THE ENANTIOSELECTIVE GENERATION OF BRIDGEHEAD ENOLATES

by Douglas Thomas Kirk, MChem

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Declaration

I declare that this thesis is the result of my own work and has not, whether in the same or a different form, been presented to this or any other university in support of an application for any degree other than that for which I am now a candidate.

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Douglas Thomas Kirk

The Alchemist

There is an old man at the top of the street,
And the end of his beard reaches down to his feet
and he's just the person I'm longing to meet,
I think that he sounds so exciting;
For he talks all the day to his tortoiseshell cat
and he asks about this, and explains about that,
And at night he puts on a big wide-awake hat*
And he sits in the writing room, writing.

He has worked all his life (and he's terribly old),
At a wonderful spell which says "Lo and Behold!
Your nursery fender is gold!" – and its gold!
(or the tongs, or the rod for the curtain);
But somehow he hasn't got hold of it quite,
Or the liquid you pour on it first isn't right,
So that's why he works at it night after night,
Till he knows he can do it for certain.

A. A. Milne

* so as not to go to sleep

Acknowledgements

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Lastly I must thank my mother and my sister for their continued support that has allowed me to flourish and achieve all that I am.

This thesis is dedicated in loving memory of my father Clifford Kirk who guided my first steps in both life and chemistry.

Table of Contents

Abstract

Chapter One gives an introduction to the key concepts of bridgehead alkene formation and its relevance to the formation of bridgehead enolates of ketones including a review of bridgehead enolates in synthesis. The review is limited to the generation of bridgehead carbanions α to a carbonyl group and does not cover bridgehead cations, radicals or any anions except those already mentioned. In addition, a brief introduction to chiral base methodology and a review of the latest developments is included.

Chapter Two describes the generation of bridgehead enolates in various bridged bicyclic ketones using chiral and achiral lithium amide bases and their subsequent interception with chlorotrimethylsilane. The chiral bridgehead silanes resulting from enantioselective deprotonation were shown to undergo silyl exchange reactions with TBAT as fluoride source in the presence of various electrophiles.

Chapter Three describes a review of bridgehead enolates of imides and describes the extension of the developed methodology in Chapter Two to the generation and trapping of bridgehead enolates in bridged bicyclic imides and lactams. In addition bridgehead enolates are shown to react in the presence of non-classical *in situ* electrophiles such as methyl iodide, allyl bromide, benzyl bromide, prenyl bromide and pivaloyl chloride in high yield and enantioselectivity. The secondary bridgehead deprotonation of *mono*-substituted imides was also achieved resulting in double bridgehead functionalised products with high ee. The bridgehead silanes are shown to undergo silyl exchange reactions and display silyl directed regioselective

reduction and thionation reactions. The mechanism of deprotonation, comparison to known examples and the origin of bridgehead carbanion stability are discussed.

Chapter Four contains the experimental procedures and analytical data for the preparation of the novel compounds described herein followed by the appendix of selected NMR and X-ray data.

Abbreviations

Ac	acetyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
18-C-6	18-crown-6
CDI	1,1'-carbonyldiimidazole
DCM	dichloromethane
DIPA	diisopropylamine
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
d	day(s)
dr	diastereoisomeric ratio
E	electrophile
ee	enantiomeric excess
EQ	external quench
Et	ethyl
h	hour(s)
HMPA	hexamethylphosphoramide
^{i}Pr	*iso*-propyl
ISQ	*in situ* quench
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamide
LiTMP	lithium 2,2,6,6-tetramethylpiperidide
mol	mole

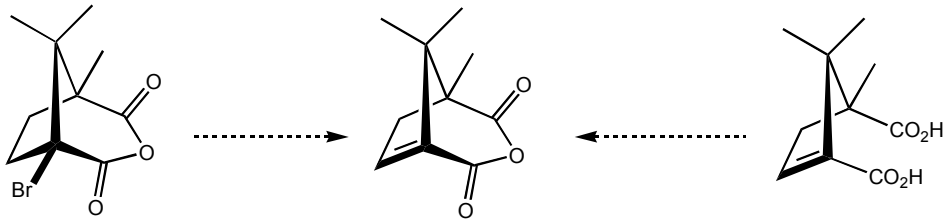
*m*CPBA	*meta*-chloroperbenzoic acid
Me	methyl
min	minutes(s)
MO	molecular orbital
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
Nu	nucleophile
Piv	pivaloyl
Ph	phenyl
PhH	benzene
PhMe	toluene
py	pyridine
R	alkyl group
TASF	tris(diethylamino)sulfonium difluoro(trimethyl)silicate
TBAF	tetra-^{n}butylammonium fluoride
TBAT	tetra-^{n}butylammonium triphenyldifluorosilicate
^{t}Bu	*tert*-butyl
THF	tetrahydrofuran
TMEDA	*N*,*N*,*N*,*N*-tetramethyl-1,2-ethylenediamine
TMS	trimethylsilyl
TMSCl	chlorotrimethylsilane
Ts	*para*-toluenesulfonyl (tosyl)
TsOH	*para*-toluenesulfonic acid

Chapter One

Introduction

1.1 Bridgehead Alkenes

In 1924 Julius Bredt introduced the concept of Bredt alkenes to explain observations made over 22 years in naturally occurring camphane and pinane systems.[1] Bredt studied the potential formation of double bonds toward a bridgehead position and found no evidence of bridgehead alkene formation. For example he found the attempted elimination of HBr from **1** or the dehydration of diacid **3** failed to produce bridgehead alkene **2** (Scheme 1).



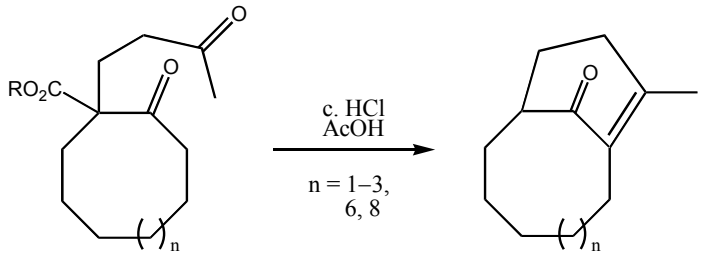
1 **2** **3**

Scheme 1

Bredt concluded that formation of a double bond originating from a bridgehead position was highly improbable and this came to be known as Bredt's rule. The failure to produce a bridgehead alkene was believed to arise from unsuitable orientation of p-orbitals that lie orthogonal and cannot overlap to form a π bond.

During the 20th century chemists have come to explore the qualitative nature of the rule, resulting in a class of molecules known as anti-Bredt alkenes.[2] In small bicyclic systems that are somewhat rigid there is little prospect for significant orbital overlap but it was recognised that increasing bridge size may allow greater flexibility and increase the likelihood of bridgehead alkene formation.

Prelog was one of the first to show the limits of Bredt's rule in a lecture at the Chemical Society in 1949 when he presented a range of medium to large bicyclic bridgehead alkenes **5** that formally broke Bredt's rule (Scheme 2).[3]



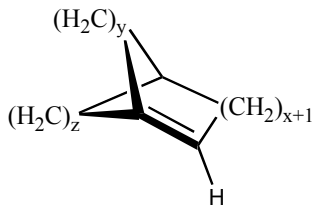
4 **5**

Scheme 2

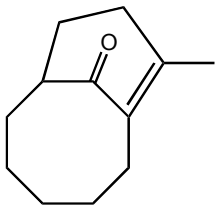
In bridged bicyclic systems ranging from n = 1 to 8, Prelog was able to observe bridgehead alkenes from Robinson type annulations and also noted that treatment of the analogous cyclohexanones and cycloheptanones gave only the products resulting from attack onto the ring ketones. This led Prelog to conclude that the "limit of applicability of Bredt's rule lies between the systems with a 7 and an 8-membered ring". Prelog also noted that decarboxylation at the bridgehead centres required milder conditions with increasing ring size, perhaps suggesting improved bridgehead carbanion stability due to resonance with the bridging ketone.

In the following year Fawcett comprehensively reviewed almost fifty years of anti-Bredt alkene literature and in the process attempted to categorise bridgehead alkenes by introducing the concept of S numbers.[2] Defined as the sum of the number of atoms present (S = x + y + z) in each of the three bridges, the S number attempted to better highlight the borderline areas between bridgehead alkenes that are; i) isolable, ii) transient reaction intermediates or

iii) unobtainable. This formula is illustrated by diagram **6** and applied to anti-Bredt alkene **7** resulting in S = 9 (Figure 1).



6



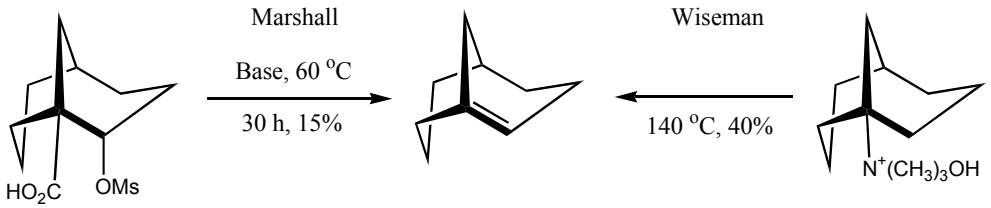
8-methylbicyclo[5.3.1]undec-7-en-11-one **7**

S = 5 + 3 + 1 = 9

Figure 1

Fawcett proposed that a bridgehead alkene with S > 8 would be isolable but those where S ≤ 8 would either be too unstable and exist only as transient reaction intermediates or be unobtainable.

The S number provided a useful framework for the discussion of bridgehead alkenes but it still could not accurately predict the existence of anti-Bredt alkenes. This was exemplified in 1967 when the synthesis and isolation of bicyclo[3.3.1]non-1-ene **9** (S = 7) was independently reported by Wiseman and Marshall (Scheme 3).[4]



8 **9** **10**

Scheme 3

Wiseman noted that to relieve strain the π-bond lies *trans* in the largest ring and so proposed that the strain of the bridgehead alkene and thus its stability is closely related to the strain of the corresponding *trans*-cycloalkene. This

proposition enhanced the understanding of why anti-Bredt alkenes are able to form because of the ample structural and theoretical data available for the smallest known *trans*-cycloalkene, *trans*-cyclooctene. In a similar fashion to anti-Bredt alkenes, *trans*-cyclooctene contains a strained and very reactive double bond because of its twisted nature, resulting from poor orbital overlap of the associated p-orbitals. Allinger, Pople and others have suggested that to regain p-orbital overlap there is partial rehybridisation of the p-orbitals with some s character.[5] The increased s character results in both carbon atoms becoming closer in character to a tetrahedral sp^3 carbon, which results in greater flexibility and better orbital overlap (Figure 2).

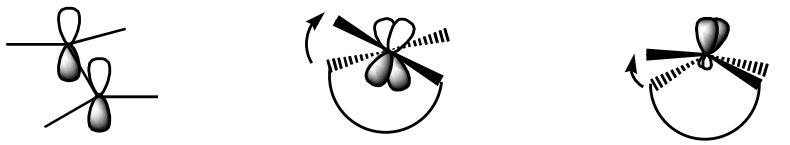
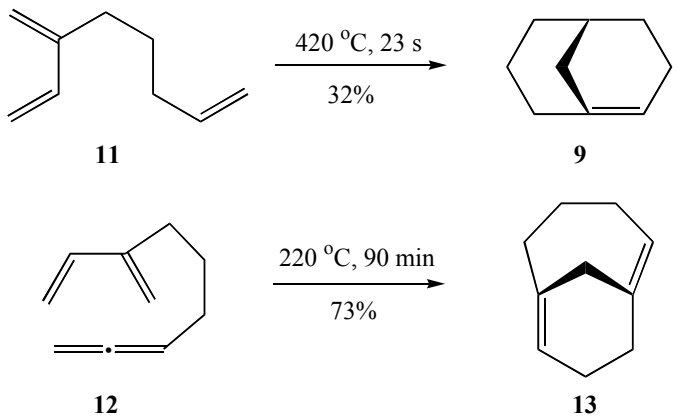


Figure 2

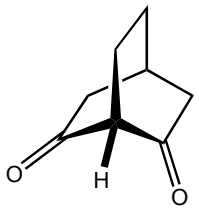
Arguably the most significant advance in preparing anti-Bredt alkenes has come from Shea with his development of the type 2 intramolecular Diels-Alder reaction.[6] Many anti-Bredt alkenes have been prepared where S = 7 (**9**) as well as products with two bridgehead alkenes **13** (Scheme 4).



Scheme 4

1.2 Bridgehead Enolates of Ketones

The anti-Bredt nature of a bridgehead enolate renders ketones in small bicyclic systems non-enolisable, but inductive effects by the ketone may still enhance the bridgehead proton acidity. In common with anti-Bredt alkenes, bridgehead enolates encounter similar strain when forming a π-bond toward a bridgehead position. The carbanion that results from deprotonation resides in a bridgehead sp^3 orbital that cannot obtain the correct orientation to form an enolate by donation into the adjacent π* carbonyl orbital. For that reason Bredt's rule can account for the reluctance of some bridged bicyclic systems to enolise under basic conditions *e.g.* **14** (Figure 3).[7]

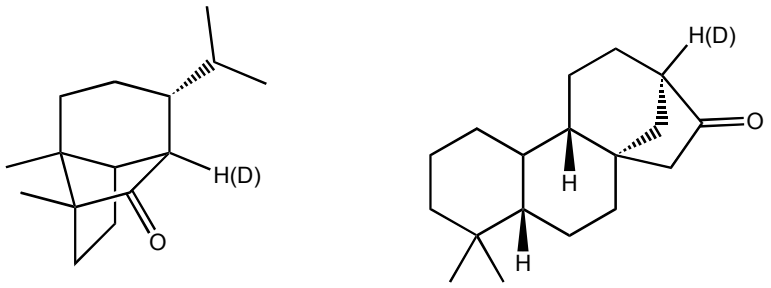


Bicyclo[2.2.2]octane-2,6-dione **14**

Figure 3

Bartlett observed that **14** showed no greater solubility in aqueous alkali than in water alone and concluded that it was 'non-enolic'.

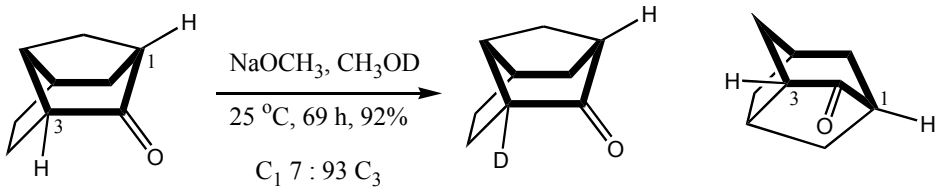
The intensive and successful research undertaken to produce anti-Bredt alkenes naturally spread to include the synthesis and isolation of bridgehead enolates. Two early studies to examine this issue concerned the deuteration of copacamphor[8] **15** and *ent*-17-norkauran-16-one[9] **16** with potassium *tert*-butoxide at 180 °C (Figure 4).



15 **16**

Figure 4

The bridgehead enolates of both of these ketones were thought to involve the formation of a *trans* double bond in a seven membered ring. The results seem to correlate with Wiseman's proposal that the double bond, in this case an enolate, is better accommodated when it lies *trans* in the largest ring. Motivated by these reports Nickon investigated the deuteration of brendan-2-one **17** to give **18**, and its isomer noradamantan-2-one **19** to provide a direct comparison between a locked boat conformation leading to a *trans* double bond and a locked chair giving the *cis* isomer (Scheme 5).[10]



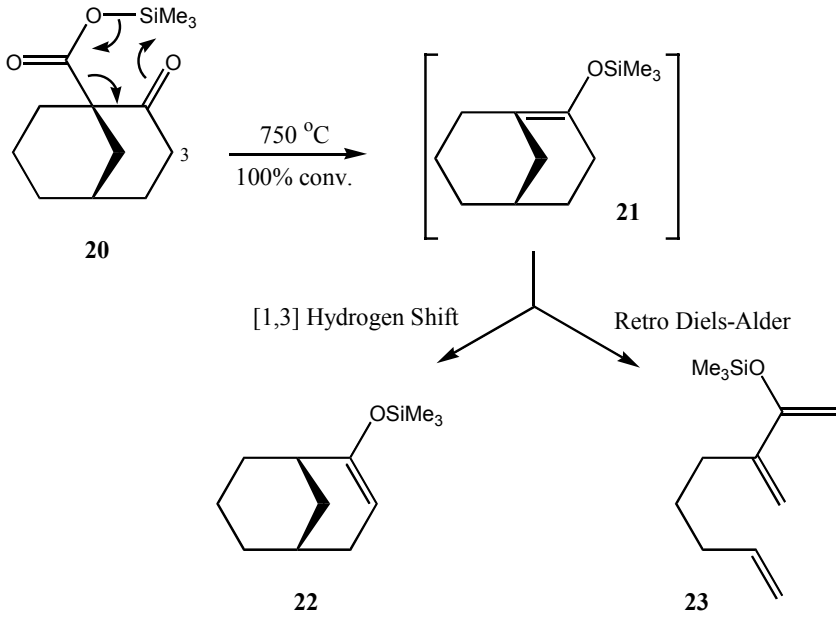
17 **18** **19**
140 °C, 69 h, 86%
C_1 10 : 90 C_3

Scheme 5

The remarkable ease with which deuteration of **17** occurs, in comparison to the forcing conditions required to deprotonate **19**, demonstrates that the bridged boat conformation significantly enhances enolate stability.

As a result Bloch revisited the bicyclo[3.3.1]nonane system, so successfully shown to accommodate an anti-Bredt alkene by Wiseman and

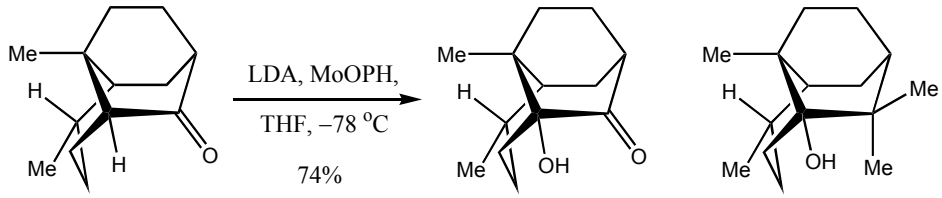
Marshall, and attempted to form a bridgehead silyl enol ether.[11] Flash thermolysis of trimethylsilyl 2-oxobicyclo[3.3.1]nonane-1-carboxylate **20** yielded two silyl enol ethers **22** and **23** that were thought to arise by [1,3] hydrogen shift and retro Diels-Alder, respectively, from the bridgehead silyl enol ether **21** (Scheme 6).



Scheme 6

Bloch stated that although such a concerted suprafacial [1,3] hydrogen shift is forbidden, according to Woodward-Hoffman rules, there is sufficient relief in strain energy involved to compensate for this violation. To confirm this proposal the thermolysis was repeated with C3 deuterium labelled ketone and gave the expected silyl enol ether **22** with deuterium incorporation at the bridgehead.

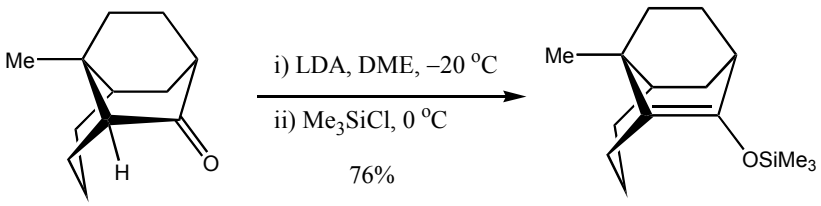
Using a closely related bicyclic system, Yamada reported the total syntheses of (±)-patchouli alcohol **26** and (±)-seychellene where bridgehead oxygenation of **24** was successfully accomplished using MoOPH to give **25** (Scheme 7).[12]



24 **25** (±)-Patchouli alcohol **26**

Scheme 7

In support of Nickon's hypothesis of a constrained boat conformation, Yamada reported the first isolation of an anti-Bredt silyl enol ether **28**.[13] Remarkably, treatment of bridged ketone **27** with LDA and subsequent trapping with TMSCl gave the enol ether with 76% yield (Scheme 8).



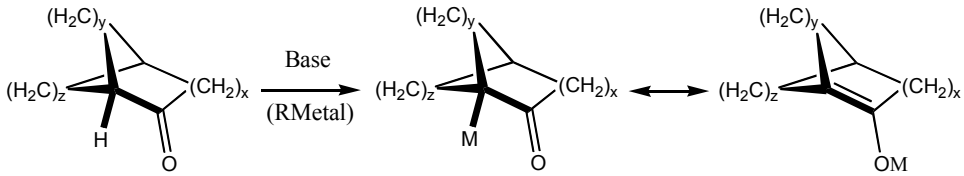
27 **28**

Scheme 8

The bridgehead silyl enol ether was shown to react with acetic acid-*d*/deuterium oxide to give the bridgehead deuterated product and also with methyl iodide and benzaldehyde in the presence of cesium fluoride to give the bridgehead alkylated products.

In discussing bridgehead enolates it is also important to recognise that their stability arises in part by resonance contribution from α-keto carbanions. In small bicyclic systems the ability to form an α-keto carbanion at a bridgehead position greatly reduces the strain compared to a bridgehead enolate even though it results in the formation of an unstable tertiary carbanion. Thus the deprotonation of small bicyclic systems **29** where S = 5 to 8 would

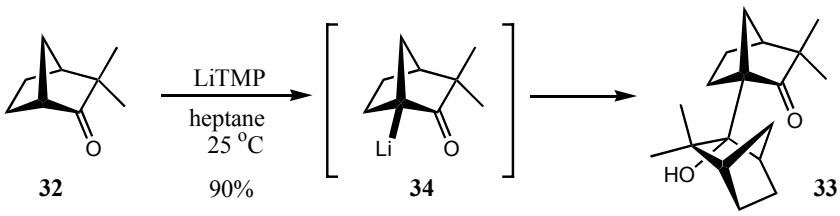
result in extremely strained enolates **31** that are presumed to exist as the relatively more stable α-keto carbanions **30** (Figure 5).



29 **30** **31**

Figure 5

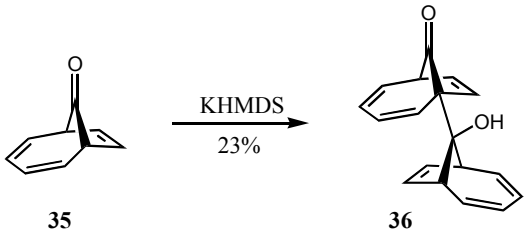
For example, Shiner reported that metallation of the non-enolisable ketone (–)-camphenilone **32** (S = 5) gave the aldol self condensation product **33**, presumably *via* the bridgehead lithiated intermediate **34** (Scheme 9).[14]



32 90% **34** **33**

Scheme 9

This intermediate was assumed to form because the aldol product obtained was a single diastereoisomer, which indicated that racemisation *via* homo-enolisation (β-deprotonation) had not occurred.[15] In a similar way, the deprotonation of bicyclo[4.2.1]nona-2,4,7-trien-9-one **35** reported by Feldman also gave an aldol self-condensation product **36** (Scheme 10).[16]

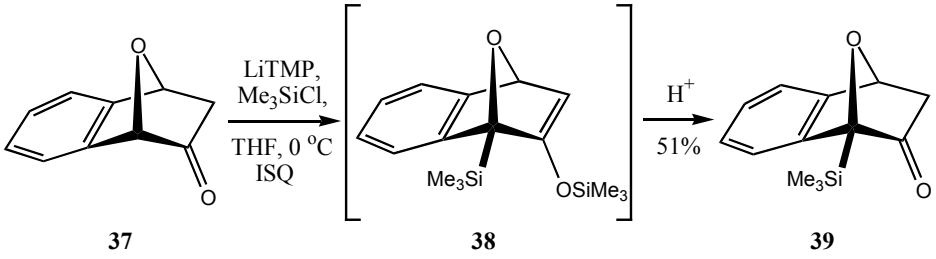


35 **36**

Scheme 10

In both cases it was reported that even in the presence of an *in situ* quench (ISQ), such as TMSCl, the presumed bridgehead lithiated intermediates could not be intercepted.

Similarly, Rickborn reported the rapid self-condensation of benzannulated 7-oxabicyclo[2.2.1]heptanone **37** despite the use of slow addition procedures.[17] However, deprotonation under ISQ conditions successfully trapped the presumed bridgehead carbanion *via* the isolable but extremely acid sensitive intermediate **38**, which upon acidic work-up gave **39** (Scheme 11).

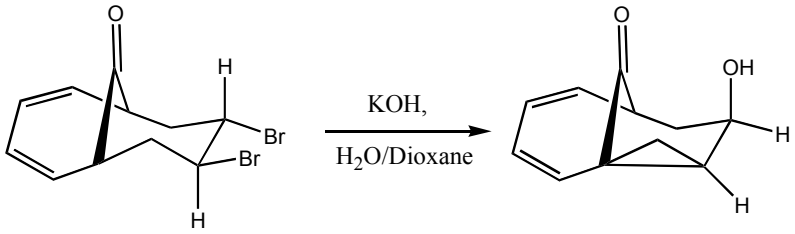


37 **38** **39**

Scheme 11

Treatment of **37** with a large excess of base resulted in secondary silylation at the methylene position presumably by vinylic deprotonation of intermediate **38**. Rickborn also demonstrated that deprotonation of benzannulated 7-oxabicyclo[2.2.1]heptene gave comparable yields of bridgehead silylation to **37**, suggesting that the benzylic nature of the bridgehead proton is the key requirement for deprotonation.

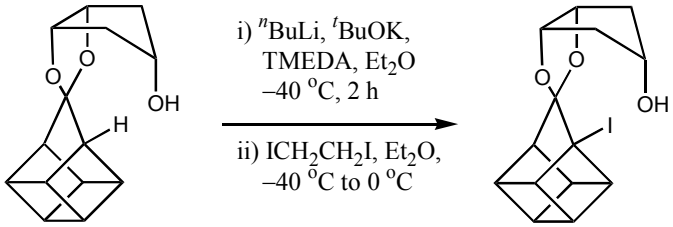
Itô reported that treatment of 8,9-dibromobicyclo[4.4.1]undeca-2,4-dien-11-one **40** with KOH in aqueous dioxane led to hydroxycyclopropyl ketone **41**, presumably *via* a bridgehead α-keto carbanion (Scheme 12).[18]



40 **41**

Scheme 12

To observe useful bridgehead chemistry in small systems required the development of indirect methods. Eaton described the 'first preparatively useful method' for bridgehead deprotonation of **42**, available from cubanone.[19] Ketal formation of cubanone with *cis*,*cis*-1,2,4-cyclopentanetriol positions a free hydroxyl, as auxiliary, in close proximity to assist bridgehead metallation that in the presence of diiodoethane gave **43** (Scheme 13).



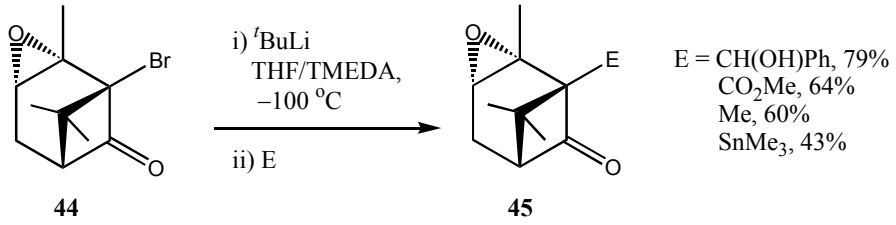
42 **43**

Scheme 13

However, the ketal auxiliary was limited in application because of its fragility and the strongly basic conditions were incompatible with other functional groups. Eaton was able to extend the methodology to a range of substrates by the use of iodobenzene diacetate under photolytic conditions to give the intermediate bridgehead radicals that were consequently trapped with iodine.

On the other hand, Wender approached the challenge by employing an efficient lithium/bromine exchange of a bridgehead bromide to generate the bridgehead lithiated intermediates.[20] Bridgehead bromide **44**, a rearrangement

product of the photolysis of bromoverbenone, was exchanged with *tert*-butyllithium and then allowed to react with various electrophiles to give the general product **45** (Scheme 14).

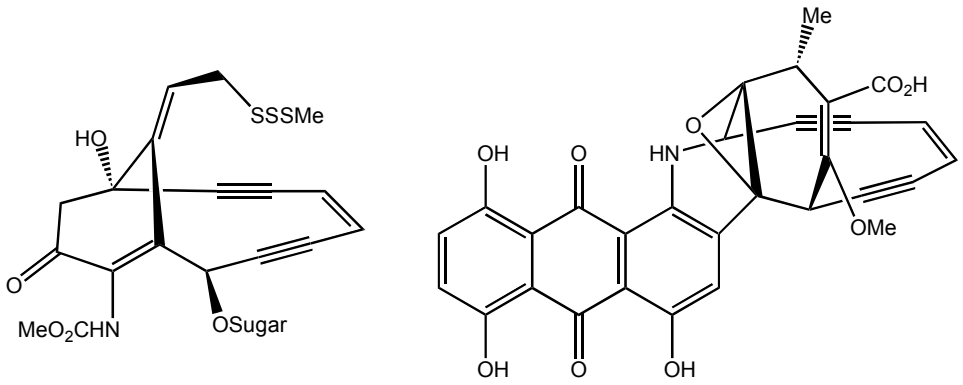


44 **45**

Scheme 14

On the whole, synthetically useful bridgehead chemistry is confined to large ring systems. The deprotonation of bridged bicyclic ketones in systems where S > 8 are expected to produce stable and controllable enolates because the flexibility of the larger ring systems are able to incorporate the π-bond.

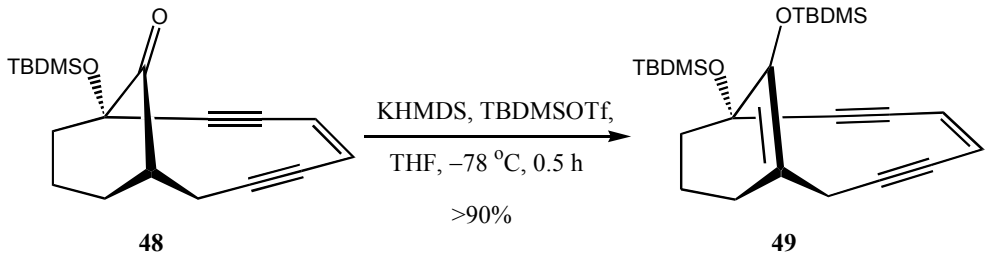
The ease with which bridgehead enolates can be formed in large ring systems was exemplified in two reports from Magnus concerning the formation of the bridgehead alkene of ene-diyne natural products, esperamycin and calicheamicin **46** and also in the synthesis of dynemicin A **47** (Figure 6).



Calicheamicin γ_1 **46** Dynemicin A **47**

Figure 6

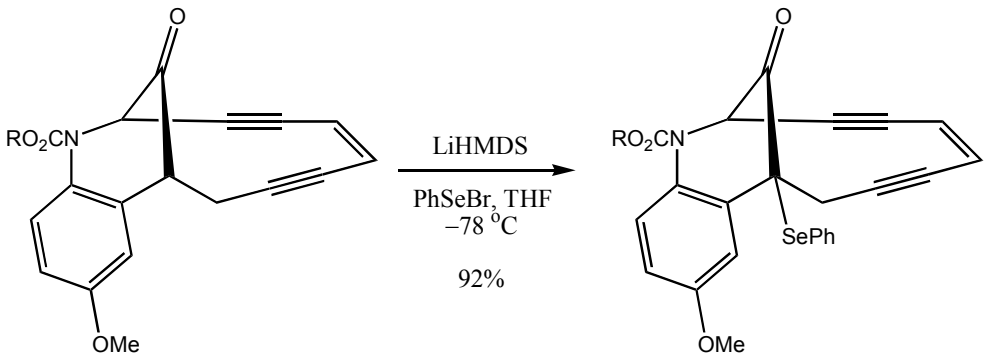
At the core of these natural products is a bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne ring system that would be expected to form a bridgehead enolate with ease due to its size. This was shown to be the case when treatment of model ketone **48** with KHMDS followed by trapping with TBDMSOTf gave the bridgehead silyl enol ether **49** in excellent yield (Scheme 15).[21]



48 **49**

Scheme 15

Subsequent oxidation of **49** with selenium dioxide produced the desired bridgehead alkene. In the synthesis toward the dynemicin core, Magnus was again able to use bridgehead enolate methodology by treating ketone **50** under similar conditions to give bridgehead phenylselenide **51** (Scheme 16).[22]

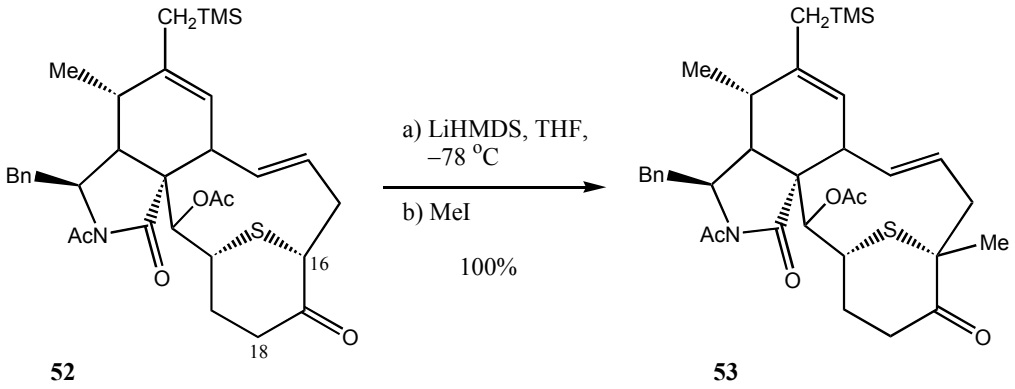


50 **51**

Scheme 16

Vedejs also demonstrated the ease of bridgehead deprotonation in a thiabicyclo[6.3.1]dodecane ring system during the total synthesis of zygosporin E.[23] While attempting to alkylate at C18 of **52** by deprotonation with LiHMDS

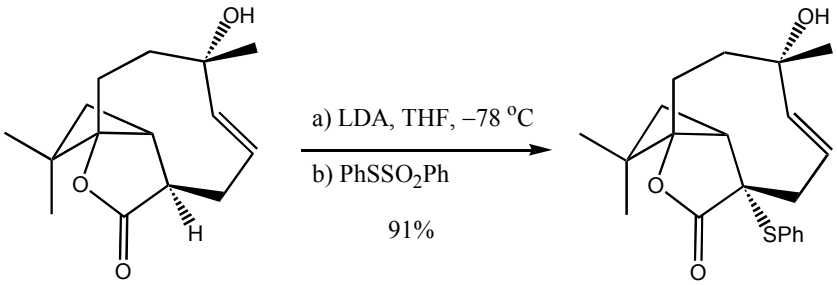
followed by methyl iodide, Vedejs found that the bridgehead alkylated product **53** was formed instead (Scheme 17).



52 **53**

Scheme 17

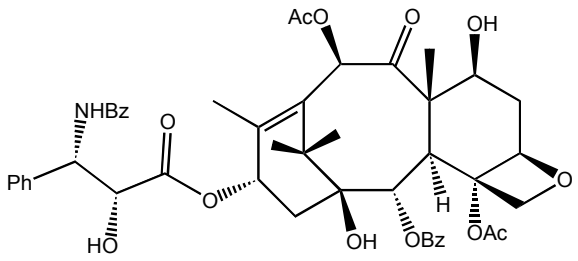
The total synthesis of (±)-punctaporonin B by Kende used the bridgehead enolate of a lactone in the 9-oxabicyclo[6.2.1]undecan-10-one system.[24] Treatment of lactone **54** with LDA followed by *S*-phenyl benzenethiosulfonate gave the thioether **55** (Scheme 18).



54 **55**

Scheme 18

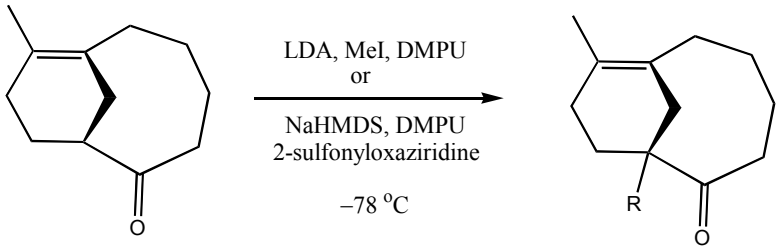
The family of taxane natural products have attracted much attention because of the biological activity associated with its many members and their interesting structural framework. Paclitaxel (Taxol™) **56** has attracted immense interest as a challenging target for modern synthetic methodology. At its heart is a bicyclo[5.3.1]undecane ring with both a bridgehead alkene and a bridgehead alcohol (Figure 7).



Paclitaxel **56**

Figure 7

Shea was first to demonstrate that bridgehead deprotonation of 8-methylbicyclo[5.3.1]undec-7-en-2-one **57** was possible.[25] Exposure of ketone **57** to base under kinetic control followed by an electrophile, gave the products **58** and **59** arising from the formation of the more highly substituted bridgehead enolate (Scheme 19).



57

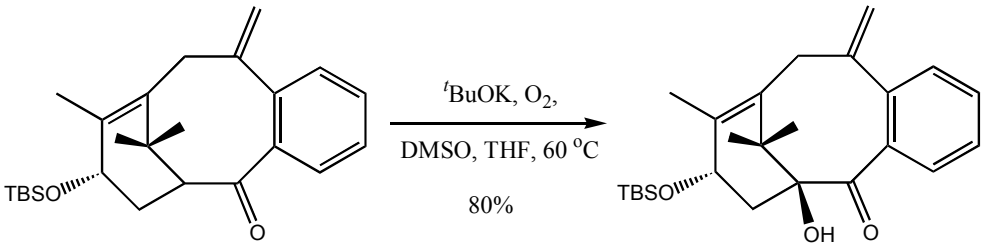
R = Me (65%, 37:1) **58**
OH (77%, 30:1) **59**

Scheme 19

Under these conditions the ratio of bridgehead substitution to methylene substitution is considerable *e.g.* R = Me, 37:1, R = OH, 30:1. The unusual selectivity observed was explained by Shea to arise from the conformational preference of the ring system. Kinetic deprotonation requires the dihedral angle for optimal stereoelectronic alignment between the bridgehead proton and the plane of the carbonyl be 90°. Examination of the low energy conformation of **57** by molecular modelling (MM2) revealed the bridgehead C–H to carbonyl dihedral angle to be 99°. In contrast, the competing methylene protons were

found to have dihedral angles of 144° and 32°. In support of this conclusion, treatment of ketone **57** under thermodynamic conditions (KHMDS, 0 °C) gave the products arising from the formation of the less highly substituted enolate with a ratio of methylene to bridgehead substitution of 40 to 1.

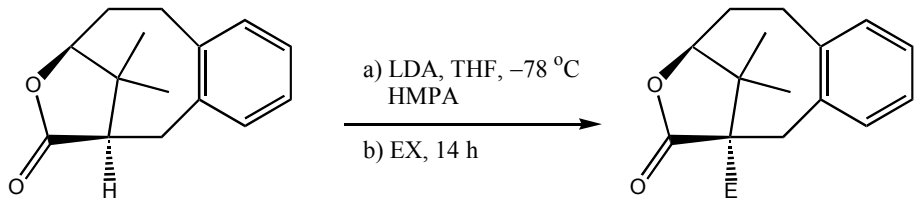
Wender was also able to show that bridgehead hydroxylation of paclitaxel model system **60** was possible to give **61** (Scheme 20).[26]



60 **61**

Scheme 20

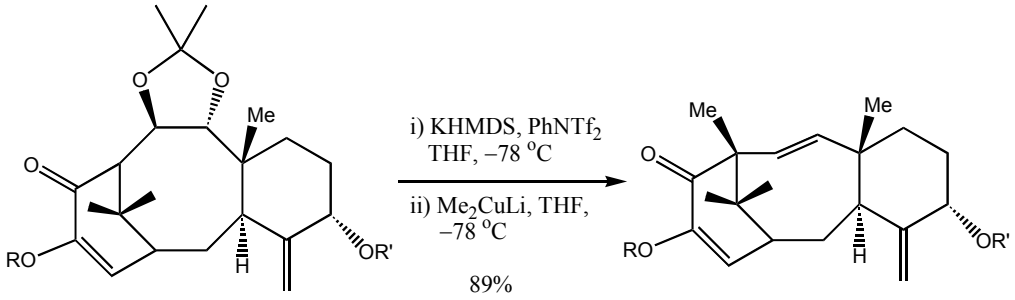
In another taxane model study, Reissig developed an efficient route to lactone **62** and was able to generate and alkylate the bridgehead enolate with various electrophiles to give the general product **63** (Scheme 21).[27]



62 **63** E = Me, 99%
Allyl, 80%
OH, 83%

Scheme 21

In addition, Paquette attempted to form the bridgehead enol triflate of **64**, as a precursor to forming a bridgehead alkene but discovered a competing rearrangement pathway to give **65** (Scheme 22).[28]

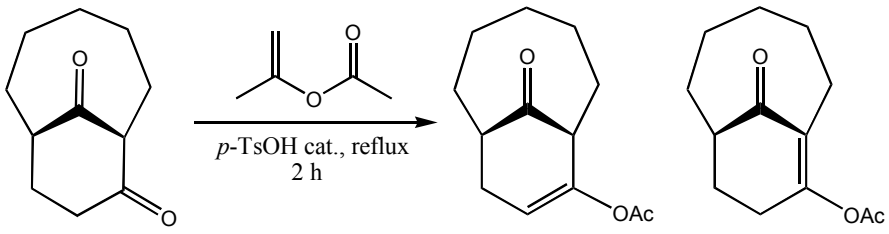


64 R = TBS, R' = MOM **65**

Scheme 22

Paquette reasoned that following successful formation of the bridgehead enolate there occurred β-elimination of the nearby protected diol to liberate acetone. Triflation of the allylic alkoxide anion was followed by [1,3] rearrangement to give the bridgehead triflate, which was substituted by the organocuprate to generate the bridgehead alkylated product **65**.

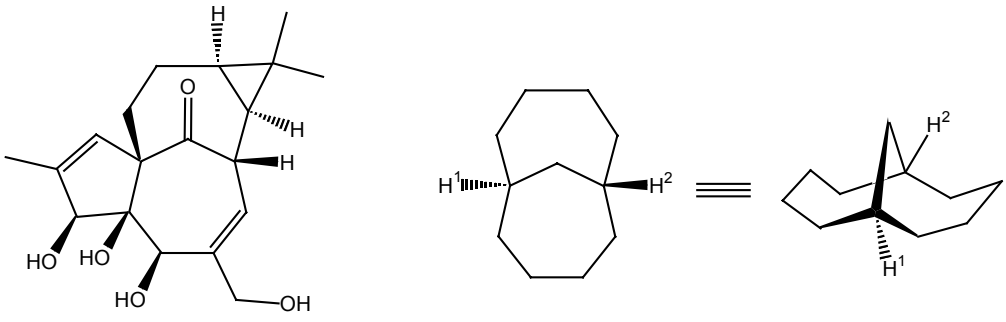
Berg, while studying the conformation of bicyclo[5.3.1]undecane-8,11-dione **66** showed that the formation of a bridgehead enolate was favoured and that the enol acetates **67** and **68** could be isolated (Scheme 23).[29]



66 **67** : **68**, 1 : 4

Scheme 23

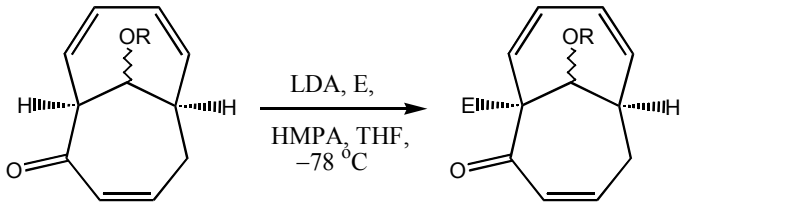
The ingenane family of natural products possess a bridged bicyclic ring system of the same number of carbon atoms as the taxanes but arranged in a bicyclo[4.4.1]undecane system with an unusual in-out bridgehead stereochemical relationship *e.g.* ingenol **69** (Figure 8).



ingenol **69** in-out

Figure 8

The unusual bridgehead relationship shown in Figure 8 is where H1 is directed 'inside' and is partially enclosed within the bicyclic ring but H2 is directed 'outside' of the bicyclic ring. Rigby pursued the total synthesis of the ingenanes using chromium arene [6 + 4] cycloaddition methodology to construct the core bicyclic ring system. As part of the strategy, bridgehead enolate formation was envisaged to install the required fragment for the fused cyclopentene at the bridgehead position. To test the approach, ketone **70** was treated with LDA followed by various electrophiles to give useful bridgehead functionalised products **71** (Scheme 24).[30]



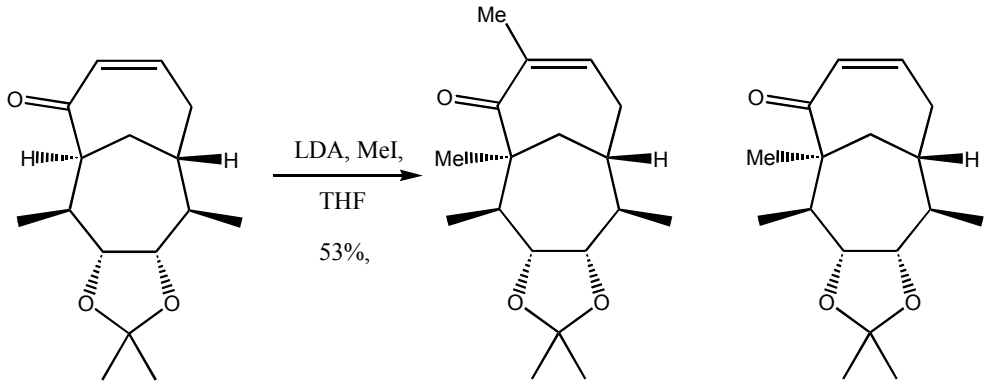
70 R = MEM

71 E = $CH_2C{\equiv}CSiMe_3$, 83%
$(CH_2)_2CH(OCH_2CH_2O)$, 68%

Scheme 24

Furthermore, Rigby successfully extended this methodology to the model ketone **72** possessing the ingenanes distinctive in-out bridgehead

stereochemical relationship and found the methylated products **73** and **74** formed in good yield (Scheme 25).[31]

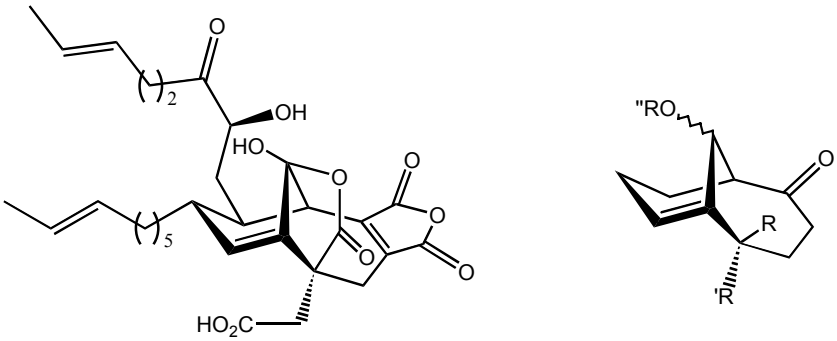


72 **73** : **74** 4.5 : 1

Scheme 25

Epimerisation at the bridgehead position does not occur because of the strain expected by forming a in-in bridgehead relationship.

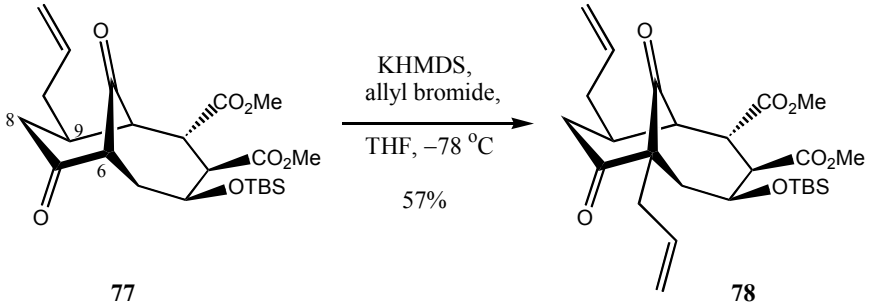
Another widely studied family of natural products are the phomoidrides A and B, designated by Pfizer as CP-263,114 and CP-225,917 (**75**), respectively. At the core of these natural products is a bicyclo[4.3.1]decane system that incorporates a bridgehead alkene. Clive alluded to a 'strong tendency' for ketone **76** to enolise towards the bridgehead and reported that blocking of the bridgehead was achieved by phenylsulfenylation (Figure 9).[32]



phomoidride B, CP-225,917 (**75**) **76**

Figure 9

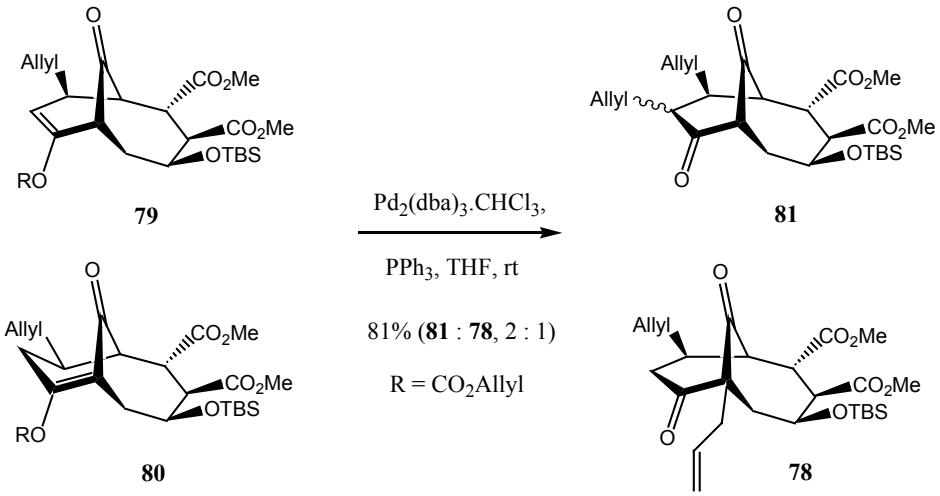
Ohmori also demonstrated a tendency to deprotonate toward the bridgehead in a similar diketone.[33] Deprotonation of diketone **77** gave the bridgehead alkylated product **78** in good yield and with no observable substitution at the adjacent methylene C8 (Scheme 26).



77 **78**

Scheme 26

However, deuteration experiments under similar conditions resulted in mostly deuteration of C8 (C8:C6, 4:1). For this reason Ohmori suggested that steric crowding of an approaching electrophile by the C9 allyl causes allylation at the less hindered bridgehead position (C6). Thus treatment of **77** with KHMDS and allyl chloroformate resulted mainly in the product of C8 deprotonation **79** accompanied by minor product **80** (Scheme 27).



79 **81**

80 **78**

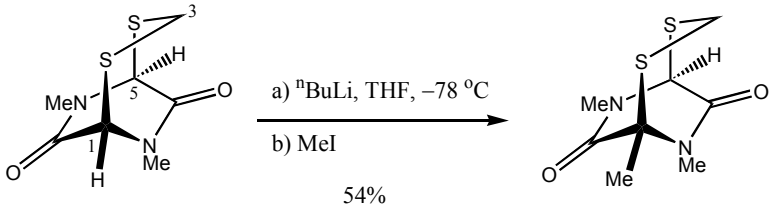
Scheme 27

This mixture was treated further with palladium to give the bridgehead alkylated product **78** and the desired product **81**.

1.3 Bridgehead Enolates of Amides and Imides

Other types of carbonyl bridgehead activation have been little studied in comparison to the ketone bridgehead chemistry already reviewed. Amides and less so imides have been widely used for conventional enolate formation but have had limited use in bridgehead enolate chemistry and for the most part are restricted to a small number of natural products.

The use of an amide to generate a bridgehead carbanion was reported by Kishi in 1981 to accomplish the total synthesis of gliotoxin.[34] The bridgehead carbanion of epidithioketopiperazine (EDKP) **82** was formed by using ^{n}BuLi followed by alkylation with methyl iodide to give *mono* methyl-dithioether **83** in 54% yield (Scheme 28).

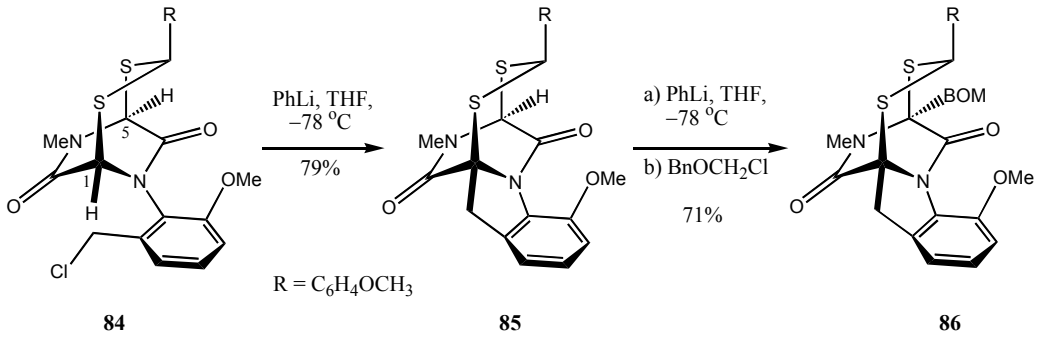


82 **83**

Scheme 28

Competing deprotonation at the methylene carbon C3 of the dithioether, similar to a dithiane, was not observed. The simple dithioether proved to be resistant to further manipulation but introduction of a *para*-methoxyphenyl (PMP) substituent allowed for the facile oxidation to the required disulfide bridge. Subsequent deprotonation of the modified EDKP **84** unexpectedly gave

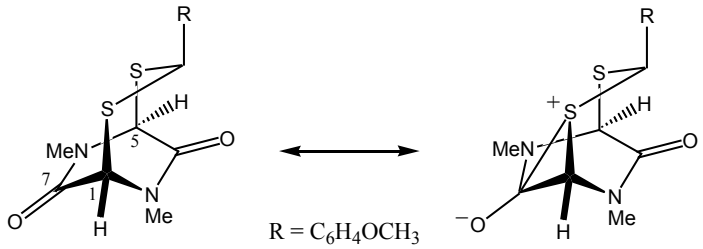
a single bridgehead substituted product **85**. Kishi took full advantage of this discovery to accomplish the diastereoselective synthesis of key intermediate **86** by a step-wise deprotonation-alkylation strategy (Scheme 29).



84 **85** **86**

Scheme 29

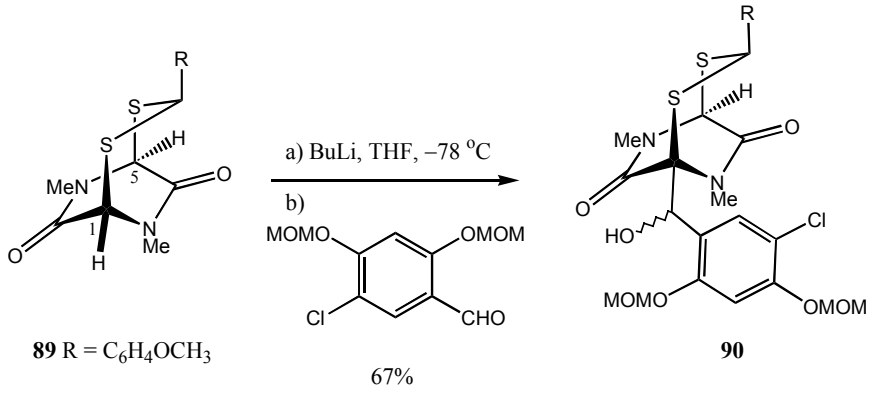
Kishi concluded that the presence of the modified dithioether group resulted in different acidities of the bridgehead protons. Furthermore it was found that changing the stereochemistry of the dithioether substituent gave the opposite sense of bridgehead deprotonation diastereoselectivity. Inspection of the X-ray crystal structure of the EDKP **87** revealed that the dihedral angles between the bridgehead protons and the dithioether bonds (H1-C1-S2-C3 & H5-C5-S4-C3) are near identical. For this reason, the observed regioselectivity could not be attributed to better orbital overlap with the 3d orbitals of the sulfur. Instead the selectivity was suggested to originate from donation of a lone pair of the sulfur atom (S2) to the sterically closer carbonyl group (C7) resulting in the increased acidity of H1 *e.g.* **87** to **88** (Figure 10).



87 **88**

Figure 10

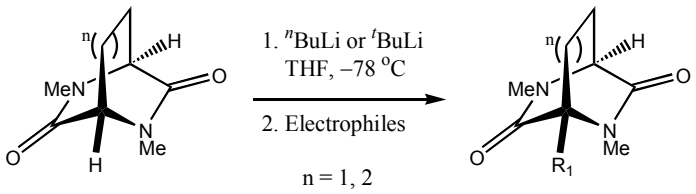
Danishefsky recently re-iterated the selectivity demonstrated by Kishi and applied it to the synthesis of the aspirochlorine family of anti-fungals. Treatment of EDKP **89** with ^{n}BuLi generated selectively the bridgehead carbanion at C1 that reacted smoothly with the appropriately functionalised benzaldehyde to give **90** (Scheme 30).[35]



89 R = $C_6H_4OCH_3$ 67% **90**

Scheme 30

Eastwood further explored the ease of bridgehead deprotonation in the diketopiperazine (DKP) system by replacing the dithioether bridge with either two or three carbon atoms. The bridgehead carbanion of **91** was efficiently generated by deprotonation with either ^{n}BuLi or ^{t}BuLi and quenched with a range of electrophiles to give various bridgehead substituted products of general structure **92** as a mixture of diastereoisomers (Scheme 31).[36]

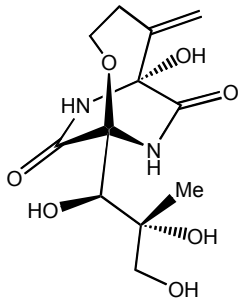


91 **92**

R_1 = D, Me, Bn, $MeOCH_2$, 31-88%

Scheme 31

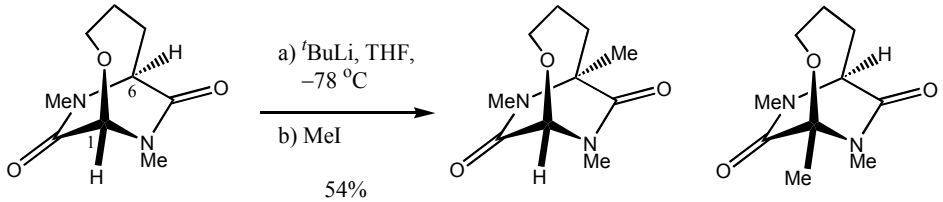
A similar bridged DKP forms the core of the antibiotic natural product bicyclomycin, which possesses both a bridgehead alcohol and an oxygenated alkyl chain. In a similar fashion to the EDKP system, Williams was able to use selective deprotonation at the bridgehead positions and complete the total synthesis of (+)-bicyclomycin **93** (Figure 11).[37]



Bicyclomycin **93**

Figure 11

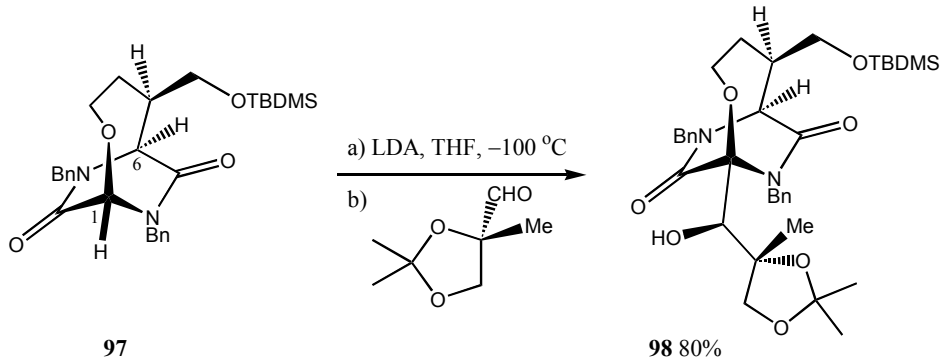
Initial model studies demonstrated that deprotonation of **94** followed by alkylation at C6 is preferred indicating that the methine at C6 is slightly more acidic than that at C1, *e.g.* **95** : **96**, 3 : 1 (Scheme 32).



94 **95** : **96**, 3 : 1

Scheme 32

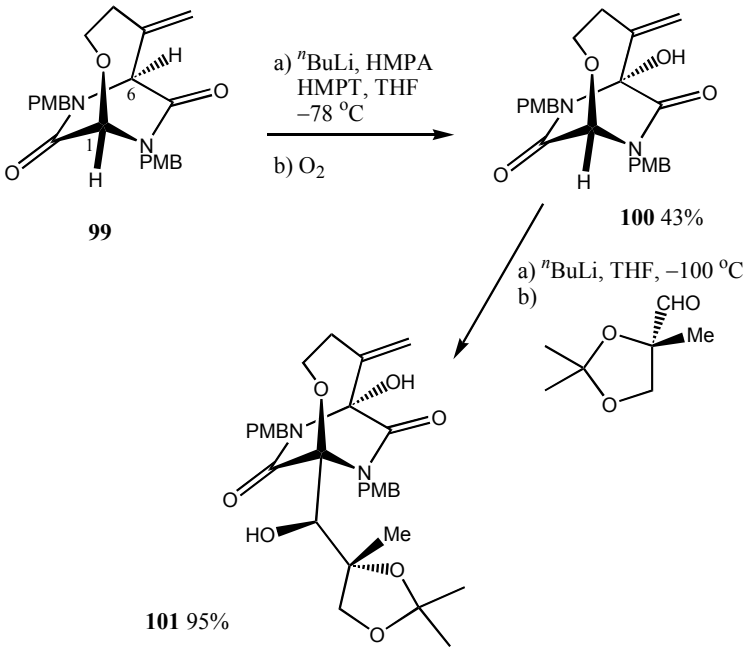
Advanced studies with **97** resulted in a complete reversal of deprotonation selectivity due to the bulky TBDMS protecting group hindering the proton at C6 (Scheme 33).



97 **98** 80%

Scheme 33

The final synthesis of (+)-bicyclomycin involved the reaction of DKP **99** with ^{n}BuLi in the presence of HMPA, HMPT and oxygen to give **100**. The remaining bridgehead proton was subsequently removed and reacted with the required aldehyde to give the double bridgehead substituted product **101** that in 3 steps was converted to (+)-bicyclomycin (Scheme 34).

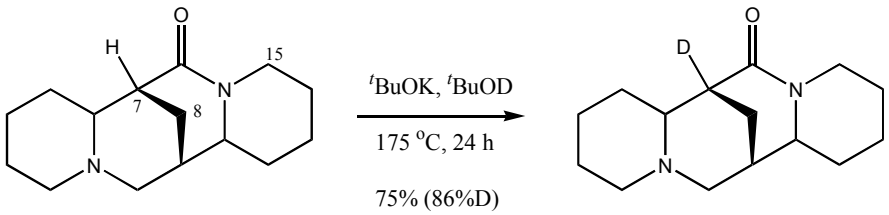


99 **100** 43%

101 95%

Scheme 34

Homo-enolisation studies of 17-oxosparteine **102** were conducted by Werstiuk to unambiguously assign the NMR spectra of sparteine by preparing the C8 deuterated analogue.[38] Heating amide **102** to 175 °C in the presence of ^{t}BuOK and ^{t}BuOD gave after 24 h the C7 bridgehead deuterated product **103** and not the intended C8 homo-enolisation product (Scheme 35).

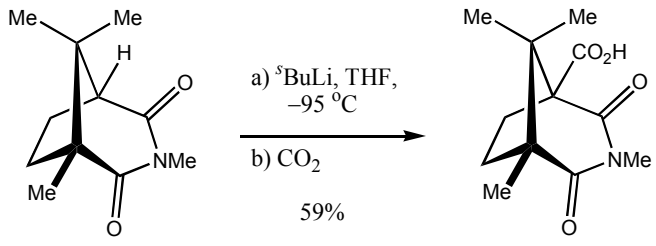


102 **103**

Scheme 35

Under more vigorous conditions (240 °C, $(CD_3)_3OK/(CD_3)_3OD$, 48 h) near complete deuterium incorporation was observed at C15 as well as C7.

In the search for a chiral auxiliary for the asymmetric alkylation of N-acyliminium ions, Wanner described the development of a camphor based auxiliary available *via* the bridgehead deprotonation of camphorimide **104** (Scheme 36).[39]



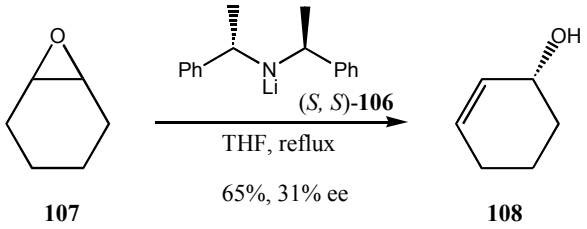
104 **105**

Scheme 36

Wanner demonstrated that low temperature deprotonation of camphorimide **104** with ^{s}BuLi followed by quenching of the carbanion with CO_2 gave after aqueous work-up the acid **105** in good yield.

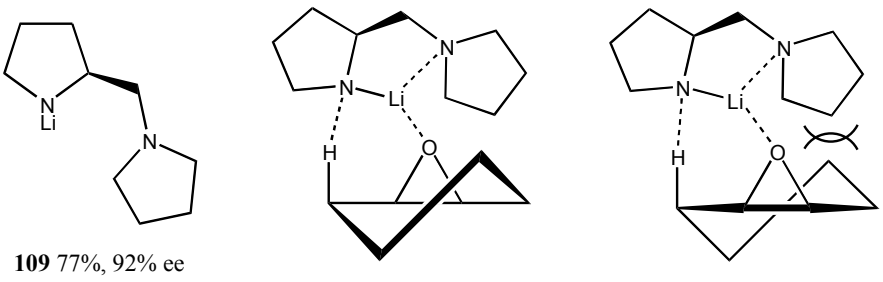
1.4 Chiral Lithium Amide Base Methodology

The use of chiral lithium amide base methodology is well established in organic synthesis and is the subject of many reviews.[40] The first significant contribution appeared in the early eighties from Whitesell and Felman concerning the enantioselective rearrangement of epoxides.[41] Using chiral lithium amide base (*S, S*)-**106** with cyclohexene oxide **107** in refluxing THF gave an enantio-enriched allylic alcohol **108** (Scheme 37).



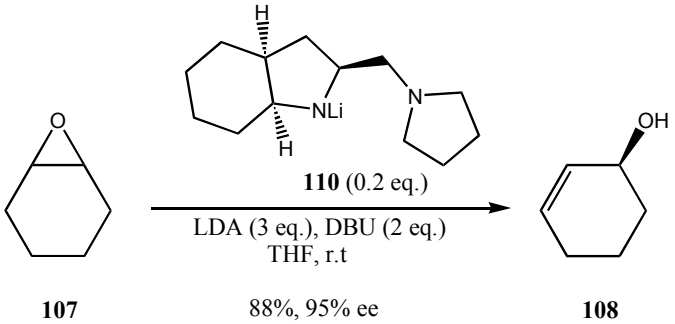
Scheme 37

Later work by Asami using chiral base **109** that incorporates a pendant chelation site and under low temperature (0 ^{o}C) conditions gave a significant improvement of asymmetric induction (Scheme 38).[42] The sense of induction was believed to arise in the transition state from steric congestion between the pendant cyclopentylamine of the base and the substrate ring.



Scheme 38

Asami has further contributed to this area by the recent development of epoxide rearrangements using catalytic quantities of a second generation chiral base **110** (Scheme 39).[43]

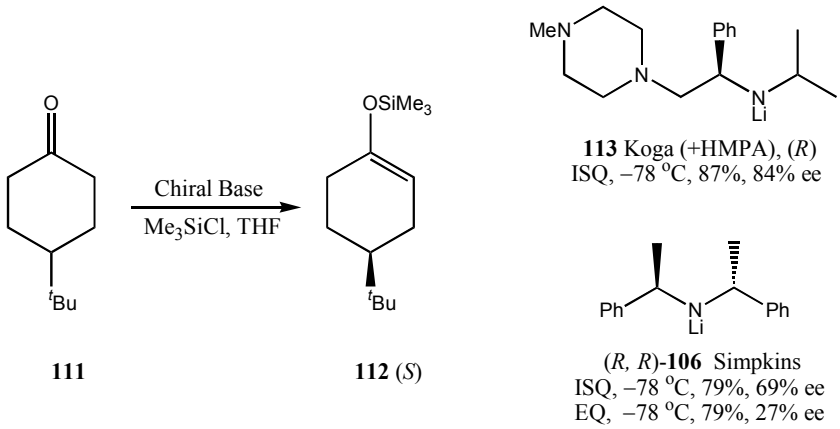


107 88%, 95% ee **108**

Scheme 39

Catalytic variants of enantioselective deprotonation reactions are rapidly developing and show great promise but are still limited in scope.[44]

The most frequent use of chiral lithium amide base reagents are for the desymmetrisation of prochiral cyclic ketones. One of the first reports by Simpkins concerned the efficient asymmetric deprotonation of *cis*-2,6-dimethyl cyclohexanone.[45] However, the description by Koga of the deprotonation of 4-*tert*-butyl cyclohexanone **111** to give silyl enol ether **112** became the benchmark reaction for testing chiral base efficacy (Scheme 40).[46]



111 **112** (*S*)

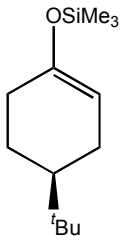
113 Koga (+HMPA), (*R*)
ISQ, –78 °C, 87%, 84% ee

(*R, R*)-**106** Simpkins
ISQ, –78 °C, 79%, 69% ee
EQ, –78 °C, 79%, 27% ee

Scheme 40

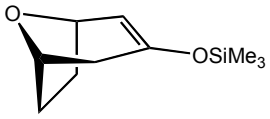
Unfortunately using chiral base **113** required the very carcinogenic additive HMPA to attain good selectivity whereas chiral base (*R, R*)-**106** only required LiCl.

One important feature for the enantioselectivity of the deprotonation was the use of an *in situ* quench (ISQ) technique. This method involves the pre-mixing of the lithium amide base and TMSCl at low temperature before addition of the substrate. Therefore as soon as the enolate forms it can immediately react with the electrophile and so will not have time to racemise by enolate equilibration. The ISQ procedure has found extensive use in chiral base reactions and is more fully discussed in Chapter Two. Another previously mentioned feature of this reaction is the use of salt additives such as LiCl to modify the chiral base and increase selectivity as shown in Scheme 40 and the following examples (Figure 12).[47]



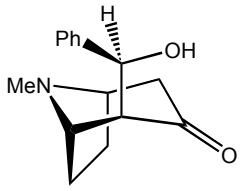
112

ISQ, 69% ee
EQ, 27% ee
EQ + LiCl, 83% ee



114

ISQ, 82% ee
EQ, 33% ee
EQ + LiCl, 82% ee



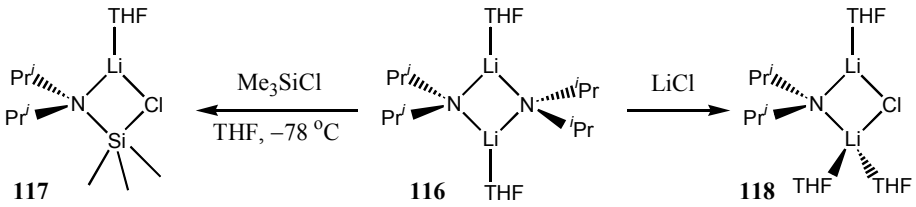
115

EQ, 24% ee
EQ + LiCl, 78% ee

Figure 12

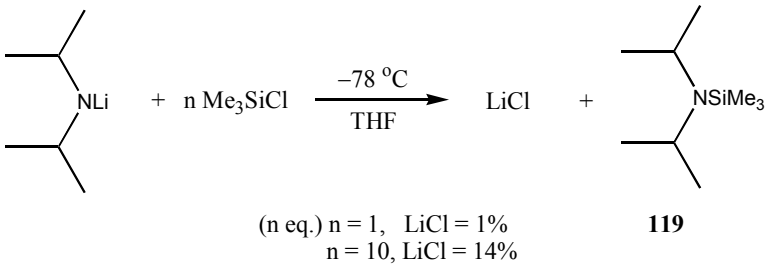
The ISQ technique is valuable for trapping very reactive carbanions or rapidly equilibrating enolates. However, the widespread use of TMSCl in such reactions requires special consideration since it was discovered to react with lithium amide bases and produce LiCl. Simpkins suggested that TMSCl as an

ISQ was a source of LiCl resulting from the reaction of LDA with TMSCl *e.g.* **116** to **117** (Scheme 41).[48]



Scheme 41

Indeed the addition of LiCl to lithium amide bases is well known to form the more reactive mixed aggregate LDA.LiCl *e.g.* **116** to **118**.[49] Confirmation of this effect was achieved when Lipshutz compared the NMR spectra of ^{7}Li isotope labelled LDA in the presence of TMSCl to a solution of LDA/LiCl.[50] Lipshutz found that 1 eq. of TMSCl mixed with LDA generated the silylated amine **119** accompanied by an equal amount of LiCl (Scheme 42).

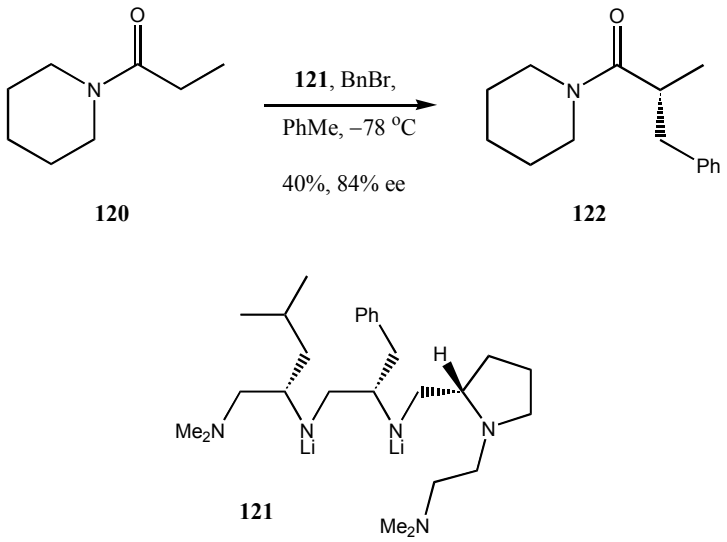


Scheme 42

Adding 10 eq. of TMSCl raised the LiCl content even further. The reasons for the observed improvements in yield and enantioselectivity involve extremely complex processes. In general, the addition of salts lead to the formation of low order mixed aggregates (dimers and monomers) that tend to be more reactive species. Computational studies by Williard of the effects of lithium halides on enolisation suggest the formation of more reactive reagents for kinetic

deprotonation.[51] The formation of mixed dimers in asymmetric deprotonation was also suggested to produce stronger binding lithium amide complexes and greater steric hindrance, both of which may be beneficial for asymmetric induction.

The enantioselective generation of acyclic enolates using chiral bases has received much less attention due to poorly controlled enolate geometry as well as effective alternative strategies such as Evans' auxiliary and asymmetric reduction. However, Kobayashi has recently described the deprotonation of **120** using the elaborate di-lithiated chiral base **121** to produce **122** with impressive ee (Scheme 43).[52]



Scheme 43

In the last 20 years, the application of chiral lithium amide base chemistry has spread to the desymmetrisation of a variety of substrates and reactions including chromium-arene complexes,[53] cyclic imides,[54] piperidine diesters,[55] ferrocenes,[56] sulfoxides,[57] phosphine oxides,[58] [2,3] Wittig rearrangement,[59] some of which are illustrated in Figure 13.

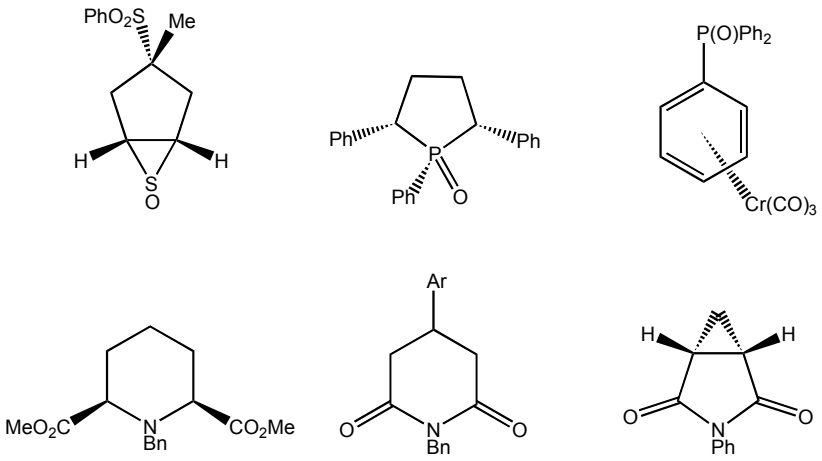
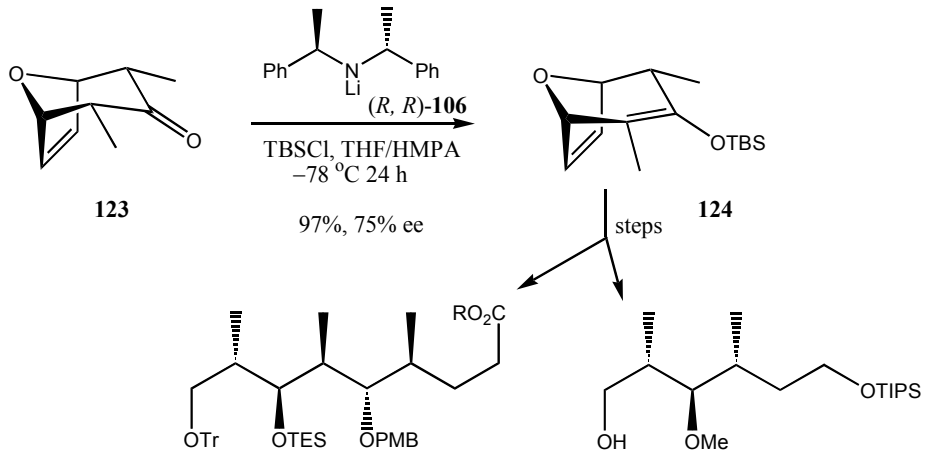


Figure 13

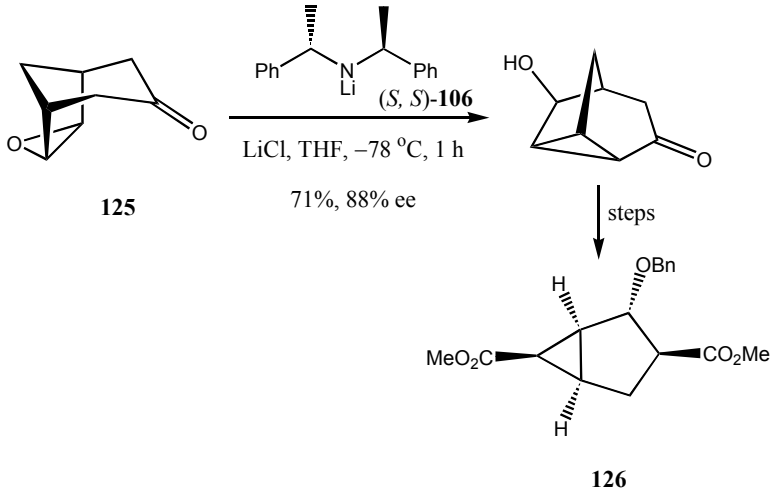
A recent application of chiral base desymmetrisation is Grieco's divergent polyol synthesis from the fragmentation of chiral silyl enol ether **124**. Treatment of ketone **123** with chiral base (*R, R*)-**106** in the presence of TBSCl for 24 h resulted in the silyl enol ether with excellent yield and good enantioselectivity (Scheme 44).[60]



Scheme 44

In contrast to previous reports, Grieco reported that deliberate addition of LiCl to this reaction was detrimental, though reaction between **106** and the chlorosilane would produce some LiCl *in situ*.

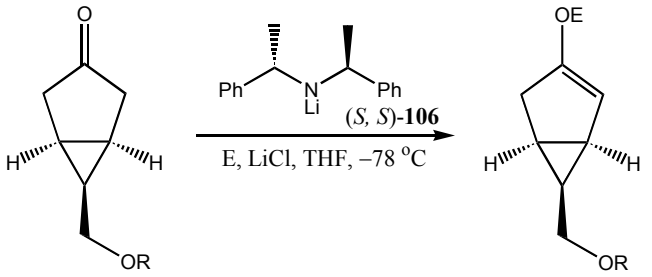
Abe and Harayama used an enantioselective deprotonation-transannular epoxide ring opening reaction of *meso* epoxy ketone **125** (Scheme 45).[61]



125 **126**

Scheme 45

Subsequent elaboration and ring cleavage led to the fused cyclopropane bicyclo[3.1.0]hexane system **126**, which is a known intermediate for the synthesis of some natural products and biologically active compounds.[62] Further exposure of the fused cyclopropane **127** to similar deprotonation conditions allowed the formation of silyl enol ether **128** and vinyl triflate **129** with good yield and high enantioselectivity (Scheme 46).

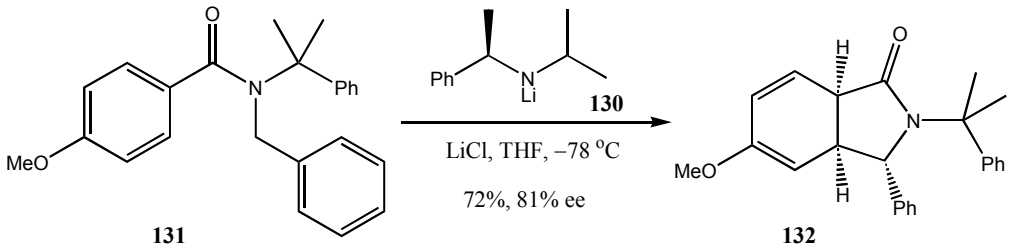


127

128 R = TBDMS, E = TMS, 52%, 86% ee
129 R = TBDPS, E = Tf, 32%, 75% ee

Scheme 46

The first example of a chiral base generated organolithium by the deprotonation of a prochiral methylene, was recently reported by Clayden. Using chiral base **130** to deprotonate **131** generated a configurationally stable, chiral benzylic organolithium that produced isoindolone **132** by a dearomatising cyclisation (Scheme 47).[63]



Scheme 47

The chiral isoindolone was enriched by crystallisation and further elaborated to (–)-kainic acid.

The current interest in the development of polymer bound reagents and catalysts has recently been extended to chiral base methodology. Using the polymer bound chiral base **133** in the well documented desymmetrisation of tropinone, Majewski was able to produce the aldol product **115** with both good yield and enantioselectivity (Figure 14).[64]

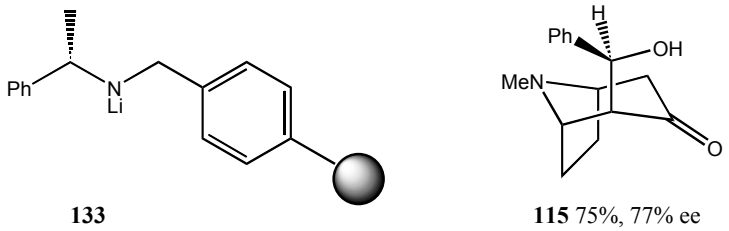
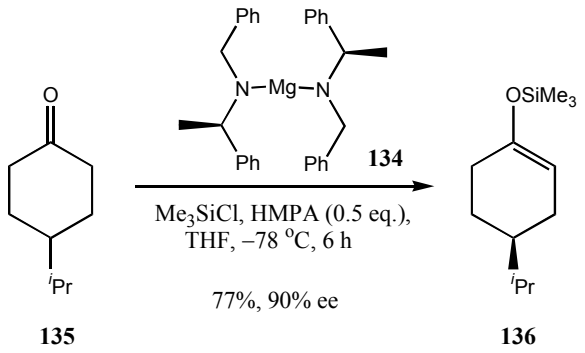


Figure 14

The most recent advance in chiral base methodology is the development of magnesium chiral amide bases. In 1947 Hauser discovered magnesium

mono-amides, but for thirty years they were unused until Solladié, Holton and others used them in synthetic chemistry.[65] Only in 2000 did Kerr report the use of chiral magnesium *bis*-amide **134** to deprotonate a prochiral cyclohexanone **135** in a similar fashion to the established lithium variants (Scheme 48).[66]



Scheme 48

The asymmetric induction observed with these reagents is comparable to chiral lithium amide reagents although they are untested with a broader range of substrates and commonly require the use of HMPA. However, Kerr has developed a polymer supported variant and has observed similarly high selectivity to those observed with the standard reagent.[67]

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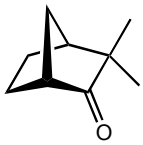
Chapter Two

Generation of the Bridgehead Enolates of Bridged Bicyclic Ketones

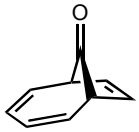
2.1 Aims and Objectives

Examples of generating bridgehead enolates in mainstream synthetic chemistry are few in number and lack general applicability. As shown in Chapter One, the generation of bridgehead enolates in large bridged bicyclic systems is relatively straightforward and has found some use in natural product chemistry. Less effort has focused on the generation of bridgehead enolates (better described as α-oxo carbanions) in small bicyclic systems. We considered the general lack of research in this area a sufficient incentive to explore the challenging generation and trapping of α-keto carbanions in small systems.

First we had to overcome the very reactive nature of the α-keto carbanions, which is illustrated by the uncontrollable aldol self-condensation of (−)-camphenilone **32** and bicyclo[4.2.1]nona-2,4,7-trien-9-one **35** discussed in Chapter One (Figure 15).



(−)-Camphenilone **32**



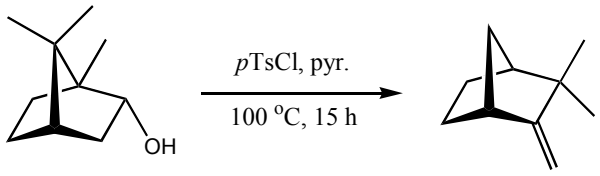
Bicyclo[4.2.1]nona-2,4,7-trien-9-one **35**

Figure 15

To begin we decided to re-investigate these self-condensation reactions, under various conditions, and attempt to form and intercept the presumed intermediate bridgehead carbanions.

2.2 Generation of the Bridgehead Enolate of (–)-Camphenilone

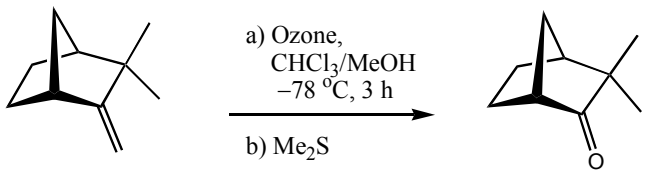
Enantiomerically pure (–)-camphenilone is not commercially available but can be produced by the ozonolysis of camphene.[1] Unfortunately, the commercially available sources of camphene are of technical grade (~80%) and are of low optical purity. Therefore we decided to make camphene from commercially available, optically pure (–)-borneol **137** using the procedure of Falorni.[2] Reaction of **137** with *para*-toluenesulfonyl chloride in pyridine at 100 ^{o}C for 15 h gave (–)-camphene **138** *via* a Wagner-Meerwin rearrangement with 67% yield and high optical purity ($[\alpha]^{25}_{D}$ –112 {*c* 1, benzene}; lit.[3] $[\alpha]^{20}_{D}$ –115 {*c* 5.6, benzene}), Scheme 49.



137 **138** 67%

Scheme 49

Ozonolysis of (–)-**138** was not straightforward because of the difficulty in monitoring the reaction, which led to inconsistent yields (39-59%, lit.[1] 91%), Scheme 50.

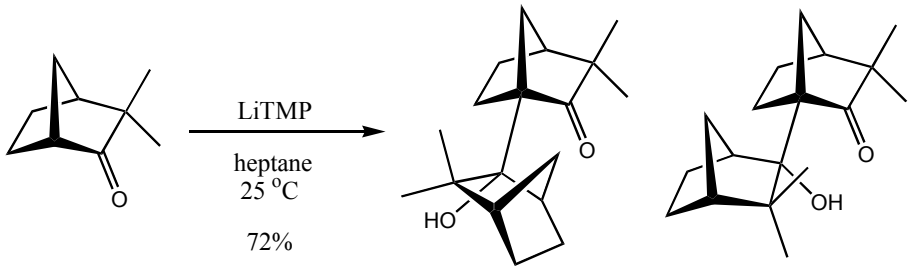


138 **32** 49%

Scheme 50

Nonetheless, (–)-camphenilone of high optical purity ($[\alpha]^{28}_D$ –58 (EtOH), *ca.* 84% ee; lit.[4] $[\alpha]_D$ –69 (EtOH) was obtained in readiness for the deprotonation studies.

Repeating Shiner's deprotonation procedure with LiTMP in heptane at room temperature gave the aldol self-condensation product but as a mixture of diastereoisomers **33a** and **33b** (Scheme 51).



32 **33a** : **33b**, 11 : 1

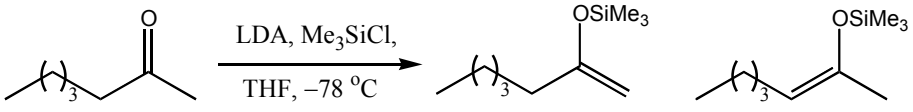
Scheme 51

The ratio of diastereoisomers is in agreement with the estimated enantiomeric excess of camphenilone as determined by optical polarity measurements and confirms that racemisation of camphenilone by homo-enolisation does not occur under these conditions.

Our next step was to find out if conventional external quench (EQ) methodology could be used to trap the presumed bridgehead lithiated intermediate. Shiner's original account and subsequent work in our group both reported the unsuccessful use of external quenches using TMSCl and D_2O.[5] Similarly, all attempts we made by adding the ketone to the base (standard addition protocol to avoid aldol reactions) and using TMSCl, D_2O and benzaldehyde as EQ led only to aldol self-condensation. This behaviour further illustrates the high reactivity of the presumed α-keto carbanion intermediate due to the lack of conventional enolate formation. Given the reactivity of the

α-keto carbanion it efficiently reacts inter-molecularly with another molecule of camphenilone before the introduction of the EQ. The result lends itself toward the use of *in situ* quench (ISQ) techniques that may intercept the reactive α-keto carbanion and produce alternative bridgehead substitution products.

The *in situ* quench (ISQ) technique was pioneered by Corey to give highly selective, kinetically controlled enolate formation with lithium amide bases in the presence of TMSCl.[6] This technique involves the pre-mixing of the lithium amide base and TMSCl at low temperature before addition of the ketone. Also, the inverse addition protocol is equally productive, *e.g.* the mixture of ketone and TMSCl is treated with a lithium amide base. In comparison to House's reported production of silyl enol ethers of 2-heptanone **139** by a two-step EQ protocol, Corey was able to show that using the ISQ technique gave significantly improved yields and enol ether regio-selectivity of **140** and **141** (Scheme 52).[7]



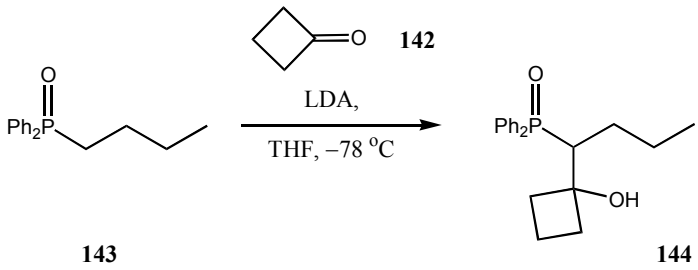
139

140 : **141**
House 65%, 86 : 14 EQ
Corey 99%, 95 : 5 ISQ

Scheme 52

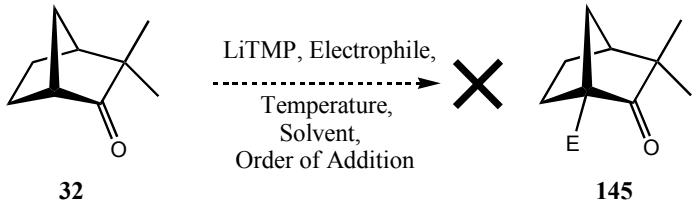
The nature of the ISQ technique requires that the electrophile be either unreactive to, or react non-destructively with the lithium amide base which therefore drastically limits useful base/electrophile combinations. The ISQ technique is primarily used with TMSCl but has been extended to a number of

electrophiles that are compatible with lithium amide bases, these include Me_3SnCl,[8] $B(O^iPr)_3$,[9] benzaldehyde,[10] MeI, EtI, 1,3-diiodopropane, 1,4-diiodobutane, 1,6-diiodohexane,[11] *E*-cinnamyl chloride,[12] cyclobutanone **142** [13] and mercury(II)chloride.[14] For example, Warren was able to trap lithiated phospine oxide **143** using cyclobutanone as an *in situ* quench (Scheme 53).



Scheme 53

In our hands, treatment of (–)-camphenilone **32** with LiTMP using the ISQ technique with various electrophiles, solvents, temperatures and orders of addition were all unsuccessful leading only to recovered starting material (Table 1).



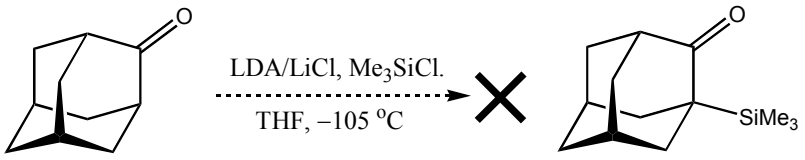
Electrophile/E	Solvent	Temperature/°C	Order of Addition
TMSCl	Heptane	rt	Base to ketone/E
Cyclobutanone	THF	–40	Ketone to base/E
Benzaldehyde	Diethyl ether	–78	
Pivaldehyde		–105	

Table 1

Using the ISQ technique suppresses the aldol self-condensation however none of the desired product formed. This suggests that bridgehead deprotonation

does not occur under these conditions perhaps because the electrophile is inhibiting the reaction between the base and the ketone. An alternative explanation may involve internal proton return where the bridgehead proton is removed but remains in close proximity to the substrate due to base-ketone complexation. Therefore in the presence of an electrophilic quench the original proton removed by the base returns to the bridgehead position.[15]

A more ambitious experiment to observe bridgehead deprotonation in adamantan-2-one **146** was attempted. Exposure of **146** to similar conditions did not produce **147** but resulted in recovery of the starting material (Scheme 54).



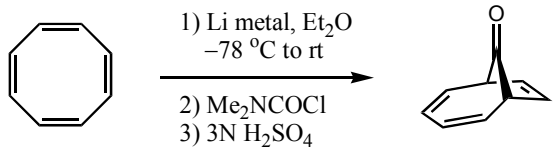
146 **147**

Scheme 54

The deprotonation of (–)-camphenilone **32** and adamantan-2-one **147** proved to be challenging and time-consuming and these substrates were not further investigated. A possible solution to the problem may be to reproduce the chelation controlled metallation strategy developed by Eaton as discussed in Chapter One. In addition to forming the ketal described by Eaton, we could form the oxime and hydrazone analogues to test chelation controlled metallation.

2.3 Generation of the Bridgehead Enolate of Bicyclo[4.2.1]nona-2,4,7-trien-9-one

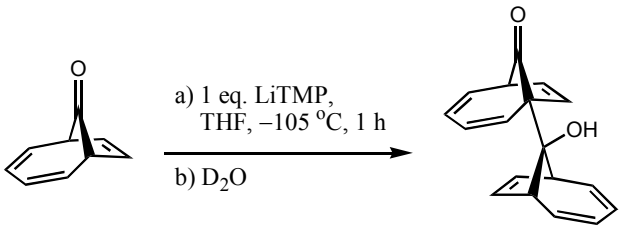
After the unsuccessful work with (−)-camphenilone **32** and adamantan-2-one **147** we turned our attention to bicyclo[4.2.1]nona-2,4,7-trien-9-one **35** reported by Feldman to exhibit aldol self-condensation. Bicyclo[4.2.1]nona-2,4,7-trien-9-one **35** was prepared by the method of Shechter from 1,3,5,7-cyclooctatetraene **148** and dimethylcarbamoyl chloride (lit.[16] 54%), Scheme 55.



148 **35** 36%

Scheme 55

Initial studies with ketone **35** demonstrated that EQ techniques were ineffective in trapping the presumed bridgehead carbanion leading only to the aldol self-condensation product **36**, albeit with an improved yield of 66% (lit.[17] 23%), Scheme 56.

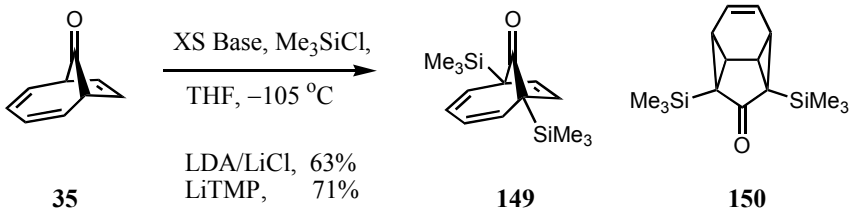


35 **36** 66%

Scheme 56

The aldol condensation occurs rapidly, consuming the starting material and the base, which means that subsequent quenching of the reaction with D_2O did not afford any bridgehead deuteration.

In view of the EQ results, we turned our attention to the deprotonation of **35** under ISQ conditions with LDA/LiCl and LiTMP in the presence of TMSCl. Thus, addition of ketone **35** to an excess of base in the presence of TMSCl (method A) at −105 °C led to the formation of an inseperable mixture of *bis*-silylated ketones **149** and **150** in a 1:4 ratio, respectively, and with respective yields of 63% and 71% (Scheme 57).



Scheme 57

The formation of the tetracyclic ketone **150** was unexpected and was confirmed following a single crystal X-ray structure determination (Figure 16).

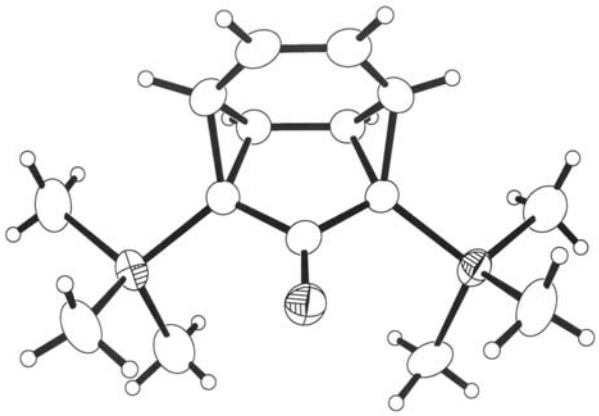
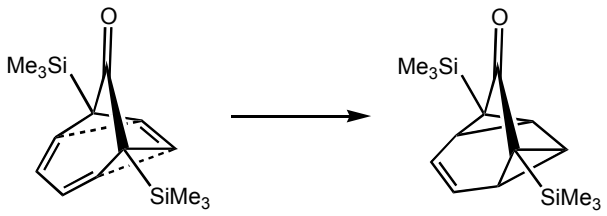


Figure 16

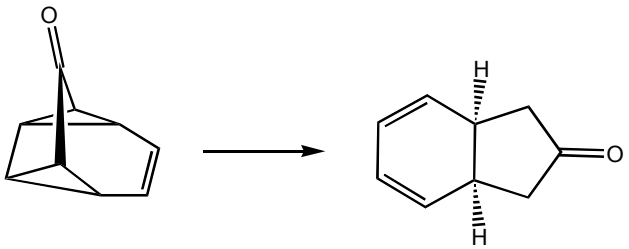
This product is believed to be the result of double bridgehead substitution followed by a transannular Diels-Alder reaction (Scheme 58).



149 **150**

Scheme 58

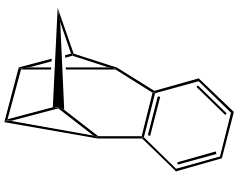
The latter process for this system is known, but the tetracyclic intermediate **151** is commonly short-lived and readily rearranges to a tetrahydroindenone **152** by a *retro* Diels-Alder pathway (Scheme 59).[18]



151 **152**

Scheme 59

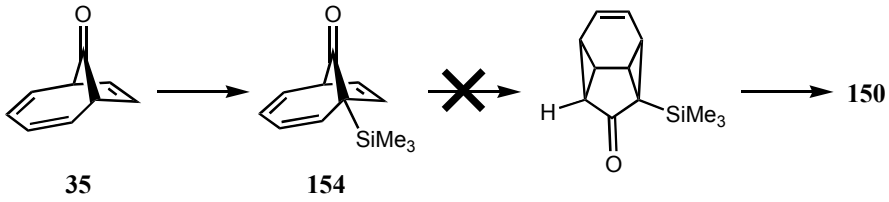
Introduction of aromatic substitution by Dolce was used to impart stability and allow isolation of the tetracyclic product **153** (Figure 17).[19]



153

Figure 17

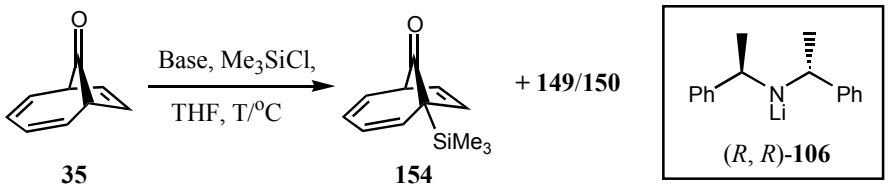
The *bis*-silylated tetracyclic ketone **150** is stable in air and can be stored indefinitely at −5 °C but decomposes in solution over several hours. When we gradually heated a $CDCl_3$ solution of ketones **149** and **150** to 65 ^{o}C we were unable to drive the Diels-Alder reaction to completion and only observed complete decomposition. At no time did we observe any *mono*-silylated ketone **154**, which points to the formation of **150** purely *via* **149** (Scheme 60).



Scheme 60

An alternative mechanism involving anion initiated cycloaddition of the carbanion of **35** followed by *bis*-silylation appears to be ruled out following further experiments described below.

Changing the mode of deprotonation to addition of the base to a mixture of ketone and TMSCl (inverse addition, method B) we hoped to minimise formation of the *bis*-silylated compounds **149** and **150**. We discovered that addition of LDA/LiCl to a solution of ketone **35** and TMSCl at −105 °C gave the *mono*-silylated ketone **154** in 38% yield, accompanied by a mixture of **149** and **150** in a 1 to 4 ratio and with a combined yield of 17%. This unprecedented result prompted us to attempt the asymmetric deprotonation of ketone **17** employing well-known chiral base (*R*, *R*)-**106**. Selected results using inverse addition (method B) are highlighted in Table 2, along with comparison data using normal addition (method A).



35 **154**

Entry	Base[a]	T/°C	Method[b]	Yield of **149**/**150** (%)	Yield of **154** (%)	Ee of **154** (%)
1	LDA/LiCl	−105	A	39	0	–
2	LDA/LiCl	−105	B	17	38	–
3	(*R*, *R*)-**106**/LiCl	−105	A	32	40	>98
4	(*R*, *R*)-**106**/LiCl	−105	B	23	76	>98
5	(*R*, *R*)-**106**/LiCl	–78	B	12	46	92

[a] 1.2 eq. used. [b] A – ketone/TMSCl added to base. B – base added to ketone/TMSCl.

Table 2

By using the inverse addition protocol with (*R*, *R*)-**106** at −105 °C we obtained *mono*-silylated ketone (–)-**154** in 76% yield and with an excellent e.e. of >98% (determined by chiral HPLC) accompanied by *bis*-silylated ketones **149**/**150** with 23% yield (entry 4). The absolute configuration of (–)-**154** was determined by single crystal X-ray structure determination (Figure 18).

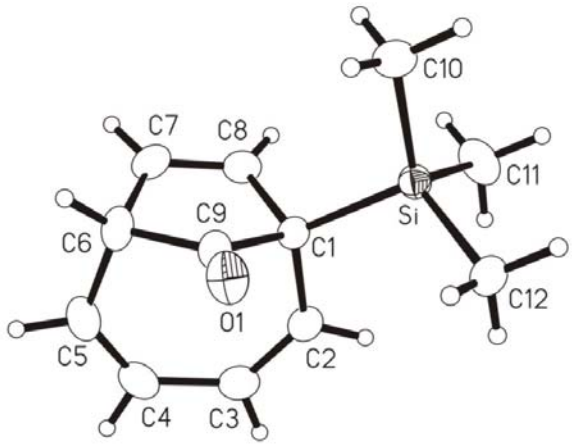
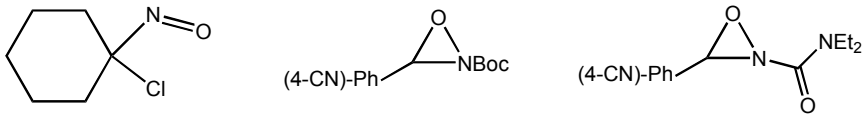


Figure 18

Performing the reaction at –78 °C, in comparison to –105 °C, gave significantly lower yields while still maintaining high enantioselectivity (entry 5). Unlike the deprotonation reactions with LDA/LiCl, the chiral base reactions

produce *mono*-silylated products regardless of the method employed due to the inherent selectivity for a single enantiotopic bridgehead proton.

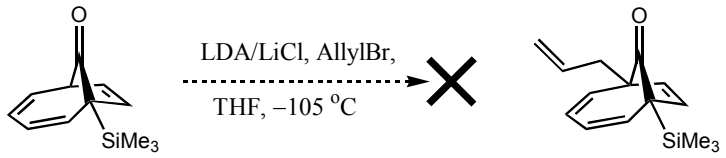
Attempts to trap the bridgehead carbanion with other ISQ electrophiles such as MeI, $B(O^iPr)_3$ and PhSSPh were all unsuccessful. More speculative electrophilic quenches such as PhSeCl, DEAD, DIAD, 1-chloro-1-nitrosocyclohexane **155** and the oxaziridines **156** and **157** were tested in an attempt to effect bridgehead selenation and amination but were unsuccessful (Figure 19).[20]



155 **156** **157**

Figure 19

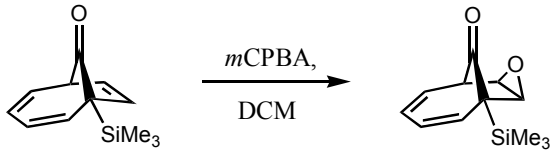
Our delight with the successful bridgehead deprotonation thus far was tempered by the inability to incorporate any functionality other than a silicon substituent. However, the production of sizeable amounts of *bis*-silanes suggested to us that secondary bridgehead substitution of the *mono*-silane becomes more facile after the initial deprotonation. We hoped that following the first bridgehead deprotonation, treatment of the *mono*-silane with more base followed by an electrophilic quench would allow the formation of alternative types of bridgehead substituted products. Unfortunately, addition of LDA/LiCl to a mixture of *mono*-silylated ketone (–)-**154** and allyl bromide at −105 °C resulted in recovery of starting material and gave none of the desired secondary bridgehead deprotonation product **158** (Scheme 61).



154 **158**

Scheme 61

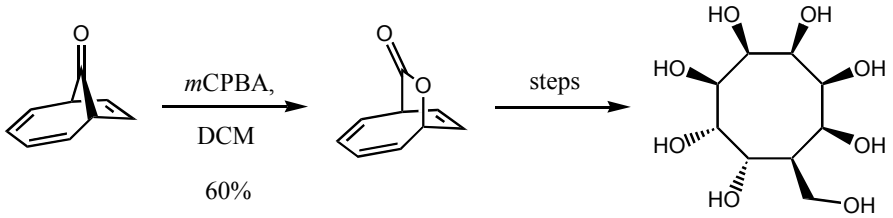
In a further attempt to explore the chemistry of *mono*-silylated ketone (–)-**154** we were interested to discover if regioselective epoxidation of one of the olefins was feasible. Treatment of (–)-**154** with an equivalent of *m*CPBA gave *mono*-epoxide (–)-**159** in 31% yield ($[\alpha]^{20}_{D}$ –206 {*c* 0.42, $CHCl_3$}), as well as recovered starting material (16%) and a mixture of various uncharacterised epoxide products (8%), Scheme 62.



(–)-**154** (–)-**159**

Scheme 62

This result was contradicted by the facile Baeyer-Villiger oxidation of the simple unsubstituted ketone **35** to give **160** reported by Mehta (Scheme 63).[21]

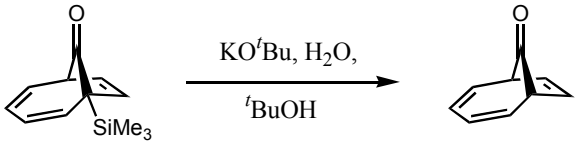


35 **160** **161**

Scheme 63

Selective transformation to various degrees of oxidation including the cyclooctitol **161** was successfully accomplished and allowed for biological evaluation of these novel carbasugar polyols.

Similarly we had no success when we attempted the Haller-Bauer cleavage of ketone (–)-**154** with potassium *tert*-butoxide, which led only to the recovery of the desilylated product **35** in good yield (Scheme 64).[22]



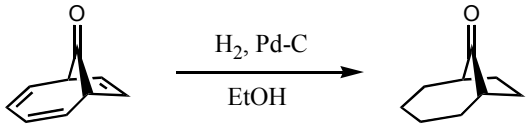
(–)-**154** **35**

Scheme 64

Returning to the original basic conditions with sodamide, discovered by Semmler, may prove more successful but the lability of the silyl group under these conditions will limit this reaction.

2.4 Generation of the Bridgehead Enolate of Bicyclo[4.2.1]nonan-9-one

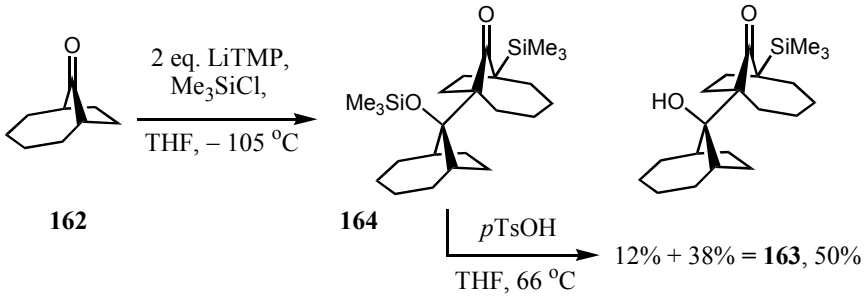
The remarkable and unprecedented results with ketone **35** prompted us to examine similar asymmetric bridgehead metallations with the saturated ketone **162**, available by hydrogenation of **35** (Scheme 65).



35 **162**

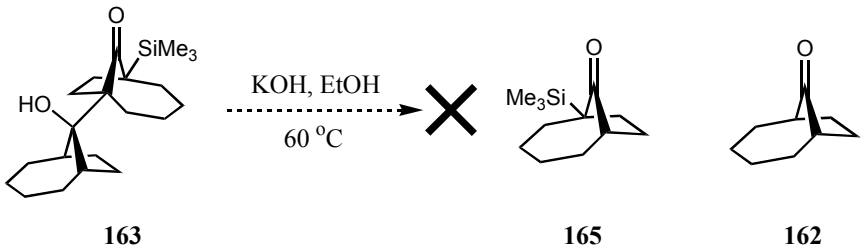
Scheme 65

All EQ reactions proved to be ineffective and so we decided to concentrate on ISQ techniques. Consequently, we found upon addition of ketone **162** to a solution of 2 eq. of LiTMP and TMSCl, the *mono*-silylated aldol self-condensation product **163** (38%) and some impure *bis*-silylated analogue **164** were isolated (Scheme 66).



Scheme 66

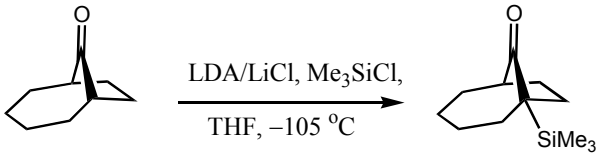
The *bis*-silylated product **164** was treated with *p*TsOH in refluxing THF to give an overall 50% yield of *mono*-silane **163**. Although the aldol self-condensation is ultimately an unproductive reaction, we considered that performing a *retro* aldol reaction with *mono*-silane **163** could produce the desired *mono*-bridgehead substituted silane **165**. Unfortunately, this reaction was unsuccessful (Scheme 67).



Scheme 67

The earlier success achieved with ketone **35** inspired us to apply the same reaction conditions for bridgehead deprotonation to ketone **162** in the hope of observing *mono*-silylation. Thus, treatment of a mixture of ketone **162**

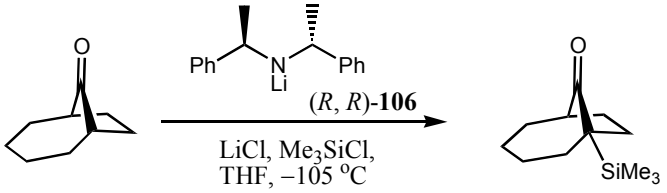
and TMSCl with LDA/LiCl at –105 °C (Method B) gave *mono*-silylated ketone **165** with 62% yield and with no observable *bis*-silylation (Scheme 68).



162 **165** 62%

Scheme 68

The enantioselective deprotonation was then attempted with chiral base (*R*, *R*)-**106** under method B conditions to give *mono*-silylated ketone **(**–)-**165** in 67% yield and with a sizeable optical rotation ($[\alpha]^{25}_{D}$ –121) (Scheme 69).

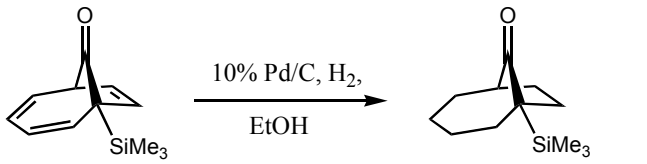


162 (–)-**165** 67% $[\alpha]^{25}_{D}$ –121

Scheme 69

Repetition of the reaction on a larger scale gave an improved yield of 78% but a lower optical rotation ($[\alpha]^{25}_{D}$ –106). Alternatively, we attempted the classical ISQ reaction conditions whereby the TMSCl is pre-mixed with the lithium amide base. Thus, addition of ketone **162** to a pre-mixed solution of chiral base (*R*, *R*)-**106** and TMSCl at –105 °C gave *mono*-silylated ketone **(**–)-**165** in 53% yield and with a higher optical rotation ($[\alpha]^{25}_{D}$ –126). Determination of the ee of *mono*-silylated ketone **(**–)-**165** by chiral HPLC was unsuccessful because of incomplete separation and also the lack of a chromophore, though an estimate of *ca.* 80% was made. We were also unable to determine the absolute configuration of ketone **(**–)-**165** due to the inability to produce X-ray quality

crystals, although we assume the sense of stereochemical induction parallels that seen with ketone (–)-**154**. To determine the absolute configuration and the enantiomeric purity, we subjected *mono*-silylated ketone **(**–)-**154**, previously determined by chiral HPLC to have an ee of greater than 98%, to catalytic hydrogenation (Scheme 70).

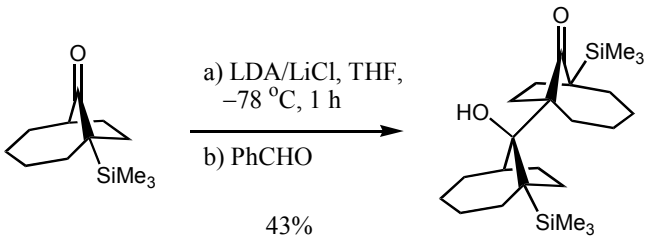


(–)-**154** (–)-**165** 45% $[\alpha]^{25}_{D}$ –131

Scheme 70

The resultant *mono*-silylated ketone **(**–)-**165** was determined to have an optical rotation greater than previously observed ($[\alpha]^{25}_{D}$ –131) and of the same sign indicating the absolute configuration is identical to ketone (–)-**154**. Comparison of the optical rotation data suggests the *mono*-silylated ketone (–)-**165**, produced by chiral lithium amide base deprotonation, has an ee between 84 and 92%. Other electrophiles tested include PhSeCl, 1-chloro-1-nitrosocyclohexane **155** and the oxaziridines **156** and **157** but none of the desired products were observed.

Despite the unsuccessful secondary bridgehead deprotonation of ketone (–)-**154** we attempted to deprotonate ketone (–)-**165**. Treatment of *mono*-silylated ketone (–)-**165** with LDA/LiCl under EQ conditions with benzaldehyde led to the bridgehead aldol self-condensation product (–)-**166** (Scheme 71).

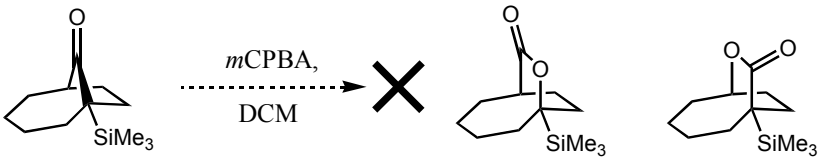


(–)-**165** (–)-**166**

Scheme 71

The reactivity of the secondary bridgehead position to deprotonation, though encouraging, does not result in a synthetically useful product under EQ conditions. Further investigation of this reaction under ISQ conditions was not conducted, though similar reactions with *mono*-silylated ketone (–)-**154** proved to be unsuccessful suggesting that aldol self-condensation may be uncontrollable.

Next, we attempted to explore the chemistry of the *mono*-silylated ketone (–)-**165** under various conditions. With the bridgehead positions successfully differentiated, we were interested to establish whether the silyl group could control the regioselective insertion of oxygen under Baeyer-Villiger conditions.[23] However treatment of (–)-**165** with *m*CPBA or peracetic acid gave none of the desired products **167** or **168** and only resulted in the recovery of starting material (Scheme 72).



(–)-**165** **167** **168**

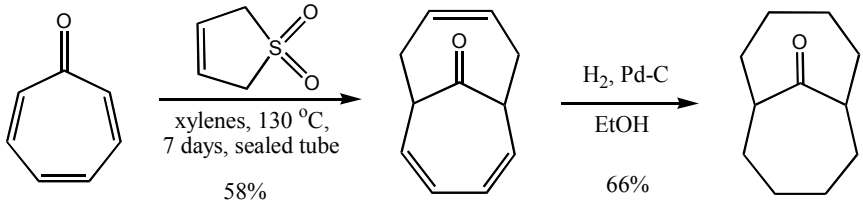
Scheme 72

Repeating the reaction under buffered conditions was also unproductive.

A discussion of the mechanism of asymmetric induction and the stability of bridgehead enolates is contained, along with further bridgehead deprotonation results, in Chapter Three.

2.5 Attempted Generation of the Bridgehead Enolate of Bicyclo[4.4.1] undeca-2,4,8-trien-11-one and Bicyclo[4.4.1]undecan-11-one

Our preliminary results offered some evidence that controllable bridgehead deprotonation is possible under certain conditions and so we turned to exploring the relationship between bridge size and the ease of deprotonation. Therefore we decided to lengthen one bridge while keeping the bridged ketone in the one carbon bridge. Bicyclo[4.4.1]undeca-2,4,8-trien-11-one **169** and the fully saturated analogue bicyclo[4.4.1]undecan-11-one **170**, obtained by hydrogenation of **169**, was reported by Itô.[24] Ketone **169** was prepared by employing Itô's strategy involving [6+4] cycloaddition of tropone **171** and butadiene sulfone in a sealed tube with xylenes at 130 ^{o}C to give **169** with 58% yield (lit. 75%) (Scheme 73).



171 **169** **170**

Scheme 73

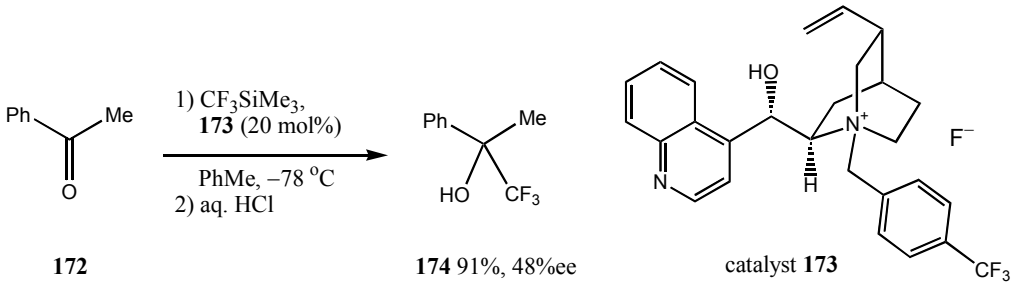
Subsequent hydrogenation of ketone **169** gave bicyclo[4.4.1]undecan-11-one **170** in 66% yield.

Attempts to deprotonate these ketones under our developed conditions led to no observable bridgehead deprotonation. Testing a variety of conditions was equally unsuccessful. From the reports described in Chapter One we might assume that increasing bridge size would facilitate deprotonation. This assumption is contradicted by ketone **169** because closer inspection of its conformation reveals that the dihedral angle between the bridgehead proton and the plane of the bridged ketone is *ca.* 5° (MM2). Such a low dihedral angle removes any contribution to stabilisation from the enolate and thus inhibits deprotonation. On the other hand, ketone **170** is relatively more flexible and displays a range of dihedral angles up to 22°, similar to that of camphenilone **32**, and yet does not show any sign of deprotonation.

2.6 Fluoride Mediated Silyl Exchange of Bridgehead Silylated Ketones

The ability to form useful quantities of *mono*-silylated products with high enantioselectivity and the failure to include more useful electrophiles with the ISQ approach led us to explore other indirect routes. Therefore we attempted to gain access to products having alternative types of bridgehead substitution by employing the fluoride mediated silyl exchange reaction. This reaction has been used successfully in a small number of applications including natural product synthesis. Kobayashi reported asymmetric trifluoromethylation of aldehydes and ketones with trifluoromethyltrimethylsilane (CF_3SiMe_3) catalysed by chiral quaternary ammonium fluorides.[25] For example, treatment of acetophenone **172** and CF_3SiMe_3 with catalytic *N*-benzylcinchonium

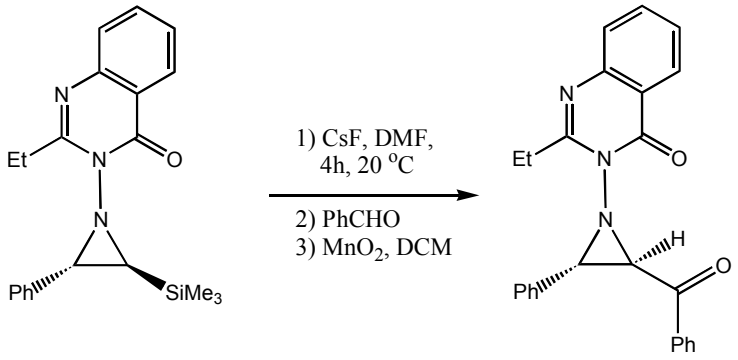
fluoride **173** gave the trifluoromethyl alcohol **174** in excellent yield but low ee (Scheme 74).



172 **174** 91%, 48%ee catalyst **173**

Scheme 74

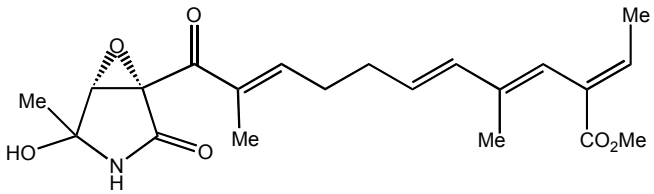
Atkinson used cesium fluoride with silylaziridine **175** and benzaldehyde to give the benzoylaziridine **176** in good yield (Scheme 75).[26]



175 **176** 80%

Scheme 75

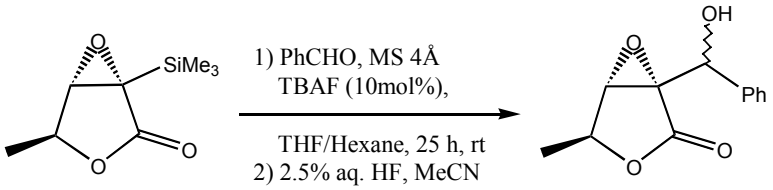
The only use of fluoride mediated silyl exchange in natural product synthesis was reported by Kobayashi in the synthesis of Epolactaene **177** (Figure 20).[27]



Epolactaene **177**

Figure 20

For example, treatment of epoxylactone **178** and benzaldehyde with catalytic tetrabutylammonium fluoride (TBAF) in the presence of molecular sieves gave the silylated aldol-type product **179** (Scheme 76).

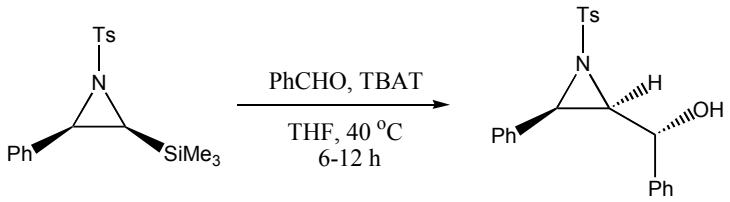


178 **179** 44% (dr 3:1)

Scheme76

When an equimolar amount of TBAF was used Kobayashi observed complete decomposition of **178**.

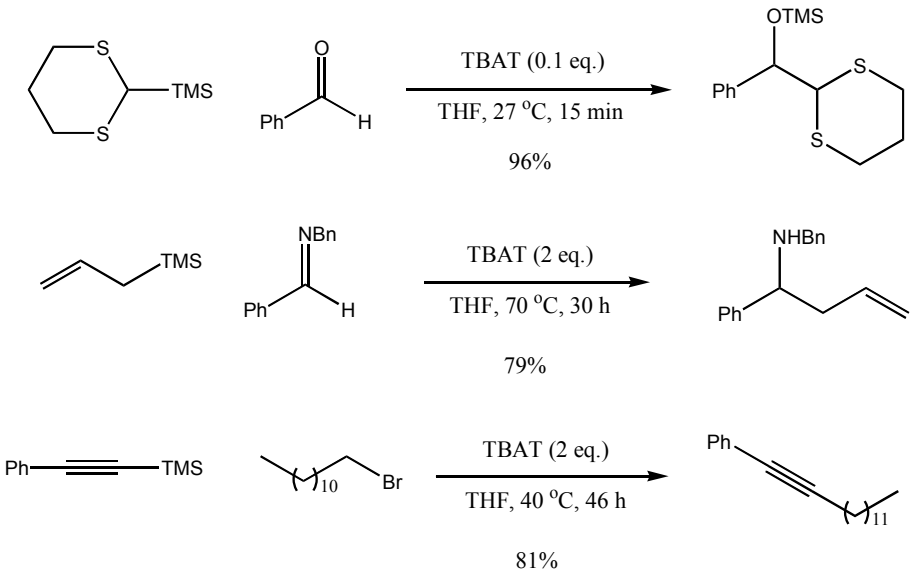
The most common sources of fluoride ion are TBAF and cesium fluoride, both of which suffer from their hygroscopic tendencies leading to simple protonation by-products. Recently, Aggarwal reported tetrabutyl-ammonium triphenyldifluorosilicate (TBAT) as an effective non-hygroscopic, non-basic fluoride source for the silyl exchange of *C*-silylaziridines *e.g.* **180** to **181** (Scheme 77).[28]



180 **181** 60%, (d.r. 98:2)

Scheme 77

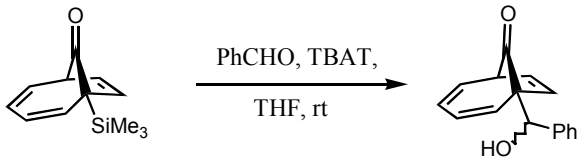
The original report of TBAT for Si–C bond cleavage by DeShong and Pilcher demonstrated its value by generating a wide range of carbanions in the presence of a variety of electrophiles (Scheme 78).[29]



Scheme 78

Selected results above illustrate the wide application of TBAT in generating and trapping carbanions of varying stability in good to excellent yields. The featured reactions treat the electrophile as the limiting reagent and did not mention the recovery of the silane and so the quantity of simple protonation products is unknown.

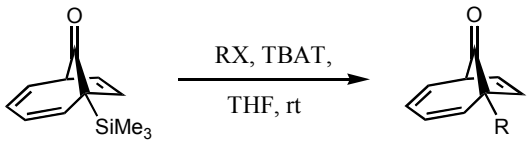
Our preliminary efforts in this area involved generating the bridgehead carbanion from *mono*-silylated ketone (–)-**154** in the presence of benzaldehyde. Thus, addition of TBAT to a solution of (–)-**154** and an excess of benzaldehyde at room temperature gave a mixture of aldol products (–)-**182a** and (–)-**182b** with a 3:2 ratio of diastereoisomers, which were separable by chromatography with an overall yield of 72% (Scheme 79).



(–)-**154** **182ab** 72% (d.r. 3:2)

Scheme 79

Both diastereoisomers possess large optical rotation values ($[\alpha]_D$ −84 and −170) and subsequent ee determination using chiral HPLC confirmed that loss of stereochemical integrity had not occurred. This encouraging outcome led us to extend the reaction to a range of electrophiles, the results of which are summarised in Table 3.



(−)-**154** (−)-**183-188**

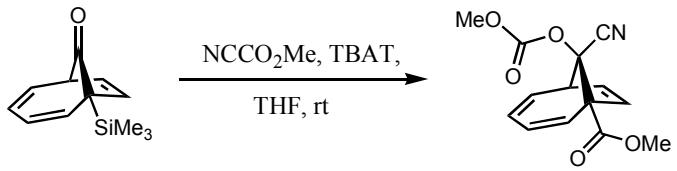
Entry	Electrophile (RX)	R	Yield (%)
1	MeI	Me (**183**)	49
2	AllylBr	Allyl (**184**)	39
3	BnBr	Bn (**185**)	41
4	$CDCl_3$	D (**186**)	32 (54% D)
5	CyCHO	CyCHOH (**187**)	78 (dr 4:1)
6[a]	$NCCO_2Me$	CO_2Me (**188**)	66

[a] See text for product.

Table 3

The yields of simple bridgehead alkylated products are generally low with the remaining material lost to the simple protonation product (entries 1 to 3). Performing these reactions under strictly anhydrous conditions and with an excess of electrophile (typically 5 to 20 equivalents) did not improve matters. Nonetheless, bridgehead deuteration proved possible by using $CDCl_3$ as the reaction solvent to give a mixture of protonated and deuterated products in 32% yield and with 54% deuterium incorporation (entry 4). Unfortunately, more ambitious silyl exchange reactions involving PhSSPh, $B(O^iPr)_3$ and the previously mentioned electrophilic nitrogen sources, 1-chloro-1-nitrosocyclohexane **155** and the oxaziridines **156** and **157** proved unsuccessful.

The initial successful silyl exchange reaction with benzaldehyde prompted a return to electrophiles with carbonyl based functional groups. Thus, TBAT promoted silyl exchange in the presence of cyclohexane carboxaldehyde gave the aldol product (–)-**187** as an inseparable 4:1 mixture of diastereoisomers with an overall yield of 78% (entry 5). Encouraged by this success, we then attempted silyl exchange with methyl cyanoformate. Treatment of (–)-**154** with methyl cyanoformate under our standard conditions gave the product (–)-**188** in 66% yield, which possesses both a bridgehead ester and an *O*-methoxycarbonyl cyanohydrin group (Scheme 80).



(–)-**154** (–)-**188**, 66%

Scheme 80

This product appeared to be the result of initial bridgehead silyl exchange with methyl cyanoformate to liberate cyanide, which attacked the bridging ketone to form the cyanohydrin. The cyanohydrin in the presence of an excess of methyl cyanoformate was trapped leading to the *O*-methoxycarbonyl cyanohydrin. Performing nOe experiments to establish the expected *exo* selectivity for the addition of cyanide failed and so the relative configuration was determined by single crystal X-ray structure determination (Figure 21).

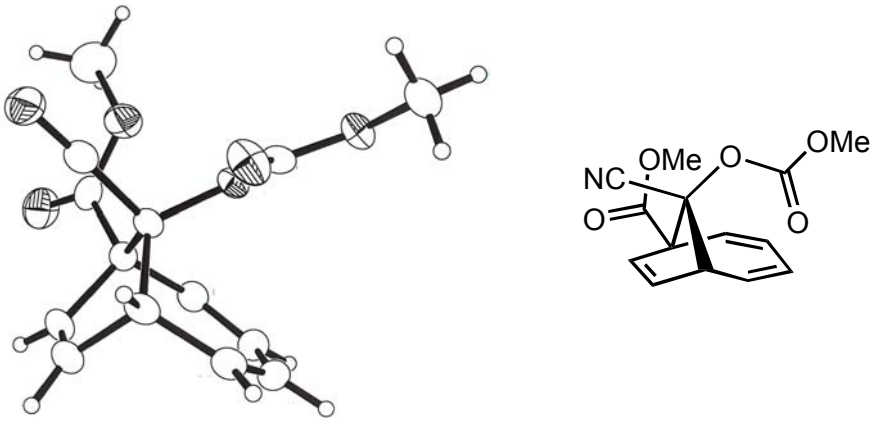
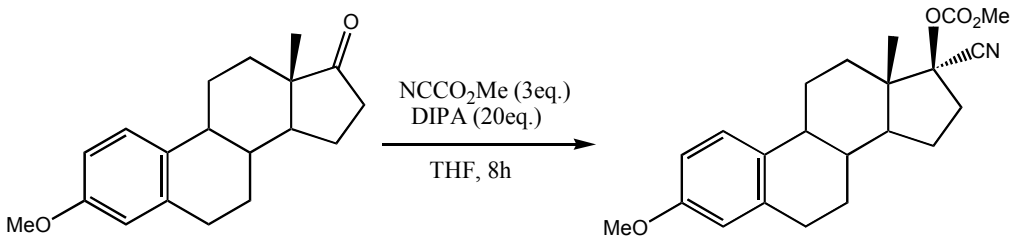


Figure 21

Two reports from Poirier detail the formation and behaviour of the *O*-methoxy carbonyl cyanohydrin group.[30] Poirier found that a variety of ketones and aldehydes in the presence of methyl cyanoformate could be converted into the *O*-methoxycarbonyl cyanohydrin under mild conditions by treatment with a secondary alkylamine such as diisopropylamine (DIPA) at room temperature. For example, treatment of 3-methyl-*O*-estrone **189** with an excess of methyl cyanoformate and DIPA gave the *O*-methoxycarbonyl cyanohydrin **190** in excellent yield (Scheme 81).



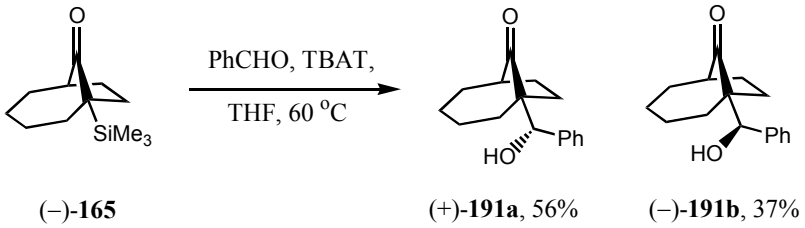
189 **190** 92%

Scheme 81

The reaction conditions enabled some selective protection of unconjugated carbonyls over conjugated carbonyls. The protecting group was found to be stable to strongly acidic and oxidising conditions as well as to

diisobutylaluminium hydride and sodium borohydride and was readily removed by treatment with 1% K_2CO_3 in $MeOH/H_2O$ solution or NaOMe/MeOH (25% w/v) solution.

Fluoride mediated silyl exchange of the saturated *mono*-silylated ketone **(**–)-**165** was also shown to be possible, but required more forcing conditions. Thus, treatment of a mixture of **(**–)-**165** and PhCHO with TBAT at 60 °C gave the aldol product mixture **191a** and **191b** with a 3:2 ratio of diastereoisomers, which were separable by chromatography with an overall yield of 93% (Scheme 81).



(–)-**165** (+)-**191a**, 56% (–)-**191b**, 37%

Scheme 81

X-ray analysis of the minor product (–)-**191b** revealed the relative configuration (Figure 22).

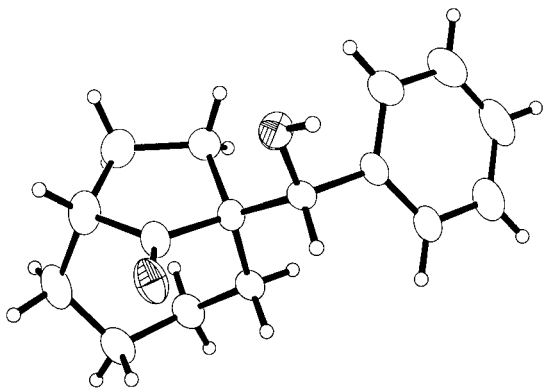
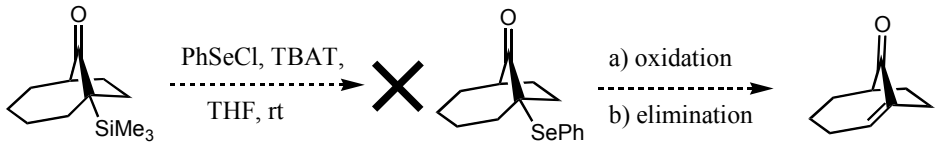


Figure 22

Both diastereoisomers possess optical activity ($[\alpha]_D$ = +33 and –61) and based on the earlier results we assumed that substitution occurs without erosion of enantiomeric purity.

An ambitious silyl exchange was attempted in the presence of PhSeCl with the aim of producing a bridgehead selenide that in turn could be oxidised and eliminated to form an anti-Bredt alkene (Scheme 82).



(–)-**165** **192**

Scheme 82

Unfortunately, addition of TBAT to a mixture of (–)-**165** and PhSeCl resulted in none of the desired product **192**.

2.7 Conclusions

The difficulty associated with deprotonation at bridgehead positions in small bicyclic systems and controlling the resultant carbanions tendency toward aldol condensation has been overcome with two ketone substrates. Our attempts to control bridgehead deprotonation and aldol self-condensation of (–)-camphenilone **32** were unsuccessful, even under ISQ conditions and the reasons for this remain unknown. However, our success in controlling the deprotonation of ketone **35** shows the potential of achieving bridgehead deprotonation in other bicyclic systems. Despite the restriction to ISQ conditions and the associated inability to incorporate other electrophiles we

were able to observe bridgehead deprotonation and use the resultant silylated products.

Even more remarkable are the high levels of asymmetric induction we have achieved using chiral base (*R*, *R*)-**106**. Not only does the asymmetric reaction produce high enantioselectivities but also increased yields by reducing the proportion of over-silylation due to the high preference by the chiral base for a single enantiotopic bridgehead proton.

Regioselective epoxidation of ketone (–)-**154** is possible though the yield is modest and as yet we have not tested the possibility of regioselective epoxide ring opening controlled by the TMS group. Oxidation of the isolated double bond in the form of dihydroxylation is a known procedure and may be of use in the future.[20] The Baeyer-Villiger oxidation of *mono*-silylated ketone (–)-**165** using some standard procedures did not give the desired product, but attempting the oxidation on the products of the silyl exchange reactions may yield better results.

Secondary bridgehead deprotonation of *mono*-silylated ketones (–)-**154** and (–)-**165** were also unsuccessful, but molecular modelling of the ketones indicates that the dihedral angle between the plane of the carbonyl to the second bridgehead hydrogen is similar or slightly worse than **35** and **162** and does not facilitate deprotonation.

The successful use of TBAT in fluoride mediated silyl exchange reactions has allowed indirect access to products having alternative types of bridgehead substituent. Noticeably the best results were obtained with carbonyl containing electrophiles whereas methyl, allyl or benzyl halides gave sizeable production of the protonation by-product. As every attempt was made to attain

completely anhydrous conditions for all the silyl exchange reactions, the possibility arises that the electrophiles interact or even react with TBAT to disrupt the desired reaction pathway. In addition the silyl exchange reaction of ketone (–)-**154** with Mander's reagent has led to the potential discovery of carbonyl protection conditions to yield *O*-methoxycarbonyl cyanohydrins.

Finally, the unsuccessful deprotonation of the larger analogue **169** demonstrated that inspection of the conformational flexibility of a target substrate in relation to dihedral angle of the bridgehead proton is unreliable. This is highlighted by ketone **170**, which based on the dihedral angle alone should be as amenable to deprotonation as camphenilone **32** or ketone **35**, but failed to react under our conditions.

2.7 References

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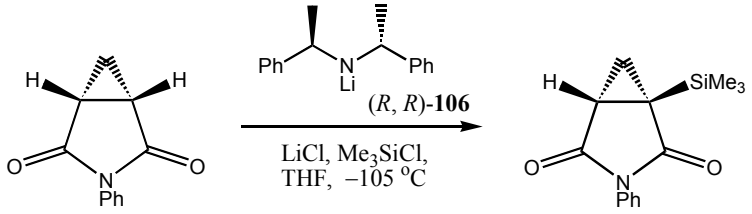
Chapter Three

Generation of the Bridgehead Enolates of Bridged Bicyclic Imides and Lactams

3.1 Aims and Objectives

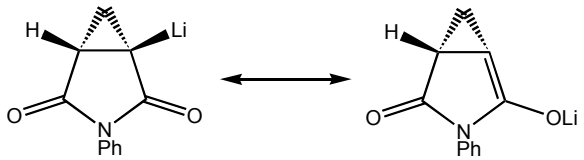
Recently our research group has demonstrated the application of chiral base chemistry to the deprotonation of systems other than conventional ketones, in particular to ring fused cyclic imides.[1] Ring fused cyclopropane imide **193** underwent deprotonation to give chiral silane **194** in 80% yield and with an excellent ee of 95% (Scheme 83).



193 **194** 80% (95% ee)

Scheme 83

Imide **193** is particularly relevant because deprotonation presumably leads to the lithiated α-oxo carbanion **195** and not the highly strained enolate **196** (Figure 23).

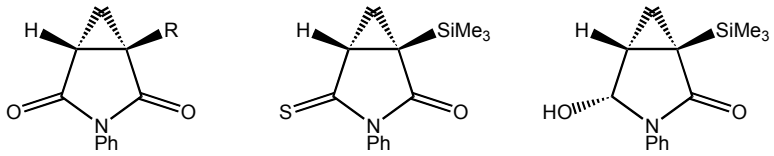


195 **196**

Figure 23

This behaviour results in reversal of the usual reactivity based on HSAB theory, which would normally lead to *O*-silylation to give a silyl enol ether, and instead results in the *C*-silylated product. The chiral silane was further elaborated using fluoride mediated silyl exchange to give **197** and also displayed regioselective thionation with Lawesson's reagent as well as DIBAL

reduction of the carbonyl distal to the silyl group leading to **198** and **199**, respectively (Figure 24).



197

R = SPh, CHOHPh, COPh

198 **199**

Figure 24

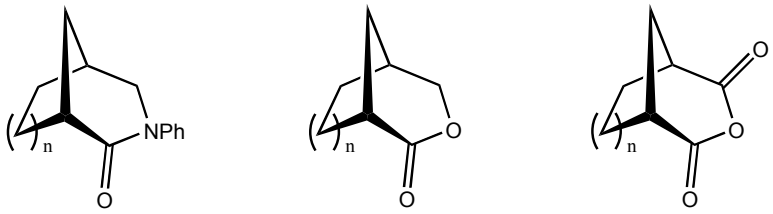
With this example in mind we were interested in testing our bridgehead deprotonation conditions with bicyclic imides **200** and **201** (Figure 25).

200 **201**

Figure 25

These imides form a pair of compounds that vary by the length of one bridge. As a result, a comparison between the different bicyclic ring conformations to the ease of deprotonation could be investigated. We were also interested to study if the change in carbonyl group from ketone to imide has an effect on deprotonation. Earlier work in our group with imides suggested the potential benefit of using imides to eliminate by-product formation such as the self-condensation observed with the ketones discussed in Chapter Two.

In addition to investigating imides, we also wanted to examine whether analogous lactams (**202**/**203**), lactones (**204**/**205)** and anhydrides (**206**/**207**) would undergo bridgehead deprotonation (Figure 26).



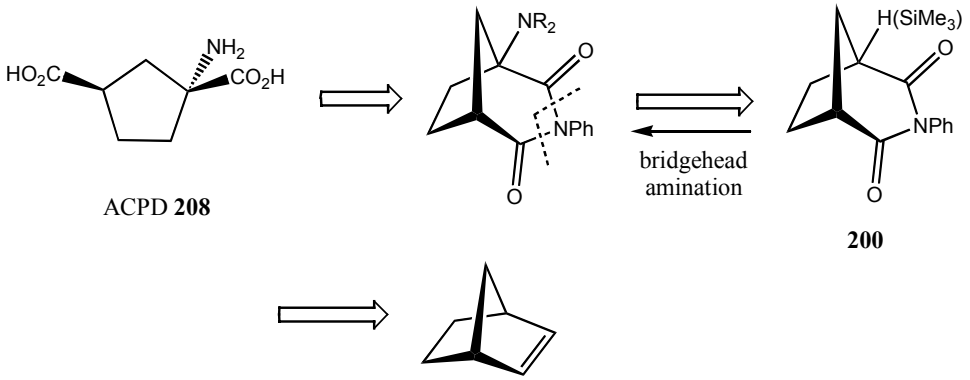
n = 1, **202**
n = 2, **203**

n = 1, **204**
n = 2, **205**

n = 1, **206**
n = 2, **207**

Figure 26

We also believed that some applications to natural product synthesis might be possible and we identified aminocyclopentane dicarboxylic acid (ACPD) **208** as a potential target.[2] We envisaged enantioselective bridgehead deprotonation of imide **200** followed by reaction with an electrophilic nitrogen source to give the direct amination product. Electrophilic amination of conventional carbanions is a difficult procedure. As an alternative we could follow an indirect silylation/exchange route to provide ACPD from norbornylene **209** (Scheme 84).

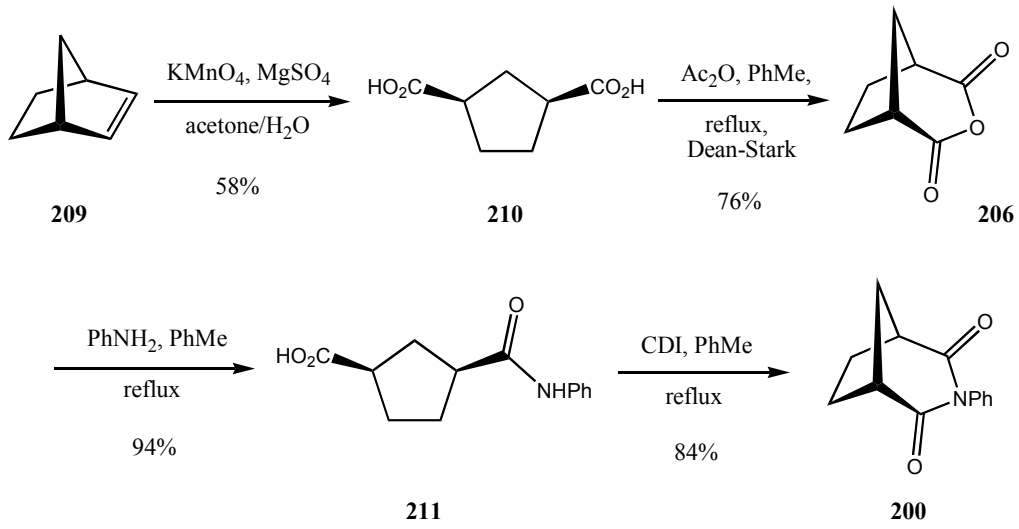


Scheme 84

However, this is a challenging objective as we reported earlier in Chapter Two that the amination reagents **155**, **156**, **157**, DEAD and DIAD were unsuccessful in achieving bridgehead amination with ketones **35** and **162**.

3.2 Generation of the Bridgehead Enolate of 3-Phenyl-3-azabicyclo-[3.2.1]octane-2,4-dione

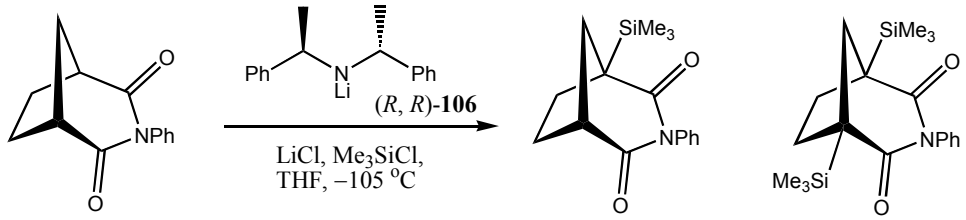
Bicyclic imide **200** was synthesised by the four-step procedure shown in Scheme 85. Firstly, norbornylene **209** was oxidised with potassium permanganate to give *cis* cyclopentane dicarboxylic acid **210**.[3] Treatment of **210** with acetic anhydride gave, after recrystallisation, anhydride **206**. This reacted cleanly with aniline to give the amido acid **211** before 1,1'-carbonyldiimidazole (CDI) mediated ring closure was accomplished to give imide **200** in good yield.



Scheme 85

Imide **200** was subjected to the conditions developed in Chapter Two for bridgehead deprotonation, thus addition of LiTMP to a mixture of imide **200** and TMSCl at –105 °C gave *mono*-silylated imide **212** in 16% yield accompanied by *bis*-silylated imide **213** in 20% yield. Enantioselective deprotonation was then performed with chiral base (*R*, *R*)-**106** to give 63% of

mono-silylated imide (–)-**212** accompanied by *bis*-silylated imide **213** in 18% yield (Scheme 86).



200 (–)-**212** 63%, 70% ee **213** 18%

Scheme 86

In common with our earlier results, the use of EQ conditions gave none of the desired product and resulted in recovery of the starting material. The enantiomeric excess of *mono*-silylated imide (–)-**212** was determined using chiral HPLC to be 70% and the absolute configuration was established by single crystal X-ray structure determination (Figure 27).

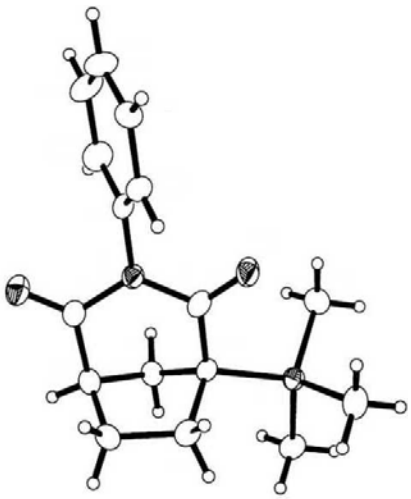
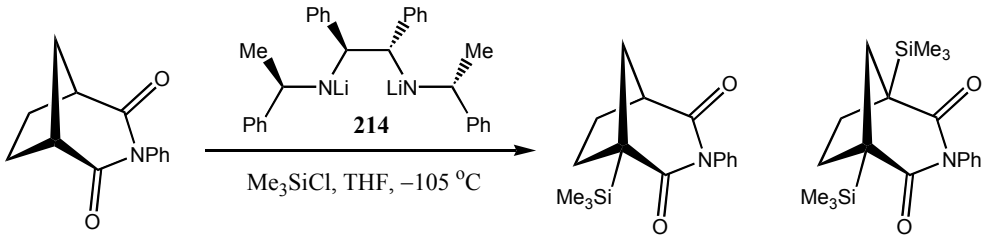


Figure 27

An analogous reaction using (*S*, *S*)-**106** gave the opposite enantiomer of the *mono*-silylated imide (+)-**212** in 56% yield and 70% ee. For both these reactions the ee was high but we attempted to improve it by using a more

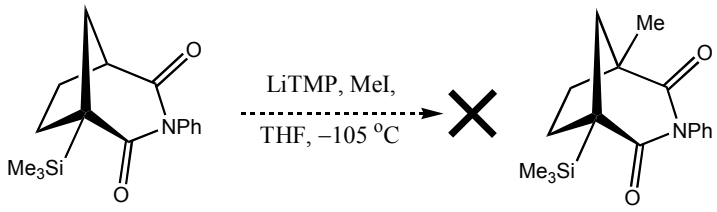
complex *bis*-amide base **214**, which is regularly used in our research group and leads to the opposite sense of stereo-induction observed with (*R*, *R*)-**106**. Treatment of imide **200** under our standard conditions gave the expected *mono*-silylated imide (+)-**212** in 47% yield but with an improved ee of 94% (Scheme 87).



200 (+)-**212** 47%, 94% ee **213** 24%

Scheme 87

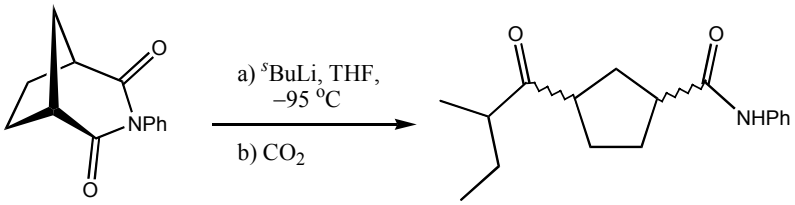
Both the optical rotation and the chiral HPLC revealed that the opposite enantiomer was formed with chiral base **214** compared to that formed with chiral base (*R*, *R*)-**106**. Further attempts to incorporate electrophiles other than TMSCl led to no observable product formation. We were also unable to achieve secondary bridgehead deprotonation of (+)-**212** other than over silylation observed in **213**. For example, treatment of (+)-**212** with LiTMP under ISQ conditions with methyl iodide resulted in recovery of the starting material (Scheme 88).



(+)-**212**

Scheme 88

As reported in Chapter One, Wanner achieved the deprotonation of camphorimide **104** by treatment with ^{s}BuLi at –95 °C followed by quenching of the carbanion with CO_2. Applying these conditions to imide **200** resulted only in nucleophilic attack of the imide by ^{s}BuLi to give the cyclopentane-carboxamide **215** (Scheme 89).



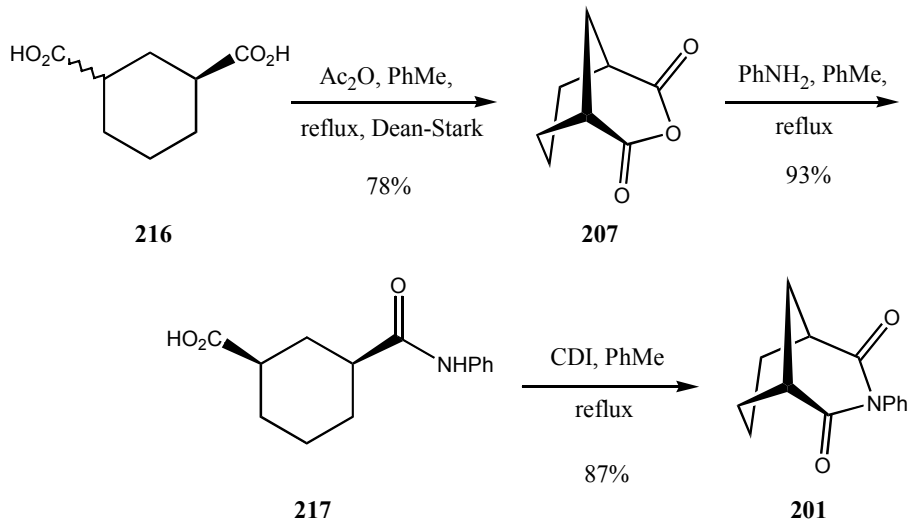
200 **215**

Scheme 89

Using chiral bases **106** and **214** under EQ conditions was also unsuccessful and led to recovery of the starting material The failure to achieve bridgehead deprotonation of imide **200** compared to camphorimide **104** is probably due to the lack of the geminal dimethyl of the one-carbon bridge in **104**, which shields the imide from nucleophilic attack.

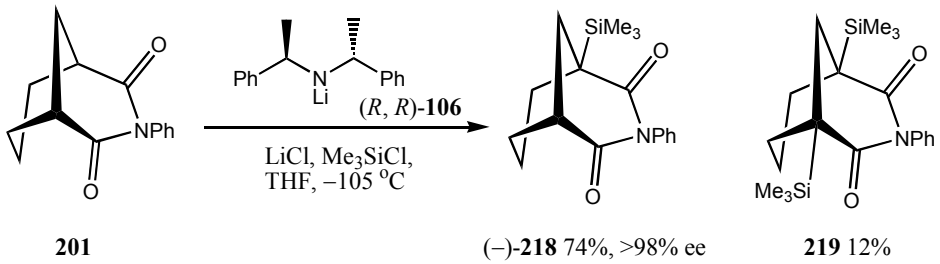
3.3 Generation of the Bridgehead Enolate of 3-Phenyl-3-azabicyclo[3.3.1] nonane-2,4-dione

The bicyclic imide **201** was synthesised by a similar three-step procedure to imide **200** as shown in Scheme 90. Thus, treatment of a *cis*/*trans* mixture of 1,3-cyclohexane dicarboxylic acid **216** with acetic anhydride gave anhydride **207**, which reacted cleanly with aniline to give amido acid **217**. Ring closure of the amido acid was accomplished with CDI to give imide **201** in good yield.



Scheme 90

Imide **201** was then subjected to the same conditions for bridgehead substitution that had proved successful with imide **200**. Thus, addition of LiTMP to a mixture of imide **201** and TMSCl at –105 °C gave *mono*-silylated imide **218** in 47% yield accompanied by *bis*-silylated imide **219** in 20% yield. Enantioselective deprotonation was then performed with chiral base (*R*, *R*)-**106** to give 74% of *mono*-silylated imide (–)-**218** accompanied by *bis*-silylated imide **219** with 12% yield (Scheme 91).



201 (–)-**218** 74%, >98% ee **219** 12%

Scheme 91

In common with our earlier results, the use of EQ conditions gave none of the desired product and resulted in recovery of the starting material. The enantiomeric excess of *mono*-silylated imide (–)-**218** was determined by chiral HPLC to be >98%. The absolute configuration was established by single crystal X-ray structure determination and exhibits the same sense of stereochemical induction by chiral base (*R*, *R*)-**106** observed with (–)-**212** (Figure 28).

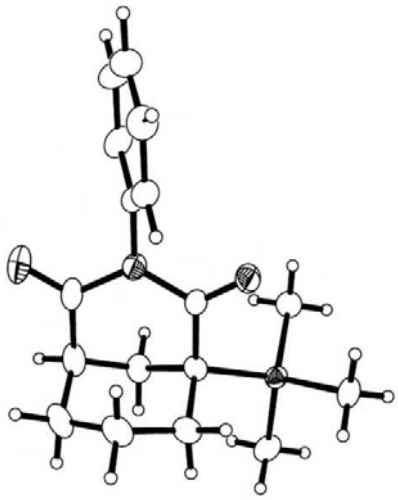
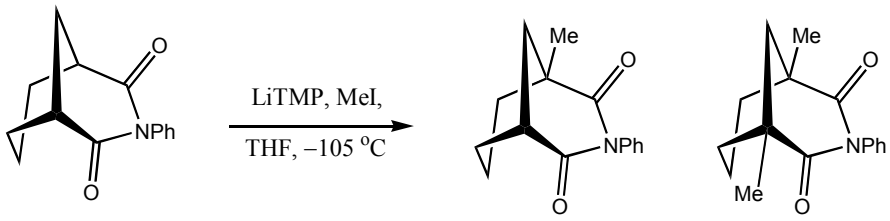


Figure 28

Performing the reaction at –78 °C with (*R*, *R*)-**106** resulted in the isolation of (–)-**218** in 53% yield and 90% ee accompanied by **219** (14%). A similar reaction using (*S*, *S*)-**106** gave the opposite enantiomer of the silylated imide (+)-**218** in 56% yield and >98% ee.

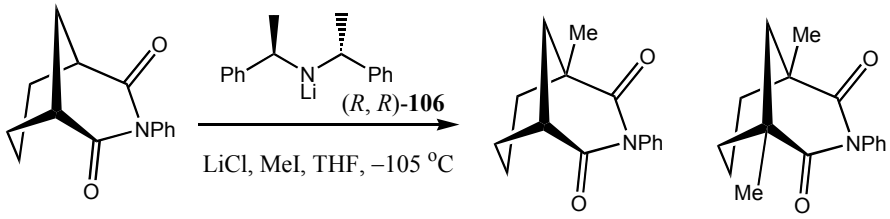
In contrast to all of the systems previously studied, imide **201** also underwent bridgehead substitution with methyl iodide as an *in situ* quench. Thus, treatment of a mixture of imide **201** and methyl iodide at –105 °C with LiTMP gave *mono*-methylated imide **220** in 40% yield accompanied by *bis*-methylated imide **221** (Scheme 92).



201 **220** 40% **221** 25%

Scheme 92

Enantioselective deprotonation was then performed with chiral base (*R*, *R*)-**106** to give 57% of *mono*-methylated imide (–)-**220** accompanied by the *bis*-methylated imide **221** (Scheme 93).

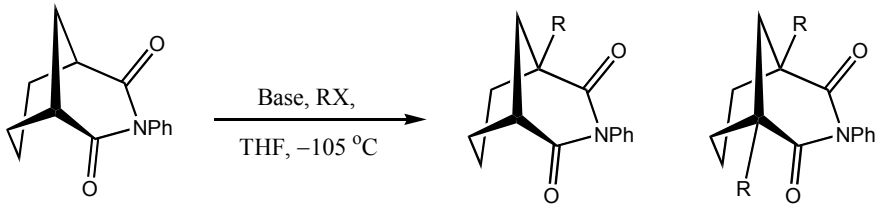


201 (–)-**220** 57%, 97% ee **221** 11%

Scheme 93

The enantiomeric excess was determined by using chiral HPLC to be 97%. The absolute stereochemistry of (–)-**220** could not be determined by X-ray crystallography due to the lack of an element heavier than silicon but was assumed to correspond to that of *mono*-silylated imide (–)-**218**. Encouraged by this result we extended the reaction to incorporate other unconventional ISQ

electrophiles including, allyl bromide, prenyl bromide, benzyl bromide and pivaloyl chloride, the results of which are shown in Table 4.



201 **220, 222, 224, 226, 228** **221, 223, 225, 227, 229**

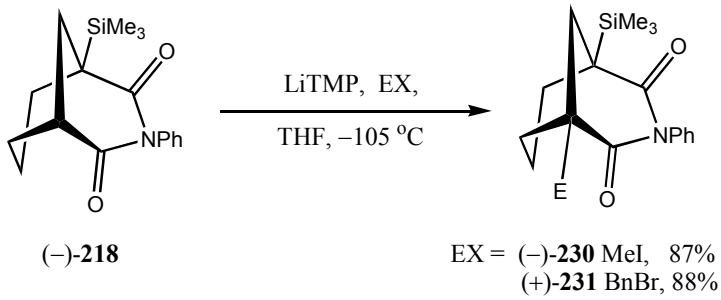
Entry	Base	Electrophile (RX)	Yield of mono (%)	Yield of bis (%)	Ee (%)
1	LiTMP	MeI	**220** (40)	**221** (25)	–
2	(*R*, *R*)-**106**/LiCl	MeI	**220** (57)	**221** (11)	97
3	LiTMP	AllylBr	**222** (25)	**223** (13)	–
4	(*R*, *R*)-**106**/LiCl	AllylBr	**222** (42)	**223** (7)	95
5	LiTMP	PrenylBr	**224** (42)	**225** (19)	–
6	(*R*, *R*)-**106**/LiCl	PrenylBr	**224** (50)	**225** (12)	98
7	LiTMP	BenzylBr	**226** (54)	**227** (19)	–
8	(*R*, *R*)-**106**/LiCl	BenzylBr	**226** (52)	**227** (3)	95
9	LiTMP	PivaloylCl	**228** (23)	**229** (34)	–
10	(*R*, *R*)-**106**/LiCl	PivaloylCl	**228** (56)	**229** (17)	99

Table 4

The results demonstrate that a range of electrophiles react with moderate overall yield (including over-alkylation) but with the racemic products generally displaying lower yields and more over-alkylation than the chiral products. The enantioselectivity observed in the silylation reaction is maintained in the alkylation and acylation reactions, which proceed in 95-99% ee. In the context of the ISQ reaction these results are remarkable in that the electrophile was not observed to react significantly with the lithium amide base and the success with pivaloyl chloride is even more surprising (entry 9 and 10). Perhaps due to the low temperatures involved, the steric bulk of pivaloyl chloride and the ease of deprotonation of imide **201** there is little interaction

between base and electrophile. The results are contrasted by the failure of imide **200** to undergo similar bridgehead alkylation and acylation reactions.

The increased potential of **201** compared to **200** led us to attempt secondary bridgehead deprotonation, which had previously been unsuccessful with our other substrates. Thus, treatment of *mono*-silylated imide (–)-**218** with LiTMP under ISQ conditions with methyl iodide gave the double bridgehead substituted products (–)-**230** in 87% yield (Scheme 94).



(–)-**218**

EX = (–)-**230** MeI, 87%
(+)-**231** BnBr, 88%

Scheme 94

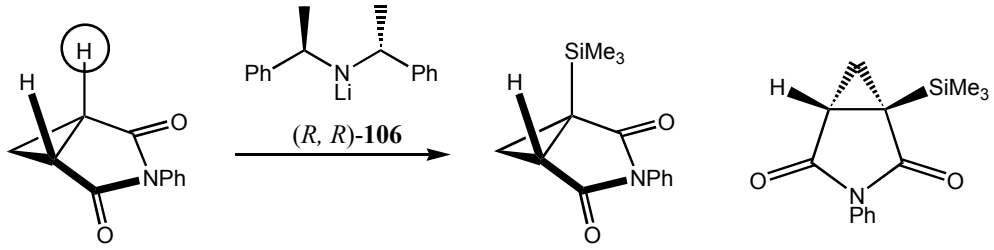
Under similar conditions with benzyl bromide as the electrophile gave (+)-**231** in 88% yield.

3.4 Discussion of Chiral Base Stereoselectivity and Bridgehead Enolate Stability

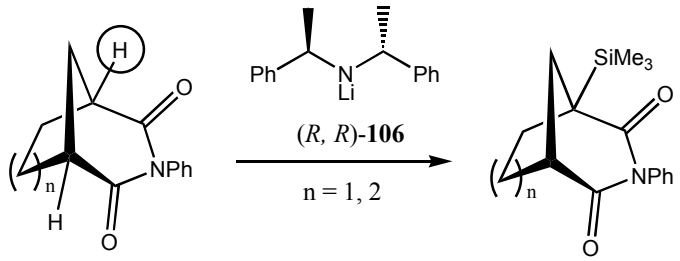
The mechanistic details of lithium amide base chemistry involve complex effects; lithium amide solution and crystal structures, aggregation, salt and additive effects.[4] As a result there is a great deal of debate regarding how the many examples of lithium amide base chemistry can be explained mechanistically. Information regarding the mechanistic details of using the chiral bases described in this thesis is limited and so we attempted to form and

isolate stable complexes of bridgehead lithiated species at very low temperatures for study. Unfortunately, X-ray structure determination of various crystals we isolated were known complexes of LiCl.[5] A description of the general features and a model for chiral base discrimination of some systems was presented by Simpkins.[6]

By comparison of the steric environments between the ring fused cyclopropane silyl imide **194** and *mono*-silylated imides (–)-**212** and (–)-**218**, we can see that the same sense of stereochemical induction is observed. For example, with imide **193** the ring fused bond is the least sterically demanding, as is the single bridging carbon in the case of imides **200** and **201** (Scheme 95).



193 **194**



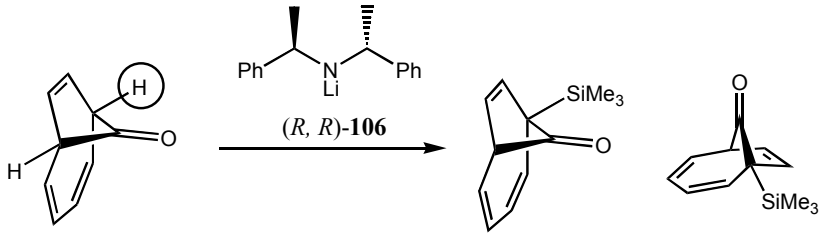
200/201 **212/218**

Scheme 95

Remarkably, the chiral base is able to significantly distinguish between a one-carbon bridge and a two-carbon bridge of **200** (70% ee). The difference in steric bulk between the one- and two-carbon bridges is accentuated because the

protons of the one-carbon bridge are orientated orthogonal to the bridgehead. The increase to a three-carbon bridge in **201** increases the steric bulk and allows better discrimination by the chiral base (>98% ee).

It is more difficult to rationalise the sense of stereo-induction of (–)-**154** and (–)-**165** with conventional ketone desymmetrisation results reported in Chapter One. However, comparing *mono*-silylated ketones (–)-**154** and (–)-**165** to the *mono*-silylated imides (–)-**212** and (–)-**218**, by placing the bridged ketone in the same plane as the imide reveals an identical trend (Scheme 96).



35 (–)-**154**

Scheme 96

In this case, the base efficiently discriminates between a two-carbon bridge and four-carbon bridge to give high ee (>98% ee).

Inductive and conjugative effects from the carbonyl adjacent to the charge affect the stability of the bridgehead carbanion. We can assume that there is a minimal contribution from enolate conjugation because of the strain required to incorporate a double bond toward the bridgehead. In our small set of substrates we can examine the inductive effect by comparing the bridged ketones **35**/**162** to the imides **200**/**201**. Due to the group electronegativity of ketones compared to imides, we would predict the ketones to display a stronger inductive effect than the imides. Unfortunately, there is no reliable experimental data to confirm this effect. For example, a crude comparison of

the yields of bridgehead silylation between ketones and imides reveals that the average yield of ketone silylation is 83% and the average yield for imides is 83.5% (**35** = 99%, **162** = 67%, **200** = 81%, **201** = 86%). Therefore we cannot predict the 'ease of deprotonation' based on inductive effects except to say that the effect contributes to the acidity of the bridgehead proton to allow removal by a lithium amide base.

Throughout this study we have referred to the relationship between the dihedral angle of the bridgehead proton to the plane of the carbonyl in relation to the formation of enolate type conjugation. All of the substrates examined possess dihedral angles equal to or less than 40°, which is significantly misaligned from the optimal 90° required to observe kinetic enolate formation (Figure 29).

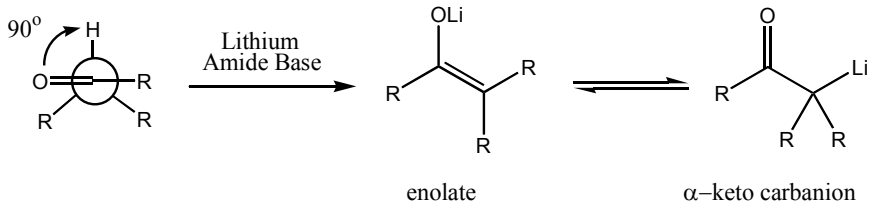


Figure 29

Enolate contribution is an incremental effect in relation to dihedral angle where enolate formation does not occur until the dihedral angle approaches 90°. The efficiency of π-type overlap depends approximately on the cosine of the dihedral angle, falling off gently for small angles of 'twist' but becoming zero at 90°. This means that the change in dihedral angle from 0° to 40° corresponds to a small decrease in the amount of carbanion present (Figure 30).

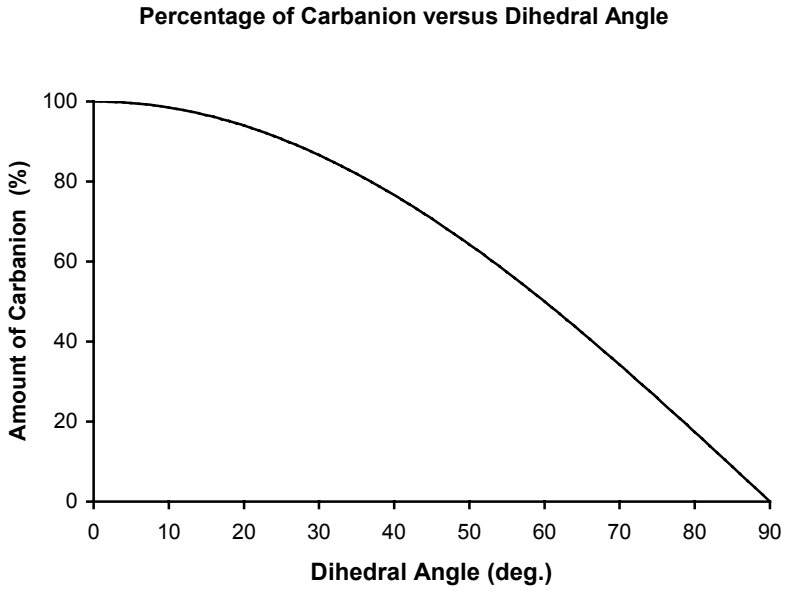


Figure 30

The range of dihedral angles produced by molecular modelling (MM2) force field calculations with the bicyclic systems we examined is presented in Table 5.

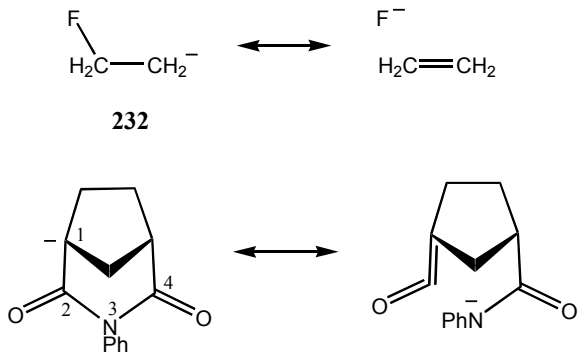
Compound Number	Dihedral Angle (deg.)	Amount of Enolate (%)
35	29	13
162	40	25
200	16.5	4
201	29	13

Table 5

In context of Figure 30 the results predict that there would be little enolate formation in compounds **35**, **162**, **200** and **201**. A partial contribution might occur by rehybridisation, as with bridgehead alkenes, but because the dihedral angles are so low, rehybridisation is unlikely to have a significant beneficial effect. Therefore the dihedral angle cannot predict the likelihood of

deprotonation in small bicyclic substrates based on stabilisation from enolate conjugation.

Another important effect to consider is negative hyperconjugation, which involves the interaction between a σ-bond molecular orbital and a p-orbital that have π symmetry on adjacent atoms (n → σ*). This effect has been studied extensively with the simple β-fluoroethyl anion **232** and is illustrated below with the bridgehead carbanion **233** of imide **200** (Figure 31).[7]



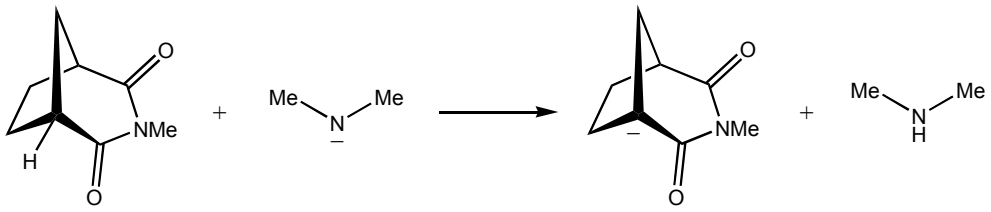
232

233

Figure 31

As a result of hyperconjugation the C1-C2 and N3-C4 bond are predicted to shorten accompanied by a complimentary lengthening of the C2-N3 bond. The strength of this effect increases with greater electronegativity of the atom at position 3. The required alignment of the orbitals implies that the interaction depends on the dihedral angle between the carbanion orbital and the σ-bond with major interactions at 0° and 180° and minor at 90°. The simple parameters for carbanions in the MM2 force field parameters are typically unreliable but modelling of imide **200** reveals that the dihedral angle H1-C1-C2-N3 is 163°, which is close to the 180° required for maximum hyperconjugation.

In collaboration with Dr. Chris Hayes at the University of Nottingham we performed *ab initio* calculations at the B3LYP/6-31G* level using Gaussian 98 on the bridgehead carbanions and lithiated intermediates of imide **234**. This imide was chosen with an *N*-Me imide rather than an *N*-Ph so that the calculation time could be reduced. Using imide **234** as a model we calculated the stabilisation energy of bridgehead deprotonation by using dimethylamide as base, which gave $\Delta E = -16.17$ kcal/mol (Scheme 97).



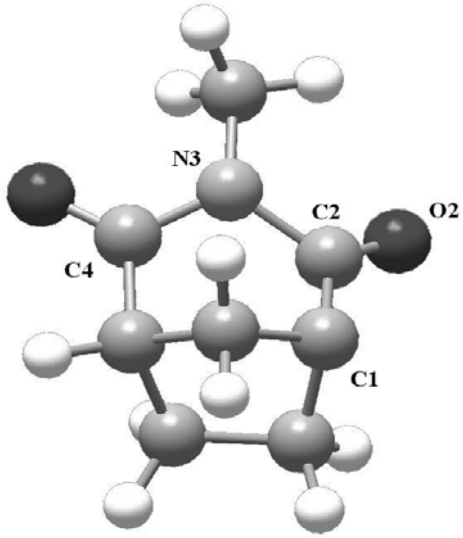
234 **235**

$\Delta E = -16.17$ kcal/mol

Scheme 97

Noticeably, this process is exothermic and the resultant imide carbanion **235** is significantly stabilised relative to imide **234**.

If the carbanion is stabilised by negative hyperconjugation we should observe the characteristic lengthening of the C2-N3 bond compared to the N3-C4 bond length as well as shortening of the C1-C2 bond. As shown in Figure **32** we do observe the predicted changes of bond length in comparison to the bond lengths of the neutral imide **234**, which suggests that negative hyperconjugation has a significant contribution to stability.

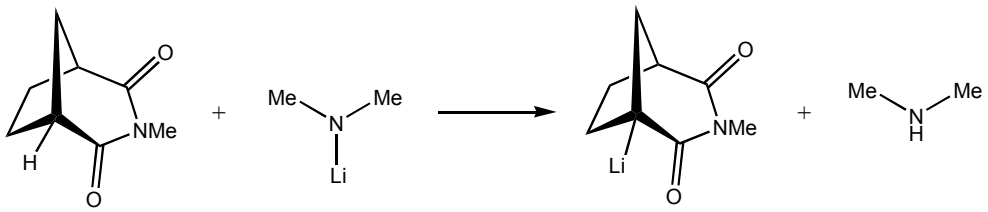


Bond	Imide **234** (Å)	Carbanion **235** (Å)
C1-C2	1.52	1.42
C2-N3	1.40	1.50
N3-C4	1.40	1.38
C2-O2	1.21	1.24

Figure 32

The carbanion **235** can also be seen to display large distortion of the C2 carbonyl in an attempt to obtain favourable alignment with the C1 lone pair and thus form an enolate. Although the C1-C2 bond length decreases, which is consistent with enolate formation, the C2-O2 bond length increases by only a small amount (0.03Å) and confirms that there is little enolate conjugation present.

Further calculations with the lithiated imide **236** produced by deprotonation with lithium dimethylamide gave a less exothermic ΔE = –2.75 kcal/mol (Scheme 98).

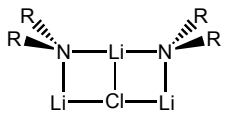


234 **236**

ΔE = –2.75 kcal/mol

Scheme 98

This result is consistent with comparisons made between carbanions and their lithiated counterparts by von Ragué Schleyer.[8] With carbanion **235** the formal charge at C1 is stabilised by de-localisation *via* negative hyperconjugation over 3 atoms (C1-C2-N3). The increase in ΔE of lithiated imide **236** is due to localisation of the charge to C1 and so **236** is less stabilised than **235**. Another reason for the increase in ΔE is the strain energy introduced by the formation of Li-O2 chelation. The square complex formed by C1-C2-O2-Li is in common with the mixed trimer **237** of (*S*, *S*)-**106** observed in solution and in the solid state by X-ray crystallography (Figure 33).[9]



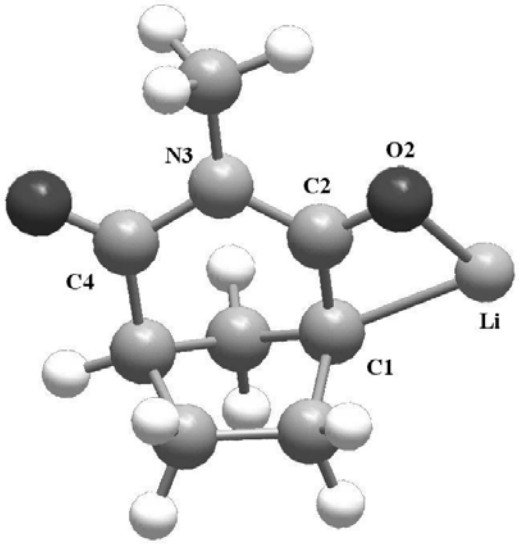
R = (*S*)-CH(CH$_3$)Ph

237

Figure 33

The Li-O2 interaction in lithiated imide **236** is favourable *in silico* but does not represent an empirically valid interaction due to the presence of solvent, lithium chloride and complexation with the base.

In a similar fashion to **235**, when we examined the bond lengths C1-C2, C2-N3, N3-C4 and C2-O2 of the lithiated imide **236** we observed a less pronounced change in bond length but with a reversal in the pattern of bond lengths measured in **235**. The major change is observed in the C2-O2 bond length, which increases by 0.06Å and is accompanied by a decrease of the C2-N3 bond (0.02Å) (Figure 34).

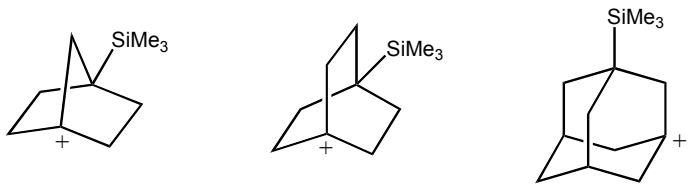


Bond	Imide **234** (Å)	Lithiated **236** (Å)
C1-C2	1.52	1.47
C2-N3	1.40	1.38
N3-C4	1.40	1.42
C2-O2	1.21	1.27

Figure 34

The results suggest that the lithiated imide **236** is stabilised by amide conjugation *via* donation of the N3 lone pair through the C2 carbonyl toward the bridgehead lithium.

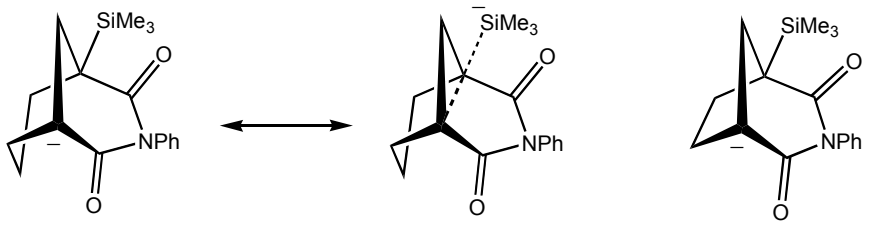
Negative hyperconjugation might also explain the ease with which secondary bridgehead deprotonation occurs with *mono*-silylated imide **213**, by invoking transannular stabilisation of the bridgehead carbanion from the silyl group. Known as homohyperconjugation, this effect has been modelled and applied to the stability of bridgehead carbocations to explain increases in the rate of solvolyses of bridgehead bromides and triflates.[10] Comparisons between the stability of *mono*-silylated norbornyl **238**, bicyclo[2.2.2]octane **239** and adamantyl **240** bridgehead carbocations revealed that the norbornyl system displays significant stabilisation (Figure 35).



238 **239** **240**

Figure 35

This effect was attributed to the conformation of the bicyclic ring systems leading to favourable inter-atomic distances and inter-orbital angles to produce 'back-lobe' through-space interactions. For example, in our case this effect would manifest itself by bridgehead deprotonation of **201** to give the bridgehead carbanion **241** (Figure 36).



241 **242**

Figure 36

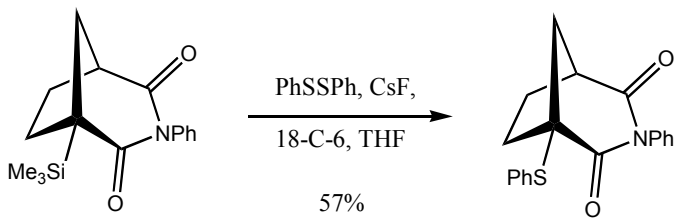
More importantly the fact that *mono*-silylated imide **212** is not amenable to secondary bridgehead deprotonation to give carbanion **242** tends to rule out this effect because it should possess more favourable inter-atomic distances and inter-orbital angles than **241**. The literature contains only two reports of negative homohyperconjugation in systems concerning oxygenated anthracene cycloadducts.[11]

The ease of deprotonation of imides **201**/**218** in comparison to imides **200**/**212** is most likely due to two factors; firstly the increase in flexibility with increasing bridge sizes resulting in greater ability to incorporate some enolate

character and secondly the contribution to stabilisation from negative hyperconjugation or amide conjugation in small bridged bicyclic systems.

3.5 Fluoride Mediated Silyl Exchange of Bridgehead Silylated Imides

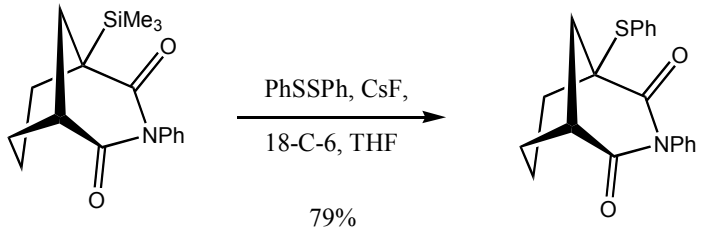
Despite the significant advance in the types of bridgehead substitution possible with imide **201** we were still unable to introduce other types of substitution with imide **200** other than TMS. Therefore we attempted fluoride mediated silyl exchange under the previously mentioned conditions using TBAT but observed no product formation. Monitoring by tlc of a test reaction of *mono*-silylated imide **212** with TBAT in the absence of an electrophile revealed very slow desilylation, typically 36 hours to completion. As an alternative we tested TBAF and observed rapid and complete desilylation in 15 min. However, treatment of *mono*-silylated imide **212** with TBAF (dried over MS 4Å) in the presence of various electrophiles led only to desilylation-protonation. Next we turned our attention to cesium fluoride, which is easier to dry than TBAF but is very limited in the range of compatible electrophiles. Subsequent treatment of imide (+)-**212** with flame dried cesium fluoride in the presence of diphenyl disulfide and 18-crown-6 gave the bridgehead phenylsulfanyl imide (+)-**243** in 57% yield (Scheme 99).



(+)-**212** (+)-**243**

Scheme 99

In a similar manner imide (–)-**218** was subjected to these conditions to give the analogous phenylsulfanyl imide (–)-**244** in 79% yield (Scheme 100).



(–)-**218** (–)-**244**

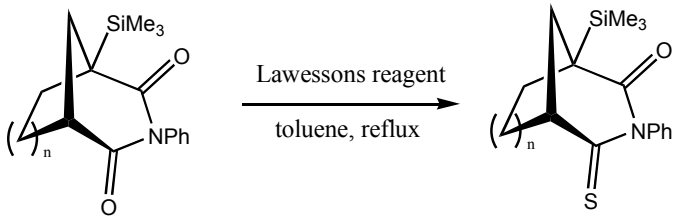
Scheme 100

These results were tempered by the previously mentioned electrophile/CsF compatibility problems, which meant that using other electrophiles such as benzoyl fluoride and benzaldehyde gave no product formation. Even electrophiles that are known to be compatible including benzoyl fluoride and benzaldehyde were unsuccessful as well as various electrophilic amination reagents. The failure to achieve bridgehead amination by either direct or indirect methods meant we were unable to complete the synthesis of ACPD **208** outlined in the aims and objectives of this Chapter.

3.6 Silyl Directed Regioselective Reactions

So far the silyl imides we had generated appeared to parallel the reactivity observed with ring fused cyclopropane silyl imide **194** mentioned at the beginning of this Chapter. For that reason we decided to investigate whether the bridgehead silyl group could similarly exert a directing influence over the regioselectivity of thionation with Lawesson's reagent and reduction with DIBAL. Thus exposure of silyl imides (–)-**212** and (–)-**218** to Lawesson's

reagent in refluxing toluene led to the production of the *mono*-thioimides (–)-**245** and (–)-**246** in 44% and 52% yields, respectively (Scheme 101).[12]



n = 1, (–)-**212**
n = 2, (–)-**218**

n = 1, (–)-**245**, 44%
n = 2, (–)-**246**, 52%

Scheme 101

The regioselectivity was confirmed by ^{1}H NMR from the change in chemical shift of the remaining bridgehead proton and by determination of the X-ray crystal structure of (–)-**246** (Figure 37).

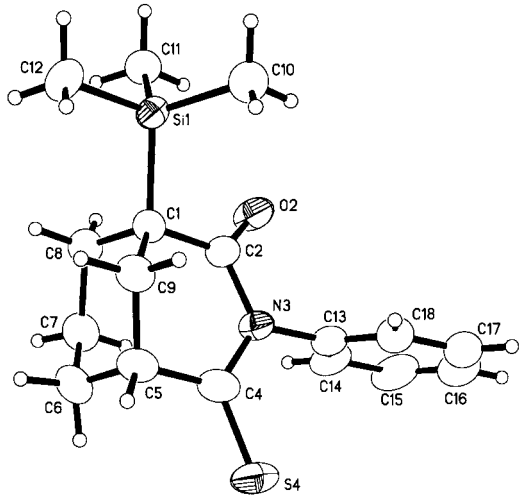


Figure 37

As shown in Figure 37 the thionation reaction introduces a sulfur atom at C4, distal to the TMS group at the bridgehead position C1.

Upon inspection of the ^{1}H NMR spectra of imide (–)-**246** there was unusual broadening and separation of the *ortho* protons of the *N*-phenyl ring (Figure 38).

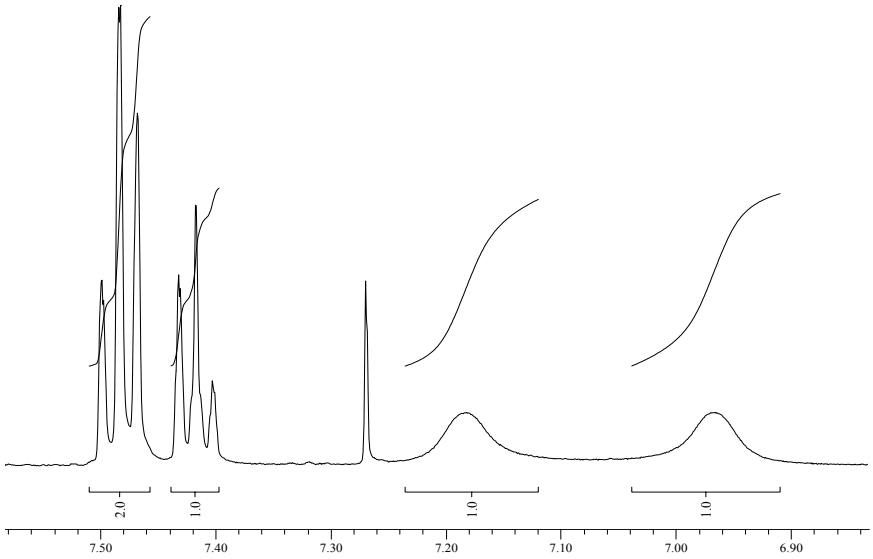
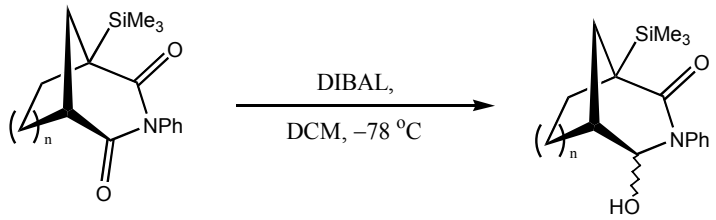


Figure 38. Imide (–)-246

The *endo* and *exo* faces of the imide are different environments and impart different chemical shifts to the *ortho* protons if it were not for free rotation around the N-C(phenyl) bond averaging the difference to give magnetic equivalence. However introduction of the larger sulfur atom causes restricted rotation to the phenyl group and allows the observation of the different environments in which the *ortho* protons reside. This atropisomerism allowed us to calculate the rate constant for the exchange to be 239.5 s^{-1} and also to calculate the Gibbs free energy ($\Delta G^{\ddagger}$) to be 62.5 $kJmol^{-1}$ (For full working see Appendix). The thioimide products could lead to the production of the analogous lactams by desulfuration, however this was more conveniently achieved by DIBAL reduction as described below.

The second regioselective reaction we examined was reduction of the *mono*-silylated imides (–)-**212** and (–)-**218** by DIBAL to give the hydroxylactams followed by further reduction *via N*-acyliminium formation to give the lactams.[13] Treatment with DIBAL lead to regioselective reduction of the carbonyl distal to the silyl group, initially leading to the product of *exo* hydride addition, which upon aqueous work-up partially epimerised to a mixture of *exo*/*endo* products (–)-**247ab** and (–)-**248ab** (Scheme 102).

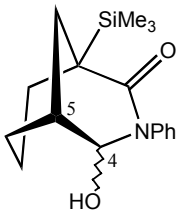


n = 1, (–)-**212**
n = 2, (–)-**218**

n = 1, (–)-**247ab**, 82% (exo/endo – 6 : 1)
n = 2, (–)-**248ab**, 79% (exo/endo – 3 : 1)

Scheme 102

The assignment of the *exo*/*endo* hydroxy lactam diastereoisomers of (–)-**248ab** was achieved by first measuring the coupling constants between H5 and H4. The dihedral angle of H4-C4-C5-H5 was then obtained for both the *exo* and *endo* isomers from molecular modelling. The assignment was then made using the Karplus equation to relate the dihedral angle to the coupling constant. The two coupling constants measured gave $J_{4,5}$ = 5.5 and 3.7 Hz and the dihedral angle determined by MM2 calculations gave *exo* = 45° and *endo* = 74°. The Karplus equation predicts that a small dihedral angle will lead to a large coupling constant, *e.g.* 0° = J_{large} and 90° = 0 Hz (Figure 39).

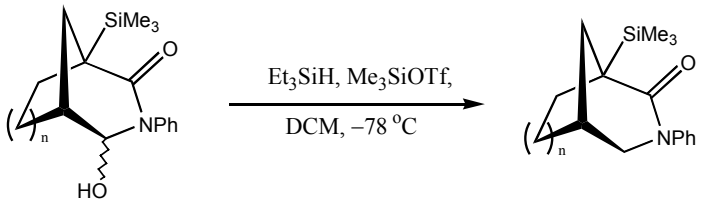


Dihedral angle (H5-C5-C4-H4)
exo - 45°
endo - 74°

Coupling Constant (*J*)	Predicted
exo - 5.5 Hz	4.9 Hz
endo - 3.7 Hz	1.7 Hz

Figure 39

The predicted coupling constants were calculating using the generalised Karplus parameter set developed by Altona and gave *exo* = 4.9 Hz and *endo* = 1.7 Hz.[14] The regioselectivity of hydride addition was confirmed upon *N*-acyliminium reduction of the hydroxylactams to give lactams (–)-**249** and (–)-**250** and the analytical data compared to the identical racemic lactams produced in Chapter 3.7 (Scheme 103).



n = 1, (–)-**247ab**
n = 2, (–)-**248ab**

n = 1, (–)-**249**, 88%
n = 2, (–)-**250**, 83%

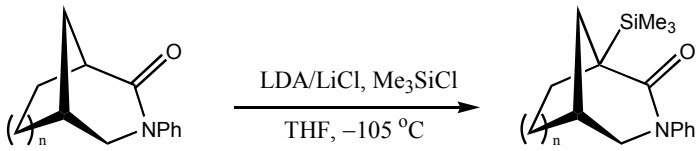
Scheme 103

We confirmed that there was no loss in enantiomeric excess by HPLC experiments in conjunction with the racemic products described in Chapter 3.6.

3.7 Generation of Bridgehead Enolate of Lactams

Due to the successful synthesis of silyl lactams (–)-**249** and (–)-**250** *via* the indirect deprotonation/reduction protocol we were interested to test if direct deprotonation of lactams **202** and **203** was possible. This was successfully

realised upon treatment of **202** and **203** with LDA/LiCl under our standard conditions, which gave the racemic silyl lactams **249** and **250** in 87% and 74% yields, respectively (Scheme 104).



n = 1, **202**
n = 2, **203**

n = 1, **249**, 87%
n = 2, **250**, 74%

Scheme 102

These reactions were equally successful when performed at –78 °C and gave **249** and **250** in 86% and 78% yields, respectively. Moreover these results allowed us to determine the enantiomeric excess of chiral lactams (–)-**236** and (–)-**237** and showed that there was no significant erosion of the ee from the *mono*-silylated precursors (–)-**212** and (–)-**218**.

In comparison to earlier imide results, the deprotonation of lactams **202**/**203** was straightforward and gave the silyl lactams with improved yields. The facile deprotonation might be due to the increased flexibility resulting from introduction of a methylene group in the three-carbon bridge of the bicyclic ring system thereby becoming better able to incorporate enolate character. Another reason might be the greater basicity of the nitrogen lone pair leading to improved bridgehead lithium coordination from the amide resonance form (Figure 40).

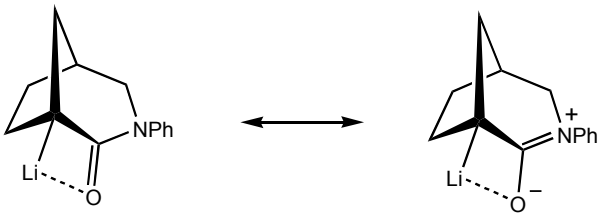
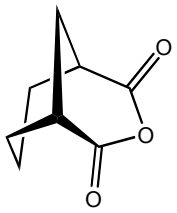


Figure 40

This contribution is also in agreement with the *ab initio* studies described earlier for the bridgehead lithiated imide **236**.

We next turned our attention to the deprotonation of anhydride **207** under our standard conditions but only observed ring opening to give the precursor diacid **216** (Figure 41).

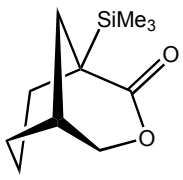


207

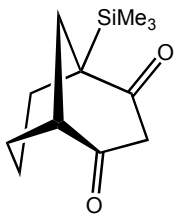
Figure 41

Deprotonation or nucleophilic attack by the base did not occur at –105 °C and it appears the aqueous work-up led to hydrolysis of the anhydride.

In regard to the other substrates illustrated in Figure 26, a senior colleague in the Simpkins group achieved the deprotonation of lactone **205** to give silyl lactone **251** in 61% yield.[15]



251



252

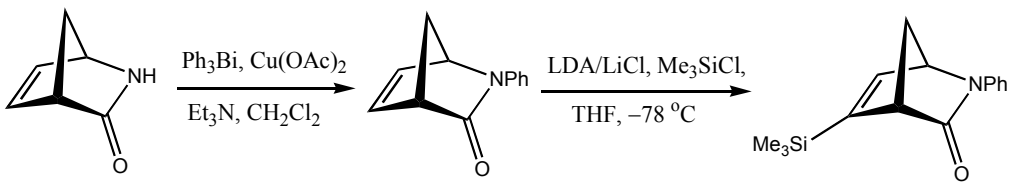
Figure 42

In conjunction with an undergraduate project we have also successfully examined the deprotonation of a bicyclic 1,3-diketone to give *mono*-silyl diketone **252** to give the bridgehead silylated product in a low 31% yield.[16] The deprotonation was achieved by using greater than 2 equivalents of base and without protection of the most acidic protons of the diketone.

3.8 Deprotonation of 2-Phenyl-2-azabicyclo[2.2.1]hept-5-en-3-one

Encouraged by the results obtained with the bicyclo[3.3.1] and [3.2.1] lactam and imide systems we turned our attention back to the bicyclo[2.2.1] system and in particular 2-azabicyclo-[2.2.1]hept-5-en-3-one **253**. Also known as Glaxo lactam, compound **253** is a valuable feedstock for the synthesis of carbocyclic nucleosides and anti-viral pharmaceuticals.[17]

Before attempting bridgehead deprotonation the lactam nitrogen was protected with a phenyl group by a modified Barton procedure developed by Chan.[18] Lactam **253** was treated with triphenylbismuth, as an electrophilic phenyl source, in the presence of copper(II)acetate and triethylamine to give *N*-Ph lactam **254** in 75% yield. Subjecting lactam **254** to LDA/LiCl in the presence of TMSCl at –78 °C did not lead to the bridgehead substituted product but the unexpected formation of the vinyl silane **255** in 86% yield (Scheme 105).



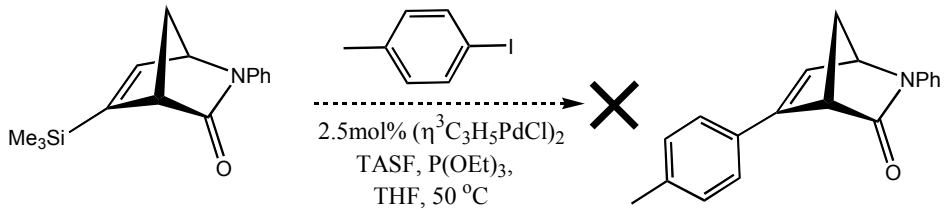
253 **254**, 75% **255**, 86%

Scheme 105

The regioselectivity of the reaction was confirmed following nOe experiments that showed significant enhancement between the trimethylsilyl protons and the bridgehead proton adjacent to the carbonyl.

Attempted formation of the corresponding vinyl stannane for palladium cross coupling chemistry by deprotonation with ISQ trimethyl or tributyltin chloride failed to produce the desired products and led only to recovered starting material. Using EQ conditions with LDA/LiCl followed by benzaldehyde, trimethyl or tributyl tin chloride gave similar results.

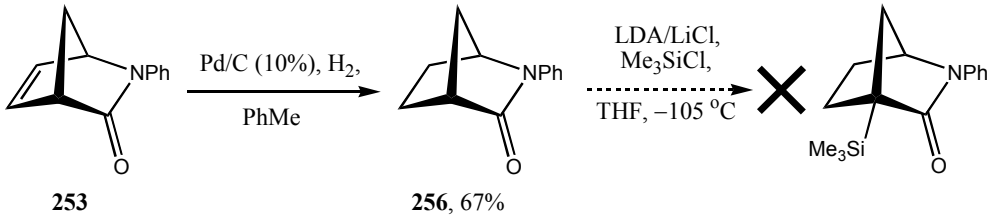
Although we could not produce any other derivatives we next investigated the further elaboration of the vinyl silane **255**. Unfortunately we discovered vinyl silane **255** was resistant to *m*CPBA[19], pivaloyl chloride/$TiCl_4$,[20] iodine,[21] and TBAT/PhCHO leading to the recovery of starting material in each case. We also attempted the palladium catalysed cross coupling with iodotoluene using Hiyama's conditions, but observed no reaction (Scheme 106).[22]



255

Scheme 106

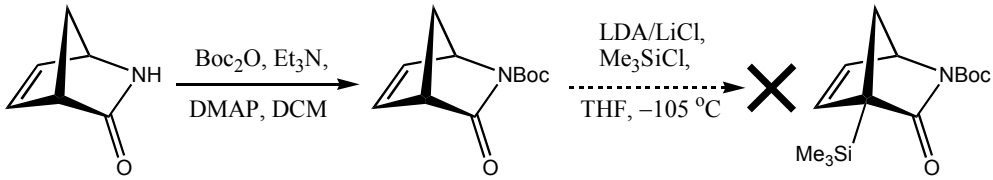
In an attempt to achieve bridgehead deprotonation we removed the double bond present in **253** by catalytic hydrogenation to give lactam **256**. However, treatment of the saturated lactam **256** with LDA/LiCl under ISQ TMSCl led only to recovery of the starting material (Scheme 107).



253 **256**, 67%

Scheme 107

Next we thought that changing the nitrogen protecting group might favourably alter the deprotonation behaviour and so lactam **253** was synthesised by a known procedure to give *N*-Boc protected lactam **257** in 92% yield (Scheme 108).[23]

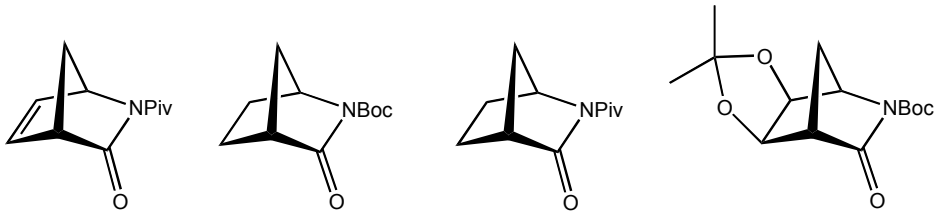


253 **257**, 92%

Scheme 108

Unfortunately, attempts to deprotonate **257** with LDA/LiCl and ISQ TMSCl gave none of the desired product.

The third protecting group we used was pivaloyl and so treatment of **253** with pivaloyl chloride and triethylamine gave lactam **258** in 74% yield. Unfortunately, lactam **258** was found to be unreactive under deprotonation conditions. Removing the double bond of both **257** and **258** by hydrogenation gave the lactams **259** and **260** both of which were susceptible to nucleophilic attack by the lithium amide base (Figure 43).



258 **259** **260** **261**

Figure 43

We also found that the protected diol lactam **261** was unreactive and attempted deprotonation under various conditions resulted in recovery of the starting material.[23]

3.9 Conclusions

We have successfully applied our standard deprotonation conditions to the enantioselective bridgehead deprotonation of imides and lactams as well as discovering novel deprotonation behaviour of lactam **253**. A significant increase in ISQ electrophile compatibility led to a variety of bridgehead substitution products with imide **201**. This promising development might allow for the asymmetric synthesis of functionally diverse products when applied to other pharmacologically active systems. Also with the effective production of double substituted products there is the potential for still greater diversity.

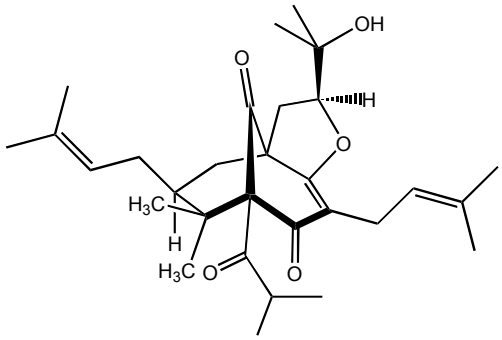
Fluoride mediated silyl exchange with TBAT was ineffective with the imides but by using cesium fluoride we observed for the first time the introduction of sulfur at the bridgehead. Instead, the silyl group was more useful achieve regioselective reduction and thionation whilst maintaining stereochemical integrity.

Given that a limited number of bicyclic substrates are presented in this thesis there remains a great many potential targets for bridgehead deprotonation. As more knowledge is gained from further studies, in particular a comprehensive investigation using *ab initio* computational calculations, then more accurate predictions and greater understanding regarding bridgehead chemistry can be gained.

The results outlined in this thesis pave the way for successful bridgehead metallation of many other types of bridged carbonyl containing compounds. Efforts to determine the scope of this chemistry are underway by others within the Simpkins group and in particular to apply the bridgehead deprotonation strategy to natural product syntheses.

3.10 Future Studies

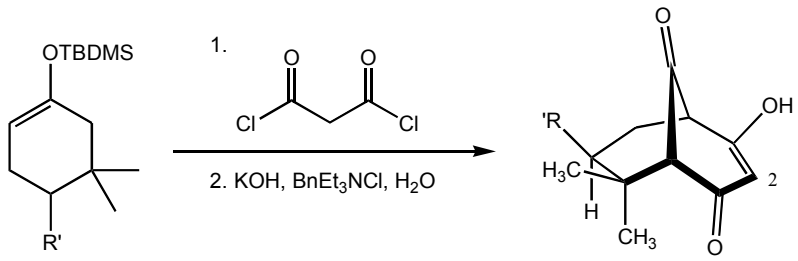
A potential application of this work is to the synthesis of Garsubellin A.[24] Garsubellin A was isolated from *Garcinia subelliptica* in 1997 and has shown promising biological activity as a choline acetyltransferase (ChAT) inducer, which is responsible for the biosynthesis of the neurotransmitter acetylcholine. Neurodegenerative diseases such as Alzheimer's have been attributed to deficiencies in acetylcholine levels and Garsubellin A was shown *in vitro* to increase ChAT activity in rat neurons by 154% at 10 μM. Garsubellin A is closely related to other structurally similar natural products including Aristophenone A, Hyperforin, Papuaforin A and Guttiferone B (Figure 44).[25]



Garsubellin A

Figure 44

Studies toward the synthesis of the bicyclic core have been reported by Shibasaki, Stoltz and Nicolaou.[26] To achieve the synthesis of Garsubellin A we could adopt the efficient approach used by Stoltz, involving the synthesis of the bicyclo[3.3.1] core **263** by a cyclisation reaction between malonyl dichloride and the enol ether of a functionalised cyclohexanone **262** (Scheme 109).[27]

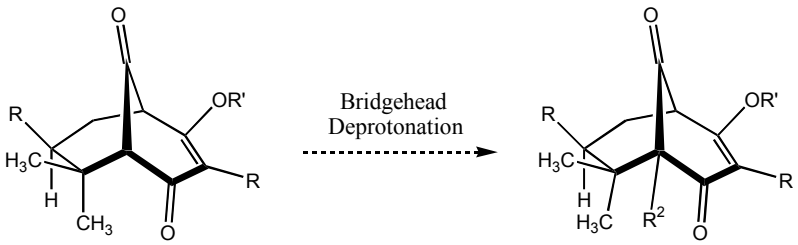


262 R' = prenyl **263**

Scheme 109

A significant limitation to this approach is that cyclisation with an enol ether containing the eventual bridgehead substituents gives poor yields (25%). Therefore we propose using a bridgehead deprotonation strategy to install the required bridgehead substituents after the cyclisation. Stoltz achieved the installation of the second prenyl group at C2 using a Claisen condensation-cross metathesis procedure. The difficulty in achieving deprotonation with an

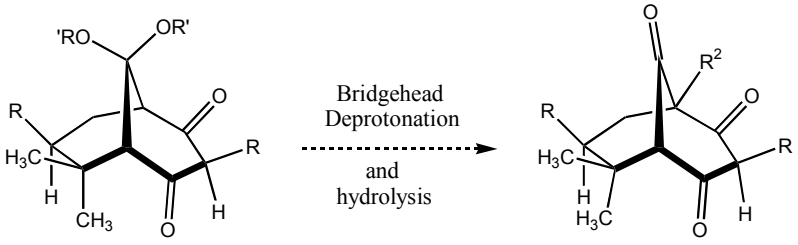
unprotected vinylogous acid would require conversion to the vinylogous ester and we could then test bridgehead deprotonation with this protected compound (Scheme 110).



R = prenyl, R' = Me

Scheme 110

Hydrolysis of the vinylogous ester might allow for subsequent introduction of the second bridgehead substituent. The difficulties associated with the vinylogous acid make it preferable to remove it altogether. This could be achieved by selective protection of the ketone in the one carbon bridge as the ketal, which in these triketone systems is known to alter the keto-enol equilibrium in favour of the ketone form.[28] In addition, the remaining acidic proton of the 1,3-diketone will need to be replaced by a suitable protecting group. After protection, we can perform selective bridgehead deprotonation by using a chiral base (Scheme 111).



R = prenyl, R' = alkyl

Scheme 111

The proposed study extends the value of the bridgehead deprotonation strategy to the synthesis of Garsubellin A and related natural products where the introduction of bridgehead functionality is difficult by other means.

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Chapter Four

Experimental Procedures

4. Experimental Procedures

General Procedures

All ^{1}H NMR and ^{13}C NMR experiments were recorded using Bruker AV400 and Bruker DRX500 NMR spectrometers. Chemical shifts are quoted in ppm and coupling constants (*J*) are quoted in Hz (s^{-1}). The 7.27 ppm resonance of residual $CHCl_3$, 77.1 ppm resonance of $CDCl_3$, 2.52 ppm resonance of DMSO and 39.5 ppm resonance of d^6-DMSO were used as internal references, respectively. The following abbreviations apply; (br) broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet, (dd) double doublet, etc. The chemical shifts of multiplets corresponding to a single proton are quoted as a point, representing the centre of the multiplet. Where the signals for two or more protons overlap, a range is quoted.

Solution infra-red spectra were recorded using a Perkin Elmer 1600 series FTIR spectrometer using chloroform as solvent unless stated otherwise. Solid infra-red spectra were recorded using a Nicolet Avatar 320 FT-IR spectrometer.

Mass spectrometry, implementing electron impact (EI), chemical ionisation and fast atom bombardment (FAB) with *meta*-nitrobenzyl alcohol as matrix, was performed using VG Micron Autospec or VG Micromass 70E spectrometers.

Elemental analysis was performed using an Exeter Analytical CE – 440.

UV experiments were recorded using Philips PU 8720 UV/vis scanning spectrophotometer.

All optical rotation experiments ($[\alpha]_D$) were recorded on a Jasco DIP-370 digital polarimeter and are quoted as 10^{-1} deg cm^2 g^{-1}. Concentration (*c*) is given in units of g/100 cm^3.

Enantiomeric excesses were determined by chiral HPLC with a Hewlett-Packard LC1100 using DAICEL chiracel-OD, OD-H and OJ columns and using HPLC grade 2-propanol and hexane as eluent.

Melting points were determined using a Stuart Scientific SMP3 melting point apparatus and are uncorrected.

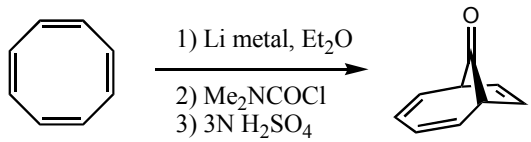
Column chromatography was performed using silica gel 60 230-400 mesh (Merck and Co.). Thin layer chromatography was conducted using pre-coated plastic backed silica gel plates (Polygram SIL G/UV_{254}) with 0.2 mm thickness, with observation by $KMnO_4$ and under UV (254 nm).

All reaction temperatures refer to values recorded by internal digital thermometer. Room temperature relates to the range 20-25 °C. A mixture of ethanol and liquid N_2 was used to obtain –105 °C whereas acetone and solid CO_2 was used to obtain –78 °C.

All reactions were performed under an atmosphere of dry nitrogen and all glass reaction flasks were dried overnight in an oven at *ca.* 120 ^oC before flame drying under flow of nitrogen. Petroleum ether (40-60 ^oC boiling fraction) was distilled before use. THF and Et_2O were distilled immediately prior to use from sodium and benzophenone. DCM was distilled from calcium hydride and stored over 4Å molecular sieves. TMSCl was distilled immediately prior to use from calcium hydride and stored over poly(4-vinylpyridine). Benzaldehyde was distilled from magnesium sulphate. All other solvents and reagents were used as received from commercial suppliers unless

stated otherwise. Compound **35** was prepared according to Antkowiak *et al.*, *J. Am. Chem. Soc.*, 1972, **94**, 5366. Compound **169** was prepared according to Itô *et al.*, *Tetrahedron Letters*, 1972, **22**, 2223. Compound **210** was prepared according to Tsanaktsidis *et al.*, *Aust. J. Chem.*, 1985, **38**, 592. Chiral amines **106** and **214** were prepared according to literature procedures as follows; chiral base **106** – C. G. Overberger, N. P. Marullo, R. G. Hiskey, *J. Am. Chem. Soc.*, 1961, **83**, 1374. M. B. Eleveld, H. Hogeveen, E. P. Schudde, *J. Org. Chem.*, 1986, **51**, 3635; chiral base **214** – K. Bambridge, N. S. Simpkins, M. J. Begley, *Tetrahedron Letters*, 1994, **35**, 3391. Bicyclic lactam 2-azabicyclo[2.2.1]hept-5-en-3-one **253** was purchased from Aldrich Chemical Co. and used as supplied. Compound **254** was prepared according to Chan, *Tetrahedron Letters*, 1996, **37**, 9013. Compound **257** was prepared according to Grieco *et al.*, *J. Org. Chem.*, 1983, **38**, 592.

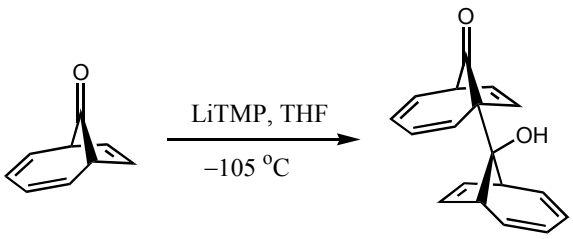
Bicyclo[4.2.1]nona-2,4,7-trien-9-one 35



148 **35**

To a flask was added dry Et_2O (200 cm^3) and shavings of lithium metal (0.80 g, 0.12 mol) under constant flow of dry N_2. The stirred mixture was cooled to –78 °C and 1,3,5,7-cyclooctatetraene **148** (5.0 g, 48 mmol) added in one portion. The reaction was stirred for 4 h at –78 °C and then allowed to warm slowly to room temperature over 3 h before leaving to stir for 14 h. The resulting mixture was dissolved by adding dry Et_2O (75 cm^3) and subsequently cooled to 0 °C before a solution of dimethylcarbamoyl chloride (2.5 cm^3, 54 mmol) in Et_2O (20 cm^3) was added dropwise over 40 min. The reaction was allowed to stir at room temperature for 4 h before being acidified with 3N sulfuric acid (48 cm^3). The organic layer was separated and the aqueous extracted further with Et_2O (3 × 50 cm^3). The combined organic extracts were dried ($MgSO_4$) and concentrated to an orange oil. Purification by vacuum distillation gave the title compound **35** as a colourless liquid (2.3 g, 59-61 °C/1 mmHg, 36%) and was stored at –25 °C where a solid formed; λ_{max} (EtOH, *c* 0.05 g/L) 207.2 (1.206), 267.2 (0.962), 275.7 (0.909), 319.0 (0.188) nm; ν_{max} (soln.)/cm^{-1} 3500, 2952, 1827, 1756 (C=O), 1588, 1381, 1287, 1147, 967, 914, 865; δ_H(400 MHz, $CDCl_3$) 3.12 (2H, dd, *J* 1.0, 7.6), 5.78-5.84 (4H, m), 5.87-5.93 (2H, m); δ_C(100 MHz, $CDCl_3$) 52.2 (CH(C=O)), 124.8 (CH), 124.9 (CH), 128.7 (CH), 214.4 (C=O). *m/z* (EI) 132.0564 (M^+, 60%). C_9H_8O requires M^+ 132.0575.

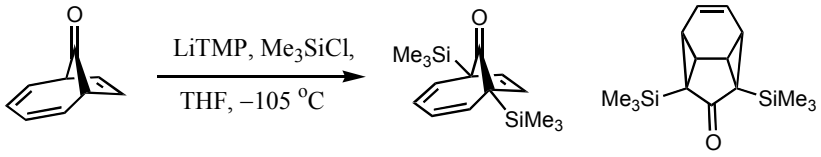
(±)-Bicyclo[4.2.1]nona-2,4,7-trien-9-one aldol dimer 36



35 **36**

A solution of LiTMP was prepared by treatment of a solution of TMP (0.30 cm^3, 2.1 mmol) in THF (5 cm^3) at –78 °C with ^{n}BuLi (1.3 cm^3, 1.47 $moldm^{-3}$ solution in hexanes, 2.0 mmol). The solution was allowed to warm to room temperature and after 10 min re-cooled to –105 °C. A solution of bicyclo[4.2.1]nona-2,4,7-trien-9-one **35** (0.132 g, 1.00 mmol) in THF (5 cm^3) was added to the base. After stirring for 1 h, D_2O (0.2 cm^3) was added to the reaction and allowed to stir for 1 h before aq. NH_4Cl (5 cm^3) and Et_2O (30 cm^3) were added. The organic extract was separated a washed with aq. NaCl (30 cm^3), dried ($MgSO_4$) and concentrated to a brown solid. Purification by flash column chromatography (15% Et_2O: petroleum ether) gave the *title compound* **36** as a white solid (86.3 mg, 66%); mp 105-107 °C (dec.); ν_{max} (soln.)/cm^{-1} 3503 (OH), 2929, 1737 (C=O), 1380, 1307, 1081, 983, 877; δ_H (400 MHz, $CDCl_3$) 2.83 (1H, dd, *J* 2.8, 7.7, C(*H*)C(OH)), 3.18 (1H, dd, *J* 1.9, 7.7, COC(*H*)), 3.34 (1H, s, OH), 3.37 (1H, dd, *J* 2.8, 7.7, C'(*H*)C(OH)), 5.15 (1H, dd, *J* 2.8, 6.1), 5.24 (1H, dd, *J* 2.8, 6.1), 5.55 (1H, d, *J* 6.9), 5.69 (1H, d, *J* 6.9), 5.81-6.25 (8H, m); *m/z* (EI) 265.1220 (MH^+, 3%), 132 (M^+–C_9H_8O, 100) 131 (M^+–C_9H_9O, 86). $C_{18}H_{16}O_2$ requires MH^+ 265.1228.

1,6-*Bis*(trimethylsilyl)bicyclo[4.2.1]nona-2,4,7-trien-9-one 149 and 1a,3b-*Bis*(trimethylsilyl)-1a,1b,3a,3b,3c,3d-hexahydro-1*H*-dicyclopropa[*cd*,*hi*]inden-1-one 150



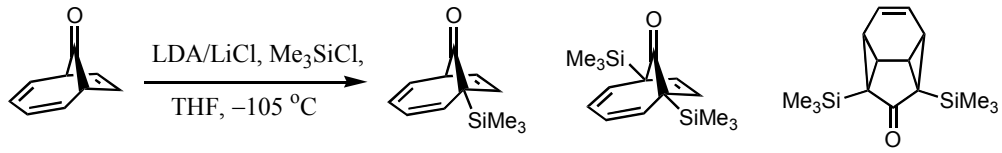
35 **149** **150**

Procedure 1. A solution of LiTMP was prepared as previously described; TMP (0.30 cm^3, 2.1 mmol), ^{n}BuLi (1.3 cm^3, 1.47 $moldm^{-3}$ solution in hexanes, 2.0 mmol) and THF (5 cm^3). The LiTMP solution was cooled to –105 °C and Me_3SiCl (1.1 cm^3, 10.0 mmol) was added followed by a solution of bicyclo[4.2.1]nona-2,4,7-trien-9-one **35** (132 mg, 1.00 mmol) in THF (5 cm^3). The reaction was allowed to warm to room temperature over 1 h and aq. NH_4Cl (5 cm^3) was added. The biphasic mixture was partitioned between Et_2O (40 cm^3) and aq. NH_4Cl (30 cm^3). The Et_2O extract was separated and washed with aq. NaCl (40 cm^3) before drying ($MgSO_4$) and concentrating to a light yellow oil. Purification by flash column chromatography (10% Et_2O: petroleum ether) gave an inseparable 1 to 4 mixture of the *title compounds* **149** and **150** as a white solid (195.3 mg, 71%). Data consistent with previously described.

Procedure 2. A solution of LDA/LiCl was prepared by flame drying LiCl (170 mg, 4.0 mmol) in a dry flask. Once the flask cooled THF (10 cm^3) and DIPA (0.59 cm^3, 4.2 mmol) were added. The flask was then cooled to –78 °C where ^{n}BuLi (2.7 cm^3, 1.49 $moldm^{-3}$ solution in hexanes, 4.0 mmol) was added before allowing the LDA/LiCl solution to warm to room temperature. After 10 min

the solution was re-cooled to −100 °C and Me_3SiCl (2.5 cm^3, 20 mmol) added followed by a solution of bicyclo[4.2.1]nona-2,4,7-trien-9-one **35** (264 mg, 2.00 mmol) in THF (10 cm^3). The reaction was stirred for 30 min at −105 °C and then allowed to warm to room temperature when aq. NH_4Cl (5 cm^3) was added. The biphasic mixture was partitioned between Et_2O (40 cm^3) and aq. NH_4Cl (30 cm^3). The Et_2O extract was separated and washed with aq. NaCl (40 cm^3) before being dried ($MgSO_4$), filtered and concentrated to a light yellow oil. Purification by flash column chromatography (10% Et_2O: petroleum ether) gave an inseparable 1 to 4 mixture of the *title compounds* **149** and **150** as a white solid (348.5 mg, 63%). Data consistent with previously described. X-ray quality crystals were obtained by slow diffusion of H_2O into an EtOH solution of **149** and **150** at room temperature.

(±)-1-(Trimethylsilyl)bicyclo[4.2.1]nona-2,4,7-trien-9-one 154, 1,6-*Bis* (trimethylsilyl)bicyclo[4.2.1]nona-2,4,7-trien-9-one 149 and 1a,3b-*Bis* (trimethylsilyl)-1a,1b,3a,3b,3c,3d-hexahydro-1*H*-bicyclopropa[*cd*,*hi*]inden -1-one 150



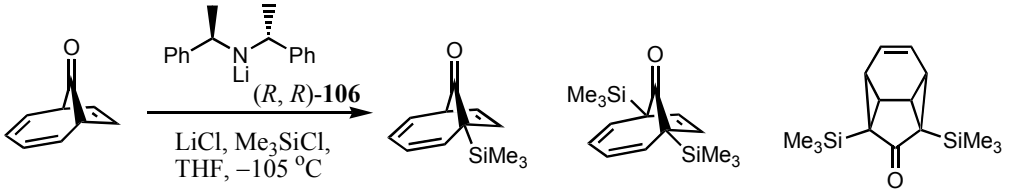
35 **154** **149** **150**

A solution of LDA/LiCl was prepared by treatment of a suspension of DIPA/HCl (151 mg, 1.10 mmol) in THF (10 cm^3) at −78 °C with ^{n}BuLi (1.6 $moldm^{-3}$ solution in hexanes; 1.37 cm^3, 2.10 mmol). The solution was allowed to warm to room temperature and after 10 min re-cooled to −105 °C. The

LDA/LiCl solution was canulated dropwise into a solution of bicyclo[4.2.1]nona-2,4,7-trien-9-one **35** (132 mg, 1.00 mmol) and Me_3SiCl (0.4 cm^3, 3 mmol) in THF (5 cm^3) at –105 °C over 25 min maintaining the internal temperature. The reaction was allowed to warm to room temperature over 3 h before quenching with aq. NH_4Cl (5 cm^3). The reaction was diluted with H_2O (10 cm^3) and Et_2O (30 cm^3). The organic extract was washed with H_2O (20 cm^3) and aq. NaCl (20 cm^3), dried ($MgSO_4$) and concentrated to give a pale yellow solid. Purification by flash column chromatography (5% Et_2O: petroleum ether) gave the *title compound* **154** as a white solid (77 mg, 38%); mp 87-89 °C; (Found: C, 70.52; H, 7.79%. $C_{12}H_{16}OSi$ requires C, 70.53; H, 7.89%); λ_{max} (EtOH, *c* 0.05 g/L) 204.5 (1.332), 267.5 (0.610), 276.9 (0.590), 325.1 (0.157) nm; ν_{max} (solid)/cm^{-1} 2951, 1732, 1250, 1243, 1151, 1060, 1031, 839, 752, 679; δ_H(400 MHz, $CDCl_3$) 0.15 (9H, s, $SiMe_3$), 3.14 (1H, dd, *J*, 2.2, 7.5), 5.62-5.66 (2H, m) 5.69-5.71 (1H, dd, *J* 2.3, 6.8) 5.84-5.97 (3H, m); δ_C(100 MHz, $CDCl_3$) –3.7 ($SiMe_3$), 51.6 (C, C1), 54.6 (CH, C6), 122.2 (=CH), 124.6 (=CH), 125.7 (=CH), 127.0 (=CH), 129.3 (=CH), 130.5 (=CH), 218.3 (C=O); *m/z* (EI) 204.0988 (M^+, 21%), 189 (M^+–CH_3, 27), 176 (M^+–C_2H_4, 17), 115 (M^+–$OSiMe_3$, 29), 73 ($SiMe_3$, 100). $C_{12}H_{16}OSi$ requires; M^+ 204.0970; and a 1 to 4 inseparable mixture of the *title compounds* **149** and **150** (47 mg, 17%); mp 82-84 °C (dec); (Found: C, 65.21; H, 8.72%. $C_{12}H_{16}OSi$ requires C, 65.19; H, 8.76%); ν_{max} (solid)/cm^{-1} 2956, 2898, 1723, 1675, 1158, 1009, 862, 840; δ_H(400 MHz, $CDCl_3$) 0.08 (18H, s, $SiMe_3$, major), 0.14 (5H, s, $SiMe_3$, minor), 2.03 (2H, m, major), 2.18 (2H, br dd, *J* 2.2, 4.8, major), 5.56 (0.6H, s, minor), 5.68 (0.6H, dd, *J* 2.9, 8.1, minor), 5.94 (0.6H, br dd, *J* 2.9, 8.1, minor), 6.30 (2H, br dd, *J* 3.3, 3.3, major); δ_C(100 MHz, $CDCl_3$) –3.5 ($SiMe_3$, minor), –2.8

($SiMe_3$, major), 25.1 (CH, major), 27.8 (CH, major), 45.5 (C, major), 54.4 (C, minor), 122.9 (=CH, major), 124.5 (=CH, minor), 125.3 (=CH, minor), 130.9 (=CH, minor), 208.4 (C=O); *m/z* (EI) 276.1368 (M^+, 8%), 261 (M^+–CH_3, 5), 203 (M^+– $SiMe_3$, 26), 73 ($SiMe_3$, 100). $C_{15}H_{24}OSi_2$ requires; M^+ 276.1365.

(–)-(1*R*,6*R*)-1-(Trimethylsilyl)bicyclo[4.2.1]nona-2,4,7-trien-9-one 154, 1,6-*Bis* (trimethylsilyl)bicyclo[4.2.1]nona-2,4,7-trien-9-one 149 and 1a,3b-*Bis*(trimethylsilyl)-1a,1b,3a,3b,3c,3d-hexahydro-1*H*-bicyclopropa[*cd*,*hi*] inden-1-one 150

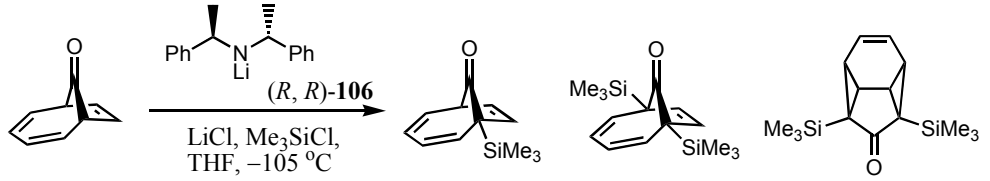


35 **(–)-154** **149** **150**

Method B. A solution of chiral lithium amide base was prepared by treatment of a suspension of the hydrochloride salt of the corresponding amine (864 mg, 3.30 mmol) in THF (15 cm^3) at −78 °C, with (1.45 $moldm^{-3}$ solution in hexanes; 4.17 cm^3, 6.15 mmol). The solution was allowed to warm to room temperature and after 10 min re-cooled to −105 °C. The chiral lithium amide base solution was canulated dropwise into a solution of bicyclo[4.2.1]nona-2,4,7-trien-9-one **35** (396 mg, 3.00 mmol), Me_3SiCl (1.2 cm^3, 9.0 mmol) in THF (30 cm^3) at −105 °C over 45 min to maintain internal temperature. The resulting solution was allowed to warm slowly to room temperature over 3 h, quenched with aq. NH_4Cl (20 cm^3) and diluted with Et_2O (50 cm^3). The two phases were separated and the organics washed with H_2O (50 cm^3) and aq. NaCl (50 cm^3), dried ($MgSO_4$) and evaporated to a pale yellow solid.

Purification by flash column chromatography (4% Et_2O: petroleum ether) gave the *title compound* (–)-**154** as a white crystalline solid (464 mg, 76%, 98%ee); $[\alpha]^{26}_D$ –182 (*c* 0.99 in $CHCl_3$); Enantiomeric excess was established by HPLC (UV detection at 205 and 215 nm) using hexane as eluent and Chiralcel OD column with a flow rate of 0.1 ml/min. Retention time of major enantiomer 67 min and minor enantiomer 61 min; and a 1 to 4 inseparable mixture of the *title compounds* **149** and **150** (63 mg, 23%). Data consistent with previously described. A similar reaction performed on 1 mmol scale at –78 °C resulted in the isolation of *title compound* (–)-**154** (46%, $[\alpha]^{19}_D$ –165 (*c* 0.5 in $CHCl_3$), 92% ee) and *title compounds* **149** and **150** (12%).

(–)-(1*R*,6*R*)-1-(Trimethylsilyl)bicyclo[4.2.1]nona-2,4,7-trien-9-one 154, 1,6-*Bis* (trimethylsilyl)bicyclo[4.2.1]nona-2,4,7-trien-9-one 149 and 1a,3b-*Bis* (trimethylsilyl)-1a,1b,3a,3b,3c,3d-hexahydro-1*H*-bicyclopropa[*cd*,*hi*]inden -1-one 150

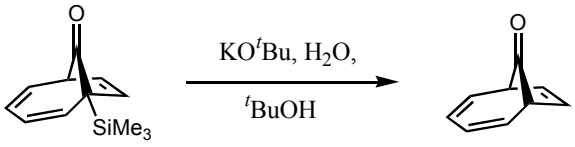


35 **(–)-154** **149** **150**

Method A. A solution of chiral lithium amide base was prepared as previously described; hydrochloride salt of amine (288 mg, 1.10 mmol), in THF (10 cm^3) with ^{n}BuLi (1.56 $moldm^{-3}$ in hexanes, 1.4 cm^3, 2.1 mmol). A solution of bicyclo[4.2.1]nona-2,4,7-trien-9-one **35** (132 mg, 1.00 mmol) and Me_3SiCl (0.4 cm^3, 3 mmol) in THF (5 cm^3) was canulated dropwise into the solution chiral lithium amide base over 25 min maintaining internal temperature. The

resulting solution was allowed to warm slowly to room temperature over 3 h, quenched with aq. NH_4Cl (5 cm^3). The reaction was diluted with H_2O (10 cm^3) and Et_2O (30 cm^3). The organic extract was washed with H_2O (20 cm^3) and aq. NaCl (20 cm^3) before drying ($MgSO_4$) and concentrating to give a yellow solid. Purification by flash column chromatography (5% Et_2O: petroleum ether) gave the *title compound* (–)-**154** as a white solid (81 mg, 40%); $[\alpha]^{21}_D$ – 186 (*c* 1.0 in $CHCl_3$); and a 1 to 4 mixture of the *title compounds* **149** and **150** (88 mg, 32%). Data consistent with previously described.

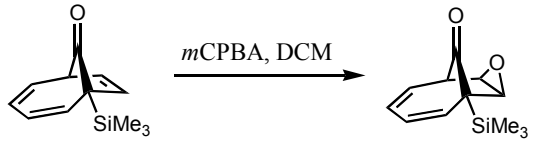
Bicyclo[4.2.1]nona-2,4,7-trien-9-one 35



(–)-**154** **35**

A solution of (–)-(1*R*,6*R*)-1-(trimethylsilyl)bicyclo[4.2.1]nona-2,4,7-trien-9-one **154** (25 mg, 0.12 mmol), KO^{t}Bu (28 mg, 0.24 mmol) and H_2O (2 drops) in ^{t}butanol was heated to reflux for 14 h. The solvent was removed and the residue partitioned between DCM (20 cm^3) and H_2O (20 cm^3). The aqueous was separated and acidified with 2N HCl before re-extracting with DCM (20 cm^3). The organic extracts were combined, dried ($MgSO_4$) and evaporated to give the title compound **35** as a yellow oil (13mg, 80%). Data consistent with previously described.

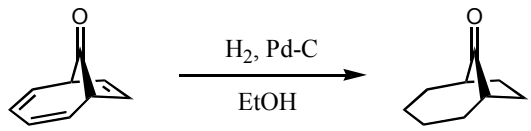
(–)-(1*R*,6*R*,7*R*,9*R*)-1-(Trimethylsilyl)-8-oxatricyclo[4.3.1.0^{7,9}]deca-2,4-dien-10-one 159



(–)-**154** (–)-**159**

To a stirred solution of (–)-(1*R*,6*R*)-1-(trimethylsilyl)bicyclo[4.2.1]nona-2,4,7-trien-9-one (–)-**154** (100 mg, 0.45 mmol, $[\alpha]^{19}_{D}$ –174 (*c* 1 in $CHCl_3$)) in DCM (10 cm^3) at room temperature was added 70% *meta*-chloroperbenzoic acid (120 mg, 0.49 mmol). The solution was stirred for 8 h and then quenched with ice cold aq. Na_2SO_3 (2 cm^3) and diluted with DCM (20 cm^3). The organic extract was separated, dried ($MgSO_4$) and concentrated to a grey solid. Purification by column chromatography (15% Et_2O: petroleum ether) gave the *title compound* (–)-**159** as a white solid (33mg, 31%); $[\alpha]^{20}_{D}$ –206 (*c* 0.42 in $CHCl_3$); mp 105-107 °C; ν_{max} (soln.)/cm^{-1} 2958, 1742 (C=O), 1374, 1135, 1076, 1024, 856, 842; δ_H(400 MHz, $CDCl_3$) 0.21 (9H, s, $SiMe_3$), 3.13 (1H, d, *J* 8.5), 3.78 (1H, d, *J* 3.5), 3.85 (1H, dd, *J* 0.6, 3.5), 5.34-5.4 (1H, m), 5.57-5.63 (1H, m), 5.84-5.92 (2H, m); δ_C(100 MHz, $CDCl_3$) –2.8 ($SiMe_3$), 50.4 (C), 54.0 (CH), 56.9 (CH), 61.6 (CH), 123.1 (=CH), 125.3 (=CH), 127.9 (=CH), 128.5 (=CH), 214.8 (C=O); *m/z* (EI) 220.0920 (M^+, 15%), 219 (M^+–H, 25), 73 ($SiMe_3$, 100). $C_{12}H_{16}O_2Si$ requires M^+ 220.0919.

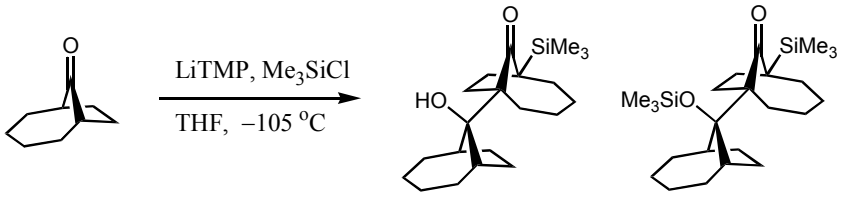
Bicyclo[4.2.1]nonan-9-one 162



35 **162**

To a solution of bicyclo[4.2.1]nona-2,4,7-trien-9-one **35** (2.24 g, 17.0 mmol) in ethanol (50 cm^3) was added 10% palladium on charcoal (0.3 g). The reaction atmosphere was evacuated and replaced with hydrogen before being stirred vigorously for 14 h. The reaction was filtered through Kieselguhr and evaporated to a yellow oil. Purification by flash column chromatography (15% Et_2O: petroleum ether) gave the *title compound* **162** as a colourless oily solid (1.75 g, 75%); ν_{max} (solid)/cm^{-1} 2926, 2858, 1733 (C=O), 1454, 840, 753; δ_H(400 MHz, $CDCl_3$) 1.36-1.42 (2H, m), 1.44-1.54 (2H, m), 1.67-1.79 (6H, m), 2.11-2.18 (2H, m), 2.44-2.48 (2H, m); δ_C(100 MHz, $CDCl_3$) 24.8 (CH_2), 26.6 (CH_2), 30.5 (CH_2), 45.7 (CH), 222.9 (C=O); *m/z* (EI) 138.1039 (M^+, 63%), 82 (84), 67 (100). $C_9H_{14}O$ requires M^+ 138.1044.

Trimethylsilyl bicyclo[4.2.1]nonan-9-one aldol condensation product 163 and *Bis* Trimethylsilyl bicyclo[4.2.1]nonan-9-one aldol condensation product 164

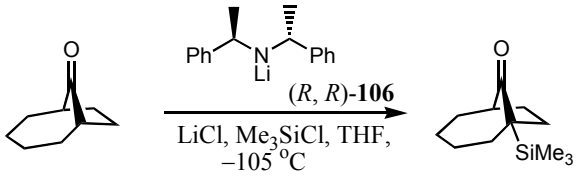


162 **163** **164**

A solution of LiTMP was prepared as previously described; TMP (0.30 cm^3, 2.1 mmol), ^{n}BuLi (1.49 $moldm^{-3}$, 1.3 cm^3, 2.0 mmol) and THF (5 cm^3). The LiTMP solution was cooled to –105 °C and Me_3SiCl (1.1 cm^3, 10 mmol) was added followed by a solution of bicyclo[4.2.1]nonan-9-one **162** (138 mg, 1.00 mmol) in THF (5 cm^3). The reaction was allowed to warm to room temperature when aq. NH_4Cl (5 cm^3) was added. The reaction was diluted with Et_2O (40 cm^3) and aq. NH_4Cl (30 cm^3). The organic extract was extracted with aq. NaCl (40 cm^3) before being dried ($MgSO_4$) and concentrated to a colourless oil. Purification by flash column chromatography (5% Et_2O: petroleum ether) gave *title mono silane* **163** as a white solid (66 mg, 38%); mp 175-177 °C; (Found: C, 72.50; H, 10.28%. $C_{21}H_{36}O_2Si$ requires C, 72.36; H, 10.41%); ν_{max} (soln.)/cm^{-1} 3461 (OH), 2917, 2859, 1686 (C=O), 1453, 1129, 1075; δ_H(400 MHz, $CDCl_3$) 0.08 (9H, s, $SiMe_3$), 0.96 (1H, ddd, *J* 2.5, 13.0, 13.0), 1.13 (1H, m), 1.26-2.01 (21H, m), 2.23 (1H, dddd, *J* 4.0, 4.0, 4.0, 4.0), 2.47 (1H, ddd, *J* 2.5, 5.9, 13.0), 4.69 (1H, s, OH); δ_C(100 MHz, $CDCl_3$) –2.8 ($SiMe_3$), 23.1 (CH_2), 24.2 (CH_2), 25.9 (CH_2), 26.1 (CH_2), 27.8 (CH_2), 28.2 (CH_2), 31.0 (CH_2), 31.8 (CH_2), 32.0 (CH_2), 32.3 (CH_2), 32.8 (CH_2), 33.0 (CH_2), 42.8 (CH), 44.4 (CH), 44.6 (C), 61.9 (C), 89.0 (C), 228.5 (C=O); *m/z* (EI) 348.2444 (M^+,

14%), 275 (M^+–$SiMe_3$, 2), 210 (M^+–$C_9H_{14}O$, 50), 137 (M^+–$C_{12}H_{13}OSi$, 14), 73 ($SiMe_3$, 100). $C_{21}H_{36}O_2Si$ requires M^+ 348.2484; and impure *title bis silane* **164** as an oil (114 mg). *Title bis silane* **164** was treated with *p*TsOH in refluxing THF for 16 h to give *title mono silane* **163** (21 mg, 12%). Overall yield of *title mono silane* **163** (87 mg, 50%).

(–)-(1*R*,6*R*)-1-(Trimethylsilyl)bicyclo[4.2.1]nonan-9-one 165

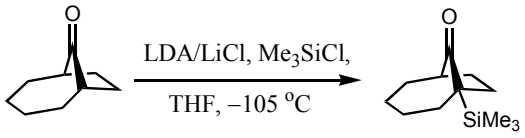


162 (–)-**165**

A solution of chiral lithium amide base was prepared as previously described; hydrochloride salt of amine (288 mg, 1.10 mmol), in THF (10 cm^3) with ^{n}BuLi (1.6 $moldm^{-3}$ solution in hexanes; 1.3 cm^3, 2.1 mmol). The chiral lithium amide base solution was canulated dropwise into a solution of bicyclo[4.2.1]nonan-9-one **162** (138 mg, 1.00 mmol), Me_3SiCl (0.4 cm^3, 3 mmol) in THF (5 cm^3) at −105 °C to maintain internal temperature. The resulting solution was allowed to warm slowly to room temperature over 1 h, quenched with aq. NH_4Cl (10 cm^3) and diluted with Et_2O (30 cm^3). The two phases were separated and the organics washed with H_2O (10 cm^3) and aq. NaCl (10 cm^3), dried ($MgSO_4$) and evaporated to a yellow oil. Purification by flash column chromatography (5% Et_2O: petroleum) gave the *title compound* (–)-**165** as a colourless oil (168 mg, 78%); $[\alpha]^{22}_D$ −126 (*c* 1 in $CHCl_3$); (Found: C, 68.52; H, 10.53%. $C_{12}H_{22}NOSi$ requires C 68.52; H, 10.55%); ν_{max} (soln.)/cm^{-1} 2929, 2860, 1707, 1453, 1309, 1101, 976, 865, 839; δ_H(400 MHz,

$CDCl_3$) 1.27-1.37 (2H, m) 1.45-1.59 (2H, m), 1.64-1.97 (7H, m), 2.12 (1H, m), 2.48 (1H, m); δ_C(100 MHz, $CDCl_3$) –3.5 ($SiMe_3$), 24.9 (CH_2), 26.2 (CH_2), 27.0 (CH_2), 30.2 (CH_2), 30.7 (CH_2), 32.3 (CH_2), 42.4 (C), 48.3 (CH, C5), 224.1 (C=O); *m/z* (EI) 210.1445 (M^+, 41), 195 (M^+–CH_3, 26), 181 (M^+–C_2H_5, 87), 73 ($SiMe_3$, 100). $C_{12}H_{22}OSi$ requires M^+ 210.1439. Enantiomeric excess was established by HPLC (UV detection at 205 and 215 nm) using 1.25 % IPA: hexane as eluent and Chiralcel OJ column with a flow rate of 1 ml/min. Retention time of major enantiomer 3.2 min and minor enantiomer 2.9 min.

(±)-1-(Trimethylsilyl)bicyclo[4.2.1]nonan-9-one 165

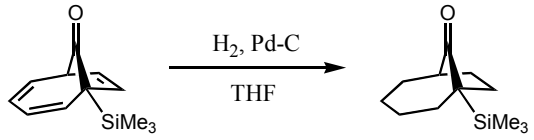


162 **165**

A solution of LDA/LiCl was prepared as previously described; DIPA/HCl (151 mg, 1.10 mmol), ^{n}BuLi (1.6 moldm^{-3} solution in hexanes, 1.3 cm^3 2.1 mmol) and THF (10 cm^3). The solution of LDA/LiCl was canulated dropwise into bicyclo[4.2.1]nonan-9-one **162** (138 mg, 1.00 mmol), Me_3SiCl (0.4 cm^3, 3 mmol) in THF (5 cm^3) at –105 °C to maintain internal temperature. The reaction was allowed to warm to room temperature before aq. NH_4Cl (5 cm^3) was added. The reaction was diluted with H_2O (10 cm^3) and Et_2O (30 cm^3). The organic layer was separated, washed with H_2O (20 cm^3) and aq. NaCl (20 cm^3), dried ($MgSO_4$) and concentrated to give a pale yellow solid. Purification by flash column chromatography (5% Et_2O: petroleum ether) gave the *title*

compound **165** (130 mg, 62%) as a colourless oil. Data consistent with previously described.

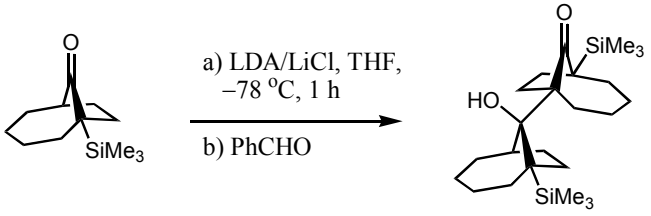
(–)-(1*R*,6*R*)-1-(Trimethylsilyl)bicyclo[4.2.1]nonan-9-one 165



(–)-**154** (–)-**165**

To a solution of (–)-(1*R*,6*R*)-1-(trimethylsilyl)bicyclo[4.2.1]nona-2,4,7-trien-9-one (–)-**154** (21 mg, 0.10 mmol, $[\alpha]^{21}_{D}$ –186) in THF (3 cm^3) was added 10% palladium on charcoal (2 mg). The reaction atmosphere was evacuated and replaced with hydrogen before being stirred vigorously for 14 h. The reaction was filtered through Kieselguhr and evaporated to a yellow oil. Purification by flash column chromatography (5% Et_2O: petroleum ether) gave the *title compound* (–)-**165** as a colourless oil (9.8 mg, 45%); $[\alpha]^{20}_{D}$ –131 (*c* 0.49 in $CHCl_3$). Data consistent with previously described.

(–)-*Bis*-trimethylsilyl bicyclo[4.2.1]nonan-9-one dimer 166

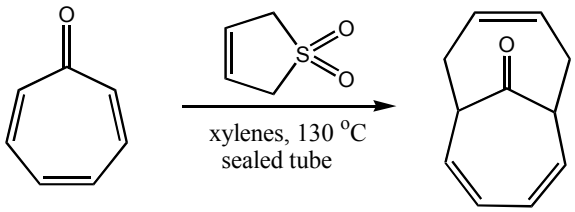


(–)-**165** (–)-**166**

A solution of LDA/LiCl was prepared as previously described; DIPA/HCl (151 mg, 1.10 mmol), ^{n}BuLi (1.6 $moldm^{-3}$ in hexanes, 1.37 cm^3, 2.10 mmol) in THF

(7.5 cm^3). The LDA/LiCl was canulated into a solution of (–)-(1*R*,6*R*)-1-(trimethylsilyl)bicyclo[4.2.1]nonan-9-one (–)-**165** (210 mg, 1.00 mmol, $[\alpha]^{20}_D$ –121 (*c* 1 in $CHCl_3$)) in THF (7.5 cm^3) at –78 °C. After 1 h, benzaldehyde (0.3 cm^3, 3 mmol) was added and the reaction allowed to warm to room temperature over 3 h. The reaction was quenched with aq. NH_4Cl (10 cm^3) and diluted with Et_2O (15 cm^3). The organic extract was dried ($MgSO_4$) and concentrated to a yellow oil. Purification by flash column chromatography (10% Et_2O: petroleum ether) gave the *title compound* (–)-**166** as a white solid (90 mg, 43%); mp 205-207 °C; $[\alpha]^{20}_D$ –171 (*c* 0.5 in $CHCl_3$); (Found: C, 68.38; H, 10.54%. $C_{24}H_{44}O_2Si_2$ requires C, 68.52; H, 10.55%); ν_{max} (soln.)/cm^{-1} 3454 (OH), 2945, 2860, 1682 (C=O), 1454, 1366, 1311, 1130, 1074, 981, 888, 876, 840; δ_H(400 MHz, $CDCl_3$) 0.07 (9H, s), 0.14 (9H, s), 1.10-1.40 (4H, m), 1.42-2.04 (20H, m), 2.44 (1H, m), 4.76 (1H, s, OH); δ_C(100 MHz, $CDCl_3$) –3.0 ($SiMe_3$), 1.1 ($SiMe_3$), 24.0 (CH_2), 25.6 (CH_2), 26.0 (CH_2), 26.1 (CH_2), 27.5 (CH_2), 29.8 (CH_2), 30.1 (CH_2), 31.6 (CH_2), 32.2 (CH_2), 32.8 (CH_2), 33.6 (CH_2), 41.4 (C), 44.2 (C), 48.3 (CH), 64.2 (C), 92.3 (C), 227.6 (C=O); *m/z* (EI) 420.2882 (M^+, 6%), 347 (M^+–$SiMe_3$, 20), 210 (M^+–$C_{12}H_{22}OSi$, 25), 73 ($SiMe_3$, 100). $C_{24}H_{44}O_2Si_2$ requires M^+ 420.2879.

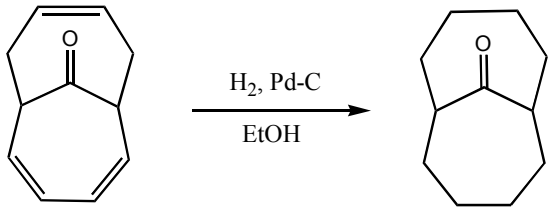
Bicyclo[4.4.1]undeca-2,4,8-trien-11-one 169



171 **169**

A pressure resistant sealed tube was charged with tropone **171** (5.0 g, 47 mmol), butadiene sulfone (51 g, 0.43 mol) and xylenes (60 cm^3). The tube was sealed and heated to 130 °C for 7 days behind a blast shield. The reaction was allowed to cooled and opened (CAUTION! Rapid release of dissolved SO_2) before partitioning between H_2O (60 cm^3) and EtOAc (60 cm^3). The organic layer was separated, dried ($MgSO_4$), filtered and concentrated to a brown oil. Purification by flash column chromatography (30% DCM: petroleum ether) gave the *title compound* **169** as a light yellow oil (4.32 g, 58%). Stored at –25 °C; ν_{max} (soln.)/cm^{-1} 3682, 2938, 2904, 2399, 1704 (C=O), 1446, 1346, 1069, 870; δ_H(400 MHz, $CDCl_3$) 2.38-2.45 (2H, m), 2.52-2.59 (2H, m), 3.51-3.56 (2H, m), 5.61-5.67 (2H, m), 5.72-5.79 (2H, m), 5.98-6.03 (2H, m); *m/z* (EI) 160.0883 (M^+, 16%), 132 (M^+ –CO, 13), 78 (C_6H_6, 100). $C_{11}H_{12}O$ requires M^+ 160.0888.

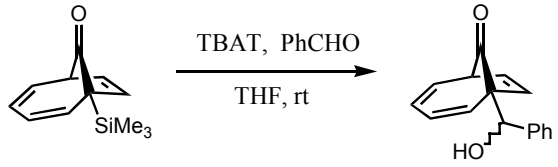
Bicyclo[4.4.1]undecan-11-one 170



169 **170**

To a solution of bicyclo[4.4.1]undecan-11-one **169** (2.0 g, 13 mmol) in ethanol (40 cm^3) was added 10% palladium on charcoal (0.13 g). The reaction atmosphere was evacuated and replaced with hydrogen before being vigorously stirred overnight. The reaction was filtered through Kieselguhr and then evaporated to give a light yellow oil. Purification by flash column chromatography (15% Et_2O: petroleum ether) gave the *title compound* **170** (1.36 g, 66%) as colourless oily solid; (Found: C, 79.67; H, 11.19%. $C_{11}H_{18}O$ requires C, 79.45; H 10.92%); ν_{max} (soln.)/cm^{-1} 2904, 2854, 1681 (C=O), 1452, 1358, 1345, 1294, 1133, 1047, 964; δ_H(400 MHz, $CDCl_3$) 1.39–1.45 (4H, m), 1.56–1.64 (4H, m), 1.75–1.84 (8H, m), 2.73–2.77 (2H, m); δ_C(67.8 MHz, $CDCl_3$) 26.3 (CH_2), 28.3 (CH_2), 54.8 (CH), 219.8 (C=O); *m/z* (EI) 166.1359 (M^+, 90%), 138 (M^+–CO, 21), 67 (C_5H_7, 100). $C_{11}H_{18}O$ requires M^+ 166.1357.

(–)-(1*S*,6*R*)-1-[(*R*)-Hydroxy(phenyl)methyl]bicyclo[4.2.1]nona-2,4,7-trien-9-one and (–)-(1*S*,6*R*)-1-[(*S*)-Hydroxy(phenyl)methyl]bicyclo[4.2.1]nona-2,4,7-trien-9-one 182ab

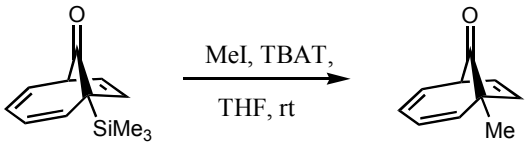


(–)-**154** (–)-**182ab**

A solution of TBAT (270 mg, 0.50 mmol) in THF (3 cm^3) was added to a solution of (–)-(1*S*,6*R*)-1-(trimethylsilyl)bicyclo[4.2.1]nona-2,4,7-trien-9-one (–)-**154** (102 mg, 0.500 mmol, $[\alpha]^{19}_D$ –174) and benzaldehyde (0.26 cm^3, 2.5 mmol) in THF (5 cm^3). The reaction was allowed to stir for 24 h before diluting with Et_2O (10 cm^3) and H_2O (10 cm^3). The organic extract was washed with aq. NaCl (10 cm^3) before being dried ($MgSO_4$) and concentrated to give a yellow oil. Purification by flash column chromatography (30% Et_2O: petroleum ether) gave the *title compound* **182a** as a white solid (51 mg, 43%); mp 122-124 °C; $[\alpha]^{25}_D$ –84 (*c* 0.5 in $CHCl_3$); ν_{max} (soln.)/cm^{-1} 3605, 3521, 2952, 2879, 1740, 1602, 1453, 1400, 1327, 1119, 1042, 1026, 949, 893, 873; δ_H(400 MHz, $CDCl_3$) 3.27 (1H, dd, *J* 2.3, 8.2), 3.68 (1H, d, *J* 1.9), 5.04 (1H, d, *J* 1.6), 5.51 (1H, dd, *J* 0.9, 6.9), 5.65 (1H, dd, *J* 2.3, 6.9), 5.80–5.86 (1H, m), 5.90–6.05 (3H, m), 7.30–7.46 (5H, m); δ_C(100 MHz, $CDCl_3$) 53.5 (CH), 61.8 (C), 73.9 (CHOH), 121.6 (CH), 124.6 (CH), 125.0 (CH), 126.4 (CH), 127.2 (CH), 127.4 (CH), 127.8 (CH), 128.0 (CH), 128.1 (CH), 128.1 (CH), 130.0 (CH), 138.9 (CH), 218.5 (C=O); *m/z* (EI) 238.1001 (M^+, 44%), 199 (100), 131 (C_9H_7O, 38), 105 (C_7H_5O, 65). $C_{16}H_{14}O_2$ requires M^+ 238.0993; and *title*

compound **182b** as a white solid (35 mg, 29%); $[\alpha]^{25}_{D}$ –170 (*c* 0.5 in $CHCl_3$); δ_H(400 MHz, $CDCl_3$) 3.28 (1H, dd, *J* 2.6, 8.2), 5.13 (1H, s), 5.64–5.70 (2H, m), 5.77 (1H, dd, *J* 0.6, 7.0), 5.84–5.99 (3H, m), 7.32–7.44 (5H, m); δ_C(100 MHz, $CDCl_3$) 53.4 (CH), 63.2 (C), 74.5 (CHOH), 121.7 (CH), 124.4 (CH), 124.6 (CH), 125.6 (CH), 127.5 (CH), 128.1 (CH), 128.3 (CH), 128.5 (CH), 128.9 (CH), 130.2 (CH), 131.9 (CH), 140.0 (CH), 217.2 (C=O); *m/z* (EI) 238.0998 (M^+, 42%), 131 (C_9H_7O, 44), 105 (C_7H_5O, 100). $C_{16}H_{14}O_2$ requires M^+ 238.0993. No erosion in ee from the starting silane (–)-**154** was established by HPLC (UV detection at 215 nm) using heptane as eluent and Chiralcel OD-H column with a flow rate of 1 ml/min. Retention time of major diastereoisomer 5.5 min and minor diastereoisomer 6.3 min.

(–)-(1*S*,6*R*)-1-Methylbicyclo[4.2.1]nona-2,4,7-trien-9-one 183

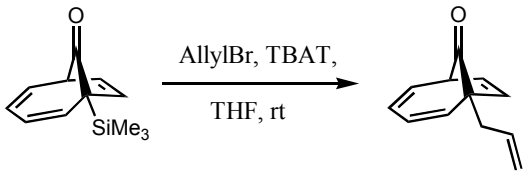


(–)-**154** (–)-**183**

A solution of tetrabutylammonium triphenyldifluorosilicate (TBAT) (291 mg, 0.538 mmol) in THF (3 cm^3) was added to a solution of (–)-(1*S*,6*R*)-1-(trimethylsilyl)bicyclo[4.2.1]nona-2,4,7-trien-9-one (–)-**154** (100 mg, 0.5 mmol, $[\alpha]^{19}_{D}$ –180) and methyl iodide (0.30 cm^3, 4.9 mmol) in THF (5 cm^3). The reaction was allowed to stir for 24 h before diluting with Et_2O (10 cm^3) and H_2O (10 cm^3). The organic extract was washed with aq. NaCl (10 cm^3) before being dried ($MgSO_4$) and concentrated to give a yellow oil. Purification by flash column chromatography (10% Et_2O: petroleum ether) gave the *title*

compound (–)-**183** as a colourless liquid (35 mg, 49%); $[\alpha]^{21}_{D}$ –19 (*c* 0.27 in $CHCl_3$); (Found: C, 81.89; H, 6.92%. $C_{10}H_{10}O$ requires C, 82.15; H, 6.90%); ν_{max} ($CDCl_3$ soln.)/cm^{-1} 3035, 2971, 2931, 2874, 1754, 1586, 1451, 1280, 1260, 1195, 1119, 1052, 837, 809; δ_H(400 MHz, $CDCl_3$) 1.24 (3H, s, CH_3), 3.18 (1H, dd, *J* 2.4, 8.2, 6-H), 5.50 (1H, m), 5.65 (1H, dd, *J* 2.4, 6.8), 5.71 (1H, dd, *J* 0.6, 6.8), 5.81-5.88 (2H, m), 5.92 (1H, m); δ_C(100 MHz, $CDCl_3$) 17.8 (CH_3, C1'), 52.7 (CH, C6), 53.7 (C, C1), 120.7 (CH), 123.4 (CH), 124.7 (CH), 129.1 (CH), 130.9 (CH), 135.9 (CH), 216.0 (C=O, C9); *m/z* (EI) 146.0728 (M^+, 75%), 131 (M^+–CH_3, 82) 117 (C_9H_9, 100), 103 (C_8H_7, 52). $C_{10}H_{10}O$ requires M^+ 146.0731.

(–)-(1*S*,6*R*)-1-Allylbicyclo[4.2.1]nona-2,4,7-trien-9-one 184

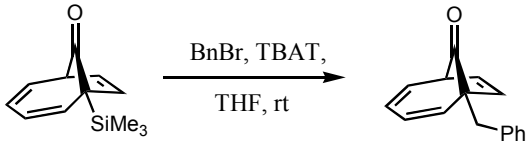


(–)-**154** (–)-**184**

A solution of TBAT (291 mg, 0.538 mmol) in THF (3 cm^3) was added to a solution of (–)-(1*S*,6*R*)-1-(trimethylsilyl)bicyclo[4.2.1]nona-2,4,7-trien-9-one (–)-**154** (100 mg, 0.5 mmol, $[\alpha]^{19}_{D}$ –180) and allyl bromide (0.42 cm^3, 4.9 mmol) in THF (5 cm^3). The reaction was allowed to stir for 24 h before diluting with Et_2O (10 cm^3) and H_2O (10 cm^3). The organic extract was washed with aq. NaCl (10 cm^3) before being dried ($MgSO_4$) and concentrated to give a yellow oil. Purification by flash column chromatography (10% Et_2O: petroleum ether) gave the *title compound* (–)-**184** as a colourless liquid (33 mg, 39%); $[\alpha]^{21}_{D}$ –94 (*c* 0.29 in $CHCl_3$); (Found: C, 83.41; H, 7.24%. $C_{12}H_{12}O$

requires C, 83.68; H, 7.03%); ν_{max} ($CDCl_3$ soln.)/cm^{-1} 3079, 3035, 2950, 1754, 1641, 1602, 1434, 1415, 1270, 1252, 1182, 1119, 1056, 1017, 992, 840, 822; δ_H(400 MHz, $CDCl_3$) 2.40 (1H, br dd, *J* 7.7, 14.1), 2.50 (1H, dddd, *J* 1.2, 1.2, 6.8, 14.1), 3.20 (1H, dd, *J* 2.2, 7.9), 5.09-5.19 (2H, m), 5.56 (1H, d, *J* 11.3), 5.68-5.80 (2H, m), 5.82-5.95 (3H, m); δ_C(100 MHz, $CDCl_3$) 35.9 (CH_2, C1'), 53.0 (CH, C6), 57.2 (c, C1), 118.7 (CH_2, C3'), 121.3 (CH), 123.6 (CH), 124.6 (CH), 128.8 (CH, C2'), 129.2 (CH), 133.3 (CH), 133.9 (CH), 215.3 (C=O, C9); *m/z* (EI) 172.0882 (M^+, 57%), 117 (C_9H_9, 25), 103 (C_8H_7, 100). $C_{12}H_{12}O$ requires M^+ 172.0888.

(–)-(1*S*,6*R*)-1-Benzylbicyclo[4.2.1]nona-2,4,7-trien-9-one 185

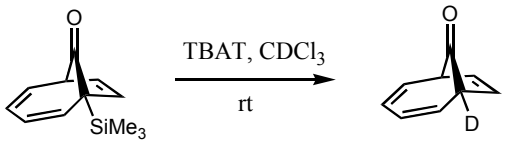


(–)-**154** (–)-**185**

A solution of TBAT (291 mg, 0.538 mmol) in THF (3 cm^3) was added to a solution of (–)-(1*S*,6*R*)-1-(trimethylsilyl)bicyclo[4.2.1]nona-2,4,7-trien-9-one (–)-**154** (100 mg, 0.5 mmol, $[\alpha]^{19}_D$ –180) and benzyl bromide (0.58 cm^3, 4.9 mmol) in THF (5 cm^3). The reaction was allowed to stir for 24 h before diluting with Et_2O (10 cm^3) and H_2O (10 cm^3). The organic extract was washed with aq. NaCl (10 cm^3) before being dried ($MgSO_4$) and concentrated to give a colourless oil. Purification by flash column chromatography (10% Et_2O: petroleum ether) gave the *title compound* (–)-**185** as a white solid (45 mg, 41%); mp 101-103 °C; $[\alpha]^{20}_D$ –194 (*c* 0.23 in $CHCl_3$); ν_{max} ($CDCl_3$ soln.)/cm^{-1} 3064, 3032, 2945, 1757, 1604, 1496, 1453, 1436, 1277, 1262, 1176, 1121,

1074, 1030, 832; δ_H(400 MHz, $CDCl_3$) 2.94 (1H, d, *J* 13.7, 1-H'), 3.13-3.19 (2H, m, 1-H' & 6-H), 5.58 (1H, dd, *J* 2.5, 6.9), 5.65 (1H, br d, *J* 11.6), 5.75 (1H, dd, *J* 0.8, 6.9), 5.83-5.98 (3H, m), 7.21-7.26 (3H, m), 7.27-7.32 (2H, m); δ_C(100 MHz, $CDCl_3$) 37.5 (CH_2, C1'), 52.9 (CH, C6), 58.7 (C, C1), 120.5 (CH), 123.5 (CH), 124.6 (CH), 126.6 (CH), 128.2 (CH, Ar), 128.3 (CH, Ar), 129.3 (CH), 130.5 (CH × 2, Ar), 134.1 (CH), 137.1 (C, Ar), 215.4 (C=O). *m/z* (EI) 222.1034 (M^+, 31%), 131 (M^+–C_7H_7, 100), 117 (C_9H_9, 25), 103 (C_8H_7, 76). $C_{16}H_{14}O$ requires M^+ 222.1044.

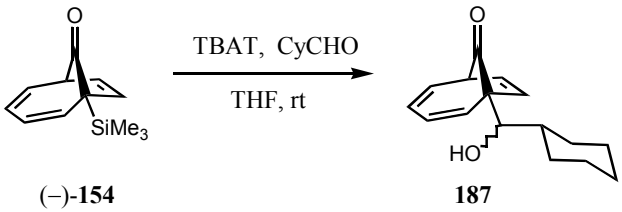
(–)-(1*S*,6*R*)-1-Deuterobicyclo[4.2.1]nona-2,4,7-trien-9-one 186



(–)-**154** **186**

A solution of tetrabutylammonium triphenyldifluorosilicate (TBAT) (146 mg, 0.270 mmol) in $CDCl_3$ (2 cm^3) was added to a solution of (–)-(1*S*,6*R*)-1-(trimethylsilyl)bicyclo[4.2.1]nona-2,4,7-trien-9-one (–)-**154** (53 mg, 0.26 mmol, $[\alpha]^{24}_D$ –166) in $CDCl_3$ (2 cm^3). The reaction was allowed to stir for 24 h before diluting with Et_2O (5 cm^3) and H_2O (5 cm^3). The organic extract was washed with aq. NaCl (5 cm^3), dried ($MgSO_4$) and concentrated to give a yellow oil. Purification by flash column chromatography (10% Et_2O: petroleum ether) gave the *title compound* **186** as a colourless liquid (10.6 mg, 32%); δ_H(400 MHz, $CDCl_3$) 3.12 (0.9H, dd, *J* 1.0, 7.6), 5.78-5.84 (4H, m), 5.87-5.93 (2H, m); ^{1}H NMR shows reduced integral intensity (0.9H) indicating 54% D insertion.

(–)-(1*S*,6*R*)-1-[(*R*/*S*)-Cyclohexyl(hydroxy)methyl]bicyclo[4.2.1]nona-2,4,7-trien-9-one 187

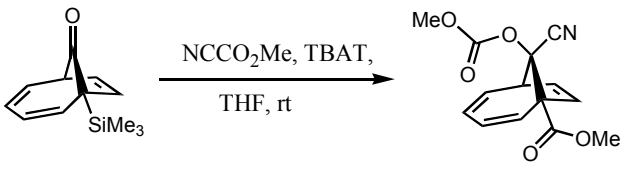


(–)-**154** **187**

A solution of TBAT (291 mg, 0.538 mmol) in THF (1 cm^3) was added to a solution of (–)-(1*S*,6*R*)-1-(trimethylsilyl)bicyclo[4.2.1]nona-2,4,7-trien-9-one (–)-**154** (50 mg, 0.25 mmol, $[\alpha]^{24}_D$ –166) and cyclohexanecarboxaldehyde (0.30 cm^3, 2.5 mmol) in THF (1 cm^3). The reaction was allowed to stir for 24 h before diluting with Et_2O (10 cm^3) and H_2O (10 cm^3). The organic extract was washed with aq. NaCl (10 cm^3) before being dried ($MgSO_4$) and concentrated to give a colourless oil. Purification by flash column chromatography (10% Et_2O: petroleum ether) gave an inseparable 4 to 1 mixture of the *title compounds* **187** as a colourless oil (47 mg, 78%) contaminated with inseparable cyclohexane carboxaldehyde; ν_{max} (soln.)/cm^{-1} 2932, 2855, 1745, 1703, 1601, 1451, 1312, 1118, 867; δ_H(400 MHz, $CDCl_3$) 1.10-1.69 (18H, m), 1.71-1.81 (4.7H, m), 1.87-1.98 (2.7H, m), 3.24 (1H, dd, *J* 2.3, 8.2), 3.29 (0.25H, d, *J* 8.2), 3.73 (1H, d, *J* 5.0), 3.78 (0.25H, br d, *J* 3.5), 5.64 (0.5H, d, *J* 0.9), 5.74 (1H, dd, *J* 2.3, 6.7), 5.78 (1H, dd, *J* 0.9, 7.0), 5.76-5.80 (4H, m), 6.11 (1H, m); δ_C(100 MHz, $CDCl_3$) 25.4 (CH_2), 25.8 (CH_2), 26.3 (CH_2), 26.5 (CH_2), 28.2 (CH_2), 28.9 (CH_2), 31.4 (CH_2), 41.3 (CH), 42.8 (CH), 53.3 (CH, C6), 62.4 (C, C1), 75.2 (CHOH, major), 79.8 (CHOH, minor), 121.7 (CH), 123.9 (CH), 124.7 (CH), 125.7 (CH), 128.4 (CH), 132.5 (CH), 217.9; *m/z* (EI) 244.1456

(M^+, 10%), 226 (M^+–H_2O, 7), 131 (M^+–$C_7H_{13}O$, 24), 117 (C_9H_9, 7), 103 (C_8H_7, 13), 82 (100). $C_{16}H_{20}O_2$ requires M^+ 244.1463.

(–)-Methyl (1*R*,6*R*,9*R*)-9-cyano-9-[(methoxycarbonyl)oxy]bicyclo[4.2.1] nona-2,4,7-triene-1-carboxylate 188

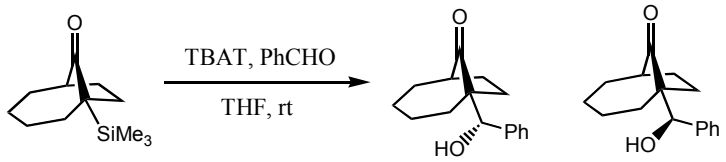


(–)-**154** (–) **188**

A solution of TBAT (146 mg, 0.280 mmol) in THF (2 cm^3) was added to a solution of (–)-(1*S*,6*R*)-1-(trimethylsilyl)bicyclo[4.2.1]nona-2,4,7-trien-9-one (–)-**154** (53 mg, 0.26 mmol, $[\alpha]^{24}_D$ –166) and methyl cyanoformate (0.10 cm^3, 1.3 mmol) in THF (2 cm^3). The reaction was allowed to stir for 24 h before diluting with Et_2O (10 cm^3) and H_2O (10 cm^3). The organic extract was washed with aq. NaCl (10 cm^3) before being dried ($MgSO_4$) and concentrated to give a yellow oil. Purification by flash column chromatography (20% Et_2O: petroleum ether) gave the *title compound* (–)-**188** as a white solid (45 mg, 66%); mp 115-117 °C; $[\alpha]^{20}_D$ –106 (*c* 0.26 in $CHCl_3$); (Found: C, 61.04; H, 4.85; N, 5.12%. $C_{14}H_{13}NO_5$ requires C, 61.07; H, 4.76; N, 5.09%); ν_{max} (soln.)/cm^{-1} 2957, 1761, 1744, 1602, 1442, 1295, 1139, 1098, 1051, 983, 968; δ_H(400 MHz, $CDCl_3$) 3.8 (3H, s), 3.9 (3H, s), 4.25 (1H, dd, *J* 3.0, 7.7), 5.37 (1H, dd, *J* 3.0, 6.1), 5.64 (1H, dd, *J* 0.5, 6.1), 5.93-5.98 (2H, m), 6.18-6.26 (2H, m); δ_C(100 MHz, $CDCl_3$) 51.1 (CH_3), 53.2 (CH_3), 55.6 (CH), 65.4 (C), 74.2 (C–O), 117.8 (C≡N), 120.7 (CH), 123.3 (CH), 126.8 (CH), 127.9 (CH), 130.3

(CH), 130.8 (CH), 153.2 (C=O), 170.4 (C=O); *m/z* (EI) 275.0794 (M^+, 30%), 216 (M^+–$C_2H_3O_2$, 18), 184 (80), 167 (100). $C_{14}H_{13}NO_5$ requires M^+ 275.0793.

(+)-(1*S*,6*R*)-1-[(*S*)-Hydroxy(phenyl)methyl]bicyclo[4.2.1]nonan-9-one 191a and (–)-(1*S*,6*R*)-1-[(*R*)-Hydroxy(phenyl)methyl]bicyclo[4.2.1]nonan-9-one 191b

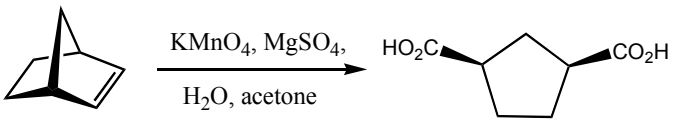


(–)-**165** (+)-**191a** (–)-**191b**

A solution of TBAT (130 mg, 0.24 mmol) in THF (3 cm^3) was added to a solution of (–)-(1*S*,6*R*)-1-(trimethylsilyl)bicyclo[4.2.1]nona-2,4,7-trien-9-one (–)-**165** (50 mg, 0.24 mmol, $[\alpha]^{22}_D$ –126) and benzaldehyde (0.10 cm^3, 0.96 mmol) in THF (3 cm^3). The reaction was heated to 60 ^oC and allowed to stir for 14 h before allowing to cool, diluted with EtOAc (10 cm^3) and extracted with H_2O (10 cm^3), 1N HCl (10 cm^3) and aq. NaCl (10 cm^3) before being dried ($MgSO_4$) and concentrated to give a yellow oil. Purification by flash column chromatography (20% Et_2O: petroleum ether) gave the *title compound* (+)-**191a** as a white solid (33 mg, 56%); $[\alpha]^{25}_D$ +33 (*c* 0.25 in $CHCl_3$); δ_H(400 MHz, $CDCl_3$) 0.95-1.02 (1H, ddd, *J* 3.8, 9.5, 13.4), 1.35-1.79 (8H, m), 2.02-2.10 (2H, m), 2.20-2.26 (1H, ddd, *J* 4.2, 7.7, 13.5), 2.63-2.66 (1H, m), 4.67 (1H, dd, *J* 1.4), 4.90 (1H, s), 7.24–7.40 (5H, m); δ_C(100 MHz, $CDCl_3$) 23.1 (CH_2), 24.6 (CH_2), 25.5 (CH_2), 29.2 (CH_2), 30.0 (CH_2), 32.2 (CH_2), 46.8 (CH), 55.4 (C), 76.7 (COH), 127.2 (=CH), 127.5 (=CH), 127.8 (=CH), 128.0 (=CH), 135.0 (=CH), 140.0 (=CH), 226.5 (C=O); *m/z* (EI) 244.1457 (M^+, 22), 226

(M^+–H_2O, 7), 138 (M^+–C_7H_6O, 100), 109 (C_7H_9O, 88), 96 (C_6H_8O, 90). $C_{16}H_{20}O_2$ requires M^+ 244.1463; and *title compound* (–)-**191b** as a glass solid (21 mg, 37%); $[\alpha]^{25}_D$ –61 (*c* 0.25 in $CHCl_3$); δ_H(400 MHz, $CDCl_3$) 0.98-1.04 (1H, m), 1.38-1.56 (5H, m), 1.60-1.73 (3H, m), 1.79-1.85 (1H, m), 2.05-2.15 (1H, m), 2.55-2.66 (3H, m) 4.95 (1H, s), 7.27-7.40 (5H, m); δ_C(100 MHz, $CDCl_3$) 24.5 (CH_2), 24.9 (CH_2), 25.2 (CH_2), 26.6 (CH_2), 30.3 (CH_2), 35.4 (CH_2), 46.7 (CH), 57.6 (C), 76.6 (COH), 127.6 (=CH), 127.6 (=CH), 127.7 (=CH), 128.0 (=CH), 128.0 (=CH), 141.1 (=CH), 223.7 (C=O); *m/z* (EI) 244.1462 (M^+, 11), 138 (M^+–C_7H_6O, 100), 109 (C_7H_9O, 68), 96 (C_6H_8O, 70). $C_{16}H_{20}O_2$ requires M^+ 244.1463.

cis-1,3-Cyclopentanedicarboxylic acid 210

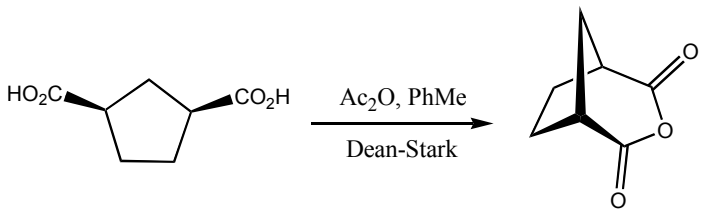


209 **210**

To a vigorously stirred solution of $KMnO_4$ (100 g, 0.63 mol) and $MgSO_4$ (10.5 g, 0.090 mol) in H_2O (800 cm^3) was added a solution of norbornylene **209** (22.1 g, 0.230 mol) in acetone (50 cm^3) at 0 °C. The ice bath was kept in place for 5 min before removing and allowing the reaction to stir at room temperature for 15 h. The reaction was filtered and the filtrate carefully treated with solid $Na_2S_2O_5$ (CAUTION! Rapid evolution of SO_2) followed by acidification to pH 1 with 12N HCl. Solid NaCl was added to the solution and the aqueous extracted with Et_2O (4 × 200 cm^3). The solid manganese oxide remaining on the filter was dissolved with aq. $Na_2S_2O_5$, treated with solid NaCl

and acidified to pH 1 before extracting the aqueous with Et_2O (4 × 200 cm^3). The combined organic extracts were dried ($MgSO_4$) and concentrated to give the title compound **210** as a white solid (21.64 g, 58%), mp 101-103 °C; ν_{max} (solid)/cm^{-1} 2959, 2963, 1683 (C=O), 1531, 1417, 1309, 1294, 1274, 1216, 1175, 1090, 941; δ_H(400 MHz, d^6 DMSO) 1.72–1.83 (4H, m, 4-H_2 & 5-H_2), 1.88 (1H, dt, *J* 12.8, 9.2, 2-H), 2.11 (1H, dt, *J* 12.8, 8.1, 2-H), 2.68–2.74 (2H, m, 1-H & 3-H); δ_C(100 MHz, d^6 DMSO) 29.8 (CH_2 × 2, C4 & C5), 33.7 (CH_2, C2), 44.1 (CH × 2, C1 & C3), 177.3 (CO_2H × 2); *m/z* (CI) 159.0657 (MH^+, 100%), 141 (M^+–H_2O, 53). $C_7H_{10}O_4$ requires MH^+ 159.0657.

3-Oxabicyclo[3.2.1]octane-2,4-dione 206

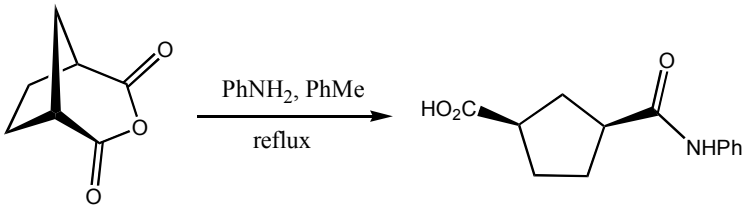


210 **206**

Acetic anhydride (25.8 cm^3, 0.280 mol) was added to a suspension of *cis*-1,3-cyclopentanedicarboxylic acid **210** (21.6 g, 0.140 mol) in toluene (200 cm^3) and heated to reflux under Dean-Stark conditions for 48 h. The toluene was removed *in vacuo* and the excess acetic anhydride was removed under high vacuum. The resultant white solid was recrystallised from pentane: Et_2O (1:1) to give the first crop of the title compound **206** (11.57 g, 60%) as a grey solid. The remaining filtrate was concentrated in volume to give a second crop of a light brown solid (2.96 g, 16%) to give a combined yield of 14.53 g, 76%; mp 119-121 °C (*lit* mp 138-140 °C, R. Carleer, *Bull. Chem. Soc. Belg.* 1978, **87**, 709; mp 164 °C, W. J. Bailey, W. B. Lawson, *J. Am. Chem. Soc.*, 1955, **77**,

1606); ν_{max} (soln.)/cm^{-1} 2956, 2884, 1817, 1766, 1708, 1131, 1072, 996, 965; δ_H(500 MHz, $CDCl_3$) 1.75 (1H, ddd, *J* 4.0, 12.4, 8-H), 2.11 (4H, m, 6-H_2 & 7-H_2), 2.25 (1H, br d, *J* 12.4, 8-H), 3.26 (2H, m, 1-H & 5-H); δ_C(125 MHz, $CDCl_3$) 26.4 (CH_2, C6 & C7), 31.2 (CH_2, C8), 41.8 (CH, C1 & C5), 169.9 (OC=O, C2 & C4); *m/z* (CI) 317 ($2MH^+.2H_2O$, 34%), 281 ($2MH^+$, 22), 159 ($M^+ + H_2O$, 100), 141.0936 (MH^+, 67). $C_7H_8O_3$ requires MH^+ 141.0551.

cis-3-(Anilinocarbonyl)cyclopentanecarboxylic acid 211

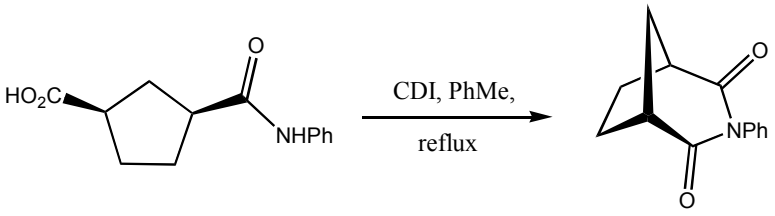


206 **211**

Aniline (8.3 cm^3, 0.09 mol) was added to a suspension of 3-oxabicyclo[3.2.1]octane-2,4-dione **206** (13 g, 0.09 mol) in toluene (250 cm^3) before heating the mixture to reflux. After 1 h the reaction was allowed to cool to room temperature and then placed in an ice bath. The resulting precipitate was filtered and washed with pentane and dried to give the *title compound* **211** as a white solid (20.38 g, 94%); mp 135-137 °C (dec.); ν_{max} (solid)/cm^{-1} 3324, 2956, 1705, 1662, 1531, 1444, 1317, 1247, 1233, 1205, 749, 691. δ_H(400 MHz, d^6 DMSO) 1.78-1.90 (4H, m), 1.95 (1H, ddd, *J* 12.6, 9.9, 9.9, 2-H), 2.15 (1H, ddd, *J* 12.6, 7.6, 7.6, 2-H), 2.71-2.89 (2H, m), 6.98-7.06 (1H, m), 7.25-7.33 (2H, m), 7.57-7.64 (2H, m), 9.3 (1H, s, NH); δ_C(100 MHz, d^6 DMSO) 29.9 (CH_2), 30.5 (CH_2), 34.4 (CH_2, C2), 44.3 (CH, C3), 46.3 (CH, C1), 120.0 (CH, Ar), 123.9 (CH, Ar), 129.5 (CH, Ar), 140.3 (C, Ar), 174.1 (NC=O), 177.4

(CO_2H); *m/z* (EI) 233.1047 (M^+, 60%), 215 (M^+–H_2O, 40), 141 (M^+–C_6H_6N, 18), 119 (M^+–C_6H_5NCO, 23) 67 (C_5H_7, 100). $C_{13}H_{15}NO_3$ requires M^+ 233.1051.

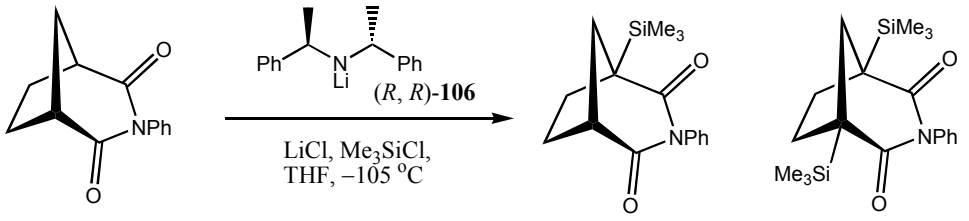
3-Phenyl-3-azabicyclo[3.2.1]octane-2,4-dione 200



211 **200**

A suspension of *cis*-3-(anilinocarbonyl)cyclopentanecarboxylic acid **211** (20.4 g, 87.0 mmol) and CDI (17.0 g, 105 mmol) in toluene (500 cm^3) was heated at reflux for 4 h. The reaction was allowed to cool and diluted with EtOAc (500 cm^3) before extracting the organic solution with 2N HCl (100 cm^3), 2N NaOH (100 cm^3), H_2O (100 cm^3) and aq. NaCl (100 cm^3). The organics were separated, dried ($MgSO_4$) and concentrated to give the *title compound* **200** as a white solid (15.82g, 84%); mp 181-183 °C; (Found: C, 72.47; H, 6.03; N, 6.36%. $C_{13}H_{13}NO_2$ requires C, 72.54; H, 6.09; N, 6.51%); ν_{max} (soln.)/cm^{-1} 2953, 2881, 1738, 1693, 1362, 1325, 1128, 1118, 993; δ_H(400 MHz, $CDCl_3$) 1.80 (1H, ddd, *J* 4.1, 4.1, 12.3, 8-H), 2.08-2.27 (4H, m, 6-H_2 & 7-H_2), 2.39 (1H, br d, *J* 12.3, 8-H), 3.32 (2H, m, 1-H & 5-H), 7.03-7.11 (2H, m), 7.37-7.51 (3H, m); δ_C(100 MHz, $CDCl_3$) 27.4 (CH_2, C6 & C7), 32.5 (CH_2, C8), 44.9 (CH, C1 & C5), 128.2 (CH, Ar), 128.5 (CH, Ar), 129.2 (CH, Ar), 134.3 (C, Ar), 176.5 (NC=O, C2 & C4); *m/z* (EI) 215.0951 (M^+, 100%), 119 (M^+–C_6H_5NCO, 47). $C_{13}H_{13}NO_2$ requires M^+ 215.0946.

(–)-(1*R*,5*R*)-3-Phenyl-1-(trimethylsilyl)-3-azabicyclo[3.2.1]octane-2,4-dione 212 and 3-phenyl-1,5-*bis*(trimethylsilyl)-3-azabicyclo[3.2.1]octane-2,4-dione 213

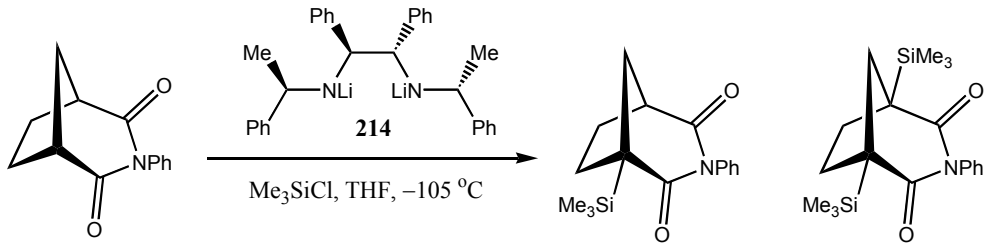


200 (–)-**212** **213**

A solution of chiral lithium amide base was prepared as previously described; hydrochloride salt of the corresponding amine (1.57 g, 6.00 mmol) in THF (20 cm^3) at −78 °C, ^{n}BuLi (1.47 $moldm^{-3}$ solution in hexanes; 8.16 cm^3, 12.0 mmol). The solution was allowed to warm to room temperature and after 10 min re-cooled to −105 °C. The chiral lithium amide base solution was canulated into a solution of imide **200** (1.08 mg, 5.00 mmol) and Me_3SiCl (6.4 cm^3, 50 mmol) in THF (120 cm^3) at −105 °C over 30 min maintaining the internal temperature. The resulting solution was allowed to warm slowly to room temperature over 3 h, quenched with aq. NH_4Cl (60 cm^3) and diluted with Et_2O (120 cm^3). The organic extract was separated and washed with H_2O (100 cm^3) and aq. NaCl (100 cm^3), dried ($MgSO_4$) and concentrated to give a yellow oil. Purification by flash column chromatography (25% EtOAc: petroleum ether) gave the *title compound* (–)-**212** as a white solid (899 mg, 63%); mp 128-130 °C; $[\alpha]^{22}_D$ –28 (*c* 0.5 in $CHCl_3$); (Found: C, 66.98; H, 7.47; N, 4.87%. $C_{16}H_{21}NO_2Si$ requires C, 66.86; H, 7.36; N, 4.87%); ν_{max} (soln.)/cm^{-1} 2954, 1728, 1679, 1359, 1136, 888, 859; δ_H(500 MHz, $CDCl_3$) 0.16 (9H, s, $SiMe_3$), 1.64 (1H, dd, *J* 4.4, 12.4, 8-H), 2.06–2.24 (4H, m, 6-H_2 & 7-H_2), 2.27

(1H, d, *J* 12.4, 8-H), 3.30 (1H, br dd, *J* 1.5, 4.4, 5-H), 7.03–7.06 (2H, m, Ar), 7.35–7.46 (3H, m, Ar); δ_C(125 MHz, $CDCl_3$) –2.9 (CH_3, $SiMe_3$), 28.9 (CH_2), 30.7 (CH_2), 34.5 (CH_2), 42.7 (C, C1), 45.3 (CH, C5), 128.3 (CH, Ar), 128.4 (CH, Ar), 129.2 (CH, Ar), 134.8 (C, Ar), 177.0, 179.0; *m/z* (EI) 287.1348 (M^+, 13%), 73 ($SiMe_3$, 100). $C_{16}H_{21}NO_2Si$ requires M^+ 287.1341. Enantiomeric excess was established by HPLC (UV detection at 205 and 215 nm) using 5% IPA in hexane as eluent and Chiralcel OJ column with a flow rate of 1 ml/min. Retention time of major enantiomer 31 min and minor enantiomer 60 min to give an ee of 70%; and the *title compound* **213** was isolated as a white solid (327 mg, 18%); mp 145-147 °C; (Found: C, 63.74; H, 8.22; N, 3.82%; $C_{19}H_{29}NO_2Si_2$ requires C, 63.46; H, 8.13; N, 3.89%); ν_{max} (soln.)/cm^{-1} 2952, 1715, 1671, 1349, 1320, 1158, 1044, 944, 885, 863; δ_H(500 MHz, $CDCl_3$) 0.17 (18H, s, $SiMe_3$), 1.48 (1H, d, *J* 12.8, 8-H), 2.02-2.17 (5H, m), 7.02-7.06 (2H, m), 7.32-7.38 (1H, m), 7.40-7.46 (2H, m); δ_C(125 MHz, $CDCl_3$) –2.8 (CH_3, $SiMe_3$), 32.1 (CH_2, C6 & C7), 36.4 (CH_2, C8), 42.9 (C, C1 & C5), 128.2 (CH, Ar), 128.3 (CH, Ar), 129.2 (CH, Ar), 135.2 (C, Ar), 179.4 (NC=O, C2 & C4); *m/z* (EI) 359.1732 (M^+, 28%), 344 (M^+–CH_3, 75), 73 ($SiMe_3$, 100). $C_{19}H_{29}NO_2Si_2$ requires M^+ 359.1736.

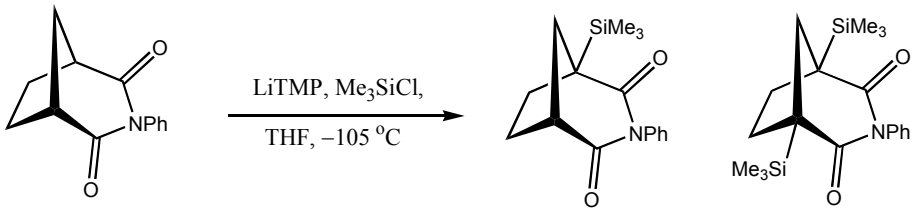
(+)-(1*S*,5*S*)-3-Phenyl-1-(trimethylsilyl)-3-azabicyclo[3.2.1]octane-2,4-dione 212 and 3-phenyl-1,5-*bis*(trimethylsilyl)-3-azabicyclo[3.2.1]octane-2,4-dione 213



200 (+)-**212** **213**

A solution of chiral lithium amide base was prepared by treatment of a solution of the corresponding *bis*-amine (2.53 g, 6.00 mmol), in THF (35 cm^3) at −78 °C, with ^{n}BuLi (1.6 $moldm^{-3}$ solution in hexanes; 7.3 cm^3, 12 mmol). The solution was allowed to warm to room temperature and after 10 min re-cooled to −105 °C. The reaction was performed as previously described with chiral base **106** using 3-phenyl-3-azabicyclo[3.2.1]octane-2,4-dione **200** (1.08 g, 5.00 mmol) and Me_3SiCl (2.0 cm^3, 15 mmol) in THF (40 cm^3). Purification by column chromatography (40% Et_2O: petroleum ether) gave the *title compound* (+)-**212** as a white solid (678 mg, 47%); $[\alpha]^{20}_D$ +39 (*c* 0.21 in $CHCl_3$) and the *title compound* **213** (428 mg, 24%). Data consistent with previously described. Enantiomeric excess was established as previously described to give an ee of 94%, but with opposite major and minor enantiomer retention times.

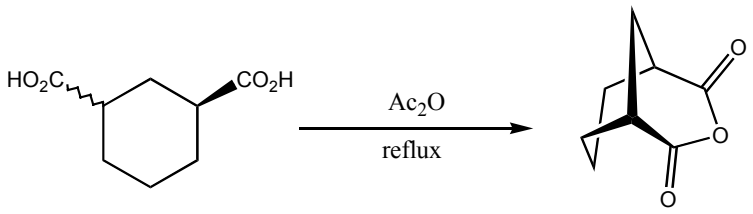
(±)-3-Phenyl-1-(trimethylsilyl)-3-azabicyclo[3.2.1]octane-2,4-dione 212 and 3-phenyl-1,5-*bis*(trimethylsilyl)-3-azabicyclo[3.2.1]octane-2,4-dione 213



200 **212** **213**

A solution of lithium amide base was prepared by as previously described; TMP (0.17 cm^3, 1.3 mmol), in THF (7 cm^3) at −78 °C, ^{n}BuLi (1.6 $moldm^{-3}$ solution in hexanes; 0.81 cm^3, 1.3 mmol). The solution was allowed to warm to room temperature and after 10 min re-cooled to −105 °C. The lithium amide base solution was canulated into a solution of imide **200** (215 mg, 1.00 mmol) and Me_3SiCl (0.38 cm^3, 3.0 mmol) in THF (13 cm^3) at −105 °C maintaining internal temperature. The resulting solution was allowed to warm slowly to room temperature over 3 h, quenched with aq. NH_4Cl (10 cm^3) and diluted with Et_2O (40 cm^3). The organic phase was extracted with H_2O (10 cm^3), dried ($MgSO_4$) and concentrated to give a yellow solid. Purification by flash column chromatography (50% Et_2O: petroleum ether) gave the *title compound* **212** as a white solid (45 mg, 16%, mono) and *title compound* **213** as a white solid (72 mg, 20%). Data consistent with previously described.

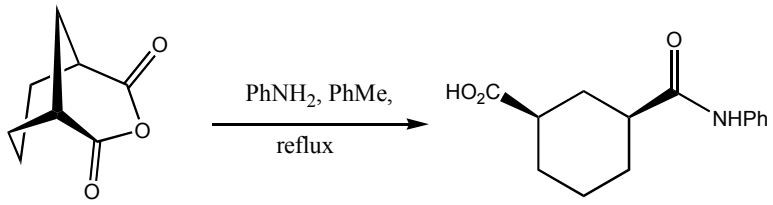
3-Oxabicyclo[3.3.1]nonane-2,4-dione 207



216 **207**

A mixture of *cis*/*trans*-1,3-cyclohexanedicarboxylic acid **216** (20 g, 0.12 mol) in acetic anhydride (80 cm^3) was heated to reflux for 5 h. A distillation head was fitted and the volatiles removed to leave a light yellow residue which was recrystallised from hot toluene by the addition of hexane and cooling to 0 °C. The precipitate was filtered, washed with hexane and dried to give the title compound **207** as a white solid (13.95 g, 78%); mp 189-191 °C; ν_{max} (solid)/cm^{-1} 2950, 1798, 1769, 1226, 1217, 1175, 1076, 1046, 1021, 999, 936, 836; δ_H(400 MHz, $CDCl_3$) 1.48 (1H, ddddd, *J* 4.4, 4.4, 5.3, 5.3 13.8, 9-H), 1.69-1.90 (4H, m), 2.06-2.17 (2H, m), 2.19-2.31 (1H, ddddd, *J* 1.5, 1.5, 2.0, 2.0, 13.7, 9-H), 3.06 (2H, br s); δ_C(100 MHz, $CDCl_3$) 20.0 (CH_2), 27.2 (CH_2), 28.5 (CH_2, C6 & C8), 36.4 (CH, C1 & C5), 170.1 (OC=O, C2 & C4); *m/z* (CI) 172 (MH^++NH_3, 100%), 155.0703 (MH^+, 49). $C_8H_{10}O_3$ requires MH^+ 155.0708.

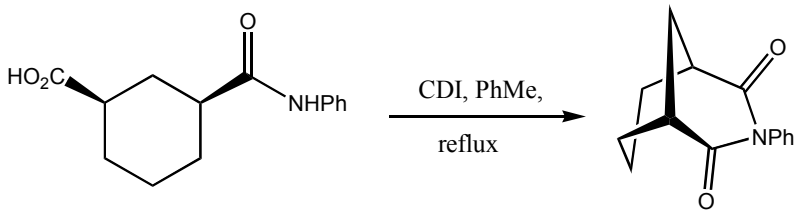
***cis*-3-(Anilinocarbonyl)cyclohexanecarboxylic acid 217**



207 **217**

Aniline (8.0 cm^3, 88 mmol) was added to a suspension of 3-oxabicyclo [3.3.1]nonane-2,4-dione **207** (13.8 g, 90.0 mmol) in toluene (250 cm^3) before heating the mixture to reflux. After 1 h the reaction was allowed to cool and the resulting precipitate was filtered and washed with pentane and dried to give the title compound **217** as a white solid (20.7 g, 93%); mp 210-212 °C; ν_{max} (solid)/cm^{-1} 2951, 1707, 1550, 1444, 1212, 1180, 755; δ_H(400 MHz, $CDCl_3$) 1.16-1.43 (3H, m), 1.54 (1H, dt, *J* 12.6, 12.6), 1.71-1.87 (3H, m), 2.05 (1H, br d, *J* 12.8), 2.10-2.27 (2H, m), 6.88 (1H, br t, *J* 7.4), 7.04-7.15 (2H, br t, *J* 8.4), 7.39-7.46 (2H, br d, *J* 7.6), 8.70 (1H, s, NH); δ_C(100 MHz, $CDCl_3$) 24.6 (CH_2), 27.9 (CH_2), 28.3 (CH_2), 31.6 (CH_2), 42.3 (CH, C3), 44.9 (CH, C1), 119.5 (CH, Ar), 123.2 (CH, Ar), 128.4 (CH, Ar), 138.6 (C, Ar), 173.7 (NC=O), 177.1 (CO_2H); *m/z* (EI) 247.1196 (M^+, 59%), 229 (M^+–H_2O, 100), 119 (M^+–C_6H_5NCO, 69). $C_{14}H_{17}NO_3$ requires M^+ 247.1208.

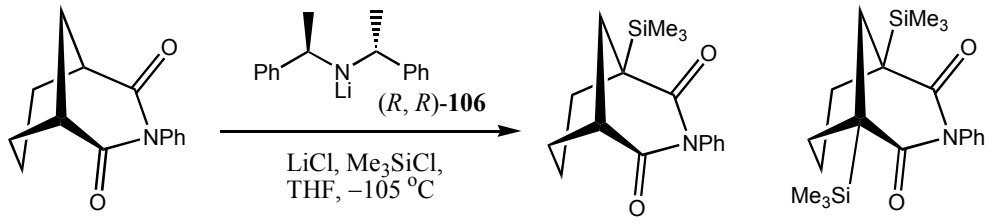
3-Phenyl-3-azabicyclo[3.3.1]nonane-2,4-dione 201



217 **201**

A suspension of *cis*-3-(anilinocarbonyl)cyclohexanecarboxylic acid **217** (20.7 g, 83.0 mmol) and CDI (16.3 g, 101 mmol) in toluene (500 cm^3) was heated at reflux for 4 h. The reaction was allowed to cool and diluted with EtOAc (500 cm^3) before extracting with 2N HCl (100 cm^3), 2N NaOH (100 cm^3), H_2O (100 cm^3) and aq. NaCl (100 cm^3). The organic extract was separated, dried ($MgSO_4$) and concentrated to give the *title compound* **201** as a white solid (16.03g, 87%); mp 181-183 °C; (Found: C, 73.41; H, 6.58; N, 6.04%. $C_{14}H_{15}NO_2$ requires C, 73.34; H, 6.59; N, 6.11%); ν_{max} (solid)/cm^{-1} 2944, 1677, 1370, 1252, 1185, 1138; δ_H(400 MHz, $CDCl_3$) 1.63-1.90 (5H, m), 2.16 (2H, br d, *J* 13.2), 2.40 (1H, br d, *J* 13.2), 3.02 (2H, br s, 1-H & 5-H), 7.10-7.18 (2H, m), 7.35-7.53 (3H, m); δ_C(100 MHz, $CDCl_3$) 19.7 (CH_2, C7), 28.1 (CH_2, C9), 28.4 (CH_2, C6 & C8), 38.5 (CH, C1 & C5), 128.4 (CH, Ar), 128.5 (CH, Ar), 129.2 (CH, Ar), 135.3 (C, Ar), 175.6 (NC=O, C2 & C4); *m/z* (EI) 229.1095 (M^+, 100%), 119 (M^+–C_6H_5NCO, 46). $C_{14}H_{15}NO_2$ requires M^+ 229.1102.

(–)-(1*R*,5*R*)-3-Phenyl-1-(trimethylsilyl)-3-azabicyclo[3.3.1]nonane-2,4-dione 218 and 3-phenyl-1,5-*bis*(trimethylsilyl)-3-azabicyclo[3.3.1]nonane-2,4-dione 219

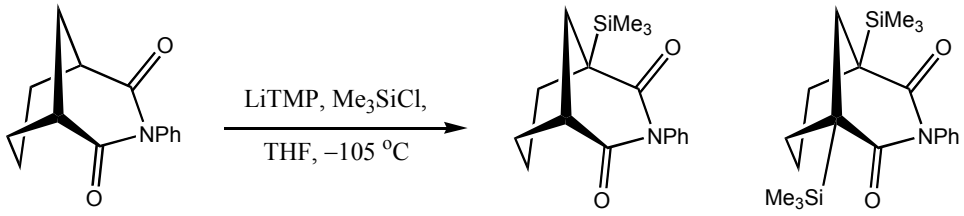


201 (–)-**218** **219**

A solution of chiral lithium amide base was prepared as previously described; hydrochloride salt of the corresponding amine (288 mg, 1.10 mmol), in THF (5 cm^3) at −78 °C, ^{n}BuLi (1.56 $moldm^{-3}$ solution in hexanes; 1.3 cm^3, 2.2 mmol). The solution was allowed to warm to room temperature and after 10 min re-cooled to −105 °C. The chiral lithium amide base solution was canulated into a solution of 3-phenyl-3-azabicyclo[3.3.1]nonane-2,4-dione **201** (229 mg, 1.00 mmol) and Me_3SiCl (0.4 cm^3, 3 mmol) in THF (30 cm^3) at −105 °C over 15 min maintaining the internal temperature. The resulting solution was allowed to warm slowly to room temperature over 3 h, quenched with aq. NH_4Cl (10 cm^3) and diluted with Et_2O (30 cm^3). The organic extract was separated and washed with H_2O (30 cm^3) and aq. NaCl (30 cm^3), dried ($MgSO_4$) and concentrated to give a white solid. Purification by flash column chromatography (40% Et_2O: petroleum ether) gave the *title compound* (–)-**218** as a white solid (224 mg, 74%); mp 119-121 °C; $[\alpha]^{20}_D$ −60 (*c* 0.26 in $CHCl_3$); (Found: C, 67.79; H, 7.75; N, 4.64%. $C_{17}H_{23}NO_2Si$ requires C, 67.73; H, 7.69; N, 4.65%); ν_{max} (soln.)/cm^{-1} 2943, 2865, 1720, 1674, 1455, 1363, 1349, 1156, 1006; δ_H(400 MHz, $CDCl_3$) 0.15 (9H, s, $SiMe_3$), 1.68-1.86 (5H, m), 2.14-2.22

(2H, m), 2.29 (1H, dddd, *J* 2.0, 2.0, 3.5, 13.4), 3.02 (1H, dddd, *J* 3.5, 3.5, 3.5, 3.5), 7.09-7.11 (2H, m), 7.39-7.43 (1H, m), 7.46-7.50 (2H, m); δ_C(100 MHz, $CDCl_3$) –3.7 ($SiMe_3$), 20.6 (CH_2), 28.3 (CH_2), 29.3 (CH_2), 30.5 (CH_2), 34.9 (C), 38.2 (CH), 128.4 (CH, Ar), 128.5 (CH, Ar), 129.3 (CH, Ar), 135.8 (C, Ar), 176.1 (C=O), 178.7 (C=O); *m/z* (EI) 301.1488 (M^+, 28%), 73 ($SiMe_3$, 100). $C_{17}H_{23}NO_2Si$ requires M^+ 301.1498. Enantiomeric excess was established by HPLC (UV detection at 205 and 215 nm) using 5% IPA in hexane as eluent and Chiralcel OJ column with a flow rate of 1 ml/min. Retention time of major enantiomer 17 min and minor enantiomer 31 min to give an ee of 98%; and the *title compound* **219** (44 mg, 12%); mp 156-158 °C; (Found: C, 64.31; H, 8.39; N 3.66 %. $C_{20}H_{31}NO_2Si_2$ requires C, 64.29; H, 8.36; N, 3.75%); ν_{max} (soln.)/cm^{-1} 2942, 2854, 1707, 1665, 1347, 1162, 1060, 1012; δ_H(500 MHz, $CDCl_3$) 0.13 (18H, s, $SiMe_3$), 1.54 (1H, d, *J* 13.5, 9-H), 1.62-1.83 (4H, m), 2.01-2.18 (3H, m), 7.02-7.10 (2H, m), 7.35-7.40 (1H, m), 7.42-7.48 (2H, m); δ_C(125 MHz, $CDCl_3$) –3.7 ($SiMe_3$), 21.3 (CH_2, C7), 30.3 (CH_2, C6, C8 & C9), 34.3 (C, C1 & C5), 128.4 (CH, Ar), 128.5 (CH, Ar), 129.3 (CH, Ar), 136.3 (C, Ar), 178.8 (NC=O, C2 & C4); *m/z* (EI) 373.1887 (40%), 73 ($SiMe_3$, 100). $C_{20}H_{31}NO_2Si_2$ requires M^+ 373.1893. A similar reaction performed on 1 mmol scale at –78 ^oC resulted in the isolation of *title compound* (–)-**218** (53%, $[\alpha]^{20}_D$ –58 (*c* 0.51 in $CHCl_3$), 90% ee) and *title compound* **219** (14%).

(±)-3-Phenyl-1-(trimethylsilyl)-3-azabicyclo[3.3.1]nonane-2,4-dione 218 and 3-Phenyl-1,5-*bis*(trimethylsilyl)-3-azabicyclo[3.3.1]nonane-2,4-dione 219

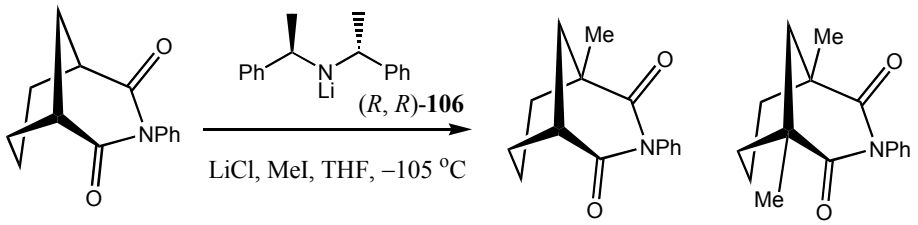


201 **218** **219**

A solution of LiTMP was prepared as previously described; TMP (0.17 cm^3, 1.3 mmol), in THF (7 cm^3) at −78 °C, with ^{n}BuLi (1.6 $moldm^{-3}$ solution in hexanes; 0.81 cm^3, 1.3 mmol). The solution was allowed to warm to room temperature and after 10 min re-cooled to −105 °C. The lithium amide base solution was canulated into a solution of 3-phenyl-3-azabicyclo[3.3.1]nonane-2,4-dione **201** (229 mg, 1.00 mmol) and Me_3SiCl (0.38 cm^3, 3.0 mmol) in THF (13 cm^3) at −105 °C maintaining the internal temperature. The resulting solution was allowed to warm slowly to room temperature over 3 h, quenched with aq. NH_4Cl (10 cm^3) and diluted with Et_2O (40 cm^3). The organic phase was extracted with H_2O (10 cm^3), dried ($MgSO_4$) and concentrated to give a yellow solid. Purification by flash column chromatography (40% Et_2O: petroleum ether) gave the *title compound* **218** as a white solid (142 mg, 47%) and *title compound* **219** as a white solid (75 mg, 20%). Data consistent with previously described.

(–)-(1*S*,5*R*)-1-Methyl-3-phenyl-3-azabicyclo[3.3.1]nonane-2,4-dione 220

and 1,5-Dimethyl-3-phenyl-3-azabicyclo[3.3.1]nonane-2,4-dione 221

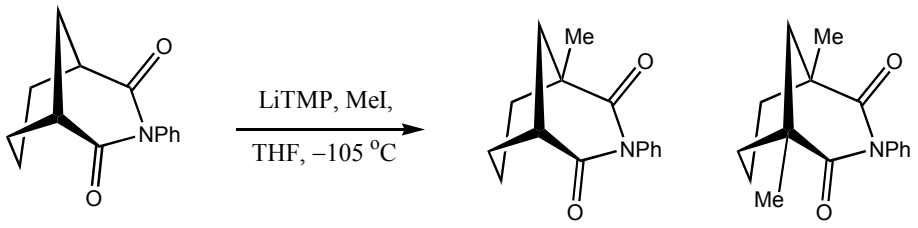


201 (–)-**220** **221**

A solution of chiral lithium amide base was prepared as previously described; hydrochloride salt of the corresponding amine (314 mg, 1.20 mmol), in THF (5 cm^3) at −78 °C, with ^{n}BuLi (1.6 $moldm^{-3}$ solution in hexanes; 1.5 cm^3, 2.4 mmol). The solution was allowed to warm to room temperature and after 10 min recooled to −105 °C. The chiral lithium amide base solution was canulated into a solution of 3-phenyl-3-azabicyclo[3.3.1]nonane-2,4-dione **201** (229 mg, 1.00 mmol) and methyl iodide (0.19 cm^3, 3.0 mmol) in THF (30 cm^3) at −105 °C over 15 min maintaining the internal temperature. The resulting solution was allowed to warm slowly to room temperature over 3 h, quenched with aq. NH_4Cl (30 cm^3) and diluted with Et_2O (60 cm^3). The organic phase was extracted with aq. citric acid (30 cm^3 × 2) and H_2O (30 cm^3), dried ($MgSO_4$) and concentrated to give a white solid. Purification by flash column chromatography (10% EtOAc in petrol) gave the *title compound* (–)-**220** as a white solid (139 mg, 57%); mp 170-172 °C; $[\alpha]^{23}_D$ –3.0 (*c* 0.5 in $CHCl_3$); (Found: C, 73.94; H, 7.02; N, 5.39%. $C_{15}H_{17}NO_2$ requires C, 74.05; H, 7.04; N, 5.76%); ν_{max} (soln.)/cm^{-1} 2937, 1730, 1682, 1362, 1137, 1104, 994; δ_H(400 MHz, $CDCl_3$) 1.32 (3H, s, CH_3), 1.51 (1H, ddd, *J* 4.8, 4.8, 13.5, 9-H), 1.63−1.77 (3H, m), 1.88 (1H, m), 2.03 (1H, m), 2.17 (1H, m), 2.31 (1H, dddd,

J 1.6, 1.6, 1.6, 13.2, 9-H), 3.10 (1H, dddd, *J* 3.3, 3.3, 3.3, 3.3, 5-H), 7.10–7.12 (2H, m), 7.4–7.43 (1H, m), 7.46–7.5 (2H, m); δ_C(100 MHz, $CDCl_3$) 20.4 (CH_2), 25.6 (CH_3), 27.9 (CH_2), 35.6 (CH_2), 36.9 (CH_2), 39.5 (CH, C5), 40.0 (C, C1), 128.4 (CH, Ar), 128.5 (CH, Ar), 129.2 (CH, Ar), 135.7 (C, Ar), 175.8, 177.7; *m/z* (EI) 243.1258 (M^+, 100%). $C_{15}H_{17}NO_2$ requires M^+ 243.1259. Enantiomeric excess was established by HPLC (UV detection at 205 nm) using 1% IPA in hexane as eluent and Chiralcel OD-H column with a flow rate of 0.5 ml/min. Retention time of major enantiomer 68 min and minor enantiomer 63 min to give an ee of 97%; and the *title compound* **221** as a white solid (29 mg, 11%); mp 137-139 °C; ν_{max} (soln.)/cm^{-1} 2934, 1729, 1681, 1380, 1359, 952; δ_H(400 MHz, $CDCl_3$) 1.31 (6H, s, $(CH_3)_2$), 1.37–1.47 (2H, ddd, *J* 1.0, 4.9, 13.5), 1.56 (1H, d, *J* 13.2, 9-H), 1.67 (1H, ddddd, *J* 4.4, 4.4, 12.7, 14.5, 14.5), 1.87 (1H, ddddd, *J* 2.1, 2.1, 4.6, 4.6, 14.5), 1.97-2.04 (2H, dddd, *J* 2.1, 2.1, 4.4, 13.5), 2.17 (1H, ddd, *J* 2.1, 2.1, 13.2), 7.03-7.09 (2H, m), 7.36-7.47 (1H, m); δ_C(100 MHz, $CDCl_3$) 21.1 (CH_2), 25.3 (CH_3), 36.4 (CH_2), 41.2 (C, C1 & C5), 43.3 (CH_2), 128.3 (CH), 128.4 (CH), 129.2 (CH), 136.2 (C), 177.8 (NC=O, C2 & C4); *m/z* (EI) 257.1404 (M^+, 93%), 109 (M^+–$C_6H_5NO_2$, 100). $C_{16}H_{19}NO_2$ requires M^+ 257.1410).

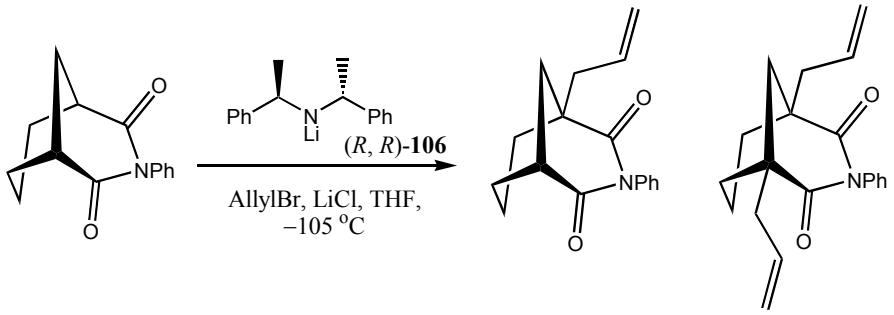
(±)-1-Methyl-3-phenyl-3-azabicyclo[3.3.1]nonane-2,4-dione 220 and 1,5-Dimethyl-3-phenyl-3-azabicyclo[3.3.1]nonane-2,4-dione 221



201 **220** **221**

A solution of lithium amide base was prepared as previously described; TMP (0.19 cm^3, 1.1 mmol), in THF (7 cm^3) at −78 °C, with ^{n}BuLi (1.56 $moldm^{-3}$ solution in hexanes; 0.67 cm^3, 1.1 mmol). The solution was allowed to warm to room temperature and after 10 min re-cooled to −105 °C. A solution of 3-phenyl-3-azabicyclo[3.3.1]nonane-2,4-dione **201** (229 mg, 1.00 mmol) and methyl iodide (0.19 cm^3, 3.0 mmol) in THF (13 cm^3) was canulated into the lithium amide base solution at −105 °C maintaining the internal temperature. The resulting solution was allowed to warm slowly to room temperature over 3 h, quenched with aq. NH_4Cl (10 cm^3) and diluted with Et_2O (40 cm^3). The organic phase was extracted with H_2O (10 cm^3), dried ($MgSO_4$) and concentrated to give a yellow solid. Purification by flash column chromatography (12% EtOAc: petroleum ether) gave the *title compound* **220** as a white solid (98 mg, 40%, mono) and *title compound* **221** as a white solid (64 mg, 25%). Data consistent with previously described.

(–)-(1*R*,5*R*)-1-Allyl-3-phenyl-3-azabicyclo[3.3.1]nonane-2,4-dione 222 and 1,5-Diallyl-3-phenyl-3-azabicyclo[3.3.1]nonane-2,4-dione 223

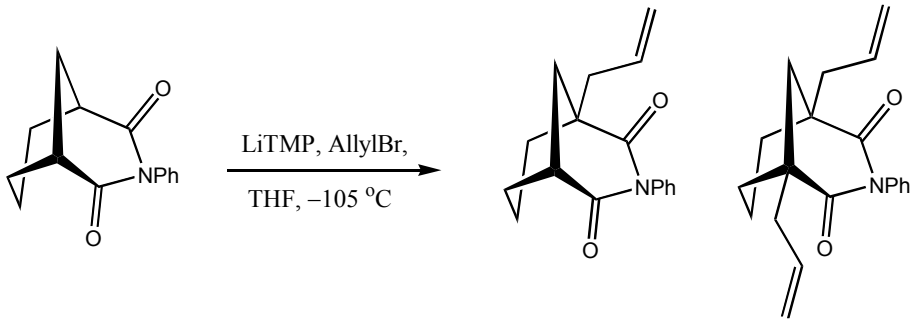


201 (–)-**222** **223**

A solution of chiral lithium amide base was prepared as previously described; hydrochloride salt of the corresponding secondary amine (314 mg, 1.20 mmol), in THF (5 cm^3) at −78 °C, with ^{n}BuLi (1.6 $moldm^{-3}$ solution in hexanes; 1.5 cm^3, 2.4 mmol). The chiral lithium amide base solution was canulated into a solution of 3-phenyl-3-azabicyclo[3.3.1]nonane-2,4-dione **201** (229 mg, 1.00 mmol) and allyl bromide (0.26 cm^3, 3.0 mmol) in THF (30 cm^3) at −105 °C over 15 min maintaining the internal temperature. The resulting solution was allowed to warm slowly to room temperature over 3 h, quenched with aq. NH_4Cl (30 cm^3) and diluted with Et_2O (60 cm^3). The organic phase was extracted with aq. citric acid (30 cm^3 × 2) and H_2O (30 cm^3), dried ($MgSO_4$) and concentrated to give a white solid. Purification by flash column chromatography (10% EtOAc: petroleum ether) gave the *title compound* (–)-**222** as a white solid (114 mg, 42%); mp 110-112 °C; $[\alpha]^{23}_D$ –61 (*c* 0.5 in $CHCl_3$); ν_{max} (soln.)/cm^{-1} 2941, 1729, 1682, 1364, 1321, 1165, 1130, 1005; δ_H(500 MHz, $CDCl_3$) 1.52-1.76 (4H, m), 1.87 (1H, m), 1.96 (1H, m), 2.14 (1H, br d, *J* 10.6), 2.21 (1H, dd, *J* 8.4, 13.5), 2.37 (1H, d, *J* 13.2), 2.70 (1H, dd, *J* 6.2, 13.5), 3.09 (1H, dd, *J* 2.6, 2.6), 5.12 (1H, d, *J* 14.6), 5.16 (1H, d, *J* 6.2),

5.76 (1H, dddd, *J* 6.2, 8.4, 10.2, 16.8), 7.02-7.14 (2H, m), 7.40 (1H, m), 7.44-7.5 (2H, m); δ_C(125 MHz, $CDCl_3$) 20.3 (CH_2), 28.1 (CH_2), 32.3 (CH_2), 35.6 (CH_2), 39.4 (CH, C5), 42.9 (CH_2, Allyl), 43.5 (C, C1), 119.3 (CH_2, Allyl), 128.4 (CH, Ar), 128.5 (CH, Ar), 129.3 (CH, Ar), 133.1 (CH, Allyl), 135.7 (C, Ar), 175.6, 176.8; *m/z* (EI) 269.1415 (M^+, 100%), 241 (M^+–CO, 17). $C_{17}H_{19}NO_2$ requires M^+ 269.1415. Enantiomeric excess was established by HPLC (UV detection at 205 nm) using 1% IPA in hexane as eluent and Chiralcel OD-H column with a flow rate of 0.8 ml/min. Retention time of major enantiomer 34 min and minor enantiomer 30 min to give an ee of 95%; and the *title compound* **223** as a white solid (22 mg, 7%); mp 129-131 °C; ν_{max} (soln.)/cm^{-1} 2938, 1728, 1681, 1364, 1311, 997; δ_H(500 MHz, $CDCl_3$) 1.37 (1H, d, *J* 13.2), 1.43-1.52 (2H, ddd, *J* 4.4, 13.2, 13.2), 1.67 (1H, ddddd, *J* 4.4, 4.4, 12.4, 14.6, 14.6), 1.89 (1H, ddddd, *J* 2.2, 2.2, 4.4, 4.4, 14.6), 1.92-1.97 (2H, dddd, *J* 2.2, 2.2, 4.0, 13.5), 2.24 (2H, dd, *J* 8.4, 13.9), 2.28 (1H, ddd, *J* 2.2, 2.2, 13.5), 2.70 (2H, dd, *J* 6.4, 13.9), 5.12 (2H, m), 5.15 (2H, dd, *J* 4.4, 5.9) 5.78 (2H, dddd, *J* 6.2, 8.4, 10.2, 16.5), 7.03-7.08 (2H, m), 7.36-7.41 (1H, m), 7.42-7.48 (2H, m); δ_C(125 MHz, $CDCl_3$) 20.8 (CH_2), 35.1 (CH_2), 36.5 (CH_2), 42.8 (CH_2, Allyl), 44.3 (C, C1 & C5), 119.3 (CH_2, Allyl), 128.4 (CH, Ar), 129.2 (CH, Ar), 133.1 (CH, Allyl), 136.0 (C, Ar), 176.7 (NC=O, C2 & C4); *m/z* (EI) 309.1740 (M^+, 100%), 268 (M^+–C_3H_5, 31), 227 (M^+–C_6H_{10}, 24). $C_{20}H_{23}NO_2$ requires M^+ 309.1728.

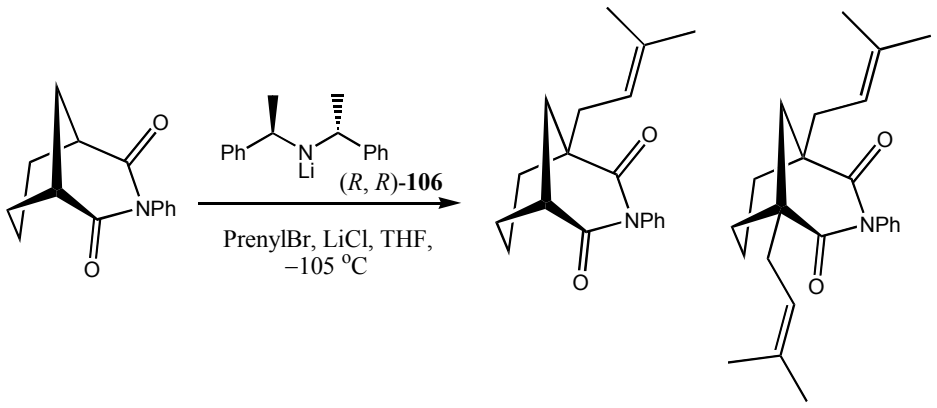
(±)-1-Allyl-3-phenyl-3-azabicyclo[3.3.1]nonane-2,4-dione 222 and 1,5-Diallyl -3-phenyl-3-azabicyclo[3.3.1]nonane-2,4-dione 223



201 **222** **223**

A solution of lithium amide base was prepared as previously described; TMP (0.20 cm^3, 1.2 mmol), in THF (5 cm^3) at −78 °C, with ^{n}BuLi (1.6 $moldm^{-3}$ solution in hexanes; 0.75 cm^3, 1.2 mmol). The solution was allowed to warm to room temperature and after 10 min re-cooled to −105 °C. The solution of lithium amide base solution was canulated into a solution of 3-phenyl-3-azabicyclo[3.3.1]nonane-2,4-dione **201** (229 mg, 1.00 mmol) and allyl bromide (0.26 cm^3, 3.0 mmol) in THF (30 cm^3) at −105 °C maintaining the internal temperature. The resulting solution was allowed to warm slowly to room temperature over 3 h, quenched with aq. NH_4Cl (30 cm^3) and diluted with Et_2O (60 cm^3). The organic phase was extracted with H_2O (30 cm^3), dried ($MgSO_4$) and concentrated to give a white solid. Purification by flash column chromatography (15% EtOAc: petroleum ether) gave the *title compound* **222** as a white solid (67 mg, 25%, mono) and *title compound* **223** as a white solid (40 mg, 13%). Data consistent with previously described.

(–)-(1*R*,5*R*)-1-(3-Methyl-2-butenyl)-3-phenyl-3-azabicyclo[3.3.1]nonane-2,4-dione 224 and 1,5-*Bis*(3-methyl-2-butenyl)-3-phenyl-3-azabicyclo [3.3.1]non ane-2,4-dione 225

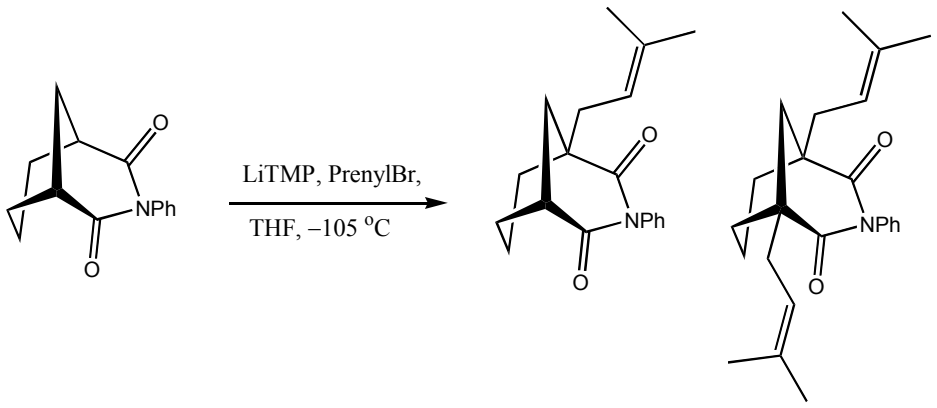


201 (–)-**224** **225**

A solution of chiral lithium amide base was prepared as previously described; hydrochloride salt of the corresponding amine (314 mg, 1.20 mmol), in THF (5 cm^3) at −78 °C, with ^{n}BuLi (1.6 $moldm^{-3}$ solution in hexanes; 1.5 cm^3, 2.4 mmol). The chiral lithium amide base solution was canulated into a solution of 3-phenyl-3-azabicyclo[3.3.1]nonane-2,4-dione **201** (229 mg, 1.00 mmol) and prenyl bromide (0.35 cm^3, 3.00 mmol) in THF (30 cm^3) at −105 °C over 15 min maintaining the internal temperature. The resulting solution was allowed to warm slowly to room temperature over 3 h, quenched with aq. NH_4Cl (30 cm^3) and diluted with Et_2O (60 cm^3). The organic phase was extracted with aq. citric acid (30 cm^3 × 2) and H_2O (30 cm^3), dried ($MgSO_4$) and concentrated to give a white solid. Purification by flash column chromatography (10% EtOAc: petroleum ether) gave the *title compound* (–)-**224** as a white solid (149 mg, 50%); mp 109-111 °C; $[\alpha]^{23}_D$ −65 (*c* 0.5 in $CHCl_3$); ν_{max} (soln.)/cm^{-1} 2938, 2870, 1729, 1682, 1363, 1321, 1152, 1097, 1004; δ_H(500 MHz, $CDCl_3$) 1.53-

1.72 (8H, m), 1.74 (3H, br s), 1.86 (1H, m), 1.93 (1H, br d, *J* 13.8), 2.14 (1H, m), 2.26 (1H, dd, *J* 8.8, 14.3), 2.34 (1H, br d, *J* 13.1), 2.53 (1H, dd, *J* 6.5, 14.3) 3.07 (1H, br dd, *J* 2.8, 2.8), 5.12 (1H, br dd, *J* 7.4, 7.4), 7.06-7.11 (2H, m), 7.37-7.42 (1H, m), 7.43-7.49 (2H, m); δ_C(125 MHz, $CDCl_3$) 18.1 (CH_3, prenyl), 20.4 (CH_2), 26.2 (CH_3, prenyl), 28.2 (CH_2), 32.3 (CH_2), 35.5 (CH_2), 36.9 (CH_2, prenyl), 39.4 (CH, C5), 44.4 (C, C1), 118.7 (CH, prenyl), 128.5 (CH, Ar), 129.3 (CH, Ar), 135.6 (C, prenyl), 135.8 (C, Ar), 175.8, 177.3; *m/z* (EI) 287.1738 (M^+, 100%). $C_{19}H_{23}NO_2$ requires; M^+ 297.1728. Enantiomeric excess was established by HPLC (UV detection at 205 nm) using 1% IPA in hexane as eluent and Chiralcel OD-H column with a flow rate of 0.8 ml/min. Retention time of major enantiomer 26 min and minor enantiomer 22 min to give an ee of 98%; and the *title compound* **225** as a white solid (44 mg, 12%); mp 72-74 °C; ν_{max} (soln.)/cm^{-1} 2932, 2858, 1726, 1681, 1454, 1367, 1352, 1307, 1174, 1111, 984; δ_H(500 MHz, $CDCl_3$) 1.38 (1H, d, *J* 13.5), 1.45-1.53 (2H, ddd, *J* 4.4, 4.4, 13.2), 1.64 (6H, s), 1.75 (6H, s), 1.83-1.92 (3H, m), 2.19 (1H, br d, *J* 13.5), 2.30 (2H, dd, *J* 8.8, 14.3), 2.51 (2H, dd, *J* 6.6, 14.3), 5.13 (2H, br dd, *J* 7.3, 7.3), 7.04-7.09 (2H, m), 7.35-7.40 (1H, m), 7.42-7.47 (2H, m); δ_C(125 MHz, $CDCl_3$) 18.2 (CH_3, prenyl), 20.9 (CH_2), 26.2 (CH_3, prenyl), 34.9 (CH_2), 36.4 (CH_2), 36.7 (CH_2), 45.1 (C, C1 & C5), 118.8 (CH, prenyl), 128.3 (CH, Ar), 128.5 (CH, Ar), 129.2 (CH, Ar), 135.5 (C, prenyl), 136.2 (C, Ar), 177.3 (NC=O, C2 & C4); *m/z* (EI) 365.2366 (M^+, 100%), 296 (M^+–C_5H_9, 68), 228 (M^+–$C_{10}H_{17}$, 22). $C_{24}H_{31}NO_2$ requires M^+ 365.2354.

(±)-1-(3-Methyl-2-butenyl)-3-phenyl-3-azabicyclo[3.3.1]nonane-2,4-dione 224 and 1,5-*Bis*(3-methyl-2-butenyl)-3-phenyl-3-azabicyclo[3.3.1]nonane-2,4-dione 225

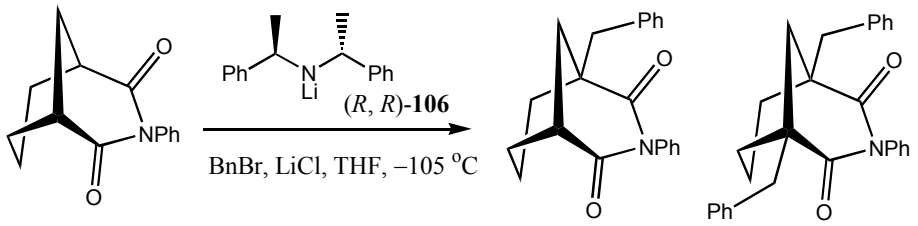


201 **224** **225**

A solution of lithium amide base was prepared as previously described; TMP (0.20 cm^3, 1.2 mmol), in THF (5 cm^3) at −78 °C, with ^{n}BuLi (1.6 $moldm^{-3}$ solution in hexanes; 0.75 cm^3, 1.2 mmol). The solution was allowed to warm to room temperature and after 10 min re-cooled to −105 °C. The solution of lithium amide base solution was canulated into a solution of 3-phenyl-3-azabicyclo[3.3.1]nonane-2,4-dione **201** (229 mg, 1.00 mmol) and prenyl bromide (0.35 cm^3, 3.0 mmol) in THF (30 cm^3) at −105 °C (internal temperature) maintaining the internal temperature. The resulting solution was allowed to warm slowly to room temperature over 3 h, quenched with aq. NH_4Cl (30 cm^3) and diluted with Et_2O (60 cm^3). The organic phase was extracted with H_2O (30 cm^3), dried ($MgSO_4$) and concentrated to give a white solid. Purification by flash column chromatography (10% EtOAc: petroleum ether) gave the *title compound* **224** as a white solid (124 mg, 42%, mono) and *title compound* **225** as a white solid (71 mg, 19%). Data consistent with previously described.

(–)-(1*S*,5*R*)-1-Benzyl-3-phenyl-3-azabicyclo[3.3.1]nonane-2,4-dione 226

and 1,5-Dibenzyl-3-azabicyclo[3.3.1]nonane-2,4-dione 227

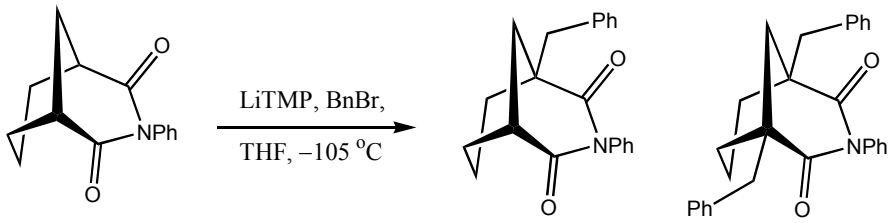


201 (–)-**226** **227**

A solution of chiral lithium amide base was prepared as previously described; hydrochloride salt of the corresponding amine (314 mg, 1.20 mmol), in THF (5 cm^3) at −78 °C, with ^{n}BuLi (1.6 $moldm^{-3}$ solution in hexanes; 1.5 cm^3, 2.4 mmol). The chiral lithium amide base solution was canulated into a solution of 3-phenyl-3-azabicyclo[3.3.1]nonane-2,4-dione **201** (229 mg, 1.00 mmol) and benzyl bromide (0.36 cm^3, 3.0 mmol) in THF (30 cm^3) at −105 °C over 15 min maintaining the internal temperature. The resulting solution was allowed to warm slowly to room temperature over 3 h, quenched with aq. NH_4Cl (30 cm^3) and diluted with Et_2O (60 cm^3). The organic phase was extracted with aq. citric acid (30 cm^3 × 2) and H_2O (30 cm^3), dried ($MgSO_4$) and concentrated to give a white solid. Purification by flash column chromatography (10% EtOAc: petroleum ether) gave the *title compound* (–)-**226** as a white solid (166 mg, 52%); mp 144-146 °C; $[\alpha]^{23}_D$ −102 (*c* 0.5 in $CHCl_3$); (Found: C, 78.66; H, 6.65; N, 4.38%. $C_{21}H_{21}NO_2$ requires C, 78.97; H, 6.63; N, 4.39%); ν_{max} (soln.)/cm^{-1} 2942, 1729, 1682, 1364, 1321, 1005; δ_H(500 MHz, $CDCl_3$) 1.60-1.79 (4H, m), 1.96 (1H, m), 2.13-2.21 (2H, m), 2.25 (1H, br d, *J* 13.2), 2.79 (1H, d, *J* 13.5), 3.10 (1H, br s, 5-H), 3.49 (1H, d, *J* 13.5), 7.09 (2H, br d, *J* 7.4),

7.25 (2H, m), 7.31-7.41 (3H, m), 7.45-7.50 (1H, m), 7.51-7.57 (2H, m); δ_C(125 MHz, $CDCl_3$) 20.4 (CH_2), 27.9 (CH_2), 31.9 (CH_2), 36.2 (CH_2), 39.3 (CH, C5), 44.2 (CH_2), 44.9 (C, C1), 126.8 (CH, Ar), 128.2 (CH, Ar), 128.4 (CH, Ar), 128.5 (CH, Ar), 129.3 (CH, Ar), 130.7 (CH, Ar), 135.7 (C, Ar), 136.7 (C, Ar), 175.4, 176.9; *m/z* (EI) 319.1587 (M^+, 100%). $C_{21}H_{21}NO_2$ requires M^+ 319.1572. Enantiomeric excess was established by HPLC (UV detection at 205 nm) using 1% IPA in hexane as eluent and Chiralcel OD-H column with a flow rate of 0.5 ml/min. Retention time of major enantiomer 95 min and minor enantiomer 86 min to give an ee of 95%; and the *title compound* **227** as a white solid (11 mg, 3%); mp 164-166 °C; (Found: C, 81.77; H, 6.65; N, 3.30%. $C_{28}H_{27}NO_2$ requires C, 82.12; H, 6.65; N, 3.42%); ν_{max} (soln.)/cm^{-1} 2939, 1727, 1683, 1454, 1365, 1176, 1073; δ_H(500 MHz, $CDCl_3$) 1.40 (1H, br d, *J* 13.5), 1.46 (2H, ddd, *J* 4.4, 13.2, 13.2), 1.75 (1H, m), 1.94 (1H, m), 2.02 (1H, br dd, *J* 1.5, 13.2), 2.84 (2H, d, *J* 13.5), 3.31 (2H, d, *J* 13.5), 7.02 (2H, br d, *J* 6.6), 7.19 (4H, m), 7.31-7.39 (6H, m), 7.45-7.54 (3H, m); δ_C(125 MHz, $CDCl_3$) 20.8 (CH_2), 34.9 (CH_2), 36.2 (CH_2), 43.8 (CH_2), 45.3 (C, C1 & C5), 126.8 (CH, Ar), 128.1 (CH, Ar), 128.4 (CH, Bn), 128.5 (CH, Ar), 129.3 (CH, Ar), 130.9 (CH, Bn), 136.1 (C, Ar), 136.6 (C, Bn), 176.8 (NC=O, C2 & C4); *m/z* (EI) 409.2036 (M^+, 100%), 318 (M^+–C_7H_7, 64). $C_{28}H_{27}NO_2$ requires M^+ 409.2041.

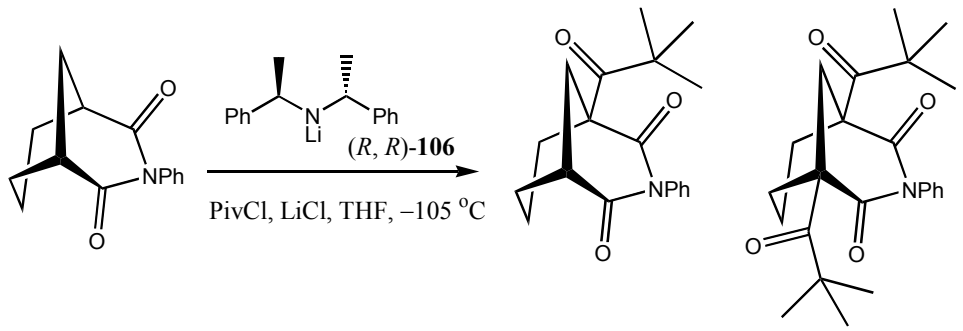
(±)-1-Benzyl-3-phenyl-3-azabicyclo[3.3.1]nonane-2,4-dione 226 and 1,5-Dibenzyl-3-azabicyclo[3.3.1]nonane-2,4-dione 227



201 **226** **227**

A solution of lithium amide base was prepared as previously described; TMP (0.20 cm^3, 1.2 mmol), in THF (5 cm^3) at −78 °C, with ^{n}BuLi (1.6 $moldm^{-3}$ solution in hexanes; 0.75 cm^3, 1.2 mmol). The solution was allowed to warm to room temperature and after 10 min re-cooled to −105 °C. The solution of lithium amide base solution was canulated into a solution of 3-phenyl-3-azabicyclo[3.3.1]nonane-2,4-dione **201** (229 mg, 1.00 mmol) and benzyl bromide (0.36 cm^3, 3.0 mmol) in THF (30 cm^3) at −105 °C maintaining the internal temperature. The resulting solution was allowed to warm slowly to room temperature over 3 h, quenched with aq. NH_4Cl (30 cm^3) and diluted with Et_2O (60 cm^3). The organic phase was extracted with H_2O (30 cm^3), dried ($MgSO_4$) and concentrated to give a white solid. Purification by flash column chromatography (10% EtOAc: petroleum ether) gave the *title compound* **226** as a white solid (171 mg, 54%, mono) and *title compound* **227** as a white solid (77 mg, 19%). Data consistent with previously described.

(–)-(1*S*,5*R*)-1-(2,2-Dimethylpropanoyl)-3-phenyl-3-azabicyclo[3.3.1]nonane -3,4-dione 228 and 1,5-*Bis*(2,2-dimethylpropanoyl)-3-phenyl-3-azabicyclo [3.3.1] nonane-2,4-dione 229

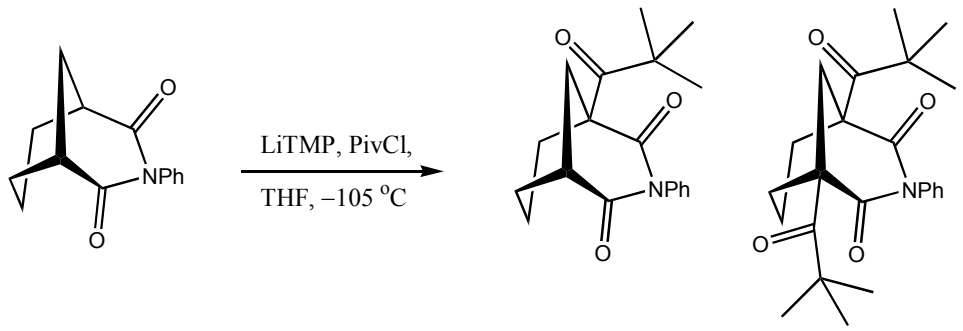


201 (–)-**228** **229**

A solution of chiral lithium amide base was prepared as previously described hydrochloride salt of the corresponding amine (314 mg, 1.20 mmol), in THF (5 cm^3) at –78 °C, with ^{n}BuLi (1.6 $moldm^{-3}$ solution in hexanes; 1.5 cm^3, 2.4 mmol). The chiral lithium amide base solution was canulated into a solution of 3-phenyl-3-azabicyclo[3.3.1]nonane-2,4-dione **201** (229 mg, 1.00 mmol) and pivaloyl chloride (0.37 cm^3, 3.0 mmol) in THF (30 cm^3) at –105 °C over 15 min maintaining the internal temperature. The resulting solution was allowed to warm slowly to room temperature over 3 h, quenched with aq. NH_4Cl (30 cm^3) and diluted with Et_2O (60 cm^3). The organic phase was extracted with aq. citric acid (30 cm^3 × 2) and H_2O (30 cm^3), dried ($MgSO_4$) and concentrated to give a white solid. Purification by flash column chromatography (15% EtOAc: petroleum ether) gave the *title compound* (–)-**228** as a white solid (175 mg, 56%); mp 200-202 °C; $[\alpha]^{22}_D$ –0.4 (*c* 0.5 in $CHCl_3$); (Found: C, 72.40; H, 7.20; N, 4.34%. $C_{19}H_{23}NO_3$ requires C, 72.80; H, 7.40; N, 4.47%); ν_{max} (soln.)/cm^{-1} 2950, 1731, 1688, 1682, 1363, 1293, 1166, 1098, 990; δ_H(500 MHz, $CDCl_3$) 1.27 (9H, s, $(CH_3)_3$), 1.60-1.80 (2H, m), 1.78 (1H, dd, *J* 2.6, 13.2, 9-H), 1.96-

2.06 (2H, m), 2.11-2.22 (2H, m), 2.95 (1H, br d, *J* 13.2, 9-H), 3.16 (1H, dddd, *J* 2.6, 2.6, 3.3, 3.3, 5-H), 7.09-7.14 (2H, m), 7.41-7.46 (1H, m), 7.46-7.50 (2H, m); δ_C(125 MHz, $CDCl_3$) 19.6 (CH_2), 28.0 (CH_2), 28.7 (CH_3), 31.5 (CH_2), 32.5 (CH_2) 38.9 (CH, C5), 45.4 (C), 56.3 (C, C1), 128.2 (CH, Ar), 128.9 (CH, Ar), 129.5 (CH, Ar), 134.8 (C, Ar), 173.7, 174.7, 210.4 (C=O); (EI) *m/z* 313.1680 (M^+, 8%), 229 (M^+–C_5H_9O, 100). $C_{19}H_{23}NO_3$ requires M^+ 313.1677. Enantiomeric excess was established by HPLC (UV detection at 205 nm) using 1% IPA in hexane as eluent and Chiralcel OD-H column with a flow rate of 0.5 ml/min. Retention time of major enantiomer 62 min and minor enantiomer was unobservable to give an ee of greater than 99%; and the *title compound* **229** as a white solid (69 mg, 17%); mp 204-206 °C; (Found: C, 72.42; H, 7.89; N, 3.43%. $C_{24}H_{31}NO_4$ requires C, 72.50; H, 7.87; N, 3.53%); ν_{max} (soln.)/cm^{-1} 2965, 2874, 1729, 1687, 1681, 1360, 1082, 967; δ_H(400 MHz, $CDCl_3$) 1.32 (18H, s, $(CH_3)_2$) 1.51-1.64 (1H, m), 1.62 (1H, d, *J* 12.8, 9-H), 2.0 (2H, ddd, *J* 4.8, 13.9, 13.9), 2.08-2.20 (3H, m), 3.45 (1H, ddd, *J* 2.2, 2.2, 12.8, 9-H), 7.10-7.15 (2H, m), 7.43-7.54 (3H, m); δ_C(100 MHz, $CDCl_3$) 19.2 (CH_2), 28.9 (CH_3), 32.2 (CH_2), 33.7 (CH_2), 45.6 (C), 56.6 (C, C1 & C5), 128.0 (CH, Ar), 129.3 (CH, Ar), 129.8 (CH, Ar), 134.3 (C, Ar), 172.9 (NC=O, C2 & C4), 209.3 (C=O); *m/z* (EI) 397.2241 (M^+, 9%), 313 (M^+–C_5H_9O, 45), 229 (M^+–$C_{10}H_{18}O_2$, 25). $C_{24}H_{31}NO_4$ requires M^+ 397.2253.

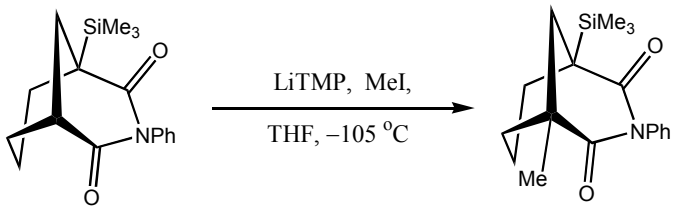
(±)-1-(2,2-Dimethylpropanoyl)-3-phenyl-3-azabicyclo[3.3.1]nonane-2,4-dione 228 and 1,5-*Bis*(2,2-dimethylpropanoyl)-3-phenyl-3-azabicyclo[3.3.1] nonane-2,4-dione 229



201 **228** **229**

A solution of lithium amide base was prepared as previously described; TMP (0.20 cm^3, 1.2 mmol), in THF (5 cm^3) at −78 °C, with ^{n}BuLi (1.6 $moldm^{-3}$ solution in hexanes; 0.75 cm^3, 1.2 mmol). The solution was allowed to warm to room temperature and after 10 min re-cooled to −105 °C. The solution of lithium amide base solution was canulated into a solution of 3-phenyl-3-azabicyclo[3.3.1]nonane-2,4-dione **201** (229 mg, 1.00 mmol) and pivaloyl chloride (0.37 cm^3, 3 mmol) in THF (30 cm^3) at −105 °C maintaining the internal temperature. The resulting solution was allowed to warm slowly to room temperature over 3 h, quenched with aq. NH_4Cl (30 cm^3) and diluted with Et_2O (60 cm^3). The organic phase was extracted with H_2O (30 cm^3), dried ($MgSO_4$) and concentrated to give a white solid. Purification by flash column chromatography (15% EtOAc: petroleum ether) gave the *title compound* **228** as a white solid (73 mg, 23%, mono) and *title compound* **229** as a white solid (137 mg, 34%). Data consistent with previously described.

(−)-(1*R*,5*R*)-1-Methyl-3-phenyl-5-(trimethylsilyl)-3-azabicyclo[3.3.1]nonane-2,4-dione 230

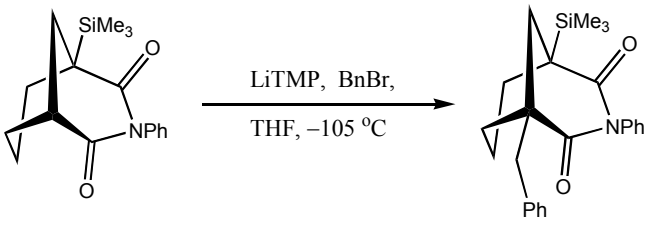


(−)-**218** (−)-**230**

A solution of lithium amide base was prepared as previously described; TMP (0.078 cm^3, 0.460 mmol), in THF (3 cm^3) at −78 °C, with ^{n}BuLi (1.6 $moldm^{-3}$ solution in hexanes; 0.28 cm^3, 0.45 mmol). The solution was allowed to warm to room temperature and after 10 min recooled to −105 °C. The lithium amide base solution was canulated into a solution of (−)-(1*R*,5*R*)-3-phenyl-1-(trimethylsilyl)-3-azabicyclo[3.3.1]nonan-2,4-dione (−)-**218** (100 mg, 0.330 mmol, ($[\alpha]^{20}_D$ −60 (*c* 0.26 in $CHCl_3$)) and methyl iodide (0.082 cm^3, 1.30 mmol) in THF (9 cm^3) at −105 °C maintaining the internal temperature. The resulting solution was allowed to warm slowly to room temperature over 3 h, quenched with aq. NH_4Cl (20 cm^3) and diluted with Et_2O (30 cm^3). The organic phase was extracted with H_2O (20 cm^3), dried ($MgSO_4$) and concentrated to give a yellow solid. Purification by flash column chromatography (15% EtOAc: petroleum ether) gave the *title compound* (−)-**230** as a yellow solid (90 mg, 87%); mp 151-153 °C; $[\alpha]^{23}_D$ −48 (*c* 0.5 in $CHCl_3$); (Found: C, 68.55; H, 7.91; N 4.37%. $C_{18}H_{25}NO_2Si$ requires C, 68.54; H, 7.99; N, 4.44%); ν_{max} (soln.)/cm^{-1} 2934, 2854, 1720, 1673, 1348, 1328, 1146, 1005, 858; δ_H(500 MHz, $CDCl_3$) 0.14 (9H, s, $SiMe_3$), 1.29 (3H, s, CH_3), 1.47 (1H, ddd, *J* 4.9, 13.5, 13.5), 1.52 (1H, d, *J* 13.5), 1.57 (1H, ddd, *J* 4.4,

13.5, 13.5), 1.69 (1H, ddddd, *J* 4.4, 4.4, 13.5, 13.5, 13.5), 1.85 (1H, m), 2.04 (1H, m), 2.10 (1H, m), 2.16 (1H, d, *J* 13.5) 6.98-7.10 (2H, m), 7.36-7.40 (1H, m), 7.43-7.47 (2H, m); δ_C(125 MHz, $CDCl_3$) –3.7 ($SiMe_3$), 21.3 (CH_2), 25.8 (CH_3), 30.0 (CH_2), 36.1 (C), 36.7 (CH_2), 36.9 (CH_2), 39.3 (C), 128.3 (CH, Ar), 128.4 (CH, Ar), 129.2 (CH, Ar), 136.2 (C, Ar), 177.9, 178.6; *m/z* (EI) 315.1649 (M^+, 45%), 300 (M^+–CH_3, 89), 73 ($SiMe_3$, 100). $C_{18}H_{25}NO_2Si$ requires M^+ 315.1654.

(+)-(1*S*,5*R*)-1-Benzyl-3-phenyl-5-(trimethylsilyl)-3-azabicyclo[3.3.1]nonane -2,4-dione 231

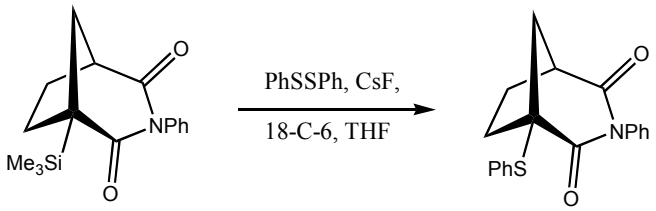


(–)-**218** (+)-**231**

A solution of lithium amide base was prepared as previously described; TMP (0.078 cm^3, 0.460 mmol), in THF (3 cm^3) at –78 °C, with ^{n}BuLi (1.6 $moldm^{-3}$ solution in hexanes; 0.28 cm^3, 0.45 mmol). The lithium amide base solution was canulated into a solution of (–)-(1*R*,5*R*)-3-phenyl-1-(trimethylsilyl)-3-azabicyclo[3.3.1]nonan-2,4-dione (–)-**218** (100 mg, 0.330 mmol) and benzyl bromide (0.16 cm^3, 1.4 mmol) in THF (9 cm^3) at –105 °C maintaining the internal temperature. The resulting solution was allowed to warm slowly to room temperature over 3 h, quenched with aq. NH_4Cl (20 cm^3) and diluted with Et_2O (30 cm^3). The organic phase was extracted with H_2O (20 cm^3), dried ($MgSO_4$) and evaporated to a white solid. Purification by flash column

chromatography (15% EtOAc: petroleum ether) gave the *title compound* (+)-**231** as a gum (115 mg, 88%); $[\alpha]^{19}_{D}$ +17 (*c* 0.515 in $CHCl_3$); (Found: C, 73.62; H, 7.59; N, 3.35%. $C_{24}H_{29}NO_2Si$ requires C, 73.62; H, 7.47; N, 3.58%); ν_{max} (soln.)/cm^{-1} 2935, 2867, 1717, 1673, 1366, 1348, 1169, 1014, 859; δ_H(400 MHz, $CDCl_3$) 0.09 (9H, s, $SiMe_3$), 1.45 (1H, d, *J* 13.2), 1.48-1.60 (2H, m) 1.71 (1H, ddddd, *J* 4.4, 4.4, 13.7, 13.7, 13.7) 1.87 (1H, m), 2.02-2.16 (3H, m), 2.82 (1H, d, *J* 13.5, $PhCH_2$), 3.32 (1H, d, *J* 13.5, $PhCH_2$), 7.02 (2H, m, Ar), 7.20 (2H, m, Ar), 7.25-7.36 (3H, m, Ar), 7.37-7.44 (1H, m, Ar), 7.44-7.52 (2H, m, Ar); δ_C(100 MHz, $CDCl_3$) –3.7 ($SiMe_3$), 21.3 (CH_2), 29.9 (CH_2), 33.2 (CH_2), 35.4 (C, C5), 35.5 (CH_2), 43.9 (C, C1), 44.3 (CH_2), 126.7 (CH, Ar), 128.1 (CH, Ar), 128.3 (CH, Ar), 128.4 (CH, Ar), 129.3 (CH, Ar), 130.8 (CH, Ar), 136.2 (C, Ar), 136.7 (C, Ar), 177.2, 178.3; *m/z* (EI) 391.1961 (M^+, 55%), 376 (M^+–CH_3, 65), 73 ($SiMe_3$, 100). $C_{24}H_{29}NO_2Si$ requires M^+ 391.1967.

(+)-(1*S*,5*S*)-3-Phenyl-1-(phenylsulfanyl)-3-azabicyclo[3.2.1]octane-2,4-dione 243

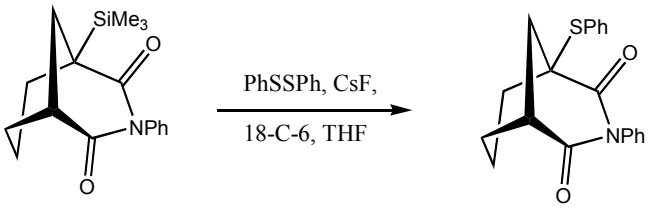


(+)-**212** (+)-**243**

Cesium fluoride (58 mg, 0.38 mmol) was flame dried under nitrogen and allowed to cool before adding 18-crown-6 (8.0 mg, 0.03 mmol) and THF (1 cm^3). A solution of (+)-(1*S*,5*S*)-3-phenyl-1-(trimethylsilyl)-3-azabicyclo[3.2.1] octane-2,4-dione (+)-**212** (72 mg, 0.25 mmol, $[\alpha]^{23}_{D}$ +37) and phenyl disulfide

(273 mg, 1.25 mmol) were added dropwise at room temperature and allowed to stir for 14 h. The reaction was diluted with Et_2O (10 cm^3) and washed with H_2O (10 cm^3). The organic extract was dried and concentrated to a yellow solid. Purification by column chromatography (50% EtOAc: petroleum ether) gave the *title compound* (+)-**243** as a white solid (46 mg, 57%); mp 164-166 °C; $[\alpha]^{22}_D$ +86 (*c* 0.5 in $CHCl_3$); ν_{max} (soln.)/cm^{-1} 2952, 1740, 1692, 1599, 1356, 1323, 1160, 1133, 1073, 957, 891; δ_H(400 MHz, $CDCl_3$) 1.98 (1H, dd, *J* 4.7, 12.0), 2.14 (1H, m), 2.24-2.37 (3H, m), 2.41 (1H, br d, *J* 12.0), 3.29 (1H, dd, *J* 4.7, 6.7), 7.01-7.05 (2H, m), 7.33-7.48 (6H, m), 7.64-7.68 (2H, m); δ_C(100 MHz, $CDCl_3$) 28.0 (CH_2), 34.7 (CH_2), 39.6 (CH_2), 45.0 (CH), 61.0 (C), 128.2 (CH, Ar), 128.8 (CH, Ar), 129.0 (CH, Ar), 129.3 (CH, Ar), 129.5 (CH, Ar), 130.8 (C), 134.6 (C), 137.1 (CH, Ar), 174.2, 175.8; *m/z* (EI) 323.0974 (M^+, 100%), 202 (20), 175 (41), 67 (42). $C_{19}H_{17}NO_2S$ requires M^+ 323.0980.

(–)-(1*R*,5*R*)-3-Phenyl-1-(phenylsulfanyl)-3-azabicyclo[3.3.1]nonane-2,4-dione 244

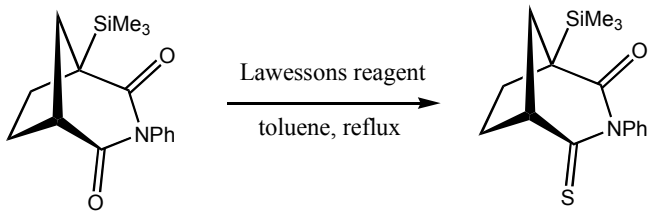


(–)-**218** (–)-**244**

Cesium fluoride (114 mg, 0.750 mmol) was flame dried under nitrogen and allowed to cool before adding 18-crown-6 (13 mg, 0.05 mmol) and THF (2 cm^3). A solution of (–)-(1*R*,5*R*)-3-phenyl-1-(trimethylsilyl)-3-azabicyclo[3.3.1] nonan-2,4-dione (–)-**218** (151 mg, 0.500 mmol, $[\alpha]^{21}_D$ –62) and phenyl

disulfide (546 mg, 2.50 mmol) was added dropwise at room temperature and allowed to stir for 14 h. The reaction was diluted with Et_2O (10 cm^3) and washed with H_2O (10 cm^3). The organic extract was dried and concentrating to a yellow solid. Purification by column chromatography (20% EtOAc: petroleum ether) gave the *title compound* (–)-**244** as a white solid (134 mg, 79%); mp 150-152 °C. $[\alpha]^{22}_D$ –133 (*c* 0.5 in $CHCl_3$); ν_{max} (soln.)/cm^{-1} 2948, 1731, 1688, 1456, 1352, 1160, 1101, 1001; δ_H(500 MHz, $CDCl_3$) 1.66-1.75 (2H, m), 1.83 (1H, m), 1.89 (1H, dd, *J* 2.9, 13.2), 1.95 (1H, m), 2.12 (1H, br d, *J* 8.8), 2.30 (1H, m), 2.47 (1H, br d, *J* 13.2), 3.06 (1H, br s, 5-H), 7.00 (2H, br d, *J* 7.3), 7.34-7.49 (6H, m), 7.60 (2H, m); δ_C(125 MHz, $CDCl_3$) 21.0 (CH_2), 27.4 (CH_2), 35.0 (CH_2), 35.8 (CH_2), 40.0 (CH, C5), 54.6 (C, C1), 128.3 (CH, Ar), 128.8 (CH, Ar), 128.9 (CH, Ar), 129.4 (CH, Ar), 129.7 (CH, Ar), 135.5 (C, Ar), 137.5 (CH, Ar), 174.0, 174.8; *m/z* (EI) 337.1121 (M^+, 100%). $C_{20}H_{19}NO_2S$ requires M^+ 337.1136.

(–)-(1*R*,5*R*)-3-Phenyl-4-thioxo-1-(trimethylsilyl)-3-azabicyclo[3.2.1]octan-2-one 245

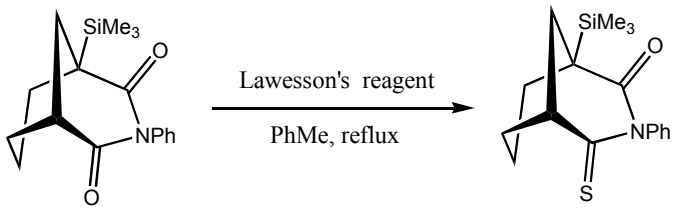


(–)-**212** (–)-**245**

A mixture of (–)-(1*R*,5*R*)-3-phenyl-1-(trimethylsilyl)-3-azabicyclo[3.2.1] octane-2,4-dione (–)-**212** (100 mg, 0.350 mmol, $[\alpha]^{19}_D$ –26 (*c* 0.512 in $CHCl_3$)) and Lawesson's reagent (170 mg, 0.420 mmol) in toluene (10 cm^3) was heated

at reflux for 38 h. The yellow solution was allowed to cool and diluted with EtOAc (15 cm^3) and H_2O (15 cm^3), extracted with aq. NaCl (15 cm^3), dried ($MgSO_4$) and concentrated to a yellow solid. Purification by column chromatography (15% EtOAc: petroleum ether) gave the *title compound* (–)-**245** as a yellow solid (47 mg, 44%); mp 156-158 °C; $[\alpha]^{19}_D$ –83 (*c* 0.5 in $CHCl_3$); (Found: C, 63.06; H, 6.79; N, 4.43%. $C_{16}H_{21}NOSSi$ requires C, 63.32; H, 6.97; N, 4.62%); ν_{max} (soln.)/cm^{-1} 2954, 1703, 1352, 1312, 1276, 1112 (C=S); δ_H(400 MHz, $CDCl_3$) 0.16 (9H, s, $SiMe_3$), 1.65 (1H, dd, *J* 4.2, 11.9, 8-H), 2.07–2.17 (3H, m), 2.28 (1H, m), 2.34 (1H, d, *J* 11.9), 4.02 (1H, dd, *J* 4.2, 6.7, 5-H), 7.03 (2H, br s), 7.38–7.42 (1H, m), 7.45–7.49 (2H, m); δ_C(100 MHz, $CDCl_3$) –2.9 ($SiMe_3$), 31.5 (CH_2), 31.8 (CH_2), 35.2 (CH_2), 43.3 (C, C1), 55.7 (CH, C5), 127.7 (CH, Ar), 128.2 (CH, Ar), 128.5 (CH, Ar), 129.4 (CH, Ar), 139.3 (C, Ar), 177.2 (C=O, C2), 216.3 (C=S, C4); *m/z* (EI) 303.1110 (M^+, 96%), 73 ($SiMe_3$, 100). $C_{16}H_{21}NOSSi$ requires M^+ 303.1113.

(–)-(1*R*,5*R*)-3-Phenyl-4-thioxo-1-(trimethylsilyl)-3-azabicyclo[3.3.1]nonan-2-one 246

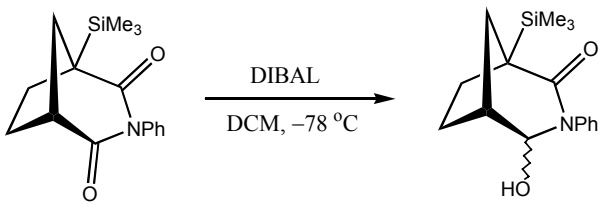


(–)-**218** (–)-**246**

A mixture of (–)-(1*R*,5*R*)-3-phenyl-1-(trimethylsilyl)-3-azabicyclo[3.3.1]nonan-2,4-dione (–)-**218** (100 mg, 0.330 mmol, $[\alpha]^{23}_D$ –62) and Lawesson's reagent (148 mg, 0.370 mmol) in toluene (10 cm^3) was heated at reflux for 14 h. The

yellow solution was diluted with EtOAc (15 cm^3) and H_2O (15 cm^3), extracted with aq. NaCl (15 cm^3), dried ($MgSO_4$) and concentrated to a yellow oily solid. Purification by column chromatography (15% EtOAc: petroleum ether) gave the *title compound* (–)-**246** as a yellow solid (54 mg, 52%); mp 147-149 °C; $[\alpha]^{19}_D$ –152 (*c* 0.5 in $CHCl_3$); (Found: C, 64.14; H, 7.31; N, 4.39%. $C_{17}H_{23}NOSSi$ requires C, 64.31; H, 7.30; N, 4.41%); ν_{max} (soln.)/cm^{-1} 2944, 1693, 1336, 1116 (C=S), 1099; δ_H(400 MHz, $CDCl_3$) 0.13 (9H, s, $SiMe_3$), 1.65-1.72 (2H, m), 1.75 (1H, dd, *J* 2.6, 13.2), 1.83-1.93 (2H, m), 2.14 (1H, br d, *J* 9.2), 2.25 (1H, br d, *J* 13.2), 2.36 (1H, br d, *J* 1.5, 13.2), 3.67 (1H, dddd, *J* 3.1, 3.1, 3.1, 3.1), 6.96 (1H, br s), 7.18 (1H, br s), 7.38-7.44 (1H, m), 7.45-7.51 (2H, m); δ_C(100 MHz, $CDCl_3$) –3.7 (CH_3, $SiMe_3$), 20.4 (CH_2), 29.9 (CH_2), 30.8 (CH_2), 31.6 (CH_2), 34.9 (C, C1), 48.1 (CH, C5), 127.2 (CH, Ar), 128.5 (CH, Ar), 129.3 (CH, Ar), 140.5 (C, Ar), 176.3 (NC=O, C2), 215.5 (NC=S, C4); *m/z* (EI) 317.1212 (M^+, 63%), 73 ($SiMe_3$, 100). $C_{17}H_{23}NOSSi$ requires M^+ 317.1269.

(–)-(1*R*,4*R*,5*R*)-4-Hydroxy-3-phenyl-1-(trimethylsilyl)-3-azabicyclo[3.2.1] octan-2-one and (1*R*,4*S*,5*R*)-4-Hydroxy-3-phenyl-1-(trimethylsilyl)-3-aza bicyclo[3.2.1]octan-2-one 247ab

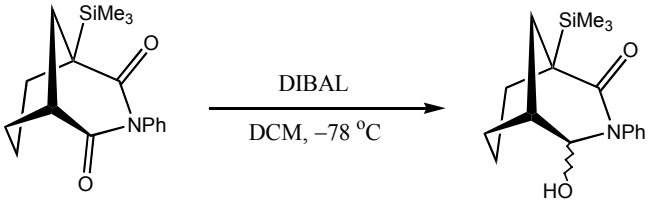


(–)-**212** (–)-**247ab**

A solution of (–)-(1*R*,5*R*)-3-phenyl-1-(trimethylsilyl)-3-azabicyclo[3.2.1] octane-2,4-dione (–)-**212** (287 mg, 1.00 mmol, $[\alpha]^{22}_{D}$ –28 (*c* 0.5 in $CHCl_3$)) in DCM (30 cm^3) was cooled to –78 °C and DIBAL (2.0 cm^3, 2.0 mmol, 1N in DCM) was added. After 20 min the reaction was quenched with EtOAc (5 cm^3), diluted with DCM (30 cm^3) and washed with aq. potassium sodium tartrate (30 cm^3). The organic extract was dried ($MgSO_4$) and concentrated to give the *title compound* (–)-**247ab** as a white solid (238 mg, 82%) as an inseparable 6 to 1 mixture of *exo*/*endo* isomers; mp 125-127 °C; $[\alpha]^{20}_{D}$ –41 (*c* 0.51 in $CHCl_3$); (Found: C, 66.27; H, 8.08; N, 4.50%. $C_{16}H_{23}NO_2Si$ requires C, 66.39; H, 8.01; N, 4.84%); ν_{max} (soln.)/cm^{-1} 3592, 2951, 2901, 2872, 1650, 1594, 1391, 1326, 1291, 1084, 1064, 1031, 894, 860; δ_H(400 MHz, $CDCl_3$) 0.10 (9H, s, $SiMe_3$, major), 0.13 (1.4H, s, $SiMe_3$, minor), 1.62 (1H, dd, *J* 5.3, 12.3), 1.71 (1.2H, dddd, *J* 4.4, 7.0, 11.4, 13.7, major & minor), 1.86 (1.2H, ddd, *J* 5.6, 11.4, 13.2, major & minor), 1.95-2.07 (2.4H, m, major & minor), 2.36 (1H, ddd, *J* 4.4, 8.8, 13.2, major), 2.42 (1H, d, *J* 5.0, major), 2.61 (0.2H, br d, *J* 5.0, minor), 2.67 (1H, ddd, *J* 5.3, 5.3, 5.3, major), 4.85 (0.2H, br s, 4-H, minor), 5.27 (1H, dd, *J* 4.7, 4.7, 4-H, major), 7.14-7.19 (2.4H, m, major & minor), 7.28-7.33 (1.2H, m, major & minor), 7.38-7.44 (2.4H, m, major & minor); δ_C(100 MHz, $CDCl_3$) –2.5 ($SiMe_3$, major), –2.4 ($SiMe_3$, minor), 22.1 (CH_2, major), 26.6 (CH_2, minor), 30.2 (CH_2, minor), 31.9 (CH_2, major), 32.6 (CH_2, minor), 33.7 (CH_2, major), 40.3 (CH, minor), 40.5 (CH, C5, major), 40.6 (C, major), 41.9 (C, minor), 84.8 (CH, C4, major), 86.8 (CH, C4, minor), 127.5 (CH, Ar, minor), 127.7 (CH, Ar, major), 128.3 (CH, Ar, minor), 128.9 (CH, Ar, major), 129.4 (CH, Ar, minor), 129.5 (CH, Ar, major), 138.6 (C, Ar, major), 140.4 (C, Ar, minor), 176.5 (C=O, minor), 177.1 (C=O, major); *m/z*

(EI) 289.1491 (M^+, 16%), 274 (M^+–CH_3, 100). $C_{16}H_{23}NO_2Si$ requires M^+ 289.1498.

(–)-(1*R*,4*R*,5*R*)-4-Hydroxy-3-phenyl-1-(trimethylsilyl)-3-azabicyclo[3.3.1] nonan-2-one and (–)-(1*R*,4*S*,5*R*)-4-Hydroxy-3-phenyl-1-(trimethylsilyl)-3-azabicyclo[3.3.1]nonan-2-one 248ab

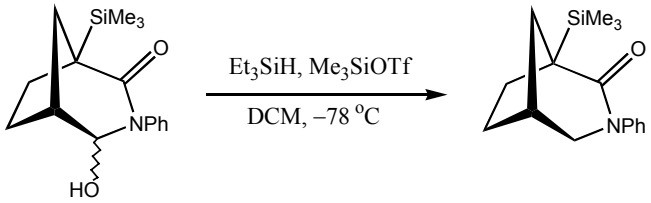


(–)-**218** (–)-**248ab**

A solution of (–)-(1*R*,5*R*)-3-phenyl-1-(trimethylsilyl)-3-azabicyclo[3.3.1] nonan-2,4-dione (–)-**218** (100 mg, 0.330 mmol, $[\alpha]^{23}_D$ –62) in DCM (10 cm^3) was cooled to –78 °C and DIBAL (0.53 cm^3, 0.53 mmol, 1N in DCM) was added. After 20 min the reaction was quenched with EtOAc (5 cm^3), diluted with DCM (30 cm^3) and washed with aq. potassium sodium tartrate (30 cm^3). The organic extract was dried ($MgSO_4$) and concentrated to give the *title compound* (–)-**248ab** as a white solid (80 mg, 79%) and an inseparable 3 to 1 mixture of *exo*/*endo* isomers; mp 116-118 °C; $[\alpha]^{20}_D$ –70 (*c* 0.23 in $CHCl_3$); ν_{max} (soln.)/cm^{-1} 3584, 2940, 1673, 1638, 1454, 1351, 1308, 1070, 892; δ_H(400 MHz, $CDCl_3$) 0.08 (9H, s, $SiMe_3$, major), 0.12 (2.7H, s, $SiMe_3$, minor), 1.46-1.62 (3H, m, major), 1.64-1.76 (m, 3H, major), 1.84 (1.3H, ddddd, *J* 4.4, 4.4, 4.4, 13.5, 13.5, major & minor), 1.92 (0.3H, br d, *J* 9.9, minor), 2.0 (1.3H, br d, *J* 13.9, major & minor), 2.05 (0.3H, br s, minor), 2.12 (1H, br d, *J* 13.2, major), 2.22 (0.3H, br s, minor), 2.34 (2.6H, m, major & minor), 2.40 (1H, d, *J* 5.1,

major), 2.53 (0.3H, d, *J* 4.0, minor), 5.07 (0.3H, br d, *J* 3.7, 4-H, minor), 5.37 (1H, dd, *J* 5.5, 5.5, 4-H, major), 7.18-7.27 (2.6H, m, major & minor), 7.31-7.36 (1.3H, m, major & minor), 7.41-7.46 (2.6H, m, major & minor); δ_C(100 MHz, $CDCl_3$) −3.4 ($SiMe_3$), 20.1 (CH_2, minor), 20.9 (CH_2, major), 24.9 (CH_2, major), 26.8 (CH_2, minor), 28.8 (CH_2, minor), 29.0 (C, minor), 29.6 (CH_2, major), 31.2 (CH_2, minor), 31.3 (CH_2, major), 31.8 (CH, major), 34.0 (CH, minor), 34.2 (C, major), 84.3 (CH, major), 86.5 (CH, minor), 127.8 (CH, Ar, minor), 127.9 (CH, Ar, minor), 128.5 (CH, Ar, minor), 129.3 (CH, Ar, major), 129.6 (CH, Ar, major), 139.2 (C, Ar, major), 141.2 (C, Ar, minor), 175.9 (NC=O, minor), 176.4 (NC=O, major); *m/z* (EI) 303.1647 (M^+, 53%), 302 (M^+–H, 28), 288 (M^+–CH_3, 100), 286 (M^+–OH, 63), 285 (M^+–OH_2, 68), 284 (M^+–OH_3, 67). $C_{17}H_{25}NO_2Si$ requires M^+ 303.1654.

(–)-(1*R*,5*R*)-3-Phenyl-1-(trimethylsilyl)-3-azabicyclo[3.2.1]octan-2-one 249

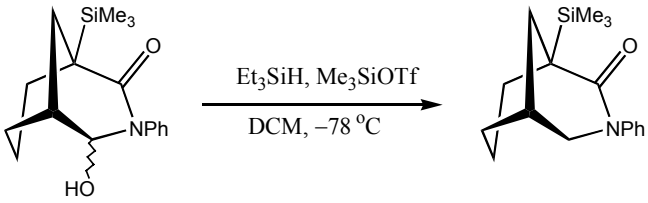


(–)-**247ab** (–)-**249**

A solution of (–)-(1*R*,(4*R*/*S*),5*R*)-4-hydroxy-3-phenyl-1-(trimethylsilyl)-3-aza bicyclo[3.2.1]octan-2-one (–)-**247ab** (153 mg, 0.530 mmol, $[\alpha]^{20}_D$ –41) in DCM (5 cm^3) was cooled to –78 °C and Me_3SiOTf (0.20 cm^3, 1.1 mmol) and Et_3SiH (0.17 cm^3, 1.1 mmol) were added. The reaction was allowed to warm to room temperature and stirred for 12 h. The reaction was quenched with aq. $NaHCO_3$ (5 cm^3) and diluted with DCM (10 cm^3). The organic layer was

separated and the aqueous extracted with DCM (10 cm^3 × 3). The combined organic extracts were dried ($MgSO_4$) and concentrated to give a yellow oil. Purification by column chromatography (15% EtOAc: petroleum ether) gave the *title compound* (–)-**249** as a white solid (127 mg, 88%); mp 63-65 °C; $[\alpha]^{23}_D$ –23 (*c* 0.5 in $CHCl_3$); (Found: C, 69.73; H, 8.58; N, 5.01%. $C_{16}H_{23}NOSi$ requires C, 70.29; H, 8.49; N, 5.13%; ν_{max} (soln.)/cm^{-1} 2949, 2871, 1639, 1593, 1488, 1328, 1289, 1150, 1122, 894, 859, 840; δ_H(500 MHz, $CDCl_3$) 0.13 (9H, s, $SiMe_3$), 1.64 (1H, ddd, *J* 1.4, 5.2, 11.7, 8-H), 1.72-1.90 (2H, m), 1.98 (1H, br d, *J* 11.7, 8-H), 2.03 (1H, m), 2.16 (1H, dddd, *J* 1.9, 3.6, 9.1, 13.0), 2.63 (1H, m) 3.33 (1H, ddd, *J* 1.4, 1.4, 11.0, 4-H), 3.70 (1H, ddd, *J* 0.7, 3.9, 11.0, 4-H), 7.15-7.25 (3H, m), 7.32-7.42 (2H, m); δ_C(125 MHz, $CDCl_3$) –2.3 (CH_3, $SiMe_3$), 30.5 (CH_2), 34.1 (CH_2), 34.4 (CH, C5), 34.7 (CH_2), 41.5 (C, C1), 59.4 (CH_2, C4), 126.4 (CH, Ar), 126.5 (CH, Ar), 129.2 (CH, Ar), 142.9 (C, Ar), 176.7 (NC=O, C2); *m/z* (EI) 273.1544 (M^+, 29%), 258 (M^+–CH_3, 100), 73 ($SiMe_3$, 79). $C_{16}H_{23}NOSi$ requires M^+ 273.1548.

(–)-(1*R*,5*R*)-3-Phenyl-1-(trimethylsilyl)-3-azabicyclo[3.3.1]nonan-2-one 250

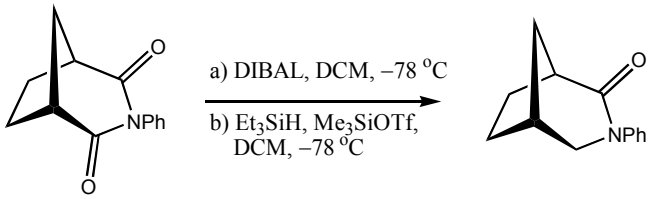


(–)-**248ab** (–)-**250**

A solution of (–)-(1*R*,(4*R*/*S*),5*R*)-4-hydroxy-3-phenyl-1-(trimethylsilyl)-3-azabicyclo[3.3.1]nonan-2-one (–)-**248ab** (52 mg, 0.17 mmol, $[\alpha]^{20}_D$ –70) in DCM (2 cm^3) was cooled to –78 °C and Me_3SiOTf (0.062 cm^3, 0.340 mmol)

and Et_3SiH (0.055 cm^3, 0.340 mmol) were added. The reaction was left for 2 h before allowing to warm to room temperature and stirring for 4 h. The reaction was quenched with EtOAc (0.5 cm^3), diluted with DCM (5 cm^3) and washed with aq. $NaHCO_3$ (2 cm^3). The aqueous was extracted with DCM (5 cm^3 × 3). The combined organic extracts were dried ($MgSO_4$) and concentrated to a colourless oil. Purification by column chromatography (10% EtOAc: petroleum ether) gave the *title compound* (–)-**250** as a white oily solid (41 mg, 83%); mp 89-91 °C; $[\alpha]^{23}_D$ –70 (*c* 0.5 in $CHCl_3$); ν_{max} (soln.)/cm^{-1} 2929, 2853, 1717, 1628, 1590, 1489, 1453, 1353, 1327, 1298, 1158, 1085, 881; δ_H(400 MHz, $CDCl_3$) 0.18 (9H, s), 1.61 (1H, m), 1.74-1.94 (5H, m), 2.08 (1H, br dd, *J* 2.2, 12.8), 2.18 (1H, m), 2.34 (1H, m), 3.59 (1H, dd, *J* 1.1, 12.1), 3.93 (1H, dd, *J* 6.2, 12.1), 7.28-7.34 (3H, m), 7.43-7.49 (2H, m); δ_C(100 MHz, $CDCl_3$) –3.2 ($SiMe_3$), 20.7 (CH_2), 27.3 (CH), 31.0 (CH_2), 31.5 (CH_2), 32.7 (CH_2), 34.1 (C), 57.5 (CH_2), 126.8 (CH, Ar), 127.0 (CH, Ar), 129.4 (CH, Ar), 143.8 (C, Ar), 176.0; *m/z* (EI) 287.1701 (M^+, 42%), 286 (31), 272 (100), 258 (57), 196 (85), 106 (23), 73 ($SiMe_3$, 82). $C_{17}H_{25}NOSi$ requires M^+ 287.1705.

(±)-3-Phenyl-3-azabicyclo[3.2.1]octan-2-one 202

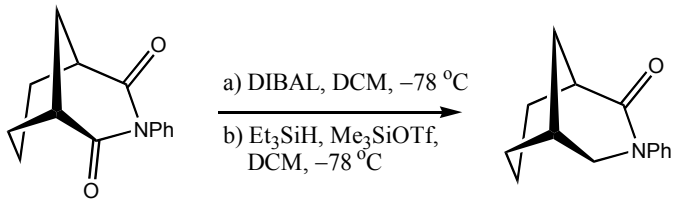


200 **202**

A solution of 3-phenyl-3-azabicyclo[3.2.1]octane-2,4-dione **200** (1.5 g, 6.9 mmol) in DCM (40 cm^3) was cooled to –78 °C and DIBAL (8.8 cm^3, 8.8 mmol, 1N in DCM) was added. After 45 min at –78 °C the reaction was

quenched with EtOAc (10 cm^3), diluted with DCM (40 cm^3) and washed with aq. potassium sodium tartrate (40 cm^3). The organic extract was separated and the aqueous extracted with DCM (40 cm^3 × 3). The combined organics were dried ($MgSO_4$) and concentrated to give 4-hydroxy-3-phenyl-3-azabicyclo[3.2.1]octan-2-one as a white solid in quantitative yield (1.52g). A solution of the hydroxylactam (1.52 g, 6.9 mmol) in DCM (50 cm^3) was cooled to –78 °C and Me_3SiOTf (2.65 cm^3, 13.8 mmol) and Et_3SiH (2.3 cm^3, 13.8 mmol) were added. The reaction was allowed to stir for 2 h before allowing to warm to room temperature and leaving to stir for 14 h. The reaction was quenched with aq. $NaHCO_3$ (30 cm^3). The organic layer was separated and the aqueous extracted with DCM (20 cm^3 × 3). The combined organic extracts were dried ($MgSO_4$) and concentrated to give a white solid. Purification by column chromatography (20% EtOAc: petroleum ether) gave the *title compound* **202** as a white solid (780 mg, 55%); mp 109-111 °C; ν_{max} (soln.)/cm^{-1} 2947, 2875, 1650, 1594, 1343, 1290, 1129, 1073; δ_H(400 MHz, $CDCl_3$) 1.72-1.81 (2H, m), 1.93-2.20 (4H, m), 2.63 (1H, br ddd, *J* 4.4, 4.4, 4.4), 2.92 (1H, br dd, *J* 4.4), 3.32 (1H, ddd, *J* 1.5, 1.5, 11.0), 3.75 (1H, ddd, *J* 1.1, 3.7, 11.0), 7.22-7.29 (3H, m), 7.37-7.43 (2H, m); δ_C(100 MHz, $CDCl_3$) 29.4 (CH_2), 31.5 (CH_2), 33.1 (CH_2), 34.4 (CH), 44.5 (CH), 59.7 (CH_2), 126.7 (CH, Ar), 127.0 (CH, Ar), 129.6 (CH, Ar), 142.9 (C, Ar), 174.8; *m/z* (EI) 201.1154 (M^+, 100%), 200 (M^+–H^+, 37). $C_{13}H_{15}NO$ requires M^+ 201.1153.

(±)-3-Phenyl-3-azabicyclo[3.3.1]nonan-2-one 203

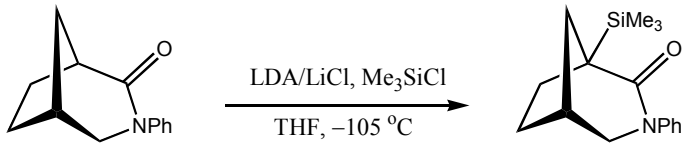


201 **203**

A solution of 3-phenyl-3-azabicyclo[3.3.1]nonane-2,4-dione **201** (2.0 g, 8.7 mmol) in DCM (50 cm^3) was cooled to –78 °C and DIBAL (10.5 cm^3, 10.5 mmol, 1N in DCM) was added. After 1 h at –78 °C the reaction was quenched with EtOAc (10 cm^3), diluted with DCM (50 cm^3) and extracted with aq. potassium sodium tartrate (25 cm^3). The aqueous was further extracted with DCM (50 cm^3 × 3). The combined organics were dried ($MgSO_4$) and concentrated to give 4-hydroxy-3-phenyl-3-azabicyclo[3.3.1]nonan-2-one as a white solid in quantitative yield (2.02 g); A solution of the hydroxylactam (2.02 g, 8.7 mmol) in DCM (75 cm^3) was cooled to –78 °C and Me_3SiOTf (3.2 cm^3, 18 mmol) and Et_3SiH (2.8 cm^3, 18 mmol) were added. The reaction was allowed to stir for 2 h before allowing to warm to room temperature and leaving to stir for 14 h. The reaction was quenched with aq. $NaHCO_3$ (35 cm^3) and diluted with DCM (75 cm^3). The organic layer was separated and the aqueous extracted with DCM (35 cm^3 × 3). The combined organic extracts were dried ($MgSO_4$) and concentrated to give a white solid. Purification by column chromatography (50% EtOAc: petroleum ether) gave the *title compound* **203** as a white solid (1.16 g, 62%); mp 81-83 °C; (Found: C, 78.16; H, 7.95; N, 6.29%. $C_{14}H_{17}NO$ requires C, 78.09; H, 7.96; N, 6.51%); ν_{max} (soln.)/cm^{-1} 2923, 2859, 1651, 1633, 1592, 1359, 1307, 1145, 1075; δ_H(400

MHz, $CDCl_3$) 1.60-1.86 (6H, m), 2.08-2.16 (2H, m), 2.26 (1H, br s), 2.73 (1H, m), 3.44 (1H, ddd, *J* 0.9, 1.7, 12.3), 3.89 (1H, ddd, *J* 0.9, 6.1, 12.3), 7.23-7.29 (3H, m), 7.37-7.43 (2H, m); δ_C(100 MHz, $CDCl_3$) 20.0 (CH_2), 27.6 (CH), 29.8 (CH_2), 30.1 (CH_2), 32.7 (CH_2), 38.4 (CH), 57.3 (CH_2), 126.6 (CH, Ar), 126.9 (CH, Ar), 129.3 (CH, Ar), 143.2 (C, Ar), 173.1; *m/z* (EI) 215.1300 (M^+, 100%), 214 (M^+–H, 43). $C_{14}H_{17}NO$ requires M^+ 215.1310.

(±)-3-Phenyl-1-(trimethylsilyl)-3-azabicyclo[3.2.1]octan-2-one 249

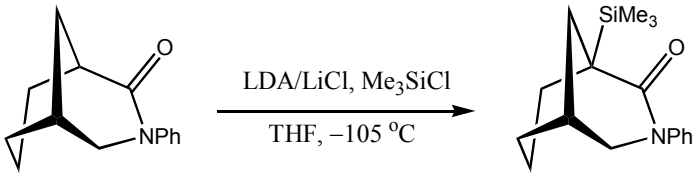


202 **249**

A solution of LDA/LiCl was prepared as previously described; DIPA/HCl (165 mg, 1.20 mmol) in THF (5 cm^3) at −78 °C, ^{n}BuLi (2.2 $moldm^{-3}$ solution in hexanes; 1.1 cm^3, 2.4 mmol). The solution was allowed to warm to room temperature and after 10 min re-cooled to −105 °C (internal temperature). The solution of LDA/LiCl was canulated dropwise into a solution of (±)-3-phenyl-3-azabicyclo[3.2.1]octan-2-one **202** (201 mg, 1.00 mmol) and Me_3SiCl (0.63 cm^3, 5.0 mmol) in THF (10 cm^3) at −105 °C over 15 min maintaining internal temperature. The resulting solution was allowed to warm slowly to room temperature over 1.5 h before leaving to stir for 14 h. The reaction was quenched with H_2O (10 cm^3) and diluted with Et_2O (30 cm^3). The organic extract was dried ($MgSO_4$) and concentrated to a yellow oil. Purification by flash column chromatography (15% EtOAc: petroleum ether) gave the *title compound* **249** as a white solid (237 mg, 87%); mp 65-67 °C; (Found: C,

70.08; H, 8.49; N, 4.92%. $C_{16}H_{23}NOSi$ requires C, 70.29; H, 8.49; N, 5.13%); ν_{max} (soln.)/cm^{-1} 2948, 2870, 1639, 1593, 1328, 1289, 1150, 860; δ_H(400 MHz, $CDCl_3$) 0.13 (9H, s, $SiMe_3$), 1.64 (1H, ddd, *J* 1.5, 5.5, 11.7), 1.74-1.89 (2H, m), 1.99 (1H, br d, *J* 11.7), 2.03 (1H, m), 2.16 (1H, dddd, *J* 2.2, 3.7, 9.1, 13.2), 2.63 (1H, m), 3.33 (1H, d, *J* 11.0), 3.70 (1H, dd, *J* 4.0, 11.0), 7.18-7.25 (3H, m), 7.38-7.40 (2H, m); δ_C(100 MHz, $CDCl_3$) –2.3 ($SiMe_3$), 30.5 (CH_2), 34.1 (CH_2), 34.4 (CH), 34.7 (CH_2), 41.5 (C), 59.4 (CH_2), 126.5 (CH), 126.5 (CH), 129.2 (CH), 143.0 (C), 176.7 (NC=O); *m/z* (EI) 273.1308 (M^+, 16%), 258 (M^+–CH_3, 100), 73 ($SiMe_3$, 58). $C_{16}H_{23}NOSi$ requires M^+ 273.1548. A similar reaction performed at –78 °C gave the *title compound* **249** in 86% yield.

(±)-3-Phenyl-1-(trimethylsilyl)-3-azabicyclo[3.3.1]nonan-2-one 250

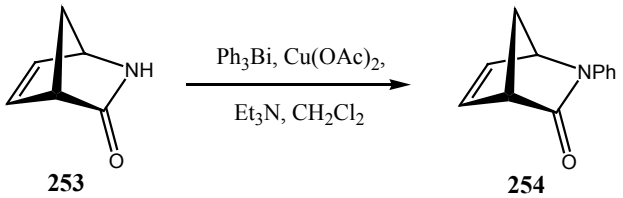


203 **250**

A solution of LDA/LiCl was prepared as previously described; DIPA/HCl (83 mg, 0.60 mmol), in THF (2.5 cm^3) at –78 °C, with ^{n}BuLi (2.2 $moldm^{-3}$ solution in hexane; 0.54 cm^3, 1.2 mmol). The solution of LDA/LiCl was canulated dropwise into the solution of (±)-3-phenyl-3-azabicyclo[3.3.1]nonan-2-one **203** (108 mg, 0.500 mmol) and Me_3SiCl (0.32 cm^3, 2.5 mmol) in THF (5 cm^3) at –105 °C (internal temperature) over 5 min maintaining the internal temperature. The resulting solution was allowed to warm slowly to room temperature over 1.5 h. The reaction was quenched with H_2O (5 cm^3) and diluted with Et_2O (15 cm^3). The organic extract was dried ($MgSO_4$) and

concentrated to a yellow oil. Purification by flash column chromatography (20% EtOAc: petroleum ether) gave the *title compound* **250** as a white solid (106 mg, 74%); Data consistent with previously described. A similar reaction performed at –78 °C gave the *title compound* **250** in 78% yield.

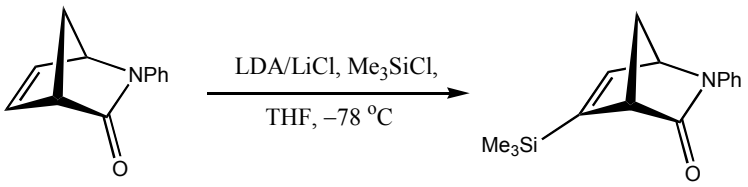
2-phenyl-2-azabicyclo[2.2.1]hept-5-en-3-one 254



253 **254**

Copper (II) acetate was recrystallised from acetic acid and dried under high vacuum at 60 ^{o}C. 2-Azabicyclo[2.2.1]hept-5-en-3-one (1.0 g, 9.2 mmol), triphenylbismuth (8.1 g, 18 mmol), copper (II) acetate (2.5 g, 14 mmol) and triethylamine (1.9 cm^3, 14 mmol) were stirred as a slurry in dichloromethane (25 cm^3) for 24 h. The reaction was dry loaded onto silica and purified by column chromatography (40% EtOAc:petrol) to give the title compound as a white solid (1.28 g, 75%). mp 92-94 °C δ_H(500 MHz, $CDCl_3$) 2.29 (1H, ddd, *J* 1.5, 1.5, 8.0), 2.49 (1H, ddd, *J* 1.5, 1.5, 8.0), 3.50-3.53 (1H, m), 4.78-4.80 (1H, m), 6.73 (1H, ddd, *J* 1.5, 3.3, 5.1), 7.04 (1H, dd, *J* 1.8, 5.1), 7.09-7.13 (1H, m), 7.33-7.41 (4H, m). δ_C(125 MHz, $CDCl_3$) 54.8 (CH_2), 57.3 (CH, C4), 64.7 (CH, C1), 118.7 (CH, Ar), 124.0 (CH, Ar), 129.0 (CH, Ar), 138.6 (=CH), 139.1 (=CH), 139.6 (C, Ar), 177.4 (NC=O). (Found: C, 77.67; H, 6.00, N, 7.59%; HRMS(EI) m/z 185.0843 (14%), 66.0467 (C_5H_6, 100%). $C_{12}H_{11}NO$ requires C, 77.81; H, 5.99; N, 7.56%; M^+ 185.0840).

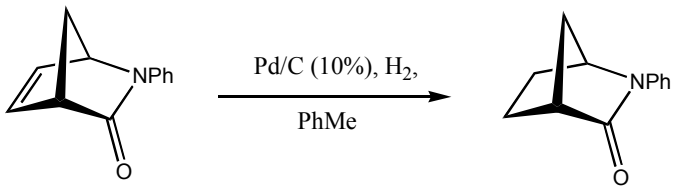
(±)-2-Phenyl-5-(trimethylsilyl)-2-azabicyclo[2.2.1]hept-5-en-3-one 255



254 **255**

A solution of LDA/LiCl was prepared as previously described; DIPA/HCl (358 mg, 1.30 mmol), in THF (10 cm^3) at −78 °C, with ^{n}BuLi (1.45 mol dm^{-3} solution in hexane; 2.0 cm^3, 2.2 mmol). The LDA/LiCl was then canulated into a solution of 2-phenyl-2-azabicyclo[2.2.1]hept-5-en-3-one **254** (370 mg, 2.00 mmol) and Me_3SiCl (1.0 cm^3, 8.0 mmol) in THF (10 cm^3) at −78 °C over 15 min maintaining internal temperature. The resulting solution was allowed to warm slowly to room temperature over 3 h, quenched with aq. NH_4Cl (20 cm^3) and diluted with Et_2O (60 cm^3). The two phases were separated and the organics washed with H_2O (60 cm^3) and aq. NaCl (60 cm^3), dried ($MgSO_4$) and evaporated to a dark brown solid. Purification by column chromatography (8% EtOAc in petrol) gave the *title compound* **255** as a tan solid (442 mg, 86%); mp 75-77 °C; ν_{max} (soln.)/cm^{-1} 2955, 2898, 2872, 1698, 1596, 1554, 1494, 1455, 1368, 1329, 1306, 1276, 1157, 1120, 1048, 1025, 996, 945, 861; δ_H(400 MHz, $CDCl_3$) 0.14 (3H, s), 2.12 (1H, ddd, *J* 1.5, 1.5, 8.0), 2.42 (1H, ddd, *J* 1.8, 1.8, 8.0), 3.58 (1H, br dd, *J* 0.7, 1.5), 4.77 (1H, br dd, *J* 1.8, 1.8**)**, 7.1 (1H, m), 7.21 (1H, br dd, *J* 0.7, 1.8), 7.32-7.40 (4H, m); δ_C(100 MHz, $CDCl_3$) −1.7 ($SiMe_3$), 56.6 (CH_2), 57.7 (CH), 65.1 (NCH), 118.7 (CH, Ar), 123.8 (CH, Ar), 128.9 (CH, Ar), 139.8 (C, Ar), 147.3 (=CH), 153.3 (SiC=), 177.4 (NC=O); *m/z* (FAB) 258.1317 (MH^+, 65%), 242 (MH^+–CH_4, 21), 73 ($SiMe_3$, 100). $C_{15}H_{19}NOSi$ requires MH^+ 258.1314.

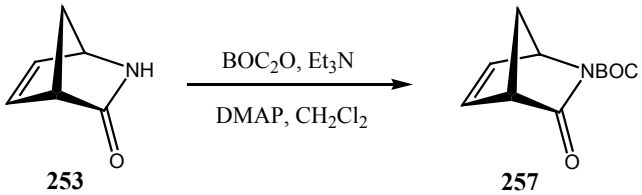
(±)-2-Phenyl-2-azabicyclo[2.2.1]heptan-3-one 256



254 **256**

A mixture of 2-phenyl-2-azabicyclo[2.2.1]hept-5-en-3-one **254** (1.0 g, 5.4 mmol) and 10% palladium on charcoal (75 mg) in toluene (5 cm^3) was stirred vigorously under an atmosphere of hydrogen for 30 h. The reaction was filtered through Kieselguhr and the filtrate concentrated to give the *title compound* **256** as an off white solid (657 mg, 67%); mp 57-59 °C; (Found: C, 76.89; H, 7.07, N, 7.30%. $C_{12}H_{13}NO$ requires C, 76.98; H 7.00; N, 7.48%); ν_{max} (soln.)/cm^{-1} 2981, 2879, 1697, 1596, 1495, 1382, 1290, 1108, 955; δ_H(400 MHz, $CDCl_3$) 1.53 (1H, ddd, *J* 1.4, 1.4, 9.5, 7-H), 1.78 (1H, m)**,** 1.84-2.10 (4H, m), 2.96 (1H, dd, *J* 1.4, 1.4, 4-H), 4.46 (1H, d, *J* 1.5, 1-H), 7.03-7.14 (1H, m), 7.30-7.40 (2H, m), 7.47-7.55(2H, m); δ_C(100 MHz, $CDCl_3$) 24.9 (CH_2), 27.9 (CH_2), 39.5 (CH_2), 47.1 (CH, C4), 60.8 (CH, C1), 119.2 (CH, Ar), 123.8 (CH, Ar), 129.0 (CH, Ar), 138.4 (C, Ar), 176.3 (NC=O, C2); *m/z* (EI) 187.1004 (100%). $C_{12}H_{13}NO$ requires M^+ 187.0997.

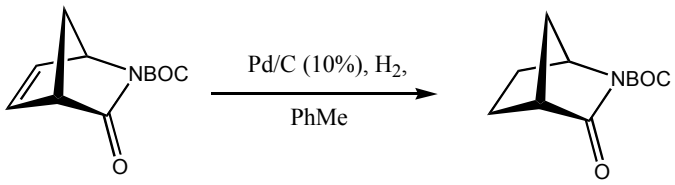
***tert*-Butyl 3-oxo-2-azabicyclo[2.2.1]hept-5-ene-2-carboxylate 257**



253 **257**

Di-*tert*-butyl dicarbonate (20.1 g, 92.0 mmol), triethylamine (6.4 cm^3, 87 mmol) and DMAP (5.6 g, 46 mmol) were added to a stirred suspension of 2-azabicyclo[2.2.1]hept-5-en-3-one (5.0 g, 46 mmol) in dichloromethane (90 cm^3). The reaction was stirred for 24 h before the volatiles were removed *in vacuo* and the residue purified by Biotage chromatography (10% EtOAc in cyclohexane) to give the title compound as an orange solid (8.85 g, 92%). mp 55-57 °C (*lit*. mp 55-57 °C, A. Toyota, M. Aizawa, C. Habutani, N. Katagiri, C. Kaneko, *Tetrahedron*, 1995, **51**, 8783). δ_H(500 MHz, $CDCl_3$) 1.50 (9H, s), 2.15 (1H, ddd, *J* 1.5, 1.5, 8.5), 2.35 (1H, *J* 1.5, 1.5, 8.5), 3.37-3.40 (1H, m), 4.95 (1H, dd, *J* 2.2, 4.0), 6.66 (1H, ddd, *J* 1.5, 3.3, 5.2), 6.89 (1H, dd, *J* 2.2, 5.2). δ_C(125 MHz, $CDCl_3$) 28.1 (CH_3), 54.4 (CH_2), 55.0 (CH, C1), 62.4 (CH, C4), 82.6 ($C(CH_3)_3$), 138.3 (=CH), 140.1 (=CH), 150.4 (C=O, Boc), 176.3 (NC=O).

(±)-*Tert*-butyl 3-oxo-2-azabicyclo[2.2.1]heptane-2-carboxylate 259

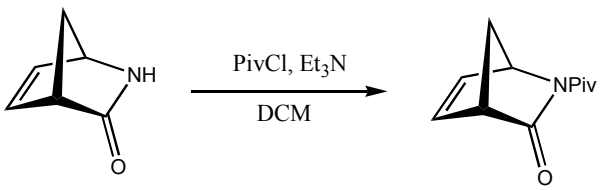


257 **259**

A mixture of *tert*-butyl 3-oxo-2-azabicyclo[2.2.1]hept-5-ene-2-carboxylate **257** (1.0 g, 4.8 mmol) and 10% palladium on charcoal (50 mg) in toluene (4 cm^3) was stirred vigorously under an atmosphere of hydrogen for 14 h. The reaction was filtered through Kieselguhr and the filtrate concentrated to give the *title compound* **259** as a white solid (863 mg, 85%); mp 96-98 °C (*lit.* mp 89-90 °C, J. Frei, J. Stanek, Ciba Geigy Co., 1996, WO9424093 (US5516806)); (Found:

C, 62.72; H, 8.16; N, 6.66%. $C_{11}H_{17}NO_3$ requires C, 62.54; H, 8.11; N, 6.63%); ν_{max} (soln.)/cm^{-1} 2981, 2881, 1782, 1748, 1708, 1369, 1354, 1313, 1154, 1127, 1098, 1054, 991; δ_H(400 MHz, $CDCl_3$) 1.42 (1H, ddd, *J* 1.3, 1.3, 9.9, 7-H), 1.52 (9H, s), 1.70-1.95 (5H, m), 2.86 (1H, dd, *J* 1.6, 3.7, 4-H), 4.53 (1H, s, 1-H); δ_C(100 MHz, $CDCl_3$) 23.9 (CH_2), 28.2 (CH_3), 28.5 (CH_2), 37.9 (CH_2), 46.8 (CH, C4), 58.9 (CH, C1), 82.6 (*C*(CH_3)$_3$), 149.6 (C=O, Boc), 175.6 (NC=O, C2); *m/z* (CI) 212.1296 (MH^+, 15%). $C_{11}H_{17}NO_3$ requires M^+ 212.1286.

(±)-2-(2,2-Dimethylpropanoyl)-2-azabicyclo[2.2.1]hept-5-en-3-one 258

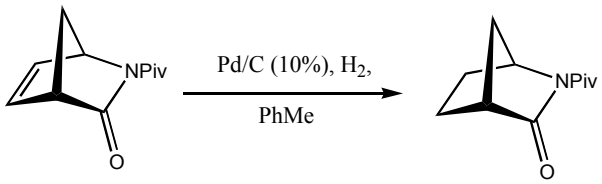


253 **258**

An ice-cold solution of 2-azabicyclo[2.2.1]hept-5-en-3-one **253** (1.0 g, 9.2 mmol) in DCM (30 cm^3) was treated with pivaloyl chloride (1.35 cm^3, 11.0 mmol) and Et_3N (1.3 cm^3, 9.2 mmol). The reaction was allowed to warm to room temperature and allowed to stir for 2 h before the addition of H_2O (15 cm^3). The aqueous extract was washed further with DCM (30 cm^3) and the combined organic extracts dried ($MgSO_4$) and concentrated to brown solid. Purification by column chromatography (30% EtOAc: petroleum ether) gave the *title compound* **258** as a light yellow solid (1.31 g, 74%); mp 46-48 °C; ν_{max} (soln.)/cm^{-1} 2962, 2874, 1747, 1673, 1396, 1364, 1317, 1281, 1157, 1121, 1087, 967, 906; δ_H(500 MHz, $CDCl_3$) 1.26 (9H, s, (CH_3)$_3$), 2.13 (1H, ddd, *J* 1.4, 8.6), 2.27 (1H, ddd, *J* 1.7, 8.6), 3.41 (1H, br s), 5.18 (1H, m), 6.62 (1H, ddd, *J* 1.5, 3.3, 5.1), 6.93 (1H, dd, *J* 2.2, 5.1); δ_C(125 MHz, $CDCl_3$) 25.8 (CH_3),

40.7 (C), 53.7 (CH_2, C7), 55.4 (CH, C4), 63.1 (CH, C1), 137.6 (CH, C5), 140.5 (CH, C6), 175.6, 179.3; *m/z* (EI) (M^+, 100%). $C_{11}H_{15}NO_2$ requires M^+ 193.1102.

(±)-2-(2,2-Dimethylpropanoyl)-2-azabicyclo[2.2.1]heptan-3-one 260



258 **260**

A mixture of 2-(2,2-dimethylpropanoyl)-2-azabicyclo[2.2.1]hept-5-en-3-one **258** (0.50 g, 2.6 mmol) and 10% palladium on charcoal (25 mg) in toluene (3 cm^3) was stirred vigorously under an atmosphere of hydrogen for 16 h. The reaction was filtered through Kieselguhr and the filtrate concentrated to give the *title compound* **260** as a white solid (413 mg, 82%); mp 71-73 °C; (Found: C, 67.76; H, 8.83; N, 7.04%. $C_{11}H_{17}NO_2$ requires C, 67.65; H, 8.78; N, 7.18%); ν_{max} (soln.)/cm^{-1} 2960, 2881, 1742, 1675, 1396, 1339, 1288, 1165, 1106, 954, 906; δ_H(400 MHz, $CDCl_3$) 1.28 (9H, s, $(CH_3)_3$), 1.45 (1H, d, *J* 10.1, 7-H), 1.67-1.80 (2H, m), 1.82-2.01 (3H, m), 2.90 (1H, dd, *J* 1.6, 3.7, 4-H), 4.81 (1H, s, 1-H); δ_C(100 MHz, $CDCl_3$) 25.6 (CH_2), 25.8 (CH_3), 28.3 (CH_2), 37.5 (CH_2, C7), 40.9 (C), 48.0 (CH, C4), 59.8 (CH, C1), 174.9, 178.9; *m/z* (EI) 195.1260 (M^+, 30%), 57 (C_4H_9, 100). $C_{11}H_{17}NO_2$ requires M^+ 195.1259.

Appendix

Appendix A. Calculations of Thermodynamic and Kinetic Data

Calculation of Rate Constant and Gibbs Free Energy of (−)-(1*R*,5*R*)-3-Phenyl-4-thioxo-1-(trimethylsilyl)-3-azabicyclo[3.3.1]nonan-2-one 246

Rate constant for exchange at coalescence point described by –

$$k = \pi\Delta\nu/\sqrt{2}$$

where $\Delta\nu$ is the difference in frequency of the two peaks. $\Delta\nu$ measured at 298 K (107.5 Hz) and at 253 K (106.6 Hz).

$\Delta\nu$(298K); $k = 337.7/1.414 = 239.5\ s^{-1}$

$\Delta\nu$(253K); $k = 334.9/1.414 = 236.8\ s^{-1}$

Gibbs free energy for the process defined as –

$$\Delta G^{\ddagger} = RT_c[23 + \ln(T_c/\Delta\nu)]$$

where T_c is the coalescence temperature and R is the gas constant. T_c determined by variable temperature NMR experiments to be 313 K.

$$\Delta G^{\ddagger} = 2.598[23 + 2.3\log_{10}(313/107.5)] = 2.598 \times 24.067 = 62.52\ kJmol^{-1}.$$

Appendix B. X-ray Crystal Structure Data

X-ray data for 1a,3b-*Bis*(trimethylsilyl)-1a,1b,3a,3b,3c,3d-hexahydro-1*H*-bicyclopropa[*cd*,*hi*]inden-1-one 150

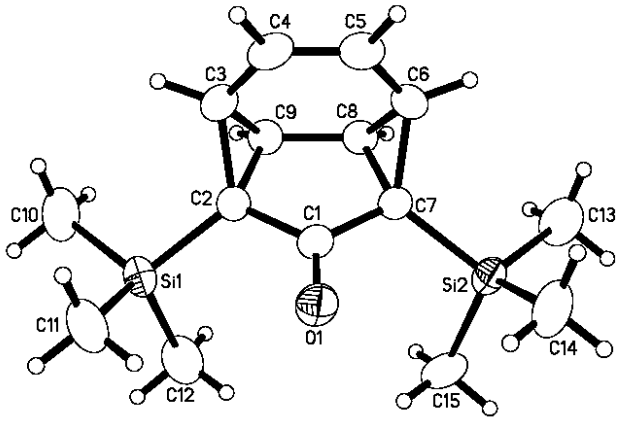


Table 1. Crystal data and structure refinement for btmsco.

CCDC	172469	
Identification code	btmsco	
Empirical formula	C15 H24 O Si2	
Formula weight	276.52	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pna2(1)	
Unit cell dimensions	a = 12.4355(7) Å	α= 90°.
	b = 13.6661(8) Å	β= 90°.
	c = 9.8989(6) Å	γ = 90°.
Volume	1682.27(17) $Å^3$	
Z	4	

Density (calculated)	1.092 Mg/m^3
Absorption coefficient	0.200 mm^{-1}
F(000)	600
Crystal size	0.51 x 0.35 x 0.15 mm^3
Theta range for data collection	2.21 to 28.85°.
Index ranges	-16<=h<=12, -17<=k<=17, -13<=l<=11
Reflections collected	10738
Independent reflections	3797 [R(int) = 0.042]
Completeness to theta = 27.50°	99.5 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3797 / 1 / 163
Goodness-of-fit on F^2	1.015
Final R indices [I>2sigma(I)]	R1 = 0.0318, wR2 = 0.0800
R indices (all data)	R1 = 0.0353, wR2 = 0.0820
Absolute structure parameter	-0.04(9)
Largest diff. peak and hole	0.393 and -0.147 $e.Å^{-3}$

X-ray data for (–)-(1*R*,6*R*)-1-(Trimethylsilyl)bicyclo[4.2.1]nona-2,4,7-trien-9-one 154

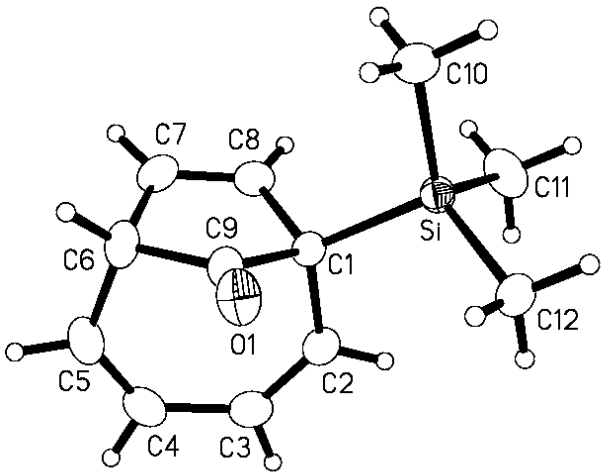


Table 2. Crystal data and structure refinement for hponme.

CCDC	172470	
Identification code	hponme	
Empirical formula	C12 H16 O Si	
Formula weight	204.34	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 6.1568(6) Å	α= 90°.
	b = 7.4191(7) Å	β= 101.996(2)°.
	c = 12.9873(12) Å	γ = 90°.
Volume	580.3(2) $Å^3$	
Z	2	
Density (calculated)	1.169 Mg/m^3	

Absorption coefficient	0.169 mm^{-1}
F(000)	220
Crystal size	0.64 x 0.40 x 0.10 mm^3
Theta range for data collection	3.18 to 28.55°.
Index ranges	-7<=h<=7, -9<=k<=9, -16<=l<=17
Reflections collected	2552
Independent reflections	2562 [R(int) = 0.023]
Completeness to theta = 27.50°	97.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.952 and 0.709
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2552 / 1 / 127
Goodness-of-fit on F^2	1.058
Final R indices [I>2sigma(I)]	R1 = 0.0266, wR2 = 0.0709
R indices (all data)	R1 = 0.0276, wR2 = 0.0719
Absolute structure parameter	0.00(8)
Largest diff. peak and hole	0.29 and -0.13 $e.Å^{-3}$

X-ray data for Trimethylsilyl bicyclo[4.2.1]nonan-9-one aldol condensation product 163

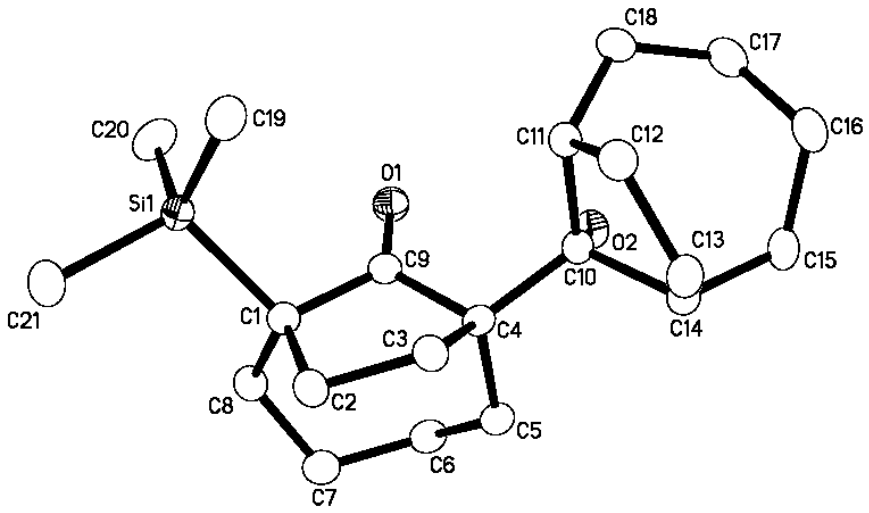


Table 3. Crystal data and structure refinement for dinosi.

Identification code	dinosi	
Empirical formula	C21 H36 O2 Si	
Formula weight	348.59	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	I2/a	
Unit cell dimensions	a = 21.0595(14) Å	α= 90°.
	b = 6.4875(4) Å	β= 90.710(1)°.
	c = 28.1672(19) Å	γ = 90°.
Volume	3848.0(4) $Å^3$	
Z	8	
Density (calculated)	1.203 Mg/m^3	
Absorption coefficient	0.133 mm^{-1}	

F(000)	1536
Crystal size	0.40 x 0.15 x 0.04 mm^3
Theta range for data collection	1.93 to 28.70°.
Index ranges	-23<=h<=27, -8<=k<=8, -30<=l<=37
Reflections collected	10873
Independent reflections	4465 [R(int) = 0.034]
Completeness to theta = 27.50°	97.7 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4465 / 0 / 218
Goodness-of-fit on F^2	1.005
Final R indices [I>2sigma(I)]	R1 = 0.0396, wR2 = 0.0916
R indices (all data)	R1 = 0.0638, wR2 = 0.1003
Largest diff. peak and hole	0.345 and -0.222 $e.Å^{-3}$

X-ray data for (–)-Methyl (1*R*,6*R*,9*R*)-9-cyano-9-[(methoxycarbonyl)oxy] bicyclo[4.2.1] nona-2,4,7-triene-1-carboxylate 188

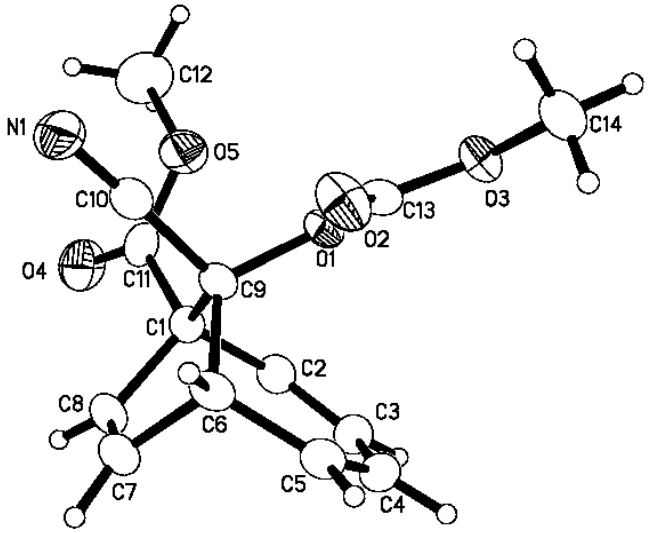


Table 4. Crystal data and structure refinement for occnme.

Identification code	occnme	
Empirical formula	C14 H13 N O5	
Formula weight	275.25	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 7.4886(9) Å	α= 90°.
	b = 7.9502(10) Å	β= 91.095(2)°.
	c = 11.2672(14) Å	γ = 90°.
Volume	670.68(14) Å^3	
Z	2	
Density (calculated)	1.363 Mg/m^3	

Absorption coefficient	0.105 mm^{-1}
F(000)	288
Crystal size	0.30 x 0.22 x 0.17 mm^3
Theta range for data collection	1.81 to 28.63°.
Index ranges	-9<=h<=9, -10<=k<=10, -14<=l<=14
Reflections collected	5994
Independent reflections	1699 [R(int) = 0.026]
Completeness to theta = 27.50°	98.4 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1694 / 1 / 183
Goodness-of-fit on F^2	1.046
Final R indices [I>2sigma(I)]	R1 = 0.0293, wR2 = 0.0771
R indices (all data)	R1 = 0.0315, wR2 = 0.0784
Largest diff. peak and hole	0.227 and -0.137 $e.Å^{-3}$

X-ray data for (−)-(1*S*,6*R*)-1-[(*R*)-Hydroxy(phenyl)methyl]bicyclo[4.2.1] nonan-9-one 191b

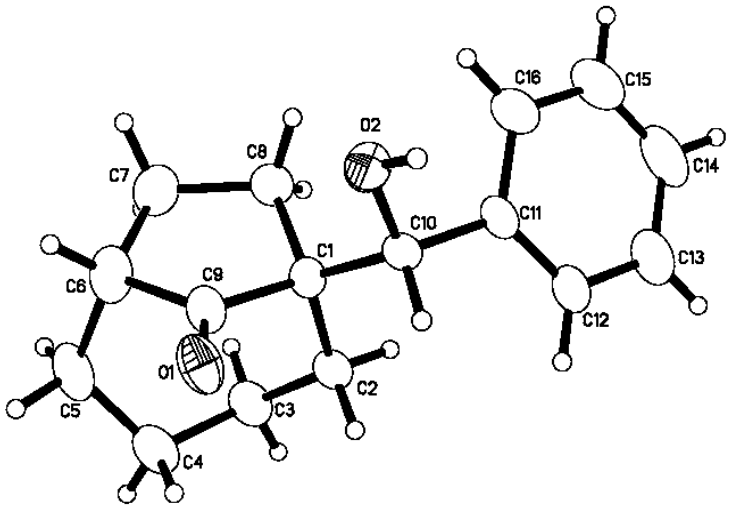


Table 5. Crystal data and structure refinement for ocbzol.

Identification code	ocbzol	
Empirical formula	C16 H20 O2	
Formula weight	244.32	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P1	
Unit cell dimensions	a = 9.3099(13) Å	α= 63.488(2)°.
	b = 12.519(2) Å	β= 83.907(2)°.
	c = 12.858(2) Å	γ = 81.996(2)°.
Volume	1326.3(3) $Å^3$	
Z	4	
Density (calculated)	1.224 Mg/m^3	
Absorption coefficient	0.079 mm^{-1}	

F(000)	528
Crystal size	0.57 x 0.46 x 0.12 mm^3
Theta range for data collection	1.77 to 28.59°.
Index ranges	-11<=h<=11, -15<=k<=15, -16<=l<=16
Reflections collected	11502
Independent reflections	5907 [R(int) = 0.082]
Completeness to theta = 27.50°	95.4 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5907 / 6 / 645
Goodness-of-fit on F^2	1.002
Final R indices [I>2sigma(I)]	R1 = 0.0493, wR2 = 0.1189
R indices (all data)	R1 = 0.0682, wR2 = 0.1285
Absolute structure parameter	not reliably determined
Largest diff. peak and hole	0.57 and -0.32 $e.Å^{-3}$

X-ray data for (–)-(1*R*,5*R*)-3-Phenyl-1-(trimethylsilyl)-3-azabicyclo[3.2.1] octane-2,4-dione 212

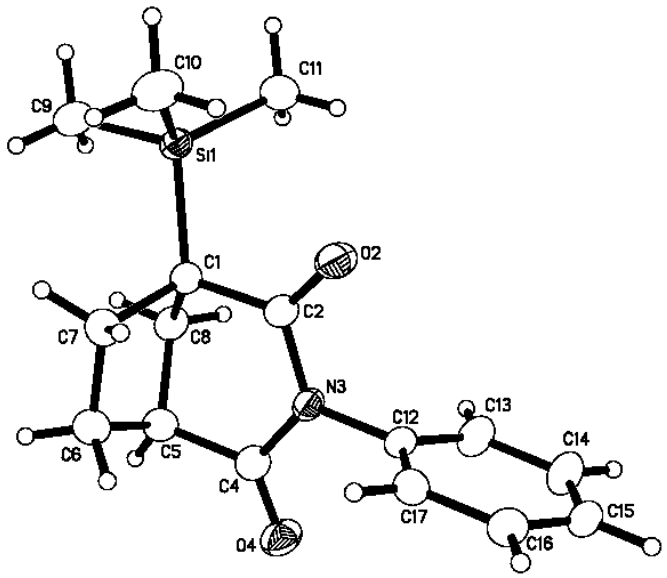


Table 6. Crystal data and structure refinement for impecx.

Identification code	impecx	
Empirical formula	C16 H21 N O2 Si	
Formula weight	287.43	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 6.1361(9) Å	α= 90°.
	b = 20.097(3) Å	β= 91.633(2)°.
	c = 25.013(4) Å	γ = 90°.
Volume	3083.3(8) $Å^3$	
Z	8	
Density (calculated)	1.238 Mg/m^3	

Absorption coefficient	0.154 mm^{-1}
F(000)	1232
Crystal size	0.50 x 0.10 x 0.10 mm^3
Theta range for data collection	1.63 to 28.82°.
Index ranges	-8<=h<=8, -27<=k<=26, -32<=l<=33
Reflections collected	27303
Independent reflections	14176 [R(int) = 0.045]
Completeness to theta = 27.50°	99.1 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.962 and 0.722
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	14151 / 1 / 722
Goodness-of-fit on F^2	1.026
Final R indices [I>2sigma(I)]	R1 = 0.0607, wR2 = 0.1445
R indices (all data)	R1 = 0.0772, wR2 = 0.1523
Absolute structure parameter	0.06(11)
Largest diff. peak and hole	0.709 and -0.329 $e.Å^{-3}$

X-ray data for (–)-(1*R*,5*R*)-3-Phenyl-1-(trimethylsilyl)-3-azabicyclo[3.3.1] nonane-2,4-dione 218

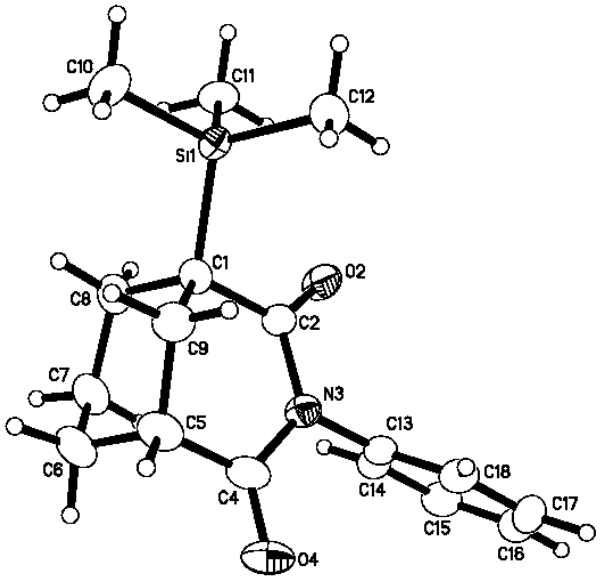


Table 7. Crystal data and structure refinement for cximph.

Identification code	cximph	
Empirical formula	C17 H23 N O2 Si	
Formula weight	301.45	
Temperature	150(2) K	
Wavelength	0.68920 Å	
Crystal system	Monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 11.0710(12) Å	α= 90°.
	b = 6.1798(7) Å	β= 102.430(2)°.
	c = 24.568(3) Å	γ = 90°.
Volume	1641.5(3) $Å^3$	
Z	4	
Density (calculated)	1.220 Mg/m^3	

Absorption coefficient	0.147 mm^{-1}
F(000)	648
Crystal size	0.16 x 0.02 x 0.02 mm^3
Theta range for data collection	1.83 to 26.00°.
Index ranges	-15<=h<=15, -8<=k<=8, -34<=l<=34
Reflections collected	14107
Independent reflections	6889 [R(int) = 0.043]
Completeness to theta = 26.00°	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.000 and 0.641
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6889 / 1 / 380
Goodness-of-fit on F^2	0.935
Final R indices [I>2sigma(I)]	R1 = 0.0534, wR2 = 0.1167
R indices (all data)	R1 = 0.0600, wR2 = 0.1191
Absolute structure parameter	0.20(12)
Largest diff. peak and hole	0.388 and -0.234 $e.Å^{-3}$

X-ray data for (–)-(1*S*,5*R*)-1-Benzyl-3-phenyl-3-azabicyclo[3.3.1]nonane-2,4-dione 226

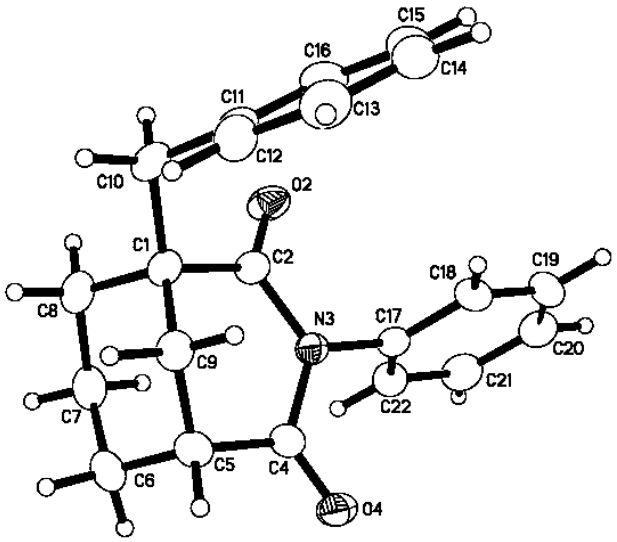


Table 8. Crystal data and structure refinement for imphcx.

Identification code	imphcx	
Empirical formula	C21 H21 N O2	
Formula weight	319.39	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 8.0351(5) Å	α= 90°.
	b = 11.7992(8) Å	β= 90°.
	c = 17.6729(12) Å	γ = 90°.
Volume	1675.5(2) $Å^3$	
Z	4	
Density (calculated)	1.266 Mg/m^3	

Absorption coefficient	0.081 mm^{-1}
F(000)	680
Crystal size	0.50 x 0.30 x 0.30 mm^3
Theta range for data collection	2.30 to 28.78°.
Index ranges	-10<=h<=10, -15<=k<=15, -23<=l<=23
Reflections collected	15320
Independent reflections	2371 [R(int) = 0.031]
Completeness to theta = 27.50°	99.7 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2346 / 0 / 217
Goodness-of-fit on F^2	1.067
Final R indices [I>2sigma(I)]	R1 = 0.0312, wR2 = 0.0773
R indices (all data)	R1 = 0.0378, wR2 = 0.0802
Absolute structure parameter	not reliably determined
Largest diff. peak and hole	0.168 and -0.193 $e.Å^{-3}$

X-ray data for (–)-(1*S*,5*R*)-1-(2,2-Dimethylpropanoyl)-3-phenyl-3-azabicyclo[3.3.1]nonane -3,4-dione 228

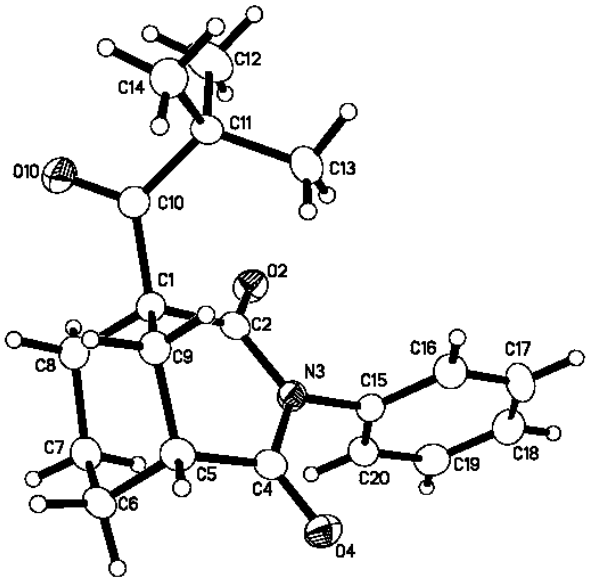


Table 9. Crystal data and structure refinement for ocphtb.

Identification code	ocphtb	
Empirical formula	C19 H23 N O3	
Formula weight	313.38	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 5.9874(6) Å	α= 90°.
	b = 10.6470(11) Å	β= 90°.
	c = 25.968(3) Å	γ = 90°.
Volume	1655.4(3) $Å^3$	
Z	4	
Density (calculated)	1.257 Mg/m^3	

Absorption coefficient	0.085 mm^{-1}
F(000)	672
Crystal size	0.46 x 0.11 x 0.09 mm^3
Theta range for data collection	2.07 to 27.50°.
Index ranges	-7<=h<=8, -11<=k<=13, -34<=l<=25
Reflections collected	7389
Independent reflections	2185 [R(int) = 0.036]
Completeness to theta = 27.50°	98.8 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2185 / 0 / 209
Goodness-of-fit on F^2	0.943
Final R indices [I>2sigma(I)]	R1 = 0.0350, wR2 = 0.0722
R indices (all data)	R1 = 0.0468, wR2 = 0.0755
Absolute structure parameter	?
Extinction coefficient	0.0038(13)
Largest diff. peak and hole	0.218 and -0.169 $e.Å^{-3}$

X-ray data for (–)-(1*R*,5*R*)-3-Phenyl-4-thioxo-1-(trimethylsilyl)-3-azabicyclo[3.3.1]nonan-2-one 246

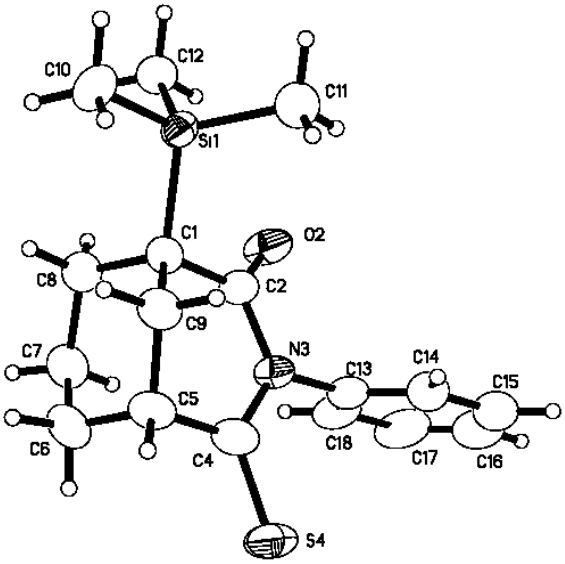
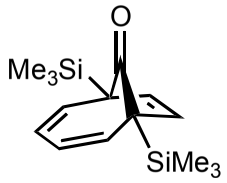


Table 10. Crystal data and structure refinement for thzone.

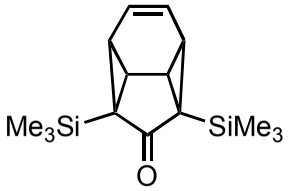
Identification code	thzone	
Empirical formula	C17 H23 N O S Si	
Formula weight	317.51	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 6.293(2) Å	α= 90°.
	b = 11.150(4) Å	β= 90°.
	c = 25.494(8) Å	γ = 90°.
Volume	1789(2) $Å^3$	
Z	4	
Density (calculated)	1.179 Mg/m^3	

Absorption coefficient	0.247 mm^{-1}
F(000)	680
Crystal size	0.06 x 0.22 x 0.66 mm^3
Theta range for data collection	1.60 to 28.09°.
Index ranges	-8<=h<=8, -14<=k<=11, -33<=l<=30
Reflections collected	10575
Independent reflections	4028 [R(int) = 0.062]
Completeness to theta = 27.50°	97.8 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4001 / 0 / 190
Goodness-of-fit on F^2	0.930
Final R indices [I>2sigma(I)]	R1 = 0.0436, wR2 = 0.0813
R indices (all data)	R1 = 0.0765, wR2 = 0.0883
Absolute structure parameter	-0.01(10)
Largest diff. peak and hole	0.321 and -0.270 $e.Å^{-3}$

Appendix C. ^{1}H NMR. 1,6-*Bis*(trimethylsilyl)bicyclo[4.2.1] nona-2,4,7-trien-9-one 149 and 1a,3b-*Bis*(trimethylsilyl)-1a,1b,3a,3b,3c,3d-hexahydro-1*H*-bicyclo-propa[*cd,hi*]inden-1-one 150

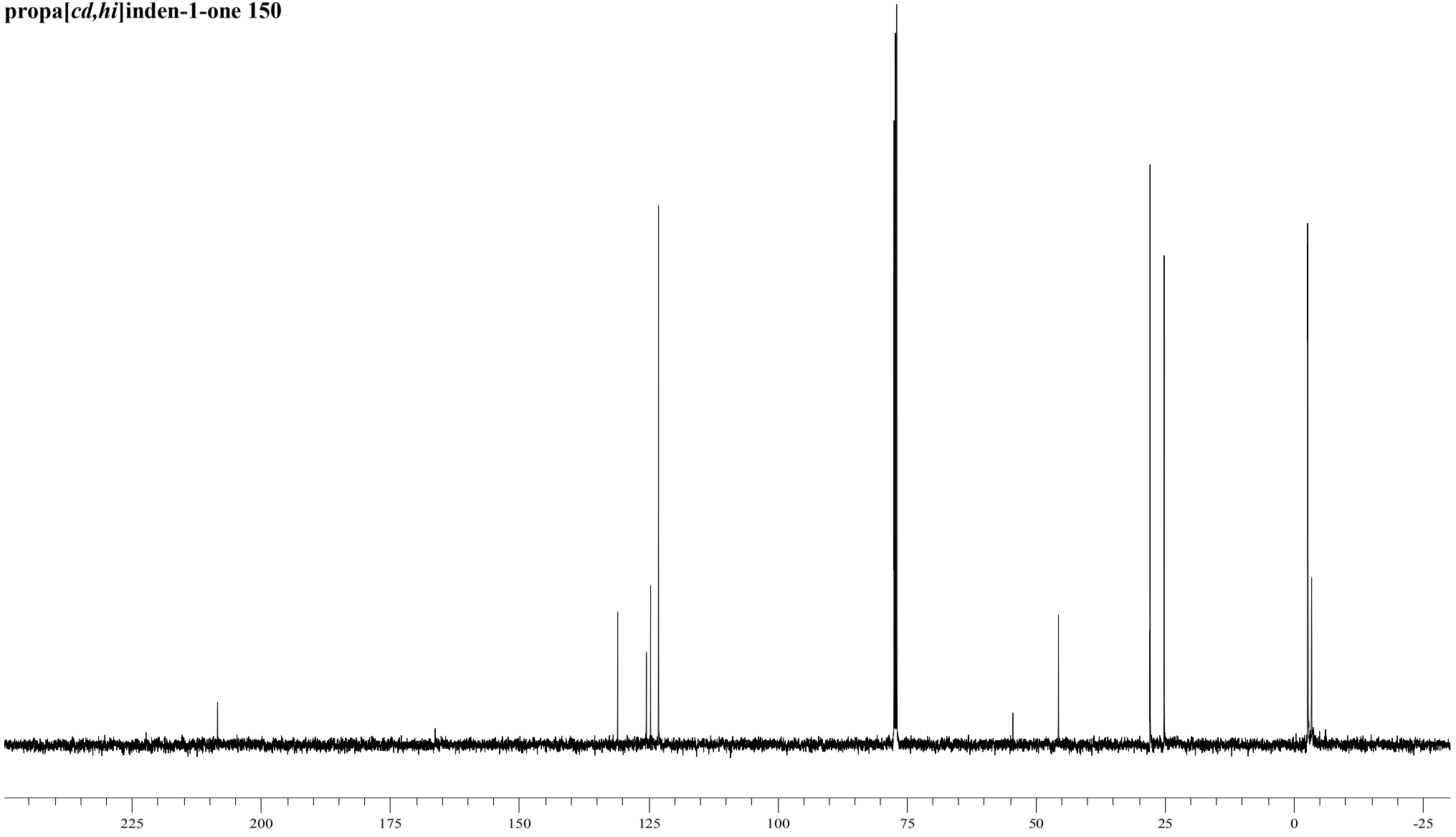


149 minor

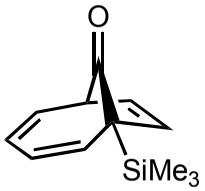


150 major

^{13}C NMR. 1,6-*Bis*(trimethylsilyl)bicyclo[4.2.1] nona-2,4,7-trien-9-one 149 and 1a,3b-*Bis*(trimethylsilyl)-1a,1b,3a,3b,3c,3d-hexahydro-1*H*-bicyclo-propa[*cd,hi*]inden-1-one 150

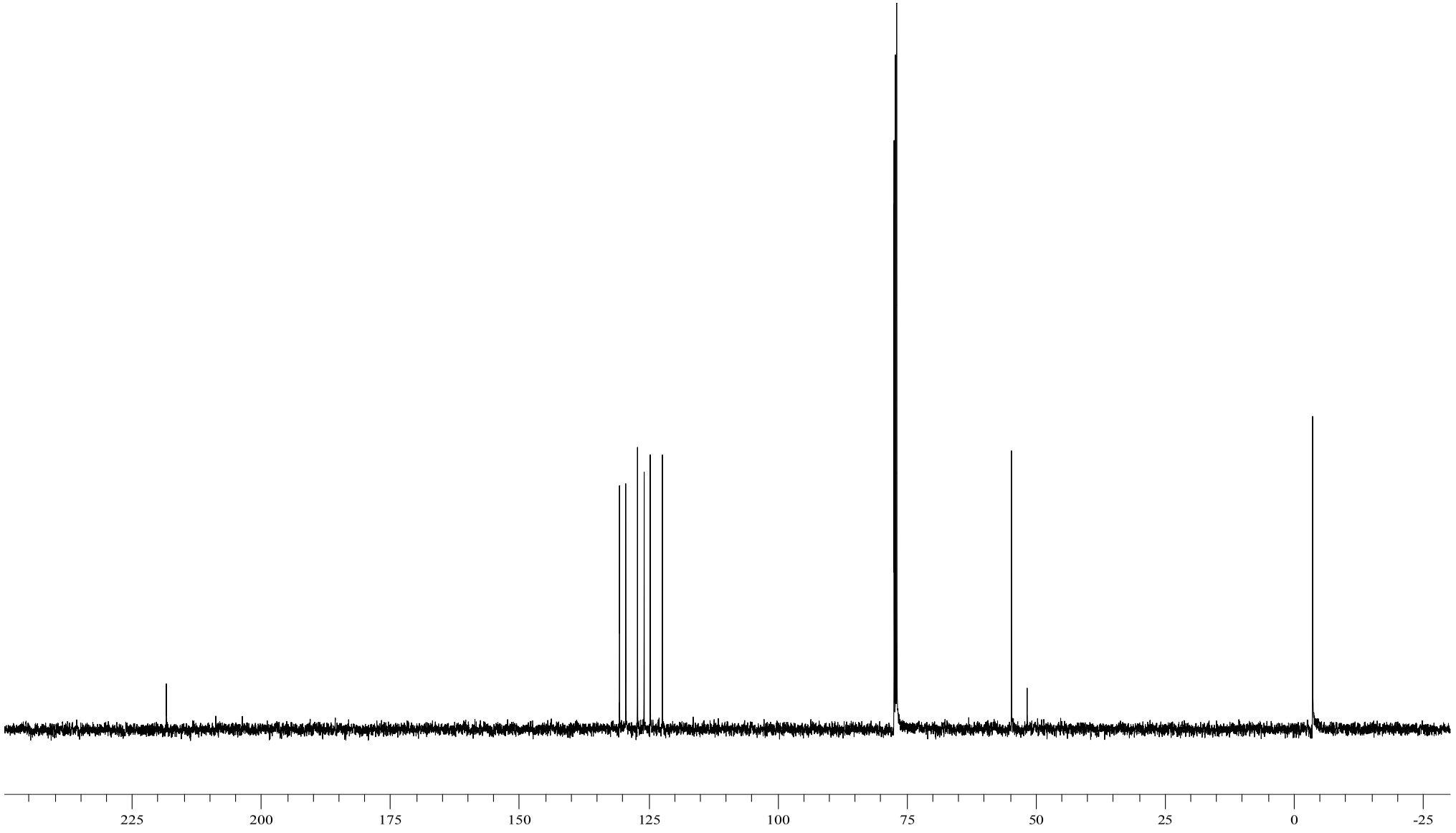


^{1}H NMR. (–)-(1*R*,6*R*)-1-(Trimethylsilyl)bicyclo[4.2.1]nona-2,4,7-trien-9-one 154.

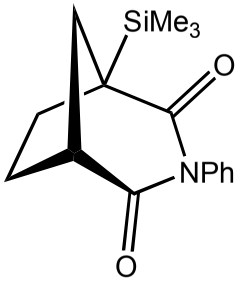


(–)-**154**

^{13}C NMR. (–)-(1*R*,6*R*)-1-(Trimethylsilyl)bicyclo[4.2.1]nona-2,4,7-trien-9-one 154.

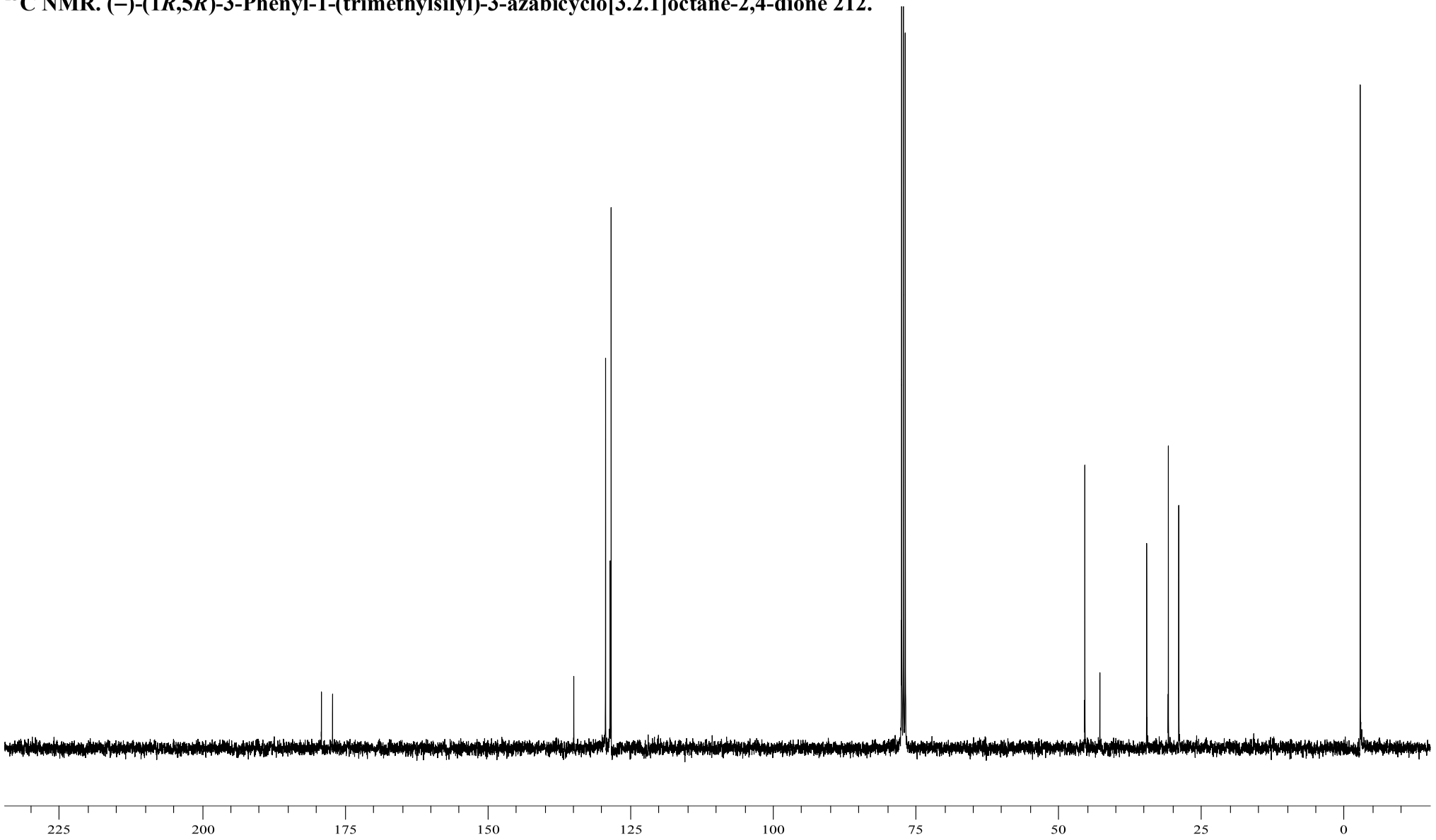


^{1}H NMR. (–)-(1*R*,5*R*)-3-Phenyl-1-(trimethylsilyl)-3-azabicyclo[3.2.1]octane-2,4-dione 212.

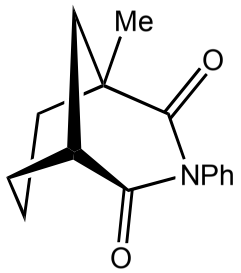


(–)-**212**

^{13}C NMR. (–)-(1*R*,5*R*)-3-Phenyl-1-(trimethylsilyl)-3-azabicyclo[3.2.1]octane-2,4-dione 212.

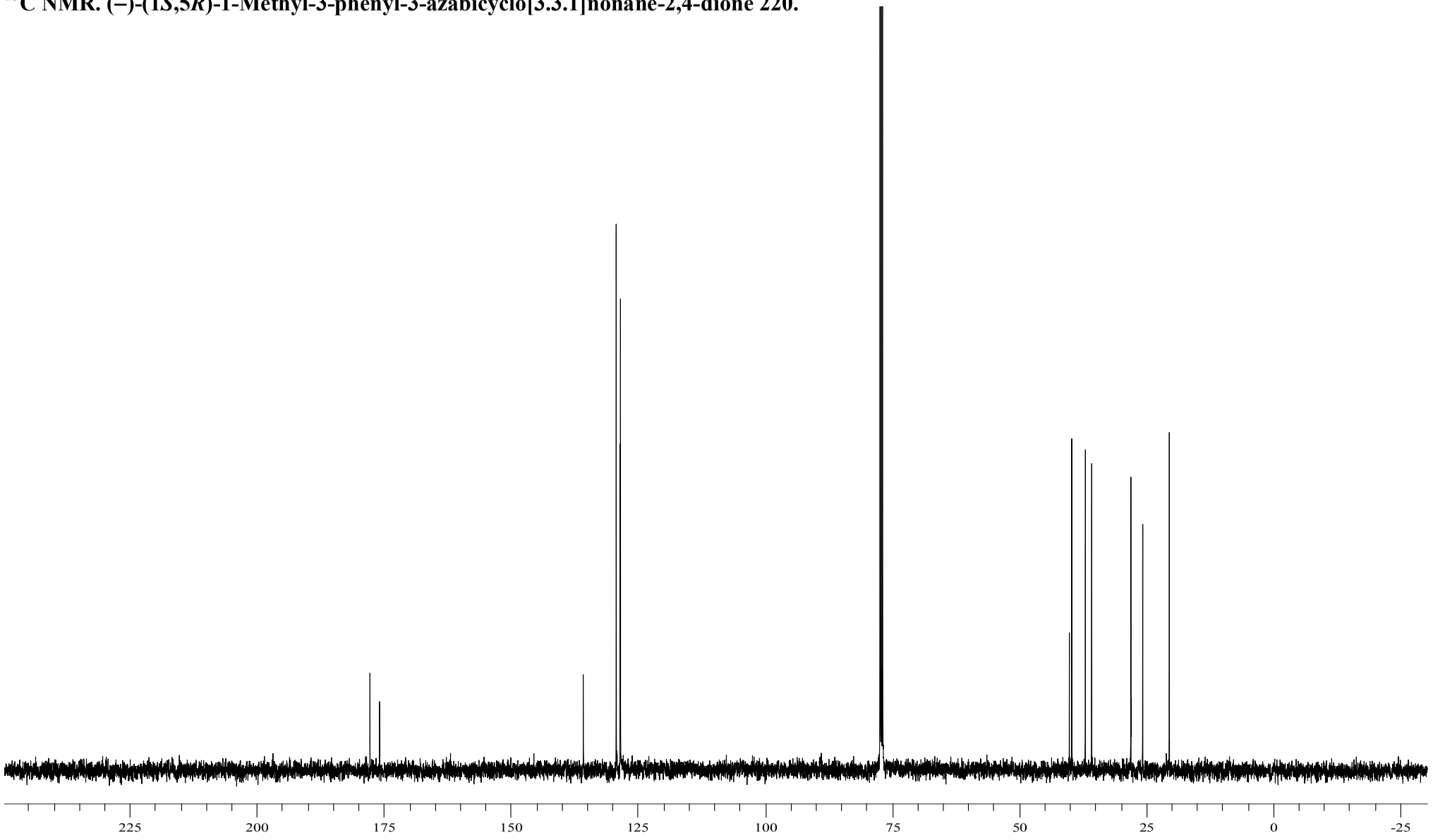


^{1}H NMR. (–)-(1*S*,5*R*)-1-Methyl-3-phenyl-3-azabicyclo[3.3.1]nonane-2,4-dione 220.

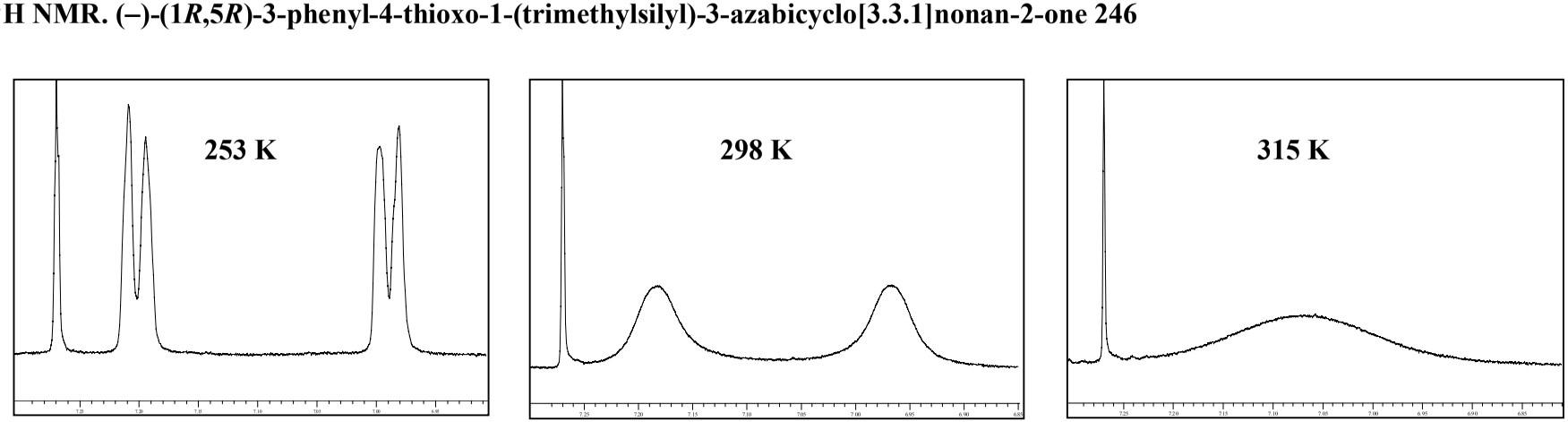


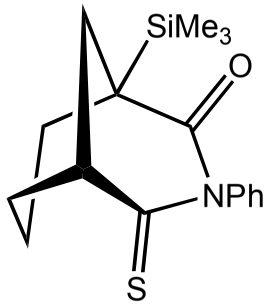
(–)-**220**

^{13}C NMR. (–)-(1*S*,5*R*)-1-Methyl-3-phenyl-3-azabicyclo[3.3.1]nonane-2,4-dione 220.



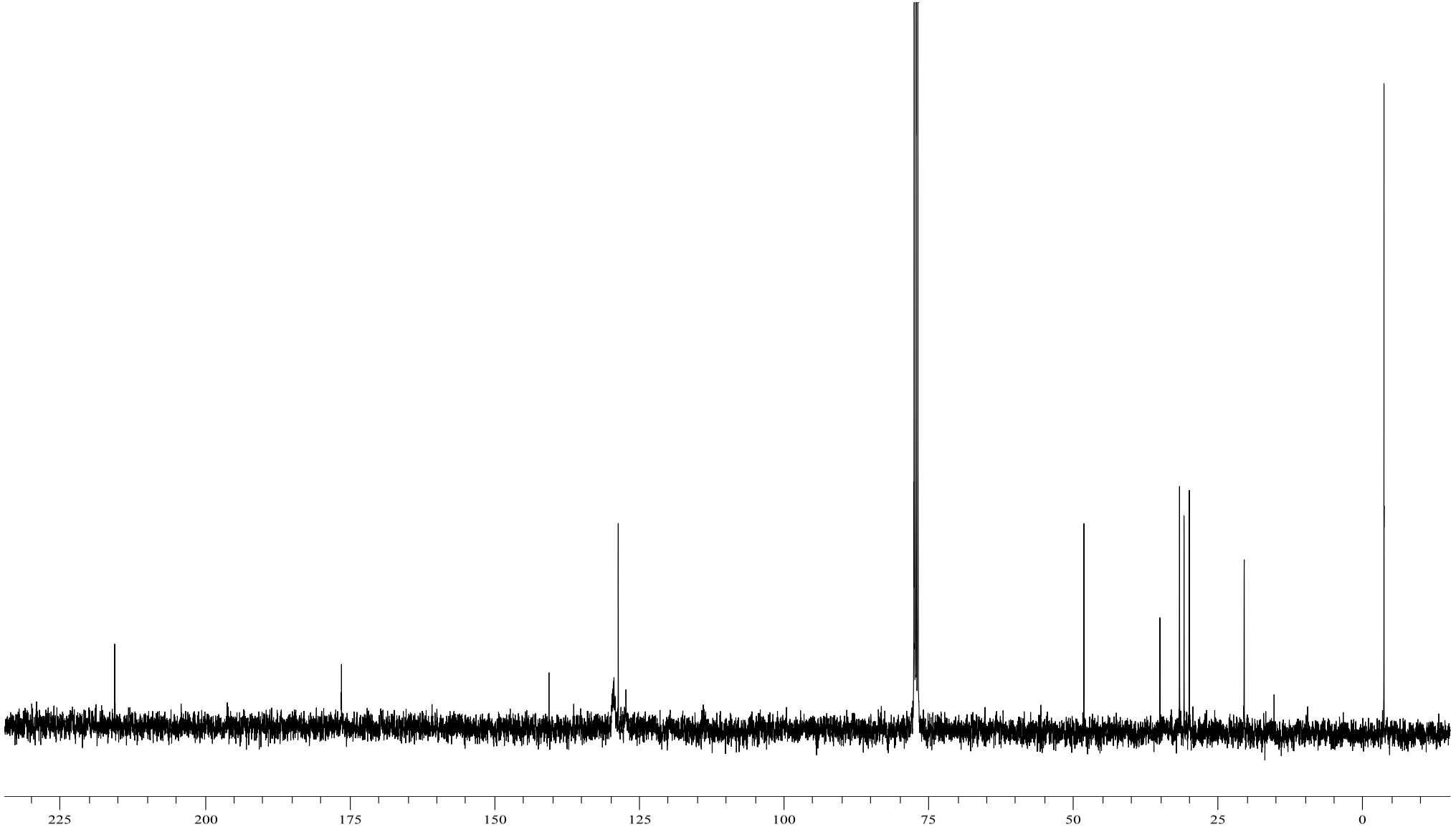
^{1}H NMR. (–)-(1*R*,5*R*)-3-phenyl-4-thioxo-1-(trimethylsilyl)-3-azabicyclo[3.3.1]nonan-2-one 246



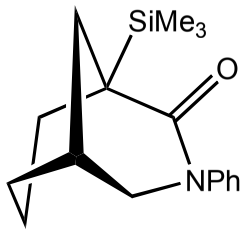


(–)-**246**

^{13}C NMR. (–)-(1*R*,5*R*)-3-phenyl-4-thioxo-1-(trimethylsilyl)-3-azabicyclo[3.3.1]nonan-2-one 246.

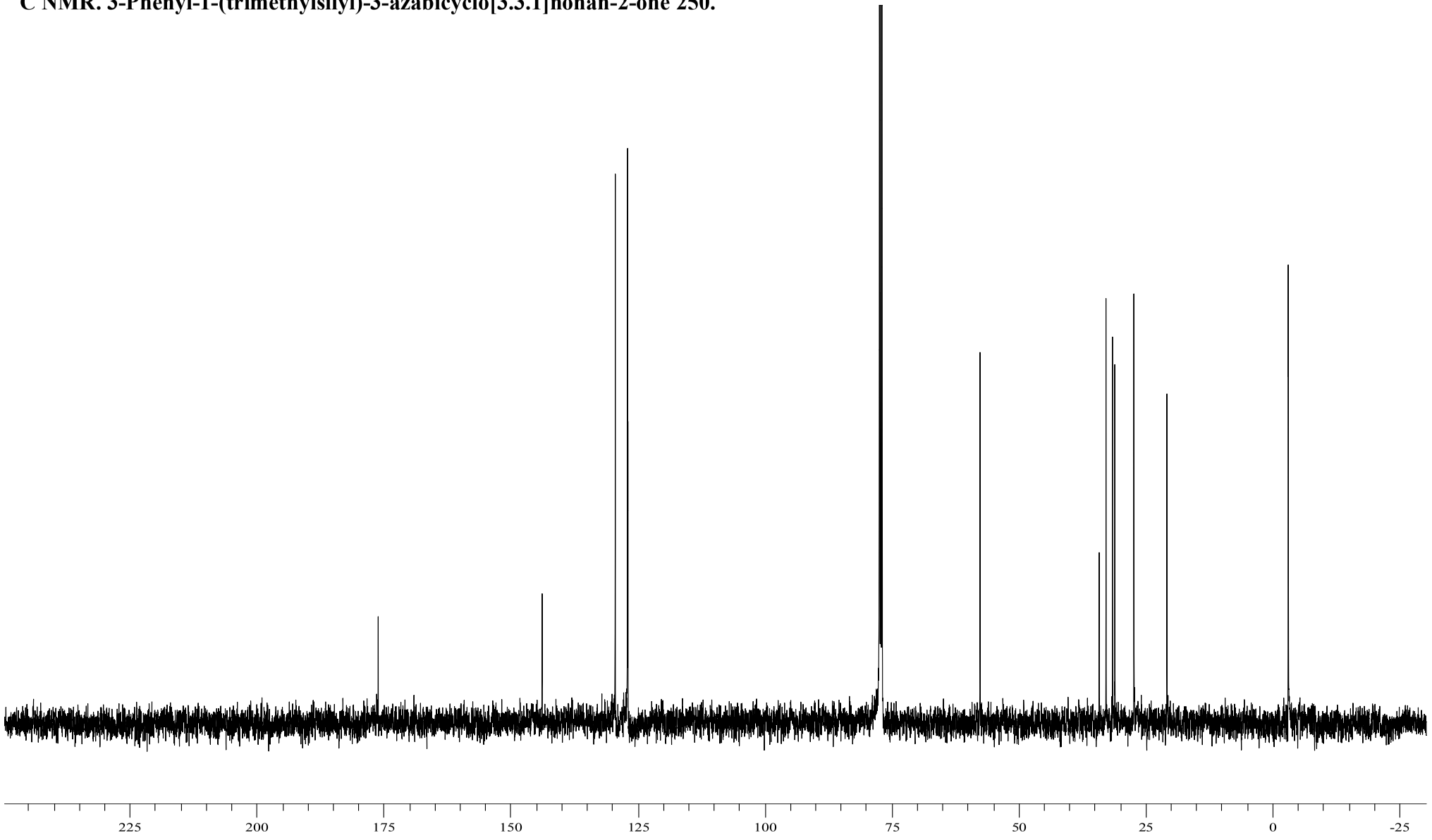


^{1}H NMR. 3-Phenyl-1-(trimethylsilyl)-3-azabicyclo[3.3.1]nonan-2-one 250.

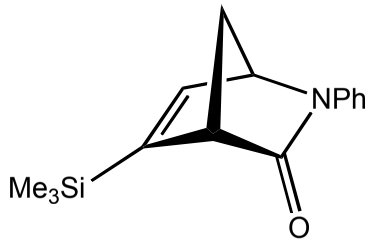


(–)-**250**

^{13}C NMR. 3-Phenyl-1-(trimethylsilyl)-3-azabicyclo[3.3.1]nonan-2-one 250.



^{1}H NMR. 3-Phenyl-5-(trimethylsilyl)-2-azabicyclo[2.2.1]hept-5-en-3-one 255.



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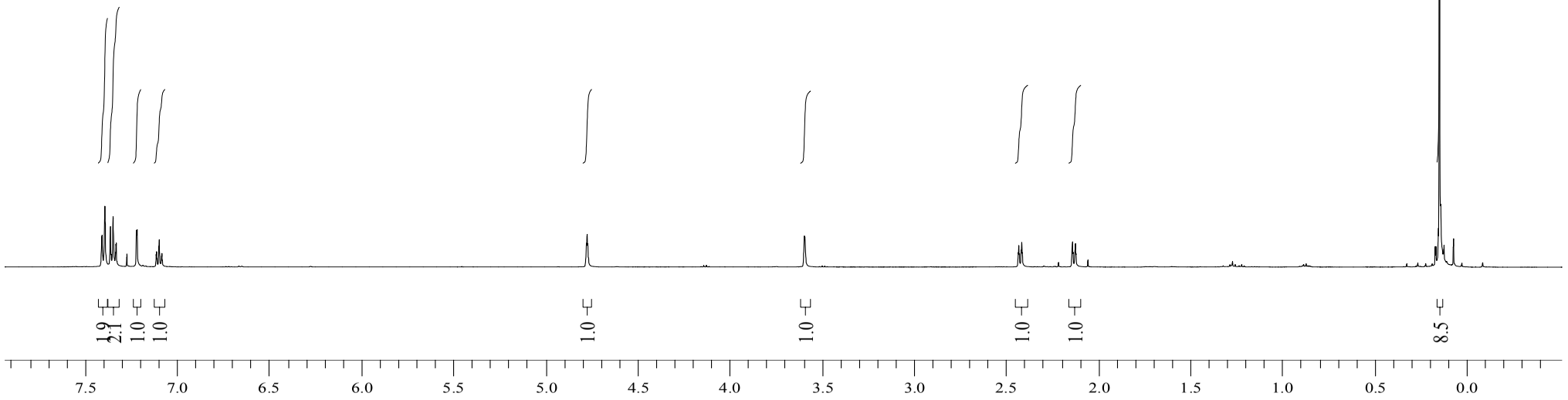
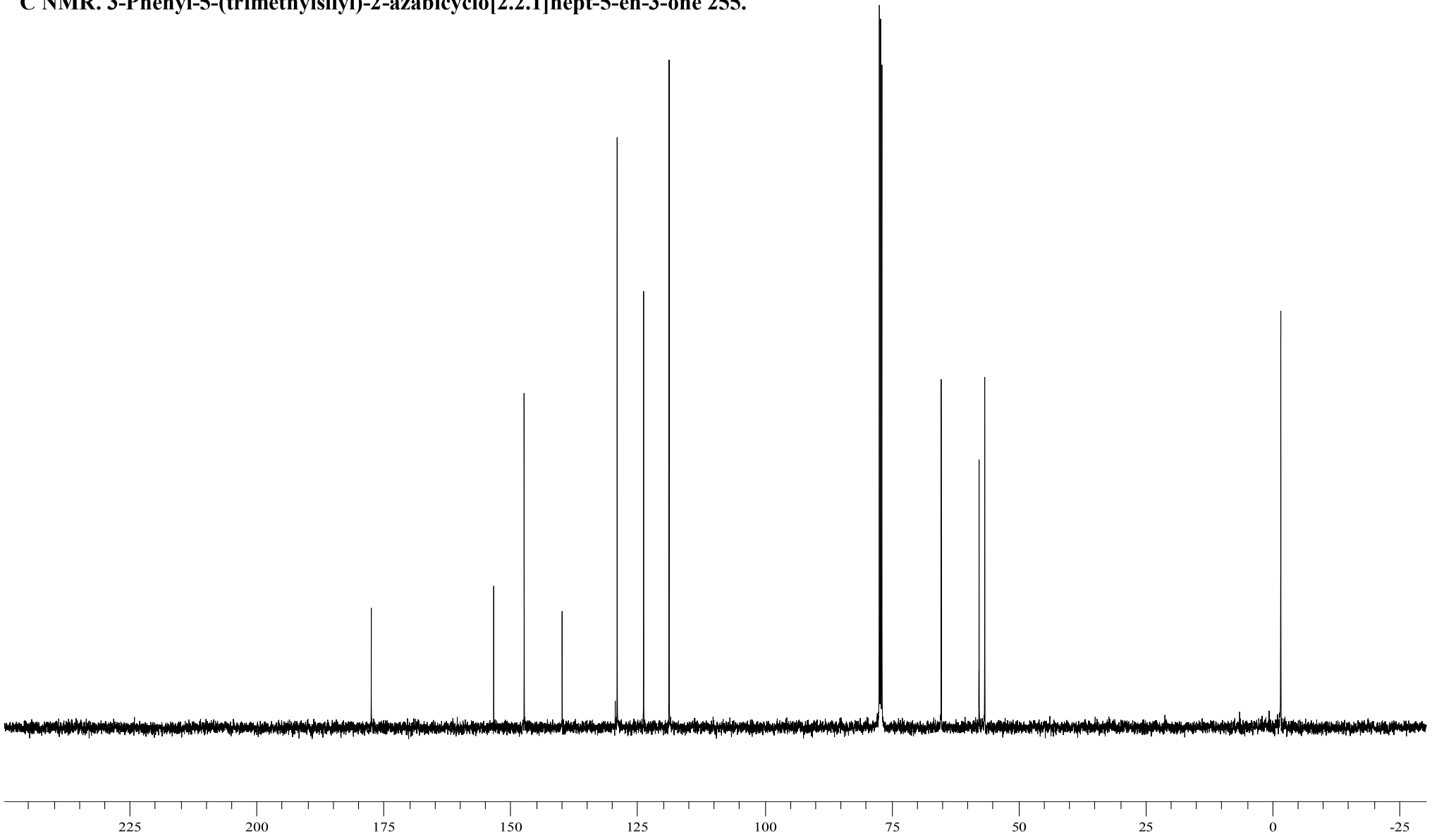


^{13}C NMR. 3-Phenyl-5-(trimethylsilyl)-2-azabicyclo[2.2.1]hept-5-en-3-one 255.



Publications

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The enantioselective generation of bridgehead enolates

Alexander J. Blake,[a] Gerard M. P. Giblin,[b] Douglas T. Kirk,[a] Nigel S. Simpkins*[a] and Claire Wilson[a]

[a] *School of Chemistry, The University of Nottingham, University Park, Nottingham, UK NG7 2RD. E-mail: Nigel.Simpkins@Nottingham.ac.uk; Fax: +44(0) 115 951 3564; Tel: +44(0) 115 951 3533*
[b] *GlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, UK SG1 2NY*

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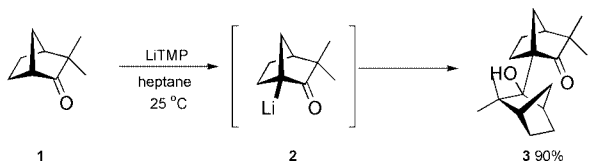
The generation and silylation of bridgehead enolates has been accomplished in high enantiomeric excess using a chiral lithium amide base.

The anti-Bredt nature of bridgehead enolates (more accurately described as α-keto carbanions) derived from ketones having small bridges is expected to make their generation difficult or impossible.[1,2] However in certain cases reactive α-keto carbanions have been formed at bridgehead positions, despite the lack of true enolate character. In these situations the intermediate anion appears highly reactive and displays chemistry that is difficult to control. An example is the metallation of (−)-camphenilone **1** with lithium tetramethylpiperidide (LiTMP).[3] Even in the presence of *in situ* trapping agents, such as Me_3SiCl, the presumed intermediate **2** could not be intercepted and only the aldol product **3** was obtained (Scheme 1).†

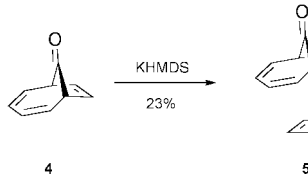


Scheme 1

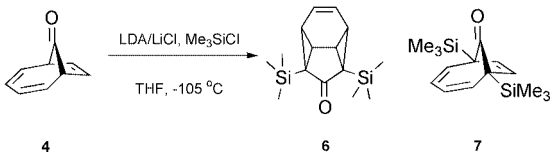
Feldman and coworkers reported that bicyclo[4.2.1]nona-2,4,7-trien-9-one **4** exhibited a similar tendency towards self-addition when treated with potassium hexamethyldisilazide (KHMDS), to give aldol product **5** in 23% yield (Scheme 2).[4]

As part of our programme of research aimed at exploring the applications of chiral lithium amide bases we became interested in the types of bridgehead enolate presumed to be intermediates in the above Schemes. Herein we describe our preliminary investigations in this area, which show that chiral lithium amide bases allow unprecedented enantioselective access to the products of bridgehead substitution in compounds such as **4**.

Initial studies with ketone **4** demonstrated that external quench protocols were ineffective in trapping the carbanion, leading only to the addition product **5**, albeit in an improved yield of 66%. Instead we turned our attention to deprotonation under *in situ* quench conditions with LDA–LiCl in the presence of Me_3SiCl, a method which we have employed in the past with success.[5] Thus addition of ketone **4** to an excess of LDA–LiCl in the presence of Me_3SiCl (method A, see later) at −105 °C led to the formation of an inseperable mixture of *bis* silylated ketones **6** and **7** in a 4 : 1 ratio and in a combined yield of 63% (Scheme 3).



Scheme 2



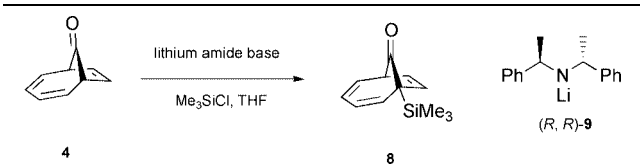
Scheme 3

The formation of the tetracyclic ketone **6** was unexpected and was confirmed following a single crystal X-ray structure determination.‡ This product is the result of double bridgehead substitution followed by a transannular Diels–Alder reaction, the latter process being precedented for this system.[6] We observed no partially silylated ketones corresponding to **6**, which points to its formation purely *via* **7**. An alternative mechanism involving anion initiated cycloaddition of **4** followed by bis-silylation appears to be ruled out following further experiments described below.

By changing the mode of deprotonation to addition of the base to a mixture of ketone and Me_3SiCl (inverse addition) we hoped to minimise formation of the unwanted bis-silyl compounds **6** and **7**. Selected results using this method (method B) are highlighted in Table 1, along with comparison data using method A. We discovered that upon addition of LDA–LiCl to a solution of ketone **4** and Me_3SiCl at −105 °C, the mono silylated ketone **8** was obtained in 38% yield, accompanied by a mixture of **6** and **7** in 17% yield (entry 2).

Next we attempted the asymmetric deprotonation of **4** by employing chiral base (*R*,*R*)-**9**.[7] By using the inverse addition protocol with (*R*,*R*)-**9** at −105 °C we obtained mono silylated ketone (−)-**8** in 76% yield and with an excellent ee of >96% in addition to bis silylated ketones **6/7** in 23% yield (entry 3).§ Conducting the reaction at −78 °C led to a lower yield and slightly lower enantiomeric excess (entry 4). The absolute configuration of (−)-**8** was determined by single crystal X-ray structure determination (Fig. 1).¶

Table 1 Bridgehead deprotonation of ketone **4** in the presence of Me_3SiCl under *in situ* quench conditions



Entry	Lithium amide base	*T*/°C	Method[a]	Yield of **6/7** (%)	Yield of **8** (%)	Ee of **8** (%)
1	LDA/LiCl	−105	A	39	0	—
2	LDA/LiCl	−105	B	17	38	—
3	(*R*,*R*)-**9**/LiCl	−105	B	23	76	>96
4	(*R*,*R*)-**9**/LiCl	−78	B	12	46	92

[a] A—ketone–Me_3SiCl added to base. B—base added to ketone–Me_3SiCl.

 DOI: 10.1039/b108986m

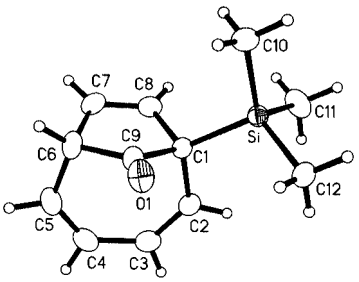


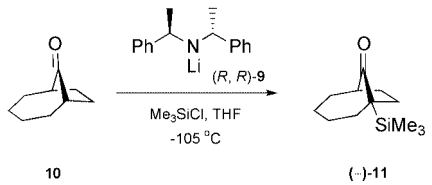
Fig. 1 X-Ray structure of (−)-**8**. Displacement ellipsoids are drawn at the 50% probability level.

We found no trace of a cyclised isomer of **8** corresponding to **6**, and attempts to induce the internal cycloaddition of **8** by heating led only to decomposition. It therefore appears that disilylation of **4** facilitates the cyclisation to give **6**.

The remarkable and unprecedented asymmetric substitution of ketone **4** prompted us to examine similar bridgehead metallations with the saturated ketone **10**, available from **4** by hydrogenation. Treatment of a mixture of ketone **10** and Me_3SiCl with (*R*,*R*)-**9** gave (−)-**11** in 53% yield and 92% optical purity (Scheme 4). The stereochemical configuration and optical purity were assigned by correlation with our earlier results, following hydrogenation of (−)-**8** to give (−)-**11**.

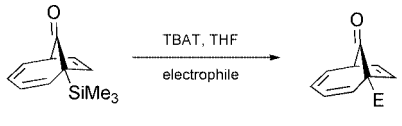
Unfortunately the *in situ* quench approach is incompatible with most electrophiles and we found that inclusion of electrophiles such as methyl iodide, allyl bromide and benzaldehyde gave none of the desired products. However, indirect access to products having alternative types of substituent was found to be possible by fluoride mediated silyl exchange reactions of (−)-**8**, using tetrabutylammonium triphenyldifluorosilicate (TBAT), Table 2.[8]

We expect that substitution occurs without erosion of enantiomeric purity, although this has only been established for entry 5 so far.



Scheme 4

Table 2 TBAT mediated silyl exchange in the presence of electrophiles



(-)-**8**

Entry	Electrophile, E	Yield (%)
1	MeI	42
2	AllylBr	29
3	BnBr	28
4	c-hexylCHO[a]	78
5	PhCHO[b]	72

[a] Obtained with diastereoisomeric ratio (dr) 4:1 [b] Obtained with dr 3:2.

Similarly, treatment of (−)-**11** in the presence of PhCHO with TBAT in refluxing THF gave the aldol product as a mixture of diastereoisomers (3:2) in 93% yield.

The remarkable enantioselective substitution of ketones **4** and **10** described above may pave the way for successful bridgehead metallation of many other types of bridged carbonyl compounds. Efforts to determine the scope of this chemistry are underway.

We are grateful to the University of Nottingham and GlaxoSmithKline for support of D. T. K. under the CASE scheme.

Notes and references

† Our efforts to control the metallation of **1** were unsuccessful leading only to aldol product **3**.

‡ *Crystal data* for compound **6**. $C_{15}H_{24}OSi_2$, M = 276.52, orthorhombic, a = 12.4355(7), b = 13.6661(8), c = 9.8989(6) Å, U = 1682.3(2) Å^3, T = 150 K, space group $Pna2_1$, Z = 4, μ(Mo-Kα) = 0.200 mm^{-1}, 10738 reflections measured, 3797 unique (R_{int} = 0.042) which were used in all calculations. The final $wR(F)$ = 0.0353, $wR(F^2)$ = 0.0820 (all data). Flack parameter refined to −0.04(9).

§ *Preparation of* (−)-**8** (Method B): A solution of chiral lithium amide base **9** (3.05 mmol), cooled to *ca.* −105 °C (internal temperature) was added dropwise *via* cannula, over 45 min, to a solution of ketone **4** (396 mg, 3 mmol) and Me_3SiCl (1.2 ml, 9 mmol) in THF (30 ml), maintained at that temperature. The resulting solution was allowed to warm slowly to rt over 3 h, quenched with saturated aqueous NH_4Cl (20 ml), and worked up in the usual way.

Purification by flash column chromatography on silica gel (4% Et_2O in light petroleum 40–60 °C as eluent) gave the title compound **8** as a white solid (464 mg, 76%); $[\alpha]_D^{26}$ −182 (*c* 0.99 in $CHCl_3$) mp 87–89 °C. ($C_{12}H_{16}OSi$: Calc: C, 70.55; H, 7.90. Found: C, 70.52; H, 7.79%). δ_H(400 MHz, $CDCl_3$) 0.15 (s, 9H), 3.14 (dd, *J* 2, 7.5 Hz, 1H), 5.62–5.66 (m, 2H), 5.69–5.71 (dd, *J* 2.3, 6.8 Hz, 1H), 5.84–5.97 (m, 3H). δ_C(125 MHz, $CDCl_3$) −3.7 (Me_3Si), 51.6 (C), 54.6 (CH), 122.2 (=CH), 124.6 (=CH), 125.7 (=CH), 127.0 (=CH), 129.3 (=CH), 130.5 (=CH), 218.3 (C=O). HRMS (EI) $C_{12}H_{16}OSi$ requires 204.097. Found 204.0984 (25%), 73.0474 (100, $SiMe_3$). Enantiomeric excess values were established by HPLC (UV detection at 205 and 215 nm) using hexane as eluent and a Chiralcel OD column.

¶ *Crystal data* for compound **8**. $C_{12}H_{16}OSi$, M = 204.34, monoclinic, a = 6.1568(6), b = 7.4191(7), c = 12.9873(12) Å, β = 101.996(2)°, U = 580.3(2) Å^3, T = 150 K, space group $P2_1$, Z = 2, μ(Mo-Kα) = 0.169 mm^{-1}, 4890 reflections measured, 2562 unique (R_{int} = 0.023). The final $wR(F)$ = 0.0276, $wR(F^2)$ = 0.0719 (2552 data). Flack parameter refined to 0.00(8). CCDC 172469 and 172470. See http://www.rsc.org/suppdata/cc/b1/b108986m/ for crystallographic data in CIF or other electronic format.

1 K. J. Shea, *Tetrahedron*, 1980, **36**, 1683; P. M. Warner, *Chem. Rev.*, 1989, **89**, 1067.

2 Previous synthetic use of bridgehead enolates is largely limited to compounds with longer bridges, see for example: P. A. Wender and T. P. Mucciaro, *J. Am. Chem. Soc.*, 1992, **114**, 5878; K. J. Shea, S. L. Gwaltney, II and S. T. Sakata, *J. Org. Chem.*, 1996, **61**, 7438; P. Magnus, D. Parry, T. Iliadis, S. A. Eisenbeis and R. A. Fairhurst, *J. Chem. Soc., Chem. Commun.*, 1994, 1543; M. Yamaura, T. Nakayama, H. Hashimoto, C. Shin and J. Yoshimura, *J. Org. Chem.*, 1988, **53**, 6035.

3 C. S. Shiner, A. H. Berks and A. M. Fisher, *J. Am. Chem. Soc.*, 1988, **110**, 957. See also: U. P. Spitz and P. E. Eaton, *Angew. Chem., Int. Ed.*, 1994, **33**, 2220.

4 K. S. Feldman, J. H. Come, B. J. Kosmider, P. M. Smith, D. P. Rotella and M.-J. Wu, *J. Org. Chem.*, 1983, **48**, 141.

5 Addition of LiCl can have a dramatic effect on rates of metallation, see for example: D. A. Price, N. S. Simpkins, A. M. MacLeod and A. P. Wyatt, *Tetrahedron Lett.*, 1994, **35**, 6159; B. J. Bunn, N. S. Simpkins, Z. Spavold and M. J. Crimmin, *J. Chem. Soc., Perkin Trans. 1*, 1993, 3113.

6 R. D. Miller and D. L. Dolce, *Tetrahedron Lett.*, 1977, 3329.

7 For a review, see: P. O'Brien, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1439.

8 A. S. Pilcher and P. DeShong, *J. Org. Chem.*, 1996, **61**, 6901.

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Bridgehead Enolates: Substitution and Asymmetric Desymmetrization of Small Bridged Carbonyl Compounds by Lithium Amide Bases

Gerard M. P. Giblin,[†] Douglas T. Kirk,[‡] Lee Mitchell,[‡] and Nigel S. Simpkins*,[‡]

GlaxoSmithKline, Department of Medicinal Chemistry, Neurology CEDD, The Frythe, Hertfordshire AL6 9AR, U.K., and School of Chemistry, University of Nottingham, University Park, Nottingham NG7 2RD, U.K.

nigel.simpkins@nottingham.ac.uk

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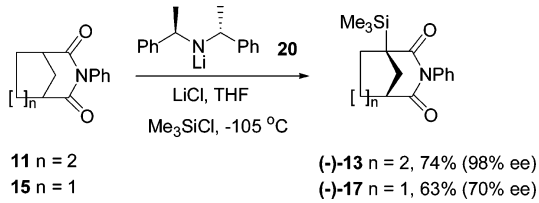
ABSTRACT



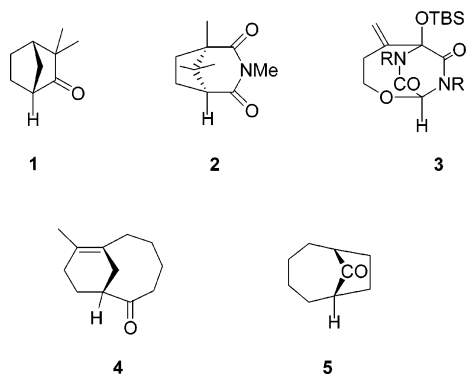
11 n = 2
15 n = 1

(-)-13 n = 2, 74% (98% ee)
(-)-17 n = 1, 63% (70% ee)

Contrary to expectations, a number of bridged carbonyl compounds undergo facile bridgehead metalation with lithium amide bases. Diketone, lactone, lactam, and imide functions are all demonstrated to participate in this type of "bridgehead enolate" chemistry, leading to a range of substituted products. Meso compounds can also be desymmetrized in very high ee by asymmetric bridgehead metalation.

Metalation of ketones such as camphenilone **1** at the bridgehead position is expected to be difficult or impossible because the conventional enolate form of the resulting anion would break Bredt's rule (Figure 1).[1] In fact, ketone **1** is readily metalated by lithium tetramethylpiperidide (LTMP), but the resulting "bridgehead enolate" (perhaps more accurately described as an α-keto carbanion) undergoes such rapid addition to the starting ketone that its interception by alternative electrophiles has not been possible.[2] A number of other bridgehead metalations have also been described, including carboxylation of imide **2** and aldol-type reaction of diketopiperazine **3**.[3,4]

While bridgehead metalation of small-bridge carbonyl compounds is expected to be problematic, with larger systems



1 **2** **3**

4 **5**

Figure 1. Carbonyl compounds known to undergo bridgehead metalation.

[†] GlaxoSmithKline.
[‡] University of Nottingham.

(1) (a) Shea, K. J. *Tetrahedron* **1980**, *36*, 1683. (b) Warner, P. M. *Chem. Rev.* **1989**, *89*, 1067. (c) Certain systems are known to undergo base-catalysed bridgehead deuteration; see: Nickon, A.; Covey, D. F.; Huang, F.; Kuo, Y.-N. *J. Am. Chem. Soc.* **1975**, *97*, 904.

(2) (a) Shiner, C. S.; Berks, A. H.; Fisher, A. M. *J. Am. Chem. Soc.* **1988**, *110*, 957. (b) The inability to trap bridgehead enolates has led to the invention of indirect approaches; see, for example: Spitz, U. P.; Eaton, P. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2220.

10.1021/ol034348l CCC: $25.00
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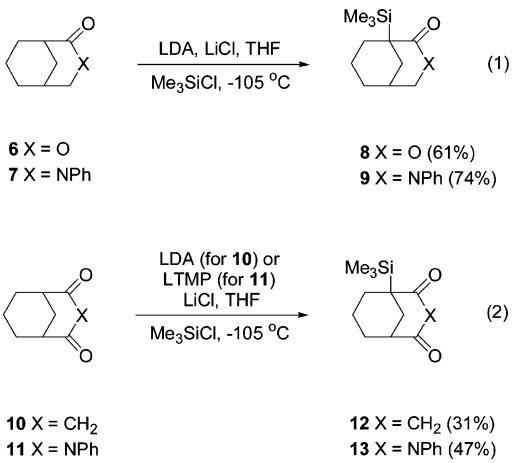
a transition to "normal" enolate chemistry should be evident.[5] Remarkably, ketone **4** undergoes kinetically controlled enolate formation at the bridgehead position despite the availability of an alternative methylene site for deprotonation.[6]

Recently, we demonstrated that bridgehead metalation−substitution of ketones such as **5** is possible in high yield by use of a lithium amide−in situ Me_3SiCl quench protocol and that enantioselective desymmetrization was possible using a chiral lithium amide base.[7] However, the scope of such bridgehead metalations remains ill-defined, especially in regard to interesting examples such as imide **2**, which appear to lie between the uncontrolled carbanion-like camphenilone system and the well-behaved large bridge systems.

Here, we demonstrate that a range of bridged systems, having small bridges (one to three atoms), with ketone, imide, lactam, or lactone activating functions undergo lithium amide mediated bridgehead metalation−substitution. We also show that very high levels of enantioselectivity can be achieved in asymmetric desymmetrization of bridged imides using the chiral base method.

The bicyclo[3.3.1]nonane systems **6**, **7**, **10**, and **11**, having various carbonyl functions in one of the three-atom bridges, provide interesting preliminary observations concerning the viability of bridgehead substitution. Under our usual low-temperature in situ quench conditions using Me_3SiCl as the electrophile, modest to good yields of the desired products were obtained, Scheme 1 (eqs 1 and 2).

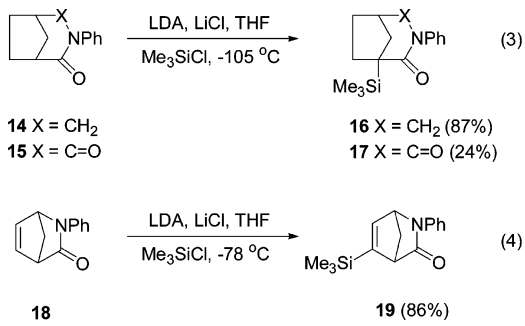
Scheme 1



The lactone **6** and lactam **7** underwent surprisingly smooth bridgehead silylation, using excess (1.2−1.8 equiv) LDA−LiCl as base (eq 1). In the diketone and imide cases (**10** and **11**), the desired product was accompanied by lesser amounts of disilylated product (typically 10−20%) and unidentified byproducts, which could be minimized by the use of LTMP in place of LDA (eq 2).[8] In the case of diketone **10**, we employed 2.5 equiv of base in the expectation that bridgehead substitution might occur via a dianion[9] although the reaction most likely proceeds via initial formation of an enol silane.

In the next phase of exploration, we examined metalation of lactam and imide compounds having shorter bridges, Scheme 2 (eqs 3 and 4).

Scheme 2



The bicyclo[3.2.1]octane lactam **14** underwent high-yielding silylation using LDA−LiCl, and we found that the use of ^sBuLi, as employed in metalations of the rather more hindered imide **2**, gave none of the desired product. Silylation of the corresponding imide **15** proved more problematic, with bis-silylation predominating. The unsaturated bicyclo[2.2.1]-heptane lactam **18** gave no products of bridgehead substitution, but instead gave a high yield of silylated alkene **19**. When we removed the double bond from **18**, either by hydrogenation or by dihydroxylation-acetonide formation, none of the desired mode of substitution could be achieved. This system is related to the classical camphenilone example **1**, and in line with previous work we were unable to intercept the anion from this ketone, even using a large excess of Me_3-SiCl at low temperature. Thus, it seems that successful metalations of these very small rigid systems still present a problem.

Asymmetric desymmetrization of the *meso*-imides **11** and **15** was carried out by use of chiral lithium amide base **20** or the bis-lithiated base **21**, Scheme 3.[10,11]

The use of (*R*,*R*)-bisphenylethylamide **20** enabled the synthesis of (−)-**13** in high yield and enantiomeric excess, the process being considerably more efficient than the corresponding reaction with LDA or LTMP. In the silylation

(3) Wanner, K. T.; Paintner, F. F. *Liebigs Ann.* **1996**, 1941.

(4) (a) Yamaura, M.; Nakayama, T.; Hashimoto, H.; Shin, C.; Yoshimura, J.; Kodama, H. *J. Org. Chem.* **1988**, *53*, 6035. (b) Williams, R. M.; Armstrong, R. W.; Dung, J.-S. *J. Am. Chem. Soc.* **1984**, *106*, 5748. (c) Eastwood, F. W.; Gunawardana, D.; Wernert, G. T. *Aust. J. Chem.* **1982**, *35*, 2289.

(5) (a) Khan, F. A.; Czerwonka, R.; Zimmer, R.; Reissig, H.-U. *Synlett* **1997**, 995. (b) Magnus, P.; Parry, D.; Iliadis, T.; Eisenbeis, S. A.; Fairhurst, R. A. *J. Chem. Soc., Chem. Commun.* **1994**, 1543. (c) Wender, P. A.; Mucciaro, T. P. *J. Am. Chem. Soc.* **1992**, *114*, 5878. (d) Rigby, J. H.; Moore, T. L. *J. Org. Chem.* **1990**, *55*, 2959.

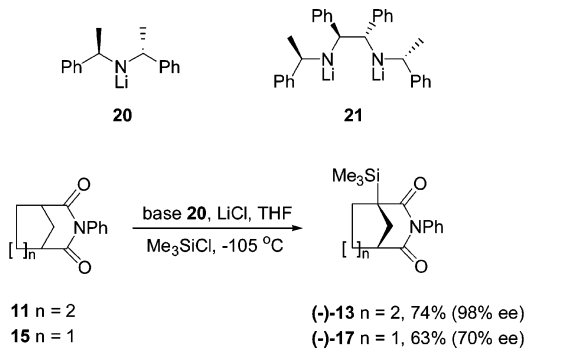
(6) Gwaltney, S. L., II; Sakata, S. T.; Shea, K. L. *J. Org. Chem.* **1996**, *61*, 7438.

(7) Blake, A. J.; Giblin, G. M. P.; Kirk, D. T.; Simpkins, N. S.; Wilson, C. *Chem. Commun.* **2001**, 2668.

(8) In cases such as **6** or **7**, excess base can be used to ensure smooth conversion to product, whereas with substrates such as imide **11** the possibility for double bridgehead substitution dictates the use of close to stoichiometric amounts of base (usually 1.1 equiv). In typical metalations, we added a solution of 1.1−1.2 equiv of base to a mixture of 1.0 equiv of substrate and 3.0 equiv of electrophile in THF at −105 °C. The mixture was then allowed to warm to room temperature before standard workup and chromatography. Further details can be found in the Supporting Information.

(9) Berry, N. M.; Darey, M. C. P.; Harwood, L. M. *Synthesis* **1986**, 476 and references therein.

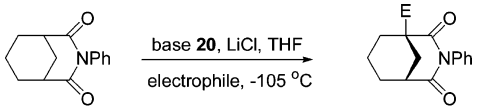
Scheme 3



of **15**, base **20** proved less selective, providing (−)-**17** in 70% ee. In this case we utilized the bis-lithium amide base **21**,[12] which then provided (+)-**17** in 47% yield and 94% ee.

Although the Me_3SiCl in situ quench procedure had provided some remarkable new bridgehead silylation results, we were interested in probing the possibilities for achieving alternative bridgehead alkylation, acylation, etc. At present, it appears that treatment of most of the aforementioned substrates with lithium amide bases, *followed* by addition of electrophiles in the conventional way, provides very low levels of substitution product. However, by addition of chiral base **20** to a mixture of imide **11** and an appropriate electrophile, asymmetric *C*-alkylation or acylation is possible (Table 1).[13]

Table 1. Asymmetric Bridgehead Substitution of Imide **11**



11 **(-)-22-26**

product	electrophile	E	yield (%)	ee (%)
(−)-**22**	methyl iodide	Me	57	97
(−)-**23**	allyl bromide	$CH_2CH{=}CH_2$	42	95
(−)-**24**	prenyl bromide	$CH_2CH{=}C(Me)_2$	50	98
(−)-**25**	benzyl bromide	CH_2Ph	52	95
(−)-**26**	pivaloyl chloride	CO^tBu	56	98

Although yields are somewhat modest at present, this being in part due to bis-alkylation, in all cases the enantiomeric excess of the product was excellent. We have not yet ascertained the full scope of this procedure in terms of substrate or electrophile, but we expect that similar substitutions will be possible on other systems.

The highly enantioselective silylation of imides **11** and **15** enables further selective transformations with synthetic potential. First, it was interesting to note that silylimide (−)-**13** undergoes rather facile and high-yielding substitution at the remaining bridgehead site, using the type of in situ quenching procedure outlined above and with LTMP as base, e.g., to give **27** and **28** (Figure 2).

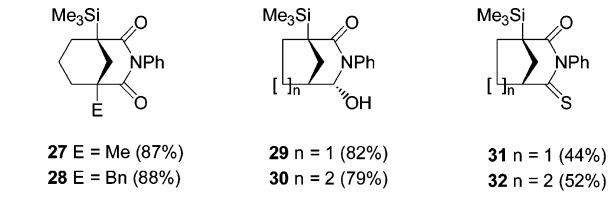


Figure 2.

Second, the bridgehead silicon substituent in chiral imides such as (−)-**13** and (−)-**17** exerts impressive control of the regiochemistry of subsequent reactions of the imide function. For example, completely regioselective reduction of these compounds was possible using DIBAL in CH_2Cl_2 at −78 °C to give **29** and **30**, which could be further reduced to **16** (88%) and **9** (83%), respectively, using Et_3SiH and Me_3SiOTf.[14]

Similarly, regioselective thionation to give **31** and **32** was possible using Lawesson's reagent,[15] and again no minor regioisomers could be detected. Although we have not checked the ee of these lactam and thioimide products they should correspond to the initial values achieved in the chiral base reactions.

In conclusion, we have demonstrated the unexpectedly wide scope of bridgehead substitution via lithium amide metalation of carbonyl compounds having relatively short bridges. The chiral lithium amide mediated desymmetrizations of *meso*-imide substrates further adds to the repertoire of these versatile reagents, and enables highly enantioselective access to certain bridged imides and lactams. Further explorations of the scope and limitations of such bridgehead metalations are ongoing, along with applications to bioactive target molecules.

Acknowledgment. We are grateful to the University of Nottingham and GlaxoSmithKline for support of this work under the CASE scheme and to the Engineering and Physical Sciences Research Council (EPSRC) for a Fellowship to L.M.

Supporting Information Available: Typical procedures for metalations, NMR data for all compounds, and HPLC data for ee determinations. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) For previous chiral base desymmetrisation of imides, see: (a) Adams, D. J.; Blake, A. J.; Cooke, P. A.; Gill, C. D.; Simpkins, N. S. *Tetrahedron* **2002**, *58*, 4603. (b) Greenhalgh, D. A.; Simpkins, N. S. *Synlett* **2002**, 2074.

(11) The absolute configurations of the chiral silylimides **13** and **17** were determined by X-ray crystallography and the *C*-alkylated compounds are assumed to belong to the same enantiomeric series; full details will be published elsewhere.

(12) Bambridge, K.; Begley, M. J.; Simpkins, N. S. *Tetrahedron Lett.* **1994**, *35*, 3391.

(13) At this time, it is not clear why this procedure is required, and we have been unable to satisfactorily monitor the course of the metalations using deuterium-quenching experiments.

(14) For contributions to the area of regioselective imide reduction, see: (a) Wijnberg, J. B. P. A.; Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 179. (b) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.

(15) Milewska, M. J.; Gdaniec, M.; Polonski, T. *J. Org. Chem.* **1997**, *62*, 1860.