A thesis submitted in part fulfilment of the requirements of the degree of Doctor of Philosophy

Titanium-based Methylenations and their Application to the Synthesis of Pipecolic Acid Derivatives

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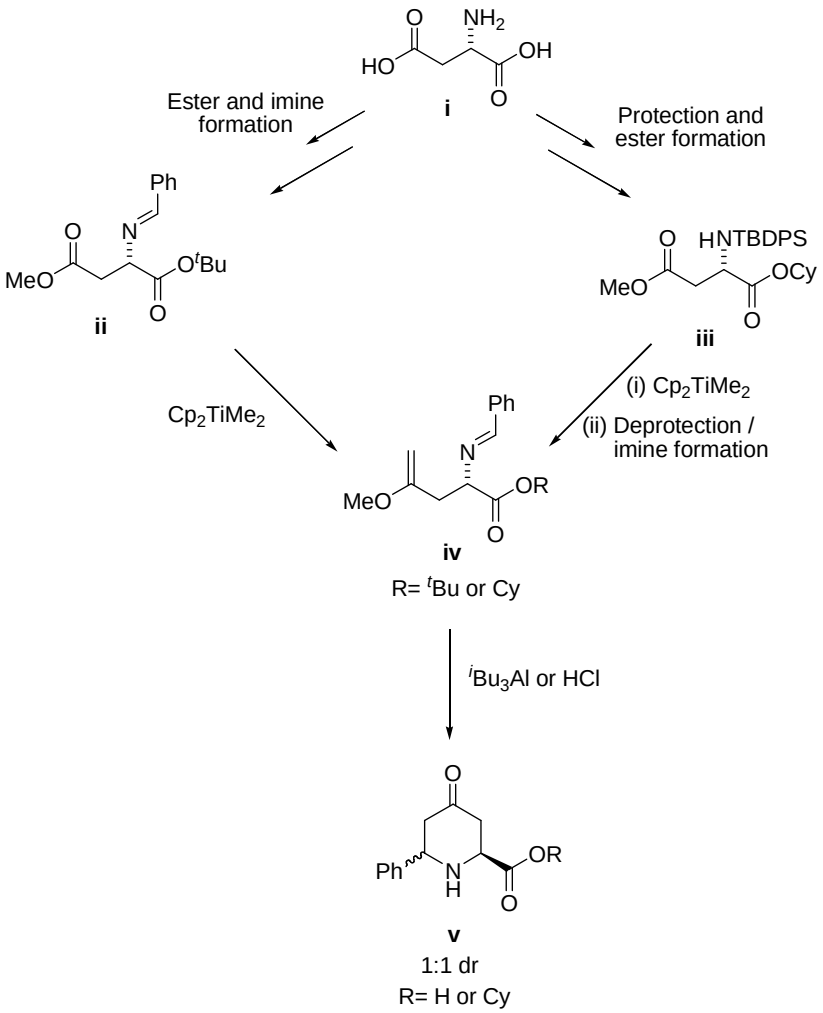
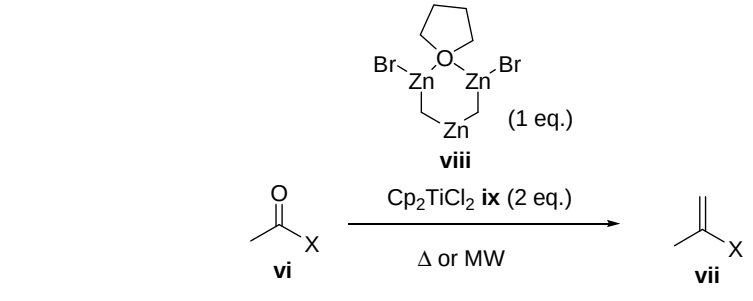
Abstract

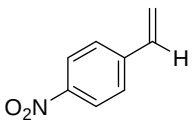
This thesis describes the use of titanium carbenoids for the synthesis of piperidinone alkaloids, in particular pipecolic acid derivatives, and the development of a new titanium-based strategy for the methylenation of carbonyl compounds including carboxylic acid derviatives

Our research focused on the synthesis of pipecolic acid derivatives **v** from (*S*)-aspartic acid **i**. A number of methods of sterically or electronically directing Petasis methylenation to give the substrate for cyclization, enol ether **iv**, were investigated. Ultimately, two routes were developed. The first used a *tert*-butyl ester to direct methylenation to the less hindered carbonyl group in imine **ii**. Reversing the order of imine formation and enol ether formation allowed the use of the bulky TBDPS-amine in diester **iii** to direct methylenation. Imino-enol ethers **iv** were cyclized in acidic conditions to give pipecolic acid derivatives **v** as a 1:1 mixture of diastereoisomers.

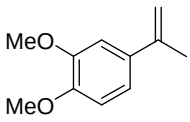


A new method for the methylenation of carbonyl compounds **vi** using a combination of the Nysted reagent **viii** and titanocene dichloride **ix** was also investigated. Following a period of optimisation, conditions for the methylenation of aldehydes, ketones, esters and lactones were developed and small libraries of methylenated products (e.g. **x**-**xiii**) were generated. Preliminary investigations into the identity of the active species were also carried out.

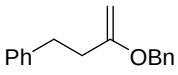




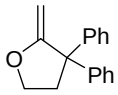
x, 59%



xi, 77%



xii, 60%



xiii, 52%

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I am also grateful for the support of my industrial supervisor, Zoran Rankovic, for making the time for many useful discussions during my PhD. Thank you also to the staff of what was MSD, Newhouse, especially Jonathon Gillespie.

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Thank you to Team Adventure for good times and showing me the importance of effective team work.

A huge thank you to my family for supporting me through the last 3-4 years while I was 'making pills' at the 'factory'.

Finally, thanks to Lynne for coming to her senses.

Author's Declaration

This thesis represents the original work of Adam Haahr unless explicitly stated otherwise in the text. The research was carried out at the University of Glasgow in the Loudon Laboratory and at MSD, Newhouse under the supervision of Dr Richard Hartley during the period October 2007 to September 2010. Portions of the work described herein have been published elsewhere as listed below.

A. Haahr, R. C. Hartley and Z. Rankovic, *Tetrahedron Letters* **2011**, *52*, 3020-3022

Abbreviations

$[\alpha]$	specific rotation
Å	Angström
Ac	acetyl
aq	aqueous
Ar	aryl
atm	atmosphere
B.p.	boiling point
Bn	benzyl
BOC	*tert*-butoxycarbonyl
br d.	broad doublet
br s.	broad singlet
Bu	butyl
^{i}Bu	isobutyl
^{t}Bu	*tert*-butyl
Bz	benzoyl
°C	degrees centigrade
cat.	catalytic
Cbz	benzyloxycarbonyl
CDI	1,1'-carbonyldiimidazole
CI	chemical ionization
COSY	correlation spectroscopy
cm	centimetre
cm^{-1}	wavenumber
Cp	cyclopentadienyl
Cy	cyclohexyl
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DFT	density functional theory
DMAP	*N*,*N*-dimethyl-4-aminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
ε'	dielectric constant
ε"	dielectric loss
Ea	activation energy
EDC.HCl	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride

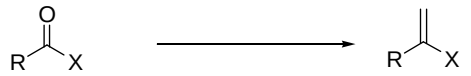
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide methiodide
ee	enantiomeric excess
eq.	equivalents
ESI	electrospray ionisation
Et	ethyl
FAB	fast atom bombardment
GABA	gamma amino butyric acid
h	hours
HOBt	hydroxybenzotriazole
HSQC	heteronuclear single quantum coherence
Hz	hertz
IR	infrared
J	coupling constant
KHMDS	potassium hexamethyldisilazide
LiHMDS	lithium hexamethyldisilazide
M	moles per litre
m	multiplet
M.p.	melting point
MAOS	microwave assisted organic synthesis
Me	methyl
mg	milligram
min	minutes
mL	millilitre
mmol	millimole
mol	moles
Ms	methylsulfonyl (mesyl)
MTBSTFA	*N*-*tert*-butyldimethylsilyl-*N*-methyltrifluoroacetamide
MW	microwave
NMO	*N*-Methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
NOESY	nuclear overhauser effect correlation spectroscopy
PG	protecting group
Ph	phenyl
PMB	paramethoxybenzyl
ppm	parts per million
^{i}Pr	isopropyl
n-Pr	propyl

P-tolyl	*para*-toluenesulfonyl (tosyl)
q	quartet
quin	quintet
R	gas constant
RCM	ring closing metathesis
R_f	retention factor
RT	room temperature
s	seconds
s-Bu	*sec*-butyl
sat.	saturated
T	temperature
t	triplet
tanδ	loss factor
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TMEDA	Tetramethylethylenediamine
TMS	trimethylsilyl
Tr	trityl
Ts	*para*-toluenesulfonyl (tosyl)
W	watts

Contents

1.0 Methylenation of Carbonyl Groups

The methylenation of carbonyl compounds **1** to give terminal alkenes **2** is an extremely useful reaction for synthetic organic chemists (Scheme 1). Depending on the type of carbonyl compound used a wide range of products **2** can be accessed, including mono- and disubstituted alkenes, enol ethers, silyl enol ethers and enamines.

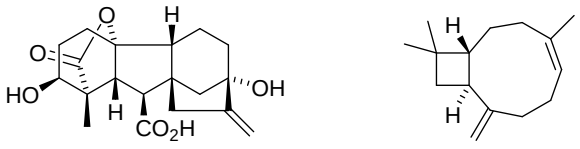


1 **2**

X=H, C, O, N, Si

Scheme 1: Methylenation of carbonyl groups

These functional groups are found in some natural products for instance gibberellic acid **3**,[1] a plant growth hormone and caryophyllene **4**,[2] a constituent of clove oil (Figure 1).



3 **4**

Figure 1: Exomethylene natural products

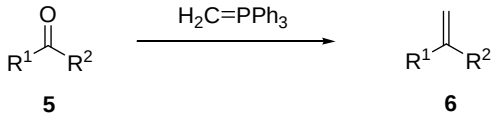
Due to the reactive nature of the methylenated compounds **2** the products of methylenation reactions are more commonly intermediates in longer syntheses. There are a large number of reactions in which they can play a role, including metathesis, epoxidation, dihydroxylation, halogenation, oxidation, hydrogenation and, in the case of carboxylic acid derived alkenes, S_N2, Mannich and aldol reactions. We were particularly interested in the use of titanium carbenoid methylenating reagents for the synthesis piperidine alkaloids.

As a consequence of the synthetic utility described above a great amount of research has been carried out in this field and there are many reported methods.[3] It should be noted that, while the depth of available synthetic methodology demonstrates the level of scientific interest, it also highlights the fact that there is no definitive method. On the contrary, there are many entries in the literature reporting the success of one method where another has failed.[3] Due to the large number of methods, only the more common and general strategies are discussed here, although use of the Nysted reagent and titanium based methods are discussed in more detail as they are very relevant to the research reported later.

1.1 Common Methylenation Methods

1.1.1 Phosphorus Based Methylenation Methods

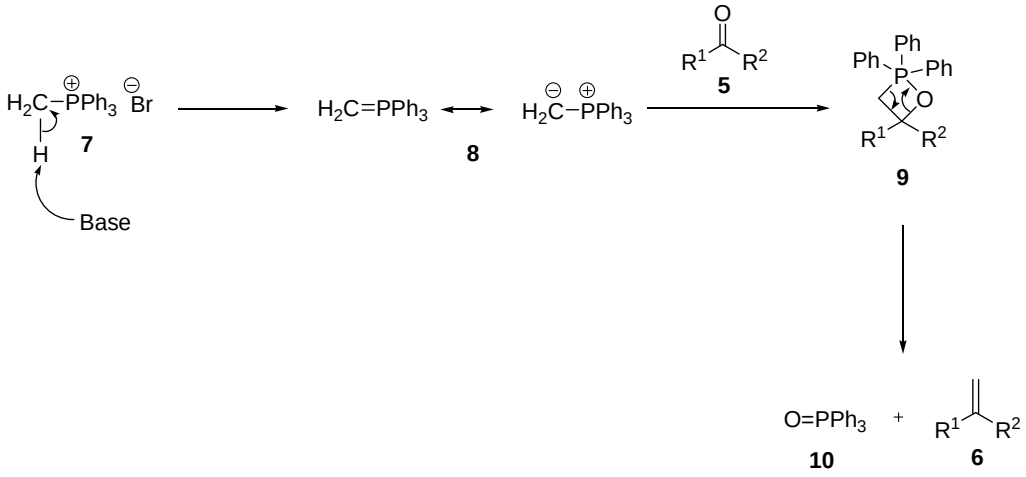
One of the most commonly used methods of carbon-carbon double bond formation is the Wittig reaction and its variants.[4] First described in 1954, the general reaction is the alkenation of carbonyl groups **5** by phosphorus ylides to give alkenes **6** (Scheme 2).[5] It earned the chemist responsible for its discovery, Georg Wittig, the Nobel Prize in 1979. Substrates for the reaction are generally aldehydes and ketones and, although it is discussed here in the context of methylenation, a wide range of alkenated products can be generated with a great degree of stereocontrol.



5 **6**

Scheme 2: The general Wittig reaction

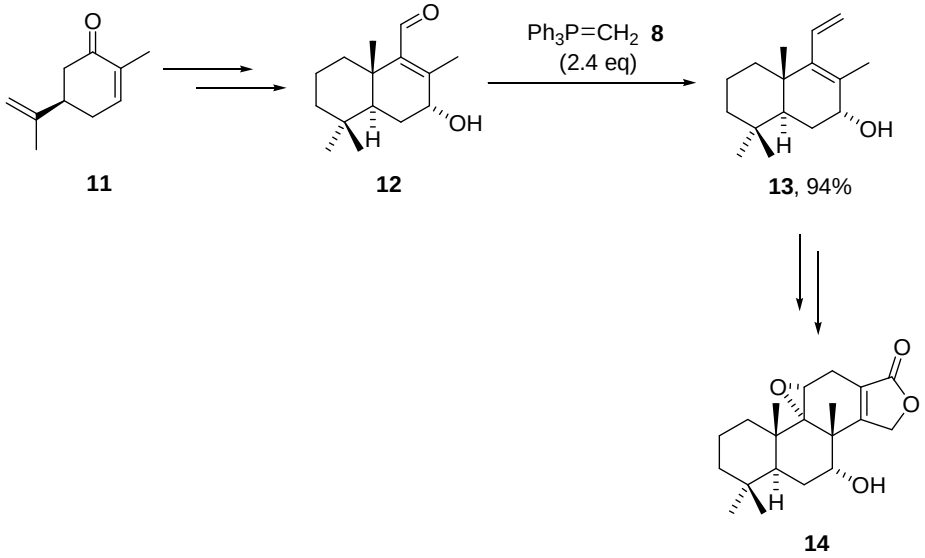
The reaction mechanism (Scheme 3) begins with the deprotonation of a phosphonium salt **7** to give a phosphonium ylide **8**.[6] Ylide **8** then reacts with carbonyl group **5** in a [2+2] addition to form oxaphosphetane ring **9**. Oxaphosphetane **9** then breaks up to generate the alkene product **6** and triphenylphosphine oxide **10**. Although not relevant to methylenation, the stereoselectivity of the reaction is controlled by the nature of the ylide used. Reactive, unstabilised ylides give *Z*-alkenes, while stabilised ylides give *E*-alkenes.



Scheme 3: Wittig reaction mechanism

When attempting to methylenate an aldehyde or ketone the Wittig reaction is likely to be one of the first reactions the modern organic chemist turns to. This is not only due to how well known this type of chemistry is, but also because the required methyl triphenylphosphonium salt **7** is cheaply commercially available. A recent example is

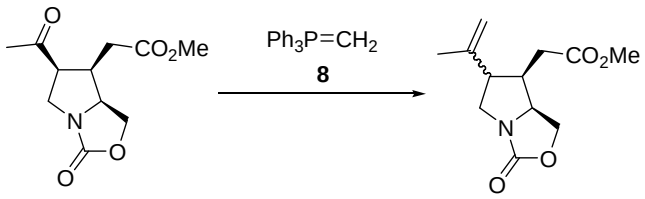
described by Abad and co-workers, using phosphonium ylide **8** they cleanly methylenated aldehyde **12** to give alkene **13**, an intermediate in their synthesis of spongaine type diterpenoid **14** (Scheme 4).[7]



11 **12** **13**, 94% **14**

Scheme 4: Synthesis of spongaine type diterpenoid

Phosphorus-based approaches to the methylenation of aldehydes and ketones are not without limitations. The reactivity of the ylide **8** is an issue and it is not generally nucleophilic enough to methylenate hindered ketones. There are others problems, ylide **8** is basic and can therefore deprotonate α-ketonic hydrogens, leading to epimerisation if the site is a chiral centre. This issue is demonstrated by Parsons and co-workers in their work toward a synthesis of kainic acid (Scheme 5).[8] When trying to methylenate ketone **15** epimerization of the adjacent chiral centre was observed, giving alkene **16** as a mixture of diastereomers.

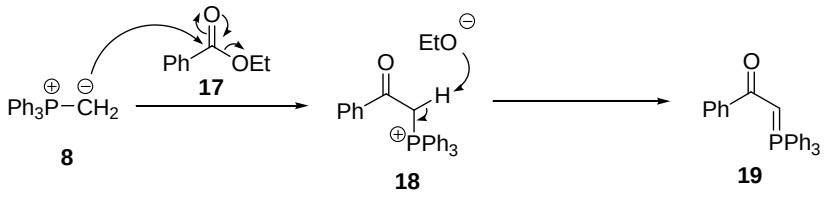


15 **16**

Scheme 5: Basic conditions lead to epimerization

While very effective in the methylenation of aldehydes and ketones, the substrate scope of the Wittig reaction and its variants does not extent much beyond here. There are some reports of the use of phosphorus based methods in the methylenation of carboxylic acid derivatives,[9] however they are not very general. Commonly the reaction of a phosphorus ylide and an ester results in displacement. For example

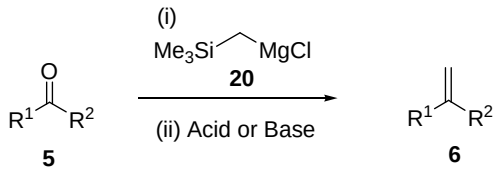
reaction between ylide **8** and ester **17** led to the formation of β-ketophosphorane **19** following deprotonation of the intermediate phosphonium salt **18** (Scheme 6).



Scheme 6: Undesirable reaction pathway in the attempted methylenation of esters

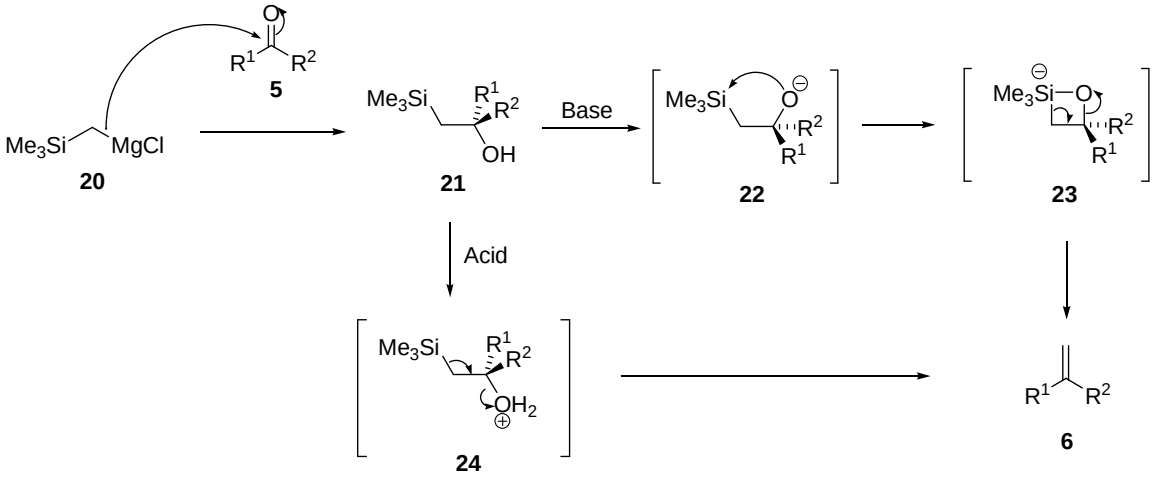
1.1.2 Silicon Based Methylenation Methods

First reported by Whitmore and co-workers in 1947,[10] though not popularised until 1968 by the chemist who lent the reaction his name, the Peterson reaction is the formation of a carbon-carbon double bond from the union of a carbonyl compound **5** and an α-silyl carbanion (for example Grignard reagent **20**) (Scheme 7).[11]



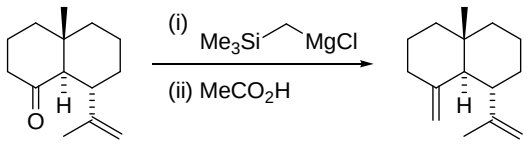
Scheme 7: The Peterson reaction

The reaction can be viewed as the silicon version of the Wittig reaction, operating by a similar mechanism (Scheme 8).[12] Firstly α-silyl carbanion **20** carries out a nucleophilic attack on carbonyl containing compound **5** giving β-hydroxysilane **21** after aqueous work-up. This is the major difference with the Wittig reaction, the β-hydroxysilane **21** is often isolable and can proceed through two different reaction pathways depending on whether it is treated with acid or base. In basic conditions deprotonation of the alcohol occurs to give alkoxide **22** which cyclizes giving oxasilacyclobutane **23**. Decompostion in the same way as the oxaphosphetane intermediate in the Wittig reaction gives the alkene product **6**. If β-hydroxysilane **21** is treated with acid an E2-like elimination of water and silicon from intermediate **24** takes place to give the product **6**. Although not of relevance to methylenation, it is possible to generate *E* and *Z* alkenes with a high degree of control using this methodology. As the elimination steps are stereospecific, isolation of single β-hydroxysilane diastereomers from the reaction of more substituted α-lithio or α-magnesio-silanes with carbonyl compounds allows the alkene geometry to be controlled by the use of acid or base.



Scheme 8: Mechanism of the Peterson reation

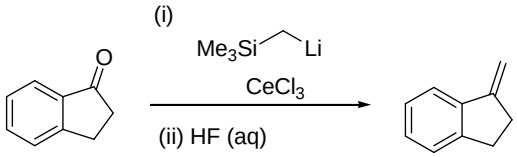
In practice, the Peterson system results in a less sterically hindered and more basic nucleophile than the analogous Wittig reagent.[13] In the field of methylenation this can be advantageous, for example Boeckmann and Silver found that Peterson methylenation succeeded where Wittig methylenation had failed in their synthesis of β-gorgonene **26** (Scheme 9).[14]



25 **26**, 16%

Scheme 9: Synthesis of *B*-gorgonene by Boeckmann and Silver

However, in general, this increased basicity and nucleophilicity has made the Peterson methodology less attractive and less widely used as a methylenating agent.[12] Modifications, such as the addition of cerium salts described by Johnson and Tait, can help to attenuate the reactivity and more cleanly generate the intermediate β-hydroxysilane.[15] In the example shown (Scheme 10), the yield of alkene **28** was more than double that of the same reaction under conventional Peterson conditions.



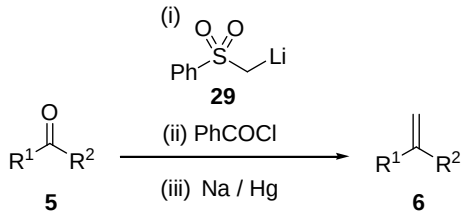
27 **28**, 73%

Scheme 10: Cerium modified Peterson methylenation conditions

The substrate scope of the Peterson methylenation is also limited to aldehydes and ketones, falling victim to the same nucleophilic acyl substitution as the Wittig reaction.[16]

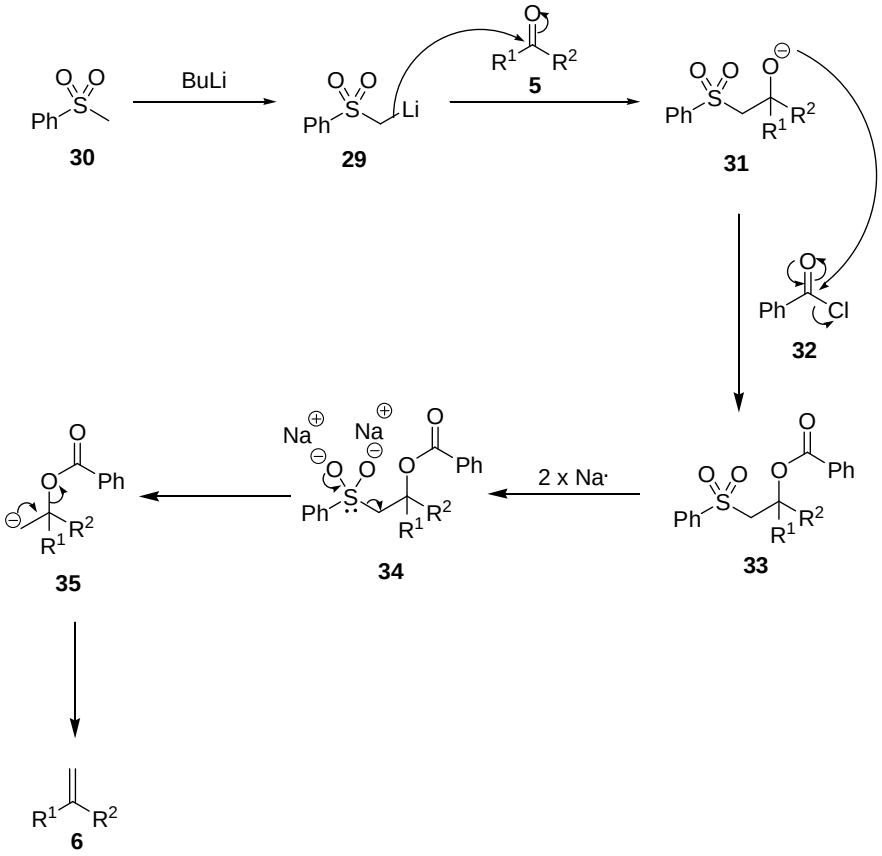
1.1.3 Sulfur Based Methylenation Methods

Sulfur based alkenation methods have also been developed, the most well know of which is the Julia olefination. First reported by Julia and Paris in 1973 the classical Julia reaction requires several chemical steps (Scheme 11).[17] Overall a carbonyl group **5** and an α-lithiated sulfone **29** come together to form an alkene **6** in the presence of a reducing agent.



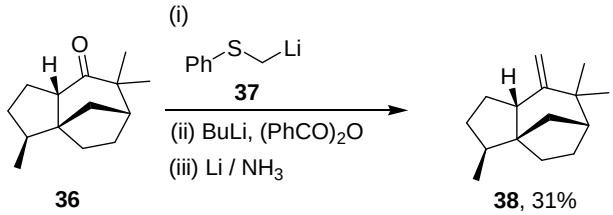
Scheme 11: Classical Julia olefination

Like the Wittig and Peterson reactions, the Julia reaction mechanism is thought to involve an elimination as the key step (Scheme 12).[18] However, unlike the previously discussed strategies, the oxygen atom is not removed by the sulfur atom. Firstly, sulfone **30** is lithiated and reacts with a carbonyl compound **5**. The resultant β-alkoxysulfone **31** is than activated by reaction with benzoyl chloride **32** giving intermediate **33**. Two sequential one-electron reductions give dianion **34** which fragments releasing carbanion **35**, which eliminates yielding the desired alkene **6**. Although not relevant to methylenation it is worth noting that that carbanion **35** has a long enough lifetime for the lowest energy conformation to form and thus the major product is predominantly the *E*-alkene when an α-substituted sulfone is used.



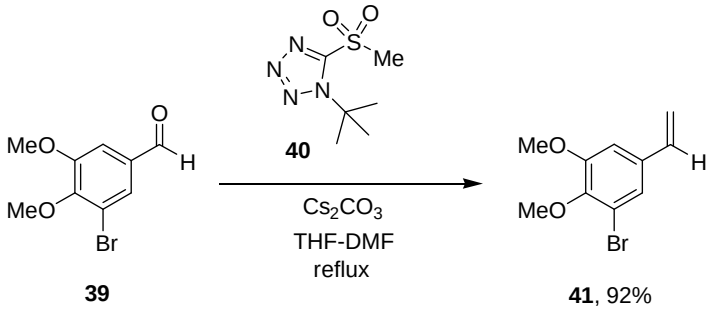
Scheme 12: Mechanism of the classical Julia reaction

Due to the number of synthetic steps involved and the availability of many simpler methods, the Julia reaction is not commonly used for methylenation.[3] However there are some examples, for instance Sowerby and Coates used analogous conditions using thioether **37** instead of a sulfone in the synthesis of zizaene **38** (Scheme 13).[19] Hindered and potentially enolizable ketone **36** was not reactive under Wittig conditions.

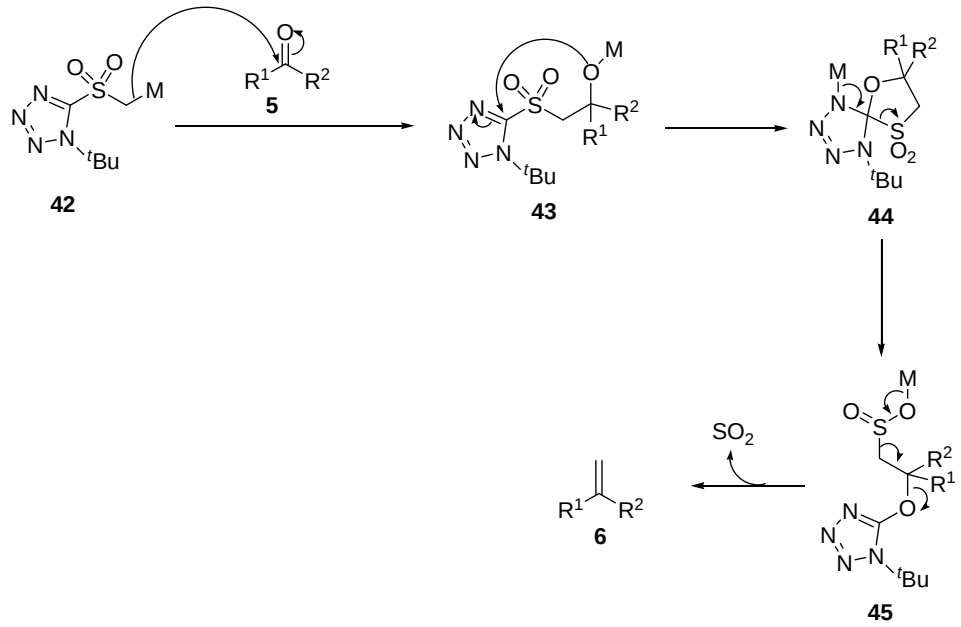


Scheme 13: Synthesis of Zizazene

More recently Aissa has described use of the modified Julia olefination to methylenate aldehydes and ketones (Scheme 14).[20] The modified Julia olefination greatly increases the practical utility of the reaction as it allows the whole procedure to occur in one pot.[18] The reaction is also thought to proceed through a different mechanism under these conditions (Scheme 15). The initial attack on the carbonyl compound **5** by metallated sulfone **42** occurs as before. However instead of being trapped as the ester, metal alkoxide intermediate **43** is set up for a Smiles rearrangement *via* intramolecular attack on the tetrazole to give spirocycle **44**. The spirocycle **44** rearranges to give intermediate **45**, which fragments losing sulfur dioxide to give the alkene product **6**.

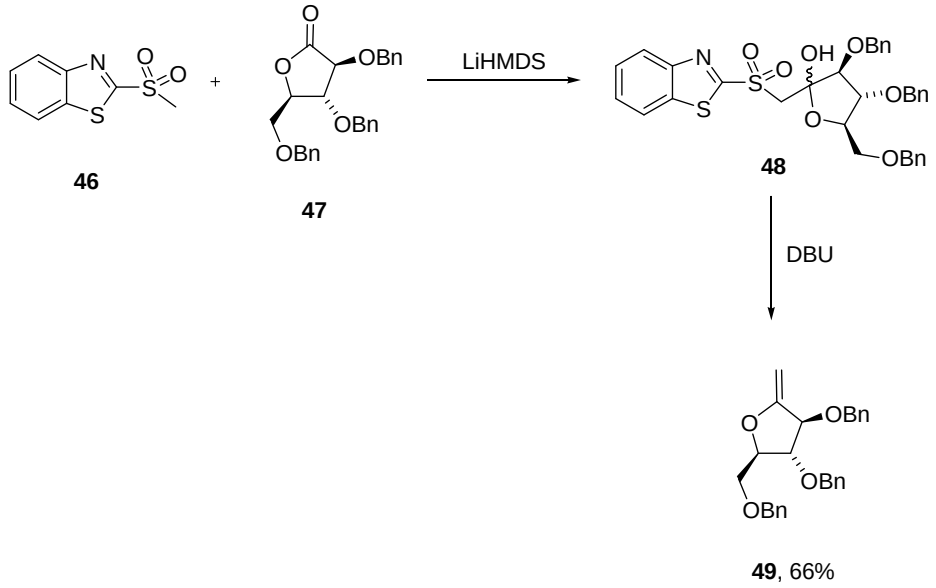


Scheme 14: Modified Julia methylenation



Scheme 15: Mechanism of the modified Julia olefination

The methylenation of esters using Julia conditions is rarely described in the literature and presumably suffers from the same displacement issues as both the Peterson and Wittig methods. There are however some reported instances of the methylenation of esters using sulfur based methodology. For example Gueyrard and co-workers used a modified step-wise Julia reaction to generate hemiacetal **48** from the reaction of lactone **47** and benzothiazole sulfone **46** (Scheme 16).[21] Treatment of the crude hemiacetal with DBU resulted in the formation of enol ether **49**. While interesting, this methodology has only been applied to sugar derived lactones to date.

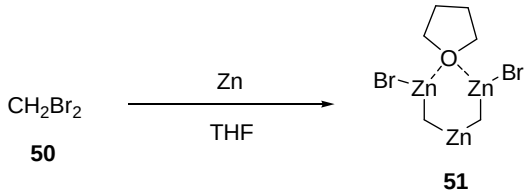


Scheme 16: Enol ether synthesis using the modified Julia olefination

Along with the phosphorus and silicon based strategies, Julia type reactions are another method in the host available for the methylenation of aldehydes and ketones. While they can carry out this transformation adequately, they are lacking in their ability to methylenate the arguably more interesting carboxylic acid derived substrates.

1.2 The Nysted Reagent and other Dizinc Species

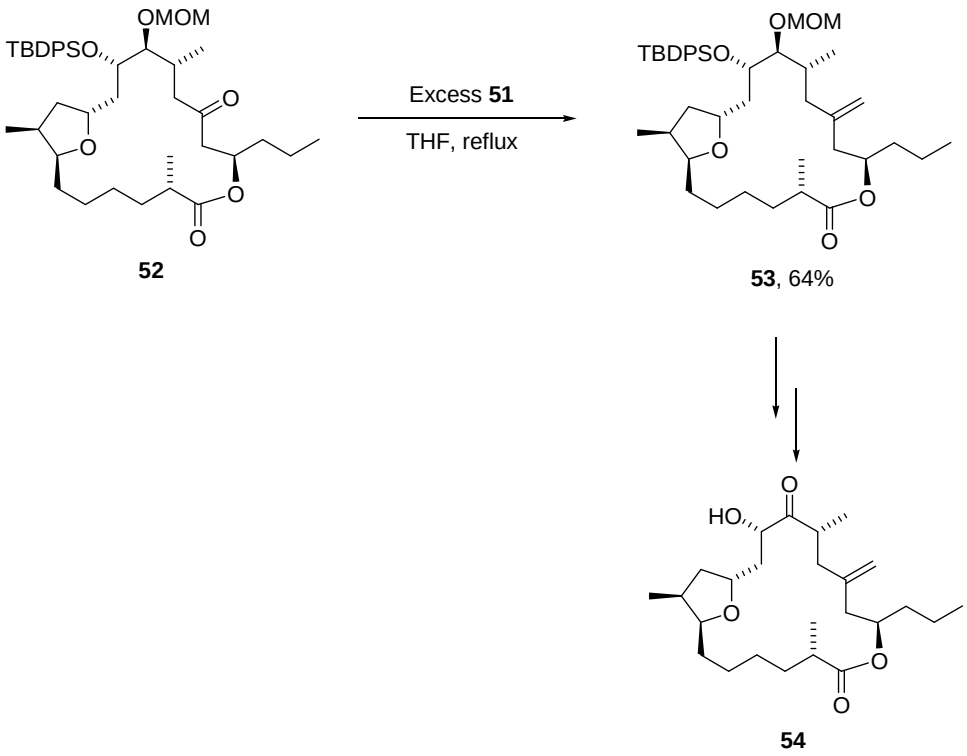
The Nysted Regeant **51** is a geminal-dizinc species first reported in 1975, and has been shown to be effective in the methylenation of aldehydes and ketones.[22] It can be synthesised by the reaction of dibromomethane **50** and zinc (Scheme 17). Evidence for its dimeric structure is based solely on ^{1}H NMR spectroscopy and therefore is not completely conclusive.[23] However it is commercially available and can be purchased from a leading chemical supplier as a suspension in THF costing approximately £1.80/mmol.



Scheme 17: Synthesis of the Nysted reagent

Due to its simplicity the Nysted Reagent **51** is quite widely used a methylenating agent, including being utilized in the late stages of complex natural product synthesis. For example Fürstner and co-workers used the reagent in their synthesis of amphidinolide T4 **54** (Scheme 18).[24] They found that Wittig reagents were too basic and led to

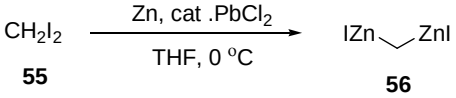
opening of the macrocycle **52**. This example also demonstrates the chemoselectivity of the Nysted reaction, even with excess reagent, methylenation of the ketone proceeded cleanly in the presence of an ester group. While this reaction used solely the Nysted reagent **51** to induce methylenation, it should be noted that others have shown that addition of Lewis acids, such as BF_3.OEt, can increase the effectiveness of the reaction.[25]



52 **53**, 64% **54**

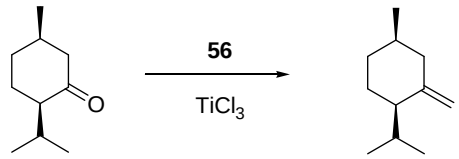
Scheme 18: Use of the Nysted reagent in the synthesis of amphidinolide T4

Matsubara and co-workers have carried out research on an analogous compound, bis(iodozincio)methane **56**, which can be generated from a lead catalysed reaction between diiodomethane **55** and zinc (Scheme 19).[25] They confirmed the monomeric structure through a neutron and X-ray scattering experiments.[26] They also showed its utility in the methylenation of various aldehydes and ketones including cyclic ketone **57**, which was found to be most effective with the addition of a stoichiometric amount of titanium(III) chloride (Scheme 20).[27]



55 **56**

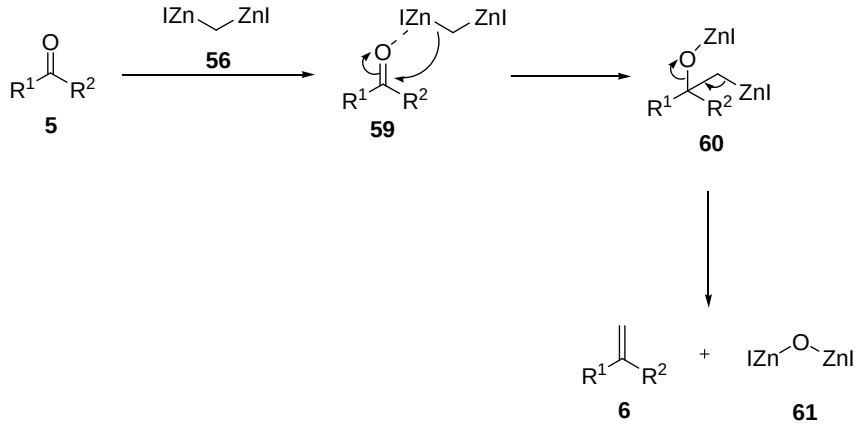
Scheme 19: Synthesis of bis(iodozincio)methane



57 **58**, 94%

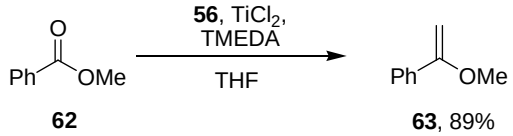
Scheme 20: Ketone methylenation with bis(iodozincio)methane

Density functional theory (DFT) calculations have allowed Matsubara and co-workers to propose a mechanism for the reaction (scheme 21).[28] The zinc atom in the reagent **56** acts as a Lewis acid to activate the carbonyl group **5** to nucleophilic attack in intermediate **59**. The resultant coordinated alkoxide **60** then eliminates forming the alkene product **6** and a zinc oxide **61**.



Scheme 21: Mechanism of methylenation with bis(iodozincio)methane

Matsubara and co-workers have also reported that a modified system using bis(iodozincio)methane **56** in combination with titanium(II) chloride and tetramethylethylenediamine (TMEDA) is effective for the methylenation of esters, for example ester **62** gave enol ether **63** (Scheme 22).[29] The reaction can be viewed as an alternative access to the active species of the Takai reaction (see Section 1.3.6), a titanium carbenoid.



62 **63**, 89%

Scheme 22: Ester methylenation with bis(iodozincio)methane

1.3 Titanium-based Methylenation Methods

Since the discovery of Tebbe's reagent in 1978, the use of titanium-based reagents has fast become a commonly used method of methylenation in organic synthesis.[30] They hold many advantages over the previously discussed methods; firstly, they are non-basic and therefore do not risk epimerisation of α-keto chiral centres, also they are small and reactive, and can successfully react with hindered carbonyl groups. Most importantly, titanium-based reagents can successfully methylenate carboxylic acid derivatives.

1.3.1 Active Species

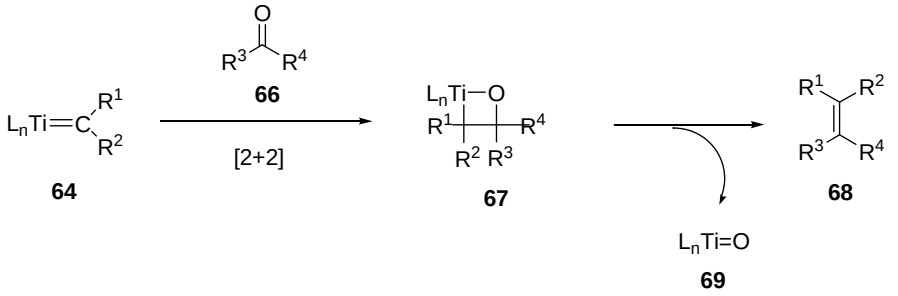
Broadly speaking the titanium-based reagents for alkylidenation of carbonyl groups are categorized as either titanium alkylidenes **64** or 1,1 bimetallic species **65** based on the identity of the proposed active species involved (Figure 2).

64 **65**

L=ligand
M=[Ti], ZnX, MgX

Figure 2: Titanium reagent active species

The majority of common titanium-based alkylidenating reagents are thought to have a titanium alkylidene **64** as the active species. The different reagents essentially represent different strategies for accessing the alkylidene **64** and their use has been extensively reviewed in the literature.[3, 31] Titanium alkylidenes **64** are Shrock carbenes, and consequently are nucleophilic at the methylidene carbon atom. They are proposed to react with carbonyl compounds **66** in the mechanism shown in Scheme 23. Firstly a concerted [2+2] addition gives oxatitanacyclobutane **67** which fragments to give the alkene product **68** and titanium oxide **69**. Evidence for this of mechanism over a Grignard type addition-elimination pathway is primarily based on isotopic labelling experiments.[32]



Scheme 23: General mechanism of titanium alkylidene-based alkylidenation

The active species titanium alkylidene **64** has not been observed experimentally under the conditions used in the alkylidenation of carbonyl compounds. However other titanium carbenoids have been characterised, for instance van der Heijden and co-workers found that phosphinoalkoxide ligands stabilised carbenoid **70** sufficiently for an X-ray crystal structure to be obtained (Figure 3).[33] The same group also synthesised titanocene dichloride-derived alkylidene **71**. Although a crystal structure could not be obtained, the spectroscopic features (^{1}H NMR peak at 12.3 ppm and ^{13}C NMR peak at 313 ppm) are typical of a titanium alkylidene.[34]

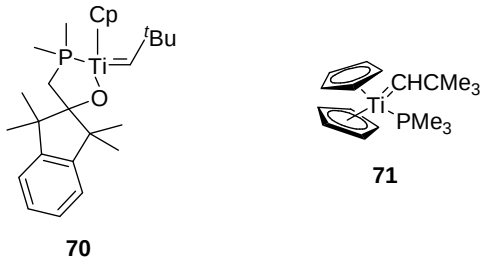
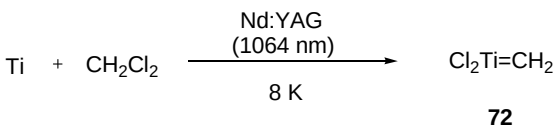


Figure 3: Relatively stable titanium alkylidene

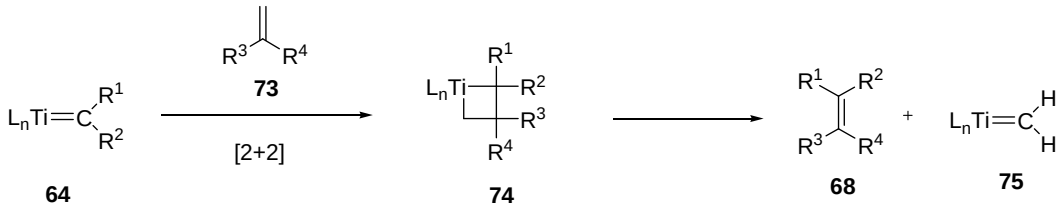
Simple titanium methylidene complexes are too unstable to be isolated, however recently Lyon and Andrews recorded the IR spectrum of titanium methylidene complex **72** formed from the laser induced reaction of titanium metal and dichloromethane at very low temperatures (Scheme 24).[35]



Scheme 24: Transient formation of a simple titanium methylidene complex

In practice, titanium alkylidenes **64** and 1,1-bimetallic species **65** are distinguished on their ability to catalyse alkene metathesis. Although much less effective than the commonly used ruthenium catalysed methods, titanium alkylidenes have been shown to promote metathesis reactions.[36] Only a titanium alkylidene **64** can undergo the [2+2]

addition onto the alkene **73** required by the reaction mechanism (Scheme 25) and hence the ability to catalyse alkene metathesis is taken as a marker of its presence.

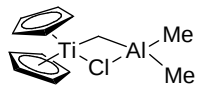


Scheme 25: Mechanism of alkene metathesis catalysed by titanium carbenoids

1,1-Bimetallic species **65** often include titanium and another metal, e.g. zinc or magnesium. They react with carbonyl groups in a similar way to bis(iodozincio)methane **56** (see Scheme 21). Titanium-based carbonyl methylenation methods that do not catalyse alkene metathesis are presumed to be 1,1-bimetallic species.

1.3.2 The Tebbe Reagent

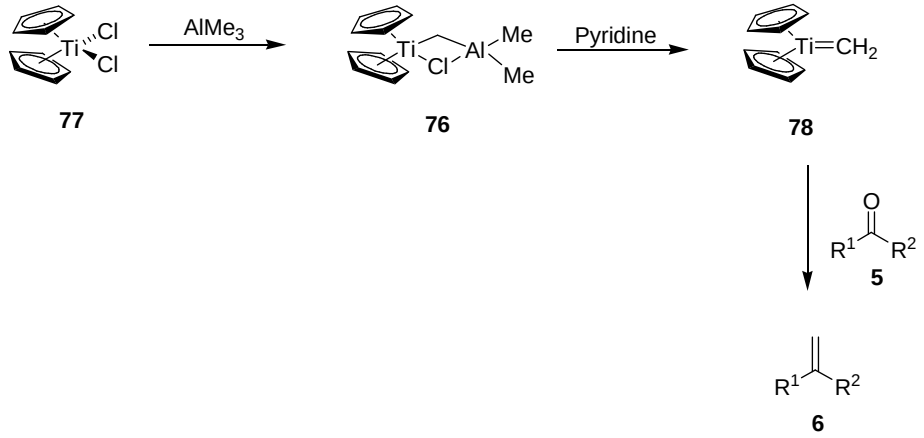
First reported in 1978 by Tebbe and co-workers the Tebbe reagent **76** ushered in a new era of carbonyl methylenation chemistry using titanium complexes (Figure 4).[30]



76

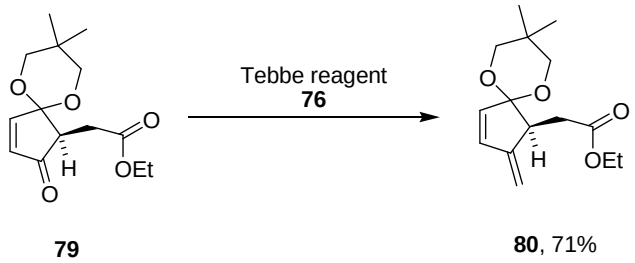
Figure 4: Structure of the Tebbe reagent

Although now commercially available, the Tebbe reagent **76** is expensive and often unsatisfactory if not freshly prepared due to its air and moisture sensitivity.[31a] It can be generated from the reaction of titanocene dichloride **77** and trimethylaluminium (Scheme 26).[30, 37] Although the Tebbe reagent **76** itself is a 1,1-bimetallic species, reaction with a Lewis base reveals the active species titanocene methylidene **78** which will methylenate a variety of carbonyl functionalities including aldehydes, ketones, esters, lactones and amides.



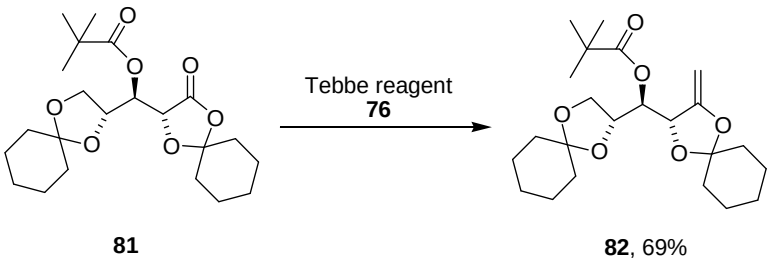
Scheme 26: Synthesis and use of the Tebbe reagent

Despite this wide range of substrates, selectivity can be achieved. As the Shrock carbene **78** is nucleophilic, the reagent reacts preferentially with the most electrophilic group present. For instance ketone **79** was selectively methylenated to give alkene **80** without reaction on the nearby ester group (Scheme 27).[38] This example also highlights the utility of the reaction with base-sensitive substrates as epimerisation was not observed at the α-keto chiral centre.



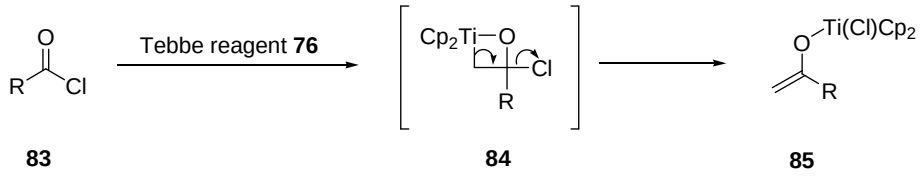
Scheme 27: Tebbe reagent electronic selectivity

While titanium-based methylenating reagents are relatively small and will react with hindered carbonyl groups, the most accessible group will react first. Sinay and co-workers used this to their advantage generating enol ether **82** from lactone **81** which contained a sterically blocked *tert*-butyl ester moiety (Scheme 28).[39]



Scheme 28: Tebbe reagent steric selectivity

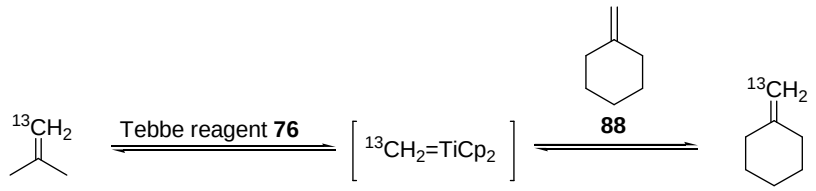
As mentioned previously, the Tebbe reagent **76** will methylenate a wide range of substrates, however there are some limitations. Activated carbonyl groups with a leaving group, e.g. acid chlorides **83**, give titanium enolate products **85**, presumably due to oxatitanacyclobutane intermediate **84** fragmenting in an undesired manner (Scheme 29).[31b, 40]



83 **84** **85**

Scheme 29: Tebbe reaction with acid chlorides

The Tebbe reagent **76** has been shown to catalyse ring closing metathesis, providing evidence that the active species is a titanium alkylidene. Tebbe and co-workers showed that the reagent **76** could facilitate transfer of an isotopically labelled methylene unit from isobutene **86** to alkene **89** under equilibrium conditions (Scheme 30).[41]

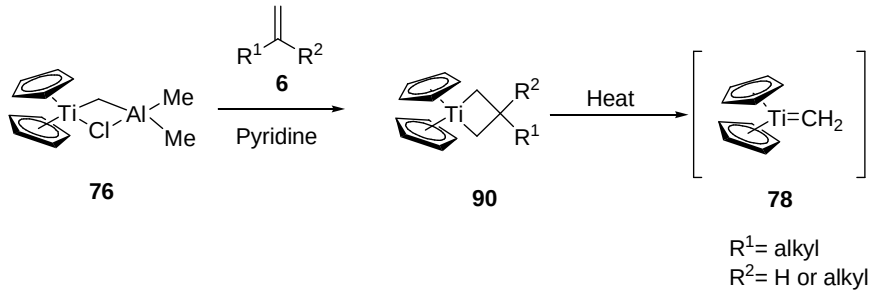


86 **87** **89**

Scheme 30: Metathesis with the Tebbe reagent

1.3.3 Grubbs Reagents

In the early 1980s Grubbs and co-workers reported the synthesis of a series of titanium metallacycles **90** from the reaction of the Tebbe reagent **76** and an alkene **6** (Scheme 31).[42] These metallocycles collapsed under mild heating to generate titanium methylidene **78**. This access to titanium methylidene **78** holds a couple of advantages over Tebbe's method, for example the removal of Lewis acidic aluminium salts allows easier isolation of particularly sensitive products, e.g. enamines. Also, the higher reaction temperature decreases reaction time.

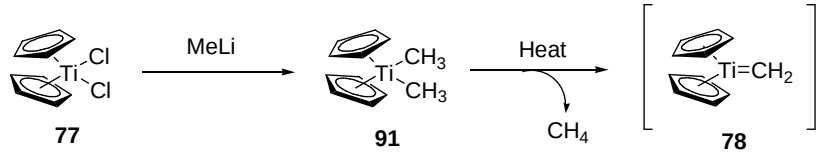


Scheme 31: Generation of titanium metallocycles and titanium methylidene using Grubbs' method.

Due to the number of synthetic steps required to generate it and the advent of the more easily accessible Petasis reagent, Grubbs reagents are not commonly used, despite being effective methylenating agents.

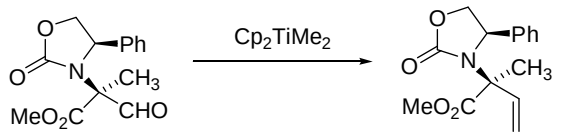
1.3.4 The Petasis Reagent

First reported in 1990 by Petasis and Bzowej, the methylenation of carbonyl compounds with dimethyltitanocene **91** demonstrated a new and simplified method of generating titanium methylidene **78** (Scheme 32).[43] Easily synthesised from the reaction of titanocene dichloride **77** and methyl lithium, dimethyltitanocene **91** is, in contrast to the Tebbe reagent **76**, relatively air and moisture stable and can be stored for more than a month without significant decomposition.[44] Titanium methylidene **78** is generated by gentle heating (60 °C) through an α-elimination process releasing methane. It should be noted that use of other organometallic nucleophiles can generate functionalised Petasis reagents for alkylidenation.[31b] These are limited to groups that cannot undergo β-elimination when bound to titanium and are far less commonly used than the methylenating reagent **91**.



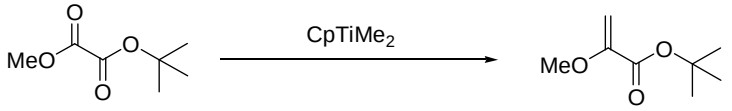
Scheme 32: Synthesis and use of the Petasis reagent

The Petasis reagent shows similar reactivity to the Tebbe reagent, methylenating a variety of carboxylic acid derivatives with electronic and steric selectivity. For example aldehyde **92** was methylenated to give alkene **93** in the presence of a less electrophilic imide moiety (Scheme 33).[45] Also ester **94** gave enol ether **95** (which was too volatile to be isolated) without reaction on the sterically hindered *tert*-butyl ester groups (Scheme 34).[46]



92 **93**, 52%

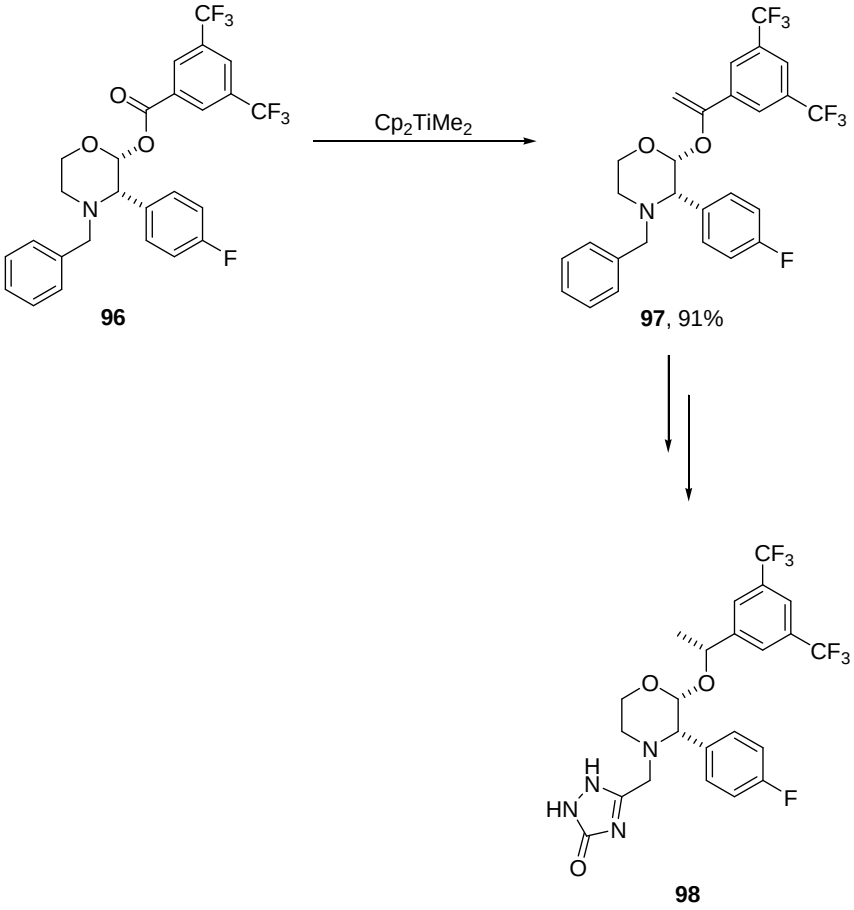
Scheme 33: Petasis reagent electronic selectivity



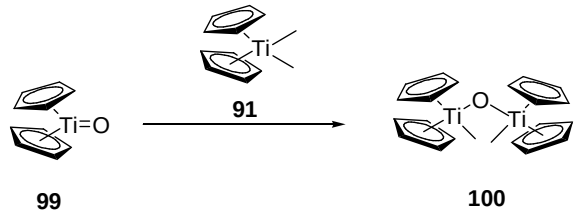
94 **95**
100% Conversion

Scheme 34: Petasis reagent steric selectivity

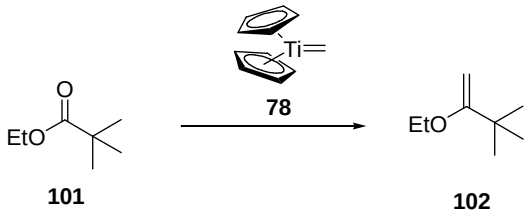
Due to its relative stability and simplicity the Petasis reagent **91** has even been used on an industrial scale. Payack and co-workers describe the large scale methylenation of ester **96** yielding 227 kg of enol ether product **97** as intermediate in the production of Emend™ **98**, an treatment for chemotherapy-induced nausea (Scheme 35).[47] Their research also highlights an important point. The titanium dioxide **99** by-product produced in the methylenation reaction can also react with titanium methylidene **78,** producing dimer **100** (Scheme 36). This side reaction means that two equivalents of the Petasis reagent are required to ensure completion of the reaction. Normally this is not a problem, however Payack and co-workers found that the excess titanium methylidene was also leading to decomposition of the enol ether product **97**. They circumvented this by the addition of a sacrificial ester, ethyl pivalate **101** (Scheme 37). Due to the sterically hindered carbonyl group, ethyl pivalate **101** is less reactive than the starting ester **96**, however it is electronically more reactive than the enol ether alkene **97**. Its addition therefore prevented reaction on enol ether **97** without affecting the desired methylenation reaction.



Scheme 35: Industrial scale use of the Petasis reagent in the production of Emend™

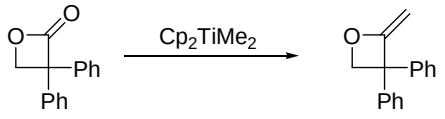


Scheme 36: Reaction of titanium methylidene with titanium oxide



Scheme 37: Reaction of titanium methylidene with ethyl pivalate

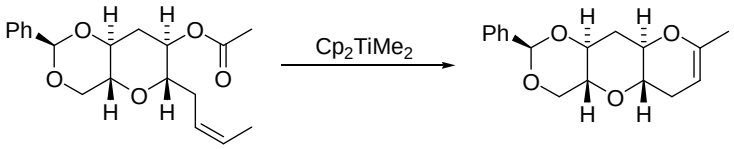
Due to the lack of strong Lewis acids the substrate scope for the Petasis reagent **91** is even greater than that of the Tebbe reagent **76**. For instance labile β-lactone **103** was methylenated cleanly giving enol ether **104** using dimethyltitanocene **91** whereas use of the Tebbe reagent **76** led to decomposition (Scheme 38).[48] Imides and anhydrides are also converted into substituted alkenes, however acid chlorides give titanium enolates in the same way as the Tebbe reagent **76**.



103 **104**, 51%

Scheme 38: Methylenation of Lewis acid-sensitive substrates with the Petasis reagent

The Petasis reagent **91** has also been shown to catalyse alkene methathesis. Nicolau and co-workers exploited this using dimethyltitanocene to convert ester **105** into the cyclic enol ether **106** in a one-pot methylenation / ring closing metathesis reaction (Scheme 39).[49] As with the Tebbe reagent **76**, the ability to induce metathesis demonstrates that a titanium methylidene **78** is the active species in the Petasis methylenation reaction.



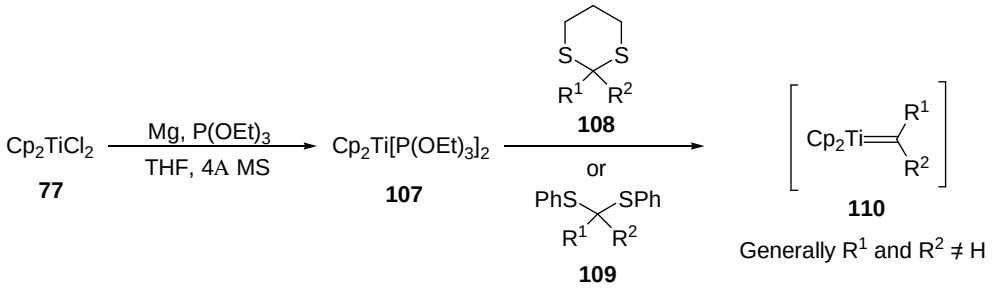
105 **106**, 60%

Scheme 39: Metathesis with the Petasis reagent

Due to the broad substrate scope and relative ease of preparation and use, the Petasis reagent is probably the most useful and commonly used titanium-based methylenating reagent.

1.3.5 Takeda Reagent

In 1997 Takeda and co-workers described new access to a titanium alkylidene active species.[50] They showed that titanium(II) complex **107**, formed from the reduction of titanocene dichloride **77** in the presence of triethylphosphite, reacts with 1,3-dithianes **108** or diphenyldithioacetals **109** to give the proposed carbenoid alkylidenating agents **110** (Scheme 40).



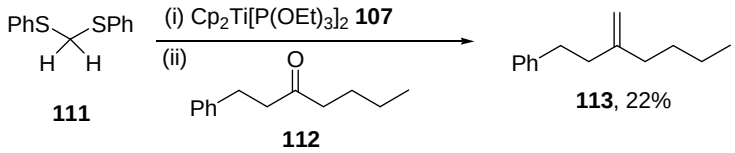
77 **107** **108** **109** **110**

Generally R^1 and $R^2 \neq H$

Scheme 40: Titanium carbenoid generation from thioacetals

The reaction is very useful, reacting with a range of carbonyls and carboxylic acid derivatives and converting a range of thioacetals into alkenes, including those with β-

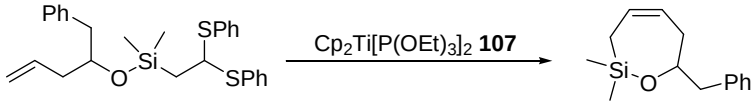
hydrogens. However it is not very effective for methylenation, with Takeda only reporting one low yielding example in his original paper (Scheme 41).[50]



111 **112** **113**, 22%

Scheme 41: Methylenation using the Takeda reagent

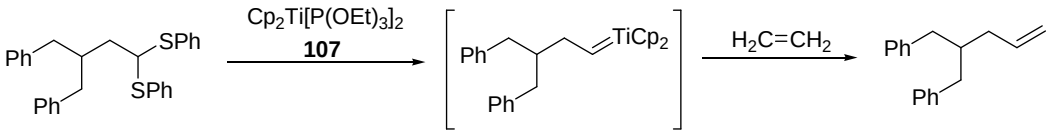
Takeda and co-workers have also shown that the reagent can induce ring closing metathesis, thus confirming the active species are titanium alkylidenes (Scheme 42).[51] Silyl tethered alkene dithioacetal **114** gave cyclic alkene **115** upon treatment with the Takeda reagent **107**. This strategy was used for the synthesis of *Z*-alkene diols.



114 **115**, 80%

Scheme 42: Ring closing metathesis

Taking inspiration from the successful metathesis reaction, Takeda and co-workers have reported a methylenation of sorts (Scheme 43).[52] By generating a titanium alkylidene **117** under an ethene atmosphere terminal alkene **118** was generated from the resulting cross metathesis reaction. This reaction is of limited utility however as aldehydes-derived dithioacetals, such as compound **116**, are the only demonstrated substrates.



116 **117** **118**, 65%

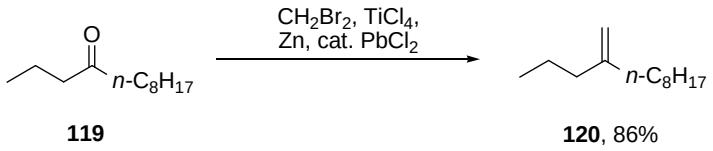
Scheme 43: Metathesis strategy for methylenation

In general, while the Takeda reagent is extremely useful for alkylidenation of a range of carbonyl groups, it is inferior to both the Petasis and Tebbe reagents in the field of methylenation.

1.3.6 Takai Reagents

Takai and co-workers have published two complementary methods for the methylenation (and alkylidenation) of carbonyl groups. Firstly, in 1978 they reported

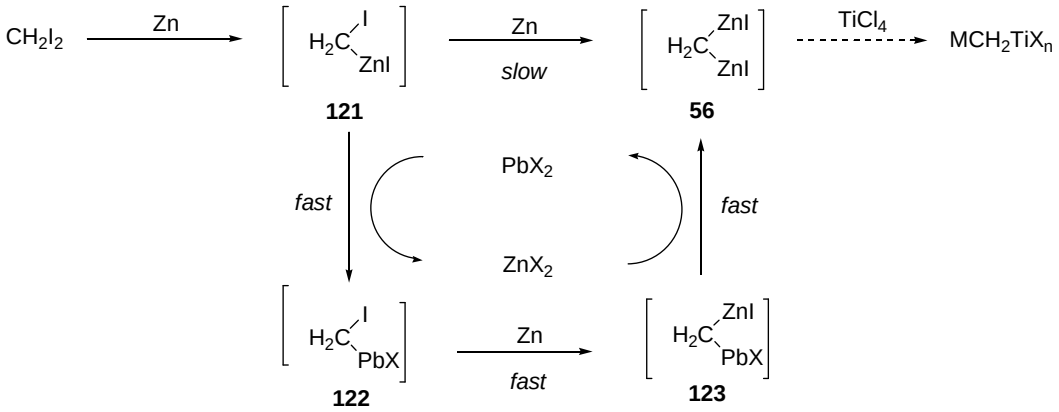
the methylenation of aldehydes and ketones using zinc, titanium tetrachloride and dibromo or diiodomethane.[53] Using this procedure ketone **119** was methylenated giving alkene **120** in high yield (Scheme 44).[54]



119 **120**, 86%

Scheme 44: Methylenation of a ketone using Takai's protocol

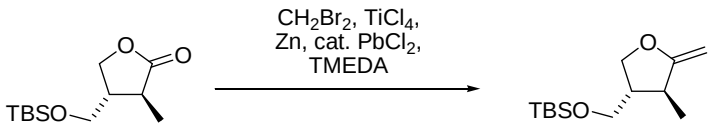
Although initially not included in the reaction mixture, Takai and co-workers found that the addition of a catalytic amount of lead was crucial to reaction success, the proposed rationale for this is shown in Scheme 45.[54] It is thought that zinc insertion into diiodomethane to give organozinc **121** is rapid, but the subsequent insertion to give bis(iodozincio)methane **56** (which is known to be formed on the basis of ^{1}H NMR evidence) is slow. The addition of lead allows a fast transmetallation of organozinc **121** to give organolead intermediate **122**. The more covalent nature of the carbon-lead bond is proposed to facilitate subsequent reduction by zinc to give intermediate **123**. A final fast trasmetallation gives bis(iodozincio)methane **56**. Takai and co-workers postulate that this may react with titanium tetrachloride to give a titanium reagent, possibly a carbenoid. However, it has been demonstrated that bis(iodozincio)methane **56** can carry out the methylenation of aldehydes without the need for titanium tetrachloride. In short, the identity of the active species is unclear, but it is likely a 1,1-bimetallic complex of zinc and/or titanium as metathesis has not been observed. Also, except in very rare activated cases, the reagent will not methylenate carboxylic acid derivatives.[55]



Scheme 45: Proposed mechanism of the Takai methylenation of aldehydes and ketones showing the catalytic effect of lead

A slight modification of these conditions has allowed Takai and co-workers to expand the substrate scope of the reaction to include carboxylic acid derivatives and allow

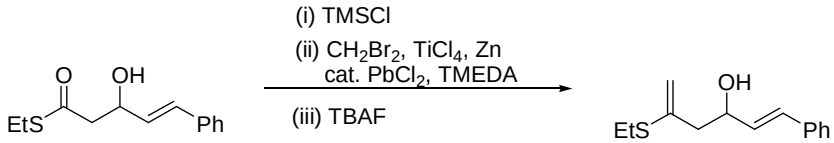
alkylidenation as well as methylenation.[54] A low valent titanium species, prepared by reducing a mixture of complexes prepared from titanium tetrachloride and TMEDA using zinc, was used to generate alkylidenating reagents from a range of 1,1-dibromoalkanes, including those with β-hydrogen atoms. These conditions allowed the alkylidenation of esters to give enol ethers. Originally Takai and co-workers reported that the reaction was low yielding for methylenation, however there are many subsequent reports of successful methylenation using this procedure. For instance Pettus and co-workers describe the methylenation of γ-lactone **124** to give enol ether **125** in good yield, without loss of the silyl protecting group (Scheme 46).[56]



124 **125**, 81%

Scheme 46: Ester methylenation using the Takai reagent

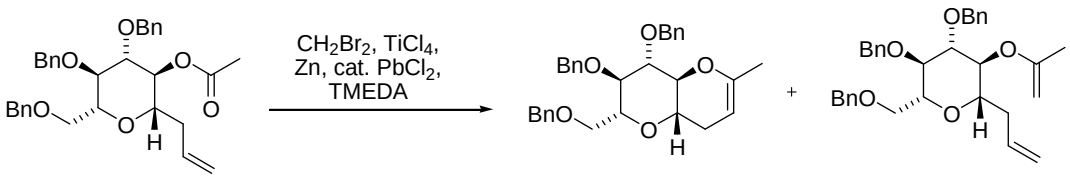
The substrate scope is not limited to carboxylic acid esters, methylenation of thioesters using the Takai reagent has been reported by Woodland *et al*. (Scheme 47).[57] Alkylidenation has also been achieved with other carboxylic acid derivatives, including amides[58] and silyl esters.[59]



126 **127**, 17%

Scheme 47: Thioester methylenation using the Takai reagent

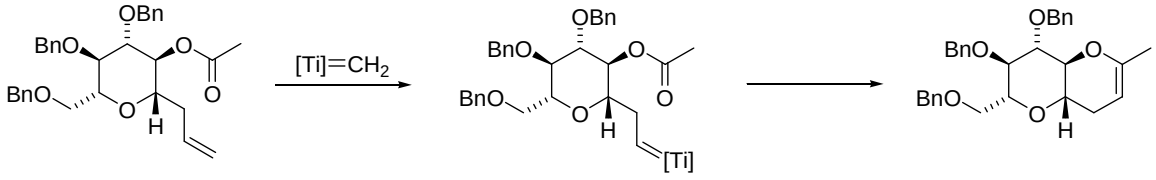
The identity of the active species in Takai ester alkylidenation is also up for debate. Rainier and co-workers have demonstrated that metathesis can be induced using the Takai methylenation conditions (Scheme 48).[60] Allylglycoside **128** gave the cyclic enol ether **129** as the major product, with a significant amount of uncyclized enol ether **130** also isolated. Interestingly, submitting uncyclized enol ether to the Takai conditions did not induce cyclization.



128 **129**, 50% **130**, 30%

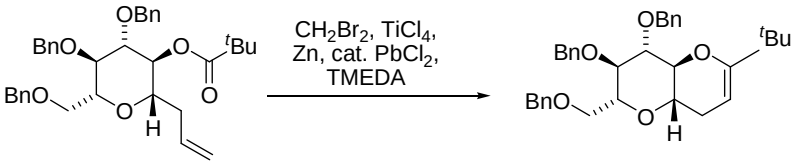
Scheme 48: Metathesis under Takai methylenation conditions

Rainier and co-workers propose that, instead of following the expected carbonyl methylenation followed by alkene metathesis pathway, a methathesis reaction occurs between the alkene **128** and postulated titanium methylidene active species **131** (Scheme 49).[61] This species **131** then undergoes an internal alkylidenation reaction to give the cyclized product **129**. The mixture of products obtained implies close competition between the methylenation and metathesis pathways. Lending credence to their mechanism, Rainier and co-workers observed that slowing down the methylenation process with the use of a butyrate derived ester **132** led to formation of the cyclic product **133** exclusively (Scheme 50).



128 **131** **129**

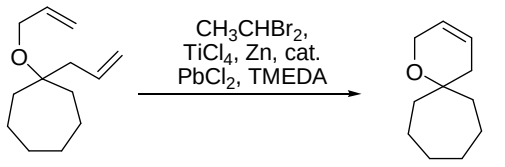
Scheme 49: Proposed internal alkylidenation mechanism of cyclic enol ether formation under Takai methylenation conditions



132 **133**, 70%

Scheme 50: Ester steric hinderance promotes cyclic product formation

Interestingly Rainier and co-workers later found that use of 1,1-dibromoethane instead of dibromomethane led to exclusive formation of the cyclized product **129**.[62] The reason for this better selectivity is not clear, though it is possibly again due to steric interactions and the use of the larger ethylidene nucleophile. Significantly, the reagent generated from 1,1-dibromoethane can induce alkene metathesis (Scheme 51), with alkene **134** being converted to spirocycle **135** in quantitative yield. The cumulative results imply that the active species are indeed titanium alkylidenes rather than 1,1-bimetallics.

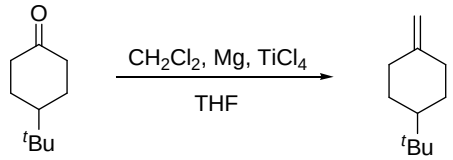


134 **135**, 100%

Scheme 51: Metathesis under Takai conditions

1.3.7 Yan Methylenation

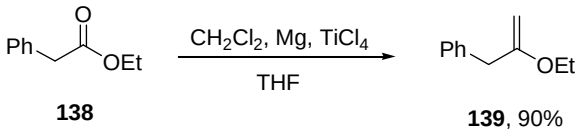
Recently Yan and co-workers have reported a simple 1,1-bimetallic-based protocol for the methylenation of aldehydes, ketones and esters.[63] Using dichloromethane as the methylene source, ketone **136** was methylenated to give alkene **137** in the presence of magnesium and titanium tetrachloride (Scheme 52). It was found that a Lewis base was necessary to induce methylenation and THF was found to be optimal following a short screening process.



136 **137**, 81%

Scheme 52: Ketone methylenation using Yan's protocol

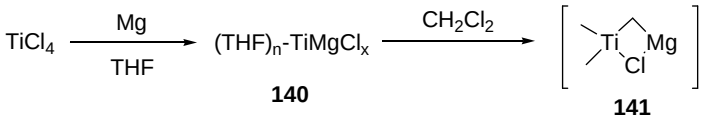
Interestingly for a 1,1-bimetallic reagent, Yan's protocol is also effective for ester methylenation. Using the same procedure with a slightly extended reaction time ester **138** gave enol ether **139**. Amides are also substrates for the reaction, however Yan and co-workers found that the resulting enamines were not isolable, instead isolating methyl ketones.[64]



138 **139**, 90%

Scheme 53: Ester methylenation using Yan's protocol

Bimetallic species **141** is proposed be the active species, thought to be generated from the insertion of the titanium-magnesium complex **140** into dichloromethane (Scheme 54).[63a]



140 **141**

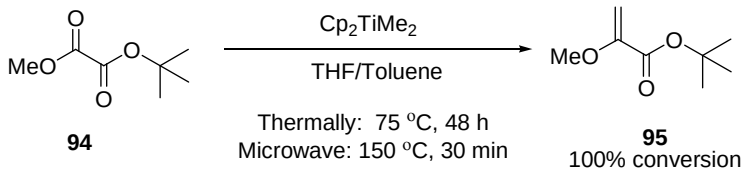
Scheme 54: Proposed active species in Yan's protocol

While there are a large number of titanium based methylenation procedures, reacting with a range of different carbonyl substrates there is no perfect method. Although they cover a broad substrate scope the more established reagents suffer from complex reaction mixtures or the requirement for the preparation of reagents before use. In this sense Yan's methylenation represents a step forward, as it is a simple one step procedure for the methylenation of carboxylic acid derivatives as well as aldehydes and ketones. However, outside of Yan's group it has been primarily used only for the methylenation of aldehydes and ketones.

2.0 Microwave Assisted Organic Synthesis

First introduced in the mid 1980s the use of microwave irradiation in organic synthesis was initially slow to catch on.[65] Early experiments were carried out using conventional kitchen appliances and suffered from a lack of control and reproducibility.[66] The relatively recent development and availability of dedicated microwave equipment for organic synthesis has led to microwave assisted organic synthesis (MAOS) becoming common place in both industry and academia. It is particularly attractive due to its ability to drastically reduce reaction times (from hours to minutes, or even seconds) and potential for automation.

For example, in the previously mentioned (see Section 1.3.4) methylenation of ester **94** to give enol ether **95** with the Petasis reagent, Gallagher and co-workers observed that use of MAOS was very advantageous.[46] It allowed them to heat the reaction mixture to 150 °C (compared with a maximum of 75 °C thermally) and resulted in a shortened reaction time of just 30 min without loss of conversion or selectivity. The Hartley group has also found the use of a microwave accelerated Petasis methylenation reaction useful in their synthesis of piperidinones (see Section 3.1.7).



Scheme 55: Comparison of thermal and microwave heating in the Petasis methylenation

The dramatic reduction in reaction time when compared to conventional heating is thought to be due to the differing mechanisms of heat transfer between the two methods. Conventional heating uses a heating mantle or hot plate and the energy is transferred to the reaction vessel *via* thermal conduction, commonly through a silicon oil medium.[67] There are several disadvantages to this, firstly heating only occurs at the sides of the reaction flask and takes time to equilibrate across the reaction mixture. There are also difficulties in controlling and monitoring the temperature as measurement often takes place in the conduction medium rather than reaction mixture. Conversely the use of microwave irradiation allows the reaction mixture to be heated uniformly and directly. As a result, heating is far faster and can be accurately controlled.

Electromagnetic radiation in the frequency range 0.3 to 300 GHz is defined as microwave radiation.[66] However all heating microwave units only emit microwaves at a

frequency of 2.45 GHz to avoid interference with telecommunications equipment. Microwaves can be used to induce heating in material through dielectric heating. When a substance is irradiated with microwaves, any molecules with dipole moments orientate to align with the resultant electromagnetic field. In a microwave heating system the microwave irradiation source oscillates and molecules move in an attempt to realign themselves. The overall effect is the conversion of microwave energy into heat energy through molecular friction and other processes. As this process depends on the existence of ionic interactions, the ability of solvents to absorb microwave radiation varies greatly. It is measured by a ratio of the medium's dielectric constant (ε') and its dielectric loss (ε"), the latter of which is a measure of how well a substance converts electromagnetic radiation into heat. This ratio is defined as the loss factor ($\tan\delta = \varepsilon''/\varepsilon'$). The loss factors of a number of common organic solvents are summarised in Table 1.[66]

Solvent	**tanδ**
DMSO	0.825
Methanol	0.659
Water	0.123
Acetonitrile	0.062
THF	0.047
DCM	0.042
Toluene	0.040
Hexane	0.020

Table 1: Loss factors of common solvents

As the table demonstrates, more polar solvents tend to be more efficient reaction media for MAOS. Non-polar solvents such as benzene are sometimes termed, "microwave transparent," as their absorption is so low, however most reaction mixtures contain enough polarity that the bulk dielectric constant is large enough to facilitate successful heating.

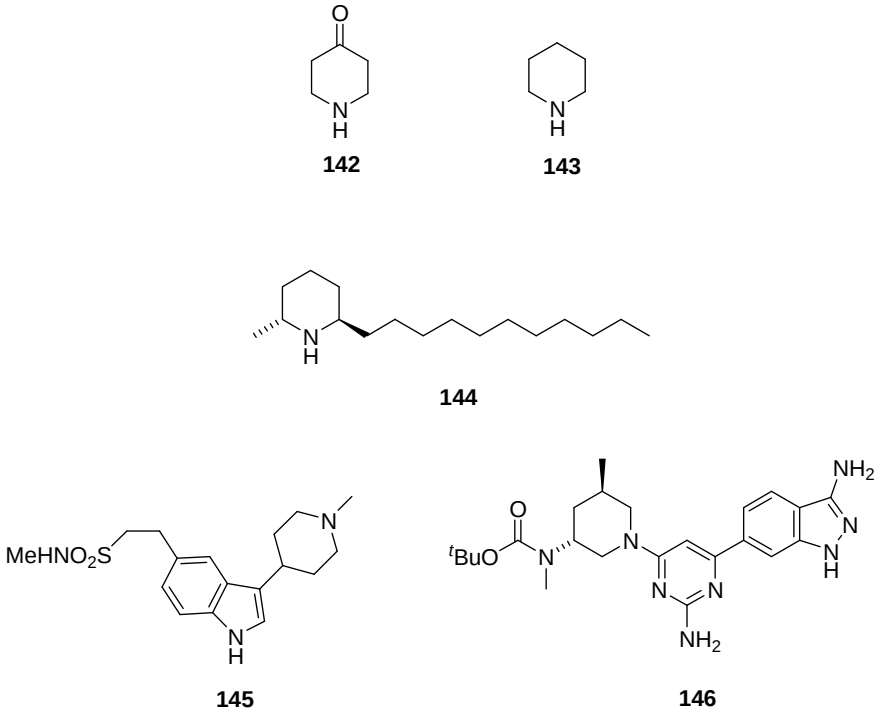
The drastically reduced reaction times observed during MAOS have led some to postulate that the observed increase in reaction rates is not solely due to thermal factors and the applied electromagnetic field elicits a genuine microwave effect.[68] They hypothesise that the ability of the electromagnetic field to affect the orientation of the molecules in the reaction medium could have an effect on the pre-exponential factor (A) in the Arrhenius equation [$K = A \exp(-E_a/RT)$] and thus affect reaction rate. It is also theorised that highly polar transition states could interact strongly with and therefore be stabilised by microwaves, which would lower reaction activation energy

(E_a). Others suggest that there is no microwave effect and the decreased reaction rates are purely the result of thermal and kinetic effects, for instance the very efficient heating of reaction mixtures and ability to reach temperatures far in excess of the solvent boiling point.[69] It has also been proposed that polar substrates could experience enhanced heating and result in local hotspots that could increase reaction rate. The debate rages on, but whether non-thermal microwave effects exist or not, the utility of MAOS cannot be denied.

Its advantages in heating efficiency, heating control, and reaction speed have taken MAOS from being a synthetic last resort to its current status as a genuine alternative to conventional heating methods. This coupled with its amenability to automation is the reason a microwave has become a common sight in organic research laboratories in both academia and industry.

3.0 Piperidines and Piperidinones

Piperidinones **142** and their parent structure piperidines **143** (Figure 5) are considered privileged structures within the drug discovery industry.[70] The piperidine scaffold is found in an enormous number of unrelated natural products, for example solenospin A **144**, a constituent of fire ant venom.[71] Watson and co-workers have noted that more than 12,000 distinct entries described in clinical or pre-clinical studies between 1988 and 1998 contain the piperidine moiety.[72] It is therefore not surprising that the structure is present in many molecules with biological activity including Naratriptan **145**, a compound used in the treatment of Alzheimer's disease and piperidine **146**, a compound with potential anticancer activity.[73]



142 **143** **144** **145** **146**

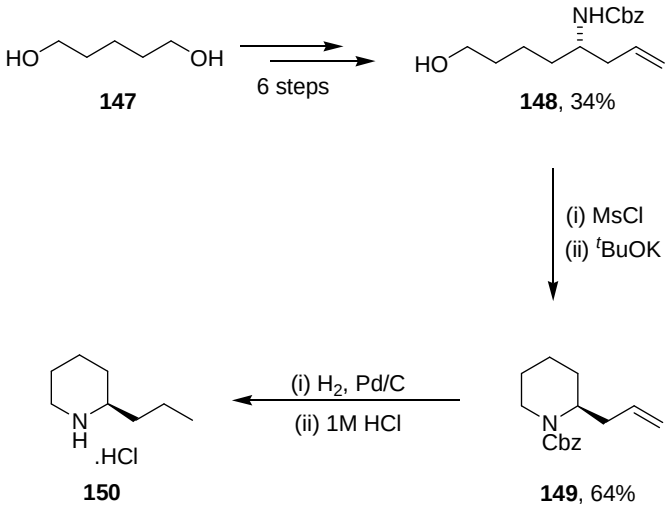
Figure 5: Piperidines and their uses

3.1 Piperidine Synthesis

As might be expected, there has been a significant amount of research carried out into the synthesis of piperidines. This work has been extensively reviewed recently by Weintraub *et al.*,[74] Buffat,[70] Cossy,[75] Källström and Leino,[76] and Girling *et al.*[77] Due to huge volume of research in this area, only selected methods of piperidine synthesis are discussed here to give an idea of the broad range of approaches.

3.1.1 Intramolecular Nucleophilic Substitution

One of the most recent examples in the literature is the synthesis of (*R*)-coniine **150** (Scheme 56) reported by Damodar *et al*. using an intramolecular nucleophilic substitution strategy to form the piperidine ring.[78] Protected amine **148** was synthesised from diol **147** in 6 steps and could be induced to cyclise under basic conditions to give carbamate **149** after the alcohol had been converted into the mesylate. Simple reduction and salt formation gave the natural product **150** as a single enantiomer.

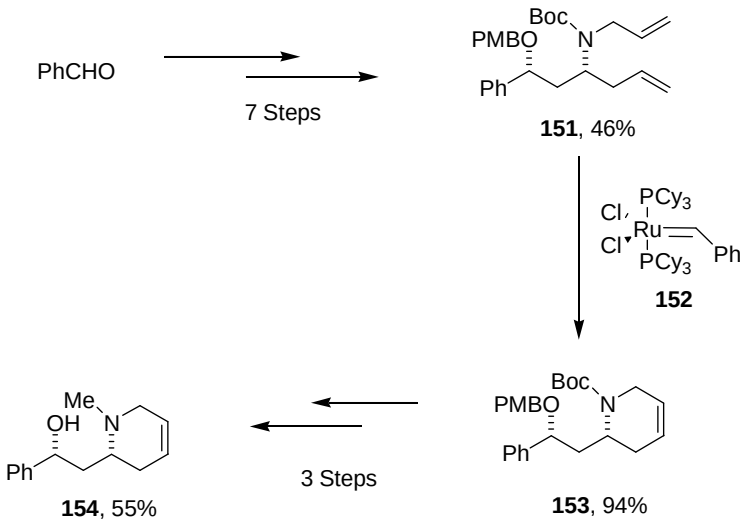


Scheme 56: Synthesis of (*R*)-coniine

3.1.2 Ring Closing Metathesis

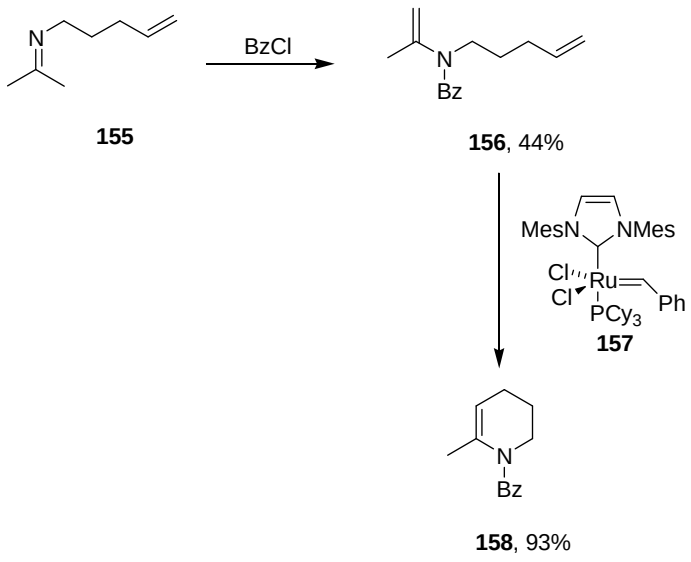
Alkene metathesis has been one of the most important advances in organic chemistry in recent years. It is especially useful in the construction of ring systems, and unsurprisingly research has been carried out to apply it to piperidine synthesis.

Cossy and co-workers used a ring closing methathesis (RCM) strategy in their synthesis of (+)-sedamine **154** (Scheme 57).[79] Synthesised from benzaldehyde in 7 steps, diene substrate **151** was cleanly cyclized to yield alkene **153** in high yield upon exposure to Grubbs 1st generation catalyst **152**. The product of this reaction **153** was then converted to the natural product **154** in 3 more steps.



Scheme 57: Synthesis of (+)-sedamine

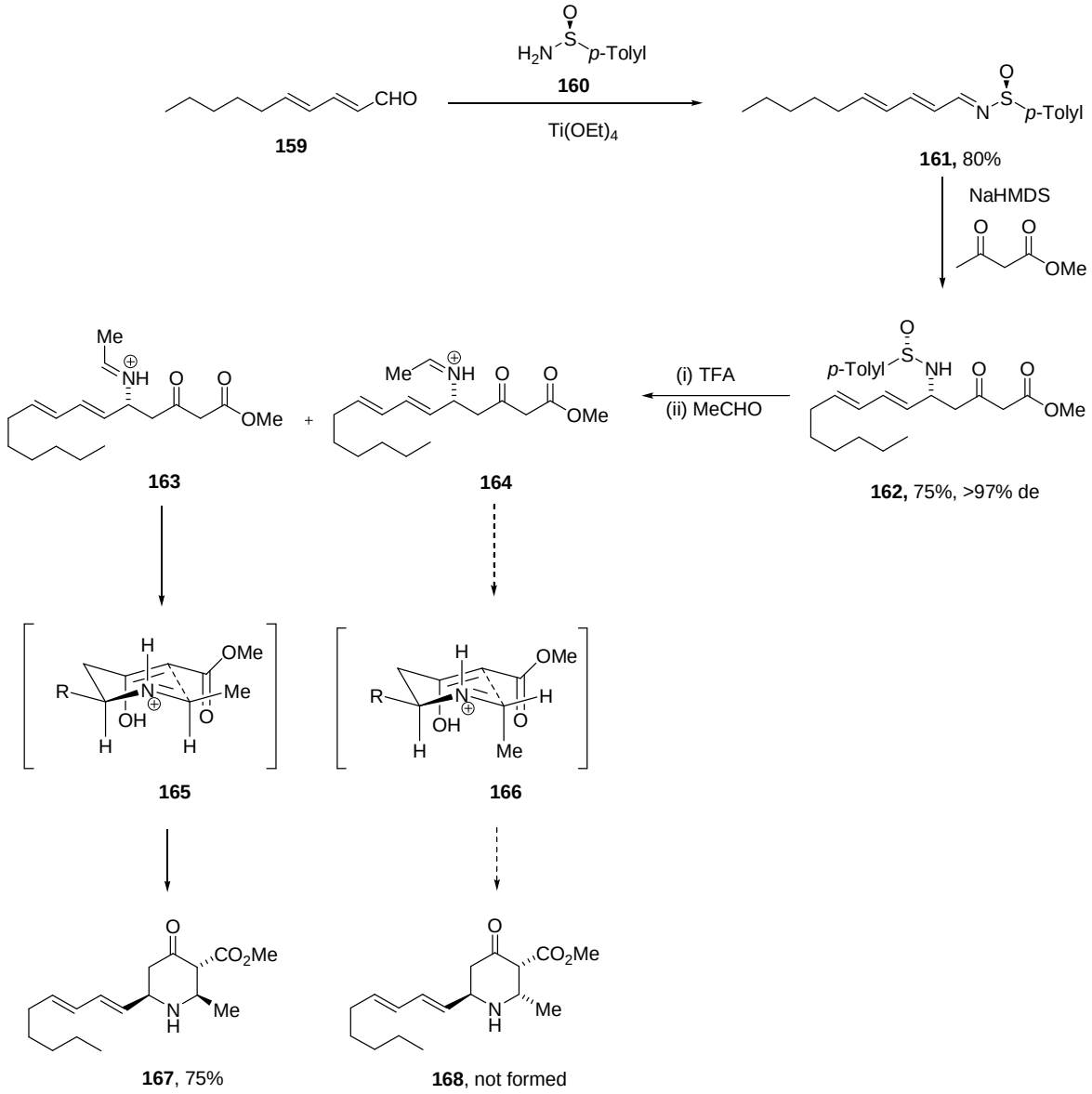
It is relatively simple to generate piperidines with a double bond at the 3,4 or 4,5 positions using RCM, however 2,3 or 5,6 alkenes are more difficult due to the requirement of sensitive enamine / enamide starting materials. Rutjes and co-workers generated enamide **156** from the reaction of the corresponding imine **155** and benzoyl chloride (Scheme 58).[80] Enamide **156** was stable enough to be purified and isolated, but only in low yield. However, cyclization with Grubbs 2nd generation catalyst **157** gave the desired product **158** with the double bond in the 2,3-position in an excellent 93% yield.



Scheme 58: Ring closing metathesis of enamides

3.1.3 Intramolecular Mannich Reaction

Davis and co-workers have developed a route to piperidinones via an intramolecular Mannich reaction (Scheme 59).[81] Beginning from aldehyde **159,** reaction with enantiopure sulfinamide **160** gave sulfinimine **161**. A highly diastereoselective enolate addition gave ester **162**, after which sequential deprotection and reversible iminium salt formation gave a mixture of geometrical isomers **163** and **164**. These are set up to cyclize through a 6-(*enolendo*)-*endo-trig* cyclization via a six-membered transition state. Maintaining the large R-group equatorial gives rise to chair-like transition states **165** and **166**. For the *Z*-iminium species, the transition state **166** is disfavoured due to larger 1,3-diaxial interactions. However, the *E*-iminium species transition state **165** has all large groups equatorial in its lowest energy conformation and thus leads to the formation of 2,6-syn-piperidinone **167** as the only isolated product due to the reversibility of the iminium forming steps.



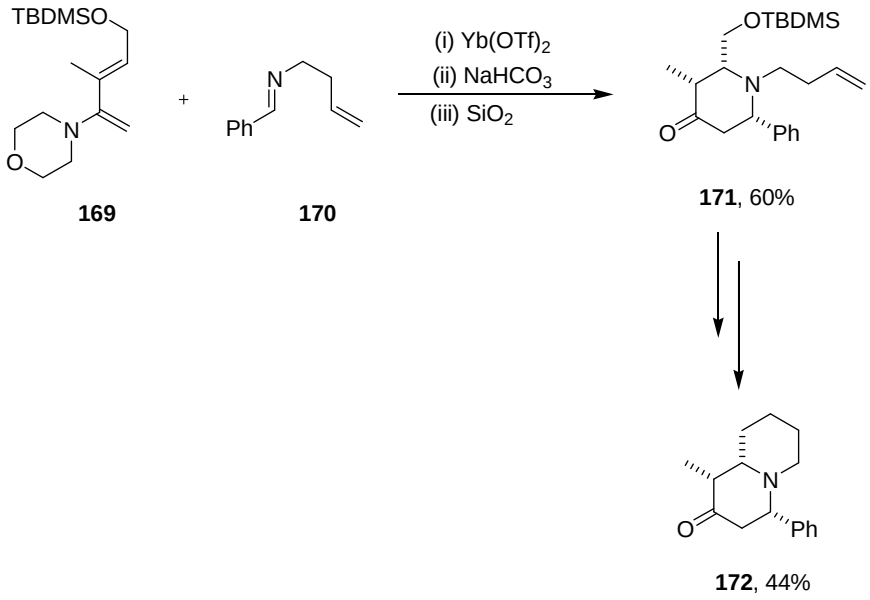
Scheme 59: Piperidinone synthesis using an intramolecular Mannich reaction

3.1.4 Aza-Diels-Alder Reaction

The Diels-Alder reaction is a powerful synthetic tool in organic chemistry allowing the synthesis of cyclohexene derivatives with good regio-, diastereo- and enantioselectivity depending on the conditions used. The analogous reaction where one of the components is an imine, the Aza-Diels-Alder reaction, is therefore an excellent method of piperidine synthesis.

Most commonly Aza-Diels-Alder reactions take place between an electron rich diene and an imine, often requiring Lewis acid catalysis to increase the reaction rate. Barluenga and co-workers used an electron-rich enamine diene **169** in combination with imine **170** in the presence of ytterbium triflate to generate 2,3,6-*syn* piperidinone **171** as a single diastereomer following flash chromatography that completely hydrolysed the

intermediate enamine (Scheme 60).[82] Piperidinone derivative **171** was subsequently used in the synthesis of quinolizidine intermediate **172**, a common structural motif in naturally occurring alkaloids.

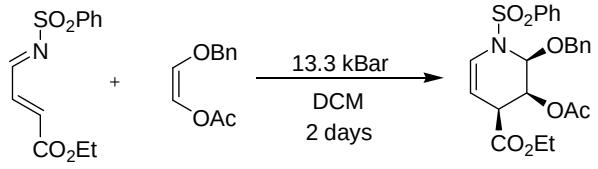


169 **170** **171**, 60%

172, 44%

Scheme 60: Aza-Diels-Alder reaction using a an imine dienophile

The inverse electron demand Diels-Alder reaction between azadienes and electron rich alkenes is less common, primarily due to problems with reaction rate and competing imine addition and/or tautomerism.[70] However, there are examples within the literature, Boger and co-workers described a series of azadiene-alkene cycloadditions and example of which is shown in Scheme 61.[83] Protected α,β-unsaturated imine **173** reacted with very electron rich alkene **174** to give the *endo* product **175** in a 20:1 ratio with its *exo* isomer. As expected the reaction was sluggish, requiring a long reaction time at elevated pressure.



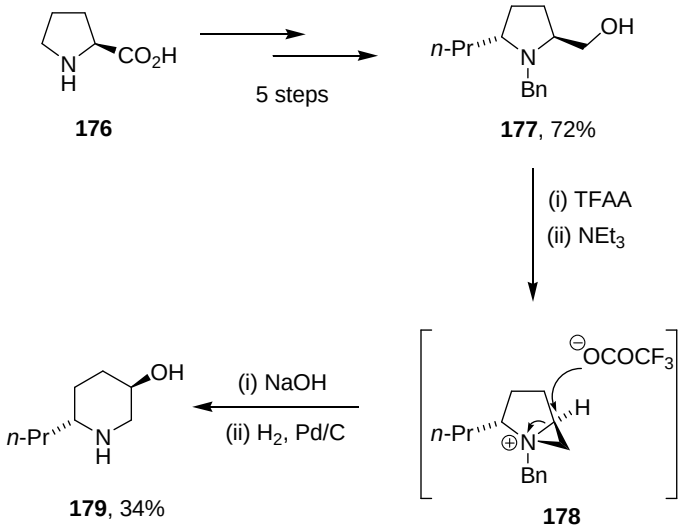
173 **174** **175**, 42%

Scheme 61: Aza-Diels-Alder reaction using an imine diene

3.1.5 Ring Expansion

The synthesis of piperidines is also possible through the ring expansion of small heterocycles. Cossy and co-workers generated protected amino-alcohol **177** from L-proline **176** in 5 steps and induced ring expansion following treatment with trifluoroacetic anhydride (TFAA) (Scheme 62).[84] They suggest that reaction with TFAA

activates alcohol **177** toward nucleophilic displacement and results in the formation of aziridinium species **178**. The addition of triethylamine reveals the trifluoroacetate anion which carries out the ring opening reaction. It is worth noting that the ring opening could also occur at the less hindered electrophilic site to regenerate the initially activated alcohol derived from **177**, presumably the driving force of the ring expansion is the formation of the thermodynamically favoured six membered ring. Addition of sodium hydroxide hydrolyses the trifluoroacetic acid ester and subsequent hydrogenation removes the benzyl group to give (−)-pseudoconhydrine **179**.

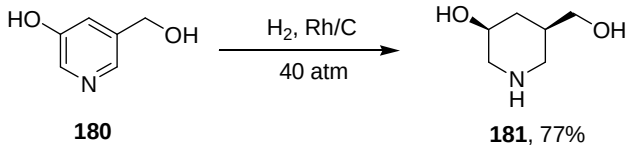


176 **177**, 72% **178** **179**, 34%

Scheme 62: Synthesis of (−)-pseudoconhydrine

3.1.6 Pyridine Reduction

Pyridines are an attractive starting point for the synthesis of piperidines as they are relatively easy to functionalise. Pyridines can be fully reduced by pressure hydrogenation, as shown in the example by Jacobsen and co-workers (Scheme 63) where pyridine derivative **180** gives piperidine **181** as the single *syn* diastereomer.[85] Unfortunately, while *syn* diastereomers are often the major products of these reactions, mixtures are obtained in many cases, limiting the usefulness of this strategy.[70, 73]



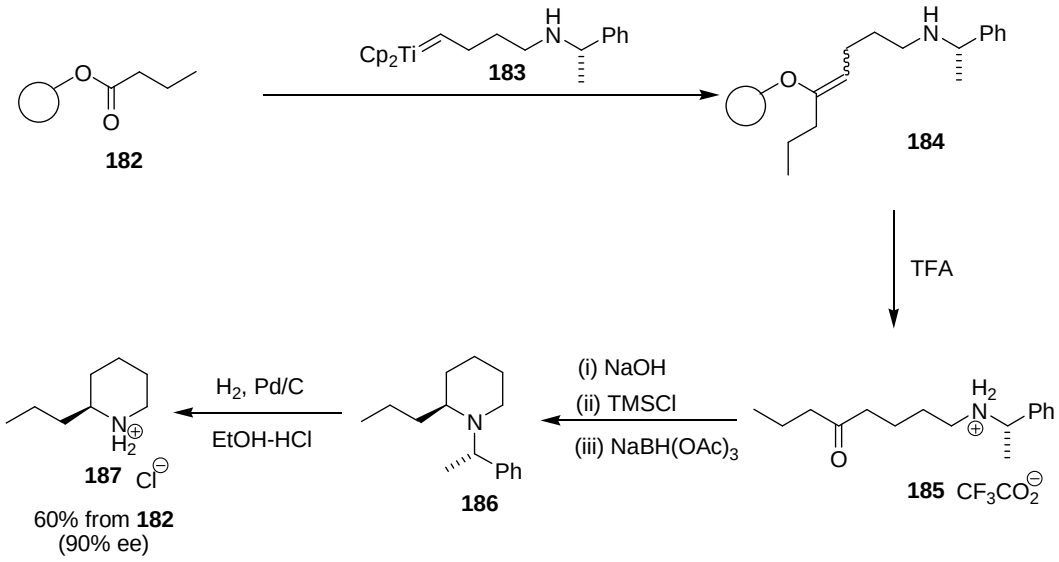
180 **181**, 77%

Scheme 63: Reduction of a pyridine derivative

3.1.7 Synthesis of Piperidines in the Hartley group

The Hartley group have also carried out research in the area of piperidine synthesis, this has resulted in two different strategies, both involving the use of titanium carbenoid chemistry.

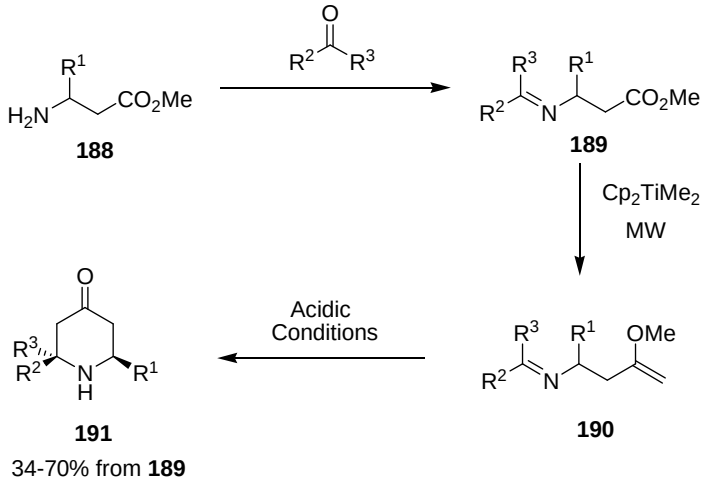
The first utilises a solid phase synthesis approach and has been used to synthesise a variety of piperdine alkaloids, including (*S*)-coniine **187** (Scheme 64).[86] Titanium alkylidene **183** (derived from the corresponding thioacetal) reacts with resin-bound ester **182** forming enol ether **184**. The resin-bound nature of the product allows excess reagents to be easily washed away, after which treatment of enol ether **184** with TFA results in simultaneous cleavage from the resin and formation of the dialkylammonium salt **185**. Neutralisation of the salt **185**, followed by addition of trimethylsilyl chloride to remove water and to provide a counter-ion, results in an iminium salt that undergoes a diastereoselective reduction giving protected piperidine **186**. Hydrogenation in acidic media gave the natural product **187** in high yield and enantiopurity.



Scheme 64: Synthesis of (*S*)-coniine

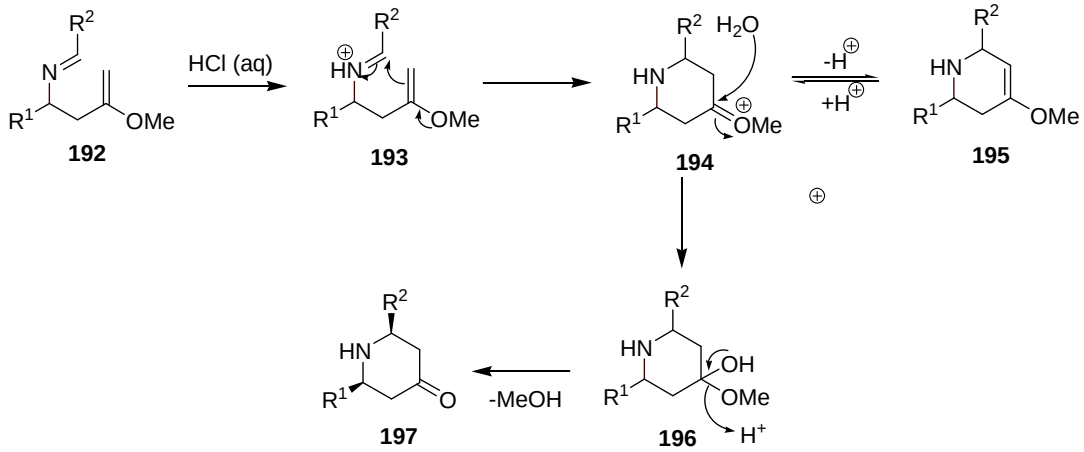
Another approach developed within the Hartley group uses imino esters **189** derived from β-amino acid methyl esters **188** as substrates for the Petasis methylenation reaction to generate imino-enol ethers **190** (Scheme 65).[87] These could be cyclized in Brønsted or Lewis acidic conditions to give 2,6-*syn* piperidinones **191** in moderate to good yield and excellent diastereoselectivity. In general R^2 was a phenyl group, giving a relatively stable imine and thereby preventing loss of yield due to decomposition. Unstabilised imine R^2=ethyl was tolerated, though as expected, gave a lower yield of 34%. Most examples used an aldehyde-derived imine (R^3=H), however one showed a ketone (R^2=Ph, R^3=Me) giving the corresponding 2,2,6-trisubstituted piperidine with a

slight loss of diastereoselectivity thought to be directly related to the *E*/*Z* ratio of the imines formed.



Scheme 65: Synthesis of 2,6-*syn* piperidinones from *β*-amino acid derivatives

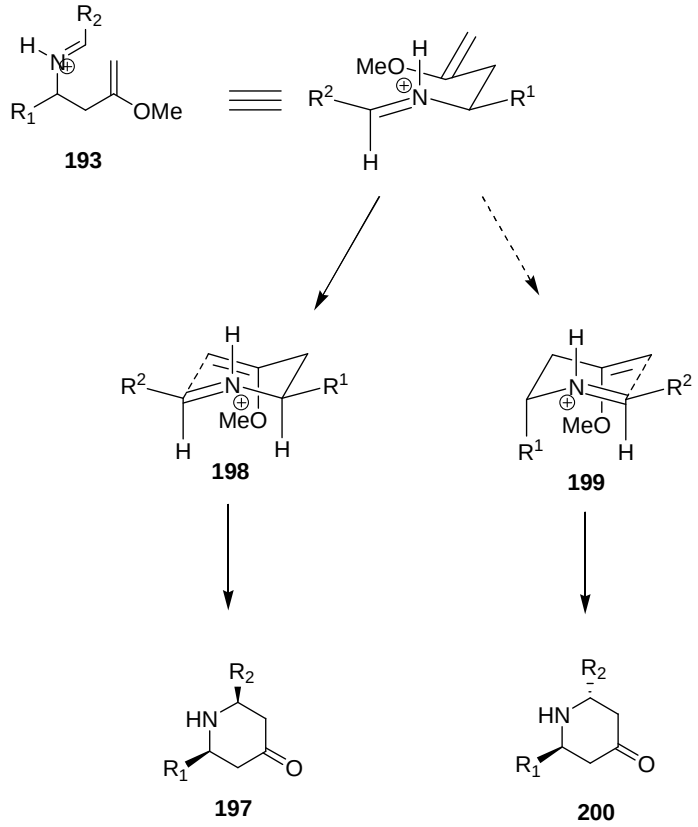
The mechanism of the key piperidinone-forming step is proposed to proceed via a 6-(*enolendo*)-*endo*-*trig* cyclization (Scheme 66). Protonation of imino-enol ether **192** in the Brønsted acidic conditions gives activated iminium ion **193**. Cyclization occurs from the enol ether nucleophile giving oxonium ion intermediate **194** (in equilibrium with its enol ether form **195**), which is subsequently hydrolysed to give the piperidinone product **197**. Under Lewis acidic conditions water is not present, so ketone **197** is not obtained until the reaction is quenched into aqueous acid.



Scheme 66: Proposed cyclization mechanism in Brønsted acid

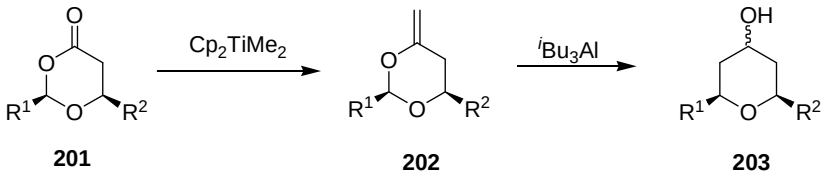
The above mechanism is similar to the one proposed by Davies and co-workers in their synthesis of piperidinones using an intramolecular Mannich reaction (Section 3.1.3). The 2,6-*syn* selectivity is also thought to occur in a analogous way (Scheme 67). The imine forming reaction gives essentially one geometric isomer when one of the substituents is hydrogen, therefore only the *E*-imine need be considered. Iminium species **193** can form

two possible chair-like 6-membered transition states (**198** and **199**), however transition state **199** experiences greater 1,3-trans-diaxial interactions due to the proximity of R^1 and the methoxy group of the enol ether and is thus of higher energy. Therefore transition state **198** gives rise to the major product **197**.



Scheme 67: Proposed rationale for stereocontrol

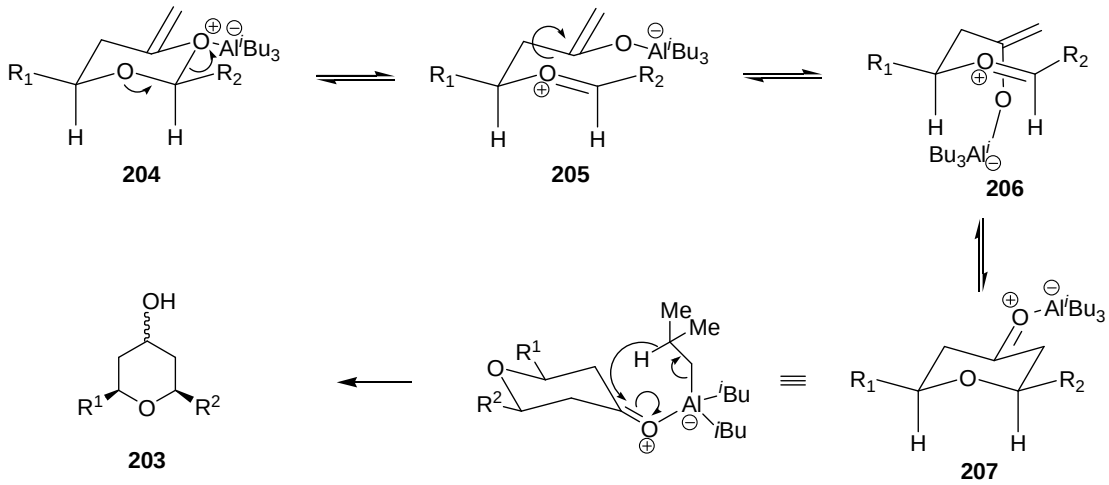
The reaction can also be viewed as a nitrogen-containing analogue of the Petasis-Ferrier rearrangement that was first observed by Ferrier while researching carbohydrate chemistry.[88] In general the reaction transforms enol ethers **202** derived from 1,2-dioxan-4-ones **201** into 2,6 *syn*-disubstituted tetrahydorpyranols **203** in Lewis acidic conditions (Scheme 68).



Scheme 68: The Petasis-Ferrier rearrangement

The mechanism proposed by Petasis and Lu first involves Lewis acid coordination of the enol ether oxygen atom **204** which reversibly results in breaking of the ring to give oxonium ion **205** (Scheme 69).[89] A simple rotation around the indicated bond gives the lowest energy transition state **206** which is analogous to transition state **198** in

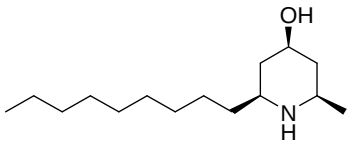
Hartley's synthesis of piperidinones (Scheme 67). The familiar 6-(*enolendo*)-*endo*-*trig* cyclization gives cyclized product **207** which, due to the fact the product is an enolate and not an enol ether, can be reduced by the Lewis acid to generate the tetrahydropyranol product **203**.



Scheme 69: Petasis-Ferrier rearrangement mechanism

3.2 Dendrobate Alkaloid (+)-241D

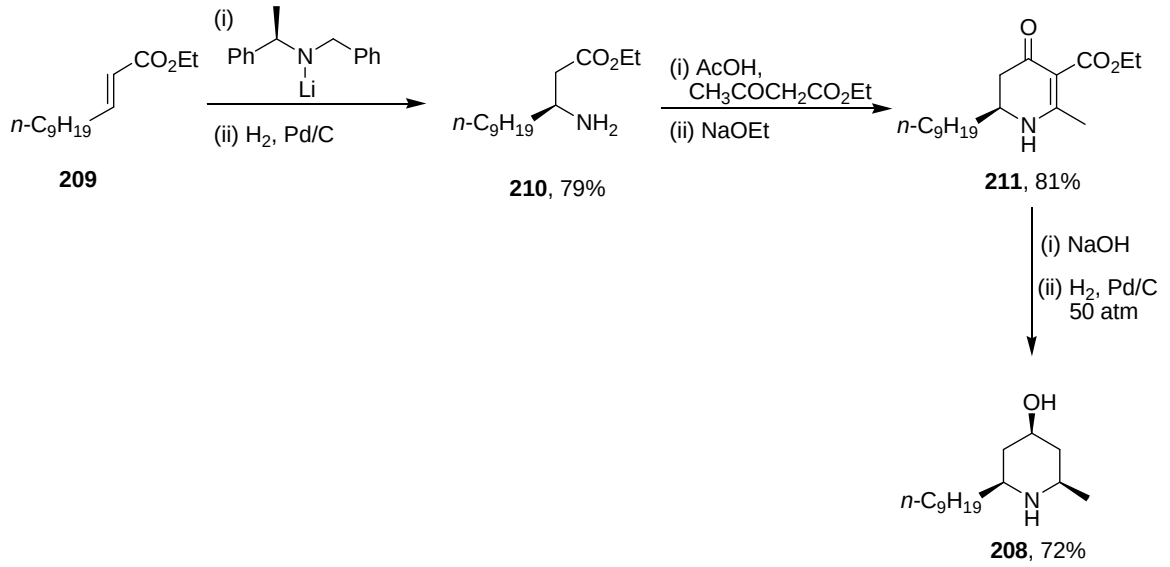
Dendrobate alkaloid (+)-241D **208** (Figure 6) is a piperidine natural product isolated from the methanolic skin extracts of *Dendrobates Speciosus*, a Panamanian species of poison dart frog.[90] As a racemate, the natural product **208** has been shown to block the action of acetylcholine by non-competitive inhibition of the nicotinic receptor.[91] Due to its interesting biological activity and relatively simple structure the synthesis of natural product **208** has been described a number of times in the literature, some of which are reported here.



208

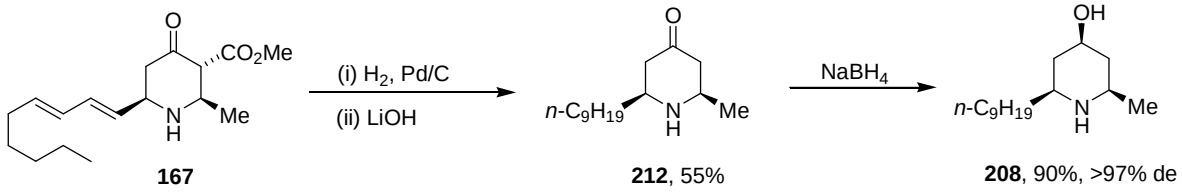
Figure 6: Dendobate alkaloid (+)-241D

One of the most efficient syntheses to date has been published by Sun and Ma (Scheme 70).[92] Beginning from commercially available enone **209** a diastereoselective aza-Michael addition followed by debenzylation gave amine **210** as a single enantiomer. A Claisen condensation in acidic conditions allows reaction at the ester of compound **210**, which cyclizes to form the imine followed by the enamine **211** on addition of base. Hydrolysis of the ester followed by a stereoselective hydrogenation reducing the double bond from the less hindered face gives the alkaloid **208** in an overall 46% yield.



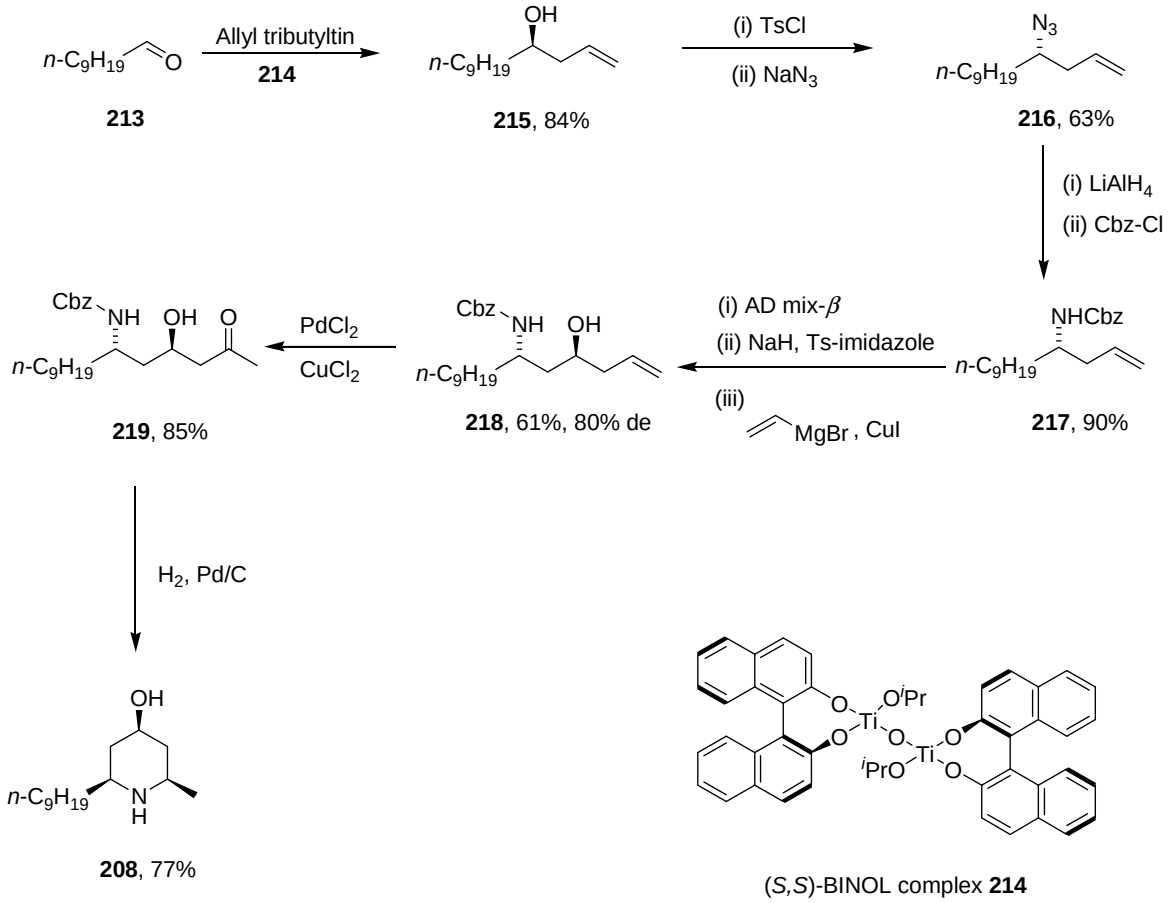
Scheme 70: Synthesis of Dendrobate alkaloid (+)-241D by Sun and Ma

Davis and co-workers have also described a synthesis of Dendrobate alkaloid (+)-241D **208** (Scheme 71).[81] As described in Section 3.1.3 piperidinone **167** was synthesised using an intramolecular Mannich reaction. Hydrogenation and decarboxylation gave piperidinone **212** which could be diastereoselectively reduced by sodium borohydride to give the target compound **208**. Troin and co-workers have also shown that use of bulky L-Selectride® as a reducing agent gives the C-4 epimer.[93]



Scheme 71: Synthesis of Dendrobate alkaloid (+)-241D by Davis and co-workers

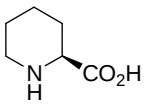
The most recently reported synthesis of alkaloid **208** is that of Rao and co-workers (Scheme 72).[94] Beginning from decanal **213** they carried out an asymmetric Marouka allylation which gave alcohol **215** with high enantioselectivity. Activation of the alcohol and displacement with sodium azide gave compound **216**, which could be reduced and protected to give carbamate **217**. Sharpless dihydroxylation gave a mixture of diastereomers which could be easily separated following by a one-pot epoxide formation and ring opening to give alcohol **218**. From here a Wacker oxidation gave ketone **219**, which is set up for a one-pot deprotection, imine formation and reduction to give the natural product **208**.



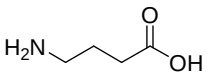
Scheme 72: Synthesis of Dendrobate alkaloid (+)-241D by Rao and co-workers

3.3 Pipecolic Acid

Another interesting piperidine-based natural product is pipecolic acid **220** (Figure 7). Pipecolic acid **220** is a naturally occurring non-proteinogenic amino acid, meaning that it is produced within the body, but not used protein synthesis.[95] Its exact role is unclear, though it has been shown to both initiate release and inhibit re-uptake of γ-aminobutyric acid **221** (GABA) *in vitro*.[96] GABA is the main inhibitory neurotransmitter in the central nervous system and therefore many anxiolytic and sedative drugs target its receptors. The pipecolic acid moiety is found in a number of drugs for instance Rapamycin **222** (Figure 8), originally discovered as a natural product isolated from *Streptomyces hygroscopicus,* but which is now marketed as Sirolimus and used as an immunosuppressive drug for patients receiving an organ transplant.[97] Considering its bioactivity and demonstrable role in drug discovery, it is not surprising that the synthesis of pipecolic acid **220** and its derivatives has been extensively researched.[95, 98] There are many strategies reported in the literature, a selection of which are described here.

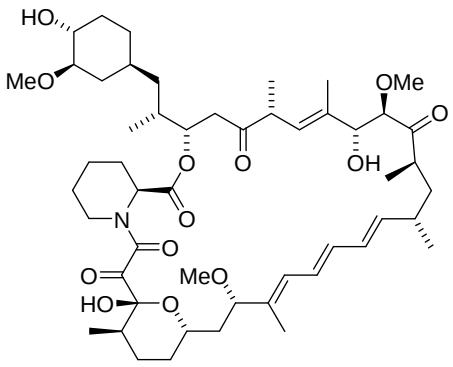


220



221

Figure 7: Pipecolic acid and GABA

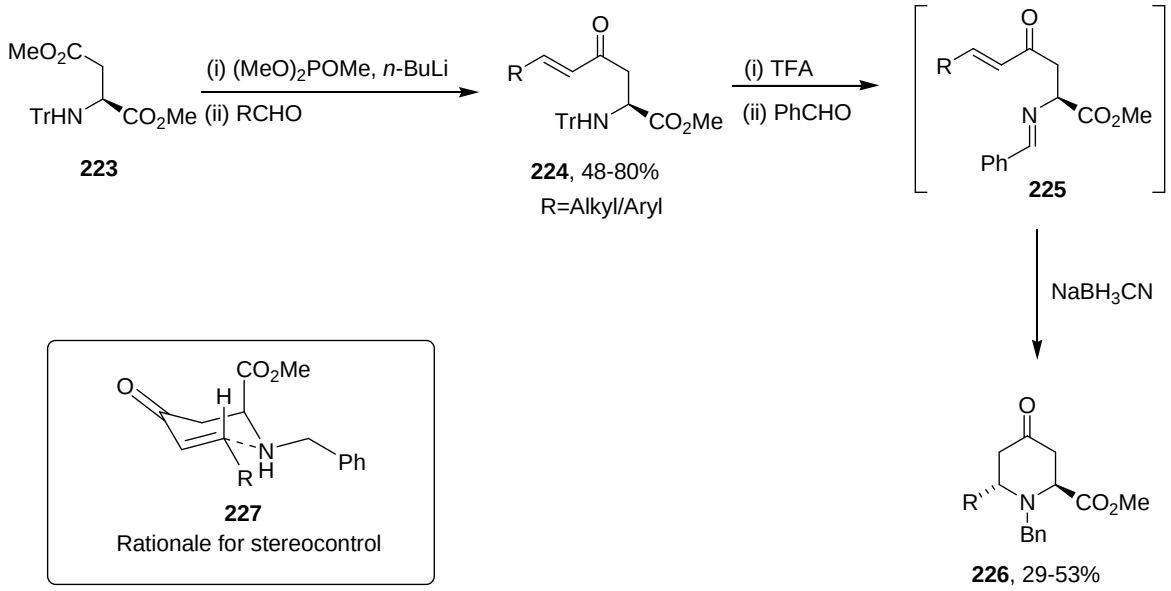


222

Figure 8: Rapamycin

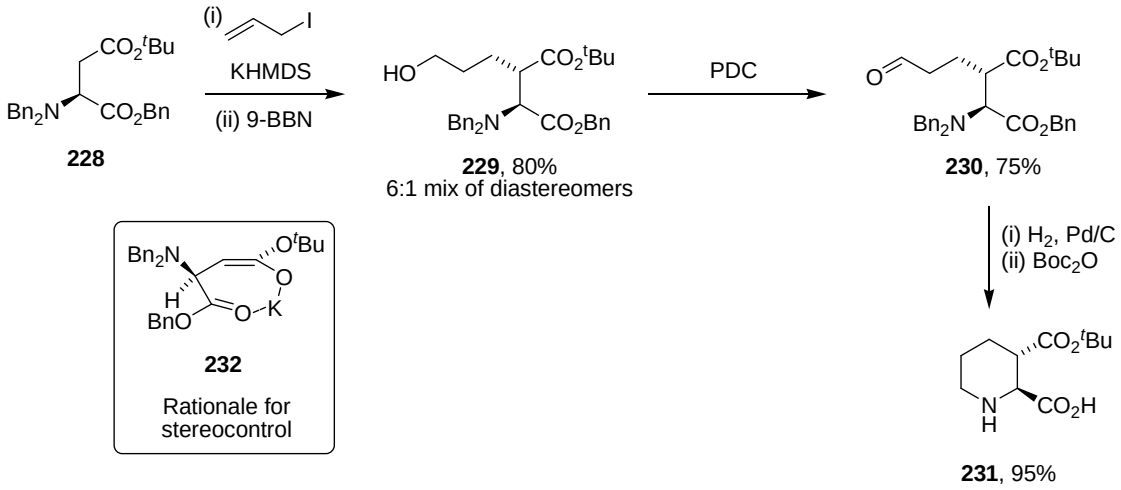
3.3.1 Pipecolic Acid Synthesis from Amino Acids

A very recently reported synthesis in the chemical literature is described by Sutherland and co-workers (Scheme 73).[99] Beginning from protected aspartic acid dertivative **223**, a variety of enones **224** were generated through formation of the phosphonate ester followed by a Horner-Wadsworth-Emmons reaction with a number of aldehydes. Removal of the trityl group follow by reaction with benzaldehyde gave imine **225** which was not isolated, instead reduction revealed the amine nucleophile which induced cyclization *via* an aza-Michael addition reaction to give 2,6-*anti* pipecolic acid esters **226**. No comment on the ratio of the diastereoisomers in the crude reaction mixture was made. The selectivity for the *anti* diastereomer presumably arises due the ester group being held in a *pseudo*-axial position to reduce 1,2 strain. It should be noted that the 1,3 diaxial interactions are relatively small due to the lack of an axial group at the carbonyl position.



Scheme 73: Synthesis of pipecolic acid derivates by Sutherland and co-workers

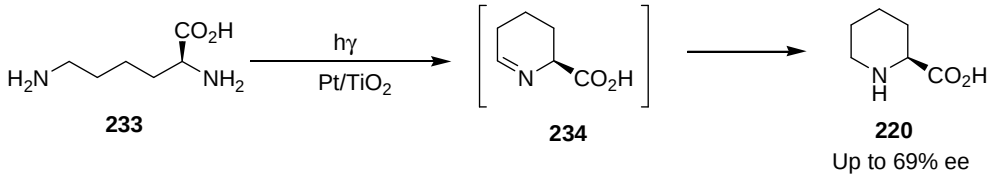
Xue and co-workers reported an earlier example of the synthesis of pipecolic acid derivatives from aspartic acid (Scheme 74).[100] Using an orthogonally protected aspartic acid derivative **228** as a start point, Xue and co-workers carried out a diastereoselective enolate addition reaction. The selectivity is thought to arise from the formation of a planar potassium chelated intermediate **232**, one face of which is blocked by the bulky dibenzyl amine.[101] The reaction gave a 6:1 mixture of diastereoisomers which were separable after the subsequent hydroboration reaction to give alcohol **229**. Oxidation to aldehyde **230** using pyridinium dichromate (PDC) set the system up for a one-pot imine formation and reduction to give the 3-functionalised pipecolic acid derivative **231**.



Scheme 74: Synthesis of pipecolic acid derivates by Xue and co-workers

Probably the simplest synthesis of pipecolic acid **220** in the literature is described by Ohtani and co-workers (Scheme 75).[102] They used a photocatalysed redox process on doped titanium oxide to convert naturally occurring lysine **233** into pipecolic acid **220**.

The variable enantioselectively was thought to be due to the possibility of the initial oxidation occurring at the undesired α-amine, thus scrambling the stereochemical information. By varying the doping agent (Pd, Rh, Pt) the group were able to selectively enhance the desired pathway, although not exclusively.

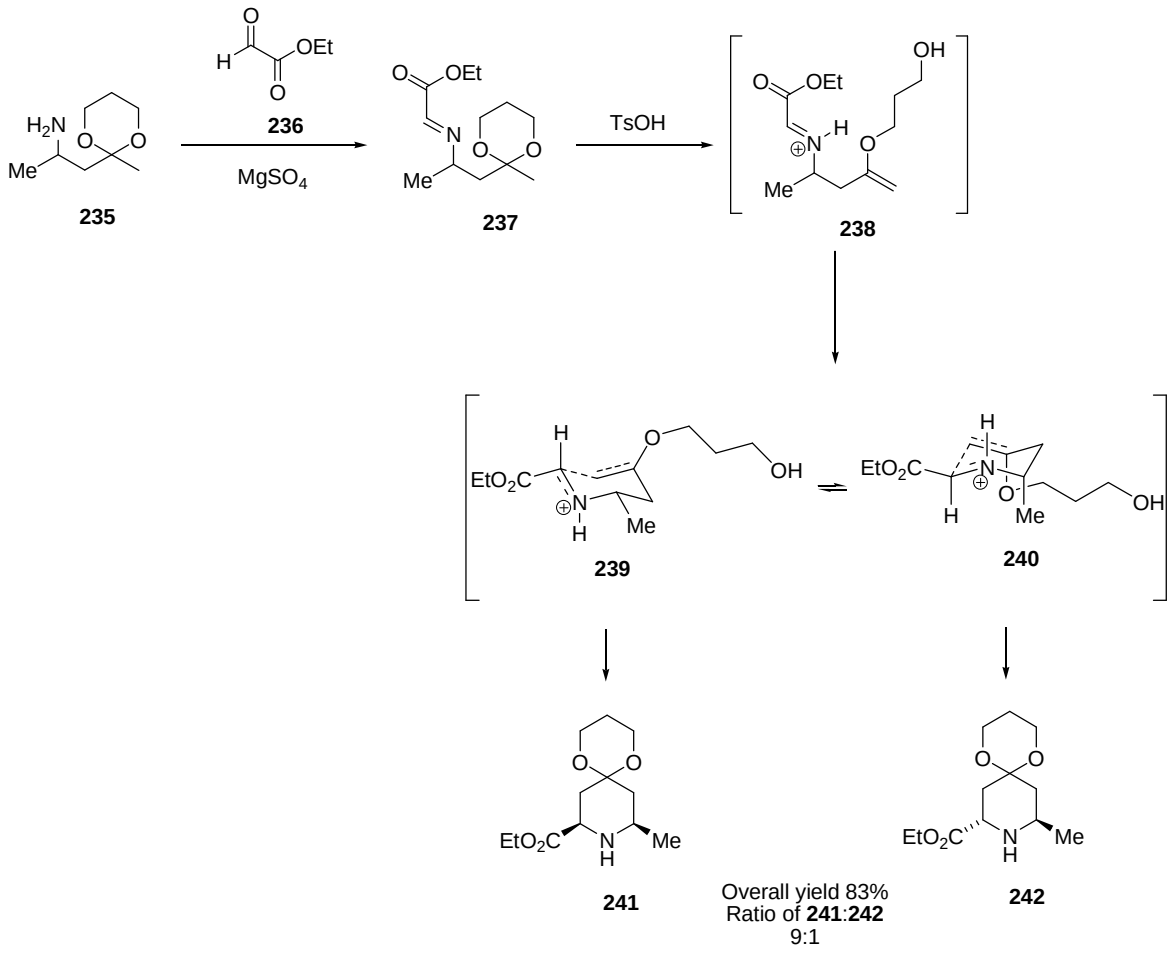


233 **234** **220**

Up to 69% ee

Scheme 75: Catalytic synthesis of pipecolic acid

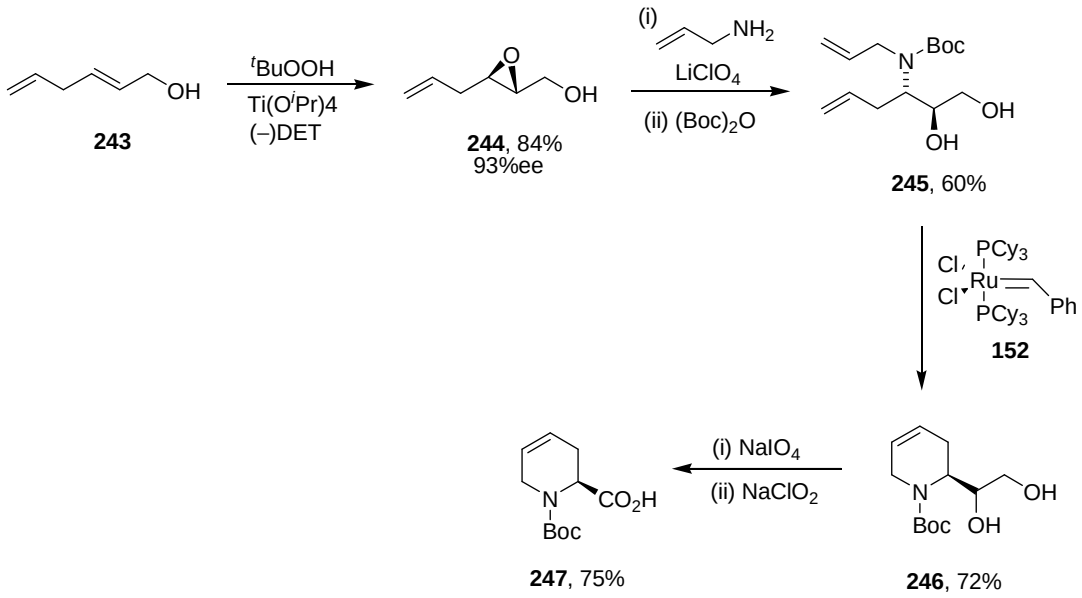
The work of Troin and co-workers was of particular relevance to our proposed synthesis of pipecolic acid derivatives (Scheme 76, also see section 5.1).[103] Beginning from protected β-amino-ketone **235**, reaction with aldehyde **236** gave imine **237**. Treating imine **237** with *p*-toluenesulfonic acid formed enol ether intermediate **238** which was set up for a 6-(*enolendo*)-*endo*-*trig* cyclization to give the 2,6-*syn* pipecolic acid ester **241** as the major product. The 2,6-*syn* selectivity of the cyclization is proposed to be derived from the energetic preference for the transition state **239**, which experiences smaller 1,3 diaxial interactions than the alternative transition state **240** that leads to formation of the 2,6-*anti* product **242**.[104]



Scheme 76: Synthesis of a Pipecolic acid derivative by Troin and co-workers

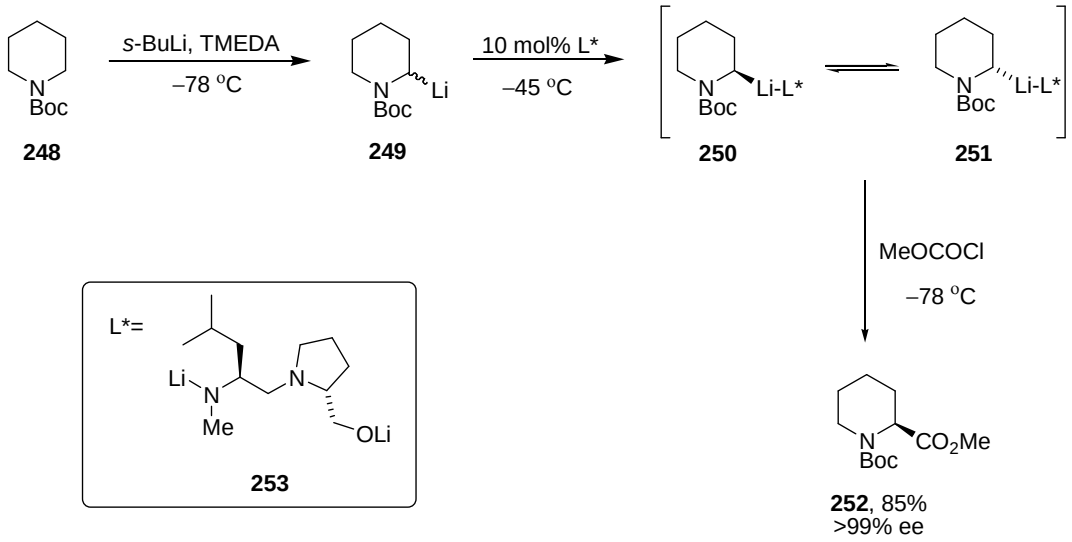
1.3.2 Pipecolic Acid Synthesis from Non-Amino Acids

When racemic starting materials are used stereoselectivity must be introduced in other ways. Ginesta and co-workers used the Sharpless asymmetric epoxidation to generate enantiopure epoxide **244** from allyic alcohol **243** as the source of chirality in their synthesis of pipecolic acid derivative **247** (Scheme 77).[105] Epoxide **244** was then regioselectively opened using Crotti's conditions and the resultant amine Boc protected to give diene **245**.[106] A ring closing metathesis reaction catalysed by Grubbs I **152** gave the piperidine product **246**, which was sequentially oxidised to avoid alkene oxidation giving the desired pipecolic acid derivative **247**.



Scheme 77: Synthesis of pipecolic acid derivates by Ginesta and co-workers

Gawley and co-workers have reported a route to pipecolic acid derivatives utilizing a catalytic dynamic resolution strategy (Scheme 78).[107] Beginning from Boc protected piperidine **248** an ortho-lithiation reaction was carried out to give racemic lithiated species **249**. The chirally pure ligand **253** was then added and the reaction mixture warmed to −45 °C. The elevated temperature allows the system to come under thermodynamic control and interconversion between the two ligand bound enantiomers **250** and **251** leads to accumulation of diastereomer **250** due to favourable diastereomeric interactions. The temperature is then lowered again, locking the lithiated species **250** as the desired enantiomer. Quenching the reaction with methylchloroformate gave the pipecolic acid derivative **252** in excellent yield and enantioselectivity.



Scheme 78: Synthesis of pipecolic acid derivates by Gawley and co-workers

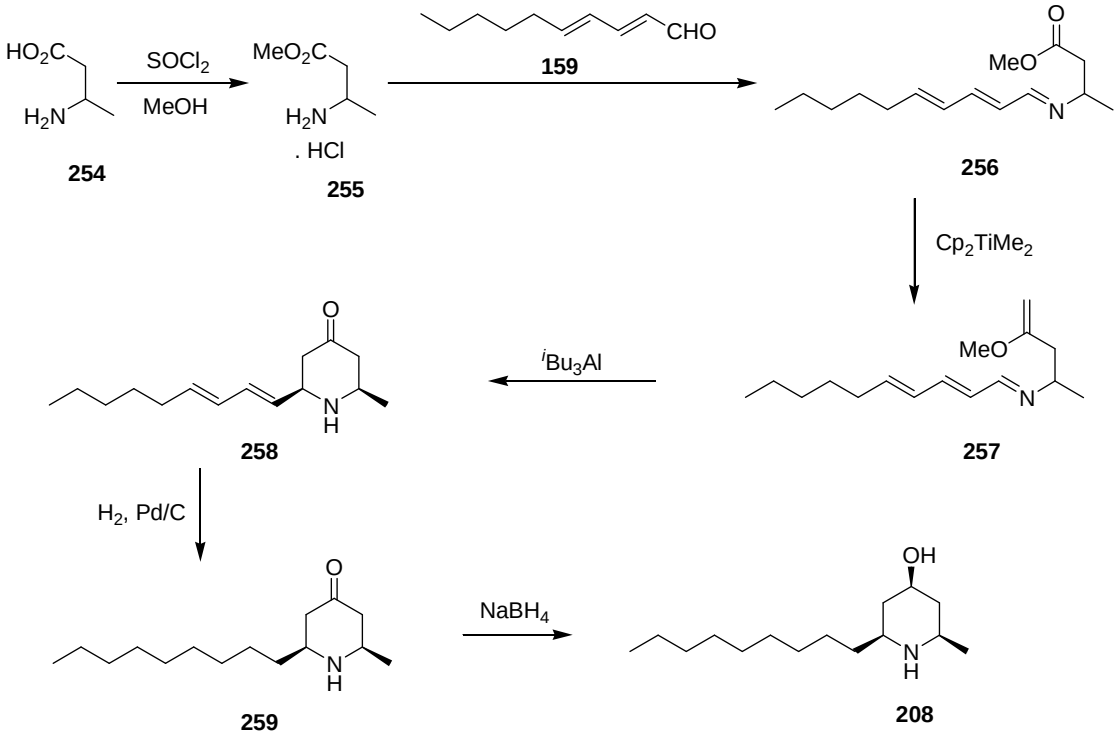
While there are many syntheses of pipecolic acid derivatives reported within the literature, there is no definitive method. This, in combination with their not yet fully explored biological activity, means that short, stereocontrolled routes to these pipecolic acid derivatives are of continuing interest to synthetic chemists.

4.0 Synthesis of Dendrobate Alkaloid (+)-241D

4.1 Proposed route

To further exemplify the imino-enol ether cyclization that has been previously described by the Hartley group[87] (see Section 3.1.7), it was decided that the initial target would be to synthesise piperidinone natural product dendrobate alkaloid (+)-241D **208**.

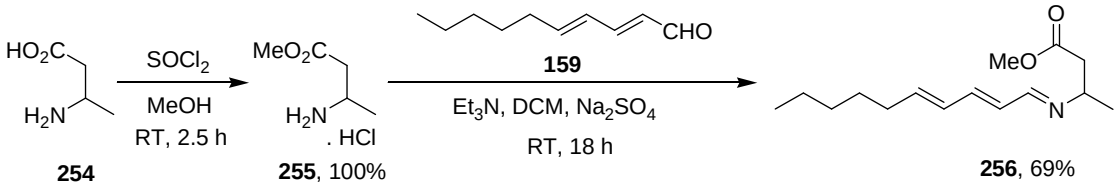
The proposed synthesis (Scheme 79) began from 3-aminobutanoic acid **254** which would be converted into its methyl ester **255**. Reaction of amine **255** with aldehyde **159** would give the imino-ester **256**. This compound contains a diene moiety that is not present in the final product, however it was hoped that the conjugated imine would be more resistant to both undesirable imine-enamine tautomerism and hydrolysis. Davis and co-workers also eschewed the use of aliphatic decanal in favour of conjugated **159** in their synthesis of the alkaloid **208** (see Sections 3.1.3 and 3.2). Imino-ester **256** is a substrate for Petasis methylenation to give enol ether **257** that could then be cyclized to give 2,6-*syn* piperidone **258** in the key sequence of the route. Hydrogenation to remove the double bond would give the piperperidinone **259**. Finally, a stereoselective reduction directed by the existing stereochemistry would give the desired natural product **208** (see Section 3.2 for precedent).



Scheme 79: Proposed synthesis of Dendrobate Alkaloid (+)-241D

4.2 First Attempted Synthesis

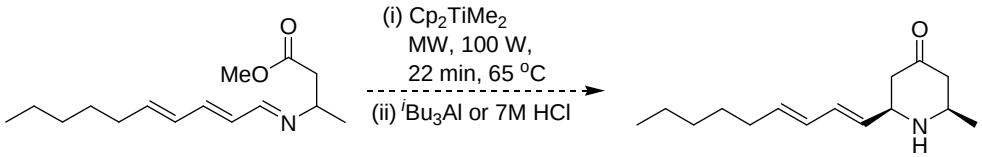
Synthesis of the imino-ester **256** was straightforward (Scheme 80). Reaction of 3-aminobutanoic acid **254** with thionyl chloride in the presence of methanol gave the desired ester **255** as the hydrochloride salt, which could be converted into the imine **256** using standard conditions in good yield.[87] One slight complication was that the aldehyde starting material **159** was a mixture of geometrical isomers containing ~10% *E,Z* or *Z,E* alkenes as well as the major *E,E* isomer, and hence the imine was also a mixture of isomers. This was not a problem however, as the alkenes would be removed by hydrogenation in a subsequent step. The imine was only moderately stable, decomposing within hours and requiring fresh preparation for each use. It is worth noting that the imine derived from propionaldehyde was too unstable to be isolated when previously synthesised within the group, implying that the use of unsaturated aldehyde **159** was beneficial.[87]



254 **255**, 100% **256**, 69%

Scheme 80: Imine formation

The imino-ester **256** was then ready for the key methylenation/cyclization step (Scheme 81). Unfortunately, despite many attempts, no enol ether product was observed after Petasis methylenation. It is worth noting that the starting material only ever remained in trace amounts, implying that side reactions competed significantly with the desired reaction. Therefore, imine **256** appears to be a poor choice of substrate for the reaction.

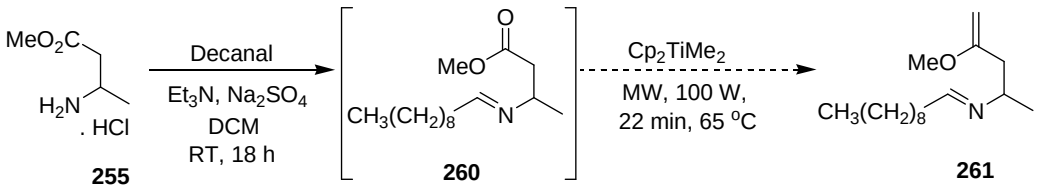


256 **258**

Scheme 81: Attempted cyclization

Despite the presumption that it would be less stable than the conjugated imine **256**, the aliphatic imino-ester **260** was investigated as a substrate for the methylenation reaction (Scheme 82). As mentioned previously, piperidinones derived from simple unstabilized imines had been synthesised previously within the Hartley group, albeit in

low yield.[87] However, it was found that the imine **260** was too unstable to be isolated and it did not survive the methylenation conditions.



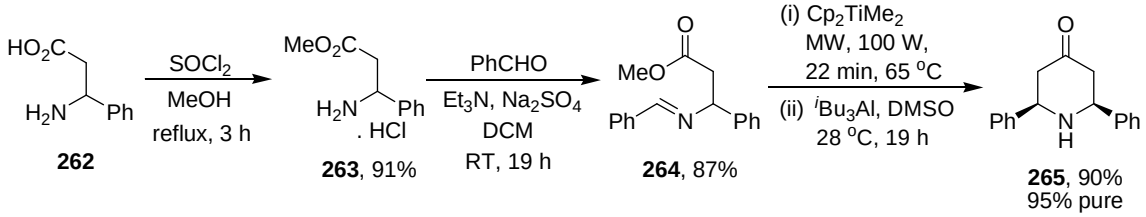
Scheme 82: Attempted methylenation of aliphatic imine

From these initial investigations it appeared that both the saturated and unsaturated ten carbon chain imines were challenging substrates for this reaction.

4.3 Validation of Reaction Conditions

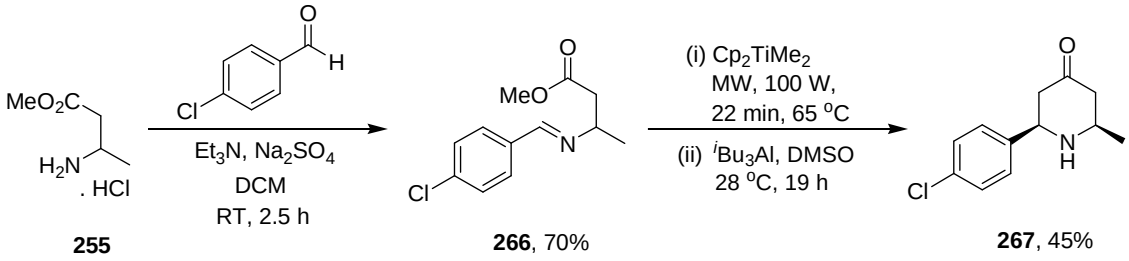
To ensure reaction conditions were being accurately reproduced two piperidinones, both derived from stable imines, were synthesised.

Firstly the synthesis of a known example was repeated (Scheme 83). The ester **263** and imine **264** were synthesised in a similar fashion to those described in Section 4.2, both in excellent yield. Usefully, the imine **264** was a stable solid, meaning that it could be stored for months without significant decomposition. Methylenation with the Petasis reagent proceeded cleanly and peaks for enol ether were clearly observed in the ^{1}H NMR spectrum as two doublets at 3.81 and 3.85 ppm. The imino-enol ether was cyclized in Lewis acidic conditions giving the 2,6-*syn* piperidinone **265** in excellent yield without purification containing only minor impurties.



Scheme 83: Synthesis of literature example

The same route was also used to generate a previously unknown piperidinone **267** which was isolated in reasonable yield (Scheme 84). The 2,6-*syn* geometry was assigned on the basis of the large coupling constants between H-2 and H-3_{ax} (10.9 Hz), and H-5_{ax} and H-6 (13.5 Hz).



Scheme 84: Synthesis of new example

The successful synthesis of the above piperidinones confirmed that the reaction conditions previously reported within the Hartley group were being faithfully reproduced and that imine **256** was indeed an unsuitable substrate for the methylenation reaction.

4.4 Characterisation of Piperidinones

There are a number of ways to confirm the stereochemical structure of piperidiones. The most definitive method is to use X-ray crystallography, however this is time consuming and limited to crystalline compounds. More commonly ^{1}H NMR spectroscopy methods are used. For example, in the 2,6-*syn* piperidinone shown Figure 9 the Nuclear Overhauser Effect (NOE) would show a correlation between H^{2}_{ax} and $H^{6}_{ax'}$ confirming a *syn* relationship between the substituents of C-2 and C-6. Analysis of coupling constants can give similar information. As described by the Karplus equation (Figure 9) the magnitude of coupling constants is maximal when the dihedral is 180°. Therefore large axial-axial couplings (8-15 Hz) between H^{2}_{ax} and H^{3}_{ax}, and H^{5}_{ax} and H^{6}_{ax} would also imply a *syn* relationship. Finally comparison of ^{1}H and ^{13}C NMR with that of similar compounds of known structure can lead to a tentative assignment of stereochemistry.

$$J(\varphi) = A\cos^2\varphi + B\cos\varphi + C$$

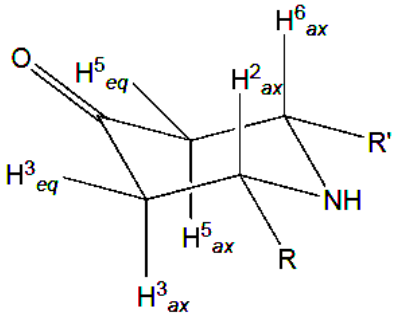
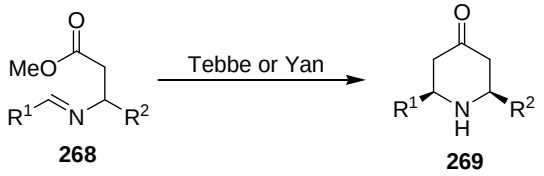


Figure 9: The Karplus equation and piperidinone structure

4.5 One-pot Methylenation/Cyclization

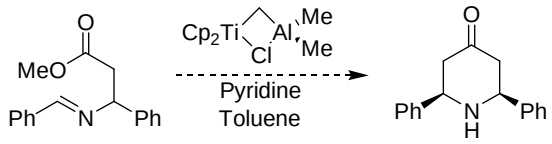
Dimethyltitanocene **91** was originally chosen as it is a relatively mild methylenating agent. Other systems, such as the Tebbe reagent **76** and Yan's methods, are less mild; this is primarily due to the Lewis acid present in both reagents. As our route involved methylenation followed by Lewis acid induced cyclization, it was hoped that the presence of a Lewis acid might present an opportunity to telescope the two steps together (Scheme 85). This would neatly avoid the need for isolation of unstable enol ethers and potentially allow them to be trapped by the cyclization before decomposition occurred.



268 **269**

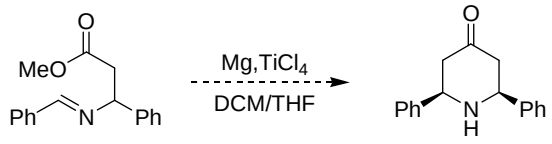
Scheme 85: Proposed one pot methylenation and cyclization

Unfortunately neither the Tebbe reagent nor Yan's methods (Schemes 86 and 87) were successful in performing this transformation, with no cyclized or enol ether product being isolated from either reaction.



264 **265**

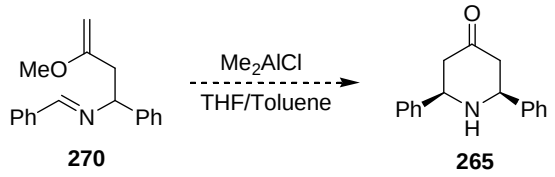
Scheme 86



264 **265**

Scheme 87

To investigate whether enol ether **270** could be cyclized using dimethyl aluminium chloride, the Lewis acid present in Tebbe's methylenation conditions in the conditions, the reaction described in Scheme 88 was performed. However, no cyclized product **265** was isolated, implying that, even if the imino-enol ether were formed, cyclization would not take place.

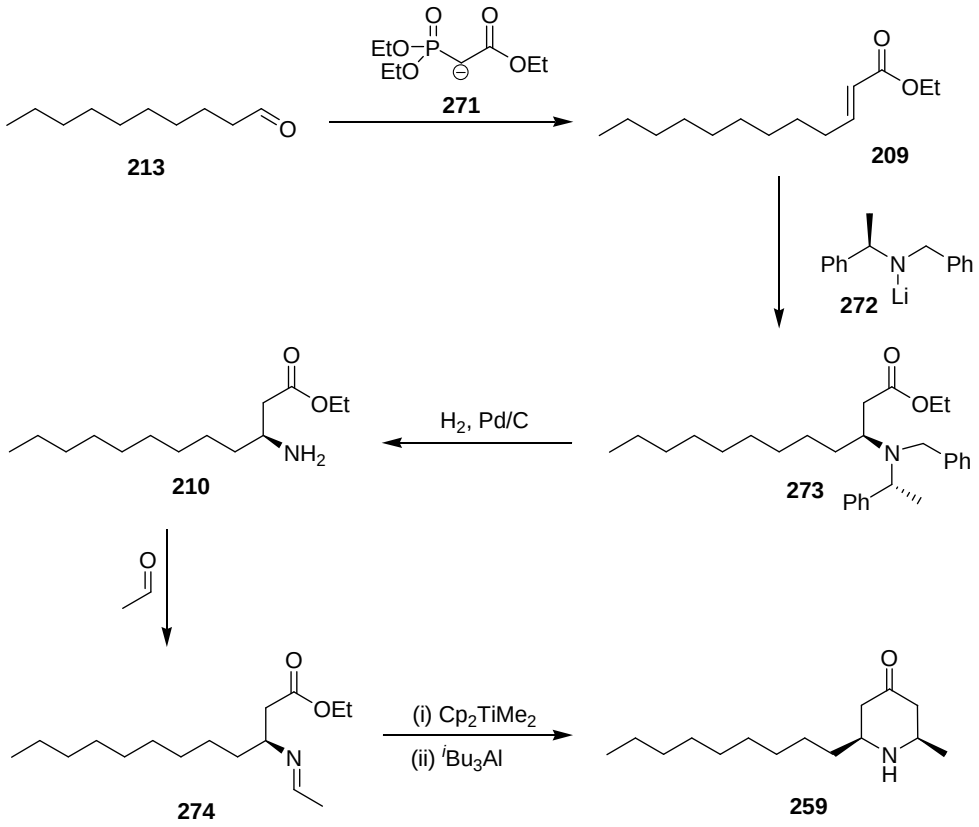


270 265

Scheme 88: Mimicking post Tebbe reaction conditions

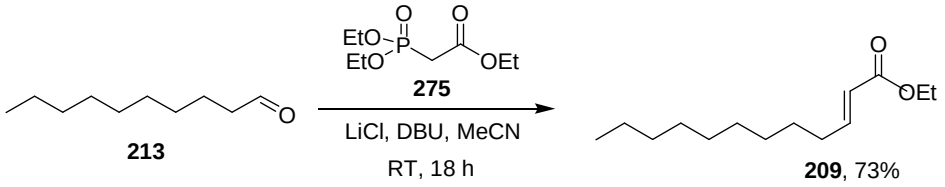
4.6 Alternative Route

Following the unsuccessful route using imine **260**, derived from decanal, whether the desired piperidinone **259** could be prepared by cyclization the other way round was investigated, i.e. using an imine derived from ethanal. Reasons for this were two-fold. Firstly, generation of the required enantiomerically pure amine **210** had already been described by Sun and Ma[92] in their previous synthesis of dendrobate alkaloid (+)-241D. Secondly, although the required imine **274** was likely to be relatively unstable, an imine derived from acetaldehyde had previously been cyclized within the Hartley group.[87] The proposed synthesis (Scheme 89) involved the generation of amine **273** from the diastereoselective aza-Michael reaction of enone **209** and secondary amine **272** described by Sun and Ma. The imino-ester **274** could then be formed, methylenated and cyclized in the normal fashion giving the desired piperidinone **259**.

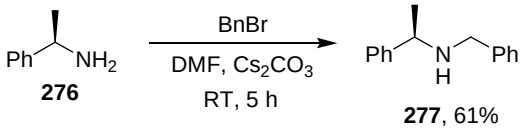


Scheme 89: Proposed althernative route

Firstly, the substrates for the aza-Michael reaction were synthesised (Schemes 90 and 91). The α,β unsaturated ester **209** was generated in a Horner-Wadsworth-Emmons reaction between decanal **213** and triethyl phosphonoacetate **275** under Masamune-Roush conditions.[108] This allowed selective formation of the *E*-alkene in good yield. The amine **277** was synthesised in a nucleophilic substitution reaction between (*R*)-methylbenzylamine **276** and benzyl bromide.[109]

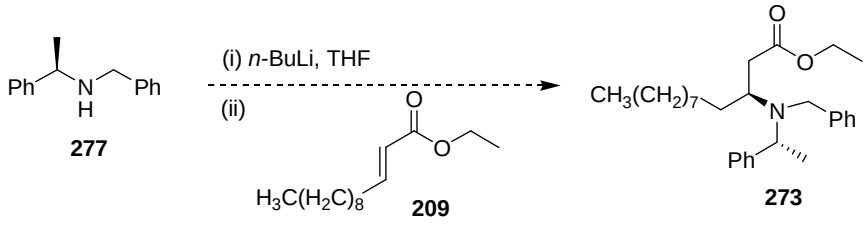


Scheme 90



Scheme 91

Despite the conjugate addition reaction to give amine **273** (Scheme 92) being described in the literature[92, 110], it was not possible to reproduce the results. Our attempts are summarised in Table 2. A variety of different coupling conditions were investigated, varying the deprotonation conditions, coupling conditions and the batch of *n*-butyllithium used. Despite this, formation of product was only observed in trace amounts. The reason for the lack of success is not entirely clear; one possibility is that the reaction is particularly moisture sensitive. The literature examples were performed on a larger scale (7-17 mmol) than those in our lab (0.5-1 mmol) and would therefore be less sensitive to small amounts of moisture.

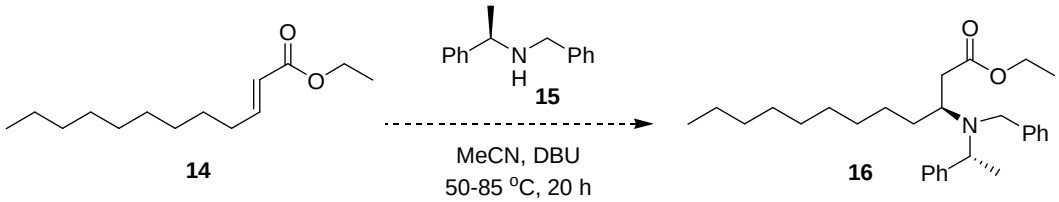


Scheme 92: Attempted aza-Michael reaction

Table 2

Entry	Deprotonation Conditions	Coupling Conditions	Result
1	−78 °C, 2 h	−78 °C, 4 min	No reaction
2	−78 °C, 2 h	−78 °C, 1 h	No significant reaction
3	−78 °C to −40 °C, 2 h	−78 °C, 1 h, allowed to warm to RT over 15 min	No significant reaction
4	−78 °C to −20 °C, 2 h	−78 °C to RT, 2 h	No significant reaction

Based on similar reactions described in the literature[111] an aza-Michael type reaction was also attempted (Scheme 93), unfortunately no reaction was observed.



Scheme 93: Alternative aza-Michael reaction conditions

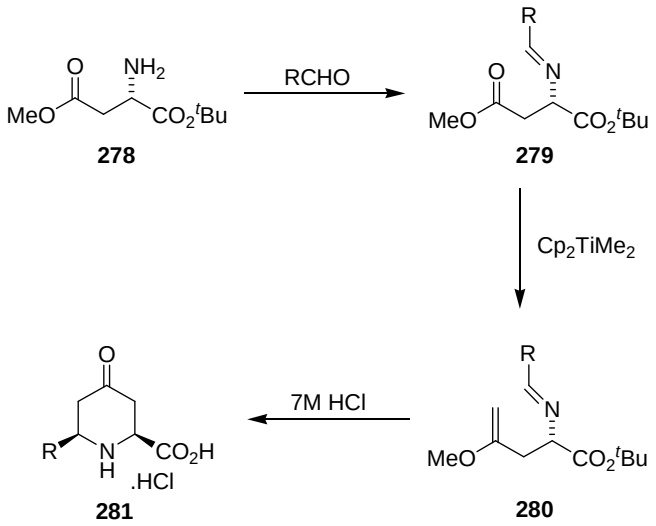
4.7 Conclusions

Our initial hope was that this first project would quickly provide a short route to dendrobate alkaloid (+)-241D **208** that would neatly exemplify the piperidinone cyclization discovered within the group. Unfortunately, it became clear that precursors to this natural product were not ideal substrates for the chemistry developed within the Hartley group and routes utilising this methodology would require significant further optimisation. For these reasons the synthesis of dendrobate alkaloid (+)-241D **208** was abandoned.

5.0 Synthesis of Pipecolic Acid Derivatives

5.1 Proposed Route

Our proposed synthesis (Scheme 94) of pipecolic acid derivatives utilized a chiral pool strategy, beginning from an orthogonally protected aspartic acid derivative **278**. The imine **279** would then be formed giving the substrate for Petasis methylenation. It was hoped that the methylenation would be selective for the less hindered methyl ester, leaving the bulky *tert*-butyl ester untouched as has been reported in the literature on unrelated compounds (see section 1.3.4). The enol ether **280** could then be cyclized in aqueous acid to give the 2,6-*syn* pipecolic acid derivative **281** as a single enantiomer.

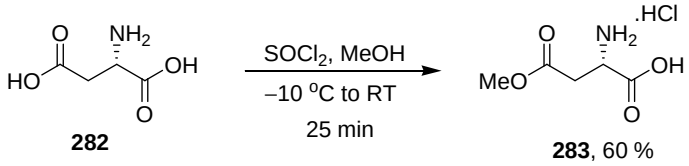


278 **279** **280** **281**

Scheme 94: Proposed synthesis of pipecolic acid derivatives

5.2 Initial Trials

Before the proposed route could be attempted, the aspartic acid diester **278** had to be synthesized. The desired mono methyl ester **283** could be synthesized from reaction between L-aspartic acid **282** and thionyl chloride in the presence of methanol under literature conditions (Scheme 95).[112] Pure material was obtained following recrystallization to remove undesired dimethyl ester. The reason for the selectivity is not entirely clear, though an investigation into the relative rates of the formation of α-, β-, and dimethyl aspartate at RT by Rapoport and co-workers showed that the proportion of β-methyl ester peaked after 15 minutes in a 6:1 ratio versus the dimethyl ester at which time no mono α-methyl ester was present.[113]



Scheme 95

It is possible that the close proximity of the amine to the α-acid disfavours protonation of the α-acid's carbonyl as this would bring the two resultant positive charges closer together than the equivalent protonation the β-acid (Figure 10) Thus, the β-acid would be more likely activated to nucleophilic attack and the rate of ester formation greater at this site.

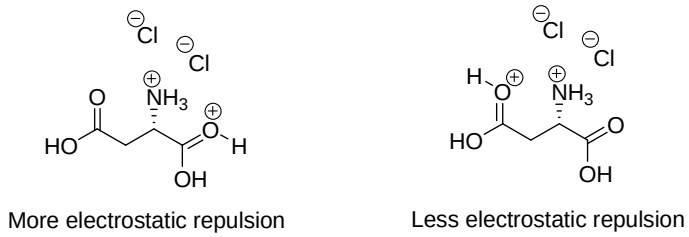
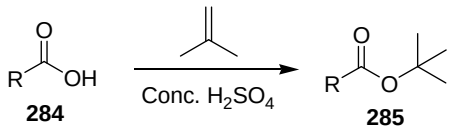


Figure 10: Proposed rational for selective ester formation

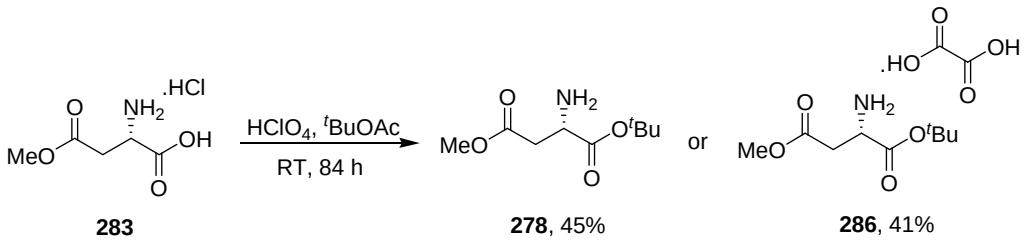
With β-methyl aspartate **283** in hand the *tert*-butyl ester **278** could then be synthesized. *Tert*-butyl ester **285** synthesis is commonly performed by reacting a carboxylic acid **284** with 2-methylpropene in a strongly acidic environment (Scheme 96).[114] The reaction proceeds through protonation of 2-methylpropene to give a *tert*-butyl cation, which is subjected to a nucleophilic attack by the carboxylic acid **284** to give the ester product **285**.



Scheme 96: *Tert*-butyl ester synthesis

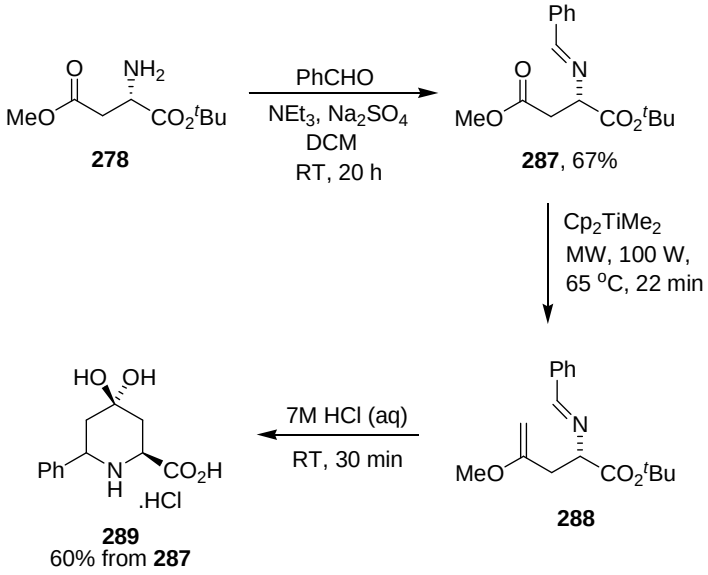
While 2-methylpropene itself is cheap, it is a gas and the equipment for its storage and use is relatively expensive. For this reason other avenues for the formation of ester **278** were investigated. There is literature precedent for *tert*-butylacetate as an alternative precursor to the *tert*-butyl cation.[115] Initial trials with hydrochloric acid were unsuccessful due to the poor solubility of the amino acid hydrochloride salt, however switching to perchloric acid solved this issue and allowed the synthesis of the desired diester **278** in reasonable yield (Scheme 97). During early attempts **278** was isolated as the free amine, however this was found to be unstable, undergoing transesterification

when stored for short periods of time. Isolating the amine as its oxalate salt **286** prevented this. Formation of an oxalate salt was chosen for practical reasons, addition of a solution of oxalic acid in diethyl ether to a solution of the amine **278** in diethyl ether precipitated the oxalate salt **286** which could be easily isolated by simple filtration. Due to the excess of oxalic acid used it was presumed that a mono salt was the product.



Scheme 97: *Tert*-butyl ester synthesis and oxalate salt formation

Having synthesised the required diester **278**, our proposed synthesis could be put into practice (Scheme 98). The imine **287** was generated in good yield from reaction of diester **278** and benzaldehyde. This was then methylenated with Petasis reagent which was pleasingly completely selective for the methyl ester giving compound **288**, showing peaks for the new methylene protons in the ^{1}H NMR spectrum at 4.05 and 4.06 ppm, with no trace of the undesired methylenation product. This was successfully cyclized in 7M hydrochloric acid to give the pipecolic acid derivative **289** in 60% yield from imine **287**, corresponding to a 10% yield from aspartic acid.

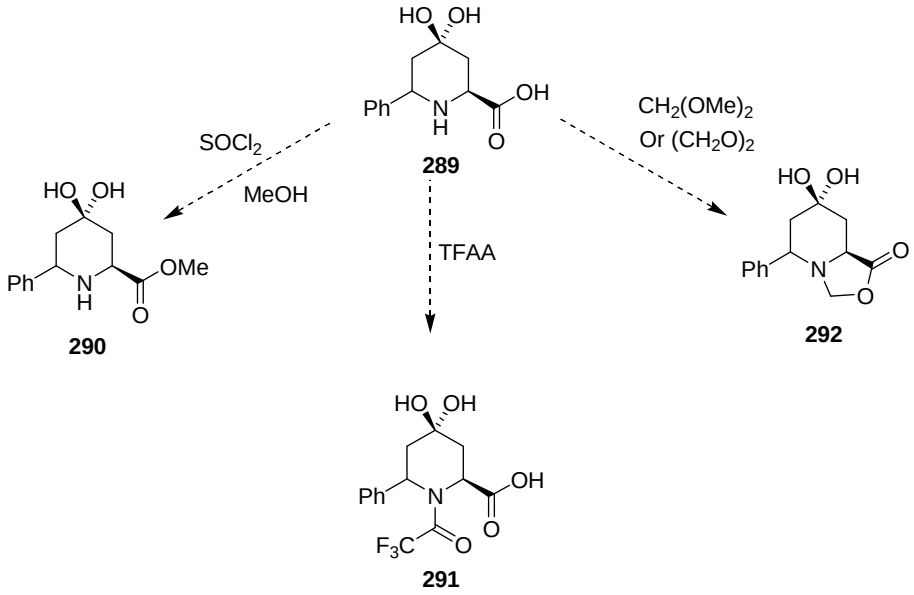


Scheme 98: Synthesis of pipecolic acid derivative **25**

Pipecolic acid derivative **289** was isolated predominantly in the geminal diol form as has be observed for similar compounds,[116] but unfortunately appeared to be a 1:1 mixture of diastereoisomers. An optical rotation for the mixture was observed, implying that the original chirality remained in some form, presumably at the amino acid derived centre. The reason for the low level of diastereoselectivity was unclear, however we proposed

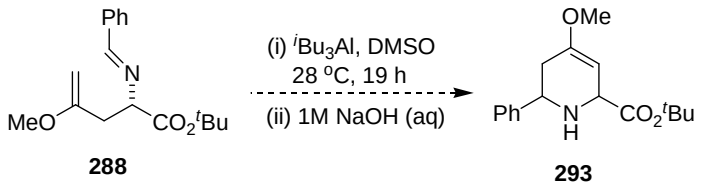
that the *tert*-butyl ester was cleaved before cyclization took place and the acid group interfered with selectivity.

Further attempts to separate and identify the diastereoisomers proved difficult. The physical form of the mixture was a foam and repeated attempts at recrystallisation failed. The highly polar zwitterionic state of the amino acid negated chromatography as an option. For this reason we attempted to generate a more easily handled derivative by preparing ester **290,** amide **291** or bicyclic amino ester **292** (Scheme 99), unfortunately none of these were successful. At the time we had yet to discover that the compound existed in the diol form **289**, something that was not observed for piperidinones we had synthesised previously. The presence of the alcohols likely contributed to the failure of the derivatization attempts.



Scheme 99: Summary of pipecolic acid derivatization attempts

To investigate whether the free acid group was interfering with the diasteroselectivity, the cyclization was repeated under Lewis acidic conditions (Scheme 100). We hoped that the Brønsted acid-free conditions would allow isolation of enol ether **293** with the *tert*-butyl ester intact. These conditions gave a complex mixture of compounds, which might not be unexpected if there were a mix of different diastereomers and enol ethers. However, when the mixture was stirred in 1M hydrochloric acid no amino acid product **289** was isolated, implying that the mixture had not contained **293**.



288 **293**

Scheme 100: Attempted cyclization without Brønsted acid

Despite the lack of success in our first attempt at cyclization with the *tert*-butyl group intact, we still felt that this was the best way forward with the project. For this reason we focussed our attention on the investigation of alternative, milder, cyclization conditions.

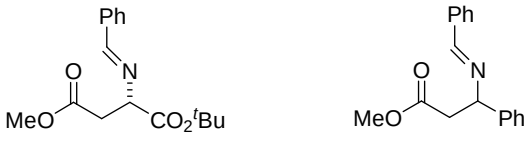
5.3 Alternative Cyclization

5.3.1 Acid Based Cyclization Methods

Our strategy to find suitable alternative cyclization conditions was two pronged:

- Take the original conditions as a starting point and modify them to allow isolation with the *tert*-butyl group intact.
- Induce cyclization with an electrophile, thereby giving the more easily handled N-protected piperidinone.

Instead of using potentially problematic imine **287** as a test substrate for these reactions we decided to use imine **264** (Figure 11). There were several reasons for this: imine **264** was much more easily synthesized and in greater yield, it is a stable solid and so did not require fresh preparation for each use, making the optimization process much quicker, finally, side products of reactions with **287** could potentially be amino acids, which would be tricky to isolate.

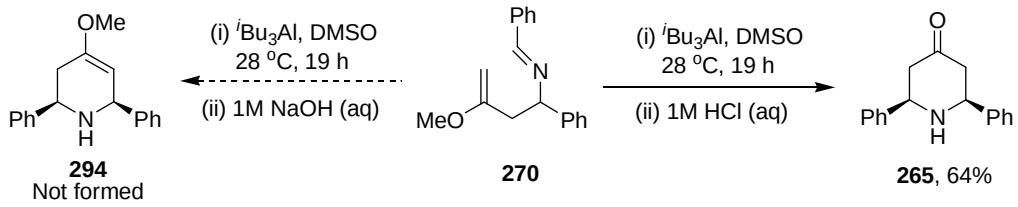


287 **264**

Figure 11

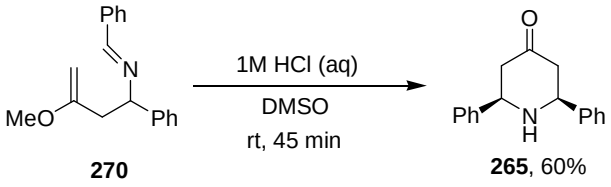
We initially tried to isolate the cyclized enol ether **294** derived from Lewis acid-induced cyclization of enol ether **270** in a repeat of the experiment shown in Scheme 100, but switching to a basic work up (Scheme 101). Interestingly, only starting material was isolated. Even when enol ether **270** was resubmitted to the reaction conditions for a

further 48 hours no cyclized product was observed, only enol ether **270** and decomposition products. An experiment run concurrently using an acid quench gave the expected piperidinone **265**.



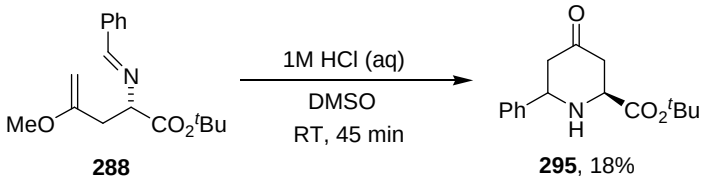
Scheme 101: Comparison of basic and acid work-up conditions

This led us to postulate that the cyclization actually occurs in the acid quench rather than in the Lewis acid. An experiment trying to mimic the quench conditions (Scheme 24) confirmed that this is indeed a possibility. Enol ether **270** was successfully cyclized in a 1:1 mixture of 1M hydrochloric acid and DMSO, giving the piperidinone **265** in a yield comparable those reported previously.



Scheme 102: Mimicking acidic work up conditions

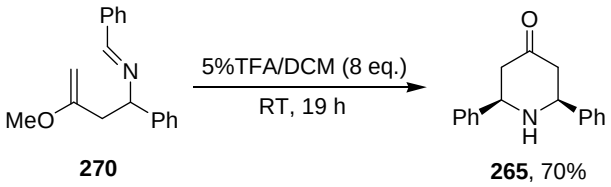
As these conditions were significantly milder than 7M hydrochloric acid, we thought it possible that the *tert*-butyl ester would survive them and so the reaction was repeated with imino-enol ether **288**. (Scheme 103) The reaction was successful, giving the desired piperidinone **295** in 18% yield. Unfortunately it was again a mixture of diastereomers, this time in a 2:1 ratio by ^{1}H NMR spectroscopy. The major (*syn*) isomer was isolated and the structure confirmed by NOESY and coupling constant analysis. The large coupling constants between H-2 and H-3_{ax} (10.4 Hz), and H-6 and H-5_{ax} (12.1 Hz) indicate the 2,6-*syn* geometry. This is corroborated by the NOESY correlation between the peaks at 3.63 and 3.93 ppm on the ^{1}H NMR spectrum. As with our first result the compound gave an optical rotation, showing retention of chiral information, presumably at the amino acid derived centre. The low yield is likely to be due to some material being lost after *tert*-butyl ester cleavage.



288 **295**, 18%

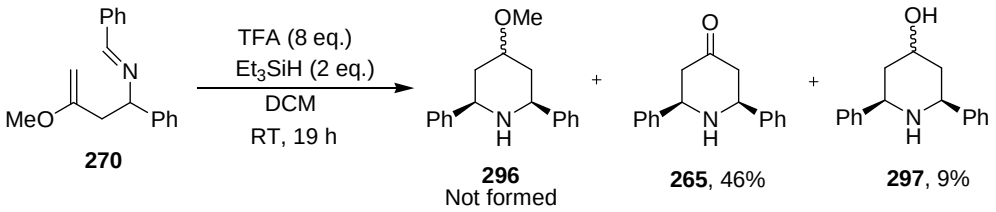
Scheme 103: Cyclization with *tert*-butyl ester intact

We felt that the *tert*-butyl ester would be more stable at lower temperatures and that this might also benefit the diastereoselectivity. We had already tested the hydrochloric acid/DMSO mixture at 0 °C, below which it will freeze, and isolated only a low yield of compound **295** with many impurities and observed no enhancement of the diastereoselectivity. So we decided to look at alternative acids. We initially tried 5% TFA in DCM (Scheme 104) on test imino-enol ether **270** and happily this gave the piperidinone **265** in 70% yield, equal to the best previously reported.[87] The product was isolated after a basic work-up, however prior to this the concentrated reaction mixture appeared to contain the TFA salt of **265**, not the oxonium intermediate as expected. This implies that these conditions both induce cyclization and oxonium cleavage in a single step, thus negating the need for an aqueous work up. There is literature precedent for this occurring resin bound enol ethers.[117] To try and confirm the presence of the oxonium intermediate, we repeated the reaction in Scheme 104, but added 2 equivalents of triethylsilane as a reductant in an attempt to generate the methyl ether (Scheme 105). The expected methyl ether product **296** was not formed, in fact the major product was piperidinone **265** and its reduction product **297** (as a 2.5:1 mixture of diastereoisomers). This suggests that, under these conditions, the oxonium cleavage is very fast.



270 **265**, 70%

Scheme 104: Cyclization in alternative acid

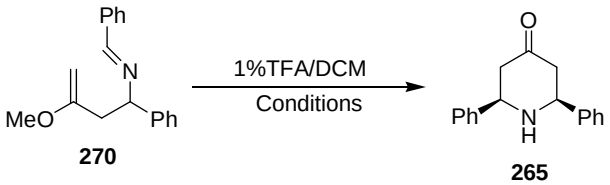


270 **296** Not formed **265**, 46% **297**, 9%

Scheme 105: Attempted trapping of oxonium intermediate

While the above cyclization conditions were very effective, they were likely to be too harsh for the *tert*-butyl ester to survive. So we investigated the effect of lowering both

the number of equivalents of TFA and the temperature (Scheme 106), the results are summarised in Table 3. Entries 1 and 2 showed that the concentration of TFA could be lowered, but that 1 equivalent was not sufficient for complete conversion. When 2 equivalents of TFA were used (entry 3) it became clear from sampling of the reaction mixture that this was not sufficient to give complete conversion, so a further 3 equivalents were added after 30 minutes. A sample after a total 1 hour reaction time showed 80-90% product, the reaction was then left overnight after which complete conversion was observed. The reaction described in entry 4 was run concurrently and so the same sequential addition was performed, showing that cyclization can also occur at low temperature.



270 **265**

Scheme 106

Table 3

Entry	Equivalents of TFA	Temperature	Reaction Time	Result	Complete conversion?
1	8	RT	45 min	Product	Yes
2	1	RT	45 min	Product, with impurites	No
3	2 to 5	RT	19 h	Product	Yes
4	2 to 5	−78 °C	5 h	Product, with minor impurities	Yes

The reason for the requirement of 2 or more equivalents of TFA can be seen in the 5.5-7.0 ppm region of the ^{1}H NMR spectrum, where the peaks for the cyclopentadienyl peaks of the titanium by-products are found (Figure 12). During purification of the enol ethers, the majority of titanium residues are precipitated out, however significant quantities remain. This shows a peak at 5.82 ppm and is presumed to be a Cp_2TiO-THF complex.[118] With two equivalents of TFA two peaks for cyclopentadienyl are observed, only when 5 equivalents are added, do the cyclopentadienyl signals converge in a peak at 6.63 ppm. This shows that titanium by-products are also reacting with TFA, thus an excess is required.

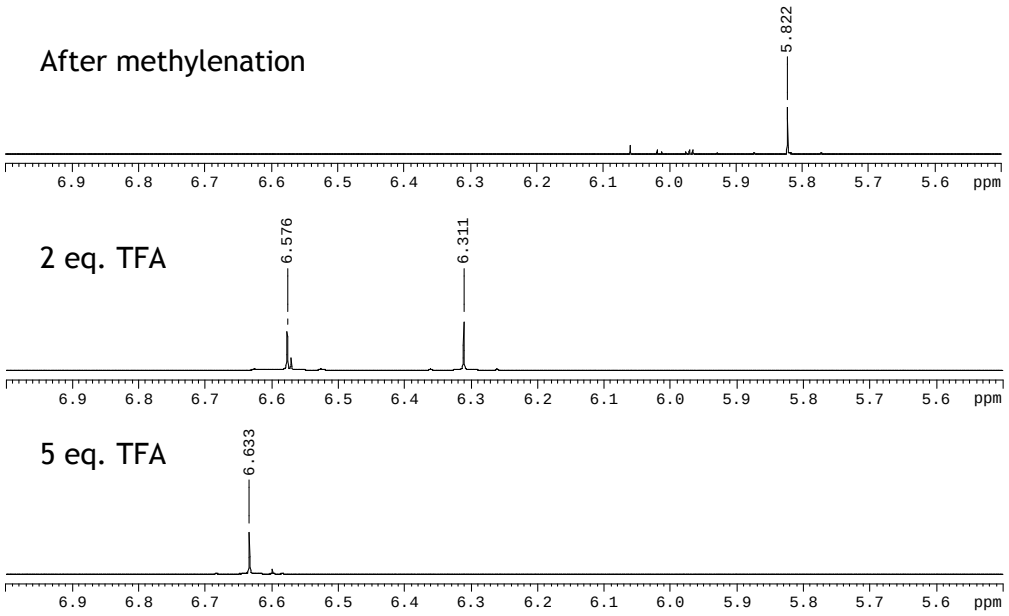
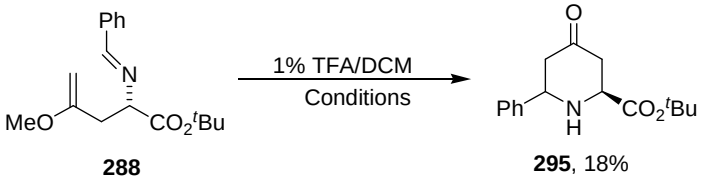


Figure 12: Reaction of titanium by-products with acid

With the optimized conditions in hand we tested them using the *tert*-butyl ester imine **288** at both room temperature and at −78 °C. (Scheme 107, Table 4) The reaction at room temperature gave no product – presumably the *tert*-butyl did not survive. At low temperature, the reaction did yield product **295**, but with many impurities remaining after chromatography. It was also a 2:1 mixture of diastereomers, similar to what had been previously observed.



288 **295**, 18%

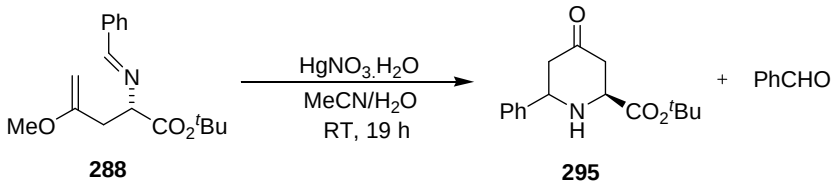
Scheme 107: Effect of temperature variation

Table 4

Entry	Equivalents of TFA	Temperature	Reaction Time	Result
1	4	RT	1 h	No product
2	4	−78 °C	6.5 h	Product with impurities, 2:1, *syn* : *anti*

The TFA system represented a Brønsted acid induced one-pot cyclization and oxonium cleavage. It would be much more advantageous to have mild Lewis acidic method, as this would not remove the *tert*-butyl group. Mander and co-workers have reported that mercury nitrate is a mild reagent for the hydrolysis of enol ethers.[119] We hoped that it

would be a strong enough Lewis acid to induce cyclization as well as hydrolyzing the resultant enol ether. (Scheme 108) While the reaction was moderately successful, product **295** was isolated as a 2:1 mixture of diastereomers with significant peaks in the ^{1}H NMR spectrum for Cp_2TiX and benzaldehyde. The presence of benzaldehyde implies that the competing imine hydrolysis is fast enough to consume large quantities of substrate **288** before cyclization takes place.



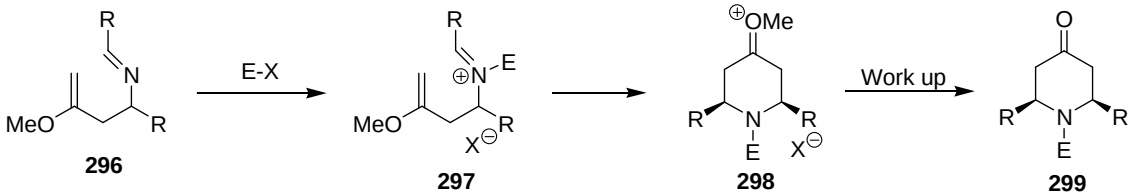
288 **295**

Scheme 108: Cyclization with mercury Lewis acid

While we had some success in developing alternative acid-based cyclization methods, it was clear that the *tert*-butyl ester was too unstable to survive Brønsted acids and give the product in acceptable yield. We also noted that the diastereoselectivity was low in all reaction conditions, implying that it would not be easily optimised.

5.3.2 Electrophile Based Cyclization Methods

We thought it was possible that cyclization could be induced by electrophiles to give *N*-functionalized products (Scheme 109). Reaction of imine **296** with an electrophile would give the iminium species **297**, which would quickly cyclize giving the oxonium salt **298**. This would be hydrolysed in the work-up, giving the N-functionalized piperidinone **299**. The advantage of this route was that, even if the *tert*-butyl ester is cleaved, the amine would be protected and the product would be more easily handled.

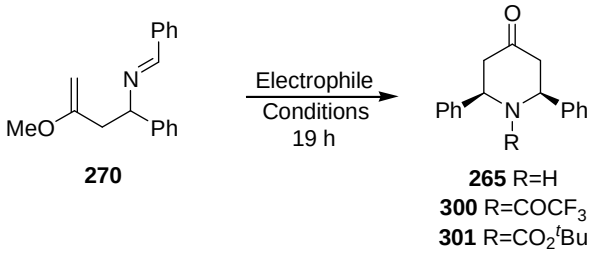


296 **297** **298** **299**

Scheme 109: Proposed cyclization with electrophiles

We investigated this cyclization method using many electrophiles, with limited success. Initial tests generated the trifluoroacetamide **300** and BOC protected **301** products, in low yield (Scheme 110, Table 5). The ^{1}H NMR spectrum of trifluoroacetamide **300** was very broad, indicating the presence of rotamers due to restricted rotation around the amide bond. Re-running the ^{1}H NMR experiment at a higher temperature solved this problem. Unfortunately these initial successes did not translate into success with more

useful electrophiles, such as those that would result in Cbz protected products. Even a relatively strong electrophile, benzyl chloroformate, in refluxing dichloromethane with DMAP as a nucleophilic catalyst (entry 12) failed to induce cyclization. The starting imino-enol ether **270** was unstable, and therefore not observed in the reaction mixture post work up, even when no cyclization had taken place. However, substantial quantities of piperidinone **265** were sometimes observed if the work up was acidic, which was seen as a marker of the presence of unreacted imino-enol ether.



270

265 R=H
300 R=$COCF_3$
301 R=$CO_2{}^tBu$

Scheme 110: Cyclization with electrophiles

Table 5

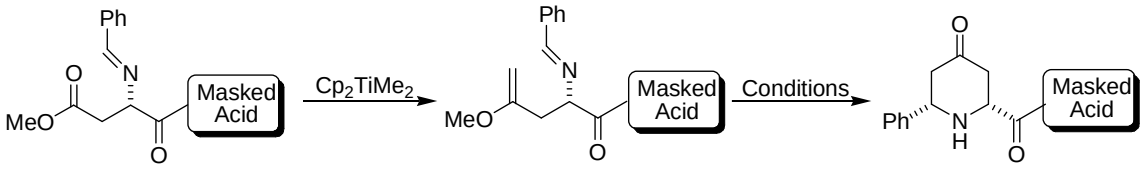
Entry	Electrophile	Solvent	Additive	Temperature	Product	Yield
1	MsCl	DCM	NEt_3	RT	**265**	N/A[a]
2	TFAA	DCM	NEt_3	RT	**300**	7%[b]
3	TFAA	Pyridine	None	RT	**300**	28%
4	TFAA	Pyridine	None	60 °C	**300**	44%[b]
5	$(Boc)_2O$	DCM	None	RT	**301**	21%[b]
6	$(Boc)_2O$	DCM	None	Reflux	**301**	21%[c]
7	$(Boc)_2O$	Pyridine	None	RT	**265**	N/A[a]
8	$(Boc)_2O$	Toluene	None	Reflux	**265**	N/A[a]
9	$(Cbz)_2O$	DCM	None	Reflux	-	N/A
10	$(Cbz)_2O$	Pyridine	None	Reflux	-	N/A
11	Benzyl chloroformate	DCM	NEt_3	Reflux	-	N/A
12	Benzyl chloroformate	DCM	NEt_3, DMAP	Reflux	-	N/A
13	Benzyl chloroformate	Toluene	NEt_3	Reflux	-	N/A

[a] Free piperidinone main component of crude reaction mixture, [b] Product contained significant impurities, [c] Product contained minor impurites

Unfortunately, despite initially promising results, our investigation in inducing cyclization with electrophiles did not provide a suitable method for the synthesis of pipecolic acid derivatives.

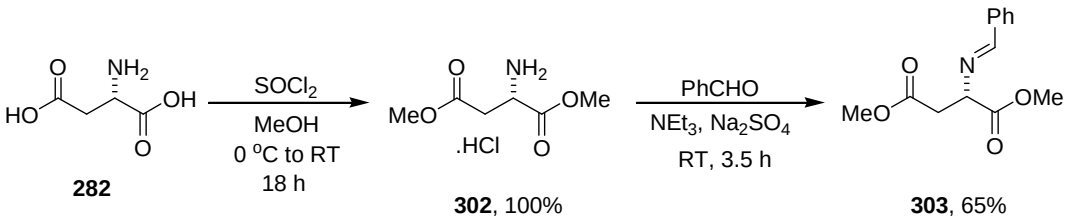
5.4 Variation of Acid Protection

Other than diastereoselectivity, the most consistent problem we encountered when trying to synthesise pipecolic acid derivatives was the ease of cleavage of the *tert*-butyl ester. We therefore decided to investigate the possibility of using other groups (Scheme 111). Obviously the masked acid group must be able to be easily transformed into a carboxylic acid, but crucially, it must also direct methylenation to the methyl ester.



Scheme 111: Generic acid protection synthesis

Before looking at different orthogonal aspartic acid esters we decided to try using dimethyl aspartate **302** to see if there was any intrinsic selectivity shown. Aspartic acid **282** was converted into its dimethyl ester **302** using standard conditions and in quantitative yield (Scheme 112). This was then converted to the imine **303** giving the substrate for Petasis methylentation.



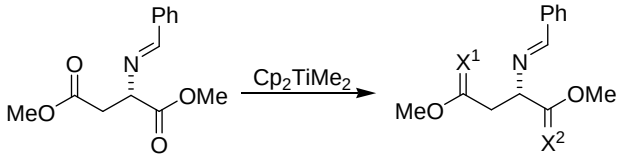
282

302, 100%

303, 65%

Scheme 112: Synthesis of dimethyl ester substrate

When the imino-ester **303** was submitted to the methylenation conditions no selectivity was observed by ^{1}H NMR spectroscopy, giving a mixture of mono-methylenated products and the di-enol ether (Scheme 113, Table 6) with a significant amount of starting material remaining. Using 3.8 equivalents of dimethyltitanocene gave almost complete conversion to di-enol ether **306**. Unfortunately cyclization of this material did not give the corresponding ketone **307** (Scheme 114).

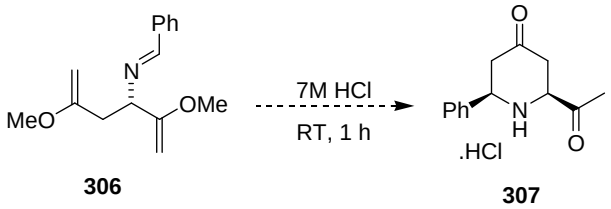


303 **304-306**

Scheme 113: Methylenation of dimethyl ester substrate

Table 6

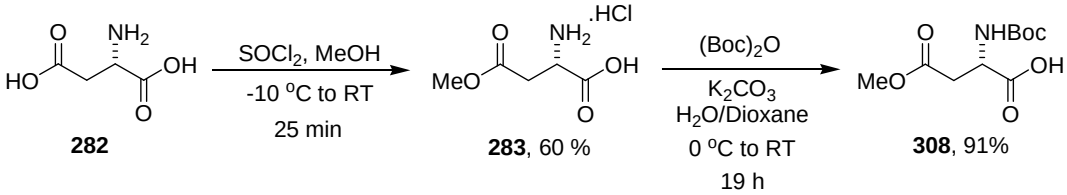
Eq. Cp_2TiMe_2	Ratio of Products in ^1H NMR			
	303 $X^1=X^2=O$	**304** $X^1=CH_2$, $X^2=O$	**305** $X^1=O$, $X^2=CH_2$	**306** $X^1=X^2=CH_2$
2	1	1	0.8	0.4
3.8	0	0	0.2	1



306 **307**

Scheme 114: Attempted cyclization of di-enol ether

The dimethyl ester result confirmed the need to chemically direct the methylenation to the desired carbonyl moiety. To this end BOC protected intermediate **308**, which could be coupled to give a variety of different acid oxidation state functionalities, was synthesised (Scheme 115). Mono methyl aspartic acid **283** was synthesised as previously described and the Boc protection proceeded in excellent yield as described by Woodard and co-workers.[120]

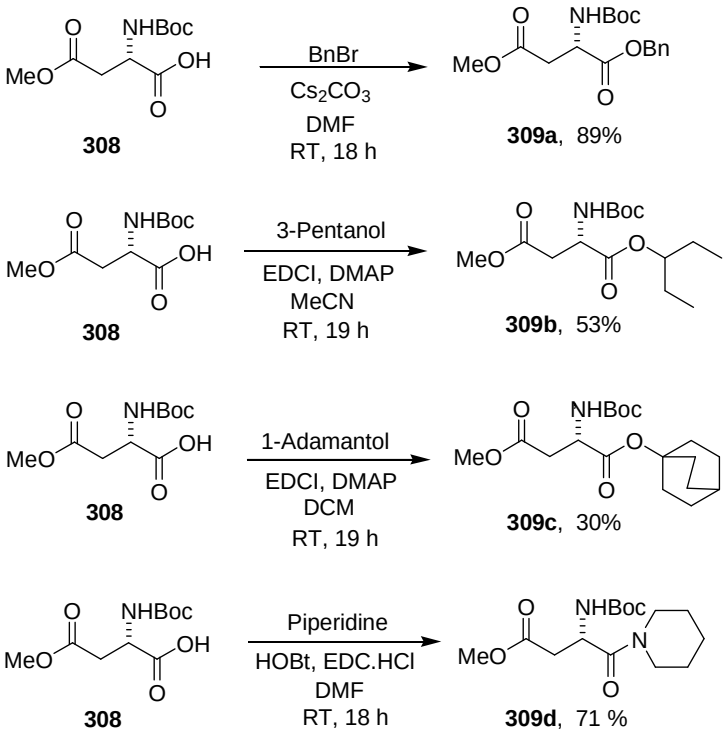


282 **283**, 60 % **308**, 91%

Scheme 115: Synthesis of BOC protected intermediate

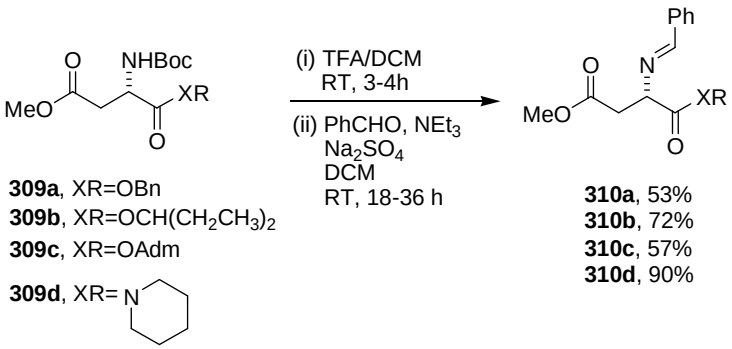
This allowed the synthesis of a range of aspartic acid derivatives (Scheme 116). In diesters **309a-c** the non-methyl ester was proposed to be the less reactive target for methylenation on the basis of steric interactions. The amide in substrate **309d** is less electrophilic than the methyl ester and should therefore be less reactive to methylenation.[121]

The derivatives were synthesised using standard coupling conditions (Scheme 116).[122] As they we required only for test reactions, the syntheses were largely unoptimised. However, on the advice of a colleague, it was found that changing the solvent from dichloromethane to acetonitrile in the synthesis of **309b** increased the yield from 42% to 53% and removed the requirement for purification by chromatography. The same improvement was not observed in the synthesis of **309c**, in fact, using acetontirile as the solvent actually lowered the yield to around 20%. The consistently low yields for this substrate are likely to be due to 1-adamantanol being such a poor nucleophile.



Scheme 116: Synthesis of a variety of masked acids

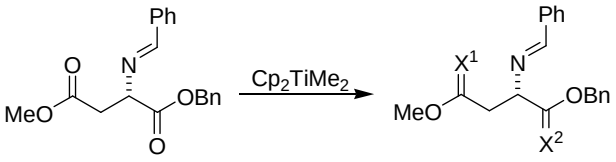
Carbamates **309a-d** could then be deprotected and reacted with benzaldehyde to give the imino-ester substrates for methylenation and cyclization (Scheme 117). In early trials the deprotection and imine formation were performed as two distinct steps. However, due to the polar nature of the free amines, excess TFA could not be washed out with water and removing it all under reduced pressure to leave the salt was time consuming. This problem was solved by concentrating the deprotection reaction mixture thoroughly on the rotary evaporator and submitting this directly to the imine formation with an extra equivalent of triethylamine to neutralise any residual TFA. These conditions allowed the synthesis of imino-esters **310a-d** in good to excellent yield.



Scheme 117: Synthesis of imino-ester substrates for methylenation

With a route to a variety of imino-aspartic acid derivatives **310a-d** in hand, their ability to direct methylenation to the desired ester could be assessed.

Benzyl ester substrate **310a** was chosen primarily for its ease of deprotection in conditions very different to those used for cyclization. Unfortunately, as we had feared, the benzyl group was insufficiently sterically different to direct methylenation solely to the methyl ester and mixtures of enol ethers were observed in a very similar fashion to the dimethyl derivative **303** (Scheme 118, Table 7). Again mirroring the dimethyl result, the dienol-ether **313** could not be induced to cyclise.



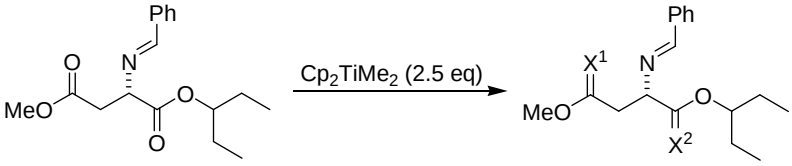
Scheme 118: Methylenation of benzyl ester derivative

Table 7

Eq. Cp_2TiMe_2	Ratio of Products in ^1H NMR			
	310a $X^1=X^2=O$	**311** $X^1=CH_2$, $X^2=O$	**312** $X^1=O$, $X^2=CH_2$	**313** $X^1=X^2=CH_2$
2.2	1.0	0.8	0.7	0.3
4.2	0	0.1	0.3	1.0

A 3-pentyl ester is significantly more sterically hindered than a benzyl ester, although less so than a *tert*-butyl ester. Its hydrolysis requires relatively strong conditions,[123] and therefore we hoped it would withstand cyclization conditions involving mild acid, but could still be removed if required. In short, we hoped it would represent a balance between the steric bulk required for methylenation selectivity and the steric bulk impeding hydrolysis to reveal the acid group. Unfortunately, while more selective than

benzyl derivative **310a**, significant quantities of the undesired methylenation product were also observed in the reaction with the 3-pentyl ester derivative **310b** (Scheme 119, Table 8). The selectivity was not good enough to be useful in our synthesis of pipecolic acids.



310b **314-316**

Scheme 119: Methylenation of 3-pentanol ester derivative

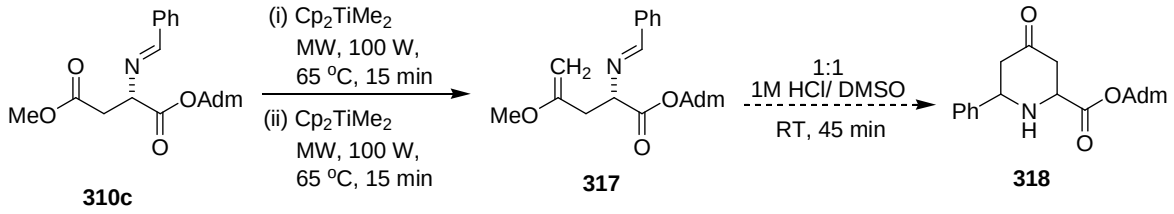
Table 8

Ratio of Products in ^{1}H NMR			
310b $X^1=X^2=O$	**314** $X^1=CH_2$, $X^2=O$	**315** $X^1=O$, $X^2=CH_2$	**316** $X^1=X^2=CH_2$
0.6	1.0	0.2	0.4

While an adamantyl ester does not fulfil the criteria of a masked acid, as it is not trivial to remove, we felt it was an interesting substrate as it should provide the same steric blocking as the *tert*-butyl ester, but should be completely stable to the cyclization conditions. We hoped this would give us some insight into whether generation of the free acid before cyclization was the reason for the loss of diastereoselectivity in the tert-butyl ester example.

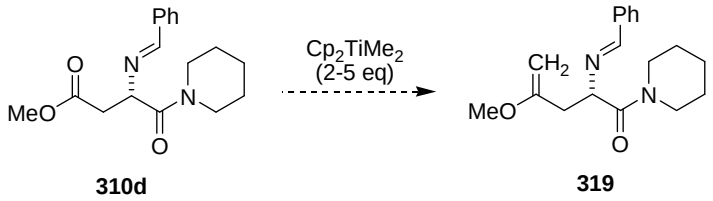
Both adamantanol ester intermediates **309c** and **310c** proved difficult substrates to work with. Deprotection/imine synthesis was often low yielding; we later discovered that, surprisingly, β-adamantyl aspartic esters are quite labile in TFA implying that our α-derivative **309c** may also be so.[124] The methylenation step was also not straightforward, early attempts with the usual 2-2.5 equivalents of the Petasis reagent gave incomplete conversion, although were completely selective for the desired ester (Scheme 120). Two successive runs in the microwave were required to consume all starting material, again with complete ester selectivity. An attempt to cyclize imino-enol ether **317** in mild acid gave impure material after chromatography. Although too impure for definitive identification the ^{1}H NMR spectrum of the major components was comparable to that seen for the mixture of *tert*-butyl analogues **295** observed in the same cyclization conditions (Scheme 103), showing the expected peaks for H-3_{eq+ax} and H-5_{eq+ax} in the 2.0-2.2 ppm and for H-2 and H-6 in the 3.9-4.1 ppm regions of the spectrum. This suggested the presence of cyclized piperidinone **318** as a mixture of

diastereomers and, in combination with previous results, implies that formation of free acid is not responsible for the loss of stereochemistry.



Scheme 120: Methylenation and cyclization of adamantanol ester derivative

As mentioned previously, selectivity in the amide derivative **310d** is based on electronics rather than sterics. As amides are less electrophilic than esters the nucleophilic titanium carbenoid should preferentially react with the ester first. Frustratingly, despite many attempts varying reagent equivalence and reaction time, only complex mixtures were isolated from the methylenation reaction (Scheme 121).



Scheme 121: Attempted methylenation of amide derivative

We felt that our investigation into the use of different carboxylic acid derivatives to direct methylenation had shown that this was not a suitable route for the synthesis of pipecolic acids. However, we thought that the strategy of blocking one carbonyl group of aspartic was still a good one, for this reason we began to look at protection of the amino group.

5.4.1 A Note on Enol Ether Analysis

Due to the unstable nature of enol ethers, it was not possible to separate and analyse the mixtures described above. The components of the mixtures therefore had to be identified by a number of other factors. Commonly the number of imine C-H peaks in the ^{1}H NMR spectrum (8.2-8.7 ppm) gave the number of products obtained in the reaction, with their relative integrations giving the product ratio. The enol ether methylene signals often overlapped in the 3.9-4.1 ppm region and therefore were less useful. Comparison of the post-methylenation chemical shift of enol ether imine peaks with known products, combined with the expected major product based on the previously demonstrated effect of sterics on ester methylenation allowed the identity of

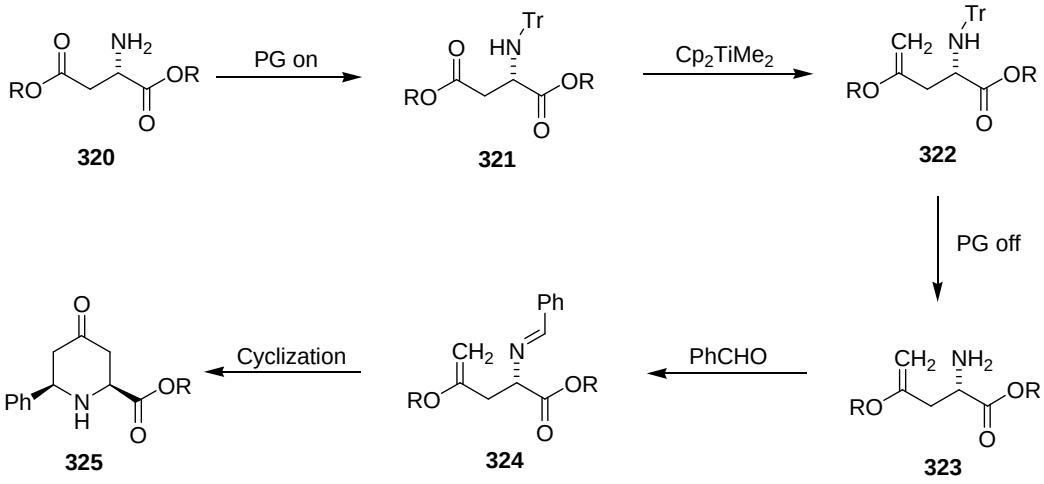
the various products to be inferred. The assignment was corroborated with the observed ratio of combined intergration of the imine C-H peaks to the combined intergration of the enol ether methylene groups.

5.5 Amine Protection

5.5.1 Trityl Protection

The idea for the amine protection strategy came about through discussion with a colleague in the lab, Lindsay Fowler. She had been struggling to hydrolyse an aspartic acid ester adjacent to a trityl group. We hoped that if its size was great enough to interfere with hydrolysis, it may also sterically block the site to methylenation.

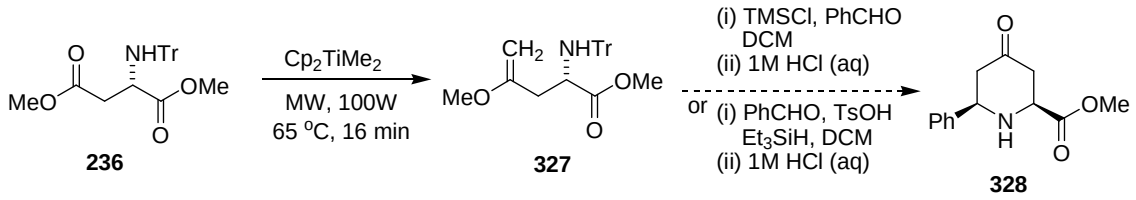
On the basis of this we designed our amine protection strategy for the synthesis of pipecolic acid derivatives (Scheme 122). We intended to synthesise the trityl aspartic acid diester **321**, which would hopefully be selectively methylenated on the desired carbonyl group to give enol ether **322**. The trityl group could then be removed giving free amine **323**, from which imine **324** could be made and subsequently cyclized to protected pipecolic acid **325**. This route represented a departure from all previous routes in that the imine would be formed after methylenation had taken place.



Scheme 122: Proposed synthesis of pipecolic acid derivatives using amine protection

The first, and most important, task was to find out whether the trityl group did indeed induce the desired selectivity. Pleasingly, reaction of trityl protected dimethyl aspartate **326** with dimethyltitanocene was completely selective for the β-carbonyl group, giving the mono enol ether **327** with titanium residues as the only impurity after flash chromatography on neutral alumina (Scheme 123). Rather ambitiously we

attempted a one pot deprotection / imine formation / cyclization, unfortunately this was unsuccessful. In both the conditions shown the reason for the failure was that the molecule was not deprotected in the first step.

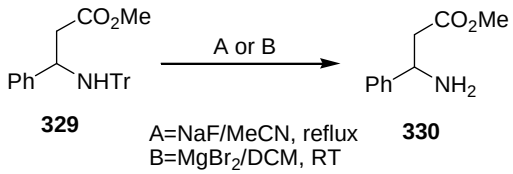


236 **327** **328**

Scheme 123: Selective methylenation of trityl protected diester

Trityl deprotection is commonly performed in acidic conditions such as TFA,[125] HCl[126] or *p*-toluenesufonic acid.[127] We had already found that *p*-toluenesufonic acid was unsuitable for the deprotection of **327** and we felt that the other acidic conditions would be too harsh for the enol ether to survive. For these reasons we looked to less common and milder methods of trityl cleavage.

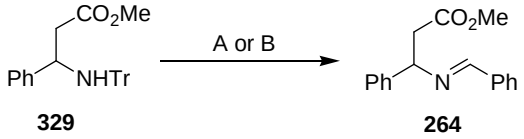
A brief literature search showed that trityl groups can also be removed using many inorganic salts including NaF[128] and $MgBr_2$.[129] We tested the effectiveness of these reagents on a model substrate, trityl protected β-amino acid **329** (Scheme 124).



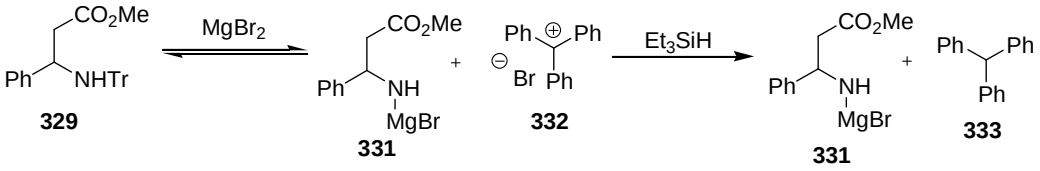
329 **330**

Scheme 124: Trityl deprotection using model system

While NaF was completely ineffective, $MgBr_2$ gave 60% deprotection after 18 h following an aqueous work up. To investigate whether the deprotection could be combined with imine formation in one step the successful reaction was repeated, this time with the addition of benzaldehyde (Scheme 125). This was also successful, however only 60% conversion to the imine product **264** was observed, the remaining material being protected amine **329**. This could have been due to the deprotection with $MgBr_2$ being an equilibrium process (Scheme 126). With this in mind, the reaction was repeated with the addition of triethylsilane giving the desired imine **264** as the major product.

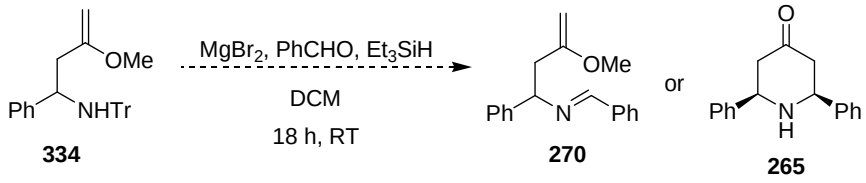


Scheme 125: One-pot deprotection and imine formation

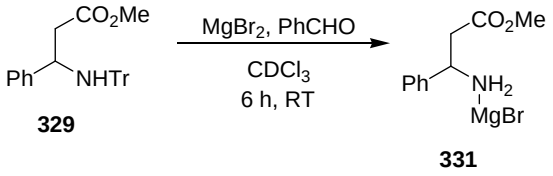


Scheme 126: Rationale for addition of triethylsilane to drive the reaction

Following the optimisation of mild trityl deprotection conditions on the model compound, we tried to apply these to enol ether containing substrate **334** (Scheme 127). We hoped that, due to the Lewis acidic $MgBr_2$, the cyclization might also occur after the imine formation. Unfortunately this was not the case, only decomposition of the starting material was observed. Carrying out the experiment without triethylsilane in a deuterated solvent in an effort to allow the imine formation to be easily followed by ^1H NMR spectroscopy highlighted an important issue (Scheme 128). It appeared that trityl deprotection and imine formation did not occur concertedly, in fact we propose that the product is magnesium-amine complex **331**. This is broken up on aqueous work up, and the imine was formed on concentration of the organic extracts.



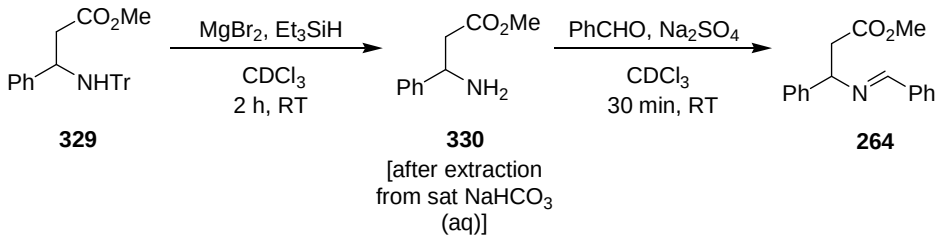
Scheme 127: Attempted one-pot deprotection / cyclization



Scheme 128: Attempted deprotection / imine formation in NMR tube

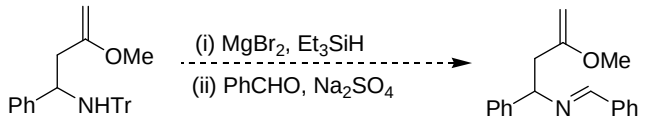
Repeating this experiment confirmed that the inclusion of an aqueous wash was necessary to form the imine after trityl deprotection had occurred (Scheme 129). With this in mind, we submitted the enol ether bearing substrate **334** to our modified conditions (Scheme 130). Sadly, the compound did not appear to be stable under these conditions and no product was isolated. As potential by-products are likely to be

volatile and/or water soluble it was unclear specifically what the substrate **334** was intolerant to.



329 **330** [after extraction from sat $NaHCO_3$ (aq)] **264**

Scheme 129: Inclusion of aqueous wash allows imine formation



334 **270**

Scheme 130: Attempted imine formation on enol ether bearing substrate

While the trityl protection route was ultimately unsuccessful, we felt that the amine protection approach was still a good one. We hoped that if we could find an amine protecting group that could both direct methylenation and be removed under mild conditions then the pipecolic acid derivatives could be synthesised using this methodology. For this reason we turned our attention to silyl protection.

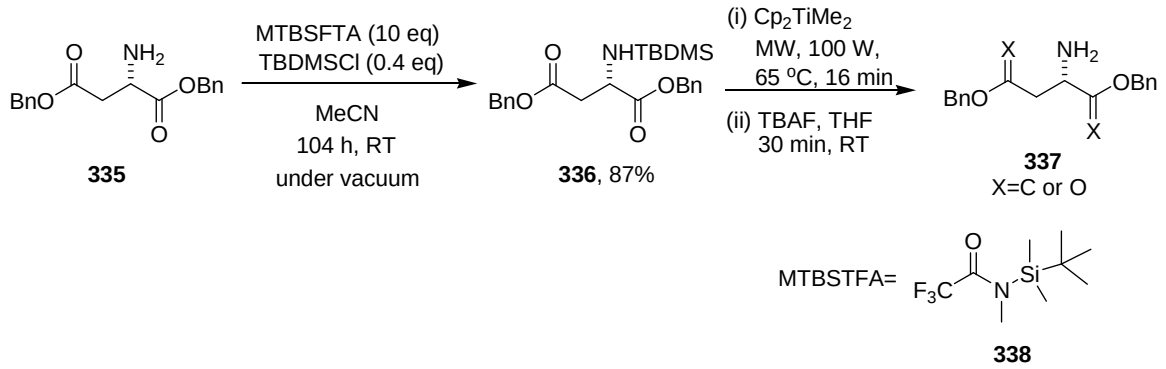
5.5.2 Silyl Protection

Silylamines are not commonly used as amine protecting groups due to their high sensitivity to both acid and moisture.[130] As we had previously found the cleavage of trityl protected amines without destruction of other sensitive functionality challenging, it was the highly labile nature of silyl amines that attracted us to them as an alternative.

For the first attempt we switched from dimethyl aspartate **302** to the corresponding dibenzyl ester **335**. There were several reasons for this, firstly we felt that the small and polar nature of **302** limited our ability to isolate products from the reaction as they had the potential to be volatile or water soluble. Also the silylation procedure for the dibenzyl ester **335** described in the literature was carried out under vacuum, conditions with which the low molecular weight **302** was unlikely to be compatible.[131] The silylation reaction was carried out as described by Baldwin and co-workers, however we found that the reaction did not proceed to completion in the described time and more time and reagent equivalents were required (Scheme 131). This was possibly due to a

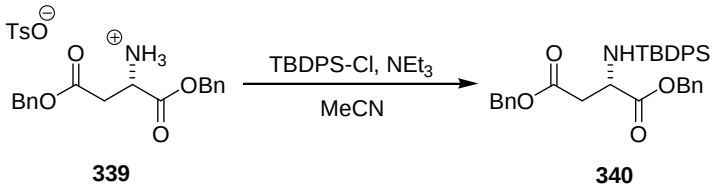
more effective vacuum removing N-tert-Butyldimethylsilyl-N-methyltrifluoroacetamide **338** (MTBSTFA) and *tert*-butyldimethylsilylchloride (TBDMSCl) before reaction could occur. The silyl protected amine **336** was submitted to the Petasis methylenation conditions, unfortunately it was insufficiently large to direct methylenation and a complex mixture of enol ether regioisomers was obtained.

Despite the failure of this initial test, the results were promising and a lot of information about handling of the silylamines was gained. Importantly, they were stable to the methylenation conditions. In fact, they were more stable than initially presumed, requiring fluoride for their removal rather just than aqueous base. Finally it was found that the deprotected amino-enol ether could be purified by flash chromatography on basic alumina.



Scheme 131: First attempt at silyl directed methylenation

To increase the steric bulk of the silyl group we turned our attention to the larger TBDPS amines. As with TBDMS amines the first issue was the silyl protection reaction (Scheme 132). Warner and co-workers had reported some success using TBDPS-Cl,[132] but, as they had seen in some cases, the reaction was very slow. The addition of silver nitrate successfully drove the reaction to completion through precipitation of insoluble silver chloride allowing the *tert*-butyldiphenylsilyl (TBDPS) amine **340** to be synthesised.



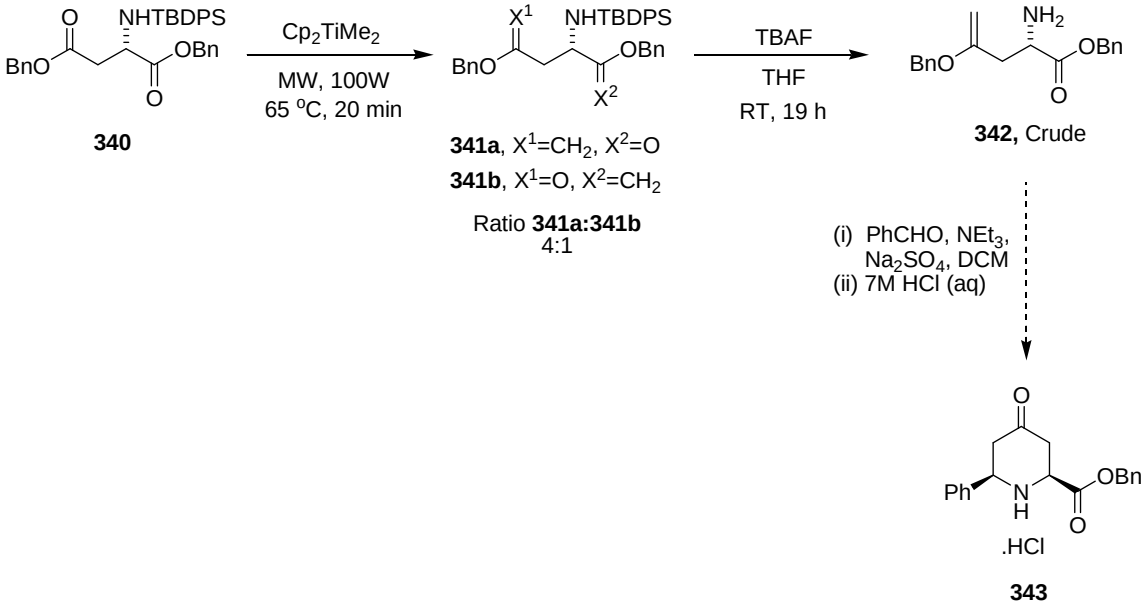
339 **340**

Scheme 132: Optimisation of TBDPS amine synthesis

Table 9

Entry	Additive	Conditions	Result
1	None	RT, 5 h	No reaction
2	None	Reflux, 19 h	20% conversion
3	$AgNO_3$	RT, 19 h, dark	Complete conversion, 80% yield.

The larger silyl group was indeed better at directing methylenation to the desired ester, giving product **341a** in a 4:1 ratio with undesired enol ether **341b** (Scheme 133), although this proved to be variable, with a ratio of 2:1 being observed in one case. As might be expected, removal of the TBDPS group was more difficult than TBDMS, requiring an increased of the reaction time from 30 min to 19 h. Due to the labile nature of the enol ether purification of amine **342** was limited to flash chromatography. This gave the amine **342** with silyl fluoride and other non-product related impurities. For this reason it was not possible to obtain an accurate yield for the reaction, though it was clear that it was significantly below 100%. Subsequent imine formation appeared successful, but upon submission to cyclization conditions no piperidinone product **343** was observed.



340

341a, $X^1=CH_2$, $X^2=O$

341b, $X^1=O$, $X^2=CH_2$

Ratio **341a:341b** 4:1

342, Crude

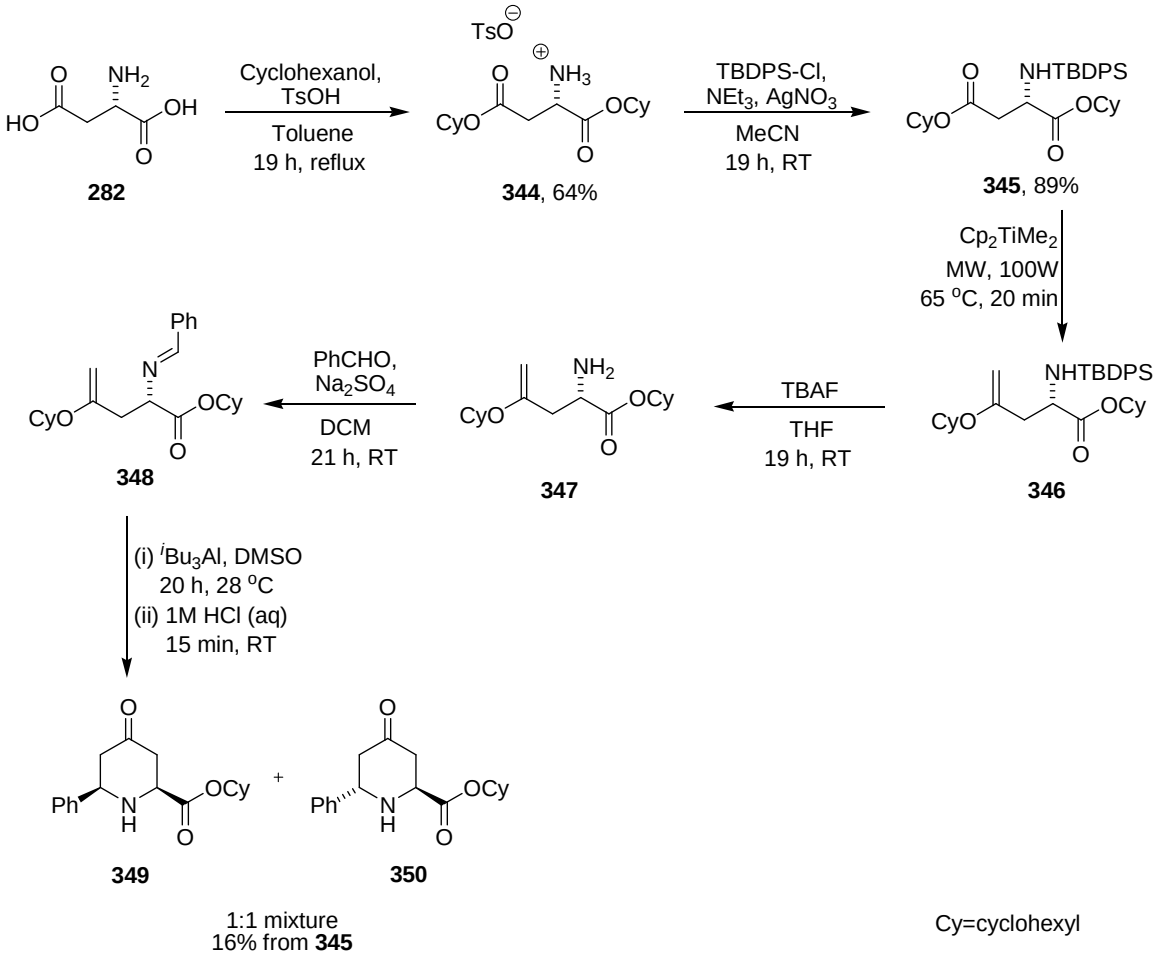
343

Scheme 133: Attempted synthesis of benzyl protected pipecolic acid derivative

At this point we faced a difficult decision due to the fact that the project was to end in three weeks time. The route shown in Scheme 133 certainly had potential, but faced a number of problems. Methylenation was not as selective as we would have liked and the selectivity was not robust, seemingly sensitive to small changes in reaction condition. Also, we were concerned that material was being lost in the silyl deprotection step, possibly due to cleavage of a benzyl group as had been observed on α-amino benzyl esters by Gawas et al.[133] We could either persevere with this route or try to solve these problems by beginning another.

We decided to change the benzyl ester to one derived from cyclohexanol, hoping that this would address the methylenation selectivity issue due to the fact that cyclohexyl has a much large steric footprint than that of a benzyl group and could help further differentiate between the two ester groups. Also, because fluoride attack would have to take place on a 2^o centre, the cleavage in TBAF was likely to be much slower.

Starting from aspartic acid **282**, dicyclohexyl aspartate **344** was synthesised in a modification of the procedure described by Wu and co-workers (Scheme 134).[134] This could then be silyl protected by the previously optimised conditions to give silylamine **345**. The methylenation reaction gave the desired enol ether **346** with about 10% unreacted starting material and hints of other enol ethers as minor impurities. As before comprehensive purification of enol ether bearing intermediates was not attempted to avoid decomposition. Consequently amine **347** and imine **348** were not isolated, but were clearly visible in the crude ^{1}H NMR spectrum for which data is provided in the experimental section. Imino-enol ether **348** was cyclized under Lewis acidic conditions and gave the desired protected pipecolic acid derivatives **349** and **350** in 16% yield from the protected amine **345** and 10% from aspartic acid. The derivatives were generated as a 1:1 mixture of diastereoisomers, one of which, proposed to be the *syn* isomer **349**, was isolated after further purification. The *syn* relationship was confirmed by NOESY and coupling constant analysis. Measurement of the optical rotation showed that the product retained some enantiomeric purity, presumably at the amino acid derived centre.



Scheme 134: Synthesis of protected pipecolic acid dervivative

The lack of diastereoselectivity shows that, whether or not a free carboxylic acid is detrimental to selectivity, it is certainly not the only reason. One possibility is that the presence of a carboxylic acid derivative at the 2-position results in an intramolecular electronic stabilisation effect of the pre-hydrolysis oxonium intermediate **351**, best illustrated by resonance form A (Figure 13). The presence of the sp^2 carbon atom of the carbonyl group at the 4-position of the piperidinones removes the possibility of 2,4 and 4,6-diaxial interactions so diaxial steric repulsions are relatively weak and the energetic gains from the intramolecular interaction in intermediate **351** are potentially of the same magnitude of those gained by having all large groups in an equatorial position in intermediate **352**. The overall result of this would be mixtures of 2,6-*syn* and 2,6-*anti* compounds. Use of a Lewis acid with two coordination sites might result in the formation of chelated intermediate **353**, circumventing the problem and improving diastereomeric purity.

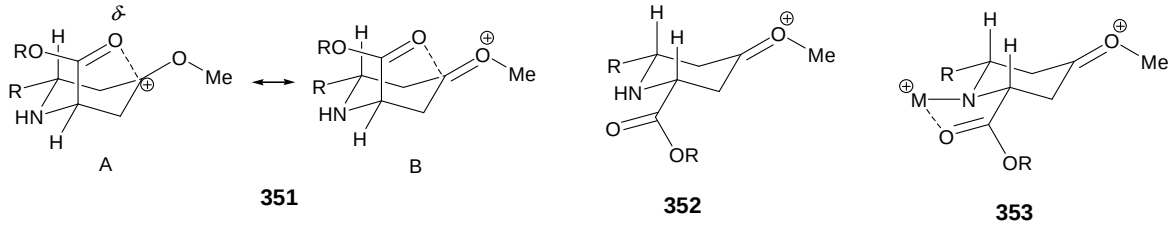
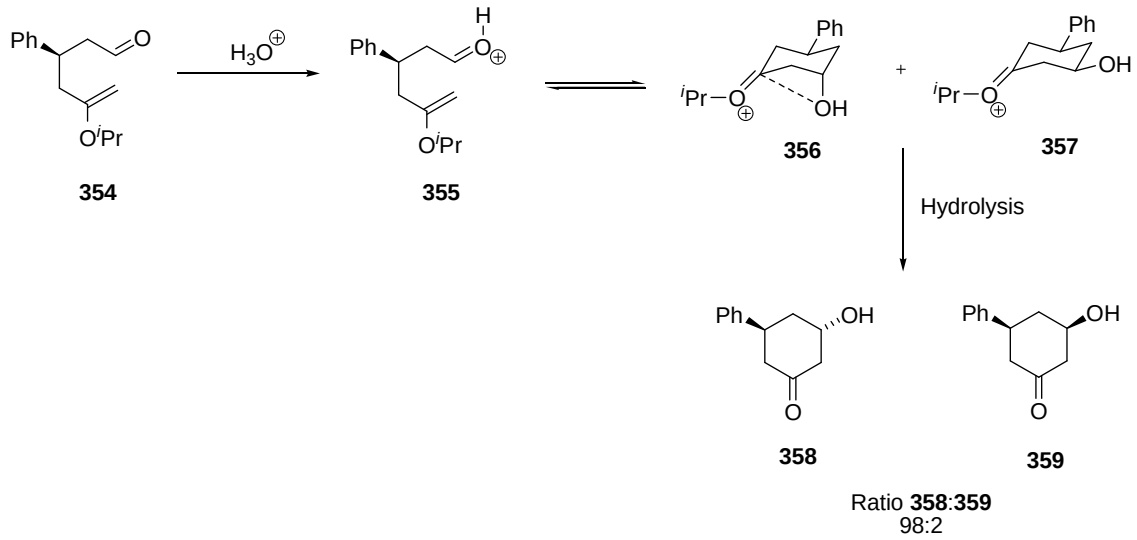


Figure 13: Comparison of proposed oxonium intermdiates

There is precedent for a similar process reported by Hartley and co-workers (Scheme 135).[135] Intramolecular aldol reaction of aldehyde **354** gave predominantly the 3,5-*anti* cyclohexanone **358**. They explained the selectivity by proposing an analogous intramolecular interaction between the hydroxyl group and the carbon of the oxonium ion in intermediate **356**. Indeed, theoretical calculations showed that the precursor to 3,5-*anti* product **358**, intermediate **356**, was energetically favoured over intermediate **357** that would give the 3,5-*syn* product **359** following hydrolysis.



Scheme 135: Precedent for the influence of intramolecular interreactions on diastereoselectivity of 6-membered ring formation

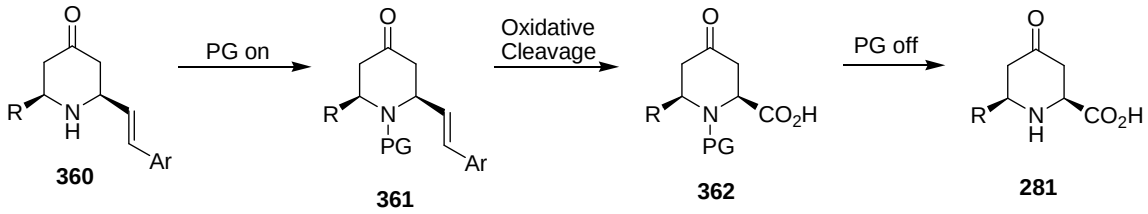
5.5.3 Conclusion

The successful synthesis of a pipecolic acid derivative demonstrated the viability of the amine protection approach. Unfortunately, as my PhD was coming to an end, there was insufficient time to optimise the process further. Future work will begin with investigation of the methylenation / deprotection / imine formation steps to try and discover where material is being lost. Also screening the cyclization in some of our other conditions, or with alternative Lewis acids may improve the diastereoselectivity.

5.6 Diastereoselective Route to Pipecolic Acid Derivatives

As the cyclization of ester-bearing imino-enol ethers was proving difficult the alternative approach of adding the acid functionality after cyclization had taken place was also considered (Scheme 136). Racemic, but diasteromerically pure, 2,6-*syn* piperidinones **360** derived from a β-amino acid and α,β-unsaturated aldehydes were chosen as a starting point. The synthesis of similar compounds had previously been reported within the Hartley group.[87] Following protection of the amine, an oxidative cleavage reaction would reveal the acid moiety **362**. Deprotection would then give the desired pipecolic acid derivative **281**.

This route has the obvious advantages that the diastereoselectivity of the cyclization is known to be high on this class of compound and that only one carbonyl group is present during the methylenation reaction so selectivity is not an issue. Also, successful synthesis of the derivative **281** where R is a phenyl group would aid our analysis of compound **289**. The disadvantages of this route are that racemic products are obtained and that the R group is derived from a β-amino acid rather than an α-amino acid, therefore limiting the product scope.



Scheme 136: Proposed diastereoselective synthesis of pipecolic acidderivative

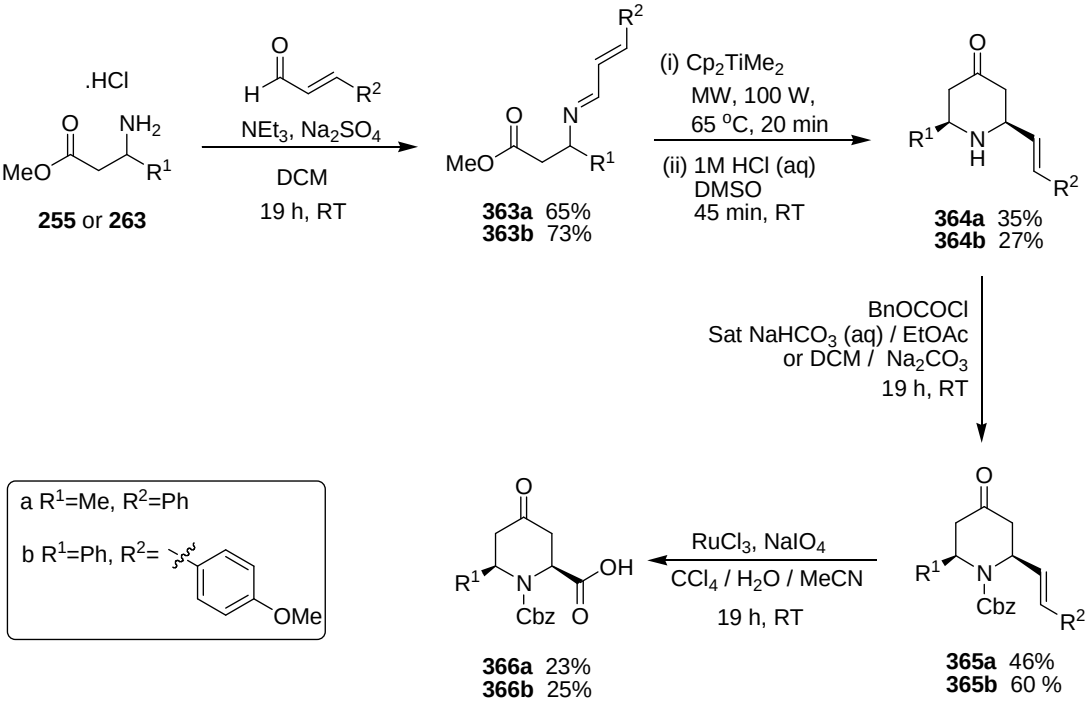
The reaction sequence was tested concurrently on two substrates bearing a methyl or phenyl R^1 group (Scheme 137). Imine formation with an electron rich or slightly electron rich α,β-unsaturated aldehydes proceeded smoothly giving compounds **363a-b**, the only modification from the previously used conditions to make benzaldehyde derived imines was that only one equivalent of the aldehyde was used as they are more difficult to remove by distillation due to their higher boiling point.

Methylenation with dimethyltitanocene and cyclization using the newly optimised HCl / DMSO conditions gave the desired 2,6-*syn* piperidinones **364a-b**. Yields were lower than expected, implying that the Lewis acid step cannot be replaced in all systems. Cyclization to give piperidinone **364b** was also attempted in TFA / DCM, but this was not successful.

Cbz was chosen as the protecting group as it had been reported to be stable to the subsequent oxidative cleavage conditions[136] and could also be easily removed in reaction conditions from which the amino acid product would be easily isolable. The moderate yield was likely to be due the sterically hindered position of the 2° amine nucleophile. In fact, the steric hindrance in the phenyl derivative **365b** was sufficiently large for the compound to show rotamers due to restricted rotation around the carbamate nitrogen-carbon bond in the ^{1}H NMR spectrum at ambient temperature. In both protected piperdinones **365a** and **365b** the preferred conformation appeared to have both 2,6 substituents in the axial position as has been observed for similar compounds.[137]

Oxidative cleavage using the procedure described by Chen and co-workers[136] gave the desired acid products **366a-b**, but in low yield and purity in both cases. Some aldehyde peaks were observed in the ^{1}H NMR spectrum of the crude material, implying that under oxidation may have been an issue.

Due to the unexpectedly low yields of some of the reactions, and the scale limiting effect of the microwave, the quantity of protected amino acids **366a-b** was very low. This was probably the major factor in our lack of success in isolating any deprotected material following hydrogenation.



Scheme 137: Diastereoselectivity synthesis of protected pipecolic acid dervivatives

Due to time constraints and the breakdown of microwave equipment it was not possible to repeat and optimise this synthesis. Increased yields could certainly be achieved for

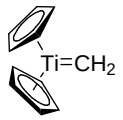
both the cyclization and protection steps, and there are other options (e.g. ozonolysis) if the oxidative cleavage reaction remained problematic. In any case, scheme 137 demonstrates that diastereomerically pure pipecolic acid derivatives can be made by this method.

5.7 Conclusions

After an initial success followed by extensive optimisation, a route to enantiomerically enriched pipecolic acid derivatives was discovered. A route to diastereomerically pure pipecolic acid derivatives was also investigated. Both of these routes successfully generated protected forms of the desired product, but further optimisation is required if they are to be synthetically useful.

6.0 A New Method for the Methylenation of Carbonyl Compounds

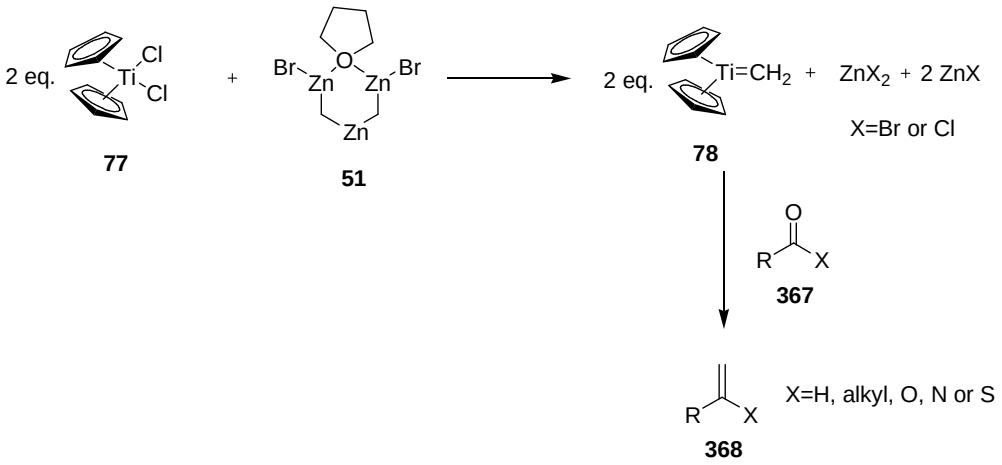
As discussed in chapter 1, there are a number of methods for accessing the titanocene methylidene complex **78** that is proposed to be the active species in carbonyl group methylenation (Figure 14). While effective, they all have the drawback that the reagents used to generate complex **78** must be synthesised before use. Although both the Petasis and Tebbe reagents are commercially available, they are expensive and often do not perform satisfactorily when not prepared in-house.



78

Figure 14: Titanocene methylidene

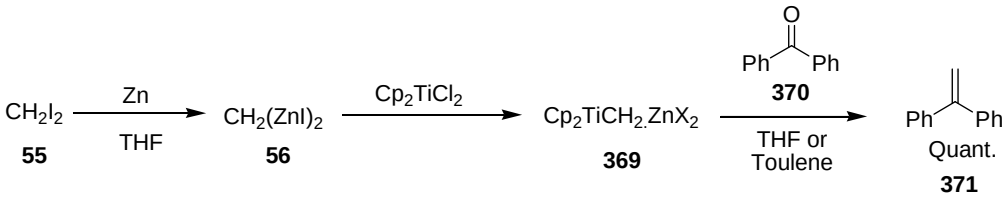
We proposed a novel and simple method for accessing titanium methylidene **78** from titanocene dichloride **77** and the Nysted reagent **51** (Scheme 138). It was hoped that that the Nysted reagent **51**, which is essentially two equivalents of geminal dizinc compound $CH_2(ZnX)_2$, would react with two equivalents of titanocene dichloride **77** to give the two equivalents of titanocene methylidene **78** required for carbonyl methylenation (see Section 1.3.1). The desired carbonyl compound **367** could then be added and methylenation could take place in a simple one-pot procedure.



Scheme 138: Proposed method to access to titanium methylidene

An analogous approach had previously been reported by J. J. Eisch and co-workers (Scheme 139).[138] They synthesised geminal dizinc compound **56** from the reaction of diiodomethane **55** and zinc dust. This then reacted with titanocene dichloride **77** and the reaction mixture then cooled to −78 °C to precipitate a solid, proposed to be the methylidene salt **369** on the basis of ^{1}H NMR spectroscopic evidence. Reaction of

complex **369** with benzophenone **370 (**and other ketones) gave the corresponding alkene **371** in high yield. It was felt that there was more progress to be made in this area for two reasons. Firstly our proposed scheme used commercially available Nysted reagent **51**, and was therefore potentially carried out far more conveniently. More importantly, Eisch and co-workers did not attempt the more interesting methylenation of carboxylic acid derivatives.

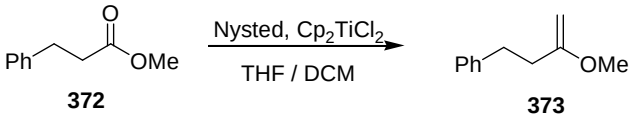


Scheme 139: Analogous approach reported by Eisch and co-workers

As has been discussed earlier, the Nysted reagent **51** is effective in the methylenation of aldehydes and ketones in the presence of a Lewis acid. It is important to note that the methylenation of carboxylic acid derivatives using the Nysted reagent **51** has not been reported in the literature. In fact, there are numerous examples of aldehyde and ketone methylenation in the presence of esters under these conditions (see Section 1.2). The proposed conditions should have broader substrate scope including carboxylic acid derivatives such as esters, lactones, thioesters and amides in line with other titanium-based methylenating agents.

6.1 Initial Trials and Optimisation

It was proposed that the reaction of the Nysted reagent **51** and titanocene dichloride **77**, would result in the in-situ generation of titanium methylidene **78** which could then be used to methylenate carbonyl compounds (Scheme 138). To eliminate any potential ambiguity between the methylenation of aldehydes and ketones using the Nysted reagent and our proposed method, the reaction conditions were initially tested on an ester substrate **372** (Scheme 140, Table 10). Along with varying the temperature (entries 1 and 2), pre-forming the reagent before the substrate was added was investigated (entry 3). There was certainly some reaction during this pre-formation by inspection, as the pale red suspension became a dark red-black solution on heating to 45 ºC. Despite these variations none of the early ester attempts were successful.

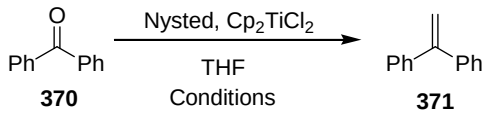


Scheme 140: First attempt at ester methylenation

Table 10

Entry	Eq. Nysted	Eq. Cp_2TlCl_2	Conditions	Pre-formed	Result
1	1	2	0 °C to RT, 2 h	No	No reaction
2	1	2	−78 °C to RT 2.5 h	No	No reaction
3	1	2	Reflux, 3 h	Yes	No reaction

As Eisch and co-workers had had success with their analogous approach, inspiration was taken from their procedure (Scheme 141, Table 11). This was only possible in the broadest sense, as no experimental proceedure was provided, and cumulated in the removal of the DCM co-solvent and the use of benzophenone **370** as a test substrate. Encouragingly, our first attempt gave complete conversion to the methylenated product **371** (entry 1). Altering the reaction stoichiometry to a 1:1 ratio of Nysted reagent **51** to titanocene dichloride **77** decreased the effectiveness of the reaction, confirming that, like the Petasis reagent, two equivalents of active species are required (entry 2). While this result was satisfying, the real challenge was to apply the reaction to esters.



Scheme 141: Methylenation of benzophenone

Table 11

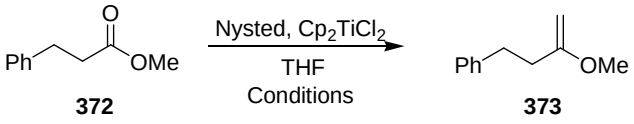
Entry	Eq. Nysted	Eq. Cp_2TlCl_2	Conditions	Pre-formed	Result
1	1	2	RT, 2.5 h	Yes	100% conversion
2	1	1	RT, 2.5 h	Yes	30 % conversion

Methyl 3-phenylpropionate **372** was selected as a test substrate for the ester methylenation reaction due to its low cost and ease of analysis (Scheme 142, Table 12). When submitted to the conditions that had successfully methylenated benzophenone **370** no reaction was observed (entry 1). Repeating the reaction in refluxing THF gave the desired enol ether **373** in a 1:1 ratio with the starting material and some minor impurities (entry 2). Following this successful result a range of different reagent stoichiometries and reaction times were trialled. Repeating our successful result with a

longer reaction time gave increased conversion to product, but at the expense of the generation of significant impurities (entry 3). It was postulated that these side products arose due to Claisen type reactions between the product **373** and unreacted starting material **372**. Leaving the reaction longer than 24 h did increase the product to starting material ratio, but the side reaction continued to generate more impurities. A study into reagent stoichiometry indicated to that a 2:1 ratio of titanocene dichloride **77** to Nysted reagent **51** was indeed optimal (entries 4-6). It was possible to push the reaction to completion by doubling the reagent equivalents (entry 7), but not without the significant generation of impurities.

The effect of various additives on the reaction was also investigated. Lewis bases (entries 8 and 9) were added in the hope that they might attenuate the Lewis acidity of the zinc present and suppress the formation of side products. However, while the reaction still occurred with these additives, the generation of impurities was unaffected. Addition of a Lewis acid (entry 10) suppressed the reaction almost entirely. This was surprising as the addition of Lewis acids has been shown to enhance the reactivity of the Nysted reagent towards aldehydes and ketones (see Section 1.2). To confirm that the Nysted reagent alone was not inducing methylenation a control experiment was performed (entry 11), showing that, without the prescence of titanocene dichloride, no reaction takes place.

The use of additives to the reaction mixture had failed to stop the side reactions, however another option was to increase the rate of the reaction and force it to completion quickly. This would decrease the opportunity for reaction between starting material and product by limiting the time they co-existed in any great concentration. Moderately high boiling THF was switched for high boiling toluene giving a slight increase in conversion, but with the impurity problem still an issue (entry 12). Our previous experiences with the methylenation of β-amino acid dervivatives using the Petasis reagent under microwave irradiation showed drastically reduced reaction times compared to those carried out thermally. This led us to consider the use of the microwave in our reaction. Pleasingly, with a reaction time of just 20 minutes, almost complete conversion to the enol ether **373** was observed with the generation of only minor impurities (entry 13).



372 **373**

Scheme 142: Successful methylenation of ester and stoichiometry study

Table 12

Entry	Eq. Nysted	Eq. Cp_2TICl_2	Conditions	Ratio 372:373 in crude ^1H NMR	Side Products
1	1	2	RT, 4 h	No reaction	No
2	1	2	reflux, 19 h	50:50	Minor
3	1	2	reflux, 24 h	33:66	Significant
4	4	2	reflux, 5 h	82:18	Minor
5	2	2	reflux, 19 h	23:76	Significant
6	1	4	reflux, 22 h	91:9	No
7	2	4	reflux, 22 h	0:100	Significant
8	1	2	reflux, 24 h, Pyridine (2 eq.)	57:43	Significant
9	1	2	reflux, 24 h, PPh_3 (2 eq.)	55:45	Significant
10	1	2	RT, 19 h, $^iBu_3Al$ (0.3 eq.)	95:5	No
11	2	0	reflux, 19 h	No reaction	No
12	1	2	reflux, 24 h[a]	26:74	Significant
13	1	2	Microwave, 80 °C, 20 min	17:83	Minor

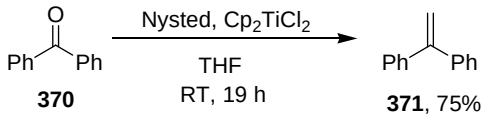
[a]Reaction carried out in toluene instead of THF

With the successful use of the microwave for ester methylenation, optimised conditions for both the methylenation of both aldehydes and ketones, and for carboxylic esters were now in hand. Our next goal was to use these conditions to generate a library of methylenated products to investigate the substrate scope of our procedure.

6.2 Aldehydes and Ketones

The first substrate used was the compound on which the intial positive result was observed, benzophenone **370** (Scheme 143). Using the optimised 2:1 titanocene dichloride to Nysted reagent ratio and pre-forming the reagent at 45 °C for 30 min before use, methylenation of benzophenone **370** occurred in 19 h at RT giving the

alkene product **371** in good yield. The procedure was then applied to electronically different aldehydes and ketones.

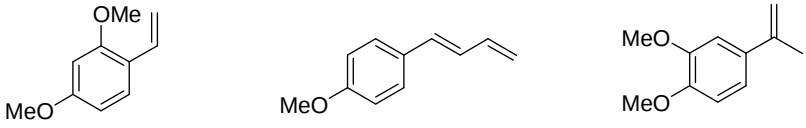


370 **371**, 75%

Scheme 143: Methylenation of benzophenone

6.2.1 Electron Rich Aldehydes and Ketones

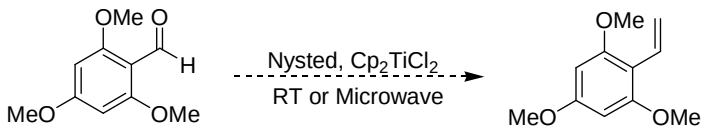
As the proposed titanium methylidene active species **78** is nucleophilic, methylenation of electron rich aldehydes and ketones should be relatively difficult. However, a number of electron rich substrates were methylenated smoothly and quickly at RT to give a range of alkenes (Figure 15). This included alkene **374**, derived from a sterically hindered and very electron rich 2,4-dimethoxybenzaldehyde and diene **375**, from an α,β-unsaturated aldehyde, 4-methoxycinnamaldehyde. As might be expected, ketone methylenation was slightly slower, with generation of alkene **376** requiring a reaction time of 5 hours to completely consume the starting material. As use of the microwave had been found to be advantageous with esters, giving shortened reaction times, these conditions were trialled with aldehyde and ketone substrates. However, they were found to be too harsh and resulted in decomposition.



374, 63% (RT, 2 h) **375**, 86% (RT, 3 h) **376**, 77% (RT, 5 h)

Figure 15: Products from the methylenation of electon rich aldehydes and ketones

The limit of the substrate scope was also investigated (Scheme 144). Extremely electron rich and sterically hindered aldehyde **377** was consumed in the reaction conditions, but a complex mixture of products that showed no alkene signals in the ^{1}H NMR spectrum was obtained under both thermal conditions and microwave irradiation.

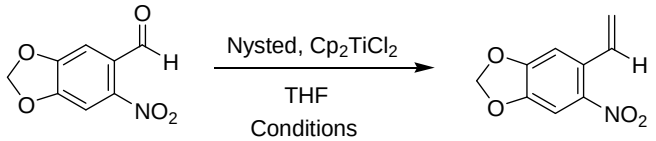


377 **378** Not formed

Scheme 144: Attempted methylenation of extremely hindered substrate

6.2.2 Electron Poor Aldehydes and Ketones

The more electrophilic electron poor aldehydes and ketones were expected to be more reactive than the electron rich substrates. This proved to be the case, nitro aldehyde **379** quickly reacted to form alkene product **380**, but with a significant amount of unidentified impurity (Scheme 145, Table 13, entry 1). In an attempt to slow the reaction and prevent or limit generation of side products, it was repeated at lower temperatures. By cooling the reaction mixture to −10 °C an immediate 19% increase in yield was observed coupled with a drop in the undesirable side reaction (entry 2). Carrying out the reaction at a lower temperature retarded the reaction rate such that complete consumption of the starting material **379** was not observed (entries 3 and 4). When the reaction described in entry 4 was allowed to warm from −78 °C to RT overnight complete consumption was observed, with the generation of side products. The best method was to carry out the reaction at −78 °C and allow it to warm to RT for 20 minutes before quenching. This gave conversion of aldehyde **379** to alkene **380** and isolation of product in high yield, with only small hints of the side product by ^{1}H NMR spectroscopy (entry 5).



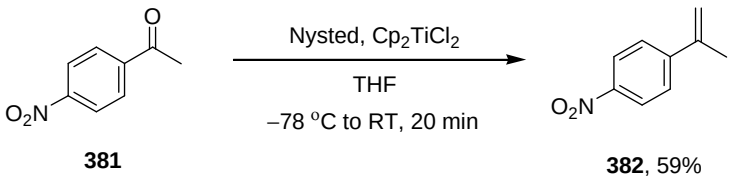
Scheme 145: Optimisation of method for electron poor substrates

Table 13

Entry	Conditions[a]	Yield	Comment
1	RT, 3 h	43%	Impurity accounts for approx. 50% isolated mass
2	−10 °C, 1 h	62%	Impurity accounts for approx. 15% isolated mass
3	−78 °C, 10 h	-	Incomplete reaction
4	−40 °C, 5 h	-	Incomplete reaction
5	−78 °C to RT, 20 min	76%	Hints of impurity in crude reaction mixture

[a] In each reaction the reagent was pre-formed at 40 °C before cooling to the designated temperature after which the substrate was added.

Formation of alkene **382** derived from an electron poor ketone **381** showed similar reactivity, generating impurities at RT and requiring the same cooling as for the formation of alkene **380** to give a reasonable yield of clean product (Scheme 146).

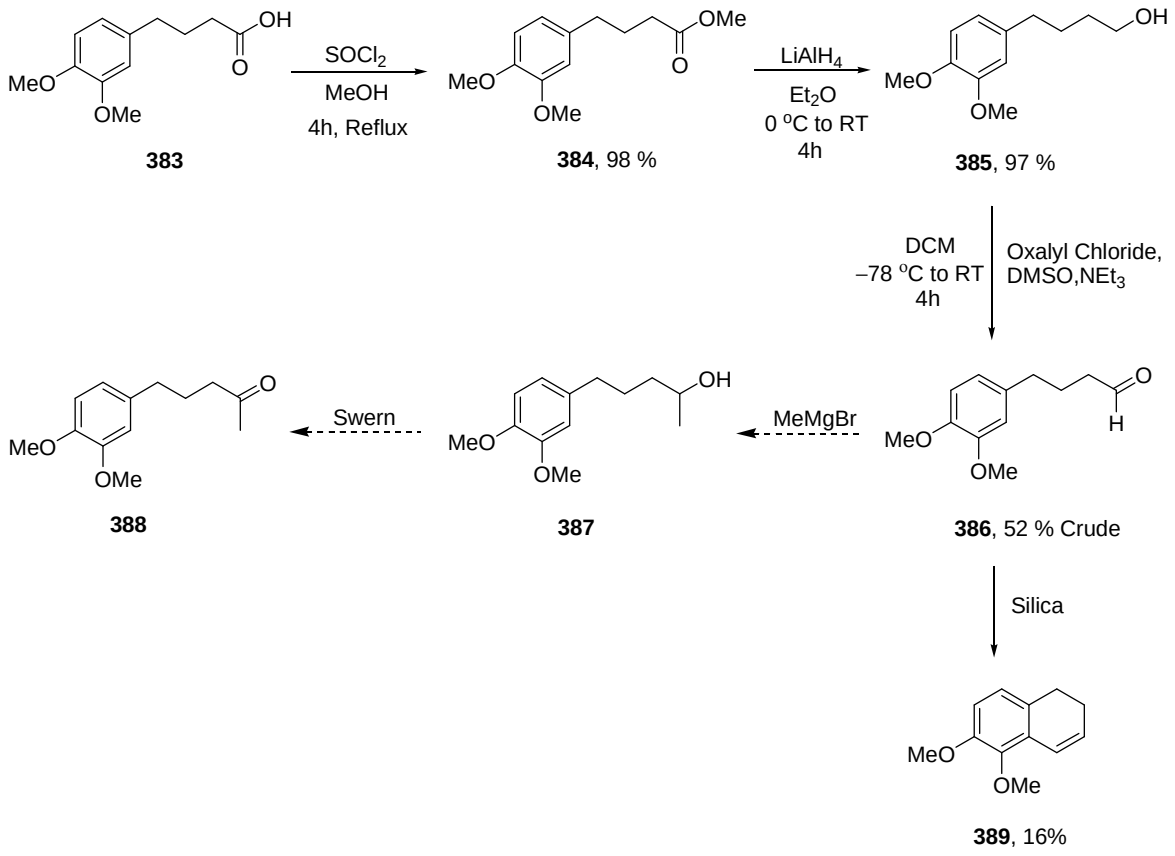


381 **382**, 59%

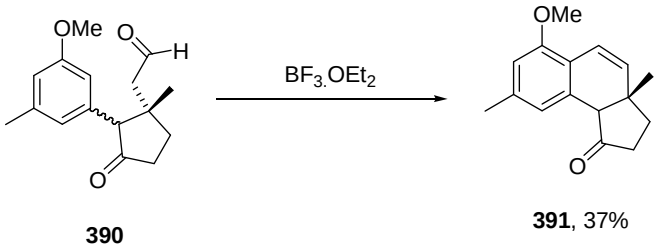
Scheme 146: Methylenation of electon poor ketone

6.2.3 Aliphatic Aldehydes and Ketones

In testing our reaction on aliphatic aldehydes and ketones the first problem was that of substrate choice. For both the aryl electron rich and electron poor substrates a wide range of substituted benzaldehydes and benzoketones were cheaply available. Also, due to the presence of polar groups, they tended to be suitably high boiling. This was not the case for aliphatic substrates, a search of common chemical suppliers revealed that available simple aldehydes and ketones were either prohibitively expensive, contained undesirable extra functionality or were too low boiling for an accurate yield to be obtained following reaction. We therefore decided to synthesise suitable substrates ourselves (Scheme 147). Acid **383** was converted into ester **384** and lithium aluminium hydride reduction gave alcohol **385** in near quantitative yield. Swern oxidation then gave the aldehyde **386** which was intended to be used as a methylenation test substrate. Potentially aldehyde **386** could also be converted to the secondary alcohol **387** and re-oxidised to give the ketone substrate **388**. Unfortuantely, aldehyde **386** was found to be unstable, undergoing a Friedel-Crafts reaction on silica to give alkene **389**. This type of reaction is known to be promoted in both Brønsted[139] and, more importantly, Lewis acidic conditions, for example Taber and Tian utilised it in their synthesis of tricycle **391** from aldehyde **390** (Scheme 148).[140] Due to this unexpected side reaction the synthesis of these substrates was not pursued any further.

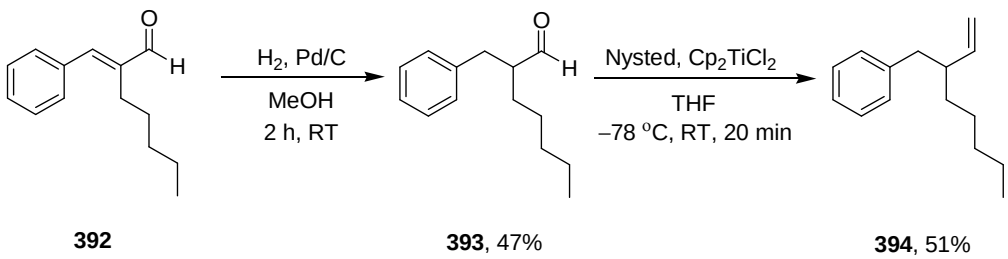


Scheme 147: Attempted synthesis of aliphatic aldehydes and ketones



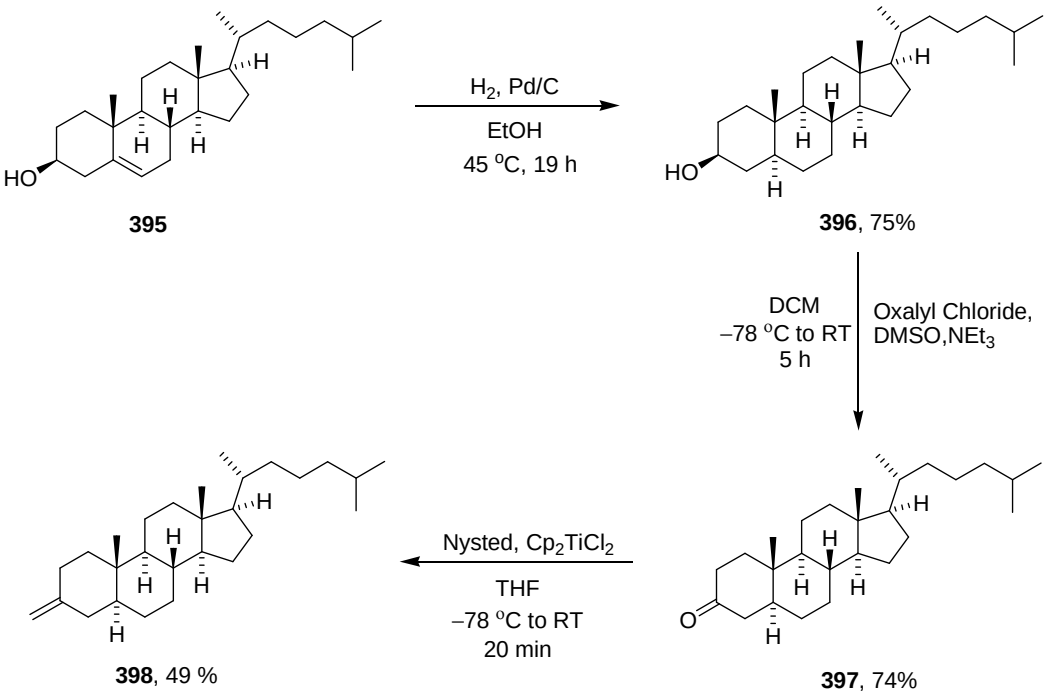
Scheme 148: Intramolecular Friedel-Crafts reaction

Instead aliphatic aldehyde **393** was prepared from the relatively inexpensive α-amylcinnamaldehyde **392** (Scheme 149). The latter was hydrogenated to remove conjugation with the phenyl group giving aldehyde **393**, the low yield in this reaction is due to partial aldehyde reduction. This could then be methylenated with the Nysted - titanocene dichloride mixture to give alkene **394**. The reason for the moderate yield was not clear, performing the reaction at RT gave similar results.



Scheme 149: Synthesis and methylenation of aldehyde substrate

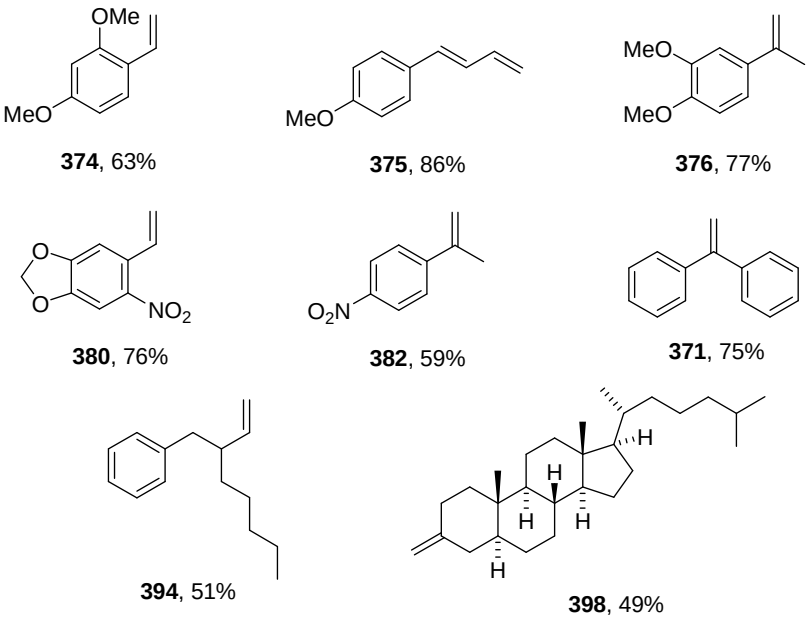
To provide an aliphatic ketone a substrate derived from cholesterol **395** was synthesised (Scheme 150). Hydrogenation of cholesterol **395** gave the expected *trans* product **396**,[141] removal of the double bond was necessary for fear the product of subsequent steps might isomerise to bring it into conjugation with the ketone or alkene. Swern oxidation of alcohol **396** proceeded cleanly to give the aliphatic ketone substrate **397**. Ketone **397** was successfully methylenated at low temperature to give alkene **398**, although in moderate yield. Again, an unidentified impurity accounted for a significant proportion of consumed starting material. Slow addition of the ketone **397** had no effect and lowering the reagent stoichiometry led to incomplete conversion.



Scheme 150: Synthesis and methylenation of ketone substrate

6.2.4 Summary

Through the generation of a small library (Figure 16), we demonstrated the applicability of our reaction conditions to a range of aldehydes and ketones, including electron rich and electon poor aryl substrates, and aliphatic substrates.



374, 63% **375**, 86% **376**, 77%

380, 76% **382**, 59% **371**, 75%

394, 51% **398**, 49%

Figure 16: Summary of methylenated aldehydes and ketones

6.3 Esters and Lactones

While the success in the methylenation of aldehydes and ketones was pleasing, demonstrating the effectiveness of our reaction on carboxylic acid derivatives was more important, as there are fewer reagents that can perform this transformation.

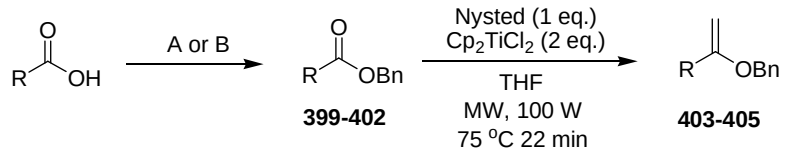
6.3.1 Esters

Optimisation of the reaction on ester substrates had used methyl ester **372**, however, due to the low boiling point of the enol ether product **373**, it was not suitable for isolation and inclusion in the library. Instead, a series of analogous benzyl esters **399**-**402** derived from an electron rich, electron poor and aliphatic acid group were synthesised (Scheme 151, Table 14). These could then be submitted to the optimised methylenation conditions.

Enol ethers are relatively sensitive functional groups that do not tolerate acidic conditions. Work-up and purification methods there had to be carefully chosen to ensure the isolation of the desired products without significant loss of yield due to hydrolysis. The standard procedure was to quench the reaction mixture directly by pouring into a saturated aqueous sodium bicarbonate solution followed by extraction with diethyl ether. The crude material was then purified by column chromatography on neutral alumina that had been deactivated to Brockmann V. Enol ether products tended to be very non-polar, often eluting in neat petroleum ether.

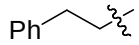
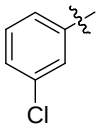
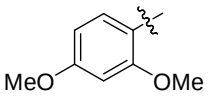
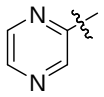
Using this procedure enol ether **403** derived from aliphatic ester **399** was isolated in good yield (Table 15, entry 1). Unfortunately this result was not replicated in aryl substrates **400** and **401**, both of which did undergo methylenation, but in low yield (entries 2 and 3). Pyrazine substrate **402** was not compatible with reaction conditions, giving a complex mixture (entry 4). The crude reaction mixture of all successfully methylenated substrates appeared to contain the desired enol ether as the major product with minor impurities by ^{1}H NMR spectroscopy. These impurities were more pronounced in enol ethers **404** and **405**, but not significant enough to account for the dramatic reduction in yield.

We considered that over reaction might be a problem. However, when the methylenation of ester **401** was repeated with a shorter reaction time at slightly lower temperature (65 °C, 12 min) only 30% conversion was observed. Alternative purification conditions were also investigated to see if material was being lost at this stage, however chromatography on silica gel with a basic eluent or sonication in hexane (as performed in the Petasis methylenation reaction) either gave a lower yield or failed to remove titanium related impurities.

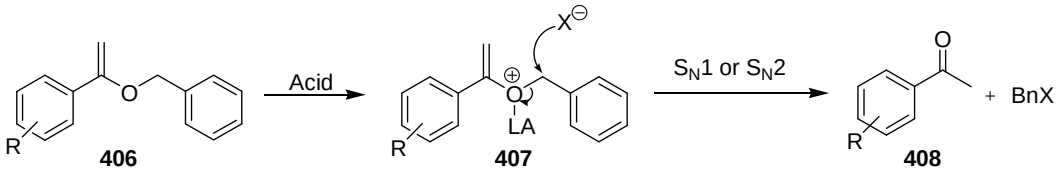


Scheme 151: Synthesis and methylenation of benzyl esters

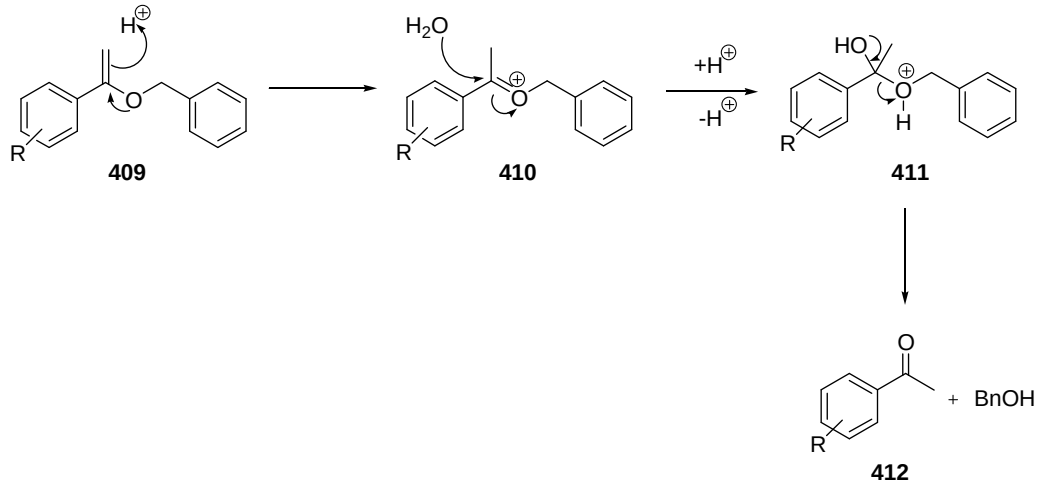
Table 14

Entry	R Group	Esterification Method	Ester Yield	Enol Ether Yield
1		A	**399**, 87%	**403**, 60%
2		A	**400**, 61%	**404**, 21%
3		A	**401**, 81%	**405**, 16%
4		B	**402**, 59%	Decomposition

It remains unclear why the aromatic benzyl esters were poor substrates for our methylenation reaction, although it is likely that product instability was a significant factor. A possibility was that benzyl group itself was responsible (Scheme 152). Potentially, coordination of metal ions to the carbonyl oxygen atom giving intermediate **407** could activate the benzyl position to cleavage either via an S_N1 or an S_N2 mechanism. Obviously the benzyl group is present in the aliphatic substrate as well, however cleavage of the benzyl group in the aryl substrate would relieve considerably more steric strain due to the combination of a bulky aromatic group and the Lewis acid interacting with the benzyl group and thus make it more labile. This is similar to a mechanism for the cleavage of esters bound to styrene resin proposed by Hartley and co-workers.[117] As they point out, normal acetal cleavage is also possible (Scheme 153), although it is unlikely in the dry reaction conditions or the basic work-up.



Scheme 152: Proposed mechanism of benzyl ester cleavage

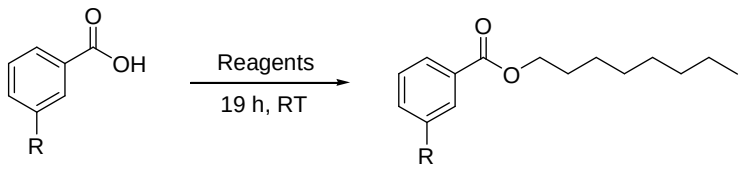


Scheme 153: Acetal hydrolysis

In order to maintain a broad substrate scope altering the group in the ester derived from the carboxylic acid was not considered. Instead the benzyl group was changed as it was likely to be lost in any subsequent synthetic step, and consequently its nature was therefore relatively unimportant.

6.3.2 Alternative esters

Esters derived from aliphatic alcohols were chosen as it was hoped that they would be less labile under the proposed decomposition mechanism. Octyl esters **413** and **414** were preferred over a shorter chain length in order to maintain a relatively high molecular weight and prevent loss of material on the rotary evaporator. The octyl esters were synthesised using standard coupling conditions in a similar fashion to the benzyl pyrazine derivative **402** (Scheme 154, Table 15). Using a moderate excess of acid was found to be advantageous ensuring complete consumption of octanol. The remaining acid could easily be removed by an aqueous base wash, negating the need for chromatography.



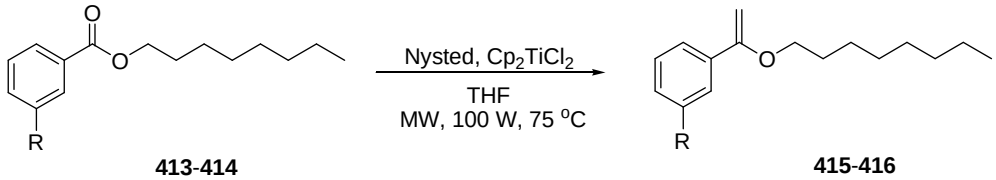
413-414

Scheme 154: Synthesis of octyl esters

Table 15

Entry	R	Eq. Acid	Reagents	Yield
1	Cl	1.1	Octanol (1 eq.), EDC. HCl (1.1 eq.), DMAP (0.1 eq.), THF	**413**, 63%
2	OMe	1.5	Octanol (1 eq.), EDC. HCl (1.5 eq.), DMAP (0.1 eq.), DMF	**414**, 90%

The octyl esters **413** and **414** were then submitted to the methylenation conditions (Scheme 155, Table 16). Surprisingly methylenation of these substrates was more difficult, only giving 50% conversion with the previously successful conditions (entry 1). A longer reaction time showed no improvement, while repeating the reaction with fresh Nysted and titanocene dichloride eliminated reagent degradation as a possibility (entries 2 and 3). Increasing the reagent stoichiometry did improve the conversion, with double the original number of equivalents required for full conversion to give enol ethers **415** and **416** (entries 4 to 6). It is interesting to note however, that achieving complete conversion only gave a modest increase in the yield, implying that excess reagents are destroying the enol ether product.



413-414 **415-416**

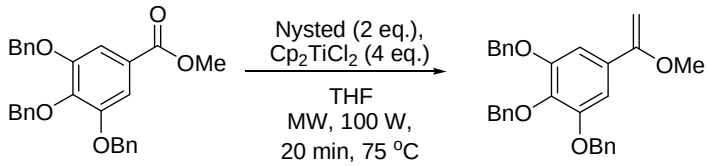
Scheme 155: Methylenation of octyl ester substrates

Table 16

Entry	R	Equivalents Nysted	Equivalents Cp_2TiCl_2	Reaction Time	Conversion	Yield
1	Cl	1	2	20 min	50%	**415,** 32%
2	Cl	1	2	40 min	50%	N/A
3	Cl	1[a]	2[b]	20 min	50%	N/A
4	Cl	2	4	20 min	100%	**415,** 38%
5	OMe	1.5	3	20 min	70%	N/A
6	OMe	2	4	20 min	95%	**416,** 37%

[a] Fresh bottle; [b] Recrystallized before use

The methylenation of methyl esters was also briefly investigated on a substrate **417** that had been synthesised by a co-worker for another project (Scheme 156). The reaction consumed all but traces of starting material **417**, however enol ether product **418** was isolated in very low yield. Methyl esters were of less interest as they would limit us to higher molecular weight acid groups for inclusion in our library. For these reasons methyl esters were not pursued further.



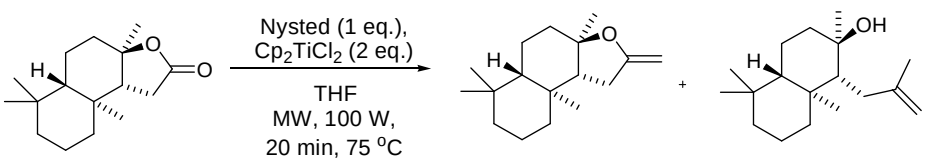
417 **418**, 20%

Scheme 156: Methylenation of a methyl ester

6.3.3 Lactones - Sclareolide

Following the successful result with esters, whether the new reagent could effectively methylenate lactones was investigated, a reaction that other titanium-based methylenating reagents are also able to carry out. The first substrate chosen was sclareolide **419**, a relatively inexpensive commercially available natural product (Scheme 157). The initial trials gave an unexpected result, the desired product **420** was formed, however it was a minor component. The major product **421** was a related compound with alkene functionality; it contained an extra carbon atom, implying that its formation was due to the incorporation of an extra methylene unit.

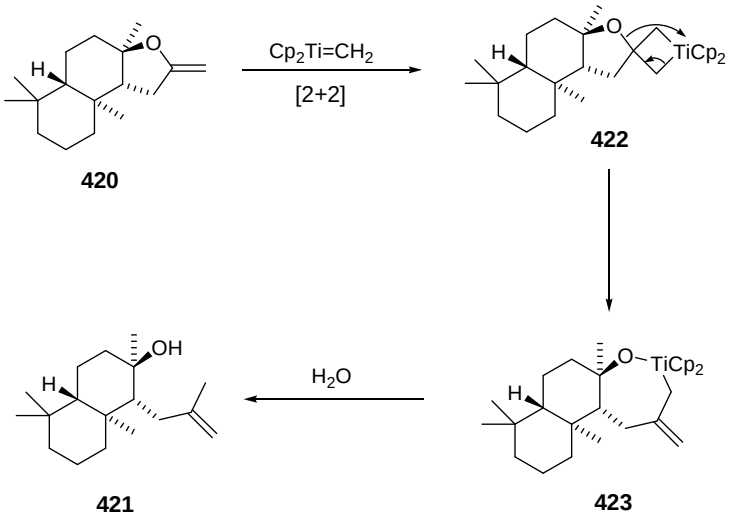
Due to the number of fused rings and aliphatic nature of sclareolide **419** and its derivatives structural analysis was not trivial. The products were identified using a combination of ^{1}H and ^{13}C NMR spectroscopy. Heteronuclear Single Quantum Coherence (HSQC) spectroscopy was particularly useful. It was this method, in combination with comparison with known compounds, that allowed these complex structures to be assigned. Tables showing the direct proton-carbon correlations observed for **420** and **427** are shown in the appendix. COSY spectra were less helpful as long range couplings were observed, meaning that one signal was shown to couple to many others.



419 **420**, 23 % **421**, 46%

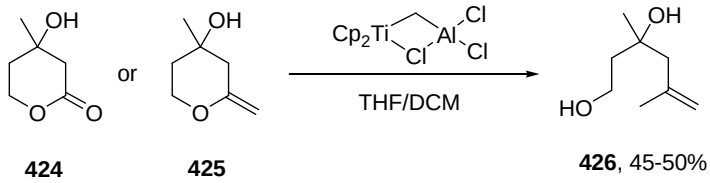
Scheme 157: Methylenation of sclareolide gave an unexpected product

It is possible that the undesired product was formed from the reaction of the desired enol ether product **420** with another molecule of the proposed active species, titanium methylidene **78** in a [2+2] addition giving **422** (Scheme 158). This would then rearrange to form allyl titanium species **423** which is hydrolysed in the aqueous work up to give the major product **421**. If this mechanism is correct it implies the active species is a titanium alkylidene rather than a 1,1-bimetallic species, which would not be able to carry out the cycloaddition.



Scheme 158: Proposed mechanism of formation of unexpected product

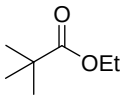
This type of reaction is reported in the literature, Bhatt and co-workers described a similar reaction (Scheme 159) where the hydroxyl-alkene product **424** is generated from the enol ether **425** or directly from the ketone **426** on reaction with the Tebbe reagent.[142]



Scheme 159: Precedent for titanium methyldene insertion into enol ether

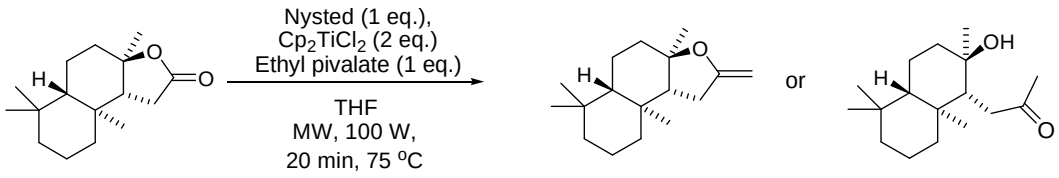
A strategy to prevent this over reaction of titanium methylidene has been developed by Payack and co-workers.[47] They found that addition of a stoichiometric quantity of ethyl pivalate **101** or another hindered ester suppressed the reaction of titanium methylidene with enol ethers without interfering with the initial methylenation of the ester group (see Section 1.3.4). The inclusion of ethyl pivalate **101** in our reaction conditions almost completely suppressed the formation of the undesired product **421** (Scheme 160), allowing isolation of the enol ether product **420**. The low yield in this case was likely

due to product instability during purification, to circumvent this the reaction was repeated and hydrolysed intentionally, giving the methyl ketone product **427** in a much improved yield.



101

Figure 17: Ethyl pivalate



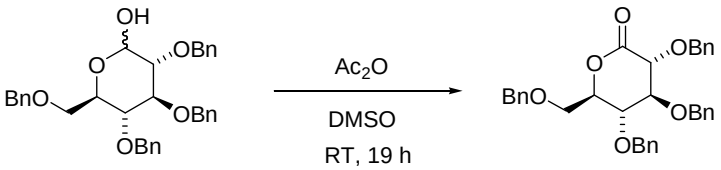
419 **420**, 30% **427** 56% after acidic work up

Scheme 160: Sclareolide methylenation with ethyl pivalate additive

It should be noted that the proposed mechanism is not the only conceivable pathway that could generate the impurity that was isolated. It is also possible that enol ether cleavage occurs in the mechanism postulated for the decomposition of the benzyl dervived enol ethers (Scheme 152) to give a methyl ketone **427**, which could undergo a second methylenation to give alkene **421**. However, this would require the presence of water. This, coupled with the fact that ethyl pivalate **101** suppresses formation of the impurity, makes the alternative mechanism unlikely, as the ketone **427** would react far more rapidly than ethyl pivalate **101**.

6.3.4 Lactones – Further Examples

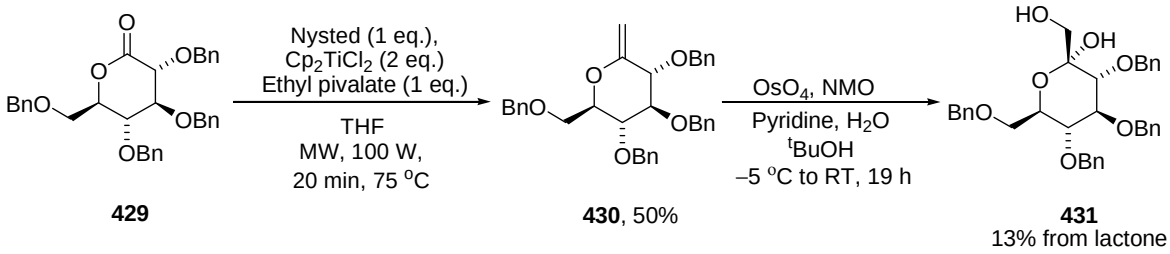
Following the optimisation of the methylenation of lactones, the substrate scope was expanded by testing the reaction on a few more examples. All but one of these was commercially available. Tetra-benzyl protected glucopyranose **428** was oxidised to the lactone **429** in a Swern-like reaction (Scheme 161).[143]



428 **429**, 96%

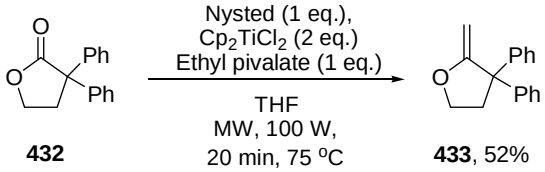
Scheme 161: Oxidation of protected glucopyranose

The sugar based lactone **429** was successfully methylenated using our optimised conditions (Scheme 162) giving the enol ether **430** in moderate yield. By adding reagents directly to the post-methylenation reaction mixture, it was possible to dihydroxylate the enol ether double bond to give diol **431**. While this did not occur in a synthetically useful yield, this approach could be useful to confirm the presence of enol ethers that were not stable enough to be isolated.



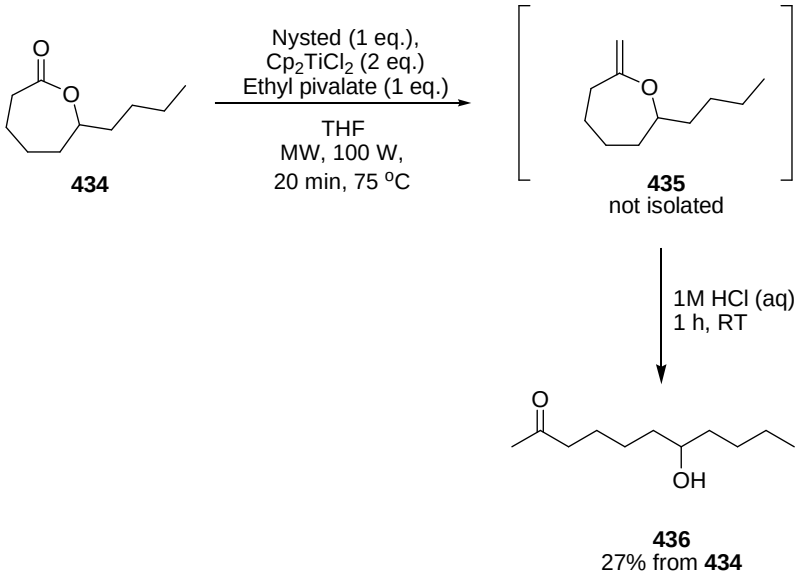
Scheme 162: Methlylenation and dihydroxylation of sugar based lactone

The methylenation reaction also works on a hindered γ-lactone **432** (Scheme 163) and a derivative of 7-membered caprolactone **434** (Scheme 164). As with the sclareolide example, an attempt was made to deliberately hydrolyse the γ-lactone derived enol ether **433**. However it was found to be relatively stable, with significant quantities of enol ether **433** surviving stirring in 1M aqueous hydrochloric acid for more than one hour. Conversely, the ε-lactone derived enol ether **435** was found to be very unstable and was not isolated. The methyl ketone **436** was isolated following an acidic work-up and is assumed to be the result of enol ether hydrolysis.



432 **433**, 52%

Scheme 163: Methylenation of γ-lactone



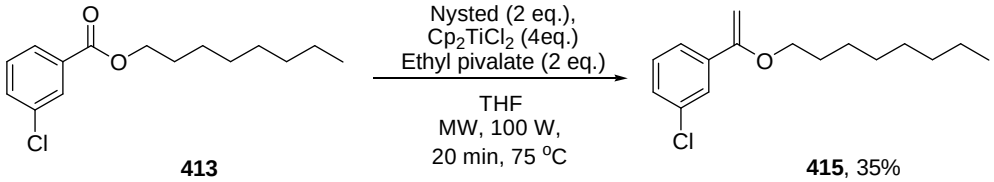
434 **435** not isolated

436 27% from **434**

Scheme 164: Synthesis of keto-alcohol **436** showing proposed enol ether intermediate

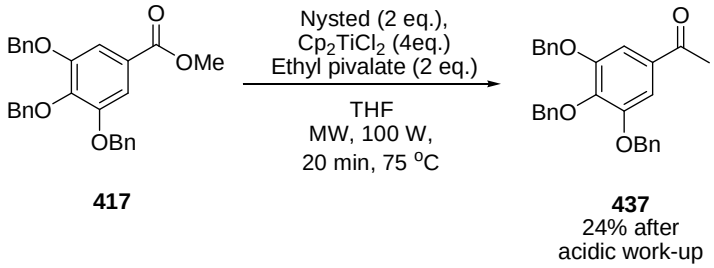
6.3.5 Ethyl Pivalate and Esters

As the addition of ethyl pivalate **101** had proved beneficial for the reaction with lactones, it was considered whether the over reaction it was preventing was also detrimental to the methylenation of esters. With this in mind, we re-tested some ester substrates with ethyl pivalate as an additive (Schemes 165 and 166). However, it was immediately obvious that ethyl pivalate **101** had no beneficial effect in these reactions, implying that the moderate yields in ester methylenation are not the result of titanium methylidene over reaction.



413 **415**, 35%

Scheme 165: Ethyl pivalate effect on methylenation of octyl esters

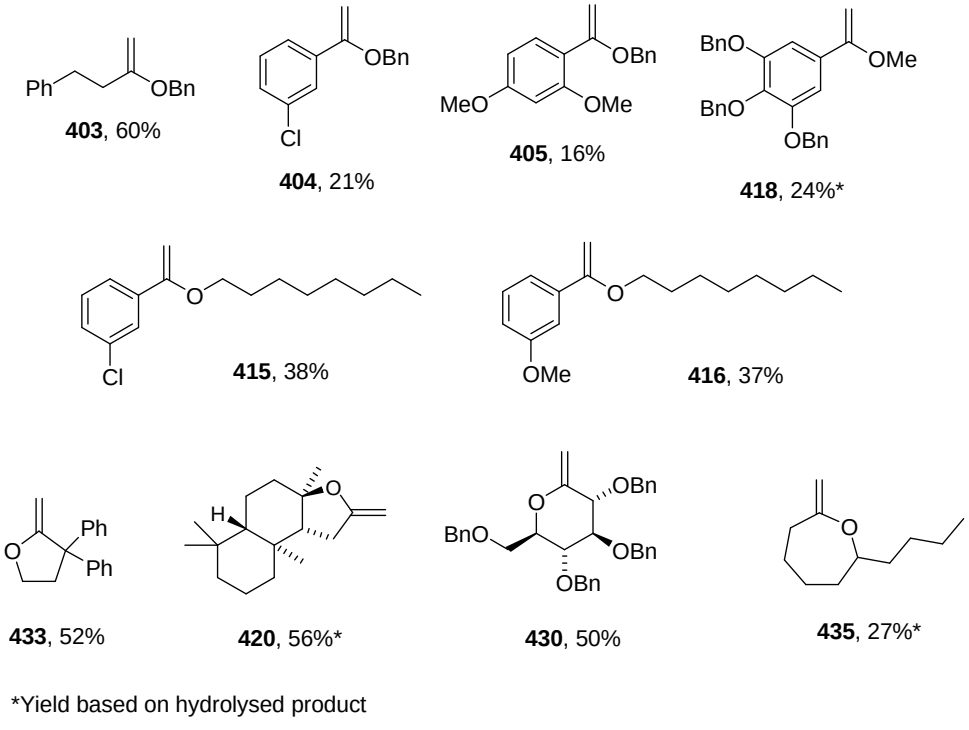


417 **437** 24% after acidic work-up

Scheme 166: Ethyl pivalate effect on methylenation of methyl esters

6.3.6 Esters and Lactones Summary

After a period of optimisation, a method for the methylenation of esters and lactones was developed and a small library synthesised (Figure 18). While the yields are modest, it should be noted that many methods of methylenation (e. g. Wittig) are not able to perform this transformation on carboxylic acid derivatives and many that can (e. g. Tebbe and Petasis) require the reagent to be synthesised before use. A simple one-pot method for the methylenation of both esters and lactones has been developed.



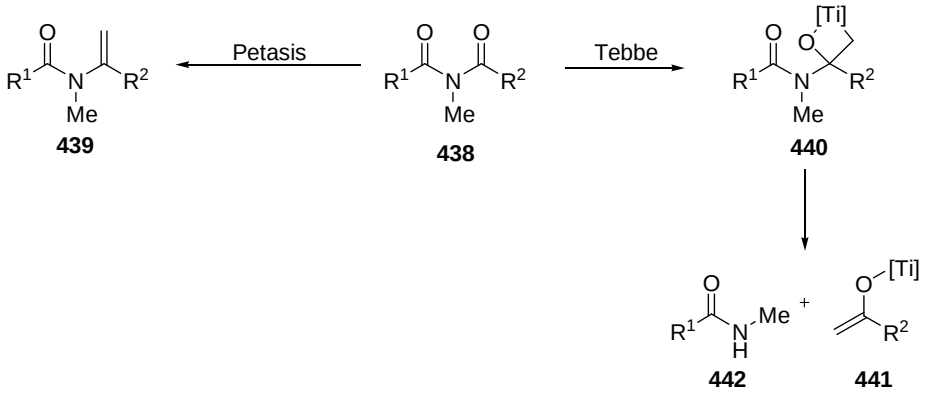
*Yield based on hydrolysed product

Figure 18: Summary of methylenated esters and lactones

6.4 Imides and Thioesters

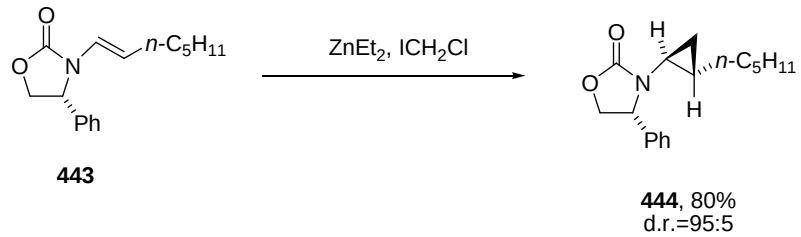
6.4.1 Imides

We were also interested in further exploring the substrate scope to include methylenation of imides **438**. This is a reaction that can be performed using the Petasis reagent to give enamines **439**, however the Tebbe reagent leads to the formation of titanium enolates **441** (Scheme 167).[144]

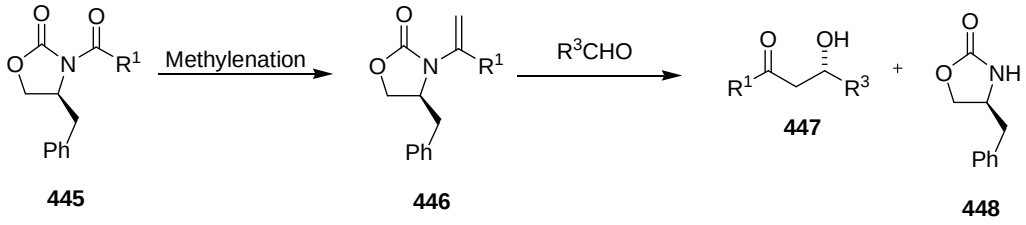


Scheme 167: Differing reactivity of the Petasis and Tebbe reagents toward imides

Imides derived from easily accessible chiral oxazolidinones were chosen as test substrates due to their potential use as chrial auxliaries (Scheme 168).[145] Hsung and co-workers described the use of enamine **443** as a substrate for a stereoselective Simmons-Smith cyclopropanation to give aminocyclopropane **444**. The selectivity is thought to be due the steric blocking of one face by the large phenyl group. We hoped to provide easy access to a range of enamine starting materials **446** that could undergo similar reactions and also potentially generate enantiomerically enriched aldol products **447** using this chiral auxiliary strategy (Scheme 169).

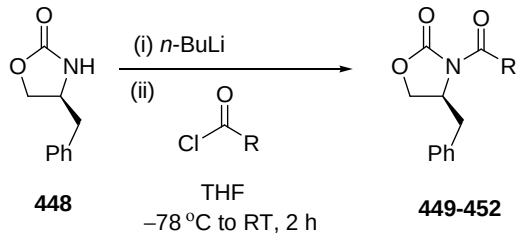


Scheme 168: Stereoselective cyclopropanation of oxazolidinone derived enamines described by Hsung and co-workers



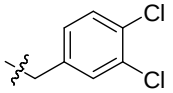
Scheme 169: Proposed methylenation of imide oxazolidinones and subsequent stereoselective aldol reaction

Throughout the optimisation process a range of imides were synthesised (Scheme 170, Table 17). Commercially available (*S*)-4-Benzyl-2-oxazolidinone **448** was deprotonated with *n*-butyllithium, this was then coupled with an acid chloride to give imides **449-452**. The acid chloride used in the synthesis of **452** was not commercially available and was synthesised by reaction of the corresponding acid and thionyl chloride immediately before use.



Scheme 170: Synthesis of imides

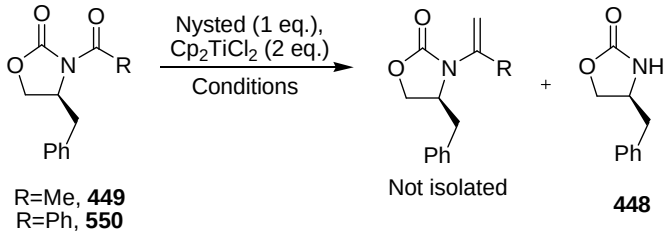
Table 17

Entry	R	Product, Yield
1	Me	**449**, 95%
2	Ph	**450**, 72%
3	$CH_2(CH_2)_{13}CH_3$	**451**, 60%
4		**452**, 43%

We then trialled these substrates in our methylenation conditions (Scheme 171, Table 18), however the desired enamides were not isolated. It was not clear whether the desired products had been formed and subsequently decomposed or if decomposition was occurring through a different mechanism. The difficulty in isolation of the enamides was surprising as, due to the nitrogen lone pair being conjugated by the adjacent carbonyl group, enamides are less nucleophilic and more difficult to hydrolyse than enol ethers.[146] It should be noted that these reactions were carried out at MSD, Newhouse with different laboratory equipment and protocols. These differences required a number of changes to our general procedure. Firstly, stringently dried solvents were not

available, so we decided to use only the THF present in the Nysted suspension. Also, MSD used a different microwave system and, by repeating known reactions, we discovered a temperature of 120 °C was required for the same conversion. The difference is likely to be a result of different temperature sensing methods (IR vs. internal probe).

To investigate and try and prevent generation of the undesired products the reaction was carried out under a variety of conditions. Lowering the temperature (entry 2) did not change the result, while carrying out the reaction thermally only led to the production of free oxazolidinone **448** at a reduced rate (entry 3). Reactions with only one of the reagents present showed that, while the substrate does react with the Nysted reagent, neither was solely responsible for the generation of the undesired product (entries 4 and 5). We wondered whether our reaction conditions were not being accurately reproduced at the MSD laboratories and therefore repeated the reaction in the university laboratory (entries 6-8). The results were the same, despite changing the reaction time and the addition of ethyl pivalate **101**.



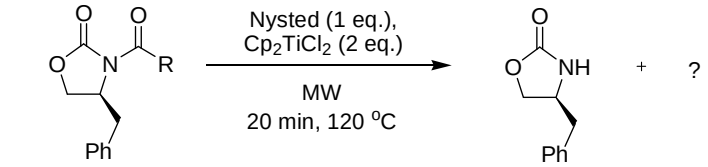
Scheme 171: Attempted methylenation of imides

Table 18

Entry	Compound	Eq. Nysted	Eq. Cp_2TiCl_2	Conditions	Result
1	**449** or **450**	1	2	MW, 120 °C, 20 min	**448**
2	**449**	1	2	MW, 100 °C, 20 min	**448**
3	**449**	1	2	RT, 24 h	Slow decomp to **448**
4	**450**	-	2	MW, 120 °C, 20 min	No reaction
5	**450**	1	-	MW, 120 °C, 20 min	Complex mixture, not **448**
6	**449**	1	2	MW, 75 °C, 22 min*	**448**
7	**449**	1	2	MW, 75 °C, 5 min*	**448**
8	**449**	1	2	MW, 75 °C, 22 min, 1 eq. ethyl pivalate*	**448**

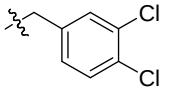
*Reaction carried out in university laboratory

Changing the reaction conditions did not lead to successful generation of the desired product. We felt that the fate of the moiety containing the R-group would give us insight into why the reaction was not working as intended. Initial attempts using an acidic work up following the reaction in Scheme 171 did not yield any carboxylic acid by-products. We reasoned that potential aldehyde or alkene products may have been too light to be isolated and synthesised imides **451** and **452**, both of which contained higher molecular weight R-groups. Unfortunately, only free oxazolidinone **448** and unreacted starting material were isolated from the reaction mixtures (Scheme 172). Evidence for other R-group containing compounds was observed, but only as a component of complex mixtures.



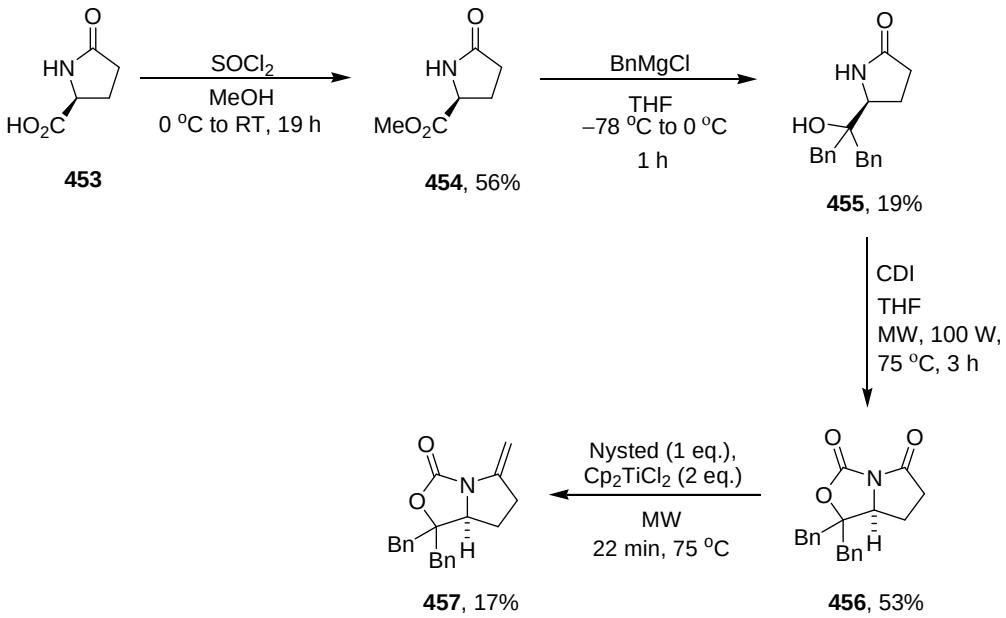
448

$R=CH_2(CH_2)_{13}CH_3$, **451**

R=  **452**

Scheme 172: Attempting to determine the fate of R-groups

Taking inspiration from our work on lactones, we resolved to synthesise a cyclic imide **456** in the hope that the fate of all components of the substrate would be clearer as they would remain tethered together (Scheme 173). The cyclic imide synthesis began from *L*-pyroglutamic acid **453** which was converted into the methyl ester **454**. Reaction with excess benzylmagnesium chloride gave the alcohol **455**, albeit in low yield, presumably due to the hindered system and the potential for side reactions. After minor optimisation, this was cyclized to give the desired cyclic imide **456** using carbonyldiimidazole (CDI). This was then subjected to our methylenation conditions, by this point my industrial placement had come to an end, so the reaction was carried out in the microwave in the university laboratory at 75 ºC. Perversely, rather than allowing the isolation of tethered decomposition products, the reaction gave a low yield of the desired enamide **457**. Imide **457** was relatively stable, with samples decomposing to the expected amido-ketone after a few days. The remaining mass from the reaction mixture was a complex mixture, showing many components by ^{1}H NMR spectroscopy. Repeating the reaction with less reagent equivalents gave a similar result.



453

454, 56%

455, 19%

456, 53%

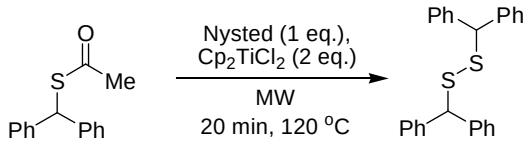
457, 17%

Scheme 173: Synthesis and methylenation of cyclic imide

With this result we finished our investigation into enamide methylenation. While the final experiment showed that it was possible using our conditions, our cumulative results had shown that was not the only available reaction pathway. The identity of the undesired reactions was not clear, although it is possible that the combination of electrophiles, nucleophiles and Lewis acids at high temperatures was the cause of their formation.

6.4.2 Thioesters

We also briefly attempted to methylenate a thioester **458** (Scheme 174), a reaction that can be carried out by other titanium based methylating reagents (see section 1.3.6). Due to time constraints the reaction was only performed once and gave a disulfide product **459**. It is possible that this was derived from decomposition of the desired product, however there was no experimental evidence for the formation of the vinyl sulfide.



458

459, 62%

Scheme 174: Attempted methylenation of a thioester

6.5 Investigation of the Active Species

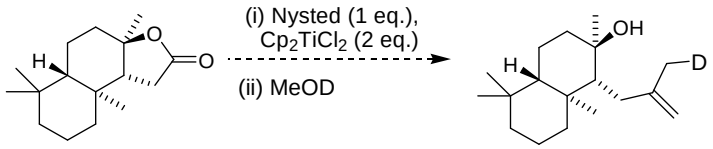
We had successfully developed a simple method for the methylenation of a variety of different carbonyl functional groups. Originally we proposed that the combination of the Nysted reagent **51** and titanocene dichloride **77** would generate titanium methylidene **78** as the methylenating agent. However it was also possible that a 1,1-bimetallic species, of a structure similar to **460**, was responsible. We were interested in determining the identity of the active species to give us insight into the mechanism of our reaction.

78 **460**

X=Br or Cl

Figure 19: Methylenation active species

As mentioned previously, the optimisation of the methylenation of lactones had already given an interesting result implying the presence of titanium methylidene **78**. On the basis of the isolated product **421**, we had proposed the mechanism shown (Scheme 158). In an attempt to provide evidence for this mechanism we repeated the reaction, this time quenching with MeOD (Scheme 175). If the oxo-titanocene ring **423** was present this should lead to deuterium incorporation in one of the methyl groups of the product **461**, which would be clearly visible on the ^{13}C NMR spectrum. This was not observed, therefore the oxo-titanocene ring **423** is not present at the end of the reaction. The lack of deuterium incorporation does not rule out the involvement of titanium methylidene **78**, but does reveal that our proposed mechanism is not entirely correct.



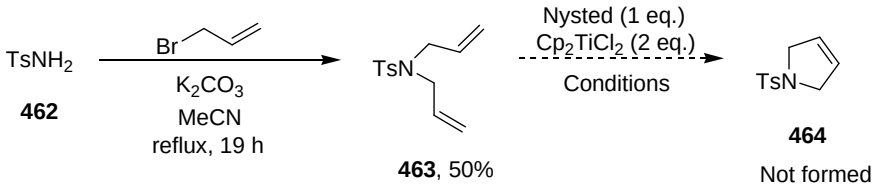
419 **461**

Scheme 175: Absence of deuterium incorporation implies mechanism is incorrect

In the literature the distinction between 1,1-bimetallic and titanium alkylidene complexes is made through metathesis. The Petasis, Tebbe, Takai and Takeda methods have all been shown to induce alkene metathesis and are therefore presumed to have a titanium alkylidene as the active species (see Section 2.3). Others, such as Yan's

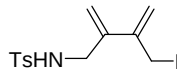
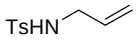
method, have not been shown to carry out metathesis and are thought to be 1,1-bimetallic species. We therefore submitted diene substrates to our reaction conditions to see if any evidence of ring closing metathesis was observed.

We first synthesised diallyl protected amine **463**, which has been shown to undergo ring closing metathesis in the presence of Grubbs I catalyst.[147] The diene **463** was then submitted to our reaction conditions (Scheme 177). No reaction was observed in thermal heating conditions, but when the reaction was heated in the microwave an unexpected diene product **465** was isolated in a 1:1 ratio with a mono de-allylated product **466**.

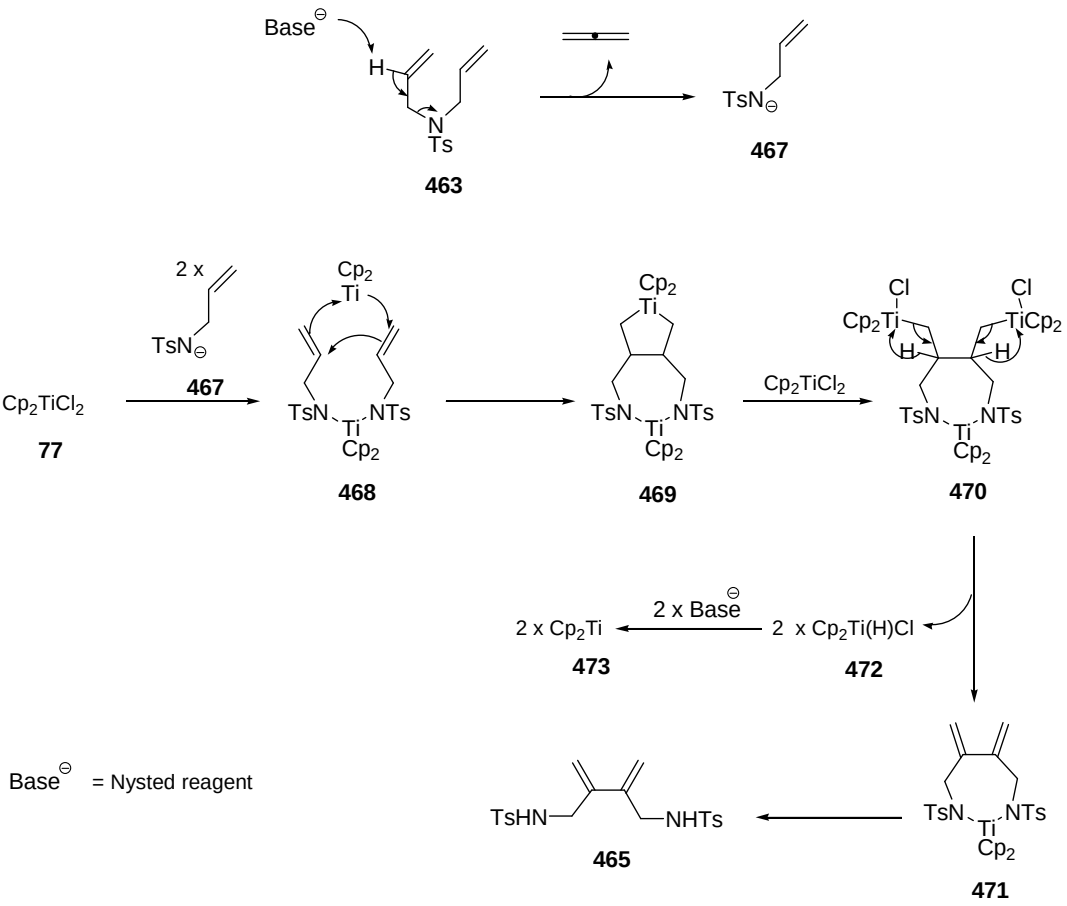


Scheme 176: Ring closing metathesis attempt

Table 19

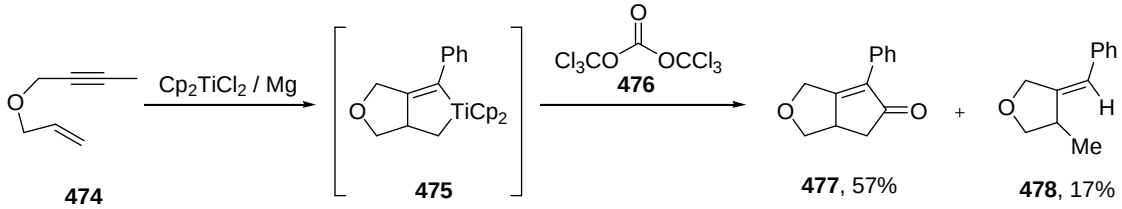
Entry	Conditions	Result
1	THF, Reflux, 20 h	No reaction
2	Microwave, 75 °C, 22 min	Mixture of starting material and  **465**, 8%  **466**, 8%

It was not obvious how the diene **465** had been formed, but we tentatively propose a mechanism (Scheme 177). Firstly, the Nysted reagent **51** may act as a base and induce an E2 elimination of diene **463** generating allene and mono-deallylated product **467**. This could then react with titanocene dichloride **77** to give complex **468**. Reaction of complex **468** with a low valent titanium species **473** would result in the formation of cyclotitanapentane **469**. Further reaction with titanocene dichloride **77** results in complex **470** which can undergo a β-elimination to give titanium complex **471** releasing diene **465** on work up. The β-elimination would also liberate titanocene hydrochloride **472**, which would regenerate low valent titanium species **473** on reaction with base.



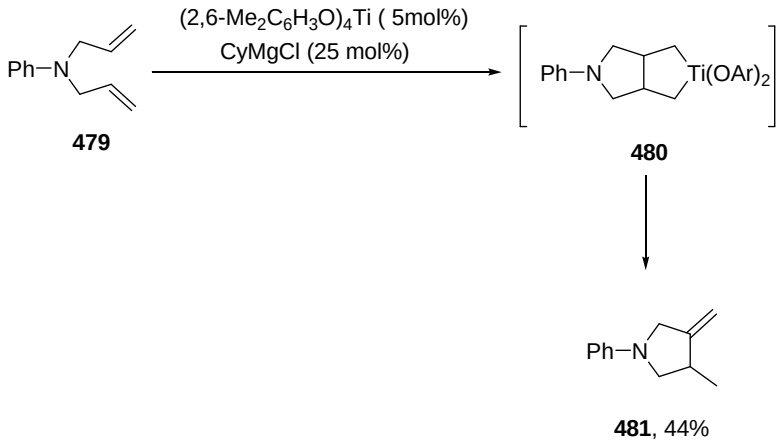
Scheme 177: Proposed mechanism for the formation of **465**

Reactions that proceed through intermdiates similar to cyclotitanapentane **469** have been reported in the literature. Ding and co-workers generated cyclotitanapentene **475** from the reaction of a low valent titanocene complex and intermediate **474** (Scheme 178).[148] Although cyclotitanapentene **475** was not isolated, they did report the isolation and characterisation of a cyclotitanapentene intermediate from an analogous reaction. Treatment of cyclotitanapentene **475** with carbonate **476** resulted in the formation of enone **477** and terminal alkene **478**. The reaction to form terminal alkene **478** is analogous to the reaction we obeserved (Scheme 176), however it is formally a reductive process, while generation of diene **465** from diallyl complex **463** requires an oxidation.



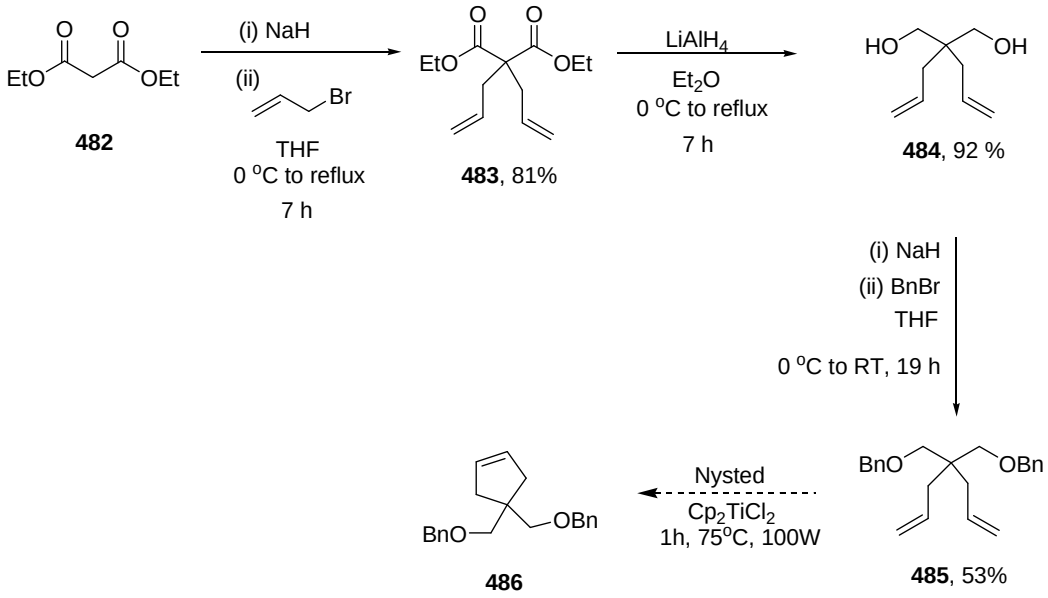
Scheme 178: Reductive cyclization reported by Ding and co-workers

Livinghouse and co-workers have described a similar process (Scheme 179).[149] Diene **479** cycloisomerized to give cyclopentane **481** in the presence of a catalytic amount of a titanium complex. This reaction is also proposed to proceed via a cyclotitanapentane intermediate **480**, although the overall process is an isomerization unlike the reduction shown by Ding (Scheme 178) or the oxidation we report (Scheme 176).



Scheme 179: Cycloisomerization reported by Livinghouse and co-workers

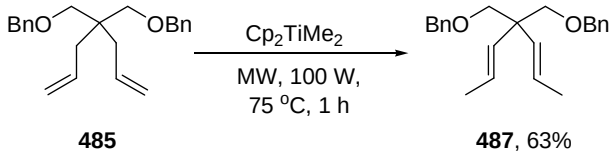
While the reaction in Scheme 176 was undoubtedly an interesting result, it did not allow us to demonstrate alkene metathesis, we therefore turned our attention to a different substrate. Protected oxy-diene **485** was synthesised in three steps from diethyl malonate **482** (Scheme 180). However, it showed no reactivity under our reaction conditions.



Scheme 180: Synthesis and attempted cyclization of a metathesis substrate

As a comparison, we tested the substrate **485** under the Petasis methylenation conditions (Scheme 181). The Petasis reagent did not induce metathesis either, instead

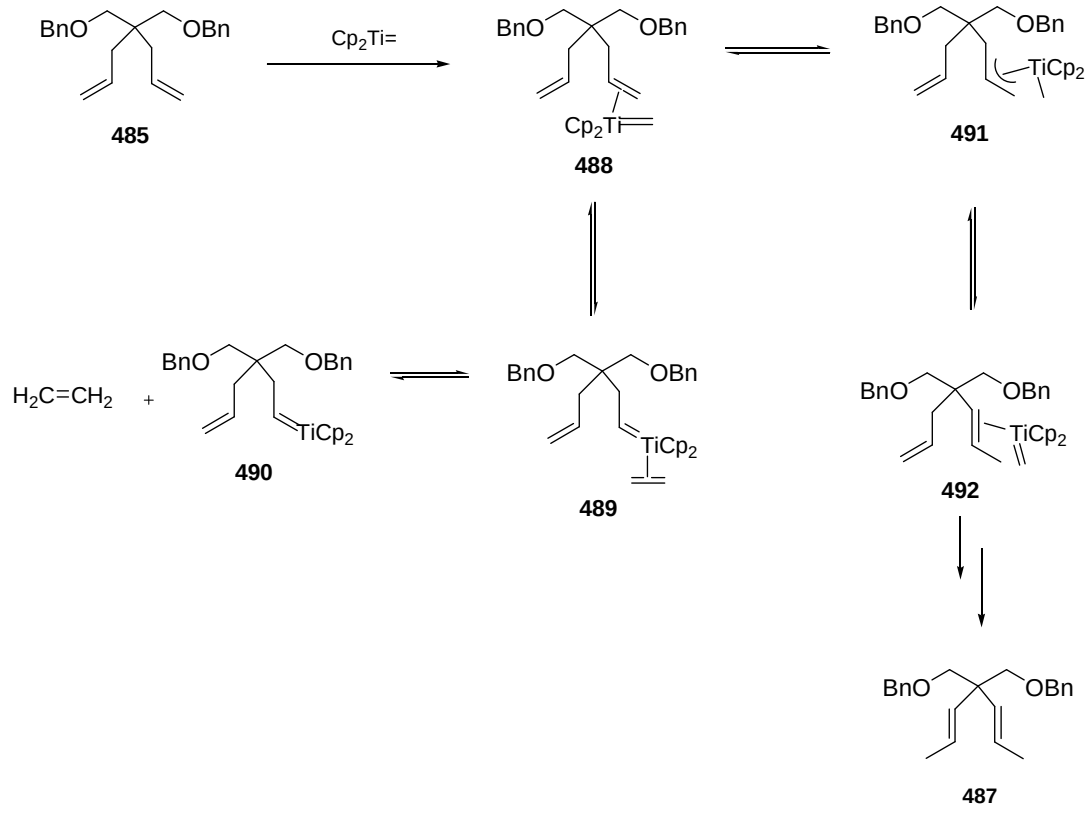
it caused isomerisation of the exomethylene groups to give an internal double bond **487**. Carrying out the reaction in a more dilute solution, with a shorter reaction time or in non-sealed conditions either gave the same product or no reaction was observed.



485 **487**, 63%

Scheme 181: Petasis reagent effect on metathesis substrate

The isomerisation is likely to come about by the mechanism shown in Scheme 182. Initial association of titanium methylidene to the double bond gives intermediate **488**, which can react further through two potential pathways. The expected [2+2] addition would give intermediate **489**, which decomplexes releasing ethane to give the titanium alkylidene **490** required for metathesis. The steps toward alkylidene **490** are reversible, and therefore could be disfavoured by the build up of ethene gas. Accumulation of intermediate **488** may allow a proton migration to take place and give η^3 complex **491**. The reaction could reverse to give the original alkene **485**, but could also generate the more stable internal double bond complex **487**. Due to the reversibility of the reaction forming titanium alkylidene **490** and greater stability of internal alkenes over terminal alkenes the result is the accumulation of diene **487.**

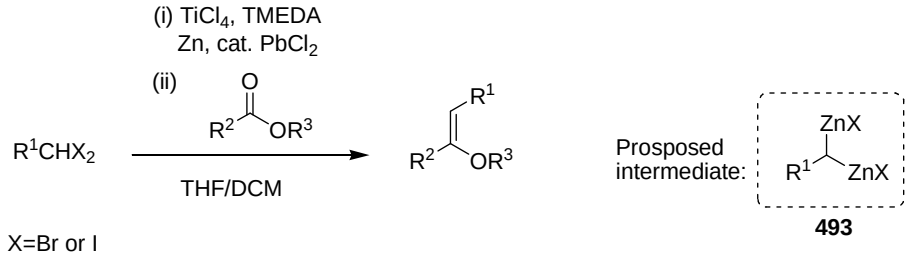


Scheme 182: Proposed mechanism leading to alkene isomerisation

Our investigation into the identity of the reactive species was inconclusive. The sclareolide result seems to imply that titanium methylidene **78** is present, however we failed to confirm this with an example of alkene metathesis. In retrospect, our substrate choice was perhaps flawed. While the compounds we tested had been shown to be metathesis substrates, it would have been more useful to use substrates that the various methylenation methods had been shown to metathesise. However, these are often complex molecules that cannot be conveniently accessed.

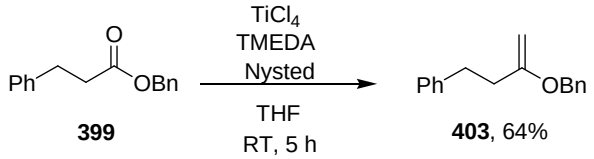
6.6 Takai Reaction

As mentioned earlier, the Takai reaction (Scheme 183) is another method of ester alkylidenation. One of the proposed intermediates **493** is essentially the Nysted reagent **51**.[54] In the same way as our previous reaction conditions could be described as a modification of the Petasis methylenation, we hoped that we could simplify the Takai reaction.



Scheme 183: The Takai alkylidentation reaction

In Takai's method the di-zinc intermediate **493** is access by a lead catalysed metal-halogen insertion reaction. As this is provided by the Nysted reagent **51** in our conditions, we hoped we could perform the same reaction without the need for added lead or zinc, or the relatively difficult to access dihaloalkane (Scheme 184). Using these conditions, an ester **399** was methylenated giving clean enol **403** ether at room temperature. The crude reaction material contained about 20% unreacted starting material and was also significantly cleaner than our other method, implying that further optimisation could improve the yield. Unfortunately, time constraints did not allow this to be fully exemplified. It should also be noted that Matsubara and co-workers have reported a similar system (Section 2.2, Scheme 22). The major difference is their use of bis(iodozincio)methane **56**, which is not commercially available and must be synthesised before use.



399 **403**, 64%

Scheme 184: Modified Takai reaction

6.7 Conclusions

Our attempt to discover a new method for the methylenation of carbonyl compounds was very successful. Beginning from our preliminary results on ester methylenation we quickly optimised to give one-pot methods for the methylenation of aldehydes, ketones, esters and lactones, and generated small libraries of each. The limits of substrate scope were explored with our investigation into imide and thioester methylenation and some insight into the reaction mechanism was gleaned. The end result is a method that, while not challenging existing methods on reaction yield, certainly is an advance in reaction simplicity. There is scope for improvement in the future, as our early results from the modified Takai reaction indicate that the reaction proceeds more cleanly while maintaining the convenience of our original reaction.

Experimental

General experimental details

All reactions were carried out using oven dried glassware and solutions added *via* syringe unless otherwise stated.

DMF and DMSO were distilled form CaH_2 under reduced pressure and stored over 4 Å molecular sieves. Diethyl ether, tetrahydrofuran, dichloromethane, toluene and acetonitrile were dried using a Puresolv© solvent drying system prior to use. Petroleum ether refers to the fraction boiling at 40-60 °C. Brine refers to a saturated sodium chloride solution.

With the exception of Cp_2TiMe_2, which was produced by the method reported by Payack *et al.*,[44] reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. Triethylamine and TMEDA were distilled form CaH_2 under reduced pressure and used immediately or stored over 4 Å molecular sieves.

Reactions were monitored by TLC performed on Merck Kieselgel 60 F_{254} plates or Alumgram® SIL G/UV_{254} and visualization was performed using UV light (365 nm) or potassium permanganate. Purification by column chromatography was carried out using Fluorochem silica gel 60 Å (mesh size 30-70 μm) or Sigma-Aldrich aluminium oxide (neutral, deactivated to Brockmann V, 150 mesh, 58 Å) as the stationary phase. All distillations were carried out bulb to bulb using Kugelrohr apparatus. Microwave assisted reactions were carried out in a CEM focussed Microwave Synthesis System, model Discover®.

Melting points were measured using Gallenkamp apparatus and are uncorrected. IR spectra were recorded using NaCl plates on a JASCO FT/IR 4100 spectrometer or on an FTIR-8400S Shimadzu infrared spectrophotometer. NMR spectra were recorded using a Bruker AV400 FT, DPX/400 or AVIII. Chemical shifts in ^1H NMR spectra are given in ppm relative to trimethylsilane. Chemical shifts in ^{13}C NMR spectra are given relative to $CDCl_3$ (77.0 ppm) as internal standard. All NMR *J* values are given in Hz. CH_3, CH_2, CH and C in ^{13}C NMR were assigned using DEPT. Mass spectra were recorded on a JEOL JMS-700 High Resolution Mass Spectrometer by the analytical services at the University of Glasgow. Optical rotations were determined using an Autopol® V automatic polarimeter. $[\alpha]_D$ values were measured at the concentration and temperature stated for a path length of 1 dm and a wavelength of 589 nm (sodium D line).

Standard Conditions

1. Methylenation of esters using the Petasis reagent

1a) The ester (1 eq.) was dissolved in a solution of the Petasis reagent (1.8-4.2 eq.), (0.62-1.38 M in 1:1 THF - toluene) and irradiated in the microwave (22-25 min, 65 ºC, 100 W). The resultant black solution was concentrated *in vacuo* and dried under high vacuum. The residue was sonicated in hexane and the liquid decanted and concentrated in vacuo to give the enol ether with some titanocene related impurities.

1b) The ester (1 eq.) was dissolved in a solution of the Petasis reagent (1.8-4.2 eq.), (0.62-1.38 M in 1:1 THF - toluene) and irradiated in the microwave (22-25 min, 65 ºC, 100 W) giving a black solution. The reaction mixture was concentrated and purified by flash chromatography (neutral alumina deactivated to Brockmann V, Et_2O/Pet. Ether) giving the enol ether with some titanocene related impurities.

2. Cyclization of imino-enol ethers

2a) A solution of $^{i}Bu_3Al$ in hexane (2 eq., 1 M) was added to a stirred solution of imino-enol ether in dry DMSO (1 eq., 0.03M) under argon at 28 ºC for 19 h, the mixture was then quenched with 1 M HCl (aq) (35 eq.) and stirred for a further 45 min. The reaction mixture was then basified with 1 M NaOH (aq) and extrated with ethyl acetate. Organics were combined, washed with sat. NH_4Cl (aq), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified using column chromatography [SiO_2, MeOH - DCM] to give the cyclized product.

2b) A solution of 1 M HCl (aq) (35 eq) was added to a stirred solution of imino-enol ether in dry DMSO (1 eq., 0.03M) and stirred for 45 min at RT then worked up as described in procedure 2a.

3. Nysted-Petasis carbonyl methylenation

3a) Titanocene dichloride (2 eq) was suspended in dry THF (5 mL) under Ar and the Nysted reagent added (1 eq, 20 %wt in THF). This was heated to 40 ºC for 30 min until a dark red/black solution formed and then allowed to cool to RT. The substrate (0.5 - 2 mmol), in dry THF (3 mL), was then added and the reaction mixture stirred until no starting material remained by TLC or NMR analysis. The reaction mixture was then quenched into sat. $NaHCO_3$ (aq) (50 mL) and extracted with Et_2O (3 x 50 mL). Organic

extracts were combined then washed with brine (100 mL), dried (Na_2SO_4) and concentrated to give a crude oily solid. Column chromatography (SiO_2, Pet. Ether - Et_2O) afforded pure alkene.

3b) Titanocene dichloride (2 eq) was suspended in dry THF (5 mL) under Ar and the Nysted reagent added (1 eq, 20 %wt in THF). This was heated to 40 °C for 30 min until a dark red/black solution formed and was to cooled to −78 °C. The substrate (0.5 -2 mmol), in dry THF (3 mL), was then added dropwise and the reaction allowed to warm to RT over 20 min. The reaction was then quenched and purified as described in procedure 3a.

3c) The ester (0.5 mmol) was dissolved in dry THF (1.5 mL) and titanocene dichloride (1 mmol) and the Nysted reagent (0.5 mmol, 20 %wt in THF) were added. The reaction mixture was irradiated in the microwave (100 W, 75 °C, 22 min). This gave a black solution which was poured into sat. $NaHCO_3$ (aq) (50 mL) and extracted with Et_2O (3 x 50 mL). Organic extracts were combined then washed with brine (100 mL), dried (Na_2SO_4) and concentrated to give a crude oily solid. Column chromatography (neutral alumina deactivated to Brockmann V, Pet. Ether/ Et_2O) yielded the enol ether.

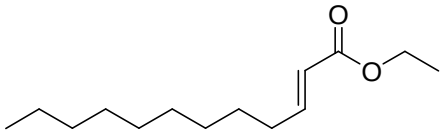
3d) The ester (0.5 mmol) was dissolved in dry THF (1.5 mL) and titanocene dichloride (2 mmol) and the Nysted reagent (1 mmol, 20 %wt in THF) were added. The reaction was performed and purified as described in procedure 3c.

3e) The ester (0.5 mmol) was dissolved in dry THF (1.5 mL) and titanocene dichloride (1 mmol), the Nysted reagent (0.5 mmol, 20 %wt in THF) and ethyl pivalate (0.5 mmol) were added. The reaction was irradiated in the microwave (100 W, 75 °C, 22 min). The reaction was then quenched and purified as described in procedure 3c.

3f) As procedure 3e except the reaction was quenched into 1 M HCl (aq) (10 mL) and stirred for 1 h and then extracted with DCM (3 x 50 mL). Further work-up was performed as described in procedure 3c. Silica gel chromatography (Pet. Ether/ EtOAc) afforded pure keto-alcohol.

Experimental Data

Ethyl 2(*E*)-Dodecenoate 209



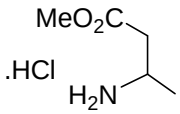
Triethylphosphonoacetate (1.14 mL, 5.76 mmol), lithium chloride (244 mg, 5.76 mmol) and DBU (810 μL, 5.76 mmol) were dissolved in dry MeCN (10 mL) and stirred under argon at RT for 30 min. The reaction mixture was then cooled to 0 °C and decanal (0.91 mL, 4.79 mmol) was added dropwise. The mixture was stirred under argon at RT for 18 h. The reaction mixture was then concentrated, re-dissolved in EtOAc (30 mL) and washed with water (3 x 30 mL) and brine (1 x 30 mL). The organic extract was dried (Na_2SO_4) and concentrated to give a crude oil. Silica gel chromatography [SiO_2, EtOAc - Pet. Ether (1:9)] gave ester **209** (784 mg, 73%) as an colourless oil.

R_f [SiO_2, EtOAc - Pet. Ether (1:4)] 0.76

δ_H (400 MHz, $CHCl_3$) 0.88 (3H, t, *J*=6.5 Hz, CH_3), 1.24-1.31 (15H, m), 1.43 (2H, qn, *J*=6.6 Hz, C*H*$_2$CH$_2$CH=CH), 2.18 (2H, q, *J*=7.4 Hz, C*H*$_2$CH=CH), 4.17 (2H, q, *J*=7.1 Hz, CH_2O), 5.80 (1H, d, *J*=15.6 Hz, CH_2CH=C*H*), 6.96 (1H, dt, *J*=15.6, 7.0 Hz, CH_2C*H*=CH); δ_C (100 MHz, $CHCl_3$) 14.1 (CH_3), 14.3 (CH_3), 22.7 (CH_2), 28.0 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 31.9 (CH_2), 32.2 (CH_2), 60.1 (CH_2), 121.2 (CH), 149.6 (CH), 166.9 (C)

All data agree with literature.[150]

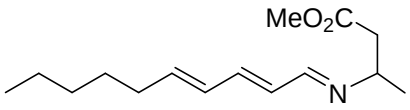
Methyl 3-aminobutanoate, hydrochloride salt 255



Following the procedure of Adriaenssens and Hartley[87] thionyl chloride (1.42 mL, 19.4 mmol) was added slowly over 5 min to a stirred suspension of 3-aminobutanoic acid (1.00 g, 9.70 mmol) in dry methanol (11.8 mL, 291 mmol) under argon at 0 °C. The resultant solution was allowed to warm to RT while stirring under argon for 2.5 h. The reaction mixture was then concentrated *in vacuo* to give the ester **255** (1.48 g, 100%) as its hydrochloride salt as a yellow oil.

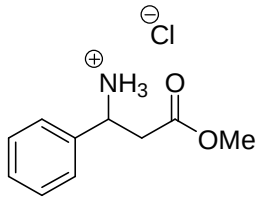
δ_H (400 MHz, D_2O) 1.16 (3H, d, *J*=6.8 Hz, CH*C*H_3), 2.57-2.60 (2H, m, CH*C*H_2), 3.55-3.60 (4H, m, CH_3O, NCH); δ_C (100 MHz, D_2O) 19.2 (CH_3), 39.3 (CH_2), 45.9 (CH), 54.1 (CH_3), 174.3 (C); m/z (CI^+) 118 [$(M+H)^+$ 100%]
All data agree with literature.[151]

Methyl 3-[2'*(E)*,4'*(E)*-decadien-(*E*)-yliden-3-amino]butanoate 256



2(*E*),4(*E*)-Decadienal (210 μL, 1.2 mmol), triethylamine (270 μL, 2.0 mmol) and Na_2SO_4 (166 mg, 1.2 mmol) were added to a suspension of methyl 3-aminobutanoate hydrochloride **255** (150 mg, 1.0 mmol) in dry dichloromethane (4 mL). The reaction mixture was stirred under argon at RT for 18 h and then washed with water (2 x 30 mL) and brine (1 x 30 mL). Organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*, excess aldehyde was removed by Kugelrohr distillation (3 h, 65 °C) giving the imine **256** (170 mg, 69%) as a brown oil. It was a mixture of geometrical isomers (90:6:1).
Data for major component:
δ_H (400 MHz, $CHCl_3$) 0.88 (3H, t, *J*=7.0 Hz, C*H*$_3$CH$_2$) 1.22 (3H, d, *J*=6.4 Hz, C*H*$_3$CH), 1.25-1.31 (4H, m, $CH_3CH_2CH_2CH_2$), 1.41 (2H, quintet, *J*=7.3 Hz, $CH_2CH_2CH_2CH$=) 2.13 (2H, q, *J*=7.2 Hz, C*H*$_2$CH=), 2.51 (1H, dd, *J*=15.5, 5.3 Hz, C*H*^{A}H^{B}CO$_2$), 2.58 (1H, dd, *J*=15.5, 8.1 Hz, CH^A*H*^{B}CO$_2$), 3.62-3.65 (4H, m, CH_3O, C*H*CH$_3$), 5.94 (1H, dt, *J*=15.5, 7.0 Hz, 5'-H), 6.13-6.21 (2H, m, 2'-H, 4'-H), 6.58 (1H, dd, *J*=15.2, 10.5 Hz, 3'-H), 7.90 (1H, d, *J*=9.1 Hz, 1'-H); δ_C (100 MHz, $CHCl_3$) 14.1 (CH_3), 22.4 (CH_3), 22.5 (CH_2), 28.6 (CH_2), 31.4 (CH_2), 32.9 (CH_2), 42.3 (CH_2), 51.5 (CH), 62.4 (CH_3), 129.1 (CH), 129.4 (CH), 140.1 (CH), 142.8 (CH), 162.4 (CH), 172.2 (C); m/z (EI^+) 251 [$M^{+\cdot}$, 59%], 80 (100). HRMS: 251.1883. $C_{15}H_{25}NO_2$ requires $M^{+\cdot}$ 251.1885.

Methyl 3-amino-3-phenylpropanoate, hydrochloride salt 263



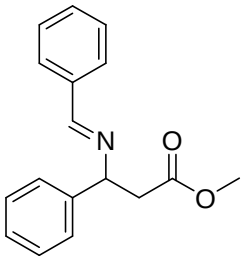
Following the procedure of Adriaenssens and Hartley[87] 3-amino-3-phenylpropanoic acid (5.00 g, 30.2 mmol) was suspended in methanol (100 mL) and cooled to 0 °C. Thionyl

chloride (4.42 mL, 60.5 mmol) was then added dropwise and the reaction heated to reflux for 18 h under argon. The reaction mixture was then cooled, concentrated *in vacuo* and washed with hexane. This gave the ester **263** (5.82 g, 89%) as a beige amorphous solid.

δ_H (400 MHz, $CDCl_3$) 3.02 (1H, dd, *J*=16.4, 6.7 Hz, C*H*^{A}H^B), 3.28 (1H, dd, *J*=16.4, 6.7 Hz, CH^A*H*^{B}), 3.63 (3H, s, OMe), 4.66-4.78 (1H, m, NCH), 7.31-7.43 (3H, m, ArH), 7.50-7.54 (2H, m, ArH), 8.85 (3H, br. s, NH_3); δ_C (100 MHz, $CDCl_3$) 38.5 (CH_2) 52.3 (CH), 52.3 (CH_3), 127.5 (CH), 129.2 (CH), 129.4 (CH), 138.3 (C), 170.0 (C); m/z (CI^+) 180 [$(M+H)^+$ 78%], 69 (100); HRMS 180.1023, $C_{10}H_{13}NO_2$ requires $(M+H)^+$ 180.1025; M.p. 143-145 °C.

All data agree with literature.[87]

Methyl 3-[(*E*)-benzylidenamino]phenylpropionate 264

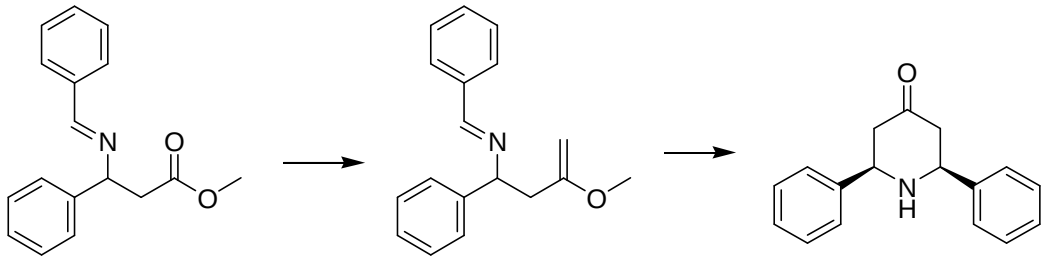


Following the procedure of Adriaenssens and Hartley[87] amine hydrochloride salt **263** (1.00 g, 4.65 mmol) was suspended in dry dichloromethane (25 mL) and benzaldehyde (520 μL, 5.12 mmol), triethylamine (1.29 mL, 9.30 mmol) and Na_2SO_4 (793 mg, 5.58 mmol) were added. The reaction mixture was stirred under argon at RT for 19 h, then washed with water (2 x 50 mL) and brine (1 x 50 mL). The organics were dried (Na_2SO_4) and concentrated *in vacuo* to give the crude imine. Excess aldehyde was removed by Kugelrohr distillation (1 h, 75 °C) affording the imine **264** (1.08 g, 87%) as a yellow solid.

δ_H (400 MHz, $CDCl_3$) 2.91 (1H, dd, *J*=15.6, 4.7 Hz, C*H*^{A}H^B), 3.05 (1H, dd, *J*=15.6, 9.2 Hz, CH^A*H*^{B}), 3.62 (3H, s, CH_3O), 4.87 (1H, dd, *J*=9.2, 4.7 Hz, NCH), 7.33-7.47 (8H, m, ArH), 7.76-7.78 (2H, m, ArH), 8.39 (1H, s, CH=N); δ_C (100 MHz, $CDCl_3$) 43.1 (CH_2), 51.6 (CH_3), 70.9 (CH), 126.9 (CH), 127.4 (CH), 128.4 (CH), 128.5 (CH), 128.7 (CH), 130.8 (CH), 136.2 (C), 142.8 (C), 161.5 (CH), 171.7 (C); m/z (CI^+), 268 [$(M+H)^+$, 100%]; HRMS: 268.1339. $C_{17}H_{17}NO_2$ requires $(M+H)^+$ 268.1338; M.p. 72-75 °C.

All data agree with literature.[87]

(2*R,6*S**)-2,6-Diphenylpiperidin-4-one 265**



264 **270** **265**

Following standard ester methylenation procedure 1a, ester **264** (200 mg, 0.75 mmol) gave the desired enol ether product **270** (>100%) with some titanium residues remaining.

δ_H (400 MHz, $CHCl_3$) 2.68 (2H, d, CHCH_2, *J*=7.0 Hz), 3.50 (3H, s, OMe), 3.81 (1H, d, C=CH^AH^B, *J*=2.0 Hz), 3.85 (1H, d, C=CH$^A H^B$, *J*=2.0 Hz), 4.58 (1H, t, NCH, *J*=7.0 Hz), 7.23 (1H, tt, ArH, *J*=7.4, 2.0 Hz), 7.33-7.41 (5H, m, ArH), 7.49 (2H, d, ArH, *J*=7.1 Hz), 7.75-7.78 (2H, d, ArH, *J*=7.1 Hz), 8.25 (1H, s, N=CH)

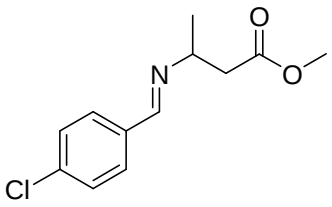
Following cyclization procedure 2b, crude imino-enol ether **270** gave the desired product **265** (112 mg, 60%) after chromatography [SiO_2, MeOH - DCM (1:199-1:99)]

R_f [SiO_2, MeOH - DCM (1:99)] 0.10

δ_H (400 MHz, $CHCl_3$) 2.49-2.60 (4H, m, 2 x CH_2), 4.01 (2H, dd, *J*=10.8, 3.5 Hz, 2 x CH), 7.21-7.42 (10H, m, ArH).

^{1}H NMR data agree with literature.[87]

Methyl [(*E*)-4'-chlorobenzylidenamino]butanoate 266

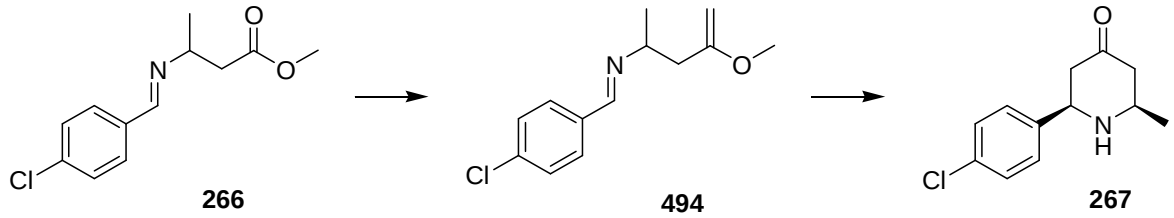


Amine hydrochloride salt **255** (150 mg, 0.98 mmol) was suspended in dry dichloromethane (5 mL) and 4-chlorobenzaldehyde (166 mg, 0.98 mmol), triethylamine (270 μL, 1.96 mmol) and Na_2SO_4 (105 mg, 1.18 mmol) were added. The reaction mixture was stirred under argon at RT for 2.5 h, then washed with water (2 x 30 mL) and brine (1 x 30 mL). The organic extract was dried (Na_2SO_4) and concentrated *in vacuo* to give the crude imine. Excess starting materials were removed by Kugelrohr distillation (0.5 h, 75 °C) affording the imine **266** (165 mg, 70%) as an orange oil.

δ_H (400 MHz, $CHCl_3$) 1.28 (3H, d, *J*= 6.4 Hz, CHCH_3), 2.58 (1H, dd, *J*=15.6, 5.2 Hz, CH^AH^B), 2.67 (1H, dd, *J*=15.6, 8.2 Hz, CH$^A H^B$), 3.62 (3H, s, OCH_3), 3.80-3.89 (1H, m, CH),

7.36 (2H, d, *J*=8.4 Hz, 3-H' and 5'-H), 7.65 (2H, d, *J*=8.5 Hz, 2-H' and 6'-H), 8.29 (1H, s, HC=N); δ_C (100 MHz, $CHCl_3$) 22.3 (CH_3), 42.2 (CH_2), 51.5 (CH), 62.7 (CH_3), 128.8 (CH), 129.4 (CH), 134.6 (C), 136.6 (C), 159.1 (CH), 172.2 (C); IR (cm^{-1}) 2970 (Ar-H), 1737 (C=O), 1644 (C=N), 825 (C-Cl); m/z (EI^+) 241 [^{37}Cl $M^{+\cdot}$, 17%], 239 [^{35}Cl $M^{+\cdot}$, 39%], 84 (100); HRMS: 241.0680 and 239.0711, $C_{12}H_{14}NO_2{}^{37}Cl$ requires $M^{+\cdot}$ 241.0687 and $C_{12}H_{14}O_2N^{35}Cl$ requires $M^{+\cdot}$ 239.0731.

(2*R,6*R**) 2-(4'-Chlorophenyl)-6-methylpiperidin-4-one 267**



Following standard ester methylenation procedure 1a, ester **266** (165 mg, 0.69 mmol) gave the desired enol ether product **494** (>100%) with some titanium residues remaining.

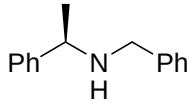
δ_H (400 MHz, $CHCl_3$) 1.41 (3H, d, CH*CH*$_3$, *J*=6.8 Hz), 2.50 (2H, d, CH*CH*$_2$, *J*=6.7 Hz), 3.64 (3H, s, OMe), 3.73 (1H, q, NCH, *J*=6.6 Hz), 4.00 (1H, d, C=C*H*^{A}H^B, *J*=2.0 Hz), 4.03 (1H, d, C=CH^A*H*^{B}, *J*=2.1 Hz), 7.51 (2H, d, 3'-H, *J*=8.4 Hz), 7.80 (2H, d, 2'-H, *J*=8.2 Hz), 8.32 (1H, s, HC=N)

Following cyclization procedure 2a, the crude imino-enol ether **494** gave the desired product **267** (69 mg, 45%) as a beige solid after chromatography [SiO_2, MeOH - DCM (1:199-1:99)] in an 97:3 ratio with a related compound – presumed to be the *anti* diastereomer.

R_f [SiO_2, MeOH - DCM (1:99)] 0.10

δ_H (400 MHz, $CHCl_3$) 1.18 (3H, d, *J*=6.1 Hz, CH_3), 1.81 (1H, br s, NH), 2.14 (1H, dd, *J*=13.5, 12.1 Hz, C*H*^{A}H^B), 2.31-2.41 (3H, m, CH^A*H*^{B} and CH_2), 2.99-3.08 (1H, m, $CHCH_3$), 3.86 (1H, dd, *J*=10.9, 3.9 Hz, ArCH), 7.19-7.29 (4H, m, ArH); COSY couplings of signal at 2.14 ppm with signal at 3.03 ppm, and signal at 2.31-2.41 ppm with signal at 3.86 ppm, combined with large coupling values confirm the *2,6 syn*- geometry; δ_C (100 MHz, $CHCl_3$) 20.7 (CH_3), 47.8 (CH_2), 48.0 (CH_2), 50.4 (CH), 58.5 (CH), 126.0 (CH), 127.0 (CH), 131.6 (C), 139.3 (C), 206.5 (C); IR (cm^{-1}) 3316 (N-H), 1708 (C=O), 828 (C-Cl); m/z (EI^+) 225 [^{37}Cl $M^{+\cdot}$, 62%], 223 [^{35}Cl $M^{+\cdot}$, 100%]; HRMS: 225.0732 and 223.0764, $C_{12}H_{14}NO^{37}Cl$ requires 225.0732 and $C_{12}H_{14}ON^{35}Cl$ requires 223.0764; M.p. 86-87 ºC.

(1*R*)-Benzyl-(1-phenylethyl)amine 277



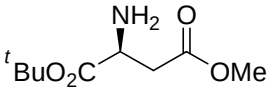
Following the procedure of Salvatore *et al.*[109] (*R*)-methylbenzylamine (210 μL, 1.65 mmol) and cesium carbonate (540 mg, 1.65 mmol) were dissolved in dry DMF (8.3 mL). The mixture was stirred under argon at RT for 30 min. Benzyl bromide (240 μL, 2.00 mmol) was then added slowly and the reaction stirred at RT for 5 h. The mixture was then filtered and concentrated to give a yellow oil which was taken up in 1 M NaOH (aq) (30 mL) and extracted with EtOAc (3 x 30 mL). Organic extracts were then washed with water (2 x 30 mL) and brine (1 x 30 mL), then dried (Na_2SO_4) and concentrated to give a crude oil. Silica gel chromatography [SiO_2, EtOH - EtOAc (1:39)] gave amine **277** (212 mg, 61%) as a yellow oil.

R_f [SiO_2, EtOH - EtOAc (1:39)] 0.57

δ_H (400 MHz, $CHCl_3$) 1.29 (3H, d, *J*=6.6 Hz, CH_3), 1.54 (1H, br. s, NH), 3.54 (1H, d, *J*=13.1 Hz, C*H*^{A}H^B), 3.58 (1H, d, *J*=13.2 Hz, CH^A*H*^{B}), 3.74 (1H, q, *J*=6.6 Hz, NCH), 7.16-7.29 (10H, m, ArH); δ_C (100 MHz, $CHCl_3$) 24.5 (CH_3), 51.7 (CH_2), 57.5 (CH), 126.7 (CH), 126.9 (CH), 127.0 (CH), 128.2 (CH), 128.4 (CH), 128.5 (CH), 140.7 (C), 145.6 (C); $[\alpha]_D$ +38.1, c=0.98 in $CHCl_3$, T=21.6 °C

All data agree with literature.[152]

(2*S*)-Aminosuccinic acid, 1-*tert*-butyl and 4-methyl diester 278



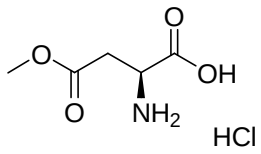
Following the procedure of Bavetsias *et al.*[115] acid **283** (500 mg, 2.70 mmol) was suspended in *tert*-butyl acetate (17.0 mL, 127 mmol) and 70% aqueous perchloric acid (0.23 mL, 2.7 mmol) was added. The reaction was stirred at RT under argon for 95 h. The reaction mixture was then cooled to 0 °C and extracted with cold 0.5 M HCl (aq) (3 x 30 mL). Combined aqueous extracts were basified with $NaHCO_3$ and extracted with diethyl ether (3 x 80 mL). Organics were dried (Na_2SO_4) and concentrated to give the *tert*-butyl ester **278** (250 mg, 45%) as a clear oil.

δ_H (400 MHz, $CHCl_3$) 1.45 (9H, s, ^{t}Bu), 1.97 (2H, br s, NH_2), 2.65 (1H, dd, *J*=16.3, 7.2 Hz, C*H*^{A}H^B), 2.74 (1H, dd, *J*=16.2, 4.8 Hz, CH^A*H*^{B}), 3.70 (1H, s, CH), 3.73 (3H, s, CH_3O); δ_C (100 MHz, $CHCl_3$) 28.0 (CH_3), 39.1 (CH_2), 51.8 (CH), 77.6 (CH_3) 81.6 (C), 171.8 (C), 173.5

(C); IR (cm^{-1}) 3386 (N-H), 2978 (Ar-H), 1735 (C=O); m/z (Cl^+), 204 [$(M+H)^+$, 70%], 148 (100); $[\alpha]_D$ −8.2, c=1.1 in $CHCl_3$, T=25.4 °C

^1H data agree with literature.[153]

(2*S*)-2-aminosuccinic acid, 4-methyl ester, hydrochloride 283

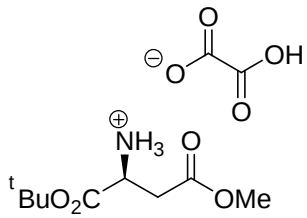


Following the procedure of Cox and Wang[112] (*S*)-aspartic acid (500 mg, 3.8 mmol) was suspended in dry methanol (2.5 mL) and cooled to −10 °C (ice/brine). Thionyl chloride (0.38 mL, 5.3 mmol) was added slowly and the reaction mixture was allowed to warm to RT over 25 min. Diethyl ether (15 mL) was then added and the mixture filtered. The precipitate was washed with diethyl ether and dried under vacuum giving the methyl ester **283 (**416 mg, 60%) as the hydrochloride salt.

δ_H (400 MHz, D_2O) 2.91-2.95 (2H, m, CH_2), 3.56 (3H, s, CH_3O), 4.09-4.17 (1H, m, CH), δ_C (100 MHz, D_2O) 33.7 (CH_2), 49.3 (CH), 52.7 (CH_3), 171.1 (C), 171.9 (C); m/z (Cl^+) 148 [$(M+H)^+$, 100%]; HRMS: 148.0609, $C_5H_{10}NO_4$ requires $(M+H)^+$ 148.0610; [α_D] +12.4 °, c=1.0 in $CHCl_3$, T=24.7 °C; M.p. 184-185 °C.

^1H NMR data agree with literature.[112]

(2*S*)-1-*tert*-butyl,4-methyl 2-aminobutanedioate, oxalate salt 286

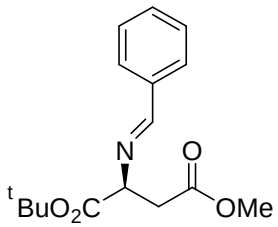


The acid **283** (980 mg, 5.3 mmol) was suspended in *tert*-butyl acetate (33.0 mL, 246 mmol) and 70% aqueous perchloric acid (460 *μ*L, 5.30 mmol) was added. The reaction was stirred at RT under argon for 84 h. The reaction mixture was then cooled to 0 °C and extracted with cold 0.5 M HCl (aq) (3 x 30 mL). Combined aqueous extracts were basified with $NaHCO_3$ and extracted with diethyl ether (3 x 80 mL). Organics were dried (Na_2SO_4) and 0.5 M oxalic acid in diethyl ether was added slowly. The resulting precipitate was collected in a Buchner funnel and washed with diethyl ether. This gave the salt **286** (540 mg, 41%) as a white solid.

δ_H (400 MHz, D_2O) 1.38 (9H, s, ^{t}Bu), 2.96 (1H, dd, *J*=17.9, 4.9 Hz, CH^AH^B), 3.09 (1H, dd, *J*=18.0, 5.6 Hz, CH^AH^B), 3.66 (3H, s, OMe), 4.26 (1H, t, NCH, *J*=5.3 Hz); δ_C (100 MHz,

D_2O) 26.9 (CH_3), 33.8 (CH_2), 49.6 (CH_3), 52.7 (CH), 86.1 (C), 165.1 (C), 167.6 (C), 171.7 (C); IR (cm^{-1}) 2880 (C-H), 1743 (C=O), 1722 (C=O); m/z (CI^+) 204 [$(M+H)^+$, 14%], 148 (100), HRMS: 204.1238, $C_9H_{13}NO_4$ requires $(M+H)^+$ 204.1236; $[\alpha]_D$ +6.6, T=25.4 °C, c=1.0 in $CHCl_3$; M.p. 153-156 ºC.

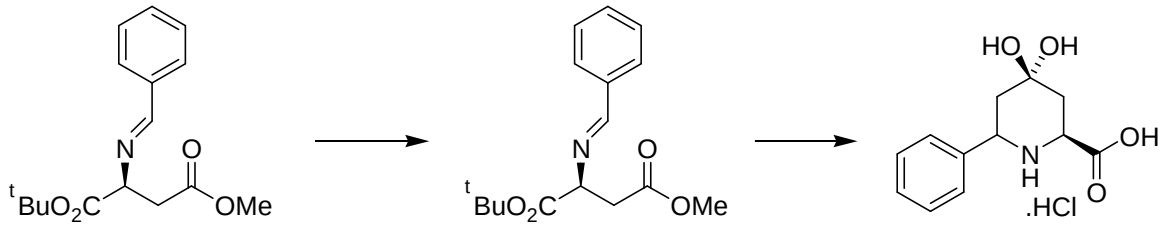
(2*S*)-[(*E*)-Benzylidenamino]succinic acid, 1-*tert*-butyl and 4-methyl diester 287



(2*S*)-Aminosuccinic acid, 1-*tert*-butyl and 4-methyl diester **278** (145 mg, 0.71 mmol) was dissolved in dry dichloromethane (7 mL) and triethylamine (0.10 mL, 0.71 mmol), Na_2SO_4 (202 mg, 1.42 mmol) and benzaldehyde (140 μL, 1.4 mmol) were added. The mixture was stirred under argon at RT for 20 h. The mixture was then washed with water (2 x 20 mL) and brine (1 x 20 mL). Organic extracts were dried (Na_2SO_4) and concentrated to give a crude yellow liquid. Excess aldehyde was removed by Kugelrohr distillation (75 ºC, 45 min) giving the imine **287** (138 mg, 67%) as an oil.

δ_H (400 MHz, $CHCl_3$) 1.46 (9H, s, ^{t}Bu), 2.83 (1H, dd, *J*=16.7, 7.2 Hz, CH^AH^B), 3.11 (1H, dd, *J*=16.6, 6.3 Hz, CH^AH^B), 3.18 (3H, s, OCH_3), 4.36 (1H, dd, CH, *J*=6.8, 6.6), 7.38-7.45 (3H, m, ArH), 7.77 (2H, d, *J*=6.9 Hz, 2'-H and 6'-H), 8.37 (1H, s, HC=N); δ_C (100 MHz, $CHCl_3$) 28.0 (CH_3), 37.5 (CH_2), 51.8 (CH), 69.6 (CH_3), 81.9 (C), 128.6 (CH), 128.6 (CH), 131.2 (CH), 135.7 (C), 164.9 (CH), 169.7 (C), 171.6 (C); IR (cm^{-1}) 2978 (Ar-H), 1735 (C=O), 1643 (C=N); m/z (CI^+), 292 [$(M+H)^+$, 100%]; $[\alpha]_D$ −37.9, c=1 in $CHCl_3$, T=24.8 ºC

(2*S*)-4,4-Dihydroxy-6-phenyl-piperidine-2-carboxylic acid 289



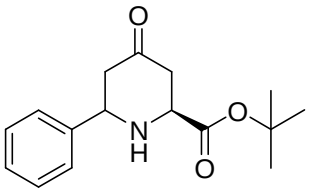
287 **288** **289**

Following standard ester methylenation procedure 1a, ester **287** (138 mg, 0.47 mmol) gave the desired enol ether product **288** (>100%) with some titanium residues remaining δ_H (400 MHz, $CHCl_3$) 1.61 (9H, s, ^{t}Bu), 2.71 (1H, dd, CHC*H*^{A}CH^B, *J*=14.2, 8.4 Hz), 2.95 (1H, dd, CHCH^{A}C*H*^{B}, *J*=13.9, 5.8 Hz), 3.60 (3H, s, OMe), 4.04-4.08 (2H, m, C=CH_2), 4.28 (1H, dd, NCH, *J*=8.3, 5.9 Hz), 7.54-7.60 (3H, m, ArH), 7.91 (2H, d, ArH, *J*=6.8 Hz), 8.34 (1H, s, HC=N)

The crude enol ether **288** (0.47 mmol) was stirred in 7 M HCl (aq) (1.7 mL) for 30 min and then washed with DCM (5 x 15 mL) The aqueous layer was retained and concentrated to give the pipecolic acid derivative **289** as a 1:1 mixture of diastereoisomers, as a brown foam (70 mg, 58%).

δ_H (400 MHz, D_2O) 2.00 (1H^{syn}, t, 3-H_{ax} or 5-H_{ax} , *J*=13.8 Hz) 2.10-2.30 (5H, m, 4H^{anti} and 1H^{syn}), 2.42 (1H^{syn}, d, 3-H_{eq} or 5-H_{eq}, *J*=14.0 Hz), 2.60 (1H^{syn}, d, 3-H_{eq} or 5-H_{eq}, *J*=14.0 Hz), 4.10 (1H^{syn}, dd, H-6, *J*=13.2 and 3.2 Hz), 4.35 (1H^{anti}, H-6, d, *J*=5.2 Hz), 4.42 (1H^{syn}, dd, 2-H, *J*=12.4 and 3.6 Hz), 4.81 (1H^{anti}, br. d, 2-H, *J*=12.0 Hz); δ_C (100 MHz, D_2O) 35.5 (CH_2), 37.0 (CH_2), 40.3 (CH_2), 40.5 (CH_2), 53.9 (CH), 55.4 (CH), 56.3 (CH), 57.8 (CH), 91.1 (C), 91.5 (C), 127.4 (CH), 127.5 (CH), 129.4 (CH), 129.5 (CH), 130.0 (CH), 130.1 (CH), 134.3 (C), 170.9 (C); m/z (EI$^+$) 219 [($M^{+\cdot}$—H_2O), 31%], 174 (63), 131 (100), HRMS: 219.0894, $C_{12}H_{13}NO_3$ requires ($M^{+\cdot}$—H_2O) 219.0895; IR (cm^{-1}) 3250 (OH), 1724 (C=O); $[\alpha]_D$ +6.0, c=1.0 in MeOH, T=22.4 °C

(2*S*)-2-(*tert*-butylcarboxylate-)-6-phenylpiperidin-4-one 295



The enol ether **288** (synthesised as described for compound **289**) (0.37 mmol) was dissolved in DMSO (12 mL) and 1 M HCl (aq) (13 mL) was added. The reaction was stirred at RT for 45 min, basified with 1 M NaOH (aq), then extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with sat. $NH_4.Cl$ (2 x 100 mL), dried (Na_2SO_4) and concentrated to give the crude piperidinone. Column chromatography [SiO_2, MeOH - DCM (1:199)] gave the product **295** as a 2:1 mixture of 2,6-*syn* : 2,6-*anti* (18 mg, 18 %), the major (2,6-*syn*) diastereoisomer was isolated after further chromatography.

R_f [SiO_2, MeOH - DCM (1:99)] 0.29

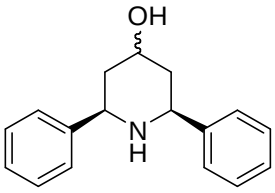
Data for major component (2,6-*syn*):

δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, ^{t}Bu), 2.51- 2.59 (3H, m, CH_2 and CH^AH^B), 2.72-2.77 (1H, m, CH^AH^B), 3.63 (1H, dd, *J*=12.1, 3.0 Hz, Ph*CH*N), 3.93 (1H, dd, *J*=10.4, 4.2 Hz, N*CH*$CO_2{}^t$Bu), 7.30-7.39 (5H, m, ArH) NOESY correlation between peaks at 3.63 and 3.93 ppm confirms *syn* geometry; δ_C (100 MHz, $CDCl_3$) 28.0 (CH_3), 44.1 (CH_2), 50.1 (CH_2), 58.6 (CH), 60.1 (CH), 82.4 (C), 126.6 (CH), 128.2 (CH), 128.7 (CH), 141.7 (C), 170.1 (C), 207.0 (C); IR (cm^{-1}) 1736 (C=O), 1709 (C=O); m/z (Cl^+), 276 [$(M+H)^+$, 100%]; HRMS: 276.1598. $C_{16}H_{21}NO_3$ requires $(M+H)^+$ 276.1600; $[\alpha]_D$ +9.3, c=0.4 in $CHCl_3$, T=19.3 ºC.

NMR data for minor component (2,6-*anti*):

δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, ^{t}Bu), 2.51- 2.59 (3H, m, CH_2 and CH^AH^B), 2.72-2.77 (1H, m, CH^AH^B), 3.98 (1H, dd, *J*=5.4, 4.0 Hz, Ph*CH*N), 4.22 (1H, dd, *J*=7.6, 6.5 Hz, N*CH*$CO_2{}^t$Bu), 7.30-7.39 (5H, m, ArH).

(2*R,6*S**)-2,6-diphenylpiperidin-4-ol 297**



The enol ether **270** (synthesised as described for piperidinone **265**) (0.58 mmol) was dissolved in dry dichloromethane (10 mL) and trifluoroacetic acid (0.44 mL, 4.46 mmol)

and triethylsilane (190 μL, 1.16 mmol) were added. The reaction was stirred at RT under argon for 19 h, then concentrated and taken up in 1 M NaOH (aq). This was washed with ethyl acetate (4 x 50 mL) and organic extracts combined, washed with brine (75 mL), dried (Na_2SO_4) and concetrated. Column chromatography [SiO_2, MeOH - DCM (1:400)] gave an oil, the alcohol **297** (13 mg, 9%) as a 2.5:1 mix of diastereomers.

R_f [SiO_2, MeOH - DCM (1:99)] 0.50

Data for major diastereomer:

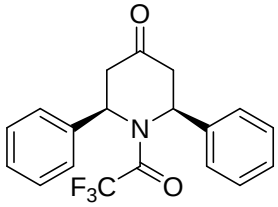
δ_H (400 MHz, $CDCl_3$) 1.73-1.83 (2H, m, CH^AH^B), 1.92 (2H, d, *J*=12.9 Hz, CH^AH^B), 4.27-4.34 (3H, m, *CH*Ph and *CH*OH), 7.23-7.54 (10H, m, ArH)

Data for minor diastereomer (2,4,6-*syn*):

δ_H (400 MHz, $CDCl_3$) 1.53 (2H, apparent q, *J*=11.4 Hz, CH^AH^B), 2.17 (2H, br. d, *J*=11.0 Hz, CH^AH^B), 3.85 (2H, br. d, *J*=11.3 Hz, *CH*Ph), 3.95 (1H, tt, *J*=10.9, 4.6 Hz, *CH*OH), 7.23-7.54 (10H, m, ArH).

Data for the *syn* isomer agree with literature.[154]

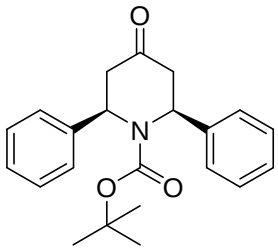
(2*R,6*S**)-2,6-Diphenyl-1-(2,2,2-trifluoro-acetyl)-piperidin-4-one 300**



The enol ether **270** (synthesised as described for piperidinone **265**) (0.62 mmol) was dissolved in dry pyridine (3.0 mL) and TFAA (170 μL, 1.25 mmol) were added. The reaction was stirred under argon at RT for 19 h, then concentrated. The residue was taken up in THF (0.5 mL) and 1 M HCl (10 mL) and stirred at RT for 1 h. The reaction mixture was partially concentrated, and then extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated to give the crude piperidinone. Column chromatography (4:1 Pet. Ether-EtOAc) gave a crude solid which was recrystallised (hot petroleum ether) to give piperidinone **300** (60 mg, 28 %) as yellow prisms.

δ_H (400 MHz, $CDCl_3$, 55 °C) 2.87 (2H, dd, *J*=16.9, 6.2 Hz, CH^AH^B), 3.28 (2H, br. d, *J*=14.9 Hz, CH^AH^B), 5.83-5.86 (2H, m, CH), 7.13-7.18 (10H, m, ArH); δ_C (100 MHz, $CDCl_3$) 43.8 (broad, CH_2), 55.9 (broad, CH), 116.7 (q, *J*=288.4 Hz, C), 127.4 (broad, CH), 128.0 (broad, CH), 128.5 (broad, CH), 137.9 (broad, C), 157.9 (q, *J*=35.7 Hz, C), 205.2 (C); IR (cm^{-1}) 1732 (C=O), 1684 (C=O); m/z (EI^+) 347 [$M^{+\cdot}$, 38%], 215 (87), 104 (100); HRMS: 347.1131 $C_{19}H_{16}NO_2F_3$ requires $M^{+\cdot}$ 347.1133; M.p. 91 °C.

(2*R,6*S**)-2,6-Diphenyl-1-(*tert*-Butoxycarbonylamino)-piperidin-4-one 301**

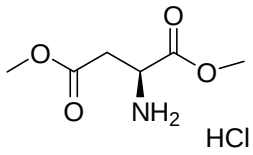


The enol ether **270** (synthesised as described for piperidinone **265**) (0.62 mmol) was dissolved in dry DCM (3.5 mL) and di-*tert*-butylcarbonate (273 mg, 1.25 mmol) was added. The reaction mixture was heated to reflux and stirred under argon for 19 h, then concentrated. The residue was taken up in 2:1 1 M HCl (aq)/THF (15 mL) and stirred at RT for 1.75 h. The reaction mixture was partially concentrated, and then extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), the dried (Na_2SO_4) and concentrated to give the crude piperidinone. Column chromatography [SiO_2, EtOAc - Pet. Ether (1:9)] gave partially impure product **301** (46 mg, 21 %) as a colourless oil.

R_f [SiO_2, EtOAc - Pet. Ether (1:4)] 0.19

δ_H (400 MHz, $CDCl_3$) 1.17 (9H, s, ^{t}Bu), 2.64 (2H, dd, *J*=17.5, 4.2 Hz, C*H*^{A}H^B), 2.90 (2H, dd, *J*=17.6, 6.8 Hz, C*H*^{A}H^B), 5.48–5.51 (2H, m, CHPh), 7.14 –7.31 (10H, m, ArH); δ_C (100 MHz, $CDCl_3$) 28.4 (CH_3), 44.3 (CH_2), 55.1 (CH), 81.1 (C), 126.3 (CH), 127.2 (CH), 128.5 (CH), 143.0 (C), 156.5 (C), 208.0 (C); IR (cm^{-1}) 2974 (Ar-H), 1726 (C=O), 1681 (C=O); m/z (Cl^+) 350 [$(M+H)^+$ 54%], 296 (100); HRMS: 350.1758, $C_{22}H_{24}NO_3$ requires $(M+H)^+$ 350.1756.

Dimethyl (2*S*)-aminosuccinate, hydrochloride salt 302

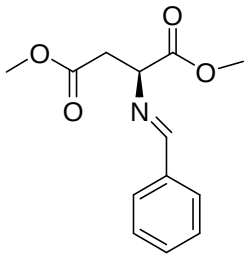


(*S*)-Aspartic acid (1.00 g, 7.5 mmol) was suspended in methanol (10 mL) and cooled to 0 °C. Thionyl chloride (1.92 mL, 26.3 mmol) was then added slowly and the resultant clear solution was allowed to warm to RT and was stirred for 18 h under argon. The reaction mixture was then concentrated to yield the diester hydrochloride salt **302** (1.38 g, 100%) as a beige solid.

δ_H (400 MHz, D_2O) 2.98 (1H, dd, *J*=18.0, 4.8 Hz, C*H*^{A}H^B), 2.99 (1H, dd, *J*=18.0, 4.9 Hz, CH^A*H*^{B}), 3.57 (3H, s, CH_3O), 3.68 (3H, s, CH_3O), 4.31 (1H, t, CH, *J*=5.1 Hz; δ_C (100 MHz,

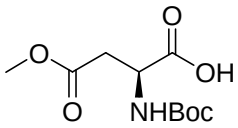
D_2O) 33.6 (CH_2), 49.1 (CH), 52.8 (CH_3), 53.8 (CH_3), 169.4 (C), 171.6 (C); m/z (Cl^+) 162 [$(M+H)^+$, 100%]; HRMS: 162.0764. $C_6H_{11}NO_4$ requires $(M+H)^+$ 162.0766; M.p. 80-85 ºC.
^{1}H NMR data agree with literature.[113]

Dimethyl-(2*S*)-[2-(*E*)-benzylidenamino]butane-1,4-dioate 303



Dimethyl *2*(*S*)-aminosuccinate hydrochloride **302** (150 mg, 0.76 mmol) was suspended in dry dichloromethane (3.5 mL) and benzaldehyde (90 *μ*L, 0.84 mmol), triethylamine (210 *μ*L, 1.52 mmol) and Na_2SO_4 (130 mg, 0.91 mmol) were added. The mixture was stirred under argon at RT for 3.5 h and then washed with water (2 x 20 mL) and brine (1 x 30 mL). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. Excess aldehyde was removed by Kugelrohr distillation (2 h, 65 ºC) yielding the imine **303** (124 mg, 65%) as a yellow oil.
δ_H (400 MHz, $CHCl_3$) 2.87 (1H, dd, *J*=16.8, 7.6 Hz, C*H*^{A}H^B), 3.16 (1H, dd, *J*=16.8, 5.7 Hz, CH^A*H*^{B}), 3.67 (3H, s, CH_3O), 3.75 (3H, s, CH_3O), 4.48 (1H, dd, *J*=7.6, 6.0 Hz, C*H*CH_2), 7.39-7.47 (3H, m, ArH), 7.75-7.77 (2H, m, ArH), 8.38 (1H, s, CH=N); δ_C (100 MHz, $CHCl_3$) 37.4 (CH_2), 51.9 (CH_3), 52.5 (CH_3), 69.0 (CH), 128.7 (CH), 128.7 (CH), 131.4 (CH), 135.5 (C) 165.4 (CH), 171.2 (C), 171.3 (C); m/z (EI^+) 249 [$M^{+\cdot}$, 18%], 190 (100); HRMS: 249.0999. $C_{13}H_{15}NO_4$ requires $M^{+\cdot}$ 249.1001.

4-Methyl (2*S*)-(*tert*-Butoxycarbonylamino)succinate 308



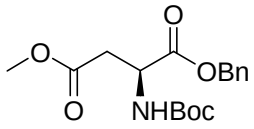
Using the procedure of Woodard and co-workers[120] amine **282** (700 mg, 3.80 mmol) was dissolved in dioxane-water (2:1, 15 mL) and the solution was cooled to 0 ºC. Sodium carbonate (525 mg, 3.80 mmol) was then added and the reaction mixture stirred for 15 min under argon. More sodium carbonate (525 mg, 3.80 mmol) was then added, followed by di-*tert*-butyl carbonate (917 mg, 4.20 mmol). The reaction mixture was stirred for 1 h and then allowed to warm to RT over 18 h. The reaction mixture was

then partially concentrated *in vacuo* and dissolved in water (50 mL). The aqueous was washed with diethyl ether (2 x 100 mL), then cooled to 0 ºC and acidified to pH 1-2 with 1 M HCl (aq). This was washed with diethyl ether (3 x 75 mL), organic extracts were combined, dried (Na_2SO_4) and concentrated to give the Boc protected amine **308** (860 mg, 91 %) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 1.45 (9H, s, ^{t}Bu), 2.84 (1H, dd, *J*=17.3, 4.8 Hz, C*H*^{A}H^B), 3.05 (1H, dd, *J*=17.2, 4.5 Hz, CH^A*H*^{B}), 3.72 (3H, s, CH_3O), 4.59-4.66 (1H, m, C*H*CH_2), 5.55 (1H, d, *J*=7.9 Hz, NH); δ_C (100 MHz, $CDCl_3$) 28.3 (CH_3), 36.3 (CH_2), 49.6 (CH), 52.2 (CH_3), 80.1 (C), 155.4 (C), 171.2 (C), 175.1 (C); m/z (CI^+) 248 [$(M+H)^+$, 9%] 191 (68), 71 (100). HRMS: 248.1136, $C_{10}H_{17}NO_6$ requires $(M+H)^+$ 248.1134; $[\alpha]_D$ +27.1, c=1.0 in $CHCl_3$, T=24.4 ºC

All data agree with literature.[120]

(2*S*)-(*tert*-Butoxycarbonylamino)succinic acid, 1-benzyl and 4-methyl ester 309a



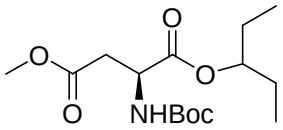
Using the procedure of Stien and Toogood[122a] acid **308** (460 mg, 1.86 mmol) was dissolved in dry DMF (20 mL) and cesium carbonate (1.25 gm, 3.83 mmol) and benzyl bromide (680 μL, 5.70 mmol) were added. The reaction mixture was stirred under argon at RT for 18 h. The reaction mixture was then diluted with water (100 mL) and washed with ethyl acetate (3 x 75 mL). Organic extracts were combined, dried (Na_2SO_4) and concentrated to give a crude oil. Column chromatography [SiO_2, EtOAc - Pet. Ether (1:4)] gave the ester **309a** (559 mg, 89 %) as a white solid.

R_f [SiO_2, EtOAc - Pet. Ether (1:4)] 0.35

δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s, ^{t}Bu), 2.82 (1H, dd, *J*=17.0, 4.6 Hz, C*H*^{A}H^B), 3.02 (1H, dd, *J*=16.9, 4.3 Hz, CH^A*H*^{B}), 3.62 (3H, s, CH_3O), 4.57-4.68 (1H, m, C*H*CH_2), 5.16 (1H, d, *J*=12.1 Hz, PhC*H*^{C}H^D), 5.19 (1H, d, *J*=12.3 Hz, PhCH^C*H*^{D}), 5.50 (1H, d, *J*=8.1 Hz, NH), 7.33-7.37 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$) 28.3, (CH_3) 36.7 (CH_2), 50.1 (CH_3), 52.0 (CH), 67.5 (CH_2), 80.2 (C), 128.3 (CH), 128.4 (CH), 128.6 (CH), 135.3 (C), 155.4 (C), 170.9 (C), 171.4 (C); m/z (CI^+) 338 [$(M+H)^+$, 10%], 282 (100); HRMS: 338.1605, $C_{17}H_{24}NO_6$ requires $(M+H)^+$ 338.1604; IR (cm^{-1}) 3377 (N-H), 2984 (Ar-H), 1737 (C=O), 1697 (C=O);$[\alpha]_D$ +7.3, c=1.0 in $CHCl_3$, T=24.8 ºC; M.p. 45-46 ºC

All data agree with literature.[122a]

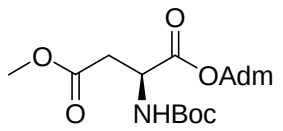
Pent-3-yl (2*S*)-(*tert*-Butoxycarbonylamino)-3-(methoxycarbonyl)propionate 309b



The acid **308** (362 mg, 1.46 mmol) was dissolved in dry acetonitrile (10 mL) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide methiodide (566 mg, 1.90 mmol), dimethylaminopyridine (178 mg, 1.46 mmol) and 3-pentanol (320 μL, 2.93 mmol) were added. The reaction mixture was stirred under argon at RT for 19 h. The mixture was then concentrated, re-dissolved in ethyl acetate (50 mL) and washed with water (2 x 50 mL), 5% $CuSO_4$ (aq.) (2 x 50 mL) and brine (1 x 50 mL). The organic extract was dried ($MgSO_4$) and concentrated to give the ester **309b** (244 mg, 53 %) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J*=7.5 Hz, CH_3), 0.92 (3H, t, *J*=7.4 Hz, CH_3), 1.48 (9H, s, 3 x CH_3), 1.58-1.65 (4H, m, 2 x CH_2), 2.84 (1H, dd, *J*=16.9, 4.8 Hz, $MeO_2CCH^AH^B$), 3.04 (1H, dd, *J*=17.1, 4.4 Hz, $MeO_2CCH^AH^B$), 3.71 (3H, s, CH_3), 4.55-4.60 (1H, m, OCH) 4.80-4.86 (1H, m, NCH), 5.52 (1H, d, *J*=8.2 Hz, NH); δ_C (100 MHz, $CDCl_3$) 9.3 (CH_3), 9.5 (CH_3), 26.2 (CH_2), 26.3 (CH_2), 28.3 (CH_3) 36.7 (CH_2), 50.1 (CH_3), 51.9 (CH), 78.6 (CH), 80.0 (C), 155.9 (C), 170.9 (C), 171.2 (C); IR (cm^{-1}) 3367 (NH), 2972 (CH), 1716 (C=O); m/z (CI^+) 318 [$(M+H)^+$, 14%], 262 (100); HRMS: 318.1919, $C_{15}H_{27}NO_6$ requires $(M+H)^+$ 318.1917; $[\alpha]_D$ +1.5, c=1.0 in $CHCl_3$, T=22.3 °C

Adamant-1-yl (2*S*)-(*tert*-Butoxycarbonylamino)-3-(methoxycarbonyl)propionate 309c



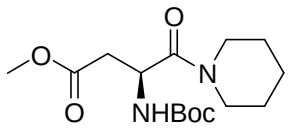
The acid **308** (500 mg, 2.02 mmol) was dissolved in dry dichloromethane (10 mL) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (503 mg, 2.63 mmol), dimethylaminopyridine (247 mg, 2.02 mmol) and 1-adamantol (308 mg, 2.02 mmol) were added. The reaction mixture was stirred for 19 h at RT under argon. The mixture was then washed with water (2 x 50 mL), 1 M $CuSO_4$ (aq.) (2 x 50 mL) and brine (1 x 50 mL). The organic extract was then dried (Na_2SO_4) and concentrated to give the crude ester. Column chromatography [SiO_2, EtOAc - Pet. Ether (1:4)] gave ester **309c** (231 mg, 30 %) as a white solid.

R_f [SiO_2, EtOAc - Pet. Ether (1:4)] 0.36

δ_H (400 MHz, $CDCl_3$) 1.47 (9H, s, ^{t}Bu), 1.66-1.70 (6H, m, 3 x CH_2), 2.11-2.13 (6H, m, 3 x CH_2), 2.17-2.20 (3H, m, 3 x CH), 2.79 (1H, dd, *J*=16.6, 5.0 Hz, $MeO_2CCH^AH^B$), 2.98 (1H,

dd, *J*=16.7, 4.4 Hz, $MeO_2CCH^AH^B$), 3.72 (3H, s, OCH_3), 4.47-4.49 (1H, m, NCH), 5.45 (1H, d, *J*=8.1 Hz, NH); δ_C (100 MHz, $CDCl_3$) 28.4 (CH_3), 30.9 (CH), 36.1 (CH_2), 37.1 (CH_2), 41.1 (CH_2), 50.5 (CH_3), 51.9 (CH), 79.9 (C), 82.4 (C), 155.5 (C), 169.7 (C), 171.4 (C); IR (cm^{-1}) 3385 (NH), 2929 (CH), 1737 (C=O), 1705 (C=O); m/z (CI^+), 382 [$(M+H)^+$, 35%], 329 (100); HRMS: 382.2226, $C_{20}H_{32}NO_6$ requires $(M+H)^+$ 382.2230; $[\alpha]_D$ +2.7, c=1.3 in $CHCl_3$, T= 25.2 °C; M.p. 82-84 °C

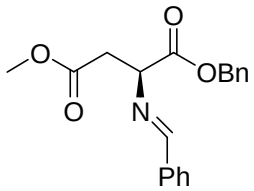
Methyl (2*S*)-3-*tert*-Butoxycarbonylamino-4-oxo-4-(piperidin-1'-yl)butanoate 309d



The acid **308** (560 mg, 2.27 mmol) was dissolved in dry DMF (20 mL) and piperidine (450 *μ*L, 4.53 mmol), 1-hydroxybenzotriazole (306 mg, 2.27 mmol) and *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (435 mg, 2.27 mmol) were added. The reaction mixture was stirred under argon at RT for 18 h after which the reaction mixture was concentrated. The residue was taken up in ethyl acetate (50 mL) and washed with water (3 x 75 mL), sat. $NaHCO_3$ (aq) (3 x 75 mL) and brine (1 x 100 mL). The organic extract was dried (Na_2SO_4) and concentrated to give the amide **309d** (506 mg, 71 %) as a solid.

δ_H (400 MHz, $CDCl_3$) 1.39 (9H, s, ^{t}Bu), 1.50-1.64 (6H, m, 3 x CH_2), 2.53 (1H, dd, *J*=15.6, 6.0 Hz, CH^AH^B), 2.73 (1H, dd, *J*=15.6, 6.6 Hz, CH^AH^B), 3.36-3.45 (2H, m, NCH_2), 3.45-3.65 (2H, m, NCH_2), 3.60 (3H, s, OCH_3), 4.92-4.97 (1H, m, $CHCH_2$), 5.57 (1H, d, *J*=9.4 Hz, NH); δ_C (100 MHz, $CDCl_3$) 22.2 (CH_2), 23.2 (CH_2), 24.1 (CH_2), 25.9 (CH_3), 35.4 (CH_2), 41.2 (CH_2), 44.4 (CH_2), 44.8 (CH), 49.5 (CH_3), 77.6 (C), 152.4 (C), 166.4 (C), 169.0 (C); IR (cm^{-1}) 3275 (NH), 2950 (CH), 1728 (C=O), 1705 (C=O), 1625 (C=O) m/z (FAB^+) 315 [$(M+H)^+$, 15%], 259 (41), 215 (77), 73 (100); HRMS: 315.1928, $C_{15}H_{26}N_2O_5$ requires $(M+H)^+$ 315.1920; $[\alpha]_D$ −18.4, c=1.0 in $CHCl_3$, T=27.0 °C; M.p. 66-68 °C

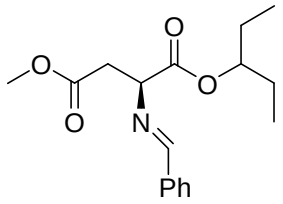
(2*S*)-[(*E*)-Benzylidenamino]succinic acid, 1-benzyl and 4-methyl ester 310a



The Boc protected amine **309a** (310 mg, 0.92 mmol) was dissolved in dry dichloromethane (10 mL) and trifluoroacetic acid (0.5 mL) was added. The reaction mixture was stirred under argon at RT for 4 h, after which it was concentrated to give a clear oil. The oil was dissolved in dry dichloromethane (10 mL) and triethylamine (320 *μ*L, 2.30 mmol), sodium sulfate (261 mg, 1.84 mmol) and benzaldehyde (190 *μ*L, 1.84 mmol) were added. The reaction mixture was stirred under argon at RT for 18 h after which it was washed with water (2 x 30 mL) and brine (1 x 30 mL). The organic extract was dried (Na_2SO_4) and concentrated to give a crude oil containing ~1:1 product:starting material by ^{1}H NMR spectroscopy. The oil was re-dissolved in dry dichloromethane (10 mL) and triethylamine (0.26 mL, 1.8 mmol), sodium sulfate (261 mg, 1.8 mmol) and benzaldehyde (0.28 mL, 2.7 mmol) were added. The reaction mixture was stirred under argon at RT for 18 h after which it was washed with water (2 x 30 mL) and brine (1 x 30 mL). The organic extract was dried (Na_2SO_4) and concentrated to give a crude oil. Removal of excess benzaldehyde by Kugelrohr distillation (75 °C, 45 min) yielded the desired imine **310a** (157 mg, 53 %) as an oil.

δ_H (400 MHz, $CDCl_3$) 2.88 (1H, dd, *J*=16.7, 7.6 Hz, C*H*^{A}H^B), 3.17 (1H, dd, *J*=16.7, 6.1 Hz, CH^A*H*^{B}), 3.63 (3H, s, OCH_3), 4.53 (1H, dd, *J*=7.1, 6.6 Hz, C*H*CH_2), 5.19 (2H, s, CH_2), 7.32-7.45 (8H, m, ArH), 7.74-7.76 (2H, m, ArH), 8.38 (1H, s, HC=N); δ_C (100 MHz, $CDCl_3$) 37.3 (CH_2), 51.8 (CH_3), 67.0 (CH_2), 68.8 (CH), 128.1 (CH), 128.3 (CH), 128.5 (CH), 128.6 (CH), 128.7 (CH), 131.4 (CH), 135.5 (C), 135.5 (C), 165.4 (CH), 170.5 (C), 171.2 (C); IR (cm^{-1}) 2990 (Ar-H), 1732 (C=O), 1639 (C=N); m/z (CI^+) 326 [$(M+H)^+$, 100%]; HRMS: 326.1393, $C_{19}H_{20}NO_4$ requires $(M+H)^+$ 326.1392; $[\alpha]_D$ −1.3, c=1.0 in $CHCl_3$, T=25.0 °C

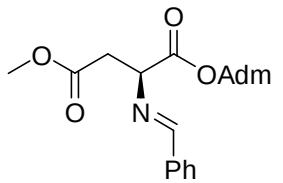
Pent-3-yl (2*S*)-[(*E*)-Benzylidenamino]-3-(methoxycarbonyl)propionate 310b



The Boc protected amine **309b** (231 mg, 0.73 mmol) was dissolved in dry dichloromethane (10 mL) and trifluoroacetic acid (1.0 mL) was added. The reaction mixture was stirred under argon at RT for 3 h, after which it was concentrated to give a clear oil. The oil was dissolved in dry dichloromethane (10 mL) and triethylamine (250 μL, 1.83 mmol), sodium sulfate (207 mg, 1.46 mmol) and benzaldehyde (150 μL, 1.46 mmol) were added. The reaction mixture was stirred under argon at RT for 18 h after which it was washed with water (2 x 30 mL) and brine (1 x 30 mL). The organic extract was dried (Na_2SO_4) and concentrated to give a crude oil. Removal of excess benzaldehyde by Kugelrohr distillation (80 ºC, 1 h) gave the desired imine **310b** (162 mg, 72 %) as an oil.

δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, *J*=7.5 Hz, CH_3), 0.92 (3H, t, *J*=7.5 Hz, CH_3), 1.53-1.68 (4H, m, 2 x CH_2), 2.90 (1H, dd, *J*=16.9, 7.5 Hz, $MeO_2CCH^AH^B$), 3.21 (1H, dd, *J*=16.8, 6.4 Hz, $MeO_2CCH^AH^B$), 4.50-4.53 (1H, m, NCH), 4.85 (1H, quin, *J*=6.3 Hz, OCH), 7.42-7.48 (3H, m, 3 x ArH), 7.80 (2H, d, *J*=6.9 Hz, 2 x ArH), 8.44 (1H, s, HC=N); δ_C (100 MHz, $CDCl_3$) 9.5 (CH_3), 9.6 (CH_3), 26.3 (CH_2), 26.5 (CH_2), 37.3 (CH_2), 51.8 (CH_3), 69.2 (CH), 78.0 (CH), 128.6 (CH), 131.3 (CH), 134.5 (CH), 135.7 (C), 165.0 (CH), 170.4 (C), 171.2 (C); IR (cm^{-1}) 2968 (Ar-H), 1732 (C=O), 1641 (C=N); m/z (CI^+) 306 [$(M+H)^+$, 100%]; HRMS: 306.1707, $C_{17}H_{23}NO_4$ requires $(M+H)^+$ 306.1705; $[\alpha]_D$ −50.5, c=1.0 in $CHCl_3$, T=24.9 ºC

Adamant-1-yl (2*S*)-[(*E*)-Benzylidenamino]-3-(methoxycarbonyl)propionate 310c

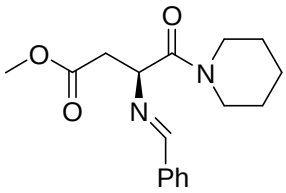


The Boc protected amine **309c** (500 mg, 1.31 mmol) was dissolved in dry dichloromethane (7 mL) and trifluoroacetic acid (1.0 mL) was added. The reaction mixture was stirred under argon at RT for 3 h, after which it was concentrated to give a clear oil. The oil was dissolved in dry dichloromethane (7 mL) and triethylamine (450 μL, 3.28 mmol), sodium sulfate (372 mg, 2.62 mmol) and benzaldehyde (270 μL, 2.62

mmol) were added. The reaction mixture was stirred under argon at RT for 18 h after which it was washed with water (2 x 30 mL) and brine (1 x 30 mL). The organic extract was dried (Na_2SO_4) and concentrated to give a crude oil. Removal of excess benzaldehyde by Kugelrohr distillation (75 ºC, 40 min) gave the desired imine **310c** (279 mg, 58 %) as an oil.

δ_H (400 MHz, $CDCl_3$) 1.67 (6H, s, 3 x CH_2), 2.11-2.14 (6H, m, 3 x CH_2), 2.16-2.20 (3H, m, 3 x CH), 2.85 (1H, dd, *J*=16.6, 7.4 Hz, $MeO_2CCH^AH^B$), 3.14 (1H, dd, *J*=16.6, 6.4 Hz, $MeO_2CCH^AH^B$), 3.70 (3H, s, OCH_3), 4.40 (1H, apparent t, *J*=6.8 Hz, NCH), 7.41-7.47 (3H, m, 3 x ArH), 7.78-7.80 (2H, m, 2 x ArH), 8.40 (1H, s, N=CH); δ_C (100 MHz, $CDCl_3$) 29.1 (CH), 34.4 (CH_2), 35.8 (CH_2), 39.5 (CH_2), 50.1 (CH_3), 67.9 (CH), 80.3 (C), 126.9 (CH), 126.9 (CH), 129.5 (CH), 134.1 (C), 163.1 (CH), 167.7 (C), 169.9 (C); IR (cm^{-1}) 2910 (Ar-H), 1729 (C=O), 1641 (C=N); m/z (EI^+) 369 [$M^{+\cdot}$, 3%], 266 (30), 234 (82), 190 (100); HRMS: 369.1939, $C_{22}H_{27}NO_4$ requires $M^{+\cdot}$ 369.1940; $[\alpha]_D$ +3.3, c=0.25 in $CHCl_3$, T=22.4 ºC

Methyl (2*S*)-4-Oxo-3-[(*E*)-Benzylidenamino]-4-(piperidin-1'-yl)butanoate 310d

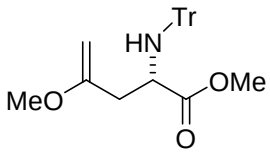


The Boc protected amine **309d** (506 mg, 1.61 mmol) was dissolved in dry dichloromethane (10 mL) and trifluoroacetic acid (1.0 mL) was added. The reaction mixture was stirred under argon at RT for 4 h, after which it was concentrated to give a clear oil. The oil was dissolved in dry dichloromethane (20 mL) and triethylamine (0.56 *μ*L, 4.03 mmol), sodium sulfate (457 mg, 3.22 mmol) and benzaldehyde (0.41 mL, 3.22 mmol) were added. The reaction mixture was stirred under argon at RT for 18 h after which it was washed with water (2 x 50 mL) and brine (1 x 50 mL). The organic extract was dried (Na_2SO_4) and concentrated to give a crude oil. Removal of excess benzaldehyde by Kugelrohr distillation (80 ºC, 1 h) gave the desired imine **310d** (435 mg, 90 %) as an oil.

δ_H (400 MHz, $CDCl_3$) 1.43-1.61 (6H, m, 3 x CH_2), 2.74 (1H, dd, *J*=16.6, 6.1 Hz, CH^AH^B), 3.13 (1H, dd, *J*=16.6, 7.8 Hz, CH^AH^B), 3.50-3.68 (4H, m, 2x CH_2), 3.55 (3H, s, OCH_3), 5.03 (1H, t, *J*=6.9 Hz, $CHCH_2$), 7.39-7.45 (3H, m, ArH), 7.73-7.75 (2H, m, ArH), 8.32 (1H, s, HC=N); δ_C (100 MHz, $CDCl_3$) 24.6 (CH_2), 25.7 (CH_2), 26.5 (CH_2), 37.3 (CH_2), 43.5 (CH_2), 46.7 (CH_2), 51.8 (CH_3), 64.3 (CH), 128.4 (CH), 128.7 (CH), 131.3 (CH), 135.8 (C), 163.0 (CH), 168.2 (C), 172.0 (C); IR (cm^{-1}) 2937 (Ar-H), 1734 (C=O), 1635 (C=N); m/z (CI^+) 303

[(M+H)$^+$, 100%]; HRMS: 303.1705, $C_{17}H_{22}N_2O_3$ requires (M+H)$^+$ 303.1709; $[\alpha]_D$ −62.6, c=1.0 in $CHCl_3$, T=26.0 °C

Methyl (2*S*)-4-methoxy-2-[(triphenylmethyl)amino]pent-4-enoate 327

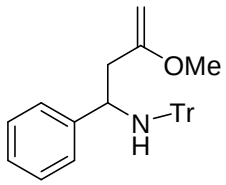


Following standard ester methylenation procedure 1b, diester **326** (205 mg, 0.50 mmol) gave the desired product **327** (>100%) with some titanium residues remaining after flash chromatography [Al_2O_3, Et_2O - Pet. Ether (3:7)].

R_f [Al_2O_3, Et_2O - Pet. Ether (3:7)] 0.71

δ_H (400 MHz, $CDCl_3$) 2.32 (1H, dd, *J*=13.6, 7.1 Hz, C*H*^{A}H^B), 2.54 (1H, dd, *J*=13.6, 6.4 Hz, CH^A*H*^{B}), 2.67 (1H, d, *J*=10.8 Hz, NH), 3.14 (3H, s, OMe), 3.47 (3H, s, OMe), 3.56 (1H, dt, *J*=10.7, 6.8 Hz, N*CH*), 3.95 (1H, d, *J*=1.9 Hz, =C*H*^{A}H^B), 3.98 (1H, d, *J*=1.9 Hz, =CH^A*H*^{B}), 7.15 (3H, t, *J*=7.2 Hz, ArH), 7.24 (6H, t, *J*=7.4 Hz, ArH), 7.49 (6H, d, *J*=7.3 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 41.8 (CH_2), 51.3 (CH), 54.8 (CH_3), 55.2 (CH_3), 71.0 (C), 83.6 (CH_2), 126.3 (CH), 127.7 (CH), 128.9 (CH), 146.0 (C), 159.9 (C) 174.9 (C); m/z (FAB$^+$) 402 [(M+H)$^+$, 31%], 324 (32), 307 (100); HRMS: 402.2066, $C_{26}H_{27}NO_3$ requires (M+H)$^+$ 402.2069.

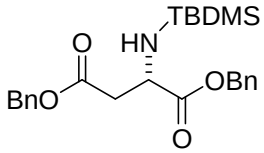
***N*-(3-Methoxy-1-phenylbut-3-en-1-yl)-*N*-(triphenylmethyl)amine 334**



Following standard ester methylenation procedure 1b, ester **329** (211 mg, 0.50 mmol) gave the desired product **334** (>100%) with some titanium residues remaining.

δ_H (400 MHz, $CDCl_3$) 1.79 (1H, dd, *J*=13.5, 7.0 Hz, C*H*^{A}H^B), 2.02 (1H, dd, *J*=13.6, 6.0 Hz, CH^A*H*^{B}), 2.60 (1H, d, *J*=6.0 Hz, NH), 3.28 (3H, s, OMe), 3.46 (1H, d, *J*=1.9 Hz, =C*H*^{A}H^B), 3.64 (1H, d, *J*=1.8 Hz, =CH^A*H*^{B}), 3.83 (1H, q, *J*=6.4 Hz, N*CH*), 7.04-7.20 (14H, m, ArH), 7.45 (6H, d, *J*=7.1 Hz, ArH).

1,4-dibenzyl (2*S*)-2-[(*tert*-butyldimethylsilyl)amino]butanedioate 336

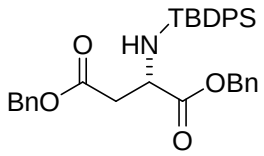


Following the procedure of Baldwin and co-workers[131] amine **335** (235 mg, 0.75 mmol) was dissolved in dry acetonitrile (5 mL) and *N*-*tert*-butyldimethylsilyl-*N*-methyltrifluoroacetamide (MTBSTFA) (520 μL, 2.25 mmol) and TBDMS-Cl (11 mg, 0.075 mmol) were added. The reaction was stirred at RT for 30 min under argon and under reduced pressure for 19 h. ^{1}H NMR analysis showed about 50% conversion so the reaction was re-submitted to the above conditions using MTBSTFA (700 μL, 3.00 mmol) and TBDMS-Cl (22 mg, 0.15 mmol) and then stirred under argon for 66 h. ^{1}H NMR showed almost complete conversion, the reaction was submitted to the original conditions for 19 h giving the product **336** (276 mg, 87%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) -0.04 (3H, s, Si*CH*$_3$), -0.03 (3H, s, Si*CH*$_3$), 0.81 (9H, s, ^{t}Bu), 2.66 (1H, dd, *J*=15.3, 6.8 Hz, CHC*H*^{A}H^B), 2.74 (1H, dd, *J*=15.3, 5.9 Hz, CHCH^A*H*^{B}), 3.81-3.93 (1H, m, N*CH*), 5.03 (1H, d, *J*=12.3 Hz, PhC*H*^{A}H^B), 5.10 (2H, s, Ph*CH*$_2$), 5.12 (1H, d, *J*=12.9 Hz, PhCH^A*H*^{B}), 7.28-7.39 (10H, m, ArH); δ_C (100 MHz, $CDCl_3$) –5.1 (CH_3), -5.0 (CH_3), 17.9 (C), 26.1 (CH_3), 41.9 (CH_2), 52.7 (CH), 66.5 (CH_2), 66.8 (CH_2), 128.3 (CH), 128.3 (CH), 128.5 (CH), 128.6 (CH), 135.7 (C), 170.7 (C), 174.5 (C); m/z (Cl^+) 428 [$(M+H)^+$, 72%], 314 (31), 137 (100), HRMS: 428.2261, $C_{24}H_{33}NO_4$ requires $(M+H)^+$ 428.2257.

All data agree with literature.[131]

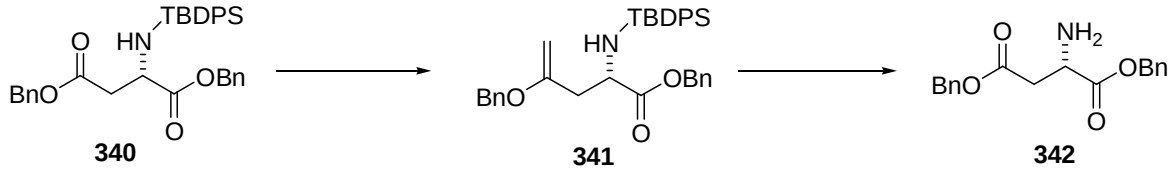
1,4-dibenzyl (2*S*)-2-[(tert-butyldiphenylsilyl)amino]butanedioate 340



The diester salt **339** (486 mg, 1.0 mmol) was suspended in dry acetonitrile (3 mL) and dry triethylamine (350 μL, 2.5 mmol) was added giving a colourless solution. Silver nitrate (425 mg, 2.50 mmol) and TBDPS-Cl (260 μL, 1.0 mmol) were then added causing precipitation of white solid, the reaction mixture was stirred in darkness for 19 h at RT under argon. The reaction mixture was then filtered and washed with diethyl ether. The filtrate was partitioned, and the organic portion washed with water (2 x 50 mL), then dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatorgraphy [SiO_2, NEt_3 - Et_2O - Pet. Ether (1:20:80)] gave silyl amine **340** (439 mg, 80%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 0.98 (9H, s, ^tBu), 1.96 (1H, d, *J*=11.9 Hz, NH), 2.54 (1H, dd, *J*=15.7, 5.8 Hz, CHCH^AH^B), 2.70 (1H, dd, *J*=15.7, 5.1 Hz, CHCH^AH^B), 3.64-3.71 (1H, m, NCH), 4.97 (1H, d, *J*=12.4 Hz, PhCH^CH^D), 4.98 (1H, d, *J*=12.1 Hz, PhCH^EH^F), 5.03 (1H, d, *J*=12.1 Hz, PhCH^CH^D), 5.04 (1H, d, *J*=12.1 Hz, PhCH^EH^F), 7.19-7.23 (2H, m, ArH), 7.25-7.41 (14H, m, ArH), 7.62 (4H, d, *J*=8.1 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 18.5 (C), 27.3 (CH_3), 41.2 (CH_2), 52.3 (CH), 66.4 (CH_2), 66.9 (CH_2), 127.5 (CH), 127.6 (CH), 128.2 (CH), 128.2 (CH), 128.3 (CH), 128.3 (CH), 128.5 (CH), 128.5 (CH), 129.4 (CH), 129.4 (CH), 134.0 (C), 134.4 (C), 135.6 (C), 135.7 (C), 136.0 (CH), 136.1 (CH), 170.7 (C), 174.2 (C); IR (cm^{-1}) 2930 (Ar-H), 1733 (C=O), 1157 (Si-N); m/z (Cl^+) 552 [$(M+H)^+$, 100%]; HRMS: 552.2569, $C_{34}H_{37}NO_4Si$ requires $(M+H)^+$ 552.2570; $[\alpha]_D$ −15.0, c=0.5 in $CHCl_3$, T=25.1 °C.

Benzyl (2*S*)-2-amino-4-(benzyloxy)pent-4-enoate 342



Conversion of ester 340 to enol ether 341

Following standard ester methylenation procedure 1b, diester **340** (197 mg, 0.36 mmol) gave the desired product **341** (>100%) with 20% of the undersired enol ether some titanium residues remaining after flash chromatography [Al_2O_3, Et_2O - Pet. Ether (3:7)]

R_f [Al_2O_3, Et_2O - Pet. Ether (3:7)] 0.74

Data for the major component: δ_H (400 MHz, $CDCl_3$) 0.98 (9H, s, ^tBu), 2.38 (1H, dd, *J*=13.5, 6.4 Hz, CHCH^AH^B), 2.48 (1H, dd, *J*=13.7, 5.3 Hz, CHCH^AH^B), 3.56-3.63 (1H, m, NCH), 3.93 (1H, d, *J*=2.0 Hz, =CH^CH^D), 4.01 (1H, d, *J*=2.1 Hz, =CH^CH^D), 4.56 (1H, d, *J*=11.2 Hz, PhCH^EH^F), 4.61 (1H, d, *J*=10.8 Hz, PhCH^EH^F), 4.78 (1H, d, *J*=12.2 Hz, PhCH^GH^H), 4.84 (1H, d, *J*=12.3 Hz, PhCH^GH^H), 7.05-7.13 (2H, m, ArH), 7.18-7.40 (14H, m, ArH), 7.61 (2H, dd, *J*=8.1, 1.4 Hz, ArH), 7.64 (2H, d, *J*=6.6 Hz, ArH); m/z (Cl^+) 550 [$(M+H)^+$, 45%], 460 (82), 402 (63), 324 (18), 312 (18), 91 (100) HRMS: 550.2781, $C_{35}H_{39}NO_3Si$ requires $(M+H)^+$ 550.2777.

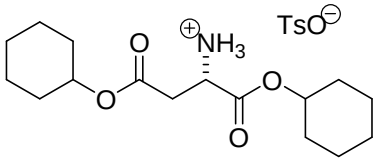
Conversion of enol ether 341 to amine 342

The crude protected amine **341** (0.36 mmol) was dissolved in tetrahydrofuran (3 mL) and 1 M TBAF (0.72 mL, 0.72 mmol) was added changing the reaction mixture from orange to dark green. The reaction was stirred at RT for 19h under argon after which ^{1}H NMR analysis showed no starting material remaining. It was then diluted with diethyl ether (20 mL) and washed with 1 M $NaHCO_3$ (aq) (2 x 20 mL). Organics were dried

(Na_2SO_4) and concentrated in vacuo to give the amine **342** (133 mg, >100%) with minor impurities for TBAF and Ti residues.

Data for the major component: δ_H (400 MHz, $CDCl_3$) 2.55 (1H, dd, *J*=13.9, 7.1 Hz, CHC*H*^{A}H^B), 2.74 (1H, dd, *J*=13.9, 5.1 Hz, CHCH^A*H*^{B}), 3.71-3.79 (1H, m, NCH), 4.04 (1H, d, *J*=2.1 Hz, =C*H*^{A}H^B), 4.09 (1H, d, *J*=2.1 Hz, =CH^A*H*^{B}), 4.68-4.70 (2H, m, $PhCH_2$), 4.96 (1H, d, *J*=12.2 Hz, PhC*H*^{A}H^B), 5.04 (1H, d, *J*=12.2 Hz, PhCH^A*H*^{B}), 7.21-7.41 (10H, m, ArH).

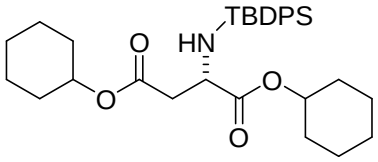
Dicyclohexyl (2*S*)-2-aminobutanedioate, *p*-toluenesulfonic acid salt 344



(*S*)-Aspartic acid (2.00 g, 15.0 mmol) and *p*-toluenesulfonic acid salt (3.56 g, 18.8 mmol) were suspended in cyclohexanol (10.1 mL, 96.0 mmol) and toluene (15 mL). The reaction mixture was heated to reflux and water removed using Dean-Stark apparatus for 19 h. The reaction mixture was then cooled and concentrated *in vacuo*. The solid residue was recrystallised (hexane / diethyl ether / methanol) to give the salt **344** (4.55 g, 64%) as a white amorphous solid.

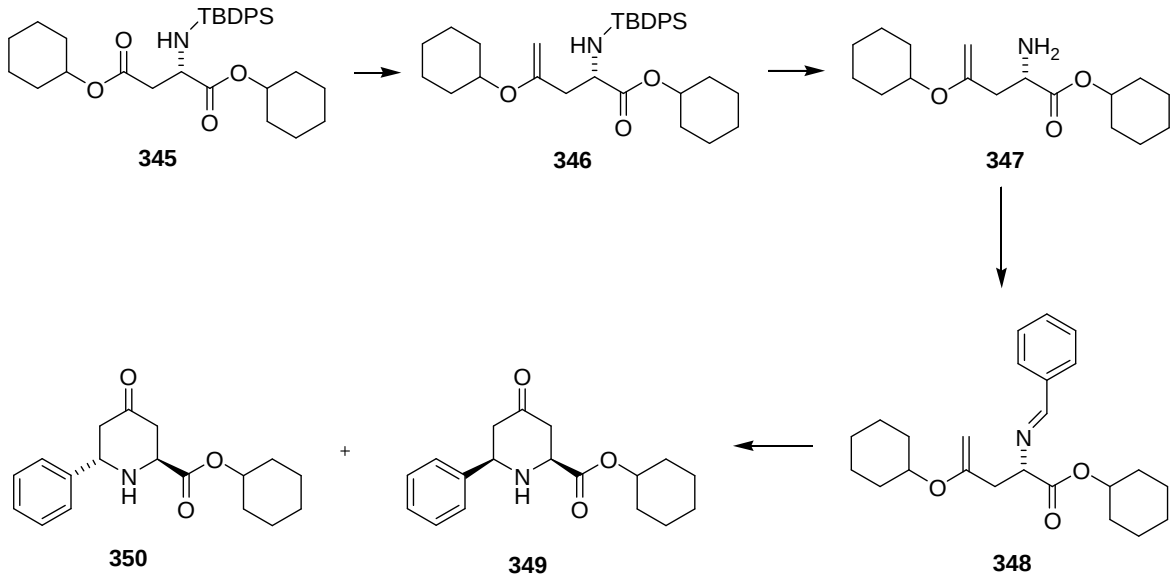
δ_H (400 MHz, $CDCl_3$) 1.12-1.82 (20H, m, cyclohexyl CH_2), 2.35 (3H, s, CH_3), 3.04 (1H, dd, *J*=18.2, 4.8 Hz, CHC*H*^{A}H^B), 3.20 (1H, dd, *J*=18.2, 4.4 Hz, CHCH^A*H*^{B}), 4.38 (1H, apparent t, *J*=4.5 Hz, NCH), 4.64-4.73 (1H, m, OCH), 4.72-4.88 (1H, m, OCH), 7.14 (2H, d, *J*=7.8 Hz, ArH), 7.74 (2H, d, *J*=8.0 Hz, ArH), 8.33 (3H, br. s, NH_3); δ_C (100 MHz, $CDCl_3$) 21.3 (CH_3), 23.4 (CH_2), 23.5 (CH_2), 23.7 (CH_2), 23.8 (CH_2), 25.1 (CH_2), 25.2 (CH_2), 31.0 (CH_2), 31.1 (CH_2), 31.3 (CH_2), 31.4 (CH_2), 33.9 (CH_2), 49.7 (CH), 74.4 (CH), 75.6 (CH), 126.1 (CH), 128.8 (CH), 140.2 (C), 141.6 (C), 167.4 (C), 169.8 (C); IR (cm^{-1}) 3250 (N-H), 2933 (Ar-H), 1739 (C=O), 1720 (C=O), 1195 (S-O), 1010 (S=O); m/z (CI^+) 298 [$(M+H)^+$, 100%]; HRMS: 298.2016, $C_{16}H_{28}NO_4$ requires $(M+H)^+$ 298.2018; $[\alpha]_D$ +19.0, c=1.0 in $CHCl_3$, T=25.3 ºC; M.p. 151-153 ºC.

Dicyclohexyl (2*S*)-2-[(*tert*-butyldiphenylsilyl)amino]butanedioate 345



The diester salt **344** (704mg, 1.50 mmol) was suspended in dry acetonitrile (5 mL) and dry triethylamine (500 μL, 3.75 mmol) was added giving a colourless solution. Silver nitrate (634 mg, 3.75 mmol) and TBDPS-Cl (390 μL, 1.50 mmol) were then added causing precipitation of white solid, the reaction mixture was stirred in darkness for 19 h at RT under argon. The reaction mixture diluted with diethyl ether and washed with water (2 x 50 mL), then dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatorgraphy [SiO_2, NEt_3 - Et_2O - Pet. Ether (1:20:80)] give silylamine **345** (715 mg, 89%) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 1.03 (9H, s, ^tBu), 1.17-1.42 (10H, m, cyclohexyl CH_2), 1.47-1.53 (2H, m, cyclohexyl CH_2), 1.62-1.86 (8H, m, cyclohexyl CH_2), 2.01 (1H, d, J=11.7 Hz, NH), 2.45 (1H, dd, *J*=15.6, 6.1 Hz, CHCH^AH^B), 2.64 (1H, dd, *J*=15.6, 4.3 Hz, CHCH^AH^B), 3.54-3.60 (1H, m, NCH), 4.70-4.77 (2H, m, OCH), 7.31-7.43 (6H, m, ArH), 7.69 (4H, td, *J*=7.8, 1.4 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 18.6 (C), 23.7 (CH_2), 23.7 (CH_2), 25.4 (CH_2), 25.4 (CH_2), 27.3 (CH_3), 31.4 (CH_2), 31.5 (CH_2), 41.6 (CH_2), 52.2 (CH), 72.9 (CH), 73.9 (CH), 127.5 (CH), 127.7 (CH), 129.3 (CH), 129.4 (CH), 134.3 (C), 134.8 (C), 136.0 (CH), 136.1 (CH), 170.4 (C), 173.9 (C);); IR (cm^{-1}) 3375 (N-H), 2933 (Ar-H), 1728 (C=O), 1175 (Si-N); m/z (FAB$^+$) 536 [(M+H)$^+$, 43%], 454 (18), 396 (15), 314 (39), 298 (100); $[\alpha]_D$ −6.4, c=1.0 in $CHCl_3$, T=25.8 ºC

Cyclohexyl (2*S,6*R**)-4-oxo-6-phenylpiperidine-2-carboxylate 349**



Conversion of ester 345 to enol ether 346

Following standard ester methylenation procedure 1b, diester **345** (427 mg, 0.80 mmol) gave enol ether **346** (326 mg, as a 9:1 mixure of enol ether **346** and diester **345**, with some titanocene residues) after flash chromatography [Al_2O_3, Et_2O - Pet. Ether (3:7)]. The product was then taken on without further purification.

NMR and MS data for major component: δ_H (400 MHz, $CDCl_3$) 1.04 (9H, s, ^tBu), 1.20-1.91 (20H, m, cyclohexyl CH_2), 2.28 (1H, dd, *J*=13.6, 6.9 Hz, CHCH^AH^B), 2.41 (1H, dd, *J*=13.7, 4.3 Hz, CHCH^AH^B), 3.45-3.53 (1H, m, NCH), 3.85 (1H, br. s, C=CH^AH^B), 3.86 (1H, br. s, C=CH^AH^B), 4.60-4.77 (2H, m, OCH), 7.30-7.42 (6H, m, ArH), 7.64-7.74 (4H, m, ArH); m/z (CI^+) 534 [$(M+H)^+$, 45%], 394 (100); HRMS: 534.3397, $C_{33}H_{48}NO_3Si$ requires $(M+H)^+$ 534.3403

Conversion of enol ether 346 to amine 347

The crude protected amine **346** was dissolved in 1 M TBAF in tetrahydrofuran (1.83 mL, 1.83 mmol) giving a dark green solution. The reaction mixture was stirred at RT for 19 h under argon after which ^1H NMR analysis showed no starting material remaining. The reaction mixture was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography [Al_2O_3, firstly Et_2O - Pet. Ether (3:17) then NEt_3 – DCM – Pet. Ether (1:50:50 – 1:99:0)] with the product **347** (200 mg, around 40% pure by NMR with TBDMS-F as the major impurity) eluting in the [NEt_3 – DCM – Pet. Ether (1:50:50)] fraction.

^1H NMR data for major component: δ_H (400 MHz, $CDCl_3$) 1.22-1.96 (20H, m, cyclohexyl CH_2), 2.23 (2H, br. s, NH_2), 2.38 (1H, dd, *J*=13.8, 7.3 Hz, CHCH^AH^B), 2.50-2.54 (2H, m, CHCH^AH^B and NCH), 3.59-3.65 (1H, m, =CO*CH*), 3.94 (1H, d, *J*=1.8 Hz, =CH^AH^B), 3.96 (1H, d, *J*=1.9 Hz, =CH^AH^B), 4.72-4.83 (1H, m, OCH).

Conversion of amine 347 to imine 348

The crude amine **347** was dissolved in dry dichloromethane (1.5 mL) and Na_2SO_4 (78 mg, 0.54 mmol) and benzaldehyde (30 μL, 0.30 mmol) were added. The reaction mixture was stirred at RT under argon and followed by ^1H NMR, after 2 h more benzaldehyde (30 μL, 0.30 mmol) was added and the reaction stirred for another 19 h. The reaction mixture was then filtered and concentrated *in vacuo* to give imine **348** (255 mg, around 35% pure by ^1H NMR with PhCHO as the major impurity) as an oil.

^1H NMR data for major component: δ_H (400 MHz, $CDCl_3$) 1.21-1.92 (20H, m, cyclohexyl CH_2), 2.56 (1H, dd, *J*=13.9, 8.6 Hz, CHCH^AH^B), 2.82 (1H, dd, *J*=14.1, 5.3 Hz, CHCH^AH^B), 3.85 (1H, d, *J*=1.5 Hz, =CH^AH^B), 3.92 (1H, d, *J*=1.7 Hz, =CH^AH^B), 3.86-3.91 (1H, m, OCH) 4.23 (1H, dd, *J*=8.6, 5.6 Hz, NCH), 4.80-4.90 (1H, m, OCH), 7.53 (2H, t, *J*=7.6 Hz, ArH), 7.64 (1H, t, *J*=7.6 Hz ArH), 7.92 (2H, d, *J*=7.8 Hz, ArH), 8.08 (1H, s, N=CH)

Conversion of imine 348 to piperidinones 349 and 350

Following cyclization procedure 2a (using 4 equivalents of 1M $^{i}Bu_3Al$ in hexane at 0.15 M concentration in DMSO) crude imine **348** gave the products **349** and **350** (39 mg, 16% from diester **345**) as a 1:1 mixture of diastereomers after column chromatography [SiO_2, MeOH - DCM (1:999-1-99)], one of which was isolated after further chromatography.

R_f [SiO_2, MeOH - DCM (1:199)] 0.30

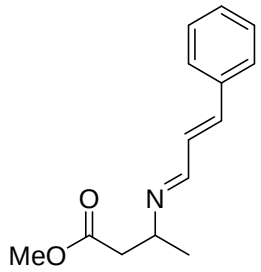
Data for the 2,6-*syn* isomer **349**:

δ_H (500 MHz, $CDCl_3$) 1.19-1.91 (10H, m, cyclohexyl CH_2), 2.49-2.64 (3H, m, 3-CH_2 and 5-H_{eq}), 2.80 (1H, ddd, *J*=14.4, 3.3, 1.7 Hz, 5-H_{ax}), 3.72 (1H, dd, *J*=12.1, 3.3 Hz, 2-H), 3.95 (1H, dd, *J*=10.3, 4.5 Hz, 6-H), 4.80-4.90 (1H, m, OCH), 7.30-7.47 (5H, m, ArH); NOESY correlation between peaks at 3.72 and 3.95 ppm confirms *syn* relationship; δ_C (125 MHz, $CDCl_3$) 23.5 (CH_2), 25.2 (CH_2), 31.4 (CH_2), 44.1 (CH_2), 50.2 (CH_2), 58.1 (CH), 60.2 (CH), 74.0 (CH), 126.6 (CH), 128.1 (CH), 128.9 (CH), 141.8 (C), 170.5 (C), 207.0 (C); IR (cm^{-1}) 2943 (Ar-H), 1732 (C=O), 1710 (C=O); m/z (FAB^+) 302 [$(M+H)^+$, 69%], 58 (100); HRMS: 302.1744, $C_{18}H_{24}NO_3$ requires $(M+H)^+$ 302.1756; $[\alpha]_D$ +37.7, c=1.0 in $CHCl_3$, T=26.1 °C; M. p. 111-112 °C.

Data for 2,6-*anti* isomer **350** (with *syn* isomer impurity):

δ_H (400 MHz, $CDCl_3$) 1.19-1.20 (10H, m, cyclohexyl CH_2), 2.50-2.60 (2H, m, 3-CH_2), 2.75 (1H, dd, *J*=14.9, 6.5 Hz, 5-H_{ax}), 2.81 (1H, dd, *J*=15.0, 3.6 Hz, 5-H_{eq}), 4.08 (1H, dd, *J*=6.5, 3.3 Hz, 6-H), 4.21 (1H, dd, *J*=9.0, 5.1 Hz, 2-H), 4.79-4.89 (1H, m, OCH), 7.22-7.43 (5H, m, ArH).

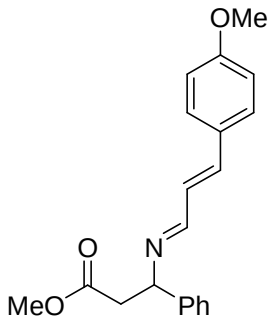
Methyl [(*E*)-[(2'*E*)-3'-phenylprop-2'-enylidene]amino]butanoate 363a



The amine **255** was suspended in dry dichloromethane (10 mL), and cinnamaldehyde (250 μL, 1.96 mmol), triethylamine (540 μL, 3.92 mmol) and Na_2SO_4 (334 mg, 2.35 mmol) were added. The reaction mixture was stirred at RT under argon for 19 h. The mixture was then washed with water (2 x 30 mL) and brine (30 mL) then dried (Na_2SO_4) and concentrated *in vacuo*. Excess starting materials were removed by kugelrohr distillation (90 °C, 40 min) giving the product **363a** (294 mg, 65%) as an oil.

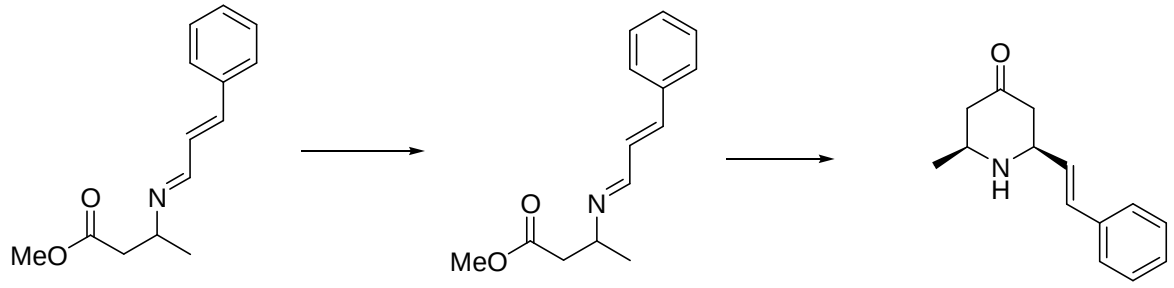
δ_H (400 MHz, $CDCl_3$) 1.26 (3H, d, *J*=6.3 Hz, CH*CH*$_3$), 2.55 (1H, dd, *J*=15.7, 5.3 Hz, C*H*^{A}H^B), 2.63 (1H, dd, *J*=15.4, 8.1 Hz, CH^A*H*^{B}), 3.65 (3H, s, OMe), 3.69-3.79 (1H, m, NCH), 6.87 (1H, dd, *J*=15.9, 8.6 Hz, 2'-H), 6.95 (1H, d, *J*=16.2, 3'-H), 7.30-7.39 (3H, m, ArH), 7.48 (2H, d, *J*=7.8 Hz, ArH), 8.08 (1H, d, *J*=8.5, 1'-H); δ_C (100 MHz, $CDCl_3$) 22.4 (CH_3), 42.3 (CH_2), 51.5 (CH_3), 62.5 (CH), 127.3 (CH), 128.0 (CH), 128.8 (CH), 129.2 (CH), 135.7 (C), 142.1 (CH), 162.2 (CH), 172.2 (C); IR (cm^{-1}) 2968 (ArH), 1734 (C=O), 1634 (C=N), 1618 (C=C); m/z (EI^+) 231 [$M^{+\cdot}$, 100%]; HRMS: 231.1257 $C_{14}H_{17}NO_2$ requires $M^{+\cdot}$ 231.1259

(1'*E*,2'*E*) Methyl 3-[3'-(4"-methoxyphenyl)prop-2'-enylidenamino]-3-phenyl propionoate 363b



The amine **263** (350 mg, 1.62 mmol) was suspended in dry DCM (8 mL) and 4-methoxycinnamaldehyde 262 mg, 1.62 mmol), triethylamine (450 μL, 3.23 mmol) and Na_2SO_4 (276 mg, 1.94 mmol) were added. The reaction mixture was stirred under argon at RT for 19 h. The reaction mixture was then washed with water (2 x 30 mL) and brine (1 x 30 mL). The organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give the crude imine (414 mg). Excess starting materials were removed by Kugelrohr distillation (45 mins, 90 °C) yielding the imine **363b** (383 mg, 73%) as a pale oil.
δ_H (400 MHz, $CDCl_3$) 2.87 (1H, dd, *J*=15.6, 4.5 Hz, C*H*^{A}H^B), 3.02 (1H, dd, *J*=15.6, 9.5 Hz, CH^A*H*^{B}), 3.64 (3H, s, ArOCH_3), 3.82 (3H, s, CO_2CH_3), 4.72 (1H, dd, *J*=9.2, 4.7 Hz, NCHPh), 6.79 (1H, dd, *J*=15.9, 8.8 Hz, NCH=C*H*-CH), 6.87-6.94 (3H, m, PhC*H*=CH and ArH), 7.32-7.41 (7H, m, ArH), 8.11 (1H, d, *J*=8.6 Hz, N=CH); δ_C (100 MHz, $CDCl_3$) 42.9 (CH_2), 51.6 (CH_3), 55.3 (CH_3), 71.0 (CH), 114.3 (CH), 125.8 (CH), 126.9 (CH), 127.4 (CH), 128.5 (C), 128.7 (CH), 128.8 (CH), 142.4 (CH), 142.6 (C), 160.6 (C), 163.8 (CH), 171.8 (C); IR (cm^{-1}) 1732 (C=O), 1633 (C=N); m/z (CI^+), 324 [$(M+H)^+$, 100%]; HRMS: 324.1599. $C_{20}H_{21}NO_3$ requires $(M+H)^+$ 324.1600.

(2*S,6*S**) 2-methyl-6-[(*E*)-2'-phenylethenyl]piperidin-4-one 364a**



363a **495** **364a**

Following standard ester methylenation procedure 1a, ester **363a** (288 mg, 1.28 mmol) gave the desired enol ether **495** (>100%) with some titanium residues remaining.

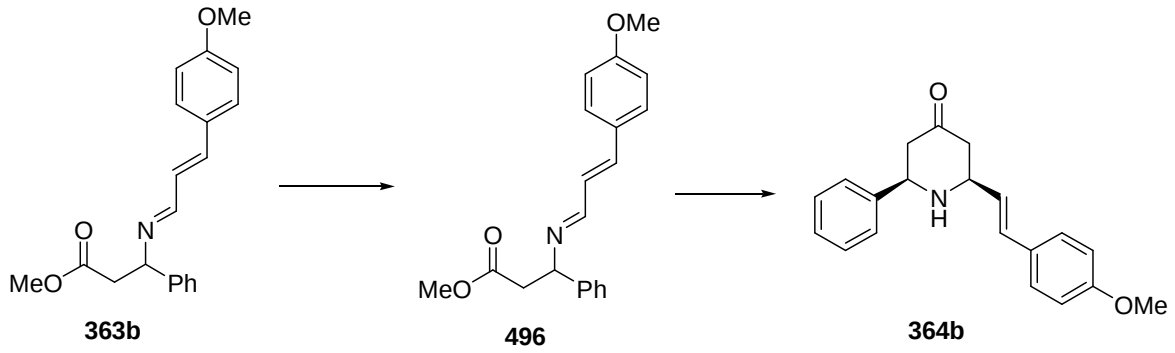
δ_H (400 MHz, $CDCl_3$) 1.24 (3H, d, CHCH_3, *J*=6.4 Hz), 2.33 (2H, d, CHCH_2, *J*=6.8 Hz), 3.48 (1H, q, NCH, *J*=6.5 Hz), 3.51 (3H, s, OMe), 3.88 (1H, d, C=CH^AH^B, *J*=2.0 Hz), 3.90 (1H, d, C=CH^AH^B, *J*=2.0 Hz), 6.90-6.92 (2H, m, 2'-H and 3'-H), 7.30-7.38 (3H, m, ArH), 7.46 (2H, d, ArH, *J*=6.9 Hz)

Following standard cyclization procedure 2b, crude enol ether **495** gave the 2,6-*syn* piperidinone **364a** (94 mg, 35% over 2 steps) as a yellow oil after chromatography [SiO_2, MeOH - DCM (1:100–1:50)].

R_f [SiO_2, MeOH - DCM (1:50)] 0.11

δ_H (400 MHz, $CDCl_3$) 1.25 (3H, d, *J*=6.1 Hz, CH_3), 1.75 (1H, br. s, NH), 2.13 (1H, dd, *J*=13.0, 12.1 Hz, CH^AH^B), 2.19-2.50 (3H, m, CH^AH^B, CH^CH^D, CH^CH^D), 3.03 (1H, m, 2-H), 3.57-3.65 (1H, m, 6-H), 6.21 (1H, dd, *J*=15.9, 7.1 Hz, 1'-H), 6.58 (1H, d, *J*=15.9 Hz, 2'-H), 7.15-7.45 (5H, m, ArH); NOE Irradiation of peak at 3.03 ppm shows an enhancement of peak at 3.57-3.65 ppm and *vice versa* confirming the *syn* relationship; δ_C (100 MHz, $CDCl_3$) 22.7 (CH_3), 47.8 (CH_2), 49.8 (CH_2), 51.9 (CH), 58.9 (CH), 126.4 (CH), 127.9 (CH), 128.6 (CH), 129.8 (CH), 130.4 (CH), 136.4 (C), 208.5 (C); IR (cm^{-1}) 3312 (N-H), 2964 (C-H), 1714 (C=O); m/z (CI^+) 216 [$(M+H)^+$, 19%], 69 (100), HRMS: 216.1389, $C_{14}H_{17}NO$ requires $(M+H)^+$ 216.1388.

(2*S,6*R**) 2-[(*E*)-2'-(4"-methoxyphenyl)ethenyl]-6-phenylpiperidin-4-one 364b**



Following standard ester methylenation procedure 1a, ester **363b** (383 mg, 1.18 mmol) gave the desired enol ether **496** (334 mg, 88%) as a 6:4 mixture with starting material and some titanium residues remaining.

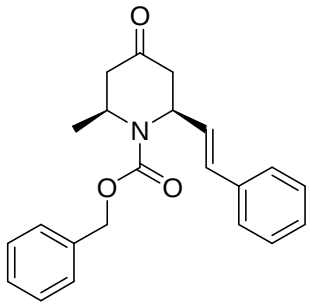
δ_H (400 MHz, $CDCl_3$) 2.67 (2H, d, CHCH_2, *J*=7.0 Hz), 3.51 (3H, s, OMe), 3.82 (3H, s, OMe), 3.85 (1H, br. s, C=CH^ACH^B), 3.88 (1H, br. s, C=CH^{A}CH^B), 4.44 (1H, t, NCH, *J*=7.9 Hz), 6.82-6.91 (4H, m, 2'-H, 3'-H and 3"-H), 7.21-7.44 (7H, m, ArH), 7.98 (1H, d, HC=N, *J*=5.6 Hz)

Following standard cyclization procedure 2b, crude enol ether **496** (0.70 mmol) gave the desired product **364b** (131 mg, 27% over 2 steps) after chromatography [SiO_2, MeOH - DCM (1:199)]

R_f [SiO_2, MeOH - DCM (1:40)] 0.63

δ_H (400 MHz, $CDCl_3$) 1.99 (1H, br. s, NH), 2.45-2.80 (4H, m, 3-H and 5-H), 3.62-3.77 (1H, m, 2-H), 3.80 (3H, s, OMe), 4.00 (1H, dd, *J*=10.6, 3.8 Hz, 6-H), 6.11 (1H, dd, *J*=15.8, 7.3 Hz, 1'-H), 6.52 (1H, d, *J*=15.9 Hz, 2'-H), 6.82 (2H, d, *J*=8.6 Hz, 3"-H and 5"-H), 7.23-7.49 (7H, m, 2"-H, 6"-H and ArH); δ_C (100 MHz, $CDCl_3$) 48.1 (CH_2), 50.1 (CH_2), 55.3 (CH), 59.4 (CH), 61.1 (CH_3), 114.0 (CH), 126.6 (CH), 127.3 (CH), 127.6 (CH), 127.9 (CH), 128.4 (CH), 128.8 (C), 130.7 (CH), 142.5 (C), 159.4 (C), 208.1 (C): IR (cm^{-1}) 3310 (N-H), 2922 (Ar-H), 1721 (C=O), 1606 (C=C); m/z (EI^+) 370 [$M^{+\cdot}$, 25%], 49 (100); HRMS: 307.1573, $C_{20}H_{21}NO_2$ requires $M^{+\cdot}$ 307.1572.

Benzyl (2*S, 6*S**)-2-methyl-4-oxo-6-[(*E*)-2'-phenylethenyl]piperidin-1-yl carboxylate 365a**

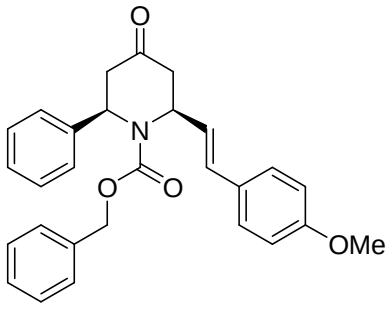


The amine **364a** (63 mg, 0.29 mmol) was dissolved in dichloromethane (1.5 mL) and Na_2CO_3 (69 mg, 0.64 mmol) was added and the mixture was cooled to 0 °C under argon. Benzyl chloroformate (50 μl, 0.32 mmol) was then added dropwise over 5 min and the reaction allowed to warm to RT over 19h. The reaction mixture was then filtered and concentrated *in vacuo* giving the carbamate **365a** (46 mg, 46%) as a dark oil after chromatography [SiO_2, EtOAc - Pet. Ether (3:7)]

R_f [SiO_2, EtOAc - Pet. Ether (3:7)] 0.18

δ_H (400 MHz, $CDCl_3$) 1.32 (3H, d, *J*=6.8 Hz, CH_3), 2.38 (1H, dd, *J*=15.2, 4.6 Hz, 3-H_{eq} or 5-H_{eq}), 2.67-2.84 (3H, m, 3-H_{ax}, 5-H_{ax} and 3-H_{eq} or 5-H_{eq}), 4.68-4.80 (1H, m, 2-H), 5.19 (1H, d, *J*=12.2 Hz, C*H*^{A}H^{B}Ph), 5.23 (1H, d, *J*=12.3 Hz, CH^A*H*^{B}Ph), 5.40-5.47 (1H, m, 6-H), 6.21 (1H, dd, *J*=16.1, 5.6 Hz, 1'-H), 6.51 (1H, d, *J*=16.1 Hz, 2'-H), 7.14-7.40 (10H, m, ArH); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 42.5 (CH_2), 44.5 (CH_2), 49.0 (CH), 53.3 (CH), 67.8 (CH_2), 126.5 (CH), 128.0 (CH), 128.1 (CH), 128.3 (CH), 128.5 (CH), 128.6 (CH), 130.7 (CH), 131.5 (CH), 136.3 (C), 155.5 (C), 171.2 (C), 207.5 (C); IR (cm^{-1}) 2965 (Ar-H), 1719 (C=O), 1695 (C=O); m/z (EI^+) 349 [$M^{+\cdot}$, 2%], 258 (51), 137 (64), 121 (100), HRMS: 349.1675, $C_{22}H_{23}NO_3$ requires $M^{+\cdot}$ 349.1678.

Benzyl (2*S,6*R**)-2-[(*E*)-2'-(4''-methoxyphenyl)ethenyl]-4-oxo-6-phenylpiperidine-1-carboxylate 364b**

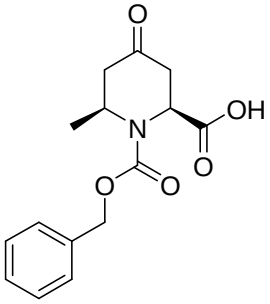


The amine **364b** (131 mg, 0.43 mmol) was dissolved in ethyl acetate (3 mL) and sat. $NaHCO_3$ (aq) (3 mL) was added. The mixture was cooled to 0 °C and stirred vigorously whilst benzyl chloroformate (90 μL, 0.59 mmol) was added dropwise over 5 min. The reaction mixture was allow to warm to RT and stirred for 19h. The reaction mixture was then diluted with ethyl acetate (10 mL), partitioned and the aqueous portion removed. The organics were washed with sat. NH_4Cl (aq) (10 mL) and brine, then were dried (Na_2SO_4) and concentrated *in vacuo* to give the carbamate **365a** (113 mg, 60 %) an oil, after chromatography [SiO_2, EtOAc - Pet. Ether (1:4)]

R_f [SiO_2, EtOAc - Pet. Ether (3:7)] 0.28

δ_H (400 MHz, $CDCl_3$, 55 °C) 2.60-2.83 (3H, m, 3-H_{ax}, 5-H_{ax} and 3-H_{eq} or 5-H_{eq}), 3.09 (1H, dd, *J*=16.8, 5.8 Hz, 3-H_{eq} or 5-H_{eq}), 3.77 (3H, s, OMe), 5.16 (2H, s, $PhCH_2$), 5.31- 5.40 (1H, m, 6-H), 5.68-5.80 (2H, m, 2-H and 1'-H), 6.31 (1H, d, *J*=15.9 Hz, 2'-H), 6.76 (2H, d, *J*=8.8 Hz, 3"-H), 7.00 (2H, d, *J*=8.6 Hz, 2"-H), 7.14-7.33 (10H, m, ArH); δ_C (100 MHz, $CDCl_3$, 55 °C) 43.7 (CH_2), 44.1 (CH_2), 53.9 (CH), 54.9 (CH), 55.2 (CH_3), 67.9 (CH_2), 114.0 (CH), 126.5 (CH), 127.3 (CH), 127.6 (CH), 128.0 (CH), 128.1 (CH), 128.4 (CH), 128.4 (CH), 128.5 (CH), 129.1 (C), 131.2 (CH), 136.2 (C), 142.2 (C), 156.2 (C), 159.6 (C), 204.4 (C); IR (cm^{-1}) 2957 (Ar-H), 1720 (C=O), 1695 (C=O), 1606 (C=C); m/z (CI^+) 442 [$(M+H)^+$, 19%], 69 (100); HRMS: 442.2016, $C_{28}H_{27}NO_4$ requires $(M+H)^+$ 442.2018.

(2*S,6*S**) 1-[(Benzyloxy)carbonyl]-6-methyl-4-oxopiperidine-2-carboxylic acid 366a**

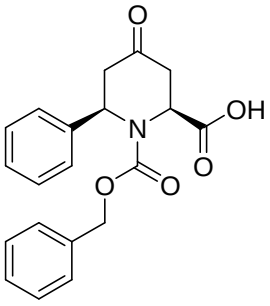


The alkene **365a** (42 mg, 0.12 mmol) was dissolved in carbon tetrachloride (0.6 mL) and acetonitrile (0.6 mL), water (0.9 mL) and $NaIO_4$ (103 mg, 0.48 mmol) were added under argon. The mixture was stirred vigorously until all $NaIO_4$ had dissolved. $RuCl_3$ (0.6 mg, 3 mol%) was then added and the reaction stirred at RT for 19 h. The reaction mixture was then extracted with dichloromethane (3 x 30 mL). Organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo* to give the acid **366a** (8 mg, 23 %) was an oil with minor impurities after chromatography [SiO_2, AcOH - EtOAc - Pet. Ether (0.25:30:70 – 0.25:50:50)].

R_f [SiO_2, AcOH - EtOAc - Pet. Ether (0.25:30:70)] 0.29

δ_H (400 MHz, $CDCl_3$, 55 °C) 1.33 (3H, d, *J*=6.2 Hz, CH_3), 2.39 (1H, dd, *J*=15.8, 4.8 Hz, 3-H_{eq}), 2.65 (1H, dd, *J*=16.0, 6.3 Hz, 3-H_{ax}), 2.71 (1H, dd, *J*=17.2, 7.9 Hz, 5-H_{ax}), 3.00 (1H, dd, *J*=17.4, 3.2 Hz, 5-H_{eq}), 4.60-4.70 (1H, m, 2-H), 5.13-5.26 (3H, m, 6-H and $PhCH_2$), 7.27-7.40 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$) 29.8 (CH_3), 37.8 (CH_2), 43.8 (CH_2), 46.8 (CH), 51.6 (CH), 66.5 (CH), 126.3 (CH), 126.6 (CH), 128.8 (CH), 134.0 (C), 173.9 (C), 174.1 (C), 203.4 (C); IR (cm^{-1}) 3430 (O-H), 2925 (Ar-H), 1740 (C=O), 1730 (C=O), 1700 (C=O).

(2*S,6*R**) 1-[(Benzyloxy)carbonyl]-4-oxo-6-phenylpiperidine-2-carboxylic acid 366b**



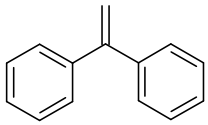
The alkene **365a** (39 mg, 0.09 mmol) was dissolved in carbon tetrachloride (0.4 mL) under argon and acetonitrile (0.4 mL), water (0.6 mL) and $NaIO_4$ (77mg, 0.36 mmol) were added. The mixture was stirred vigorously until all $NaIO_4$ had dissolved. $RuCl_3$ (0.6 mg, 3 mol%) was then added and the reaction stirred at RT for 19 h. The reaction mixture was then extracted with dichloromethane (3 x 20 mL). Organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo* to give the acid **366b** (8 mg, 25 %)

as a dark oil with impurities remaining after chromatography [SiO_2, AcOH - EtOAc - Pet. Ether (0.25:30:70)]

R_f [SiO_2, AcOH - EtOAc - Pet. Ether (0.25:30:70)] 0.13

δ_H (400 MHz, $CDCl_3$) 2.55 (1H, dd, *J*=17.3, 7.4 Hz, 3-H_{ax} or 5-H_{ax}), 2.78-3.02 (3H, m, 3-H_{eq}, 5-H_{eq} and 3-H_{ax} or 5-H_{ax}), 4.91-5.05 (1H, m, 6-H), 5.21 (1H, d, *J*=12.1 Hz, C*H*^{A}H^{B}Ph), 5.26 (1H, d, *J*=12.1 Hz, CH^A*H*^{B}Ph), 5.72-5.88 (1H, m, 2-H), 7.15-7.41 (10H, m, ArH), 9.27 (1H, br. s, CO_2H).

1,1-Diphenylethene 371



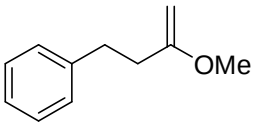
Following methylenation procedure 3a, benzophenone **370** (182 mg, 1 mmol) gave alkene **371** (135 mg, 75%) as a colourless oil, after chromatography [SiO_2, Et_2O - Pet. Ether (1:19)]

R_f [SiO_2, Et_2O - Pet. Ether (1:4)] 0.68

δ_H (400 MHz, $CDCl_3$) 5.50 (2H, s, CH_2), 7.31-7.42 (10H, m, ArH); δ_C (100 MHz, $CDCl_3$) 114.3 (CH_2), 127.7 (CH), 128.2 (CH), 128.3 (CH), 141.5 (C), 150.0 (C); m/z (EI$^+$) 180 [$M^{+\cdot}$, 100%].

All data agree with literature.[155]

(3-Methoxybut-3-en-1-yl)benzene 373



Conventional heating:

Titanocene dichloride (608 mg, 2.44 mmol) was suspended in dry THF (8 mL) under argon and the Nysted reagent (20 %wt in THF, 2.34 mL, 1.22 mmol) was added. This was heated to 40 °C for 45 min until a dark red/black solution formed and then allowed to cool. Methyl 3-phenylpropanoate (190 μL, 1.22 mmol) was then added and the reaction mixture heated to reflux for 19 h. The reaction was then allowed to cool and quenched into sat. $NaHCO_3$ (aq) (70 mL). This was then extracted with dichloromethane (3 x 70 mL) and the combined organics washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product **373**. ^{1}H NMR showed 50 % conversion to product.

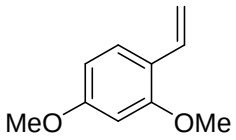
Microwave assisted:

Titanocene dichloride (149 mg, 0.6 mmol) was suspended in dry THF (2 mL) under argon in a microwave vial and the Nysted reagent (20 %wt in THF, 0.58 mL, 0.3 mmol) and methyl 3-phenylpropanoate (0.05 mL, 0.3 mmol) were added. The mixture was irradiated in the microwave (20 min, 80 °C, 100 W) and the resultant black solution quenched into sat. $NaHCO_3$ (aq) (50 mL). This was then extracted with dichloromethane (3x 40 mL) and the combined organics washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product **373**. ^{1}H NMR showed impurities, but no starting material remaining.

δ_H (400 MHz, $CDCl_3$) 2.40 (2H, t, *J*=7.8 Hz, $=CCH_2$), 2.81 (2H, t, *J*=7.7 Hz, $PhCH_2$), 3.56 (3H, s, OMe), 3.86 (1H, d, *J*=2.2 Hz, CH^AH^B), 3.87 (1H, d, *J*=2.0 Hz, CH^AH^B), 7.17-7.25 (2H, m, ArH), 7.27-7.35 (3H, m, ArH)

All data agree with literature.[156]

2,4-Dimethoxybenzene-1-vinylbenzene 374



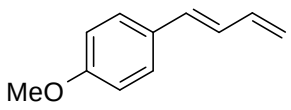
Following methylenation procedure 3a, 2,4-dimethoxybenzaldehyde (332 mg, 2 mmol) gave alkene **374** (208 mg, 63%) as a colourless oil, after chromatography [SiO_2, Et_2O - Pet. Ether (1:9)]

R_f [SiO_2, Et_2O - Pet. Ether (1:1)] 0.62

δ_H (400 MHz, $CDCl_3$) 3.85 (3H, s, OMe), 3.86 (3H, s, OMe), 5.17 (1H, d, *J*=11.2 Hz, CH^AH^B), 5.64 (1H, d, *J*=17.8 Hz, CH^AH^B), 6.47 (1H, s, 3-H), 6.50 (1H, d, *J*=8.5 Hz, 5-H), 6.97 (1H, dd, *J*=17.8, 11.2 Hz, ArCH=), 7.42 (1H, d, *J*=8.4 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 55.4 (CH_3), 55.5 (CH_3), 98.4 (CH), 104.7 (CH), 112.3 (CH_2), 119.9 (C), 127.3 (CH), 131.2 (CH), 157.8 (C), 160.5 (C); m/z (CI^+) 165 [$(M+H)^+$, 15%], 82 (100).

All data agree with literature.[157]

1-[(*1'E*)-1',3'-Butadien-1'-yl]-4-methoxybenzene 375



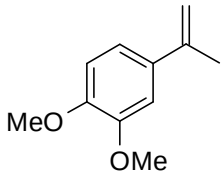
Following methylenation procedure 3a, 4-methoxycinnamaldehyde (324mg, 2 mmol) gave alkene **375** (276 mg, 86%) as an orange oil, after chromatography [SiO_2, Et_2O - Pet. Ether (1:9)]

R_f [SiO_2, Et_2O - Pet. Ether (1:1)] 0.76

δ_H (400 MHz, $CDCl_3$) 3.84 (3H, s, OMe), 5.14 (1H, dd, *J*=10.7, 1.6 Hz, C*H*^{A}H^B), 5.32 (1H, dd, *J*=16.1, 1.6 Hz, CH^A*H*^{B}), 6.50 (1H, dd, *J*=16.7, 10.1 Hz, 3'-H), 6.54 (1H, d, *J*=15.5, 1'-H), 6.69 (1H, dd, *J*=15.4 Hz, 10.5 Hz, 2'-H), 6.89 (2H, d, *J*=8.8, 3-H + 5-H), 7.37 (2H, d, *J*=8.7, 2-H + 6-H); δ_C (100 MHz, $CDCl_3$) 55.3 (CH_3), 114.1 (CH), 116.5 (CH_2), 127.3 (CH), 127.6 (CH) 129.9 (C), 132.4 (CH), 137.4 (CH), 159.3 (C); m/z (EI$^+$) 160 [M$^{+\cdot}$, 37%], 84 (100).

All data agree with literature.[158]

1,2-Dimethoxy-4-(propen-2'-yl)benzene 376



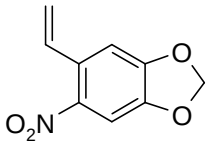
Following methylenation procedure 3a, 3',4'-dimethoxyacetophenone (360 mg, 2 mmol) gave alkene **376** (276 mg, 77%) as pale needles, after chromatography [SiO_2, Et_2O - Pet. Ether (1:9)]

R_f [SiO_2, Et_2O - Pet. Ether (1:9)] 0.53

δ_H (400 MHz, $CDCl_3$) 2.17 (3H, s, CH_3), 3.92 (3H, s, OMe), 3.94 (3H, s, OMe), 5.05 (1H, s, C*H*^{A}H^B), 5.32 (1H, s, CH^A*H*^{B}), 6.86 (1H, d, *J*=8.8 Hz, 6-H), 7.04-7.06 (2H, m, 3-H and 5-H); δ_C (100 MHz, $CDCl_3$) 22.0 (CH_3), 55.8 (CH_3), 55.9 (CH_3), 108.7 (CH), 110.7 (CH), 111.0 (CH_2), 118.0 (CH), 134.2 (C), 142.8 (C), 148.6 (C), 148.6 (C); IR (cm^{-1}) 1602 (C=C), 1580 (Ar); m/z (EI$^+$) 178 [M$^{+\cdot}$, 100%]; HRMS: 178.0990, $C_{11}H_{14}O_2$ requires M$^{+\cdot}$ 178.0994; M.p. 33-34 °C

^{1}H NMR and IR data agree with literature.[159]

5-Vinyl-6-nitro-1,3-benzodioxole 380



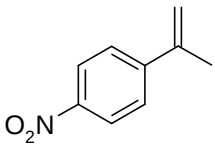
Following methylenation procedure 3b, aldehyde 6-nitropiperonal (390 mg, 2 mmol) gave alkene **380** (292 mg, 76%) as yellow needles, after chromatography [SiO_2, Et_2O - Pet. Ether (1:9-1:1)]

R_f [SiO_2, Et_2O - Pet. Ether (1:1)] 0.48

δ_H (400 MHz, $CDCl_3$) 5.45 (1H, d, *J*=10.9 Hz, C*H*^{A}H^B), 5.65 (1H, d, *J*=17.2 Hz, CH^A*H*^{B}), 6.15 (2H, s, CH_2O_2), 7.02 (1H, s, 4-H), 7.23 (1H, dd, *J*=17.2, 10.9 Hz, ArCH=), 7.52 (1H, s, 7-H); δ_C (100 MHz, $CDCl_3$) 102.6 (CH_2), 104.9 (CH), 106.8 (CH), 117.5 (CH_2), 130.4 (C), 132.8 (CH), 141.5 (C), 147.1 (C), 151.5 (C); IR (cm^{-1}) 3090 (Ar-H), 2925 (Ar-H), 1602 (C=C), 1499 (NO_2), 1329 (NO_2); m/z (CI^+) 194 [$(M+H)^+$, 100%]; HRMS: 194.0457, $C_9H_7NO_4$ requires $(M+H)^+$ 194.0453; M.p. 59-63 ºC

All data agree with literature.[160]

1-(Propen-2'-yl)-4-nitrobenzene 382



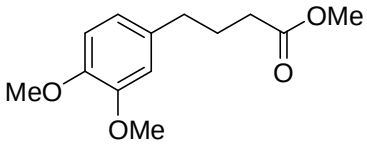
Following methylenation procedure 3b, 4'-nitroacetophenone (330 mg, 2 mmol) gave alkene **382** (191 mg, 59%) as a yellow amorphous solid, after chromatography [SiO_2, Et_2O - Pet. Ether (1:19)]

R_f [SiO_2, Et_2O - Pet. Ether (2:8)] 0.74

δ_H (400 MHz, $CDCl_3$) 2.21 (3H, s, CH_3), 5.31 (1H, s, C*H*^{A}H^B), 5.65 (1H, s, CH^A*H*^{B}), 7.62 (2H, d, *J*=9.0 Hz, 2-H and 6-H), 8.22 (2H, d, *J*=9.0 Hz, 3-H and 5-H); δ_C (100 MHz, $CDCl_3$) 21.6 (CH_3), 116.4 (CH_2), 123.6 (CH), 126.3 (CH), 141.6 (C), 147.0 (C), 147.7 (C); m/z (CI^+) 164 [$(M+H)^+$, 100%]; HRMS: 164.0717, $C_9H_9O_2N$ requires $(M+H)^+$ 164.0712; M.p. 50-53 ºC.

All data agree with literature.[161]

Methyl 4-(3',4'-dimethoxyphenyl)butanoate 384



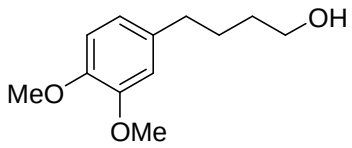
4-(3',4'-dimethoxyphenyl)butanoic acid (500 mg, 2.23 mmol) was dissolved in methanol (15 mL) and cooled to 0 ºC. Thionyl chloride (0.24 mL, 3.3 mmol) was then added dropwise and the reaction mixture heated to reflux for 4 h under argon. The reaction mixture was then concentrated and taken up in ethyl acetate (50 mL) and washed with sat. $NaHCO_3$ (aq) (2 x 50 mL) and brine (50 mL). The organic layer was then dried ($MgSO_4$) and concentrated in vacuo to give the ester **384** (518 mg, 98%) as an oil.

R_f [SiO_2, EtOAc - Pet. Ether (3:7)] 0.25

δ_H (400 MHz, $CDCl_3$) 1.94 (2H, quintet, *J*=7.6 Hz, 3-H), 2.33 (2H, t, *J*=7.4 Hz, 4-H), 2.60 (2H, t, *J*=7.5 Hz, 2-H), 3.67 (3H, s, OMe), 3.86 (3H, s, OMe), 3.88 (3H, s, OMe), 6.68-6.73 (2H, m, 2'-H and 5'-H), 6.79 (1H, d, *J*=7.8 Hz, 6'-H); δ_C (100 MHz, $CDCl_3$) 26.7 (CH_2), 33.3 (CH_2), 34.7 (CH_2), 51.5 (CH_3), 55.8 (CH_3), 55.9 (CH_3), 111.1 (CH), 111.7 (CH), 120.3 (CH), 134.0 (C), 147.3 (C), 148.8 (C), 174.0 (C); m/z (EI^+) 238 [$M^{+\cdot}$, 70%], 207 (20), 164 (82), 151 (100), HRMS: 238.1206, $C_{13}H_{18}O_4$ requires $M^{+\cdot}$ 238.1205.

All data agree with literature.[162]

4-(3',4'-Dimethoxyphenyl)butanol 385



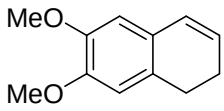
Lithium aluminium hydride (512 mg, 13.5 mmol) was suspended in dry diethyl ether (15 mL) and cooled to 0 ºC under argon. The ester **384** (1.46 g, 6.1 mmol) in dry diethyl ether (15 mL) was then added dropwise and the reaction allowed to warm to RT over 4h. The reaction was then quenched with acetone and then water and the resultant mixture extracted with diethyl ether (3 x 50 mL). Organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give the alcohol **385** (1.25 g, 97%) as a colourless oil.

R_f [SiO_2, EtOAc - Pet. Ether (3:7)] 0.10

δ_H (400 MHz, $CDCl_3$) 1.28 (1H, br. s, OH), 1.56-1.74 (4H, m, 2-H and 3-H), 2.60 (2H, t, *J*=7.3 Hz, 4-H), 3.67 (2H, t, *J*=6.5 Hz, 1-H), 3.87 (3H, s, OMe), 3.89 (3H, s, OMe), 6.70 (1H, s, 2'-H), 6.71 (1H, d, *J*=8.4 Hz, 5'-H), 6.79 (1H, d, *J*=8.3 Hz, 6'-H); δ_C (100 MHz, $CDCl_3$) 27.8 (CH_2), 31.0 (CH_2), 32.3 (CH_2), 55.8 (CH_3), 55.9 (CH_3), 62.9 (CH_2), 111.1 (CH),

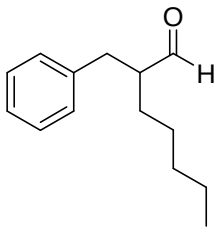
111.6 (CH), 120.1. (CH), 135.0 (C), 147.1 (C), 148.7 (C); m/z (CI^+) 211 [$(M+H)^+$, 100%]; HRMS: 211.1328, $C_{12}H_{19}O_3$ requires $(M+H)^+$ 211.1334.
All data agree with literature.[163]

6,7-Dimethoxy-1,2-dihydronaphthalene 389



Oxalyl chloride (0.99 mL, 8.3 mmol) was dissolved in dry dichloromethane (20 mL) and cooled to −78 °C under argon. Dry DMSO (1.05 mL, 15.9 mmol) was added dropwise and the reaction stirred for 15 min. The alcohol **385** (1.26 g, 6.0 mmol) in dry dichloromethane (10 mL) was then added dropwise and the reaction stirred for 20 min. Finally dry triethylamine (4.15 mL, 29.8 mmol) was added dropwise and the reaction mixture stirred for 30 min before being allowed to warm to RT over 3 h. The reaction mixture was then partially concentrated and taken up in diethyl ether (50 mL). It was then washed with water (2 x 50 mL) and brine (50 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to give a crude oil. Chromatography [SiO_2, EtOAc - Pet. Ether (3:7–1:1)] gave an impure sample of the undesired cyclized product **389** (183 mg, 16%).
R_f [SiO_2, EtOAc - Pet. Ether (3:7)] 0.34
δ_H (400 MHz, $CDCl_3$) 2.25-2.33 (2H, m, 2-H), 2.73 (2H, t, *J*=8.3 Hz, 1-H), 3.87 (3H, s, OMe), 3.88 (3H, s, OMe), 5.93 (1H, dt, *J*=9.5, 4.4 Hz, 3-H), 6.38 (1H, d, *J*=9.6 Hz, 1-H), 6.60 (1H, s, 5-H), 6.71 (1H, s, 8-H)
All data agree with literature.[164]

2-Benzylheptanal 393

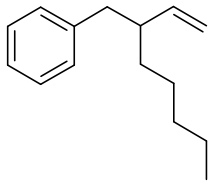


α-Amylcinnamaldehyde (1.00 g, 4.90 mmol), was dissolved in methanol (15 mL) and 10% palladium on carbon (100 mg, 10%wt) was added. The reaction mixture was stirred under a hydrogen atmosphere for 1 h at RT. The reaction mixture was then filtered through celite and the filtrate concentrated *in vacuo*. Chromatography [SiO_2, Et_2O - Pet. Ether (1:9)] gave aldehyde **393** (470 mg, 47%) as an oil.

R_f [SiO_2, EtOAc - Pet. Ether (1:4)] 0.29

δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, *J*=7.1 Hz, CH_3), 1.20-1.41 (6H, m, 4-H, 5-H and 6-H), 1.42-1.51 (1H, m, 3-H^AH^B) 1.60-1.70 (1H, m, 3-H^AH^B), 2.56-2.67 (1H, m, 2-H), 2.71 (1H, dd, *J*=14.0, 6.8 Hz, PhCH^CH^D), 2.99 (1H, dd, *J*=13.9, 7.3 Hz, PhCH^CH^D), 7.17 (2H, d, *J*=6.8 Hz, ArH), 7.22 (1H, tt, *J*=7.4, 1.3 Hz, ArH), 7.26-7.31 (2H, m, ArH), 9.66 (1H, d, *J*=2.6 Hz, 1-H); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 22.4 (CH_2), 26.6 (CH_2), 28.6 (CH_2), 31.8 (CH_2), 35.0 (CH_2), 53.5 (CH), 126.4 (CH), 128.5 (CH), 129.0 (CH), 138.9 (C), 204.8 (CH); IR (cm^{-1}) 2929 (Ar-H), 1724 (C=O); m/z (EI^+) 204 [$M^{+\cdot}$, 19%], 148 (27), 133 (75), 105 (36), 91 (100); HRMS: 204.1512, $C_{14}H_{20}O$ requires $M^{+\cdot}$ 204.1514.

(2'-Vinylhept-1'-yl)benzene 394

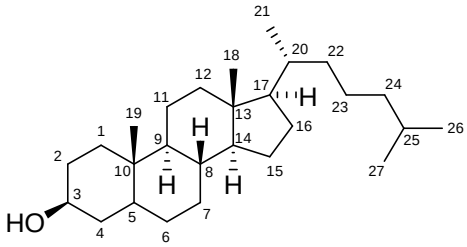


Following procedure 3b, aldehyde **393** (204 mg, 1.0 mmol) gave alkene **394** (103 mg, 51%) as an colourless oil, after chromatography [SiO_2, Et_2O - Pet. Ether (0:1-1:1)]

R_f [SiO_2, Et_2O - Pet. Ether (1:1)] 0.66

δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, *J*=6.8 Hz, CH_3), 1.16-1.44 (8H, m, 4 x CH_2), 2.22-2.32 (1H, m, 2'-H), 2.60 (1H, dd, *J*=13. Hz 4, 7.6 Hz, 1'-H^AH^B), 2.65 (1H, dd, *J*=13.5 Hz, 6.7 Hz, 1'-H^AH^B), 4.85 (1H, ddd, *J*=17.0 Hz, 2.0 Hz, 0.8 Hz, =CH^CH^D), 4.92 (1H, ddd, *J*=10.3 Hz, 2.0 Hz, 0.3 Hz, =CH^CH^D) 5.53-5.59 (1H, m, =CH), 7.11-7.19 (3H, m, ArH), 7.23-7.30 (2H, m, ArH); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.6 (CH_2), 23.8 (CH_2), 31.9 (CH_2), 34.1 (CH_2), 41.8 (CH_2), 45.7 (CH), 114.4 (CH_2), 125.7 (CH), 128.0 (CH), 129.3 (CH), 140.7 (C), 142.6 (CH); IR (cm^{-1}) 3150 (Ar-H) 2926 (C-H), 1641 (C=C); m/z (EI^+) 202 [$M^{+\cdot}$, 36%], 104 (30), 91 (100); HRMS: 202.1720, $C_{15}H_{22}$ requires $M^{+\cdot}$ 202.1722.

3β-Hydroxy-5α-cholestane 396



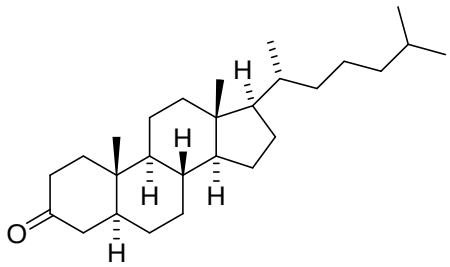
Cholesterol (1.50 g, 3.88 mmol) was dissolved in ethanol (20 mL) and 10% palladium on carbon (150 mg, 10%wt.) was added. The reaction mixture was heated to 45 °C for 19 h under a hydrogen atmosphere, then cooled and filtered through celite. The celite was washed with ethyl acetate and the combined filtrates were concentrated *in vacuo*. Chromatography [SiO_2, EtOAc - Pet. Ether (1:9-3:7)] gave the hydrogenated product **396** (1.12 g, 74%) as a white solid.

R_f [SiO_2, EtAcO - Pet. Ether (1:4)] 0.25

δ_H (400 MHz, $CDCl_3$) 0.65 (3H, s, 18-CH_3), 0.80 (3H, s, 19-CH_3), 0.86 (3H, d, 26-CH_3, *J*=6.7 Hz), 0.87 (3H, d, 27-CH_3, *J*=6.6 Hz), 0.90 (3H, d, 21-CH_3, *J*=6.6 Hz), 0.92-1.59 (27H, m, alkyl-H), 1.62-1.73 (2H, m, alkyl-H), 1.75-1.86 (2H, m, alkyl-H), 1.96 (1H, dt, 4-H_{eq}, *J*=12.9, 3.6 Hz), 3.54-3.63 (1H, m, 3-H); δ_C (100 MHz, $CDCl_3$) 12.1 (CH_3), 12.3 (CH_3), 18.7 (CH_3), 21.1 (CH_2), 22.5 (CH_3), 23.8 (CH_3), 24.2 (CH_2), 24.3 (CH_2), 28.0 (CH), 28.3 (CH_2), 28.8 (CH_2), 31.5 (CH_2), 32.1 (CH_2), 35.5 (CH), 35.8 (CH), 36.5 (CH_2), 37.3 (CH_2), 38.2 (CH_2), 38.2 (C), 39.5 (CH_2), 40.1 (CH_2), 42.6 (C), 44.9 (CH), 54.4 (CH), 56.3 (CH), 56.5 (CH), 71.4 (CH); m/z (EI^+) 388 [$M^{+\cdot}$, 100%]; HRMS: 388.3702, $C_{27}H_{48}O$ requires $M^{+\cdot}$ 388.3705; M.p. 121-123 °C.

All data agree with literature.[165]

5α-cholestan-3-one 397



Oxalyl chloride (0.30 mL, 3.6 mmol) was dissolved in dry dichloromethane (8 mL) and cooled to −78 °C under argon. Dry DMSO (460 μL, 6.43 mmol) was added dropwise and the reaction stirred for 15 min. Alcohol **396** (1.00 g, 2.57 mmol) in dry dichloromethane (10 mL) was then added dropwise and the reaction stirred for 20 min. Finally dry triethylamine (1.80 mL, 12.9 mmol) was added dropwise and the reaction mixture stirred for 30 min before being allowed to warm to RT over 5 h. The reaction mixture was then partially concentrated and taken up in diethyl ether (70 mL). The mixture was

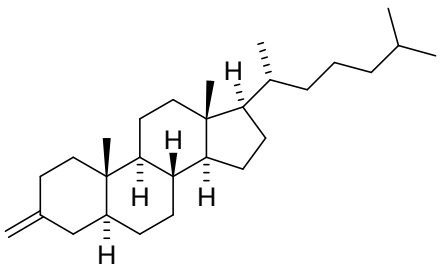
washed with water (2 x 100 mL) and brine (100 mL) then dried ($MgSO_4$) and concentrated *in vacuo* to give crude product. Chromatography [SiO_2, EtOAc - Pet. Ether (1:19)] gave the ketone **397** (731 mg, 74%) as a white amorphous solid.

R_f [SiO_2, EtOAc - Pet. Ether (1:4)] 0.56

δ_H (400 MHz, $CDCl_3$) 0.67 (3H, s, CH_3), 0.68-0.76 (1H, m, CH), 0.86 (3H, d, *J*=6.7 Hz, CH_3), 0.87 (3H, d, *J*=6.6 Hz, CH_3), 0.90 (3H, d, *J*=6.6 Hz, CH_3), 0.98-1.43 (17H, 8 x CH_2 and 1 x CH), 1.00 (3H, s, CH_3), 1.45-1.61 (5H, m, 2 x CH_2 and 1 x CH), 1.69 (1H, dq, *J*=13.2, 3.1 Hz, CH), 1.78-1.86 (1H, m, CH), 1.96-2.05 (2H, m, CH_2), 2.08 (1H, ddd, *J*=14.6, 3.8, 2.1 Hz, CH), 2.21-2.32 (2H, m, CH_2), 2.37 (1H, qd, *J*=15.3, 6.5 Hz, CH); δ_C (100 MHz, $CDCl_3$) 11.5 (CH_3), 12.1 (CH_3), 18.7 (CH_3), 21.5 (CH_2), 22.6 (CH), 22.9 (CH), 23.8 (CH_2), 24.3 (CH_2), 28.0 (CH), 28.3 (CH_2), 29.0 (CH_2), 31.7 (CH_2), 35.4 (CH_3), 35.7 (C), 35.8 (CH_3), 36.2 (CH_2), 38.2 (CH_2), 38.6 (CH_2), 39.5 (CH_2), 39.9 (CH_2), 42.6 (C), 44.8 (CH_2), 46.7 (CH), 53.8 (CH), 56.3 (CH), 56.3 (CH), 212.3 (C); IR (cm^{-1}) 2930 (C-H), 1711 (C=O); m/z (EI^+) 386 [$M^{+\cdot}$, 100%]; HRMS: 386.3553, $C_{27}H_{46}O$ requires $M^{+\cdot}$ 386.3549; $[\alpha]_D$ +43.9, c=1.0 in $CHCl_3$, T=25.2 ºC; M.p. 124-126 ºC.

All data agree with literature.[166]

3-Methylen-5α-cholestane 398



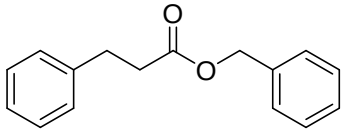
Following methylenation procedure 3d, ketone **397** (193 mg, 0.5 mmol) gave alkene **398** (94 mg, 49%) as a white amorphous solid, after chromatography [SiO_2, EtOAc - Pet. Ether (0:1-1:4)]

R_f [SiO_2, EtOAc - Pet. Ether (1:9)] 0.68

δ_H (400 MHz, $CDCl_3$) 0.64 (3H, s, CH_3), 0.85 (3H, s, CH_3), 0.86 (3H, d, *J*=6.6 Hz, CH_3), 0.86 (3H, d, *J*=6.6 Hz, CH_3), 0.89 (3H, d, *J*=6.6 Hz, CH_3), 0.95-1.40 (19H, m, 7 x CH_2, 5 x CH), 1.45-1.59 (4H, m, 2 x CH_2), 1.61-1.68 (1H, m, CH), 1.74-1.83 (2H, m, CH_2), 1.89 (1H, dd, *J*=13.2, 2.6 Hz, CH) 1.92-2.04 (2H, m, CH_2), 2.10-2.24 (2H, m, CH_2), 4.55-4.56 (2H, m, =CH_2); δ_C (100 MHz, $CDCl_3$) 11.8 (CH_3), 12.1 (CH_3), 18.7 (CH_3), 21.1 (CH_2), 22.6 (CH), 22.8 (CH), 23.8 (CH_2), 24.2 (CH_2), 28.0 (CH_2), 28.3 (CH), 28.9 (CH_2), 31.0 (CH_2), 32.0 (CH_2), 35.5 (CH_3), 35.8 (CH_3), 36.0 (C), 36.2 (CH_2), 38.0 (CH_2), 39.5 (CH_2), 39.9 (CH_2), 40.0 (CH_2), 42.6 (C), 48.1 (CH), 54.4 (CH), 56.3 (CH), 56.5 (CH), 105.9 (CH_2),

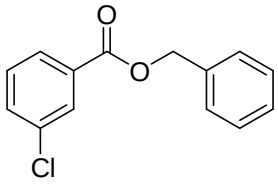
150.3 (C); m/z (EI^+) 384 [$M^{+\cdot}$, 40%], 229 (42), 44 (100); $[\alpha]_D$ +20.1, c=0.5 in $CHCl_3$, T=21.6 °C; M.p. 65-66 °C.
All data agree with literature.[20]

Benzyl 3-phenylpropanoate 399



Following the procedure of Roy *et al.*[167] 3-phenylpropanoic (1.00 g, 6.66 mmol) and K_2CO_3 (920 mg, 6.66 mmol) were suspended in acetone (15 mL) and benzyl bromide (0.86 mL, 7.3 mmol) was added. The reaction mixture was heated to reflux for 19 h under argon and then cooled, filtered and concentrated *in vacuo*. The residue was taken up in diethyl ether (50 mL), washed with water (2 x 50 mL) and brine (50 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by chromatography [SiO_2, Et_2O - Pet. Ether (1:9)] giving ester **399** (1.40 g, 87 %) as a colourless oil.
R_f [SiO_2, Et_2O - Pet. Ether (1:9)] 0.29
δ_H (400 MHz, $CDCl_3$) 2.69 (2H, t, *J*=8.1 Hz, $PhCH_2$), 2.96 (2H, t, *J*=8.0 Hz, $CH_2C{=}O$), 5.11 (2H, s, OCH_2Ph), 7.14-7.22 (3H, m, ArH), 7.24-7.39 (7H, m, ArH); δ_C (100 MHz, $CDCl_3$) 30.9 (CH_2), 35.9 (CH_2), 66.3 (CH_2), 126.3 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 128.5 (CH), 135.9 (C), 140.4 (C), 172.7 (C); m/z (EI^+) 240 [$M^{+\cdot}$, 6%]; 149 (32),91 (100); HRMS: 240.1151, $C_{16}H_{16}O$ requires $M^{+\cdot}$ 240.1150.
All data agree with literature.[168]

Benzyl 3-chlorobenzoate 400



3-Chlorobenzoic acid (1.00 g, 6.39 mmol) and K_2CO_3 (883 mg, 6.39 mmol) were suspended in acetone (15 mL) and benzyl bromide (0.84 mL, 7.0 mmol) was added. The reaction was heated to reflux for 19 h under argon and then cooled, filtered and concentrated *in vacuo*. The residue was taken up in diethyl ether (50 mL), washed with water (2 x 50 mL) and brine (50 mL), then dried ($MgSO_4$) and concentrated *in vacuo*.

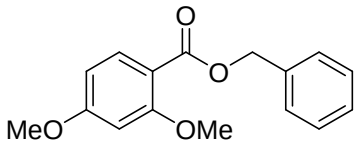
Chromatography [SiO_2, Et_2O - Pet. Ether (0:1-8:92)] gave ester **400** (0.97 gm, 61%) as an oil.

R_f [SiO_2, Et_2O - Pet. Ether (1:9)] 0.30

δ_H (400 MHz, $CDCl_3$) 5.37 (2H, s, Ph*CH*$_2$), 7.33-7.46 (6H, m, PhH and 5-H), 7.54 (1H, ddd, *J*=8.0, 2.2, 1.1 Hz, 4-H), 7.95 (1H, ddd, *J*=7.8, 1.5, 1.2 Hz, 6-H), 8.05 (1H, t, *J*=2.0 Hz, 2-H); δ_C (100 MHz, $CDCl_3$) 67.1 (CH_2), 127.8 (CH), 128.3 (CH), 128.4 (CH), 128.7 (CH), 129.7 (CH), 129.7 (CH), 131.8 (C), 133.1 (C), 134.5 (CH), 135.6 (C), 165.2 (C); m/z (Cl^+) 249 [$(M+H)^+$ (^{37}Cl), 17%], 247 [$(M+H)^+$ (^{35}Cl), 48%], 91 (100); HRMS 249.0508 and 247.0537, $C_{14}H_{11}O_2{}^{37}Cl$ requires $(M+H)^+$ 249.0501 and $C_{14}H_{11}O_2{}^{35}Cl$ requires $(M+H)^+$ 247.0526.

All data agree with literature.[169]

Benzyl 2,4-dimethoxybenzoate 401



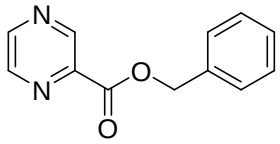
2,4-dimethoxybenzoic acid (1.00 g, 5.49 mmol) and K_2CO_3 (759 mg, 5.49 mmol) were suspended in acetone (15 mL) and benzyl bromide (0.84 mL, 7.0 mmol) was added. The reaction mixture was heated to reflux for 19 h under argon and then cooled, filtered and concentrated *in vacuo*. The residue was taken up in diethyl ether (50 mL), washed with water (2 x 50 mL) and brine (50 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography [SiO_2, Et_2O - Pet. Ether (1:9)] gave ester **401** (1.20 g, 81%) as a white amorphous solid.

R_f [SiO_2, Et_2O - Pet. Ether (1:4)] 0.15

δ_H (400 MHz, $CDCl_3$) 3.85 (3H, s, OMe), 3.90 (3H, s, OMe), 5.32 (2H, s, Ph*CH*$_2$), 6.45-6.50 (2H, m, 3-H and 5-H), 7.29-7.40 (3H, m, 3'-H, 4'-H and 5'-H), 7.45 (2H, d, *J*=6.8 Hz, 2'-H and 6'-H), 7.90 (1H, d, *J*=9.3 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 55.5 (CH_3), 55.9 (CH_3), 66.1 (CH_2), 98.8 (CH), 104.4 (CH), 112.0 (C), 127.9 (CH), 128.0 (CH), 128.5 (CH), 134.0 (CH), 136.5 (C), 161.6 (C), 164.3 (C), 165.2 (C); m/z (Cl^+) 273 [$(M+H)^+$ 100%]; HRMS: 273.1124, $C_{16}H_{16}O_4$ requires $(M+H)^+$ 273.1127; M.p. 44-46 °C.

All data agree with literature.[170]

Benzyl pyrazine-2-carboxylate 402



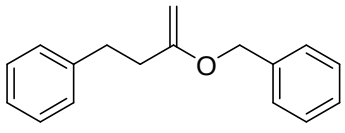
Following the procedure of Seitz *et al.*[171] 2-pyrazinecarboxylic acid (500 mg, 4.03 mmol) was dissolved in dry DMF (10 mL) and DMAP (49 mg, 0.4 mmol) and benzyl alcohol (460 μL, 4.43 mmol) were added. The reaction mixture was cooled to 0 ºC, then EDC. HCl (850 mg, 4.43 mmol) was added and the mixture heated to 25 ºC for 19 h. The reaction mixture was then partially concentrated and partitioned between water (50 mL) and ethyl acetate (50 mL). The organic layer was extracted, then washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography [SiO_2, EtAcO - Pet. Ether (1:3-1:1)] giving the ester **402** (507 mg, 59%) as an amorphous solid.

R_f [SiO_2, EtAcO - Pet. Ether (1:4)] 0.28

δ_H (400 MHz, $CDCl_3$) 5.49 (2H, s, PhCH_2), 7.33-7.46 (3H, m, 3'-H, 4'-H and 5'-H), 7.50 (2H, d, *J*=7.8 Hz, 2'-H and 6'-H), 8.74 (1H, dd, *J*=2.5, 1.5 Hz, 5-H), 8.77 (1H, d, *J*=2.7 Hz, 6-H), 9.35 (1H, d, *J*=1.3 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 68.0 (CH_2), 128.7 (CH), 128.7 (CH), 128.7 (CH), 135.0 (C), 143.4 (C), 144.5 (CH), 146.4 (CH), 147.7 (CH), 163.8 (C); m/z (EI$^+$) 202 [$M^{+\cdot}$, 10%], 108 (84), 91 (100), HRMS: 214.0743, $C_{12}H_{10}N_2O_2$ requires $M^{+\cdot}$ 214.0742; M.p. 38-39 °C.

All data agree with literature.[171]

3-(Benzyloxy)but-3-en-1-ylbenzene 403



A) Following procedure 3c, ester **399** (170 mg, 0.5 mmol) gave enol ether **403** (71 mg, 60%) as an oil, after chromatography [Al_2O_3, Et_2O - Pet. Ether (0:1-1:9)].

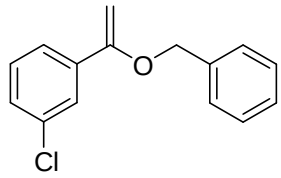
B) $TiCl_4$ (0.44 mL, 4.0 mmol) was added to dry tetrahydrofuran (3 mL) at 0 ºC giving a bright yellow solution. Freshly distilled TMEDA (1.20 mL, 8.0 mmol) was then added and the mixture stirred for 2 min under argon. The Nysted reagent (4.24 mL, 2.20 mmol, 20 %wt in THF) and ester **399** (240 mg, 1.0 mmol) in dry tetrahydrofuran (3 mL) were added. The reaction mixture was allowed to warm to RT and stirred for 5 h before being quenched with sat $NaHCO_3$ (aq) (40 mL). The mixture was extracted with diethyl ether

(3 x 50 mL) and combined organics were washed with brine (100 mL), dried ($MgSO_4$) and concentrated. Column chromatography [Al_2O_3, Et_2O - Pet. Ether (0:1-1:9)] gave enol ether **403** (153 mg, 63%) as an oil.

R_f [Al_2O_3, Et_2O - Pet. Ether (1:9)] 0.77

δ_H (400 MHz, $CDCl_3$) 2.48 (2H, t, *J*=7.2 Hz, CH_2), 2.86 (2H, t, *J*=7.2 Hz, CH_2), 3.93 (1H, d, *J*=2.1 Hz, =C*H*^{A}H^B), 3.97 (1H, d, *J*=2.1 Hz, =CH^A*H*^{B}), 4.36 (2H, s, OCH_2), 7.10-7.41 (10H, m, ArH); δ_C (100 MHz, $CDCl_3$) 33.7 (CH_2), 36.9 (CH_2), 69.2 (CH_2), 82.1 (CH_2), 125.8 (CH), 125.8 (CH), 127.4 (CH), 127.7 (CH), 128.3 (CH), 128.4 (CH), 137.3 (C), 161.7 (C), 162.4 (C); IR (cm^{-1}) 3027 (Ar-H), 2924 (C-H), 1654 (A), 1495 (Ar); m/z (Cl^+) 239 [$(M+H)^+$ 37%], 71 (100); HRMS: 239.1434, $C_{17}H_{18}O$ requires $(M+H)^+$ 239.1346.

1-[1'-(Benzyloxy)ethenyl]-3-chlorobenzene 404

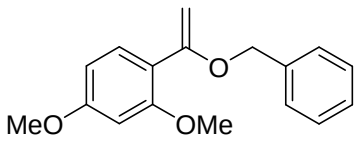


Following procedure 3c, ester **400** (123 mg, 0.5 mmol) gave enol ether **404** (25 mg, 21%) as an oil, after chromatography [Al_2O_3, Pet. Ether].

R_f [Al_2O_3, Et_2O - Pet. Ether (1:9)] 0.83

δ_H (400 MHz, $CDCl_3$) 4.36 (1H, d, *J*=3.0 Hz, =C*H*^{A}H^B), 4.76 (1H, d, *J*=3.0 Hz, =CH^A*H*^{B}), 4.95 (2H, s, Ph*CH*$_2$), 7.09-7.46 (7H, m, 4-H, 5-H and PhH), 7.54 (1H, dt, *J*=7.0, 1.8 Hz 6-H), 7.65 (1H, t, *J*=2.0 Hz, 2-H); δ_C (100 MHz, $CDCl_3$) 70.0 (CH_2), 84.2 (CH_2), 123.6 (CH), 125.5 (CH), 127.5 (CH), 127.9 (CH), 128.3 (CH), 128.5 (CH), 129.4 (CH), 134.2 (C), 136.8 (C), 138.1 (C), 158.4 (C); IR (cm^{-1}) 2923 (Ar-H), 1595 (C=C), 697 (C-Cl); m/z (Cl^+) 247 [$(M+H)^+$ (^{37}Cl), 19%], 245 [$(M+H)^+$ (^{35}Cl), 52%], 91 (100).

1-[1'-(Benzyloxy)ethenyl]-2,4-dimethoxybenzene 405



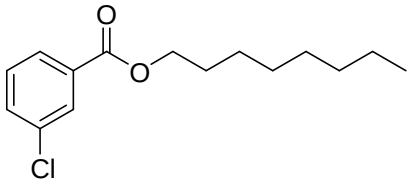
Following procedure 3c, ester **401** (136 mg, 0.5 mmol) gave enol ether **405** (22 mg, 16%) as an oil, after chromatography [Al_2O_3, Et_2O - Pet. Ether (0:1-1:9)]

R_f [Al_2O_3, Et_2O - Pet. Ether (1:4)] 0.45

δ_H (400 MHz, $CDCl_3$) 3.81 (3H, s, OMe), 3.86 (3H, s, OMe), 4.46 (1H, d, *J*=2.0 Hz, =C*H*^{A}H^B), 4.73 (1H, d, *J*=2.0, =CH^A*H*^{B}), 4.92 (2H, s, Ph*CH*$_2$), 6.47 (1H, dd, *J*=8.5, 2.5 Hz, 5-H), 6.48 (1H, d, *J*=2.5 Hz, 3-H), 7.30-7.33 (1H, m, Ar-H), 7.35-7.40 (2H, m, Ph), 7.42-

7.46 (2H, m, Ph), 7.48 (1H, dd, *J*=8.0, 0.8 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 55.3 (CH_3), 55.6 (CH_3), 69.5 (CH_2), 86.7 (CH_2), 98.8 (CH), 104.9 (CH), 119.0 (C), 127.1 (CH), 127.6 (CH), 128.2 (CH), 130.1 (CH), 137.4 (C), 157.3 (C), 1581 (C), 160.8 (C); IR (cm^{-1}) 2919 (Ar-H), 1609 (C=C); m/z (CI^+) 271 [$(M+H)^+$ 10%], 181 (100), HRMS: 271.1327, $C_{17}H_{18}O_3$ requires $(M+H)^+$ 271.1334.

Octyl 3-chlorobenzoate 413

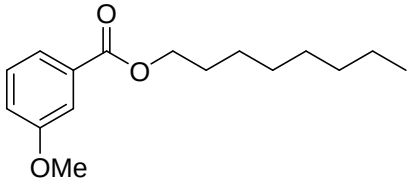


3-Chlorobenzoic acid (1.00 g, 6.39 mmol) was dissolved in dry tetrahydrofuran (15 mL) and DMAP (78 mg, 0.64 mmol) and octanol (0.92 mL, 5.8 mmol) were added. The reaction mixture was cooled to 0 ºC, then EDC.HCl (1.22 g, 6.39 mmol) was added and the mixture stirred at RT for 19 h. The reaction mixture was then concentrated and taken up in ethyl acetate (50 mL). The organic layer was washed with water (2 x 100 mL), 5% $CuCl_2$ (aq) (100 mL), sat. $NaHCO_3$ (aq) (100 mL) and brine (100 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography [SiO_2, EtOAc - Pet. Ether (1:9)] giving the ester **413** (1.00 g, 63%) as a colourless oil.

R_f [SiO_2, EtAcO - Pet. Ether (3:7)] 0.63

δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J*=7.1 Hz, CH_3), 1.24-1.46 (10H, m, 5 x CH_2), 1.77 (2H, quintet, *J*=6.8 Hz, 2'-H), 4.32 (2H, t, *J*=6.8 Hz, 1'-H), 7.38 (1H, t, *J*=7.8 Hz, 5-H), 7.52 (1H, ddd, *J*=8.1, 2.3, 1.3 Hz, 4-H), 7.92 (1H, dt, *J*=7.8, 1.5 Hz, 6-H), 8.01 (1H, t, *J*=1.8 Hz, 2-H); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.7 (CH_2), 26.0 (CH_2), 28.7 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 31.8 (CH_2), 65.6 (CH_2), 127.7 (CH), 129.6 (CH), 129.7 (CH), 132.3 (C), 132.9 (CH), 134.5 (C), 165.5 (C); IR (cm^{-1}) 2926 (Ar-H), 1724 (C=O), 748 (C-Cl); m/z (EI^+) 270 [$M^{+\cdot}(^{37}Cl)$, 3%], 268 [$M^{+\cdot}(^{35}Cl)$, 8%], 159 (19), 157 (58), 141 (33), 139 (100); HRMS 270.1210 and 268.1224, $C_{15}H_{21}O_2{}^{37}Cl$ requires $M^{+\cdot}$ 270.1205 and $C_{15}H_{21}O_2{}^{35}Cl$ requires $M^{+\cdot}$ 268.1230.

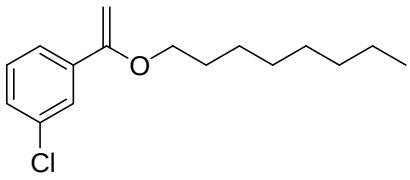
Octyl 3-methoxybenzoate 414



3-Methoxybenzoic acid (600 mg, 3.94 mmol) was dissolved in dry DMF (10 mL) and DMAP (32 mg, 0.26 mmol) and octanol (410 μL, 2.63 mmol) were added. The reaction mixture was cooled to 0 ºC, then EDC.HCl (755 mg, 3.94 mmol) was added and the reaction stirred at RT for 19 h. The reaction mixture was then concentrated and taken up in ethyl acetate (50 mL). The organic layer washed with sat. $NaHCO_3$ (aq) (2 x 100 mL), 1 M, HCl (aq) (100 mL), 5% $CuCl_2$ (aq) (100 mL) and brine (100 mL), then dried ($MgSO_4$) and concentrated *in vacuo* giving the ester **414** (622 mg, 90%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J*=7.0 Hz, CH_3), 1.21-1.49 (10H, m, 5 x CH_2), 1.76 (2H, quintet, *J*=6.9 Hz, 2'-H), 3.86 (3H, s, OMe), 4.31 (2H, t, *J*=6.7 Hz, 1'-H), 7.10 (1H, ddd, *J*=8.2, 2.7, 1.0 Hz, 4-H), 7.34 (1H, t, *J*=7.9 Hz, 5-H), 7.56 (1H, dd, *J*=2.6, 1.5 Hz, 2-H), 7.64 (1H, dt, *J*=7.7, 1.5 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.7 (CH_2), 26.0 (CH_2), 28.7 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 31.8 (CH_2), 55.4 (CH_3), 65.3 (CH_2), 114.1 (CH), 119.2 (CH), 121.9 (CH), 129.3 (CH), 131.9 (C), 159.5 (C), 166.6 (C); IR (cm^{-1}) 2927 (Ar-H), 1717 (C=O); m/z (EI^+) 264 [$M^{+\cdot}$, 24%], 152 (100); HRMS: 264.1728, $C_{16}H_{24}O_3$ requires $M^{+\cdot}$ 264.1725.

1-Chloro-3-(1'-octyloxyvinyl)benzene 415



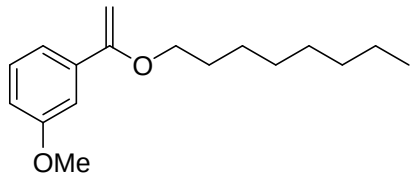
Following methylenation procedure 3d, ester **413** (136 mg, 0.5 mmol) gave enol ether **415** (50 mg, 38%) as an oil, after chromatography [Al_2O_3, Et_2O - Pet. Ether (0:1-1:9)].

R_f [Al_2O_3, Et_2O - Pet. Ether (1:9)] 0.83

δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J*=6.7 Hz, CH_3), 1.19-1.42 (8H, m, 4 x CH_2), 1.43-1.52 (2H, m, CH_2), 1.79 (2H, quintet, *J*=6.6 Hz, OCH_2CH_2), 3.84 (2H, t, *J*=6.5 Hz, OCH_2), 4.22 (1H, d, *J*=2.8 Hz, $=CH^AH^B$), 4.63 (1H, d, *J*=2.8 Hz, $=CH^AH^B$), 7.24-7.29 (2H, m, ArH), 7.50 (1H, dt, *J*=6.8, 1.8 Hz, 4-H or 6-H), 7.60 (1H, d, *J*=2.0 Hz, 2-H); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.7 (CH_2), 26.3 (CH_2), 29.0 (CH_2), 29.3 (CH_2), 29.7 (CH_2), 31.8 (CH_2), 68.0 (CH_2), 83.0 (CH_2), 123.5 (CH), 126.3 (CH), 129.3 (CH), 129.4 (CH), 134.1 (C), 138.6 (C), 157.7

(C); IR (cm^{-1}) 2925 (Ar-H) 1564 (C=C), 786 (C-Cl); m/z (EI^+) 266 [$M^{+\cdot}$(^{35}Cl), 81%], 268 [$M^{+\cdot}$(^{37}Cl), 40%], 134 (47), 91 (100); HRMS 266.1465 and 268.1455, $C_{16}H_{23}O^{35}Cl$ requires $M^{+\cdot}$ 266.1437 and $C_{16}H_{23}O^{37}Cl$ requires $M^{+\cdot}$ 268.1413.

1-Methoxy-3-(1'-octyloxyvinyl)benzene 416

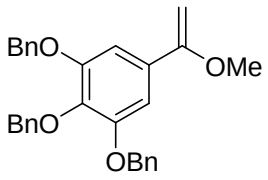


Following methylenation procedure 3d, ester **414** (132 mg, 0.5 mmol) gave enol ether **416** (48 mg, 37%) as an oil, after chromatography [Al_2O_3, Et_2O - Pet. Ether (0:1-1:9)].

R_f [Al_2O_3, Et_2O - Pet. Ether (1:9)] 0.87

δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J*=7.0 Hz, CH_3), 1.20-1.38 (8H, m, 4 x CH_2), 1.50-1.52 (2H, m, CH_2), 1.79 (2H, quintet, *J*=6.5 Hz, OCH_2CH_2), 3.82 (3H, s, OMe), 3.84 (2H, t, *J*=6.4 Hz, OCH_2), 4.18 (1H, d, *J*=2.5 Hz, $=CH^AH^B$), 4.62 (1H, d, *J*=2.5 Hz, $=CH^AH^B$), 6.85 (1H, dt, *J*=7.0, 2.4 Hz, 4-H or 6-H), 7.17-7.33 (3H, m, ArH); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.3 (CH_2), 26.3 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 31.8 (CH_2), 55.2 (CH_3), 67.8 (CH_2), 82.3 (CH_2), 111.1 (CH), 113.8 (CH), 118.0 (CH), 129.1 (CH), 138.2 (C), 159.4 (C), 159.8 (C); IR (cm^{-1}) 2928 (Ar-H), 1599 (C=C); m/z (CI^+) 263 [$(M+H)^+$ 100%]; HRMS 263.2018, $C_{17}H_{26}O_2$ requires $(M+H)^+$ 263.2011

1,2,3-Tris(benzyloxy)-5-(1'-methoxyethenyl)benzene 418



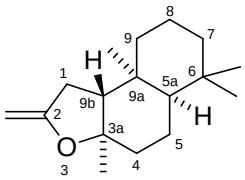
Following methylenation procedure 3d, methyl 1,2,3-tris(benzyloxy)benzoate (227 mg, 0.5 mmol) gave enol ether **418** (46 mg, 20%) as an oil after chromatography [Al_2O_3, Et_2O - Pet. Ether (0:1-1:9)].

R_f [Al_2O_3, Et_2O - Pet. Ether (3:7)] 0.47

δ_H (400 MHz, $CDCl_3$) 3.72 (3H, s, OMe), 4.17 (1H, d, *J*=2.8 Hz, $=CH^AH^B$), 4.52 (1H, d, *J*=2.9 Hz, $=CH^AH^B$), 5.05 (2H, s, CH_2Ph), 5.11 (4H, s, 2 x CH_2Ph), 6.95 (2H, s, ArH), 7.29-7.45 (15H, m, ArH); δ_C (100 MHz, $CDCl_3$) 55.4 (CH_3), 71.3 (CH_2), 75.2 (CH_2), 81.6 (CH_2), 105.5 (CH), 127.5 (CH), 127.8 (CH), 128.0 (CH), 128.1 (CH), 128.5 (CH), 128.6 (CH), 132.1 (C), 137.1 (C), 137.8 (C), 139.0 (C), 152.6 (C), 160.5 (C); IR (cm^{-1}) 2921 (Ar-H),

1680 (C=C); m/z (EI^+) 452 [$M^{+\cdot}$, 8%], 438 (24), 347 (25), 91 (100), HRMS: 452.1982, $C_{28}H_{28}O_4$ requires $M^{+\cdot}$ 452.1988.

(3a*R*,5a*R*,9a*S*,9b*R*)-3a,6,6,9a-Tetramethyl-2-methylidene-dodecahydronaphthol [2,1-b]furan 420

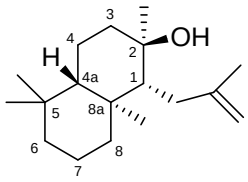


Following methylenation procedure 3e, sclareolide (125 mg, 0.5 mmol) gave enol ether **420** (37 mg, 30%) as a beige amorphous solid, after chromatography [Al_2O_3, Et_2O - Pet. Ether (0:1-1:9)] (with 10% hydrolysed product impurity).

R_f [SiO_2, Et_2O - Pet. Ether (1:19)] 0.67

δ_H (400 MHz, $CDCl_3$) 0.83 (3H, s, 6'-Me), 0.86 (3H, s, 6'-Me), 0.88 (3H, s, 9a'-Me), 1.00 (1H, dd, 5a'-H, *J*=12.5, 2.7 Hz), 1.05 (1H, dd, 7'-H_{ax}, *J*=13.3, 2.5 Hz), 1.10-1.48 (5H, m, 4'-C*H*^{A}H^B, 5'-C*H*^{A}H^B, 7'-H_{eq}, 8'-C*H*^{A}H^B, 9'-C*H*^{A}H^B), 1.19 (3H, s, 3b'-Me), 1.52-1.73 (3H, m, 5'-CH^A*H*^{B}, 8'-CH^A*H*^{B}, 9'-*C*H^A*H*^{B}), 1.81 (1H, dq, 4'-CH^A*H*^{B}, *J*=13.9, 3.8 Hz), 2.00 (1H, dt, 9b-H, *J*=11.7, 3.3 Hz), 2.28-2.43 (2H, m, 1-H), 3.89 (1H, s, =CH_2), 4.22 (1H, s, =CH_2); δ_C (100 MHz, $CDCl_3$) 15.2 (CH_3), 18.3 (CH_2), 20.8 (CH_2), 21.0 (CH_3), 21.5 (CH_3), 27.5 (CH_2), 33.0 (CH), 33.4 (C), 36.2 (C), 39.1 (CH_2), 39.7 (CH_2), 42.3 (CH_2), 55.9 (CH_3), 59.8 (CH), 81.3 (CH_2), 84.4 (C), 161.9 (C); IR (cm^{-1}) 2927 (C-H), 1706 (C=C), 1671 (C=C); m/z (EI^+) 248 [$M^{+\cdot}$ 21%], 84 (100); HRMS 248.2138, $C_{17}H_{28}O$ requires $M^{+\cdot}$ 248.2140; $[\alpha]_D$ +32.1, c=0.8 in $CHCl_3$, T=24.9 ºC; M.p. 72-74 ºC.

(1*R*,2*R*,4a*S*,8a*S*)-2,5,5,8a-Tetramethyl-1-(2'-methylprop-2'-en-1-yl)-decahydronaphth-2-ol 421



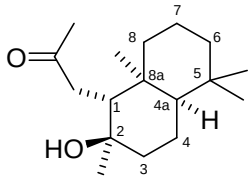
Following methylenation procedure 3c, sclareolide (123 mg, 0.5 mmol) gave alkene **421** (61 mg, 46%) as a colourless oil, after chromatography [Al_2O_3, Pet. Ether].

R_f [Al_2O_3, Et_2O - Pet. Ether (1:19)] 0.65

δ_H (400 MHz, $CDCl_3$) 0.77 (3H, s, 8a-Me), 0.87 (3H, s, 5-Me), 0.85-0.93 (1H, m, 6-H^AH^B), 0.90 (3H, s, 5-Me) 0.96 (1H, dd, *J*=12.1, 2.1 Hz, 4a-H), 1.10-1.20 (1H, m, 6-H^AH^B), 1.21-1.30 (4H, m, 2-Me and 4-H^AH^B), 1.34-1.48 (3H, m, 4-H^AH^B, 7-H^AH^B and 8-H^AH^B), 1.55-1.68 (3H, m, 1-H, 4-H^AH^B and 8-H^AH^B), 1.70-1.76 (1H, m, 6-H^AH^B), 1.79-1.84 (4H, m, 2'-Me and 3-H^AH^B), 2.13 (1H, br. d, *J*=14.5 Hz ,1'-H^AH^B), 2.25-2.33 (1H, dd, *J*=15.0, 8.5 Hz, 1'-H^AH^B), 4.78 (1H, br. s, 3'-H^AH^B), 4.86 (1H, br. s, 3'-H^AH^B); δ_C (100 MHz, $CDCl_3$) 15.3 (CH_3), 18.7 (CH_2), 20.1 (CH_2), 21.6 (CH_3), 22.3 (CH_3), 24.2 (CH_3), 33.4 (C), 33.5 (CH_3), 33.8 (CH_2), 38.6 (C), 40.0 (CH_2), 41.8 (CH_2), 43.5 (CH_2), 56.2 (CH), 57.6 (CH), 74.8 (C), 111.6 (CH_2), 149.4 (C); IR (cm^{-1}) 3449 (O-H), 2935 (C-H), 1638 (C=C); m/z (CI^+) 249 [$(M+H)^+$-CH_4 89%], 191 (100); HRMS: 249.2222, $C_{17}H_{29}O$ requires $(M+H)^+$-CH_4, 249.2218; $[\alpha]_D$ −18.9, c=1.1 in $CHCl_3$, T=21.6 °C.

See appendix for detailed NMR correlation table.

1-[(1*R*,2*R*,4a*S*,8a*S*)-2-Hydroxy-2,5,5,8a-tetramethyl-decahydronaphth-1-yl]-propan-2-one 427



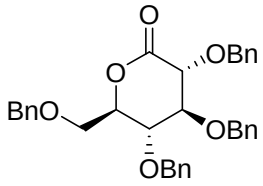
Following methylenation procedure 3f, sclareolide (125 mg, 0.5 mmol) gave keto-alcohol **427** (74 mg, 56%) as a beige amorphous solid, after chromatography [SiO_2, EtOAc - Pet. Ether (3:7)].

R_f [SiO_2, EtOAc - Pet. Ether (3:7)] 0.15

δ_H (400 MHz, $CDCl_3$) 0.78 (6H, m, 5'-Me, 8a-Me), 0.88 (3H, s, 5'-Me), 0.92 (1H, dd, 6'-H_{ax}, *J*=10.0, 3.3 Hz), 1.04 (1H, dd, 4a'-H, *J*= 12.3, 2.2 Hz), 1.11 (3H, s, 2'-Me), 1.14 (1H, td, 7'-H_{ax}, *J*=13.6, 4.2 Hz) 1.20-1.47 (5H, m, 3'-CH^AH^B, 4'-H_{ax}, 6'-H_{eq}, 7'-H_{eq}, 8'-CH^AH^B),

1.51-1.63 (1H, m, 8'-CH^A*H^B*), 1.69 (1H, dq, 4'-H$_{eq}$, *J*=13.5, 2.6 Hz), 1.90-1.97 (2H, m, 1'-H, 3-CH^A*H^B*), 2.21 (3H, s, 3-H), 2.45 (1H, dd, 1-C*H^A*H^B, *J*=17.6, 5.6 Hz), 2.54 (1H, dd, 1-CH^A*H^B*, *J*=17.6, 4.3 Hz); δ_C (100 MHz, $CDCl_3$) 15.7 (CH_3), 18.4 (CH_2), 20.6 (CH_2), 21.4 (CH_3), 23.1 (CH_3), 30.3 (CH_3), 33.2 (C), 33.3 (CH_3), 38.3 (C), 39.3 (CH_2), 39.6 (CH_2), 41.7 (CH_2), 44.6 (CH_2), 55.8 (CH), 55.9 (CH), 73.2 (C), 210.3 (C); IR (cm^{-1}) 3451 (O-H), 2921 (C-H), 1695 (C=O); m/z (CI^+) 249 [$(M+H)^+$-H_2O 78%], 137 (100); HRMS: 249.2215, $C_{17}H_{28}O$ requires [$(M+H)^+$-H_2O] 249.2218; $[\alpha]_D$ −3.0, c=0.8 in $CHCl_3$, T=21.5 ºC; M.p. 52-53 ºC.
See appendix for detailed NMR correlation table.

2,3,4,6-Tetra-O-benzyl-D-glucopyranolactone 429



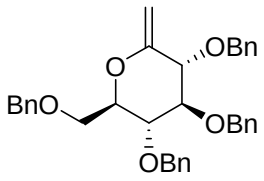
Following the procedure of Labeguere *et al.*[172] 2,3,4,6-tetra-O-benzyl-D-glucopyranose (500 mg, 0.92 mmol) was dissolved in DMSO (2.9 mL, 41 mmol) and acetic anhydride (1.9 mL, 20.3 mmol) was added. The reaction was stirred at RT for 19 h under argon. The reaction mixture was then poured into water (50 mL) and extracted with diethyl ether (4 x 50 mL). Organic extracts were combined and washed with sat. $NaHCO_3$ (aq) (100 mL) and brine (100 mL), then were dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography [SiO_2, EtOAc - Pet. Ether (3:7)] gave the lactone **429** (475 mg, 96%) as a colourless oil.

R_f [SiO_2, EtOAc - Pet. Ether (3:7)] 0.44

δ_H (400 MHz, $CDCl_3$) 3.66 (1H, dd, 6-C*H^A*H^B, *J*=11.0, 3.3 Hz), 3.72 (1H, dd, 6-CH^A*H^B*, *J*=11.0, 2.5 Hz), 3.88-3.97 (2H, m, 3-H_{ax} and 4-H_{ax}), 4.12 (1H, d, 2-H_{ax}, *J*=6.7 Hz), 4.41-4.74 (8H, m, 5-H_{ax} and 7 x PhC*H^x*H^y), 4.99 (1H, d, PhC*H^x*H^y, *J*= 11.8 Hz), 7.13-7.34 (20H, m, ArH); δ_C (100 MHz, $CDCl_3$) 68.3 (CH_2), 73.6 (CH_2), 73.7 (CH_2), 73.7 (CH_2), 74.0 (CH_2), 76.1 (CH), 77.4 (CH), 78.2 (CH), 81.0 (CH), 127.8 (CH), 127.8 (CH), 128.0 (CH), 128.0 (CH), 128.0 (CH), 128.0 (CH), 128.1 (CH), 128.4 (CH), 128.4 (CH), 128.4 (CH), 128.5 (CH), 128.5 (CH), 137.0 (C), 137.5 (C), 137.5 (C), 137.6 (C), 169.3 (C); m/z (FAB^+) 561 [$(M+Na)^+$, 12%], 92 (100); HRMS: 561.2260, $C_{34}H_{34}O_6$ requires $(M+Na)^+$ 561.2253; $[\alpha]_D$ +73.1, c=0.5 in $CHCl_3$, T=25.3 ºC.

^{1}H NMR and ^{13}C NMR data agree with literature.[173]

2,3,4,6-Tetra-O-benzyl-1-deoxy-1-methylidene-D-glucopyranose 430



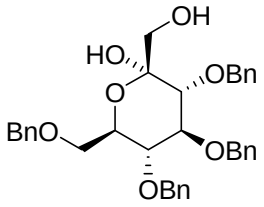
Following procedure 3e, ester **429** (269 mg, 0.5 mmol) gave enol ether **430** (133 mg, 50%) a as an oil, after chromatography [Al_2O_3, Et_2O - Pet. Ether (0:1-3:7)].

R_f [Al_2O_3, Et_2O - Pet. Ether (1:4)] 0.25

δ_H (400 MHz, $CDCl_3$) 3.67-3.79 (5H, m, 3-H_{ax}, 4-H_{ax}, 5-H_{ax}, 6-CH_2), 3.96 (1H, d, *J*=7.1 Hz, 2-H_{ax}), 4.51 (1H, d, *J*= 11.1 Hz, PhCH^AH^B), 4.53 (1H, d, *J*= 12.1 Hz, PhCH^AH^B), 4.62 (1H, s, =CH^IH^J), 4.64 (1H, d, *J*= 11.6 Hz, PhCH^CH^D), 4.64 (1H, d, *J*= 12.4 Hz, PhCH^CH^D), 4.71 (1H, d, *J*= 11.1 Hz, PhCH^EH^F), 4.75 (1H, s, =CH^IH^J), 4.76 (1H, d, *J*= 11.4 Hz, PhCH^GH^H), 4.77 (1H, d, *J*= 11.1 Hz, PhCH^EH^F), 4.85 (1H, d, *J*= 11.4 Hz, PhCH^GH^H), 7.12-7.16 (2H, m, ArH), 7.24-7.37 (18H, m, ArH); δ_C (100 MHz, $CDCl_3$) 68.7 (CH_2), 72.8 (CH_2), 73.5 (CH_2), 74.5 (CH_2), 74.5 (CH_2), 77.5 (CH), 78.6 (CH), 79.0 (CH), 84.7 (CH), 94.8 (CH_2), 127.7 (CH), 127.7 (CH), 127.7 (CH) 127.8 (CH), 127.8 (CH), 127.9 (CH), 127.9 (CH), 128.0 (CH), 128.4 (CH), 128.4 (CH), 128.4 (CH), 128.5 (CH), 137.9 (C), 138.0 (C), 138.0 (C), 138.3 (C), 156.3 (C); IR (cm^{-1}) 3030 (Ar-H), 1659 (C=C); m/z (EI^+) 536 [$M^{+\cdot}$ 8%], 181 (100); $[\alpha]_D$ +60.0, c=0.5 in $CHCl_3$, T=25.3 °C.

All data agree with literature.[174]

3,4,5,7-Tetra-O-benzyl-D-gluco-2-heptulopyranose 431



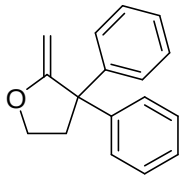
Ester **429** (193 mg, 0.35 mmol) was methylenated using procedure 3e and the reaction mixture cannulated directly into a mixture of N-methylmorpholine-N-oxide (308 mg, 2.62 mmol), 2.5%wt osmium tetroxide in *tert*-butanol (90 μL, 0.007 mmol), pyridine (100 μL, 1.24 mmol) and water (70 μL, 3.89 mmol) in tert-butanol (2.5 mL) at −5 °C. The reaction was allowed to warm to RT and stirred for 19 h under argon then quenched by addition of Na_2SO_3 (148 mg, 1.40 mmol). This was stirred for 10 mins, then florisil (1g) was added and the reaction mixture filtered and washed with EtOAc (50 mL). The filtrate was washed with 1 M HCl in brine (50 mL) and organic extracts dried (Na_2SO_4) and concentrated. Chromatography [SiO_2, Et_2O - Pet. Ether (3:7] gave the diol **431** (25 mg, 13%) as an oil.

R_f [SiO_2, Et_2O - Pet. Ether (3:7] 0.31

δ_H (400 MHz, $CDCl_3$) 3.39 (1H, d, 3-H_{ax}, *J*=9.6 Hz), 3.59-3.77 (4H, m, 1-CH_2, 5-H_{ax} and 6-H_{ax}), 4.13 (1H, t, 4-H_{ax}, *J*=9.2 Hz), 4.48-4.63 (5H, m, 5 x PhCH^AH^B), 4.72 (1H, d, PhCH^AH^B, *J*=11.5 Hz), 4.83 (1H, d, PhCH^AH^B, *J*=10.8 Hz), 4.87 (1H, d, PhCH^AH^B, *J*=11.0 Hz), 4.92 (1H, d, PhCH^AH^B, *J*=11.0 Hz), 4.96 (1H, d, PhCH^AH^B, *J*=11.5 Hz), 7.23-7.38 (20H, m, ArH); δ_C (100 MHz, $CDCl_3$) 62.6 (CH_2), 68.8 (CH_2), 71.7 (CH), 73.4 (CH_2), 74.4 (CH_2), 75.4 (CH_2), 75.5 (CH_2), 78.7 (CH), 83.1 (CH), 84.3 (CH), 100.9 (C), 127.2 (CH), 127.4 (CH), 127.5 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 127.9 (CH), 128.0 (CH), 128.2 (CH), 128.3 (CH), 128.3 (CH), 128.4 (CH), 138.4 (C), 138.6 (C), 138.8 (C), 140.0 (C); IR (cm^{-1}) 3450 (O-H), 2920 (Ar-H); $[\alpha]_D$ +54.5, c=0.6 in $CHCl_3$, T=21.8 ºC.

^{1}H NMR data agrees with literature.[175]

2-Methylidene-3,3-diphenyltetrahydrofuran 433

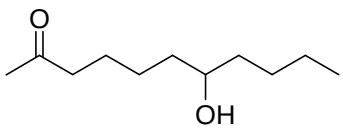


Following methylenation procedure 3e, α,α-Diphenyl-γ-butyrolactone (119 mg, 0.5 mmol) gave enol ether **433** (64 mg, 52%) as an oil, after chromatography [Al_2O_3, Et_2O - Pet. Ether (0:1-1:9)].

R_f [Al_2O_3, Et_2O - Pet. Ether (1:9)] 0.53

δ_H (400 MHz, $CDCl_3$) 2.78 (2H, t, *J*=6.3 Hz, 4-CH_2), 3.64 (1H, d, *J*=1.8 Hz, =CH^AH^B), 4.00 (1H, t, *J*=6.3 Hz, OCH_2), 4.55 (1H, d, *J*=1.8 Hz, =CH^AH^B), 7.25-7.32 (10H, m, ArH); δ_C (100 MHz, $CDCl_3$) 40.0 (CH_2), 58.9 (C), 67.2 (CH_2), 84.7 (CH_2), 126.7 (CH), 128.2 (CH), 128.5 (CH), 143.6 (C), 167.4 (C); IR (cm^{-1}) 3058 (Ar-H), 1666 (Ar), 1491 (C=C); m/z (FAB$^+$) 237 [(M+H)$^+$, 20%], 84 (100); HRMS 237.1264, $C_{17}H_{16}O$ requires (M+H)$^+$ 237.1279.

7-Hydroxyundecan-2-one 436

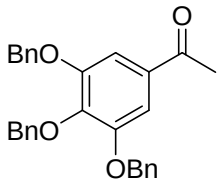


Following methylenation procedure 3f, ε-Decalactone (90 μL, 0.5 mmol) gave keto-alcohol **436** (25 mg, 27%) as an oil, after chromatography [SiO_2, EtOAc - Pet. Ether (1:1)].

R_f [SiO_2, EtOAc - Pet. Ether (1:1)] 0.10

δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, *J*=7.0 Hz, CH_2CH_3), 1.15-1.48 (10H, m, 5 x CH_2), 1.50-1.67 (2H, m, $COCH_2CH_2$), 2.13 (3H, s, $COCH_3$), 2.46 (2H, t, *J*=7.3 Hz, $COCH_2$), 3.52-3.63 (1H, m, *CH*OH); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.7 (CH_2), 23.3 (CH_2), 25.2 (CH_2), 27.8 (CH_2), 29.9 (CH_3), 37.1 (CH_2), 37.2 (CH_2), 43.7 (CH_2), 71.7 (CH), 209.3 (C); IR (cm^{-1}) 3421 (O-H), 2931 (C-H), 1710 (C=O), m/z (CI^+) 187 [$(M+H)^+$, 40%], 169 (78), 85 (80), 69 (100); HRMS: 187.1695, $C_{11}H_{22}O_2$ requires $(M+H)^+$ 187.1698.

3,4,5-tris(benzyloxy)acetophenone 437

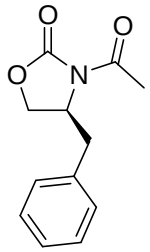


Methyl 1,2,3-tris(benzyloxy)benzoate (227 mg, 0.5 mmol) was dissolved in dry THF (1.5 mL) and titanocene dichloride (498 mg, 2.0 mmol) and the Nysted reagent (1.92 mL, 1.0 mmol, 20 %wt in THF) were added. The reaction was irradiated in the microwave (100W, 75 °C, 22 min). This gave a black solution which was quenched into 1 M HCl (aq) (20 mL) and stirred for 1 h at RT. This was then extracted with dichloromethane (3 x 50 mL) and organic extracts combined, washed with brine (100 mL), dried (Na_2SO_4) and concentrated to give a crude oily solid. Column chromatography [SiO_2, EtOAc - Pet. Ether (1:19-1:4)] yielded the ketone (52 mg, 24%) as an amorphous solid.

R_f [SiO_2, EtOAc - Pet. Ether (1:4)] 0.27

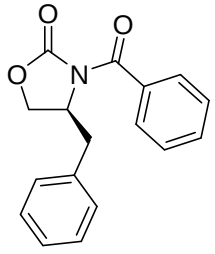
δ_H (400 MHz, $CDCl_3$) 2.50 (3H, s, Me), 5.14 (2H, s, CH_2Ph), 5.15 (4H, s, CH_2Ph), 7.21-7.45 (17H, m, ArH); δ_C (100 MHz, $CDCl_3$) 26.5 (CH_3), 71.4 (CH_2), 75.2 (CH_2), 108.3 (CH), 127.0 (CH), 127.3 (CH), 127.6 (CH), 128.0 (CH), 128.1 (CH), 128.6 (CH), 132.4 (C), 136.6 (C), 137.4 (C), 142.9 (C), 152.6 (C), 196.9 (C); IR (cm^{-1}) 2927 (Ar-H), 1680 (C=O); m/z (EI^+) 438 [$M^{+\cdot}$, 9%], 91 (100); HRMS: 438.1834, $C_{29}H_{26}O_4$ requires $M^{+\cdot}$ 438.1831.

(4*S*)-3-Acetyl-4-benzyl-1,3-oxazolidin-2-one 449



Following the procedure described by Theurer *et al*.[176] (4*S*)-4-Benzyl-1,3-oxazolidin-2-one (531 mg, 3.0 mmol) was dissolved in dry tetrahydrofuran (10 mL) and cooled to −78 °C. 1.6 M butyllithium in hexane (2.25 mL, 3.6 mmol) was then added dropwise followed by acetyl chloride (0.24 mL, 3.3 mmol). The reaction mixture was stirred at −78 °C for 45 min and then allowed to warm to RT over 30 min. The reaction was then quenched by addition of sat. $NH_4.Cl$ (aq) (10 mL) and partially concentrated. The mixture was basified with 1 M NaOH (aq) (25 mL) and partitioned with dichloromethane (50 mL). Organics were extracted and dried using a Biotage® ISOLUTE phase separator, then concentrated *in vacuo* to give the imide **449** (625 mg, 95 %) as a white amorphous solid.
δ_H (400 MHz, $CDCl_3$) 2.56 (3H, s, CH_3), 2.78 (1H, dd, *J*=13.4, 8.9 Hz, OC*H*^{A}H^B), 3.31 (1H, dd, *J*=13.4, 3.3 Hz, OCH^A*H*^{B}), 4.18 (2H, m, Ph*CH*$_2$), 4.69 (1H, m, NCH), 7.21 (2H, d, *J*=7.0 Hz, ArH), 7.30-7.40 (3H, m, ArH); δ_C (100 MHz, $CDCl_3$) 23.9 (CH_3), 37.8 (CH_2), 55.0 (CH), 66.1 (CH_2), 127.4 (CH), 129.0 (CH), 129.4 (CH), 135.2 (C), 153.6 (C), 170.3 (C); m/z (EI^+) 219 [$M^{+\cdot}$, 59%] 83 (100); HRMS: 219.0897, $C_{12}H_{13}NO_3$ requires $M^{+\cdot}$ 219.0895; $[\alpha]_D$ +64.9, c=1.0 in $CHCl_3$, T=25.2 °C; M.p. 100-102 °C.
All data agree with literature.[176]

(4*S*)-3-Benzoyl-4-benzyl-1,3-oxazolidin-2-one 450



(4*S*)-4-Benzyl-1,3-oxazolidin-2-one (531 mg, 3.0 mmol) was dissolved in dry tetrahydrofuran (10 mL) and cooled to −78 °C. 1.6 M butyllithium in hexane (2.25 mL, 3.6 mmol) was then added dropwise followed by benzoyl chloride (0.24 mL, 3.3 mmol). The reaction was stirred at −78 °C for 45 min and then allowed to warm to RT over 30 min. The reaction mixture was then quenched by addition of sat. $NH_4.Cl$ (aq) (10 mL) and partially concentrated. The mixture was basified with 1 M NaOH (aq) (25 mL) and

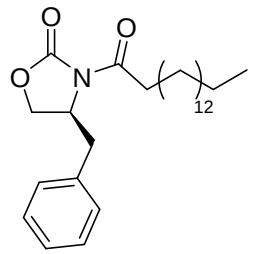
partitioned with dichloromethane (50 mL). Organics were extracted and dried using a Biotage® ISOLUTE phase separator, then concentrated *in vacuo* to give crude product. Chromatography using a Biotage® SNAP KP-Sil cartridge (25 g) [SiO_2, EtOAc - Heptane (1:4)] gave the imide **450** (604 mg, 72%) as a white amorphous solid.

R_f [SiO_2, EtOAc - Heptane (3:7)] 0.23

δ_H (400 MHz, $CDCl_3$) 2.97 (1H, dd, *J*=13.5, 9.2 Hz, OC*H*^{A}H^B), 3.45 (1H, dd, *J*=13.6, 4.1 Hz, OCH^A*H*^{B}), 4.24 (1H, dd, *J*=9.0, 5.5 Hz, PhC*H*^{A}H^B), 4.34 (1H, t, *J*=8.2 Hz, PhCH^A*H*^{B}), 4.88-4.91 (1H, m, NCH), 7.20-7.38 (5H, m, ArH), 7.44 (2H, t, *J*=7.4 Hz, ArH), 7.56 (1H, t, *J*=7.5 Hz, ArH), 7.65 (2H, d, *J*=7.0 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 37.5 (CH_2), 55.8 (CH), 66.4 (CH_2), 127.5 (CH), 127.9 (CH), 129.0 (CH), 129.1 (CH), 129.5 (CH), 132.5 (C), 133.1 (C), 135.0 (CH), 153.3 (C), 169.9 (C); m/z (EI$^+$) 281 [$M^{+\cdot}$, 21%], 105 (100), HRMS: 281.1053, $C_{17}H_{15}NO_3$ requires $M^{+\cdot}$ 281.1053; $[\alpha]_D$ +115.3, c=1 in $CHCl_3$, T=25.3 ºC; M.p. 134-138 ºC.

All data agree with literature.[177]

(4*S*)-4-Benzyl-3-hexadecanoyl-1,3-oxazolidin-2-one 451



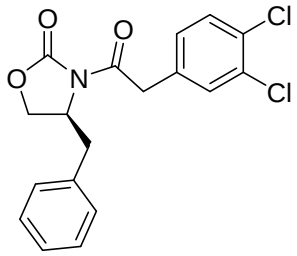
(4*S*)-4-Benzyl-1,3-oxazolidin-2-one (354 mg, 2.0 mmol) was dissolved in dry tetrahydrofuran (6.5 mL) and cooled to −78 ºC. 1.6 M butyllithium in hexane (1.5 mL, 2.4 mmol) was then added dropwise followed by palmitoyl chloride (0.67 mL, 2.2 mmol). The reaction mixture was stirred at −78 ºC for 45 min and then allowed to warm to RT over 1 h. The reaction was then quenched by addition of sat. NH_4.Cl (aq) (10 mL) and partially concentrated. The mixture was basified with 1 M NaOH (aq) (25 mL) and partitioned with dichloromethane (50 mL). Organics were extracted and dried using a Biotage® ISOLUTE phase separator, then concentrated *in vacuo* to give crude product. Chromatography using a Biotage® SNAP KP-Sil cartridge (25 g) [SiO_2, EtOAc - Cyclohexane (0:1-1:19)] gave imide **451** (496 mg, 60%) as a white amorphous solid.

R_f [SiO_2, EtOAc - Cyclohexane (1:4)] 0.59

δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J*=7.0 Hz, CH_3), 1.25-1.43 (24H, m, 12 x CH_2), 1.55 (2H, quintet, *J*=7.1 Hz, NCOCH$_2$*CH*$_2$), 2.77 (1H, dd, *J*=13.4, 9.7 Hz, OC*H*^{A}H^B), 2.90 (1H, dt *J*=24.6, 7.5 Hz, NCOC*H*^{A}H^B), 2.96 (1H, dt *J*=24.5, 7.5 Hz, NCOCH^A*H*^{B}), 3.29 (1H, dd, *J*=13.4, 3.3 Hz, OCH^A*H*^{B}), 4.12-4.23 (2H, m, PhCH$_2$), 4.61-4.71 (1H, m, NCH), 7.21 (2H,

d, *J*=7.0 Hz, ArH), 7.26-7.42 (3H, m, ArH); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.7 (CH_2), 24.3 (CH_2), 29.1 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 31.9 (CH_2), 35.6 (CH_2), 37.9 (CH_2), 55.2 (CH), 66.1 (CH_2), 127.3 (CH), 129.0 (CH), 129.4 (CH), 135.3 (C), 153.5 (C), 173.5 (C); IR (cm^{-1}) 2917 (C-H), 1781 (C=O), 1767 (C=O); m/z (CI^+) 416 [$(M+H)^+$, 100%], 266 (100), HRMS: 416.3159, $C_{26}H_{41}NO_3$ requires $(M+H)^+$ 416.3165; $[\alpha]_D$ +48.3, c=1.0 in $CHCl_3$, T=20.7 ºC.

(4*S*)-4-Benzyl-3-[2'-(3'',4''-dichlorophenyl)acetyl]-1,3-oxazolidin-2-one 452

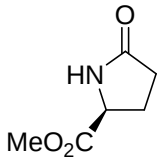


(4*S*)-4-Benzyl-1,3-oxazolidin-2-one (354 mg, 2.3 mmol) was dissolved in dry tetrahydrofuran (5 mL) and cooled to −78 ºC. 1.6 M butyllithium in hexane (1.51 mL, 2.41 mmol) was then added dropwise followed by 2-(3',4'-dichlorophenyl)acetyl chloride (494 mg, 2.41 mmol). The reaction mixture was stirred at −78 ºC for 1 h and then allowed to warm to RT over 1 h. The reaction was then quenched by addition of sat. NH_4.Cl (aq) (10 mL) and partially concentrated. The mixture was basified with 1 M NaOH (aq) (25 mL) and partitioned with dichloromethane (50 mL). Organics were extracted and dried using a Biotage® ISOLUTE phase separator, then concentrated *in vacuo* to give crude product. Chromatography using a Biotage® SNAP KP-Sil cartridge (25 g) [SiO_2, EtOAc - Heptane (1:9-1:4)] gave imide **452** (364 mg, 43%) as an oily solid.

R_f [SiO_2, EtOAc - Heptane (1:4)] 0.18

δ_H (400 MHz, $CDCl_3$) 2.77 (1H, dd, *J*=13.4, 9.4 Hz, OC*H*^{A}H^B), 3.26 (1H, dd, *J*=13.4, 3.3 Hz, OCH^A*H*^{B}), 4.18-4.32 (4H, m, $PhCH_2$ and $ArCH_2$), 4.61-4.74 (1H, m, NCH), 7.10-7.23 (3H, m, ArH), 7.24-7.37 (3H, m, ArH), 7.42 (1H, d, *J*=8.2 Hz, 5"-H), 7.44 (1H, d, *J*=2.0 Hz, 2"-H); δ_C (100 MHz, $CDCl_3$) 37.8 (CH_2), 40.7 (CH_2), 55.3 (CH), 66.3 (CH_2), 127.5 (CH), 129.0 (CH), 129.3 (CH), 129.4 (CH), 130.5 (CH), 131.6 (C), 131.9 (CH), 132.6 (C), 133.5 (C), 134.9 (C), 153.4 (C), 170.2 (C); IR (cm^{-1}) 1775 (C=O), 1696 (C=O), 760 (C-Cl), 737 (C-Cl); m/z (CI^+) 368 [$(M+H)^+$ (^{37}Cl ^{37}Cl), 7%], 366 [$(M+H)^+$ (^{35}Cl ^{37}Cl), 33%], 364 [$(M+H)^+$ ($^{35}Cl^{35}Cl$), 47%], 71 (100); HRMS: 368.0454, 366.0475 and 364.0505, $C_{18}H_{15}O^{37}Cl_2$ requires $(M+H)^+$ 368.0461, $C_{18}H_{15}O^{35}Cl^{37}Cl$ requires $(M+H)^+$ 366.0481 and $C_{18}H_{15}O^{35}Cl_2$ requires $(M+H)^+$ 364.0507; $[\alpha]_D$ +72.1, c=1.0 in $CHCl_3$, T=21.0 ºC.

Methyl (*S*)-pyroglutamate 454

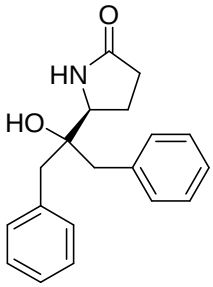


(*S*)-pyroglutamic acid (3.0 g, 22.3 mmol) was suspended in methanol (25 mL) and cooled to 0 °C. Thionyl chloride (0.33 mL, 4.5 mmol) was then added dropwise and the reaction heated to reflux for 18 h under nitrogen. The reaction mixture was then cooled, concentrated *in vacuo* and the residue taken up in dichloromethane. This was passed through a Biotage® ISOLUTE NH cartridge to remove excess acid and the eleunt concentrated to give ester **454** (1.84 gm, 56 %) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 2.20-2.53 (4H, m, 2 x CH_2), 3.78 (3H, s, OMe), 4.27 (1H, dt, *J*=8.7, 6.0 Hz, NCH), 5.95 (1H, br. s, NH); δ_C (100 MHz, $CDCl_3$) 24.8 (CH_2), 29.1 (CH_2), 52.6 (CH), 55.2 (CH_3), 172.4 (C), 177.6 (C); m/z (Cl^+) 144 [$(M+H)^+$, 100%], HRMS: 144.0657 $C_6H_9NO_3$ requires $(M+H)^+$ 144.0661; $[\alpha]_D$ +10.3, c=0.1 in $CHCl_3$, T=21.3 °C

All data agree with literature.[178]

(5*S*)-5-(2'-Hydroxy-1',3'-diphenylpropan-2'-yl)pyrrolidin-2-one 455



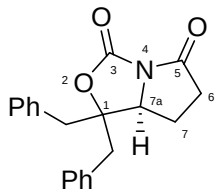
The ester **454** (1.84 gm, 12.9 mmol) was dissolved in dry tetrahydrofuran (15 mL) and cooled to −78 °C. 2 M benzylmagnesium chloride in tetrahyrofuran (20.0 mL, 40.0 mmol) was then added over 25 min and the reaction mixture allowed to −40 °C warm to for 15 min, followed by 0 °C for 30 min. The reaction was then quenched by addition of 1 M HCl (aq) (100 mL) and extracted with dichloromethane (5 x 100 mL). Combined organics were combined, dried and concentrated *in vacuo*. The residue was purified by chromatography using a Biotage® SNAP KP-Sil cartridge (100 g) [SiO_2, EtOAc – *iso*-hexane (7:3-1:0)] gave alcohol **455** (706 mg, 19%) as a beige amorphous solid.

R_f [SiO_2, EtOAc - Cyclohexane (4:1)] 0.28

δ_H (400 MHz, $CDCl_3$) 2.03-2.17 (1H, m, NCHCH^AH^B) 2.18-2.29 (1H, m, NCHCH^AH^B), 2.30-2.46 (2H, m, $COCH_2$), 2.71 (1H, d, *J*=13.6 Hz, PhCH^AH^B), 2.77 (2H, s, $PhCH_2$), 3.00 (1H, d, *J*=13.4 Hz, PhCH^AH^B), 3.64 (1H, dd, *J*=8.4, 6.5 Hz, NCH), 5.60 (1H, br. s, NH), 7.13 (2H, d, *J*=6.3 Hz, ArH), 7.21 (8H, m, ArH); δ_C (100 MHz, $CDCl_3$) 21.7 (CH_2), 30.1 (CH_2),

40.2 (CH_2), 42.5 (CH_2), 59.5 (CH), 75.4 (C), 127.1 (CH), 127.1 (CH), 128.7 (CH), 128.7 (CH), 130.2 (CH), 130.9 (CH), 135.6 (C), 135.8 (C), 177.7 (C); IR (cm^{-1}) 3364 (O-H), 1682 (C=O), 1651 (N-H); m/z (CI^+) 296 [$(M+H)^+$, 21%], 144 (48), 71 (100), HRMS: 296.1653, $C_{19}H_{21}NO_2$ requires $(M+H)^+$ 296.1651; ;$[\alpha]_D$ +52.0, T=20.8 °C, c=1.0 in $CHCl_3$; M.p. decomp at 180 °C.

(7a*S*)-1,1-Dibenzyl-hexahydropyrrolo[1,2-c][1,3]oxazole-3,5-dione 556

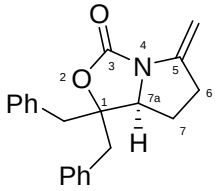


The amide **455** (250 mg, 0.85 mmol) was dissolved in dry tetrahydrofuran (3 mL) and carbonyldiimidazole (686 mg, 4.23 mmol) was added. The reaction mixture was irradiated in the microwave (100 W, 75 °C, 3 h), then cooled and concentrated *in vacuo*. The crude material was chromatographed [SiO_2, EtOAc - Pet. Ether (1:1-1:0)] to give the imide **456** (133 mg, 53%) as a solid.

R_f [SiO_2, EtOAc] 0.57

δ_H (400 MHz, $CDCl_3$) 1.93-2.02 (1H, m, 7-C*H*^{A}H^B), 2.14-2.26 (1H, m, 7-CH^A*H*^{B}), 2.62 (1H, ddd, *J*=17.4, 8.8, 1.5 Hz, 6-H_{eq}), 2.72 (1H, ddd, *J*=17.4, 12.0, 8.4 Hz, 6-H_{ax}), 2.82 (1H, d, *J*=14.3 Hz, PhC*H*^{A}H^B), 2.83 (1H, d, *J*=14.5 Hz, PhC*H*^{C}H^D), 3.09 (1H, d, *J*=14.5 Hz, PhCH^C*H*^{D}), 3.23 (1H, d, *J*=14.3 Hz, PhCH^A*H*^{B}), 4.55 (1H, dd, *J*=10.0, 6.7 Hz, 7a-H), 7.16 (2H, d, *J*=8.0 Hz, ArH), 7.29-7.39 (8H, m, ArH); δ_C (100 MHz, $CDCl_3$) 21.5 (CH_2), 36.0 (CH_2), 40.8 (CH_2), 41.8 (CH_2), 61.9 (CH), 86.2 (C), 127.5 (CH), 127.6 (CH), 128.6 (CH), 128.9 (CH), 130.6 (CH), 130.9 (CH), 133.6 (C), 133.9 (C), 148.1 (C), 170.3 (C); IR (cm^{-1}) 1795 (C=O), 1718 (C=O); m/z (CI^+) 322 [$(M+H)^+$, 100%]; HRMS: 322.1444, $C_{20}H_{19}NO_3$ requires $(M+H)^+$ 322.1443 ;$[\alpha]_D$ +116.2, T=25.3 °C, c=0.5 in $CHCl_3$; M.p. 163-164 °C.

(7a*S*)-1,1-Dibenzyl-5-methylidene-hexahydropyrrolo[1,2-c][1,3]oxazol-3-one 457



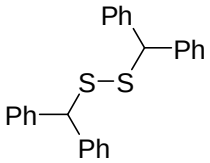
Following methylenation procedure 3c, ester **456** (269 mg, 0.5 mmol) gave enamine **457** (11 mg, 17%) as an oil after chromatography [Al_2O_3, Et_2O - Pet. Ether (0:1-1:4)] and [SiO_2, Et_2O - Pet. Ether (1:9)].

R_f [Al_2O_3, Et_2O - Pet. Ether (1:1)] 0.50

R_f [SiO_2, Et_2O - Pet. Ether (1:1)] 0.24

δ_H (400 MHz, $CDCl_3$) 1.71-1.80 (1H, m, 7-C*H*^{A}H^B), 1.85-1.99 (1H, m, 7-CH^A*H*^{B}), 2.60-2.80 (2H, m, 6-CH_2), 2.71 (1H, d, *J*=14.2 Hz, PhC*H*^{A}H^B), 2.73 (1H, d, *J*=14.4 Hz, PhC*H*^{C}H^D), 3.03 (1H, d, *J*=14.4 Hz, PhCH^C*H*^{D}), 3.24 (1H, d, *J*=14.2 Hz, PhCH^A*H*^{B}), 4.30 (1H, dd, *J*=10.9, 5.6 Hz, 7a-H), 4.39 (1H, s, =C*H*^{A}H^B), 5.06 (1H, s, =CH^A*H*^{B}) 7.16 (2H, d, *J*=8.0 Hz, ArH), 7.20-7.38 (8H, m, ArH); δ_C (100 MHz, $CDCl_3$) 25.0 (CH_2), 35.3 (CH_2), 41.7 (CH_2), 42.3 (CH_2), 65.9 (CH), 77.6 (C), 83.8 (C), 90.3 (CH_2), 127.1 (CH), 127.2 (CH), 128.4 (CH), 128.5 (CH), 130.6 (CH), 130.9 (CH), 134.7 (C), 134.9 (C), 141.4 (C); IR (cm^{-1}) 2933 (Ar-H), 1750 (C=O), 1495 (C=C); m/z (CI^+) 320 [$(M+H)^+$, 34%], 338 [$(M+H_2O+H)^+$, 100%]; HRMS: 320.1649, $C_{21}H_{21}NO_2$ requires $(M+H)^+$ 320.1651.

Diphenylmethyl disulfide 459



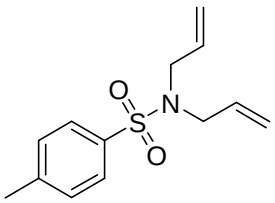
Diphenylmethanethiol acetate (121 mg, 0.5 mmol), titanocene dichloride (498 mg, 2 mmol) and the Nysted reagent (1.92 mL, 1.0 mmol, 20 %wt in THF) were mixed in a microwave vial. The reaction mixture was irradiated in the microwave (120 °C, 20 min). This gave a black solution which was quenched into 1 M HCl (aq) (20 mL) and partitioned with dichloromethane (50 mL). Organics were extracted and dried using a Biotage® ISOLUTE phase separator, then concentrated *in vacuo* to give crude product. Chromatography using a Biotage® SNAP KP-Sil cartridge (11 g) [SiO_2, EtOAc - cyclohexane (1:9)] gave disulfide **459** (74 mg, 62%) as an oil.

R_f [SiO_2, EtOAc - Cyclohexane (3:7)] 0.88

δ_H (400 MHz, $CDCl_3$) 4.77 (2H, s, SCH), 6.98-7.03 (4H, m, ArH), 7.08-7.35 (16H, m, ArH); δ_C (100 MHz, $CDCl_3$) 56.3 (CH), 125.8 (CH), 128.1 (CH), 128.5 (CH), 143.4 (C).

All data agree with literature.[179]

***N*,*N*-bis(prop-2'-en-1'-yl)-4-methylbenzenesulfonamide 463**



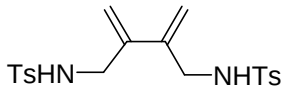
Following the procedure of Terada *et al*.[180] tosylamide (300 mg, 1.75 mmol) and K_2CO_3 (346 mg, 4.38 mmol) were suspended in dry acetonitrile (17 mL) and allyl bromide (380 μL, 4.38 mmol) was added. The reaction mixture was stirred at RT for 19 h under argon. The reaction was then filtered and concentrated *in vacuo* to give the diene **463** (217 mg, 50%) as a yellow oil after chromatography [SiO_2, EtOAc - Pet. Ether (1:5)]

R_f [SiO_2, EtOAc - Pet. Ether (1:5)] 0.37

δ_H (400 MHz, $CDCl_3$) 2.43 (3H, s, CH_3), 3.80 (4H, d, *J*=6.2 Hz, 1'-H), 5.10-5.13 (2H, m, 3'-H), 5.14-5.20 (2H, m, 3'-H), 5.53-5.71 (2H, m, 2'-H), 7.30 (2H, d, *J*=8.0 Hz, 3-H and 5-H), 7.70 (2H, d, *J*=8.2 Hz, 2-H and 6-H); δ_C (100 MHz, $CDCl_3$) 21.5 (CH_3), 49.3 (CH_2), 119.0 (CH_2), 127.2 (CH), 129.7 (CH), 132.6 (CH), 137.4 (C), 143.2 (C); IR (cm^{-1}) 1620 (C=C),1597 (Ar), 1342 (S=O), 1153 (S=O); m/z (EI^+) 251 [$M^{+\cdot}$, 21%], 224 (15), 155 (49), 91 (100), HRMS: 251.0976, $C_{13}H_{17}NO_2S$ requires $M^{+\cdot}$ 251.0980.

All data agree with literature.[181]

2,3-Bis(4-methylbenzenesulfonamide)but-1,3-diene 465



The diene **463** (103 mg, 0.41 mmol) was dissolved in dry THF (1.5 mL) and titanocene dichloride (204 mg, 0.82 mmol) and the Nysted reagent (0.79 mL, 0.41 mmol, 20 %wt in THF) were added. The reaction was irradiated in the microwave (100W, 75 ºC, 22 min). This gave a black solution which was quenched into sat. $NaHCO_3$ (aq) (20 mL) and extracted with Et_2O (3 x 20 mL). Organic extracts were combined then washed with brine (100 mL), dried ($MgSO_4$) and concentrated to give a crude oily solid. [SiO_2, EtOAc - Pet. Ether (1:5)] gave a 1:2 mixture (15 mg) of dimerised compound **465** and *N*-allyl-4-methylbenzenesulfonamide **466**.

Data for dimerised compound **465**:

δ_H (400 MHz, $CDCl_3$) 2.43 (6H, s, $ArCH_3$), 3.48 (4H, d, *J*=6.3 Hz, NCH_2) signal becomes a singlet on D_2O shake, 4.50-4.60 (2H, m, NH) signal dissapears on D_2O shake, 4.83 (2H, s, $=CH^AH^B$), 4.86 (2H, s, $=CH^AH^B$), 7.31 (4H, d, *J*=7.7 Hz, ArH), 7.75 (4H, d, *J*=7.5 Hz, ArH);

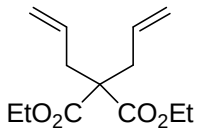
δ_C (100 MHz, $CDCl_3$) 20.2 (CH_3), 49.0 (CH_2), 112.8 (CH_2), 127.2 (CH), 129.8 (CH), 136.9 (C), 140.5 (C), 143.5 (C); IR (cm^{-1}) 3350 (N-H),1655 (C=C), 1310 (S=O).

Data for *N*-allyl-4-methylbenzenesulfonamide **466**:

δ_H (400 MHz, $CDCl_3$) 2.43 (3H, s, $ArCH_3$), 3.59 (2H, t, *J*=5.9 Hz, NCH_2) signal becomes a doublet on D_2O shake, 4.50-4.60 (1H, m, NH) signal dissapears on D_2O shake, 5.10 (1H, d, *J*=9.3 Hz, CH=CH^AH^B), 5.17 (1H, d, *J*=18.1 Hz, CH=CH^AH^B), 5.66-5.77 (1H, m, *CH*=CH_2), 7.31 (2H, d, *J*=7.7 Hz, ArH), 7.75 (2H, d, *J*=7.5 Hz, ArH)

Data for *N*-allyl-4-methylbenzenesulfonamide **466** agrees with literature.[182]

1,3-Diethyl 2,2-bis(prop-2'-en-1'-yl)propanedioate 483



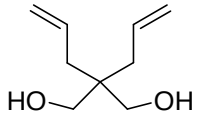
Following the procedure of BouzBouz *et al*.[183] diethyl malonate (0.95 mL, 6.2 mmol) was dissolved in dry tetrahydrofuran (30 mL) and cooled to 0 °C. Sodium hydride (60% disp. in mineral oil, 998 gm, 25.0 mmol) was added portionwise and the mixture allowed to warm to RT over 90 min under argon. The reaction was the re-cooled to 0 °C and allyl bromide (2.16 mL, 25.0 mmol) was added. The mixture was then heated to reflux for 6 h before being cooled and quenched into sat. NH_4Cl (aq) (70 mL). This was partitioned and extracted with ethyl acetate (2 x 70 mL), combined organics were washed with brine (70 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a crude oil. Chromatography [SiO_2, EtOAc - Pet. Ether (0:1–1:19)] gave pure diene **483** (1.21 g, 81%) as a colourless oil.

R_f [SiO_2, EtOAc - Pet. Ether (1:9)] 0.37

δ_H (400 MHz, $CDCl_3$) 1.25 (6H, t, *J*=7.1 Hz, 2 x CH_3CH_2O), 2.64 (4H, d, *J*=7.4 Hz, 1'-H), 4.18 (4H, q, *J*=7.1 Hz, 2 x CH_3CH_2O), 5.10 (2H, d, *J*=10.9 Hz, 3'-H), 5.11 (2H, d, *J*=16.5 Hz, 3'-H), 5.56 (2H, m, 2'-H); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 36.7 (CH_2), 57.2 (C), 61.3 (CH_2), 119.2 (CH_2), 132.3 (CH), 170.8 (C); m/z (CI^+) 241 [$(M+H)^+$, 100%], HRMS: 241.1443, $C_{13}H_{20}O_4$ requires $(M+H)^+$ 241.1440.

All data agree with literature.[183]

2,2-Bis(prop-2'-en-1'-yl)propane-1,3-diol 484



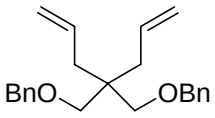
Following the procedure of Adrio *et al.*[184] lithium aluminium hydride (459 mg, 12.1 mmol) was suspended in dry diethyl ether (20 mL) and cooled to 0 °C under argon. The diester **483** (1.21 g, 5.04 mmol) in dry diethyl ether (10 mL) was then added dropwise and the reaction refluxed for 6 h. The reaction mixture was then cooled to 0 °C and quenched with firstly sat. NH_4Cl (aq) (1 mL) followed by 1 M NaOH (aq) (2.5 mL). The mixture was then refluxed for 19 h before being cooled, dried ($MgSO_4$) and filtered. After copious washing of the solid with diethyl ether the filtrate was concentrated *in vacuo* giving the diol **484** (723 mg, 92%) as a colourless oil.

R_f [SiO_2, EtOAc - Pet. Ether (1:9)] 0.10

δ_H (400 MHz, $CDCl_3$) 2.06 (2H, t, *J*=5.5 Hz, OH), 2.10 (4H, d, *J*=7.5 Hz, 1'H), 3.60 (4H, d, *J*=5.4 Hz, CH_2OH), 5.10 (2H, d, *J*=10.7 Hz, 2 x 3'-H_{cis}), 5.13 (2H, d, *J*=16.7 Hz, 2 x 3'-H_{trans}), 5.85 (2H, m, 2'-H); δ_C (100 MHz, $CDCl_3$) 36.2 (CH_2), 42.2 (C), 66.4 (CH_2), 118.2 (CH_2), 134.0 (CH); m/z (Cl^+) 157 [$(M+H)^+$, 100%]; HRMS: 157.1227, $C_9H_{16}O_2$ requires $(M+H)^+$ 157.1229.

All data agree with literature.[184]

4,4-Bis(benzyloxymethyl)hepta-1,6-diene 485



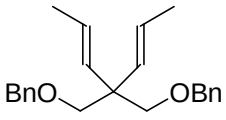
Following the procedure of Perch *et al.*[185] the diol **484** (647 mg, 4.14 mmol) was dissolved in dry tetrahyrofuran (15 mL) and cooled to 0 °C, sodium hydride (60% disp. in mineral oil, 745 mg, 18.6 mmol) was then added portionwise. Benzyl bromide (1.48 mL, 12.4 mmol) in dry tetrahydrofuran (10 mL) was then added dropwise and the reaction stirred at RT for 19 h under argon. The reaction was then quenched with ice and extracted with DCM (3 x 30 mL). Combined organics were dried ($MgSO_4$) and concentrated *in vacuo*, and excess benzyl bromide removed by kugelrohr distillation (100 °C, 2 h). The residue was purified by chromatography [SiO_2, EtOAc - Pet. Ether (0:1–1:9)] giving the benzylated product **485** (1.23 g, 88%) as a clear oil.

R_f [SiO_2, EtOAc - Pet. Ether (1:4)] 0.60

δ_H (400 MHz, $CDCl_3$) 2.12 (4H, d, *J*=7.4 Hz, =CHCH_2), 3.31, (4H, s, CH_2OBn), 4.48 (4H, s, CH_2Ph), 5.02 (2H, d, *J*=10.3 Hz, 2 x =CH^AH^B), 5.05 (2H, d, *J*=16.6 Hz, 2 x =CH^AH^B), 5.79

(2H, m, 2 x *HC*=CH_2) 7.26-7.39 (10H, m, ArH); δ_C (100 MHz, $CDCl_3$) 36.6 (CH_2), 42.0 (C), 72.6 (CH_2), 73.2 (CH_2), 117.6 (CH_2), 127.4 (CH), 127.6 (CH), 128.4 (CH), 134.4 (CH), 138.9 (C); IR (cm^{-1}) 2856 (ArH), 1638 (C=C), 1094 (C-O); m/z (CI^+) 337 [$(M+H)^+$, 100%]; HRMS: 337.2170, $C_{23}H_{28}O_2$ requires $(M+H)^+$ 337.2168.
All data agree with literature.[185]

4,4 Bis(benzyloxymethyl)hepta-2*E*, 5*E*-diene 487



The diene **485** (168 mg, 0.5 mmol) was dissolved in an solution of the Petasis reagent (0.43 mL, 0.5 mmol, 1.18 M in 1:1 THF - toluene) and further diluted with dry THF (0.25 ml) and toluene (0.25 mL). The reaction mixture was irradiated in the microwave (20 min, 75 °C, 100 W). The resultant black solution was concentrated *in vacuo* and residual solvent removed under high vacuum. The residue was sonicated in hexane and the liquid decanted and concentrated *in vacuo*. Column chromatography [SiO_2, Et_2O - Pet. Ether (1:39-1:19)] gave an 85:15 mixture of dienes **485** and **487** (105 mg, corresponding to 10% yield of diene **487** and 53% of recovered starting material).
R_f [SiO_2, Et_2O - Pet. Ether (1:9)] 0.44
δ_H (400 MHz, $CDCl_3$) 1.69 (6H, d, *J*=4.6 Hz, CH_3), 3.47 (4H, s, CCH_2), 4.52 (4H, s, OCH_2), 5.43-5.51 (4H, m, C=*CH* and =*CH*CH_3), 7.21-7.39 (10H, m, ArH); δ_C (100 MHz, $CDCl_3$) 18.5 (CH_3), 47.4 (C), 73.2 (CH_2), 73.3 (CH_2), 125.4 (CH), 127.3 (CH), 127.4 (CH), 128.2 (CH), 133.0 (CH), 138.9 (C); IR (cm^{-1}) 2854 (Ar-H), 1094 (C-O); m/z (CI^+) 337 [$(M+H)^+$, 100%]; HRMS: 337.2166, $C_{23}H_{29}O_2$ requires $(M+H)^+$ 337.2168.

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Appendix

Combined ^{1}H and ^{13}C NMR data for (1*R*,2*R*,4a*S*,8a*S*)-2,5,5,8a-tetramethyl-1-(2'-methylprop-2'-en-1-yl)-decahydronaphthalen-2-ol **421** assigned using HSQC

			^{1}H NMR													
			Shift	0.77-0.84	0.85-0.93	0.96	1.10-1.20	1.21-1.30	1.34-1.48	1.55-1.68	1.70-1.76	1.79-1.84	2.13	2.25-2.33	4.78	4.86
			Multiplicity	m	m	dd	m	m	m	m	m	m	d	m	br. s	br. s
^{13}C NMR	Shift	DEPT	Assignment	8a-Me, 5-Me	5-Me, 6-$H^{A}H^{B}$	4a-H	7-$H^{A}H^{B}$	4-$H^{A}H^{B}$, 2-Me	3-$H^{A}H^{B}$, 7-$H^{A}H^{B}$, 8$H^{A}H^{B}$	1-H, 4-$H^{A}H^{B}$, 8-$H^{A}H^{B}$,	6-$H^{A}H^{B}$,	2'-Me, 3-$H^{A}H^{B}$	1'-$H^{A}H^{B}$	1'-$H^{A}H^{B}$	3'-$H^{A}H^{B}$	3'-$H^{A}H^{B}$
	15.3	CH_3	8a-Me	X												
	18.7	CH_2	8						X	X						
	20.1	CH_2	4					X		X						
	21.6	CH_3	5-Me	X												
	22.3	CH_3	2'-Me									X				
	24.2	CH_3	2-Me					X								
	33.4	C	5													
	33.5	CH_3	5-Me		X											
	33.8	CH_2	1'										X	X		
	38.6	C	8a													
	40.0	CH_2	6		X						X					
	41.8	CH_2	7				X		X							
	43.5	CH_2	3						X			X				
	56.2	CH	4a			X										
	57.6	CH	1							X						
	74.8	C	2													
	111.6	CH_2	3'												X	X
	149.4	C	2'													

Combined ^{1}H and ^{13}C NMR data for 1-[(1*R*,2*R*,4a*S*,8a*S*)-2-Hydroxy-2,5,5,8a-tetramethyl-decahydronaphthalen-1-yl]-propan-2-one **427** assigned using HSQC

			^{1}H NMR													
			Shift	0.78	0.88	0.92	1.04	1.11	1.14	1.20-1.47	1.51-1.63	1.69	1.90-1.97	2.21	2.45	2.54
			Multiplicity	m	s	td	dd	s	td	m	m	dq	m	s	dd	dd
^{13}C NMR	Shift	DEPT	Assignment	5'-Me 8a-Me	5'-Me	6'-H_{ax}	4a-H	2'-Me	7'-H_{ax}	3'-C*H*^{A}H^{B} 4'-H_{ax} 6'-H_{eq} 7'-H_{eq} 8'-C*H*^{A}H^{B}	8'-CH^{A}*H*^{B}	4'-H_{eq}	1'-H 3'-CH^{A}*H*^{B}	3-H	1-C*H*^{A}H^{B}	1-CH^{A}*H*^{B}
	15.7	CH_3	8a-Me	X												
	18.4	CH_2	8'							X	X					
	20.6	CH_2	4'							X		X				
	21.4	CH_3	5'-Me	X												
	23.1	CH_3	2'Me					X								
	30.3	CH_3	3											X		
	33.2	C	5'													
	33.3	CH_3	5'-Me		X											
	38.3	C	8a													
	39.3	CH_2	6'			X				X						
	39.6	CH_2	1												X	X
	41.7	CH_2	7'						X	X						
	44.6	CH_2	3'							X			X			
	55.8	CH	4a				X									
	55.9	CH	1'										X			
	73.2	C	2'													
	210.3	C	2													