

# Memory of Chirality in 1,4-Benzodiazepin-2-ones

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## ABSTRACT

Memory of chirality (MOC) is an emerging strategy in asymmetric synthesis. It has been applied to enolate chemistry, reactions involving carbocation intermediates, and to radical systems. In this strategy the chirality of an enantiopure reactant is transferred to the dynamic chirality of a reactive intermediate to produce stereospecific product.

1,4-Benzodiazepin-2-ones have been described as a “privileged” structure in medicinal chemistry. In addition to their uses as anxiolytics (Valium®) and anti-epileptic agents (Clonopin®), they have shown activity as HIV Tat antagonist, ras farnesyltransferase inhibitors in cancer cells, and antiarrhythmic agents. Because of the utility of this scaffold in the area of medicinal chemistry, it has served as a template in libraries for tens of thousands of compounds. Despite the vast diversity of 1,4-benzodiazepin-2-ones, there are few routes to enantiomerically enriched 3,3-disubstituted benzodiazepines containing a “quaternary” stereogenic center. This research will discuss the stereochemical properties of 1,4-benzodiazepin-2-ones, and provide a novel approach to synthesize enantiomerically enriched “quaternary” benzodiazepines with stereogenic centers through MOC, without the use of external chiral sources.

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# **Dedication**

To my parents.

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# Chapter 1. Memory of Chirality

## 1.1. Introduction

This chapter will discuss memory of chirality (MOC) by distinguishing between the static and dynamic chirality in certain compounds. Requirements for the MOC protocol will also be provided, followed by examples of MOC in enolate chemistry, reactions involving carbocation intermediates, and radical systems. Chapter 1 will conclude with a discussion on MOC in comparison to Seebach's Self-Regeneration of Stereocenters (SRS).

## 1.2. Static and dynamic chirality

In describing chirality, Fuji and Kawabata make a distinction between the static chirality in molecules such as the *S* and *R* enantiomers of phenylalanine and the conformational or dynamic chirality in molecules such as  $\beta$ -phenylpropionic acid (Figure 1-1).<sup>1,2</sup>

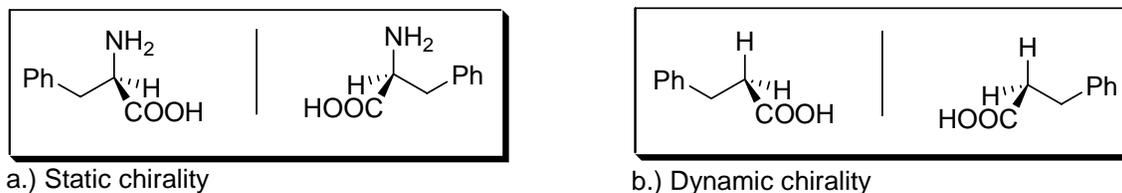


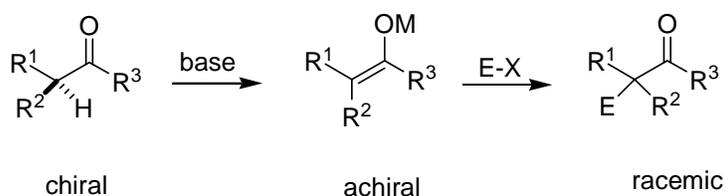
Figure 1-1. Static chirality and dynamic chirality

In Figure 1-1a the conversion from the *R* to the *S* enantiomer would require the breaking of a bond followed by bond formation. In contrast  $\beta$ -phenylpropionic acid in Figure 1-1b can be converted to its mirror image by bond rotation. It does not possess static chirality because it does not have a carbon with a stereogenic center. However, on a limited time

scale it can exist in an enantiomerically pure form. Because one enantiomer can be converted to the other by bond rotation this phenomenon is called conformational chirality. Fuji and Kawabata also propose the term dynamic chirality since the chiral properties of these molecules are time and temperature dependent.<sup>1,2</sup>

### 1.3. Memory of chirality (MOC)

Under conditions of dynamic chirality, enantiopure starting material undergoing reactions in which one might expect racemized product (Scheme 1-1) could proceed stereospecifically to enantiomerically enriched product.<sup>1</sup>



Scheme 1-1. Racemized product from enantiomerically enriched starting material

At short timescales, an enolate could possess axial chirality **1** or planar chirality **2** as in Figure 1-2.<sup>1</sup>

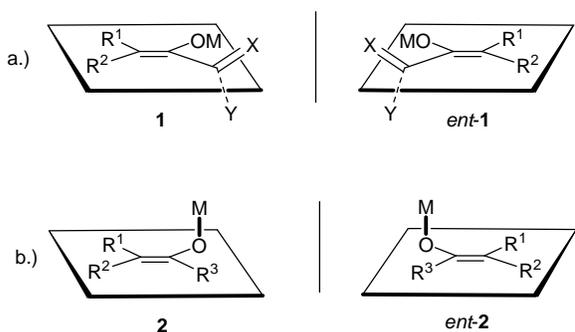
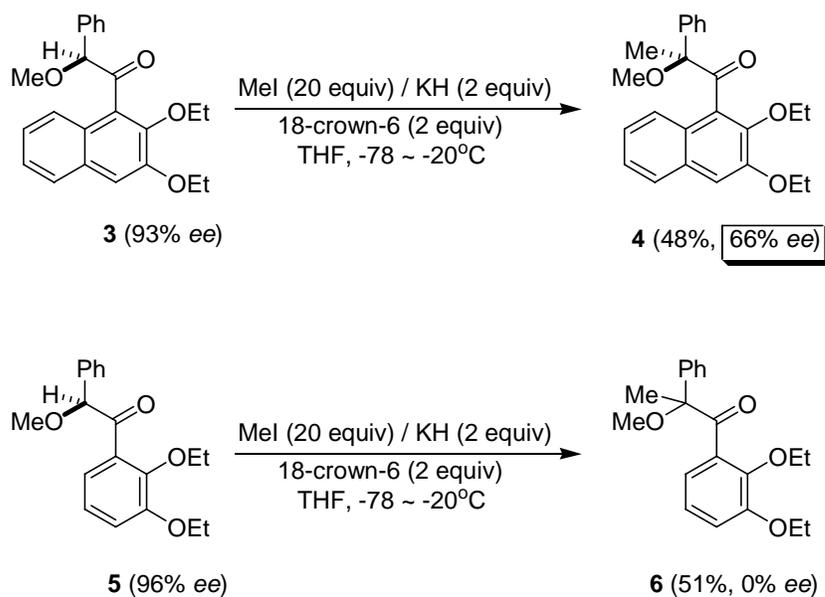


Figure 1-2. Enantiomeric forms of enolates with a.) axial chirality **1** and b.) planar chirality **2**  
(Adapted from *Chem. Eur. J.* **1998**, *4*, 373-376)

In investigating this concept Fuji and Kawabata prepared enantiomerically enriched chiral ketone **3** which upon treatment with potassium hydride and methyl iodide in the presence of 18-crown-6 afforded **4** in 66% *ee* without the use of any chiral auxiliaries (Scheme 1-2).<sup>1,3</sup> In addition ethylation of **3** occurred in 65% *ee* while benzylation and allylation went in 67 and 48% *ee* respectively.



Scheme 1-2. Asymmetric methylation of **3** in a nonchiral environment

To explain these results Fuji and Kawabata propose that the “*central chirality at a carbon  $\alpha$  to a carbonyl group is preserved as transient axial chirality of the intermediate enolate and is then regenerated as central chirality in the reaction product (memory of chirality).*”<sup>3</sup> The transient or dynamic axial chirality referred to in the enolate intermediate **7** is shown in Figure 1-3 along the C<sub>1</sub>-C<sub>2</sub> bond. Fuji and Kawabata were the first to design experiments which utilized this protocol, although Seebach was the first to propose that MOC could account for the enantioselectivity of certain reactions.<sup>4</sup>

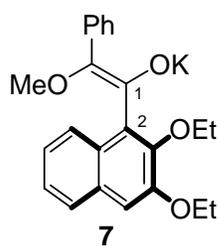


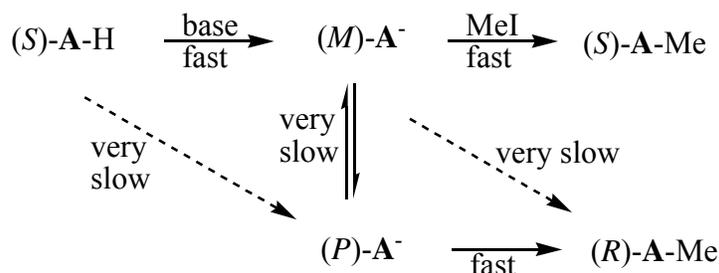
Figure 1-3. Axial chirality along the C<sub>1</sub>-C<sub>2</sub> bond

The (*E*)-enolate was determined to be the major intermediate because the corresponding methyl enol ether was also isolated.<sup>3</sup> The racemization half-life of **7** was found to be 53 min at 21 °C.<sup>1</sup> This restricted bond rotation along the C<sub>1</sub>-C<sub>2</sub> axis is analogous to the atropisomerism found in 1,1'-binaphthyls. As a further proof of this concept, when compound **5** underwent deprotonation and alkylation under conditions identical to compound **3** racemic **6** was obtained (Scheme 1-2).<sup>3</sup> In Fuji and Kawabata's memory of chirality (MOC) the chirality of the starting material is preserved in a reactive intermediate for a limited time.<sup>1</sup>

Two other definitions of MOC worth considering are those of Matsumura and Carlier. Matsumura<sup>5</sup> defines MOC as “*a phenomenon in which the chirality of the starting material having a chiral sp<sup>3</sup>-carbon is preserved in the reaction product even though the reaction proceeds at the chiral carbon as a reaction center through reactive intermediates such as carbanions, singlet monoradicals, biradicals, or carbenium ions.*” For the purpose of this thesis the definition of Carlier will be used in which it is stated: A ‘*memory of chirality*’ reaction can be defined as a formal substitution at an sp<sup>3</sup> stereogenic center that proceeds stereospecifically, even though the reaction proceeds by trigonalization of that center, and despite the fact that no other permanently chiral elements are present in the system.<sup>6</sup>

## 1.4. Requirements for MOC

Based on the definition of Carlier the requirements for MOC are illustrated in Scheme 1-3.<sup>6</sup>



Scheme 1-3. Requirements for memory of chirality

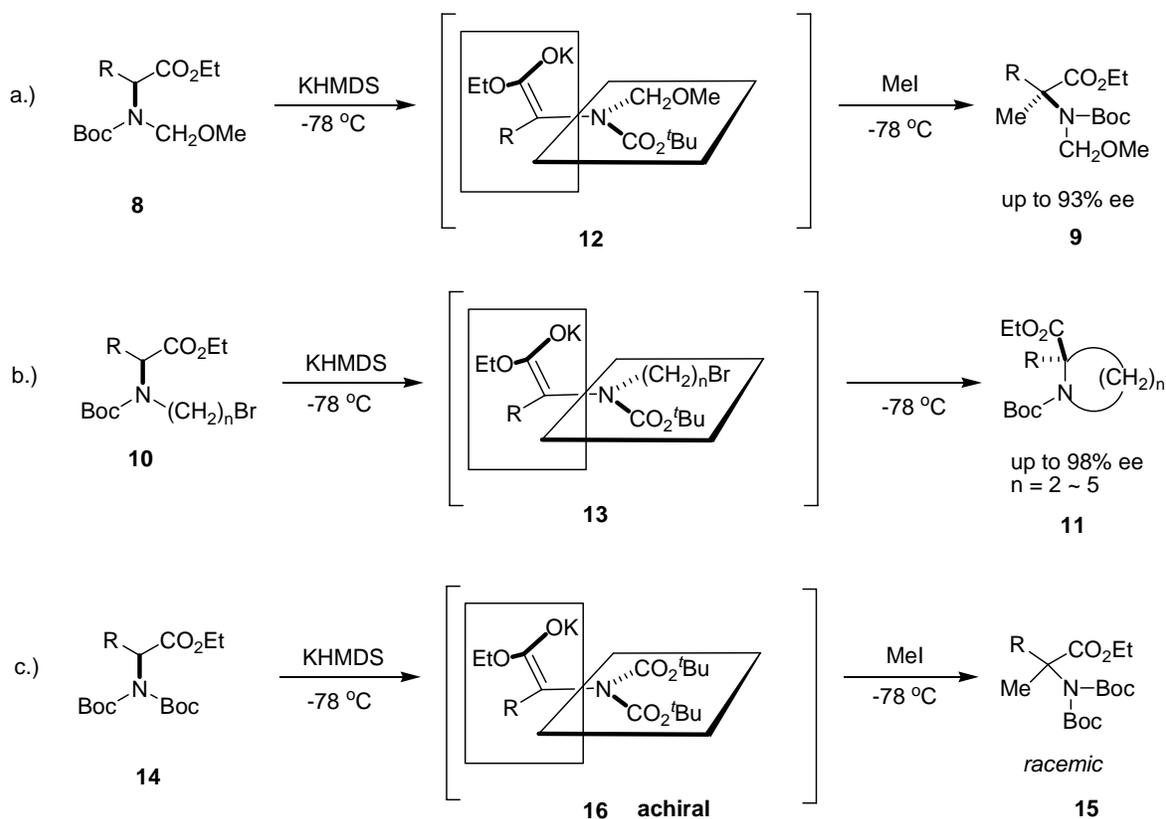
From this scheme, the first step for a successful MOC protocol involves the deprotonation of the stereogenic center in the enantiopure reactant (*S*)-**A**-H to form the conformationally chiral reactive intermediate (*M*)-**A**<sup>-</sup> with high enantioselectivity. The helical descriptors (*M*)- and (*P*)- are used to describe the chirality of the intermediates. The assignments of the helical descriptors are arbitrary. The second criterion in this MOC protocol is that the conformationally chiral intermediate (*M*)-**A**<sup>-</sup> must not readily racemize on the time scale of the desired subsequent reaction. The final criterion is that the conformationally chiral intermediate must react with an electrophile (MeI) with high stereospecificity to produce (*S*)-**A**-Me (the choice of (*S*)-configuration here is arbitrary). From Scheme 1-3 it can be seen that the static chirality present in the starting material (*S*)-**A**-H is transferred to the dynamic chirality of the reactive intermediate (*M*)-**A**<sup>-</sup> and finally to the static chirality of the product (*S*)-**A**-Me. Failure to fulfill any of the above criteria within the MOC protocol would result in product with little or no enantioselectivity.<sup>6</sup>

## 1.5. Applications of MOC

To date the applications of MOC have expanded in the field of asymmetric synthesis to produce a wide variety of compounds.<sup>1,2,6</sup> In the following section, specific examples of MOC will be cited. In these schemes it will be shown how the MOC protocol is used to synthesize products stereospecifically without the use of chiral auxiliaries.

### 1.5.1. MOC strategies in the synthesis of $\alpha,\alpha$ -disubstituted amino acid derivatives

Fuji and Kawabata use the MOC strategy to enantioselectively synthesize  $\alpha,\alpha$ -disubstituted amino acid derivatives **9** (Scheme 1-4a)<sup>7,8</sup> including cyclic amino acids with quaternary stereocenters **11** (Scheme 1-4b)<sup>8,9</sup> from enantiomerically enriched starting material amino acids **8** and **10**.  $\alpha,\alpha$ -Disubstituted amino acids have been shown to be an important class of compounds in biological and medicinal chemistry.<sup>10-13</sup>

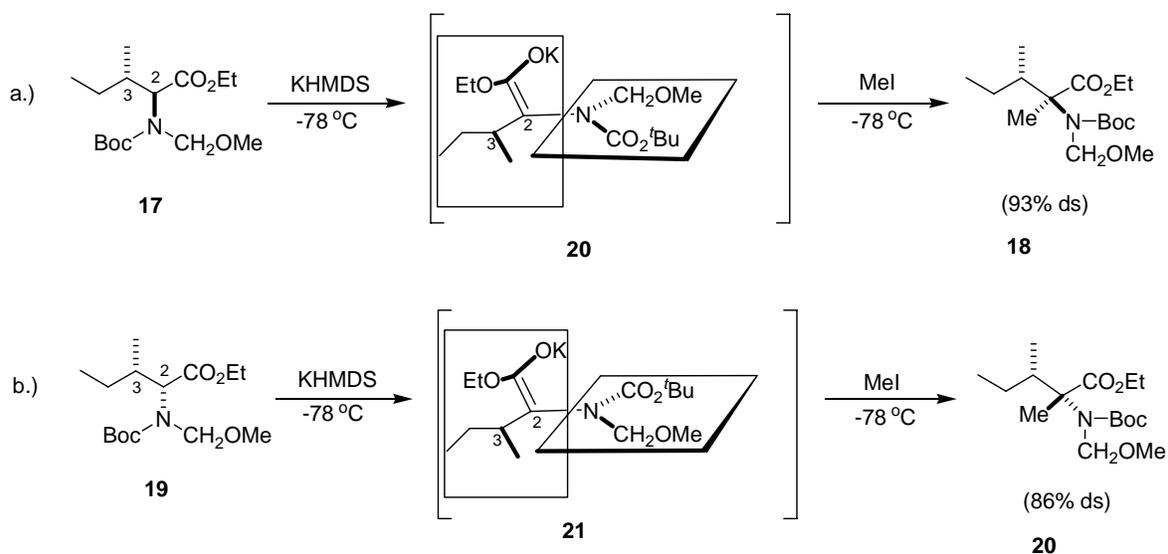


Scheme 1-4. Synthesis of  $\alpha,\alpha$ -disubstituted amino acids using MOC

In Scheme 1-4 Fuji and Kawabata propose that upon deprotonation of the  $\alpha$ -amino acids **8** and **10**, the static chirality of the chiral carbon is transferred to the dynamic chirality of the C-N axis in enolate intermediates **12** and **13** respectively. As in the requirements for MOC (Scheme 1-3) the racemization barrier of these intermediate must be sufficient to prevent racemization before alkylation. Alkylation is proposed to occur from the less sterically hindered side of the enolates opposite the Boc group, resulting in stereoselective methylation **9** (Scheme 1-4a) and stereoselective cyclization **11** (Scheme 1-4b). Hence, the dynamic chirality of the enolate intermediates is transferred to the static chirality of the  $\alpha,\alpha$ -disubstituted amino acid derivatives, fulfilling the MOC requirements. To test this proposal, Fuji and Kawabata also synthesized the di-Boc

protected amino acid **14** which upon deprotonation followed by methylation yielded racemic product **15** (Scheme 1-4c). The key difference here is that upon deprotonation, di-Boc protected amino acid **14** goes through an achiral enolate **16** in which the electrophile has no preference of approach leading to racemic product **15**.<sup>7</sup>

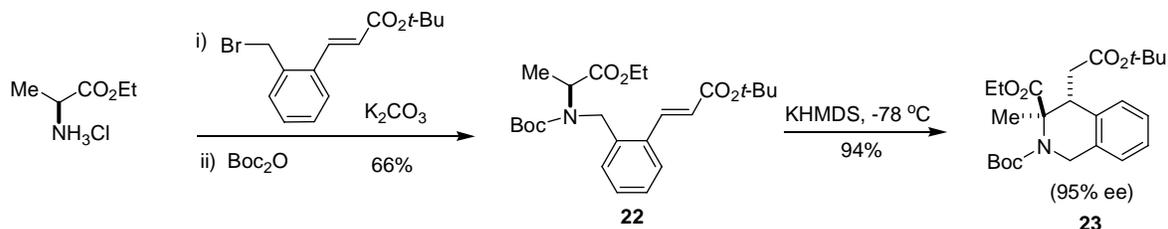
As a further proof of their concept Fuji and Kawabata conducted experiments in which they placed a (*S*) chiral center at C(3) in their molecules **17** and **18** (Scheme 1-5).<sup>14</sup> In doing this they would be able to see whether the stereochemical course of the reaction determined by the dynamic chirality of the C-N axis in the enolate intermediate (Scheme 1-4) would be affected.



Scheme 1-5. Effect of C(3) substituent on the synthesis of  $\alpha,\alpha$ -disubstituted amino acids using MOC

Despite the presence of an additional source of chirality in the enolate intermediates **20** and **21** at C(3) stereoselective alkylation occurred with retention. This selectivity can be attributed to alkylation from the less sterically hindered methoxy methyl side of the enolates along the C-N axis leading to diastereomerically enriched products **18** and **20** with the (*S*) chiral center at C(3) having little effect on diastereoselectivity (Scheme 1-5).

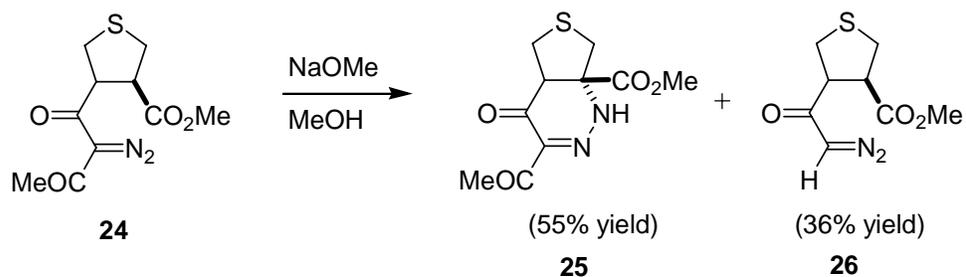
Most recently Kawabata has utilized the MOC strategy to synthesize nitrogen heterocycles with contiguous quaternary and tertiary stereocenters (Scheme 1-6).<sup>15</sup> Precursor **22** was synthesized from alanine ethyl ester and (*E*)-*tert*-butyl-3-(2-bromomethylphenyl)acrylate followed by Boc protection. Upon cyclization of **22** product **23** was obtained in 94% yield and 95% ee.



Scheme 1-6. Synthesis of nitrogen heterocycles with contiguous quaternary and tertiary stereocenters using MOC

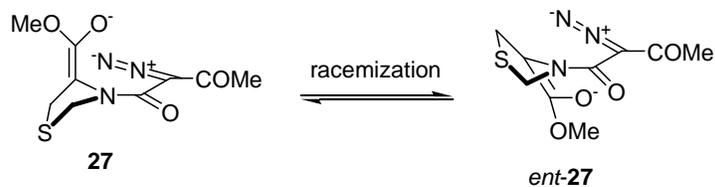
### 1.5.2. MOC involving other cyclization reactions with axially chiral enolate intermediates

In the same year that Fuji and Kawabata proposed their MOC strategies Stoodley and co-workers also reported the stereoselective cyclization reaction of **24** to **25** in an attempt to produce **26** (Scheme 1-7).<sup>16</sup>



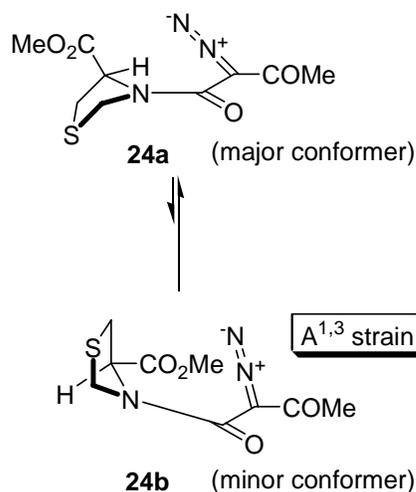
Scheme 1-7. MOC involving other cyclization reactions with axially chiral enolate intermediates

Stoodley's explanation for this result was that the reaction proceeds through enolate **27** in which the cyclization reaction occurs more rapidly than racemization to *ent*-**27** (Scheme 1-8).<sup>16</sup>



Scheme 1-8. Axially chiral enolate intermediate **27**

Preference for formation of enolate **27** comes from deprotonation of the major conformer of the starting material **24a** which does not contain the severe  $A^{1,3}$  interactions between the acyl substituent and the methoxycarbonyl group found in the minor conformer **24b** (Scheme 1-9).<sup>16</sup> More recently Stoodley and co-workers have expanded their MOC schemes to include derivatives of proline and oxaproline esters through axially chiral enolate intermediates.<sup>17</sup>

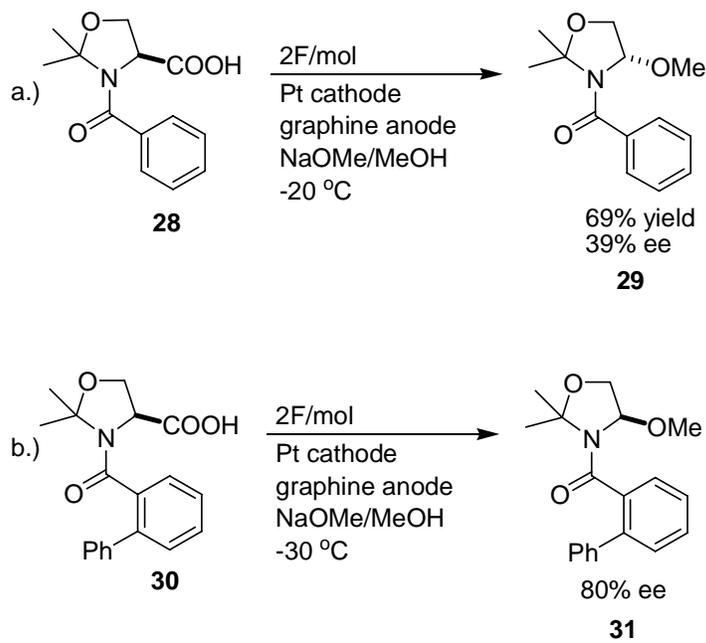


Scheme 1-9. Major conformer **24a** due to  $A^{1,3}$  strain in **24b**

### 1.5.3. MOC involving carbocation intermediates

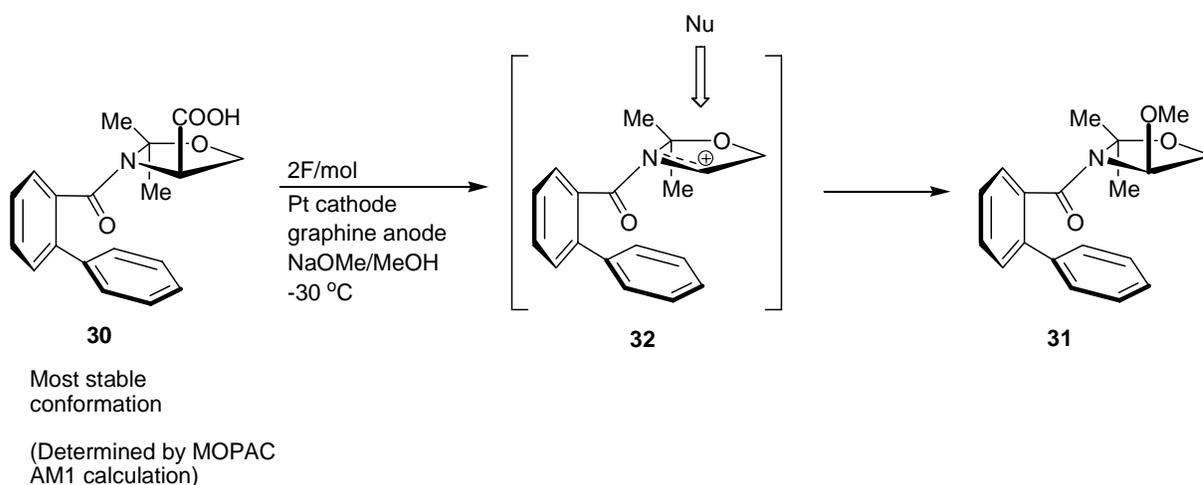
As mentioned above by Matsumura<sup>5</sup> MOC strategies can go through a variety of reactive intermediates. In their enantioselective oxidative decarboxylation/methoxylation

protocol of *N*-acylated serine derivatives **28** and **30** to products **29** and **31** (Scheme 1-10)<sup>5,18,19</sup> Matsumura and co-workers present an explanation for the retentive stereochemical reaction in Scheme 1-10b.<sup>5</sup>



Scheme 1-10. MOC in decarboxylation/methoxylation of *N*-acylated serine

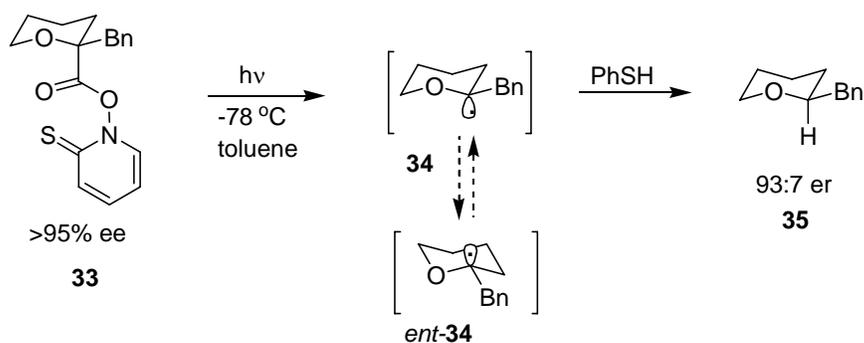
They propose that the main contributing factor for the enhanced enantioselectivity in Scheme 1-10b over Scheme 1-10a is the bulky *o*-phenyl benzoyl *N*-protecting group. As seen in Scheme 1-11 upon decarboxylation of **30** the reaction goes through a chiral iminium ion **32** which is shielded on the bottom face by the *o*-phenyl group to give retentive product **31**.<sup>5</sup>



Scheme 1-11. Chiral iminium ion

### 1.5.4. MOC in radical systems

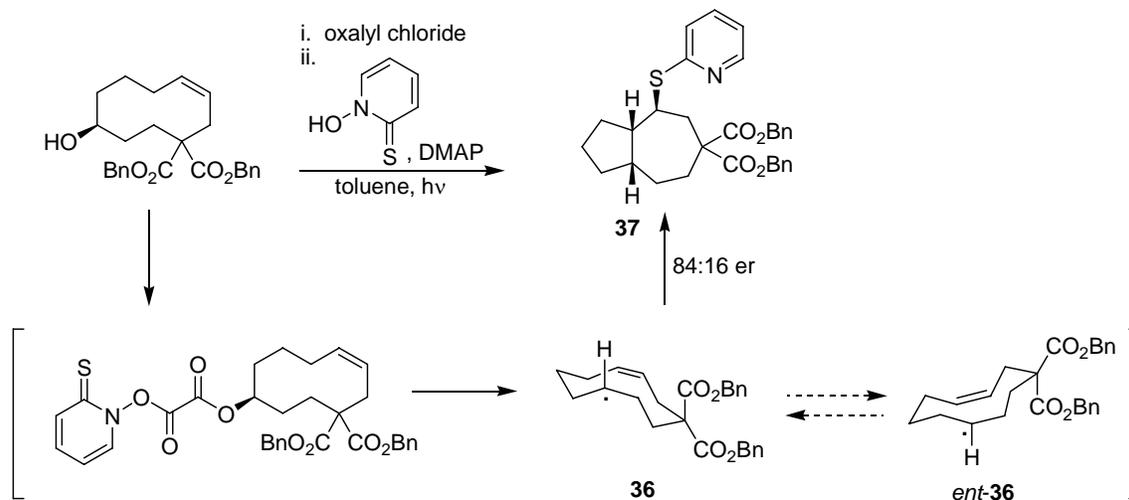
MOC strategies have also been applied to radical systems. Rychnovsky's work shows that hydrogen abstraction of anomeric-stabilized tetrahydropyranyl radicals can occur stereoselectively (Scheme 1-12).<sup>20,21</sup>



Scheme 1-12. MOC in hydrogen abstraction of a tetrahydropyranyl radical

In the above example the static chirality at the chiral carbon in the starting material **33** is transferred to the dynamic chirality of the radical intermediate **34** upon radical decarboxylation. It is important to note that it is the conformation of the radical intermediate and **not** the radical center that is dynamically chiral. Interconversion of **34**

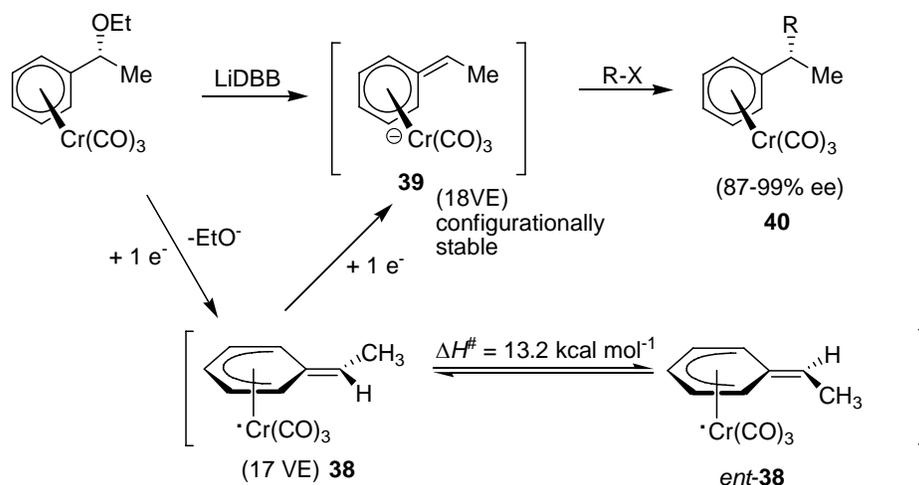
to *ent*-**34** involves a chair ring inversion with a barrier between 5 and 10 kcal/mol<sup>21,22</sup> accompanied by radical inversion barrier of  $\leq 0.5$  kcal/mol.<sup>23</sup> Ring inversion of this intermediate is slow compared to the radical reaction to form the enantiomerically enriched product **35** (Scheme 1-12). More recently Rychnovsky has applied MOC strategies in the transannular cyclization of cyclodecenyl radicals (Scheme 1-13).<sup>24</sup>



Scheme 1-13 MOC in radical cyclization

As in the previous scheme, the dynamic chirality in Scheme 1-13 is dependent on the conformational chirality of the radical intermediate **36** not the inversion of the radical center. Because the transannular cyclization reaction occurs faster than the ring inversion of the radical intermediate **36**, optically enriched product **37** is obtained upon transfer of the 2-thiopyridyl moiety. In both cases (Schemes 1-12 and 1-13) stereoselective reactions are achieved due to the stable conformational chirality in the ring systems of the radical intermediates.

Schmalz and co-workers utilize the dynamic planar chirality of arene radical intermediates in their MOC strategies to obtain enantioselective alkylations at the benzylic carbon (Scheme 1-14).<sup>25,26</sup>



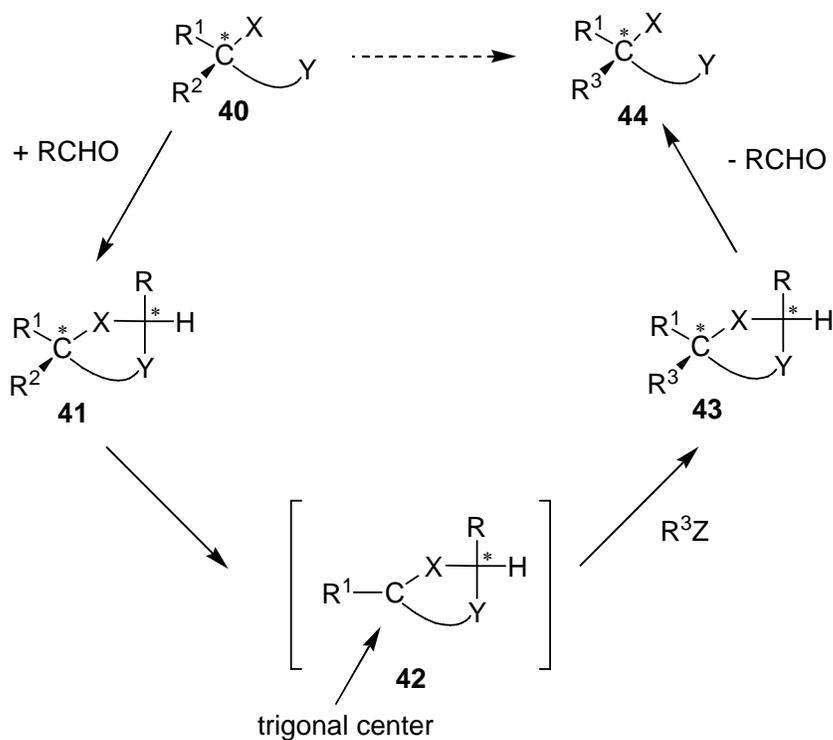
Scheme 1-14. Dynamic planar chirality of arene radical intermediates

In Scheme 1-14 Schmalz describes the radical intermediate **38** as a 17-valence electron complex with a racemization barrier of 13.2 kcal/mol determined by DFT calculations. Single electron reduction of this intermediate leads to the configurationally stable 18-valence electron benzylic anion species **39**.<sup>27</sup> Stereoselective alkylation of the anion species occurs in 87-99% ee to yield **40**. Once again the static chirality at the carbon center in the starting material is transferred to the dynamic chirality of the planar intermediate and finally to the static chirality in the carbon center of the product.

## 1.6. MOC in comparison to Self-Regeneration of Stereocenters (SRS)

It is important to note that MOC is conceptually different from Seebach's Self-Regeneration of Stereocenters (SRS)<sup>28</sup> despite the fact that enantiomerically enriched product can be obtained in both methods without the use of a chiral auxiliary. In the SRS method (Scheme 1-15),<sup>28</sup> first a chiral starting material **40** with one stereogenic center and two functional groups reacts with an aldehyde to form an acetal **41** with a preference for one diastereomer. In doing this a temporary static chiral center is formed selectively.

Second, a ligand is removed from the original chiral center, which then becomes trigonalized. The intermediate **42** formed in this step is chiral due to the temporary chiral center at the acetal carbon. In the third step a new ligand is attached to the trigonalized center **43**. This is done diastereoselectively due to the temporary static chiral center. Finally, the temporary static chiral center is removed by hydrolysis of the acetal unit, regenerating the aldehyde and producing stereospecific product **44**.<sup>28</sup> The key difference between SRS and MOC is that SRS is dependent upon the static chirality of the chiral carbon (formed from an external reagent, i.e. aldehyde in Scheme 1-15) in the intermediate step while MOC relies upon the dynamic or conformational chirality of the intermediate itself (without any external reagents). As such MOC is a time dependent method.<sup>20</sup>



Scheme 1-15. Self-Regeneration of Stereocenters

## 1.7. Conclusion

In conclusion, under MOC conditions, the static chirality present in the starting material is transferred to the dynamic chirality of a reactive intermediate and finally to the static chirality of the product. The MOC protocol has been applied to enolate chemistry, reactions involving carbocation intermediates, and to radical systems. Finally, MOC is conceptually different from SRS. While SRS depends on the static chirality of a chiral carbon in the intermediate step, MOC relies upon the dynamic chirality of the intermediate itself.

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## Chapter 2. Significance of 1,4-Benzodiazepin-2-ones

### 2.1. Introduction

This chapter will discuss the significance of 1,4-benzodiazepin-2-ones from a historical perspective. They are an important structure in medicinal chemistry with drug discoveries, such as Librium® and Valium®, resulting in libraries of tens of thousands of these compounds. Other medicinal uses of these compounds will also be looked at. In addition, the stereochemistry of these structures will be discussed, which will include NMR studies on these compounds. Finally, synthetic routes to 3,3-disubstituted 1,4-benzodiazepin-2-ones possessing a quaternary center will be examined.

### 2.2. History of 1,4-benzodiazepin-2-ones

1,4-Benzodiazepines **45** (Figure 2-1) have been an important structure in medicinal chemistry ever since the discovery of the anxiolytic chlordiazepoxide **46** (Librium®) (Figure 2-2) in the late 1950's by Sternbach and co-workers.<sup>1</sup>

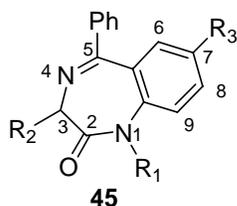


Figure 2-1. 1,4-Benzodiazepin-2-one

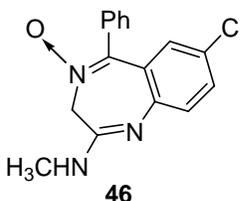


Figure 2-2. Chlordiazepoxide (Librium®)

The success of this drug quickly led to research to find better products. Because chlordiazepoxide **46** is metabolized in the body to the 1,4-benzodiazepin-2-one,<sup>2,3</sup> diazepam **47** (Valium®) (Figure 2-3) was developed in 1963 which proved to be a more potent anxiolytic. Other 1,4-benzodiazepin-2-one derivatives used in anti-anxiety

treatments include: oxazepam (Sereax®) **48**, clorazepate (Tranxene®) **49**, lorazepam (Ativan®) **50**, and prazepam (Verstran®) **51**. In addition flurazepam (Dalmane®) **52** is a hypnotic while clonazepam (Clonopin®) **53** is used in anti-epileptic treatments (Figure 2-3).<sup>1</sup>

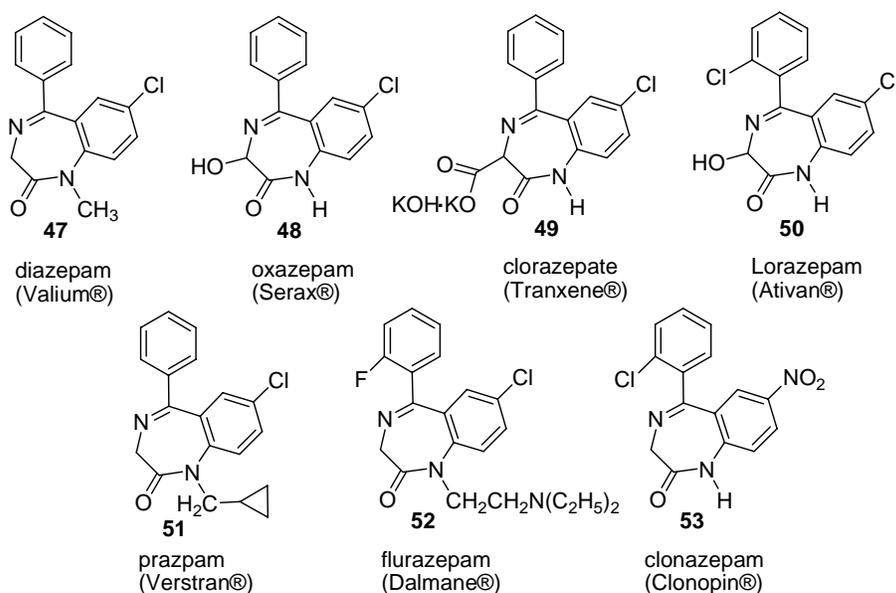


Figure 2-3. 1,4-Benzodiazepin-2-ones used as pharmaceuticals

In addition to the 1,4-benzodiazepin-2-one derivatives triazolobenzodiazepines (Figure 2-4), such as alprazolam (Xanax®) **54** and triazolam (Halcion®) **55**, have been developed which were found to be more potent than benzodiazepin-2-ones.<sup>1,4,5</sup>

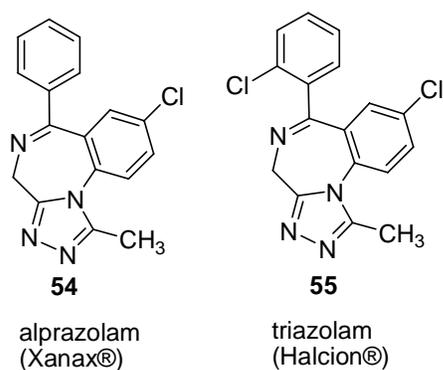


Figure 2-4. Triazolobenzodiazepines

### 2.3. Usefulness of 1,4-benzodiazepin-2-ones

1,4-benzodiazepin-2-ones **45** have been referred to as a “privileged”<sup>6</sup> structure in medicinal chemistry. Because of their effectiveness as anxiolytics, such as diazepam (Valium®) **47**, these structures have served as templates in libraries for tens of thousands of compounds.<sup>7,8</sup> As a result 1,4-benzodiazepin-2-ones have also been shown to be antagonists of the peptide hormone cholecystokinin A (CCK-A) **56**<sup>6,9</sup> in the gastrointestinal system and CCK-B **57** in the central nervous system.<sup>10,11</sup> They have also shown activity as HIV Tat antagonists **58**,<sup>12</sup> ras farnesyltransferase inhibitors in cancer cells **59**,<sup>13</sup> antagonists for the Bradykinin B<sub>2</sub> receptor **61**,<sup>14</sup> and antiarrhythmic agents **60**<sup>15</sup> (Figure 2-5). Furthermore derivatives of these structures have also shown activity as agonists and antagonists on the GABA<sub>A</sub> receptor.<sup>16-19</sup>

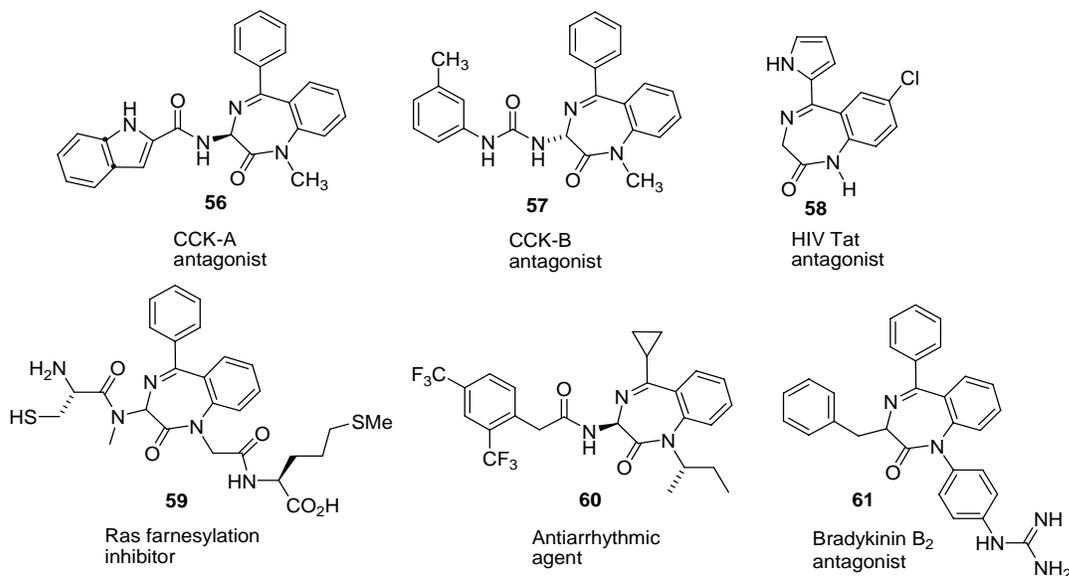


Figure 2-5. Medical uses of 1,4-benzodiazepin-2-ones

It is important to note, however, that despite the vast diversity of 1,4-benzodiazepin-2-ones there are few routes to enantiomerically enriched 3,3-disubstituted benzodiazepines containing a “quaternary” stereogenic center.<sup>20</sup> This paucity exists

because the corresponding quaternary amino acids<sup>21</sup> from which they would be synthesized<sup>22</sup> are usually not commercially available. This issue will be addressed later in this thesis.

## 2.4. Stereochemistry of 1,4-benzodiazepin-2-ones

### 2.4.1. Conformational chirality of the benzodiazepine ring

1,4-Benzodiazepin-2-ones exist in a 7-membered boat formation **47** with the substituents at C3 in axial and equatorial positions (Figure 2-6). In addition, molecules such as diazepam without a stereogenic center can exist as (*M*)-**47** and (*P*)-**47** conformational enantiomers<sup>23,24</sup> despite the fact that they have no chiral center (Figure 2-7). These aspects are of importance during the discussions on inversion barriers and substituent effects on C3 in the benzodiazepine ring system below.

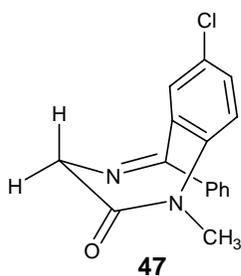


Figure 2-6. 1,4-Benzodiazepin-2-one in 7-membered boat

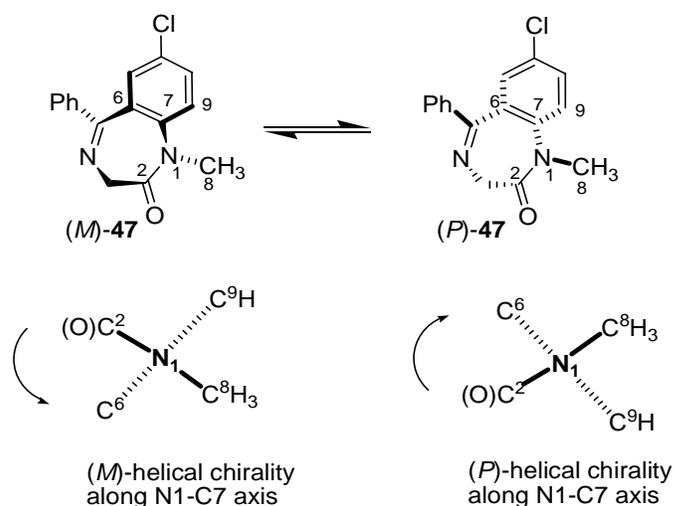
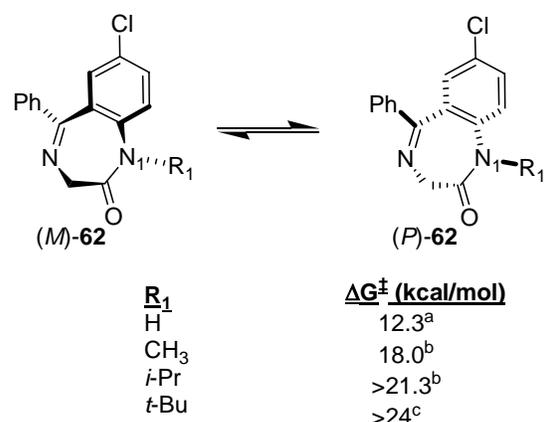


Figure 2-7. *(M)*- and *(P)*-conformers of the benzodiazepine ring

#### 2.4.2. Inversion barriers of 1,4-benzodiazepin-2-ones

It is known that increasing the size of the N1 substituent R<sub>1</sub> in the benzodiazepine ring system increases the inversion barrier of the ring (Figure 2-8).<sup>23,25,26</sup> The placement of a large substituent such as a *tert*-butyl group at the N1 position increases the racemization barrier of the benzodiazepine ring to over 24 kcal/mol allowing for preparative resolution of the *(M)*-**62** and *(P)*-**62** enantiomers.<sup>24,25</sup> Smaller N1 substituents (i.e. H, Me, *i*-Pr) prevent resolution of these compounds at room temperature due to the lower racemization barriers (Figure 2-8).<sup>24</sup>



<sup>a</sup>Linscheid, P.; Lehn, J. M., *Bull. Chim. Soc. Fr.* **1967**, 3, 992-997  
<sup>b</sup>Lam, P.C.-H.; Carlier, P.R., *J. Org. Chem.*, **2005**, 70, 1530-1538  
<sup>c</sup>Gilman, N.W.; Rosen, P.; Earley, J. V.; Cook, C.; Todaro, L.J.,  
*J. Am. Chem. Soc.*, **1990**, 112, 3969-3978

Figure 2-8. Inversion barriers of 1,4-benzodiazepin-2-ones

Interestingly, Salvadori and co-workers have discovered that placing a fluorine atom at the C2' position on N-*t*-Bu benzodiazepine ((*M*)-**63** and (*P*)-**63**) decreases the inversion barrier to 21 kcal/mol (Figure 2-9)<sup>27</sup>, which is between the diazepam (R1 = Me) and N-*t*-Bu benzodiazepine (Figure 2-8). While it is known that the placement of a halogen substituent at the C2' position enhances benzodiazepine activity<sup>28</sup> the authors do not provide an explanation for the decrease in inversion barrier.

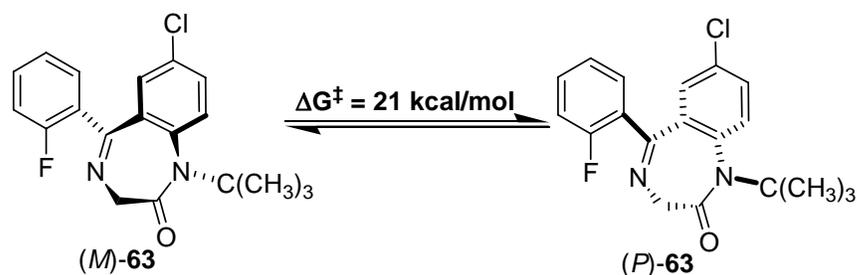


Figure 2-9. Inversion barrier of 7-chloro-5-(2-fluorophenyl)-1-(1,1-dimethylethyl)-1,4-benzodiazepin-2-one

### 2.4.3. NMR studies on 1,4-benzodiazepin-2-ones

<sup>1</sup>H NMR studies show that, when the N1 substituent is hydrogen, the corresponding inversion barrier of 12.3 kcal/mol<sup>24</sup> (Figure 2-8) is not high enough to resolve the methylene protons in the equatorial and axial positions of the benzodiazepine ring on the NMR time scale at room temperature. These protons appear as one broad signal at 4.34 ppm (Figure 2-10a) because of the interconversion from the (*M*)-**64** to the (*P*)-**64** conformer through the ring flipping is fast on the NMR timescale. However, once the N1 substituent is increased to the size of a methyl group (thereby increasing the inversion barrier to 18.0 kcal/mol<sup>26</sup>) (Figure 2-8), the equatorial and axial methylene protons in the diazepam ring ((*M*)-**47** and (*P*)-**47**) can be resolved on the NMR timescale at room temperature (Figure 2-10b). The equatorial proton at 4.84 ppm is split into a doublet by the axial proton (<sup>2</sup>*J*<sub>HH</sub> = 10.8 Hz) while the axial proton is also split into a doublet by the equatorial proton and is shifted upfield to 3.78 ppm (<sup>2</sup>*J*<sub>HH</sub> = 10.8 Hz) due to the shielding cone of the benzene ring (Figure 2-10b).

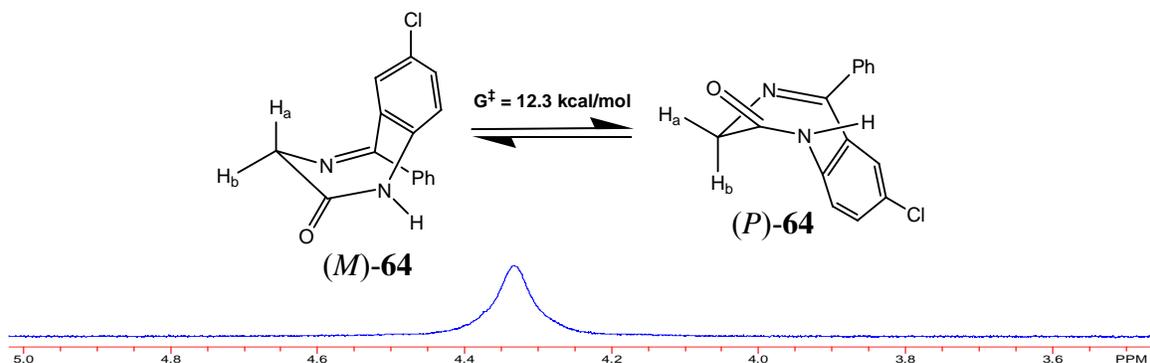


Figure 2-10a. NMR studies on *des*-methyl diazepam

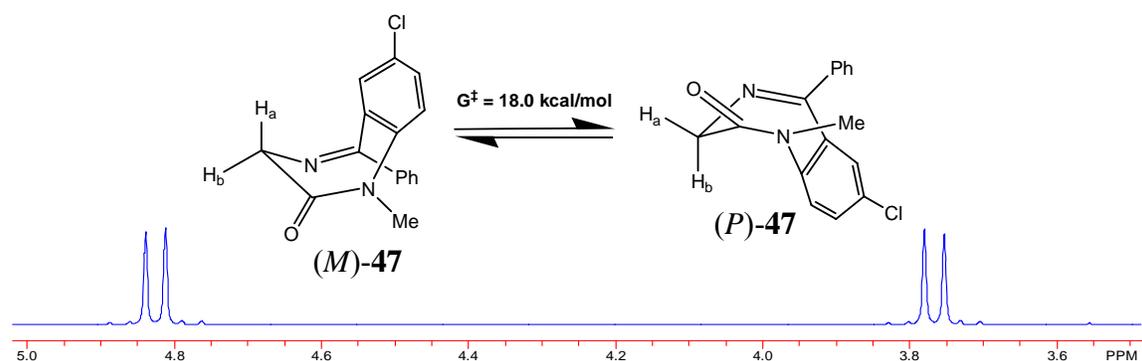


Figure 2-10b.  $^1\text{H}$  NMR studies on diazepam in  $\text{CDCl}_3$

Spectra supplied by the author

#### 2.4.4. Effect of a chiral center at C3 on the benzodiazepine ring

It is known<sup>23,25,29,30</sup> that if 1,4-benzodiazepin-2-ones possess a chiral center at the C3 carbon the conformational equilibrium of these molecules would be shifted towards the conformer having the larger substituent in the equatorial position in the benzodiazepine ring (*M*)-65. In the case of the 1,4-benzodiazepin-2-one ring systems the

(*S*)-stereochemistry at the C3 carbon induces the (*M*)-axial chirality (*M*)-**65** in the benzodiazepine ring. (Figure 2-11).

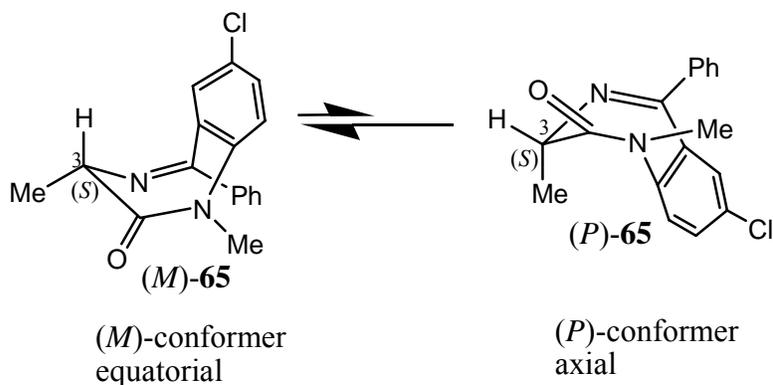


Figure 2-11. (*M*)-axial chirality induced by (*S*)-stereochemistry at C3

NMR studies done on 3-substituted 1,4-benzodiazepin-2-ones also reveal the equatorial preference for the larger substituent at the C3 position on the ring. As seen above when the N1 substituent on the benzodiazepine ring is a methyl group the equatorial and axial methylene protons at the C3 position of the diazepam ring **47** are resolvable at 4.84 ppm and 3.78 ppm respectively (Figures 2-10b & 2-12). Substitution of one of the methylene protons at C3 with a methyl group would cause an equilibrium shift towards the conformer with the larger methyl group in the equatorial position of the benzodiazepine ring (*M*)-**65**. Hence the signal of the equatorial methylene proton is replaced by the equatorial methyl group at 1.73 ppm while the axial proton is still present at 3.70 ppm (Figure 2-12). Further substitution of the axial proton at the C3 position with a methyl group to give the 3,3-dimethyl diazepam (*M*)-**66** shows that the equatorial methyl group is still present at 1.83 ppm while the axial methyl group is shifted to 0.90 ppm due to the shielding cone of the benzene ring, as in the case of the axial proton.

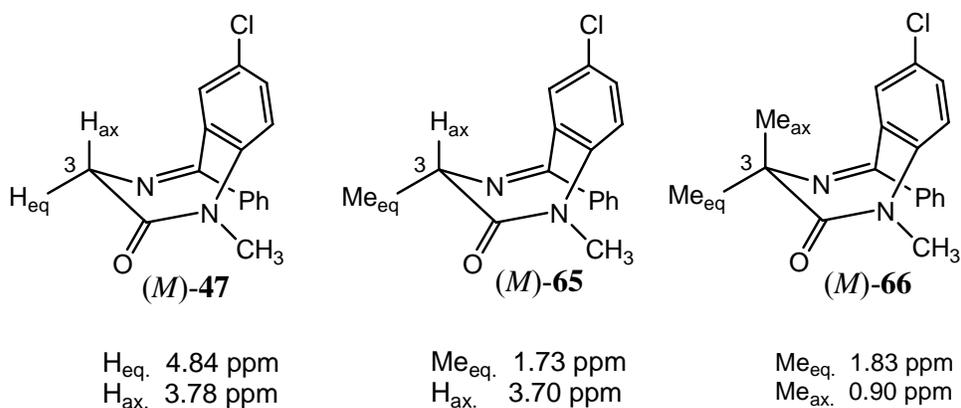


Figure 2-12.  $^1\text{H}$  NMR studies in  $\text{CDCl}_3$  for equatorial preference of larger substituent at C3  
 Data supplied by the author

#### 2.4.5. Biological implications of 1,4-benzodiazepin-2-one stereochemistry

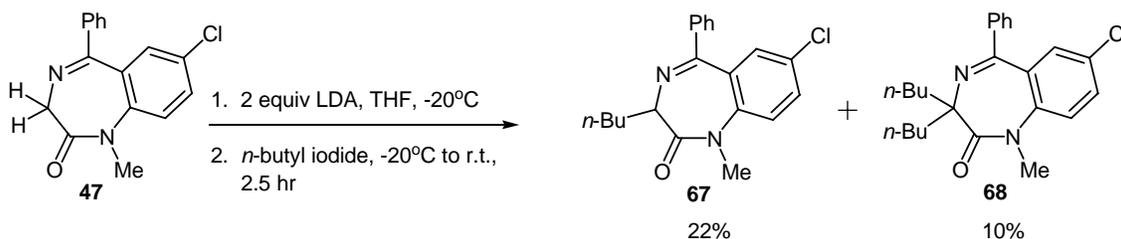
It is of interest to note that receptors in the central nervous system (CNS)<sup>31</sup> and human serum albumin (HSA)<sup>32,33</sup> have shown enantioselectivity in binding to the (*S*) enantiomer of 1,4-benzodiazepin-2-ones. In addition, studies done on the CNS receptor<sup>34</sup> and on HSA<sup>35</sup> with 1,4-benzodiazepin-2-ones without a chiral center, such as diazepam, have suggested that chiral recognition at specific binding sites is achieved by the (*M*)-conformation of the benzodiazepine ring rather than the (*S*)-chiral center at C3. This implication is consistent with the above explanation of (*S*)-stereochemistry at C3 inducing (*M*)-axial chirality on the benzodiazepine ring. This particular aspect will also be important in addressing methods for stereoselective alkylations to produce enantiopure 3,3-disubstituted benzodiazepines containing a “quaternary” stereogenic center later in this thesis.

## 2.5. Synthetic routes to 3,3-disubstituted 1,4-benzodiazepin-2-ones possessing a quaternary center

As mentioned above, there are few routes to 3,3-disubstituted benzodiazepines possessing a quaternary center. This section will discuss two routes to these compounds. In the first method 3,3-disubstituted benzodiazepines without a stereogenic center will be generated.<sup>36</sup> The second will employ lipase-catalyzed acylation to produce enantiopure 3,3-disubstituted 1,4-benzodiazepin-2-ones.<sup>20</sup>

### 2.5.1. Synthesis of 3,3-di-*n*-butyl-1,4-benzodiazepin-2-one

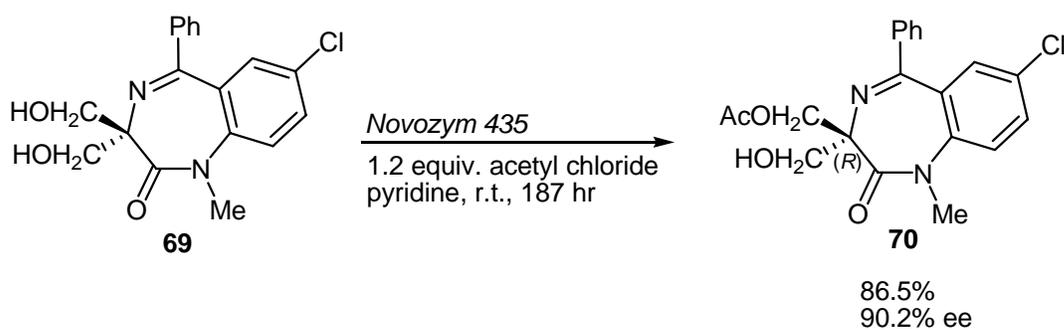
In their attempts to synthesize 3,3-dialkyl benzodiazepines from diazepam **47** using 2 equivalents of LDA at -20°C, Wolfe and co-workers<sup>36</sup> isolated both mono-**67** and di-alkylated product **68** in the reaction with *n*-butyl iodide in 22% and 10% yield respectively (Scheme 2-1). While this product does not contain a chiral center it is an example of the 3,3-disubstituted quaternary benzodiazepine. Interestingly, when this reaction was done using methyl iodide as the electrophile, only mono-methylated product was obtained.



Scheme 2-1. Synthesis of 3,3-di-*n*-butyl-1,4-benzodiazepin-2-one

## 2.5.2. Enantioselective acylation of 3,3-bis(hydroxymethyl)-1,4-benzodiazepin-2-one

In addition to the work of Carlier and co-workers addressed in this thesis, in which 3,3-disubstituted 1,4-benzodiazepin-2-ones are enantioselectively synthesized based on the intrinsic chirality of the benzodiazepine ring using the MOC protocol, Sunjic and co-workers<sup>20</sup> have also acquired these compounds in high enantiomeric excess. Using *Novozym 435*, in their lipase-catalyzed acylation of 3,3-bis(hydroxymethyl)-1,4-benzodiazepin-2-one **69**, they were able to obtain the (*R*)-acylated product **70** in both high yield and enantiomeric excess (Scheme 4-18). Sunjic's explanation for the stereochemistry in the product is that compound **69** is prevalently bound to the enzyme in the (*P*) conformation to affording the (*R*)-acetylated product **70**.<sup>20</sup> The key difference between their procedure and the work presented in this research is that external chiral sources (such as enzymes) were not employed in the synthesis of our compounds.



Scheme 2-2. Enantioselective acylation of 3,3-bis(hydroxymethyl)-1,4-benzodiazepin-2-ones by *Novozym 435*

## 2.6. Conclusion

In conclusion, 1,4-benzodiazepin-2-ones have proven to be a “privileged” structure in medicinal chemistry. In examining the stereochemistry of these compounds, benzodiazepines without a chiral center can exist as (*M*)- and (*P*)- conformational enantiomers. Increasing the size of the N1 substituent increases the inversion barrier of the benzodiazepine ring. It is also known that in benzodiazepines with a chiral center, there is an equilibrium shift towards the conformer having the larger substituent in the equatorial position of the ring. Finally, there are few routes to synthesize enantiomerically enriched quaternary 1,4-benzodiazepin-2-ones with quaternary stereogenic centers.

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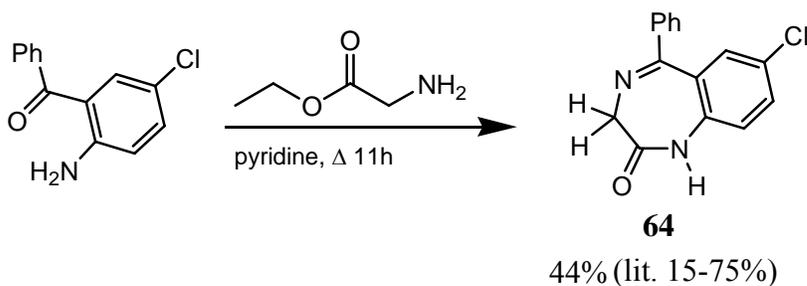
## Chapter 3. Synthesis of 1,4-benzodiazepin-2-one scaffolds

### 3.1. Introduction

In this chapter the synthesis of the benzodiazepine scaffolds used in this research is discussed. It was found that DCC coupling to of enantiopure *N*-Boc amino acids to 2-amino benzophenone followed by cyclization of the amide intermediate worked best. The enantiopure amino acids used in this research were alanine, phenylalanine, 2-aminobutyric acid, methionine, and leucine. It is known that increasing the size of the N1 substituent increases the inversion barrier of the benzodiazepine ring. Because of this, benzodiazepines derivatives were synthesized with the methyl, isopropyl, and di(*p*-anisyl)methyl (DAM) group at the N1 position. Enantioselective reactions performed on these scaffolds are discussed in Chapter 4.

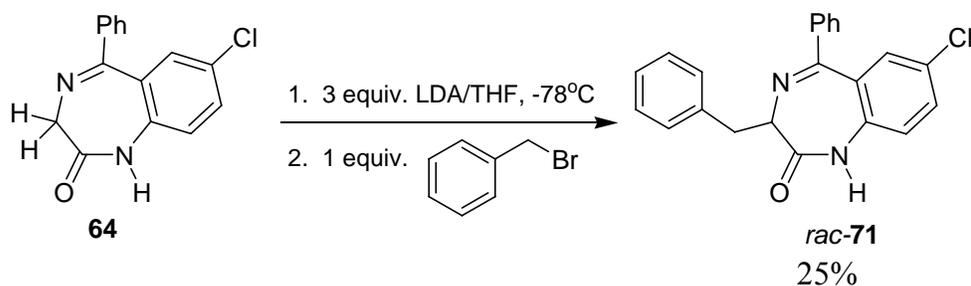
### 3.2. Early work

At the beginning of our studies in these ring systems we first synthesized benzodiazepine **64** derived from 2-amino-5-chlorobenzophenone and the achiral amino acid glycine using the method of Sternbach<sup>1</sup> (Scheme 3-1).



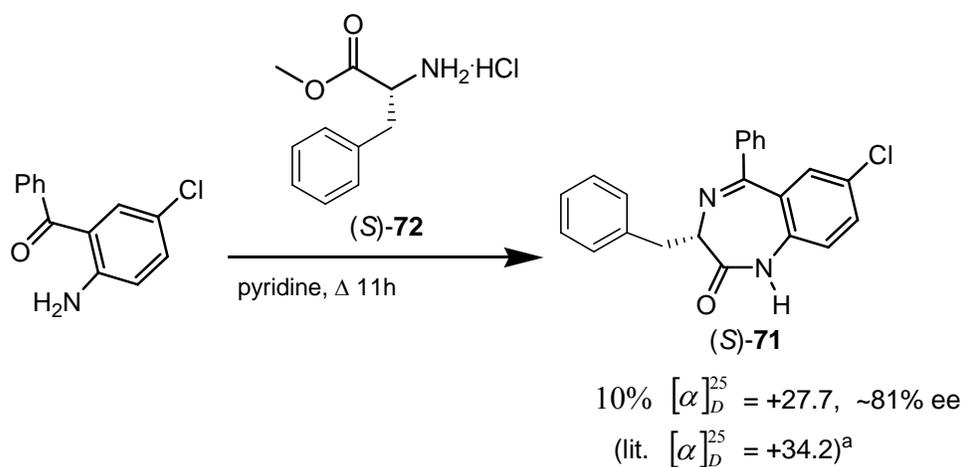
Scheme 3-1. Synthesis of *des*-methyl diazepam

Our initial yields were modest (44%). Compound **64** was functionalized at the C3 position under conditions developed by Sunjic<sup>2</sup> using LDA at -78°C in THF followed by alkylation with benzyl bromide to give racemic 3-benzyl-1-hydro-1,4-benzodiazepine, *rac*-**71** in 25% yield (Scheme 3-2).



Scheme 3-2. C3 benzylation of *des*-methyl diazepam

Early attempts at synthesizing enantiomerically enriched benzodiazepines under similar conditions<sup>1</sup> by reacting enantiomerically pure (*S*)-phenyl alanine hydrochloride (*S*)-**72** with 2-amino-5-chlorobenzophenone by refluxing in pyridine led to a disappointing 10% yield (Scheme 3-1). Furthermore the 3-benzyl-7-chloro-1,3-dihydro-5-phenyl-1,4-benzodiazepin-2-one product (*S*)-**71** evidenced partial racemization (Scheme 3-3).



Scheme 3-3. Partial racemization in synthesis of (*S*)-**71**

<sup>a</sup>Hart, B. R.; Rush, D. J.; Shea, K. J. *J. Am. Chem. Soc.* **2000**, *122*, 460-465

As stated in Chapter 2 of this thesis, a chiral center at the C3 carbon in 1,4-benzodiazepin-2-ones causes an equilibrium shift towards the conformer having the larger substituent in the equatorial position in the benzodiazepine ring.<sup>3-6</sup> Thus, the 3-substituted 1-hydro-benzodiazepine (*S*)-**71** appears as one conformer by NMR because of the equatorial preference of the larger benzyl substituent. The (*S*)-chirality of the amino acids incorporated into these ring systems induces the (*M*)-axial chirality in the benzodiazepine ring.

### 3.3. Synthesis of enantiopure 1,4-benzodiazepin-2-ones via DCC coupling

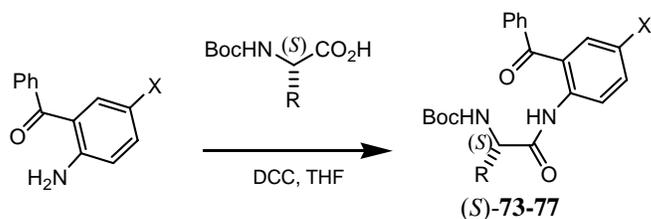
In light of initial attempts to synthesize enantiopure 1,4-benzodiazepin-2-ones which resulted in low yield (Scheme 3-3), alternative methods were sought which would increase reaction yield and avoid racemization at the C3 carbon. Shea and co-workers used a modified procedure of Sunjic,<sup>7</sup> to develop a protocol which incorporated DCC

coupling in their synthesis of enantiomerically pure benzodiazepines. They used these compounds for their studies on molecularly imprinted polymers (MIPs) used to separate enantiomers.<sup>8</sup> A variety of enantiomerically pure amino acid starting materials were used to expand the diversity of the benzodiazepine scaffolds used in this research. As will be described below, DCC was employed in coupling these amino acids.

It is worth noting that Ellman and co-workers synthesized libraries of structurally diverse 1,4-benzodiazepine derivatives using combinatorial synthesis.<sup>9-11</sup> They reported that standard coupling procedures, such as the use of carbodiimides, were not successful in their solid phase synthesis reactions. As a result  $\alpha$ -*N*-Fmoc amino acid fluorides developed by Carpino<sup>12</sup> were employed to obtain amide products en route to 1,4-benzodiazepines.

### **3.3.1 Synthesis of amide products from enantiomerically pure *N*-protected amino acids**

The modifications done on the protocol of Shea and co-workers<sup>8</sup> to obtain the amide precursor and the 1,4-benzodiazepine product are described below. Purification procedures for the removal of DCU in the coupling step of the reaction were optimized by the author. Reaction conditions for the cyclization of the amide were optimized by Dr. Polo Lam (Carrier research group, Virginia Tech, 2003). The first step of this synthesis is shown in Scheme 3-4, in which 2-amino-5-chlorobenzophenone is coupled to enantiomerically pure *N*-Boc-amino acid using DCC to form the corresponding amides (*S*)-**73-77**.



product	amino acid	R-	X-	% yield	% ee <sup>b</sup>
(S)-73	phenylalanine	-CH <sub>2</sub> Ph	-Cl	73	>99.5
(S)-74	2-aminobutyric acid	-CH <sub>2</sub> CH <sub>3</sub>	-Cl	77	>99.5
(S)-75	methionine	-CH <sub>2</sub> CH <sub>2</sub> SCH <sub>3</sub>	-Cl	74 <sup>a</sup>	nd
(S)-76	leucine	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-Cl	80	>99.5
(S)-77	alanine	-CH <sub>3</sub>	-H	70	nd <sup>c</sup>

<sup>a</sup>Including DCU contaminant

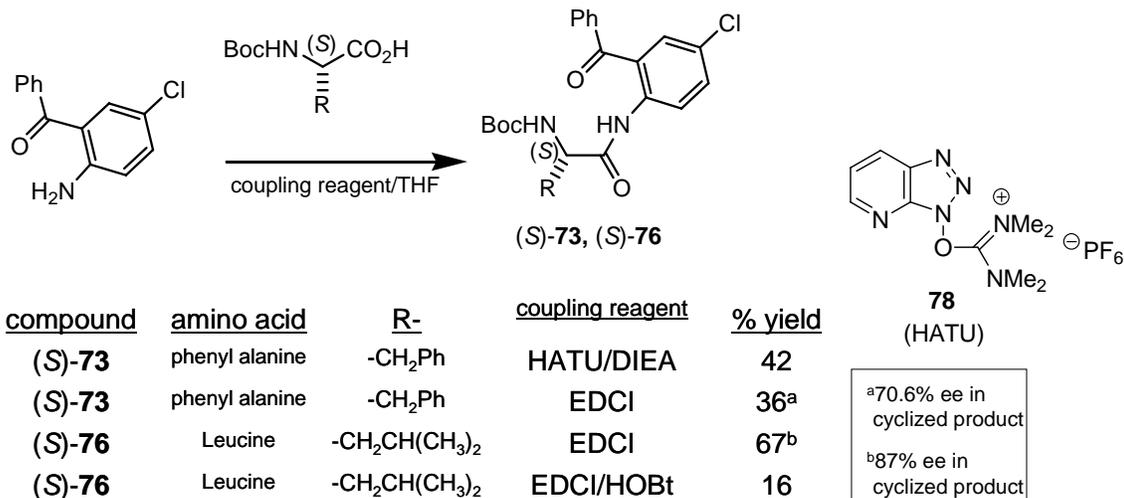
<sup>b</sup>Determined by chiral stationary phase HPLC

<sup>c</sup>Racemate not available

Scheme 3-4. Synthesis of amides using DCC

As shown in Scheme 3-4 coupling of the enantiomerically pure amino acid to the benzophenone occurs in a respectable 70-80% yield and excellent enantiomeric excess (>99.5% ee, HPLC). The enantiomeric excess for the methionine derived amide (S)-75 was not determined due to trace amounts of dicyclohexylurea (DCU) impurity in the sample. However upon cyclization of (S)-75 the impurity could be removed by column chromatography. Enantiomeric excess of the *des*-chloro alanine derived amide 77 (Scheme 3-4) was not determined at this stage. The enantiomeric excess for these compounds were determined by chiral stationary phase HPLC.

One problem encountered in this DCC coupling reaction was the removal of the dicyclohexylurea (DCU) by-product. According to the literature procedure of Shea and co-workers<sup>8</sup> the impurity is filtered off after the reaction is complete. While most of the DCU formed in the coupling reaction could be filtered off, approximately 20% still remained by <sup>1</sup>H NMR analysis. In an attempt to bypass this problem other coupling agents were employed in reacting the enantiomerically pure amino acids with the 2-amino-benzophenone to form the amides (S)-73 and (S)-76 (Scheme 3-5).



Scheme 3-5. Synthesis of amides using other coupling reagents

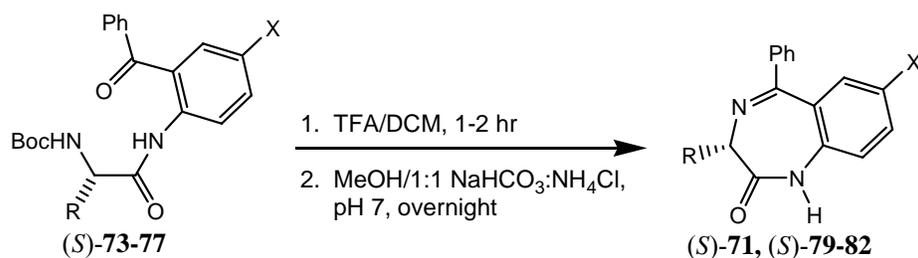
From Scheme 3-5 it is seen that when HATU<sup>13</sup> **78** is used in conjunction with diisopropyl ethylamine (DIEA),<sup>14</sup> the yield for amide (S)-73 is only 42%. Use of EDCI gave only 36% yield for (S)-73 and 70.6% ee in the cyclized product. In the coupling reaction with leucine using EDCI a 67% yield of amide (S)-76 was obtained however it was found that enantiomeric excess was lowered to 87% in the cyclized product. Addition of 1-hydroxybenzotriazole (HOBt) to the leucine coupling reaction using EDCI lowered the yield of the amide product (S)-76 to 16%. In conclusion, DCC works best for reacting the enantiopure amino acid starting material with the benzophenone. The amide products (S)-73-77 are obtained in high yields and without racemization with this coupling reagent (Scheme 3-4).

Eventually we were able to purify the amide product from the DCU impurity by two chromatographies. The first chromatography consists of 100% dichloromethane (DCM) to separate excess 2-amino-5-chlorobenzophenone starting material from the

amide products (*S*)-**73-77** and the DCU impurity. In the second chromatography a 1:20 mixture of Et<sub>2</sub>O:DCM is used to separate the amide product ( $R_f = 0.322$ ) from the DCU impurity ( $R_f = 0.203$ ). Ninhydrin is used to track the DCU impurity in the second chromatography. Using DCC coupling with these purification conditions enabled us to obtain the amide (*S*)-**73-77** products from enantiomerically pure amino acids in high yield without racemization (Scheme 3-4).

### **3.3.2. De-blocking and cyclization of amides to enantiomerically pure 1,4-benzodiazepin-2-ones**

In the optimized cyclization conditions developed by Dr. Polo Lam of the Carlier research group (Virginia Tech, 2003) de-blocking of the carbamate occurs with trifluoroacetic acid (TFA) in dichloromethane (DCM) to give the free amine. This is followed by cyclization under conditions of a 1:1 mixture of NaHCO<sub>3</sub>:NH<sub>4</sub>Cl at pH 7 in methanol (Scheme 3-6). Under these conditions higher yields with less racemization is obtained than when the reaction is done using Shea's protocol of de-blocking with HCl (g) followed by cyclization in methanol/water at pH 8.5.<sup>8</sup>



<u>compound</u>	<u>R-</u>	<u>X-</u>	<u>starting material</u>	<u>% yield</u>	<u>%ee<sup>a</sup></u>
(S)-71	-CH <sub>2</sub> Ph	-Cl	(S)-73	100	>99.5
(S)-79	-CH <sub>2</sub> CH <sub>3</sub>	-Cl	(S)-74	89	>99.5
(S)-80	-CH <sub>2</sub> CH <sub>2</sub> SCH <sub>3</sub>	-Cl	(S)-75	82	>99.5
(S)-81	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-Cl	(S)-76	100	>99.5
(S)-82	-CH <sub>3</sub>	-H	(S)-77	92	nd <sup>b</sup>

<sup>a</sup>Determined by chiral stationary phase HPLC

<sup>b</sup>Racemate not available

Scheme 3-6. Cyclization of amides to enantiopure 1,4-benzodiazepin-2-ones (Procedure developed by Dr. Polo Lam for alanine analog, Carrier reserach group, Virginia Tech 2003)

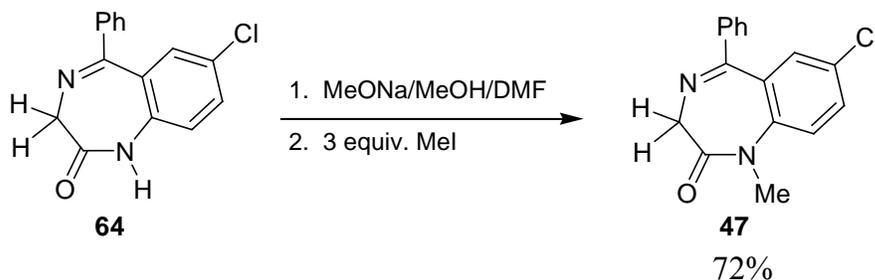
From Scheme 3-6 it is shown that cyclization of the amides (S)-73-77 to the 3-substituted, 1-hydro 1,4-benzodiazepin-2-ones (S)-71 and (S)-79-82 can be achieved in high yield (82-100%). In addition the enantiopurity of the amino acid starting materials is retained (>99.5% ee) in both the reaction coupling to the benzophenone (Scheme 3-4) as well as the cyclization to the benzodiazepine scaffolds (S)-71 and (S)-79-82 (Scheme 3-6). This same procedure is used in the cyclization of the *des*-chloro amide derived from Boc-L-alanine (S)-77 to give the *des*-chloro 1-hydro-3-methyl-1,4-benzodiazepin-2-one (S)-82 in 92% yield (Scheme 3-6). As will be seen below the *N*-DAM alkylated analog of (S)-82 was synthesized in >99.5% ee, confirming no racemization had occurred during coupling or cyclization

### 3.4. Installation of *N*-methyl group on the benzodiazepine scaffold

For enantioselective reactions to occur on the benzodiazepine scaffold the inversion barrier of the benzodiazepine ring must be increased. This is done by increasing the size of the N1 substituent on the benzodiazepine ring. As seen in Chapter 2, when the size of the N1 substituent is increased from a proton to a methyl group in diazepam the inversion barrier of the ring is increased from 12.3 kcal/mol<sup>15</sup> to 18.0 kcal/mol.<sup>16</sup> Enantioselective reactions done on *N*-methylated benzodiazepines derived from enantiopure amino acids will be discussed in chapter 4 of this thesis.

#### 3.4.1. Method 1. Synthesis of diazepam

In our early studies on glycine derived benzodiazepines **64**, methylation at the N1 position was achieved by deprotonation with sodium methoxide in methanol/dimethyl formamide solution, followed by alkylation with methyl iodide (Scheme 3-7).<sup>1</sup>

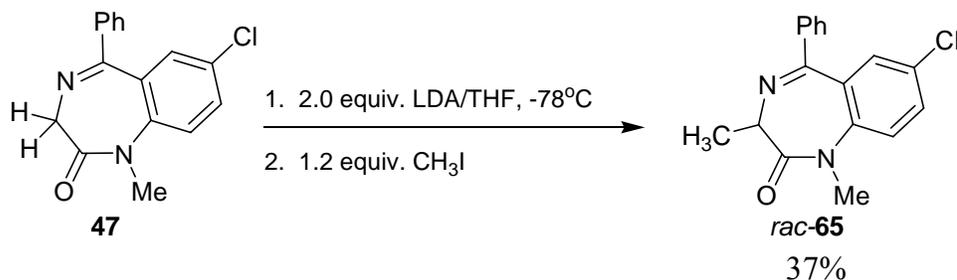


Scheme 3-7. *N*-methylation of *des*-methyl diazepam

Methylation at the N1 position of *des*-methyl diazepam **64** occurred in a respectable 72% yield to give diazepam **47**.

### 3.4.1.1. C3 methylation on diazepam

Following the protocol of Wolfe and co-workers,<sup>17</sup> compound **47** underwent methylation at the C3 carbon by deprotonation with LDA in THF at -78°C followed by addition of methyl iodide to provide racemic 3-methyl-*N*-methyl benzodiazepine *rac*-**65** in 37% yield (Scheme 3-8).

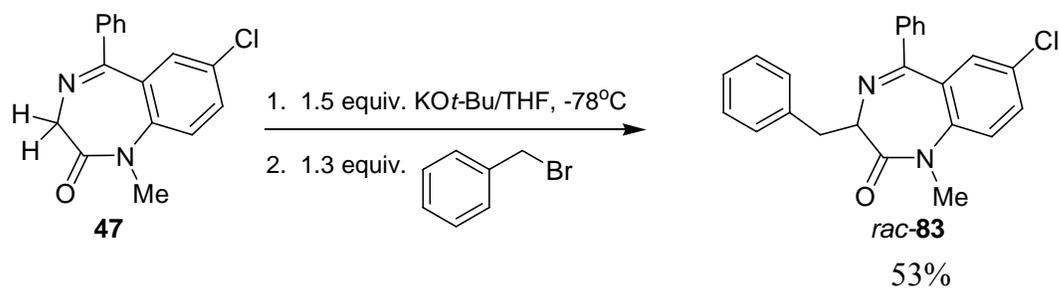


Scheme 3-8. Methylation of diazepam

Although compound *rac*-**65** is racemic, it is a useful standard for optimizing chiral stationary phase HPLC conditions.

### 3.4.1.2. C3 benzylation on diazepam

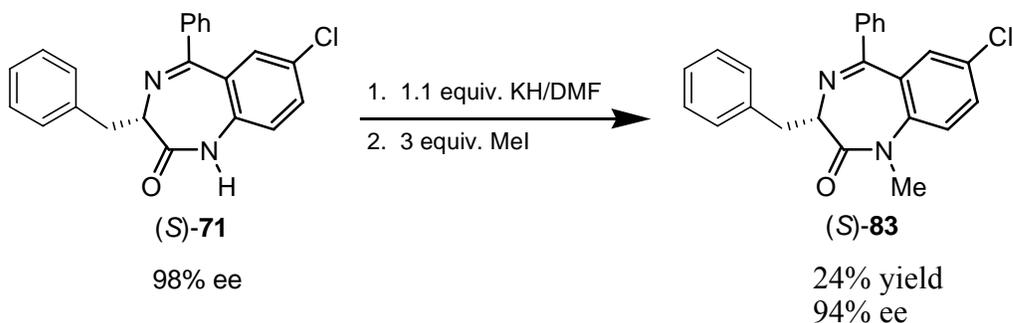
Using a method developed by Ellman and co-workers,<sup>18</sup> benzylation at the C3 position of diazepam **47** was achieved by deprotonation with KO*t*-Bu in THF at -78°C, followed by treatment with benzyl bromide to give racemic 3-benzyl-*N*-methyl benzodiazepine *rac*-**83** in 53% yield<sup>18</sup> (Scheme 3-9). Just as in the previous example, *rac*-**83** can be used for optimizing HPLC conditions.



Scheme 3-9. Benzoylation of diazepam

### 3.4.2. Method 2. *N*-methylation of (*S*)-Phe derived benzodiazepine

Initial attempts at *N*-methylation of enantiomerically enriched Phe-derived benzodiazepine (*S*)-**71** by treatment with potassium hydroxide in dimethylformamide (DMF) followed by addition of methyl iodide, the desired product (*S*)-**83** was obtained in only 24% yield with 94% ee (Scheme 3-10).



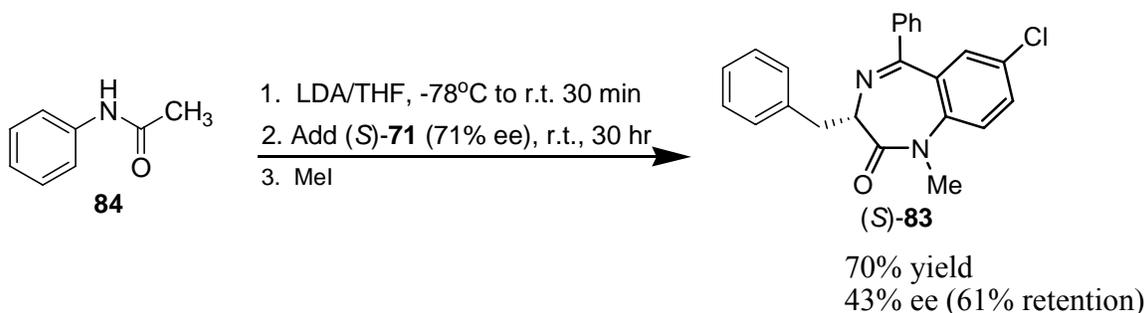
Scheme 3-10. *N*-methylation (*S*)-3-benzyl benzodiazepine

### 3.4.3. Method 3. *N*-methylation of enantiomerically enriched benzodiazepines using acetanilide

In their synthesis of 1,4-benzodiazepin-2,5-diones, Ellman and co-workers employ the lithium salt of acetanilide as a base in their *N*-alkylation procedure of their compounds.<sup>19</sup> In this way they were able to obtain *N*-alkylated 1,4-benzodiazepin-2,5-diones in high yield and without loss of optical purity in their compounds derived from

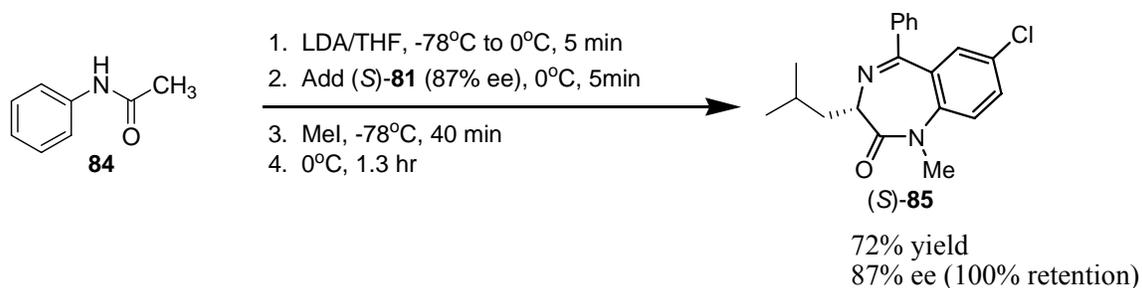
enantiopure amino esters. Ellman and co-workers chose to use acetanilide **84** in their studies because it has a  $pK_a$  of 21.5 in DMSO.<sup>20</sup> Since the  $pK_a$ 's of the  $C_\alpha$  proton acidities of amides, esters, and carbamates are greater than 24 in DMSO, deprotonation and alkylation of these functional groups does not occur, and racemization is thus avoided.

Following the protocol of Ellman,<sup>19</sup> acetanilide **84** was treated with LDA at  $-78^\circ\text{C}$  and allowed to warm to room temperature over 30 min. The benzodiazepine (*S*)-**71** was then added and allowed to react for 30 hr at room temperature, followed by addition of methyl iodide. The reaction yield of product (*S*)-**83** increased to 70%, however the enantiomeric excess decreased to 43% ee, most likely due to the prolonged deprotonation time and high temperature (Scheme 3-11).



Scheme 3-11. *N*-methylation (*S*)-3-benzyl benzodiazepine using acetanilide

*N*-methylation of the leucine derived benzodiazepine (*S*)-**81** (Scheme 3-12) with acetanilide **84** under reduced deprotonation time (15 min) and a total methylation time of 2 hr at temperatures ranging from  $-78^\circ\text{C}$  to  $0^\circ\text{C}$  gave comparable yields (72%) without racemization of product (*S*)-**85** (100% retention), as shown in Scheme 3-12.

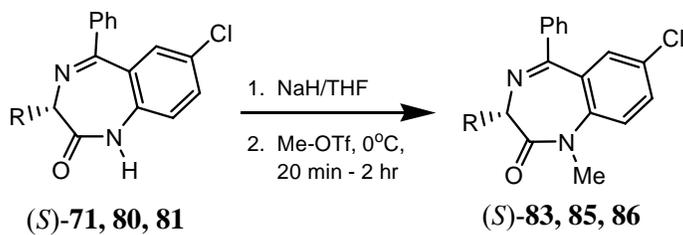


Scheme 3-12. *N*-methylation (*S*)-3-isobutyl benzodiazepine using acetanilide

#### 3.4.4. Method 4. *N*-methylation of enantiomerically enriched benzodiazepines using methyl triflate

For *N*-methylation on benzodiazepines derived from other enantiomerically pure amino acids (*S*)-71, (*S*)-80, and (*S*)-81 (Scheme 3-13) we utilized the methyl trifluoromethanesulfonate (methyl triflate)<sup>21</sup> reagent. Installation of the methyl group at the N1 position of the benzodiazepine ring occurs by deprotonation with sodium hydride followed by addition of methyl triflate to produce the *N*-methylated benzodiazepines (*S*)-83, (*S*)-85, and (*S*)-86. *N*-methylation with methyl triflate occurs in good yield (87-95%) for the phenyl alanine (*S*)-71 and leucine (*S*)-81 derived benzodiazepines and in excellent % ee (>99%) for all benzodiazepines (*S*)-83, (*S*)-85, and (*S*)-86 synthesized (Scheme 3-13). The increase in yield of *N*-methylated product in this method over the previous methods is attributed to the triflate being a good leaving group for this reaction. The low yields obtained with the methionine derived benzodiazepine (*S*)-86 are puzzling. Methyl triflate shows high reactivity towards the phenylalanine (*S*)-71 and leucine (*S*)-81 derived enolates, producing high yields in reaction times as short as 20 minutes. However, in the methionine derived benzodiazepine, starting material is still present by TLC after 2 hours. Therefore it is proposed that the sulfur atom on compound (*S*)-80 coordinates with the N-H proton in such a way as to hinder deprotonation of this analog,

or interferes with the alkylation of the amide nitrogen. Another possible explanation for the low yield of the methionine analog is that methylation could be occurring at the sulfur atom. This methylated sulfur product could revert back to starting material during chromatography.



<u>product</u>	<u>R-</u>	<u>starting material</u>	<u>% yield</u>	<u>%ee<sup>a</sup></u>
(S)-83	-CH <sub>2</sub> Ph	(S)-71	95	>99.5
(S)-85	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	(S)-81	87	99
(S)-86	-CH <sub>2</sub> CH <sub>2</sub> SCH <sub>3</sub>	(S)-80	30	99

<sup>a</sup>determined by chiral stationary phase HPLC

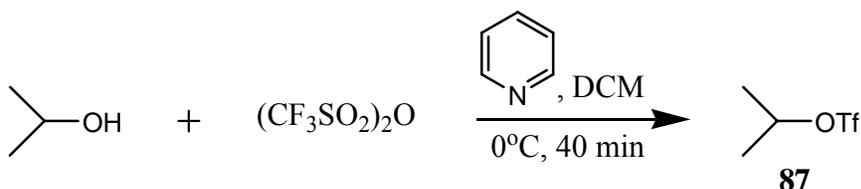
Scheme 3-13. *N*-methylation of enantiopure 1,4-benzodiazepin-2-ones using methyl triflate

As stated above when the size of the N1 substituent is increased from a hydrogen to the size of a methyl group, the inversion barrier of the derived benzodiazepine is increased from 12.3 kcal/mol<sup>15</sup> to 18.0 kcal/mol.<sup>16</sup> We expected that a similar trend would be observed in benzodiazepine enolates. A high inversion barrier of the enolate would be required to achieve enantioselective alkylation. Thus we sought to install larger N1 substituents.

### 3.5. Installation of *N*-isopropyl group on the benzodiazepine scaffold

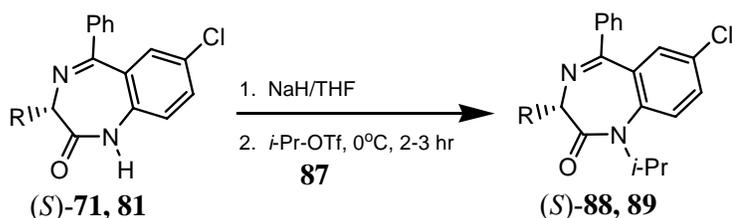
Because triflate was a good leaving group for *N*-methylation of these compounds we used it for *N*-isopropylation. Isopropyl triflate **87** (Scheme 3-14) is synthesized using

a modified procedure of Beard and co-workers<sup>21</sup> in which a mixture of isopropyl alcohol and pyridine in dichloromethane is added dropwise to trifluoromethanesulfonic anhydride in dichloromethane.



Scheme 3-14. Synthesis of isopropyl triflate

*N*-isopropyl benzodiazepines (*S*)-**88** and (*S*)-**89** (Scheme 3-15) were synthesized by deprotonation of the *N*-H benzodiazepines (*S*)-**71** and (*S*)-**81** with sodium hydride and alkylation with isopropyl triflate **87**.<sup>21</sup> Isopropylation at the N1 position of the benzodiazepine ring occurs in good yield (73-74%) and without racemization at the C3 position (>99.5% ee).



<u>product</u>	<u>R-</u>	<u>starting material</u>	<u>% yield</u>	<u>% ee<sup>a</sup></u>
( <i>S</i> )- <b>88</b>	-CH <sub>2</sub> Ph	( <i>S</i> )- <b>71</b>	74	>99.5
( <i>S</i> )- <b>89</b>	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	( <i>S</i> )- <b>81</b>	73	>99.5

<sup>a</sup>determined by chiral stationary phase HPLC

Scheme 3-15. *N*-isopropylation of enantiopure 1,4-benzodiazepin-2-ones

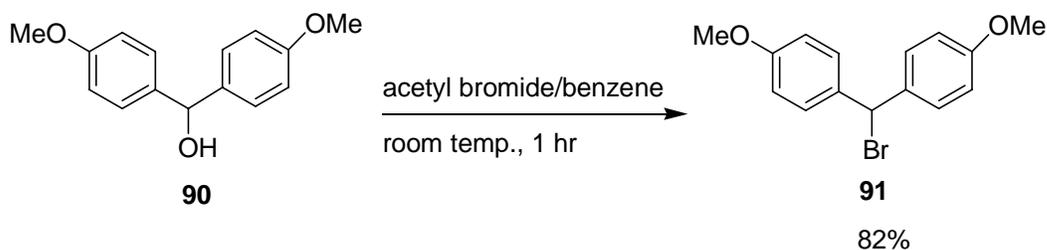
When hexamethylphosphoramide (HMPA) was used in the *N*-isopropylation reaction of phenylalanine-derived benzodiazepine, yields were typically lower (42%) than when the

reaction was done in the absence of HMPA. In addition to recovered *N*-H benzodiazepine starting material, *O*-alkylated product, as much as 10%, could be detected in the reactions done with HMPA. As stated in Chapter 2 placing an isopropyl group at the N1 position in the benzodiazepine ring causes an inversion barrier of 21 kcal/mol in glycine derived benzodiazepines.<sup>16</sup>

### 3.6. Installation of *N*-DAM group on the benzodiazepine scaffold

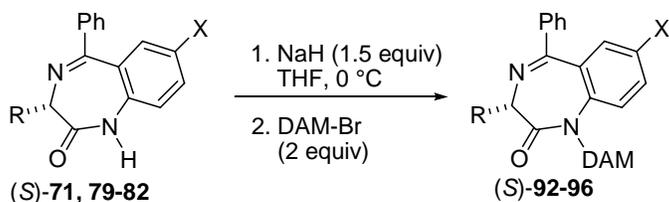
The di-(*p*-anisyl)methyl (DAM) group is a well known protecting group for  $\beta$ -lactam amides.<sup>22,23</sup> In addition the DAM group has been used in protection of uridines, acyclic amides, and anilines.<sup>24,25</sup> Removal of the DAM group can occur by oxidation,<sup>22,26</sup> reduction,<sup>27</sup> or hydrolysis.<sup>23</sup> The DAM group was employed in our studies to allow for wider diversity at the N1 position of the benzodiazepine scaffold. Two methods were used to synthesize the DAM-Br starting material. Our initial attempts to synthesize DAM-Br using a procedure based on that of Sekine and co-workers<sup>28</sup> in which 4,4'-dimethoxybenzhydrol and acetyl bromide were refluxed in benzene resulted in impure product which led to moderate reaction yields (39-62%) in the subsequent *N*-DAM installation reactions of the enantiopure 1,4-benzodiazepin-2-ones.

Modifications of the procedure of Sekine and co-workers<sup>28</sup> in which DAM-Br **91** (Scheme 3-16) was synthesized at room temperature, followed by recrystallization from hexane led to purer product **91** in 82% yield. This procedure was developed by Dr. Hongwu Zhao of the Carlier research group (Virginia Tech 2003) in his attempts to install the DAM group on alanine derived benzodiazepine and later applied to other examples.



Scheme 3-16. Synthesis of DAM-Br  
 (Developed by Dr. Hongwu Zhao, Carlier research group, Virginia Tech, 2003)

*N*-DAM installation of the benzodiazepines (*S*)-**71**, and (*S*)-**79-82** was achieved by deprotonation with sodium hydride in THF at 0°C, followed by addition of DAM-Br (Scheme 3-17). Good product yields for (*S*)-**92-94**, and (*S*)-**96** (56 – 96%) and high % ee (94 - >99.5% ee) were obtained for these reactions. The *N*-DAM installation yield on the methionine derived benzodiazepine scaffold (*S*)-**80** was lower than the other benzodiazepine derivatives (Scheme 3-17), just as with the *N*-methylation yields (Scheme 3-13) on this scaffold. Once again this could be due to interference of the sulfur atom on the substituted C3 position of the benzodiazepine ring making this substrate less reactive towards alkylation at the N1 position by hindering the deprotonation step. Evidence of this hypothesis was suggested by the presence of starting material by TLC, which was recovered at the end of the reaction.



<u>product</u>	<u>R-</u>	<u>X-</u>	<u>starting material</u>	<u>% yield</u>	<u>%ee<sup>a</sup></u>
(S)-92	-CH <sub>2</sub> Ph	-Cl	(S)-71	83	>99.5
(S)-93	-CH <sub>2</sub> CH <sub>3</sub>	-Cl	(S)-79	96	94
(S)-94	-CH <sub>2</sub> CH <sub>2</sub> SCH <sub>3</sub>	-Cl	(S)-80	56	98
(S)-95	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-Cl	(S)-81	75	>99.5
(S)-96	-CH <sub>3</sub>	-H	(S)-82	71	>99.5

<sup>a</sup>determined by chiral stationary phase HPLC

Scheme 3-17. *N*-DAM installation of enantiopure 1,4-benzodiazepin-2-ones

While *N*-DAM installation on the 1,4-benzodiazepin-2-ones with DAM-Br synthesized at room temperature (Scheme 3-20) gave much improved yields, purification of the *N*-DAM product from the excess DAM-Br in the reaction proved to be problematic since DAM-Br degrades on silica gel. Attempts to purify DAM-Br itself via column chromatography showed that this compound was unstable to these purification conditions. The majority of the DAM-Br degraded to DAM-ether **97**, a clear colorless oil, ( $R_f = 0.718$ , 1 Et<sub>2</sub>O:20 DCM) (HRMS) FAB mass spectrometry: 469 m/z), while a small portion degraded into DAM-ketone **98** ( $R_f = 0.487$ , 1 Et<sub>2</sub>O:20 DCM) by NMR and mass spectrometry ( $[M+H]^+$ : 243 m/z) (Figure 3-1). Interestingly, Marchand-Brynaert and co-workers have also isolated DAM-ether in their *N*-DAM installation attempts of their amide compounds using DAM-OH.<sup>24</sup>

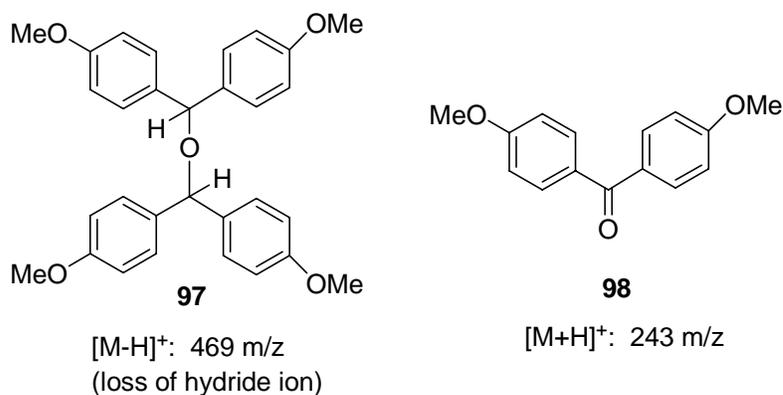
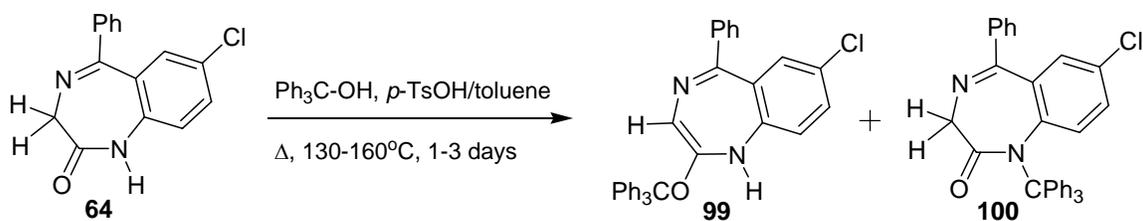


Figure 3-1. Reactivity of DAM-Br

As a result at least two chromatographies were employed to purify the *N*-DAM benzodiazepine. In the first chromatography (Et<sub>2</sub>O:DCM, 1:20) the *N*-DAM benzodiazepine product was separated from the unreacted *N*-H benzodiazepine starting material. The DAM-Br degraded in this first chromatography and co-eluted with the product. In the second chromatography a solution of EtOAc:Hex (1:4) was used to separate the degraded DAM-Br from the *N*-DAM benzodiazepine product. The *N*-DAM methionine derived benzodiazepine required three chromatographies of Et<sub>2</sub>O:DCM (1:20) to separate the DAM-impurity from the product.

### 3.7. Installation of *N*-trityl group on the benzodiazepine scaffold

Attempts to introduce the trityl group into the benzodiazepine ring **64** using a procedure of Reddy and co-workers<sup>29</sup> gave *O*-alkylated or a mixture of *O*-alkylated **99** and *N*-alkylated **100** products in low yield (Scheme 3-18).



entry	temp.(°C)	time(d)	%yield
1	130	3	3% mixture <i>N</i> - and <i>O</i> -alkylated
2	150	1	3% mixture <i>N</i> - and <i>O</i> -alkylated
3	160	2	25% <i>O</i> -alkylated

Scheme 3-18. Attempts at *N*-tritylation on 1,4-benzodiazepin-2-one

$^1\text{H}$  NMR (Figure 3-2) shows a mixture of *O*- **99** to *N*-tritylated **100** benzodiazepine in a ratio of 4:1. The broad peak at 8.72 ppm is indicative of the N-H proton in *O*-tritylated **99**. The singlet at 4.89 ppm accounts for the C3 methine proton in compound **99**. These chemical shifts correspond to the chemical shifts in the  $^1\text{H}$  NMR spectra of the pure *O*-tritylated product **99** (Figure 3-3). The peaks at 3.91 ppm and 4.74 ppm are indicative of the axial and equatorial methylene protons in compound **100** split into doublets (recall the axial and equatorial protons in the  $^1\text{H}$  NMR of diazepam Figure 2-10b). Mass spectroscopy of the *N*- and *O*-tritylated mixture as well as the pure *O*-tritylated product correspond with these structures giving a molecular ion peak of  $([\text{M}+\text{H}]^+)$ :  $m/z$  513.18) in both cases. Another possible structure that has been considered for compound **100** is the *O*-tritylated imidate ester, **alt-100** (Figure 3-4), a tautomer of compound **99**. The structure of **alt-100** could also account for the chemical shifts of the methylene protons in the  $^1\text{H}$  NMR (Figure 3-2) and would show an identical molecular ion peak in mass spectroscopy.

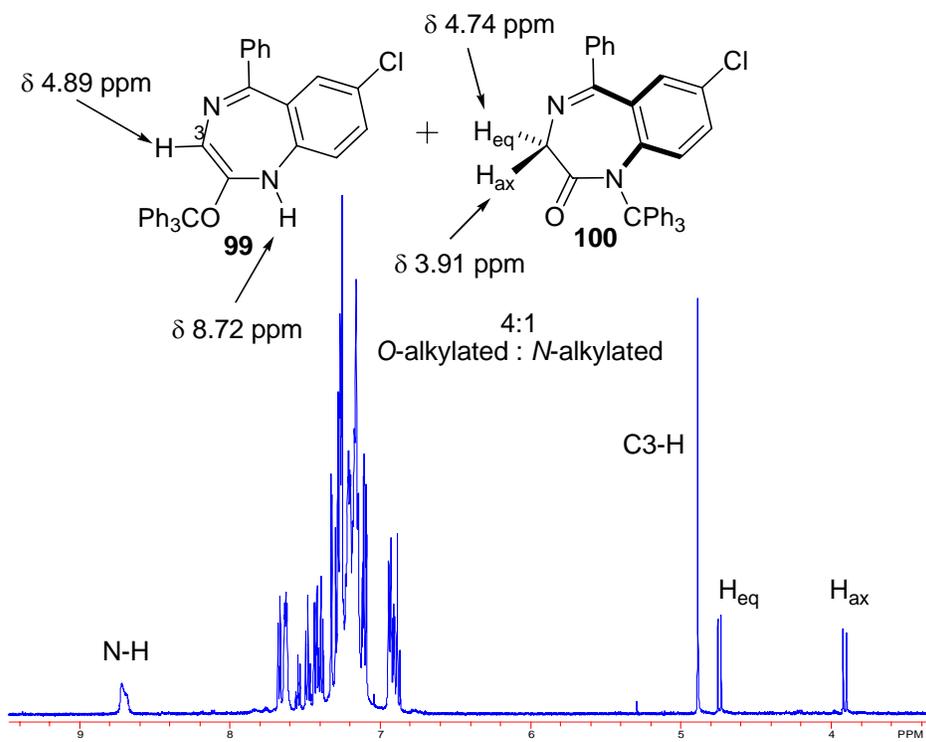


Figure 3-2.  $^1\text{H}$  NMR: O- and N-tritylated 1,4-benzodiazepin-2-ones **99** and **100**

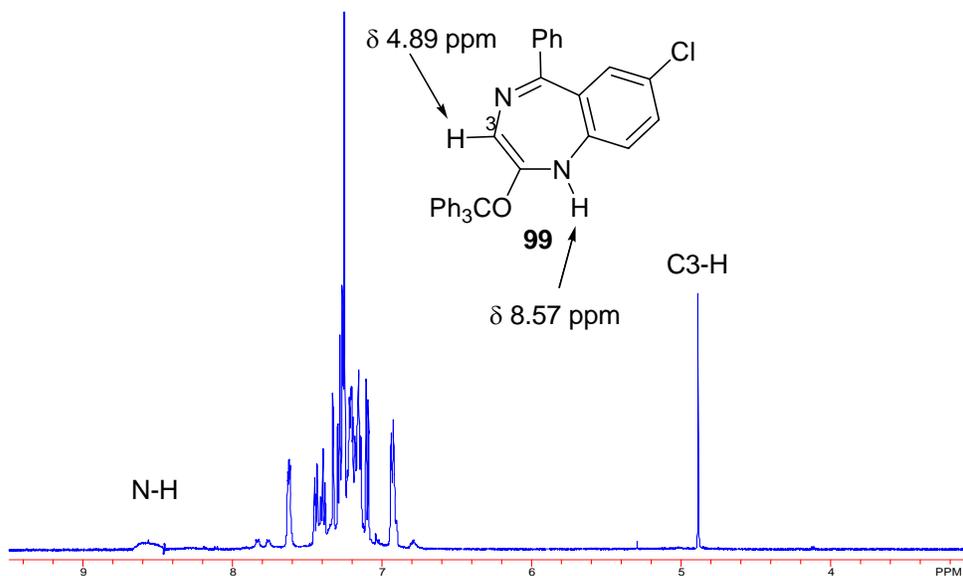


Figure 3-3.  $^1\text{H}$  NMR: O-tritylated 1,4-benzodiazepin-2-one **99**

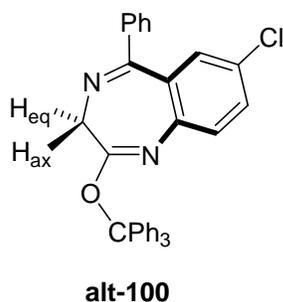


Figure 3-4. O-tritylated imidate ester **alt-100**

The chromatogram (Figure 3-5) of the tritylated benzodiazepine shows a racemic mixture comprising four peaks. The two larger peaks at 20 and 30 min correspond to the (*M*)- and (*P*)-conformers of the *O*-alkylated product **99** while the two smaller peaks at 25 and 34 min correspond to the (*M*)- and (*P*)-conformers of the *N*-alkylated product **100** (or **alt-100**). The integration ratios from the chromatogram (Figure 3-4) match the integration ratios of the NMR of the *O*- and *N*-tritylated mixture, 4:1 (Figure 3-2).

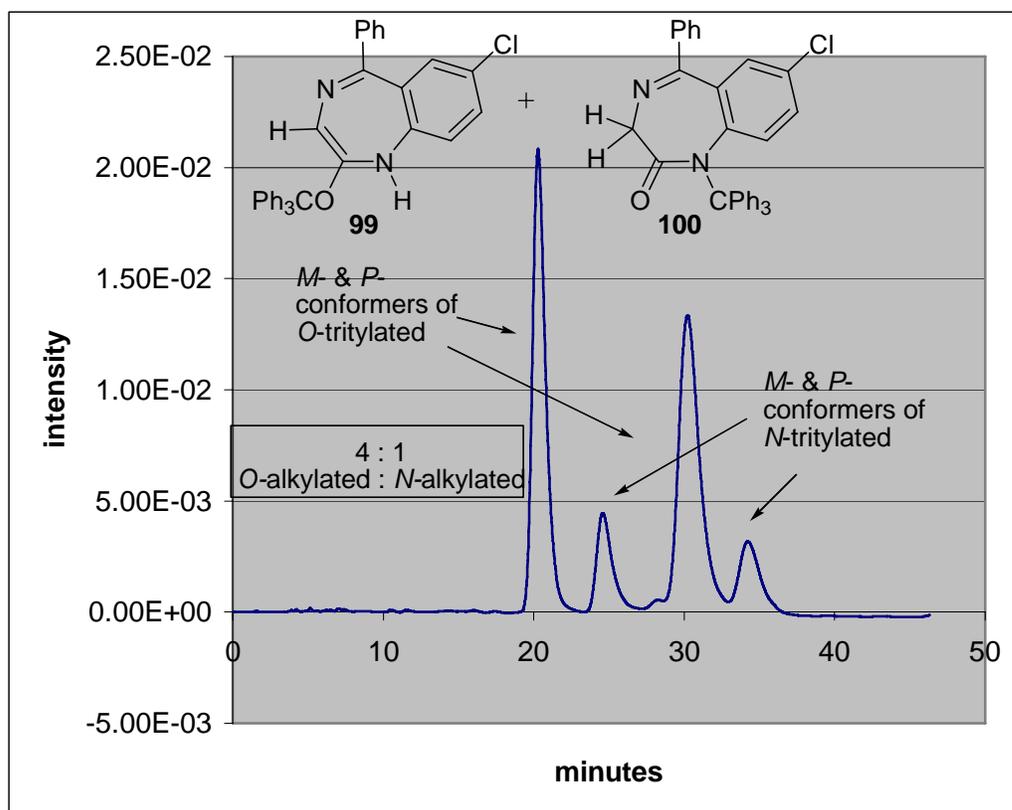


Figure 3-5. Chromatogram: *O*- and *N*-tritylated 1,4-benzodiazepin-2-ones **99** and **100**

### 3.8. Conclusion

In conclusion, the benzodiazepine scaffolds used in this research can be synthesized in good yield and without racemization. Coupling of the enantiopure *N*-Boc protected amino acids to the 2-amino benzophenone worked best with DCC. The resulting amide was then deblocked with TFA in DCM. Cyclization occurred by treatment with  $\text{NaHCO}_3:\text{NH}_4\text{Cl}$  (1:1) in methanol at pH 7.

*N*-methylation of the benzodiazepine scaffolds worked best by treatment with sodium hydride in THF and methyl triflate. *N*-methylation occurred in high yield for Phe and Leu-derived benzodiazepines and in excellent % ee for all benzodiazepines synthesized. *N*-isopropylation also occurred in good yield and without racemization by

treatment with sodium hydride in THF and isopropyl triflate. Finally, *N*-DAM installation on the benzodiazepine scaffold occurred in good yield and high % ee. Treatment of 4,4'-dimethoxybenzhydrol with acetyl bromide in benzene at room temperature followed by recrystallization from hexane gave purer DAM-Br, which was used in this reaction. The enantioselective reactions done on these benzodiazepine scaffolds are discussed in Chapter 4.

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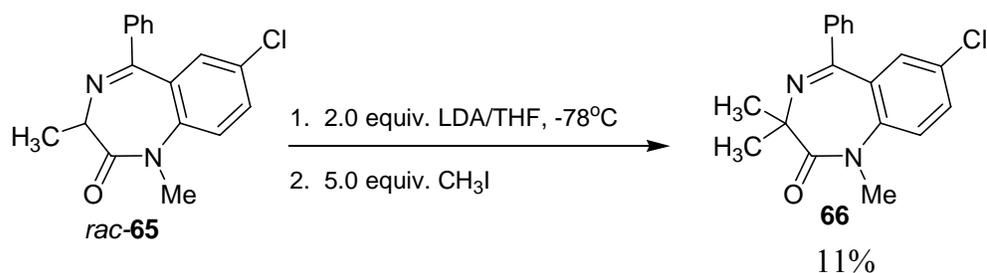
## Chapter 4. MOC studies on 1,4-benzodiazepin-2-ones

### 4.1. Introduction

This chapter discusses the enantioselective reactions performed on the 1,4-benzodiazepin-2-one scaffolds using the MOC protocol. Enantioselective H-D exchanges on the *N*-methyl benzodiazepine substrates will be examined, along with enantioselective alkylations performed in the *N*-isopropyl and *N*-DAM analogs. De-blocking of the DAM group occurred in high yield and high enantiomeric excess to allow for further diversity at the N1 position of these compounds.

### 4.2. Synthesis of 3,3-disubstituted “quaternary” benzodiazepines

In our initial studies to synthesize 3,3-disubstituted “quaternary” benzodiazepines, racemic C3-monosubstituted benzodiazepine *rac*-**65** was used in determining optimum deprotonation alkylation conditions. Using a procedure based on Wolfe and co-workers<sup>1</sup> we were able to synthesize the 3,3-dimethyl derivative of diazepam **66** in 11% yield (Scheme 4-1).



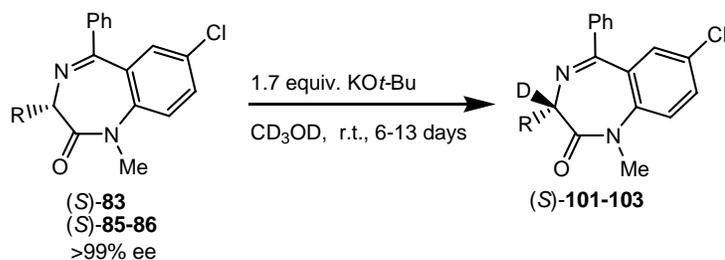
Scheme 4-1. C3 methylation of 3-methyl diazepam

Although Wolfe and co-workers were unable to synthesize compound **66**, they were able to synthesize the di-butyl analogue in 10% yield.<sup>1</sup> Despite the low yield and the fact that methylation of 3-methyl diazepam destroys the stereogenic center of the starting material,

this result suggested the possibility of synthesizing enantiomerically enriched 3,3-disubstituted benzodiazepines containing a “quaternary” stereogenic center.

### 4.3. Enantioselective deuterations on *N*-methyl 1,4-benzodiazepin-2-ones

Because enantioselective alkylations on these scaffolds looked unusually challenging, we thought we would start with H-D exchange on enantiomerically enriched benzodiazepines (*S*)-**83**, (*S*)-**85**, and (*S*)-**86** (Scheme 4-2). Although such a reaction would not create a quaternary stereogenic center if successful, it would demonstrate the intermediacy of a non-racemic, conformationally chiral enolate. As it happens, this line of research was successful,<sup>2</sup> although it did not appear in our first publication in this area.<sup>3</sup>



<u>product</u>	<u>R-</u>	<u>starting material</u>	<u>%yield</u>	<u>%deuteration<sup>a</sup></u>	<u>%ee<sup>b</sup></u>	
( <i>S</i> )-(+)- <b>101</b>	-CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	( <i>S</i> )-(+)- <b>83</b>	99	100	97	<sup>a</sup> Determined by NMR <sup>b</sup> Determined by chiral stationary phase HPLC
( <i>S</i> )-(+)- <b>102</b>	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	( <i>S</i> )-(+)- <b>85</b>	75	99	94	
( <i>S</i> )-(-)- <b>103</b>	-CH <sub>2</sub> CH <sub>2</sub> SCH <sub>3</sub>	( <i>S</i> )-(-)- <b>86</b>	88	94	99	

Scheme 4-2. Enantioselective H-D exchange on *N*-methyl 1,4-benzodiazepin-2-ones. Retention is demonstrated by HPLC and polarimetry

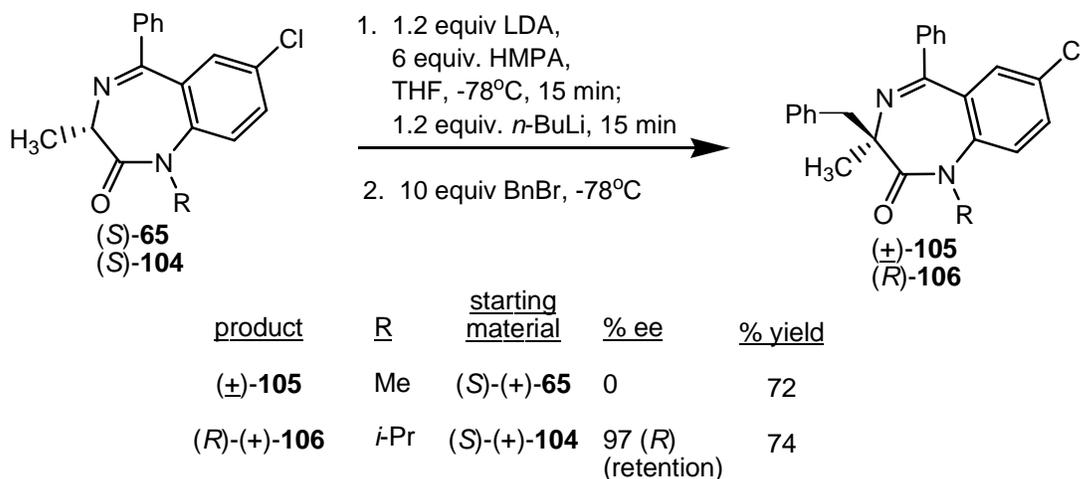
From Scheme 4-2 it is shown that enantioselective deuteration can occur in good yield (75-99%), high % deuteration (94-100%), and with little racemization (94-99% ee) to give deuterated benzodiazepines (*S*)-**101-103**. Retentive deuteration was established based

on chiral stationary phase HPLC and polarimetry measurements of the deuterio products in comparison to the protio starting material. Even though enantioselective deuteration reactions are done at higher temperatures than enantioselective alkylations (usually done at -78°C to -42°C) and undergo longer reaction times (enantioselective alkylation reactions usually run 1-2 hours) both high yields and enantiomeric excess are obtained. This excellent outcome is realized because upon deprotonation with potassium *tert*-butoxide, the enolate formed is immediately trapped by the deuterated methanol solvent. The deuterated compounds (*S*)-**101-103**, like their protio starting material (*S*)-**83**, (*S*)-**85**, and (*S*)-**86** exist as one conformer. From Chapter 2 we know that the large steric demands of the C3 substituent in relation to the deuterium atom cause the substituent to adopt the equatorial position in the benzodiazepine ring. The (*S*)-chiral center at the C3 carbon induces the (*M*)-conformational chirality in the ring. Being able to acquire deuterated products (*S*)-**101-103** enantioselectively, along with the synthesis of the 3,3-dimethyl diazepam derivative **66** (Scheme 4-1), provided a good basis that enantioselective alkylations could be performed on the benzodiazepine scaffolds without the use of chiral auxiliaries, to produce enantiomerically enriched 1,4-benzodiazepine-2-ones with “quaternary” stereogenic centers.

#### **4.4. Attempts at enantioselective alkylation on *N*-methyl 1,4-benzodiazepin-2-ones**

Following our successful enantioselective H-D exchange of (*S*)-**101-103**, Dr. Hongwu Zhao of the Carlier research group (Virginia Tech, 2003) attempted enantioselective alkylations on the *N*-methyl Ala-derived benzodiazepine (*S*)-**65**. The

3,3-disubstituted “quaternaly” benzodiazepine **105** was obtained in good yield (72%), however the product was racemic (Scheme 4-3).<sup>3</sup>



Scheme 4-3. Benzoylation of *N*-substituted (*S*)-3-methyl-1,4-benzodiazepin-2-one (Hongwu Zhao, Carlier research group, Virginia Tech, 2003)

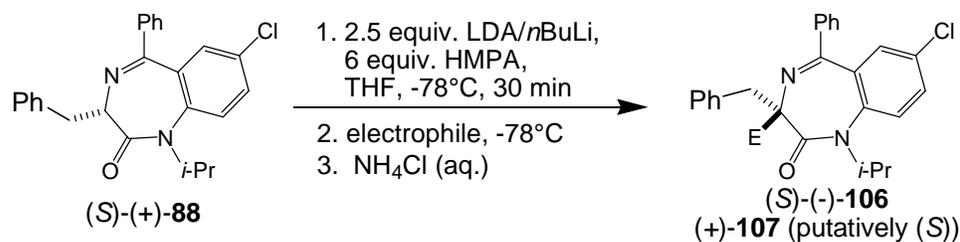
As seen in Scheme 4-3 in changing the N1 substituent from a methyl group to an isopropyl group as in (*S*)-**104**, benzoylated product (*S*)-**106** was produced in similar yield, 74% but in 97% ee. We propose the reason for this dichotomy in results relates to the size of the N1 substituent. When the N1 substituent is methyl, the inversion barrier of the enolate formed upon deprotonation is small, resulting in fast racemization (recall the 18 kcal/mol inversion barrier for diazepam).<sup>4</sup> However when the N1 substituent is increased to the size of an isopropyl group, thereby increasing the inversion barrier<sup>4-6</sup> of the enolate, benzoylation occurs in high enantiomeric excess (recall the >21.3 kcal/mol inversion barrier for *N*-isopropyl diazepam)<sup>4</sup>. We propose this process is an example of memory of chirality (MOC),<sup>7</sup> because the original stereogenic center is trigonalized during the reaction, and the product is obtained in high enantiomeric excess without the use of external chiral sources. Furthermore, we propose the deprotonation of the (*S*)-chiral

center at the C3 carbon of the benzodiazepine ring leads to the formation of the conformationally chiral (*M*)-enolate intermediate, which reacts with the benzyl bromide with high stereospecificity (Scheme 1-3).

If LDA was used as the only base, and *n*-butyl lithium was omitted, yields of the benzylated *N*-isopropyl Ala-derived benzodiazepine product, (*R*)-**106**, were low and starting material was recovered. It was suspected that enolate-diisopropylamine complexes were being formed, which re-protonated the enolate via an internal return mechanism. Such complexes have been reported in the work of Seebach.<sup>8</sup> His solution was to add *n*-butyl lithium to deprotonate the diisopropyl amine. This technique was applied to the deprotonation protocol of our research and increased reaction yields.

#### **4.5. Enantioselective alkylations on *N*-isopropyl 3-benzyl benzodiazepine**

In light of Dr. Zhao's results with the *N*-isopropyl Ala-derived benzodiazepine (*S*)-**104** (Scheme 4-3), the author attempted enantioselective alkylations on *N*-isopropyl benzodiazepines derived from other amino acid starting materials. Enantioselective alkylations on the *N*-isopropyl Phe-derived benzodiazepine (*S*)-**88**, done under similar conditions to those of the Ala-derived benzodiazepine, occur in good yield and high enantiomeric excess to produce compounds (*S*)-**106** and (+)-**107** (Scheme 4-4).<sup>3</sup> Methylation of this compound occurs in 64% yield and 95% ee while allylation using allyl bromide gave 57% yield and 86% ee.



<u>product</u>	<u>electrophile</u>	<u>% yield</u>	<u>%ee</u>
( <i>S</i> )-(-)- <b>106</b>	MeI	64	95
(+)- <b>107</b> putatively ( <i>S</i> )	allyl-Br	57	86

Scheme 4-4. Enantioselective alkylations on *N*-isopropyl (*S*)-3-benzyl-1,4-benzodiazepin-2-one

Alkylation of the *N*-isopropyl Phe-derived benzodiazepine (*S*)-**88** occurs with retention of stereochemistry to give methylated product (*S*)-**106**. Evidence of this is provided by the following: Dr. Hongwu Zhao showed that retentive substitution of the (*S*)-alanine derived benzodiazepine gave (+)-**106**. Compound (+)-**106** was subsequently hydrolyzed to (*R*)-(-)- $\alpha$ -methyl-Phe-OH. By this observation we can conclude that (-)-**106** is (*S*)-configured. From this result we propose that allylation of benzodiazepine (*S*)-**88** also occurs with retention to give (*S*)-(+)-**107** (Scheme 4-4).

In addition to alkylations on the *N*-isopropyl Phe-derived benzodiazepine, alkylations were attempted on the Leu-analog. Alkylation yields on the *N*-isopropyl Leu-derived benzodiazepine were between 24-28% for methylation, allylation, and benzylation. Enantiomeric excess of these products was not determined because of the low chemical yields. Enantiomeric excess of recovered leucine starting material was >99.5% ee, indicating possible deprotonation difficulty due to the sterically hindered isobutyl substituent. Because these difficulties encountered with the *N*-isopropyl benzodiazepine analogs, and because another versatile N1 group emerged (see below),

we did not further explore reactions of the N1-isopropyl benzodiazepines derived from other amino acids.

#### **4.6. Enantioselective alkylations on *N*-DAM 1,4-benzodiazepin-2-ones**

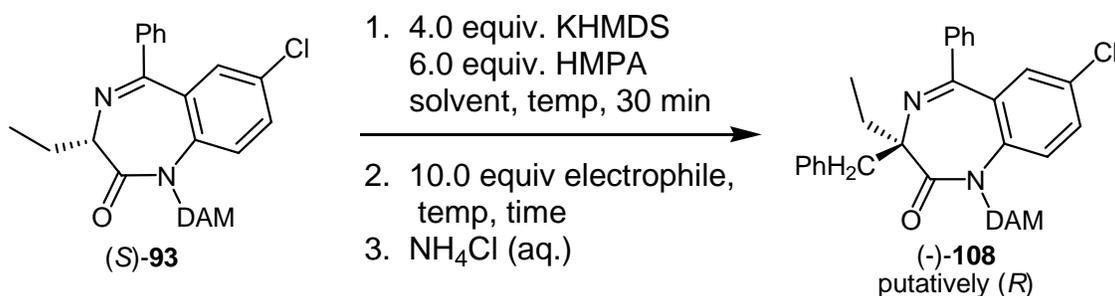
As mentioned earlier in Chapter 3, the dianisyl methyl (DAM) group was introduced into the 1,4-benzodiazepin-2-one scaffold to allow for more variability at the N1 substituent in the benzodiazepine ring. As will be shown below de-blocking of the *N*-DAM group occurs in both excellent yield and enantiomeric excess to allow for further substitution at the N1 position.

##### **4.6.1. Enantioselective alkylations on *N*-DAM amino butyric acid (Abu) derived benzodiazepine**

Initial trials in benzylating the *N*-DAM Abu-derived benzodiazepine (*S*)- **93** at -78°C (dry ice/acetone bath) using KHMDS as base led to enantiomerically enriched 3,3-disubstituted “quaternary” benzodiazepine (-)-**108** in a moderate 39% yield, but >99.5% ee (Scheme 4-5, entry 1). Cyanated product (+)-**109** occurred in only 28% yield, although without racemization (Scheme 4-6, entry 1). Note that the use of LDA as base was replaced with KHMDS when it was discovered by Dr. Hongwu Zhao of the Carlier research group (Virginia Tech, 2003) that the *N*-DAM group was unstable to LDA. In an attempt to increase the yield of the reaction, reaction temperatures were increased to -42°C (acetonitrile/dry ice). The results of these experiments are summarized below (Scheme 4-5 to Scheme 4-7).

#### 4.6.1.1. Enantioselective benzylation on *N*-DAM Abu-derived benzodiazepine

Deprotonation of *N*-DAM Abu-derived benzodiazepine (*S*)-**93** occurs using KHMDS as base in the presence of HMPA at -78°C. Upon benzylation with benzyl bromide, product (-)-**108** is obtained in only 39% yield, although without racemization (Scheme 4-5, entry 1). Increasing the reaction temperature to -42°C in DME increased the yield of compound (-)-**108** to 65% while maintaining high enantiomeric excess (Scheme 4-5, entry 3). Using the more reactive electrophile, benzyl iodide, did not significantly improve the yield of the reaction at -42°C and gave 94% ee (Scheme 4-5, entry 2). Based on the precedent described above, we propose that alkylation at the C3 carbon occurs with retention of configuration. The changes in absolute configuration from the starting material (*S*)-**93** to the product, putatively (*R*)-(-)-**108** is due to the replacement of the C3 proton with the higher priority benzyl group in this ring system, a so-called “priority switch.” Racemate **108** was synthesized at elevated temperature (0°C) as a standard for chiral stationary phase HPLC. As shown in Scheme 4-5 (entry 4) racemized product **108** is obtained in 85% yield under these conditions after a 7 min reaction time.



<u>entry</u>	<u>temp./solvent</u>	<u>electrophile</u>	<u>time (hours)</u>	<u>% yield</u>	<u>%ee</u>
1	-78°C/THF,	BnBr	6.0	39	>99.5
2	-42°C/THF	BnI	1.3	67	94
3	-42°C/DME	BnBr	1.2	65	94
4	0°C/THF	BnI	7 min	85	racemic <sup>a</sup>

<sup>a</sup>deprotonation time 10 min

Scheme 4-5. Enantioselective benzylation on *N*-DAM (*S*)-3-ethyl-1,4-benzodiazepin-2-one

It is important to note that all the quaternary *N*-isopropyl 1,4-benzodiazepin-2-ones (Scheme 4-4) and the quaternary *N*-DAM 1,4-benzodiazepin-2-ones (with the exception of the C3 cyanated compounds) discussed in this thesis show a mixture of (*M*)- and (*P*)-conformers in their <sup>1</sup>H and <sup>13</sup>C NMR spectra. The ratios of these conformers are consistent with the local steric demands of the C3 substituents.<sup>3</sup> A table of conformer ratios is provided at the end of this chapter (Figure 4-8). As seen in Figure 4-1 for the NMR of benzylated *N*-DAM Abu-derived benzodiazepine, putatively (*R*)-(-)-**108**, there is a 70:30 equatorial to axial preference for the benzyl substituent at the C3 position of the benzodiazepine ring represented by compounds (*P*)-(*R*)-**108** and (*M*)-(*R*)-**108** respectively (Figure 4-1). From Chapter 2 it is known for 1,4-benzodiazepin-2-ones possessing a chiral center at the C3 carbon, equilibrium favors the conformer having the larger substituent in the equatorial position of the benzodiazepine ring.<sup>5,6,9,10</sup> In the *N*-DAM Abu-derived benzodiazepine starting material (*S*)-**93**, the steric demands of the C3

ethyl group compared to the C3 proton are such that the larger ethyl group stays in the equatorial position of the benzodiazepine ring, resulting in one conformer. When the C3 proton is replaced with a benzyl group as in the product, putatively (*R*)-(-)-**108** in Scheme 4-5, the local steric demands at the C3 position are more similar. However, the slightly larger size of the benzyl group causes it to favor the equatorial position of the benzodiazepine ring making (*P*)-(*R*)-**108** the major conformer (Figure 4-1).

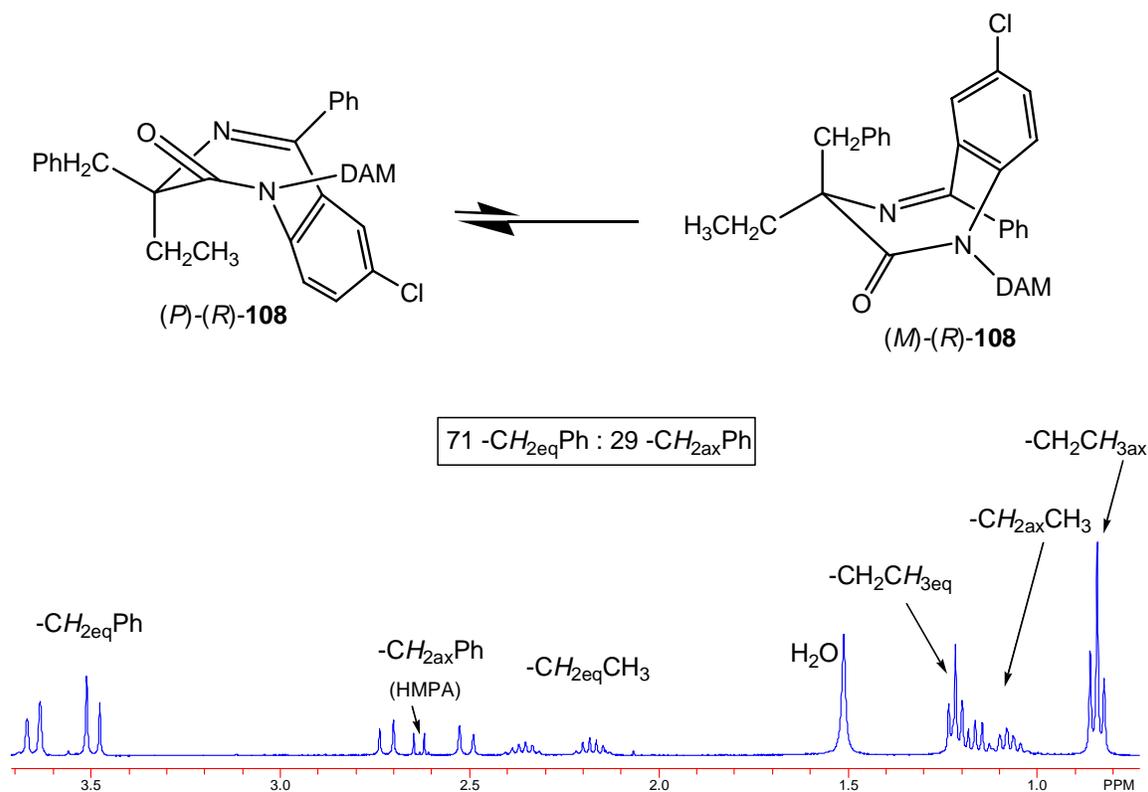
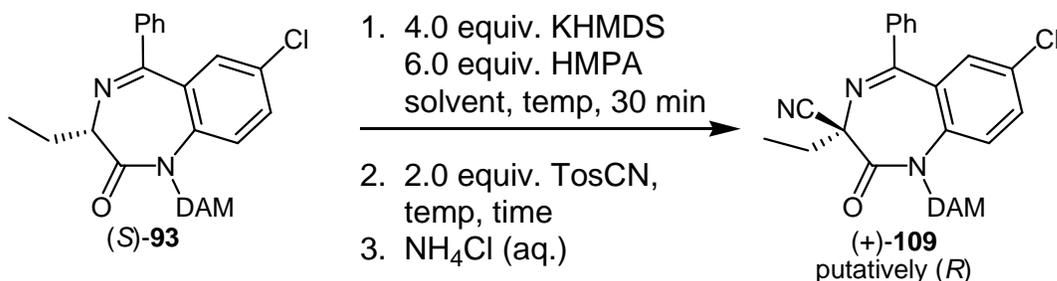


Figure 4-1. NMR: (*R*)-3-benzyl-7-chloro-1-dianisylmethyl-3-ethyl-5-phenyl-1,4-benzodiazepin-2-one

#### 4.6.1.2. Enantioselective cyanation on *N*-DAM amino butyric acid derived benzodiazepine

Cyanation on the *N*-DAM Abu-derived benzodiazepine (*S*)-**93** also occurs with little racemization at  $-78^{\circ}\text{C}$  to produce compound (+)-**109** (Scheme 4-6, entry 1). Just as

in the case of benzylation of compound (*S*)-**93** (Scheme 4-5), increasing the reaction temperature to  $-42^{\circ}\text{C}$  also increases the yield of cyanated product (+)-**109** without causing significant racemization (Scheme 4-6, entries 1-2). Decrease in reaction time is also observed at these elevated temperatures, as expected.



<u>entry</u>	<u>temp./solvent</u>	<u>time</u>	<u>% yield</u>	<u>%ee</u>
1	$-78^{\circ}\text{C}/\text{THF}$	2.5 h	28	$>99.5$
2	$-42^{\circ}\text{C}/\text{DME}$	33 min	86	96

Scheme 4-6. Enantioselective cyanation on *N*-DAM (*S*)-3-ethyl-1,4-benzodiazepin-2-one

Figure 4-2 shows the  $^1\text{H}$  NMR of the cyanated product (+)-**109**. Unlike other the other “quaternary” benzodiazepines discussed in this thesis the “quaternary” cyanated product of the *N*-DAM amino butyric acid derived benzodiazepine and all “quaternary” cyanated benzodiazepines in this research exist as one conformer in their NMR spectra.

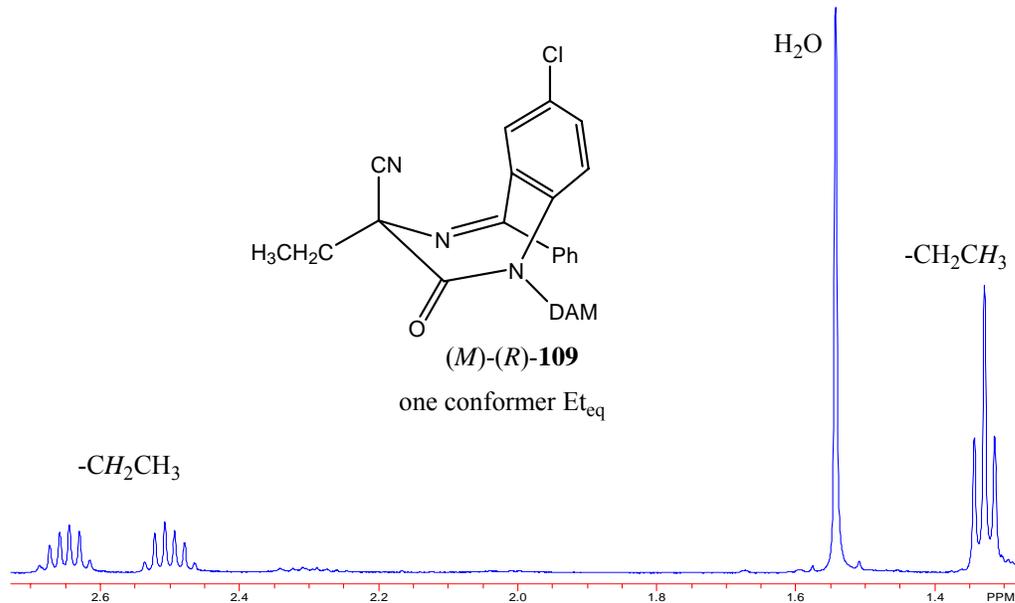


Figure 4-2.  $^1\text{H}$  NMR: (*R*)-7-chloro-3-cyano-1-dianisylmethyl-3-ethyl-5-phenyl-1,4-benzodiazepin-2-one

We propose that due to the larger steric demands of the ethyl group at C3 in comparison to the cyano group causes it to occupy only the equatorial position. The distinguishable methylene protons are split into a multiplet at 2.51 and 2.64 ppm while there is only one signal for the  $-\text{CH}_3$  protons on the ethyl group at 1.34 ppm which is split into a triplet by the methylene protons ( $t$ ,  $^3J_{\text{HH}} = 7.5 \text{ Hz}$ , 3H).

To explain the contrasting conformer distributions of (*-*)-**108** and (*+*)-**109**, A-values for the conformational energies,  $-\Delta G$ , of cyano<sup>11</sup> substituted and ethyl<sup>12</sup> substituted cyclohexane were compared. From Figure 4-3 it is shown that the A-value for the ethyl group on the cyclohexane ring is 1.8 kcal/mol, nearly ten times that of the cyano group, 0.2 kcal/mol. This explains the strong equatorial preference of the ethyl group over the cyano group in the cyclohexane ring. This effect is also used to explain the strong equatorial preference of the ethyl group over the cyano in the seven membered benzodiazepine ring.

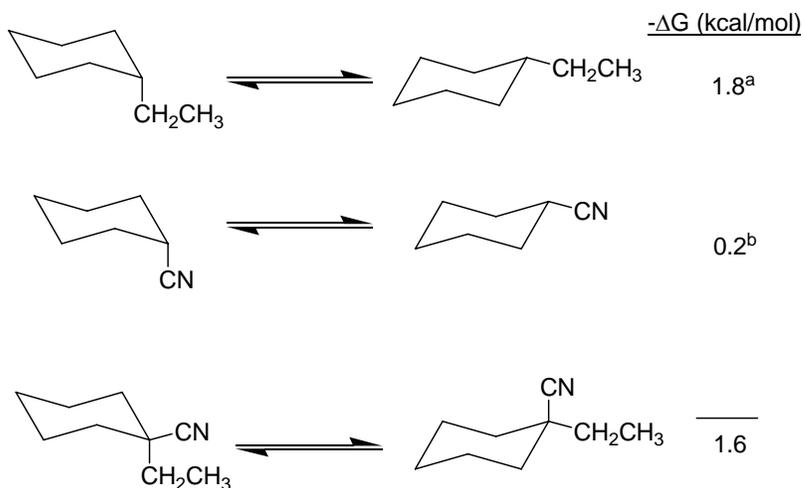


Figure 4-3. A-values for the equatorial preference of cyano substituted and ethyl substituted cyclohexane  
<sup>a</sup>ElieI, E.L.; Wilen, S. H. *Stereochemistry of Organic Compounds*, John Wiley & Sons Inc.: New York, 1994, p. 697

<sup>b</sup>Schneider, H.-J.; Hoppen, V. *J. Org. Chem.* **1978**, 43, (20), 3866-3873

In addition to steric effects the possibility of the anomeric effect was considered in the axial preference of the cyano group. Booth and co-workers<sup>13</sup> note that upon placement of a cyano group at the 2 position of the piperidine ring the axial cyano conformer was strongly preferred with equilibrium constants ranging from  $K = 17.5$  (at 190K) to 0.86 (at 227K) (Figure 4-4).<sup>13</sup> This enhancement is due to interaction of the lone pair electrons on the cyclic nitrogen with the C-CN  $\sigma^*$  orbital; this interaction can occur in the CN-axial conformation, but not in the CN-equatorial conformation.

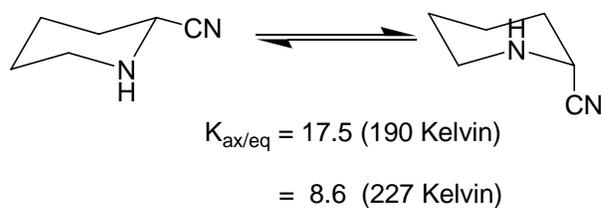


Figure 4-4. Conformational equilibrium of 2-cyanopiperidine  
 Booth H.; Dixon, J. M.; Khedair, K. A.. *Tetrahedron* **1992**, *48*, (29), 6161-6174

The possibility of an anomeric effect was examined on the cyanated *N*-DAM Abu-derived benzodiazepine (+)-**109** (Figure 4-5). The imine lone pair and the electronegative cyano group at carbon 3 could provide the  $n \rightarrow \sigma^*$  orbital interaction needed as in Figure 4-4. However, since this interaction effectively forms a cumulene functionality by resonance the importance of the anomeric effect in (+)-**109** may be less than that in 2-cyano piperidine.

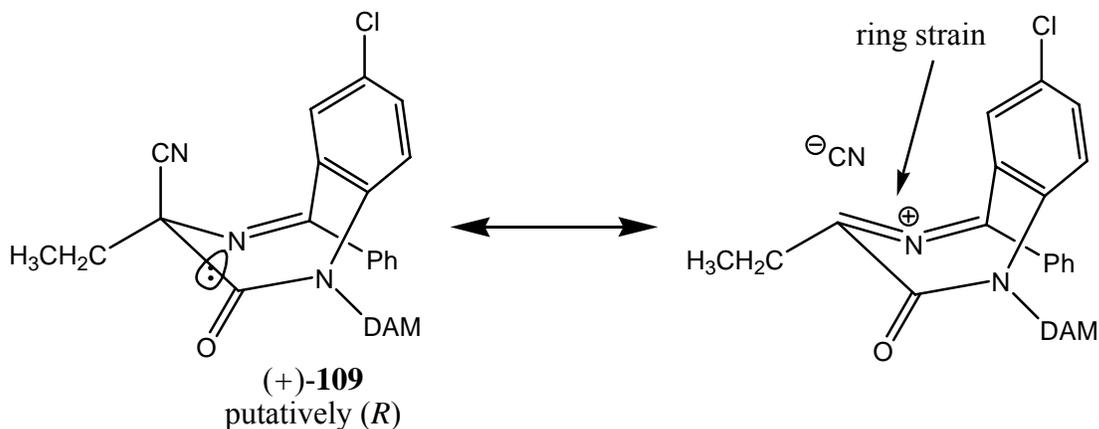
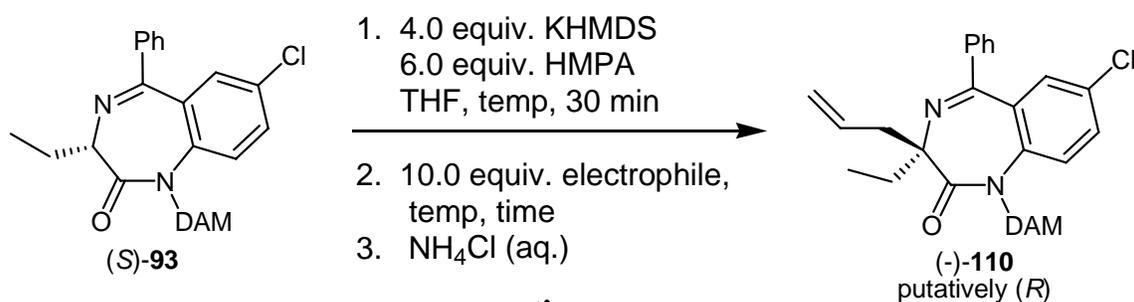


Figure 4-5. Examining the Anomeric Effect on **109**

### 4.6.1.3. Enantioselective allylation on *N*-DAM amino butyric acid derived benzodiazepine

Allylations on the *N*-DAM Abu-derived benzodiazepine (*S*)-**93** (Scheme 4-7) further emphasize the importance of reaction temperature on this substrate. As seen in Scheme 4-7 (entries 1-2) the type of solvent has little effect on the yield of product (-)-**110** or enantiomeric excess when reactions are done at -42°C with KHMDS and HMPA using allyl iodide as the electrophile. Allylation yields of 54% and 58% can be obtained with allyl iodide in THF or DME respectively in 94% ee in both cases (entries 1 & 2). Allyl iodide seems to react better with this substrate resulting in slightly higher yields and enantioselectivities than allyl bromide when the reaction is done under identical solvent conditions at -42°C (Scheme 4-7, entries 2 & 3). Racemic **110** is also obtained in good yield for by deprotonation at 0°C and an 18 min reaction time (Scheme 4-7, entry 4).



<u>entry</u>	<u>temp./solvent</u>	<u>electrophile</u>	<u>time</u> <u>(hours)</u>	<u>% yield</u>	<u>% ee</u>
1	-42°C/THF	allyl-I	2.0	54	94
2	-42°C/DME	allyl-I	2.2	58	94
3	-42°C/DME	allyl-Br	1.2	50	85
4	0°C/THF	allyl-I	18 min	68	racemic <sup>a</sup>

<sup>a</sup>deprotonation  
time 10 min

Scheme 4-7. Enantioselective allylation on *N*-DAM (*S*)-3-ethyl-1,4-benzodiazepin-2-one

The lower enantiomeric excess obtained in entry 3 of Scheme 4-7 could be due to a leaving group effect. Allyl iodide having a softer leaving group would favor C-alkylation in the enolate.<sup>14</sup> Allyl bromide would be more inclined towards *O*-alkylation than allyl iodide. If upon work-up the *O*-allylated product **alt-110** were converted to *C*-allylated product **110** through a -sigmatropic rearrangement (Figure 4-6), this could account for the lower enantiomeric excess in entry 3 (Scheme 4-7).

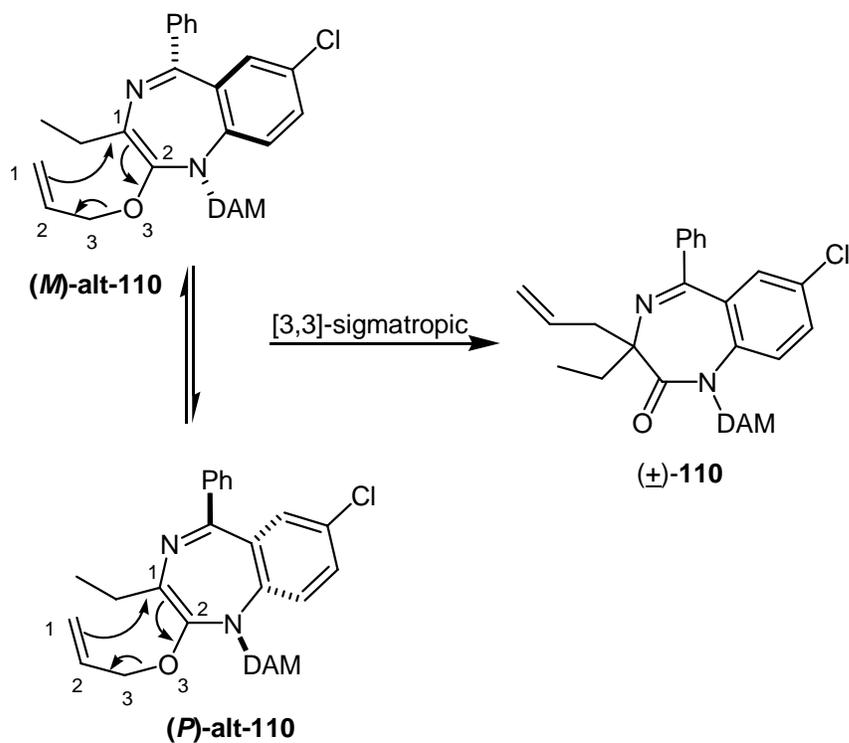
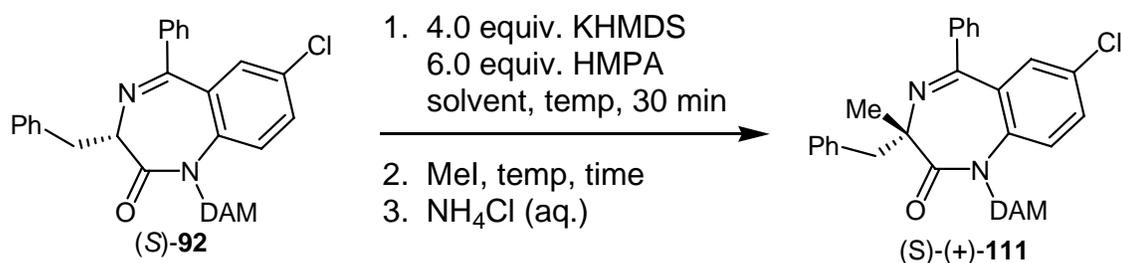


Figure 4-6. Claisen rearrangement of *O*-allylated **alt-110** to *C*-allylated **110**

## 4.6.2. Enantioselective alkylations on *N*-DAM phenylalanine derived benzodiazepine

### 4.6.2.1. Enantioselective methylation on *N*-DAM phenylalanine derived benzodiazepine

Methylation of the *N*-DAM Phe-derived benzodiazepine (*S*)-**92** occurs in moderate yield without racemization at -42°C using THF or diethyl ether as solvent (Scheme 4-8, entries 1 & 2). Methylated product can be obtained in 51% yield in THF and 43% in diethyl ether to afford product (*S*)-**111** with >99.5% ee in both cases. Absolute configuration is known with certainty based on Dr. Zhao's correlation of the benzylated *N*-DAM Ala-derived benzodiazepine product. When this same reaction is done using DME (dimethoxyethane) as the solvent, the yield is increased to 79% without racemization (Scheme 4-8, entry 3). From these results it is seen that the type of solvent is very important in increasing reaction yields. As in the case of the *N*-DAM Abu-derived benzodiazepine (*S*)-**93**, racemic **111** is obtained when (*S*)-**92** is subject to deprotonation at 0°C (Scheme 4-8, entry 4).



<b>entry</b>	<b>temp./solvent</b>	<b>time (hours)</b>	<b>% yield</b>	<b>%ee</b>
1	-42°C/THF	1.9	51	>99.5
2	-42°C/Et <sub>2</sub> O	2.1	43	>99.5
3	-42°C/DME	1.4	79	>99.5
4	0°C/THF	10 min	59 <sup>a</sup>	racemic <sup>b</sup>

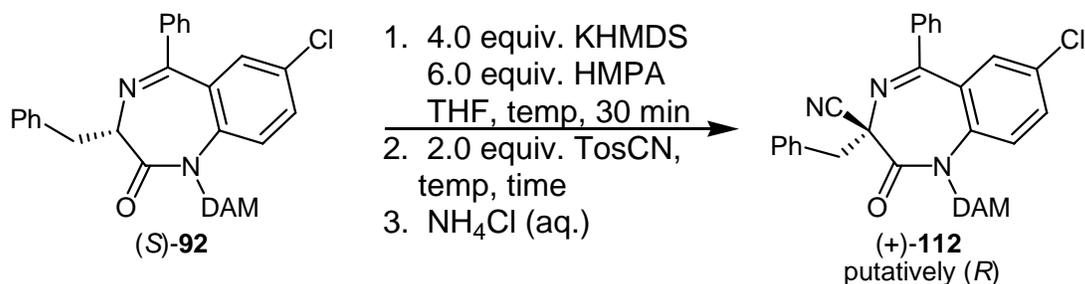
<sup>a</sup>isolated *N*-Me 3-benzyl-1,4-benzodiazepin-2-one  
~10% yield

<sup>b</sup>deprotonation  
time 10 min

Scheme 4-8. Enantioselective methylation on *N*-DAM (*S*)-3-benzyl-1,4-benzodiazepin-2-one

#### 4.6.2.2. Enantioselective cyanation on *N*-DAM phenylalanine derived benzodiazepine

As a result of the increase in cyanated product yield on the *N*-DAM Abu-derived benzodiazepine, (*S*)-93 when reaction temperatures were increased to -42°C (Scheme 4-6), enantioselective cyanations were also done on the *N*-DAM Phe-derived benzodiazepine (*S*)-92 at this temperature. In light of the solvent effects on the methylation of compound (*S*)-92 with DME giving high % yield without racemization (Scheme 4-8), this solvent was also used in the cyanation reactions of this compound. From Scheme 4-9 (entry 1) it is shown that cyanation of (*S*)-92 can occur in 68% yield and 96 % ee when the reaction is done in DME at -42°C to give product (+)-112. Racemic 112 can be prepared in good yield at 0°C in THF (Scheme 4-9, entry 2).



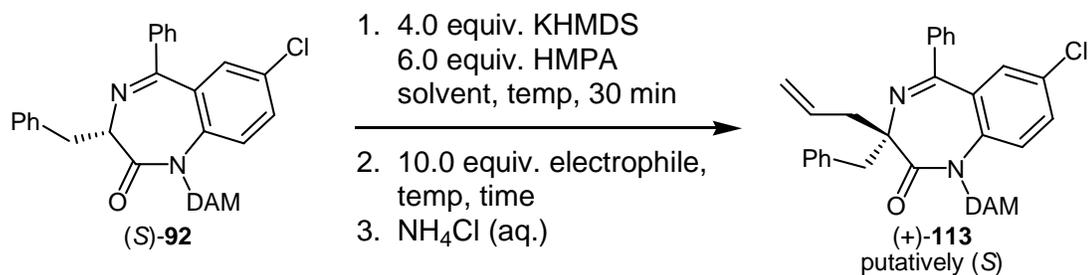
<u>entry</u>	<u>temp./solvent</u>	<u>time (min)</u>	<u>% yield</u>	<u>%ee</u>	
1	-42°C/DME	47	68	96	<sup>a</sup> deprotonation time 10 min
2	0°C/THF	10	63	racemic <sup>a</sup>	

Scheme 4-9. Enantioselective cyanation on *N*-DAM (*S*)-3-benzyl-1,4-benzodiazepin-2-one

#### 4.6.2.3. Enantioselective allylation on *N*-DAM phenylalanine derived benzodiazepine

Because a reaction temperature of -42°C in DME gave high enantiomeric excess and high yield for the methylated product (+)-**111** (Scheme 4-8) and cyanated product (+)-**112** (Scheme 4-9) these conditions were also chosen for enantioselective allylations on compound (*S*)-**92** (Scheme 4-10). Unlike Scheme 4-7 the use of allyl iodide with THF or DME at -42°C gave only moderate yields of the allylated product (+)-**113** in Scheme 4-10 (entries 1 & 2). Only when allyl bromide was used as the electrophile were acceptable allylation (58%) obtained, although reduced enantioselectivity (92% ee) was observed (Scheme 4-10, entry 3). As in the allylation case of the Abu-analog (*S*)-**93** (Scheme 4-7), allylation with allyl bromide occurs with more racemization than allyl iodide for the Phe-derived benzodiazepine (*S*)-**92**. As mentioned above this phenomena could be possibly due to *O*-allylated product being formed with the allyl bromide since

bromide is not as soft a leaving group than iodide. If the *O*-allylated product were to rearrange to *C*-alkylated product (+)-**113** via a Claisen rearrangement (Figure 4-6), it could cause racemization in that compound. *O*-alkylation could be responsible for both the increase in yield and decrease in enantiomeric excess in entry 3 of Scheme 4-10.



<b>entry</b>	<b>temp./solvent</b>	<b>electrophile</b>	<b>time (hours)</b>	<b>% yield</b>	<b>% ee</b>
1	-42°C/THF	allyl-I	2.1	44	>99.5
2	-42°C/DME	allyl-I	1.2	29	>99.5
3	-42°C/DME	allyl-Br	1.9	58	92
4	0°C/THF	allyl-I	21 min	66	racemic <sup>a</sup>

<sup>a</sup>deprotonation time 10 min

Scheme 4-10. Enantioselective allylation of *N*-DAM (*S*)-3-benzyl-1,4-benzodiazepin-2-one

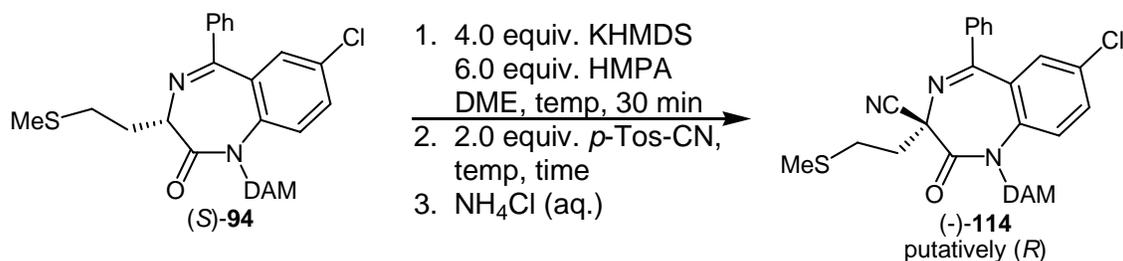
### 4.6.3. Enantioselective alkylations on *N*-DAM methionine derived benzodiazepines

In considering reaction conditions for enantioselective alkylations on the *N*-DAM Met-derived benzodiazepine (*S*)-**94**, variables that were significant in increasing product yield without racemization in the *N*-DAM Abu-derived benzodiazepine (*S*)-**93** and *N*-DAM Phe-derived benzodiazepine (*S*)-**92** were considered. Reaction temperature proved to be important for alkylations done on the *N*-DAM Abu-derived benzodiazepine (*S*)-**93** (Scheme 4-5 and Scheme 4-6), while the combination of reaction temperature and solvent were key in increasing product yields in the *N*-DAM Phe-derived benzodiazepine (*S*)-**92**

(Scheme 4-8). These components were incorporated into the alkylation schemes of the *N*-DAM Met-derived benzodiazepine (*S*)-**94** (Scheme 4-11 to Scheme 4-13).

#### 4.6.3.1. Enantioselective cyanation on *N*-DAM methionine derived benzodiazepine

In Scheme 4-11 low cyanation yields on the *N*-DAM methionine derived benzodiazepine (*S*)-**94** are observed when the reaction temperature is  $-78^{\circ}\text{C}$  (Scheme 4-11, entry 1). Increasing the temperature to  $-42^{\circ}\text{C}$  and using DME as solvent increases the yield of product (-)-**114** to 80% (Scheme 4-11, entry 2). As with the previous *N*-DAM benzodiazepine substrates the *N*-DAM group provides a sufficient racemization barrier upon deprotonation to the enolate for enantioselective cyanations to occur. It is uncertain what causes the slight decrease to 87% ee, although it could be attributed to interaction with the sulfur atom and the carbanion formed upon deprotonation. Racemic **114** is also obtained in good yield at  $0^{\circ}\text{C}$  and a 15 min reaction time (Scheme 4-11, entry 3).



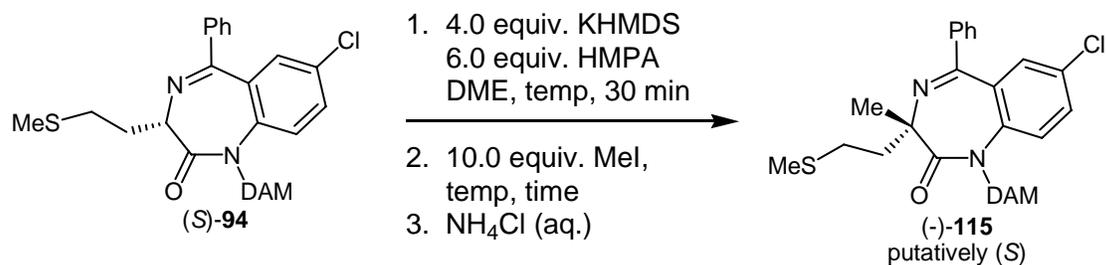
<u>entry</u>	<u>temp./solvent</u>	<u>time (min)</u>	<u>% yield</u>	<u>% ee</u>
1	-78°C/THF	20	36	87
2	-42°C/DME	30	80	87
3	0°C/DME	15	71	racemic <sup>a</sup>

<sup>a</sup>deprotonation time 10 min

Scheme 4-11. Enantioselective cyanation on *N*-DAM (*S*)-3-(2-(methylthio)ethyl)-1,4-benzodiazepin-2-one

#### 4.6.3.2. Enantioselective methylation on *N*-DAM methionine derived benzodiazepine

Following the protocol of the cyanation reactions on the *N*-DAM methionine derived benzodiazepine (*S*)-**94** (Scheme 4-11), enantioselective methylations on this compound were also done at -42°C in DME (Scheme 4-12). Under these conditions methylated product (-)-**115** is obtained in 67% yield and 87 % ee (entry 1). As mentioned above, the slight decrease in enantiomeric excess could be due to interactions with the sulfur atom and the carbanion just as in the case of cyanation on compound (*S*)-**94** (Scheme 4-11). Racemizing methylation yields of this substrate indicate that although a 10 minute deprotonation time at 0°C is sufficient to obtain racemic enolate, a reaction time longer than 17 minutes is needed to increase the alkylation yield of *rac*-**115** (Scheme 4-12, entry 2).



<u>entry</u>	<u>temp.</u>	<u>time</u> <u>(hours)</u>	<u>% yield</u>	<u>% ee</u>
1	-42°C	1.3	67	87
2	0°C	17 min	23 <sup>a</sup>	racemic <sup>b</sup>

<sup>a</sup>51% recovered starting material

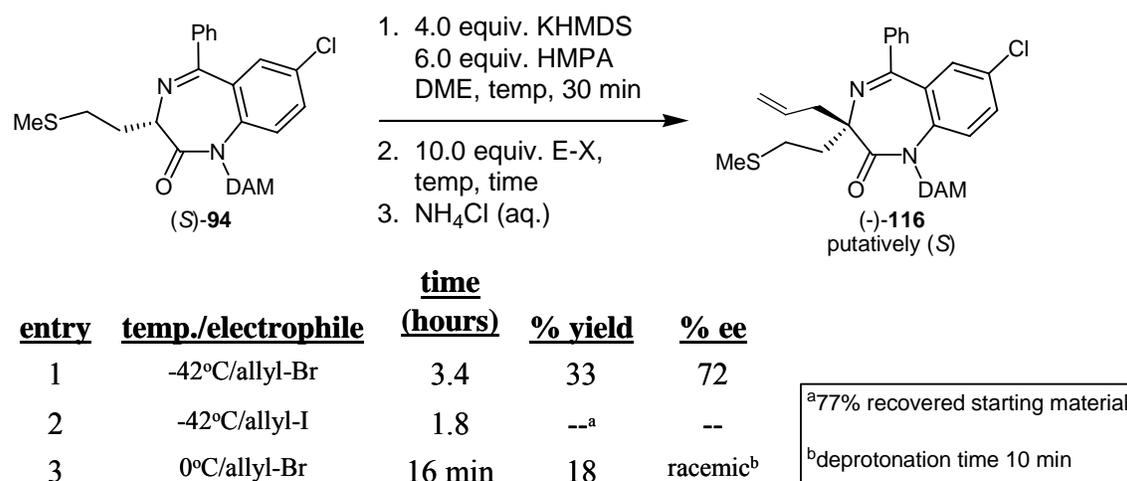
<sup>b</sup>deprotonation time 10 min

Scheme 4-12. Enantioselective methylation on *N*-DAM (*S*)-3-(2-(methylthio)ethyl)-1,4-benzodiazepin-2-one

#### 4.6.3.3. Enantioselective allylation on *N*-DAM methionine derived benzodiazepine

In the allylation of (*S*)-**94** (Scheme 4-13) the alkylation protocol of -42°C in DME used in the cyanations (Scheme 4-11) and methylations (Scheme 4-12) of this compound was employed. From Scheme 4-13 it is shown that allylated product (-)-**116** is obtained in 33 % yield and 72 % ee under these conditions, with allyl bromide as the electrophile (entry 1). When allyl iodide was used in the reaction 77% starting material was recovered and no allylated product was formed (entry 2). These results demonstrate the enhanced reactivity of allyl bromide over allyl iodide on the *N*-DAM Met-derived analog, (*S*)-**94**. This preference for allyl bromide over allyl iodide is also noticed in Scheme 4-10 (entries 2 and 3), with the allylation of *N*-DAM Phe-derived benzodiazepine (*S*)-**92**, at -42°C in DME. Just as in Figure 4-6, it is speculated that *O*-alkylated product could be formed in this reaction, which rearranges into *C*-alkylated product through a -sigmatropic rearrangement, accounting for the decrease in enantiomeric excess to 72% ee. Similar to Scheme 4-12, reaction times longer than 16 minutes are needed to increase the yield of

racemic **116** (Scheme 4-13, entry 3). The yields of these racemate reactions suggest that the reactivity of the enolate derived from (*S*)-**94** is less than those derived from (*S*)-**93** or (*S*)-**92**. This could be possibly due to the sulfur atom coordinating with the carbanion formed upon deprotonation, decreasing the reactivity of the enolate. These results also illustrate that in going from methylations (Scheme 4-12) to allylations (Scheme 4-13) on compound (*S*)-**94** reaction yields are greatly decreased showing decreased reactivity towards less reactive electrophiles.

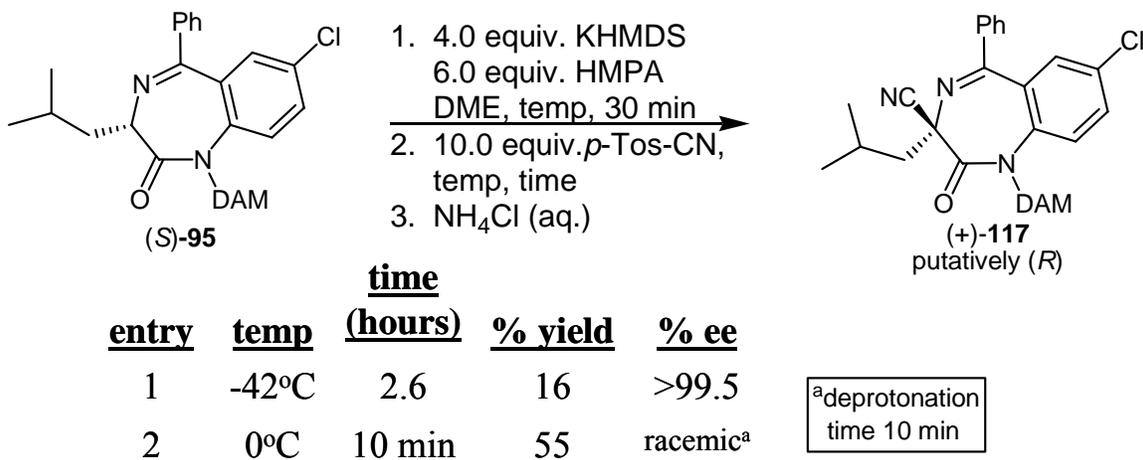


Scheme 4-13. Enantioselective allylation on *N*-DAM (*S*)-3-(2-(methylthio)ethyl)-1,4-benzodiazepin-2-one

#### 4.6.4. Enantioselective cyanation on *N*-DAM leucine derived benzodiazepine

Like the other cyanation reactions performed on these scaffolds (Schemes 4-6, 4-9, 4-11) enantioselective cyanations on *N*-DAM Leu-derived benzodiazepine (*S*)-**95** occur in high % ee under reaction conditions of -42°C in DME. However unlike the other *N*-DAM benzodiazepines the reaction yield using tosyl cyanide to give compound (+)-**117** is poor (Scheme 4-14, entry 1). This result suggests that reactivity of the *N*-

DAM Leu-derived benzodiazepine (*S*)-**95** is even less than that of the *N*-DAM Met-derived benzodiazepine (*S*)-**94** possibly due to steric effects of the C3 isobutyl substituent on the benzodiazepine ring. Like the other *N*-DAM benzodiazepines used in this study the racemic cyanated product **117** is obtained in good yield, 55% for this substrate (Scheme 4-14, entry 2).



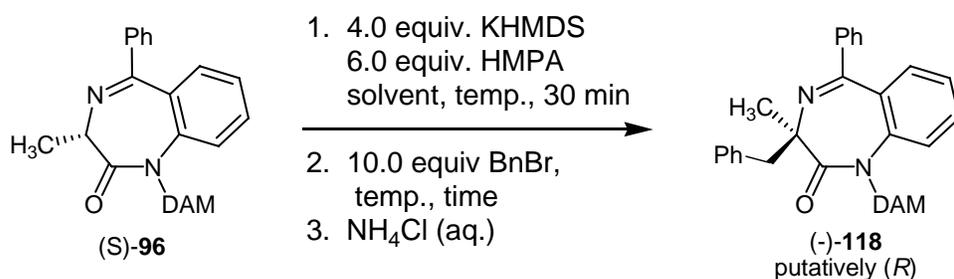
Scheme 4-14. Enantioselective cyanation on *N*-DAM (*S*)-3-isobutyl-1,4-benzodiazepin-2-one

#### 4.6.5. Enantioselective benzylation on *N*-DAM alanine derived *des*-chloro benzodiazepine

The reader will note that a chlorine atom is present in all the benzodiazepine substrates used thus far. The reason for this stems from our use of 2-amino-5-chloro-benzophenone starting material, which is commercially available and inexpensive due to its use in the synthesis of diazepam. In this research we wanted to show that the chlorine atom is not needed for enantioselective reactions to occur on the benzodiazepine scaffold.

Similar to the results of the methylation of the *N*-DAM Phe-derived benzodiazepine (*S*)-**92** (Scheme 4-8), benzylation of the *N*-DAM Ala-derived *des*-chloro benzodiazepine (*S*)-**96** occurs in high enantiomeric excess when the reaction is done in

THF or DME, however the yield of the product (-)-**118** increases when the reaction is done in DME (Scheme 4-15, entries 1 & 2). The optical rotation sign of (-)-**118** correlates with that of the (*R*)-configured benzylated *N*-DAM Ala-derived benzodiazepine synthesized by Dr. Hongwu Zhao (Carrier research group, Virginia Tech, 2003). Using the 10 minute deprotonation protocol at 0°C racemic cyanated product **118** is obtained in high yield after a 14 minute reaction time in DME (Scheme 4-15, entry 3). These results show that lack of the chlorine atom on the benzodiazepine scaffold does not seem to have any significant effect on product yield or racemization in these enantioselective alkylation reactions.



<u>entry</u>	<u>temp./solvent</u>	<u>time (hours)</u>	<u>% yield</u>	<u>% ee</u>
1	-42°C/THF	1.4	47	96
2	-42°C/DME	1.5	78	98
3	0°C/DME	14 min	84	racemic <sup>a</sup>

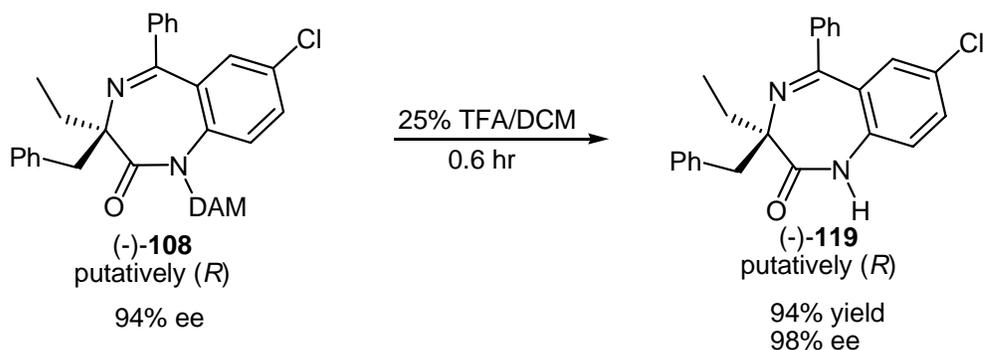
<sup>a</sup>deprotonation  
time 10 min

Scheme 4-15. Enantioselective benzylation of *N*-DAM (*S*)-3-methyl *des*-chloro 1,4-benzodiazepin-2-one

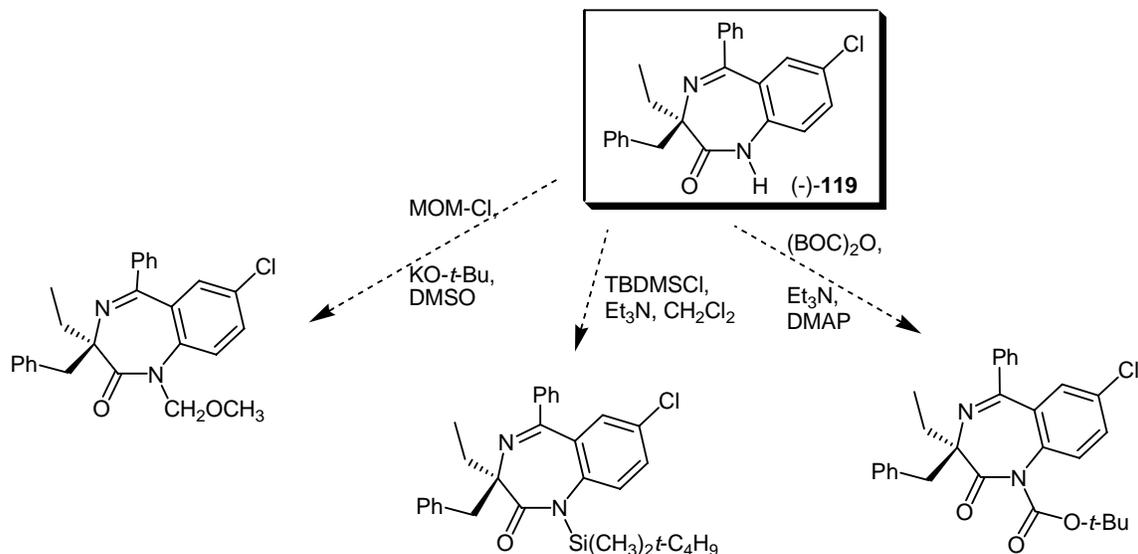
#### 4.7. De-blocking of *N*-DAM group on *N*-DAM 3-benzyl amino butyric acid derived benzodiazepine

The results in this chapter demonstrate that *N*-DAM group provides a sufficient racemization barrier for enantioselective alkylations to be performed in the benzodiazepine scaffold. Once these enantiomerically enriched “quaternary” 1,4-

benzodiazepin-2-ones have been synthesized, removal of the *N*-DAM group can occur by treatment with TFA in dichloromethane, to give enantiomerically enriched *N*-H “quaternary” benzodiazepine (-)-**119** in excellent yield and enantiomeric excess (Scheme 4-16). The discrepancy between the 94% ee in the *N*-DAM starting material (-)-**108** in Scheme 4-16 and the 98% ee in the *N*-H product (-)-**119** is attributed to a DAM impurity present in the starting material which co-elutes with one of the enantiomers on the chiral phase HPLC chromatogram. Upon de-blocking of the DAM group and purification by column chromatography (1:4 ethyl acetate:hexane followed by 1:10 diethyl ether:dichloromethane), the DAM group and DAM impurity are no longer present in the sample giving the “quaternary” *N*-H 1,4-benzodiazepin-2-one product (-)-**119** in 94% yield and 98% ee. Compound (-)-**119** can undergo further functionalization at the N1 position to expand the diversity of these substrates (Scheme 4-17).



Scheme 4-16. De-blocking of *N*-DAM group on *N*-DAM 3-benzyl amino butyric acid derived benzodiazepine



Scheme 4-17. Further functionalization of enantiomerically enriched "quaternary" 1,4-benzodiazepin-2-one

It is of interest to note that unlike the *N*-DAM 3-benzyl amino butyric acid derived benzodiazepine (-)-**108**, in the  $^1\text{H}$  NMR of the de-blocked *N*-H 3-benzyl amino butyric acid derived benzodiazepine (-)-**119** only one set of signals appear in the NMR spectrum (Figure 4-5). This spectral simplicity is due to rapid conformational interconversion on the NMR time scale when the N1 substituent is a proton (recall NMR spectra for *des*-methyl diazepam and diazepam from chapter 2). Hence only one average signal appears for the two conformers in the NMR spectrum.

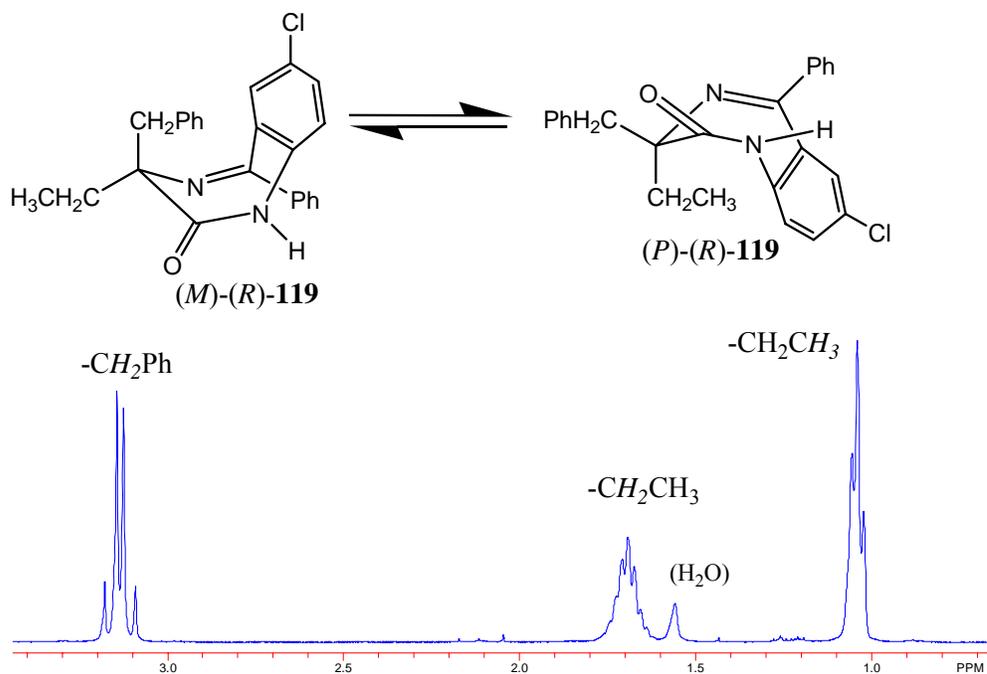
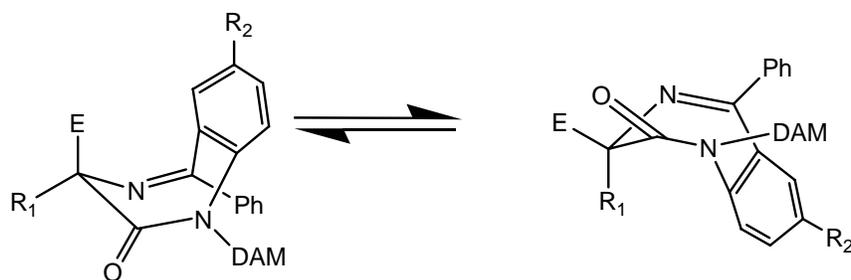


Figure 4-7.  $^1\text{H}$  NMR: *(R)*-3-benzyl-7-chloro-3-ethyl-1-hydro-5-phenyl-1,4-benzodiazepin-2-one

When the *N*-DAM group is present, conformational interconversion is slow on the NMR timescale. This chapter concludes with Figure 4-8, which describes the conformer ratios for all the “quaternary” *N*-DAM benzodiazepines discussed in this chapter.



<u>compound</u> <sup>a</sup>	<u>R</u> <sub>1</sub>	<u>E</u>	<u>R</u> <sub>2</sub>	<u>mol% R</u> <sub>1</sub> <u>equatorial</u> <sup>b</sup>
<b>(R)-(-)-108</b>	-CH <sub>2</sub> CH <sub>3</sub>	-CH <sub>2</sub> Ph	-Cl	30
<b>(R)-(+)-109</b>	-CH <sub>2</sub> CH <sub>3</sub>	-CN	-Cl	100
<b>(R)-(-)-110</b>	-CH <sub>2</sub> CH <sub>3</sub>	-CH <sub>2</sub> CHCH <sub>2</sub>	-Cl	40
<b>(S)-(+)-111</b>	-CH <sub>2</sub> Ph	-CH <sub>3</sub>	-Cl	65
<b>(R)-(+)-112</b>	-CH <sub>2</sub> Ph	-CN	-Cl	100
<b>(R)-(+)-113</b>	-CH <sub>2</sub> Ph	-CH <sub>2</sub> CHCH <sub>2</sub>	-Cl	65
<b>(R)-(-)-114</b>	-CH <sub>2</sub> CH <sub>2</sub> SCH <sub>3</sub>	-CN	-Cl	100
<b>(S)-(-)-115</b>	-CH <sub>2</sub> CH <sub>2</sub> SCH <sub>3</sub>	-CH <sub>3</sub>	-Cl	65
<b>(S)-(-)-116</b>	-CH <sub>2</sub> CH <sub>2</sub> SCH <sub>3</sub>	-CH <sub>2</sub> CHCH <sub>2</sub>	-Cl	60
<b>(R)-(+)-117</b>	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-CN	-Cl	100
<b>(R)-118</b>	-CH <sub>3</sub>	-CH <sub>2</sub> Ph	-H	40

Figure 4-8. Conformational preference for R1 equatorial in *N*-DAM 1,4-benzodiazepin-2-ones

<sup>a</sup>Putative designations

<sup>b</sup>Determined by <sup>1</sup>H NMR

## 4.8. Conclusion

We have established a synthetic route to enantiomerically enriched 3,3-disubstituted 1,4-benzodiazepin-2-ones containing a “quaternary” stereogenic center. The *N*-methyl group does not provide a sufficient racemization barrier in the enolate formed upon deprotonation to allow slow bimolecular reactions to proceed enantioselectively (Scheme 4-3). However, H-D exchange (Scheme 4-2) occurs enantioselectively on the *N*-methyl substrates (*S*)-(+)-**83**, (*S*)-(+)-**85**, and (*S*)-(+)-**86** because in the H-D exchange the enolate is immediately trapped by the deuterated solvent. Increasing the size of the N1 substituent to an isopropyl group allows for standard sequential deprotonation/trapping reactions to be performed enantioselectively, due to an increased inversion barrier in the enolate (Schemes 4-3 and 4-4). The *N*-DAM group also provides a sufficient racemization barrier in the enolate to allow enantioselective deprotonation/trapping. Raising the reaction temperature from -78°C to -42°C was the major contributor that allowed for an increase in % yield, while maintaining high enantiomeric excess on enantioselective alkylations done on the *N*-DAM Abu-derived benzodiazepine (*S*)-**93** (Scheme 4-5). The combination of a reaction temperature of -42°C and the use of the solvent DME was responsible for the increase in alkylation yield on the *N*-DAM Phe-derived benzodiazepine (Scheme 4-8). The -42°C temperature in the DME protocol was also successful on cyannations and methylations on the *N*-DAM Met- analog (*S*)-**94**. In the *N*-DAM Leu-derived benzodiazepine (*S*)-**95**, steric effects of the isobutyl substituent seem to contribute to the low cyanation yield of this substrate. Finally de-blocking of the *N*-DAM group occurs in high yield and high

enantiomeric excess to allow installation of diverse N1 functionality on these substrates (Schemes 4-16 and 4-17).

#### **4.9. Future work**

Future work in this study would involve investigations into how to improve the work-up for the *N*-DAM installation reaction. Excess DAM-Br could be quenched before chromatography and thus allow for easier purification. In addition, because of the utility of the 1,4-benzodiazepine scaffold in medicinal chemistry, and the lack of enantiomerically enriched 3,3-disubstituted benzodiazepines containing quaternary stereogenic centers, biological assays would be explored on these novel benzodiazepines synthesized. Furthermore these enantiomerically enriched quaternary benzodiazepine scaffolds could be hydrolyzed to provide for a synthetic route to quaternary amino acids in enantiomeric excess.

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## Chapter 5: Experimental

### 5.1. General methods:

THF was distilled from Na/benzophenone. DME was also distilled from Na/benzophenone. Dichloromethane, diethyl ether, acetone, ethyl acetate, hexanes, and methanol were reagent grad and used as received. *N*-Boc protected amino acids were purchased from Advanced ChemTech. <sup>1</sup>H NMR Spectra were recorded on JEOL Eclipse 500, Varian Inova 400, and Varian Unity 400 MHz NMR Spectrometers. Enantiomeric excess was assessed by HPLC (Chiralcel OD) (Chiralpak AD or AD-H).

**Tabulation of HPLC conditions and retention times for 1,4-benzodiazepin-2-ones**

compound	column	solvent, flowrate	fast enantiomer retention time (config)	slow enantiomer retention time (config)
( <i>S</i> )- <b>71</b>	OD	3% isopropanol-hexane, 1mL/min	23.7 min ( <i>R</i> )	26.9 min ( <i>S</i> )
( <i>S</i> )- <b>80</b>	AD	10% isopropanol-hexane, 1mL/min	10.3 min ( <i>R</i> )	12.0 min ( <i>S</i> )
( <i>S</i> )- <b>81</b>	AD	10% isopropanol-hexane, 1mL/min	7.1 min ( <i>R</i> )	7.9 min ( <i>S</i> )
( <i>S</i> )-(+)- <b>83</b>	OD	5% isopropanol-hexane, 1mL/min	12.3 min ( <i>R</i> )	14.3 min ( <i>S</i> )
( <i>S</i> )-(+)- <b>85</b>	OD	3% isopropanol-hexane, 1mL/min	9.7 min ( <i>R</i> )	11.1 min ( <i>S</i> )
( <i>S</i> )-(-)- <b>86</b>	AD	3% isopropanol-hexane, 1mL/min	20.3 min ( <i>S</i> )	23.6 min ( <i>R</i> )
( <i>S</i> )-(+)- <b>88</b>	AD	5% isopropanol-hexane, 1mL/min	9.7 min ( <i>R</i> )	10.6 min ( <i>S</i> )
( <i>S</i> )- <b>89</b>	OD	1% isopropanol-hexane, 1mL/min	6.8 min ( <i>R</i> )	7.9 min ( <i>S</i> )
( <i>S</i> )-(+)- <b>92</b>	OD	1% isopropanol-hexane, 1mL/min	40.2 min ( <i>S</i> )	46.7 min ( <i>R</i> )
( <i>S</i> )-(+)- <b>93</b>	OD	1% isopropanol-hexane, 1mL/min	25.1 min ( <i>R</i> )	28.9 min ( <i>S</i> )
( <i>S</i> )-(-)- <b>94</b>	OD	1% isopropanol-hexane, 1mL/min	41.6 min ( <i>S</i> )	46.9 min ( <i>R</i> )
( <i>S</i> )-(+)- <b>95</b>	OD	1% isopropanol-hexane, 1mL/min	26.6 min ( <i>S</i> )	31.6 min ( <i>R</i> )
( <i>S</i> )-(+)- <b>96</b>	OD	3% isopropanol-hexane, 1mL/min	16.3 min ( <i>R</i> )	19.7 min ( <i>S</i> )
( <i>S</i> )-(+)- <b>101</b>	AD	5% isopropanol-hexane, 1mL/min	18.1 min ( <i>S</i> )	20.2 min ( <i>R</i> )
( <i>S</i> )-(+)- <b>102</b>	OD	3% isopropanol-hexane, 1mL/min	9.7 min ( <i>R</i> )	11.1 min ( <i>S</i> )
( <i>S</i> )-(-)- <b>103</b>	AD	3% isopropanol-hexane, 1mL/min	20.5 min ( <i>S</i> )	23.8 min ( <i>R</i> )
( <i>S</i> )-(-)- <b>106</b>	AD-H	1% isopropanol-hexane, 1mL/min	20.1 min ( <i>S</i> )	22.5 min ( <i>R</i> )
(+)- <b>107</b> putatively ( <i>S</i> )	AD-H	1% isopropanol-hexane, 1mL/min	13.1 min ( <i>S</i> )	14.3 min ( <i>R</i> )
(-)- <b>108</b> Putatively ( <i>R</i> )	AD	3% isopropanol-hexane, 1mL/min	27.2 min ( <i>S</i> )	34.6 min ( <i>R</i> )
(+)- <b>109</b> putatively ( <i>R</i> )	OD	1% isopropanol-hexane, 1mL/min	21.5 min ( <i>R</i> )	26.5 min ( <i>S</i> )

(-)- <b>110</b> putatively ( <i>R</i> )	OD	1% isopropanol- hexane, 1mL/min	21.2 min ( <i>S</i> )	23.7 min ( <i>R</i> )
( <i>S</i> )-(+)- <b>111</b>	OD	1% isopropanol- hexane, 1mL/min	22.1 min ( <i>S</i> )	24.7 min ( <i>R</i> )
(+)- <b>112</b> putatively ( <i>R</i> )	OD	1% isopropanol- hexane, 1mL/min	26.5 min ( <i>R</i> )	32.7 min ( <i>S</i> )
(+)- <b>113</b> putatively ( <i>S</i> )	AD	3% isopropanol- hexane, 1mL/min	22.1 min ( <i>S</i> )	31.0 min ( <i>R</i> )
(+)- <b>114</b> putatively ( <i>R</i> )	OD	10% isopropanol- hexane	9.0 min ( <i>R</i> )	14.3 min ( <i>S</i> )
(-)- <b>115</b> putatively ( <i>S</i> )	AD	3% isopropanol- hexane, 1mL/min	20.5 min ( <i>R</i> )	25.1 min ( <i>S</i> )
(-)- <b>116</b> putatively ( <i>R</i> )	AD-H	3% isopropanol- hexane, 1mL/min	16.7 min ( <i>R</i> )	20.7 min ( <i>S</i> )
(+)- <b>117</b> putatively ( <i>R</i> )	OD	1% isopropanol- hexane, 1mL/min	16.3 min ( <i>R</i> )	22.2 min ( <i>S</i> )
(-)- <b>118</b> putatively ( <i>R</i> )	OD	1% isopropanol- hexane, 1mL/min	26.8 min ( <i>S</i> )	30.2 min ( <i>R</i> )
(-)- <b>119</b> putatively ( <i>R</i> )	AD-H	3% isopropanol- hexane, 1mL/min	17.9 min ( <i>R</i> )	20.2 min ( <i>S</i> )

## 5.2. Synthesis of benzodiazepine scaffolds

### [(*S*)-71] 3-benzyl-7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one

Benzodiazepines (*S*)-**71** was synthesized using a modified protocol of Shea and co-workers.<sup>1</sup> To a stirred solution of 2-amino-5-chloro-benzophenone (1.9216 g, 8.29 mmol) and *N*-Boc-phenylalanine ((2.0000 g, 7.54 mmol) in 10 mL THF was added dicyclohexylcarbodiimide (DCC) ( 1.7116 g, 8.29 mmol) in methylene chloride (DCM) (10 mL) dropwise, over 30 min at 0°C. The reaction mixture was stirred for an additional 8 hr at room temperature. The dicyclohexyl urea formed was filtered off and the filtrate concentrated. The intermediate amide product (*S*)-**73** underwent additional chromatography in 100% DCM to separate excess 2-amino-5-chlorobenzophenone starting material from the (*S*)-**73** amide product and dicyclohexylurea (DCU) impurity. A

second chromatography of 1:20 Et<sub>2</sub>O:DCM was used to separate the amide product (*S*)-**73** from the DCU impurity. Ninhydrin was used to track the DCU impurity in the second chromatography. The intermediate amide product (*S*)-**73** was obtained in 2.6334 g, 73 % yield.

To a stirred solution of amide (*S*)-**73** (2.6 g, 5.5 mmol) in DCM (30 mL) was added trifluoroacetic acid (TFA) (9 mL). The reaction mixture was stirred 1-2 hr. Reaction mixture was concentrated and redissolved in methanol (30 mL). A 1:1 solution of NaHCO<sub>3</sub> : NH<sub>4</sub>Cl was added until the reaction mixture was pH 7. The reaction mixture was stirred overnight. The solution was extracted with DCM (3 × 30 mL) and the organic layer was dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated. The crude product was purified by chromatography 30:70 EtOAc:hexanes to afford (*S*)-**71** in 1.9839 g, 100% yield, >99.5% ee

### 5.3. Synthesis of *N*-methyl benzodiazepines

#### **[(*S*)-(+)-83] 3-benzyl-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one**

At 0°C to a stirred mixture of compound (*S*)-**71** (0.7000 g, 1.94 mmol, 1.0 equiv.) in anhydrous THF (15 mL) was added NaH (0.1008 g, 6.28 mmol, 1.3 equiv., 60% suspension in mineral oil) in one portion. The resulting solution was stirred for 20 min. methyl triflate (0.276 mL, 2.52 mmol, 1.3 equiv.) was added to the solution. The reaction mixture was stirred for 20 min at 0°C, at which point TLC (1:4 EtOAc / hexanes) indicated the reaction was complete. The reaction was quenched with 20 mL H<sub>2</sub>O and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 20 mL). The combined organic extracts were dried over

Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified with flash column chromatography on silica gel (eluent: EtOAc/Hex = 1:4) to afford (*S*)- **83** as white foam. 0.6918 g, yield 95%,

$[\alpha]_D^{25} = +73.5$  ( $c = 1.10$ , CHCl<sub>3</sub>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.56–7.53 (m, 2H), 7.49–7.44 (m, 2H), 7.41–7.38 (m, 2H), 7.36–7.34 (d,  $J = 7.1$  Hz, 2H), 7.30–7.23 (m, 4H), 7.21–7.18 (t,  $J = 7.3$  Hz, 1H) 3.75 (t,  $J = 6.6$  Hz, 1H), 3.59 (d,  $J = 6.9$  Hz, 2H), 3.41 (s, 3H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  170.1, 167.1, 142.3, 139.3, 138.2, 131.5, 130.7, 130.4, 130.0, 129.9, 129.7, 129.3, 128.5, 128.3, 126.3, 122.9, 65.4, 38.2, 35.4;

HRMS calcd. for C<sub>23</sub>H<sub>20</sub>ClN<sub>2</sub>O (M+1) 375.1264, found 375.1264 (+0.0 ppm, +0.0 mmu).

HPLC  $t_r(R)$ : 12.3 min;  $t_r(S)$ : 14.3 min [Chiralcel OD (0.46 cm × 25 cm) (from Daicel Chemical Ind., Ltd.) Hexane/*i*-PrOH: 95/5, 1.0 mL/min, >99.5% ee.

**[(*S*)-(+)-85] 7-chloro-1,3-dihydro-1-methyl-5-phenyl-3-(2-methylpropyl)-2*H*-1,4-benzodiazepin-2-one**

At 0°C to a stirred mixture of compound (*S*)-**81** (0.3000 g, 1.03 mmol, 1.0 equiv.) in anhydrous THF (6 mL) was added NaH (53.6 mg, 1.34 mmol, 1.3 equiv., 60% suspension in mineral oil) in one portion. The resulting solution was stirred for 20 min. methyl triflate (0.147 mL, 1.34 mmol, 1.3 equiv.) was added to the solution. The reaction mixture was stirred for 30 min at 0°C, at which point TLC (1:1 EtOAc / hexanes) indicated the reaction was complete. The reaction was quenched with 6 mL H<sub>2</sub>O and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 6 mL). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was

purified with flash column chromatography on silica gel (eluent: EtOAc/Hex = 1:1) to afford (*S*)- **85** as white foam. 0.2722 g, yield 87%,

$[\alpha]_D^{25} = +180$  ( $c = 1.11$ ,  $\text{CHCl}_3$ ).

$^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.59–7.57 (m, 2H), 7.52–7.50 (dd,  $J = 8.8$  Hz, 2.4Hz, 1H), 7.47–7.44 (m, 1H), 7.41–7.39 (m, 2H), 7.31–7.29 (m, 2H), 3.59–3.56 (dd,  $J = 9.3$  Hz, 8.5 Hz, 1H), 3.40 (s, 3H), 2.35–2.28 (m, 1H), 1.96–1.91 (m, 2H), 1.00–0.99 (d,  $J = 6.5$  Hz, 3H), 0.82–0.80 (d,  $J = 6.2$  Hz, 3H);

$^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  170.8, 167.1, 142.5, 138.4, 131.5, 130.6, 130.5, 129.7, 129.6, 129.2, 128.5, 122.7, 61.8, 40.3, 35.3, 24.7, 23.6, 22.0;

HRMS calcd. for  $\text{C}_{20}\text{H}_{22}\text{ClN}_2\text{O}$  ( $M+1$ ) 341.1421, found 341.14087(–3.4 ppm, –1.2 mmu).

HPLC  $t_r(R)$ : 9.7 min;  $t_r(S)$ : 11.1 min [Chiralcel OD (0.46 cm  $\times$  25 cm) (from Daicel Chemical Ind., Ltd.) Hexane/*i*-PrOH: 97/3, 1.0 mL/min, 99% ee.

**[(*S*)-(-)-**86**] 7-chloro-1,3-dihydro-1-methyl-5-phenyl-3-(2-thiomethyl)ethyl-2*H*-1,4-benzodiazepin-2-one**

At 0°C to a stirred mixture of compound (*S*)-**80** (0.2000 g, 0.58 mmol, 1.0 equiv.) in anhydrous THF (3.2 mL) was added NaH (30.2 mg, 0.754 mmol, 1.3 equiv., 60% suspension in mineral oil) in one portion. The resulting solution was stirred for 20 min. methyl triflate (0.083 mL, 0.754 mmol, 1.3 equiv.) was added to the solution. The reaction mixture was stirred for 2 h at 0°C. The reaction was quenched with 6 mL  $\text{H}_2\text{O}$  and extracted with  $\text{CH}_2\text{Cl}_2$  (3  $\times$  6 mL). The combined organic extracts were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. The crude product was

purified with flash column chromatography on silica gel (eluent: EtOAc/Hex = 1:1) to afford (*S*)- **86** as white foam. 0.0616 g, yield 30%,

$[\alpha]_D^{25} = -170$  ( $c = 0.29$ , CHCl<sub>3</sub>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  2.09 (s, 3H), 2.41-2.48 (m, 1H), 2.55-2.62 (m, 1H), 2.69-2.82 (m, 2H), 3.40 (s, 3H), 3.73-3.76 (m, 1H), 7.30-7.31 (m, 2H), 7.39-7.42 (m, 2H), 7.45-7.49 (m, 1H), 7.51-7.53 (dd,  $J = 8.9$ ,  $J = 2.6$ , 1H), 7.58-7.60 (m, 2H);

<sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  15.48, 30.70, 30.85, 35.22, 61.84, 122.73, 128.43, 129.28, 129.55, 129.76, 130.43, 130.69, 131.54, 138.12, 142.27, 167.50, 170.30.

HPLC  $t_r$  20.3 min (*S*);  $t_r$  23.6 min (*R*) [Chiralcel AD (0.46 cm  $\times$  25 cm) (from Daicel Chemical Ind., Ltd.) Hexane/*i*-PrOH, 97/3, 1.0 mL/min, 99% ee.

## 5.4. Synthesis of *N*-isopropyl benzodiazepines

### **[(*S*)-(+)-**88**] 3-benzyl-7-chloro-1,3-dihydro-1-isopropyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one**

At 0°C to a stirred mixture of compound (*S*)-**71** (2.0242 g, 5.61 mmol, 1.0 equiv.) in anhydrous THF (40 mL) was added NaH (0.2513 g, 6.28 mmol, 1.12 equiv., 60% suspension in mineral oil) in one portion. The resulting solution was stirred for 30 min. Isopropyl triflate (3.234 g, 16.83 mmol, 3.0 equiv.) was added to the solution. The reaction mixture was stirred for 1.5 h at 0°C, at which point TLC (1:8 EtOAc / hexanes) indicated the reaction was complete. The reaction was quenched with 40 mL H<sub>2</sub>O and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3  $\times$  40 mL). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was

purified with flash column chromatography on silica gel (eluent: EtOAc/Hex = 1:6) to afford (*S*)- **88** as white foam. 1.6656 g, yield 74%,

$[\alpha]_D^{21} = +64.4^\circ$  (c = 0.5, CHCl<sub>3</sub>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.56-7.15 (several multiplets, 13H), 4.58 (septet, *J* = 6.9 Hz, 1H), 3.70 (dd, *J* = 8.2, 5.4 Hz, 1H), 3.586 (dd, *J* = 13.9, 8.2 Hz, 1H), 3.525 (dd, *J* = 13.9, 5.4 Hz, 1H), 1.56 (s, 3H), 1.47 (d, *J* = 6.7 Hz, 3H), 1.19 (d, *J* = 7.1 Hz, 3H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): 169.8, 166.8, 140.2, 139.5, 138.1, 132.7, 130.66, 130.62, 130.4, 129.9, 129.39, 129.33, 128.5, 128.2, 126.1, 125.4, 66.0, 51.5, 37.8, 22.3, 20.6.

HRMS: calcd for C<sub>25</sub>H<sub>23</sub>N<sub>2</sub>OCl (M+1) 403.1577, found 403.1583 (+1.4 ppm, +0.6 mmu).

HPLC *t*<sub>r</sub> 9.7 min (*R*); *t*<sub>r</sub> 10.6 min (*S*) [Chiralpak AD (0.46 cm × 25 cm) (from Daicel Chemical Ind., Ltd.) Hexane/*i*-PrOH, 95/5, 1.0 mL/min, >99.5% ee.

**[(*S*)-**89**] 7-chloro-1,3-dihydro-1-isopropyl-3-(2-methylpropyl)-5-phenyl-2*H*-1,4-benzodiazepin-2-one**

At 0°C to a stirred mixture of compound (*S*)-**81** (0.8000 g, 2.75 mmol, 1.0 equiv.) in anhydrous THF (20 mL) was added NaH (123 mg, 3.08 mmol, 1.12 equiv., 60% suspension in mineral oil) in one portion. The resulting solution was stirred for 30 min. Isopropyl triflate (1.5855 g, 8.25 mmol, 3.0 equiv.) was added to the solution. The reaction mixture was stirred for 1 h at 0°C, at which point TLC (3:7 EtOAc / hexanes) indicated the reaction was complete. The reaction was quenched with 20 mL H<sub>2</sub>O and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 20 mL). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified with flash column chromatography on silica gel (eluent: EtOAc/Hex = 1:9) to afford (*S*)- **89** as white foam. 0.7410g, yield 73%,

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.84 (d,  $J = 6.0$  Hz, 3H), 1.03 (d,  $J = 6.8$  Hz, 3H), 1.24 (d,  $J = 7.2$  Hz, 3H), 1.51 (d,  $J = 6.4$  Hz, 3H), 2.00-1.95 (m, 2H), 2.31-2.26 (m, 1H), 3.60-3.56 (m, 1H), 4.62-4.58 (m, 1H), 7.31 (d,  $J = 2.8$  Hz, 1H), 7.53-7.40 (m, 5H), 7.64-7.62 (m, 2H);

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) (20 resonances found for a possible 20 unique carbons):  $\delta$  20.61, 22.06, 22.25, 23.48, 24.78, 39.92, 51.28, 62.64, 125.24, 128.48, 129.17, 129.27, 130.23, 130.49, 130.61, 132.78, 138.21, 140.44, 166.64, 170.20.

HPLC  $t_r$  6.8 min (*R*);  $t_r$  7.9 min (*S*) [Chiralcel OD (0.46 cm  $\times$  25 cm) (from Daicel Chemical Ind., Ltd.) Hexane/*i*-PrOH, 99/1, 1.0 mL/min, >99.5% ee.

## 5.5. Synthesis of *N*-DAM benzodiazepines

### Synthesis of 4,4'-Dimethoxybenzhydryl bromide (DAM-Br)

At r.t. to a stirred solution of 4,4'-dimethoxybenzhydrol (2.20 g, 9.8 mmol) in anhydrous benzene (23 mL) was added acetyl bromide (3.21 mL, 43.1 mmol) dropwise by syringe. After addition the resulting solution was stirred for r.t. for 1.0 hr. The excess benzene was removed in vacuo below 40°C. The resulting residue was placed under high vacuum for 1.0 hr while being cooled down by liquid nitrogen. Recrystallization from dried hexane afforded 2.450g (82%) of a pink-ish solid.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 3.80 (s, 6H), 6.31 (s, 1H), 6.87-6.84 (m, 4H), 7.39-7.37 (m, 4H)

### **[(*S*)-(+)-92] 1-di(*p*-anisyl)methyl-3-benzyl-7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one**

At 0°C to a stirred mixture of compound (*S*)-**71** (0.1000 g, 0.277 mmol, 1.0 equiv.) in anhydrous THF (2 mL) was added NaH (21.8 mg, 0.554 mmol, 2.0 equiv., 60% suspension in mineral oil) in one portion. The resulting solution was stirred for 30 min.

DAM-Br (0.1702 g, 0.554 mmol, 2.0 equiv.) was added to the solution. The reaction mixture was stirred for a further 4 h at 0°C, at which point TLC (3:7 EtOAc / hexanes) indicated the reaction was complete. The reaction was quenched with 5 mL H<sub>2</sub>O and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 5 mL). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified with flash column chromatography on silica gel (1<sup>st</sup> eluent: Et<sub>2</sub>O/DCM=1:20, 2<sup>nd</sup> eluent: ethyl acetate/*n*-hexane=1:4) to afford (*S*)-(+)-**92** as colorless oil. 0.1314g, yield 83%,

$[\alpha]_D^{25} = +101$  ( $c = 1.25$ , CHCl<sub>3</sub>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.65 (dd, <sup>2</sup>J<sub>HH</sub> = 46.0 Hz, <sup>3</sup>J<sub>HH</sub> = 17.8 Hz, 2H), 3.75 (s, 3H), 3.84 (s, 3H), 3.95 (q, <sup>3</sup>J<sub>HH</sub> = 5.5 Hz, 1H), 6.64 (d, <sup>3</sup>J<sub>HH</sub> = 9.0 Hz, 3H), 6.90-6.93 (m, 5H), 6.99 (d, <sup>4</sup>J<sub>HH</sub> = 2.5 Hz, 1H), 7.06 (s, 1H), 7.10-7.17 (m, 2H), 7.21-7.38 (m, 9H), 7.44 (t, <sup>3</sup>J<sub>HH</sub> = 7.5 Hz, 1H);

<sup>13</sup>C NMR (CDCl<sub>3</sub>) (29 resonances found for a possible 29 unique carbons): δ 38.14, 55.45, 55.59, 64.14, 65.99, 113.84, 113.93, 114.11, 126.18, 126.43, 128.46, 128.49, 129.09, 129.34, 129.72, 130.09, 130.23, 130.39, 130.47, 130.82, 131.51, 133.13, 138.10, 139.58, 139.68, 158.98, 159.21, 167.47, 169.92.

HRMS (FAB) calcd for C<sub>37</sub>H<sub>32</sub>N<sub>2</sub>O<sub>3</sub>Cl [M+H]<sup>+</sup>: 587.2101. Found: 587.2120 (+3.1 ppm, +1.8 mmu).

HPLC t<sub>r</sub> 40.2 min (*S*); t<sub>r</sub> 46.7 min (*R*) [Chiralcel OD (0.46 cm × 25 cm) (from Daicel Chemical Ind., Ltd.) Hexane/*i*-PrOH, 99/1, 1.0 mL/min, >99.5% ee.

**[(S)-(+)-93] 1-di(*p*-anisyl)methyl-7-chloro-3-ethyl-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one**

At 0°C to a stirred mixture of compound (*S*)-**79** (0.1000 g, 0.335 mmol, 1.0 equiv.) in anhydrous THF (2 mL) was added NaH (26.8 mg, 0.670 mmol, 2.0 equiv., 60% suspension in mineral oil) in one portion. The resulting solution was stirred for 30 min. DAM-Br (0.2058 g, 0.670 mmol, 2.0 equiv.) was added to the solution. The reaction mixture was stirred for a further 3 h at 0°C, at which point TLC (3:7 EtOAc / hexanes) indicated the reaction was complete. The reaction was quenched with 5 mL H<sub>2</sub>O and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 5 mL). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified with flash column chromatography on silica gel (1<sup>st</sup> eluent: Et<sub>2</sub>O/DCM=1:20, 2<sup>nd</sup> eluent: ethyl acetate/*n*-hexane=1:4) to afford (*S*)-(+)-**93** as white foam. 0.1687g, yield 96%,

$[\alpha]_D^{25} = +186$  ( $c = 1.46$ , CHCl<sub>3</sub>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.07 (t, <sup>3</sup>J<sub>HH</sub> = 7.5 Hz, 3H), 2.26-2.36 (m, 2H), 3.61 (t, <sup>3</sup>J<sub>HH</sub> = 7.0 Hz, 1H), 3.76 (s, 3H), 3.84 (s, 3H), 6.64 (d, <sup>3</sup>J<sub>HH</sub> = 8.5 Hz, 2H), 6.91-6.93 (m, 4H), 7.05 (s, 1H), 7.07 (d, <sup>4</sup>J<sub>HH</sub> = 2.5 Hz, 1H), 7.13-7.21 (m, 2H), 7.24-7.29 (m, 4H), 7.35 (t, <sup>3</sup>J<sub>HH</sub> = 7.5 Hz, 2H), 7.44 (t, <sup>3</sup>J<sub>HH</sub> = 7.5 Hz, 1H);

<sup>13</sup>C NMR (CDCl<sub>3</sub>) (26 resonances found for a possible 26 unique carbons): δ 10.98, 24.95, 55.44, 55.58, 63.92, 65.87, 113.81, 114.11, 126.19, 128.44, 129.08, 129.21, 129.67, 130.11, 130.27, 130.53, 130.66, 130.72, 131.52, 133.34, 138.20, 139.87, 158.94, 159.17, 167.44, 170.23.

HRMS (FAB) calcd for C<sub>32</sub>H<sub>30</sub>N<sub>2</sub>O<sub>3</sub>Cl [M+H]<sup>+</sup>: 525.1945. Found: 525.1938 (-1.4 ppm, -0.7 mmu).

HPLC  $t_r$  25.1 min (*R*);  $t_r$  28.9 min (*S*) [Chiralcel OD (0.46 cm × 25 cm) (from Daicel Chemical Ind., Ltd.) Hexane/*i*-PrOH, 99/1, 1.0 mL/min, >94% ee.

**[(*S*)-(-)-**94**] 1-di(*p*-anisyl)methyl-7-chloro-1,3-dihydro-5-phenyl-3-(2-thiomethyl)ethyl-2*H*-1,4-benzodiazepin-2-one**

At 0°C to a stirred mixture of compound (*S*)-**80** (0.1000 g, 0.290 mmol, 1.0 equiv.) in anhydrous THF (2 mL) was added NaH (23.2 mg, 0.580 mmol, 2.0 equiv., 60% suspension in mineral oil) in one portion. The resulting solution was stirred for 30 min. DAM-Br (0.1782 g, 0.580 mmol, 2.0 equiv.) was added to the solution. The reaction mixture was stirred for a further 4 h at 0°C, at which point TLC (3:7 EtOAc / hexanes) indicated the reaction was complete. The reaction was quenched with 5 mL H<sub>2</sub>O and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 5 mL). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified with flash column chromatography on silica gel (eluent: Et<sub>2</sub>O/DCM=1:20, three times) to afford (*S*)-(-)-**94** as white foam. 0.0931g, yield 56%,

$[\alpha]_D^{25} = -127$  ( $c = 0.86$ , CHCl<sub>3</sub>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.12 (s, 3H), 2.55-2.64 (m, 2H), 2.72-2.84 (m, 2H), 3.75 (s, 3H), 3.84 (s, 3H), 3.95 (t, <sup>3</sup>*J*<sub>HH</sub> = 8.3 Hz, 1H), 6.64 (d, <sup>3</sup>*J*<sub>HH</sub> = 11.0 Hz, 2H), 6.90-6.95 (m, 4H), 7.03 (s, 1H), 7.07 (d, <sup>4</sup>*J*<sub>HH</sub> = 3.5 Hz, 1H), 7.14-7.23 (m, 2H), 7.25-7.29 (m, 4H), 7.36 (t, <sup>3</sup>*J*<sub>HH</sub> = 9.5 Hz, 2H), 7.45 (t, <sup>3</sup>*J*<sub>HH</sub> = 9.5 Hz, 1H);

<sup>13</sup>C NMR (CDCl<sub>3</sub>) (26 resonances found for a possible 27 unique carbons): δ 15.78, 31.01, 31.03, 55.44, 55.56, 62.70, 64.10, 113.83, 114.12, 126.28, 128.48, 129.07, 129.25,

129.67, 130.29, 130.44, 130.50, 130.86, 131.51, 133.21, 138.04, 139.70, 158.97, 159.20, 167.87, 169.99.

HRMS (FAB) calcd for C<sub>33</sub>H<sub>32</sub>N<sub>2</sub>O<sub>3</sub>Cl [M+H]<sup>+</sup>: 571.1822. Found: 571.1802 (-3.6 ppm, -2.0 mmu).

HPLC t<sub>r</sub> 41.6 min (*S*); t<sub>r</sub> 46.9 min (*R*) [Chiralcel OD (0.46 cm × 25 cm) (from Daicel Chemical Ind., Ltd.) Hexane/*i*-PrOH, 99/1, 1.0 mL/min, 98% ee.

**[(*S*)-(+)-**95**] 1-di(*p*-anisyl)methyl-7-chloro-3-(2-methyl)propyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one**

At 0°C to a stirred mixture of compound (*S*)-**81** (0.1000 g, 0.307 mmol, 1.0 equiv.) in anhydrous THF (2 mL) was added NaH (24.6 mg, 0.614 mmol, 2.0 equiv., 60% suspension in mineral oil) in one portion. The resulting solution was stirred for 30 min. DAM-Br (0.1886 g, 0.614 mmol, 2.0 equiv.) was added to the solution. The reaction mixture was stirred for a further 4 h at 0°C, at which point TLC (1:10 Et<sub>2</sub>O/DCM) indicated the reaction was complete. The reaction was quenched with 5 mL H<sub>2</sub>O and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 5 mL). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified with flash column chromatography on silica gel (1<sup>st</sup> eluent: Et<sub>2</sub>O/DCM=1:20, 2<sup>nd</sup> eluent: EtOAc/Hex=1:4) to afford (*S*)-(-)-**95** as white foam. 0.1278 g, yield 75%,  $[\alpha]_D^{25} = +153$  (*c* = 1.74, CHCl<sub>3</sub>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.85 (d, <sup>3</sup>J<sub>HH</sub> = 6.5 Hz, 3H), 1.01 (d, <sup>3</sup>J<sub>HH</sub> = 6.5 Hz, 3H), 1.93-1.98 (m, 1H), 2.05-2.11 (m, 1H), 2.30-2.36 (m, 1H), 3.75 (s, 3H), 3.79 (dd, <sup>3</sup>J<sub>HH</sub> = 5.0 Hz, <sup>3</sup>J<sub>HH</sub> = 9.0 Hz, 1H), 3.84 (s, 3H), 6.63 (d, <sup>3</sup>J<sub>HH</sub> = 8.0 Hz, 2H), 6.92 (t, <sup>3</sup>J<sub>HH</sub> = 8.0 Hz, 4H), 7.04

(s, 1H), 7.07 (d,  $^4J_{\text{HH}} = 2.5$  Hz, 1H), 7.14-7.22 (m, 2H), 7.24-7.27 (m, 4H), 7.35 (t,  $^3J_{\text{HH}} = 7.5$  Hz, 2H), 7.44 (t,  $^3J_{\text{HH}} = 7.5$  Hz, 1H);

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) (27 resonances found for a possible 27 unique carbons):  $\delta$  22.44, 23.68, 25.13, 40.31, 55.43, 55.57, 62.53, 64.01, 113.81, 114.09, 126.19, 128.42, 129.08, 129.13, 129.67, 130.19, 130.34, 130.53, 130.70, 131.50, 133.27, 138.18, 139.90, 158.92, 159.17, 167.31, 170.35;

HRMS (FAB) calcd for  $\text{C}_{34}\text{H}_{34}\text{N}_2\text{O}_3\text{Cl}$   $[\text{M}+\text{H}]^+$ : 553.2258. Found: 553.2241 (-3.0 ppm, -1.7 mmu).

HPLC  $t_r$  26.6 min (*S*);  $t_r$  31.6 min (*R*) [Chiralcel OD (0.46 cm  $\times$  25 cm) (from Daicel Chemical Ind., Ltd.) Hexane/*i*-PrOH, 99/1, 1.0 mL/min, >99.5% ee.

**[(*S*)-(+)-**96**] 1-di(*p*-anisyl)methyl-1,3-dihydro-3-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one**

At 0°C to a stirred mixture of compound (*S*)-**82** (0.5000 g, 2.0 mmol, 1.0 equiv.) in anhydrous THF (12 mL) was added NaH (160.0 mg, 4.0 mmol, 2.0 equiv., 60% suspension in mineral oil) in one portion. The resulting solution was stirred for 30 min. DAM-Br (1.2288 g, 4.0 mmol, 2.0 equiv.) was added to the solution. The reaction mixture was stirred for a further 4 h at 0°C, at which point TLC (3:7 EtOAc / hexanes) indicated the reaction was complete. The reaction was quenched with 10 mL  $\text{H}_2\text{O}$  and extracted with  $\text{CH}_2\text{Cl}_2$  (3  $\times$  10 mL). The combined organic extracts were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. The crude product was purified with flash column chromatography on silica gel (1<sup>st</sup> eluent: ethyl acetate/*n*-hexane=35:65, 2<sup>nd</sup> eluent:  $\text{Et}_2\text{O}/\text{DCM}$ =1:15) to afford (*S*)-(+)-**96** as white foam. 0.6717g, yield 71%,

$[\alpha]_D^{25} = +182$  ( $c = 0.48$ ,  $\text{CHCl}_3$ ).

$^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.78 (d,  $^3J_{\text{HH}} = 6.5$  Hz, 3H), 3.74 (s, 3H), 3.84 (s, 3H), 3.94 (q,  $^3J_{\text{HH}} = 6.5$  Hz, 1H), 6.62 (d,  $^3J_{\text{HH}} = 8.5$  Hz, 2H), 6.91-6.95 (m, 4H), 7.02-7.10 (m, 3H), 7.20 (t,  $^3J_{\text{HH}} = 8.5$  Hz, 1H), 7.26-7.34 (m, 6H), 7.42 (t,  $^3J_{\text{HH}} = 7.0$  Hz, 1H);

$^{13}\text{C NMR}$  ( $\text{CDCl}_3$ ) (25 resonances found for a possible 25 unique carbons):  $\delta$  17.57, 55.28, 55.42, 59.27, 64.14, 113.49, 113.83, 124.67, 124.76, 128.09, 129.04, 129.55, 129.62, 129.94, 130.25, 130.73, 131.00, 131.44, 131.97, 138.60, 141.17, 158.67, 158.89, 168.33, 171.19.

HRMS (FAB) calcd for  $\text{C}_{31}\text{H}_{29}\text{N}_2\text{O}_3$   $[\text{M}+\text{H}]^+$ : 477.2178. Found: 577.2161 (-3.6 ppm, -1.7 mmu).

HPLC  $t_r$  16.3 min (*R*);  $t_r$  19.7 min (*S*) [Chiralcel OD (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) Hexane/*i*-PrOH, 3/97 mL/min, >99.5% ee.

## 5.6. Deuterations on *N*-methylated benzodiazepines

### [(*S*)-(+)-**101**] 7-chloro-1,3-dihydro-3-d-1-methyl-5-phenyl-3-(phenylmethyl)-2*H*-1,4-benzodiazepin-2-one

A mixture of (*S*)-**83** (22.0 mg, 0.059 mmol, 100% ee) and *t*-BuOK (11.2 mg, 0.010mmol) in  $\text{CD}_3\text{OD}$  (2.0 mL) for 6 days. The excess solvent was evaporated in vacuo. The crude product was purified with flash column chromatography on silica gel (Eluent: Ethyl Acetate/*n*-Hexane=3:7) to afford 21.8 mg (99%) of (*S*)-(+)-**101** as yellow oil (100% D by  $^1\text{H NMR}$ ).

$[\alpha]_D^{25} = +90$  ( $c = 1.06$ ,  $\text{CHCl}_3$ ).

$^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.55–7.53 (m, 2H), 7.49–7.44 (m, 2H), 7.41–7.38 (t,  $J = 7.4\text{Hz}$ , 2H),

7.36–7.34 (d,  $J = 7.1$  Hz, 2H), 7.30–7.23 (m, 4H), 7.21–7.23 (t,  $J = 7.3$ Hz, 1H) 3.58 (s, 1H), 3.41 (s, 3H)

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  170.1, 167.1, 142.3, 139.3, 138.53, 131.5, 130.7, 130.4, 130.0, 129.9, 129.7, 129.3, 128.5, 128.3, 126.3, 122.9, 65.0 ( $^1J_{\text{DC}} = 19.1$ Hz), 38.1, 35.4;

HRMS calcd. for  $\text{C}_{23}\text{H}_{19}\text{ClDN}_2\text{O}$  ( $\text{M}+1$ ) 376.1327, found 376.13184(–2.4 ppm, –0.9 mmu).

HPLC  $t_{\text{r}}(\text{S})$ : 12.3 min;  $t_{\text{r}}(\text{R})$ : 14.3 min [Chiralcel OD (0.46 cm  $\times$  25 cm) (from Daicel Chemical Ind., Ltd.) Hexane/*i*-PrOH: 95/5, 1.0 mL/min, 97% ee.

**[(*S*)-(+)-102] 7-chloro-1,3-dihydro-3-d-1-methyl-3-(2-methylpropyl)-5-phenyl-2*H*-1,4-benzodiazepin-2-one**

A mixture of (*S*)- **85** (22.0 mg, 0.072 mmol, 99% ee) and *t*-BuOK (13.7 mg, 0.122 mmol) in  $\text{CD}_3\text{OD}$  (2.0 mL) and stirred for 13 days. The excess solvent was evaporated in vacuo. The crude product was purified with flash column chromatography on silica gel (Eluent: Ethyl Acetate/*n*-Hexane=3:7) to afford 16.5 mg (94%) of (*S*)-(+)-**102** as colorless oil (99% D by  $^1\text{H}$  NMR).

$[\alpha]_{\text{D}}^{25} = +187$  ( $c = 0.35$ ,  $\text{CHCl}_3$ ).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.60–7.59 (m, 2H), 7.58–7.57 (m, 1H), 7.52–7.50 (dd,  $J = 8.7$  Hz, 2.5 Hz, 1H), 7.48–7.44 (m, 1H), 7.42–7.38 (m, 1H), 7.31–7.29 (m, 2H) 3.59–3.54 (m, 1.0%  $\times$  1H), 3.40 (s, 3H), 2.34–2.28 (m, 1H), 1.95–1.90 (m, 2H), 1.00–0.99 (d,  $J = 6.5$  Hz, 3H), 0.81–0.80 (d,  $J = 6.2$ Hz, 3H)

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  170.7, 167.1, 142.5, 138.4, 137.6, 131.5, 130.6, 130.5, 129.7, 129.6, 129.2, 128.5, 122.8, 40.2, 35.2, 24.7, 23.6, 22.0;

HRMS calcd. for C<sub>20</sub>H<sub>21</sub>ClDN<sub>2</sub>O (M+1) 342.1483, found 342.1482 (−0.4 ppm, −0.1 mmu).

HPLC *t<sub>r</sub>*(*R*): 9.7 min; *t<sub>r</sub>*(*S*): 11.1 min [Chiralcel OD (0.46 cm × 25 cm) (from Daicel Chemical Ind., Ltd.) Hexane/*i*-PrOH: 97/3, 1.0 mL/min, 94% ee.

**[(*S*)-(-)-103] 7-chloro-1,3-dihydro-3-d-1-methyl-5-phenyl-3-(2-thiomethyl)ethyl-2*H*-1,4-benzodiazepin-2-one**

A mixture of (*S*)- **86** (20.0 mg, 0.056 mmol, 99% ee) and *t*-BuOK (10.6 mg, 0.095 mmol) in CD<sub>3</sub>OD (2.0 mL) and stirred for 8 days. The excess solvent was evaporated in vacuo. The crude product was purified with flash column chromatography on silica gel (Eluent: Ethyl Acetate/*n*-Hexane=3:7) to afford 17.6 mg (88%) of (*S*)-(-)-**103** as colorless oil (94% D by <sup>1</sup>H NMR).

$[\alpha]_D^{25} = -14.2$  (*c* = 0.88, CHCl<sub>3</sub>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.63–7.59 (m, 2H), 7.53–7.51 (m, 1H), 7.48–7.46 (m, 1H), 7.42–7.39 (m, 2H), 7.31–7.30 (m, 2H), 3.75–3.73 (m, 6.0% × 1H), 3.40 (s, 3H), 2.82–2.69 (m, 2H), 2.61–2.55 (m, 1H), 2.46–2.41 (mz, 1H), 2.09(s, 3H)

<sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 170.2, 167.5, 142.2, 138.1, 137.6, 131.5, 130.6, 130.4, 129.7, 129.5, 129.2, 128.4, 122.7, 61.4, 35.2, 30.7, 30.6, 15.4;

HRMS calcd. for C<sub>19</sub>H<sub>18</sub>ClDN<sub>2</sub>OS (M+1) 360.0985, found 360.1023 (−0.4 ppm, −0.1 mmu).

HPLC *t<sub>r</sub>*(*R*): 23.8 min; *t<sub>r</sub>*(*S*): 20.5 min [Chiralpak AD (0.46 cm × 25 cm) (from Daicel Chemical Ind., Ltd.) Hexane/*i*-PrOH: 97/3, 1.0 mL/min, 99% ee.

## 5.7. Alkylations of *N*-isopropyl benzodiazepines

### [(*S*)-(-)-106] 3-benzyl-7-chloro-1,3-dihydro-1-isopropyl-3-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one

At  $-78\text{ }^{\circ}\text{C}$  under nitrogen, to a stirred solution of (*S*)-(+)-**88** (50 mg, 0.124 mmol) and HMPA (130  $\mu\text{L}$ , 0.745 mmol) in anhydrous THF (3.0 mL) was added LDA (99  $\mu\text{L}$ , 0.149 mmol, 1.5M in hexanes). After 15 minutes, *n*-BuLi (60  $\mu\text{L}$ , 0.149 mmol, 2.5M in hexanes) was added and the mixture stirred for a further 10 min. Methyl iodide (77  $\mu\text{L}$ , 1.24 mmol) was then added dropwise via syringe at  $-78\text{ }^{\circ}\text{C}$  and The reaction mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for 1.5 hr. The reaction was quenched at  $-78\text{ }^{\circ}\text{C}$  by the addition of saturated aqueous  $\text{NH}_4\text{Cl}$  (5.0 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 5 mL). The combined extracts were dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. Purification with flash column chromatography on silica gel (1 EtOAc: 6 Hex) provided 32.9 mg (64%) of (*S*)-(-)-**106**

$[\alpha]_{\text{D}}^{24} = -31.4^{\circ}$  ( $c = 0.15$ ,  $\text{CHCl}_3$ ).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) indicated a 55:45 mixture of the axial-Me and equatorial-Me conformers:  $\delta$  7.60-7.15 (m, 12H), 6.94-6.86 (m, 1H), 4.62-4.52 (two overlapping septets, 1H), 3.74 (d,  $J = 13.5$  Hz, 1H  $\times$  0.55 ax-Me), 3.22 (d,  $J = 13.5$  Hz, 1H  $\times$  0.55 ax-Me), 2.54 (d,  $J = 13.9$  Hz, 1H  $\times$  0.45 eq-Me), 2.39 (d,  $J = 13.8$  Hz, 1H  $\times$  0.45 eq-Me), 1.71 (s, 3H  $\times$  0.45 eq-Me), 1.54 (two overlapping doublets,  $J = 6.9$  Hz, 6H  $\times$  0.45 eq-Me), 1.33 (d,  $J = 7.1$  Hz, 3H  $\times$  0.55 ax-Me), 1.29 (d,  $J = 7.1$  Hz, 0.55 ax-Me), 0.72 (s, 3H  $\times$  0.55 ax-Me).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) was consistent with an approximate 1:1 mixture of axial-Me and equatorial-Me conformers (44 resonances found for a possible 2 x 22 unique carbons):  $\delta$

173.4, 172.1, 165.3, 164.9, 140.64, 140.58, 139.77, 139.7, 138.6, 137.0, 134.2, 133.9, 132.3, 131.1, 130.8, 130.43, 130.40, 129.9, 129.77, 129.71, 129.47, 129.45, 129.39, 129.2, 128.5, 128.4, 128.2, 127.5, 126.7, 126.2, 124.7, 124.6, 68.5, 66.3, 53.6, 53.3, 47.6, 37.7, 28.5, 22.3, 22.0, 20.8, 20.6, 17.6.

HRMS calcd. for C<sub>26</sub>H<sub>26</sub>ClN<sub>2</sub>O (M+1) 417.1734, found 417.1743 (+2.2 ppm, +0.9 mmu).

Chiral stationary phase HPLC (Chiralcel AD-H) indicated 95 %ee.

HPLC t<sub>r</sub> 20.1 min (*S*); t<sub>r</sub> 22.5 min (*R*) [Chiralpak AD-H (0.46 cm × 25 cm) (from Daicel Chemical Ind., Ltd.) Hexane/*i*-PrOH, 99/1, 1.0 mL/min, 95% ee.

**[(*S*)-(+)-107] 3-allyl-3-benzyl-7-chloro-1,3-dihydro-1-isopropyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one**

At -78 °C under nitrogen, to a stirred solution of (*S*)-(+)-**88** (20 mg, 0.0496 mmol) and HMPA (52 μL, 0.298 mmol) in anhydrous THF (3.0 mL) was added LDA (40 μL, 0.0595 mmol, 1.5M in hexanes). After 10 minutes, *n*-BuLi (24 μL, 0.0595 mmol, 2.5M in hexanes) was added and the mixture stirred for a further 10 min. Allyl bromide (43 μL, 0.496 mmol) was then added dropwise via syringe at -78 °C and The reaction mixture was stirred at -78 °C for 16 minutes. The reaction was quenched at -78 °C by the addition of saturated aqueous NH<sub>4</sub>Cl (5.0 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 5 mL). The combined extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Purification with flash column chromatography on silica gel (1 EtOAc: 8 Hex) provided 12.1 mg (57%) of (*S*)-(+)-**107**

[α]<sub>D</sub><sup>21</sup> = +72.1° (c = 0.315, CHCl<sub>3</sub>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) indicated a 60:40 mixture of conformers: δ 7.6-6.96 (several multiplets, 13H), 6.41-6.32 (m, 1H x 0.4), 5.71-5.62 (m, 1H x 0.6), 5.27 (apparent d, *J* =

10.0 Hz, 1H x 0.4), 5.23 (apparent d,  $J = 16.3$  Hz, 1H x 0.4), 5.01 (dd,  $J = 10.0, 1.6$  Hz, 1H x 0.6), 4.65 (dd,  $J = 16.8, 1.6$  Hz, 1H x 0.6), 4.56 (two overlapped septets,  $J = 6.9$  Hz, 1H), 3.67 (d,  $J = 14.6$  Hz, 1H x 0.6), 3.39 (d,  $J = 14.6$  Hz, 1H x 0.6), 3.03 (complex d,  $J = 14.7$  Hz, 1H x 0.4), 2.69 (dd,  $J = 14.7, 8.7$  Hz, 1H x 0.4), 2.46 (d,  $J = 14.3$  Hz, 1H x 0.4), 2.42 (d,  $J = 14.3$  Hz, 1H x 0.4), 1.88 (dd,  $J = 15.0, 6.8$  Hz, 1H x 0.6), 1.59-1.54 (m, 1H x 0.6), 1.52 (two overlapped doublets,  $J = 6.9$  Hz, 6H x 0.4), 1.30 (d,  $J = 7.0$  Hz, 3H x 0.6), 1.285 (d,  $J = 7.0$  Hz, 3H x 0.6).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) was consistent with a near 1:1 mixture of conformers (48 resonances found for 2 x 24 unique carbons):  $\delta$  171.9, 171.6, 165.0, 164.7, 140.4, 140.0, 139.8, 139.6, 138.5, 136.6, 135.9, 134.1, 133.6, 132.9, 132.3, 130.9, 130.50, 130.48, 130.4, 129.8, 129.7, 129.6, 129.5, 129.4, 129.3, 129.2, 128.43, 128.36, 128.2, 127.5, 126.6, 126.3, 124.74, 124.70, 118.4, 118.2, 70.4, 70.0, 53.4, 53.3, 43.2, 42.6, 34.5, 32.5, 22.1, 21.9, 20.5, 20.4.

HRMS: calcd for  $\text{C}_{28}\text{H}_{27}\text{N}_2\text{OCl}$  443.1890, found 443.1898 (+1.7 ppm, +0.8 mmu).

HPLC  $t_r$  13.1 min (*S*);  $t_r$  14.3 min (*R*) [Chiralpak AD-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) Hexane/*i*-PrOH, 99/1, 1.0 mL/min, 86% ee.

## 5.8. Alkylation on *N*-DAM benzodiazepines

### [(*R*)-(-)-108] 1-di(*p*-anisyl)methyl-3-benzyl-7-chloro-3-ethyl-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one

At  $-42^\circ\text{C}$  under nitrogen, to a stirred solution of (*S*)-**93** (200.0 mg, 0.382 mmol, 1.0 equiv) and HMPA (398  $\mu\text{L}$ , 2.29 mmol, 6.0 equiv) in anhydrous DME (11.0 mL) was added KHMDS (3.06 mL, 1.53 mmol, 4.0 equiv, 0.5 M in toluene). The resulting solution was stirred for a further 30.0 min at  $-42^\circ\text{C}$  and then transferred via a cannula into

a solution of benzyl bromide (457  $\mu\text{L}$ , 3.82 mmol, 10.0 equiv) and HMPA (200  $\mu\text{L}$ , 1.15 mmol) in dried DME (5.6 mL) at  $-42^\circ\text{C}$ . The reaction was stirred at  $-42^\circ\text{C}$  for 1.2 h at which the starting benzodiazepine (*S*)-**93** was consumed (TLC, 1:3 EtOAc/hexanes). The reaction was quenched at  $-42^\circ\text{C}$  with sat.  $\text{NH}_4\text{Cl}$  (aq) (5.0 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 5 mL). The combined organic extracts were dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (1:4 EtOAc/hexanes) to afford 152.0 mg (65%) of (*R*)-(-)-**108** as clear yellow oil.

$[\alpha]_D^{25} = -45.3$  ( $c = 0.78$ ,  $\text{CHCl}_3$ ).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) indicated a 70:30 mixture of axial-Et and equatorial-Et conformers  $\delta$  0.87 (t,  $^3J_{\text{HH}} = 7.2$  Hz, 3H x 0.70 ax-Et), 1.10 (q,  $^3J_{\text{HH}} = 7.6$  Hz, 1H x 0.70 ax-Et), 1.20 (q,  $^3J_{\text{HH}} = 7.2$  Hz, 1H x 0.70 ax-Et), 1.26 (t,  $^3J_{\text{HH}} = 3.6$  Hz, 3H x 0.30 eq-Et, overlapping with peak at 1.20), 2.20 (q,  $^3J_{\text{HH}} = 6.8$  Hz, 1H x 0.30 eq-Et), 2.39 (q,  $^3J_{\text{HH}} = 6.8$  Hz, 1H x 0.30 eq-Et), 2.54 (d,  $^2J_{\text{HH}} = 14.8$  Hz, 1H x 0.30 eq-Et), 2.75 (d,  $^2J_{\text{HH}} = 14.4$  Hz, 1H x 0.30 eq-Et), 3.52 (d,  $^2J_{\text{HH}} = 14.0$  Hz, 1H x 0.70 ax-Et), 3.68 (d,  $^2J_{\text{HH}} = 14.4$  Hz, 1H x 0.70 ax-Et), 3.77 (s, 3H), 3.82 (s, 3H x 0.30 one conformer), 3.85 (s, 3H x 0.70 one conformer), 6.67 (dd,  $^3J_{\text{HH}} = 8.8$  Hz,  $^4J_{\text{HH}} = 2.4$  Hz, 2H), 6.82 (d,  $^3J_{\text{HH}} = 8.8$  Hz, 1H), 6.89 (d,  $^4J_{\text{HH}} = 2.4$  Hz, 1H), 6.95 (m, 4H), 7.03 (d,  $^3J_{\text{HH}} = 8.4$  Hz, 1H), 7.06-7.10 (m, 2H), 7.16 (s, 1H x 0.70 ax-Et), 7.18 (s, 1H x 0.30 eq-Et), 7.24-7.32 (m, 4H), 7.34-7.40 (m, 4H), 7.45 (t,  $^3J_{\text{HH}} = 7.2$  Hz, 1H), 7.59 (d,  $^3J_{\text{HH}} = 7.2$  Hz, 1H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) was consistent with a 70:30 mixture of axial-Et and equatorial-Et conformers (53 resonances found for a possible 2 x 31 unique carbons):  $\delta$  8.44, 10.02, 21.66, 31.81, 35.23, 43.03, 55.31, 55.43, 66.21, 66.63, 70.71, 71.70, 113.65, 113.74,

113.96, 125.81, 126.25, 126.37, 126.72, 127.61, 128.18, 128.29, 128.33, 128.62, 128.90, 128.97, 129.07, 129.52, 129.59, 129.85, 129.94, 130.16, 130.32, 130.42, 130.70, 130.78, 131.03, 131.45, 131.56, 132.09, 132.31, 135.02, 136.91, 138.83, 139.15, 139.69, 139.79, 158.61, 158.76, 159.03, 164.87, 172.74, 172.96.

HRMS (FAB) calcd for C<sub>39</sub>H<sub>36</sub>N<sub>2</sub>O<sub>3</sub>Cl [M+H]<sup>+</sup>: 615.2414. Found: 615.2424 (+1.5 ppm, +0.9 mmu).

HPLC t<sub>r</sub> 27.2 min (*S*); t<sub>r</sub> 34.6 min (*R*) [Chiralpak AD (0.46 cm × 25 cm) (from Daicel Chemical Ind., Ltd.) Hexane/*i*-PrOH, 97/3, 1.0 mL/min, 94% ee.

**[(*R*)-(+)-109] 1-di(*p*-anisyl)methyl-7-chloro-3-cyano-3-ethyl-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one**

At -42°C under nitrogen, to a stirred solution of (*S*)-**93** (50.0 mg, 0.095 mmol, 1.0 equiv) and HMPA (100 μL, 0.572 mmol, 6.0 equiv) in anhydrous DME (2.8 mL) was added KHMDS (0.764 mL, 0.382 mmol, 4.0 equiv, 0.5 M in toluene). The resulting solution was stirred for a further 30.0 min at -42°C and then transferred via a cannula into a solution of *p*-toluenesulfonyl cyanide (37.1 mg, 0.950 mmol, 2.0 equiv) and HMPA (50 μL, 0.286 mmol) in dried DME (1.4 mL) at -42°C. The reaction was stirred at -42°C for 33 min at which the starting benzodiazepine (*S*)-**93** was consumed (TLC, 1:20 Et<sub>2</sub>O/DCM). The reaction was quenched at -42°C with sat. NH<sub>4</sub>Cl (aq) (5.0 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 5 mL). The combined organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (1<sup>st</sup> eluent 1:20 Et<sub>2</sub>O/DCM, 2<sup>nd</sup> eluent 1:3 EtOAc/hexanes) to afford 45.0 mg (86%) of (*R*)-(+)-**109** as clear yellow oil.

$[\alpha]_D^{25} = +143$  ( $c = 2.25$ , CHCl<sub>3</sub>).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.34 (t,  $^3J_{\text{HH}} = 7.5$  Hz, 3H), 2.48-2.54 (m, 1H), 2.63-2.69 (m, 1H), 3.76 (d, 2 conformers, 3H), 3.84 (d, 2 conformers, 3H), 6.66 (dd,  $^3J_{\text{HH}} = 8.0$  Hz,  $^4J_{\text{HH}} = 2.8$  Hz, 2H), 6.90-6.97 (m, 4H), 7.01 (s, 1H), 7.12 (s, 1H), 7.24-7.30 (m, 4H), 7.33-7.35 (m, 2H), 7.38-7.43 (m, 2H), 7.50-7.53 (m, 1H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) One conformer CN axial ( 26 resonances found for a possible 27 unique carbons):  $\delta$  8.39, 31.86, 55.33, 55.46, 63.28, 65.75, 113.81, 114.20, 115.02, 126.28, 128.55, 128.81, 129.40, 129.61, 129.89, 131.38, 131.55, 131.71, 131.76, 132.73, 137.43, 138.85, 159.06, 159.29, 164.90, 170.47. HRMS (FAB) calcd for  $\text{C}_{33}\text{H}_{29}\text{N}_3\text{O}_3\text{Cl}$   $[\text{M}+\text{H}]^+$ : 550.1897. Found: 550.1876 (-3.9 ppm, -2.1 mmu). HPLC  $t_r$  21.5 min (R);  $t_r$  26.5 min (S) [Chiralcel OD (0.46 cm  $\times$  25 cm) (from Daicel Chemical Ind., Ltd.) Hexane/*i*-PrOH, 99/1, 1.0 mL/min, 96% ee.

**[(R)-(-)-110] 3-allyl-1-di(*p*-anisyl)methyl-7-chloro-3-ethyl-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one**

At  $-42^\circ\text{C}$  under nitrogen, to a stirred solution of (*S*)-**93** (50.0 mg, 0.095 mmol, 1.0 equiv) and HMPA (100  $\mu\text{L}$ , 0.572 mmol, 6.0 equiv) in anhydrous DME (2.8 mL) was added KHMDS (0.764 mL, 0.382 mmol, 4.0 equiv, 0.5 M in toluene). The resulting solution was stirred for a further 30.0 min at  $-42^\circ\text{C}$  and then transferred via a cannula into a solution of allyl iodide (86.9  $\mu\text{L}$ , 0.950 mmol, 10.0 equiv) and HMPA (50  $\mu\text{L}$ , 0.286 mmol) in dried DME (1.4 mL) at  $-42^\circ\text{C}$ . The reaction was stirred at  $-42^\circ\text{C}$  for 2.2 h at which the starting benzodiazepine (*S*)-**93** was consumed (TLC, 1:3 EtOAc/hexanes). The reaction was quenched at  $-42^\circ\text{C}$  with sat.  $\text{NH}_4\text{Cl}$  (aq) (5.0 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  (3  $\times$  5 mL). The combined organic extracts were dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. The crude product was purified by flash

chromatography on silica gel (1:3 EtOAc/hexanes) to afford 31.1 mg (58%) of (*R*)-(-)-**110** as clear yellow oil.

$[\alpha]_D^{25} = -14.7$  (*c* 1.56, CHCl<sub>3</sub>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) indicated a 60:40 mixture of axial-Et and equatorial-Et conformers  
δ 0.77-0.82 (m, 3H × 0.60 ax-Et), 1.18-1.22 (m, 3H × 0.40 eq-Et), 1.25-1.32 (m, 1H × 0.60 ax-Et), 1.32-1.40 (m, 1H × 0.60 ax-Et, overlapping with peaks at 1.32-1.40), 2.00 (dd, <sup>2</sup>J<sub>HH</sub> = 13.8 Hz, <sup>3</sup>J<sub>HH</sub> = 8.0 Hz, 1H × 0.40 eq-Et), 2.12 (dd, <sup>2</sup>J<sub>HH</sub> = 14.8 Hz, <sup>3</sup>J<sub>HH</sub> = 6.4 Hz, 1H × 0.40 eq-Et), 2.21-2.27 (m, 1H × 0.40 eq-Et), 2.37 (dd, <sup>2</sup>J<sub>HH</sub> = 9.2 Hz, <sup>3</sup>J<sub>HH</sub> = 2.0 Hz, 1H × 0.40 eq-Et), 2.99 (dd, <sup>2</sup>J<sub>HH</sub> = 8.6 Hz, <sup>3</sup>J<sub>HH</sub> = 2.4 Hz, 1H × 0.60 ax-Et), 3.10 (d, <sup>2</sup>J<sub>HH</sub> = 13.2 Hz, 1H × 0.60 ax-Et), 3.76 (d, 2 conformers overlapping, 3H), 3.84 (m, 2 conformers overlapping, 3H), 4.76 (d, <sup>2</sup>J<sub>HH</sub> = 16.0 Hz, 1H × 0.40 eq-Et), 5.08 (d, <sup>2</sup>J<sub>HH</sub> = 9.2 Hz, 1H × 0.40 eq-Et), 5.19 (d, <sup>2</sup>J<sub>HH</sub> = 10.0 Hz, 1H × 0.60 ax-Et), 5.26 (d, <sup>2</sup>J<sub>HH</sub> = 17.2 Hz, 1H × 0.60 ax-Et), 5.68-5.76 (m, 1H × 0.40 eq-Et), 6.23-6.33 (m, 1H × 0.60 ax-Et), 6.66 (dd, <sup>3</sup>J<sub>HH</sub> = 13.3 Hz, <sup>4</sup>J<sub>HH</sub> = 2.4 Hz, 2H), 6.89-6.97 (m, 4H), 6.99-7.02 (m, 2H), 7.08-7.13 (m, 1H), 7.15-7.18 (m, 1H), 7.24-7.27 (m, 2H), 7.31-7.39 (m, 4H), 7.45 (t, <sup>3</sup>J<sub>HH</sub> = 6.4 Hz, 1H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>) was consistent with a 60:40 mixture of axial-Et and equatorial-Et conformers (48 resonances found for a possible 2 × 29 unique carbons): δ 8.12, 9.22, 22.03, 31.26, 33.15, 42.80, 55.31, 55.42, 65.95, 66.01, 69.62, 70.76, 113.59, 113.62, 113.79, 113.92, 117.63, 118.30, 125.77, 125.96, 128.28, 128.72, 128.92, 129.06, 129.45, 129.73, 129.94, 130.00, 130.40, 130.70, 130.77, 131.47, 133.28, 134.51, 134.57, 135.97, 139.29, 139.38, 139.57, 139.70, 158.69, 158.72, 158.94, 158.97, 165.17, 165.46, 172.69, 172.74.

HRMS (FAB) calcd for C<sub>35</sub>H<sub>34</sub>N<sub>2</sub>O<sub>3</sub>Cl [M+H]<sup>+</sup>: 565.2258. Found: 565.2281 (+4.1 ppm, +2.3 mmu).

HPLC t<sub>r</sub> 21.2 min (*S*); t<sub>r</sub> 23.7 min (*R*) [Chiralcel OD (0.46 cm × 25 cm) (from Daicel Chemical Ind., Ltd.) Hexane/*i*-PrOH, 99/1, 1.0 mL/min, 94% ee.

**[(*S*)-(+)-111] 1-di(*p*-anisyl)methyl-3-benzyl-7-chloro-1,3-dihydro-3-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one**

At -42°C under nitrogen, to a stirred solution of (*S*)-**92** (50.0 mg, 0.085 mmol, 1.0 equiv) and HMPA (90 μL, 0.512 mmol, 6.0 equiv) in anhydrous DME (2.4 mL) was added KHMDS (0.682 mL, 0.341 mmol, 4.0 equiv, 0.5 M in toluene). The resulting solution was stirred for a further 30.0 min at -42°C and then transferred via a cannula into a solution of methyl iodide (53 μL, 0.853 mmol, 10.0 equiv) and HMPA (45 μL, 0.256 mmol) in dried DME (1.2 mL) at -42°C. The reaction was stirred at -42°C for 1.4 h at which the starting benzodiazepine (*S*)-**92** was consumed (TLC, 1:3 EtOAc/hexanes). The reaction was quenched at -42°C with sat. NH<sub>4</sub>Cl (aq) (5.0 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 5 mL). The combined organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (1:3 EtOAc/hexanes) to afford 40.5 mg (79%) of (*S*)-(+)-**111** as white foam.

$[\alpha]_D^{25} = +39.6$  ( $c = 2.03$ , CHCl<sub>3</sub>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) indicated a 65:35 mixture of axial-Me and equatorial-Me conformers δ 0.91 (s, 3H × 0.65 ax-Me), 1.88 (3H × 0.35 eq-Me), 2.61 (d, <sup>2</sup>J<sub>HH</sub> = 14.0 Hz, 1H × 0.35 eq-Me), 2.78 (d, <sup>2</sup>J<sub>HH</sub> = 14.0 Hz, 1H × 0.35), 3.30 (d, <sup>2</sup>J<sub>HH</sub> = 13.6 Hz, 1H × 0.65), 3.77 (d, 2 conformers, 3H), 3.81-3.85 (m, 4H), 6.677 (dd, <sup>3</sup>J<sub>HH</sub> = 8.6 Hz, <sup>4</sup>J<sub>HH</sub> = 1.6 Hz, 2H),

6.86-7.00 (m, 6H), 7.05-7.17 (m, 5H), 7.24-7.29 (m, 2H), 7.31-7.40 (m, 5H), 7.46 (t,  $^3J_{\text{HH}} = 6.8$  Hz, 1H), 7.59 (d,  $^3J_{\text{HH}} = 7.4$  Hz, 1H);

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) was consistent with a 65:35 mixture of axial-Me and equatorial-Me conformers (53 resonances found for a possible  $2 \times 30$  unique carbons):  $\delta$  17.72, 29.33, 38.77, 47.68, 55.32, 55.43, 55.46, 65.38, 66.23, 66.29, 68.49, 113.62, 113.64, 113.86, 114.02, 125.50, 126.30, 126.81, 127.59, 128.26, 128.29, 128.40, 128.86, 128.99, 129.43, 129.52, 129.62, 129.98, 130.07, 130.29, 130.32, 130.43, 130.47, 130.59, 130.64, 130.71, 131.49, 132.26, 134.54, 134.63, 136.79, 138.53, 139.57, 139.66, 139.79, 158.66, 158.75, 158.95, 159.02, 165.39, 165.85, 172.67, 173.30;

HRMS (FAB) calcd for  $\text{C}_{38}\text{H}_{34}\text{N}_2\text{O}_3\text{Cl}$   $[\text{M}+\text{H}]^+$ : 601.2258. Found: 601.2257 (-0.1 ppm, -0.1 mmu).

HPLC  $t_r$  22.1 min (*S*);  $t_r$  24.7 min (*R*) [Chiralcel OD (0.46 cm  $\times$  25 cm) (from Daicel Chemical Ind., Ltd.) Hexane/*i*-PrOH, 99/1, 1.0 mL/min, >99.5% ee.

**[(*R*)-(+)-112] 1-di(*p*-anisyl)methyl-3-benzyl-7-chloro-3-cyano-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazpin-2-one**

At  $-42^\circ\text{C}$  under nitrogen, to a stirred solution of (*S*)-**92** (50.0 mg, 0.085 mmol, 1.0 equiv) and HMPA (90  $\mu\text{L}$ , 0.512 mmol, 6.0 equiv) in anhydrous DME (2.4 mL) was added KHMDS (0.682 mL, 0.341 mmol, 4.0 equiv, 0.5 M in toluene). The resulting solution was stirred for a further 30.0 min at  $-42^\circ\text{C}$  and then transferred via a cannula into a solution of *p*-toluenesulfonyl cyanide (58.4 mg, 0.320 mmol, 2.0 equiv) and HMPA (45  $\mu\text{L}$ , 0.256 mmol) in dried DME (1.2 mL) at  $-42^\circ\text{C}$ . The reaction was stirred at  $-42^\circ\text{C}$  for 47 min at which the starting benzodiazepine (*S*)-**92** was consumed (TLC, 1:20  $\text{Et}_2\text{O}/\text{DCM}$ ). The reaction was quenched at  $-42^\circ\text{C}$  with sat.  $\text{NH}_4\text{Cl}$  (aq) (5.0 mL) and

extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 5 mL). The combined organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (1<sup>st</sup> eluent 1:20 Et<sub>2</sub>O/DCM, 2<sup>nd</sup> eluent 1:3 EtOAc/hexanes) to afford 35.4 mg (68%) of (*R*)-(+)-**112** as clear yellow oil.

$[\alpha]_D^{25} = +122$  ( $c = 1.77$ , CHCl<sub>3</sub>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.61 (d, <sup>2</sup>J<sub>HH</sub> = 13.6 Hz, 1H), 3.76 (s, 3H), 3.86 (s, 3H), 4.05 (d, <sup>2</sup>J<sub>HH</sub> = 14.0 Hz, 1H), 6.67 (d, <sup>2</sup>J<sub>HH</sub> = 8.4 Hz, 2H), 6.92-6.99 (m, 5H), 7.05 (s, 1H), 7.20-7.34 (m, 6H), 7.37-7.41 (m, 4H), 7.51 (t, <sup>3</sup>J<sub>HH</sub> = 7.2 Hz, 1H), 7.60 (d, <sup>3</sup>J<sub>HH</sub> = 7.6 Hz, 2H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>) One conformer CN axial (29 resonances found for a possible 30 unique carbons): δ 43.75, 55.34, 55.48, 63.30, 65.97, 113.85, 114.24, 114.64, 126.18, 127.62, 128.12, 128.52, 128.86, 129.36, 129.44, 129.55, 129.99, 131.42, 131.52, 131.74, 131.82, 132.78, 134.54, 137.51, 138.82, 159.22, 159.34, 164.27, 170.20.

HRMS (FAB) calcd for C<sub>38</sub>H<sub>31</sub>N<sub>3</sub>O<sub>3</sub>Cl [M+H]<sup>+</sup>: 612.2054. Found: 612.1997 (-9.3 ppm, -5.7 mmu).

HPLC t<sub>r</sub> 26.5 min (*R*); t<sub>r</sub> 32.7 min (*S*) [Chiralcel OD (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) Hexane/*i*-PrOH, 99/1, 1.0 mL/min, 96% ee.

**[(*S*)-(+)-113] 3-allyl-1-di(*p*-anisyl)methyl-3-benzyl-7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one**

At -42°C under nitrogen, to a stirred solution of (*S*)-**92** (50.0 mg, 0.085 mmol, 1.0 equiv) and HMPA (90 μL, 0.512 mmol, 6.0 equiv) in anhydrous DME (2.4 mL) was added KHMDS (0.682 mL, 0.341 mmol, 4.0 equiv, 0.5 M in toluene). The resulting solution was stirred for a further 30.0 min at -42°C and then transferred via a cannula into a solution of allyl bromide (74 μL, 0.850 mmol, 10.0 equiv) and HMPA (45 μL, 0.256

mmol) in dried DME (1.2 mL) at -42°C. The reaction was stirred at -42°C for 1.9 h at which the starting benzodiazepine (*S*)-**92** was consumed (TLC, 1:3 EtOAc/hexanes). The reaction was quenched at -42°C with sat. NH<sub>4</sub>Cl (aq) (5.0 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 5 mL). The combined organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (1<sup>st</sup> eluent 1:3 EtOAc/hexanes, 2<sup>nd</sup> eluent 1:4 EtOAc/hexanes) to afford 30.9 mg (58%) of (*S*)-(+)-**113** as clear yellow oil.

$[\alpha]_D^{25} = +68.2$  ( $c = 1.55$ , CHCl<sub>3</sub>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) indicated a 65:35 mixture of axial-allyl and equatorial-allyl conformers  $\delta$  1.80 (dd, <sup>2</sup> $J_{\text{HH}} = 14.8$  Hz, <sup>3</sup> $J_{\text{HH}} = 8.4$  Hz, 1H  $\times$  0.65 ax-allyl), 2.03 (dd, <sup>2</sup> $J_{\text{HH}} = 15.2$  Hz, <sup>3</sup> $J_{\text{HH}} = 5.6$  Hz, 1H  $\times$  0.65 ax-allyl), 2.46 (d, <sup>2</sup> $J_{\text{HH}} = 14.4$  Hz, 1H  $\times$  0.35 eq-allyl), 2.87 (d, <sup>2</sup> $J_{\text{HH}} = 14.4$  Hz, 1H  $\times$  0.35 eq-allyl), 3.03 (dd, <sup>2</sup> $J_{\text{HH}} = 16.0$  Hz, <sup>3</sup> $J_{\text{HH}} = 8.8$  Hz, 1H  $\times$  0.35 eq-allyl), 3.22 (dd, <sup>2</sup> $J_{\text{HH}} = 5.0$  Hz, <sup>3</sup> $J_{\text{HH}} = 0.8$  Hz, 1H  $\times$  0.35 eq-allyl), 3.53 (d, <sup>2</sup> $J_{\text{HH}} = 14.0$  Hz, 1H  $\times$  0.65 ax-allyl), 3.75 (d, <sup>2</sup> $J_{\text{HH}} = 8.4$  Hz, 1H  $\times$  0.65 ax-allyl), 3.76 (s, 3H  $\times$  0.35 one conformer, overlapping with peak at 3.75), 3.77 (s, 3H  $\times$  0.65 one conformer), 3.82 (s, 3H  $\times$  0.35 one conformer), 3.85 (s, 3H  $\times$  0.65 one conformer), 4.69 (d, <sup>2</sup> $J_{\text{HH}} = 16.0$  Hz, 1H  $\times$  0.65 ax-allyl), 5.65 (d, <sup>2</sup> $J_{\text{HH}} = 10.4$  Hz, 1H  $\times$  0.65 ax-allyl), 5.27-5.31 (m, 2H  $\times$  0.35 eq-allyl), 5.85-5.91 (m, 1H  $\times$  0.65 ax-allyl), 6.31-6.42 (m, 1H  $\times$  0.35 eq-allyl), 6.65 (t, <sup>3</sup> $J_{\text{HH}} = 7.6$  Hz, 2H), 6.79 (d, <sup>3</sup> $J_{\text{HH}} = 8.4$  Hz, 1H), 6.90-6.97 (m, 6H), 7.04 (s, 1H), 7.08-7.18 (m, 2H), 7.24-7.26 (m, 1H), 7.28-7.40 (m, 7H), 7.44-7.48 (m, 1H), 7.61 (d, <sup>3</sup> $J_{\text{HH}} = 6.8$  Hz, 1H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>) was consistent with a 65:35 mixture of axial-allyl and equatorial-allyl conformers (59 resonances found for a possible 2  $\times$  32 unique carbons):  $\delta$  33.51, 36.13,

43.64, 44.10, 55.31, 55.40, 55.44, 66.14, 66.47, 70.34, 70.74, 113.61, 113.76, 113.80, 118.53, 118.78, 126.25, 126.39, 126.70, 126.81, 127.66, 128.23, 128.31, 128.35, 128.75, 128.91, 129.02, 129.13, 129.55, 129.64, 129.84, 129.92 (2 overlapping peaks), 130.12, 130.43, 130.55, 130.58, 130.64, 130.69, 130.84, 131.55, 131.64, 132.36, 133.36, 134.64, 135.04, 135.98, 136.78, 138.50, 138.97, 139.35, 139.57, 139.72, 158.59, 158.75, 159.02, 165.23, 165.55, 172.23, 172.48.

HRMS (FAB) calcd for  $C_{40}H_{36}N_2O_3Cl$   $[M+H]^+$ : 627.2414. Found: 627.2411 (-0.6 ppm, -0.4 mmu).

HPLC  $t_r$  22.1 min (*S*);  $t_r$  31.0 min (*R*) [Chiralpak AD (0.46 cm × 25 cm) (from Daicel Chemical Ind., Ltd.) Hexane/*i*-PrOH, 97/3, 1.0 mL/min, 92% ee.

**[(*R*)-(-)-114] 1-di(*p*-anisyl)methyl-7-chloro-3-cyano-1,3-dihydro-5-phenyl-3-(3-thiomethyl)ethyl-2*H*-1,4-benzodiazepin-2-one**

At -42°C under nitrogen, to a stirred solution of (*S*)-**94** (50.0 mg, 0.088 mmol, 1.0 equiv) and HMPA (92 μL, 0.528 mmol, 6.0 equiv) in anhydrous DME (2.6 mL) was added KHMDS (0.704 mL, 0.352 mmol, 4.0 equiv, 0.5 M in toluene). The resulting solution was stirred for a further 30.0 min at -42°C and then transferred via a cannula into a solution of *p*-toluenesulfonyl cyanide (31.9 mg, 0.176 mmol, 2.0 equiv) and HMPA (46 μL, 0.264 mmol) in dried DME (1.3 mL) at -42°C. The reaction was stirred at -42°C for 30 min at which the starting benzodiazepine (*S*)-**94** was consumed (TLC, 1:3 EtOAc/hexanes). The reaction was quenched at -42°C with sat.  $NH_4Cl$  (aq) (5.0 mL) and extracted with  $CH_2Cl_2$  (3 x 5 mL). The combined organic extracts were dried over anhydrous  $Na_2SO_4$ , filtered, and concentrated under reduced pressure. The crude product

was purified by flash chromatography on silica gel (1:3 EtOAc/hexanes) to afford 41.7 mg (80%) of (*R*)-(-)-**114** as clear yellow oil.

$[\alpha]_D^{25} = -121$  (*c* 2.09, CHCl<sub>3</sub>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.24 (s, 3H), 2.75-3.04 (m, 4H), 3.77 (s, 3H), 3.85 (s, 3H), 6.66 (d, <sup>2</sup>*J*<sub>HH</sub> = 8.8 Hz, 2H), 6.89-6.99 (m, 5H), 7.12 (s, 1H), 7.24-7.28 (m, 4H), 7.32-7.34 (m, 2H), 7.41 (t, <sup>3</sup>*J*<sub>HH</sub> = 8.0 Hz, 2H), 7.51-7.55 (m, 1H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>) One conformer CN axial ( 26 resonances found for a possible 28 unique carbons): δ 15.67, 28.54, 38.52, 55.34, 55.47, 62.04, 65.91, 113.84, 114.23, 114.73, 126.33, 128.58, 128.79, 129.25, 129.43, 129.94, 131.39, 131.74, 131.90, 132.61, 137.15, 138.66, 159.11, 159.34, 163.69, 170.63.

HRMS (FAB) calcd for C<sub>38</sub>H<sub>31</sub>N<sub>3</sub>O<sub>3</sub>Cl [M+H]<sup>+</sup>: 612.2054. Found: 612.1997 (-9.3 ppm, -5.7 mmu).

HPLC *t*<sub>r</sub> 9.0 min (*R*); *t*<sub>r</sub> 14.3 min (*S*) [Chiralcel OD (0.46 cm × 25 cm) (from Daicel Chemical Ind., Ltd.) Hexane/*i*-PrOH, 90/10, 1.0 mL/min, 87% ee.

**[(*S*)-(-)-**115**] 1-di(*p*-anisyl)methyl-7-chloro-1,3-dihydro-3-methyl-5-phenyl-3-(2-thiomethyl)ethyl-2*H*-1,4-benzodiazepin-2-one**

At -42°C under nitrogen, to a stirred solution of (*S*)-**94** (50.0 mg, 0.088 mmol, 1.0 equiv) and HMPA (92 μL, 0.528 mmol, 6.0 equiv) in anhydrous DME (2.6 mL) was added KHMDS (0.704 mL, 0.352 mmol, 4.0 equiv, 0.5 M in toluene). The resulting solution was stirred for a further 30.0 min at -42°C and then transferred via a cannula into a solution of methyl iodide (55 μL, 0.880 mmol, 10.0 equiv) and HMPA (46 μL, 0.264 mmol) in dried DME (1.3 mL) at -42°C. The reaction was stirred at -42°C for 1.3 h at which the starting benzodiazepine (*S*)-**94** was consumed (TLC, 1:3 EtOAc/hexanes). The

reaction was quenched at  $-42^{\circ}\text{C}$  with sat.  $\text{NH}_4\text{Cl}$  (aq) (5.0 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 5 mL). The combined organic extracts were dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (1:3 EtOAc/hexanes) to afford 38.3 mg (67%) of (*S*)-(-)-**115** as clear yellow oil.

$[\alpha]_D^{25} = -72.6$  ( $c = 1.92$ ,  $\text{CHCl}_3$ ).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) indicated a 65:35 mixture of axial-Me and equatorial-Me conformers  $\delta$  1.04 (s, 3H  $\times$  0.65 ax-Me), 1.59-1.76 (m, 2H  $\times$  0.35 eq-Me), 1.78 (s, 3H  $\times$  0.35 eq-Me), 1.91 (s, 3H  $\times$  0.35 eq-Me), 2.20 (s, 3H  $\times$  0.65 ax-Me), 2.23-2.48 (m, 2H  $\times$  0.65 ax-Me), 2.65-2.73 (m, 2H  $\times$  0.35 eq-Me), 2.84-3.00 (m, 2H  $\times$  0.65 ax-Me), 3.76 (d, 2 conformers, 3H), 3.84 (s, 3H), 6.67 (dd,  $^3J_{\text{HH}} = 8.6$  Hz,  $^4J_{\text{HH}} = 3.6$  Hz, 2H), 6.92-6.97 (m, 4H), 6.99-7.03 (m, 2H), 7.10-7.24 (m, 4H), 7.32-7.40 (m, 4H), 7.44-7.46 (m, 1H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) was consistent with a 65:35 mixture of axial-Me and equatorial-Me conformers (47 resonances found for a possible  $2 \times 28$  unique carbons):  $\delta$  15.37, 15.63, 18.63, 28.36, 29.23, 29.40, 32.74, 43.32, 55.31, 55.43, 65.40, 65.87, 65.98, 67.55, 113.61, 113.67, 113.99, 125.64, 125.85, 128.29, 128.38, 128.84, 128.88, 128.92, 128.98, 129.45, 129.57, 129.91, 130.06, 130.26, 130.51 (2 overlapping peaks), 130.58, 130.60, 131.38, 131.43, 132.32, 134.13, 139.24, 139.37, 139.46, 158.74, 158.94, 159.02, 165.50, 165.96, 172.50, 172.99.

HRMS (FAB) calcd for  $\text{C}_{34}\text{H}_{34}\text{N}_2\text{O}_3\text{ClS}$   $[\text{M}+\text{H}]^+$ : 585.1979. Found: 585.2003 (+4.2 ppm, +2.4 mmu).

HPLC  $t_r$  20.5 min (*R*);  $t_r$  25.1 min (*S*) [Chiralpak AD (0.46 cm  $\times$  25 cm) (from Daicel Chemical Ind., Ltd.) Hexane/*i*-PrOH, 97/3, 1.0 mL/min, 87% ee

**[(S)-(-)-116] 3-allyl-1-di(*p*-anisyl)methyl-7-chloro-1,3-dihydro-5-phenyl-3-(2-thiomethyl)ethyl-2*H*-1,4-benzodiazepin-2-one**

At -42°C under nitrogen, to a stirred solution of (*S*)-**94** (50.0 mg, 0.088 mmol, 1.0 equiv) and HMPA (92 µL, 0.528 mmol, 6.0 equiv) in anhydrous DME (2.6 mL) was added KHMDS (0.704 mL, 0.352 mmol, 4.0 equiv, 0.5 M in toluene). The resulting solution was stirred for a further 30.0 min at -42°C and then transferred via a cannula into a solution of allyl bromide (77 µL, 0.880 mmol, 10.0 equiv) and HMPA (46 µL, 0.264 mmol) in dried DME (1.3 mL) at -42°C. The reaction was stirred at -42°C for 3.4 h (TLC, 1:3 EtOAc/hexanes). The reaction was quenched at -42°C with sat. NH<sub>4</sub>Cl (aq) (5.0 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 5 mL). The combined organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (1:3 EtOAc/hexanes) to afford 17.6 mg (33%) of (*S*)-(-)-**116** as clear yellow oil.

$[\alpha]_D^{25} = -71.4$  ( $c = 0.88$ , CHCl<sub>3</sub>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) indicated a 60:40 mixture of axial-allyl and equatorial-allyl conformers δ 1.52-1.73 (m, 2H x 0.40 eq-allyl), 1.81 (s, 3H x 0.40 eq-allyl), 2.09-2.11 (m, 2H x 0.60 ax-allyl), 2.20 (s, 3H x 0.60 ax-allyl), 2.33-2.41 (m, 2H x 0.60 ax-allyl), 2.67-2.74 (m, 2H x 0.40 eq-allyl), 2.88-2.96 (m, 2H x 0.60 ax-allyl), 3.05 (dd, <sup>2</sup>J<sub>HH</sub> = 14.4 Hz, <sup>3</sup>J<sub>HH</sub> = 8.0 Hz, 1H x 0.40 eq-allyl), 3.11 (dd, <sup>2</sup>J<sub>HH</sub> = 14.6 Hz, <sup>3</sup>J<sub>HH</sub> = 5.6 Hz, 1H x 0.40 eq-allyl), 3.76 (s, 3H), 3.84-3.85 (d, 2 overlapping conformers, 3H), 4.76 (d, <sup>2</sup>J<sub>HH</sub> = 17.0 Hz, 1H x 0.60 ax-allyl), 5.09 (d, <sup>2</sup>J<sub>HH</sub> = 9.8 Hz, 1H x 0.60 ax-allyl), 5.21 (d, <sup>2</sup>J<sub>HH</sub> = 10.4 Hz, 1H x 0.40 eq-allyl), 5.26 (d, <sup>2</sup>J<sub>HH</sub> = 10.0 Hz, 1H x 0.40 eq-allyl), 5.65-5.76 (m, 1H x 0.60 ax-allyl), 6.23-6.33 (m, 1H x 0.40 eq-allyl), 6.66 (d, <sup>3</sup>J<sub>HH</sub> = 8.8 Hz, 2H), 6.90-6.96 (m, 5H),

7.02 (d,  $^4J_{\text{HH}} = -2.4$  Hz, 1H), 7.10-7.18 (m, 2H), 7.23-7.26 (d,  $^3J_{\text{HH}} = 10.8$  Hz, 2H), 7.30-7.39 (m, 4H), 7.46 (t,  $^3J_{\text{HH}} = 6.8$  Hz, 1H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) was consistent with a 60:40 mixture of axial-allyl and equatorial-allyl conformers (48 resonances found for a possible  $2 \times 30$  unique carbons):  $\delta$  15.42, 15.64, 28.99, 29.35, 29.40, 35.31, 39.85, 43.74, 55.31, 55.43, 66.08, 69.55, 69.58, 113.61, 113.67, 113.85, 113.99, 118.15, 118.86, 125.97, 128.27, 128.35, 128.88, 128.92, 129.00, 129.45, 129.86, 130.05, 130.23, 130.40, 130.52, 130.61, 131.44, 132.64, 134.28, 135.55, 139.16, 139.20, 139.28, 139.34, 158.74, 158.79, 158.98, 159.03, 165.50, 165.65, 171.99, 172.26.

HRMS (FAB) calcd for  $\text{C}_{36}\text{H}_{36}\text{N}_2\text{O}_3\text{ClS}$   $[\text{M}+\text{H}]^+$ : 611.2135. Found: 611.2168 (+5.4 ppm, +3.3 mmu).

HPLC  $t_{\text{r}}$  16.7 min (*S*);  $t_{\text{r}}$  20.7 min (*R*) [Chiralpak AD-H (0.46 cm  $\times$  25 cm) (from Daicel Chemical Ind., Ltd.) Hexane/*i*-PrOH, 97/3, 1.0 mL/min, 72% ee.

**[(*R*)-(+)-117] 1-di(*p*-anisyl)methyl-7-chloro-3-cyano-3-(2-methylpropyl)-5-phenyl-2*H*-1,4-benzodiazepin-2-one**

At  $-42^\circ\text{C}$  under nitrogen, to a stirred solution of (*S*)-**95** (50.0 mg, 0.091 mmol, 1.0 equiv) and HMPA (94  $\mu\text{L}$ , 0.543 mmol, 6.0 equiv) in anhydrous DME (2.6 mL) was added KHMDS (0.724 mL, 0.362 mmol, 4.0 equiv, 0.5 M in toluene). The resulting solution was stirred for a further 30.0 min at  $-42^\circ\text{C}$  and then transferred via a cannula into a solution of *p*-toluenesulfonyl cyanide (33.8 mg, 0.187 mmol, 2.1 equiv) and HMPA (47  $\mu\text{L}$ , 0.272 mmol) in dried DME (1.3 mL) at  $-42^\circ\text{C}$ . The reaction was stirred at  $-42^\circ\text{C}$  for 2.6 h (TLC, 1:20 EtOAc/hexanes). The reaction was quenched at  $-42^\circ\text{C}$  with sat.  $\text{NH}_4\text{Cl}$  (aq) (5.0 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  (3  $\times$  5 mL). The combined organic extracts

were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure.

The crude product was purified by flash chromatography on silica gel (1:3 EtOAc/hexanes) to afford 8.2 mg (16%) of (*R*)-(+)-**117** as clear yellow oil.

$[\alpha]_D^{25} = +144$  (*c* 0.41, CHCl<sub>3</sub>),

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.14 (d, <sup>3</sup>J<sub>HH</sub> = 7.0 Hz, 3H), 1.22 (d, <sup>3</sup>J<sub>HH</sub> = 7.0 Hz, 3H), 2.23 (m, 1H), 2.45 (dd, <sup>2</sup>J<sub>HH</sub> = 14.5 Hz, <sup>3</sup>J<sub>HH</sub> = 5.5 Hz, 1H), 2.62 (dd, <sup>2</sup>J<sub>HH</sub> = 14.0 Hz, <sup>3</sup>J<sub>HH</sub> = 7.5 Hz, 1H), 3.77 (s, 3H), 3.85 (s, 3H), 6.66 (d, <sup>3</sup>J<sub>HH</sub> = 8.5 Hz, 2H), 6.91 (d, <sup>3</sup>J<sub>HH</sub> = 8.5 Hz, 2H), 6.95 (d, <sup>3</sup>J<sub>HH</sub> = 8.5 Hz, 2H), 7.01 (s, 1H), 7.12 (d, <sup>4</sup>J<sub>HH</sub> = 2.5 Hz, 1H), 7.24-7.27 (m, 4H), 7.29-7.32 (m, 2H), 7.40 (t, <sup>3</sup>J<sub>HH</sub> = 8.0 Hz, 2H), 7.52 (t, <sup>3</sup>J<sub>HH</sub> = 7.5 Hz, 1H);

<sup>13</sup>C NMR (CDCl<sub>3</sub>) One conformer CN axial ( 30 resonances found for a possible 29 unique carbons): δ 24.04, 24.07, 25.23, 29.79, 45.75, 55.33, 55.46, 62.23, 65.81, 113.80, 114.17, 115.25, 126.17, 128.55, 128.81, 129.36, 129.42, 129.61, 129.90, 131.39, 131.51, 131.66, 131.77, 132.80, 137.50, 138.89, 159.04, 159.27, 164.14, 169.79;

HRMS (FAB) calcd for C<sub>35</sub>H<sub>33</sub>N<sub>3</sub>O<sub>3</sub>Cl [M+H]<sup>+</sup>: 578.2210. Found: 578.2243 (+5.6 ppm, +3.3 mmu).

HPLC t<sub>r</sub> 16.3 min (*R*); t<sub>r</sub> 22.2 min (*S*) [Chiralcel OD (0.46 cm × 25 cm) (from Daicel Chemical Ind., Ltd.) Hexane/*i*-PrOH, 99/1, 1.0 mL/min, >99.5% ee.

**[(*R*)-(-)-118] 1-di(*p*-anisyl)methyl-3-benzyl-1,3-dihydro-3-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one**

At -42°C under nitrogen, to a stirred solution of (*S*)-**96** (50.0 mg, 0.105 mmol, 1.0 equiv) and HMPA (110 μL, 0.630 mmol, 6.0 equiv) in anhydrous DME (3.1 mL) was added KHMDS (0.840 mL, 0.420 mmol, 4.0 equiv, 0.5 M in toluene). The resulting solution was stirred for a further 30.0 min at -42°C and then transferred via a cannula into a

solution of benzyl bromide (126  $\mu\text{L}$ , 1.05 mmol, 10.0 equiv) and HMPA (55  $\mu\text{L}$ , 0.315 mmol) in dried DME (1.6 mL) at  $-42^\circ\text{C}$ . The reaction was stirred at  $-42^\circ\text{C}$  for 1.5 h at which the starting benzodiazepine (*S*)-**96** was consumed (TLC, 1:3 EtOAc/hexanes). The reaction was quenched at  $-42^\circ\text{C}$  with sat.  $\text{NH}_4\text{Cl}$  (aq) (5.0 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 5 mL). The combined organic extracts were dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (1:3 EtOAc/hexanes) to afford 46.5 mg (78%) of (*R*)-(-)-**118** as white foam.

$[\alpha]_D^{25} = -10.8$  ( $c = 0.023$ ,  $\text{CHCl}_3$ ).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) indicated a 60:40 mixture of axial-methyl and equatorial-methyl conformers  $\delta$  0.87 (s, 3H x 0.60 ax-methyl), 1.87 (s, 3H x 0.40 eq-methyl), 2.59 (d,  $^2J_{\text{HH}} = 14.0$  Hz, 1H x 0.40 eq-methyl), 2.75 (d,  $^2J_{\text{HH}} = 13.5$  Hz, 1H x 0.40 eq-methyl), 3.31 (d,  $^2J_{\text{HH}} = 13.5$  Hz, 1H x 0.60 ax-methyl), 3.71 (d,  $^2J_{\text{HH}} = 11$  Hz, 1H x 0.60 ax-methyl), 3.74 (s, 3H x 0.60, one conformer), 3.75 (s, 3H x 0.40, one conformer), 3.83 (s, 3H x 0.40, one conformer), 3.85 (s, 3H x 0.40, one conformer), 6.67 (t,  $^3J_{\text{HH}} = 7.5$  Hz, 2H), 6.86-6.97 (m, 5H), 7.01 (d,  $^3J_{\text{HH}} = 7.0$  Hz, 2H), 7.09-7.16 (m, 2H), 7.20-7.29 (m, 5H), 7.32-7.36 (m, 5H), 7.42-7.44 (m, 1H), 7.60 (d,  $^3J_{\text{HH}} = 7.5$  Hz, 1H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) was consistent with a 60:40 mixture of axial-methyl and equatorial-methyl conformers (57 resonances found for a possible 2 x 38 unique carbons):  $\delta$  17.51, 29.16, 38.33, 47.74, 55.31, 55.41, 55.44, 65.64, 66.10, 66.59, 68.36, 113.45, 113.48, 113.57, 113.75, 113.90, 124.07, 124.14, 124.69, 124.85, 126.19, 126.65, 127.55, 128.09, 128.13, 128.21, 128.98, 129.09, 129.42, 129.61, 129.73, 129.96, 130.12, 130.19, 130.35, 130.84, 130.98, 131.01, 131.22, 131.51, 132.32, 133.12, 133.18, 137.09, 138.86, 140.39,

140.49, 141.07, 141.19, 158.57, 158.64, 158.80, 158.88, 166.69, 167.24, 172.96, 173.61.

HRMS (FAB) calcd for C<sub>38</sub>H<sub>35</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 567.2648. Found: 567.2646 (-0.3 ppm, -0.2 mmu).

HPLC t<sub>r</sub> 16.3 min (*R*); t<sub>r</sub> 19.7 min (*S*) [Chiralcel OD (0.46 cm × 25 cm) (from Daicel Chemical Ind., Ltd.) Hexane/*i*-PrOH, 97/3, 1.0 mL/min, 98% ee.

**[(*R*)-(-)-119] 3-benzyl-7-chloro-3-ethyl-1,3-dihydro-3-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one**

Compound (*R*)-(-)-**108** (144.7 mg, 0.236 mmol) was dissolved in a solution of 25% TFA in CH<sub>2</sub>Cl<sub>2</sub> (8.0 mL) and stirred for 35 min at which the starting benzophenone (*R*)-(-)-**108** was consumed (TLC, 1:3 EtOAc/hexanes). The reaction was quenched with H<sub>2</sub>O (10 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 mL). The combined organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (1<sup>st</sup> eluent 1:4 EtOAc/hexanes, 2<sup>nd</sup> eluent 1:10 Et<sub>2</sub>O/DCM) to afford 85.9 mg (94%) of (*R*)-(-)-**119** as white foam.

$[\alpha]_D^{25} = -19.9$  (*c* 4.62, CHCl<sub>3</sub>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.04 (t, <sup>3</sup>J<sub>HH</sub> = 6.4 Hz, 3H), 1.69 (m, 2H), 3.11 (d, <sup>2</sup>J<sub>HH</sub> = 14.0 Hz, 1H), 3.16 (d, <sup>2</sup>J<sub>HH</sub> = 13.6 Hz, 1H), 6.99 (d, <sup>3</sup>J<sub>HH</sub> = 9.2 Hz, 1H), 7.22-7.33 (m, 6H), 7.34-7.43 (m, 3H), 7.45-7.49 (m, 1H), 7.51-7.53 (m, 2H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>) One conformer Et axial (20 resonances found for a possible 20 unique carbons): δ 8.76, 25.70, 38.20, 70.33, 121.58, 126.59, 127.98, 128.04, 128.31, 129.19, 129.88, 130.23, 130.34, 131.00, 131.88, 136.96, 137.35, 140.92, 165.61, 174.61.

HRMS (FAB) calcd for  $C_{24}H_{22}N_2OCl [M+H]^+$ : 389.1421. Found: 389.1410 (-2.8 ppm, -1.1 mmu).

HPLC  $t_r$  17.9 min (*R*);  $t_r$  20.2 min (*S*) [Chiralpak AD-H (0.46 cm  $\times$  25 cm) (from Daicel Chemical Ind., Ltd.) Hexane/*i*-PrOH, 97/3, 1.0 mL/min, 98% ee.

## References for Chapter 5.

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**Omnia ad maiorem Dei gloriam.**

*Everything for the greater glory of God.*