figure M.1) were assigned to the aromatic protons of the benzoate. Signal **d** at δ 5.09 ppm appears as a broad *doublet* and can be assigned to the *exo* proton on C-7. Signal **e** at δ 2.65 ppm appears as a *doublet of*

*triplets* and can be assigned to the *exo* proton on C-2 due to the *cis* coupling (8 Hz) with the *exo* proton on C-3, *trans* coupling (2.1 Hz) with the *endo* proton on C-3, and coupling to the bridgehead proton on C-1 (4.5 Hz). This peak alone suggests the proton at the C-2 stereocenter is *exo* and is consistent with the structure shown above. The structure was confirmed by x-ray diffraction (Figure M.2).

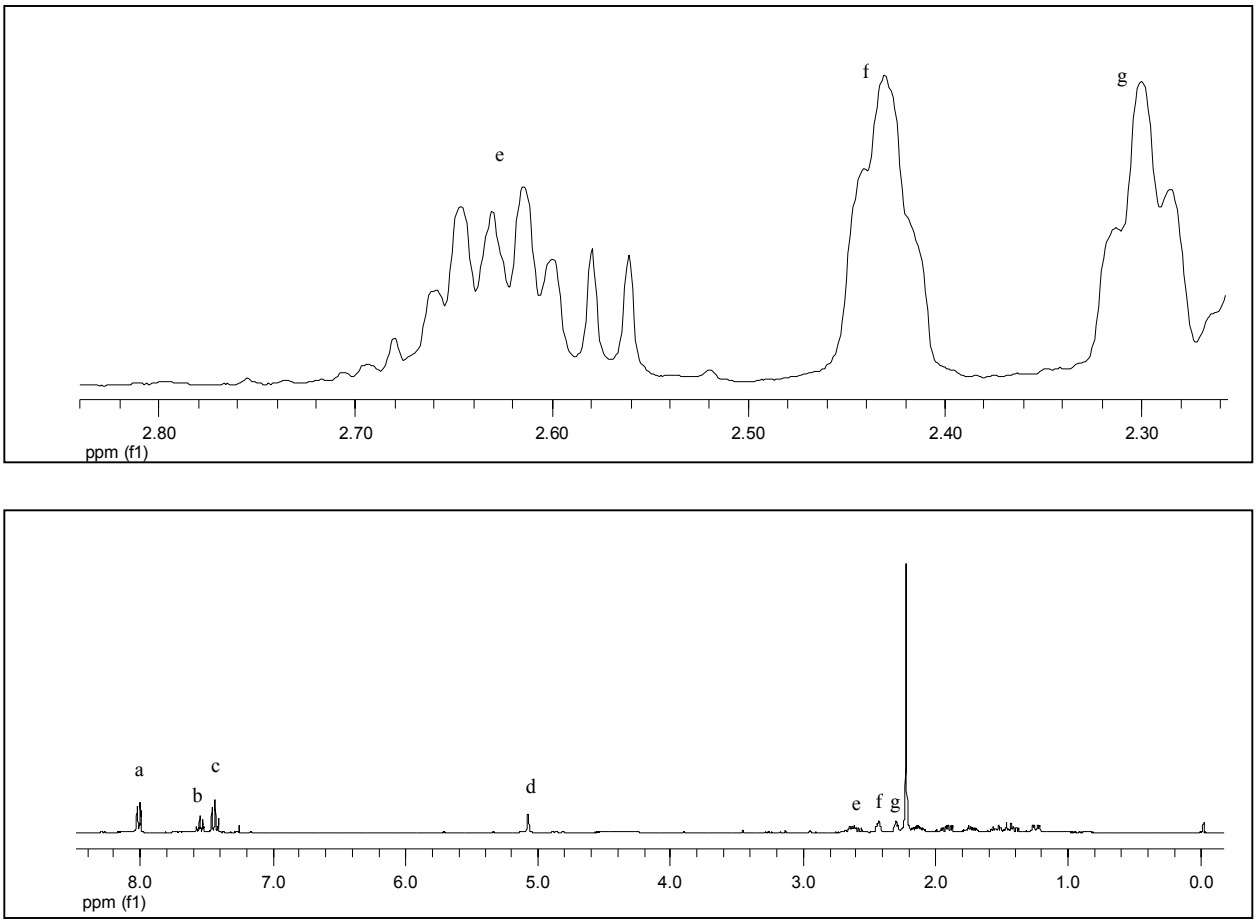



**Figure M.1.** The $^{1}$H NMR spectrum of keto benzoate **68**.

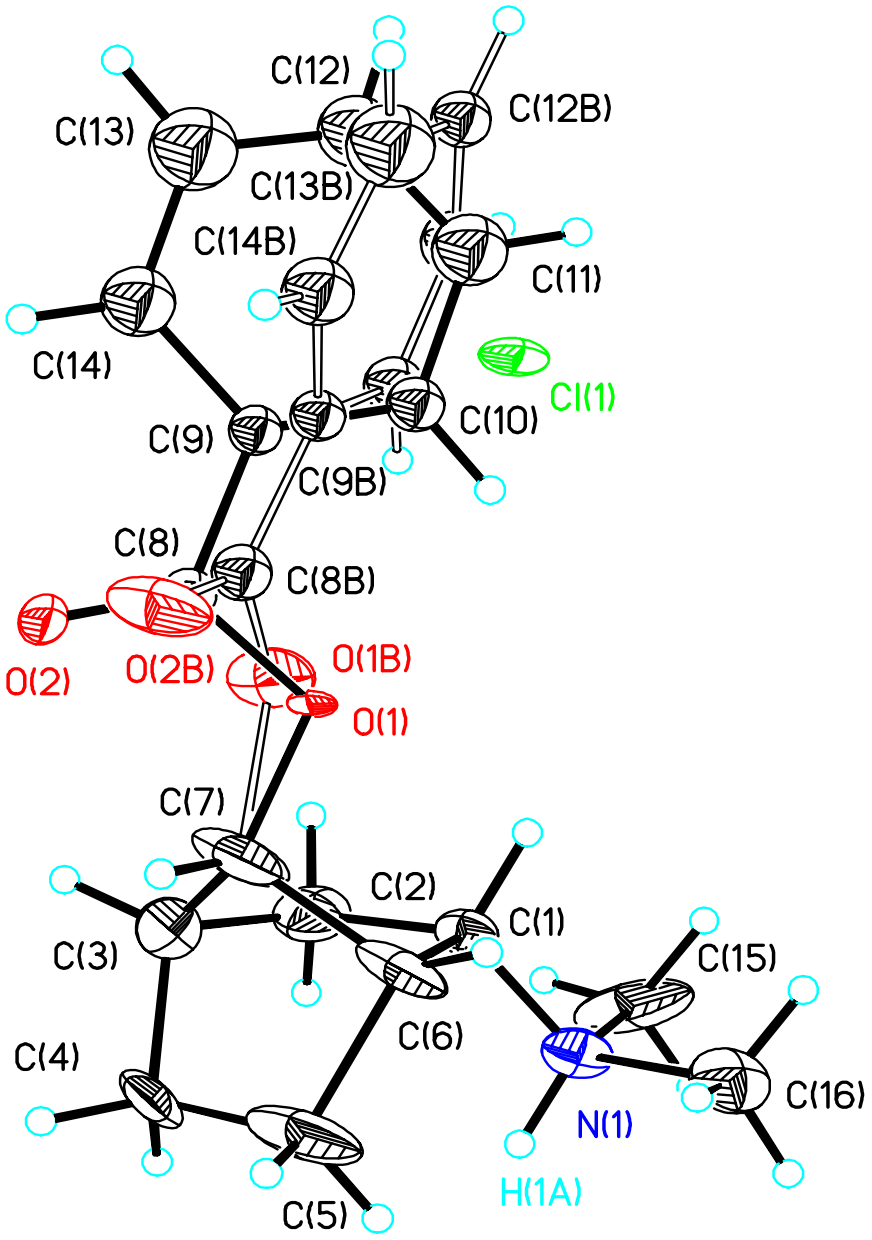



**Figure M.2.** The Ellipsoid structure of amino-benzoate **68**.

**Table M.1.** Crystal data and structure refinement for benzoate **68**.

| | | |
|---|---|---|
| Identification code | SC_05_32 | |
| Empirical formula | C16 H22 Cl N O2 | |
| Formula weight | 295.80 | |
| Temperature | 173(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/n | |
| Unit cell dimensions | a = 5.9958(16) Å | α= 90°. |
| | b = 10.766(3) Å | β= 95.822(5)°. |
| | c = 24.750(7) Å | γ = 90°. |
| Volume | 1589.3(7) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.236 $Mg/m^3$ | |
| Absorption coefficient | 0.242 $mm^{-1}$ | |
| F(000) | 632 | |
| Crystal size | 0.27 x 0.13 x 0.04 $mm^3$ | |
| Theta range for data collection | 1.65 to 23.53°. | |
| Index ranges | -6<=h<=6, -12<=k<=12, -27<=l<=27 | |
| Reflections collected | 13757 | |
| Independent reflections | 2360 [R(int) = 0.1488] | |
| Completeness to theta = 23.53° | 100.0 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 1.000 and 0.876477 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 2360 / 7 / 195 | |
| Goodness-of-fit on $F^2$ | 1.262 | |
| Final R indices [I>2sigma(I)] | R1 = 0.1771, wR2 = 0.4184 | |
| R indices (all data) | R1 = 0.1966, wR2 = 0.4299 | |
| Largest diff. peak and hole | 0.710 and -0.794 $e.Å^{-3}$ | |

**Table M.2**. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters (Å$^2$x $10^3$) for benzoate **68**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| Cl(1) | 3902(4) | 2300(2) | 2252(1) | 45(1) |
| C(1) | 7767(16) | 9477(8) | 1749(4) | 31(2) |
| C(2) | 5743(19) | 9041(12) | 1367(5) | 56(3) |
| C(3) | 6170(30) | 9581(14) | 821(5) | 85(5) |
| C(4) | 5710(30) | 10955(14) | 838(5) | 95(6) |
| C(5) | 7680(30) | 11485(12) | 1211(6) | 85(5) |
| C(6) | 9100(20) | 10307(10) | 1393(5) | 58(3) |
| C(7) | 8690(30) | 9555(13) | 852(6) | 83(5) |
| O(1) | 9900(30) | 8456(12) | 964(6) | 25(4) |
| O(2) | 9560(30) | 8202(12) | 62(5) | 52(4) |
| C(8) | 10060(30) | 7828(17) | 505(8) | 29(4) |
| C(9) | 11026(7) | 6550(13) | 618(7) | 26(4) |
| C(10) | 11516(13) | 6092(16) | 1132(8) | 32(4) |
| C(11) | 12410(20) | 4850(20) | 1220(10) | 56(9) |
| C(12) | 12720(20) | 4180(20) | 765(9) | 56(6) |
| C(13) | 12250(20) | 4610(20) | 242(11) | 73(7) |
| C(14) | 11380(20) | 5818(19) | 159(9) | 51(5) |
| O(1B) | 9240(40) | 8100(20) | 874(10) | 55(7) |
| O(2B) | 11650(30) | 8534(15) | 290(8) | 61(5) |
| C(8B) | 11020(40) | 7850(20) | 603(9) | 32(5) |
| C(9B) | 12021(17) | 6640(14) | 747(5) | 27(4) |
| C(10B) | 11010(30) | 5771(19) | 1098(7) | 35(6) |
| C(11B) | 12140(30) | 4710(30) | 1191(7) | 46(9) |
| C(12B) | 14020(30) | 4338(19) | 1015(7) | 34(5) |
| C(13B) | 14880(30) | 5170(20) | 694(7) | 69(8) |
| C(14B) | 13950(30) | 6290(20) | 557(7) | 45(6) |
| C(15) | 5900(30) | 9247(11) | 2586(5) | 103(6) |
| C(16) | 9080(17) | 10616(11) | 2588(5) | 54(3) |
| N(1) | 7057(13) | 10114(7) | 2244(3) | 35(2) |

**Table M.3.** Bond lengths [Å] and angles [°] for benzoate **68**.

| | |
|---|---|
| C(1)-N(1) | 1.503(12) |
| C(1)-C(2) | 1.535(15) |
| C(1)-C(6) | 1.536(14) |
| C(2)-C(3) | 1.516(18) |
| C(3)-C(4) | 1.505(19) |
| C(3)-C(7) | 1.51(2) |
| C(4)-C(5) | 1.53(2) |
| C(5)-C(6) | 1.568(15) |
| C(6)-C(7) | 1.563(19) |
| C(7)-O(1) | 1.402(18) |
| C(7)-O(1B) | 1.60(2) |
| O(1)-C(8) | 1.34(2) |
| O(2)-C(8) | 1.18(2) |
| C(8)-C(9) | 1.51(2) |
| C(9)-C(10) | 1.37(2) |
| C(9)-C(14) | 1.42(3) |
| C(10)-C(11) | 1.45(3) |
| C(11)-C(12) | 1.37(3) |
| C(12)-C(13) | 1.38(3) |
| C(13)-C(14) | 1.40(3) |
| O(1B)-C(8B) | 1.34(3) |
| O(2B)-C(8B) | 1.16(3) |
| C(8B)-C(9B) | 1.46(3) |
| C(9B)-C(14B) | 1.35(3) |
| C(9B)-C(10B) | 1.45(3) |
| C(10B)-C(11B) | 1.33(3) |
| C(11B)-C(12B) | 1.32(3) |
| C(12B)-C(13B) | 1.33(3) |
| C(13B)-C(14B) | 1.36(4) |
| C(15)-N(1) | 1.478(14) |
| C(16)-N(1) | 1.509(13) |
| | |
| N(1)-C(1)-C(2) | 111.8(8) |
| N(1)-C(1)-C(6) | 114.2(8) |
| C(2)-C(1)-C(6) | 104.4(9) |
| C(3)-C(2)-C(1) | 103.8(10) |
| C(4)-C(3)-C(7) | 101.5(14) |
| C(4)-C(3)-C(2) | 107.8(11) |
| C(7)-C(3)-C(2) | 101.9(10) |
| C(3)-C(4)-C(5) | 104.6(11) |
| C(4)-C(5)-C(6) | 103.5(11) |
| C(1)-C(6)-C(7) | 98.3(10) |
| C(1)-C(6)-C(5) | 109.6(9) |
| C(7)-C(6)-C(5) | 98.0(10) |

| | |
|---|---|
| O(1)-C(7)-C(3) | 121.5(14) |
| O(1)-C(7)-C(6) | 103.5(11) |
| C(3)-C(7)-C(6) | 96.0(10) |
| O(1)-C(7)-O(1B) | 21.0(11) |
| C(3)-C(7)-O(1B) | 102.8(15) |
| C(6)-C(7)-O(1B) | 117.6(12) |
| C(8)-O(1)-C(7) | 109.7(14) |
| O(2)-C(8)-O(1) | 126.0(17) |
| O(2)-C(8)-C(9) | 122.8(17) |
| O(1)-C(8)-C(9) | 111.2(15) |
| C(10)-C(9)-C(14) | 120.6(14) |
| C(10)-C(9)-C(8) | 123.0(15) |
| C(14)-C(9)-C(8) | 116.4(15) |
| C(9)-C(10)-C(11) | 121.0(18) |
| C(12)-C(11)-C(10) | 116(2) |
| C(11)-C(12)-C(13) | 124(2) |
| C(12)-C(13)-C(14) | 119(2) |
| C(13)-C(14)-C(9) | 119(2) |
| C(8B)-O(1B)-C(7) | 110.6(18) |
| O(2B)-C(8B)-O(1B) | 122(2) |
| O(2B)-C(8B)-C(9B) | 125(2) |
| O(1B)-C(8B)-C(9B) | 112.8(19) |
| C(14B)-C(9B)-C(10B) | 117.2(16) |
| C(14B)-C(9B)-C(8B) | 120.7(17) |
| C(10B)-C(9B)-C(8B) | 122.0(14) |
| C(11B)-C(10B)-C(9B) | 114.6(16) |
| C(12B)-C(11B)-C(10B) | 130(2) |
| C(11B)-C(12B)-C(13B) | 113(2) |
| C(12B)-C(13B)-C(14B) | 125(2) |
| C(9B)-C(14B)-C(13B) | 120(2) |
| C(15)-N(1)-C(1) | 111.5(8) |
| C(15)-N(1)-C(16) | 107.5(10) |
| C(1)-N(1)-C(16) | 110.2(8) |

Symmetry transformations used to generate equivalent atoms:

**Table M.4**. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for benzoate **68**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| Cl(1) | 48(2) | 18(1) | 70(2) | -3(1) | 8(1) | 5(1) |
| C(1) | 35(5) | 24(5) | 35(5) | 6(4) | 11(4) | 3(4) |
| C(2) | 41(6) | 58(7) | 67(8) | -17(6) | 3(6) | 18(6) |
| C(3) | 132(13) | 78(9) | 41(7) | -9(7) | -8(8) | 58(9) |
| C(4) | 151(13) | 92(10) | 37(7) | 7(7) | -8(8) | 100(10) |
| C(5) | 128(12) | 49(7) | 89(10) | 45(7) | 65(9) | 51(8) |
| C(6) | 58(7) | 46(6) | 72(8) | 30(6) | 20(6) | 33(6) |
| C(7) | 114(11) | 72(9) | 68(8) | 35(7) | 38(8) | 71(8) |
| O(1) | 37(8) | 7(7) | 28(7) | -5(5) | -6(6) | 8(6) |
| O(2) | 104(12) | 30(7) | 21(6) | -3(5) | -8(7) | 25(8) |
| O(1B) | 82(17) | 36(13) | 53(14) | 14(10) | 35(12) | 10(11) |
| O(2B) | 67(12) | 35(9) | 85(13) | 20(9) | 31(10) | 17(9) |
| C(15) | 230(20) | 20(6) | 72(9) | 11(6) | 89(11) | 8(9) |
| C(16) | 29(6) | 53(7) | 78(8) | -3(6) | 0(6) | 5(5) |
| N(1) | 29(4) | 23(4) | 54(5) | 5(4) | 8(4) | -6(3) |

**Table M.5.** Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters (Å$^2$x $10^3$) for benzoate **68**.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(1) | 8702 | 8738 | 1867 | 37 |
| H(2A) | 5671 | 8123 | 1351 | 67 |
| H(2B) | 4325 | 9362 | 1486 | 67 |
| H(3) | 5387 | 9140 | 500 | 102 |
| H(4A) | 4272 | 11122 | 986 | 114 |
| H(4B) | 5665 | 11323 | 470 | 114 |
| H(5A) | 7143 | 11912 | 1528 | 102 |
| H(5B) | 8564 | 12077 | 1013 | 102 |
| H(6) | 10704 | 10461 | 1530 | 69 |
| H(7) | 9248 | 10016 | 541 | 99 |
| H(10) | 11269 | 6596 | 1435 | 38 |
| H(11) | 12755 | 4522 | 1574 | 67 |
| H(12) | 13294 | 3363 | 812 | 67 |
| H(13) | 12505 | 4105 | -59 | 87 |
| H(14) | 11035 | 6135 | -198 | 61 |
| H(10B) | 9644 | 5943 | 1249 | 42 |
| H(11B) | 11480 | 4141 | 1420 | 55 |
| H(12B) | 14702 | 3558 | 1106 | 40 |
| H(13B) | 16239 | 4964 | 551 | 82 |
| H(14B) | 14671 | 6832 | 325 | 54 |
| H(15A) | 4663 | 8842 | 2364 | 154 |
| H(15B) | 5313 | 9708 | 2882 | 154 |
| H(15C) | 6966 | 8616 | 2738 | 154 |
| H(16A) | 9939 | 9925 | 2762 | 80 |
| H(16B) | 8589 | 11169 | 2867 | 80 |
| H(16C) | 10025 | 11079 | 2358 | 80 |
| H(1A) | 6097 | 10767 | 2137 | 42 |

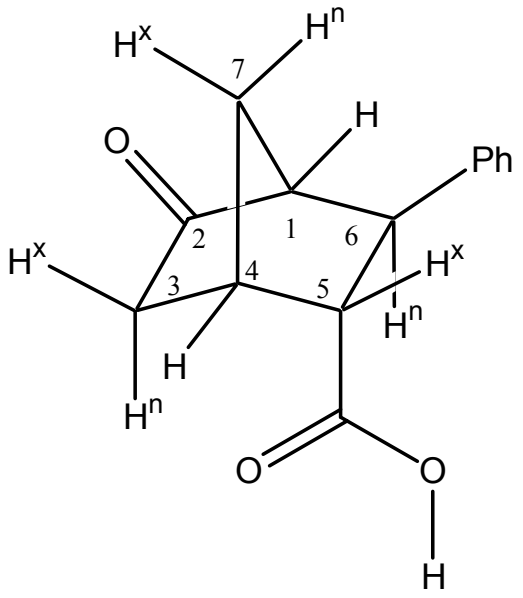
**Table M.6.** Hydrogen bonds for benzoate **68** [Å and °].

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|
| N(1)-H(1A)...Cl(1)#1 | 0.93 | 2.15 | 3.021(8) | 155.8 |

Symmetry transformations used to generate equivalent atoms:
#1 x,y+1,z

## APPENDIX N

**Structural Assignment of 78.**




n= endo
x=exo

The connectivity of the atoms is established based on the mechanism of the reaction of the double-Michael addition of *tert*-butyl acrylate and cyclopentenone. Deprotection of the *t*-butyl ester does not change the connectivity or the stereochemistry. Signal **a** at δ 8.80 ppm (br s) in the $^{1}$H NMR spectrum of **78** (Figure N.1) was assigned to the OH of the carboxylic acid. Signal **b** at δ 7.20-7.37 appears as a multilplet and can be

assigned to the aromatic protons on the phenyl ring at C-6. Signal **c** at δ 3.53 ppm was assigned to the *endo* proton on C-6. The multiplicity of signal **c** is consistent with a proton with *trans* coupling (*d*, 4.5 Hz) to the proton at C-5. Since no coupling is seen between signal **c** and the bridgehead proton on C-1, this indicates the proton must be in the *endo* position. To further corroborate this stereochemical assignment, signal **d** at δ 3.25 ppm was assigned to the proton at C-5. The multiplicity of this peak, a *triplet* (4.8 Hz) is consistent with a *exo* proton at C-5 that *trans* couples to the *endo* proton on C-6 and couples with the bridgehead proton on C-4 with a similar coupling constant. This establishes the stereochemistry at the C-5 and C-6 stereocenters of the bicycle. The peak at δ 3.16 (br s) was assigned to the bridgehead proton on C-4, signal **e**. The peak at δ 2.90 ppm (singlet) was assigned to the proton on C-1, signal **f**. Signal **g**, was assigned to the *endo* and *exo* proton on C-3 and one of the protons on C-7. The peak at δ 1.92 ppm (d) was assigned to one of the protons on C-7, signal **h**. The coupling of 10.5 Hz is consistent with geminal coupling at C-7.

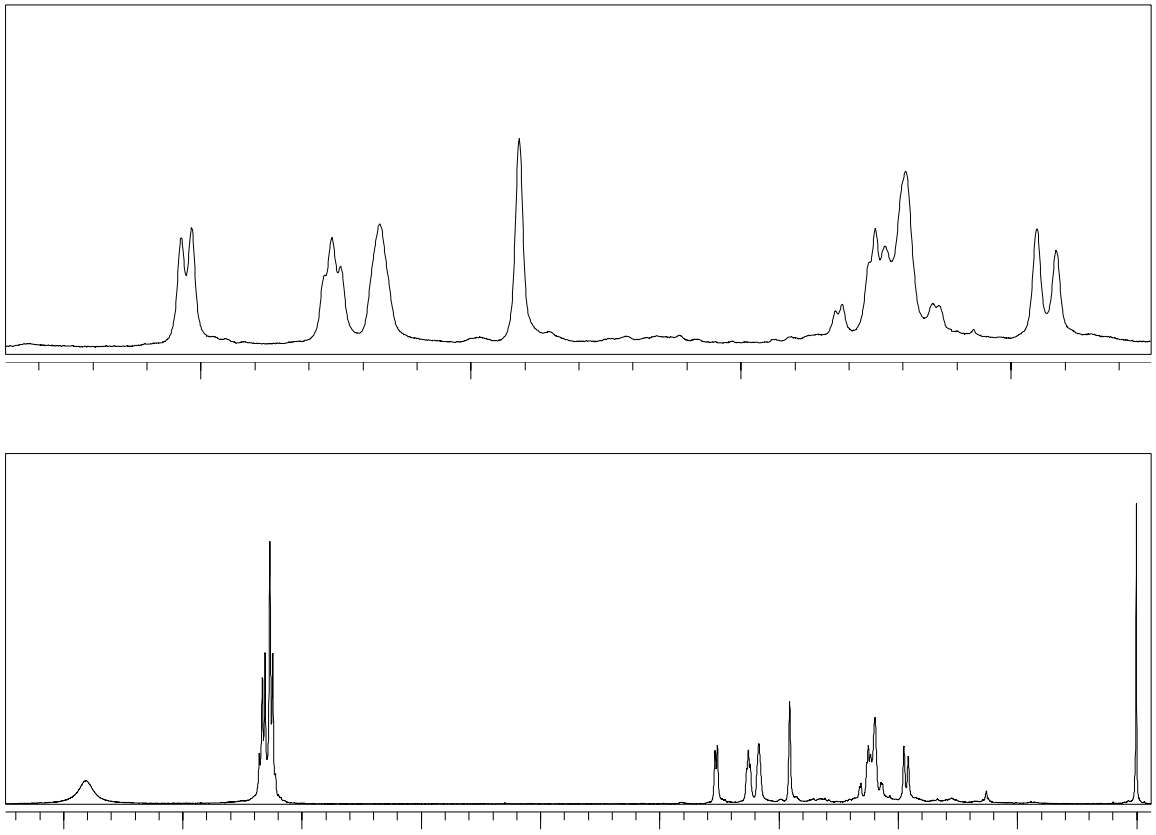
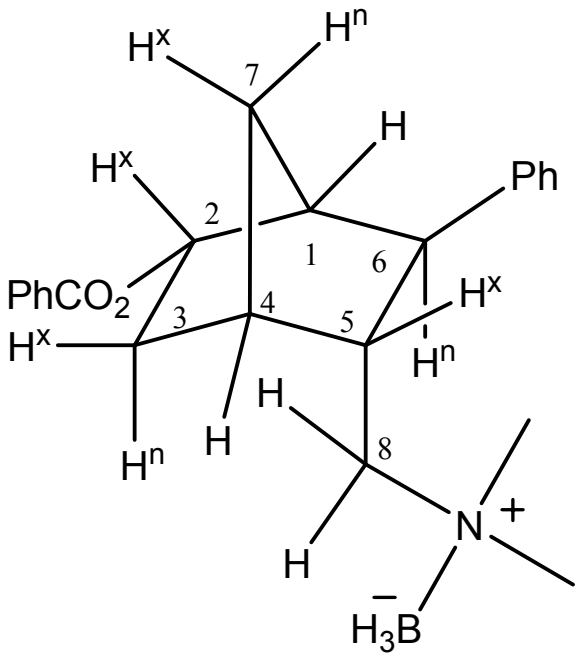


**Figure N.1**. $^{1}$H NMR spectrum(Gemini 300MHz, $CDCl_3$) of carboxylic acid **78**.

## APPENDIX O

**Structural Assignment of 82.**




n= endo
x=exo

The signals at δ 8.10 ppm (2H, signal **a**), δ 7.61 ppm (1H, signal **b**), δ 7.50 ppm (2H, signal **c**) and δ 7.34 - 7.18 ppm (5H, signal **d**) account for all of the protons of the two phenyl rings in the $^{1}$H NMR spectrum of benzoate **82** (Figure O.1). The absorption at δ 5.27 ppm (1H, signal **e**) was assigned to the proton at C-2. The absorptions at δ 3.16

ppm (1H, 13.8 Hz, 6.9 Hz, signal **f**) and δ 3.02 ppm (1H, 13.8 Hz, 4.5 Hz, signal **g**) were assigned to the protons at C-8. The doublet at δ 2.98 (1H, 6.9 Hz, signal **h**) was assigned to the proton at C-6. This shows *trans* stereochemistry between the protons on C-6 and C-5. There doesn't appear to be coupling to the bridgehead proton at C-1 and the proton at C-6, signal **f**, so this suggests the proton at C-6 is *endo*. The multiplet at δ 2.84 – 2.77 ppm (1H, signal **i**) was assigned to the proton of C-3. The absorptions at δ 2.65 ppm (1H, *singlet*, signal **j**) and δ 2.63 ppm (1H, *singlet*, signal **k**) were assigned to the bridgehead protons of C-1 and C-4. The singlets at δ 2.49 ppm (3H, *singlet*, signal **l**) and 2.47 ppm (3H, *singlet*, signal **m**) were assigned to the two methyl groups on the amine. The signal at δ 2.17 ppm (1H, 14.4 Hz, 10.2 Hz, 4.5 Hz, 1.8 Hz, signal **n**) was assigned to the *exo* proton on C-5. The COSY NMR spectrum (Figure O.2) shows that the proton on C-5 is coupled to signal **i**, corresponding to the proton on C-3. The only possible stereochemical assignment which allows coupling between the protons on C-5 and C-3 is when both protons are *exo*. The signal at δ 1.96 ppm (1H, signal **o**) corresponds to one of the protons on C-7. The absorption at δ 1.60 – 1.53 ppm (signal **p**) corresponds to the *endo* proton on C-5 and C-7.

The structure of compound **82** was also confirmed by x-ray analysis (Figure O.3).

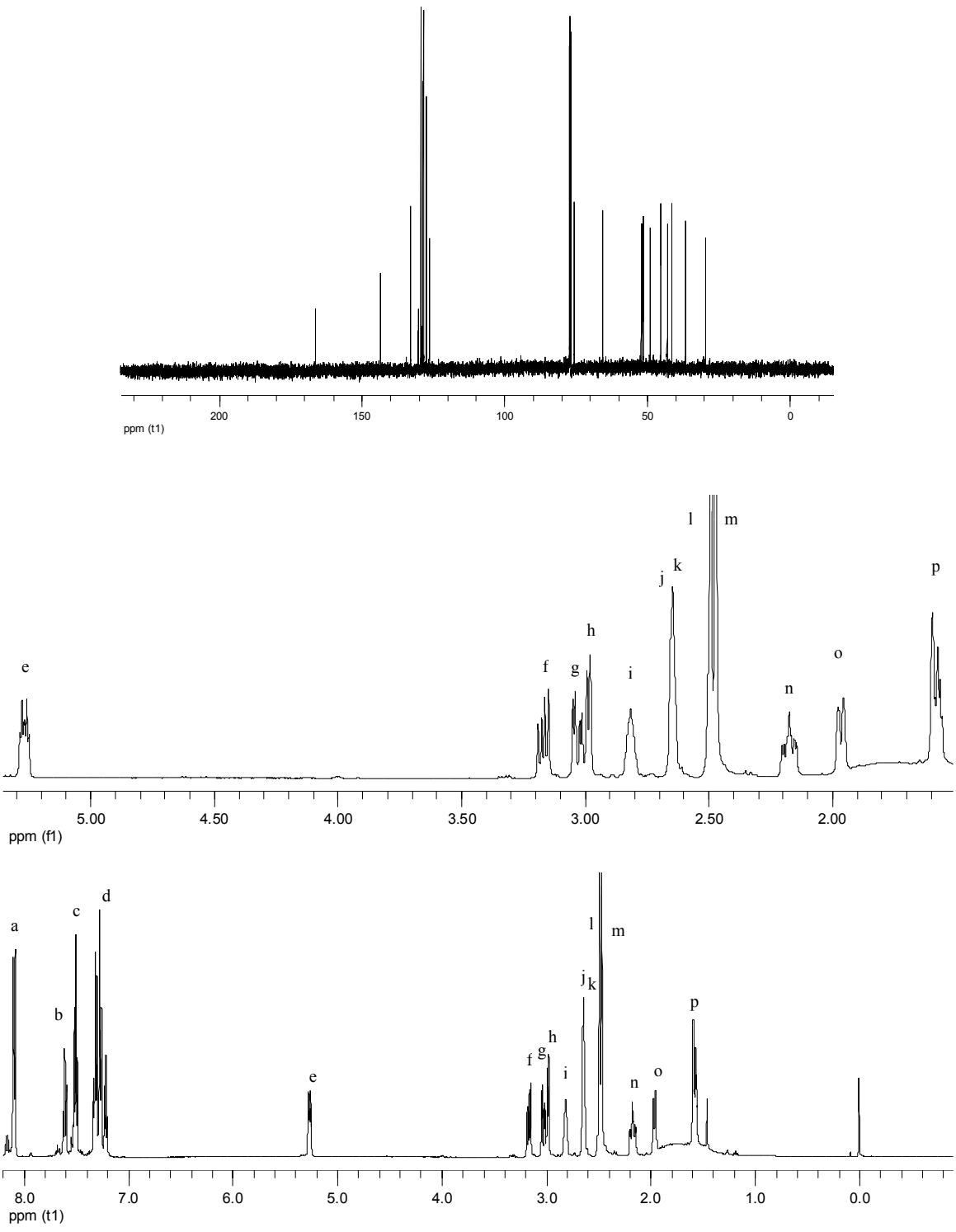



**Figure O.1.** The $^{1}H$ NMR (Gemini 300 MHz, $CDCl_3$) and $^{13}C$ (Bruker AMX 500 MHz, $CDCl_3$) spectra for benzoate **82**.

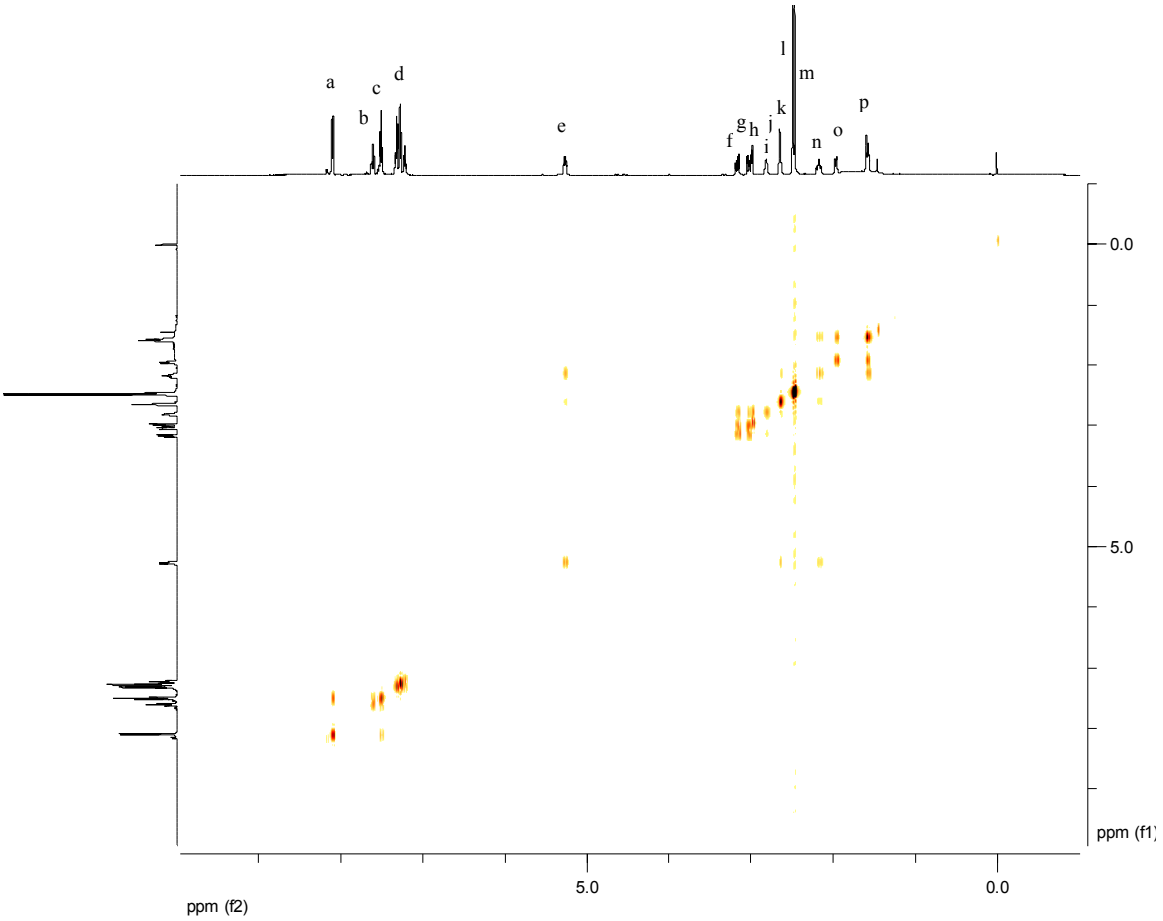



**Figure O.2.** The COSY NMR (Bruker AMX 500 MHz, $CDCl_3$) spectrum for benzoate **82**.

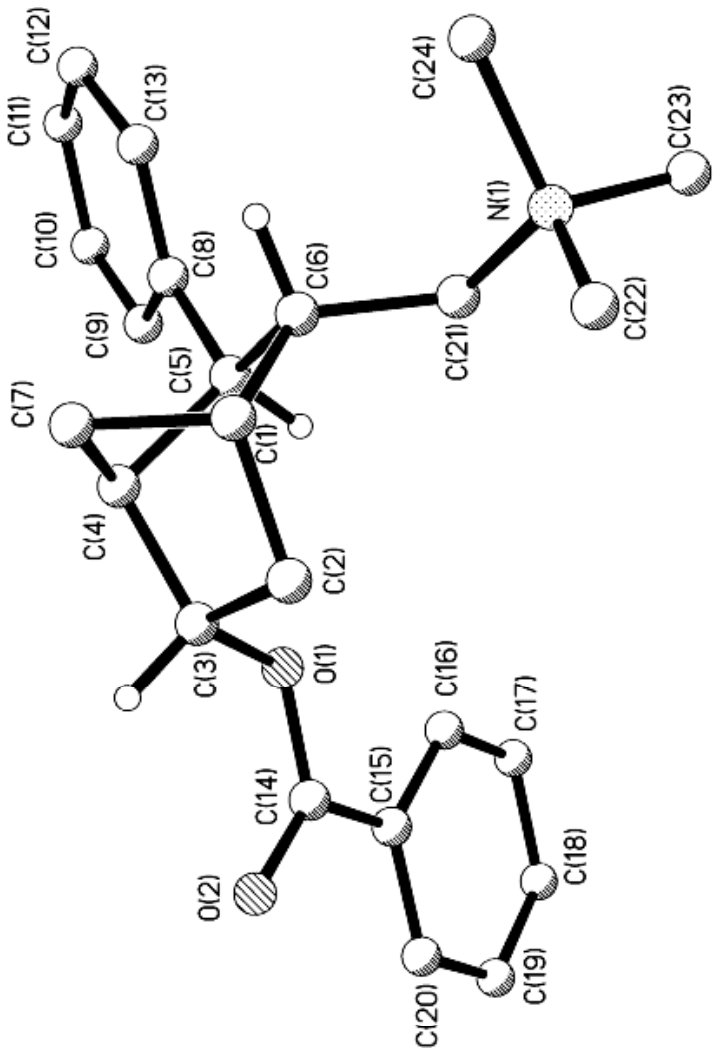



**Figure O.3.** The ORTEP diagram of possible structure of benzoate **82**.

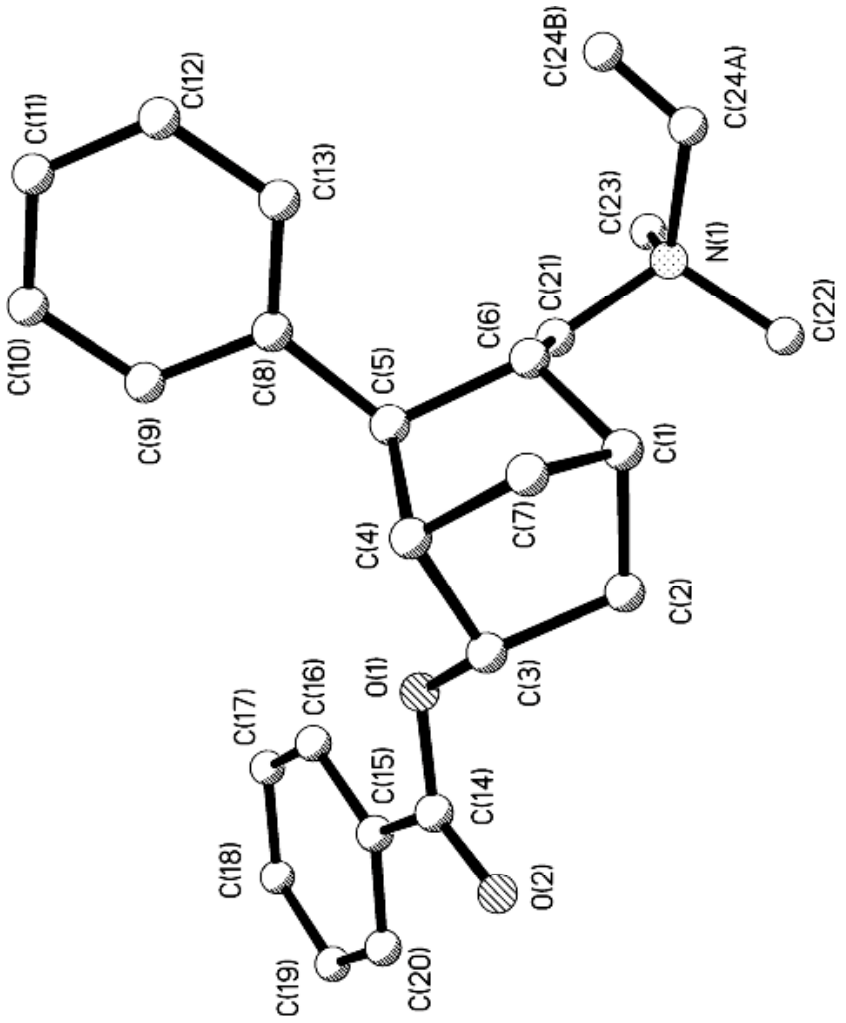



**Figure O.4.** The ORTEP diagram of possible structure of benzoate **82**.

# APPENDIX P

Relative Stereochemical Assignment of Compounds **31**, **32**, **39**, **41**, **10**, **22**, **21**, **50**, **51**, **54**, **55**, **69**, **70**.

## Introduction

In most cases throughout this thesis, stereochemistry assignments of diastereomers has been assigned based on 1- and 2-D spectroscopy techniques and either validated or determined by x-ray diffraction. *exo*-Amino-*endo*- benzoate **69** and *endo*-amino-*exo*-benzoate **70** is the only case in this thesis where the assignment of the relative stereochemistry could not be done with a certain level of confidence and further evaluation was needed to provide additional evidence. A common feature that may not

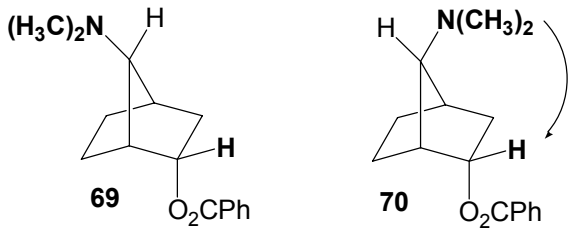



**Figure P.1.** Comparison of amines **69** and **70**.

seem immediately apparent found in some sets of diastereomers is the proximity of a proton to the dimethylamine group, whose 1H NMR chemical shift could be affected by the electronegative nitrogen atom. These protons can be assigned in the $^{1}$H NMR of certain compounds and allow for a direct comparison with the corresponding diastereomer (Figure P.1). The protons *syn* to the nitrogen, either directly above (i.e. amine **41**) or below (i.e. amines **70**) should be shifted further downfield than their corresponding diastereomers in the free amine. In the case of final products where the amine is converted to an HCl salt, the difference in chemical shifts between the two free amines and two salts should increase due to the protonation of the nitrogen.

## Results

A table was constructed with all the compounds synthesized in this thesis that contain the same relationship as noted above: a proton on the same face of the bicycle as the nitrogen which can be assigned in the $^{1}$H NMR (Table P.1). Only final products were converted to HCl salts and some HCl salts were evaluated in different solvents. As a result, not all the compounds allow for comparison of the difference in chemical shifts between the free amine and salt. In all cases illustrated in the table with respect to the free amine, the diastereomer with the *syn* proton either directly above or below the dimethylamine is further downfield than its corresponding diastereomer. For example, the benzylic proton on amine **31** is shifted further at δ 3.31 ppm than amine **32** at δ 2.98 ppm. The structure assignment of amine **31** was verified by x-ray analysis (Appendix E). The proton α to the benzoate in amine **26a** is also further downfield (δ 5.41 ppm) than amine **10** (δ 5.15 ppm). These results were confirmed by x-ray diffraction of amine **10**.[1] This

trend is consistent throughout the table, even when the proton is four carbons away, as is the case with alcohols **50** and **51** (δ 3.90 ppm vs δ 3.73 ppm, respectively; Appendix H) and benzoates **54** and **55** (δ 5.15 ppm and δ 5.03 ppm).

The difference in chemical shifts between the two diastereomers when comparing the free amine and the HCl salt does not show a clear trend with respect to the relative stereochemistry. For example, the difference in the chemical shift of the proton α to the benzoate in the free amines **26a** and **10** is 0.26 while in the HCl salt the difference is 0.09. For benzoates **54** and **55** there wasn't a difference between seen between the free amine and the salts, the difference in both cases is 0.05. In the case of amines **69** and **70**, the difference between the free amines is 0.34 and 0.53 for the salts, the opposite of that seen between **26a** and **10**.

Table P.1 indicates the proton α to the benzoate in amine **70** is further downfield at δ 5.50 ppm than the same proton on amine **69** at δ 5.16 ppm. Using the same argument that the nitrogen affects the chemical shifts of protons in close proximity, the amine of compound **70** is *endo*, while the amine of compound **69** must be *exo*.

**Table P.1.** Comparison of *endo* vs *exo* Substituents Directly Above or Below a Nitrogen in a variety of [2.2.1] and [2.2.2]bicycles.

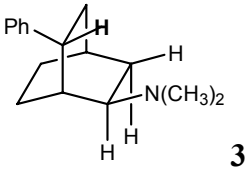
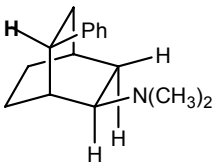
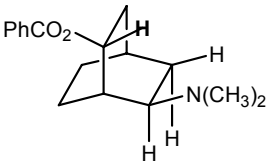
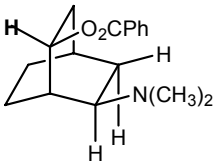
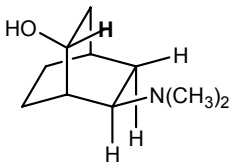
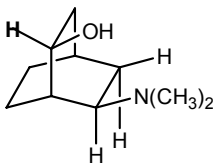
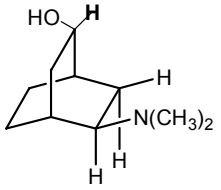
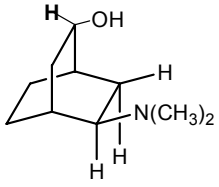
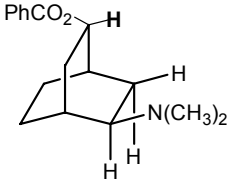
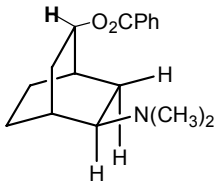
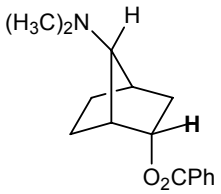
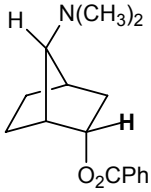
| Compound | Chemical shift (ppm) of free amine (A) | Chemical shift (ppm) of HCl salt (B) | Same face – opposite face |
|---|---|---|---|
|  **31** | 3.31 (benzylic proton) | * | 3.31 – 2.98 = **0.33** (Free amine: **31-32**) |
|  **32** | 2.98 (benzylic proton) | * | |
|  **26a** | 5.41 (proton α to benzoate) | 5.12 (proton α to benzoate, $D_2O$) | 5.41-5.15 = 0.26 (Free amine: **26a – 10**) |
|  **10** | 5.15 (proton α to benzoate) | 5.03 (proton α to benzoate, $D_2O$) | 5.12 – 5.03 = **0.09** (salt: **26a – 10**) |
|  **22** | 4.20 (carbinol proton) | ** | 4.90 – 3.90 = **0.30** (Free amine: **22 – 21**) |
|  **21** | 3.90 (carbinol proton) | ** | |

**Table P.1.** Comparison of *endo* vs *exo* Substituents Directly Above or Below a Nitrogen in a variety of [2.2.1] and [2.2.2]bicycles.

| Compound | Chemical shift (ppm) of free amine (A) | Chemical shift (ppm) of HCl salt (B) | Same face-opposite face |
|---|---|---|---|
|  **50** | 3.90 (carbinol proton) | ** | 3.90 – 3.73 = **0.17**<br>(free amine: **50** – **52**) |
|  **51** | 3.73 (carbinol proton) | ** | |
|  **54** | 5.15 (proton α to benzoate) | 4.93 (proton α to benzoate, $D_2O$) | 5.15 – 5.03 = **0.12**<br>(free amine: **54** – **55**) |
|  **55** | 5.03 (proton α to benzoate) | 4.88 (proton α to benzoate, $D_2O$) | 4.93 – 4.88 = **0.05**<br>(salt: **54** – **55**) |
|  **69** | 5.16 (proton α to benzoate) | 5.21 (proton α to benzoate, $CDCl_3$) | 5.50 – 5.16 = 0.34<br>(free amine: **70** – **69**) |
|  **70** | 5.50 (proton α to benzoate) | 5.74 (proton α to benzoate, $CDCl_3$) | 5.74 – 5.21 = 0.53<br>(salt: **70** – **69**) |

*The salts were not evaluated in the same solvents.
**The compounds were not converted to HCl salts.

## References

1. Coons, S. Synthesis and pharmacology of site-specific cocaine abuse treatment agents-(6-*N*,*N*-dimethylamino)-5-(4-chlorophenyl)bicylco[2.2.2]octan-2-yl benzoate and 6-(*N*,*N*-dimethylamino)bicyclo[2.2.2]octan-2-yl benzoate. Masters Thesis (1998), Georgia Institute of Technology.