Enantioselective Synthesis of Drug-like Molecules via Axially-chiral Intermediates

Gary Michael Richoux Jr.

Dissertation submitted to the faculty of the Virginia Polytechnic Institute and State University in partial fulfillment of the requirements for the degree of

Doctor of Philosophy
In
Chemistry

Paul R. Carlier, Committee Chair
Felicia A. Etzkorn
David G. Kingston
Webster L. Santos

06/09/2016
Blacksburg, VA

Keywords: Memory of Chirality, benzodiazepine, rearrangement, SRSvSACI

Enantioselective Synthesis of Drug-like Molecules via Axially-chiral Intermediates

Gary Richoux

ABSTRACT

The self-regeneration of stereocenters via stereolabile axially-chiral intermediates (SRSvSACI) is a synthetic strategy in which the configuration of a starting material, possessing only a single stereocenter, directs the formation of a chiral axis in an intermediate. The reaction proceeds stereospecifically, although the original stereocenter is destroyed through trigonalization. This is due to the stereochemical information encoded in the chiral axis, which is transformed into the configuration of a stereocenter in the product. In this research, we investigate the generation of axially chiral intermediates arising from both (*S*)-methyl lactate derivatives and 1,4-benzodiazepin-2,5-dione derivatives.

For the deprotonation/alkylation of *O*-Bn and *O*-TBS substituted (*S*)-methyl lactate derivatives containing achiral oxazolidinones, we hypothesized that a twisted amide enolate featuring a chiral C(O^-)-N axis could sufficiently impart stereochemical information and control the selectivity of the reaction. Previous work completed by Kobayashi showed in related compounds (*E*)- vs (*Z*)-enolate formation could be controlled through the identity of the 2′-oxygen substituent with –Bn affording the (*E*)-enolate and –TBS affording the (*Z*)-enolate. We investigated the utilization of achiral oxazolidinone moieties to selectively generate axial chiral intermediates that could then control the facial selectivity of sequential alkylations. Unfortunately, unforeseen synthetic difficulties prevented successful accomplishment of our project goals.

We also utilized axially chiral intermediates in the generation of 3,3-disubstituted quinolone-2,4-diones. The target compounds serve as potentially useful drug scaffolds, yet synthetic access to them has remained limited due to the lack of commercial availability of the corresponding enantiopure quaternary substituted amino acids. Prior work in the Carlier group demonstrated the preferential (*M*)-conformer deprotonation demonstrated by 1,4-benzodiazepin-2,5-diones, and through the installation of an *N*4-*tert*-butyloxycarbonyl protecting group, we were able to take advantage of this preferential (*M*)-conformer deprotonation and generate 3,3-disubstituted quinolone-2,5-diones through an acyl-amino variant of the Chan rearrangement. In general, these reactions were highly enantioselective proceeding with little to no loss of enantiomeric excess. Finally, we collaborated with Professor Bloomquist to test the topical toxicity of selected ring-contracted products against adult *Anopheles gambiae*, the African vector of malaria.

Acknowledgments

My sincerest thanks and appreciation go to my advisor Dr. Paul Carlier and my committee members Dr. Etzkorn, Dr. Kingston, and Dr. Santos. Your wisdom and knowledge have shaped my research and molded me into the chemist that I am today. I am grateful for all the guidance shared over these five years, and I am excited to take and use the education you have imparted to me as I step into the world.

I would also like to thank my colleagues at Virginia Tech. Mr. Chris Presley, you have been a constant source of support and laughter. From pulling all-nighters completing assignments to pulling all-nighters playing games, you have helped me get through the good times and the bad. Dr. Eugene Camerino, not only have you been a great friend, you have helped guide me through all the twists and turns of graduate school. You are always willing to help, and for that I am so thankful. To my fellow group members Mr. Joe Clements and Ms. Maryam Ghavami, thank you for all the help you have given me these past five years. Both of you have shared knowledge and kindness with me, and I am truly grateful for that.

Dedicated

To my wonderful family. Words cannot express what you mean to me. My parents, Elizabeth Simms, Will Simms, and Gary Richoux Sr., thank you for raising me in households filled with love. You didn't just instill in me a drive to better myself. You lifted me up on your shoulders and let me know that you were always there to catch me should I need it. To my brothers, Tilon and Noah, you two have believed and cheered for me in every endeavor I've ever undertaken. In many trying times, your unyielding support has given me the resolve to push through. To Marguerite and Bryon Chambers, thank you for taking me into your family with open arms. You opened up your home, showered me with love and support, and you treated me like a son from the very beginning.

To my incredible wife whose unwavering love, constant support, and endless patience has given me the strength needed to complete this journey. Walking by my side, not only have you shared in excitement and joy; you've readily taken on the burdens and tribulations I've been faced with. You are my best friend, and God truly blessed me when he brought you into my life.

Table of Contents

1. Introduction to the Self-regeneration of Stereocenters via Stereolabile Axially-chiral Intermediates (SRSvSACI) 1-1
1.1 Definition 1-1
1.2 SRSvSACI: Rational design 1-3
1.3 Requirements for SRSvSACI 1-4
1.4 Dynamic chirality 1-5
1.5 SRSvSACI in literature 1-7
1.5.1. Enolate chemistry: The pioneer application of SRSvSACI 1-7
1.5.2. Asymmetric synthesis of quaternary *α*-amino acids 1-7
1.5.3. SRSvSACI in imino-aldol reactions 1-9
1.5.4. Carbonyl migration of *α*-amino acid derivatives 1-11
1.5.5. First example of asymmetric intermolecular aldol reaction through SRSvSACI 1-13
1.5.6. Base-free generation of ammonium enolates and subsequent trapping 1-14
1.5.7. Asymmetric synthesis of (*S*)-α-methylDOPA 1-16
1.5.8. Enantiodivergent synthesis of chiral benzo[*d*]sultams 1-17
1.5.9. Asymmetric α-arylation of amino acid derivatives 1-19
1.5.10. Application of SRSvSACI for the conjugate addition of amino acids 1-21
1.5.11. Synthesis of *β*-hydroxy quaternary *α*-amino acids 1-23
1.6 SRSvSACI through radical intermediates 1-25
1.6.1. Double SRSvSACI 1-25
1.6.2. Aryl radical phosphanylations 1-28
1.6.3. Cascade rearrangement of enediynes 1-29
1.7 SRSvSACI reactions of carbocations 1-34
1.7.1. Friedel-Crafts alkylation using *α*-aryl alcohols 1-34
1.8 Conclusion 1-36
1.9 Bibliography 1-38
2. Exploring SRSvSACI Reactions of (*S*)-Methyl Lactate Derivatives 2-1
2.1 Abstract of Chapter 2 2-1
2.2 SRSvSACI: Application to amide enolates in the Carlier group 2-3
2.3 Control of lactate oxazolidinone enolization 2-4
2.4 (S)-lactic acid coupled achiral oxazolidinones 2-9
2.5 Synthesis of 5,5-dimethyloxazolidinone 2-10
2.6 Synthesis of (S)-methyl lactate derivatives 2-11
2.7 Oxazolidinone coupling 2-12
2.8 Aldol reaction of the protected lactate oxazolidinones 2-13
2.9 Attempted alkylation of the enolates derived from protected lactate oxazolidinone 2-9a and 2-9b 2-18
2.10 Synthesis and alkylation of glycolate derivatives 2-20
2.11 Deuteration of (S)-methyl lactate derivatives 2-22
2.12 Synthesis of an alternate achiral oxazolidinone 2-24
2.13 (S)-methyl lactate project conclusion 2-25
2.14 Bibliography 2-27
3. Enantioselective Ring-Contraction of 1,4-Benzodiazepin-2,5-diones 3-1
3.1 Abstract 3-1

3.2 Applications of SRSvSACI to 1,4-benzodiazepin-2-ones and 1,4-benzodiazepin-2,5-diones by the Carlier group 3-3
3.3 Chan-type rearrangement of 1,4-benzodiazepin-2,5-diones 3-10
3.4 Enantioselective ring contraction of N1-methyl-N4-Boc-benzo[e][1,4]diazepin-2,5-diones 3-14
3.4.1. Path B synthesis of (*S*)-phenylalanine derived 1,4-benzodiazepin-2,5-dione (*S*)-3-35e 3-18
3.4.2. Path C synthesis of (*S*)-phenylalanine derived 1,4-benzodiazepin-2,5-dione (*S*)-3-35e 3-19
3.4.3. A new discovery in the Path A synthesis of (*S*)-phenylalanine derived 1,4-benzodiazepin-2,5-dione (*S*)-3-35e 3-22
3.4.4. Rearrangement of 1,4-benzodiazepin-2,5-dione derivatives 3-35a-e 3-25
3.5 Ring contraction on aryl substituted 1,4-benzodiazepin-2,5-diones 3-28
3.6 Attempted group migration of 1,4-benzodiazepin-2,5-dione N4-substituent . 3-40
3.7 1,4-benzodiazepin-2,5-dione project conclusion 3-45
3.8 Bibliography 3-47
4. Experimental Procedures and Analytical Data 4-1
4.1 Materials and general information 4-1
4.2 Tabulation of HPLC conditions and retention rimes for 1,4-benzodiazepin-2,5-diones 4-2
4.3 Synthetic procedures 4-6
4.3.1. Chapter 2 (*S*)-methyl lactate project 4-6
4.3.2. Chapter 3 1,4-benzodiazepin-2,5-dione project 4-19
4.4 Bibliography 4-89

1. Introduction to the Self-regeneration of Stereocenters via Stereolabile Axially-chiral Intermediates (SRSvSACI)

1.1 Definition

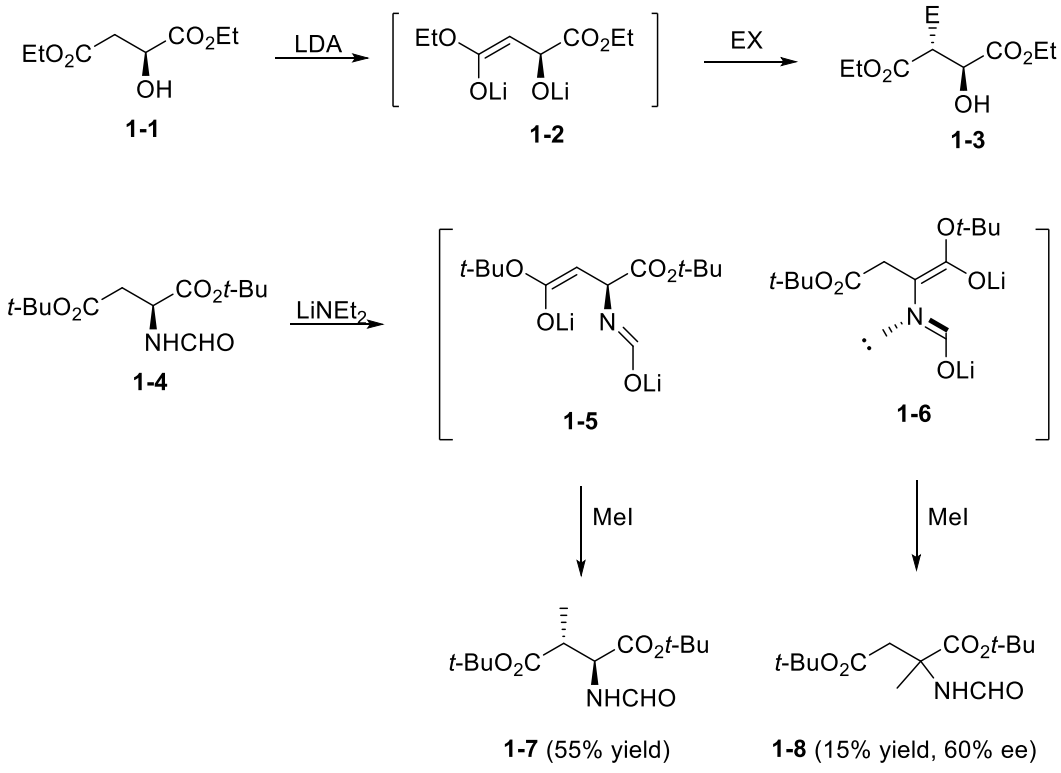
"Memory of Chirality" (MOC), also referred to as "self-regeneration of stereocenters via stereolabile axially-chiral intermediates" (SRSvSACI),[1] has been defined by Carlier as

"A formal substitution at an sp^3 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."[2]

The term "Memory of Chirality" was coined by Fuji in 1991 and has the considerable advantage of brevity.[3] However, this term is imprecise and tends to evoke misunderstanding. For example, it is not the "chirality" of the starting material that is remembered, but rather the configuration. The chirality never vanishes, but the configuration does. Furthermore the term does not convey any linkage to previous important historical developments in asymmetric synthesis, such as Seebach's "self-regeneration of stereocenters" (SRS) concept.[4] For these reasons and more Carlier devised the longer term, which I will abbreviate as "SRSvSACI".[1] It is the configuration of the stereocenter in the starting material that directs the "configuration" of the chiral axis in the intermediate; upon reaction, the stereochemical information encoded in the chiral axis is transformed into the configuration of a stereocenter in the product. The key axially-chiral intermediate is subject to racemization, hence the term "stereolabile."

SRSvSACI is a fascinating phenomenon wherein a single stereogenic center in a molecule is destroyed, and yet, further substitution at that previously chiral carbon leads to a stereoselective result. The possibility of this phenomenon was first hinted at in Seebach's 1981 paper in which he and his coworker applied their previous work of *α*-alkylation on di-lithiated species **1-2** (derived from diethyl malate **1-1**) to the *N*-formyl aspartic acid ester analog **1-4** (**Scheme 1-1**).[5] Along with obtaining the expected β-alkylated compound, **1-7,** they also obtained **1-8** in 15% yield. This *α*-alkylated product isolated in 60% enantiomeric excess (ee) in spite of having apparently originated from **1-6**, which has no chiral center.

To account for this result, Seebach inferred two possibilities. One, the formation of **1-8** proceeded through a mixed aggregate of enolates **1-5** and **1-6**, whereby **1-5** acted as a

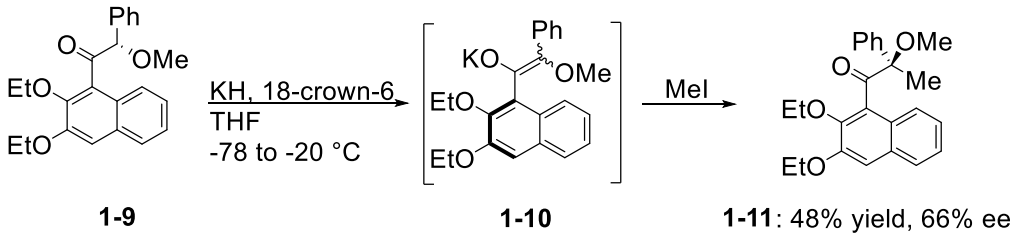


Scheme 1-1 *α*-Alkylation of Aspartic acid ester **1-4**.[5]

chiral controller in the methylation of **1-6**. Two, enolate **1-6,** itself, could possess axial chirality as depicted along the C2-N bond, leading to asymmetric *α*-alkylation. While discrimination between these possibilities was not described in this paper, Seebach would later report that the mixed aggregate mechanism was responsible.[4, 5] Thus, although Seebach's work was later discovered to work through a different pathway than SRSvSACI, the ideas in this paper would outline the foundation for reactions that would appear to proceed through achiral intermediates, yet transfer stereochemical information in the reactants to their products.

1.2 SRSvSACI: Rational design

Fuji was the first to employ the phenomenon of SRSvSACI in a rational synthesis,[3] although he used the term "Memory of Chirality" to describe his work. Fuji successfully achieved enantioselective alkylation of the enolate derived from **1-9** (66%



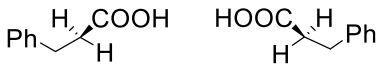
Scheme 1-2 Fuji's enantioselective deprotonation/alkylation of **1-9**.[3]

ee, **Scheme 1-2**) He proposed that this chirality transfer proceeded by a two-step process. Firstly, the initial central chirality of **1-9** is transferred to axial chirality in the enolate intermediate **1-10**. Through a series of trapping experiments and measurement of optical rotation on this intermediate, it was determined that the % ee of their product was time and temperature dependent. If **1-10** was exposed to ambient temperatures, enantiomeric purity would decrease over time. Thus, enolate **1-10** possessed transient axial chirality.

Secondly, in the two-step chirality transfer, the regeneration of the central chirality in **1-11** was obtained through reaction of their axially chiral enolate with an electrophile. It was determined that the enantioselectivity of the product was not affected by the steric bulk of the electrophile. These two observations led to the conclusion that the % ee of the product was mainly dependent upon the formation of the axially chiral enolate.

1.3 Requirements for SRSvSACI

As discovered by Fuji, the formation of a dynamically chiral intermediate is of the utmost importance while invoking SRSvSACI[4]. He would later state in a review article that chirality must not simply be thought of as 3-dimensional, but that a fourth dimension must be considered, namely timescale.[3, 6] To illustrate this, consider *β*-phenylpropionic acid **1-12.** It has no permanent chirality (i.e. static chirality), but if it is observed on a

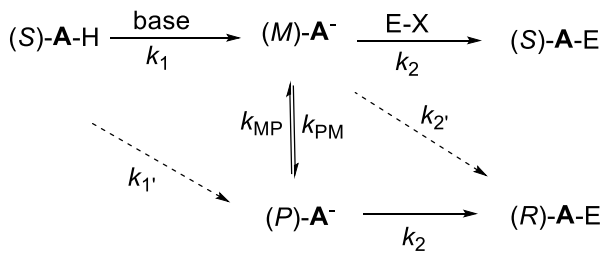


1-12-g+ **1-12-g-**

Figure 1-1 Chiral gauche conformations of β-phenylpropionic acid

short enough timescale, *β*-phenylpropionic acid can be seen to have multiple conformers, two of which are shown in **Figure 1-1**. While normal reaction conditions would result in the rapid interconversion of these enantiomeric conformations, certain conditions could be envisioned in which the conformational chirality of a starting material could affect the chirality of a product in a reaction.

However, simply forming a conformationally chiral intermediate is not sufficient to ensure enantioselective reactions; it is necessary that the intermediate meet certain conditions. As described by Carlier (**Scheme 1-3**), the formation of conformationally



Scheme 1-3 Hypothetical SRSvSACI deprotonation/alkylation. **Requirements for asymmetric induction**: 1) Enantioselective formation of stereo-labile, axially-chiral reactive intermediate; $k_1 >> k_{1'}$. 2) Enantiomerization of the stereolabile chiral reactive intermediate is slow on the trapping reaction time scale: $k_{MP} << k_2$[E-X]. 3) Trapping reaction is stereoselective: $k_2 >> k_{2'}$.[1]

chiral intermediate (*M*)-**A**$^-$ from starting material (S)-**A**-H must be enantiospecific.[1] The assignment of the (*M*)-**A**$^-$ and (*P*)-**A**$^-$ helical, (*R*) and (*S*), descriptors here is purely arbitrary and will be explained later in specific detail. The rate at which the reactive intermediate (*M*)-**A**$^-$ is formed must be much faster than the rate at which (*P*)-**A**$^-$ is formed to ensure the intermediate has a high % ee ($k_1 >> k_{1'}$). Next, the intermediate must not readily enantiomerize on the specific timescale at which the reaction is run ($k_{MP} << k_2$[E-X]). For this to occur alkylation must be fast and enantiomerization from (*M*)-**A**$^-$ to (*P*)-**A**$^-$ must be relatively slow. Finally, the electrophile must enantioselectively react with (*M*)-**A**$^-$ to form (*S*)-**A**-E over (*R*)-**A**-E ($k_2 >> k_{2'}$).

1.4 Dynamic chirality

When employing conformationally chiral intermediates, the speed at which the reaction takes place in comparison with how fast the conformationally chiral intermediates racemize is of paramount importance to the overall enantioselectivity of the reaction. If this process is unimolecular and the barrier to enantiomerization can be estimated, then the Eyring equation can be applied to determine k_{rac} and the racemization $t_{1/2}$ at a given temperature. Comparison of these values at 25 and -78 °C allows one to see

Table 1-1 Effects of enantiomerization barrier and temperature on racemization $t_{1/2}$

Enantiomerization barrier $\Delta G^{\ddagger}$ (kcal/mol)	Racemization $t_{1/2}$ at -78 °C[a]	Racemization $t_{1/2}$ at 25 °C[a]
12	2.4 s	3.5×10^{-5} s
13	30.1 s	1.9×10^{-4} s
14	7 min	1.0×10^{-3} s
15	89 min	5.5×10^{-3} s
16	20 h	3.0×10^{-2} s
17	4 d	1.6×10^{-1} s
18	148 d	0.9 s
19	5 years	4.72 s
20	70 years	26 s

[a]Racemization $t_{1/2} = \ln 2/k_{rac}$, where $k_{rac} = 2*(k_BT/h)*\exp(-\Delta G^{\ddagger}/RT)$.

under which conditions SRSvSACI could be practical as a synthetic strategy (**Table 1-1**).[7] At room temperature compared to -78 °C, the $t_{1/2}$ values are significantly shorter. For a given conformer with an enantiomerization barrier of 20 kcal/mol the racemization $t_{1/2}$ at 25 °C is only 26 seconds. However, at -78 °C the racemization half-lives are dramatically increased. The same conformer with an enantiomerization barrier of 20 kcal/mol would exhibit a racemization $t_{1/2}$ of 70 years at -78 °C, 8.5 million times longer. This understanding allows for rational design when planning a synthesis containing the principle of SRSvSACI. What has become a common theme is the use of sp^2-sp^2 bonds as a source of dynamic chirality, since a rotational barrier of 16 kcal/mol can be easily attained and exceeded for such bonds, in comparison to rotations of sp^3-sp^3 bonds which typically exhibit barriers to rotation less than 7 kcal/mol.[8] As can be seen, a barrier of 16 kcal/mol at -78 °C gives a racemization half-life of 20 hours. Decreasing the barrier to 14 kcal/mol at this temperature reduces the racemization $t_{1/2}$ to only seven minutes. It should also be noted that while highly enantioselective intermolecular reactions necessitate cold temperatures to facilitate increased racemization half-lives, there are a few instances in which intramolecular reactions proceed in an enantioselective manner via SRSvSACI at

ambient temperatures.[9-11] To obtain high enantioselectivity for these intramolecular reactions, it is required that the chiral enolate intermediates react faster than the timescale of their racemization.

1.5 SRSvSACI in literature

SRSvSACI has been reviewed several times by authors such as Fuji,[6, 12] Griesbeck,[13] and Carlier.[1, 2] Thus below I will review the published work in SRSvSACI from early 2009 to the present.

1.5.1. Enolate chemistry: The pioneer application of SRSvSACI

The first work with SRSvSACI involved enolate chemistry. It is here that the idea was born and developed into what it is today. More than 20 years after the first SRSvSACI reactions were being designed by Fuji,[3] the boundaries of SRSvSACI are still being pushed by enolate related reactions.

1.5.2. Asymmetric synthesis of quaternary *α*-amino acids

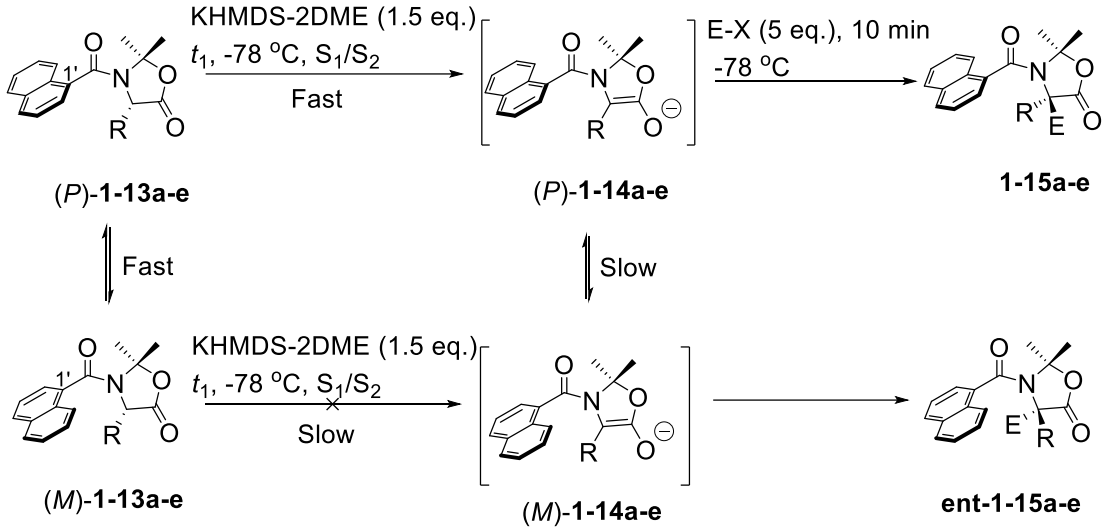
Enantiopure quaternary *α*-amino acids have proven to be an important resource for peptide synthesis due to their ability to restrict peptide conformations and slow proteolytic cleavage. Changes in peptide conformation have been shown in several instances to increase a peptide's biological activity. Because of this important aspect, many synthetic methods have been developed towards the creation of these asymmetric quaternary *α*-amino acids, but very few are achieved without the use of chiral catalysts[14-16] or chiral auxiliaries.[17-19]

Branca et al. have reported the development and optimization for the synthesis of asymmetric quaternary *α*-amino acids, derived from 5 different L-amino acids: valine,

leucine, alanine, and methionine, through the implementation of SRSvSACI.[20] They first formed an oxazolidin-5-one (**Table 1-2**, (*P*)-**1-13a-e**/(*M*)-**1-13a-e**), which contained a tertiary aromatic amide group derived from one of the 5 corresponding L-amino acids

(Val, Leu, Ala, Phe, Met) which was subsequently deprotonated and alkylated to form the quaternary *α*-amino acid **1-15a-e**. Their key insight into the synthesis is the axial chirality formed from the slow rotation about the C(O)-N and C(O)-Ar bond in their tertiary aromatic amides. The rotation about the C(O)-C1′ bond in (*P*)-**1-13a-e**/(*M*)-**1-13a-e** to give both *M*- and *P*-conformers is fast, but while the *M*-conformer exists,

Table 1-2 Optimized SRSvSACI Alkylations on L-Amino Acid derived **1-13a-e**[20]

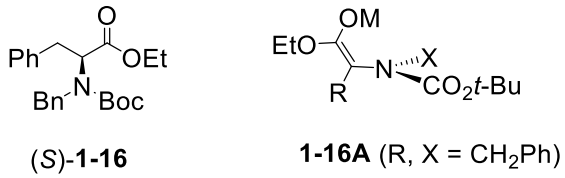


S.M	R	S_1	S_2	S_1:S_2	t_1 (min)	E-X	Product	Yield (%)	ee (%)
1-13a	$CH(CH_3)_2$	Et_2O	toluene	-	8	ethyl iodoacetate	**1-15a**	80	96
1-13b	$CH_2CH(CH_3)_2$	Et_2O	Et_2O	55/45	8	ethyl iodoacetate	**1-15b**	96	94
1-13c	CH_3	THF	THF	70/30	3	ethyl iodoacetate	**1-15c**	94	91
1-13d	$CH_2C_6H_5$	THF	THF	70/30	3	ethyl iodoacetate	**1-15d**	85	89
1-13e	$CH_2CH_2SCH_3$	THF	toluene	55/45	3	*tert*-butyl bromo acetate	**1-15e**	75	91

deprotonation is sterically blocked ((*M*)-**1-13a-e**). However, rotation of the C(O)-C1′ bond in the enolate (*P*)-**1-14a-e**/(*M*)-**1-14a-e** is apparently much slower than that of (*P*)-**1-13a-e**/(*M*)-**1-13a-e**. If deprotonation of the *P*-conformer and alkylation from the *Re* face is rapid, stereoselective results can be obtained. From this knowledge, optimized reaction conditions were obtained for their L-amino acid derivatives **1-13a-e** to afford **1-15a-e** in 75-96% yields with 89-96% ee through the use of SRSvSACI. Following hydrolysis of **1-15a-e** they were able to obtain the correlating asymmetric quaternary *α*-amino acids, derived from five different L-amino acids, in high yield and % ee (not shown).

1.5.3. SRSvSACI in imino-aldol reactions

Ghorai *et al*. have also reported the use of *α*-amino acid esters for SRSvSACI-based synthesis towards the creation of *α*,*β*-diamino acid derivatives.[21] Hoping to capitalize on a chiral C-N axis, such as that demonstrated in **1-16A** (**Figure 1-2**, derived from (*S*)-**1-16**), gained through the deprotonation of *N*-substituted *α*-amino acids, which was

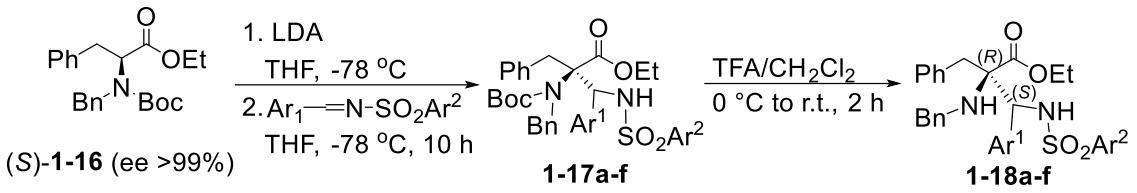


(*S*)-**1-16** **1-16A** (R, X = CH_2Ph)

Figure 1-2 Amino acid ester derivative and chiral enolate.[21]

introduced and established by Fuji and Kawabata,[3, 6, 12, 22-25] they proposed the new substrate *N*-benzyl-*N*-Boc-phenylalanine ethyl ester (*S*)-**1-16.** Treatment of (*S*)-**1-16** with LDA followed by addition of several N-activated imines gave the corresponding *α*,*β*-diamino acid derivatives (**1-17a-f**) which were determined to be non-racemic by HPLC analysis of **1-18a-f** (**Table 1-3**). The stereomers of these reactions could only be

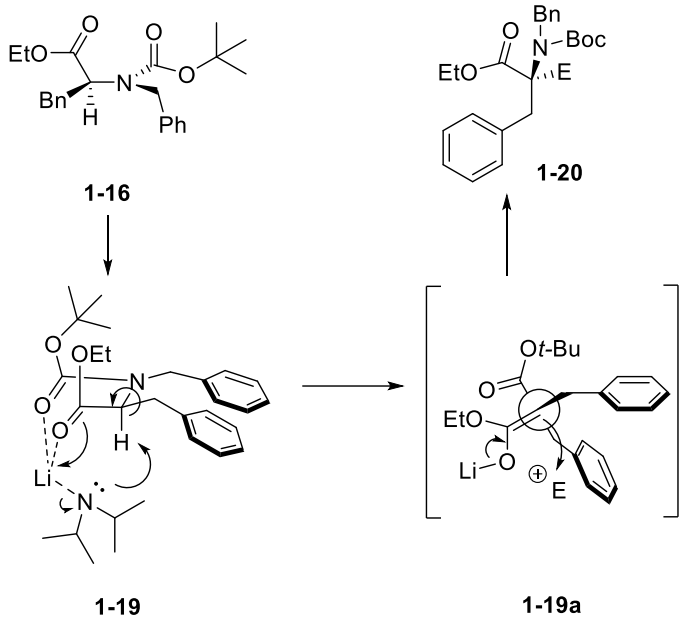
Table 1-3 Synthesis of *α*,*β*-di-amino acid derivatives.[26]



Entry	Ar^1	Ar^1	Intermediate	yield (%)	Product	yield (%)	dr	ee (%)
1	Ph	4-MeC_6H_4	**1-17a**	84	**1-18a**	88	83:17	92
2	Ph	Ph	**1-17b**	62	**1-18b**	70	71:29	80
3	3-BrC_6H_4	4-MeC_6H_4	**1-17c**	68	**1-18c**	87	71:29	84
4	2-ClC_6H_4	4-MeC_6H_4	**1-17d**	74	**1-18d**	80	79:21	74
5	2-furyl	4-MeC_6H_4	**1-17e**	74	**1-18e**	87	67:33	80
6	Ph	4-$NO_2C_6H_4$	**1-17f**	80	**1-18f**	84	83:17	88

separated after removal of the Boc group. For all cases, they reported moderate diastereoselectivity and moderate to high enantioselectivity ranging from 74-92% ee for major diastereomers and 62-88% ee for minor diastereomers. A crystal structure of the major diastereomer of racemic **1-18a** was obtained which identified the relative configuration as trans (described as (2*R**, 3*S**) arbitrarily in their paper). The absolute configuration of the products was not determined.

While the authors did not propose an explanation for the major diastereomer, it can be seen that with chelation of the base cation, a 7-membered ring intermediate can be achieved in which the *N*-Boc group is cis to the α-H (**Scheme 1-4, 1-19**). With subsequent deprotonation, attack on an electrophile from the *β*-face of enolate **1-19a** will be sterically hindered by the *N*-Boc protecting group, and attack will proceed through the *α*-face. The substituents change in priority after alkylation and this results in an overall inversion of configuration but the reaction proceeds through retention at the chiral center (**Scheme 1-4**).

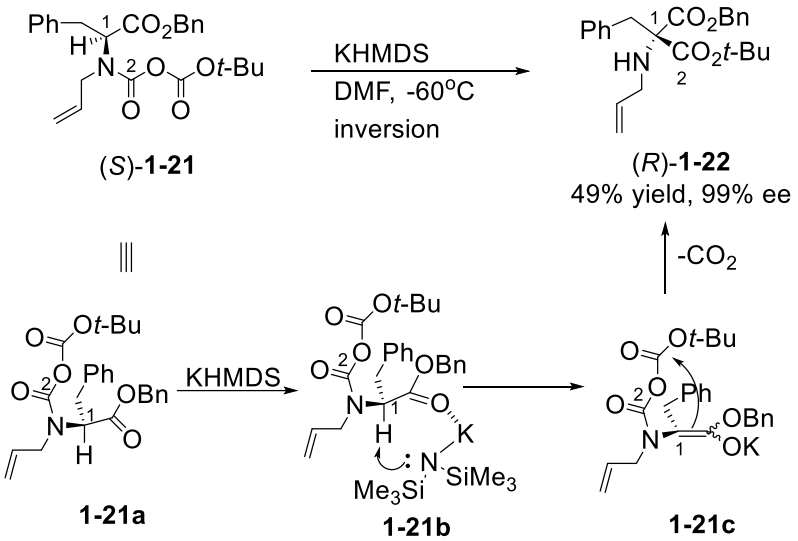


Scheme 1-4 Deprotonation of N-substituted *α*-amines.

1.5.4. Carbonyl migration of *α*-amino acid derivatives

Recently, Kawabata *et al.*[27] extended a protocol they previously developed for asymmetric alkylations and conjugate additions through SRSvSACI to carbonyl migrations of α-amino acid derivatives. The ability to generate axially chiral enolates is vitally important, and specifically, the choice of nitrogen substituents is critical for the generation of enantioenriched chiral enolate intermediates. Through studies of various *N*-substituted α-amino acid derivatives, they discovered that *N*-allyl-*N*-*tert*-butoxycarbonylcarbamate amino acid derivatives afforded them with axially chiral intermediates that underwent intramolecular carbonyl migration with inversion of configuration to give new amino acid derivatives containing a tetra-substituted carbon and an additional ester group in up to 99% ee (**Scheme 1-5**). Using a previously reported reaction, they obtained *N*-allyl-*N*-*tert*-butoxycarbonylcarbamate derivative (*S*)-**1-21** from phenylalanine benzyl ester in 71% yield. Next, they optimized the reaction conditions for the following deprotonation and found that, at 20 °C with KHMDS, asymmetric

induction was strongly dependent on the polarity of the solvent. DMSO gave the best results, giving carbonyl migration product (*R*)-**1-22** in 65% ee. Reactions run at lower temperatures with toluene or THF gave low yields but higher % ee. The use of more equivalents of KHMDS did not afford better results, and other bases, such as NaHMDS, LiHMDS, and LiTMP gave both lower yield and enantioselectivity. It was determined that treatment of (*S*)-**1-21** with 1.2 equivalents KHMDS in DMF at -60 °C for 2h gave the

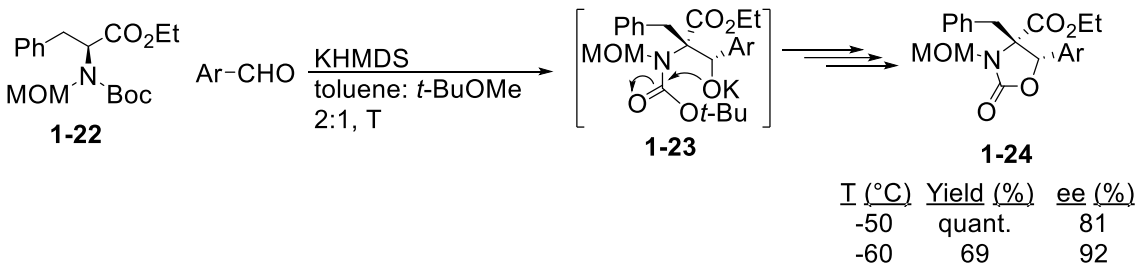


Scheme 1-5 Carbonyl migration in allyl-N-tertbutoxycarbonylcarbamate derivative.[27]

best results (49% yield, 99% ee) (**Scheme 1-5**). Next, in an attempt to improve yield, they developed a one-pot reaction for the synthesis of and alkylation on *N-tert*-butoxycarbonylcarbamate analogs. For analogs derived from L-valine and L-alanine they were able to obtain yields of 49 and 64% and enantioselectivities of 98 and 97% ee, respectively (not shown). Next, to determine a rationale for the transformation of (*S*)-**1-21** into (*R*)-**1-22**, they performed a conformational search and determined that **1-21a** was the most stable conformer of (*S*)-**21**. Deprotonation of the C(α)-H would lead to the axially chiral intermediate **1-21c**, which would give rapid carbonyl migration to produce the final alkylated product with inversion of configuration **1-22**.

1.5.5. First example of asymmetric intermolecular aldol reaction through SRSvSACI

Because conformationally chiral enolates undergo time dependent racemization, intermolecular applications of SRSvSACI have generally been limited to irreversible reactions. Aldol reactions are notoriously reversible which could lead to eventual degradation of % ee. Watanabe et al. reported the first asymmetric intermolecular aldol reaction between axially chiral enolates derived from *α*-amino acids and aromatic aldehydes.[28] Based on the previously studied axial chirality of *N*-Boc-*N*-MOM α-amino acids enolate intermediates, they chose **1-22** for this application. Through a series of



T (°C)	Yield (%)	ee (%)
-50	quant.	81
-60	69	92

Scheme 1-6 Asymmetric intermolecular aldol reaction.[28]

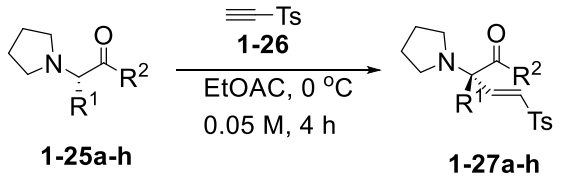
optimizations it was discovered that for Ar = Ph and KHMDS as base, a 2:1 mixture of toluene and *t*-BuOMe, at -50 or -60 °C for 12 h gave them the best results with quantitative yield and 81% ee or 69% yield and 92% ee, respectively (**Scheme 1-6**). They then applied these conditions to a variety of aryl aldehydes, including *p*-substituted benzaldehydes, *o*-methoxybenzaldehyde, and 2-napthaldehyde, resulting in a range of 44-95% yields and 78-92% ee (not shown). They also noted the use of aliphatic aldehydes did not result in significant amounts of aldolates or their corresponding oxazolidinones.

1.5.6. Base-free generation of ammonium enolates and subsequent trapping

Tayama et al. have recently reported an interesting application of SRSvSACI where deprotonation and asymmetric electrophilic addition on *N*,*N*-dialkyl acyclic amino acid ester can be accomplished without the addition of base.[29] Extending a previous method they developed for the asymmetric α-2-tosylethenylation of *N*-alkyl-L-proline esters using ethynyl tolyl sulfone (**Table 1-4**, **1-26**) as a highly reactive Michael acceptor and various electrophiles, it was determined that a variety of L-amino acid derivatives could undergo stereoselective 2-tosylethenylation.

The optimized reaction conditions were generalized to a variety of L-amino acid derivatives to determine the substituent effects on the chiral induction (**Table 1-4**). It was seen that for primary esters (entry 1 and 2), decreased yield was observed due to the formation of an undesired side product. Phenylalanine and leucine-derived substrates, **1-**

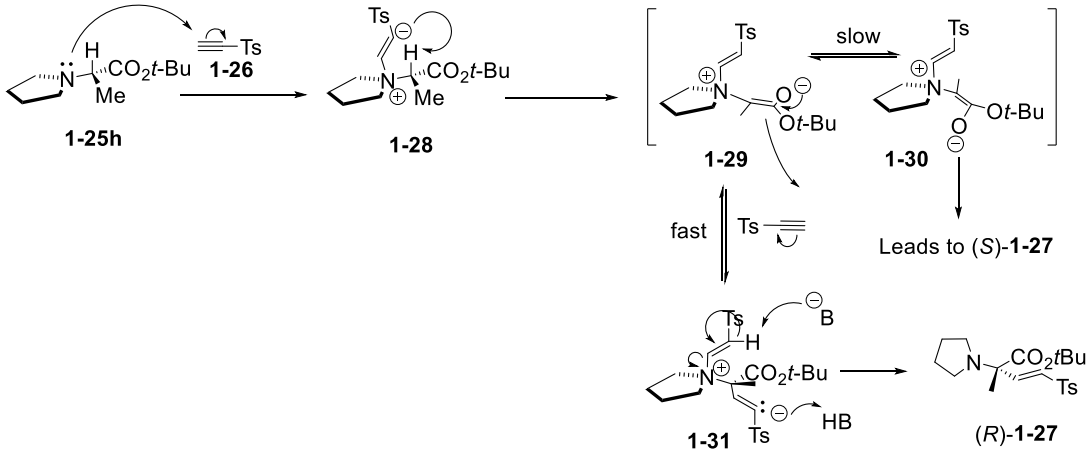
Table 1-4 Asymmetric *α*-2-tosylethenylation of acyclic L-amino acid derivatives.[29]



Entry	S.M	R^1	R^2	Equiv. of **28**	Product	Yield (%)	ee (%)
1	**1-25a**	Me	O*n*-Bu	2.0	**1-27a**	40	88
2	**1-25b**	Me	OCH_2Ph	2.0	**1-27b**	11	90
3	**1-25c**	CH_2Ph	O*t*-Bu	2.0	**1-27c**	99	81
4	**1-25d**	*i*-Bu	O*t*-Bu	2.0	**1-27d**	80	92
5	**1-25e**	*i*-Pr	O*t*-Bu	2.0	**1-27e**	27	95
6	**1-25e**	*i*-Pr	O*t*-Bu	2.0	**1-27e**	54	95
7	**1-25f**	Ph	O*t*-Hex	2.0	**1-27f**	90	40
8	**1-25g**	Me	NEt_2	2.0	**1-27g**	0	-
9	**1-25h**	Me	O*t*Bu	1.5	**1-27h**	90	93
10	**1-25h**	Me	O*t*Bu	1.0	**1-27h**	86	91

25c and **1-25d** reacted with high yields and % ee. The valine derivative **1-25e**, was much less reactive and gave a decreased yield (entry 5), but this was improved by increasing the reaction time to 48h (entry 6). Unfortunately, the phenylglycine derivative **1-25f** (entry 7) gave decreased % ee, and the *N*,*N*-diethyl amide derivative (entry 8) gave no product at all. It is possible that for entry 7, the steric bulk from the phenyl group at R^1 slows down the nucleophilic attack of the intermediate on the second equivalent of **1-26** which allows enantiomerization of the enolate intermediate. The failure of the *N*,*N*-dimethylamide to react may be due to the lower acidity of amides relative to esters.

The reaction and a proposed mechanism is shown in **Scheme 1-7**. Intermediate **1-28** is generated through conjugate addition of **1-26** and **1-25h**, which subsequently undergoes intramolecular deprotonation to afford **1-29**. The transfer of chirality here is achieved through the generation of the chiral ammonium intermediate **1-29.** To attain (*R*)-**1-27** stereoselectively, rotation about the C-N bond in **1-29** and **1-30** must be relatively slow compared to nucleophilic attack on **1-28**. Because of the axial chirality generated in the intermediate **1-29**, only one face is available for conjugate addition with

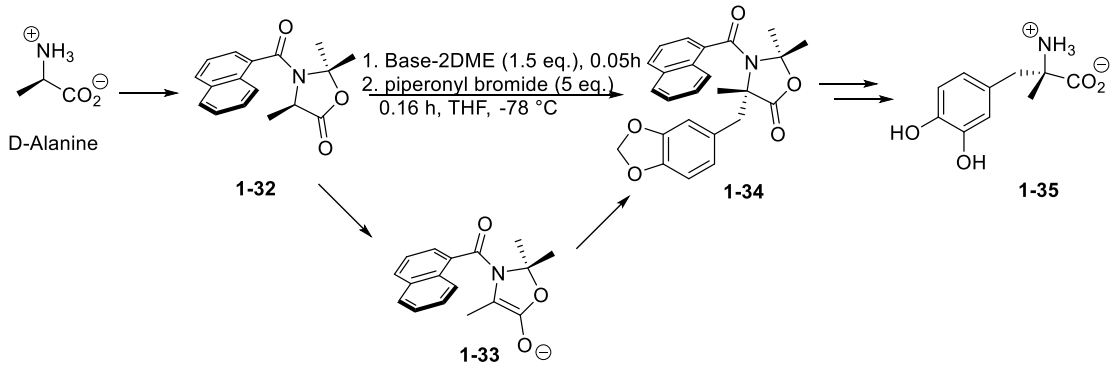


Scheme 1-7 Proposed mechanism for SRSvSACI α-2-tosylethenylation.[29]

1-28, leading selectively to **1-31**. Subsequent deprotonation/protonation of **1-31** leads to the final 2-tosylethenyl derivative product obtained stereoselectively with inversion of chirality of the original stereocenter.

1.5.7. Asymmetric synthesis of (*S*)-α-methylDOPA

Similar to the previous work by Branca[20] involving the use of a naphthoyl amide to induce axial chirality, Mai et al. reported the use of SRSvSACI towards the synthesis



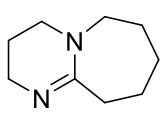
Scheme 1-8 Alkylation of oxazolidinone **1-32**[30]

of (*S*)-α-MethylDOPA with the only source of chirality being that generated from the starting material D-alanine.[30] As shown in **Scheme 1-8**, oxazolidinone **1-32** was synthesized from D-alanine. Treatment with base at cold temperatures is proposed to afford axially chiral enolate **1-33**. Subsequent addition of electrophile enantioselectively gives product **1-34**, which is ultimately transformed to the final product (*S*)-α-methylDOPA (**1-35**). Through optimization of the synthesis of **1-34** from **1-32**, it was observed that the use of KHMDS on **1-32** in THF at -78 °C followed by treatment with piperonyl bromide led to product **1-34** in 82% yield and 81% ee. The product was then recrystallized up to 98% ee and successfully used to synthesize (*S*)-α-methylDOPA.

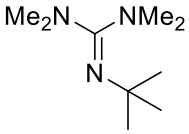
1.5.8. Enantiodivergent synthesis of chiral benzo[*d*]sultams

Starting from α-arylglycine (polyfluorobenzo)sulfonamides, Foschi *et al.*[31] reported the enantiodivergent cyclization to benzo[*d*]sultams through the use of different base/solvent combinations. While exploring the preparation of racemic *N*-substituted 3-aryl-3-carboxytetrafluorobenzo[*d*]sultam **1-37 (Table 1-5**), it was observed that although the use of DBU in acetonitrile afforded racemic products (entry 1), use of DME as the solvent gave the product in 36% ee in favor of the *R*-isomer (retentive product, priority switch, entry 2). Further exploration of varying solvents showed that THF gave slightly

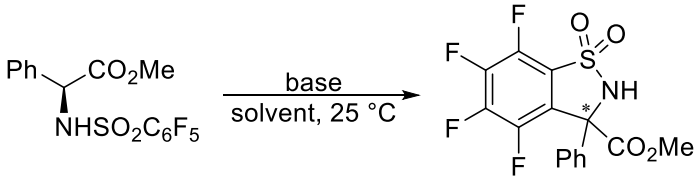
Table 1-5 Varying base/solvent conditions for the synthesis of **1-37**[31]



DBU



BTMG



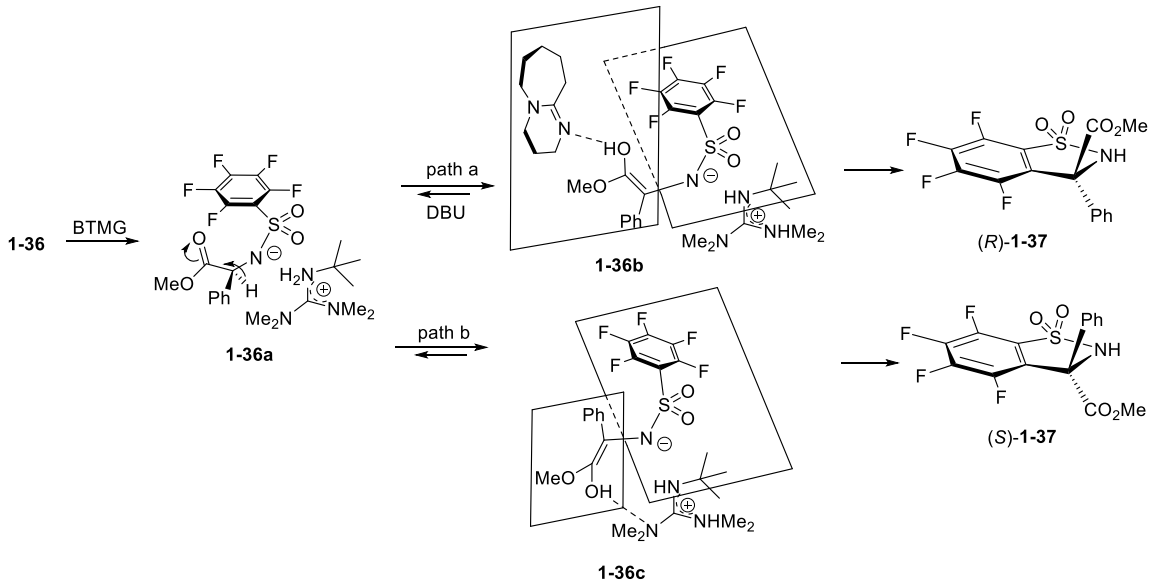
1-36 **1-37**

Entry	Base[a]	Solvent	*t* (h)	yield (%)	ee (%)
1	DBU	MeCN	16	98	0
2	DBU	DME	8	98	36 (*R*)
3	DBU	THF	8	95	24 (*R*)
4	DBN	DME	16	94	14 (*R*)
5	TBD	DME	16	98	4 (*R*)
6	MTBD	DME	20	56	38 (*R*)
7	TMG	DME	16	90	4 (*R*)
8	BTMG	DME	90	95	80 (*S*)
9	DBU/BTMG[b]	DME	8	98	68 (*R*)

[a]DBN = 1,5-diazabicyclo(4.3.0)non-5-ene; TBD = 1,5,7-triazabicyclo-[4.4.0]dec-5-ene; MTBD = 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene; TMG = 1,1,3,3-tetramethyl-guanidine; BTMB = 2-*tert*-butyl-1,1, 3,3-tetramethylguanidine. [b]7:97 molar ratio

less selective results (entry 3) and DMSO, DMF, DCM, toluene, and chlorobenzene all afforded racemic products (not shown). Interestingly, while exploring bases similar to DBU (entries 4-8), it was discovered that use of BTMG reversed the enantioselectivity, giving 80% ee in favor of the *S*-isomer (inversion product, entry 8). Further exploration of varying base/solvent combinations showed that using increasing amounts of BTMG with DBU had a synergistic effect on enantioselectivities, giving a maximum 68% ee of (*R*)-**1-37** with a 7:93 DBU/BTMG molar ratio (entry 10).

The proposed mechanism for this enantiodivergent synthetic pathway first involves deprotonation of **1-36** *N*-H proton by the sterically demanding base BTMG, forming a tight ion pair to give compound **1-36a** as seen in **Scheme 1-9**. Tautomerization leads to enols **1-36b**/**1-36c**, but further choice of either mechanistic pathway a or b is dependent on the presence of DBU. If DBU is present in the reaction mixture, as seen in path a, then it is possible that an intermolecular H-bond is formed on the less crowded



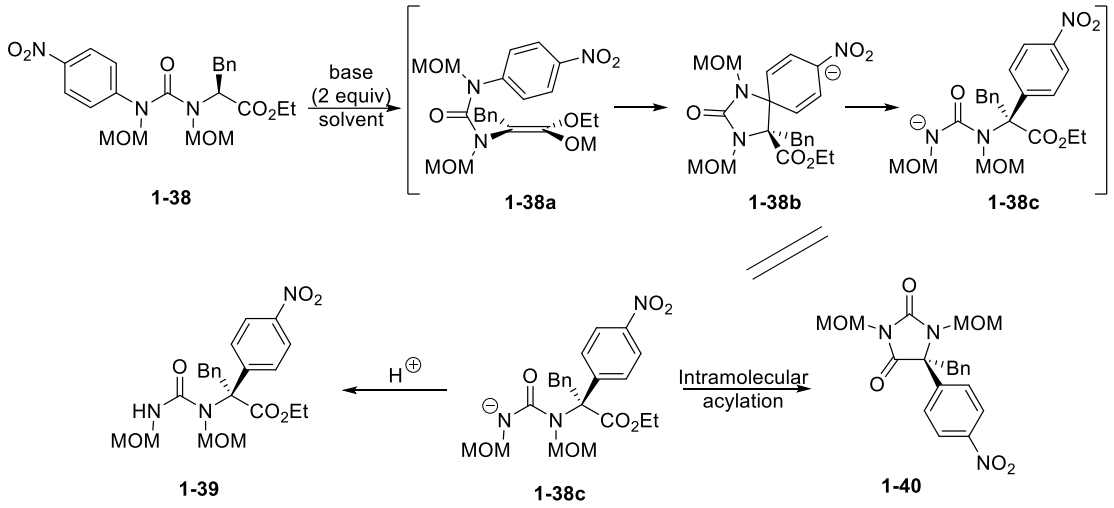
Scheme 1-9 Mechanistic explanation for enantiodivergent sultam synthesis[31]

side of the molecule between DBU and the enol, giving rise to **1-36b**. This would, in turn, give rise to the retentive product (*R*)-**1-37**. Alternatively, if DBU is absent, then it can be hypothesized that enol formation will proceed with an intramolecular H-bond on the more crowded side with BTMG, giving rise to conformer **1-36c**. This conformer, would then cyclize to give the inverted sultam (*S*)-**1-37**. An interesting addition to note is that axial chirality is generated along the C_α-N axis of an amino acid enolate with only a single substituent at nitrogen (sulfonamide). Typically, in reactions of amino acid enolates proceeding through SRSvSACI conditions it is observed that an unsymmetrically *N*,*N*-disubstituted ion is required, but in this case, it appears that there is a very tight ion pair formed between the BTMG and substrate which mimics the unsymmetrically *N*,*N*-disubstituted sulfonamide. This gives rise to the ability to apply SRSvSACI conditions to a variety of amino acid containing compounds without the need of using two different *N*-protecting groups.

1.5.9. Asymmetric α-arylation of amino acid derivatives

Tomohara *et al*. have developed a methodology for the synthesis of chiral hydantoins with an aryl-substituted tetrasubstituted carbon via SRSvSACI generated from α-amino acid esters.[32] Starting from **1-38** (**Table 1-6**), which was synthesized according to Clayden's protocol,[33] treatment with base affords axially chiral intermediate **1-38a**. Subsequent, intramolecular nucleophilic addition leads to the higher energy species **1-38b**. While formation of **1-38b** was expected to be difficult, once formed it can be transformed to the more stable urea anion **1-38c**. The authors observed that the use of KHMDS in 3:2 DMF/THF gave hydantoins **1-40** in 93% yield and 83% ee (entry 1). Use of NaHMDS gave **1-40** in 43% yield and 93% ee as well as **1-39** in 24% yield (entry 2). LiHMDS,

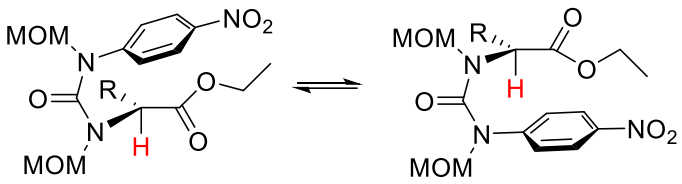
Table 1-6 Synthetic pathway to chiral hydantoins through SRSvSACI and results for the synthesis of **1-40**[32]



Entry	Base	Solvent	T (°C)	*t* (h)	Yield of **1-40** (%)	ee of **1-40** (%)	Yield of **1-39** (%)
1	KHMDS	3:2 DMF/THF	-60	0.5	93	83 (*S*)	-
2	NaHMDS	8:1 DMF/THF	-60	0.5	64	93 (*S*)	24
3	LiHMDS	4:1 DMF/THF	-60	0.5	59	99 (*S*)	15
4	LiHMDS	4:1 DMF/THF	-60 to 15	0.5	68	97 (*S*)	-
5	KHMDS	toluene	0	0.5	55	25 (*R*)	42
6	NaHMDS	toluene	0	0.5	51	83 (*R*)	29
7	LiHMDS	toluene	0	1	37	74 (*R*)	11

while giving **1-40** an improved 99% ee, only proceeded in 59% yield (entry 3). Interestingly, the use of elevated temperatures, from -60 ° to 15 °C, gave **1-40** in 68% yield and 97% ee (entry 4), while the use of toluene at elevated temperatures gave products with absolute configuration opposite those obtained from reactions run in DMF/THF (entries 5-7). Chirality was assigned based on comparison to the x-ray crystal structure of a related compound.

The divergent solvent effects are explained through examination of the coordinative strength of the solvents. For more coordinating solvents deprotonation of **1-38a′** (**Scheme 1-10**) is sterically preferred, giving way to the invertive product. For less



Scheme 1-10 Amino acid derivative conformers[32]

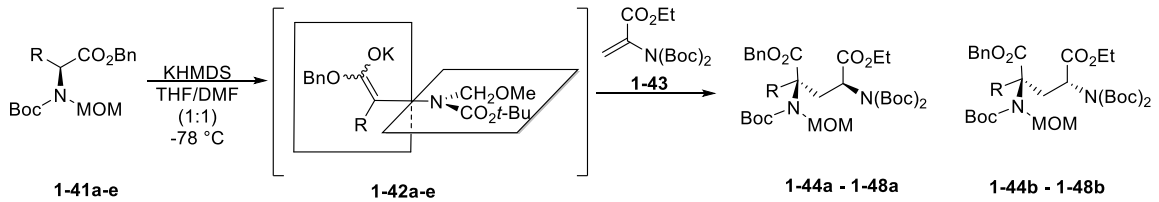
coordinating solvents, countercation coordination of the base with the carbonyl of the urea plays a much greater role, leading to the deprotonation of **1-38b** which gives the retentive product.

This methodology was also extended to urea derivatives with a variety of aryl substituents. It was generally observed that electron withdrawing containing aryl groups proceeded with high enantioselectivities and good yield to afford α-arylated hydantoins. Anionic aryl migration was not observed for electron donating aryl groups, and surprisingly, unactivated aryl groups did proceed to give α-arylated hydantoins in moderate to good % ee and yield (not shown).

1.5.10. Application of SRSvSACI for the conjugate addition of amino acids

While SRSvSACI conditions have previously been applied to intramolecular aldol, alkylation, and acyl migration reactions, intermolecular conjugate addition reaction is one area that has not been exploited. Yoshimura *et al*. bridged this gap by looking at the conjugate addition of **1-43** (**Table 1-7**) with varying *N*-Boc-*N*-MOM substituted amino acids, **1-41a-e**.[34] Prior SRSvSACI methodology work on L-phenylalanine derived **1-41b** could not be applied to L-alanine derived **1-41a** due to the differences in racemization half-life at -78 °C: 22 h for L-phenylalanine derived **1-41b** and 1 h for L-alanine derived **1-41a**. L-Alanine derived **1-41a** was of interest to the authors since it is a useful intermediate in the total synthesis of manzacidin A. It was discovered that L-

Table 1-7 Asymmetric intermolecular conjugate addition.[35]



1-41a-e **1-42a-e** **1-44a - 1-48a** **1-44b - 1-48b**

Entry	S.M.	R	Product (yield)	**a**:**b**	ee (%) **a**, **b**
1	**1-41a**	CH_3	**1-44** (quant)	1:2	97, 97
2	**1-41b**	$PhCH_2$	**1-45** (quant)	3:2	97, 97
3	**1-41c**	*i*-Pr	**1-46** (50%)	1:0	87
4	**1-41d**	*i*-Bu	**1-47** (62%)	1:2	97, 97
5	**1-41e**	$MeS(CH_2)_2$	**1-48** (quant)	1:2	91, 92

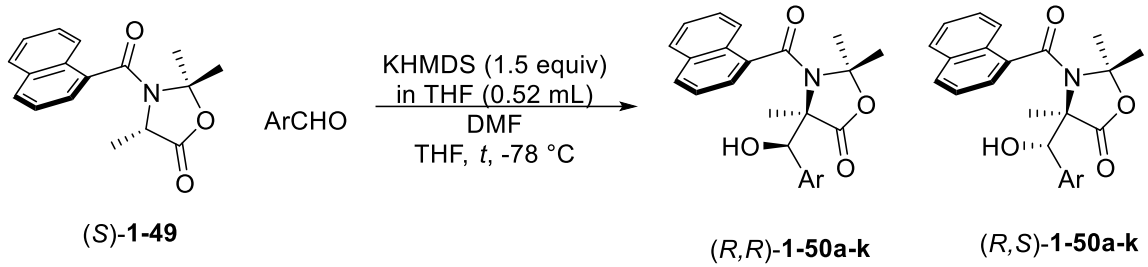
alanine derived **1-41a** and **1-43** (slow addition of KHMDS in a 1:1 mixture of THF/DMF) provided a 1:2 diastereomeric mixture of **1-44a** and **1-44b** in quantitative yield and 97% ee for both diastereomers.

The importance of this in situ deprotonation/conjugate addition protocol was confirmed by comparing it to the procedure developed in their previous methodology for asymmetric methylation on L-phenylalanine. Following their previous protocol, treatment of L-alanine derived **1-41a** with KHMDS for 30 min followed by the addition of **1-43** only proceeded in 70% yield and 22% ee for both diastereomers. Further investigation of the new reaction protocol showed that it could be generalized for a variety of other *N*-MOM-*N*-Boc amino acid ester derivatives, namely L-phenylalanine (entry 2, **1-41b** to **1-45a**/**1-45b**), L-valine (entry 3, **1-41c** to **1-46a**/**1-46b**), L-leucine (entry 4, **1-41d** to **1-47a**/**1-47b**), and L-methionine (entry 5, **1-41e** to **1-48a**/**1-48b**). L-Alanine derivative **1-44a** and **1-44b** was then successfully taken forward in the total synthesis of manzacidin A showing how SRSvSACI can viably be used in the total synthesis of natural products.

1.5.11. Synthesis of *β*-hydroxy quaternary *α*-amino acids

Viswambharan *et al*.[36] have applied the same utilization of SRSvSACI protocol with naphthoyl amide containing oxazolidinones as Branca and Mai[20, 30] to induce axial chirality in the synthesis of enantiopure *β*-hydroxy quaternary α-amino acids. Using L-alanine as their starting material, oxazolidinone (*S*)-**1-49** (**Table 1-8**) was generated from known procedures, and used in combination with benzaldehyde for optimization of SRSvSACI protocol. The best conditions consisted of 1.5 equivalents KHMDS added dropwise to a pre-cooled (-78 °C) mixture of benzaldehyde and **1-49**, which was

Table 1-8 Aldol through SRSvSACI[36]



(*S*)-**1-49**

(*R,R*)-**1-50a-k**

(*R,S*)-**1-50a-k**

Entry	Ar-	*t* (min)	Product	dr (*R,R*)/(*R,S*)	ee (%) (*R,R*)/(*R,S*)	Yield (%)
1	Ph	10	**1-50a**	89:11	84/74	85
2	*o*-Me-C_6H_4	12	**1-50b**	>98:2	82/-	48
3	*p*-Me-C_6H_4	12	**1-50c**	78:22	82/78	73
4	*p*-OMe-C_6H_4	12	**1-50d**	88:12	73/56	67
5	*m*-Br-C_6H_4	15	**1-50e**	92/8	79/65	90
6	*o*-Br-C_6H_4	12.5	**1-50f**	93:7	75/90	91
7	3-pyridine	12	**1-50g**	79:21	85/92	71
8	2-thiophene	12	**1-50h**	50:50	75/71	68
9	*o*-F-C_6H_4	15	**1-50i**	30:70	88/78	56
10	2-furan	12	**1-50j**	10:90	77/94	75
11	1-Me-isatin	12	**1-50k**	42:58	53/87	49

subsequently quenched after 10 min. The reaction proceeded in 78% yield and afforded (*R,R*)-**1-50** and (*R,S*)-**1-50** in a diastereomeric mixture of 89:11 at 83% ee and 75% ee, respectively. This optimized methodology was then applied using (*S*)-**1-49** with a wide variety of aromatic aldehydes, heteroaromatic aldehydes, and the ketone 1-methyl-isatin. Absolute configuration was determined by X-ray structures obtained for multiple products, and the remaining compounds were assigned based on comparison of chiral

HPLC elution order of the major enantiomers. The major diastereomers (entries 1-11) were obtained with % ee ranging from 73% (entry 4) to 94% (entry 10). It was observed that the dr was highly dependent on the aldehyde used. For 2-bromobenzaldehyde (entry 6) the major diastereomer obtained was observed to be (*R*,*R*)-**1-50**, whereas 2-fluorobenzaldehyde (entry 9) afforded (*R*,*S*)-**1-50** as the major diastereomer. It was also seen for some aldehydes containing a donor atom on the aromatic ring such as 2-furaldehyde (entry 10) the major diastereomer was **1-50j**.

The major diastereomer was typically (*R*,*R*)-**1-50**, which originates from a transition state similar to that demonstrated by **1-51** (arising from (*S*)-**1-49** and

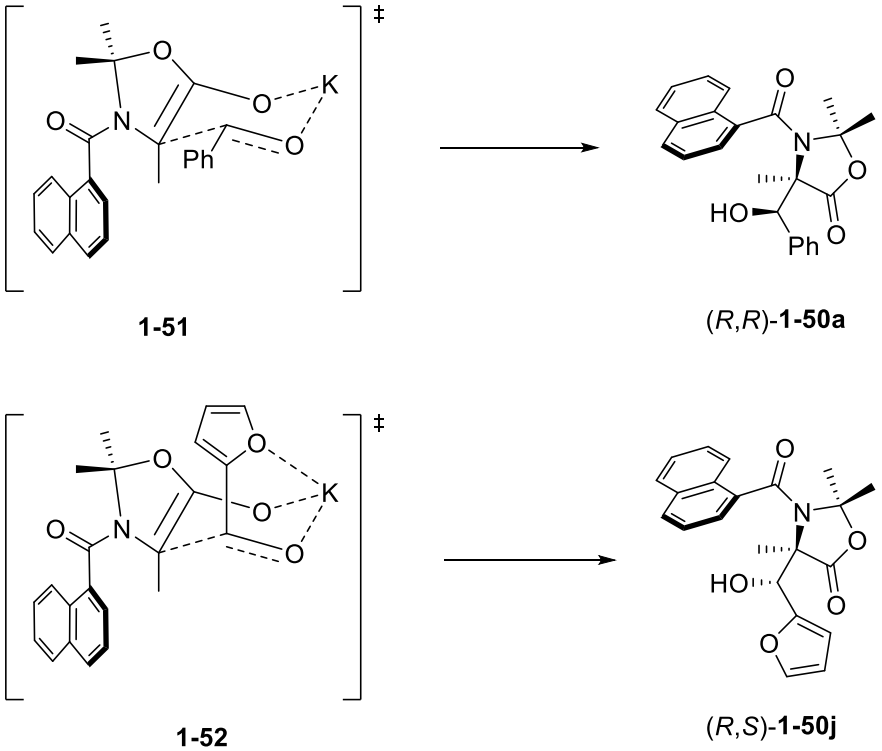


Figure 1-3 Explanation for observed diastereoselectivity for the synthesis of **1-50a-k**.[36]

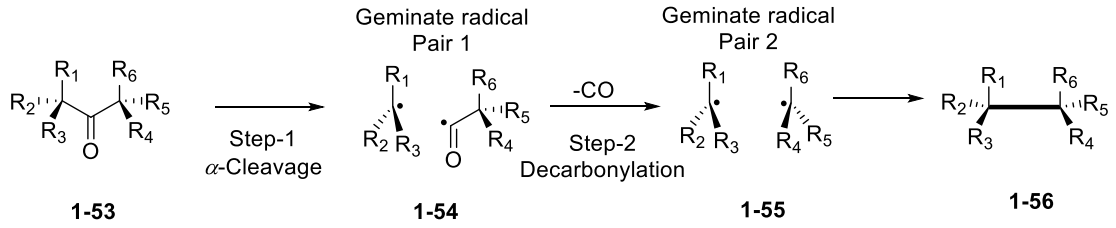
benzaldehyde **Figure 1-3**) and can be explained through a chair-like Zimmerman-Traxler transition state in which the C-N bond is oriented in a pseudoequatorial position and the approaching aldehyde can orient in a pseudoequatorial position. The presence of a donor

atom presents an extra anchoring position between the heteroatom and metal cation. This in turn stabilizes transition structures in a similar fashion as **1-52** (derived from (*S*)-**1-49** and 2-furaldehyde) leading to major diastereomer (*R*,*S*)-**1-50j**. This protocol opens the possibility to not only easily synthesize *β*-hydroxy quaternary *α*-amino acids but it allows substrate control from the aldehyde over the stereoselectivity.

1.6 SRSvSACI through radical intermediates

1.6.1. Double SRSvSACI

Through the succession of a Norrish type-1 *α*-cleavage of chiral **1-53** affording **1-54** followed by decarbonylation to generate **1-55** and subsequent radical-radical combination leading to **1-56**, it is expected that the stepwise two bond cleavage will lead to the loss of the stereochemical information (**Scheme 1-11**). For the starting chirality to be preserved,

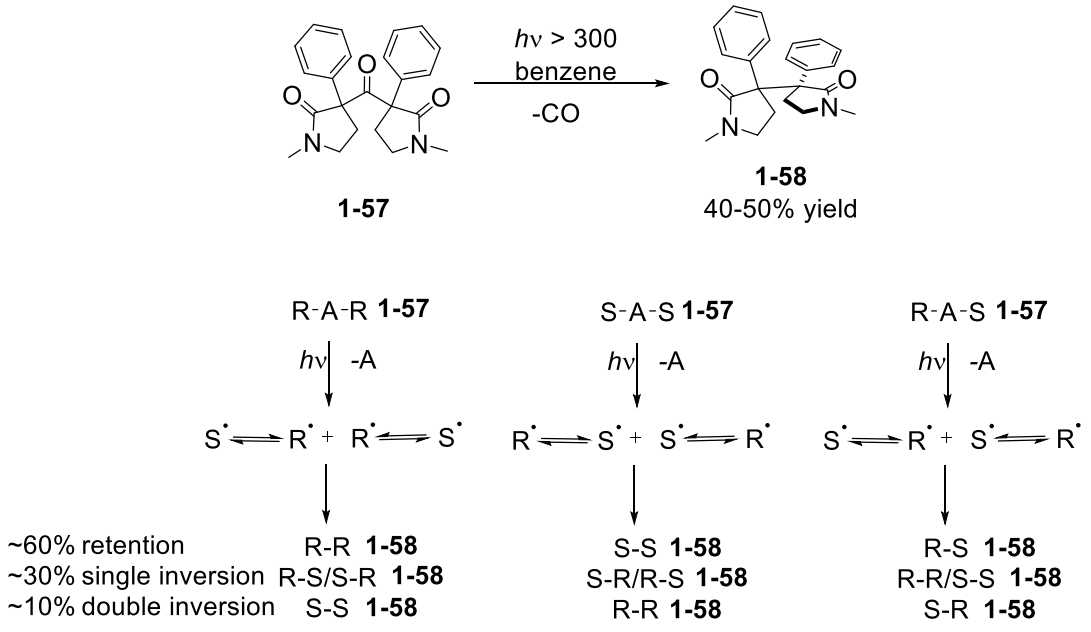


Scheme 1-11 Norrish type-1, decarbonylation, and radical-radical combination.[37]

the timescale for decarbonylation and bond formation would have to be faster than the time needed for the two radicals to rotate. Previously, Garcia-Garibay reported that if the radical pairs are created within crystalline ketones, racemization can be limited through the application of SRSvSACI.[37] Because of the high energetic cost of large amplitude molecular motions in solid-state reactions, the bond formation between radicals **1-55** is much faster than the time of their rotation in the solid. With the previously studied time

constants for rotation of medium-sized molecules in liquid (5-20 ps for benzene) Garcia-Garibay *et al.* questioned if the rotation time in solution could be overcome to produce stereospecific results. They discerned that, for a SRSvSACI photochemical reaction to occur, two things must be true. The reactions must "occur from the singlet excited state with reactants that have essentially no barrier for each of the two bond-cleavage steps, and which also have a spin allowed bond forming reaction."[37]

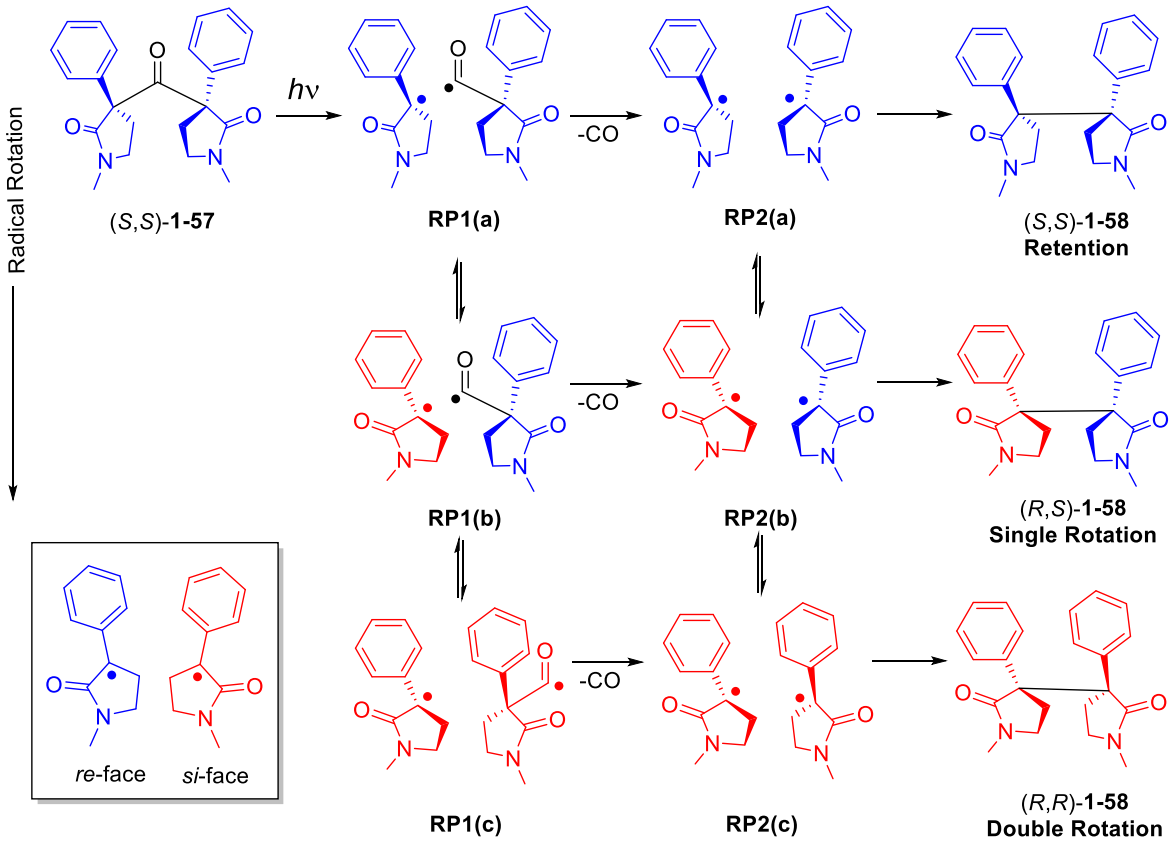
Using previously published work, where a radical application of SRSvSACI with significant stereoselectivity at a single chiral carbon was reported, they deduced that the use of *bis*-(*N*-methyl-phenylpyrrolidinonyl)-ketone (*R,S*)-**1-57**, (*R,R*)-**1-57**, and (*S,S*)-**1-57** (**Scheme 1-17**) could possibly afford them the results they wanted as it had the qualities required. They were pleased to discover that the reaction did proceed stereoselectively, and the respective retention, single inversion, and double inversion arising from the three different starting materials are demonstrated in **Scheme 1-12**. For all cases, the retention



Scheme 1-12 Double SRSvSACI through Norrish type-1 reaction for the synthesis of **1-58**[37]

product was obtained in around 60% yield ((*R,R*)-**1-58** derived from (*R,R*)-**1-57** and (*S,S*)-**1-58** derived from (*S,S*)-**1-57**). The product arising from epimerization of a single chiral center was made in 30% yield ((*R,S*)-**1-58** for both (*R,R*)-**1-57** (*S,S*)-**1-57**). The double inversion product was obtained in around 10% yield ((*S,S*)-**1-58** derived from (*R,R*)-**1-57** and (*R,R*)-**1-58** derived from (*S,S*)-**1-57**). Note that *meso*-(*R,S*)-**1-57**, gave a 2:1 diastereoselective ratio of (*R,S*)-**1-58**:mixture of (*R,R*)-**1-58** and (*S,S*)-**1-58**, which is consistent with the selectivity observed for starting materials (*R,R*)-**1-57** and (*S,S*)-**1-57** since the retentive and double inversion products for the meso starting material are identical.

Scheme 1-13 demonstrates the bond cleavage of (*S,S*)-**1-57** to generate radical pair

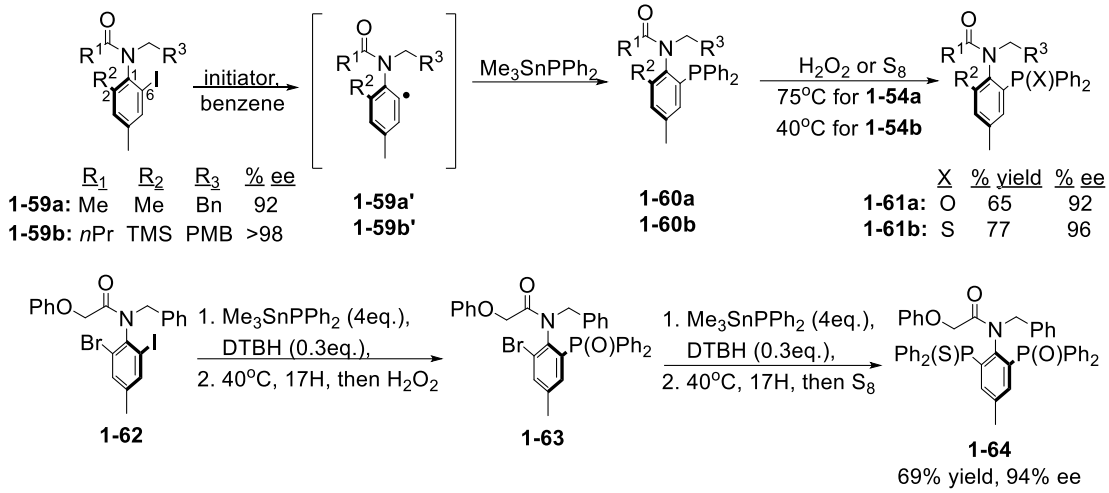


Scheme 1-13 Pathways leading to three possible **1-58** products[37]

RP1(a). If decarbonylation followed by bond formation is rapid, then **RP2(a)** is generated followed by final product (*S*,*S*)-**1-58**. Single rotation of **RP1(a)** or **RP2(a)** will afford intermediates **RP1(b)** or **RP2(b)**, respectively, which will ultimately lead to *meso*-(*R*,*S*)-**1-58**. If double rotation occurs for either **RP1(a)** or **RP2(a)** then the double inversion product (*R*,*R*)-**1-58** is obtained. As discussed for **Scheme 1-12**, the percentages obtained for the retention:single inversion:double inversion products were 60:30:10. While the starting material chirality is not completely retained, this reaction importantly illustrates how photochemical SRSvSACI reactions can procced with minimal radical rotation in liquids.

1.6.2. Aryl radical phosphanylations

While chirality transfer from a centrosymmetric carbon to a product through a SRSvSACI radical reaction has been elegantly displayed in previous publications, Curran et al. reported the first ever chirality transfer from an axially chiral intermediate to an axially chiral product through a radical mechanism without the use of any external chiral sources.[38] SRSvSACI here is achieved from the high rate of radical phosphanylation compared to the rate of rotation about the N-Ar bond in the axially chiral intermediate. Previous kinetic studies of phosphanylations on aryl radicals showed that for *o*-indoanisole the k_{phos} = 9 X 10^8 $M^{-1}s^{-1}$. It was because of this large rate constant that aryl iodides were used in this application. While **1-59a** and **1-59b** (**Scheme 1-14**) do not possess any central chirality, the 2,6-disubstituted aryl ring has hindered rotation which translates into axial chirality. This axial chirality is preserved in the generation of **1-60a,b** (which proceeds through radical **1-59a′,b′**). The axial chirality was retained in the intermediate after removing the ortho substituent and rapidly trap it to provide the final

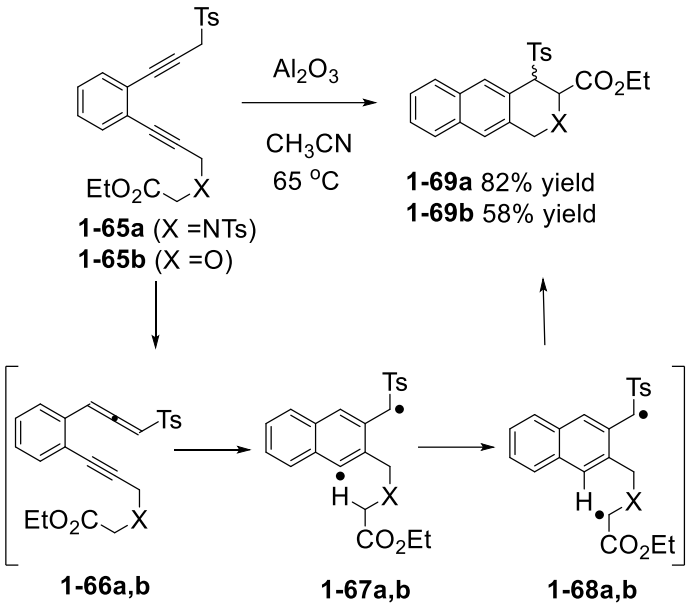


Scheme 1-14 Phosphanylation on axially chiral aryl radicals.[38]

product with the same axial chirality without racemization of the radical intermediates **1-59a′** and **1-59b′**. Structure **1-60a,b** was found to be conformationally stable even up to 80 °C. Treatment of **1-60a** with H_2O_2 led to the phosphine oxide **1-61a**, obtained in 65% yield and 92% ee. Treatment of **1-60b** under similar conditions with S_8 as the oxidant afforded **1-61b** in 77% yield and 96% ee. Due to the high SRSvSACI obtained in these results, this method was applied to the sequential double phosphanylation of the axially chiral *ortho,ortho*-2-bishaloanilide **1-62.** As was seen previously, there is high % ee in both steps of this phosphanylation, giving the final product **1-64** with 94% ee.

1.6.3. Cascade rearrangement of enediynes

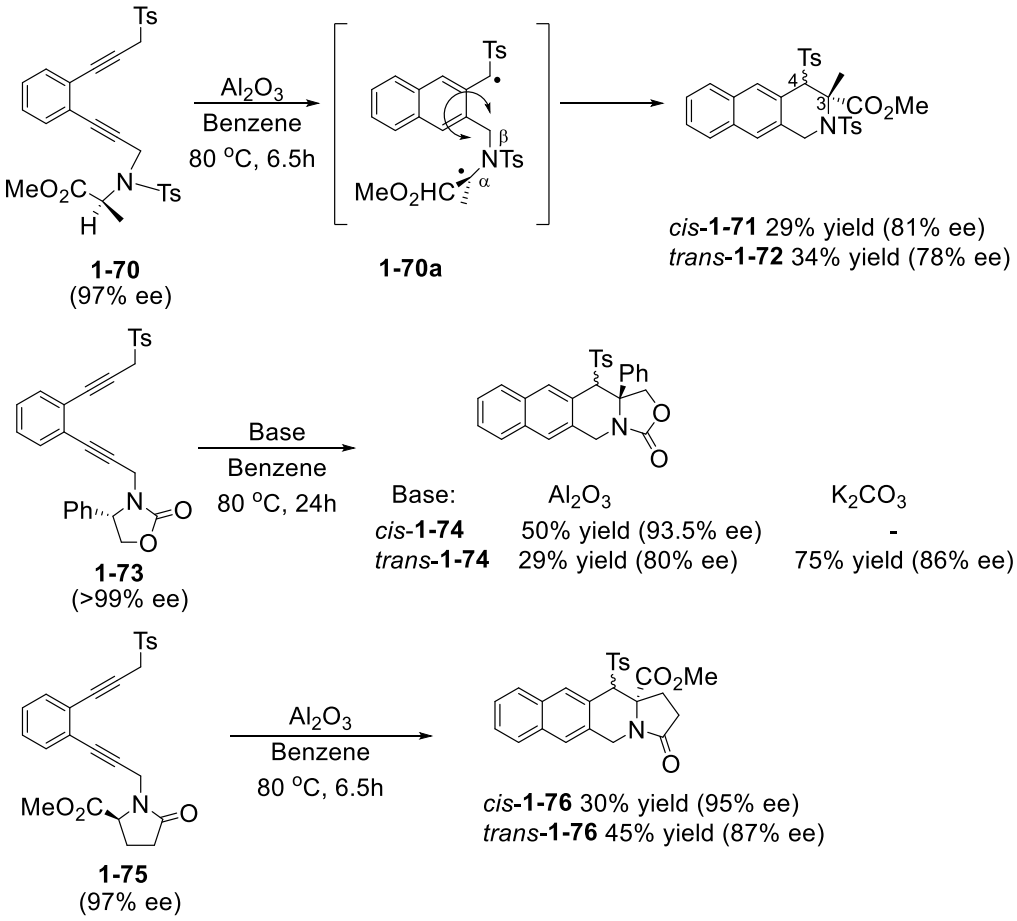
With the goal of developing an asymmetric synthesis of heterocycles containing a quaternary stereogenic center, Nechab *et al* studied the reactions of glycine derived **1-65a** and glycolic acid derived **1-65b**[39] proceeding through a 1,3-proton shift forming enynallenes **1-66a,b** (**Scheme1-15**). Following this, Saito-Myers cyclization generates biradicals **1-67a,b**. 1,5-Hydrogen atom transfer affords **1-68a,b** which subsequently undergoes intramolecular coupling to give products **1-69a,b** in 82% and 58% yield,



Scheme 1-15 Cascade rearrangement of chiral enediynes **1-65a,b**[39]

respectively. By first optimizing reaction conditions on an achiral **1-65a,b** (**Scheme 1-15**), it was determined that benzene as their choice of solvent and Al_2O_3 as their base at 80 °C, with varying reaction times, provided the best results.

They determined that for the best chiral induction, the enediyne they choose to use should have only one conformation where the hydrogen atom of their *N*-substituted side chain can transfer (i.e. chiral), as seen for the starting compounds **1-70 1-73**, and **1-75** (**Scheme 1-16)**. The captodative radical center (radical stabilized by neighboring electron withdrawing and electron donating groups) should retain its original conformation and rotation about both the sp^2 C-N bond (**1-70a**, α) and sp^3 C-N bond (**1-70a**, β) should be hindered to prevent racemization of that center. If the chirality is properly preserved from the starting material then the expected product can form two possible diastereomers and four possible products due to the two chiral centers generated in the product **1-71** (chiral centers at C3 and C4). If rotations about the α and β bonds of **1-70** are limited, then ring closure through coupling of the two reactive radical centers can occur either on the front

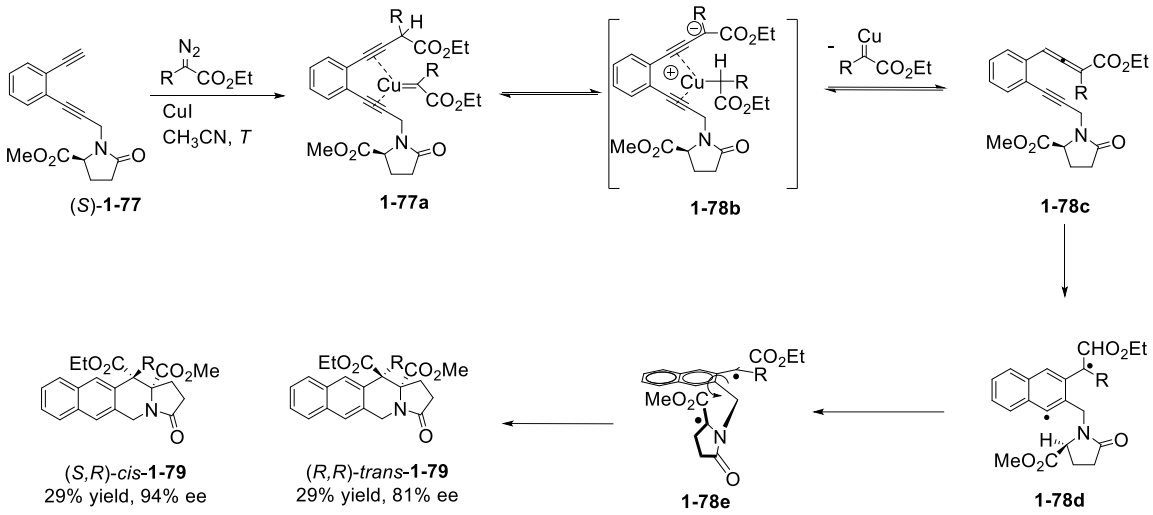


Scheme 1-16 Enediyne radical cascade rearrangement of **1-70**, **1-73**, and **1-75**[39]

or back face of **1-70a** leading to either the *cis*- or *trans*-diastereomers of **1-71**. This is observed for all cases demonstrated in **Scheme 1-16**, and the reaction proceeded with retention of the original chiral center. It was also noted that for **1-73**, the use of K_2CO_3 as base afforded only *trans*-**1-74** in 75% yield and 86% ee, whereas the use of Al_2O_3 gave both *trans*- and *cis*-**1-74**. Compound **1-75** led to *cis*-**1-76** in 30% yield and 95% ee and *trans*-**1-76** in 45% yield and 87% ee.

Using this same principle in SRSvSACI, Bertrand *et al*. have reported the ability to both form and cyclize these types of enediynes in a one-pot diazo coupling enediyne cascade rearrangement reaction.[40] Starting with a variety of enediyne derivatives, **1-77**,

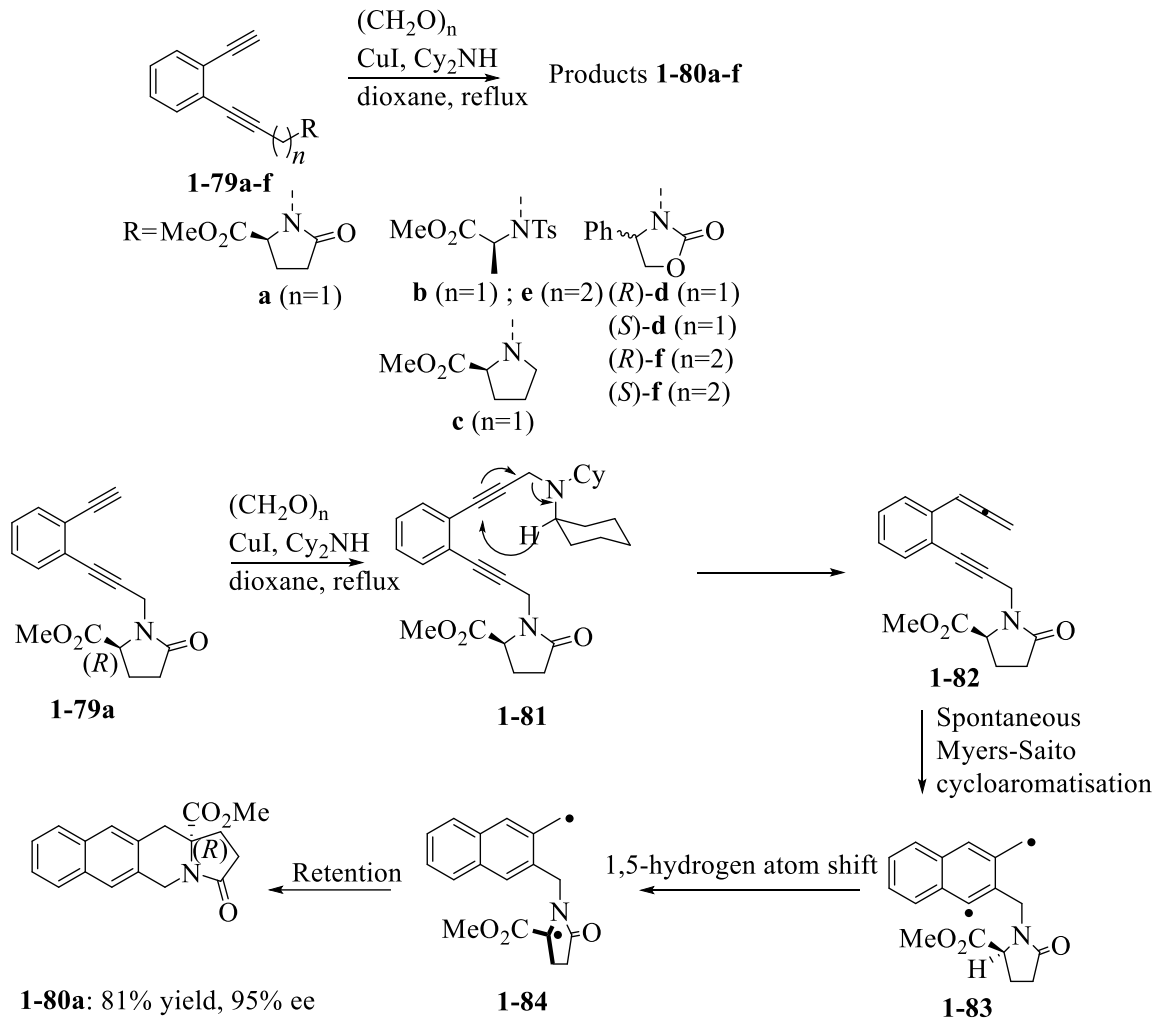
Table 1-9 One-pot diazo coupling enediyne cascade rearrangement of **1-77**[40]



Entry	S.M	R	*T* (°C)	Product	dr *cis*:*trans*	ee (%) (*R*,*S*)/(*R*,*R*)	Yield (%)
1	(*S*)-**1-77**	H	80	**1-79a**	1:1	94/81	58
2	(*S*)-**1-77**	Ph	80	**1-79b**	44:56	91/79	63
3	(*R*)-**1-77**	Ph	24	**1-79b**	46:54	97/89	83

1.4 equivalents of diazo ester were added in the presence of CuI (5% mol) in acetonitrile (**Table 1-9**). For **1-79a**, the cyclized final product was obtained in a total yield of 58% Diastereomer (*S*,*R*)-*cis*-**1-79** was obtained in 29% yield and 94% ee while diastereomer (*R*,*R*)-*trans*-**1-79** was obtained in 29% yield and 81% ee (entry 1). It was discovered that lowering the temperature led not only to increased % ee of the diastereomers, but also gave greater yields. Reactions run at 80 °C were tried first and found to be successful (entry 2: 63% yield, 11:56 dr, 91% and 71% ee respectively), and subsequent reactions at room temperature were found to proceed with higher yield and % ee (entry 3: 83% yield, 46:54 dr, 97% and 89% ee respectively.

Because of the lack of diastereoselectivity in this method, Bertrand et al. devised a more efficient synthetic pathway towards the creation of six and seven membered α-amino acid esters bearing a quaternary stereocenter through this radical enediyne rearrangement with SRSvSACI.[41] The previous diastereoselectivity problem was due to



Scheme 1-17 Stereoselective enediyne cascade Rearrangement.[41]

the necessity of having an electron withdrawing group on the terminus of the allene moiety. To overcome this problem, a modified Mannich type reaction reported by Ma and co-workers,[42-44] where dicyclohexylamine and CuI refluxed in dioxane with terminal allenes **1-79a-f**, was used to stereoselectively produce **1-80a-f** (**Scheme 1-17**) in a stereoselective manner through a one-pot Crabbé homologation-radical cascade cyclisation. The reaction was shown to be general and all products were obtained with moderate to good yields with high % ee and retention of configuration.

Bertrand and co-workers were also pleased to report that this method could be extended to homopropargylic amines with n=2 towards the synthesis of 7-membered heterocycle rings **1-80e-f** where increased rotation of the amine moiety in the conformationally chiral intermediate only slightly reduced the % ee of the products.

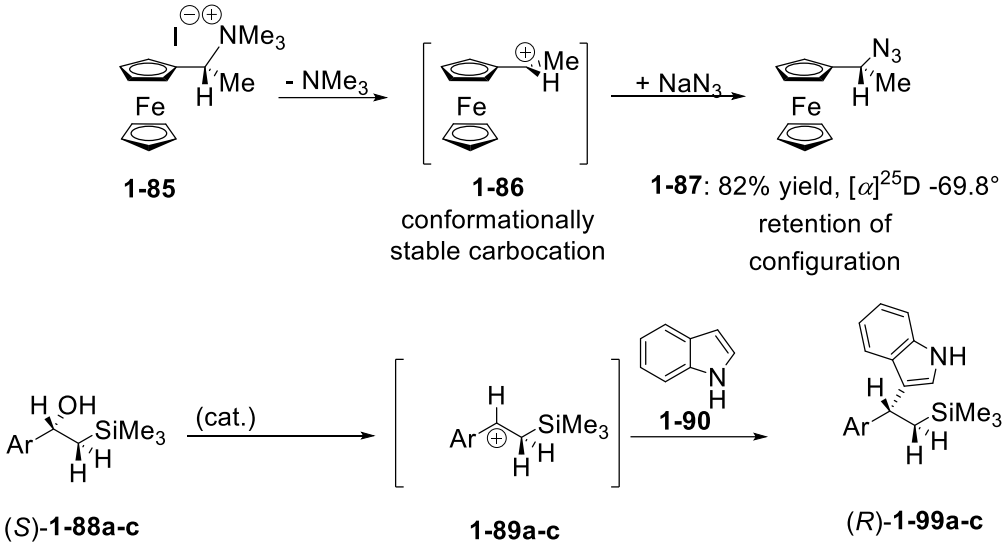
Surprisingly, for enediyne **1-79c**, where there are two possible locations for hydrogen abstraction only the captodative stereocenter hydrogen went through the 1,5-hydrogen atom shift. Product with hydrogen transfer from the methylene group was not seen in the product mixture and could be attributed to the increased stability of the more substituted radical.

1.7 SRSvSACI reactions of carbocations

1.7.1. Friedel-Crafts alkylation using *α*-aryl alcohols

Previously, Ugi *et al* showed that electrophilic substitution of chiral *α*-substituted alkyl ferrocenes can proceed stereoselectively through an intermediate possessing axial chirality and no central elements of chirality.[45, 46] Following the removal of a leaving group from **1-85 (Table 1-10**), the ferrocenylalkyl cation **1-86** is generated. It was seen that substitution on this intermediate, leading to **1-87**, proceeded with complete retention of the starting chirality. While electrophilic substitutions of chiral starting materials proceeding via a carbocation intermediates typically produce racemic products, **1-86** was found to be conformationally stable, which led stereoselectively to **1-87**. While investigating iron salt catalyzed Friedel-Crafts alkylation on aromatic compounds, Itoh *et al* discovered that SRSvSACI could be applicable to reactions using *α*-aryl alcohols as alkylating agents that possessed a silyl group at the *β*-position.[47]

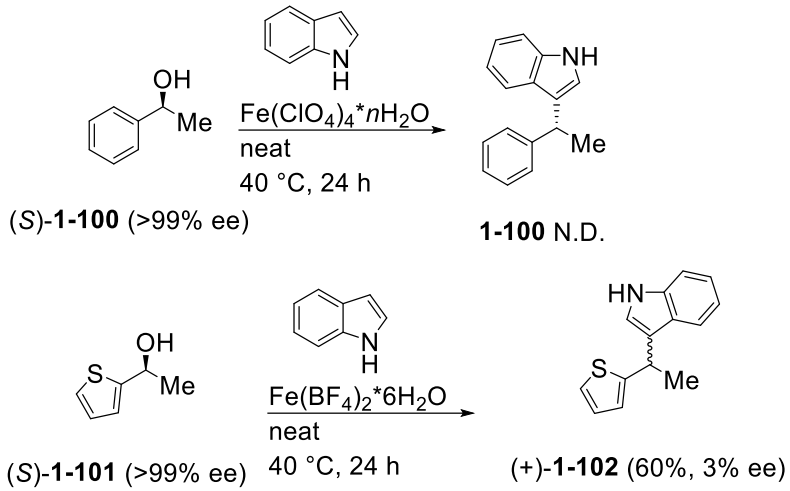
Table 1-10 Electrophilic Substitution through Friedel-Crafts alkylation[47]



Entry	S.M	R	Acid catalyst	Product	Yield (%)	ee (%)
1	(*S*)-**1-88a**	Ph	$Fe(ClO_4)_3$*$n$$H_2O$	**1-99a**	67	91
2	(*S*)-**1-88b**	2-furyl	$Sc(OTf)_3$	**1-99b**	66	93
3	(*R*)-**1-88c**	2-thienyl	$Fe(BF_4)_2$*$6H_2O$	**1-99b**	60	66

While the reaction proceeds via the loss of the chiral center by means of the $–OH^-$ leaving group ((*S*)-**1-88a-c** to **1-89a-c**), (*R*)-**1-99a** was generated stereoselectively in 91% ee using $Fe(ClO_4)_3$*$n$$H_2O$ as the iron salt (entry 1). This protocol was also applied to 2-furyl and 2-thienyl alcohols to afford **1-99b** in 66% yield and 93% ee and **1-99c** in 60% yield and 66% ee (entries 2 and 3. It was seen that conventional Lewis acids such as $AlCl_3$, $FeCl_3$, and $Sc(OTf)_3$ could be used without significant loss in % ee, although the yields were lower.

Furthermore, it was seen that the *β*-trimethylsilyl group was necessary for both increased reactivity as well as the enantioselectivity of the reaction (**Figure 1-18**). As demonstrated from the attempted alkylations of (*S*)-**1-100** and (*S*)-**1-101** (, both of which are lacking the *β*-trimethylsilyl group, the reaction proceeds in poor yield, and almost no enantioselectivity. They hypothesized that the trimethylsilyl group occupies the opposite face of the hydroxyl leaving group for the generation of the carbocation intermediate. In



Scheme 1-18 Attempted alkylation on derivatives without trimethylsilyl[47]

the subsequent step, nucleophilic attack on the cationic intermediate can sterically only attack from the opposite face of the trimethylsilyl group. The leads stereoselectively to the final product with retention of configuration.

1.8 Conclusion

Asymmetric synthesis utilizing the self-regeneration of stereocenters via stereolabile axially chiral intermediates typically involves the formation of axially chiral intermediates without any permanent forms of chirality and is generated from enantiopure starting material possessing a single stereocenter. The starting material's chiral stereocenter must impart sufficient stereochemical control on the formation of the intermediate such that it is generated as only a single conformer (either *M*- or *P*-conformer). The intermediate must not readily racemize on the reaction timescale, and subsequent trapping must afford an enantiopure chiral product. As discussed in this chapter this principle has been applied successfully in a wide variety of reactions, such as those utilizing enolate, radical, and carbocation intermediates. The next chapter will discuss the application of SRSvSACI protocol towards the asymmetric synthesis of *α*-

quaternary substituted benzyl and silyl protected (*S*)-methyl lactate derivatives coupled with achiral oxazolidinones.

1.9 Bibliography

1. Carlier, P. R.; Hsu, D. C.; Bryson, S. A. Self-Regeneration of Stereocenters (Srs) Via Stereolabile Axially Chiral Intermediates. In *Stereochemical Aspects of Organolithium Compounds*, Verlag Helvetica Chimica Acta: 2010; pp 53-91.

2. Zhao, H. W.; Hsu, D. C.; Carlier, P. R. Memory of Chirality: An Emerging Strategy for Asymmetric Synthesis. *Synthesis* **2005**, 1-16.

3. Kawabata, T.; Yahiro, K.; Fuji, K. Memory of Chirality: Enantioselective Alkylation Reactions at an Asymmetric Carbon Adjacent to a Carbonyl Group. *J. Am. Chem. Soc.* **1991**, *113*, 9694-9696.

4. Seebach, D.; Sting, A. R.; Hoffmann, M. Self-Regeneration of Stereocenters (Srs)—Applications, Limitations, and Abandonment of a Synthetic Principle. *Angew. Chem. Int. Ed.* **1996**, *35*, 2708-2748.

5. Seebach, D.; Wasmuth, D. Alkylation of Amino Acids without Loss of Optical Activity: A- and B-Alkylation of an Aspartic Acid Derivative. *Angew. Chem. Int. Ed.* **1981**, *20*, 971.

6. Fuji, K.; Kawabata, T. Memory of Chirality—a New Principle in Enolate Chemistry. *Chem. Eur. J.* **1998**, *4*, 373-376.

7. Eyring, H. The Activated Complex and the Absolute Rate of Chemical Reactions. *Chem. Rev.* **1935**, *17*, 65-77.

8. Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*. Wiley-Interscience: New York, 1994.

9. Kawabata, T.; Moriyama, K.; Kawakami, S.; Tsubaki, K. Powdered Koh in Dmso: An Efficient Base for Asymmetric Cyclization Via Memory of Chirality at Ambient Temperature. *J. Am. Chem. Soc.* **2008**, *130*, 4153-4157.

10. Moriyama, K.; Sakai, H.; Kawabata, T. Direct Asymmetric Intramolecular Alkylation of B-Alkoxy-A-Amino Esters Via Memory of Chirality. *Org. Lett.* **2008**, *10*, 3883-3886.

11. Farran, D.; Archirel, P.; Toupet, L.; Martinez, J.; Dewynter, G. Enantiodivergent Transannular Rearrangement of 3-Isopropyl-1,4-Benzodiazepine-2,5-Dione by Memory of Chirality. *Eur, J. Org. Chem.* **2011**, *2011*, 2043-2047.

12. Kawabata, T.; Fuji, K. Memory of Chirality: Asymmetric Induction Based on the Dynamic Chirality of Enolates. In *Topics in Stereochemistry*, John Wiley & Sons, Inc.: 2003; pp 175-205.

13. Kramer, W. H.; Griesbeck, A. G. The Same and Not the Same: Chirality, Topicity, and Memory of Chirality. *J. Chem. Educ.* **2008**, *85*, 701-709.

14. Chowdari, N. S.; Barbas, C. F. Total Synthesis of Lfa-1 Antagonist Birt-377 Via Organocatalytic Asymmetric Construction of a Quaternary Stereocenter. *Org. Lett.* **2005**, *7*, 867-870.

15. Lee, Y.-J.; Lee, J.; Kim, M.-J.; Kim, T.-S.; Park, H.-g.; Jew, S.-s. Highly Enantioselective Synthesis of (R)-A-Alkylserines Via Phase-Transfer Catalytic Alkylation of O-Biphenyl-2-Oxazoline-4-Carboxylic Acid Tert-Butyl Ester Using Cinchona-Derived Catalysts. *Org. Lett.* **2005**, *7*, 1557-1560.

16. Maruoka, K.; Ooi, T.; Kano, T. Design of Chiral Organocatalysts for Practical Asymmetric Synthesis of Amino Acid Derivatives. *Chem. Commun.* **2007**, 1487-1495.

17. Jones, M. C.; Marsden, S. P.; Muñoz Subtil, D. M. Efficient Asymmetric Synthesis of Quaternary (E)-Vinylglycines by Deconjugative Alkylation of Dehydroamino Acids. *Org. Lett.* **2006**, *8*, 5509-5512.

18. Satoh, T.; Hirano, M.; Kuroiwa, A.; Kaneko, Y. A Synthesis of Optically Active A-Quaternary A-Amino Acids and Esters by Assembling Three Components, Ketones, (R)-Chloromethyl P-Tolyl Sulfoxide, and Sodium Azide, Via Sulfinyloxiranes. *Tetrahedron* **2006**, *62*, 9268-9279.

19. Davies, S. G.; Christopher Garner, A.; Ouzman, J. V. A.; Roberts, P. M.; Smith, A. D.; Snow, E. J.; Thomson, J. E.; Tamayo, J. A.; Vickers, R. J. Diastereoselective Synthesis of Quaternary [Small Alpha]-Amino Acids from Diketopiperazine Templates. *Org. Biomol. Chem.* **2007**, *5*, 2138-2147.

20. Branca, M.; Pena, S. b.; Guillot, R. g.; Gori, D.; Alezra, V. r.; Kouklovsky, C. Memory of Chirality of Tertiary Aromatic Amides: A Simple and Efficient Method for the Enantioselective Synthesis of Quaternary A-Amino Acids. *J. Am. Chem. Soc.* **2009**, *131*, 10711-10718.

21. Ghorai, M. K.; Ghosh, K.; Yadav, A. K. Enantioselective Synthesis of A,B-Diamino Ester Derivatives: Memory of Chirality in Imino-Aldol Reactions. *Tetrahedron Lett.* **2009**, *50*, 476-479.

22. Kawabata, T.; Wirth, T.; Yahiro, K.; Suzuki, H.; Fuji, K. Direct Asymmetric .Alpha.-Alkylation of Phenylalanine Derivatives Using No External Chiral Sources. *J. Am. Chem. Soc.* **1994**, *116*, 10809-10810.

23. Kawabata, T.; Chen, J.; Suzuki, H.; Nagae, Y.; Kinoshita, T.; Chancharunee, S.; Fuji, K. Memory of Chirality in Diastereoselective A-Alkylation of Isoleucine and Allo-Isoleucine Derivatives. *Org. Lett.* **2000**, *2*, 3883-3885.

24. Kawabata, T.; Suzuki, H.; Nagae, Y.; Fuji, K. A Chiral Nonracemic Enolate with Dynamic Axial Chirality: Direct Asymmetric A-Methylation of A-Amino Acid Derivatives. *Angew. Chem. Int. Ed.* **2000**, *39*, 2155-2157.

25. Sakamoto, M.; Iwamoto, T.; Nono, N.; Ando, M.; Arai, W.; Mino, T.; Fujita, T. Memory of Chirality Generated by Spontaneous Crystallization and Asymmetric Synthesis Using the Frozen Chirality. *J. Org. Chem.* **2002**, *68*, 942-946.

26. Ghorai, M. K.; Ghosh, K.; Yadav, A. K.; Nanaji, Y.; Halder, S.; Sayyad, M. Memory of Chirality (Moc) Concept in Imino-Aldol Reaction: Enantioselective Synthesis of A,B-Diamino Esters and Aziridines. *J. Org. Chem.* **2013**, *78*, 2311-2326.

27. Kawabata, T.; Teraoka, F.; Fuji, K.; Ozturk, O.; Yoshimura, T. Asymmetric Carbonyl Migration of A-Amino Acid Derivatives Via Memory of Chirality. *Synlett* **2011**, *2011*, 543-546.

28. Watanabe, H.; Yoshimura, T.; Kawakami, S.; Sasamori, T.; Tokitoh, N.; Kawabata, T. Asymmetric Aldol Reaction Via Memory of Chirality. *Chem. Commun.* **2012**, *48*, 5346-5348.

29. Tayama, E.; Igarashi, T.; Iwamoto, H.; Hasegawa, E. Asymmetric Alpha-2-Tosylethenylation of N,N-Dialkyl-L-Amino Acid Esters Via the Formation of Non-Racemic Ammonium Enolates. *Org. Biomol. Chem.* **2012**, *10*, 339-345.

30. Mai, T. T.; Viswambharan, B.; Gori, D.; Kouklovsky, C.; Alezra, V. Memory of Chirality of Tertiary Aromatic Amide: Application to the Asymmetric Synthesis of (S)-A-Methyldopa. *J. Org. Chem.* **2012**, *77*, 8797-8801.

31. Foschi, F.; Tagliabue, A.; Mihali, V.; Pilati, T.; Pecnikaj, I.; Penso, M. Memory of Chirality Approach to the Enantiodivergent Synthesis of Chiral Benzo[D]Sultams. *Org. Lett.* **2013**, *15*, 3686-3689.

32. Tomohara, K.; Yoshimura, T.; Hyakutake, R.; Yang, P.; Kawabata, T. Asymmetric A-Arylation of Amino Acid Derivatives by Clayden Rearrangement of Ester Enolates Via Memory of Chirality. *J. Am. Chem. Soc.* **2013**, *135*, 13294-13297.

33. Clayden, J.; Dufour, J.; Grainger, D. M.; Helliwell, M. Substituted Diarylmethylamines by Stereospecific Intramolecular Electrophilic Arylation of Lithiated Ureas. *J. Am. Chem. Soc.* **2007**, *129*, 7488-7489.

34. Yoshimura, T.; Kinoshita, T.; Yoshioka, H.; Kawabata, T. Asymmetric Intermolecular Conjugate Addition of Amino Acid Derivatives Via Memory of Chirality: Total Synthesis of Manzacidin A. *Org. Lett.* **2013**, *15*, 864-867.

35. Yoshimura, T.; Kinoshita, T.; Yoshioka, H.; Kawabata, T. Asymmetric Intermolecular Conjugate Addition of Amino Acid Derivatives Via Memory of Chirality: Total Synthesis of Manzacidin A. *Org. Lett.* **2013**.

36. Viswambharan, B.; Gori, D.; Guillot, R.; Kouklovsky, C.; Alezra, V. Substrate Control in Enantioselective and Diastereoselective Aldol Reaction by Memory of Chirality: A Rapid Access to Enantiopure B-Hydroxy Quaternary A-Amino Acids. *Org. Lett.* **2014**, *16*, 788-791.

37. Resendiz, M. J. E.; Family, F.; Fuller, K.; Campos, L. M.; Khan, S. I.; Lebedeva, N. V.; Forbes, M. D. E.; Garcia-Garibay, M. A. Radical Reactions with Double Memory of Chirality (2moc) for the Enantiospecific Synthesis of Adjacent Stereogenic Quaternary Centers in Solution: Cleavage and Bonding Faster Than Radical Rotation. *J. Am. Chem. Soc.* **2009**, *131*, 8425-8433.

38. Bruch, A.; Ambrosius, A.; Fröhlich, R.; Studer, A.; Guthrie, D. B.; Zhang, H.; Curran, D. P. Memory of Axial Chirality in Aryl Radical Phosphanylations. *J. Am. Chem. Soc.* **2010**, *132*, 11452-11454.

39. Nechab, M.; Campolo, D.; Maury, J.; Perfetti, P.; Vanthuyne, N.; Siri, D.; Bertrand, M. l. P. Memory of Chirality in Cascade Rearrangements of Enediynes. *J. Am. Chem. Soc.* **2010**, *132*, 14742-14744.

40. Mondal, S.; Nechab, M.; Campolo, D.; Vanthuyne, N.; Bertrand, M. P. Copper Carbenoid, Reactant and Catalyst for One-Pot Diazo Ester Coupling Cascade Rearrangement of Enediynes: Formation of Two Contiguous Tetrasubstituted Stereocenters. *Adv. Synth. Catal.* **2012**, *354*, 1987-2000.

41. Mondal, S.; Nechab, M.; Vanthuyne, N.; Bertrand, M. P. One-Pot Crabbe Homologation-Radical Cascade Cyclisation with Memory of Chirality. *Chem. Commun.* **2012**, *48*, 2549-2551.

42. Kuang, J.; Ma, S. An Efficient Synthesis of Terminal Allenes from Terminal 1-Alkynes. *J. Org. Chem.* **2009**, *74*, 1763-1765.

43. Kuang, J.; Ma, S. One-Pot Synthesis of 1,3-Disubstituted Allenes from 1-Alkynes, Aldehydes, and Morpholine. *J. Am. Chem. Soc.* **2010**, *132*, 1786-1787.

44. Kitagaki, S.; Komizu, M.; Mukai, C. Can the Crabbé Homologation Be Successfully Applied to the Synthesis of 1,3-Disubstituted Allenes? *Synlett* **2011**, *2011*, 1129-1132.

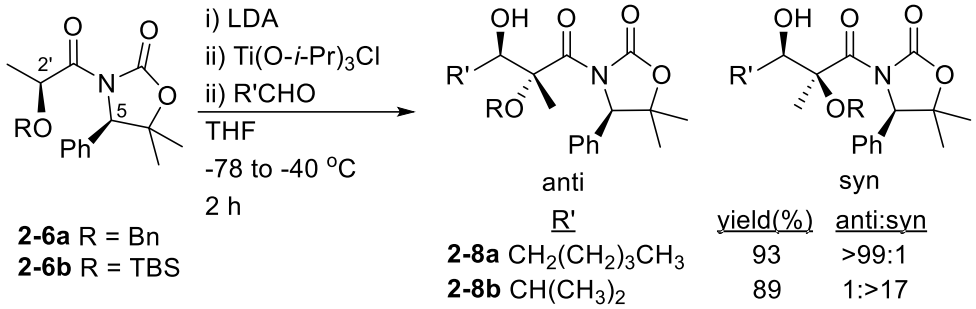
45. Marquarding, D.; Klusacek, H.; Gokel, G.; Hoffmann, P.; Ugi, I. Stereoselective Syntheses. Vi. Correlation of Central and Planar Chirality in Ferrocene Derivatives. *J. Am. Chem. Soc.* **1970**, *92*, 5389-5393.

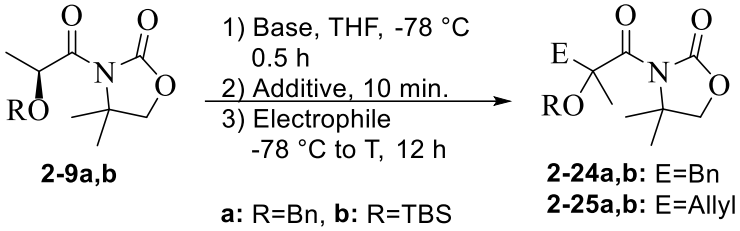
46. Gokel, G. W.; Marquarding, D.; Ugi, I. K. Stereoselective Syntheses. Viii. Retentive Nucleophilic Displacements of A-Substituted Alkylferrocenes. *J. Org. Chem.* **1972**, *37*, 3052-3058.

47. Nokami, T.; Yamane, Y.; Oshitani, S.; Kobayashi, J.-k.; Matsui, S.-i.; Nishihara, T.; Uno, H.; Hayase, S.; Itoh, T. The B-Silyl Effect on the Memory of Chirality in Friedel–Crafts Alkylation Using Chiral A-Aryl Alcohols. *Org. Lett.* **2015**, *17*, 3182-3185.

2. Exploring SRSvSACI Reactions of (*S*)-Methyl Lactate Derivatives

2.1 Abstract of Chapter 2





Previous work performed by Kobayashi *et al.*[1] showed how enolate geometry formation could be controlled by the directing effects of the *O*-benzyl and *O*-TBS substituents of compounds **2-6a** and **2-6b**. We believed that a twisted amide enolate featuring a chiral C(O^-)-N axis can sufficiently impart stereochemical information and control the selectivity of the reaction such that the stereocenter of the oxazolidinone is not necessary for the selectivity of the reaction

Following this hypothesis, *O*-benzyl and *O*-TBS protected (*S*)-methyl lactate derivatives **2-9a** and **2-9b**, respectively, were synthesized. Subsequent aldol reaction with crotonaldehyde was then performed according to the protocol used by Kobayashi *et al*. The diastereoselectivity was 2:1 for **2-9a** and 2:1 for **2-9b**, significantly lower than that observed by Kobayashi. Both because of the low selectivity and the complexity of the

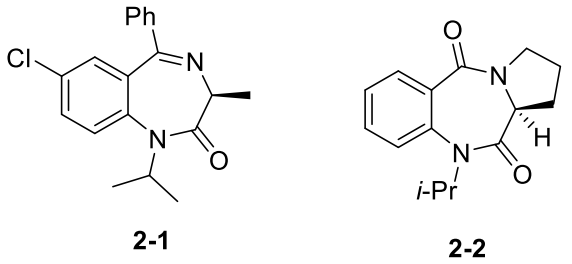
products, having multiple stereocenters, our focus switched away from an aldol reaction and to attempted alkylation.

Unfortunately, as outlined in **Table 2-1**, no attempts at alkylation were successful. We suspected steric crowding around the α-carbon to be the problem, and to verify this we synthesized glycolate derivative **2-28** and successfully allylated and benzylated it. We then attempted to prove that derivatives **2-9a** and **2-9b** were being deprotonated and the problem lay with the size of our electrophiles during alkylation. Surprisingly, it was discovered that in our deprotonation/alkylation reactions our starting material was not being deprotonated. As proven by **Figure 2-3,** attempted deprotonation and subsequent quenching with D_2O returned protio-starting material indicating that deprotonation had not taken place.

In an attempt to remedy the steric problems with **2-9**, alternate oxazolidinone **2-35** was synthesized, but attempts to couple this new achiral oxazolidinone with *O*-benzyl and *O*-TBS protected (*S*)-methyl lactate derivatives **2-18a** and **2-18b** proved unsuccessful. It is suspected that the steric bulk from bromine prevented **2-18** to successfully approach and couple with oxazolidinone **2-35**, and it was here that work involving these (*S*)-methyl lactate derivatives was concluded.

2.2 SRSvSACI: Application to amide enolates in the Carlier group

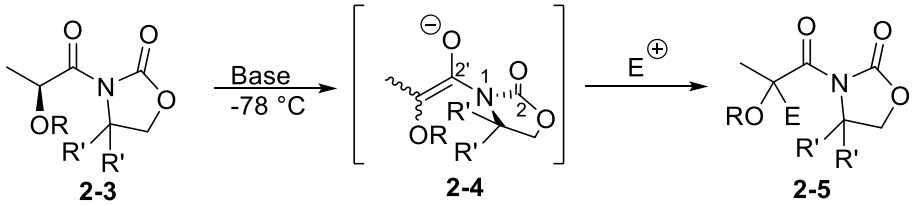
While the Carlier group was the first to utilize SRSvSACI protocol with the benzodiazepine class of compounds such as compounds **2-1** and **2-2**, discussed in chapter



2-1 **2-2**

Figure 2-1 Previously explored benzodiazepine class compounds by the Carlier group[2, 3]

3, we believed that asymmetric induction through axial chirality could be obtained in deprotonation/alkylation of much simpler molecules, such as **2-3** (**Scheme 2-1**). These compounds would be generated by coupling (*S*)-methyl lactate derivatives to achiral oxazolidinones. It is well known that amide resonance is significantly reduced in amide



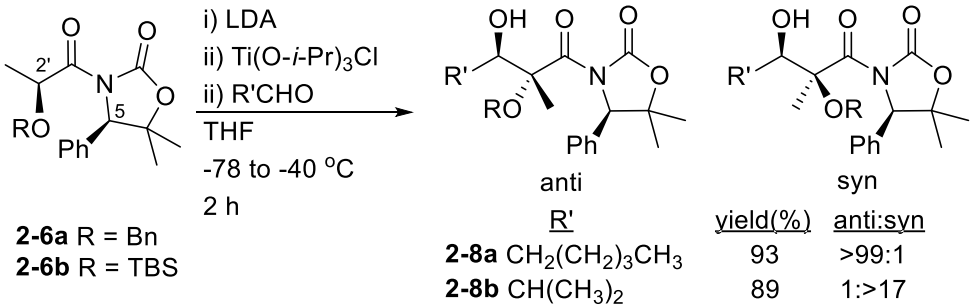
2-3 **2-4** **2-5**

Scheme 2-1 Potential Applications of SRSvSACI to (*S*)-Methyl Lactate Derivatives

enolates, and with a twist along the C2'-N1 of **2-4**, axial chirality results. If **2-4** can be generated in high enantioenrichment (selectively from either the *M*- or *P*-conformer starting material but not both), is slowly racemizing, and exhibits preferential facial selectivity for electrophilic addition, then it would be possible to transfer stereochemical information from statically chiral starting material **2-3** through stereolabile intermediate **2-4** into statically chiral products **2-5**.

2.3 Control of lactate oxazolidinone enolization

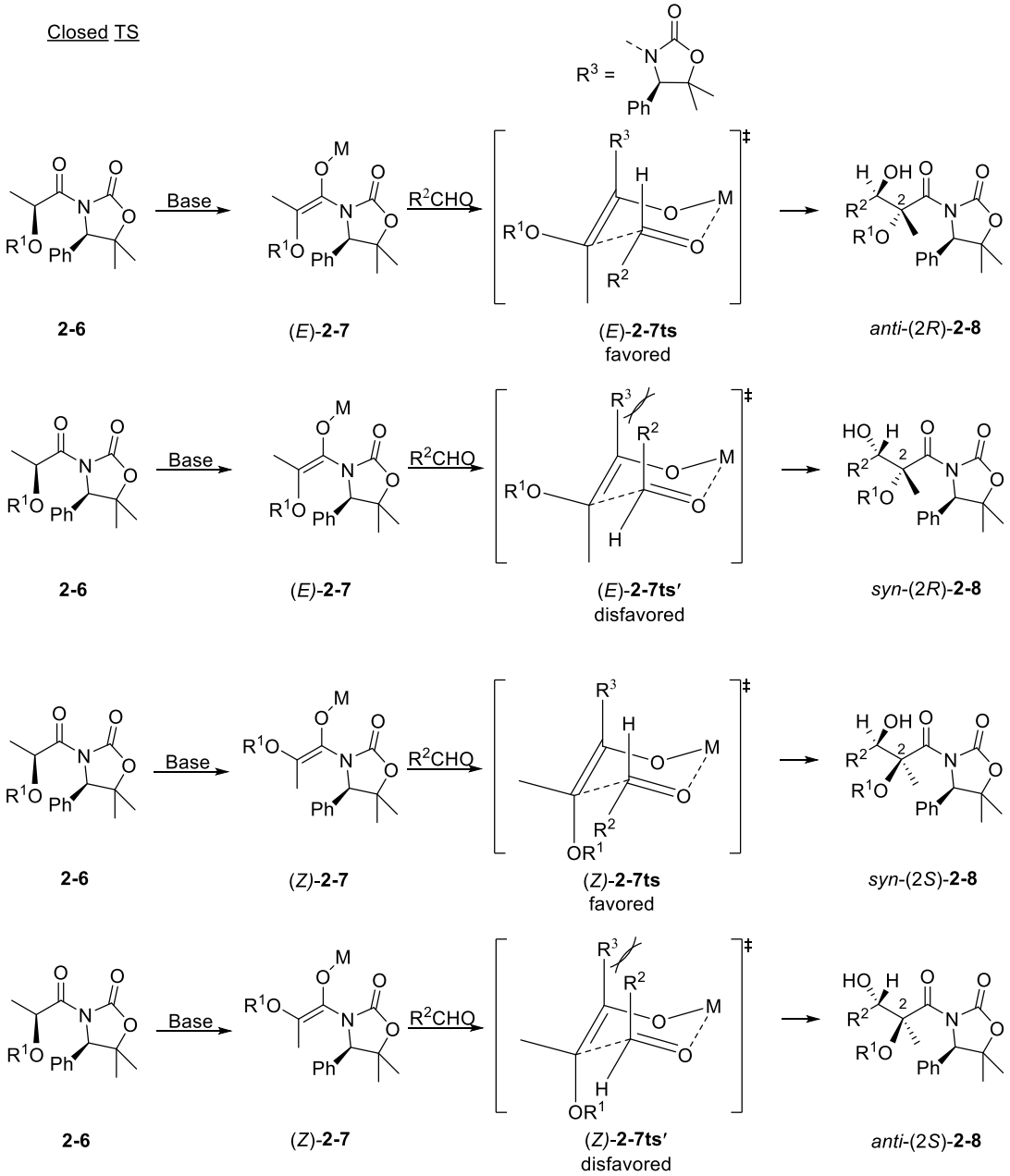
To place our proposed work in context, we must first review the work of Kobayashi *et al.*[1, 4] who reported the asymmetric aldol reaction of (*S*)-methyl lactate derivatives containing an enantiopure oxazolidinone auxiliary. The Evans aldol reaction offers diastereoselectivity through the installation and utilization of a chiral oxazolidinone auxiliary.[5] Enantiomers have equal energies, and as such their reaction activation energies are equal and lead to racemic mixtures of products. Through the addition of a chiral oxazolidinone, the starting lactate derivatives are now diastereomers, differ in energy, and have a difference in transition state energies. This difference in energy is manifested as facial selectivity for approach of the aldehyde in this reaction. It was shown that oxazolidinone enolate geometry can be controlled through the 2'-oxygen substituents and its stereochemical relationships with the oxazolidinone moiety as seen in **Scheme 2-2**. Since the products **2-8a**,**b** contain two chiral centers apart from the oxazolidinone auxiliary, in principle, four products could be obtained. However, only two compounds were isolated, the depicted *anti*- and *syn*-isomers (**2-8a**,**b**). Note that these descriptors classify the orientation of the OR and OH groups. For the synthesis of aldol products **2-8**, when R = Bn, treatment of **2-6a** with LDA, $Ti(O\text{-}i\text{-}Pr)_3Cl$, and crotonaldehyde at cold temperatures led selectively to **2-8a** in an anti:syn ratio of >99:1.



Scheme 2-2 Bn and TBS Protected (*S*)-methyl lactate selectivity[4]

In contrast, when R = TBS, the *syn*-diastereomer, **2-8b**, predominated with an anti:syn = 1:>17 selectivity. Assuming the reaction proceeds via a closed transition structure, two aspects of the reaction must be controlled: 1) enolate geometry (i.e. *E* vs *Z* enolate) and 2) facial selectivity of the enolate.

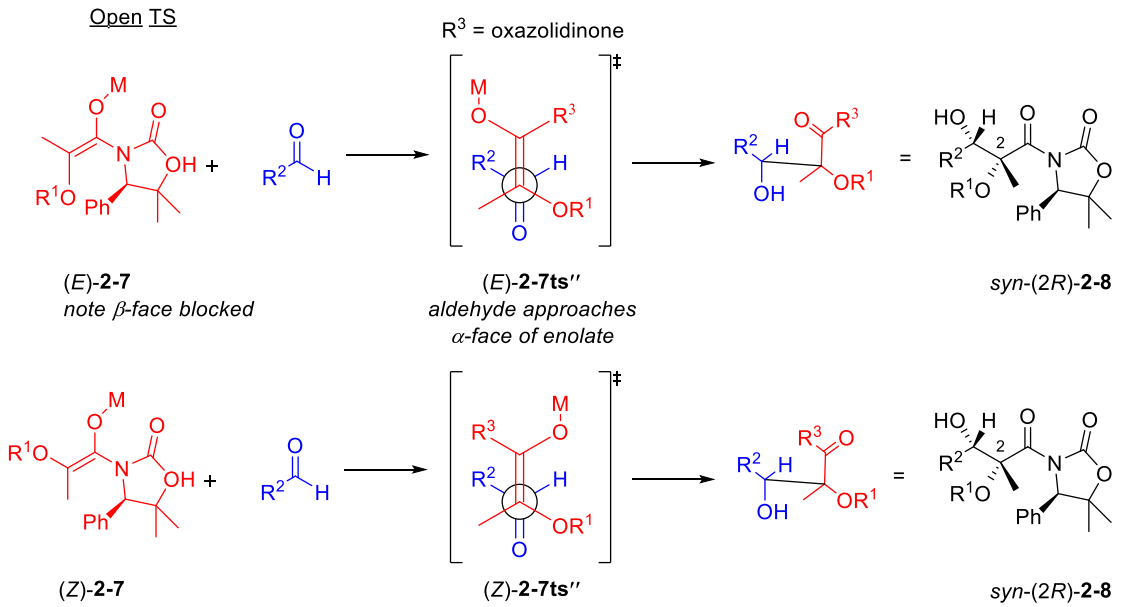
As previously stated, four possible products may be obtained in the aldol



Scheme 2-3 Possible stereochemical outcome for the aldol reaction of **2-6** proceeding through closed transition states

reactions of **2-6a** or **2-6b**, and mechanistic explanations for each of these products are shown in **Scheme 2-3**. Enolate formation, occurring through deprotonation of **2-6,** leads to either (*E*)-**2-7** or (*Z*)-**2-7**. If subsequent nucleophilic attack on the aldehyde occurs through a closed transition state, a Zimmerman-Traxler model can be used to explain the selectivity in which the (*E*)-enolate leads preferentially to the *anti*-product and the (*Z*)-enolate leads to the *syn*-product.[6] For (*E*)-**2-7** two possible closed transition state structures can be envisioned: (*E*)-**2-7ts** leading to *anti*-(2*R*)-**2-8** and (*E*)-**2-7ts′** leading to *syn*-(2*R*)-**2-8**. Of these two, (*E*)-**2-7ts** is preferred due to minimizing 1,3-diaxial strain between R^2 and R^3. For enolate (*Z*)-**2-7**, the favored closed transition state structure (*Z*)-**2-7ts** affords *syn*-(2*S*)-**2-8** whereas disfavored (*Z*)-**2-7ts′** leads to *anti*-(2*S*)-**2-8**.

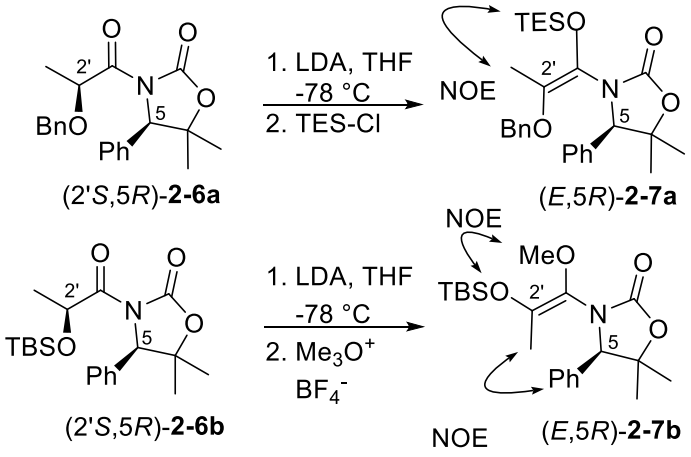
If the aldol reaction proceeds through an open transition state (**Scheme 2-4**) and the substituent sizes are sufficiently large enough, both (*E*)- and (*Z*)-enolates will afford the *syn*-product. As demonstrated in (*E*)-**2-7ts″** and (*Z*)-**2-7ts″**, the approach of the



Scheme 2-4 Possible stereochemical outcome for the aldol reaction of enolate **2-7** proceeding through open transition states

aldehyde to enolate (*E*)-**2-7** and (*Z*)-**2-7**, respectively, is aligned in such a way that OR^1 and R^2 are *anti* to each other. Subsequent bond formation leads to *syn*-(2*R*)-**2-8** for both cases. For these reactions, **2-6a** led to *anti* as the major product whereas **2-6b** led to *syn*. This appears to rule out an open transition state model for these reactions and indicates that enolate formation of **2-6a** and **2-6b** must afford the (*E*)- and (*Z*)-isomers, respectively, which then proceed through a closed transition state.

Control of enolate geometry was demonstrated with enolate trapping experiments (**Scheme 2-5**). Deprotonation of benzyl protect **2-6a** followed by treatment with TES-Cl afforded a single isomeric enol ether **2-7a** in 70% yield. NOE experiments showed this isomer to have (*E*)-configuration. In contrast, *O*-silyl protected **2-6b** was converted to enol ether **2-7b**, which an NOE experiment demonstrated to have the (*Z*)-configuration. In the case of *O*-benzyl protected **2-6a**, it was hypothesized that the (*E*)-enolate geometry would be thermodynamically preferred due to the electronic repulsion between the α-alkoxyl group and the enolate ion leading to product (*E,5R*)-**2-7a**. For a closed transition

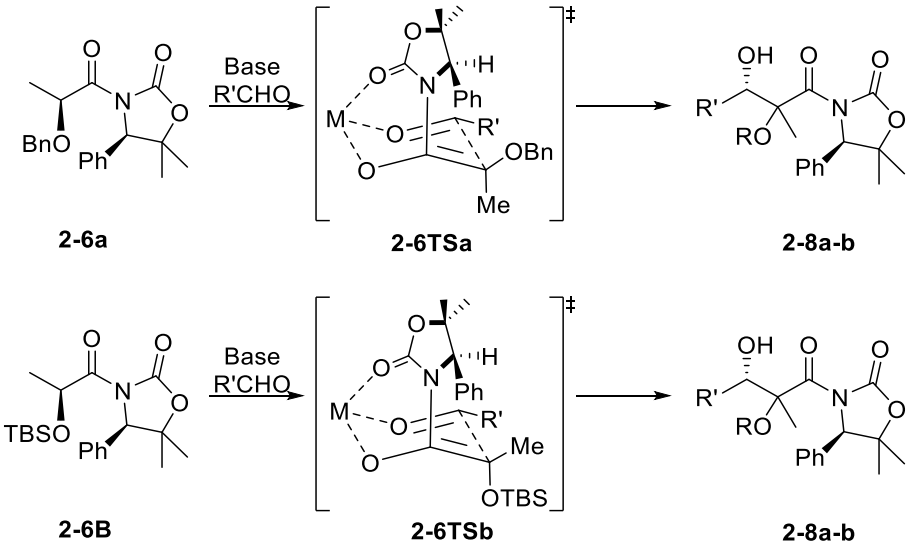


Scheme 2-5 Enolate trapping experiments of **2-6a** and **2-6b**[1]

structure under the Zimmerman-Traxler model[6] this would lead to the expected *anti*-product (*2R,3R*)-**2-8a** in the case of *O*-benzyl protected **2-6a**. However, where R = TBS

(**2-6b**), steric repulsion between the TBS and oxazolidinone moiety C-3 group must play a significant role, leading to (*Z*)-enolate (**2-7b**) and ultimately affords the *syn*-product (*2S,3R*)-**2-8b**.

While the enolate configuration and closed transition structure dictates whether the products will be *anti* or *syn*, the *anti*-(2*R*)- and *syn*-(2*S*)-**2-8** diastereomers afforded are not accompanied by the *syn*-(2*R*)- and *anti*-(2*S*)-**2-8** diastereomers. This is due to a second element of stereocontrol in which the Davies SuperQuat[7] oxazolidinone directs approach of the aldehyde to only one face of the enolate. The Davies SuperQuat auxiliary is a modification of the well-known Evans oxazolidinone.[5] Kobayashi had earlier investigated the Evans oxazolidinone in the lactate aldol reaction,[4] but the low stereoselectivity obtained no doubt motivated him to explore the Davies SuperQuat auxiliary. We would expect that approach would occur from the less sterically hindered

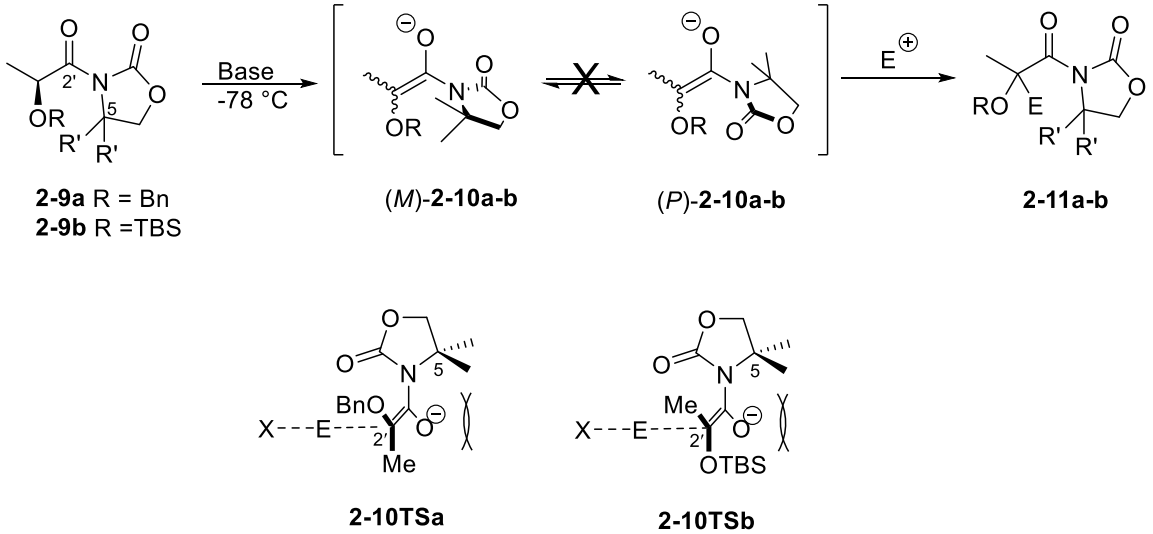


Scheme 2-6 Demonstration of facial selectivity for approach of aldehyde[4]

side (**Scheme 2-6**), and for reactions involving Bn and TBS protected **2-6**, approach appears to occur from the *β*-face, leading to an (*R*)- assignment for the OH containing stereocenter.

2.4 (S)-lactic acid coupled achiral oxazolidinones

Based on our understanding of SRSvSACI, we hypothesized that results similar to those Kobayashi *et al.*[1, 4] reported might be achievable through the use of achiral oxazolidinones. In effect, we proposed that the use of the chiral, Evans type oxazolidinone was superfluous.[5] Instead of using the oxazolidinone C5-substituent to control facial selectivity of the enolate, we proposed to stereoselectively generate a chiral C(O^-)-N axis, as depicted in **2-10a, b** (**Scheme 2-7**). Approach of the electrophile would likely occur opposite to the $C(Me)_2$ group (**2-10TSa** and **2-10TSb**). Following Kobayashi's observations, it appeared likely that enolate geometry could be controlled by the identity of the 2'-oxygen substituent. Fulfillment of these two conditions, and slow racemization along the C(O^-)-N axis would result in a high degree of stereochemical control. A key requirement of the achiral oxazolidinone would be sufficient steric bulk at the C5 position, which would cause the oxazolidinone to rotate out of plane upon enolization and to create a high energy barrier to racemization. Based on these considerations, derivative **2-9**, synthesized from achiral 5,5-dimethyl oxazolidin-2-one,

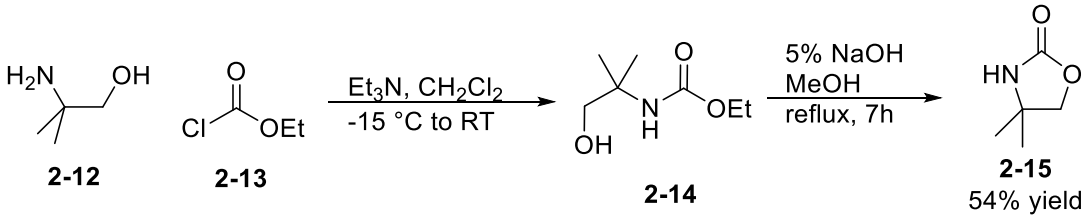


Scheme 2-7 Proposed enantioselective deprotonation/alkylation reactions of lactate derivatives bearing an achiral auxiliary

was our first target compound. It is feasible that the 5,5-dimethyl oxazolidin-2-one moiety would provide axial chirality providing facial selectivity for the electrophile, which would approach from the sterically less hindered side, opposite the methyl groups, and would stereoselectively lead to either retention or inversion **2-11** from starting material **2-9a** and **2-9b** respectively. The 5,5-dimethyl substitution would also create hindered rotation around the C-N axis, and enough steric mass to direct the *O*-TBS protected enolate **2-10b** to the *Z* enolate geometry. Finally, though for simplicity we depict a free oxyanion, it is likely that the associated solvated cation might further increase the barrier to rotation of the C-N axis.

2.5 Synthesis of 5,5-dimethyloxazolidinone

Synthesis of achiral 5,5-dimethyloxazolidin-2-one **2-15** was performed according to the procedure reported by Seebach *et al*.[8] As shown in **Scheme 2-8**, 2-amino-2-methyl-1-propanol (**2-12**) was reacted with ethyl chloroformate (**2-13**) to generate intermediate **2-14** following an aqueous HCl quench. The crude reaction mixture was taken forward, and subsequent ester hydrolysis yielded 5,5-dimethyloxazolididnone **2-15** in an overall yield of 54% across two steps and was ready to be taken forward for coupling with our *O*-benzyl and *O*-silyl protected (*S*)-methyl lactate derivatives.

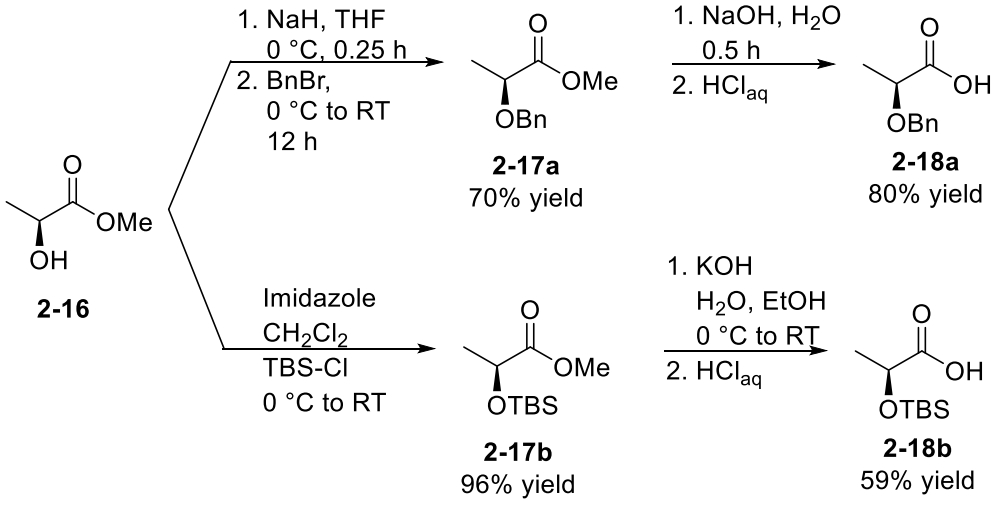


Scheme 2-8 Synthesis of 5,5-dimethyloxazolidin-2-one

2.6 Synthesis of (S)-methyl lactate derivatives

O-benzyl protection of (*S*)-methyl lactate **2-16** was performed according to protocol used by Chavan *et al*.[9] as seen in **Scheme 2-9** by deprotonation of (*S*)-methyl lactate with sodium hydride followed by treatment with benzyl bromide to afford **2-17a** in 70% yield. Carboxylic acid **2-18a** was synthesized in 80% yield by ester hydrolysis through the treatment of **2-17a** with sodium hydroxide followed by acidic quench.

Synthesis of *O-tert*-butyldimethylsilyl protected (*S*)-methyl lactate derivative **2-17b** (**Scheme 2-9**) was accomplished following a procedure similar to that used by Teck-Peng *et al*.[10] by addition of *tert*-butyldimethylsilyl chloride to a mixture of (*S*)-methyl lactate **2-16** and imidazole in methylene chloride to afford the product **2-17b** in 96% yield. Subsequent ester hydrolysis of **2-17b** was first attempted in a similar fashion as that performed on **2-17a**, but no product was obtained. It was suspected that solubility of **2-17b** in water was most likely the problem, as a literature search provided an alternate ester hydrolysis procedure by McIntosh et al.[11] which afforded carboxylic acid **2-18b** in 58% yield by first dissolving ester **2-17** in ethanol prior to the addition of potassium

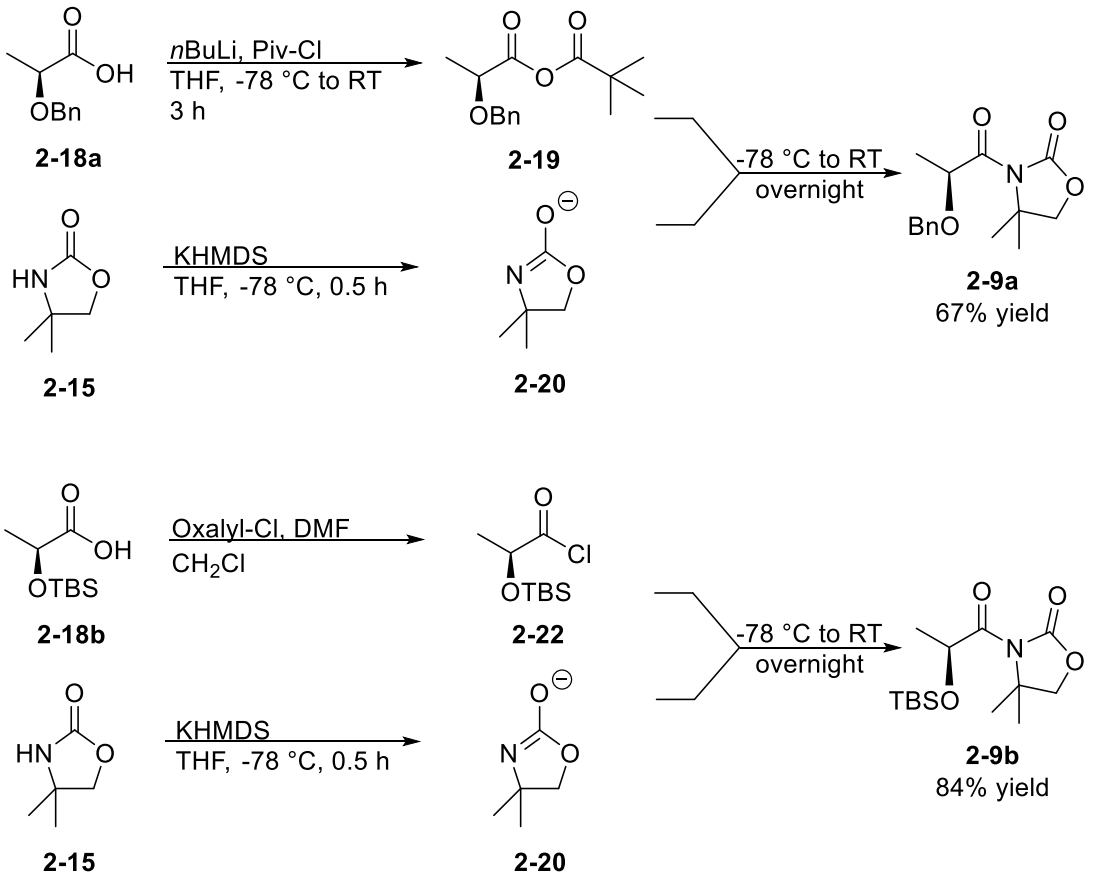


Scheme 2-9 Synthesis of *O*-Bn Protected Lactate Derivative **2-18a**

hydroxide in water.

2.7 Oxazolidinone coupling

Coupling product **2-19** was synthesized as seen in **Scheme 2-10** following a protocol similar to that done by Toshima *et al*.[12] in which *O*-benzyl protected carboxylic acid **2-18a** was treated with *n*-butyllithium (*n*BuLi) followed by pivaloyl chloride (Piv-Cl) to afford the mixed anhydride intermediate **2-19**, which was immediately taken forward to the next step. Achiral oxazolidinone **2-15** following treatment with potassium bis(trimethylsilyl)amide (KHMDS) generating deprotonated intermediate **2-20**, was subsequently added to **2-19** to afford *O*-benzyl protected acyl oxazolidinone **2-9a** in 67%

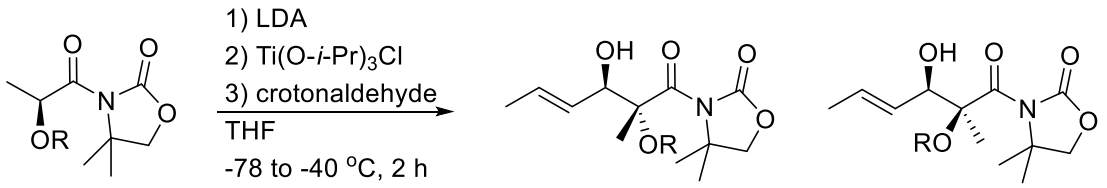


Scheme 2-10 Benzyl and TBS Protected Lactate Derivative Coupling with **2-15**

yield. Following the successful synthesis of **2-9a,** O-TBS protected **2-9b** was synthesized according to the protocol by Doi *et al*.[13] by first generating the crude acid chloride **2-22** which was taken directly forward to the next step. As in the synthesis of **2-9a**, oxazolidinone anion **2-20** was generated by deprotonation of oxazolidinone **2-15**. To this solution, the acid chloride **2-22** was added. The mixture was warmed to room temperature overnight, and this afforded the target TBS-protected acyl oxazolidinone **2-9b** in 84% yield.

2.8 Aldol reaction of the protected lactate oxazolidinones

With the *O*-benzyl and *O*-TBS protected lactate derivatives successfully coupled with achiral 5,5-dimethyloxazolidin-2-one, our first attempts at electrophilic addition involved aldol reaction, according to the procedure by Kobayashi *et al*.[1] Following treatment of **2-9a** or **2-9b** (**Scheme 2-11**) with lithium diisopropylamide (LDA) and Ti(O-*i*-Pr)$_3$Cl, presumably forming the titanium enolate, crotonaldehyde was added, followed by an aqueous ammonia chloride quench and purification to afford the final aldol products **2-23a** in 83% yield and **2-23b** in 33% yield, both as inseparable mixtures of the *anti*- and *syn*-diastereomers.



2-9a R = Bn
2-9b R = TBS

anti
(% ee unknown)

syn
(% ee unknown)

	Yield	diastereomeric ratio
2-23a	83%	2:1
2-23b	33%	2:1

Scheme 2-11 Aldol reactions of **2-9a**, **b** with crotonaldehyde

For the synthesis of **2-23a**, four possible structures can be obtained, as shown in **Figure 2-2**. If the enolate formation proceeds similarly for reactions involving **2-9a-b** as was reported by Kobayashi *et al* (**Scheme 2-2**), then Bn protected **2-9a** should form the (*E*)-enolate. If the reaction proceeds through a closed transition state the major product

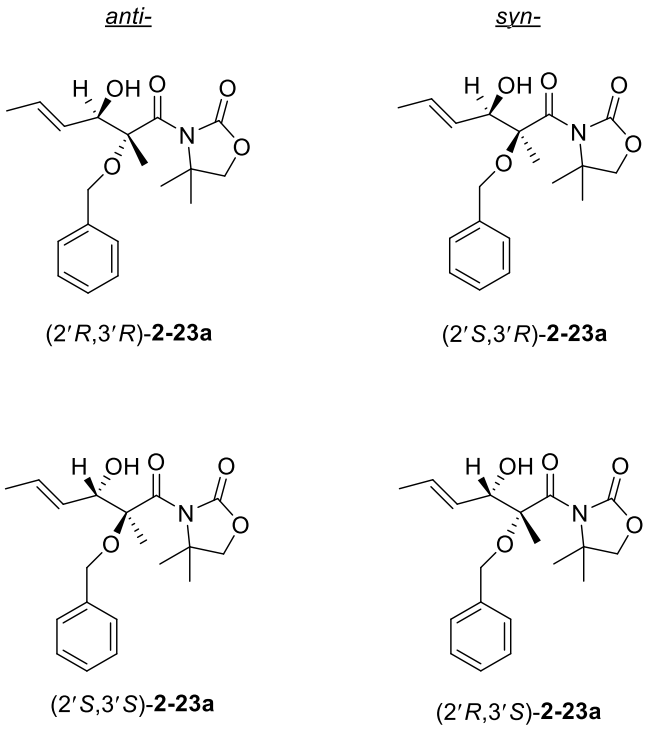


Figure 2-2 Possible Products Generated in the Synthesis of **2-23a**

diastereomer should be *anti*-configured. Whether asymmetric induction is achieved will depend on the ability to generate the axially chiral enolate in high % ee and whether its racemization rate is much slower than addition of the aldehyde.

The identity of aldol products **2-23a** and **2-23b** were confirmed by ^{1}H and ^{13}C NMR spectroscopy. All peaks were assigned by HMBC and HMQC. Benzyl protected **2-23a** was verified by high resolution mass spectrometry, showing the $(M+Na)^{+}$ peak at *m/z* = 370.1620 Daltons (exact mass = 347.17 Da). Interestingly, with first glance at the ^{1}H NMR spectra, the region containing the alkene protons from the crotonaldehyde moiety appeared to be very complex and/or contain impurities (**Figure 2-3**). Upon a closer look, it becomes apparent that the pattern is perfectly explained and identified as a pair of *anti*/*syn* diastereomers through analysis of the expected coupling. It should be noted, that while the diastereomeric ratio (dr) can be gleaned from the obtained NMR spectra, the enantiomeric excess was not determined. Also, the absolute configurations of the

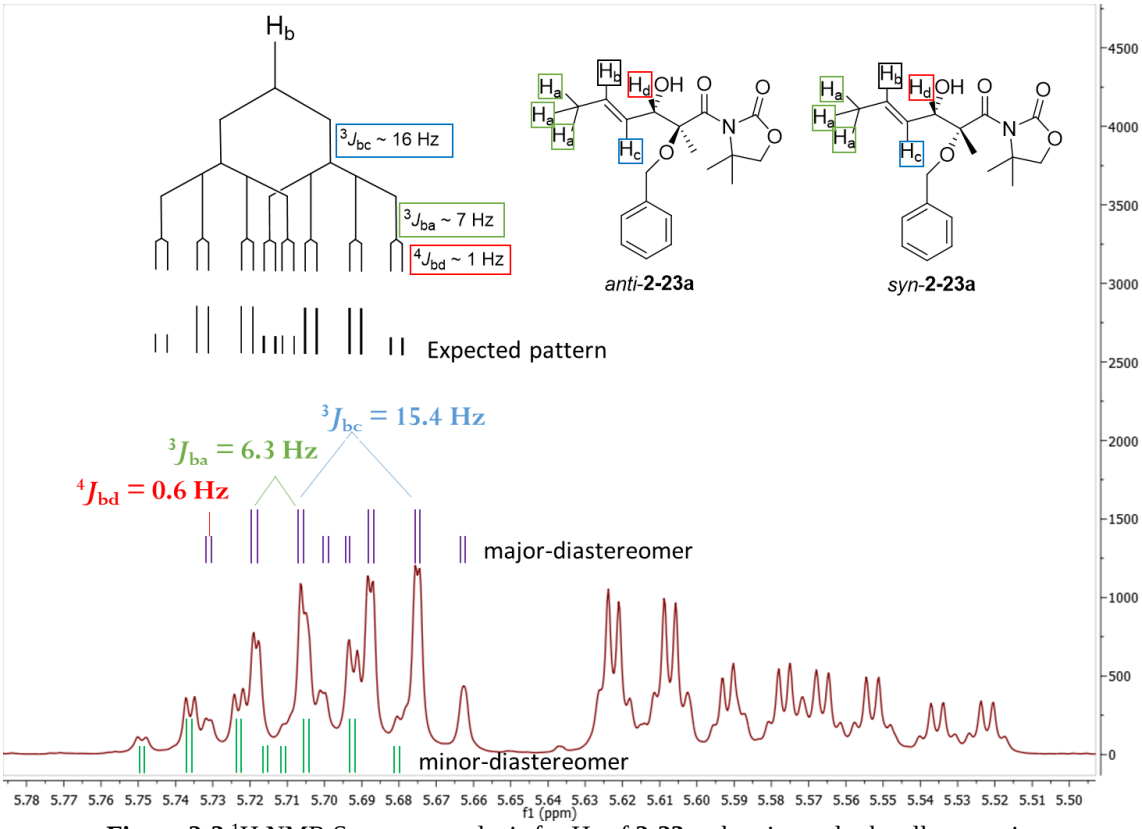


Figure 2-3 ^{1}H NMR Spectrum analysis for H_b of **2-23a**, showing only the alkene region.

structure in **Figure 2-3** are arbitrarily shown as (2′*S*,3′*S*)-**2-23a** and (2′*S*,3′*S*)-**2-23a**. The ^{1}H NMR diastereomer peaks are simply labeled as major and minor. When looking at proton H_b for **2-23a**, the largest expected coupling is with H_c across the double bond ($^3J_{bc}$ ≈ 16 Hz). The next largest coupling should be with the three H_a protons ($^3J_{ba}$ ≈ 7 Hz). The last splitting that should appear is the four bond coupling with H_d ($^4J_{bd}$ ≈ 1 Hz). Thus, the expected splitting pattern should be a doublet of quartet of doublets for each diastereomer (expected J ≈ 16, 7 ,1 Hz). If the expected splitting patterns for proton H_b are overlaid on the ^{1}H NMR spectra, it is apparent the signal from 5.66 ppm to 5.75 ppm is from H_b, both *anti*- and *syn*-diastereomers. The major diastereomer dqd ranges from 5.66 to 5.73 ppm. The minor diastereomer dqd ranges from 5.68 to 5.75 ppm For the major diastereomer the actual *J*-coupling values were obtained, and were very close to the expected values. $^3J_{bc}$ was 15.4 Hz, $^3J_{ba}$ was 6.3 Hz, and $^4J_{bd}$ was 0.6 Hz.

Similarly, the splitting pattern for proton H_C was elucidated in the same manner, and is shown in **Figure 2-4**. The expected pattern for each diastereomer was a doublet of doublet of quartets (expected J ≈ 16, 7, 1), and thus the signal from 5.51 ppm to 5.63 ppm was assigned to proton H_C on *anti*- and *syn*-**2-23a**. The measured coupling constants of the major diastereomer for H_c are as follows: $^3J_{cb}$ = 15.3 Hz; $^3J_{cd}$ = 7.6 Hz; $^4J_{bd}$ = 1.4 Hz. The major diastereomer ddq ranges from 5.57 to 5.63 ppm; the minor diastereomer ranges from 5.51 to 5.57 ppm. Due to overlapping of peaks from the major and minor diastereomers, the best estimation of diastereomeric ratio was obtained through integration of the major and minor diastereomer H_c peaks. The dr was identified as 2:1 for **2-23a**. The same analysis was applied to *O*-TBS protected **2-23b** and dr was discovered to be 2:1. Therefore, contrary to our expectation based on the Kobayashi work (**Scheme**

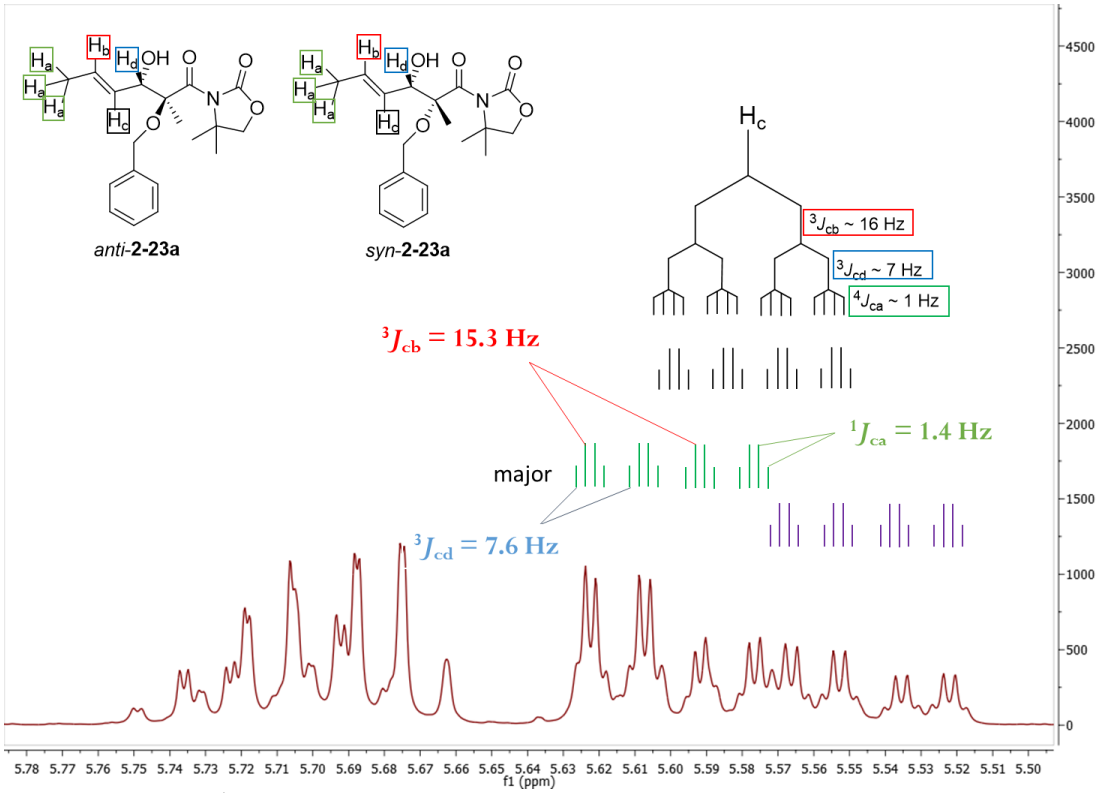


Figure 2-4 ^{1}H NMR Spectrum analysis for H_c of **2-23a**, showing only the alkene region.

2-2), Bn-protected **2-9a** and TBS-protected **2-9b** did not give high and opposite diastereoselectivity. This fact alone makes it impossible to deduce the stereochemistry of the major aldol diastereomer. How can this poor diastereoselectivity be rationalized? First, it is possible that both **2-9a** and **2-9b** give similar (*E*)-/(*Z*)- ratios of the corresponding enolates. Poor (*E*)-/(*Z*)-selectivity in the enolate will therefore translate to poor *anti*-/*syn*- ratios if the aldol reaction proceeds via a closed chair-like TS. Secondly, it is possible that the aldol reaction proceeds through both open- and closed-transition structures.

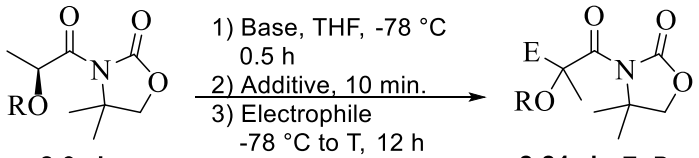
Due to the unanticipated poor diastereoselectivity seen in aldol reactions of **2-9a** and **2-9b**, to hopefully obtain greater stereoselectivity, we then focused our attention on alkylation instead of aldolation. In deprotonation/alkylation of **2-9a** and **2-9b**, we would

generate a single stereocenter and the stereochemical analysis would be limited to determination of % ee.

2.9 Attempted alkylation of the enolates derived from protected lactate oxazolidinone 2-9a and 2-9b

Since aldol reaction of crotonaldehyde with the titanium enolates of **2-9a** and **2-9b** did not afford good diastereoselectivity, we explored alkylation of the corresponding potassium and lithium enolates. If we were to alkylate with electrophiles such as allyl iodide or benzyl bromide, the products of such reactions would only contain a single chiral center as seen with compounds **2-24a,b** and **2-25a,b** (**Table 2-1**). This would remove the possibility of diastereomers and give us a more concrete look at the reaction stereoselectivity. Enantiomeric enrichment could then be determined by chiral HPLC,

Table 2-1 Attempted Alkylation of **2-9**



2-9a,b

a: R=Bn, **b:** R=TBS

2-24a,b: E=Bn
2-25a,b: E=Allyl

Entry	Substrate	Base	Additive (1.2 equiv)	Electrophile (EX)	Equiv.	T (°C)	Conversion (%)
1	**2-9b**	KHMDS	-	BnBr	1	-78	<5
2	**2-9b**	LiHMDS	-	BnBr	2	-78	<5
3	**2-9b**	KHMDS	-	BnBr	5	21	<5
4	**2-9b**	KHMDS	HMPA	BnBr	1.2	21	<5
5	**2-9b**	KHMDS	-	Allyl Iodide	5	-45	<5
6	**2-9b**	LDA	-	BnBr	10	-78	<5
7	**2-9a**	KHMDS	-	Allyl Iodide	5	-45	<5
8	**2-9a**	KHMDS	-	Allyl Iodide	5	21	<5
9	**2-9a**	KHMDS	HMPA	Allyl Iodide	5	21	<5
10	**2-9a**	KHMDS	HMPA	BnBr	1.2	21	<5

with NMR spectroscopy using a chiral shift reagent, or if a solid were obtained we could possibly perform x-ray crystallography. We also believed that using $Ti(O\text{-}i\text{-}Pr)_3Cl$ might possibly compromise the axial chirality generated in the intermediate by chelation with both the enolate and oxazolidinone carbonyl to prevent a twist at the C(O)-N axis. Due to this, reactions from this point on did not contain the Lewis acid.

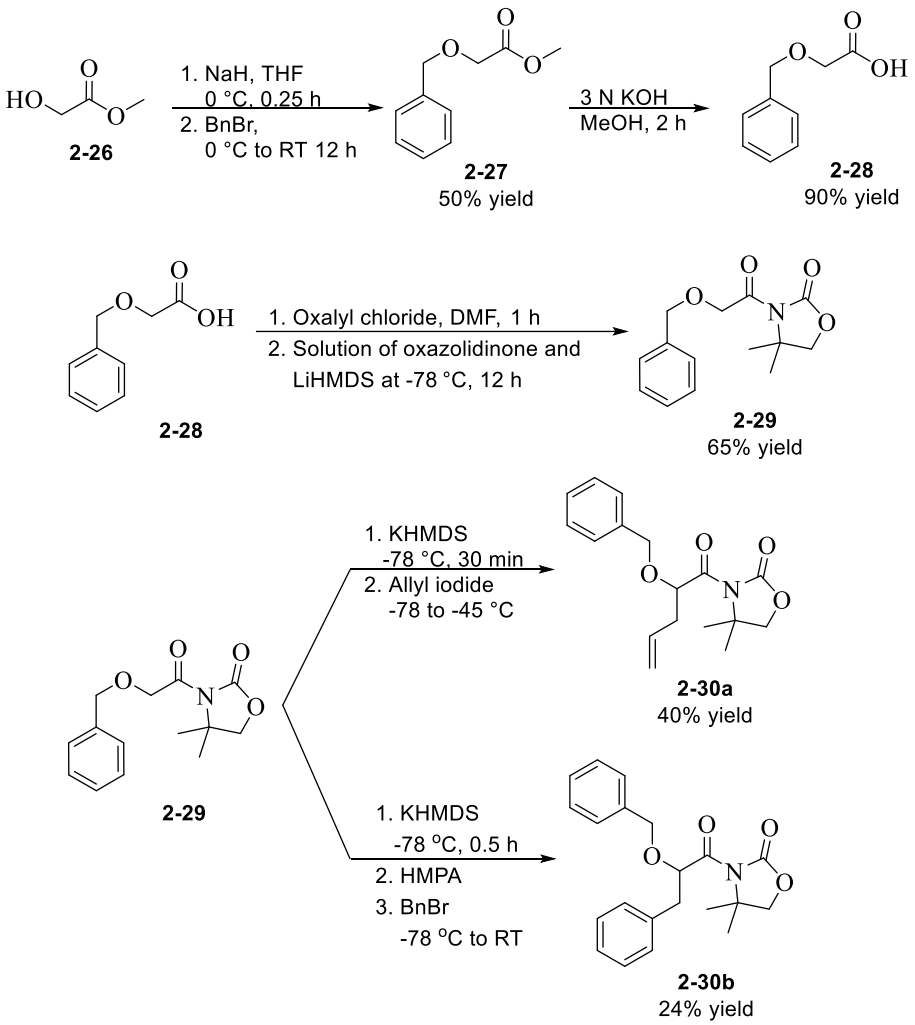
Our first attempt involved deprotonation of **2-9b** by KHMDS in THF at -78 °C, followed by addition of BnBr. After 12 hours at -78 °C, the reaction was quenched, but none of the desired product was detected (Entry 1). Using LiHMDS instead of KHMDS (entry 2 vs. 1) yielded the same results. Next, we tried using more base (5 equiv.) and raising the temperature of the final mixture from -78 °C to room temperature (entry 3), but again no product was observed. With the addition of base, a color change from colorless to yellow was observed. This led us to believe that starting material **2-9a,b** was being successfully deprotonated but that the resulting enolate intermediate was not reactive enough. To address this issue, HMPA (a common enolate additive),[14, 15] was added following the addition of base in the hopes of generating a more reactive, naked anion. Regrettably, no product was observed for this reaction (entry 4).

Another, explanation for why the electrophile was not reacting with the formed enolate could be steric hindrance. To this end, allyl iodide was used in the hopes that the reaction might proceed through an S_N2' mechanism. As seen in entry 5, the reaction did not proceed to desired products. It was then suspected that the observed color change did not signify enolate formation, and that in fact, deprotonation with KHMDS and LiHMDS was not successful. To address this possibility, lithium diisopropyl amide (LDA) was used (entry 6), since it had been successful in the aldol reaction with crotonaldehyde (see

Scheme 2-7 above). However, surprisingly this reaction also failed. Unfortunately, the results observed for *O*-Bn protected **2-9a** were the same as *O*-TBS protected **2-9b** although LDA was not tried again (entries 7-9). In all cases, no product was observed.

2.10 Synthesis and alkylation of glycolate derivatives

Since the attempted deprotonation/alkylation reactions of **2-9a,b** failed, we considered various possibilities for the lack of reaction. One obvious possibility was that steric bulk on the enolate, combined with the 5,5-dimethyl substitution on the oxazolidinone, reduced reactivity to alkylation as opposed to reaction with an aldehyde. It is possible that backside attack on the sp^3-carbon electrophile by the enolate might be more difficult than approach on sp^2-carbon electrophiles, yet it was for this reason that we investigated allyl iodide. Another possibility for the lack of reaction could be unsuccessful deprotonation, and this possibility is explored below in section ***2.11***. Whether steric bulk impeded enolate generation or alkylation we thus decided to investigate derivatives of methyl glycolate, because it lacked an α-methyl group, yet retained an α-oxygen like (*S*)-methyl lactate. Without a chiral center like (*S*)-methyl lactate, methyl glycolate would not be a candidate for applications of SRSvSACI, but with the removal of the α-methyl group, enolate alkylation might be easier. We have previously seen that the synthesis of our *O*-benzylated oxazolidinone derivatives proceeded cleaner and in higher yields than those of the *O*-TBS derivatives. Because of this we decided to focus our attention on generating *O*-benzyl protected glycolate derivatives and did not investigate *O*-TBS protected glycolate derivatives. Applying the same synthetic protocol as was used previously, **2-26** (**Scheme 2-12**) was benzylated by



Scheme 2-12 Synthesis and alkylation of methyl glycolate derivative **2-29**

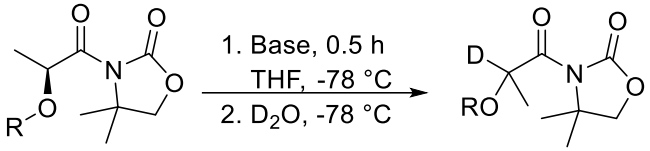
deprotonation in THF at 0 °C, followed by addition of benzyl bromide, and subsequent stirring for 12 hours. The expected product, **2-27** was obtained in 50% yield. Successful ester hydrolysis was performed with 3 N methanolic potassium hydroxide to give **2-28** in 90% yield. A similar protocol for coupling *O*-benzyl protected **2-28** with our previously made 5,5-dimethyloxazolidin-2-one **2-15** as shown in **Scheme 2-10** was performed, and coupled product **2-30** was obtained in 65% yield. Deprotonation with KHMDS, followed by treatment with allyl iodide or benzyl bromide afforded allylated product **2-30** in 40% yield and benzylated product **2-31** in 24% yield. Although these yields are low, these results indicated to us that 1) the glycolated derivative **2-29** could be deprotonated by

KHMDS, and 2) that the resulting enolate was sufficiently reactive towards allyl iodide and benzyl bromide. Clearly, reduced steric bulk around the *α*-carbon of the *O*-Bn glycolate derivative **2-29** could facilitate both deprotonation and enolate alkylation. These experiments motivated us to determine whether deprotonation of the *O*-protected lactate derivatives **2-9a,b** was the key difficulty, or whether the low enolate reactivity was responsible for the failed alkylations.

2.11 Deuteration of (S)-methyl lactate derivatives

During the deprotonation/alkylation reactions involving **2-9a** and **2-9b**, a color change was observed with the addition of base (KHMDS, LiHMDS). Initially we believed this color change could be attributed to the formation of the enolate. Since D_2O is an extremely small electrophile, it and other deuterating agents (e.g. CH_3OD) are

Table 2-2 Attempted Deuteration of **2-9**



2-9a,b → **2-31**

Entry	Substrate	Base	Equiv.	Conversion (%)
1	**2-9b**	KHMDS	1	<5
2	**2-9b**	LiHMDS	2	<5
3	**2-9a**	KHMDS	1	<5
4	**2-9a**	LiHMDS	1	<5
5	**2-9a**	MeLi	1	<5

commonly used to confirm the generation of carbanionic species that do not efficiently react with electrophiles.[16-18] Thus deprotonation/deuteration of **2-9a,b** was attempted with KHMDs and LiHMDS as shown in **Table 2-2** (entry 1-4). Very surprisingly, in all cases,

no deuterated product was obtained. Increased equivalents of base (entry 2) did not produce product either. Methyl lithium was also used as the base (entry 5), because it was substantially smaller than KHMDS and LiHMDS, but there was no observed product. Upon revisiting the MeLi results, it is odd that not only did MeLi not deprotonate **2-9a**, it did not act as a nucleophile. It is possible that the MeLi solution had degraded and therefore entry 5 might not be accurate.

It was expected, that if product was successfully deprotonated and then quenched with D_2O, then the α-hydrogen ^1H NMR signal would decrease in intensity or disappear altogether. As seen in **Figure 2-5**, following addition of LiHMDS and D_2O quench for

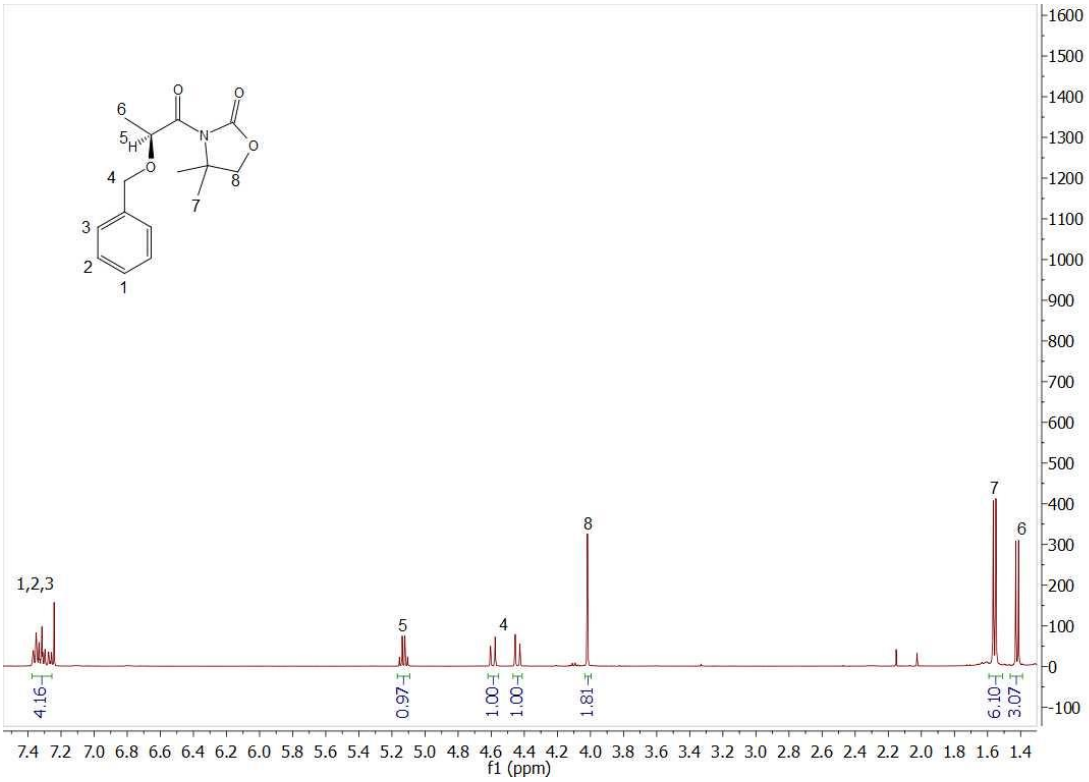
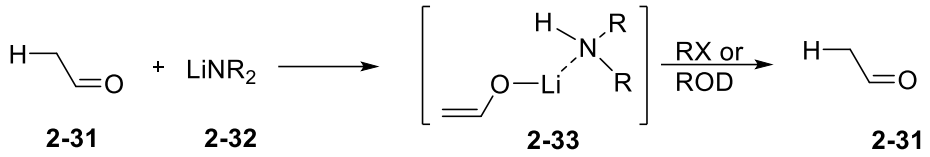


Figure 2-5 Treatment of **2-9a** with LiHMDS Followed by D_2O Quench

entry 4 in **Table 2-2**, the α-hydrogen, designated 5, did not decrease in intensity.

These experiments seem to prove that the starting material was not extensively deprotonated. While it can be argued that steric bulk of the base might be preventing

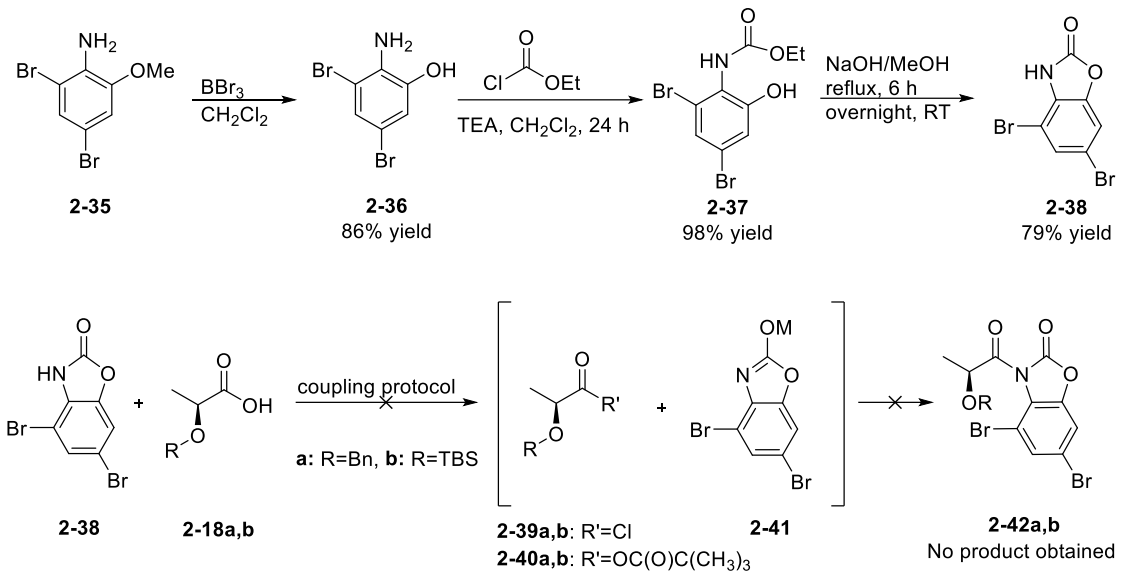


Scheme 2-13 Internal return phenomenon of generic aldehyde **2-31**[19]

deprotonation by LiHMDS and KHMDs, there is a reported internal return mechanism[19] that has been observed in the attempted deuteration or alkylation of some lithium enolates in which the lithium enolate (**Scheme 2-13**, **2-33**) complexes with the amine conjugate acid to protonate the enolate and return the protio starting material (**2-31**) instead of deuterated product. This internal return mechanism offers a possible explanation as to the reaction color changes yet return of protio starting material **2-9**. In any event, it was clear the 5,5-dimethyloxazolidinone auxiliary was not functioning as intended. Our attention thus turned to another oxazolidinone.

2.12 Synthesis of an alternate achiral oxazolidinone

While we could not decrease the steric bulk directly attached to the α-carbon of our lactate derivative, we could focus on attempts at changing how steric bulk was displayed in the oxazolidinone. It was still necessary that the oxazolidinone be achiral, and it needed to exhibit some degree of steric bulk so that it would help direct enolate facial selectivity as depicted in geometry formation as previously outlined in section 2.3 (**Scheme 2-6**) and section 2.4 (**Scheme 2-7**). For this purpose, achiral oxazolidinone **2-38** (**Scheme 2-14**) was synthesized. Demethylation of **2-35** with BBr_3 in methylene chloride gave **2-36** in 86% yield. Following the protocol used for the synthesis of the previously made oxazolidinone **2-15**, compound **2-37** was made in 98% yield, and successful ring closure provided the new oxazolidinone **2-38** in 79% yield. All the coupling methodologies used previously for the (*S*)-methyl lactate and methyl glycolate derivatives



Scheme 2-14 Synthesis of new oxazolidinone **2-35** and attempted coupling with **2-18**

(**Schemes 2-10** and **2-12**), were applied to oxazolidinone **2-38** and *O*-benzyl and *O*-TBS derivatives **2-18a** and **2-18b**. To our dismay, neither **2-42a** nor **2-42b** were obtained with any of these procedures, and instead starting materials were obtained. We believe that the bromine located next to the carbamate nitrogen on **2-38** prevented approach of **2-39a, b** and **2-40a, b**, preventing successful coupling to give **2-42a, b**.

2.13 (S)-methyl lactate project conclusion

At this point my work on these (*S*)-methyl lactate derivatives terminated. Substantial time and resources had been invested, and it no longer appeared that a successful outcome could be realized. Although *O*-Bn and *O*-TBS protected derivatives **2-9a**,**b** were generated, subsequent aldol reaction with crotonaldehyde did not generated products **2-23a**,**b** with the desired selectivities. Unfortunately, alkylation to afford products **2-24a**,**b** and **2-25a**,**b** could not be realized either. The achiral glycolate derivative **2-29** was successfully made and alkylated to afford **2-30a**,**b**, and this seems to indicate that steric interactions could be hindering successful alkylation of the chiral

lactate derivatives. Attempted deuteration of **2-9a**,**b** did not indicate successful deprotonation, and attempts at generating and attaching an alternate achiral oxazolidinone functionality to the protected lactate derivatives were not successful. My future research will focus on benzodiazepines, a scaffold on which the Carlier group had successfully developed SRSvSACI deprotonation/alkylations.[2, 3, 20-24] The following chapter will contain work applying the SRSvSACI protocol to various 1,4-benzodiazepin-2,5-diones.

2.14 Bibliography

1. Murata, Y.; Kamino, T.; Hosokawa, S.; Kobayashi, S. Stereocontrolled Preparation of 1,2-Diol with Quaternary Chiral Center. *Tetrahedron Lett.* **2002**, *43*, 8121-8123.

2. MacQuarrie-Hunter, S.; Carlier, P. R. Highly Enantioselective Synthesis of Rigid, Quaternary 1,4-Benzodiazepine-2,5-Diones Derived from Proline. *Org. Lett. 7*, 5305-5308.

3. Carlier, P. R.; Zhao, H.; DeGuzman, J.; Lam, P. C. H. Enantioselective Synthesis of "Quaternary" 1,4-Benzodiazepin-2-One Scaffolds Via Memory of Chirality. *J. Am. Chem. Soc.* **2003**, *125*, 11482-11483.

4. Kamino, T.; Murata, Y.; Kawai, N.; Hosokawa, S.; Kobayashi, S. Stereochemical Control of Tertiary Alcohol: Aldol Condensation of Lactate Derivatives. *Tetrahedron Lett.* **2001**, *42*, 5249-5252.

5. Evans, D. A.; Bartroli, J.; Shih, T. L. Enantioselective Aldol Condensations. 2. Erythro-Selective Chiral Aldol Condensations Via Boron Enolates. *J. Am. Chem. Soc.* **1981**, *103*, 2127-2129.

6. Zimmerman, H. E.; Traxler, M. D. The Stereochemistry of the Ivanov and Reformatsky Reactions. I. *J. Am. Chem. Soc.* **1957**, *79*, 1920-1923.

7. Davies, S. G.; Sanganee, H. J.; Szolcsanyi, P. The 'Superquat' (R)-4-Phenyl-5,5-Dimethyl Oxazolidin-2-One as an Effective Chiral Auxiliary for Conjugate Additions: Asymmetric Synthesis of (−)-Aplysillamide B. *Tetrahedron* **1999**, *55*, 3337-3354.

8. Gaul, C.; Arvidsson, P. I.; Bauer, W.; Gawley, R. E.; Seebach, D. Computational, Reactir-, and Nmr-Spectroscopic Investigations on the Chiral Formyl Anion Equivalent N-(A-Lithiomethylthiomethyl)-4-Isopropyl-5,5-Diphenyloxazolidin-2-One and Related Compounds. *Chem. Eur. J.* **2001**, *7*, 4117-4125.

9. Fernandes, R. A.; Chavan, V. P. A Concise Asymmetric Synthesis of (–)-Hongconin and (–)-1-Epi-Hongconin. *Eur, J. Org. Chem.* **2010**, *2010*, 4306-4311.

10. Chin, Y.-J.; Wang, S.-Y.; Loh, T.-P. Synthesis of Iriomoteolide-1a C13−C23 Fragment Via Asymmetric Conjugate Addition and Julia−Kocienski Coupling Reaction. *Org. Lett.* **2009**, *11*, 3674-3676.

11. Qi, W.; McIntosh, M. C. Acyclic 1,4-Stereocontrol Via Reductive 1,3-Transpositions. *Org. Lett.* **2008**, *10*, 357-359.

12. Ohtani, T.; Tsukamoto, S.; Kanda, H.; Misawa, K.; Urakawa, Y.; Fujimaki, T.; Imoto, M.; Takahashi, Y.; Takahashi, D.; Toshima, K. Total Synthesis of Incednam, the Aglycon of Incednine. *Org. Lett.* **2010**, *12*, 5068-5071.

13. Yoshida, M.; Takeuchi, H.; Ishida, Y.; Yashiroda, Y.; Yoshida, M.; Takagi, M.; Shin-ya, K.; Doi, T. Synthesis, Structure Determination, and Biological Evaluation of Destruxin E. *Org. Lett.* **2010**, *12*, 3792-3795.

14. Carlier, P. R.; Lo, C. W. S. 7li/31p Nmr Studies of Lithiated Arylacetonitriles in Thf−Hmpa Solution: Characterization of Hmpa-Solvated Monomers, Dimers, and Separated Ion Pairs. *J. Am. Chem. Soc.* **2000**, *122*, 12819-12823.

15. Carlier, P. R.; Lo, C. W. S.; Lo, M. M. C.; Wan, N. C.; Williams, I. D. Hmpa Promotes Retro-Aldol Reaction, Resulting in Syn-Selective Addition of Lithiated 1-Naphthylacetonitrile to Aromatic Aldehydes. *Org. Lett.* **2000**, *2*, 2443-2445.

16. Carlier, P. R.; Zhang, Y. The First Enantioenriched Metalated Nitrile Possessing Macroscopic Configurational Stability. *Org. Lett.* **2007**, *9*, 1319-1322.

17. Patwardhan, N. N.; Gao, M.; Carlier, P. R. Incremental Solvation Precedes Ion-Pair Separation in Enantiomerization of a Cyano-Stabilized Grignard Reagent. *Chem. Eur. J.* **2011**, *17*, 12250-12253.

18. Gao, M.; Patwardhan, N. N.; Carlier, P. R. Stereochemical Inversion of a Cyano-Stabilized Grignard Reagent: Remarkable Effects of the Ethereal Solvent Structure and Concentration. *J. Am. Chem. Soc.* **2013**, *135*, 14390-14400.

19. Seebach, D. Structure and Reactivity of Lithium Enolates. From Pinacolone to Selective C-Alkylations of Peptides. Difficulties and Opportunities Afforded by Complex Structures. *Angew. Chem. Int. Ed.* **1988**, *27*, 1624-1654.

20. Carlier, P. R. Experimental and Computational Studies of Ring Inversion of 1,4-Benzodiazepin-2-Ones: Implications for Memory of Chirality Transformations. *J. Org. Chem.* **2005**, *70*, 1530-1538.

21. Carlier, P. R.; Lam, P. C. H.; DeGuzman, J. C.; Zhao, H. Memory of Chirality Trapping of Low Inversion Barrier 1,4-Benzodiazepin-2-One Enolates. *Tetrahedron: Asymmetry* **2005**, *16*, 2998-3002.

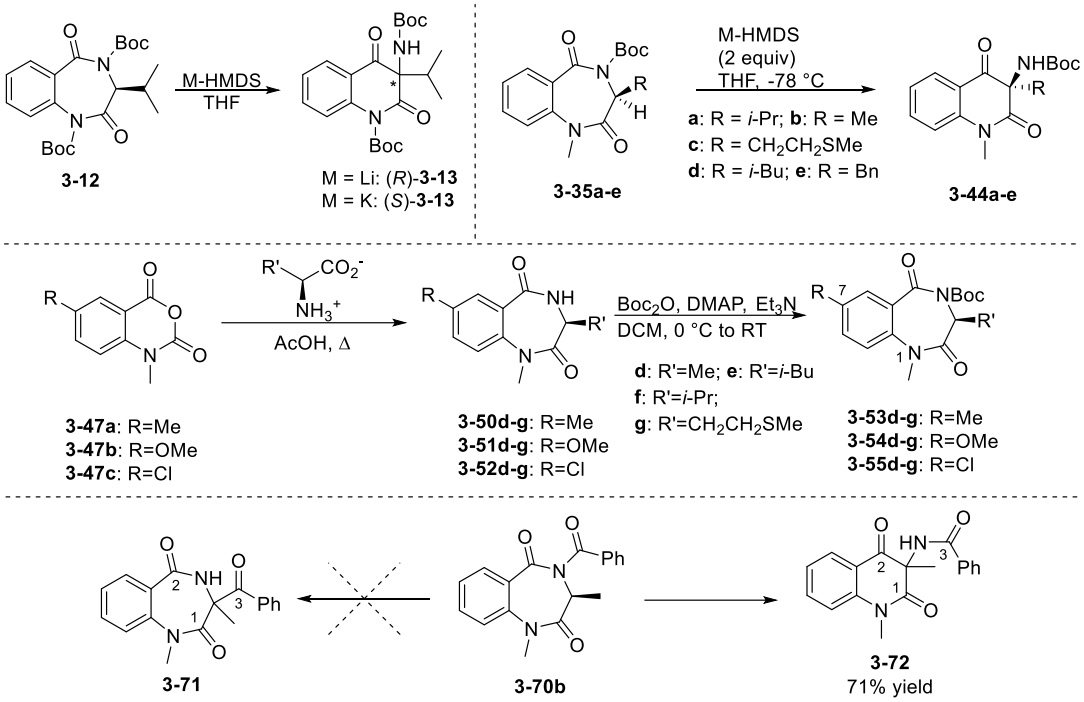
22. Carlier, P. R.; Sun, Y.-S.; Hsu, D. C.; Chen, Q.-H. Axial-Selective H/D Exchange of Glycine-Derived 1h-Benzo[E][1,4]Diazepin-2(3h)-Ones: Kinetic and Computational Studies of Enantiomerization. *J. Org. Chem.* **2010**, *75*, 6588-6594.

23. Hsu, D. C.; Lam, P. C. H.; Slebodnick, C.; Carlier, P. R. Complete Mapping of the Stereochemical Course of Retentive Deprotonation/Alkylation of 1h-Benzo[E][1,4]Diazepin-2(3h)-Ones. *J. Am. Chem. Soc.* **2009**, *131*, 18168-18176.

24. Carlier, P. R.; Zhao, H.; MacQuarrie-Hunter, S. L.; DeGuzman, J. C.; Hsu, D. C. Enantioselective Synthesis of Diversely Substituted Quaternary 1,4-Benzodiazepin-2-Ones and 1,4-Benzodiazepine-2,5-Diones. *J. Am. Chem. Soc.* **2006**, *128*, 15215-15220.

3. Enantioselective Ring-Contraction of 1,4-Benzodiazepin-2,5-diones

3.1 Abstract



In this chapter, I describe the enantioselective ring-contraction of a variety of 1,4-benzodiazepin-2,5-diones. Dewynter *et al.*[1] was the first to report this reaction, which afforded quinolone-2,4-dione **3-13** from 1,4-benzodiazepin-2,5-dione **3-12** (**Table 3-3**). This ring contraction was only applied to valine derived **3-12** because preparation of analogous BZD derivatives from other amino acids proved unsuccessful. These works are reviewed in sections 3.2 and 3.3.

Starting with section 3.4 the successful synthesis of varied *N*1-Me-*N*4-Boc-benzodiazepin-2,5-dione derivatives is reported. Application of the ring contraction protocol developed by Dewynter to these 1,4-benzodiazepin-2,5-diones (**Table 3-7**) is discussed as my research began with the synthesis and optimization (*S*)-phenylalanine derived 1,4-benzodiazepin-2,5-dione (*S*)-**3-35e**. Following our successful

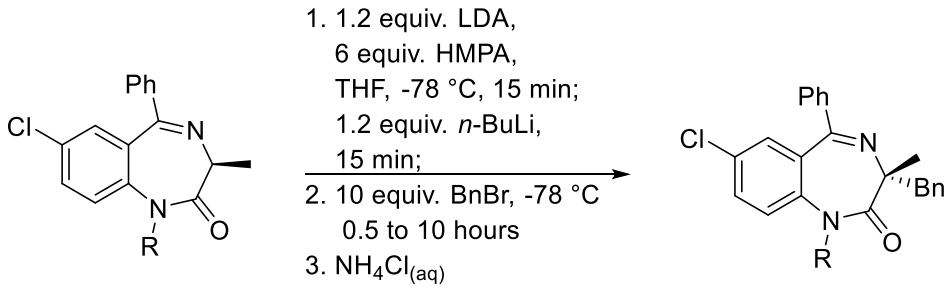
enantioselective rearrangement of compounds **3-35a-e**, we investigated the substituent effect of varying aromatic substituents on reaction enantioselectivity. Following the synthesis and treatment of (*S*)-alanine, (*S*)-valine, (*S*)-leucine, and (*S*)-methionine derived BZDs **3-53d-g**, **3-54d-g**, and **3-55d-g** with LiHMDS, it was observed that while yield varied, enantiomeric enrichment remained consistent with little to no loss (**Table 3-12**).

Ring contraction of the discussed benzodiazepines proceeds through an acyl-amino variant of the Chan reaction that is dependent on the *N*4-acyl activation provided by the installed Boc-protecting group (**Table 3-4**). Theoretically, installation of an electron withdrawing substituent at *N*4 could lead preferentially to an enantioselective acyl-migration as demonstrated in **Scheme 3-12**. While we were not successful in installing a strongly electron withdrawing substituent at the *N*4 position, we were able to generate benzoyl-protected **3-70b**. However, it was seen that treatment with LiHMDS led enantioselectively to the ring contracted product **3-72** instead of acyl migrated product **3-71.**

3.2 Applications of SRSvSACI to 1,4-benzodiazepin-2-ones and 1,4-benzodiazepin-2,5-diones by the Carlier group

Believed to be beta-turn peptidomimetics,[2] benzodiazepines are an important privileged scaffold in medicinal chemistry and exhibit a wide variety of biological activity.[3-9] Key starting materials for these benzodiazepine class compounds are proteinogenic amino acids, and while there are a wide array of preparations for benzodiazepines[6, 10] there are very few examples possessing quaternary stereogenic center at C3. This is most likely due to the lack of commercial availability of the corresponding enantiopure quaternary substituted amino acids. Previous work by the Carlier group investigated the enantioselective synthesis of C3-quaternary substituted 1,4-benzodiazepin-2-ones and 1,4-benzodiazepin-2,5-diones through the application of SRSvSACI.[11-18]

Previous work by the Carlier group with 1,4-benzodiazepin-2-ones showed that a bulky group attached at N1 is necessary to impart sufficient conformational stability to the enolate ring and facilitate enantioselective alkylation on the deprotonation/alkylation timescale at cold temperatures (-78 to -100 °C) (**Scheme 3-1**).[11, 13] When the *N*1-substituent is methyl, deprotonation and alkylation of (*S*)-**3-1a** led to racemic **3-2**. But application of the same protocol to N1-*i*Pr substituted (*S*)-**3-1b** afforded (*R*)-**3-2b** in 97% ee, demonstrating the importance of an increased steric interaction at the N1 substituent. The size of the N1-substituent is believed to control the rate of racemization of the axially chiral enolate.



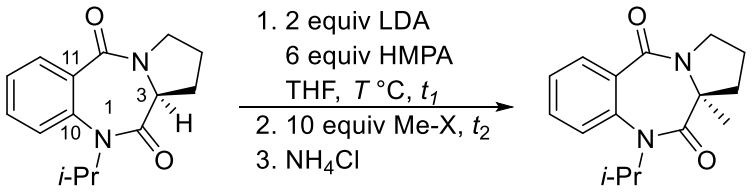
(*S*)-**3-1a**: R = Me
(*S*)-**3-1b**: R = *i*-Pr

3-2a: 72% yield, 0% ee
3-2b: 74% yield, 97% ee (*R*)

Scheme 3-1 Dependence of enantioselectivity on the N1-substituent in deprotonation/alkylation of 1,-benzodiazepin-2-ones.[11]

To extend this reaction to the related 1,4-benzodiazepin-2,5-diones, an isopropyl (*i*Pr) group was installed at the N1 position of proline derived **3-3** (**Table 3-1**).[15] Subsequent treatment with LDA and HMPA in THF at -78 °C for five minutes followed by addition of methyl iodide for 10 minutes and quench with ammonium chloride led to racemic product **3-4** (entry 1). It was observed that reducing the deprotonation time to one minute led to retentive product (*R*)-**3-4** in 93% ee but only 10% yield (entry 2). Enantioselectivity and yield were increased by using methyl trifluoromethanesulfonate

Table 3-1 Enantioselective alkylation of proline derived 1,4-benzodiazepin-2,5-dione.[15]



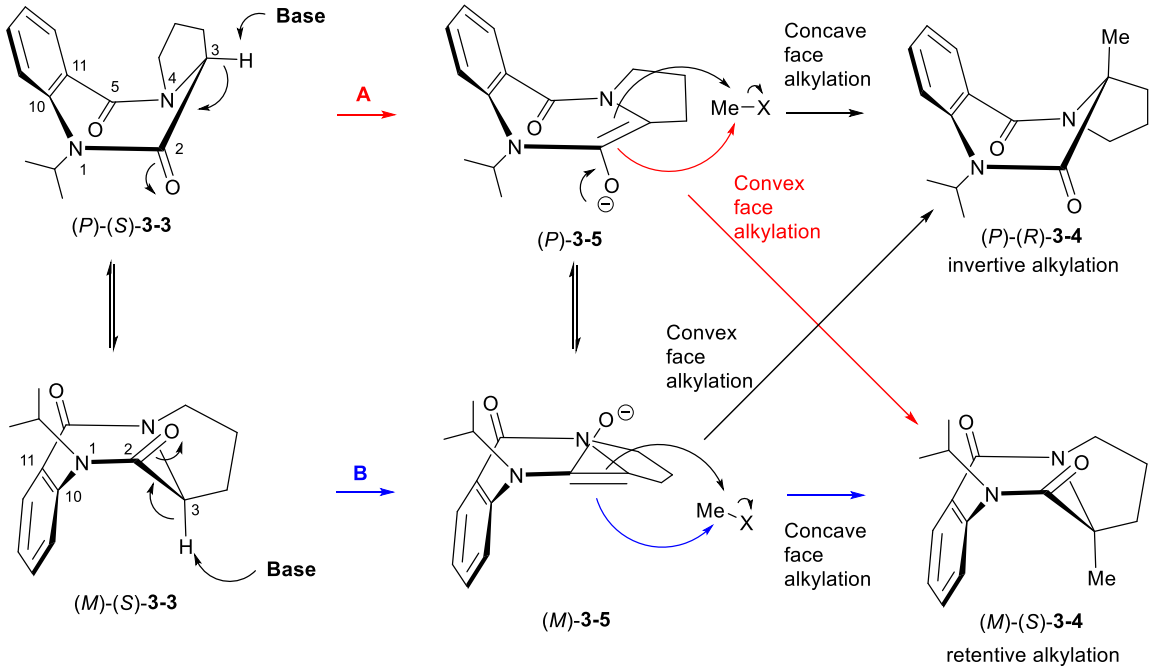
3-3 **3-4**

Entry	Me-X	*T* (°C)	t_1 (min)	t_2 (min)	% yield	% ee
1	MeI	-78	5	10	22	0
2	MeI	-78	1	10	10	93
3	MeOTf	-100	1	5	52	>99.5
4	MeOTf	-100	1	10	69	>99.5

(MeOTf) and reducing the temperature to -100 °C (entries 3-4). The best results obtained were those with a reaction time of 10 minutes (entry 4).

This time and temperature dependency suggests that the dynamically chiral enolate formed from the deprotonation of **3-3** interconverts between (*M*)- and (*P*)-conformers rapidly at -78 °C but more slowly at -100 °C. The helical descriptors (*M*)- and (*P*)- used to assign the sense of chirality here are assigned according to the sign of C2N1C10C11 dihedral angle. Note that this dihedral has the same sign as the dihedral angle C2C3N4C5, which historically has been used to define conformational chirality in 1,4-benzodiazepin-2-ones.[19]

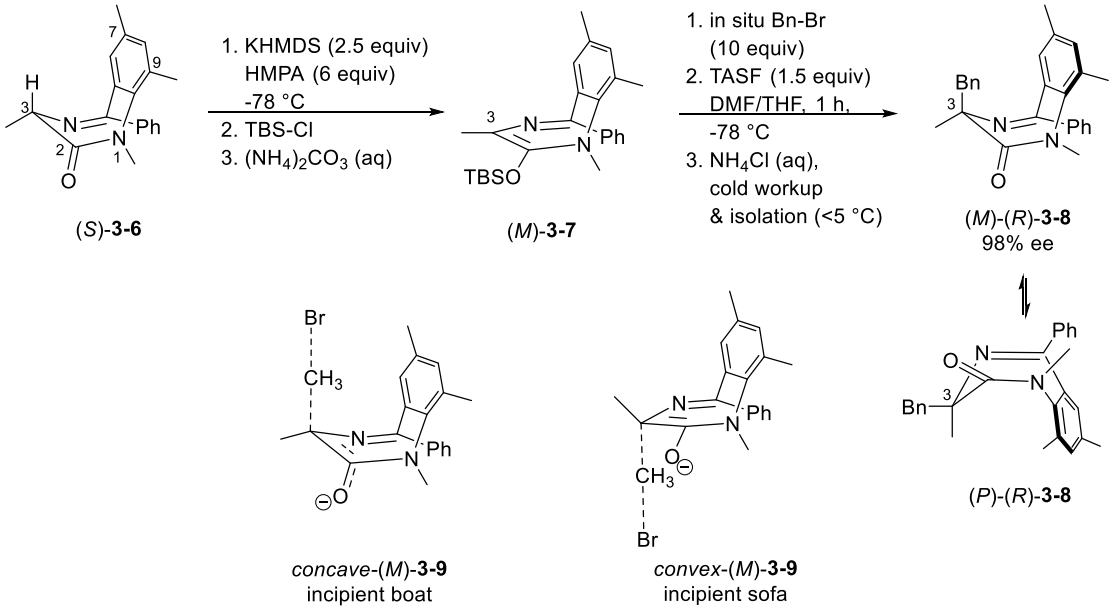
Scheme 3-2 illustrates the possible mechanistic pathways for the formation of **3-4**. As can be seen, to achieve retentive product (*S*)-**3-4**, either path **A** or path **B** must be followed. For path **A**, deprotonation must happen selectively from the *P* conformer.



Scheme 3-2 Possible mechanistic pathways for the formation of **3-4**

Subsequently, attack on the electrophile must come from the convex face of the enolate. Alternately, path B will lead to the retentive alkylation product (*S*)-**3-4** through deprotonation from the *M* conformer and concave face alkylation. From stereoelectronic considerations it can be reasoned that the *M* conformer is more susceptible to deprotonation due to better alignment of the C3-H σ orbital with the C2 carbonyl π* orbital than can be achieved in the *P* conformer. Further supporting this hypothesis, B3LYP/6-31G* calculations of **3-3** indicate that (*P*)-(*S*)-**3-3** is 17.8 kcal/mol higher in energy than (*M*)-(*S*)-**3-3.** Thus the (*P*)-(*S*)-**3-3** should only be present in insignificant amounts at equilibrium. For the deprotonation of (*P*)-(*S*)-**3-3** and (*M*)-(*S*)-**3-3**, it was seen that the transition structure arising from the deprotonation of (*M*)-(*S*)-**3-3** is 11.9 kcal/mol lower in energy than the transition structure afforded from the deprotonation of (*P*)-(*S*)-**3-3**. This high energy difference supports our qualitative reasoning based on stereoelectronic effects and indicates that deprotonation of (*M*)-(*S*)-**3-3** leading to (*M*)-**3-5** is preferred.

Following analysis for the deprotonation of (*M*)-(*S*)-**3-3**, a cursory glance of the alkylation step would seem to indicate that sterically, convex-face alkylation would be preferred to concave-face alkylation, but this would lead to the retentive product (*R*)-**3-4** instead of the obtained invertive product (*S*)-**3-4** . Later work by the Carlier group on 1,4-benzodiazepin-2-one (*S*)-**3-6** (**Scheme 3-3**) indicated that the preferred deprotonation is likely relevant to reactions on 1,4-benzodiazepin-2,5-diones.[17] First, starting (*S*)-alanine derived 1,4-benzodiazepin-2-one **3-6** was successfully deprotonated and trapped to form the silyl enol ether **3-7**. ^{1}H NMR spectra of **3-7** showed diastereotopic methyl protons at silicon, indicating that this structure is chiral. Compound **3-7** was obtained in optically active form with $[a]_D^{25} = +959$ and X-ray crystallography demonstrated that it possessed *M* axial chirality which originated in the (*M*)-(*S*)-**3-6** compound. Compound **3-7** was then deprotected and benzylated to yield the retentive product (*R*)-**3-8**, which at equilibrium exists as a mixture of (*M*)- and (*P*)- conformers. However, proton NMR spectroscopy of



Scheme 3-3 The stereochemical course of the retentive deprotonation/alkylation of (*S*)-**3-6**, illustrated by the trapping and reaction of silyl enol ether (*M*)-**3-7**.[17]

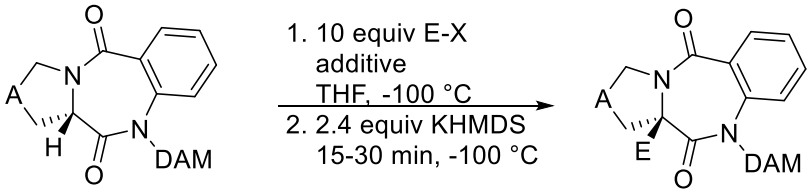
the product directly after reaction showed that alkylation of the enolate derivative from (*M*)-**3-7** gives product (*M*)-(*R*)-**3-8** exclusively. Thus, concave-face alkylation was confirmed.

How can this contra-steric alkylation be rationalized? Closer inspection of the crystal structure obtained of (*M*)-**3-7** shows slight pyramidalization at C3 to slightly orient a virtual sp^3 orbital toward the preferred concave-face alkylation. This idea is illustrated in transition state *concave*-(*M*)-**3-9**. The slight pyramidalization at the ground state reflects interactions that would have larger energetic consequences in the transition state,[20, 21] and this can help explain why *concave*-(*M*)-**3-9** is the preferred transition state over *convex*-(*M*)-**3-9**. Further explanation as to why preferential concave face alkylation occurs was demonstrated through the use of density functional calculations. Minimum energy B3LYP/6-31G* transition structures for alkylation (MeBr) indicated that for *concave*-(*M*)-***3*-9** an incipient boat conformation was adopted in contrast to the sofa conformation observed for *convex*-(*M*)-***3*-9**. For benzodiazepines the boat conformation is the preferred conformation[22] as this minimizes torsional strain along the MeC3C2O dihedral and maximizes π overlap in the amide functional group. The MeN1C2O dihedral angle for *concave*-(*M*)-**3-9** is 16.3° and 30.1° for *convex*-(*M*)-**3-9**. This indicates decreased amide π overlap for *convex*-(*M*)-**3-9**. While 1,4-benodiazepin-2,5-dione enolate (*M*)-**3-5** and 1,4-benzodiazepin-2-one (*M*)-**3-9** do differ in structure, both 1,4-benzodiazepin-2,5-diones and 1,4-benzodiazepin-2-ones undergo retentive deprotonation/alkylation. Given the calculated preference of deprotonation of (*M*)-(*S*)-**3-3** we therefore conclude that retentive deprotonation/alkylation of (*S*)-**3-3** occurs via path **B**

(**Scheme 3-2**). This as well as the calculations demonstrating preferential deprotonation of (*M*)-**3-3** supports path **B** as the correct mechanistic route.

While previous work provided a pathway to quaternary substituted 1,4-benzodiazepin-2- ones and proline-derived 1,4-benzodiazepin-2,5-diones, the appeal of this methodology is limited due to the requirement for an *i*-Pr group at N1. Because of this, Carlier et al.[16] began investigations on employing an alternate bulky *N*1 substituent that could easily be removed following enantioselective deprotonation/alkylation. For this cause, the di-(*p*-anisyl)methyl (DAM) group was used. As seen from **Table 3-2** the proline and thioproline derived *N*1-DAM protected **3-10a** and **3-10b** were successfully

Table 3-2 Alkylation on N1-DAM protected **3-10**. Table modified from Carlier *et al*.[16]



3-10a A = CH_2
3-10b A = S

3-11a A = CH_2
3-11b A = S

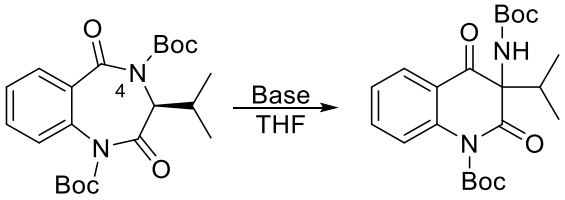
Entry	A	E	additive	% yield	% ee
1	CH_2	Bn	HMPA	98	98 *R*
2	CH_2	Bn	HMPA	90	0 (-78 °C)
3	CH_2	Bn	na	83	99 *R*
4	CH_2	4-Me-$C_6H_4CH_2$-	HMPA	93	>99.5 *R*
5	CH_2	4-Me-$C_6H_4CH_2$-	na	83	99 *R*
6	CH_2	2-Me-$C_6H_4CH_2$-	HMPA	94	99 *R*
7	CH_2	2-Me-$C_6H_4CH_2$-	na	87	94 *R*
8	CH_2	allyl	HMPA	65	93
9	CH_2	allyl	na	90	92
10	S	Bn	na	98	99
11	S	allyl	na	89	95

alkylated in high yields and excellent % ee. It was observed that -100 °C temperatures were required to ensure enantioselective reaction (entry 1 vs entry 2), but the use of HMPA was not necessary to obtain high yields. The DAM groups of the generated quaternary substituted benzodiazepines **3-11** were then successfully removed using 25% TFA in CH_2Cl_2 within 3 hours to afford the corresponding *N*-H analogues in near quantitative yields.

3.3 Chan-type rearrangement of 1,4-benzodiazepin-2,5-diones

Further application of SRSvSACI principle to benzodiazepines was reported by Farran *et al.*[1] in which base mediated transannular rearrangement of 3-isopropyl-1,4-benzodiazepine-2,5-dione **3-12** (**Table 3-3**) affords the corresponding 3-aminoquinolone-2,4-dione **3-13**. These reactions proceed in an enantioselective manner similar to the deprotonation/alkylation reactions involving proline- and thioproline- derived 1,4-benzodiazepin-2,5-diones observed by Carlier *et al*,[15] with one exception. Whereas the

Table 3-3 Transannular rearrangement of **3-12**[1]

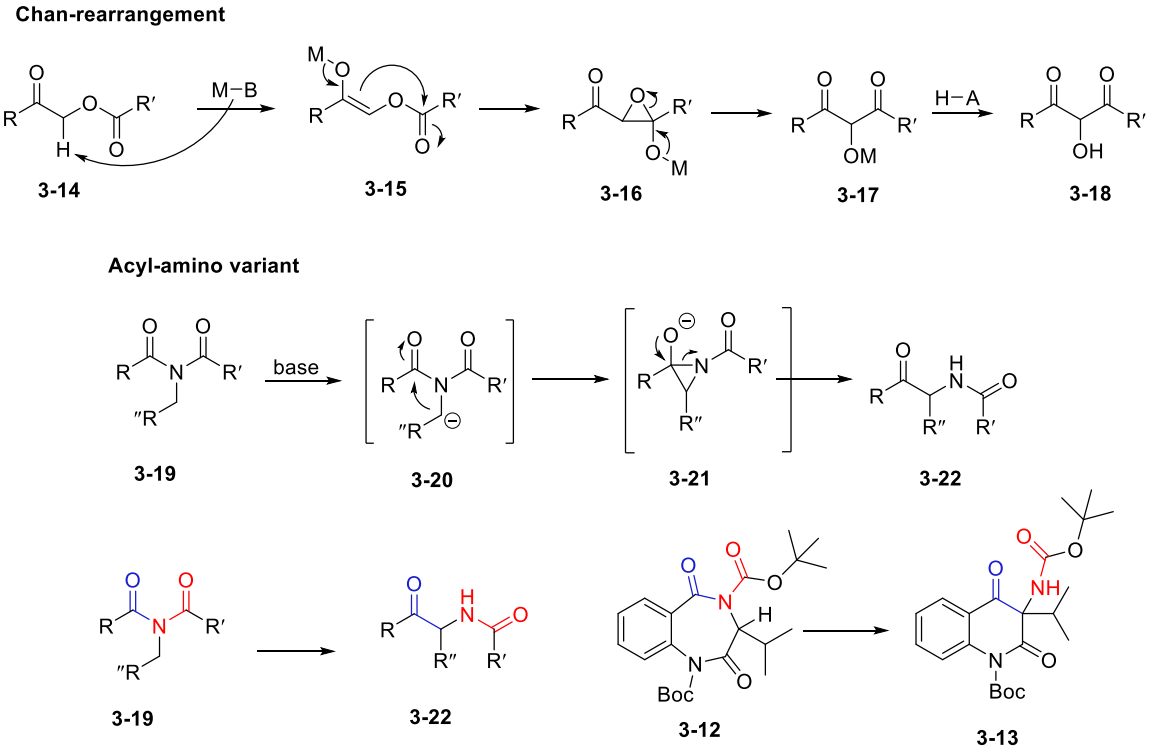


(*S*)-**3-12** **3-13**

Entry	**3-12**	Base	T (°C)	configuration, yield (%)	ee (%)
1	(3S)	LDA	-78	-, 0	-
2	(3*S*)	*n*BuLi	-78	-, 0	-
3	(3*S*)	NaH	0	(3S), 5	66
4	(3*S*)	*t*BuOK	0	(3S), 52	44
5	(3*S*)	LiHMDS	-78	(3R), 75	94
6	(3*S*)	KHMDS	-78	(3S), 87	62

latter substrates could be converted to enolates and then alkylated, Dewynter's substrate (*S*)-**3-12** undergoes an intramolecular reaction following enolization. The key difference here is that **3-12** contains an *N*4-*tert*-butyloxycarbonyl (Boc) protecting group which was not used for any of the prior examples of SRSvSACI involving benzodiazepines by Carlier *et al.*[11, 15-18] Due to the electron-withdrawing *N*4-Boc protecting group, deprotonation of C3 leads to an intramolecular ring contraction, which is an acyl-amino variant[23] of the Chan rearrangement.[24]

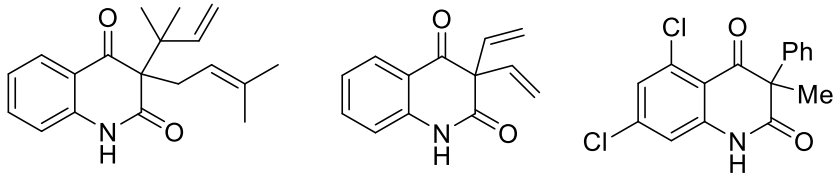
The Chan rearrangement, as demonstrated in the transformation of **3-14** to **3-18** (**Scheme 3-4**), is a reaction proceeding through the base-mediated rearrangement of an acyloxy acetate, **3-14**, leading to a 2-hydroxy-3-keto-ester, **3-18**. An acyl-amino variant



Scheme 3-4 Chan-rearrangement of **3-14** and **3-12**[1, 23, 24]

of the Chan-rearrangement was investigated by Hamada *et al.*[23] and occurs through the deprotonation of an acyl-activated amide, illustrated by the transformation of **3-19** to **3-22**. It can be seen how **3-12** closely resembles **3-19**, as similar functionalities are highlighted in blue and red in **Scheme 3-4**, which shows how **3-12** is a viable candidate for the Chan-rearrangement as reported by Dewynter *et al.*[1]

Prior to this work, there was no known stereoselective pathway to 3-alkyl-3-aminoquinolone-2,4-diones, and only one racemic preparation.[28, 29] Yet, quinolone-2,4-diones possessing a quaternary substituted C3 serve as a potentially useful drug scaffold, as is observed in buchapine **3-23**[25] (**Figure 3-1**) and **3-24**[26] which demonstrates anti-HIV activity and with **3-25** which exhibits 5-HT_6 serotonin receptor antagonism.[27]



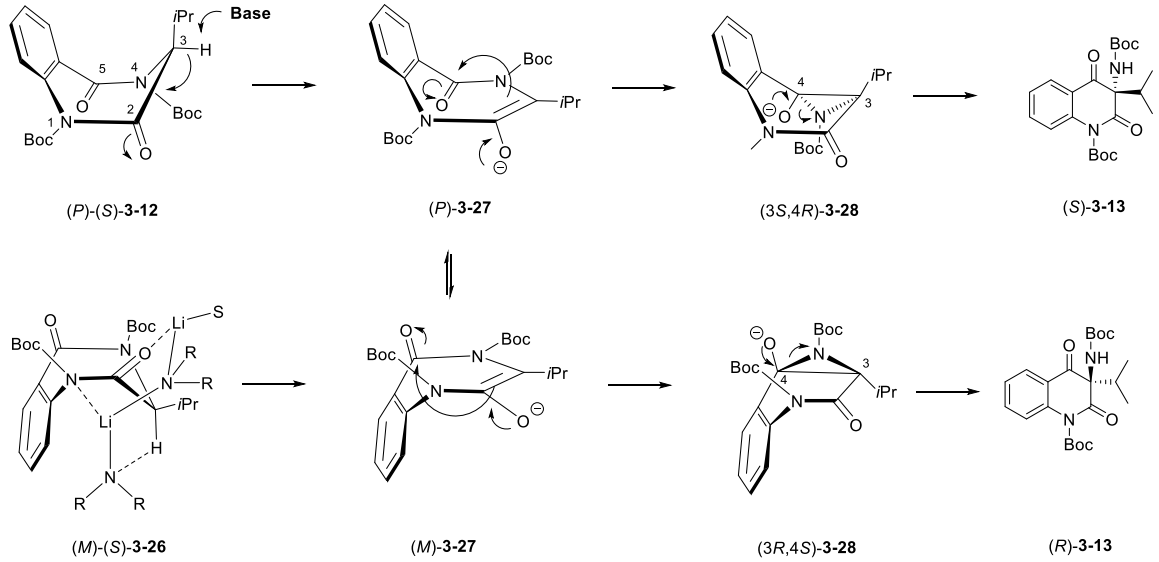
3-23 **3-24** **3-25**

Figure 3-1 Potential Quinolone-2,4-dione Drug Scaffolds[25-27]

Dewynter reported that for (*S*)-**3-12**, use of LDA and *n*BuLi for deprotonation (**Table 3-3**, entry 1 and 2) were unsuccessful and gave complicated mixtures of compounds that were too difficult to analyze. Sodium hydride and potassium *tert*-butoxide gave less than desirable yields and poor % ee (**Table 3-3**, entry 3 and 4). However, when treated with LiHMDS, at -78 °C, (*R*)-**3-13** was afforded in 75% yield and 94% ee (entry 5). The most striking results were those involving KHMDS in comparison to LiHMDS (entry 5 and 6). Starting from the same enantiopure benzodiazepine (*S*)-**3-12**, it is possible to obtain both enantiomers of **3-13** by changing the cation of the base. For

LiHMDS the reaction leads to the invertive product, whereas KHMDS preferentially leads to retention of configuration.

The authors explain the divergent results through the conformational equilibrium of the starting material. To obtain the retentive product (*S*)-**3-13** (**Scheme 3-5**) starting material must be the (*P*)-(*S*)-**3-12** conformer, which gives enolate (*P*)-**3-27**, that forms aziridine (*3S,4R*)-**3-28**. DFT/PCM calculations at the B3LYP/SDD level of theory and careful examination of the ^{1}H NMR spectrum of (*S*)-**3-12** showed that the *P*-conformer, with the isopropyl group in the pseudoaxial position is the most stable and preferred conformer, which is in stark contrast to DFT calculations of proline derived (*S*)-**3-3** which indicate the *M*-conformer as preferred. Furthermore, in all previous calculations of deprotonation of 1,4-benzodiazepin-2-ones and 1,4-benzodiazepin-2,5-diones there has been a significant energetic preference for deprotonation of (*M*)-(*S*)-conformers, in which the C3-H is pseudoaxial. If Dewynter's proposal of preferential deprotonation of (*P*)-(*S*)-



Scheme 3-5 Mechanistic explanation for stereoselectivity in the formation of **3-13**[1]

3-12 is correct, then it is likely that the additional acyl groups at N1 and N4 (Boc) are responsible. For (*S*)-**3-12,** it might be that *N*1- and *N*4-exocyclic amide resonance plays a larger role than *N*1- and *N*4-endocyclic resonance with the *C*2- and *C*5-carbonyl groups. Reduced endocyclic resonance could allow for greater flexibility within the 1,4-benzodiazepin-2,5-dione ring of (*S*)-**3-12**. As we will discuss below, a stereoelectronically acceptable HC3C2O torsion angle might be obtained which leads to the KHMDS deprotonation of (*P*)-(*S*)-**3-12**. Proline derived (*S*)-**3-3**, lacking the *N*1- and *N*4-Boc protecting groups, can only participate in endocyclic resonance, and thus this electronic difference must be key in directing preferential conformation.

The authors propose that KHMDS base deprotonation would occur from the most stable conformer leading to retention of configuration in the product. LiHMDS, on the other hand, is known to exist as a monomer-dimer equilibrium in ethereal solvents.[30] Deprotonation of carbonyl compounds by dimeric LiHMDS can proceed via "open-dimer" transition states.[31] Dewynter proposed that such an open-dimer TS might be more favorable for (*M*)-(*S*)-**3-12** than for (*P*)-(*S*)-**3-12** (**Scheme 3-5**). As can be seen TS (*M*)-(*S*)-**3-37** leads to the invertive product, (*R*)-**3-13**. Note that enantiodivergent outcomes from Li and KHMDS have precedent in the literature as Kawabata reported the same phenomenon in deprotonation/alkylation reactions for the synthesis of α,α-disubstituted-α-amino acids from α-amino acids using SRSvSACI.[32, 33]

3.4 Enantioselective ring contraction of N1-methyl-N4-Boc-benzo[e][1,4]diazepin-2,5-diones

Interested in the enantiodivergent paths taken by the lithium and potassium enolate derivatives of **3-12** as well as the potential usefulness of 3,3-disubstituted

quinolone-2,4-diones as drug scaffolds, our group[34] began an investigation into generating a broader scope of 1,4-benzodiazepin-2,5-diones which could undergo the Chan-type ring contraction reaction. This effort was begun by a former graduate student, Stephanie Antolak, and a postdoctoral researcher, Dr. Zhongke Yao, also played a major role. My involvement began with the synthesis of (*S*)-**3-34e** and will be clearly marked below.

As Farran *et al.* reported,[1] valine derived **3-29a** (**Figure 3-2**) was easily transformed into the *N*1,*N*4-di-Boc Val-derived **3-31a**, but for L-Ala, Ile, Phe, and phenylglycine this was not possible, as only the mono- or tri-Boc derivatives **3-30b-e** and **3-32b-e** were obtained, respectively. Reactions were carried out by dissolving **3-29b-e** and Boc_2O in either THF, DMF, or pyridine along with Et_3N and/or DMAP. In all cases, the major/only product was tri-Boc protected **3-32b-e**, without even trace amounts of **3-31b-e**. In one peculiar case, using **3-29e**, mono-Boc protected **3-30e** was obtained at 0 °C whereas increasing the temperature to 10 °C afforded only tri-Boc protected **3-32e**.

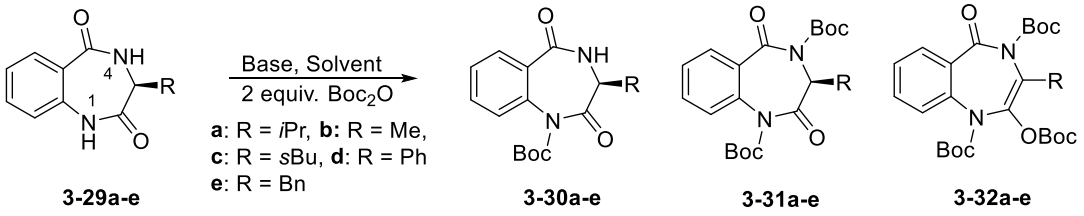
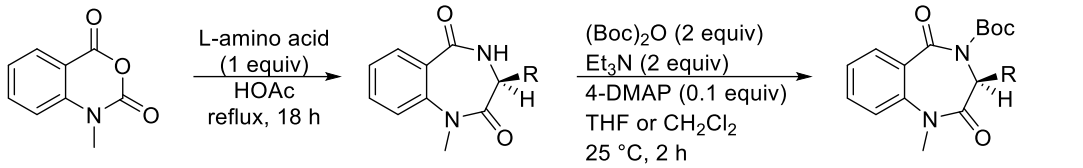


Figure 3-2 Attempted *N*1, *N*4-di-Boc protection of 1,4-benzodiazepin-2,5-diones[1]

In any event, since the Dewynter group could prepare only one *N*1-Boc, *N*4-Boc-1,4-benzodiazepin-2,5-dione, their very interesting study was restricted to a single substrate. To broaden the scope of this ring contraction, Antolak and Yao (the Carlier group) investigated replacing the *N*1-Boc substituent with methyl, as we presumed that

only *N*4 required electron withdrawing activation by an acyl group to facilitate the ring contraction. This was accomplished by reacting L-Val, Ala, Met, Leu, and Phe with *N*-methylisatoic anhydride **3-33** (**Scheme 3-6**) in refluxing acetic acid for 18 hours, affording the corresponding *N*1-Me benzodiazepin-2,5-diones, (*S*)-**3-34a-e**. Partial racemization occurred during these reactions, and for all but L-Phe derived **3-34e** the products could be recrystallized to >99% ee. Final yields for **3-34a-e** were moderate to good ranging from 56-81%. Treatment with di-*tert*-butyl dicarbonate (Boc_2O), triethylamine (Et_3N), and 4-dimethylaminopyridine (DMAP) in THF or DCM afforded *N*1-Me-*N*4-Boc-benzodiazepine-2,5-diones (*S*)-**3-35a-d** in good to excellent yields (62-95%) and excellent % ee (>94%).



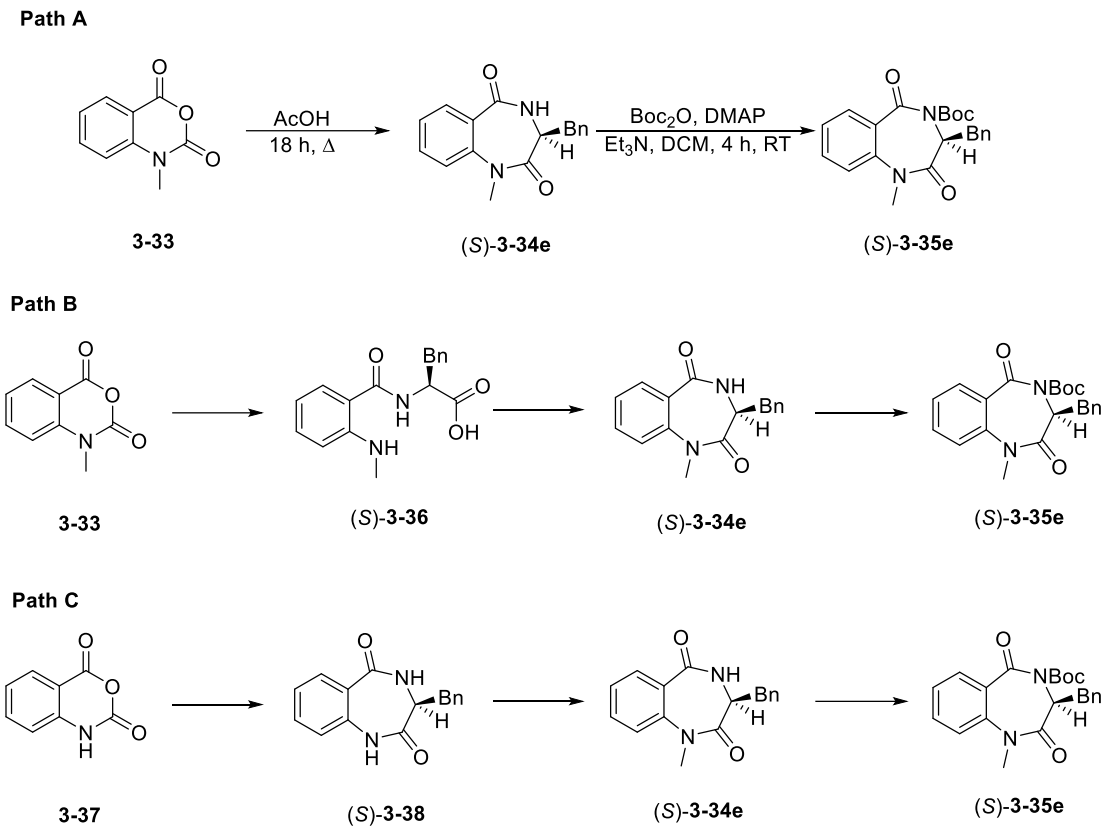
3-33

	R	Yield (%)
(*S*)-**3-34a**:	*i*-Pr	56
(*S*)-**3-34b**:	Me	74
(*S*)-**3-34c**:	CH_2CH_2SMe	60
(*S*)-**3-34d**:	*i*-Bu	81
(*S*)-**3-34e**:	CH_2Ph	57

	Yield (%)	ee (%)
(*S*)-**3-35a**:	95	98
(*S*)-**3-35b**:	82	94
(*S*)-**3-35c**:	90	>99
(*S*)-**3-35d**:	62	96
(*S*)-**3-35e**:	96	80(85)

Scheme 3-6 Preparation of Ring-Contraction Reaction Substrates (S)-**3-35a-e**. Scheme modified from Carlier *et al*.[34]

Neither L-Phe derived (*S*)-**3-34e** nor its *N*4-Boc derivative (*S*)-**3-35e** was a highly crystalline solid, and they could not be obtained in excellent enantiomeric enrichment using the current synthetic protocol. Originally Stephanie Antolak prepared (*S*)-**3-35e** in 80% ee, and Dr. Zhongke Yao obtained (*S*)-**3-35e** in a slightly higher 85% ee. It was at this point that I joined the project, and my research involved increasing % ee through optimizing the synthesis of (*S*)-**3-35e**. Three separate methods were investigated as demonstrated in **Scheme 3-7. Path A** demonstrates the original procedure previously



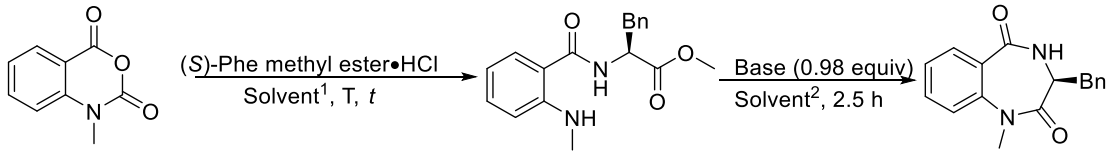
Scheme 3-7 Alternate pathways to synthesize **3-35e**

discussed in which **3-35e** was obtained in 80-85% ee. Transformation of **3-33** into 1,4-benzodiazepin-2,5-dione (S)-**3-34e** likely proceeds via rapid formation of ring-opened intermediate (*S*)-**3-36** (as observed through TLC), followed by the slow ring-closure step to give (*S*)-**3-34e**. Partial racemization, most likely occurs during the slow ring closure, which requires high temperatures for an extended period of time in acetic acid. For **Path B** we investigated alternate reaction protocols utilizing various solvents and reagents in which elevated temperature conditions were limited in time or removed altogether to limit racemization in the synthesis of (*S*)-**3-34e**. For **Path C**, we anticipated that (*S*)-**3-38** could be recrystallized to >99% ee, after which we would strive to achieve non-racemizing *N*1-selective methylation to afford (*S*)-**3-34e**.

3.4.1. Path B synthesis of (*S*)-phenylalanine derived 1,4-benzodiazepin-2,5-dione (*S*)-3-35e

Our first attempts at obtaining (*S*)-**3-34e** in higher % ee involved following **Path B** exploiting an alternate ring closure protocol utilizing (*S*)-Phe methyl ester in an attempt to determine if an alternate leaving group (-OMe vs –OH) would facilitate a faster ring closing (**Table 3-4**). Instead of a one-pot transformation of **3-33** to (*S*)-**3-34e**, as described previously, methyl ester ring-opened intermediate (*S*)-**3-36** was first obtained by workup after either treatment with either Et_3N (24 °C) or pyridine (reflux), and ring closure was then attempted on the crude intermediate (*S*)-**3-36.** For the ring closure step, KHMDS in either methylene chloride or Et_2O gave an exceptionally complicated reaction mixture, and product (*S*)-**3-34e** was not isolated (entry 1 and 2). While treatment of (*S*)-**3-36** with KHMDS in toluene did give some of the expected product, it was only obtained in 19% yield (entry 3). Previously, for 1,4-benzodiazepin-2,5-diones enantiomeric excess was checked by chiral HPLC once *N*4 was Boc-protected, and because the yield was already so low for (*S*)-**3-34e** obtained from entry 3 prior to Boc-protecting, we did not

Table 3-4 Alternate ring closure protocol for the synthesis of (*S*)-**3-34e**



3-33 (*S*)-**3-36** (*S*)-**3-34e**

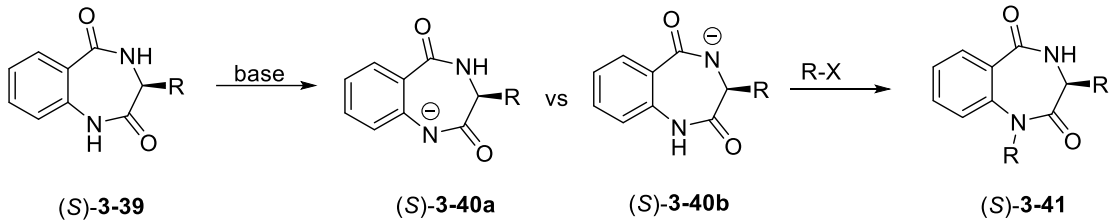
Entry	Solvent[1]	*T* (°C)	*t* (h)	Base	Solvent[2]	Total yield (%)	ee (%)
1	Et_3N	24	4.5	KHMDS	Et_2O	0	-
2	Pyridine	115	2.5	KHMDS	DCM	0	-
3	Pyridine	115	2.5	KHMDS	Toluene	19	-
4	Pyridine	115	2.5	*t*BuOK	THF	54	29
5	Et_3N	24	4.5	*t*BuOK	THF	47	22

move forward with investigation of this base, and % ee is not reported for entry 3. Instead, we attempted ring closure with potassium *tert*-butoxide (*t*BuOK). Product (*S*)-**3-34e** was obtained in 54% and 47% yields of for entry 4 and entry 5, respectively. Unfortunately, once *N*4 was Boc-protected to (*S*)-**3-35e**, it was observed that % ee was less than 30% for both entries.

Through investigation into the literature, work by Sivakua *et al.*[35] was discovered which offers insight into the low % ee we have obtained in the synthesis of (*S*)-phenylalanine derived 1,4-benzodiazepin-2,5 diones. In investigation of racemization rates of (*S*)-amino acids, the authors reported that (*S*)-phenylalanine has a relative rate of racemization approximately 2-6 times faster than (*S*)-alanine, (*S*)-leucine, and *(S*)-valine, the cause of which is most likely due to the electron withdrawing nature of the aromatic ring. It was also seen through studying the pH profile of these amino acids that the rate of racemization increases at higher pH values. This highlights how attempts to synthesize (*S*)-**3-35e** through base mediated ring opening/closing **Path B** is not optimal, and clearly an alternate route needs to be investigated.

3.4.2. Path C synthesis of (*S*)-phenylalanine derived 1,4-benzodiazepin-2,5-dione (*S*)-3-35e

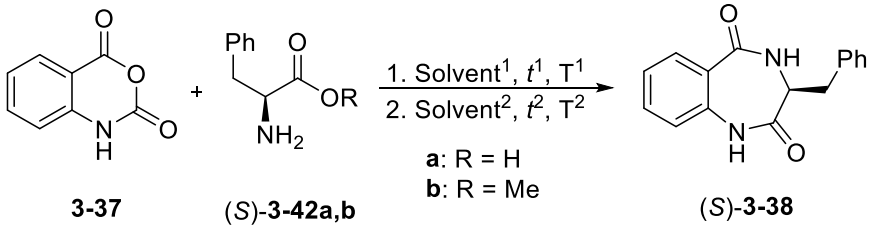
Because attempts at using an alternate ring closure protocol (**Path B**) did not provide us with the desired results, we then decided to try a different approach to synthesize (*S*)-**3-34e** in higher % ee. In our experience, 1,4-benzodiazepin-2,5-diones lacking substituents at *N*1-nitrogen are highly crystalline and thus we were confident they could be recrystallized to high % ee. From the work of Fang et al.[5] it is known that di-*N*H 1,4-benzodiazepin-2,5-diones structures like (*S*)-**3-39** (**Scheme 3-8**) could be selectively



Scheme 3-8 Selective *N*1-alkylation of **3-39**

mono-alkylated at *N*1. We reasoned that *N*1 deprotonation leading to (*S*)-**3-40a** should be preferred over *N*4 deprotonation leading to (*S*)-**3-40b** due to the extra resonance stabilization of the *N*1 lone pair both through the aromatic ring and with both the *C*2 and *C*5 carbonyl functionalities. If this selective *N*1 alkylation could be achieved without racemization, then (*S*)-**3-41** could be obtained in high % ee. Investigation into the synthesis of di-*N*H 1,4-benzodiazepin-2,5-dione (*S*)-**3-38** began with the typical protocol used previously in the synthesis of *N*1-methyl-*N*4-H-benzodiazepin-2,5-dione (*S*)-**3-34e** (**Scheme 3-6**). It should be noted that it was important to recrystallize isatoic anhydride **3-37** before reacting with the amino acid (*S*)-**3-42a** (or ester (*S*)-**3-42b**) as it appears that isatoic anhydride may degrade upon standing. A two-step protocol for the synthesis of

Table 3-5 Synthesis of di-*N*H 1,4-benzodiazepin-2,5-dione (*S*)-**3-38**



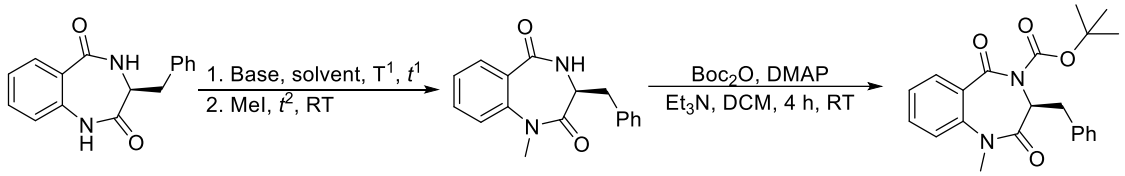
Entry	S.M.	Solvent[1]	T[1] (°C)	t^1 (h)	Solvent[2]	T[2] (°C)	t^2 (h)	Yield (%)	ee (%)
1	**3-42b**	Et_3N/H_2O	24	2	pyridine	115	16	<5%	-
2	**3-42b**	Et_3N/H_2O	24	2.5	AcOH	116	16	44	81
3	**3-42a**	Et_3N/H_2O	24	24	AcOH	116	45	81 (34[a])	78 (>99[a])
4	**3-42b**	Et_3N/H_2O	24	2	AcOH	116	48	77 (35[a])	>99[a]

[a]recrystallized product. [b]product repeatedly recrystallized in $EtOH/H_2O$ until optical rotation remained consistent. Further, ee was assigned based on this rotation.

(*S*)-**3-38** was applied (**Table 3-5**, entry 1-4). It was seen that for ring opening with Et_3N/H_2O and attempted ring closure in refluxing pyridine, only a very small quantity of product (*S*)-**3-38** was formed (entry 1). Ring opening in Et_3N/H_2O followed by reflux in AcOH for 16 hours afforded the expected product in 44% yield and 81% ee, but the reaction had not yet reached completion as starting material was evident on TLC (entry 2). The best results obtained were those where ring closure was performed in refluxing acetic acid for 45-48 hours, to afford (*S*)-**3-38** in 34% yield and >99% ee (entry 3) and 35% yield and >99% ee (entry 4) following recrystallization. Using either (*S*)-Phe or (*S*)-Phe methyl ester gave similar outcomes (**Table 3-5**, entries 1, 3).

With di-*N*H (*S*)-Phe derived (*S*)-**3-38** in hand, selective *N*1-methylation was attempted. As previously discussed, Fang *et al*.[5] reported the mono-alkylation of 1,4-benzodiazepin-2,5-dione derivatives similar to (*S*)-**3-39** (**Scheme 3-8**). They accomplished this with the use of potassium carbonate (K_2CO_3) in dimethylformamide (DMF). Alternately, Blass *et al*. reported the mono-methylation of di-*N*H 1,4-benzodiazepin-2,5-diones with iodomethane (MeI) and potassium fluoride on alumina (KF/Al_2O).[36] Our attempt at mono-methylation with KF/Al_2O was not successful giving a 1:1 mixture of the desired mono-methyl product (*S*)-**3-34e** and the undesired *N*1,*N*4-dimethyl product. To determine the enantiomeric excess of (*S*)-**3-34e**, in each case it was converted to the *N*4-Boc derivative (*S*)-**3-35e**. For entry 1, it was seen that poor yield and only 81% ee were achieved (**Table 3-6**). Use of K_2CO_3 afforded (*S*)-**3-34e** in high yield, and significantly higher enantiomeric excess (94 % ee, entry 2). In an attempt to increase yield, cesium carbonate was used. Although the alkylation was improved, the enantiomeric excess of the final product (*S*)-**3-34e** was lower than that obtained with

Table 3-6 *N*1 and *N*4 protection of **3-38**



(*S*)-**3-38** (*S*)-**3-34e** (*S*)-**3-35e**

Entry	Base	Solvent	T^1 (°C)	t^1 (h)	t^2 (h)	(*S*)-**3-34e** yield (%)	(*S*)-**3-35e** yield (%)	ee (%)
1	KF/Al_2O	DMF	25	-	48	33[a]	99	81
2	K_2CO_3	DMF	25	1	7	56	99	94
3	Cs_2CO_3	DMF	25	1	31	90	85	85
4	MeLi	THF	-78	2	2	na[b]	-	-

[a]*N*1,*N*4-di-methylated product observed as well (~1:1). [b]A mixture of S.M. and *N*1,*N*4-di-methylated product was obtained, but the mixture was not separated

K_2CO_3 (85% vs 94% ee). Finally, the use of methyl lithium (MeLi) as base was also explored, and although mono methyl product (*S*)-**3-34e** was initially observed by TLC, it was quickly converted to the *N*1,*N*4-dimethyl product.

3.4.3. A new discovery in the Path A synthesis of (*S*)-phenylalanine derived 1,4-benzodiazepin-2,5-dione (*S*)-3-35e

It was at this time that an interesting observation was made of *N*1-Me, *N*4-Boc phenylalanine derived (*S*)-**3-35e**. While it had previously been reported as a viscous glassy solid that could not be recrystallized, a standing vial of racemic **3-35e**, which was used for HPLC comparison of enantioenriched (*S*)-**3-35e**, appeared to have a small amount of crystal growth along the edges of the vial. From this observation, we reasoned that under the right conditions, **3-35e** might be coaxed into a crystalline state. Starting with glassy solid **3-35e** (**Figure 3-3,** picture **A**), methylene chloride was added and stripped off under vacuum followed by addition and stripping of hexane. Cloudiness was observed with the first addition of hexane. This was repeated multiple times, and after the 4th addition of hexane, a spatula was scratched on the glass in the mixture, and a fluffy

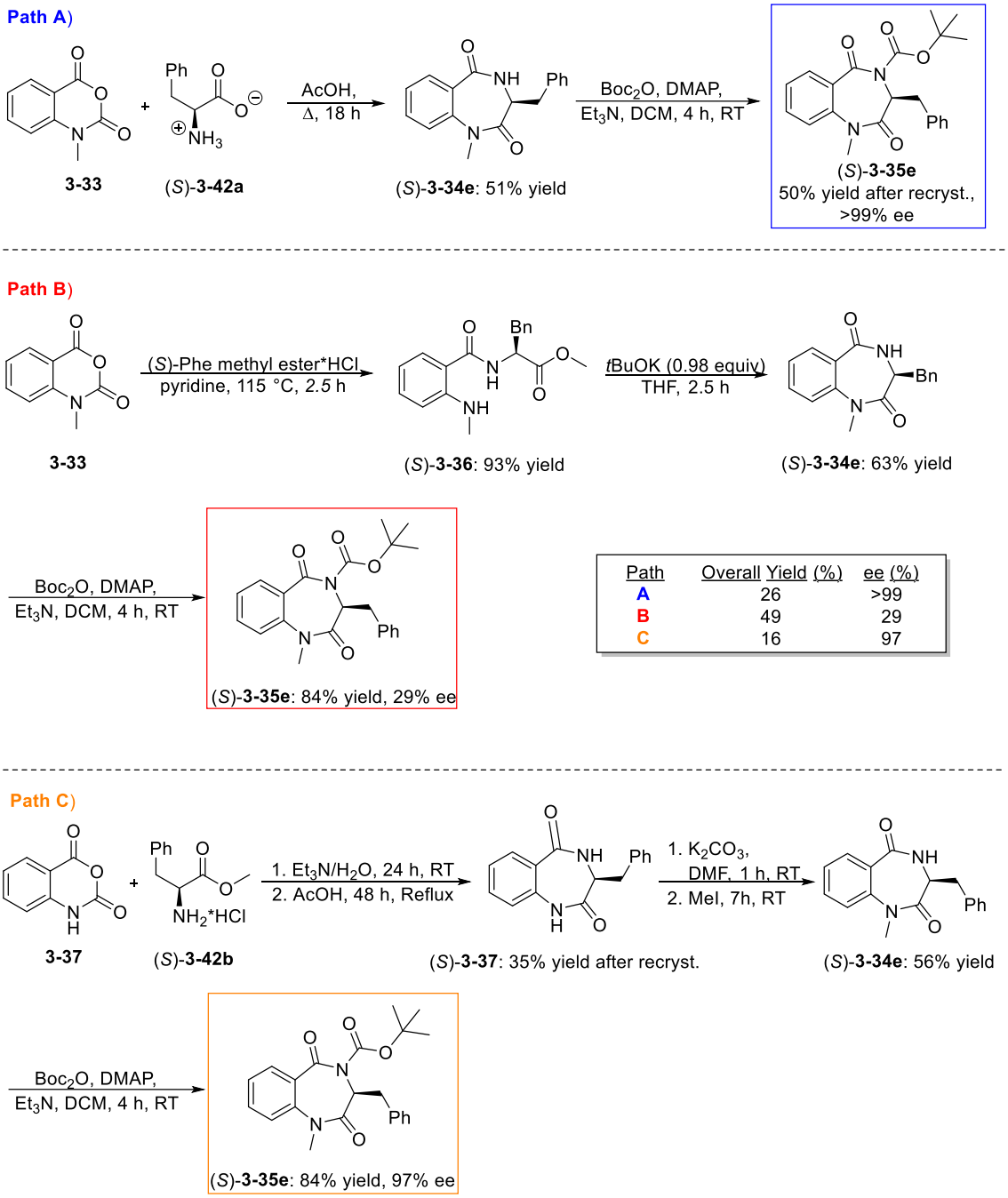
A **B** **C**

Figure 3-3 Recrystallization of **3-35e**

white solid of **3-35e** (**Figure 3-3**, picture **B**) crashed out of solution. Solid was filtered off, and it was discovered that it could be recrystallized in 100% hot hexane to afford crystalline **3-35e** (**Figure 3-3**, picture **C**). Enantiomeric enrichment of **3-35e** was raised to >99% through this recrystallization method, and x-ray crystallography was also able to be performed, which confirmed C3 to have *S* stereochemistry.

With the ability to recrystallize (*S*)-**3-35e** to high enantiomeric enrichment, we had three separate pathways to proceed (**Scheme 3-9**). **Path A** uses the original protocol of acetic acid reflux of (*S*)-phenylalanine with *N*-methyl isatoic anhydride to give (*S*)-**3-34e,** which is then Boc-protected and recrystallized to give (*S*)-**3-35e** in 26% total yield and >99% ee. **Path B** proceeds through a two-step ring opening/ring closing procedure under basic conditions followed by *N*4-Boc protection to afford final product (*S*)-**3-35e** in

better overall yield (49%) although at lower % ee (29%). **Path C**, in which we synthesize di-*N*H 1,4-benzodiazepin-2,5-dione (*S*)-**3-37**, recrystallize to high % ee, selectively methylate at *N*1, and then install the Boc protecting group at *N*4 to afford (*S*)-



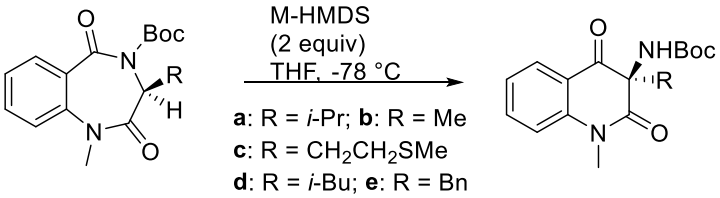
Scheme 3-9 Path A-C in the overall synthesis of (*S*)-**3-35e**

3-35e in 16% yield overall and 97% ee. With these three protocols, it is apparent that method **A** is the superior pathway to generating (*S*)-**3-35e** in high ee.

3.4.4. Rearrangement of 1,4-benzodiazepin-2,5-dione derivatives 3-35a-e

All *N*1-Me, *N*4-Boc BZDs (*S*)-**3-35a-e** were deprotonated using both LiHMDS and KHMDS, and as can be seen in **Table 3-7** underwent the desired ring-contraction to afford **3-44a-e**. The rearrangement of **3-35a-d** was pioneered by Stephanie Antolak and subsequently optimized by Zhongke Yao. I then applied this same protocol to the rearrangement of phenylalanine derived **3-35e**. X-ray crystallography was performed for (–)-**3-44a** (generated by Stephanie Antolak) and (–)-**3-44e** (generated by me), and the

Table 3-7 Ring Contraction Reactions of **3-35a-e**[34]



(*S*)-**3-35a-e** **3-44a-e**

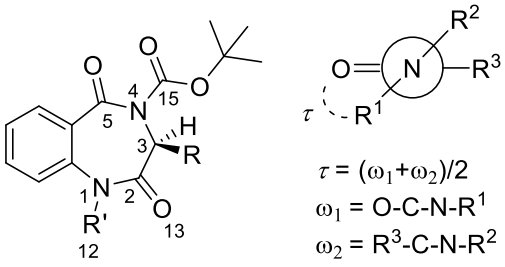
Entry	Substrate	M	Product	% yield	% ee (config)
1	(*S*)-(–)-**3-35a**	Li	(–)-**3-44a**	84	98 (*R*)[a]
2	(S)-(–)-**3-35a**	K	(–)-**3-44a**	84	98 (*R*)[a]
3	(S)-(+)-**3-35b**	Li	(–)-**3-44b**	69	92 (*R*)[b]
4	(S)-(+)-**3-35b**	K	(+)-**3-44b**	57	97 (*R*)[b]
5	(S)-(–)-**3-35c**	Li	(–)-**3-44c**	91	>99 (*R*)[b]
6	(S)-(–)-**3-35c**	K	(–)-**3-44c**	63	>99 (*R*)[b]
7	(S)-(–)-**3-35d**	Li	(–)-**3-44d**	56	84 (*R*)[b]
8	(S)-(–)-**3-35d**	K	(–)-**3-44d**	58	92 (*R*)[b]
9	(S)-(–)-**3-35e**	Li	(–)-**3-44e**	85	98 (*R*)[b]
10	(S)-(–)-**3-35e**	K	(–)-**3-44e**	82	92 (*R*)[b]

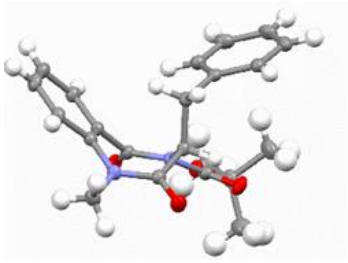
[a]The absolute configuration of (–)-**3-44a** was established as (*R*)- by X-ray crystallography. [b]The products of rearrangement of (*S*)-**3-35a-e** (**3-44a-e**) are assigned an (*R*)-configuration based on HPLC elution order and conformity of optical rotation (in every case the sign of rotation is preserved from (*S*)-**3-35a-e** to **3-44a-e**).

absolute configuration was identified as (*R*). For the remainder of the compounds, stereochemistry at C3 was assigned based on two observations. First, in every case the major enantiomer of the products derived from (*S*)-**3-35a-e** elutes first on the Chiralcel OD column. Second, we noticed that the sign of the optical rotation of (*S*)-**3-35a-e** (whether plus or minus) was preserved in the product. Based on these observations (*R*)-stereochemistry was assigned to all the ring-contracted products. All products were obtained in moderate to good yields and good to excellent % ee. LiHMDS gave slightly better % ee in most cases except with **3-35b** and **3-35d**. Interestingly, all products were found to have (*R*) stereochemistry regardless of whether LiHMDS or KHMDS was used, suggesting that in each case deprotonation of the (*M*)-conformer occurred. As noted in previous work by Carlier *et al.*[17] involving (*S*)-configured 1,4-benzodiazepin-2-one or 1,4-benzodiazepin-2,5-diones, deprotonation is stereoelectronically predisposed to occur from the (*M*)-conformer due to the pseudoaxial C3-H σ and C2-O π* orbital overlap. This appears to be the case for all instances except for deprotonation with KHMDS of Dewynter and co-workers' valine-derived *N*1, *N*4-di-Boc protected 1,4-benzodiazepin-2,5-dione **3-12** (**Table 3-3**).

While a detailed computational study of possible transition structures would be necessary to account for Dewynter's proposed pseudoequatorial deprotonation of **3-12** with KHMDS, X-ray analysis of *N*1,*N*4-di-Boc substrate **3-12** in comparison to the *N*1-methyl-*N*4-Boc substrate **3-35e** shows some differences in the conformation these structures adopt (**Table 3-5**). Although both (*S*)-configured compounds adopt a (*P*)-conformation in the solid state, we know from ^{1}H NMR spectroscopy that (*S*)-**3-35**e exists in a 0.3:0.7 mixture of the (*M*)- and (*P*)-conformers, in which the *C*3-H is

Table 3-8 Analysis of torsion angles for (*S*)-**3-35e** and **3-12**





3-35e

	(*P*)-(*S*)-**3-35e**	(*P*)-(*S*)-**3-12**
R′	Me	Boc
R	Bn	*i*-Pr
$\tau_{1\text{-}2}$	-1.4°	-36.4°
$\tau_{4\text{-}5}$	9.7°	-31.9°
$\tau_{4\text{-}15}$	16.6°	-19.4°
$\tau_{1\text{-}12}$	na	3.3°
HC3C2O13	3.1°	21.6°

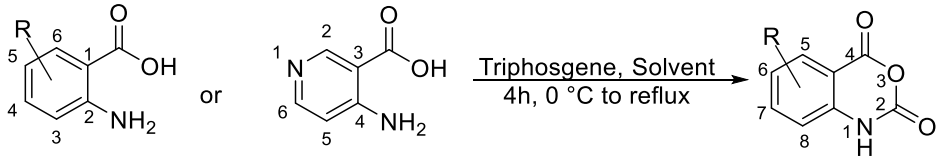
pseudoaxial and pseudoequatorial, respectively. But looking at the (*P*)-conformers in the solid state, there are some differences in the extent of amide resonance within and external to the 1,4-benzodiazepin-2,5-dione ring. The extent of amide resonance is judged according to the amide twist angles (τ)[37, 38] along the N1-C2, N4-C5, N4-C15, and N1-C12 bonds. For amide twist angles closer to zero, it can be assumed that amide resonance is high. As is seen in **Table 3-8** the crystal structure obtained for (*S*)-**3-35e** exhibits smaller torsion angles for both endocyclic amide functionalities ($\tau_{1\text{-}2}$, $\tau_{4\text{-}5}$) in comparison to (*S*)-**3-12**. These observations suggest that (*S*)-**3-35e** has greater endocyclic amide resonance in comparison to (*S*)-**3-12**. For example, the $\tau_{1\text{-}2}$ value of (*S*)-**3-35e** is -1.4°, whereas for **3-12** it is -36.4°. The loss of amide resonance along the N1-C2 bond of **3-12** is apparently compensated by strong amide resonance of N1 with the attached *N*-Boc group ($\tau_{1\text{-}12}$ = 3.3°). From this observation we conclude that (*S*)-**3-12** has greater flexibility along the N1-C2 axis and N4-C5 axes. A similar observation can be made

along the N4-C5 bond of these two compounds. The greater flexibility of the N1-C2 and N4-C5 torsions of **3-3** compared to **3-35e** could allow for a more stereoelectronically acceptable HC3C2O torsion angle in the (*P*)-(*S*)-**3-12** KHMDS deprotonation transition structure than could be obtained in the corresponding transition state with (*P*)-(*S*)-**3-35e**.

3.5 Ring contraction on aryl substituted 1,4-benzodiazepin-2,5-diones

Previous applications of SRSvSACI to 1,4-benzodiazepin-2,5-dione derivatives (**Table 3-1**, **3-2**, and **Scheme 2-5**) in the Carlier group involved varying *N*1- and C3 substituents.[11, 15-17] To further the scope of the recently discovered enantioselective ring-contraction detailed above,[34] we began investigation into the preparations of (*S*)-1,4-benzodiazepin-2,5-diones that feature substitution on the aryl ring. We began with the synthesis of substituted isatoic anhydrides **3-46a-h** (**Table 3-9**). 6-Me and 6-OMe substituted isatoic anhydrides **3-46a,b** were easily synthesized by refluxing the

Table 3-9 Synthesis of Aryl Substituted Isatoic Anhydrides[a]

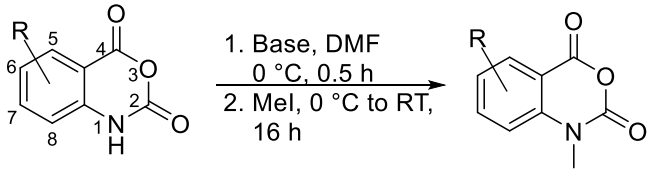


3-45a-f		**3-45h**				**3-46a-h**
Entry	S.M	R	Solvent	Product	R	Yield (%)
1	**3-45a**	5-Me	THF	**3-46a**	6-Me	99
2	**3-45b**	5-OMe	THF	**3-46b**	6-OMe	97
3	**3-45c**	5-Cl	-	**3-46c**	6-Cl	Purchased
4	**3-45d**	6-Cl	THF	**3-46d**	5-Cl	75
5	**3-45e**	4-Cl	THF	**3-46e**	7-Cl	80
6	**3-45f**	5-Cl, 3-Me	THF	**3-46f**	6-Cl, 8-Me	92
7	**3-45g**	5,3-dibromo	THF	**3-46g**	6,8-dibromo	68
8	**3-45h**	na	THF	**3-46h**	pyrido[4,3-d]	0
9	**3-45h**	na	Pyr	**3-46h**	pyrido[4,3-d]	na

[a]na designates "not applicable"

corresponding substituted benzoic acid **3-38a,b** with triphosgene to give the product in 99% and 97% yield, respectively (entry 1 and 2). 6-Cl substituted **3-46c** was not synthesized as it was commercially available (entry 3). Compounds **3-39d-g** were made in moderate to good yields (entry 4-7). For **3-45h**, because of solubility issues, the reaction in THF returned starting material (entry 8). Unfortunately, although solubility issues were solved for the starting material by utilizing pyridine (entry 9), whatever product was formed was not soluble in any available solvents. Isatoic anhydrides **3-46f** and **3-46g** were interesting to us due to the substituent at C8, proximal to N1. As previously reported in our enantioselective reactions involving BZDs, the *N*1-substituent must be sufficiently large enough to impart enough conformational stability on the enolate intermediate to prevent racemization on the reaction timescale.[11, 15] A C8-substituted isatoic anhydride would give a C9-substituted 1,4-benzodiazepin-2,5-dione (see **Table 3-10**). We envisioned that a C9-substituent would sterically impede

Table 3-10 Methylation of **3-46a-g**



3-46a-g **3-47a-g**

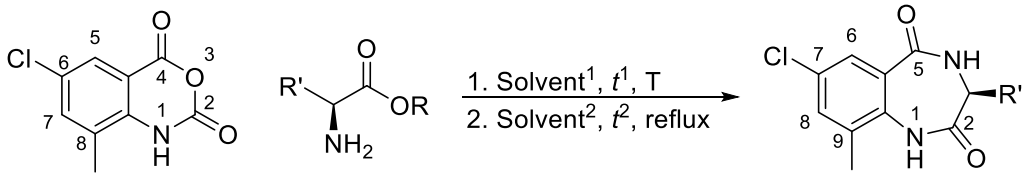
Entry	S.M	R	Base	Yield (%)
1	**3-46a**	6-Me	KOH	26
2	**3-46c**	6-Cl	KOH	54
3	**3-46d**	5-Cl	KOH	68
4	**3-46g**	6,8-dibromo	KOH	9
5	**3-46a**	6-Me	NaH	83
6	**3-46b**	6-OMe	NaH	84
7	**3-46c**	6-Cl	NaH	85
8	**3-46d**	5-Cl	NaH	51
9	**3-46f**	6-Cl, 8-Me	NaH	6
10	**3-46g**	6,8-dibromo	NaH	32

conformational interconversion in the enolate intermediate; a similar effect had been seen in studies of C9-substituted 1,4-benzodiazepin-2-one (*S*)-**3-6** (**Scheme 3-3**).[17] We were also highly interested in isatoic anhydrides **3-46a-c** as they provided a range of electron donating and withdrawing groups para-to N1 on the aromatic ring which could uncover possible substituent effects on the enantioselective ring contraction.

Methylation of isatoic anhydrides **3-46a-g** in either potassium hydroxide (KOH) or sodium hydride (NaH) was performed as seen in **Table 3-10**. While KOH yields ranged from poor to moderate (entry 1-4), NaH gave moderate to good yields in most cases (entry 5-8) except for methylation of disubstituted isatoic anhydrides **3-46f** (6%) and **3-46g** (32%) (entry 9 and 10). We believe that the low yield in these cases is due in part to the steric bulk of both of these isatoic anhydrides at C8.

To address these low yields we attempted to couple *N*H-isatoic anhydride **3-46f** with amino acids/esters **3-48a-d** (**Table 3-11**) anticipating that selective methylation could be performed on the corresponding 1,4-benzodiazepin-2,5-diones as was discussed in ***section 3.4***. Synthesis of 1,4-benzodiazepin-2,5-dione **3-49a-d** gave the expected

Table 3-11 Synthesis of (*S*)-**3-49a-d**



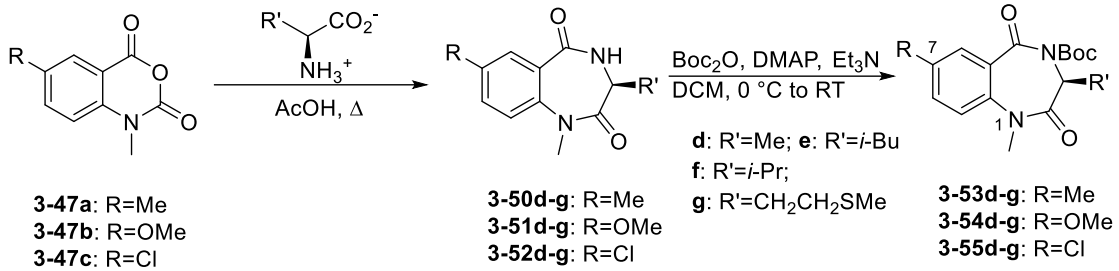
3-46f (*S*)-**3-48a-d** (*S*)-**3-49a-d**

Entry	S.M.	R	R'	Solvent[1]	t^1 (h)	T^1 (°C)	Solvent[2]	t^2 (h)	Product	Yield (%)
1	(*S*)-**3-48a**	Me	Bn	Pyr	16	115	-	-	(*S*)-**3-49a**	5
2	(*S*)-**3-48a**	Me	Bn	Pyr	16	115	AcOH	25	(*S*)-**3-49a**	15
3	(*S*)-**3-48b**	H	$CH_2CH(CH_3)_2$	Et_3N/H_2O	17	24	AcOH	20	(*S*)-**3-49b**	58
4	(*S*)-**3-48c**	H	$CH(CH_3)_2$	Et_3N/H_2O	17	24	AcOH	39	(*S*)-**3-49c**	5
5	(*S*)-**3-48d**	H	4-nitro benzyl	Et_3N/H_2O	17	24	AcOH	39	(*S*)-**3-49d**	7

products in very poor yield for all cases except for (*S*)-leucine derived 1,4-benzodiazepin-2,5-dione **3-92b**, which was still obtained in only 58% yield (entry 1-5), relatively low in comparison to prior synthesized di-*N*H 1,4-benzodiazepin-2,5-diones (**Table 3-5**). As we've noted before, for the synthesis of 1,4-benzodiazepin-2,5-diones from isatoic anhydride, ring closure appears to be the most difficult step. When the C8 substituent is larger than hydrogen, it appears that the difficulty in ring-closure is increased. Due to the difficulty encountered in synthesizing C9-substituted 1,4-benzodiazepin-2,5-diones, our focus shifted back to 7-substituted 1,4-benzodiazepin-2,5-diones, which could be prepared from 6-Me, 6-OMe, and 6-Cl *N*-Me isatoic anhydrides **3-47a-c**.

The C6-substituted *N*1-Me isatoic anhydrides **3-47a-c** were then reacted with four (*S*)-amino acids (Ala, Leu, Val, and Met) according to the procedure we used to prepare Phe-derived (*S*)-**3-34e** (AcOH, 116 °C, 16 h) (**Table 3-12**). For 6-Me, 6-OMe, and 6-Cl derivatives **3-47a-c**, reactions with valine consistently gave the lowest yields (8-48% before recrystallization, entries 3, 7, and 11). Steric crowding from the bulky isopropyl group most likely slowed the rate of ring closure. The reactions of the other three amino acids **3-47a-c** proceeded in moderate to good yields (76-83% for **3-50d, e,** and **g,** 61-90% for **3-51d, e,** and **g**, and 55-72% for **3-52d**, **e**, and **g**). With respect to the C6-substituent, synthesis from 6-Me and 6-OMe *N*-Me isatoic anhydrides **3-47a** and **3-47b** appeared in higher yield than those for 6-Cl **3-47c** for all amino acids except alanine, in which entry 9 proceeds in slightly higher yield than entry 5 (*cf.* entries 2, 6 vs. 10; 3, 7 vs. 11; 4, 8 vs. 12). Since the difficult ring closure step occurs through nucleophilic attack of the aniline nitrogen on the amino acid carboxylate, and the C6-substituents are para to that nitrogen, such a trend in yield might derive from electronic effects. In this position chlorine is

Table 3-12 Synthesis of BZDs from Aryl Substituted Isatoic Anhydrides



3-47a: R=Me
3-47b: R=OMe
3-47c: R=Cl

3-50d-g: R=Me
3-51d-g: R=OMe
3-52d-g: R=Cl

3-53d-g: R=Me
3-54d-g: R=OMe
3-55d-g: R=Cl

Entry	R	R'	Product[1]	yield (%)	ee (%)	Product[2]	yield (%)	ee (%)
1	Me	Me	(*S*)-**3-50d**	83 (65[a])	>99[a]	(*S*)-**3-53d**	85	>99
2	Me	*i*-Bu	(*S*)-**3-50e**	78 (51[a])	>99[a]	(*S*)-**3-53e**	91	>99
3	Me	*i*-Pr	(*S*)-**3-50f**	32 (3[a,b])	>99[a,b]	(*S*)-**3-53f**	67[d]	>99
4	Me	CH_2CH_2SMe	(*S*)-**3-50g**	76 (27[a,b])	99[a,b]	(*S*)-**3-53g**	91	97
5	OMe	Me	(*S*)-**3-51d**	61[c]	76[c]	(*S*)-**3-54d**	>99	69
6	OMe	*i*-Bu	(*S*)-**3-51e**	90 (4[a])	99[a]	(*S*)-**3-54e**	59[d]	98
7	OMe	*i*-Pr	(*S*)-**3-51f**	48 (13[a,b])	99[a,b]	(*S*)-**3-54f**	96	98
8	OMe	CH_2CH_2SMe	(*S*)-**3-51g**	75 (57[a])	>99[a]	(*S*)-**3-54g**	>99	90
9	Cl	Me	(*S*)-**3-52d**	68[c]	94[c]	(*S*)-**3-55d**	95	94
10	Cl	*i*-Bu	(*S*)-**3-52e**	72 (45[a])	>99[a]	(*S*)-**3-55e**	>99	>99
11	Cl	*i*-Pr	(*S*)-**3-52f**	8 (3[a,b])	98[a]	(*S*)-**3-55f**	>99	99
12	Cl	CH_2CH_2SMe	(*S*)-**3-52g**	55 (41[a])	>99[a]	(*S*)-**3-55g**	93	83

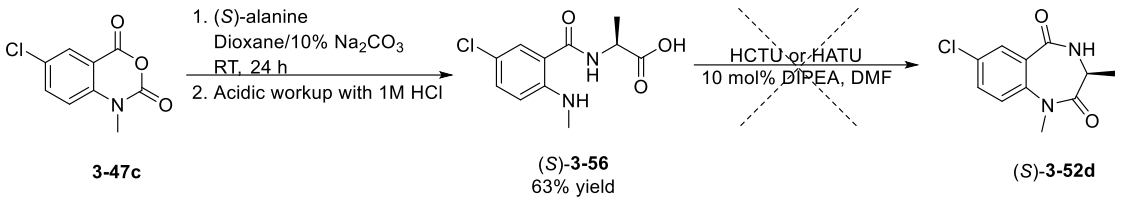
[a]Recrystallized results. [b]Enantioenriched crop obtained from mother liquor. [c]Mass lost due to bumping under high-vac.

weakly electron-withdrawing while methyl is weakly electron-releasing, and methoxy is strongly electron releasing. Electron donating groups should increase the nucleophilicity of the aniline nitrogen and better facilitate ring closure.

In our previous studies (***Section 3.4***) we had operated under the misconception that our Chiralcel columns could not operate with more than 15% *i*-PrOH in the mobile phase. Consequently, HPLC measurement of the % ee of *N*1-Me, *N*4-H-1,4-benzodiazepin-2,5-diones, was deemed impractical since they were polar. We subsequently discovered that the Chiralcel columns could accommodate 100% *i*-PrOH, and thus % ee for these compounds could be determined by HPLC as shown in **Table 3-12**.

For all cases except for product **3-51d**, enantiomeric enrichment was achieved through recrystallization. In the case of **3-51d**, the compound was not very crystalline, and enantiomeric enrichment was not achieved. In most cases *N*1-Me, *N*4-Boc 1,4-benzodiazepin-2,5-diones could be recrystallized to ≥ 98% ee (entries 1, 2, 6, 8, and 10-12). Enantiomeric enrichment of **3-51e** through recrystallization was only obtainable through the use of a large excess of solvent, as using minimal solvent led to rapid recrystallization and no change in % ee. We presume that the enantiomerically enriched product must have similar solubility to the racemic crystal. Therefore, an excess of solvent is necessary to ensure that very slow recrystallization occurs. Although **3-51e** was obtained in high % ee, the overall yield suffered considerably following recrystallization. In the case of valine derived **3-50f**, **3-51f**, **3-52f**, and Met-derived **3-50g**, we found that recrystallization did not increase enantioenrichment of the collected solid, but did enrich the mother liquor. This behavior can be rationalized if the racemic compound is slightly less soluble than the enantiopure compound. Thus, by repeated recrystallization of both racemate and enantiopure compound the mixture is slowly depleted of racemate, but at the cost of a dramatic yield loss, since so much enantiopure compound concurrently crystallizes.

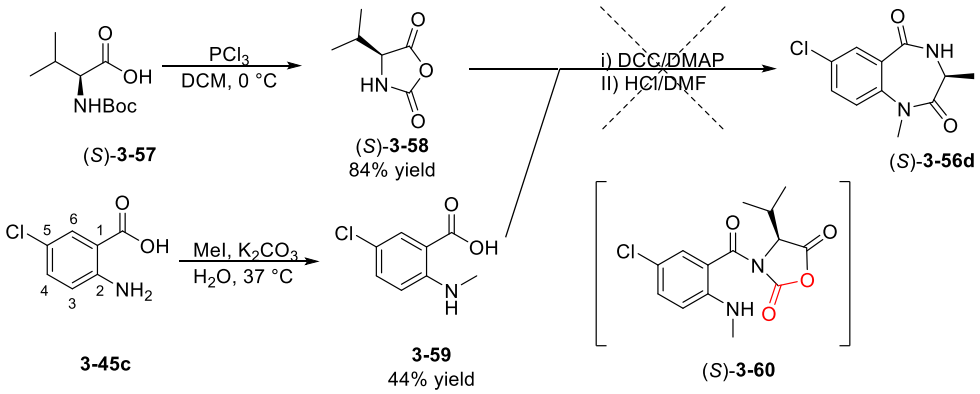
Because of the poor yields obtained for *N*1-Me, *N*4-H 1,4-benzodiazepin-2,5-dione derivatives **3-50f**, **3-51e**, and **3-52f** (**Table 3-12**, entries 3, 6, and 11), we decided to look once again at alternate ways to synthesize these products. In our previous attempts to synthesize similar 1,4-benzodiazepin-2,5-diones (**Section *3.4***), we did not attempt to use any peptide coupling reagents. For 6-Cl substituted alanine derived **3-47c** we first made the ring opened product **3-56** in 63% yield by treatment of 6-Cl substituted



Scheme 3-10 Unsuccessful use of HCTU or HATU to prepare **3-52d**

N-Me isatoic anhydride **4-47c** with (*S*)-alanine in dioxane/sodium carbonate followed by acidic workup (**Scheme 3-10**). Reactions were attempted with either peptide coupling reagent HCTU or HATU in conjunction with **3-56** in DIPEA and DMF, but neither reaction led to product **3-52d**, and both returned starting material.

An alternate procedure toward the synthesis of both *N*1-Me and *N*1-H 1,4-benzodiazepin-2,5-diones using *N*-carboxy α-amino acid anhydrides (NCA) and anthranilic acids was reported by Akssira et al.[39] Though the paper did not measure the enantiomeric excess of the products, and despite several errors in the paper, we decided to apply the method to the synthesis of **3-56d**. Using Akssira's procedure Boc-protected amino acid **3-57**[40] (**Scheme 3-11**) was transformed into the corresponding NCA **3-58** using PCl_3 in methylene chloride in 84% yield. 5-Chloroanthranilic acid **3-45c** was mono-methylated using a modification of the protocol of Aitken *et al.*[41] to afford **3-59**.

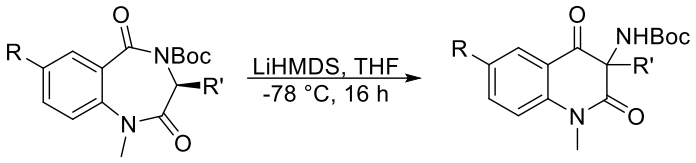


Scheme 3-11 NCA Utilization for Synthesis of **3-56d**

By running the reaction at 37 °C rather than the recommended 100 °C, **3-59** was obtained in 44% yield. In the work by Akssira *et al*. they reported the synthesis of *N*1-Me/H, *N*4-H BZD derivatives from glycine and alanine. We then applied the Akssira protocol to NCA **3-58** and *N*-methyl anthranilic acid **3-59** with DCC/DMAP followed by HCl in DMF. Our reasoning for attempting this reaction was that the CO_2 portion of the NCA moiety in intermediate **3-60** (-CO_2 portion indicated in red), generated *in situ,* was expected to constitute a better leaving group than our previously used hydroxyl- and methoxy-leaving groups. Unfortunately, this reaction did not provide product **3-56d**. Historically, synthesis of valine derived 1,4-benzodiazepin-2,5-diones gave the lowest yields (**Tables 3-11** and **3-12**), and we believe steric hindrance due to the *i*Pr group to be the issue. Note that Akssira reported this method for the synthesis of 1,4-benzodiazepin-2,5-diones from NCAs derived from Gly, Ala, Phe, PhGly, and Tyr but not for Val. At this point we stopped investigation into alternate synthesis protocols for **3-52d**.

With *N*1-Me, *N*4-Boc 1,4-benzodiazepin-2,5-diones in hand (**3-53d-g**, **3-54d-g**, **3-55d-g**), enantioselective base-mediated ring-contraction was performed with LiHMDS at -78 °C in THF. As seen in **Table 3-13**, deprotonation and rearrangement of 1,4-benzodiazepin-2,5-diones **3-53d-g**, **3-54d-g**, and **3-55d-g** led to the successful synthesis of quinolone-2,4-diones **3-61d-g**, **3-62d-g**, and **3-63d-g**. For all reactions, % ee was maintained with little to no loss (entry 1-12). Note that in the case of **3-61d** the % ee obtained matches the enantiopurity of the starting material **3-54d**. The lower than desired enantiopurities of **3-62g** and **3-63g** can be explained in the same way. Rearrangement yields range from poor (26%, **3-63g**) to good (90%, **3-63d**) for our 7-substituted 1,4-benzodiazepin-2,5-diones, worse than yields reported in our earlier study (57-84% yield,

Table 3-13 Rearrangement of 7-substituted 1,4-benzodiazepin-2,5-diones



(*S*)-**3-53d-g**
(*S*)-**3-54d-g**
(*S*)-**3-55d-g**

3-61d-g
3-62d-g
3-63d-g

Entry	R	R'	S.M.	S.M. ee (%)	Product	yield (%)	ee (%)
1	Me	Me	(*S*)-**3-53d**	>99	**3-61d**	79	98
2	Me	*i*-Bu	(*S*)-**3-53e**	>99	**3-61e**	55	>99
3	Me	*i*-Pr	(*S*)-**3-53f**	98	**3-61f**	42	98
4	Me	CH_2CH_2SMe	(*S*)-**3-53g**	97	**3-61g**	54	98
5	OMe	Me	(*S*)-**3-54d**	69	**3-62d**	67	68
6	OMe	*i*-Bu	(*S*)-**3-54e**	84[a]	**3-62e**	(22)77[b]	98(84[b])
7	OMe	*i*-Pr	(*S*)-**3-54f**	98	**3-62f**	35	98
8	OMe	CH_2CH_2SMe	(*S*)-**3-54g**	90	**3-62g**	48	88
9	Cl	Me	(*S*)-**3-55d**	95	**3-63d**	5(90[b])	94(90[b])
10	Cl	*i*-Bu	(*S*)-**3-55e**	>99	**3-63e**	31	97
11	Cl	*i*-Pr	(*S*)-**3-55f**	99	**3-63f**	27	98
12	Cl	CH_2CH_2SMe	(*S*)-**3-55g**	83	**3-63g**	26	82

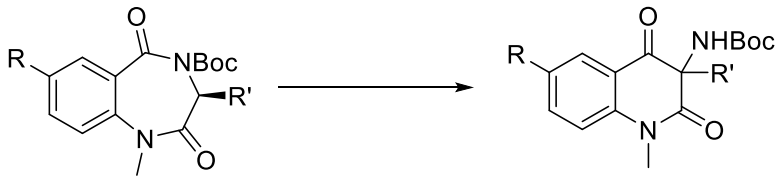
[a]Previously obtained in 98% ee, but first rearrangement attempt gave poor yield. (*S*)-**3-54e** was remade, but due to time constraints, starting material leading to (*S*)-**3-54e** was not recrystallized to high % ee. [b]New bottle of 1 M LiHMDS

Table 3-7). The majority of the 1,4-benzodiazepin-2,5-dione rearrangements presented in **Table 3-13** were run from the same bottle of 1 M LiHMDS which, although opened fresh for these reactions, appeared slightly yellow tinted. Previously, we have observed that 1 M LiHMDS, which is colorless when first opened, turns yellow once exposed to atmosphere. We believe this is due to the formation of LiOH in the mixture, and in some cases rearrangement yields and/or % ee has shown to be significantly decreased when using old/yellow 1 M LiHMDS. In our original attempt to synthesize **3-62e** and **3-63d**, yields were 22% and <5%, respectively. Because of these low yields, **3-54e** and **3-55d** were remade. New 1 M LiHMDS was purchased, and deprotonation/rearrangement was

attempted again. As is reported, **3-61e** was obtained in 77% yield, and **3-62d** was obtained in 90% yield (entry 6 and 9, respectively). These yields are significantly higher than was originally obtained, and indicate that the slightly yellow tinted 1 M LiHMDS was in fact bad. While the compromised base appears to have no deleterious effect on the enantioselectivity of the reaction, the apparent yields are most likely depressed.

In our previous work (**Scheme 3-5**), the absolute configuration of the final rearranged quinolone-2,4-diones was assigned as (*R*) using the logic described in **section *3.3.4***. Based on the close relationship of (*S*)-**3-61d-g**, (*S*)-**3-62d-g**, and (*S*)-**3-63d-g** to those previously studied, we expect ring contraction to proceed with inversion, and thus at the outset assume all the products are (*R*)-configured. However, to date we have not

Table 3-14 Optical rotation of 7-substituted 1,4-benzodiazepin-2,5-diones and their rearranged products



3-53d-g
3-54d-g
3-55d-g

3-61d-g
3-62d-g
3-63d-g

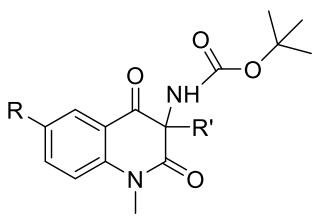
Entry	R	R'	S.M	S.M. Opt. Rot (°)	Product	Product Opt. Rot (°)
1	Me	Me	(*S*)-**3-53d**	+55.88	**3-61d**	+50.49
2	Me	*i*-Bu	(*S*)-**3-53e**	-29.23	**3-61e**	-22.11
3	Me	*i*-Pr	(*S*)-**3-53f**	-140.98	**3-61f**	-43.05
4	Me	CH_2CH_2SMe	(*S*)-**3-53g**	-35.53	**3-61g**	-46.91
5	OMe	Me	(*S*)-**3-54d**	+42.50	**3-62d**	+10.53
6	OMe	*i*-Bu	(*S*)-**3-54e**	-74.11	**3-62e**	-17.65
7	OMe	*i*-Pr	(*S*)-**3-54f**	-94.66	**3-62f**	-55.34
8	OMe	CH_2CH_2SMe	(*S*)-**3-54g**	-14.93	**3-62g**	-54.05
9	Cl	Me	(*S*)-**3-55d**	+84.15	**3-63d**	+88.41
10	Cl	*i*-Bu	(*S*)-**3-55e**	-94.12	**3-63e**	-8.86
11	Cl	*i*-Pr	(*S*)-**3-55f**	-186.43	**3-63f**	-0.98
12	Cl	CH_2CH_2SMe	(*S*)-**3-55g**	-22.08	**3-63g**	+9.48

obtained any X-ray structures to confirm this assumption, and HPLC enantiomer separations were obtained using three separate chiral columns (Chiralcel OD-H, Chiralcel AD-H, and (*R,R*) Whelk-O2). Therefore, comparison of major enantiomer elution order is not a viable method for assignment of stereochemistry. Thus, we investigated whether the sign of optical rotation for starting materials **3-53d-g**, **3-54d-g**, and **3-55d-g** was preserved with their respective products **3-61d-g**, **3-62d-g**, and **3-63d-g** (**Table 3-14**). Although this relationship is not required by first principles, in our previous study we demonstrated that the sign of optical rotation of the starting material was preserved in the products. Interestingly, this same optical rotation conformity is observed here in 11 of 12 cases (entries 1-11). Although, **3-55g** and **3-63g** (entry 12) do exhibit opposite optical rotation signs, we believe this discontinuity does not reflect a change in reaction stereochemistry. We thus concluded that ring contractions of (*S*)-**3-53g-d**, **3-54g-d**, **3-55g-d** occurs in each case to give (*R*)-configured products.

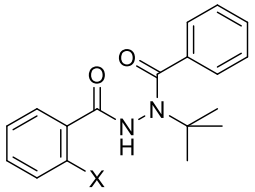
We noted earlier that the quinolonedione structure embodied by ring-contracted products (±)-**3-61d-g**, **3-62d-g**, and **3-63d-g** is similar to that found in known 5-HT_6 antagonists and anti-HIV structures **3-23**, **3-24**, and **3-25** (***Section 3.3***). To date we have not identified a collaborator who could test our compounds for activity against these targets. However, these compounds also bear a passing resemblance to known diacylhydrazine insecticides RH-1266 and RH-5849 (**Table 3-15**). These compounds were developed to target the ecdysone receptor of insect larvae, but were subsequently found to cause neurotoxic symptoms in adult insects, due to blockade of the voltage-gated potassium channel.[42] The Carlier and Bloomquist group had a funded collaboration to explore compounds like RH-1266 and RH-5849 as potential potassium channel-

blocking insecticides for the malaria mosquito *Anopheles gambiae*. We thus sent compounds (±)-**3-61d-g**, **3-62d-g**, and **3-63d-g** to Professor Bloomquist (University of Florida) to test toxicity to adult *An. gambiae*, using the topical application protocol.[43] In brief, groups of mosquitos (size ranging from 11-26) were anesthetized by cooling on ice, and then 200 nL of an ethanolic solution of the text compounds (500 ng/200 nL) was

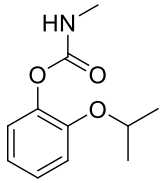
Table 3-15 Topical toxicity of ring-contracted compounds **3-61d** - **3-63f**, diacylhydrazines RH-1266 & RH-5849, and carbamate insecticide controls to adult *Anopheles gambiae* (G3 strain 3-5 days old).[a]



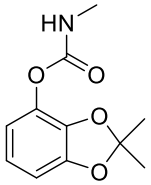
(±)-**3-61d-g**, **62d-g** **63d**,**e**,**f**



X = Br: RH-1266
X = H: RH-5849



propoxur



bendiocarb

Compound	R	R'	24 h LD_{50} ng/mosquito (95%CI)[b]	24 h mortality at 500 ng/mosquito	48 h mortality at 500 ng/mosquito[b]
propoxur	-	-	3 (2-4)[44]	100	100
bendiocarb	-	-	2(1-4)[44]	100	100
RH-1266			504 (393-648)[45]	nr	nd
RH-5849			735 (583-945)[45]	nr	nd
(±)-**3-61d**	Me	Me	>500	37	32
(±)-**3-61e**	Me	*i*-Bu	>500	35	35
(±)-**3-61f**	Me	*i*-Pr	>500	31	38
(±)-**3-61g**	Me	CH_2CH_2SMe	>500	19	24
(±)-**3-62d**	OMe	Me	>500	8	17
(±)-**3-62e**	OMe	*i*-Bu	>500	17	25
(±)-**3-62f**	OMe	*i*-Pr	>500	8	15
(±)-**3-63g**	OMe	CH_2CH_2SMe	>500	0	18
(±)-**3-63d**	Cl	Me	>500	17	17
(±)-**3-63e**	Cl	*i*-Bu	>500	24	24
(±)-**3-63f**	Cl	CH_2CH_2SMe	>>500	0	0

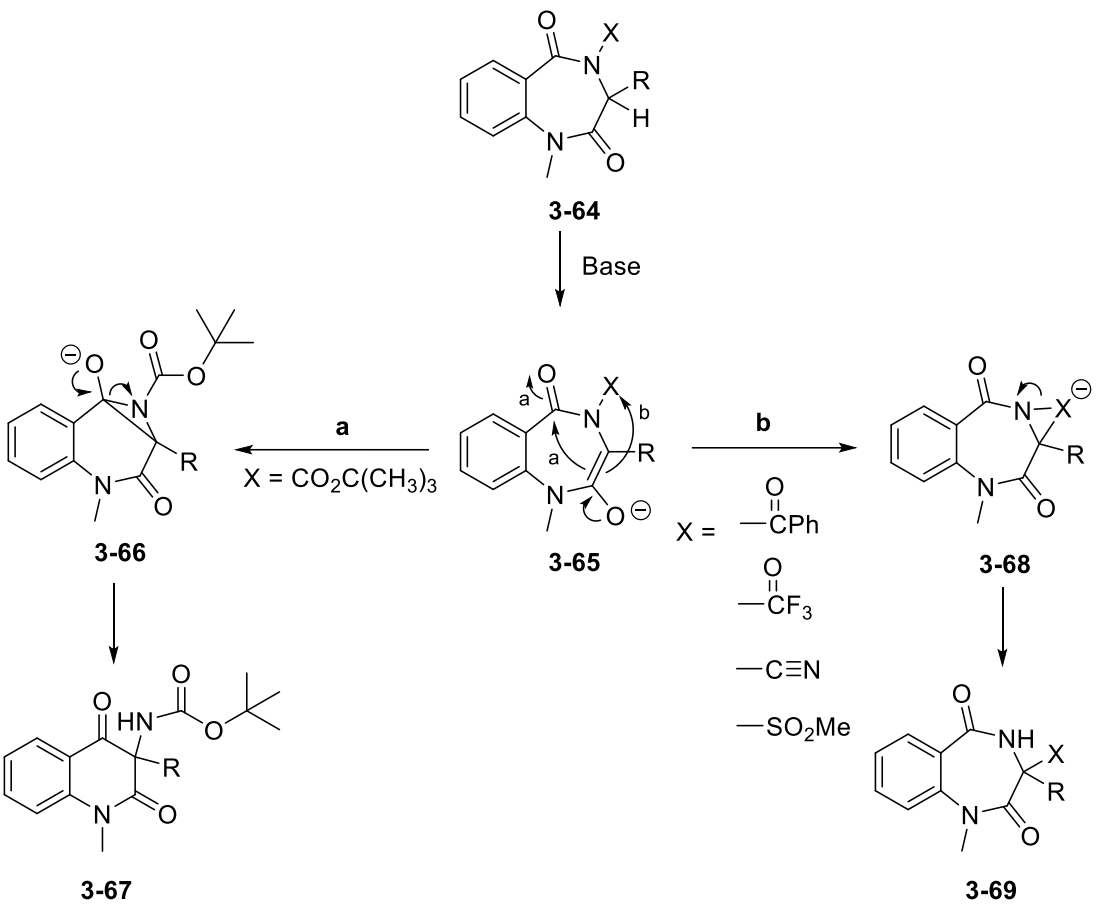
[a] Topical toxicity to G3 strain adult (3-5 days old) An. gambiae was measured using the method of Pridgeon et al.[43] The abbreviation nr designates that the mortality data measured at 500 ng/insect could not be retrieved from available records, though these data were used earlier to calculate the LD_{50} value given in the table. The abbreviation nd designates that mortality at 48 was not measured. [b] LD_{50} values were determined from measurements of 24 h mortality at at least 4 doses; probit analysis was carried out using PoloPlus (Robertson, J.L, H.K. Preisler, and R. M. Russell. 2002. PoloPlus Probit and Logit Analysis. LeOra Software).

applied to the dorsal thorax of the insect. Mosquitoes were then allowed to warm up and provided free access to air and sugar water. Mortality was noted at 24 h and 48 h. The most toxic quinolonediones proved to be (±)-**3-61d-f**, which at 500 ng/mosquito exhibited 31-37% mortality at 24 h and 32-38% mortality at 48 h. Thus the LD_{50} value for these compounds is greater than 500 ng/insect. For comparison, the diacylhydrazine insecticides RH-1266 and RH-5849 had LD_{50} values of 504 and 735 ng/insect respectively, and are not much more toxic than (±)-**3-61d-f**. However, as can be seen, the carbamate insectides propoxur and bendiocarb (which target acetylcholinesterase) are much more toxic than any of the diacylhydrazines or ring-contraction products. We thus ended our evaluation of these compounds as potential malaria mosquitocides

With these results, we have succeeded in enantioselectively generating 6-aryl substituted quinolone-2,4-diones by ring contraction through an acyl-amino variant of the Chan reaction using SRSvSACI protocol. While we cannot speak definitively about the aryl-substituent effect on reaction yield, it can be seen that little to no loss is obtained in all cases. It was also seen that 6-methyl substituted quinolone-2,4-diones are not viable insecticidal candidates for adult Anopheles gambiae.

3.6 Attempted group migration of 1,4-benzodiazepin-2,5-dione N4-substituent

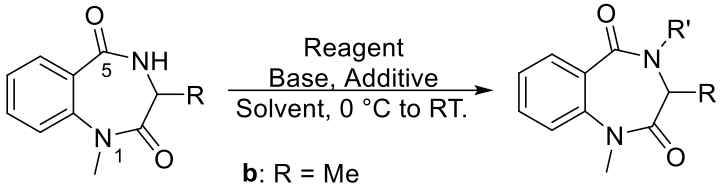
Our previous work with enantioselective ring contractions of 1,4-benzodiazepin-2,5-diones necessitated the use of the *N*4-Boc protecting group for acyl activation of *N*4 in the Chan-type reaction which led to ring contracted products **3-67** through pathway **a** (**Scheme 3-12**). We believed that through the use of an alternative electron-deficient *N*4-substituent X, it might be possible to divert the enolate to achieve an enantioselective acyl migration to generate product **3-69** through the mechanism shown in pathway **b**. If



Scheme 3-12 Mechanistic Route for the Ring Contraction or Acyl Migration of **3-57**

the X group were more electrophilic then than the C5-carbonyl, pathway **b** might predominate. Thus installation of various electron withdrawing groups at *N*4 was attempted on alanine and leucine derived *N*1-Me, *N*4-H 1,4-benzodiazepin-2,5-diones **3-34b,d** (**Table 3-16**). First, acylation of leucine derived **3-34d** was attempted with both benzoyl chloride and benzoic anhydride (entry 1 and 2). While reaction of benzoic anhydride with Leu-derived (*S*)-**3-34** did not afford the desired compound, benzoyl chloride gave the expected leucine derived (*S*)-**3-70a** in 46% yield. A similar protocol was applied to alanine-derived 1,4-benzodiazepin-2,5-dione **3-34b** and the expected product (*S*)-**3-70b** was obtained in 87% yield (entry 3). While our early success with

Table 3-16 Alternate *N*4 acylating group Attempts

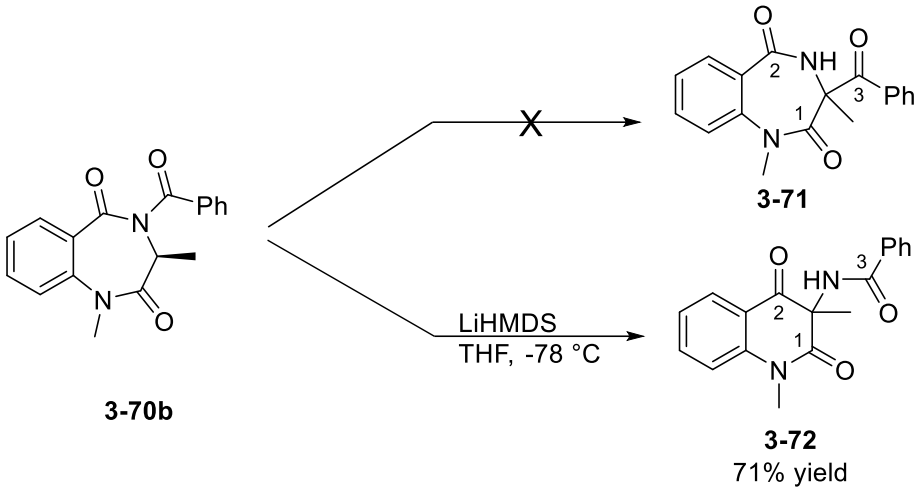


3-34b,d **3-70a-g**

Entry	S.M.	**Reagent**	Base	Additive	Solvent	R'	Product	yield (%)
1	(*S*)-**3-34d**	$O(COC_6H_5)_2$	Et_3N	DMAP	DCM	COC_6H_5	(*S*)-**3-70a**	-
2	(*S*)- **3-34d**	$ClCOC_6H_5$	Et_3N	-	DCM	COC_6H_5	(*S*)-**3-70a**	46
3	(*S*)- **3-34b**	$ClCOC_6H_5$	Et_3N	-	DCM	COC_6H_5	(*S*)-**3-70b**	87
4	(*R/S*)- **3-34b**	$(CF_3CO)_2O$	Et_3N	DMAP	DCM	$COCF_3$	(*R/S*)- **3-70c**	-
5	(*R/S*)- **3-34b**	$(CF_3CO)_2O$	-	-	Toluene	$COCF_3$	(*R/S*)- **3-70c**	-
6	(*R/S*)- **3-34b**	$(CF_3CO)_2O$	-	-	-	$COCF_3$	(*R/S*)- **3-70c**	-
7	(*R/S*)- **3-34b**	CF_3CO_2Me	$NaOH_{(aq)}$	-	MeOH	$COCF_3$	(*R/S*)- **3-70c**	-
8	(*R/S*)- **3-34b**	CF_3CO_2Me	LiHMDS	-	THF	$COCF_3$	(*R/S*)- **3-70c**	-
9	(*R/S*)- **3-34b**	CF_3CO_2Me	Et_3N	DMAP	DCM	$COCF_3$	(*R/S*)- **3-70c**	-
10	(*R/S*)- **3-34b**	CNBr	Et_3N	-	DCM	CN	(*R/S*)- **3-70d**	-
11	(*S*)- **3-34d**	TsCl	Et_3N	DMAP	DCM	Ts	(*S*)-**3-70e**	-
12	(*S*)- **3-34b**	TsCl	Et_3N	DMAP	DCM	Ts	(*S*)-**3-70f**	-
13	(*R/S*)- **3-34b**	TsCl	$NaOH_{(aq)}$	Tetrabutyl-ammonium bisulfate	DCM	Ts	(*R/S*)- **3-70g**	-
14	(*R/S*)- **3-34b**	TsCl	-	-	Pyridine	Ts	(*R/S*)- **3-70g**	-
15	(*R/S*)- **3-34b**	TsCl	LiHMDS	-	THF	Ts	(*R/S*)- **3-70g**	-

benzoylation of **3-34b,d** appeared promising, unfortunately *N*4-protection with other electron deficient groups proved troublesome. Installation of a trifluoro acetate group ($COCF_3$) was not accomplished using either trifluoroacetic anhydride ($(CF_3CO)_2O$) (entry 4-6) or methyl trifluoroacetate (CF_3CO_2Me) (entry 7-9). Installation of a cyano group (CN) through the use of cyanogen bromide also proved unsuccessful (entry 10). Protection of *N*4 with the electron-withdrawing tosyl group (Ts) was not successful (entries 11-15). Electronically, these reagents are more electron withdrawing than benzoyl chloride, so they should be more electrophilic and therefore more susceptible to attack by BZD derivatives **3-34b,d**. In all cases, starting material was returned. So, it is

possible that nucleophilic attack occurred from the *C*5-oxygen, and subsequent aqueous work-up led to hydrolysis of the products to afford the starting material.



Scheme 3-13 Deprotonation of *N*4-benzoyl Protected Alanine BZD **3-52**

Benzoylated alanine derivative 1,4-benzodiazepin-2,5-dione **3-70b** was treated with LiHMDS in THF at -78 °C and a product was obtained in 71% yield (**Scheme 3-13**). To identify whether the product was acyl migrated product **3-71** or ring-contracted product **3-72**, HMBC HSQC and selective NOE spectroscopies were performed on the compound obtained. For **3-71,** amide carbonyl carbon 2 would be located farther up-field than ketone carbonyl carbon 3. Inversely, for **3-72,** ketone carbonyl carbon 2 should be shifted farther downfield than amide carbonyl carbon 3.

Figure 3-4 is a relevant section pulled from the HSQC spectra of **3-72**. It was necessary to identify which carbonyl carbons corresponded with the three carbon peaks between 168.8 and 193.3 ppm. Proton and carbon assignments are labeled **A**-**O** and correlate with their respective peaks on the HSQC spectra. *N*1-Methyl protons **A** (δ 3.5) and *C*-methyl protons **B** (δ 1.6) were easily assigned based on chemical shift. Irradiation of methyl **A** through selective NOE spectroscopy was used to identify aromatic proton **K**

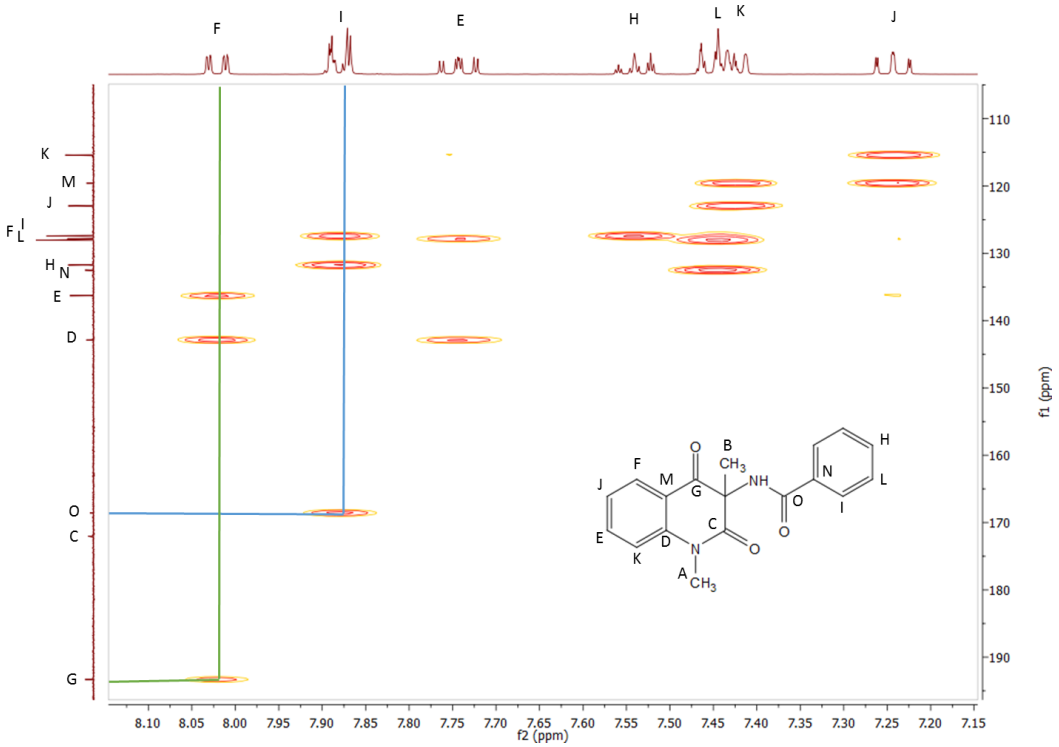


Figure 3-4 Section of HSQC for **3-72**. Amide carbonyl carbon **O** and aromatic hydrogen **I** correlation shown in blue, and ketone carbonyl carbon **G** and aromatic hydrogen **F** correlation shown in green.

(δ 7.4). The remaining aromatic protons in that ring (**E**, **J**, **F**) were identified through correlation with proton **K** using HSQC and HMBC. The three remaining unidentified aromatic protons (**I**, **L**, **H**) belong to the benzoyl moiety. Proton **H** was assigned based on integration, and protons **I** and **L** were assigned based on scalar coupling. With all the aromatic peaks assigned, HSQC indicated that proton **I** (δ 7.9) correlated with amide carbonyl carbon **O**, and aromatic proton **F** (δ 8.0) showed correlation with ketone carbonyl carbon **G** (δ 193.3). Through this analysis, the product was revealed to be ring contracted product **3-60**. While a benzoyl-protecting group is less electron donating than a Boc-protecting group, it appears that the reaction still progresses through a ring contraction similar to what has been previously discussed.

3.7 1,4-benzodiazepin-2,5-dione project conclusion

This concludes my work with 1,4-benzodiazepin-2,5-diones. I successfully generated phenylalanine derived **3-35e** in high % ee and subsequently, performed ring contraction to generate **3-44e** in 98% ee. I then investigated the substituent effect for rearrangement on 7-Me, 7-OMe, and 7-Cl substituted 1,4-benzodiazepin-2,5-diones in the synthesis of the corresponding quinolone-2,4-diones. Racemic 6-substituted quinolone-2,4-diones were then submitted for toxicity assay, but were found to demonstrate no improvement over the diacylhydrazine insecticides RH-1266 and RH-5849. Lastly, *N*4-benzoyl substituted 1,4-benzodiazepin-2,5-dione **3-63b** was synthesized, and it was seen that treatment with base led to ring contracted **3-65** and not acyl-migrated product **3-64**.

As I covered in chapter 1, axially chiral intermediates with enantiomerization barriers equal to or greater than 16 kcal/mol are typically sought after for applications of SRSvSACI in intermolecular reactions. It is for this reason that bulky *N*1-groups were utilized in the enantioselective alkylation reactions of 1,4-benzodiazepin-2-one and 1,4-benzodiazepin-2,5-diones investigated previously by the Carlier group. It has been shown that for intramolecular reactions, high enantioselectivity can still be obtained where enantiomerization barriers are less than 16 kcal/mol.[46] Following the newly investigated ring-contraction of *N*1-Me,*N*4-Boc-benzodiazepin-2,5-diones, I believe highly enantioselective rearrangement can occur from *N*1-H protected benzodiazepines. Not only would this afford structures that more closely resemble the potential drug scaffolds **3-28**, **3-29**, and **3-30**, they would give access to *N*1-H-quinolon-2,4-diones which could then be easily derivatized for further medicinal investigations/applications. The following

chapter contains all of the experimental procedures and data for **Chapter 2** and **Chapter 3**.

3.8 Bibliography

1. Farran, D.; Archirel, P.; Toupet, L.; Martinez, J.; Dewynter, G. Enantiodivergent Transannular Rearrangement of 3-Isopropyl-1,4-Benzodiazepine-2,5-Dione by Memory of Chirality. *Eur, J. Org. Chem.* **2011**, *2011*, 2043-2047.

2. Ripka, W. C.; De Lucca, G. V.; Bach Ii, A. C.; Pottorf, R. S.; Blaney, J. M. Protein B-Turn Mimetics I. Design, Synthesis, and Evaluation in Model Cyclic Peptides. *Tetrahedron* **1993**, *49*, 3593-3608.

3. Joseph, C. G.; Wilson, K. R.; Wood, M. S.; Sorenson, N. B.; Phan, D. V.; Xiang, Z.; Witek, R. M.; Haskell-Luevano, C. The 1,4-Benzodiazepine-2,5-Dione Small Molecule Template Results in Melanocortin Receptor Agonists with Nanomolar Potencies. *J. Med. Chem.* **2008**, *51*, 1423-1431.

4. Loudni, L.; Roche, J.; Potiron, V.; Clarhaut, J.; Bachmann, C.; Gesson, J.-P.; Tranoy-Opalinski, I. Design, Synthesis and Biological Evaluation of 1,4-Benzodiazepine-2,5-Dione-Based Hdac Inhibitors. *Bioorg. Med. Chem.* **2007**, *17*, 4819-4823.

5. Cheng, M.-F.; Yu, H.-M.; Ko, B.-W.; Chang, Y.; Chen, M.-Y.; Ho, T.-I.; Tsai, Y.-M.; Fang, J.-M. Practical Synthesis of Potential Endothelin Receptor Antagonists of 1,4-Benzodiazepine-2,5-Dione Derivatives Bearing Substituents at the C3-, N1- and N4-Positions. *Org. Biomol. Chem.* **2006**, *4*, 510-518.

6. Boojamra, C. G.; Burow, K. M.; Thompson, L. A.; Ellman, J. A. Solid-Phase Synthesis of 1,4-Benzodiazepine-2,5-Diones. Library Preparation and Demonstration of Synthesis Generality. *J. Org. Chem.* **1997**, *62*, 1240-1256.

7. Papageorgiou, C.; Borer, X. A Non-Peptide Ligand for the Somatostatin Receptor Having a Benzodiazepinone Structure. *Bioorg. Med. Chem.* **1996**, *6*, 267-272.

8. Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S. Methods for Drug Discovery: Development of Potent, Selective, Orally Effective Cholecystokinin Antagonists. *J. Med. Chem.* **1988**, *31*, 2235-2246.

9. Wright, W. B.; Brabander, H. J.; Greenblatt, E. N.; Day, I. P.; Hardy, R. A. Derivatives of 1,2,3,11a-Tetrahydro-5h-Pyrrolo[2,1-C][1,4]Benzodiazepine-5,11(10h)-Dione as Anxiolytic Agents. *J. Med. Chem.* **1978**, *21*, 1087-1089.

10. Spencer, J.; Rathnam, R. P.; Harvey, A. L.; Clements, C. J.; Clark, R. L.; Barrett, M. P.; Wong, P. E.; Male, L.; Coles, S. J.; Mackay, S. P. Synthesis and Biological Evaluation of 1,4-Benzodiazepin-2-Ones with Antitrypanosomal Activity. *Bioorg. Med. Chem.* **2011**, *19*, 1802-1815.

11. Carlier, P. R.; Zhao, H.; DeGuzman, J.; Lam, P. C. H. Enantioselective Synthesis of "Quaternary" 1,4-Benzodiazepin-2-One Scaffolds Via Memory of Chirality. *J. Am. Chem. Soc.* **2003**, *125*, 11482-11483.

12. Carlier, P. R. Experimental and Computational Studies of Ring Inversion of 1,4-Benzodiazepin-2-Ones: Implications for Memory of Chirality Transformations. *J. Org. Chem.* **2005**, *70*, 1530-1538.

13. Carlier, P. R.; Lam, P. C. H.; DeGuzman, J. C.; Zhao, H. Memory of Chirality Trapping of Low Inversion Barrier 1,4-Benzodiazepin-2-One Enolates. *Tetrahedron: Asymmetry* **2005**, *16*, 2998-3002.

14. Lam, P. C. H.; Carlier, P. R. Experimental and Computational Studies of Ring Inversion of 1,4-Benzodiazepin-2-Ones: Implications for Memory of Chirality Transformations. *J. Org. Chem.* **2005**, *70*, 1530-1538.

15. MacQuarrie-Hunter, S.; Carlier, P. R. Highly Enantioselective Synthesis of Rigid, Quaternary 1,4-Benzodiazepine-2,5-Diones Derived from Proline. *Org. Lett. 7*, 5305-5308.

16. Carlier, P. R.; Zhao, H.; MacQuarrie-Hunter, S. L.; DeGuzman, J. C.; Hsu, D. C. Enantioselective Synthesis of Diversely Substituted Quaternary 1,4-Benzodiazepin-2-Ones and 1,4-Benzodiazepine-2,5-Diones. *J. Am. Chem. Soc.* **2006**, *128*, 15215-15220.

17. Hsu, D. C.; Lam, P. C. H.; Slebodnick, C.; Carlier, P. R. Complete Mapping of the Stereochemical Course of Retentive Deprotonation/Alkylation of 1h-Benzo[E][1,4]Diazepin-2(3h)-Ones. *J. Am. Chem. Soc.* **2009**, *131*, 18168-18176.

18. Carlier, P. R.; Sun, Y.-S.; Hsu, D. C.; Chen, Q.-H. Axial-Selective H/D Exchange of Glycine-Derived 1h-Benzo[E][1,4]Diazepin-2(3h)-Ones: Kinetic and Computational Studies of Enantiomerization. *J. Org. Chem.* **2010**, *75*, 6588-6594.

19. Konował, A.; Snatzke, G.; Alebić-Kolbah, T.; Kajfež, F.; Rendić, S.; Šunjić, V. General Approach to Chiroptical Characterization of Binding of Prochiral and Chiral 1,4-Benzodiazepin-2-Ones to Human Serum Albumin. *Biochem. Pharmacol.* **1979**, *28*, 3109-3113.

20. Rondan, N. G.; Paddon-Row, M. N.; Caramella, P.; Houk, K. N. Nonplanar Alkenes and Carbonyls: A Molecular Distortion Which Parallels Addition Stereoselectivity. *J. Am. Chem. Soc.* **1981**, *103*, 2436-2438.

21. Seebach, D.; Zimmermann, J.; Gysel, U.; Ziegler, R.; Ha, T. K. Totally Stereoselective Additions to 2,6-Disubstituted 1,3-Dioxin-4-Ones (Chiral Acetoacetic Acid Derivatives). Synthetic and Mechanistic Aspects of Remote Stereoselectivity. *J. Am. Chem. Soc.* **1988**, *110*, 4763-4772.

22. Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*. Wiley-Interscience: New York, 1994.

23. Hara, O.; Ito, M.; Hamada, Y. Novel N → C Acyl Migration Reaction of Acyclic Imides: A Facile Method for A-Aminoketones and B-Aminoalcohols. *Tetrahedron Lett.* **1998**, *39*, 5537-5540.

24. Lee, S. D.; Chan, T. H.; Kwon, K. S. Rearrangement of A-Acyloxyacetates into 2-Hydroxy-3-Ketoesters. *Tetrahedron Lett.* **1984**, *25*, 3399-3402.

25. McCormick, J. L.; McKee, T. C.; Cardellina, J. H.; Boyd, M. R. Hiv Inhibitory Natural Products. 26. Quinoline Alkaloids from Euodia Roxburghiana. *J. Nat. Prod.* **1996**, *59*, 469-471.

26. Ahmed, N.; Brahmbhatt, K. G.; Sabde, S.; Mitra, D.; Singh, I. P.; Bhutani, K. K. Synthesis and Anti-Hiv Activity of Alkylated Quinoline 2,4-Diols. *Bioorg. Med. Chem.* **2010**, *18*, 2872-2879.

27. Seong, C. M.; Park, W. K.; Park, C. M.; Kong, J. Y.; Park, N. S. Discovery of 3-Aryl-3-Methyl-1h-Quinoline-2,4-Diones as a New Class of Selective 5-Ht6 Receptor Antagonists. *Bioorg. Med. Chem.* **2008**, *18*, 738-743.

28. Harfenist, M.; Magnien, E. Tetracyclic Phenothiazines and Related Compounds. Iv. Ketoamides Alkylated and Aminoalkylated on Oxygen, and Alkylated and Aminated on Carbon1. *J. Org. Chem.* **1963**, *28*, 538-543.

29. Kafka, S.; Klásek, A.; Polis, J.; Kosmrlj, J. Synthesis of 3-Aminoquinoline-2,4(1*h*,3*h*)-Diones. *Heterocycles* **2002**, *57*, 1659-1682.

30. Lucht, B. L.; Bernstein, M. P.; Remenar, J. F.; Collum, D. B. Polydentate Amine and Ether Solvates of Lithium Hexamethyldisilazide (Lihmds): Relationship of Ligand Structure, Relative Solvation Energy, and Aggregation State. *J. Am. Chem. Soc.* **1996**, *118*, 10707-10718.

31. Zhao, P.; Lucht, B. L.; Kenkre, S. L.; Collum, D. B. Lithium Hexamethyldisilazide-Mediated Ketone Enolization: The Influence of Hindered Dialkyl Ethers and Isostructural Dialkylamines on Reaction Rates and Mechanisms. *J. Org. Chem.* **2004**, *69*, 242-249.

32. Kawabata, T.; Wirth, T.; Yahiro, K.; Suzuki, H.; Fuji, K. Direct Asymmetric .Alpha.-Alkylation of Phenylalanine Derivatives Using No External Chiral Sources. *J. Am. Chem. Soc.* **1994**, *116*, 10809-10810.

33. Kawabata, T.; Matsuda, S.; Kawakami, S.; Monguchi, D.; Moriyama, K. Stereochemical Diversity in Asymmetric Cyclization Via Memory of Chirality. *J. Am. Chem. Soc.* **2006**, *128*, 15394-15395.

34. Antolak, S. A.; Yao, Z.-K.; Richoux, G. M.; Slebodnick, C.; Carlier, P. R. Enantioselective Deprotonative Ring Contraction of N1-Methyl-N4-Boc-Benzo[E][1,4]Diazepine-2,5-Diones. *Org. Lett.* **2014**, *16*, 5204-5207.

35. Smith, G. G.; Sivakua, T. Mechanism of the Racemization of Amino Acids. Kinetics of Racemization of Arylglycines. *J. Org. Chem.* **1983**, *48*, 627-634.

36. Blass, B. E.; Burt, T. M.; Liu, S.; Portlock, D. E.; Swing, E. M. A Facile Kf/Al2o3 Mediated, Selective Alkylation of Benzodiazepin-2,5-Diones. *Tetrahedron Lett.* **2000**, *41*, 2063-2066.

37. Otani, Y.; Nagae, O.; Naruse, Y.; Inagaki, S.; Ohno, M.; Yamaguchi, K.; Yamamoto, G.; Uchiyama, M.; Ohwada, T. An Evaluation of Amide Group Planarity in 7-Azabicyclo[2.2.1]Heptane Amides. Low Amide Bond Rotation Barrier in Solution. *J. Am. Chem. Soc.* **2003**, *125*, 15191-15199.

38. Dunitz, J. D.; Winkler, F. K. Amide Group Deformation in Medium-Ring Lactams. *Acta Crystallographica Section B* **1975**, *31*, 251-263.

39. Akssira, M.; Boumzebra, M.; Kasmi, H.; Dahdouh, A.; Roumestant, M. L.; Viallefont, P. New Routes to 1,4- Benzodiazepin-2,5-Diones. *Tetrahedron* **1994**, *50*, 9051-9060.

40. Levkin, P. A.; Ruderisch, A.; Schurig, V. Combining the Enantioselectivity of a Cyclodextrin and a Diamide Selector in a Mixed Binary Gas-Chromatographic Chiral Stationary Phase. *Chirality* **2006**, *18*, 49-63.

41. Aitken, R. A.; Murray, L. New Gas-Phase Cascade Reactions of Stabilized Phosphorus Ylides Leading to Ring-Fused Indoles and to Quinolines. *J. Org. Chem.* **2008**, *73*, 9781-9783.

42. Salgado, V. L. The Neurotoxic Insecticidal Mechanism of the Nonsteroidal Ecdysone Agonist Rh-5849: K+ Channel Block in Nerve and Muscle. *Pestic. Biochem. Physiol.* **1992**, *43*, 1-13.

43. Pridgeon, J. W.; Becnel, J. J.; Clark, G. G.; Linthicum, K. J. A High-Throughput Screening Method to Identify Potential Pesticides for Mosquito Control. *J. Med. Entomol.* **2009**, *46*, 335-341.

44. Swale, D. R.; Carlier, P. R.; Hartsel, J. A.; Ma, M.; Bloomquist, J. R. Mosquitocidal Carbamates with Low Toxicity to Agricultural Pests: An Advantageous Property for Insecticide Resistance Management. *Pest Manag. Sci* **2015**, *71*, 1158-1164.

45. Bloomquist, J. R.; Mutunga, J. M.; Islam, R. M.; Verma, A.; Ma, M.; Totrov, M. M.; Carlier, P. R. Voltage-Sensitive Potassium Kv2 Channels as New Targets for Insecticides. In *Biopesticides: State of the Art and Future Opportunities*, American Chemical Society: 2014; Vol. 1172, pp 71-81.

46. Zhao, H. W.; Hsu, D. C.; Carlier, P. R. Memory of Chirality: An Emerging Strategy for Asymmetric Synthesis. *Synthesis* **2005**, 1-16.

4. Experimental Procedures and Analytical Data

4.1 Materials and general information

NMR spectra were obtained on a Varian Inova-400 MHz spectrometer at 400 (^{1}H) and 101 (^{13}C) MHz, a Bruker Avance-II 500 MHz spectrometer at 500 (^{1}H) and 126 (^{13}C) MHz, or an Avance-III 600 MHz spectrometer at 600 (^{1}H) and 151 (^{13}C). Variable temperature ^{1}H and ^{13}C NMR were performed on an Avance-III 600 MHz spectrometer. The chemical shifts for ^{1}H and ^{13}C are reported in δ (ppm) against tetramethylsilane as an internal standard for reference, and coupling constants are given in Hz. Deuterated solvents were purchased from Cambridge Isotope Laboratories. The following abbreviations are used to show coupling in the spectra: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (sextet), hept (heptet), nonet (n), and m (multiplet). High-resolution electronspray ionization (ESI) mass spectroscopy (HRMS) was performed on an Agilent 6220 LC/MS time-of-flight mass spectrometer. Tetrahydrofuran (THF) for moisture sensitive reactions was distilled from sodium/benzophenone ketyl immediately prior to use in reactions. Reactions at -78 °C were maintained using the standard acetone/dry-ice bath or Thermo NESLAB cc-100 immersion cooler. Column chromatography was performed using silica gel (ZEOprep 60 HYD 40-63 μm) purchased from AIC. Thin layer chromatography (TLC) was performed on XG silica gel w/UV254 plates purchased from SORBTECH. Enantiomeric excess of all synthesized compounds was assessed by HPLC (Chiralcel OD, OD-H, AD-H, or (*R,R*)-Whelk 02). For chiral stationary phase HPLC analyses of enantiomeric purity, racemic samples were prepared for each of the compounds. Reagents were purchased from Sigma-Aldrich and were used without purification, unless otherwise noted. Compounds prepared for mosquito bioassay

were > 95% pure as judged by ^{1}H and ^{13}C NMR spectroscopy. All hexane used is a mixture of hexanes.

4.2 Tabulation of HPLC conditions and retention rimes for 1,4-benzodiazepin-2,5-diones

The retention times reported here are determined from racemic and enantiomerically enriched/pure samples. HPLC columns are not thermostatted, and consequently retention times are subject to day-to-day variability.

Compound	Column	Solvent, flow rate	Fast enantiomer retention time	Slow enantiomer retention time
(*R/S*)-**3-34e**	OD-H	85/15 hexane/*i*-PrOH, 1 ml/min	24.8	27.6
(*S*)-**3-34e**	OD-H	85/15 hexane/*i*-PrOH, 1 ml/min	25.1	27.7 (major)
(*R/S*)-**3-50e**	OD-H	90/10 hexane/*i*-PrOH, 1 ml/min	35.1	54.3
(*S*)-**3-50d**	OD-H	90/10 hexane/*i*-PrOH, 1 ml/min	-	53.9 (major)
(*R/S*)-**3-50e**	OD-H	90/10 hexane/*i*-PrOH, 1 ml/min	27.6	39.0
(*S*)-**3-50e**	OD-H	90/10 hexane/*i*-PrOH, 1 ml/min	27.7	39.1 (major)
(*R/S*)-**3-51d**	OD-H	90/10 hexane/*i*-PrOH, 1 ml/min	21.5	37.9
(*S*)-**3-51d**	OD-H	90/10 hexane/*i*-PrOH, 1 ml/min	21.6	37.8 (major)
(*R/S*)-**3-51e**	OD-H	90/10 hexane/*i*-PrOH, 1 ml/min	21.0	37.6
(*S*)-**3-51e**	OD-H	90/10 hexane/*i*-PrOH, 1 ml/min	21.2	37.8 (major)
(*R/S*)-**3-51f**	OD-H	80/20 hexane/*i*-PrOH, 1 ml/min	28.8	46.1
(*S*)-**3-51f**	OD-H	80/20 hexane/*i*-PrOH, 1 ml/min	28.4	45.3 (major)
(*R/S*)-**3-51g**	OD-H	92/8 hexane/*i*-PrOH, 1 ml/min	124.4	139.4
(*S*)-**3-51g**	OD-H	92/8 hexane/*i*-PrOH, 1 ml/min	122.5	138.7 (major)
(*R/S*)-**3-52d**	OD-H	88/12 hexane/*i*-PrOH, 1 ml/min	22.9	32.7
(*S*)-**3-52d**	OD-H	88/12 hexane/*i*-PrOH, 1 ml/min	22.8	32.3 (major)

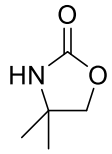
Compound	Column	Solvent, flow rate	Fast enantiomer retention time	Slow enantiomer retention time
(*R/S*)-**3-52e**	OD-H	85/15 hexane/*i*-PrOH, 1 ml/min	22.2	32.5
(*S*)-**3-52e**	OD-H	85/15 hexane/*i*-PrOH, 1 ml/min	22.2	32.4 (major)
(*R/S*)-**3-52g**	OD-H	95/5 hexane/*i*-PrOH, 1 ml/min	126.8	147.7
(*S*)-**3-52g**	OD-H	95/5 hexane/*i*-PrOH, 1 ml/min	-	146.8 (major)
(*R/S*)-**3-53d**	OD-H	96/4 hexane/*i*-PrOH, 1 ml/min	31.1	42.2
(*S*)-**3-53d**	OD-H	96/4 hexane/*i*-PrOH, 1 ml/min	-	42.1 (major)
(*R/S*)-**3-53e**	OD-H	93/7 hexane/*i*-PrOH, 1 ml/min	20.1	24.8
(*S*)-**3-53e**	OD-H	93/7 hexane/*i*-PrOH, 1 ml/min	-	25.1 (major)
(*R/S*)-**3-53f**	(*R,R*)-Whelk02	85/15 hexane/*i*-PrOH, 1 ml/min	27.6	39.0
(*S*)-**3-53f**	(*R,R*)-Whelk02	85/15 hexane/*i*-PrOH, 1 ml/min	27.7	39.1 (major)
(*R/S*)-**3-53g**	OD-H	95/5 hexane/*i*-PrOH, 1 ml/min	32.7	41.2
(*S*)-**3-53g**	OD-H	95/5 hexane/*i*-PrOH, 1 ml/min	32.3	41.7 (major)
(*R/S*)-**3-54d**	OD-H	95/5 hexane/*i*-PrOH, 1 ml/min	27.7	44.9
(*S*)-**3-54d**	OD-H	95/5 hexane/*i*-PrOH, 1 ml/min	28.1	45.5 (major)
(*R/S*)-**3-54e**	OD-H	95/5 hexane/*i*-PrOH, 1 ml/min	16.9	26.6
(*S*)-**3-54e**	OD-H	95/5 hexane/*i*-PrOH, 1 ml/min	16.2	25.5 (major)
(*R/S*)-**3-54f**	OD-H	99/1 hexane/*i*-PrOH, 1 ml/min	31.3	45
(*S*)-**3-54f**	OD-H	99/1 hexane/*i*-PrOH, 1 ml/min	32.6	39.2 (major)
(*R/S*)-**3-54g**	OD-H	90/10 hexane/*i*-PrOH, 1 ml/min	20.8	29.2
(*S*)-**3-54g**	OD-H	90/10 hexane/*i*-PrOH, 1 ml/min	21.3	30.0 (major)
(*R/S*)-**3-55d**	OD-H	97/3 hexane/*i*-PrOH, 1 ml/min	37.1	44.1
(*S*)-**3-55d**	OD-H	97/3 hexane/*i*-PrOH, 1 ml/min	40.2 (major)	48.3
(*R/S*)-**3-55e**	OD-H	98/2 hexane/*i*-PrOH, 1 ml/min	18.0	21.0
(*S*)-**3-55e**	OD-H	98/2 hexane/*i*-PrOH, 1 ml/min	-	21.0 (major)

Compound	Column	Solvent, flow rate	Fast enantiomer retention time	Slow enantiomer retention time
(*R/S*)-**3-55f**	OD-H	98/2 hexane/*i*-PrOH, 1 ml/min	16.8	20.3
(*S*)-**3-55f**	OD-H	98/2 hexane/*i*-PrOH, 1 ml/min	16.9	20.3 (major)
(*R/S*)-**3-55g**	OD-H	98/2 hexane/*i*-PrOH, 1 ml/min	61.1	76.2
(*S*)-**3-55g**	OD-H	98/2 hexane/*i*-PrOH, 1 ml/min	61.8	74.0 (major)
(*R/S*)-**3-61d**	AD-H	85/15 hexane/*i*-PrOH, 1 ml/min	21.9	32.4
(*S*)-**3-61d**	AD-H	85/15 hexane/*i*-PrOH, 1 ml/min	22.2	32.2 (major)
(*R/S*)-**3-61e**	OD-H	85/15 hexane/*i*-PrOH, 1 ml/min	12.2	14.4
(*S*)-**3-61e**	OD-H	85/15 hexane/*i*-PrOH, 1 ml/min	-	13.2 (major)
(*R/S*)-**3-61f**	AD-H	85/15 hexane/*i*-PrOH, 1 ml/min	31.4	40.2
(*S*)-**3-61f**	AD-H	85/15 hexane/*i*-PrOH, 1 ml/min	31.0	39.5 (major)
(*R/S*)-**3-61f**	(*R,R*)-Whelk02	95/5 hexane/*i*-PrOH, 1 ml/min	34.9	43.2
(*S*)-**3-61f**	(*R,R*)-Whelk02	95/5 hexane/*i*-PrOH, 1 ml/min	34.5 (major)	44.3
(*R/S*)-**3-62d**	AD-H	85/15 hexane/*i*-PrOH, 1 ml/min	26.5	37.9
(*S*)-**3-62d**	AD-H	85/15 hexane/*i*-PrOH, 1 ml/min	27.2	39.0 (major)
(*R/S*)-**3-62e**	OD-H	85/15 hexane/*i*-PrOH, 1 ml/min	12.2	15.5
(*S*)-**3-62e**	OD-H	85/15 hexane/*i*-PrOH, 1 ml/min	12.3 (major)	15.6
(*R/S*)-**3-62f**	AD-H	85/15 hexane/*i*-PrOH, 1 ml/min	40.4	52.4
(*S*)-**3-62f**	AD-H	85/15 hexane/*i*-PrOH, 1 ml/min	41.5	54.0 (major)
(*R/S*)-**3-62g**	(*R,R*)-Whelk02	85/15 hexane/*i*-PrOH, 1 ml/min	52.8	69.6
(*S*)-**3-62g**	(*R,R*)-Whelk02	85/15 hexane/*i*-PrOH, 1 ml/min	52.4 (major)	70.7
(*R/S*)-**3-63d**	AD-H	85/15 hexane/*i*-PrOH, 1 ml/min	19.8	36.4
(*S*)-**3-63d**	AD-H	85/15 hexane/*i*-PrOH, 1 ml/min	19.5	33.5 (major)
(*R/S*)-**3-63e**	AD-H	85/15 hexane/*i*-PrOH, 1 ml/min	17.4	25.6
(*S*)-**3-63e**	AD-H	85/15 hexane/*i*-PrOH, 1 ml/min	17.3	25.6 (major)

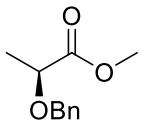
Compound	Column	Solvent, flow rate	Fast enantiomer retention time	Slow enantiomer retention time
(*R/S*)-**3-63f**	AD-H	85/15 hexane/*i*-PrOH, 1 ml/min	24.6	38.0
(*S*)-**3-63f**	AD-H	85/15 hexane/*i*-PrOH, 1 ml/min	24.5	38.0 (major)
(*R/S*)-**3-63g**	AD-H	85/15 hexane/*i*-PrOH, 1 ml/min	21.4	29.7
(*S*)-**3-63g**	AD-H	85/15 hexane/*i*-PrOH, 1 ml/min	21.5	30.2 (major)

4.3 Synthetic procedures

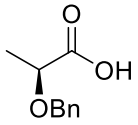
4.3.1. Chapter 2 (*S*)-methyl lactate project



4,4-Dimethyloxazolidin-2-one (**2-15**): Adapted from the procedure by Gaul *et al.*[1] Et_3N (12.9 mL, 92.2 mmol, 0.7255 g/mL, 1.1 equiv) was added at -15 °C to a solution of 2-amino-2-methyl-1-propanol (8.0 mL, 84 mmol, 0.934 g/mL, 1 equiv) in DCM (2 ml/mmol). Ethyl chloroformate (7.0 mL, 84 mmol, 1.14 g/mL, 1 equiv) was added dropwise to the solution, and the reaction mixture was stirred for 12 hours at room temperature. The reaction was quenched with $HCl_{(aq)}$ (1 M, 0.6 mL/mmol) and diluted with DCM. The resulting mixture was extracted with DCM (2 × 15 ml), dried with $MgSO_4$, and concentrated under reduced pressure. The residue was dissolved in 5% methanolic NaOH (4 g in 80 mL, 0.95 mL/mmol) and heated to reflux for 7 hours. The reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$. Methanol was removed under reduced pressure, and the residual mixture was extracted with DCM (2 × 15 ml). The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure. The product was purified by trituration in pentane to afford the achiral oxazolidinone **2-15** as a white solid. (5.32 g, 54%); mp: 48-49 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.37 (s, 1H), 4.03 (s, 2H), 1.31 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7, 76.8, 55.1, 27.5. Spectra matched the literature.[1] (**GMR-I-001**)

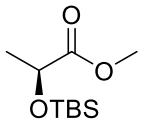


Methyl (*S*)-2-(benzyloxy)propanoate (**2-17a**): Adapted from the procedure by Chavan *et al*.[2] To a solution of (*S*)-methyl lactate (4.9 mL, 51 mmol, 1.09 g/mL, 1.0 equiv) in dry THF (60 mL, 1 mL/mmol) at 0 °C, NaH (60% suspension in mineral oil, 2.47 g, 1.2 equiv.) was added, and the mixture was stirred for 15 min. Benzyl bromide (7.4 mL, 62 mmol, 1.44 g/mL, 1.2 equiv) was added, and the reaction mixture warmed to room temperature and stirred for 12 hours. The reaction mixture was quenched with water and extracted into EtOAc (3 × 15 mL). The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. Purification by silica gel column chromatography (1:5 EtOAc:Hex) afforded the product as a colorless oil (7.03 g, 70%). ^{1}H NMR (500 MHz, CD_3OD) δ 7.79 – 7.05 (m, 5H), 5.04 (s, 1H), 4.68 (d, *J* = 11.7 Hz, 1H), 4.45 (d, *J* = 11.7 Hz, 1H), 4.07 (d, *J* = 6.7 Hz, 1H), 1.42 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ 176.8, 139.1, 129.4, 129.1, 128.8, 75.0, 72.9, 52.5 19.0. Spectra matched the literature.[3] $[a]_D^{25} = -89.07$ (c = 0.083, MeOH) (**GMR-I-067**)

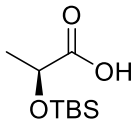


(*S*)-2-(Benzyloxy)propanoic acid (**2-18a**): **2-17a** (1.92 g, 9.88 mmol, 1 equiv) was added to a premixed solution of KOH (3 M, 5.55 g, 93.9 mmol, 9.50 equiv) in EtOH (31 mL) and stirred for 4 hours. The solution was neutralized (pH ~ 3) with $HCl_{(aq)}$ (1 N) and extracted with Et_2O. The organic layer dried with $MgSO_4$, and the volume was reduced *in vacuo* to afford product **2-18a** as a white solid (1.42 g, 80%). ^{1}H NMR (500 MHz, CD_3OD) δ 8.23 – 7.01 (m, 5H), 5.03 (s, 1H), 4.68 (d, *J* = 11.5 Hz, 1H), 4.45 (d, *J* = 11.5

Hz, 1H), 4.07 (q, J = 6.8 Hz, 1H), 1.42 (d, J = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ 176.8, 139.1, 129.4, 129.1, 128.8, 75.0, 72.9, 19.0, 19.0. Spectra matched the literature.[4] $[a]_D^{25} = -69.09$ (c = 0.77, MeOH) **(GMR-I-154)**

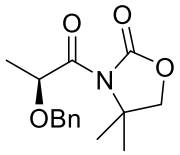


Methyl (*S*)-2-((tert-butyldimethylsilyl)oxy)propanoate (**2-17b**): Adapted from the procedure by Chin *et al*.[5] (*S*)-methyl lactate (4.37 mL, 45.8 mmol, 1.09 g/mL, 1.0 equiv) was added dropwise to a mixture of imidazole (6.24 g, 91.6 mmol, 2.0 equiv) and DCM (1.6 mL/mmol) under nitrogen and cooled to 0 °C. TBS-Cl (12.0 g, 67.7 mmol, 1.5 equiv) was added slowly and the resulting mixture was stirred over night at room temperature. The mixture was diluted with DCM and water, and the product was extracted into DCM. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (5% EtOAc in Hex) to afford **2-17b** as a clear oil. (7.43 g, 74%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.26 (q, J = 6.7 Hz, 1H), 3.65 (s, 3H), 1.33 (d, J = 6.8 Hz, 3H), 0.83 (s, 9H), 0.03 (s, 3H), -0.00 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.54, 68.38, 51.84, 25.70, 21.35, 18.30, -5.00, -5.29. Spectra matched the literature.[5] $[a]_D^{25} = -28.03$ (c = 0.37, MeOH) (**GMR-I-027**)



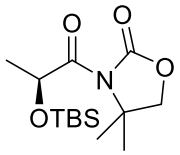
(*S*)-2-((tert-Butyldimethylsilyl)oxy)propanoic acid (**2-18b**): Adapted from the procedure by Wei *et al*.[6] KOH (0.88 g, 15.6 mmol, 1.0 equiv) in water (15.6 mL) was added dropwise to a solution of **2-17b** (3.40 mg, 15.6 mmol, 1.0 equiv) in EtOH (15.6) at 0 °C, and the reaction was stirred for 30 min. The mixture was extracted with Et_2O to

remove impurities. The aqueous phase was neutralized with 1 M HCl, and the desired carboxylic acid was extracted with Et_2O (3 × 15 mL). The combined ether extracts were dried with $MgSO_4$, filtered, and concentrated *in vacuo* to afford **2-18b** as a tan solid (1.25 g, 59%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.16 (q, *J* = 6.8 Hz, 1H), 1.29 (d, *J* = 6.8 Hz, 3H), 0.80 (s, 9H), 0.00 (s, 3H), -0.03 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.30, 68.98, 25.54, 21.34, 18.29, -4.87, -5.38. Spectra matched the literature.[7] $[a]_D^{25} = -34.33$ (c = 0.40, MeOH) (**GMR-I-73**)



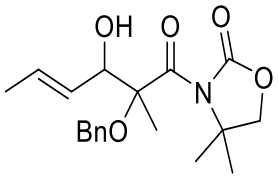
(*S*)-3-(2-(Benzyloxy)propanoyl)-4,4-dimethyloxazolidin-2-one (**2-9a**): Adapted from the procedure by Toshima *et al*.[8] Under N_2, **2-18a** (1.169 g, 6.48 mmol, 1.0 equiv) was added to dry THF (14.9 mL) and cooled to -78 °C. *n*BuLi (2.5 M, 2.6 mL, 6.5 mmol, 1.0 equiv) was added followed by pivaloyl chloride (0.80 g, 6.48 mmol, 0.980 g/mL, 1.0 equiv). The flask was warmed to room temperature and stirred for three hours. Compound **2-15** (0.746 g, 6.48 mmol, 1.0 equiv) was stirred separately with KHMDS (0.5 M, 13.0 mL, 6.48 mmol, 1.0 equiv) in THF for 30 min. at -78 °C. The deprotonated oxazolidinone solution was then added to the flask containing mixed anhydride intermediate at -78 °C. The solution was warmed to room temperature and stirred overnight. The solvent was removed *in vacuo*, and the residue was extracted with ethyl acetate, dried with $MgSO_4$, and concentrated *in vacuo*. The crude mixture was purified on a silica gel column (1:7 EtOAc: Hex) to afford the product **2-9a** as a yellow oil (1.21 g, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.22 (m, 5H), 5.13 (q, *J* = 6.6 Hz, 1H), 4.59

(d, *J* = 11.3 Hz, 1H), 4.44 (d, *J* = 11.3 Hz, 1H), 4.01 (s, 2H), 1.56 (s, 3H), 1.55 (s, 3H), 1.42 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3, 153.6, 137.7, 128.3, 128.0, 127.7, 75.6, 74.4, 72.1, 60.6, 24.8, 24.5, 18.4; HRMS (ESI) calculated for $C_{15}H_{19}NO_4$ $[M+H]^+$: 278.1383, exact mass found 278.1383; $[a]_D^{25} = +52.27$ (c = 0.22, MeOH) (**GMR-I-071**)



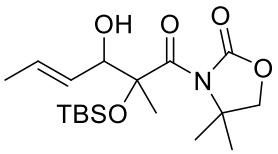
(*S*)-3-(2-((tert-Butyldimethylsilyl)oxy)propanoyl)-4,4-dimethyloxazolidin-2-one (**2-9b**): Adapted from the procedure by Doi *et al.*[9] Compound **2-18b** (0.61 g, 3.0 mmol, 1.0 equiv) was dissolved in DCM (7.5 mL). Oxalyl chloride (0.51 mL, 6.0 mmol, 2.0 equiv) was added followed by DMF (2 drops), and the reaction was stirred for one hour. The solvent was removed *in vacuo*. KHMDS (0.5 M in toluene, 5.8 mL, 2.9 mmol, 0.98 equiv) was added to a separate solution of oxazolidinone **2-15** (0.33 g, 2.9 mmol, 0.98 equiv) in THF (9 mL) at -78 °C and stirred for 30 min. The acid chloride intermediate derivative **2-18b** was dissolved in THF and added to the deprotonated oxazolidinone. The mixture was slowly warmed to room temperature and stirred overnight. Saturated NH_4Cl and Et_2O were added. The mixture was extracted with Et_2O (3 × 15 mL), and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (1:5 EtOAc:Hex) to afford product **2-9b** as a slightly yellow oil (0.76 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (q, *J* = 6.5 Hz, 1H), 3.98 (s, 2H), 1.53 (s, 3H), 1.50 (s, 3H), 1.32 (d, *J* = 6.5 Hz, 3H), 0.84 (s,

9H), 0.03 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6, 153.8, 75.7, 68.4, 60.7, 25.9, 24.9, 24.6, 21.4, 18.4, -4.7, -4.9; HRMS (ESI) calculated for $C_{14}H_{27}NO_4Si$ $[M+H]^+$: 302.1788, exact mass found 302.1776; $[a]_D^{25} = -20.83$ (c = 0.096, MeOH) (**GMR-I-161**)



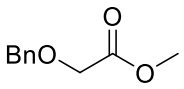
(*E*)-3-(2-(benzyloxy)-3-hydroxy-2-methylhex-4-enoyl)-4,4-dimethyloxazolidin-2-one (**2-23a**): Procedure adapted from protocol by Murata *et al.*[10] Diisopropylamine (97.0 μL, 692 μmol, 1.5 equiv) and *n*BuLi (2.5 M in hexane, 277 μL, 692 μmol, 1.5 equiv) were stirred in THF under nitrogen at -78 °C for 15 min. **2-9a** (128 mg, 0.46 mmol, 1.0 equiv) was added at -78 °C, and the mixture was stirred for 30 min. $Ti(O\text{-}i\text{-}Pr)_3Cl$ (1 M in hexane, 1.85 mL, 1.85 mmol, 4.0 equiv) was added, and the mixture was warmed to -40 °C and stirred for 1 hour. The reaction was then cooled to -78 °C, and crotonaldehyde (46 μL, 550 μmol, 1.2 equiv) was added. The mixture was warmed to -40 °C and stirred for 2 hours. The mixture was quenched with aq. NH_4Cl (saturated, 2 mL) and stirred with celite (2 spatula tips full) for one hour at room temperature. The celite was filtered, and the filtrate was concentrated *in vacuo*. The residue was dissolved in Et_2O, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The product was purified on a silica gel column (1:4 EtOAc:Hex) to afford **2-23a** as a yellow oil (132.4 mg, 83%). The NMR spectra was identified as a mixture of two diastereomers in 2:1 ratio (determined by integrations of peak at 5.75 ppm and 5.66 ppm): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.25 (m, 5H), 5.69 (a mixture of major and minor diastereomers with each having a dqd, $^3J_{bc}$ = 16, $^3J_{ba}$

= 7 Hz $^4J_{bd}$ = 1 Hz, 1H, a detailed description of the splitting pattern is described in **section 2.8** and **Figure 2-2**), 5.60 (a mixture of major and minor diastereomers with each having a ddq, $^3J_{cb}$ = 15.3 Hz; $^3J_{cd}$ = 7.6 Hz; $^4J_{bd}$ = 1.4 Hz, a detailed description of the splitting pattern is described in **section 2.8** and **Figure 2-3**), 4.77 – 4.33 (m, 3H) 3.93 – 3.85 (m, 3H), 1.67 – 1.61 (m, 6H), 1.51 – 1.35 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$ $CDCl_3$) δ 177.5, 176.8, 153.1, 153.0, 138.2, 138.1, 129.8, 129.4, 129.0, 128.7, 128.5, 128.3, 127.8, 127.7, 127.6, 127.5, 85.4, 85.1, 76.9, 76.8, 75.7, 75.6, 67.0, 66.7, 62.5, 62.4, 24.3, 24.2, 23.9, 23.6, 17.9, 17.8, 17.8, 17.8; HRMS (ESI) calculated for $C_{19}H_{25}NO_5$ $[M+Na]^+$: 370.1630, exact mass found 370.1620; $[a]_D^{21} = +4.38$ (c = 0.160, MeOH) (**GMR-I-041**)



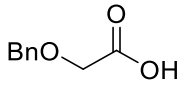
(E)-3-(2-((tert-Butyldimethylsilyl)oxy)-3-hydroxy-2-methylhex-4-enoyl)-4,4-dimethyloxazolidin-2-one (**2-23b**): Procedure adapted from protocol by Murata *et al*.[10] Diisopropylamine (48.8 μL, 348 μmol, 1.5 equiv) and *n*BuLi (2.5 M in hexane, 350 μL, 350 μmol, 1.5 equiv) were stirred in THF under nitrogen at -78 °C for 15 min. Compound **2-9b** (0.07 g, 0.23 mmol, 1.0 equiv) was added at -78 °C, and the mixture was stirred for 30 min. Ti(O-*i*-Pr)$_3$Cl (1 M in hexane, 0.9 mL, 0.9 mmol, 4.0 equiv) was added. The mixture was warmed to -40 °C and stirred for 1 hour, cooled to -78 °C, and crotonaldehyde (35 μL, 418 μmol, 1.2 equiv) was added. The mixture was warmed to -40 °C and stirred for 2 hours. The mixture was quenched with aq. NH_4Cl (saturated, 2 mL) and stirred with celite (2 spatula tips full) for one hour at room temperature. The celite was filtered, and the filtrate was concentrated *in vacuo*. The residue was dissolved in

Et_2O, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified on a silica gel column (1:4 EtOAc:Hex) to afford the product as a yellow oil (28.7 mg, 33%). The NMR spectra indicated a mixture of two diastereomers (ratio 1:2 based off integration of doublet of quartet peaks at 5.39 ppm, 5.32 ppm: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.64 – 5.47 (m, 1H), 5.36 (tdq, *J* = 15.2, 8.1, 1.6 Hz, 1H), 4.34 (d, *J* = 8.2 Hz, 1H), 3.81 (d, *J* = 8.0 Hz, 1H), 3.78 (d, *J* = 8.0 Hz, 1H), 1.50 (dd, *J* = 6.5, 1.5 Hz, 3H), 1.37 (s, 3H), 1.07 (s, 6H), 0.71 (s, 9H), -0.01 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.1, 179.1, 155.7, 155.4, 132.2, 131.6, 131.4, 131.2, 87.3, 86.1, 80.0, 79.7, 7.0, 77.9, 64.9, 62.6, 32.0, 31.9, 28.3, 28.3, 27.0, 26.6, 26.4, 25.9, 20.9, 20.8, 20.2, 20.0, 0.2, 0.0, -0.0, -0.1; HRMS (ESI) calculated for $C_{18}H_{33}NO_5Si$ $[M+Na]^+$: 394.2026, exact mass 394.2021; $[a]_D^{21} = +4.90$ (c = 0.102, MeOH) (**GMR-I-033**)

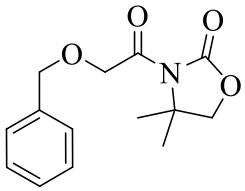


Methyl 2-(benzyloxy)acetate (**2-27)**: Adapted from the procedure by Chavan *et al*.[2] To a solution of methyl glycolate (2.57 mL, 33.3 mmol, 1.67 g/mL, 1.0 equiv) in dry THF (1 mL/mmol) at 0 °C, NaH (60% dispersion in mineral oil, 1.6 g, 40 mmol, 1.2 equiv) was added, and the mixture was stirred for 15 min. Benzyl bromide (5.9 mL, 50 mmol, 1.44 g/mL, 1.2 equiv) was added, and the reaction mixture was warmed to room temperature and stirred for 12 hours. The reaction mixture was quenched with water and extracted into EtOAc (3 × 15 mL). The combined EtOAc extract was washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. The crude mixture was purified on a silica gel column (1:5 EtOAc:Hex) to afford the product **2-27** as a yellow oil (3.01 g, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 5H), 4.61 (s, 2H), 4.08 (s, 2H), 3.74

(s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 137.0, 128.4, 128.0, 127.9, 73.3, 67.0, 60.3. Spectra matched the literature.[11] (**GMR-I-095**)

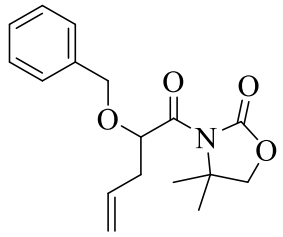


2-(Benzyloxy)acetic acid (**2-28**): Modified from the procedure by Wei *et al.*[6] To a solution methyl 2-(benzyloxy)acetate (3.535 g, 19.61 mmol, 1.0 equiv) in MeOH (26 mL) was added 3 N methanolic KOH (4.46 g, 78.5 mmol, 4.0 equiv), and the reaction was stirred for two hours. Methanol was removed *in vacuo* and the residue was extracted with Et_2O. The aqueous phase was neutralized with 1 M HCl, and the product was extracted into Et_2O (3 × 15 mL). The combined Et_2O extract was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to afford the product **2-28** as a colorless oil (2.98 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.13 (s, 1H), 7.38 – 7.35 (m, 4H), 7.35 (s, 1H), 4.64 (s, 2H), 4.14 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 136.5, 128.5, 128.2, 128.1, 73.4, 66.5. Spectra matched the literature.[12] (**GMR-I-101**)



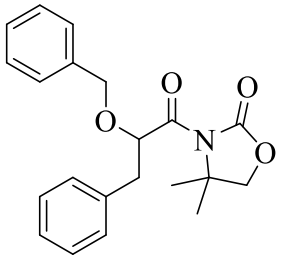
3-(2-(Benzyloxy)acetyl)-4,4-dimethyloxazolidin-2-one (**2-29**): Adapted from the procedure by Doi *et al.*[9] **2-28** (432 mg, 2.6 mmol, 1 equiv) was dissolved in DCM (2.5 mL/mmol). Oxalyl chloride (0.45 mL, 5.2 mmol, 1.48 g/mL, 2 equiv) was added followed by DMF (2 drops), and the reaction was stirred for one hour. The solvent was removed *in vacuo*. LiHMDS (1 M in THF, 2.5 mL, 2.5 mmol, 0.98 equiv) was added to a separate solution of **2-15** (300 mg, 2.6 mmol, 0.98 equiv) in THF (7.8 mL) at -78 °C and

stirred for 30 min. The acid chloride intermediate was dissolved in THF and was added to the deprotonated oxazolidinone. The mixture was slowly warmed to room temperature and stirred overnight. The solvent was removed *in vacuo*. Saturated NH_4Cl (15 mL) and Et_2O (15 mL) were added to the mixture. The product was extracted with Et_2O (3 × 15 mL) and the combined Et_2O extract was dried with Na_2SO_4, filtered, concentrated *in vacuo*, and purified on a silica gel column (1:5 EtOAc:Hex) to afford **2-29** as a white solid (425 mg, 65% yield). mp: 80 – 82 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.19 (m, 5H), 4.63 (s, 2H), 4.61 (s, 2H), 4.04 (s, 2H), 1.59 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 153.9, 137.2, 128.4, 127.9, 127.8, 76.1, 73.4, 70.4, 60.3, 24.8; HRMS (ESI) calculated for $C_{14}H_{17}NO_4$ $[M+H]^+$: 264.1236, exact mass found 264.1223 (**GMR-I-102**)



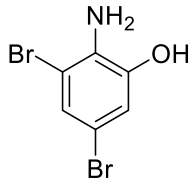
3-(2-(Benzyloxy)pent-4-enoyl)-4,4-dimethyloxazolidin-2-one (**2-30a**): **2-28** (100 mg, 0.595 mmol, 1.0 equiv) was dissolved in THF (5 mL) at -78 °C. KHMDS (0.5 M in toluene, 1.785 mL, 0.8925 mmol 1.5 equiv) was added dropwise and stirred for 30 min. Allyl iodide (0.27 mL, 3.0 mmol, 1.83 g/mL, 5 equiv) was added dropwise and stirred for 5 min. The solution was warmed to -45 °C and stirred until the reaction was at completion. The reaction was quenched with saturated ammonia chloride (20 mL), solvent was removed *in vacuo*, and the crude residue was extracted into Et_2O (3 × 15 mL). The combined Et_2O extract was dried with $MgSO_4$, concentrated *in vacuo*, and the

residue was purified on a silica gel column (1:5 EtOAc:Hex) to afford product **2-30a** as a clear oil (71.4 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.22 (m, 5H), 5.88 (ddt, *J* = 17.1, 10.1, 6.8 Hz, 1H), 5.17 (dd, *J* = 6.8, 4.7 Hz, 1H), 5.14 – 5.05 (m, 2H), 4.60 (d, *J* = 11.5 Hz, 1H), 4.46 (d, *J* = 11.5 Hz, 1H), 3.98 (s, 2H), 2.59 – 2.41 (m, 2H), 1.52 (s, 3H), 1.50 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 153.7, 137.6, 133.3, 127.6, 127.3, 126.9, 116.5, 77.1, 76.8, 75.6, 60.7, 37.3, 24.8, 24.3. HRMS (ESI) calculated for $C_{17}H_{21}NO_4$ $[M+H]^+$: 304.1549, exact mass found 304.1559 (**GMR-I-104**)

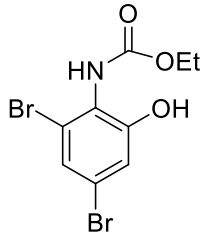


3-(2-(Benzyloxy)-3-phenylpropanoyl)-4,4-dimethyloxazolidin-2-one (**2-30b**): KHMDS (0.5 M in toluene, 1.4 mL, 0.71 mmol, 1.2 equiv) was added to a -78 °C mixture of **2-29** (100 mg, 0.595 mmol, 1.0 equiv) in THF (6.0 mL) and stirred for 25 min. HMPA (0.12 mL, 0.71 mmol, 1.03 g/mL, 1.2 equiv) was added and stirred for 10 min. BnBr (85 µL, 0.71 mmol, 1.44 g/mL, 1.2 equiv) was added, and the mixture was warmed to room temperature overnight. The reaction was quenched with H_2O, concentrated *in vacuo*, and the residue was extracted with Et_2O (3 × 15). The organic layer was washed with brine, dried with $MgSO_4$, concentrated *in vacuo*, and purified on a silica gel column (1:3 EtOAc:Hex) to afford the product as a yellow oil (51.2 mg, 24% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 7.5 Hz, 2H), 7.19 (t, *J* = 7.5 Hz, 2H), 7.18 – 7.11 (m, 4H), 7.09 (dd, *J* = 7.3, 1.7 Hz, 2H), 5.24 (dd, *J* = 8.8, 3.9 Hz, 1H), 4.43 (d, *J* = 11.7 Hz, 1H), 4.29 (d, *J* = 11.7 Hz, 1H), 3.88 (d, *J* = 8.4 Hz, 1H), 3.82 (d, *J* = 8.4 Hz, 1H), 3.00

(dd, *J* = 13.6, 3.9 Hz, 1H), 2.87 (dd, *J* = 13.6, 8.8 Hz, 1H), 1.43 (s, 3H), 1.35 (s, 3H); HRMS (ESI) calculated for $C_{21}H_{23}NO_4$ $[M+H]^+$: 354.1700, exact mass found 354.1707 (**GMR-I-105**)

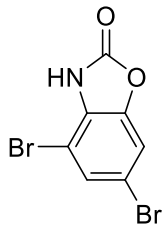


2-Amino-3,5-dibromophenol (**2-36**): Borontribromide (1 M in methylene chloride, 13.5 mL, 13.5 mmol, 2.0 equiv) was slowly added to a solution of 4-dibromo-6-methoxyaniline (1.89 g, 6.74 mmol, 1 equiv) in methylene chloride (40 mL) at 0 °C. The mixture was stirred for 30 min, at which point H_2O was added, and solid precipitated out of solution. The solid was filtered, washed with H_2O (15 mL), and air dried to afford **2-36** as a brown solid. (1.54 g, 86% yield). mp: 143 – 145 °C, ^{1}H NMR (400 MHz, CD_3OD) δ 7.02 (s, 1H), 6.80 (s, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ 146.2, 132.8, 124.5, 115.7, 108.7, 108.5. Known compound[13] but NMR spectra is not reported in literature. HRMS (ESI) calculated for $C_6H_5Br_2NO$ $[M-H]^-$: 263.8665, exact mass found 263.8665 (**GMR-I-158**)



Ethyl (2,4-dibromo-6-hydroxyphenyl)carbamate (**2-37**): Under N_2, Et_3N (0.30 mL, 2.16 mmol, 0.7255 g/mL, 1.1 equiv) was added to **2-36** (524 mg, 1.96 mmol, 1.0 equiv) at -10 °C. Ethylchloroformate (0.21 mL, 2.16 mmol, 1.14 g/mL, 1.1 equiv) was added

dropwise to the mixture. The mixture was stirred until completion as monitored by TLC. The reaction was acidified with 1 M HCl until precipitation ceased. The precipitate was collected by filtration, dissolved in methylene chloride (10 mL), washed with brine (2 × 15 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo* to afford **2-37** as a brown solid (654 mg, 98% yield). mp: 121 – 122 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 2.1 Hz, 1H), 7.24 (d, *J* = 2.1 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.5, 138.1, 136.3, 131.9, 124.2, 109.8, 108.1, 65.5, 14.1; HRMS (ESI) calculated for $C_9H_9Br_2NO_3$ $[M+H]^+$: 337.9022, exact mass found 337.9022 (**GMR-I-163**)



4,6-Dibromobenzo[d]oxazol-2(3H)-one (**2-38**): Compound **2-37** (654 mg, 1.93 mmol, 1.0 equiv) was dissolved in 5% methanolic NaOH (92.64 mg, 2.32 mmol, 1.2 equiv in 2.23 mL MeOH) and refluxed for four hours. The reaction was quenched with aq. NH_4Cl (sat., 10 mL), MeOH was removed *in vacuo*, and the residue was extracted into EtOAc (3 × 15 mL). The organic layers were dried with $MgSO_4$, filtered, concentrated *in vacuo*, and purified on a silica gel column (3:7 EtOAc:Hex) to afford **2-38** as a yellow solid (447.5 mg, 79% yield). mp: 138 – 144 °C ^{1}H NMR (500 MHz, CD_3OD) δ 6.91 (d, *J* = 2.1 Hz, 1H), 6.69 (d, *J* = 2.1 Hz, 1H). ^{13}C NMR (126 MHz, CD_3OD) δ 155.7, 145.9, 133.8, 124.4, 115.5, 107.9, 107.9; HRMS (ESI) calculated for $C_7H_3Br_2NO_2$ $[M+H]^+$: 291.8603, exact mass found 291.8431 (**GMR-I-164**)

4.3.2. Chapter 3 1,4-benzodiazepin-2,5-dione project

General procedure for synthesis *N*1-Me 1,4-benzodiazepin-2,5-diones

Method A. Procedure is based on protocol by Mohiuddin;[1] we found that an 18 hour reflux was necessary to achieve a reasonable conversion. The amino acid (1 equiv), and *N*-methyl isatoic anhydride (1 equiv) were combined in acetic acid (2.5 mL/mmol) and refluxed for 18 hours. The reaction was cooled to room temperature and concentrated *in vacuo*. The oily residue was diluted in EtOAc and stirred in saturated $NaHCO_{3(aq)}$ for 10 minutes. The aqueous layer was separated and extracted with EtOAc. The organic layers were collected, dried with Na_2SO_4, and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography or by trituration to afford the product.

General procedure for *N*4-Boc protection of 1,4-benzodiazepin-2,5-diones

Method B. Boc_2O (2.6 equiv) was added to a solution of *N*4-H BZD (1 equiv) in THF or DCM (3.5 mL/mmol). Et_3N (2.6 equiv) was added followed by DMAP (1.26 equiv), and the mixture was stirred under N_2 for 2 hours. The mixture was concentrated *in vacuo,* and EtOAc and 0.1N HCl were added. The aqueous layer was extracted with EtOAc. The organic layers were collected, dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The crude products were purified by column chromatography.

Method C. Boc_2O (2 equiv) was added to a solution of *N*4-H BZD (1 equiv) in DCM (10 mL/mmol). Et_3N (2 equiv) was added followed by DMAP (0.2 equiv), and the mixture was stirred for 2 hours. The mixture was concentrated *in vacuo,* and EtOAc and H_2O were added. The aqueous layer was extracted with EtOAc. The organic layers were collected, dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The crude products were purified by silica gel column chromatography.

General procedure for synthesis of *N*-H isatoic anhydrides

Method D. Procedure adapted from protocol by Sheng.[14] 2-aminobenzoic acid derivatives (3 equiv) were dissolved in THF (4 mL/mmol). Triphosgene (1 equiv) was added, and the mixture was refluxed for four hours. The reaction was cooled, quenched with aq. NH_4Cl (sat.), and the solvent was removed *in vacuo*. H_2O was added to precipitate the product. The precipitate was filtered out and washed with cold H_2O, methylene chloride, and Et_2O to afford the product.

General procedure for *N*-methylation

Method E. Procedure adapted from protocol by Bjork.[15] The Isatoic anhydride (1 equiv) was dissolved in DMF (2 mL/mmol) and cooled to 0 °C. 60% NaH (dispersion in mineral oil, 1.2 equiv) was added and stirred for 30 min. MeI (1.2 equiv) was added dropwise and the reaction was warmed to room temperature and stirred overnight. Water was added to precipitate the product, and excess MeI was removed *in vacuo*. The precipitate was filtered out and washed with H_2O, hexane, and Et_2O to afford the product.

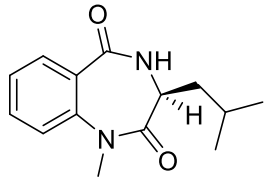
Method F. Amino acid (1 equiv) and *N*-H isatoic anhydride (1 equiv) were dissolved in H_2O (2.5 mL/mmol) and Et_3N (1 equiv) and stirred until starting material was used up. The reaction was diluted with brine and extracted into EtOAc. The organic layers were collected, washed with brine, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting residue was dissolved in AcOH (2.5 mL/mmol) and refluxed. The reaction was cooled, AcOH was removed *in vacuo*, and the residue was dissolved in EtOAc. The organic layer was washed with brine, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified on a silica gel column to afford the product.

General procedure for the ring contraction of 1,4-benzodiazepin-2,5-diones

Method G. At -78 °C under N_2, to a stirred solution of BZD (1 equiv) in THF (7 mL/mmol), M-HMDS (2 equiv) was added and the reaction was stirred overnight. The reaction was quenched with 0.1N HCl and concentrated *in vacuo*. The mixture was extracted with EtOAc. The organic layers were collected, dried with $MgSO_4$, filtered, concentrated *in vacuo*, and purified on a silica gel column to afford the product.

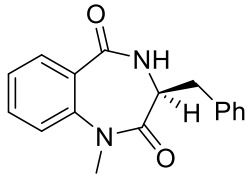
General procedure for the *N*-benzoyl protection of 1,4-benzodiazepin-2,5-diones

Method H. BZD (1 equiv) was dissolved in methylene chloride, and Et_3N (2 equiv) was added. The mixture was cooled to 0 °C under N_2, and benzoyl chloride (2 equiv) was added. The reaction was warmed to room temperature and stirred for 18 hours. Methylene chloride was removed *in vacuo*, and aq. NH_4C (sat.) was added. The mixture was extracted with EtOAc. The organic layers were collected, washed with brine, dried with Na_2SO_4, filtered, concentrated *in vacuo*, and purified on a silica gel column.

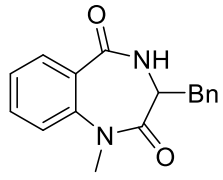


(*S*)-3-Isobutyl-1-methyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione[16] (**(*S*)-3-34d**): Prepared from the general procedure above (*Method A*) from *N*-methyl isatoic anhydride (1.35 g, 7.6 mmol), (*S*)-leucine (1 g, 7.6 mmol), and acetic acid (15 mL). The crude product was purified by silica gel column chromatography (1:1 EtOAc) to give product as a tan solid (1.4302g, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.5 Hz, 1H), 7.57 (t, *J* = 7.8, 7.5, Hz, 1H), 7.32 (t, *J* = 7.8, 7.5 Hz, 1H), 7.24 (d, *J* = 7.5 Hz, 1H), 3.76 (dd, *J* = 13.1, 7.4 Hz, 1H), 3.41 (s, 3H), 1.97 – 1.58 (m, 3H), 0.93 (d, *J* =

6.5 Hz, 3H), 0.85 (d, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2, 163.1, 135.8, 127.3, 124.9, 122.7, 120.4, 116.4, 71.3, 45.1, 30.6. $[a]_D^{25} = +2.56$ (c = 0.084, CH_2Cl_2] (**GMR-I-167**)

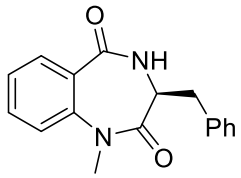


(*S*)-3-Benzyl-1-methyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione[16] (**(*S*)-3-34e**): Prepared from the general procedure above (*Method A*) from *N*-methyl isatoic anhydride (1.06 g, 6 mmol), (*S*)-phenylalanine (1 g, 6 mmol), and acetic acid (15 mL). The crude product was purified by silica gel column chromatography (1:1 EtOAc) to give the product as a tan solid (855.7 mg, 51% yield). mp: 170 – 172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 7.7 Hz, 1H), 7.55 (t, J = 7.8, 1.5 Hz, 1H), 7.37 – 7.12 (m, 7H), 4.01 (q, J = 7.7, 2.5 Hz, 1H), 3.46 (t, J = 3.5, 2.5 Hz, 1H), 3.42 (s, 3H), 3.07 (dd, J = 14.5, 7.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 168.7, 141.0, 136.5, 132.5, 130.3, 129.3, 128.6, 128.1, 126.9, 125.7, 121.7, 53.8, 35.9, 34.8. $[a]_D^{25} = +243.01$ (c = 0.465, MeOH) (**GMR-I-166**)



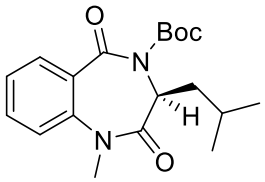
(*R/S*)-3-Benzyl-1-methyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione[16] (**(*R/S*)-34e**): Adapted from protocol by Mackay.[17] 90% *N*-methyl isatoic anhydride (0.2 g, 1.1 mmol, 1.0 equiv) and (*R/S*)-phenylalanine methyl ester*HCl (254 mg, 1.18 mmol, 1.07 equiv) were mixed together in pyridine (0.7 mL) and refluxed for 16 hours. The reaction

was poured into ice water to precipitate out solid. The solid was extracted into EtOAc (15 mL). The organic layer was collected, dried with $MgSO_4$, concentrated *in vacuo*, and the crude residue was taken directly forward. The following procedure was adapted from protocol by Lu.[18] Under N_2 *t*BuOK (1 M in THF, 1.1 mL, 1.1 mmol, 1 equiv) was added to the ring opened isatoic anhydride crude mixture in THF (2.2 mL) and stirred at room temperature for one hour. The mixture was concentrated *in vacuo*, and the resulting residue was extracted into EtOAc (3 × 15 mL). The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified on a silica gel column (1:1 EtOAc:Hex) to afford the product as a yellow oil (188.7 mg, 61% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.53 (td, *J* = 8.3, 1.5 Hz, 1H), 7.36 – 7.17 (m, 6H), 7.12 (d, *J* = 4.8 Hz, 1H), 3.99 (dd, *J* = 13.9, 4.8 Hz, 1H), 3.47 – 3.37 (m, 4H), 3.04 (dd, *J* = 13.9, 8.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 168.7, 140.9, 136.4, 132.5, 130.3, 129.3, 128.6, 128.0, 126.9, 125.7, 121.7, 53.8, 36.0, 34.8. (**GMR-II-015**)



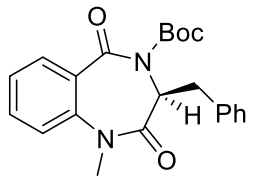
(*S*)-3-Benzyl-1-methyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione[16] (**3-34e**). Procedure adapted from protocol by Jim-min.[19] Under N_2, **3-23** (250 mg, 0.94 mmol, 1.0 equiv) and K_2CO_3 (128 mg, 0.93 mmol) were stirred together at room temperature for one hour in DMF (1 mL). MeI (70 μL, 0.9 mmol, 2.28 g/mL, 1 equiv) was added, and the reaction was stirred overnight. The reaction was quenched by pouring it into ice water, and the mixture was extracted into EtOAc (3 × 15 mL). The organic phase was washed with brine, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude mixture was

purified on a silica gel column (20:1 DCM:EtOH) to afford the product as a tan solid (147.4 mg, 56% yield). mp: 219 – 221 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.54 (td, *J* = 8.3, 1.7 Hz, 1H), 7.34 – 7.17 (m, 7H), 6.60 (s, 1H), 4.01 (dt, *J* = 8.3, 6.0 Hz, 1H), 3.52 – 3.35 (m, 4H), 3.03 (dd, *J* = 14.6, 8.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 168.4, 140.9, 136.2, 132.5, 130.3, 129.3, 128.7, 128.0, 127.0, 125.7, 121.7, 53.6, 36.0, 34.9. $[a]_D^{25} = +243.01$ (c = 0.5, MeOH) (**GMR-II-041**)

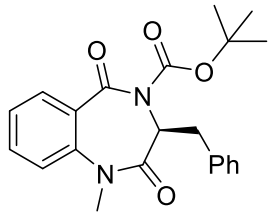


***tert*-Butyl (*S*)-3-isobutyl-1-methyl-2,5-dioxo-1,2,3,5-tetrahydro-4H-benzo[e][1,4]diazepine-4-carboxylate** (**(*S*)-35d**): Prepared from the general procedure above (*Method B*) from (*S*)-3-isobutyl-1-methyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (1.43 g, 5.80 mmol), Boc_2O (4.4 g, 20 mmol), and DMAP (1.18 g, 9.68 mmol). The crude mixture was purified by silica gel column chromatography (1:1 EtOAc:Hex) to afford the product as a tan solid (1.13 g, 53% yield). mp: 219 – 221 °C; Two conformers were observed in the NMR spectra. NMR tabulations are taken from spectra recorded at 0 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.7 Hz, 1H), 7.57 (t, *J* = 7.7 Hz, 1H), 7.29 (q, *J* = 7.5 Hz, 1H), 7.20 (d, *J* = 8.2 Hz, 0.29H), 7.16 (d, *J* = 8.2 Hz, 0.71H), 5.27 (t, *J* = 8.1 Hz, 0.71H), 4.14 (t, *J* = 7.3 Hz, 0.29H), 3.40 (s, 0.87H), 3.38 (s, 2.13H), 1.97 (dt, *J* = 14.0, 6.6 Hz, 0.29H), 1.90 – 1.79 (m, 0.71H), 1.65 – 1.52 (m, 9.71H), 1.47 (dq, *J* = 13.3, 6.7 Hz, 0.87H), 1.16 (t, *J* = 8.1 Hz, 1.42H), 0.83 (d, *J* = 6.6 Hz, 0.87H), 0.79 – 0.74 (m, 5.13H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 165.6, 152.0, 139.9, 133.2, 132.8, 131.6, 130.9, 128.6, 126.0, 125.5, 125.5, 120.8, 120.7, 84.8, 84.5, 59.5, 53.5, 38.3, 35.8, 35.7,

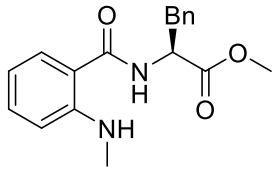
35.1, 27.9, 27.7, 25.7, 24.7, 22.6, 22.3, 22.0. $[a]_D^{25} = -108.99$ (c = 1.353, CH_2Cl_2] (**GMR-I-169**)



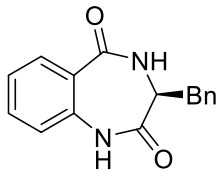
(*S*)- *tert*-Butyl 3-benzyl-1-methyl-2,5-dioxo-1,2,3,5-tetrahydro-4H-benzo[e][1,4]diazepine-4-carboxylate (**(*S*)-3-35e**): Prepared from the general procedure above (*Method B*) from (*S*)-3-benzyl-1-methyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (810 mg, 2.88 mmol), Boc_2O (1.7 g, 7.6 mmol), and DMAP (0.446 g, 3.65 mmol). The crude mixture was purified by silica gel column chromatography (1:1 EtOAc:Hex) to afford the product as a tan solid (0.829 g, 76% yield). mp: 100 – 102 °C; At room temperature the conformers are nearly coalesced in the ^{1}H NMR spectrum, but two conformers were observed in the NMR spectra at 0 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.9 Hz, 0.68H), 7.89 (d, *J* = 9.1 Hz, 0.32H), 7.67 (t, *J* = 8.5 Hz, 0.68H), 7.55 (t, *J* = 8.5, 7.6 Hz, 0.32H), 7.41 (t, *J* = 7.6 Hz, 0.68H), 7.33 – 7.16 (m, 5.04H), 6.95 (d, *J* = 7.0 Hz, 1.28H), 5.54 (dd, *J* = 10.2, 7.4 Hz, 0.68H), 4.39 (dd, *J* = 8.5, 5.5 Hz, 0.32H), 3.67 (dd, *J* = 14.0, 8.5 Hz, .32H), 3.43 (s, 1H), 3.41 (s, 2H), 3.20 (dd, *J* = 14.0, 5.5 Hz, 0.32H), 2.72 (dd, *J* = 13.8, 7.4 Hz, 0.68H), 2.54 (dd, *J* = 13.8, 10.2 Hz, 0.68H), 1.59 (s, 3H), 1.42 (s, 6H). $[a]_D^{25} = -165.22$ (c = 0.115, MeOH) (**GMR-I-168**)



tert-Butyl (*S*)-3-benzyl-1-methyl-2,5-dioxo-1,2,3,5-tetrahydro-4H-benzo[e][1,4]diazepine-4-carboxylate[16] (**3-35e**). Prepared using the general procedure above (*Method B*) from (*S*)-3-benzyl-1-methyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (125 mg, 0.45 mmol), Boc_2O (244 mg, 1.12 mmol), DMAP (66 mg, 0.54 mmol), Et_3N (0.16 mL, 1.1 mmol), and THF (1.5 mL). The crude mixture was purified on a silica gel column (7:3 EtOAc: Hex). The product was obtained as a white crystal (144.3 mg, 85% yield, 94% ee). mp: 100 – 102 °C; % ee measured by chiral HPLC. Two conformers were observed by NMR at room temperature in a 7:3 ratio. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.9 Hz, 0.7H), 7.87 (d, *J* = 6.9 Hz, 0.3H), 7.62 (t, *J* = 7.9 Hz, 0.7H), 7.55 – 7.47 (m, 0.3H), 7.36 (t, *J* = 6.8 Hz, 0.7H), 7.29 – 7.10 (m, 5.3H), 6.92 (d, *J* = 6.8 Hz, 1H), 5.51 (t, *J* = 9.4, 7.7 Hz, 0.7H), 4.44 – 4.31 (m, 0.3H), 3.69 – 3.56 (m, 0.3H), 3.38 (s, 3H), 3.18 (d, *J* = 11.7 Hz, 0.3H), 2.68 (dd, *J* = 13.9, 7.6 Hz, 0.7H), 2.52 (dd, *J* = 13.6, 10.2 Hz, 0.7H), 1.56 (s, 2.7H), 1.41 (s, 6.3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 169.3, 168.3, 165.4, 163.0, 151.3, 139.6, 135.4, 133.2, 132.9, 132.9, 131.7, 131.1, 129.4, 129.4, 129.2, 128.8, 128.6, 127.1, 126.8, 126.8, 125.8, 125.6, 125.5, 121.0, 121.0, 120.9, 84.4, 76.7, 62.1, 56.9, 35.8, 35.3, 35.2, 33.5, 28.0, 27.7. $[a]_D^{25} = -165.22$ (c = 0.5, MeOH) (**GMR-II-044**)

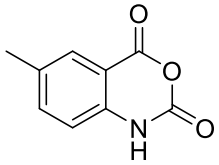


Methyl (2-(methylamino)benzoyl)-L-phenylalaninate (**3-36**). Adapted from protocol by Mackay.[17] *N*-methyl isatoic anhydride (150 mg, 0.762 mmol, 1.0 equiv) and (*S*)-**4-1** (179 mg, 0.815 mmol, 1.07 equiv) were mixed together in pyridine (0.6 mL) and refluxed for 16 hours. The reaction was poured into ice water to precipitate out solid. The solid was extracted into EtOAc (15 mL). The organic extract was collected, dried with $MgSO_4$, concentrated *in vacuo*, and purified on a silica gel column (1:1 EtOAc:Hex) to afford the product as a yellow oil (237.8 mg, 93% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.35 – 7.19 (m, 5H), 7.17 – 7.08 (m, 2H), 6.45 (d, *J* = 7.1 Hz, 1H), 4.99 (dt, *J* = 7.1, 5.8 Hz, 1H), 3.74 (s, 3H), 3.20 (qd, *J* = 13.8, 5.8 Hz, 2H), 2.83 (d, *J* = 3.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 169.1, 150.7, 135.9, 133.1, 129.2, 128.6, 127.4, 127.1, 114.4, 114.1, 111.0, 53.2, 52.3, 37.9, 2.5. $[a]_D^{25} = -24.81$ (c = 0.128, MeOH) (**GMR-II-011**)



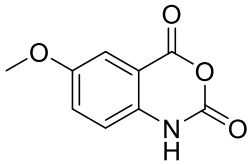
(*S*)-3-Benzyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (**3-38**). *N*-H isatoic anhydride (1.55 g, 9.52 mmol, 1.0 equiv) and 98.5% (*S*)-phenylalanine (1.6 g, 9.5 mmol, 1.0 equiv) were dissolved in H_2O (24 mL) at room temperature and stirred. Et_3N (1.3 mL, 9.5 mmol, 0.7255 g/mL, 1.0 equiv) was added, and the mixture was stirred for 16 hours. The mixture was concentrated *in vacuo*, and the residue was dissolved in AcOH (24 mL)

and refluxed for 45 hours. AcOH was removed *in vacuo*. The mixture was diluted with H_2O (30 mL) and extracted into EtOAc (3 × 15 mL). The combined organic layers were washed with sodium bicarbonate (2 × 15 mL). The organic layer was concentrated *in vacuo*. The product was recrystallized in EtOH/H_2O to afford a white solid, and the enantiomeric excess was observed through optical rotation. (0.87 g, 34% yield, >99% ee). mp: 221 – 225 °C; Two conformers were observed by NMR at room temperature. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.65 (s, 0.2H), 10.40 (s, 0.8H), 8.49 (d, J = 6.4 Hz, 0.8H), 8.28 (d, J = 8.4 Hz, 0.2H), 7.76 – 6.99 (m, 9H), 4.68 (dd, J = 5.1, 2.9 Hz, 0.2H), 3.95 – 3.78 (m, 0.8H), 3.31 – 3.26 (m, 0.2H), 3.22 – 2.98 (m, 1H), 2.89 – 2.73 (m, 0.8H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.2, 171.7, 168.5, 168.1, 139.0, 138.3, 137.8, 137.1, 137.0, 132.6, 132.4, 130.7, 129.7, 129.5, 128.6, 128.5, 126.9, 126.7, 126.7, 124.4, 122.9, 121.3, 121.3, 120.9, 54.2, 52.5, 36.5, 33.7. Spectra matched the literature.[20] $[a]_D^{21} = +227.33$ (c = 0.5, MeOH) (**GMR-II-035**)

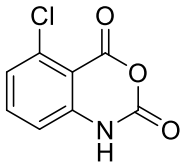


6-Methyl-2H-benzo[d][1,3]oxazine-2,4(1H)-dione (**3-46a**). Prepared using the general procedure above (*Method D*) from 2-amino-5-methylbenzoic acid (499 mg, 2.97 mmol), triphosgene (0.3 g, 1.0 mmol), and THF (12 mL). The obtained product is a tan solid (261 mg, 88% yield). mp: 269 – 271 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.59 (s, 1H), 7.65 (d, J = 1.1 Hz, 1H), 7.50 (ddd, J = 8.6, 21.8 1H), 7.00 (d, J = 8.6 Hz, 1H), 2.28 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 160.3, 147.5, 139.6, 138.3, 133.4, 128.7, 115.7, 110.3,

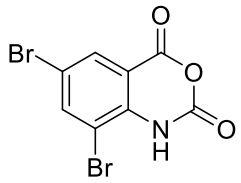
20.4. Spectra matched the literature.[21] HRMS (ESI) calculated for $C_9H_7NO_3$ $[M-H]^-$: 176.0353, exact mass found 176.0351 (**GMR-I-165**)



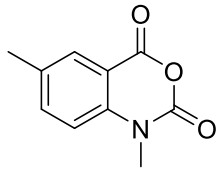
6-Methoxy-2H-benzo[d][1,3]oxazine-2,4(1H)-dione (**3-46b**). Prepared using the general procedure above (*Method D*) from 97% 2-amino-5-methoxybenzoic acid (3.64 g, 21.1 mmol), triphosgene (2.2 g, 7.4 mmol), and THF (87 mL). The obtained product was a yellow solid (3.92 g, 97% yield). mp: >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.58 (s, 1H), 7.35 (dd, J = 8.9, 2.9 Hz, 1H), 7.30 (d, J = 2.9 Hz, 1H), 7.08 (d, J = 8.9 Hz, 1H), 3.77 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.2, 155.5, 147.3, 135.9, 126.1, 117.3, 111.1, 110.2, 56.1. Spectra matched the literature.[22] (**GMR-III-014**)



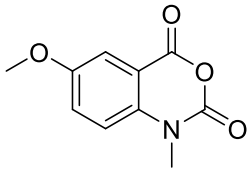
5-Chloro-2H-benzo[d][1,3]oxazine-2,4(1H)-dione (**3-46d**). Prepared using the general procedure above (*Method D*) from 2-amino-6-chlorobenzoic acid (0.515 g, 3 mmol), triphosgene (0.303 g, 1.02 mmol), and THF (12 mL). The obtained product was a white solid (0.45 g, 75% yield). mp: 273 -276 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 11.82 (s, 1H), 7.82 (d, J = 2.3 Hz, 1H), 7.73 (dd, J = 8.7, 2.4 Hz, 1H), 7.12 (d, J = 8.7 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d6) δ 159.3, 147.1, 140.6, 137.0, 128.0, 127.5, 117.8, 112.4. Spectra matches literature.[23] (**GMR-I-173**)



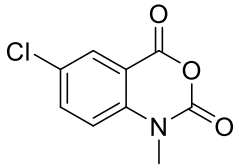
6,8-Dibromo-2H-benzo[d][1,3]oxazine-2,4(1H)-dione[24] (**3-46g**). Prepared using the general procedure above (*Method D*) from 2-amino-3,5-dibromobenzoic acid (2.00 g, 6.78 mmol), triphosgene (0.68 g, 2.1 mmol), and THF (81 mL). The obtained product was a white solid (1.47 g, 68% yield). mp: 172 -173 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 11.22 (s, 1H), 8.22 (d, *J* = 2.2 Hz, 1H), 7.98 (d, *J* = 2.2 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d6) δ 158.6, 146.6, 141.8, 139.5, 130.7, 115.1, 114.8, 109.7. Known compound[24] (**GMR-I-181**)



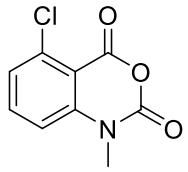
1,6-Dimethyl-2H-benzo[d][1,3]oxazine-2,4(1H)-dione (**3-47a**). Prepared using the general procedure above (*Method E*) from **3-29a** (500 mg, 2.82 mmol), 60% NaH (147 mg, 3.67 mmol), MeI (228 mL, 3.67 mmol, 2.28 g/mL), and DMF (7.2 mL). The obtained product is a yellow solid (368.4 mg, 68% yield). mp: 170 – 171 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 1.5 Hz, 1H), 7.64 – 7.46 (m, 1H), 7.06 (d, *J* = 8.5 Hz, 1H), 3.53 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5, 147.9, 139.8, 138.2, 134.0, 130.3, 113.7, 111.3, 31.7, 20.3. Spectra matched the literature.[25] (**GMR-I-179**)



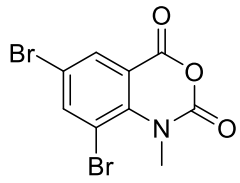
6-Methoxy-1-methyl-2H-benzo[d][1,3]oxazine-2,4(1H)-dione (**3-47b**). Prepared using the general procedure above (*Method E*) from **3-46b** (1.58 g, 8.16 mmol), 60% NaH (424 mg, 10.6 mmol), MeI (0.66 mL, 11 mmol), and DMF (14.7 mL). The obtained product was a yellow solid (1.34 g, 79% yield). mp: 234 – 237 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.48 – 7.32 (m, 3H), 3.80 (s, 3H), 3.41 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.34, 155.60, 148.00, 136.77, 125.47, 117.03, 112.60, 111.22, 56.25, 32.19. Spectra matched the literature.[25] (**GMR-III-091**)



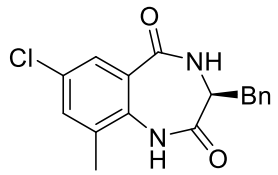
6-Chloro-1-methyl-2H-benzo[d][1,3]oxazine-2,4(1H)-dione (**3-47c**). Prepared using the general procedure above (*Method E*) from 6-chloro-2H-benzo[d][1,3]oxazine-2,4(1H)-dione (4 g, 20 mmol), 60% NaH (1.053 g, 26.32 mmol), MeI (1.64 mL, 26.3 mmol), and DMF (36.4 mL). The obtained product was a yellow solid (3.43 g, 80% yield). mp: 200 – 201 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, J = 2.7 Hz, 1H), 7.86 (dd, J = 8.9, 2.6 Hz, 1H), 7.44 (d, J = 8.9 Hz, 1H), 3.42 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.4, 147.8, 141.5, 137.0, 128.3, 128.0, 117.5, 113.7, 32.3. Known compound[23] (**GMR-III-085**)



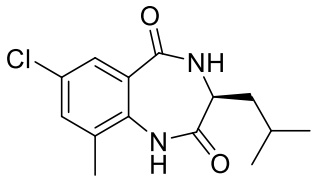
5-Chloro-1-methyl-2H-benzo[d][1,3]oxazine-2,4(1H)-dione (**3-47d**). Prepared using the general procedure above (*Method E*) from **3-29d** (1 g, 5 mmol), 60% NaH (242 mg, 6.07 mmol), MeI (0.38 mL, 6.1 mmol, 2.28 g/mL), and DMF (9 mL). The obtained product was a yellow solid (513 mg, 51% yield). mp: 219 – 220 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 7.91 (d, *J* = 2.5 Hz, 1H), 7.86 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.44 (d, *J* = 8.9 Hz, 1H), 3.42 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d6) δ 158.4, 147.8, 141.5, 137.0, 128.3, 128.0, 117.5, 113.7, 32.3. Spectra matched the literature.[23] (**GMR-I-182**)



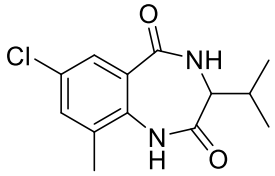
6,8-Dibromo-1-methyl-2H-benzo[d][1,3]oxazine-2,4(1H)-dione (**3-47g**). Prepared using the general procedure above (*Method E*) from 6,8-dibromo-2H-benzo[d][1,3]oxazine-2,4(1H)-dione (0.75 g, 2.3 mmol), 60% NaH (0.122 mg, 3.05 mmol), MeI (0.19 mL, 3.05 mmol), and DMF (4.2 mL). The obtained product was a white solid (256 mg, 33% yield). mp: 140 -142 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 – 7.77 (m, 1H), 6.77 (s, 1H), 3.79 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.62, 147.32, 139.25, 132.80, 112.19, 111.09, 107.24, 105.36, 52.74. (**GMR-II-113**)



(*S*)-3-Benzyl-7-chloro-9-methyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (**3-49a**). 6-chloro-8-methyl-2H-benzo[d][1,3]oxazine-2,4(1H)-dione (1.5 g, 7.5 mmol, 1.0 equiv) and (*S*)-phenylalanine methyl ester (1.6 g, 7.5 mmol, 1.0 equiv) were mixed together in pyridine and refluxed for 16 hours. The reaction was cooled and poured into iced water. The mixture was extracted with chloroform. The organic layer was collected, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude mixture was dissolved in AcOH (18.7 mL) and refluxed for 25 hours. The reaction was cooled and poured into cold water to precipitate the crude product. Filtrate was extracted into EtOAc (25 mL). The organic layer was washed with brine (2 × 15 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified on a silica gel column (1:1 EtOAc:Hex) to afford the product as an orange solid (0.325 g, 15% yield). mp: 177 – 179 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.75 (s, 1H), 8.68 (d, J = 6.2 Hz, 1H), 7.46 (d, J = 1.9 Hz, 1H), 7.40 (s, 1H), 7.33 – 7.07 (m, 5H), 3.93 – 3.81 (m, 1H), 3.13 – 3.04 (m, 1H), 2.90 – 2.81 (m, 1H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.3, 167.3, 138.2, 134.3, 133.4, 133.1, 130.2, 129.7, 128.8, 128.6, 127.2, 126.7, 53.6, 33.4, 18.3. HRMS (ESI) calculated for $C_{17}H_{15}ClN_2O_2$ $[M+H]^+$: 315.0895, exact mass found 315.0903; $[a]_D^{25} = +400.00$ (c = 0.128, MeOH) (**GMR-II-090**)

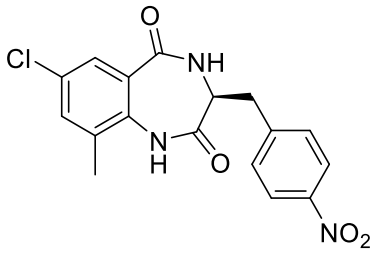


(*S*)-7-Chloro-3-isobutyl-9-methyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (**3-49b**). Prepared using the general procedure above (*Method F*) from (*S*)-leucine (0.124 g, 0.945 mmol), 6-chloro-8-methyl-2H-benzo[d][1,3]oxazine-2,4(1H)-dione (0.2 g, 0.9 mmol), Et_3N (0.145 mL, 1.04 mmol, 0.7255 g/mL), and AcOH (2.5 mL). The crude mixture was purified on a silica gel column to afford the product as a tan solid (0.14 g, 50% yield). mp: 183 – 184 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.14 (dd, *J* = 8.0, 1.3 Hz, 1H), 5.99 (d, *J* = 7.6 Hz, 1H), 3.84 – 3.76 (m, 1H), 3.36 (s, 3H), 1.85 – 1.71 (m, 2H), 1.68 – 1.59 (m, 1H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.85 (d, *J* = 6.3 Hz, 3H). HRMS (ESI) calculated for $C_{14}H_{17}ClN_2O_2$ $[M+H]^+$: 281.1051, exact mass found 281.1056; $[a]_D^{25} = -264.13$ (c = 0.092, MeOH) (**GMR-II-106**)

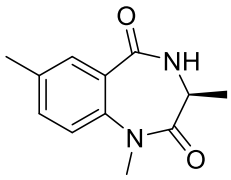


(*R/S*)-7-Chloro-3-isopropyl-9-methyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (**3-49c**). Prepared using the general procedure above (*Method F*) from (*R/S*)-valine (0.111 g, 0.945 mmol), 6-chloro-8-methyl-2H-benzo[d][1,3]oxazine-2,4(1H)-dione (0.20 g, 0.95 mmol), Et_3N (0.145 mL, 1.04 mmol, 0.7255 g/mL), and AcOH (2.5 mL). The crude mixture was purified on a silica gel column (1:1 EtOAc:Hex) to afford the product as a tan solid (0.012 g, 5% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.14 (dd, *J* = 8.1, 1.2 Hz, 1H), 6.52 (d, *J* = 7.6 Hz, 1H), 3.41 (t, *J* = 8.4 Hz,

1H), 3.36 (s, 3H), 2.30 (ddt, *J* = 13.3, 8.5, 6.8 Hz, 1H), 1.07 (d, *J* = 6.8 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 166.0, 142.5, 133.7, 131.5, 128.1, 120.2, 109.9, 57.8, 35.7, 26.9, 20.2, 18.4. HRMS (ESI) calculated for $C_{13}H_{15}ClN_2O_2$ $[M+H]^+$: 267.0895, exact mass found 267.0899 (**GMR-II-108**)

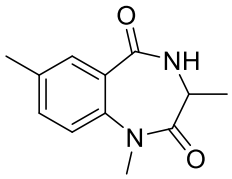


(*S*)-7-Chloro-9-methyl-3-(4-nitrobenzyl)-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (**3-49d**). Prepared using the general procedure above (*Method F*) from (S)-2-amino-3-(4-nitrophenyl)propanoic acid (0.216 g, 0.945 mmol), 6-chloro-8-methyl-2H-benzo[d][1,3]oxazine-2,4(1H)-dione (0.20 g, 0.95 mmol), Et_3N (0.145 mL, 1.04 mmol, 0.7255 g/mL), and AcOH (2.5 mL). The crude mixture was purified on a silica gel column (1:1 EtOAc:Hex) to afford the product as a yellow solid (23.5 mg, 7% yield). mp: 270 – 275 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.14 – 8.09 (m, 2H), 7.54 – 7.47 (m, 2H), 7.37 (dd, *J* = 11.7, 8.2 Hz, 2H), 4.18 (dd, *J* = 8.7, 6.0 Hz, 1H), 3.40 – 3.33 (m, 4H), 3.12 (dd, *J* = 14.5, 8.7 Hz, 1H). HRMS (ESI) calculated for $C_{17}H_{14}ClN_3O_4$ $[M+H]^+$: 360.0746, exact mass found 360.0753; $[a]_D^{25} = +87.30$ (c = 0.063, MeOH) (**GMR-II-109**)

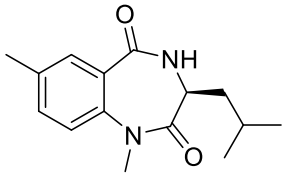


(*S*)-1,3,7-Trimethyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione ((S)-**3-50a**). Prepared according to the general procedure above (*Method A*) from **3-47a** (303.0 mg,

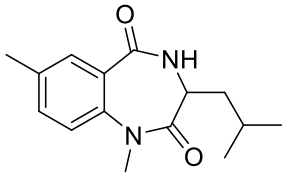
1.58 mmol), (*S*)-alanine (142.18 mg, 1.58 mmol), and AcOH (3.17 mL). The crude product was triturated in Et_2O to afford the product as a white solid. The product was recrystallized in toluene. The enantiomeric enrichment was observed by optical rotation. (209.9 mg, 65% yield, >99% ee). mp: 181 – 184 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.32 (d, *J* = 8.3 Hz, 1H), 7.09 (d, *J* = 8.3 Hz, 1H), 6.79 (s, 1H), 3.87 (q, *J* = 6.8, 5.4 Hz, 1H), 3.37 (s, Hz, 3H), 2.37 (s, 3H), 1.45 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 168.8, 138.7, 135.6, 133.2, 130.2, 127.8, 121.5, 48.0, 35.8, 20.6, 14.4; HRMS (ESI) calculated for $C_{12}H_{14}N_2O_2$ $[M+Na]^+$: 241.0947, exact mass found 241.0943; $[a]_D^{23} = +367.67$ (c = 0.5, MeOH) (**GMR-II-191**)



(*R/S*)-1,3,7-Trimethyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione ((*R/S*)-**3-50a**). Prepared according to the general procedure above (*Method A*) from **3-47a** (215 mg, 1.12 mmol), (*R/S*)-alanine (100.19 mg, 1.12 mmol), and AcOH (2 mL). The crude product was triturated in Et_2O to afford a white solid product (184.6 mg, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 1.7 Hz, 1H), 7.35 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 6.85 (s, Hz, 1H), 3.90 (q, *J* = 6.7 Hz, 1H), 3.39 (s, 3H), 2.39 (s, 3H), 1.48 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 171.2, 141.2, 138.1, 135.7, 132.7, 130.2, 124.0, 50.5, 38.3, 23.1, 16.9. (**GMR-II-164**)

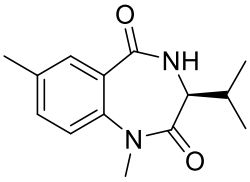


(*S*)-3-Isobutyl-1,7-dimethyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione ((S)-**3-50b**). Prepared according to the general procedure above (*Method A*) from **3-47a** (575 mg, 3.01 mmol), (*S*)-leucine (394.51 mg, 3.01 mmol), and AcOH (6 mL). The crude product was triturated in Et_2O to afford the product as a white solid. The product was recrystallized in toluene. The enantiomeric enrichment was observed by optical rotation and chiral HPLC. (399.8 mg, 51% yield, >99% ee). mp: 176 – 178°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 1.9 Hz, 1H), 7.33 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.10 (d, *J* = 8.1 Hz, 1H), 6.64 (d, *J* = 5.8 Hz, 1H), 3.73 (dt, *J* = 8.4, 5.8 Hz, 1H), 3.36 (s, 3H), 2.38 (s, 3H), 1.92 – 1.60 (m, 3H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.83 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 168.8, 138.7, 135.6, 133.3, 130.2, 127.8, 121.6, 50.5, 37.5, 35.8, 24.3, 22.9, 21.9, 20.6; $[a]_D^{23} = +282.93$ (c = 0.5, MeOH) (**GMR-II-161**)

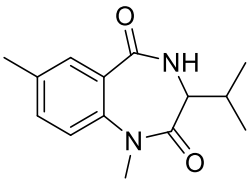


(*R/S*)-3-Isobutyl-1,7-dimethyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione ((*R/S*)-**3-50b**). Prepared according to the general procedure above (*Method A*) from **3-47a** (230 mg, 1.2 mmol), (*R/S*)-leucine (157.8 mg, 1.2 mmol), and AcOH (2.4 mL). The crude product was triturated in Et_2O to afford solid product (263 mg, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 1.8 Hz, 1H), 7.34 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.11 (d, *J* = 7.9 Hz, 1H), 6.55 (d, *J* = 5.9 Hz, 1H), 3.73 (dt, *J* = 8.4, 5.9 Hz, 1H), 3.36 (s, 3H), 2.38 (s,

3H), 1.91 – 1.58 (m, 3H), 0.90 (d, *J* = 6.4 Hz, 3H), 0.83 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 168.8, 138.7, 135.7, 133.3, 130.2, 127.8, 121.6, 50.5, 37.5, 35.8, 24.3, 22.9, 21.9, 20.6. (**GMR-II-165**)

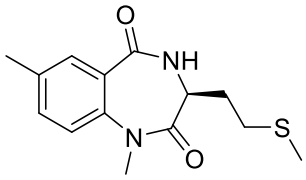


(*S*)-3-Isopropyl-1,7-dimethyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione ((S)-**3-50c**). Prepared according to the general procedure above (*Method A*) from **3-47a** (350 mg, 1.8 mmol), (*S*)-valine (215.95 mg, 1.8 mmol), and AcOH (3.6 mL). The crude product was triturated in Et_2O to afford the product as a white solid. The product was recrystallized in toluene. The enantiomeric enrichment was observed by optical rotation and chiral HPLC. (14.3 mg, 3% yield, >99% ee). mp: 215 – 217°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 1.6 Hz, 1H), 7.33 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.11 (d, *J* = 8.3 Hz, 1H), 6.66 (s, 3H), 3.41 – 3.33 (m, 4H), 2.41 – 2.26 (m, 4H), 1.07 (d, *J* = 6.7 Hz, 3H), 1.01 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 168.9, 138.9, 135.7, 133.2, 130.2, 127.9, 121.7, 57.9, 35.7, 27.05, 20.6, 20.3, 18.4; HRMS (ESI) calculated for $C_{14}H_{18}N_2O_2$ $[M+H]^+$: 247.1441, exact mass found 247.1437; $[a]_D^{23} = +222.6$ (c = 0.09, MeOH) (**GMR-III-029**)

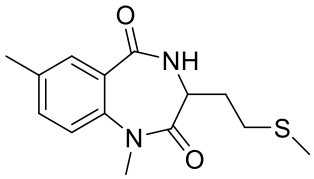


(*R/S*)-3-Isopropyl-1,7-dimethyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione ((*R/S*)-**3-50c**). Prepared according to the general procedure above (*Method A*) from **3-47a**

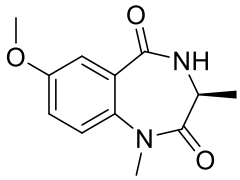
(230 mg, 1.2 mmol), (*R/S*)-valine (140.94 mg, 1.2 mmol), and AcOH (2.4 mL). The crude product was triturated in Et_2O to afford a white solid product (138.5 mg, 60% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.37 – 7.27 (m, 1H), 7.11 (d, *J* = 8.3 Hz, 1H), 6.64 (d, *J* = 27.7 Hz, 1H), 3.42 – 3.31 (m, 4H), 2.41 – 2.25 (m, 4H), 1.06 (d, *J* = 6.8 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 168.8, 138.9, 135.7, 133.2, 130.2, 127.9, 121.7, 57.9, 35.7, 27.0, 20.6, 20.3, 18.4; (**GMR-II-166**)



(*S*)-1,7-Dimethyl-3-(2-(methylthio)ethyl)-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione ((S)-**3-50d**). Prepared according to the general procedure above (*Method A*) from **3-47a** (298 mg, 1.56 mmol), (*S*)-methionine (235 mg, 1.56 mmol), and AcOH (3.1 mL). The crude product was triturated in Et_2O to afford the product as a white solid. The product was recrystallized in toluene. The enantiomeric enrichment was observed by optical rotation (91.1 mg, 27% yield, >99% ee). mp: 159 - 160°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, 2.1 Hz, 1H), 7.34 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.11 (d, *J* = 8.3 Hz, 1H), 6.79 (s, 1H), 3.95 (dd, *J* = 7.1, 6.7 Hz, 1H), 3.37 (s, 3H), 2.65 (t, *J* = 6.7 Hz, 2H), 2.38 (s, 3H), 2.33 (dt, *J* = 14.1, 7.1 Hz, 1H), 2.12 – 1.98 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 165.7, 138.6, 135.8, 133.4, 130.3, 127.7, 121.6, 51.0, 35.8, 30.1, 28.1, 20.6, 15.3; $[a]_D^{23} = +219.8$ (c = 0.129, MeOH) (**GMR-II-190**)

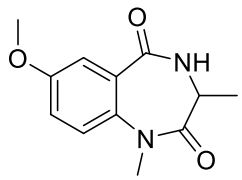


(*R/S*)- 1,7-Dimethyl-3-(2-(methylthio)ethyl)-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione ((*R/S*)-**3-50d**). Prepared according to the general procedure above (*Method A*) from **3-47a** (230 mg, 1.2 mmol), (*R/S*)-methionine (179.5 mg, 1.2 mmol), and AcOH (2.4 mL). The crude product was triturated in Et_2O to afford a white solid product (265.7 mg, >99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 1.8 Hz, 1H), 7.36 – 7.29 (dd, *J* = 8.3, 1.8 Hz, 2H), 7.11 (d, *J* = 8.3 Hz, 1H), 3.95 (q, *J* = 6.4 Hz, 1H), 3.37 (s, 3H), 2.64 (t, *J* = 6.4 Hz, 2H), 2.40 – 2.26 (m, 4H), 2.09 – 1.96 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 169.2, 138.6, 135.8, 133.3, 130.3, 127.7, 121.6, 51.0, 35.8, 30.1, 28.0, 20.6, 15.3. (**GMR-II-163**)

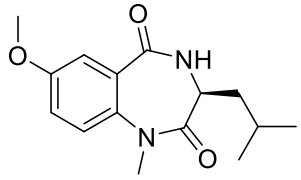


(*S*)-7-Methoxy-1,3-dimethyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione ((*S*)-**3-51a**) Prepared according to the general procedure above (*Method A*) from **3-47b** (325 mg, 1.6 mmol), (*S*)-alanine (141.16 mg, 1.6 mmol), and AcOH (3 mL). The crude product was triturated in Et_2O to afford the product as a white solid. The product was recrystallized in toluene. The enantiomeric enrichment was observed by chiral HPLC (223.7 mg, 60.8% yield, >78% ee). mp: 174 - 176°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 2.7 Hz, 1H), 7.12 (d, *J* = 9.0 Hz, 1H), 7.06 (dd, *J* = 9.0, 2.7 Hz, 1H), 3.95 – 3.79 (m, 4H), 3.35 (s, 3H), 1.45 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9,

168.6, 156.9, 134.3, 129.0, 123.2, 119.9, 112.7, 55.7, 48.1, 35.9, 14.4; $[a]_D^{25}$ = +257.26 (c = 0.124, MeOH) (**GMR-III-026**)

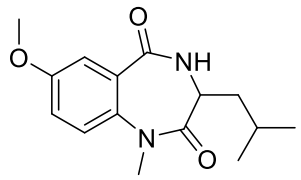


(*R/S*)-7-Methoxy-1,3-dimethyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione ((*R/S*)-3-51a). Prepared according to the general procedure above (*Method A*) from **3-47b** (100 mg, 0.5 mmol), (*R/S*)-alanine (44.72 mg, 0.5 mmol), and AcOH (1 mL). The crude product was purified by silica gel column chromatography (7:3 EtOAc:Hex) to afford a white solid product (77.9 mg, 67% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 2.7 Hz, 1H), 7.12 (d, *J* = 9.0 Hz, 1H), 7.06 (dd, *J* = 9.0, 2.7 Hz, 1H), 3.95 – 3.79 (m, 4H), 3.35 (s, 3H), 1.45 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 168.6, 156.9, 134.3, 129.0, 123.2, 119.9, 112.7, 55.7, 48.1, 35.9, 14.4; HRMS (ESI) calculated for $C_{12}H_{14}N_2O_3$ $[M+H]^+$: 235.1083, exact mass found 235.1070; (**GMR-III-018**)

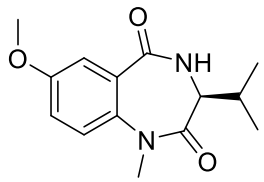


(*S*)-3-Isobutyl-7-methoxy-1-methyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione ((*S*)-3-51b) Prepared according to the general procedure above (*Method A*) from **3-47b** (275 mg, 1.3 mmol), (*S*)-leucine (175.86 mg, 1.3 mmol), and AcOH (3 mL). The crude product was purified on a silica gel column to afford the product as a white solid. The product was recrystallized in toluene. The enantiomeric enrichment was observed by chiral HPLC (14.5 mg, 4% yield, 99% ee). mp: 173 - 174°C; ^{1}H NMR (400 MHz,

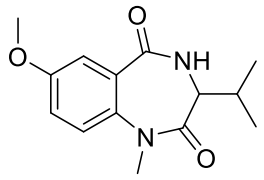
$CDCl_3$) δ 7.32 (d, *J* = 3.0 Hz, 1H), 7.13 (d, *J* = 9.0 Hz, 1H), 7.07 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.97 (d, *J* = 5.8 Hz, 1H), 3.72 (dt, *J* = 8.4, 5.8 Hz, 1H), 1.90 – 1.59 (m, 3H), 0.89 (dd, *J* = 6.4, 2.5 Hz, 3H), 0.82 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 168.8, 156.9, 134.4, 129.1, 123.2, 119.8, 112.7, 55.6, 50.6, 37.3, 35.8, 24.3, 22.9, 21.9; HRMS (ESI) calculated for $C_{15}H_{20}N2O_3$ $[M+H]^+$: 277.1552, exact mass found 277.1542; $[a]_D^{25} = +91.53$ (c = 0.5, MeOH) (**GMR-III-027**)



(*R/S*)-3-Isobutyl-7-methoxy-1-methyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione ((*R/S*)-**3-51b).** Prepared according to the general procedure above (*Method A*) from **3-47b** (100 mg, 0.5 mmol), (*R/S*)-leucine (65.85 mg, 0.5 mmol), and AcOH (5 mL). The crude product was purified by silica gel column chromatography (7:3 EtOAc:Hex) to afford a white solid product (110.3 mg, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.42 (m, 1H), 7.36 (d, *J* = 1.9 Hz, 1H), 7.24 – 7.05 (m, 1H), 3.88 (s, 3H), 3.76 (s, 1H), 3.38 (s, 3H), 1.96 – 1.66 (m, 3H), 1.02 – 0.76 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 168.8, 156.9, 134.4, 129.1, 123.2, 119.8, 112.7, 55.6, 50.6, 37.3, 35.8, 24.3, 22.9, 21.9; HRMS (ESI) calculated for $C_{15}H_{20}N2O_3$ $[M+H]^+$: 277.1552, exact mass found 277.1538 (**GMR-III-019**)

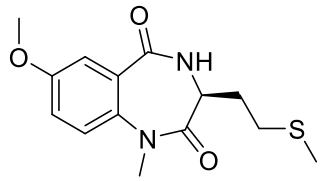


(S)-3-Isopropyl-7-methoxy-1-methyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione ((*S*)-**3-51c**) Prepared according to the general procedure above (*Method A*) from **3-47b** (540 mg, 2.6 mmol), (*S*)-valine (308.43 mg, 2.6 mmol), and AcOH (5 mL). The crude product was purified on a silica gel column to afford the product as a white solid. The product was recrystallized in toluene. The enantiomeric enrichment was observed by chiral HPLC (32.9 mg, 5% yield, >99% ee). mp: 154 – 157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 1H), 7.18 (d, *J* = 8.8 Hz, 1H), 7.08 (d, *J* = 8.8 Hz, 1H), 3.88 (s, 3H), 3.37 (s, 4H), 2.38 (dq, *J* = 13.5, 6.6 Hz, 1H), 1.16 – 0.99 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 168.7, 156.9, 134.5, 129.3, 123.4, 119.7, 112.6, 58.1, 55.6, 35.7, 27.0, 20.3, 18.5; HRMS (ESI) calculated for $C_{14}H_{18}N_2O_3$ $[M+H]^+$: 263.1396, exact mass found 263.1389; $[a]_D^{25} = +264.44$ (c = 0.09, MeOH) (**GMR-III-028**)

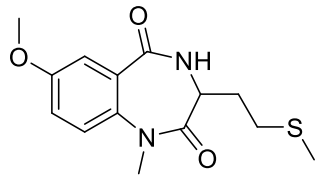


(*R/S*)-3-Isopropyl-7-methoxy-1-methyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione ((*R/S*)-**3-51c).** Prepared according to the general procedure above (*Method A*) from **3-47b** (100 mg, 0.5 mmol), (*R/S*)-valine (58.82 mg, 0.5 mmol), and AcOH (1 mL). The crude product was purified by silica gel column chromatography (7:3 EtOAc:Hex) to afford a white solid product (53.8 mg, 41% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 1H), 7.18 (d, *J* = 8.8 Hz, 1H), 7.08 (d, *J* = 8.8 Hz, 1H), 3.88 (s, 3H), 3.37 (s, 4H), 2.38

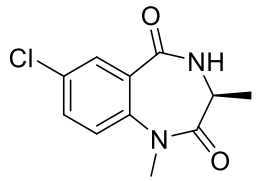
(dq, *J* = 13.5, 6.6 Hz, 1H), 1.16 – 0.99 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 168.7, 156.9, 134.5, 129.3, 123.4, 119.7, 112.6, 58.1, 55.6, 35.7, 27.0, 20.3, 18.5. (**GMR-III-020**)



(S)-7-Methoxy-1-methyl-3-(2-(methylthio)ethyl)-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione ((*S*)-**3-51c**) Prepared according to the general procedure above (*Method A*) from **3-47b** (360 mg, 1.7 mmol), (*S*)-methionine (261.9 mg, 1.7 mmol), and AcOH (3 mL). The crude product was purified on a silica gel column to afford the product as a white solid. The product was recrystallized in toluene. The enantiomeric enrichment was observed by chiral HPLC (168.8 mg, 33% yield, >99% ee). mp: 142 – 144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 2.8 Hz, 1H), 7.15 (d, *J* = 8.9 Hz, 1H), 7.09 (dd, *J* = 8.9, 2.8 Hz, 1H), 3.96 (q, *J* = 6.5 Hz, 1H), 3.85 (s, 3H), 3.36 (s, 3H), 2.65 (h, *J* = 7.8, 7.3 Hz, 2H), 2.34 (dq, *J* = 14.0, 7.3 Hz, 1H), 2.11 – 1.96 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0, 134.2, 128.8, 124.7, 123.3, 120.0, 112.8, 109.9, 55.7, 51.0, 35.9, 30.1, 28.1, 15.3; HRMS (ESI) calculated for $C_{14}H_{18}N_2O_3S$ $[M+H]^+$: 295.1116, exact mass found 295.1128; $[a]_D^{25} = +198.33$ (c = 0.12, MeOH) (**GMR-III-025**)

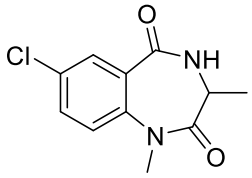


(*R/S*)-7-Methoxy-1-methyl-3-(2-(methylthio)ethyl)-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione ((*R/S*)-**3-51c).** Prepared according to the general procedure above (*Method A*) from **3-47b** (100 mg, 0.5 mmol), (*R/S*)-methionine (74.9 mg, 0.5 mmol), and AcOH (1 mL). The crude product was purified by silica gel column chromatography (7:3 EtOAc:Hex) to afford the product as a white solid (88 mg, 60% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 2.8 Hz, 1H), 7.15 (d, *J* = 8.9 Hz, 1H), 7.09 (dd, *J* = 8.9, 2.8 Hz, 1H), 3.96 (q, *J* = 6.5 Hz, 1H), 3.85 (s, 3H), 3.36 (s, 3H) 2.71 – 2.56 (m, 2H), 2.34 (dq, *J* = 14.0, 6.5 Hz, 1H), 2.11 – 1.96 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0, 134.2, 128.8, 124.7, 123.3, 120.0, 112.8, 109.9, 55.7, 51.0, 35.9, 30.1, 28.1, 15.3. (**GMR-III-017**)



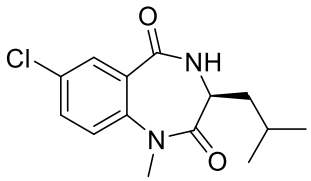
(S)-7-Chloro-1,3-dimethyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione ((*S*)-**3-52a**) Prepared according to the general procedure above (*Method A*) from **3-47c** (1 g, 4.7 mmol), (*S*)-alanine (425.3 mg, 4.7 mmol), and AcOH (10 mL). The crude product was triturated in Et_2O to afford the product as a white solid. The product was recrystallized in toluene. The enantiomeric enrichment was observed by chiral HPLC (487.8 mg, 51% yield, 89% ee). mp: 181 – 186 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 2.6 Hz, 1H), 7.48 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.30 (d, *J* = 5.4 Hz, 1H), 7.15 (d, *J* = 8.8 Hz, 1H),

3.86 (qd, J = 6.7, 5.4 Hz, 1H), 3.37 (s, 3H), 1.47 (d, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 167.6, 139.5, 132.5, 131.3, 129.9, 129.4, 123.1, 48.1, 35.9, 14.3; HRMS (ESI) calculated for $C_{11}H_{11}ClN_2O_2$ $[M+H]^+$: 239.0582, exact mass found 239.0579; $[a]_D^{25} = +360.78$ (c = 0.5, MeOH) (**GMR-III-089**)



(*R/S*)-7-Chloro-1,3-dimethyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione

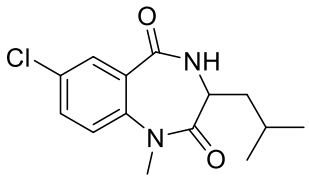
((*R/S*)-**3-52a).** Prepared according to the general procedure above (*Method A*) from **3-47c** (154.2 mg, 0.7 mmol), (*R/S*)-alanine (64.9 mg, 0.7 mmol), and AcOH (1.5 mL). The crude product was purified by silica gel column chromatography (7:3 EtOAc:Hex) to afford a tan solid product. (mass lost by spilling) (17.3 mg, 9.9% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 2.3 Hz, 1H), 7.48 (dd, J = 8.7, 2.3 Hz, 1H), 7.15 (d, J = 8.7 Hz, 1H), 7.12 – 6.96 (m, 1H), 3.94 – 3.78 (m, 1H), 3.37 (s, 2H), 2.14 (s, 3H), 1.46 (d, J = 6.7 Hz, 3H)**.** ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 167.4, 139.5, 132.5, 131.3, 129.9, 129.4, 123.1, 48.1, 35.8, 14.4. (**GMR-II-170**)



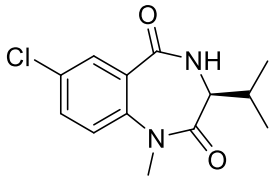
(S)-7-Chloro-3-isobutyl-1-methyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione

((*S*)-**3-52b**) Prepared according to the general procedure above (*Method A*) from **3-47c** (384.2 mg, 1.8 mmol), (*S*)-leucine (240.57 mg, 1.8 mmol), and AcOH (3.6 mL). The crude product was triturated in Et_2O to afford the product as a white solid. The product

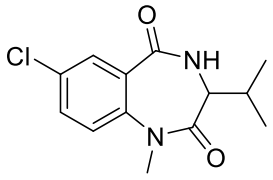
was recrystallized in toluene. The enantiomeric enrichment was observed by optical rotation. (367.5 mg, 72% yield, >99% ee). mp: 207 – 208 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 2.6 Hz, 1H), 7.50 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.17 (d, *J* = 8.8 Hz, 1H), 7.05 (d, *J* = 6.0 Hz, 1H), 3.71 (dt, *J* = 7.8, 6.0 Hz, 1H), 3.37 (s, 3H), 1.94 – 1.50 (m, 2H), 0.93 (d, *J* = 6.4 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$)) δ 170.2, 167.5, 139.6, 132.5, 131.3, 129.9, 129.4, 123.1, 50.5, 37.4, 35.9, 24.3, 22.9, 21.8; $[a]_D^{23} = +307.4$ (c = 0.5, MeOH) (**GMR-II-171**)



(*R/S*)-7-Chloro-3-isobutyl-1-methyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione ((*R/S*)-**3-52b).** Prepared according to the general procedure above (*Method A*) from **3-47c** (198.1 mg, 0.9 mmol), (*R/S*)-leucine (122.8 mg, 0.9 mmol), and AcOH (2 mL). The crude product was purified by silica gel column chromatography (7:3 EtOAc:Hex) to afford the product as a white solid. (146 mg, 56% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 2.6 Hz, 1H), 7.50 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.17 (d, *J* = 8.7 Hz, 1H), 6.69 (d, *J* = 5.6 Hz, 1H), 3.72 (dt, *J* = 8.3, 5.6 Hz, 1H), 3.37 (s, 3H), 1.94 – 1.58 (m, 2H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.84 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 167.3, 139.6, 132.5, 131.3, 129.9, 129.4, 123.2, 50.5, 37.5, 35.9, 24.3, 22.8, 21.9; (**GMR-III-111**)

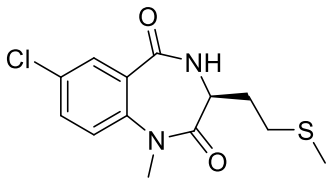


(S)-7-Chloro-3-isopropyl-1-methyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione ((*S*)-**3-52c**) Prepared according to the general procedure above (*Method A*) from **3-47c** (1.6292 g, 7.7 mmol), (*S*)-valine (911.1 mg, 7.7 mmol), and AcOH (15.5 mL). Crude product purified on a silica gel column to afford the product as a white solid. The product was recrystallized in toluene. The enantiomeric enrichment was observed by chiral HPLC (158 mg, 8% yield, 98% ee). mp: 220 – 225 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 2.6 Hz, 1H), 7.49 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.17 (d, *J* = 8.7 Hz, 1H), 7.06 (d, *J* = 5.8 Hz, 1H), 3.44 – 3.28 (m, 4H), 2.45 – 2.26 (m, 1H), 1.08 (d, *J* = 6.5 Hz, 3H), 1.02 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$)) δ 169.4, 167.6, 139.7, 132.4, 131.3, 129.9, 129.6, 123.3, 57.9, 35.7, 27.0, 20.3, 18.4; HRMS (ESI) calculated for $C_{13}H_{15}ClN_2O_2$ $[M+H]^+$: 267.0900, exact mass found 267.0917; $[a]_D^{25} = +225.94$ (c = 0.5, MeOH) (**GMR-III-033**)

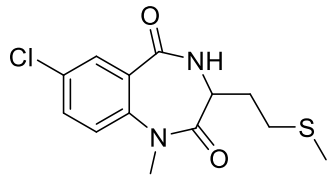


(*R/S*)-7-Chloro-3-isopropyl-1-methyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione ((*R/S*)-**3-52c**)**.** Prepared according to the general procedure above (*Method A*) from **3-47c** (541 mg, 2.5 mmol), (*R/S*)-valine (299.52 mg, 2.5 mmol), and AcOH (5 mL). The crude product was purified by silica gel column chromatography (7:3 EtOAc:Hex) to afford the product as a tan solid. (138.1 mg, 20% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ

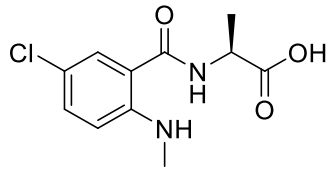
7.81 (d, *J* = 2.5 Hz, 1H), 7.48 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.37 – 7.25 (m, 1H), 7.16 (d, *J* = 8.7 Hz, 1H), 3.42 – 3.26 (m, 4H), 2.35 (dq, *J* = 13.4, 6.5 Hz, 1H), 1.08 (d, *J* = 6.7 Hz, 3H), 1.01 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 167.7, 139.7, 132.4, 131.2, 129.8, 126.8, 123.3, 58.0, 35.7, 27.0, 20.3, 18.4; HRMS (ESI) calculated for $C_{13}H_{15}ClN_2O_2$ $[M+H]^+$: 267.0900, exact mass found 267.0897; (**GMR-II-174**)



(S)-7-Chloro-1-methyl-3-(2-(methylthio)ethyl)-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione ((*S*)-**3-52d**) Prepared according to the general procedure above (*Method A*) from **3-47c** (200 mg, 0.9 mmol), (*S*)-methionine (142.45mg, 0.9 mmol), and AcOH (2 mL). The crude product was triturated in Et_2O to afford the product as a white solid. The product was recrystallized in toluene. The enantiomeric enrichment was observed by chiral HPLC (124.6 mg, 44% yield, >99% ee). mp: 157 – 160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 2.5 Hz, 1H), 7.71 (d, *J* = 5.6 Hz, 1H), 7.50 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.17 (d, *J* = 8.8 Hz, 1H), 3.95 (q, *J* = 5.6 Hz, 1H), 3.37 (s, 3H), 2.66 (t, *J* = 6.8 Hz, 2H), 2.33 (dd, *J* = 14.2, 6.8 Hz, 1H), 2.14 – 1.99 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 168.0, 139.5, 132.6, 131.4, 129.9, 129.3, 123.2, 50.9, 35.8, 30.0, 27.8, 15.3; HRMS (ESI) calculated for $C_{13}H_{15}ClN_2O_2S$ $[M+H]^+$: 299.0616, exact mass found 299.0596; $[a]_D^{25} = +242.95$ (c = 0.5, MeOH) (**GMR-III-009**)

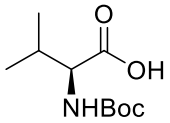


(*R/S*)-7-Chloro-1-methyl-3-(2-(methylthio)ethyl)-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione ((*R/S*)-**3-52d).** Prepared according to the general procedure above (*Method A*) from **3-47c** (541 mg, 2.5 mmol), (*R/S*)-methionine (299.52 mg, 2.5 mmol), and AcOH (5 mL). The crude product was purified by silica gel column chromatography (7:3 EtOAc:Hex) to afford a tan solid product. (138.1 mg, 20% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 2.6 Hz, 1H), 7.74 (d, *J* = 5.6 Hz, 1H), 7.50 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.17 (d, *J* = 8.8 Hz, 1H), 3.95 (q, *J* = 5.6 Hz, 1H), 3.37 (s, 3H), 2.64 (t, *J* = 6.8 Hz, 2H), 2.33 (dd, *J* = 14.3, 6.8 Hz, 1H), 2.11 – 1.97 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 168.0, 139.5, 132.6, 131.4, 130.0, 129.3, 123.2, 50.9, 35.8, 30.0, 27.8, 15.3. (**GMR-II-168**)

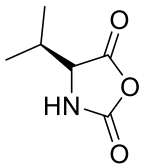


5-Chloro-2-(methylamino)benzoyl)-L-alanine (**3-56**). **3-47c** (20.6 mg, 0.116 mmol, 1.0 equiv) and (*S*)-alanine (10.5 mg, 0.116 mmol, 1.0 equiv) were mixed together in 1,4-dioxane (1 mL, 10 mL/mmol). Aq. Na_2CO_3 (10%) (1 mL, 10 mL/mmol) was added, and the mixture was stirred overnight. The mixture was diluted with H_2O, acidified with 1 M HCl (pH~3). The aqueous layer was extracted with methylene chloride, combined, washed with brine, dried with $MgSO_4$, filtered, and dried *in vacuo* to afford the product as a yellow viscous oil (22.5 mg, 63% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.50 (s, 1H), 7.50 (d, *J* = 2.5 Hz, 1H), 7.23 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.62 (d, *J* = 8.9 Hz, 1H),

4.34 (q, J = 7.1 Hz, 1H), 2.79 (s, 3H), 1.41 (d, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 178.9, 168.5, 148.4, 131.6, 127.3, 118.8, 117.4, 111.7, 54.5, 28.1, 22.3. $[a]_D^{25} = +20.69$ (c = 0.116, MeOH) (**GMR-III-40**)

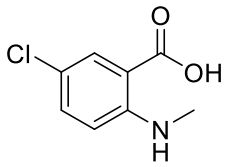


(tert-Butoxycarbonyl)-L-valine (**3-57**). Procedure is based on protocol by Schurig.[26] Et_3N (2.6 mL, 19 mmol, 0.7255 g/mL, 1.1 equiv) was added to a solution of amino acid (99% (*S*)-valine (2.00 g, 16.9 mmol, 1.0 equiv) in H_2O (18 mL). Boc_2O (4.43 g, 20.3 mmol, 1.2 equiv) in dioxane (11.3 mL) was added dropwise, and the mixture was stirred at room temperature overnight. The solution was concentrated to half volume *in vacuo* and adjusted to pH 2 with 1N HCl. The mixture was extracted with EtOAc (3 × 15 mL) and the organic layers were collected, washed with brine, dried with Na_2SO_4, filtered, and concentrated *in vacuo* to afford the product as a yellow oil (3.8 g, >99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.01 (d, J = 9.0 Hz, 1H), 4.28 – 4.18 (m, 1H), 2.28 – 2.14 (m, 1H), 1.45 (s, 9H), 1.01 (d, J = 6.9 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.8, 155.8, 80.0, 58.3, 30.9, 28.2, 19.0, 17.4. Spectra matched the literature.[27] $[a]_D^{25} = -26.31$ (c = 0.038, MeOH) (**GMR-III-043**)

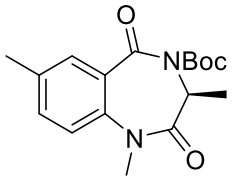


(*R*)-4-Isopropyloxazolidine-2,5-dione (**3-58**). Procedure adapted from the protocol by Vaillefont.[28] To a solution of **3-57** (3.84 g, 17.68 mmol, 1 equiv) in methylene chloride at 0 °C under N_2, PCl_3 (2 M in methylene chloride, 10.6 mL, 21.2 mmol, 1.2 equiv) was

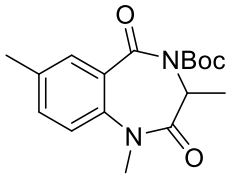
added, and the reaction was stirred for 3 hours. The solvent was concentrated *in vacuo* and the residue was washed with carbon tetrachloride to afford the product as a white solid (2.1158 g, 84% yield). mp: 227 – 229 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (s, 1H), 4.19 (dd, *J* = 4.4, 1.0 Hz, 1H), 2.23 (pd, *J* = 6.9, 4.4 Hz, 1H), 1.07 (d, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 152.8, 62.9, 30.7, 18.2, 16.5. Proton spectra matched the literature.[29] $[a]_D^{25} = -8.63$ (c = 0.139, MeOH) (**GMR-III-048**)



5-Chloro-2-(methylamino)benzoic acid (**3-59**). Procedure adapted from protocol by Murray.[30] To a solution of K_2CO_3 (205 mg, 1.50 mmol, 1.0 equiv) in H_2O (2 mL), 2-amino-5-chlorobenzoic acid (500 mg, 2.94 mmol, 1.96 equiv) was added and stirred. MeI (218 μL, 2.94, 2.33 equiv, 2.28 g/mL, 1.2 equiv) was added to the solution, and the mixture was heated to 37 °C for one hour. The precipitate that formed during the reaction was filtered and collected to afford the product as a yellow solid (238 mg, 44% yield). mp: 189 – 192 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.58 (d, *J* = 2.7 Hz, 1H), 7.20 (dd, *J* = 8.9, 2.7 Hz, 1H), 6.73 (d, *J* = 8.9 Hz, 1H), 2.78 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.8, 133.9, 130.2, 118.7, 117.9, 113.2, 110.9, 29.7. Known compound[31] (**GMR-III-051**)

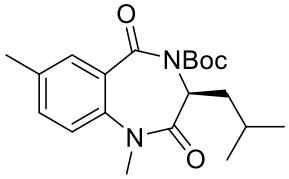


tert-Butyl (*S*)-1,3,7-trimethyl-2,5-dioxo-1,2,3,5-tetrahydro-4H-benzo[e][1,4]diazepine-4-carboxylate ((*S*)-**3-53a**) Prepared according to the general procedure above (*Method C*) from (*S*)- **3-50a** (103.6 mg, 0.5 mmol), Boc_2O (201.12 mg, 1.0 mmol), DMAP (11.59 mg, 0.1 mmol), Et_3N (132.36 µL, 1.0 mmol, 0.7255 g/mL), and methylene chloride (5 mL). The crude product was purified on a silica gel column to afford a white tacky solid product. The enantiomeric enrichment was observed by chiral HPLC (128.1 mg, 85% yield, >99% ee). Diastereomers were observed by room temperature NMR (0.45:0.55) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 2.3 Hz, 1H), 7.33 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.05 (d, *J* = 8.3 Hz, 1H), 5.43 – 5.21 (m, 0.45H), 4.41 – 4.15 (m, 0.55H), 3.40 – 3.28 (m, 3H), 2.35 (t, *J* = 0.7 Hz, 3H), 1.62 – 1.37 (m, 10.65H), 1.18 – 1.02 (m, 1.35H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.5, 165.8, 152.1, 137.5, 135.5, 134.0, 133.6, 131.6, 130.8, 127.9, 120.8, 84.6, 84.4, 59.6, 56.4, 53.7, 38.3, 35.7, 35.4, 30.9, 29.6, 29.2, 27.7, 25.7, 22.6, 22.3, 22.0, 20.5, 15.1, 12.7; HRMS (ESI) calculated for $C_{17}H_{22}N_2O_4$ $[M+Na]^+$: 341.1472, exact mass found 341.1458; $[a]_D^{25} = +55.88$ (c = 0.17, MeOH) (**GMR-III-006**)



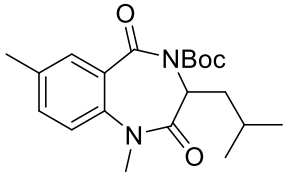
(*R/S*)-tert-Butyl 1,3,7-trimethyl-2,5-dioxo-1,2,3,5-tetrahydro-4H-benzo[e][1,4]diazepine-4-carboxylate ((*R/S*)-**3-53a).** Prepared according to the general

procedure above (*Method C*) from (*R/S*)- **3-50a** (180.3 mg, 0.8 mmol), Boc_2O (360.11 mg, 1.6 mmol), DMAP (20.16 mg, 0.16 mmol), Et_3N (230.13 µL, 1.65 mmol, 0.7255 g/mL), and methylene chloride (8.3 mL). The crude product was purified on a silica gel column to afford a white tacky solid product. (244.2 mg, 93% yield). Diastereomers were observed by room temperature NMR (0.45:0.55) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 2.3 Hz, 1H), 7.33 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.05 (d, *J* = 8.3 Hz, 1H), 5.43 – 5.21 (m, 0.45H), 4.41 – 4.15 (m, 0.55H), 3.40 – 3.28 (m, 3H), 2.35 (t, *J* = 0.7 Hz, 3H), 1.62 – 1.37 (m, 10.65H), 1.18 – 1.02 (m, 1.35H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.5, 165.8, 152.1, 137.5, 135.5, 134.0, 133.6, 131.6, 130.8, 127.9, 120.8, 84.6, 84.4, 59.6, 56.4, 53.7, 38.3, 35.7, 35.4, 30.9, 29.6, 29.2, 27.7, 25.7, 22.6, 22.3, 22.0, 20.5, 15.1, 12.7. (**GMR-II-181**)



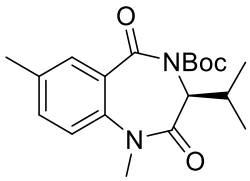
tert-Butyl (*S*)-3-isobutyl-1,7-dimethyl-2,5-dioxo-1,2,3,5-tetrahydro-4H-benzo[e][1,4]diazepine-4-carboxylate ((*S*)-**3-53b**) Prepared according to the general procedure above (*Method C*) from (*S*)- **3-50b** (103.6 mg, 0.5 mmol), Boc_2O (201.12 mg, 1.0 mmol), DMAP (11.59 mg, 0.1 mmol), Et_3N (132.36 µL, 1.0 mmol, 0.7255 g/mL), and methylene chloride (5 mL). The crude product was purified on a silica gel column to afford a white tacky white solid product. The enantiomeric enrichment was observed by chiral HPLC (128.1 mg, 85% yield, >99% ee). Two diastereomers were observed by NMR (0.7:0.3). 0 °C ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 – 7.67 (m, 1H), 7.40 – 7.35 (m, 1H), 7.14 – 7.04 (m, 1H), 5.26 (t, *J* = 8.1 Hz, 0.7H), 4.16 (t, *J* = 7.4 Hz, 0.3H), 3.39 (m, 0.3H), 2.39 (d, *J* = 2.0 Hz, 3H), 1.98 (ddd, *J* = 13.8, 7.4, 5.9 Hz, 0.3H), 1.90 – 1.82 (m,

0.7H)1.66 – 1.44 (m, 10H), 1.19 (dd, *J* = 8.0, 6.9 Hz, 1.8H), 0.83 – 0.76 (m, 4.2H). 23 °C ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 169.0, 167.1, 165.8, 152.1, 150.2, 138.6, 138.6, 137.5, 135.5, 135.3, 134.0, 133.6, 131.68, 130.9, 128.2, 127.9, 120.7, 84.7, 84.4, 59.6, 55.3, 53.5, 38.3, 35.7, 35.7, 35.0, 27.8, 27.7, 25.7, 24.7, 22.6, 22.3, 22.8, 22.0, 20.5; HRMS (ESI) calculated for $C_{17}H_{22}N_2O_4$ $[M+Na]^+$: 383.1941, exact mass found 383.1933; $[a]_D^{25} = -29.23$ (c = 0.065, MeOH) (**GMR-III-006**)

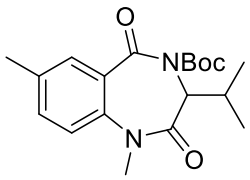


(*R/S*)-tert-Butyl 3-isobutyl-1,7-dimethyl-2,5-dioxo-1,2,3,5-tetrahydro-4H-benzo[e][1,4]diazepine-4-carboxylate ((*R/S*)-**3-53b).** Prepared according to the general procedure above (*Method C*) from (*R/S*)- **3-50b** (226.3 mg, 0.87 mmol), Boc_2O (379.4 mg, 1.7 mmol), DMAP (21.2 mg, 0.17 mmol), Et_3N (242.5 µL, 1.7 mmol, 0.7255 g/mL), and methylene chloride (8.5 mL). The crude product was purified on a silica gel column to afford a white tacky solid product. (333.4 mg, 83% yield). Two diastereomers were observed by NMR (0.7:0.3). 0 °C ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 – 7.67 (m, 1H), 7.40 – 7.35 (m, 1H), 7.14 – 7.04 (m, 1H), 5.26 (t, *J* = 8.1 Hz, 0.7H), 4.16 (t, *J* = 7.4 Hz, 0.3H), 3.39 (m, 0.3H), 2.39 (d, *J* = 2.0 Hz, 3H), 1.98 (ddd, *J* = 8.1, 7.4, 5.9 Hz, 0.3H), 1.90 – 1.82 (m, 0.7H)1.66 – 1.44 (m, 10H), 1.19 (dd, *J* = 8.0, 6.9 Hz, 1.8H), 0.83 – 0.76 (m, 4.2H). 23 °C ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 169.0, 167.1, 165.8, 152.1, 150.2, 138.6, 138.6, 137.5, 135.5, 135.3, 134.0, 133.6, 131.6, 130.9, 128.2, 127.9, 120.7, 84.7, 84.4, 59.6, 55.3, 53.5, 38.3, 35.7, 35.7, 35.0, 27.8, 27.7, 25.7, 24.7, 22.6, 22.3, 22.0, 22.0,

20.5; HRMS (ESI) calculated for $C_{17}H_{22}N_2O_4$ $[M+Na]^+$: 383.1941, exact mass found 383.1932 (**GMR-II-183**)

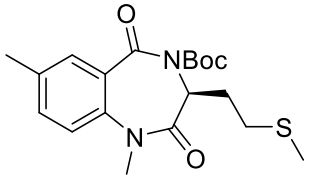


tert-Butyl (*S*)-3-isopropyl-1,7-dimethyl-2,5-dioxo-1,2,3,5-tetrahydro-4H-benzo[e][1,4]diazepine-4-carboxylate ((*S*)-**3-53c**) Prepared according to the general procedure above (*Method C*) from (*S*)- **3-50c** (43.2 mg, 0.2 mmol), Boc_2O (76.56 mg, 0.35 mmol), DMAP (4.28 mg, 0.035 mmol), Et_3N (48.8 µL, 0.35 mmol, 0.7255 g/mL), and methylene chloride (1.75 mL). The crude product was purified on a silica gel column to afford a tacky brown solid product. The enantiomeric enrichment was observed by chiral HPLC (53.3 mg, 88% yield, 98% ee). mp: 215 – 216 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.63 (m, 1H), 7.32 (ddd, *J* = 8.3, 2.2, 1.5 Hz, 1H), 7.02 (d, *J* = 8.3 Hz, 1H), 4.71 (dd, *J* = 16, 1.5 Hz, 1H), 3.34 (t, *J* = 1.5 Hz, 3H), 2.34 (d, *J* = 1.9 Hz, 3H), 1.53 (t, *J* = 1.5 Hz, 9H), 1.41 – 1.30 (m, 1H), 0.84 – 0.72 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 165.6, 152.4, 137.3, 135.4, 134.0, 131.5, 128.2, 120.7, 84.3, 67.7, 35.7, 27.8, 27.7, 20.5, 19.6, 19.4; HRMS (ESI) calculated for $C_{19}H_{26}N_2O_4$ $[M+Na]^+$: 369.1785, exact mass found 369.1770; $[a]_D^{25} = -140.98$ (c = 0.061, MeOH) (**GMR-III-119**)



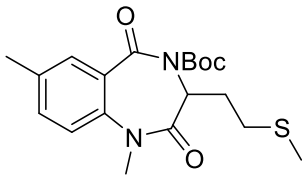
(*R/S*)-tert-Butyl 3-isopropyl-1,7-dimethyl-2,5-dioxo-1,2,3,5-tetrahydro-4H-benzo[e][1,4]diazepine-4-carboxylate ((*R/S*)-**3-53c).** Prepared according to the general

procedure above (*Method C*) from (*R/S*)- **3-50c** (19.2 mg, 0.08 mmol), Boc_2O (34mg, 0.16 mmol), DMAP (1.9 mg, 0.016 mmol), Et_3N (21.8 µL, 0.16 mmol, 0.7255 g/mL), and methylene chloride (0.78 mL). The crude product was purified on a silica gel column to afford a white tacky solid product. (23.4 mg, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.63 (m, 1H), 7.32 (ddd, *J* = 8.3, 2.2, 1.5 Hz, 1H), 7.02 (d, *J* = 8.3 Hz, 1H), 4.71 (dd, *J* = 16, 1.5 Hz, 1H), 3.34 (t, *J* = 1.5 Hz, 3H), 2.34 (d, *J* = 1.9 Hz, 3H), 1.53 (t, *J* = 1.5 Hz, 9H), 1.41 – 1.30 (m, 1H), 0.84 – 0.72 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 165.6, 152.4, 137.3, 135.4, 134.0, 131.5, 128.2, 120.7, 84.3, 67.7, 35.7, 27.8, 27.7, 20.5, 19.6, 19.4; HRMS (ESI) calculated for $C_{19}H_{26}N_2O_4$ $[M+Na]^+$: 369.1785, exact mass found 369.1771; (**GMR-III-112**)

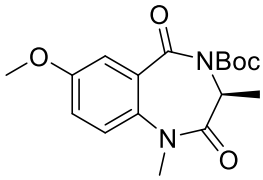


tert-Butyl (*S*)-1,7-dimethyl-3-(2-(methylthio)ethyl)-2,5-dioxo-1,2,3,5-tetrahydro-4H-benzo[e][1,4]diazepine-4-carboxylate ((*S*)-**3-53d**) Prepared according to the general procedure above (*Method C*) from (*S*)- **3-50d** (223.4 mg, 0.8 mmol), Boc_2O (350.3 mg, 1.6 mmol), DMAP (19.6 mg, 0.16 mmol), Et_3N (223.9 µL, 1.6 mmol, 0.7255 g/mL), and methylene chloride (8 mL). The crude product was purified on a silica gel column to afford the product as a yellow oil. The enantiomeric enrichment was observed by chiral HPLC (248 mg, 82% yield, 97% ee). Two diastereomers were observed by NMR at room temperature (0.53:0.47). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 7.3 Hz, 1H), 7.09 – 6.93 (m, 1H), 5.19 (d, *J* = 8.2 Hz, 0.53H), 4.29 (d, *J* = 7.5 Hz, 0.47H), 3.40 – 3.23 (m, 3H), 2.59 – 2.21 (m, 5H), 2.22 – 2.07 (m, 0.94H), 1.97 – 1.76 (m,

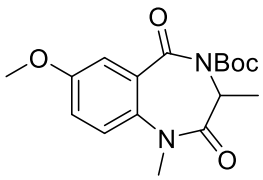
2.94H), 1.64 – 1.39 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 168.6, 167.1, 165.4, 152.0, 150.2, 138.4, 137.3, 135.5, 135.5, 134.1, 133.8, 131.6, 131.0, 127.8, 127.6, 120.8, 84.8, 84.6, 60.1, 53.8, 50.9, 35.8, 35.0, 30.5, 30.5, 28.6, 27.8, 27.7, 26.6, 20.5, 15.2; HRMS (ESI) calculated for $C_{14}H_{18}N2O_2S$ $[M+Na]^+$: 401.1505, exact mass found 401.1491; $[a]_D^{25} = -35.53$ (c = 0.076, MeOH) (**GMR-III-096**)



(*R/S*)-tert-Butyl 1,7-dimethyl-3-(2-(methylthio)ethyl)-2,5-dioxo-1,2,3,5-tetrahydro-4H-benzo[e][1,4]diazepine-4-carboxylate ((*R/S*)-**3-53d).** Prepared according to the general procedure above (*Method C*) from (*R/S*)- **3-50d** (240.6 mg, 0.85 mmol), Boc_2O (377.35 mg, 1.7 mmol), DMAP (21.12 mg, 0.17 mmol), Et_3N (241.1 µL, 1.7 mmol, 0.7255 g/mL), and methylene chloride (8 mL). The crude product was purified on a silica gel column to afford the product as a yellow oil. (241.6 mg, 74% yield). Two diastereomers were observed by NMR at room temperature (0.53:0.47). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 7.3 Hz, 1H), 7.09 – 6.93 (m, 1H), 5.19 (d, *J* = 8.2 Hz, 0.53H), 4.29 (d, *J* = 7.5 Hz, 0.47H), 3.40 – 3.23 (m, 3H), 2.59 – 2.21 (m, 5H), 2.22 – 2.07 (m, 0.94H), 1.97 – 1.76 (m, 2.94H), 1.64 – 1.39 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 168.6, 167.1, 165.4, 152.0, 150.2, 138.4, 137.3, 135.5, 135.5, 134.1, 133.8, 131.6, 131.0, 127.8, 127.6, 120.8, 84.8, 84.6, 60.1, 53.8, 50.9, 35.8, 35.0, 30.5, 30.5, 28.6, 27.8, 27.7, 26.6, 20.5, 15.2; HRMS (ESI) calculated for $C_{14}H_{18}N2O_2S$ $[M+Na]^+$: 401.1505, exact mass found 401.1486 (**GMR-III-097**)

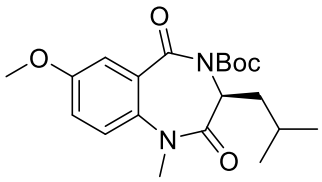


tert-Butyl (*S*)-7-methoxy-1,3-dimethyl-2,5-dioxo-1,2,3,5-tetrahydro-4H-benzo[e][1,4]diazepine-4-carboxylate ((*S*)-**3-54a**) Prepared according to the general procedure above (*Method C*) from (*S*)- **3-51a** (40 mg, 0.17 mmol), Boc_2O (74.2 mg, 0.34 mmol), DMAP (4.15 mg, 0.034 mmol), Et_3N (47.4 µL, 0.34 mmol, 0.7255 g/mL), and methylene chloride (1.7 mL). The crude product was purified on a silica gel column to afford a white glassy solid product. The enantiomeric enrichment was observed by chiral HPLC (94.9 mg, >99% yield, 69% ee). Diastereomers were observed by NMR (0.5:0.5) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.18 (m, 1H), 7.06 – 6.99 (m, 2H), 5.31 – 5.11 (m, 0.5H), 4.26 – 4.08 (m, 0.5H), 3.80 – 3.69 (m, 3H), 3.33 – 3.15 (m, 3H), 1.55 – 1.27 (m, 10.5H), 1.06 (d, *J* = 29.5 Hz, 1.5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 169.2, 166.3, 165.3, 165.2, 156.7, 151.9, 150.1, 134.0, 133.2, 128.8, 122.4, 120.2, 114.1, 113.4, 84.7, 60.2, 56.3, 55.6, 55.6, 50.6, 35.8, 35.3, 30.8, 29.1, 27.6, 20.9, 15.1, 14.1, 12.7; HRMS (ESI) calculated for $C_{17}H_{22}N_2O_5$ $[M+Na]^+$: 357.1421, exact mass found 357.1433; $[a]_D^{25} = +42.50$ (c = 0.12, MeOH) (**GMR-III-038**)



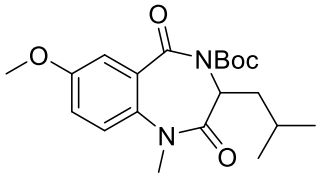
(*R/S*)-tert-Butyl 7-methoxy-1,3-dimethyl-2,5-dioxo-1,2,3,5-tetrahydro-4H-benzo[e][1,4]diazepine-4-carboxylate ((*R/S*)-**3-54a).** Prepared according to the general procedure above (*Method C*) from (*R/S*)- **3-51a** (64.4 mg, 0.275 mmol), Boc_2O (120 mg,

0.55 mmol), DMAP (6.7 mg, 0.055 mmol), Et_3N (76.7 µL, 0.55 mmol, 0.7255 g/mL), and methylene chloride (2.75 mL). The crude product was purified on a silica gel column to afford the product as a yellow oil. (91.7 mg, >99% yield). Diastereomers were observed by NMR (0.5:0.5) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.18 (m, 1H), 7.06 – 6.99 (m, 2H), 5.31 – 5.11 (m, 0.5H), 4.26 – 4.08 (m, 0.5H), 3.80 – 3.69 (m, 3H), 3.33 – 3.15 (m, 3H), 1.55 – 1.27 (m, 10.5H), 1.06 (d, *J* = 29.5 Hz, 1.5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 169.2, 166.3, 165.3, 165.2, 156.7, 151.9, 150.1, 134.0, 133.2, 128.8, 122.4, 120.2, 114.1, 113.4, 84.7, 60.2, 56.3, 55.6, 55.6, 50.6, 35.8, 35.3, 30.8, 29.1, 27.6, 20.9, 15.1, 14.1, 12.7. (**GMR-III-022**)

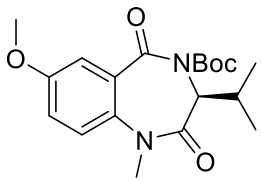


tert-Butyl (*S*)-3-isobutyl-7-methoxy-1-methyl-2,5-dioxo-1,2,3,5-tetrahydro-4H-benzo[e][1,4]diazepine-4-carboxylate ((*S*)-**3-54b**) Prepared according to the general procedure above (*Method C*) from (*S*)-**3-51b** (13 mg, 0.047 mmol), Boc_2O (20.51 mg, 0.094 mmol), DMAP (1.15 mg, 0.0094 mmol), Et_3N (13.1 µL, 0.094 mmol, 0.7255 g/mL), and methylene chloride (0.5 mL). The crude product was purified on a silica gel column to afford the product as a yellow oil. The enantiomeric enrichment was observed by chiral HPLC (93 mg, 59% yield, 98% ee). Two diastereomers were observed by NMR at room temperature (0.68:0.32). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 2.8 Hz, 1H), 7.16 – 7.04 (m, 2H), 5.24 (t, *J* = 8.1 Hz, 0.68H), 4.14 (t, *J* = 7.3 Hz, 0.32H), 3.86 (s, 3H), 3.42 – 3.34 (m, 3H), 1.92 (t, *J* = 7.3 Hz, 0.68H), 1.64 – 1.46 (m, 6.4H), 1.30 – 1.13 (m, 4.24H), 0.94 – 0.71 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 165.5, 156.7, 152.1,

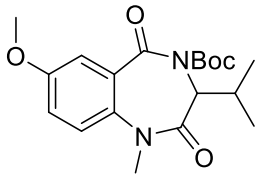
133.3, 129.4, 122.4, 120.6, 120.2, 114.1, 113.4, 84.5, 77.1, 59.7, 55.7, 53.5, 38.4, 35.9, 35.2, 29.6, 27.8, 27.7, 25.8, 24.7, 22.6, 22.3, 22.1, 22.0; HRMS (ESI) calculated for $C_{20}H_{28}N_2O_5$ $[M+Na]^+$: 399.1890, exact mass 399.1896; $[a]_D^{25} = -74.11$ (c = 0.112, MeOH) (**GMR-III-057**)



(*R/S*)-tert-Butyl 3-isobutyl-7-methoxy-1-methyl-2,5-dioxo-1,2,3,5-tetrahydro-4H-benzo[e][1,4]diazepine-4-carboxylate ((*R/S*)-**3-54b).** Prepared according to the general procedure above (*Method C*) from (*R/S*)-**3-51b** (91.2 mg, 0.33 mmol), Boc_2O (144.05 mg, 0.66 mmol), DMAP (8.6 mg, 0.066 mmol), Et_3N (92.1 µL, 0.66 mmol, 0.7255 g/mL), and methylene chloride (3.3 mL). The crude product was purified on a silica gel column to afford the product as a yellow oil. (123 mg, 99% yield). Two diastereomers observed by NMR at room temperature (0.68:0.32). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 2.8 Hz, 1H), 7.16 – 7.04 (m, 2H), 5.24 (t, *J* = 8.1 Hz, 0.68H), 4.14 (t, *J* = 7.3 Hz, 0.32H), 3.86 (s, 3H), 3.42 – 3.34 (m, 3H), 1.92 (t, *J* = 7.3 Hz, 0.68H), 1.64 – 1.46 (m, 6.4H), 1.30 – 1.13 (m, 4.24H), 0.94 – 0.71 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 165.5, 156.7, 152.1, 133.3, 129.4, 122.4, 120.6, 120.2, 114.1, 113.4, 84.5, 77.1, 59.7, 55.7, 53.5, 38.4, 35.9, 35.2, 29.6, 27.8, 27.7, 25.8, 24.7, 22.6, 22.3, 22.1, 22.0. (**GMR-III-023**)

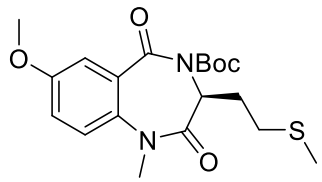


tert-Butyl (*S*)-3-isopropyl-7-methoxy-1-methyl-2,5-dioxo-1,2,3,5-tetrahydro-4H-benzo[e][1,4]diazepine-4-carboxylate ((*S*)-**3-54c**) Prepared according to the general procedure above (*Method C*) from (*S*)-**3-51c** (30.9 mg, 0.12 mmol), Boc_2O (51.5 mg, 0.24 mmol), DMAP (2.88 mg, 0.024 mmol), Et_3N (32.9 µL, 0.24 mmol, 0.7255 g/mL), and methylene chloride (1.2 mL). The crude product was purified on a silica gel column to afford the product as a tacky white solid. The enantiomeric enrichment was observed by chiral HPLC (41.2 mg, 96% yield, 98% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 2.1, 1.5 Hz, 1H), 7.11 (t, *J* = 2.1, 1.5 Hz, 2H), 4.75 (dd, *J* = 11.6, 2.2 Hz, 1H), 3.86 (s, 3H), 3.38 (s, 3H), 1.58 (s, 9H), 1.44 – 1.34 (m, 1H), 0.89 – 0.76 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 165.4, 156.7, 152.4, 133.0, 129.3, 122.4, 120.5, 114.0, 84.4, 67.8, 55.6, 35.8, 27.8, 27.8, 19.6, 19.5; HRMS (ESI) calculated for $C_{19}H_{26}N_2O_5$ $[M+Na]^+$: 385.1734, exact mass 385.1740; $[a]_D^{25} = -94.66$ (c = 0.131, MeOH) (**GMR-III-058**)

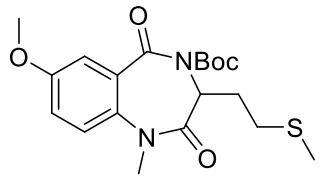


(*R/S*)-tert-Butyl 3-isopropyl-7-methoxy-1-methyl-2,5-dioxo-1,2,3,5-tetrahydro-4H-benzo[e][1,4]diazepine-4-carboxylate ((*R/S*)-**3-54c).** Prepared according to the general procedure above (*Method C*) from (*R/S*)-**3-51c** (40.3 mg, 0.15 mmol), Boc_2O (67 mg, 0.3 mmol), DMAP (3.7 mg, 0.03 mmol), Et_3N (42.8 µL, 0.3 mmol, 0.7255 g/mL), and methylene chloride (1.5 mL). The crude product was purified on a silica gel column to

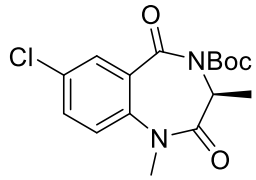
afford the product as a yellow solid. (42.9 mg, 77% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 2.1, 1.5 Hz, 1H), 7.11 (t, *J* = 2.1, 1.5 Hz, 2H), 4.75 (dd, *J* = 11.6, 2.2 Hz, 1H), 3.86 (s, 3H), 3.38 (s, 3H), 1.58 (s, 9H), 1.44 – 1.34 (m, 1H), 0.89 – 0.76 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 165.4, 156.7, 152.4, 133.0, 129.3, 122.4, 120.5, 114.0, 84.4, 67.8, 55.6, 35.8, 27.8, 27.8, 19.6, 19.5. (**GMR-III-024**)



tert-Butyl (*S*)-7-methoxy-1-methyl-3-(2-(methylthio)ethyl)-2,5-dioxo-1,2,3,5-tetrahydro-4H-benzo[e][1,4]diazepine-4-carboxylate ((*S*)-**3-54d**) Prepared according to the general procedure above (*Method C*) from (*S*)-**3-51d** (223.4 mg, 0.8 mmol), Boc_2O (350.3 mg, 1.6 mmol), DMAP (19.6 mg, 0.16 mmol), Et_3N (223.9 µL, 1.6 mmol, 0.7255 g/mL), and methylene chloride (8 mL). The crude product was purified on a silica gel column to afford the product as a yellow oil. The enantiomeric enrichment was observed by chiral HPLC (248 mg, 82% yield, 97% ee). Two diastereomers were observed by NMR at room temperature (0.55:0.45). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 1H), 7.15 – 6.95 (m, 2H), 5.25 (t, *J* = 8.2 Hz, 0.55H), 4.36 (s, 0.45H), 3.83 (d, *J* = 1.1 Hz, 3H), 3.36 (s, 3H), 2.64 – 2.32 (m, 3H), 1.99 (s, 0.55H), 1.90 (s, 3H), 1.66 – 1.50 (m, 9.45H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 156.8, 133.1, 122.5, 120.7, 120.3, 114.2, 113.5, 109.9, 85.1, 84.8, 60.3, 55.7, 53.8, 49.0, 35.9, 35.9, 35.2, 30.6, 28.8, 27.8, 27.8, 27.7, 26.5, 15.4; HRMS (ESI) calculated for $C_{19}H_{26}N_2O_5S$ $[M+Na]^+$: 417.1455, exact mass 417.1459; $[a]_D^{25} = -14.93$ (c = 0.067, MeOH) (**GMR-III-036**)

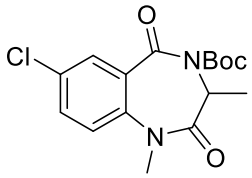


(*R/S*)-tert-Butyl 7-methoxy-1-methyl-3-(2-(methylthio)ethyl)-2,5-dioxo-1,2,3,5-tetrahydro-4H-benzo[e][1,4]diazepine-4-carboxylate ((*R/S*)-**3-54d).** Prepared according to the general procedure above (*Method C*) from (*R/S*)-**3-51d** (75.8 mg, 0.26 mmol), Boc_2O (112.4 mg, 0.52 mmol), DMAP (6.3 mg, 0.052 mmol), Et_3N (71.8 µL, 0.52 mmol, 0.7255 g/mL), and methylene chloride (2.6 mL). The crude product was purified on a silica gel column to afford the product as a yellow oil. (76.6 mg, 75% yield). Two diastereomers were observed by NMR at room temperature (0.55:0.45). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 1H), 7.15 – 6.95 (m, 2H), 5.25 (t, *J* = 8.2 Hz, 0.55H), 4.36 (s, 0.45H), 3.83 (d, *J* = 1.1 Hz, 3H), 3.36 (s, 3H), 2.64 – 2.32 (m, 3H), 1.99 (s, 0.55H), 1.90 (s, 3H), 1.66 – 1.50 (m, 9.45H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 156.8, 133.1, 122.5, 120.7, 120.3, 114.2, 113.5, 109.9, 85.1, 84.8, 60.3, 55.7, 53.8, 49.0, 35.9, 35.9, 35.2, 30.6, 28.8, 27.8, 27.8, 27.7, 26.5, 15.4. (**GMR-III-021**)



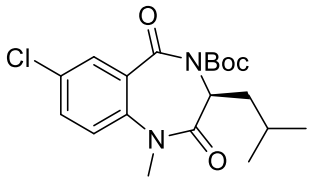
***tert*-Butyl (*S*)-7-chloro-1,3-dimethyl-2,5-dioxo-1,2,3,5-tetrahydro-4H-benzo[e][1,4]diazepine-4-carboxylate** ((*S*)-**3-55a**) Prepared according to the general procedure above (*Method C*) from (*S*)-**3-51a** (126.9 mg, 0.5 mmol), Boc_2O (232.09 mg, 1.0 mmol), DMAP (12.99 mg, 0.1 mmol), Et_3N (148.3 µL, 1.0 mmol, g/mL), and methylene chloride (5.3 mL). The crude product was purified on a silica gel column to

afford the product as a white solid. The enantiomeric enrichment was observed by chiral HPLC (171.8 mg, 95% yield, 95% ee). Two diastereomers observed at room temperature (0.43:0.57). 0°C ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.94 – 7.82 (m, 1H), 7.53 (t, *J* = 8.7 Hz, 1H), 7.17 (d, *J* = 8.7 Hz, 1H), 5.36 (q, *J* = 7.4 Hz, 0.43H), 4.28 (q, *J* = 6.7 Hz, 0.57H), 3.40 (d, *J* = 13.5 Hz, 3H), 1.62 – 1.44 (m, 10.41H), 1.17 (d, *J* = 7.4 Hz, 1.59H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.3, 169.1, 165.4, 164.2, 151.6, 149.7, 139.3, 138.3, 133.3, 132.9, 131.3, 131.1, 131.0, 130.4, 129.5, 129.2, 122.5, 122.4, 85.4, 85.0, 56.0, 50.6, 36.1, 35.4, 27.8, 27.6, 15.4, 12.8; HRMS (ESI) calculated for $C_{16}H_{19}ClN_2O_4$ $[M+Na]^+$: 361.0926, exact mass found 361.0911; $[a]_D^{25} = +84.15$ (c = 0.164, MeOH) (**GMR-III-188**)

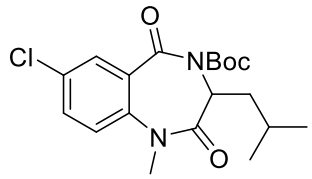


(*R/S*)-*tert*-Butyl 7-chloro-1,3-dimethyl-2,5-dioxo-1,2,3,5-tetrahydro-4H-benzo[e][1,4]diazepine-4-carboxylate ((*R/S*)-**3-55a).** Prepared according to the general procedure above (*Method C*) from (*R/S*)-**3-52a** (19.4 mg, 0.08 mmol), Boc_2O (35.49 mg, 0.16 mmol), DMAP (1.99 mg, 0.016 mmol), Et_3N (22.7 µL, 0.16 mmol, 0.7255 g/mL), and methylene chloride (0.813 mL). The crude product was purified on a silica gel column to afford the product as a yellow oil. (23.3 mg, 85% yield). Two diastereomers observed at room temperature (0.43:0.57). 0°C ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.94 – 7.82 (m, 1H), 7.53 (t, *J* = 8.7 Hz, 1H), 7.17 (d, *J* = 8.7 Hz, 1H), 5.36 (q, *J* = 7.4 Hz, 0.43H), 4.28 (q, *J* = 6.7 Hz, 0.57H), 3.40 (d, *J* = 13.5 Hz, 3H), 1.62 – 1.44 (m, 10.41H), 1.17 (d, *J* = 7.4 Hz, 1.59H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.3, 169.1, 165.4, 164.2,

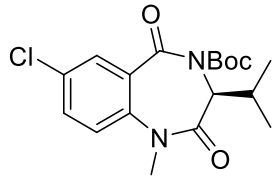
151.6, 149.7, 139.3, 138.3, 133.3, 132.9, 131.3, 131.1, 131.0, 130.4, 129.5, 129.2, 122.5, 122.4, 85.4, 85.0, 56.0, 50.6, 36.1, 35.4, 27.8, 27.6, 15.4, 12.8; HRMS (ESI) calculated for $C_{16}H_{19}ClN_2O_4$ $[M+Na]^+$: 361.0926, exact mass found 361.0909 (**GMR-III-189**)



***tert*-Butyl (*S*)-7-chloro-3-isobutyl-1-methyl-2,5-dioxo-1,2,3,5-tetrahydro-4H-benzo[e][1,4]diazepine-4-carboxylate** ((*S*)-**3-55b**) Prepared according to the general procedure above (*Method C*) from (*S*)-**3-52b** (152.1 mg, 0.5 mmol), Boc_2O (222.18 mg, 1.0 mmol), DMAP (12.45 mg, 0.1 mmol), Et_3N (142.0 µL, 1.0 mmol, 0.7255 g/mL), and methylene chloride (5.09 mL). The crude product was purified on a silica gel column to afford the product as a clear oil. The enantiomeric enrichment was observed by chiral HPLC (199.6 mg, >99% yield, >99% ee). Two diastereomers were observed by NMR at room temperature (0.68:0.32). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.80 (m, 1H), 7.53 – 7.44 (m, 1H), 7.17 – 7.04 (m, 1H), 5.24 (tt, *J* = 8.1, 2.2 Hz, 0.68H), 4.07 (t, *J* = 7.1 Hz, 0.32H), 3.42 – 3.22 (m, 3H), 1.96 – 1.82 (m, 0.68H), 1.66 – 1.42 (m, 9.96H), 1.19 (t, *J* = 8.1, 7.1 Hz, 1.36H), 0.94 – 0.73 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 168.6, 165.6, 164.3, 151.7, 149.8, 139.4, 138.4, 133.1, 132.8, 131.2, 131.0, 130.5, 129.8, 129.5, 123.2, 122.3, 122.2, 85.1, 84.8, 59.3, 53.5, 38.5, 35.8, 35.6, 35.1, 27.8, 27.6, 25.8, 24.7, 22.8, 22.6, 22.3, 22.0; $[a]_D^{25} = -94.12$ (c = 0.102, MeOH) (**GMR-III-057**)

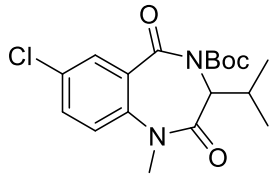


(*R/S*)-*tert*-Butyl 7-chloro-3-isobutyl-1-methyl-2,5-dioxo-1,2,3,5-tetrahydro-4H-benzo[e][1,4]diazepine-4-carboxylate ((*R/S*)-**3-55b).** Prepared according to the general procedure above (*Method C*) from (*R/S*)-**3-52b** (109.9 mg, 0.37 mmol), Boc_2O (160.54 mg, 0.74 mmol), DMAP (8.99 mg, 0.074 mmol), Et_3N (102.6 µL, 0.74 mmol, 0.7255 g/mL), and methylene chloride (4 mL). The crude product was purified on a silica gel column to afford the product as clear oil. (151.3 mg, >99% yield). Two diastereomers were observed by NMR at room temperature (0.68:0.33). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.80 (m, 1H), 7.53 – 7.44 (m, 1H), 7.17 – 7.04 (m, 1H), 5.24 (tt, *J* = 8.1, 2.2 Hz, 0.68H), 4.07 (t, *J* = 7.1 Hz, 0.33H), 3.42 – 3.22 (m, 3H), 1.96 – 1.82 (m, 0.68H), 1.66 – 1.42 (m, 9.96H), 1.19 (t, *J* = 8.2, 7.1 Hz, 1.36H), 0.94 – 0.73 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 168.6, 165.6, 164.3, 151.7, 149.8, 139.4, 138.4, 133.1, 132.8, 131.2, 131.0, 130.5, 129.8, 129.5, 123.2, 122.3, 122.2, 85.1, 84.8, 59.3, 53.5, 38.5, 35.8, 35.6, 35.1, 27.8, 27.6, 25.8, 24.7, 22.8, 22.6, 22.3, 22.0. (**GMR-III-023**)



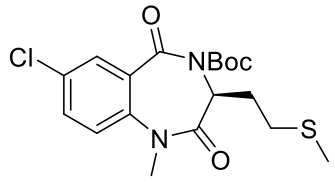
***tert*-Butyl (*S*)-7-chloro-3-isopropyl-1-methyl-2,5-dioxo-1,2,3,5-tetrahydro-4H-benzo[e][1,4]diazepine-4-carboxylate** ((*S*)-**3-55c**) Prepared according to the general procedure above (*Method C*) from (*S*)-**3-52c** (56.4 mg, 0.2 mmol), Boc_2O (92.3 mg, 0.4 mmol), DMAP (5.2 mg, 0.04 mmol), Et_3N (59 µL, 0.4 mmol, 0.7255 g/mL), and

methylene chloride (2.1 mL). The crude product was purified on a silica gel column to afford the product as a tacky white solid. The enantiomeric enrichment was observed by chiral HPLC (76.9 mg, 99% yield, 99% ee). Two diastereomers were observed by NMR (0.82:0.18). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.79 (m, 1H), 7.55 – 7.48 (m, 1H), 7.21 – 7.06 (m, 1H), 4.75 (dt, *J* = 11.6, 1.9 Hz, 0.82H), 3.60 (d, *J* = 10.5 Hz, 0.18H), 3.41 – 3.30 (m, 3H), 1.54 (s, 9H), 1.44 – 1.32 (m, 1H), 1.09 – 0.99 (m, 1.08H), 0.81 (ddt, *J* = 23.3, 6.5, 1.9 Hz, 4.92H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 169.3, 164.1, 152.1, 138.1, 133.1, 132.8, 132.4, 131.0, 129.9, 129.8, 123.3, 122.3, 122.2, 109.9, 84.8, 67.4, 57.8, 35.8, 34.9, 28.1, 28.0, 27.8, 27.7, 27.0, 25.9, 21.1, 20.3, 19.6, 19.4, 18.3; HRMS (ESI) calculated for $C_{18}H_{23}ClN_2O_4$ $[M+Na]^+$: 389.1239, exact mass found 389.1228; $[a]_D^{25} = -186.43$ (c = 0.14, MeOH) (**GMR-III-060**)

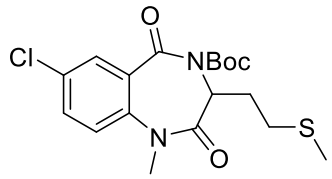


(*R/S*)-*tert*-Butyl 7-chloro-3-isopropyl-1-methyl-2,5-dioxo-1,2,3,5-tetrahydro-4H-benzo[e][1,4]diazepine-4-carboxylate ((*R/S*)-**3-55c).** Prepared according to the general procedure above (*Method C*) from (*R/S*)-**3-52c** (27.1 mg, 0.1 mmol), Boc_2O (44.4 mg, 0.2 mmol), DMAP (2.5 mg, 0.02 mmol), Et_3N (28.5 µL, 0.2 mmol, 0.7255 g/mL), and methylene chloride (1 mL). The crude product was purified on a silica gel column to afford the product as a yellow oil. (25.3 mg, 68% yield). Two diastereomers were observed by NMR (0.82:0.18). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.79 (m, 1H), 7.55 – 7.48 (m, 1H), 7.21 – 7.06 (m, 1H), 4.75 (dt, *J* = 11.6, 1.9 Hz, 0.82H), 3.60 (d, *J* = 10.5 Hz, 0.18H), 3.41 – 3.30 (m, 3H), 1.54 (s, 9H), 1.44 – 1.32 (m, 1H), 1.09 – 0.99 (m,

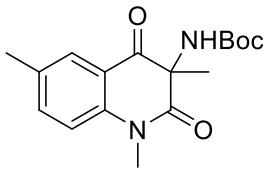
1.08H), 0.81 (ddt, *J* = 23.3, 6.5, 1.9 Hz, 4.92H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 169.3, 164.1, 152.1, 138.1, 133.1, 132.8, 132.4, 131.0, 129.9, 129.8, 123.3, 122.3, 122.2, 109.9, 84.8, 67.4, 57.87 35.8, 34.9, 28.1, 28.0, 27.8, 27.7, 27.0, 25.9, 21.1, 20.3, 19.6, 19.4, 18.3. (**GMR-III-109**)



***tert*-Butyl (*S*)-7-chloro-1-methyl-3-(2-(methylthio)ethyl)-2,5-dioxo-1,2,3,5-tetrahydro-4H-benzo[e][1,4]diazepine-4-carboxylate** ((*S*)-**3-55d**) Prepared according to the general procedure above (*Method C*) from (*S*)-**3-52d** (50 mg, 0.17 mmol), Boc_2O (73.3 mg, 0.34 mmol), DMAP (4.1 mg, 0.034 mmol), Et_3N (46.7 µL, 0.34 mmol, 0.7255 g/mL), and methylene chloride (1.7 mL). The crude product was purified on a silica gel column to afford the product as a yellow oil. The enantiomeric enrichment was observed by chiral HPLC (82.5 mg, >99% yield, 80% ee). Two diastereomers were observed by NMR at room temperature (0.55:0.45). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.84 (s, 1H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.12 (d, *J* = 7.5 Hz, 1H), 5.28 (t, *J* = 7.2 Hz, 0.55H), 4.34 (d, *J* = 6.6 Hz, 0.45H), 3.35 (s, 3H), 2.62 – 2.27 (m, 2.45H), 2.27 – 2.11 (m, 0.55H), 2.07 – 1.81 (m, 3H), 1.70 – 1.46 (m, 10H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 168.3, 165.6, 164.0, 151.7, 149.8, 139.3, 138.2, 133.3, 132.9, 131.2, 131.2, 130.6, 129.4, 129.3, 123.2, 122.4, 85.3, 85.1, 59.9, 53.7, 50.8, 35.9, 35.2, 30.5, 30.0, 28.9, 28.1, 27.8, 27.7, 26.4, 15.3; HRMS (ESI) calculated for $C_{18}H_{23}ClN_2O_4S$ $[M+Na]^+$: 421.0959, exact mass found 421.0938; $[a]_D^{25} = -22.08$ (c = 0.48, MeOH) (**GMR-III-117**)

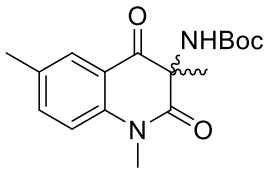


(*R/S*)-*tert*-Butyl 7-chloro-1-methyl-3-(2-(methylthio)ethyl)-2,5-dioxo-1,2,3,5-tetrahydro-4H-benzo[e][1,4]diazepine-4-carboxylate ((*R/S*)-**3-55d).** Prepared according to the general procedure above (*Method C*) from (*R/S*)-**3-52d** (175.8 mg, 0.59 mmol), Boc_2O (256.8 mg, 1.18 mmol), DMAP (14.38 mg, 0.118 mmol), Et_3N (164.13 µL, 1.18 mmol, 0.7255 g/mL), and methylene chloride (5.9 mL). The crude product was purified on a silica gel column to afford the product as a yellow oil. (171.8 mg, 73% yield). Two diastereomers were observed by NMR at 0 °C (0.53:0.47). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.55 (ddd, *J* = 8.6, 4.4, 2.5 Hz, 1H), 7.18 (dd, *J* = 19.9, 8.6 Hz, 1H), 5.35 (dd, *J* = 8.8, 7.5 Hz, 0.53H), 4.41 (t, *J* = 7.4, 6.9 Hz, 0.47H), 3.42 (s, 1.41H), 3.40 (s, 1.59H), 2.60 – 2.38 (m, 2.47H), 2.26 – 2.19 (m, 0.51H), 2.03 (s, 1.41H), 1.94 (s, 1.59H), 1.74 – 1.55 (m, 10H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 168.3, 165.6, 164.0, 151.7, 149.8, 139.3, 138.2, 133.3, 132.9, 131.3, 131.2, 130.7, 129.5, 122.3, 85.3, 85.1, 59.9, 53.7, 35.9, 35.2, 30.9, 30.5, 29.2, 28.9, 27.8, 27.7, 26.4; HRMS (ESI) calculated for $C_{18}H_{23}ClN_2O_4S$ $[M+Na]^+$: 421.0959, exact mass found 421.0949 (**GMR-II-187**)

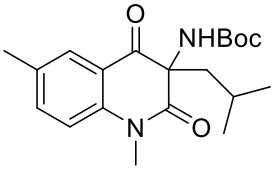


(*R* or *S*)-*tert*-Butyl (1,3,6-trimethyl-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl)carbamate ((*R* or *S*)-**3-61d**). Prepared according to the general procedure above

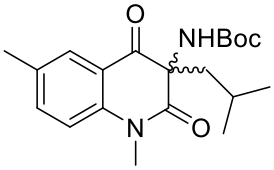
(*Method G*) from *tert*-butyl (*S*)- **3-53d** (54 mg, 0.17 mmol), LiHMDS (1 M in THF, 0.34 mL, 0.34 mmol), and THF (1.19 mL). The crude mixture was purified on a silica gel column to afford the product as a yellow solid. The enantiomeric enrichment was observed by chiral HPLC. (42.6 mg, 79% yield, 98% ee). mp: 187 – 188 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 1.4 Hz, 1H), 7.44 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 5.47 (s, 1H), 3.50 (s, 3H), 2.35 (s, 3H), 1.50 (s, 3H), 1.41 (s, 7.8H), 1.13 (s, 1.2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.6, 171.8, 155.1, 140.7, 136.9, 132.8, 128.7, 119.2, 114.9, 80.7, 64.8, 30.3, 28.2, 23.8, 20.2; HRMS (ESI) calculated for $C_{17}H_{22}N_2O_4$ $[M+H]^+$: 319.1658, exact mass found 319.1670; $[a]_D^{25} = +50.49$ (c = 0.101, MeOH) (**GMR-III-062**)



(*R/S*)-*tert*-Butyl (1,3,6-trimethyl-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl)carbamate ((*R/S*)-**3-61d**) Prepared according to the general procedure above (*Method G*) from *tert*-butyl (*R/S*)-**3-53d** (255.2 mg, 0.8 mmol), LiHMDS (1 M in THF, 1.6 mL, 1.6 mmol), and THF (5.6 mL). The crude mixture was purified on a silica gel column to afford the product as a yellow solid (85.6 mg, 56% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 1.4 Hz, 1H), 7.44 (dd, *J* = 8.8, 1.4 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 5.47 (s, 1H), 3.50 (s, 3H), 2.35 (s, 3H), 1.50 (s, 3H), 1.41 (s, 7.8H), 1.13 (s, 1.2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.6, 171.8, 155.1, 140.7, 136.9, 132.8, 128.7, 119.2, 114.9, 80.7, 64.8, 30.3, 28.2, 23.8, 20.2; HRMS (ESI) calculated for $C_{17}H_{22}N_2O_4$ $[M+H]^+$: 319.1658, exact mass found 319.1636 (**GMR-III-061**)

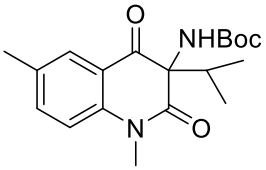


(*R* or *S*)-*tert*-Butyl (3-isobutyl-1,6-dimethyl-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl)carbamate ((*R* or *S*)-**3-61e**). Prepared according to the general procedure above (*Method G*) from *tert*-butyl (*S*)-**3-53e** (21.9 mg, 0.06 mmol), LiHMDS (1 M in THF, 0.12 mL, 0.1 mmol), and THF (0.42 mL). The crude mixture was purified on a silica gel column to afford the product as a yellow solid. The enantiomeric enrichment was observed by chiral HPLC. (5.7 mg, 26% yield, >99% ee). mp: 167 – 169 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 2.2 Hz, 1H), 7.42 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 5.38 (s, 1H), 3.48 (s, 3H), 2.35 (s, 3H), 1.84 – 1.68 (m, 3H), 1.41 (s, 7.5H), 1.12 (s, 1.5H), 0.87 – 0.82 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.2, 171.2, 155.1, 140.5, 136.7, 132.7, 128.4, 120.2, 114.8, 80.5, 68.5, 46.2, 30.2, 28.2, 24.2, 23.8, 23.8, 20.2; HRMS (ESI) calculated for $C_{20}H_{28}N_2O_4$ $[M+Na]^+$: 383.1947, exact mass found 383.1922; $[a]_D^{25} = -22.11$ (c = 0.095, MeOH) (**GMR-III-064**)

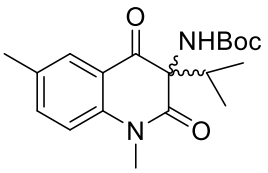


(*R/S*)-*tert*-Butyl (3-isobutyl-1,6-dimethyl-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl)carbamate ((*R/S*)-**3-61e**) Prepared according to the general procedure above (*Method G*) from (*R/S*)-**3-53e** (254.9 mg, 0.7 mmol), LiHMDS (1 M in THF, 1.364 mL, 1.4 mmol), and THF (4.77 mL). The crude mixture was purified on a silica gel column to afford the product as a yellow solid (140.7 mg, 55% yield). ^{1}H NMR (400 MHz, $CDCl_3$)

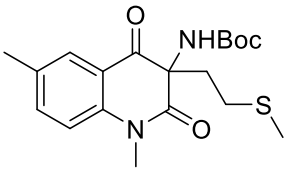
δ 7.85 (d, *J* = 2.2 Hz, 1H), 7.42 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 5.38 (s, 1H), 3.48 (s, 3H), 2.35 (s, 3H), 1.84 – 1.68 (m, 3H), 1.41 (s, 7.5H), 1.12 (s, 1.5H), 0.87 – 0.82 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$)) δ 193.2, 171.2, 155.1, 140.5, 136.7, 132.7, 128.4, 120.2, 114.8, 80.5, 68.5, 46.2, 30.2, 28.2, 24.2, 23.8, 23.8, 20.2; HRMS (ESI) calculated for $C_{20}H_{28}N_2O_4$ $[M+Na]^+$: 383.1947, exact mass found 383.1930 (**GMR-III-063**)



(*R* or *S*)-*tert*-Butyl (3-isopropyl-1,6-dimethyl-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl)carbamate ((*R* or *S*)-**3-61f**). Prepared according to the general procedure above (*Method G*) from (*S*)-**3-53f** (121.3 mg, 0.35 mmol), LiHMDS (1 M in THF, 0.70 mL, 0.70 mmol), and THF (2.45 mL). The crude mixture was purified on a silica gel column to afford the product as a yellow solid. The enantiomeric enrichment was observed by chiral HPLC. (51.2 mg, 42% yield, 98% ee). mp: 146 – 149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 2.2 Hz, 1H), 7.36 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.00 (d, *J* = 8.6 Hz, 1H), 5.28 (s, 1H), 3.45 (d, *J* = 2.2 Hz, 3H), 2.31 (s, 3H), 2.20 – 2.11 (m, 1H), 1.37 (s, 7.5H), 1.08 (s, 1.5H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.9, 170.8, 155.4, 140.7, 136.5, 132.5, 128.0, 121.3, 114.7, 80.5, 71.4, 35.6, 30.1, 28.2, 20.2, 17.0, 16.9; HRMS (ESI) calculated for $C_{19}H_{26}N_2O_4$ $[M+Na]^+$: 369.1790, exact mass found 369.1779; $[a]_D^{25} = -43.05$ (c = 0.072, MeOH) (**GMR-III-066**)

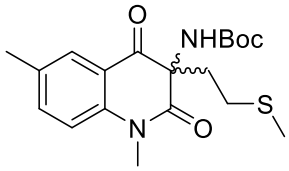


(*R/S*)-*tert*-Butyl (3-isopropyl-1,6-dimethyl-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl)carbamate ((*R/S*)-**3-61f**) Prepared according to the general procedure above (*Method G*) from (*R/S*)-**3-53f** (128.1 mg, 0.37 mmol), LiHMDS (1 M in THF, 0.74 mL, 0.74 mmol), and THF (2.6 mL). The crude mixture was purified on a silica gel column to afford the product as a yellow solid (33.8 mg, 26% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 2.2 Hz, 1H), 7.36 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.00 (d, *J* = 8.6 Hz, 1H), 5.28 (s, 1H), 3.45 (d, *J* = 1.2 Hz, 3H), 2.31 (s, 3H), 2.20 – 2.11 (m, 1H), 1.37 (s, 7.5H), 1.08 (s, 1.5H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $cdcl_3$) δ 192.9, 170.8, 155.4, 140.7, 136.5, 132.5, 128.0, 121.3, 114.7, 80.5, 71.4, 35.6, 30.1, 28.2, 20.2, 17.0, 16.9; HRMS (ESI) calculated for $C_{19}H_{26}N_2O_4$ $[M+Na]^+$: 369.1790, exact mass found 369.1775 (**GMR-III-065**)

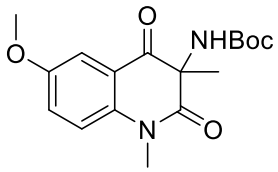


(*R* or *S*)-*tert*-Butyl (1,6-dimethyl-3-(2-(methylthio)ethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl)carbamate ((*R* or *S*)-**3-61g**). Prepared according to the general procedure above (*Method G*) from (*S*)-**3-53g** (47.9 mg, 0.13 mmol), LiHMDS (1 M in THF, 0.26 mL, 0.26 mmol), and THF (0.89 mL). The crude mixture was purified on a silica gel column to afford the product as a white solid. The enantiomeric enrichment was observed by chiral HPLC. (25.9 mg, 54% yield, 98% ee). mp: 152 – 153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 2.2 Hz, 1H), 7.43 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.06 (d, *J* =

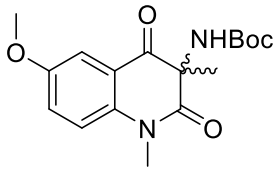
8.5 Hz, 1H), 5.77 (s, 1H), 3.49 (s, 3H), 2.46 (ddd, *J* = 8.8, 6.6, 2.4 Hz, 2H), 2.35 (s, 3H), 2.21 – 2.05 (m, 2H), 2.04 (s, 3H), 1.41 (s, 7.5H), 1.13 (s, 1.5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.5, 170.6, 155.2, 140.5, 137.0, 132.9, 128.6, 119.8, 115.0, 80.8, 68.3, 36.0, 30.3, 28.2, 27.5, 20.2, 15.4; HRMS (ESI) calculated for $C_{19}H_{26}N_2O_4S$ $[M+Na]^+$: 401.1511, exact mass found 401.1496; $[a]_D^{25} = -46.91$ (c = 0.081, MeOH) (**GMR-III-068**)



(*R/S*)-*tert*-Butyl (1,6-dimethyl-3-(2-(methylthio)ethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl)carbamate ((*R/S*)-**3-61g**) Prepared according to the general procedure above (*Method G*) from (*R/S*)-**3-61g** (246.1 mg, 0.65 mmol), LiHMDS (1 M in THF, 1.3 mL, 1.3 mmol), and THF (4.55 mL). The crude mixture was purified on a silica gel column to afford the product as a yellow solid (30.1 mg, 12% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 2.2 Hz, 1H), 7.43 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.06 (d, *J* = 8.5 Hz, 1H), 5.77 (s, 1H), 3.49 (s, 3H), 2.46 (ddd, *J* = 8.8, 6.6, 2.4 Hz, 2H), 2.35 (s, 3H), 2.21 – 2.05 (m, 2H), 2.04 (s, 3H), 1.41 (s, 7.5H), 1.13 (s,1.5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.5, 170.6, 155.2, 140.5, 137.0, 132.9, 128.6, 119.8, 115.0, 80.8, 68.3, 36.0, 30.3, 28.2, 27.5, 20.2, 15.4; HRMS (ESI) calculated for $C_{19}H_{26}N_2O_4S$ $[M+Na]^+$: 401.1511, exact mass found 401.1496 (**GMR-III-067**)

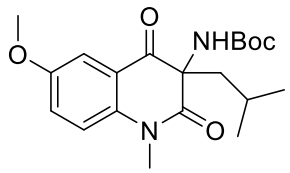


(*R* or *S*)-*tert*-Butyl (6-methoxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl)carbamate ((*R* or *S*)-**3-62d**). Prepared according to the general procedure above (*Method G*) from *tert*-butyl (*S*)-**3-54d** (45.3 mg, 0.14 mmol), LiHMDS (1 M in THF, 0.28 mL, 0.28 mmol), and THF (1 mL). The crude mixture was purified on a silica gel column to afford the product as a yellow solid. The enantiomeric enrichment was observed by chiral HPLC. (30.5 mg, 67% yield, 68% ee). mp: 218 – 220 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 3.1 Hz, 1H), 7.18 (dd, *J* = 9.0, 3.1 Hz, 1H), 7.09 (d, *J* = 9.0 Hz, 1H), 5.47 (s, 1H), 3.82 (s, 3H), 3.47 (s, 3H), 1.48 (s, 3H), 1.38 (s, 7.5H), 1.11 (s, 1.5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.4, 171.5, 155.3, 155.1, 137.0, 124.2, 120.0, 116.5, 110.3, 80.7, 64.7, 55.7, 30.4, 28.2, 23.9; HRMS (ESI) calculated for $C_{17}H_{22}N_2O_5$ $[M+Na]^+$: 357.1426, exact mass found 357.1407; $[a]_D^{25} = +10.53$ (c = 0.38, MeOH) (**GMR-III-070**)

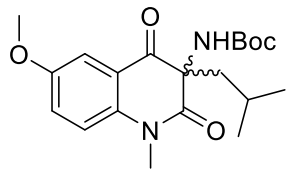


(*R/S*)-*tert*-Butyl (6-methoxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl)carbamate ((*R/S*)-**3-62d**) Prepared according to the general procedure above (*Method G*) from (*R/S*)-**3-54d** (81 mg, 0.24 mmol), LiHMDS (1 M in THF, 0.48 mL, 0.48 mmol), and THF (1.694 mL). The crude mixture was purified on a silica gel column to afford the product as a yellow solid (25.5 mg, 31% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J*

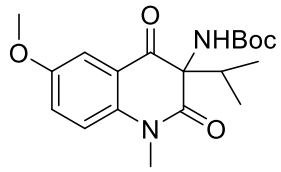
= 3.1 Hz, 1H), 7.18 (dd, *J* = 9.0, 3.1 Hz, 1H), 7.09 (d, *J* = 9.0 Hz, 1H), 5.47 (s, 1H), 3.82 (s, 3H), 3.47 (s, 3H), 1.48 (s, 3H), 1.38 (s, 7.5H), 1.11 (s, 1.5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.4, 171.5, 155.3, 155.1, 137.0, 124.2, 120.0, 116.5, 110.3, 80.7, 64.7, 55.7, 30.4, 28.2, 23.9; HRMS (ESI) calculated for $C_{17}H_{22}N_2O_5$ $[M+Na]^+$: 357.1426, exact mass found 357.1414 (**GMR-III-069**)



(*R* or *S*)-*tert*-Butyl (3-isobutyl-6-methoxy-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl)carbamate ((*R* or *S*)-**3-62e**). Prepared according to the general procedure above (*Method G*) from (*S*)-**3-54e** (95 mg, 0.25 mmol), LiHMDS (1 M in THF, 0.5 mL, 0.5 mmol), and THF (1.7 mL). The crude mixture was purified on a silica gel column to afford the product as a yellow solid. The enantiomeric enrichment was observed by chiral HPLC. (73.6 mg, 77% yield, 84% ee). mp: 167 – 169 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 3.1 Hz, 1H), 7.17 (dd, *J* = 9.0, 3.1 Hz, 1H), 7.07 (d, *J* = 9.0 Hz, 1H), 5.35 (s, 1H), 3.82 (s, 3H), 3.45 (s, 3H), 1.81 – 1.64 (m, 3H), 1.38 (s, 7.5H), 1.10 (s, 1.5H), 0.82 (dd, *J* = 6.4, 4.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.0, 170.9, 155.3, 155.1, 136.9, 123.9, 121.0, 116.4, 110.1, 80.6, 68.4, 55.7, 46.3, 30.3, 29.6, 28.2, 24.2, 23.8, 23.8; HRMS (ESI) calculated for $C_{20}H_{28}N_2O_5$ $[M+H]^+$: 377.2071, exact mass found 377.2058; $[a]_D^{25} = -17.65$ (c = 0.102, MeOH) (**GMR-III-113**)

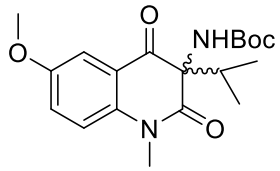


(*R/S*)-*tert*-Butyl (3-isobutyl-6-methoxy-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl)carbamate ((*R/S*)-**3-62e**) Prepared according to the general procedure above (*Method G*) from (*R/S*)-**3-54e** (112.7 mg, 0.3 mmol), LiHMDS (1 M in THF, 0.6 mL, 0.6 mmol), and THF (2 mL). The crude mixture was purified on a silica gel column to afford the product as a yellow solid (24.5 mg, 22% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 3.1 Hz, 1H), 7.17 (dd, *J* = 9.0, 3.1 Hz, 1H), 7.07 (d, *J* = 9.0 Hz, 1H), 5.35 (s, 1H), 3.82 (s, 3H), 3.45 (s, 3H), 1.81 – 1.64 (m, 3H), 1.38 (s, 7.5H), 1.10 (s, 1.5H), 0.82 (dd, *J* = 6.4, 4.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.0, 170.9, 155.3, 155.1, 136.9, 123.9, 121.0, 116.4, 110.1, 80.6, 68.4, 55.7, 46.3, 30.3, 29.6, 28.2, 24.2, 23.8, 23.8; HRMS (ESI) calculated for $C_{20}H_{28}N_2O_5$ $[M+Na]^+$: 399.1896, exact mass found 399.1875 (**GMR-III-071**)

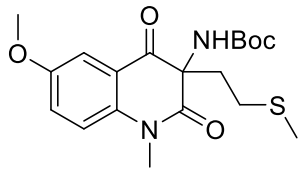


(*R* or *S*)-*tert*-Butyl (3-isopropyl-6-methoxy-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl)carbamate ((*R* or *S*)-**3-62f**). Prepared according to the general procedure above (*Method G*) from *tert*-butyl (*S*)-**3-54f** (37.9 mg, 0.1 mmol), LiHMDS (1 M in THF, 0.2 mL, 0.2 mmol), and THF (0.73 mL). The crude mixture was purified on a silica gel column to afford the product as a yellow solid. The enantiomeric enrichment was observed by chiral HPLC. (13.4 mg, 35% yield, 98% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 3.1 Hz, 1H), 7.15 (dd, *J* = 9.0, 3.1 Hz, 1H), 7.05 (d, *J* = 9.0 Hz,

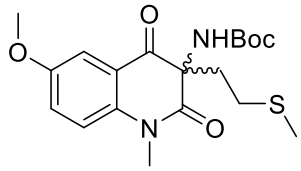
1H), 5.28 (s, 1H), 3.82 (s, 3H), 3.46 (s, 3H), 2.23 – 2.11 (m, 2H), 1.39 (s, 7.5H), 1.10 (s, 1.5H), 0.94 (d, J = 6.9 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$)) δ 192.7, 170.5, 155.4, 155.2, 137.1, 123.7, 122.1, 116.3, 109.8, 80.6, 71.2, 55.7, 35.8, 30.2, 28.2, 27.7, 17.0, 16.9; HRMS (ESI) calculated for $C_{19}H_{26}N_2O_5$ $[M+Na]^+$: 385.1739, exact mass found 385.1731; $[a]_D^{25} = -55.34$ (c = 0.103, MeOH) (**GMR-III-074**)



(*R/S*)-*tert*-Butyl (3-isopropyl-6-methoxy-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl)carbamate ((*R/S*)-**3-62f**) Prepared according to the general procedure above (*Method G*) from (*R/S*)-**3-54f** (32.3 mg, 0.09 mmol), LiHMDS (1 M in THF, 0.18 mL, 0.18 mmol), and THF (0.36 mL). The crude mixture was purified on a silica gel column to afford the product as a yellow solid (5.9 mg, 18% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 3.1 Hz, 1H), 7.15 (dd, J = 9.0, 3.1 Hz, 1H), 7.05 (d, J = 9.0 Hz, 1H), 5.28 (s, 1H), 3.82 (s, 3H), 3.46 (s, 3H), 2.23 – 2.11 (m, 2H), 1.39 (s, 7.5H), 1.10 (s, 1.5H), 0.94 (d, J = 6.9 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.7, 170.5, 155.4, 155.2, 137.1, 123.7, 122.1, 116.3, 109.8, 80.6, 71.2, 55.7, 35.8, 30.2, 28.2, 27.7, 17.0, 16.9; HRMS (ESI) calculated for $C_{19}H_{26}N_2O_5$ $[M+Na]^+$: 385.1739, exact mass found 385.1730 (**GMR-III-073**)

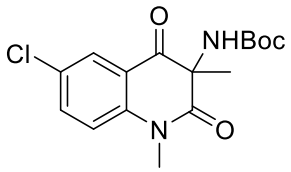


(*R* or *S*)-*tert*-Butyl (6-methoxy-1-methyl-3-(2-(methylthio)ethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl)carbamate ((*R* or *S*)-**3-62g**). Prepared according to the general procedure above (*Method G*) from (*S*)-**3-54g** (123.5 mg, 0.31 mmol), LiHMDS (1 M in THF, 0.62 mL, 0.62 mmol), and THF (2.19 mL). The crude mixture was purified on a silica gel column to afford the product as a yellow solid. The enantiomeric enrichment was observed by chiral HPLC. (59.5 mg, 48% yield, 88% ee). mp: 132 – 134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 3.1 Hz, 1H), 7.17 (dd, *J* = 9.1, 3.1 Hz, 1H), 7.07 (d, *J* = 9.1 Hz, 1H), 5.80 (s, 1H), 3.82 (s, 3H), 3.45 (s, 3H), 2.43 (ddd, *J* = 8.5, 6.7, 1.7 Hz, 2H), 2.07 (ddd, *J* = 16.1, 8.5, 6.7 Hz, 2H), 2.01 (s, 3H), 1.38 (s,7.5H), 1.12 – 1.07 (m, 1.5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.3, 170.3, 155.4, 155.3, 136.8, 124.2, 120.6, 116.6, 110.2, 80.8, 68.1, 55.7, 36.1, 30.4, 28.2, 27.7, 27.5, 15.4; HRMS (ESI) calculated for $C_{19}H_{26}N_2O_5S$ $[M+Na]^+$: 417.1460, exact mass found 417.1448; $[a]_D^{25} = -54.05$ (c = 0.111, MeOH) (**GMR-III-076**)

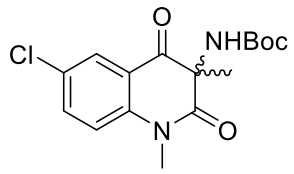


(*R/S*)-*tert*-Butyl (6-methoxy-1-methyl-3-(2-(methylthio)ethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl)carbamate ((*R/S*)-**3-62g**) Prepared according to the general procedure above (*Method G*) from (*R/S*)-**3-54g** (64.9 mg, 0.16 mmol), LiHMDS (1 M in THF, 0.32 mL, 0.32 mmol), and THF (1.15 mL). The crude mixture was purified on a

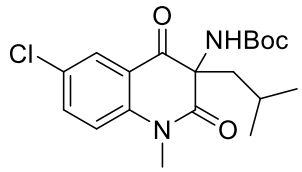
silica gel column to afford the product as a yellow solid (20.3 mg, 31% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 3.1 Hz, 1H), 7.17 (dd, *J* = 9.1, 3.1 Hz, 1H), 7.07 (d, *J* = 9.1 Hz, 1H), 5.80 (s, 1H), 3.82 (s, 3H), 3.45 (s, 3H), 2.43 (ddd, *J* = 8.5, 6.7, 1.7 Hz, 2H), 2.07 (ddd, *J* = 16.1, 8.5, 6.7 Hz, 2H), 2.01 (s, 3H), 1.38 (s, 7.5H), 1.12 – 1.07 (m, 1.5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.3, 170.3, 155.4, 155.3, 136.8, 124.2, 120.6, 116.6, 110.2, 80.8, 68.1, 55.7, 36.1, 30.4, 28.2, 27.7, 27.5, 15.4; HRMS (ESI) calculated for $C_{19}H_{26}N_2O_5S$ $[M+Na]^+$: 417.1460, exact mass found 417.1433 (**GMR-III-075**)



(*R* or *S*)-*tert*-Butyl (6-chloro-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl)carbamate ((*R* or *S*)-**3-63d**). Prepared according to the general procedure above (*Method G*) from (*S*)-**3-55d** (141 mg, 0.42 mmol), LiHMDS (1 M in THF, 0.84 mL, 0.84 mmol), and THF (2.91 mL). The crude mixture was purified on a silica gel column to afford the product as a white solid. The enantiomeric enrichment was observed by chiral HPLC. (87.1 mg, 90% yield, 90% ee). mp: 202 - 207 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.8 Hz, 1H), 7.50 (d, *J* = 12.3 Hz, 1H), 7.08 (dd, *J* = 8.9, 2.9 Hz, 1H), 5.80 (s, 1H), 3.43 (s, 3H), 1.46 (s, 3H), 1.33 (s, 7.5H), 1.07 (s, 1.5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.5, 171.8, 155.2, 141.3, 135.7, 128.8, 128.1, 120.5, 116.7, 80.8, 64.9, 30.5, 28.1, 27.7, 23.4; HRMS (ESI) calculated for $C_{16}H_{19}ClN_2O_4$ $[M+Na]^+$: 361.0901, exact mass found 361.0906; $[a]_D^{25} = +88.41$ (c = 0.164, MeOH) (**GMR-III-114**)

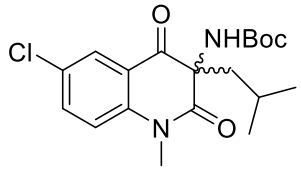


(*R/S*)-*tert*-Butyl (6-chloro-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl)carbamate ((*R/S*)-**3-63d**) Prepared according to the general procedure above (*Method G*) from (*R/S*)-**3-55d** (17.7 mg, 0.05 mmol), LiHMDS (1 M in THF, 0.104 mL, 0.10 mmol), and THF (0.365 mL). The crude mixture was purified on a silica gel column to afford the product as a yellow solid (18.4 mg, >99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.8 Hz, 1H), 7.50 (d, *J* = 2.9 Hz, 1H), 7.08 (dd, *J* = 8.8, 2.9 Hz, 1H), 5.80 (s, 1H), 3.43 (s, 3H), 1.46 (s, 3H), 1.33 (s, 7.5H), 1.07 (s, 1.5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.5, 171.8, 155.2, 141.3, 135.7, 128.8, 128.1, 120.5, 116.7, 80.8, 64.9, 30.5, 28.1, 27.7, 23.4; HRMS (ESI) calculated for $C_{16}H_{19}ClN_2O_4$ $[M+Na]^+$: 361.0901, exact mass found 361.0907 (**GMR-III-078**)

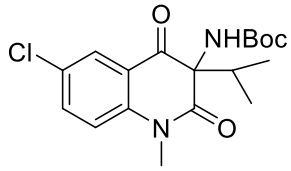


(*R* or *S*)-*tert*-Butyl (6-chloro-3-isobutyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl)carbamate ((*R* or *S*)-**3-63e**). Prepared according to the general procedure above (*Method G*) from (*S*)-**3-55e** (144.9 mg, 0.38 mmol), LiHMDS (1 M in THF, 0.76 mL, 0.76 mmol), and THF (2.66 mL). The crude mixture was purified on a silica gel column to afford the product as a yellow solid. The enantiomeric enrichment was observed by chiral HPLC. (13.1 mg, 9% yield, 97% ee). mp: 180 - 183 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 2.6 Hz, 1H), 7.53 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.09 (d, *J* = 8.9 Hz, 1H), 5.36 (s, 1H), 3.46 (s, 3H), 1.80 – 1.59 (m, 3H), 1.38 (s, 7.5H), 1.10 (s, 1.5H),

0.82 (dd, *J* = 6.3, 4.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.0, 171.1, 155.1, 141.2, 135.5, 128.8, 127.9, 121.4, 116.5, 80.9, 68.6, 46.0, 30.4, 28.2, 27.7, 24.2, 23.8; HRMS (ESI) calculated for $C_{19}H_{25}ClN_2O_4$ $[M+Na]^+$: 403.1401, exact mass found 403.1376; $[a]_D^{25} = -8.86$ (c = 0.079, MeOH) (**GMR-III-081**)

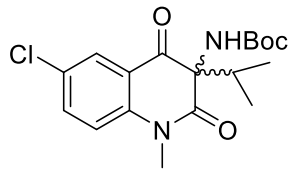


(*R/S*)-*tert*-Butyl (6-chloro-3-isobutyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl)carbamate ((*R/S*)-**3-63e**) Prepared according to the general procedure above (*Method G*) from (*R/S*)-**3-63e** (144.2 mg, 0.3 mmol), LiHMDS (1 M in THF, 0.6 mL, 0.6 mmol), and THF (2.1 mL). The crude mixture was purified on a silica gel column to afford the product as a yellow solid (35.1 mg, 31% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 2.6 Hz, 1H), 7.53 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.09 (d, *J* = 8.9 Hz, 1H), 5.36 (s, 1H), 3.46 (s, 3H), 1.80 – 1.59 (m, 3H), 1.38 (s, 7.5H), 1.10 (s, 1.5H), 0.82 (dd, *J* = 6.3, 4.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.0, 171.1, 155.1, 141.2, 135.5, 128.8, 127.9, 121.4, 116.5, 80.9, 68.6, 46.0, 30.4, 28.2, 27.7, 24.2, 23.8; HRMS (ESI) calculated for $C_{19}H_{25}ClN_2O_4$ $[M+Na]^+$: 403.1401, exact mass found 403.1407 (**GMR-III-080**)

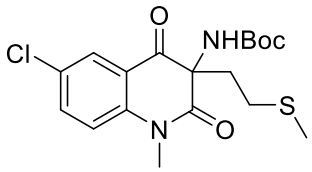


(*R* or *S*)-*tert*-Butyl (6-chloro-3-isopropyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl)carbamate ((*R* or *S*)-**3-63f**). Prepared according to the general procedure above (*Method G*) from (*S*)-**3-55f** (72.6 mg, 0.2 mmol), LiHMDS (1 M in

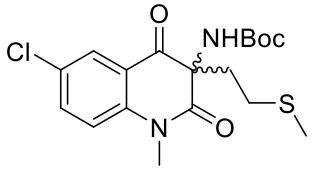
THF, 0.4 mL, 0.4 mmol), and THF (1.37 mL). The crude mixture was purified on a silica gel column to afford the product as a yellow solid. The enantiomeric enrichment was observed by chiral HPLC. (19.3 mg, 27% yield, 95% ee). mp: 109 - 110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 2.6 Hz, 1H), 7.51 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.07 (d, *J* = 8.8 Hz, 1H), 5.30 (s, 1H), 3.47 (s, 3H), 2.24 – 2.11 (m, 1H), 1.38 (s, 7.5H), 1.10 (s, 1.5H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.88 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.7, 170.7, 155.5, 141.4, 135.4, 128.7, 127.5, 122.4, 116.4, 80.8, 71.4, 35.7, 30.3, 28.1, 27.7, 17.0, 16.9; HRMS (ESI) calculated for $C_{19}H_{25}ClN_2O_4$ $[M+Na]^+$: 389.1244, exact mass found 389.1258; $[a]_D^{25} = -0.98$ (c = 1.02, MeOH) (**GMR-III-082**)



(*R/S*)-*tert*-Butyl (6-chloro-3-isopropyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl)carbamate ((*R/S*)-**3-63f**) Prepared according to the general procedure above (*Method G*) from (*R/S*)-**3-55f** (20.1 mg, 0.06 mmol), LiHMDS (1 M in THF, 0.12 mL, 0.12 mmol), and THF (0.39 mL). The crude mixture was purified on a silica gel column to afford the product as a yellow solid (5.6 mg, 28% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 2.6 Hz, 1H), 7.51 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.07 (d, *J* = 8.8 Hz, 1H), 5.30 (s, 1H), 3.47 (s, 3H), 2.24 – 2.11 (m, 1H), 1.38 (s, 7.5H), 1.10 (s, 1.5H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.88 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.7, 170.7, 155.5, 141.4, 135.4, 128.7, 127.5, 122.4, 116.4, 80.8, 71.4, 35.7, 30.3, 28.1, 27.7, 17.0, 16.9; HRMS (ESI) calculated for $C_{19}H_{25}ClN_2O_4$ $[M+Na]^+$: 389.1244, exact mass found 389.1230 (**GMR-III-115**)

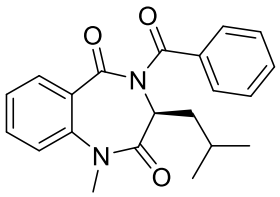


(*R* or *S*)-*tert*-Butyl (6-chloro-1-methyl-3-(2-(methylthio)ethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl)carbamate ((*R* or *S*)-**3-63g**). Prepared according to the general procedure above (*Method G*) from (*S*)-**3-55g** (34.1 mg, 0.0.9 mmol), LiHMDS (1 M in THF, 0.18 mL, 0.18 mmol), and THF (0.6 mL). The crude mixture was purified on a silica gel column to afford the product as a tacky yellow solid. The enantiomeric enrichment was observed by chiral HPLC. (23.3 mg, 68% yield, 82% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 2.6 Hz, 1H), 7.55 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.10 (d, *J* = 8.8 Hz, 1H), 5.79 (s, 1H), 3.47 (s, 3H), 2.44 (ddd, *J* = 8.5, 6.7, 2.0 Hz, 2H), 2.14 – 1.99 (m, 5H), 1.38 (s, 7.5H), 1.11 (s, 1.5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.3, 170.5, 155.3, 141.2, 135.8, 129.0, 128.1, 121.0, 116.6, 81.1, 68.2, 35.8, 30.5, 28.1, 27.7, 27.4, 15.5; HRMS (ESI) calculated for $C_{18}H_{23}ClN_2O_4S$ $[M+H]^+$: 421.0959, exact mass found 421.0960; $[a]_D^{25} = +9.48$ (c = 0.116, MeOH) (**GMR-III-116**)



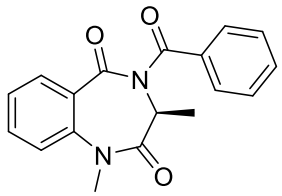
(*R/S*)-*tert*-Butyl (6-chloro-1-methyl-3-(2-(methylthio)ethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl)carbamate ((*R/S*)-**3-63g**) Prepared according to the general procedure above (*Method G*) from (*R/S*)-**3-55g** (153.1mg, 0.38 mmol), LiHMDS (1 M in THF, 0.76 mL, 0.76 mmol), and THF (2.69 mL). The crude mixture was purified on a silica gel column to afford the product as a tacky yellow solid (12.2 mg, 8% yield). ^{1}H

NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 2.6 Hz, 1H), 7.55 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.10 (d, *J* = 8.8 Hz, 1H), 5.79 (s, 1H), 3.47 (s, 3H), 2.44 (ddd, *J* = 8.5, 6.7, 2.0 Hz, 2H), 2.14 – 1.99 (m, 5H), 1.38 (s, 7.5H), 1.11 (s, 1.5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.3, 170.5, 155.3, 141.2, 135.8, 129.0, 128.1, 121.0, 116.6, 81.1, 68.2, 35.8, 30.5, 28.1, 27.7, 27.4, 15.5; HRMS (ESI) calculated for $C_{18}H_{23}ClN_2O_4S$ $[M+H]^+$: 399.1140, exact mass found 399.1111 (**GMR-III-083**)

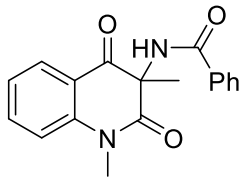


(*S*)-4-Benzoyl-3-isobutyl-1-methyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione ((*S*)-**3-70a**). Prepared using the general procedure above (*Method H*) from (*S*)-**3-34d** (150 mg, 0.61 mmol), benzoyl chloride (0.142 mL, 1.22 mmol), Et_3N (0.17 mL, 1.22 mmol, 0.7255 g/mL), and Methylene chloride (10 mL/mmol). The crude mixture was purified on a silica gel column (1:1 EtOAc:Hex) to afford the product as a clear oil (98.3 mg, 46% yield). mp: 97 – 101 °C; Two Ddiastereomers were observed by NMR at room temperature (0.7:0.3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.78 (m, 1H), 7.66 – 7.54 (m, 2.8H), 7.52 – 7.42 (m, 1.2H), 7.41 – 7.35 (m, 1.2H), 7.33 – 7.21 (m, 2.8H), 5.39 (t, *J* = 8.2 Hz, 0.7H), 4.10 (q, *J* = 7.1 Hz, 0.3H), 3.52 – 3.44 (m, 3H), 1.99 – 1.83 (m, 0.3H), 1.59 (dp, *J* = 13.3, 6.7 Hz, 0.7H), 1.31 (ddd, *J* = 8.2, 6.7, 1.8 Hz, 06H), 1.24 (t, *J* = 7.1 Hz, 1.4H), 0.87 – 0.75 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 173.2, 171.1, 170.9, 167.6, 167.3, 140.9, 140.6, 135.1, 134.7, 134.0, 133.4, 132.9, 132.2, 131.7, 130.3, 130.0, 129.7, 128.3, 128.2, 127.2, 125.7, 125.5, 121.1, 121.0, 60.3, 59.0, 54.4, 38.3, 36.2, 35.2, 25.8, 22.5, 22.1, 22.0, 21.0, 14.1. HRMS (ESI) calculated for $C_{21}H_{22}N_2O_3$ $[M+H]^+$:

351.1703, exact mass found 351.1714; $[a]_D^{25} = +69.12$ (c = 0.136, MeOH) (**GMR-II-121**)

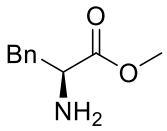


(*S*)-4-Benzoyl-1,3-dimethyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione ((*S*)-**3-70b**). Prepared using the general procedure above (*Method H*) from (*S*)-**3-34d** (0.5 mg, 2.45 mmol), benzoyl chloride (0.57 mL, 4.9 mmol), Et_3N (0.68 mL, 4.9 mmol, 0.7255 g/mL), and Methylene chloride (25 mL/mmol). The crude mixture was purified on a silica gel column (1:1 EtOAc:Hex) to afford the product as a white solid (564.9 mg, 75% yield). mp: 179 - 180°C; Two diastereomers observed at room temperature by NMR (0.6:0.4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.19 (m, 9H), 5.46 (d, *J* = 7.3 Hz, 0.6H), 4.52 (d, *J* = 7.0 Hz, 0.4H), 3.50 (s, 3H), 4.52 (d, *J* = 7.0 Hz, 1.2H), 1.24 (d, *J* = 7.3 Hz, 1.8H). HRMS (ESI) calculated for $C_{18}H_{16}N_2O_3$ $[M+H]^+$: 309.1234, exact mass found 309.1239; $[a]_D^{25} = -34.71$ (c = 0.193, MeOH) (**GMR-II-136**)



(*R or S*)-*N*-(1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl)benzamide (**3-72**). Prepared using the general procedure above (*Method G*) from **3-70b** (50 mg, 0.16 mmol), LiHMDS (1 M in THF, 0.32 mL, 0.32 mmol), and THF (2.43 mL). The crude mixture was purified on a silica gel column (1:1 EtOAc:Hex) to afford the product as a tan solid (39.3 mg, 79% yield). mp: 227 - 228 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.02

(d, *J* = 7.5 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 2H), 7.74 (t, *J* = 8.7, 8.0 Hz, 1H), 7.54 (t, *J* = 8.0, 7.1 Hz, 1H), 7.43 (td, *J* = 7.5, 5.6 Hz, 3H), 7.24 (t, *J* = 8.3 Hz, 1H), 3.51 (s, 3H), 1.59 (s, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 193.3, 172.0, 168.5, 142.8, 136.3, 132.5, 131.7, 128.0, 127.8, 127.4, 122.9, 119.6, 115.4, 65.1, 29.2, 21.4. HRMS (ESI) calculated for $C_{18}H_{16}N_2O_3$ $[M+H]^+$: 309.1234, exact mass found 309.1243; $[a]_D^{25} = -10.87$ (c = 0.092, MeOH) (**GMR-II-138**)



Methyl L-phenylalaninate (**4-1**): Under N_2, thionyl chloride (0.96 mL, 13 mmol, 1.64 g/mL, 1.1 equiv) was added to L-phenylalanine (2.0 g, 13 mmol, 1 equiv) in MeOH (9.7 mL, 0.8 mL/mmol). The reaction was refluxed for four hours. The mixture was cooled, concentrated *in vacuo*, MeOH was added/stripped three times, and the obtained solid was recrystallized in EtOH to afford the product as a white solid (1.9371 g, 74% yield). mp: 241 – 244 °C; ^{1}H NMR (400 MHz, D_2O) δ 7.36 – 7.25 (m, 3H), 7.18 (dd, *J* = 7.8, 1.4 Hz, 2H), 4.33 (dd, *J* = 7.5, 5.9 Hz, 1H), 3.73 (s, 3H), 3.24 (dd, *J* = 14.5, 5.9 Hz, 1H), 3.13 (dd, *J* = 14.5, 7.5 Hz, 1H). ^{13}C NMR (101 MHz, D_2O) δ 169.9, 133.6, 129.3, 129.2, 128.0, 54.0, 53.5, 35.5. Spectra matched the literature.[32] $[a]_D^{25} = -28.21$ (c = 0.078, MeOH) (**GMR-II-009**)

4.4 Bibliography

1. Gaul, C.; Arvidsson, P. I.; Bauer, W.; Gawley, R. E.; Seebach, D. Computational, Reactir-, and Nmr-Spectroscopic Investigations on the Chiral Formyl Anion Equivalent N-(A-Lithiomethylthiomethyl)-4-Isopropyl-5,5-Diphenyloxazolidin-2-One and Related Compounds. *Chem. Eur. J.* **2001**, *7*, 4117-4125.

2. Fernandes, R. A.; Chavan, V. P. A Concise Asymmetric Synthesis of (–)-Hongconin and (–)-1-Epi-Hongconin. *Eur, J. Org. Chem.* **2010**, *2010*, 4306-4311.

3. Shang, S.; Iwadare, H.; Macks, D. E.; Ambrosini, L. M.; Tan, D. S. A Unified Synthetic Approach to Polyketides Having Both Skeletal and Stereochemical Diversity. *Org. Lett.* **2007**, *9*, 1895-1898.

4. Uraguchi, D.; Kizu, T.; Ohira, Y.; Ooi, T. Enantioselective Protonation of [Small Alpha]-Hetero Carboxylic Acid-Derived Ketene Disilyl Acetals under Chiral Ionic Bronsted Acid Catalysis. *Chem. Commun.* **2014**, *50*, 13489-13491.

5. Chin, Y.-J.; Wang, S.-Y.; Loh, T.-P. Synthesis of Iriomoteolide-1a C13−C23 Fragment Via Asymmetric Conjugate Addition and Julia−Kocienski Coupling Reaction. *Org. Lett.* **2009**, *11*, 3674-3676.

6. Qi, W.; McIntosh, M. C. Acyclic 1,4-Stereocontrol Via Reductive 1,3-Transpositions. *Org. Lett.* **2008**, *10*, 357-359.

7. Mayer, S. C.; Ramanjulu, J.; Vera, M. D.; Pfizenmayer, A. J.; Joullie, M. M. Synthesis of New Didemnin B Analogs for Investigations of Structure/Biological Activity Relationships. *J. Org. Chem.* **1994**, *59*, 5192-5205.

8. Ohtani, T.; Tsukamoto, S.; Kanda, H.; Misawa, K.; Urakawa, Y.; Fujimaki, T.; Imoto, M.; Takahashi, Y.; Takahashi, D.; Toshima, K. Total Synthesis of Incednam, the Aglycon of Incednine. *Org. Lett.* **2010**, *12*, 5068-5071.

9. Yoshida, M.; Takeuchi, H.; Ishida, Y.; Yashiroda, Y.; Yoshida, M.; Takagi, M.; Shin-ya, K.; Doi, T. Synthesis, Structure Determination, and Biological Evaluation of Destruxin E. *Org. Lett.* **2010**, *12*, 3792-3795.

10. Murata, Y.; Kamino, T.; Hosokawa, S.; Kobayashi, S. Stereocontrolled Preparation of 1,2-Diol with Quaternary Chiral Center. *Tetrahedron Lett.* **2002**, *43*, 8121-8123.

11. Desage-El Murr, M.; Nowaczyk, S.; Le Gall, T.; Mioskowski, C. Synthesis of Pulvinic Acid and Norbadione a Analogues by Suzuki–Miyaura Cross-Coupling of Benzylated Intermediates. *Eur, J. Org. Chem.* **2006**, *2006*, 1489-1498.

12. Seizert, C. A.; Ferreira, E. M. An Examination of the Scope and Stereochemistry of the Ireland–Claisen Rearrangement of Boron Ketene Acetals. *Chem. Eur. J.* **2014**, *20*, 4460-4468.

13. Bagmanov, B. T. Effect of Structural Factors and Solvent Nature in Bromination of Anilines. *Russ. J. Appl. Chem.* **2009**, *82*, 1570-1576.

14. Dong, G.; Wang, S.; Miao, Z.; Yao, J.; Zhang, Y.; Guo, Z.; Zhang, W.; Sheng, C. New Tricks for an Old Natural Product: Discovery of Highly Potent Evodiamine Derivatives as Novel Antitumor Agents by Systemic Structure–Activity Relationship Analysis and Biological Evaluations. *J. Med. Chem.* **2012**, *55*, 7593-7613.

15. Jönsson, S.; Andersson, G.; Fex, T.; Fristedt, T.; Hedlund, G.; Jansson, K.; Abramo, L.; Fritzson, I.; Pekarski, O.; Runström, A.; Sandin, H.; Thuvesson, I.; Björk, A.

Synthesis and Biological Evaluation of New 1,2-Dihydro-4-Hydroxy-2-Oxo-3-Quinolinecarboxamides for Treatment of Autoimmune Disorders: Structure−Activity Relationship. *J. Med. Chem.* **2004**, *47*, 2075-2088.

16. Antolak, S. A.; Yao, Z.-K.; Richoux, G. M.; Slebodnick, C.; Carlier, P. R. Enantioselective Deprotonative Ring Contraction of N1-Methyl-N4-Boc-Benzo[E][1,4]Diazepine-2,5-Diones. *Org. Lett.* **2014**, *16*, 5204-5207.

17. Clark, R. L.; Carter, K. C.; Mullen, A. B.; Coxon, G. D.; Owusu-Dapaah, G.; McFarlane, E.; Duong Thi, M. D.; Grant, M. H.; Tettey, J. N. A.; Mackay, S. P. Identification of the Benzodiazepines as a New Class of Antileishmanial Agent. *Bioorg. Med. Chem.* **2007**, *17*, 624-627.

18. Leonard, K.; Marugan, J. J.; Raboisson, P.; Calvo, R.; Gushue, J. M.; Koblish, H. K.; Lattanze, J.; Zhao, S.; Cummings, M. D.; Player, M. R.; Maroney, A. C.; Lu, T. Novel 1,4-Benzodiazepine-2,5-Diones as Hdm2 Antagonists with Improved Cellular Activity. *Bioorg. Med. Chem.* **2006**, *16*, 3463-3468.

19. Cheng, M.-F.; Yu, H.-M.; Ko, B.-W.; Chang, Y.; Chen, M.-Y.; Ho, T.-I.; Tsai, Y.-M.; Fang, J.-M. Practical Synthesis of Potential Endothelin Receptor Antagonists of 1,4-Benzodiazepine-2,5-Dione Derivatives Bearing Substituents at the C3-, N1- and N4-Positions. *Org. Biomol. Chem.* **2006**, *4*, 510-518.

20. Bräuer, A.; Beck, P.; Hintermann, L.; Groll, M. Structure of the Dioxygenase Asqj: Mechanistic Insights into a One-Pot Multistep Quinolone Antibiotic Biosynthesis. *Angew. Chem. Int. Ed.* **2016**, *55*, 422-426.

21. Tedesco, R.; Shaw, A. N.; Bambal, R.; Chai, D.; Concha, N. O.; Darcy, M. G.; Dhanak, D.; Fitch, D. M.; Gates, A.; Gerhardt, W. G.; Halegoua, D. L.; Han, C.;

Hofmann, G. A.; Johnston, V. K.; Kaura, A. C.; Liu, N.; Keenan, R. M.; Lin-Goerke, J.; Sarisky, R. T.; Wiggall, K. J.; Zimmerman, M. N.; Duffy, K. J. 3-(1,1-Dioxo-2h-(1,2,4)-Benzothiadiazin-3-Yl)-4-Hydroxy-2(1h)-Quinolinones, Potent Inhibitors of Hepatitis C Virus Rna-Dependent Rna Polymerase. *J. Med. Chem.* **2006**, *49*, 971-983.

22. Charoensutthivarakul, S.; David Hong, W.; Leung, S. C.; Gibbons, P. D.; Bedingfield, P. T. P.; Nixon, G. L.; Lawrenson, A. S.; Berry, N. G.; Ward, S. A.; Biagini, G. A.; O'Neill, P. M. 2-Pyridylquinolone Antimalarials with Improved Antimalarial Activity and Physicochemical Properties. *Med. Chem. Comm.* **2015**, *6*, 1252-1259.

23. Tomassoli, I.; Ismaili, L.; Pudlo, M.; de los Ríos, C.; Soriano, E.; Colmena, I.; Gandía, L.; Rivas, L.; Samadi, A.; Marco-Contelles, J.; Refouvelet, B. Synthesis, Biological Assessment and Molecular Modeling of New Dihydroquinoline-3-Carboxamides and Dihydroquinoline-3-Carbohydrazide Derivatives as Cholinesterase Inhibitors, and Ca Channel Antagonists. *Eur. J. Med. Chem.* **2011**, *46*, 1-10.

24. Sheibley, F. E. 6,8-Diiodobenzoyleneurea, and the Interaction of 5,7-Dihalogenoisatoic Anhydrides with Ammonia and with Ethylamine; 3-Ethyl-6,8-Dihalogenobenzoyleneureas. *J. Org. Chem.* **1947**, *12*, 743-751.

25. Guan, Z.-H.; Chen, M.; Ren, Z.-H. Palladium-Catalyzed Regioselective Carbonylation of C–H Bonds of N-Alkyl Anilines for Synthesis of Isatoic Anhydrides. *J. Am. Chem. Soc.* **2012**, *134*, 17490-17493.

26. Levkin, P. A.; Ruderisch, A.; Schurig, V. Combining the Enantioselectivity of a Cyclodextrin and a Diamide Selector in a Mixed Binary Gas-Chromatographic Chiral Stationary Phase. *Chirality* **2006**, *18*, 49-63.

27. Kantam, M. L.; Annapurna, M.; Likhar, P. R.; Srinivas, P.; Mirzadeh, N.; Bhargava, S. K. Palladium Complexes Containing Multidentate Phenoxy–Pyridyl–Amidate Ligands: Highly Efficient Catalyst for Heck Coupling of Deactivated Aryl Halides. *J. Organomet. Chem.* **2013**, *723*, 129-136.

28. Akssira, M.; Boumzebra, M.; Kasmi, H.; Dahdouh, A.; Roumestant, M. L.; Viallefont, P. New Routes to 1,4- Benzodiazepin-2,5-Diones. *Tetrahedron* **1994**, *50*, 9051-9060.

29. Coste, J.; Frerot, E.; Jouin, P. Coupling N-Methylated Amino Acids Using Pybrop and Pyclop Halogenophosphonium Salts: Mechanism and Fields of Application. *J. Org. Chem.* **1994**, *59*, 2437-2446.

30. Aitken, R. A.; Murray, L. New Gas-Phase Cascade Reactions of Stabilized Phosphorus Ylides Leading to Ring-Fused Indoles and to Quinolines. *J. Org. Chem.* **2008**, *73*, 9781-9783.

31. Wang, Y.; Zhang, M.; Cao, S.; Lin, H.; Gao, M.; Li, Z. Synthesis of 1-Substituted 4(1h)-Quinazolinones under Solvent-Free Conditions. *Synth. Commun.* **2012**, *42*, 2715-2727.

32. Martinez-Montero, L.; Diaz-Rodriguez, A.; Gotor, V.; Gotor-Fernandez, V.; Lavandera, I. Broadening the Chemical Scope of Laccases: Selective Deprotection of N-Benzyl Groups. *Green Chem.* **2015**, *17*, 2794-2798.