Claisen Rearrangements of Heterocycles

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Abstract

This thesis is divided into five chapters.

Chapter 1 is a review of de-aromatisation processes achieved by sigmatropic rearrangement. It covers the two main types of sigmatropic rearrangements, namely [2,3]- and [3,3]-rearrangement.

Chapter 2 introduces the decarboxylative Claisen rearrangement (dCr) reaction and the aim to investigate its viability on more elaborate heterocyclic substrates is discussed. Research efforts into the synthesis of 3-sulfonyl-6-alkenyl-1,4-dioxan-2-ones are detailed.

Chapter 3 discusses the extension of this methodology towards *N*-alkylmorpholinones. The first section examines 5,6-divinyl *cis*-morpholinones and L-alanine-derived *trans*-morpholinones as Claisen precursors, whereby stereospecific Ireland–Claisen rearrangement of L-alanine-derived *trans*-morpholinones was achieved. The second section details the synthesis of a novel L-proline-derived bicyclic morpholinone. However, attempted rearrangement led to degradation of product instead. The third section details the synthesis of 6-thienyl and 6-furanyl morpholinones, along with attempted Ireland–Claisen rearrangements and dCr reactions.

Chapter 4 describes research efforts into the de-aromatising sigmatropic rearrangement of azide- and phthalimide-containing thienyl acyclic precursors. dCr Reaction of a cyanoacetate-containing substrate followed by unprecedented cyclisation led to the formation a highly-conjugated tetracycle and the mechanism of its formation is discussed.

Chapter 5 provides experimental procedures and characterisation data.

Declaration

I certify that all work in this thesis is solely my own, except where explicitly stated and appropriately referenced. No part of the thesis has been submitted previously for a degree at this, or any other, university.

Acknowledgements

Firstly, I would like to thank Professor Donald Craig for this invaluable opportunity as well as providing support and guidance since my time as an undergraduate. I would also like to thank Mr. Toby Underwood for his helpful input as my CASE supervisor, particularly during my placement at Pfizer.

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Lastly, I want to thank my family and extended family at home for their love and concern. This thesis is dedicated to my father, who believed in the importance of my education and without whom, I would not have been able to be what I am.

List of Abbreviations

$[\alpha]_D$	specific optical rotation
Å	Ångström(s)
a	antarafacial
Ac	acetyl
Ar	aryl
atm	atmosphere(s)
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
bp	boiling point
BSA	*N,O*-bis(trimethylsilyl)acetamide
*n*Bu or Bu	*normal*-butyl
*s*Bu	*secondary* or *sec*-butyl
*t*Bu	*tertiary* or *tert*-butyl
c or [ ]	concentration
°C	degree centigrade
cat.	catalytic
CBz	benzyloxycarbonyl
conc.	concentrated
calcd	calculated
cm	centimetre(s)
Cy	cyclohexyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DCE	dichloroethane
dCr	decarboxylative Claisen rearrangement
de	diastereomeric excess
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DIC	*N,N*′-diisopropylcarbodiimide
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane

DMF	dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethyl sulfoxide
dppm	bis(diphenylphosphino)methane
dr	diastereomeric ratio
E1cB	elimination unimolecular conjugate base
ee	enantiomeric excess
eq	equivalent(s)
Et	ethyl
g	gram(s)
h	hour(s)
HATU	*O*-(7-Azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate
HMPA	hexamethylphosphorictriamide
HOMO	highest occupied molecular orbital
HNIB	[hydroxy(*para*-nitrobenzenesulfonyloxy)iodo]benzene
HTIB	[hydroxy(tosyloxy)iodo]benzene
IR	infrared
K	Kelvin
kcal	kilocalorie(s)
KHMDS	potassium bis(trimethylsilyl)amide
kJ	kilojoule(s)
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
liq.	liquid
LUMO	lowest unoccupied molecular orbital
M	$moldm^{-3}$
m/w	microwave
mCPBA	*meta*-chloroperbenzoic acid
Me	methyl
mg	milligram(s)
min	minor or minute(s)
mL	millilitre(s)
mmol	millimole(s)

MMPP	magnesium monoperoxyphthalate hexahydrate
mol	mole(s)
mp	melting point
Ms	methanesulfonyl
MS	mass spectrometry
n	normal
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMR	nuclear magnetic resonance
O/N	overnight
p	*para*
Ph	phenyl
*i*Pr	*iso*-propyl
*n*Pr	*normal*-propyl
PTAB	phenyltrimethylammonium tribromide
*p*TSA	*para*-toluenesulfonic acid
R	alkyl group
R_f	retention factor
rt	room temperature
s	suprafacial
S_N2	bimolecular nucleophilic substitution
SOMO	singly occupied molecular orbital
SCX	strong cation exchange
t	time
T3P®	propylphosphonic anhydride
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBME	*tert*-butyl methyl ether
Temp.	temperature
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyranyl

TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*para*-toluenesulfonyl (tosyl)
TS	transition state(s)
X	heteroatom or halide
Δ	reflux

NMR

D	dimensional
δ	chemical shift
Hz	Hertz
J	coupling constant
MHz	megahertz
NOESY or nOe	nuclear Overhauser effect
ppm	parts per million
s	singlet
d	doublet
t	triplet
q	quartet
m	multiplet
br	broad

IR

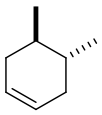
cm^{-1}	wavenumbers
υ_{max}	maximum absorption

MS

CI	chemical ionisation
EI	electron impact
ESI	electrospray ionisation
HRMS	high resolution mass spectrometry
m/z	mass / charge
$[M]^+$	molecular ion

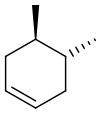
Stereochemical Notation

It should be noted that the Maehr convention for indicating relative and absolute stereochemistry has been used throughout this report.[1] Therefore, solid and broken lines are used to denote racemates, and solid and broken wedges denote absolute configuration. Narrowing of the wedges implies increasing distance from the reader in the latter case.



Racemate

Relative stereochemistry



Single enantiomer

Absolute stereochemistry

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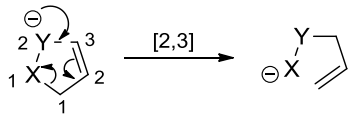
1. De-aromatising sigmatropic rearrangements

Since the discovery of benzene by Kekulé in 1865, scientific research has been pushed into a new dimension. Kekulé assigned the benzene structure as a six-membered ring of carbon atoms with alternating single and double bonds and its physical properties have been studied in detail. Most importantly, the unusual stability of benzene through resonance energy[2] has led to a new understanding of the concept of aromaticity. Since then, many other carbocyles and heterocycles have been classified as aromatics, which are extremely important for both fundamental and applied chemistry. Despite the high resonance energy of benzene, nature has shown that microorganisms can effect de-aromatisation by oxidation with oxygenases or reduction with reductases. [3] Synthetically, this remains a challenge. De-aromatisation can often produce highly reactive intermediates which could lead to facile bond formations or even new heterocycles with different properties. This powerful strategy has also been widely utilised in the synthesis of complex natural products.[4]

This chapter intends to explore some de-aromatisation processes achieved by sigmatropic rearrangement, where the de-aromatised cyclic nucleus could be part of either an intermediate or product in the reaction.

1.1. [2,3]-Sigmatropic rearrangements

The [2,3]-sigmatropic rearrangement is a six-electron pericyclic reaction that proceeds *via* a five-membered cyclic transition state with a simultaneous σ bond-breaking and a σ bond-formation, generalised by Scheme 1. It constitutes versatile bond reorganisation which encompasses useful variations in terms of the atom pair (X, Y) and the type of electron pair on Y (anions, non-bonding electron pairs or ylides).



Scheme 1: [2,3]-Sigmatropic rearrangement.

The pericyclic reaction is a concerted, thermally-allowed sigmatropic reaction which obeys the Woodward–Hoffmann rules [5] (Fig. 1, left). The transition state has an "envelope" conformation, which allows a head-on σ-overlap and side-on π-overlap. This is illustrated as a [$\sigma^2s + \omega^2s + \pi^2s$] reaction with an overall suprafacial component (e.g. no inversion of centre). Alternatively, this rearrangement also obeys Fukui's frontier orbital theory [6] (Fig. 1, right), where the new bond is formed by orbital interaction between the HOMO of the conjugated system into the LUMO of the π bond.

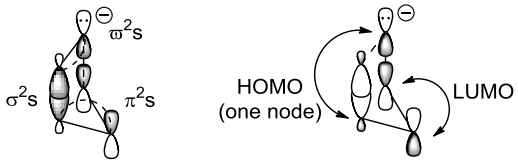
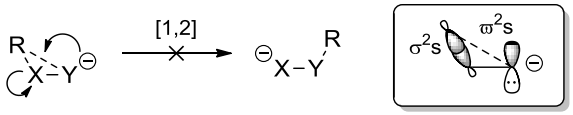


Fig. 1: Pericyclic TS obeys the Woodward–Hoffman rules (left) or Fukui's frontier orbital theory (right).

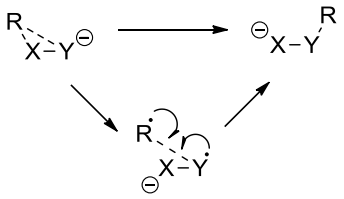
Notably when Y is an anion, the [1,2]-rearrangement [7] often competes with the [2,3]-rearrangement pathway. Despite its outward appearance as a concerted [1,2]-rearrangement, this process is actually forbidden by the Woodward–Hoffmann

rules (Scheme 2, left). The four-electron [σ^2s + ω^2s] process (Scheme 2, right) is symmetry-forbidden whereas the symmetry-allowed [σ^2s + ω^2a] or [σ^2a + ω^2s] geometries are unattainable.



Scheme 2: Disallowed concerted mechanism of [1,2]-rearrangement (left) and its symmetry-forbidden TS (right).

Instead, the [1,2]-rearrangement proceeds *via* a radical dissociation–recombination mechanism[8] which involves the homolytic cleavage of R-X and the homolytic bond formation of R-Y (Scheme 3).



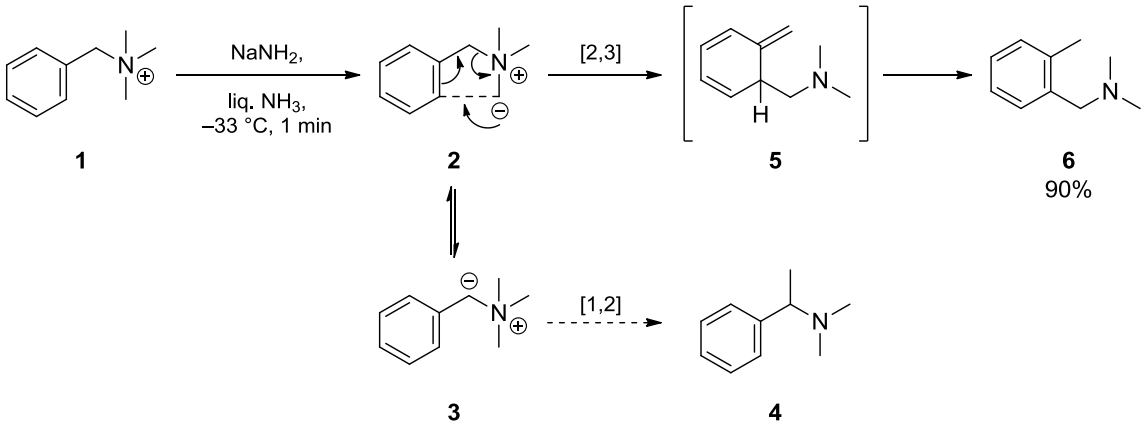
Scheme 3: Radical dissociation–recombination mechanism of [1,2]-rearrangement.

This section focuses on several classes of [2,3]-rearrangements represented by different atom pairs (X = N, S or O; Y = C) which involves the de-aromatisation of an aromatic nucleus during the rearrangement process.

1.1.1. Rearrangements involving X = N, Y = C (Sommelet–Hauser)

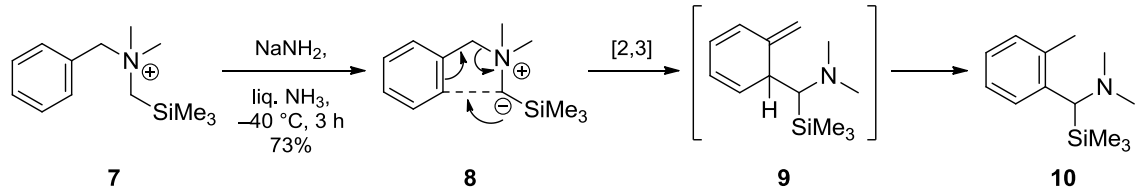
[2,3]-Rearrangements where X = N and Y = C (Scheme 1) are normally known as the Sommelet–Hauser reaction. Sommelet first realised such rearrangement of a benzyl quaternary ammonium salt in 1937.[9] These rearrangements were further elaborated by Hauser where benzyltrimethylammonium salt **1** was treated with sodium amide in liquid ammonia to give the carbanion **2** (Scheme 4).[10] This carbanion would be in equilibrium with the more stabilised isomeric carbanion **3**, which is capable of undergoing a Stevens

[1,2]-rearrangement to give **4**. However, this did not occur as it would require more vigorous conditions as compared to the [2,3]-rearrangement of anion **2** which occurred very readily in one minute to give the de-aromatised intermediate **5**. Concomitant re-aromatisation gave the Sommelet–Hauser product **6** as the only product in 90% yield.



Scheme 4: Hauser's [2,3]-rearrangement of benzyltrimethylammonium iodide **1**.

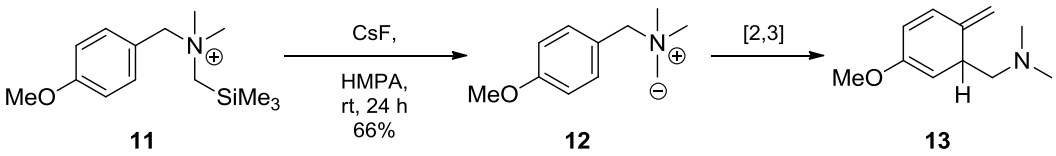
In another example, Sato reported that α-silyl ammonium salt **7**, when deprotonated with base, formed silyl-stabilised ylide **8** (Scheme 5).[11] It underwent [2,3]-rearrangement to give the de-aromatised product **9** followed by re-aromatisation to give the Sommelet–Hauser product **10** in 73% yield. Once again, no Stevens rearrangement product was observed.



Scheme 5: [2,3]-Rearrangement of silyl-stabilised ylide **8**.

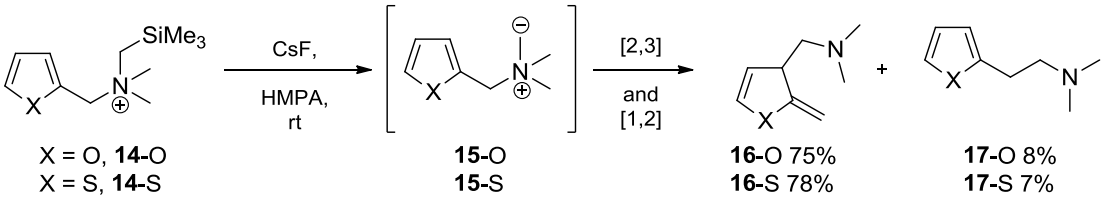
The [2,3]-rearrangements of *para*-substituted analogues of **7** were also reported by Sato.[12] It was found that electron-donating *para*-substituents stabilised the Sommelet–Hauser de-aromatised intermediate. In particular, fluoride-induced desilylation of

para-methoxybenzyl substrate **11** gave ylide **12**, which rearranged at room temperature to give isotoluene **13** (Scheme 6). This derivative was exceptionally stable (as compared to other Me, NO_2, CO_2tBu derivatives) and was isolated as the only product in 66% yield.



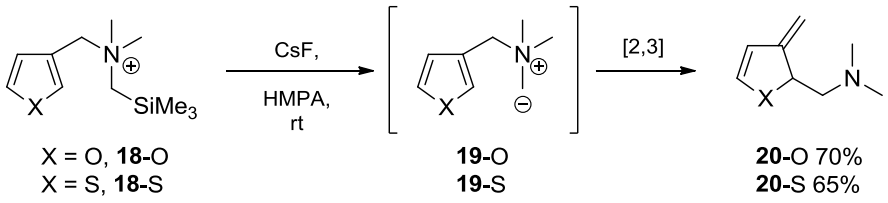
Scheme 6: [2,3]-Rearrangement of 3-methoxy-substituted **11** to give isotoluene **13**.

This result suggested that rearrangement of ylides of an electron-rich aromatic ring could similarly stop at the de-aromatised intermediates. Sato then examined the rearrangements of electron-rich (furylmethyl)ammonium and (thienylmethyl)ammonium *N*-methylides. CsF-induced desilylation of 2-substituted furan **14**-O gave ylide **15**-O which underwent rearrangement to give de-aromatised dihydrofuran **16**-O in 75% yield (Scheme 7).[13] The competing [1,2]-rearrangement of ylide **15**-O gave Stevens product **17**-O in 8% yield. Similarly, the rearrangement of thiophene **14**-S gave a 78% yield of the [2,3]-product **16**-S and 7% of the [1,2]-product **17**-S.



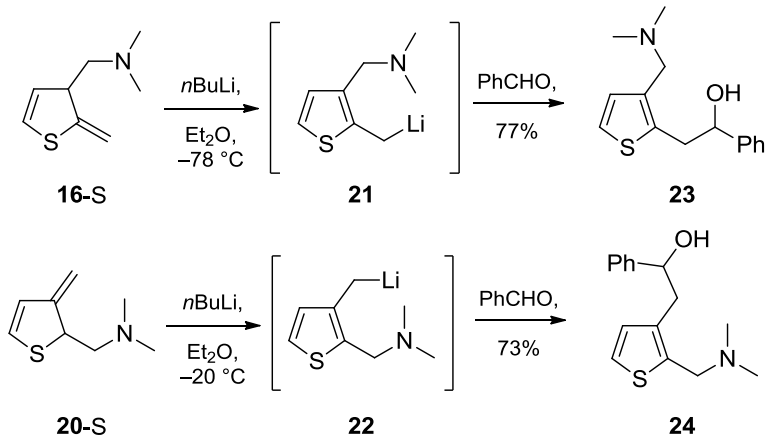
Scheme 7: [2,3]-Rearrangements 2-substituted heteroaromatics **14**.

In addition, 3-substituted furan **18**-O and thiophene **18**-S underwent [2,3]-rearrangements to give de-aromatised furan **20**-O in 70% yield and thiophene **20**-S in 65% yield, respectively (Scheme 8). The Stevens rearrangements of ylides **19** were not observed and this was hypothesised to have arisen from the stability of heterocycles **20** over its isomers **16**.



Scheme 8: [2,3]-Rearrangement of 3-substituted heteroaromatics **18**.

The de-aromatised dihydrothiophenes **16**-S and **20**-S were subsequently treated with 1 eq of *n*BuLi and benzaldehyde at −78 °C and −20 °C respectively to give re-aromatised aldol products **23** and **24** in good yields *via* lithium intermediates **21** and **22** (Scheme 9).

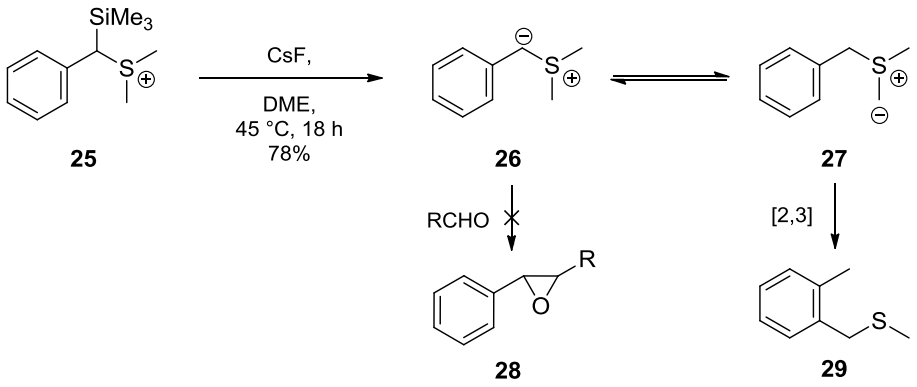


Scheme 9: Aldol reactions of thiophenes **20**-S and **16**-S with benzaldehyde to give thiophenes **23** and **24**.

1.1.2. Rearrangements involving X = S, Y = C

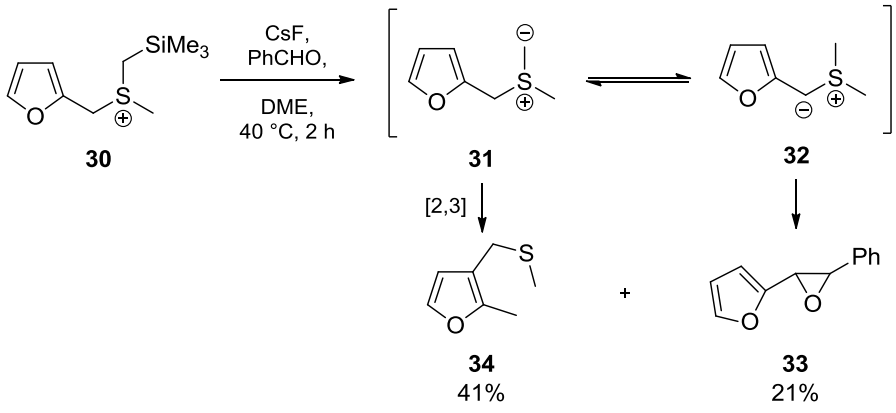
Another type of [2,3]-rearrangement may occur, involving the formation of a sulfur ylide in the rearrangement mechanism. Padwa [14] also employed the CsF-desilylation methodology in the formation of sulfur-stabilised ylide **26** from benzyl α-trimethylsilylsulfonium salt **25** and tried to trap the ylide with aldehydes (R = Ph, *p*-$CH_3C_6H_4$, furanyl, cinnamyl) to give epoxides **28** (Scheme 10). It was observed that the ylide isomers **26** and **27** rapidly interconverted *via* proton transfer (verified by deuterium NMR study) and the reaction could be competitive with both [2,3]-rearrangement and formation of epoxide **28**. However, the rearrangement product

29 was isolated as the only product in 78% yield, which seemed to suggest that the [2,3]-rearrangement is a more facile process. This parallels Hauser's observation (see Section 1.2.2) that the Sommelet–Hauser rearrangement was faster than the Stevens rearrangement.



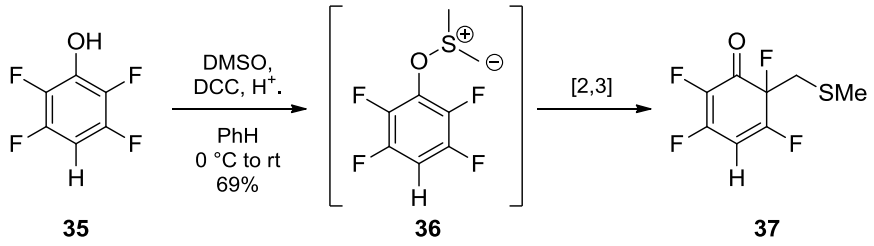
Scheme 10: [2,3]-Rearrangement of aryl **25** to give aryl **29**.

When the reaction was repeated with a more electron-rich heteroaromatic such as furan **30**, the initially-formed ylide **31** rapidly equilibrated with the thermodynamically more stable ylide **32 (**Scheme 11). In the presence of benzaldehyde, it was possible to trap ylide **32** to give epoxide **33** and this was isolated in 21% yield. However, the [2,3]-rearrangement still proceeded more rapidly than the bimolecular trapping reaction, giving furan **34** as the major product in 41% yield.



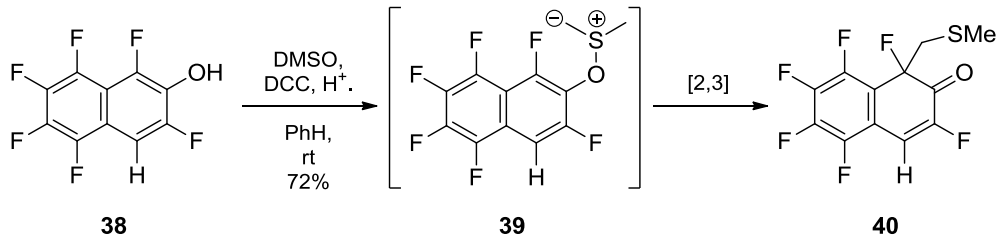
Scheme 11: Formation of furan **34** from [2,3]-rearrangement and epoxide **33** from intermolecular trapping.

The [2,3]-rearrangements of polyfluoro-arenols were also extensively studied.[15] Treatment of phenol **35** with activated DMSO–DCC–H^+ gave intermediate ylide **36** (Scheme 12).[15(e)] Rearrangement of the ylide gave de-aromatised cyclohexadienone **37** in 69% yield. Since **37** is unable to re-aromatise, this could be a powerful method for the formation of quarternary centres.



Scheme 12: [2,3]-Rearrangement of polyfluoro-phenol **35** to give de-aromatised product **37**.

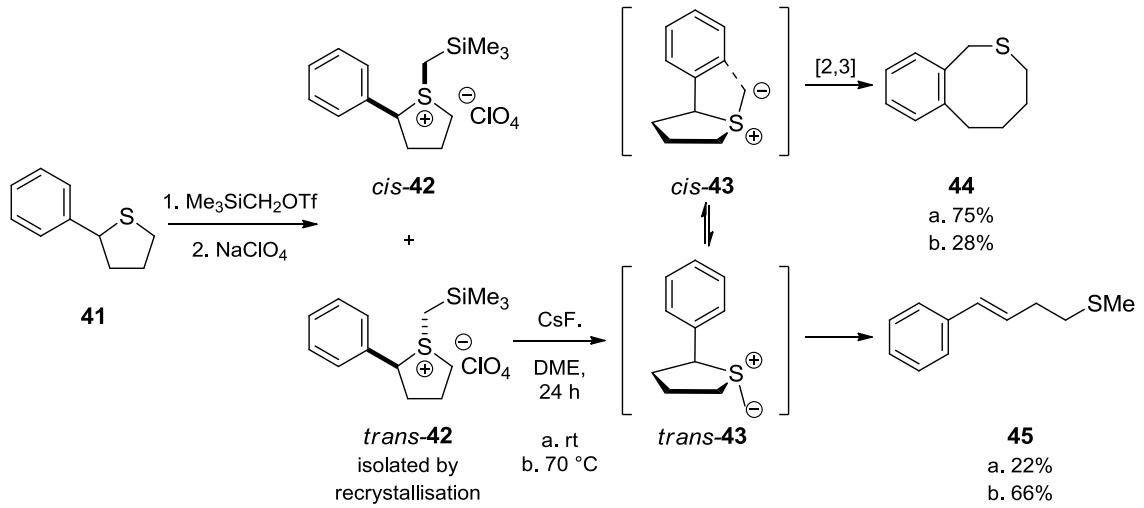
Under similar reaction conditions, naphthol **38** and DMSO–DCC–H^+ gave ylide **39** (Scheme 13). It was followed by [2,3]-rearrangement to give de-aromatised product **40** in 72% yield. The rearrangement was regioselective for the C-1 position rather than the C-3 position in formation of the new C–C bond in order to prevent disruption of the adjacent aromatic nucleus.



Scheme 13: [2,3]-Rearrangement of polyfluoro-naphthol **38** to give de-aromatised product **40**.

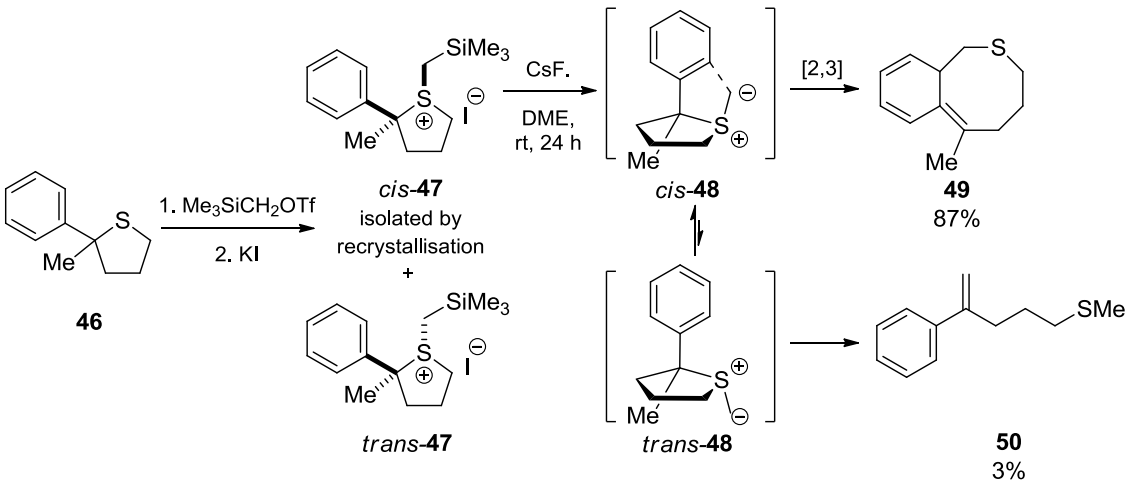
This method was also applied extensively by Sato in the formation of 8-, 9- and 10-membered heterocyclic compounds by [2,3]-rearrangement–ring expansion of 2-aryl-1-[(trimethylsilyl)methyl]-substituted six- or seven-membered ammonium[16] or sulfonium[17] salts. A recent example[18] reported that tetrahydrothiophene **41** was silylated

to give sulfonium salts **42** in which the *trans*-isomer was isolated by recrystallisation and its configuration confirmed by NOESY analysis (Scheme 14). Isomer *trans*-**42** was desilylated with CsF which resulted in an equilibrating mixture of ylides **43**. At room temperature, [2,3]-rearrangement was faster than elimination to give the 8-membered bicyclic product **44** in 75% yield and Hofmann elimination product **45** in 22% yield. In contrast, when the reaction mixture was heated at 70 °C, Hofmann elimination was predominant over [2,3]-rearrangement and gave 28% of **44** and 66% of **45**.



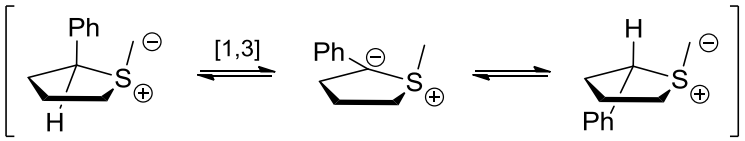
Scheme 14: [2,3]-Rearrangement of sulfonium salt *trans*-**42** to give product **44** and elimination product **45**.

Similarly, 2-methyl-2′-phenyltetrahydrothiophenium salts **47** were prepared from substrate **46** and sulfonium salt *cis*-**47** was isolated from recrystallisation of the mixture (Scheme 15).[18] The *cis*-isomer was treated with CsF and this gave the rearrangement product **49** in 87% yield and only 3% of elimination product **50** *via* an equilibrating mixture of ylides **48**. The de-aromatised product **49** was stable when isolated possibly due to the extra stabilisation gained from the increased substitution of the olefin.



Scheme 15: [2,3]-Rearrangement of sulfonium salt *cis*-**47** to give product **49** and elimination product **50**.

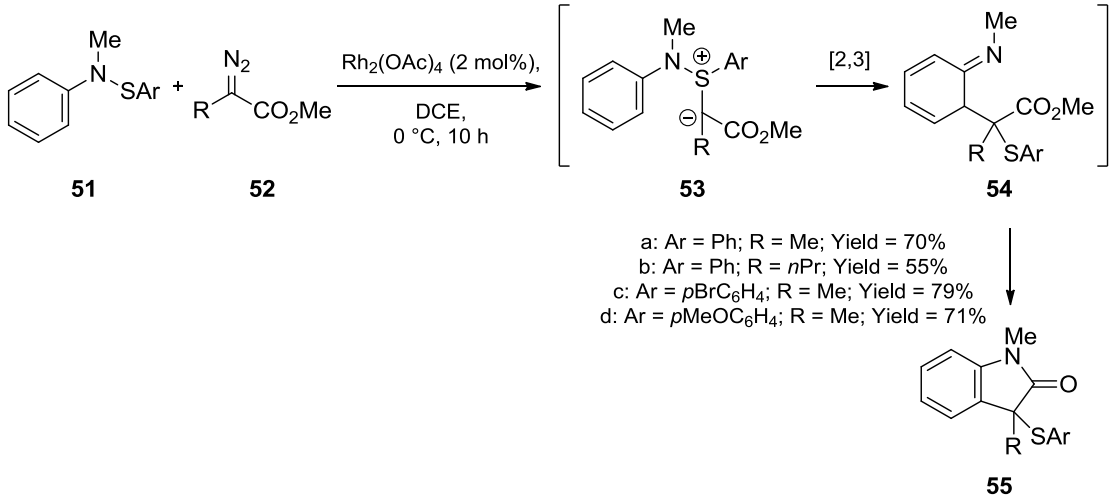
This result suggested that it was unfavourable for *cis*-**48** to convert into *trans*-**48** and provided an insight to the isomerisation mechanism of the ylides. It was reported that the isomerisation of ylides might have proceeded *via* an inversion of the phenyl group on the carbon atom by [1,3]-proton migration (Scheme 16) instead of an inversion at the sulfur centre.



Scheme 16: Isomerisation mechanism of ylide *cis*-**43** into *trans*-**43**.

Early work on a similar type of thia-Sommelet–Hauser rearrangement involving a nitrogen atom adjacent to the sulfonium ylide was investigated by Gassman in the synthesis of oxindoles.[19] More recently, Li reported a catalytic variation in the formation of Gassman's sulfonium ylide **53** (Scheme 17).[20] The Rh(II)-catalysed reaction of sulfenamide **51** and diazoacetate **52** under neutral conditions at 0 °C gave ylide **53** which rearranged to give de-aromatised product imine **54**. This unstable compound simultaneously converted into oxindole **55** with a quaternary centre on the 3-position. It

was observed that polar solvent disfavoured this reaction and optimal conditions were achieved with a low catalytic loading of 2 mol% $Rh_2(OAc)_4$ in DCE. A library of oxindoles were synthesised by Li *via* this method; this demonstrated that increasing size of the R-group led to increased steric hindrance of ylide **53** and in turn a poorer yield (conditions a and b). However, the stereoelectronic effect of *para*-substitutents on Ar did not affect the rearrangements (conditions c and d).



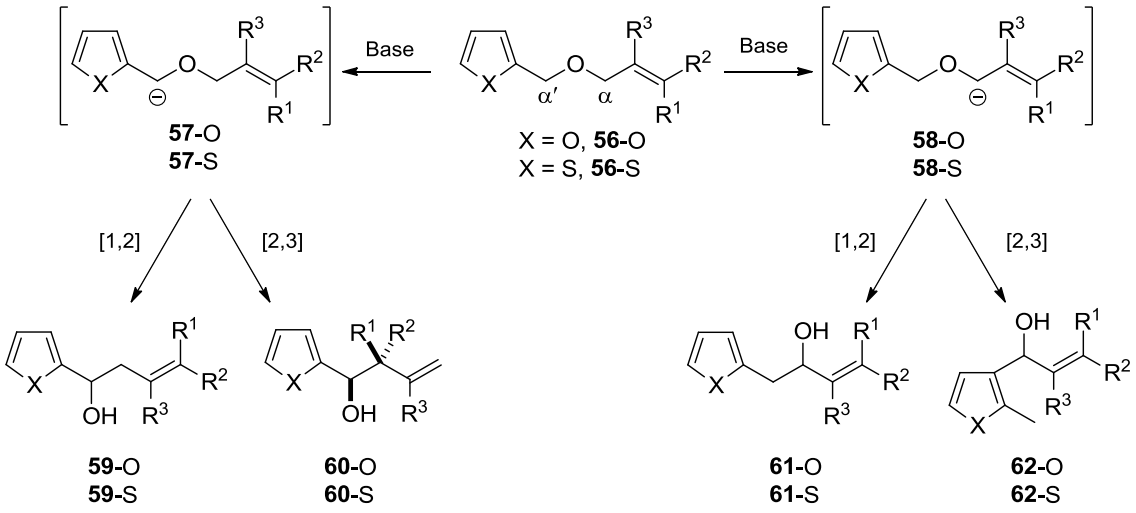
Scheme 17: Synthesis of oxindole **55** *via* [2,3]-rearrangement of sulfonium ylide **53**.

1.1.3. Rearrangements involving X = O, Y = C (Wittig)

The [2,3]-Wittig rearrangement[21] is another class of [2,3]-sigmatropic rearrangement involving an oxycarbanion (Scheme 1, X = O, Y = C) as the migrating terminus. This originates from the fact that it formally represents a [2,3]-sigmatropic version of the classic Wittig rearrangement,[22] a well-known 1,2-alkyl shift of oxycarbanions. However at higher temperature, the [1,2]-Wittig rearrangement could be a competitive process.

Tsubuki extensively studied the Wittig-rearrangements of allyl and propargyl 2-furyl- and 2-thienyl-methyl ethers.[23] 2-Furyl- or 2-thienyl-methyl ethers **56** were deprotonated with a strong base at either the α- or α′-position to give ylides **57** or **58** (Scheme 18). This

gave rise to four different rearrangement products, notably heteroaromatic **62** was formed *via* a [2,3]-rearrangement de-aromatised intermediate. Table 1 summarises some of the results obtained by Tsubuki with 2-substituted furans and thiophenes. It was generally observed that *t*BuLi promoted α′-deprotonation whereas *s*BuLi favoured α-deprotonation (Entries 1-4). In addition, increased substitution at the allylic end of thiophene **56**-S deterred formation of [2,3]-product **62**-S (Entries 3-4). On the other hand, [2,3]-rearrangements of 2-furyl substrates **56**-O involving the de-aromatisation pathway were disfavoured even when the allylic end was not substituted (Entries 5-6).

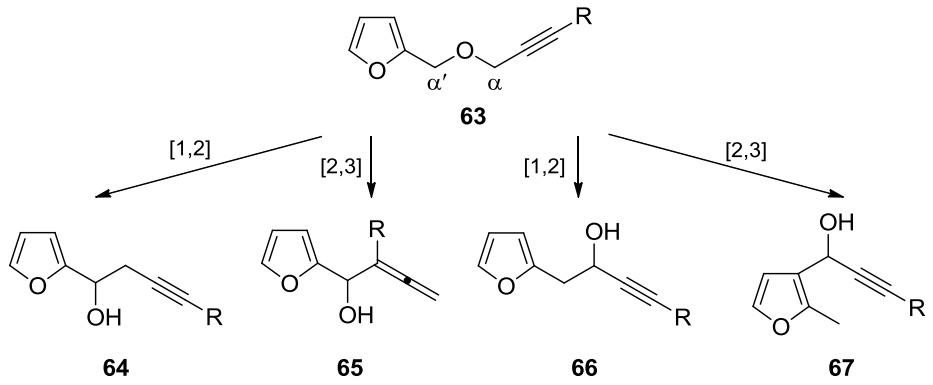


Scheme 18: Wittig-rearrangements of heteroaromatics **56** and their possible products (**59**-**62**).

Entry	X	Substrate	Base[+]	Yield	Product Distribution			
					59	**60 (*syn*/*anti*)**	**61**	**62**
1	S	$R^1 = R^2 = R^3 = H$	*s*BuLi	74%	-	-	39	61
2	S	$R^1 = R^2 = R^3 = H$	*t*BuLi	84%	44*		31	25
3	S	$R^1 = R^3 = H$, $R^2 = Me$	*s*BuLi	96%	-	18 (56/44)	49	33
4	S	$R^1 = R^2 = R^3 = Me$	*t*BuLi	76%	4	76	20	-
5	O	$R^1 = R^2 = R^3 = H$	*s*BuLi	61%	30	-	54	16
6	O	$R^1 = R^3 = H$, $R^2 = Me$	*n*BuLi	79%	-	74 (66/34)	26	-

Table 1: Reaction conditions for the Wittig-rearrangements of heteroaromatics **56**.
[+] Reactions carried out in THF at −78 °C; *Combined for **59** and **60** as they are the same product.

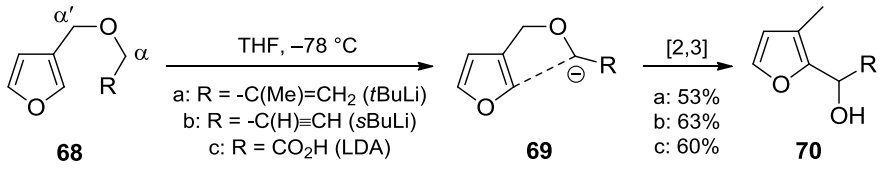
In comparison, 2-furyl methylpropargyl ether **63** was deprotonated with *s*BuLi and rearranged to give products **64** to **67** (Scheme 19).[23(b)] When R = H at the terminal alkynyl end, deprotonation at the α′-position was favoured and it rearranged to give [1,2]-product **64** as the major product. Increased substitution at the propargylic end (when R = Me) in contrast led to preferential deprotonation at the α-position to give the [2,3]-product **67** as the major product.



	Product Distribution			
R = H, 62% yield	65	-	21	14
R = Me, 64% yield	-	12	3	85

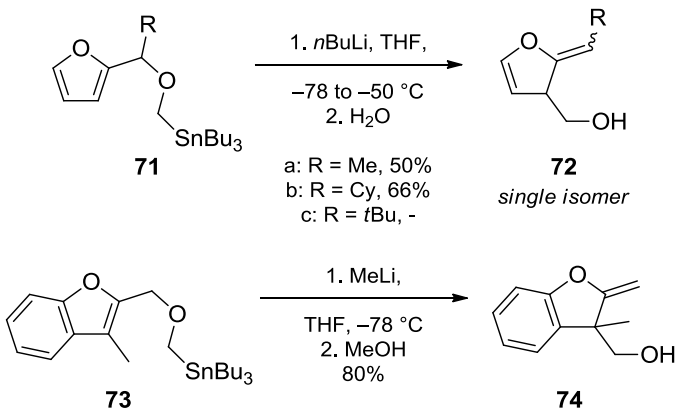
Scheme 19: Wittig rearrangements of heteroaromatics **63** and their possible products (**64**-**67**).

The Wittig rearrangements of 3-furylmethyl ethers **68** were also examined and were notably different in reactivity as compared to the 2-substituted furans (Scheme 20).[24, 25] Tsubuki reported that the deprotonation of furans **68** with base preferentially occurred at the α-position to give carbanions **69**.[24] [2,3]-Rearrangements next gave the re-aromatised products **70** in 53-63% yields. The by-products formed from [1,2]-rearrangements of ylides **69** were also observed, but in small amounts. Tsubuki also performed calculations of the carbanions formed at the α- and α′-position and found that carbanion **69** had lower energy minimum of at least 7.9 kJmol^{-1} compared to the α′-isomer.



Scheme 20: [2,3]-Rearrangements of furans **68** to give products **70**.

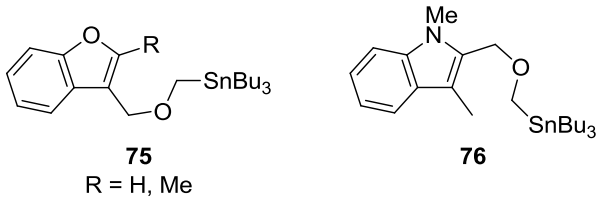
The permanent destruction of an aromatic system is more elusive, but Frontier managed to report the first examples of de-aromatised heterocycles isolated from [2,3]-Wittig rearrangements.[26] For example, 2-substituted furans **71** were deprotonated with *n*BuLi to form carbanions adjacent to the stannyl group, and rearrangements gave the de-aromatised products **72** as a single geometric isomer (geometry not elucidated) (Scheme 21). These products were expected to isomerise but they were surprisingly robust and survived silica gel chromatography conditions. It was found that increased substitution at the homo-furanylic position of the system retarded rearrangement. Substrate **71**-a (R = Me) rearranged at −78 °C but **71**-b (R = Cy) required warming up to −50 °C. When R = *t*Bu, no rearrangement occurred at all and this might have been prevented by the increased steric repulsion of the product after rearrangement.



Scheme 21: [2,3]-Rearrangements of heterocycles **71** and **73** to give de-aromatised products **72** and **74**.

In addition, the ylide of benzofuran stannane **73** also underwent rearrangement to give enol ether **74** in 80% yield on a 7 mmol scale. This rearrangement proceeded with efficient formation of a new quaternary centre which prevented

re-aromatisation of the heterocycle. On the other hand, it was also reported that 3-substituted benzofuryl methyl ethers **75** and 2-substituted indole **76** did not rearrange (Fig. 2).



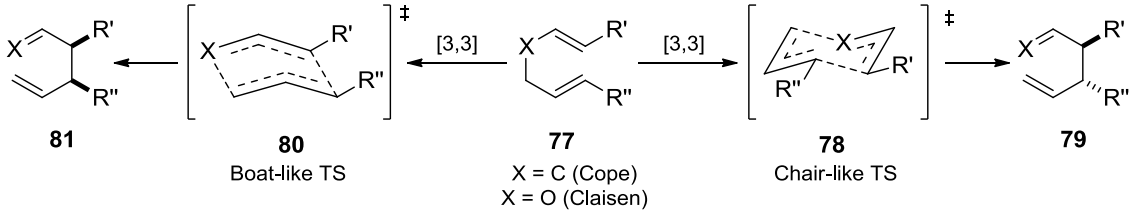
75
R = H, Me

76

Fig. 2: Substrates **75** and **76** which did not undergo [2,3]-rearrangements.

1.2. [3,3]-Sigmatropic rearrangements

The first observation of a thermally-induced rearrangement of vinyl allyl ether **77** (X = O) to the corresponding homoallylic carbonyl compound was reported by Claisen in 1912.[27] The corresponding rearrangement of 1,5-hexadienes **77** (X = C) was first discovered by Cope in 1940 as the carbon analogue of the Claisen rearrangement.[28] Today, it is recognised that such transformations fall within the general category of [3,3]-sigmatropic rearrangements [29] and that considerable variation may be accommodated in the basic requirement of a system of six atoms with terminal unsaturated linkages. Under normal circumstances, the rearrangement of **77** proceeds *via* a chair-like transition state **78** to give **79** with R′ and R″ in an *anti* relationship (Scheme 22). However for some cyclic or sterically-demanding substrates, the reaction is forced to proceed *via* a boat-like transition state **80** to give product **81** in the opposite configuration.



Scheme 22: [3,3]-Rearrangements and their transition states **78** and **80**.

In order for six electron pericyclic reactions to be thermally-allowed by the Woodward–Hoffmann rules, the total number of $[(4q+2)_s + (4r)_a]$ components should be odd.[5] This could be illustrated as a $[\sigma^2s + \pi^2s + \pi^2s]$ or $[\sigma^2s + \pi^2a + \pi^2a]$ reaction with an overall suprafacial component (e.g. no inversion of centre). The former is depicted in Fig. 3 (left) as a chair-like or boat-like transition state, which confirms that both transition states are symmetry-allowed. Alternatively, this could be explained by frontier molecular orbital theory (Fig. 3, right), where the new bond is formed by bonding interactions of the

HOMO of the four-electron component (made up by combination of one σ and one π bond) with the LUMO of the π bond.[6] With either model, both the chair and boat-like transition states can be rationalised by their orbital descriptions. The boat-like transition state is disfavoured because it is destabilised by the non-bonding secondary orbital interactions between C-2 and C-5.

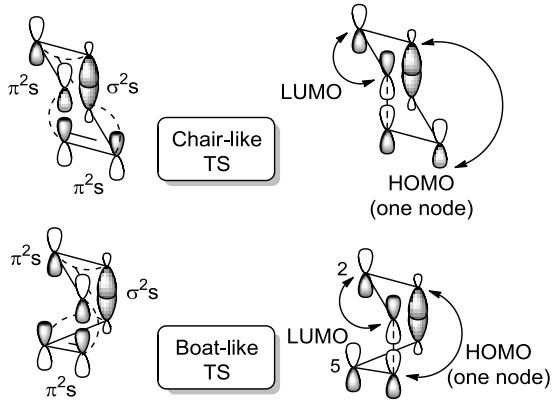
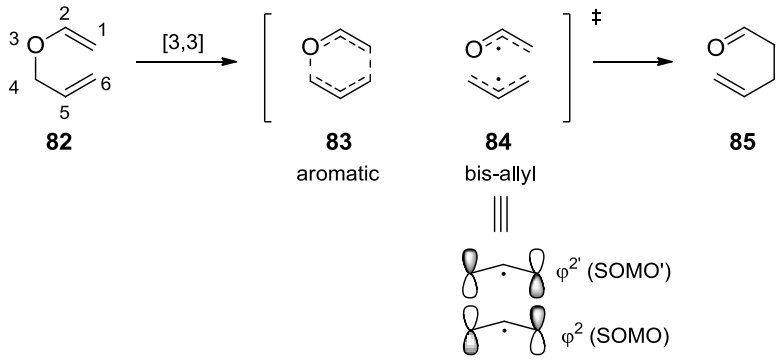


Fig. 3: Orbital description of TS: Woodward–Hoffman rules (left) or Fukui's frontier orbital theory (right).

It is generally accepted that the transition state of ether **82** has cyclic aromatic character (**83**) (Scheme 23), however it was sometimes found that this transition state alone could not account for all of the observations, so it was reasoned that the transition state could adopt a bis-allyl configuration (**84**).[30] This transition state is also symmetry-allowed by the Woodward–Hoffman rules where the SOMOs of the bis-allyl groups have bonding interactions with each other.



Scheme 23: Claisen rearrangement of **82** and possible transition states **83** and **84** in the formation of aldehyde **85**.

This section will focus on some Claisen rearrangements involving de-aromatisation of an aromatic nucleus. However, due to the vast accumulation of such rearrangements reported since 1912, only recent examples of heteroaromatics will be discussed (limited to recent decades). We would like to present this review in two sections – one in which the vinyl bond is part of a heteroaromatic ring (**A**), and the other in which the allyl bond is part of a heteroaromatic ring (**B**) (Fig. 4).

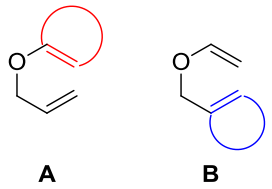
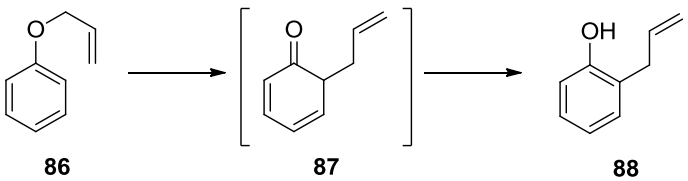


Fig. 4: Allyl vinyl ethers of heteroaromatics where the vinyl bond is part of the heteroaromatics ring (**A**) or where the allyl bond is part of the heteroaromatics ring (**B**).

1.2.1. Ethers where the vinyl bond is part of a heteroaromatic ring

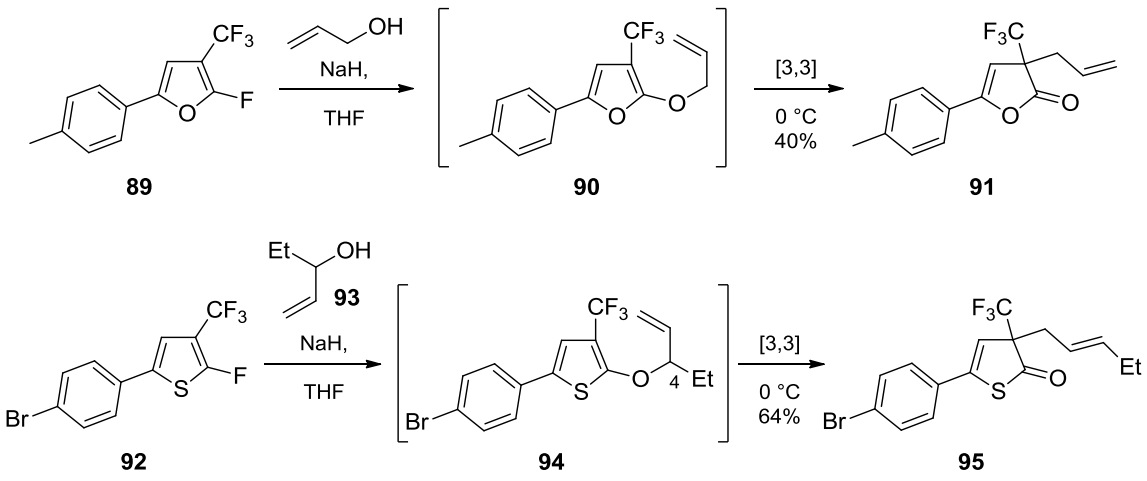
The thermal [3,3]-rearrangement discovered by Claisen included the rearrangement of allyl aryl ethers **86** to give *o*-allyl phenol **88** (Scheme 24).[27(a), 31] [3,3]-Rearrangement of ether **86** proceeded *via* de-aromatised *ortho*-dienone intermediate **87**, followed by facile re-aromatisation of the intermediate due to a rapid enolisation process. This is called the aromatic Claisen rearrangement. The aromatic Claisen rearrangement is a well-known process in the syntheses of substituted aromatics and has recently been extensively reviewed.[27(b), 32] Hence, this section will not include these common aromatic Claisen rearrangement reactions.



Scheme 24: Aromatic Claisen rearrangement of ether **86**.

1.2.1.1. Furan and thiophene

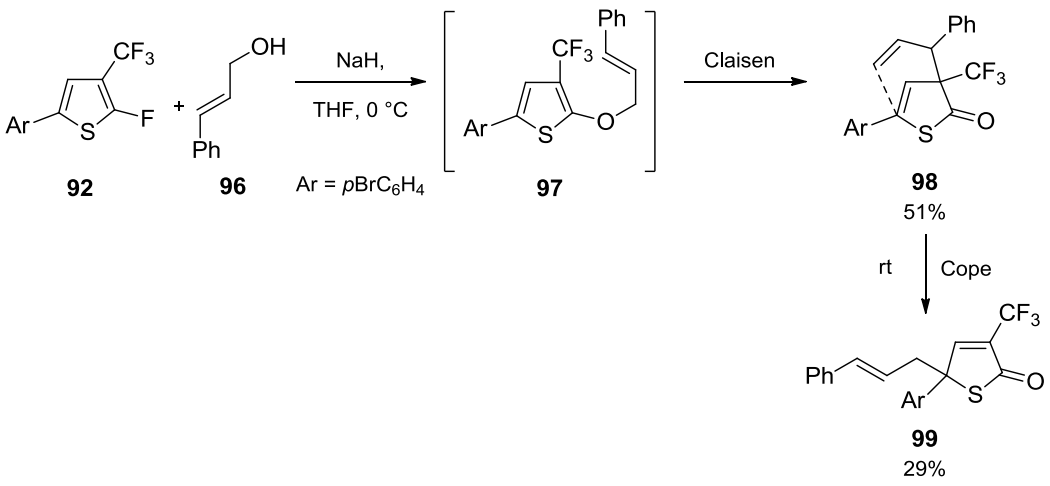
Examples of Claisen rearrangement where the ether vinyl bond is part of a five-membered heteroaromatic ring are scarce. In 2005, Burger reported a novel approach in the formation of substituted butenolides and their thio-analogues utilising [3,3]-rearrangement.[33] Displacement of the 2-fluoride of furan **89** with allyl alcohol was facile under mild conditions to afford intermediate allyl ether **90**. This readily rearranged at 0 °C to give butenolide **91** in 40% yield, which was stable at room temperature (Scheme 25). The formation of a new quaternary centre prevented re-aromatisation and the product was stabilised by the formation of a new C=O bond. Similarly, the thiophene analogue **92** reacted with 2-substituted allyl alcohol **93** to give ether **94**, which rearranged to give product **95** in an improved yield of 64%. Despite the lower reactivity of thiophene compared to furan, electron-donating substitution at the C-4 position of the Claisen framework possibly accelerated the rearrangement.



Scheme 25: Claisen rearrangement of intermediate ethers **90** and **94**.

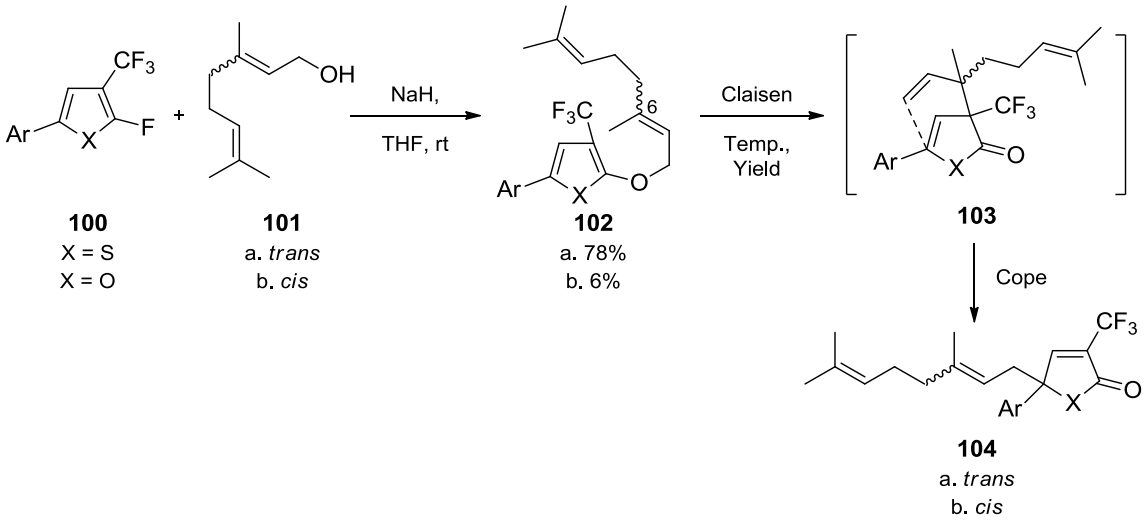
A novel domino Claisen–Cope rearrangement was also reported by Burger in the same paper. Displacement of thiophene **92** with alcohol **96** gave ether **97**, which readily

rearranged at low temperature to give Claisen product **98** (Scheme 26). Prolonged standing of this product at room temperature subsequently gave the Cope product **99**.



Scheme 26: Claisen–Cope rearrangement of ether intermediate **97** to give **99**.

This methodology was further utilised by Burger in the incorporation of lipidic anchors into biologically relevant compounds by displacement of the fluorides of **100** with terpenes such as geraniol or nerol **101**, to form ethers **102** with long aliphatic side chains (Scheme 27).[33] [3,3]-Claisen rearrangement of **102** followed by Cope rearrangement of **103**, gave products **104** in good yields with thiophene substrates (Table 2, Entries 1 and 2) and in poorer yields with furan substrates (Table 2, Entries 3 and 4). In comparison with ether **97**, it was observed that increased substitution at the C-6 position of the Claisen framework and the presence of electron-donating substituents (alkyl groups) as opposed to electron-withdrawing substituents (Ph), led to increased yields. Bond-formation was accelerated by the donation of electron-density from the alkyl substituents at the C-6 allyl terminal to the inductively electron-poor 3-heteroaromatic position.



100
X = S
X = O

101
a. *trans*
b. *cis*

102
a. 78%
b. 6%

103

104
a. *trans*
b. *cis*

Scheme 27: Claisen–Cope rearrangement of intermediate ethers **102** to give **104**.

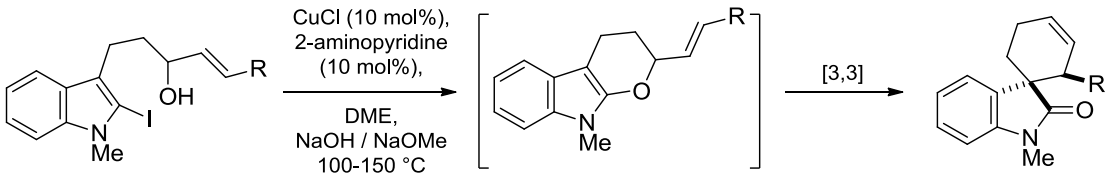
Entry	100	101	Ar	Temp.	104	Yield
1	X = S	a	Ph	65 °C	a	79%
2	X = S	b	Ph	65 °C	b	61%
3	X = O	a	*p*BrC$_6$H$_4$	0 °C	a	33%
4	X = O	b	*p*BrC$_6$H$_4$	0 °C	b	53%

Table 2: Conditions for Claisen–Cope rearrangement of intermediate ethers **102** to give **104**.

1.2.1.2. Indole

The Claisen rearrangement is also a well-established method for the installation of new stereocentres due to its highly stereoselective nature. Oxindoles possessing a quaternary stereogenic centre at C-3 are attractive targets as they often have interesting biological activities, or are synthetic intermediates of complex indole alkaloids.[34] It is possible to achieve stereoselective formation of such oxindoles from Claisen rearrangements of carefully-designed indoles. In 2006, Kobayashi reported a highly diastereoselective one-pot synthesis of spirocyclic oxindoles through an intramolecular Ullmann coupling–Claisen rearrangement reaction.[35] C–O Bond formation was achieved from 2-iodoindoles **105** with Cu(I) as the Ullmann coupling catalyst to give pyranoindoles **106** (Scheme 28).

These intermediates were unstable and rearrangement proceeded cleanly to give oxindoles **107** in excellent yields and diastereoselectivities.



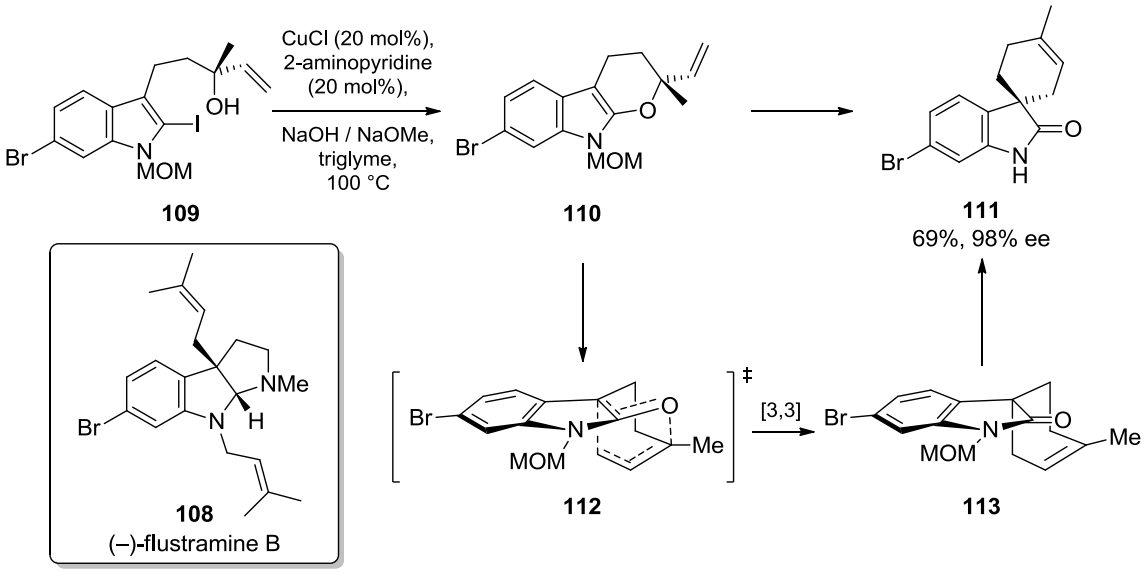
105
a: R = H
b: R = Me
c. R = *n*Bu
d. R = Ph
e. R = CH_2CH_2OH

106

107
a: 84% (> 95% de)
b: 89% (> 95% de)
c. 92% (> 95% de)
d. 84% (> 95% de)
e. 93% (> 95% de)

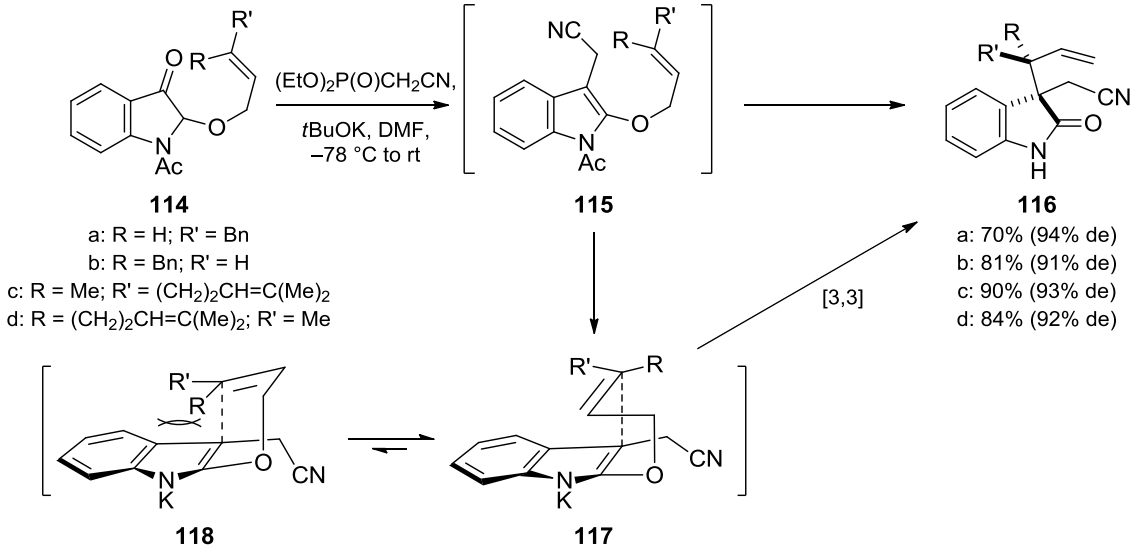
Scheme 28: A one-pot Ullmann coupling–Claisen rearrangement of indole **105**.

This methodology was applied by Kobayashi in the syntheses of some indoline alkaloids.[36] An enantioenriched Claisen rearrangement step was utilised in the total synthesis of (−)-flustramine B **108** (Scheme 29).[36(b)] Indole **109** was derived from (−)-linalool and *o*-iodoaniline, and subjected to previously developed Ullmann–Claisen conditions to give pyranoindole **110**, which rearranged to give deprotected spirocyclic oxindole **111** with 98% ee. The high ee suggested that the reaction was stereospecific and that rearrangement had proceeded *via* a boat-like transition state **112** due to cyclic constraints, to give intermediate **113**.



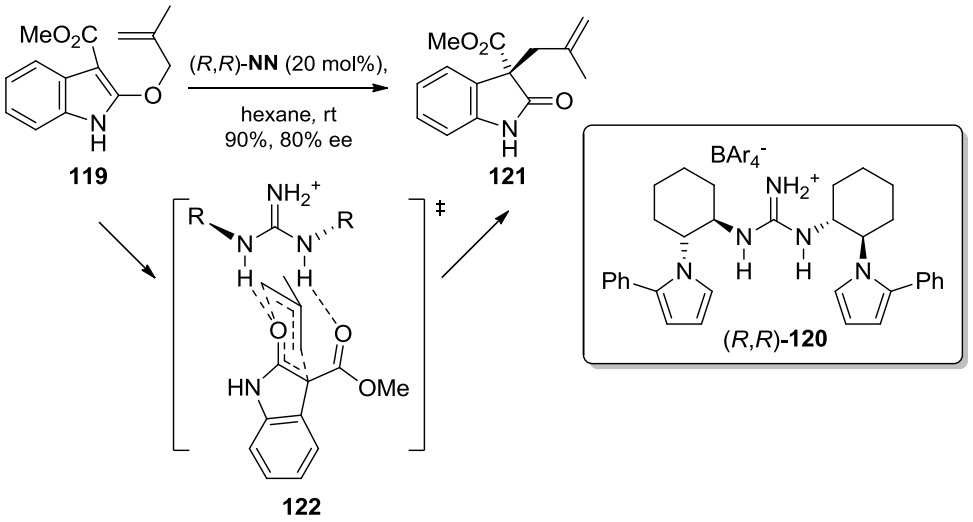
Scheme 29: Key step involving Ullmann coupling–Claisen rearrangement of indole **109**.

Another highly diastereoselective Claisen rearrangement of indoles was reported by Kawasaki in the synthesis of oxindoles with two adjacent quaternary centres.[37] This cascade reaction first proceeded with olefination–isomerisation of indolinones **114** to give indoles **115** (Scheme 30). The acetyl protecting group was next removed under basic conditions and Claisen rearrangement gave lactone–spirooxindoles **116** in good yields and high diastereoselectivity. The diastereomeric excesses were indicative that the reaction favoured the boat-like intermediate **117** over chair-like intermediate **118** even though it was not bound by cyclic constraints. The chair-like intermediate was rendered more unstable by the steric repulsion of the R and R′ substituents with the indole ring. Notably, the Claisen rearrangement proceeded smoothly at lower temperatures without the need for heating as the reactions may have been accelerated by the nitrogen anion formed from de-acetylation.[38]



Scheme 30: Domino reaction of indolinones **114** to give oxindoles **116**.

Some diastereoselective rearrangement reactions of 2-substituted-3-carboxylic esters of indole were screened by Booker-Milburn,[39] but a novel catalytic enantioselective rearrangement of one such ester was reported by Jacobsen in 2010.[40] Rearrangement of indole **119** with 20 mol% (*R*,*R*)-**120** at room temperature gave oxindole **121** in 90% yield and 80% ee at the C-3 stereocentre (Scheme 31). The rearrangement proceeded through a highly dipolar transition state **122**, which was amenable to rate acceleration by hydrogen bond donations. Computational studies were conducted for a simple cyclic *O*-allyl β-ketoester substrate and it was observed that binding of substrate with the catalyst effectively lowered the energy of the catalyst-bound substrate as well as lowered the activation barrier for rearrangement by 5.3 kcalmol^{-1}. It is likely that hydrogen bonding alleviates the developing negative charge on the ether oxygen and accelerates C–O bond breaking. Similarly, rate acceleration and improved yields were also observed in some Au(I)-catalysed de-aromatising Claisen rearrangement of indoles.[41]

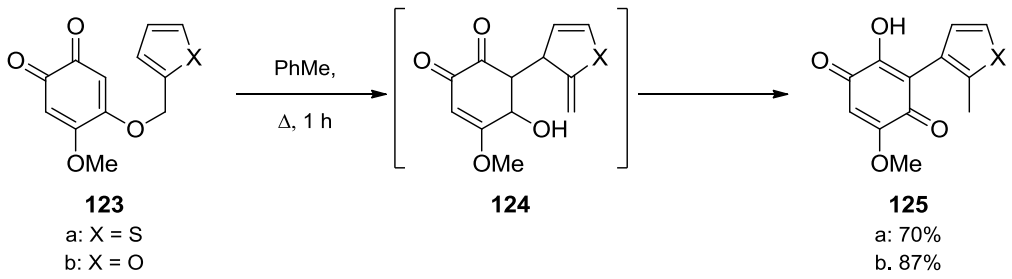


Scheme 31: Organocatalytic enantioselective rearrangement of indole **119** to give oxindoles **121**.

1.2.2. Ethers where the allyl bond is part of a heteroaromatic ring

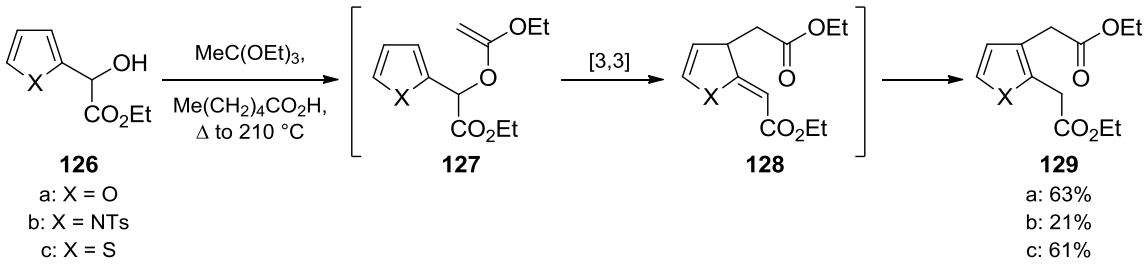
1.2.2.1. Furan and thiophene

Rearrangements of substituted vinyl benzyl ethers are generally difficult to achieve[42] due to the higher aromatic stabilisation of the benzene nuclei. However, electron-rich heterocycles such as furan and thiophene have been observed to undergo rearrangements because of the stability of the reaction intermediates. [43] Maumy reported the rearrangements of furfuryloxy- and (2-thienyl)methylbenzoquinone **123** to give substituted benzoquinones **125** in good yields *via* de-aromatised intermediates **124** (Scheme 32).[44] This strategy has been shown to be useful in the formation of a new C–C bond between two heterocycles.[45]



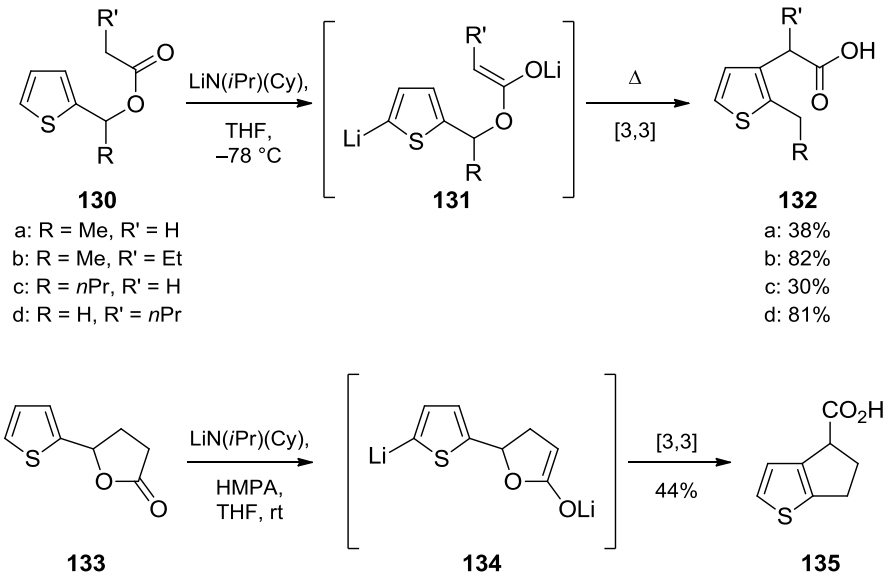
Scheme 32: [3,3]-Rearrangement of heteroaromatics **123** to give products **125**.

The Johnson–Claisen rearrangement of heteroaromatics such as furan, *N*-tosylpyrrole and thiophene were performed by Raucher.[46] Reaction of heteroaromatics **126** with triethyl orthoester and hexanoic acid gave ketene acetals **127** (Scheme 33). Rearrangement under thermal conditions gave de-aromatised intermediates **128** which concomitantly re-aromatised to give 2,3-disubstituted heteroaromatics **129**. The presence of the ethyl ester adjacent to the exocyclic double bond contributed to increased stabilisation of de-aromatised intermediates **128**.[42(a)] It was also observed that the pyrrole substrate was less reactive than its furan and thiophene analogues.



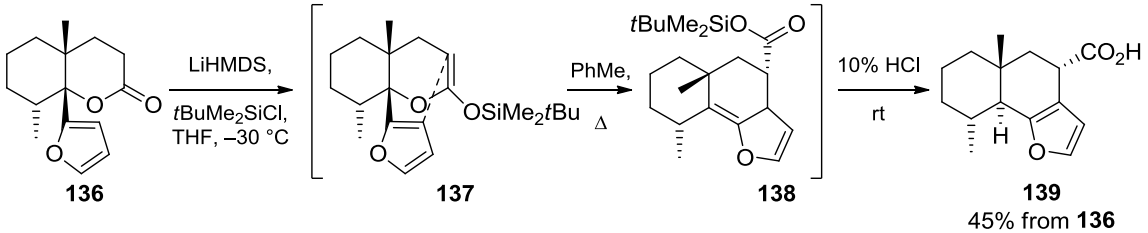
Scheme 33: Johnson–Claisen rearrangement of heteroaromatics **126** to give products **129**.

The enolate Claisen rearrangement is another variant of the Claisen reaction, which is widely employed due to the simplicity of its reaction conditions. An example of an enolate Claisen rearrangement was reported by Kumamoto where lithium enolates **131** of homo-substituted esters **130** were formed using lithium *N*-isopropylcyclohexylamide as base (Scheme 34).[47] Rearrangements of the enolates gave acids **132**. Substitution at the R′-position resulted in better yields whereas substitution at the R-position did not matter. The rearrangements could have been accelerated by positive interactions between the electron-rich substituted terminal vinyl end and the electron-poor C-3 position of the thiophene. Similarly, rearrangement of 4-(2-thienyl)-4-butanolide **133** at room temperature gave bicyclic compound **135** in 44% from enolate **134**.



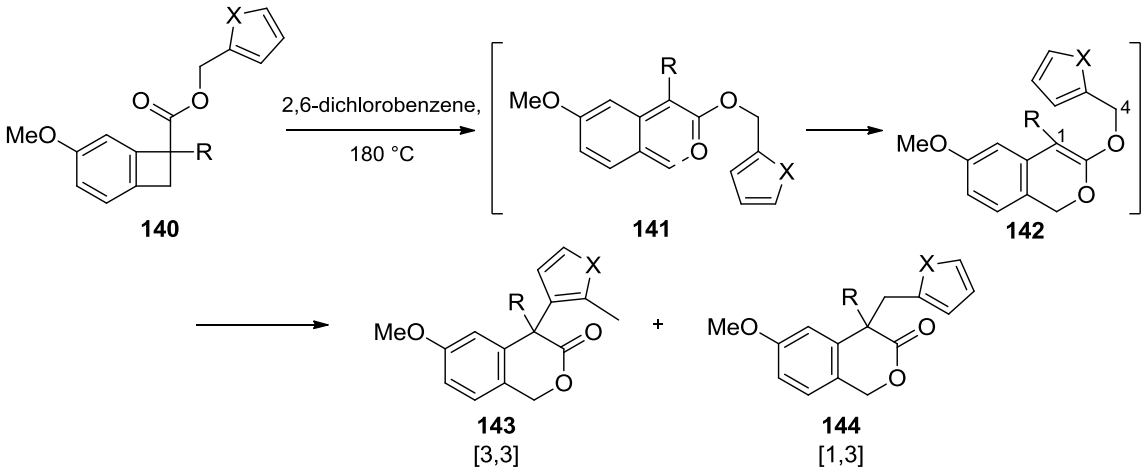
Scheme 34: Enolate Claisen rearrangement of thiophenes **130** and **133**.

Rearrangement of systems where the allylic double bond is incorportated in a furan ring was investigated under mild Ireland–Claisen conditions by Fukumoto.[48] In particular, a novel stereospecific synthesis of a potential intermediate of eudesmane type sesquiterpenes was synthesised from lactone **136** (Scheme 35).[49] Silyl ketene acetal **137** was formed by reacting **136** with LiHMDS and *t*BuMe$_2$SiCl at −30 °C, and thermal heating gave rearranged product **138**. Acid hydrolysis of the silyl ester finally gave substituted furanodecalin **139** in 45% yield from **136**. This rearrangement was stereospecific and proceeded *via* a boat-like transition state due to the cyclic nature of the silyl ketene acetal.



Scheme 35: Ireland–Claisen rearrangement of lactone **136** to give product **139**.

A tandem electrocyclic–sigmatropic reaction of benzocyclobutenes was also reported by Fukumoto in the construction of 4,4-disubstituted isochromanones.[50] Thermolysis of benzocyclobutene **140** gave de-aromatised electrocyclic intermediate **141** which underwent a second electrocyclic reaction to give acetal **142**, which is the rearrangement substrate (Scheme 36). Sigmatropic rearrangement proceeded concomitantly and gave a mixture of [3,3]-product **143** and [1,3]-product[51] **144**.



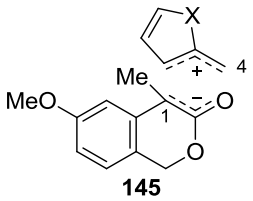
Scheme 36: Tandem electrocyclic–sigmatropic reaction of benzocyclobutene **140** to give products **143** and **144**.

Entry	X	R	Ratio of 143:144	Combined Yield
1	O	Me	1:2	73%
2	S	Me	1:5	49%
3	O	-CH_2OMe	3.7:1	62%

Table 3: Reaction conditions for tandem electrocyclic–sigmatropic reaction of benzocyclobutene **140**.

Some observations may be made from the results summarised in Table 3. When R = Me, [1,3]-rearrangement predominates over [3,3]-rearrangement possibly due to the presence of dipolar transition state **145** (formed from an early bond-breaking pathway), which is stabilised by the methyl substituent (Fig. 5). Bond formation occurs between C-1 and C-4 so as not to disrupt the aromatic nucleus. Next, the ratio of product **144** was

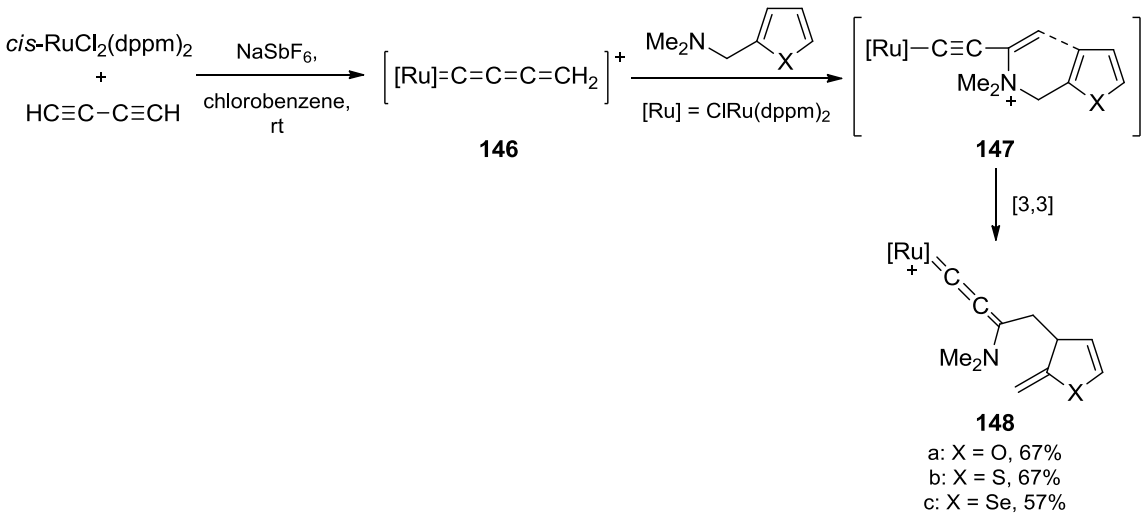
higher for the thiophene than the furan analogue. Furan is intrinsically more reactive than thiophene and is more susceptible to de-aromatisation *via* [3,3]-rearrangement compared to its thiophene counterpart, which might also account for the higher yields obtained with furans. However, when R = CH_2OMe (Entry 3), [3,3]-rearrangement was favoured over [1,3]-rearrangement giving **143** as the major product. It is unclear why product selectivity was reversed in this case.



145

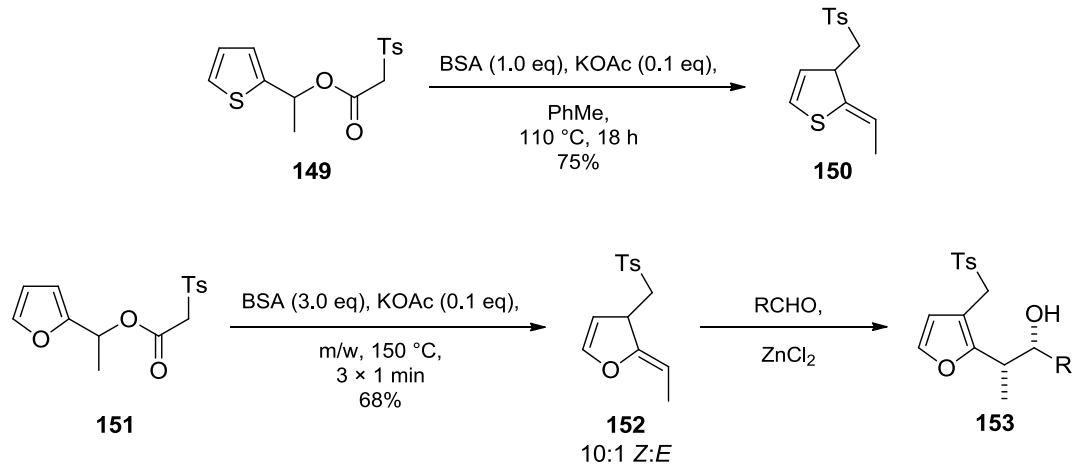
Fig. 5: Possible transition state of **142** when R = Me.

All of the examples discussed up to now involved transiently de-aromatised intermediates from [3,3]-rearrangement, which re-aromatised again to give their products. However, there are some instances where non-aromatic products could be isolated. Trapping of primary butatrienylidene ruthenium intermediate **146**, formed from *cis*-$RuCl_2(dppm)_2$ and an excess of butadiyne, with five-membered 2-(dimethylamino)methyl-substituted heteroaromatics (furan, thiophene and selenophene) gave intermediates **147** (Scheme 37).[52] Prolonged stirring of the intermediates at room temperature for 2-3 days subsequently gave aza-Claisen rearrangement products **148** in moderate yields. The de-aromatised 2-methylene-2,3-dihydro heterocycles **148** attached to an aminoallenylidene ligand are stable in solid state and are re-aromatised only when in solution or when heated.



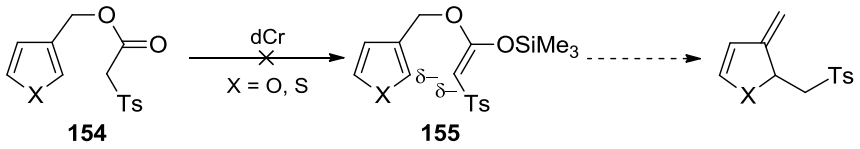
Scheme 37: Aza-Claisen type rearrangement involving Ru-complexes **147** to give products **148**.

The de-aromatising decarboxylative Claisen rearrangement (dCr) reaction was developed by the Craig group and will be discussed again in Section 2.1.1. This methodology led to the isolation of some de-aromatised heterocyclic products.[53] For example, when thien-2-yl tosylacetate **149** was subjected to standard thermal dCr conditions with stoichiometric BSA, de-aromatised heterocycle **150** was obtained in 75% yield as a single geometric isomer (Scheme 38). Similarly, furan-2-yl tosylacetate **151** gave de-aromatised product **152** in a 10:1 *Z*:*E* ratio.[53(b)] The geometric configuration of these exocyclic olefins were determined by NOESY[54] and the *cis*-configuration is thought to minimise allylic 1,3-strain. Isolation of the de-aromatised products was made possible due to the enhanced stabilisation afforded by substitution on the exocyclic olefin. In addition, re-aromatisation of the heterocycle is disfavoured since it would lead to an increase in the steric buttressing between the 2-substituent and the 3-methyltosyl group. Furthermore, the nucleophilicity of the exocyclic double bond promoted further reactions of dihydrofuran **152** with some aldehydes in the presence of zinc(II) chloride to give chelation-controlled *syn* alcohols **153** as the major products.



Scheme 38: De-aromatising dCr reactions of thiophene **149** and furan **151**.

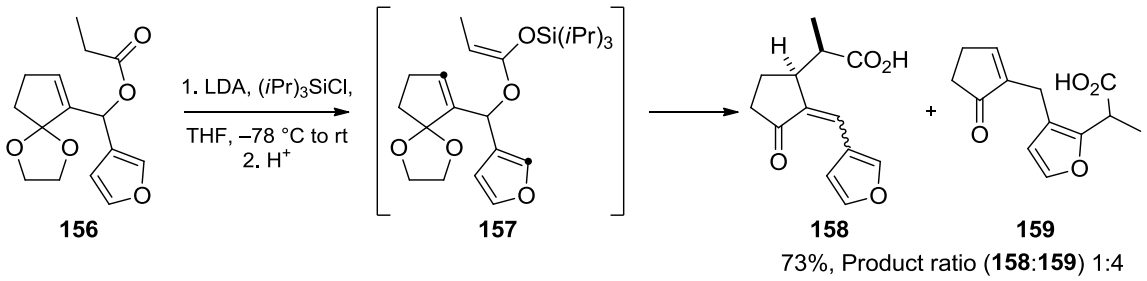
Conversely, no dCr reaction was observed with 3-tosylacetates of furan and thiophene **154** (Scheme 39). It is predicted that the greater electron density at the 2-position of furans and thiophenes relative to the 3-position disfavours [3,3]-rearrangement due to a mismatch in partial charges between the 2-position and the electron-rich terminal carbon of silyl ketene acetal **155**.[53(a)]



Scheme 39: Disfavoured de-aromatising dCr reactions of 3-substituted heteroaromatics **154**.

All of the examples discussed up to this point involved 2-methyloxysubstituted heteroaromatics (e.g. C-3 carbon of five-membered heteroaromatics as the terminal allyl end). Rearrangement involving 3-methyloxysubstituted heteroaromatics are rare, although homolytic cleavage of the C–O ether bond could occur at a high temperature (350 °C).[43(d)] However, an example of a [3,3]-rearrangement of 3-methyloxysubstituted furan has been reported.[55] Treatment of ester **156** with chlorosilane and LDA formed silyl ketene acetal **157**[56] (Scheme 40). [3,3]-Rearrangement was regioselective for the

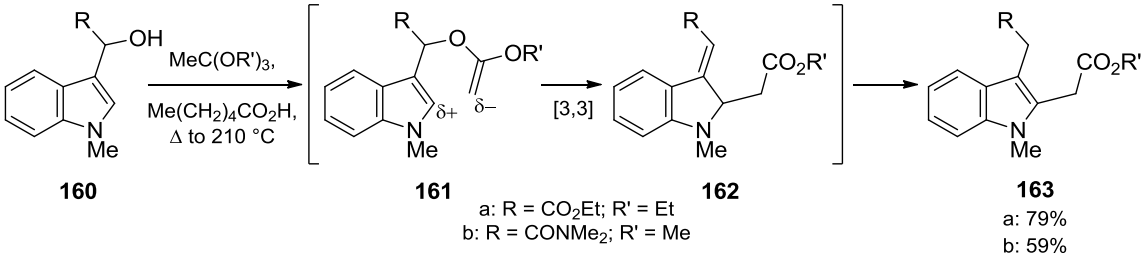
2-position of the furanyl ring over the cyclopentene alkenyl end, to give products **158** and **159** in a ratio of 1:4.



Scheme 40: A rare example of [3,3]-rearrangement of 3-substituted furan **156**.

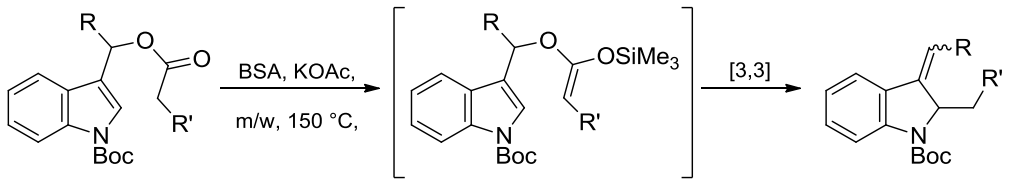
1.2.2.2. Indole and pyridine

Aside from five-membered heteroaromatics, Claisen rearrangements have been reported for substituted indoles, where the allyl ether fragment is part of the indole ring. 3-Substituted indoles **160** were reacted with trimethyl or triethyl orthoesters to give acetals **161**, which rearranged to give de-aromatised indolines **162** (Scheme 41).[42(a)] This new C–C bond was formed between the electron-rich vinylic end and the electron-poor C-2-position of the indole. Concomitant re-aromatisation gave indoles **163**. Once again, it was demonstrated that the presence of electron-withdrawing groups such as an ester or amide adjacent to the exocyclic double bond could stabilise de-aromatised intermediates such as **162** by resonance.



Scheme 41: Johnson–Claisen rearrangement of indole **161** to give product **163**.

Another example of a rearrangement of C-3-substituted indoles was recently reported by Craig.[53(c)] The dCr reaction of *N*-Boc indoles **164** under microwave conditions gave silyl ketene acetals **165**, which rearranged to give isolated de-aromatised indolines **166** in good yields (Scheme 42). When R = Me, an increase in yield was observed compared to the less-substituted analogues, which was in agreement with the hypothesis that substitution on the exocyclic double bond of **166** led to increased stabilisation of the de-aromatised indolines.



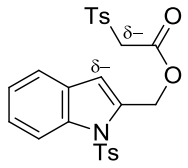
164
a: R = H; R' = Ts
b: R = H; R' = CN
c: R = Me; R' = Ts
d: R = Me; R' = CN

165

166
a: 68%
b: 70%
c: 87% (*E*/*Z*-mixture)
d: 82% (*E*/*Z*-mixture)

Scheme 42: De-aromatising dCr reactions of indoles **164** to give indolines **166**.

In contrast, 2-substituted tosylacetate **167** was inert to dCr reaction (Fig. 6).[53(a)] This can be explained as a mismatch of orbital interactions between the greater electron densities at the 3-indole position and at the α-position of the carbonyl of the silyl ketene acetal.

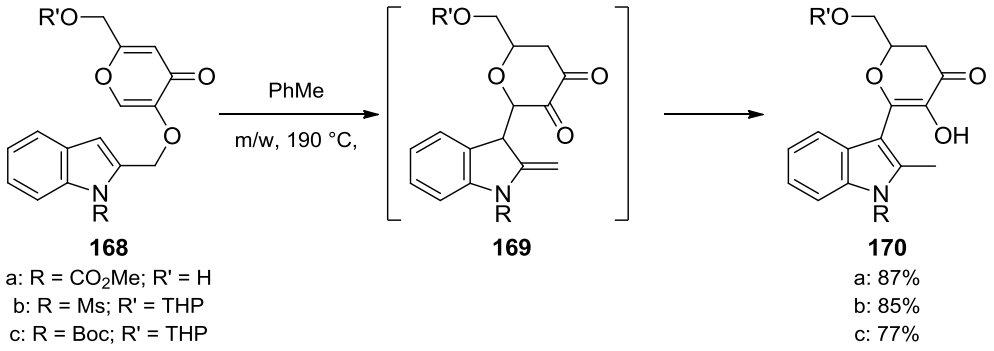


167

Fig. 6: 3-Substituted indole **167** inert to dCr reaction.

On the other hand, unusual examples of rearrangement of C-2-substituted indoles have been reported by Pirrung in the formation of (indolyl)kojic acids as anti-diabetic agents. [57] *N*-Protected (indole)methyl kojates **168** when subjected to microwave

irradiation gave transiently de-aromatised indolines **169** (Scheme 43). Tautomerisation and re-aromatisation brought the molecule back into conjugation to give (indolyl)kojic acids **170** in good yields.



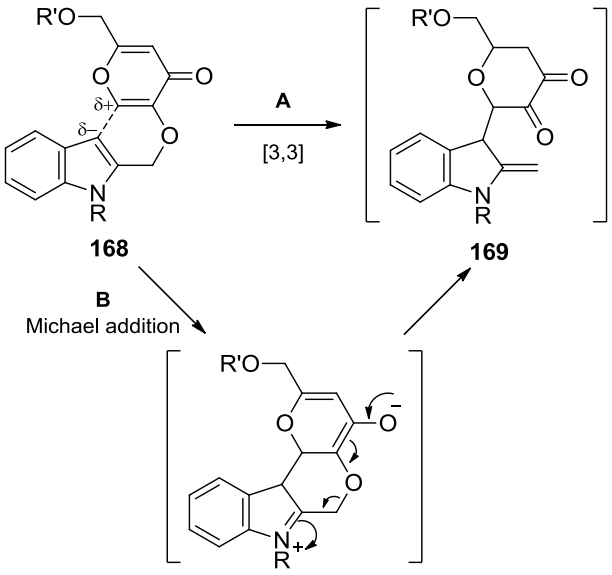
168
a: R = CO_2Me; R' = H
b: R = Ms; R' = THP
c: R = Boc; R' = THP

169

170
a: 87%
b: 85%
c: 77%

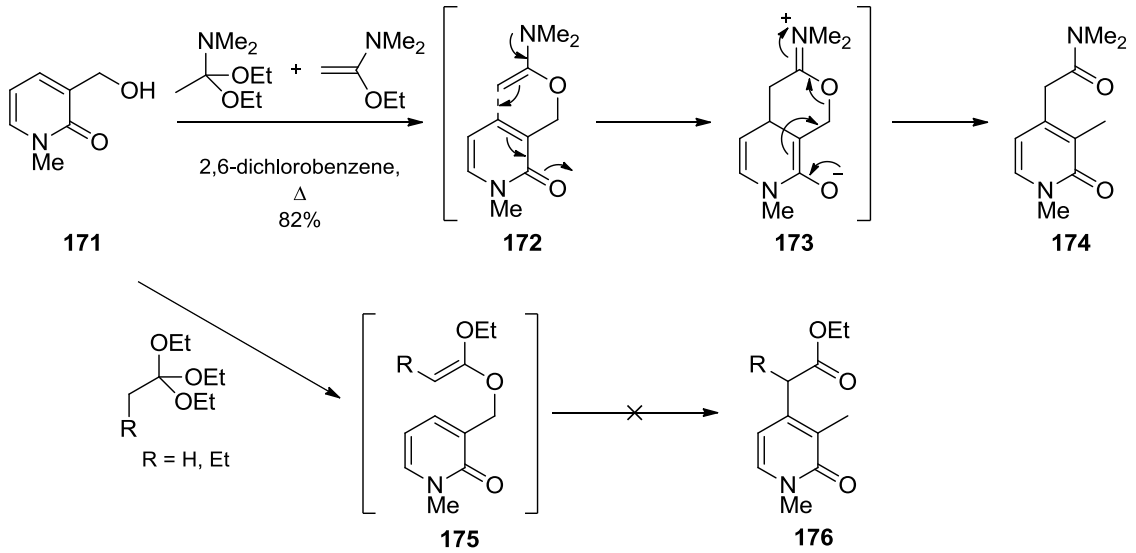
Scheme 43: Rearrangements of (indole)methyl kojates **168** to give (indolyl)kojic acids **170**.

Therefore, [3,3]-rearrangements of C-2-substituted indoles can be made possible by carefully placed substitutents. In this case, it was hypothesised that bond formation was encouraged by positive interactions between the greater electron densities of the C-3 position of indole **168** and the electrophilic vinylic terminal carbon (Scheme 44). On careful inspection, the reaction could proceed in a concerted [3,3]-sigmatropic rearrangement where bond-formation is predominant over bond-breaking (**A**). However, the electrophilic end could also act as a good Michael acceptor and bond formation could be described as a Michael addition of an enamine to an α,β-unsaturated carbonyl group, followed by cleavage of the ether bond to give **169** in a second step (**B**).



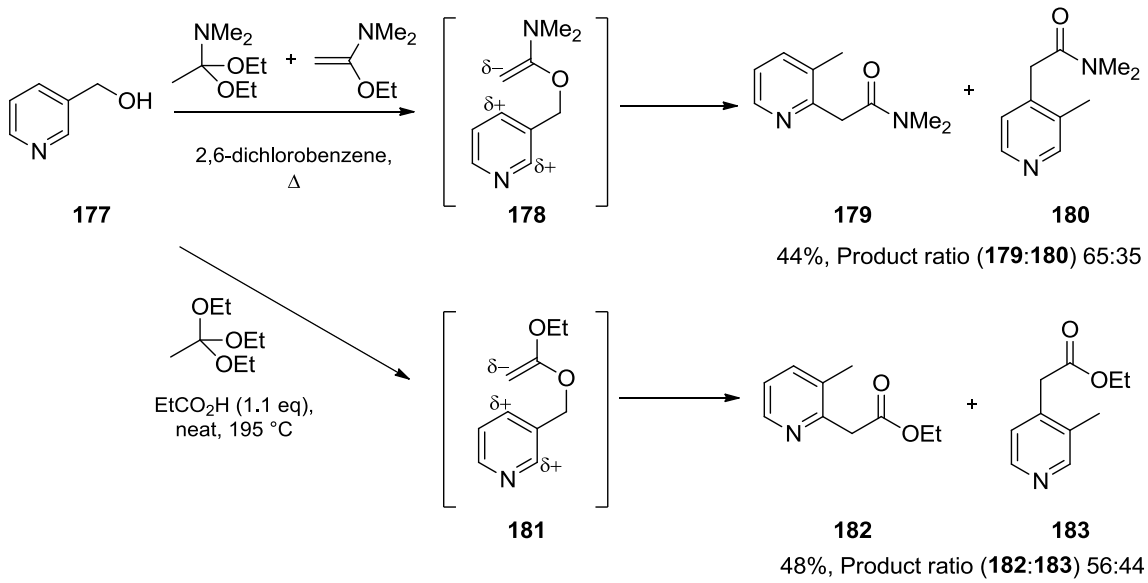
Scheme 44: Plausible mechanisms (**A** or **B**) for the formation of indoline intermediate **169**.

Apparent [3,3]-rearrangement product formation was observed by Rapoport whereby pyridone **171** gave product **174** in 82% yield when treated with a mixture of *N*,*N*-dimethylacetamide diethyl acetal and 1-ethoxy-1-dimethylaminoethylene (Scheme 45).[58] However, it was postulated that the reaction had proceeded by a stepwise Michael addition mechanism whereby the enamine of **172** adds to the α,β-unsaturated amide intramolecularly followed by cleavage of the weakened C–O bond of **173**. On the other hand, formation of ketene acetal **175** from triethyl orthoester did not give [3,3]-rearrangement product **176**. The inability of **175** to undergo Michael addition hence supports the possibility of a step-wise Michael addition–elimination mechanism.



Scheme 45: Reaction of pyridone **171** to give product **170** *via* stepwise Michael addition.

Not surprisingly, the reactivity of pyridine analogue **177** differed from pyridone **171**. Formation of amide acetal **178** using the same procedure gave a mixture of 2,3- and 3,4-disubstituted pyridines **179** and **180** (Scheme 46). Similarly, rearrangement of ketene acetal **181** gave an almost equivalent amount of disubstituted pyridines **182** and **183**. Bond-formation took place between the electron-rich vinylic end and the electron-deficient C-2- or C-4-positions of pyridine. Since product formation was obtained with both amide and ketene acetals, this suggested that the reactions underwent concerted [3,3]-sigmatropic rearrangement instead of a stepwise Michael addition mechanism.



Scheme 46: [3,3]-Rearrangements of amide acetal **178** or ketene acetal **181** to give products **179**, **180**, **182** and **183**.

1.3. Conclusion

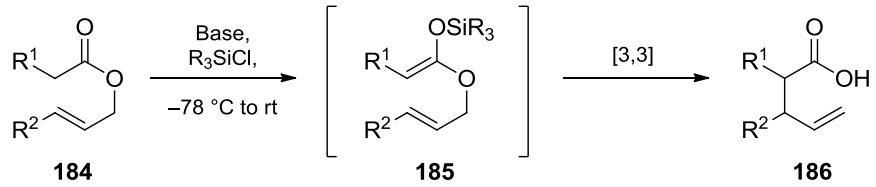
[2,3]-Sigmatropic rearrangements with mechanisms involving the de-aromatisation of a range of substituted carboaromatics and heteroaromatics have been described. [1,2]-Rearrangement is often a competitive process adjacent to [2,3]-rearrangement, however, this can be controlled by altering reaction conditions. In most cases, the de-aromatised intermediates concomitantly re-aromatised into their products but in some rare cases, they can be isolated as stable products or trapped with electrophiles intramolecularly (e.g. **54** to **55**). In addition, there is no clear regioselectivity explanation as 3-substituted furans or thiophenes are as likely to undergo rearrangement as 2-substituted furans or thiophenes.

[3,3]-Sigmatropic rearrangements of heteroaromatics were classified into two sections – where the ether vinyl bond is part of the ring or where the allyl ether bond is part of the ring. In the former, rearrangements involving de-aromatisation mechanisms are often utilised in the formation of desirable quaternary centres, which also prevented re-aromatisation of the heterocycles. In addition, the de-aromatised products (e.g. oxindoles, thiophenones, butenolides) are usually stable to re-aromatisation as the new C=O bond formed is adjacent to a heteroatom and is hence stabilised by resonance or simply by the energy gained from formation of a new C=O bond. In the latter case where the allyl ether bond is part of a ring, the ethers are almost always substituted at the C-2 position of furan or thiophene or at the C-3 position of indole in order to maximise interaction of partial charges across the site of bond-formation. In some cases, the de-aromatised heterocyclic products can be isolated as the exocyclic double bond is stabilised by substitution.

2. Rearrangements of dioxanones

2.1. Background

The Claisen rearrangement[27] is an important and powerful carbon–carbon bond-forming tool in organic synthesis since its discovery a century ago. Several variations on the original Claisen procedure have been developed since then. The Ireland−Claisen rearrangement[59] was reported by Ireland in 1972 and is one of the most well-used variants of the Claisen rearrangement. Reaction of an allyl ester **184** with a silylating reagent and a base forms a silyl ketene acetal intermediate **185** which undergoes a [3,3]-sigmatropic rearrangement to give a γ,δ-unsaturated carboxylic acid **186** on hydrolysis of the silyl ester. Such rearrangement reactions are very facile and typically take place at temperatures between –78 °C and room temperature (Scheme 47).



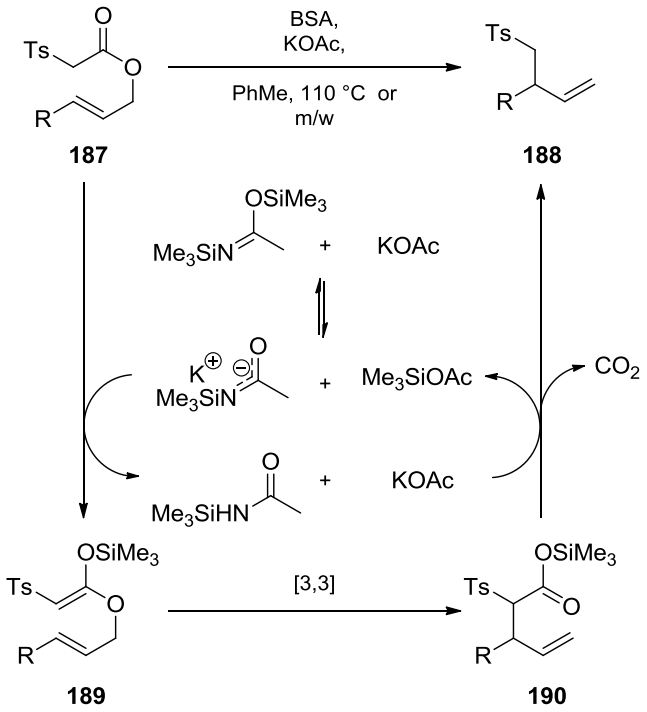
Scheme 47: The Ireland–Claisen rearrangement.

The widespread success of the Claisen rearrangement reaction lies in the ease of synthesis of the allyl ester substrates, the reliable stereoselectivities obtained based on well-established empirical trends and the mild reaction conditions to facilitate the rearrangement.

2.1.1 The decarboxylative Claisen rearrangement (dCr)

In 2005, Craig and co-workers reported the decarboxylative Claisen rearrangement (dCr) reaction, which is a novel variant of the Ireland–Claisen reaction. It involves the direct conversion of tosylacetic esters **187** of allylic alcohols into homoallylic sulfones **188**

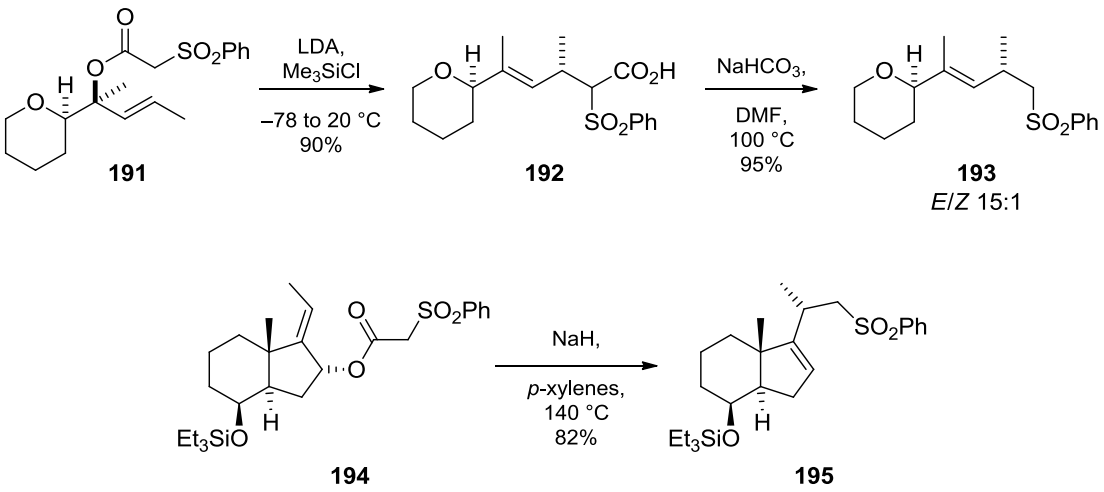
upon exposure to sub-stoichiometric amounts of bis(trimethylsilyl)acetamide (BSA) and potassium acetate under conventional thermal or microwave conditions (Scheme 48).[60]



Scheme 48: Proposed catalytic cycle of the dCr rearrangement.

The proposed mechanism involved the initial, reversible reaction of potassium acetate and BSA to generate the conjugate base of *N*-trimethylsilylacetamide and trimethylsilyl acetate. The former deprotonates ester **187**, the resultant enolate is silylated by the latter to give the silyl ketene acetal **189** and potassium acetate is regenerated. Following the [3,3]-sigmatropic rearrangement of silyl ketene acetal **189**, the γ,δ-unsaturated silyl ester **190** is desilylated with potassium acetate. The carboxylate species spontaneously fragments to release carbon dioxide, trimethylsilyl acetate and the strongly basic conjugate base of **188**. Protonation of the anion to give the homoallylic product **188** can occur from either from proton abstraction of the *N*-trimethylsilylacetamide generated during the catalytic cycle, or directly from another molecule of substrate **187**. In both cases, the catalytic cycle would still be propagated.

Prior to the dCr methodology, there was only one example of a decarboxylative Ireland–Claisen rearrangement. Davidson treated allylic aryl sulfonylacetate **191** with LDA and chlorotrimethylsilane and obtained the corresponding α-phenylsulfonyl carboxylic acid **192**.[61] Upon heating with a weak base in a separate step, the decarboxylated product **193** was obtained (Scheme 49, top). In comparison, the dCr rearrangement gives concomitant decarboxylation together in the same step using sub-stoichiometric amounts of BSA and potassium acetate. More recently, Posner reported a Carroll-type rearrangement of α-sufonylacetate **194** derived from vitamin D_3, which rearranged and decarboxylated in the same step to give sulfone **195** in 82% yield (Scheme 49, bottom).[62]



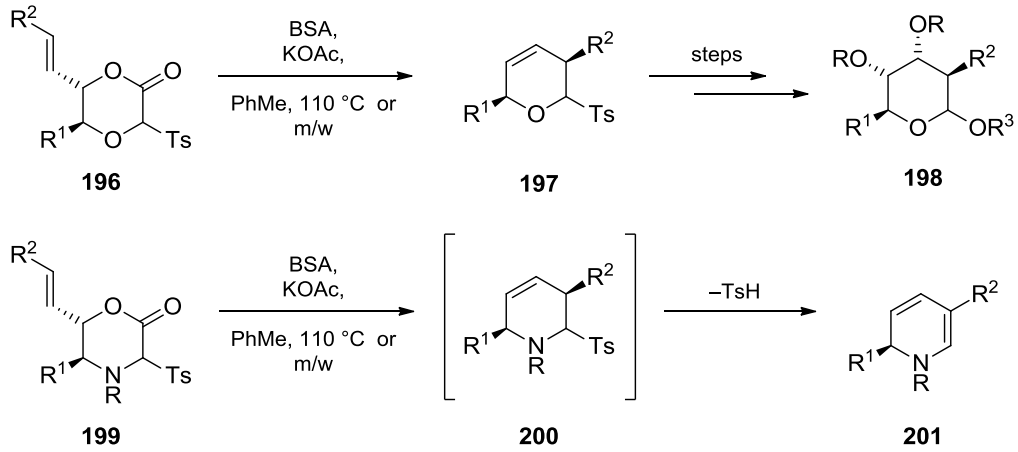
Scheme 49: Davidson's rearrangement–decarboxylation reaction of α-sulfonylacetate **191** (top) and Posner's Carroll-type rearrangement of α-sulfonylacetate **194** (bottom).

The versatility and scope of the dCr reaction was demonstrated on a variety of substrates and it was found to be tolerant to different oxygen-, nitrogen- and sulfur-containing functional groups and of different substitution levels at the olefinic carbons. This methodology has been extended to heteroaromatic systems,[53] acyclic systems,[63] double dCr reactions in the formation of pyridines,[64] transannular systems[65] and applied in the formation of natural products.[65(b), 66] The dCr rearrangement is stereoselective and can exhibit high levels of acyclic stereoselectivity.[67]

2.2. Decarboxylative Claisen rearrangements of dioxanones

2.2.1. Aims and Objectives

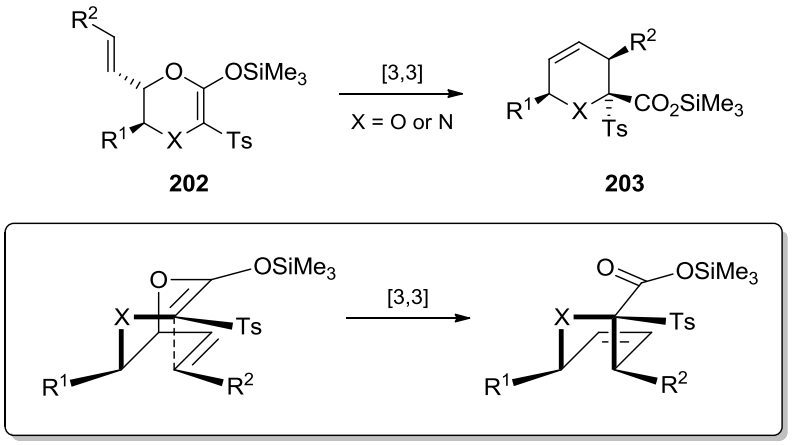
As an extension of the current decarboxylative Claisen rearrangement methodology, an investigation of its viability with more elaborate heterocyclic substrates was carried out. It was hypothesised that rearrangements of 1,4-dioxan-2-ones **196** under typical dCr conditions would give tosylated dihydropyrans **197**, which could be used as precursors in the syntheses of unnatural polysubstituted glycosidic fragments **198** (Scheme 50). Similarly, rearrangements of the analogous 1,4-morpholin-2-ones **199** would give *N*-alkyltetrahydropyridines **200**, which would be expected to undergo spontaneous loss of TsH under the mildly basic dCr conditions to give *N*-alkyldihydropyridines **201**.



Scheme 50: Proposed dCr reactions of dioxanones **196** and morpholinones **199**.

It was predicted that the [3,3]-rearrangement of the cyclic silyl ketene acetals **202**, generated from substrates **196** or **199** with BSA (Scheme 51, top), would proceed *via* a 6-membered boat-like conformation (Scheme 51, bottom) to give silyl esters **203**. The boat-like conformation is favoured over the chair-like conformation since rearrangement of the cyclic chair-like conformation is restricted. The stereospecific nature of the

rearrangement could provide a route into diastereomerically or enantiomerically pure 6-membered heterocycles.



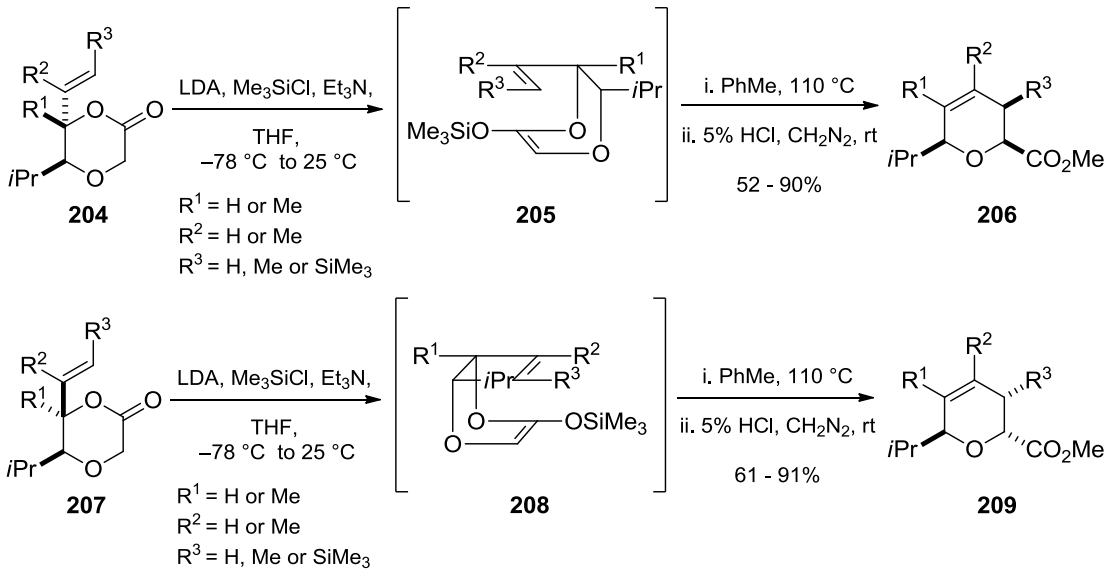
Scheme 51: [3,3]-rearrangements of cyclic ketene acetals (top) and their boat-like conformations during rearrangements (bottom)

2.2.2. Previous Ireland–Claisen rearrangement work on 1,4-dioxan-2-ones

The Ireland–Claisen rearrangements of 6-alkenyl-1,4-dioxan-2-one to dihydropyrans have been established as an efficient and stereocontrolled entry into diastereomeric *C*-pyranosides from appropriately functionalised precursors.[68-71]

Burke investigated a series of Ireland–Claisen rearrangements of dioxanones **204** and reported the formation of diastereomerically-pure dihydropyrans **206** in good yields *via* the boat-like conformation of silyl ketene acetals **205** (Scheme 52).[68] The rearrangements of the opposite diastereomers **207** also gave diastereomerically-pure dihydropyrans **209** *via* silyl ketene acetals **208**. Since both dioxanones **204** and **207** gave the corresponding products in good to excellent yields, it was concluded that the projection of the isopropyl group in both pericyclic boat-like transition states offered no impediment to the rearrangements. On the other hand, no rearrangements were observed with terminal *cis*-substituted alkenyl dioxanones.

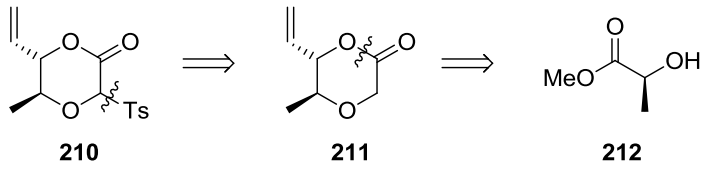
Burke later applied this methodology in the syntheses of macrolides,[69] ionophores[68, 70] and carbohydrates[71] that contained tetrahydropyran subunits.



Scheme 52: Ireland–Claisen rearrangements of 6-alkenyl-1,4-dioxan-2-ones.

2.2.3. Synthesis of methyl lactate-derived dioxanone

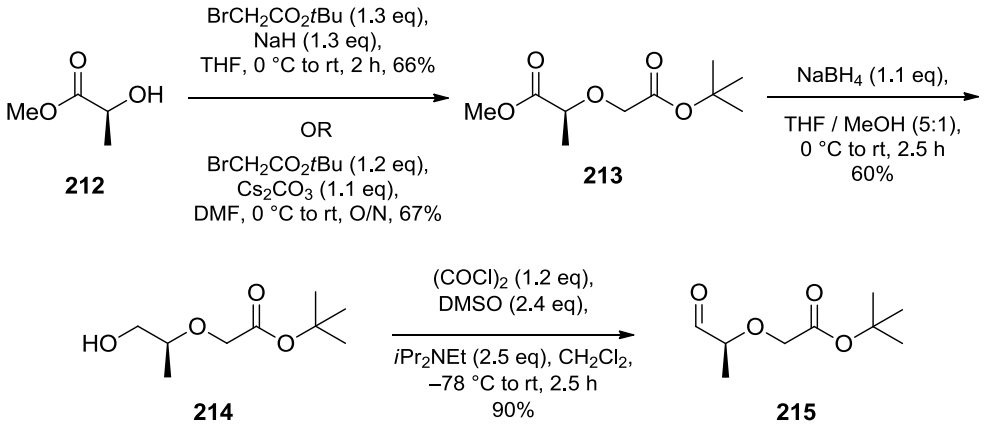
Firstly, 5-methyl-3-tosyl-6-vinyl-1,4-dioxanone **210** was selected as the initial substrate to be investigated using the dCr methodology. It was planned to prepare **210** by the tosylation of dioxanone **211** using a TsF-base methodology[63(a), 72] used previously for the tosylation of malonates (Scheme 53). The 5,6-disubstituted dioxanone **211** could be derived from commercially available (*S*)-methyl lactate **212**.



Scheme 53: Planned retrosynthetic route for the formation of dioxanone **210**.

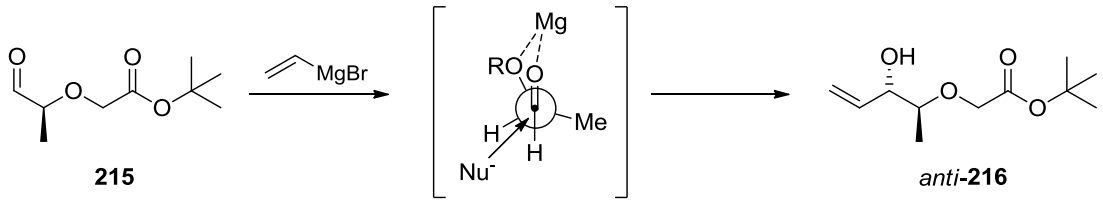
The synthesis of aldehyde **215** was carried out using a three-step procedure. (*S*)-Methyl lactate **212** was *O*-alkylated with *tert*-butyl bromoacetate to give diester **213** (Scheme 54). Selective reduction of the methyl ester over the *tert*-butyl ester using sodium

borohydride was achieved using a mixed solvent system of THF and methanol.[73] Finally, oxidation of alcohol **214** to the corresponding aldehyde **215** proceeded smoothly under Swern conditions.



Scheme 54: Formation of aldehyde **215** from (*S*)-methyl lactate **212**.

The chelation-controlled addition of a vinylmetal to aldehyde **215** was next investigated in order to introduce the necessary double bond. It was proposed that the addition of vinylmagnesium bromide would proceed *via* a 5-membered cyclic transition state in which the magnesium atom would coordinate to the carbonyl group and the β-oxygen atom of the aldehyde. Subsequent nucleophilic attack along the Bürgi–Dunitz trajectory would give the desired *anti*-**216** as the major product (Scheme 55).

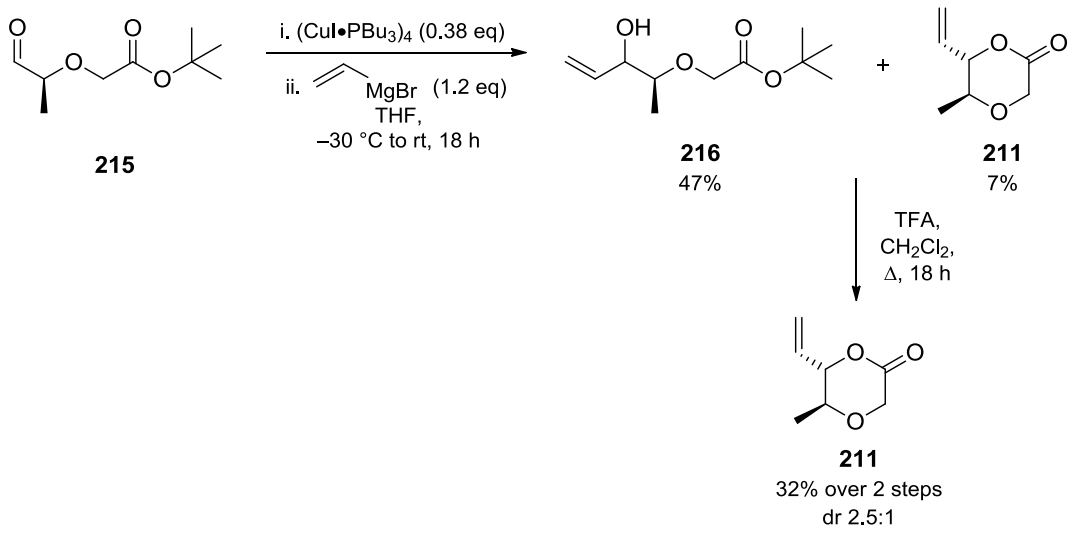


Scheme 55: Proposed *anti*-selective chelation-controlled addition to aldehyde **215**.

Direct vinylmagnesium bromide addition to aldehyde **215** was first attempted and found to give a 1:1 diastereomeric mixture of alcohol **216**. It was postulated that the use of a copper reagent might enhance the selectivity of the addition.[74] Interestingly, addition of

copper(I) bromide as chelating reagent gave no diastereoselectivity in the formation of alcohol **216** whereas copper(I) iodide exhibited some selectivity and gave *anti*-**216** in a 1.8:1 dr.

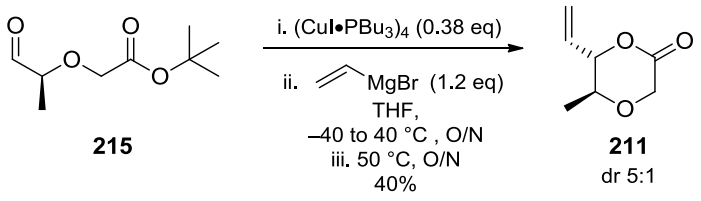
The best diastereoselectivity was obtained when the addition was mediated by copper(I) iodide–tributylphosphine complex.[75] When used as an additive in the reaction (Scheme 56), an inseparable mixture of alcohol **216** and cyclised dioxanone **211** was isolated in 47% and 7% yields respectively (yields determined from ^{1}H NMR analysis of the mixture). The mixture was subsequently treated with TFA and heated for 18 h to induce complete cyclisation and dioxanone **211** was obtained in 32% yield over 2 steps with a dr of 2.5:1. The *trans*-methine hydrogens of the six-membered ring displayed a coupling constant of 9 Hz, as compared to the 3 Hz observed with the *cis*-methine hydrogens. The novel compound **211** was also fully characterised by standard analytical techniques.



Scheme 56: Copper(I)-mediated vinylmagnesium bromide addition of **215** followed by cyclisation with TFA to give dioxanone **211**.

A one-pot procedure for the addition–cyclisation reaction was also developed (Scheme 57). In order to ensure complete cyclisation, the reaction was performed with increased time and temperature. This was essential since it was not possible to separate the product

211 from the uncyclised alcohol **216**. Furthermore, dioxanone **211** was obtained in an improved dr of 5:1.

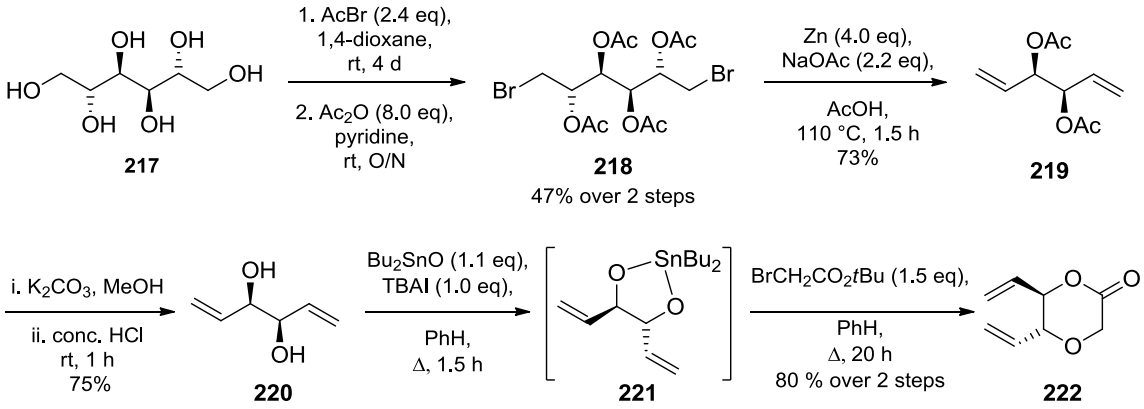


Scheme 57: A one-pot copper(I)-mediated vinylmagnesium bromide addition of aldehyde **215**.

Although it was possible to form dioxanone **211** in moderate yield with good selectivity using the one-pot copper(I)-mediated reaction, the reaction often gave incomplete cyclisation on a larger scale and rendered purification difficult. Therefore the focus was shifted to another dioxanone substrate which could be easily synthesised on multi-gram scale for dCr investigations.

2.2.4. Synthesis of mannitol-derived dioxanone

It was decided to synthesise an enantiopure dioxanone for the dCr reaction to allow for easy structural elucidation of the system. Dioxanone **222** was synthesised by de-symmetrisation of diene-diol **220,** which was derived from commercially available D-mannitol **217** (Scheme 58). Following literature precedent,[76] D-mannitol **217** was first brominated with acetyl bromide and acetylation of the resulting bromide gave tetraacetate **218**. Dehomologation *via* a Zn-mediated reduction gave acetate **219** and acetyl deprotection with potassium carbonate gave diene-diol **220**. The synthesis was performed on a forty-gram scale of D-mannitol to provide 7 g of diene-diol **220** without any need for purification by column chromatography.



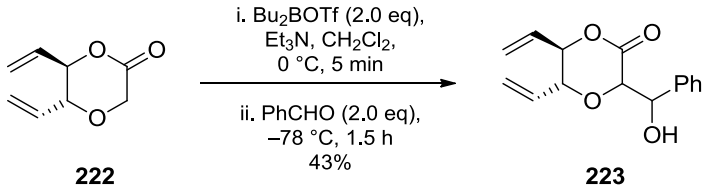
Scheme 58: Synthesis of diene-diol **220** from D-mannitol **217** and formation of dioxanone **222**.

Next, enantiopure dioxanone **222** was prepared by heating diene-diol **220**, di-*n*-butyltin oxide and tetrabutylammonium iodide (TBAI) in benzene using a Dean–Stark apparatus.[71] The TBAI, which is a catalyst for the subsequent alkylation reaction, was heated under reflux in the first step to ensure that any water present in the hygroscopic reagent was removed. The intermediate stannylene acetal **221** was alkylated with *tert*-butyl bromoacetate and subsequent cyclisation under thermal conditions gave dioxanone **222**. This procedure could be reproduced easily on a two-gram scale in a good yield.

2.2.5. C-3 functionalisation of mannitol-derived dioxanone

The alkylation at the 3-position of dioxanone **222** was next investigated. In 2000, Andrus reported that the boron enolate of 5,6-diphenyl-1,4-dioxan-2-one underwent aldol reaction with a variety of aldehyde electrophiles.[77] Applying the same methodology, the boron enolate of dioxanone **222** was first generated with dibutylboron triflate and triethylamine at 0 ^{o}C (Scheme 59). The resultant dark brown solution of the boron enolate was quenched with benzaldehyde at −78 ˚C to give alcohol **223** as a mixture of 4 diastereomers. Encouraged by the result, a variety of electrophiles (tosyl fluoride, ethyl chloroformate, $PhSSO_2Ph$, NBS, PTAB and CBr_4) was screened with the boron enolate.

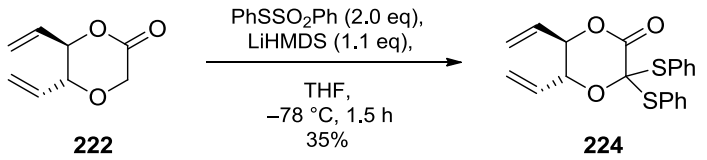
However, the boron enolate was unreactive and the starting material was retrieved in all cases. It was concluded that the enolate was not nucleophilic enough to react with these weaker electrophiles.



222 **223**

Scheme 59: Formation of boron enolate of **222** and quenching with benzaldehyde.

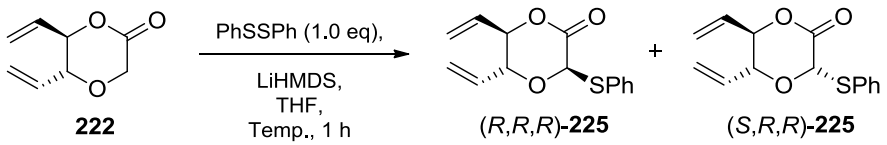
A direct deprotonation / alkylation method was next attempted. Dioxanone **222** was first premixed with excess $PhSSO_2Ph$ so that the enolate generated by LiHMDS could be quenched immediately (Scheme 60). The reaction initially gave bis-sulfide **224** in 35% yield when 2 eq of the electrophile was used. Reducing the amount of electrophile to 1 eq of $PhSSO_2Ph$ gave an inseparable mixture of bis-sulfide **224** and mono-sulfide **225** in a 2.5:1 ratio.



222 **224**

Scheme 60: Reaction of dioxanone **222** with LiHMDS and $PhSSO_2Ph$.

Employing a less reactive electrophile, diphenyl disulfide, gave sulfide **225** as the only product (Scheme 61). The reaction was performed under a variety of reaction conditions (Table 4) and it consistently gave sulfide **225** in poor yields in a dr of 1:2 [(*R*,*R*,*R*):(*S*,*R*,*R*)]. The configuration of the new stereocentre was determined using 1D selective NOESY. It was found that the order of addition determined the success of the reaction. When LiHMDS was added to a solution of dioxanone **222** and PhSSPh at –78 ˚C (reversed order of addition), only a trace amount (< 1%) of product was isolated.



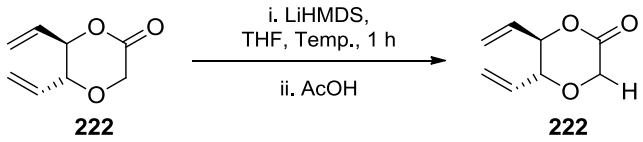
222 (*R*,*R*,*R*)-**225** (*S*,*R*,*R*)-**225**

Scheme 61: Reaction of dioxanone **222** with LiHMDS and PhSSPh.

Entry[a]	LiHMDS	Temp.	Yield of 225 [(*R*,*R*,*R*):(*S*,*R*,*R*)][a]
1	2 eq	−78 ˚C	14% (1:2)
2[b]	1 eq	−78 ˚C	16% (1:2)
3	2 eq	−50 ˚C	12% (1:2)

Table 4: Reaction conditions for the reaction of dioxanone **222** with LiHMDS and PhSSPh. [a]Addition of premixed solution of dioxanone **222** and PhSSPh to base. [b] Slow addition over 1 h using a syringe pump. [c] Ratio determined by crude ^{1}H NMR.

Since it was unclear why the alkylation proceeded in low yields, hence the stability of the lithium enolate was investigated by treating dioxanone **222** with 2 eq of LiHMDS followed by quenching with 2 eq of 10% acetic acid in THF (Scheme 62). Reactions carried out at –78 ˚C and –90 ˚C led to 20% and 13% recovery in the starting material respectively. TLC analysis of the reaction mixture before acidic work-up revealed a complicated mixture of decomposition products at both temperatures.



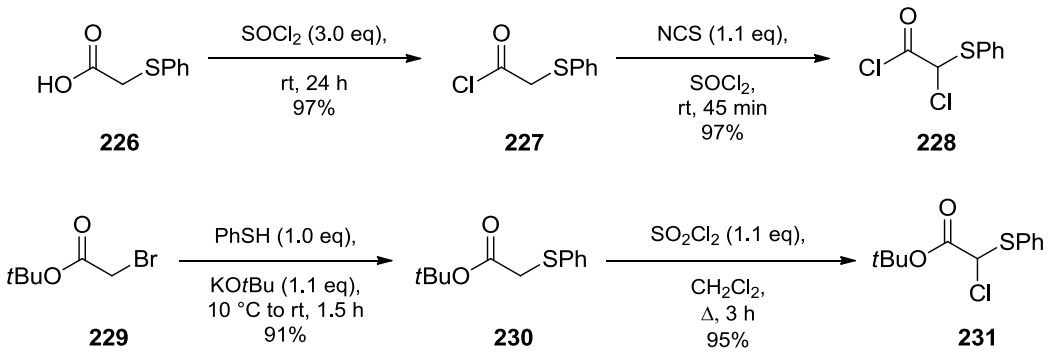
222 **222**

Scheme 62: Control deprotonation experiment of dioxanone **222**.

Other base (LDA) and electrophiles (TsF, NBS and iodomethane) were also investigated using the direct deprotonation / alkylation methodology. However, all reactions gave no desired product and in most cases led to decomposition of the starting material.

2.2.6. Synthesis of mannitol-derived dioxanones *via* a stannylene acetal

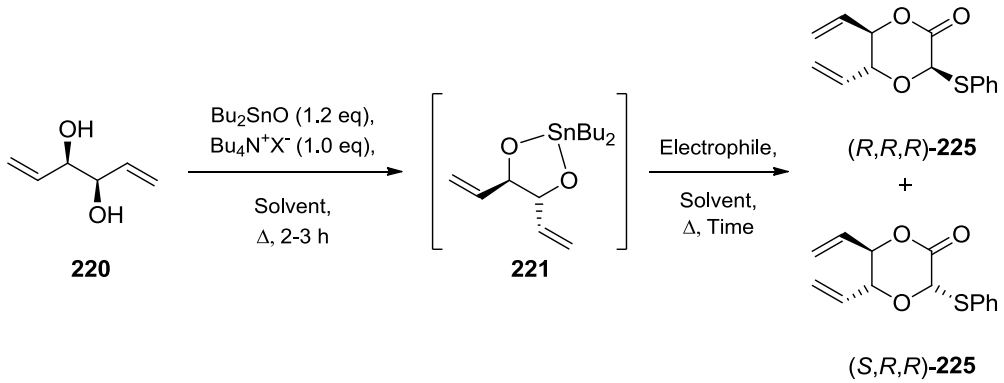
Following up on the previous positive result in the formation of dioxanone **222** *via* the stannylene acetal **221** and *tert*-butyl bromoacetate, we next wanted to evaluate a more convergent route using a similar electrophile with a phenylthio group already incorporated at the appropriate position. Therefore, two chloro-electrophiles, **228** and **231** were separately synthesised *via* a two-step procedure (Scheme 63). Starting from phenylthioacetic acid **226**, acid chloride **227** was obtained by treatment with thionyl chloride and the resulting product was α-chlorinated with NCS in thionyl chloride to give α-chloroacetyl chloride **228**.[78] *tert*-Butyl bromoacetate **229** was subjected to S_N2 reaction with thiophenol to give sulfide **230**,[79] which was then chlorinated with sulfuryl chloride to give chloride **231**.[80] Both electrophiles were prepared in multi-gram quantities.



Scheme 63: Synthesis of α-chloro electrophiles **228** and **231**.

Stannylene acetal **221** was prepared from diene-diol **220** using the same procedure with a Dean–Stark apparatus. Addition of the electrophiles **228** or **231** in a subsequent step then led to sulfide **225** (Scheme 64). The reaction conditions are summarised in Table 5. The electrophilic addition and cyclisation steps proceeded *via* different pathways with the two different electrophiles. Electrophile **231** followed the same mechanism as *tert*-butyl bromoacetate whereas electrophile **228** was first acylated before the α-chloro group was displaced. When acid chloride **228** was used as electrophile, 21% of

(*R*,*R*,*R*)- **225** was isolated exclusively (Entry 1). The poor yield was attributed to the incomplete cyclisation of α-chloroacetate formed after acylation which led to the conclusion that the acylation proceeded faster than the alkylation. Interestingly, no product formation was observed with TBAI as catalyst (Entries 2 and 4). The best conditions involved prolonged heating which gave the product **225** in 45% yield (Entry 5).

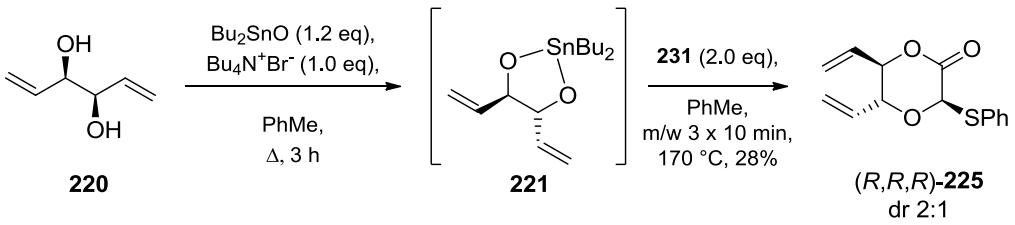


Scheme 64: Formation of dioxanones **225** *via* stannylene acetal **221**.

Entry	$Bu_4N^+X^-$	Solvent	Electrophile	Time	Yield	(*R*,*R*,*R*):(*S*,*R*,*R*)
1	TBAI	PhH	**228** (1.3 eq)	18 h	21%	1:0
2	TBAI	PhH	**231** (2.0 eq)	15.5 h	0%	-
3	TBAB	PhH	**231** (2.0 eq)	18 h	20%	2:1
4	TBAI	PhMe	**231** (2.0 eq)	18 h	0%	-
5	TBAB	PhMe	**231** (2.0 eq)	68 h	45%	2:1

Table 5: Reaction conditions for the formation of dioxanones **225** *via* stannylene acetal **221**.

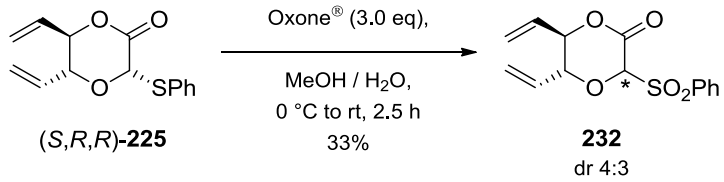
It was found that the rate of the addition–cyclisation could be increased by microwave irradiation of the crude stannylene acetal mixture and chloride **231** at 170 °C (Scheme 65). Although the time taken for the reaction was significantly shortened, a lower yield was obtained for product **225** compared to the reaction carried out under thermal conditions. The diastereoselectivity of the product remained 2:1 under both conditions.



Scheme 65: Formation of dioxanones **225** *via* stannylene acetal **221** under microwave irradiation.

2.2.7. Oxidation of mannitol-derived dioxanone

The oxidation of (*S*,*R*,*R*)-sulfide **225** with Oxone® in methanol and water (Scheme 66) gave sulfone **232** in only 33% yield despite complete consumption of starting material. The reaction also led to epimerisation at the C-3 position to give sulfone **232** as a mixture of diastereomers in a 4:3 ratio (diastereomers unassigned).



Scheme 66: Oxidation of sulfide **225** to sulfone **232**.

In all the stannylation reactions, the products were contaminated with tin by-products from di-*n*-butyltin oxide which could not be removed with Celite®, alumina or by washing the product with acids and bases. In addition, the relatively non-polar tin by-products leached through the silica gel during column chromatography and persistently remained in subsequent steps. The presence of the tin impurity and impracticality made large-scale synthesis difficult and therefore this line of investigation was abandoned.

2.3. Conclusion

A method was developed for the synthesis of 5-methyl-6-vinyl-dioxanone **211** in moderate yield and good selectivity using a one-pot procedure from aldehyde **215**. Aldehyde **215** could be derived from (*S*)-methyl lactate **212**.

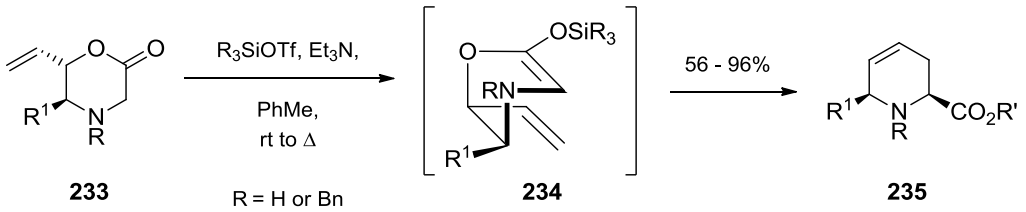
A model system was also employed and enantiopure 5,6-divinyl-dioxanone **222** was formed by de-symmetrisation of diene-diol **220** which could be derived from D-mannitol **217**. A direct base / alkylation method was investigated on dioxanone **222** but it gave 3-phenylthio-dioxanone **225** in low yields. It was later discovered in a control reaction that the ketene acetal of **222** had decomposed upon treatment with base.

It was also possible to synthesise 3-phenylthio-dioxanone **225** using a more convergent route from diene-diol **220** and pre-functionalised electrophiles **228** and **231** using either thermal or microwave conditions. The oxidation of 3-phenylthio-dioxanone **225** into sulfone **232** has also been successfully carried out with Oxone®.

3. Rearrangements of morpholinones

3.1. Background

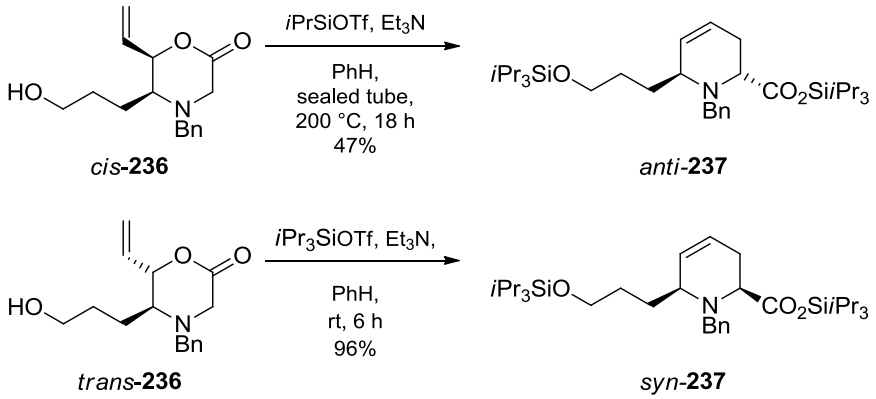
The Ireland–Claisen rearrangements for the analogous *N*-alkylmorpholinones have been examined extensively by Angle. *Trans* 5,6-substituted morpholinones **233** derived from amino acids such as alanine (R^1 = Me),[81] phenylalanine (R^1 = CH_2Ph),[81(a)] valine (R^1 = *i*Pr),[81(a), 82] glutamic acid (R^1 = $(CH_2)_3OH$),[83] methionine (R^1 = $(CH_2)_2OH$)[84] have been shown to rearrange to give tetrahydropyridines **235** in a stereocontrolled manner in good yields (Scheme 67). The rearrangements are hypothesised to proceed *via* a boat-like transition state **234** to give its predicted diastereomers. Angle subsequently applied this methodology in the formation of pipecolic acid derivatives [81(a), 85] and alkaloids.[81(b), 82-84]



Scheme 67: Ireland–Claisen rearrangement of amino-derived morpholinones **233**.

In contrast to the dioxanone system, the stereoconfiguration of the six-membered ring of morpholinones determines their reactivity in Claisen rearrangements. For example, rearrangement of the silyl ketene acetal of *cis*-**236** required harsher reaction conditions which involved heating in a sealed tube at 200 ˚C for 18 h in order to obtain tetrahydropyridine *anti*-**236** (Scheme 68, top).[83] On the other hand, rearrangement of the analogous *trans*-**236** occurred readily at room temperature to give *syn*-**236** in 96% yield (Scheme 68, bottom). It was postulated that the steric interactions between the alkyl chain and the alkenyl group in the boat-like transition state were more significant for the

cis-substituted morpholinone and therefore required more energy for its formation. This will be discussed in greater detail later in this section.



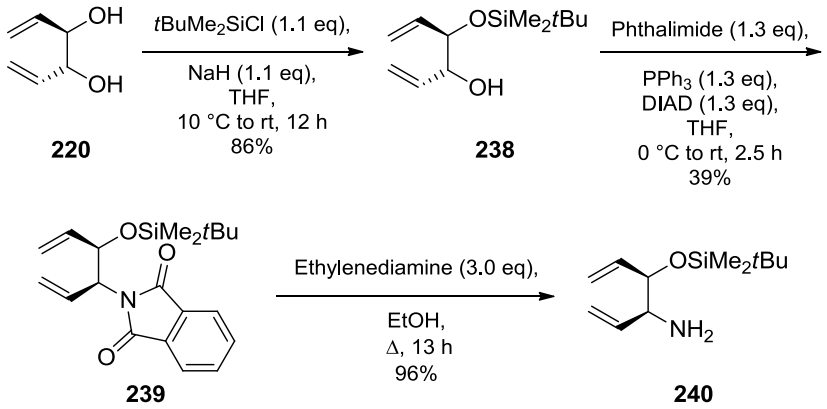
Scheme 68: Ireland–Claisen rearrangement of *cis*- (top) and *trans*-substituted (bottom) morpholinone **236**.

3.2. Claisen rearrangements of divinyl morpholinones

Building on earlier synthetic work in the large-scale preparation of diene-diol **220** from D-mannitol, the diene-diol was converted into an amino-alcohol in order to incorporate the nitrogen atom of the morpholinone.

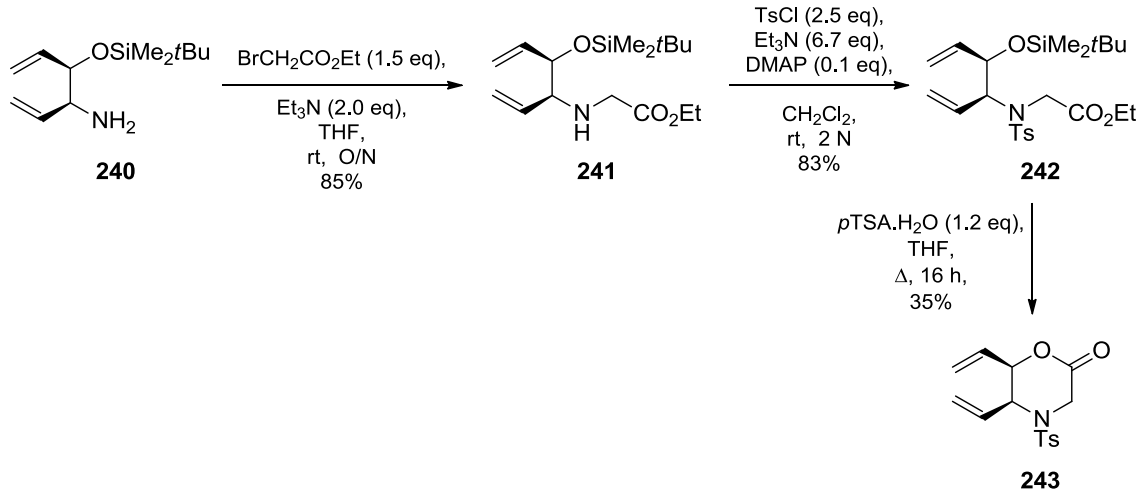
3.2.1. Synthesis of *N*-Ts divinyl morpholinones

Diene-diol **220** was first mono-protected as silyl ether **238** (Scheme 69). The remaining alcohol group was subjected to a Mitsunobu reaction with phthalimide,[86] which proceeded with inversion of the stereocentre to give phthalimide **239** in 39% yield. Deprotection of phthalimide **239** with ethylenediamine[87] gave amine **240** in excellent yield.



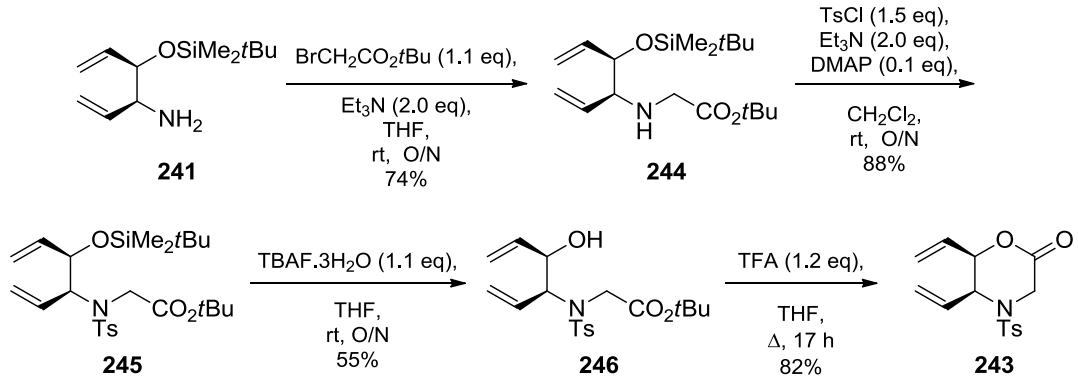
Scheme 69: Synthesis of amine **240** from diene-diol **220**.

Next, amine **240** was *N*-alkylated with ethyl bromoacetate to give secondary amine **241** (Scheme 70). Tosylation with TsCl and sub-stoichiometric DMAP gave the tertiary amine **242** in good yield. It was found that the use of DMAP was crucial for the success of this reaction. A one-step silyl ether deprotection–cyclisation facilitated by *p*TSA gave the desired morpholinone **243** in 35% yield.



Scheme 70: Synthesis of morpholinone **243** from amine **240**.

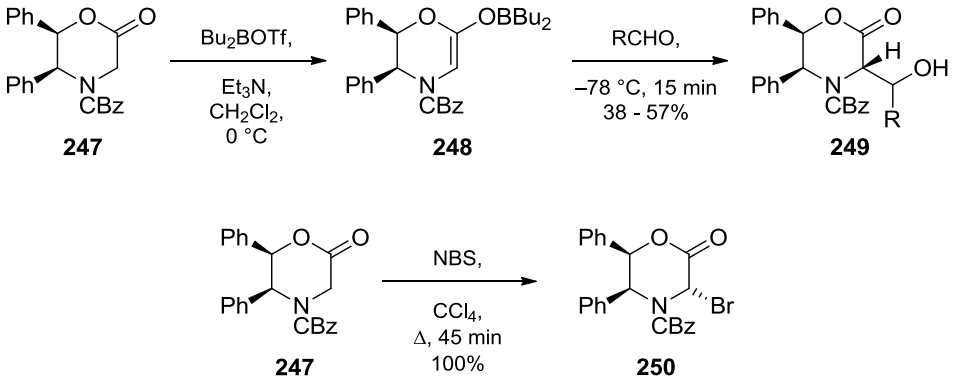
A strategy similar to that used for morpholinone **243** involved the use of *tert*-butyl bromoacetate as electrophile in the alkylation of amine **240**. Amine **244** was obtained in 74% before it was tosylated as tertiary amine **245** (Scheme 71). A separate deprotection–cyclisation step was examined where the silyl group was first deprotected with TBAF to give alcohol **246**. Cyclisation of alcohol **246** with stoichiometric amount of TFA gave morpholinone **243** in 45% over two steps.



Scheme 71: Synthesis of morpholinone **243** from *tert*-butyl ester **244**.

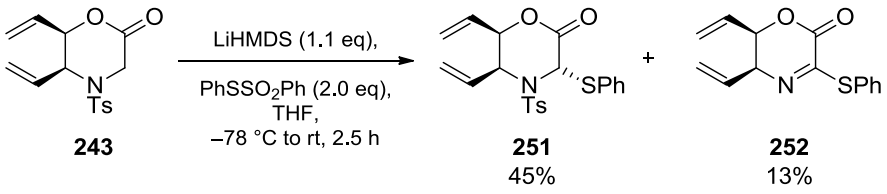
The C-3 functionalisation of morpholinone **247** has been described previously by Williams.[88, 89] For example, morpholinone **247** underwent C-3 functionalisation *via* boron enolate **248**, whose stereoselective aldol reactions with aliphatic aldehydes gave

alcohols **249** (Scheme 72, top).[88(c)] In addition, C3-halogenation of morpholinone **247** was achieved with NBS to give bromide **250** as a single diastereomer (Scheme 72, bottom).[88(e)] Disappointingly, these methods were unsuccessful in functionalising the C-3 position of morpholinone **243** as it was unreactive under the enolation and halogenation conditions.



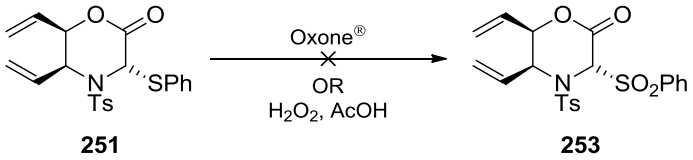
Scheme 72: William's C-3 functionalisations of morpholinone **247** using Bu_2BOTf (top) or NBS (bottom).

Therefore, morpholinone **243** was investigated using the deprotonation–sulfinylation approach discussed earlier in Section 2.2.5 with the dioxanone system. Unlike the dioxanone system, it did not matter if the base was added to the substrate or *vice versa*. The reaction was carried out by adding a solution of LiHMDS to a premixed solution of morpholinone **243** and $PhSSO_2Ph$ at –78 ˚C (Scheme 73). After work-up, sulfide **251** was obtained as a single diastereomer and the phenylsulfide group was tentatively assigned as being in *anti*-relationship to the two vinyl groups.[89] Notably, imine **252** was also isolated in a significant amount of 13% due to the elimination of the tosyl group on product **251** under the basic conditions. In contrast to the dioxanone system, use of PhSSPh as electrophile did not give morpholinone **251**.



Scheme 73: Sulfinylation at the C-3 position of *N*-Ts morpholinone **243**.

With sulfide **251** in hand, oxidations with Oxone® or H_2O_2 in acetic acid were investigated (Scheme 74). However, both reactions gave only the starting material or the sulfoxide; no sulfone product **253** was detected.

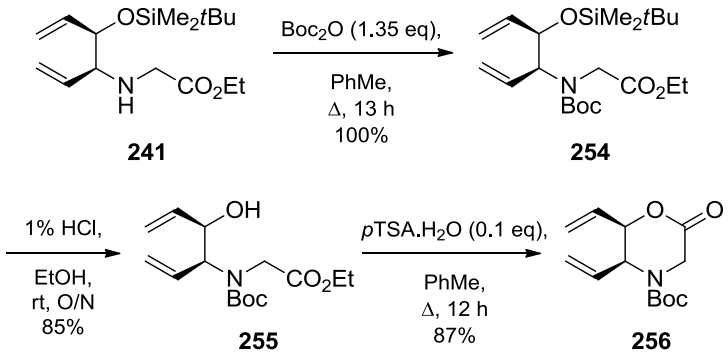


Scheme 74: Attempted oxidation of sulfide **251**.

3.2.2. Synthesis of *N*-Boc divinyl morpholinones

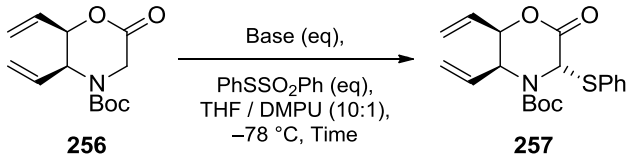
It was decided to evaluate Boc instead of tosyl as a protecting group since it is not susceptible to elimination under basic conditions. It would also allow closer comparison with the C-3 functionalisation reactions of *N*-Boc morpholinones previously described by Williams.[88(a), (e)]

According to a modified procedure,[90] amine **241** was protected with Boc_2O to give carbamate **254** in quantitative yield (Scheme 75). Remarkably, deprotection of the silyl ether using 1% HCl in ethanol was superior to TBAF and *p*TSA and gave a clean conversion of **254** to alcohol **255** in 85% yield. Lastly, cyclisation was facilitated using sub-stoichiometric *p*TSA to give *N*-Boc morpholinone **256** in 87% yield. This route is diversifiable and allows access to a range of other *N*-protecting groups during later stages of the synthesis.



Scheme 75: Synthesis of Boc-morpholinone **256**.

Morpholinone **256** was sulfinylated using the procedure described previously in Section 3.2.1 (Scheme 76). In addition, DMPU was employed as a co-solvent to promote solvation. Both KHMDS and LiHMDS were investigated as base and they both exhibited similar reactivities (Table 6, Entries 1 and 2). The yields improved when the amount of base and $PhSSO_2Ph$ used were increased (Entries 3 and 4). The reaction was further optimised with 2.5 eq of base and 3 eq of $PhSSO_2Ph$ (Entry 4) and this gave sulfide **257** in an excellent yield of 85% as a single diastereomer.



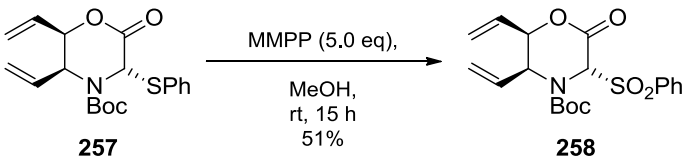
Scheme 76: Sulfinylation at the C-3 position of *N*-Boc-morpholinone **256**.

Entry	Base (eq)	$PhSSO_2Ph$ (eq)	Time (h)	Yield
1	KHMDS (1.5)	2	2.5	50%
2	LiHMDS (1.5)	2	2.0	57%
3	LiHMDS (2.0)	3	2.5	76%
4	LiHMDS (2.5)	3	2.5	85%

Table 6: Reaction conditions for the base / sulfinylation reaction of morpholinone **256**.

TsF and phenylsulfonyl chloride also were investigated as electrophiles, but no reaction was observed. Attempts to halogenate at the C-3 position with NBS or NCS were also unsuccessful.

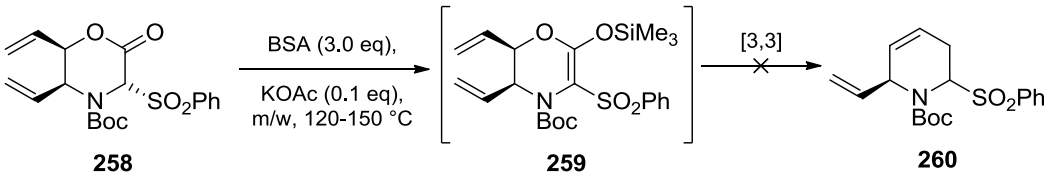
Oxidation of sulfide **257** using a mild oxidant, magnesium monoperoxyphthalate hexahydrate (MMPP), gave sulfone **258** in 51% yield (Scheme 77). Pleasingly, X-ray crystallographic analysis of sulfone **258** confirmed the predicted configuration at the C-3 position, in which the sulfur group is *anti* to the vinyl groups (Appendix I).



Scheme 77: Oxidation of sulfide **257** to sulfone **258**.

3.2.3. Claisen rearrangements of *N*-Boc divinyl morpholinones

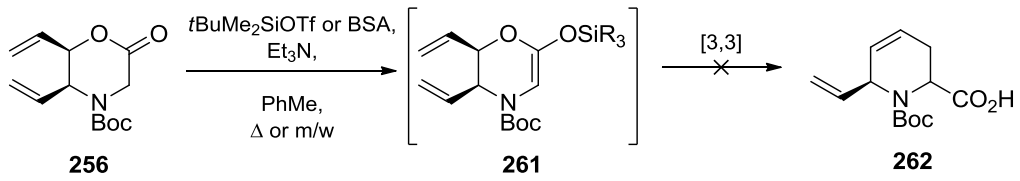
With substrate **258** in hand, the dCr rearrangement of sulfone **258** was attempted under microwave conditions with BSA and KOAc at 120 to 150 °C (Scheme 78). However, no product **260** was observed despite the formation of the silyl ketene acetal **259** as determined by 2D-TLC analysis and IR spectroscopy. 2D-TLC analysis suggested the presence of silyl ketene acetal **259** as a new spot which subsequently was converted back into starting material **258**. Further confirmation was obtained with IR spectroscopy of the crude reaction mixture, which indicated the disappearance of two strong carbonyl stretches at 1758 and 1708 cm^{-1} belonging to sulfone **258** and the appearance of a new broad band at 1658 cm^{-1}. Unfortunately, it was not possible to isolate silyl ketene acetal **259**.



258 259 260

Scheme 78: Attempted dCr of morpholinone **258** to give tetrahydropyridine **260**.

In order to test the feasibility of [3,3]-rearrangement of divinyl-substituted morpholinones, the Ireland–Claisen rearrangement of morpholinone **256** was investigated. Addition of *t*BuMe$_2$SiOTf to a solution of morpholinone and Et$_3$N in toluene at room temperature resulted in the formation of two colourless liquid phases (Scheme 79). TLC analysis of the top layer indicated that a new product had formed, presumed to be silyl ketene acetal **261**. Thermal heating or microwave irradiation at 140 °C of the mixture resulted only in decomposition of the starting material and no product formation of acid **262**. Milder rearrangement conditions[91] using BSA and Et$_3$N in toluene failed to facilitate formation of the silyl ketene acetal **261**.

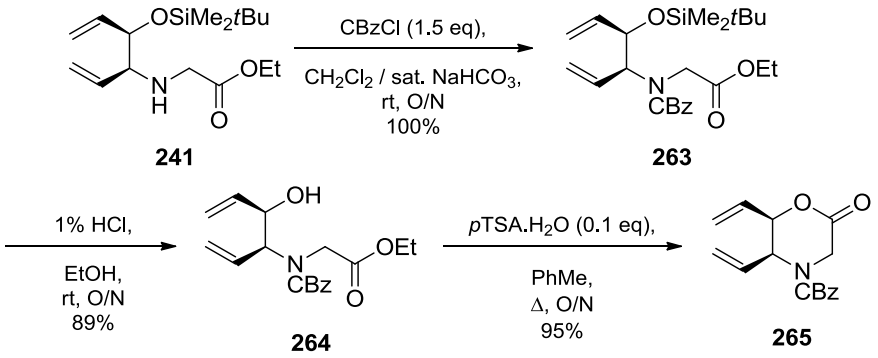


256 261 262

Scheme 79: Attempted rearrangements of morpholinone **256** to give acid **262**.

3.2.4. Synthesis of *N*-CBz divinyl morpholinone

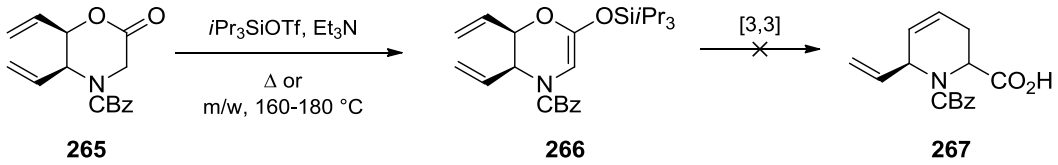
It was envisaged that *N*-CBz protected morpholinone would be more thermally stable and less acid-labile than the *N*-Boc derivative. Therefore, morpholinone **265** was synthesised in three high-yielding steps from amine **241**. The first step involved phase-transfer reaction of **241** with CBz-Cl to give the carbamate **263** (Scheme 80). Silyl deprotection under acidic conditions followed by *p*TSA-catalysed cyclisation of alcohol **264** gave morpholinone **265**.



Scheme 80: Synthesis of *N*-CBz-morpholinone **265**.

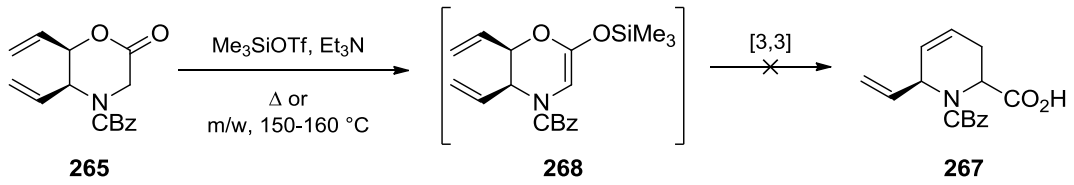
3.2.5. Ireland–Claisen rearrangement of *N*-CBz divinyl morpholinone

The Ireland–Claisen rearrangement of morpholinone **265** was investigated under similar silyl triflate–Et_3N conditions (Scheme 81). Treatment of morpholinone **265** with *i*Pr_3SiOTf in the presence of Et_3N at room temperature gave the corresponding silyl ketene acetal **266**. It was possible to isolate and characterise (^1H NMR and IR spectroscopy) the TIPS-derived silyl ketene acetal **266** by passage of the crude solution through commercially-available TMS-functionalised silica gel. Further heating of the crude mixture (both thermally and microwave irradiation at 160-180 °C) did not result in the formation of acid **267** but instead led to the recovery of starting material. It was predicted that the bulkier TIPS-group might have increased the stability of the silyl ketene acetal which had made it possible to isolate. On the other hand, this might have rendered it too stable towards rearrangement.



Scheme 81: Attempted rearrangement of morpholinone **265** to give acid **267** using *i*Pr_3SiOTf as silylating reagent.

In addition, the TMS-derived silyl ketene acetal **268** was formed by treatment of **265** with Me_3SiOTf, as verified by ^1H NMR (Scheme 82). Heating of the crude mixture thermally in the rearrangement step led to recovery of the starting material after quenching, whereas microwave irradiation of the mixture at 150-160 °C led to decomposition of the silyl ketene acetal. Once again, the BSA–Et_3N conditions were too mild even to initiate the formation of the silyl ketene acetal.



Scheme 82: Attempted rearrangement of morpholinone **265** to give acid **267** using Me_3SiOTf as silylating reagent.

According to Angle's boat-like model, silyl ketene acetals of 5,6-divinyl *cis*-morpholinones could undergo [3,3]-rearrangements as depicted in Fig. 7.

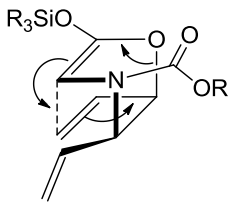
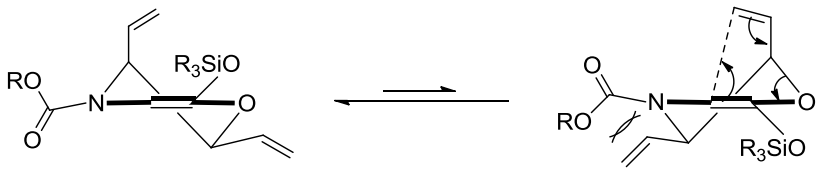


Fig. 7: Angle's boat-like model of silyl ketene acetal.

However, since substrates **256** and **265** failed to undergo rearrangements, it was proposed that the silyl ketene acetals might have preferred to adopt a half-chair conformations **269** and **270** (Scheme 83). The two conformers are in equilibrium whereby which the major conformer (**269**) is that in which the 5-vinyl group and the *N*-protecting group exert the least steric interactions. The sp^2 orbitals of the silyl ketene acetal and the 6-vinyl group required for the rearrangement, however, are not in overlap and therefore rearrangement is impossible. In order for rearrangement to occur, the silyl

ketene acetal has to adopt the energetically disfavoured minor conformer (**270)** so that sp^2 orbital of the 6-vinyl group could overlap with the orbital of the silyl ketene acetal.



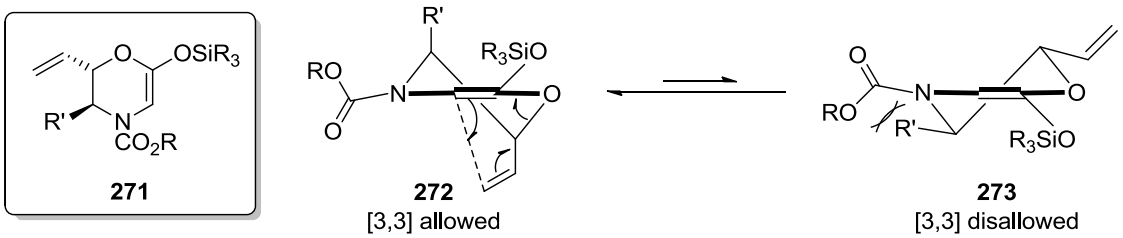
269
[3,3] disallowed

270
[3,3] allowed

Scheme 83: Half-chair conformations of silyl ketene acetals of 5,6-divinyl *cis* morpholinones.

3.3. Claisen rearrangements of alanine-derived morpholinones

We examined the possibility of directing our research towards a *trans* 5,6-disubstituted morpholinone in order to investigate our hypothesis concerning the lack of reactivity of the *cis*-morpholinones. It was predicted that the preferred conformation of silyl ketene acetal **271** would be the less energetic conformation **272**, where the 5- and 6-substituents adopt *trans*-diaxial positions (Scheme 84). The R′ substituent would be situated away from the adjacent to the *N*-protecting group and this conformation could facilitate rearrangement. The minor conformer **273** is energetically disfavoured due to the increased steric interactions between the *N*-protecting group and the equatorial 5-substituent.

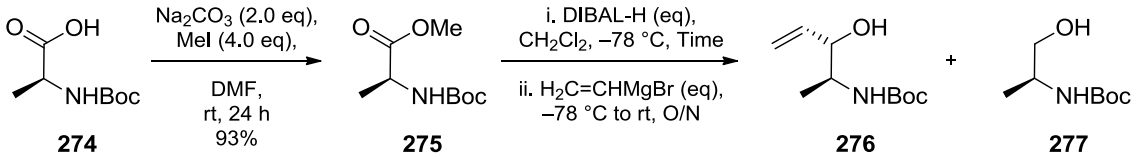


Scheme 84: Half-chair conformations of *trans* 5,6-disubstituted silyl ketene acetal **271**.

3.3.1. Synthesis of *N*-CBz alanine-derived morpholinones

N-Boc L-alanine **274** was first converted into its corresponding methyl ester **275** according to a literature procedure (Scheme 85).[92] The resultant methyl ester **275** was subjected to a one-pot DIBAL-H reduction / vinylmagnesium bromide addition reaction[93] to give the desired alcohol **276** (Table 7). A large excess of DIBAL-H reagent (Entries 1-3) was initially employed as described by literature procedures, but the over-reduced product **277** was isolated in significant amounts. By reducing the amount of DIBAL-H (< 1.2 eq), over-reduction was suppressed (Entries 4-7), although the yields and diastereomeric ratios obtained from the reaction were inconsistent. Optimal reaction

conditions involved treatment of ester **275** with 1.2 eq of DIBAL-H for 5 h before addition of 2.0 eq of vinylmagnesium bromide. This gave the product in 60% yield with 5:1 dr on an eight-gram scale (Entry 7).



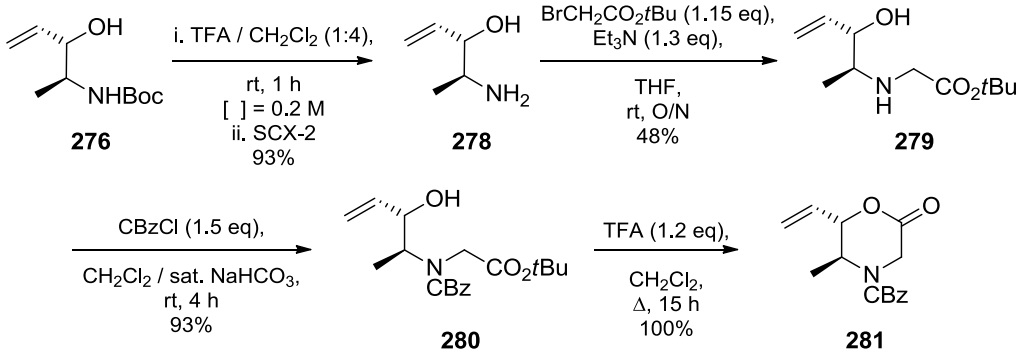
Scheme 85: Synthesis of allyl alcohol **276** from L-alanine **274**.

Entry	DIBAL-H (eq)	H_2C=CHMgBr (eq)	Time /h	Yield (276) /%	Yield (277) /%	dr
1	2.2	3.0	3.75	33	8	7:1
2	2.2	3.0	3	48	44	5.5:1
3	2.2	3.0	3.5	28	60	5:1
4	1.15	3.0	3.5	84	-	3:1
5	1.15	3.0	3	69	-	3:1
6	1.15	2.0	3.5	53	-	3:1
7	1.2	2.0	5	60	-	5:1

Table 7: Reaction conditions for the one-pot reduction / addition reaction of methyl ester **275**.

Direct alkylation on the nitrogen atom could not be achieved for carbamate **276** since the nucleophilicity of the nitrogen is significantly reduced by the presence of the electron-withdrawing Boc-group. Therefore carbamate **276** had to be first deprotected with TFA to give amino-alcohol **278** in 93% yield (Scheme 86). The reaction was concentration-dependent; 0.2 M was necessary to achieve complete consumption of amine **276**. A major challenge lay in the purification of the water-soluble amino-alcohol **278**, which required an SCX-2 ion-exchange method for purification. *N*-alkylation of amino-alcohol **278** with *tert*-butyl bromoacetate gave the secondary amine **279** in a best yield of 48%. Protection with benzyl chloroformate afforded the carbamate **280** and

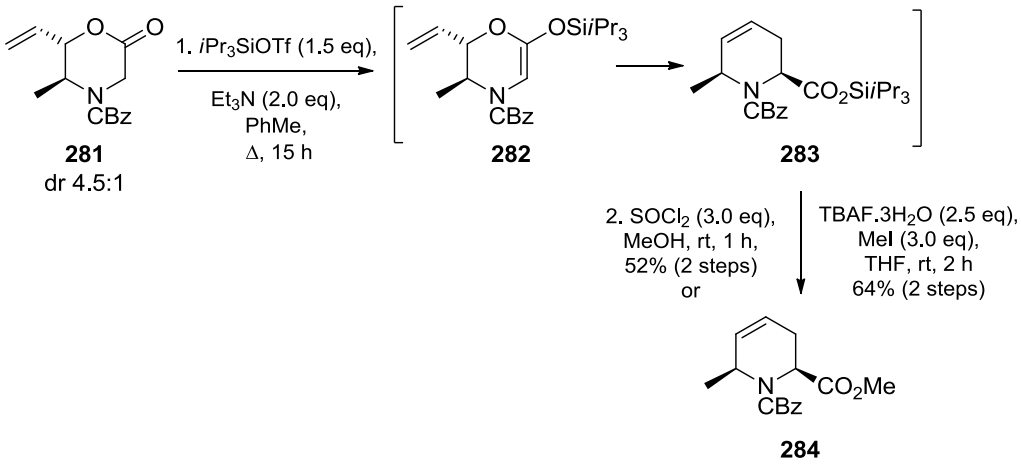
cyclisation under with 1.2 eq of TFA gave the desired *trans*-5,6-substituted morpholinone **281** in a quantitative yield.



Scheme 86: Synthesis of morpholinone **281** from alcohol **276**.

3.3.2. Novel Ireland–Claisen rearrangement of *N*-CBz alanine-derived morpholinone

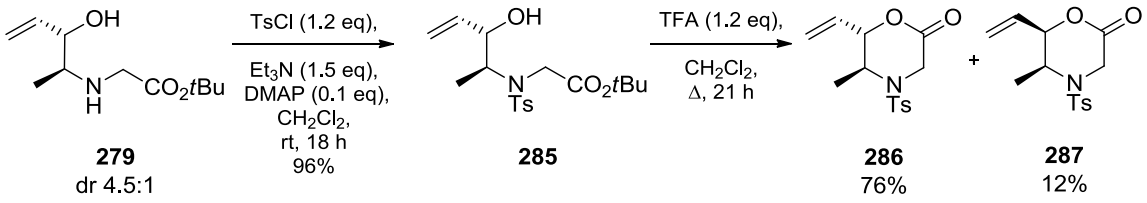
The Ireland–Claisen rearrangement of morpholinone **281** was next investigated. A 4.5:1 diastereomeric mixture of morpholinone **281** was subjected to standard *i*Pr_3SiOTf–Et_3N conditions at room temperature to generate the silyl ketene acetal **282** *in situ* (Scheme 87). Thermal conditions facilitated the stereospecific rearrangement to give silyl ester product **283**. The silyl ester was isolated as methyl ester **284** as a single isomer in 52% over two steps by treatment of the crude mixture with $SOCl_2$ in methanol. Alternatively, methylation could be carried out under slightly basic conditions using TBAF and MeI[94] to give methyl ester **284** as a single isomer in an improved yield of 64%. Unfortunately, the fate of the minor diastereomer **281** could not be determined due to broadening of peaks in ^{1}H NMR spectra at room temperature.



Scheme 87: Ireland–Claisen rearrangement of morpholinone **281**.

3.3.3. Synthesis of *N*-Ts alanine-derived morpholinone

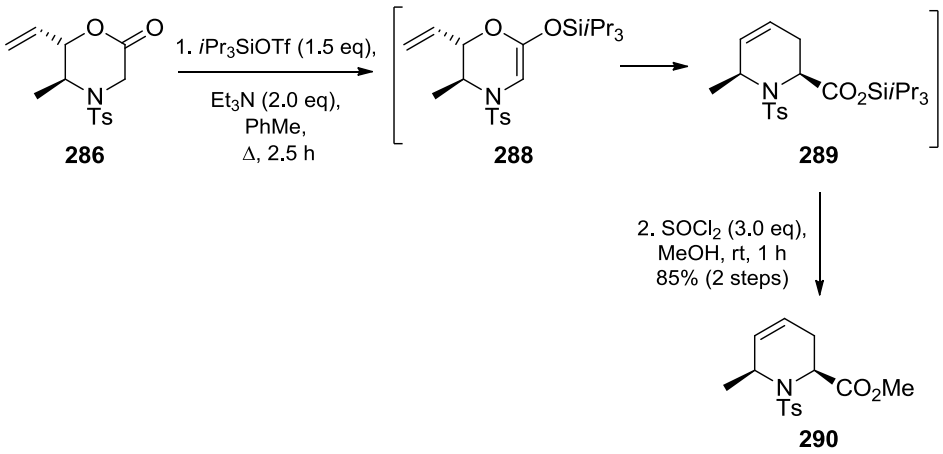
Encouraged by the novel rearrangement of morpholinone **281**, we proceeded to investigate other alanine-derived morpholinones as rearrangement substrates by incorporation of different *N*-protecting groups. Amine **279** was tosylated under standard condition to furnish tertiary amine **285** in excellent yield (Scheme 88). Cyclisation was achieved with TFA to give the tosyl-protected morpholinones **286** and **287** in which the cyclic diastereomers **286** and **287** could be resolved by silica-gel chromatography.



Scheme 88: Synthesis of *N*-Ts morpholinones **286** and **287** from alcohol **279**.

3.3.4. Novel Ireland–Claisen rearrangement of *N*-Ts alanine-derived morpholinone

The Ireland–Claisen rearrangement with enantiopure *trans*-morpholinone **286** was next investigated (Scheme 89). As with the CBz-analogue, silyl ketene acetal **288** was formed instantaneously at room temperature and rearrangement proceeded thermally, requiring a shorter period of 2.5 h. The crude silyl ester product **289** was methylated subsequently with thionyl chloride in MeOH to afford the novel methyl ester **290** in good yield and as a single isomer.

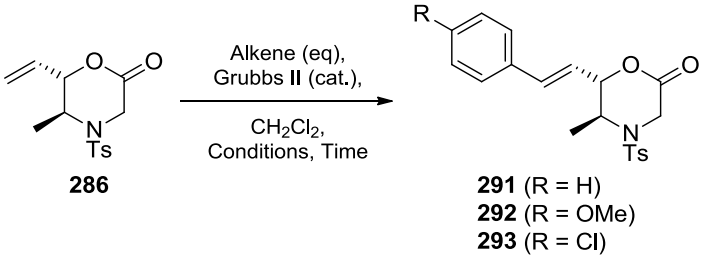


Scheme 89: Ireland–Claisen rearrangement of morpholinone **286**.

3.3.5. Cross-metathesis reactions of *N*-Ts alanine-derived morpholinone

Since the rearrangements of alanine-derived morpholinones **281** and **286** were successful, morpholinone **286** was synthesised on a larger scale so that other derivatives could be investigated. It was envisaged that alteration of the substitution of the vinyl group could alter the reactivity of morpholinone **286** in the [3,3]-rearrangement. Furthermore, an electron-rich substituent such as *para*-methoxystyene could increase the rate of rearrangement[95] by weakening of the allylic C-O bond through vinylogous anomeric effect ($\pi \rightarrow \sigma^*$).[96]

Morpholinones **291**, **292** and **293** were prepared by cross-metathesis of **286** with styrene (A), *para*-methoxystyrene (B), or *para*-chlorostyrene (C) as coupling partners (Scheme 90, Table 8). The cross-metathesis reactions were *trans*-selective and the products were obtained as a single geometric isomer with catalytic amount of Grubbs II catalyst (5-10 mol%) either under thermal or microwave conditions. Initial coupling reactions with alkenes (B) and (C) by heating at 40 °C in a sealed tube overnight led to incomplete reactions, and the mixtures had to be irradiated subsequently in the microwave in order to attain total conversion (Entries 3 and 5). Carrying out the cross-metathesis reactions solely in the microwave gave total conversions in one hour (Entries 2, 4 and 6).



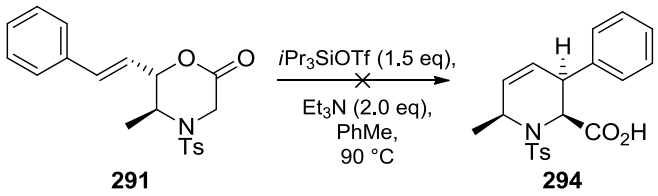
Scheme 90: Cross-metathesis reactions of morpholinone **286** with alkenes A (styrene), B (*para*-methoxystyrene) or C (*para*-chlorostyrene).

Entry	Alkene (eq)	Grubbs II (cat.)	Conditions	Product	Yield
1	A	10 mol%	Δ, 4.5 h	**291**	73%
2	A	10 mol%	m/w, 100 °C, 2 × 30 min	**291**	75%
3	B	10 mol%	Δ, O/N then m/w, 70 °C, 30 min	**292**	84%
4	B	7.5 mol%	m/w, 70 °C, 2 × 30 min	**292**	70%
5	C	5 mol%	Δ, O/N then m/w, 70 °C, 2 × 30 min, 100 °C, 20 min	**293**	61%
6	C	10 mol%	m/w, 100 °C, 1 h	**293**	86%

Table 8: Reaction conditions for the cross-metathesis reactions of morpholinone **286** with alkenes A (styrene), B (*para*-methoxystyrene) or C (*para*-chlorostyrene).

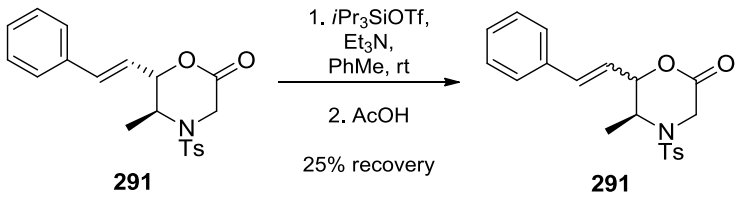
3.3.6. Ireland–Claisen rearrangements of *N*-Ts alanine-derived aryl morpholinone

Morpholinone **291** was initially subjected to the same rearrangement condition obtained previously using 1.5 eq of *i*Pr_3SiOTf, 2.0 eq of Et_3N at 90 °C (Scheme 91). However, no product **294** had formed and decomposition of the starting material was observed.



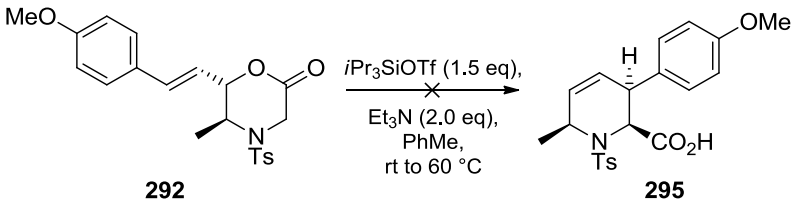
Scheme 91: Ireland–Claisen rearrangement of morpholinone **291**.

In a simple control experiment, *i*Pr_3SiOTf and Et_3N were added to **291** at room temperature and it was quenched with 1 M AcOH in THF (Scheme 92). The starting material was retrieved in less than 25% and unexpectedly obtained as a 1:1 mixture of epimers.



Scheme 92: Control experiment of morpholinone **291**.

The rearrangement of morpholinone **292** into product **295** was also unsuccessful (Scheme 93). Substrate **292** epimerised at room temperature under the mildly basic reaction condition and started to decompose when the mixture was heated up to 60 °C.

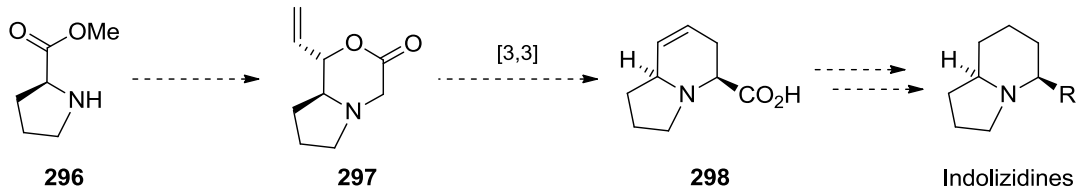


Scheme 93: Ireland–Claisen rearrangement of morpholinone **292**.

Since morpholinones **291** and **292** did not undergo [3,3]-rearrangements, this line of investigation was abandoned.

3.4. Claisen rearrangement of proline-derived morpholinone

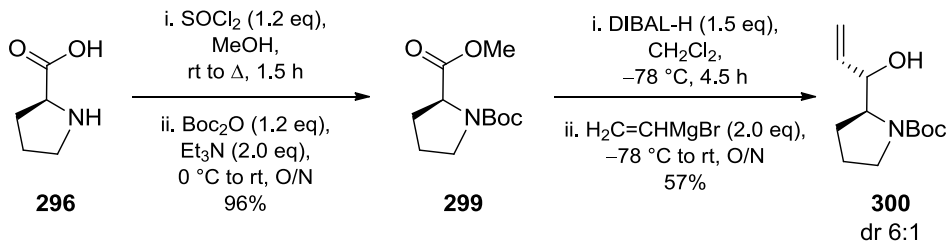
Given that the rearrangements of alanine-derived morpholinones **281** and **286** have been successful, we set out to investigate the chemistry of other amino acid-derived morpholinones. It was decided to synthesise morpholinone **297** derived from L-proline **296** using a similar strategy previously described for morpholinones **281** and **286** (Scheme 94). An intrinsic advantage of mopholinone **297** is that the tertiary nitrogen does not require a protecting group. Furthermore, the bicyclic rearrangement product **298** could be further elaborated towards the formation of indolizidines,[97] which is an important core structure of some alkaloids such as lepadiformine and monomorine.



Scheme 94: Proposed Ireland–Claisen rearrangement of morpholinone **297**.

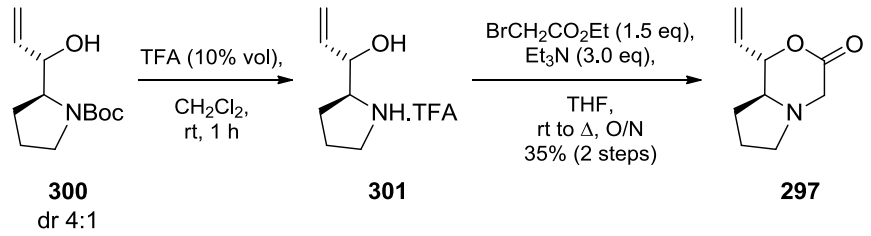
3.4.1. Synthesis of proline-derived morpholinone

L-Proline **296** was first esterified with methanol as its corresponding methyl ester and the nitrogen atom was subsequently protected with Boc_2O to give methyl ester **299** (Scheme 95).[98] A one-pot DIBAL-H reduction of the ester and vinyl Grignard addition gave alcohol **300** in 57% yield with a dr of 6:1, in line with the reported procedure.[93(d)]



Scheme 95: Synthesis of alcohol **300** from L-proline **296**.

The preparation of morpholinone **297** from alcohol **300** was performed as a one-pot reaction. Boc deprotection with TFA gave amine **301** as a yellow oil (Scheme 96). The crude mixture was redissolved in THF and alkylated with ethyl bromoacetate in the presence of Et_3N at room temperature. This gave a mixture of *N*-alkylated product and morpholinone **297** which suggested that cyclisation could be carried out under mildly basic conditions. Pleasingly, heating of the mixture under reflux gave the desired bicyclic morpholinone **297** in 35% yield as a single diastereomer after work-up and purification.



300
dr 4:1

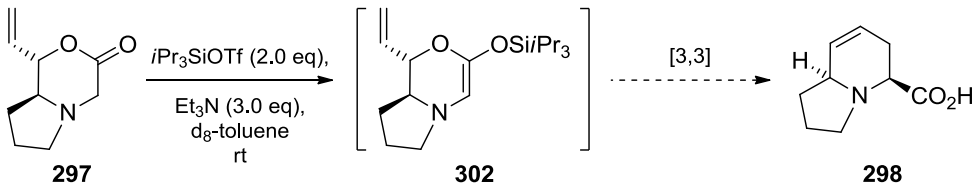
301

297

Scheme 96: Synthesis of morpholinone **297**.

3.4.2. Ireland–Claisen rearrangement of proline-derived morpholinone

The rearrangement reaction of morpholinone **297** into acid **298** was followed by ^1H NMR spectroscopy (Scheme 97). Fig. 8, (top) is a ^1H NMR spectrum of morpholinone **297** in d_8-toluene recorded at room temperature. Addition of Et_3N and $i Pr_3SiOTf$ instantaneously formed silyl ketene acetal **302** (Fig. 8, bottom). At this point, two layers were observed in the reaction mixture and the bottom layer was presumed to be ammonium triflate which was insoluble in toluene. The silyl ketene acetal **302** was identified by the disappearance of the methylene hydrogens of **297** at δ 2.6 and 3.5 ppm and the appearance of a new methine peak at δ 5.1 ppm.



Scheme 97: Ireland–Claisen rearrangement of morpholinone **297**.

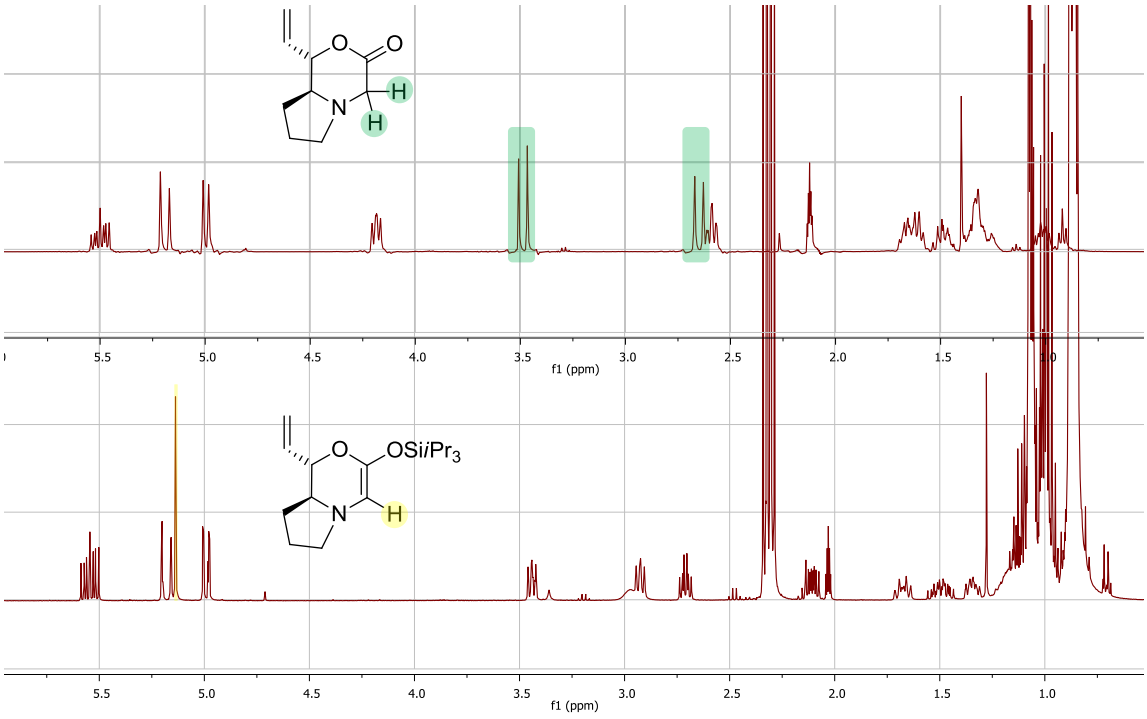
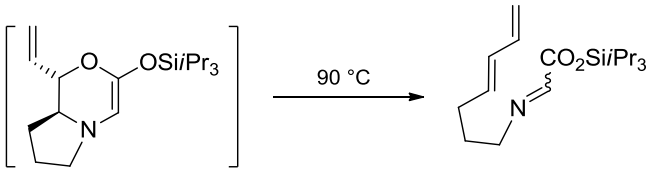


Fig. 8: ^{1}H NMR spectra of morpholinone **297** (top) and silyl ketene acetal **302** (bottom).

Heating the reaction at 90 °C in the NMR probe revealed that the starting material was completely consumed after 1.5 h (Fig. 9, t = 1.5 h). In addition, a new set of peaks was observed at δ 4.7 to 6.0 ppm and the chemical shifts and splitting patterns were consistent with a terminal 1,3-diene which suggested that diene **303** (Scheme 98) had formed.



302 **303**

Scheme 98: Formation of diene **303** from silyl ketene acetal **302**.

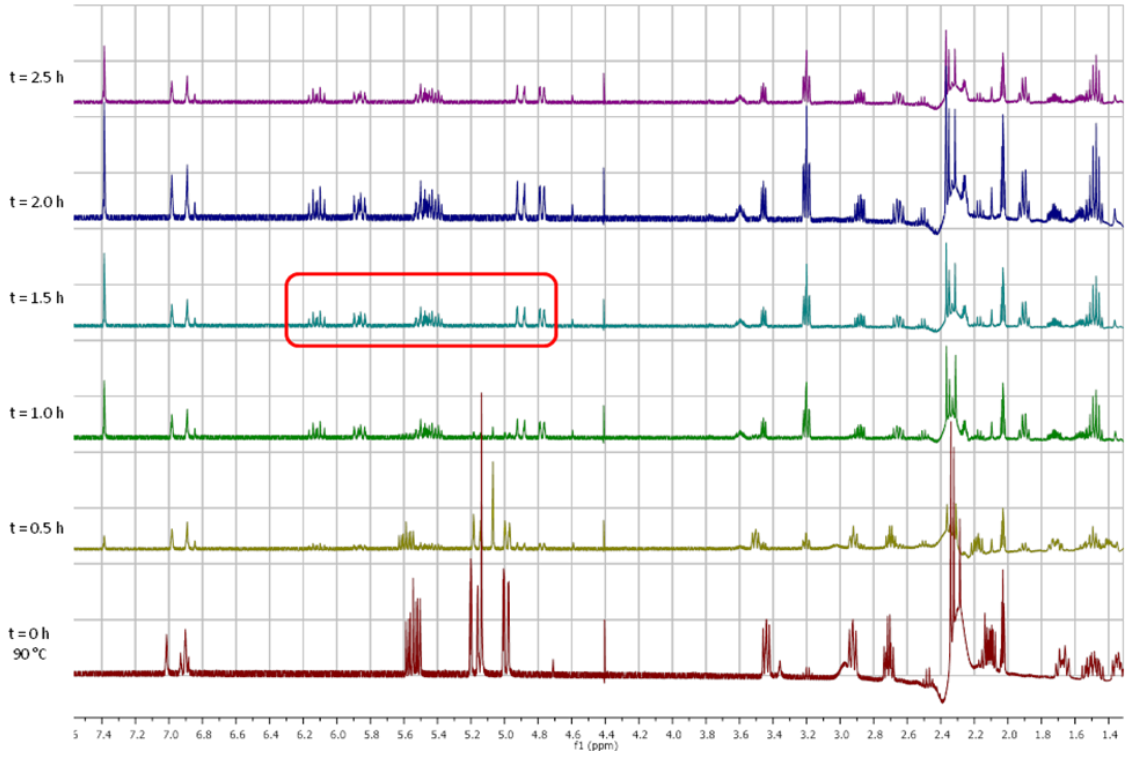


Fig. 9: ^{1}H NMR-overlays of the Ireland–Claisen rearrangement of morpholinone **297**.

The imine methine hydrogen (h) of **303** was assigned at δ 8.56 ppm as a singlet (Fig. 10). The terminal diene hydrogens (a to d) were found between δ 4.8 and 6.4 ppm whereby the chemical shifts and coupling constants are consistent with that of a similar molecule, (*E*)-hepta-4,6-dien-1-ylamine.[99]

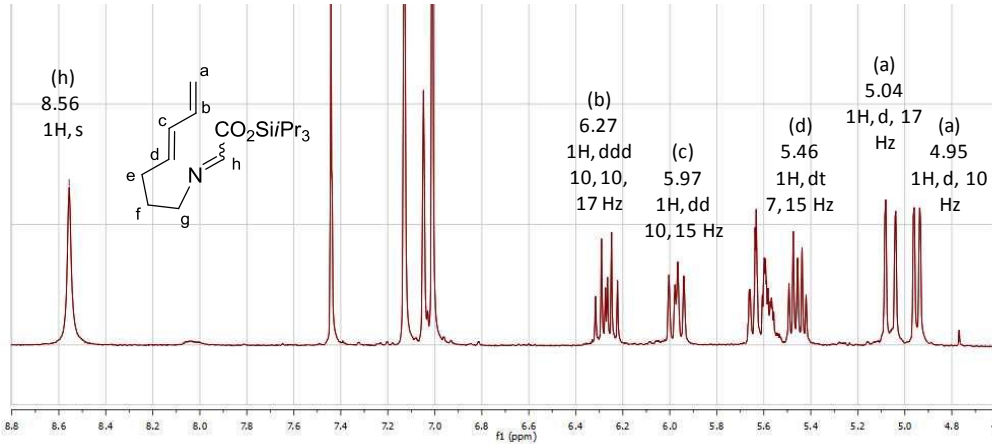
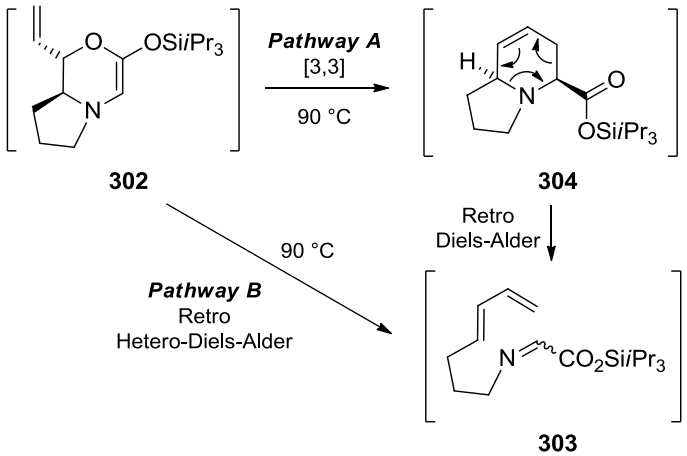


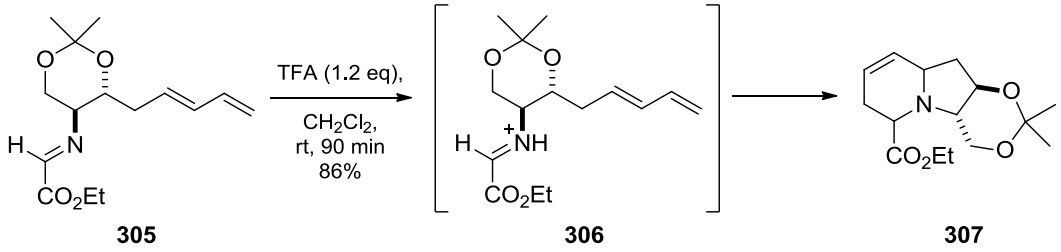
Fig. 10: Expanded ^{1}H-NMR spectrum of the reaction mixture at 1.5 h in d_8-toluene at 90 °C.

It was hypothesised that diene **303** could have formed either by Pathway A or Pathway B (Scheme 99). In Pathway A, silyl ketene acetal **302** rearranged to give silyl ester **304** followed by a retro Diels–Alder reaction while in Pathway B, silyl ketene acetal **302** undergoes a direct retro hetero-Diels–Alder reaction. Both pathways would give the same end-product **303**. In order to track intermediate **304**, the reaction was repeated at 40 °C. However, silyl ketene acetal **302** remained unreactive at this temperature. Further heating at 60 °C gave diene **303** at a slower reaction rate but intermediate **304** was not observed. Disappointingly, attempts to isolate the diene as a methyl ester by treating the crude solution of **303** with TBAF and iodomethane resulted in decomposition of the silyl ester.



Scheme 99: Two possible pathways for the formation of diene **303** from morpholinone **297**.

The formation of diene **303** could have been induced by traces of triflic acid present in *i*Pr_3SiOTf. Vallée reported a TFA-induced cycloaddition of a similar substrate whereby diene **305** was treated with TFA to induce the formation iminium cation **306** and this underwent an intramolecular Diels–Alder cycloaddition to give the tricyclic product **307** (Scheme 100).[100] This is in effect the reverse reaction of the retro Diels–Alder reaction of silyl ester **304** to diene **303**.

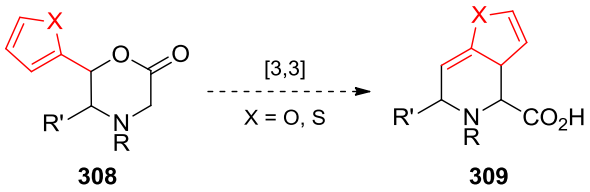


Scheme 100: TFA-catalysed Diels–Alder cycloaddition of diene **305**.

3.5. De-aromatising Claisen rearrangements of 6-aryl morpholinones

3.5.1. Aims

We planned to incorporate a heteroaromatic such as thiophene or furan on the 6-position of a morpholinone and utilise the aromatic double bond in a [3,3]-rearrangement. For example, rearrangements of morpholinones **308** could lead to unusual de-aromatised bicyclic heterocycles **309** which could act as potential pharmaceutical targets (Scheme 101).[101]

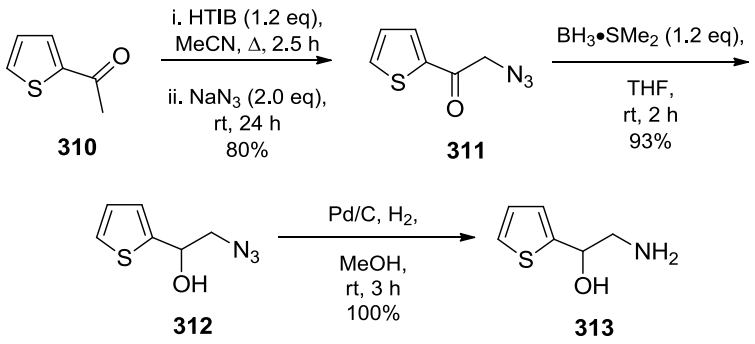


308 **309**

Scheme 101: Planned de-aromatising dCr reactions of morpholinones **308**.

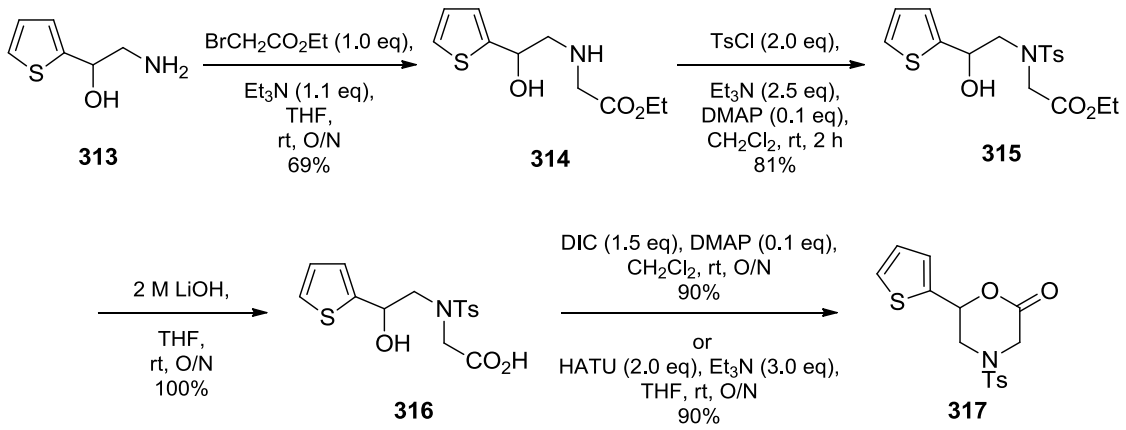
3.5.2. Synthesis of 2-acetylthiophene-derived morpholinone

A one-pot α-functionalisation of 2-acetylthiophene **310** was performed according to a modified procedure employing commercially available [hydroxy(tosyloxy)iodo]benzene (HTIB) instead of [hydroxy(*p*-nitrobenzenesulfonyloxy)iodo]benzene (HNIB) (Scheme 102) as tosylating reagent.[102] Treatment of ketone **310** with HTIB gave the α-tosylate which was subsequently subjected to S_N2 reaction with sodium azide. The reaction was reproducible with HTIB and gave azide **311** in better yield than reported with HNIB. Reduction of the ketone with borane following a modified procedure gave racemic alcohol **312** in 93% yield.[103] Hydroxy-azide **312** was subsequently hydrogenated over Pd/C and amino-alcohol **313** was obtained quantitatively without the need for any further purification.[104]



Scheme 102: Synthesis of amino-alcohol **313** from 2-acetylthiophene **310**.

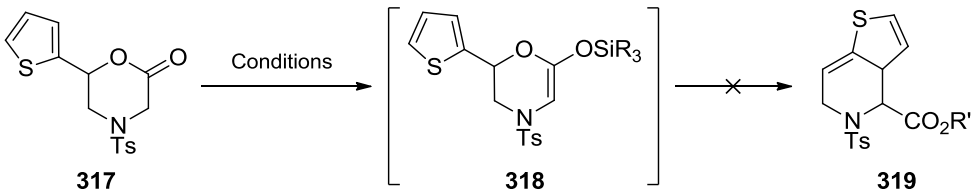
Mono *N*-alkylation of amine **313** was effected by treatment with 1 eq of ethyl bromoacetate and 1.1 eq of base to give ester **314** in 69% yield (Scheme 103). Despite careful control of stoichiometry, the bis-alkylated product persistently formed. Tosylation of ester **314** subsequently gave the tertiary amine **315** in 81% yield. Initial attempts to cyclise amine **315** directly using *p*TSA were unsuccessful. It was thought that the acidic thermal condition might have initiated decomposition of the thiophene. Hence, a neutral cyclisation method was employed instead. Saponification of the ethyl ester with 2 M LiOH gave acid **316** in quantitative yield without the need for any purification. Intramolecular condensation of acid **316** either with DIC or HATU both gave morpholinone **317** in good yields.



Scheme 103: Synthesis of morpholinone **317** from amino-alcohol **313**.

3.5.3. De-aromatising Ireland–Claisen rearrangement of 2-acetylthiophene-derived morpholinone

The Ireland–Claisen rearrangement of morpholinone **317** to bicyclic product **319** was investigated under various conditions (Scheme 104). Treatment of morpholinone **317** with 2 eq of *i*Pr_3SiOTf and 3 eq of Et_3N in d_8-toluene at room temperature gave the silyl ketene acetal **318** as evidenced by ^1H NMR spectroscopic analysis (Fig. 11). The crude solution was heated incrementally from room temperature to 90 °C and the reaction was followed by ^1H NMR spectroscopy. However, the silyl ketene acetal did not undergo rearrangement. Similarly, no rearrangement was observed when repeated with other conditions (BSA and Me_3SiOTf).



Scheme 104: De-aromatising rearrangement of morpholinone **317**.

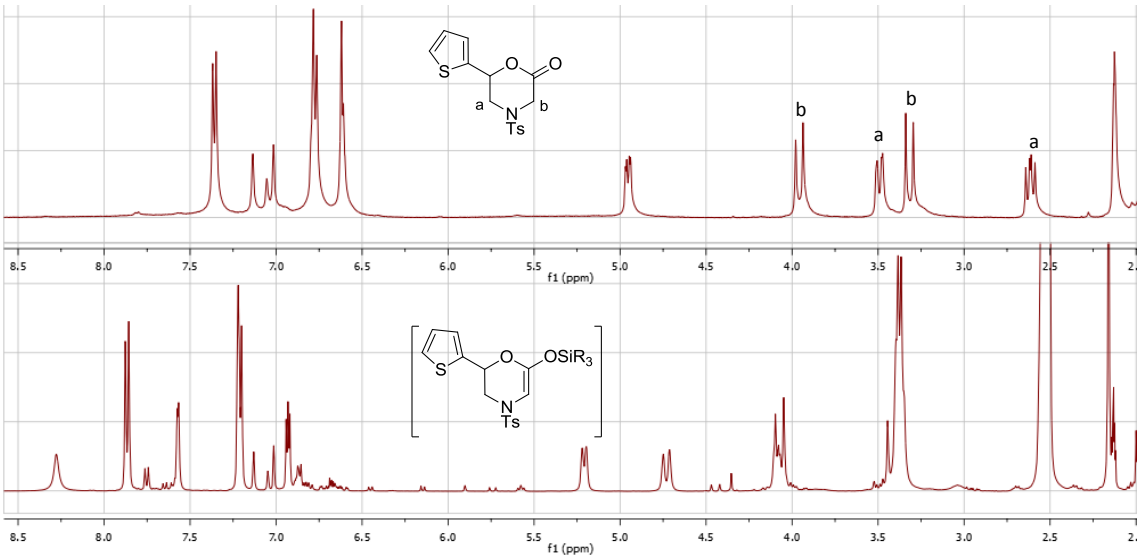
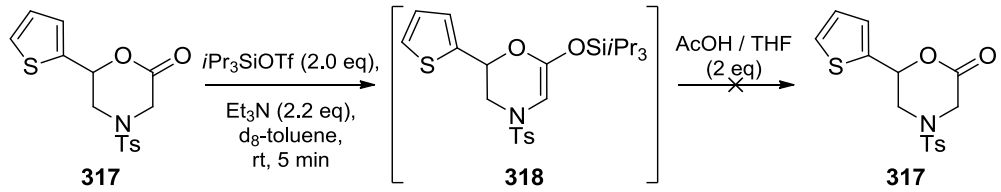


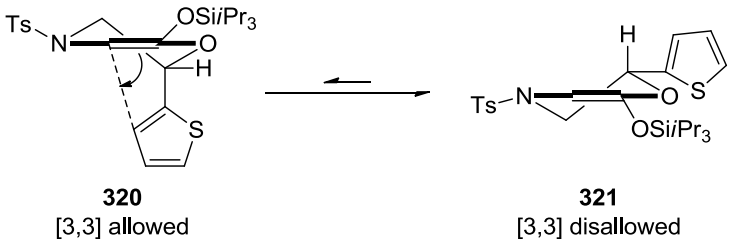
Fig. 11: ^1H NMR spectra of **317** in d_8-toluene at rt (top) and after addition of Et_3N and *i*Pr_3SiOTf at rt (bottom).

In a separate control experiment monitored by ^{1}H NMR spectroscopy, the crude silyl ketene acetal mixture **318** was quenched with a stoichiometric amount of acetic acid but no starting material **317** could be observed (Scheme 105). It was suspected that silyl ketene acid **318** could have decomposed under acidic conditions.



Scheme 105: Control experiment for the formation of silyl ketene acetal **318** from morpholinone **317**.

The failure of this rearrangement was attributed to the silyl ketene acetal **318** adopting a more thermodynamically stable conformation (**321**) with the thiophene substituent in the equatorial position (Scheme 106). However, in order for rearrangement to be allowed, the thiophene group is required to adopt the axial position as in **320** so that the sp^2 orbitals of the aromatic ring and the silyl ketene acetal would overlap in order to form the new carbon–carbon bond.



Scheme 106: Half-chair conformations of silyl ketene acetal **318**.

An X-ray crystal structure of morpholinone **317** was obtained (Fig. 12, Appendix II) and verified our hypothesis that, at least in the solid state, the thiophene group lies in the equatorial position, a conformation not disposed towards rearrangement.

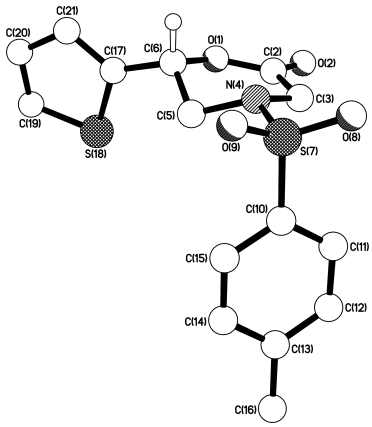
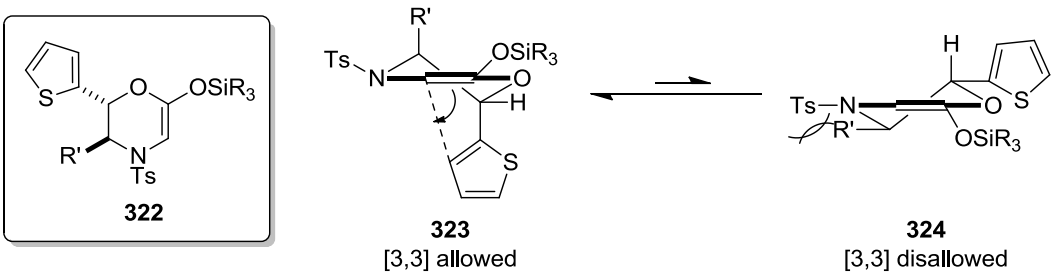


Fig. 12: X-Ray crystal structure of morpholinone **317**.

3.5.4. Synthesis of 2-propionylthiophene-derived morpholinone

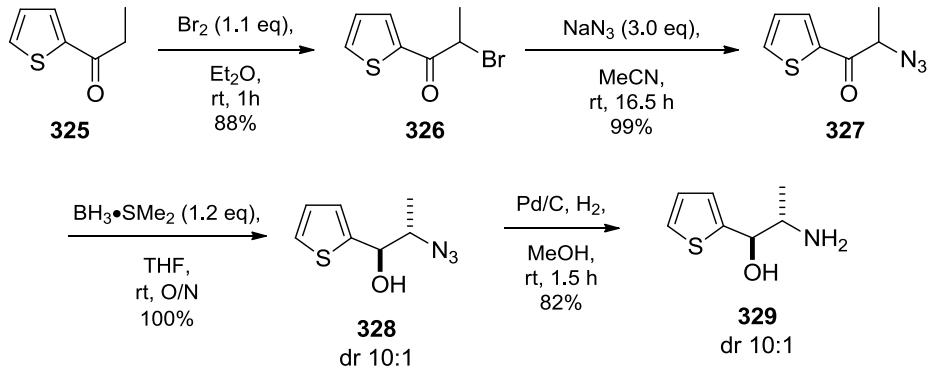
In light of the above conclusion, it was proposed to overcome conformation problems by synthesising a 5,6-disubstituted *trans*-morpholinone. By installing a substituent on the 5-position in *trans*-configuration adjacent to the 6-thienyl group, the energetically stable conformation (**323**) of silyl ketene acetal **322** would minimise steric interactions between the Ts group and the R′ substituent as well as allowing rearrangement (Scheme 107). The minor conformation (**324**) is energetically less stable as the *N*-Ts group experiences steric clashes with the equatorial 5-substituent.



Scheme 107: Half-chair conformations of silyl ketene acetal **322**.

In order to employ a similar synthetic strategy as the previously-developed route, the synthesis started from the commercially available 2-propionylthiophene **325**, which is a one-carbon homologue of thiophene **310** (Scheme 108). Bromination at the α-position

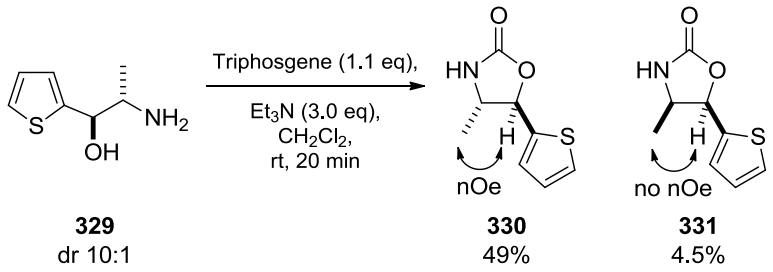
according to a reported procedure yielded bromide **326** which was stable over silica gel during purification.[105] Displacement of the bromide with sodium azide gave α-azide **327** in an excellent yield. Reduction of the carbonyl was performed as previously by addition of borane dimethyl sulfide complex to a solution of ketone **327**. Alcohol **328** was unexpectedly obtained as a mixture in 10:1 dr and in quantitative yield. At this point, we were unable to determine the identity of the major diastereomer because it was not possible to crystallise the oily product. By reversing the order of addition, where the substrate was added to an environment of excess borane complex, a low dr of 3:1 was obtained (determined by crude ^{1}H NMR and the product was not isolated). Hydrogenation of the azide in methanol gave amino-alcohol **329** in 82% yield.



Scheme 108: Synthesis of amino-alcohol **329** from 2-propionylthiophene **325**.

The selectivity of the borane reduction was further examined. Amino-alcohol was treated with triphosgene to form oxazolidinones **330** and **331** in hope that the cyclic diastereomers could be resolved and identified by comparing the coupling constants between the cyclic methine hydrogens (Scheme 109). Resolution of the *cis*- (**331**) and *trans*-diastereomers (**330**) were successful. However, both diastereomers exhibited similar coupling constants of 7.5 Hz between the methine hydrogens. Pleasingly, a NOESY coupling could be observed for the major diastereomer **330** between the methyl

group and the methine hydrogen next to the thiophene whereas the minor diastereomer **331** did not display such NOESY coupling.



329 dr 10:1 | **330** 49% | **331** 4.5%

Scheme 109: Synthesis of oxazolidinones **330** and **331** from amino-alcohol **329**.

Furthermore, it was possible to selectively recrystallise the major diastereomer of amino-alcohol **329** from hexane–ethyl acetate (Fig. 13, Appendix III). This verified that the borane reduction proceeded with *anti*-selectivity to give the desired *trans*-morpholinone.

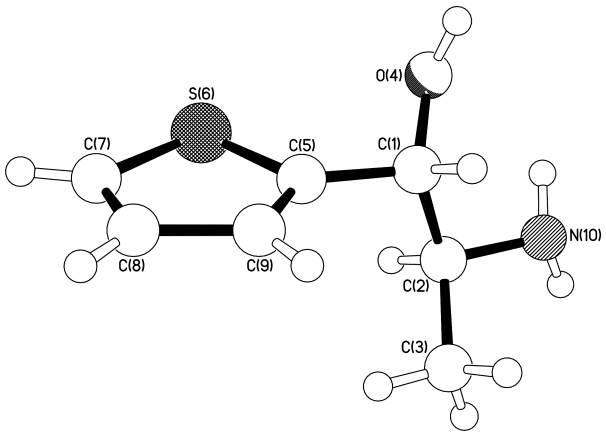


Fig. 13: X-Ray crystal structure of amino-alcohol **329**.

The *anti*-selectivity from the reduction of ketone **327** is postulated to have arisen from Felkin–Anh selectivity in which the azide group is assigned as the largest group (Fig. 14). Addition of borane to racemic ketone **327** would result in the formation of the major product **328** as a mixture of *anti*-diastereomers.

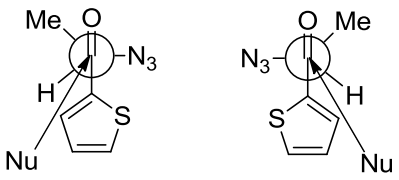
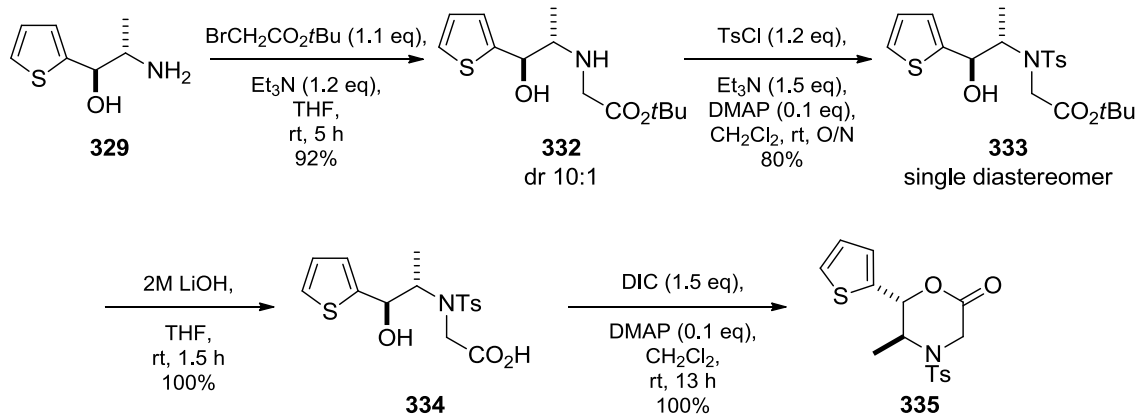


Fig. 14: Felkin–Anh models for the reduction of ketone **327**.

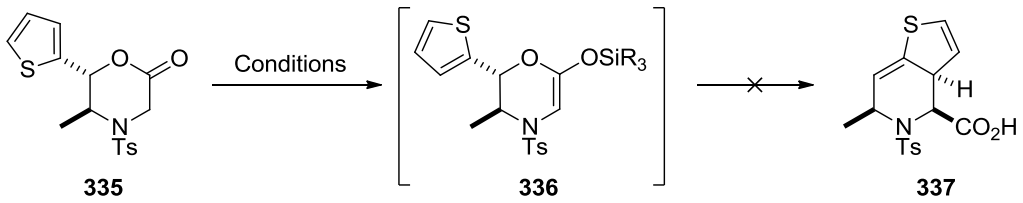
With a methyl substituent adjacent to the free amine group in **329**, bis *N*-alkylation was not observed unlike with the previous amino-alcohol **313** and gave secondary amine **332** in an excellent yield of 92% (Scheme 110). Next, a mixture of amine **332** (dr 10:1) was tosylated with TsCl and the tertiary amine **333** was obtained as a single diastereomer in 80% yield (of the possible 91%) by triturating the product mixture in TBME. The minor diastereomer was soluble in TBME and filtration gave the major diastereomer as the residue. Saponification of the *tert*-butyl ester with aqueous LiOH yielded acid **334** quantitatively. Finally, cyclisation was achieved with DIC-mediated intramolecular condensation of hydroxy-acid **334** to give *trans* 5,6-disubstituted morpholinone **335**.



Scheme 110: Synthesis of morpholinone **335** from amino-alcohol **329**.

3.5.5. De-aromatising Ireland–Claisen rearrangement of 2-propionylthiophene-derived morpholinone

The de-aromatising rearrangement was attempted under a variety of conditions, all of which proved unsuccessful and did not form acid **337** (Scheme 111, Table 9). Standard *i*Pr_3SiOTf conditions with different bases at 60-70 °C led to decomposition of the starting material **335** (Entries 1-3). When the reactions were repeated at room temperature with or without base, it was observed by ^1H NMR spectroscopy that silyl ketene acetal **336** had not formed (Entries 4 and 5). Instead, epimerisation of morpholinone **335** had occurred. Morpholinone **335** might have been very acid-sensitive such that a trace amount of triflic acid in *i*Pr_3SiOTf would have triggered epimerisation *via* an ionisation–reassociation pathway.

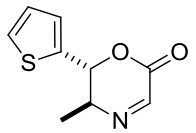


Scheme 111: Attempted de-aromatising rearrangement of morpholinone **335**.

Entry	Conditions	Result
1	*i*Pr_3SiOTf, Et_3N, PhMe, 70 °C, O/N	Decomposition
2	*i*Pr_3SiOTf, *i*Pr_2NEt, PhMe, 60 °C, 5 h	Decomposition
3	*i*Pr_3SiOTf, DBU, PhMe, 70 °C, O/N	Decomposition
4	*i*Pr_3SiOTf, Et_3N, d_8-toluene, rt, 5 min	Epimerisation of **335**
5	*i*Pr_3SiOTf, d_8-toluene, rt, 5 min	Epimerisation of **335**
6	LiHMDS, Me_3SiCl, THF, −78 °C to rt, O/N	75% **335**
7	LiHMDS, *t*$BuMe_2SiCl$, THF, −78 °C, 1 h	68% **335**
8	LiHMDS, *t*$BuMe_2SiCl$, THF, −78 °C to rt, O/N	Mixture of **335** and **338**

Table 9: Reaction conditions for the rearrangement of morpholinone **335**.

Under basic rearrangement conditions using LiHMDS and *t*BuMe$_2$SiCl at −78 °C, no rearrangement was observed after work-up with 1 M AcOH (Entry 7). When the experiment was repeated and warmed up to room temperature, the tosyl group was eliminated and imine **338** was isolated (Entry 8, Fig. 15).



338

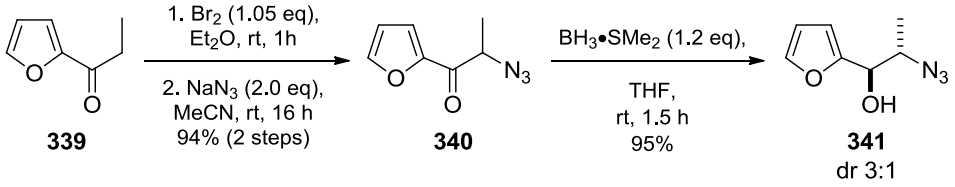
Fig. 15: Imine **338**.

3.5.6. Synthesis of 2-propionylfuran-derived morpholinones

The failure of the rearrangement of thienyl-substituted morpholinone **335** could have been attributed to the high resonance energy and stability of the thiophene ring. Our focus was next shifted on synthesising a furan-substituted morpholinone in hope that the furan ring, having lower resonance energy, might be more reactive.

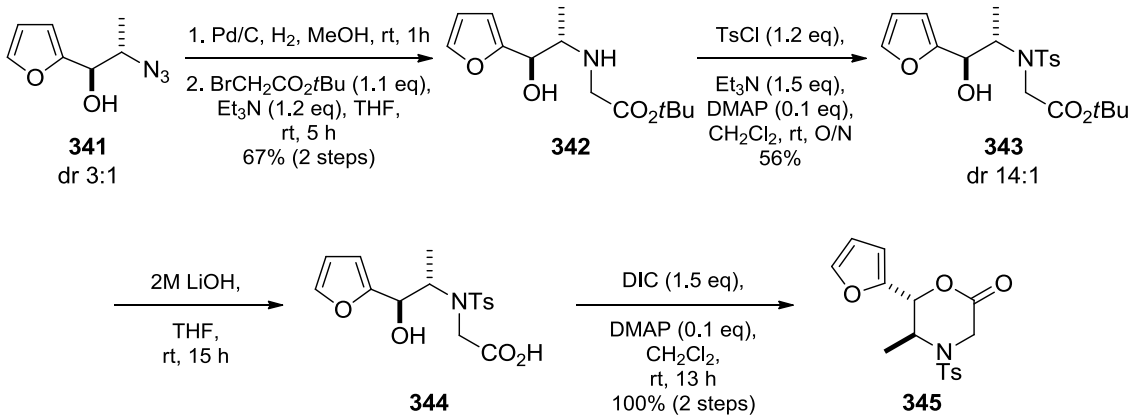
Employing an identical synthetic route to that developed previously, 2-propionylfuran **339** was first brominated at the α-position (Scheme 112). Mono-bromination of ketone **339** was carefully controlled by using only 1.05 eq of bromine followed by quenching the reaction as soon as the bromine addition was completed. The bromide product was unstable over silica gel and therefore the crude mixture was treated directly with sodium azide to give azide **340** in 94% over two steps. Reduction of the ketone was performed by adding borane dimethylsulfide complex to azide **340** and this gave alcohol **341** in 95% yield. Unfortunately, reaction of the furan derivative was less selective than that of its thiophene counterpart, giving a dr of only 3:1 (*anti* / *syn*). It was assumed that the reduction had proceeded with *anti*-selectivity similar to thiophene **328**. Reversing the

order of addition led to a poorer selectivity and gave alcohol **341** in a dr of 2:1 (as determined from the crude ^{1}H NMR spectrum).



Scheme 112: Synthesis of alcohol **341** from 2-propionylfuran **339**.

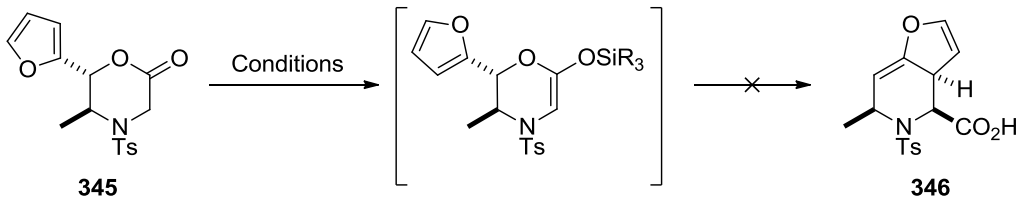
Hydrogenation of a 3:1 diastereomeric mixture of azide **341** followed by mono *N*-alkylation of the crude amino-alcohol with *tert*-butyl bromoacetate gave ester **342** in 67% over two steps (Scheme 113). Protection of the amine with TsCl gave the product as a 3:1 mixture of diastereomers. As before, trituration of the products in TBME improved the dr of major diastereomer **343** significantly. Saponification followed by DIC-mediated cyclisation of hydroxy-acid **344** finally gave the desired morpholinone **345** in quantitative yield over two steps.



Scheme 113: Synthesis of morpholinone **345** from amine **341**.

3.5.7. De-aromatising Ireland–Claisen rearrangement of 2-propionylfuran-derived morpholinone

Rearrangement of **345** was investigated under several conditions, which are summarised in Table 10 (Scheme 114). Disappointingly, standard *i*Pr_3SiOTf–Et_3N condition only led to decomposition of the starting material (Entry 1). Other rearrangement conditions with BSA or *t*$BuMe_2$SiCl did not give product **346** (Entries 2 and 3).



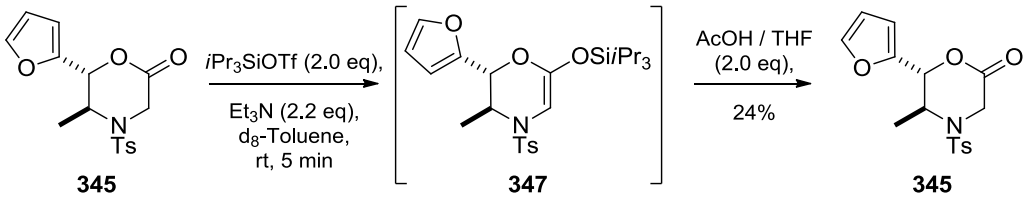
345 **346**

Scheme 114: Attempted de-aromatising rearrangement of morpholinone **345**.

Entry	Conditions	Result
1	*i*Pr_3SiOTf, Et_3N, PhMe, 85 °C, 6 h	Decomposition
2	BSA, Et_3N, MeCN, m/w, 170 °C, 30 min	No reaction
3	LiHMDS, *t*$BuMe_2$SiCl, THF, −78 °C to rt, O/N	No reaction

Table 10: Reaction conditions for the rearrangement of morpholinone **335**.

A control experiment was carried out, using ^{1}H NMR spectroscopy to verify the presence of silyl ketene acetal **347** (Scheme 115). Morpholinone **345** was first treated with *i*Pr_3SiOTf and Et_3N, and then the crude silyl ketene acetal was hydrolysed with stoichiometric amount of acetic acid. However, morpholinone **345** was only obtained in 24% yield and no other organic materials could be observed or isolated. The ^{1}H NMR spectrum of the mixture after addition of *i*Pr_3SiOTf to the substrate (Fig 16, bottom) indicated that the starting material (Fig 16, top) had been consumed, but the spectrum of the new product formed did not resemble that of silyl ketene acetal **347**.



Scheme 115: Control experiment of morpholinone **345**.

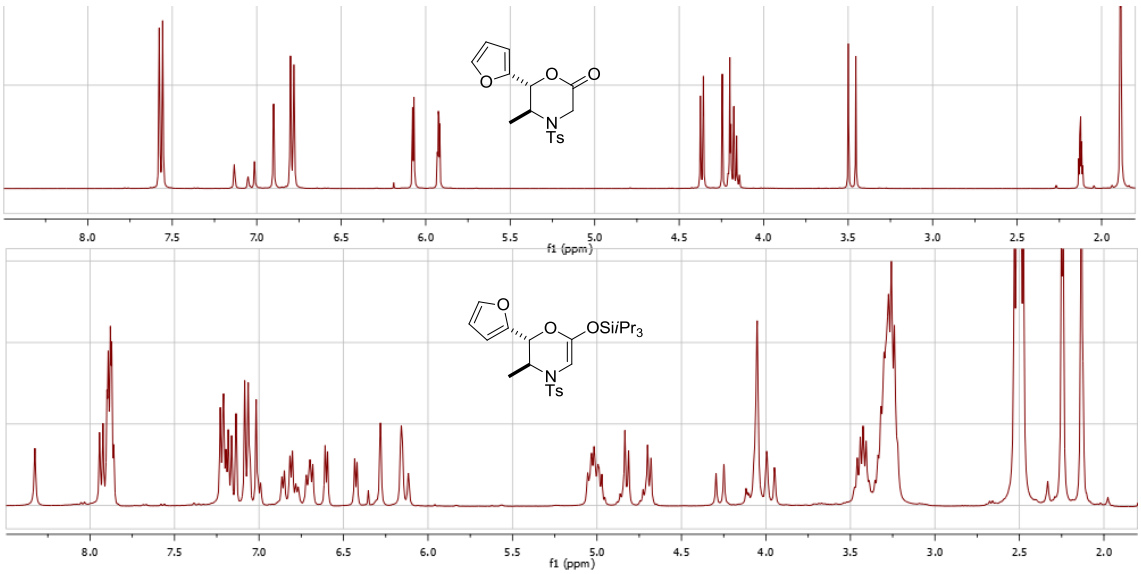


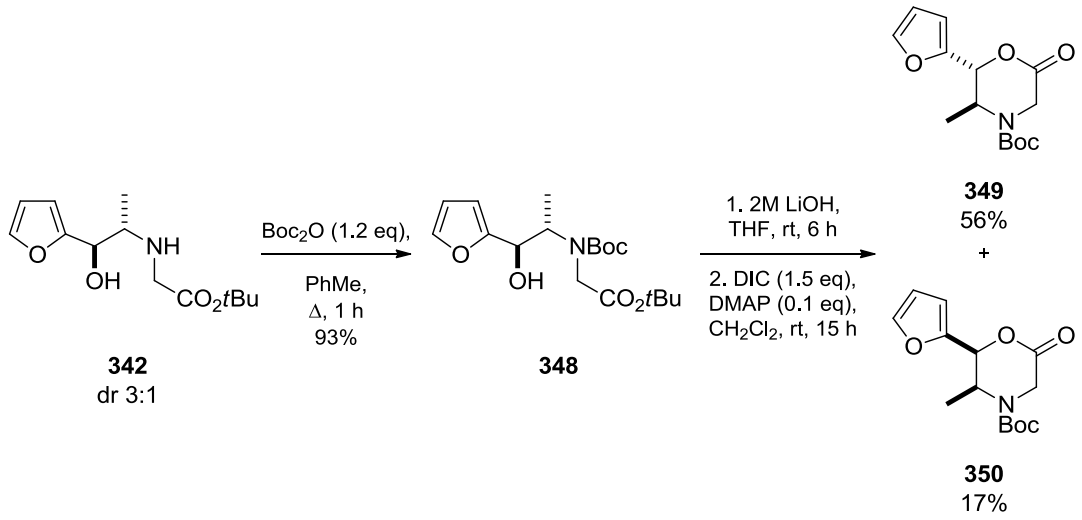
Fig. 16: ^{1}H NMR spectra of morpholinone **345** (top) and silyl ketene acetal **347** (bottom) in d_8-toluene at room temperature.

3.5.8. Investigation of 2-propionylfuran-derived morpholinones as dCr precursors

It was unclear if the failure of the rearrangement was due to the lack of reactivity of the substrate, or if the rearrangement conditions were too harsh, thus leading to decomposition. On the other hand, typical dCr conditions are relatively mild and it was therefore planned to investigate dCr rearrangements of some α-sulfonylfuran precursors in hope that it might eliminate any decomposition issues.

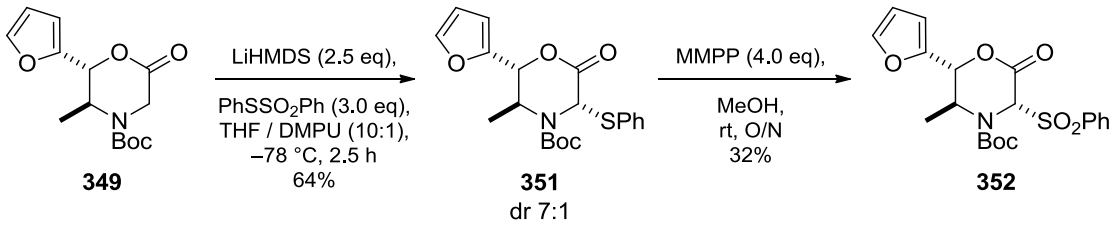
It was known that *N*-Ts morpholinones are unsuitable substrates for the base–sulfinylation methodology (see section 3.2.1). Hence, an *N*-Boc morpholinone substrate was prepared instead.

Starting from a 3:1 diastereomeric mixture of amine **342**, the secondary nitrogen was protected with Boc_2O to give carbamate **348** (Scheme 116). Saponification with aqueous LiOH followed by DIC-mediated cyclisation gave the desired morpholinones **349** and **350**, and the diastereomers could be resolved at this stage.



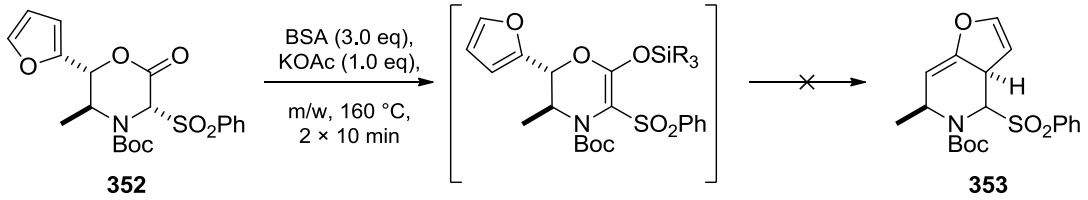
Scheme 116: Synthesis of morpholinones **349** and **350** from amine **342**.

Morpholinone **349** was first premixed with $PhSSO_2Ph$ followed by addition of LiHMDS at –78 °C. The reaction was stirred for 2.5 h and sulfide **351** was obtained in 64% yield with a dr of 7:1 (Scheme 117). Oxidation of the sulfide with MMPP gave sulfone **352** in only 32% yield even though the starting material was consumed. The poor yield was attributed to loss of product during work-up as sulfone **352** is water-soluble. Other oxidants such as mCPBA, Oxone®, or AcOH / H_2O_2 were tried, but were found to be inferior to MMPP.



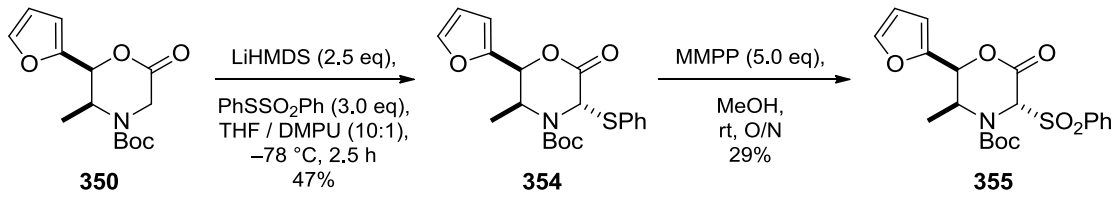
Scheme 117: α-Sulfinylation and oxidation of morpholinone **349**.

The dCr reaction of sulfone **352** was performed using the standard dCr procedure with 3 eq of BSA and 1 eq of KOAc under microwave irradiation at 160 °C (Scheme 118). After two pulses of 10 min, all the starting material was consumed and there were two liquid layers formed in the microwave vial. Analysis of the crude mixture indicated no formation of product **353** and the starting material had decomposed into an intractable mixture.



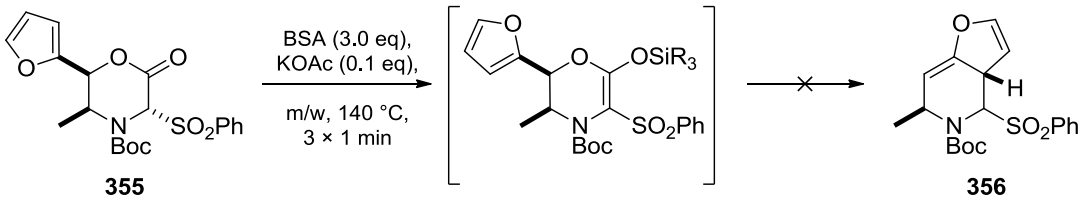
Scheme 118: Attempted de-aromatising dCr reaction of morpholinone **352**.

We were disappointed with the above result and wanted to further investigate the reactivity of the minor diastereomer. The dCr substrate of the minor diastereomer was prepared by sulfinylation of morpholinone **350** using the same procedure and sulfide **354** was obtained in 47% yield as a single diastereomer (Scheme 119). Unlike its other diastereomer **349**, bis-sulfinylation occurred with morpholinone **350** and gave a significant amount of bis-sulfide product in 20% yield. Oxidation to sulfone **355** was also not straightforward and the best conditions were with MMPP, which gave sulfone **355** in 29% yield.



Scheme 119: α-Sulfinylation and oxidation of morpholinone **350**.

Rearrangement was repeated with the minor diastereomer **355** under microwave irradiation conditions (Scheme 120) to give sulfone **356**. However after 3 pulses of 1 min, decomposition of the starting material was observed. This was confirmed by ^{1}H NMR spectroscopic analysis of the crude mixture.



355 **356**

Scheme 120: Attempted de-aromatising dCr reaction of minor diastereomer **355**.

3.6. Conclusion

A variety of novel 5,6-divinyl *cis*-morpholinones with different *N*-protecting groups was synthesised *via* a reliable route. Functionalisation of the C-3 positions of morpholinones **243** and **256** with LiHMDS and $PhSSO_2Ph$ was achieved. Disappointingly, the Ireland–Claisen and dCr reactions of *N*-Boc and *N*-CBz morpholinones **256** and **265** were unsuccessful. It was hypothesised that steric interactions between the *N*-protecting group and the non-participating vinyl groups on C-5 caused the 5,6-divinyl *cis*-morpholinone substrates to adopt half-chair conformations which prevented mutual approach of the ketene acetal and participating C-6 vinyl groups.

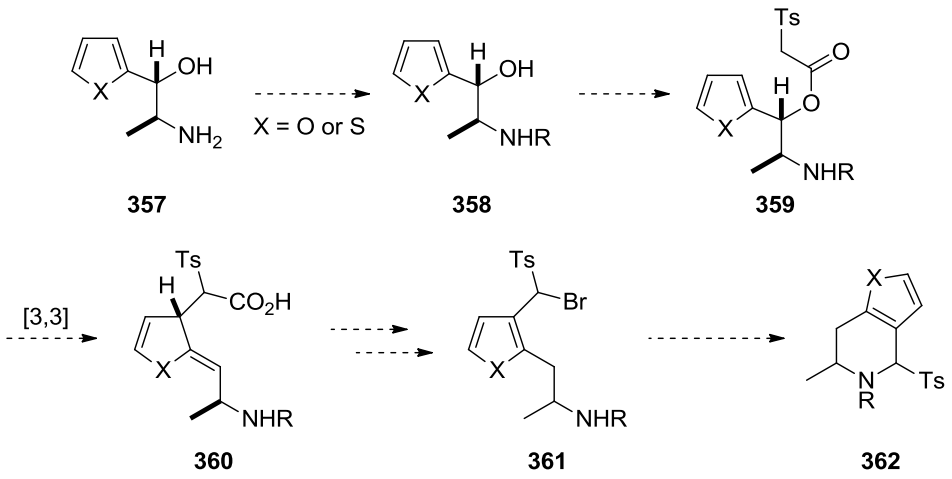
Next, the synthesis of some L-alanine-derived *trans*-morpholinones was developed. Ireland–Claisen rearrangements of morpholinones **281** and **286** were stereospecific and gave novel tetrahydropyridines **284** and **290** respectively in good yields. The vinyl bond of morpholinone **286** could be functionalised by cross-coupling metathesis with styryl derivatives in good yields. However, no rearrangement products could be obtained from styryl-substituted products.

It was anticipated that rearrangement of the novel L-proline-derived bicyclic morpholinone **297** would give indolizidine intermediate **298**. However, ^{1}H NMR studies of the rearrangement showed that degradation of **297** had occurred, giving diene **303** instead.

Lastly, some 6-thienyl and 6-furanyl morpholinones were synthesised. During the investigation, a highly diastereoselective reduction of 2-thienyl ketone **327** was achieved though reaction of the furanyl analogue **340** was less selective. Attempts to effect rearrangement of these morpholinones under Ireland–Claisen and dCr conditions were unsuccessful.

4. De-aromatising dCr reactions of acyclic thienyl precursors

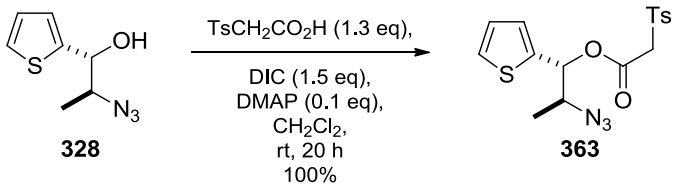
An alternative strategy towards the formation of some unusual bicyclic heterocycles could be achieved with Claisen rearrangements prior to cyclisation. For example, the amino-alcohol **357** of furan or thiophene could be mono-protected as amine **358** (Scheme 121). Esterification with tosylacetic acid would give the Claisen substrates **359** in a concise route employing previously-developed procedures. The de-aromatising dCr reactions of acyclic substrates are well-documented within the Craig group as discussed earlier (see section 1.2.2.1, **149** and **151**) and we hope that the rearrangements would give the de-aromatised products **360**. Re-aromatisation of **360** followed by dehomologation would give bromides **361**. Finally, a late-stage 6-*exo* cyclisation would give heteroaromatic products **362**.



Scheme 121: Proposed alternative towards the formation of heteroaromatic **362**.

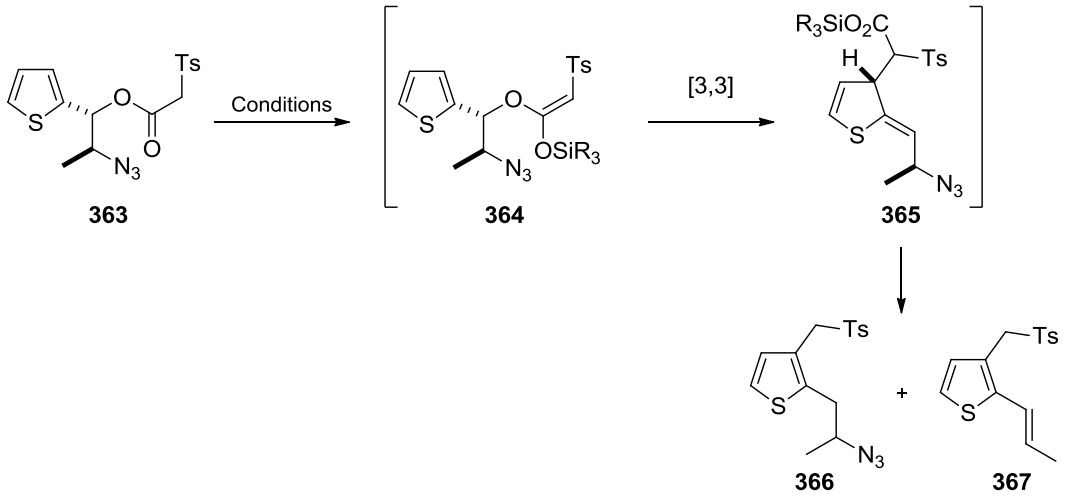
4.1. Claisen rearrangement of azide-containing tosylacetate

First, it was planned to utilise the azide functional group of azide **328** as a masked amine. Prior experiences within the Craig group demonstrated the stability of azides under Claisen rearrangement conditions[91] and the azide group could be easily hydrogentated to reveal the amine when necessary. Therefore, esterification of the previously synthesised alcohol **328** was performed with tosylacetic acid which gave ester **363** in a quantitative yield (Scheme 122).



Scheme 122: DIC-mediated esterification for the formation of ester **363**.

With the Claisen precursor in hand, ester **363** was subjected to a variety of Ireland–Claisen rearrangement conditions (Table 11). Silyl ketene acetal **364** should rearrange to give the silyl ester **365** (Scheme 123). In all cases, total conversion was attained (except Entry 3) and decarboxylation could not be prevented; hence it was not possible to isolate the de-aromatised heterocyclic product.



Scheme 123: [3,3]-Rearrangement of ester **363**.

Entry	Conditions	366	367 (*E*/*Z*)
1	iPr$_3$SiOTf (2 eq), Et$_3$N (1.5 eq), PhMe, Δ, 18 h	11%	41% (10:1)
2	BSA (3 eq), Et$_3$N (1.5 eq), MeCN, Δ, 14 h	8%	59% (15:1)
3[*]	BSA (3 eq), Et$_3$N (1.2 eq), MeCN, 60 °C, 18 h	4%	22% (19:1)
4	BSA (3 eq), Et$_3$N (1.2 eq), MeCN, rt, 4 d	-	-
5	BSA (2 eq), MeCN, Δ, 18 h	-	57% (5:1)
6	BSA (2 eq), MeCN, 60 °C, 18 h	-	-

Table 11: Reaction conditions for the rearrangement of ester **363**.
[*] **363** retrieved in 54%

Trace amounts of the re-aromatised rearrangement product **366** were isolated in some cases (Entries 1-3). However, the major product of the rearrangement was alkene **367**, which was predominantly obtained as an *E*-isomer resulting from elimination of the azido-group of **366**. Lowering the temperature did not prevent re-aromatisation of product **365**. At 60 °C, alkene **367** was obtained as the major product and the reaction was incomplete (Entry 3). It was suspected that the mildly basic conditions could have initiated the decarboxylation and elimination processes. Switching to base-free conditions led solely to the formation of alkene **367** under reflux conditions (Entry 5) whereas at 60 °C, no rearrangement occurred (Entry 6).

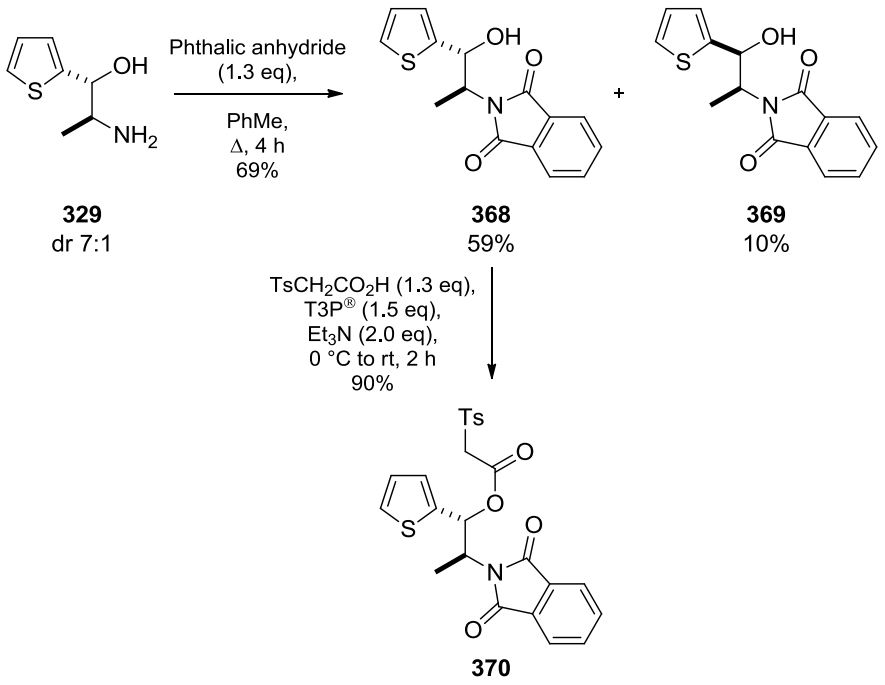
It was concluded that the silyl ester **365** was susceptible to decarboxylation as soon as it had formed. This was immediately followed by concomitant re-aromatisation of the heterocycle. In addition, elimination of azide **366** was favoured and gave the thermodynamically-stable conjugated alkene **367** as the major product of this rearrangement.

4.2. Claisen rearrangements of phthalimide-containing acetates

4.2.1. Synthesis of phthalimide-containing tosylacetate

Encouraged by the rearrangement reactions of the azide precursor, it was decided to protect the amino group as a phthalimide so that the rearrangements of phthalimido precursors could be investigated. The phthalimide group served two purposes; it is not as good a leaving group as the azide as well as protects both the acidic protons of the nitrogen at the same time.

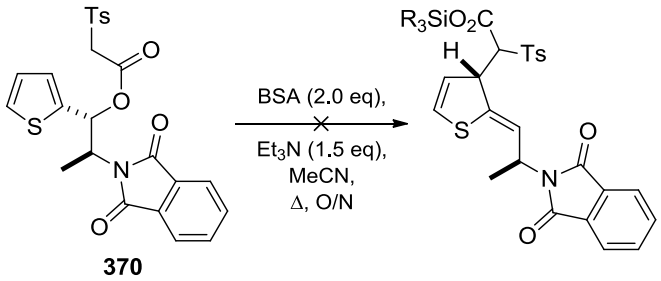
A 7:1 diastereomeric mixture of amino-alcohol **329** was heated with phthalic anhydride for 4 h and phthalimides **368** and **369** were obtained in 69% (Scheme 124). It was crucial not to heat the reaction mixture for more than 4 h as a loss in the diastereomeric ratio was observed. On a small scale, diastereomers **368** and **369** could be resolved over silica gel but on a larger scale, it was more efficient to obtain the major diastereomer by recrystallisation of the mixture from hexane–ethyl acetate. Esterification of the major diastereomer **368** with tosylacetic acid under DIC and DMAP-mediated condition did not give total conversion to ester **370** even after 48 h. It was also difficult to separate the product from the urea by-product of DIC. By switching to T3P®-mediated coupling, a highly efficient and low-toxicity coupling reagent, the esterification proceeded with total conversion and gave clean formation of tosylacetate **370** in just 2 h.



Scheme 124: Synthesis of rearrangement precursor **370**.

4.2.2. De-aromatising dCr reaction of phthalimide-containing tosylacetate

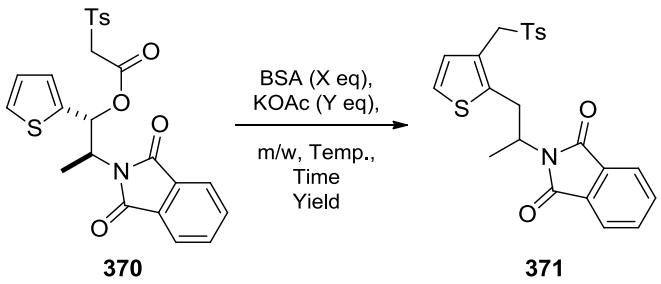
The Ireland–Claisen rearrangement of **370** was initially investigated under typical BSA and Et_3N conditions but no rearrangement occurred, unlike with the previous azide substrate (Scheme 125).



Scheme 125: Ireland–Claisen rearrangement of ester **370**.

Therefore, it was decided to focus on the dCr reactions of **370** instead (Scheme 126, Table 12). Treatment of acetate **370** under standard dCr conditions with BSA and sub-stoichiometric KOAc at 160 °C in the microwave gave the re-aromatised product

371 in 37% yield (Entry 1). The reaction seemed to be indifferent when a stoichiometric amount of KOAc was used (Entry 6) but the presence of KOAc was found to be essential (Entry 5). It was hoped that by lowering the temperature, the de-aromatised product could be isolated. However, no rearrangement was observed at 125 °C (Entry 3). At 140 °C, the reaction proceeded with 50% conversion (as determined by ^{1}H NMR spectroscopy) to give product **371** (Entries 2 and 4). No attempts were made to isolate **371** in entries 2 and 4 because it was not possible to distinguish **370** from **371** by TLC analysis.



370 **371**

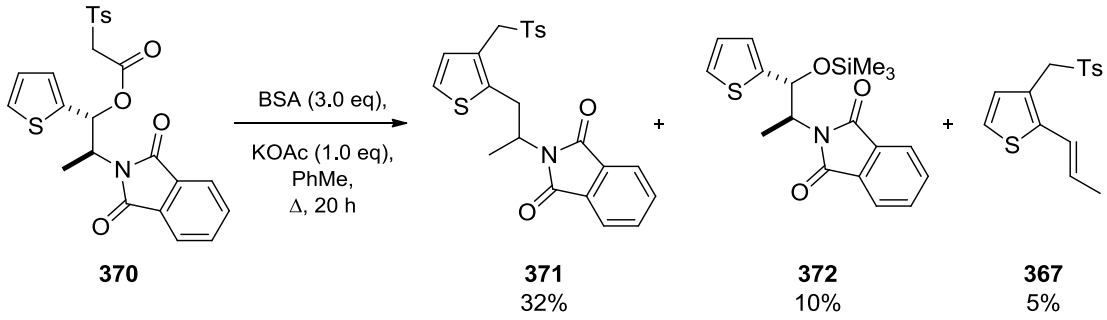
Scheme 126: dCr Reactions of ester **370** under microwave conditions.

Entry	X	Y	Temp.	Time	Yield
1	6.0	0.1	160 °C	2 × 1 min	37%
2	6.0	0.1	140 °C	1 min	50%*
3	6.0	0.1	125 °C	1 min	-
4	6.0	1.5	140 °C	1 min, then 2 × 3 min	50%*
5	6.0	-	140 °C	1 min, then 2 × 3 min	-
6	6.0	1.1	170 °C; then 160 °C	5 min; then 5 min	40%

Table 12: Reaction conditions for the rearrangement of ester **370**.
* 50% conversion as determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

The rearrangement also proceeded under thermal conditions in toluene (Scheme 127). Aside from obtaining re-aromatised product **371** in 32% yield, it gave other by-products such as ether **372** in 10% yield and alkene **367** in 5% yield. The formation of the

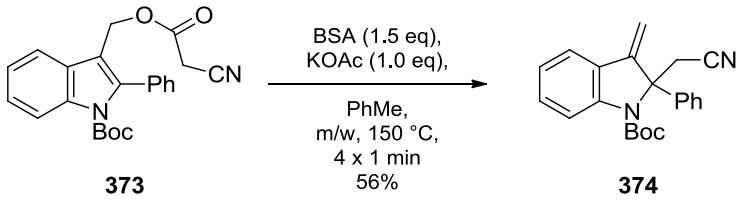
by-products was probably initiated by the prolonged heating conditions as compared to the rapid microwave conditions. In all cases, no de-aromatised rearrangement product was observed by TLC analysis or ^{1}H NMR spectroscopy.



Scheme 127: dCr Reaction of ester **370** under thermal condition.

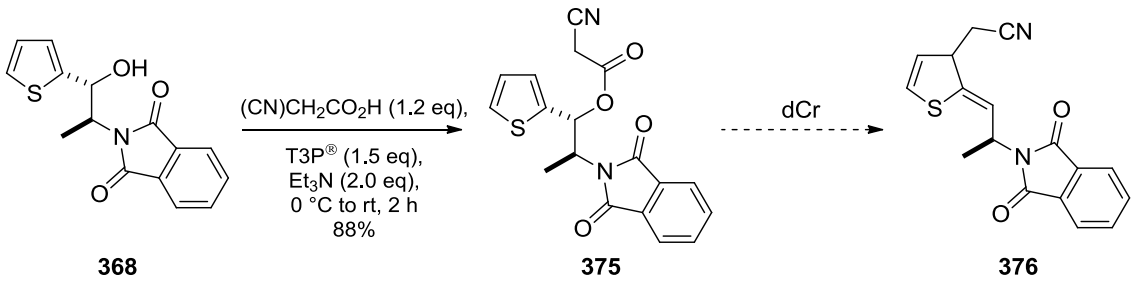
4.2.3. Synthesis of phthalimide-containing cyanoacetate

Aside from having a tosyl group at the α-position in place for dCr reactions, it has been established that the dCr reaction could proceed with other α-substituents such as a sulfoximine.[65(a), 67] More recently, it was established that 3-substituted indole α-cyanoacetate **373** underwent dCr reaction to give de-aromatised 3-methyleneindoline **374** in 56% yield (Scheme 128).[53(c)]



Scheme 128: De-aromatising dCr reaction of cyanoacetate **373**.

We planned to also investigate the de-aromatising dCr methodology on the cyanoacetic ester of alcohol **368**. Ester **375** was prepared by the coupling reaction of alcohol **368** and cyanoacetic acid mediated by T3P® (Scheme 129). With precursor **375** in hand, dCr reaction would give the desired de-aromatised product **376**.

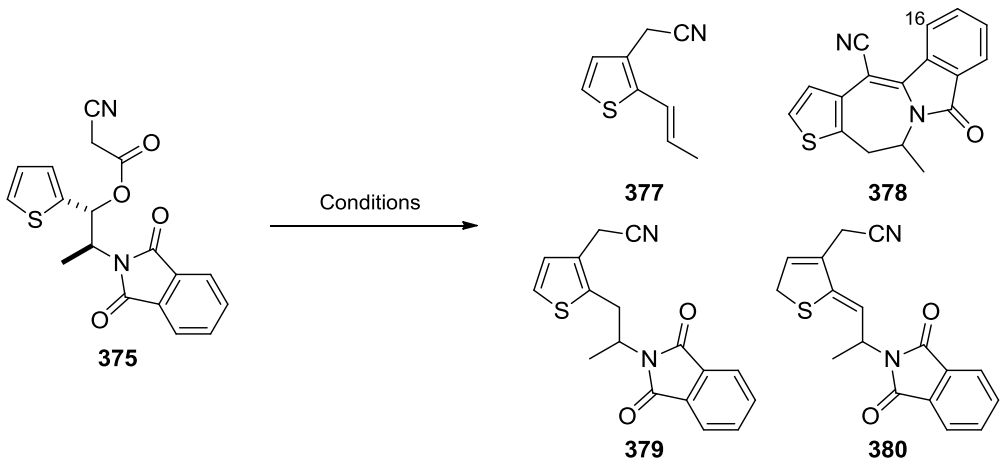


368 **375** **376**

Scheme 129: Synthesis of cyanoacetate **375**.

4.2.4. De-aromatising dCr reaction of phthalimide-containing cyanoacetate

The dCr reaction of cyanoacetate **375** was investigated under a variety of conditions with BSA and KOAc (Scheme 130, Table 13). The reaction gave a mixture of products **377**-**380**, all of which were isolated and characterised by standard analytical techniques. In all cases, no de-aromatised product **376** could be obtained. In some cases, it re-aromatised to give thiophene **379** (Entries 1, 2 and 5). Moreover, dihydrothiophene **380** was isolated in trace amounts (Entries 1 and 5) and it was predicted that **380** is more thermodynamically-stable than **376** due to conjugation with the exocyclic double bond. Dihydrothiophene **380** was confirmed by mass spectrometry to have the same mass as its regioisomer **379**. In addition, the ^{1}H NMR spectrum displayed two sets of AB quartet methylene peaks and also a doublet at δ 5.80 ppm corresponding to the methine hydrogen of the exocyclic double bond.



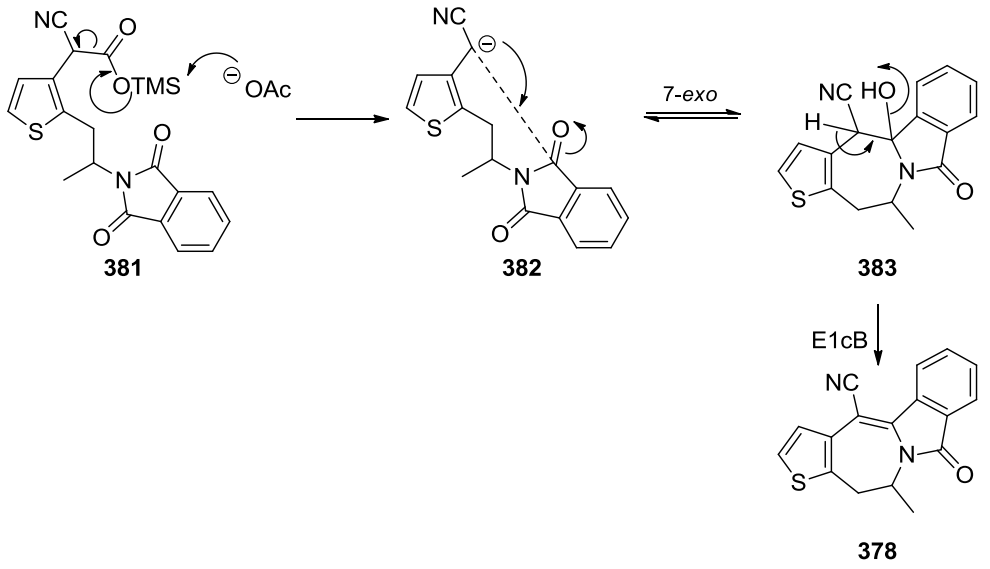
Scheme 130: dCr Reaction of ester **375**.

Entry	Conditions	377	378	379	380
1	BSA (3 eq), KOAc (0.1 eq), m/w, 160 °C, 2 × 1 min	1%	13%	14%	4%
2[#]	BSA (4 eq), KOAc (1.5 eq), m/w, 120 °C, 2 × 1 min then 5 min	10%	25%	5%	-
3[*]	BSA (6 eq), KOAc (1.5 eq), K_2CO_3, m/w, 120 °C, 1 × 1 min, 1 × 5 min then 1 × 10 min	8%	23%	-	-
4	BSA (3 eq), KOAc (1.0 eq), PhMe, m/w, 120 °C, 49 min[+], 130 °C, 2 × 60 min then 135 °C, 60 min	17%	30%	-	-
5	BSA (3 eq), KOAc (1 eq), PhMe, 100 °C heated in sealed tube, 15 h	6%	41%	22%	5%

Table 13: Reaction conditions for the rearrangement of ester **375**.
[*] **372** also isolated in 3%; [#] Ester **375** retrieved in 6%; [+] Total time of 4 pulses (1, 3, 15 and 30 min).

Unexpectedly, the major product obtained from this reaction was a relatively non-polar unknown compound. This compound was later identified to be the highly-conjugated novel tetracycle **378**. The identity of **378** was confirmed by IR spectroscopy which indicated that the nitrile band was still present at 2212 cm^{-1}. Furthermore, ^1H NMR spectroscopy indicated an unusually low-field doublet at δ 8.79 ppm which corresponds to the most electron-deficient H-16 of the benzene ring.[106] The optimal reaction conditions are detailed in Entry 5. When the mixture was heated in a sealed tube at 100 °C for 15 h, 41% of tetracycle **378** and 22% of dihydrothiophene **379** were obtained.

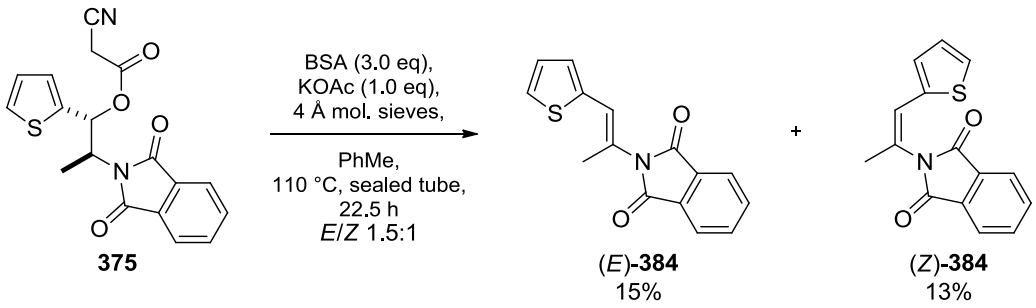
Tetracycle **378** was predicted to have formed *via* an intermediate of the dCr mechanism. It was assumed that re-aromatisation occurred before decarboxylation to give silyl ester **381** (Scheme 131). Desilylation and decarboxylation of **381** with a molecule of acetate gave the corresponding anion **382**. Instead of proton-abstraction to furnish the dCr product as in the dCr mechanism, condensation of the anion with the phthalimide gave the cyclised 7-*exo*-product **383**. This reversible addition could be promoted by the subsequent E1cB step with loss of a water molecule to give the final condensation product **378**, which is highly-stabilised by conjugation. We are pleased to report this as the first example where the anion intermediate could be further manipulated instead of protonation after decarboxylation in a dCr reaction. This might have been possible because the cyano-group could stabilise the anion by resonance rather than by inductive effect in the case of a tosyl-group.



Scheme 131: Postulated mechanism for the formation of condensation product **378**.

Encouraged by these precedents, optimisation of the dCr reaction was further attempted under thermal conditions. With the aid of 4 Å molecular sieves, it was hoped that it might promote the E1cB step, thus giving the total conversion of dihydrothiophene **379** into tetracycle **378**. However, no previously observed products (**377**-**380**) were formed

(Scheme 132). Instead, alkenes **384** were obtained as a mixture of geometric isomers in a ratio of 1.5:1 (*E*/*Z*) and the isomers were resolved over silica gel. It was suspected that the aluminosilicate composition of the molecular sieves might have acted as a Lewis-acid in mediating the elimination of the cyanoacetate group.



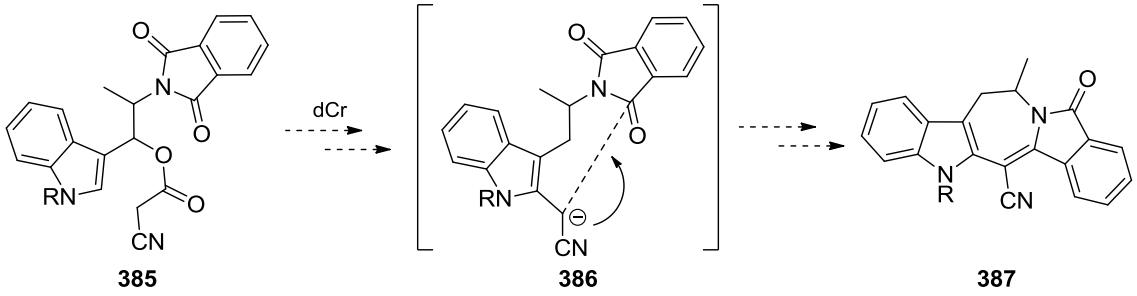
Scheme 132: dCr Reaction of ester **375** with molecular sieves.

4.3. Conclusion

The initial plan for the synthesis of bicyclic heterocycle **362** could not be realised because attempts to generate **360** *via* the Ireland-Claisen rearrangement were unsuccessful. [3,3]-Rearrangements of substrate **359** with different *N*-protecting groups (azide and phthalimide) were investigated. Under different reaction conditions, the rearrangement mechanism always proceeded with decarboxylation and de-aromatisation, followed by re-aromatisation of the thiophene intermediate. However, interesting results were obtained with dCr reactions involving phthalimide-containing cyanoacetate **375**. Notably, a highly conjugated intermediate **378** was isolated in 41% yield. This was believed to have resulted from intramolecular condensation instead of protonation of the anionic intermediate after decarboxylation in the dCr reaction.

4.4. Future work

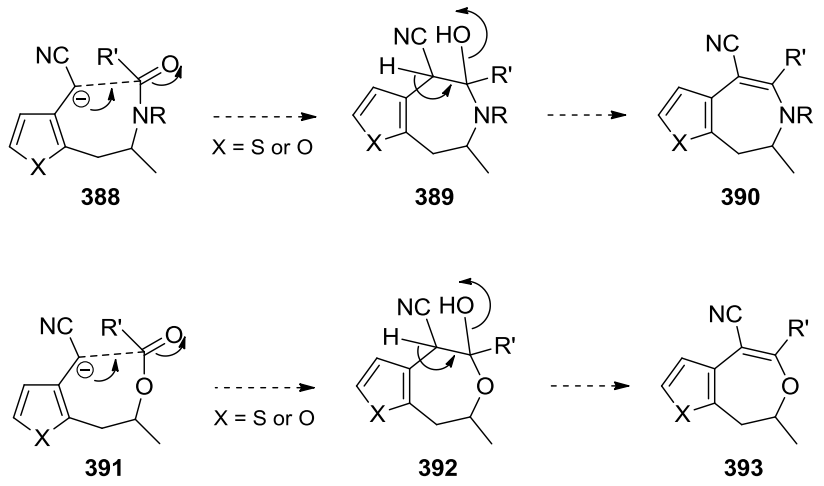
In addition to further optimisation of the dCr reaction involving 2-substituted cyanoacetate **375**, the reaction could be repeated for 3-substituted indole **385** (Scheme 133). This would form anion **386** as an intermediate after dCr reaction and re-aromatisation. Intramolecular acylation of the anion with the phthalimide group would give highly conjugated polycyclic product **387**.



385 **386** **387**

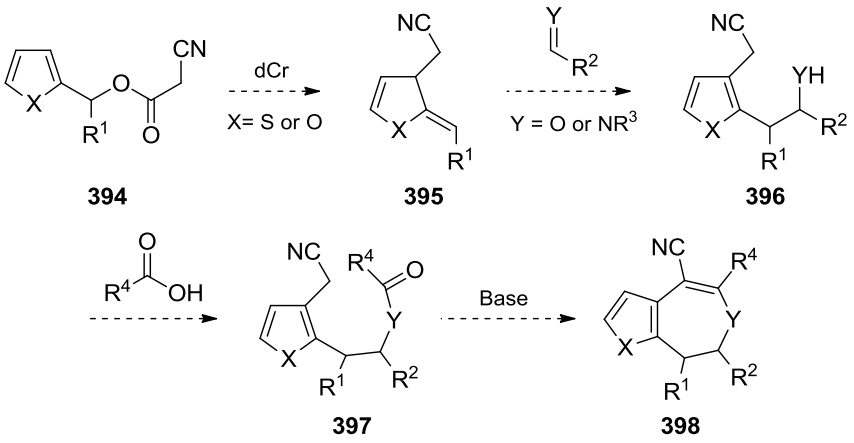
Scheme 133: Proposed dCr reaction of **385** to form polycyclic product **387**.

In addition, the behaviour of the anionic dCr intermediate could be investigated. It is envisaged that amino-alcohol **329** could be protected as amides (Scheme 134). Subsequent transformations and dCr reaction would form intermediate anions **388** which could be intramolecularly acylated with the amide group to give **389**. It is envisaged that this would eliminate to give conjugated bicyclic products **390**. Similarly, esters **391** could also be investigated as electrophiles to give hemiacetal intermediates **392** and eventually products **393**. This route could provide an access into unusual poly-substituted furan- or thiophene-fused bicyclic heterocycles which could be potential pharmacophores.



Scheme 134: Proposed intramolecular trapping of dCr intermediates **388** and **391** to form bicylic products.

Another route in the formation of such bicyclic heterocycles could be attempted from cyanoacetate **394** (Scheme 135). The dCr reaction of the analogous tosylacetate (eg. **149** to **150**) has already been investigated, and it is expected that dCr reaction of **394** would give heterocycle **395**. Lewis acid-mediated intermolecular addition of **395** to an imine or aldehyde would give **396**. Subsequent intermolecular condensation with a carboxylic acid would give either ester or amide **397**, which would cyclise under basic conditions to give highly substituted bicyclic product **398**.

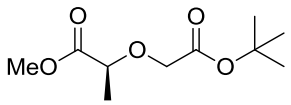


Scheme 135: Proposed dCr reaction of **394** to form bicyclic product **398**.

5. Experimental

General: All reactions and manipulations were performed under an inert atmosphere of nitrogen unless otherwise stated. Diethyl ether and tetrahydrofuran were distilled over sodium benzophenone ketyl and used immediately. Dichloromethane, triethylamine, acetonitrile and DMPU were distilled from calcium hydride. Toluene was distilled from sodium. All other chemicals were used as purchased from commercial sources. Thin layer chromatography (TLC) was performed on Merck Kieselgel aluminium-back 60 F_{254} plates, using UV light (254 nm) as visualising agent and vanillin or potassium permanganate as developing agents. Preparative TLC was performed using Merck Kieselgel glass-back 60 F_{254} plates. Flash column chromatography was performed using BDH silica gel (particle size 40–63 μm). Melting points were recorded on a Stuart Scientific SMP1 melting point apparatus in open capillaries and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter using a 1 dm path length; concentrations are given as g / 100 mL. Infrared spectra were recorded on Perkin–Elmer Spectrum RX and 100 FT-IR spectrometers. NMR spectra were recorded at room temperature on Bruker DRX 400, AV 400 or AV 500 instruments in $CDCl_3$, unless otherwise stated. *J* values are reported in hertz and chemical shifts in ppm. Mass spectra were recorded on Micromass Platform II and Micromass AutoSpec-Q instruments by the mass spectrometry service at Imperial College London. Elemental analyses were performed by the London Metropolitan University microanalytical service. Microwave reactions were performed in a Biotage Initiator instrument.

(*S*)-Methyl 2-(2-*tert*-butoxy-2-oxoethoxy)propanoate (213)



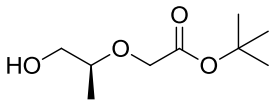
213

(Method A) To a stirred suspension of prewashed sodium hydride (1.27 g of a 60% dispersion in mineral oil, 31.8 mmol, 1.3 eq) in THF (30 mL) at 0 °C was added methyl (*S*)-(–)-lactate **212** (4.00 g, 38.4 mmol, 1.0 eq). The suspension was warmed to rt and stirred for 75 min before adding *tert*-butyl bromoacetate (8.06 mL, 50.5 mmol, 1.3 eq) dropwise. After 2 h, the mixture was poured into saturated aqueous NH_4Cl (50 mL), the layers were separated and the aqueous layer was further extracted with Et_2O (100 mL). The combined organic extracts were washed with water (200 mL), brine (200 mL) and dried over $MgSO_4$. Concentration under reduced pressure and chromatography of the crude mixture over silica gel (17→20% Et_2O–petrol) gave (*S*)-methyl 2-(2-*tert*-butoxy-2-oxoethoxy)propanoate **213** (5.49 g, 66%) as a colourless oil.

(Method B) To a solution of methyl (*S*)-(–)-lactate **212** (0.5 mL, 5.24 mmol, 1.0 eq) in DMF (25 mL) at 0 °C was added caesium carbonate (2.03 g, 5.76 mmol, 1.1 eq) in 2 portions over 15 min before adding *tert*-butyl bromoacetate (0.97 mL, 6.03 mmol, 1.15 eq) dropwise. After 6 h, the reaction was warmed to rt and left to stir overnight. The mixture was filtered, and the filtrate was diluted with water (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (60 mL), water (2 × 60 mL), brine (60 mL) and dried over $MgSO_4$. Concentration under reduced pressure and chromatography of the crude mixture over silica gel (7% EtOAc–petrol) gave (*S*)-methyl 2-(2-*tert*-butoxy-2-oxoethoxy)propanoate **213** (761 mg, 67%) as a colourless oil.

R_f 0.40 (30% Et_2O–petrol); $[\alpha]_D^{23}$ –83.8 (*c* 1.1, CH_2Cl_2); ν_{max} (neat) 1743, 1369, 1228, 1209, 1127, 1042 cm^{-1}; δ_H (400 MHz) 4.18 (1H, d, *J* 15.5 Hz, C*H*H'), 4.17 (1H, q, *J* 7.0 Hz, C*H*CH_3), 3.97 (1H, d, *J* 15.5 Hz, CH*H'*), 3.77 (3H, s, OCH_3), 1.50 (3H, d, *J* 7.0 Hz, CHC*H*$_3$), 1.49 (9H, s, $(CH_3)_3$); δ_C (100 MHz) 173.1 (*C*O_2CH_3), 169.2 (*C*$O_2(CH_3)_3$), 81.8 (*C*$(CH_3)_3$), 74.9 (*C*HCH_3), 67.4 (CH_2), 52.0 (OCH_3), 28.1 ($(CH_3)_3$) 18.5 (CH*C*H_3); *m/z* (CI) 236 $[M+NH_4]^+$, 180 $[M+H+NH_4-t\text{Bu}]^+$ (Found: $[M+NH_4]^+$, 236.1504. $C_{10}H_{18}O_5$ requires $[M+NH_4]^+$, 236.1498).

(*S*)-*tert*-Butyl 2-(1-hydroxypropan-2-yloxy)acetate (214)

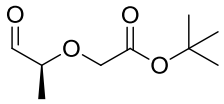


214

To a stirred suspension of diester **213** (14.28 g, 65.4 mmol, 1 eq) and $NaBH_4$ powder (2.79 g, 72.0 mmol, 1.1 eq) in THF (180 mL) at 0 °C was added methanol (36 mL) dropwise *via* a syringe pump over 1 h. Effervescence was observed and the solution was warmed to rt after the addition. After another 1.5 h, citric acid (10 mL) and water (10 mL) was added and THF was removed under reduced pressure. The mixture was diluted with citric acid (100 mL), Et_2O (100 mL) and the organic layer was separated. The aqueous phase was extracted again with Et_2O (100 mL). The combined organic extracts were washed with water (200 mL), brine (200 mL), dried ($MgSO_4$) and filtered over a pad of silica gel. Concentration of the filtrate under reduced pressure gave (*S*)-*tert*-butyl 2-(1-hydroxypropan-2-yloxy)acetate **214** (7.42 g, 60%) as a colourless oil; R_f 0.22 (50% Et_2O–CH_2Cl_2); $[\alpha]_D^{23}$ +68.7 (*c* 1.1, CH_2Cl_2); ν_{max} (neat) 3471 (br), 2971, 2933, 1735, 1369, 1229, 1124, 1047 cm^{-1}; δ_H (400 MHz) 4.16 (1H, d, *J* 17.0 Hz, C*H*H'CO_2), 3.92 (1H, d, *J* 17.0 Hz, CH*H'*CO_2), 3.62-3.49 (3H, m, C*H*CH_3 and C*H*$_2$OH), 2.53 (1H, br, OH), 1.50 (9H, s, $(CH_3)_3$), 1.50 (3H, d, *J* 6.0 Hz, CHC*H*$_3$); δ_C (100 MHz) 171.3

($CO_2(CH_3)_3$), 82.3 ($C(CH_3)_3$), 78.9 ($CHCH_3$), 66.8 (CH_2CO_2), 66.2 (CH_2OH), 28.1 ($(CH_3)_3$) 16.1 ($CHCH_3$); *m/z* (CI) 208 $[M+NH_4]^+$, 152 $[M+H+NH_4-t\text{Bu}]^+$ (Found: $[M+NH_4]^+$, 208.1550. $C_9H_{18}O_4$ requires $[M+NH_4]^+$, 208.1549).

(*S*)-*tert*-Butyl 2-(1-oxopropan-2-yloxy)acetate (215)



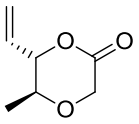
To a stirred solution of oxalyl chloride (1.1 mL, 12.6 mmol, 1.2 eq) in dry CH_2Cl_2 (80 mL) at −78 °C was added DMSO (1.8 mL, 25.2 mmol, 2.4 eq) dropwise and the solution stirred for 30 min before adding a solution of alcohol **214** (2.00 g, 10.5 mmol, 1.0 eq) in CH_2Cl_2 (10 mL). The clear solution was then stirred at −78 °C for 1.5 h in which it gradually turned cloudy. *N*,*N*-Diisopropylethylamine (5.0 mL, 26.3 mmol, 2.5 eq) was added dropwise and the suspension gradually turned clear and it was stirred for another 30 min at −78 °C. It was warmed to rt and stirred for a further 30 min. Saturated aqueous NH_4Cl (20 mL) and water (20 mL) was added to the flask and the layers were separated. The aqueous phase was extracted again with CH_2Cl_2 (40 mL), the combined organic extracts were washed with water (100 mL), brine (100 mL) and dried over $MgSO_4$. Concentration under reduced pressure and chromatography of the crude mixture over silica gel (30% Et_2O–petrol) gave (*S*)-*tert*-butyl 2-(1-oxopropan-2-yloxy)acetate **215** (1.83 g, 93%) as a yellow oil; R_f 0.27 (50% Et_2O–petrol); ν_{max} (neat) 2980, 2937, 1732, 1369, 1231, 1136, 1016 cm^{-1}; δ_H (400 MHz) 9.74 (1H, d, *J* 1.5 Hz, CHO), 4.16 (1H, d, *J* 16.5 Hz, C*H*H'), 4.11 (1H, d, *J* 16.5 Hz, CH*H'*), 3.96 (1H, dq, *J* 7.0, 1.5 Hz, C*H*CH_3), 1.51 (9H, s, $(CH_3)_3$), 1.38 (3H, d, *J* 7.0 Hz, CHC*H*$_3$), δ_C (100 MHz) 202.7 (CHO), 169.2 ($CO_2(CH_3)_3$), 82.2 ($C(CH_3)_3$), 80.8 ($CHCH_3$), 67.7 (CH_2), 28.1 ($(CH_3)_3$), 15.3 ($CHCH_3$).

m/z (CI) 206 $[M+NH_4]^+$, 188 $[M]^+$, 150 $[M+H+NH_4-tBu]^+$ (Found: $[M+NH_4]^+$, 206.1383. $C_9H_{16}O_4$ requires $[M+NH_4]^+$, 206.1392).

Tetrakis[iodo(tri-*n*-butylphosphine)copper(I)] $(CuI{\cdot}PBu_3)_4$ [107]

Copper(I) iodide (10.0 g, 52.6 mmol, 1.1 eq) was dissolved in saturated aqueous sodium iodide (60 mL) and a solution of tributylphosphine (10 g, 49.5 mmol, 1.0 eq) in Et_2O (40 mL) was transferred into the flask *via* a cannula and the solution stirred at rt for 1 h. The layers were separated and the organic layer was washed with saturated aqueous sodium iodide (50 mL) and water (50 mL). Concentration under reduced pressure gave a yellow oil which solidified into a waxy yellow solid when dried *in vacuo*. The solid was dissolved in 9:1 acetone–methanol (25 mL) at rt. The solution was cooled to −20 °C and gave $(CuI{\cdot}PBu_3)_4$ (12.0 g, 58%) as colourless needle; mp 70 °C (lit.[107] mp 75 °C); Further cooling of the filtrate at −10 °C gave a second crop of $(CuI{\cdot}PBu_3)_4$ (1.47 g, 7%) as a colourless solid; mp 70 °C. The copper complex was stored in the freezer in order to slow down the decomposition rate.

(5*S*,6*S*)-5-Methyl-6-vinyl-1,4-dioxan-2-one (211)

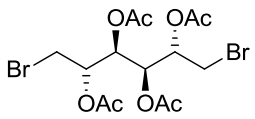


211

To a stirred solution of aldehyde **215** (250 mg, 1.33 mmol, 1.0 eq) in THF (60 mL) was added $(CuI{\cdot}PBu_3)_4$ (784 mg, 0.50 mmol, 0.375 eq) at rt. The solution was cooled to −40 °C and vinylmagnesium bromide (2.28 mL of a 0.7 M solution in THF, 1.60 mmol, 1.2 eq) was added dropwise over 5 min. The dark solution was stirred for 1 h at −40 °C and then allowed to warm to rt and subsequently heated to 40 °C overnight. TLC indicated that the reaction was incomplete, and it was heated to 50 °C for another night.

The solution was poured into saturated aqueous NH_4Cl (100 mL) and the layers were separated. The aqueous phase was extracted with with Et_2O (100 mL) and the combined organic extracts were stirred in saturated aqueous $NaHSO_3$ (150 mL) for 1 h at rt before the layers were separated. The organic phase was washed with brine (200 mL), dried over $MgSO_4$ and filtered over Celite®. Concentration under reduced pressure and chromatography of the crude mixture over silica gel (20% TBME–petrol) gave a 5:1 (*trans* / *cis*) diastereomeric mixture of (5*S*,6*S*)-5-methyl-6-vinyl-1,4-dioxan-2-one **211** (80.0 mg, 40%) as a pale yellow oil; R_f 0.50 (*trans*), 0.40 (*cis*) (5:6 TBME–petrol); ν_{max} (neat) 1743, 1258, 1229, 1152, 1113, 1069, 1019, 941, 904, 872 cm^{-1}; δ_H (400 MHz) 6.00 (1H, ddd, *J* 17.0, 10.5, 7.5 Hz, *cis* C*H*=CH_2), 5.80 (1H, ddd, *J* 17.0, 10.5, 7.0 Hz, *trans* C*H*=CH_2), 5.57 (1H, d, *J* 17.0 Hz, *trans* CH=C*H*H'), 5.49 (1H, d, *J* 10.5 Hz, *cis* CH=C*H*H'), 5.45 (1H, d, *J* 17.0 Hz, *cis* CH=CH*H*'), 5.43 (1H, d, *J* 10.5 Hz, *trans* CH=CH*H*'), 4.79 (1H, dd, *J* 7.5, 3.0 Hz, *cis* CHOCO), 4.66 (1H, dd, *J* 9.0, 7.0 Hz, *trans* CHOCO), 4.50 (1H, d, *J* 17.5 Hz, *trans* C*H*H'), 4.47 (1H, d, *J* 18.0 Hz, *cis* C*H*H'), 4.38 (1H, d, *J* 18.0 Hz, *cis* CH*H*'), 4.30 (1H, d, *J* 17.5 Hz, *trans* CH*H*'), 4.06 (1H, dq, *J* 6.5, 3.0 Hz, *cis* C*H*CH_3), 3.57 (1H, dq, *J* 9.0, 6.5 Hz, *trans* C*H*CH_3), 1.28 (3H, d, *J* 6.5 Hz, *trans* CHC*H*$_3$), 1.22 (3H, d, *J* 6.5 Hz, *cis* CHC*H*$_3$); δ_C (100 MHz) 170.0 (*trans C*=O), 166.9 (*cis C*=O), 131.6 (*trans* vinyl CH), 130.7 (*cis* vinyl CH), 121.5 (*cis* vinyl CH_2), 121.1 (*trans* vinyl CH_2), 85.3 (*trans* CHOCO), 83.2 (*cis* CHO), 72.3 (*trans C*HCH_3), 70.3 (*cis C*HCH_3), 66.8 (*trans* CH_2), 65.3 (*cis* CH_2), 16.5 (*trans* CH*C*H$_3$), 15.5 (*cis* CH*C*H$_3$); *m/z* (CI) 160 $[M+NH_4]^+$ (Found: $[M+NH_4]^+$, 160.0971. $C_7H_{10}O_3$ requires $[M+NH_4]^+$, 160.0974).

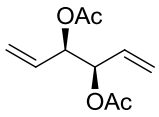
(2*S*,3*S*,4*S*,5*S*)-1,6-Dibromohexane-2,3,4,5-tetrayl tetraacetate (218)[76]



218

D-mannitol **217** (40.0 g, 0.22 mol, 1.0 eq) was suspended in 1,4-dioxane (450 mL), acetyl bromide (40 mL, 0.53 mol, 2.4 eq) was slowly added and the clear solution was stirred for 4 d at rt. The orange solution was concentrated under reduced pressure and the viscous residue was redissolved in anhydrous pyridine (200 mL). Acetic anhydride (166 mL, 1.76 mol, 8.0 eq) was slowly added to it and the solution was stirred at rt overnight. The volatiles were removed under reduced pressure and gave a brown residue which was dissolved in minimal ethanol (70 mL) and left to crystallise overnight to give (2*S*,3*S*,4*S*,5*S*)-1,6-dibromohexane-2,3,4,5-tetrayl tetraacetate **218** (48.9 g, 47%) as colourless crystals; mp 117–120 °C; (lit.[76] mp 120–122 °C); R_f 0.15 (30% Et_2O–hexane); $[\alpha]_D^{23}$ +28.7 (*c* 1.1, CH_2Cl_2); {lit.[76] $[\alpha]_D^{20}$ +29.6 (*c* 0.95, CH_2Cl_2)}; ν_{max} (film) 1744, 1428, 1367, 1203, 1044, 967 cm^{-1}; δ_H (400 MHz) 5.44 (2H, d, *J* 8.0 Hz, H-3), 5.14 (2H, m, H-2), 3.57 (2H, dd, *J* 11.5, 3.5 Hz, C*H*H'Br), 3.40 (2H, dd, *J* 11.5, 6.0 Hz, CH*H'*Br), 2.16 (6H, s, CH_3), 2.15 (6H, s, CH_3); δ_C (100 MHz) [169.8 and 169.7 (4 × C=O)], 69.2 (2 × C-3), 68.9 (2 × C-2), 30.6 (2 × CH_2), [20.8 and 20.7 (4 × CH_3)]; *m/z* (ESI) 499 $[M+Na]^+$, 417 $[M-OAc]^+$, 397 $[M-Br]^+$ (Found: $[M+Na]^+$, 496.9402. $C_{14}H_{20}O_8Br_2$ requires $[M+Na]^+$, 496.9423); data in agreement with published data.[76]

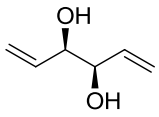
(3*R*,4*R*)-Hexa-1,5-diene-3,4-diyl diacetate (219)[76]



219

A suspension of tetraacetate **218** (48.0 g, 0.10 mol, 1.0 eq), sodium acetate (18.2 g, 0.22 mol, 2.2 eq) and zinc dust (activated; 26.4 g, 0.40 mol, 4.0 eq) in glacial acetic acid (500 mL) was heated to 110 °C. It was stirred for 1.5 h until evolution of gas had ceased and the solution became clear. After cooling, the zinc dust was filtered off and the solution was concentrated under reduced pressure. The viscous colourless residue was dissolved in water and then extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with minimal saturated aqueous K_2CO_3 (until gas evolution ceases; caution – vigorous gas evolution), dried over $MgSO_4$ and the solvent was removed under reduced pressure to yield a colourless crude product. Distillation under vacuum (bp 76–78 °C at 4 Torr) (lit.[76] bp 59–61 °C at 0.6 Torr) afforded (3*R*,4*R*)-hexa-1,5-diene-3,4-diyl diacetate **219** (14.6 g, 73%) as a colourless oil; R_f 0.39 (30% Et_2O–hexane); $[\alpha]_D^{23}$ +56.6 (*c* 0.9, CH_2Cl_2); ν_{max} (neat) 1740, 1372, 1215, 1022, 985, 928 cm^{-1}; δ_H (400 MHz) 5.78 (2H, m, C*H*=CH_2), 5.43 (2H, m, CHO), 5.35 (2H, d, *J* 17.0 Hz, C*H*H'), 5.30 (2H, d, *J* 17.0 Hz, CH*H*'), 2.11 (6H, s, CH_3); δ_C (100 MHz) 169.8 (2 × C=O), 132.1 (2 × *C*H=CH_2), 119.2 (2 × CH=*C*H_2), 74.4 (2 × COAc), 21.0 (2 × CH_3); *m/z* (CI) 216 $[M+NH_4]^+$; data in agreement with published data.[76]

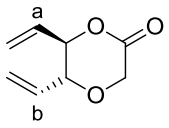
(3*R*,4*R*)-Hexa-1,5-diene-3,4-diol (220)[76]



220

To a solution of diacetate **219** (14.5 g, 72.9 mmol, 1.0 eq) in methanol (200 mL) was added saturated aqueous K_2CO_3 until pH ~ 11 was achieved and the white suspension was stirred at rt for 2 h. Conc. HCl was added in portions until pH ~ 6 was achieved. The mixture was dried over $MgSO_4$, the solvent was removed under reduced pressure and the residue was diluted with Et_2O (100 mL) and dried again over $MgSO_4$. Concentration under reduced pressure gave a crude yellow oil. Distillation under vacuum (bp 80 °C at 4 Torr) (lit.[76] bp 43 °C at 0.3 Torr) afforded (3*R*,4*R*)-hexa-1,5-diene-3,4-diol **220** (6.22 g, 75%) as a colourless oil; R_f 0.13 (50% Et_2O–hexane); $[\alpha]_D^{23}$ +42.3 (*c* 1.4, CH_2Cl_2); {lit.[108] $[\alpha]_D^{20}$ +43.1 (*c* 0.91, CH_2Cl_2)}; ν_{max} (neat) 3343, 1424, 1251, 1118, 1032, 988, 923 cm^{-1}; δ_H (400 MHz) 5.90 (2H, ddd, *J* 17.0, 10.5, 6.0 Hz, C*H*=CH_2), 5.40 (2H, d, *J* 17.0, C*H*H′), 5.28 (2H, d, *J* 10.5 Hz, CH*H*′), 4.03 (2H, d, *J* 6.5 Hz, C*H*(OH)), 2.67 (2H, s, OH); δ_C (100 MHz) 136.6 (2 × *C*H=CH_2), 117.4 (2 × CH=*C*H_2), 75.7 (2 × COH); *m/z* (CI) 132 $[M+NH_4]^+$ (Found: $[M+NH_4]^+$, 132.1023. $C_6H_{10}O_2$ requires $[M+NH_4]^+$, 132.1025); data in agreement with published data.[76]

(5*R*,6*R*)-5,6-divinyl-1,4-dioxan-2-one (222)[71, 109]

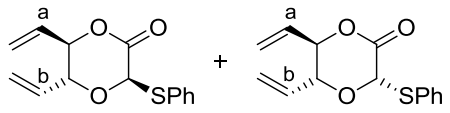


222

To a solution of diene-diol **220** (1.00 g, 8.76 mmol, 1.0 eq) in benzene (45 mL) was added di-*n*-butyltin oxide (2.40 g, 9.63 mmol, 1.1 eq) and tetra-*n*-butylammonium iodide

(3.24 g, 8.76 mmol, 1.0 eq) and the white suspension was heated under reflux in a Dean–Stark apparatus (trap filled with 4 Å molecular sieves) until water evolution was completed (~1.5 h). The homogenous reaction mixture was cooled to rt and two liquid phases were observed. To the mixture was added *tert*-butyl bromoacetate (2.83 mL, 17.5 mmol, 2.0 eq), the Dean–Stark apparatus was replaced with a condenser and the yellow solution was heated under reflux for 20 h. The reaction mixture was cooled to rt, filtered over a short pad of Celite® and silica before it was concentrated under reduced pressure. The crude brown oil was purified by chromatography of the crude mixture over silica gel (10% Et_2O–hexane) to yield the product as a crude yellow oil. The oil was diluted with Et_2O (20 mL) and washed with saturated aqueous $Na_2S_2O_3$ (2 × 20 mL), saturated aqueous $NaHCO_3$ (2 × 20 mL) and brine (20 mL) to remove any iodide and acetate contaminations. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to yield (5*R*,6*R*)-5,6-divinyl-1,4-dioxan-2-one **222** (1.08 g, 80%) as a pale yellow oil; R_f 0.49 (50% Et_2O–hexane); ν_{max} (neat) 1747, 1427, 1340, 1257, 1223, 1113, 1008, 985, 936, 832, 736 cm^{-1}; δ_H (400 MHz) 5.83 (1H, ddd, *J* 17.0, 10.5, 6.5 Hz, C*H*=CH_2 a), 5.79 (1H, ddd, *J* 17.0, 10.5, 5.5 Hz, C*H*=CH_2 b), 5.52 (2H, 2 × d, *J* 17.0 Hz, CH=C*H*H' a and b), 5.43 (2H, 2 × d, *J* 10.5 Hz, CH=CH*H'* a and b), 4.76 (1H, ddt, *J* 9.0, 6.5, 1.0 Hz, CHOCO), 4.57 (1H, d, *J* 17.5 Hz, OC*H*H'), 4.35 (1H, d, *J* 17.5 Hz, OCH*H'*), 3.96 (1H, ddt, *J* 9.0, 5.5, 1.0 Hz, C*H*OCH_2); δ_C (100 MHz) 166.6 (C=O), [131.3 and 131.1 (*C*H=CH_2 of a and b)], [120.7 and 120.6 (CH=*C*H_2 of a and b)], 83.0 (*C*HOCO), 76.7 (*C*HOCH_2), 65.3 (CH_2); *m/z* (CI) 172 $[M+NH_4]^+$ (Found: $[M+NH_4]^+$, 172.0976. $C_8H_{10}O_3$ requires $[M+NH_4]^+$, 172.0974); data in agreement with published data.[109]

(3*R*,5*R*,6*R*)-3-(phenylthio)-5,6-divinyl-1,4-dioxan-2-one [(*R*,*R*,*R*)-225] and (3*S*,5*R*,6*R*)-3-(phenylthio)-5,6-divinyl-1,4-dioxan-2-one [(*S*,*R*,*R*)-225]



(*R*,*R*,*R*)-**225** (*S*,*R*,*R*)-**225**

(Method A: Base / Alkylation) To a solution of LiHMDS (0.57 mL of a 1 M in THF solution, 0.57 mmol, 1.1 eq) in THF (1 mL) at −78 °C was added a solution of dioxanone **222** (80 mg, 0.52 mmol, 1.0 eq) and PhSSPh (113.5 mg, 0.52 mmol, 1 eq) in THF (1 mL) using a syringe pump at a rate of 1 mLh^{-1}. The reaction mixture was quenched with saturated aqueous NH_4Cl (2 mL) and the solution was warmed to rt before the layers were separated. The aqueous phase was extracted with Et_2O (2 × 2 mL), the organic layers were combined and washed with brine (10 mL) and dried over $MgSO_4$. Concentration of the filtrate under reduced pressure and chromatography of the crude mixture over silica gel (10% Et_2O–hexane) gave a 1:2 [(*R*,*R*,*R*) / (*S*,*R*,*R*)] diastereomeric mixture of 3-(phenylthio)-5,6-divinyl-1,4-dioxan-2-ones **225** (22.4 mg, 16%) as a yellow oil.

(Method B: Thermal Heating) To a solution of diene-diol **220** (135 mg, 1.18 mmol, 1.0 eq) in toluene (7 mL) was added di-*n*-butyltin oxide (351 mg, 1.41 mmol, 1.2 eq) and tetra-*n*-butylammonium bromide (362 mg, 1.12 mmol, 1.05 eq) and the white suspension was heated under reflux in a Dean–Stark apparatus (trap filled with 4 Å molecular sieves) for 3 h. The mixture was cooled to rt before chloride **231** (610 mg, 2.36 mmol, 2.0 eq) was added. The Dean–Stark apparatus was replaced with a condenser and the yellow solution was heated under reflux for 68 h. The reaction mixture was cooled to rt, filtered over a short pad of Celite® and silica before it was concentrated under reduced pressure. The crude brown oil was directly chromatographed over silica gel (0→10% Et_2O–hexane)

and gave a 2:1 [(*R*,*R*,*R*) / (*S*,*R*,*R*)] diastereomeric mixture of 3-(phenylthio)-5,6-divinyl-1,4-dioxan-2-ones **225** (138 mg, 45%) as a brown oil.

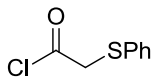
(Method C: Microwave irradiation) To a solution of diene-diol **220** (300 mg, 2.63 mmol, 1.0 eq) in toluene (12 mL) was added di-*n*-butyltin oxide (785 mg, 3.15 mmol, 1.2 eq) and tetra-*n*-butylammonium bromide (890 mg, 2.76 mmol, 1.05 eq) and the white suspension was heated under reflux in a Dean–Stark apparatus (trap filled with 4 Å molecular sieves) for 3 h. The mixture was cooled to rt before it was transferred into a microwave vial with a syringe and chloride **231** (1.36 g, 5.26 mmol, 2.0 eq) was added. The mixture was subjected to microwave irradiation at 170 ˚C with 3 × 10 min pulses. In between the pulses, the pressure in the vial was released with a needle. The mixture was concentrated under reduced pressure and the crude brown oil was directly chromatographed over silica gel (0→10% Et_2O–hexane) and gave a 2:1 [(*R*,*R*,*R*) / (*S*,*R*,*R*)] diastereomeric mixture of 3-(phenylthio)-5,6-divinyl-1,4-dioxan-2-ones **225** (194 mg, 28%) as a brown oil.

[Data for (*R*,*R*,*R*)-225] R_f 0.60 (50% Et_2O–hexane); δ_H (400 MHz) 7.61-7.58 (2H, m, *ortho* C_6H_5), 7.40-7.36 (3H, m, *meta* and *para* C_6H_5), 5.93 (1H, s, CHS), 5.86-5.76 (2H, m, C*H*=CH_2), 5.53 (1H, d, *J* 17.0 Hz, CH=C*H*H' a), 5.49 (1H, d, *J* 17.5 Hz, CH=C*H*H' b), 5.46 (1H, d, *J* 11.0 Hz, CH=CH*H'* a), 5.42 (1H, d, *J* 10.5 Hz, CH=CH*H'* b), 4.81-4.72 (2H, m, CHOCO and CHOCS); δ_C (100 MHz) 163.9 (C=O), 133.9 (*ortho* C_6H_5), 132.0 (*C*H=CH_2 b), 130.5 (*ipso* C_6H_5), 130.3 (*C*H=CH_2 a), [129.2, 128.9 (*meta* and *para* C_6H_5)], 121.4 (CH=*C*H_2 a), 120.8 (CH=*C*H_2 b), 83.5 (*C*HOCO), 82.9 (CSPh), 70.8 (*C*OCS).

[Data for (*S*,*R*,*R*)-225] R_f 0.66 (50% Et_2O–hexane); ν_{max} (neat) 2990, 1741, 1441, 1262, 1149, 1025, 1069, 984, 930, 801, 742, 689 cm^{-1}; δ_H (500 MHz, $(CD_3)_2CO$, 276 K) 7.62-7.60 (2H, m, *ortho* C_6H_5), 7.42-7.39 (3H, m, *meta* and *para* C_6H_5), 5.83 (1H, s, CHS),

5.81 (1H, ddd, *J* 17.5, 10.5, 6.5 Hz, C*H*=CH_2 b), 5.78 (1H, ddd, *J* 17.5, 10.5, 7.0 Hz, C*H*=CH_2 a), 5.47 (1H, ddd, *J* 17.5, 1.5, 1.5 Hz, CH=C*H*H' a), 5.38 (1H, ddd, *J* 17.5, 1.0, 1.0 Hz, CH=CH*H'* b), 5.35-5.33 (2H, m, CH=CH*H'*), 4.53 (1H, ddt, *J* 9.5, 7.0, 1.5 Hz, CHOCO), 4.32 (1H, ddt, *J* 9.5, 6.5, 1.0 Hz, C*H*OCS); δ_C (100 MHz, $(CD_3)_2CO$, 276 K) 165.1 (C=O), 134.7 (*ortho* C_6H_5), 133.0 (*C*H=CH_2 a), 132.4 (*C*H=CH_2 b), 132.2 (*ipso* C_6H_5), [130.1, 129.8 (*meta* and *para* C_6H_5)], 121.3 (CH=*C*H_2 b), 120.6 (CH=*C*H_2 a), 83.0 (*C*HOCO), 82.0 (CSPh), 77.8 (*C*OCS); *m/z* (CI) 280 $[M+NH_4]^+$, 263 $[M+H]^+$ (Found: $[M+H]^+$, 263.0750. $C_{14}H_{14}O_3S$ requires $[M+H]^+$, 263.0742).

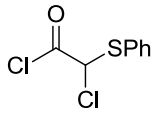
2-(Phenylthio)acetyl chloride (227)[78]



227

Phenylthioacetic acid **226** (3.00 g, 17.8 mmol, 1.0 eq) was stirred in thionyl chloride (3.9 mL, 53.6 mmol, 3.0 eq) at rt for 24 h. The volatiles were removed under reduced pressure and the crude orange oil was distilled under vacuum (bp 84–90 °C at 4 Torr) (lit.[78] bp 80 °C at 0.3 Torr) afforded 2-(phenylthio)acetyl chloride **227** (3.23 g, 97%) as a colourless oil; R_f 0.70 (60% EtOAc–hexane); ν_{max} (neat) 1781, 1482, 1440, 1175, 1007, 950, 739, 688 cm^{-1}; δ_H (400 MHz) 7.50-7.47 (2H, m, *ortho* C_6H_5), 7.40-7.34 (3H, m, *meta* and *para* C_6H_5), 4.09 (2H, s, CH_2); δ_C (100 MHz) 169.8 (CO), 132.9 (*ipso* C_6H_5), 131.6 (*ortho* C_6H_5), [129.4, 128.3 (*meta* and *para* C_6H_5)], 48.6 (CH_2); *m/z* (CI) 185 $[M-Cl+NH_2+NH_4]^+$ (Found: $[M-Cl+NH_2+NH_4]^+$, 185.0751. C_8H_7OSCl requires $[M-Cl+NH_2+NH_4]^+$, 185.0749); data in agreement with published data.[78]

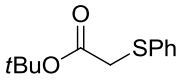
2-Chloro-2-(phenylthio)acetyl chloride (228)[78]



228

To a stirred solution of acid chloride **227** (2.06 g, 11.0 mmol, 1.0 eq) in thionyl chloride (1.5 mL) at rt was added *N*-chlorosuccinimide (1.66 g, 12.5 mmol, 1.1 eq) in portions over 5 min. After 45 min, the precipitate was filtered off and washed with hexane, the volatiles were removed under reduced pressure and the crude yellow oil was distilled under vacuum (bp 95–100 °C at 0.3 Torr) (lit.[78] bp 115 °C at 0.45 Torr) afforded 2-chloro-2-(phenylthio)acetyl chloride **228** (2.36 g, 97%) as a pale yellow oil; ν_{max} (neat) 2972, 1790, 1473, 1441, 974, 732, 702, 687 cm^{-1}; δ_H (400 MHz) 7.66-7.64 (2H, m, *ortho* C_6H_5), 7.54-7.43 (3H, m, *meta* and *para* C_6H_5), 5.71 (1H, s, CH); δ_C (100 MHz) 165.6 (CO), 137.2 (*ipso* C_6H_5). 135.6 (*ortho* C_6H_5), 130.8 (*para* C_6H_5), 129.6 (*meta* C_6H_5), 70.8 (CH); *m/z* (CI) 219 $[M-Cl+NH_2+NH_4]^+$, 201 $[M-Cl+NH_2]^+$ (Found: $[M-Cl+NH_2+NH_4]^+$, 219.0365. $C_8H_6OSCl_2$ requires $[M-Cl+NH_2+NH_4]^+$, 219.0359); data in agreement with published data.[78]

***tert*-Butyl 2-(phenylthio)acetate (230)**[79]

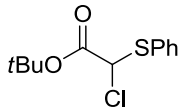


230

To a solution of thiophenol (6.30 mL, 61.9 mmol, 1.0 eq) in THF (mL) at 10 °C was added potassium *tert*-butoxide (7.65 g, 68.1 mmol, 1.1 eq) and the suspension was stirred for 10 min. *tert*-Butyl bromoacetate (10.0 mL, 61.9 mmol, 1.0 eq) was added dropwise in 2 portions over 15 min. After 10 min, the suspension was warmed to rt and stirred for

another 1 h. The mixture quenched with water (4 mL) and $MgSO_4$ was added to remove the excess water. Filtration and concentration under reduced pressure yielded a colourless crude product. Distillation under vacuum (bp 104 °C at 1 Torr) afforded ester **230** (12.6 g, 91%) as a colourless oil; R_f 0.22 (3% Et_2O–hexane); ν_{max} (neat) 2978, 1724, 1482, 1440, 1393, 1368, 1289, 1124, 1025, 950, 837, 738, 689 cm^{-1}; δ_H (400 MHz) 7.44 (2H, dd, *J* 7.5, 1.0 Hz, *ortho* C_6H_5), 7.34-7.29 (2H, m, *meta* C_6H_5), 7.24 (1H, tt, *J* 7.5, 1.0 Hz, *para* C_6H_5), 3.59 (2H, s, CH_2), 1.43 (9H, s, $(CH_3)_3$); δ_C (100 MHz) 168.8 (CO), 135.3 (*ipso* C_6H_5). 129.9 (*ortho* C_6H_5), 128.9 (*para* C_6H_5), 126.7 (*meta* C_6H_5), 81.9 ($C(CH_3)_3$), 37.8 (CH_2), 27.9 ($(CH_3)_3$); *m/z* (CI) 242 $[M+NH_4]^+$, 225 $[M+H]^+$ (Found: $[M+H]^+$, 225.0952. $C_{12}H_{16}O_2S$ requires $[M+H]^+$, 225.0949); data in agreement with published data.[79]

***tert*-Butyl 2-chloro-2-(phenylthio)acetate (231)**[80]



231

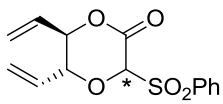
(Method A)[80(a)] To a refluxing solution of ester **230** (1.48 g, 6.60 mmol, 1.0 eq) in CH_2Cl_2 (6 mL) was added dropwise a solution of sulfuryl chloride (0.62 mL, 7.66 mmol, 1.1 eq) in CH_2Cl_2 (1 mL) *via* a syringe pump at a rate such that a gentle reflux is maintained (~ 1 h). The yellow solution was heated to reflux for 3 h in total before it was cooled to rt and solid K_2CO_3 was added. Filtration and concentration under reduced pressure yielded a crude yellow oil which was purified by chromatography of the crude mixture over silica gel (0→2% Et_2O–hexane) to give *tert*-butyl 2-chloro-2-(phenylthio)acetate **231** (1.62 g, 95%) as a colourless oil.

On a scale of less than 2 g, the product was stable when purified by silica gel chromatography. On a larger scale (> 5 g), dehalogenation occurred when purified over silica gel hence Method B was the preferred route since there was less by-products formed during the reaction and the crude oil could be used directly in the next step.

(Method B)[80(b)] To a solution of ester **230** (8.00 g, 35.7 mmol, 1.0 eq) in carbon tetrachloride (35 mL) at rt was added *N*-chlorosuccinimide (5.71 g, 42.8 mmol, 1.2 eq) in 3 portions over 30 min and the suspension was stirred overnight. The yellow suspension was filtered over Celite® and the residues were washed with hexane. The filtrate was concentrated under reduced pressure and dried over the vacuum pump overnight to give crude *tert*-butyl 2-chloro-2-(phenylthio)acetate **231** (11.2 g) as a colourless oil which was used directly in the next step without further purification.

R_f 0.41 (3% Et_2O–hexane); ν_{max} (neat) 2981, 1738, 1370, 1288, 1259, 1135, 850, 738 cm^{-1}; δ_H (400 MHz) 7.63-7.61 (2H, m, *ortho* C_6H_5), 7.42-7.40 (3H, m, *meta* and *para* C_6H_5), 5.46 (1H, s, CH), 1.50 (9H, s, $(CH_3)_3$); δ_C (100 MHz) 164.8 (CO), 137.2 (*ipso* C_6H_5). 133.8 (*ortho* C_6H_5), [129.3, 129.2 (*meta* and *para* C_6H_5)], 86.0 ($C(CH_3)_3$), 65.9 (CHCl), 27.7 ($(CH_3)_3$); *m/z* (CI) 276 $[M+NH_4]^+$, 258 $[M]^+$ (Found: $[M+NH_4]^+$, 276.0824. $C_{12}H_{15}O_2SCl$ requires $[M+NH_4]^+$, 276.0825); data in agreement with published data.[80]

(5*R*,6*R*)-3-(Phenylsulfonyl)-5,6-divinyl-1,4-dioxan-2-one (232)

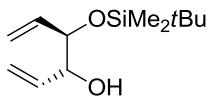


232

To a stirred solution of sulfide (*S*,*R*,*R*)-**225** (24.5 mg, 0.09 mmol, 1.0 eq) in methanol (1.0 mL) at 0 °C was added a solution of Oxone® ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$; 172 mg, 0.28 mmol, 3.0 eq) in water (1.0 mL). The solution was stirred for 1 h at 0 °C before it

was warmed to rt and stirred for a further 1.5 h. All the organic volatiles were removed under reduced pressure, the aqueous solution was diluted with CH_2Cl_2 (5 mL) and the organic layer was separated using a phase separator. Concentration under reduced pressure gave a crude colourless oil. Purification by preparative silica gel thin layer chromatography (50% Et_2O–hexane) gave a 4:3 (unassigned) diastereomeric ratio of (5*R*,6*R*)-3-(phenylsulfonyl)-5,6-divinyl-1,4-dioxan-2-one **232** (8 mg, 33%) as a colourless oil; R_f 0.44 (50% Et_2O–hexane); ν_{max} (neat) 1751, 1327, 1310, 1300, 1260, 1234, 1152, 1120, 1077, 985, 942, 719 cm^{-1}; δ_H (400 MHz) 8.04-7.97 (4H, m, *ortho* C_6H_5), 7.80-7.23 (2H, m, *para* C_6H_5), 7.67-7.61 (4H, m, *meta* C_6H_5), 5.86-5.69 (4H, m, C*H*=CH_2), 5.58-5.44 (8H, m, CH=CH_2), 5.40 (1H, s, minor $CHSO_2$), 5.36 (1H, s, major $CHSO_2$), 5.03 (1H, dd, *J* 9.5, 6.5 Hz, minor CHOCO), 4.94 (1H, dd, *J* 9.0, 6.5 Hz, major CHOCO), 4.80 (1H, dd, *J* 9.0, 6.5 Hz, major CHOCS), 4.20 (1H, dd, *J* 9.5, 6.5 Hz, minor CHOCS); δ_C (100 MHz) 159.7 (minor C=O), 159.1 (major C=O), [136.7, 135.9, 135.0, 134.8, 131.9, 130.3, 129.9, 129.8, 129.7, 129.5, 129.4, 129.3, 129.2, 125.5, 125.0 (C_6H_5 and CH_2=*C*H)], [122.1, 121.9, 121.8 (*C*H_2=CH)], 89.2 (minor *C*SPh), 88.3 (major *C*SPh), 83.9 (major *C*OCO), 83.5 (minor *C*OCO), 74.6 (major *C*OCS), 65.8 (minor *C*OCS); *m/z* (CI) 312 $[M+NH_4]^+$, 296 $[M+H_2]^+$ (Found: $[M+NH_4]^+$, 312.0912. $C_{14}H_{14}O_5S$ requires $[M+NH_4]^+$, 312.0906).

(3*R*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)hexa-1,5-dien-3-ol (238)

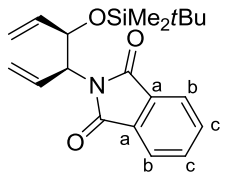


238

To a stirred suspension of prewashed sodium hydride (2.33 g of a 60% dispersion in mineral oil, 58.3 mmol, 1.1 eq) in THF (120 mL) at 10 °C was added a solution of (3*R*,4*R*)-hexa-1,5-diene-3,4-diol **220** (6.05 g, 53.0 mmol, 1.0 eq) in THF (5 mL). The

suspension was warmed to rt and stirred for 15 min before adding a solution of *tert*-butyldimethylchlorosilane (8.97 g, 58.3 mmol, 1.1 eq) in THF (10 mL) dropwise. After 12 h, saturated aqueous NH_4Cl (4 mL) was added to the white suspension and the excess water was dried by addition of $MgSO_4$. The mixture was filtered, concentrated under reduced pressure and purification by chromatography of the crude mixture over silica gel (0→5% Et_2O−hexane) gave (3*R*,4*R*)-4-(*tert*-butyldimethylsilyloxy)hexa-1,5-dien-3-ol **238** (10.5 g, 86%) as a colourless oil; R_f 0.33 (10% Et_2O−hexane); $[\alpha]_D^{23}$ +10.0 (*c* 1.0, CH_2Cl_2); ν_{max} (neat) 3446, 2955, 2930, 2886, 2858, 1252, 1074, 991, 923, 834, 775 cm^{-1}; δ_H (400 MHz) 5.91-5.80 (2H, m, C*H*=CH_2), 5.36 (1H, dd, *J* 17.5, 1.5 Hz, C*H*H′=CHCHOH), 5.28 (1H, dd, *J* 17.0, 1.0 Hz, C*H*H′=CHCHOSi), 5.26-5.21 (2H, m, CH*H′*=CH), 4.02-3.95 (2H, m, C*H*OH and CHOSi), 2.41 (1H, br s, OH), 0.94 (9H, s, $C(CH_3)_3$), 0.11 (3H, s, $SiCH_3$), 0.09 (3H, s, $SiCH_3$′); δ_C (100 MHz) [137.8, 136.9 (*C*H=CH_2)], [117.1, 116.5 (CH=*C*H_2)], [77.5, 75.7 (CHO)], 25.9 ($(CH_3)_3$), 18.2 (*C*$(CH_3)_3$), [−4.1 and −4.9 ($Si(CH_3)_2$)]; *m/z* (CI) 246 $[M+NH_4]^+$, 229 $[M+H]^+$, (Found: $[M+H]^+$, 229.1627. $C_{12}H_{24}O_2Si$ requires $[M+H]^+$, 229.1624); data in agreement with published data.[110]

2-((3*S*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)hexa-1,5-dien-3-yl)isoindoline-1,3-dione (239)

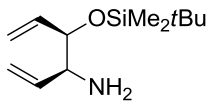


239

To a solution of alcohol **238** (1.93 g, 8.43 mmol, 1.0 eq), triphenylphosphine (2.88 g, 11.0 mmol, 1.3 eq) and phthalimide (1.61 g, 11.0 mmol, 1.3 eq) in THF (100 mL) at 0 °C was added diisopropylazodicarboxylate (2.18 mL, 11.0 mmol, 1.3 eq) dropwise and the

yellow solution was allowed to warm up to rt. After 2.5 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (100 mL) and the organic layer was separated. The aqueous phase was extracted with Et_2O (50 mL), the combined organic extracts were washed with brine (150 mL) and dried over $MgSO_4$. Concentration of the filtrate under reduced pressure and chromatography of the crude mixture over silica gel (0→2% Et_2O−hexane) gave 2-((3*S*,4*R*)-4-(*tert*-butyldimethylsilyloxy)hexa-1,5-dien-3-yl)isoindoline-1,3-dione **239** (1.16 g, 39%) as a white solid; mp 38–40 °C; R_f 0.47 (15% Et_2O−hexane); $[\alpha]_D^{23}$ −14.5 (*c* 1.2, CH_2Cl_2); ν_{max} (neat) 2930, 2858, 1774, 1710, 1382, 1252, 1077, 929, 871, 835, 776, 713 cm^{-1}; δ_H (400 MHz) 7.85 (1H, d, *J* 3.0 Hz, C_6H_4), 7.83 (1H, d, *J* 3.0 Hz, C_6H_4), 7.74 (1H, d, *J* 3.0 Hz, C_6H_4), 7.72 (1H, d, *J* 3.0 Hz, C_6H_4), 6.35 (1H, ddd, *J* 17.5, 10.0, 7.5 Hz, H_2C=C*H*CHN), 5.73 (1H, ddd, *J* 17.0, 10.5, 8.0 Hz, H_2C=C*H*CHO), 5.30-5.25 (2H, m, *H*$_2$C=CHCHN), 5.13 (1H, d, *J* 17.0 Hz, *H*H′C=CHCHO), 5.00 (1H, d, *J* 10.5 Hz, H*H*′C=CHCHO), 4.77-4.73 (1H, m, CHO), 4.69-4.64 (1H, m, CHN), 0.92 (9H, s, $C(CH_3)_3$), 0.12 (3H, s, $SiCH_3$), 0.07 (3H, s, $SiCH_3$′); δ_C (100 MHz) 167.9 (C=O), 138.6 (H_2C=*C*HCHO), 133.9 (C_6H_4 a), 133.1 (H_2C=*C*HCHN), [131.9 and 123.2 (C_6H_4 of b and c)], 119.1 (H_2C=CHCHN), 117.6 (H_2C=CHCHO), 73.7 (CHO), 58.8 (CHN), 25.8 ($(CH_3)_3$), 18.1 (*C*$(CH_3)_3$), −4.1 and −4.6 ($Si(CH_3)_2$); *m/z* (CI) 375 $[M+NH_4]^+$, 358 $[M+H]^+$, 226 $[M-Phth+H]^+$ (Found: $[M+H]^+$, 358.1841. $C_{20}H_{27}NO_3Si$ requires $[M+H]^+$, 358.1838).

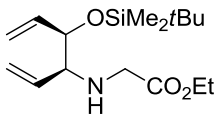
(3*S*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)hexa-1,5-dien-3-amine (240)



240

To a stirred solution of silyl ether **239** (155 mg, 0.43 mmol, 1.0 eq) in absolute ethanol (5 mL) was added ethylenediamine (0.09 mL, 1.30 mmol, 3.0 eq) and the solution was heated to reflux for 13 h. All the volatiles were removed under reduced pressure (Caution! Product is volatile and could be removed under vacuum) and chromatography of the crude mixture over silica gel (60% Et_2O−hexane) gave (3*S*,4*R*)-4-(*tert*-butyldimethylsilyloxy)hexa-1,5-dien-3-amine **240** (94.1 mg, 96%) as a colourless oil; R_f 0.06 (50% Et_2O−hexane); $[\alpha]_D^{23}$ +7.1 (*c* 1.1, CH_2Cl_2); ν_{max} (neat) 2955, 2930, 2886, 2858, 1253, 1078, 1029, 992, 919, 834, 774 cm^{-1}; δ_H (400 MHz) 5.87 (1H, ddd, *J* 17.0, 10.5, 6.5 Hz, H_2C=C*H*CHN), 5.80 (1H, ddd, *J* 17.0, 10.5, 6.0 Hz, H_2C=C*H*CHO), 5.30-5.14 (4H, m, CH=CH_2), 4.16-4.13 (1H, m, CHOSi), 3.40-3.37 (1H, m, CHN), 1.90 (2H, br s, NH_2), 0.94 (9H, s, $C(CH_3)_3$), 0.10 (3H, s, $SiCH_3$), 0.07 (3H, s, $SiCH_3'$); δ_C (100 MHz) 138.4 (H_2C=*C*HCHO), 137.4 (H_2C=*C*HCHN), [116.6 and 115.6 (H_2C=CHCHO and H_2C=CHCHN)], 77.0 (CHO), 59.3 (CHN), 25.9 ($(CH_3)_3$), 18.2 ($C(CH_3)_3$), [−4.1 and −4.9 ($Si(CH_3)_2$)]; *m/z* (CI) 228 $[M+H]^+$ (Found: $[M+H]^+$, 228.1783. $C_{12}H_{25}NOSi$ requires $[M+H]^+$, 228.1784).

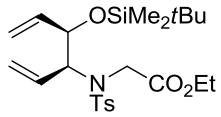
Ethyl 2-((3*S*,4*R*)-4-(*tert*-butyldimethylsilyloxy)hexa-1,5-dien-3-ylamino)acetate (241)



241

To a stirred solution of amine **240** (149 mg, 0.65 mmol, 1.0 eq) in THF (3 mL) at rt was added Et_3N (0.18 mL, 1.30 mmol, 2.0 eq), ethyl bromoacetate (0.11 mL, 0.98 mmol, 1.5 eq) and the suspension was stirred at rt overnight. The volatiles were removed under reduced pressure and chromatography of the crude mixture over silica gel (10% Et_2O−hexane) gave ethyl 2-((3*S*,4*R*)-4-(*tert*-butyldimethylsilyloxy)hexa-1,5-dien-3-ylamino)acetate **241** (174 mg, 85%) as a colourless oil; R_f 0.09 (10% Et_2O−hexane); $[\alpha]_D^{23}$ +27.0 (*c* 1.4, CH_2Cl_2); ν_{max} (neat) 2956, 2931, 2858, 1742, 1253, 1194, 1069, 1027, 922, 835, 775 cm^{-1}; δ_H (400 MHz) 5.87 (1H, ddd, *J* 17.0, 10.5, 6.5 Hz, H_2C=C*H*CHO), 5.64 (1H, *J* 17.0, 10.5, 8.5 Hz, H_2C=C*H*CHN), 5.27-5.16 (4H, m, CH=CH_2), 4.19 (2H, q, *J* 7.0 Hz, CO_2CH_2), 4.18-4.15 (1H, m, CHOSi), 3.44 (1H, d, *J* 17.5 Hz, NC*H*H′), 3.32 (1H, d, *J* 17.5 Hz, NCH*H*′), 3.09 (1H, dd, *J* 8.5, 4.5 Hz, CHN), 2.10 (1H, br s, NH), 1.29 (3H, t, *J* 7.0 Hz, $CO_2CH_2CH_3$), 0.94 (9H, s, $C(CH_3)_3$), 0.11 (3H, s, $SiCH_3$), 0.07 (3H, s, $SiCH_3$′); δ_C (100 MHz) 172.4 (C=O), 138.3 (H_2C=*C*HCHO), 136.9 (H_2C=*C*HCHN), 118.6 (H_2C=CHCHO), 116.4 (H_2C=CHCHN), 77.0 (CHOSi), 66.6 (CHN), 60.6 (CO_2CH_2), 48.5 (NCH_2), 25.8 ($C(CH_3)_3$), 18.2 ($C(CH_3)_3$), 14.2 ($CO_2CH_2CH_3$), [−4.3 and −4.8 ($Si(CH_3)_2$)]; *m/z* (CI) 314 $[M+H]^+$, 400 $[M+CH_2CO_2Et]^+$ (Found: $[M+H]^+$, 314.2147. $C_{16}H_{31}NO_3Si$ requires $[M+H]^+$, 314.2151).

Ethyl 2-(*N*-((3*S*,4*R*)-4-(*tert*-butyldimethylsilyloxy)hexa-1,5-dien-3-yl)-4-methylphenylsulfonamido)acetate (242)

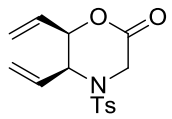


242

To a stirred solution of amine **241** (1.00 g, 3.19 mmol, 1.0 eq) in CH_2Cl_2 (6 mL) at rt was added Et_3N (0.89 mL, 6.38 mmol, 2.0 eq) and DMAP (39.0 mg, 0.32 mmol, 0.1 eq). *para*-Toluenesulfonyl chloride (1.22 g, 6.38 mmol, 2.0 eq) was added in two portions over 1 h and the resultant orange solution was stirred at rt overnight. TLC indicated that reaction was incomplete and another portion of Et_3N (3 mL) and *para*-toluenesulfonyl chloride (0.60 g) were added. After 24 h, the mixture was filtered, the filtrate was concentrated under reduced pressure and chromatography of the crude mixture over silica gel (0→5% Et_2O–hexane) gave ethyl 2-(*N*-((3*S*,4*R*)-4-(*tert*-butyldimethylsilyloxy)hexa-1,5-dien-3-yl)-4-methylphenylsulfonamido)acetate **242** (1.25 g, 83%) as a colourless oil; R_f 0.13 (30% Et_2O–hexane); ν_{max} (neat) 2971, 2949, 1757, 1741, 1338, 1253, 1178, 1156, 1089, 927 cm^{-1}; δ_H (400 MHz) 7.86 (2H, d, *J* 8.0 Hz, *ortho* Ts), 7.30 (2H, d, *J* 8.0 Hz, *meta* Ts), 5.80 (1H, ddd, *J* 17.5, 10.5, 7.5 Hz, H_2C=C*H*CHN), 5.76 (1H, ddd, *J* 17.5, 10.5, 7.5 Hz, H_2C=C*H*CHO), 5.20-5.09 (4H, m, *H*$_2$C=CHCHO and *H*$_2$C=CHCHN), 4.48 (1H, dd, *J* 7.5, 3.5 Hz, CHOSi), 4.27 (1H, d, *J* 18.0 Hz, NC*H*H′), 4.19 (1H, d, *J* 18.0 Hz, NCH*H*′), 4.14 (2H, q, *J* 7.0 Hz, CO_2CH_2), 4.04 (1H, dd, *J* 7.5, 3.5 Hz, CHN), 2.44 (3H, s, *para* Ts), 1.24 (3H, t, *J* 7.0 Hz, $CO_2CH_2CH_3$), 0.89 (9H, s, $C(CH_3)_3$), 0.06 (3H, s, $SiCH_3$), 0.01 (3H, s, $SiCH_3$′); δ_C (100 MHz) 170.0 (C=O), 143.3 (*para* Ts), 139.0 (H_2C=*C*HCHO), 137.4 (*ipso* Ts), 130.6 (H_2C=*C*HCHN), 129.3 (*meta* Ts), 128.1 (*ortho* Ts), 120.8 (H_2C=CHCHO), 116.6 (H_2C=CHCHN), 77.0 (CHOSi), 64.5 (CHN), 61.1 (CO_2CH_2), 46.7 (NCH_2), 25.9 ($C(CH_3)_3$), 21.5 ($ArCH_3$),

18.0 ($C(CH_3)_3$), 14.0 ($CO_2CH_2CH_3$), [−3.8 and −4.8 ($Si(CH_3)_2$)]; *m/z* (CI) 485 $[M+NH_4]^+$, 468 $[M+H]^+$ (Found: $[M+H]^+$, 468.2248. $C_{23}H_{37}NO_5SSi$ requires $[M+H]^+$, 468.2240).

(5*S*,6*R*)-4-Tosyl-5,6-divinylmorpholin-2-one (243)



243

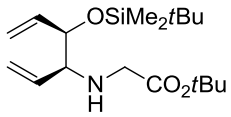
(Method A) A solution of ester **246** (186 mg, 0.49 mmol, 1.0 eq) and TFA (0.045 mL, 0.58 mmol, 1.2 eq) in THF (2 mL) was heated to reflux for 17 h. The volatiles were removed under reduced pressure and chromatography of the crude mixture over silica gel (20% Et_2O−hexane) gave (5*S*,6*R*)-4-tosyl-5,6-divinylmorpholin-2-one **243** (124 mg, 82%) as a colourless oil.

(Method B) A solution of ester **245** (1.18 g, 2.52 mmol, 1.0 eq) and *para*-toluenesulfonic acid (0.58 g, 3.03 mmol, 1.2 eq) in THF (50 mL) was heated to reflux for 16 h. The volatiles were removed under reduced pressure and chromatography of the crude mixture over silica gel (10→25% Et_2O−hexane) gave (5*S*,6*R*)-4-tosyl-5,6-divinylmorpholin-2-one **243** (269 mg, 35%) as a colourless oil.

R_f 0.33 (50% Et_2O−hexane); ν_{max} (neat) 1749, 1350, 1270, 1239, 1160, 1092, 172, 985, 936, 815 cm^{-1}; δ_H (400 MHz) 7.72 (2H, d, *J* 8.0 Hz, *ortho* Ts), 7.36 (2H, d, *J* 8.0 Hz, *meta* Ts), 5.76 (1H, ddd, *J* 17.5, 10.5, 6.0 Hz, H_2C=C*H*CHO), 5.66 (1H, ddd, *J* 17.0, 10.5, 6.5 Hz, H_2C=C*H*CHN), 5.48 (1H, d, *J* 17.5 Hz, *H*H'C=CHCHO), 5.42 (1H, d, *J* 10.5 Hz, CH*H'*=CHCHO), 5.36 (1H, d, *J* 10.5 Hz, *H*H'C=CHCHN), 5.33 (1H, d, *J* 17.0 Hz, CH*H'*=CHCHN), 4.93-4.90 (1H, m, CHO), 4.67-4.64 (1H, m, CHN), 4.29 (1H, d, *J* 18.0 Hz, CH*H'*), 3.98 (1H, d, *J* 18.0 Hz, C*H*H'), 2.48 (3H, s, *para* Ts); δ_C (100 MHz) 164.6 (C=O), 144.6 (*para* Ts), 134.8 (*ipso* Ts), 131.0 (H_2C=*C*HCHO), 130.0 (*meta* Ts), 127.6

(*ortho* Ts), 127.5 (H_2C=*C*HCHN), 122.3 (H_2C=CHCHO), 120.1 (H_2C=CHCHN), 81.3 (CHO), 57.2 (CHN), 43.8 (CH_2), 21.6 (ArCH_3), *m/z* (CI) 325 $[M+NH_4]^+$, 308 $[M+H]^+$ (Found: $[M+H]^+$, 308.0954. $C_{15}H_{17}NO_4S$ requires $[M+H]^+$, 308.0957).

tert-Butyl 2-((3*S*,4*R*)-4-(_tert_-butyldimethylsilyloxy)hexa-1,5-dien-3-ylamino)acetate (244)

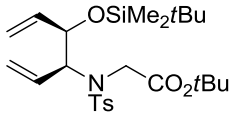


244

To a stirred solution of amine **240** (72 mg, 0.32 mmol, 1.0 eq) in THF (2 mL) at rt was added Et_3N (0.09 mL, 0.64 mmol, 2.0 eq), *tert*-butyl bromoacetate (0.07 mL, 0.35 mmol, 1.1 eq) and the suspension was stirred at rt overnight. Saturated aqueous NH_4Cl (2 mL) was added to the flask and the layers were separated, the aqueous phase was extracted with Et_2O (2 mL) and the combined organic extracts were dried over $MgSO_4$. Concentration of the filtrate under reduced pressure and chromatography of the crude mixture over silica gel (0→5% Et_2O−hexane) gave *tert*-butyl 2-((3*S*,4*R*)-4-(*tert*-butyldimethylsilyloxy)hexa-1,5-dien-3-ylamino)acetate **244** (80.4 mg, 74%) as a colourless oil; R_f 0.17 (10% Et_2O−hexane); ν_{max} (neat) 2930, 2858, 1736, 1368, 1252, 1154, 1069, 920, 825, 774 cm^{-1}; δ_H (400 MHz) 5.86 (1H, ddd, *J* 17.5, 10.5, 7.0 Hz, H_2C=C*H*CHO), 5.70-5.61 (1H, m, H_2C=C*H*CHN), 5.28-5.16 (4H, m, CH=CH_2), 4.18-4.15 (1H, m, CHOSi), 3.34 (1H, d, *J* 17.0 Hz, C*H*H′), 3.23 (1H, d, *J* 17.0 Hz, CH*H*′), 3.06 (1H, dd, *J* 8.5, 4.5 Hz, CHN), 2.50-1.70 (1H, br, NH), 1.48 (9H, s, $CO_2C(CH_3)_3$), 0.93 (9H, s, $C(CH_3)_3$), 0.11 (3H, s, $SiCH_3$), 0.06 (3H, s, $SiCH_3$′); δ_C (100 MHz) 171.3 (C=O), 138.4 (H_2C=*C*HCHO), 136.8 (H_2C=*C*HCHN), 118.8 (H_2C=CHCHO), 116.6 (H_2C=CHCHN), 81.0 (CO_2C), 77.0 (CHOSi), 66.6 (CHN), 49.2 (NCH_2), 28.1 ($CO_2C(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 18.2 ($SiC(CH_3)_3$), [−4.3 and −4.8

($Si(CH_3)_2$)]; *m/z* (CI) 342 $[M+H]^+$ (Found: $[M+H]^+$, 342.2467. $C_{18}H_{35}NO_3Si$ requires $[M+H]^+$, 342.2464).

tert-Butyl 2-(_N_-((3_S_,4_R_)-4-(_tert_-butyldimethylsilyloxy)hexa-1,5-dien-3-yl)-4-methylphenylsulfonamido)acetate (245)

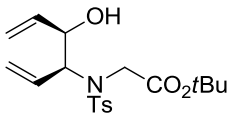


245

To a stirred solution of amine **244** (390 mg, 1.14 mmol, 1.0 eq) in CH_2Cl_2 (5 mL) at rt was added Et_3N (0.32 mL, 2.28 mmol, 2.0 eq), *para*-toluenesulfonyl chloride (327 mg, 1.71 mmol, 1.5 eq), DMAP (14 mg, 0.11 mmol, 0.1 eq) and the solution stirred at rt overnight. Water (5 mL) was added to the flask and the layers were separated, the organic phase was washed with saturated aqueous NH_4Cl (5 mL), brine (5 mL) and dried over $MgSO_4$. Concentration under reduced pressure and chromatography of the crude mixture over silica gel (0→5% Et_2O−hexane) gave *tert*-butyl 2-(*N*-((3*S*,4*R*)-4-(*tert*-butyldimethylsilyloxy)hexa-1,5-dien-3-yl)-4-methylphenyl-sulfonamido)acetate **245** (450 mg, 88%) as a colourless oil; R_f 0.42 (20% Et_2O−hexane); ν_{max} (neat) 2931, 2858, 1751, 1732, 1339, 1254, 1151, 1089, 924, 826, 810, 776 cm^{-1}; δ_H (400 MHz) 7.85 (2H, d, *J* 8.0 Hz, *ortho* Ts), 7.30 (2H, d, *J* 8.0 Hz, *meta* Ts), 5.86-5.73 (2H, m, H_2C=C*H*CHO and H_2C=C*H*CHN), 5.20-5.09 (4H, m, *H*$_2$C=CHCHO and *H*$_2$C=CHCHN), 4.43 (1H, dd, *J* 7.5, 4.0 Hz, CHOSi), 4.17 (1H, d, *J* 18.0 Hz, C*H*H′), 4.10 (1H, d, *J* 18.0 Hz, CH*H*′), 4.02 (1H, dd, *J* 7.5, 4.0 Hz, CHN), 2.44 (3H, s, *para* Ts), 1.45 (9H, s, $CO_2C(CH_3)_3$), 0.90 (9H, s, $SiC(CH_3)_3$), 0.06 (3H, s, $SiCH_3$), 0.01 (3H, s, $SiCH_3$′); δ_C (100 MHz) 168.9 (C=O), 143.3 (*para* Ts), 139.0 (H_2C=*C*HCHO), 137.6 (*ipso* Ts), 131.0 (H_2C=*C*HCHN), 129.3 (*meta* Ts), 128.1 (*ortho* Ts), 120.5 (H_2C=CHCHO), 116.4 (H_2C=CHCHN), 81.5 (CO_2C), 77.6 (CHOSi), 64.7 (CHN), 47.5 (CH_2), 28.0 ($CO_2C(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 21.5

(Si*C*$(CH_3)_3$), 18.0 (Ar*C*H_3), [−3.8 and −4.8 (Si$(CH_3)_2$)]; *m/z* (CI) 513 $[M+NH_4]^+$, 457 $[M-t\text{Bu}+H]^+$ (Found: $[M+NH_4]^+$, 513.2816. $C_{25}H_{41}NO_5SSi$ requires $[M+NH_4]^+$, 513.2818).

tert-Butyl 2-(*N*-((3*S*,4*R*)-4-hydroxyhexa-1,5-dien-3-yl)-4-methylphenylsulfonamido)acetate (246)

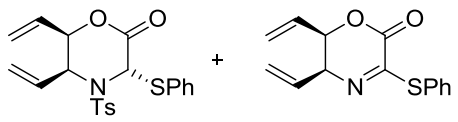


246

A solution of ester **245** (478 mg, 0.96 mmol, 1.0 eq) and tetrabutylammonium fluoride trihydrate (333 mg, 1.06 mmol, 1.1 eq) in THF (5 mL) was stirred at rt overnight. The volatiles were removed under reduced pressure and chromatography of the crude mixture over silica gel (10→15% Et_2O−hexane) gave *tert*-butyl 2-(*N*-((3*S*,4*R*)-4-hydroxyhexa-1,5-dien-3-yl)-4-methylphenylsulfonamido)acetate **246** (201 mg, 55%) as a colourless oil; R_f 0.42 (50% Et_2O−hexane); ν_{max} (neat) 3417 (br), 2981, 1751, 1730, 1344, 1244, 1153, 1091, 986, 927, 814 cm^{-1}; δ_H (400 MHz) 7.78 (2H, d, *J* 8.0 Hz, *ortho* Ts), 7.32 (2H, d, *J* 8.0 Hz, *meta* Ts), 5.82 (1H, ddd, *J* 17.0, 10.5, 4.5 Hz, H_2C=C*H*CHO), 5.82 (1H, ddd, *J* 17.5, 10.5, 6.0 Hz, H_2C=C*H*CHN), 5.36 (1H, d, *J* 17.0 Hz, C*H*H′=CHCHO), 5.22 (1H, d, *J* 10.5 Hz, CH*H′*=CHCHN), 5.17 (1H, d, *J* 10.5 Hz, CH*H′*=CHCHO), 4.91 (1H, d, *J* 17.5 Hz, C*H*H′=CHCHN), 4.58 (1H, br s, C*H*OH), 4.47-4.45 (1H, m, CHN), 4.05 (1H, d, *J* 18.0 Hz, C*H*H′), 3.74 (1H, d, *J* 18.0 Hz, CH*H′*), 2.45 (3H, s, *para* Ts), 1.80 (9H, s, C$(CH_3)_3$); δ_C (100 MHz) 171.2 (C=O), 143.7 (*ipso* Ts), 136.7 (*para* Ts), 136.2 (H_2C=*C*HCHO), 130.4 (H_2C=*C*HCHN), 129.6 (*meta* Ts), 129.6 (*ortho* Ts), 120.6 (H_2C=CHCHN), 116.1 (H_2C=CHCHO), 82.9 (CO_2C), 74.2 (CHOH), 63.8 (CHN), 47.1 (CH_2), 28.0 (C(*C*$H_3)_3$), 21.6 (Ar*C*H_3); *m/z* (ESI) 404 $[M+Na]^+$, 420 $[M+K]^+$ (Found: $[M+Na]^+$, 404.1512. $C_{19}H_{27}NO_5S$ requires $[M+Na]^+$, 404.1508).

(5*S*,6*R*)-3-(Phenylthio)-4-tosyl-5,6-divinylmorpholin-2-one (251) and

(5*S*,6*R*)-3-(phenylthio)-5,6-divinyl-5,6-dihydro-1,4-oxazin-2-one (252)



251 **252**

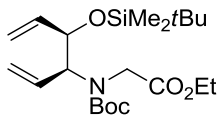
To a solution of morpholinone **243** (80 mg, 0.26 mmol, 1.0 eq) and $PhSSO_2Ph$ (130 mg, 0.52 mmol, 2.0 eq) in THF (3 mL) at −78 °C was added a solution of LiHMDS (0.39 mL of a 1 M in THF / PhEt solution, 0.57 mmol, 1.1 eq). The yellow solution was stirred at −78 °C for 1.5 h, then warmed up to rt over 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (3 mL), the organic phase was separated, washed with brine (3 mL) and dried ($MgSO_4$). Concentration of the filtrate under reduced pressure and chromatography of the crude mixture over silica gel (5→10% Et_2O−hexane) gave (5*S*,6*R*)-3-(phenylthio)-4-tosyl-5,6-divinylmorpholin-2-one **251** (48.5 mg, 45%) as a single diastereomer as a pale yellow oil which solidified into a pale yellow solid on drying *in vacuo* over 3 days and (5*S*,6*R*)-3-(phenylthio)-5,6-divinyl-5,6-dihydro-1,4-oxazin-2-one **252** (9.0 mg, 13%) as a colourless oil.

(Data for 251) mp 70–72 °C; R_f 0.38 (50% Et_2O−hexane); ν_{max} (neat) 1754, 1355, 1263, 1162, 1090, 981, 909, 729 cm^{-1}; δ_H (400 MHz) 7.80 (2H, d, *J* 8.5 Hz, *ortho* Ts), 7.64-7.62 (2H, m, *ortho* C_6H_5), 7.46-7.40 (3H, m, *meta* and *para* C_6H_5), 7.33 (2H, d, *J* 8.5 Hz, *meta* Ts), 5.75 (1H, ddd, *J* 17.0, 10.5, 6.0 Hz, H_2C=C*H*CHO), 5.60 (1H, d, *J* 1.0 Hz, CHS), 5.55-5.42 (3H, m, H_2C=C*H*CHN and *H*$_2$C=CHCHO), 5.33-5.26 (3H, m, CHO and *H*$_2$C=CHCHO), 4.44 (1H, s, CHN), 2.47 (3H, s, *para* Ts); δ_C (100 MHz) 163.5 (C=O), 144.7 (*para* Ts), 136.7 (*ipso* Ts), 135.0 (*ortho* C_6H_5), 130.8 (*ipso* C_6H_5), 130.4 (H_2C=*C*HCHO), 129.8 (H_2C=*C*HCHN), [129.7, 129.6, 129.5 (*meta* and *para* C_6H_5, *meta*

Ts)], 128.2 (*ortho* Ts), 121.8 (H_2C=CHCHN), 120.7 (H_2C=CHCHO), 78.6 (CHO), 64.0 (CHS), 59.7 (CHN), 21.6 (ArCH_3), *m/z* (CI) 433 $[M+NH_4]^+$, 306 $[M-SPh]^+$ (Found: $[M+NH_4]^+$, 433.1269. $C_{21}H_{21}NO_4S_2$ requires $[M+NH_4]^+$, 433.1256).

(Data for 252) R_f 0.51 (50% Et_2O−hexane); δ_H (400 MHz) 7.57-7.53 (2H, m, *ortho* C_6H_5), 7.47-7.44 (3H, m, *meta* and *para* C_6H_5), 5.84 (1H, ddd, *J* 17.5, 11.5, 6.5 Hz, H_2C=C*H*CHO), 5.74 (1H, ddd, *J* 17.0, 11.0, 6.5 Hz, H_2C=C*H*CHN), 5.47 (1H, d, *J* 17.5 Hz, H*H'*C=CHCHO), 5.44 (1H, d, *J* 11.5 Hz, *H*H'C=CHCHO), 5.34 (1H, d, *J* 11.0 Hz, H*H'*C=CHCHN), 5.17 (1H, d, *J* 17.0 Hz, *H*H'C=CHCHN), 5.07-5.04 (1H, m, CHO), 4.48-4.45 (1H, m, CHN); δ_C (100 MHz) 160.4 (C=O), 154.6 (C=N), 135.4 (*ortho* C_6H_5), [130.5 and 130.4 (H_2C=*C*HCHO and H_2C=*C*HCHN)], 129.7 (*ipso* C_6H_5), [129.3 and 127.3 (*meta* and *para* C_6H_5)], 120.6 (H_2C=CHCHN), 120.1 (H_2C=CHCHO), 80.2 (CHO), 62.8 (CHN); *m/z* (ESI) 260 $[M+H]^+$ (Found: $[M+H]^+$, 260.0757. $C_{14}H_{13}NO_2S$ requires $[M+H]^+$, 260.0745).

Ethyl 2-(*tert*-butoxycarbonyl((3*S*,4*R*)-4-(*tert*-butyldimethylsilyloxy)hexa-1,5-dien-3-yl)amino)acetate (254)

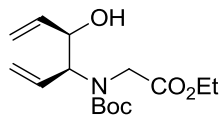


254

A solution of amine **241** (2.30 g, 7.34 mmol, 1.0 eq) and di-*tert*-butyl dicarbonate (2.16 g, 9.90 mmol, 1.35 eq) in toluene (25 mL) was heated to reflux for 13 h. The colourless solution was concentrated under reduced pressure and chromatography of the crude mixture over silica gel (5→10% Et_2O−hexane) gave ethyl 2-(*tert*-butoxycarbonyl((3*S*,4*R*)-4-(*tert*-butyldimethylsilyloxy)hexa-1,5-dien-3-yl)amino)acetate **254** (3.04 g, 100%) as a colourless oil; R_f 0.30 (20% Et_2O−hexane); $[\alpha]_D^{23}$ +6.4 (*c* 0.31,

CH_2Cl_2); ν_{max} (neat) 2931, 2858, 1758, 1700, 1390, 1367, 1251, 1190, 1161, 1090, 1028, 923, 833, 774 cm^{-1}; δ_H (400 MHz, DMSO, 368 K) 5.89 (1H, ddd, *J* 17.5, 10.5, 7.0 Hz, H_2C=C*H*CHO), 5.79 (1H, ddd, *J* 17.5, 10.5, 7.0 Hz, H_2C=C*H*CHN), 5.25-5.16 (3H, m, H*H′*C=CHCHN and H_2C=CHCHO), 5.10 (1H, d, *J* 10.5 Hz, *H*H′C=CHCHN), 4.39 (1H, dd, *J* 7.0, 7.0 Hz, CHOSi), 4.23 (1H, br s, CHN), 4.06 (2H, q, *J* 7.0 Hz, CO_2CH_2), 3.86 (1H, d, *J* 17.5 Hz, NC*H*H′), 3.77 (1H, d, *J* 17.5 Hz, NCH*H′*), 1.37 (9H, s, $CO_2C(CH_3)_3$), 1.17 (3H, t, *J* 7.0 Hz, $CO_2CH_2CH_3$), 0.86 (9H, s, $SiC(CH_3)_3$), 0.02 (3H, s, $SiCH_3$), 0.00 (3H, s, $SiCH_3'$); δ_C (100 MHz, DMSO, 368 K) 174.2 (CO_2Et), 159.1 (NC=O), 143.9 (H_2C=CHCHO), 137.8 (H_2C=CHCHN), 123.8 (H_2C=CHCHO), 120.7 (H_2C=CHCHN), 84.3 ($CO_2C(CH_3)_3$), 79.7 (CHOSi), 64.9 (CO_2CH_2), 52.4 (NCH_2), 35.3 (CHN), 32.7 ($CO_2C(CH_3)_3$), 30.5 ($SiC(CH_3)_3$), 22.5 ($SiC(CH_3)_3$), 18.7 ($CO_2CH_2CH_3$), [0.0 and −0.1 ($Si(CH_3)_2$)]; *m/z* (ESI) 436 $[M+Na]^+$, 414 $[M+H]^+$, 314 $[M-Boc+H_2]^+$ (Found: $[M+H]^+$, 414.2682. $C_{21}H_{39}NO_5Si$ requires $[M+H]^+$, 414.2676) (Found: C, 61.13; H, 9.48; N, 3.43. $C_{21}H_{39}NO_5Si$ requires C, 60.98; H, 9.50; N, 3.39%).

Ethyl 2-(*tert*-butoxycarbonyl((3*S*,4*R*)-4-(hydroxy)hexa-1,5-dien-3-yl)amino)acetate (255)

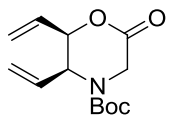


255

To a solution of silyl ether **254** (1.31 g, 3.17 mmol, 1.0 eq) in ethanol (32 mL) at rt was added conc. HCl (1% vol, 0.86 mL) and the solution was stirred overnight. Solid $NaHCO_3$ was added carefully until effervescence stopped. The suspension was filtered and the filtrate was concentrated under reduced pressure. Column chromatography of the crude mixture over silica gel (15% Et_2O−hexane) gave ethyl 2-(*tert*-butoxycarbonyl((3*S*,4*R*)-4-(hydroxy)hexa-1,5-dien-3-yl)amino)acetate **255** (803 mg,

85%) as a colourless oil; R_f 0.39 (50% Et_2O−hexane); ν_{max} (neat) 3451, 2979, 1755, 1697, 1392, 1367, 1191, 1161, 1028, 989, 924, 894, 773 cm^{-1}; δ_H (400 MHz) 5.97-5.78 (2H, m, H_2C=C*H*CHO and H_2C=C*H*CHN), 5.58-3.67 (10H, m, all *H*$_2$C=CH, CHN, CHO, NCH_2 and CO_2CH_2), 1.51-1.46 (9H, 2 × s, $(CH_3)_3$), 1.33-1.28 (3H, 2 × t, *J* 7.0 Hz, $CO_2CH_2CH_3$); δ_C (100 MHz) (peak splitting due to *N*-Boc rotamers) 172.3 (*C*O_2Et), 155.3 (NC=O), [137.3, 137.1, 131.8, 131.5, 131.2 (H_2C=*C*H)], [120.3, 120.1, 115.7 (H_2C=CH)], 80.9 (*C*$(CH_3)_3$), 73.7, 63.2, 62.5, 61.6, 61.4, 47.4, 46.5, [28.3, 28.2 (C(*C*$H_3)_3$)], 14.2 (CH_3); *m/z* (CI) 300 $[M+H]^+$, 317 $[M+NH_4]^+$ (Found: $[M+NH_4]^+$, 317.2081. $C_{15}H_{25}NO_5$ requires $[M+NH_4]^+$, 317.2076).

(2*R*,3*S*)-*tert*-Butyl 6-oxo-2,3-divinylmorpholine-4-carboxylate (256)

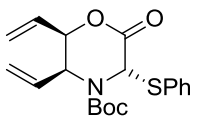


256

A solution of ester **255** (304 mg, 1.01 mmol, 1.0 eq) and *para*-toluenesulfonic acid (19.0 mg, 0.10 mmol, 0.1 eq) in toluene (10 mL) was heated to reflux. After 12 h, solid $NaHCO_3$ was added carefully until effervescence stopped. The suspension was filtered and the filtrate was concentrated under reduced pressure. Column chromatography of the crude mixture over silica gel (20% Et_2O−hexane) gave (2*R*,3*S*)-*tert*-butyl 6-oxo-2,3-divinylmorpholine-4-carboxylate **256** (269 mg, 87%) as a colourless oil; R_f 0.32 (50% Et_2O−hexane); $[\alpha]_D^{23}$ +0.4 (*c* 1.2, CH_2Cl_2); ν_{max} (neat) 2979, 2933, 1755, 1694, 1393, 1367, 1346, 1273, 1251, 1159, 1135, 1109, 1071, 928, 893, 768 cm^{-1}; δ_H (400 MHz, 328 K) 5.84 (1H, ddd, *J* 17.5, 11.0, 6.5 Hz, H_2C=C*H*CHO), 5.79 (1H, ddd, *J* 17.0, 12.0, 6.5 Hz, H_2C=C*H*CHN), 5.52 (1H, dd, *J* 17.5, 1.0 Hz, *H*H'C=CHCHO), 5.41 (1H, dd, *J* 10.5, 1.0 Hz, H*H'*C=CHCHO), 5.35 (1H, d, *J* 12.0 Hz, *H*H'C=CHCHN), 5.23 (1H, d,

J 17.0 Hz, H*H'*C=CHCHN), 5.01 (1H, m, CHO), 4.67 (1H, br s, CHN), 4.26 (1H, d, *J* 19.0 Hz, CH*H'*), 4.17 (1H, d, *J* 19.0 Hz, C*H*H'), 1.49 (9H, s, $C(CH_3)_3$); δ_C (100 MHz) 166.2 (C=O lactone), 153.4 (NC=O), 131.5 (H_2C=*C*HCHO), 129.3 (H_2C=*C*HCHN), 119.9 (H_2C=CHCHN), 119.5 (H_2C=CHCHO), 86.5 (*C*$(CH_3)_3$), 80.2 (CHO), 55.5 (CHN), 44.3 (CH_2), 28.3 ($C(CH_3)_3$); *m/z* (CI) 271 $[M+NH_4]^+$, 215 $[M-t\text{Bu}+H+NH_4]^+$, 254 $[M+H]^+$ (Found: $[M+H]^+$, 254.1395. $C_{13}H_{19}NO_4$ requires $[M+H]^+$, 254.1392) (Found: C, 61.83; H, 7.64; N, 5.46. $C_{13}H_{19}NO_4$ requires C, 61.64; H, 7.56; N, 5.53%).

(3*S*,5*S*,6*R*)-*tert*-Butyl 2-oxo-3-(phenylthio)-5,6-divinylmorpholine-4-carboxylate (257)

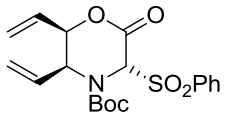


257

To a solution of morpholinone **256** (432 mg, 1.71 mmol, 1.0 eq) and $PhSSO_2Ph$ (1.28 g, 5.12 mmol, 3.0 eq) in THF (8 mL) and DMPU (0.8 mL) at −78 °C was added dropwise a solution of LiHMDS (4.26 mL of a 1.0 M in THF / PhEt solution, 4.26 mmol, 2.5 eq). The orange suspension gradually turned pink and it was stirred at −78 °C for 2.5 h. The suspension was poured saturated aqueous NH_4Cl (20 mL) and diluted with ether (10 mL). The organic phase was separated, the aqueous layer was extracted with ether (20 mL) and the combined organic extracts were washed with brine (40 mL) and dried ($MgSO_4$). Concentration of the filtrate under reduced pressure and chromatography of the crude mixture over silica gel (0→4% Et_2O−hexane) gave (3*S*,5*S*,6*R*)-*tert*-butyl 2-oxo-3-(phenylthio)-5,6-divinylmorpholine-4-carboxylate **257** (528 mg, 85%) as a single diastereomer as a colourless oil; R_f 0.66 (50% Et_2O−hexane); $[\alpha]_D^{23}$ +102.1 (*c* 1.1, CH_2Cl_2); ν_{max} (neat) 2979, 2931, 1753, 1703, 1367, 1328, 1272, 1241, 1151, 1066,

983 cm^{-1}; δ_H (400 MHz, DMSO, 363 K) 7.60-7.53 (2H, m, *ortho* C_6H_5), 7.49-7.31 (3H, m, *meta* and *para* C_6H_5), 5.91 (1H, ddd, *J* 17.5, 12.0, 6.5 Hz, H_2C=C*H*CHO), 5.71 (1H, ddd, *J* 17.0, 11.5, 6.5 Hz, H_2C=C*H*CHN), 5.65 (1H, s, CHS), 5.49 (1H, dd, *J* 17.5, 1.5 Hz, *H*H'C=CHCHO), 5.41 (1H, dd, *J* 12.0, 1.5 Hz, H*H'*C=CHCHO), 5.33-5.23 (2H, m, *H*H'C=CHCHN and CHO), 5.07 (1H, d, *J* 17.0 Hz, H*H'*C=CHCHN), 4.62-4.56 (1H, m, CHN), 1.42 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, DMSO, 363 K) 163.6 (C=O lactone), 151.3 (NC=O), 136.8 (*ipso* C_6H_5), 136.5 (*meta* C_6H_5), 133.0 (*para* C_6H_5), 130.8 (H_2C=*C*HCHO), 128.9 (*ortho* C_6H_5), 128.5 (H_2C=*C*HCHN), 118.8 (H_2C=CHCHO), 118.0 (H_2C=CHCHN), 81.3 ($C(CH_3)_3$), 77.0 (CHO), 61.9 (CSO_2), 57.7 (CHN), 27.3 ($C(CH_3)_3$); *m/z* (CI) 379 $[M+NH_4]^+$ (Found: $[M+NH_4]^+$, 379.1689. $C_{19}H_{23}NO_4S$ requires $[M+NH_4]^+$, 379.1692) (Found: C, 63.26; H, 6.53; N, 3.84. $C_{19}H_{23}NO_4S$ requires C, 63.13; H, 6.41; N, 3.88%).

(3*R*,5*S*,6*R*)-*tert*-Butyl 2-oxo-3-(phenylsulfonyl)-5,6-divinylmorpholine-4-carboxylate (258)

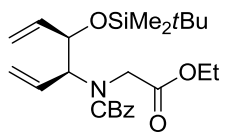


258

To a solution of sulfide **257** (528 mg, 1.46 mmol, 1.0 eq) in methanol (7 mL) was added magnesium monoperoxyphthalate hexahydrate (MMPP) (80% purity, 4.50 g, 7.30 mmol, 5.0 eq) and the white suspension was stirred at rt overnight. The suspension was concentrated and the residue was diluted with water (40 mL) and ether (40 mL). The organic phase was separated, the aqueous layer was extracted again with ether (40 mL) and the combined organic extracts were dried ($MgSO_4$). Concentration of the filtrate under reduced pressure and chromatography of the crude mixture over silica gel

(0→10% Et_2O−hexane) gave (3*R*,5*S*,6*R*)-*tert*-butyl 2-oxo-3-(phenylsulfonyl)-5,6-divinylmorpholine-4-carboxylate **258** (292 mg, 51%) as a single diastereomer as a white solid; mp 107–111 °C (Et_2O/hexane); R_f 0.43 (50% Et_2O−hexane); $[\alpha]_D^{23}$ +67.4 (*c* 0.8, CH_2Cl_2); ν_{max} (neat) 2979, 2935, 1758, 1708, 1368, 1310, 1270, 1247, 1145, 1076, 985 cm^{-1}; δ_H (400 MHz, DMSO, 363 K) 7.94 (2H, d, *J* 7.5 Hz, *ortho* C_6H_5), 7.83 (1H, t, *J* 7.5 Hz, *para* C_6H_5), 7.72 (2H, d, *J* 7.5 Hz, *meta* C_6H_5), 5.99-5.90 (2H, m, H_2C=C*H*CHO and $CHSO_2$), 5.72 (1H, ddd, *J* 17.0, 11.0, 6.5 Hz, H_2C=C*H*CHN), 5.51 (1H, d, *J* 17.5 Hz, *H*H'C=CHCHO), 5.46-5.42 (2H, m, H*H'*C=CHCHO and CHO), 5.29 (1H, d, *J* 11.0 Hz, *H*H'C=CHCHN), 5.08 (1H, d, *J* 17.0 Hz, H*H'*C=CHCHN), 4.79-4.66 (1H, br s, CHN), 1.47 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, DMSO, 363 K) 159.7 (C=O lactone), 151.7 (NC=O), 137.5 (*ipso* C_6H_5), 134.4 (*para* C_6H_5), 131.4 (H_2C=*C*HCHO), 130.4 (H_2C=*C*HCHN), 129.1 (*meta* C_6H_5), 128.2 (*ortho* C_6H_5), 119.0 (H_2*C*=CHCHO), 118.5 (H_2*C*=CHCHN), 82.1 (*C*$(CH_3)_3$), 80.7 (CHO), 78.0 (CSO_2), 55.9 (CHN), 27.4 (C(*C*$H_3)_3$); *m/z* (CI) 411 $[M+NH_4]^+$, 355 $[M-t\text{Bu}+H+NH_4]^+$, 269 $[M-SO_2Ph+H+NH_4]^+$ (Found: $[M+NH_4]^+$, 411.1591. $C_{19}H_{24}NO_6S$ requires $[M+NH_4]^+$, 411.1590) (Found: C, 58.13; H, 5.78; N, 3.48. $C_{19}H_{23}NO_6S$ requires C, 58.00; H, 5.89; N, 3.56%).

Ethyl 2-(benzyloxycarbonyl((3*S*,4*R*)-4-(*tert*-butyldimethylsilyloxy)hexa-1,5-dien-3-yl)amino)acetate (263)

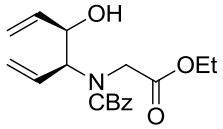


263

To a solution of amine **241** (1.51 g, 4.83 mmol, 1.0 eq) in CH_2Cl_2 (20 mL) and sat. $NaHCO_3$ solution (15 mL) at rt was added benzyl chloroformate (1.00 mL, 7.00 mmol, 1.45 eq) and the solution was stirred for 2 h. The solution was passed over a phase

separator, the organic phase was concentrated under reduced pressure and chromatography of the crude mixture over silica gel (0→10% Et_2O−hexane) gave ethyl 2-(benzyloxycarbonyl((3*S*,4*R*)-4-(*tert*-butyldimethylsilyloxy)hexa-1,5-dien-3-yl)amino)-acetate **263** (2.16 g, 100%) as a colourless oil; R_f 0.61 (50% Et_2O−hexane); $[\alpha]_D^{25}$ +4.5 (*c* 0.37, CH_2Cl_2); ν_{max} (neat) 2955, 2930, 2857, 1756, 1704, 1442, 1401, 1251, 1189, 1091, 1027, 928, 832, 772 cm^{-1}; δ_H (400 MHz, DMSO, 368 K) 7.37-7.31 (5H, m, C_6H_5), 5.92 (1H, ddd, *J* 17.5, 10.0, 7.0 Hz, H_2C=C*H*CHO), 5.78 (1H, ddd, *J* 17.5, 10.5, 7.0 Hz, H_2C=C*H*CHN), 5.28-5.08 (6H, m, *H*$_2$C=CHCHO, *H*$_2$C=CHCHN and C*H*$_2$Ph), 4.41 (1H, br s, CHOSi), 4.30 (1H, br s, CHN), 4.04 (2H, q, *J* 7.0 Hz, $CO_2CH_2CH_3$), 3.98 (1H, d, *J* 17.5 Hz, NC*H*H′), 3.90 (1H, d, *J* 17.5 Hz, NCH*H*′), 1.13 (3H, t, *J* 7.0 Hz, $CO_2CH_2CH_3$), 0.86 (9H, s, $C(CH_3)_3$), 0.00 (3H, s, $SiCH_3$), −0.04 (3H, s, $SiCH_3$′); δ_C (100 MHz, DMSO, 368 K) 168.7 (*C*O_2Et), 154.7 (NC=O), 138.4 (H_2C=*C*HCHN), 136.1 (*ipso* C_6H_5), 132.3 (H_2C=*C*HCHO), [127.7, 127.3, 127.0 (*ortho*, *meta and para* C_6H_5)], 119.0 (H_2C=CHCHO), 115.7 (H_2C=CHCHN), 74.3 (CHOSi), 66.2 (*C*H_2Ph), 63.7 (CHN), 59.8 (NCH_2), 47.0 ($CO_2CH_2CH_3$), 25.2 ($C(CH_3)_3$), 17.2 ($C(CH_3)_3$), 13.4 ($CO_2CH_2CH_3$), [−4.7 and −5.3 ($Si(CH_3)_2$)]; *m/z* (CI) 448 $[M+H]^+$, 465 $[M+NH_4]^+$, 314 $[M-CBz+H]^+$ (Found: $[M+H]^+$, 448.2520. $C_{24}H_{37}NO_5Si$ requires $[M+H]^+$, 448.2519) (Found: C, 64.55; H, 8.33; N, 3.10. $C_{24}H_{37}NO_5Si$ requires C, 64.39; H, 8.33; N, 3.13%).

Ethyl 2-(benzyloxycarbonyl((3*S*,4*R*)-4-(hydroxy)hexa-1,5-dien-3-yl)amino)acetate (264)

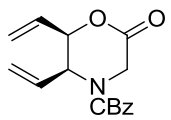


264

To a solution of silyl ester **25** (140 mg, 0.31 mmol, 1.0 eq) in ethanol (1.5 mL) at rt was added conc. HCl (1.5% vol, 0.06 mL) and the solution was stirred overnight. Solid

$NaHCO_3$ was added carefully until effervescence stopped. The suspension was filtered and the filtrate was concentrated under reduced pressure. Column chromatography of the crude mixture over silica gel (10→20% Et_2O−hexane) gave ethyl 2-(benzyloxycarbonyl((3*S*,4*R*)-4-(hydroxy)hexa-1,5-dien-3-yl)amino)acetate **264** (104 mg, 89%) as a colourless oil; R_f 0.31 (50% Et_2O−hexane); $[\alpha]_D^{25}$ −12.8 (*c* 0.45, CH_2Cl_2); ν_{max} (neat) 3458, 2983, 1752, 1697, 1444, 1403, 1256, 1193, 1115, 1027, 988, 925 cm^{-1}; δ_H (400 MHz, DMSO, 368 K) 7.34-7.28 (5H, m, C_6H_5), 5.93 (1H, ddd, *J* 17.0, 11.0, 6.5 Hz, H_2C=C*H*CHO), 5.85 (1H, ddd, *J* 16.5, 11.0, 6.0 Hz, H_2C=C*H*CHN), 5.26-5.05 (3H, m, *H*$_2$C=CHCHO and *H*H'C=CHCHN), 5.09-5.05 (3H, m, H*H'*C=CHCHN and C*H*$_2$Ph), 4.83 (1H, d, *J* 5.5 Hz, OH), 4.45 (1H, br s, CHOH), 4.29-4.25 (1H, m, CHN), 4.05 (2H, q, *J* 7.0 Hz, $CO_2CH_2CH_3$), 3.99 (2H, ABq, *J* 17.5 Hz, NCH_2), 1.14 (3H, t, *J* 7.0 Hz, $CO_2CH_2CH_3$); δ_C (100 MHz, DMSO, 368 K) 169.0 (*C*O_2Et), 155.0 (NC=O), 139.1 (H_2C=*C*HCHN), 136.2 (*ipso* C_6H_5), 132.5 (H_2C=*C*HCHO), [127.7, 127.2, 126.8 (*ortho*, *meta and para* C_6H_5)], [118.0, 114.5 (H_2C=CHCHO and H_2C=CHCHN)], 72.3 (CHN), 66.2 (*C*H_2Ph), 62.0 (CHOH), 59.7 (NCH_2), 46.3 ($CO_2CH_2CH_3$), 13.4 ($CO_2CH_2CH_3$); *m/z* (CI) 334 $[M+H]^+$, 351 $[M+NH_4]^+$ (Found: $[M+H]^+$, 334.1659. $C_{18}H_{23}NO_5$ requires $[M+H]^+$, 334.1654) (Found: C, 64.49; H, 6.92; N, 3.74. $C_{18}H_{23}NO_5$ requires C, 64.85; H, 6.95; N, 4.20%).

(2*R*,3*S*)-Benzyl 6-oxo-2,3-divinylmorpholine-4-carboxylate (265)

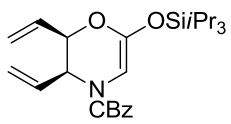


265

A solution of ester **264** (1.73 g, 5.18 mmol, 1.0 eq) and and *para*-toluenesulfonic acid (98.5 mg, 0.52 mmol, 0.1 eq) in toluene (30 mL) was heated to reflux overnight. The

brown solution was concentrated under reduced pressure and column chromatography of the crude mixture over silica gel (10→25% Et_2O−hexane) gave (2*R*,3*S*)-benzyl 6-oxo-2,3-divinylmorpholine-4-carboxylate **265** (1.49 g, 95%) as a pale yellow oil; R_f 0.31 (50% Et_2O−hexane); $[\alpha]_D^{25}$ +4.0 (*c* 0.3, CH_2Cl_2); ν_{max} (neat) 2953, 1699 (2 C=O bands overlapping), 1525, 1453, 1296, 1210, 1173, 1068, 1028 cm^{-1}; δ_H (400 MHz, DMSO, 368 K) 7.38-7.29 (5H, m, C_6H_5), 5.94 (1H, ddd, *J* 17.5, 11.0, 5.5 Hz, H_2C=C*H*CHO), 5.79 (1H, ddd, *J* 17.0, 10.5, 5.0 Hz, H_2C=C*H*CHN), 5.44 (1H, dd, *J* 17.5, 1.5 Hz, *H*H'C=CHCHO), 5.38 (1H, dd, *J* 11.0, 1.5 Hz, H*H'*C=CHCHO), 5.31-5.26 (2H, m, H_2C=CHCHN), 5.18-5.11 (3H, m, CHO and CH_2Ph), 4.74-4.70 (1H, m, CHN), 4.40 (1H, d, *J* 17.5 Hz, NCH*H'*), 4.15 (1H, d, *J* 17.5 Hz, NC*H*H'); δ_C (100 MHz, DMSO, 368 K) 165.8 (C=O lactone), 153.3 (NC=O), 136.1 (*ipso* C_6H_5), 131.8 (H_2C=*C*HCHO), 130.1 (H_2C=*C*HCHN), [128.0, 127.6, 127.2 (*ortho*, *meta* and *para* C_6H_5)], 118.6 (H_2C=CHCHN), 118.2 (H_2C=CHCHO), 78.4 (CHO), 66.5 (*C*H_2Ph), 54.9 (CHN), 44.0 (NCH_2); *m/z* (CI) 305 $[M+NH_4]^+$, 288 $[M+H]^+$ (Found: $[M+H]^+$, 288.1244. $C_{16}H_{17}NO_4$ requires $[M+H]^+$, 288.1236) (Found: C, 66.00; H, 6.11; N, 4.90. $C_{16}H_{17}NO_4$ requires C, 66.89; H, 5.96; N, 4.88%).

(2*R*,3*S*)-Benzyl 6-(triisopropylsilyloxy)-2,3-divinyl-2,3-dihydro-1,4-oxazine-4-carboxylate (266)

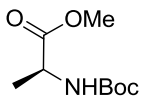


266

To a solution of morpholinone **265** (60.0 mg, 0.21 mmol, 1.0 eq) in dry toluene (0.5 mL) at rt was added Et_3N (0.33 mL, 2.30 mmol, 11 eq) and *i*Pr_3SiOTf (0.06 mL, 0.23 mmol, 1.1 eq). A cloudy solution was formed which separated into two liquid phases upon immediate addition of *i*Pr_3SiOTf. After 2 min, the volatiles were removed under reduced

pressure. The crude oil was redissolved in $CDCl_3$ and filtered over a small pad of TMS-functionalised silica gel to give a crude yellow solution of (2*R*,3*S*)-benzyl 6-(triisopropylsilyloxy)-2,3-divinyl-2,3-dihydro-1,4-oxazine-4-carboxylate **266**; R_f 0.08 (50% Et_2O−hexane); ν_{max} (neat) 2943, 2866, 1755, 1703, 1412, 1296, 1275, 1241, 1214, 1162, 1107, 1030, 985, 934 cm^{-1}; δ_H (400 MHz) 7.42-7.32 (5H, m, C_6H_5), 5.93-5.72 (3H, m, H_2C=C*H* and CHCOSi), 5.43 (1H, d, *J* 17.5, 1.5 Hz, *H*H'C=CHCHO), 5.37-5.14 (5H, m, H*H'*C=CHCHO, *H*$_2$C=CHCHN and CH_2), 4.75-4.58 (1H, m, CHO), 4.57-4.45 (1H, m, CHN), 1.25-1.08 (21H, m, *i*Pr).

(*S*)-Methyl 2-(*tert*-butoxycarbonylamino)propanoate (275)[92]

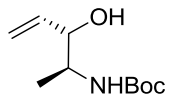


275

To a solution of Boc-L-alanine (1.00 g, 5.29 mmol, 1.0 eq) in DMF (2 mL) at rt was added anhydrous Na_2CO_3 (1.12 g, 10.6 mmol, 2.0 eq), then iodomethane (1.32 mL, 21.1 mmol, 4.0 eq) dropwise. After 24 h, the reaction mixture was diluted with EtOAc (50 mL), water (50 mL) and the organic layer was separated, washed with water (3 × 50 mL), brine (3 × 50 mL) and dried over $MgSO_4$. Concentration of the filtrate under reduced pressure and chromatography of the crude mixture over silica gel (10% Et_2O−hexane) gave (*S*)-methyl 2-(tert-butoxycarbonylamino)propanoate **275** (998 mg, 93%) as a white solid; mp 29–31 °C; R_f 0.53 (50% Et_2O−hexane); $[\alpha]_D^{25}$ −4.0 (*c* 0.3, $CHCl_3$); {lit.[111] $[\alpha]_D^{20}$ −3.4 (*c* 1.0, $CHCl_3$)}; ν_{max} (neat) 3358, 2979, 1742, 1696, 1514, 1453, 1366, 1249, 1214, 1160, 1067, 1024 cm^{-1}; δ_H (400 MHz) 5.06 (1H, br s, NH*)*, 4.28-4.27 (1H, m, CH), 4.76 (3H, s, OCH_3), 1.46 (9H, s, $C(CH_3)_3$), 1.39 (3H, d, *J* 7.0 Hz, CH_3); δ_C (100 MHz) 173.9 (*C*O_2CH_3), 155.1 (NC=O), 79.9 (*C*$(CH_3)_3$), 52.3 (OCH_3), 49.1

(CH), 28.3 (C(CH_3)$_3$), 15.3 (CH_3); *m/z* (CI) 221 $[M+NH_4]^+$, 204 $[M+H]^+$, 165 $[M-tBu+H+NH_4]^+$; data in agreement with published data.[111]

***tert*-Butyl (2*S*,3*S*)-3-hydroxypent-4-en-2-ylcarbamate (276)**[93]

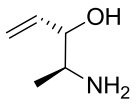


276

To a stirred solution of ester **275** (8.00 g, 39.4 mmol, 1.0 eq) in CH_2Cl_2 (40 mL) at −78 °C was added a solution of DIBAL-H (47.2 mL of a 1 M in hexane solution, 47.2 mmol, 1.2 eq) at a rate of 20 mLh^{-1} using a syringe pump. After 5 h, vinylmagnesium bromide (113 mL of a 0.7 M solution in THF, 78.8 mmol, 2.0 eq) was added dropwise over 1.5 h *via* a cannula. The colourless solution gradually turned brown and was allowed to warm up to rt gradually overnight. The solution was poured into aqueous 1 M HCl (200 mL), the organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL). The combined organic extracts were washed with brine (500 mL) and dried ($MgSO_4$). Concentration under reduced pressure and chromatography of the crude mixture over silica gel (0→15% Et_2O−hexane) gave a 5:1 diastereomeric mixture of *tert*-butyl (2*S*,3*S*)-3-hydroxypent-4-en-2-ylcarbamate **276** (4.79 g, 60%) as a colourless oil; R_f 0.29 (50% Et_2O−hexane); ν_{max} (neat) 3426, 2979, 1684, 1505, 1367, 1247, 1163, 1050, 1026, 737 cm^{-1}; (Major diastereomer) δ_H (400 MHz) 5.88 (1H, ddd, *J* 17.0, 11.0, 6.5 Hz, H_2C=C*H*), 5.31 (1H, dd, *J* 17.0, 1.5 Hz, H′*H*C=CH), 5.20 (1H, dd, *J* 11.0, 1.5 Hz, *H*′HC=CH), 4.76 (1H, br s, NH), 4.03-4.00 (1H, m, C*H*OH), 3.74-3.63 (1H, m, C*H*N), 2.87 (1H, br s, OH), 1.44 (9H, s, C(CH_3)$_3$), 1.17 (3H, d, *J* 7.0 Hz, CH_3); δ_C (100 MHz) 156.3 (C=O), 137.9 (H_2C=*C*H), 116.6 (H_2C=CH), 79.5 (*C*(CH_3)$_3$), 75.8 (COH), 50.6 (CHN), 28.4 (C(*C*H_3)$_3$), 17.5 (CH_3); *m/z* (CI) 202 $[M+H]^+$,

219 $[M+NH_4]^+$, 163 $[M-Boc+H+NH_4]^+$ (Found: $[M+H]^+$, 202.1436. $C_{10}H_{19}NO_3$ requires $[M+H]^+$, 202.1443); data in agreement with published data.[93(b)]

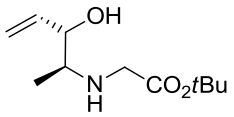
(3*S*,4*S*)-4-Aminopent-1-en-3-ol (278)[81(b)]



278

To a solution of 5:1 diastereomeric mixure of *tert*-butyl (2*S*,3*S*)-3-hydroxypent-4-en-2-ylcarbamate **276** (2.86 g, 14.2 mmol, 1.0 eq) in CH_2Cl_2 (35 mL) at rt was added TFA (9 mL) dropwise and the brown solution was stirred for 1 h. The volatiles were removed under reduced pressure and the residue was purified by a SCX-2 column (100% MeOH then 1% NH_3 in MeOH) to give a 5.5:1 diastereomeric mixture of (3*S*,4*S*)-4-aminopent-1-en-3-ol **278** (998 mg, 93%) as a brown oil; R_f 0.14 (1% NH_4OH−10% MeOH−CH_2Cl_2); ν_{max} (neat) 3277, 3067, 2976, 1647, 1451, 1379, 1042, 991, 928 cm^{-1}; (Major diastereomer) δ_H (400 MHz) 5.84 (1H, ddd, *J* 17.0, 10.5, 6.5 Hz, H_2C=C*H*), 5.33 (1H, d, *J* 17.0 Hz, C*H*H′), 5.20 (1H, d, *J* 10.5 Hz, CH*H*′), 3.73 (1H, dd, *J* 6.5, 6.5 Hz, CHO), 2.83 (1H, dq, *J* 6.5, 6.5 Hz, CHN), 2.45-1.65 (3H, br s, OH, NH_2), 1.11 (3H, d, *J* 6.5 Hz, CH_3); δ_C (100 MHz) 138.9 (H_2C=*C*H), 116.4 (CH_2), 77.0 (COH), 50.9 (CHN), 20.3 (CH_3); *m/z* (CI) 102 $[M+H]^+$, 84 $[M-OH]^+$ (Found: $[M+H]^+$, 102.0919. $C_5H_{11}NO$ requires $[M+H]^+$, 102.0919).

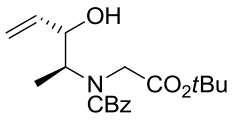
***tert*-Butyl 2-((2*S*,3*S*)-3-hydroxypent-4-en-2-ylamino)acetate (279)**



279

To a stirred solution of 5.5:1 diastereomeric mixture of amino-alcohol **278** (1.11 mg, 11.0 mmol, 1.0 eq) in THF (35 mL) at rt was added *N*,*N*-diisopropylethylamine (2.49 mL, 14.3 mmol, 1.3 eq) then *tert*-butyl bromoacetate (1.86 mL, 12.6 mmol, 1.15 eq) dropwise and the brown suspension was stirred at rt overnight. The mixture was filtered, the filtrate was removed under reduced pressure and chromatography of the crude mixture over silica gel (0.1% NH_4OH−40% EtOAc−hexane) gave a 4.5:1 diastereomeric mixture of *tert*-butyl 2-((2*S*,3*S*)-3-hydroxypent-4-en-2-ylamino)acetate **279** (1.14 g, 48%) as a brown solid; mp 44–46 °C; R_f 0.20 (80% Et_2O−hexane); ν_{max} (neat) 3345, 2976, 1730, 1368, 1229, 1151, 1043, 993, 923 cm^{-1}; (Major diastereomer) δ_H (400 MHz) 5.82 (1H, ddd, *J* 17.0, 10.5, 6.5 Hz, H_2C=C*H*), 5.34 (1H, d, *J* 17.0 Hz, *H*H′C=CH), 5.19 (1H, d, *J* 10.5 Hz, H*H*′C=CH), 3.73 (1H, dd, *J* 6.5, 6.5 Hz, CHO), 3.37 (1H, d, *J* 17.5 Hz, NC*H*H′), 3.29 (1H, d, *J* 17.5 Hz, NCH*H*′), 2.54 (1H, dq, *J* 6.5, 6.5 Hz, CHN), 1.47 (9H, s, $(CH_3)_3$), 1.06 (3H, d, *J* 6.5 Hz, CH_3), no NH peak observed; δ_C (100 MHz) 171.9 (C=O), 138.7 (H_2C=*C*H), 116.7 (H_2C=CH), 81.4 (*C*$(CH_3)_3$), 72.6 (COH), 57.6 (CHN), 49.4 (NCH_2), 28.1 (C(*C*$H_3)_3$), 16.8 (CH_3); *m/z* (CI) 216 $[M+H]^+$, 158 $[M-t\text{Bu}]^+$, 102 $[M-CH_2CO_2t\text{Bu}+2H]^+$ (Found: $[M+H]^+$, 216.1590. $C_{11}H_{21}NO_3$ requires $[M+H]^+$, 216.1600).

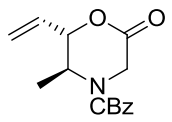
***tert*-Butyl 2-(benzyloxycarbonyl(2*S*,3*S*)-3-hydroxypent-4-en-2-ylamino)acetate (280)**



280

To a solution of 4.5:1 diastereomeric mixture of amine **279** (36.0 mg, 0.17 mmol, 1.0 eq) in CH_2Cl_2 (2 mL) and sat. $NaHCO_3$ solution (1 mL) at rt was added benzyl chloroformate (0.04 mL, 0.25 mmol, 1.5 eq). After 4 h, the solution was passed over a phase separator, the organic phase was concentrated under reduced pressure and chromatography of the crude mixture over silica gel (20% Et_2O−hexane) gave a 4.5:1 diastereomeric mixture of *tert*-butyl 2-(benzyloxycarbonyl(2*S*,3*S*)-3-hydroxypent-4-en-2-ylamino)acetate **280** (55.1 mg, 93%) as a colourless oil; R_f 0.31 (50% Et_2O−hexane); ν_{max} (neat) 3452, 2979, 1746, 1698, 1442, 1408, 1368, 1331, 1243, 1207, 1151, 1015, 994, 925, 771 cm^{-1}; (Major diastereomer) δ_H (500 MHz, DMSO, 363 K) 7.36-7.27 (5H, m, C_6H_5), 5.82 (1H, ddd, *J* 17.0, 11.5, 6.5 Hz, H_2C=C*H*), 5.24 (1H, d, *J* 17.0 Hz, *H*H′C=CH), 5.09-5.03 (3H, m, H*H′*C=CH and CH_2Ph), 4.69 (1H, m, OH), 4.10-3.97 (2H, m, CHO and CHN), 3.92 (1H, d, *J* 18.0 Hz, NC*H*H′), 3.87 (1H, d, *J* 18.0 Hz, NCH*H′*), 1.37 (9H, s, $(CH_3)_3$), 1.12 (3H, d, *J* 7.0 Hz, CH_3); δ_C (125 MHz, DMSO, 363 K) 168.9 (*C*O_2*t*Bu), 155.0 (NC=O), 138.8 (H_2C=*C*H), 136.4 (*ipso* C_6H_5), [127.7, 127.1, 126.8 (*ortho*, *meta* and *para* C_6H_5)], 114.7 (H_2C=CH), 80.2 (*C*$(CH_3)_3$), 73.0 (COH), 65.8 (*C*H_2Ph), 55.5 (CHN), 46.1 (NCH_2), 27.2 (C(*C*$H_3)_3$), 14.5 (CH_3); *m/z* (CI) 350 $[M+H]^+$, 367 $[M+NH_4]^+$, 311 $[M-tBu+H+NH_4]^+$, 294 $[M-tBu+2H]^+$ (Found: $[M+H]^+$, 350.1962. $C_{19}H_{27}NO_5$ requires $[M+H]^+$, 350.1967).

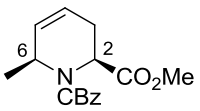
(2*S*,3*S*)-Benzyl 3-methyl-6-oxo-2-vinylmorpholine-4-carboxylate (281)



281

A solution of a 4.5:1 diastereomeric mixture of ester **280** (140 mg, 0.40 mmol, 1.0 eq) and TFA (0.04 mL, 0.48 mmol, 1.2 eq) in CH_2Cl_2 (4 mL) was heated to reflux. After 15 h, the volatiles were removed under reduced pressure and chromatography of the crude mixture over silica gel (40% Et_2O−hexane) gave a 4.5:1 diastereomeric mixture of (2*S*,3*S*)-benzyl 3-methyl-6-oxo-2-vinylmorpholine-4-carboxylate **281** (113 mg, 100%) as a colourless oil; R_f 0.31 (50% Et_2O−hexane); ν_{max} (neat) 1749, 1699, 1411, 1308, 1208, 1114, 1019, 983, 938, 915, 765, 736 cm^{-1}; (Major diastereomer) δ_H (400 MHz, DMSO, 363 K) 7.40 (5H, m, C_6H_5), 5.94 (1H, ddd, *J* 17.0, 11.5, 6.5 Hz, H_2C=C*H*), 5.36-5.30 (2H, m, H_2C=CH), 5.14 (2H, s, CH_2Ph), 4.89 (1H, ddt, J 5.5, 4.5, 1.5 Hz, CHO), 4.32 (1H, d, *J* 18.0 Hz, NC*H*H'), 4.16 (1H, dq, *J* 6.5, 4.5 Hz, CHN), 4.08 (1H, d, *J* 18.0 Hz, NCH*H'*), 1.24 (3H, d, *J* 6.5 Hz, CH_3); δ_C (100 MHz, DMSO. 363 K) 165.7 (lactone C=O), 153.4 (NC=O), 136.0 (*ipso* C_6H_5), 134.1 (H_2C=*C*H), [127.9, 127.4, 127.0 (*ortho*, *meta* and *para* C_6H_5)], 118.1 (H_2C=CH), 80.6 (CHO), 66.4 (*C*H_2Ph), 48.6 (CHN), 42.5 (NCH_2), 15.1 (CH_3); *m/z* (ESI) 276 $[M+H]^+$, 208 $[M-CH_2Ph+H+Na]^+$ (Found: $[M+H]^+$, 276.227. $C_{15}H_{17}NO_4$ requires $[M+H]^+$, 276.1236) (Found: C, 65.55; H, 6.09; N, 4.96. $C_{15}H_{17}NO_4$ requires C, 65.44; H, 6.22; N, 5.09%).

(2*S*,6*S*)-1-Benzyl 2-methyl 6-methyl-2,3-dihydropyridine-1,2(6*H*)-dicarboxylate (284)

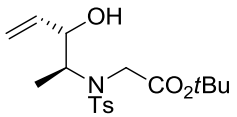


284

To a solution of a 4.5:1 diastereomeric mixture of morpholinone **281** (51.0 mg, 0.19 mmol, 1.0 eq) in toluene (1 mL) at rt was added Et_3N (0.05 mL, 0.37 mmol, 2.0 eq), *i*Pr_3SiOTf (0.08 mL, 0.28 mmol, 1.5 eq) and the colourless solution was heated to reflux. After 4 h, the volatiles were removed under reduced pressure to give the crude silyl ester product as a colourless oil. The residue was redissolved in THF (1 mL) to give a colourless solution, then TBAF.$3H_2O$ (145 mg, 0.46 mmol, 2.5 eq) and iodomethane (0.03 mL, 0.56 mmol, 3.0 eq) were added consecutively at rt. After 2 h, the yellow solution was quenched with saturated aqueous NH_4Cl (1 mL) and concentrated under reduced pressure. The solution was diluted with CH_2Cl_2 (5 mL) and passed over a phase separator. The organic phase was concentrated under reduced pressure and chromatography of the crude mixture over silica gel (10% Et_2O−hexane) gave (2*S*,6*S*)-1-benzyl 2-methyl 6-methyl-2,3-dihydropyridine-1,2(6*H*)-dicarboxylate **284** (34.0 mg, 64% of a maximum possible yield of 82%) as a colourless oil as a single diastereomer; R_f 0.45 (50% Et_2O−hexane); $[\alpha]_D^{25}$ +40.7 (*c* 1.5, CH_2Cl_2); ν_{max} (neat) 2952, 1740, 1695, 1408, 1321, 1296, 1200, 1096, 1070, 1034, 972, 769 cm^{-1}; δ_H (400 MHz, 323K) 7.37-7.29 (5H, m, C_6H_5), 5.81-5.76 (1H, m, H-4), 5.60 (1H, br s, H-5), 5.23 (2H, s, C*H*$_2$Ph), 5.15 (1H, br s, H-2), 4.47 (1H, br s, H-6), 3.68 (3H, s, OCH_3), 2.70 (1H, dd, *J* 17.5, 6.5 Hz, H-3), 2.40-2.31 (1H, m, H-3), 1.27 (3H, d, *J* 6.5 Hz, CH_3); δ_C (100 MHz) 172.4 (CO_2CH_3), 155.6 (NC=O), 136.8 (*ipso* C_6H_5), 129.2 (C-4), [128.5, 128.0, 127.9 (*ortho*, *meta* and *para* C_6H_5)], 121.8 (C-5), 67.5 (OCH_2), 52.0 (OCH_3), 50.7 (C-2), 48.3 (C-6),

25.2 (C-3), 20.3 (C*C*H$_3$); *m/z* (CI) 274 [M+H]$^+$, 290 [M+OH]$^+$, 307 [M+(OH)$_2$]$^+$ (Found: [M+OH]$^+$, 290.1392. $C_{16}H_{19}NO_3$ requires [M+OH]$^+$, 290.1392) (Found: C, 66.33; H, 6.52; N, 4.75. $C_{16}H_{19}NO_3$ requires C, 65.42; H, 6.62; N, 4.84%).

***tert*-Butyl 2-(*N*-((2*S*,3*S*)-3-hydroxypent-4-en-2-yl)-4-methylphenylsulfonamido)acetate (285)**

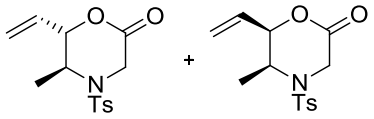


285

To a solution of a 4.5:1 diastereomeric mixture of amine **279** (74.6 mg, 0.35 mmol, 1.0 eq) in CH_2Cl_2 (2 mL) at rt was added Et_3N (0.07 mL, 0.52 mmol, 1.5 eq), *para*-toluenesulfonyl chloride (79.0 mg, 0.42 mmol, 1.2 eq), DMAP (4.20 mg, 0.03 mmol, 0.1 eq) and the yellow solution was stirred at rt. After 18 h, the resultant precipitate was filtered off, concentration of the filtrate under reduced pressure and chromatography of the crude oil over silica gel (20% Et_2O−hexane) gave a 4.5:1 diastereomeric mixture of *tert*-butyl 2-(*N*-((2*S*,3*S*)-3-hydroxypent-4-en-2-yl)-4-methylphenylsulfonamido)acetate **285** (122 mg, 96%) as a white solid; mp 100–102 °C; R_f 0.35 (50% Et_2O−hexane); ν_{max} (neat) 3444 (br), 2985, 1724, 1369, 1345, 1241, 1153, 1087, 1065, 907, 927, 816 cm^{-1}; (Major diastereomer) δ_H (400 MHz) 7.79 (2H, d, *J* 8.0 Hz, *ortho* Ts), 7.32 (2H, d, *J* 8.0 Hz, *meta* Ts), 5.79 (1H, ddd, *J* 17.0, 10.5, 7.0 Hz, H_2C=C*H*), 5.36 (1H, dd, *J* 17.0, 1.5 Hz, *H*H′C=CH), 5.24 (1H, d, *J* 10.5 Hz, H*H*′C=CH), 4.42 (1H, d, *J* 2.5 Hz, OH), 4.13 (1H, d, *J* 18.0 Hz, NC*H*H′), 3.80-3.75 (1H, m, CHN), 3.69-3.64 (1H, m, CHO), 3.60 (1H, d, *J* 18.0 Hz, NCH*H*′), 2.45 (3H, s, *para* Ts), 1.52 (9H, s, C(CH_3)$_3$), 0.91 (3H, d, *J* 7.0 Hz, CH_3); δ_C (100 MHz) 170.6 (C=O), 143.7 (*para* Ts), 136.9 (*ipso* Ts), 136.4 (H_2C=*C*H), 129.7 (*meta* Ts), 127.6 (*ortho* Ts), 118.4 (H_2*C*=CH), 83.3 (CO_2*C*), 74.4 (COH), 58.8

(CHN), 44.2 (CH_2), 27.9 ($C(CH_3)_3$), 21.6 ($ArCH_3$), 14.3 (CH_3); *m/z* (CI) 331 $[M-t\text{Bu}+H+NH_4]^+$, 387 $[M+NH_4]^+$ (Found: $[M+NH_4]^+$, 387.1956. $C_{18}H_{27}NO_5S$ requires $[M+NH_4]^+$, 387.1954).

(5*S*,6*S*)-5-Methyl-4-tosyl-6-vinylmorpholin-2-one (286) and (5*S*,6*R*)-5-methyl-4-tosyl-6-vinylmorpholin-2-one (287)



286 **287**

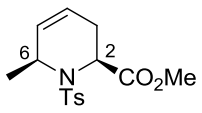
A solution of a 4.5:1 diastereomeric mixture of ester **285** (112 mg, 0.30 mmol, 1.0 eq) and TFA (0.03 mL, 0.36 mmol, 1.2 eq) in CH_2Cl_2 (3 mL) was heated to reflux for 21 h. The volatiles were removed under reduced pressure and chromatography of the crude mixture over silica gel (25% Et_2O−hexane) gave a separated 4.5:1 diastereomeric ratio of (5*S*)-5-methyl-4-tosyl-6-vinylmorpholin-2-ones **286** and **287** (78.2 mg, 88%) as colourless oils.

(Major diastereomer 286) 67.5 mg; 76%; R_f 0.16 (50% Et_2O−hexane); $[\alpha]_D^{25}$ −25.7 (*c* 1.2, CH_2Cl_2); ν_{max} (neat) 1756, 1597, 1369, 1346, 1221, 1157, 1089, 1029, 1008, 990 cm^{-1}; δ_H (400 MHz) 7.71 (2H, d, *J* 8.0 Hz, *ortho* Ts), 7.35 (2H, d, *J* 8.0 Hz, *meta* Ts), 5.74 (1H, ddd, *J* 17.5, 11.5, 6.5 Hz, H_2C=C*H*), 5.35 (1H, d, *J* 17.5 Hz, *H*H'C=CH), 5.32 (1H, d, *J* 11.5 Hz, H*H'*C=CH), 4.62-4.59 (1H, m, CHO), 4.24 (1H, d, *J* 18.0 Hz, CH*H'*), 4.00 (1H, dq, *J* 6.5, 4.5 Hz, CHN), 3.90 (1H, d, *J* 18.0 Hz, C*H*H'), 2.46 (3H, s, *para* Ts), 1.29 (3H, d, *J* 6.5 Hz, CH_3); δ_C (100 MHz) 165.5 (C=O), 144.5 (*para* Ts), 134.9 (*ipso* Ts), 133.2 (H_2C=*C*H), 130.0 (*meta* Ts), 127.4 (*ortho* Ts), 120.1 (H_2C=CH), 82.4 (CHO), 51.2 (CHN), 43.3 (CH_2), 21.6 ($ArCH_3$), 16.4 (CH_3); *m/z* (CI) 313 $[M+NH_4]^+$, 296 $[M+H]^+$

(Found: $[M+H]^+$, 296.0948. $C_{14}H_{17}NO_4S$ requires $[M+H]^+$, 296.0957) (Found: C, 57.07; H, 5.68; N, 4.82. $C_{14}H_{17}NO_4S$ requires C, 56.93; H, 5.80; N, 4.74%).

(Minor diastereomer 287) 10.7 mg; 12%; R_f 0.29 (50% Et_2O−hexane); ν_{max} (neat) 1748, 1597, 1347, 1249, 1157, 1090, 1029, 986, 952 cm^{-1}; δ_H (400 MHz) 7.71 (2H, d, *J* 8.5 Hz, *ortho* Ts), 7.36 (2H, d, *J* 8.5 Hz, *meta* Ts), 5.69 (1H, ddd, *J* 17.5, 10.5, 6.5 Hz, H_2C=C*H*), 5.43 (1H, dd, *J* 17.5, 1.0 Hz, *H*H'C=CH), 5.36 (1H, dd, *J* 10.5, 1.0 Hz, H*H'*C=CH), 4.86-4.83 (1H, m, CHO), 4.25 (1H, d, *J* 18.0 Hz, CH*H'*), 4.18 (1H, dq, *J* 7.0, 3.0 Hz, CHN), 3.90 (1H, d, *J* 18.0 Hz, C*H*H'), 2.45 (3H, s, *para* Ts), 1.02 (3H, d, *J* 7.0 Hz, CH_3); δ_C (100 MHz) 164.7 (C=O), 144.6 (*para* Ts), 135.1 (*ipso* Ts), 131.1 (H_2C=*C*H), 130.2 (*meta* Ts), 127.3 (*ortho* Ts), 119.4 (H_2C=CH), 81.8 (CHO), 50.4 (CHN), 42.9 (CH_2), 21.6 (Ar*C*H_3), 10.7 (CH_3); *m/z* (CI) 313 $[M+NH_4]^+$, 296 $[M+H]^+$ (Found: $[M+NH_4]^+$, 313.1218. $C_{14}H_{17}NO_4S$ requires $[M+NH_4]^+$, 313.1222).

(2*S*,6*S*)-Methyl 6-methyl-1-tosyl-1,2,3,6-tetrahydropyridine-2-carboxylate (290)

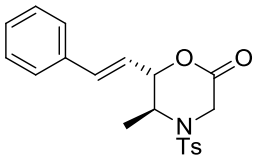


290

To a solution of morpholinone **286** (67.0 mg, 0.23 mmol, 1.0 eq) in toluene (1 mL) at rt was added Et_3N (0.06 mL, 0.45 mmol, 2.0 eq), *i*Pr_3SiOTf (0.09 mL, 0.34 mmol, 1.5 eq) and the colourless solution was heated to reflux after which the solution turned yellow. After 2.5 h, the volatiles were removed under reduced pressure to give the crude silyl ester product as yellow oil. The residue was redissolved in MeOH (1 mL) and thionyl chloride (0.08 mL, 0.68 mmol, 3.0 eq) was added at rt. After 3 h, the yellow solution was concentrated under reduced pressure and chromatography of the crude oil over silica gel (20% Et_2O−hexane) gave (2*S*,6*S*)-methyl 6-methyl-1-tosyl-1,2,3,6-tetrahydropyridine-2-

carboxylate **290** (60.0 mg, 85%) as a white solid; mp 74–78 °C; R_f 0.37 (50% Et_2O−hexane); $[\alpha]_D^{25}$ +42.4 (*c* 1.4, CH_2Cl_2); ν_{max} (neat) 2931, 1739, 1334, 1161, 1099, 1023, 1015, 980, 847, 815, 722 cm^{-1}; δ_H (400 MHz) 7.72 (2H, d, *J* 8.0 Hz, *ortho* Ts), 7.29 (2H, d, *J* 8.0 Hz, *meta* Ts), 5.73-5.66 (1H, m, H-4), 5.53 (1H, dd, *J* 10.5, 3.0 Hz, H-5), 4.85 (1H, d, *J* 6.5 Hz, H-2), 4.40-4.32 (1H, m, H-6), 3.71 (3H, s, OCH_3), 2.56 (1H, dd, *J* 17.5, 6.5 Hz, H-3), 2.43 (3H, s, *para* Ts), 2.00 (1H, ddd, *J* 17.5, 6.5, 3.0 Hz, H-3), 1.29 (3H, d, *J* 6.5 Hz, CH_3); δ_C (100 MHz) 171.8 (C=O), 143.3 (*para* Ts), 137.6 (*ipso* Ts), 129.7 (*meta* Ts), 128.4 (C-5), 127.0 (*ortho* Ts), 122.2 (C-4), 52.4 (OCH_3), 51.5 (C-2), 49.3 (C-6), 24.2 (C-3), 21.8 (CCH_3), 21.5 ($ArCH_3$); *m/z* (CI) 327 $[M+NH_4]^+$, 310 $[M+H]^+$ (Found: $[M+H]^+$, 310.1122. $C_{15}H_{19}NO_4S$ requires $[M+H]^+$, 310.1113) (Found: C, 58.34; H, 6.25; N, 4.58. $C_{15}H_{19}NO_4S$ requires C, 58.23; H, 6.19; N, 4.53%).

(5*S*,6*S*,*E*)-5-Methyl-6-styryl-4-tosylmorpholin-2-one (291)

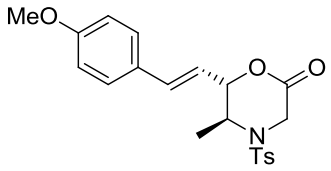


291

A solution of morpholinone **286** (46.0 mg, 0.16 mmol, 1.0 eq), styrene (0.05 mL, 0.47 mmol, 3.0 eq) and Grubbs II catalyst (14.0 mg, 16.0 μmol, 10 mol%) in CH_2Cl_2 (0.5 mL) was subjected to microwave irradiation at 100 °C for 2 × 30 min. The volatiles were removed under reduced pressure and chromatography of the crude mixture over silica gel (20→30% Et_2O−hexane) gave (5*S*,6*S*,*E*)-5-methyl-6-styryl-4-tosylmorpholin-2-one **291** (43.4 mg, 75%) as a colourless gum as a single geometric isomer; R_f 0.16 (50% Et_2O−hexane); $[\alpha]_D^{25}$ +15.1 (*c* 2.0, CH_2Cl_2); ν_{max} (neat) 1751, 1598, 1347, 1268, 1159, 1139, 1089, 1027, 1007, 966, 713 cm^{-1}; δ_H (400 MHz) 7.70 (2H, d, *J* 8.5 Hz, *ortho* Ts), 7.37-7.26 (7H, m, *meta* Ts and C_6H_5), 6.63 (1H, d, *J* 16.0 Hz, C_6H_5CH), 5.96 (1H, dd,

J 16.0, 6.5 Hz, C_6H_5CH=C*H*), 4.79 (1H, ddd, *J* 6.5, 4.5, 1.0 Hz, CHO), 4.26 (1H, d, *J* 18.0 Hz, CH*H'*), 4.07 (1H, dq, *J* 6.5, 4.5 Hz, CHN), 4.02 (1H, d, *J* 18.0 Hz, C*H*H′), 2.40 (3H, s, *para* Ts), 1.39 (3H, d, *J* 6.5 Hz, CH_3); δ_C (100 MHz) 165.5 (C=O), 144.5 (*para* Ts), 135.2 (C_6H_5*C*H), [135.2 and 134.9 (*ipso* C_6H_5 and *ipso* Ts)], 130.1 (*meta* Ts), [128.7 and 128.6 (*meta* and *para* C_6H_5)], 127.3 (*ortho* Ts), 126.9 (*ortho* C_6H_5), 123.8 (C_6H_5CH=*C*H), 82.6 (CHO), 51.6 (CHN), 43.4 (CH_2), 21.6 (Ar*C*H_3), 16.9 (CH_3); *m/z* (CI) 313 $[M-C_6H_5+H+NH_4]^+$, 372 $[M+H]^+$, 389 $[M+NH_4]^+$ (Found: $[M+H]^+$, 372.1260. $C_{20}H_{21}NO_4S$ requires $[M+H]^+$, 372.1270).

(5*S*,6*S*,*E*)-6-(4-Methoxystyryl)-5-methyl-4-tosylmorpholin-2-one (292)

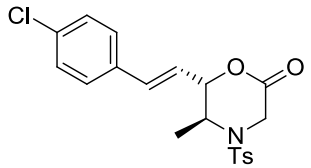


292

A solution of morpholinone **286** (52.0 mg, 0.18 mmol, 1.0 eq), *para*-methoxystyrene (0.07 mL, 0.53 mmol, 3.0 eq) and Grubbs II catalyst (7.5 mg, 8.80 μmol, 5 mol%) in CH_2Cl_2 (0.5 mL) was heated in a sealed tube at 40 °C overnight. The reaction was still not completed hence it was subjected to microwave irradiation at 70 °C for another 30 min. The volatiles were removed under reduced pressure and chromatography of the crude mixture over silica gel (30% Et_2O−hexane) gave (5*S*,6*S*,*E*)-6-(4-methoxystyryl)-5-methyl-4-tosylmorpholin-2-one **292** (59.3 mg, 84%) as a colourless gum as a single geometric isomer; R_f 0.09 (50% Et_2O−hexane); $[\alpha]_D^{25}$ +31.6 (*c* 1.0, CH_2Cl_2); ν_{max} (neat) 1751, 1601, 1512, 1348, 1249, 1160, 1139, 1089, 1029, 1005, 967, 733 cm^{-1}; δ_H (400 MHz) 7.71 (2H, d, *J* 8.0 Hz, *ortho* Ts), 7.29 (2H, d, *J* 8.0 Hz, *meta* Ts), 7.22 (2H, d, *J* 8.5 Hz, *meta* Ar), 6.58 (2H, d, *J* 8.5 Hz, *ortho* Ar), 6.58 (1H, d, *J* 16.0 Hz, ArC*H*), 5.80 (1H, dd, *J* 16.0, 6.5 Hz, ArCH=C*H*), 4.76-4.73 (1H, m, CHO), 4.26 (1H, d, *J* 18.0 Hz, CH*H'*),

4.07-4.01 (1H, m, CHN), 3.99 (1H, d, *J* 18.0 Hz, C*H*H′), 3.84 (3H, s, OCH_3), 2.42 (3H, s, *para* Ts), 1.37 (3H, d, *J* 7.0 Hz, CH_3); δ_C (100 MHz) 165.7 (C=O), 160.1 (*para* Ar), 144.4 (*para* Ts), 135.0 (Ar*C*H), 134.9 (*ipso* Ts), 130.1 (*meta* Ts), 128.2 (*meta* Ar), 127.9 (*ipso* Ar), 127.4 (*ortho* Ts), 121.3 (ArCH=*C*H), 114.1 (*ortho* Ar), 82.9 (CHO), 55.3 (OCH_3), 51.8 (CHN), 43.4 (CH_2), 21.6 (Ar*C*H_3), 17.0 (CH_3); *m/z* (CI) 402 $[M+H]^+$, 419 $[M+NH_4]^+$ (Found: $[M+H]^+$, 402.1367. $C_{21}H_{23}NO_5S$ requires $[M+H]^+$, 402.1375).

(5*S*,6*S*,*E*)-6-(4-Chlorostyryl)-5-methyl-4-tosylmorpholin-2-one (293)

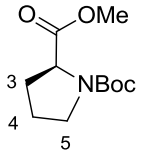


293

A solution of morpholione **286** (47.7 mg, 0.16 mmol, 1.0 eq), *para*-chlorostyrene (0.10 mL, 0.81 mmol, 5.0 eq) and Grubbs II catalyst (13.5 mg, 16.0 μmol, 10 mol%) in CH_2Cl_2 (0.5 mL) was subjected to microwave irradiation at 100 °C for 1 h. The volatiles were removed under reduced pressure and chromatography of the crude mixture over silica gel (30% Et_2O−hexane) gave (5*S*,6*S*,*E*)-6-(4-chlorostyryl)-5-methyl-4-tosylmorpholin-2-one **293** (55.7 mg, 86%) as a colourless gum as a single geometric isomer; R_f 0.18 (20% Et_2O−hexane); $[\alpha]_D^{25}$ +4.9 (*c* 2.8, CH_2Cl_2); ν_{max} (neat) 1753, 1595, 1491, 1349, 1265, 1161, 1139, 1090, 1030, 1010, 968, 732 cm^{-1}; δ_H (400 MHz) 7.69 (2H, d, *J* 8.0 Hz, *ortho* Ts), 7.31 (2H, d, *J* 8.5 Hz, *meta* Ar), 7.28 (2H, d, *J* 8.0 Hz, *meta* Ts), 7.21 (2H, d, *J* 8.5 Hz, *ortho* Ar), 6.59 (1H, d, *J* 16.0 Hz, ArC*H*), 5.96 (1H, dd, *J* 16.0, 6.0 Hz, ArCH=C*H*), 4.80-4.77 (1H, m, CHO), 4.27 (1H, d, *J* 18.0 Hz, CH*H'*), 4.09 (1H, dq, *J* 7.0, 4.0 Hz, CHN), 4.00 (1H, d, *J* 18.0 Hz, C*H*H′), 2.41 (3H, s, *para* Ts), 1.37 (3H, d, *J* 7.0 Hz, CH_3); δ_C (100 MHz) 165.3 (C=O), 144.5 (*para* Ts), [135.0 and 134.5 (*ipso* Ar and Ts)], 133.9 (Ar*C*H), 133.7 (*para* Ar), 130.1 (*ortho* Ts), 128.9 (*meta* Ar), 128.1 (*meta* Ar), 127.3

(*ortho* Ts), 124.6 (ArCH=*C*H), 82.4 (CHO), 51.5 (CHN), 43.4 (CH_2), 21.6 (Ar*C*H_3), 16.7 (CH_3); *m/z* (ESI) 406 $[M+H]^+$ (Found: $[M+H]^+$, 406.0884. $C_{20}H_{20}NO_4SCl$ requires $[M+H]^+$, 406.0880).

Methyl *N*-(*tert*-butyloxycarbonyl)-L-prolinate (299)[98]

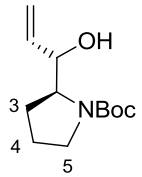


299

To a solution of L-proline **296** (1.00 g, 8.69 mmol, 1.0 eq) in methanol (10 mL) at 0 °C was added thionyl chloride (0.73 mL, 10.1 mmol, 1.2 eq) dropwise stirred for 1.5 h before the colourless solution was heated to reflux. After 1.5 h, the volatiles were removed under reduced pressure to give the crude hydrochloric salt of L-proline methyl ester (1.47 g) as colourless oil. The crude oil (200 mg, 1.21 mmol, 1.0 eq, <100% purity) was redissolved in CH_2Cl_2 (2 mL) and the solution was cooled to 0 °C before adding Et_3N (0.34 mL, 2.44 mmol, 2.0 eq) and di-*tert*-butyl dicarbonate (317 mg, 1.45 mmol, 1.2 eq). The white suspension was allowed to warm to rt overnight before it was diluted with saturated aqueous NH_4Cl (1 mL) and CH_2Cl_2 (5 mL). The organic layer was separated using a phase separator and it was concentrated under reduced pressure. Chromatography of the crude mixture over silica gel (30% Et_2O−hexane) gave methyl *N*-(*tert*-butyloxycarbonyl)-L-prolinate **299** (267 mg, 96%) as a colourless oil; R_f 0.40 (50% Et_2O−hexane); $[\alpha]_D^{25}$ −51.7 (*c* 1.1, CH_2Cl_2); {lit.[112] $[\alpha]_D^{27}$ −54.5 (*c* 1.1, CH_2Cl_2)}; ν_{max} (neat) 2978, 2881, 1748, 1696, 1392, 1365, 1200, 1158, 1117, 1087, 1069 cm^{-1}; δ_H (400 MHz) 4.35-4.22 (1H, m, H-2*)*, 3.74 (3H, s, CH_3), 3.60-3.37 (2H, m, H-5), 2.29-2.12 (1H, m, H-3a), 2.02-1.83 (3H, m, H-3b and H-4), 1.48-1.43 (9H, m, $(CH_3)_3$); δ_C (100 MHz) 173.8 (*C*O_2CH_3), 153.8 (NC=O), 79.8 (*C*$(CH_3)_3$), 59.1 (C-2), 52.0 (OCH_3),

46.3 (C-5), 30.9 (C-3), 28.4 (C(CH_3)$_3$), 24.3 (C-4); *m/z* (ESI) 252 $[M+Na]^+$ (Found: $[M+Na]^+$, 252.1218. $C_{11}H_{19}NO_4$ requires $[M+Na]^+$, 252.1212); data in agreement with published data.[98]

(*S*)-*tert*-Butyl 2-((*S*)-1-hydroxyallyl)pyrrolidine-1-carboxylate (300)[93(d)]

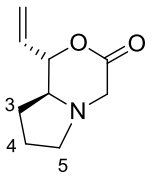


300

To a stirred solution of ester **299** (2.00 g, 8.72 mmol, 1.0 eq) in CH_2Cl_2 (25 mL) at −78 °C was added a solution of DIBAL-H (13.1 mL of a 1 M in hexane solution, 13.1 mmol, 1.5 eq) dropwise. After 4.5 h, vinylmagnesium bromide (25.0 mL of a 0.7 M solution in THF, 78.8 mmol, 2.0 eq) was added dropwise over 2 h *via* a syringe pump. The colourless solution gradually turned brown and allowed to warm up to rt gradually overnight. The solution was poured into aqueous 1 M HCl (50 mL), the organic layer was removed *in vacuo*. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL), the combined organic extracts were washed with brine (100 mL) and dried ($MgSO_4$). Concentration under reduced pressure and chromatography of the crude mixture over silica gel (20→25% Et_2O−hexane) gave a 6:1 diastereomeric mixture of (*S*)-*tert*-butyl 2-((*S*)-1-hydroxyallyl)pyrrolidine-1-carboxylate **300** (1.14 g, 58%) as a colourless oil; R_f 0.27 (50% Et_2O−hexane); ν_{max} (neat) 3428, 2976, 2933, 2880, 1691, 1669, 1391, 1366, 1256, 1163, 1114, 995, 921 cm^{-1}; (Major diastereomer) δ_H (400 MHz) 5.82 (1H, ddd, *J* 17.0, 10.5, 7.0 Hz, H_2C=C*H*), 5.32 (1H, dd, *J* 17.0, 1.0 Hz, *H*H′C=CH), 5.19 (1H, dd, *J* 10.5, 1.0 Hz, H*H′*C=CH), 4.10-3.92 (1H, br m, C*H*OH), 3.87-3.82 (1H, m, H-2), 3.51-3.45 (1H, m, H-5a), 3.36-3.30 (1H, m, H-5b), 1.95-1.69 (4H, m, H-3 and H-4), 1.49 (9H, s, $(CH_3)_3$), no OH peak observed; δ_C (100 MHz) 156.0 (C=O), 138.4 (H_2C=*C*H),

116.9 H_2C=CH), 80.6 ($C(CH_3)_3$), 77.0 (COH), 62.4 (C-2), 47.4 (C-5), 28.4 ($C(CH_3)_3$), [24.0 and 23.8 (C-3 and C-4)]; *m/z* (CI) 228 $[M+H]^+$, 172 $[M-t\text{Bu}+2H]^+$, 172 $[M-\text{Boc}+2H]^+$ (Found: $[M+H]^+$, 228.1602. $C_{12}H_{21}NO_3$ requires $[M+H]^+$, 228.1600); data in agreement with published data.[113]

(1*S*,8a*S*)-1-Vinyl-tetrahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3(4*H*)-one (297)

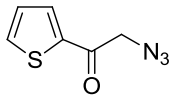


297

To a solution of a 4:1 diastereomeric mixture of alcohol **300** (100 mg, 0.44 mmol, 1.0 eq) in CH_2Cl_2 (2 mL) at rt was added TFA (0.2 mL) dropwise. After 1 h, the yellow solution was concentrated under reduced pressure to give a crude amine as a yellow oil. The crude residue was redissolved in THF (2 mL) before Et_3N (0.18 mL, 1.32 mmol, 3.0 eq) and ethyl bromoacetate (0.07 mL, 0.66 mmol, 1.5 eq) were added dropwise at rt. After 1 h, the suspension was heated to reflux and left overnight. The mixture was filtered, the filtrate was concentrated under reduced pressure and chromatography of the crude mixture over silica gel (10→20% Et_2O−hexane) gave (1*S*,8a*S*)-1-vinyl-tetrahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3(4*H*)-one **297** (25.7 mg, 35%) as a pale yellow oil isolated as a single diastereomer; R_f 0.15 (50% Et_2O−hexane); $[\alpha]_D^{25}$ −10.6 (*c* 1.4, CH_2Cl_2); ν_{max} (neat) 2960, 2796, 1738, 1431, 1319, 1244, 1212, 1140, 1120, 1015, 985 cm^{-1}; δ_H (400 MHz) 5.83 (1H, ddd, *J* 17.0, 10.5, 6.5 Hz, H_2C=C*H*), 5.47 (1H, d, *J* 17.0 Hz, *H*H′C=CH), 5.34 (1H, d, *J* 10.5, H*H′*C=CH), 4.63 (1H, dd, *J* 9.0, 6.5 Hz, CHO), 3.88 (1H, d, *J* 17.0 Hz, C*H*H′CO), 3.16 (2H, m, CH*H′*CO and H-5a), 2.36-2.25 (2H, m, H-5b and H-2), 2.01-1.51 (4H, m, H-3 and H-4); δ_C (100 MHz) 167.7 (C=O), 133.0 (H_2C=*C*H), 119.3 (H_2C=CH), 85.1 (CHO), 63.0 (C-2), 55.1 (CH_2CO_2), 54.1 (C-5), 26.5 (C-3), 22.1 (C-4);

m/z (CI) 168 $[M+H]^+$, 185 $[M+NH_4]^+$ (Found: $[M+H]^+$, 168.1021. $C_9H_{13}NO_2$ requires $[M+H]^+$, 168.1025).

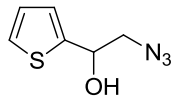
2-Azido-1-(thiophen-2-yl)ethanone (311)



311

A solution of 2-acetylthiophene (1.10 mL, 10.0 mmol, 1.0 eq) and [hydroxy(tosyloxy)iodo]benzene (4.70 g, 12.0 μmol, 1.2 eq) in acetonitrile (30 mL) was heated at reflux. After 2.5 h, the brown solution was cooled to rt, NaN_3 (1.30 g, 20.0 mmol, 2.0 eq) was added and stirring was continued at rt for another 24 h. The brown suspension was concentrated under reduced pressure, the residue was diluted with water (20 mL) and CH_2Cl_2 (20 mL). The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic fractions were washed with saturated aqueous Na_2SO_3 (50 mL), brine (50 mL), dried ($MgSO_4$) and concentrated. Chromatography of the crude mixture over silica gel (0→3% EtOAc−hexane) gave 2-azido-1-(thiophen-2-yl)ethanone **311** (1.33 g, 80%) as a brown solid; mp 52–55 °C; R_f 0.42 (50% Et_2O−hexane); ν_{max} (neat) 2107, 1670, 1412, 1232, 1061, 892, 854 cm^{-1}; δ_H (400 MHz) 7.78-7.76 (2H, m, H-3 and H-5), 7.21 (1H, dd, *J* 5.0, 4.5 Hz, H-4), 4.49 (2H, s, CH_2); δ_C (100 MHz) 186.3 (C=O), 140.7 (C-2), [134.9 and 132.5] (C-3 and C-5), 128.4 (C-4), 54.9 (CH_2); *m/z* (CI) 185 $[M+NH_4]^+$ (Found: $[M+NH_4]^+$, 185.0510. $C_6H_5N_3OS$ requires $[M+NH_4]^+$, 185.0497); data in agreement with published data.[114]

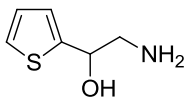
2-Azido-1-(thiophen-2-yl)ethanol (312)



312

To a solution of ketone **311** (341 mg, 2.04 mmol, 1.0 eq) in THF (7 mL) at rt was added BH_3•SMe_2 (0.23 mL, 2.45 mmol, 1.2 eq) dropwise in which the brown solution turned yellow. After 2 h, methanol was added dropwise until effervescence ceased and the volatiles were removed under reduced pressure. Chromatography of the crude mixture of the crude yellow oil over silica gel (5→10% Et_2O−hexane) gave 2-azido-1-(thiophen-2-yl)ethanol **312** (321 mg, 93%) as a colourless oil; R_f 0.32 (20% Et_2O−hexane); ν_{max} (neat) 3381, 2096, 1437, 1264, 1066, 1039, 877, 851, 835, 700 cm^{-1}; δ_H (400 MHz) 7.33 (1H, dd, *J* 5.0, 1.5 Hz, H-5), 7.07 (1H, d, *J* 3.5 Hz, H-3), 7.04 (1H, dd, *J* 5.0, 3.5 Hz, H-4), 5.16 (1H, dd, *J* 7.5, 4.5 Hz, CH), 3.62 (1H, dd, *J* 12.5, 7.5 Hz, C*H*H′), 3.57 (1H, dd, *J* 12.5, 4.5 Hz, CH*H*′), 2.55 (1H, br s, OH); δ_C (100 MHz) 143.9 (C-2), 127.0 (C-4), 125.6 (C-5), 124.7 (C-3), 69.6 (COH), 57.9 (CH_2); *m/z* (CI) 169 $[M]^+$, 152 $[M-OH]^+$, 187 $[M+NH_4]^+$ (Found: $[M+NH_4]^+$, 187.0653. $C_6H_7N_3OS$ requires $[M+NH_4]^+$, 187.0654).

2-Amino-1-(thiophen-2-yl)ethanol (313)

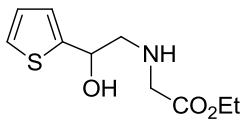


313

A suspension of azide **312** (297 mL, 1.76 mmol, 1.0 eq) and 10% Pd/C (123 mg) in methanol (7 mL) was hydrogenated at rt using a hydrogen balloon. After 3 h, the suspension was filtered over a pad of Celite® and the filtrate was concentrated under reduced pressure to give 2-amino-1-(thiophen-2-yl)ethanol **313** (252 mg, 100%) as a yellow oil which solidified on cooling after 4 days; mp 75–80 °C; (lit.[115] mp 81–82 °C);

ν_{max} (neat) 3357, 3102, 2922, 2859, 1577, 1478, 1438, 1312, 1065, 1037, 849, 830, 731 cm^{-1}; δ_H (400 MHz) 7.26 (1H, dd, *J* 4.5, 1.5 Hz, H-5), 7.01 (1H, d, *J* 3.5 Hz, H-3), 6.99-6.98 (1H, m, H-4), 5.90 (1H, dd, *J* 7.5, 4.5 Hz, CH), 3.05 (1H, dd, *J* 13.0, 4.5 Hz, C*H*H′), 2.95 (1H, dd, *J* 13.0, 7.5 Hz, CH*H*′), 2.55 (3H, br s, OH and NH_2); δ_C (100 MHz) 146.6 (C-2), 126.8 (C-4), 124.5 (C-5), 123.6 (C-3), 70.4 (COH), 49.1 (CH_2); *m/z* (CI) 144 $[M+H]^+$, 126 $[M-OH]^+$, 161 $[M+NH_4]^+$ (Found: $[M+H]^+$, 144.0480. C_6H_9NOS requires $[M+H]^+$, 144.0483); data in agreement with published data.[115]

Ethyl 2-(2-hydroxy-2-(thiophen-2-yl)ethylamino)acetate (314)

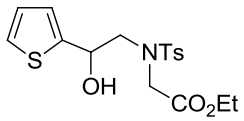


314

To a stirred solution of amine **313** (907 mg, 6.33 mmol, 1.0 eq) in THF (35 mL) at rt was added Et_3N (0.97 mL, 6.96 mmol, 1.1 eq), ethyl bromoacetate (0.70 mL, 6.33 mmol, 1.0 eq) dropwise and the resultant yellow suspension was stirred overnight. The mixture was filtered, the filtrate was concentrated under reduced pressure and chromatography of the crude mixture over silica gel (0.5% NH_4OH−80% Et_2O−hexane) gave ethyl 2-(2-hydroxy-2-(thiophen-2-yl)ethylamino)acetate **314** (1.00 g, 69%) as a white solid; mp 188–192 °C; R_f 0.09 (80% Et_2O−hexane); ν_{max} (neat) 3311, 3076, 2911, 2832, 1734, 1454, 1336, 1224, 1130, 1069, 1024, 905, 857, 704 cm^{-1}; δ_H (400 MHz) 7.25 (1H, dd, *J* 4.5, 1.5 Hz, H-5), 7.00-6.97 (2H, m, H-3 and H-4), 4.98 (1H, ddd, *J* 8.0, 4.0, 0.5 Hz, CH), 4.21 (2H, q, *J* 7.0 Hz, CO_2CH_2), 3.46 (2H, s, NCH_2CO_2), 3.18-2.60 (2H, br s, NH and OH), 3.02 (1H, dd, *J* 12.5, 4.0 Hz, CH(OH)C*H*H′), 2.92 (1H, dd, *J* 12.5, 8.0 Hz, CH(OH)CH*H*′), 1.29 (3H, t, *J* 7.0 Hz, CH_3); δ_C (100 MHz) 172.5 (C=O), 146.0 (C-2), 126.7 (C-4), 124.5 (C-5), 123.7 (C-3), 64.8 (COH), 61.0 (CO_2CH_2), 56.7 (CH(OH)CH_2),

50.6 (N*C*H$_2$CO$_2$), 14.2 (CH$_3$); *m/z* (CI) 230 [M+H]$^+$, 212 [M−OH]$^+$ (Found: [M+H]$^+$, 230.0849. $C_{10}H_{15}NO_3S$ requires [M+H]$^+$, 230.0851) (Found: C, 52.28; H, 6.56; N, 6.00. $C_{10}H_{15}NO_3S$ requires C, 52.38; H, 6.59; N, 6.11%).

Ethyl 2-(*N*-(2-hydroxy-2-(thiophen-2-yl)ethyl)-4-methylphenylsulfonamido)acetate (315)

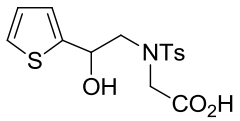


315

To a solution of amine **314** (972 mg, 4.24 mmol, 1.0 eq) in CH_2Cl_2 (20 mL) at rt was added Et_3N (1.48 mL, 10.6 mmol, 2.5 eq), *para*-toluenesulfonyl chloride (1.62 mg, 8.48 mmol, 2.0 eq) and DMAP (51.0 mg, 0.42 mmol, 0.1 eq) consecutively. After 2 h, the suspension was quenched with water (20 mL) and the organic layer was separated. Concentration of the organic layer under reduced pressure and chromatography of the crude oil over silica gel (15→30% Et_2O−hexane) gave ethyl 2-(*N*-(2-hydroxy-2-(thiophen-2-yl)ethyl)-4-methylphenylsulfonamido)acetate **315** (1.32 mg, 81%) as a yellow solid; mp 70–72 °C; R_f 0.22 (50% Et_2O−hexane); ν_{max} (neat) 3482, 2982, 2938, 1733, 1337, 1213, 1154, 1090, 1022, 942, 812, 703 cm^{-1}; δ_H (400 MHz) 7.75 (2H, d, *J* 8.5 Hz, *ortho* Ts), 7.34 (2H, d, *J* 8.5 Hz, *meta* Ts), 7.27 (1H, dd, *J* 4.5, 2.0 Hz, H-5), 7.02-6.99 (2H, m, H-3 and H-4), 5.25 (1H, dd, *J* 9.5, 2.5 Hz, CH), 4.19 (2H, q, *J* 7.5 Hz, CO_2CH_2), 4.16 (1H, d, *J* 18.0 Hz, NC*H*H′CO_2), 4.03 (1H, d, *J* 18.0 Hz, NCH*H*′CO_2), 3.56 (1H, dd, *J* 14.5, 2.5 Hz, CH(OH)C*H*H′), 3.37 (1H, dd, *J* 14.5, 9.5 Hz, CH(OH)CH*H*′), 2.45 (3H, s, *para* Ts), 1.28 (3H, t, *J* 7.5 Hz, CH_3), OH peak not observed; δ_C (100 MHz) 170.5 (C=O), 144.2 (C-2), 144.0 (*para* Ts), 135.9 (*ipso* Ts), 129.8 (*meta* Ts), 127.4 (*ortho* Ts), 126.8 (C-4), 124.9 (C-5), 124.0 (C-3), 69.4 (COH), 62.0 (CO_2CH_2),

58.2 (CH(OH)*C*H_2), 50.9 (N*C*H_2CO_2), 21.6 (Ar*C*H_3), 14.0 (CH_3); *m/z* (ESI) 406 $[M+Na]^+$ (Found: $[M+Na]^+$, 406.0750. $C_{17}H_{21}NO_5S_2$ requires $[M+Na]^+$, 406.0759) (Found: C, 53.37; H, 5.45; N, 3.55. $C_{17}H_{21}NO_5S_2$ requires C, 53.24; H, 5.52; N, 3.65%).

2-(*N*-(2-Hydroxy-2-(thiophen-2-yl)ethyl)-4-methylphenylsulfonamido)acetic acid (316)

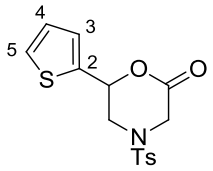


316

To a solution of amine **315** (23.5 mg, 0.06 mmol, 1.0 eq) in THF (1 mL) at rt was added 2 M LiOH (0.05 mL). After 24 h, the suspension was diluted with EtOAc (5 mL) and acidified to pH 2 with aqueous 2 M HCl. The organic layer was removed, the aqueous layer was diluted with water (5 mL), extracted with EtOAc (3 × 5 mL) and the combined organic extracts were dried ($MgSO_4$). Concentration under reduced pressure gave, without further purification, 2-(*N*-(2-hydroxy-2-(thiophen-2-yl)ethyl)-4-methylphenylsulfonamido)acetic acid **316** (20.7 mg, 100%) as a white solid; mp 142–145 °C; ν_{max} (neat) 3281, 2941, 2633, 1706, 1340, 1276, 1260, 1238, 1154, 1091, 1005, 951, 752, 702 cm^{-1}; δ_H (400 MHz, DMSO) 13.40-12.30 (1H, br s, CO_2H), 7.69 (2H, d, *J* 8.5 Hz, *ortho* Ts), 7.40 (1H, dd, *J* 5.5, 1.0 Hz, H-5), 7.39 (2H, d, *J* 8.5 Hz, *meta* Ts), 6.99 (1H, dd, *J* 5.5, 3.5 Hz, H-4), 6.94 (1H, d, *J* 3.5 Hz, H-3), 6.30-5.60 (1H, br s, OH), 4.96 (1H, dd, *J* 8.5, 4.5 Hz, CH), 4.13 (1H, d, *J* 18.0 Hz, NC*H*H′CO_2), 3.92 (1H, d, *J* 18.0 Hz, NCH*H*′CO_2), 3.44 (1H, dd, *J* 14.5, 4.5 Hz, CH(OH)C*H*H′), 3.35 (1H, dd, *J* 14.5, 8.5 Hz, CH(OH)CH*H*′), 2.40 (3H, s, *para* Ts); δ_C (100 MHz, DMSO) 170.4 (C=O), [146.8 and 143.1 (C-2 and *para* Ts)], 136.8 (*ipso* Ts), 129.4 (*meta* Ts), 127.0 (*ortho* Ts), 126.8 (C-4), 124.8 (C-5), 123.4 (C-3), 68.3 (COH), 55.3 (N*C*H_2CO_2), 49.1

(CH(OH)*C*H_2), 21.0 (Ar*C*H_3); *m/z* (CI) 355 $[M]^+$, 338 $[M-OH]^+$ (Found: $[M-OH]^+$, 338.0521. $C_{15}H_{17}NO_5S_2$ requires $[M-OH]^+$, 338.0521) (Found: C, 50.66; H, 4.73; N, 3.85. $C_{15}H_{17}NO_5S_2$ requires C, 50.69; H, 4.82; N, 3.94%).

6-(Thiophen-2-yl)-4-tosylmorpholin-2-one (317)



317

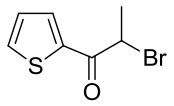
(Method A) To a solution of acid **316** (17.4 mg, 0.05 mmol, 1.0 eq) in CH_2Cl_2 (1 mL) was added DIC (0.01 mL, 0.08 mmol, 1.5 eq), DMAP (0.6 mg, 5.00 μmol, 0.1 eq) and the solution was stirred at rt for 24 h. The volatiles were removed under reduced pressure and chromatography of the crude oil over silica gel (25% Et_2O−hexane) gave 6-(thiophen-2-yl)-4-tosylmorpholin-2-one **317** (14.9 mg, 90%) as a white solid.

(Method B) To a solution of acid **316** (21.0 mg, 0.06 mmol, 1.0 eq) in THF (1 mL) was added Et_3N (0.03 mL, 0.19 mmol, 3.0 eq), HATU (48.0 mL, 0.13 mmol, 2.0 eq) and the solution was stirred at rt overnight. The precipitate was filtered off, concentration of the filtrate under reduced pressure and chromatography of the crude oil over silica gel (25% Et_2O−hexane) gave 6-(thiophen-2-yl)-4-tosylmorpholin-2-one **317** (17.8 mg, 90%) as a white solid.

mp 130–132 °C; R_f 0.21 (10% Et_2O−hexane); ν_{max} (neat) 2925, 2854, 1750, 1600, 1447, 1352, 1251, 1162, 1090, 976, 948, 712 cm^{-1}; **δ_H (500 MHz, DMSO)** 7.74 (2H, d, *J* 8.5 Hz, *ortho* Ts), 7.61 (1H, dd, *J* 5.0, 1.0 Hz, H-5), 7.47 (2H, d, *J* 8.5 Hz, *meta* Ts), 7.26 (1H, dd, *J* 3.5, 1.0 Hz, H-3), 7.06 (1H, dd, *J* 5.0, 3.5 Hz, H-4), 5.93 (1H, dd, *J* 8.5, 3.5 Hz, CH), 4.06 (1H, d, *J* 17.0 Hz, C*H*H′CO_2), 3.84 (1H, d, *J* 17.0 Hz, CH*H*′CO_2), 3.78 (1H,

dd, *J* 12.5, 3.5 Hz, CHC*H*H′), 3.33 (1H, dd, *J* 12.5, 8.5 Hz, CHCH*H*′), 2.40 (3H, s, *para* Ts); **δ_H (400 MHz, d_8–toluene)** 7.36 (2H, d, *J* 8.0 Hz, *ortho* Ts), 6.78-6.61 (5H, m, H-3, H-4, H-5 and *meta* Ts), 4.96 (1H, dd, *J* 9.0, 2.5 Hz, CH), 3.96 (1H, d, *J* 17.5 Hz, C*H*H′CO_2), 3.49 (1H, dd, *J* 12.5, 2.5 Hz, CHC*H*H′), 3.32 (1H, d, *J* 17.5 Hz, CH*H*′CO_2), 2.62 (1H, dd, *J* 12.5, 9.0 Hz, CHCH*H*′), 1.97 (3H, s, *para* Ts); **δ_C (125 MHz, DMSO)** 164.2 (C=O), [144.4, 138.2 and 131.8 (C-2, *para* Ts and *ipso* Ts)], 130.1 (*meta* Ts), 127.8 (*ortho* Ts), 127.4 (C-5), 127.2 (C-3), 126.9 (C-4), 74.9 (CHO), 47.1 (CH*C*H_2), 49.1 (*C*H_2CO_2), 21.0 (Ar*C*H_3); *m/z* (CI) 355 $[M+NH_4]^+$, 338 $[M+H]^+$ (Found: $[M+H]^+$, 338.0527. $C_{15}H_{14}NO_4S_2$ requires $[M+H]^+$, 338.0521) (Found: C, 53.30; H, 4.39; N, 4.17. $C_{15}H_{14}NO_4S_2$ requires C, 53.39; H, 4.48; N, 4.15%).

2-Bromo-1-(thiophen-2-yl)propan-1-one (326)[105]

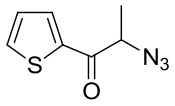


326

To a solution of 2-propionylthiophene **325** (3.44 mL, 27.6 mmol, 1.0 eq) in Et_2O (40 mL) was added bromine (1.56 mL, 30.3 mmol, 1.1 eq) in portions at rt over 1 h. On completion of bromine addition, the brown solution was quenched with 10% aqueous K_2CO_3 (40 mL). The organic layer was separated and washed with saturated aqueous $Na_2S_2O_7$ (40 mL), dried ($MgSO_4$) and concentrated. Chromatography of the crude oil over silica gel (0→15% CH_2Cl_2–hexane) gave 2-bromo-1-(thiophen-2-yl)propan-1-one **326** (5.53 g, 91%) as a pale yellow oil; R_f 0.28 (50% CH_2Cl_2–hexane); ν_{max} (neat) 1659, 1410, 1242, 1166, 1057 cm^{-1}; δ_H (400 MHz) 7.87 (1H, dd, *J* 4.0, 1.0 Hz, H-5), 7.72 (1H, dd, *J* 5.0, 1.0 Hz, H-3), 7.18 (1H, dd, *J* 5.0, 4.0 Hz, H-4), 5.17 (1H, q, *J* 6.5 Hz, CH), 1.92 (3H, t, *J* 6.5 Hz, CH_3); δ_C (100 MHz) 186.8 (C=O), 140.9 (C-2), 134.9 (C-3), 133.1 (C-5), 128.3 (C-4), 42.4 (CH), 20.3 (CH_3); *m/z* (CI) 236, 238 $[M+NH_4]^+$, 219, 221

$[M+H]^+$ (Found: $[M+H]^+$, 218.9479. C_7H_7OSBr requires $[M+H]^+$, 218.9472); data in agreement with published data.[105]

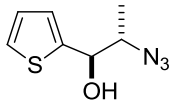
2-Azido-1-(thiophen-2-yl)propan-1-one (327)



327

A solution of bromide **326** (5.53 g, 25.2 mmol, 1.0 eq) and NaN_3 (4.90 g, 75.6 mmol, 3.0 eq) in acetonitrile (30 mL) was stirred at rt for 16.5 h. The precipitate was filtered off, concentration of the filtrate under reduced pressure and chromatography of the crude oil over silica gel (10% Et_2O−hexane) gave 2-azido-1-(thiophen-2-yl)propan-1-one **327** (4.50 g, 99%); R_f 0.40 (20% Et_2O−hexane); ν_{max} (neat) 2097 (N_3), 1661, 1411, 1235, 1217, 1056, 914, 828, 723 cm^{-1}; δ_H (400 MHz) 7.83 (1H, dd, *J* 4.0, 1.0 Hz, H-5), 7.77 (1H, dd, *J* 5.0, 1.0 Hz, H-3), 7.21 (1H, dd, *J* 5.0, 4.0 Hz, H-4), 4.55 (1H, q, *J* 7.0 Hz, CH), 1.64 (3H, d, *J* 7.0 Hz, CH_3); δ_C (100 MHz) 189.7 (C=O), 140.9 (C-2), 135.2 (C-3), 133.2 (C-5), 128.4 (C-4), 59.7 (CH), 17.0 (CH_3); *m/z* (CI) 199 $[M+NH_4]^+$, 182 $[M+H]^+$ (Found: $[M+H]^+$, 182.0387. $C_7H_7N_3OS$ requires $[M+H]^+$, 182.0387).

(1*R*,2*S*)-2-Azido-1-(thiophen-2-yl)propan-1-ol (328)

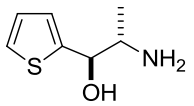


328

To a solution of azide **327** (800 mg, 4.40 mmol, 1.0 eq) in THF (20 mL) was added BH_3•SMe_2 (0.50 mL, 5.30 mmol, 1.2 eq) dropwise at rt and the yellow solution was stirred overnight. Methanol (~1 mL) was added dropwise until effervescence ceased, the volatiles were removed under reduced pressure and chromatography of the crude yellow

oil over silica gel (15→20% Et_2O−hexane) gave a 10:1 diastereomeric mixture of (1*R*,2*S*)-2-azido-1-(thiophen-2-yl)propan-1-ol **328** (846 mg, 100%) as a colourless oil; R_f 0.19 (15% Et_2O−hexane); ν_{max} (neat) 3402, 2980, 2892, 2100 (N_3), 1249, 1023, 700 cm^{-1}; (Major diastereomer) δ_H (400 MHz) 7.34 (1H, dd, *J* 5.0, 1.0 Hz, H-5), 7.06-7.00 (2H, m, H-3 and H-4), 4.78 (1H, dd, *J* 7.0, 3.5 Hz, C*H*OH), 3.76 (1H, dq, *J* 6.5, 6.5 Hz, CHN_3), 2.78 (1H, br s, OH), 1.23 (3H, d, *J* 6.5 Hz, CH_3); δ_C (100 MHz) 143.7 (C-2), 126.8 (C-4), 125.7 (C-5), 125.5 (C-3), 74.0 (COH), 63.4 (CHN_3), 16.0 (CH_3); *m/z* (CI) 201 $[M+NH_4]^+$, 183 $[M]^+$, 166 $[M-OH]^+$ (Found: $[M+NH_4]^+$, 201.0801. $C_7H_9N_3OS$ requires $[M+NH_4]^+$, 201.0810).

(1*R*,2*S*)-2-Amino-1-(thiophen-2-yl)propan-1-ol (329)



329

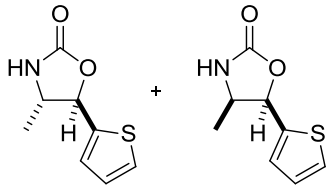
A suspension of a 10:1 diastereomeric mixture of azide **328** (2.46 g, 13.4 mmol, 1.0 eq) and 10% Pd/C (962 mg) in methanol (60 mL) was hydrogenated at rt using a hydrogen balloon. After 1.5 h, the suspension was filtered over a pad of Celite® and the filtrate was concentrated under reduced pressure to give a 10:1 diastereomeric mixure of (1*R*,2*S*)-2-amino-1-(thiophen-2-yl)propan-1-ol **329** (2.02 g, 82%) as a white solid.

(Data for major diastereomer obtained from recrystallisation) White crystals; mp 75–78 °C (hexane–EtOAc); ν_{max} (neat) 3348, 3280, 1590, 1441, 1378, 1363, 1300, 1278, 1136, 1054, 1034, 828, 709, 696 cm^{-1}; δ_H (400 MHz) 7.29-7.27 (1H, m, H-5), 7.03-6.99 (2H, m, H-3 and H-4), 4.55 (1H, d, *J* 6.5 Hz, CHO), 3.14 (1H, dq, *J* 6.5, 6.5 Hz, CHN), 3.08 (3H, br s, OH and NH_2), 1.13 (3H, *J* 6.5 Hz, CH_3); δ_C (125 MHz) 146.7 (C-2), 126.6 (C-3), [124.6 and 124.3 (C-4 and C-5)], 74.6 (COH), 53.2 (CNH_2), 20.5 (CH_3); *m/z* (CI)

158 $[M+H]^+$, 140 $[M-OH]^+$ (Found: $[M+H]^+$, 155.0640. $C_7H_{11}NOS$ requires $[M+H]^+$, 158.0640) (Found: C, 53.68; H, 7.20; N, 9.01. $C_7H_{11}NOS$ requires C, 53.47; H, 7.05; N, 8.91%).

(4*S*,5*R*)-4-Methyl-5-(thiophen-2-yl)oxazolidin-2-one (330) and

(4*R*,5*R*)-4-methyl-5-(thiophen-2-yl)oxazolidin-2-one (331)



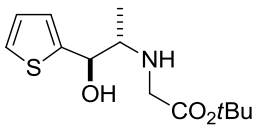
330 **331**

To a solution of a 10:1 diastereomeric mixture of amino-alcohol **329** (57.7 mg, 0.36 mmol, 1.0 eq) in CH_2Cl_2 (2 mL) was added Et_3N (0.13 mL, 0.93 mmol, 3.0 eq) and triphosgene (103 mg, 0.35 mmol, 1.1 eq) at rt. After 20 min, the yellow suspension was quenched with saturated aqueous NH_4Cl (5 mL) and diluted with CH_2Cl_2 (5 mL). The organic layer was separated and concentrated under reduced pressure. Chromatography of the crude oil over silica gel (50% Et_2O–hexane) gave a separated 10:1 diastereomeric ratio of (5*R*)-4-methyl-5-(thiophen-2-yl)oxazolidin-2-ones **330** and **331** (35.1 mg, 54%) as colourless oils.

(Major diastereomer 330) 32.1 mg; 49%; R_f 0.16 (80% Et_2O–hexane); ν_{max} (neat) 3277, 2974, 1737, 1375, 1317, 1297, 1231, 998, 942, 706 cm^{-1}; δ_H (400 MHz) 7.37 (1H, d, *J* 5.0 Hz, H-5), 7.14 (1H, dd, *J* 3.5, 0.5 Hz, H-3), 7.02 (1H, dd, *J* 5.0, 3.5 Hz, H-4), 6.63 (1H, br s, NH), 5.27 (1H, d, *J* 7.5 Hz, CHO), 4.01 (1H, dq, *J* 7.5, 6.5 Hz, CHN), 1.36 (3H, *J* 6.5 Hz, CH_3); δ_C (100 MHz) 158.6 (C=O), 139.6 (C-2), 127.0 (C-4), 126.8 (C-5), 126.7 (C-3), 81.2 (CHO), 56.7 (CHN), 19.5 (CH_3); *m/z* (CI) 201 $[M+NH_4]^+$, 184 $[M+H]^+$ (Found: $[M+H]^+$, 184.0428. $C_8H_9NO_2S$ requires $[M+H]^+$, 184.0432).

(Minor diastereomer 331) 3.0 mg; 4.5%; R_f 0.11 (80% Et_2O−hexane); ν_{max} (neat) 3277, 2942, 1740, 1374, 1316, 1228, 1121, 1102, 1003, 947, 772, 704 cm^{-1}; δ_H (400 MHz) 7.34 (1H, d, *J* 5.0 Hz, H-5), 7.07-7.02 (2H, m, H-3 and H-4), 5.92 (1H, d, *J* 6.5 Hz, CHO), 5.50 (1H, br s, NH), 4.21 (1H, dq, *J* 7.5, 6.5 Hz, CHN), 1.00 (3H, *J* 6.5 Hz, CH_3); δ_C (100 MHz) 158.4 (C=O), 137.1 (C-2), 126.9 (C-4), 126.1 (C-5), 125.9 (C-3), 78.1 (CHO), 52.6 (CHN), 17.0 (CH_3); *m/z* (CI) 201 $[M+NH_4]^+$, 184 $[M+H]^+$ (Found: $[M+H]^+$, 184.0423. $C_8H_9NO_2S$ requires $[M+H]^+$, 184.0432).

***tert*-Butyl 2-((1*R*,2*S*)-1-hydroxy-1-(thiophen-2-yl)propan-2-ylamino)acetate (332)**

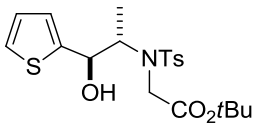


332

To a stirred solution of amino-alcohol **329** (97.0 mg, 0.53 mmol, 1.0 eq) in THF (35 mL) was added *N*,*N*-diisopropylethylamine (0.10 mL, 0.58 mmol, 1.1 eq) and *tert*-butyl bromoacetate (0.08 mL, 0.56 mmol, 1.05 eq) dropwise at rt. After 3 h, the reaction was still incomplete as monitored by TLC. Hence another portion of base (0.01 mL) and bromide (0.008 mL) were added and the suspension was stirred an additional 2 h. The suspension was filtered, the filtrate was removed under reduced pressure and chromatography of the crude oil over silica gel (50% Et_2O−hexane) gave a 10:1 diastereomeric mixture of *tert*-butyl 2-((1*R*,2*S*)-1-hydroxy-1-(thiophen-2-yl)propan-2-ylamino)acetate **332** (133 g, 92%) as a white solid; mp 76–78 °C; R_f 0.23 (80% Et_2O−hexane); ν_{max} (neat) 3313, 2976, 2931, 1729, 1452, 1367, 1230, 1151, 1037, 841 cm^{-1}; (Major diastereomer) δ_H (400 MHz) 7.28 (1H, dd, *J* 5.0, 1.0 Hz, H-5), 7.03 (1H, d, *J* 3.5 Hz, H-3), 6.99 (1H, dd, *J* 5.0, 3.5 Hz, H-4), 4.55 (1H, d, *J* 7.5 Hz, CHO), 3.38 (1H, d, *J* 17.5 Hz, C*H*H′), 3.34 (1H, d, *J* 17.5 Hz, CH*H*′), 2.85 (1H, dq, *J* 6.5, 6.5

Hz, CHN), 1.51 (9H, s, $(CH_3)_3$), 1.07 (3H, d, *J* 6.5 Hz, CH_3); δ_C (100 MHz) 171.9 (C=O), 146.3 (C-2), 126.5 (C-4), [124.8 and 124.7 (C-3 and C-5)], 81.5 ($C(CH_3)_3$), 73.8 (COH), 60.1 (CHN), 49.5 (CH_2), 28.1 ($(CH_3)_3$), 17.0 (CH_3); *m/z* (CI) 272 $[M+H]^+$ (Found: $[M+H]^+$, 272.1314. $C_{13}H_{21}NO_3S$ requires $[M+H]^+$, 272.1320).

tert-Butyl 2-(*N*-((1*R*,2*S*)-1-hydroxy-1-(thiophen-2-yl)propan-2-yl)-4-methylphenylsulfonamido)acetate (333)

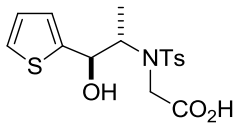


333

To a solution of a 10:1 diastereomeric mixture of amine **332** (1.29 g, 4.74 mmol, 1.0 eq) in CH_2Cl_2 (20 mL) was added Et_3N (1.00 mL, 7.11 mmol, 1.5 eq), *para*-toluenesulfonyl chloride (1.08 g, 5.68 mmol, 1.2 eq), DMAP (57.0 mg, 0.47 mmol, 0.1 eq) and the yellow suspension was stirred at rt overnight. The mixture was quenched with saturated aqueous NH_4Cl (20 mL), the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude yellow oil was filtered over a pad of silica gel and washed with CH_2Cl_2. The filtrate was concentrated to give a white solid which was triturated in TBME. The residue was obtained from filtration and dried to give *tert*-butyl 2-(*N*-((1*R*,2*S*)-1-hydroxy-1-(thiophene-2-yl)propan-2-yl)-4-methylphenylsulfonamido)acetate **333** (1.62 mg, 80%) as a single diastereomer as a white solid; mp 130–133 °C; R_f 0.38 (50% Et_2O–hexane); ν_{max} (neat) 3431, 2980, 1726, 1370, 1343, 1291, 1153, 1089, 1032, 706 cm^{-1}; δ_H (400 MHz) 7.83 (2H, d, *J* 8.0 Hz, *ortho* Ts), 7.34 (2H, d, *J* 8.0 Hz, *meta* Ts), 7.30-7.28 (1H, m, H-5), 6.99 (1H, dd, *J* 3.5, 1.0 Hz, H-3), 6.96 (1H, dd, *J* 5.0, 3.5 Hz, H-4), 4.89 (1H, d, *J* 2.5 Hz,

OH), 4.49 (1H, dd, *J* 9.5, 2.5 Hz, CHO), 4.20 (1H, d, *J* 18.5 Hz, C*H*H′), 4.04 (1H, dq, *J* 9.5, 7.0 Hz, CHN), 3.66 (1H, d, *J* 18.5 Hz, CH*H*′), 2.45 (3H, s, *para* Ts), 1.54 (9H, s, $(CH_3)_3$), 0.81 (3H, d, *J* 7.0 Hz, CH_3); δ_C (100 MHz) 170.6 (C=O), [143.9 and 143.3 (C-2 and *para* Ts)], 136.7 (*ipso* Ts), 129.7 (*meta* Ts), 127.7 (*ortho* Ts), 126.4 (C-4), [125.4 and 125.3 (C-3 and C-5)], 83.6 ($C(CH_3)_3$), 71.6 (COH), 60.8 (CHN), 44.3 (CH_2), 28.0 ($C(CH_3)_3$), 21.6 ($ArCH_3$), 14.4 (CH_3); *m/z* (CI) 369 $[M-t\text{Bu}+H]^+$, 352 $[M-t\text{Bu}-OH+H]^+$, 408 $[M-OH+H]^+$, 443 $[M+NH_4]^+$ (Found: $[M+NH_4]^+$, 443.1665. $C_{20}H_{27}NO_5S_2$ requires $[M+NH_4]^+$, 443.1674) (Found: C, 56.60; H, 6.34; N, 3.35. $C_{20}H_{27}NO_5S_2$ requires C, 56.45; H, 6.39; N, 3.29%).

2-(*N*-((1*R*,2*S*)-1-Hydroxy-1-(thiophen-2-yl)propan-2-yl)-4-methylphenylsulfonamido)acetic acid (334)

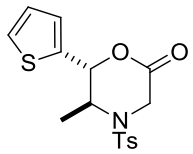


334

To a solution of ester **333** (1.61 g, 3.77 mmol, 1.0 eq) in THF (20 mL) was added 2 M LiOH (5 mL) at rt. After 1.5 h, the suspension was diluted with EtOAc (10 mL) and acidified to pH 2 with aqueous 2 M HCl (~4.8 mL). The organic layer was removed under reduced pressure, the aqueous layer was diluted with water (40 mL), extracted with EtOAc (4 × 40 mL) and the combined organic extracts were dried (Na_2SO_4). Concentration under reduced pressure gave, without further purification, 2-(*N*-((1*R*,2*S*)-1-hydroxy-1-(thiophen-2-yl)propan-2-yl)-4-methylphenylsulfonamido)acetic acid **334** (1.42 g, 100%) as a white solid; mp 162–168 °C; δ_H (500 MHz, d_6-acetone) 12.48-10.90 (1H, br, CO_2H), 7.81 (2H, d, *J* 8.5 Hz, *ortho* Ts), 7.42 (2H, dd, *J* 8.5, 0.5 Hz, *meta* Ts), 7.39 (1H, dd, *J* 5.0, 1.0 Hz, H-5), 7.01 (1H, dd, *J* 3.5, 1.0 Hz, H-3), 6.94 (1H, dd, *J* 5.0,

3.5 Hz, H-4), 5.23 (1H, br s, OH), 4.78 (1H, d, *J* 9.5 Hz, CHO), 4.14 (1H, d, *J* 18.5 Hz, C*H*H′), 4.08 (1H, d, *J* 18.5 Hz, CH*H*′), 4.02 (1H, dq, *J* 9.5, 7.0 Hz, CHN), 2.42 (3H, s, *para* Ts), 0.72 (3H, d, *J* 7.0 Hz, CH_3); δ_C (125 MHz) 173.7 (C=O), [145.3 and 144.6 (C-2 and *para* Ts)], 138.3 (*ipso* Ts), 130.6 (*meta* Ts), 128.3 (*ortho* Ts), 127.1 (C-4), 126.3 (C-3), 126.0 (C-5), 71.7 (COH), 61.7 (CHN), 44.5 (CH_2), 21.4 (Ar*C*H_3), 14.0 (CH_3); *m/z* (ESI) 368 $[M-H]^-$ (Found: $[M-H]^-$, 368.0614. $C_{16}H_{19}NO_5S_2$ requires $[M-H]^-$, 368.0626).

(5*S*,6*R*)-5-Methyl-6-(thiophen-2-yl)-4-tosylmorpholin-2-one (335)

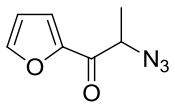


335

To a solution of acid **334** (1.37 g, 3.70 mmol, 1.0 eq) in CH_2Cl_2 (18 mL) was added DIC (0.87 mL, 5.56 mmol, 1.5 eq), DMAP (45.0 mg, 0.37 mmol, 0.1 eq) and the white suspension was stirred at rt for 13 h. The mixture was filtered, the filtrate was concentrated under reduced pressure and chromatography of the crude oil over silica gel (30→40% Et_2O−hexane) gave (5*S*,6*R*)-5-methyl-6-(thiophen-2-yl)-4-tosylmorpholin-2-one **335** (1.30 g, 100%) as a white solid; mp 95–99 °C; R_f 0.17 (50% Et_2O−hexane); ν_{max} (neat) 1738, 1754, 1349, 1160, 1030, 1008, 816, 710 cm^{-1}; **δ_H (400 MHz)** 7.67 (2H, d, *J* 8.5 Hz, *ortho* Ts), 7.38 (1H, dd, *J* 5.0, 1.5 Hz, H-5), 7.35 (2H, d, *J* 8.5 Hz, *meta* Ts), 7.05 (1H, d, *J* 3.5 Hz, H-3), 7.00 (1H, dd, *J* 5.0, 3.5 Hz, H-4), 5.35 (1H, d, *J* 6.0 Hz, CHO), 4.31 (1H, d, *J* 18.0 Hz, C*H*H′), 4.29 (1H, dq, *J* 6.5, 6.0 Hz, CHN), 3.97 (1H, d, *J* 17.0 Hz, CH*H*′), 2.47 (3H, s, *para* Ts), 1.37 (3H, d, *J* 6.5 Hz, CH_3); **δ_H (400 MHz, d_8–toluene)** 7.59 (2H, d, *J* 8.0 Hz, *ortho* Ts), 6.84-6.80 (3H, m, H-5 and *meta* Ts), 6.69-6.66 (1H, m, H-5), 6.61-6.59 (1H, m, H-4), 4.54-4.46 (1H, m, CHO), 4.27 (1H, d,

J 18.0 Hz, C*H*H′), 3.96 (1H, dq, *J* 6.5, 6.5 Hz, CHN), 3.45 (1H, d, *J* 18.0 Hz, CH*H*′), 1.91 (3H, s, *para* Ts), 0.99 (3H, d, *J* 6.5 Hz, CH_3); **δ_C (100 MHz)** 165.5 (C=O), [144.7 and 138.6 (C-2 and *para* Ts)], 134.2 (*ipso* Ts), 130.1 (*meta* Ts), 127.6 (*ortho* Ts), [127.1, 127.0 and 126.9 (C-3, C-4 and C-5)], 79.6 (CHO), 53.2 (CHN), 43.4 (CH_2), 21.6 (Ar*C*H_3), 17.0 (CH_3); *m/z* (ESI) 352 $[M+H]^+$ (Found: $[M+H]^+$, 352.0682. $C_{16}H_{17}NO_4S_2$ requires $[M+H]^+$, 352.0677) (Found: C, 54.81; H, 4.95; N, 3.88. $C_{16}H_{17}NO_4S_2$ requires C, 54.68; H, 4.88; N, 3.99%).

2-Azido-1-(furan-2-yl)propan-1-one (340)

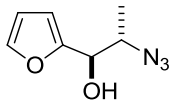


340

To a solution of 2-propionylfuran (2.28 g, 18.3 mmol, 1.0 eq) in Et_2O (60 mL) was added bromine (0.99 mL, 19.2 mmol, 1.05 eq) dropwise in portions at rt over 1 h. On completion of bromine addition, the brown solution was quenched with 20% aqueous K_2CO_3 (100 mL), the organic layer was separated and washed with saturated aqueous $Na_2S_2O_7$ (100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated to give the bromide as a crude yellow oil. The oil was redissolved in acetonitrile (24 mL) and NaN_3 (2.38 g, 36.6 mmol, 2.0 eq) was added at rt and the suspension was stirred for 16 h. The precipitate was filtered off, concentration of the filtrate under reduced pressure and chromatography of the crude brown oil over silica gel (0→20% Et_2O−hexane) gave 2-azido-1-(furan-2-yl)propan-1-one **340** (2.85 mg, 94%); R_f 0.27 (20% Et_2O−hexane); ν_{max} (neat) 2113, 2094 (N_3), 1676, 1463, 1243, 1016, 975, 763 cm^{-1}; δ_H (400 MHz) 7.67 (1H, dd, *J* 1.5, 0.5 Hz, H-5), 7.36 (1H, dd, *J* 3.5, 0.5 Hz, H-3), 6.63 (1H, dd, *J* 3.5, 1.5 Hz, H-4), 4.57 (1H, q, *J* 7.0 Hz, CH), 1.59 (3H, d, *J* 7.0 Hz, CH_3); δ_C (100 MHz) 185.7 (C=O), 150.5 (C-2), 147.3 (C-5), 119.1 (C-3), 112.8 (C-4), 58.9 (CH), 16.3 (CH_3); *m/z*

(CI) 183 $[M+NH_4]^+$, 166 $[M+H]^+$ (Found: $[M+NH_4]^+$, 183.0876. $C_7H_7N_3O_2$ requires $[M+NH_4]^+$, 183.0882).

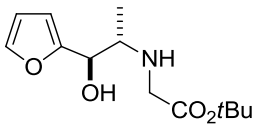
(1*R*,2*S*)-2-Azido-1-(furan-2-yl)propan-1-ol (341)



341

To a solution of azide **340** (3.77 mg, 22.8 mmol, 1.0 eq) in THF (75 mL) was added BH_3•SMe_2 (2.60 mL, 27.4 mmol, 1.2 eq) dropwise *via* a syringe pump at a rate of 2 mLh^{-1} at rt. After 1.5 h, methanol (~9 mL) was cautiously added dropwise until effervescence ceased, the volatiles were removed under reduced pressure and chromatography of the crude yellow oil over silica gel (0→20% Et_2O−hexane) gave a 3:1 diastereomeric mixture of (1*R*,2*S*)-2-azido-1-(furan-2-yl)propan-1-ol **341** (3.63 mg, 95%) as a colourless oil; R_f 0.12 (10% Et_2O−hexane); ν_{max} (neat) 3392, 2982, 2096 (N_3), 1249, 1148, 1010, 738 cm^{-1}; (Major diastereomer) δ_H (400 MHz) 7.42 (1H, dd, *J* 2.0, 1.0 Hz, H-5), 6.40-6.36 (2H, m, H-3 and H-4), 4.54 (1H, dd, *J* 6.5, 5.5 Hz, C*H*OH), 3.91 (1H, dq, *J* 6.5, 6.5 Hz, CHN_3), 2.59 (1H, d, *J* 5.5 Hz, OH), 1.21 (3H, d, *J* 6.5 Hz, CH_3); δ_C (100 MHz) 153.0 (C-2), 142.5 (C-5), [110.4 and 108.0 (C-3 and C-4)], 71.6 (COH), 61.3 (CHN_3), 15.9 (CH_3); *m/z* (CI) 167 $[M]^+$, 150 $[M-OH]^+$, 185 $[M+NH_4]^+$ (Found: $[M+NH_4]^+$, 185.1030. $C_7H_9N_3O_2$ requires $[M+NH_4]^+$, 185.1039).

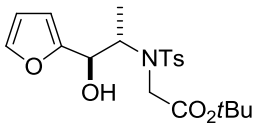
***tert*-Butyl 2-((1*R*,2*S*)-1-(furan-2-yl)-1-hydroxypropan-2-ylamino)acetate (342)**



342

A suspension of a 3:1 diastereomeric mixture of azide **341** (3.62 g, 21.7 mmol, 1.0 eq) and 10% Pd/C (1.60 mg) in methanol (80 mL) was hydrogenated at rt using a hydrogen balloon. After 1 h, the suspension was filtered over a pad of Celite® and the filtrate was concentrated under reduced pressure to give the amino-alcohol (2.97 g) as a yellow oil. The oil was redissolved in THF (100 mL), Et_3N (3.22 mL, 23.1 mmol, 1.1 eq) and *tert*-butyl bromoacetate (3.26 mL, 22.1 mmol, 1.05 eq) was added dropwise at rt. After 14 h, the mixture was filtered, the filtrate was concentrated under reduced pressure and chromatography of the crude oil over silica gel (20% EtOAc−hexane) gave a 3:1 diastereomeric mixture of *tert*-butyl 2-((1*R*,2*S*)-1-hydroxy-1-(furan-2-yl)propan-2-ylamino)acetate **342** (3.70 g, 67%) as a yellow oil; R_f 0.20 (40% EtOAc−hexane); ν_{max} (neat) 3311, 2976, 1730, 1368, 1229, 1150, 1041, 1008, 811, 737 cm^{-1}; (Major diastereomer) δ_H (400 MHz) 7.36-7.38 (1H, m, H-5), 6.35-6.33 (1H, m, H-4), 6.30 (1H, d, *J* 3.0 Hz, H-3), 4.30 (1H, d, *J* 7.0 Hz, C*H*OH), 3.32 (1H, d, *J* 17.5 Hz, C*H*H′), 3.27 (1H, d, *J* 17.5 Hz, CH*H*′), 3.02 (1H, dq, *J* 7.0, 6.5 Hz, CHN), 1.47 (9H, s, $(CH_3)_3$), 1.00 (3H, d, *J* 6.5 Hz, CH_3), OH and NH peaks not observed; δ_C (100 MHz) 171.9 (C=O), 155.0 (C-2), 141.9 (C-5), 110.2 (C-4), 107.4 (C-3), 81.4 ($C(CH_3)_3$), 71.2 (COH), 56.9 (CHN), 49.4 (CH_2), 28.1 ($C(CH_3)_3$), 17.0 (CH_3); *m/z* (CI) 256 $[M+H]^+$ (Found: $[M+H]^+$, 256.1549. $C_{13}H_{21}NO_4$ requires $[M+H]^+$, 256.1549).

***tert*-Butyl 2-(*N*-((1*R*,2*S*)-1-(furan-2-yl)-1-hydroxypropan-2-yl)-4-methylphenylsulfonamido)acetate (343)**

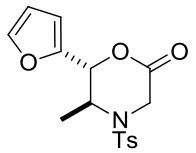


343

To a solution of a 3:1 diastereomeric mixture of amine **342** (768 mg, 3.01 mmol, 1.0 eq) in CH_2Cl_2 (15 mL) was added Et_3N (0.63 mL, 4.52 mmol, 1.5 eq), *para*-toluenesulfonyl chloride (688 mg, 3.61 mmol, 1.2 eq), DMAP (37.0 mg, 0.30 mmol, 0.1 eq) and the yellow suspension was stirred at rt overnight. The mixture was quenched with water (40 mL) and diluted with CH_2Cl_2 (20 mL), the organic layer was separated and washed with saturated aqueous NH_4Cl (40 mL), brine (40 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude yellow precipitate was triturated in TBME and filtered. The residue was collected and dried to give a 14:1 diastereomeric mixture of *tert*-butyl 2-(*N*-((1*R*,2*S*)-1-(furan-2-yl)-1-hydroxypropan-2-yl)-4-methylphenylsulfonamido)acetate **343** (687 mg, 56%) as a white solid; mp 139–142 °C; R_f 0.18 (40% Et_2O−hexane); ν_{max} (neat) 3435, 2982, 1724, 1345, 1245, 1154, 1090, 1034, 1010, 875, 814, 738 cm^{-1}; (Major diastereomer) δ_H (400 MHz) 7.82 (2H, d, *J* 8.5 Hz, *ortho* Ts), 7.32 (2H, d, *J* 8.0 Hz, *meta* Ts), 7.38 (1H, dd, *J* 1.5, 1.5 Hz, H-5), 6.34-6.32 (2H, m, H-3 and H-4), 4.70 (1H, d, *J* 2.5 Hz, OH), 4.29-4.24 (2H, m, C*H*OH and CHN), 4.17 (1H, d, *J* 18.5 Hz, C*H*H′), 3.65 (1H, d, *J* 18.5 Hz, CH*H*′), 2.43 (3H, s, *para* Ts), 1.51 (9H, s, $(CH_3)_3$), 0.76 (3H, d, *J* 6.5 Hz, CH_3); δ_C (100 MHz) 170.7 (C=O), [152.7 and 143.8 (C-2 and *para* Ts)], 142.3 (C-5), 136.9 (*ipso* Ts), 129.7 (*meta* Ts), 127.7 (*ortho* Ts), [110.3 and 108.3 (C-3 and C-4)], 83.5 ($C(CH_3)_3$), 69.1 (COH), 58.3 (CHN), 44.2 (CH_2), 27.9 ($C(CH_3)_3$), 21.6 ($ArCH_3$), 14.3 (CH_3); *m/z* (CI) 427 $[M+NH_4]^+$, 392 $[M-OH]^+$ (Found:

$[M+NH_4]^+$, 427.1894. $C_{20}H_{27}NO_6S$ requires $[M+NH_4]^+$, 427.1903) (Found: C, 58.80; H, 6.52; N, 3.42. $C_{20}H_{27}NO_6S$ requires C, 58.66; H, 6.65; N, 3.42%).

(5*S*,6*R*)-6-(Furan-2-yl)-5-methyl-4-tosylmorpholin-2-one (345)

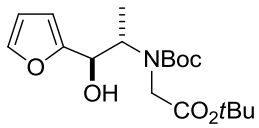


345

To a solution of ester **343** (140 mg, 0.34 mmol, 1.0 eq) in THF (20 mL) was added 2 M LiOH (3 mL) at rt. After 15 h, the white suspension was diluted with EtOAc (10 mL) and acidified to pH 2 with aqueous 1 M HCl. The organic layer was removed under reduced pressure, the aqueous layer was diluted with water (15 mL), extracted with EtOAc (2 × 15 mL) and the combined organic extracts were dried ($MgSO_4$). Concentration under reduced pressure gave the crude hydroxyl-acid (140 mg) as a colourless gum. The gum was redissolved in CH_2Cl_2 (2 mL), DIC (0.08 mL, 0.51 mmol, 1.5 eq) and DMAP (4.0 mg, 34.0 μmol, 0.1 eq) was added at rt and stirred for 5.5 h. The mixture was filtered, the filtrate was concentrated under reduced pressure and chromatography of the crude oil over silica gel (35% Et_2O−hexane) gave (5*S*,6*R*)-6-(furan-2-yl)-5-methyl-4-tosylmorpholin-2-one **345** (115 mg, 100%) as a white solid; mp 96–98 °C; R_f 0.18 (20% EtOAc−hexane); ν_{max} (neat) 1761, 1347, 1225, 1157, 1089, 1004, 899, 814, 749 cm^{-1}; **δ_H (400 MHz)** 7.65 (2H, d, *J* 8.0 Hz, *ortho* Ts), 7.36 (1H, d, *J* 1.5 Hz, H-5), 7.32 (2H, d, *J* 8.0 Hz, *meta* Ts), 6.41 (1H, d, *J* 3.5 Hz, H-3), 6.36 (1H, dd, *J* 3.5, 1.5 Hz, H-4), 5.16 (1H, d, *J* 6.0 Hz, CHO), 4.44 (1H, dq, *J* 6.5, 6.0 Hz, CHN), 4.26 (1H, d, *J* 18.0 Hz, C*H*H′), 4.00 (1H, d, *J* 18.0 Hz, CH*H*′), 2.45 (3H, s, *para* Ts), 1.36 (3H, d, *J* 6.5 Hz, CH_3); **δ_H (400 MHz, d_8–toluene)** 7.57 (2H, d, *J* 8.0 Hz, *ortho* Ts), 6.90 (1H, dd, *J* 2.0, 0.5 Hz, H-5), 6.79 (2H, d, *J* 8.0 Hz, *meta* Ts), 6.07 (1H, d, *J* 3.5 Hz, H-3), 5.92 (1H, dd, *J* 3.5,

2.0 Hz, H-4), 4.37 (1H, d, *J* 7.0 Hz, CHO), 4.22 (1H, d, *J* 18.0 Hz, C*H*H′), 4.18 (1H, dq, *J* 7.0, 6.5 Hz, CHN), 3.48 (1H, d, *J* 18.0 Hz, CH*H′*), 1.89 (3H, s, *para* Ts), 0.98 (3H, d, *J* 6.5 Hz, CH_3); **δ_C (100 MHz)** 165.5 (C=O), [148.4 and 144.5 (C-2 and *para* Ts)], 143.5 (C-5), 134.6 (*ipso* Ts), 130.0 (*meta* Ts), 127.5 (*ortho* Ts), 110.7 (C-4), 109.9 (C-3), 77.0 (CHO), 50.5 (CHN), 43.3 (CH_2), 21.6 (Ar*C*H_3), 17.2 (CH_3); *m/z* (CI) 353 $[M+NH_4]^+$, 336 $[M+H]^+$ (Found: $[M+H]^+$, 336.0898. $C_{16}H_{17}NO_5S$ requires $[M+H]^+$, 336.0906) (Found: C, 57.45; H, 4.96; N, 4.10. $C_{16}H_{17}NO_5S$ requires C, 57.30; H, 5.11; N, 4.18%).

tert-Butyl 2-(_tert_-butoxycarbonyl((1_R_,2_S_)-1-(furan-2-yl)-1-hydroxypropan-2-yl) amino)acetate (348)

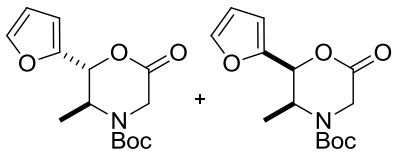


348

A solution of a 3:1 diastereomeric mixture of amine **342** (1.00 g, 3.92 mmol, 1.0 eq) and di-*tert*-butyl dicarbonate (1.03 g, 4.70 mmol, 1.2 eq) in toluene (20 mL) was heated to reflux for 1 h. The colourless solution was concentrated under reduced pressure and chromatography of the crude mixture over silica gel (20% Et_2O−hexane) gave a 3:1 diastereomeric mixture of *tert*-butyl 2-(*tert*-butoxycarbonyl((1*R*,2*S*)-1-(furan-2-yl)-1-hydroxypropan-2-yl) amino)acetate **348** (1.30 g, 93%) as a white solid; mp 58–62 °C; R_f 0.22 (30% Et_2O−hexane); ν_{max} (film) 3418, 2979, 1694, 1455, 1394, 1368, 1250, 1152, 1009, 737 cm^{-1}; (Major diastereomer) δ_H (400 MHz, DMSO, 373 K) 7.50 (1H, dd, *J* 2.0, 1.0 Hz, H-5), 6.37 (1H, dd, *J* 3.0, 2.0 Hz, H-4), 6.26 (1H, d, *J* 3.0 Hz, H-3), 5.03 (1H, d, *J* 4.5 Hz, C*H*OH), 4.59 (1H, dd, *J* 7.0, 4.5 Hz, CHN), 4.37-4.08 (1H, br, OH), 3.76 (2H, s, CH_2), 1.43 (9H, s, $(CH_3)_3$), 1.38 (9H, s, $(CH_3)_3$), 1.02 (3H, d, *J* 7.0 Hz, CH_3); δ_C (100 MHz) 169.2 (CO_2tBu), 155.3 (NC=O), 154.1 (C-2), 141.1 (C-5), 109.6 (C-4), 105.3

(C-3), [80.0 and 79.7 ($C(CH_3)_3$ of Boc and CO_2tBu)], 78.5 (COH), 68.1 (CHN), 46.4 (CH_2), [27.5 and 27.3 ($(CH_3)_3$) of Boc and CO_2tBu], 13.8 (CH_3); *m/z* (CI) 299 $[M-tBu+H]^+$, 356 $[M+H]^+$, 373 $[M+NH_4]^+$ (Found: $[M+H]^+$, 356.2069. $C_{18}H_{29}NO_6$ requires $[M+H]^+$, 356.2073).

(2*R*,3*S*)-*tert*-Butyl 2-(furan-2-yl)-3-methyl-6-oxomorpholine-4-carboxylate (349) and (2*S*,3*S*)-*tert*-Butyl 2-(furan-2-yl)-3-methyl-6-oxomorpholine-4-carboxylate (350)



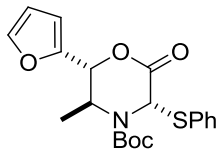
349 **350**

To a solution of a 3:1 diastereomeric mixture of ester **348** (1.20 g, 3.37 mmol, 1.0 eq) in THF (30 mL) was added 2 M LiOH (7.5 mL) at rt. After 6 h, the solvent was removed under reduced pressure, the residue was diluted with EtOAc (30 mL) and acidified to pH 1 with aqueous 1 M HCl (~20 mL). The organic layer was separated, the aqueous layer was diluted with water (30 mL) and extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine (90 mL) and dried ($MgSO_4$). Concentration under reduced pressure gave the crude hydroxyl-acid as a colourless gum. The gum was redissolved in CH_2Cl_2 (2 mL) and DIC (0.08 mL, 0.51 mmol, 1.5 eq) and DMAP (4.0 mg, 34.0 μmol, 0.1 eq) were added at rt. After 15 h, the mixture was filtered, the filtrate was concentrated under reduced pressure and chromatography of the crude orange oil over silica gel (10→30% Et_2O−hexane) gave a separated 3:1 diastereomeric ratio of (3*S*)-*tert*-butyl 2-(furan-2-yl)-3-methyl-6-oxomorpholine-4-carboxylates **349** and **350** (115 mg, 73%) as white solids.

(Major diastereomer 349) 534 mg, 56%; mp 58–59 °C; R_f 0.17 (30% Et_2O−hexane); ν_{max} (film) 2977, 2934, 1754, 1702, 1400, 1367, 1336, 1211, 1164, 1125, 1012, 751 cm^{-1}; δ_H (400 MHz) 7.43 (1H, br s, H-5), 6.39-6.36 (2H, m, H-3 and H-4), 5.29 (1H, d, *J* 3.0 Hz, CHO), 4.62 (1H, br s, CHN), 4.44 (1H, d, *J* 19.0 Hz, C*H*H′), 4.01 (1H, d, *J* 19.0 Hz, CH*H*′), 1.45 (9H, s, $(CH_3)_3$), 1.38 (3H, d, *J* 7.0 Hz, CH_3); δ_C (100 MHz) 166.4 (lactone C=O), 153.3 (NC=O), 149.9 (C-2), 143.4 (C-5), [110.6 and 108.8 (C-3 and C-4)], 81.2 ($C(CH_3)_3$), 76.9 (CHO), 47.6 (CHN), 43.1 (CH_2), 28.3 ($C(CH_3)_3$), 16.5 (CH_3); *m/z* (CI) 243 $[M-t\text{Bu}+H+NH_4]^+$, 226 $[M-t\text{Bu}+2H]^+$, 282 $[M+H]^+$ (Found: $[M+H]^+$, 282.1337. $C_{14}H_{19}NO_5$ requires $[M+H]^+$, 282.1341) (Found: C, 59.85; H, 6.76; N, 4.88. $C_{14}H_{19}NO_5$ requires C, 59.78; H, 6.81; N, 4.98%).

(Minor diastereomer 350) 160 mg; 17%; mp 72–76 °C; R_f 0.25 (30% Et_2O−hexane); ν_{max} (film) 2980, 1760, 1694, 1395, 1369, 1334, 1262, 1168, 1119, 1038, 1008 cm^{-1}; δ_H (400 MHz) 7.45 (1H, br s, H-5), 6.48 (1H, br s, H-3), 6.42 (1H, br s, H-4), 5.61 (1H, d, *J* 2.5 Hz, CHO), 4.71-4.44 (1H, m, CHN), 4.40 (1H, d, *J* 19.5 Hz, C*H*H′), 4.16 (1H, d, *J* 19.5 Hz, CH*H*′), 1.51 (9H, s, $(CH_3)_3$), 1.11 (3H, d, *J* 7.0 Hz, CH_3); δ_C (100 MHz) 166.1 (lactone C=O), 153.1 (NC=O), 148.1 (C-2), 142.9 (C-5), 110.6 (C-4), 108.8 (C-3), 81.5 ($C(CH_3)_3$), 77.0 (CHO), 47.6 (CHN), 43.6 (CH_2), 28.3 (($CH_3)_3$), 11.6 (CH_3); *m/z* (CI) 243 $[M-t\text{Bu}+H+NH_4]^+$, 226 $[M-t\text{Bu}+2H]^+$, 282 $[M+H]^+$ (Found: $[M+H]^+$, 282.1339. $C_{14}H_{19}NO_5$ requires $[M+H]^+$, 282.1341) (Found: C, 59.84; H, 6.68; N, 4.88. $C_{14}H_{19}NO_5$ requires C, 59.78; H, 6.81; N, 4.98%).

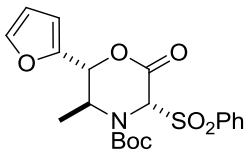
(2*R*,3*S*,5*S*)-*tert*-Butyl 2-(furan-2-yl)-3-methyl-6-oxo-5-(phenylthio)morpholine-4-carboxylate (351)



351

To a solution of morpholinone **349** (50 mg, 0.18 mmol, 1.0 eq) and $PhSSO_2Ph$ (133 mg, 0.53 mmol, 3.0 eq) in THF (1 mL) and DMPU (0.1 mL) at −78 °C was added dropwise a solution of LiHMDS (0.45 mL of a 1.0 M in THF / PhEt solution, 0.45 mmol, 2.5 eq). After 2.5 h, the yellow suspension was poured into saturated aqueous NH_4Cl (10 mL) and diluted with ether (10 mL). The organic phase was separated, washed with brine (10 mL) and dried ($MgSO_4$). Concentration of the filtrate under reduced pressure and chromatography of the crude mixture over silica gel (0→8% Et_2O−hexane) gave the major diastereomer (2*R*,3*S*,5*S*)-*tert*-butyl 2-(furan-2-yl)-3-methyl-6-oxo-5-(phenylthio)-morpholine-4-carboxylate **351** (44 mg, 64%) as a colourless gum; dr 7:1; R_f 0.34 (30% Et_2O−hexane); ν_{max} (film) 2978, 2934, 1764, 1706, 1370, 1303, 1249, 1159, 1026, 1006, 747 cm^{-1}; δ_H (400 MHz) 7.69-7.67 (2H, m, *ortho* C_6H_5), 7.51 (1H, d, *J* 2.0 Hz, H-5), 7.47-7.36 (3H, br, *meta* and *para* C_6H_5), 6.58 (1H, d, *J* 3.5 Hz, H-3), 6.45 (1H, dd, *J* 3.5, 2.0 Hz, H-4), 6.24-5.93 (1H, m, CHS), 5.67 (1H, d, *J* 10.0 Hz, CHO), 4.54-4.23 (1H, m, CHN), 1.57-1.21 (12H, m, $(CH_3)_3$ and CH_3); δ_C (100 MHz) 165.4 (lactone C=O), 154.2 (NC=O), 147.9 (C-2), 143.9 (C-5), [134.7 and 134.2 (*ipso* and *ortho* C_6H_5)], [129.4 and 129.3 (*meta* and *para* C_6H_5)], 111.3 (C-3), 110.8 (C-4), 82.3 ($C(CH_3)_3$), 75.1 (CHO), 62.5 (CHS), 49.5 (CHN), 28.0 ($(CH_3)_3$), 17.8 (CH_3); *m/z* (CI) 407 $[M+NH_4]^+$, 351 $[M-tBu+H+NH_4]^+$, 297 $[M-SPh+OH]^+$, 280 $[M-SPh]^+$ (Found: $[M+NH_4]^+$, 407.1639. $C_{20}H_{23}NO_5S$ requires $[M+NH_4]^+$, 407.1641).

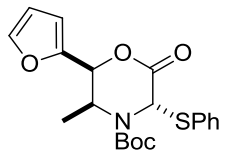
(2*R*,3*S*,5*S*)-*tert*-Butyl 2-(furan-2-yl)-3-methyl-6-oxo-5-(phenylsulfonyl)morpholine-4-carboxylate (352)



352

To a solution of sulfide **351** (26.9 mg, 0.07 mmol, 1.0 eq) in methanol (1 mL) was added magnesium monoperoxyphthalate hexahydrate (MMPP) (80% purity, 170 mg, 0.28 mmol, 4.0 eq) and the white suspension was stirred at rt overnight. The mixture was filtered, the filtrate was concentrated under reduced pressure and diluted with chloroform and water. The organic phase was removed with a phase separator, concentrated under reduced pressure and purified using preparative silica gel TLC (20% EtOAc−hexane) to give (2*R*,3*S*,5*S*)-*tert*-butyl 2-(furan-2-yl)-3-methyl-6-oxo-5-(phenylsulfonyl)morpholine-4-carboxylate **352** (9.4 mg, 32%) as a colourless gum; R_f 0.36 (20% EtOAc−hexane); ν_{max} (film) 1766, 1715, 1449, 1371, 1312, 1255, 1150, 1082, 1007 cm^{-1}; δ_H (400 MHz) 8.05 (2H, d, *J* 7.5 Hz, *ortho* C_6H_5), 7.80-7.71 (1H, m, *para* C_6H_5), 7.65 (2H, dd, *J* 7.5, 7.5 Hz, *meta* C_6H_5), 7.54-7.49 (1H, m, H-5), 6.60 (1H, d, *J* 3.5 Hz, H-3), 6.45 (1H, dd, *J* 3.5, 2.0 Hz, H-4), 6.27-5.90 (1H, m, CHS), 5.89-5.74 (1H, m, CHO), 4.64-4.34 (1H, m, CHN), 1.64-1.34 (12H, m, $(CH_3)_3$ and CH_3); δ_C (100 MHz) 161.4 (lactone C=O), 155.4 (NC=O), 147.4 (C-2), 144.1 (C-5), 138.0 (*ipso* C_6H_5), 134.7 (*para* C_6H_5), [111.9 and 110.8 (*meta* and *ortho* C_6H_5)], 111.9 (C-3), 110.8 (C-4), 83.4 ($C(CH_3)_3$), 75.3 (CHO), 75.1 (CHS), 49.3 (CHN), 30.3 (CH_3), 28.1 ($(CH_3)_3$); *m/z* (CI) 439 $[M+NH_4]^+$, 297 $[M-SO_2Ph+OH]^+$ (Found: $[M+NH_4]^+$, 439.1544. $C_{20}H_{23}NO_7S$ requires $[M+NH_4]^+$, 439.1539).

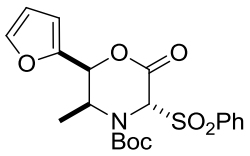
(2*S*,3*S*,5*S*)-*tert*-Butyl 2-(furan-2-yl)-3-methyl-6-oxo-5-(phenylthio)morpholine-4-carboxylate (354)



354

To a solution of morpholinone **350** (52 mg, 0.19 mmol, 1.0 eq) and $PhSSO_2Ph$ (139 mg, 0.53 mmol, 3.0 eq) in THF (1 mL) and DMPU (0.1 mL) at −78 °C was added dropwise a solution of LiHMDS (0.46 mL of a 1.0 M in THF / PhEt solution, 0.46 mmol, 2.5 eq). After 2.5 h, the yellow suspension was poured into saturated aqueous NH_4Cl (10 mL) and diluted with ether (10 mL). The organic phase was separated, washed with brine (10 mL) and dried ($MgSO_4$). Concentration of the filtrate under reduced pressure and chromatography of the crude mixture over silica gel (0→5% Et_2O−hexane) gave (2*S*,3*S*,5*S*)-*tert*-butyl 2-(furan-2-yl)-3-methyl-6-oxo-5-(phenylthio)morpholine-4-carboxylate **354** (44 mg, 47%) as a colourless gum; R_f 0.56 (30% Et_2O−hexane); ν_{max} (film) 2981, 1760, 1714, 1372, 1354, 1306, 1249, 1162, 1042, 1006, 744 cm^{-1}; δ_H (400 MHz) 7.73-7.57 (2H, m, *ortho* C_6H_5), 7.49-7.45 (1H, m, H-5), 7.41-7.37 (3H, m, *meta* and *para* C_6H_5), 6.53 (1H, dd, *J* 10.0, 3.0 Hz, H-4), 6.47-6.42 (1H, m, H-3), 6.00-5.96 (1H, m, CHO), 6.65-5.58 (1H, m, CHS), 4.51-4.28 (1H, m, CHN), 1.51 (9H, s, $(CH_3)_3$), 1.10 (3H, d, *J* 6.5 Hz, CH_3); δ_C (100 MHz) 164.6 (lactone C=O), 152.3 (NC=O), 147.5 (C-2), 142.9 (C-5), 137.5 (*ipso* C_6H_5), 134.3 (*ortho* C_6H_5), [129.4 and 129.1 (*meta* and *para* C_6H_5)], 110.6 (C-3), 109.1 (C-4), 82.5 ($C(CH_3)_3$), 74.6 (CHO), 62.6 (CHS), 49.9 (CHN), 28.2 ($(CH_3)_3$), 13.0 (CH_3); *m/z* (CI) 351 $[M-tBu+H+NH_4]^+$, 407 $[M+NH_4]^+$, 297 $[M-SPh+OH]^+$, 390 $[M+H]^+$ (Found: $[M+H]^+$, 390.1376. $C_{20}H_{23}NO_5S$ requires $[M+H]^+$, 390.1375).

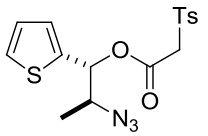
(2*S*,3*S*,5*S*)-*tert*-Butyl 2-(furan-2-yl)-3-methyl-6-oxo-5-(phenylsulfonyl)morpholine-4-carboxylate (355)



355

To a solution of sulfide **354** (46.5 mg, 0.12 mmol, 1.0 eq) in methanol (1 mL) was added magnesium monoperoxyphthalate hexahydrate (MMPP) (80% purity, 369 mg, 0.60 mmol, 5.0 eq) and the white suspension was stirred at rt overnight. The suspension was concentrated under reduced pressure and the residue was diluted with water (8 mL) and EtOAc (8 mL). The organic phase was separated, the aqueous layer was extracted again with EtOAc (8 mL) and the combined organic extracts were dried ($MgSO_4$). Concentration of the filtrate under reduced pressure and chromatography of the crude mixture over silica gel (10% Et_2O−hexane) gave (2*S*,3*S*,5*S*)-*tert*-butyl 2-(furan-2-yl)-3-methyl-6-oxo-5-(phenylsulfonyl)morpholine-4-carboxylate **355** (14.6 mg, 29%) as a colourless gum; R_f 0.41 (20% EtOAc−hexane); ν_{max} (film) 1765, 1714, 1370, 1311, 1257, 1147, 1080 cm^{-1}; δ_H (400 MHz) 8.10-8.04 (2H, m, *ortho* C_6H_5), 7.80-7.71 (1H, m, *para* C_6H_5), 7.67-7.62 (2H, m, *meta* C_6H_5), 7.51-7.48 (1H, m, H-5), 6.59-6.53 (1H, m, H-3), 6.47-6.44 (1H, m, H-4), 6.24-6.13 (1H, m, CHS), 5.87-5.77 (1H, m, CHO), 4.68-4.49 (1H, m, CHN), 1.58-1.44 (9H, m, $(CH_3)_3$), 1.19-1.15 (3H, m, CH_3); *m/z* (CI) 439 $[M+NH_4]^+$, 297 $[M-SO_2Ph+OH]^+$ (Found: $[M+NH_4]^+$, 439.1537. $C_{20}H_{23}NO_7S$ requires $[M+NH_4]^+$, 439.1539).

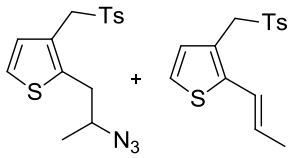
(1*R*,2*S*)-2-Azido-1-(thiophen-2-yl)propyl 2-tosylacetate (363)



363

To a solution of a 7:1 diastereomeric mixture of alcohol **328** (510 mg, 2.78 mmol, 1.0 eq) and tosylacetic acid (775 mg, 3.62 mmol, 1.3 eq) in CH_2Cl_2 (1.5 mL) was added DIC (0.65 mL, 4.17 mmol, 1.5 eq) and DMAP (34.0 mg, 0.28 mmol, 0.1 eq) at rt. After 20 h, the yellow suspension was diluted with water (20 mL) and CH_2Cl_2 (20 mL), the organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and chromatography of the crude mixture over silica gel (10% EtOAc−hexane) gave a 7:1 diastereomeric mixture of (1*R*,2*S*)-2-azido-1-(thiophen-2-yl)propyl 2-tosylacetate **363** (1.05 g, 100%) as a colourless oil; R_f 0.22 (40% EtOAc−hexane); ν_{max} (film) 2981, 2940, 2112 (N_3), 1747, 1704, 1598, 1455, 1385, 1336, 1149, 1085, 982, 813, 718 cm^{-1}; (Major diastereomer) δ_H (400 MHz) 7.71 (2H, d, *J* 8.5 Hz, *ortho* Ts), 7.38 (1H, dd, *J* 5.0, 1.0 Hz, H-5), 7.30 (2H, d, *J* 8.5 Hz, *meta* Ts), 7.11 (1H, dd, *J* 3.0, 1.0 Hz, H-3), 7.03 (1H, dd, *J* 5.0, 3.0 Hz, H-4), 5.92 (1H, d, *J* 7.0 Hz, CHO), 4.18 (1H, d, *J* 14.5 Hz, C*H*H′), 4.15 (1H, d, *J* 14.5 Hz, CH*H*′), 3.84 (1H, dq, *J* 7.0, 7.0 Hz, CHN), 3.06 (3H, s, *para* Ts), 1.19 (3H, d, *J* 7.0 Hz, CH_3); δ_C (100 MHz) 161.4 (C=O), 145.4 (*para* Ts), 137.6 (C-2), 135.4 (*ipso* Ts), 129.9 (*meta* Ts), 128.5 (*ortho* Ts), 128.1 (C-3), 127.0 (C-5), 126.8 (C-4), 75.7 (CHO), 60.8 (CH_2), 60.1 (CHN), 21.7 (Ar*C*H_3), 16.1 (CH_3); *m/z* (CI) 397 $[M+NH_4]^+$ (Found: $[M+NH_4]^+$, 397.1006. $C_{16}H_{17}N_3O_4S_2$ requires $[M+NH_4]^+$, 397.1004).

2-(2-Azidopropyl)-3-(tosylmethyl)thiophene (366) and (*E*)-2-(prop-1-enyl)-3-(tosylmethyl)thiophene (367)



366 **367**

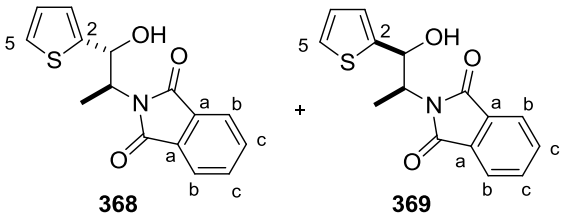
A solution of azide **363** (42.2 mg, 0.11 mmol, 1.0 eq), BSA (0.08 mL, 0.33 mmol, 3.0 eq) and Et_3N (0.02 mL, 0.17 mmol, 1.5 eq) in acetonitrile (1 mL) was heated at 90 °C overnight. The yellow solution was concentrated under reduced pressure and chromatography of the crude mixture over silica gel (20% Et_2O−hexane) gave 2-(2-azidopropyl)-3-(tosylmethyl)thiophene **366** (3.0 mg, 8%) as a colourless oil and (*E*)-2-(prop-1-enyl)-3-(tosylmethyl)thiophene **367** (19.1 mg, 59%, *E*/*Z*: 15:1) as a white solid.

(Data for 366) R_f 0.34 (10% Et_2O−hexane); ν_{max} (film) 2925, 2109 (N_3), 1598, 1456, 1316, 1303, 1254, 1187, 1146, 1087 cm^{-1}; δ_H (400 MHz) 7.57 (2H, d, *J* 8.0 Hz, *ortho* Ts), 7.31 (2H, d, *J* 8.0 Hz, *meta* Ts), 7.15 (1H, d, *J* 5.0 Hz, H-4), 6.76 (1H, d, *J* 5.0 Hz, H-5), 4.39 (1H, d, *J* 14.5 Hz, C*H*H′SO_2), 4.33 (1H, d, *J* 14.5 Hz, CH*H*′ SO_2), 3.57 (1H, dq, *J* 6.5, 6.5 Hz, CHN_3), 2.68-2.64 (2H, m, CH_2CN_3), 2.46 (3H, s, *para* Ts), 1.27 (3H, d, *J* 6.5, 1.5 Hz, CH_3); *m/z* (CI) 353 $[M+NH_4]^+$, 310 $[M-N_3+OH]^+$ (Found: $[M+NH_4]^+$, 353.1110. $C_{15}H_{17}N_3O_2S_2$ requires $[M+NH_4]^+$, 353.1106).

(Data for 367) mp 112–120 °C; R_f 0.40 (50% Et_2O−hexane); ν_{max} (film) 2918, 1598, 1453, 1317, 1302, 1151, 1087, 948, 761 cm^{-1}; (Major diastereomer) δ_H (400 MHz) 7.53 (2H, d, *J* 8.5 Hz, *ortho* Ts), 7.27 (2H, d, *J* 8.5 Hz, *meta* Ts), 7.02 (1H, d, *J* 5.5 Hz, H-4), 6.80 (1H, d, *J* 5.5 Hz, H-5), 6.02 (1H, dd, *J* 15.5, 1.5 Hz, *H*C=CH(CH_3)), 5.90 (1H, dq, *J* 15.5, 6.5 Hz, HC=C*H*(CH_3)), 4.33 (2H, s, CH_2), 2.44 (3H, s, *para* Ts), 1.71 (3H, dd,

J 6.5, 1.5 Hz, CH_3); δ_C (100 MHz) [144.7, 142.6 and 134.7 (C-3, *ipso* Ts and *para* Ts)], 130.2 (C-5), 129.5 (*meta* Ts), 128.7 (*ortho* Ts), 128.2 (C=*C*H(CH_3)), 123.2 (C-2), 122.4 (C-4), 121.0 (*C*=CH(CH_3)), 55.8 (CH_2), 21.6 (Ar*C*H_3), 18.4 (CH_3); *m/z* (CI) 310 $[M+NH_4]^+$, 292 $[M+H]^+$ (Found: $[M+NH_4]^+$, 310.0939. $C_{15}H_{16}O_2S_2$ requires $[M+NH_4]^+$, 310.0935) (Found: C, 61.51; H, 5.41; $C_{15}H_{16}O_2S_2$ requires C, 61.61; H, 5.52%).

2-((1*R*,2*S*)-1-Hydroxy-1-(thiophen-2-yl)propan-2-yl)isoindoline-1,3-dione (368) and 2-((1*S*,2*S*)-1-Hydroxy-1-(thiophen-2-yl)propan-2-yl)isoindoline-1,3-dione (369)



368 **369**

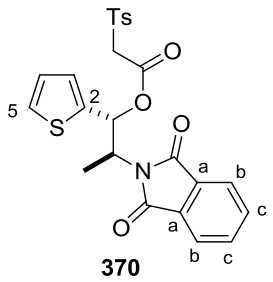
A solution of a 7:1 diastereomeric mixture of amino-alcohol **55** (332 mg, 2.11 mmol, 1.0 eq) and phthalic anhydride (406 mg, 2.75 mmol, 1.3 eq) in toluene (10 mL) was heated at 100 °C for 4 h. The mixture was concentrated under reduced pressure and chromatography of the crude mixture over silica gel (15→20% EtOAc−hexane) gave a separated 7:1 diastereomeric ratio of 2-((2*S*)-1-hydroxy-1-(thiophen-2-yl)propan-2-yl)isoindoline-1,3-diones **368** and **369** (420 mg, 69%) as white solids.

(Major diastereomer 368) 358 mg; 59%; mp 126–128 °C; R_f 0.31 (30% EtOAc−hexane); ν_{max} (film) 3454, 1770, 1704, 1697, 1393, 1026, 719 cm^{-1}; δ_H (400 MHz) 7.83-7.81 (2H, m, C_6H_4 b), 7.72-7.70 (2H, m, C_6H_4 c), 7.22 (1H, dd, *J* 5.0, 1.0 Hz, H-5), 7.03 (1H, d, *J* 3.5 Hz, H-3), 6.94 (1H, dd, *J* 5.0, 3.5 Hz, H-4), 5.40 (1H, dd, *J* 7.5, 7.0 Hz, CHO), 4.75 (1H, dq, *J* 7.0, 7.0 Hz, CHN), 3.85 (1H, br s, OH), 1.46 (3H, d, *J* 7.0 Hz, CH_3); δ_C (100 MHz) 169.0 (C=O), 145.8 (C-2), 134.1 (C_6H_4 c), 131.7 (C_6H_4 a), 126.9 (C-4), 125.0 (C-5), 124.3 (C-3), 134.1 (C_6H_4 b), 71.5 (COH), 52.9 (CHN), 15.6

(CH_3); *m/z* (CI) 270 $[M-OH]^+$, 287 $[M+H]^+$, 305 $[M+NH_4]^+$ (Found: $[M+NH_4]^+$, 305.0961. $C_{15}H_{13}NO_3S$ requires $[M+NH_4]^+$, 305.0960).

(Minor diastereomer 369) 62 mg; 10%; R_f 0.38 (30% EtOAc−hexane); δ_H (400 MHz) 7.82-7.78 (2H, m, C_6H_4 b), 7.73-7.70 (2H, m, C_6H_4 c), 7.19 (1H, d, *J* 5.0 Hz, H-5), 6.99 (1H, d, *J* 3.0 Hz, H-3), 6.89 (1H, dd, *J* 5.0, 3.0 Hz, H-4), 5.50 (1H, dd, *J* 6.0, 1.5 Hz, CHO), 4.63 (1H, dq, *J* 7.0, 6.0 Hz, CHN), 3.88 (1H, br s, OH), 1.55 (3H, d, *J* 7.0 Hz, CH_3); δ_C (100 MHz) 168.6 (C=O), 145.1 (C-2), 134.2 (C_6H_4 c), 131.6 (C_6H_4 a), 126.9 (C-4), 124.9 (C-5), 124.3 (C-3), 123.4 (C_6H_4 b), 71.7 (COH), 53.8 (CHN), 13.7 (CH_3).

(1*R*,2*S*)-2-(1,3-Dioxoisoindolin-2-yl)-1-(thiophen-2-yl)propyl 2-tosylacetate (370)

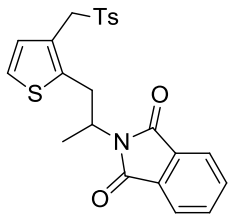


370

To a solution of alcohol **368** (500 mg, 1.74 mmol, 1.0 eq) and tosylacetic acid (480 mg, 2.26 mmol, 1.3 eq) in CH_2Cl_2 (1.0 mL) was added Et_3N (0.49 mL, 3.48 mmol, 2.0 eq) and a solution of T3P® (1.6 mL of a 50% w/w EtOAc solution, 2.61 mmol, 1.5 eq) at 0 °C and the yellow solution was allowed to warmed up to rt. After 2 h, the solution was quenched with 1 M NaOH (10 mL) and diluted with EtOAc (10 mL), the organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with brine (30 mL) and dried ($MgSO_4$). Concentrated of the filtrate under reduced pressure and chromatography of the crude mixture over silica gel (10→20% EtOAc−hexane) gave (1*R*,2*S*)-2-(1,3-dioxoisoindolin-2-yl)-1-(thiophen-2-yl)propyl 2-tosylacetate **370** (757 mg, 90%) as a white solid;

mp 60–66 °C; R_f 0.17 (30% EtOAc−hexane); ν_{max} (film) 1745, 1713, 1381, 1329, 1157, 1082, 1026, 723 cm^{-1}; δ_H (400 MHz) 7.89 (2H, dd, *J* 5.5, 3.0 Hz, C_6H_4 b), 7.73 (2H, dd, *J* 5.5, 3.0 Hz, C_6H_4 c), 7.50 (2H, d, *J* 8.5 Hz, *ortho* Ts), 7.38 (1H, d, *J* 5.0 Hz, H-5), 7.26-7.22 (3H, m, *meta* Ts and H-3), 7.02 (1H, dd, *J* 5.0, 3.0 Hz, H-4), 6.72 (1H, d, *J* 10.5 Hz, CHO), 4.84 (1H, dq, *J* 10.5, 7.0 Hz, CHN), 3.92 (1H, d, *J* 13.5 Hz, C*H*H′), 3.84 (1H, d, *J* 13.5 Hz, CH*H*′), 2.43 (3H, s, *para* Ts), 1.35 (3H, d, *J* 7.0 Hz, CH_3); δ_C (100 MHz) [168.2 and 161.3 (C=O of phthalimide and ester)], [138.9 and 135.4 (*para* Ts and C-2)], 134.1 (*ipso* Ts), 134.0 (C_6H_4 c), 132.1 (C_6H_4 a), 129.7 (*meta* Ts), 128.5 (C-3), 128.3 (*ortho* Ts), 126.9 (C-5), 126.9 (C-4), 123.3 (C_6H_4 b), 72.8 (CHO), 60.9 (CH_2), 50.1 (CHN), 21.7 (Ar*C*H_3), 15.4 (CH_3); *m/z* (CI) 501 $[M+NH_4]^+$ (Found: $[M+NH_4]^+$, 501.1160. $C_{24}H_{21}NO_6S_2$ requires $[M+NH_4]^+$, 501.1154) (Found: C, 59.66; H, 4.25; N, 2.81. $C_{24}H_{21}NO_6S_2$ requires C, 59.61; H, 4.38; N, 2.90%).

2-(1-(3-(Tosylmethyl)thiophen-2-yl)propan-2-yl)isoindoline-1,3-dione (371)

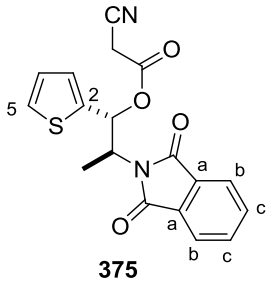


371

A solution of ester **370** (50.0 mg, 0.10 mmol, 1.0 eq), BSA (0.15 mL, 0.62 mmol, 6.0 eq) and KOAc (1.0 mg, 0.01 mmol, 0.1 eq) was subjected to microwave irradiation at 160 °C for 1 min, then at 170 °C for 5 min. The reaction was incompleted; more KOAc (10.0 mg, 0.1 mmol, 1.0 eq) was added and it was irradiated at 160 °C for another 5 min. The mixture was co-evaporated with PhMe (3 × 7 mL) to remove the BSA. Chromatography of the residue over silica gel (10% Et_2O−hexane) gave 2-(1-(3-(tosylmethyl)thiophen-2-yl)propan-2-yl)isoindoline-1,3-dione **371** (17.8 mg, 40%) as a yellow oil; R_f 0.31 (30%

EtOAc−hexane); ν_{max} (film) 2927, 2770, 1714, 1698, 1394, 1360, 1318, 1147, 1087, 1028, 722 cm^{-1}; δ_H (400 MHz) 7.79 (2H, dd, *J* 5.5, 3.0 Hz, C_6H_4 b), 7.70 (2H, dd, *J* 5.5, 3.0 Hz, C_6H_4 c), 7.59 (2H, d, *J* 8.5 Hz, *ortho* Ts), 7.29 (2H, d, *J* 8.5 Hz, *meta* Ts), 7.00 (1H, d, *J* 5.0 Hz, H-4), 6.71 (1H, d, *J* 5.0 Hz, H-5), 4.54-4.45 (1H, m, CHN), 4.40 (1H, d, *J* 14.5 Hz, C*H*H′SO_2), 4.27 (1H, d, *J* 14.5 Hz, CH*H*′SO_2), 3.32 (1H, dd, *J* 15.5, 10.0 Hz, C*H*H′CN), 2.85 (1H, dd, *J* 15.5, 6.0 Hz, CH*H*′CN), 2.44 (3H, s, *para* Ts), 1.46 (3H, d, *J* 7.0 Hz, CH_3); δ_C (100 MHz) 168.2 (C=O), [144.8, 140.8 and 135.2 (C-3, *ipso* Ts and *para* Ts)], 134.0 (C_6H_4 c), 131.8 (C_6H_4 a), 129.7 (*meta* Ts), 129.6 (C-5), 128.6 (*ortho* Ts), 125.1 (C-2), 123.3 (C-4), 123.2 (C_6H_4 b), 55.6 (CH_2SO_2), 45.2 (CHN), 31.3 (*C*H_2CN), 21.6 (Ar*C*H_3), 18.5 (CH_3); *m/z* (ESI) 462 $[M+Na]^+$, 440 $[M+H]^+$ (Found: $[M+H]^+$, 440.0976. $C_{23}H_{21}NO_4S_2$ requires $[M+H]^+$, 440.0990).

(1*R*,2*S*)-2-(1,3-dioxoisoindolin-2-yl)-1-(thiophen-2-yl)propyl 2-cyanoacetate (375)

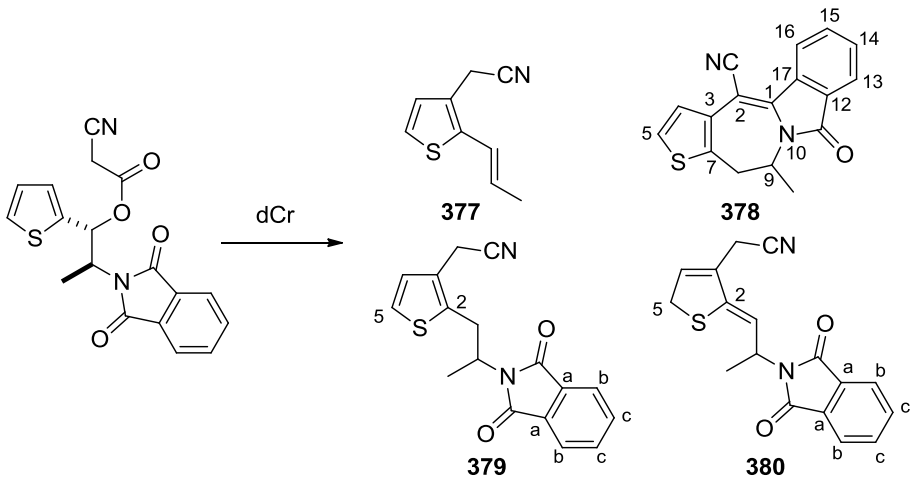


375

To a solution of alcohol **368** (500 mg, 1.74 mmol, 1.0 eq) and cyanoacetic acid (178 mg, 2.09 mmol, 1.2 eq) in CH_2Cl_2 (2 mL) was added Et_3N (0.49 mL, 3.48 mmol, 2.0 eq) and a solution of T3P® (1.6 mL of a 50% w/w EtOAc solution, 2.61 mmol, 1.5 eq) at 0 °C and the yellow solution was allowed to warmed up to rt. After 2 h, the solution was quenched with water (30 mL), diluted with EtOAc (30 mL) and the organic phase was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic extracts were washed with brine (60 mL), dried ($MgSO_4$). Concentration of the filtrate under reduced pressure and chromatography of the crude mixture over silica gel

(20→25% EtOAc−hexane) gave (1*R*,2*S*)-2-(1,3-dioxoisoindolin-2-yl)-1-(thiophen-2-yl)propyl 2-cyanoacetate **375** (542 mg, 88%) as a white solid; mp 114–118 °C; R_f 0.38 (30% EtOAc−hexane); ν_{max} (film) 2940, 2261 (CN), 1756, 1714, 1393, 1382, 1253, 1177, 1026, 720 cm^{-1}; δ_H (400 MHz) 7.88 (2H, dd, *J* 5.5, 3.0 Hz, C_6H_4 b), 7.76 (2H, dd, *J* 5.5, 3.0 Hz, C_6H_4 c), 7.40 (1H, d, *J* 5.0 Hz, H-5), 7.29 (1H, d, *J* 3.5 Hz, H-5), 7.05 (1H, dd, *J* 5.0, 3.5 Hz, H-4), 6.70 (1H, d, *J* 10.0 Hz, CHO), 4.82 (1H, dq, *J* 10.0, 7.0 Hz, CHN), 3.25 (2H, s, CH_2), 1.37 (3H, d, *J* 7.0 Hz, CH_3); δ_C (100 MHz) [168.0 and 161.7 (C=O of phthalimide and ester)], 138.4 (C-2), 134.3 (C_6H_4 c), 131.6 (C_6H_4 a), 128.6 (C-3), 127.2 (C-5), 127.1 (C-4), 123.5 (C_6H_4 b), 112.3 (CN), 73.8 (CHO), 50.1 (CHN), 24.7 (CH_2), 15.6 (CH_3); *m/z* (CI) 270 $[M-CH_2(CN)CO_2]^+$, 372 $[M+NH_4]^+$, 287 $[M-CH_2(CN)CO+H]^+$ (Found: $[M+NH_4]^+$, 372.1017. $C_{18}H_{14}N_2O_4S$ requires $[M+NH_4]^+$, 372.1018) (Found: C, 61.15; H, 3.90; N, 7.88. $C_{18}H_{14}N_2O_4S$ requires C, 61.01; H, 3.98; N, 7.90%).

Procedure for dCr reaction of ester 375



A solution of ester **375** (35.0 mg, 0.10 mmol, 1.0 eq), BSA (0.07 mL, 0.30 mmol, 3.0 eq) and KOAc (9.7 mg, 0.10 mmol, 1.0 eq) in toulene (1 mL) was heated in a sealed tube at 100 °C for 15 h. The mixture was co-evaporated with PhMe (3 ×7 mL) to remove BSA.

Purification of the crude residue using preparative silica gel TLC (2 × 30% Et_2O−hexane) gave products **377**-**380** in their respective yields.

(*E*)-2-(2-(Prop-1-enyl)thiophen-3-yl)acetonitrile (377)

(Data for 377): 1.0 mg; 6%; yellow oil; R_f 0.67 (30% EtOAc−hexane); ν_{max} (film) 2915, 2193, 1450, 1378, 1253, 1157, 1080, 949 cm^{-1}; δ_H (400 MHz) 7.11 (1H, d, *J* 5.0 Hz, H-4), 6.98 (1H, d, *J* 5.0 Hz, H-5), 6.46 (1H, dd, *J* 15.5, 1.5 Hz, *H*C=CH(CH_3)), 6.13 (1H, dq, *J* 15.5, 6.5 Hz, HC=C*H*(CH_3)), 3.68 (2H, s, CH_2), 1.92 (3H, dd, *J* 6.5, 1.5 Hz, CH_3); *m/z* (CI) 181 $[M+NH_4]^+$, 163 $[M+H]^+$ (Found: $[M+NH_4]^+$, 181.0802. C_9H_9NS requires $[M+NH_4]^+$, 181.0799).

9-Methyl-11-oxo-6-thia-10-azatetracyclo[8.7.0.0^{3,7}.0^{12,17}]heptadeca-1,3(7),4,12,14,16-hexaene-2-carbonitrile (378)

(Data for 378) 12.0 mg; 41%; yellow oil; R_f 0.62 (30% EtOAc−hexane); ν_{max} (film) 2940, 2975, 2932, 2212 (CN), 1728, 1714, 1599, 1584, 1472, 1303, 1255, 1157, 1095, 1032, 720 cm^{-1}; δ_H (500 MHz) 8.79 (1H, d, *J* 8.0 Hz, H-16), 7.92 (1H, d, *J* 7.5 Hz, H-13), 7.72 (1H, ddd, *J* 8.0, 7.5 1.0 Hz, H-15), 7.61 (1H, ddd, *J* 8.0, 7.5, 1.0 Hz, H-14), 7.44 (1H, d, *J* 5.5 Hz, H-4), 7.19 (1H, d, *J* 5.5 Hz, H-5), 5.36 (1H, ddq, *J* 7.0, 5.0, 2.5 Hz, H-9), 3.31 (1H, dd, *J* 16.0, 5.0 Hz, C*H*H′), 3.22 (1H, dd, *J* 16.0, 2.5 Hz, C*H*H′), 1.10 (3H, d, *J* 7.0 Hz, CH_3); δ_C (125 MHz) 165.7 (C-11), [142.6, 137.2 and 135.1 (3°)], 133.5 (C-15), 130.8 (C-14), [129.9, 129.3, 128.2 (3°)], [124.1 and 124.0 (C-16, C-13)], 123.0 (C-5), 119.1 (CN), 87.8 (C-2), 46.9 (C-9), 34.0 (CH_2), 18.4 (CH_3); *m/z* (CI) 293 $[M+H]^+$, 310 $[M+NH_4]^+$ (Found: $[M+H]^+$, 293.0753. $C_{17}H_{12}N_2OS$ requires $[M+H]^+$, 293.0749).

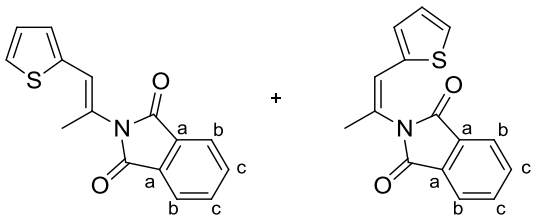
2-(2-(2-(1,3-Dioxoisoindolin-2-yl)propyl)thiophen-3-yl)acetonitrile (379)

(Data for 379) 6.9 mg; 22%; yellow oil; R_f 0.38 (30% EtOAc−hexane); ν_{max} (film) 2247 (CN), 1770, 1704, 1394, 1361, 1029, 881, 720 cm^{-1}; δ_H (400 MHz) 7.81 (2H, dd, *J* 5.5, 3.0 Hz, C_6H_4 b), 7.72 (2H, dd, *J* 5.5, 3.0 Hz, C_6H_4 c), 7.12 (1H, d, *J* 5.5 Hz, H-4), 6.93 (1H, d, *J* 5.5 Hz, H-5), 4.69-4.60 (1H, m, CHN), 3.69 (2H, m, CH_2CN), 3.63 (1H, dd, *J* 15.0, 10.0 Hz, C*H*H′CN), 3.24 (1H, dd, *J* 15.0, 6.0 Hz, CH*H*′CN), 1.60 (3H, d, *J* 7.0 Hz, CH_3); δ_C (100 MHz) 168.3 (C=O), 136.9 (C-3), 134.0 (C_6H_4 c), 131.6 (C_6H_4 a), 129.7 (C-5), 126.3 (C-2), 124.2 (C-4), 123.2 (C_6H_4 b), 117.5 (CN), 48.2 (CHN), 31.7 (*C*H_2C(CH_3)), 18.5 (CH_3), 16.8 (*C*H_2CN); *m/z* (CI) 328 $[M+NH_4]^+$, 270 $[M-CH_2CN]^+$ (Found: $[M+NH_4]^+$, 328.1123. $C_{17}H_{14}N_2O_2S$ requires $[M+NH_4]^+$, 328.1120).

(*Z*)-2-(2-(2-(1,3-Dioxoisoindolin-2-yl)propylidene)-2,5-dihydrothiophen-3-yl)acetonitrile (380)

(Data for 380) 1.8 mg; 5%; yellow oil; R_f 0.30 (30% EtOAc−hexane); ν_{max} (film) 2250 (CN), 1773, 1711, 1386, 1141, 1080, 1023, 881, 720 cm^{-1}; δ_H (400 MHz) 7.85 (2H, dd, *J* 5.5, 3.0 Hz, C_6H_4 b), 7.79 (2H, dd, *J* 5.5, 3.0 Hz, C_6H_4 c), 6.47-6.44 (1H, m, H-4), 5.80 (1H, d, *J* 8.0 Hz, C*H*CH(CH_3)), 5.02 (1H, dq, *J* 8.0, 7.0 Hz, C*H*(CH_3)), 3.96 (1H, d, *J* 18.0 Hz, H-5), 3.88 (1H, d, *J* 18.0 Hz, H-5), 3.32-3.31 (2H, m, CH_2CN), 1.62 (3H, d, *J* 7.0 Hz, CH_3); *m/z* (CI) 328 $[M+NH_4]^+$, 270 $[M-CH_2CN]^+$ (Found: $[M+NH_4]^+$, 328.1124. $C_{17}H_{14}N_2O_2S$ requires $[M+NH_4]^+$, 328.1120).

(*E*)-2-(1-(Thiophen-2-yl)prop-1-en-2-yl)isoindoline-1,3-dione [*(E)*-384] and (*Z*)-2-(1-(thiophen-2-yl)prop-1-en-2-yl)isoindoline-1,3-dione [(*Z*)-384]



(*E*)-384 (*Z*)-384

A solution of ester **375** (42.0 mg, 0.12 mmol, 1.0 eq), BSA (0.09 mL, 0.36 mmol, 3.0 eq), KOAc (12.0 mg, 0.12 mmol, 1.0 eq) and some 4 Å molecular sieves in toulene (1 mL) was heated in a sealed tube at 120 °C for 22.5 h. The mixture was co-evaporated with PhMe (3 ×7 mL) to remove BSA. The residue was diluted with CH_2Cl_2 (5 mL), brine (5 mL) and the organic layer was separated with a phase separator. The filtrate was concentrated under reduced pressure and purified using preparative silica gel TLC (2 × 30% Et_2O–hexane) to give 2-(1-(thiophen-2-yl)prop-1-en-2-yl)isoindoline-1,3-diones **384** (9.0 mg, 28%, *E*/*Z* 1.5:1) as colourless oils.

[Major (*E*)-384] 4.8 mg; 15%; R_f 0.56 (30% EtOAc–hexane); ν_{max} (film) 1722, 1713, 1378, 1105, 866, 716, 686 cm^{-1}; δ_H (400 MHz) 7.93 (2H, dd, *J* 5.5, 3.0 Hz, C_6H_4 b), 7.79 (2H, dd, *J* 5.5, 3.0 Hz, C_6H_4 c), 7.40 (1H, d, *J* 5.0 Hz, H-5), 7.15 (1H, d, *J* 3.5 Hz, H-3), 7.10 (1H, dd, *J* 5.0, 3.5 Hz, H-5), 6.76 (1H, s, CH), 2.39 (3H, s, CH_3); *m/z* (CI) 287 $[M+NH_4]^+$, 270 $[M+H]^+$ (Found: $[M+H]^+$, 270.0586. $C_{15}H_{11}NO_2S$ requires $[M+H]^+$, 270.0589).

[Minor (*Z*)-384] 4.2 mg; 13%; R_f 0.49 (10% Et_2O–hexane); δ_H (400 MHz) 7.97 (2H, dd, *J* 5.5, 3.0 Hz, C_6H_4 b), 7.82 (2H, dd, *J* 5.5, 3.0 Hz, C_6H_4 c), 7.10 (1H, d, *J* 5.0 Hz, H-5), 7.02 (1H, d, *J* 3.5 Hz, H-3), 6.98 (1H, s, CH), 6.93 (1H, dd, *J* 5.0, 3.5 Hz, H-5), 2.19 (3H, s, CH_3).

6. Appendices

6.1. Appendix I – 258

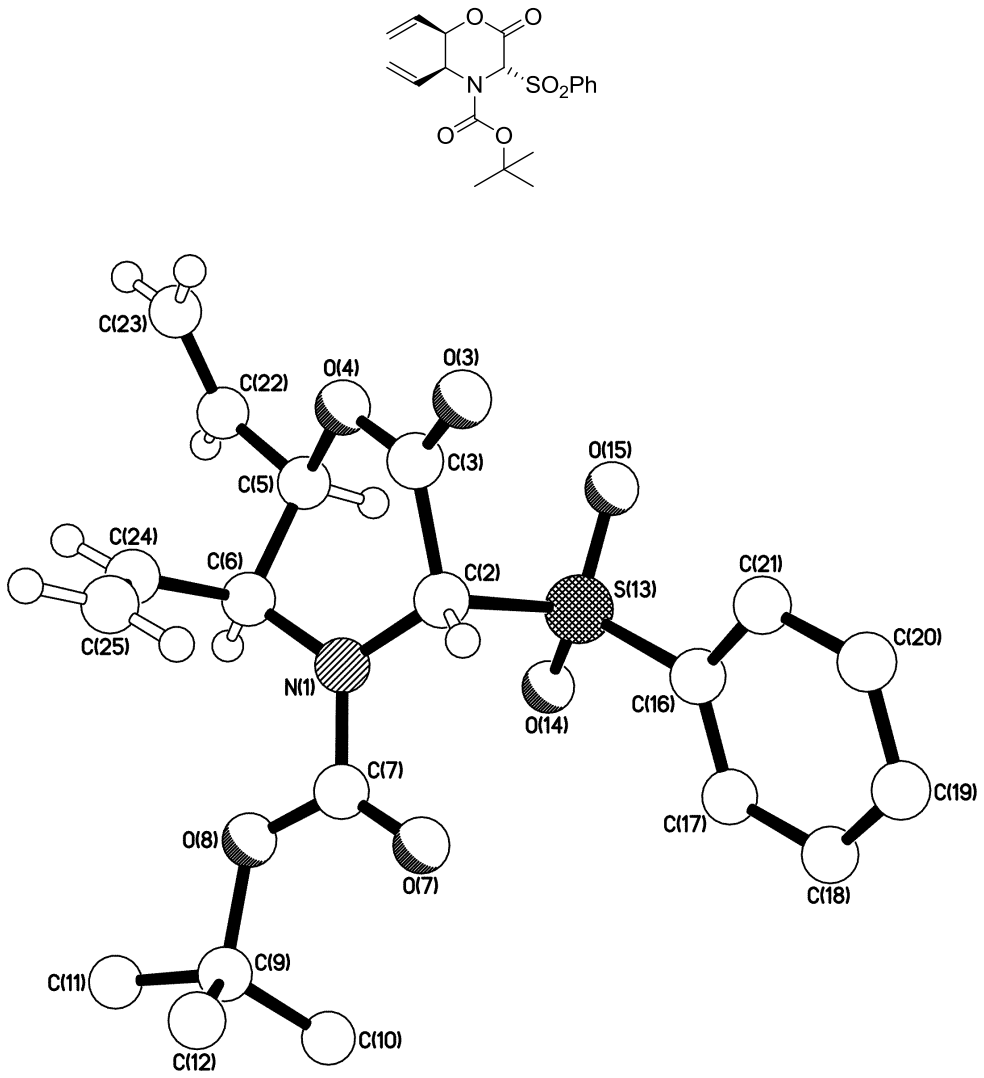


Table 1. Crystal data and structure refinement for **258**.

Identification code	DC1006
Formula	C19 H23 N O6 S
Formula weight	393.44
Temperature	173(2) K
Diffractometer, wavelength	OD Xcalibur 3, 0.71073 Å
Crystal system, space group	Monoclinic, P2(1)
Unit cell dimensions	a = 9.4631(2) Å α = 90°
	b = 11.2899(2) Å β = 116.356(3)°
	c = 10.4846(3) Å γ = 90°
Volume, Z	1003.72(4) $Å^3$, 2
Density (calculated)	1.302 Mg/m^3
Absorption coefficient	0.195 mm^{-1}
F(000)	416
Crystal colour / morphology	Colourless blocks
Crystal size	0.43 x 0.42 x 0.31 mm^3
θ range for data collection	3.61 to 32.73°
Index ranges	-14<=h<=14, -17<=k<=16, -15<=l<=15
Reflns collected / unique	21921 / 6826 [R(int) = 0.0414]
Reflns observed [F>4σ(F)]	5602
Absorption correction	Analytical
Max. and min. transmission	0.960 and 0.936
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6826 / 1 / 245
Goodness-of-fit on F^2	1.089
Final R indices [F>4σ(F)]	R1 = 0.0433, wR2 = 0.0961
	R1+ = 0.0433, wR2+ = 0.0961
	R1- = 0.0443, wR2- = 0.0992
R indices (all data)	R1 = 0.0595, wR2 = 0.1036
Absolute structure parameter	x+ = 0.00(5), x- = 1.03(5)
Extinction coefficient	0.021(2)
Largest diff. peak, hole	0.241, -0.254 $eÅ^{-3}$
Mean and maximum shift/error	0.000 and 0.001

Table 2. Bond lengths [Å] and angles [°] for **258**.

N(1)-C(7)	1.3831(18)
N(1)-C(2)	1.4256(18)
N(1)-C(6)	1.4586(19)
C(2)-C(3)	1.522(2)
C(2)-S(13)	1.8773(15)
C(3)-O(3)	1.2003(19)
C(3)-O(4)	1.3291(19)
O(4)-C(5)	1.4592(18)
C(5)-C(22)	1.496(2)
C(5)-C(6)	1.5362(19)
C(6)-C(24)	1.506(2)
C(7)-O(7)	1.2106(19)
C(7)-O(8)	1.3230(18)
O(8)-C(9)	1.4951(16)
C(9)-C(11)	1.509(2)
C(9)-C(10)	1.511(2)
C(9)-C(12)	1.515(2)
S(13)-O(14)	1.4337(13)
S(13)-O(15)	1.4392(12)
S(13)-C(16)	1.7584(16)
C(16)-C(17)	1.374(2)
C(16)-C(21)	1.379(2)
C(17)-C(18)	1.389(3)
C(18)-C(19)	1.370(3)
C(19)-C(20)	1.374(3)
C(20)-C(21)	1.385(3)
C(22)-C(23)	1.307(3)
C(24)-C(25)	1.310(3)

C(7)-N(1)-C(2)	115.30(12)
C(7)-N(1)-C(6)	124.45(12)
C(2)-N(1)-C(6)	120.01(11)
N(1)-C(2)-C(3)	114.06(12)
N(1)-C(2)-S(13)	111.13(10)
C(3)-C(2)-S(13)	107.16(10)
O(3)-C(3)-O(4)	120.89(14)
O(3)-C(3)-C(2)	121.14(15)
O(4)-C(3)-C(2)	117.97(13)
C(3)-O(4)-C(5)	116.84(11)
O(4)-C(5)-C(22)	108.02(12)
O(4)-C(5)-C(6)	109.10(11)
C(22)-C(5)-C(6)	113.33(13)
N(1)-C(6)-C(24)	113.12(12)
N(1)-C(6)-C(5)	107.04(11)
C(24)-C(6)-C(5)	111.40(12)
O(7)-C(7)-O(8)	127.80(14)
O(7)-C(7)-N(1)	121.14(14)
O(8)-C(7)-N(1)	111.06(13)
C(7)-O(8)-C(9)	119.95(12)
O(8)-C(9)-C(11)	101.68(12)
O(8)-C(9)-C(10)	109.65(12)
C(11)-C(9)-C(10)	111.04(14)
O(8)-C(9)-C(12)	109.85(13)
C(11)-C(9)-C(12)	111.30(15)
C(10)-C(9)-C(12)	112.76(15)
O(14)-S(13)-O(15)	119.34(8)
O(14)-S(13)-C(16)	109.19(8)
O(15)-S(13)-C(16)	108.66(8)
O(14)-S(13)-C(2)	107.46(7)

O(15)-S(13)-C(2)	106.69(7)
C(16)-S(13)-C(2)	104.48(7)
C(17)-C(16)-C(21)	121.38(16)
C(17)-C(16)-S(13)	119.63(13)
C(21)-C(16)-S(13)	118.99(12)
C(16)-C(17)-C(18)	118.76(18)
C(19)-C(18)-C(17)	120.43(17)
C(18)-C(19)-C(20)	120.25(18)
C(19)-C(20)-C(21)	120.16(19)
C(16)-C(21)-C(20)	119.02(17)
C(23)-C(22)-C(5)	126.37(17)
C(25)-C(24)-C(6)	126.02(17)

6.2. Appendix II – 317

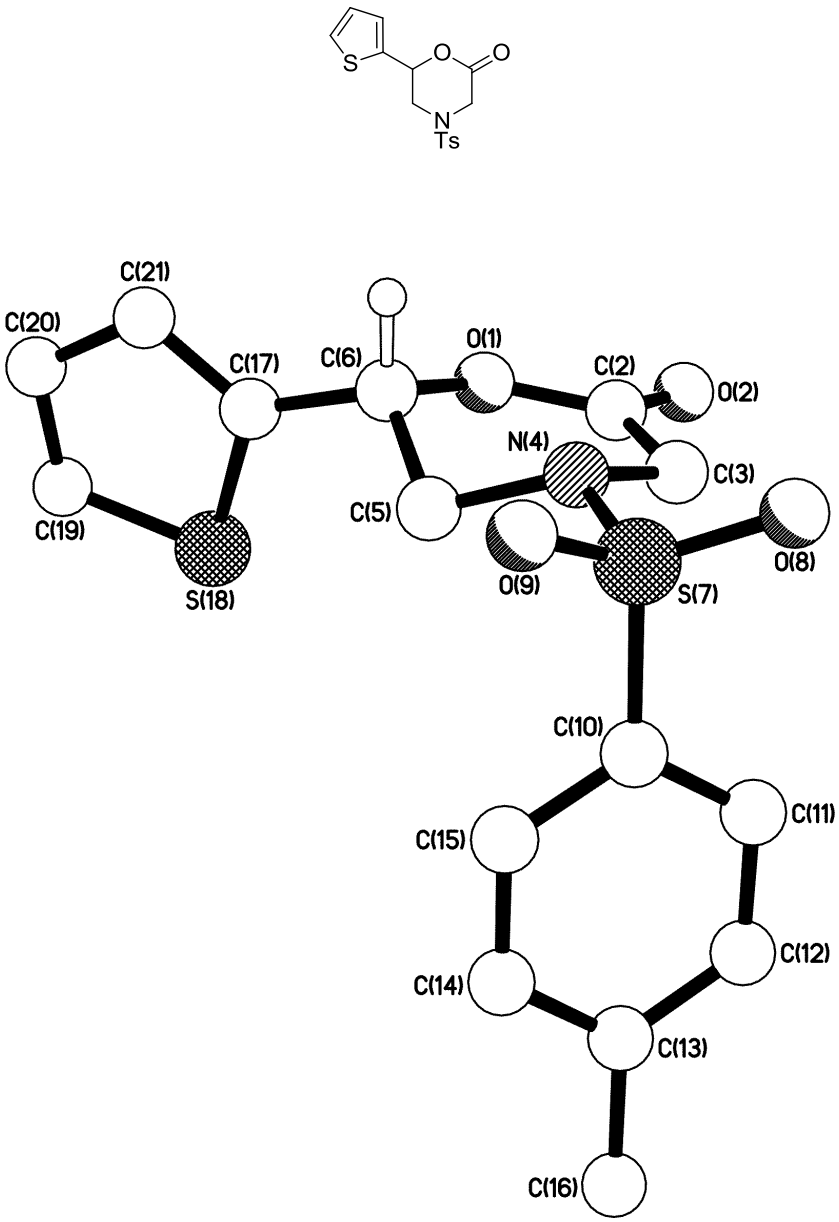


Table 1. Crystal data and structure refinement for **317**.

Identification code	DC1101
Formula	C15 H15 N O4 S2
Formula weight	337.40
Temperature	173 K
Diffractometer, wavelength	OD Xcalibur 3, 0.71073 Å
Crystal system, space group	Monoclinic, P2(1)/n
Unit cell dimensions	a = 13.4621(4) Å α = 90°
	b = 5.42045(13) Å β = 102.628(3)°
	c = 21.4779(5) Å γ = 90°
Volume, Z	1529.34(7) $Å^3$, 4
Density (calculated)	1.465 Mg/m^3
Absorption coefficient	0.365 mm^{-1}
F(000)	704
Crystal colour / morphology	Colourless needles
Crystal size	0.50 x 0.07 x 0.05 mm^3
θ range for data collection	3.10 to 32.93°
Index ranges	-20<=h<=20, -7<=k<=8, -31<=l<=27
Reflns collected / unique	15448 / 5181 [R(int) = 0.0240]
Reflns observed [F>4σ(F)]	3989
Absorption correction	Analytical
Max. and min. transmission	0.983 and 0.901
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5181 / 0 / 200
Goodness-of-fit on F^2	1.033
Final R indices [F>4σ(F)]	R1 = 0.0458, wR2 = 0.1132
R indices (all data)	R1 = 0.0648, wR2 = 0.1221
Largest diff. peak, hole	0.456, -0.279 $eÅ^{-3}$
Mean and maximum shift/error	0.000 and 0.001

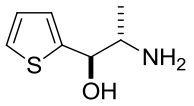
Table 2. Bond lengths [Å] and angles [°] for **317**.

O(1)-C(2)	1.3415(18)
O(1)-C(6)	1.4598(18)
C(2)-O(2)	1.1996(19)
C(2)-C(3)	1.501(2)
C(3)-N(4)	1.470(2)
N(4)-C(5)	1.4734(18)
N(4)-S(7)	1.6474(12)
C(5)-C(6)	1.5089(19)
C(6)-C(17)	1.489(2)
S(7)-O(9)	1.4296(13)
S(7)-O(8)	1.4300(13)
S(7)-C(10)	1.7548(15)
C(10)-C(11)	1.390(2)
C(10)-C(15)	1.393(2)
C(11)-C(12)	1.387(2)
C(12)-C(13)	1.388(2)
C(13)-C(14)	1.388(2)
C(13)-C(16)	1.511(2)
C(14)-C(15)	1.380(2)
C(17)-C(21)	1.362(2)
C(17)-S(18)	1.7174(15)
S(18)-C(19)	1.7065(17)
C(19)-C(20)	1.339(3)
C(20)-C(21)	1.421(2)

C(2)-O(1)-C(6)	121.99(11)
O(2)-C(2)-O(1)	118.33(14)
O(2)-C(2)-C(3)	120.77(14)
O(1)-C(2)-C(3)	120.83(13)
N(4)-C(3)-C(2)	113.59(12)
C(3)-N(4)-C(5)	112.62(11)
C(3)-N(4)-S(7)	115.35(10)
C(5)-N(4)-S(7)	116.47(9)
N(4)-C(5)-C(6)	107.06(11)
O(1)-C(6)-C(17)	106.95(12)
O(1)-C(6)-C(5)	109.69(11)
C(17)-C(6)-C(5)	114.30(12)
O(9)-S(7)-O(8)	120.60(8)
O(9)-S(7)-N(4)	105.89(7)
O(8)-S(7)-N(4)	106.21(7)
O(9)-S(7)-C(10)	107.87(8)
O(8)-S(7)-C(10)	108.98(7)
N(4)-S(7)-C(10)	106.45(7)
C(11)-C(10)-C(15)	120.38(14)
C(11)-C(10)-S(7)	120.02(11)
C(15)-C(10)-S(7)	119.47(11)
C(12)-C(11)-C(10)	118.90(14)
C(11)-C(12)-C(13)	121.61(14)
C(12)-C(13)-C(14)	118.32(14)
C(12)-C(13)-C(16)	120.60(16)
C(14)-C(13)-C(16)	121.08(15)
C(15)-C(14)-C(13)	121.39(15)
C(14)-C(15)-C(10)	119.40(14)
C(21)-C(17)-C(6)	126.88(14)
C(21)-C(17)-S(18)	110.65(12)
C(6)-C(17)-S(18)	122.47(10)
C(19)-S(18)-C(17)	91.80(8)
C(20)-C(19)-S(18)	112.38(13)
C(19)-C(20)-C(21)	112.24(14)

C(17)-C(21)-C(20) 112.93(14)

6.3. Appendix III – 329



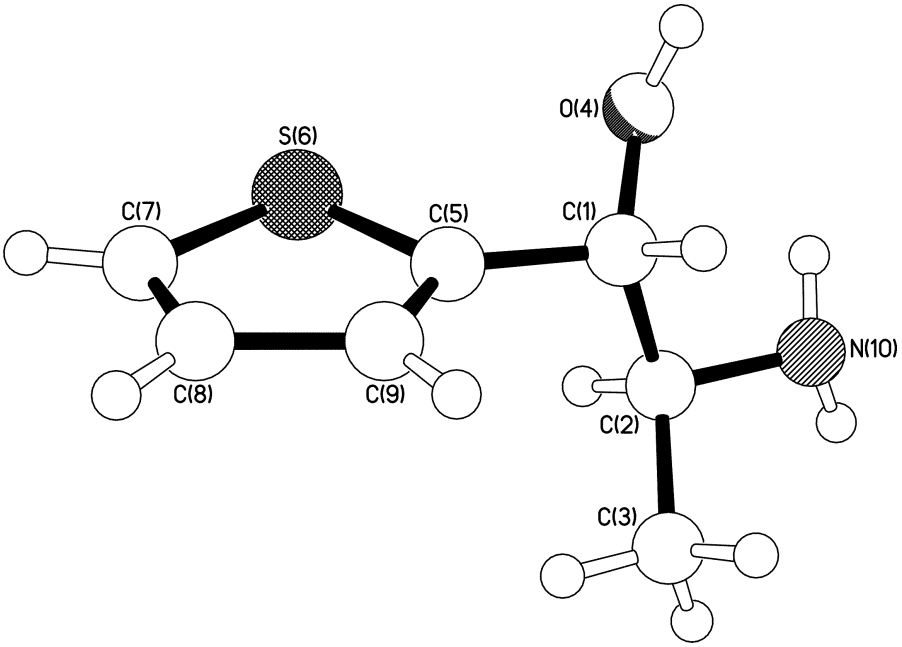


Table 1. Crystal data and structure refinement for **329**.

Identification code	DC1102
Formula	C7 H11 N O S
Formula weight	157.23
Temperature	173 K
Diffractometer, wavelength	OD Xcalibur 3, 0.71073 Å
Crystal system, space group	Orthorhombic, Pca2(1)
Unit cell dimensions	a = 9.3517(15) Å α = 90°
	b = 11.7376(16) Å β = 90°
	c = 7.4239(13) Å γ = 90°
Volume, Z	814.9(2) $Å^3$, 4
Density (calculated)	1.282 Mg/m^3
Absorption coefficient	0.330 mm^{-1}
F(000)	336
Crystal colour / morphology	Colourless platy needles
Crystal size	0.34 x 0.09 x 0.01 mm^3
θ range for data collection	3.47 to 27.86°
Index ranges	-11<=h<=8, -14<=k<=13, -9<=l<=6
Reflns collected / unique	2158 / 1165 [R(int) = 0.0339]
Reflns observed [F>4σ(F)]	906
Absorption correction	Analytical
Max. and min. transmission	0.997 and 0.952
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1165 / 4 / 103
Goodness-of-fit on F^2	1.016
Final R indices [F>4σ(F)]	R1 = 0.0480, wR2 = 0.1121
	R1+ = 0.0480, wR2+ = 0.1121
	R1- = 0.0485, wR2- = 0.1133
R indices (all data)	R1 = 0.0702, wR2 = 0.1237
Absolute structure parameter	x+ = 0.0(2), x- = 1.0(2)
Largest diff. peak, hole	0.224, -0.424 $eÅ^{-3}$
Mean and maximum shift/error	0.000 and 0.000

Table 2. Bond lengths [Å] and angles [°] for **329**.

C(1)-O(4)	1.418(5)
C(1)-C(5)	1.502(6)
C(1)-C(2)	1.521(6)
C(2)-N(10)	1.481(6)
C(2)-C(3)	1.497(6)
C(5)-C(9)	1.353(6)
C(5)-S(6)	1.716(4)
S(6)-C(7)	1.704(5)
C(7)-C(8)	1.353(8)
C(8)-C(9)	1.428(7)

O(4)-C(1)-C(5)	110.5(4)
O(4)-C(1)-C(2)	108.5(3)
C(5)-C(1)-C(2)	111.8(4)
N(10)-C(2)-C(3)	108.4(4)
N(10)-C(2)-C(1)	108.0(3)
C(3)-C(2)-C(1)	113.6(4)
C(9)-C(5)-C(1)	128.8(4)
C(9)-C(5)-S(6)	111.1(4)
C(1)-C(5)-S(6)	120.0(3)
C(7)-S(6)-C(5)	92.3(3)
C(8)-C(7)-S(6)	111.4(4)
C(7)-C(8)-C(9)	112.7(4)
C(5)-C(9)-C(8)	112.4(4)

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