The Asymmetric Synthesis of Oxo-piperidines and Oxo-pyrrolidines

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DECLARATION STATEMENT

I, Kin Cheung Yau, confirm that the work presented in this thesis is my own. Where information has been derivied from other sources, I confirm that this has been indicated in the thesis.

Kin Cheung Yau

ABSTRACT

Chapter 1 describes the attempts to synthesize piperidin-2-ones via an aza-Michael-Michael annulation, which were unsuccessful. A general route for the synthesis of piperidin-2,4-diones from *β*-keto esters via a Dieckmann cyclisation was proposed and five piperidin-2,4-diones with different substituents at positions-5 and -6 were prepared. An asymmetric route to 1-unsubstituted piperidin-2,4-diones was also developed which involved the use of Davies' chiral auxiliary to induce an asymmetric Michael addition.

Chapter 2 describes a new approach to the synthesis of codeine. The piperidin-4-one ring was prepared by a Dieckmann cyclisation; a Robinson annulation was performed to construct the cyclohexenone ring and the key bicyclic intermediate was made. However, attempts to prepare the corresponding benzomorphan via a Grewe cyclisation of the *α*,*β*-unsaturated ketone were not successful. Synthesis of various 2,3-disubstituted piperidin-4-ones using the same strategy as the codeine synthesis was attempted; six different piperidin-4-ones with alkyl and aryl substituents at the 2-position were prepared.

Chapter 3 describes the attempts to synthesize 1,2-dihydropyrrol-3-ones employing the same strategy used to make piperidin-4-ones in Chapter 2. Seven different diester intermediates were successfully prepared but attempts for Dieckman cyclisation failed. The focus was changed to prepare 5-substituted pyrrolidin-3-ones by the protocol used to make piperidin-2,4-diones in chapter 1 and four pyrrolidin-3-ones were made. Enantioselective syntheses using the Davies' chiral auxiliary were attempted and enantiopure 5-methylpyrrolidin-3-one was prepared.

ACKNOWLEDGMENTS

I cannot find any words to express my gratitude to my supervisor, Professor Charles Marson for his continuous guidance and support. I would also like to thank my secondary supervisor, Dr. Erik Arstad for his support.

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Last but not least, I would like to thank my parents, Sandy and Benny and my sister Candy for their unconditional emotional support. Had it not been for their encouragement and understanding, this thesis would not have come about.

ABBREVIATIONS

Ac	acetyl
Ar	aryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad
n-Bu	*n*-butyl
t-Bu	*tert*-butyl
campSO_3H	camphorsulfonic acid
CAN	cerium(IV) ammonium nitrate
d	doublet
DBS	dibenzosuberylamine
DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublet of doublets
de	diastereoisomeric excess
DIPEA	diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide

dt	doublet of triplets
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EI	electron impact
ee	enantiomeric excess
eq	equivalent
ESI	electrospray ionisation
Et	ethyl
EWG	electron-withdrawing group
GABA	γ-aminobutyric acid
gem	geminal
h	hour
HIV	human immunodeficiency virus
HOBt	1-hydroxybenzotriazole
HRMS	high resolution mass spectroscopy
Hz	hertz
IR	infra red
J	coupling constant
KHMDS	potassium hexamethyldisilazide
L	ligand
LDA	lithium diisopropylamine
m	meta
m	multiplet
M	molar
Me	methyl

min	minute
mL	millilitre
mp	melting point
Ms	methanesulfonyl
MVK	methyl vinyl ketone
m/z	mass-to-charge ratio
μL	microlitre
NaHMDS	sodium hexamethyldisilazide
NBS	*N*-bromosuccinimide
NDMBA	1,3-dimethylbarbituric acid
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
o	*ortho*
p	*para*
PG	protecting group
Ph	phenyl
PMP	pentamethylpiperidine
Pr	propyl
i-Pr	isopropyl
q	quartet
R	alkyl
RT	room temperature
s	singlet
t	triplet

TBAF	tetra *n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetra-*n*-propylammonium perruthenate
Ts	*p*-toluenesulfonyl
UV	ultraviolet

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CHAPTER 3

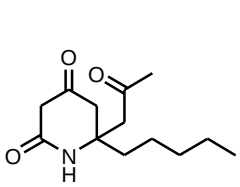
Synthesis of Substituted Pyrrolidin-3-ones and Related Ring Systems

CHAPTER 1

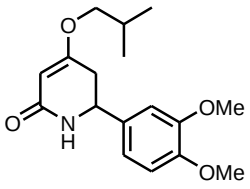
Synthesis of Substituted Piperidin-2,4-diones and Related Ring Systems

1.1 Introduction

The piperidine ring plays an important role in pharmaceutically active compounds and is commonly found in natural compounds such as the alkaloids.[1–5] The oxopiperidines such as piperidin-2-ones are also present in natural alkaloids[3–5] or as a part of various biologically active compounds.[6–8] A scaleable synthetic route to diversely substituted piperidines and oxopiperidines, though very important to drug development, is still challenging.[9,10] Enantioselective synthesis of the substituted piperidines is even more difficult; although the groups of Meyers,[11] Marazano,[12] and Comins,[13] have made progress in the preparation of enantiopure piperidines, there are limitations for the types and positions of substituents that can be introduced in the ring. Piperidin-2,4-diones are also present in various pharmaceutical compounds,[14–18] but routes to 6-substituted piperidin-2,4-diones are limited.[19]



Adalinine

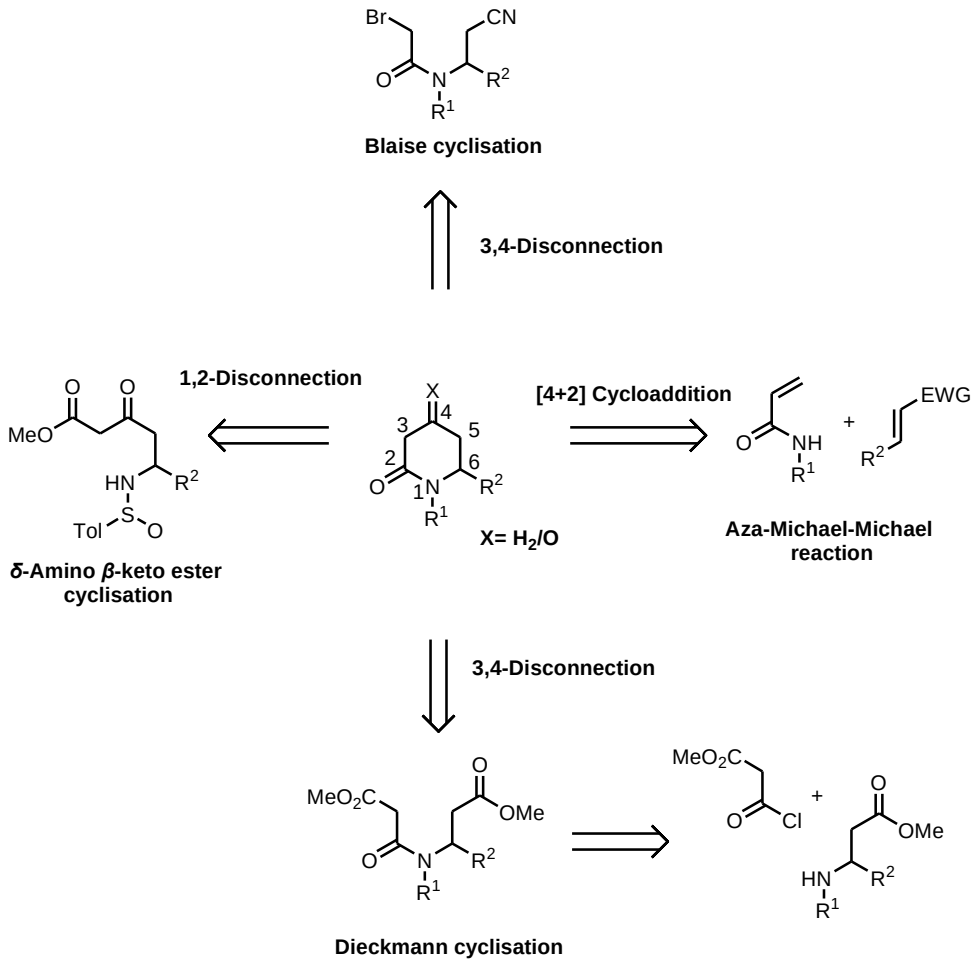


Anti-hypogpycaemic agent[16]

Figure 1.1 Some substituted piperidin-2,4-diones with biological or pharmaceutical activity

1.1.1 Retrosynthetic Analysis for Oxo-Piperidines

Unlike piperidines, straightforward synthetic routes to substituted piperidin-2,4-diones are limited.[19] Retrosynthesis of piperidin-2,4-diones usually involves 3,4-disconnection or 1,2-disconnection (Scheme 1.1). The synthetic strategies are usually based on δ-amino β-ketoester cyclisation,[15,16,20–23] Dieckmann cyclisation,[15,24–26] or Blaise cyclisation.[27] For piperidin-2-ones a [4+2] cycloaddition is also feasible.



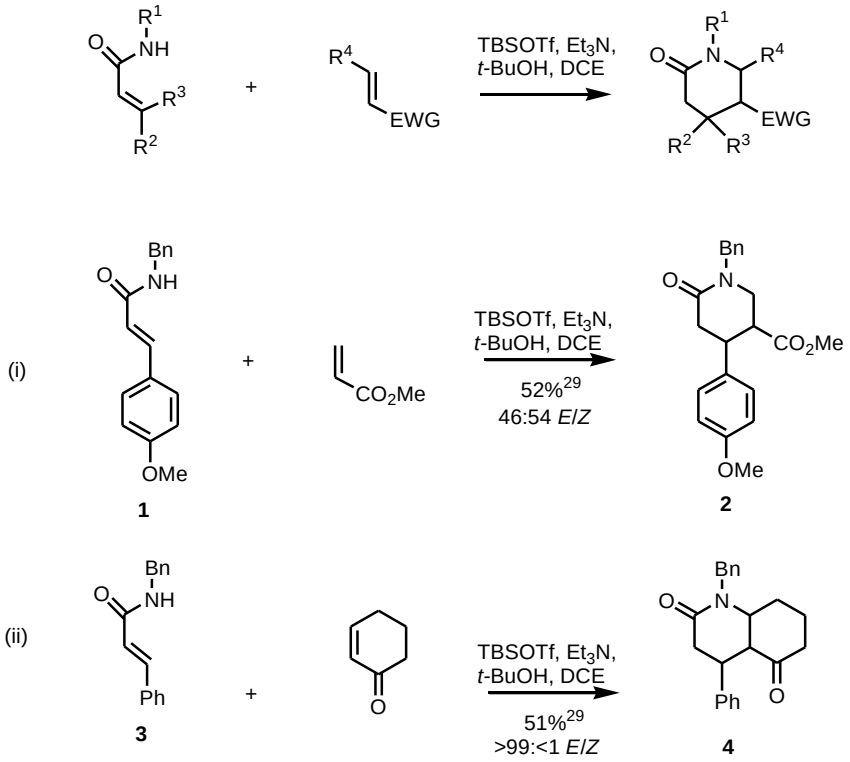
Scheme 1.1 Retrosynthetic analysis of oxopiperidines

1.1.2 Approaches to the Synthesis of Oxo-piperidines

(i) [4+2] Cycloaddition to Piperidin-2-ones

In 2005, Ihara reported a one-pot synthesis of piperidin-2-ones by reaction of an electrophilic alkene with an *α,β*-unsaturated amide in an aza-Michael-Michael process,[28,29] a very powerful method for the synthesis of piperidin-2-ones with 4- and 6-substitutions. Bicyclic piperidin-2-ones **4** were also synthesized (eq(ii), Scheme 1.2). However, only *N*-substituted piperidin-2-ones could be prepared and it is quite difficult to incorporate a 3-substituent. It is suprising that this method has not been advanced

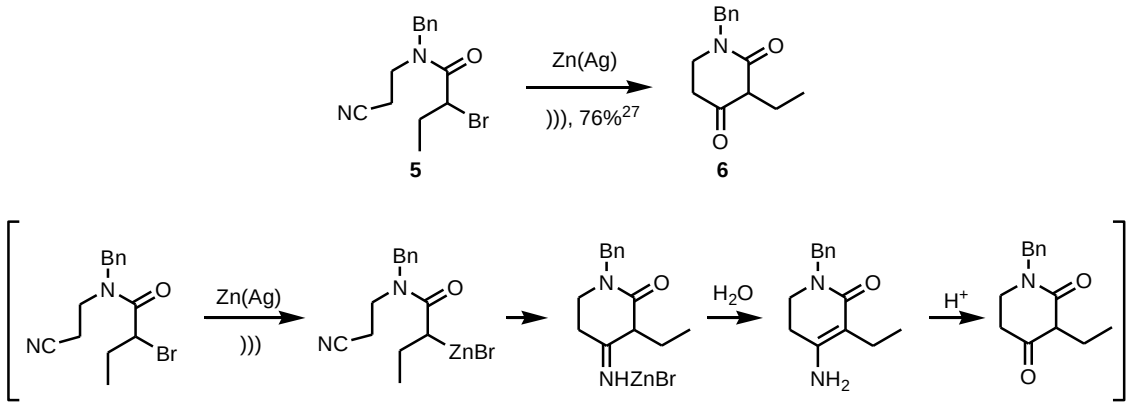
since it was first reported in 2005 by Ihara.[29] Thus, it appeared of interest to exploit the Ihara reaction and extend the scope to make various piperidin-2-ones.



Scheme 1.2 A [4+2] annulation to give piperidin-2-ones

(ii) Intramolecular Blaise cyclisation to piperidin-2,4-diones

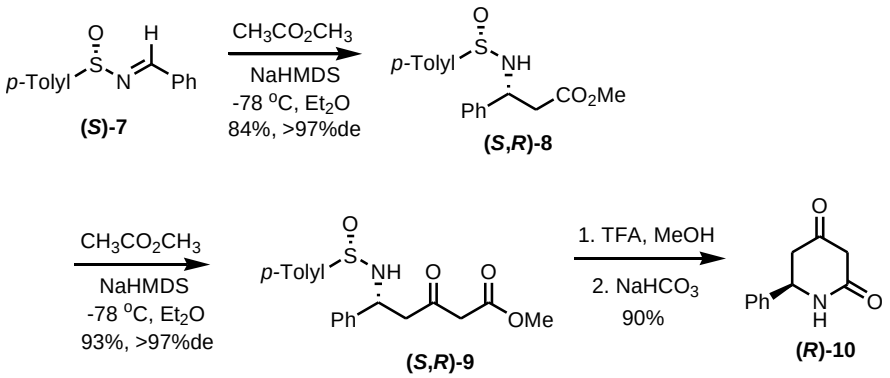
In 1991, Meyers reported the asymmetric synthesis of the *Corynantheine* alkaloids in which the piperidin-2,4-dione ring was formed by an intramolecular Blaise reaction.[27] An organozinc complex is formed by the reaction of zinc with the bromine *alpha* to the amide to give the *alpha*-carbon nucleophile which then attacks the nitrile, leading after hydrolysis to the piperidin-2,4-dione (Scheme 1.3). The limitations is that there is no straightforward synthesis of the precursor α-bromo ester **5**.



Scheme 1.3 Intramolecular Blaise reaction

(iii) *δ*-Amino *β*-ketoester cyclisation to piperidin-2,4-diones

In 2000, Davis reported the asymmetric synthesis of 6-substituted piperidin-2,4-diones by a *δ*-amino *β*-ketoester cyclisation.[23] An asymmetric Michael reaction of the imine **7** with methyl acetate was induced by the chiral *N*-sulfinyl group of **7** to afford the *N*-sulfinyl *β*-phenylalanine **8** (Scheme 1.4). The *δ*-amino *β*-ketoester **9** was made by a Claisen condensation of the amino ester **8** with methyl acetate in the presence of excess NaHMDS.[23] The chiral auxiliary was removed by the use of TFA and then a *δ*-amino *β*-ketoester cyclisation was effected under basic conditions to give the 6-phenylpiperidin-2,4-dione **10**. Davis' approach is powerful because enantiopure *N*-unsubstituted piperidin-2,4-diones can be prepared in a few steps. However, it is difficult to prepare piperidin-2,4-diones with 3- and/or 5-substitutions by this method.



Scheme 1.4 *δ*-Amino *β*-ketoester cyclisation[23]

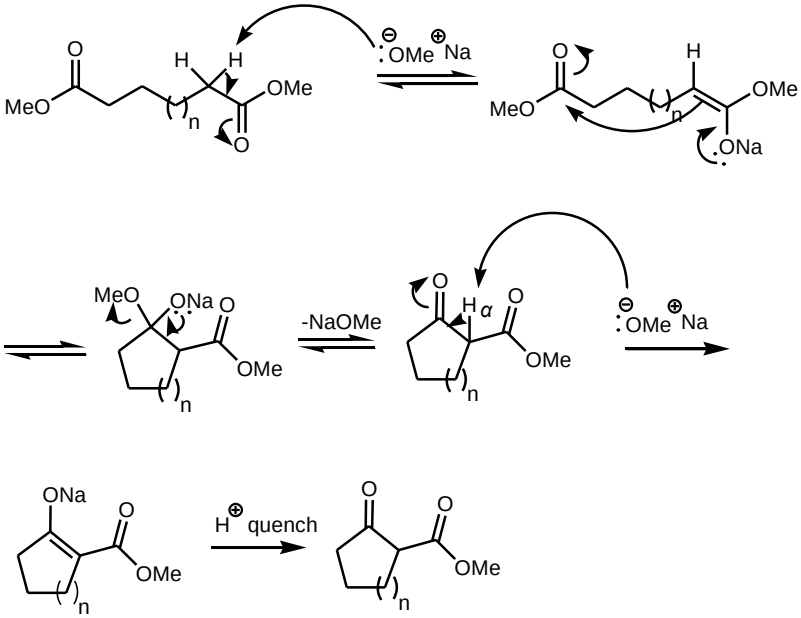
(iv) Dieckmann cyclisation to piperidin-2,4-diones

Dieckmann cyclisation is a widely used approach for making substituted cyclohexanones and cyclopentanones. This can also be applied to the synthesis of oxopiperidines. Using Dieckmann cyclisation to make piperidin-2,4-diones has the advantages that the precursor diesters are easily prepared and the reaction conditions are usually mild. To our knowledge, there are few enantioselective Dieckmann cyclisations that afford 1-unsubstituted piperidin-2,4-diones,[26] although the construction of a bridged piperidin-4-one ring via a diastereoselective Dieckmann reaction has been described.[30]

1.1.3 Background of Dieckmann Cyclisation

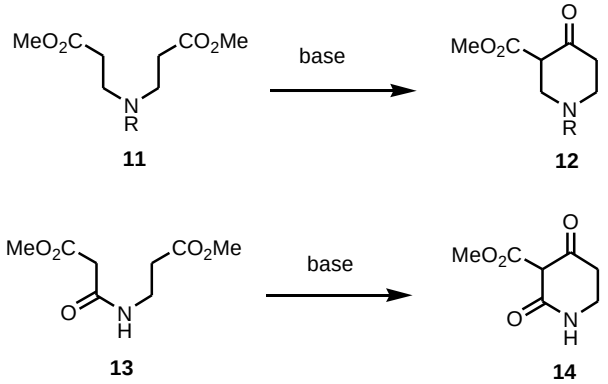
Dieckmann cyclisation is an intramolecular Claisen condensation reaction; the mechanism is shown in Scheme 1.5. A base abstracts a proton from the *alpha* carbon to give the enolate of the ester which reacts with another ester, leading via addition-elimination to ring formation. Once the alkoxy group is displaced to form a ketone, a base abstracts the most acidic proton *alpha* to the ester (marked in diagram) to form an enolate and this step is irreversible. After neutralisation, the desired cyclic

keto ester is formed.



Scheme 1.5 Mechanism of Dieckmann cyclisation

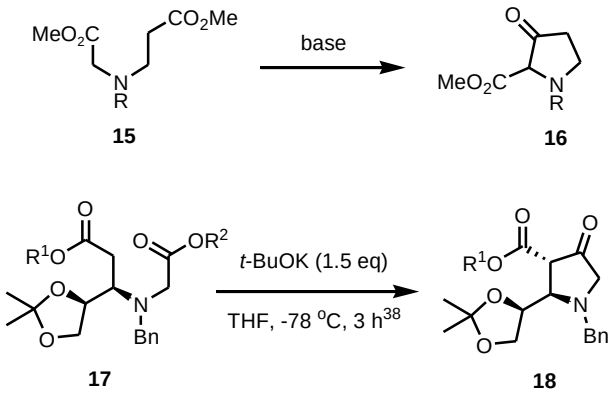
Dieckmann cyclisation has also been used to synthesize piperidin-2-one rings. The amine nitrogen must usually be protected. For the synthesis of piperidin-2,4-diones, although most use protected amides for the Dieckmann cyclisation, there are some cases of unprotected amides affording *N*-unsubstituted piperidin-2,4-diones.[24,31,32]



Scheme 1.6 Representative Dieckmann cyclisations giving 4-oxopiperidines

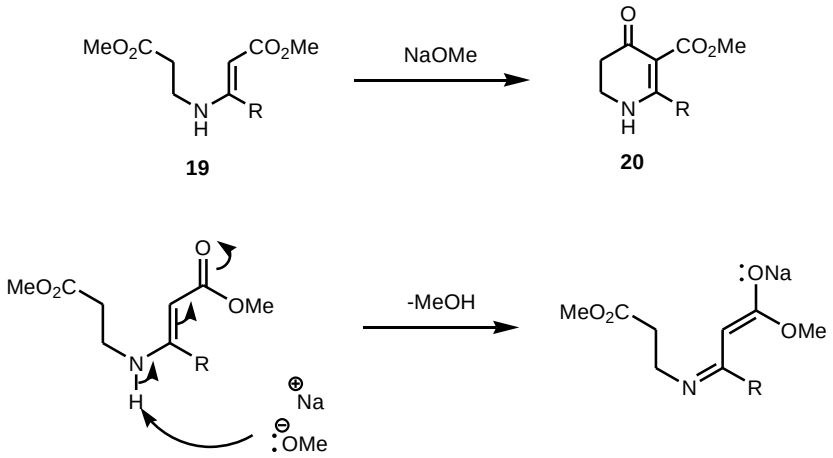
Although Dieckmann cyclisation is widely used to construct cyclopentane rings, there

are only around twenty examples using the reaction to prepare pyrrolidin-3-ones **16**.[33–36] Few of them afford 5-substitution[37] or proceed enantioselectively[38] (Scheme 1.7).



Scheme 1.7 Dieckmann cyclisation to pyrrolidin-3-ones

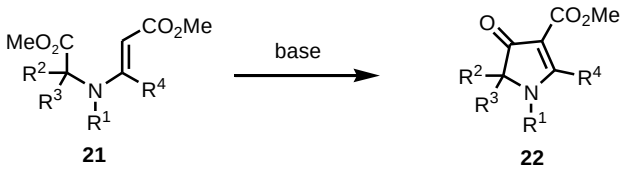
In 1961, Becker showed that enamino esters **19** are also substrates for Dieckmann cyclisations, and afford 5,6-dihydro-3-methoxy-4-pyridones **20**.[39] Sodium methoxide deprotonates the amine group to give an imine enolate (Scheme 1.8) which then participates in a Dieckmann cyclisation to give 5,6-dihydro-3-methoxy-4-pyridones **20**.



Scheme 1.8 Dieckmann cyclisation of enamino esters **19**

Although it seems that Dieckmann cyclisation of enamino esters **21** to give 1,2-dihydropyrrol-3-ones **22** is feasible and convenient, to our knowledge only

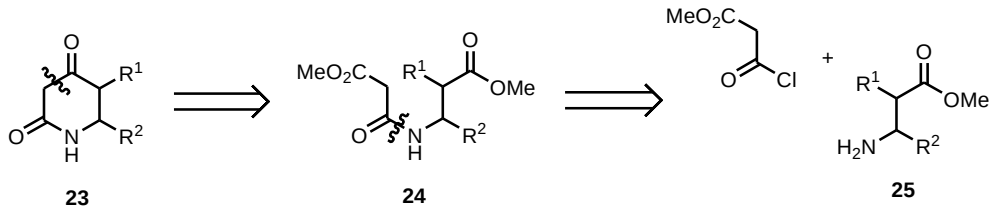
Cambon[35] attempted to do so and reported that **21** did not undergo a Dieckmann cyclisation to give 1,2-dihydropyrrol-3-ones **22**.



Scheme 1.9 Dieckmann cyclisation to 1,2-dihydropyrrol-3-ones **22**

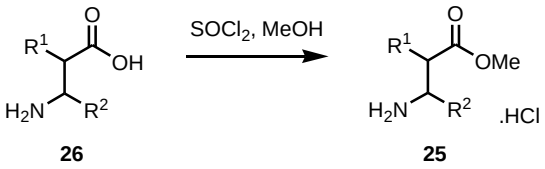
1.1.4 Preparation of *β*-Amino Esters

The main objective of this section is the synthesis of 5,6-disubstituted piperidin-2,4-diones **23** by a Dieckmann cyclisation approach; the retrosynthetic plan is shown in Scheme 1.10. Therefore, an effective preparation of intermediate *β*-amino esters **25** with various R^1 and R^2 is required.



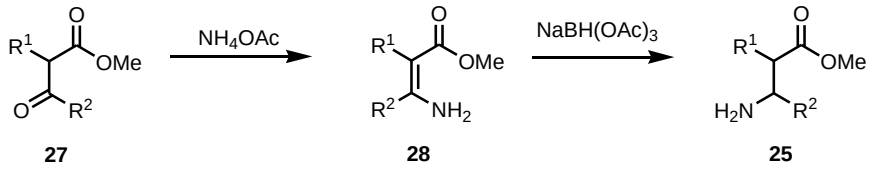
Scheme 1.10 Retrosynthetic plan of piperidin-2,4-diones **23**

The most convenient way of making *β*-amino esters **25** is the traditional $SOCl_2$-activated esterification of *β*-amino acids **26** (Scheme 1.11). However, the choice of commercially-avaliable *β*-amino acids **26** is very limited so other methods will usually be required for making various *β*-amino esters **25**.



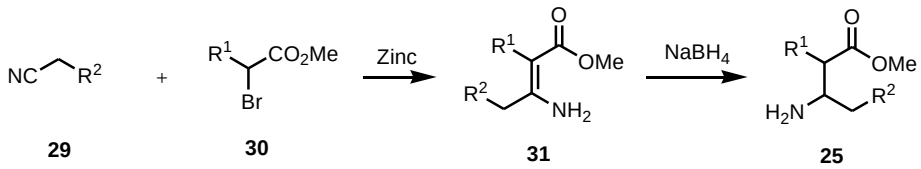
Scheme 1.11 Esterification of *β*-amino acids **25**

Another method of preparing *β*-amino esters is by reduction of the corresponding vinylogous carbamates **28** (Scheme 1.12), in turn prepared from *β*-keto esters **27**. The latter can be prepared from methyl acetoacetate (see Section 1.2.3). Reaction of *β*-keto esters **27** with ammonium acetate gives enamino esters **28** which are then reduced by sodium triacetoxyborohydride to afford the desired *β*-amino esters **25** (Scheme 1.12). Many *β*-amino esters **25** can be prepared by this method which is particularly useful when the *β*-amino acids are unavailable.



Scheme 1.12 Reductive amination of *β*-keto esters **27**

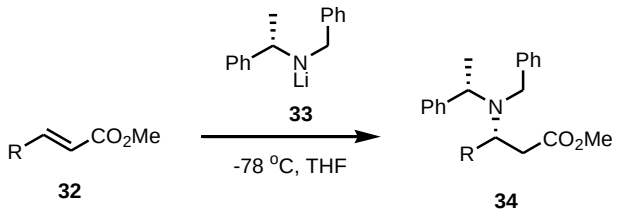
The Blaise reaction is a limited method of preparing *β*-enamino esters. For example, nitriles **29** react with bromo esters **30** to give *β*-enamino esters **31** which are then reduced by sodium borohydride to give *β*-amino esters **25** (Scheme 1.13).[40]



Scheme 1.13 Blaise reaction to *β*-amino esters **25**

1.1.5 Davies' Chiral Auxiliary Approach for Asymmetric Syntheses

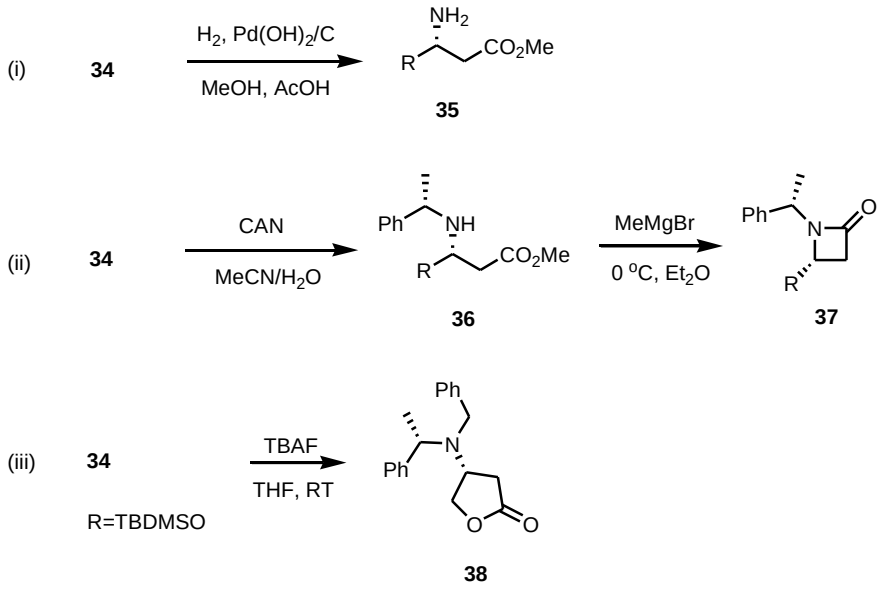
Asymmetric induction is central to the synthesis of chiral compounds. This can be achieved by using starting materials from chiral pool (which uses readily avaliable enantiopure substrates for the synthesis), or by using a chiral auxiliary or chiral catalysts. Davies reported the use of enantiopure *α*-phenylethylamine as a chiral auxiliary in asymmetric Michael addition of the amine **33** to *α*,*β*-unsaturated esters **32** to give enantiopure adducts **34** in over 98% ee (Scheme 1.14).[41–44] Since both enantiomers of *α*-phenylethylamine are commercially-avaliable and inexpensive, Michael adducts **34** can be made with (*S*,*R*)- or (*R*,*S*)- configuration. This auxiliary can be removed by catalytic hydrogenation.



Scheme 1.14 Chiral auxiliary-induced asymmetric Michael reaction

Adducts **34** are key building blocks which can be converted to various amine derivatives (Scheme 1.15). Hydrogenation of adducts **34** removed both the auxiliary and benzyl group to give various *β*-amino esters **35**.[41] The benzyl group of **34** was removed selectively with the use of CAN by an unknown mechanism[44] and intermediates **36** were then cyclised by a base to afford *β*-lactams **37**.[42,43] If R of adducts **34** is an ether, treating **34** with a base induced transesterification to give the lactone **38**.[43] Since this chiral auxiliary approach is powerful and effective, one of our objectives was to exploit and extend this approach for the synthesis of

piperidin-2,4-diones enantioselectively.

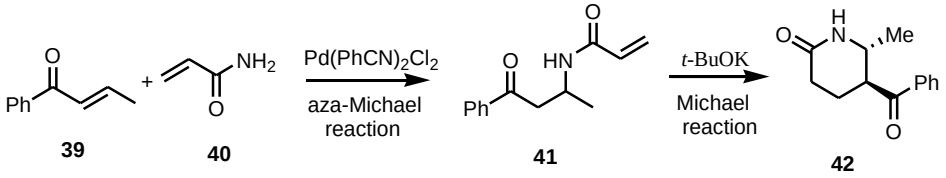


Scheme 1.15 Applications of enantiopure adducts **34**[41-44]

1.2 Results and Discussion

1.2.1 Attempted Synthesis of Piperidin-2-ones via a Palladium-catalyzed Aza-Michael Reaction

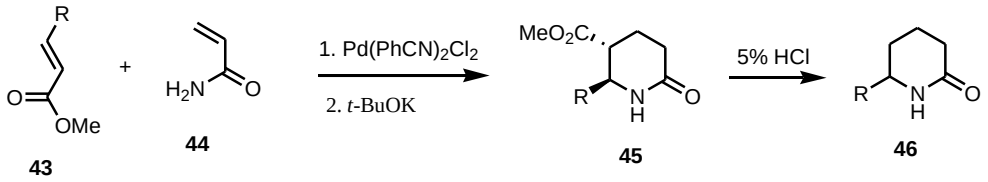
One method of preparing a piperidin-2-one ring involves a palladium-catalyzed aza-Michael reaction followed by a Michael reaction.[28] The piperidinones can then be reduced to afford the corresponding piperidines.[29] In Ihara's route, the first step was the aza-Michael reaction of an *α,β*-unsaturated amide with a Michael acceptor, catalyzed by $Pd(PhCN)_2Cl_2$. In the second step, an intramolecular Michael reaction using potassium *tert*-butoxide formed the ring. This route to piperidin-2-ones appears powerful because the aza-Michael reaction takes place under mild conditions and does not involve the use of strong bases such as *n*-butyllithium. The convenience of this method of making a piperidinone ring gives it potential in the synthesis of many natural products. However the reaction has only been reported by Ihara's group and it is not well-established.



Scheme 1.16 Route to piperidin-2-ones

The proposed route for making piperidin-2-ones **46** is shown in Scheme 1.17. The electrophilic alkenes **43** reacted with the *α,β*-unsaturated amide **44** by the palladium-catalyzed aza-Michael reaction and the adducts formed were cyclised by a Michael reaction to give 5-methoxypiperidin-2-ones **45** which were then

decarboxylated to give the desired piperidin-2-ones **46** with various substituents at position-6. Since the limitations for such palladium-catalyzed aza-Michael reaction were not fully understood, in our hands they were investigated using various *α,β*-unsaturated amides and alkenes. Secondary amines were employed to see if *N*-substituted piperidin-2-ones could be made by this method. Also, synthesis of bicyclic piperidin-2-ones was attempted using cyclohex-2-en-1-one as the electrophilic alkene.



Scheme 1.17 Proposed route to 6-substituted piperidin-2-ones **46**

As stated by Ihara, secondary amides were too bulky to participate in such aza-Michael reaction; there were no reactions of the benzylamide **47** with either methyl acrylate or cyclohex-2-en-1-one (Table 1.1) in our hands as well.[28] Coupling of 1-phenylbut-2-en-1-one (**40**) with the amide **39** was then attempted since it was reported in 85 % yield.[28] However, only a few milligrams of the desired product were isolated in the first time, and no product was isolated when this reaction was repeated. Nor was the coupling of the amide **39** and cyclohex-2-en-1-one a successful reaction in our hands. Therefore, another strategy for making the piperidinone ring was considered, namely aza-Michael-Michael annulation reactions.

Table 1.1 Aza-Michael reaction of *α,β*-unsaturated amides with *α,β*-unsaturated ketones and esters

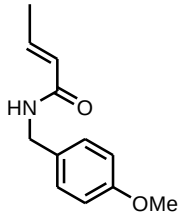
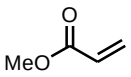
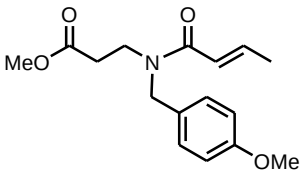
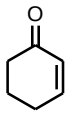
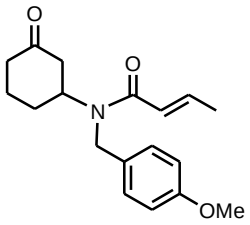
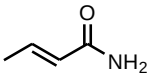
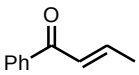
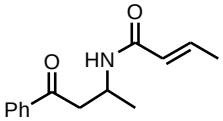
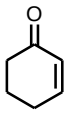
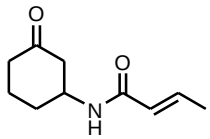
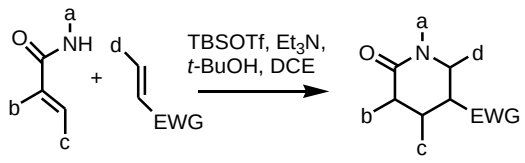
α,β-Unsaturated amide	Electrophile alkene	Expected product
 **47**		 **48**
47		 **49**
 **39**	 **40**	 **41**
50		 **51**

Table 1.1 *Reagents and conditions:* $Pd(PhCN)_2Cl_2$, neat, 60 ^oC, overnight.

1.2.2 Attempted Synthesis of Piperidin-2-ones via an Aza-Michael Michael Annulation Reaction

Ihara also reported a [4+2] annulation (Scheme 1.18) for the synthesis of the piperidin-2-one ring from an electrophilic alkene with an *α,β*-unsaturated amide. This annulation is a powerful reaction since the two bond-forming steps can be carried out in one laboratory operation. Although the mechanism has not been examined, it is

believed that an aza-Michael reaction occurs first followed by Michael reaction rather than two bonds forming simultaneously, since the aza-Michael adduct can be isolated in some cases.[29]



Scheme 1.18 A [4+2] annulation to give piperidin-2-ones

The synthesis of substituted piperidin-2-ones in one operation from an α,β-unsaturated amide and a Michael acceptor in the presence of TBSOTf has been described (Scheme 1.18).[29] This reaction is sensitive to water and the amount of triethylamine added. To make this reaction work, the amount of triethylamine should be within the range of 0.5-1.0 equivalents.[29] In our hands, the piperidinone **55** could not be made from the benzylamide **52** and methyl acrylate, only the starting material **52** being recovered (Table 1.2) even though the solvent 1,2-dichloroethane was dried by molecular sieves and the glassware was dried over a naked flame. The benzylamide **47** and **53** were also reacted with methyl acrylate, but no desired piperidinones were formed. Therefore, the acrylamide **57** was prepared since it was reported to react with cyclohex-2-en-1-one to give the piperidin-2-one **59** in 51% yield.[29] However, in our hands, no annulation between **57** and either cyclohex-2-en-1-one or methyl acrylate could be achieved under the reported conditions. Since it was difficult to make any progress, a much more reliable and well-established Dieckmann cyclisation was used to make piperidinones.

Table 1.2 [4+2] Annulation to piperidin-2-ones

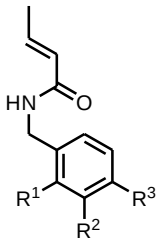
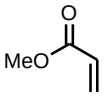
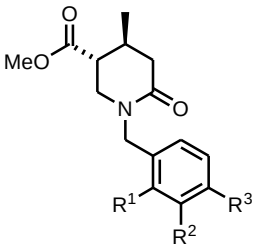
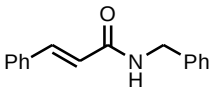
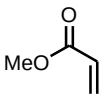
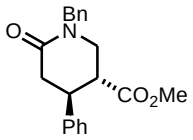
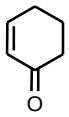
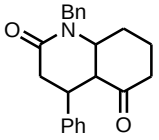
α,β-Unsaturated amide	Electrophilic alkene	Expected product
		
47: R^1=H, R^2=H, R^3= OMe **52:** R^1=H, R^2=OMe, R^3= OMe **53:** R^1=OMe, R^2=H, R^3= OMe		**54:** R^1=H, R^2=H, R^3= OMe **55:** R^1=H, R^2=OMe, R^3= OMe **56:** R^1=OMe, R^2=H, R^3= OMe
 **57**		 **58**
57		 **59**

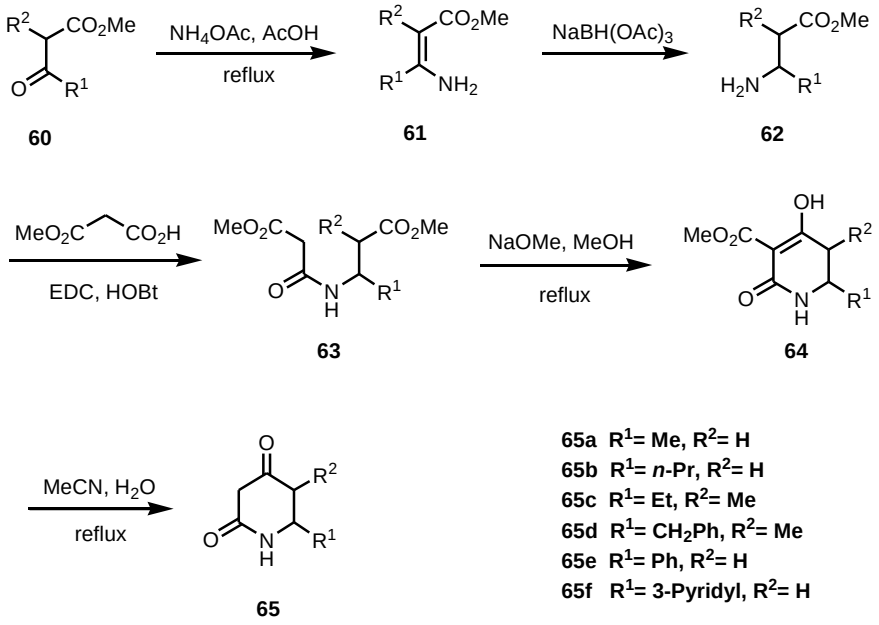
Table 1.2 *Reagents and conditions:* Et_3N (0.7 eq), TBSOTf (1.2 eq), *t*-BuOH (0.25 eq), $ClCH_2CH_2Cl$, RT, overnight.

1.2.3 Synthesis of Piperidin-2,4-diones via a Dieckmann Cyclisation

The main objective was to exploit and extend the scope of Dieckmann cyclisation to make piperidin-2,4-diones without any *N*-protective groups. It was desired to develop a systematic method to prepare piperidin-2,4-diones with various substitutions at positions-2, -3, and -5 in only a few steps. With the ability to construct the ring with different substituents, syntheses of natural piperidine-containing compounds could be

advanced.

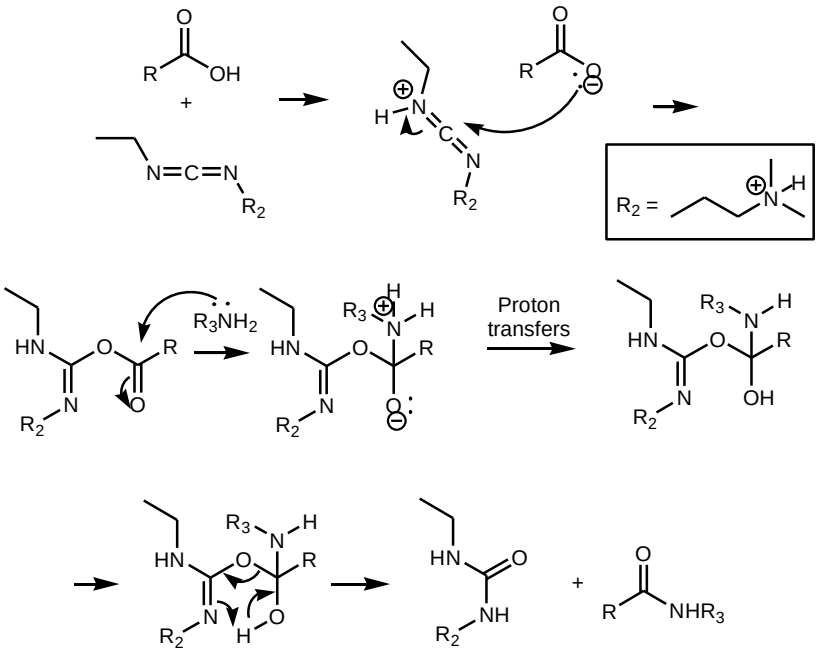
Our general route began with *β*-keto esters **60** (Scheme 1.19). Amination of **60** with ammonium acetate gave enamines **61** which were then reduced to *β*-amino esters **62** upon treatment with sodium triacetoxyborohydride. Acylation of *β*-amino esters **62** using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) afforded diesters **63** which were substrates for Dieckmann cyclisation. When treated with sodium methoxide, diesters **63** underwent ring closure and the desired products **65** were formed after decarboxylation (modified from Vanotti's synthesis)[15]. Piperidin-2,4-diones **65** with different 5- and 6- substitutents were made successfully by this route.



Scheme 1.19 General route to piperidin-2,4-diones **65**

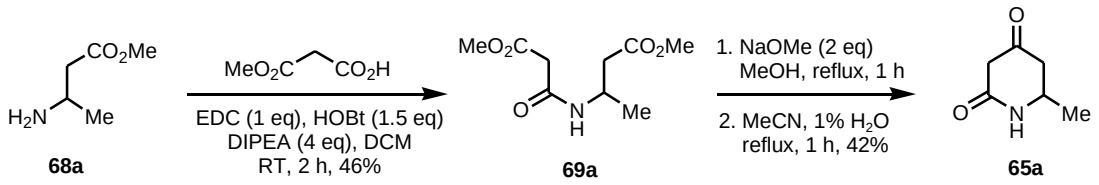
The mechanism of EDC-activated acylation of *β*-amino esters is shown in Scheme 1.20. A carboxylate ion attacks the electrophilic carbon of EDC. The adduct formed activates the carbonyl carbon for nucleophilic attack from an amide due to the

electron-withdrawing effect of EDC. After the formation of an amide bond, EDC leaves as an urea byproduct and an amide is formed. EDC is a better coupling agent than DCC because the urea byproduct is ionic and remains in the aqueous phase during extraction of the product.



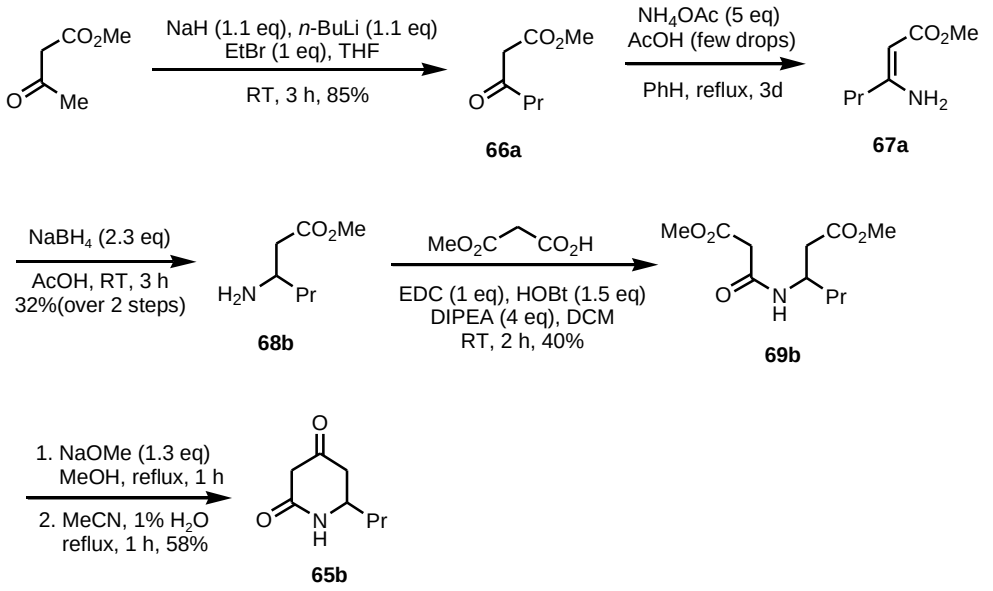
Scheme 1.20 Mechanism of EDC-activated acylation

The 6-methylpiperidin-2,4-dione **65a** was our first target due to its simplicity (Scheme 1.21). The precusor *β*-amino ester **68a** could be easily prepared in 97% yield from methyl 3-aminobutanoic acid using thionyl chloride. Acylation of **68a** with methyl malonate using DIPEA and EDC gave **69a** in moderate yield (procedure modified from Weis's synthesis).[45] The 6-methylpiperidin-2,4-dione **65a** was prepared by Dieckmann cyclisation and decarboxylation[15] of the diester **69a** in 42% yield over two steps.



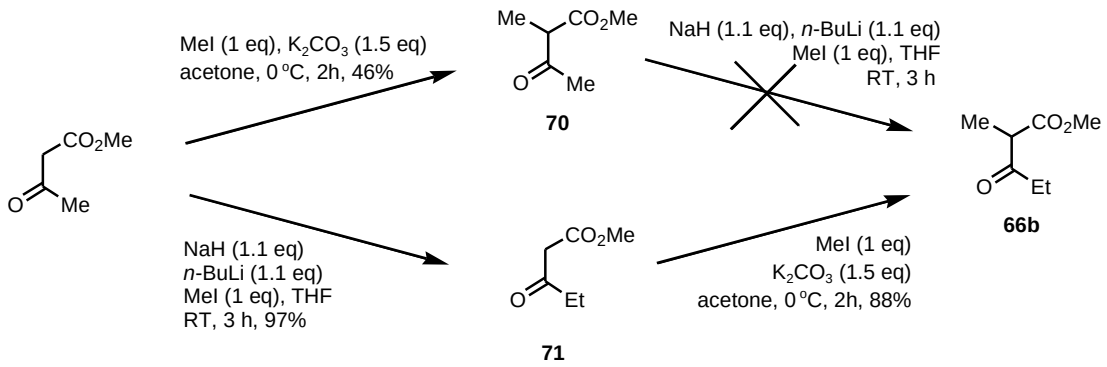
Scheme 1.21 Synthesis of the piperidin-2,4-dione **65a**

The 6-propylpiperidin-2,4-dione **65b** was prepared to show that piperidin-2,4-diones with different alkyl groups at position-6 could be made from methyl acetoacetate (Scheme 1.22). Weiler dianion alkylation is a useful method for addition of an alkyl group to the carbon with a less acidic proton by the use of two equivalents of strong bases. By this method, the methyl group *gamma* to the ester of methyl acetoacetate could be converted into different R groups and that would become the 6-substituents of piperidin-2,4-diones. The *β*-keto ester **66a** was prepared in good yield via a Weiler dianion alkylation with ethyl bromide using one equivalent of sodium hydride and one equivalent of *n*-butyllithium.[46] Reductive amination modified from Shipman synthesis[47] afforded the *β*-amino ester **68b** in 32% yield. Treating **68b** with methyl malonate and EDC gave the diester **69b** (40% yield). The subsequent cyclisation and decarboxylation[15] gave the product **65b** in 58%, which was better than that of the 6-methylpiperidin-2,4-dione **65a** (42%). This may be due to the fact that a bulkier propyl group constrains the bond rotation of **69b** and facilitates Dieckmann cyclisation.

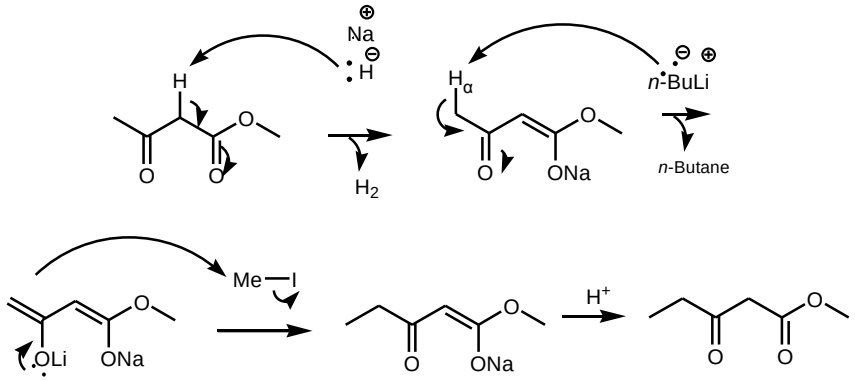


Scheme 1.22 Synthesis of the piperidin-2,4-dione **65b**

The next targets were 5,6-disubstituted piperidin-2,4-diones. It was desired to investigate whether the precursor **66b** could be made from methyl acetoacetate (Scheme 1.23). Methylation of methyl acetoacetate with mild base K_2CO_3 gave **70** in moderate yield.[48] However, the newly-added methyl group prevented the formation of the Weiler dianion when treated with two equivalents of strong bases and failed to give the desired product **66b**. Therefore, the order of reactions was changed and the intermediate **71** was prepared first. By treating with one equivalent of sodium hydride, the most acidic proton *alpha* to the ester (pK_a around 14) of **71** was removed. Then one equivalent of *n*-butyllithium was added to remove the less acidic proton *alpha* to the ketone (pK_a around 26, marked in diagram) and a Weiler dianion was formed. Alkylation of the dianion with methyl iodide occurred at the more reactive carbon to form **66b** (Scheme 1.24).[46] It was found to be a clean reaction with an excellent yield (97%). To our suprise, methylation of **71** with K_2CO_3 gave the desired β-keto ester **66b** in a much better yield than that of methyl acetoacetate (88% and 46%). Thus, the overall yield was over 85%.

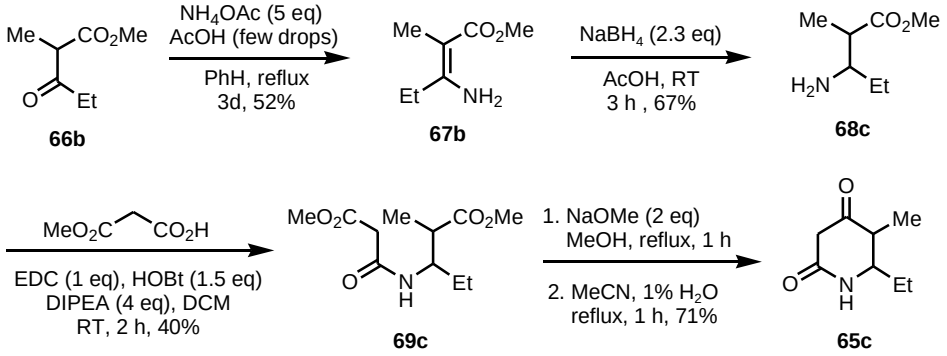


Scheme 1.23 Synthesis of the keto ester **66b**



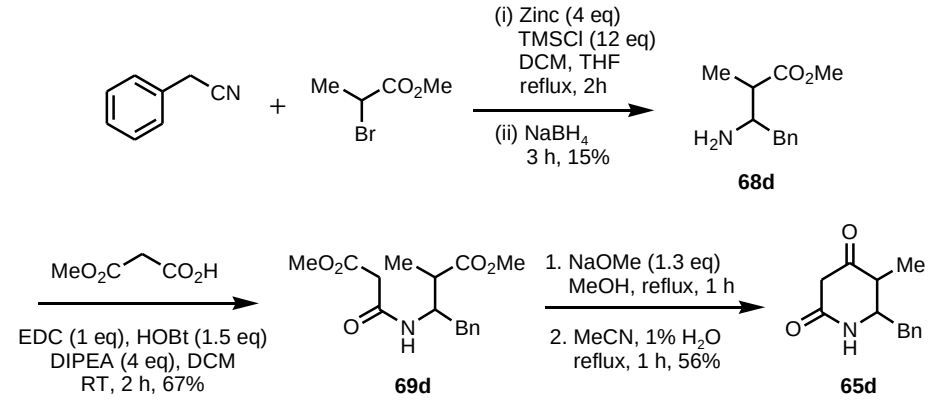
Scheme 1.24 Mechanism of Weiler dianion methylation

With the *β*-keto ester **66b** in hand, the 6-ethyl-5-methylpiperidin-2,4-dione **65c** was prepared according to the general route (Scheme 1.25). Amination with ammonium acetate and subsequent reduction with sodium triacetoxyborohydride generated *in situ* (procedure modified from Cohen's synthesis)[49] gave the *β*-amino ester **67b** (35% over two steps) which was then acylated to form the diester **69c** in 40% yield. The methyl group *alpha* to the ester found not to affect the subsequent Dieckmann cyclisation and decarboxylation[15] which gave the desired 5,6-disubstituted piperidin-2,4-dione **65c** in 71% yield over two steps. From the NMR spectra of the piperidin-2,4-dione **65c**, it was found to be a 1:1 mixture of diastereoisomers, as expected.



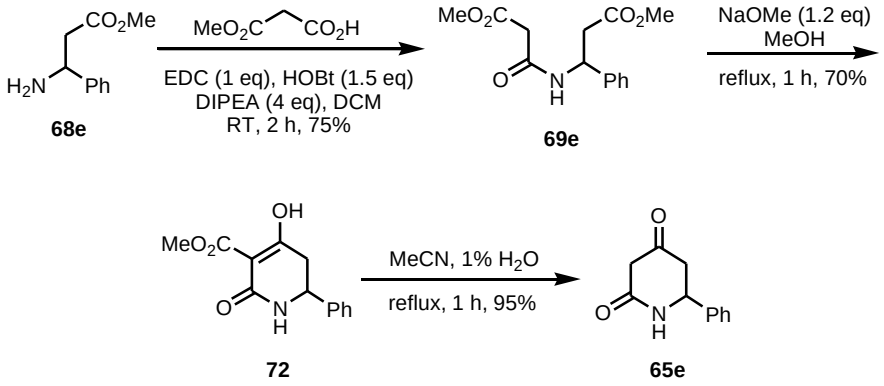
Scheme 1.25 Synthesis of the piperidin-2,4-dione **65c**

By a reductive amination based on Grauert's procedure using TMSCl and zinc dust,[40] benzyl cyanide was coupled with methyl 2-bromopropanoate to form the *β*-amino ester **68d** in 15% yield. This reductive amination is very convenient as the *β*-amino ester can be prepared in one step. However, the yield was poor in our hands so the synthesis of other piperidin-2,4-diones followed the original route. The *β*-amino ester **68d** was acylated in 67% yield. A benzyl group next to nitrogen was found to be compatible with Dieckmann cyclisation; the 5,6-disubstituted piperidin-2,4-dione **65d** was isolated in 56% yield over two steps (Scheme 1.26). The piperidin-2,4-dione **65d** was obtained as a 1:1 mixture of diastereoisomers.



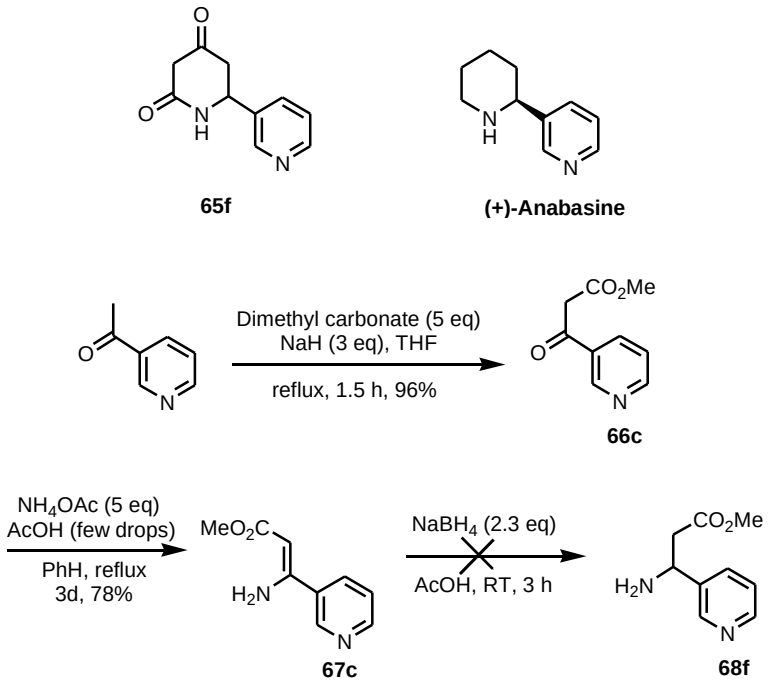
Scheme 1.26 Synthesis of the piperidin-2,4-dione **65d**

Whether the 6-phenylpiperidin-2,4-dione **65e** could be prepared by this route was of interest. Esterification of commercially-avaliable 3-amino-3-phenylpropionic acid using thionyl chloride gave the *β*-amino ester **68e** in 87% yield. Coupling the *β*-amino ester **68e** with methyl malonate afforded the diester **69e** in good yield. The diester **69e** was cyclised to give the piperidin-2,4-dione **72** in 70% yield which was then decarboxylated[15] in excellent yield to afford the desired product **65e** (Scheme 1.27). This showed that piperidin-2,4-diones with another ring (including an aromatic one) directly connected could be prepared by this route.



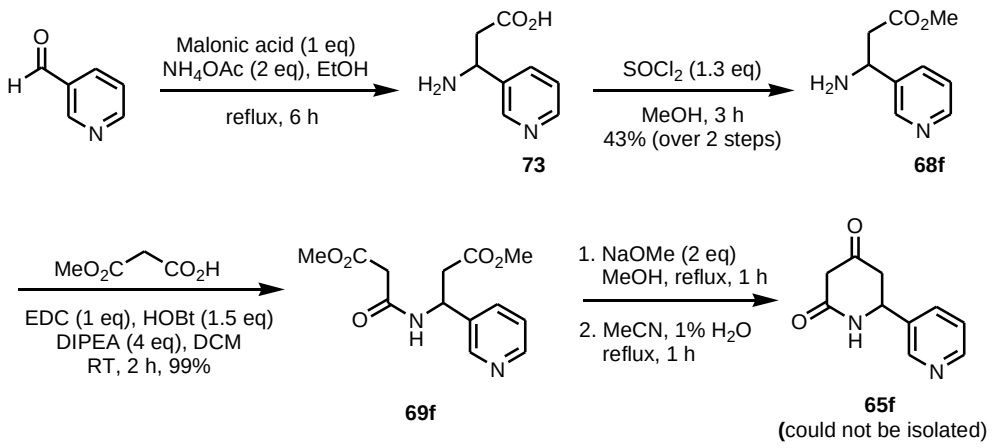
Scheme 1.27 Synthesis of the piperidin-2,4-dione **65e**

Since the 6-phenylpiperidin-2,4-dione **65e** was prepared in good yield, the final target compound would be the 6-pyridin-3-ylpiperidin-2,4-dione **65f** because it shares the structure of the natural alkaloid anabasine. Claisen condensation of commercially-avaliable 3-acetylpiperidine with dimethyl carbonate gave the *β*-amino ester **66c** in excellent yield.[50] **66c** was then treated with ammonium acetate to give the enamine **67c**.[51] However, reduction of the enamine **67c** using sodium triacetoxyborohydride made *in situ* gave a complex mixture of products suggesting pyridinylenamine is not stable under acidic conditions or the pyridine ring affects the enamine reduction (Scheme 1.28).



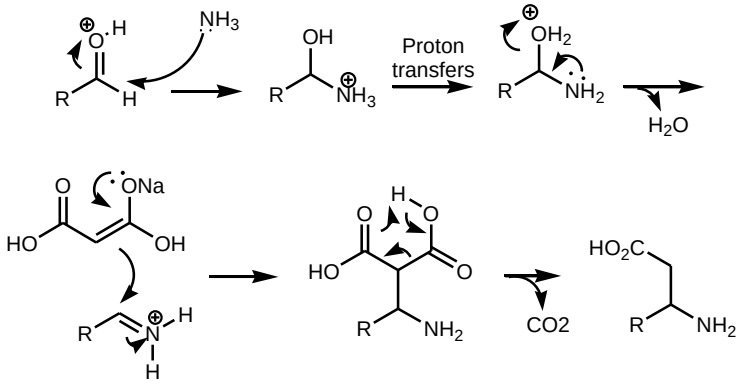
Scheme 1.28 Attempted reduction of the enamine **68f**

Another route to the *β*-amino ester **68f** was developed (Scheme 1.29). Knoevenagel condensation[52,53] of commercially-avaliable 3-pyridinecarboxaldehyde with malonic acid afforded the *β*-amino acid **73** which was then treated with thionyl chloride in methanol to give the *β*-amino ester **68f** in moderate yield (43% over two steps). The *β*-amino ester **68f** was then acylated to give the diester **69f** quantitatively. Dieckmann cyclisation and subsequent decarboxylation[15] gave the desired piperidin-2,4-dione **65f** (molecular ion was identified in the mass spectrum) but it was found to be too water-soluble and could not be extracted from the aqueous phase.



Scheme 1.29 Synthesis of the piperidin-2,4-dione **65f**

The mechanism of Knoevenagel condensation is shown in Scheme 1.30. Ammonia attacks the carbonyl carbon of the aldehyde. After proton transfers, a water molecule leaves and an iminium ion is formed. Malonic acid is deprotonated and attacks the iminium ion to form an adduct. At high temperature, one carboxylic acid leaves as carbon dioxide and β-amino acid is formed.



Scheme 1.30 Mechanism of Knoevenagel condensation

The piperidin-2,4-dione **65f** is ionic at various pH (as shown in Figure 1.2) and cannot be extracted into the organic phase. Under acidic conditions, the nitrogen atom of the pyridine ring protonates and possesses a positive charge. Whereas under basic conditions, the β-keto amide deprotonates to form the enolate and negatively charged.

Since it was too difficult to extract the piperidin-2,4-dione **65f** from the aqueous phase, 2-pyridin-3-ylpiperidin-4-one was the next target molecule as it should not form an enolate under mild basic conditions lacking a β-amide group.

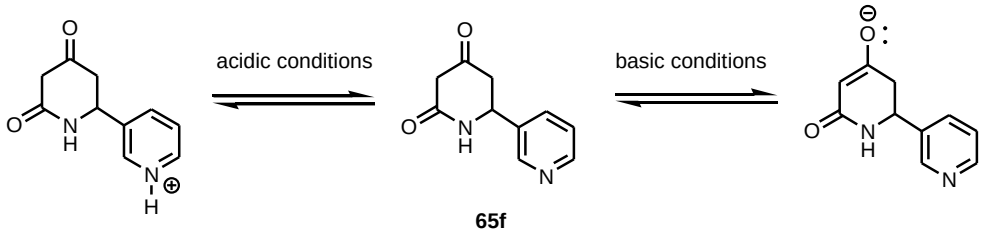


Figure 1.2 Major forms of the piperidin-2,4-dione **65f** depending upon the pH

In order to solve the solubility problem of oxopiperidines containing a pyridine ring, the pyridylpiperidin-4-one **74**, rather than the pyridylpiperidin-2,4-dione **65f**, became the target. Since the pK_a of a piperidin-4-one is much higher than a piperidin-2,4-dione, the pyridylpiperidin-4-one would not deprotonate to form an enolate under mild basic conditions and would be extractable from the aqueous phase (Figure 1.3).

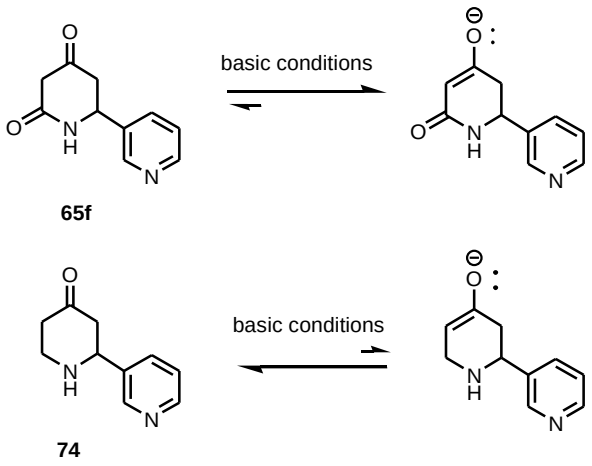
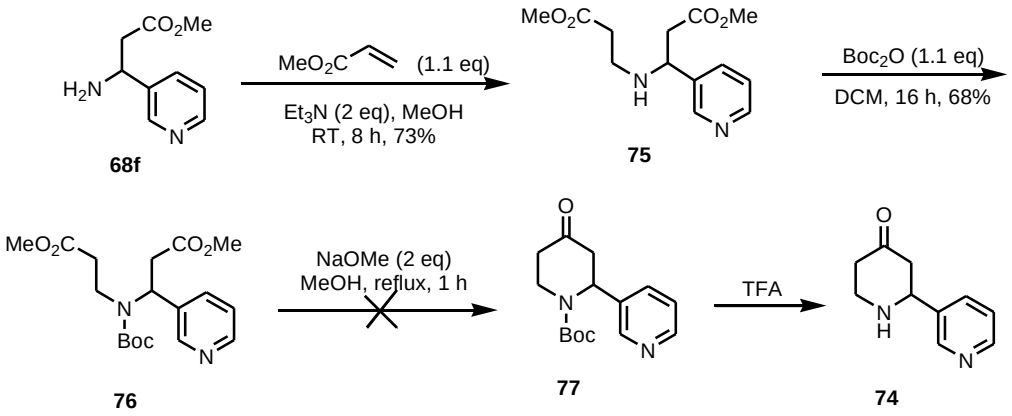


Figure 1.3 Major forms of the piperidin-2,4-dione **65f** and the piperidin-4-one **74** under mild basic conditions

The proposed route for making the 2-pyridin-3-ylpiperidin-4-one **74** is shown in Scheme 1.31. The β-amino ester **68f** was coupled with methyl acrylate by an

aza-Michael reaction to give the diester **75** in 73% yield (procedure modified from Schlewer's synthesis).[54] The amine of **75** was then protected by a Boc group in 68% yield. However, treating the diester **76** with sodium methoxide resulted in a complex mixture of products and the piperidin-4-one **77** could not be isolated from this mixture. Owing to these difficulties, attempts to make the 6-pyridin-3ylpiperidinone ring by this route were abandoned.

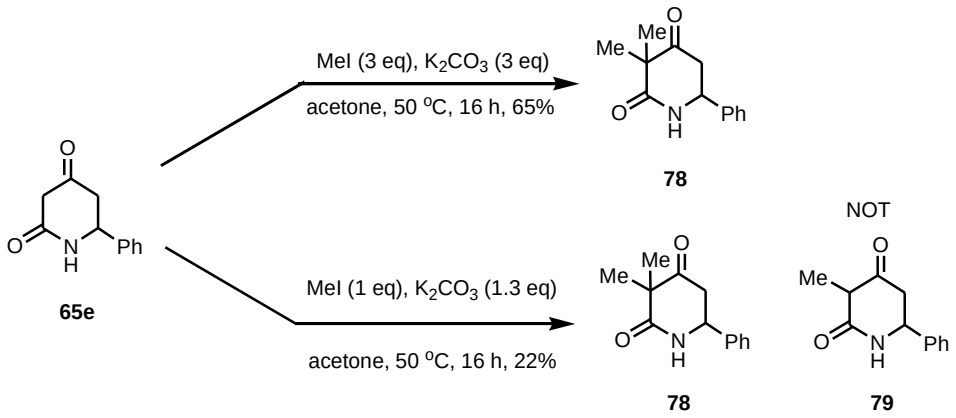


Scheme 1.31 Attempted synthesis of the piperidin-4-one **74**

1.2.4 Attempted Alkylations of Piperidin-2,4-diones at Position-3

Using the general route of *N*-acylation-Dieckmann cyclisation (Scheme 1.19), piperidin-2,4-diones with different substituents at positions-5 and -6 were made. Our next goal would be adding substituents to position-3. Dimethylation of the piperidin-2,4-dione **65e** with excess methyl iodide and potassium carbonate afforded the 3,3-dimethylpiperidin-2,4-dione **78** in 65%. Then, monomethylation of the piperidin-2,4-dione **65e** using one equivalent of methyl iodide was attempted but only the 3,3-dimethylpiperidin-2,4-dione **78** was formed, in 22% yield (Scheme 1.32). One possible solution would be the change of the mild base K_2CO_3 to one equivalent of stronger bases such as *t*-BuOK so as to give 100% enolate conversion of **65e** for

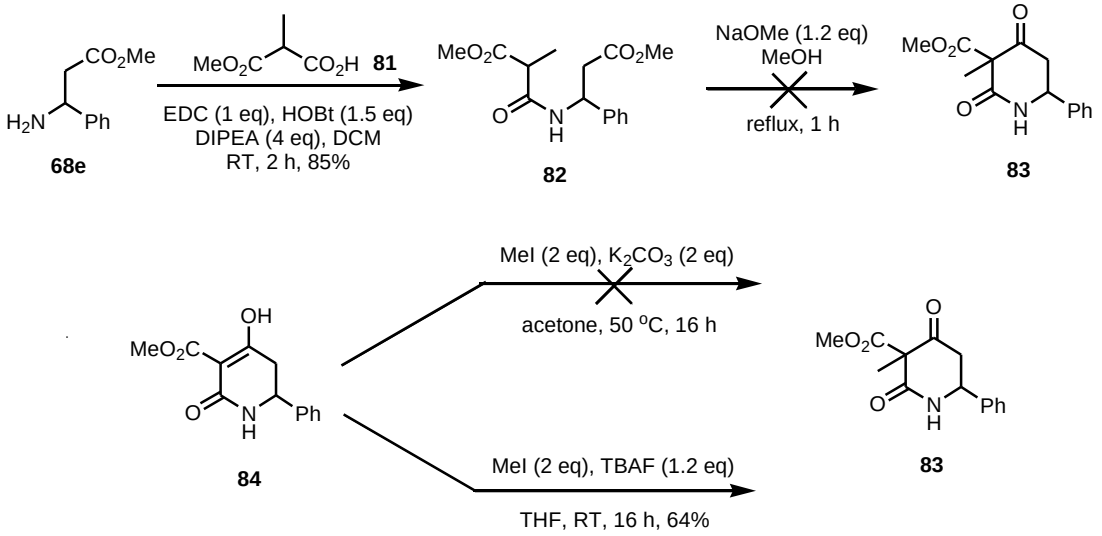
monomethylation.



Scheme 1.32 Alkylations of the piperidin-2,4-dione **65e**

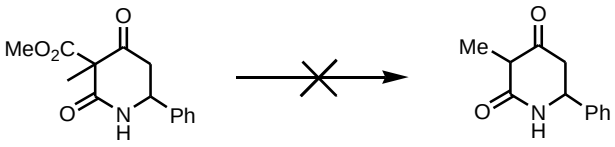
Since it was difficult to add a single methyl group to 3-position after the ring formation, a possible solution would be methylating at an earlier stage (Scheme 1.33). Methyl 2-methylmalonate **81** was prepared from commercially-avaliable ethyl 2-methylmalonate using potassium hydroxide in methanol (55% yield).[55] The *β*-amino ester **68e** was coupled with methyl 2-methylmalonate **81** activated by EDC to give the diester **82** in 85% yield. However, Dieckmann cyclisation was not performed when **82** was treated with sodium methoxide, a complex mixture was formed instead.

Additionally, 3-methylation of the precusor **72** was attempted which should give 3-methylpiperidin-2,4-dione **79** after decarboxylation. Methylation using potassium carbonate in acetone at 50 °C for 16 hours failed and gave complex mixture. Then methylation which was modified from Prof. Philip Page's synthesis[56] was tried. TBAF was used as a mild base (1.2 equivalents) and the mixture was stirred at room temperature for 16 hours. The 3-methoxy-3-methylpiperidin-2,4-dione **83** was isolated in 64% yield and the desired 3-methylpiperidin-2,4-dione **79** could be made if the subsequent decarboxylation suceeded.



Scheme 1.33 Synthesis of the 3-methoxy-3-methylpiperidin-2,4-dione **83**

Decarboxylation of the 3-methoxy-3-methylpiperidin-2,4-dione **83** was found to be very challenging. Several attempts were made including acidic, neutral, and basic conditions but none of them were successful (Scheme 1.34). Krapcho decarboxylation[57] by heating **83** with NaCl in DMSO under reflux was tried but the piperidin-2,4-dione **83** remained unchanged.

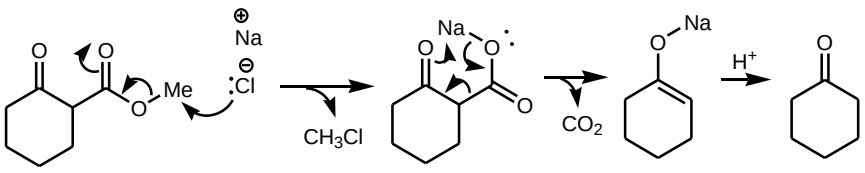


83 **85**

Entry	Conditions
1	5% HCl, water, reflux, 2 h
2	MeCN, 1% H_2O, reflux, 3 h
3	NaCl (1.1 eq), H_2O (2 eq), DMSO, reflux, 2 h
4	LiI (5 eq), pyridine, reflux, 2 h

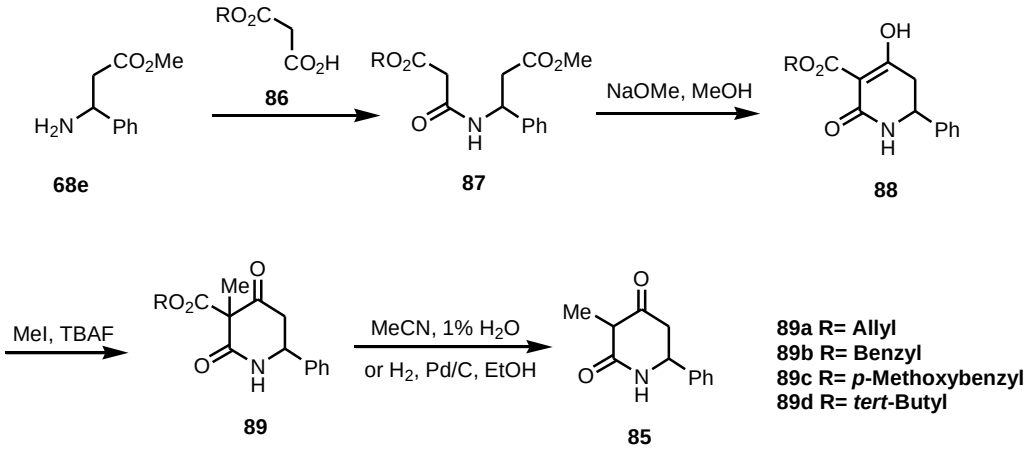
Scheme 1.34 Attempted decarboxylation of the piperidin-2,4-dione **83**

The mechanism of Krapcho decarboxylation is shown in Scheme 1.35. A chloride ion attacks the carbon of methyl ester via a S_N2 reaction and the byproduct chloromethane is lost as a gas. Then the carboxylate leaves as a carbon dioxide and the enolate converts into a ketone in the presence of water in wet DMSO. The reaction equilibrium shifts towards right since the byproducts are both gases and would leave the reaction system once formed.



Scheme 1.35 Mechanism of Krapcho decarboxylation

Since methoxy ester could not be removed from the piperidin-2,4-dione **83** in our hands, routes to the piperidin-2,4-dione **77** using other esters were investigated (Scheme 1.36). Synthesis of the allyl ester **89a** and the *tert*-butyl ester **89d** were attempted because they are more likely to be removed by traditional decarboxylation methods. The benzyl ester **89b** and the *p*-methoxybenzyl ester **89c** were target compounds as well since Prof. Philip Page[56] showed that related benzyl esters could be removed by hydrogenation with palladium on activated carbon.



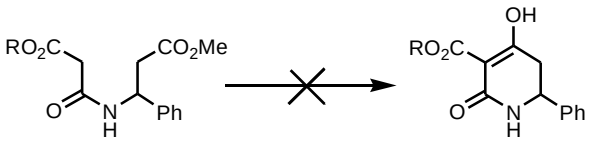
Scheme 1.36 Proposed route to the 3-methylpiperidin-2,4-dione **85**

Allyl malonate (**90a**) was prepared by reacting malonic acid with allyl alcohol activated by dicyclohexylcarbodiimide (DCC) in 67% yield.[58] The *β*-amino ester **68e** was coupled with allyl malonate (**90a**) to give the diester **89a** (77% yield). However, when the diester **89a** was treated with sodium methoxide, transesterification occurred along with Dieckmann cyclisation to form the unwanted 3-methoxycarboxylpiperidin-2,4-dione **72**. Therefore, potassium *tert*-butoxide was used instead to prevent transesterification. Suprisingly, the allyl ester was found to be too good a leaving group and decarboxylation took place immediately after Dieckmann cyclisation to give the piperidin-2,4-dione **65e**, so that no allyl ester **91** could be

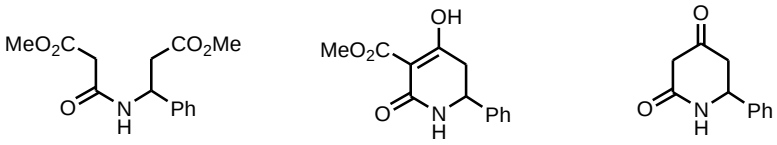
isolated (Scheme 1.37).

Benzyl malonate (**90b)** and *p*-methoxybenzyl malonate (**90c**) were prepared by DCC-activated esterification of malonic acid in 26% and 28% respectively.[59] Acylation of the *β*-amino ester **68e** with **90b** and **90c** gave the diester **89b** (83%) and the diester **89c** (79%) respectively. When they were treated with sodium methoxide, no Dieckmann cyclisation occurred. Instead, the dimethoxyester **69e** was formed (transesterification). Sodium hydride was used to cyclise the diester **89b** but decarboxylation also occurred to give the piperidin-2,4-dione **65e**. Then potassium *tert*-butoxide was used to cyclise the diester **89c**, the reaction was performed at room temperature to avoid decarboxylation. However, no cyclisation took place and only the diester **89c** was recovered.

Esterification of malonic acid afforded *tert*-butyl malonate (**90d**) in 75% yield.[58] The *β*-amino ester **68e** was acylated with **90d** to give the diester **89d** in 80% yield. As for the diester **89d**, using sodium methoxide caused transesterification to give the 3-methoxypiperidin-2,4-dione **72** while using potassium *tert*-butoxide caused decarboxylation to give the piperidin-2,4-dione **65e**. Since decarboxylation of the esters **88** were too rapid, the idea of methylating these esters for making 3-methylpiperidin-2,4-dione had to be abandoned.



87 **88**



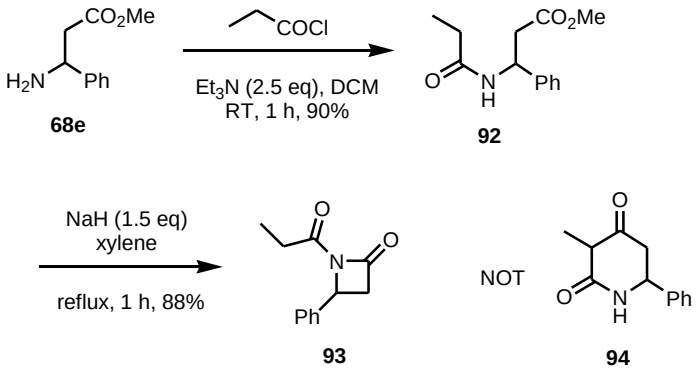
69e **72** **65e**

Entry	Cpd	R	Conditions	Product
1	**89a**	Allyl	NaOMe (1.3 eq), MeOH, reflux, 1 h	**72** (transesterification)
2	**89a**	Allyl	KO^{t}Bu (2 eq), PhMe, 80 ^{o}C, 1 h	**65e** (decarboxylation)
3	**89b**	Benzyl	NaOMe (1.3 eq), MeOH, reflux, 1 h	**69e** (transesterification)
4	**89b**	Benzyl	NaH (1.2 eq), PhMe, reflux, 2 h	**65e** (decarboxylation)
5	**89c**	*p*-Methoxybenzyl	NaOMe (1.3 eq), MeOH, reflux, 1 h	**69e** (transesterification)
6	**89c**	*p*-Methoxybenzyl	KO^{t}Bu (2 eq), THF, RT, 24 h	unchanged
7	**89d**	*tert*-Butyl	NaOMe (1.3 eq), MeOH, reflux, 1 h	**72** (transesterification)
8	**89d**	*tert*-Butyl	KO^{t}Bu (2 eq), PhMe, 80 ^{o}C, 1 h	**65e** (decarboxylation)

Scheme 1.37 Attempted formation of piperidin-2,4-dione alkyl esters **88**

In order to avoid the decarboxylation step, which had proved so problematic, a route

that gave piperidin-2,4-diones with a 3-methyl group and did not possess an ester group after Dieckmann cyclisation was proposed (Scheme 1.38). The *β*-amino ester **68e** was coupled with propionyl chloride to give the amide **89d** in excellent yield. The hope was that treatment of the amide **89d** with base would lead to sufficient *α*-deprotonation of the amide that a Dieckmann-like cyclisation would occur to give the desired 3-methylpiperdin-2,4-dione **77**. However, treatment of the amide **89d** with sodium hydride gave only the azetidin-2-one **93** as the only product in 88% yield. That means that the amide nitrogen atom, which was throught to be inert, was in fact deprotonated and attacked the ester to form an azetidinone. This may be explained by Pearson's hard and soft acids and bases (HSAB) theory that the ester being a hard acid prefers the deprotonated amide (hard base) rather than the enolate (soft base) for better orbital overlapping. Since attempts to block the amide with an *N*-Boc protection were unsuccessful, the focus was shifted to 3-methylation of chiral piperidin-2,4-diones, as discussed in Section 1.2.6.



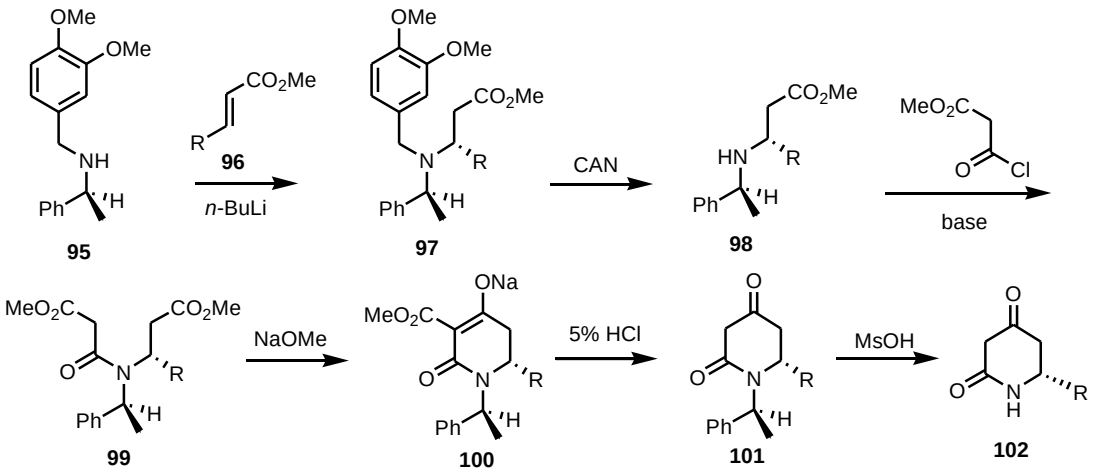
Scheme 1.38 Attempted synthesis of the 3-methylpiperidin-2,4-dione **94**

1.2.5 Enantioselective Synthesis of Piperidin-2,4-diones

Piperidine alkaloids play a central role in pharmaceutically-active compounds, and most of them are optically active. Thus, enantiocontrolled strategies to substituted

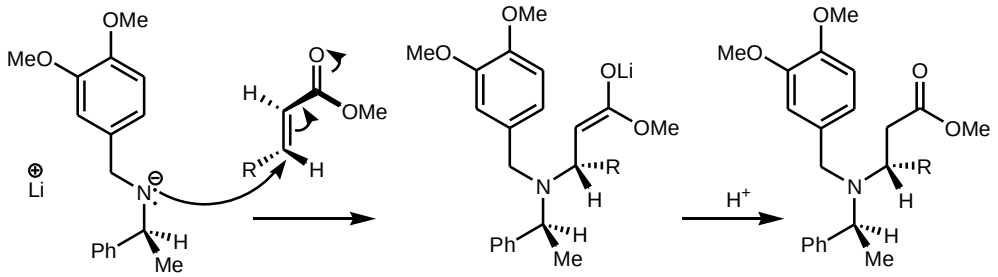
oxopiperidines would be very useful in drug development. The groups of Meyers, Marazano, and Comins,[24] have made progressed in this area, but their syntheses have limitations on the types and positions of substituents that can be introduced in the ring. Our goal was to extend to prepare diversely substituted piperidin-2,4-diones enantioselectively.

Davies[60,61] showed commercially-avaliable (*S*)-*α*-methylbenzylamine can act as a chiral auxiliary to induce asymmetric aza-Michael reaction of the amine **95** with *α*,*β*-unsaturated esters **96** to afford adducts **97**. The 3,4-dimethoxybenzyl group can then be eliminated using cerium(IV) ammonium nitrate (CAN). Thus an enantioselective route to piperidin-2,4-diones was proposed using the Davies protocol (Scheme 1.39). Once the blocking group was removed using CAN, amines **98** were acylated with acid chloride to give diesters **99**. Dieckmann cyclisation and subsequent decarboxylation afforded the enantiopure piperidin-2,4-diones **101**. The Davies' auxiliary in **101** was then removed by methanesulfonic acid to give 1-unsubstituted piperidin-2,4-diones **102**.



Scheme 1.39 Proposed route to enantiopure piperidin-2,4-diones **102**

The mechanism of asymmetric aza-Michael reaction is shown in Scheme 1.40. The amine is deprotonated by *n*-butyllithium and attacks the *α*,*β*-unsaturated esters. Due to the bulkness of the phenyl group of the chiral auxiliary, the phenyl group stays away from the *α*,*β*-unsaturated esters during the nucleophilic addition. The R group of the *α*,*β*-unsaturated esters stays away from the methyl group of the auxiliary due to steric hindrance so the thermodynamically more stable enolate adducts form. As the amine is chiral due to the presence of the auxiliary, the adducts formed would also be a single enantiomer. After aqueous workup, the enolate converts into an ester and the desired enantiopure adducts are formed.

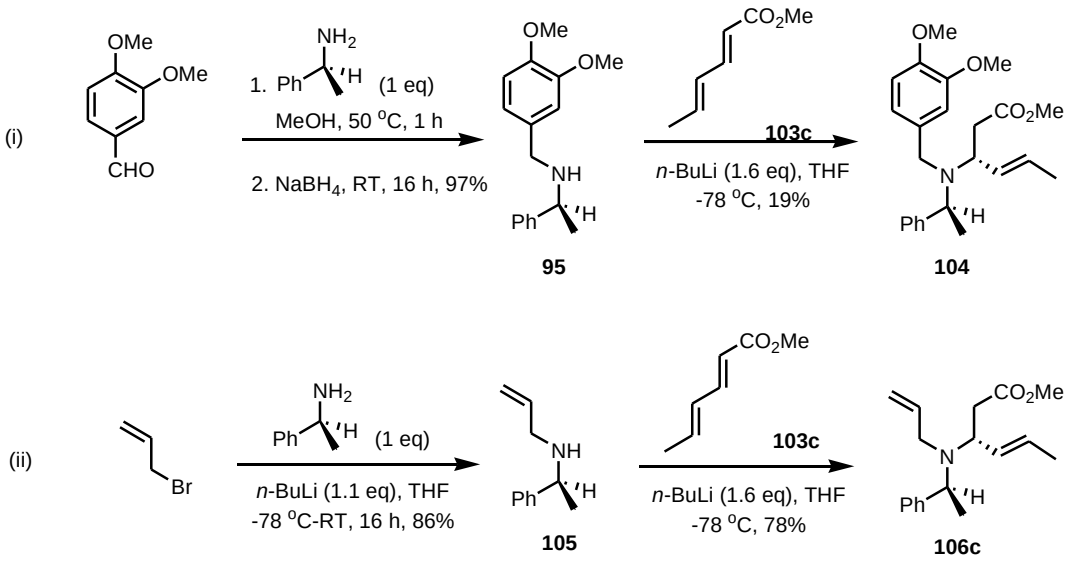


Scheme 1.40 Mechanism of asymmetric aza-Michael reaction

Reductive amination of 3,4-dimethoxybenzaldehyde with (*S*)-*α*-methylbenzylamine and sodium borohydride afforded the amine **95** in 97% yield. However, aza-Michael reaction of the amine **95** with methyl sorbate (**103c**) gave the adduct **104** in 19% yield only, although was reported in 90% yield by Davies.[60] Consequently, another blocking group was needed (Scheme 1.41).

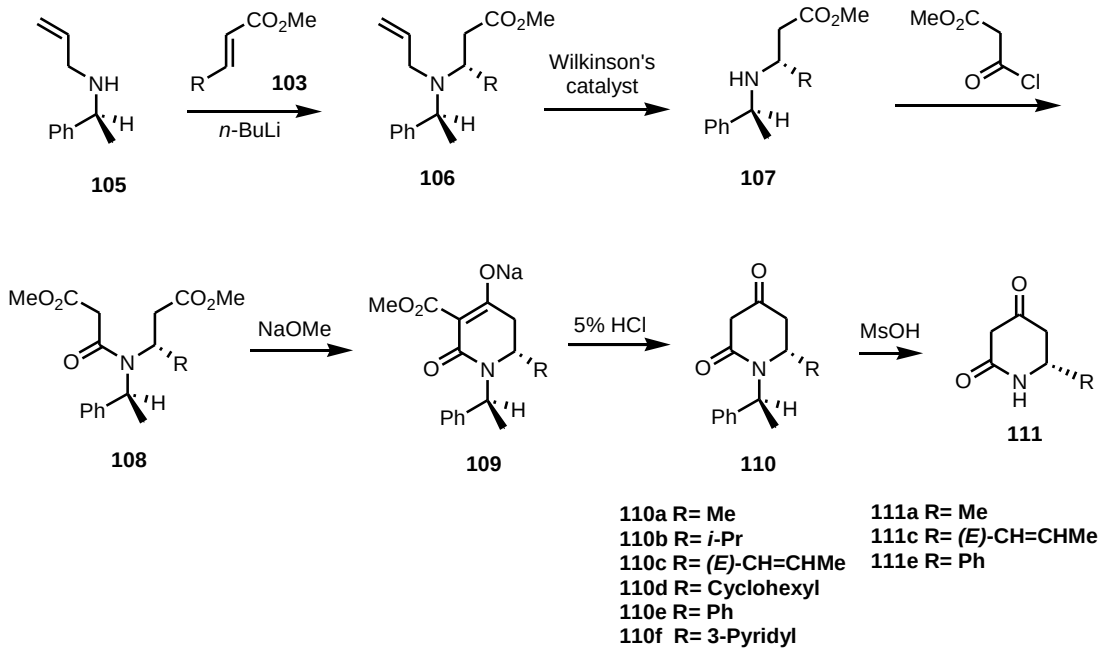
An allyl group was then used to block the amine, and could be removed using tris(triphenylphosphine)rhodium(I) chloride (Wilkinson's catalyst)[62] in a later step. Allylation of (*S*)-*α*-methylbenzylamine using *n*-butyllithium (1.1 equivalents) and allyl bromide (1 equivalent) at room temperature gave the monallylated amine **105** in 86% yield. The amine **105** was then coupled with methyl sorbate (**103c**) by aza-Michael

reaction to afford the adduct **106c** in 78% yield.



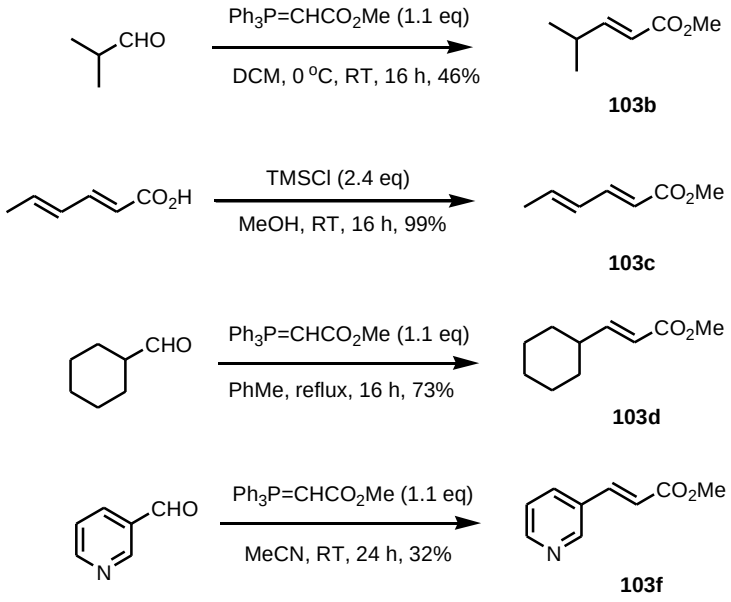
Scheme 1.41 Synthesis of intermediates **104** and **106c** via an aza-Michael reaction

Since an allyl group could be efficiently added and removed, our synthetic route was modified as shown in Scheme 1.42; six enantiopure piperidin-2,4-diones **110** with various 6-substituents were prepared.



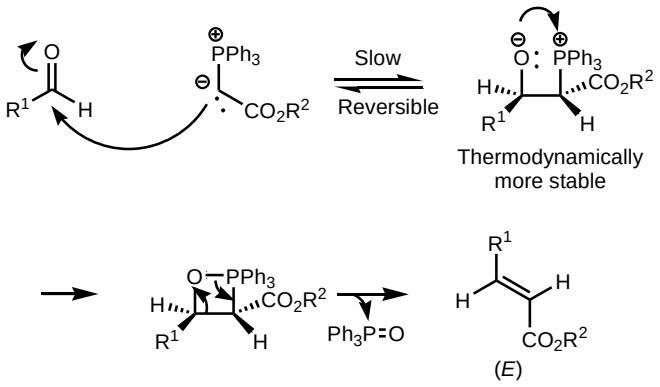
Scheme 1.42 General route to enantiopure piperidin-2,4-diones **111**

(*E*)-Methyl but-2-enoate (**103a**) and methyl *trans*-cinnamate (**103e**) were purchased, other *α*,*β*-unsaturated esters had to be prepared. Methyl sorbate (**103c**) was prepared quantitatively from sorbic acid by TMSCl-activated esterification.[63] *α*,*β*-Unsaturated esters **103b**, **103d**, and **103f** were prepared from relevant aldehydes by Wittig reactions using carbomethoxymethylene triphenylphosphorane and were obtained in 46%, 73%, and 32% respectively (Scheme 1.43).[64–66]



Scheme 1.43 Preparation of *α,β*-unsaturated esters **103**

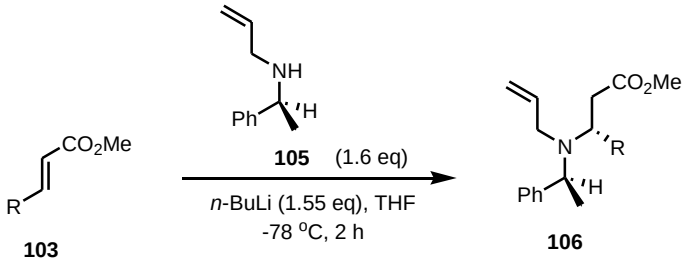
The mechanism of Wittig reaction using a stablized ylide is shown in Scheme 1.44. The ylide attacks the carbonyl carbon to form adducts. Since this step is the rate-determining step and is reversible, the thermodynamically more stable adducts with two bulky groups far from each other form predominantly. Oxygen anion then attacks phosphrous cation and oxaphosphetanes are formed. Then, Ph_3PO leaves and (*E*)-alkenes are formed.



Scheme 1.44 Mechanism of Wittig reaction using a stablized ylide

The enantiomerically pure tertiary amines **106** were prepared by metalation of the

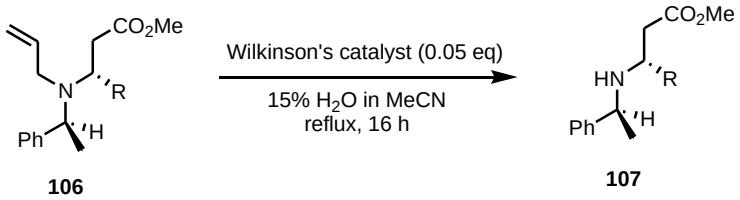
amine **105** using *n*-butyllithium and reaction with *α,β*-unsaturated esters **103** at -78 ^{o}C (Scheme 1.45).[61] This aza-Michael reaction gave adducts **106a-e** in good yield (68-90%) and gave the 3-pyridyl adduct **106f** in moderate yield (48%). From the ^{1}H NMR and ^{13}C NMR spectra, no opposite diastereoisomers of adducts **106** were identified.



Cpd	R	yield (%)
103a	Me	85
103b	*i*-Pr	69
103c	(*E*)-CH=CHMe	78
103d	Cyclohexyl	68
103e	Ph	90
103f	3-Pyridyl	48

Scheme 1.45 Synthesis of tertiary amines **106** via aza-Michael reactions

The allyl group of adducts **106** was then cleaved by heating under reflux overnight in water/acetonitrile mixture in the presence of Wilkinson's catalyst.[67] The deprotection was clean and gave *β*-amino esters **107** in good yield (53-87%) except the adduct **107f**. Presumably, the pyridyl group of the adduct **106f** interacted with the catalyst, causing various side reactions to occur, as indicated by TLC (Scheme 1.46).

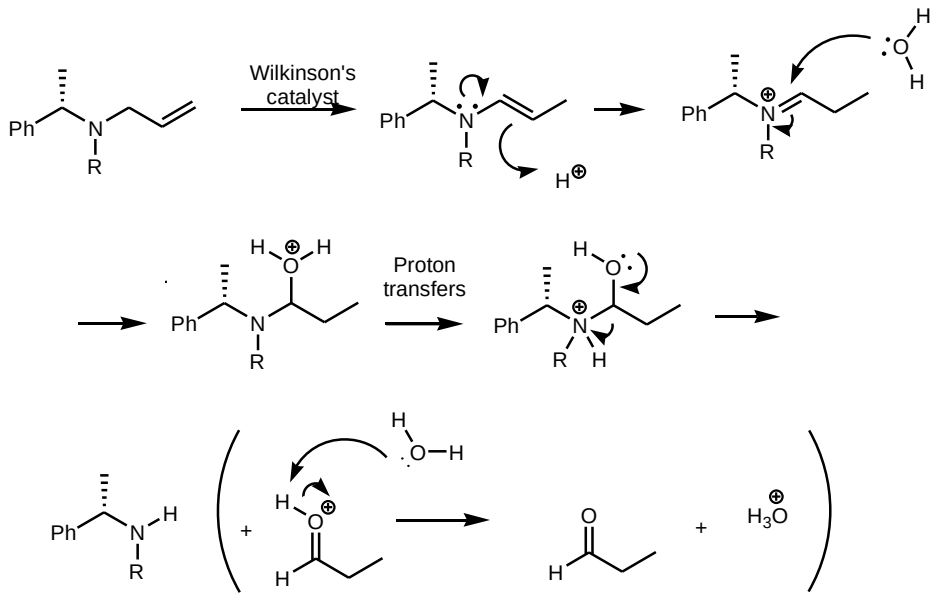


106 **107**

Cpd	R	yield (%)
106a	Me	87
106b	*i*-Pr	59
106c	(*E*)-CH=CHMe	84
106d	Cyclohexyl	53
106e	Ph	76
106f	3-Pyridyl	0

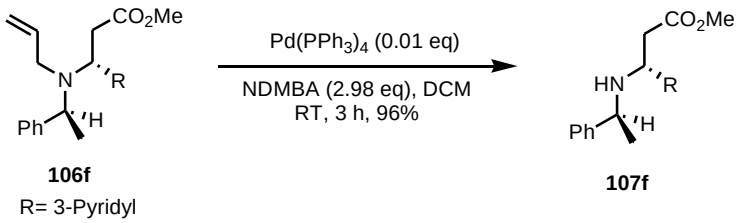
Scheme 1.46 Deallylation of tertiary amines **106** using Wilkinson's catalyst

The mechanism of deallylation of amine **106** using Wilkinson's catalyst is shown in Scheme 1.47. Wilkinson's catalsyt catalyzes the isomerization of *N*-allyl amines to enamines.[68,69] Then the enamines convert to iminium ions which are attacked by a water molecule. After proton transfers, the imines are hydrolyzed to aldehydes and the amines **106** are deallylated.



Scheme 1.47 Mechanism of the deallylation of amines **106** using Wilkinson's catalyst

As deallylation using Wilkinson's catalyst was not compatible with the presence of a pyridyl group, other deallylating agents were investigated. 1,3-Dimethylbarbituric acid (NDMBA) with a catalytic amount of tetrakis(triphenylphosphine)palladium(0) was found to be an ideal deallylating agent, and gave the *β*-amino ester **107f** in 96% yield (procedure modified from Avenoza's synthesis,[70] Scheme 1.48). Although a small amount of catalyst co-ordinated with the product and could not be removed by column chromatography, this did not affect the following acylation step and the product would be purified.



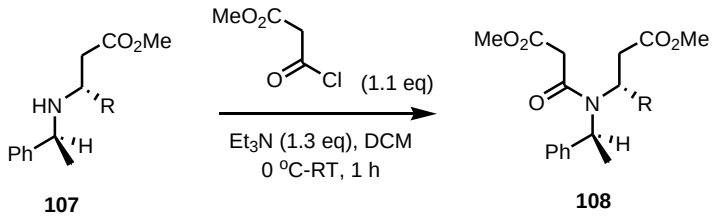
106f
R= 3-Pyridyl

107f

Scheme 1.48 Deallylation of the tertiary amine **106f**

Probably owing to the bulkness of the chiral auxiliary, acylation using methyl malonate activated by EDC failed and the more reactive acid chloride was needed. *β*-Amino

esters **107** were acylated with methyl malonyl chloride using triethylamine as a base to give diesters **108** in fair to high yields (50-94%, Scheme 1.49).



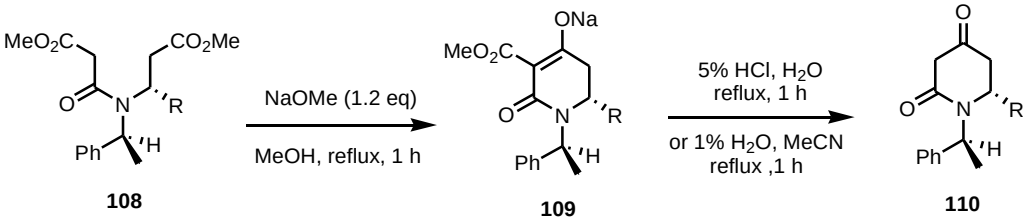
107 **108**

Cpd	R	yield (%)
107a	Me	58
107b	*i*-Pr	50
107c	(*E*)-CH=CHMe	94
107d	Cyclohexyl	66
107e	Ph	80
107f	3-Pyridyl	75

Scheme 1.49 Synthesis of diesters **108**

Dieckmann cyclisation of diesters **108** by heating under reflux for 1 hour with sodium methoxide in methanol gave cyclised products **109**. Cyclised products **109c** and **109e** were isolated as the sodium salts in order to confirm the formation of piperidin-2,4-dione ring, while others were decarboxylated directly. Decarboxylation using either HCl or neutral conditions[15] worked well to give piperidin-2,4-diones **110**

in good to excellent yields (70-97% over two steps, Scheme 1.50).

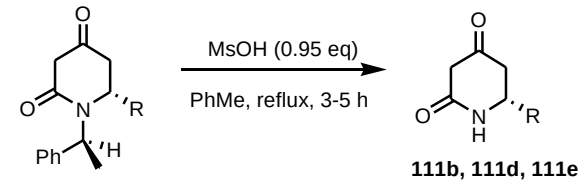


Cpd	R	Yield (%, over 2 steps)
108a	Me	97
108b	*i*-Pr	95
108c	(*E*)-CH=CHMe	70
108d	Cyclohexyl	76
108e	Ph	83
108f	3-Pyridyl	99

Scheme 1.50 Synthesis of piperidin-2,4-diones **110**

The piperidin-2,4-diones **110b, 110d, 110e** were selected for the removal of the chiral auxiliary by treatment with methanesulfonic acid to give the corresponding 1-unsubstituted piperidin-2,4-diones **111a, 111c, 111e** in moderate yields (42-56%, procedure modified from Paik's synthesis,[71] Scheme 1.51). 6-Pyridylpiperidin-2,4-dione (**111f**) would be very water-soluble once the auxiliary was removed and could not be extracted from the aqueous phase, as in the Section 1.2.3.

6-Methylpiperidin-2,4-dione (**111a**) was quite polar and would be difficult to purify by column chromatography. The 6-propenylpiperidin-2,4-dione **110c** should react with methanesulfonic acid normally but insufficient quantities prevented this experiment. From the above three successful cases, this route was found as a feasible synthesis of enantiomerically-pure 1-unsubstituted piperidin-2,4-diones with various substitutions at position-6.



110b,110d,110e **111b, 111d, 111e**

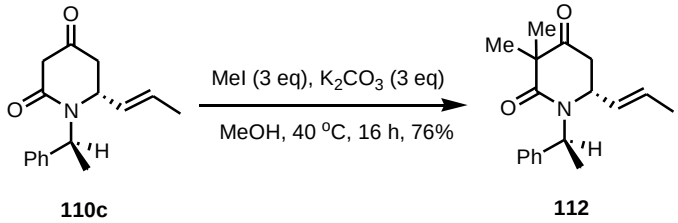
Cpd	R	yield (%)
110b	*i*-Pr	48
110d	Cyclohexyl	42
110e	Ph	56

Scheme 1.51 Deprotection of piperidin-2,4-diones **110b, 110d, 110e**

1.2.6 Alkylations and Reductions of Chiral Piperidin-2,4-diones

Several attempts were made to introduce a methyl group at position-3 of the achiral piperidin-2,4-dione **65e** but only dimethylation was achieved, as previously observed in Scheme 1.32. With the chiral auxiliary blocking the amide, it may be the right substrate for making 3-substituted piperidin-2,4-diones.

The piperidin-2,4-dione **110c** was methylated twice by reacting with excess methyl iodide and potassium carbonate to give the 3,3-dimethylpiperidin-2,4-dione **112** in 76% yield (Scheme 1.52). As expected, the 3-methylpiperidin-2,4-dione **114** could not be made by reacting **110c** with one equivalent of methyl iodide and only the 3,3-dimethylpiperidin-2,4-dione **112** was isolated.

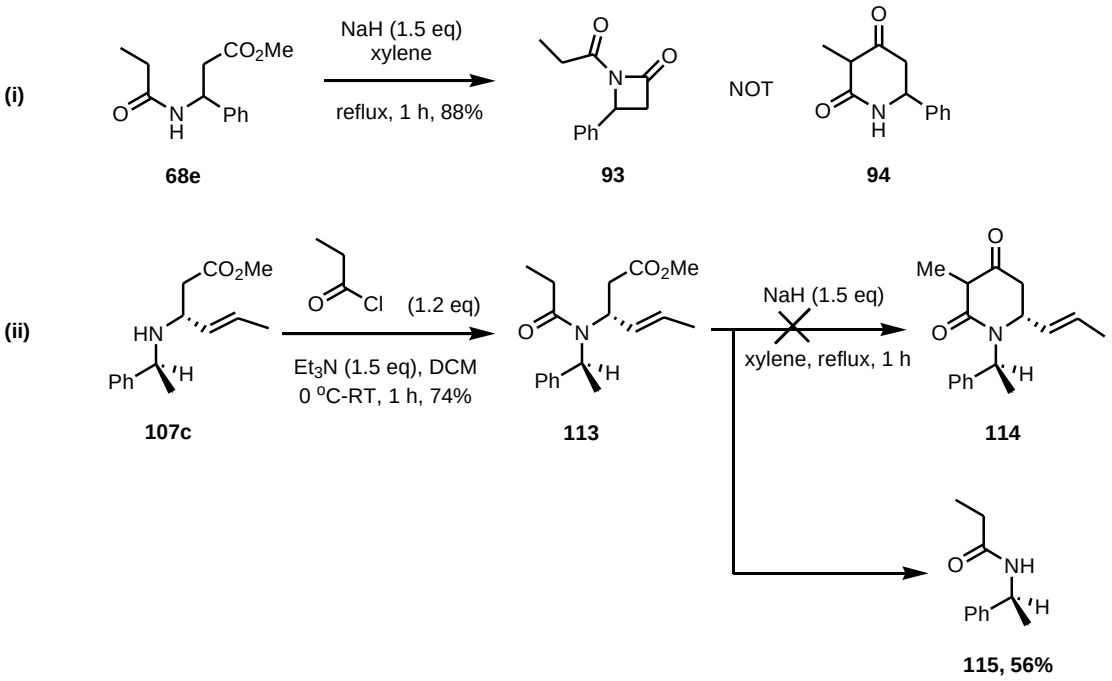


110c **112**

Scheme 1.52 Dimethylation of the piperidin-2,4-dione **110c**

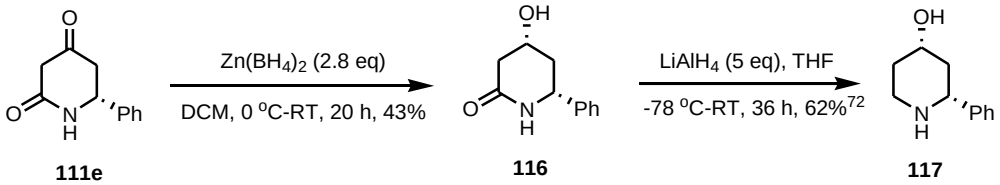
Given that the auxiliary also acts as a blocking group of nitrogen, it was hoped that Dieckmann cyclisation would now take place, since azetidin-2-one formation, as previously observed, could not occur (Scheme 1.53).

The *β*-amino ester **107c** was acylated with propionyl chloride to give the amide **113** in 74% (Scheme 1.53) which was then heated under reflux with sodium hydride in xylene for 1 hour. Unfortunately, reverse Michael reaction occurred to give the amide **115**, and not the cyclised product **114**. Owing to time limitations, further investigation of 3-methylation was not undertaken.



Scheme 1.53 Attempted synthesis of the 3-methylpiperidin-2,4-dione **114**

Stereoselective reduction of chiral piperidin-2,4-diones would be very helpful for drug synthesis since 4-hydroxypiperidine motif is commonly found in alkaloids. Reaction of the piperidin-2,4-dione **110e** with zinc borohydride at room temperature gave the enantiomerically-pure 4-hydroxypiperidin-2-one **116** in 43% yield (procedure modified from Davis' synthesis,[72] Scheme 1.54). The 4-hydroxypiperidin-2-one **116** is in *cis*-form since both phenyl and hydroxy groups are equatorial. Szewczyk reported the reduction of **116** by lithium aluminium hydride to afford the 4-hydroxypiperidine **117** in 62% yield.[72] Therefore, enantiomerically pure 4-hydroxypiperidines can be prepared by our general route.

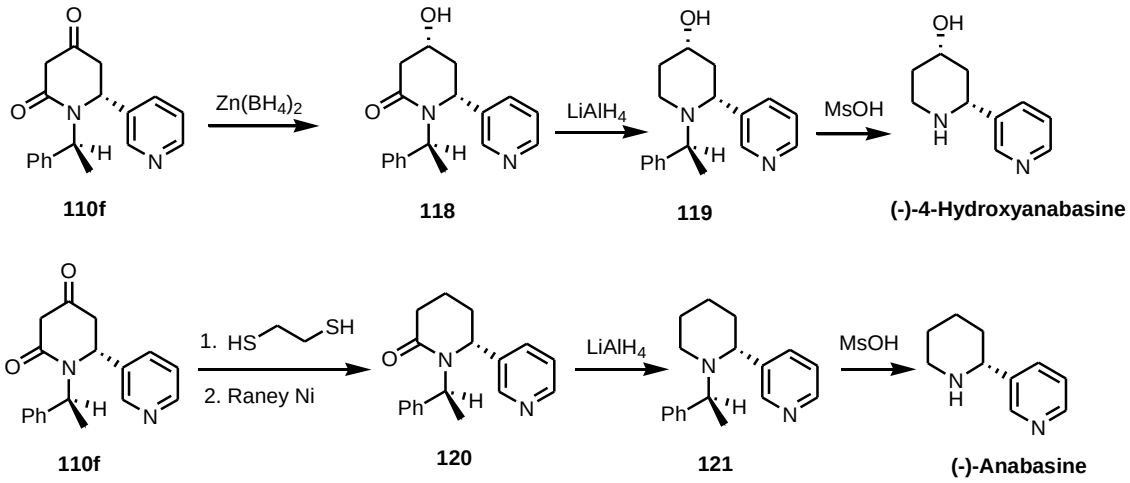


Scheme 1.54 Reduction of the piperidin-2,4-dione **111e**

1.2.7 Future Work

Having developed an asymmetric synthesis of 4-hydroxypiperidines, it is of interest to make (-)-4-hydroxyanabasine using this route. As 1-unsubstituted 6-pyridylpiperidin-2,4-diones are very water-soluble, it was planned to reduce the piperidin-2,4-dione **110f** to the 4-hydroxypiperidine **119** and then remove the auxiliary to give (-)-4-hydroxyanabasine (Scheme 1.55).

(-)-Anabasine could also be synthesized as shown in Scheme 1.54. The piperidin-2,4-dione **110f** would react with 1,2-ethanedithiol to give the corresponding thioketal which would be reduced by Raney nickel to give the piperidin-2-one **120**.[23] Subsequent amide reduction by lithium aluminium hydride and auxiliary removal should give enantiomerically pure anabasine.



Scheme 1.55 Synthesis of (-)-anabasine and its derivative

1.3 Conclusions

Syntheses of piperidin-2-ones via a palladium-catalyzed aza-Michael reaction of *α,β*-unsaturated amides with Michael acceptors were attempted but none of them were successful. Aza-Michael-Michael annulation reported by Ihara[29] was also employed for making such ring but it failed as well.

Then a route for preparing piperidin-2,4-diones involved a Dieckmann cyclisation was proposed (Scheme 1.19). Piperidin-2,4-diones with various substituents at positions-5 and -6 were prepared by this method. Dimethylation at position-3 could be achieved but introduction of a single methyl group at that position failed.

An asymmetric route to 1-unsubstituted piperidin-2,4-diones using a chiral auxiliary was also developed (Scheme 1.42). Dimethylation at position-3 was in good yield but monomethylation at that position was not achieved. Reduction of piperidin-2,4-diones gave enantiomerically-pure 4-hydroxypiperidin-2-ones which would be useful for drug development. In future, it is hoped to make anabasine and related compounds by this synthetic route.

1.4 Experimental

All moisture-sensitive reactions were performed under a nitrogen atmosphere and the glassware was pre-dried in an oven (130 ^{o}C). Evaporation refers to the removal of solvent under reduced pressure. Melting points were measured by a microscope hot-stage Electrothermal 9100 apparatus and are uncorrected. Infra-red (IR) spectra were recorded on a Perkin-Elmer PE-983 spectrophotometer; absorptions are quoted in wavenumbers (ν_{max} in cm^{-1}). ^{1}H NMR spectra were recorded on a Bruker AC300 (300 MHz) spectrometer or a Bruker AMX 500 (125 MHz) spectrometer; data are reported in parts per million (δ). Coupling constants (J) are given in Hertz (Hz). The following abbreviations were used in signal assignments: singlet (s), broad singlet (br s), doublet (d), triplet (t), quartet (q), and multiplet (m). ^{13}C NMR spectra were recorded on a Bruker AC300 (300 MHz) spectrometer or a Bruker AMX 500 (125 MHz) spectrometer; data are reported in parts per million (δ), with $CHCl_3$ as an internal standard. Mass spectra were recorded on a VG7070H mass spectrometer with Finigan Incos II data system at University College London. Thin-layer chromatography was performed on Merck 0.2 mm aluminium-backed silica gel 60 F_{254} plates and visualized by ultra violet light (254 nm) or staining with potassium permanganate with subsequent heating. Flash column chromatography was performed using Merck 0.040-0.063 mm, 230-400 mesh silica gel. Temperatures below 0 ^{o}C were obtained from various mixtures of water, salt and ice, acetone and dry ice.

General procedure 1 for amidation

A solution of acryloyl chloride (1.1 equiv) in dichloromethane was added to a 250 mL round-bottom flask equipped with a pressure-equalizing dropping funnel. The solution

was then cooled to -15 ^{o}C in an ethylene glycol/dry ice bath. The dropping funnel was charged with a solution of amines (1 equiv) and triethylamine in dichloromethane. This solution was added dropwise to the acid chloride solution over 25 min, stirred for 30 min more at -15 ^{o}C, and slowly warmed to ambient temperature over 1.5 h. The mixture was then poured into an aqueous sodium hydroxide and extracted by dichloromethane. The combined organic layers were dried ($MgSO_4$), and evaporated.

General procedure 2a for amidation to diesters

To a stirred solution of *β*-amino esters (1 equiv) in dichloromethane at 0 ^{o}C under nitrogen, anhydrous 1-hydroxybenzotriazole (1.5 equiv) and *N*,*N*-diisopropylethylamine (4 equiv) were added. Methyl malonate (3 equiv) in dichloromethane was added dropwise. *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (1 equiv) was added and the mixture was then allowed to warm to room temperature and stirred for 2 h. Saturated aqueous sodium hydrogen carbonate was added. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated.

General procedure 2b for amidation to diesters

To a stirred solution of *β*-amino esters (1 equiv) in dichloromethane at 0 ^{o}C under nitrogen, triethylamine (1.3 equivl) and methyl 3-chloro-3-oxopropanoate (1.2 equiv) were added. The mixture was then allowed to warm to room temperature and stirred for 1 h. The mixture was diluted with dichloromethane and washed with saturated aqueous sodium hydrogen carbonate. The aqueous layer was extracted with dichloromethane and the combined organic layers were dried ($MgSO_4$) and evaporated.

General procedure 3 for Dieckmann cyclisation

To a stirred solution of diesters (1 equiv) in methanol at room temperature under nitrogen, sodium methoxide in methanol (1.2 equiv) was added. The mixture was then heated under reflux for 1 h. The mixture was allowed to cool to room temperature, then acidifed with 1M hydrochloric acid to around pH 6. The aqueous phase was extracted with dichloromethane, dried ($MgSO_4$), and evaporated. The oily residue was added to 1% water in acetonitrile and the mixture was heated under reflux for 1 h. The mixture was allowed to cool to room temperature and evaporated

General procedure 4 for Michael addition

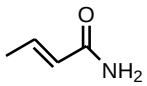
To a stirred solution of amines (1.6 equiv) in anhydrous THF at -78 ^{o}C under nitrogen, *n*-butyllithium (1.55 equiv) was added dropwise via syringe. The mixture was stirred at -78 ^{o}C for a further 30 min. A solution of α,β-unsaturated esters (1 equiv) in anhydrous THF was added dropwise via syringe at -78 ^{o}C and the mixture was stirred for further 3 h at the same temperature. The mixture was quenched with aqueous saturated ammonium chloride and was allowed to warm to room temperature over 15 min. Evaporation gave a pale yellow liquid which was partitioned between dichloromethane and aqueous 10% citric acid. The aqueous layer was extracted with dichloromethane and the combined organic layers were washed with saturated aqueous sodium hydrogen carbonate and then brine, dried ($MgSO_4$), and evaporated.

General procedure 5 for deallylation

To a stirred solution of β-amino esters (1 equiv) in acetonitrile/water (85:15) at room temperature, tris(triphenylphosphine)rhodium(I) chloride (Wilkinson's catalyst) (5 mol%) was added in one portion. The mixture was then heated under reflux for 16 h.

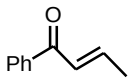
The mixture was allowed to cool to room temperature and extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$) and evaporated.

(*E*)-But-2-enamide (39)[73]



0.880 Aqueous ammonia (9 mL, 0.313 mol) was cooled in an ice bath. Methyl acrylate (3 mL, 31.3 mmol) was added dropwise over 5 min. The white solid was filtered and recrystallized from deionized water to give **39** (1.91 g, 72%) as white microprisms, mp 150-152 ^oC (lit.[74] mp 155-156 ^oC); IR ν_{max} 3322 (N-H), 3151 (N-H), 1674 (amide C=O), 1610, 1407, 1142, 662 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.87 (1H, dq, *J*= 17.7, 7.8 Hz, =C*H*CH_3) 5.86 (1H, dq, *J*= 17.7, 1.7 Hz, =CHCO) 5.45 (1H, s, NH) 1.88 (3H, dd, *J*= 7.8, 1.7 Hz, C*H*$_3$CH=).

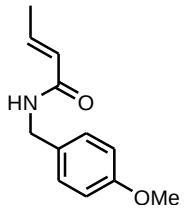
(*E*)-1-Phenylbut-2-en-1-one (40)[73]



Aluminium chloride (freshly ground, 1.84 g, 13.7 mmol) was added to benzene (6.67 mL). The mixture was stirred vigorously while (*E*)-crotonyl chloride (1.03 mL, 10.8 mmol) was added dropwise over 5 min. The mixture was stirred for further 15 min, and then poured into a mixture of ice (33 mL) and hydrochloric acid (17 mL, 2M). The mixture was extracted with diethyl ether (2 x 10 mL), washed with sodium hydroxide (10 mL, 4M), dried ($MgSO_4$), and evaporated. The resulting yellow oil was purified by distillation to give **40** as colourless oil (0.65 g, 42%), bp 120 ^oC/760 mmHg (lit.[75] bp 90-95 ^oC/2.0 mmHg); R_f 0.76 (30% ethyl acetate/hexane); IR ν_{max} 2972 (C-H), 1668 (ketone C=O), 1621 (C=C), 1446, 1293, 1217, 963, 756, 689 cm^{-1}; ^1H NMR (300 MHz,

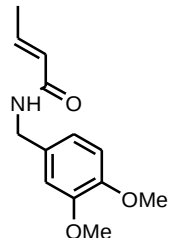
$CDCl_3$) δ 7.94-7.91 (2H, m, Ph) 7.73-7.53 (1H, m, Ph) 7.49-7.46 (2H, m, Ph) 7.08 (1H, dq, *J*= 19.5, 6.6 Hz, =C*H*CH_3) 6.88 (1H, dd, *J*= 19.5 ,0.5 Hz, =CHCO) 2.00 (3H, dd, *J*= 6.6, 0.5 Hz, C*H*$_3$CH=).

(2*E*)-*N*-[(4-Methoxyphenyl)methyl]but-2-enamide (47)



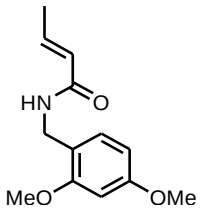
Following general procedure 1, reaction of crotonyl chloride (1.31 mL, 11.8 mmol) in dichloromethane (45 mL), 4-methoxybenzylamine (1.43 mL, 10.9 mmol) and triethylamine (1.53 mL) in dichloromethane (45 mL) gave a pale yellow solid that was triturated with cyclohexane (4 x 55 mL) to give **47** (1.79 g, 80%) as white microprisms, mp 115-117 ^{o}C; R_f 0.82 (ethyl acetate), IR ν_{max} (solution in $CHCl_3$) 3284 (N-H), 2835 (C-H), 1668 (amide C=O), 1620, 1418, 1252, 1225 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (1H, s, Ph) 7.22 (2H, d, *J*= 8.6 Hz, Ph) 6.86 (2H, d, *J*= 8.6 Hz, Ph) 6.87 (1H, dq, *J*= 15.2, 6.9 Hz, =C*H*CH_3) 5.78 (1H, dq, *J*= 15.2, 1.6 Hz, =CHCO) 5.60 (1H, br d, *J*= 5.6 Hz, NH) 4.43 (2H, d, *J*= 5.6 Hz, C*H*$_2$Ar) 3.79 (3H, s, OCH_3) 1.85 (3H, dd, *J*= 6.9, 1.6 Hz, C*H*$_3$CH=); ^{13}C NMR (300 MHz, $CDCl_3$) δ 165.7 (CONH) 159.1 (Ar*C*OCH_3) 140.2 (=*C*HCH_3) 130.5 (=*C*HCO) 129.2 (ArC) 124.9 (ArC) 114.1 (ArC) 55.3(CH_3O) 43.1 (CH_2Ar) 17.7 (*C*H_3CH=); m/z (Cl+) 228 (100%, M+Na^+), 174 (5%, M^+-OMe); HRMS $C_{12}H_{15}NO_2Na$ calcd. 228.1000, found 228.1011.

(2*E*)-*N*-[(3,4-Dimethoxyphenyl)methyl]but-2-enamide (52)



Following general procedure 1, reaction of crotonyl chloride (0.26 mL, 2.71 mmol) in dichloromethane (12 mL), veratrylamine (0.44 mL, 3.03 mmol) and triethylamine (0.42 mL) in dichloromethane (12 mL) gave a pale yellow solid that was triturated with cyclohexane (4 x 55 mL) to give **52** (0.39 g, 61%) as white microprisms, mp 71-75 ^{o}C; R_f 0.52 (ethyl acetate); IR ν_{max} 3280 (N-H), 2835 (C-H), 1669 (amide C=O), 1626, 1419, 1262, 1225 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (1H, s, Ph) 7.00 (1H, dq, *J*= 15.2, 6.9 Hz, =C*H*CH_3) 6.90-6.79 (2H, m, Ph) 5.80 (1H, dq, *J*= 15.2, 1.6 Hz, =CHCO) 5.65 (1H, br d, *J*= 5.7 Hz, NH) 4.44 (2H, d, *J*= 5.7 Hz, C*H*$_2$Ar) 3.87 (6H, s, 2 x OCH_3) 1.89 (3H, dd, *J*= 6.9, 1.6 Hz, C*H*$_3$CH=); ^{13}C NMR (300 MHz, $CDCl_3$) δ 165.8 (CONH) 149.1 (Ar*C*OCH_3) 148.5 (Ar*C*OCH_3) 140.3 (=*C*HCH_3) 130.9 (Ar*C*CH_2) 124.9 (=*C*HCO) 120.2 (ArC) 111.3 (ArC) 111.2 (ArC) 55.9 (CH_3O) 55.9 (CH_3O) 43.4 (CH_2Ar) 17.7 (*C*H_3CH=).

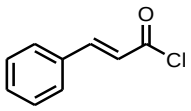
(2*E*)-*N*-[(2,4-Dimethoxyphenyl)methyl]but-2-enamide (53)



Following general procedure 1, reaction of crotonyl chloride (0.31 mL, 2.64 mmol) in dichloromethane (12 mL), 2,4-dimethoxybenzylamine (0.45 mL, 3.00 mmol) and

triethylamine (0.42 mL) in dichloromethane (12 mL) gave a pale yellow solid that was triturated with cyclohexane (4 x 55 mL) to give **53** (0.55 g, 88%) as white microprisms, mp 132-132.6 ^{o}C; R_f 0.70 (ethyl acetate), IR ν_{max} 3283 (N-H), 2835 (C-H), 1668 (amide C=O), 1613, 1419, 1262, 1222 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (1H, d, *J*= 8.1 Hz, Ph) 6.91-6.76 (1H, m, Ph) 6.45 (1H, s, Ph) 6.42 (1H, dq, *J*= 15.5, 1.9 Hz, =C*H*CH_3) 5.88 (1H, br d, *J*= 5.8 Hz, NH) 5.76 (1H, dq, *J*= 15.5, 5.4 Hz, =CHCO) 4.42 (2H, d, *J*= 5.8 Hz, C*H*$_2$Ar) 3.86 (3H, s, OCH_3) 3.83 (3H, s, OCH_3) 1.83 (3H, dd, *J*= 5.4, 1.9 Hz, C*H*$_3$CH=); ^{13}C NMR (300 MHz, $CDCl_3$) δ 165.5 (CONH) 160.5 (Ar*C*OCH_3) 158.6 (Ar*C*OCH_3) 139.6 (=*C*HCH_3) 130.7 (Ar*C*CH_2) 125.3 (=*C*HCO) 119.0 (ArC) 104.0 (ArC) 98.6 (ArC) 55.4 (CH_3O) 55.4 (CH_3O) 38.8 (CH_2Ar) 17.7 (*C*H_3CH=); m/z (Cl+) 235 (25%, M^+), 220 (5%, M^+-CH_3), 166 (8%, M^+-$CH_3CHCHCO$), 151 (100%, M^+-$CH_3CHCHCONH$), 98 (4%, M^+-$CH_3CHCHCONHCH_2$); HRMS $C_{13}H_{17}NO_3$ calcd. 235.1203, found 235.1208.

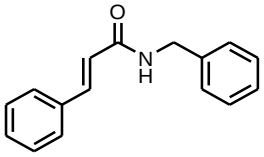
(*E*)-3-Phenylprop-2-enoyl chloride (122)[76]



trans-Cinnamic acid (1.00 g, 7.46 mmol) was added in a 25 mL round-bottom flask and dissolved in toluene (10 mL) under nitrogen. Then thionyl chloride (0.75 mL, 10.3 mmol) was added and the mixture was heated under reflux for 2 h. The pale yellow liquid was evaporated to give **122** (quantitative) as white microprisms, mp 35-36 ℃ (lit.[77] mp 35-37 ℃); R_f 0.60 (ethyl acetate); IR ν_{max} 2942 (C-H), 1689 (acid chloride C=O), 1631 (C=C), 1264, 731, 703 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (1H, d, *J*= 16.0 Hz, =C*H*Ar) 7.57-7.51 (2H, m, Ph) 7.50-7.44 (2H, m, Ph) 7.41-7.23 (1H, m,

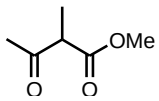
Ph) 6.60 (1H, d, *J*= 16.0 Hz, =CHCO).

(*E*)-*N*-Benzyl-3-phenylpro-2-enamide (57)[78]



Benzylamine (1.72 mL, 15.8 mmol) was stirred vigorously in crushed ice while 3-phenylpro-2-enoyl chloride (1.31 g, 7.89 mmol) was being added dropwise. The reaction mixture was then filtered and washed with distilled water (15 mL). Recrystallization from methanol gave white microprisms of **57** (1.32 g, 70%), mp 106-109 ^{o}C (lit. [79] 106-108 ^{o}C); R_f 0.30 (ethyl acetate); IR ν_{max} 3275 (N-H), 2925 (C-H), 1656 (amide C=O), 1617 (C=C), 1536, 1220, 977, 732, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (1H, d, *J*= 15.7 Hz, =C*H*Ar) 7.50-7.49 (2H, m, Ph) 7.37-7.26 (8H, m, Ph) 6.41 (1H, d, *J*= 15.7 Hz, =CHCO) 5.88 (1H, br d, *J*= 5.7 Hz, NH) 4.59 (2H, d, *J*= 5.7 Hz, C*H*$_2$Ar).

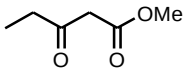
Methyl 2-methyl-3-oxobutanoate (70)[48]



To a stirred mixture of methyl acetoacetate (1 mL, 9.26 mmol) and methyl iodide (0.58 mL, 9.26 mmol) in acetone (3 mL), potassium carbonate (1.91 g, 13.89 mmol) was added slowly at 0 ^{o}C and the mixture was stirred for 2 h at 0 ^{o}C and then stirred at room temperature for 16 h. Diethyl ether (10 mL) was added and the mixture was filtered. The filtrate was washed with brine (5 mL), dried (Na_2SO_4), and evaporated. The resulting pale yellow oil was purified by flash chromatography (10% ethyl

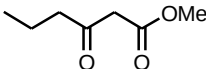
acetate/hexane) to give **70** (0.53 g, 46%) as a colourless oil, R_f 0.18 (15% ethyl acetate/hexane); IR ν_{max} 2955 (C-H), 1740 (ketone C=O), 1708 (ester C=O), 1457, 1166, 1084, 878, 670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.74 (3H, s, OCH_3) 3.52 (1H, q, *J*= 7.5 Hz, C*H*CH_3) 2.24 (3H, s, CH_3CO) 1.33 (3H, d, *J*= 7.5 Hz, C*H*$_3$CHCO);^{13}C NMR (300 MHz, $CDCl_3$) δ 203.6 (*C*OCH_3) 171.0 (*C*$OOCH_3$) 53.4 (*C*HCOO) 52.4 (OCH_3) 28.4 (*C*H_3CH) 12.8 (*C*H_3CO).

Methyl 3-oxopentanoate (71)[46]



To a stirred solution of sodium hydride (2.05 g, 0.102 mol, 60% in mineral oil, washed with petroleum ether and THF) in THF (75 mL) at 0 ℃, methyl acetoacetate (5 mL, 46.4 mmol) was added dropwise. The mixture was cooled to -20 ℃ after stirring at 0 ℃ for 10 min. *n*-Butyllithium (20.5 mL, 2.5 M, 50.9 mmol) was added over 10 min and the mixture was stirred at -20 ℃ for 5 min. Methyl iodide (2.9 mL, 46.6 mmol) was added dropwise and the mixture was stirred at room temperature for 3 h. The mixture was then poured to saturated ammonium chloride solution (50 mL), extracted with diethyl ether (3 x 50 mL), dried ($MgSO_4$), and evaporated to give **71** (5.84 g, 97%) as a pale yellow oil, ^1H NMR (300 MHz, $CDCl_3$) δ 3.73 (3H, s, OCH_3) 3.46 (2H, s, C*H*$_2$$CO_2CH_3$) 2.57 (2H, t, *J*= 7.2 Hz, C*H*$_2$$CH_3$) 1.08 (3H, t, *J*= 7.2 Hz, C*H*$_3$$CH_2$).

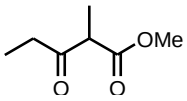
Methyl 3-oxohexanoate (66a)[46]



To a stirred solution of sodium hydride (4.10 g, 0.102 mol, 60% in mineral oil, washed with petroleum ether and THF) in THF (150 mL) at 0 ℃, methyl acetoacetate (10 mL,

92.8 mmol) was added dropwise. The mixture was cooled to -20 ℃ after stirring at 0 ℃ for 10 min. *n*-Butyllithium (41 mL, 0.102 mol, 2.5 M) was added over 10 min and the mixture was stirred at -20 ℃ for 5 min. Bromoethane (7 mL, 93.1 mmol) was added dropwise and the mixture was stirred at room temperature for 3 h. The mixture was then poured to saturated ammonium chloride solution (100 mL), extracted with diethyl ether (3 x 100 mL), dried ($MgSO_4$), and evaporated. The resulting orange solid was purified by distillation (105 ℃/1.6 mmbar) to give **66a** (11.33 g, 85%) as a colourless oil, IR ν_{max} 2923 (C-H), 1752 (ketone C=O), 1736 (ester C=O), 1438, 1319, 1261, 1163 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.72 (3H, s, OCH_3) 3.46 (2H, s, $CH_2CO_2CH_3$) 2.51 (2H, t, *J*= 7.2 Hz, $CH_2CH_2CH_3$) 1.62 (2H, qt, *J*= 7.4, 7.2 Hz, CH_2CH_3) 0.92 (3H, t, *J*= 7.4 Hz, CH_3CH_2); ^{13}C NMR (300 MHz, $CDCl_3$) δ 202.7 ($COCH_2$) 167.7 ($COOCH_3$) 52.3 (OCH_3) 49.0 (CH_2COOCH_3) 44.9 (CH_2COCH_2)) 16.9 (CH_2CH_3) 13.5 (CH_3CH_2).

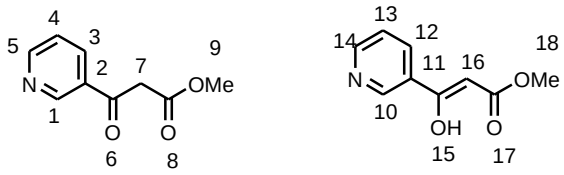
Methyl 2-methyl-3-oxopentanoate (66b)



To a stirred mixture of methyl 3-oxopentanoate (1.00 g, 7.68 mmol) and methyl iodide (0.48 mL, 7.68 mmol) in acetone (10 mL), potassium carbonate (1.60 g, 11.52 mmol) was added slowly at 0 ^oC and the mixture was stirred for 2 h at 0 ^oC and then stirred at room temperature for 16 h. Diethyl ether (20 mL) was added and the mixture was filtered. The filtrate was washed with brine (5 mL), dried (Na_2SO_4), and evaporated to give **66b** (0.98 g, 88%) as a yellow oil, IR ν_{max} 2955 (C-H), 1742 (ketone C=O), 1707 (ester C=O), 1598, 1456, 1260, 1147 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.72 (3H, s, OCH_3) 3.54 (1H, q, *J*= 7.7 Hz, $CHCH_3$) 2.54 (2H, d, *J*= 3.2 Hz, CH_2CO) 1.34 (3H, d,

J= 7.7 Hz, C*H*$_3$CHCO) 1.08 (3H, t, *J*= 3.2 Hz, C*H*$_3$CH$_2$); ^{13}C NMR (300 MHz, $CDCl_3$) δ 206.4 (*C*OCH$_2$) 171.1 (*C*OOCH$_3$) 52.4 (*C*HCOO) 52.4 (OCH$_3$) 34.7 (*C*H$_2$CO) 12.9 (*C*H$_3$CH) 7.7 (*C*H$_3$CH$_2$).

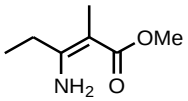
Methyl 3-oxo-3-(pyridin-3-yl)propanoate (66c)[50]



To a stirred solution of sodium hydride (9.90 g, 0.246 mol, 60% in mineral oil, washed with petroleum ether and THF) in THF (60 mL), dimethyl carbonate (14.7 g, 0.423 mol) was added. The mixture was heated under reflux for 10 min. 3-Acetylpyridine (9.90 g, 81.7 mmol) in THF (24 mL) was added over 15 min and the mixture was heated under reflux for 1.5 h. The mixture was then poured to ice water (100 mL) and neutralized by 1M hydrochloric acid. The mixture was then extracted with ethyl acetate (3 x 100 mL), dried ($MgSO_4$), and evaporated. The resulting yellow oil was purified by flash chromatography (30% ethyl acetate/hexane) to give **66c** (14.1 g, 96%) as yellow microprisms, mp 72-73 ^{o}C (lit.[80] 73-74 ^{o}C); R_f 0.17 (30% ethyl acetate/hexane); IR ν_{max} 3315 (O-H), 2955 (C-H), 1738 (seter C=O), 1687 (alkenyl C=C), 1625, 1585, 1270, 1209, 987, 801, 701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) (2:1 keto-enol mixture) δ 8.85 (1H, d, *J*= 1.9 Hz, C_1H) 8.67 (1H, d, *J*= 1.9 Hz, $C_{10}H$) 8.49-8.48 (1H, m, C_5H) 8.38-8.34 (1H, m, $C_{14}H$) 7.96-7.92 (1H, m, C_3H) 7.75-7.73 (1H, m, $C_{12}H$) 7.17-7.13 (1H, m, C_4H) 7.05-7.03 (1H, m, $C_{13}H$) 3.72 (3H, s, OCH_3) 5.44 (1H, s, $C_{16}H$) 3.85 (2H, s, C_7H) 3.48 (3H, s, $C_{18}H$) 3.44 (3H, s, C_9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 191.5 (C_6) 172.8 (C_{15}) 168.5 (C_{18}) 167.2 (C_9) 153.7 (C_1) 151.6 (C_{10}) 149.7 (C_5) 147.1 (C_{13}) 135.6 (C_3) 133.2 (C_{12}) 131.1 (C_2) 128.8 (C_{11}) 123.5 (C_4) 123.2 (C_{13}) 88.1 (C_{16}) 52.2 (C_9) 51.4

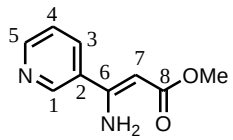
(C_{18}) 45.4 (C_7); m/z (Cl+) 180 (100%, $M+H^+$); HRMS $C_9H_{10}NO_3$ calcd. 180.0655, found 180.0658.

Methyl 3-amino-2-methylpent-2-enoate (67b)



To a stirred solution of methyl 2-methyl-3-oxopentanoate (0.98 g, 6.77 mmol) in benzene (50 mL), ammonium acetate (2.60 g, 33.76 mmol) and a few drops of acetic acid were added. The mixture was heated under reflux for 3 d with the azeotropic removal of water. The mixture was allowed to cool to room temperature, then diluted with ethyl acetate (50 mL), washed with saturated aqueous sodium hydrogen carbonate (15 mL), dried (Na_2SO_4), and evaporated to give **67b** (0.51 g, 52%) as an orange oil, IR ν_{max} 3303 (N-H), 2924 (C-H), 1744 (ester C=O), 1656 (alkenyl C=C), 1610, 1462, 1161 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.72 (3H, s, OCH_3) 2.25 (2H, q, J= 7.6 Hz, CH_2CH_3) 1.75 (3H, s, CH_3CCOO) 1.15 (3H, t, J= 7.6 Hz, CH_3CH_2); m/z (Cl+) 144 (65%, $M+H^+$); HRMS $C_7H_{14}NO_2$ calcd. 144.1025, found 144.1019.

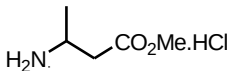
Methyl 3-amino-3-(pyridin-3-yl)propenoate (67c)[51]



To a stirred solution of methyl 3-oxo-3-(pyridin-3-yl)propanoate (1.89 g, 10.57 mmol) in benzene (40 mL), ammonium acetate (4.07 g, 52.84 mmol) and a few drops of acetic acid were added. The mixture was heated under reflux for 3 d with the azeotropic removal of water. The mixture was allowed to cool to room temperature, then diluted with ethyl acetate (30 mL), washed with saturated aqueous sodium hydrogen carbonate

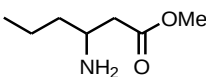
(5 mL), dried (Na_2SO_4), and evaporated to give **67c** (1.46 g, 78%) as yellow microprisms, mp 112-114 ^oC; IR ν_{max} 3396 (N-H), 3301 (N-H), 2955 (C-H), 1664 (ester C=O), 1620 (alkenyl C=C), 1559, 1475, 1312, 1171, 793, 712 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.67-8.62 (1H, m, C_1H) 8.52-8.47 (1H, m, C_5H) 7.77-7.71 (1H, m, C_3H) 7.26-7.19 (1H, m, C_4H) 4.82 (1H, s, =CHCOO) 3.59 (3H, s, OCH_3); ^{13}C NMR (500 MHz, $CDCl_3$) δ 170.4 (C_8) 157.5 (C_6) 151.3 (C_1) 147.5 (C_5) 133.9 (C_3) 133.5 (C_2) 123.6 (C_4) 85.6 (C_7) 50.6 (C_8).

Methyl 3-aminobutanoate hydrochloride (68a)



To a stirred solution of methyl 3-aminobutanoic acid (4.80 g, 46.5 mmol) in methanol (80 mL) in a salt-ice bath, thionyl chloride (7 mL, 96.5 mmol) was added dropwise via an addition funnel. The resulting solution was heated under reflux for 3 h. The mixture was then concentrated and washed with hot hexane to give **68a** (6.93 g, 97%) as a yellow oil, IR ν_{max} 3397 (N-H), 2917 (C-H), 1716 (ester C=O), 1611 (C=C), 1497, 1439, 1188, 1103, 1005 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.38 (3H, br s, NH_2) 3.82-3.80 (1H, m, C*H*CH_3) 3.69 (3H, s, OCH_3) 2.98 (1H, dd, *J*= 15.8, 5.0 Hz, C*H*$_2$CH) 2.76 (1H, dd, *J*= 15.8, 5.0 Hz, C*H*$_2$CH) 1.51 (3H, d, *J*= 4.9 Hz, C*H*$_3$$CH_2$); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.1 (*C*$OOCH_3$) 52.4 (OCH_3) 45.1 (CHNH) 38.1 (*C*H_2COOCH_3) 18.6 (*C*H_3CH_2).

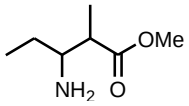
Methyl 3-aminohexanoate (68b)



To a stirred solution of methyl 3-oxohexanoate (11.21 g, 77.7 mmol) in benzene (160

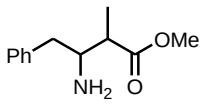
mL), ammonium acetate (30 g, 0.388 mol) and a few drops of acetic acid were added. The mixture was heated under reflux for 3 d with the azeotropic removal of water. The mixture was allowed to cool to room temperature, then diluted with ethyl acetate (150 mL), washed with saturated aqueous sodium hydrogen carbonate (15 mL), dried (Na_2SO_4), and evaporated to give *β*-enamino ester as a pale orange oil. Sodium borohydride (7.15 g, 189 mmol) was added portion wise to a stirred solution of glacial acetic acid (200 mL) whilst the temperature was maintained at around 20 ℃. The mixture was then stirred for 30 min until there was no hydrogen gas evolved. The *β*-enamino ester was then added in one portion and the mixture was stirred at room temperature for 3 h. The acetic acid was removed in vacuo and the residue was dissolved in ethyl acetate (100 mL). The mixture was extracted with water (4 x 100 mL), and the pH of the aqueous phase was adjusted to pH 12 by potassium carbonate. The mixture was extracted with chloroform (3 x 150 mL) and the combined organic layers were dried ($MgSO_4$), and evaporated to give **68b** (3.61 g, 32%) as an orange oil, IR ν_{max} 3272 (N-H), 2957 (C-H), 1736 (ester C=O), 1553, 1436, 1379, 1174 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.73 (3H, s, OCH_3) 3.20-3.16 (1H, m C*H*NH_2) 2.46 (1H, dd, *J*= 15.7, 3.9 Hz, C*H*$_2$$COOCH_3$) 2.25 (1H, dd, *J*= 15.7, 9.0 Hz, C*H*$_2$$COOCH_3$) 2.03 (2H, br s, NH_2) 1.36-1.33 (4H, m, C*H*$_2$$CH_3$ + C*H*$_2$$CH_2CH_3$) 0.91 (3H, t, *J*= 2.5 Hz, C*H*$_3$$CH_2$); ^{13}C NMR (300 MHz, $CDCl_3$) δ 173.1 (*C*$OOCH_3$) 51.5 (OCH_3) 48.0 (*C*HNH_2) 42.3 (*C*H_2COOCH_3) 39.7 (*C*$H_2CH_2CH_3$) 19.2 (*C*H_2CH_3) 14.0 (*C*H_3CH_2).

Methyl 3-amino-2-methylpentanoate (68c)



Sodium borohydride (0.64 g, 16.8 mmol) was added portion wise to a stirred solution of glacial acetic acid (11 mL) whilst the temperature was maintained at around 20 ℃. The mixture was then stirred for 30 min until there was no hydrogen gas evolved. Methyl 3-amino-2-methylpent-2-enoate (0.93 g, 6.47 mmol) was then added in one portion and the mixture was stirred at room temperature for 3 h. The acetic acid was removed in vacuo and the residue was dissolved in ethyl acetate (10 mL). The mixture was extracted with water (4 x 10 mL), and the pH of the aqueous phase was adjusted to pH 12 by potassium carbonate. The mixture was extracted with chloroform (3 x 15 mL) and the combined organic layers were dried ($MgSO_4$), and evaporated to give **68c** (0.63 g, 67%) as an orange oil, IR ν_{max} 3321 (N-H), 2961 (C-H), 1731 (ester C=O), 1569, 1457, 1402, 1198, 975 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (1:1 mixture of diastereoisomers) δ 3.67 (3H, s, OCH_3) 3.66 (3H, s, OCH_3) 2.90-2.43 (2H, m C*H*NH_2 + C*H*$COOCH_3$) 1.53 (2H, br s, NH_2) 1.42-1.16 (2H, m, C*H*$_2CH_3$) 1.14-1.11 (3H, m, C*H*$_3CH$) 0.96-0.90 (3H, m, C*H*$_3CH_2$).

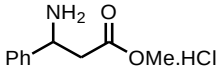
Methyl 3-amino-2-methyl-4-phenylbutanoate (68d)



To a stirred mixture of zinc dust (2.60 g, 39.28 mmol) in dichloromethane (13 mL) under nitrogen, trimethylsilylchloride (0.26 ml, 0.109 mol) was added. The mixture was stirred for 30 min at room temperature. Tetrahydrofuran (8 mL) was added and the

mixture was heated to 42 ^{o}C. A mixture of benzyl cyanide (1.00 g, 8.54 mmol) and methyl 2-bromopropanoate (2.85 g, 17.07 mmol) was added to the mixture and was heated under reflux for 2 h. The mixture was left to cool down and filtered. Sodium borohydride (0.60 g, 15.37 mmol) and ethanol (2.5 mL) was added cautiously to the filtrate and the mixture was stirred for 3 h. Hydrochloric acid (9 mL, 2M) was then added and the aqueous layer was extracted with dichloromethane (2 x 10 ml). The combined organic layers were dried ($MgSO_4$) and evaporated. The oily residue was diluted with toluene (4 mL) and alkalized with concentrated ammonia (3 ml). The aqueous phase was then extracted with toluene (2 x 4 mL), dried ($MgSO_4$) and evaporated. The resulting oil was purified by flash chromatography (20% ethyl acetate/hexane) to give **68d** (0.27 g, 15%) as a yellow oil, R_f 0.75 (30% ethyl acetate/hexane); IR ν_{max} 3368 (N-H), 2948 (C-H), 1726 (ester C=O), 1664, 1453, 1166, 740 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) (1:1 mixture of diastereoisomers) δ 7.38-7.30 (5H, m, Ph) 3.69 (3H, s, OCH_3) 3.40-3.21 (1H, m C*H*NH_2) 2.92-2.73 (1H, m, C*H*$COOCH_3$) 2.60-2.40 (2H, m, C*H*$_2$Ar) 1.65 (2H, br s, NH_2) 1.26-1.18 (3H, m, C*H*$_3$CH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 176.1 (*C*$OOCH_3$) 175.9 (*C*$OOCH_3$) 139.1 (ArC) 139.1 (ArC) 129.4 (ArC) 129.3 (ArC) 129.1 (ArC) 128.6 (ArC) 126.5 (ArC) 55.5 (*C*HNH_2) 54.4 (*C*HNH_2) 51.7 (OCH_3) 51.6 (OCH_3) 45.7 (*C*$HCOOCH_3$) 44.6 (*C*$HCOOCH_3$) 41.8 (*C*H$_2$Ar) 41.6 (*C*H$_2$Ar) 14.5 (*C*H$_3$CH) 11.7 (*C*H$_3$CH).

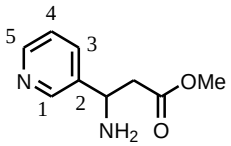
Methyl 3-amino-3-phenylpropanoate hydrochloride (68e)



To a stirred solution of 3-amino-3-phenylpropionic acid (6.00 g, 36.0 mmol) in methanol (150 mL) in a salt-ice bath, thionyl chloride (18 mL, 0.24 mol) was added

dropwise via an addition funnel. The resulting solution was stirred at room temperature for 24 h. Diethyl ether (150 mL) was added and the solution was left to crystallize. The microprisms were filtered, washed with diethyl ether to give **68e** (6.82 g, 87%) as white microprisms, mp 143-144 ^{o}C (lit.[81] 145-147 ^{o}C); IR ν_{max} 3351 (N-H), 3215 (N-H), 2952 (C-H), 1734 (ester C=O), 1650 (C=C), 1498, 1456, 1214, 762, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43-7.19 (5H, m, Ph) 4.43 (1H, t, *J*= 5.9 Hz, C*H*NH_2) 3.68 (3H, s, OCH_3) 2.80 (2H, d, *J*= 5.9 Hz, CH_2COO) 1.77 (2H, br s, NH); ^{13}C NMR (500 MHz, CD_4OD) δ 170.0 (*C*$OOCH_3$) 135.4 (ArC) 129.4 (ArC) 129.2 (ArC) 127.6 (ArC) 52.3 ($CHNH_2$) 52.3 (OCH_3) 38.5 (*C*H_2COO).

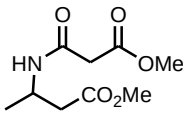
Methyl 3-amino-3-(pyridin-3-yl)propanoate (68f)[53]



To a stirred solution of 3-pyridinecarboxaldehyde (8.24 g, 76.8 mmol) in ethanol (15 mL), malonic acid (8.00 g, 76.8 mmol) and ammonium acetate (12.00 g, 0.156 mol) were added. The mixture was heated under reflux for 6 h and was then filtered, redissolved in methanol (150 mL) and cooled to 0 ^{o}C. Thionyl chloride (2.7 mL, 99.8 mmol) was added dropwise, stirred at 0 ^{o}C for 30 mins and at room temperature for 3 h. The mixture was then heated under reflux for 1 h. Diethyl ether (200 mL) was added and the precipitate was filtered to give **68f** (5.42 g, 43%) as white microprisms, mp 202-205 ^{o}C (lit.[82] 197-199 ^{o}C); IR ν_{max} 3296 (N-H), 2953 (C-H), 1737 (ester C=O), 1657 (C=C), 1516, 1248, 1168, 701 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) δ 8.55-8.53 (1H, m, C_1H) 8.50-8.50 (1H, m, C_5H) 7.91-7.89 (1H, m, C_3H) 7.49-7.46 (1H, m, C_4H) 4.74 (1H, dd, *J*= 7.9 , 6.6 Hz, C*H*NH_2) 2.88 (1H, dd, *J*= 16.3 , 7.9 Hz, CH_2CH) 2.80 (1H, dd,

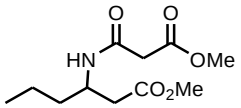
J= 16.3 , 6.6 Hz, C*H*$_2$CH); ^{13}C NMR (300 MHz, $CDCl_3$) δ 170.9 (*C*OOCH$_3$) 149.3 (C_1) 147.8 (C_5) 134.8 (C_2) 134.4 (C_3) 123.8 (C_4) 52.2 (CH_3O) 48.3 (CHNH) 38.5 (*C*H$_2$COO).

Methyl 3-(2-methoxycarbonylacetylamino)butanoate (69a)



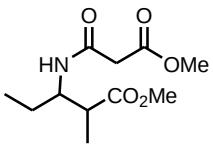
Following general procedure 2a, reaction of methyl 3-aminobutanoate hydrochloride (0.50 g, 3.30 mmol) in dichloromethane (7 mL), 1-hydroxybenzotriazole (0.66 g, 4.9 mmol), *N*,*N*-diisopropylethylamine (2.3 mL, 13.0 mmol), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (0.59 g, 3.30 mmol), and methyl malonate (1.52 g, 9.80 mmol) in dichloromethane (10 mL) gave a pale yellow solid that was purified by flash chromatography (60% ethyl acetate/hexane) to give **69a** (0.33 g, 46%) as a yellow gum, R_f 0.33 (75% ethyl acetate/hexane); IR ν_{max} 3293 (N-H), 2956 (C-H), 1730 (ketone C=O), 1650 (amide C=O), 1545, 1436, 1196, 1015, 569 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (1H, br s, NH) 4.48-4.25 (1H, m, C*H*CH$_2$CO$_2$CH$_3$) 3.63 (3H, s, OCH_3) 3.58 (3H, s, OCH_3) 3.19 (2H, s, CH_2CON) 2.51-2.36 (2H, m, C*H*$_2$CHN) 1.13 (3H, d, *J*= 6.7 Hz, C*H*$_3$CHN); ^{13}C NMR (500 MHz, $CDCl_3$) δ 171.7 (*C*OOCH$_3$) 169.4 (*C*OOCH$_3$) 164.3 (CON) 52.3 (OCH_3) 51.6 (OCH_3) 42.2 (*C*HCH$_2$CO$_2$Me) 41.3 (*C*H$_2$CON)) 39.8 (*C*H$_2$CHN) 19.8 (*C*H$_3$CH); m/z (Cl+) 218 (100%, M+H$^+$); HRMS $C_9H_{16}NO_5$ calcd. 218.1023, found 218.1022.

Methyl 3-(2-methoxycarbonylacetylamino)hexanoate (69b)



Following general procedure 2a, reaction of methyl 3-aminohexanoate (0.47 g, 3.30 mmol) in dichloromethane (7 mL), 1-hydroxybenzotriazole (0.66 g, 4.90 mmol), *N*,*N*-diisopropylethylamine (2.3 mL, 13.0 mmol), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (0.59 g, 3.30 mmol), and methyl malonate (1.52 g, 9.80 mmol) in dichloromethane (10 mL) gave a pale yellow solid that was purified by flash chromatography (55% ethyl acetate/hexane) to give **69b** (0.32 g, 40%) as a colourless gum, R_f 0.44 (75% ethyl acetate/hexane); IR ν_{max} 3292 (N-H), 2956 (C-H), 1734 (ester C=O), 1649 (amide C=O), 1545, 1436, 1169, 1015, 573 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22 (1H, br s, NH) 4.52-4.24 (1H, m, C*H*$CH_2CO_2CH_3$) 3.74 (3H, s, OCH_3) 3.69 (3H, s, OCH_3) 3.31 (2H, s, CH_2CON) 2.56-2.54 (2H, m, C*H*$_2CO_2CH_3$) 1.56-1.49 (2H, m, C*H*$_2CH_2CH_3$) 1.39-1.32 (2H, m, C*H*$_2CH_3$) 0.91 (3H, d, *J*= 7.3 Hz, C*H*$_3CH_2$); ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.1 (*C*$OOCH_3$) 169.7 (*C*$OOCH_3$) 164.3 (CON) 52.4 (OCH_3) 51.7 (OCH_3) 46.0 (*C*$HCH_2CO_2CH_3$) 41.2 (*C*H_2COOCH_3) 38.4 (*C*$H_2CH_2CH_3$) 36.1 (*C*H_2CON) 19.3 (*C*H_2CH_3) 13.8 (*C*H_3CH_2); m/z (Cl+) 246 (100%, $M+H^+$); HRMS $C_{11}H_{20}NO_5$ calcd. 246.1336, found 246.1332.

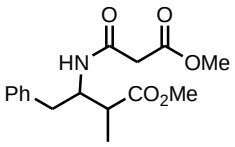
Methyl 3-(2-methoxycarbonylacetylamino)-2-methylpentanoate (69c)



Following general procedure 2b, reaction of methyl 3-amino-2-methylpentanoate (0.30

g, 2.07 mmol), triethylamine (0.38 mL, 2.70 mmol), and methyl 3-chloro-3-oxopropanoate (0.27 mL, 2.48 mmol) in dichloromethane (8 mL) gave a pale yellow oil that was purified by flash chromatography (40% ethyl acetate/hexane) to give **69c** (0.20 g, 40%) as a pale yellow oil, R_f 0.56 (75% ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) (mixture of diastereoisomers) δ 7.49-7.20 (1H, m, NH) 4.23-4.11 (1H, m, C*H*CH_2CH_3) 3.75 (3H, s, OCH_3) 3.74 (3H, s, OCH_3) 3.69 (3H, s, OCH_3) 3.66 (3H, s, OCH_3) 3.34-3.30 (2H, m, CH_2CON) 2.71-2.64 (1H, m, C*H*CH_3) 1.61-1.55 (2H, m, C*H*$_2CH_3$) 1.16 (3H, d, *J*= 11.1 Hz, C*H*$_3CH$) 1.15 (3H, d, *J*= 7.2 Hz, C*H*$_3CH$) 0.92 (3H, t, *J*= 7.2 Hz, C*H*$_3CH_2$); ^{13}C NMR (300 MHz, $CDCl_3$) δ 175.7 (*C*$OOCH_3$) 174.8 (*C*$OOCH_3$) 169.6 (*C*$OOCH_3$) 169.3 (*C*$OOCH_3$) 165.0 (CONH) 164.8 (CONH) 52.8 (OCH_3) 52.7 (OCH_3) 52.4 (OCH_3) 52.3 (OCH_3) 51.7 (CHNH) 48.6 (CHNH) 43.3 (*C*H$COOCH_3$) 42.0 (*C*H$COOCH_3$) 41.5 (*C*H_2COOCH_3) 41.2 (*C*H_2COOCH_3) 26.4 (*C*H_2CH_3) 24.7 (*C*H_2CH_3) 14.7 (*C*H_3CH) 12.8 (*C*H_3CH) 10.6 (*C*H_3CH_2); m/z (Cl+) 246 (100%, $M+H^+$); HRMS $C_{11}H_{20}NO_5$ calcd. 246.1342, found 246.1345.

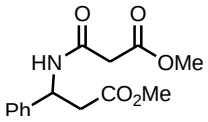
Methyl 3-(2-methoxycarbonylacetylamino)-2-methyl-4-phenylbutanoate (69d)



Following general procedure 2b, reaction of methyl 3-amino-2-methyl-4-phenylbutanoate (0.13 g, 0.60 mmol), *N*,*N*-diisopropylethylamine (0.21 mL, 1.21 mmol), and methyl 3-chloro-3-oxopropanoate (0.10 mL, 0.90 mmol) in dichloromethane (4 mL) gave a pale yellow oil that was purified by flash chromatography (40% ethyl acetate/hexane) to give **69d** (0.13 g, 67%) as a colourless

oil, R_f 0.83 (75% ethyl acetate/hexane); IR ν_{max} 3301 (N-H), 2953 (C-H), 1733 (ester C=O), 1657 (amide C=O), 1554, 1436, 1165, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (mixture of diastereoisomers) δ 7.29-7.16 (5H, m, Ph) 4.51-4.13 (1H, m, C*H*CH_2Ph) 3.72 (3H, s, OCH_3) 3.66 (3H, s, OCH_3) 3.27-3.12 (2H, m, CH_2CON) 2.84-2.67 (2H, m, C*H*$_2$Ph + C*H*CH_3) 1.22-1.18 (3H, m, C*H*$_3$CH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 175.9 (*C*$OOCH_3$) 174.8 (*C*$OOCH_3$) 169.8 (*C*$OOCH_3$) 169.4 (*C*$OOCH_3$) 164.8 (CONH) 164.3 (CONH) 137.8 (ArC) 137.6 (ArC) 129.3 (ArC) 129.2 (ArC) 128.5 (ArC) 128.4 (ArC) 126.7 (ArC) 126.6 (ArC) 53.1 (OCH_3) 52.4 (OCH_3) 52.3 (OCH_3) 51.9 (OCH_3) 42.9 (CHNH) 42.6 (CHNH) 41.5 (*C*H$COOCH_3$) 41.0 (*C*H$COOCH_3$) 40.7 (CH_2Ar) 39.9 (CH_2Ar) 37.8 (*C*H_2COOCH_3) 37.8 (*C*H_2COOCH_3) 13.2 (*C*H_3CH) 12.9 (*C*H_3CH).

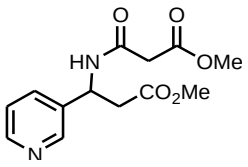
Methyl 3-(2-methoxycarbonylacetylamino)-3-phenylpropanoate (69e)



Following general procedure 2a, reaction of methyl 3-amino-3-phenylpropanoate (0.65 g, 3.00 mmol) in dichloromethane (6 mL), 1-hydroxybenzotriazole (0.61 g, 4.50 mmol), *N*,*N*-diisopropylethylamine (2.1 mL, 12.0 mmol), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (0.55 g, 3.00 mmol), and methyl malonate (1.40 g, 9.00 mmol) in dichloromethane (8 mL) gave a pale yellow solid that was purified by flash chromatography (40% ethyl acetate/hexane) to give **69e** (0.63 g, 75%) as white microprisms, mp 67-69 ^oC (lit.[45] 65 ^oC); R_f 0.50 (75% ethyl acetate/hexane); IR ν_{max} 3293 (N-H), 2954 (C-H), 1734 (ester C=O), 1649 (amide C=O), 1540, 1435, 1270, 1158, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (presence of rotamers) δ 7.94 (1H, d, *J*= 8.4 Hz, NH) 7.39-7.16 (5H, m, Ph) 5.39-5.35 (1H, m,

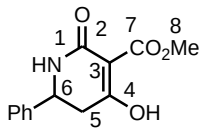
C*H*CH_2CO_2Me) 3.64 (3H, s, OCH_3) 3.53 (3H, s, OCH_3) 3.23 (2H, s, CH_2CON) 2.87-2.82 (1H, m, CH_2CHN) 2.77-2.73 (1H, m, C*H*$_2$CHN); ^{13}C NMR (500 MHz, $CDCl_3$) δ 171.2 (*C*$OOCH_3$) 169.4 (*C*$OOCH_3$) 164.6 (CON) 140.5 (ArC) 128.5 (ArC) 127.8 (ArC) 126.6 (ArC) 52.1 (*C*HCH_2CO_2Me) 50.7 (OCH_3) 50.0 (OCH_3) 41.6 (*C*H_2CON)) 40.4 (*C*H_2CHN); m/z (Cl+) 280 (98%, $M+H^+$); HRMS $C_{14}H_{18}NO_5$ calcd. 280.1180, found 280.1176.

Methyl 3-(2-methoxycarbonylacetylamino)-4-(pyridin-3-yl)butanoate (69f)



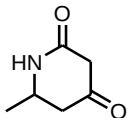
Following general procedure 2b, reaction of methyl 3-amino-3-(pyridin-3-yl)propanoate (0.50 g, 1.98 mmol), *N*,*N*-diisopropylethylamine (1.4 mL, 7.93 mmol), and methyl 3-chloro-3-oxopropanoate (0.32 mL, 2.98 mmol) in dichloromethane (12 mL) gave a pale yellow oil that was purified by flash chromatography (50% ethyl acetate/hexane) to give **69f** (0.55 g, 99%) as a yellow oil, R_f 0.08 (75% ethyl acetate/hexane); IR ν_{max} 3273 (N-H), 2954 (C-H), 1733 (ester C=O), 1656 (amide C=O), 1546, 1481, 1166, 713 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) (mixture of rotamers) δ 8.67 (1H, s, aryl) 8.57-8.49 (1H, m, aryl) 7.64-7.55 (1H, m, aryl) 7.26-7.18 (1H, m, aryl) 5.38 (1H, dd, *J*= 6.4, 5.3 Hz, C*H*NH) 3.67 (3H, s, OCH_3) 3.53 (3H, s, OCH_3) 3.26 (2H, s, CH_2CON) 2.86 (1H, dd, *J*= 16.0, 6.4 Hz, C*H*$_2$CH) 2.79 (1H, dd, *J*= 16.0, 5.3 Hz, C*H*$_2$CH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 170.8 (*C*$OOCH_3$) 169.3 (*C*$OOCH_3$) 164.8 (CONH) 148.8 (ArC) 148.1 (ArC) 136.2 (ArC) 134.4 (ArC) 123.6 (ArC) 123.3 (ArC) 52.5 (OCH_3) 52.0 (OCH_3) 47.9 (CHNH) 41.3 (*C*H_2CONH) 39.6 (*C*H_2CH).

3-Methoxy-6-phenylpiperidine-2,4-dione (72)



To a stirred solution of methyl 3-(2-methoxycarbonylacetylamino)-3-phenylpropanoate (1.40 g, 5.01 mmol) in methanol (15 mL) at room temperature under nitrogen, sodium methoxide in methanol (3.1 mL, 6.02 mmol, 1.97 M) was added. The mixture was then heated under reflux for 2 h. The mixture was allowed to cool to room temperature, then diluted with diethyl ether and filtered. The white precipitate was dissolved in water, which was then acidified to pH 2-3 by 1M hydrochloric acid. The product was then extracted into ethyl acetate (3 x 20 mL) and the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and evaporated to give **72** (0.86 g, 70%) as white microprisms, mp 122-125 ^oC (lit.[24] 128-130 ^oC); R_f 0.26 (5% methanol/chloroform); IR ν_{max} 3311 (O-H), 2952 (C-H), 1713 (ester C=O), 1638 (amide C=O), 1571, 1448, 1265, 730, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27-7.14 (5H, m, Ph) 6.22 (1H, br s, NH) 4.64 (1H, t, J= 7.5 Hz, C_6H) 3.68 (3H, s, OCH_3) 2.81 (2H, d, J= 7.5 Hz, C_5H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 183.5 (C_4) 172.0 (C_7) 164.8 (C_2) 139.6 (ArC) 129.1 (ArC) 128.7 (ArC) 126.5 (ArC) 97.4 (C_3) 52.7 (C_8) 52.3 (C_5) 37.8 (C_6).

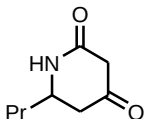
6-Methylpiperidine-2,4-dione (65a)



Following general procedure 3, reaction of methyl 3-(2-methoxycarbonylacetylamino)butanoate (0.30 g, 1.38 mmol) in methanol (2.0 mL), and sodium methoxide in methanol (1.5 mL, 2.76 mmol, 1.84 M) gave **65a** (74

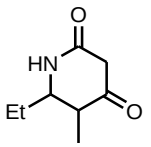
mg, 42%) as a yellow microprism, mp 115-118 ^{o}C; IR ν_{max} 3217 (N-H), 2968 (C-H), 1726 (ketone C=O), 1663 (amide C=O), 1445, 1331, 1198, 742, 556 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.98-3.77 (1H, m, C*H*CH_3) 3.26 (1H, d, *J*= 19.8 Hz, CH_2CON) 3.19 (1H, d, *J*= 19.8 Hz, CH_2CON) 2.64 (1H, dd, *J*= 16.4, 3.9 Hz, C*H*$_2$CHNH) 2.30 (1H, dd, *J*= 16.4, 9.6 Hz, C*H*$_2$CHNH) 1.30 (3H, d, *J*= 6.5 Hz, C*H*$_3$CH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 203.4 (*C*OCH_2) 169.8(CONH) 47.0 (*C*HCH_3) 46.2 (*C*H_2CONH) 44.6 (*C*H_2CH) 21.3 (*C*H_3CH); m/z (Cl+) 128 (100%, M+H$^+$); HRMS $C_6H_{10}NO_2$ calcd. 128.0711, found 128.0714.

6-Propylpiperidine-2,4-dione (65b)



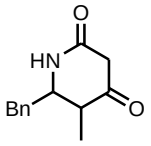
Following general procedure 3, reaction of methyl 3-(2-methoxycarbonylacetylamino)hexanoate (0.17 g, 0.70 mmol) in methanol (1.0 mL), and sodium methoxide in methanol (0.54 mL, 1.05 mmol, 2.00 M) gave **65b** (63 mg, 58%) as white microprisms, mp 112-116 ^{o}C; IR ν_{max} 3249 (N-H), 2925 (C-H), 1736 (ketone C=O), 1664 (amide C=O), 1516, 1302, 1172 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.65 (1H, m, C*H*NH) 3.25 (2H, m, CH_2CON) 2.68-2.64 (1H, m, C*H*$_2$CHCH_2CH_2) 2.37-2.29 (1H, m, C*H*$_2$CHCH_2CH_2) 1.50-1.22 (4H, m C*H*$_2$$CH_3$ + C*H*$_2$$CH_2CH_3$) 0.93 (3H, m, C*H*$_3$$CH_2$); ^{13}C NMR (500 MHz, $CDCl_3$) δ 208.0 (*C*OCH_2) 176.1 (CONH) 36.9 (*C*H_2COCH_2CONH) 34.0 (*C*H_2CONH) 29.7 (CHNH) 21.1 (*C*$H_2$$CH_2CH_3$) 18.4 (*C*$H_2$$CH_3$) 13.9 (*C*$H_3$$CH_2$); m/z (Cl+) 156 (35%, M+H$^+$); HRMS $C_8H_{14}NO_2$ calcd. 156.1025, found 156.1022.

6-Ethyl-5-methylpiperidine-2,4-dione (65c)



Following general procedure 3, reaction of methyl 3-(2-methoxycarbonylacetylamino)-2-methylpentanoate (0.12 g, 0.48 mmol) in methanol (3.0 mL), and sodium methoxide in methanol (0.53 mL, 0.92 mmol, 1.74 M) gave **65c** (53 mg, 71%) as a yellow oil, R_f 0.08 (75% ethyl acetate/hexane); IR ν_{max} 3280 (N-H), 2925 (C-H), 1725 (ketone C=O), 1661 (amide C=O), 1458, 1343, 1203 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (mixture of diastereoisomers) δ 7.95 (1H, br s, NH) 7.79 (1H, br s, NH) 3.75-3.69 (1H, m, C*H*CH_2CH_3) 3.22 (2H, m, CH_2CON) 2.67-2.63 (1H, m, C*H*CH_3) 2.41-2.36 (1H, m, C*H*CH_3) 1.73-1.70 (2H, m, C*H*$_2CH_3$) 1.59-1.52 (2H, m, C*H*$_2CH_3$) 1.19-1.05 (3H, m, C*H*$_3CH$) 0.99-0.83 (3H, m, C*H*$_3CH_2$); ^{13}C NMR (300 MHz, $CDCl_3$) δ 205.7 (*C*OCH) 170.0 (CONH) 55.6 (*C*HCH_3) 54.5 (*C*HCH_3) 46.4 (CHNH) 46.4 (CHNH) 46.0 (*C*H_2CO) 41.0 (CH_2Ar) 26.2 (*C*H_2CH_3) 24.4 (*C*H_2CH_3) 11.6 (*C*H_3CH_2) 10.1 (*C*H_3CH_2) 10.0 (*C*H_3CH) 8.5 (*C*H_3CH); m/z (Cl+) 156 (100%, $M+H^+$); HRMS $C_8H_{14}NO_2$ calcd. 156.2023, found 156.2021.

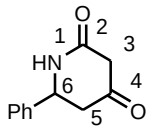
6-Benzyl-5-methylpiperidine-2,4-dione (65d)



Following general procedure 3, reaction of methyl 3-(2-methoxycarbonylacetylamino)-2-methyl-4-phenylbutanoate (0.09 g, 0.30 mmol) in methanol (1.2 mL), and sodium methoxide in methanol (0.2 mL, 0.38 mmol, 1.97 M) gave **65d** (36 mg, 56%) as a yellow oil, IR ν_{max} 3245 (N-H), 2923 (C-H), 1721 (ketone

C=O), 1661 (amide C=O), 1454, 1345, 1209, 702 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) (mixture of diastereoisomers) δ 7.63-7.19 (5H, m, Ph) 3.92-3.83 (1H, m, C*H*CH_2Ph) 3.27-3.13 (2H, m, CH_2CON) 2.90 (1H, m, C*H*CH_3) 2.65-2.61 (1H, m, C*H*$_2$Ph) 2.51-2.46 (1H, m, C*H*$_2$Ph) 1.28-1.25 (3H, m, C*H*$_3$CH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 204.8 (*C*OCH) 204.7 (*C*OCH) 169.2 (CONH) 168.4 (CONH) 136.0 (ArC) 135.5 (ArC) 129.5 (ArC) 129.4 (ArC) 129.3 (ArC) 129.1 (ArC) 127.7 (ArC) 127.4 (ArC) 55.8 (*C*HCH$_3$) 54.5 (*C*HCH$_3$) 47.4 (CHNH) 46.6 (CHNH) 46.1 (*C*H$_2$CO) 46.1 (*C*H$_2$CO) 41.0 (*C*H$_2$Ar) 37.9 (*C*H$_2$Ar) 12.1(*C*H$_3$CH) 10.5 (*C*H$_3$CH); m/z (Cl+) 218 (100%, M+H$^+$); HRMS $C_{13}H_{16}NO_2$ calcd. 218.1181, found 218.1189.

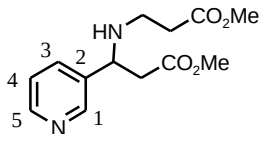
6-Phenylpiperidine-2,4-dione (65e)[15]



3-Methoxy-6-phenylpiperidine-2,4-dione (0.31 g, 1.25 mmol) was added to 1% water in acetonitrile (6 mL). The mixture was heated under reflux for 2 h. The mixture was allowed to cool to room temperature and evaporated. The residue was purified by flash chromatography (1% methanol/chloroform) to give **65e** (0.25 g, 95%) as white microprisms, mp 160-163 ^{o}C (lit.[83] 167-169 ^{o}C); R_f 0.26 (5% methanol/chloroform); IR ν_{max} 3248 (N-H), 2927 (C-H), 1722 (ketone C=O), 1664 (amide C=O), 1374, 762, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47-7.28 (5H, m, Ph) 6.87 (1H, br s, NH) 4.80 (1H, dd, *J*= 8.7, 4.5 Hz, C_6H) 3.34 (2H, s, C_3H) 2.88 (1H, dd, *J*= 16.0, 4.5 Hz, C_5H) 2.87 (1H, dd, *J*= 16.0, 8.7 Hz, C_5H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 202.3 (C_4) 169.0 (C_2) 139.3 (ArC) 129.4 (ArC) 128.9 (ArC) 126.0 (ArC) 52.9 (C_5) 47.2 (C_3) 47.0 (C_6); m/z (Cl+) 190 (95%, M+H$^+$); HRMS $C_{11}H_{12}NO_2$ calcd. 190.0863, found

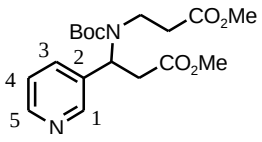
190.0859.

Methyl 3-(2-methoxycarbonylethylamino)-3-(pyridin-3-yl)propanoate (75)



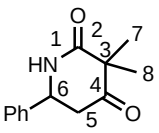
To methyl 3-amino-3-(pyridin-3-yl)propanoate hydrochloride (0.60 g, 2.38 mmol) in methanol (6 mL) was added methyl acrylate (0.24 mL, 2.62 mmol) and triethylamine (0.7 mL). The mixture was stirred for 8 h at room temperature. The mixture was concentrated in vacuo and was then diluted with water (5 mL), acidied with 1M hydrochloric acid to pH 4, and washed with ethyl acetate (2 x 10 mL). The aqueous phase was then neutralized by saturated sodium bicarbonate solution, extracted with ethyl acetate (2 x 10 mL), washed with water (2 x 5 mL), dried ($MgSO_4$) and evaporated to give **75** (0.46 g, 73%,) as a yellow oil, IR ν_{max} 3310 (N-H), 2953 (C-H), 1728 (ester C=O), 1434, 1168, 1123, 1024, 715 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.60-8.50 (2H, m, C_1H + C_5H) 7.84-7.82 (1H, m, C_3H) 7.28-7.26 (1H, m, C_4H) 4.12-4.10 (1H, m, C*H*CH_2COO) 3.66 (3H, s, OCH_3) 3.64 (3H, s, OCH_3) 2.72-2.61 (4H, m, C*H*$_2$NH + C*H*$_2$CH) 2.46-2.44 (2H, m, C*H*$_2$$CH_2$NH) 1.95 (1H, br s, NH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 173.0 (*C*$OOCH_3$) 171.6 (*C*$OOCH_3$) 149.2 (C_1) 149.2 (C_5) 137.9 (C_2) 134.6 (C_3) 123.7 (C_4) 57.2 (*C*HCH_2) 51.8 (CH_3O) 51.7 (CH_3O) 42.7 (*C*H_2CH) 42.5 (*C*H_2NH) 34.5 (*C*$H_2$$CH_2$NH).

Methyl 3-[(*tert*-butoxycarbonyl)-(2-methoxycarbonylethyl)amino]-3-(pyridin-3-yl)propanoate (76)



To methyl 3-(2-methoxycarbonylethylamino)-3-(pyridin-3-yl)propanoate (0.30 g, 1.13 mmol) in dichloromethane (3 mL) was added di-*tert*-butyl dicarbonate (0.29 mL, 1.24 mmol). The mixture was stirred for 16 h at room temperature. The mixture was concentrated in vacuo. The residue was then diluted with water (5 mL), acidied with 1M hydrochloric acid to pH 4, and washed with ethyl acetate (2 x 10 mL). The aqueous phase was then neutralized by saturated sodium bicarbonate solution, extracted with ethyl acetate (2 x 10 mL), washed with water (2 x 5 mL), dried ($MgSO_4$) and evaporated. The resulting oil was purified by flash chromatography (50% ethyl acetate/hexane) to give **76** (0.25 g, 68%) as a colourless oil, R_f 0.58 (75% ethyl acetate/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57-8.51 (2H, m, C_1H + C_5H) 7.70-7.64 (1H, m, C_3H) 7.53-7.51 (1H, m, C_4H) 5.53-5.58 (1H, m, C*H*CH_2COO) 3.68 (3H, s, OCH_3) 3.61 (3H, s, OCH_3) 3.39 (2H, m, C*H*$_2$$CH_2$N) 3.31-3.01 (2H, m, C*H*$_2$CH) 2.54-2.52 (2H, m, C*H*$_2$N) 1.44 (9H, s, (C*H*$_3$)$_3$C); ^{13}C NMR (500 MHz, $CDCl_3$) δ 172.1 (*C*$OOCH_3$) 171.0 (*C*$OOCH_3$) 149.0 (C_1) 149.2 (C_5) 123.5 (C_4) 52.1 (*C*HCH_2) 52.0 (CH_3O) 51.7 (CH_3O) 28.4 ((*C*H_3)$_3$C).

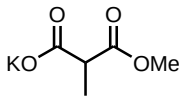
3,3-Dimethyl-6-phenylpiperidine-2,4-dione (78)



To 6-phenylpiperidine-2,4-dione (0.12 g, 0.61 mmol) in acetone (3 mL) was added

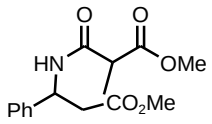
potassium carbonate (0.25 g, 1.84 mmol) and iodomethane (0.11 ml, 1.84 mmol). The mixture was stirred at 50 ^{o}C for 16 h. The solution was filtered and the filtrate was evaporated. The resulting yellow solid was purified by flash chromatography (60% ethyl acetate/hexane) to give **78** (0.09 g, 65%) as white microprisms, mp 165-168 ^{o}C (lit.[84] 168-169 ^{o}C); R_f 0.72 (ethyl acetate); IR ν_{max} 3199 (N-H), 2978 (C-H), 1714 (ester C=O), 1649 (amide C=O), 1463, 1400, 1325, 768, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.26 (5H, m, Ph) 6.60 (1H, br s, NH) 4.71 (1H, dd, *J*= 4.7, 2.5 Hz, C_6H) 2.91 (1H, dd, *J*= 15.5, 4.7 Hz, C_5H) 2.84 (1H, dd, *J*= 15.5, 2.5 Hz, C_5H) 1.39 (3H, s, C_7H) 1.38 (3H, s, C_8H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 208.2 (C_4) 175.8 (C_2) 140.0 (ArC) 129.3 (ArC) 128.8 (ArC) 126.0 (ArC) 52.1 (C_5) 52.0 (C_3) 45.3 (C_6) 23.1 (C_7) 22.8 (C_8).

Methyl 2-methylmalonate potassium salt (81)[55]



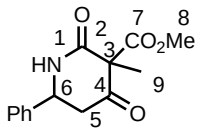
To a stirred solution of diethyl 2-methylmalonate (5.00 g, 28.7 mmol) in methanol (100 mL), potassium hydroxide (2.50 g, 44.6 mmol) was added. The mixture was then stirred at room temperature for 16 h and concentrated in vacuo. The residue was washed with diethyl ether (2 x 30 mL) to give **81** (2.00 g, 55%) as white microprisms, IR ν_{max} 2924 (C-H), 1716 (ester C=O), 1457, 1166, 1085, 877 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.56 (1H, br s, OH) 3.76 (3H, s, OCH_3) 3.40 (1H, q, *J*= 7.2 Hz, C*H*CO) 1.45 (3H, d, *J*= 7.2 Hz, CH_3CH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 175.0 (*C*OOCH_3) 170.7 (COOH) 52.7 (OCH_3) 45.8 (*C*HCH_3) 13.5 (*C*H_3CH).

Methyl 3-(2-methoxycarbonylpropionylamino)-3-phenylpropanoate (82)



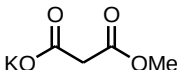
Following general procedure 2a, reaction of methyl 3-amino-3-phenylpropanoate (0.50 g, 2.32 mmol) in dichloromethane (6 mL), 1-hydroxybenzotriazole (0.47 g, 3.48 mmol), *N*,*N*-diisopropylethylamine (1.7 mL, 9.30 mmol), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (0.43 g, 2.32 mmol), and methyl 2-methylmalonate (0.92 g, 6.95 mmol) in dichloromethane (8 mL) gave a pale yellow oil that was purified by flash chromatography (40% ethyl acetate/hexane) to give **82** (0.57 g, 85%) as white microprisms, mp 59-62 ^{o}C; R_f 0.80 (75% ethyl acetate/hexane); IR ν_{max} 3297 (N-H), 2962 (C-H), 1734 (ester C=O), 1649 (amide C=O), 1538, 1435, 1165, 915, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) (1:1 mixture of diastereoisomers) δ 7.55 (1H, br d, *J*= 7.8 Hz, NH) 7.35-7.23 (5H, m, Ph) 5.45-5.37 (1H, m, C*H*$CH_2CO_2CH_3$) 3.75 (3H, s, OCH_3) 3.73 (3H, s, OCH_3) 3.61 (3H, s, OCH_3) 3.39-3.30 (1H, m, CHCON) 2.95-2.79 (2H, m, CH_2CHN) 1.29-1.20 (3H, m, CH_3CH); ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.6 (*C*$OOCH_3$) 172.4 (*C*$OOCH_3$) 171.5 (*C*$OOCH_3$) 171.4 (*C*$OOCH_3$) 168.2 (CON) 140.3 (ArC) 128.8 (ArC) 128.7 (ArC) 127.7 (ArC) 127.6 (ArC) 126.2 (ArC) 126.1 (ArC) 52.6 (*C*$HCH_2CO_2CH_3$) 51.9 (OCH_3) 49.7 (OCH_3) 46.8 (*C*HCON) 46.7 (*C*HCON) 40.0 (*C*H_2CHN) 39.9 (*C*H_2CHN) 14.9 (*C*H_3CH) 14.7 (*C*H_3CH).

3-Methoxy-3-methyl-6-phenylpiperidine-2,4-dione (83)



To 3-methoxy-6-phenylpiperidine-2,4-dione (0.16 g, 0.64 mmol) in THF (2 mL) was added tetrabutylammonium fluoride (0.8 mL, 1M in THF) and iodomethane (0.08 mL, 1.28 mmol). The mixture was stirred at room temperature for 24 h. The solution was neutralized with 1M hydrochloric acid and extracted with chloroform. After evaporation, the resulting yellow oil was purified by flash chromatography (55% ethyl acetate/hexane) to give **83** (0.11 g, 64%) as white microprisms, R_f 0.83 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) (1:1 mixtures of diastereoisomers) δ 7.47-7.21 (5H, m, Ph) 6.60 (1H, br s, NH) 4.82-4.49 (1H, m, C_6H) 4.69-4.64 (1H, m, C_6H) 3.69 (3H, s, C_7H) 3.64 (3H, s, C_7H) 3.04-2.90 (2H, m, C_5H) 2.82-2.73 (2H, m, C_5H) 1.57 (3H, s, C_9H) 1.51 (3H, s, C_9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 201.7 (C_4) 201.6 (C_4) 170.3 (C_2) 169.6 (C_2) 167.5 (C_7) 167.5 (C_7) 139.3 (ArC) 139.2 (ArC) 129.4 (ArC) 129.3 (ArC) 129.0 (ArC) 128.9 (ArC) 126.2 (ArC) 126.1 (ArC) 63.8 (C_3) 63.7 (C_3) 53.5 (C_8) 53.4 (C_8) 52.4 (C_5) 52.0 (C_5) 45.7 (C_6) 45.7 (C_6) 18.3 (C_9) 18.3 (C_9); m/z (Cl+) 262 (100%, $M+H^+$); HRMS $C_{14}H_{16}NO_4$ calcd. 262.1074, found 262.1067.

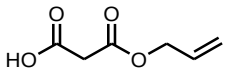
Methyl malonate potassium salt (123)



To a stirred solution of ethyl malonate (1.84 g, 11.5 mmol) in methanol (60 mL), potassium hydroxide (1.00 g, 17.8 mmol) was added. The mixture was then stirred at room temperature for 16 h and concentrated in vacuo. The residue was washed with

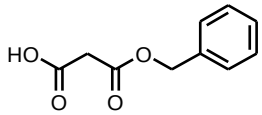
diethyl ether (2 x 30 mL) to give **123** (1.49 g, 84%) as white microprisms, mp 206-210 ^{o}C (lit.[85] 204-207 ^{o}C); IR ν_{max} 2959 (C-H), 1726 (ester C=O), 1594, 1401, 1287, 1227, 1147, 1023, 875, 700, 611, 569 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.67 (3H, s, OCH_3) 3.16 (2H, s, CH_2COO); ^{13}C NMR (500 MHz, D_2O) δ 174.6 (COOK) 172.3 ($COOCH_3$) 52.9 (OCH_3) 44.7 (CH_2COO).

Allyl malonate (90a)[86]



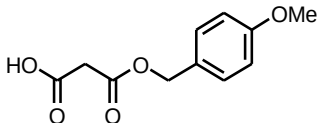
To a stirred solution of malonic acid (5.20 g, 50 mmol) and allyl alcohol (6.8 mL, 100 mmol) in acetonitrile (150 mL), dicyclohexylcarbodiimide (11.35 g, 11.0 mmol) in acetonitrile (50 mL) was added dropwise. The mixture was stirred at room temperature for 30 min. The mixture was then filtered and concentrated. The residue was redissolved in diethyl ether (250 mL) and extracted with saturated sodium bicarbonate solution (2 x 100 mL). The aqueous phase was then acidified with 1M hydrochloric acid to pH 1, extracted with ethyl acetate (2 x 200 mL), dried ($MgSO_4$), and evaporated to give **90a** (4.83 g, 67%) as an orange oil, IR ν_{max} 3400 (N-H), 2952 (C-H), 1713 (ester C=O), 1649 (C=C), 1412, 1149, 989, 929 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.96-5.88 (1H, m, C*H*=CH_2) 5.36 (1H, dd, *J*= 17.2, 8.5 Hz, C*H*$_2$=$CHCH_2O$) 5.28 (1H, dd, *J*= 17.2, 10.4 Hz, C*H*$_2$=$CHCH_2O$) 4.68 (1H, d, *J*= 5.8 Hz, CH_2O) 3.47 (2H, s, CH_2COO); ^{13}C NMR (500 MHz, $CDCl_3$) δ 171.6 (COOH) 166.4 (*C*$OOCH_2$) 131.3 (*C*HCH_2) 119.2 (CH_2*C*HCH_2O) 66.5 (CH_2O) 40.9 (CH_2*C*OO).

Benzyl malonate (90b)



To a stirred solution of malonic acid (2.08 g, 20.0 mmol) and benzyl alcohol (1.08 g, 10.0 mmol) in ethyl acetate (20 mL) at -10 ℃, dicyclohexylcarbodiimide (2.06 g, 10.0 mmol) in ethyl acetate (4 mL) was added dropwise. The mixture was stirred at room temperature for 16 h. The mixture was then filtered. The filtrate was washed with water (20 mL) and extracted with saturated sodium bicarbonate solution (3 x 20 mL). The aqueous phase was then acidified with 4M hydrochloric acid, extracted with ethyl acetate (3 x 20 mL), dried ($MgSO_4$), and evaporated to give **90b** (1.08 g, 26%) as a yellow oil, IR ν_{max} 3201 (O-H), 2948 (C-H), 1714 (ester C=O), 1318, 1146, 986, 736, 695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.11 (1H, br s, OH) 7.61-7.21 (5H, m, Ph) 5.21 (2H, s, CH_2Ar) 3.48 (2H, s, CH_2CO_2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 171.1 (COOH) 166.8 (*C*OOCH_2) 135.1 (ArC) 128.7 (ArC) 128.6 (ArC) 127.3 (ArC) 67.7 (CH_2Ar) 41.3 (*C*H_2COO).

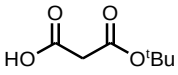
4-Methoxybenzyl malonate (90c)[59]



To a stirred solution of malonic acid (2.08 g, 20.0 mmol) and 4-methoxybenzyl alcohol (1.38 g, 10.0 mmol) in ethyl acetate (20 mL) at -10 ℃, dicyclohexylcarbodiimide (2.06 g, 10.0 mmol) in ethyl acetate (4 mL) was added dropwise. The mixture was stirred at room temperature for 16 h. The mixture was then filtered. The filtrate was washed with water (20 mL) and extracted with saturated sodium bicarbonate solution (3 x 20 mL).

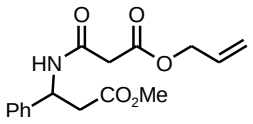
The aqueous phase was then acidified with 4M hydrochloric acid, extracted with ethyl acetate (3 x 20 mL), dried ($MgSO_4$), and evaporated. The resulting yellow solid was recrystallised from toluene to give **90c** (1.23 g, 28%) as white microprisms, mp 72-75 ^oC (lit.[59] 78 ^oC); IR ν_{max} 3351 (N-H), 2957 (C-H), 1715 (ester C=O), 1612 (C=C), 1514, 1243, 1147, 1029, 816, 517 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.18-7.13 (2H, m, Ph) 6.74-6.72 (2H, m, Ph) 5.10 (2H, s, CH_2Ar) 3.81 (3H, s, OCH_3) 3.42 (2H, s, CH_2CO_2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 171.0 (COOH) 167.0 (*C*$OOCH_2$) 160.0 (ArC) 130.4 (ArC) 127.1 (ArC) 114.1 (ArC) 67.6 (CH_2Ar) 55.4 (OCH_3) 40.7 (*C*H_2COO); m/z (Cl+) 224 (5%, $M+H^+$); HRMS $C_{11}H_{12}O_5$ calcd. 224.0685, found 224.0683.

***tert*-Butyl malonate (90d)**[58]



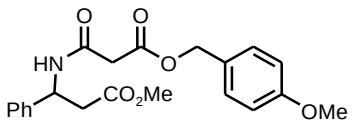
To a stirred solution of malonic acid (1.04 g, 10.0 mmol) and *tert*-butanol (1.48 g, 20.0 mmol) in acetonitrile (50 mL), dicyclohexylcarbodiimide (2.27 g, 11.0 mmol) in acetonitrile (10 mL) was added dropwise. The mixture was stirred at room temperature for 30 min. The mixture was then filtered and concentrated. The residue was redissolved in diethyl ether (20 mL) and extracted with saturated sodium bicarbonate solution (3 x 20 mL). The aqueous phase was then acidified with 1M hydrochloric acid to pH 1, extracted with ethyl acetate (3 x 20 mL), dried ($MgSO_4$), and evaporated to give **90d** (1.31 g, 75%) as a colourless oil, IR ν_{max} 3220 (O-H), 2980 (C-H), 1712 (ester C=O), 1369, 1327, 1140, 835 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.30 (2H, s, CH_2COO) 1.49 (9H, s, $(CH_3)_3C$); ^{13}C NMR (500 MHz, $CDCl_3$) δ 83.6 (*C*$(CH_3)_3$) 41.1 (*C*H_2COO) 28.0 ($(CH_3)_3C$).

Methyl 3-[2-(allyloxycarbonyl)acetylamino]-3-phenylpropanoate (89a)



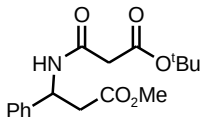
Following general procedure 2a, reaction of methyl 3-amino-3-phenylpropanoate hydrochloride (1.00 g, 4.65 mmol) in dichloromethane (13 mL), 1-hydroxybenzotriazole (0.94 g, 7.00 mmol), *N*,*N*-diisopropylethylamine (3.6 mL, 20.90 mmol), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (0.85 g, 4.65 mmol), and allyl malonate (2.00 g, 13.94 mmol) in dichloromethane (13 mL) gave a pale yellow solid that was purified by flash chromatography (50% ethyl acetate/hexane) to give **89a** (1.09 g, 77%) as a colourless oil, R_f 0.75 (75% ethyl acetate/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (1H, br d, *J*= 7.9 Hz, NH) 7.34-7.25 (5H, m, Ph) 5.92-5.91 (1H, m, =C*H*CH_2O) 5.46-5.45 (1H, m, C*H*$CH_2CO_2CH_3$) 5.33 (1H, ddd, *J*= 17.2, 7.8, 1.4 Hz, C*H*$_2$=$CHCH_2O$) 5.27 (1H, ddd, *J*= 17.2, 11.6, 1.4 Hz, C*H*$_2$=$CHCH_2O$) 4.66-4.64 (1H, m, CH_2O) 3.62 (3H, s, OCH_3) 3.37 (2H, s, C*H*$_2$CONH) 2.92-2.87 (1H, m, C*H*$_2$CHN) 2.86-2.85 (1H, m, C*H*$_2$CHN); ^{13}C NMR (500 MHz, $CDCl_3$) δ 171.3 (*C*$OOCH_3$) 169.0 (*C*$OOCH_2$) 164.2 (CON) 140.3 (ArC) 131.4 (*C*HCH_2O) 128.8 (ArC) 127.8 (ArC) 126.3 (Ar*C*) 119.3 (*C*H_2CHCH_2O) 66.2 (CH_2O) 51.9 (OCH_3) 49.8 (*C*HCH_2CO_2Me) 41.3 (*C*H_2CHN) 40.2 (*C*H_2CON); m/z (Cl+) 306 (100%, M+H$^+$); HRMS $C_{16}H_{20}NO_5$ calcd. 306.1342, found 306.1343.

Methyl 3-[2-(4-methoxybenzyloxycarbonyl)acetylamino]-3-phenylpropanoate (89b)



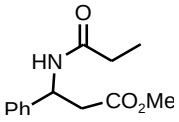
Following general procedure 2a, reaction of methyl 3-amino-3-phenylpropanoate hydrochloride (0.48 g, 2.23 mmol) in dichloromethane (7 mL), 1-hydroxybenzotriazole (0.45 g, 3.40 mmol), *N*,*N*-diisopropylethylamine (1.6 mL, 8.90 mmol), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (0.41 g, 2.20 mmol), and 4-methoxybenzyl malonate (1.00 g, 4.46 mmol) in dichloromethane (6 mL) gave a pale yellow solid that was purified by flash chromatography (60% ethyl acetate/hexane) to give **89b** (0.68 g, 79%) as a yellow oil, R_f 0.76 (75% ethyl acetate/hexane); IR ν_{max} 3295 (N-H), 2953 (C-H), 1732 (ester C=O), 1649 (amide C=O), 1514, 1244, 1152, 1029, 823, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.98 (1H, br d, *J*= 7.7 Hz, NH) 7.50-7.26 (7H, m, Ph) 6.90-6.88 (2H, m, Ph) 5.47-5.42 (1H, m, C*H*$CH_2CO_2CH_3$) 5.12 (2H, s, C*H*$_2$Ar) 3.81 (3H, s, OCH_3) 3.63 (3H, s, OCH_3) 3.36 (2H, s, CH_2CON) 2.96 (1H, dd, *J*= 15.7, 4.6 Hz, C*H*$_2$CHN) 2.82 (1H, dd, *J*= 15.7, 6.2 Hz, C*H*$_2$CHN); ^{13}C NMR (500 MHz, $CDCl_3$) δ 171.9 (*C*$OOCH_3$) 169.2 (*C*$OOCH_2$) 164.2 (CON) 160.0 (ArC) 140.3 (ArC) 130.4 (ArC) 128.8 (ArC) 127.7 (ArC) 127.2 (ArC) 126.3 (ArC) 114.1 (ArC) 67.3 (CH_2Ar) 55.4 (OCH_3) 51.9 (OCH_3) 49.9 (*C*$HCH_2CO_2CH_3$) 41.4 (*C*H_2CHN) 40.2 (*C*H_2CON).

Methyl 3-(2-*tert*-butoxycarbonyacetylamino)-3-phenylpropanoate (89c)



Following general procedure 2a, reaction of methyl 3-amino-3-phenylpropanoate hydrochloride (0.48 g, 2.23 mmol) in dichloromethane (7 mL), 1-hydroxybenzotriazole (0.45 g, 3.40 mmol), *N*,*N*-diisopropylethylamine (1.6 mL, 8.90 mmol), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (0.41 g, 2.20 mmol), and *tert*-butyl malonate (0.78 g, 4.50 mmol) in dichloromethane (6 mL) gave a pale yellow solid that was purified by flash chromatography (50% ethyl acetate/hexane) to give **89c** (0.57 g, 80%) as white microprisms, mp 60-62 ^{o}C; R_f 0.87 (75% ethyl acetate/hexane); IR ν_{max} 3293 (N-H), 2979 (C-H), 1730 (ester C=O), 1649 (amide C=O), 1539, 1367, 1256, 1143, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (1H, br d, *J*= 8.3 Hz, NH) 7.26-7.16 (5H, m, Ph) 5.41-5.37 (1H, m, C*H*$CH_2CO_2CH_3$) 3.68 (3H, s, OCH_3) 3.19 (2H, s, CH_2CON) 2.87 (1H, dd, *J*= 15.6, 6.5 Hz, C*H*$_2$CHN) 2.77 (1H, dd, *J*= 15.6, 4.8 Hz, C*H*$_2$CHN) 1.40 (9H, s, $(CH_3)_3C$); ^{13}C NMR (500 MHz, $CDCl_3$) δ 171.1 (*C*$OOCH_3$) 168.2 (*C*OOCC) 165.0 (CON) 140.6 (ArC) 128.9 (ArC) 127.6 (ArC) 126.4 (ArC) 82.3 (*C*$(CH_3)_3$) 51.7 (*C*$HCH_2CO_2CH_3$) 49.8 (OCH_3) 42.6 (*C*H_2CON) 40.3 (*C*H_2CHN) 28.0 ((*C*$H_3)_3C$).

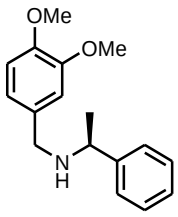
Methyl 3-phenyl-3-propionylaminopropanoate (89d)



To a stirred solution of methyl 3-amino-3-phenylpropanoate hydrochloride (0.50 g, 2.32 mmol) in dichloromethane (8 mL) at 0 ^{o}C under nitrogen, triethylamine (0.78 mL,

5.58 mmol) and 1-chloro-1-oxopropane (0.27 mL, 3.02 mmol) was added. The mixture was then allowed to warm to room temperature and stirred for 1 h. The mixture was diluted with dichloromethane (30 mL) and washed with saturated aqueous sodium hydrogen carbonate (10 mL). The aqueous layer was extracted with dichloromethane (2 x 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated. The resulting pale yellow oil was purified by flash chromatography (60% ethyl acetate/hexane) to give **89d** (0.49 g, 90%) as white microprisms, mp 60-64 ^oC; R_f 0.18 (50% ethyl acetate/hexane); IR ν_{max} 3280 (N-H), 2951 (C-H), 1736 (ester C=O), 1643 (amide C=O), 1536, 1435, 1230, 1164, 761, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29-7.16 (5H, m, Ph) 7.01 (1H, br d, *J*= 8.2 Hz, NH) 5.42-5.22 (1H, m, C*H*Ph) 3.55 (3H, s, OCH_3) 2.86 (1H, dd, *J*= 15.6, 4.7 Hz, CH_2CHN) 2.75 (1H, dd, *J*= 15.6, 6.5 Hz, CH_2CHN) 2.14 (2H, q, *J*= 7.6 Hz, CH_2CON) 1.09 (3H, t, *J*= 7.6 Hz, CH_3CH_2CO); ^{13}C NMR (300 MHz, $CDCl_3$) δ 173.3 (*C*$OOCH_3$) 171.6 (CONH) 140.9 (ArC) 128.6 (ArC) 127.5 (ArC) 126.3 (ArC) 51.7 (OCH_3) 49.5 (CHPh) 40.0 (*C*H_2COO) 29.6 (*C*H_2CON) 9.8 (*C*H_3CH_2CON).

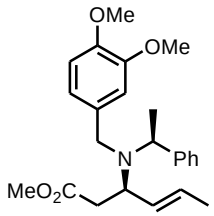
(*S*)-(3,4-Dimethoxybenzyl)-(1-phenylethyl)amine (95)[87]



(*S*)-1-Phenylethylamine (4.6 mL, 35.5 mmol) was added at 50 ^oC in a thin stream to a solution of 3,4-dimethoxybenzaldehyde (6.00 g, 36.0 mmol) in methanol (21.4 mL). The mixture was stirred for 1 h at the same temperature. Then sodium borohydride (0.81 g, 37.8 mmol) was added to the mixture at 25 ^oC and was stirred for 16 h. The

mixture was extracted by toluene (2 x 60 mL) and evaporated to give **95** (8.89 g, 97%) as a colourless oil, R_f 0.44 (ethyl acetate); IR ν_{max} 3211 (N-H), 2958 (C-H), 1611 (C=C), 1587, 1504, 1437, 1286, 1154, 1132, 760, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60-7.31 (3H, m, Ph) 7.28-7.17 (2H, m, Ph) 6.86-6.80 (3H, m, Ph) 3.88 (3H, s, OCH_3) 3.84 (3H, s, OCH_3) 3.80 (1H, q, *J*= 6.6 Hz, C*H*Ar) 3.68 (1H, d, *J*= 17.3 Hz, CH_2Ar) 3.60 (1H, d, *J*= 17.3 Hz, CH_2Ar) 1.69 (1H, s, NH) 1.31 (3H, d, *J*= 6.6 Hz, CH_3CH); ^{13}C NMR (300 MHz, $CDCl_3$) δ 148.9 (ArC) 148.0 (ArC) 145.7 ArC) 133.4 (ArC) 128.5 (ArC) 127.0 (ArC) 126.7 (ArC) 120.2 (ArC) 111.5 (ArC) 111.1 (ArC) 57.5 (CH_2NH) 55.9 (CH_3O) 55.8 (CH_3O) 51.5 (CHAr) 21.5 (*C*H_3CH).

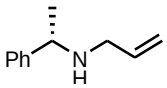
(*R*)-Methyl 3-{(3,4-dimethoxybenzyl)-[(1*S*)-1-phenylethyl]amino}hex-4-enoate (104)[43]



Following general procedure 4, reaction of (*S*)-(3,4-dimethoxybenzyl) (1-phenylethyl)amine (2.79 g, 10.3 mmol) in anhydrous THF (10 mL), *n*-butyllithium (1.6 M in hexanes, 6.2 mL, 9.95 mmol), and (*E*,*E*)-methyl hexa-2,4-dienoate (0.81 g, 6.42 mmol) in anhydrous THF (10 mL) gave a pale yellow oil that was purified by flash chromatography (20% ethyl acetate/hexane) to give **104** (0.49 g, 19%) as a pale yellow oil, R_f 0.54 (30% ethyl acetate/hexane); IR ν_{max} 2935 (C-H), 1734 (ester C=O), 1512, 1449, 1260, 1133, 1027, 970, 765, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60-7.12 (5H, m, Ph) 6.91 (1H, s, Ph) 6.79 (2H, q, *J*= 8.3 Hz, Ph) 5.64-5.48 (2H, m, C*H*=CHCHN + C*H*=CHCH$_3$) 4.00 (1H, q, *J*= 6.7 Hz, C*H*Ar) 3.86 (3H, s, OCH_3) 3.81

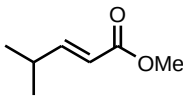
(3H, s, OCH_3) 3.78 (1H, dd, *J*= 7.3 Hz, C*H*$CH_2CO_2CH_3$) 3.71 (1H, d, *J*= 14.3 Hz, C*H*$_2$Ar) 3.44 (1H, d, *J*= 8.2, 7.3 Hz, C*H*$_2$Ar) 3.44 (3H, s, CH_3OOC) 2.53 (2H, dd, *J*= 14.6, 8.2 Hz, C*H*$_2CO_2CH_3$) 2.28 (2H, dd, *J*= 14.6, 7.3 Hz, C*H*$_2CO_2CH_3$) 1.71 (3H, d, *J*= 4.9 Hz, C*H*$_3$CH=CH) 1.38 (3H, d, *J*= 6.7 Hz, C*H*$_3$CHAr).

(*S*)-(1-Phenylethyl)(prop-2-enyl)amine (105)[88]



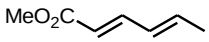
To a solution of (*S*)-1-phenylethylamine (6.06 g, 60.0 mmol) in anhydrous THF (150 mL) at -78 ^oC under nitrogen, *n*-butyllithium (1.6 M in hexanes, 41.3 mL, 66.0 mmol) and allyl bromide (6.8 mL, 62.0 mmol) was added dropwise via syringe. The solution was stirred at -78 ^oC for 3 h and at room temperature for 15 h. The mixture was quenched with water (20 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried (Na_2SO_4), and evaporated. The resulting pale yellow oil was purified by flash chromatography (30% ethyl acetate/hexane) to give **105** (8.27 g, 86%) as a pale yellow oil, R_f 0.55 (50% ethyl acetate/hexane); IR ν_{max} 3062 (N-H), 2972 (C-H), 1642 (C=C), 1449, 1119, 993, 914, 756, 698 cm^{-1}; $[\alpha]^{25}_D$ = -50.2 (*c* 0.98, CH_2Cl_2) (lit.[89] $[\alpha]^{25}_D$ = -58.8 *c* 1.04, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.08 (5H, m, Ph) 5.96-5.82 (1H, m, C*H*=CH_2) 5.15-5.05 (2H, m, C*H*$_2$=CHCH_2NH) 3.80 (1H, q, *J*= 6.6 Hz, C*H*CH_3) 3.10 (2H, d, *J*= 5.9 Hz, C*H*$_2$CH=) 1.51 (1H, br s, NH) 1.36 (3H, d, *J*= 6.6 Hz, C*H*$_3$CH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 145.6 (Ar*C*) 137.1 (*C*HCH_2) 128.5 (Ar*C*) 127.2(Ar*C*) 126.7 (Ar*C*) 115.8 (*C*HCH_2) 57.6 (CHPh) 50.3 (CH_2NH) 24.3 (*C*H_3CH).

(*E*)-Methyl 4-methylpent-2-enoate (103b)[64]



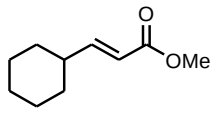
Isobutyraldehyde (2 mL, 22.0 mmol) was added dropwise to a solution of carbomethoxymethylene triphenylphosphorane (6.44 g, 25.2 mmol) in dichloromethane (20 mL) at 0 ^{o}C. The mixture was stirred for 16 h at room temperature, then evaporated. Hexane (20 mL) was added and the solid was filtered off. The filtrate was evaporated to give **103b** (1.30 g, 46%) as a colourless oil, IR ν_{max} 2961 (C-H), 1721 (ester C=O), 1656 (alkenyl C=C), 1436, 1287, 1168, 982, 723, 541 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (1H, dd, *J*= 15.0, 6.7 Hz, C*H*=CHCOO) 5.77 (1H, dd, *J*= 15.0, 1.5 Hz, =CHCOO) 3.71 (3H, s, CH_3O) 2.49-2.42 (1H, m, C*H*CH_3) 1.06 (6H, d, *J*= 6.7 Hz, C*H*$_3$CH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 167.6 (*C*OOCH_3) 155.9 (*C*HCHCOO) 118.3 (*C*HCOO) 51.5 (OCH_3) 31.0 (*C*HCH_3) 21.3 (*C*H_3CH).

(*E*,*E*)-Methyl hexa-2,4-dienoate (103c)[63]



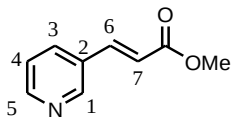
A solution of chlorotrimethylsilane (12 mL, 2M) was added dropwise to a solution of sorbic acid (1.12 g, 10.0 mmol) in dry methanol (10 mL) via a cannula. The mixture was stirred for 16 h, then evaporated. The resulting pale yellow oil was purified by flash chromatography (30% ethyl acetate/hexane) to give **103c** (1.05 g, 99%) as a colourless oil, R_f 0.71 (30% ethyl acetate/hexane); IR ν_{max} 2951 (C-H), 1715 (ester C=O), 1644 (C=C), 1434, 1329, 1242, 1137, 996 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.15 (1H, m, C*H*=CHCOO) 6.19-6.06 (2H, m, =C*H*CH_3 + C*H*=CHCH_3) 5.76 (1H, d, *J*= 15.4 Hz, =CHCOO) 3.85 (3H, s, CH_3O) 1.84 (3H, d, *J*= 5.3 Hz, C*H*$_3$CH).

(*E*)-Methyl 3-cyclohexylprop-2-enoate (103d)[65]



Cyclohexanecarboxaldehyde (2 mL, 16.5 mmol) was added to a solution of carbomethoxymethylene triphenylphosphorane (6.07 g, 18.2 mmol) in toluene (40 mL). The mixture was heated under reflux for 16 h and then quenched with water (20 mL), extracted with diethyl ether (2 x 20 mL), dried ($MgSO_4$), and evaporated. Hexane (20 mL) was added and the solid was filtered off. The filtrate was evaporated to give **103d** (2.03 g, 73%) as a pale yellow oil, IR ν_{max} 2924 (C-H), 1721 (ester C=O), 1652 (alkenyl C=C), 1447, 1312, 1167, 982, 721, 541 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.92 (1H, dd, *J*= 15.8, 6.8 Hz, C*H*=CHCOO) 5.76 (1H, dd, *J*= 15.8, 1.4 Hz, =CHCOO) 3.73 (3H, s, CH_3O) 2.14-2.12 (1H, m, 1'-cyclohexyl-CH) 1.76-1.73 (5H, m, cyclohexyl-CH_2) 1.30-1.12 (5H, m, cyclohexyl-CH_2); ^{13}C NMR (500 MHz, $CDCl_3$) δ 167.7 (*C*$OOCH_3$) 154.7 (*C*HCHCOO) 118.5 (*C*HCOO) 51.5 (OCH_3) 40.5 (1'-cyclohexyl-C) 31.7 (2'- and 6'-cyclohexyl-C) 26.0 (3'- and 5'-cyclohexyl-C) 25.8 (4'-cyclohexyl-C).

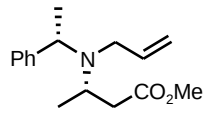
(*E*)-Methyl 3-(pyridin-3-yl)propenoate (103f)[66]



To 3-pyridinecarboxaldehyde (1.5 mL, 16.0 mmol) in saturated sodium hydrogen carbonate solution (32 mL) was added triphenylphosphine (6.30 g, 24.0 mmol) and methyl bromoacetate (2.4 mL, 26.0 mmol). The mixture was stirred for 24 h at room temperature. The mixture was then filtered and the filtrate was extracted with diethyl

ether (2 x 30 mL), washed with brine (15 mL), dried ($MgSO_4$) and evaporated. The resulting oil was purified by flash chromatography (40% ethyl acetate/hexane) to give **103f** (0.84 g, 32%) as an orange oil; R_f 0.20 (30% ethyl acetate/hexane); IR ν_{max} 2950 (C-H), 1713 (ester C=O), 1638 (alkenyl C=C), 1435, 1119, 805, 720, 541 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.73 (1H, s, C_1H) 8.57 (1H, d, J= 4.5 Hz, C_5H) 7.82 (1H, d, J= 7.9 Hz, C_3H) 7.70 (1H, d, J= 19.8 Hz, C_6H) 7.33-7..26 (1H, m, C_4H) 6.53 (1H, d, J= 19.8 Hz, C_7H) 3.81 (3H, s, OCH_3); ^{13}C NMR (500 MHz, $CDCl_3$) δ 166.8 ($COOCH_3$) 152.1 (C_1) 149.1 (C_5) 141.2 (C_6) 134.3 (C_3) 130.2 (C_2) 123.8 (C_7) 120.1 (C_4) 52.0 (CH_3O).

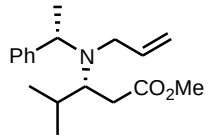
(*R*)-Methyl 3-{[(1*S*)-1-phenylethyl](prop-2-enyl)amino})butanoate (106a)



Following general procedure 4, reaction of (*S*)-(1-phenylethyl)(prop-2-enyl)amine (2.15 g, 13.3 mmol) in anhydrous THF (18 mL), *n*-butyllithium (1.6 M in hexanes, 8.0 mL, 12.9 mmol), and methyl but-2-enoate (0.83 g, 8.30 mmol) in anhydrous THF (9 mL) gave a pale yellow oil that was purified by flash chromatography (15% ethyl acetate/hexane) to give **106a** (1.85 g, 85%) as a pale yellow oil, R_f 0.40 (15% ethyl acetate/hexane); $[\alpha]^{21}_D$ = +18.7 (*c* 0.75, $CHCl_3$); IR ν_{max} 2970 (C-H), 1737 (ester C=O), 1463, 1295, 1200, 700; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.20 (5H, m, Ph) 5.87-5.82 (1H, m, =C*H*CH_2N) 5.15 (1H, dd, J= 17.2, 10.4 Hz, C*H*$_2$=CHCH_2N) 5.04 (1H, dd, J= 17.2, 4.6 Hz, C*H*$_2$=CHCH_2N) 3.97 (1H, q, J= 6.8 Hz, C*H*Ph) 3.56 (3H, s, OCH_3) 3.51-3.47 (1H, m, C*H*$CH_2CO_2CH_3$) 3.18 (2H, d, J= 6.3 Hz, CH_2N) 2.40 (1H, dd, J= 14.2, 7.0 Hz, C*H*$_2CO_2CH_3$) 2.19 (1H, dd, J= 14.2, 7.5 Hz, C*H*$_2CO_2CH_3$) 1.37 (3H, d,

J= 6.8 Hz, C*H*$_3$CHPh) 1.07 (3H, d, *J*= 6.7 Hz, C*H*$_3$CHCH$_2$); ^{13}C NMR (500 MHz, CDCl$_3$) δ 172.9 (*C*OOCH$_3$) 145.2 (ArC) 139.2 (*C*HCH$_2$N) 128.1 (ArC) 127.6 (ArC) 126.8 (ArC) 115.6 (*C*H$_2$CHCH$_2$N) 57.7 (CHPh) 51.4 (*C*HCH$_2$COO) 50.6 (CH$_2$N) 48.6 (OCH$_3$) 40.4 (*C*H$_2$COO) 18.8 (*C*H$_3$CHN) 17.5 (*C*H$_3$CHN).

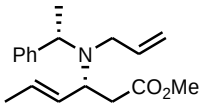
(*R*)-Methyl 4-methyl-3-{[(1*S*)-1-phenylethyl](prop-2-enyl)amino})pentanoate (106b)[7]



Following general procedure 4, reaction of (*S*)-(1-phenylethyl)(prop-2-enyl)amine (2.22 g, 13.7 mmol) in anhydrous THF (28 mL), *n*-butyllithium (2.5 M in hexanes, 5.3 mL, 13.3 mmol), and methyl 4-methylpent-2-enoate (1.10 g, 8.58 mmol) in anhydrous THF (22 mL) gave a pale yellow oil that was purified by flash chromatography (12% ethyl acetate/hexane) to give **106b** (1.70 g, 69%) as a pale yellow oil, R_f 0.75 (30% ethyl acetate/hexane); $[\alpha]^{21}_D$ = +18.00 (*c* 5.00, CHCl$_3$); IR ν_{max} 2969 (C-H), 1736 (ester C=O), 1452, 1195, 1158, 914, 701; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.31-7.21 (5H, m, Ph) 5.96-5.85 (1H, m, =C*H*CH$_2$N) 5.22-5.17 (1H, m, C*H*$_2$=CHCH$_2$N) 5.08-5.06 (1H, m, C*H*$_2$=CHCH$_2$N) 3.91 (1H, q, *J*= 7.1 Hz, C*H*Ph) 3.58 (3H, s, OCH$_3$) 3.20-3.17 (1H, m, C*H*CH$_2$CO$_2$CH$_3$) 3.09-3.06 (2H, m, CH$_2$N) 2.11 (1H, dd, *J*= 15.6, 7.8 Hz, C*H*$_2$CO$_2$CH$_3$) 2.02 (1H, dd, *J*= 15.6, 4.0 Hz, C*H*$_2$CO$_2$CH$_3$) 1.70-1.67 (1H, m, C*H*(CH$_3$)$_2$) 1.43 (3H, d, *J*= 7.1 Hz, C*H*$_3$CHPh) 0.98 (3H, d, *J*= 6.7 Hz, (C*H*$_3$)$_2$CHCH) 0.81 (3H, d, *J*= 6.7 Hz, (C*H*$_3$)$_2$CHCH); ^{13}C NMR (500 MHz, CDCl$_3$) δ 174.0 (*C*OOCH$_3$) 143.9 (ArC) 139.2 (*C*HCH$_2$N) 128.3 (ArC) 127.9 (ArC) 126.8 (ArC) 115.4 (*C*H$_2$CHCH$_2$N) 59.8 (*C*HCH$_2$COO) 58.9 (CHPh) 51.4 (CH$_2$N) 49.7 (OCH$_3$) 35.0

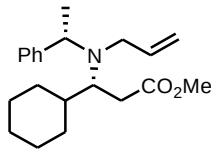
(CH_2COO) 32.8 ($CH(CH_3)_2$) 21.0 (($CH_3)_2CH$) 20.9 (($CH_3)_2CH$) 19.8 (CH_3CHN); m/z (Cl+) 290 (40%, $M+H^+$) 246 (100%, $M+H^+-C_3H_7$) 105 (30%, $C_9H_9^+$); HRMS $C_{18}H_{28}NO_2$ calcd. 290.2120, found 290.2123.

(*R*)-Methyl 3-{[(1*S*)-1-phenylethyl](prop-2-enyl)amino})hex-4-enoate (106c)[61]



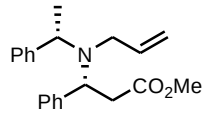
Following general procedure 4, reaction of (*S*)-(1-phenylethyl)(prop-2-enyl)amine (3.00 g, 18.6 mmol) in anhydrous THF (15 mL), *n*-butyllithium (1.6 M in hexanes, 11.3 mL, 18.0 mmol), and (*E*,*E*)-methyl hexa-2,4-dienoate (1.47 g, 11.6 mmol) in anhydrous THF (15 mL) gave a pale yellow oil that was purified by flash chromatography (10% ethyl acetate/hexane) to give **106c** (2.61 g, 78%) as a pale yellow oil, R_f 0.79 (30% ethyl acetate/hexane); $[\alpha]^{21}_D$ = +3.4 (*c* 2.95, $CHCl_3$) (lit.[61] opposite enantiomer $[\alpha]^{13}_D$ = -2.4 *c* 1.00, $CHCl_3$); IR ν_{max} 2970 (C-H), 1736 (ester C=O), 1436 , 1172, 993, 876, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.17 (5H, m, Ph) 5.85-5.72 (1H, m, =C*H*CH_2N) 5.53-5.49 (2H, m, C*H*=CHCHN + =C*H*CHN) 5.12-5.00 (2H, m, C*H*$_2$=CHCH_2N) 4.02 (1H, q, *J*= 6.8 Hz, C*H*Ph) 3.88-3.81 (1H, m, C*H*$CH_2CO_2CH_3$) 3.56 (3H, s, OCH_3) 3.16-3.09 (2H, m, CH_2N) 2.51 (1H, dd, *J*= 14.3, 5.8 Hz, C*H*$_2CO_2CH_3$) 2.34 (1H, dd, *J*= 14.3, 7.5 Hz, C*H*$_2CO_2CH_3$) 1.69 (3H, d, *J*= 4.6 Hz, C*H*$_3$CH=CH) 1.35 (3H, d, *J*= 6.8 Hz, C*H*$_3$CHPh); ^{13}C NMR (500 MHz, $CDCl_3$) δ 172.5 (*C*$OOCH_3$) 145.2 (ArC) 138.8 (*C*HCH_2N) 130.6 (*C*HCHN) 128.0 (ArC) 127.6 (ArC) 127.1 (ArC) 126.5 (*C*HCHCHN) 115.7 (*C*H_2CHCH_2N) 56.9 (CHPh) 56.8 (*C*HCH_2COO) 51.4 (CH_2N) 49.6 (OCH_3) 38.9 (*C*H_2COO) 18.1 (*C*H_3CHN) 18.0 (*C*$H_3CHCHCHN$).

(*R*)-Methyl 3-cyclohexyl-3-{[(1*S*)-1-phenylethyl](prop-2-enyl)amino})propanoate (106d)



Following general procedure 4, reaction of (*S*)-(1-phenylethyl)(prop-2-enyl)amine (2.76 g, 17.1 mmol) in anhydrous THF (34 mL), *n*-butyllithium (2.5 M in hexanes, 6.6 mL, 16.6 mmol), and methyl 3-cyclohexylpropenoate (1.80 g, 10.7 mmol) in anhydrous THF (27 mL) gave a pale yellow oil that was purified by flash chromatography (12% ethyl acetate/hexane) to give **106d** (2.40 g, 68%) as a pale yellow oil, R_f 0.87 (30% ethyl acetate/hexane); $[\alpha]^{25}_D$ = +11.0 (*c* 6.69, $CHCl_3$); IR ν_{max} 2923 (C-H), 1735 (ester C=O), 1449, 1171, 1156, 914, 701; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.19 (5H, m, Ph) 5.86-5.84 (1H, m, =C*H*CH_2N) 5.21-5.17 (1H, m, C*H*$_2$=CHCH_2N) 5.08-5.06 (1H, m, C*H*$_2$=CHCH_2N) 3.90 (1H, q, *J*= 7.0 Hz, C*H*Ph) 3.57 (3H, s, OCH_3) 3.17-3.12 (2H, m, C*H*$CH_2CO_2CH_3$ + CH_2N) 3.07-3.05 (1H, m, CH_2N) 2.17-2.08 (2H, m, C*H*$_2CO_2CH_3$ + 1'-cyclohexyl-CH) 2.00 (1H, dd, *J*= 15.7, 3.7 Hz, C*H*$_2CO_2CH_3$) 1.57-1.42 (4H, m, cyclohexyl-CH_2) 1.39 (3H, d, *J*= 7.0 Hz, C*H*$_3$CHPh) 1.17-1.12 (4H, m, cyclohexyl-CH_2) 0.88-0.76 (2H, m, 4'-cyclohexyl-CH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 174.0 (*C*$OOCH_3$) 143.9 (ArC) 139.2 (*C*HCH_2N) 128.3 (ArC) 127.9 (ArC) 126.8 (ArC) 115.4 (*C*H_2CHCH_2N) 58.8 (CHPh) 51.4 (OCH_3) 49.8 (CH_2N) 42.7 (*C*HCH_2COO) 34.7 (*C*H_2COO) 31.1 (1'-cyclohexyl-C) 30.2 (4'-cyclohexyl-C) 27.0 (2'- and 6'-cyclohexyl-C) 26.6 (3'- and 5'-cyclohexyl-C) 21.0 (*C*H_3CHPh); m/z (Cl+) 330 (20%, M+H$^+$) 246 (100%, M-$C_7H_{11}^+$); HRMS $C_{21}H_{32}NO_2$ calcd. 330.2433, found 330.2439.

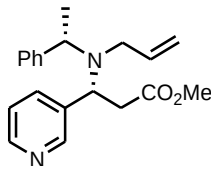
(*R*)-Methyl 3-{[(1*S*)-1-phenylethyl](prop-2-enyl)amino})-3-phenylpropanoate (106e)



Following general procedure 4, reaction of (*S*)-(1-phenylethyl)(prop-2-enyl)amine (1.59 g, 9.86 mmol) in anhydrous THF (20 mL), *n*-butyllithium (2.5 M in hexanes, 3.8 mL, 9.56 mmol), and methyl *trans*-cinnamate (1.00 g, 6.17 mmol) in anhydrous THF (16 mL) gave a pale yellow oil that was purified by flash chromatography (10% ethyl acetate/hexane) to give **106e** (1.80 g, 90%) as a pale yellow oil, R_f 0.50 (15% ethyl acetate/hexane); $[\alpha]^{21}_D$ = +1.5 (*c* 4.10, $CHCl_3$); IR ν_{max} 2973 (C-H), 1736 (ester C=O), 1451, 1167, 914, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.55-7.33 (10H, m, Ph) 5.85-5.72 (1H, m, =C*H*CH_2N) 5.17 (1H, ddd, *J*= 17.2, 8.6, 1.4 Hz, C*H*$_2$=CHCH_2N) 5.08 (1H, ddd, *J*= 17.2, 10.1, 1.4 Hz, C*H*$_2$=CHCH_2N) 4.55-4.52 (1H, m, C*H*$CH_2CO_2CH_3$) 4.08 (1H, q, *J*= 6.7 Hz, C*H*CH_3) 3.57 (3H, s, OCH_3) 3.22-3.18 (2H, m, CH_2N) 2.91 (1H, dd, *J*= 14.6, 5.6 Hz, C*H*$_2CO_2CH_3$) 2.69 (1H, dd, *J*= 14.6, 8.3 Hz, C*H*$_2CO_2CH_3$) 1.18 (3H, d, *J*= 6.7 Hz, C*H*$_3$CHPh); ^{13}C NMR (500 MHz, $CDCl_3$) δ 172.5 (*C*$OOCH_3$) 144.9 (ArC) 141.5 (ArC) 138.8 (*C*HCH_2N) 128.4 (ArC) 128.1 (ArC) 127.7 (ArC) 127.5 (ArC) 127.3 (ArC) 126.7 (ArC) 116.0 (*C*H_2CHCH_2N) 58.9 (*C*HCH_3) 56.3 (*C*HCH_2COO) 51.5 (CH_2N) 49.8 (OCH_3) 38.0 (*C*H_2COO) 16.6 (*C*H_3CHN); m/z (Cl+) 324 (100%, M+H^+); HRMS $C_{12}H_{25}NO_2$ calcd. 324.1964, found 324.1958.).

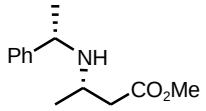
(*R*)-Methyl

3-(pyridin-3-yl)-3-{[(1*S*)-1-phenylethyl](prop-2-enyl)amino}propanoate (106f)



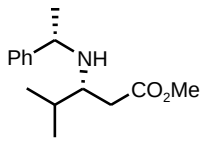
Following general procedure 4, reaction of (*S*)-(1-phenylethyl)(prop-2-enyl)amine (0.95 g, 4.09 mmol) in anhydrous THF (10 mL), *n*-butyllithium (2.5 M in hexanes, 1.9 mL, 4.75 mmol), and methyl 3-(pyridin-3-yl)propenoate (0.50 g, 3.06 mmol) in anhydrous THF (5 mL) gave a pale yellow oil that was purified by flash chromatography (50% ethyl acetate/hexane) to give **106f** (0.52 g, 48%) as a yellow oil, R_f 0.65 (75% ethyl acetate/hexane); $[\alpha]^{21}_D$ = -0.6 (*c* 1.70, $CHCl_3$); IR ν_{max} 2972 (C-H), 1735 (ester C=O), 1434, 1202, 1167, 1024, 701; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (1H, s, aryl) 8.51-8.49 (1H, m, aryl) 7.67 (1H, d, *J*= 7.9 Hz, aryl) 7.37-7.22 (6H, m, aryl + Ph) 5.80-5.75 (1H, m, =C*H*CH_2N) 5.16 (2H, ddd, *J*= 17.2, 4.8, 1.5 Hz, C*H*$_2$=CHCH_2N) 5.07 (2H, ddd, *J*= 17.2, 10.2, 1.5 Hz, C*H*$_2$=CHCH_2N) 4.55-4.52 (1H, m, C*H*$CH_2CO_2CH_3$) 4.02 (1H, q, *J*= 6.8 Hz, C*H*Ph) 3.55 (3H, s, OCH_3) 3.19-3.13 (2H, m, CH_2N) 2.81 (1H, dd, *J*=15.2, 6.0 Hz, C*H*$_2CO_2CH_3$) 2.67 (1H, dd, *J*=15.2, 9.0 Hz, C*H*$_2CO_2CH_3$) 1.23 (3H, d, *J*= 6.8 Hz, C*H*$_3$CHPh); ^{13}C NMR (500 MHz, $CDCl_3$) δ 172.0 (*C*$OOCH_3$) 149.7 (ArC) 148.6 (ArC) 144.2 (ArC) 138.2 (ArC) 137.2 (ArC) 135.3 (*C*HCH_2N) 128.3 (ArC) 127.5 (ArC) 127.0 (ArC) 123.3 (ArC) 116.4 (*C*H$_2$CHCH_2N) 56.9 (CHPh) 56.6 (OCH_3) 51.7 (*C*HCH_2COO) 49.8 (CH_2N) 36.7 (*C*H$_2$COO) 17.6 (*C*H$_3$CHN).

(*R*)-Methyl 3-{[(1*S*)-1-phenylethyl]amino}butanoate (107a)



Following general procedure 5, reaction of (*R*)-methyl 3-{[(1*S*)-1-phenylethyl](prop-2-enyl)amino})butanoate (1.00 g, 3.83 mmol), and Wilkinson's catalyst (180 mg, 0.19 mmol) in acetonitrile/water (20 mL) gave a pale yellow oil that was purified by flash chromatography (15% ethyl acetate/hexane) to give **107a** (0.73 g, 87%) as a pale brown oil, R_f 0.25 (30% ethyl acetate/hexane); $[\alpha]^{21}_D$ = -22.5 (*c* 1.29, $CHCl_3$); IR ν_{max} 2960 (N-H), 2923 (C-H), 1731 (ester C=O), 1436, 1192, 1119, 699, 540; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69-7.22 (5H, m, Ph) 3.87 (1H, q, *J*= 6.6 Hz, C*H*CH_3) 3.66 (3H, s, OCH_3) 3.02-2.97 (1H, m, C*H*$CH_2CO_2CH_3$) 2.48-2.44 (1H, m, C*H*$_2CO_2CH_3$) 2.39-2.35 (1H, m, C*H*$_2CO_2CH_3$) 1.68 (1H, br s, NH) 1.33 (3H, d, *J*= 6.6 Hz, C*H*$_3$CHPh) 1.06 (3H, d, *J*= 6.7 Hz, C*H*$_3$CHCH$_2$); ^{13}C NMR (500 MHz, $CDCl_3$) δ 172.8 (*C*OOCH_3) 132.0 (ArC) 128.6 (ArC) 127.0 (*C*HCH_2N) 126.6 (ArC) 55.3 (*C*HCH_3) 51.5 (OCH_3) 47.8 (*C*HCH_2COO) 40.6 (*C*H$_2$COO) 24.6 (*C*H$_3$CHCH$_2$) 21.5 (*C*H$_3$CHAr).

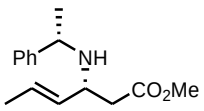
(*R*)-Methyl 4-methyl-3-[(1*S*)-1-phenylethylamino]pentanoate (107b)



Following general procedure 5, reaction of (*R*)-methyl 4-methyl-3-{[(1*S*)-1-phenylethyl](prop-2-enyl)amino})pentanoate (1.50 g, 5.18 mmol), and Wilkinson's catalyst (0.24 g, 0.26 mmol) in acetonitrile/water (30 mL) gave a pale yellow oil that was purified by flash chromatography (18% ethyl acetate/hexane) to

give **107b** (0.77 g, 59%) as a pale yellow oil, R_f 0.66 (30% ethyl acetate/hexane); $[\alpha]^{21}_D$ = -48.1 (*c* 2.35, $CHCl_3$); IR ν_{max} 2957 (C-H), 1733 (ester C=O), 1436, 1265, 1168, 761, 701; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.20 (5H, m, Ph) 3.86-3.81 (1H, m, C*H*$CH_2CO_2CH_3$) 3.67 (3H, s, OCH_3) 2.65 (1H, q, *J*= 6.3 Hz, C*H*Ph) 2.45 (1H, dd, *J*= 14.6, 9.0 Hz, C*H*$_2CO_2CH_3$) 2.37 (1H, dd, *J*= 14.6, 5.5 Hz, C*H*$_2CO_2CH_3$) 1.70-1.64 (1H, m, C*H*$(CH_3)_2$) 1.31 (3H, d, *J*= 6.3 Hz, C*H*$_3$CHPh) 0.87 (3H, d, *J*= 6.9 Hz, C*H*$_3$CHCH) 0.80 (3H, d, *J*= 6.8 Hz, C*H*$_3$CHCH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 173.5 (*C*$OOCH_3$) 128.3 (ArC) 126.9 (ArC) 57.6 (*C*HCH_2COO) 55.5 (CHPh) 51.5 (OCH_3) 35.9 (*C*H_2COO) 31.4 (*C*$H(CH_3)_2$) 24.9 (*C*H_3CHN) 18.6 ((*C*$H_3)_2CHCH$) 18.5 ((*C*$H_3)_2CHCH$); m/z (Cl+) 250 (100%, M+H$^+$) 206 (53%, M+H$^+$-$(CH_3)_2CH$) 133 (8%, PhCHNCO+H$^+$) 105 (47%, PhCHCH_3^+); HRMS $C_{15}H_{24}NO_2$ calcd. 250.1807, found 250.1805.

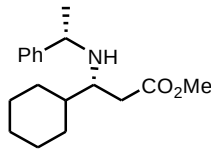
(*R*)-Methyl 3-{[(1*S*)-1-phenylethyl]amino}hex-4-enoate (107c)[67]



Following general procedure 5, reaction of (*R*)-methyl 3-{[(1*S*)-1-phenylethyl] (prop-2-enyl)amino})hex-4-enoate (5.10 g, 17.8 mmol), and Wilkinson's catalyst (0.82 g, 0.89 mmol) in acetonitrile/water (120 mL) gave a pale yellow oil that was purified by flash chromatography (10% ethyl acetate/hexane) to give **107c** (3.69 g, 84%) as a pale yellow oil, R_f 0.70 (30% ethyl acetate/hexane); $[\alpha]^{21}_D$ = -38.9 (*c* 0.72, $CHCl_3$); IR ν_{max} 3061 (N-H), 2965 (C-H), 1734 (ester C=O), 1626, 1419, 1261, 1241 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57-7.04 (5H, m, Ph) 5.59-5.51 (1H, m, C*H*=CHCHN) 5.31-5.22 (1H, m, =C*H*CHN) 3.83 (1H, q, *J*= 6.5 Hz, C*H*Ph) 3.66 (3H, s, OCH_3)

3.51-3.44 (1H, m, C*H*$CH_2CO_2CH_3$) 2.52-2.46 (2H, m, C*H*$_2CO_2CH_3$) 1.63 (3H, dd, *J*= 6.5, 1.4 Hz, C*H*$_3$CH=CH) 1.31 (3H, d, *J*= 6.5 Hz, C*H*$_3$CHPh); ^{13}C NMR (500 MHz, $CDCl_3$) δ 172.5 (*C*OOCH_3) 146.2 (ArC) 132.7 (ArC) 128.5 (ArC) 127.1 (*C*HCHCHN) 126.9 (*C*HCHNH) 126.7 (ArC) 54.9 (*C*HPh) 54.7 (*C*HCH_2COO) 51.5 (OCH_3) 40.5 (*C*H_2COO) 23.3 (*C*H_3CHN) 17.8 (*C*H_3CHCHCHN).

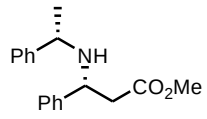
(*R*)-Methyl 3-cyclohexyl-3-[(1*S*)-1-phenylethyl]amino]propanoate (107d)



Following general procedure 5, reaction of (*R*)-methyl 3-cyclohexyl-3-{[(1*S*)-1-phenylethyl](prop-2-enyl)amino})propanoate (1.86 g, 5.65 mmol), and Wilkinson's catalyst (0.30 g, 0.32 mmol) in acetonitrile/water (35 mL) gave a pale yellow oil that was purified by flash chromatography (12% ethyl acetate/hexane) to give **107d** (0.79 g, 53%) as a yellow oil, R_f 0.72 (30% ethyl acetate/hexane); $[\alpha]^{25}_D$ = -35.2 (*c* 1.90, $CHCl_3$); IR ν_{max} 2985 (N-H), 2922 (C-H), 1732 (ester C=O), 1448, 1191, 1167, 760, 700; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.20 (5H, m, Ph) 3.87-3.71 (1H, m, C*H*$CH_2CO_2CH_3$) 3.67 (3H, s, OCH_3) 2.63 (1H, q, *J*= 5.9 Hz, C*H*Ph) 2.49 (1H, dd, *J*= 14.7, 5.5 Hz, C*H*$_2CO_2CH_3$) 2.37 (1H, dd, *J*= 14.7, 6.3 Hz, C*H*$_2CO_2CH_3$) 1.79-1.62 (5H, m, 1'-cyclohexyl-CH + cyclohexyl-CH_2) 1.31 (3H, d, *J*= 5.9 Hz, C*H*$_3$CHPh) 1.17-1.08 (4H, m, cyclohexyl-CH_2) 0.96-0.86 (2H, m, 4'-cyclohexyl-CH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 173.5 (*C*OOCH_3) 128.3 (ArC) 127.0 (ArC) 126.9 (ArC) 57.0 (CHN) 55.5 (CHPh) 51.5 (OCH_3) 41.8 (*C*H_2COO) 35.9 (1'-cyclohexyl-C) 29.3 (4'-cyclohexyl-C) 29.1 (2'- and 6'-cyclohexyl-C) 26.6 (3'- and 5'-cyclohexyl-C) 26.5 (*C*H_3CHPh); m/z (Cl+) 290 (100%, M+H$^+$); HRMS $C_{18}H_{28}NO_2$

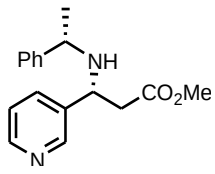
calcd. 290.2120, found 290.2112.

(*R*)-Methyl 3-{[(1*S*)-1-phenylethyl]amino}-3-phenylpropanoate (107e)



Following general procedure 5, reaction of (*R*)-methyl 3-{[(1*S*)-1-phenylethyl](prop-2-enyl)amino})-3-phenylpropanoate (0.50 g, 1.55 mmol), and Wilkinson's catalyst (72 mg, 0.08 mmol) in acetonitrile/water (10 mL) gave a pale yellow oil that was purified by flash chromatography (20% ethyl acetate/hexane) to give **107e** (0.33 g, 76%) as a pale yellow oil, R_f 0.52 (30% ethyl acetate/hexane); $[\alpha]^{21}_D$ = -13.5 (*c* 7.47, $CHCl_3$) (lit.[90] $[\alpha]^{20}_D$ = -16.3 *c* 1.00, $CHCl_3$); IR ν_{max} 3050 (N-H), 2964 (C-H), 1732 (ester C=O), 1451, 1080, 761, 588 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33-7.21 (10H, m, Ph) 4.23-4.20 (1H, m, C*H*$CH_2CO_2CH_3$) 3.66 (1H, q, *J*= 6.6 Hz, C*H*CH_3) 3.62 (3H, s, OCH_3) 2.79-2.75 (1H, m, $CH_2CO_2CH_3$) 2.70-2.66 (1H, m, $CH_2CO_2CH_3$) 1.85 (1H, br s, NH) 1.23 (3H, d, *J*= 6.6 Hz, C*H*$_3$CHPh); ^{13}C NMR (500 MHz, $CDCl_3$) δ 172.2 (*C*OOCH_3) 128.6 (ArC) 128.5 (ArC) 127.5 (*C*HCH_2N) 127.1 (ArC) 126.7 (ArC) 56.9 (*C*HCH_3) 54.8 (OCH_3) 51.6 (*C*HCH_2COO) 42.5 (*C*H_2COO) 22.2 (*C*H_3CHN); m/z (Cl+) 284 (100%, $M+H^+$); HRMS $C_{18}H_{21}NO_2$ calcd. 284.1651, found 284.1638.

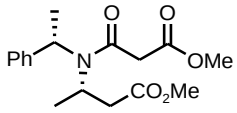
(*R*)-Methyl 3-(pyridin-3-yl)-3-{[(1*S*)-1-phenylethyl]amino}propanoate (107f)[70]



To a stirred solution of (*R*)-methyl

3-(pyridin-3-yl)-3-{[(1*S*)-1-phenylethyl](prop-2-enyl)amino}propanoate (0.54 g, 1.51 mmol) in anhydrous dichloromethane (80 mL) at 30 ^{o}C under nitrogen, tetrakis(triphenylphosphine)palladium(0) (0.16 g, 0.01 mmol) and dimethylbarbituric acid (0.73 g, 2.98 mmol) was added. The solution was stirred at 30 ^{o}C for a further 3 h. The reaction mixture was washed with saturated sodium carbonate solution (2 x 10 mL) and the organic layer was dried ($MgSO_4$), and evaporated. The resulting orange oil was purified by flash chromatography (60% ethyl acetate/hexane) to give **107f** (0.41 g, 96%) as an orange oil, R_f 0.33 (75% ethyl acetate/hexane); IR ν_{max} 2982 (N-H), 2921 (C-H), 1732 (ester C=O), 1435, 1202, 701; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (1H, s, aryl) 8.42-8.38 (1H, m, aryl) 7.66-7.64 (1H, m, aryl) 7.43-7.14 (6H, m, aryl + Ph) 4.17 (1H, dd, *J*=7.5, 6.3 Hz, C*H*$CH_2CO_2CH_3$) 3.65 (1H, q, *J*= 6.4 Hz, C*H*Ph) 3.58 (3H, s, OCH_3) 2.75 (1H, dd, *J*=15.5, 7.5 Hz, C*H*$_2CO_2CH_3$) 2.63 (1H, dd, *J*=15.5, 6.3 Hz, C*H*$_2CO_2CH_3$) 2.25 (1H, br s, NH) 1.33 (3H, d, *J*= 6.4 Hz, C*H*$_3$CHPh); ^{13}C NMR (500 MHz, $CDCl_3$) δ 171.7 (*C*$OOCH_3$) 149.3 (ArC) 148.8 (ArC) 145.4 (ArC) 138.2 (ArC) 133.7 (ArC) 132.0 (ArC) 132.0 (ArC) 128.9 (ArC) 128.5 (ArC) 127.1 (ArC) 123.5 (ArC) 55.4 (CHPh) 54.9 (OCH_3) 51.7 (*C*HCH_2COO) 41.8 (*C*H_2COO) 22.9 (*C*H_3CHN); m/z (Cl+) 285 (100%, M+H$^+$); HRMS $C_{17}H_{21}N_2O_2$ calcd. 285.1603, found 285.1637.

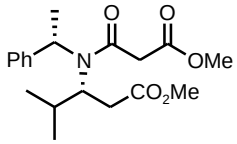
(*R*)-Methyl 3-{(2-methoxycarbonylacetyl)[(1*S*)-1-phenylethyl]amino}butanoate (108a)



Following general procedure 2b, reaction of (*R*)-methyl 3-{[(1*S*)-1-phenylethyl]amino}butanoate (0.30 g, 1.36 mmol), triethylamine (0.22 mL,

1.63 mmol), and methyl 3-chloro-3-oxopropanoate (0.16 mL, 1.49 mmol) in dichloromethane (6 mL) gave a pale yellow oil that was purified by flash chromatography (50% ethyl acetate/hexane) to give **108a** (0.25 g, 58%) as a colourless oil, R_f 0.60 (75% ethyl acetate/hexane); $[\alpha]^{21}_D$ = -2.5 (*c* 0.80, $CHCl_3$); IR ν_{max} 2952 (C-H), 1736 (ester C=O), 1646 (amide C=O), 1438, 1331, 1201, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.22 (5H, m, Ph) 4.95 (1H, q, *J*= 6.8 Hz, C*H*CH_3) 3.78 (3H, s, OCH_3) 3.60 (3H, s, OCH_3) 3.46 (2H, s, CH_2CON) 3.12-3.06 (1H, m, C*H*CH_3) 2.45-2.40 (1H, m, CH_2CHN) 2.10-2.06 (1H, m, C*H*$_2$CHN) 1.66 (3H, d, *J*= 6.8 Hz, C*H*$_3$CHPh) 1.43 (3H, d, *J*= 6.7 Hz, C*H*$_3$CHCH$_2$); ^{13}C NMR (500 MHz, $CDCl_3$) δ 172.3 (*C*$OOCH_3$) 168.3 (*C*$OOCH_3$) 165.6 (CONH) 139.0 (ArC) 128.3 (ArC) 128.1 (ArC) 127.3 (ArC) 56.9 (OCH_3) 52.6 (OCH_3) 51.4 (CH_2N) 48.6 (*C*H_2CHCH$_3$) 42.9 (*C*HCH$_3$) 39.1 (*C*H_2CONH) 18.7 (*C*H_3CHAr) 17.3 (*C*H_3CHCH$_2$); m/z (Cl+) 321 (5%, $M+H^+$) 220 (85%, $M+H^+$-$COCH_2COOCH_3^+$) 105 (100%, $C_8H_9^+$); HRMS $C_{17}H_{23}NO_5$ calcd. 321.1576, found 321.1571.

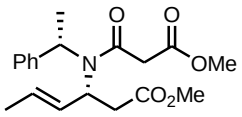
(*R*)-Methyl 3-{(2-methoxycarbonylacetyl)[(1*S*)-1-phenylethyl]amino}-4-methylpentanoate (108b)



Following general procedure 2b, reaction of (*R*)-methyl 4-methyl-3-[(1*S*)-1-phenylethylamino]pentanoate (0.25 g, 1.00 mmol), triethylamine (0.18 mL, 1.30 mmol), and methyl 3-chloro-3-oxopropanoate (0.13 mL, 1.20 mmol) in dichloromethane (4 mL) gave a pale yellow oil that was purified by flash

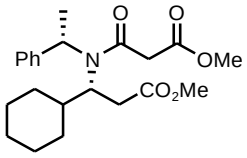
chromatography (50% ethyl acetate/hexane) to give **108b** (0.18 g, 50%) as a pale yellow oil, R_f 0.75 (75% ethyl acetate/hexane); $[\alpha]^{21}_D$ = +74.3 (*c* 0.35, $CHCl_3$); IR ν_{max} 2953 (C-H), 1738 (ester C=O), 1647 (amide C=O), 1437, 1327, 1165 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (presence of rotamers) δ 7.35-7.22 (5H, m, Ph) 5.01-4.98 (1H, m, C*H*$CH_2CO_2CH_3$) 4.30-4.28 (1H, m, C*H*$CH_2CO_2CH_3$) 3.95 (1H, d, *J*= 15.7 Hz, CH_2CON) 3.79 (3H, s, OCH_3) 3.78 (3H, s, OCH_3) 3.72 (1H, d, *J*= 15.2 Hz, CH_2CON) 3.68 (1H, d, *J*= 15.7 Hz, CH_2CON) 3.60 (1H, d, *J*= 15.2 Hz, CH_2CON) 3.46 (3H, s, OCH_3) 3.36 (3H, s, OCH_3) 3.33-3.22 (1H, m, C*H*CH_3) 2.72 (1H, dd, *J*= 18.0, 6.9 Hz, C*H*$_2$CHN) 2.58-2.42 (3H, m, C*H*CHN + C*H*$_2$CHN) 2.24 (2H, dd, *J*= 18.0, 2.5 Hz, C*H*$_2$CHN) 2.04 (1H, m, C*H*CHN) 1.88 (3H, d, *J*= 7.0 Hz, C*H*$_3$CHPh) 1.65 (3H, d, *J*= 7.0 Hz, C*H*$_3$CHPh) 1.11 (3H, d, *J*= 6.7 Hz, (C*H*$_3$)$_2$CH) 0.99 (3H, d, *J*= 6.7 Hz, (C*H*$_3$)$_2$CH) 0.92 (3H, d, *J*= 6.8 Hz, (C*H*$_3$)$_2$CH) 0.81 (3H, d, *J*= 6.8 Hz, (C*H*$_3$)$_2$CH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 172.7 (*C*$OOCH_3$) 171.9 (*C*$OOCH_3$) 168.6 (*C*$OOCH_3$) 168.4 (*C*$OOCH_3$) 167.6 (CON) 165.9 (CON) 139.2 (ArC) 128.8 (ArC) 128.3 (ArC) 127.9 (ArC) 127.7 (ArC) 126.8 (ArC) 126.6 (ArC) 62.3 (*C*HCH_3) 58.3 (*C*HCH_3) 56.6 (*C*$HCH_2CO_2CH_3$) 55.6 (*C*$HCH_2CO_2CH_3$) 52.6 (OCH_3) 52.4 (OCH_3) 51.9 (OCH_3) 51.4 (OCH_3) 43.0 (*C*H_2CON) 42.8 (*C*H_2CON) 39.6 (*C*H_2CHN) 35.9 (*C*H_2CHN) 31.2 (*C*$H(CH_3)_2$) 30.9 (*C*$H(CH_3)_2$) 21.4 (*C*H_3CH) 21.2 (*C*H_3CH) 20.7 ((*C*H_3)$_2$CH) 20.1 ((*C*H_3)$_2$CH) 19.9 ((*C*H_3)$_2$CH) 18.3 ((*C*H_3)$_2$CH); m/z (Cl+) 372 (100%, $M+Na^+$); HRMS $C_{19}H_{27}NO_5Na$ calcd. 372.1787, found 372.1783.

(*R*)-Methyl 3-{(2-methoxycarbonylacetyl)[(1*S*)-1-phenylethyl]amino}hex-4-enoate (108c)



Following general procedure 2b, reaction of (*R*)-methyl 3-{[(1*S*)-1-phenylethyl]amino}hex-4-enoate (1.20 g, 4.85 mmol), triethylamine (0.80 mL, 5.82 mmol), and methyl 3-chloro-3-oxopropanoate (0.57 mL, 5.33 mmol) in dichloromethane (25 mL) gave a pale yellow oil that was purified by flash chromatography (30% ethyl acetate/hexane) to give **108c** (1.58 g, 94%) as a colourless oil, R_f 0.17 (30% ethyl acetate/hexane); $[\alpha]^{21}_D$ = +5.5 (*c* 1.82, $CHCl_3$); IR ν_{max} 3030 (N-H), 2952 (C-H), 1733 (ester C=O), 1641 (ketone C=O), 1434, 1246, 1202 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.21 (5H, m, Ph) 5.97-5.89 (1H, m, C*H*CH=CHCH$_3$) 5.65-5.56 (2H, m, C*H*=CHCHN + =C*H*CHN) 5.04 (1H, q, *J*= 6.7 Hz, C*H*Ph) 3.78 (3H, s, OCH_3) 3.51 (2H, s, CH_2CON) 3.45 (3H, s, OCH_3) 1.74 (2H, d, *J*= 4.9 Hz, C*H*$_2$CO$_2$CH$_3$) 1.64 (3H, d, *J*= 6.7 Hz, C*H*$_3$CHPh) 1.58 (3H, m, C*H*$_3$CHCH); m/z (Cl+) 370 (100%, M^+), 311 (2%, M^+-CO_2CH_3); HRMS $C_{19}H_{25}NO_5Na$ calcd. 370.1630, found 370.1626.

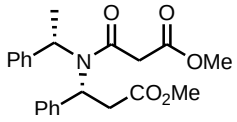
(*R*)-Methyl 3-cyclohexyl-3-{(2-methoxycarbonylacetyl)[(1*S*)-1-phenylethyl]amino}propanoate (108d)



Following general procedure 2b, reaction of (*R*)-methyl 3-cyclohexyl-3-[(1*S*)-1-phenylethyl]amino]propanoate (0.25 g, 0.86 mmol), triethylamine (0.16 mL, 1.12 mmol), and methyl 3-chloro-3-oxopropanoate (0.11 mL, 1.04 mmol) in dichloromethane (4 mL) gave a pale yellow oil that was purified by flash chromatography (50% ethyl acetate/hexane) to give **108d** (0.22 g, 66%) as a pale yellow oil, R_f 0.75 (75% ethyl acetate/hexane); $[\alpha]^{25}_D$ = +22.5 (*c* 1.00, $CHCl_3$); IR ν_{max} 2925 (C-H), 1737 (ester C=O), 1648 (amide C=O), 1437, 1167 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (presence of rotamers) δ 7.32-7.16 (5H, m, Ph) 4.99-4.95 (1H, m, C*H*$CH_2CO_2CH_3$) 4.30-4.28 (1H, m, C*H*$CH_2CO_2CH_3$) 3.77 (3H, s, OCH_3) 3.76 (3H, s, OCH_3) 3.65 (1H, s, CH_2CON) 3.60 (1H, s, CH_2CON) 3.45 (3H, s, OCH_3) 3.33 (3H, s, OCH_3) 2.72 (1H, d, *J*= 7.0 Hz, C*H*CH_3) 2.46 (1H, d, *J*= 7.0 Hz, C*H*CH_3) 2.45-2.32 (2H, m, C*H*$_2$CHN) 2.22-2.18 (2H, m, C*H*$_2$CHN) 1.85-1.83 (3H, d, *J*= 7.0 Hz, C*H*$_3$CHPh) 1.73-1.61 (8H, m, C*H*$_3$CHPh + cyclohexyl-C*H*) 1.29-0.82 (6H, m, cyclohexyl-C*H*); ^{13}C NMR (500 MHz, $CDCl_3$) δ 173.5 (*C*$OOCH_3$) 172.7 (*C*$OOCH_3$) 168.7 (*C*$OOCH_3$) 168.4 (*C*$OOCH_3$) 167.6 (CON) 165.8 (CON) 142.6 (ArC) 139.3 (ArC) 128.7 (ArC) 128.3 (ArC) 128.2 (ArC) 127.9 (ArC) 126.9 (ArC) 126.8 (ArC) 61.4 (*C*HCH_3) 57.2 (*C*HCH_3) 57.0 (*C*$HCH_2CO_2CH_3$) 55.5 (*C*$HCH_2CO_2CH_3$) 52.5 (OCH_3) 51.5 (OCH_3) 51.3 (OCH_3) 50.0 (OCH_3) 43.0 (*C*H_2CON) 42.8 (*C*H_2CON) 41.8 (*C*H_2CHN) 40.8

(*C*H_2CHN) 35.9 (cyclohexyl-C) 31.5 (cyclohexyl-C) 30.6 (cyclohexyl-C) 30.1 (cyclohexyl-C) 29.2 (cyclohexyl-C) 29.1 (cyclohexyl-C) 26.6 (cyclohexyl-C) 26.5 (cyclohexyl-C) 26.4 (cyclohexyl-C) 26.4 (cyclohexyl-C) 26.1 (cyclohexyl-C) 26.1 (cyclohexyl-C) 25.0 (*C*H_3CH) 21.2 (*C*H_3CH); m/z (Cl+) 412 (100%, M+Na^+); HRMS $C_{22}H_{31}NO_5Na$ calcd. 412.2100, found 412.2115.

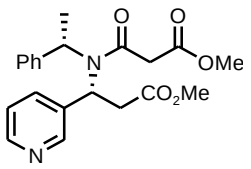
(*R*)-Methyl 3-{(2-methoxycarbonylacetyl)[(1*S*)-1-phenylethyl]amino}-3-phenylpropanoate (108e)



Following general procedure 2b, reaction of (*R*)-methyl 3-{[(1*S*)-1-phenylethyl]amino}-3-phenylpropanoate (4.16 g, 14.7 mmol), triethylamine (2.73 mL, 19.1 mmol), and methyl 3-chloro-3-oxopropanoate (1.9 mL, 17.6 mmol) in dichloromethane (45 mL) gave a pale yellow oil that was purified by flash chromatography (35% ethyl acetate/hexane) to give **108e** (4.48 g, 80%) as a colourless oil, R_f 0.50 (50% ethyl acetate/hexane); $[\alpha]^{21}_D$ = +25.0 (*c* 1.56, $CHCl_3$); IR ν_{max} 2951 (C-H), 1735 (ester C=O), 1647 (amide C=O), 1435, 1330, 1161, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) (presence of rotamers) δ 7.37-7.17 (10H, m, Ph) 5.32 (1H, m, C*H*$CH_2CO_2CH_3$) 5.26-5.22 (1H, m, C*H*$CH_2CO_2CH_3$) 4.98 (1H, q, *J*= 6.1 Hz, C*H*CH_3) 3.71 (3H, s, OCH_3) 3.56 (2H, s, CH_2CON) 3.51 (3H, s, OCH_3) 3.36-3.31 (2H, m, C*H*$_2$CHN) 2.98-2.94 (1H, m, C*H*$_2$CHN) 2.73-2.65 (1H, m, C*H*$_2$CHN) 1.25 (3H, *J*= 6.1 Hz, C*H*$_3$CHPh); ^{13}C NMR (500 MHz, $CDCl_3$) δ 171.9 (*C*$OOCH_3$) 171.1 (*C*$OOCH_3$) 168.4 (*C*$OOCH_3$) 168.2 (*C*$OOCH_3$) 167.2 (CON) 166.5 (CON) 141.4 (ArC) 140.4

(ArC) 139.9 (ArC) 139.0 (ArC) 129.1 (ArC) 129.0 (ArC) 128.6 (ArC) 128.5 (ArC) 128.2 (ArC) 128.0 (ArC) 127.4 (ArC) 127.2 (ArC) 127.0 (ArC) 126.6 (ArC) 126.5 (ArC) 56.8 (*C*HCH$_3$) 56.4 (*C*HCH$_3$) 55.2 (*C*HCH$_2$CO$_2$CH$_3$) 54.7 (*C*HCH$_2$CO$_2$CH$_3$) 52.6 (OCH$_3$) 52.5 (OCH$_3$) 52.1 (OCH$_3$) 51.8 (OCH$_3$) 43.0 (*C*H$_2$CON) 40.8 (*C*H$_2$CON) 38.9 (*C*H$_2$CHN) 38.3 (*C*H$_2$CHN) 18.6 (*C*H$_3$CH); m/z (Cl+) 384 (100%, M+H$^+$); HRMS $C_{22}H_{26}NO_5Na$ calcd. 384.1811, found 384.1803.

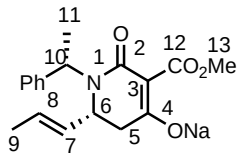
(*R*)-Methyl 3-(pyridin-3-yl)-3-{(2-methoxycarbonylacetyl)[(1*S*)-1-phenylethyl]amino}propanoate (108f)



Following general procedure 2b, reaction of (*R*)-methyl 3-(pyridin-3-yl)-3-{[(1*S*)-1-phenylethyl]amino}propanoate (0.16 g, 0.56 mmol), triethylamine (0.11 mL, 0.73 mmol), and methyl 3-chloro-3-oxopropanoate (0.07 mL, 0.67 mmol) in dichloromethane (3 mL) gave a pale yellow oil that was purified by flash chromatography (50% ethyl acetate/hexane) to give **108f** (0.16 g, 75%) as a colourless oil, R_f 0.12 (75% ethyl acetate/hexane); $[\alpha]^{21}_D$ = +15.0 (*c* 1.00, $CHCl_3$); IR ν_{max} 2952 (C-H), 1735 (ester C=O), 1648 (amide C=O), 1496, 1436, 1165, 702 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) (presence of rotamers) δ 8.57 (1H, s, aryl) 8.44-8.37 (1H, m, aryl) 7.82 (1H, d, *J*= 7.3 Hz, aryl) 7.66-7.62 (1H, m, aryl) 7.45-7.17 (5H, m, aryl) 5.08 (1H, q, *J*= 6.5 Hz, C*H*CH$_3$) 4.86 (1H, dd, *J*= 7.7, 5.6 Hz, C*H*CH$_2$CO$_2$CH$_3$) 3.74 (3H, s, OCH$_3$) 3.58 (2H, s, CH$_2$CON) 3.43 (3H, s, OCH$_3$) 2.74-2.69 (2H, m, C*H*$_2$CHN) 2.48 (2H, dd, *J*= 17.1, 7.7 Hz, C*H*$_2$CHN) 2.27 (2H, dd, *J*= 17.1, 5,6 Hz, C*H*$_2$CHN)

1.60 (3H, d, *J*= 6.5 Hz, C*H*$_3$CHPh); ^{13}C NMR (500 MHz, $CDCl_3$) δ 171.6 (*C*OOCH$_3$) 168.1 (*C*OOCH$_3$) 166.2 (CON) 149.0 (ArC) 148.5 (ArC) 136.1 (ArC) 135.7 (ArC) 132.1 (ArC) 132.0 (ArC) 129.1 (ArC) 128.8 (ArC) 128.4 (ArC) 127.2 (ArC) 123.3 (ArC) 57.3 (*C*HCH$_3$) 53.3 (*C*HCH$_2$CO$_2$CH$_3$) 52.6 (OCH$_3$) 51.8 (OCH$_3$) 42.7 (*C*H$_2$CON) 38.7 (*C*H$_2$CHN) 18.4 (*C*H$_3$CH); m/z (Cl+) 385 (100%, M+H$^+$) 279 (55%, M+H$^+$-PhCHCH$_3$); HRMS $C_{21}H_{25}N_2O_5$ calcd. 385.1764, found 385.1761.

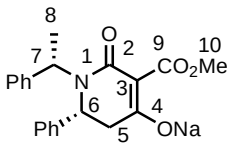
3-Methoxy-1-[(1*S*)-phenylethyl]-(6*R*)-propenylpiperidine-2,4-dione sodium salt (109c)



To a stirred solution of (*R*)-methyl 3-{(2-methoxycarbonylacetyl)[(1*S*)-1-phenylethyl]amino}hex-4-enoate (1.58 g, 4.60 mmol) in methanol (6 mL) at room temperature under nitrogen, sodium methoxide in methanol (2.3 mL, 5.0 mmol, 2.14 M) was added. The mixture was then heated under reflux for 1 h. The mixture was allowed to cool to room temperature, then diluted with diethyl ether and filtered to give **109c** (1.46 g, 95%) as white microprisms, mp 203-207 ^{o}C; IR ν_{max} 3064 (O-H), 2974 (C-H), 1660 (amide C=O), 1521, 1435, 1134, 1087, 733, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.22 (5H, m, Ph) 6.04 (1H, q, *J*= 7.2 Hz, C_{10}H) 5.68-5.64 (1H, m, C_7H) 5.56-5.51 (1H, m, C_8H) 3.66 (3H, s, OCH$_3$) 3.61-3.59 (1H, m, C_6H) 2.33 (1H, dd, *J*= 15.7, 6.2 Hz, C_5H) 2.18 (1H, dd, *J*= 15.7, 2.4 Hz, C_5H) 1.61 (3H, d, *J*= 6.3 Hz, C_9H) 1.49 (3H, d, *J*= 7.2 Hz, C_{11}H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 188.1 (C_4) 170.8 (C_{12}) 170.7 (C_2) 144.1 (Ar*C*) 132.7 (C_7) 129.4 (Ar*C*) 128.2 (Ar*C*) 128.2 (C_8) 127.3 (Ar*C*) 96.4 (C_3) 51.8 (C_{13}) 51.4 (C_{10}) 50.4 (C_5) 43.4 (C_6) 17.8

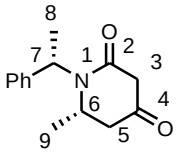
(C_9) 17.3 (C_{11}); HRMS $C_{18}H_{21}NO_4Na$ calcd. 338.1368, found 338.1360.

3-Methoxy-1-[(1*S*)-phenylethyl]-(6*R*)-phenylpiperidine-2,4-dione sodium salt (109e)



To a stirred solution of (*R*)-methyl 3-{(2-methoxycarbonylacetyl)[(1*S*)-1-phenylethyl]amino}-3-phenylpropanoate (0.13 g, 0.34 mmol) in methanol (0.7 mL) at room temperature under nitrogen, sodium methoxide in methanol (0.2 mL, 0.38 mmol, 1.97 M) was added. The mixture was then heated under reflux for 1 h. The mixture was allowed to cool to room temperature, then diluted with diethyl ether and filtered to give **109e** (0.12 g, 97%) as white microprisms, mp 230 ^{o}C (decomposed); IR ν_{max} 3220 (O-H), 2972 (C-H), 1671 (amide C=O), 1650 (C=C), 1589, 1529, 1438, 1110, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.14 (10H, m, Ph) 6.21 (1H, q, *J*= 7.2 Hz, C_7H) 4.33 (1H, dd, *J*= 6.9, 1.3 Hz, C_6H) 3.67 (3H, s, OCH_3) 2.64 (1H, dd, *J*= 15.7, 6.9 Hz, C_5H) 2.15 (1H, dd, *J*= 15.7, 1.3 Hz, C_5H) 1.24 (3H, d, *J*= 7.2 Hz, C_8H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 186.6 (C_4) 171.8 (C_9) 170.6 (C_2) 144.1 (ArC) 143.9 (ArC) 129.5 (ArC) 129.2 (ArC) 128.3 (ArC) 128.1 (ArC) 127.9 (ArC) 127.7 (ArC) 97.5 (C_3) 53.6 (C_{10}) 51.4 (C_7) 50.5 (C_5) 44.9 (C_6) 17.0 (C_8).

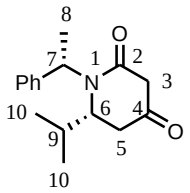
(6*R*)-Methyl-1-[(1*S*)-phenylethyl]piperidine-2,4-dione (110a)



Following general procedure 3, reaction of

3-{(2-methoxycarbonylacetyl)[(1*S*)-1-phenylethyl]amino}butanoate (0.23 g, 0.70 mmol), and sodium methoxide in methanol (0.7 mL, 1.40 mmol, 2.00 M) in methanol (5 mL) gave **110a** (0.16 g, 97%) as a pale yellow oil, $[\alpha]^{21}_{D}$ = -198.1 (*c* 3.09, $CHCl_3$); IR ν_{max} 2975 (C-H), 1730 (ester C=O), 1642 (amide C=O), 1439, 1280, 1181, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.25 (5H, m, Ph) 6.10 (1H, q, *J*= 6.9 Hz, C_7H) 3.60-3.50 (1H, m, C_6H) 3.41-3.29 (2H, m, C_3H) 2.24 (1H, dd, *J*= 16.5, 8.6 Hz, C_5H) 2.17 (1H, dd, *J*= 16.5, 5.0 Hz, C_5H) 1.59 (3H, d, *J*= 6.9 Hz, C_8H) 1.25 (3H, d, *J*= 6.7 Hz, C_9H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 204.6 (C_4) 166.2 (C_2) 140.0 (ArC) 128.8 (ArC) 128.1 (ArC) 127.2 (ArC) 50.9 (C_5) 47.4 (C_7) 46.5 (C_3) 45.1 (C_6) 22.7 (C_8) 16.9 (C_9); m/z (Cl+) 232 (100%, $M+H^+$), 105 (35%, $PhCHCH_3^+$); HRMS $C_{14}H_{18}NO_2$ calcd. 232.1338, found 232.1334.

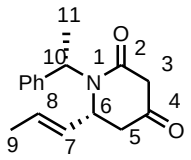
(6*R*)-Isopropyl-1-[(1*S*)-phenylethyl]piperidine-2,4-dione (110b)



Following general procedure 3, reaction of 3-{(2-methoxycarbonylacetyl)[(1*S*)-1-phenylethyl]amino}-4-methylpentanoate (0.15 g, 0.47 mmol), and sodium methoxide in methanol (0.5 mL, 1.00 mmol, 2.00 M) in methanol (3 mL) gave **110b** (0.12 g, 95%) as a pale yellow oil, $[\alpha]^{21}_{D}$ = -177.9 (*c* 1.31, $CHCl_3$); IR ν_{max} 2968 (C-H), 1726 (ester C=O), 1644 (amide C=O), 1443, 1319, 1170, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.26 (5H, m, Ph) 6.07 (1H, q, *J*= 7.1 Hz, C_7H) 3.42 (1H, d, *J*= 21.3 Hz, C_3H) 3.20 (1H, d, *J*= 21.3 Hz, C_3H) 3.17-3.15 (1H, m, C_6H) 2.53-2.50 (1H, dd, *J*= 16.7, 5.0 Hz, C_5H) 2.02-1.96 (2H, m, C_5H + C_9H) 1.65 (3H, d, *J*= 7.1 Hz, C_8H) 0.90 (3H, d, *J*= 6.9 Hz, $C_{10}H$) 0.84 (3H, d, *J*= 6.9 Hz, $C_{10}H$); ^{13}C

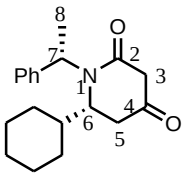
NMR (500 MHz, $CDCl_3$) δ 208.2 (C_4) 170.2 (C_2) 142.5 (ArC) 131.5 (ArC) 130.7 (ArC) 130.2 (ArC) 58.3 (C_7) 55.4 (C_6) 50.1 (C_3) 43.7 (C_5) 35.9 (C_9) 22.9 (C_8) 20.4 (C_{10}) 20.2 (C_{10}); m/z (El+) 259 (100%, M^+), 216 (99%, M^+-$(CH_3)_2CH$), 147 (5%, $PhCH(CH_3)NCO^+$), 132 (8%, $PhCHNCO^+$) 105 (75%, $PhCHCH_3^+$), 77 (40%, Ph^+); HRMS $C_{16}H_{21}NO_2$ calcd. 259.1572, found 259.1575.

1-[(1*S*)-Phenylethyl]-(6*R*)-propenylpiperidine-2,4-dione (110c)



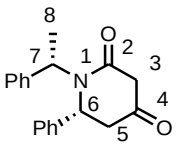
3-Methoxy-1-[(1*S*)-phenylethyl]-(6*R*)-phenylpiperidine-2,4-dione sodium salt (1.00 g, 2.96 mmol) was added to aqueous 5% hydrochloric acid (30 mL). The mixture was heated under reflux for 1 h. The mixture was allowed to cool to room temperature and extracted with dichloromethane (2 x 30 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to give **110c** (0.56 g, 74%) as a pale yellow oil, $[\alpha]^{21}_D$ = -203.8 (*c* 2.08, $CHCl_3$); IR ν_{max} 3060 (N-H), 2938 (C-H), 1726 (amide C=O), 1650 (ketone C=O), 1438, 1268, 1206 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52-7.26 (5H, m, Ph) 6.14 (1H, q, *J*= 7.2 Hz, $C_{10}H$) 5.55 (1H, dtq, *J*= 18.0, 6.2, 1.4 Hz, C_7H) 5.41 (1H, dq, *J*= 18.0, 1.7 Hz, C_8H) 3.93-3.90 (1H, m, C_6H) 3.41-3.24 (2H, m, C_3H) 2.42 (1H, dd, *J*= 17.0, 2.1 Hz, C_5H) 2.16 (1H, dd, *J*= 17.0, 5.1 Hz, C_5H) 1.68 (3H, dd, *J*= 6.2, 1.7 Hz, C_9H) 1.54 (3H, d, *J*= 7.2 Hz, $C_{11}H$); ^{13}C NMR (300 MHz, $CDCl_3$) δ 204.1 (C_4) 166.6 (C_2) 139.9 (ArC) 129.8 (C_7) 128.7 (C_8) 128.0 (ArC) 127.9 (ArC) 127.3 (ArC) 51.1 (*C*HPh) 50.2 (C_5) 48.4 (C_3) 44.9 (C_6) 17.7 (C_{11}) 16.5 (C_9); m/z (Cl+) 257 (70%, M^+), 147 (5%, $PhCH(CH_3)NCO^+$), 132 (15%, $PhCHNCO^+$) 105 (39%, $PhCHCH_3^+$), 77 (15%, Ph^+); HRMS $C_{16}H_{19}NO_2$ calcd. 257.1416, found 257.1428.

(6*R*)-Cyclohexyl-1-[(1*S*)-phenylethyl]piperidine-2,4-dione (110d)



Following general procedure 3, reaction of (*R*)-methyl 3-cyclohexyl-3-{(2-methoxycarbonylacetyl)[(1*S*)-1-phenylethyl]amino}propanoate (0.22 g, 0.57 mmol), and sodium methoxide in methanol (0.6 mL, 1.20 mmol, 2.00 M) in methanol (3 mL) gave **110d** (0.13 g, 76%) as a colourless oil, $[\alpha]^{25}_{D}$ = -133.1 (*c* 3.40, $CHCl_3$); IR ν_{max} 2926 (C-H), 1726 (ester C=O), 1640 (amide C=O), 1444, 1317, 1172, 762, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46-7.25 (5H, m, Ph) 6.03 (1H, q, *J*= 7.2 Hz, C_7H) 3.38 (1H, d, *J*= 21.2 Hz, C_3H) 3.26 (1H, d, *J*= 21.2 Hz, C_3H) 3.14-3.12 (1H, m, C_6H) 2.49 (1H, dd, *J*= 16.7, 3.6 Hz, C_5H) 1.95 (1H, dd, *J*= 16.7, 6.5 Hz, C_5H) 1.76-1.72 (2H, m, cyclohexyl-CH_2) 1.61 (3H, d, *J*= 7.2 Hz, C_8H) 1.59-1.47 (3H, m, cyclohexyl-CH_2) 1.14-0.80 (6H, m, cyclohexyl-CH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 205.6 (C_4) 169.5 (C_2) 139.9 (ArC) 128.8 (ArC) 128.0 (ArC) 127.5 (ArC) 55.2 (C_7) 52.8 (C_6) 47.7 (C_3) 43.6 (C_5) 41.7 (1'-cyclohexyl-C) 30.7 (4'-cyclohexyl-C) 28.6 (2'-cyclohexyl-C) 26.6 (6'-cyclohexyl-C) 26.4 (3'- cyclohexyl-C) 26.0 (5'-cyclohexyl-C) 17.6 (C_8) ; m/z (Cl+) 300 (100%, $M+H^+$); HRMS $C_{19}H_{26}NO_2$ calcd. 300.1964, found 300.1953.

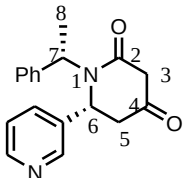
1-[(1*S*)-Phenylethyl]-(6*R*)-phenylpiperidine-2,4-dione (110e)



3-Methoxy-1-[(1*S*)-phenylethyl]-(6*R*)-phenylpiperidine-2,4-dione sodium salt (0.10 g,

0.28 mmol) was added to aqueous 5% hydrochloric acid (5 mL). The mixture was heated under reflux for 1 h. The mixture was allowed to cool to room temperature and extracted with dichloromethane (2 x 5 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. The resulting pale yellow oil was purified by flash chromatography (50% ethyl acetate/hexane) to give **110e** (69 mg, 85%) as pale yellow microprisms, mp 104-107 ^oC; R_f 0.42 (50% ethyl acetate/hexane); $[\alpha]^{21}_D$ = +103.4 (*c* 2.95, $CHCl_3$) (lit.[61] opposite enantiomer $[\alpha]^{13}_D$ = -107.7 *c* 1.04, $CHCl_3$); IR ν_{max} 2923 (C-H), 1730 (ester C=O), 1648 (amide C=O), 1453, 1323, 1207, 755, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39-7.11 (10H, m, Ph) 6.31 (1H, q, *J*= 7.2 Hz, C_7H) 4.65 (1H, dd, *J*= 6.1, 2.2 Hz, C_6H) 3.39 (2H, s, C_3H) 2.68 (1H, dd, *J*= 16.4, 2.2 Hz, C_5H) 2.51 (1H, dd, *J*= 16.4, 6.1 Hz, C_5H) 1.35 (3H, d, *J*= 7.2 Hz, C_8H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 203.2 (C_4) 167.4 (C_2) 140.0 (ArC) 140.0 (ArC) 129.2 (ArC) 128.9 (ArC) 128.1 (ArC) 128.0 (ArC) 127.5 (ArC) 125.7 (ArC) 53.0 (C_5) 51.6 (C_7) 48.8 (C_3) 47.9 (C_6) 16.4 (C_8); m/z (El+) 293 (100%, M^+), 105 (35%, $PhCHCH_3^+$), 77 (10%, Ph^+); HRMS $C_{19}H_{19}NO_2$ calcd. 293.1416, found 293.1413.

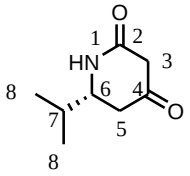
(6*R*)-Pyridin-3-yl-1-[(1*S*)-phenylethyl]piperidine-2,4-dione (110f)



Following general procedure 3, reaction of (*R*)-methyl 3-(pyridin-3-yl)-3-{(2-methoxycarbonylacetyl)[(1*S*)-1-phenylethyl]amino}propanoate (0.25 g, 0.65 mmol), and sodium methoxide in methanol (0.65 mL, 1.30 mmol, 2.00 M) in methanol (3 mL) gave **110f** (0.19 g, 99%) as a brown oil, $[\alpha]^{25}_D$ = -84.7 (*c* 1.00, $CHCl_3$); IR ν_{max} 2977 (C-H), 1730 (ester C=O), 1642 (amide C=O), 1414, 1206, 747,

697, 540 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (1H, d, *J*= 4.5 Hz, aryl) 8.48 (1H, s, aryl) 7.67-7.63 (1H, m, aryl) 7.53-7.26 (6H, m, aryl + Ph) 6.31 (1H, q, *J*= 7.2 Hz, C_7H) 4.66 (1H, dd, *J*= 6.0, 1.8 Hz, C_6H) 3.46 (1H, d, *J*= 20.6 Hz, C_3H) 3.35 (1H, d, *J*= 20.6 Hz, C_3H) 2.66 (1H, dd, *J*= 16.4, 1.8 Hz, C_5H) 2.56 (1H, dd, *J*= 16.4, 6.0 Hz, C_5H) 1.34 (3H, d, *J*= 7.2 Hz, C_8H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 202.1 (C_4) 167.1 (C_2) 149.6 (ArC) 147.6 (ArC) 139.5 (ArC) 135.7 (ArC) 133.2 (ArC) 132.2 (ArC) 129.1 (ArC) 128.6 (ArC) 128.3 (ArC) 127.4 (ArC) 123.8 (ArC) 51.6 (C_5) 51.1 (C_7) 48.6 (C_3) 47.7 (C_6) 16.6 (C_8); m/z (El+) 294 (15%, M^+); HRMS $C_{18}H_{18}N_2O_2$ calcd. 294.1368, found 294.1366.

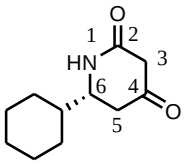
(6*R*)-Isopropylpiperidine-2,4-dione (111a)



To a stirred solution of (6*R*)-isopropyl-1-[(1*S*)-phenylethyl]piperidine-2,4-dione (76 mg, 0.29 mmol) in toluene (2 mL) at room temperature under nitrogen, methanesulfonic acid (0.02 mL, 0.26 mmol) was added. The mixture was then heated under reflux for 3 h. The mixture was allowed to cool to room temperature and evaporated. The resulting pale yellow oil was purified by flash chromatography (ethyl acetate) to give **111a** (22 mg, 48%) as a pale yellow oil, R_f 0.20 (ethyl acetate); $[\alpha]^{21}_D$ = +30.6 (*c* 0.49, $CHCl_3$) (lit.[22] $[\alpha]^{13}_D$ = +35.3 *c* 1.00, MeOH); IR ν_{max} 3212 (N-H), 2922 (C-H), 1722 (ester C=O), 1665 (amide C=O), 1464, 1347 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (1H, br s, NH) 3.50-3.48 (1H, m, C_6H) 3.28 (2H, s, C_3H) 2.63 (1H, dd, *J*= 16.1, 4.4 Hz, C_5H) 2.45 (1H, dd, *J*= 16.1, 9.1 Hz, C_5H) 1.85-1.81 (1H, m, C_7H) 1.01-0.95 (6H, m, C_8H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 203.5 (C_4) 170.2 (C_2) 54.3 (C_6)

47.2 (C_3) 41.6 (C_5) 32.5 (C_7) 18.2 (C_8) 17.9 (C_8).

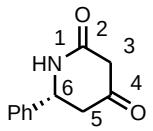
(6*R*)-Cyclohexylpiperidine-2,4-dione (111c)



To a stirred solution of (6*R*)-cyclohexyl-1-[(1*S*)-phenylethyl]piperidine-2,4-dione

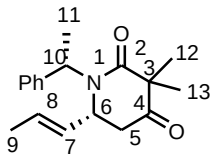
(0.14 g, 0.47 mmol) in toluene (3 mL) at room temperature under nitrogen, methanesulfonic acid (0.04 mL, 0.61 mmol) was added. The mixture was then heated under reflux for 5 h. The mixture was allowed to cool to room temperature and evaporated. The resulting pale yellow oil was purified by flash chromatography (ethyl acetate) to give **111c** (38 mg, 42%) as yellow microprisms, mp 125-127 ^{o}C; R_f 0.24 (ethyl acetate); $[\alpha]^{21}_{D}$ = +14.2 (*c* 1.26, MeOH); IR ν_{max} 3223 (N-H), 2925 (C-H), 1724 (ester C=O), 1665 (amide C=O), 1449, 1337, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (1H, br s, NH) 3.66-3.45 (1H, m, C_6H) 3.25 (2H, s, C_3H) 2.61 (1H, dd, *J*= 16.1, 4.8 Hz, C_5H) 2.50 (1H, dd, *J*= 16.1, 8.1 Hz, C_5H) 1.80-1.74 (3H, m, cyclohexyl-CH) 1.70-1.69 (2H, m, cyclohexyl-CH) 1.52-1.64 (1H, m, cyclohexyl-CH) 1.25-1.14 (3H, m, cyclohexyl-CH) 1.02-0.98 (2H, m, cyclohexyl-CH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 203.9 (C_4) 169.4 (C_2) 53.6 (C_6) 47.3 (C_3) 42.4 (C_5) 41.7 (1'-cyclohexyl-C) 28.8 (4'-cyclohexyl-C) 28.5 (2'-cyclohexyl-C) 26.1 (6'-cyclohexyl-C) 25.9 (3'-cyclohexyl-C) 25.9 (5'-cyclohexyl-C); m/z (El+) 195 (2%, M^+) 112 (100%, M^+-cyclohexyl) 83 (5%, cyclohexyl$^+$); HRMS $C_{11}H_{17}NO_2$ calcd. 195.1259, found 195.1255.

(6*R*)-Phenylpiperidine-2,4-dione (111e)[71]



To a stirred solution of 1-[(1*S*)-phenylethyl]-(6*R*)-phenylpiperidine-2,4-dione (1.00 g, 3.41 mmol) in toluene (15 mL) at room temperature under nitrogen, methanesulfonic acid (0.23 mL, 3.07 mmol) was added. The mixture was then heated under reflux for 3 h. The mixture was allowed to cool to room temperature and evaporated. The resulting pale yellow oil was purified by flash chromatography (90% ethyl acetate/hexane) to give **111e** (0.36 g, 56%) as white microprisms, mp 163-166 ^{o}C (lit.[23] 166-168 ^{o}C); R_f 0.20 (ethyl acetate); $[\alpha]^{25}_{D}$ = +119.1 (*c* 1.00, $CHCl_3$) (lit.[23] $[\alpha]^{20}_{D}$ = +123.4 *c* 0.35, $CHCl_3$); IR ν_{max} 3185 (N-H), 2899 (C-H), 1716 (ester C=O), 1665 (amide C=O), 1409, 1369, 1329, 701, 660 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43-7.21 (5H, m, Ph) 7.13 (1H, br s, NH) 4.80-4.77 (1H, m, C_6H) 3.33 (2H, s, C_3H) 2.85 (1H, dd, *J*= 16.1, 4.5 Hz, C_5H) 2.73 (1H, dd, *J*= 16.1, 8.9 Hz, C_5H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 202.5 (C_4) 169.2 (C_2) 139.4 (ArC) 129.4 (ArC) 128.9 (ArC) 126.1 (ArC) 52.9 (C_5) 47.3 (C_3) 47.0 (C_6); m/z (El+) 189 (100%, M^+); HRMS $C_{11}H_{11}NO_2$ calcd. 189.0790, found 189.0787.

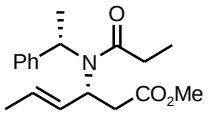
3,3-Dimethyl-1-[(1*S*)-phenylethyl]-(6*R*)-propenylpiperidine-2,4-dione (112)



To 1-[(1*S*)-phenylethyl]-(6*R*)-propenylpiperidine-2,4-dione (0.13 g, 0.51 mmol) in ethanol (2 mL) was added potassium carbonate (0.21 g, 1.52 mmol) and iodomethane (0.1 ml, 1.52 mmol). The mixture was stirred at 40 ^{o}C for 16 h. The solution was

filtered and the filtrate was evaporated. Chloroform (5 mL) was added and the solution was filtered again. After evaporation, the resulting yellow oil was purified by flash chromatography (15% ethyl acetate/hexane) to give **112** (0.11 g, 76%) as a colourless oil, $[\alpha]^{21}_{D}$ = -142.9 (*c* 0.35, $CHCl_3$); IR ν_{max} 2923 (C-H), 1724 (amide C=O), 1640 (ketone C=O), 1429, 1185, 701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.24 (5H, m, Ph) 6.07 (1H, q, *J*= 6.5 Hz, $C_{10}H$) 5.50-5.43 (1H, m, C_7H) 5.29-5.22 (1H, m, C_8H) 3.83-3.81 (1H, m, C_6H) 2.65 (1H, dd, *J*= 13.8, 5.7 Hz, C_5H) 2.30 (1H, dd, *J*= 13.8, 2.5, C_5H) 1.63 (3H, d, *J*= 6.5 Hz, $C_{11}H$) 1.51 (3H, dd, *J*= 7.2, 1.8 Hz, C_9H) 1.39 (3H, d, *J*= 1.9 Hz, $C_{12}H$) 1.35 (3H, d, *J*= 1.9 Hz, $C_{13}H$); ^{13}C NMR (300 MHz, $CDCl_3$) δ 209.2 (C_4) 174.0 (C_2) 140.5 (ArC) 131.1 (C_7) 128.7 (C_8) 128.3 (ArC) 127.7 (ArC) 127.3 (ArC) 52.4 (CHPh) 52.1 (C_5) 50.6 (C_3) 44.4 (C_6) 26.5 (C_{12}) 21.7 (C_{13}) 17.6 (C_{11}) 16.8 (C_9).

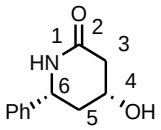
Methyl 3-[(1-phenylethyl)propionylamino]hex-4-enoate (113)



To a stirred solution of (*R*)-methyl 3-{[(1*S)*-1-phenylethyl]amino}hex-4-enoate (0.10 g, 0.42 mmol) in dichloromethane (1.5 mL) at 0 ^{o}C under nitrogen, triethylamine (0.01 mL, 0.62 mmol) and 1-chloro-1-oxopropane (0.05 mL, 0.52 mmol) was added. The mixture was then allowed to warm to room temperature and stirred for 1 h. The mixture was diluted with dichloromethane (5 mL) and washed with saturated aqueous sodium hydrogen carbonate (3 mL). The aqueous layer was extracted with dichloromethane (2 x 3 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated. The resulting pale yellow oil was purified by flash chromatography (30% ethyl acetate/hexane) to give **113** (0.09 g, 74%) as a colourless oil, R_f 0.72 (75% ethyl

acetate/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.23 (5H, m, Ph) 5.92-5.87 (1H, m, C*H*CH=CHCH$_3$) 5.54-5.50 (2H, m, C*H*=CHCHN + =C*H*CHN) 5.06 (1H, q, *J*= 6.7 Hz, C*H*Ph) 3.98-3.94 (1H, m, CH_2CON) 3.51 (3H, s, OCH_3) 3.12-3.09 (1H, m, CH_2CON) 2.50-2.38 (2H, m, C*H*$_2$CO$_2$CH$_3$) 1.58-1.57 (6H, m, C*H*$_3$CH=CH + C*H*$_3$CHPh) 1.14-1.11 (3H, m, C*H*$_3$CH$_2$CO); ^{13}C NMR (500 MHz, $CDCl_3$) δ 173.2 (*C*OOCH$_3$) 172.0 (*C*ONH) 140.1 (ArC) 130.1 (ArC) 128.7 (ArC) 128.3 (*C*HCHCHN) 127.6 (*C*HCHNH) 127.2 (ArC) 55.6 (OCH_3) 54.6 (CHPh) 51.3 (*C*HCH$_2$COO) 38.7 (*C*H$_2$COO) 28.0 (*C*H$_2$CON) 18.0 (*C*H$_3$CHPh) 17.6 (*C*H$_3$CHCHCHN) 9.6 (*C*H$_3$CH$_2$CON).

(4*R*,6*R*)-4-Hydroxy-6-phenylpiperidine-2-one (116)



To a stirred solution of (6*R*)-phenylpiperidine-2,4-dione (0.19 g, 0.98 mmol) in anhydrous dichloromethane (2 mL) at 0 ^{o}C under nitrogen, zinc borohydride (2.0 mL, 1.37 M, 2.74 mmol) was added. The mixture was then stirred at room temperature for 20 h. Water (5 mL) was then added to the mixture. The mixture was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was then recrystallised from isopropanol/hexane to give **116** (0.08 g, 43%) as white microprisms, mp 206-210 ^{o}C (lit.[91] 213 ^{o}C) ; R_f 0.36 (10% methanol/50% ethyl acetate/40% chloroform); $[\alpha]^{25}_{D}$ = +53.3 (*c* 1.20, MeOH) (lit.[91] $[\alpha]^{20}_{D}$ = +52.3 *c* 0.88, MeOH); IR ν_{max} 3269 (O-H), 2896 (C-H), 1648 (amide C=O), 1319, 1069, 761, 699 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 7.38-7.28 (5H, m, Ph) 4.51 (1H, dd, *J*= 11.6, 4.3 Hz, C_6H) 4.12-4.10 (1H, m, C_4H) 2.71 (1H, ddd, *J*= 17.1, 5.6, 2.3

Hz, C_3H) 2.33-2.26 (2H, m, C_3H + C_5H) 1.62 (1H, ddd, *J*= 15.6, 11.6, 10.8 Hz, C_5H); ^{13}C NMR (500 MHz, CD_3OD) δ 174.1 (C_2) 143.5 (ArC) 129.8 (ArC) 129.0 (ArC) 127.4 (ArC) 65.6 (C_4) 56.2 (C_5) 42.7 (C_6) 41.4 (C_3); m/z (Cl+) 192 (100%, $M+H^+$); HRMS $C_{11}H_{14}NO_2$ calcd. 192.1025, found 192.1028.

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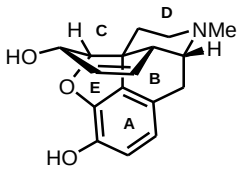
CHAPTER 2

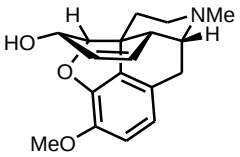
Synthesis of Codeine and Piperidin-4-ones

2.1 Introduction

Codeine, also called 3-methylmorphine, is an analgesic opium alkaloid that has long been used to alleviate pain and relieve coughing. Codeine has attracted the interest of synthetic chemists due to its compact pentacyclic structure; it contains a phenyl ring (A ring), two unsaturated cyclohexane rings (B and C rings), a piperidine ring (D ring), and a dihydrofuran ring (E ring). Since the first total synthesis of codeine reported by Gates[1] in 1956, various syntheses have been described by several groups[2–7] in the last fifty years. However, most syntheses are long and of little commercial use; of the racemic syntheses, only Magnus' and Rice's are practical.[8,9]



(-)-Morphine

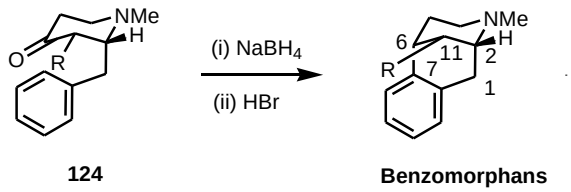


(-)-Codeine

Figure 2.1 Structure of (-)-morphine and (-)-codeine

2.1.1 Conversion of 2,3-Disubstituted Piperidin-4-ones into Benzomorphans by the Grewe Cyclisation

The benzomorphan ring system (Scheme 2.1) is a substructure in morphine, codeine and related alkaloids and thus has important pharmacological properties.[10] The benzomorphan ring is mostly synthesized by Grewe cyclisation of a benzene ring onto an alcohol at C-6, thereby forming the 6,7-bond (Scheme 2.1). 2,3-Disubstituted piperidin-4-ones **124** would be key for the syntheses of opium alkaloids such as codeine, which requires assembly of the demanding 2,3,4-trisubstitued piperidine ring (D ring, Figure 2.1). Reduction of piperidin-4-ones **124** followed by Grewe cyclisation would afford the benzomorphan system; with a suitable 2-substituent, the cyclohexenol ring (C ring) could be assembled. However, syntheses of 2,3-disubstituted piperidin-4-ones are not routine and involve many steps, few being enantioselective. The groups of Meyers,[11] Marazano,[12] and Comins,[10] have addressed that but their strategies have not been advanced beyond the synthesis of alkyl-substituted benzomorphans. Thus, it was of interest to develop a general route to 2,3-disubstituted piperidin-4-ones **124**.

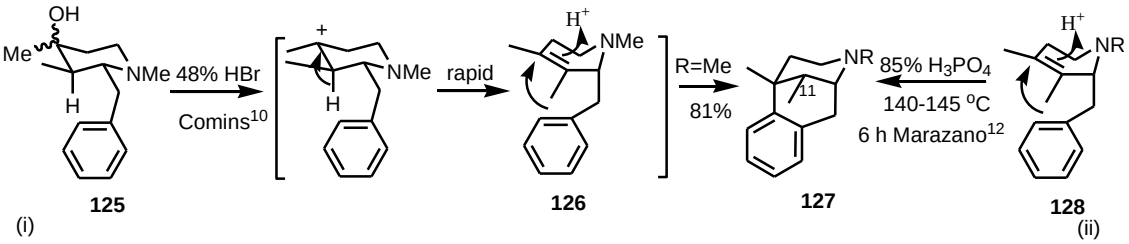


124 **Benzomorphans**

Scheme 2.1 A Grewe cyclisation to benzomorphans

Comins[10] prepared the benzomorphan **127** from **125** which has the *trans*-configuration (Scheme 2.2, eq (i)) suggesting that direct cyclisation of the tertiary carbocation is not the correct mechanism for Grewe cyclisation, since only the equatorial methyl group at

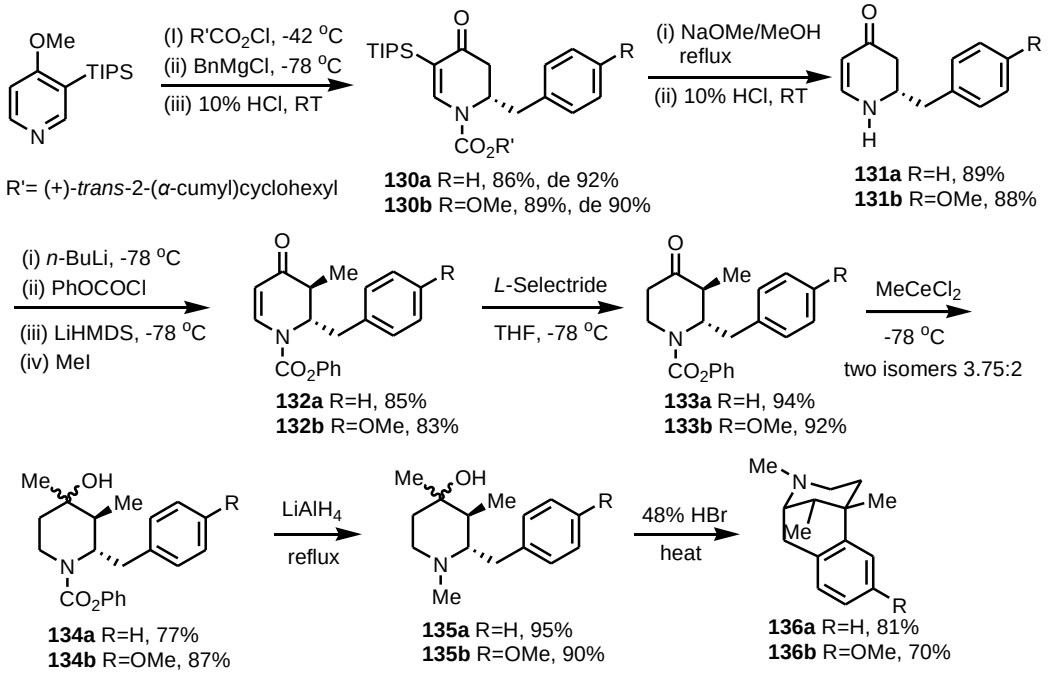
C-11 was found in the product **127**. It is proposed that the tetrasubstituted alkene **126**, as in eq (i), is formed first and then *trans*-diaxial protonation-cyclisation undergoes to give the product **125** with solely equatorial C-11 methyl group (Scheme 2.2). Therefore, it is believed that both *cis*- and *trans*-2,3-disubstituted piperidin-4-ones would undergo Grewe cyclisations, and thus afford benzomorphans.



Scheme 2.2 Proposed mechanism for Grewe cyclisations

2.1.2 Comins' Asymmetric Synthesis of Benzomorphans

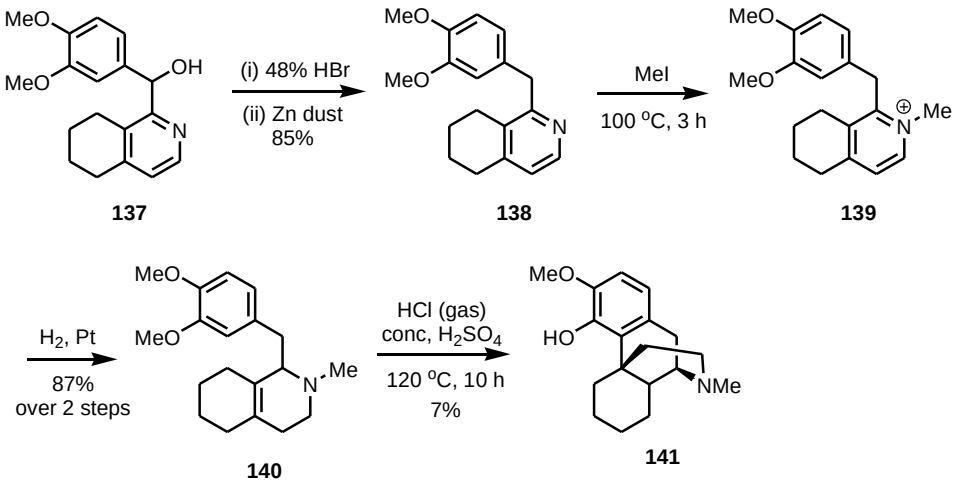
In 1999, Comins described an asymmetric synthesis of benzomorphans (Scheme 2.3).[10] Asymmetric alkylation of 4-methoxy-3-(triisopropylsilyl)pyridine with benzylic Grignard reagents was induced by the addition of the chiral auxiliary to afford dihydropyridones **130** (Scheme 2.3). After the removal of the chiral auxiliary and triisopropylsilyl group, methylation using LiHMDS and then olefinic reduction using *L*-selectride were performed to give 2,3-disubstituted piperidin-4-ones **133**. Methylation of the ketone and then reduction of the *N*-protective group gave 4-hydroxypiperidines **135** which were ready for a Grewe cyclisation to afford enantiopure benzomorphans **136**. However, only a methyl group was introduced at C-11 and so assembly of the complete structure of codeine or other opium alkaloids using this route was not addressed.



Scheme 2.3 Comins' asymmetric synthesis of benzomorphans **136**[10]

2.1.3 Grewe's Total Synthesis of Tetrahydrodeoxycodeine

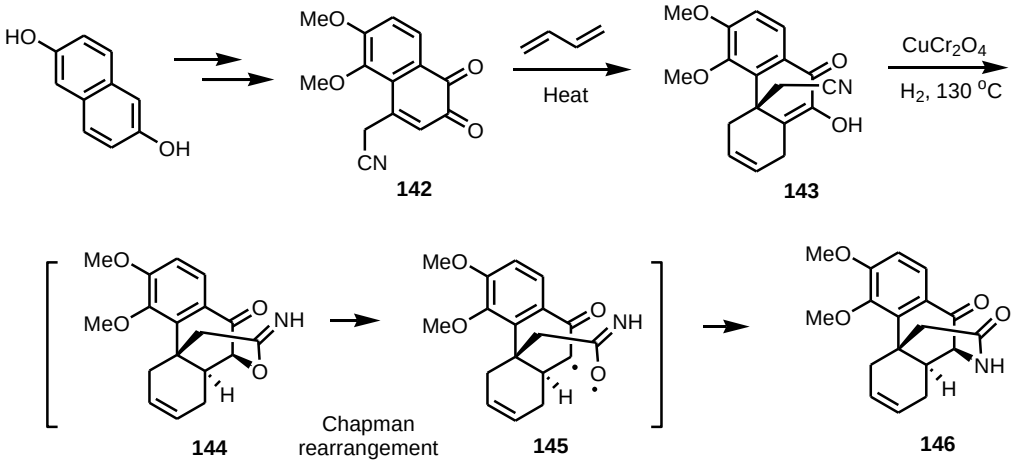
In 1949, Grewe reported the total synthesis of the tetrahydrodeoxycodeine **141** (Scheme 2.4).[13] **137** was first treated with 48% HBr in acetic acid at room temperature for 24 hours; zinc dust was then added to the mixture and stirred at 25-30 °C for 2 hours to give **138** in 85% yield. *N*-Methylation of **138** by heating with methyl iodide at 100 °C for 3 hours afforded **139** which was then hydrogenated over platinum to give **140** in 87% over two steps. Grewe cyclisation was performed by bubbling hydrogen chloride gas through a solution of **140** in concentrated sulfuric acid at 120 °C for 10 hours to give the tetrahydrodeoxycodeine **141** in 7% yield. Although the yield of **141** was quite low, this synthesis showed the potential of a Grewe cyclisation to synthesize codeine and benzomorphans.



Scheme 2.4 Synthesis of the tetrahydrodeoxycodeine **141** via a Grewe cyclisation

2.1.4 Key Steps in Gates' Total Synthesis of Codeine

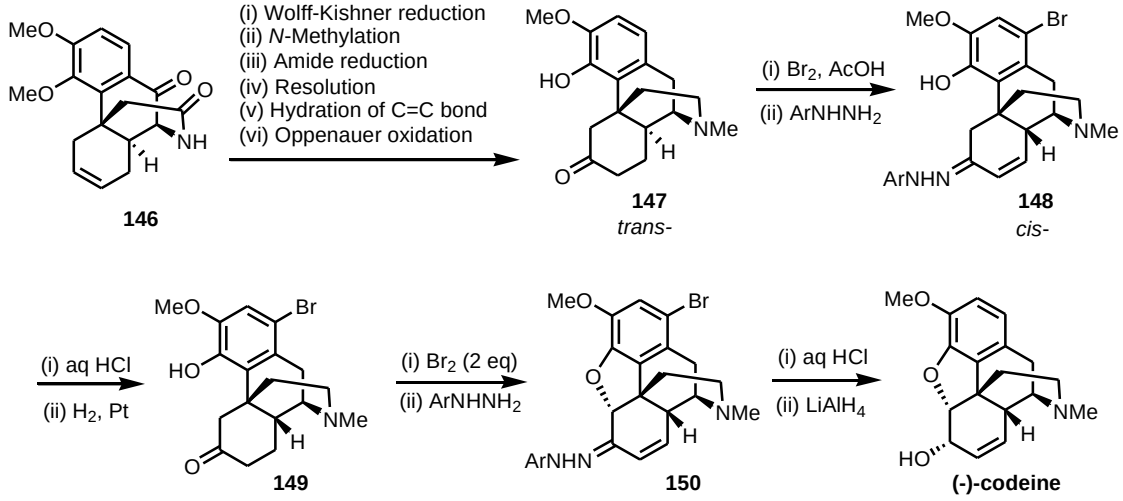
In 1956, the first total synthesis of (-)-codeine was described by Gates, and involved resolution.[1] Diels-Alder addition of **142** with 1,3-butadiene was used to constuct the cyclohexene ring (C ring). Reductive cyclisation of **143** using copper chromite under hydrogen afforded the keto lactam **146** (construction of piperidine ring D, Scheme 2.5).



Scheme 2.5 Formation of the tetracyclic intermediate **146**

Through a series of reactions shown in Scheme 2.6, the keto lactam **146** was converted into the *β*-dihydrothebainone **147**. However, since *β*-dihydrothebainone **147** had the inappropriate *trans*-configuration, epimerisation was required, and was achieved

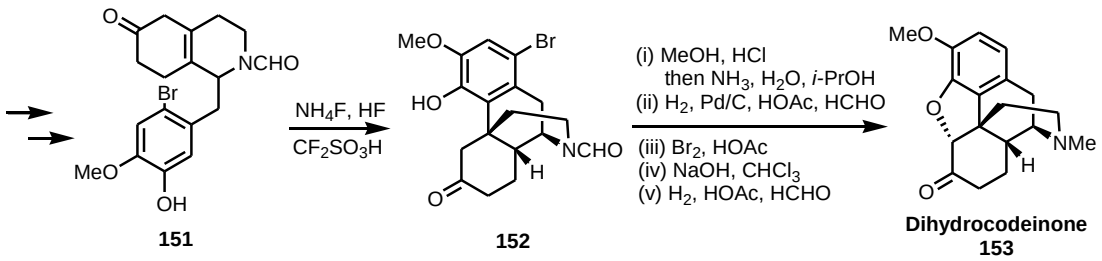
through the preparation of the *α,β*-unsaturated hydrazone **148** which was hydrolysed to give *cis*-fused 1-bromodihydrothebainone (**149**). Dibromination of **149** (2 equivalents of bromine) afforded the *α*-bromo ketone that under the basic conditions underwent cyclisation to the dihydrofuran E ring and hence **150**. After the hydrolysis of the hydrazone under acidic conditions to give the corresponding enone, treatment with lithium aluminium hydride reduced the ketone and debrominated the aromatic ring, affording (-)-codeine. This total synthesis involves 31 steps and requires resolution to generate enantiopure (-)-codeine.



Scheme 2.6 Gates' total synthesis

2.1.5 Key Steps in Rice's Formal Synthesis of (±)-Codeine

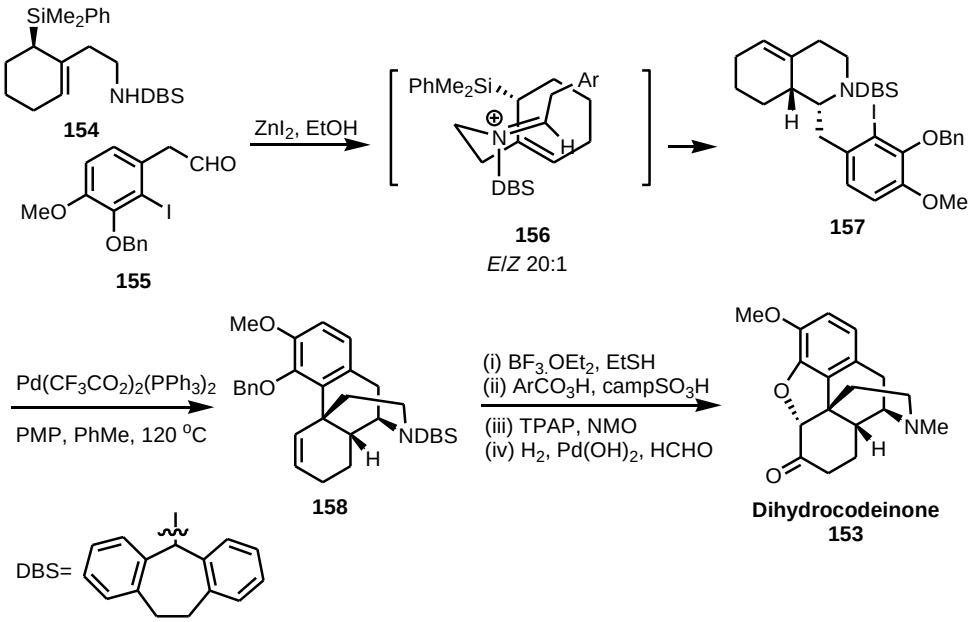
In 1980, Rice described the shortest formal synthesis of (±)-codeine (Scheme 2.7), at that time.[14] The key step is the Grewe cyclisation of **151** to give the morphinan **152**. A series of reactions including *N*-deprotection, debromination, dihydrofuran E ring formation (bromination and displacement), and *N*-methylation of **152** were performed to give the dihydrocodeinone **153** which was converted into (±)-codeine in five steps. The overall yield of the synthesis of (±)-**153** was 29%.



Scheme 2.7 Synthesis of dihydrocodeinone **153** via a Grewe cyclisation

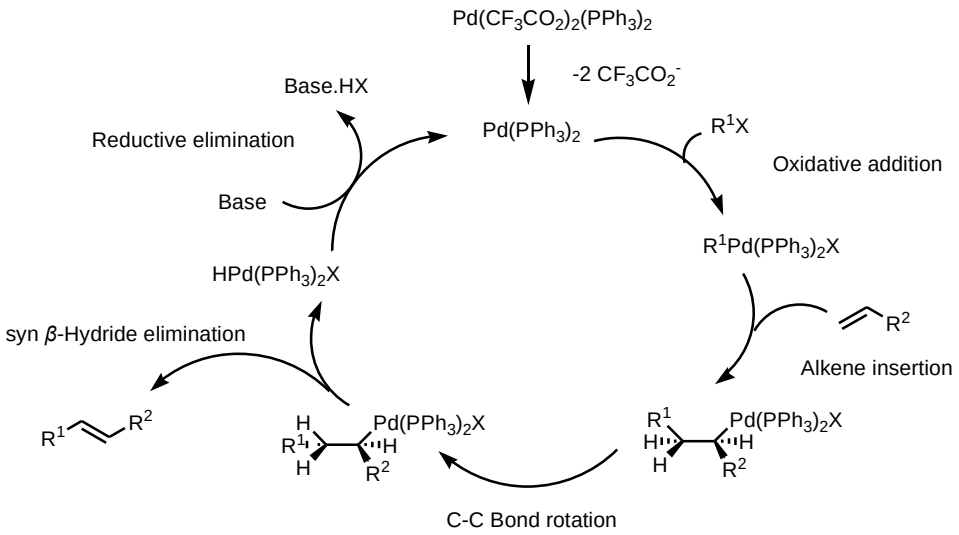
2.1.6 Outline of Overman's Formal Synthesis of Codeine

In 1993, Overman described the formal synthesis of (-)-codeine which employed an enantioselective catechol borane reduction as a source of asymmetric induction.[3] In the presence of zinc iodide, reaction of the amine **154** with the arylacetaldehyde **155** gave the iminium intermediate **156** which underwent an iminium-allylsilane cyclisation to give the octahydroisoquinoline **157** in excellent ee (formation of piperidine D ring, Scheme 2.8). The second key step was the intramolecular Heck reaction of **157** which gave the morphinan **158**. After the formation of dihydrofuran E ring (by epoxidation[15] and subsequent intramolecular displacement), oxidation of the alcohol, and hydrogenolysis of the *N*-DBS group, the dihydrocodeinone **153** was obtained. The most characteristic feature of this synthesis is the use of an intramolecular Heck reaction to construct the cyclohexene B ring instead of a Grewe cyclisation.



Scheme 2.8 Synthesis of the dihydrocodeinone **153** via an intramolecular Heck reaction

The mechanism of the Heck reaction is shown in Scheme 2.9. The first step is the oxidative addition of palladium(0) to the R^1-X bond. The second step is the syn addition of the palladium complexes to alkenes. C-C bond rotation permits a *syn-β*-hydride elminiation, resulting in (*E*)-alkenes. Reductive elimination regenerates the palladium(0) compound and the cycle continues.



Scheme 2.9 Mechanism of the Heck reaction

Other total syntheses of codeine by different strategies have been reported; for example, Parker (2006) described a tandem radical cyclisation that constructed both the dihydrofuran E ring and the cyclohexene B ring; the piperidine D ring was formed by a reductive hydroamination.[5] The source of asymmetric induction was a catechol borane reduction, as in Overman's synthesis.[3] Metz's racemic synthesis (2011) employed a nitrone cycloaddition followed by an Eschenmoser–Claisen rearrangement to construct the cyclohexene B ring and the piperidine D ring.[7] However, no asymmetric synthesis of (-)-codeine of commercial application has yet been described.

2.2 Results and Discussion

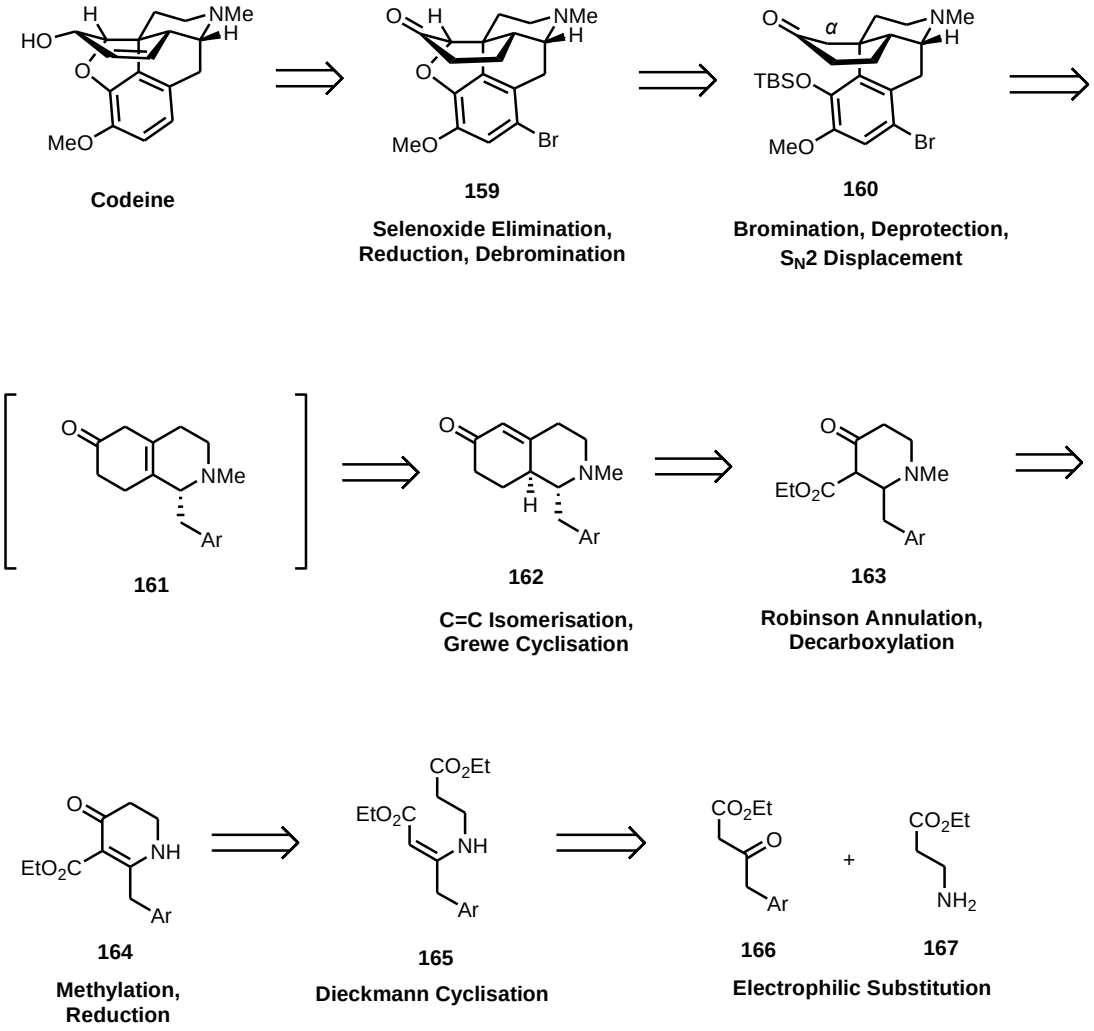
2.2.1 Retrosynthetic Analysis of Codeine

The retrosynthetic plan to codeine is shown in Scheme 2.1. The allylic alcohol unit of codeine would be converted from a ketone of **159** via selenoxide elimination-ketone reduction following White's synthesis.[4] A bromine atom would be introduced to the aryl ring to define the location for a Grewe cyclisation to occur; debromination would occur concurrently with the ketone reduction by treating **159** with lithium aluminium hydride to afford codeine.[4]

Disconnection of the dihydrofuran ring of **159** would give **160**; a bromine would be added to the *alpha* carbon of the ketone (marked in diagram) of **160** as a leaving group which would then be displaced by the hydroxy group of the aryl ring (after TBS-deprotection using TBAF) to form the pentacyclic structure of **159** (similar strategy as Metz's synthesis).[7]

A Grewe cyclisation[16] of **162** was planned for assembling the cyclohexane B ring of **160**. By treating **162** with acid, C=C bond isomerisation would occur to give the *β*,γ-unsaturated ketone (**161**); Grewe cyclisation would then take place to give **160** in the presence of acid.

162 would be derived from the piperidin-4-one **163** via a Robinson annulation; while **163** itself would be prepared from the 5,6-dihydro-4-pyridone **164** via *N*-methylation and C=C reduction. A Dieckmann cyclisation[17] would be employed to make **164** from the diester **165**; while **165** would be prepared by an electrophilic substitution of the *β*-keto ester **166** and the *β*-amino ester **167**.

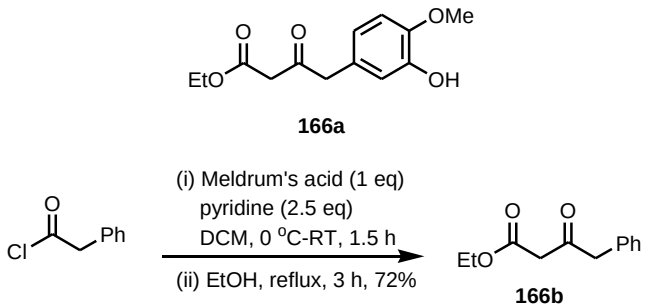


Scheme 2.10 Retrosynthetic analysis of codeine

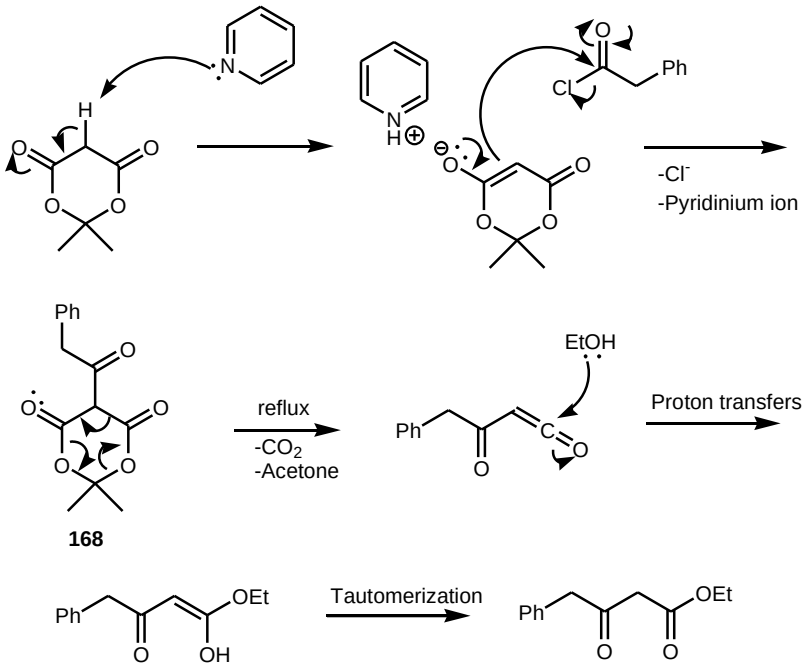
2.2.2 Synthesis of the 5,6-Dihydro-4-pyridone **172a** by a Dieckmann Cyclisation

The synthesis of codeine started with the preparation of the *β*-keto ester **166a**. This could be done by an acylation of 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) with subsequent heating.[18] For the fully-substituted aromatic ring of codeine, the aryl group of the *β*-keto ester **166a** should contain functionality appropriate to the desired 3-hydroxy and 4-methoxy groups (Scheme 2.11). In our studies, the *β*-keto ester **166b** with an unsubstituted phenyl group was prepared first to test the feasibility of first few steps. Once the route to benzomorphans was developed, the *β*-keto ester **166** with a substituted aryl group would be used to synthezise codeine.

Meldrum's acid was acylated with phenylacetyl chloride using pyridine to give an adduct which was then heated under reflux in ethanol to afford the *β*-keto ester **166b** in 72% (Scheme 2.11); and the mechanism is shown in Scheme 2.12. Pyridine deprotonates the *alpha* carbon of the esters of the Meldrum's acid to give an enolate which attacks the acid chloride to form the adduct **168**. On heating, **168** decomposed to give the electrophilic ketene. Ethanol acts as the nucleophile, attacking the ketene to afford an enolate which is converted into the *β*-keto ester after tautomerization.



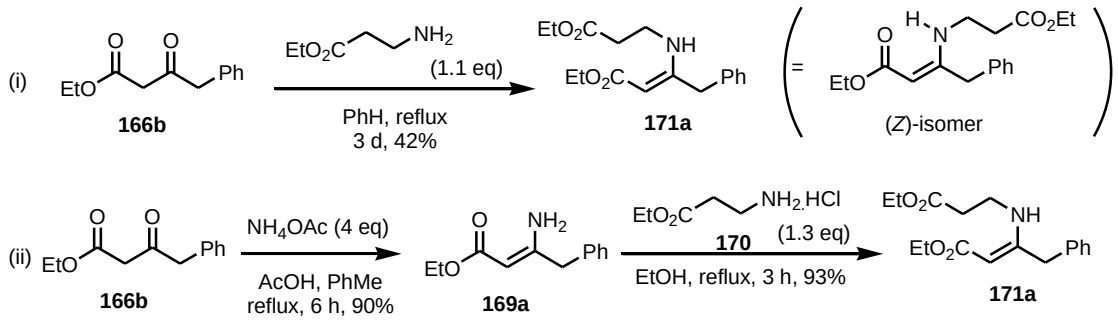
Scheme 2.11 Synthesis of the *β*-keto ester **166b**



Scheme 2.12 Mechanism of acylation using Meldrum's acid

Amination of the *β*-keto ester **166b** with *β*-alanine ethyl ester by heating under reflux in benzene with the azeotropic removal of water afforded the diester **171a** in 42% yield (Scheme 2.13).[19] Since the yield was not satisfactory and the reaction time was long (3 days), another route to the diester **171a** was sought.

The *β*-keto ester **166b** was condensed with ammonium acetate to give the enamino ester **169a** in 90% yield (procedure modified from Karg's synthesis).[20] *β*-Alanine ethyl ester (**170**) then displaced the amine group to afford the diester **171a** in 93% yield as described by Becker (Scheme 2.13).[17] The yield was excellent because the by-product ammonium chloride is precipitated from ethanol, thereby shifting the equilibrium to the right. Only the *cis*-isomer of **171a** was obtained because there is hydrogen bonding between the ester and the amine in this conformation (Scheme 2.13).[21]

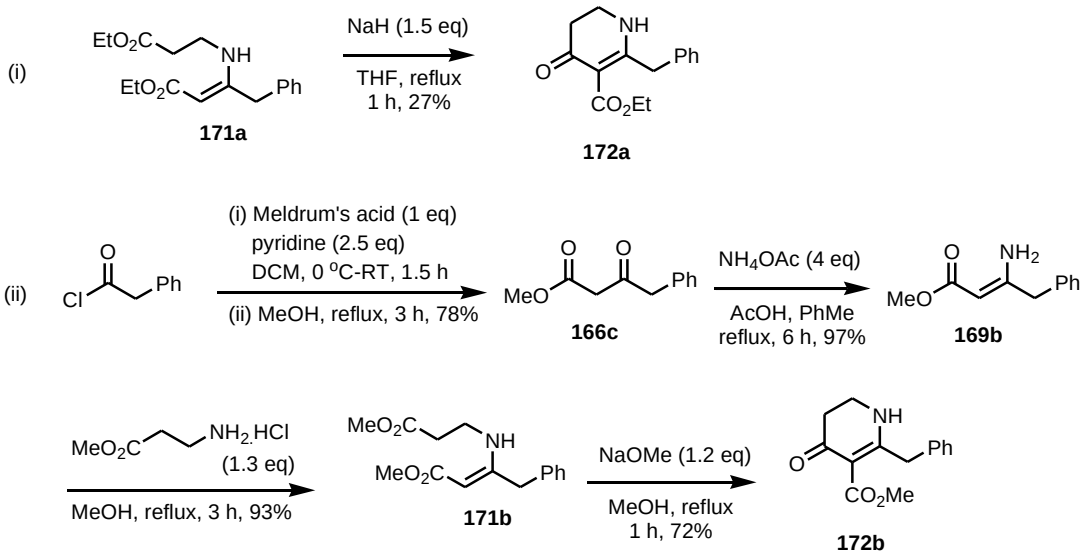


Scheme 2.13 Synthesis of the diester **171a**

Several attempts at Dieckmann cyclisations of the diethyl ester **171a** were made but the 5,6-dihydro-4-pyridone **172a** was isolated in low yield (Table 2.1). Cyclisation using sodium hydride gave a poor yield (27%, Scheme 2.14). In our studies, the Dieckmann cyclisation proceeded much better with high concentrations of reactants. Although the yield was better (56%) when sodium methoxide was used, incomplete trans-esterification occurred. Pure sodium ethoxide solution could not be obtained in high concentration while more dilute solution (0.6 M) was not efficient (25% yield). Accordingly, ethoxide ion was generated by adding *tert*-butoxide to ethanol. Potassium *tert*-butoxide was not efficient (28%) while sodium *tert*-butoxide provided a moderate yield of **172a** (50%). These studies show that the counter ion participates in the reaction and that sodium facilitates the cyclisation.

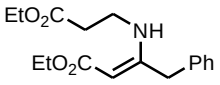
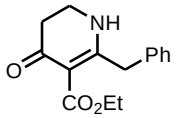
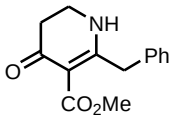
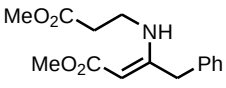
In order to achieve a higher yield of 5,6-dihydro-4-pyridones, synthesis of the methyl ester analog **172b** was attempted since Becker had reported that in 84% yield using sodium methoxide.[17] The yields of the *β*-keto ester **166c**, the enamino ester **169b**, and the diester **171b** were similar to those of the ethyl analogs (78%, 97%, and 93% respectively, Scheme 2.14). Dieckmann cyclisation of the dimethyl ester **171b** using sodium methoxide gave the 5,6-dihydro-4-pyridone **172b** in 72% yield, much higher than that using other reagents. In other syntheses, the aryl group is often introduced by

metalation which is not so convenient on a large scale; whereas our route is suitable for a large scale synthesis, since this does not involve the use of any air-sensitive reagents.



Scheme 2.14 Dieckmann cyclisations to 5,6-dihydro-4-pyridones

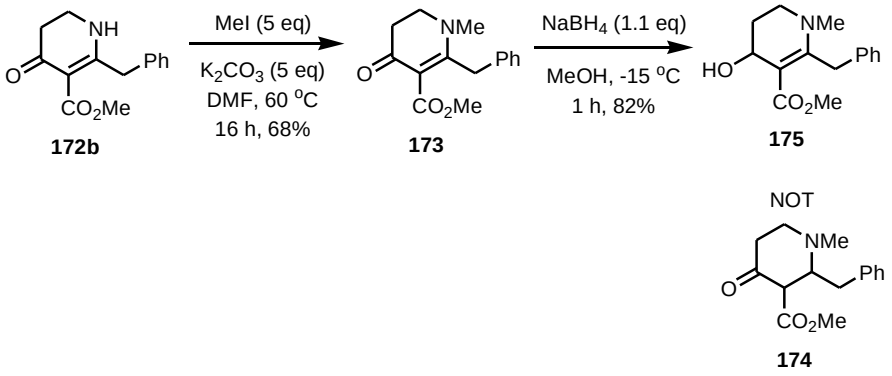
Table 2.1 Dieckmann cyclisations of enamino esters

Entry	Substrate	Reaction conditions	Product
1	 **171a**	NaH (1.5 eq) THF, reflux, 1h	 **172a**, 27%
2	**171a**	Na (1.3 eq), MeOH reflux, overnight	 **172b** mixture of **172b**, and **172a**, ~8:1, 56%
3	**171a**	Na (1.3 eq), EtOH reflux, overnight	**172a**, 25%
4	**171a**	KO*t*-Bu (2 eq), EtOH reflux, overnight	**172a**, 28%
5	**171a**	NaO*t*-Bu (2 eq), EtOH reflux, overnight	**172a**, 50%
6	 **171b**	Na (1.3 eq), MeOH reflux, overnight	**172b**, 72%

2.2.3 Reduction of the 5,6-Dihydro-4-pyridone **172b** to the Piperidin-4-one **174**

N-Methylation of the 5,6-dihydro-4-pyridone **172b** using methyl iodide and potassium carbonate proceeded in 68% yield. The methylated product **173** was reduced by sodium borohydride but ketone reduction, instead of the desired C=C bond reduction, took place to give the unwanted 4-hydroxy-1,4,5,6-tetrahydro-4*H*-pyridine **175** in 82%

yield (Scheme 2.15). Diisobutylaluminium hydride was also employed but ketone reduction occurred again.[22]

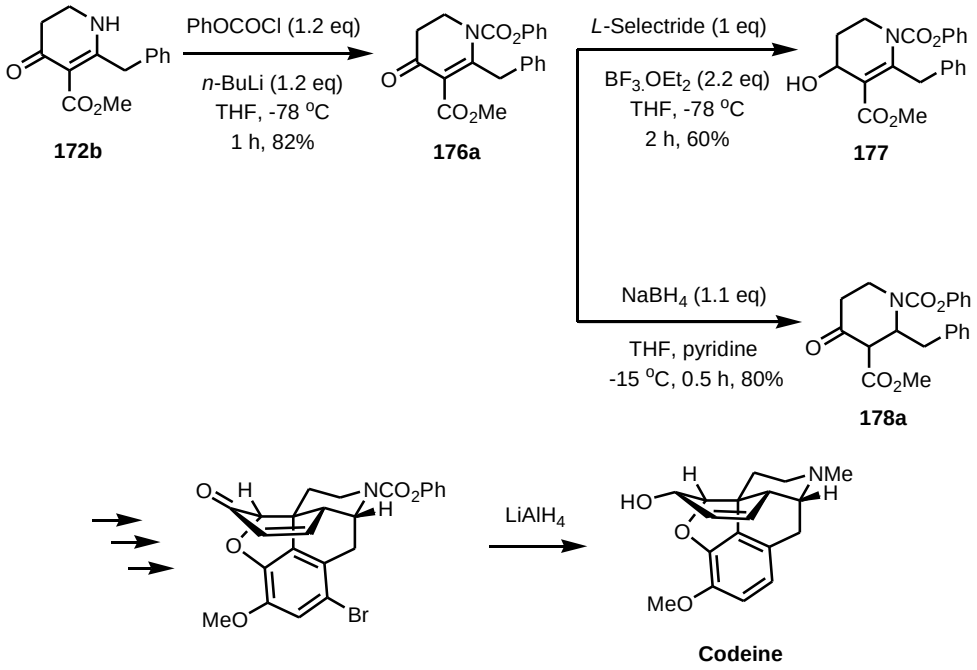


Scheme 2.15 Reduction of the 5,6-dihydro-4-pyridone **173**

Comins has shown that similar 5,6-dihydro-4-pyridones were reduced by *L*-selectride to give piperidin-4-ones, once the amino group was deactivated by a phenoxycarbonyl group;[23] the electron-withdrawing nature of the deactivating group makes the C=C bond more electrophilic, so that it is attacked by hydride. Accordingly, the amino group of **172b** was deactivated by reacting with *n*-butyllithium and phenylchloroformate to give **176a** (82%). However, *L*-selectride reduced the ketone instead of the C=C bond to give the undesired 4-hydroxy-5,6-dihydro-4*H*-pyridine **177** in 60% yield (Scheme 2.16). Undesired reduction of the ketone also occurred when sodium borohydride in methanol was employed (91%).

A literature survey revealed that Schultz and co-workers had reduced the C=C bond in a protected dihydropyridones related to **176a** using sodium borohydride in an aprotic solvent at low temperature; they reported that ketone reduction took place predominantly at room temperature while olefinic reduction was the major reaction at -15 °C. [24] Once the C=C bond was reduced, further ketone reduction was suppressed by adding benzaldehyde to quench the remaining sodium borohydride prior to acidic

workup.[24] In our hands, it was found that the C=C bond of the 5,6-dihydro-4-pyridone **176a** was selectively reduced to afford the desired piperidin-4-one **178a** in 80% yield. If required, the deactivating *N*-phenoxycarbonyl group would be reduced into the desired *N*-methyl group by lithium aluminium hydride at the last step concurrently with the ketone reduction to afford codeine (Scheme 2.16).

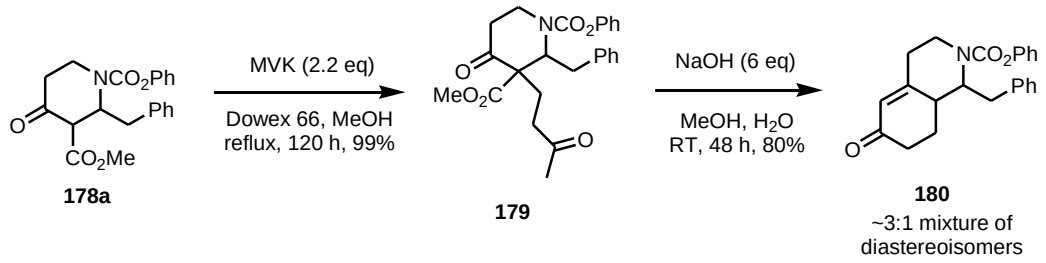


Scheme 2.16 Reduction of the 5,6-dihydro-4-pyridone **176a**

2.2.4 Robinson Annulation of the Piperidin-4-one **178a**

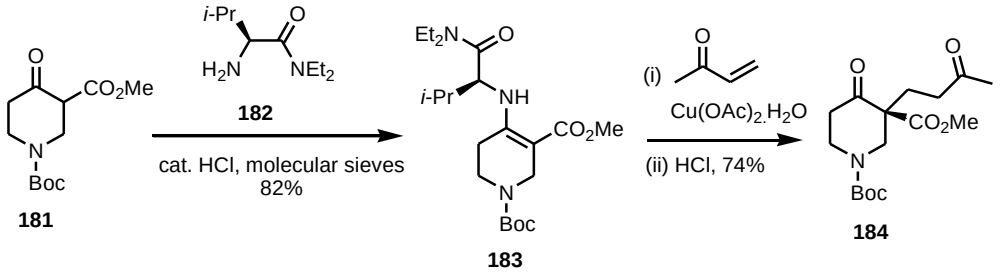
Rodriguez reported that the anionic resin Dowex 66 promoted Michael addition of cyclic *β*–keto esters with methyl vinyl ketone.[25] In our hands, by employing the anionic resin, the Michael adduct **179** was prepared from **178a** in 99% yield (Scheme 2.17). When the reaction was scaled up to gram scale, the yield dropped to 70%. Claisen condensation of the Michael adduct **179** using sodium hydroxide gave the cyclised product **180** in 80% yield as a 3:1 mixture of diastereoisomers. The major isomer of

180 would be *cis*-isomer so that both bulky groups are equatorial.



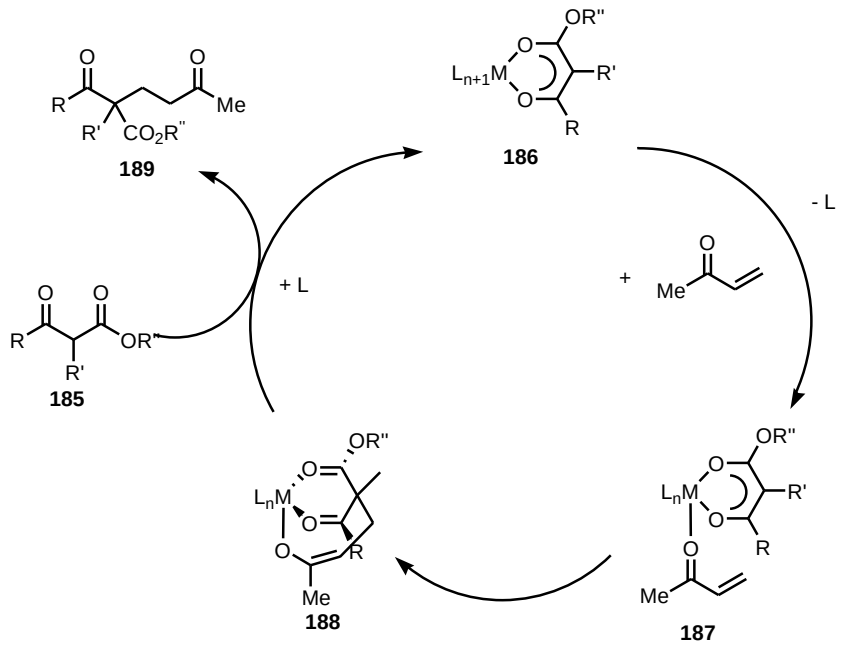
Scheme 2.17 Robinson annulation of the piperidin-4-one **178a**

Christoffers developed an asymmetric copper-catalyzed Michael addition of a related *N*-protected 3-methoxycarbonylpiperidin-4-one with methyl vinyl ketone using *L*-valine diethylamide (**182**) as the chiral auxiliary (Scheme 2.18).[26] It would be useful if this can be applied to synthesize enantiopure (-)-codeine.



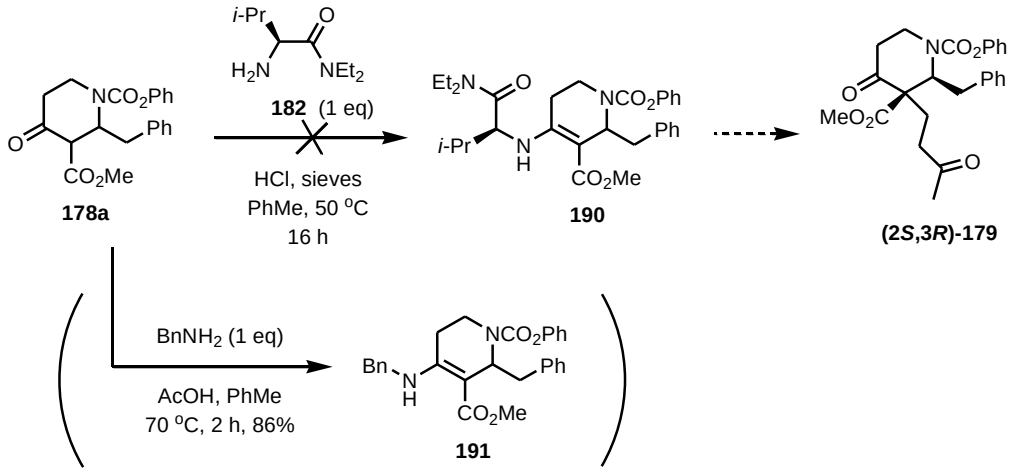
Scheme 2.18 *L*-Valine derivative-induced asymmetric Michael reaction[26]

The mechanism of metal-catalyzed Michael reaction was proposed by Christoffers and is shown in Scheme 2.19.[27,28] The metal would form complexes **186** with *β*-keto esters **185**. By ligand exchange, methyl vinyl ketone would coordinate at a vacant site of metal to form **187**. The function of the metal catalyst is to bring two reactants close to each other and to activate methyl vinyl ketone by the Lewis acidity of the metal. Once the Michael reaction has occurred, the adducts **189** leave the metal and other *β*-keto esters **185** would form complexes with the metal again.[27,28] With the presence of the chiral auxiliary, methyl vinyl ketone would coordinate to the metal at the opposite side of the bulky isopropyl group of the auxiliary to give the enantiopure adduct **184**.



Scheme 2.19 Proposed mechanism of metal-catalyzed Michael reaction

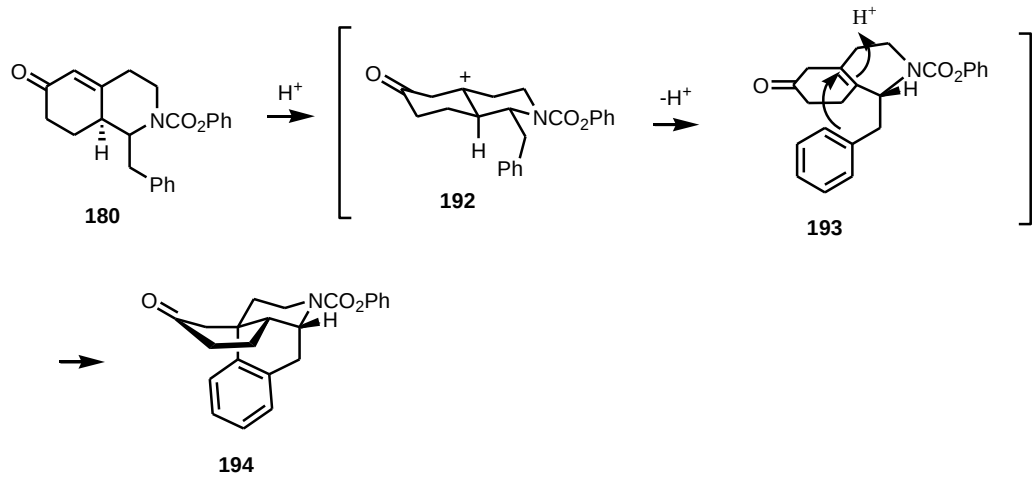
Amination of the piperidin-4-one **178a** with *L*-valine diethylamide **182** was attempted following the Christoffers' procedure[26] but a complex mixture resulted and no desired product **190** could be isolated (Scheme 2.20). Amination of the piperidin-4-one **178a** with benzylamine gave the enamine **191** in 86% yield but the enamine **190** could not be prepared under the same conditions. Since there is difficulty in making the enamine **190**, the asymmetric Michael reaction was abandoned and the cyclohex-2-enone ring of **180** was cyclised by the original route involving the use of the anionic resin Dowex 66.



Scheme 2.20 Attempted amination with the chiral auxiliary **182**

2.2.5 Attempted Grewe Cyclisation to Give the Benzomorphan **194**

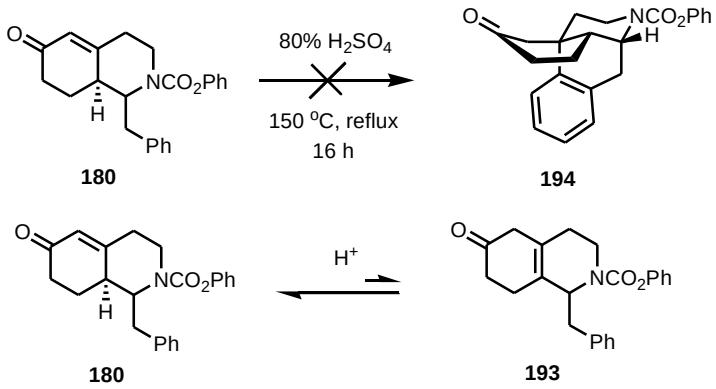
It was proposed to prepare the benzormorphan **194** from **180** by treatment with acid, during which it was hoped that the olefinic bond of **180** would isomerise to give the β,γ-unsaturated ketone **193**, an ideal substrate for a Grewe cyclisation that would afford the benzomorphan **194** (Scheme 2.21).



Scheme 2.21 Proposed Grewe cyclisation to the benzomorphan **194**

However, a Grewe cyclisation using 80% sulphuric acid with heating under reflux was

attempted but decomposition occurred. Other acids such as hydrochloric acid were employed but none gave the desired product. Wang reported that *β*,γ-unsaturated ketones underwent Grewe cyclisation whereas *α*,*β*-unsaturated ketone such as **180** did not.[29] It is because under acidic conditions, the equilibrium shifts towards the *α*,*β*-unsaturated ketone **180** and almost no *β*,γ-unsaturated ketone **193** is formed (Scheme 2.22).[9,14,29] Thus, an effective way to convert the *α*,*β*-unsaturated ketone **180** into a *β*,γ-unsaturated ketone is needed for the benzomorphan synthesis. However, further investigation was not undertaken due to time limitation.

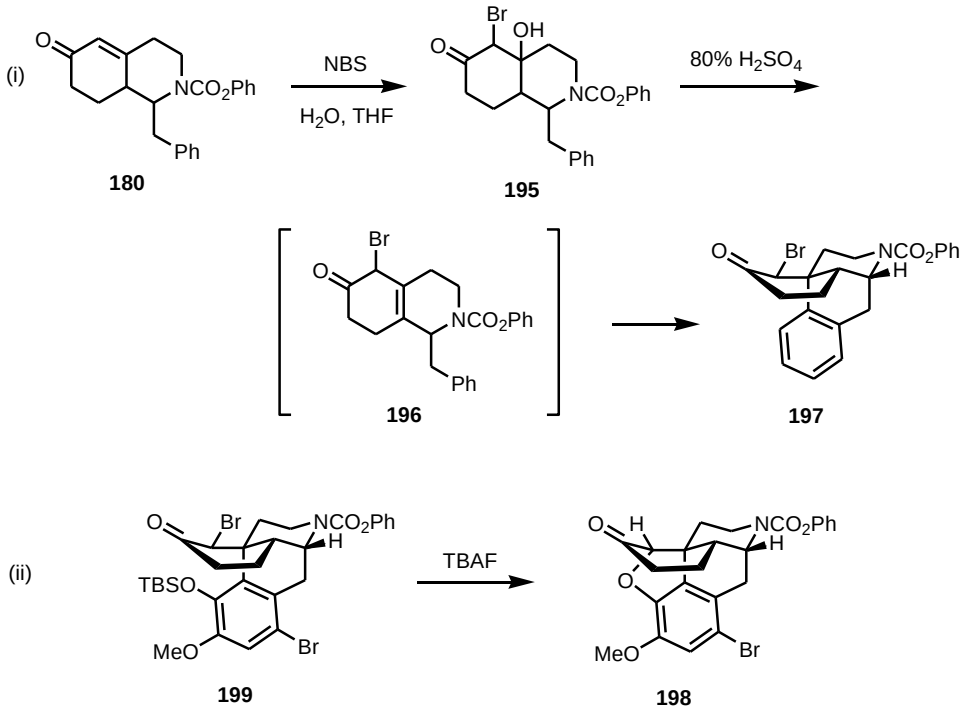


Scheme 2.22 Attempted Grewe cyclisation

2.2.6 Modified Synthetic Plan for Codeine

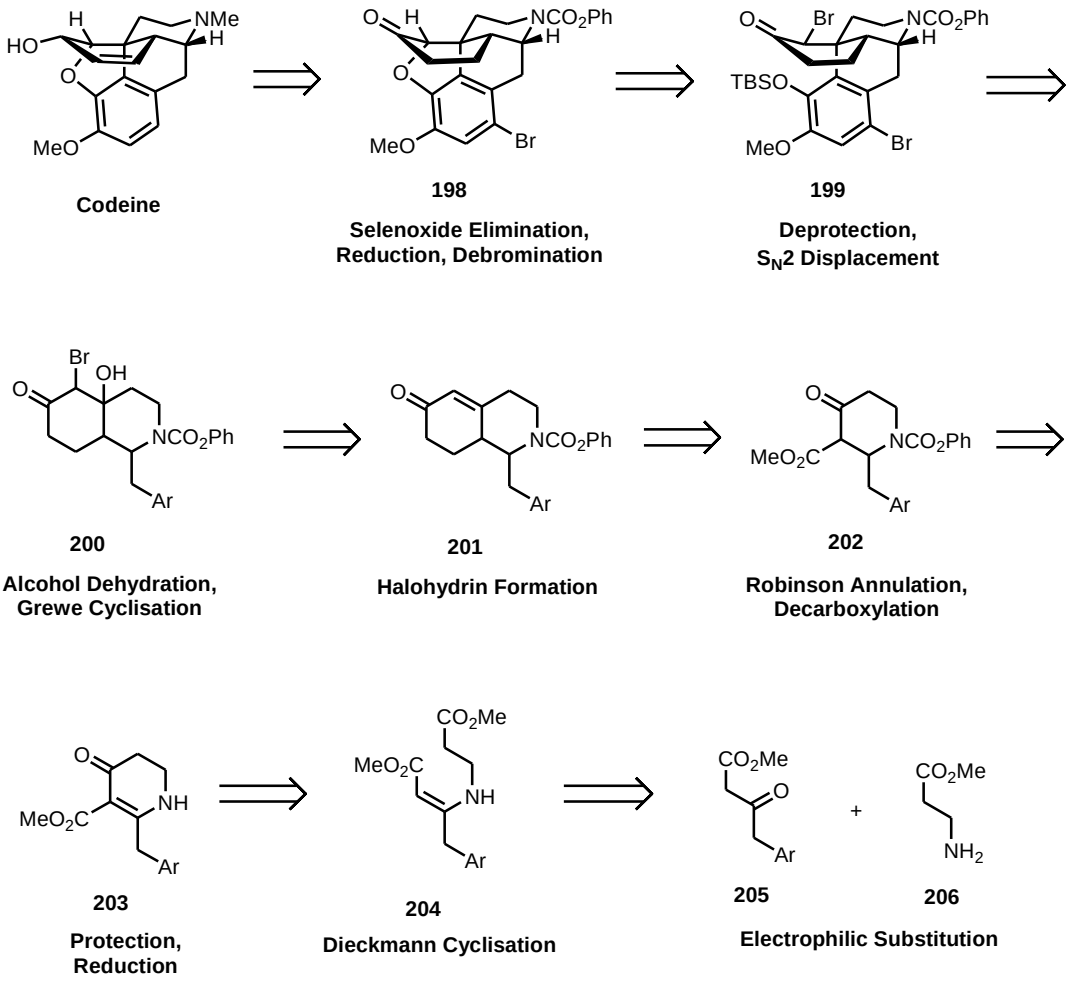
One possible solution would be the conversion of the *α*,*β*-unsaturated ketone **180** into the halohydrin **195** which would be a potential substrate for Grewe cyclisation. When the halohydrin **195** was treated with acid, dehydration would take place to form the *β*,γ-unsaturated ketone **196** (Scheme 2.23, eq i). The formation of the unwanted *α*,*β*-unsaturated ketone would be avoided since the olefinic bond formed would be thermodynamically less stable due to the presence of the electron-withdrawing bromine. Grewe cyclisation of **196** could occur to afford the benzormorphan **197**.

Moreover, the bromine atom would be ideally located for the construction of the dihydrofuran ring by intramolecular etherification (Scheme 2.23, eq ii).



Scheme 2.23 Proposed Grewe cyclisation of the halohydrin **195**

If the benzormorphan **197** can be prepared from the halohydrin **195**, it is believed that codeine can be synthesized by this route because the formation of the dihydrofuran ring of **198** is related to that of the Metz's synthesis;[7] while the final selenoxide elimination-reduction sequence giving codeine is close to White's synthesis (Scheme 2.24).[4] This route would be 12-13 steps, much shorter than most of the total syntheses of codeine (usually over 20 steps). An enantioselective synthesis of codeine would also be feasible if an asymmetric Michael addition of **202** could be developed.

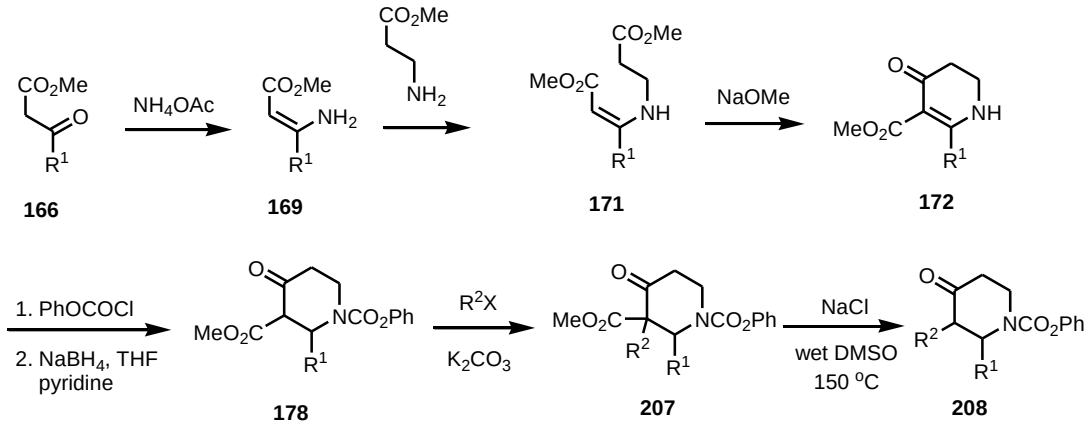


Scheme 2.24 New retrosynthetic plan for codeine

2.2.7 Attempted Synthesis of 2,3-Disubstituted Piperidin-4-ones

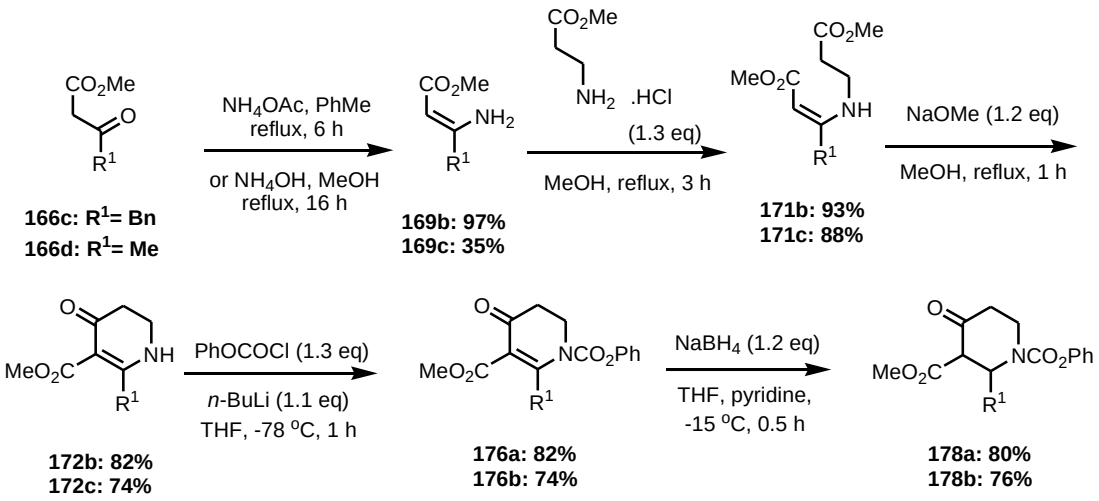
Since 2,3-disubstitued piperidin-4-ones could be key compounds for the synthesis of benzomorphans and opium alkaloids as discussed in the Section 2.1.1, it was of interest to develop a general route which does not involve many steps. In Section 2.2.3, the 2-benzyl 3-methoxycarbonylpiperidin-4-one **178a** was prepared as an intermediate in the synthesis of codeine. Therefore, synthesis of different 2,3-disubstituted piperidin-4-ones **208** using a related route was attempted (Scheme 2.25). The same strategy was applied for the preparation of 3-methoxycarbonylpiperidin-4-ones **178**

from *β*-keto esters **166**. Alkylation of **178** with alkyl halides following decarboxylation would afford 2,3-disubstituted piperidin-4-ones **208**. This would be a powerful route since different 2,3-disubstituted piperidin-4-ones could be prepared from simple starting materials such as *β*-keto esters **166** and *β*-alanine methyl ester only.



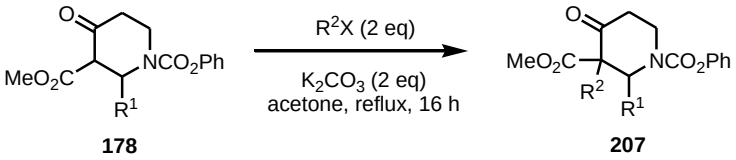
Scheme 2.25 Proposed route to 2,3-disubstituted piperidin-4-ones **208**

Two *β*-keto esters **166** (R^1 being a methyl and a benzyl) were employed to see whether 2,3-disubstituted piperidin-4-ones **208** could be made by the proposed route (Scheme 2.26). Amination of the *β*-keto ester **166c** with ammonium acetate gave the enamine **169b** in 97% yield;[20] while amination of the *β*-keto ester **166d** with ammonium hydroxide gave the enamine **169c** in 35% yield (procedure modified from Hansen's synthesis).[30] Displacement of enamines **169** with *β*-alanine methyl ester afforded diesters **171** in excellent yields which were then cyclised by sodium methoxide to give 5,6-dihydro-4-pyridones **172** (82% and 74% respectively).[17] *N*-Protection of 5,6-dihydro-4-pyridones **172** using phenylchloroformate proceeded well (82% and 74%, procedure modified from Comins' synthesis).[23] Olefinic reduction using sodium borohydride in anhydrous THF at -15 ^oC afforded 3-methoxycarbonylpiperidin-4-ones **178** in good yields (procedure modified from Schultz's synthesis).[24]



Scheme 2.26 Synthesis of piperidin-4-ones **178**

With 3-methoxycarbonylpiperidin-4-ones **178** in hand, 3-substitution could be attempted using alkyl halides and potassium carbonate (Scheme 2.27). Methylation using methyl iodide gave excellent yields (around 90% for both substrates, Scheme 2.27); while allylation using allyl bromide proceeded well (around 70% for both substrates). If removal of the methoxycarbonyl group of **207** can be achieved, different 2,3-disubstituted piperidin-4-ones **208** can be made by this route.

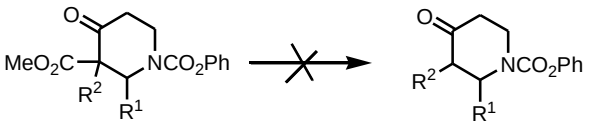


178 **207**

Cpd	R^1	R^2X	yield (%)
178a	Bn	Methyl iodide	89
178a	Bn	Allyl bromide	74
178b	Me	Methyl iodide	88
178b	Me	Allyl bromide	70

Scheme 2.27 Alkylations of piperidin-4-ones **178**

Krapcho decarboxylation of **207** using lithium chloride in wet DMSO was attempted but no reaction took place.[31] Decarboxylation under neutral conditions by heating under reflux in acetonitrile was also tried but not successful.[32] Various reagents including hydrochloric acid, TFA,[33] and sodium hydroxide were investigated but none were effective (Scheme 2.28). In view of these surprising difficulties encountered, this route to 2,3-disubstituted piperidin-4-ones **208** was abandoned.



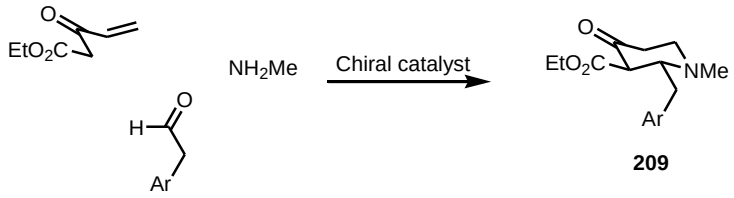
207 **208**

Entry	Conditions
1	LiCl (1.1 eq), H_2O (2 eq), DMSO, reflux, 4 h
2	MeCN, 1% H_2O, reflux, 3 h
3	5% HCl, water, reflux, 3 h
4	TFA, PhMe, MeOH, reflux, 4 h
5	NaOH, MeOH, H_2O, RT, 2 d

Scheme 2.28 Attempted decarboxylation of the piperidin-4-ones **207**

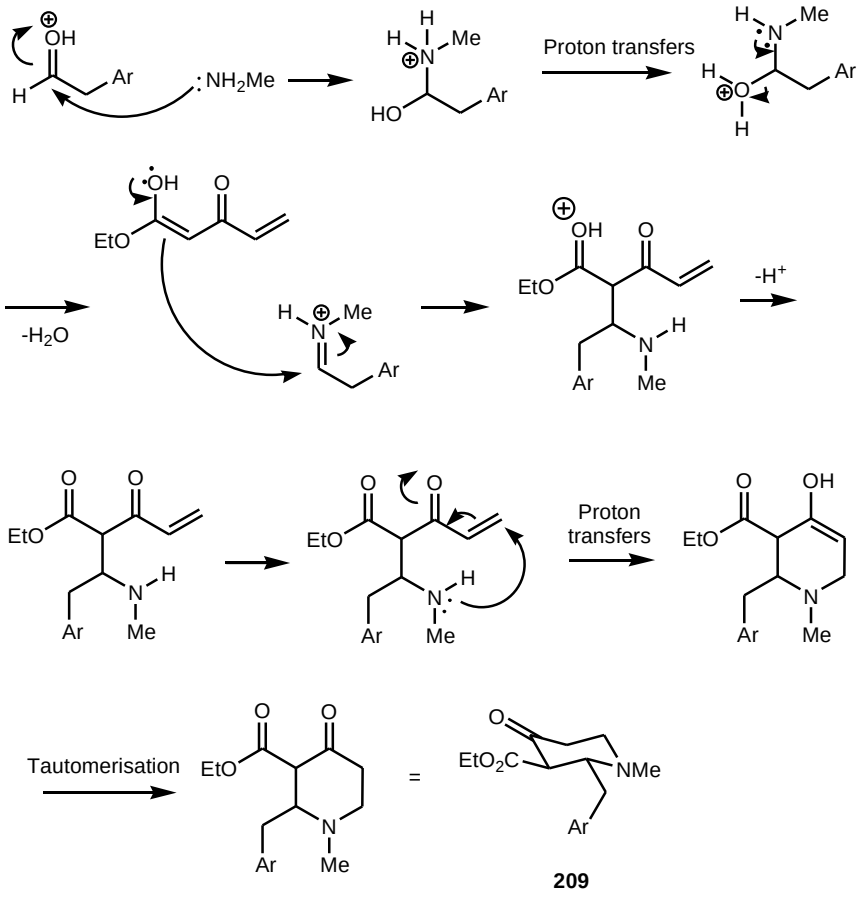
2.2.8 Future Work

Hohenlohe-Oeringen described a one-pot synthesis of the piperidin-4-one **209,** which is closely related to **202**, using Nazarov's reagent (ethyl 3-oxo-4-pentenoate) via a tandem Mannich aza-Michael cyclisation, achieved in 29% (scheme 2.29).[34] With the advent of asymmetric Mannich reactions, it is possible to make piperidin-4-ones enantioselectively.[35,36] Chiral imines, β-keto esters, or catalysts could be potential reagents for such enantioselective condensations. If the important intermediate **202** could be synthesized asymmetrically in one step by this tandem Mannich aza-Michael cyclisation, the synthetic route of (-)-codeine would be greatly shortened.



Scheme 2.29 A one-pot enantioselective synthesis of the piperidin-4-one **209** via a tandem Mannich aza-Michael cyclisation

The mechanism of a tandem Mannich aza-Michael cyclisation is shown in Scheme 2.30. Methylamine reacts with the aldehyde to give an iminium ion via an electrophilic substitution. The enol form of ethyl 3-oxo-4-pentenoate attacks the iminium ion to afford an adduct. An intramolecular Michael addition undergoes to afford the piperidin-4-one **209**.

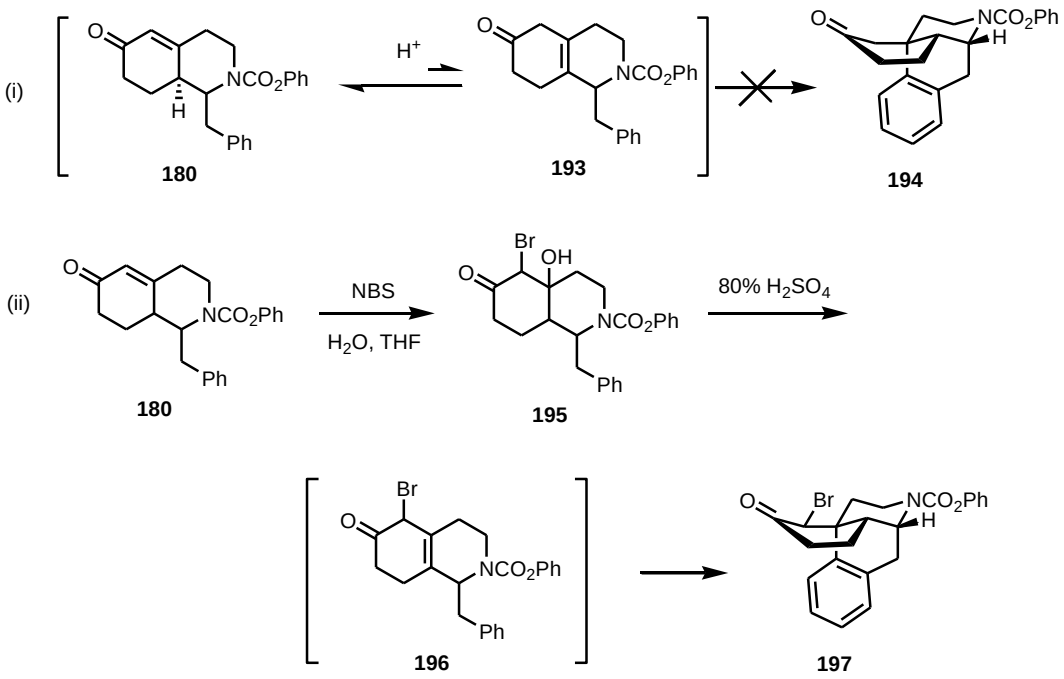


Scheme 2.30 Mechanism of tandem Mannich aza-Michael cyclisation

2.3 Conclusions

The main objective was to develop a synthetic route to codeine with a relatively short path; the retrosynthetic plan is shown in Scheme 2.24. The bicyclic compound **180** was prepared by a Robinson annulation from the piperidin-4-one **178a**. The original plan was to make the benzomorphan **194** by treating **180** with acid (Scheme 2.31). However, C=C bond isomerisation of **197** did not occur to give the *β*,γ-unsaturated ketone **193** under acidic conditions; thus, no Grewe cyclisation to afford the benzomorphan **194** could be attempted. Owing to time limitations, further investigation was not undertaken.

It was proposed that the halohydrin **195** would undergo a Grewe cyclisation to give the benzomorphan **197** under acidic conditions. The formation of the unwanted *α*,*β*-unsaturated ketone is avoided since the olefinic bond formed would be thermodynamically less stable due to the presence of the electron-withdrawing bromine (Scheme 2.31). If this happens, it is very likely that codeine can be synthesized by this route because the remaining steps have similar strategies as White's and Metz's syntheses.[4,7]

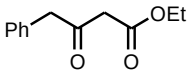


Scheme 2.31 Proposed Grewe cyclisation to benzomorphan **197**

Synthesis of 2,3-disubstituted piperidin-4-ones **208** from *β*-keto esters **168** using a related route was attempted (Scheme 2.26). Although different 2,3-disubstituted 3-methoxycarbonylpiperidin-4-ones **207** were prepared, there was difficulty with the removal of the methoxycarbonyl group and therefore, this route was abandoned.

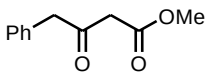
2.4 Experimental

Ethyl 3-oxo-4-phenylbutanoate (166b)



To a stirred solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (14.4 g, 0.100 mol) in dichloromethane (60 mL) at 0 ℃, pyridine (20 mL, 0.247 mol) was added over 10 min. A solution of phenylacetyl chloride (13.3 mL, 0.100 mol) in dichloromethane (140 mL) was added over 30 min and the mixture was stirred at 0 ℃ for 30 min. The mixture was then allowed to warm to room temperature and stirred for a further 1 h. The solution was diluted with dichloromethane (200 mL), washed with water (4 x 300 mL), dried ($MgSO_4$), and evaporated. The orange solid was dissolved in ethanol (200 mL) and the solution was heated under reflux for 3 h. The solution was then evaporated to give an orange oil that was purified by flash chromatography (30% ethyl acetate/hexane) to give **166b** (14.9 g, 72%) as a pale yellow oil, R_f 0.69 (30% ethyl acetate/hexane); IR ν_{max} 2985 (C-H), 1743 (ketone C=O), 1717 (ester C=O), 1265, 1025, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.09 (5H, m, Ph) 4.20 (2H, q, J= 7.2 Hz, OCH_2) 3.83 (2H, s, CH_2Ar) 3.45 (2H, s, C$H_2CO_2CH_2$) 1.26 (3H, t, J= 7.2 Hz, CH_3CH_2O). Spectroscopic data were consistent with reported values in the literature.[37]

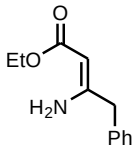
Methyl 3-oxo-1-phenylbutanoate (166c)[18]



To a stirred solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (6.20 g, 43.1 mmol) in dichloromethane (30 mL) at 0 ℃, pyridine (9 mL, 111 mmol) was added over 5 min. A

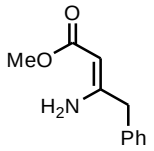
solution of phenylacetyl chloride (5.73 mL, 43.1 mmol) in dichloromethane (70 mL) was added over 10 min and the mixture was stirred at 0 ℃ for 30 min. The mixture was then allowed to warm to room temperature and stirred for a further 1 h. The solution was diluted with dichloromethane (100 mL), washed with water (4 x 150 mL), dried ($MgSO_4$), and evaporated to give an orange solid which was dissolved in methanol (150 mL) and the solution was heated under reflux for 3 h. The solution was then evaporated. The resulting orange oil was purified by flash chromatography (30% ethyl acetate/hexane) to give **166c** (6.41 g, 78%) as a pale yellow oil, R_f 0.8 (30% ethyl acetate/hexane); IR ν_{max} 2954 (C-H), 1744 (ketone C=O), 1715 (ester C=O), 1436, 1260, 1201 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60-7.19 (5H, m, Ph) 3.82 (2H, s, CH_2Ar) 3.71 (3H, s, OCH_3) 3.46 (2H, s, C$H_2CO_2CH_3$).

Ethyl 3-amino-4-phenylbut-2-enoate (169a)[20]



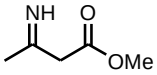
Ethyl 3-oxo-1-phenylbutanoate (11.8 g, 57.0 mmol), ammonium acetate (20.0 g, 0.259 mol), and acetic acid (5 mL) were dissolved in dry toluene (150 mL). The solution was heated under reflux for 6 h with the azeotropic removal of water. The mixture was allowed to cool to room temperature, then washed with saturated aqueous sodium hydrogen carbonate (30 mL), dried (Na_2SO_4), and evaporated to give **169a** (10.5 g, 90%) as a pale orange oil, R_f 0.79 (30% ethyl acetate/hexane); IR ν_{max} 3437 (N-H), 3332 (N-H), 2979 (C-H), 1717 (ester C=O), 1663 (C=C), 1613, 1265, 1153, 1039, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49-7.22 (5H, m, Ph) 4.64 (1H, s, CHCOO) 4.12 (2H, q, J= 7.2 Hz, CH_2CH_3) 3.46 (2H, s, CH_2Ar) 1.26 (3H, t, J= 7.2 Hz, CH_3CH_2O).

Methyl 3-amino-4-phenylbut-2-enoate (169b)[20]



Methyl 3-oxo-1-phenylbutanoate (4.00 g, 20.8 mmol), ammonium acetate (8.02 g, 0.104 mol), and acetic acid (2 mL) were dissolved in dry toluene (70 mL). The solution was heated under reflux for 6 h with the azeotropic removal of water. The mixture was allowed to cool to room temperature, then washed with saturated aqueous sodium hydrogen carbonate (15 mL), dried (Na_2SO_4), and evaporated to give **169b** (3.85 g, 97%) as a pale orange gum, R_f 0.45 (30% ethyl acetate/hexane); IR ν_{max} 3449 (N-H), 3333 (N-H), 2947 (C-H), 1716 (ester C=O), 1665 (C=C), 1613, 1449, 1266, 1156, 1030, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36-7.22 (5H, m, Ph) 4.65 (1H, s, CHCOO) 3.65 (3H, s, OCH_3) 3.47 (2H, s, CH_2Ar).

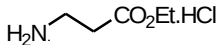
Methyl 3-iminobutanoate (169c)



To a solution of methyl 3-oxobutanoate (2.00 g, 17.4 mmol) in methanol (8 mL) was added 0.880 ammonia solution (2 mL, 70 mmol) dropwise. The mixture was heated under reflux for 16 h. The mixture was allowed to cool to room temperature and evaporated. The resulting solution was extracted with chloroform (3 x 10 mL). The combined organic layers were evaporated to give **169c** (0.70 g, 35%) as white microprisms, mp 76-79 ℃ (lit.[38] mp 81-83 ℃); R_f 0.72 (50% ethyl acetate/hexane); IR ν_{max} 3319 (N-H), 2953 (C-H), 1735 (ester C=O), 1436, 1201, 1174, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.92 (1H, br s, NH) 4.52 (2H, s, C$H_2CO_2CH_3$) 3.63 (3H, s, OCH_3)

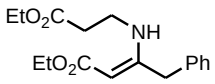
1.90 (3H, s, C*H*$_3$CNH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 170.6 (*C*OOCH$_3$) 159.9 (CNH) 83.8 (*C*H$_2$CO$_2$Me) 50.2 (OCH$_3$) 22.4 (*C*H$_3$CNH). Spectroscopic data were consistent with reported values in the literature.[38]

Ethyl 3-aminopropanoate hydrochloride (170)[37]



To a stirred solution of *β*-alanine (17.8 g, 0.200 mol) in ethanol (50 mL) in a salt-ice bath, thionyl chloride (32.8 g, 0.275 mol) was added dropwise via an addition funnel. The resulting solution was stirred for 2 d at room temperature. Acetone (50 mL) was added and the solution was left to crystallize. Filtration, washing with acetone and then with diethyl ether gave **206** (29.0 g, 94%) as white microprisms, mp 58-59 ℃ (lit.[39] mp 58 ℃); IR ν_{max} 3402 (N-H), 2981 (C-H), 1722 (ester C=O), 1614, 1378, 1212, 1021 cm^{-1}.

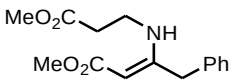
Ethyl 3-(2-ethoxycarbonylethyl)amino-4-phenylbut-2-enoate (171a)[17]



To ethyl 3-amino-4-phenylbut-2-enoate (4.50 g, 21.9 mmol) in ethanol (5 mL) was added ethyl 3-aminopropanoate hydrochloride (4.33 g, 28.2 mmol). The mixture was heated under reflux for 3 h, then allowed to cool to room temperature and diluted with diethyl ether (10 mL). The solution was filtered and the filtrate was evaporated to give **171a** (6.05 g, 93%) as an orange oil, R_f 0.79 (30% ethyl acetate/hexane); IR ν_{max} 3445 (N-H), 2980 (C-H), 1729 (ester C=O), 1650 (C=C), 1599, 1373, 1181, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (1H, br d, *J*= 6.6 Hz, NH) 7.33-7.19 (5H, m, Ph) 4.49 (1H, s, CHCOO) 4.18-4.05 (4H, m, 2 x CH$_2$OOC) 3.57 (2H, s, C*H*$_2$Ar) 3.39 (2H, q, *J*=

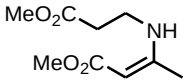
6.6 Hz, CH_2NH) 2.35 (2H, t, *J*= 6.6 Hz, CH_2COO) 1.27-1.19 (6H, m, 2 x CH_3CH_2).

Methyl 3-(2-methoxycarbonylethyl)amino-4-phenylbut-2-enoate (171b)[17]



To methyl 3-amino-4-phenylbut-2-enoate (4.50 g, 23.5 mmol) in methanol (5 mL) was added methyl 3-aminopropanoate hydrochloride (3.94 g, 28.2 mmol) and the solution was heated under reflux for 3 h. The mixture was allowed to cool to room temperature and diluted with diethyl ether (10 mL). The solution was filtered and the filtrate was evaporated to give **171b** (6.05 g, 93%,) as an orange oil, R_f 0.56 (30% ethyl acetate/hexane); IR ν_{max} 3345 (N-H), 2951 (C-H), 1734 (ester C=O), 1653 (C=C), 1598, 1435, 1246, 1165, 729, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (1H, br d, *J*= 6.6 Hz, NH) 7.33-7.22 (5H, m, Ph) 4.51 (1H, s, =CHCOO) 3.68 (3H, s, OCH_3) 3.64 (3H, s, OCH_3) 3.57 (2H, s, CH_2Ar) 3.39 (2H, q, *J*= 6.6 Hz, CH_2NH) 2.36 (2H, t, *J*= 6.6 Hz, CH_2COO).

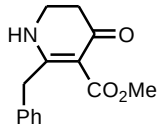
Methyl 3-(2-methoxycarbonylethyl)aminobut-2-enoate (171c)[17]



To methyl 3-aminobut-2-enoate (2.00 g, 17.4 mmol) in methanol (3 mL) was added methyl 3-aminopropanoate hydrochloride (2.80 g, 20.9 mmol) and the solution was heated under reflux for 3 h. The mixture was allowed to cool to room temperature and diluted with diethyl ether (8 mL). The solution was filtered and the filtrate was evaporated. The pale yellow oil was purified by flash chromatography (20% ethyl acetate/hexane) to give **171c** (3.06 g, 88%,) as a colourless oil, R_f 0.30 (30% ethyl acetate/hexane); IR ν_{max} 3346 (N-H), 2952 (C-H), 1734 (ester C=O), 1651 (C=C), 1599,

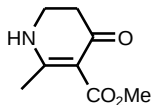
1436, 1166, 1047, 783, 701 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (1H, br d, J= 6.7 Hz, NH) 4.43 (1H, s, CHCOO) 3.68 (3H, s, OCH_3) 3.58 (3H, s, OCH_3) 3.48 (2H, q, J= 6.7 Hz, CH_2NH) 2.54 (2H, t, J= 6.7 Hz, CH_2COO) 1.90 (3H, s, CH_3CH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 171.8 (*C*$OOCH_3$) 170.8 (*C*$OOCH_3$) 161.4 (=CNH) 82.8 (*C*H=CNH) 52.0 (OCH_3) 50.1 (OCH_3) 38.6 (CH_2NH) 35.3 (*C*H_2COO) 19.3 (*C*H_3CNH).

2-Benzyl-5,6-dihydro-3-(methoxycarbonyl)-4-pyridone (172b)[17]



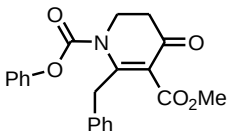
To methyl 3-(2-methoxycarbonylethyl)amino-4-phenylbut-2-enoate (9.57 g, 34.5 mmol) in methanol (7 mL) was added sodium methoxide in methanol (17.8 mL, 38.0 mmol, 2.14 M) and the solution was heated under reflux for 6 h under nitrogen. The mixture was allowed to cool to room temperature and evaporated. The resulting brown residue was purified by flash chromatography (5% ethanol/ethyl acetate) to give **172b** (6.05 g, 72%) as white microprisms, mp 116-117 ^{o}C (lit.[17] mp 116-118 ^{o}C); R_f 0.13 (ethyl acetate); IR ν_{max} 3239 (N-H), 2855 (C-H), 1691 (ketone C=O), 1616, 1452, 1288, 1218 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.22 (5H, m, Ph) 5.69 (1H, br d, J= 2.8 Hz, NH) 4.08 (2H, s, CH_2Ar) 3.76 (3H, s, OCH_3) 3.49 (2H, td, J= 7.6, 2.8 Hz, CH_2NH) 2.47 (2H, t, J= 7.6 Hz, CH_2CO); ^{13}C NMR (300 MHz, $CDCl_3$) δ 188.7 (*C*OCH_2) 168.2 (*C*$OOCH_3$) 167.2 (=CNH) 135.2 (ArC) 129.5 (ArC) 129.4 (ArC) 129.0 (ArC) 128.9 (ArC) 127.5 (ArC) 103.2 (=*C*CO) 51.3 (CH_3O) 40.6 (*C*H_2CO) 39.5 (CH_2NH) 35.5 (CH_2Ph); m/z (Cl+) 268 (90%, M^+); HRMS $C_{14}H_{15}NO_3Na$ calcd. 268.0950, found 268.0960.

5,6-dihydro-3-(methoxycarbonyl)-2-methyl-4-pyridone (172c)[17]



To methyl 3-(2-methoxycarbonylethyl)aminobut-2-enoate (6.00 g, 29.8 mmol) in methanol (1.0 mL) was added sodium methoxide in methanol (20.4 mL, 32.8 mmol, 1.61 M) and the solution was heated under reflux for 6 h under nitrogen. The mixture was allowed to cool to room temperature and evaporated to give a brown residue which was purified by flash chromatography (10% ethanol/chloroform) to give **172c** (2.90 g, 58%) as white microprisms, mp 128-130 ^{o}C (lit.[17] mp 142-154 ^{o}C); R_f 0.35 (15% ethanol/chloroform); IR ν_{max} 3246 (N-H), 2947 (C-H), 1710 (ketone C=O), 1683 (ester C=O), 1569, 1390, 1218, 1169, 1110, 534 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (1H, br s, NH) 3.67 (3H, s, OCH_3) 3.54 (2H, t, J= 7.2 Hz, CH_2NH) 2.42 (2H, t, J= 7.2 Hz, CH_2CO) 2.35 (3H, s, CH_3CNH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 189.1 (*C*OCH_2) 168.9 (*C*OOCH_3) 167.3 (=CNH) 101.8 (=*C*CO) 50.9 (CH_3O) 40.3 (*C*H_2CO) 35.6 (CH_2NH) 22.0 (*C*H_3CNH); m/z (Cl+) 170 (100%, M+H^{+}) 138 (60%, M^{+}-OCH_3); HRMS $C_8H_{11}NO_3$ calcd. 170.0817, found 170.0813.

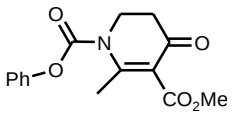
2-Benzyl-5,6-dihydro-3-(methoxycarbonyl)-1-(phenoxycarbonyl)-4-pyridone (176a)



To 2-benzyl-5,6-dihydro-3-(methoxycarbonyl)-4-pyridone (0.30 g, 1.22 mmol) in THF (9.4 mL) was added *n*-butyllithium (1.6 M in hexanes, 0.84 mL) dropwise at -78 ^{o}C under nitrogen and the mixture was stirred for 20 min. Phenyl chloroformate (0.2 mL,

1.59 mmol) was added to the mixture which was then stirred for 1 h at -78 ^{o}C. The mixture was quenched by addition of saturated aqueous sodium hydrogen carbonate (3 mL), after allowing to warm to room temperature, water (3 mL) was added. The mixture was extracted with diethyl ether (4 x 3 mL) and the combined organic layers were washed with brine (1.5 mL), dried ($MgSO_4$), and evaporated to give **176a** (0.32 g, 82%) as white microprisms, mp 109-112 ^{o}C; R_f 0.76 (50% ethyl acetate/hexane); IR ν_{max} 2951 (C-H), 1723 (ketone C=O), 1671 (ester C=O), 1591, 1581, 1296, 1254 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.22 (8H, m, Ph) 6.86-6.83 (2H, m, Ph) 4.24 (2H, s, C*H*$_2$Ar) 4.15 (2H, t, *J*= 6.5 Hz, CH_2N) 3.88 (3H, s, OCH_3) 2.73 (2H, t, *J*= 6.5 Hz, CH_2CO); ^{13}C NMR (300 MHz, $CDCl_3$) δ 190.6 (*C*OCH_2) 166.4 (*C*OOCH_3) 157.3 (CON) 151.3 (*C*CH_2) 150.1 (ArC) 136.0 (ArC) 129.6 (ArC) 128.9 (ArC) 128.8 (ArC) 127.3 (ArC) 126.4 (ArC) 122.6 (*C*CO) 121.2 (ArC) 52.8 (CH_3O) 47.2 (*C*H_2CO) 38.4 (CH_2N) 37.3 (CH_2Ar); m/z (Cl+) 388 (40%, M^+); HRMS $C_{21}H_{19}NO_5Na$ calcd. 388.1161, found 388.1146.

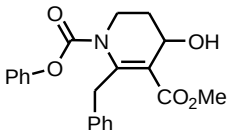
5,6-Dihydro-3-(methoxycarbonyl)-2-methyl-1-(phenoxycarbonyl)-4-pyridone (176b)



To 5,6-dihydro-3-(methoxycarbonyl)-2-methyl-4-pyridone (1.00 g, 5.91 mmol) in THF (120 mL) was added *n*-butyllithium (2.5 M in hexanes, 2.6 mL, 6.50 mmol) dropwise at -78 ^{o}C under nitrogen and the mixture was stirred for 20 min. Phenyl chloroformate (1.0 mL, 7.68 mmol) was added to the mixture which was then stirred for 1 h at -78 ^{o}C. The mixture was quenched by addition of saturated aqueous sodium hydrogen

carbonate (15 mL), after allowing to warm to room temperature, water (15 mL) was added. The mixture was extracted with diethyl ether (4 x 15 mL) and the combined organic layers were washed with brine (7 mL), dried ($MgSO_4$), and evaporated to give **176b** (1.26 g, 74%) as a pale yellow microprism, mp 152-155 ^oC; R_f 0.56 (50% ethyl acetate/hexane); IR ν_{max} 2952 (C-H), 1723 (ketone C=O), 1667 (ester C=O), 1587, 1348, 1249, 1189, 1154, 751 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (2H, dd, *J*= 7.8, 7.1 Hz, Ph) 7.26 (1H, t, *J*= 7.1 Hz, Ph) 7.13 (2H, d, *J*= 7.8 Hz, Ph) 4.22 (2H, t, *J*= 6.5 Hz, CH_2N) 3.82 (3H, s, OCH_3) 2.63 (2H, t, *J*= 6.5 Hz, CH_2CO) 2.42 (3H, s, CH_3CN); ^{13}C NMR (500 MHz, $CDCl_3$) δ 190.0 (*C*OCH_2) 166.6 (*C*$OOCH_3$) 156.2 (ArC) 151.7 (CON) 150.3 (*C*CH_3) 129.5 (ArC) 126.5 (ArC) 121.3 (ArC) 120.8 (*C*CO) 52.7 (CH_3O) 46.3 (*C*H_2CO) 36.8 (CH_2N) 21.1 (CH_3C); m/z (Cl+) 290 (100%, $M+H^+$) 258 (24%, M^+-OCH_3); HRMS $C_{15}H_{15}NO_5$ calcd. 290.1028, found 290.1026.

2-Benzyl-4-hydroxy-3-(methoxycarbonyl)-1-(phenoxycarbonyl)-1,4,5,6-tetrahydro-4*H*-pyridine (177)

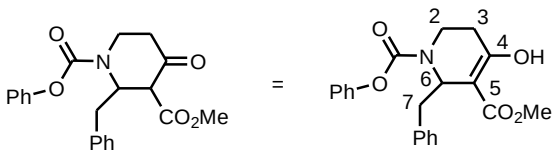


(a) Using *L*-selectride: To 2-benzyl-5,6-dihydro-3-(methoxycarbonyl)-1-(phenoxycarbonyl)-4-pyridone (0.31 g, 0.85 mmol) in THF (8.8 mL) was added borontrifluoride diethyletherate (0.24 mL, 1.95 mmol) dropwise at -78 ^oC under nitrogen and the mixture was stirred for 1 h. *L*-selectride (0.84 mL, 0.85 mmol) was added to the mixture which was then stirred for 2 h at -15 ^oC. The mixture was quenched by adding saturated aqueous sodium hydrogen carbonate (30 mL). The mixture was allowed to warm to room temperature,

then extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine (3.5 mL), dried ($MgSO_4$), and evaporated. The resulting yellow oil was purified by flash chromatography (30% ethyl acetate/hexane) to give **177** (0.19 g, 60%) as white microprisms, mp 117-119 ^oC; R_f 0.62 (50% ethyl acetate/hexane); IR ν_{max} 2948 (C-H), 1735 (ester C=O), 1676 (ester C=O), 1607, 1430, 1282, 1251 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36-7.18 (8H, m, Ph) 6.48-6.46 (2H, m, Ph) 4.63 (1H, d, *J*= 4.6 Hz, C*H*OH) 4.60 (1H, d, *J*= 16.0 Hz, CH_2Ar) 4.46 (1H, d, *J*= 16.0 Hz, CH_2Ar) 4.15 (1H, dt, *J*= 11.0, 3.0 Hz, CH_2N) 3.80 (3H, s, OCH_3) 3.39 (1H, dt, *J*= 13.0, 3.0 Hz, CH_2N) 2.12-1.97 (2H, m, CH_2CHOH); ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.1 (*C*OOCH_3) 152.0 (ArC) 150.5 (CON) 149.9 (ArC) 138.4 (*C*CH_2Ar) 129.4 (ArC) 128.5 (ArC) 128.4 (ArC) 126.4 (ArC) 125.9 (ArC) 121.4 (ArC) 119.6 (*C*CO_2CH_3) 63.0 (CHOH) 52.1 (*C*H_2CHOH) 42.5 (CH_2Ar) 36.7 (CH_2N) 31.1 (*C*H_3OOC); m/z (Cl+) 390 (40%, M^+); HRMS $C_{21}H_{21}NO_5Na$ calcd. 390.1317, found 390.1320.

(b) Using sodium borohydride: To 2-benzyl-5,6-dihydro-3-(methoxycarbonyl)-1-(phenoxycarbonyl)-4-pyridone (1.00 g, 2.70 mmol) in methanol (16 mL) was added sodium borohydride (0.13 g, 3.30 mmol) at 0 ^oC and the mixture was stirred for 1 h. The mixture was quenched by adding water (10 mL), then allowed to warm to room temperature and then was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried ($MgSO_4$), and evaporated to give a residue that was purified by flash chromatography (30% ethyl acetate/hexane) to give **177** (0.91 g, 91%) as white microprisms with mp and spectroscopic data as above.

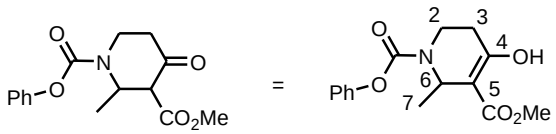
2-Benzyl-3-(methoxycarbonyl)-1-(phenoxycarbonyl)piperidin-4-one (178a)



To 2-benzyl-5,6-dihydro-3-(methoxycarbonyl)-1-(phenoxycarbonyl)-4-pyridone (0.30 g, 0.82 mmol) in THF-pyridine (6.5 mL, 10:1) was added sodium borohydride (0.04 g, 0.98 mmol) at -15 ^{o}C under nitrogen; the mixture was stirred for 0.5 h at -15 ^{o}C. Benzaldehyde (0.66 mL, 6.6 mmol) was then added and the mixture was stirred for 10 min at room temperature. After cooling to -78 ^{o}C, a mixture of hydrochloric acid (0.9 mL, 10 M) and ethanol (1.6 mL) was added and the mixture was stirred for 5 min at -78 ^{o}C and 10 min at room temperature. Water (5 mL) was then added and the mixture was extracted with dichloromethane (3 x 10 mL), dried ($MgSO_4$), and evaporated. The resulting orange oil was purified by flash chromatography (25% ethyl acetate/hexane) to give **178a** (0.24 g, 80%) as white microprisms, mp 137-139 ^{o}C; R_f 0.67 (50% ethyl acetate/hexane); IR ν_{max} 1714 (ester C=O), 1657 (ester C=O), 1618, 1422, 1260, 1236 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) (presence of rotamers) δ 7.38-7.07 (8H, m, Ph) 6.77 (2H, d, *J*= 7.5 Hz, Ph) 5.32-5.25 (1H, m, C_2H) 4.33 (1H, dd, *J*= 13.9, 7.2 Hz, C_6H) 3.81 (3H, s, OCH_3) 3.44-3.34 (1H, m, C_3H) 3.19-3.13 (1H, m, C_7H) 2.86-2.78 (1H, m, C_2H) 2.87-2.60 (1H, m, C_3H) 2.37-2.30 (1H, m, C_7H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.5 ($COOCH_3$) 171.2 ($COOCH_3$) 171.1 (C_4) 170.8 (C_4) 153.5 (CON) 153.3 (CON) 151.3 (ArC) 151.0 (ArC) 138.6 (ArC) 138.0 (ArC) 129.5 (ArC) 129.4 (ArC) 129.4 (ArC) 129.2 (ArC) 129.0 (ArC) 128.6 (ArC) 128.3 (ArC) 127.7 (ArC) 127.0 (ArC) 126.7 (ArC) 126.6 (ArC) 125.3 (ArC) 121.7 (ArC) 121.6 (ArC) 100.5 (C_5) 100.5 (C_5) 52.2 (OCH_3) 52.0 (OCH_3) 51.9 (C_6) 51.0 (C_6) 40.2 (C_2) 40.0 (C_2) 36.9 (C_7) 35.5 (C_7)

28.8 (C_3) 28.6 (C_3); m/z (Cl+) 368 (8%, M^+) 276 (95%, M^+-$ArCH_2$); HRMS $C_{21}H_{21}NO_5Na$ calcd. 368.1495, found 368.1498.

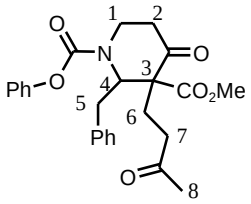
3-(Methoxycarbonyl)-2-methyl-1-(phenoxycarbonyl)piperidin-4-one (178b)



To 5,6-dihydro-3-(methoxycarbonyl)-2-methyl-1-(phenoxycarbonyl)-4-pyridone (0.20 g, 0.69 mmol) in THF-pyridine (5.5 mL, 10:1) was added sodium borohydride (0.03 g, 0.82 mmol) at -15 ^oC under nitrogen; the mixture was stirred for 0.5 h at -15 ^oC. Benzaldehyde (0.28 mL, 2.8 mmol) was then added to the mixture and subsequently stirred for 10 min at room temperature. After cooling to -78 ^oC, a mixture of hydrochloric acid (0.9 mL, 10 M) and ethanol (1.6 mL) was added and the mixture was stirred for 5 min at -78 ^oC and 10 min at room temperature. Water (5 mL) was then added and the mixture was extracted with dichloromethane (3 x 10 mL), dried ($MgSO_4$), and evaporated. The resulting orange oil was purified by flash chromatography (25% ethyl acetate/hexane) to give **178b** (0.15 g, 76%) as a colourless oil, R_f 0.76 (50% ethyl acetate/hexane); IR ν_{max} 3300 (O-H), 2960 (C-H), 1718 (ester C=O), 1660 (C=C), 1419, 1303, 1200, 746 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (presence of rotamers) δ 7.38-7.11 (5H, m, Ph) 5.14 (1H, q, J= 6.4 Hz, C_6H) 5.08 (1H, q, J= 6.4 Hz, C_6H) 4.33-4.27 (1H, m, C_2H) 3.81 (3H, s, OCH_3) 3.79 (3H, s, OCH_3) 3.38 (1H, td, J= 7.9, 3.4 Hz, C_2H) 3.23 (1H, td, J= 7.9, 1.5 Hz, C_2H) 2.67-2.62 (2H, m, C_3H) 2.34-2.29 (2H, m, C_3H) 1.43 (3H, d, J= 6.4 Hz, C_7H) 1.37 (3H, d, J= 6.4 Hz, C_7H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 171.3 ($COOCH_3$) 171.2 ($COOCH_3$) 170.8 (C_4) 170.1 (C_4) 153.4 (CON) 152.9 (CON) 151.3 (ArC) 129.1 (ArC) 129.1 (ArC) 125.7

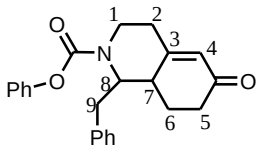
(ArC) 125.4 (ArC) 121.9 (ArC) 121.8 (ArC) 101.6 (C_5) 101.0 (C_5) 51.8 (OCH_3) 51.5 (OCH_3) 46.4 (C_2) 46.0 (C_2) 36.2 (C_6) 35.5 (C_6) 29.1 (C_3) 28.7 (C_3) 19.4 (C_7) 19.3 (C_7).

2-Benzyl-3-(methoxycarbonyl)-3-(3-oxobutyl)-1-(phenoxycarbonyl)piperidin-4-one (179)



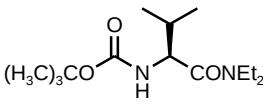
To 2-benzyl-3-(methoxycarbonyl)-1-(phenoxycarbonyl)piperidin-4-one (0.20 g, 0.35 mmol) in methanol (5.0 mL) was added Dowex 66 anionic resin (0.40 g) and methyl vinyl ketone (0.10 ml, 0.82 mmol). The mixture was heated under reflux for 5 d. The solution was filtered and the filtrate was evaporated to give a yellow oil which was purified by flash chromatography (20% ethyl acetate/hexane) to give **179** (0.23 g, 99%) as white microprisms, mp 71-73 ^{o}C; R_f 0.27 (50% ethyl acetate/hexane); IR ν_{max} 2953 (C-H), 1754 (ketone C=O), 1711 (ester C=O), 1410, 1267, 1199, 735, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) (3:1 mixture of diastereomers) δ 7.30-7.20 (8H, m, Ph) 6.46 (2H, d, J= 8.2 Hz, Ph) 5.29-5.27 (1H, m, C_4H) 3.86 (3H, s, OCH_3) 3.82 (3H, s, OCH_3) 3.58-3.54 (1H, m, C_1H) 3.21-3.18 (1H, m, C_1H) 2.61-1.81 (8H, m, C_2H + C_5H + C_6H + C_7H) 1.42 (3H, s, C_8H) 1.29 (3H, s, C_8H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 206.1 ($COCH_3$) 205.6 ($COCH_3$) 171.1 ($COOCH_3$) 154.0 (CON) 150.6 (ArC) 137.5 (ArC) 129.4 (ArC) 129.2 (ArC) 126.9 (ArC) 125.7 (ArC) 121.6 (ArC) 121.4 (ArC) 64.9 (C_3) 60.7 (C_4) 59.0 (C_1) 52.8 (OCH_3) 42.5 (C_2) 34.6 (C_7) 34.2 (C_5) 32.6 (C_6) 27.9 (C_8); m/z (Cl+) 438 (100%, $M+H^+$) 346 (80%, M^+-$ArCH_2$); HRMS $C_{25}H_{28}NO_6Na$ calcd. 438.1917, found 438.1911.

1-Benzyl-6-oxo-2-(phenoxycarbonyl)-3,4,6,7,8,8a-hexahydro-1*H*-isoquinoline (180)



To 2-benzyl-3-(methoxycarbonyl)-3-(3-oxobutyl)-1-(phenoxycarbonyl)piperidin-4-one (0.20 g, 0.45 mmol) in methanol/water (6 mL, 2:1) was added sodium hydroxide (0.12 g, 2.70 mmol). The mixture was stirred at room temperature for 48 h. The solution was neutralized by aqueous 5% hydrochloric acid, extracted into dichloromethane (3 x 10 mL), and the combined organic layers were dried ($MgSO_4$), and evaporated to give **180** (0.13 g, 80%) as a brown gum; IR ν_{max} 2959 (C-H), 1700 (ketone C=O), 1652 (amide C=O), 1423, 1201, 748, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (3:1 mixture of diastereomers) δ 7.35-7.08 (8H, m, Ph) 6.92-6.37 (2H, m, Ph) 5.29 (1H, s, C_4H) 4.16-4.13 (1H, m, C_8H) 3.73-3.57 (2H, m, C_5H) 3.16-3.12 (1H, m, C_7H) 2.48-2.13 (6H, m, C_1H + C_2H + C_9H) 1.79-1.76 (1H, m C_6H) 1.61-1.58 (1H, m, C_6H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 207.1 ($COCH_3$) 154.6 (C_3) 151.0 (CON) 150.6 (ArC) 138.5 (ArC) 129.3 (ArC) 129.1 (ArC) 128.4 (ArC) 126.8 (ArC) 121.5 (ArC) 121.4 (ArC) 115.4 (C_4) 60.3 (C_8) 54.0 (C_1) 38.0 (C_5) 35.7 (C_7) 34.8 (C_9) 33.5 (C_2) 29.9 (C_6); m/z (Cl+) 362 (100%, M^+); HRMS $C_{25}H_{28}NO_6Na$ calcd. 362.1751, found 362.1755.

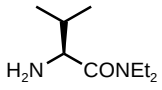
***tert*-Butyl (1-diethylcarbamoyl-2-methylpropyl)carbamate (210)**[40]



To valine (0.59 g, 5.00 mmol) in methanol/water (30 mL, 1:1) was added *tert*-butyl dicarbonate (1.09 g, 5.00 mmol) and sodium carbonate (0.53 g, 5.10 mmol) and the

mixture was stirred for 16 h at room temperature. The solution was evaporated and the residue was acidified by citric acid. The mixture was extracted with dichloromethane (3 x 20 mL), dried ($MgSO_4$), and evaporated to give *N*-Boc valine (0.86 g, 80%) as white microprisms. It was used directly for the next step without further purification. To *N*-Boc valine (0.86 g, 4.00 mmol) in dichloromethane (4.5 mL) was added dicyclohexylcarbodiimide (DCC) (0.94 g, 4.60 mmol) in small portions at 0 ^{o}C. Diethylamide (0.58 g, 7.90 mmol) in dichloromethane (1.5 mL) was added to the mixture which was then stirred at room temperature for 16 h. The solution was filtered and the filtrate was evaporated. The resulting yellow oil was purified by flash chromatography (20% ethyl acetate/hexane) to give **210** (0.58 g, 43%) as a colourless oil; R_f 0.42 (50% methyl *tert*-butyl ether/hexane); IR ν_{max} 3035 (N-H), 2971 (C-H), 1703 (ester C=O), 1634 (amide C=O), 1453, 1365, 1247, 1171, 1016 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.25 (1H, br d, *J*= 9.4 Hz, NH) 4.39-4.34 (1H, m, C*H*NH) 3.64-3.11 (4H, m, CH_2CH$_3$ x2) 1.95-1.89 (1H, m, C*H*CH$_3$) 1.42 (9H, s, CH_3CO x3) 1.22 (3H, t, *J*= 7.2 Hz, CH_3CH$_2$) 1.11 (3H, t, *J*= 7.2 Hz, CH_3CH$_2$) 0.94 (3H, d, *J*= 6.9 Hz, CH_3CH) 0.91 (3H, d, *J*= 6.9 Hz, CH_3CH); m/z (El+) 272 (5%, M$^+$) 116 (100%, BocNH$^+$); HRMS $C_{14}H_{28}N_3O_2$ calcd. 272.2094, found 272.2097.

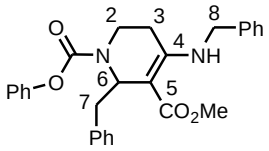
(1-Diethylcarbamoyl-2-methylpropyl)carbamic acid (182)[40]



To *tert*-butyl (1-diethylcarbamoyl-2-methylpropyl)carbamate (0.58 g, 2.10 mmol) in dichloromethane (5 mL) was added trifloroacetic acid (TFA) (0.70 mL, 9.00 mmol) and the mixture was stirred for 24 h at 30 ^{o}C. The mixture was cooled to 0 ^{o}C and neutralized with 10% aqueous potassium hydroxide. The mixture was extracted with

dichloromethane (3 x 5 mL), dried ($MgSO_4$), and the combined organic layers were evaporated to give **182** (0.28 g, 78%) as a colourless oil; R_f 0.71 (75% methyl *tert*-butyl methyl ether/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (2H, br s, NH_2) 4.28-4.32 (1H, m, C*H*NH_2) 3.61-3.21 (4H, m, C*H*$_2$CH$_3$ x2) 2.21-2.14 (1H, m, C*H*CH_3) 1.23 (3H, t, *J*= 7.2 Hz, C*H*$_3$CH$_2$) 1.14 (3H, t, *J*= 7.4 Hz, C*H*$_3$CH$_2$) 1.04 (3H, d, *J*= 6.9 Hz, C*H*$_3$CH) 0.97 (3H, d, *J*= 6.0 Hz, C*H*$_3$CH).

2-Benzyl-4-benzylamino-5,6-dihydro-2*H*-3-(methoxycarbonyl)-1-(phenoxycarbonyl)pyridine (191)



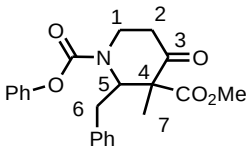
To 2-benzyl-5,6-dihydro-3-(methoxycarbonyl)-1-(phenoxycarbonyl)-4-pyridone (0.20 g, 0.55 mmol) in toluene (3.0 mL) was added benzylamine (0.06 mL, 0.55 mmol).Acetic acid (3 drops) was added and the mixture was heated to 70 ^{o}C for 2 h. Saturated aqueous sodium hydrogen carbonate (3 mL) was then added and the mixture was extracted with dichloromethane (3 x 5 mL), dried ($MgSO_4$), and evaporated. The resulting yellow oil was purified by flash chromatography (25% ethyl acetate/hexane) to give **191** (0.22 g, 86%) as a colourless viscous oil, R_f 0.62 (50% ethyl acetate/hexane); IR ν_{max} 3335 (N-H), 3027 (C-H), 1713 (ester C=O), 1655 (C=C), 1595, 1425, 1202, 746, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) (presence of rotamers) δ 7.35-7.12 (13H, m, Ph) 6.74 (2H, d, *J*= 7.4 Hz, Ph) 5.41-5.37 (1H, m, C_2H) 4.45-4.41 (2H, m, C_8H) 4.41-3.93 (1H, m, C_6H) 3.81 (3H, s, OCH_3) 3.43-3.38 (1H, m, C_3H) 3.25-3.20 (1H, m, C_7H) 2.88-2.80 (1H, m, C_2H) 2.55-2.52 (1H, m, C_3H) 2.44-2.39 (1H, m, C_7H); m/z (Cl+) 457 (65%, M^+) 365 (100%, M^+-C_7H_7); HRMS $C_{28}H_{29}N_4O_2$ calcd.

457.2127, found 457.2135.

General procedure for alkylation of 207

To 3-(methoxycarbonyl)-1-(phenoxycarbonyl)piperidin-4-ones **207** (1.0 equiv) in acetone was added potassium carbonate (2.0 equiv) and alkyl halides (2.0 equiv). The mixture was heated under reflux for 16 h. The solution was filtered and the filtrate was evaporated. Chloroform was added and the solution was filtered again. The filtrate was then evaporated.

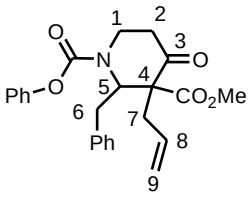
2-Benzyl-3-(methoxycarbonyl)-3-methyl-1-(phenoxycarbonyl)piperidin-4-one (207a)



Following general procedure, reaction of 2-benzyl-3-(methoxycarbonyl)-1-(phenoxycarbonyl)piperidin-4-one (0.80 g, 2.18 mmol), potassium carbonate (0.60 g, 4.36 mmol), and iodomethane (0.3 ml, 4.36 mmol) in acetonitrile (7 mL) gave a yellow oil that was purified by flash chromatography (25% ethyl acetate/hexane) to give **207a** (0.74 g, 89%) as a pale yellow oil, R_f 0.25 (30% ethyl acetate/hexane); IR ν_{max} 2951 (C-H), 1734 (ketone C=O), 1707 (ester C=O), 1411, 1191, 941, 734, 689 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (presence of rotamers) δ 7.35-7.13 (8H, m, Ph) 6.80-6.60 (2H, m, Ph) 5.01 (1H, dd, J= 11.9, 3.5 Hz, C_5H) 4.42-4.38 (1H, m, C_1H) 3.82 (3H, s, OCH_3) 3.75 (3H, s, OCH_3) 3.64-3.60 (1H, m, C_1H) 3.22-3.18 (1H, m, C_2H) 2.93-2.85 (2H, m, C_6H) 2.65-2.62 (1H, m, C_2H) 1.72 (3H, s, C_7H) 1.64 (3H, s, C_7H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 205.2 (C_3) 204.9 (C_3) 171.2 ($COOCH_3$) 171.1 ($COOCH_3$) 154.2 (CON) 150.8 (CON) 137.2 (ArC) 136.8 (ArC)

129.3 (ArC) 129.1 (ArC) 128.8 (ArC) 128.5 (ArC) 127.1 (ArC) 126.9 (ArC) 125.6 (ArC) 125.5 (ArC) 121.7 (ArC) 121.5 (ArC) 60.7 (C_4) 60.5 (C_4) 52.6 (OCH_3) 39.5 (C_5) 38.7 (C_5) 36.9 (C_1) 36.5 (C_1) 36.2 (C_2) 35.7 (C_2) 22.7 (C_6) 22.3 (C_6) 21.1 (C_7) 20.9 (C_7); m/z (Cl+) 382 (100%, $M+H^+$); HRMS $C_{22}H_{24}NO_5$ calcd. 382.1654, found 382.1655.

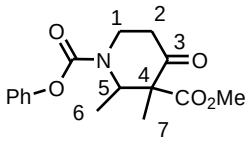
3-Allyl-2-benzyl-3-(methoxycarbonyl)-1-(phenoxycarbonyl)piperidin-4-one (207b)



Following general procedure, reaction of 2-benzyl-3-(methoxycarbonyl)-1-(phenoxycarbonyl)piperidin-4-one (0.50 g, 1.36 mmol), potassium carbonate (0.38 g, 2.72 mmol), and allyl bromide (0.45 ml, 4.08 mmol) in acetonitrile (5 mL) gave a solid that was purified by flash chromatography (22% ethyl acetate/hexane) to give **207b** (0.41 g, 74%) as a milky gum, R_f 0.26 (30% ethyl acetate/hexane); IR ν_{max} 2955 (C-H), 1742 (ketone C=O), 1707 (ester C=O), 1407, 1189, 973, 736, 689 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (presence of rotamers) δ 7.33-7.23 (8H, m, Ph) 6.79-6.55 (2H, m, Ph) 5.82-5.66 (1H, m, C_8H) 5.22-5.12 (3H, m, C_9H + C_5H) 4.52-4.43 (1H, m, C_1H) 3.81 (3H, s, OCH_3) 3.76 (3H, s, OCH_3) 3.71-3.61 (1H, m, C_1H) 3.24-3.22 (1H, m, C_2H) 3.05-3.04 (1H, m, C_7H) 2.85-2.77 (3H, m, C_7H + C_6H) 2.57-2.532 (1H, m, C_2H) 1.72 (3H, s, C_7H) 1.64 (3H, s, C_7H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 203.2 (C_3) 203.2 (C_3) 169.7 ($COOCH_3$) 169.5 ($COOCH_3$) 154.1 (CON) 154.0 (CON) 151.2 (ArC) 150.7 (ArC) 137.2 (C_8) 136.9 (C_8) 131.6 (ArC) 131.2 (ArC) 129.2(ArC) 128.8 (ArC) 128.4 (ArC) 127.0 (ArC) 126.9 (ArC) 125.6 (ArC) 125.5 (ArC) 121.4 (ArC) 120.2 (C_9) 120.0 (C_9) 65.1 (C_4) 59.9 (C_5) 58.7 (C_5) 52.4 (OCH_3) 39.8 (C_1) 39.6 (C_1) 38.8 (C_2) 37.8 (C_6) 37.2 (C_6) 35.4 (C_7) 34.9 (C_7); m/z (Cl+) 408

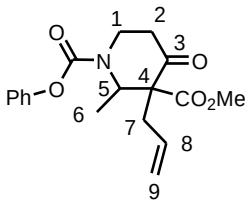
(100%, $M+H^+$); HRMS $C_{24}H_{26}NO_5$ calcd. 408.1811, found 408.1813.

3-(Methoxycarbonyl)-2,3-dimethyl-1-(phenoxycarbonyl)piperidin-4-one (207c)



Following general procedure, reaction of 3-(methoxycarbonyl)-2-methyl-1-(phenoxycarbonyl)piperidin-4-one (0.20 g, 0.69 mmol), potassium carbonate (0.19 g, 1.37 mmol), and iodomethane (0.1 ml, 1.37 mmol) in acetonitrile (2 mL) gave a yellow oil that was purified by flash chromatography (35% ethyl acetate/hexane) to give **207c** (0.18 g, 88%) as a colourless oil, R_f 0.35 (30% ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.10 (5H, m, Ph) 4.70 (1H, q, *J*= 6.5 Hz, C_5H) 4.36-4.01 (1H, m, C_1H) 3.69 (3H, s, OCH_3) 3.69-3.68 (1H, m, C_1H) 2.87-2.76 (1H, m, C_2H) 2.66-2.61 (1H, m, C_2H) 1.61 (3H, s, C_7H) 1.45 (3H, d, *J*= 6.5 Hz, C_6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 205.1 (C_3) 170.8 (*C*$OOCH_3$) 153.8 (CON) 151.0 (ArC) 129.4 (ArC) 125.7 (ArC) 121.6 (ArC) 60.6 (C_4) 56.1 (OCH_3) 52.4 (C_5) 39.1 (C_1) 36.9 (C_2) 21.8 (C_6) 17.2 (C_7).

3-Allyl-3-(methoxycarbonyl)-2-methyl-1-(phenoxycarbonyl)piperidin-4-one (207d)



Following general procedure, reaction of 3-(methoxycarbonyl)-2-methyl-1-(phenoxycarbonyl)piperidin-4-one (0.20 g, 0.69

mmol), potassium carbonate (0.19 g, 1.37 mmol), and allyl bromide (0.15 ml, 1.37 mmol) in acetonitrile (2 mL) gave a yellow oil that was purified by flash chromatography (35% ethyl acetate/hexane) to give **207d** (0.168 g, 70%) as a colourless oil, R_f 0.32 (30% ethyl acetate/hexane); IR ν_{max} 2952 (C-H), 1735 (ketone C=O), 1710 (ester C=O), 1414, 1200, 751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63-7.09 (5H, m, Ph) 5.72-5.65 (1H, m, C_8H) 5.17-5.09 (2H, m, C_9H) 4.77 (1H, q, *J*= 6.9 Hz, C_5H) 4.37-4.31 (1H, m, C_1H) 3.73 (3H, s, OCH_3) 3.67-3.50 (1H, m, C_1H) 2.93-2.92 (1H, m, C_2H) 2.79-2.65 (2H, m, C_7H) 2.54-2.48 (1H, m, C_2H) 1.40 (3H, d, *J*= 6.9 Hz, C_6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 203.4 (C_3) 169.6 ($COOCH_3$) 153.7 (CON) 151.0 (ArC) 131.6 (C_8) 129.4 (ArC) 125.7 (ArC) 121.6 (ArC) 119.8 (C_9) 65.0 (C_4) 54.0 (OCH_3) 52.3 (C_5) 39.3 (C_1) 39.0 (C_2) 37.6 (C_7) 16.7 (C_6); m/z (Cl+) 332 (100%, $M+H^+$); HRMS $C_{18}H_{22}NO_5$ calcd. 332.1498, found 332.1487.

2.5 References

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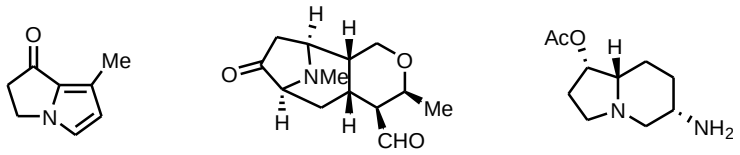
CHAPTER 3

Synthesis of Substituted Pyrrolidin-3-ones and Related Ring Systems

3.1 Introduction

The pyrrolidine ring, whether present as a single ring or as a part of a fused ring system, is commonly found in pharmaceutically active compounds and natural compounds including alkaloids.[1–8] Oxopyrrolidines are also found in some alkaloids; pyrrolidin-2-ones being the most abundant.[9–11] In contrast, pyrrolidin-3-ones are much less common; however, they are sometimes found in alkaloids.[12–16] Some pyrrolidin-3-one derivatives are used as potent HIV protease inhibitors;[17,18] while others are key intermediates for making agonists for metabotropic glutamate receptors,[19] inhibitors of tripeptidylpeptidase II,[20] androgen receptor antagonists,[21] and GABA uptake inhibitors.[22] Furthermore, pyrrolidin-3-ones are precusors for the synthesis of pyrrolidin-3-ol-containing natural compounds like preussin and bulgecinine;[23] or quinocarcin[24] and stemofoline[25] in which pyrrolidin-3-ol acts as a part of a fused ring system. Although this area has significant potential for drug development, there are few methods of synthesizing pyrrolidin-3-ones. Therefore, developing synthetic routes to pyrrolidin-3-ones would be useful for exploiting this area.

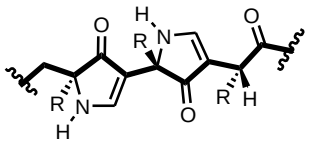


Danaidone **(+)-Angustimalal** **(-)-Slaframine**

Figure 3.1 Some pyrrolidin-3-one- and pyrrolidin-3-ol-based alkaloids

3.1.1 Approaches to 1,2-Dihydropyrrol-3-ones

1,2-Dihydropyrrol-3-ones, also named pyrrolinones, are present in pharmaceutically active compounds as a peptidomimetic scaffold.[26–29] Moreover, 1,2-dihydropyrrol-3-one derivatives are key intermediates for the synthesis of pyrrolidin-3-one- and pyrrolidin-3-ol-containing natural compounds. However, there are few papers[29,30] describing the synthesis of this ring system and general routes to 1,2-dihydropyrrol-3-ones are not well developed.

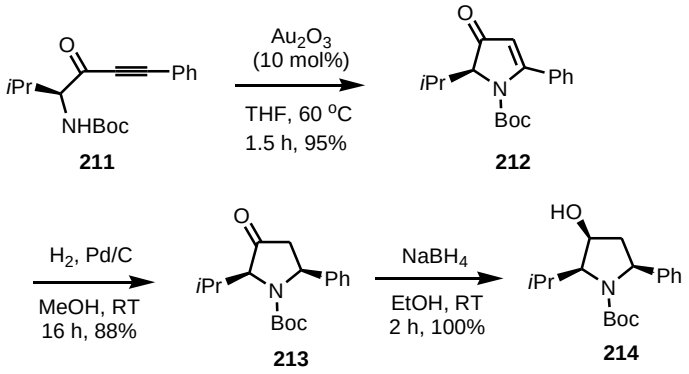


Pyrrolinone scaffold

Figure 3.2 1,2-Dihydropyrrol-3-ones as part of a peptidomimetic scaffold[26]

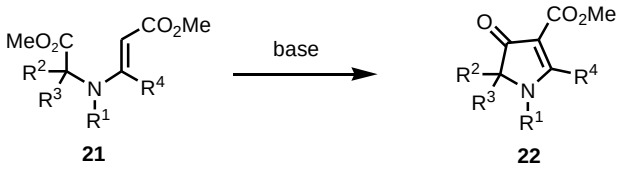
In 2009, Gouault reported a gold-catalysed cyclisation of α-amino-ynones to give enantiopure 1,2-dihydropyrrol-3-ones (Scheme 3.1).[30] Gold was chosen because of its ability to coordinate and activate C-C mutiple bonds through its Lewis acidity.[30] Enantiopure α-amino-ynones were prepared from α-amino acids (chiral pool synthesis). Gouault also showed that the 1,2-dihydropyrrol-3-one **212** could be converted into the pyrrolidin-3-one **213** and then into the pyrrolidin-3-ol **214** in excellent ee.[30] In 2013,

Lamaty employed $PtCl_2$ as the catalyst and was able to do this reaction in a more environmentally-friendly way.[29]



Scheme 3.1 A gold-catalyzed approach to the 1,2-dihydropyrrol-3-one **212**[30]

Although it seems that Dieckmann cyclisation of enamino esters **21** to afford 1,2-dihydropyrrol-3-ones **22** is feasible and convenient, to our knowledge the only attempt is by Cambon[31] who in 1990 reported that **21** did not undergo a Dieckmann cyclisation by the treatment of sodium in xylene to give 1,2-dihydropyrrol-3-ones **22** (refers to Section 1.1.3). Since little is known about the potential of this Dieckmann cyclisation to give 1,2-dihydropyrrol-3-ones **22**, it would be of interest to investigate its feasibility using different substrates and conditions.

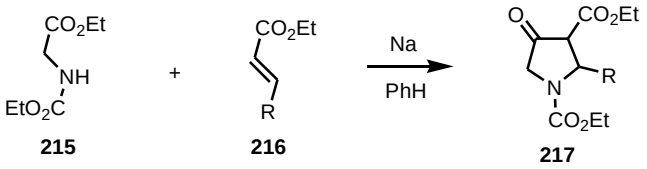


Scheme 3.2 Dieckmann cyclisation to 1,2-dihydropyrrol-3-ones **22**

3.1.2 Approaches to Pyrrolidin-3-ones

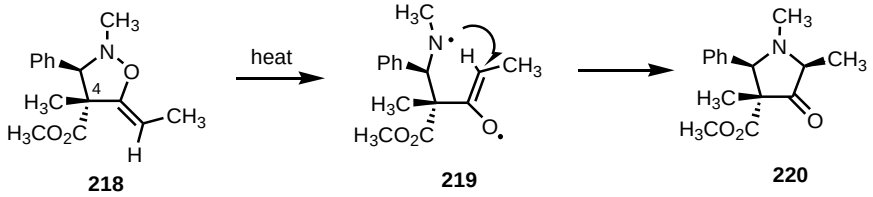
In 1922, Ruzicka and Seidel attempted to prepare pyrrolidin-3-ones via a Dieckmann-like cyclisation by heating diesters under reflux with sodium in xylene but they could not characterise the product.[32] In 1956, Kuhn and Osswald developed a

one-pot aza-Michael addition-Dieckmann cyclisation of the *N*-protected glycine ethyl ester **215** with *β*-substituted acrylates **216** using sodium in benzene to give *N*-protected pyrrolidin-3-ones **217** (Scheme 3.3).[33] They were able to prepare the pyrrolidin-3-one hydrochloride and the pyrrolidin-3-ol, which were first described in 1957, using this method.[34]



Scheme 3.3 Michael addition-Dieckmann cyclisation to pyrrolidin-3-ones **217**[33]

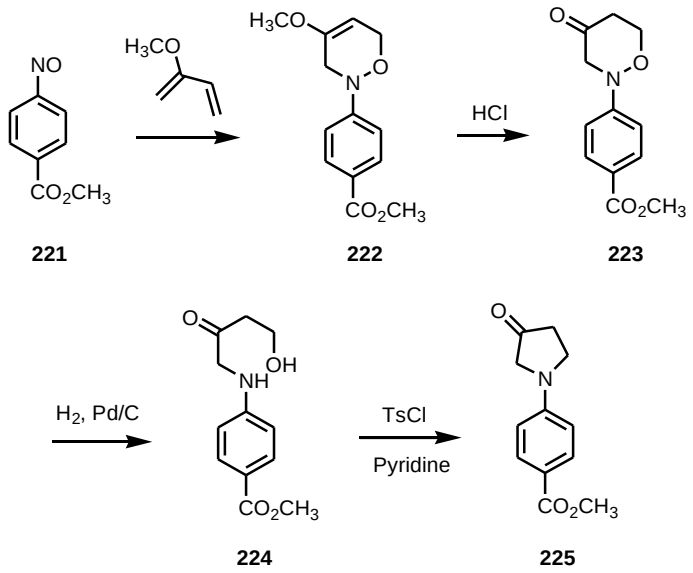
In 1987, Padwa reported a radical rearrangement of the 5-exomethyleneisoxazolidine derivative **218** to prepare the pyrrolidin-3-one **220**.[35] Since C^4 (marked in diagram, Scheme 3.4) is fully substituted, rearrangement of **218** by 1,3-hydrogen shift is prohibited.[35] By heating, N-O bond breaks and the nitrogen radical attacks the C=C bond to form the pyrrolidin-3-one **220**.



Scheme 3.4 Rearrangement of the 5-exomethyleneisoxazolidine derivative **220**[35]

In 1984, Taylor described a Diels-Alder route to the pyrrolidin-3-one **225** (Scheme 3.5).[36] Diels-Alder addition of the methyl 4-nitrosobenzoate **221** with 2-methoxy-1,3-butadiene gave the 3,6-dihydro-2*H*-1,2-oxazine **222** which was converted into tetrahydro-2*H*-1,2-oxazin-4-one **223** in the presence of acid. The N-O bond of **223** was cleaved by hydrogenation, and subsequent dehydrative ring closure afforded the pyrrolidin-3-one **225**. Despite these advances, scaleable routes to

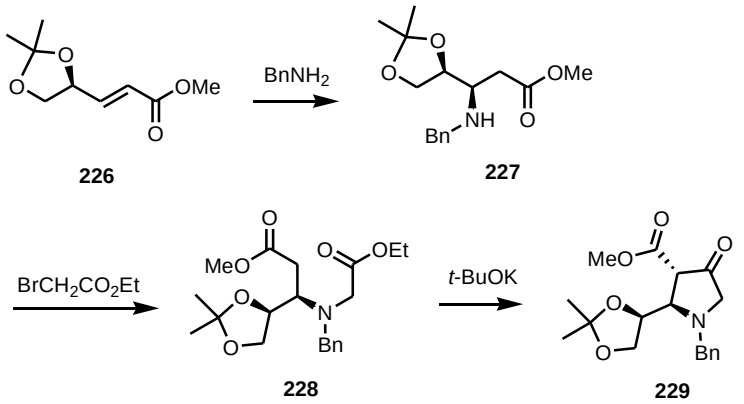
pyrrolidin-3-ones with different substitutions are in demand.



Scheme 3.5 A Diels-Alder route to the pyrrolidin-3-one **225**[36]

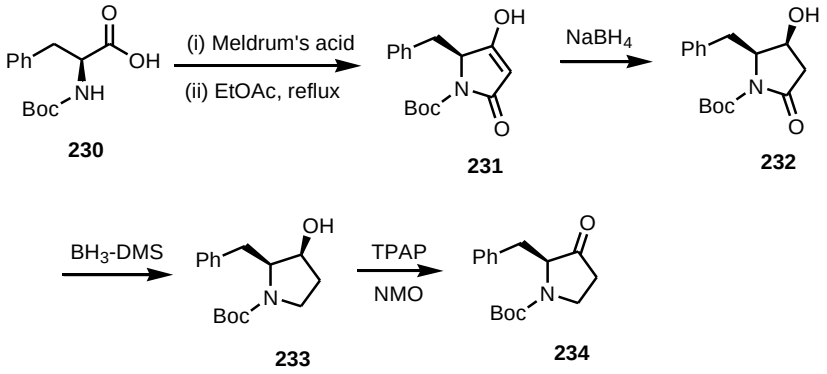
3.1.3 Enantiocontrolled Strategies to Pyrrolidin-3-ones

Enantioselective syntheses of pyrrolidin-3-ones are useful for drug development but only a few have been reported. Costa employed the chiral acrylate **226** derived from D-(+)-mannitol to induce asymmetric Michael addition to give the enantiopure *β*-keto ester **227** (Scheme 3.6).[1] Dieckmann cyclisation of the diester **228** afforded the pyrrolidin-3-one derivative **229** in a single enantiomer. Using a similar approach, Li used a diester derived from a chiral *β*-amino ester to prepare enantiopure *N*-benzyl-5-methylpyrrolidin-3-one by a Dieckmann cyclisation.[37]



Scheme 3.6 Preparation of the enantiopure pyrrolidin-3-one **229** from D-(+)-mannitol derivatives[1]

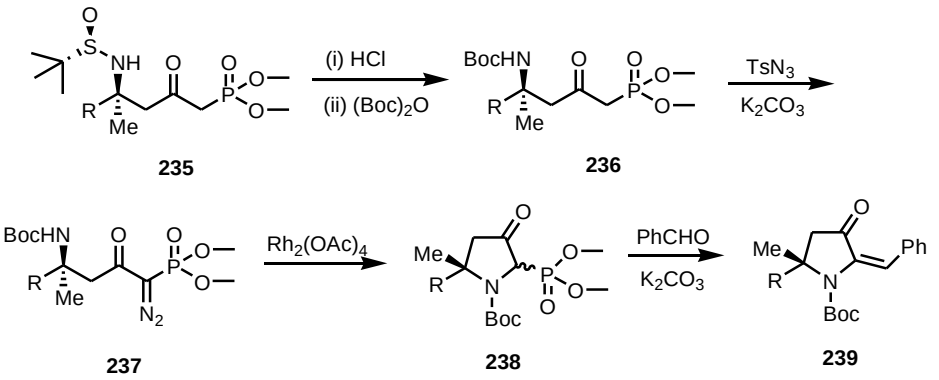
Kraus prepared the chiral tetramic acid **231** by the treatment of Boc-L-phenylalanine with Meldrum's acid.[18] After subsequent reduction and oxidation, enantiopure (2*S*)-2-benzyl-1-(*tert*-butyloxycarbonyl)pyrrolidin-3-one (**234**) was synthesized (Scheme 3.7).



Scheme 3.7 Preparation of the enantiopure pyrrolidin-3-one **234** from Boc-L-phenylalanine[18]

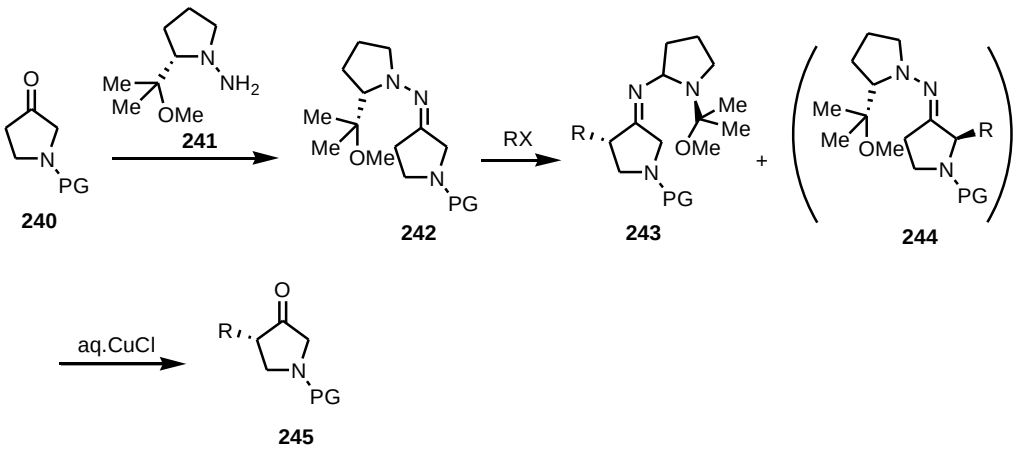
Yuan prepared enantiopure oxophosphonates **235** by the treatment of Ellman's sulfinylimines with 2-oxophosphonates (Scheme 3.8).[38] Oxophosphonates **235** were converted into 1-diazo derivatives **237** which were then cyclised by N-H insertion. The cyclised products **238** were subjected to Horner-Wadsworth-Emmons olefination to give 5,5-disubstituted 2-benzylidenepyrrolidin-3-ones **239**. Yang also reported the

synthesis of enantiopure 5-substituted pyrrolidin-3-ones by an N-H insertion approach with the use of chiral *N*-Boc-amino acids.[39]



Scheme 3.8 Preparation of the enantiopure pyrrolidin-3-one **239** via an N-H insertion[38]

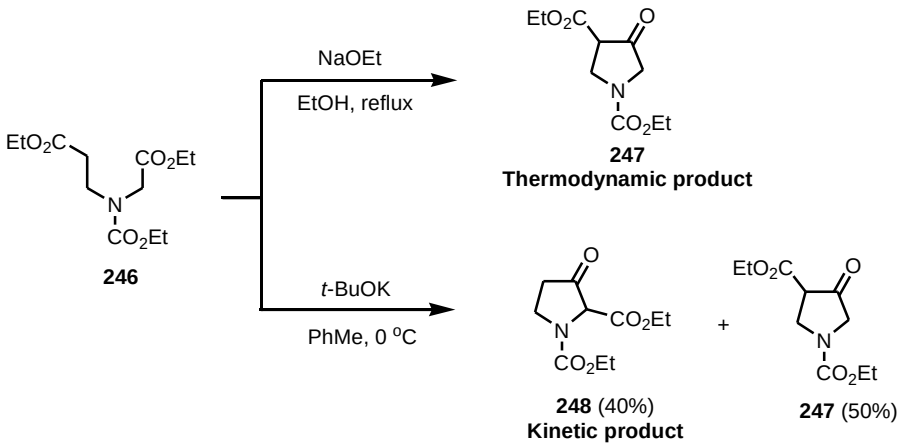
In 2002, Quirion prepared enantiopure 4-substituted pyrrolidin-3-ones **245** via a diastereoselective alkylation using Enders' chiral hydrazone protocol (Scheme 3.9).[24] This approach afforded **245** in high regioselectivity and acceptable diastereoselectivity; the bulkier the R is, the higher the regioselectivity due to the steric hindrance between R and PG in minor products **244**.



Scheme 3.9 Regio- and diastereoselective alkylation of hydrazones **241** to give enantiopure pyrrolidin-3-ones **245**[24]

3.1.4 Mode of Cyclisation of Diesters to Pyrrolidin-3-ones

When the diester **246** is treated with a base, Dieckmann cyclisation could in principle ocurr at both sides to afford the 4-ethoxycarbonylpyrrolidin-3-one **247** and the 2-ethoxycarbonylpyrrolidin-3-one **248** as products. Rapoport demonstrated that the 4-ethoxycarbonylpyrrolidin-3-one **247**, being the thermodynamic product, was the only product when the reaction was performed at high temperature; while at low temperature, the 2-ethoxycarbonylpyrrolidin-3-one **248**, being the kinetic product, was identified together with **247** (Scheme 3.10).[40] Other groups were also able to isolate the kinetic products using the same approach.[41–43] The 4-ethoxycarbonylpyrrolidin-3-one **247** is the thermodynamic product because there is no steric hindrance between the alkoxy group and the *N*-protecting group; while the 2-ethoxycarbonylpyrrolidin-3-one **248** is the kinetic product since the glycine-type methylene is more acidic than the propionic methylene due to the inductive effect of the *N*-ethoxycarbonyl group.[40]



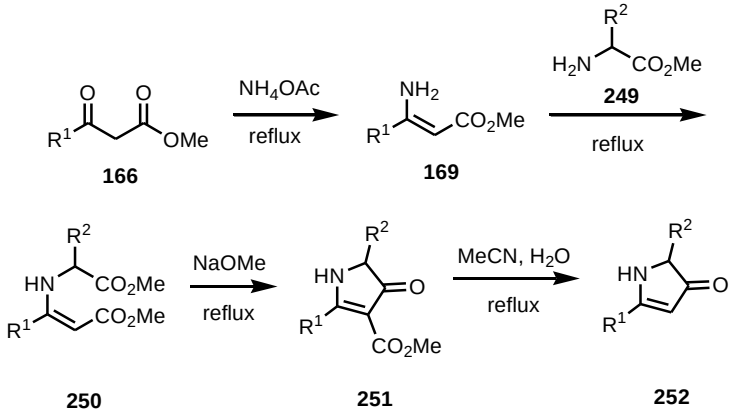
Scheme 3.10 Mode of cyclisation of the diester **246**

3.2 Results and Discussion

3.2.1 Attempted Synthesis of 1,2-Dihydropyrrol-3-ones

In Section 2.2.7, 2-substituted piperidin-4-ones were efficiently prepared by a Dieckmann cyclisation approach. It was of interest to see if this synthetic strategy could be applied to make the five-membered-ring counterpart, *i.e. 1,2-dihydropyrrol-3-one derivatives*, especially to have various substituents at the 2- and/or 5-positions.

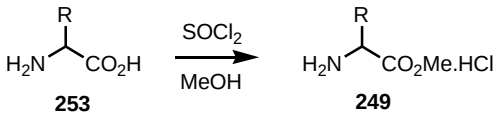
The proposed route, shown in Scheme 3.11, began with *β*-keto esters **166**. Amination of *β*-keto esters **166** using ammonium acetate gave enamines **169** which were coupled with amino esters **249** to give diesters **250**. Dieckmann cyclisation of diesters **250** using sodium methoxide and subsequent decarboxylation gave the desired 1,2-dihydropyrrol-3-ones **252**. Depending on *β*-keto esters **166** and amino esters **249** used, it was hoped that 1,2-dihydropyrrol-3-ones **252** with various 2- and 5-substitutions could be made in a few steps.



Scheme 3.11 Proposed route to 1,2-dihydropyrrol-3-ones **252**

Amino esters **249** were made from their corresponding amino acids **253** using the

traditional thionyl chloride-activated esterification, except for the alanine-derived amino ester **253b** which was commercially-avaliable.[44,45] The yields were good to excellent (75-97%, Scheme 3.12). Five different amino esters **249** were prepared to investigate the limitations of the proposed route. First, whether this route was feasible or not was tested using the glycine amino ester **253a** (R=H). Then, monosubstituted amino esters **253b** (R= methyl), **253c** (R= isopropyl), and **253d** (R= benzyl) were used to find out if dihydropyrrol-3-ones with bulky R groups could be synthesized by this route. Finally, the disubstituted amino ester **253e** (R=*gem*-dimethyl) was employed to see if 2,2-disubstituted 1,2-dihydropyrrol-3-ones could be synthesized.



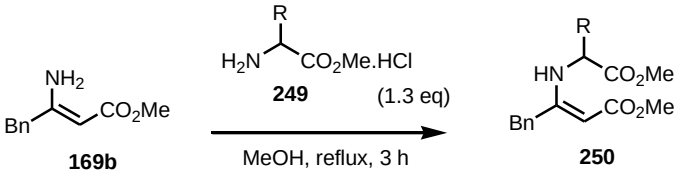
253 **249**

Cpd	R	yield (%)
253a	H	90
253c	*i*-Propyl	78
253d	Benzyl	97
253e	*gem*-Dimethyl	75

Scheme 3.12 Synthesis of amino esters **249** HCl salt

The enamine **169b** was made from the *β*-keto ester **166c** by amination in 97% yield.[46] The amine group of the enamine **169b** was then displaced by amino esters **249** to

afford diesters **250** (Scheme 3.13).[47] This was a very good reaction for monosubstituted amino esters **253a-d** (87-93% yields). However, no reaction of the *gem*-dimethyl animo ester **253e** with the enamine **169b** was observed, suggesting that steric hindrance from the *gem*-dimethyl groups was too large for displacement to occur.

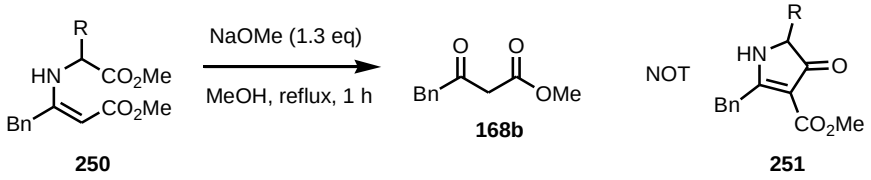


Cpd	R	yield (%)
253a	H	87
253b	Methyl	87
253c	*i*-Propyl	93
253d	Benzyl	90
253e	*gem*-Dimethyl	0

Scheme 3.13 Synthesis of diesters **250**

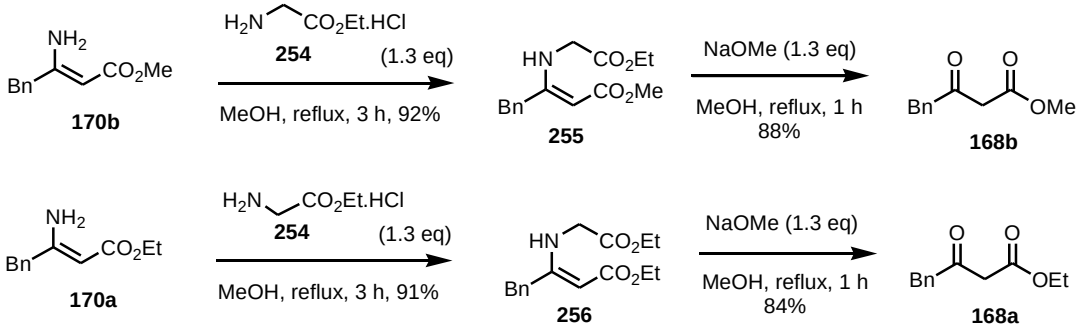
Cyclisations of diesters **250** by a Dieckmann cyclisation to form 1,2-dihydropyrrol-3-ones **251** were attempted but none of them were successful (Scheme 3.14). When diesters **250** were heated under reflux with sodium methoxide in methanol, a hydrolysis reaction took place instead of a Dieckmann cyclisation and the precusor **168b** was isolated as the single product in over 80% yield. Other bases

including sodium hydride and poatssium *tert*-butoxide were used but were also ineffective.



Scheme 3.14 Attempted synthesis of 1,2-dihydropyrrol-3-ones **4**

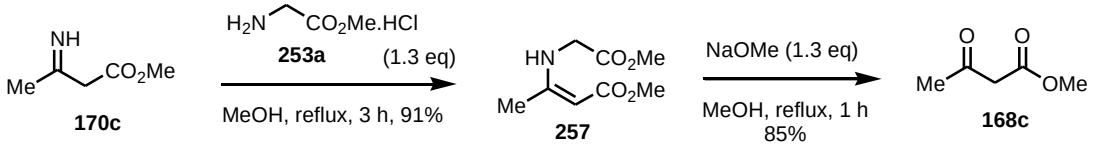
The ester groups of the diester **250a** were changed in the hope that a Dieckmann cyclisation would take place with these substrates. It is because it was found in Section 2.2.2 that Dieckmann cyclisation affording 5,6-dihydro-4-pyridones was affected by the type of ester groups involved. The mixed diester **255** and ethyl diester **256** were prepared by the same approach in excellent yields (Scheme 3.15). However, hydrolysis reaction occurred again to give *β*-keto esters **168** as the products.



Scheme 3.15 Attempted synthesis of 1,2-dihydropyrrol-3-ones **252** with ethyl esters

From the above result, it was suspected that hydrolysis reaction was facilitated by the benzyl group of diesters **250** so cyclisation of the diester **257** was attempted (Scheme 3.16). The diester **257** was prepared from the imine **170c** by a substitution in 91% yield. When the diester **257** was treated with sodium methoxide, hydrolysis also occurred, affording the *β*-keto ester **168c** in 85% yield. Since the problem of hydrolysis reaction

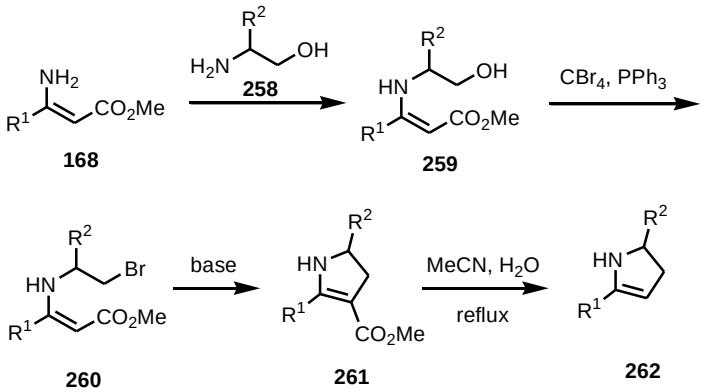
could not be solved, focus was changed to cyclise a related ring system by a S_N2 substitution reaction.



Scheme 3.16 Attempted synthesis of 2-methyl-1,2-dihydropyrrol-3-ones **252**

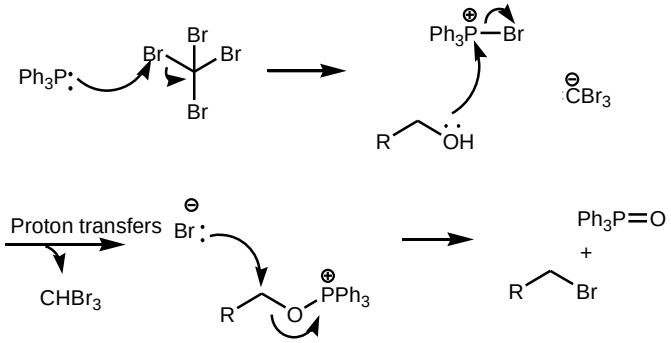
3.2.2 Attempted Synthesis of 1,2-Dihydropyrroles

Owing to the difficulty of making 1,2-dihydropyrrol-3-ones **252** by a Dieckmann cyclisation, diesters **250** were replaced by bromo esters **260** in the hope that esters **260** would cyclise in the presence of a base by a S_N2 substitution reaction. The proposed route is shown in Scheme 3.17. Amino alcohols **258** were prepared from the corresponding amino acids by reduction and were coupled with enamines **168** to give hydroxy esters **259**. By an Appel reaction[48] with tetrabromomethane, bromo esters **260** were formed. Bromo esters **260** were then treated with a base to afford 4-methoxycarbonyl-1,2-dihydropyrroles **261** by a S_N2 substitution reaction. Decarboxylation would then give the desired 2,5-disubstituted 1,2-dihydropyrroles **262**.



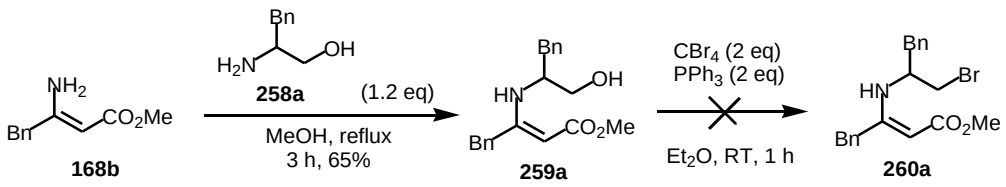
Scheme 3.17 Poposed route to 1,2-dihydropyrroles **262**

The mechanism of the Appel reaction is shown in Scheme 3.18. The triphenylphosphine attacks the bromine atom of the tetrabromomethane to form the electrophilic phosphonium cation which undergoes nucleophilic displacement by an alcohol. The adduct is electrophilic and it is ready for the S_N2 displacement reaction by the bromide because $Ph_3P{=}O$ is a very good leaving group.



Scheme 3.18 Mechanism of the Appel reaction

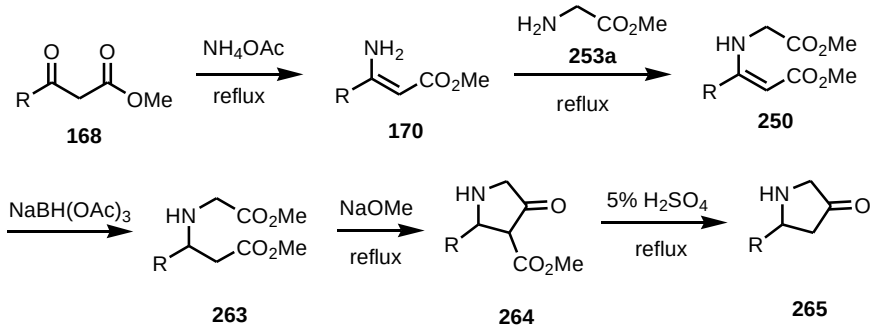
Phenylalanine was reduced by sodium borohydride to give the amino alcohol **258a** in 83% yield (Scheme 3.19).[49] It was then coupled with the enamine **168b** to give the hydroxy ester **259a** in 65% yield. However, when the latter was treated with triphenylphosphine and tetrabromomethane at room temperature for 1 hour, a complex mixture was obtained and no desired bromo ester **260a** was isolated, perphaps beacuse the bromo ester **260a** is very reactive, leading to side reactions. Owing to these difficulties, this route was abandoned and the synthesis of a related ring system using the synthetic route of piperidin-2,4-diones (Section 1.2.3) was investigated.



Scheme 3.19 Attempted substitution of an alcohol with a bromide

3.2.3 Synthesis of Pyrrolidin-3-ones via a Dieckmann Cyclisation

5,6-Disubstituted piperidin-2,4-diones were made successfully in Section 1.2.3 via a Dieckmann cyclisation starting from *β*-keto esters **168**. It was hoped that pyrrolidin-3-ones with various substituents at position-5 could also be prepared by this strategy. The proposed route is shown in Scheme 3.20. Amination of *β*-keto esters **168** with ammonium acetate afforded enamines **170** which were coupled with the amino ester **253a** to give diesters **250**. The diesters **250** were reduced by sodium triacetoxyborohydride.[50] Dieckmann cyclisation of diesters **263** and subsequent decarboxylation would give the desired pyrrolidin-3-ones **265**.

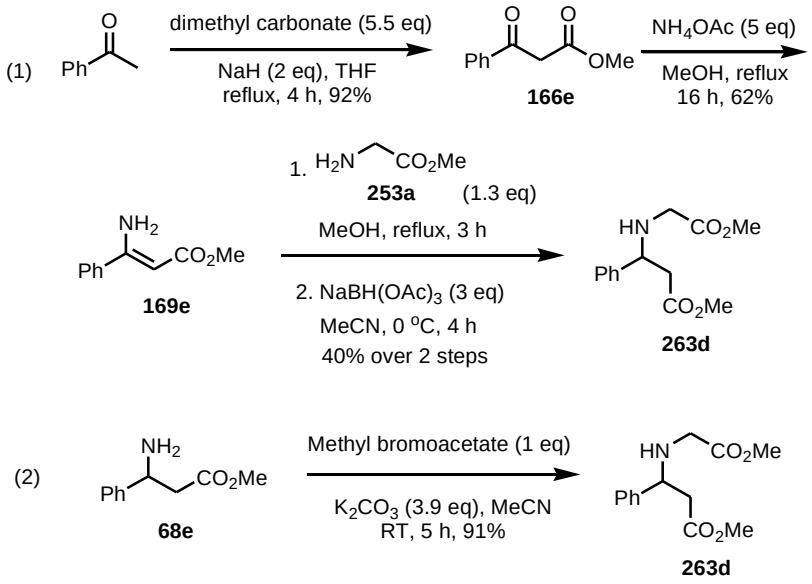


Scheme 3.20 Proposed route to pyrrolidin-3-ones **265**

5-Phenylpyrrolidin-3-one (**265a**) was the first target since 6-phenylpiperidin-2,4-dione (**65e**) was prepared in good yield by a closely-related synthetic route in Section 1.2.3. The intermediate diester **263d** could be prepared from acetophenone or *β*-phenylalanine methyl ester (Scheme 3.21). Acetophenone was converted into its enolate by sodium hydride and was then reacted with dimethyl carbonate to give the *β*-keto ester **166e** in 92% yield.[51] Amination gave the enamine **169e** in 62% which was coupled with the amino ester **253a** to give the diester **250f**. Reduction of **250f** using

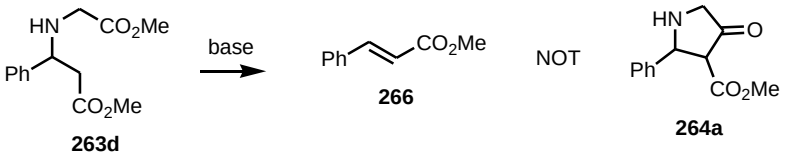
sodium triacetoxyborohydride gave the diester **263d** in 40% over two steps.

Another feasible route to the diester **263d** is the displacement reaction of *β*-phenylalanine methyl ester with methyl bromoacetate in the presence of potassium carbonate. Since the yield was excellent (91%) and the diester **263d** could be prepared in one step, this route was used to make **263d** in grams quantities.



Scheme 3.21 Synthesis of the diester **263d** by 2 routes

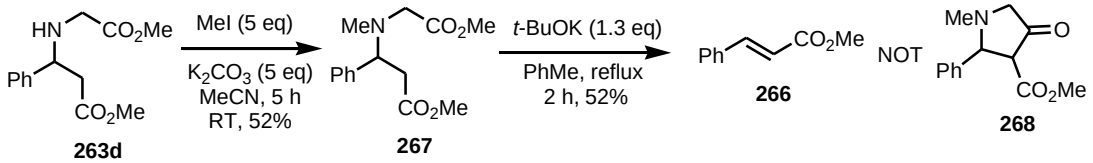
The diester **263d** was then heated under reflux with sodium methoxide in methanol for 1 hour. However, instead of a Dieckmann cyclisation, a reverse-Michael reaction took place to give the α,*β*-unsaturated ester **266** in 62% yield. Potassium *tert*-butoxide and sodium hydride were employed but both of them also gave the unwanted product **266** (Scheme 3.22).



Entry	Conditions
1	NaOMe (1.2 eq), MeOH, reflux, 1 h
2	*t*-BuOK (1.2 eq), PhMe, reflux, 1 h
3	NaH (1.3 eq), THF, reflux, 1 h

Scheme 3.22 Attempted cyclisation of the diester **263d**

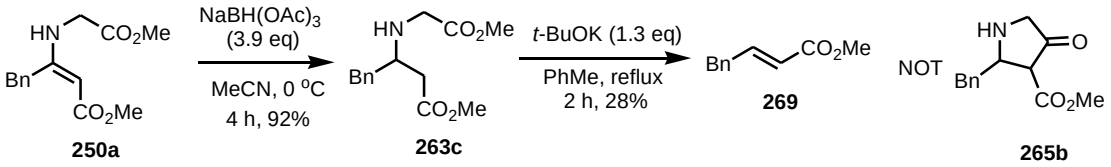
The *N*-methyl diester **267** was prepared in the hope that no reverse-Michael reaction would occur since the nitrogen is fully substituted. The diester **263d** was methylated using potassium carbonate and methyl iodide in moderate yield (52%). The resulting *N*-methyl diester **267** was heated under reflux with potassium *tert*-butoxide in toluene for 2 hours; however, a reverse-Michael reaction took place again to give the α,*β*-unsaturated ester **266** in 52% yield (Scheme 3.23).



Scheme 3.23 Attempted cyclisation of the *N*-methyl diester **267**

It was suspected that the phenyl group of the diester **263d** facilitates the reverse-Michael reaction so the diester **263c** with a benzyl group was prepared. The diester **263c** was synthesized by a sodium triacetoxyborohydride reduction of the

diester **250a** in 92% yield. The diester **263c** was treated with potassium *tert*-butoxide but again reverse-Michael reaction occurred to give the α,*β*-unsaturated ester **269** in 52% yield (Scheme 3.24).

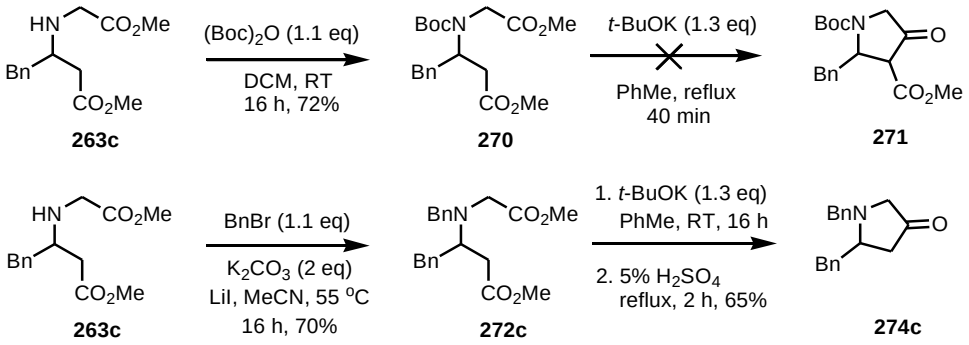


Scheme 3.24 Attempted cyclisation of the diester **263c**

The deactivating Boc group was then added to the diester **263c** in the hope of preventing the undesired reverse-Michael reaction. The Boc group could be easily added by treating the diester **263c** with di-*tert*-butyl dicarbonate in 72% yield. However, when the *N*-Boc diester **270** was heated with potassium *tert*-butoxide for 40 minutes, a complex mixture resulted and no desired product could be isolated (Scheme 3.25).

A literature search for the synthesis of pyrrolidin-3-ones via a Dieckmann cyclisation revealed only one patent that described such an approach. In that patent, the *N*-benzyl diester was cyclised by treating with 1M potassium *tert*-butoxide solution in toluene at room temperature for 16 hours.[52] Since 1-benzyl-5-methylpyrrolidin-3-one (**274a**) was the only pyrrolidin-3-one described in that patent, the scope was evaluated by using the same conditions to prepare the *N*-benzyl diester **272c**; which was via a displacement reaction of the diester **263c** and benzyl bromide using potassium carbonate in 70% yield. A trace amount of lithium iodide was added to generate benzyl iodide which is a better substrate for a S_N2 reaction because iodide is a better leaving group. The *N*-benzyl diester **272c** was then reacted with 1M potassium *tert*-butoxide solution at room temperature. The Dieckmann cyclisation took place and after decarboxylation,

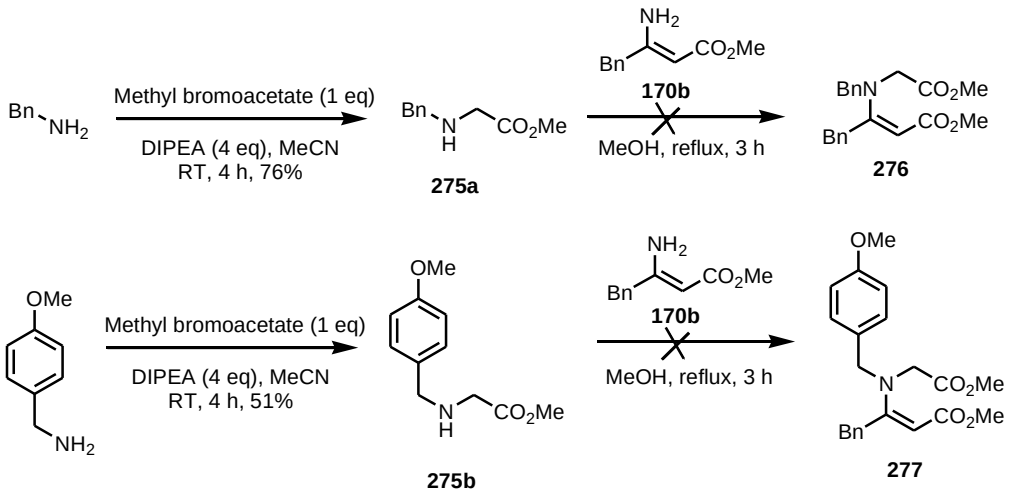
the desired pyrrolidin-3-one **274c** was isolated in 65% over two steps (Scheme 3.25). 1M Potassium *tert*-butoxide solution was also an important factor for a clean Dieckmann cyclisation; when potassium *tert*-butoxide powder was used instead, the reaction was not complete after 3 days and the pyrrolidin-3-one **274c** was isolated in only 38%.



Scheme 3.25 Dieckmann cyclisation of *N*-protected diesters

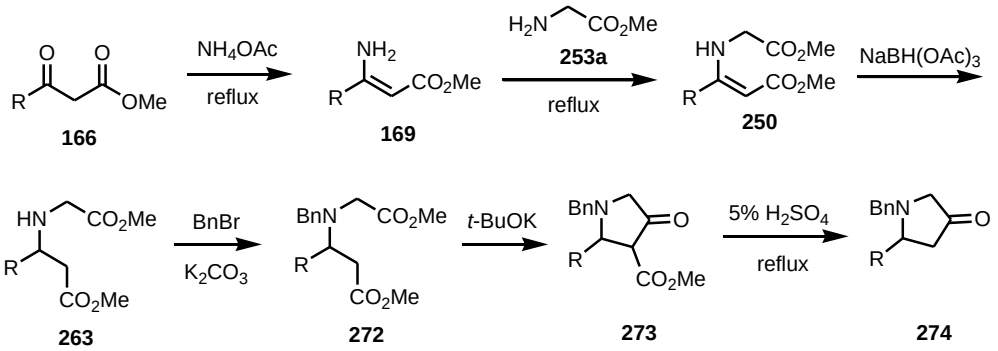
Since the presence of a *N*-benzyl group is vital for a satisfied Dieckmann cyclisation, the benzyl amino ester **275a** was prepared so as to shorten the synthetic route (Scheme 3.26). The *para*-methoxybenzyl amino ester **275b** was also prepared because if a *para*-methoxybenzyl group can block the reverse-Michael reaction, this can then be removed easily in later step by cerium(IV) ammonium nitrate (CAN).

The amino esters **275a** and **275b** were prepared by displacement of methyl bromoacetate with the corresponding amines in the presence of diisopropylethylamine. The yields were moderate (76% and 51% respectively, Scheme 3.26). However, when they were heated under reflux with the enamine **170b** in methanol for 3 hours, no displacement took place and a complex mixture was resulted, perphaps because the secondary amines are too bulky for a displacement reaction to take place. Therefore, the original synthetic route was used to make other pyrrolidin-3-ones **274**.



Scheme 3.26 Attempted synthesis of *N*-protected enamines

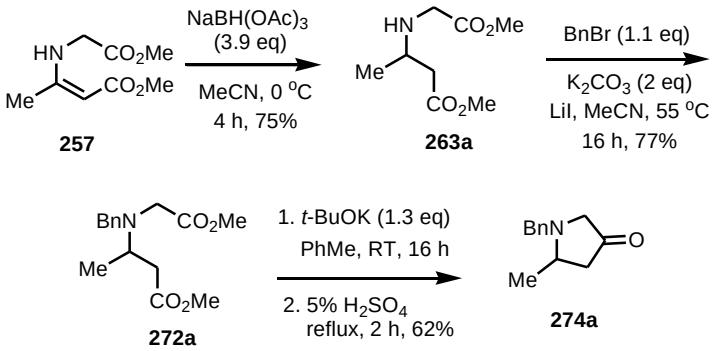
From the above result, a general route to pyrrolidin-3-ones **274** was generated (Scheme 3.27). The 5-benzyl pyrrolidin-3-one **274c** had already been prepared by this route (Scheme 3.25). Synthesis of four more different pyrrolidin-3-ones were attempted in order to outline the scope and limitations of this route. Two of them possess a 5-alkyl substitution (methyl and propyl) and a third has a 5-phenyl group. The fourth, 5-(3-pyridyl)pyrrolidin-3-one, possesses the same skeleton as the alkaloid nicotine.



Scheme 3.27 General route to pyrrolidin-4-ones **274**

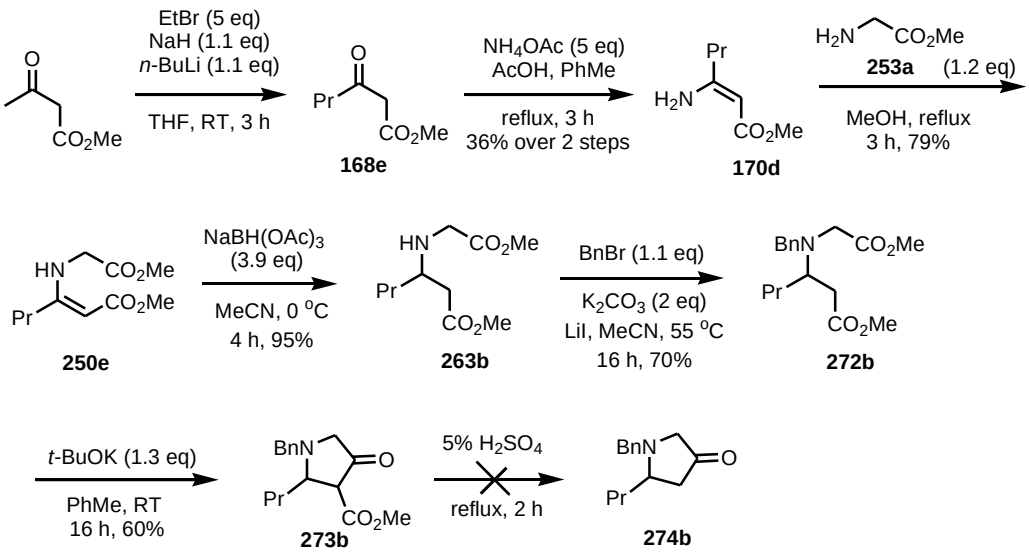
Since the 5-methylpyrrolidin-3-one **274a** is the only known *N*-benzylpyrrolidin-3-one, it was prepared by our synthetic route so that the formation of such ring could be confirmed by comparing the spectroscopic data with the literature values. Reduction of

the enamine **257** gave the diester **263a** in 75% yield. *N*-Benzylation of the diester **263a** proceeded in good yield. The diester **272a** was then cyclised and decarboxylated to give the 5-methylpyrrolidin-3-one **274a** in 62% yield (Scheme 3.28).[52] Since the spectroscopic data for **274a** matched with the literature values, synthesis of other pyrrolidin-3-ones **274** was attempted.



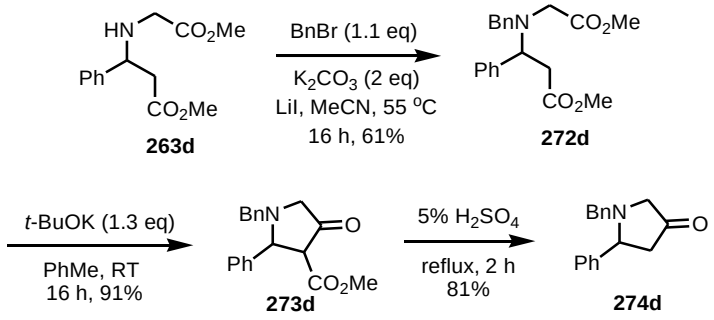
Scheme 3.28 Synthesis of the pyrrolidin-3-one **274a**

For the preparation of 5-propylpyrrolidin-3-one, the *β*-keto ester **168e** was prepared by a Weiler dianion alkylation and was coupled with ammonium acetate to give the enamine **170d** in 35% over two steps (Scheme 3.29). Displacement with the amino ester **253a** gave the diester **250e** in 79% and reduction with sodium triacetoxyborohydride proceeded in excellent yield. *N*-Benzylation proceeded in 70% yield and a subsequent Dieckmann cyclisation gave the 4-(methoxycarbonyl)pyrrolidin-3-one **273b** in 60% yield. However, decarboxylation of **273b** using 5% sulfuric acid gave a complex mixture. Since the diester **272b** was consumed, Krapcho decarboxylation was not tried here although it was found to be an effective decarboxylation method for such ring system later on.



Scheme 3.29 Attempted synthesis of the pyrrolidin-3-one **274b**

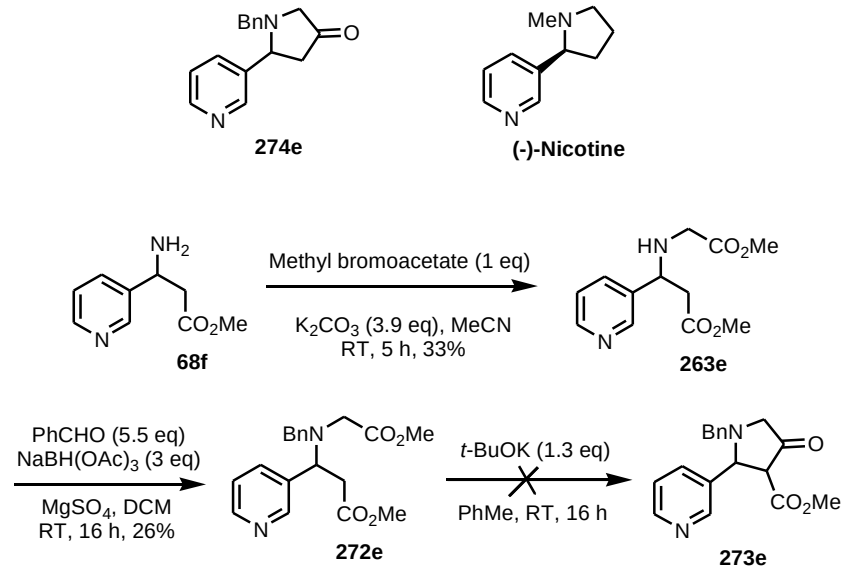
Synthesis of the 5-phenylpyrrolidin-3-one **274d** was attempted using the general route (Scheme 3.30). Treatment of the diester **263d** with benzyl bromide gave the benzyl diester **272d** in 61% yield which underwent a Dieckmann cyclisation in 91% yield to give the cyclised product **273d** which was decarboxylated using 5% sulfuric acid to give the 5-phenylpyrrolidin-3-one **274d** in 81% yield. Since the yield of cyclisation was very good, grams of **274d** were prepared for the investigation of the reactivity of pyrrolidin-3-ones in Section 3.2.4.



Scheme 3.30 Synthesis of the pyrrolidin-3-one **274d**

The final attempted to be synthesized was a 5-(3-pyridyl)pyrrolidin-3-one. It was of interest because it shares the same structure with nicotine. The diester **263e** was

prepared from the *β*-amino ester **68f** by a displacement reaction in 33% yield (Scheme 3.31). However, when the diester **263e** was treated with benzyl bromide and potassium carbonate, a complex mixture resulted, probably because the pyridine ring interacted with benzyl bromide to afford unwanted side products. The benzyl diester **272e** was prepared by a reductive amination of benzaldehyde and the diester **263e** in 26% yield (by a modification of Ley's synthesis).[53] However, when the diester **263e** was treated with 1M potassium *tert*-butoxide solution at room temperature for 16 hours, side reactions took place to give a complex mixture. Since the pyridine ring was too reactive, synthesis of the 5-(3-pyridyl)pyrrolidin-3-one **274e** was abandoned.



Scheme 3.31 Attempted synthesis of the 4-(methoxycarbonyl)pyrrolidin-3-one **273e**

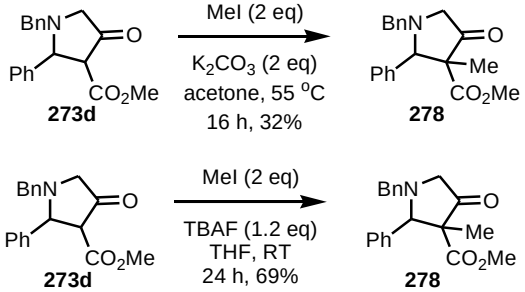
To sum up, the synthesis of five different 5-substituted pyrrolidin-3-ones using the general route was attempted. Dieckmann cyclisation using 1M potassium *tert*-butoxide solution gave four different 5-substituted 4-(methoxycarbonyl)pyrrolidin-3-ones in 60-91% yields except the 5-(3-pyridyl)pyrrolidin-3-one **273e**. Three of them could be decarboxylated using 5% sulfuric acid (62-81% yields) but not the 5-propylpyrrolidin-3-one **273b**. It is believed that a Krapcho decarboxylation of **273b**

could have been successful but it was not attempted owing to the lack of the starting materials. The 5-phenylpyrrolidin-3-one **274d** would be used to investigate the reactivity of pyrrolidin-3-ones which will be discussed in the next section.

3.2.4 Methylation, Reduction, and Deprotection of Pyrrolidin-3-ones

By the general route shown in Scheme 3.27, pyrrolidin-3-ones with various 5-substitutions were synthesized. Our next objective was the addition of another substituent to the 4-position. It was proposed that alkylation of 4-(methoxycarbonyl)pyrrolidin-3-ones **273** with alkyl halide and subsequent decarboxylation would give 5,6-disubstituted pyrrolidin-3-ones.

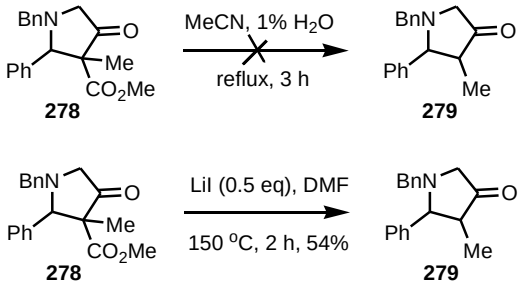
The tradition methylation procedure using potassium carbonate as a base was first applied to the 4-(methoxycarbonyl)pyrrolidin-3-one **273d**; heating the mixture at 55 ^{o}C in acetone for 16 hours gave the methylated product **278** in 32% yield. However, modification of the method sued by Prof. Philip Page[54], using TBAF as a base and stirring at room temperature in THF for 24 hours, gave **278** in much higher yield (69%, Scheme 3.32).



Scheme 3.32 Methylation of the 4-(methoxycarbonyl)pyrrolidin-3-one **273d**

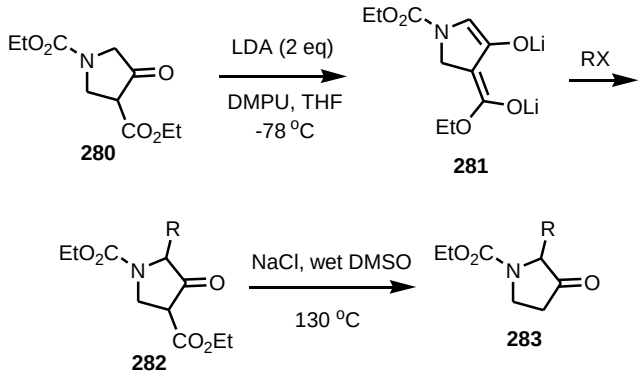
Decarboxylation of 4-(methoxycarbonyl)-4-methylpyrrolidin-3-one **278** by heating

under reflux in 1% water/acetonitrile for 3 hours was attempted but no reaction took place (Scheme 3.33). Then a Krapcho decarboxylation (modified from Hashizume's synthesis[55]) was employed by heating **278** with lithium iodide at 150 ^{o}C in DMF for 2 hours; this gave the desired *trans*-4-methylpyrrolidin-3-one **279** in 54% yield.



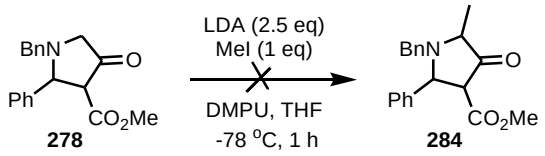
Scheme 3.33 Decarboxylation of the 4-(methoxycarbonyl)-4-methylpyrrolidin-3-one **278**

Since 4,5-disubstituted pyrrolidin-3-ones had been successfully prepared, the next ojective was the synthesis of 2,5-disubstituted pyrrolidin-3-ones. Giles reported that 2-substituted pyrrolidin-3-ones **283** could be made from 4-(ethoxycarbonyl)pyrrolidin-3-ones **280** (Scheme 3.34).[56] By treating **280** with 2 equivalents of lithium diisopropylamine (LDA), the dianion **281** was formed, in the presence of dimethylpropyleneurea (DMPU) as a co-solvent.[56] Giles had showed that alkylation of dianions of type **281** occurred at the 2-position since that enolate was more reactive.[56] After decarboxylation, 2-substituted pyrrolidin-3-ones **283** were synthesized. It was hoped that this strategy could be applied to make 2,5-disubstituted pyrrolidin-3-ones.



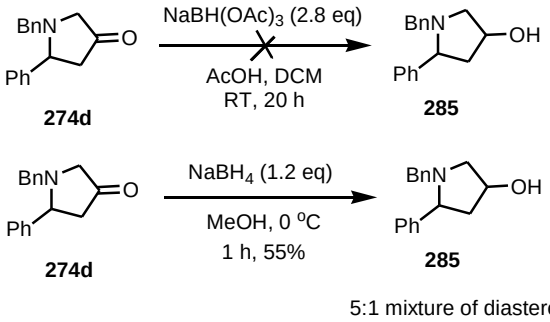
Scheme 3.34 Giles' alkylation of 4-(ethoxycarbonyl)pyrrolidin-3-ones **280**[56]

When the 4-(methoxycarbonyl)pyrrolidin-3-one **278** was treated with 2 equivalents of LDA using the Giles' method, no reaction took place and **278** was recovered (Scheme 3.35). It was suspected that the system was not anhydrous enough to form the highly reactive dianion. Extra attention was paid to make sure everthing was anhydrous but the problem could not be solved. Due to the difficulty of generating the dianion, synthesis of 2,5-disubstituted pyrrolidin-3-ones was abandoned.



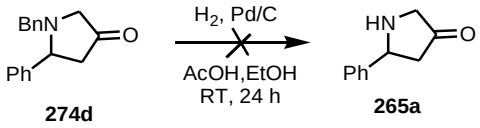
Scheme 3.35 Attempted methylation of the 4-(methoxycarbonyl)pyrrolidin-3-one **278** using 2 equivalents of LDA

Reduction of pyrrolidin-3-ones to give 5-substituted pyrrolidin-3-ols was also of interest. Sodium triacetoxyborohydride[57] was employed to reduce the pyrrolidin-3-one **274d** but no reduction of **274d** was observed after 20 hours (Scheme 3.36). Then the more reactive sodium borohydride was used which reduced the pyrrolidin-3-one **274d** to the pyrrolidin-3-ol **285** in 55% yield, as a 5:1 mixture of (*E*)- and (*Z*)-diastereoisomers. The major isomer would be the (*Z*)-isomer so that the steric hindrance is minimized.



Scheme 3.36 Reduction of the pyrrolidin-3-one **274d**

The final objective was the removal of benzyl group to give *N*-unsubstituted pyrrolidin-3-ones. Traditional hydrogenation deprotection was attempted using palladium on activated carbon and hydrogen gas. However, no change was observed by TLC after stirring for 3 days. A few drops of acetic acid were added to the reaction mixture to facilitate hydrogenation. A complex mixture had formed after 1 day (Scheme 3.36), perhaps because after removal of the benzyl group the *N*-unsubstituted pyrrolidin-3-one **265a** was unstable and was decomposed even under mild acidic conditions. Due to time limitations, further attempts to remove the benzyl group were abandoned.

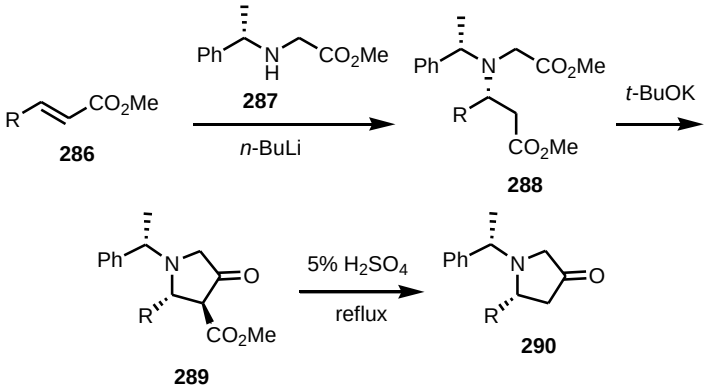


Scheme 3.36 Deprotection of the pyrrolidin-3-one **274d**

3.2.5 Enantioselective Synthesis of Pyrrolidin-3-ones

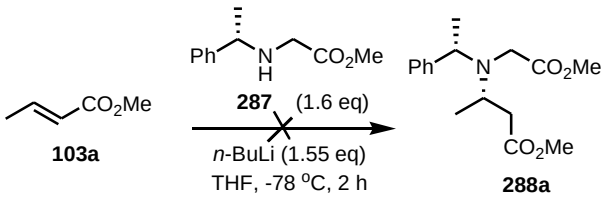
In Section 1.2.4, enantiopure piperidin-2,4-diones were prepared with the use of a chiral auxiliary. It was desired to extend this methodology to the synthesis of enantiopure pyrrolidin-3-ones. The proposed route is shown in Scheme 3.37. Aza-Michael addition of the chiral amino ester **287** to α,β-unsaturated esters **286** would give diesters **288**. Dieckmann cyclisation followed by decarboxylation would afford

enantiopure piperidin-2,4-diones **290**.



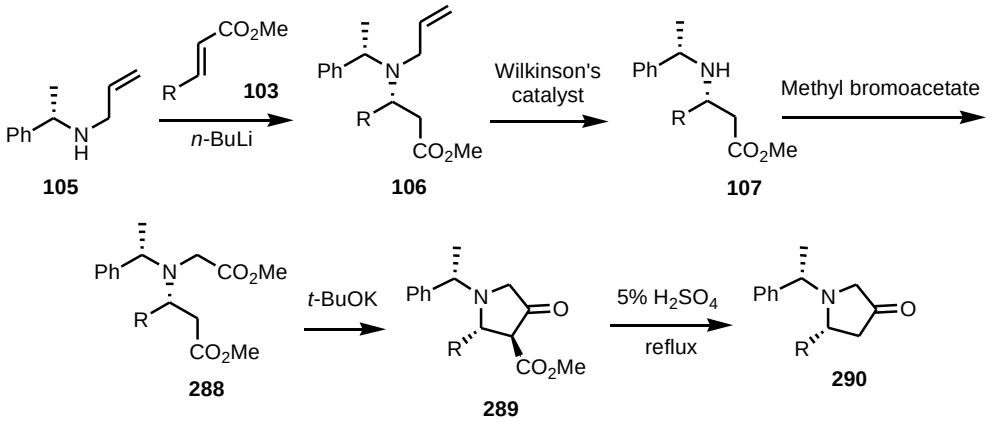
Scheme 3.37 Proposed route to enantiopure pyrrolidin-3-ones **290**

The chiral amino ester **287** was prepared in 32% yield by a displacement reaction of methyl bromoacetate with (*S*)-1-phenylethylamine using triethylamine.[58] However, when the chiral amino ester **287** was treated with the *α*,*β*-unsaturated ester **103a** and *n*-butyllithium at -78 ^{o}C, a complex mixture resulted and no desired diester **288a** could be isolated (Scheme 3.38). Presumably the strong base *n*-butyllithium had reacted at the ester group of amino ester **287** giving various side products. Therefore, the proposed route needed to be modified to prevent such interactions.



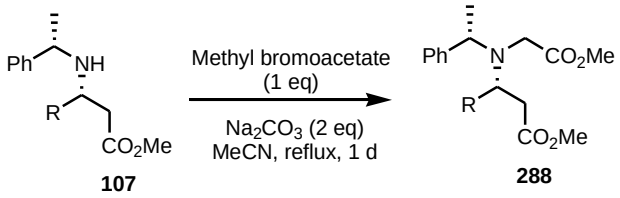
Scheme 3.38 Attempted aza-Michael reaction to the diester **288a**

The modified route to enantiopure pyrrolidin-3-ones **290** is shown in Scheme 3.39. The first two steps were in common with the enantioselective synthesis of piperidin-2,4-diones (Scheme 1.42). Diesters **288** were made from amines **107** by reaction with methyl bromoacetate. The desired pyrrolidin-3-ones **290** were then formed by a Dieckmann cyclisation followed by a decarboxylation.



Scheme 3.39 Modified route to enantiopure pyrrolidin-3-ones **290**

To examine the feasibility of this synthetic route, synthesis of five enantiopure 5-substituted pyrrolidin-3-ones **290** was attempted; three had an aliphatic chain (methyl, isopropyl, and propenyl) and two had a ring (cyclohexyl and phenyl). Amines **107** were prepared as in Section 1.2.4, using Wilkinson's catalyst.[59] Amines **107** were then alkylated with methyl bromoacetate to give diesters **288** in moderate to excellent yields (51-96%, Scheme 3.40).

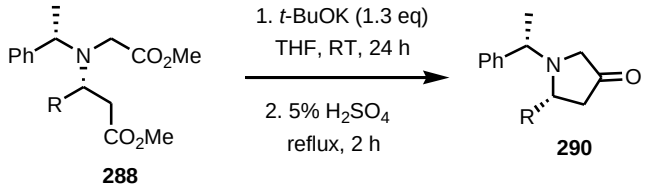


Cpd	R	yield (%)
107a	Me	96
107b	*i*-Pr	56
107c	(*E*)-CH=CHMe	84
107d	Cyclohexyl	51
107e	Ph	58

Scheme 3.40 Synthesis of diesters **288**

Dieckmann cyclisations of diesters **288** were attempted using 1M potassium *tert*-butoxide solution in THF at room temperature (Scheme 3.41). After decarboxylation, the enantiopure 5-methylpyrrolidin-3-one **290a** was isolated in 40% yield over two steps. However, treating diesters **288b** (R= isopropyl), **288c** (R= propenyl), and **288d** (R= cyclohexyl) with potassium *tert*-butoxide gave complex mixtures. Dieckmann cyclisation of the diester **288e** gave the enantiopure 4-(methoxycarbonyl)-5-phenylpyrrolidin-3-one **289a** in 55% yield. However, decarboxylation of **289a** using 5% sulfuric acid gave the 5-phenylpyrrolidin-3-one **290b** as a 3:1 mixture of diastereoisomers in 28% yield over two steps. Krapcho

decarboxylation of **289a** by heating with lithium iodide in DMF at 150 ^{o}C for 1 hour gave **290b** as a 1:1 mixture of diastereoisomers. Because of time limitations, synthesis of further enantiopure pyrrolidin-3-ones **290** could not be carried out.



288 **290**

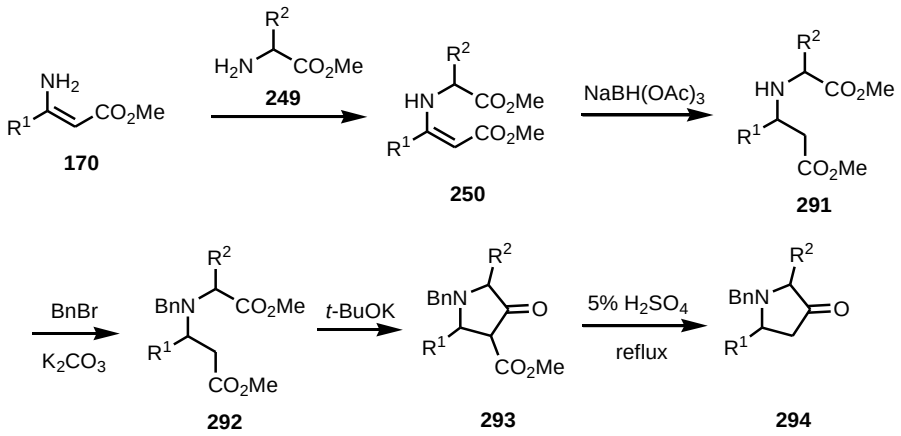
Cpd	R	yield (%)
288a	Me	40
288b	*i*-Pr	0 (decomposed)
288c	(*E*)-CH=CHMe	0 (decomposed)
288d	Cyclohexyl	0 (decomposed)
288e	Ph	28 (mixture of diastereoisomers)

Scheme 3.41 Synthesis of pyrrolidin-3-ones **288**

3.2.6 Future Work

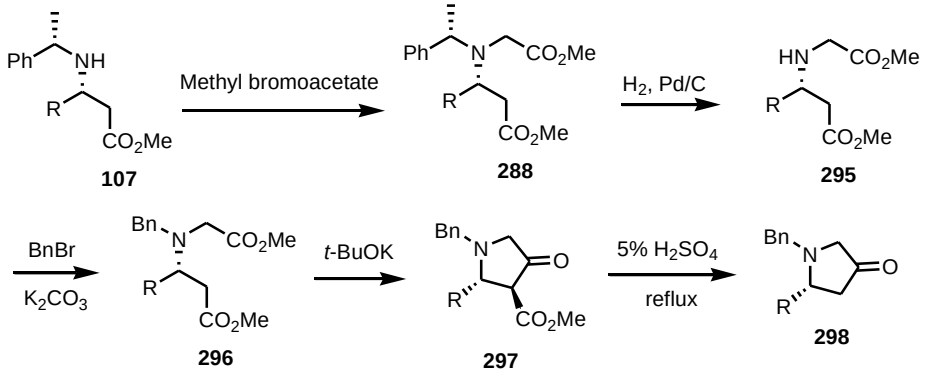
2,5-Disubstituted pyrrolidin-3-ones **294** could not be prepared by using the dianion procedure (Scheme 3.35). Therefore, another route was proposed (Scheme 3.42) in which the 5-substituents were supplied from amino esters **249**. The presence of the R^2 group in diesters **291** may facilitate the Dieckmann cyclisation since a bulky group

constrains the bond rotation of **291** and brings the ester close to the enolate.



Scheme 3.42 Proposed route to 2,5-disubstituted pyrrolidin-3-ones **294**

For the enantioselective synthesis of pyrrolidin-3-ones, the presence of the auxiliary, instead of a *N*-benzyl group, hindered the ring formation and only enantiopure 5-methylpyrrolidin-3-one **290a** could be prepared (Scheme 3.41). Thus, the solution would be that diesters **288** have their auxiliary removed by hydrogenation and are reprotected by a benzyl group prior to a Dieckmann cyclisation.



Scheme 3.43 Modified route to enantiopure pyrrolidin-3-ones **298**

3.3 Conclusions

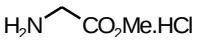
The synthesis of 1,2-dihydropyrrolidin-3-ones was attempted (Scheme 3.11) employing the same strategy used to make piperidin-4-ones (Section 2.2.7) but a hydrolysis reaction, rather than a Dieckmann cyclisation, occurred to give *β*-keto esters **168**. Then diesters **250** were replaced by bromo esters **260** and it was hoped that 1,2-dihydropyrroles **262** could be made by a S_N2 substitution reaction (Scheme 3.17). However, the bromo esters **260** could not be prepared from hydroxy esters **259** so this route was abandoned.

Pyrrolidin-3-ones **274** were prepared by the protocol used to make piperidin-2,4-diones (Section 1.2.3). Dieckmann cyclisation using 1M potassium *tert*-butoxide solution at room temperature afforded the 4-(methoxycarbonyl)pyrrolidin-3-ones **273** (Scheme 3.27). The 4,5-disubstituted pyrrolidin-3-one **279** and the 5-substituted pyrrolidin-3-ol **285** were prepared but the *N*-benzyl could not be removed.

Enantioselective synthesis of pyrrolidin-3-ones **290** was attempted (Scheme 3.39) by asymmetric induction using the Davies' chiral auxiliary. The enantiopure 5-methylpyrrolidin-3-one **290a** was prepared by this route, but other diesters **288** decomposed when treated with potassium *tert*-butoxide.

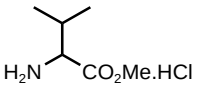
3.4 Experimental

Methyl aminoethanoate hydrochloride (253a)[60]



To a stirred solution of glycine (2.00 g, 26.0 mmol) in methanol (40 mL) in a salt-ice bath, thionyl chloride (1.2 mL, 28.0 mmol) was added dropwise via an addition funnel. The resulting solution was heated under reflux for 30 min. Diethyl ether (40 mL) was added and the solution was left to crystallize. The microprisms were filtered, washed with diethyl ether to give **253a** (2.94 g, 90%) as white microprisms, mp 170-172 ℃ (lit.[60] mp 177 ℃); IR ν_{max} 3389 (N-H), 2952 (C-H), 1739 (ester C=O), 1612, 1512, 1437, 1247, 1178, 1033 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 3.85 (3H, s, OCH_3) 3.83 (2H, s, CH_2NH_2); ^{13}C NMR (500 MHz, $CDCl_3$) δ 169.0 ($COOCH_3$) 53.5 (OCH_3) 41.0 (CH_2NH_2).

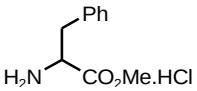
Methyl 2-amino-3-methylbutanoate hydrochloride (253c)[45]



To a stirred solution of valine (2.00 g, 17.1 mmol) in methanol (20 mL) in a salt-ice bath, thionyl chloride (3.7 mL, 50.2 mmol) was added dropwise via an addition funnel. The resulting solution was stirred at room temperature for 16 h. Diethyl ether (20 mL) was added and the solution was left to crystallize. The microprisms were filtered, washed with diethyl ether to give **253c** (2.23 g, 78%) as white microprisms, ^{1}H NMR (500 MHz, CD_3OD) δ 3.93 (1H, d, J= 4.7 Hz, $CHNH_2$) 3.84 (3H, s, OCH_3) 2.32-2.25 (1H, m, $CHCH_3$) 1.07 (3H, d, J= 5.2 Hz, CH_3CHCH_3) 1.06 (3H, d, J= 5.1 Hz, CH_3CHCH_3); ^{13}C NMR (500 MHz, $CDCl_3$) δ 170.4 ($COOCH_3$) 59.4 ($CHNH_2$) 53.5

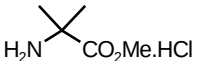
(OCH_3) 31.0 ($CHCH_3$) 18.4 (CH_3CH) 18.2 (CH_3CH).

Methyl 2-amino-3-phenylpropanoate hydrochloride (253d)[61]



To a stirred solution of 2-amino-3-phenylpropionic acid (3.00 g, 18.1 mmol) in methanol (16 mL) in a salt-ice bath, thionyl chloride (1.5 mL, 20.0 mmol) was added dropwise via an addition funnel. The resulting solution was heated under reflux for 2 h. Diethyl ether (30 mL) was added and the solution was left to crystallize. The microprisms were filtered, washed with diethyl ether to give **253d** (3.70 g, 97%) as white microprisms, mp 156-157 ℃ (lit.[61] 158-160 ℃); IR ν_{max} 3457 (N-H), 2847 (C-H), 1745 (ester C=O), 1497, 1240, 701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (2H, br s, NH_2) 7.33-7.26 (5H, m, Ph) 4.40 (1H, s, C*H*NH_2) 3.69 (3H, s, OCH_3) 3.47-3.32 (2H, m, C*H*$_2$Ar); ^{13}C NMR (500 MHz, CD_4OD) δ 170.5 (*C*$OOCH_3$) 135.3 (ArC) 130.4 (ArC) 130.2 (ArC) 129.0 (ArC) 55.2 ($CHNH_2$) 53.6 (OCH_3) 47.4 (CH_2Ar).

Methyl 2-amino-2-methylpropanoate hydrochloride (253e)[44]



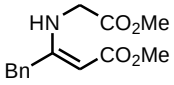
To a stirred solution of aminoisobutyric acid (2.00 g, 17.1 mmol) in methanol (20 mL) in a salt-ice bath, thionyl chloride (1.5 mL, 20.0 mmol) was added dropwise via an addition funnel. The resulting solution was stirred for 4 h at 55 ^{o}C and stirred overnight at room temperature. Diethyl ether (30 mL) was added and the solution was left to crystallize. The microprisms were filtered, washed with diethyl ether to give **253e** (2.30 g, 75%) as white microprisms, mp 182-183 ℃ (lit.[62] 182-183 ℃); IR ν_{max} 3368 (N-H), 2922 (C-H), 1741 (ester C=O), 1634, 1521, 1322, 1197, 875 cm^{-1}; ^{1}H NMR

(300 MHz, $CDCl_3$) δ 8.97 (2H, br s, NH_2) 3.86 (3H, s, OCH_3) 1.73 (6H, s, CH_3CCH_3).

General procedure for enamino esters 250

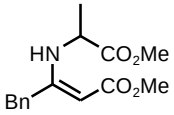
To enamino esters **250** (1.0 equiv) in methanol was added amino esters (1.1 equiv) and the solution was heated under reflux for 3 h. The mixture was allowed to cool to room temperature, then diluted with diethyl ether. The solution was filtered and the filtrate was evaporated.

Methyl 3-(1-methoxycarbonylmethyl)amino-4-phenylbut-2-enoate (250a)



Following general procedure, reaction of methyl 3-amino-4-phenylbut-2-enoate (1.00 g, 5.20 mmol) and methyl aminoethanoate hydrochloride (0.79 g, 6.30 mmol) in methanol (1.1 mL) gave **250a** (1.45 g, 87%) as a milky gum, R_f 0.24 (30% ethyl acetate/hexane); IR ν_{max} 3340 (N-H), 2954 (C-H), 1745 (ester C=O), 1656 (C=C), 1605, 1436, 1209 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.87 (1H, br d, J= 6.1 Hz, NH) 7.34-7.21 (5H, m, Ph) 4.62 (1H, s, =CHCOO) 3.87 (2H, d, J= 6.1 Hz, CH_2NH) 3.69 (3H, s, OCH_3) 3.67 (3H, s, OCH_3) 3.51 (2H, s, CH_2Ar).

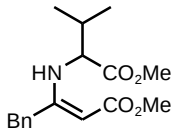
Methyl 3-(1-methoxycarbonylethyl)amino-4-phenylbut-2-enoate (250b)



Following general procedure, reaction of methyl 3-amino-4-phenylbut-2-enoate (0.80 g, 4.18 mmol) and methyl 2-aminopropanoate hydrochloride (0.70 g, 5.02 mmol) in methanol (1 mL) gave **250b** (1.01 g, 87%) as an orange oil, R_f 0.72 (50% ethyl

acetate/hexane); IR ν_{max} 3245 (N-H), 2950 (C-H), 1741 (ester C=O), 1657 (C=C), 1598, 1452, 1251, 1146, 729 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (1H, br d, *J*= 8.6 Hz, NH) 7.33-6.91 (5H, m, Ph) 4.57 (1H, s, C*H*=CNH) 4.17-4.12 (1H, m, C*H*NH) 3.66 (3H, s, OCH_3) 3.64 (3H, s, OCH_3) 3.50 (2H, s, CH_2CNH) 1.34 (3H, d, *J*= 7.4 Hz, CH_3CHCOO); ^{13}C NMR (500 MHz, $CDCl_3$) δ 173.2 (*C*$OOCH_3$) 170.7 (*C*$OOCH_3$) 161.4 (=CNH) 136.0 (ArC) 129.1 (ArC) 128.6 (ArC) 127.0 (ArC) 86.1 (=*C*CO) 52.3 (CH_2N) 51.2 (CH_3O) 50.2 (CH_3O) 39.1 (CH_2Ar) 19.5 (*C*H_3CH); m/z (Cl+) 278 (100%, $M+H^+$); HRMS $C_{15}H_{20}NO_4$ calcd. 278.1392, found 238.1371.

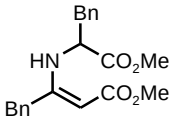
Methyl 3-(1-methoxycarbonyl-2-methylpropyl)amino-4-phenylbut-2-enoate (250c)



Following general procedure, reaction of methyl 3-amino-4-phenylbut-2-enoate (0.50 g, 2.61 mmol) and methyl 2-amino-3-methylbutanoate hydrochloride (0.57 g, 3.40 mmol) in methanol (0.6 mL) gave **250c** (0.74 g, 93%) as yellow microprisms, mp 48-50 ℃; R_f 0.76 (50% ethyl acetate/hexane); IR ν_{max} 3247 (N-H), 2964 (C-H), 1741 (ester C=O), 1657 (C=C), 1609, 1248, 1146, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.90 (1H, br d, *J*= 10.0 Hz, NH) 7.35-7.14 (5H, m, Ph) 4.60 (1H, s, C*H*=CNH) 3.84 (1H, dd, *J*= 10.0, 5.5 Hz, C*H*NH) 3.69 (3H, s, OCH_3) 3.61 (3H, s, OCH_3) 3.47 (2H, s, CH_2CNH) 2.10-1.99 (1H, m, C*H*CHCOO) 0.86 (3H, d, *J*= 6.9 Hz, CH_3CHCH_3) 0.82 (3H, d, J= 6.9 Hz, CH_3CHCH_3); ^{13}C NMR (500 MHz, $CDCl_3$) δ 172.4 (*C*$OOCH_3$) 170.9 (*C*$OOCH_3$) 162.0 (=CNH) 136.1 (ArC) 129.0 (ArC) 128.6 (ArC) 127.0 (ArC) 86.0 (=*C*CO) 61.2 (CH_2N) 52.0 (CH_3O) 50.3 (CH_3O) 39.3 (CH_2Ar) 31.6 (*C*HCH_3) 19.1 (*C*H_3CH) 17.7 (*C*H_3CH); m/z (Cl+) 306 (100%, $M+H^+$); HRMS $C_{17}H_{24}NO_4$ calcd.

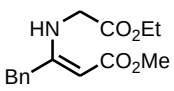
306.1705, found 306.1693.

Methyl 3-(1-methoxycarbonyl-2-phenylethyl)amino-4-phenylbut-2-enoate (250d)



Following general procedure, reaction of methyl 3-amino-4-phenylbut-2-enoate (0.80 g, 4.18 mmol) and methyl 2-amino-3-phenylpropanoate hydrochloride (1.08 g, 5.02 mmol) in methanol (1 mL) gave **250d** (1.21 g, 90%) as orange microprisms, mp 59-63 ℃; R_f 0.42 (30% ethyl acetate/hexane); IR ν_{max} 3256 (N-H), 2949 (C-H), 1743 (ester C=O), 1657 (C=C), 1609, 1493, 1249, 1164, 1123, 729, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.95 (1H, br d, *J*= 9.9 Hz, NH) 7.26-6.83 (10H, m, Ph) 4.50 (1H, s, C*H*=CNH) 4.24 (1H, ddd, *J*= 9.9, 8.5, 5.3 Hz, C*H*NH) 3.69 (3H, s, OCH_3) 3.61 (3H, s, OCH_3) 3.27 (2H, s, CH_2CNH) 3.03 (1H, dd, *J*= 13.6, 5.3 Hz, CH_2CHCOO) 2.81 (1H, dd, *J*= 13.6, 8.5 Hz, CH_2CHCOO); ^{13}C NMR (500 MHz, $CDCl_3$) δ 172.0 (*C*$OOCH_3$) 170.7 (*C*$OOCH_3$) 161.3 (=CNH) 136.3 (ArC) 135.9 (ArC) 129.6 (ArC) 129.2 (ArC) 129.0 (ArC) 128.6 (ArC) 127.1 (ArC) 127.0 (ArC) 86.1 (=*C*CO) 57.5 (CHN) 52.4 (CH_3O) 50.3 (CH_3O) 40.2 (CH_2Ar) 39.0 (CH_2Ar); m/z (Cl+) 354 (100%, $M+H^+$); HRMS $C_{21}H_{24}NO_4$ calcd. 354.1705, found 354.1718.

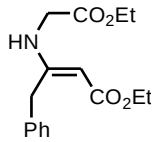
Methyl 3-(ethoxycarbonylmethyl)amino-4-phenylbut-2-enoate (255)



Following general procedure, reaction of methyl 3-amino-4-phenylbut-2-enoate (1.30 g, 6.80 mmol) and ethyl aminoethanoate hydrochloride (1.33 g, 9.50 mmol) in methanol (1.5 mL) gave **255** (1.73 g, 92%) as white microprisms, mp 88-91 ^oC; R_f 0.86 (ethyl

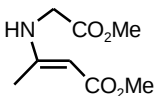
acetate); IR ν_{max} 3296 (N-H) 2944 (C-H), 1743 (ester C=O), 1655 (ester C=O), 1595, 1413 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (1H, br d, *J*= 3.6 Hz, NH) 7.32-7.21 (5H, m, Ph) 4.60 (1H, s, =C*H*COO) 4.16 (2H, q, *J*= 4.2 Hz, CH_2OOC) 3.85 (2H, d, *J*= 3.6 Hz, C*H*$_2$NH) 3.66 (3H, s, OCH_3) 3.51 (2H, s, C*H*$_2$Ar) 1.25 (3H, t, *J*= 4.2 Hz, C*H*$_3$CH$_2$); ^{13}C NMR (300 MHz, $CDCl_3$) δ 170.7 (*C*OOCH$_2$) 169.7 (*C*OOCH$_3$) 161.6 (=CNH) 135.8 (ArC) 129.2 (ArC) 128.6 (ArC) 127.0 (ArC) 86.0 (=*C*CO) 61.5 (CH_2N) 50.3 (CH_2O) 44.7 (CH_3O) 39.1 (CH_2Ar) 14.1 (*C*H_3CH_2); m/z (Cl+) 278 (100%, M^+); HRMS $C_{15}H_{20}NO_4Na$ calcd. 278.1392, found 238.1406.

Ethyl 3-(ethoxycarbonylmethyl)amino-4-phenylbut-2-enoate (256)



Following general procedure, reaction of ethyl 3-amino-4-phenylbut-2-enoate (0.20 g, 1.00 mmol) and ethyl aminoethanoate hydrochloride (0.18 g, 1.30 mmol) in methanol (0.3 mL) gave **256** (0.26 g, 91%) as a yellow oil; R_f 0.57 (30% ethyl acetate/hexane); IR ν_{max} 3222 (N-H), 2923 (C-H), 1741 (ester C=O), 1660 (C=C), 1518, 1435, 1359, 1198, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.89 (1H, br d, *J*= 6.0 Hz, NH) 7.33-7.22 (5H, m, Ph) 4.60 (1H, s, =C*H*COO) 4.20-4.11 (4H, m, C*H*$_2$CH$_3$ x2) 3.85 (2H, d, *J*= 6.0 Hz, C*H*$_2$NH) 3.51 (2H, s, C*H*$_2$Ar) 0.89-0.84 (6H, m, C*H*$_3$CH$_2$ x2).

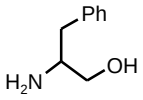
Methyl 3-(methoxycarbonylmethyl)aminobut-2-enoate (257)



Following general procedure, reaction of methyl 3-iminobutanoate (0.50 g, 4.34 mmol) and methyl aminoethanoate hydrochloride (0.71 g, 5.65 mmol) in methanol (0.8 mL)

gave **257** (0.74 g, 91%) as an orange oil, R_f 0.46 (30% ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.81 (1H, br d, *J*= 6.3 Hz, NH) 4.58 (1H, s, C*H*=CNH) 4.00 (2H, d, *J*= 6.3 Hz, CH_2NH) 3.80 (3H, s, OCH_3) 3.64 (3H, s, OCH_3) 1.89 (3H, s, CH_3CNH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 170.7 (*C*$OOCH_3$) 170.3 (*C*OOCH3) 160.6 (=CNH) 84.4 (=*C*HCO_2Me) 52.5 (OCH_3) 50.2 (OCH_3) 44.7 (CH_2NH) 19.3 (*C*H_3CNH); m/z (Cl+) 188 (100%, M+H^+) 156 (55%, M^+-OCH_3); HRMS $C_8H_{14}N_4O$ calcd. 188.0923, found 188.0925.

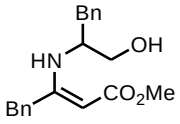
2-Amino-3-phenylpropan-1-ol (258a)[49]



To a two-neck flask fitted with a condenser, phenylalanine (2.48 g, 15.0 mmol) was dissolved in dry THF (40 mL). Sodium borohydride (1.36 g, 36.1 mmol) was added to the mixture and it was cooled to 0 ^{o}C. Iodine (3.80 g, 15.0 mmol) dissolved in dry THF (10 mL) was added via a dropping funnel over 30 min. The resulting solution was heated under reflux for 16 h. The mixture was allowed to cool to room temperature and methanol was added slowly until the solution became clear. The mixture was stirred for 30 min and evaporated. The resulting white paste was dissolved in 20% potassium hydroxide (30 mL) and was stirred for 4 h. The mixture was extracted with dichloromethane (3 x 30 mL) and the combined organic layers were washed with brine (15 mL), dried (Na_2SO_4), and evaporated to give a white solid which was recrystalised from toluene to give **258a** (1.89 g, 83%) as white microprisms, mp 89-91 ^{o}C (lit.[49] 90-92 ℃); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.18 (5H, m, Ph) 3.64 (1H, dd, *J*= 10.7, 3.8 Hz, CH_2OH) 3.39 (1H, dd, *J*= 10.7, 7.2 Hz, CH_2OH) 3.14-3.09 (1H, m, CHN) 2.79 (1H, dd, *J*= 13.5, 5.2 Hz, CH_2Ph) 2.53 (1H, dd, *J*= 13.5, 8.7 Hz, CH_2Ph) 2.02 (3H, br s,

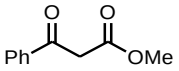
NH_2 and OH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 138.8 (ArC) 129.3 (ArC) 128.7 (ArC) 126.5 (ArC) 66.3(CH_2OH) 54.3 (CHN) 40.9 (CH_2Ar).

Methyl 3-(1-benzyl-2-hydroxyethyl)amino-4-phenylbut-2-enoate (259a)



To methyl 3-amino-4-phenylbut-2-enoate (0.20 g, 1.04 mmol) in methanol (0.4 mL) was added 2-amino-3-phenylpropan-1-ol (0.19 g, 1.25 mmol) and the solution was heated under reflux for 3 h. The mixture was allowed to cool to room temperature and evaporated. The resulting oil was purified by flash chromatography (10% ethyl acetate/hexane) to give **259a** (0.22 g, 65%) as a colourless oil, R_f 0.22 (30% ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (1H, br d, *J*= 10.4 Hz, NH) 7.32-7.01 (10H, m, Ph) 4.50 (1H, s, C*H*=CNH) 3.71-3.55 (1H, m, C*H*NH) 3.66 (3H, s, OCH_3) 3.55-3.45 (2H, m, CH_2OH) 3.36 (2H, d, *J*= 16.0 Hz, CH_2CNH) 3.21 (2H, d, *J*= 16.0 Hz, CH_2CNH) 2.95 (1H, br s, OH) 2.80 (1H, dd, *J*= 13.4, 6.0 Hz, CH_2CHCH_2OH) 2.62 (1H, dd, *J*= 13.4, 7.8 Hz, CH_2CHCH_2OH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 171.3 (*C*OCH_2) 169.5 (*C*CH) 138.1 (ArC) 136.6 (ArC) 129.3 (ArC) 128.9 (ArC) 128.8 (ArC) 126.9 (ArC) 126.6 (ArC) 84.1 (*C*HCOO) 65.1 (CH_2OH) 56.6 (CHN) 50.3 (OCH_3) 39.5 (CH_2Ar) 39.2 (CH_2Ar).

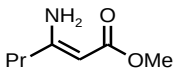
Methyl 3-oxo-3-phenylpropanoate (166e)[51]



To a solution of sodium hydride (60% dispersion in mineral oil, 1.00 g, 25.7 mmol) in THF (15 mL) was added a solution of acetophenone (1.5 mL, 12.8 mmol) in THF (1

mL) dropwise. The mixture was stirred for 30 min at room temperature, then dimethyl carbonate (6 mL, 70.2 mmol) was added dropwise. The mixture was stirred for 20 min at room temperature and was heated under reflux for 4 h. The mixture was allowed to cool to room temperature and 3M acetic acid was added until all solids dissolved. The aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate (10 mL) and then brine (10 mL), dried ($MgSO_4$), and evaporated to give **166e** (2.10 g, 92%) as an orange oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96-7.42 (5H, m, Ph) 5.68 (s, from enol) 4.02 (2H, s, CH_2CO$_2$CH$_3$) 3.80 (d, J= 5.6 Hz, from enol) 3.76 (3H, s, OCH_3); ^{13}C NMR (500 MHz, $CDCl_3$) δ 192.6 (*C*OCH_2) 168.1 (*C*OOCH_3) 133.9 (ArC) 128.9 (ArC) 128.8 (ArC) 126.1 (ArC) 52.6 (OCH_3) 45.7 (*C*H_2CO).

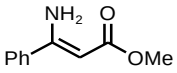
(*E*)-Methyl 3-aminohex-2-enoate (169d)[63]



To a stirred solution of sodium hydride (0.82 g, 20.4 mmol, 60% in mineral oil, washed with petroleum ether and THF) in THF (30 mL) at 0 ℃, methyl acetoacetate (2 mL, 18.6 mmol) was added dropwise. The mixture was cooled to -20 ℃ after stirring at 0 ℃ for 10 min. *n*-Butyllithium (8.2 mL, 20.4 mmol, 2.5 M) was added over 10 min and the mixture was stirred at -20 ℃ for 5 min. Bromoethane (1.4 mL, 93.1 mmol) was added dropwise and the mixture was stirred at room temperature for 3 h. The mixture was then poured to saturated ammonium chloride solution (100 mL), extracted with dithyl ether (3 x 100 mL), dried ($MgSO_4$), and evaporated. The orange solid was dissolved in toluene (70 mL). Ammonium acetate (7.16 g, 92.8 mmol) and a few drops of acetic acid were added. The mixture was heated under reflux for 3 h with the

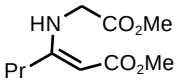
azeotropic removal of water. The mixture was allowed to cool to room temperature, then diluted with ethyl acetate (50 mL), washed with saturated aqueous sodium hydrogen carbonate (15 mL), dried (Na_2SO_4), and evaporated to give *β*-enamino ester as a pale orange oil. The resulting oil was purified by flash chromatography (20% ethyl acetate/hexane) to give **169d** (0.96 g, 36%) as a yellow oil, R_f 0.45 (30% ethyl acetate/hexane); IR ν_{max} 3453 (N-H), 3335 (N-H), 2962 (C-H), 1713 (ester C=O), 1666 (alkenyl C=C), 1437, 1265, 1159, 1042, 788 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.54 (1H, s, C*H*$COOCH_3$) 3.64 (3H, s, OCH_3) 2.10 (2H, t, *J*= 7.4 Hz, C*H*$_2CH_2CH_3$) 1.61-1.55 (2H, m, C*H*$_2CH_3$) 0.94 (3H, t, *J*= 7.4 Hz, C*H*$_3CH_2$). Spectroscopic data were consistent with reported calues in the literature.[63]

Methyl 3-amino-3-phenylpropenoate (169e)[64]



To a solution of methyl 3-oxo-3-phenylpropanoate (0.50 g, 2.80 mmol) in methanol (5 mL) was added ammonium acetate (1.50 g, 14.0 mmol). The mixture was heated under reflux for 16 h. The mixture was allowed to cool to room temperature and water (5 mL) was added. The mixture was extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried (Na_2SO_4), evaporated to give **169e** (0.31 g, 62%) as an orange oil, ^1H NMR (300 MHz, $CDCl_3$) δ 7.56-7.52 (2H, m, Ph) 7.43-7.26 (3H, m, Ph) 4.97 (1H, s, C*H*CO_2CH_3) 3.69 (3H, s, OCH_3).

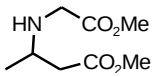
Methyl 3-(methoxycarbonylmethylamino)hex-2-enoate (250e)



To methyl 3-aminohex-2-enoate (0.48 g, 3.31 mmol) in methanol (0.5 mL) was added

methyl 2-aminoethanoate hydrochloride (0.50 g, 3.98 mmol) and the solution was heated under reflux for 3 h. The mixture was allowed to cool to room temperature and diluted with diethyl ether (5 mL). The solution was filtered and the filtrate was evaporated to give **250e** (0.56 g, 79%,) as a yellow oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.85 (1H, br d, *J*= 6.2 Hz, NH) 4.58 (1H, s, CHCOO) 3.99 (2H, d, *J*= 6.2 Hz, CH_2COO) 3.77 (3H, s, OCH_3) 3.64 (3H, s, OCH_3) 2.10 (2H, t, *J*= 10.5 Hz, C$H_2CH_2CH_3$) 1.53 (2H, tq, *J*= 10.5, 7.5 Hz, CH_2CH_3) 0.98 (3H, t, *J*= 7.5 Hz, CH_3CH_2); ^{13}C NMR (500 MHz, $CDCl_3$) δ 171.0 (*C*$OOCH_3$) 170.3 (*C*$OOCH_3$) 164.2 (CNH) 83.5 (*C*HCOO) 52.5 (CH_3O) 50.2 (CH_3O) 44.4 (CH_2Ar) 34.2 (*C*$H_2CH_2CH_3$) 21.0 (*C*H_2CH_3) 13.8 (*C*H_3CH_2).

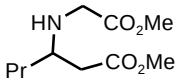
Methyl 3-(methoxycarbonylmethylamino)butanoate (263a)[50]



To sodium triacetoxyborohydride (0.68 g, 3.21 mmol) in glacial acetic acid (1.8 mL) was added methyl 3-(methoxycarbonylmethylamino)but-2-enoate (0.20 g, 1.07 mmol) in acetonitrile (1.8 mL) in one portion at 0 ^{o}C. The mixture was stirred for 4 h at 0 ^{o}C. The mixture was evaporated and the residue was then diluted with dichloromethane (10 mL), washed with saturated sodium carbonate solution (2 x 5 mL), dried ($MgSO_4$) and evaporated to give **263a** (0.15 g, 75%) as a brown oil, R_f 0.10 (75% ethyl acetate/hexane); IR ν_{max} 3350 (N-H), 2954 (C-H), 1730 (ester C=O), 1435, 1195, 1004, 768 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.75 (3H, s, OCH_3) 3.69 (3H, s, OCH_3) 3.45 (2H, d, *J*= 5.4 Hz, CH_2NH) 3.15-3.12 (1H, m, C*H*NH) 2.48 (1H, dd, *J*= 15.4, 6.7 Hz, CH_2CHCH$_3$) 2.37 (1H, dd, *J*= 15.4, 6.2 Hz, CH_2CHCH$_3$) 1.89 (1H, br d, *J*= 5.4 Hz, NH) 1.11 (3H, d, *J*= 6.5 Hz, CH_3CH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 172.6 (*C*$OOCH_3$)

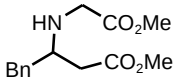
172.5 (*C*OOCH$_3$) 52.0 (CH$_3$O) 51.7 (CH$_3$O) 50.1 (CH$_2$Ar) 48.3 (CHN) 41.3 (*C*H$_2$CHCH$_3$) 20.3 (*C*H$_3$CH).

Methyl 3-(methoxycarbonylmethylamino)hexanoate (263b)



To sodium triacetoxyborohydride (1.64 g, 7.74 mmol) in glacial acetic acid (4.4 mL) was added methyl 3-(methoxycarbonylmethylamino)hex-2-enoate (0.56 g, 2.58 mmol) in acetonitrile (4.4 mL) in one portion at 0 ^{o}C. The mixture was stirred for 4 h at 0 ^{o}C. The mixture was evaporated and the residue was then diluted with dichloromethane (30 mL), washed with saturated sodium carbonate solution (2 x 10 mL) ,dried (MgSO$_4$) and evaporated to give **263b** (0.53 g, 95%,) as a pale yellow oil, IR ν_{max} 3350 (N-H), 2956 (C-H), 1732 (ester C=O), 1435, 1199, 1172, 1012, 734 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.72 (3H, s, OCH$_3$) 3.68 (3H, s, OCH$_3$) 3.43 (2H, s, C*H*$_2$NH) 3.15-3.12 (1H, m, C*H*NH) 2.40 (2H, d, *J*= 5.1 Hz, C*H*$_2$CHCH$_2$CH$_2$CH$_3$) 2.07 (1H, br s, NH) 1.47-1.35 (4H, m, C*H*$_2$CH$_2$CH$_3$ + C*H*$_2$CH$_3$) 0.90 (3H, t, *J*= 5.4 Hz, C*H*$_3$CH$_2$); ^{13}C NMR (500 MHz, CDCl$_3$) δ 172.9 (*C*OOCH$_3$) 172.8 (*C*OOCH$_3$) 54.4 (CH$_2$NH) 51.9 (CH$_3$O) 51.6 (CH$_3$O) 48.3 (CHN) 39.2 (*C*H$_2$CHCH$_2$CH$_2$CH$_3$) 36.7 (*C*H$_2$CH$_2$CH$_3$) 18.9 (*C*H$_2$CH$_3$) 14.2 (*C*H$_3$CH$_2$).

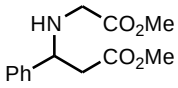
Methyl 3-(methoxycarbonylmethylamino)-4-phenylbutanoate (263c)



To sodium triacetoxyborohydride (2.20 g, 10.35 mmol) in glacial acetic acid (5.8 mL) was added methyl 3-(methoxocarbonylmethylamino)-4-phenylbut-2-enoate (0.91 g, 3.45 mmol) in acetonitrile (5.8 mL) in one portion at 0 ^{o}C. The mixture was stirred for

4 h at 0 ^{o}C. The mixture was evaporated and the residue was then diluted with dichloromethane (30 mL), washed with saturated sodium carbonate solution (2 x 15 mL), dried ($MgSO_4$) and evaporated to give **263c** (0.84 g, 92%) as a brown oil, IR ν_{max} 3350 (N-H), 2952 (C-H), 1731 (ester C=O), 1435, 1199, 1148, 748, 701 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46-7.19 (5H, m, Ph) 3.70 (3H, s, OCH_3) 3.67 (3H, s, OCH_3) 3.46 (2H, s, CH_2NH) 3.29 (1H, ddd, *J*= 7.1, 6.2, 5.7 Hz, C*H*NH) 2.85 (1H, dd, *J*= 13.5, 6.2 Hz, CH_2CHN) 2.75 (1H, dd, *J*= 13.5, 7.1 Hz, CH_2CHN) 2.43 (2H, d, *J*= 5.7 Hz, CH_2Ph) 2.09 (1H, br s, NH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 172.6 (*C*$OOCH_3$) 172.5 (*C*$OOCH_3$) 138.1 (ArC) 129.4 (ArC) 128.6 (ArC) 126.7 (ArC) 56.1 (CH_2N) 52.0 (CH_3O) 51.7 (CH_3O) 48.5 (CHN) 40.8 (CH_2Ar) 38.6 (*C*H_2CHCH_2Ar).

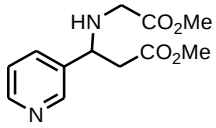
Methyl 3-(methoxycarbonylmethylamino)-3-phenylpropanoate (263d)



To a stirred solution of methyl 3-amino-3-phenylpropanoate (10.52 g, 98.9 mmol) in acetonitrile (260 mL), methyl bromoacetate (7.56 g, 98.9 mmol) and potassium carbonate (26.30 g, 138.2 mmol) were added. The mixture was stirred for 5 h at room temperature and was then diluted with ethyl acetate (300 mL), washed with water (2 x 150 mL) and brine (2 x 30 mL), dried ($MgSO_4$), and evaporated to give an oil that was purified by flash chromatography (50% ethyl acetate/hexane) to give **263d** (11.19 g, 91%) as a colourless oil, R_f 0.67 (50% ethyl acetate/hexane); IR ν_{max} 3350 (N-H), 2952 (C-H), 1735 (ester C=O), 1453, 1199, 1167, 763, 702 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (1H, br s, NH) 7.37-7.25 (5H, m, Ph) 4.10 (1H, dd, *J*= 8.5, 5.3 Hz, ArC*H*) 3.67 (3H, s, OCH_3) 3.65 (3H, s, OCH_3) 3.27 (1H, d, *J*= 17.4 Hz, CH_2NH) 3.21 (1H, d, *J*= 17.4 Hz, CH_2NH) 2.76 (1H, dd, *J*= 15.6, 8.5 Hz, CH_2CH) 2.64 (1H, dd, *J*= 15.6, 5.3

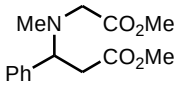
Hz, C*H*$_2$CH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 172.6 (*C*OOCH$_3$) 172.0 (*C*OOCH$_3$) 141.6 (ArC) 128.7 (ArC) 127.8 (ArC) 127.2 (ArC) 59.1 (CHNH) 51.8 (CH_3O) 51.8 (CH_3O) 48.5 (CH_2NH) 42.7 (*C*H$_2$CH); HRMS $C_{13}H_{17}NO_4$ calcd. 252.1236, found 252.1230.

Methyl 3-(methoxycarbonylmethylamino)-3-(pyridin-3-yl)propanoate (263e)



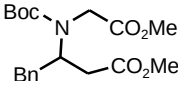
To a stirred solution of methyl 3-amino-3-(pyridin-3-yl)propanoate (0.60 g, 2.38 mmol) in acetonitrile (15 mL), methyl bromoacetate (0.37 g, 2.38 mmol) and potassium carbonate (1.61 g, 11.66 mmol) were added. The mixture was stirred for 5 h at room temperature and was then diluted with ethyl acetate (10 mL), washed with water (2 x 5 mL) and brine (2 x 3 mL), dried ($MgSO_4$), and evaporated. The resulting oil was purified by flash chromatography (1% methanol/chloroform) to give **263e** (0.20 g, 33%) as a yellow oil, R_f 0.14 (3% methanol/chloroform); IR ν_{max} 3332 (N-H), 2953 (C-H), 1730 (ester C=O), 1433, 1199, 1164, 715 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57-8.51 (2H, m, aryl) 7.71-7.69 (1H, m, aryl) 7.28-7.26 (1H, m, aryl) 4.16 (1H, dd, *J*= 8.2, 5.7 Hz, C*H*Ar) 3.67 (3H, s, OCH_3) 3.65 (3H, s, OCH_3) 3.26 (1H, d, *J*= 17.4 Hz, C*H*$_2$NH) 3.19 (1H, d, *J*= 17.4 Hz, C*H*$_2$NH) 2.77 (1H, dd, *J*= 15.7, 8.2 Hz, C*H*$_2$CHN) 2.63 (1H, dd, *J*= 15.7, 5.7 Hz, C*H*$_2$CHN); ^{13}C NMR (500 MHz, $CDCl_3$) δ 172.4 (*C*OOCH$_3$) 171.4 (*C*OOCH$_3$) 149.4 (ArC) 149.4 (ArC) 137.2 (ArC) 134.8 (ArC) 123.7 (ArC) 56.8 (CHNH) 52.3 (CH_3O) 51.9 (CH_3O) 48.4 (CH_2NH) 42.4 (*C*H$_2$CH).

Methyl 3-(methoxycarbonylmethylmethylamino)-3-phenylpropanoate (267)



To a stirred solution of methyl 3-(methoxycarbonylmethylamino)-3-phenylpropanoate (0.40 g, 1.57 mmol) in acetonitrile (10 mL), methyl iodide (0.50 ml, 7.85 mmol) and potassium carbonate (1.08 g, 7.85 mmol) were added. The mixture was stirred for 5 h at room temperature and was then diluted with ethyl acetate (10 mL), washed with water (2 x 5 mL) and brine (2 x 3 mL), dried ($MgSO_4$), and evaporated. The resulting oil was purified by flash chromatography (12% ethyl acetate/hexane) to give **267** (0.22 g, 52%) as a colorless oil, R_f 0.15 (15% ethyl acetate/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.24 (5H, m, Ph) 4.23 (1H, dd, *J*= 8.3, 6.7 Hz, ArC*H*) 3.67 (3H, s, OCH_3) 3.58 (3H, s, OCH_3) 3.28 (1H, d, *J*= 16.6 Hz, C*H*$_2$NH) 3.11 (1H, d, *J*= 16.6 Hz, C*H*$_2$NH) 2.99 (1H, dd, *J*= 14.9, 6.7 Hz, C*H*$_2$CH) 2.73 (1H, dd, *J*= 14.9, 8.3 Hz, C*H*$_2$CH) 2.34 (3H, s, NCH_3); ^{13}C NMR (500 MHz, $CDCl_3$) δ 171.9 (*C*$OOCH_3$) 171.5 (*C*$OOCH_3$) 138.8 (ArC) 128.4 (ArC) 128.3 (ArC) 127.8 (ArC) 64.2 (NCH_3) 55.6 (CHN) 51.7 (CH_3O) 51.6 (CH_3O) 39.3 (CH_2NH) 38.5 (*C*H_2CH); HRMS $C_{14}H_{19}NO_4$ calcd. 265.1314, found 265.1302.

Methyl 3-[(*tert*-butoxycarbonyl)(methoxycarbonylmethyl)amino]-4-phenylbutanoate (270)



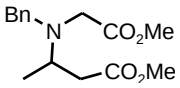
To methyl 3-(methoxycarbonylmethylamino)-4-phenylbutanoate (0.20 g, 0.75 mmol) in dichloromethane (2 mL) was added di-*tert*-butyl dicarbonate (0.18 mL, 0.83 mmol).

The mixture was stirred for 16 h at room temperature. The mixture was evaporated and the residue was then diluted with water (3 mL), acidied with 1M hydrochloric acid to pH 4, and washed with ethyl acetate (2 x 6 mL). The aqueous phase was then neutralized by saturated sodium hydrogen carbonate solution, extracted with ethyl acetate (2 x 6 mL), washed with water (2 x 3 mL), dried ($MgSO_4$) and evaporated. The resulting oil was purified by flash chromatography (10% ethyl acetate/hexane) to give **270** (0.20 g, 72%) as a colourless oil, R_f 0.75 (30% ethyl acetate/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.13 (5H, m, Ph) 4.34-4.28 (1H, m, C*H*NH) 3.77 (3H, s, OCH_3) 3.65 (3H, s, OCH_3) 3.60 (2H, s, C*H*$_2$NH) 3.06-2.93 (1H, m, C*H*$_2$Ph) 2.87-2.79 (2H, m, C*H*$_2$Ph + C*H*$_2$CHN) 2.60-2.55 (1H, m, C*H*$_2$CHN) 1.38 (4H, s, $(CH_3)_3C$) 1.35 (5H, s, $(CH_3)_3C$); ^{13}C NMR (500 MHz, $CDCl_3$) δ 172.2 (*C*$OOCH_3$) 171.9 (*C*$OOCH_3$) 170.7 (*C*$OOCH_3$) 170.7 (*C*$OOCH_3$) 155.1 (CON) 154.3 (CON) 138.4 (ArC) 129.4 (ArC) 129.2 (ArC) 129.0 (ArC) 128.6 (ArC) 126.6 (ArC) 126.5 (ArC) 80.2 (*C*$(CH_3)_3$) 80.4 (*C*$(CH_3)_3$) 57.3 (CH_2N) 52.0 (CH_3O) 51.9 (CH_3O) 51.7 (CH_3O) 51.7 (CH_3O) 48.9 (CHN) 39.6 (CH_2Ar) 38.7 (CH_2Ar) 38.1 (*C*H_2CHCH_2Ar) 37.3 (*C*H_2CHCH_2Ar) 28.4 ((*C*$H_3)_3C$) 28.2 ((*C*$H_3)_3C$); m/z (Cl+) 366 (10%, $M+H^+$) 266 (100%, $M+H^+$-$CO_2C(CH_3)_3$); HRMS $C_{19}H_{27}NO_6$ calcd. 366.1917, found 366.1917.

General procedure for benzylation

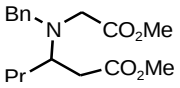
To diesters **272** (1.0 equiv) in acetonitrile was added potassium carbonate (2.0 equiv), lithium iodide (catalytic amount) and benzyl bromide (1.1 equiv). The mixture was stirred for 16 h at 55 ^{o}C. The mixture was then evaporated and redissolved in dicholomethane. The mixture was washed with water and the organic layer was dried ($MgSO_4$) and evaporated.

Methyl 3-(benzylmethoxycarbonylmethylamino)butanoate (272a)



Following general procedure, reaction of methyl 3-(methoxycarbonylmethylamino)butanoate (1.00 g, 5.30 mmol), potassium carbonate (1.46 g, 10.6 mmol), lithium iodide (50 mg), and benzyl bromide (0.69 mL, 5.81 mmol) in acetonitrile (100 mL) gave an oil that was purified by flash chromatography (20% ethyl acetate/hexane) to give **272a** (1.13 g, 77%) as a yellow oil; R_f 0.66 (30% ethyl acetate/hexane); IR ν_{max} 2952 (C-H), 1734 (ester C=O), 1436, 1197, 1004, 744, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.17 (5H, m, Ph) 3.75 (2H, s, CH_2Ar) 3.62 (3H, s, OCH_3) 3.59 (3H, s, OCH_3) 3.39-3.34 (1H, m, CHN) 3.25 (2H, s, CH_2NCH_2Ar) 2.59 (1H, dd, J= 14.4, 5.9 Hz, CH_2CHCH_3) 2.26 (1H, dd, J= 14.4, 7.3 Hz, CH_2CHCH_3) 1.09 (3H, d, J= 6.7 Hz, CH_3CH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 172.7 (*C*$OOCH_3$) 172.6 (*C*$OOCH_3$) 139.2 (ArC) 128.8 (ArC) 128.3 (ArC) 127.0 (ArC) 54.1 (CH_2Ar) 53.6 (*C*H_2NCH_2Ar) 51.7 (CHN) 51.6 (CH_3O) 51.5 (CH_3O) 39.5 (*C*H_2CHCH_3) 15.8 (*C*H_3CH).

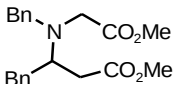
Methyl 3-(benzylmethoxycarbonylmethylamino)hexanoate (272b)



Following general procedure, reaction of methyl 3-(methoxycarbonylmethylamino)hexanoate (0.30 g, 1.38 mmol), potassium carbonate (0.38 g, 2.72 mmol), lithium iodide (10 mg), and benzyl bromide (0.18 mL, 1.52 mmol) in acetonitrile (25 mL) gave an oil that was purified by flash chromatography (15% ethyl acetate/hexane) to give **272b** (0.30 g, 70%) as a yellow oil; R_f 0.60 (30% ethyl

acetate/hexane); IR ν_{max} 2954 (C-H), 1734 (ester C=O), 1436, 1195, 1175, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.21 (5H, m, Ph) 3.87 (1H, d, *J*= 13.7 Hz, C*H*$_2$Ar) 3.72 (1H, d, *J*= 13.7 Hz, C*H*$_2$Ar) 3.67 (3H, s, OCH_3) 3.63 (3H, s, OCH_3) 3.28 (2H, s, C*H*$_2$NCH$_2$Ar) 3.21-3.19 (1H, m, CHN) 2.62 (1H, dd, *J*= 14.5, 6.7 Hz, C*H*$_2$CHCH$_2$CH$_2$CH$_3$) 2.29 (1H, dd, *J*= 14.5, 7.3 Hz, C*H*$_2$CHCH$_2$CH$_2$CH$_3$) 1.60-1.57 (2H, m, C*H*$_2$CH$_2$CH$_3$) 1.33-1.28 (2H, m, C*H*$_2$CH$_3$) 0.87 (3H, t, *J*= 7.3 Hz, C*H*$_3$CH$_2$); ^{13}C NMR (500 MHz, $CDCl_3$) δ 173.1 (*C*OOCH$_3$) 172.6 (*C*OOCH$_3$) 139.2 (ArC) 129.0 (ArC) 128.2 (ArC) 127.1 (ArC) 58.1 (CH$_2$Ar) 54.3 (*C*H$_2$NCH$_2$Ar) 51.6 (CHN) 51.5 (CH$_3$O) 51.2 (CH$_3$O) 36.5 (*C*H$_2$CHCH$_2$CH$_2$CH$_3$) 34.2 (*C*H$_2$CH$_2$CH$_3$) 19.9 (*C*H$_2$CH$_3$) 14.1 (*C*H$_3$CH$_2$).

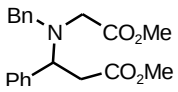
Methyl 3-(benzylmethoxycarbonylmethylamino)-4-phenylbutanoate (272c)



Following general procedure, reaction of methyl 3-(methoxycarbonylmethylamino)-4-phenylbutanoate (0.25 g, 0.94 mmol), potassium carbonate (0.26 g, 1.88 mmol), lithium iodide (10 mg), and benzyl bromide (0.12 mL, 1.03 mmol) in acetonitrile (18 mL) gave an oil that was purified by flash chromatography (20% ethyl acetate/hexane) to give **272c** (0.23 g, 70%) as a yellow oil; R_f 0.87 (50% ethyl acetate/hexane); IR ν_{max} 2950 (C-H), 1731 (ester C=O), 1435, 1198, 1151, 1028, 734, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40-7.15 (10H, m, Ph) 3.90 (1H, d, *J*= 13.9 Hz, C*H*$_2$NCH$_2$COO) 3.82 (1H, d, *J*= 13.9 Hz, C*H*$_2$NCH$_2$COO) 3.64 (3H, s, OCH_3) 3.60 (3H, s, OCH_3) 3.59-3.48 (1H, m, CHN) 3.43 (1H, d, *J*= 12.8 Hz, C*H*$_2$NCH$_2$Ar) 3.37 (1H, d, *J*= 12.8 Hz, C*H*$_2$NCH$_2$Ar) 3.07 (1H, m, C*H*$_2$CHCH$_2$COO) 2.60-2.52 (2H, m, C*H*$_2$CHCH$_2$COO + C*H*$_2$CHCH$_2$Ar) 2.34 (1H, dd, *J*= 14.7 Hz, 6.0

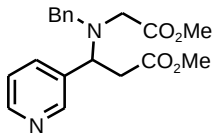
Hz, C*H*$_2$CHCH$_2$Ar); ^{13}C NMR (500 MHz, CDCl$_3$) δ 172.6 (*C*OOCH$_3$) 172.6 (*C*OOCH$_3$) 139.2 (ArC) 139.1 (ArC) 129.3 (ArC) 128.9 (ArC) 128.5 (ArC) 128.2 (ArC) 127.2 (ArC) 126.3 (ArC) 60.5 (CH$_2$Ar) 54.4 (*C*H$_2$NCH$_2$Ar) 51.6 (CHN) 51.4 (CH$_3$O) 37.6 (*C*H$_2$CHCH$_2$COO) 37.0 (*C*H$_2$CHCH$_2$Ar).

Methyl 3-(benzylmethoxycarbonylmethylamino)-3-phenylpropanoate (272d)



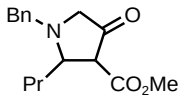
Following general procedure, reaction of methyl 3-(methoxycarbonylmethylamino)-3-phenylpropanoate (1.93 g, 7.67 mmol), potassium carbonate (2.12 g, 15.3 mmol), lithium iodide (82 mg), and benzyl bromide (0.82 mL, 8.43 mmol) in acetonitrile (110 mL) gave an oil that was purified by flash chromatography (20% ethyl acetate/hexane) to give **272d** (1.59 g, 61%) as pale yellow microprisms and also methyl 3-(methoxycarbonylmethylamino)-3-phenylpropanoate (0.80 g), mp 45-47 ^{o}C; R$_f$ 0.50 (30% ethyl acetate/hexane); IR ν_{max} 2950 (C-H), 1732 (ester C=O), 1434, 1195, 1167, 1081, 735, 697 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.39-7.23 (10H, m, Ph) 4.47 (1H, dd, *J*= 8.1, 7.3 Hz, CHN) 3.83 (1H, d, *J*= 14.5 Hz, C*H*$_2$NCH$_2$COO) 3.62 (3H, s, OCH$_3$) 3.60 (3H, s, OCH$_3$) 3.59 (1H, d, *J*= 14.5 Hz, C*H*$_2$NCH$_2$COO) 3.38 (1H, d, *J*= 17.1 Hz, C*H*$_2$NCH$_2$Ar) 3.16 (1H, d, *J*= 17.1 Hz, C*H*$_2$NCH$_2$Ar) 3.05 (2H, dd, *J*= 14.1, 7.3 Hz, C*H*$_2$CHAr) 2.75 (1H, dd, *J*= 14.1, 8.1 Hz, C*H*$_2$CHAr); ^{13}C NMR (500 MHz, CDCl$_3$) δ 172.1 (*C*OOCH$_3$) 172.0 (*C*OOCH$_3$) 139.1 (ArC) 139.0 (ArC) 129.1 (ArC) 128.9 (ArC) 128.4 (ArC) 128.3 (ArC) 127.7 (ArC) 127.2 (ArC) 61.6 (CH$_2$Ar) 54.8 (*C*H$_2$NCH$_2$Ar) 51.7 (CHN) 51.5 (CH$_3$O) 51.1 (CH$_3$O) 37.9 (*C*H$_2$CHCH$_2$COO); m/z (Cl+) 342 (100%, M+H$^+$); HRMS C$_{20}$H$_{23}$NO$_4$ calcd. 342.1705, found 342.1709.

Methyl 3-(benzylmethoxycarbonylmethylamino)-3-(pyridin-3-yl)propanoate (272e)



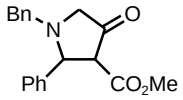
To a stirred solution of methyl 3-(methoxycarbonylmethylamino)-3-(pyridin-3-yl)propanoate (0.11 g, 0.45 mmol) in dichloromethane (6 mL), benzaldehyde (0.28 ml, 2.71 mmol) and $MgSO_4$ (20 mg) was added. The mixture was stirred for 5 min at room temperature. Sodium triacetoxyborohydride (0.29 g, 1.36 mmol) was then added and the mixture was stirred for 16 h. The mixture was diluted with dichloromethane (20 mL), washed with saturated sodium carbonate solution (2 x 5 mL), dried ($MgSO_4$), and evaporated. The resulting oil was purified by flash chromatography (22% ethyl acetate/hexane) to give **272e** (0.04 g, 26%) as a yellow oil, R_f 0.48 (30% ethyl acetate/hexane); IR ν_{max} 2952 (C-H), 1731 (ester C=O), 1433, 1199, 1025, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.63-8.55 (2H, m, aryl) 7.80 (1H, d, *J*= 7.8 Hz, aryl) 7.35-7.22 (6H, m, aryl + Ph) 4.53 (1H, dd, *J*= 8.6, 6.6 Hz, C*H*Ar) 3.78 (2H, s, CH_2Ar) 3.62 (3H, s, OCH_3) 3.60 (3H, s, OCH_3) 3.38 (1H, d, *J*= 17.3 Hz, CH_2NCH_2Ar) 3.18 (1H, d, *J*= 17.3 Hz, CH_2NCH_2Ar) 3.07 (1H, dd, *J*= 15.0, 6.6 Hz, CH_2CHN) 2.78 (1H, dd, *J*= 15.0, 8.6 Hz, CH_2CHN); ^{13}C NMR (500 MHz, $CDCl_3$) δ 171.8 (*C*$OOCH_3$) 171.4 (*C*$OOCH_3$) 148.9 (ArC) 148.3 (ArC) 138.3 (ArC) 136.6 (ArC) 135.8 (ArC) 128.9 (ArC) 128.3 (ArC) 127.5 (ArC) 123.7 (ArC) 59.3 (CHN) 54.7 (CH_2Ar) 52.0 (CH_3O) 51.7 (CH_3O) 50.9 (*C*H_2NHCH_2Ar) 36.7 (*C*H_2CH).

Methyl 1-benzyl-4-methoxy-5-propylpyrrolidin-3-one (273b)



To methyl 3-(benzylmethoxycarbonylmethylamino)hexanoate (0.19 g, 0.61 mmol) in toluene (2 mL) was added potassium *tert*-butoxide (0.8 mL, 1M solution in THF) at 0 ^{o}C. The mixture was stirred for 16 h at room temperature under nitrogen. The mixture was diluted with dichloromethane (10 mL), washed with hydrochloric acid (2 mL, 1M), dried ($MgSO_4$), and evaporated to give **273b** (0.10 g, 60%) as an yellow oil, R_f 0.83 (30% ethyl acetate/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.22 (5H, m, Ph) 4.24 (1H, d, *J*= 13.1 Hz, CH_2CO) 3.76 (3H, s, OCH_3) 3.35-3.23 (4H, m, CH_2CO+C*H*$_2$Ar+CHCOO+CHN) 2.79 (1H, d, *J*= 17.7 Hz, C*H*$_2$Ar) 1.90-1.89 (2H, m, C*H*$_2$$CH_2CH_3$) 1.41-1.33 (2H, m, C*H*$_2$$CH_3$) 0.97 (3H, t, *J*= 7.3 Hz, C*H*$_3$$CH_2$); ^{13}C NMR (500 MHz, $CDCl_3$) δ 206.2 (*C*OCH_2N) 168.5 (*C*OOCH_3) 137.7 (ArC) 128.6 (ArC) 128.5 (ArC) 127.0 (ArC) 65.0 (*C*H_2CO) 61.6 (*C*HCOO) 60.5 (CH_2Ar) 57.4 (CH_3O) 52.7 (CHN) 34.1 (*C*$H_2CH_2CH_3$) 18.1 (*C*H_2CH_3) 14.5 (*C*H_3CH_2).

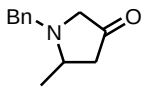
Methyl 1-benzyl-4-methoxy-5-phenylpyrrolidin-3-one (273d)



To methyl 3-(benzylmethoxycarbonylmethylamino)-3-phenylpropanoate (0.44 g, 1.28 mmol) in toluene (4.5 mL) was added potassium *tert*-butoxide (1.7 mL, 1M solution in THF) at 0 ^{o}C. The mixture was stirred for 16 h at room temperature under nitrogen. The mixture was acidified with hydrochloric acid (3 mL, 1M), neutralized by sodium carbonate to around pH 6, extracted with ethyl acetate (10 mL), dried ($MgSO_4$), and evaporated to give **273d** (0.36 g, 91%) as an orange oil, IR ν_{max} 3318 (O-H), 2951

(C-H), 1664 (ester C=O), 1603 (alkenyl C=C), 1436, 1204, 1110, 732, 696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61-7.27 (10H, m, Ph) 4.31 (1H, d, *J*= 10.5 Hz, C*H*CHCOO) 4.00 (1H, d, *J*= 13.1 Hz, CH_2Ar) 3.71 (3H, s, OCH_3) 3.57 (1H, d, *J*= 17.9 Hz, CH_2CO) 3.49 (1H, d, *J*= 10.5 Hz, CHCOO) 3.20 (1H, d, *J*= 13.1 Hz, CH_2Ar) 2.93 (1H, d, *J*= 17.9 Hz, CH_2CO); ^{13}C NMR (500 MHz, $CDCl_3$) δ 204.9 (*C*OCH_2N) 167.3 (*C*OOCH_3) 139.1 (ArC) 137.5 (ArC) 129.1 (ArC) 129.0 (ArC) 128.6 (ArC) 128.2 (ArC) 128.0 (ArC) 127.7 (ArC) 69.4 (*C*HCOO) 64.1 (*C*H_2CO) 61.0 (CH_2Ar) 57.2 (CH_3O) 52.7 (*C*HCHCOO); m/z (Cl+) 310 (100%, $M+H^+$); HRMS $C_{19}H_{20}NO_3$ calcd. 310.1443, found 310.1444.

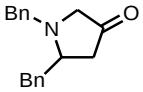
1-Benzyl-5-methylpyrrolidin-3-one (274a)[52]



To methyl 3-(benzylmethoxycarbonylmethylamino)butanoate (0.46 g, 1.63 mmol) in toluene (6 mL) was added potassium *tert*-butoxide (2.2 mL, 1M solution in THF) at 0 ^{o}C. The mixture was stirred for 16 h at room temperature under nitrogen. The mixture was diluted with dichloromethane (30 mL), washed with hydrochloric acid (6 mL, 1M), dried ($MgSO_4$), and evaporated. The resulting oil was added to 5% sulfuric acid solution (5 mL) and the mixture was heated under reflux for 2 h. The mixture was then neutralized with saturated sodium carbonate solution, extracted with ethyl acetate, dried ($MgSO_4$), and evaporated. The resulting oil was purified by flash chromatography (10% ethyl acetate/hexane) to give **274a** (0.19 g, 62%) as a yellow oil, R_f 0.47 (30% ethyl acetate/hexane); IR ν_{max} 2924 (C-H), 1699 (ketone C=O), 1640, 1495, 1452, 1352, 733, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48-7.26 (5H, m, Ph) 4.16 (1H, d, *J*= 11.6 Hz, CH_2NCH_2Ar) 3.30-3.22 (2H, m, CH_2NCH_2Ar + CH_2Ar)

3.01-2.95 (1H, m, C*H*CH_3) 2.65 (1H, d, *J*= 17.4 Hz, CH_2Ar) 2.50 (1H, dd, *J*= 18.3, 6.1 Hz, CH_2CHN) 2.15 (1H, dd, *J*= 18.3, 9.9 Hz, CH_2CHN) 1.35 (3H, d, *J*= 6.1 Hz, CH_3CH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 213.4 (*C*OCH_2N) 138.0 (ArC) 128.8 (ArC) 128.5 (ArC) 127.4 (ArC) 61.9 (*C*H_2NCH_2Ar) 57.3 (*C*H_2CHN) 57.2 (CH_2Ar) 46.1 (CHN) 18.4 (*C*H_3CH).

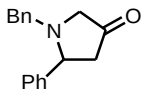
1,5-Dibenzylpyrrolidin-3-one (274c)



Methyl 3-(benzylmethoxycarbonylmethylamino)-4-phenylbutanoate (0.41 g, 1.16 mmol) in toluene (4.5 mL) was added potassium *tert*-butoxide (1.5 mL, 1M solution in THF) at 0 ^{o}C. The mixture was stirred for 16 h at room temperature under nitrogen. The mixture was acidified with hydrochloric acid (3 mL, 1M), neutralized by sodium carbonate to around pH 6, extracted with ethyl acetate (10 mL), dried ($MgSO_4$), and evaporated. The residue was added to aqueous 5% sulfuric acid (5 mL) and the mixture was heated under reflux for 2 h. The mixture was then neutralized with saturated sodium carbonate solution, extracted with ethyl acetate, dried ($MgSO_4$), and evaporated. The resulting oil was purified by flash chromatography (18% ethyl acetate/hexane) to give **274c** (0.20 g, 65%) as a yellow oil, R_f 0.33 (15% ethyl acetate/hexane); IR ν_{max} 2923 (C-H), 1700 (ketone C=O), 1452, 1203, 1076, 735, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.20 (10H, m, Ph) 4.38 (1H, d, *J*= 13.1 Hz, CH_2NCH_2Ar) 3.42 (1H, d, *J*= 13.1 Hz, CH_2NCH_2Ar) 3.33-3.28 (2H, m, CH_2NCH_2CO + CH_2CHCH_2CO) 3.21-3.18 (1H, m, CHN) 2.77-2.69 (2H, m, CH_2NCH_2CO + CH_2CHCH_2CO) 2.30 (1H, dd, *J*= 18.3, 6.3 Hz, CH_2CHCH_2Ar) 2.21 (1H, dd, *J*= 18.3, 9.5 Hz, CH_2CHCH_2Ar); ^{13}C NMR (500 MHz, $CDCl_3$) δ 212.9 (*C*OCH_2N) 138.2 (ArC)

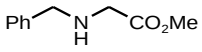
137.9 (ArC) 129.3 (ArC) 129.1 (ArC) 128.6 (ArC) 128.6 (ArC) 127.5 (ArC) 126.6 (ArC) 63.2 (CH_2NCH_2Ar) 62.0 (CH_2NCH_2CO) 57.8 (CHN) 43.6 (CH_2CHN) 39.2 (CH_2CHCH_2CO); m/z (Cl+) 266 (100%, $M+H^+$); HRMS $C_{18}H_{20}NO$ calcd. 266.1545, found 266.1545.

1-Benzyl-5-phenylpyrrolidin-3-one (274d)



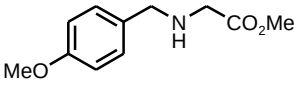
Methyl 1-benzyl-4-methoxy-5-phenylpyrrolidin-3-one (0.31 g, 1.00 mmol) was added to aqueous 5% sulfuric acid (5 mL) and the mixture was heated under reflux for 1 h. After allowing to cool, the mixture was then neutralized with saturated sodium carbonate solution, extracted with ethyl acetate, dried ($MgSO_4$), and evaporated. The resulting oil was purified by flash chromatography (12% ethyl acetate/hexane) to give **274d** (0.20 g, 81%) as an yellow oil, R_f 0.38 (15% ethyl acetate/hexane); IR ν_{max} 2952 (C-H), 1712 (ketone C=O), 1668, 1451, 1203, 764, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.56-7.23 (10H, m, Ph) 3.99 (1H, d, J= 13.2 Hz, CH_2NCH_2Ar) 3.90-3.87 (1H, m, CHN) 3.48 (1H, d, J= 13.2 Hz, CH_2Ar) 3.19 (1H, d, J= 13.2 Hz, CH_2NCH_2Ar) 2.78-2.72 (2H, m, CH_2Ar + CH_2CHN) 2.47 (1H, dd, J= 18.2, 10.6 Hz, CH_2CHN); ^{13}C NMR (500 MHz, $CDCl_3$) δ 212.4 ($COCH_2N$) 140.9 (ArC) 137.9 (ArC) 129.3 (ArC) 129.01 (ArC) 128.6 (ArC) 128.5 (ArC) 127.6 (ArC) 127.4 (ArC) 66.9 (CH_2NCH_2Ar) 61.6 (CH_2NCH_2CO) 57.6 (CHN) 48.2 (CH_2CHN); m/z (Cl+) 252 (100%, $M+H^+$); HRMS $C_{17}H_{18}NO$ calcd. 252.1388, found 252.1387.

Methyl benzylaminoethanoate (275a)



To a mixture of benzylamine (1.0 mL, 9.20 mmol) and diethylpropylamine (6.4 mL, 36.6 mmol) in acetonitrile (70 mL) was added methyl bromoacetate (1.40 g, 9.20 mmol) at 0 ^{o}C. The mixture was stirred for 4 h at room temperature. The mixture was then washed with water (30 mL) and the aqueous phase was extracted with dichloromethane (2 x 30 mL), dried ($MgSO_4$) and evaporated. The resulting oil was purified by flash chromatography (30% ethyl acetate/hexane) to give **275a** (1.24 g, 76%) as a yellow oil; R_f 0.22 (30% ethyl acetate/hexane); IR ν_{max} 3340 (N-H), 2951 (C-H), 1738 (ester C=O), 1667, 1435, 1199, 738, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.23 (5H, m, Ph) 3.81 (2H, s, CH_2Ar) 3.73 (3H, s, OCH_3) 3.43 (2H, s, CH_2COO) 1.96 (1H, br s, NH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 172.9 (*C*$OOCH_3$) 139.5 (ArC) 128.5 (ArC) 128.3 (ArC) 127.3 (ArC) 53.4 (CH_3O) 51.8 (CH_2Ar) 50.0 (*C*H_2COO).

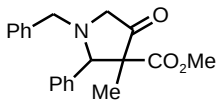
Methyl 4-methoxybenzylaminoethanoate (275b)



To a mixture of 4-methoxyphenylethylamine (2.00 g, 14.6 mmol) and triethylamine (2.1 mL, 14.6 mmol) in dichloromethane (7 mL) was added methyl bromoacetate (1.40 g, 14.6 mmol) at 0 ^{o}C. The mixture was stirred for 3 h at room temperature. The mixture was then washed with water (2 x 5 mL), dried ($MgSO_4$) and evaporated. The resulting oil was purified by flash chromatography (50% ethyl acetate/hexane) to give **275b** (1.57 g, 51%) as a colourless oil; R_f 0.18 (30% ethyl acetate/hexane); IR ν_{max} 2951 (C-H), 1737 (ester C=O), 1611, 1510, 1243, 1173, 1031, 815, 733, 520 cm^{-1}; ^{1}H

NMR (500 MHz, $CDCl_3$) δ 7.25 (2H, d, *J*= 10.1 Hz, Ph) 6.90 (2H, d, *J*= 10.1 Hz, Ph) 3.79 (3H, s, ArOC*H*$_3$) 3.76 (2H, s, C*H*$_2$Ar) 3.72 (3H, s, OCH_3) 3.45 (2H, s, CH_2COO) 1.75 (1H, br s, NH).

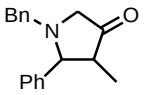
Methyl 1-benzyl-4-methyl-4-methoxy-5-phenylpyrrolidin-3-one (278)



To methyl 1-benzyl-4-methoxy-5-phenylpyrrolidin-3-one (0.17 g, 0.54 mmol) in THF (3 mL) was added tetrabutylammonium fluoride (0.65 mL, 1M in THF) and methyl iodide (0.07 mL, 1.09 mmol). The mixture was stirred for 24 h at room temperature under nitrogen. The mixture was neutralized with 1M hydrochloic acid, extracted by chloroform, filtered and evaporated. The resulting oil was purified by flash chromatography (12% ethyl acetate/hexane) to give **278** (0.12 g, 69%) as a yellow oil, R_f 0.22 (15% ethyl acetate/hexane); IR ν_{max} 2924 (C-H), 1762 (ketone C=O), 1736 (ester C=O), 1453, 1237, 1203, 1077, 755, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) (5:1 mixture of diasteriomers) δ 7.55-7.26 (10H, m, Ph) 4.13 (1H, d, *J*= 13.8 Hz, C*H*$_2$Ar) 4.06 (1H, d, *J*= 13.8 Hz, C*H*$_2$Ar) 3.88 (1H, s, C*H*Ar) 3.75 (1H, s, C*H*Ar) 3.50 (3H, s, OCH_3) 3.48 (3H, s, OCH_3) 3.20 (1H, d, *J*= 13.8 Hz, CH_2CO) 2.99 (1H, d, *J*= 18.0 Hz, CH_2CO) 2.87 (1H, d, *J*= 18.0 Hz, CH_2CO) 1.40 (3H, s, CH_3C) 1.09 (3H, s, CH_3C); ^{13}C NMR (500 MHz, $CDCl_3$) δ 210.6 (*C*OCH_2N) 209.5 (*C*OCH_2N) 170.9 (*C*OOCH_3) 169.8 (*C*OOCH_3) 137.8 (ArC) 137.5 (ArC) 136.7 (ArC) 136.0 (ArC) 128.8 (ArC) 128.7 (ArC) 128.6 (ArC) 128.6 (ArC) 128.6 (ArC) 128.5 (ArC) 128.5 (ArC) 128.4 (ArC) 128.3 (ArC) 127.5 (ArC) 127.4 (ArC) 127.3 (ArC) 73.2 (*C*CH_3) 70.4 (*C*CH_3) 61.8 (*C*H_2CO) 61.5 (*C*H_2CO) 60.7 (CH_2Ar) 60.5 (CH_2Ar) 58.1 (CHAr) 57.4 (CHAr) 52.8 (CH_3O) 52.1 (CH_3O) 17.3 (*C*H_3C) 15.5 (*C*H_3C); m/z (Cl+) 324 (100%, $M+H^+$);

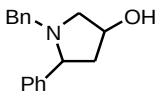
HRMS $C_{20}H_{22}NO_3$ calcd. 324.1600, found 324.1598.

1-Benzyl-4-methyl-5-phenylpyrrolidin-3-one (279)



To methyl 1-benzyl-4-methyl-4-methoxy-5-phenylpyrrolidin-3-one (0.13 g, 0.39 mmol) in DMF (3 mL) was added lithium iodide (0.27 g, 0.20 mmol). The mixture was stirred for 2 h at 150 ^{o}C under nitrogen. The mixture was diluted with water (8 mL), extracted with ethyl acetate (4 x 8 mL), washed with brine (8 mL), dried ($MgSO_4$), and evaporated. The resulting oil was purified by flash chromatography (12% ethyl acetate/hexane) to give **279** (56 mg, 54%) as an orange oil, R_f 0.72 (15% ethyl acetate/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70-7.26 (10H, m, Ph) 3.98 (1H, d, *J*= 13.2 Hz, CH_2CO) 3.55 (1H, d, *J*= 17.8 Hz, C*H*$_2$Ar) 3.34 (1H, d, *J*= 6.2 Hz, C*H*Ar) 3.12 (1H, d, *J*= 13.2 Hz, CH_2CO) 2.73 (1H, d, *J*= 17.8 Hz, C*H*$_2$Ar) 2.26 (1H, qt, *J*= 7.1, 6.2 Hz, C*H*CH_3) 1.04 (3H, d, *J*= 7.1 Hz, C*H*$_3$CH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 214.7 (*C*OCH_2N) 140.4 (ArC) 138.0 (ArC) 128.9 (ArC) 128.7 (ArC) 128.5 (ArC) 128.4 (ArC) 127.6 (ArC) 127.3 (ArC) 74.6 (*C*H_2CO) 60.9 (CH_2Ar) 57.7 (*C*HCH_3) 53.2 (CHAr) 10.5 (*C*H_3CH); m/z (Cl+) 266 (100%, M+H$^+$); HRMS $C_{18}H_{20}NO$ calcd. 266.1545, found 266.1540.

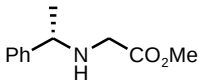
1-Benzyl-4-hydroxy-2-phenylpyrrolidine (285)



To 1-benzyl-5-phenylpyrrolidin-3-one (0.20 g, 0.80 mmol) in methanol (3 mL), sodium borohydride (0.03 g, 0.80 mmol) was added at 0 ^{o}C and the mixture was stirred for 1 h at 0 ^{o}C. The mixture was diluted with water (5 mL), acidified by aqueous 1%

hydrochloric acid to around pH 9, extracted with ethyl acetate (3 x 5 mL), dried ($MgSO_4$), and evaporated. The resulting oil was purified by flash chromatography (30% ethyl acetate/hexane) to give **285** (0.11 g, 55%) as an orange oil, R_f 0.56 (50% ethyl acetate/hexane); IR ν_{max} 3365 (O-H), 2935 (C-H), 1601, 1452, 1169, 757, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (5:1 mixture of diastereoisomers) δ 7.62-7.21 (10H, m, Ph) 4.28-4.25 (1H, m, C*H*OH) 3.89 (1H, d, *J*= 13.2 Hz, CH_2Ar) 3.38 (1H, dd, *J*= 8.4, 4.9 Hz, CHN) 3.08-3.04 (2H, m, CH_2Ar + CH_2NCH_2Ar) 2.69-2.63 (1H, m, CH_2NCH_2Ar) 2.35 (1H, dd, *J*= 10.4, 4.9 Hz, CH_2CHAr) 2.05 (1H, br s, OH) 1.76 (1H, dd, *J*= 10.4, 8.4 Hz, CH_2CHAr); ^{13}C NMR (500 MHz, $CDCl_3$) δ 142.7 (ArC) 138.7 (ArC) 128.8 (ArC) 128.8 (ArC) 128.4 (ArC) 128.3 (ArC) 127.6 (ArC) 127.4 (ArC) 70.2 (*C*H_2CHAr) 68.4 (CH_2OH) 62.2 (CH_2Ar) 57.2 (CHN) 46.0 (CHAr); m/z (Cl+) 253 (10%, M^+) 176 (25%, M^+-Ph) 162 (10%, M^+-$PhCH_2$) 91 (100%, $PhCH_2^+$) 77 (10%, Ph^+); HRMS $C_{17}H_{19}NO$ calcd. 253.1467, found 253.1462.

(*S*)-Methyl 1-phenylethylaminoethanoate (287)[58]



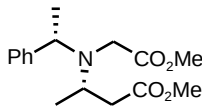
To a mixture of (*S*)-1-phenylethylamine (1.00 g, 8.3 mmol) and triethylamine (1.2 mL, 8.3 mmol) in dichloromethane (4 mL) was added methyl bromoacetate (0.80 g, 8.3 mmol) at 0 ^oC. The mixture was stirred for 3 h at 20 ^oC then washed with water (2 x 3 mL), dried ($MgSO_4$) and evaporated to give **kc0 40** (0.51 g, 32%) as a pale yellow oil, $[\alpha]^{21}_D$ = -64.2 (*c* 6.20, $CHCl_3$); IR ν_{max} 3005 (N-H), 2955 (C-H), 1736 (ester C=O), 1435, 1199, 761, 700; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.24 (5H, m, Ph) 3.79 (1H, q, *J*= 6.6 Hz, C*H*Ar) 3.69 (3H, s, OCH_3) 3.30 (2H, d, *J*= 17.4 Hz, CH_2COO) 3.24 (2H, d, *J*= 17.4 Hz, CH_2COO) 1.89 (1H, br s, NH) 1.38 (3H, d, *J*= 6.6 Hz, CH_3CH); ^{13}C

NMR (500 MHz, $CDCl_3$) δ 173.1 (*C*$OOCH_3$) 144.7 (ArC) 128.6 (ArC) 127.3 (ArC) 126.8 (ArC) 57.8 (CH_3O) 51.8 (CHAr) 48.8 (*C*H_2COO) 24.3 (*C*H_3CH).

General procedure for diesters 288

To a stirred solution of β-amino esters **288** (1.0 equiv) in acetonitrile at room temperature, sodium carbonate (2.0 equiv) and methyl bromoacetate (1.0 equiv) were added. The mixture was then heated under reflux for 16 h. The mixture was allowed to cool to room temperature and diluted with diethyl ether. The mixture was then washed with water, dried ($MgSO_4$) and evaporated.

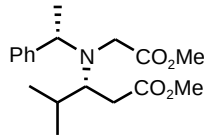
(*R*)-Methyl 3-{methoxycarbonylmethyl-[(1*S*)-1-phenylethyl]amino}butanoate (288a)



Following general procedure, reaction of (*R*)-methyl 3-{[(1*S*)-1-phenylethyl]amino}butanoate (0.50 g, 2.36 mmol), sodium carbonate (0.50 g, 4.72 mmol), and methyl bromoacetate (0.25 ml, 2.60 mmol) in acetonitrile (6 mL) gave a pale yellow oil that was purified by flash chromatography (10% ethyl acetate/hexane) to give **288a** (0.66 g, 96%) as a pale yellow oil, R_f 0.52 (30% ethyl acetate/hexane); $[\alpha]^{21}_D$ = +5.6 (*c* 10.2, $CHCl_3$); IR ν_{max} 2971 (C-H), 1731 (ester C=O), 1435, 1194, 1160, 701; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.20 (5H, m, Ph) 4.08 (1H, q, *J*= 6.7 Hz, C*H*CH_3) 3.64 (3H, s, OCH_3) 3.62 (3H, s, OCH_3) 3.54-3.48 (1H, m, C*H*$CH_2CO_2CH_3$) 3.35 (2H, s, CH_2N) 2.54 (1H, dd, *J*= 14.6, 6.2 Hz, CH_2CH) 2.18 (1H, dd, *J*= 14.6, 7.9 Hz, CH_2CH) 1.33 (3H, d, *J*= 5.3 Hz, CH_3CHCH_2) 1.05 (3H, d, *J*= 6.7 Hz, CH_3CHPh); ^{13}C NMR (500 MHz, $CDCl_3$) δ 173.9 (*C*$OOCH_3$) 172.7 (*C*$OOCH_3$)

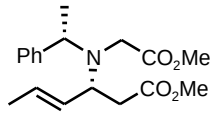
145.2 (ArC) 128.3 (ArC) 127.6 (ArC) 127.0 (ArC) 59.6 (*C*HCH$_3$) 51.6 (OCH$_3$) 51.5 (OCH$_3$) 51.2 (CH$_2$N) 47.6 (*C*HCH$_2$COO) 39.6 (*C*H$_2$CHCH$_3$) 20.7 (*C*H$_3$CHCH$_2$) 17.4 (*C*H$_3$CHAr).

(*R*)-Methyl 3-{methoxycarbonylmethyl-4-methyl-[(1*S*)-1-phenylethyl]amino}pentanoate (288b)



Following general procedure, reaction of (*R*)-methyl 4-methyl-3-[(1*S*)-1-phenylethylamino]pentanoate (0.46 g, 1.85 mmol), sodium carbonate (0.40 g, 3.69 mmol), and methyl bromoacetate (0.22 ml, 2.03 mmol) in acetonitrile (5 mL) gave a pale yellow oil that was purified by flash chromatography (2% ethyl acetate/chloroform) to give **288b** (0.33 g, 56%) as a pale yellow oil, R_f 0.66 (2% ethyl acetate/chloroform); $[\alpha]^{21}_D$ = +15.2 (*c* 0.33, CHCl$_3$); IR ν_{max} 2954 (C-H), 1736 (ester C=O), 1436, 1196, 1171, 703; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.42-7.18 (5H, m, Ph) 3.94 (1H, q, *J*= 6.6 Hz, C*H*Ph) 3.65 (3H, s, OCH$_3$) 3.59 (3H, s, OCH$_3$) 3.35 (2H, s, CH$_2$N) 2.91-2.87 (1H, m, C*H*CH$_2$CO$_2$CH$_3$) 2.32 (1H, dd, *J*= 15.5, 4.4 Hz, C*H*$_2$CO$_2$CH$_3$) 2.21 (1H, dd, *J*= 15.5, 6.9 Hz, C*H*$_2$CO$_2$CH$_3$) 1.66-1.62 (1H, m, C*H*(CH$_3$)$_2$) 1.33 (3H, d, *J*= 6.6 Hz, C*H*$_3$CHPh) 0.95 (3H, d, *J*= 6.9 Hz, C*H*$_3$CHCH) 0.74 (3H, d, *J*= 6.9 Hz, C*H*$_3$CHCH); ^{13}C NMR (500 MHz, CDCl$_3$) δ 173.9 (*C*OOCH$_3$) 173.6 (*C*OOCH$_3$) 144.7 (ArC) 128.3 (ArC) 128.1 (ArC) 127.1 (ArC) 60.6 (*C*HCH$_2$COO) 60.3 (CHAr) 51.6 (OCH$_3$) 51.5 (OCH$_3$) 48.4 (CH$_2$N) 34.7 (*C*H$_2$CHN) 32.7 (*C*H(CH$_3$)$_2$) 21.2 (*C*H$_3$CHN) 20.8 ((*C*H$_3$)$_2$CHCH) 19.7 ((*C*H$_3$)$_2$CHCH).

(*R*)-Methyl 3-{methoxycarbonylmethyl-[(1*S*)-1-phenylethyl]amino}hex-4-enoate (288c)

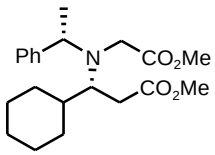


Following general procedure, reaction of (*R*)-methyl 3-{[(1*S*)-1-phenylethyl]amino}hex-4-enoate (0.20 g, 0.81 mmol), sodium carbonate (0.17 g, 1.62 mmol), and methyl bromoacetate (0.09 ml, 0.89 mmol) in acetonitrile (3 mL) gave a pale yellow oil that was purified by flash chromatography (20% ethyl acetate/hexane) to give **288c** (0.22 g, 84%) as a pale yellow oil, R_f 0.67 (30% ethyl acetate/hexane); $[\alpha]^{21}_D$ = +5.3 (*c* 1.33, $CHCl_3$); IR ν_{max} 2952 (C-H), 1737 (ester C=O), 1436, 1195, 1173, 702; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53-7.20 (5H, m, Ph) 5.59-5.54 (1H, m, C*H*=CHCH$_3$) 5.45-5.42 (1H, m, C*H*=CHCHN) 4.11 (1H, q, *J*= 6.7 Hz, C*H*CH$_3$) 3.89-3.88 (1H, m, C*H*CH$_2$CO$_2$CH$_3$) 3.62 (3H, s, OCH$_3$) 3.60 (3H, s, OCH$_3$) 3.31 (2H, s, CH$_2$N) 2.62 (1H, dd, *J*= 14.6, 6.3 Hz, C*H*$_2$CO$_2$CH$_3$) 2.37 (1H, dd, *J*= 14.6, 8.4 Hz, C*H*$_2$CO$_2$CH$_3$) 1.68 (3H, d, *J*= 2.3 Hz, C*H*$_3$CHCH) 1.36 (3H, d, *J*= 6.7 Hz, C*H*$_3$CHPh); ^{13}C NMR (500 MHz, $CDCl_3$) δ 173.7 (*C*OOCH$_3$) 172.3 (*C*OOCH$_3$) 144.9 (ArC) 129.7 (ArC) 128.3 (ArC) 127.7 (ArC) 127.7 (=*C*HCHN) 127.0 (*C*H=CHCHN) 59.2 (*C*HCH$_3$) 57.4 (CH$_2$N) 51.6 (OCH$_3$) 51.5 (OCH$_3$) 48.5 (*C*HCH$_2$COO) 37.7 (*C*H$_2$CHN) 19.8 (*C*H$_3$CH=CH) 18.1 (*C*H$_3$CHAr).

(*R*)-Methyl

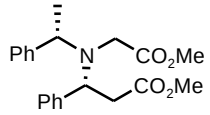
3-cyclohexyl-3-{methoxycarbonylmethyl-[(1*S*)-1-phenylethyl]amino}propanoate

(288d)



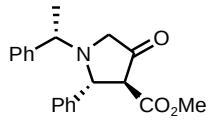
Following general procedure, reaction of (*R*)-methyl 3-cyclohexyl-3-[(1*S*)-1-phenylethyl]amino]propanoate (0.42 g, 1.45 mmol), sodium carbonate (0.32 g, 2.90 mmol), and methyl bromoacetate (0.17 ml, 1.59 mmol) in acetonitrile (5 mL) gave a pale yellow oil that was purified by flash chromatography (2% ethyl acetate/chloroform) to give **288d** (0.26 g, 51%) as a pale yellow oil, R_f 0.70 (2% ethyl acetate/chloroform); $[\alpha]^{25}_D$ = +11.7 (*c* 1.00, $CHCl_3$); IR ν_{max} 2923 (C-H), 1734 (ester C=O), 1434, 1193, 1169, 702; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48-7.19 (5H, m, Ph) 3.94 (1H, q, *J*= 6.8 Hz, C*H*Ph) 3.66 (3H, s, OCH_3) 3.59 (3H, s, OCH_3) 3.35 (2H, s, CH_2N) 2.95-2.92 (1H, m, C*H*$CH_2CO_2CH_3$) 2.31 (1H, dd, *J*= 15.6, 4.1 Hz, C*H*$_2CO_2CH_3$) 2.21 (1H, dd, *J*= 15.6, 7.3 Hz, C*H*$_2CO_2CH_3$) 1.67-1.44 (5H, m, 1'-cyclohexyl-CH + cyclohexyl-CH_2) 1.34 (3H, d, *J*= 6.8 Hz, C*H*$_3$CHPh) 1.30-1.04 (4H, m, cyclohexyl-CH_2) 0.76-0.71 (2H, m, 4'-cyclohexyl-CH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 173.9 (*C*$OOCH_3$) 173.7 (*C*$OOCH_3$) 144.8 (ArC) 128.5 (ArC) 128.4 (ArC) 127.1 (ArC) 60.9 (*C*HCH_2COO) 60.3 (CHPh) 51.5 (OCH_3) 51.4 (OCH_3) 48.4 (CH_2N) 42.4 (*C*H_2CHN) 34.5 (1'-cyclohexyl-C) 30.7 (4'-cyclohexyl-C) 30.0 (2'- cyclohexyl-C) 26.6 (6'-cyclohexyl-C) 26.5 (3'- cyclohexyl-C) 26.5 (5'-cyclohexyl-C) 21.3 (*C*H_3CHPh); m/z (Cl+) 362 (100%, M+H^+); HRMS $C_{21}H_{32}NO_4$ calcd. 362.2331, found 362.2322.

(*R*)-Methyl 3-{methoxycarbonylmethyl-3-phenyl-[(1*S*)-1-phenylethyl]amino}propanoate (288e)



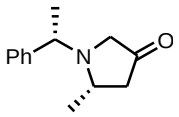
Following general procedure, reaction of (*R*)-methyl 3-phenyl-{[(1*S*)-1-phenylethyl]amino}propanoate (0.70 g, 2.47 mmol), sodium carbonate (0.54 g, 4.94 mmol), and methyl bromoacetate (0.29 ml, 2.70 mmol) in acetonitrile (9 mL) gave a pale yellow oil that was purified by flash chromatography (20% ethyl acetate/hexane) to give **288e** (0.50 g, 58%) as a colourless oil, R_f 0.62 (30% ethyl acetate/hexane); $[\alpha]^{21}_D$ = -10.0 (*c* 2.91, $CHCl_3$); IR ν_{max} 2950 (C-H), 1733 (ester C=O), 1435, 1196, 1169, 761, 700; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58-7.25 (10H, m, Ph) 4.51 (1H, dd, *J*= 9.2, 5.6 Hz, C*H*$CH_2CO_2CH_3$) 4.11 (1H, q, *J*= 6.7 Hz, C*H*CH_3) 3.59 (3H, s, OCH_3) 3.55 (3H, s, OCH_3) 3.32 (2H, s, CH_2N) 2.95 (1H, dd, *J*= 15.0, 5.6 Hz, C*H*$_2CO_2CH_3$) 2.73 (1H, dd, *J*= 15.0, 9.2 Hz, C*H*$_2CO_2CH_3$) 1.33 (3H, d, *J*= 6.7 Hz, C*H*$_3$CHPh); ^{13}C NMR (500 MHz, $CDCl_3$) δ 173.6 (*C*$OOCH_3$) 172.2 (*C*$OOCH_3$) 144.4 (ArC) 141.0 (ArC) 128.4 (ArC) 128.3 (ArC) 128.0 (ArC) 127.7 (ArC) 127.5 (ArC) 127.1 (ArC) 59.9 (*C*HCH_3) 58.3 (*C*HCH_2COO) 51.6 (OCH_3) 51.6 (OCH_3) 48.2 (*C*H_2N) 37.2 (*C*H_2CHN) 17.8 (*C*H_3CHAr).

(5*R*, 4*S*)-Methyl 4-methoxy-5-phenyl-[(1*S*)-1-phenylethyl]pyrrolidin-3-one (289a)



To (*R*)-methyl 3-{methoxycarbonylmethyl-3-phenyl-[(1*S*)-1-phenylethyl]amino}propanoate (0.32 g, 0.91 mmol) in toluene (3 mL) was added potassium *tert*-butoxide (1.2 mL, 1M solution in THF) at 0 ^{o}C. The mixture was stirred for 16 h at room temperature under nitrogen. The mixture was acidified with hydrochloric acid (2 mL, 1M), neutralized by sodium carbonate to around pH 6, extracted with ethyl acetate (10 mL). The combined organic extracts were dried ($MgSO_4$), and evaporated to give **289a** (0.16 g, 55%) as a yellow oil, R_f 0.58 (30% ethyl acetate/hexane); $[\alpha]^{21}_D$ = -13.7 (*c* 1.53, $CHCl_3$); IR ν_{max} 2922 (C-H), 1731 (ester C=O), 1669 (ketone C=O), 1453, 1263, 1336, 759, 699; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58-7.24 (10H, m, Ph) 4.58 (1H, d, *J*= 10.1 Hz, C*H*CHCOO) 4.02 (1H, q, *J*= 6.7 Hz, C*H*CH_3) 3.68 (3H, s, OCH_3) 3.48 (1H, d, *J*= 10.1 Hz, CHCOO) 3.20 (2H, s, CH_2N) 1.30 (3H, d, *J*= 6.7 Hz, C*H*$_3$CH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 205.4 (*C*OCH_2N) 167.4 (*C*OOCH_3) 142.3 (ArC) 139.1 (ArC) 129.3 (ArC) 128.7 (ArC) 128.3 (ArC) 128.0 (ArC) 127.6 (ArC) 127.2 (ArC) 66.1 (*C*HCOO) 64.3 (*C*H_2CO) 53.7 (*C*HCH_3) 53.0 (CH_3O) 52.6 (*C*HCHCOO) 8.6 (*C*H_3CH); m/z (Cl+) 323 (55%, M+H$^+$) 105 (100%, $C_8H_9^+$); HRMS $C_{20}H_{21}NO_3$ calcd. 323.1521, found 323.1526.

(5*S*)-5-Phenyl-[(1*S*)-1-phenylethyl]pyrrolidin-3-one (290a)



(*R*)-Methyl 3-{methoxycarbonylmethyl-[(1*S*)-1-phenylethyl]amino}butanoate (0.30 g,

1.04 mmol) in toluene (3.5 mL) was added potassium *tert*-butoxide (1.4 mL, 1M solution in THF) at 0 ^{o}C. After stirring for 16 h at room temperature under nitrogen, the mixture was acidified with hydrochloric acid (3 mL, 1M), neutralized by sodium carbonate to around pH 6, extracted with ethyl acetate (10 mL), dried ($MgSO_4$), and evaporated. The residue was added to aqueous 5% sulfuric acid (5 mL) and the mixture was heated under reflux for 2 h, then allowed to cool, and neutralized with saturated sodium carbonate solution. The mixture was extracted with ethyl acetate, dried ($MgSO_4$), and evaporated. The resulting oil was purified by flash chromatography (15% ethyl acetate/hexane) to give **290a** (85 mg, 40%) as a yellow oil, R_f 0.28 (15% ethyl acetate/hexane); $[\alpha]^{21}_{D}$ = +186.5 (*c* 0.52, $CHCl_3$); IR ν_{max} 2923 (C-H), 1654 (ketone C=O), 1451, 1378, 1208, 761, 700; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.22 (5H, m, Ph) 3.93 (1H, q, *J*= 6.7 Hz, C*H*Ar) 3.56-3.52 (1H, m, C*H*CH_2) 2.88 (2H, s, CH_2N) 2.60 (1H, dd, *J*= 17.9, 6.4 Hz, C*H*$_2$CH) 2.12 (1H, dd, *J*= 17.9, 6.0 Hz, C*H*$_2$CH) 1.38 (3H, d, *J*= 6.7 Hz, C*H*$_3$CHAr) 1.20 (3H, d, *J*= 6.7 Hz, C*H*$_3$CHCH_2); ^{13}C NMR (500 MHz, $CDCl_3$) δ 214.6 (*C*OCH_2N) 144.2 (ArC) 128.3 (ArC) 127.1 (ArC) 125.6 (ArC) 57.5 (*C*H_2NCH_2Ar) 56.3 (*C*H_2NCH_2CO) 53.2 (*C*HCH_2) 46.6 (*C*H_2CHN) 16.3 (*C*H_3CHAr) 16.1 (*C*H_3CHCH_2); m/z (Cl+) 204 (85%, M+H$^+$) 105 (100%, $C_9H_9^+$); HRMS $C_{13}H_{18}NO$ calcd. 204.1388, found 204.1388.

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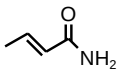
List of Compounds



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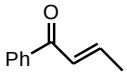

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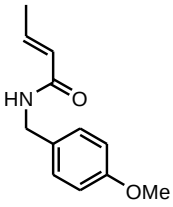

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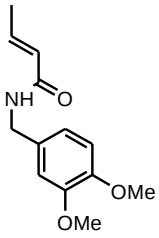

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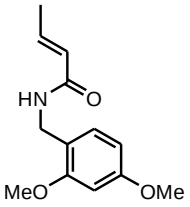

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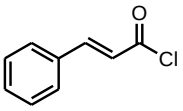

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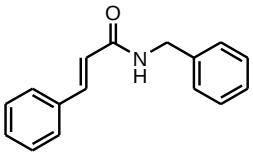

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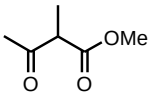

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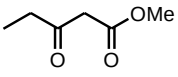
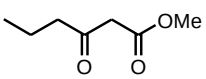
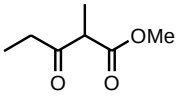


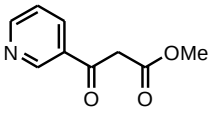
71 P.71



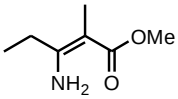
66a P.71



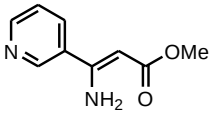
66b P.72



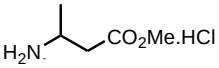
66c P.73



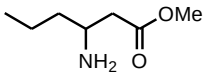
67b P.74



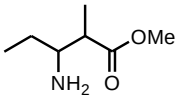
67c P.74



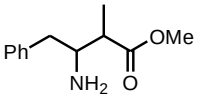
68a P.75



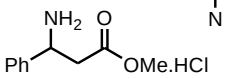
68b P.75



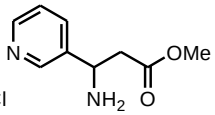
68c P.77



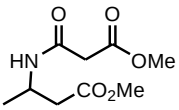
68d P.77



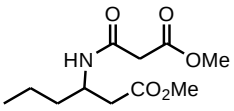
68e P.78



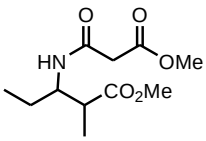
68f P.79



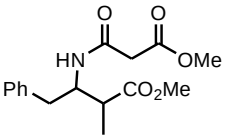
69a P.80



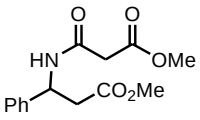
69b P.81



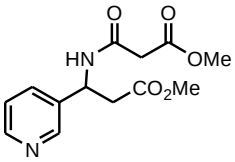
69c P.81



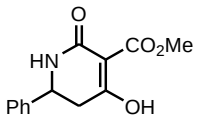
69d P.82



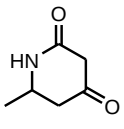
69e P.83



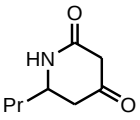
69f P.84



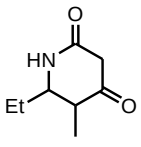
72 P.85



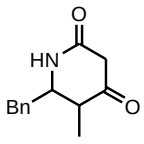
65a P.85



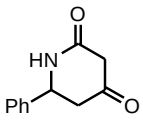
65b P.86



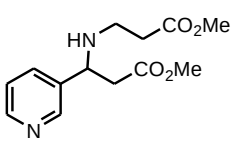
65c P.87



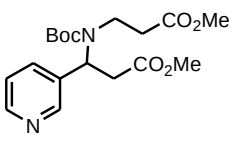
65d P.87



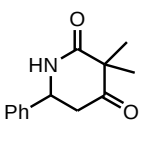
65e P.88



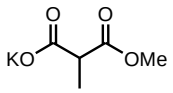
75 P.89



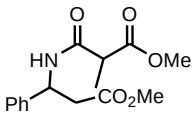
76 P.90



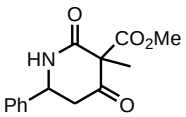
78 P.90



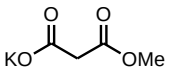
81 P.91



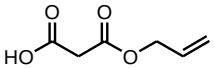
82 P.92



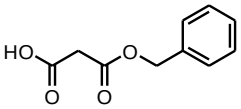
83 P.93



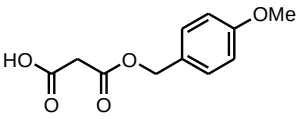
123 P.93



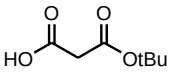
90a P.94



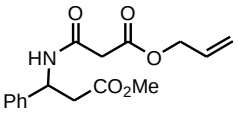
90b P.95



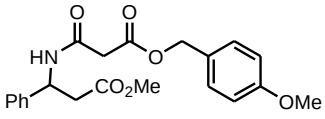
90c P.95



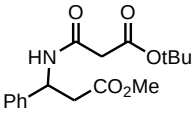
90d P.96



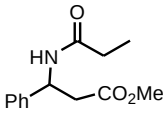
89a P.97



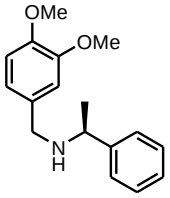
89b P.98



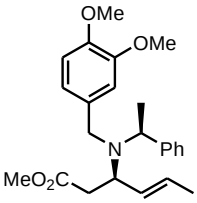
89c P.99



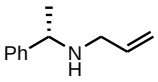
89d P.99



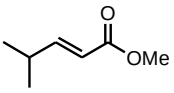
95 P.100



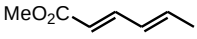
104 P.101



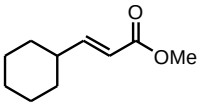
105 P.102



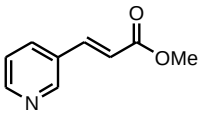
103b P.103



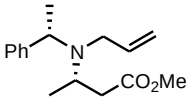
103c P.103



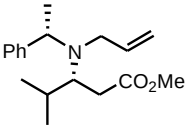
103d P.104



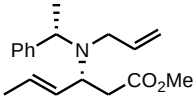
103f P.104



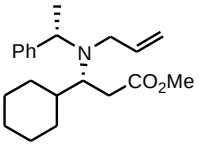
106a P.105



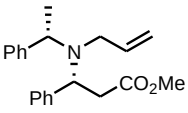
106b P.106



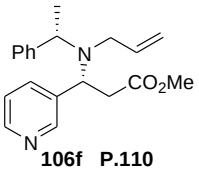
106c P.107



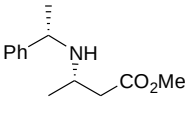
106d P.108



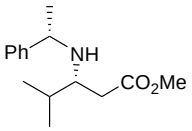
106e P.109



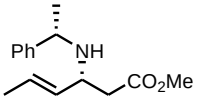
106f P.110



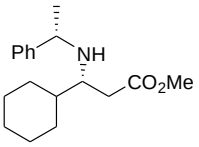
107a P.111



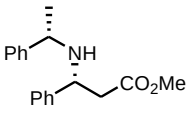
107b P.111



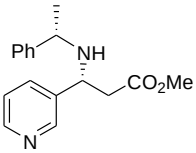
107c P.112



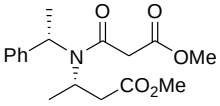
107d P.113



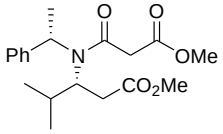
107e P.114



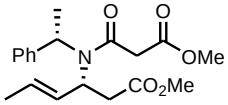
107f P.114



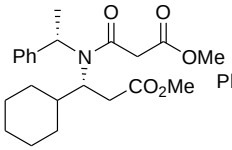
108a P.115



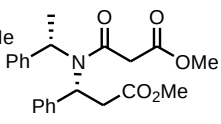
108b P.116



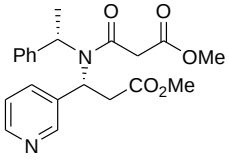
108c P.118



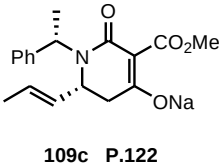
108d P.119



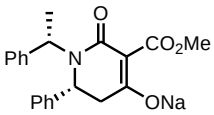
108e P.120



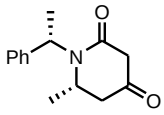
108f P.121



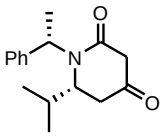
109c P.122



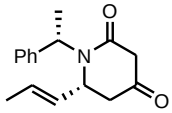
109e P.123



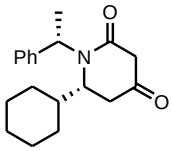
110a P.123



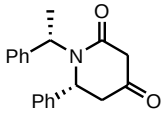
110b P.124



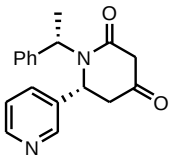
110c P.125



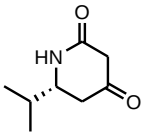
110d P.126



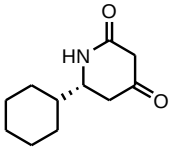
110e P.126



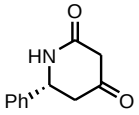
110f P.127



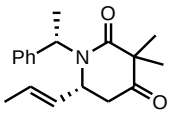
111a P.128



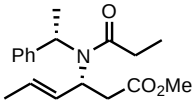
111c P.129



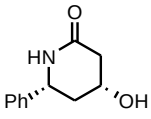
111e P.130



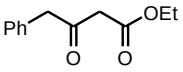
112 P.130



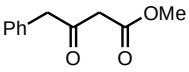
113 P.131



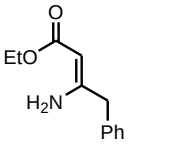
116 P.132



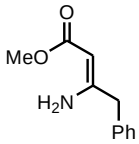
166b P.173



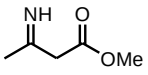
166c P.173



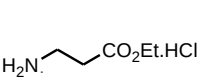
169a P.174



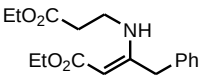
169b P.175



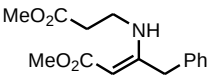
169c P.175



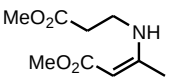
170 P.176



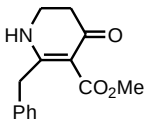
171a P.176



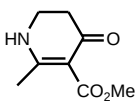
171b P.177



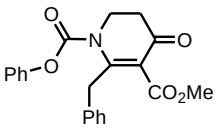
171c P.177



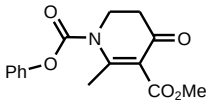
172b P.178



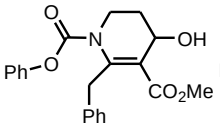
172c P.179



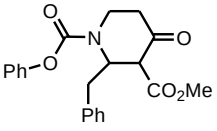
176a P.179



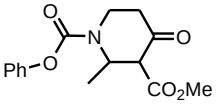
176b P.180



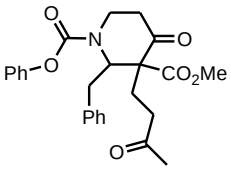
177 P.181



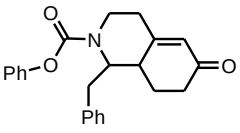
178a P.183



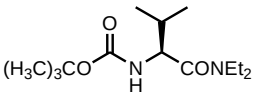
178b P.184



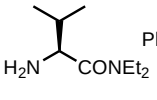
179 P.185



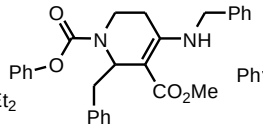
180 P.186



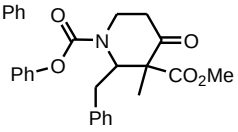
210 P.186



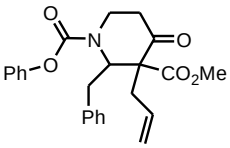
182 P.187



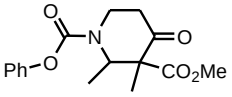
191 P.188



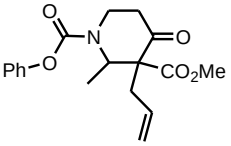
207a P.189



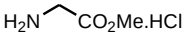
207b P.190



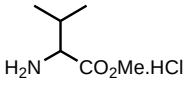
207c P.191



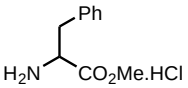
207d P.191



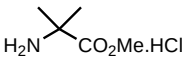
253a P.229



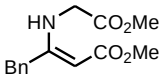
253c P.229



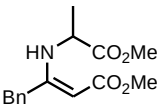
253d P.230



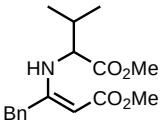
253e P.230



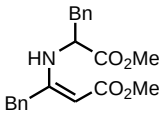
250a P.231



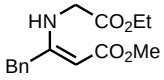
250b P.231



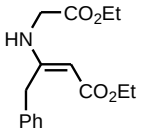
250c P.232



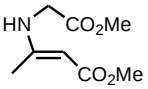
250d P.233



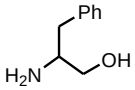
255 P.233



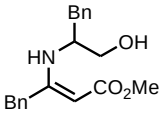
256 P.234



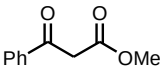
257 P.234



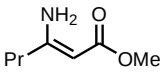
258 P.235



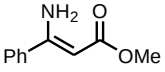
259a P.236



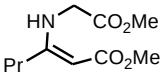
166e P.236



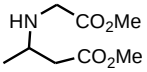
169d P.237



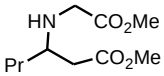
169e P.238



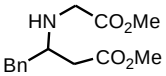
250e P.238



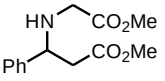
263a P.239



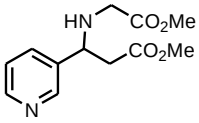
263b P.240



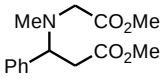
263c P.240



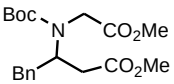
263d P.241



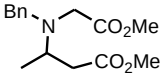
263e P.242



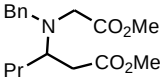
267 P.243



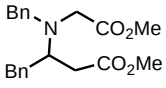
270 P.243



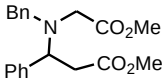
272a P.245



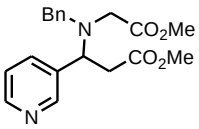
272b P.245



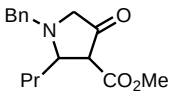
272c P.246



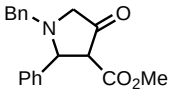
272d P.247



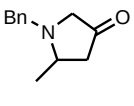
272e P.248



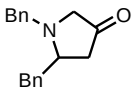
273b P.249



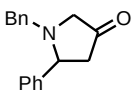
273d P.249



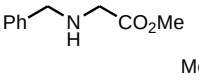
274a P.250



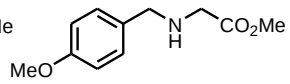
274c P.251



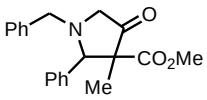
274d P.252



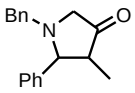
275a P.253



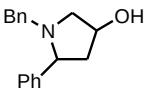
275b P.253



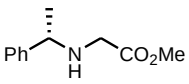
278 P.254



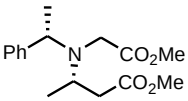
279 P.255



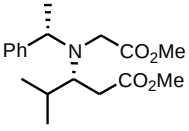
285 P.255



287 P.256



288a P.257



288b P.258

288c P.259

288d P.260

288e P.261

289a P.262

290a P.262