Pericyclic Reactions of Vinyl-Heteroaromatics: Multi-Component Domino and Sequential Processes

by

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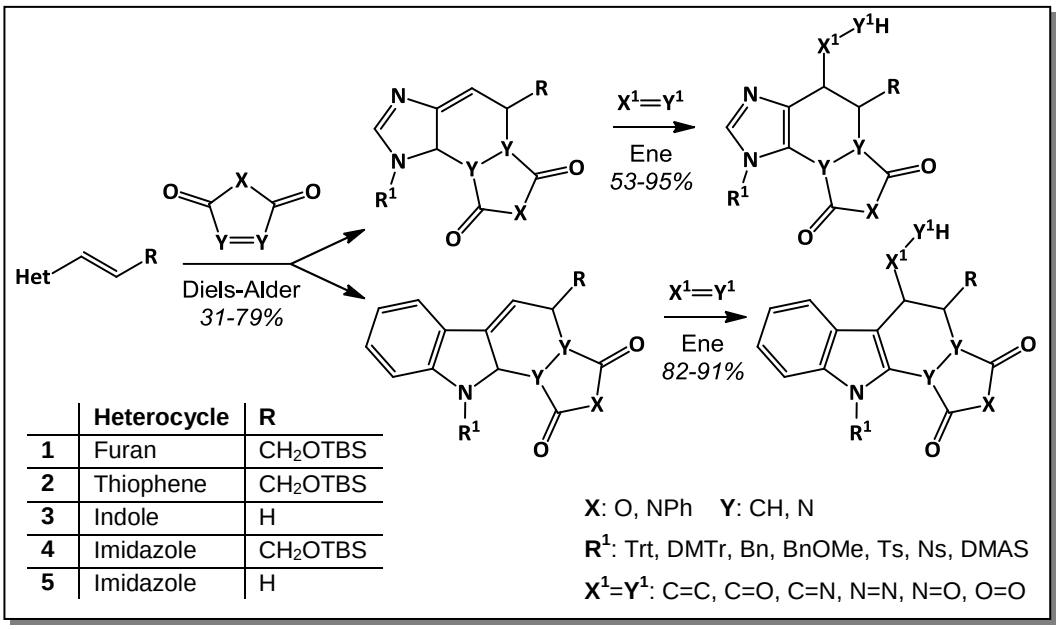
Abstract

Sequential intermolecular Diels-Alder/intermolecular ene reactions of electron-rich vinyl-heteroaromatics have been investigated, as the basis for a new class of three component coupling reactions. This relatively unexplored reaction sequence provides access to the biologically important scaffolds 4,5,6,7-tetrahydro-1*H*-benzo[*d*]imidazole and 2,3,4,9-tetrahydro-1*H*-carbazole, with high atom economy and diastereocontrol of up to 5 new stereocentres, following a two-step reaction process involving three simple molecules (a diene, a dienophile and an enophile).

2-Vinylfuran (**1**), 2-vinylthiophene (**2**), *N*-protected-3-vinylindole (**3**) and *N*-protected-4-vinyl-1*H*-imidazoles (**4** and **5**) were found to react as dienes in Diels-Alder reactions under thermal conditions, without the need for Lewis acid catalysis. **4** and **5** were then subjected to a program of *N*-protecting group and dienophile optimisation, and the resulting Diels-Alder adducts were isolated in moderate to high yields (31-79 %) as single diastereoisomers, arising from exclusively *endo*-cycloaddition (Scheme 1).



	Heterocycle	R
1	Furan	CH_2OTBS
2	Thiophene	CH_2OTBS
3	Indole	H
4	Imidazole	CH_2OTBS
5	Imidazole	H

Scheme 1. Sequential Diels-Alder/Ene reactions.

The cycloadducts arising from the Diels-Alder reaction of *N*-trityl-4-vinylimidazole and *N*-phenylmaleimide (NPM) were shown to undergo hitherto unreported, facile, sterically driven N→N trityl migrations. These migrations were a key step in several novel, highly diastereoselective domino reaction sequences (Diels−Alder, [1,3]-H shift, [1,3]-trityl migration and Diels−Alder, [1,3]-H shift, [1,3]-trityl migration, Michael reaction), leading to architecturally complex molecules.

The cycloadducts arising from the Diels-Alder reaction of 1-benzyl-4-vinyl-1*H*-imidazole, (*E*)-1-benzyl-4-(3-((*tert*-butyldimethylsilyl)oxy)prop-1-en-1-yl)-1*H*-imidazole and *N*,*N*-dimethyl-3-vinyl-1*H*-indole-1-sulfonamide were obtained in high yields, and were then tested in ene reactions with a range of reactive enophiles (Scheme 1). The resulting ene adducts were successfully isolated in moderate to excellent yields (53-95%).

Publications from this work

Chapter 2

Thermal 1,3-trityl migrations in Diels-Alder domino reactions of 1-trityl-4-vinyl-1*H*-imidazoles; Cotterill, L. J.; Harrington, R. W.; Clegg, W.; Hall, M. J. *J. Org. Chem.* **2010,** *75*, 4604-4607 (Appendix 1).

Chapter 4

Diastereoselective intermolecular ene reactions: synthesis of 4,5,6,7-tetrahydro-1*H*-benzo[*d*]imidazoles; Watson, L. J.; Harrington, R. W.; Clegg, W.; Hall, M. J. *Org. Biomol. Chem.* **2012**, *10*, 6649-6655 (Appendix 2).

List of Abbreviations

Å	Ångström
Aq	Aqueous
Ar	Aromatic
Bn	Benzyl
br	Broad
calcd.	Calculated
COSY	Correlation spectroscopy
d	Day(s)
DCE	1,2-Dichloroethane
DEAD	Diethyl azodicarboxylate
DEPT	Distortionless enhancement by polarisation transfer
DiBAl-H	Diisobutylaluminium hydride
DMAD	Dimethyl acetylenedicarboxylate
DMAP	4-(Dimethylamino)pyridine
DMAS	*N*,*N*-dimethylaminosulfonyl
DMF	*N*,*N*'-dimethylformamide
DMSO	Dimethyl sulfoxide
equiv.	Equivalent(s)
Et	Ethyl
g	Gram(s)
h	Hour(s)
HRMS	High-resolution mass spectrometry
Hz	Hertz
IR	Infrared
LDA	Lithium diisopropylamide
M	Molar
m.p.	Melting point
Me	Methyl
mg	Milligram(s)
MHz	MegaHertz
MOM	Methoxymethyl
min	Minute(s)
mL	Millilitre(s)

mmol	Millimole(s)
MTAD	4-Methyl-1,2,4-triazoline-3,5-dione
NDMA	*N,N*-Dimethyl-4-nitrosoaniline
NMM	*N*-Methylmaleimide
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect spectroscopy
NPM	*N*-Phenylmaleimide
Ns	Nosyl
Ph	Phenyl
ppm	Parts per million
PTAD	4-Phenyl-1,2,4-triazoline-3,5-dione
r.t.	Room temperature
R_f	Retention factor
ROESY	Rotating frame nuclear Overhauser effect spectroscopy
SEM	(2-(Trimethylsilyl)ethoxy)methyl
TAD	Triazolinedione
TBS	*tert*-Butyldimethylsilyl
*t*Bu	*tert*-Butyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
Trityl	Triphenylmethane
Ts	Tosyl
UV	Ultra-violet

Table of Contents

Chapter 1. Introduction

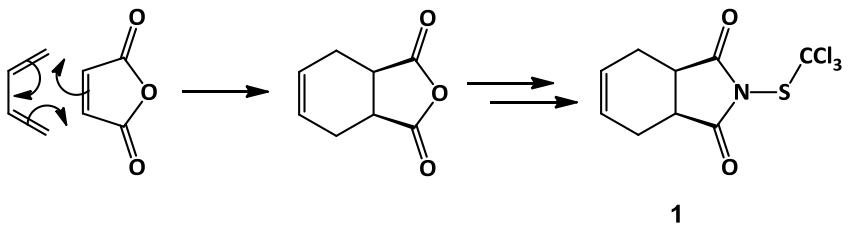
1.1 The Diels-Alder Reaction

1.1.1 Introduction

The Diels-Alder [4+2] cycloaddition is widely acknowledged to be the most important reaction in the synthesis of 6-membered ring systems, and has been extensively studied since its discovery in 1928. It is popular due to the high level of regio- and stereoselectivity that is typically displayed and the ease with which it allows access to highly structurally complex compounds.

The Diels-Alder reaction is concerted and occurs in one-step between the 4π electrons of a conjugated diene and 2π electrons of a dienophile to form two new σ-bonds and a 6-membered ring containing up to 4 chiral centres (Scheme 1.1). The scope and versatility of both the inter- and intramolecular Diels-Alder reaction can be attributed to the extensive range of dienes and dienophiles to which this reaction can be applied, from the all-carbon version to a great number of heteroatom based examples.

The utility of the reaction was first hinted at by the pioneers, Otto Diels and Kurt Alder, in their initial publication describing the Diels-Alder reaction. They immediately recognised the potential for application to the synthesis of natural products, but imposed a stark warning on the synthetic community that they explicitly reserved the reaction for their own synthesis.[1]



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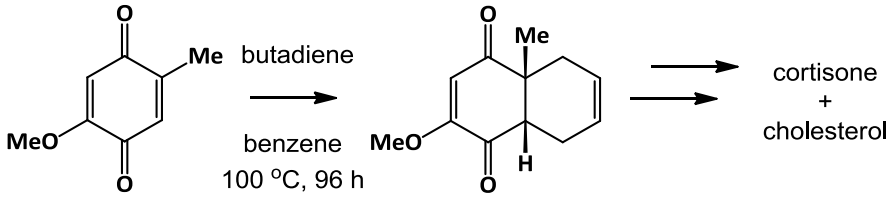
Scheme 1.1. Diels-Alder [4+2] cycloaddition in the synthesis of Captan (**1**).

Preceding their award of the Nobel Prize in 1950 for their discovery and development of the diene synthesis,[2] it seems that this warning was heeded by the synthetic community. It was not until the synthesis of cantharidin by Stork[3] in 1951, the first total synthesis of morphine by Gates and Tschudi,[4] and Sarett's work on cortisone[5] that the Diels-Alder reaction played a prominent role in total synthesis.

Woodward *et al.* were one of the first groups to employ the Diels-Alder reaction in directed synthesis, applying a regioselective [4+2] cycloaddition of disubstituted quinone with butadiene to access the steroids cortisone and cholesterol (Scheme 1.2).[6]

This work is a clear example of the potential of the Diels-Alder reaction to create molecular complexity from relatively simple starting materials, and subsequently there have been numerous partial and total syntheses reported which feature the Diels-Alder reaction.[7,8,9]



Scheme 1.2. Quinone-based Diels-Alder reaction in the total synthesis of cortisone and cholesterol.

1.1.2 Diels-Alder Reactions of Heteroaromatics

Whilst the number of examples of [4+2] cycloadditions with acyclic dienes is extensive, and despite furan being among those dienes first investigated by Diels and Alder,[1] heteroaromatics are largely uninvestigated as dienes. However, Diels-Alder chemistry can be applied to a variety of heteroaromatics, and furan,[10,11] thiophene[11] and pyrrole[11] are known to undergo [4+2] cycloadditions as 4π-dienes. This occurs despite their aromaticity, which would be expected to decrease their reactivity (see subsequent examples).

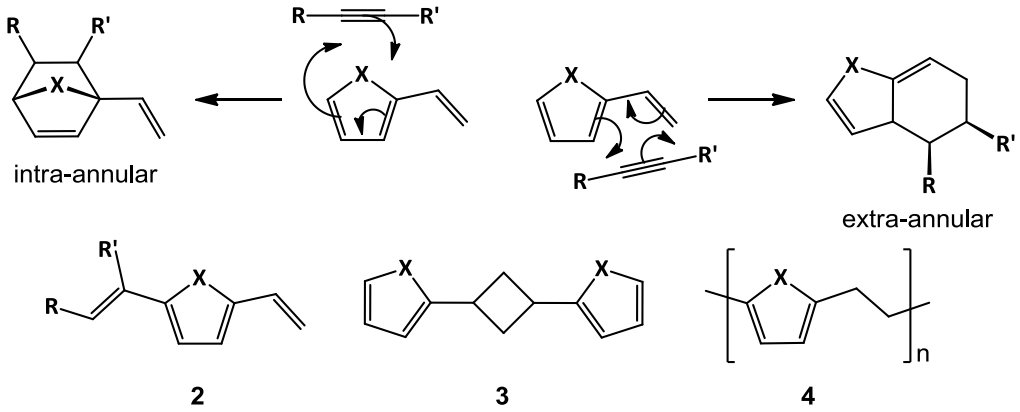
The Diels-Alder reactions of heteroaromatic dienes are very useful tools in synthesis as they allow access to a much wider variety of systems through the incorporation of a heteroatom, and this is particularly true when combined with heteroatom containing dienophiles.

1.1.3 Diels-Alder Reactions of Vinyl-Heteroaromatics

The Diels-Alder reactions of heteroaromatics have been employed to access natural products, novel heterocycles and polycyclic heterocycles of interest. The variety of accessible products can be further expanded through the use of substituted-heterocycles, and also *via* the introduction of a vinyl group to a heteroaromatic ring.

The vinyl group provides the Diels-Alder reaction with an alternative pathway, extending the range of possible reactions. Whilst intra-annular cycloaddition across the π-system of the heteroaromatic is still possible, the addition of a vinyl group allows the exocyclic vinyl π-bond and one of the heteroaromatic π-bonds to participate as the 4π element of the Diels-Alder reaction, resulting in extra-annular cycloaddition (Scheme 1.3).[12]

However, there is also the possibility of competing reactions taking place at either the heteroaromatic or the vinylic bond, including Michael addition (**2**), [2+2]-cycloaddition (**3**) and polymerisation (**4**).[13]

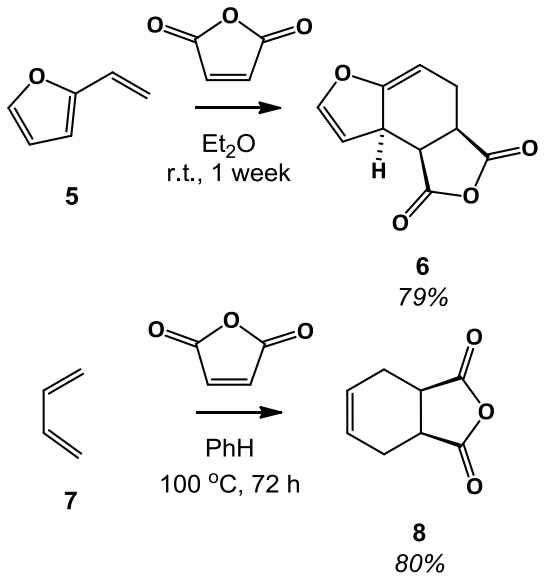


Scheme 1.3. Intra- and extra-annular cycloaddition pathways and possible by-products.

1.1.3.1 Vinylfurans

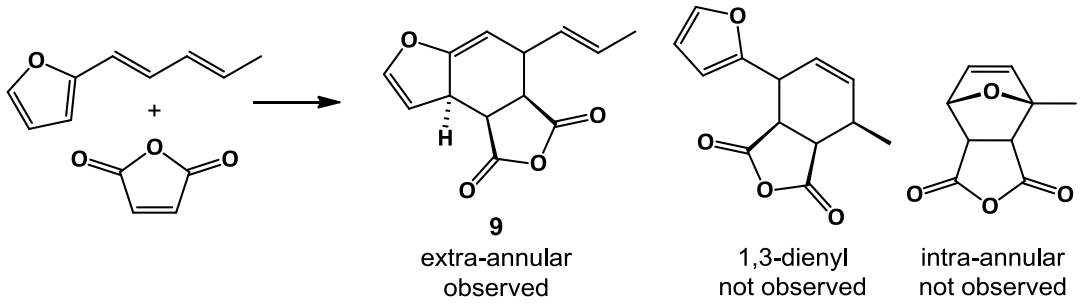
The first example of a vinyl-substituted heteroaromatic participating as a 4π-donor in the Diels-Alder reaction was reported with maleic anhydride by Paul in 1939.[14,15] 2-Vinylfuran (**5**) was reacted with maleic anhydride in diethyl ether at r.t. affording the initial Diels-Alder adduct (**6**) in 79% yield after 1 week (Scheme 1.4).

Previous studies have indicated that much higher temperatures are required (>80 ^{o}C) to achieve similar reaction yields when employing the all-carbon butadiene (**7**) and maleic anhydride to synthesise cycloadduct **8**.[16,17,18] It appears therefore that 2-vinylfuran is more reactive at lower temperatures, due to the increased electron-donation of the oxygen heteroatom in vinylfuran increasing the electron density of the diene. A more electron-rich diene component is more inclined to undergo cycloaddition with an electron-poor dienophile, and thus the Diels-Alder reaction occurs more readily at lower temperatures.



Scheme 1.4. Diels-Alder reaction of 2-vinylfuran and butadiene with maleic anhydride.

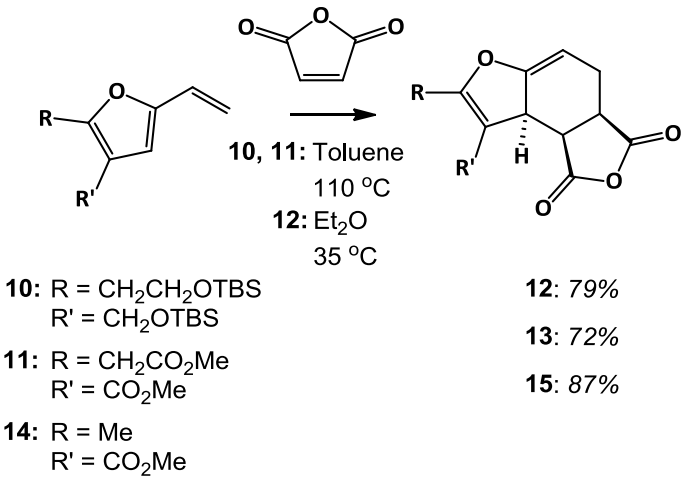
Diels-Alder cycloadditions of 2-vinylfuran with maleic anhydride prefer to occur *via* the extra-annular pathway, incorporating the vinylic double bond, in an *endo* manner. Extra-annular reactions have also been observed for substituted-vinylfurans, for example by Schmidt, who investigated the cycloaddition of 2-(penta-1,3-dien-1-yl)-furan with maleic anhydride, and obtained the Diels-Alder cycloadduct **9** (Scheme 1.5).[19] Cycloaddition occurred in this case at the exocyclic π-bond in preference to intra-annular cycloaddition or reaction at the penta-1,3-dienyl substituent.



Scheme 1.5. Diels-Alder reaction of 2-(penta-1,3-dien-1-yl)-furan with maleic anhydride.

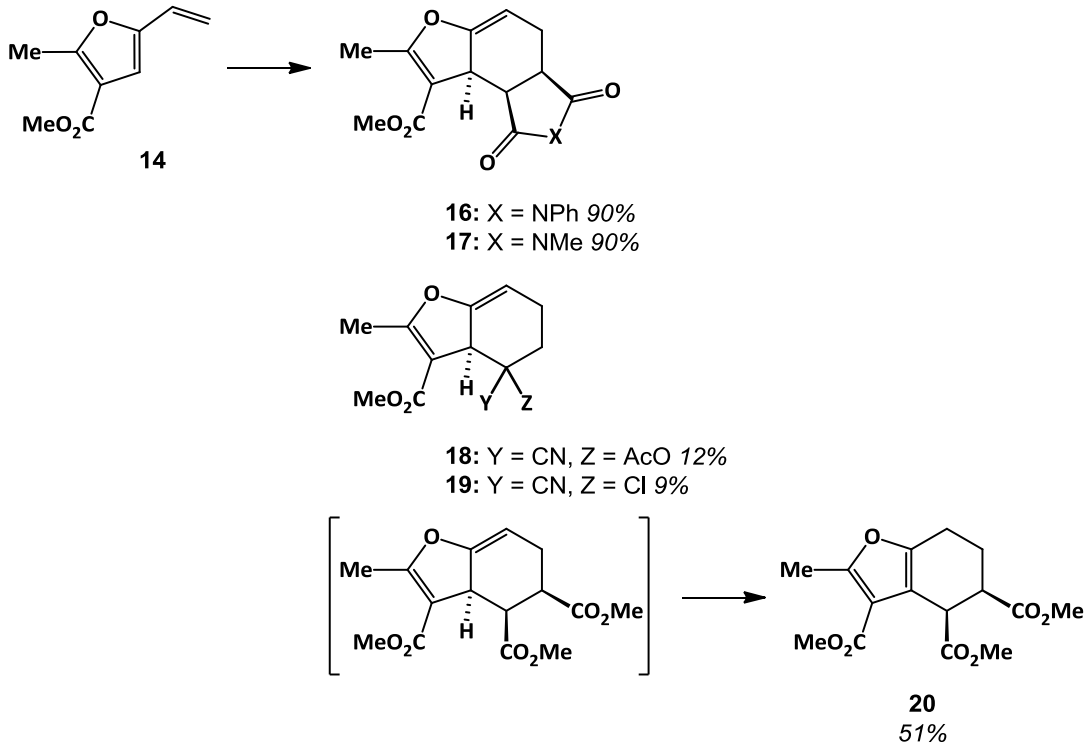
The preference for extra-annular cycloaddition was also observed by Ghobsi *et al.*,[20] who noted that varying the substituents of vinylfuran had little effect on the Diels-Alder reaction. Vinylfurans **10** and **11** would readily undergo extra-annular cycloaddition with maleic anhydride to afford to the Diels-Alder cycloadducts **12** and **13** in 79% and 72% yield, respectively. Similarly, in the work of Drew and co-workers,[21] methyl 2-methyl-5-vinyl-3-furoate **14** was found to undergo cycloaddition with maleic anhydride,

resulting in the formation of the Diels-Alder cycloadduct **15** exclusively in 87% yield (Scheme 1.6).



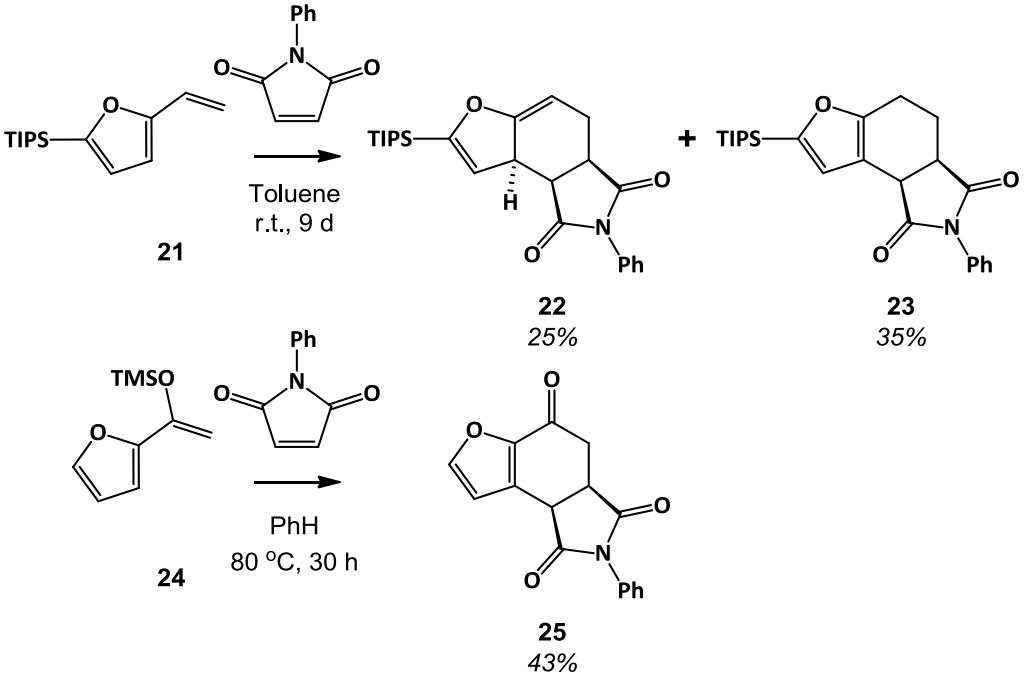
Scheme 1.6. Diels-Alder reactions of substituted-vinylfurans.

The Drew group extended their investigations of **14** to assess the viability of the Diels-Alder reaction with other dienophiles. They found that the Diels-Alder adduct could be obtained as the only product with a number of dienophiles; *N*-phenylmaleimide (NPM) (**16**), *N*-methylmaleimide (NMM) (**17**), 1-acetoxyacrylonitrile (**18**) and 2-chloroacrylonitrile (**19**) (Scheme 1.7). In the case of dimethyl maleate however, it was found that only the rearomatised product **20** could be isolated, with the initial Diels-Alder cycloadduct having undergone a rearomatisation to reform the furan.[21]



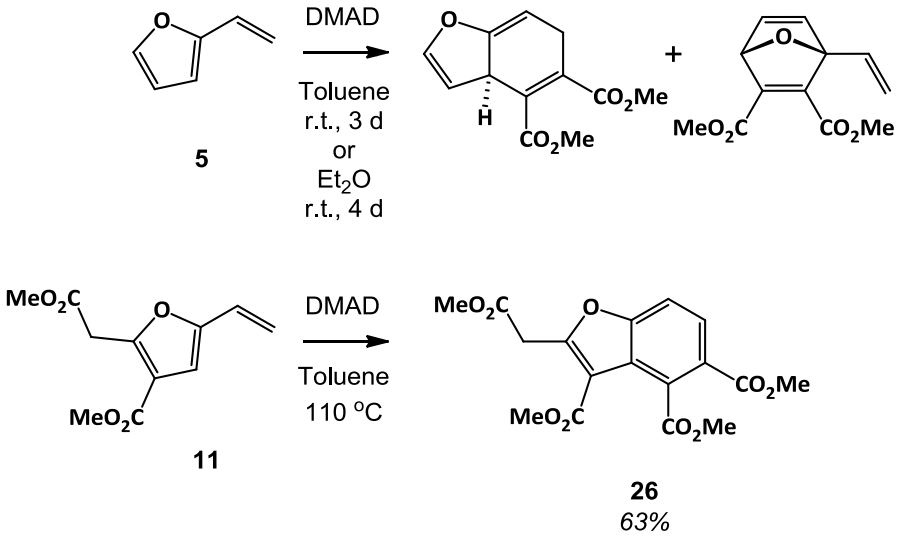
Scheme 1.7. Diels-Alder reaction of **14** with a range of dienophiles.

Rearomatisation was also observed by Avalos and co-workers[22] who reacted 5-triisopropylsilyl-2-vinylfuran (**21**) with NPM and obtained both the initial Diels-Alder adduct **22** and the rearomatised compound **23** in a (1:1.4) ratio. Sasaki *et al.*[12] also found reaction of 2-(1-trimethylsilyloxyvinyl)furan **24** with NPM afforded the rearomatised product **25** exclusively (Scheme 1.8).



Scheme 1.8. Rearomatisation observed following the Diels-Alder reaction.

Interestingly, when the highly reactive dienophile dimethyl acetylenedicarboxylate (DMAD) was employed with both 2- and 3-vinylfuran, Benitez[23] and Davidson[24] were able to observe both intra- and extra-annular cycloadditions occurring in reactions at r.t. over 72-96 h. In a similar experiment, Ghobsi *et al.*[20] obtained the aromatic compound **26** exclusively, in 63% yield, arising from extra-annular Diels-Alder reaction and subsequent air-oxidation (Scheme 1.9).



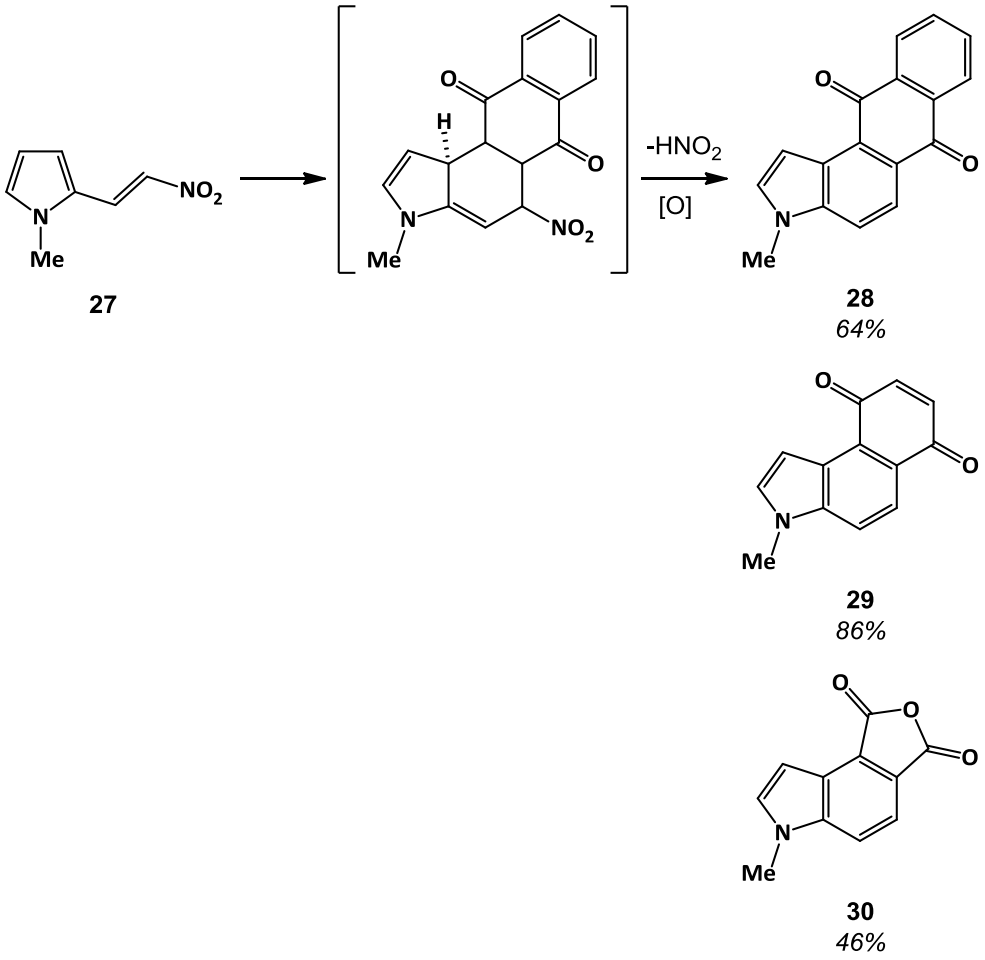
Scheme 1.9. Intra- and extra-annular cycloaddition products observed on reaction with DMAD.

1.1.3.2 Vinylpyrroles

The first vinylpyrroles to be investigated in the Diels-Alder reaction were β-nitrovinyl-*N*-methylpyrroles. These dienes were stable and readily available from condensation of the corresponding carboxaldehydes with nitromethane, and were found to be more effective as dienes than their vinyl analogues.[25]

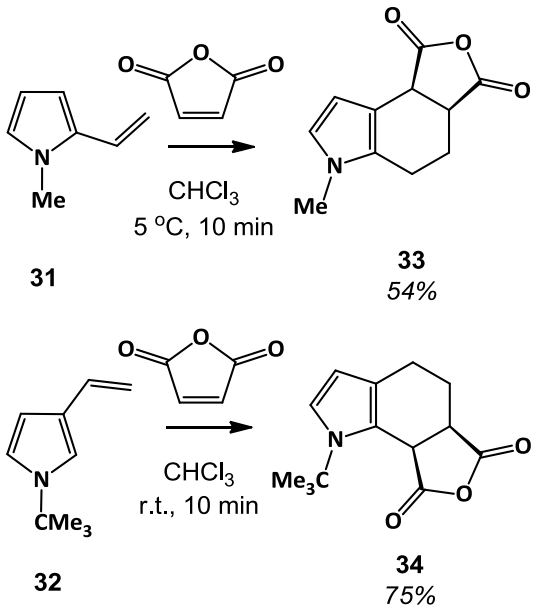
Hosmane and Hiremath found that β-nitrovinyl-*N*-methylpyrrole **27** would readily undergo Diels-Alder reaction with naphthaquinone, benzoquinone, and maleic anhydride leading to the fully aromatic adducts **28**, **29** and **30**, respectively. They postulated that following Diels-Alder [4+2] cycloaddition, the loss of nitrous acid was the driving force for rearomatisation in all cases, and that subsequent dehydrogenation gave fully aromatic products (Scheme 1.10).

Interestingly, Diels-Alder reaction with maleic acid led to the same aromatic product, *N*-methylindole-4,5-dicarboxylic anhydride **30**, as when maleic anhydride was employed as the dienophile. They theorised that dehydration of maleic acid occurred in the acidic conditions created by the loss of nitrous acid.



Scheme 1.10. Diels-Alder reactions of β-nitrovinyl-*N*-methylpyrrole **27**.

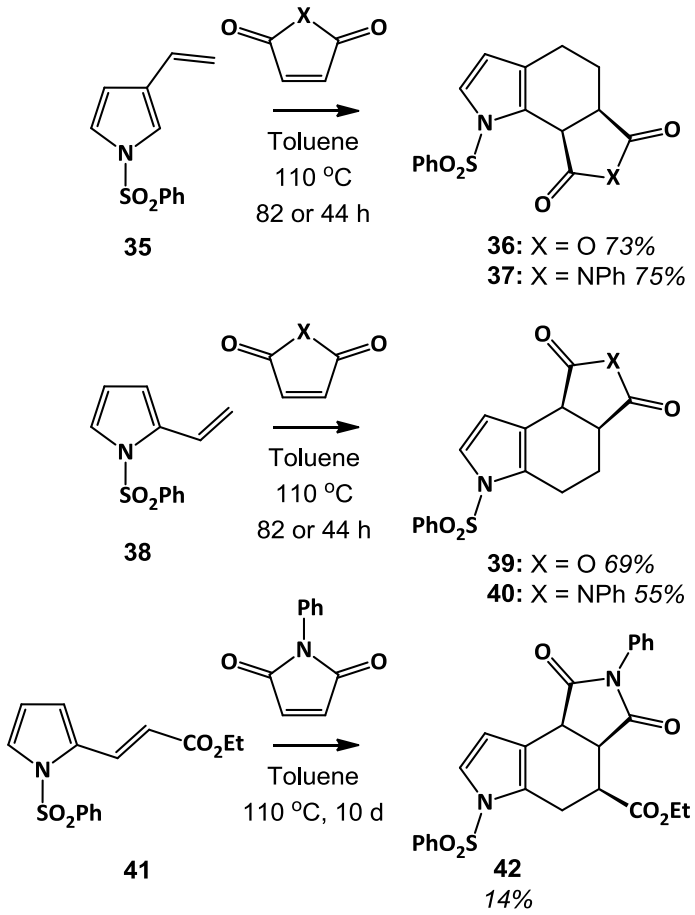
Jones *et al.*[26] found that a [4+2] cycloaddition reaction between 2- and 3-vinylpyrrole (**31**, **32**) and maleic anhydride would occur extremely rapidly at r.t.. They were unable to isolate the initial Diels-Alder cycloadduct, and found the major products to be the rearomatised adducts **33** and **34** (Scheme 1.11).



Scheme 1.11. Diels-Alder reactions of 2- and 3-vinylpyrroles with maleic anhydride.

Xiao and Ketcha[27] also found the reactions of vinylpyrroles to be successful with maleimide dienophiles; 1-(phenylsulfonyl)-3-vinylpyrrole (**35**) reacted readily with both maleic anhydride and NPM to give rearomatised Diels-Alder adducts **36** and **37** in 73% and 75% respectively, whilst 1-(phenylsulfonyl)-2-vinylpyrrole (**38**) gave rearomatised adducts **39** and **40** in 69% and 55% respectively.

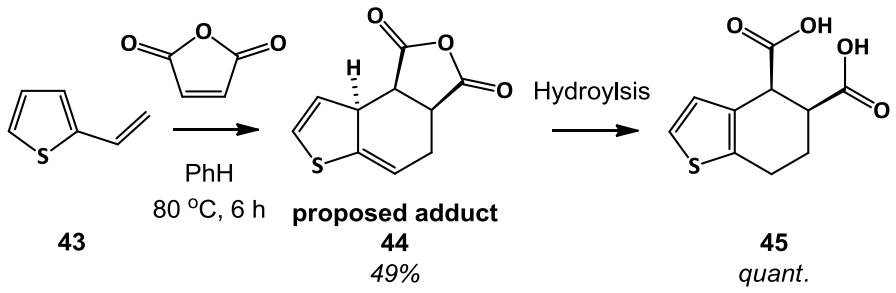
Additionally, they found that further substitution of the vinyl with electron withdrawing groups greatly reduced the Diels-Alder reactivity of the diene. Ethyl ester substituted derivative **41** yielded only 14% of rearomatised adduct **42** after 10 days in refluxing toluene (Scheme 1.12).



Scheme 1.12. Diels-Alder reaction of 2- and 3-vinylpyrroles with maleic anhydride and NPM.

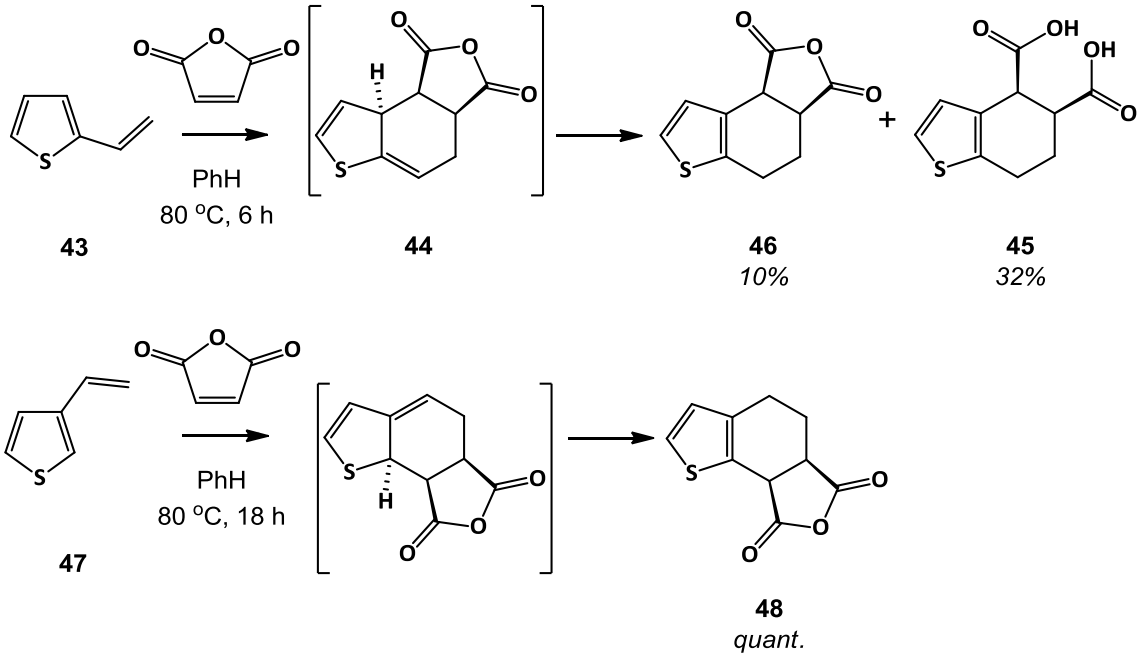
1.1.3.3 Vinylthiophenes

Vinylthiophenes have been investigated to a lesser extent as it was initially thought that thiophene, being highly aromatic, would not participate in Diels-Alder reactions.[28,29] Scully and Brown were the first to investigate the cycloaddition of 2-vinylthiophene (**43**) with maleic anhydride in 1953,[30] and proposed the structure of the initial Diels-Alder adduct **44**, with 2-vinylthiophene having undergone extra-annular cycloaddition through an *endo*-mechanism (Scheme 1.13). However, they were unable to purify the product and instead converted it directly to the dicarboxylic acid **45** through hydrolysis with aqueous sodium hydroxide. These results were later mirrored by Davies and Porter[31] who, under similar conditions, were able to isolate a product with the same proposed structure (**44**) before hydrolysing to the corresponding dicarboxylic acid.



Scheme 1.13. Proposed structures arising from Diels-Alder reaction of 2-vinylthiophene and maleic acid.

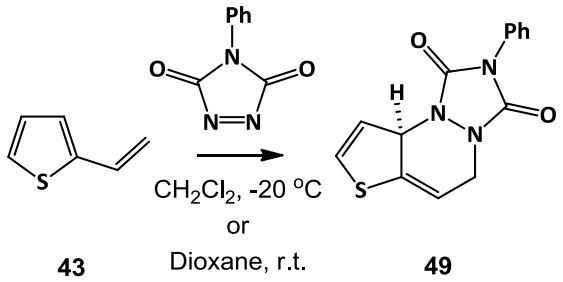
It would seem from these initial reports that the reactivity of 2-vinylthiophene with maleic anhydride is directly comparable to that of 2-vinylfuran. However, Abarca *et al.* re-examined this reaction in 1985[32] and were able to successfully isolate and characterise the products of the reaction as the rearomatised adduct **46** and the corresponding dicarboxylic acid **45**, appearing in a 1:3.2 ratio. They also achieved similar results with 3-vinylthiophene **47**, obtaining the rearomatised adduct **48** as a single product in quantitative yield following cycloaddition with maleic anhydride (Scheme 1.14).[33]



Scheme 1.14. Diels-Alder reaction of 2- and 3-vinylthiophene with maleic anhydride.

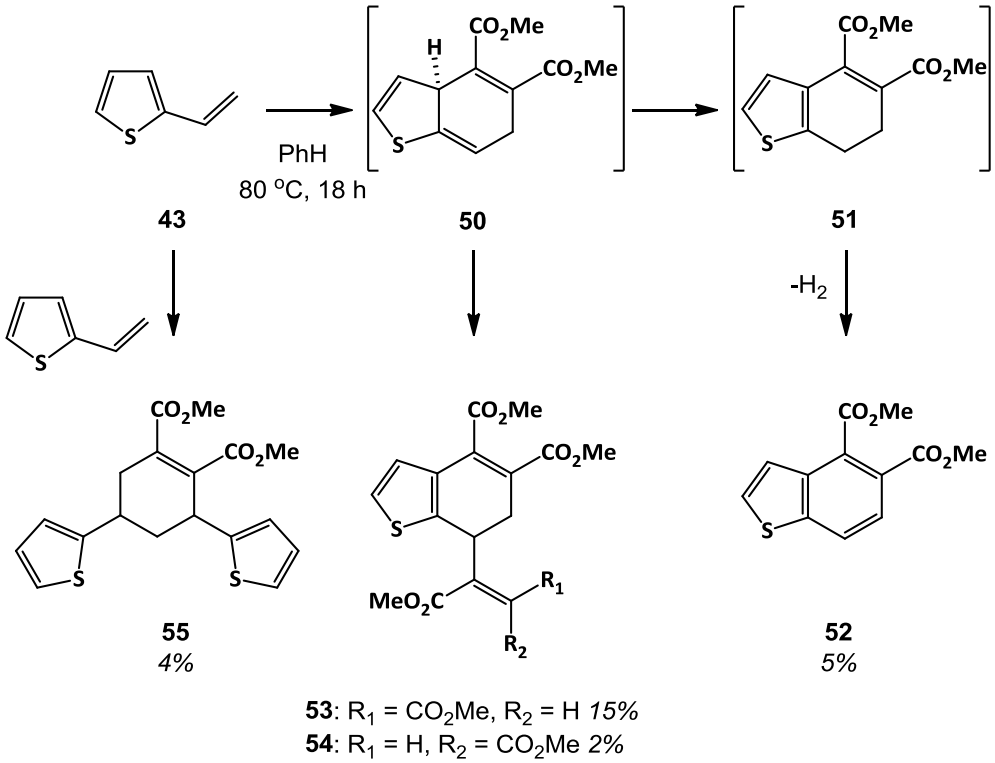
These results indicate that the greater resonance energy of thiophene over furan provides a higher thermodynamic impetus towards subsequent rearomatisation following a Diels-Alder cycloaddition. However, Pryor[34] and Moody *et al.*[35] have shown that it is possible to isolate the initial Diels-Alder cycloadduct (**49**) when using the very reactive dienophile 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) at low temperatures (Scheme

1.15).



Scheme 1.15. Diels-Alder reaction of 2-vinylthiophene and PTAD.

Analogous to the vinylfuran and vinylpyrrole examples, on reaction with DMAD, Abarca *et al.*[32] found that 2-vinylthiophene produced a number of products, summarised in Scheme 1.16. Interestingly, neither the initial Diels-Alder cycloadduct **50** nor the rearomatised cycloadduct **51** were isolated, but instead further *in situ* domino reactions of these compounds led to the dehydrogenated diester **52** (5%), the isomeric ene adducts **53** (15%) and **54** (2%), and dithiophene **55** (4%), arising from a formal [2+2+2] cycloaddition with DMAD and a second molecule of **43**.



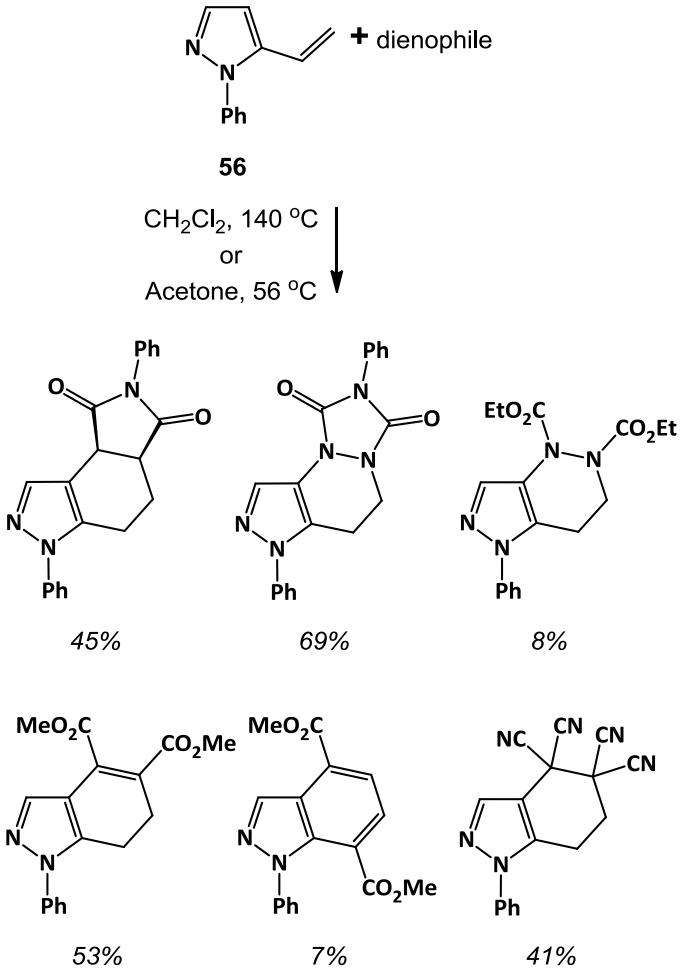
Scheme 1.16. Products isolated from reaction of 2-vinylthiophene with DMAD.

1.1.3.4 Vinylpyrazoles

There are a very limited number of examples of vinylpyrazoles participating as

dienes in Diels-Alder reactions, and they very rarely give the expected Diels-Alder cycloadducts. Work by Sepulveda-Arques *et al.* has shown that whilst vinylpyrazoles are reluctant to undergo [4+2] cycloadditions under standard conditions, successful reactions can be observed under high temperatures and pressures (120-140 ^{o}C, 8-10 atm), although under these conditions by-products from competing reactions and retro-Diels-Alder reactions are often observed.[36,37]

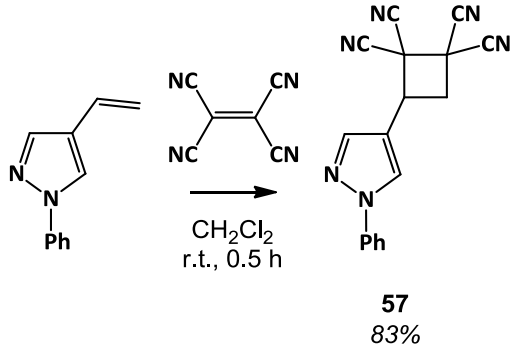
The Sepulveda-Arques group also investigated the Diels-Alder cycloaddition of 1-phenyl-5-vinylpyrazole (**56**) with a range of dienophiles in either CH_2Cl_2 at 140 ^{o}C or acetone at 56 ^{o}C, and found that the rearomatised cycloadducts were obtained consistently (Scheme 1.17).[38]



Scheme 1.17. Diels-Alder reactions of 5-vinylpyrazole **56** with range of dienophiles.

The Sepulveda-Arques group found 4-vinylpyrazoles to be much more reactive towards dienophiles, giving products from Diels-Alder reactions and other domino reaction pathways.[36,37] Analogous to the 5-vinylpyrazoles, the 4-vinylpyrazoles were subjected to a series of [4+2] cycloadditions with a range of dienophiles. However, only

with NPM was the expected rearomatised Diels-Alder cycloadduct obtainable. With all other dienophiles, with the exception of tetracyanoethylene, further reactions occurred leading to formation of the ene adduct with a second molecule of dienophile, or to the fully aromatised molecule *via* air oxidation. With tetracyanoethylene, the 4-vinylpyrazoles underwent formal [2+2] cycloaddition with the vinylic double bond giving cyclobutane **57** (Scheme 1.18).

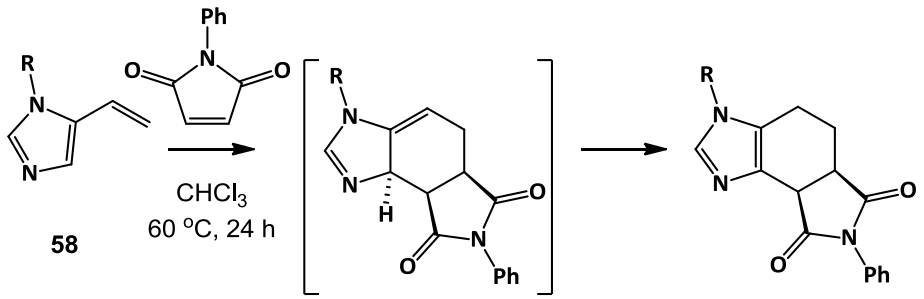


57
83%

Scheme 1.18. [2+2] cycloaddition of 4-vinylpyrazole with tetracyanoethylene.

1.1.3.5 Vinylimidazoles

Walters and Lee were the first to investigate vinylimidazoles as Diels-Alder dienes in 1994.[39] They showed that methyl and methoxymethyl (MOM) protected 5-vinylimidazoles (**58**) underwent [4+2] Diels-Alder reactions with NPM, however the initial Diels-Alder adducts (**59** and **60**) were only identifiable by NMR spectroscopy and were unstable to chromatography. Rearomatised Diels-Alder cycloadducts **61** and **62** were isolable in low to reasonable yields of 41% and 14% after 24 h at 60 ^{o}C (Scheme 1.19).



58

59: R = Me
60: R = MOM

61: R = Me *41%*
62: R = MOM *41%*

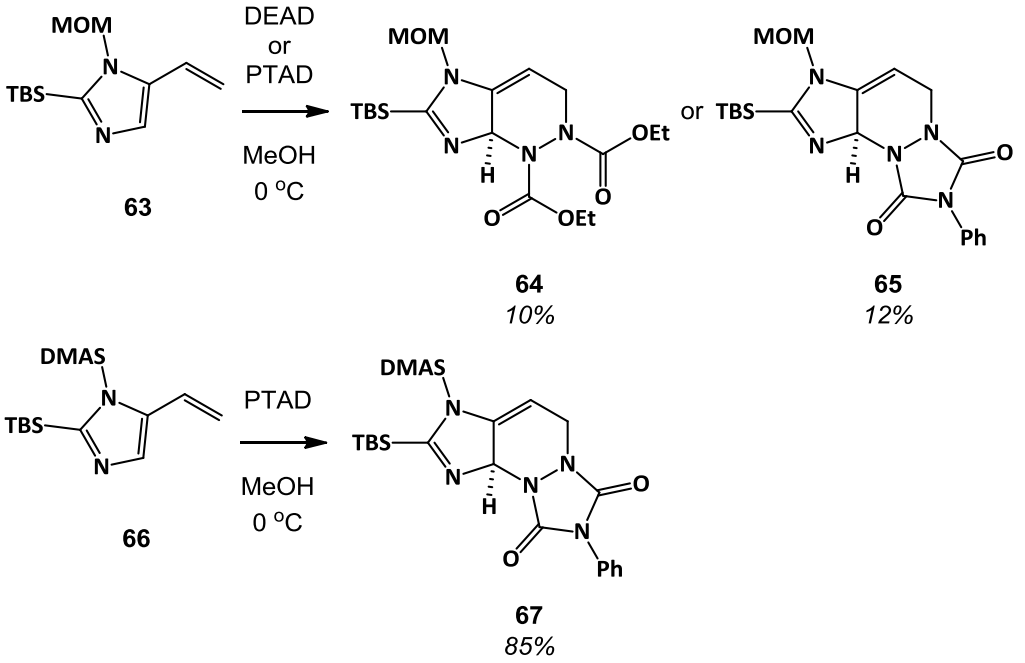
Scheme 1.19. Diels-Alder reaction of 5-vinylimidazoles with NPM.

Walters and Lee also observed that addition of a catalytic quantity of *p*-toluenesulfonic acid to the reaction mixture rapidly facilitated rearomatisation, and

significantly improved their yield of **62** from 14 to 41%.

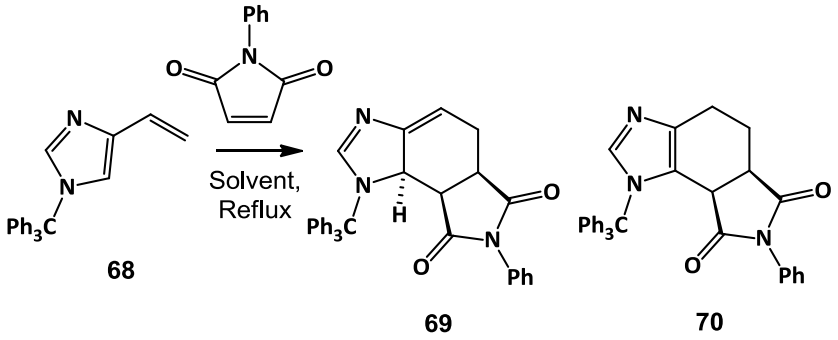
Deghati *et al.*[40] also investigated the Diels-Alder reactions of 5-vinylimidazoles as an approach to purine analogues. **63** underwent Diels-Alder reactions with both diethyl azodicarboxylate (DEAD) and PTAD, both resulting in low yields of the initial Diels-Alder cycloadducts **64** and **65** (Scheme 1.20).

However, with the electron-poor protecting group *N*,*N*-dimethylaminosulfonyl (DMAS), 5-vinylimidazole **66** underwent rapid cycloaddition with PTAD at 0 °C, to give the expected Diels-Alder cycloadduct (**67**) in 85% yield.



Scheme 1.20. Diels-Alder reaction of N1-protected 5-vinyl imidazoles.

It appears that the electronics of the N1 protecting group may have a significant effect on the product distribution of intermolecular Diels-Alder reactions of vinylimidazoles. As part of an investigation into the synthesis of pyrrole-imidazole alkaloids, Lovely *et al.*[41] studied the effects of reaction solvent/temperature and N1-protecting group on reactions of 4-vinylimidazoles. Initial studies looked at the intermolecular cycloaddition of trityl-protected 4-vinylimidazole **68** with NPM at reflux in a range of solvents, with a comparison of the yields of the initial Diels-Alder adduct **69** and rearomatised adduct **70** (Scheme 1.21, Table 1.1).



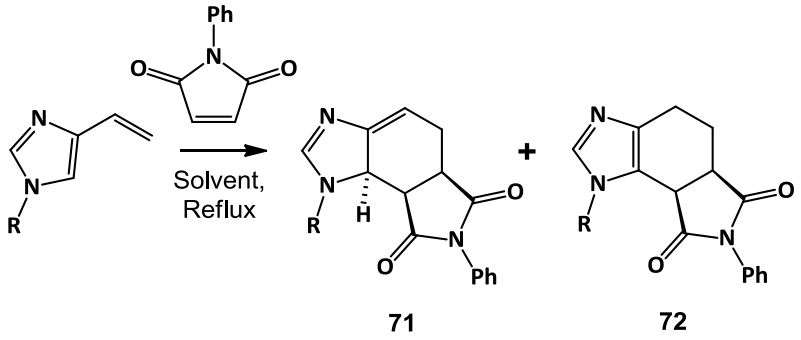
Scheme 1.21. Diels-Alder reaction of **68** with NPM in a range of solvents.

Entry	Solvent (Reaction Time/h)	69/%	70/%
1	Xylene (1)	0	0
2	Toluene (3)	52	8
3	Benzene (12)	63	8
4	Benzene (30)	60	3
5	Chloroform (24)	84	0
6	Dichloromethane (24)	52	0

Table 1.1. Solvent dependence of isolated product yield.

The desired initial Diels-Alder cycloadduct was obtained with the best yields in refluxing chloroform at 60 ^{o}C. The authors hypothesised that the reduced yields observed at higher temperature were related to thermal sensitivity of either the vinylimidazole or Diels-Alder cycloadducts, and indeed decomposition of vinylimidazole **68** was observed in refluxing xylene. The authors attributed this decomposition to the lability of the trityl group at elevated temperatures.[42]

The Lovely group also studied the effect of protecting group on the Diels-Alder reaction of vinylimidazoles (Scheme 1.22).[41,43,44] Higher yields of the Diels-Alder cycloadduct (80-94%) were achieved when using the electron-withdrawing protecting groups tosyl- (Ts) and DMAS (Table 1.2).[39]

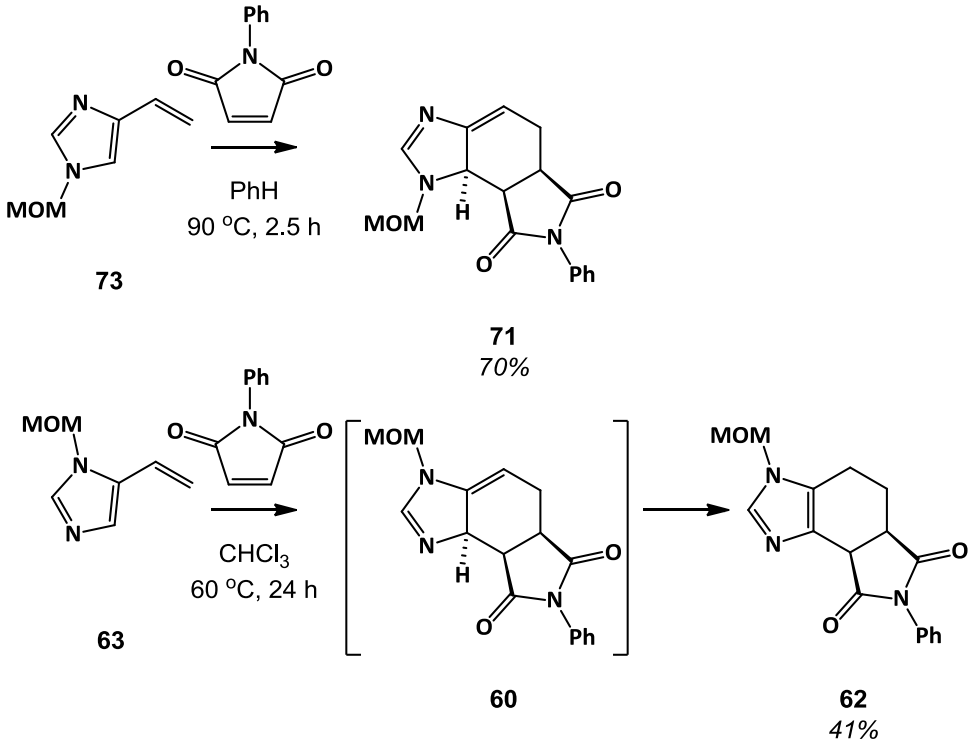


Scheme 1.22. Intermolecular Diels-Alder reaction of *N*-protected-4-vinylimidazoles with NPM.

Entry	R	Solvent	Temp/^{o}C	Time/h	71/%	72/%
1	Me	PhH	90	6	**0**	**46**
2		CH_2Cl_2	50	13	**0**	**76**
3	Trityl	PhH	90	12	**63**	**8**
4		CH_2Cl_2	50	24	**52**	**0**
5	MOM	PhH	90	2.5	**70**	**0**
6		CH_2Cl_2	50	17	**86**	**0**
7	SEM	PhH	90	5	**85**	**0**
8		CH_2Cl_2	50	6	**78**	**0**
9	Bn	PhH	90	21	**0**	**18**
10		CH_2Cl_2	50	10	**88**	**0**
11	Ts	PhH	90	27	**80**	**0**
12		CH_2Cl_2	50	48	**89**	**0**
13	DMAS	PhH	90	9	**93**	**0**
14		CH_2Cl_2	50	48	**94**	**0**

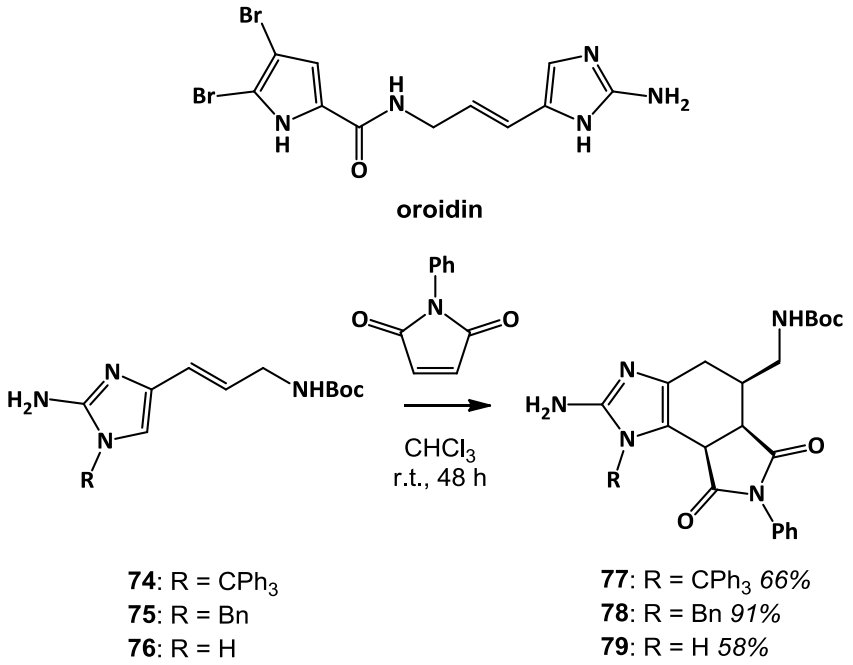
Table 1.2. Protecting group dependence of isolated product yield.

The Diels-Alder cycloadducts arising from the reaction of 4-vinylimidazoles with NPM are more stable than the corresponding 5-vinylimidazole derived compounds. This can be observed by comparing the reaction of methoxymethyl- (MOM) protected 4- and 5-vinylimidazole (**73** and **63**) with NPM. The Diels-Alder cycloadduct **71** was isolated in 70% yield from reaction at 90 ^{o}C in benzene,[41] whilst Walters and Lee were unable to isolate cycloadduct **60** as rapid rearomatisation occurred even at lower temperatures (Scheme 1.23).[39]



Scheme 1.23. Diels-Alder reactions of 4- and 5-vinylimidazoles with NPM.

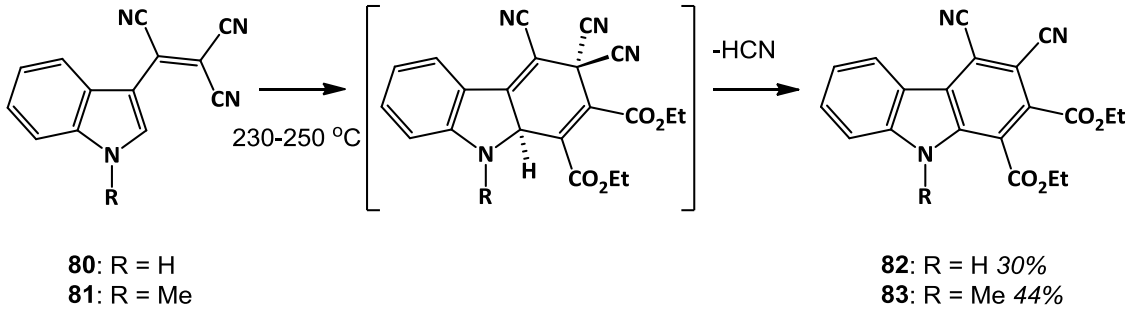
Poverlein *et al.*[45] also studied the cycloadditions of 4-vinylimidazoles **74**-**76** with NPM, as model compounds for the synthesis of oroidin-like pyrrole-imidazole alkaloids. 2-amino-4-vinylimidazoles readily underwent intermolecular Diels-Alder reactions with NPM at r.t. in chloroform, providing exclusively rearomatised products in good to excellent yields (58-91%). The unprotected 2-amino-4-vinylimidazole **76** also readily underwent an intermolecular Diels-Alder reaction with NPM to give the corresponding cycloadduct **79**, although in lower yield than trityl- (**77**) and benzyl- (**78**) protected systems (Scheme 1.24). The electron-donating 2-amino group makes the 4-vinylimidazole a more reactive diene, leading to fast intermolecular Diels-Alder reactions and subsequent rapid rearomatisation.



Scheme 1.24. Diels-Alder reaction of 2-amino-4-vinylimidazoles with NPM.

1.1.3.6 Vinylindoles

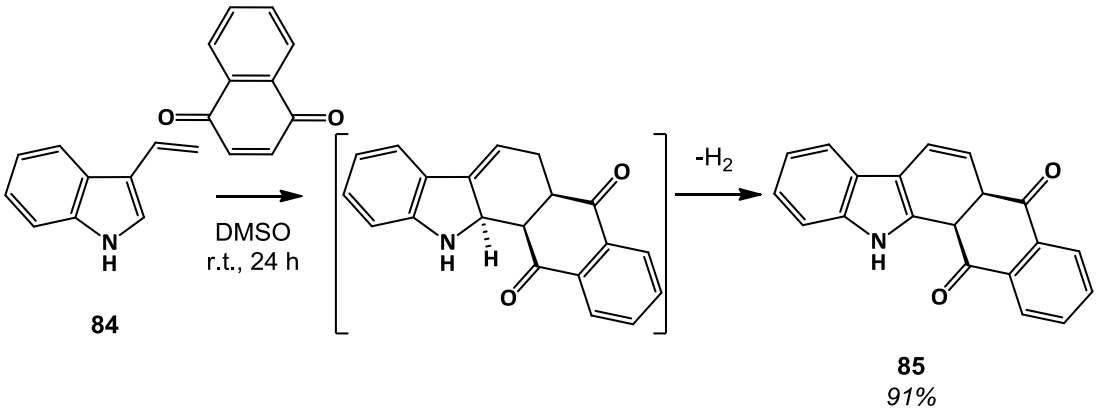
By comparison to other heteroaromatics, the Diels-Alder reactions of 2- and 3-vinylindoles have been examined extensively, largely inspired by the wealth of natural products based on the indole scaffold. Substituted 3-vinylindoles were first examined in Diels-Alder reactions as early as 1959 by Noland *et al.*[46] who reacted 3-tricyanovinylindoles **80** and **81** with DMAD to give intermolecular Diels-Alder cycloadducts **82** and **83**, following extrusion of HCN (Scheme 1.25).



Scheme 1.25. Reaction of substituted 3-vinylindoles with DMAD.

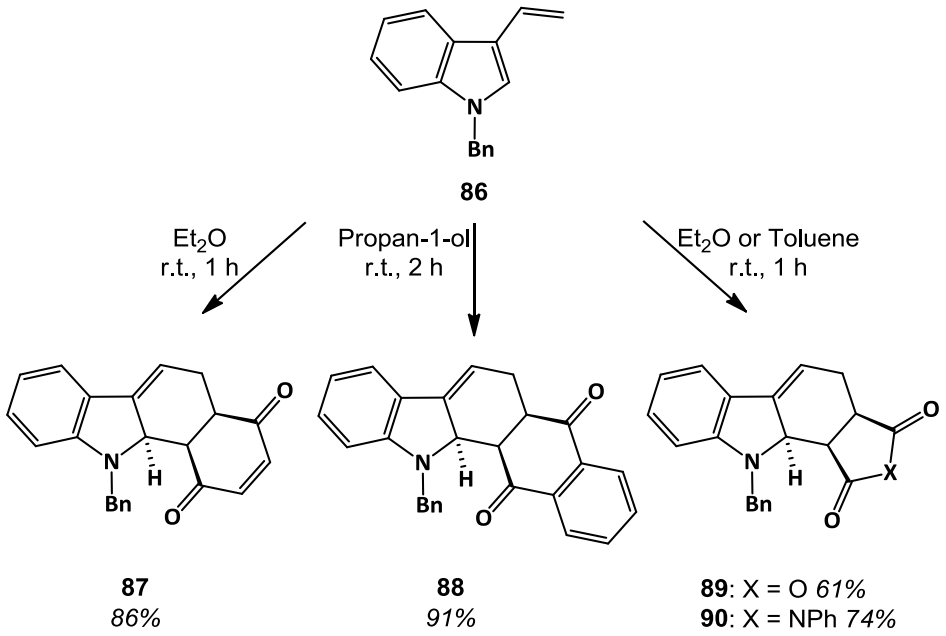
In subsequent work, the Noland group also reported the synthesis of the parent compound 3-vinylindole (**84**) in 1963,[47] and examined its reactivity in intermolecular Diels-Alder reactions. 3-Vinylindole underwent a Diels-Alder cycloaddition with 1,4-naphthoquinone at r.t. over 24 h, and subsequent air oxidation led to adduct **85** in 91%

yield (Scheme 1.26).



Scheme 1.26. Diels-Alder reaction of 3-vinylindole with 1,4-naphthoquinone.

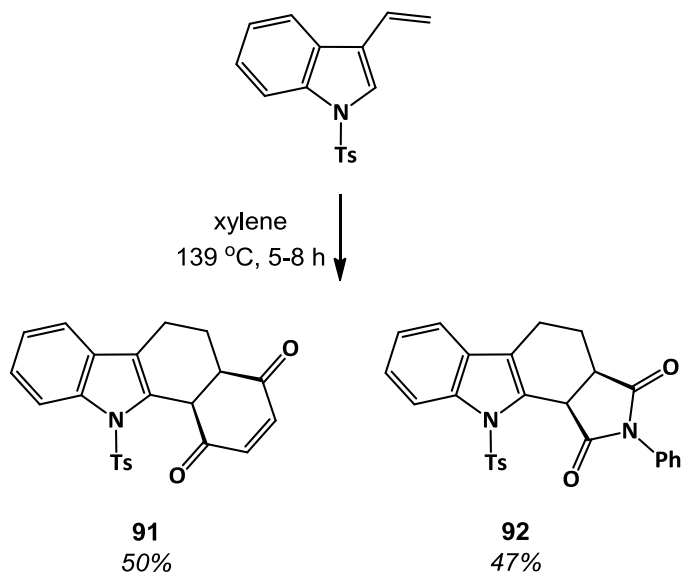
In contrast to this, Lambert *et al.*[48] studied reactions of 1-benzyl-3-vinylindole (**86**) with a range of dienophiles and found that despite the increased electron-donation provided through the electron-rich benzyl protecting group, Diels-Alder cycloadducts could be successfully isolated at r.t. in 1-2 hours with *p*-benzoquinone (**87**), 1,4-naphthoquinone (**88**), maleic anhydride (**89**) and NPM (**90**) (Scheme 1.27).



Scheme 1.27. Diels-Alder reactivity of 1-benzyl-3-vinylindole.

Saroja and Srinivasan examined the Diels-Alder reactions of 3-vinylindoles protected with the electron-withdrawing tosyl group,[49] and found that rearomatised cycloadducts could only be obtained in moderate yields when refluxing in xylene for 5-8 hours with *p*-benzoquinone (**91**) or NPM (**92**) (Scheme 1.28). This reduction in reactivity

is due to the electron-withdrawing tosyl groups deactivating the system towards Diels-Alder reaction and subsequent rearomatisation.

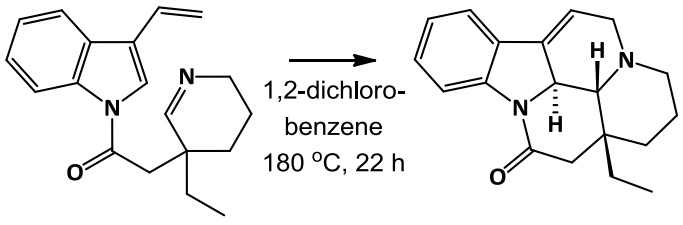


91
50%

92
47%

Scheme 1.28. Diels-Alder reactions of 1-tosyl-3-vinylindole.

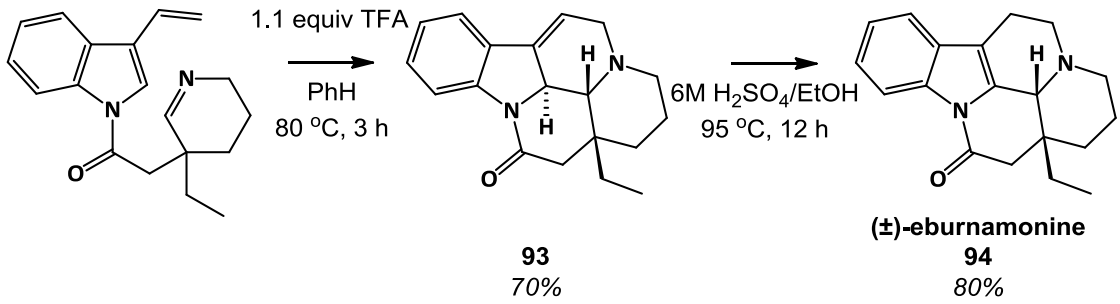
The Diels-Alder reactions of vinylindoles have also been employed in numerous total syntheses. Grieco and Kaufman[50] utilised an intramolecular imino-Diels-Alder reaction of a substituted-3-vinylindole in their studies towards the total synthesis of the vasodilator (±)-eburnamonine (**94**). The desired Diels-Alder reaction proved relatively slow, despite the use of forcing conditions, giving low yields of the initial intramolecular Diels-Alder cycloadduct **93** (Scheme 1.29), with no rearomatisation to **94**.



93
32%

Scheme 1.29. Intramolecular imino-Diels-Alder reaction in the synthesis of (±)-eburnamonine **94**.

In agreement with results observed previously by Walters and Lee,[39] the reaction was much more efficient in the presence of an acid catalyst. The addition of 1.1 equivalents of TFA afforded the initial Diels-Alder cycloadduct after 3 h at 80 °C, and rearomatisation with 6.0 M H_2SO_4/EtOH at 95 °C for 12 h gave (±)-eburnamonine in 56% yield over 2 steps (Scheme 1.30).



Scheme 1.30. Acid catalysed Diels-Alder reaction and rearomatisation.

1.1.4 Conclusions

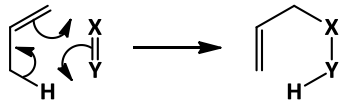
Diels-Alder reactions of vinyl-heteroaromatics occur mainly *via* the extra-annular pathway, incorporating the vinylic double bond, in an *endo* manner. The more electron-rich vinyl-heteroaromatics are typically more reactive as dienes due to their high energy HOMO's. For moderately reactive vinyl-heteroaromatics, mild reaction conditions can provide simple Diels-Alder cycloadducts, whilst under more forcing conditions, rearomatisation and other competing reactions are observed.

Importantly, the reactivity of a vinyl-heteroaromatic towards Diels-Alder reaction can be tailored by modifying the electronics of protecting groups and substituents. For example Lovely *et al.* have shown that employing Ts and DMAS as electron-withdrawing *N*-protecting groups for 4-vinylimidazole allows selective Diels-Alder cycloaddition. Similarly, other groups have demonstrated that rearomatisation of vinylindole Diels-Alder cycloadducts can be hindered through the use of deactivating *N*-protecting groups such as Ts, phenylsulfonyl and acetyl, leading to clean Diels-Alder reactions for these systems.[51,52,53,54]

1.2 Ene Reactions

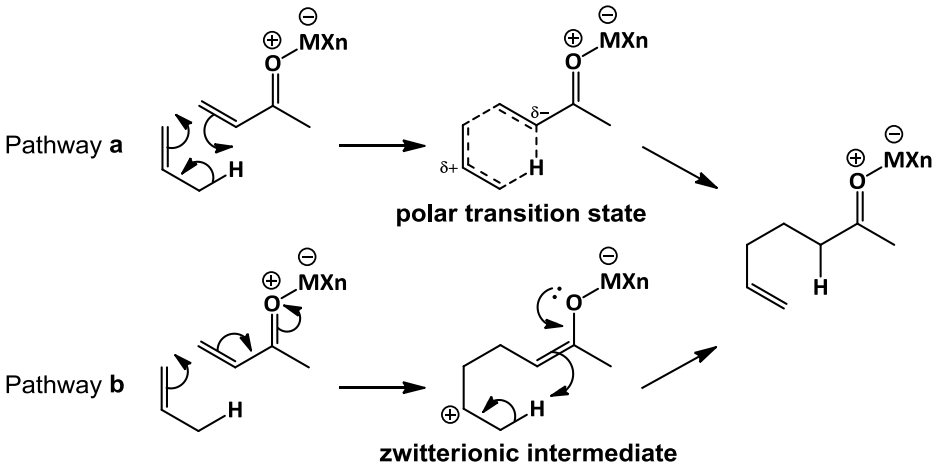
Another pericyclic reaction which has gained some synthetic utility is the ene reaction. It was first recognised by Kurt Alder in 1943[55] and initially described as an 'indirect substitution' in his Nobel Lecture in 1950.[2] Ene reactions are defined as six-electron pericyclic processes which occur between an alkene possessing a hydrogen in the allylic position (the "ene") and an electron deficient π-system (the "enophile"). The reaction involves the [1,5]-sigmatropic shift of the allylic hydrogen, migration of the π-bond, and the formation of a new C-C σ-bond (Scheme 1.31).

The ene reaction is mechanistically similar to the Diels-Alder reaction, with enophiles oriented either *exo* or *endo* with respect to the ene component. Energy is required to activate the σ C-H and π X-Y bonds, whilst energy is gained from the formation of the σ X-C and σ Y-H bonds.



Scheme 1.31. Ene reaction of propene with an enophile, X=Y.

There is dispute, as with the Diels-Alder reaction, whether this reaction occurs *via* a concerted or stepwise mechanism. For many ene reactions, the mechanism is undefined, or can be shown to proceed either by a concerted or stepwise pathway depending on the reaction conditions. Lewis acid catalysed ene reactions may undergo either a concerted mechanism with a polar transition state, or a stepwise mechanism with a zwitterionic intermediate (Scheme 1.32).[56]



Scheme 1.32. Zwitterionic (a) and polar (b) pathways of the Lewis acid catalysed ene reaction.

The scope, synthetic potential and applications of the ene reaction have previously been reviewed extensively.[56,57,58,59] Despite its atom efficiency and tolerance for a range of enophiles, and although the formation of C-C bonds and C-H activation are important reactions in synthesis, the ene reaction has been utilised to a much lesser extent in comparison to the Diels-Alder reaction. The main factor limiting the scope of ene reactions is the high activation barrier arising from the highly ordered nature of the transition state. This leads to a negative entropy of activation, of the order -30 cal mol K^{-1}, generally requiring temperatures in excess of 400 ^{o}C for an intermolecular reaction of an all carbon species.[60]

This difficulty has been overcome to some extent through the use of intramolecular substrates, intramolecular tethers, strained/reactive enes, and enophiles possessing electron-withdrawing groups. Lewis acid catalysts or promoters containing basic groups are also often employed to activate the enophile and facilitate ene reactions at ambient temperatures or below. The most common of these promoters are aluminium salts, for example $AlMe_2Cl$, which can enable the ene reaction to occur at low temperatures, usually -78 ^{o}C.[61] In many of these reactions a number of equivalents of $AlMe_2Cl$ are required for reaction, as the aluminium ligands are subject to degradation *via* alcoholysis, leading to the term promoter rather than catalyst. In addition, it is known that ene reactions can also be facilitated by classic Lewis acid catalysts, the more common of which are $SnCl_4$,[62] $BF_3.OEt_2$,[61] $Sc(OTf)_3$ and $Yb(OTf)_3$.

1.2.1 Ene reaction classification

The ene reaction can be divided into two categories depending on the nature of the components: (1) 'all-carbon' ene reaction, taking place between an olefin (carba-ene) and an activated alkene or alkyne (carba-enophile), and (2) hetero-ene reaction, taking place between an ene and enophile, either of which contains at least one heteroatom.[63,64]

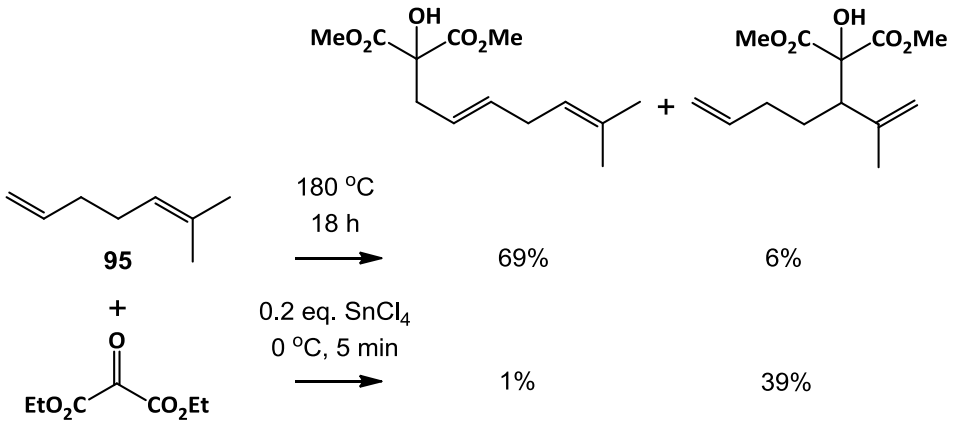
The hetero-ene reaction may then be further subdivided into three subcategories; (a) all-carbon ene components with hetero-enophiles, (b) hetero-ene components with all-carbon enophiles, and (c) hetero-ene components with hetero-enophiles.

1.2.2 Common ene substrates

In general terms, 1,1-disubstituted and 1,1,2-trisubstituted alkenes are much more reactive in the ene reaction than mono- or 1,2-disubstituted alkenes, due to the stabilisation effect they infer on any partial positive charge developed during the reaction. This is a significant factor in Lewis acid catalysed reactions, whilst for thermal reactions,

the steric accessibility of the double bond and allylic hydrogen are more important.[58]

The influences of the steric effects in thermal reactions *vs*. the electronic effects in Lewis-acid catalysed reactions have been highlighted in the work by Salomon *et al*.,[63] who observed that ene reaction of 6-methylhepta-1,5-diene (**95**) with diethyl ketomalonate would occur preferentially at the least sterically hindered ene in a thermal reaction, and at the ene most stabilised by σ-conjugation in the Lewis-acid catalysed reaction (Scheme 1.33).



Scheme 1.33. Thermal *vs*. Lewis acid catalysed ene reaction of 6-methylhepta-1,5-diene (**95**).

1.2.3 Common enophiles

In terms of the electron-deficient enophile component, as with the Diels-Alder reaction, the ene reaction can tolerate a vast range of variation, and the most common categories of enophile are summarised below.

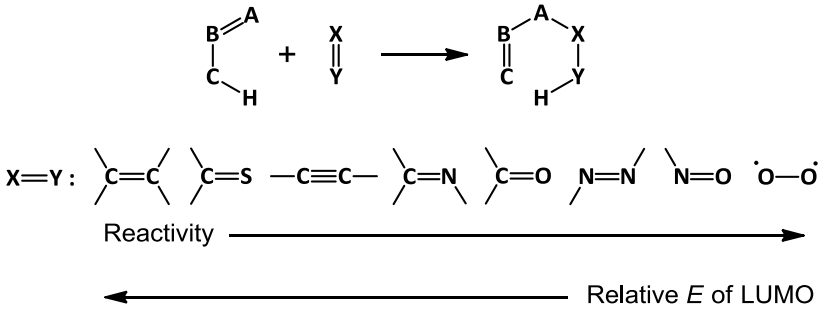


Figure 1.1. Examples of the most common enophiles.

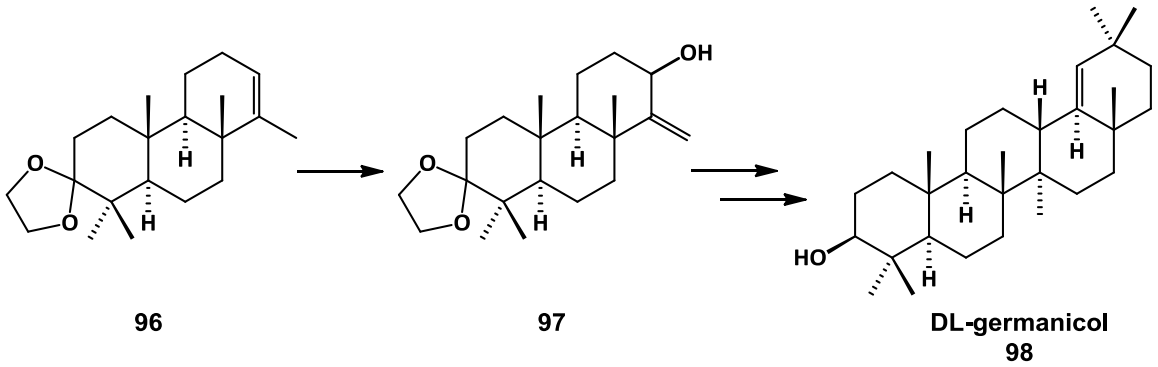
Enophiles with the lowest energy LUMO will be the most reactive with electron-rich dienes. The orbitals of electronegative heteroatoms like oxygen and nitrogen are of lower energy than the corresponding orbitals of carbon, and so serve to reduce the energy of the LUMO, and thus increase the reactivity of the enophile. For the same reason, a similar enhancement in reactivity is observed when the enophile is substituted with

electron-withdrawing groups.

1.2.3.1 Singlet oxygen ene reactions

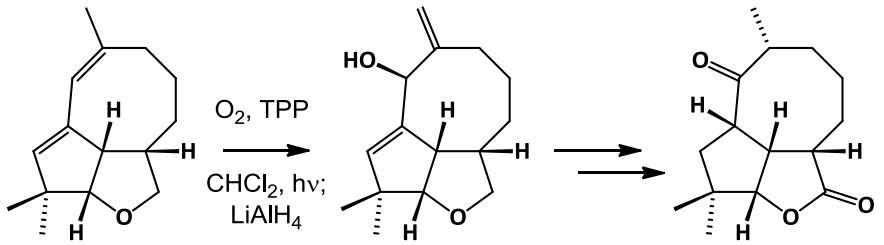
Of all of the ene reactions, it is those employing singlet-oxygen as the enophile that have received the most synthetic attention. Following the initial discovery of this reaction in 1948 by Schenck,[64] it wasn't until almost 40 years later that the active oxidant was identified as singlet oxygen.[65,66] The reactive oxygen species is commonly generated *in situ* by dye sensitised photoexcitation of molecular oxygen, commonly using methylene blue (MB), Rose Bengal (RB) or tetraphenylporphyrin (TPP). Singlet oxygen then reacts with olefins to yield allylhydroperoxides. The reaction, sometimes referred to as the Schenck ene reaction, has subsequently found numerous applications in synthesis as a method of introducing O-R functionality into a molecule.

Ireland *et al.*[67] utilised a singlet-oxygen ene reaction in their multi-step synthesis of the pentacyclic natural product DL-germanicol (**98**) from the tetracyclic alkene **96.** Following photooxygenation and reduction of the resulting hydroperoxide to the α-methylene allylic alcohol, **97** was converted to **98** in a total of 32 steps, with a 0.1% overall yield (Scheme 1.34).



Scheme 1.34. Singlet-ene reaction in the synthesis of DL-germanicol (**98**).

More recently, Paquette *et al.*[68] employed a singlet oxygen ene reaction in their route towards (+)-asteriscanolide (**101**). **99** was converted to a hydroperoxide *via* a singlet-oxygen ene reaction with TPP as the sensitiser, and was successfully transformed to the diallylic carbinol **100** with direct hydride reduction in 61% yield. Three subsequent steps led to (+)-asteriscanolide **101** in 4% overall yield (Scheme 1.35).



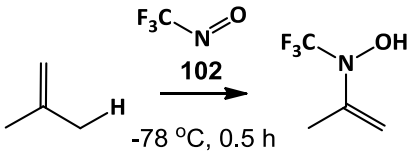
99 **100** *61%* **101** *4% over 16 steps*

Scheme 1.35. Singlet-oxygen ene reaction in the synthesis of (+)-asteriscanolide **101**.

1.2.3.2 Nitroso ene reactions

Ene reactions employing nitroso compounds as the enophile are synthetically useful as a mild and convenient method of generating a new nitrogen-carbon bond. However, since the discovery of the nitroso-ene reaction by Banks and co-workers in 1965,[69] it is yet to be afforded a great deal of synthetic attention, despite the low energy of the LUMO placing nitroso compounds among the most reactive class of enophiles.

As part of a study of the Diels-Alder reaction of butadiene with trifluoronitrosomethane (**102**), Banks *et al*. investigated the reaction of **102** with isobutene. They found that carrying out the reaction at -78 ^{o}C resulted in the successful isolation of the nitroso-ene product **103**, in 96% yield (Scheme 1.36).[69]

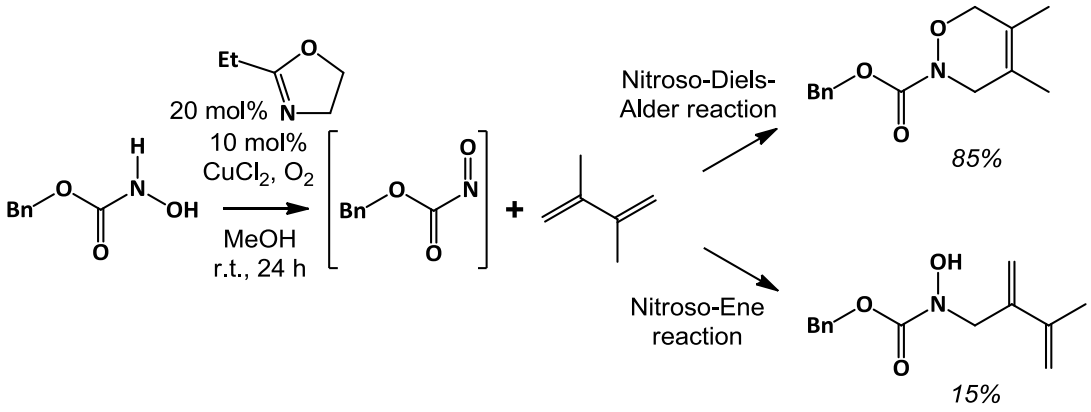


103 *96%*

Scheme 1.36. Nitroso-ene reaction of isobutene and trifluoronitrosomethane.

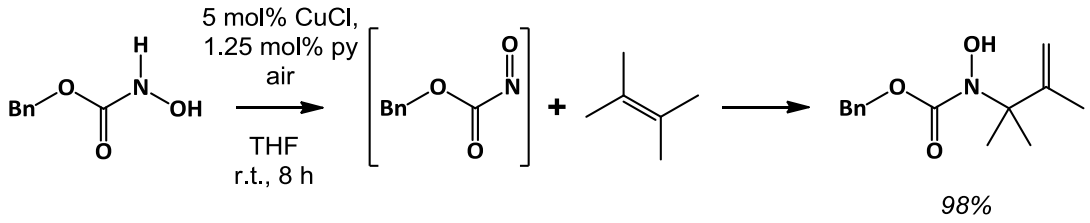
The nitroso-ene reaction represents a direct regioselective and stereoselective method of the allylic nitrogen functionalisation of alkenes, however, nitrosos may also succumb to a variety of *in-situ* side-reactions, such as dimerisation, addition and reduction.[70] The occurrence of these *in situ* transformations and the potential for side-reactions of the nitroso starting materials are a limitation to the suitability of these compounds in ene reactions. Therefore the majority of the synthetic attention in recent years has surrounded the *in situ* generation and reaction of acyl nitroso species.[71,72,73,74,75] Through the copper(II) chloride catalysed air oxidation of hydroxamic acids, Whiting *et*

al. have shown it is possible to successfully obtain both Diels-Alder and ene adducts of dienes under facile conditions (Scheme 1.37).[75]



Scheme 1.37. *In situ* generation and Diels-Alder/ene reaction of acyl nitroso species.

Frazier and co-workers have also successfully employed copper(I) chloride and air to oxidise hydroxamic acids to reactive acyl nitroso species *in situ*, and shown them to be reactive with a range of enes affording good selectivity (Scheme 1.38).[76]

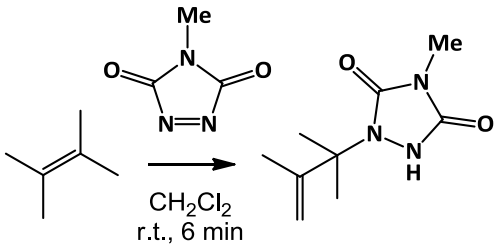


Scheme 1.38. *In situ* generation of acyl nitrosos from the catalytic air oxidation of hydroxamic acids.

1.2.3.3 Aza enophiles

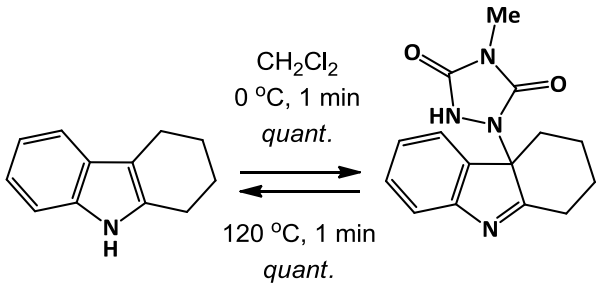
Another class of synthetically useful nitrogen-based enophiles are the aza compounds, including the cyclic 4-alkyl-1,2,4-triazoline-3,5-diones (TAD) and the related linear molecule DEAD.[77,78,79,80] This method of allylic amination of alkenes is an attractive alternative approach to the use of sulfur or selenium diimido compounds,[81] or *N*-sulfinylbenzenesulfonamide,[82] as the low LUMO energy of these compounds makes them very reactive as enophiles and dienophiles.[78]

The first reported use of a triazolinedione in an ene reaction was by Pirkle and Stickler in 1967,[79] who found that 4-methyl-1,2,4-triazoline-3,5-dione (MTAD) would react rapidly at r.t. with a range of mono-olefins containing an allylic hydrogen, including 2,3-dimethyl-but-2-ene (Scheme 1.39), to produce the expected ene adduct.



Scheme 1.39. Reaction of MTAD with 2,3-dimethyl-but-2ene.

More recently, Baran *et al.*[83,84] employed an aza-ene reaction with MTAD to protect the 2,3-π bond of indoles. They found the reaction proceeded extremely rapidly, with the disappearance of the pink colour of MTAD occurring within seconds at 0 ^{o}C, yielding the urazole-derivatives in good to quantitative yields. They were then able to simply revert these urazoles to the starting indoles on heating (120 – 280 ^{o}C) *via* a retro-ene reaction (Scheme 1.40).

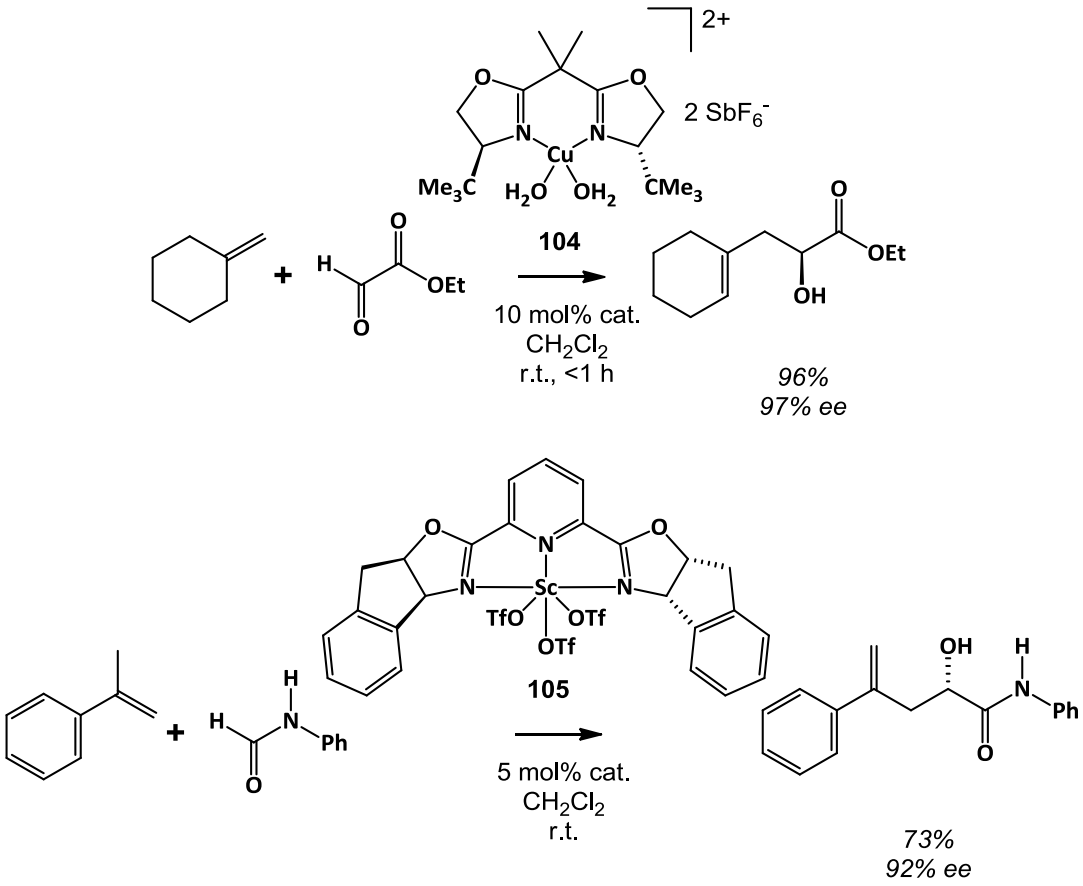


Scheme 1.40. Aza-ene reaction to protect indole 2,3-π bond.

1.2.3.4 Carbonyl enophiles

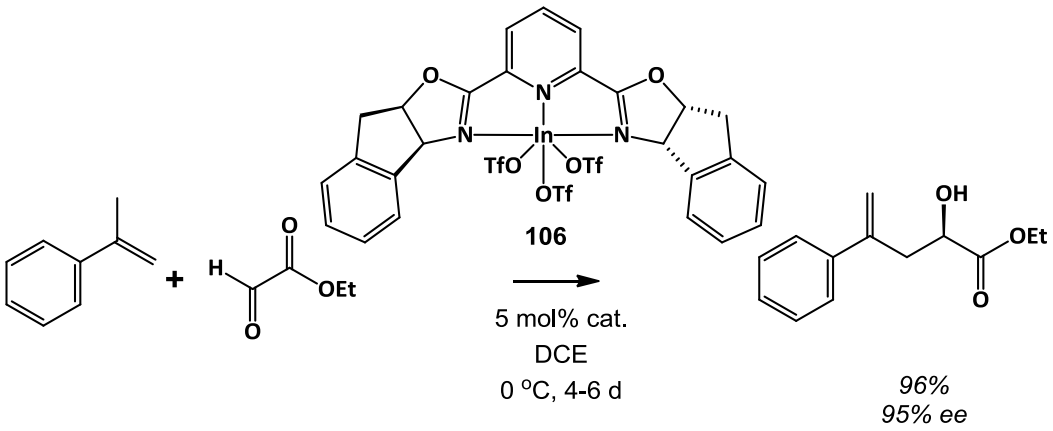
The carbonyl ene reaction has been used extensively in synthesis, exclusively forming alcohols as the ene product.[56,57,85] The inherent low LUMO energy of the simplest carbonyl enophile, formaldehyde, is decreased further through the incorporation of electron-withdrawing groups, and indeed chloral, pyruvate and glyoxalate esters are among the most frequently employed carbonyl enophiles.

Evans *et al.* have reported that both the chiral metal complexes Cu-Box (**104**) and Sc-PyBox (**105**) are efficient catalysts for mediating the asymmetric carbonyl-ene reaction.[86,87] They demonstrated excellent diastereoselectivities could be obtained when employing Cu-Box and Sc-Pybox at 10 and 5 mol% respectively for the carbonyl ene reactions of methylene cyclohexane and α-methylstyrene with ethyl glyoxalate and *N*-phenyl glyoxamide (Scheme 1.41).



Scheme 1.41. Carbonyl ene reactions with chiral metal catalysts.

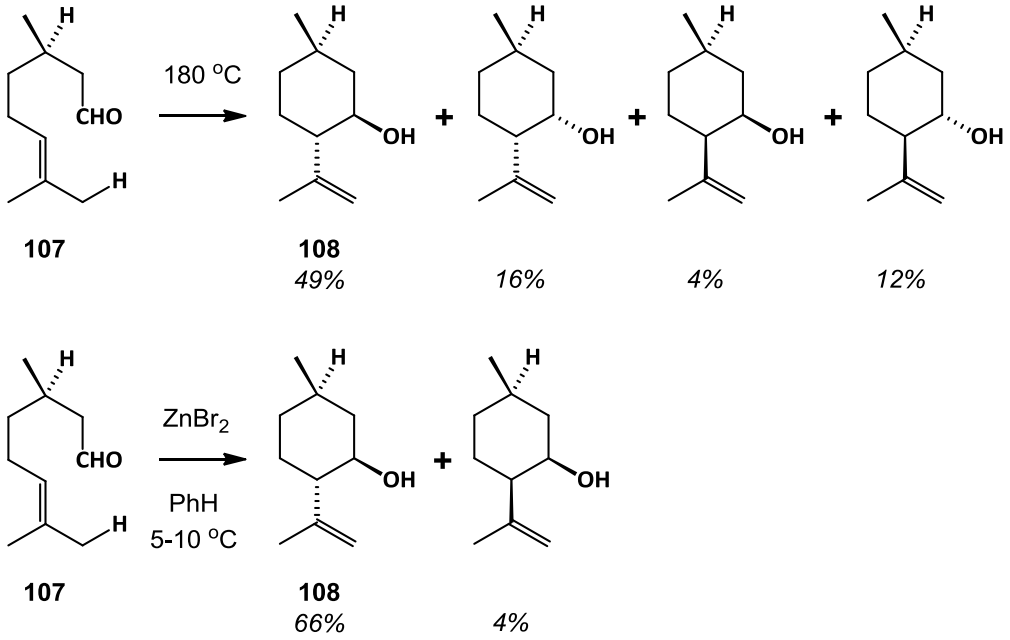
These results were consistent with the later work by Zhao and co-workers, indicating In(III)-PyBox (**106**) was also an excellent catalyst for the asymmetric carbonyl-ene reaction of α-methylstyrene with ethyl glyoxalate (Scheme 1.42).[88]



Scheme 1.42. Carbonyl ene reaction with In(III)-PyBox catalyst.

The use of intramolecular substrates or an intramolecular tether are often employed to overcome the high activation energy observed in carbonyl ene reactions.

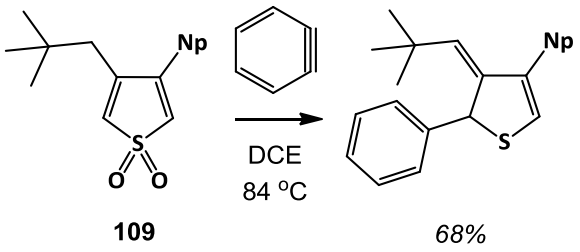
One such example is the intramolecular carbonyl-ene reaction of citronellal (**107**) to isopulegol (**108**), which gives a mixture of four diastereomers in which the *trans*-β-alcohol is the major product.[89] Addition of the Lewis acid $ZnBr_2$ to this reaction allows lower temperatures to be employed and provides improved yields through better regio- and stereocontrol. In the presence of $ZnBr_2$, only two isomers are formed of which the *trans*-β-isomer is the major product (Scheme 1.43).



Scheme 1.43. Intramolecular thermal and Lewis acid catalysed ene reactions of citronellal **107**.

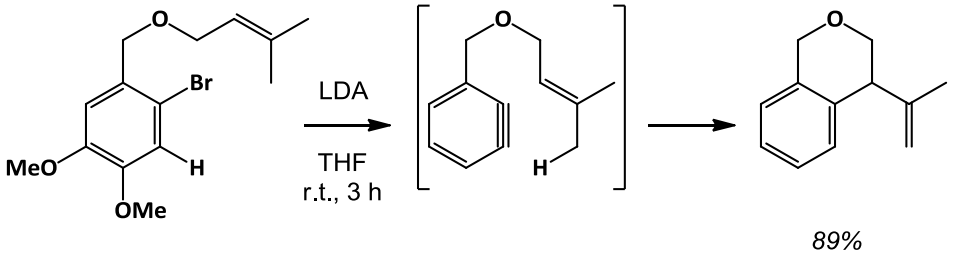
1.2.3.5 Aryne enophiles

Aryne enophiles participate much more readily in ene reactions than their alkene or alkyne counterparts, due to the lower energy of the aryne LUMO. Although the aryne-ene reaction is well-known, most notably since Nakayama's observation of an unexpected ene reaction of 3,4-dineopentylthiophene-1,1-dioxide (**109**) with benzyne during Diels-Alder investigations (Scheme 1.44),[90] it is yet to see much synthetic application as a result of poor yields and regioselectivities.



Scheme 1.44. Ene reaction of **109** with benzyne.

The reactive nature of aryne enophiles necessitate their *in situ* generation, and competing [2+2] or [4+2] cycloadditions are still possible. There are only a limited number of examples of efficient aryne-ene reactions appearing in the literature which afford good yields or regioselectivities,[91] although Candito *et al.* have attempted to overcome this by using an intramolecular tether. They were able to successfully prepare a number of benzofused carbo- and hetero-cycles, using deprotonation with LDA as a method of generating benzyne *in situ* (Scheme 1.45).[92]



Scheme 1.45. Intramolecular aryne ene reaction.

1.2.4 Conclusions

The ene reaction has been shown to be a powerful, versatile transformation with a broad scope in terms of both substrate and enophile. The high activation energies that are typically observed often require high temperatures for reactions to proceed, although Lewis acid promoted reactions can proceed rapidly at moderate temperatures. These limitations have led to the ene reaction being studied to a lesser extent than the closely related Diels-Alder reaction, although the ene reaction has still found numerous applications in synthesis.

High levels of stereoselectivity are typically observed in the ene reaction, and through the use of chiral Lewis acid catalysts, synthetically useful enantioselective reactions can be performed.

1.3 One-Pot Reactions

1.3.1 Introduction

"One-pot" reactions (in which three or more components react together in a single chemical operation) have appeared in the literature for well over a century. Many of the more well-known one-pot reactions including the Strecker amino acid synthesis (1850),[93,94] the Hantsch dihydropyridine synthesis (1882),[95] the Biginelli synthesis of pyrimidinones (1891),[96,97] and the Mannich (1912)[98] and Passerini reactions (1922)[99] are now nearly 100 years old. The Ugi four-component reaction (1959)[100,101] is perhaps the most utilised one-pot reaction in recent years, despite being over 50 years old itself.

In the last twenty years this class of reaction has witnessed a surge in interest with the desire to rapidly generate large and varied libraries of compounds for use with high-throughput screening systems.[102,103,104,105] Subsequently, this increased attention has led to a number of expressions appearing in the literature to describe different facets of these one-pot reactions, with the terms multi-component, domino, cascade, tandem, consecutive and serial used freely and interchangeably. In recent years however, there has been an increasing effort to standardise the nomenclature:

1. Domino: Tietze defines a "domino reaction" as one in which the formation of two or more bonds occurs under the same conditions (without the addition of further reagents or catalysts), and in which subsequent reactions occur as a result of functionality formed in the previous reaction.[106]
2. Tandem: Denmark has employed the term "tandem reactions" to encompass all reactions which occur one after the other, and uses the modifiers cascade, consecutive and sequential to specify how the subsequent reactions occur.[107]
3. Cascade: Nicolaou has adopted the broader term "cascade reaction" to classify reactions that occur consecutively in the same reaction vessel, regardless of whether a change in conditions or additional reagent is required, but where each subsequent reaction is dependent on the functionality generated in the previous step.[108]
4. One-Pot: All of the above reactions fall under the overall classification of a one-pot reaction, in which the combination of three or more components in one reaction vessel leads to a new product incorporating a portion of all of the components.

1.3.2 Domino Reactions

For purposes of clarity in this thesis I will use the term one-pot to describe all reactions carried out consecutively in the same reaction vessel with the following modifiers:

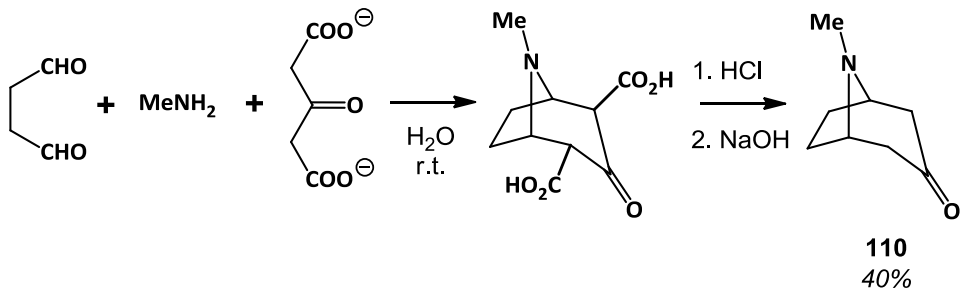
Domino: 2 or more bond-forming transformations occurring without a change in reaction conditions or the addition of further reagents or catalysts.

Sequential: 2 or more bond forming transformations which require a change in conditions, or the addition of an additional reagent or catalyst. Furthermore, subsequent transformations must occur as a consequence of functionality introduced in the previous step, and any additional reagents must be incorporated into the products.

One-pot domino reactions can be carried out as unimolecular, bimolecular and multicomponent transformations, and therefore most of the known multicomponent processes, but not all, can also be defined as a subgroup of domino reactions.[109,110]

The first recognised one-pot domino reaction was Robinson's designed multicomponent synthesis of the natural bicyclic alkaloid tropinone (**110**, Scheme 1.46) in 1917.[111] Robinson reasoned that by looking at the structure of tropinone and using "imaginary hydrolysis" that suitable starting materials could be elucidated. He subsequently reacted succinaldehyde with methylamine and an acetonedicarboxylate salt to generate tropinone (**110**) *via* a domino double Mannich reaction and subsequent decarboxylation, in 40% yield.

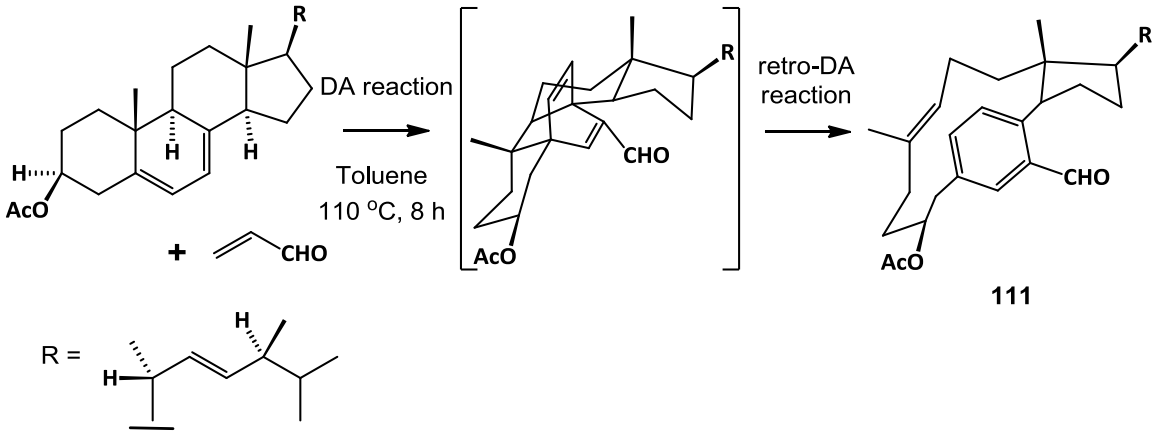
This reaction was a vast improvement on the existing linear synthesis described by Willstater in 1901[112] which involved a 15-step sequence from cycloheptanone, resulting in an overall yield of only 0.75%.



Scheme 1.46. Domino reaction in the synthesis of tropinone **110**.

Winterfeldt and co-workers employed a domino Diels-Alder/retro-Diels-Alder reaction as a route towards the synthesis of ansa-secosteroids (Scheme 1.47).[113]

Following a cycloaddition with acrylaldehyde, the steroid framework is dismantled through retro-Diels-Alder to provide the macrocycle **111**.

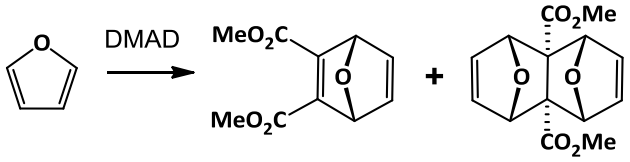


Scheme 1.47. Diels-Alder/retro-Diels-Alder domino reaction in synthesis of macrocycle **111**.

Intermolecular pericyclic reactions are powerful tools in synthetic organic chemistry due to their ability to generate multiple covalent bonds and stereocentres in a single step. Thus the combination of an intermolecular Diels-Alder reaction with another pericyclic process would allow the rapid (2 step) synthesis of complex and highly regio- and stereoselective products. More than one type of cycloaddition may also be combined, as can other pericyclic transformations such as sigmatropic rearrangements and ene reactions, and many other reactions.

1.3.2.1 Domino Diels-Alder/Diels-Alder Reactions

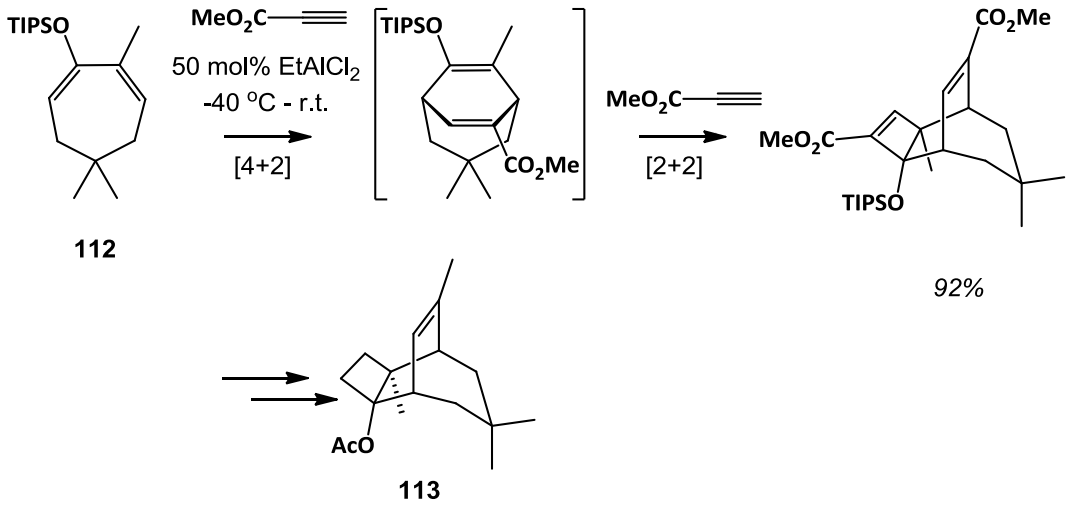
The majority of domino pericyclic reactions published in the literature involve two consecutive cycloadditions, namely [4+2]/[4+2], although there are examples of other combinations, e.g. [2+2]/[2+5]. This combination of two successive [4+2] Diels-Alder reactions was documented in the literature as early as 1931[114] by Diels and Alder themselves for the reaction of DMAD with an excess of furan (Scheme 1.48).



Scheme 1.48. [4+2]/[4+2] reaction observed by Diels and Alder.

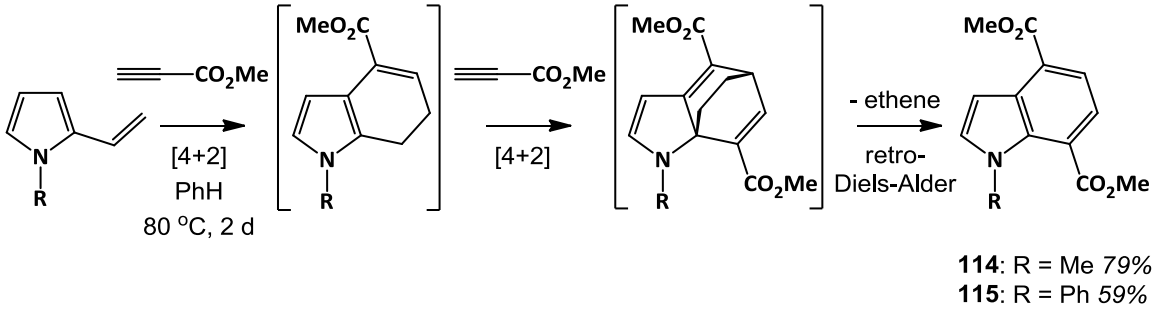
More recently, Ihara and co-workers carried out a domino [4+2]/[2+2] Diels-Alder cycloaddition in their synthesis towards (±)-Paesslerin A (**113**, Scheme 1.49),

which incorporates methyl propiolate as the dienophile in both cycloadditions with diene **112**. In the presence of the Lewis acid catalyst $EtAlCl_2$, the product could be obtained in 92% yield with complete diastereoselectivity, which led to (±)-Paesslerin A (**113**) in six further steps.[115]



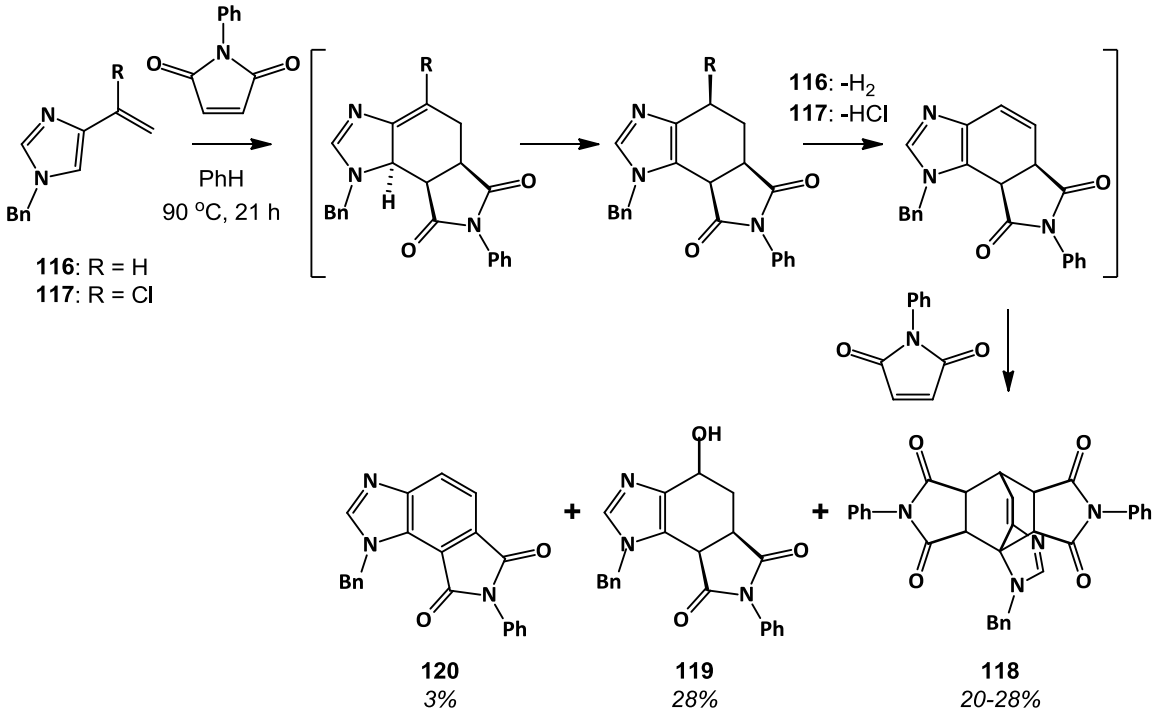
Scheme 1.49. Domino [4+2]/[2+2] reaction in the synthesis of (±)-Paesslerin A (**113**).

Jones *et al.*[26] also witnessed an interesting domino [4+2]/[4+2]/retro-Diels-Alder reaction in their studies of the cycloadditions of 2-vinylpyrroles with methyl propiolate. They found 1-methyl- and 1-phenyl-2-vinylpyrroles would undergo [4+2] cycloaddition *via* extra-annular addition, then undergo a second extra-annular [4+2] cycloaddition *via* the newly installed exocyclic double bond with a second molecule of dienophile. This was followed by the extrusion of ethene *via* a retro-Diels-Alder, leading to the indole-4,7-dicarboxylates **114** and **115** in 73 and 59% yield respectively (Scheme 1.50). Similar products were observed by Abarca *et al.*[32] in reactions of 2-vinylthiophene with methyl propiolate, and by the Sepulveda Arques group[38] from reactions of 1-phenyl-5-vinylpyrazole with methyl propiolate.



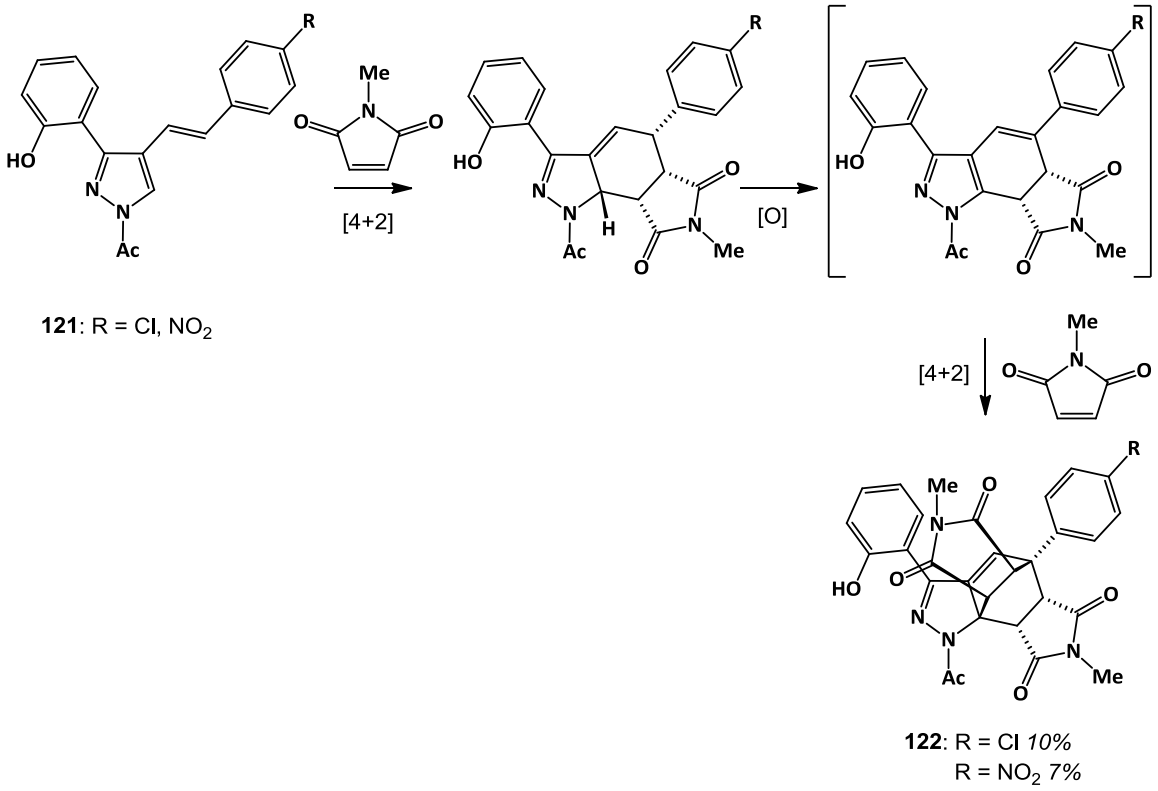
Scheme 1.50. Domino [4+2]/[4+2]/retro-Diels-Alder reaction.

Lovely *et al.*[44,116] witnessed the formation of an intriguing bis-Diels-Alder adduct resulting from a domino [4+2]-Diels-Alder/oxidation/[4+2]-Diels Alder reaction. In a study of the Diels-Alder reactions of 4-vinylimidazoles it was found that upon heating 1-benzyl-4-vinylimidazoles **116** and **117** with NPM in benzene at 90 °C, the bis-Diels-Alder adduct **118** could be isolated in low yields, along with a number of other interesting adducts arising from oxygenation (**119**) and full aromatisation (**120**, Scheme 1.51).



Scheme 1.51. Domino reaction leading to bis-Diels-Alder adduct **118**.

A further example of this domino [4+2]-Diels-Alder/oxidation/[4+2]-Diels-Alder reaction occurring with maleimides was witnessed by Silva *et al.*[117] The bis-Diels-Alder adduct **122** appeared in low yields (7-10%) as a by-product of Silva's investigations of the cycloaddition reactions of substituted vinyl-pyrazole **121** and NMM (Scheme 1.52).

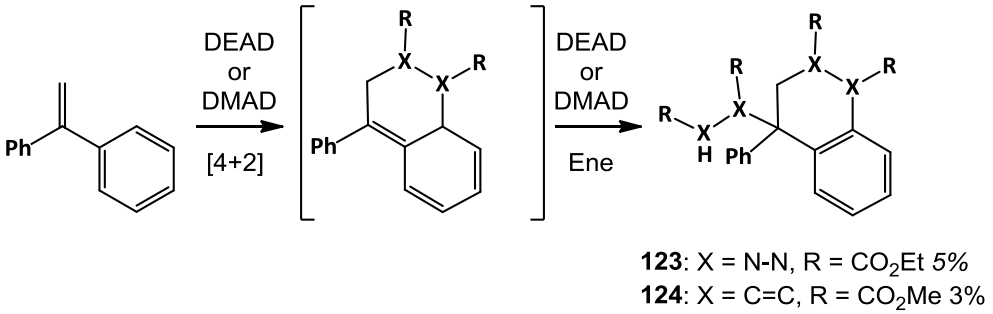


Scheme 1.52. Domino reaction leading to bis-Diels-Alder adduct **122**.

1.3.2.2 Domino Diels-Alder/Ene Reactions

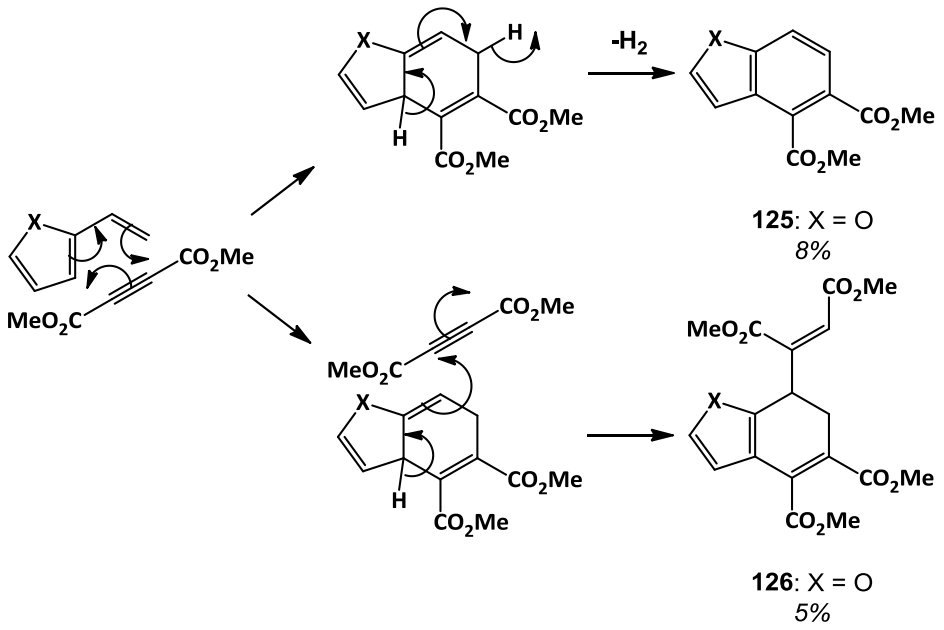
Domino Diels-Alder/ene reactions appear, by comparison, relatively infrequently in the literature. They appear most often as by-products of Diels-Alder reactions, usually in low yields (>10%). However, the occurrence of this reaction is not unreasonable, as many of the reactive electron-poor dienophiles employed in Diels-Alder reactions are also reactive enophiles. In a number of the initial Diels-Alder adducts arising from vinyl-heterocycles, the allylic C-H σ-bond is held co-planar with the newly formed electron-rich exocyclic C=C π-bond, in a geometry suitable for ene reaction. The occurrence of ene reaction could then allow rearomatisation of the heterocycle, which would be a further driving force for the reaction.

The earliest example of this reaction was reported by Alder in 1954,[118] as the reaction of 1,1-diphenylethylene with an excess of DEAD led to the 2:1 adduct **123** as the major component following a domino Diels-Alder/aza ene reaction. Very similar results were later observed by Millar and Richards,[119] who reacted 1,1-diphenylethylene with DMAD and obtained the 2:1 ene adduct **124** as the major product in 21% yield *via* a domino Diels-Alder/carba-ene reaction process (Scheme 1.53).



Scheme 1.53. Domino Diels-Alder/ene reactions with 1,1-diphenylethylene.

Davidson and Elix[24] were the first to observe this reaction with a vinyl-heteroaromatic, noting that reaction of 2-vinylfuran with DMAD at reflux in benzene over 24 h led to isolation of the oxidised adduct **125**, and the 2:1 ene adduct **126**, both in low yield (8 and 5% respectively), which the authors attributed to polymerisation of 2-vinylfuran. A general mechanism of this domino Diels-Alder/ene reaction and oxidation is shown in Scheme 1.54.

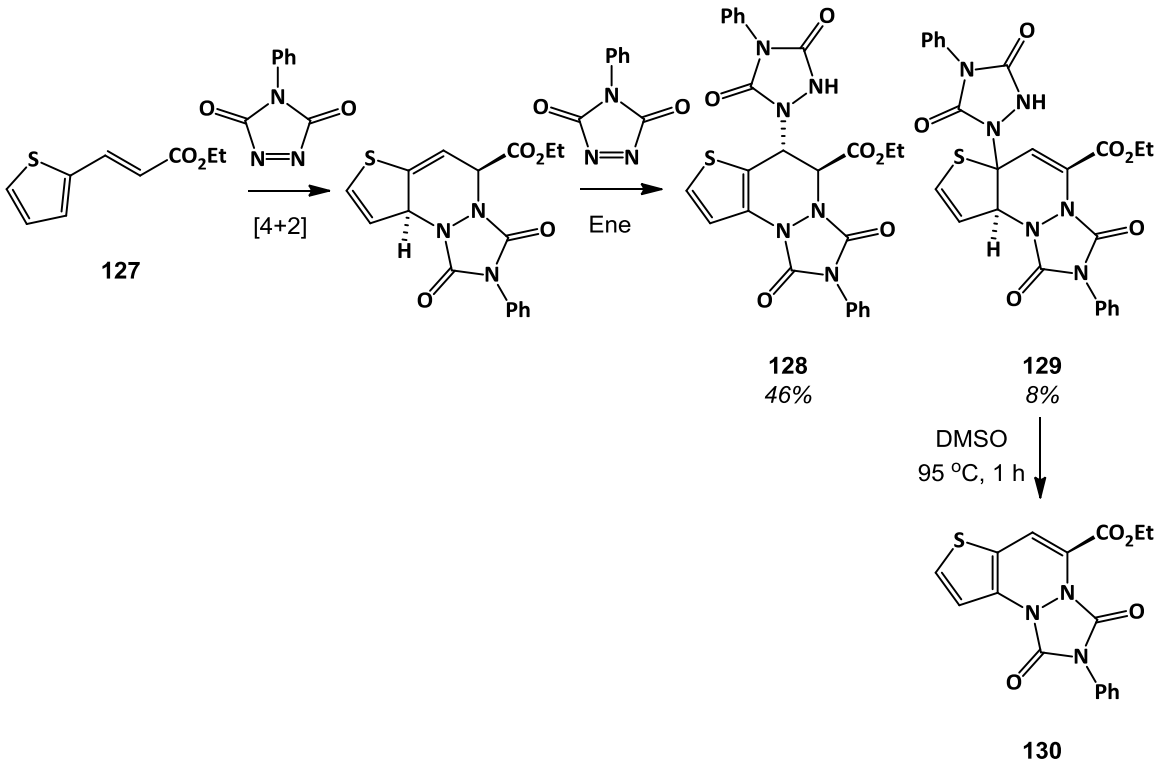


Scheme 1.54. General mechanism of cycloaddition, oxidation and ene reaction.

Analogous results were observed by Abarca *et al.* from reaction of both 2- and 3-vinylthiophene[32,33] and 4-vinylpyrazole[120] with DMAD, and by the Sepulveda-Arques group from reaction of 2-vinylpyrrole with diethyl azodicarboxylate.[121]

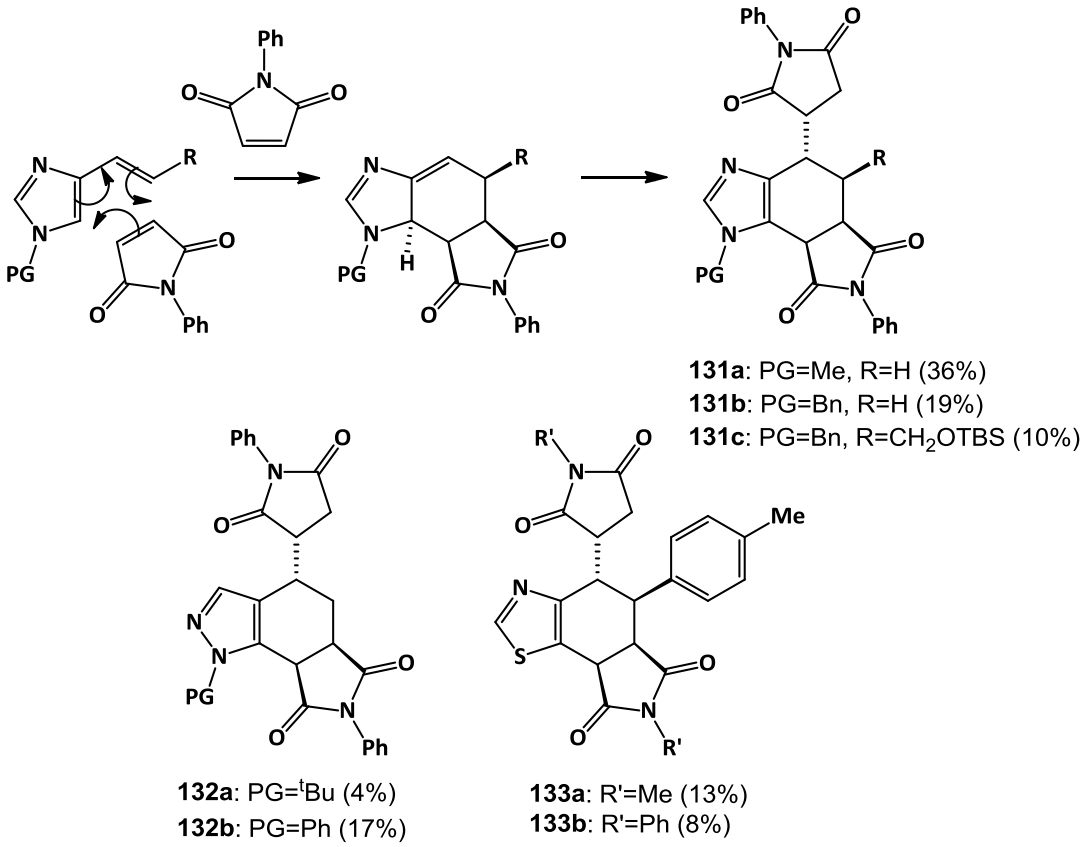
Moody *et al.*[35] found that addition of PTAD, one of the most reactive aza dienophiles, to vinylthiophene **127** resulted in two compounds, each appearing to be 2:1

adducts by mass spectrometry. On the basis of NMR data, Moody assigned them the structures **128** and **129**, both having resulted from an ene reaction at either end of the newly installed exocyclic double bond. The formation of the major adduct **128** involves rearomatisation of the thiophene, and this driving force and greater stability are reflected in the higher yield. The minor adduct **129** was much less stable and slowly decomposed, with a loss of PTAD on standing or within 1 h at 95 °C in DMSO to give **130** (Scheme 1.55).



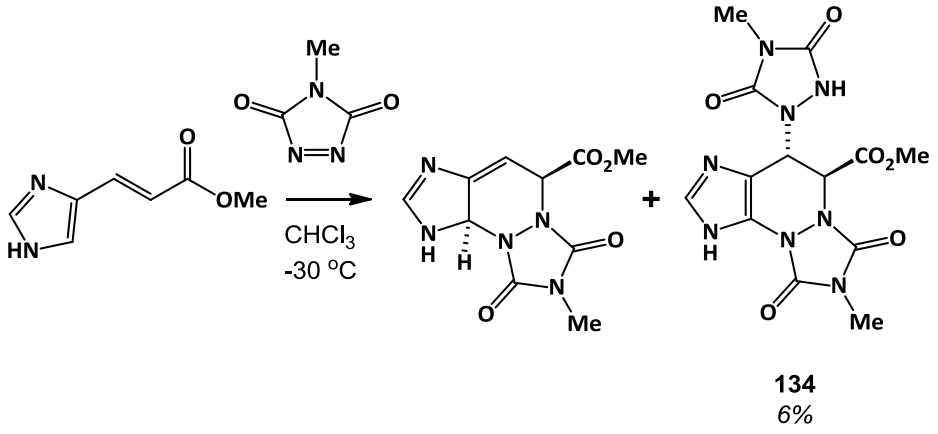
Scheme 1.55. Diels-Alder/ene reactions observed with vinylthiophene and PTAD.

Other groups have observed similar reactions with *N*-methyl-, *N*-ethyl- and NPM. Lovely *et al.*[44] noted the formation of ene-adduct **131** as a by-product from the reaction of 4-vinylimidazoles with NPM. Analogous results were reported by Sepulveda-Arques[36,37] for reactions of 4-vinylpyrazole with NPM (**132**), and by Cabrera *et al.*[122] for reactions of 4-vinylthiazole with *N*-methyl- and NPM (**133**, Scheme 1.56).



Scheme 1.56. Domino Diels-Alder/ene reactions observed with NPM.

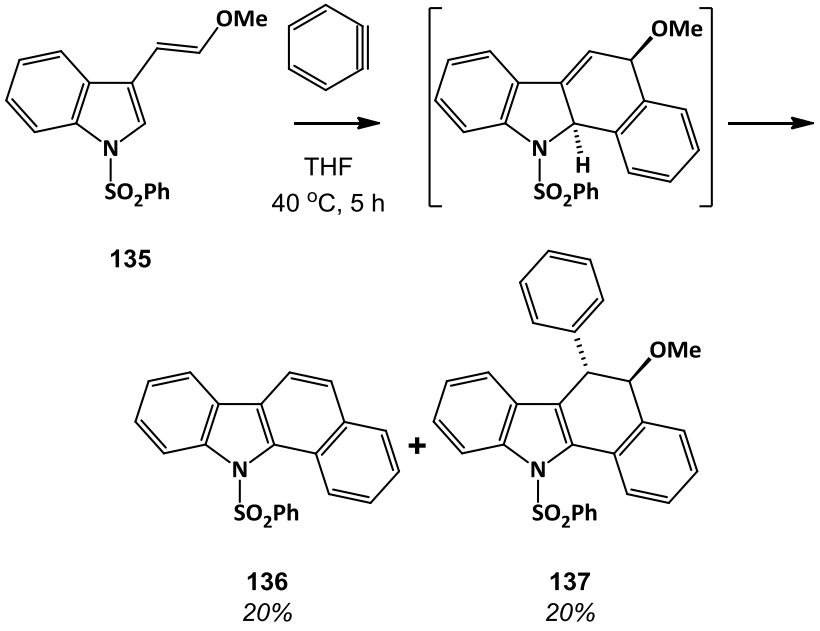
In work akin to that of the Lovely group, Roa and O'Shea[123] also observed the formation of the 2:1 ene adduct **134** upon reaction of methyl urocanate with MTAD at elevated temperatures. However, this product was only isolated in low yields (6%) in the presence of the initial Diels-Alder adduct, and readily decomposed (Scheme 1.57).



Scheme 1.57. Ene adduct formed from methyl urocanate and MTAD.

In an isolated aryne example, Gonzalez *et al.* also observed the formation of this 2:1 adduct in their studies of the Diels-Alder reaction of 3-vinylindoles with arynes.[124]

They found that on reaction with benzyne, substituted indole **135** gave the rearomatised Diels-Alder adduct **136** with the extrusion of methanol, and the 2:1 adduct **137** in equal quantities after 5 h at r.t. (Scheme 1.58).



Scheme 1.58. Domino reactions observed with benzyne.

The Gonzalez group were then able to structurally characterise this 2:1 adduct *via* single-crystal X-ray analysis (Figure 1.2). The crystal structure of **137** indicates the second equivalent of benzyne has added to the same face from which the hydrogen was abstracted. This is consistent with a concerted ene reaction occurring between benzyne and the *endo*-derived initial Diels-Alder adduct.

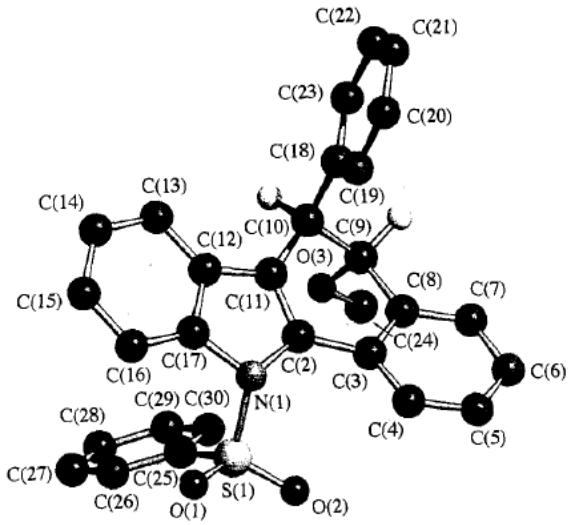
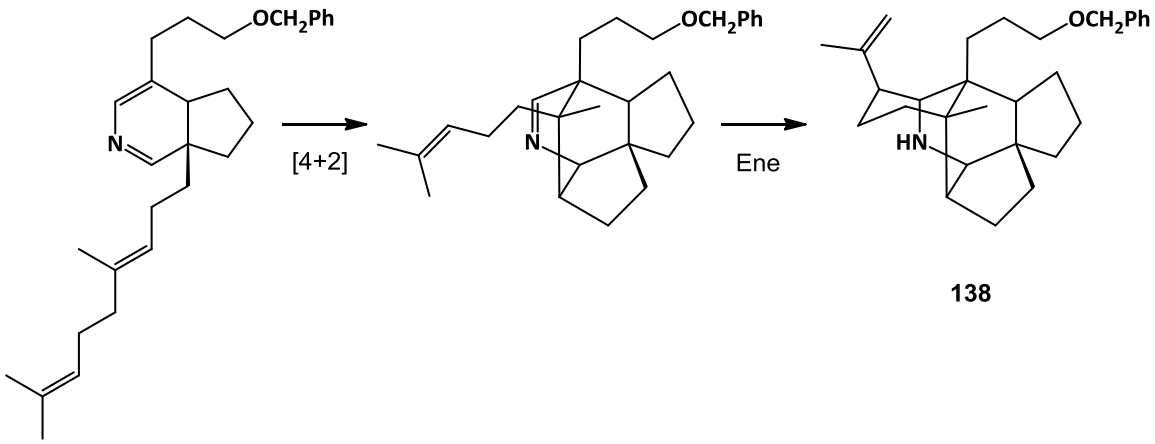


Figure 1.2. Gonzalez X-ray crystal structure of **137**.

The vast majority of the instances of this 2:1 domino ene adduct were reported as minor by-products in low yields (4-36%), usually in the presence of more substantial quantities of the initial Diels-Alder and rearomatised adducts. However, a small number of groups have purposefully employed selective Diels-Alder/ene domino reactions to access complex targets.

1.3.2.2.1 Selective Diels-Alder/Ene Domino Reactions

Heathcock *et al.*[125] were the first group to employ a selective domino Diels-Alder/ene reaction in their synthesis of the *Daphniphyllum* alkaloids. They utilised a domino hetero-Diels-Alder/ene reaction to afford the pentacyclic unsaturated amine **138**, as a precursor to (±)-methylhomosecodaphniphyllate (Scheme 1.59). They were able to successfully carry out the selective domino pericyclic reactions on up to 10 mmol scale, in excellent yields (~70-80%).



Scheme 1.59. Domino Diels-Alder/ene reaction in the synthesis of (±)-methylhomosecodaphniphyllate.

1.4 Conclusions

Vinyl- and substituted vinyl-heteroaromatics have been extensively studied and shown to undergo successful Diels-Alder reactions with a range of dienophiles. In addition, many of these reactions were found to be highly regio- and stereoselective, with the vast majority proceeding *via* extra-annular cycloaddition through an *endo*-transition state. Lewis-acid catalysis is generally not required as thermal reactions will proceed at accessible temperatures, ranging from -78 ^{o}C to 95 ^{o}C.

Whilst rearomatisation of the initially formed Diels-Alder adduct is a common occurrence with electron-rich heteroaromatics, this can be impeded by tailoring the reaction conditions in favour of lower temperatures and shorter reaction times.

In a limited number of examples, further reactions were observed, for example with a second molecule of diene or dienophile, leading to bis-Diels-Alder and ene adducts respectively. These adducts were typically observed in low yields as minor by-products. A single-crystal X-ray structure determination of the ene adduct **137** derived from 3-vinylindole **135** and *in-situ* generated benzyne was consistent with a concerted, *endo*-derived transition state for the ene reaction.

Chapter 2. Synthesis and Diels-Alder Chemistry of Vinyl-Heteroaromatics

2.1 Research Aims

The foregoing introduction has provided a broad overview of the intriguing chemistry associated with Diels-Alder reactions of vinyl-heteroaromatics, and has demonstrated the potential to synthesise structurally complex molecules from simple achiral precursors. In addition, the inclination of Diels-Alder cycloadducts to undergo further reaction was indicated *via* a number of examples of domino Diels-Alder/Diels-Alder and Diels-Alder/ene reactions, and two isolated examples of Diels-Alder/Michael-addition reaction sequences (see Scheme 2.30).

Within the scope of these reactions, the ultimate objective of the current research programme was to synthesise molecularly diverse, structurally complex molecules inspired by bioactive alkaloid-like architectures based on vinyl-heteroaromatics through a one-pot sequence. This objective comprises two key steps, which form the essence of the research described herein.

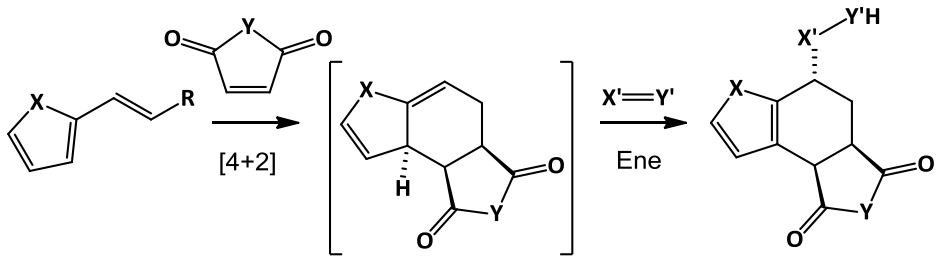
Step 1: the intermolecular Diels-Alder reaction of vinyl- and substituted vinyl-heteroaromatics with a range of dienophiles.

Step 2: the intermolecular ene reaction of Diels-Alder cycloadducts with a range of enophiles.

In view of this outlook, the primary focus of the research was to find a suitable method for the synthesis of vinyl- and substituted vinyl-heteroaromatics, and to examine their behaviour in intermolecular Diels-Alder reactions.

Following the identification of successful routes to vinyl-heteroaromatics and their corresponding cycloadducts, subsequent investigations will involve the optimisation of reaction conditions including temperature, solvent, reaction time, dienophile and protecting group (where applicable), as studies in the literature (see Chapter 1) have already highlighted these factors as instrumental in determining the product distribution.

We then aim to subject optimised Diels-Alder cycloadducts to selective sequential ene reactions with a range of reactive enophiles to create rapid two-step routes to functionally diverse, structurally complex compounds. Successful sequential Diels-Alder/ene reactions will then be examined in a one-pot synthesis to assess their viability for domino Diels-Alder/ene reaction sequences.

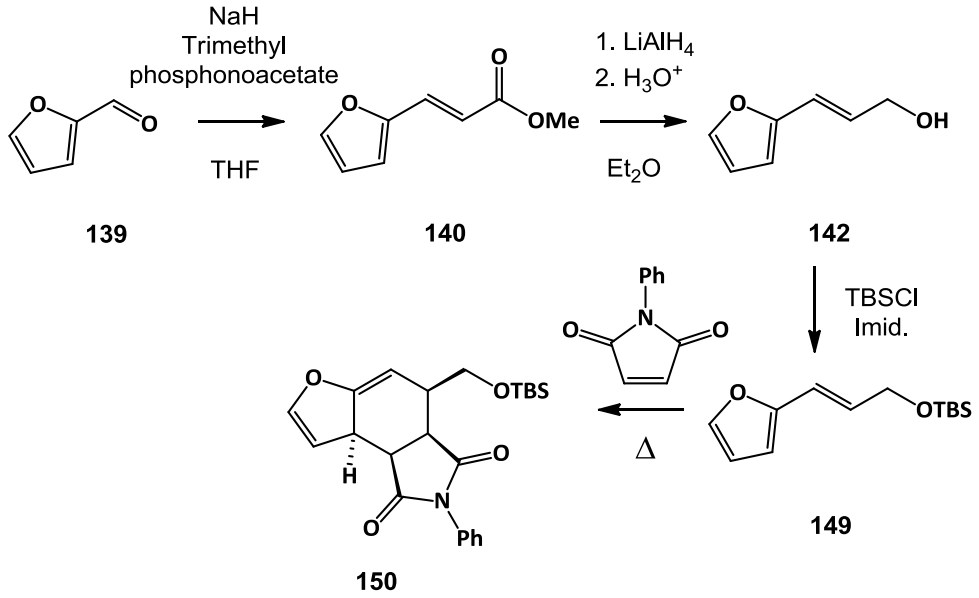


Scheme 2.1. One-pot domino Diels-Alder/ene reaction sequence.

2.2 Vinylfurans

2.2.1 Synthesis and Diels-Alder Cycloaddition of 149

In order to examine the Diels-Alder reactivity of substituted vinylfurans, furan-2-carboxaldehyde **139** was submitted to a Horner-Wadsworth-Emmons reaction, and the subsequent ester reduced to the primary alcohol and TBS protected to afford **149**. This was then submitted to Diels-Alder reaction with NPM (Scheme 2.2).



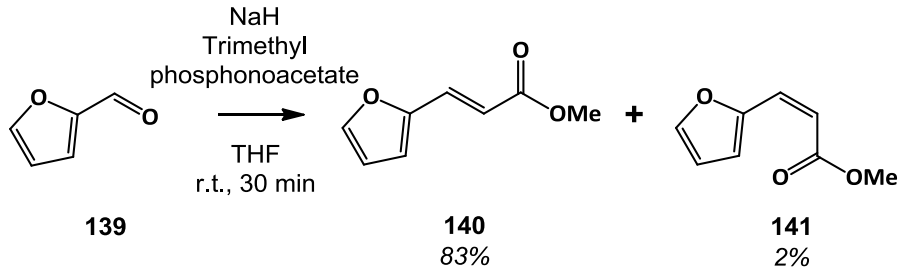
Scheme 2.2. Synthesis and Diels-Alder reaction of **149**.

2.2.1.1 Synthesis of (*E*)-Methyl 3-(furan-2-yl)acrylate (140)

The synthesis of 140 is shown in Scheme 2.3, and follows a literature preparation.[126] A Horner-Wadsworth-Emmons reaction was carried out on furan-2-carboxaldehyde **139**, using sodium hydride and trimethyl phosphonoacetate in THF at 0 ^{o}C. Following aqueous work-up, analysis of the crude reaction mixture by ^{1}H NMR spectroscopy indicated the loss of the singlet relating to the H of the aldehyde group of **139** at 9.64 ppm. In addition, the formation of two new compounds was evident, each with a pair of doublets, corresponding to the newly formed vinyl bonds in the *E* (**140**) and

Z (**141**) isomers of methyl 3-(furan-2-yl)acrylate.

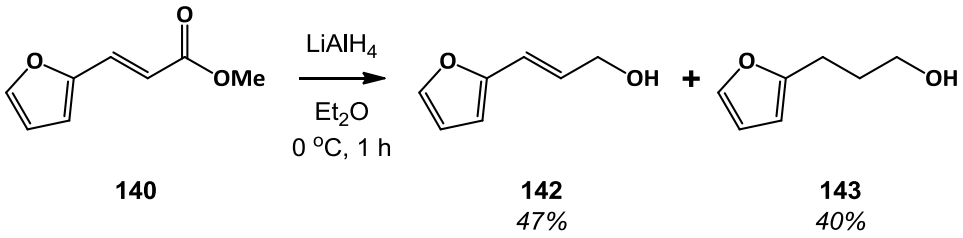
Both isomers could be distinguished by ^{1}H NMR spectroscopy, with the pair of doublets corresponding to the alkene in the *E*-isomer having the larger *trans* coupling constant of 15.8 Hz, compared to the *cis* coupling constant of 12.9 Hz of the *Z*-isomer. The *E* isomer was formed as the major product in 83% yield.



Scheme 2.3. Horner-Wadsworth-Emmons reaction to give **140**.

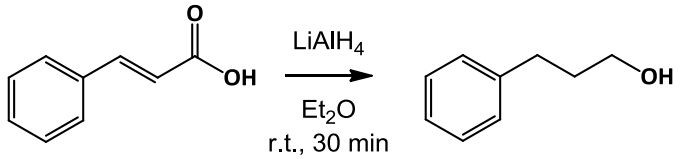
2.2.1.2 Synthesis of (*E*)-3-(furan-2-yl)prop-2-en-1-ol (142)

With **140** in hand, a suitable reducing agent was then required to reduce the α,β-unsaturated ester to the allylic alcohol. Following a literature procedure,[127] $LiAlH_4$ was stirred with the unsaturated ester **140** for 1 h at 0 ^oC in diethyl ether and the formation of a new, more polar compound was observed by TLC. Excess $LiAlH_4$ was then quenched with 28% $NH_4OH_{(aq)}$, and stirred for 2 h before the mixture was filtered through a pad of Celite. Following purification by flash column chromatography, analysis by ^{1}H NMR spectroscopy indicated the yellow oil contained two compounds of near identical R_f values. These were identified as the allylic alcohol **142**, and the over-reduced alcohol **143** which had suffered additional reduction of the alkene (Scheme 2.4).



Scheme 2.4. Reduction of **140** with $LiAlH_4$.

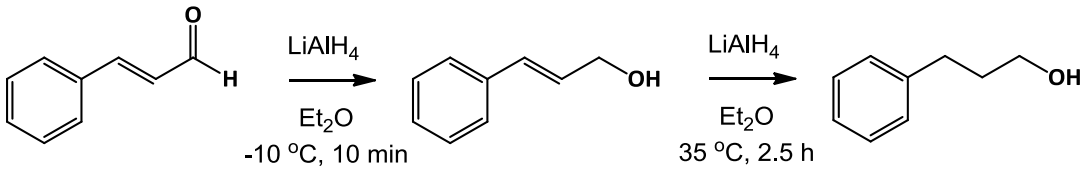
Examination of the literature showed precedent for this reaction, first reported by Nystrom and Brown in 1947.[128] In their studies of the reduction of a series of cyclic and acyclic carboxylic esters, they noted that cinnamic acid **144** underwent concurrent reduction of the carboxylic acid and the alkene double bond to give hydrocinnamyl alcohol **145** in 85% yield (Scheme 2.5).



144 **145**
85%

Scheme 2.5. Reduction of cinnamic acid with $LiAlH_4$ to give hydrocinnamyl alcohol.

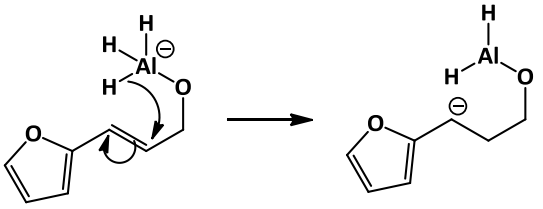
Further investigation by Hochstein and Brown[129] identified that reacting one equivalent of $LiAlH_4$ with compounds such as cinnamaldehyde **146** at low temperatures would yield cinnamyl alcohol **147** exclusively. A second equivalent and higher temperatures were required to afford the reduction to hydrocinnamyl alcohol **145** (Scheme 2.6), indicating that the reduction occurs sequentially, with the reduction of the alkene occurring more slowly than reduction of the carbonyl.



146 **147** **145**
90% *93%*

Scheme 2.6. Sequential reduction of cinnamic acid with $LiAlH_4$.

Franzus and Snyder[130] proposed the following mechanism; after reduction of the carbonyl, the resulting aluminium alkoxide is well placed to facilitate the transfer of a hydride intramolecularly to the alkene double bond (**148**). The resulting benzylic carbanion could then be stabilised through conjugation with the furan π-system (Scheme 2.7).



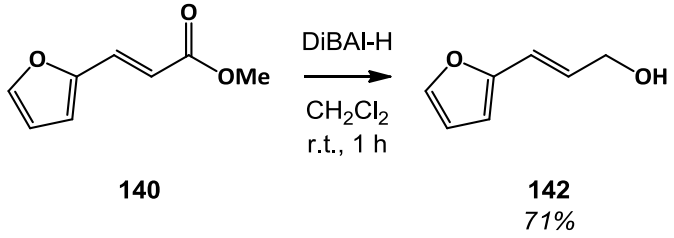
148

Scheme 2.7. Intramolecular hydride reduction of vinylic alkene by $LiAlH_4$.

In order to prevent the occurrence of over-reduction, diisobutylaluminium hydride

(DiBAl-H) was employed. The use of DiBAl-H leads to the generation of a tetrahedral intermediate which is unable to facilitate a hydride to the vinylic alkene, thus preventing over-reduction.

After stirring for 1 h at -78 ^{o}C the reaction was quenched with water/NaOH and filtered through a pad of Celite. Analysis of the crude material by ^{1}H NMR spectroscopy revealed the loss of the singlet relating to the methyl group of the ester at 3.80 ppm, and no evidence of double bond reduction was observed. The product could then be isolated by flash column chromatography.

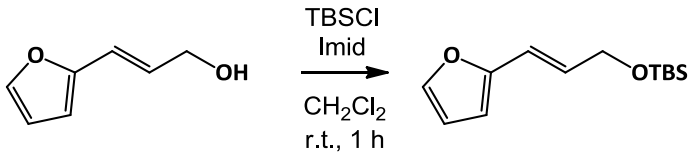


140 **142**
71%

Scheme 2.8. DiBAl-H reduction of α,β-unsaturated ester **140.**

2.2.1.3 Synthesis of ((*E*)-3-(furan-2-yl)allyloxy)(*tert*-butyl)dimethylsilane (149)

The silyl protection of the terminal alcohol of (*E*)-3-(furan-2-yl)prop-2-en-1-ol **142** was performed with *tert*-butylchlorodimethylsilane (TBS) and imidazole in CH_2Cl_2 at r.t., as shown in Scheme 2.9. It proceeded cleanly, giving the product (**149**) in modest yield (49%). The ^{1}H NMR spectrum clearly showed a gain of 15 protons, with singlet peaks integrating to 6H and 9H at 0.95 and 0.12 ppm, corresponding to the *tert*-butyl and dimethyl protons respectively.



142 **149**
49%

Scheme 2.9. Protection of allylic alcohol **142** with *tert*-butylchlorodimethylsilane.

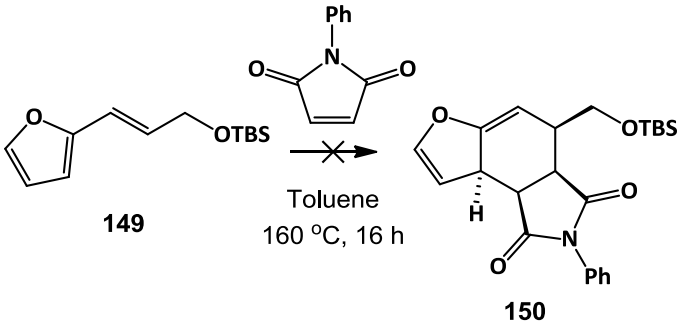
2.2.1.4 Synthesis of (3a*R*,4*R*,8b*S*)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-phenyl-3a,4,8a,8b-tetrahydro-1*H*-furo[3,2-*e*]isoindole-1,3(2*H*)-dione (150)

With ((*E*)-3-(furan-2-yl)allyloxy)(*tert*-butyl)dimethylsilane (**149**) in hand, its ability to engage in Diels-Alder reactions was then investigated. NPM has been

successfully employed as a reactive dienophile in a large number of Diels-Alder reactions (see Chapter 1), and so this was the dienophile utilised initially.

149 was heated in toluene to 50 ^{o}C in a sealed tube with 2.5 equivalents of NPM for 16 h, and monitored by TLC and ^{1}H NMR spectroscopy. No reaction was observed to occur over this time and so the reaction was heated to 110 ^{o}C in toluene for a further 16 h. The reaction still failed to progress and so was heated to 160 ^{o}C and stirred for an additional 16 h. Analysis by TLC showed the formation of three additional spots, and the ^{1}H NMR spectrum showed a number of new multiplets between 2.0 and 4.5 ppm, which would be consistent with a cycloadduct.

Purification by column chromatography yielded three fractions; the first eluted was recovered NPM, the second and third compounds, despite repeated attempts, could not be isolated cleanly. It is possible that the product was subject to further *in situ* domino reactions, or suffered from degradation, as furan species are prone to hydrolysis to 1,4-dicarbonyls.



Scheme 2.10. Diels-Alder reaction of **149** with NPM.

2.2.2 Conclusions

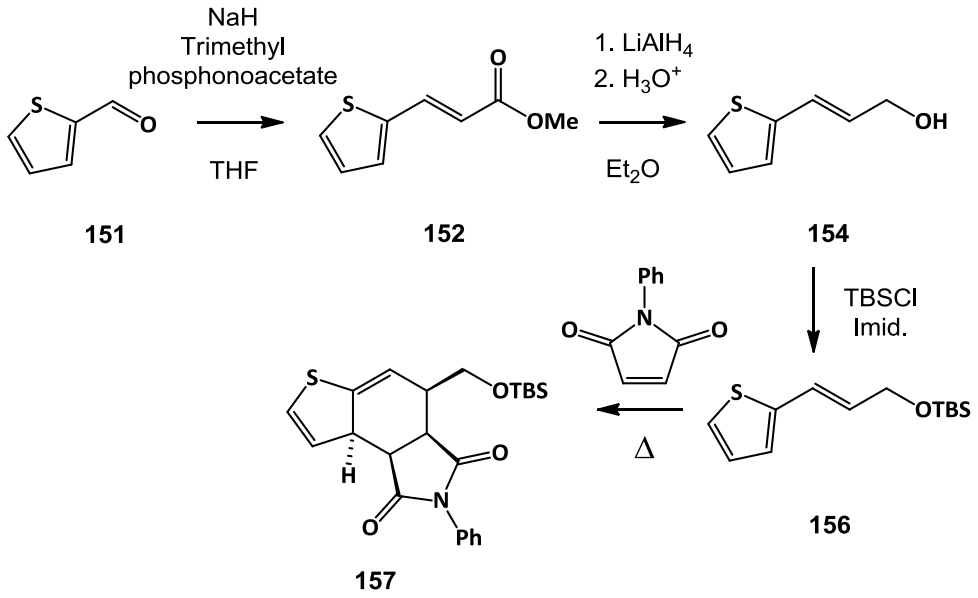
The [4+2] cycloaddition reaction of vinylfuran **149** and NPM did not proceed cleanly, and no Diels-Alder cycloadducts could be successfully isolated. However, the appearance of a number of complex multiplets in the ^{1}H NMR spectrum is encouraging, but it is likely that these cycloadducts are undergoing further reaction (i.e. rearomatisation, ene reaction, decomposition etc.) before they are isolated.

This is consistent with examples in the literature in which electron-rich vinylfurans will undergo Diels-Alder cycloaddition with NPM, but then undergo subsequent rearomatisation under the reaction conditions to give the rearomatised and air oxidised species (see Chapter 1).[12,21,22]

2.3 Vinylthiophenes

2.3.1 Synthesis and Diels-Alder Cycloaddition of 156

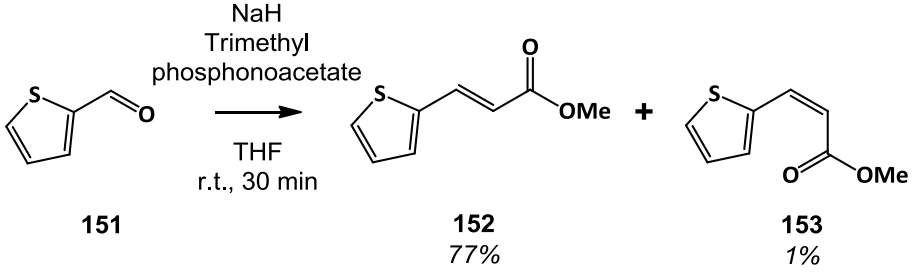
The Diels-Alder reactivity of substituted vinylthiophenes was examined analogously to that of vinylfurans. Thiophene-2-carboxaldehyde **151** was submitted to a Horner-Wadsworth-Emmons reaction, and the subsequent ester reduced to the primary alcohol and TBS protected to afford **156**. This was then submitted to Diels-Alder reaction with NPM (Scheme 2.11).



Scheme 2.11. Synthesis and Diels-Alder reaction of **156**.

2.3.1.1 Synthesis of (*E*)-methyl 3-(thiophen-2-yl)acrylate (152)

The Horner-Wadsworth-Emmons reaction of thiophene-2-carbaldehyde (**151**) was carried out analogously to that of the furan derivative with trimethyl phosphonoacetate and sodium hydride in THF at 0 ^{o}C (Scheme 2.12). No starting materials were visible by TLC after 1 h, and following aqueous work-up and purification by chromatography, the desired compound was isolated in 77% yield of *E*-isomer (**152**), and 1% yield of *Z*-isomer (**153**).

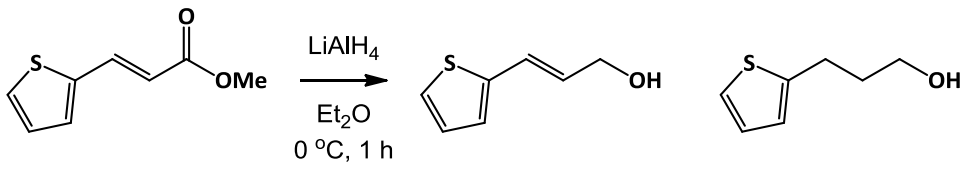


Scheme 2.12. Horner-Wadsworth-Emmons reaction of **151**.

The ^{1}H NMR spectra of these compounds were comparable to those of the furan derivatives, with the alkene double bond of the *E*-isomer having the larger *trans* coupling constant of 15.7 Hz compared to the 12.5 Hz *cis* coupling constant of the *Z*-isomer.

2.3.1.2 (*E*)-3-(thiophen-2-yl)prop-2-en-1-ol (154)

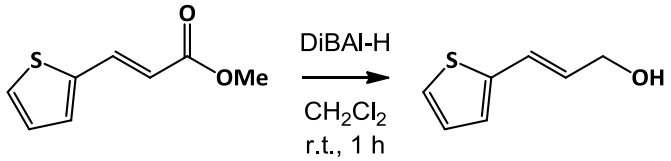
Subsequent reduction of the α,β-unsaturated ester **152** to allylic alcohol **154** was carried out analogously to the vinylfuran case, initially employing $LiAlH_4$ in diethyl ether at 0 ^oC. The reaction was monitored by TLC and appeared to proceed cleanly to a single product spot of lower polarity, consistent with an ester-alcohol transformation. Following purification by flash column chromatography however, the desired allylic alcohol **154** was evident alongside the over-reduced species **155**, which appeared to be the major product (Scheme 2.13). All efforts to obtain either compound cleanly by chromatography failed due to the great similarity in R_f of both compounds.



152 **154** *32%* **155** *54%*

Scheme 2.13. Reduction of **152** with $LiAlH_4$, yields calculated by comparison of ^{1}H NMR intensity.

As with the furan case, the milder reducing agent DiBAl-H was then adopted. Following stirring for 1 h in CH_2Cl_2 at -78 ^oC, the allylic alcohol **154** was the only observable product by analysis of the crude mixture by ^{1}H NMR spectroscopy. This was evidenced by the loss of the methyl ester singlet at 3.81 ppm, the formation of a doublet of doublet of doublets at 4.30 ppm corresponding to the allylic CH_2, and the doublet and doublet of triplets at 6.77 and 6.22 ppm relating to the intact vinylic HC=CH bond. Following purification by flash column chromatography, the desired product was isolated in near quantitative yield (Scheme 2.14).

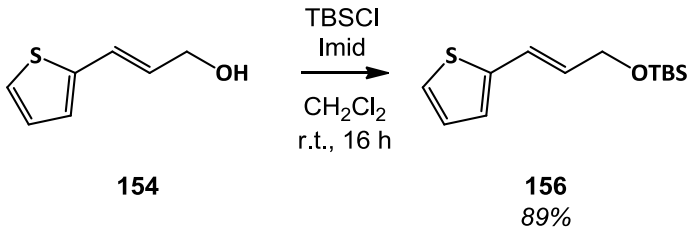


152 **154** *98%*

Scheme 2.14. Reduction of **152**with DiBAl-H.

2.3.1.3 Synthesis of ((*E*)-3-thiophen-2-yl)allyloxy)(*tert*-butyl)dimethylsilane (156)

Silyl protection of the terminal alcohol of (*E*)-3-(thiophene-2-yl)prop-2-en-1-ol **154** was carried out with *tert*-butyldimethylsilyl chloride and imidazole in CH_2Cl_2 at r.t., as shown in Scheme 2.15. The product was obtained in good yield, and isolated by flash column chromatography. Analysis by ^{1}H NMR spectroscopy was consistent with the loss of the OH signal at 1.66 ppm, and the gain of 15 protons corresponding to the *tert*-butyl and dimethyl protons of the TBDMS group at 0.96 ppm and 0.13 ppm respectively.

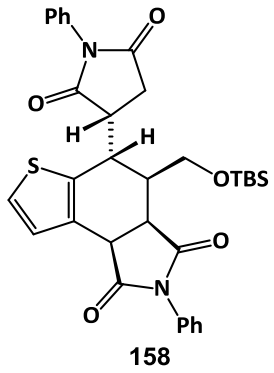


Scheme 2.15. TBS protection of allylic alcohol **154**.

2.3.1.4 Synthesis of (3a*S*,4*S*,8b*S*)-4,5-dihydro-4-*tert*-butyldimethylsilyloxymethyl-5-((3*S*)2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-phenyl-2*H*-thieno[3,2-*e*]isoindole-1,3(3a*H*,8b*H*)-dione (157)

Following silyl protection, the substituted vinylthiophene **156** was then subjected to Diels-Alder reaction conditions, analogous to the furan case, with 2.5 equivalents of NPM in toluene in a sealed tube. As with furan, no reaction was observed at temperatures lower than 160 ^{o}C, but following 16 h at 160 ^{o}C, a single new spot was evident by TLC. Purification by flash column chromatography led to the recovery of minor quantities of starting material and NPM, and a third compound (**158**) in 29% yield which appeared to be a cycloadduct on examination of the ^{1}H NMR spectrum. The purified compound was subjected to mass spectrometry which gave a parent ion of m/z 623.2022, consistent with a formula of $C_{33}H_{36}N_2O_5SSi.Na$, thus suggesting a reaction between vinylthiophene **156** and two molecules of NPM as a 2:1 adduct.

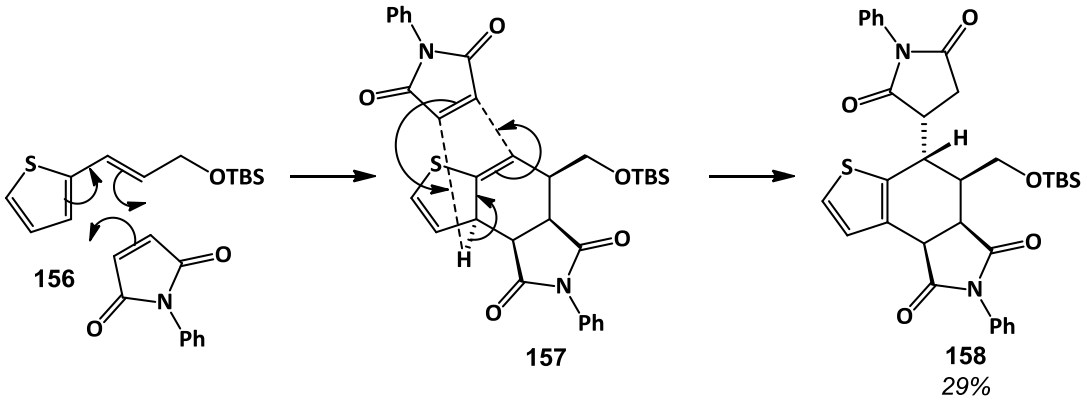
Literature precedent[32,33,35] would suggest that the second molecule of NPM should be incorporated *via* an ene reaction, to give the structure shown in Figure 2.1. ^{1}H and ^{13}C NMR spectroscopy were consistent with this structure, and further analysis by COSY, NOESY and DEPT ^{13}C NMR spectroscopy indicated two CH_2 environments, which would also be consistent with **158**.



158

Figure 2.1. Proposed structure of **158**.

We propose that compound **156** has undergone a Diels-Alder reaction with NPM to give **157**, followed by a concerted ene reaction with a second equivalent of NPM to give the 2:1 ene adduct **158** (Scheme 2.16).



Scheme 2.16. Domino Diels-Alder/ene reaction of **156**.

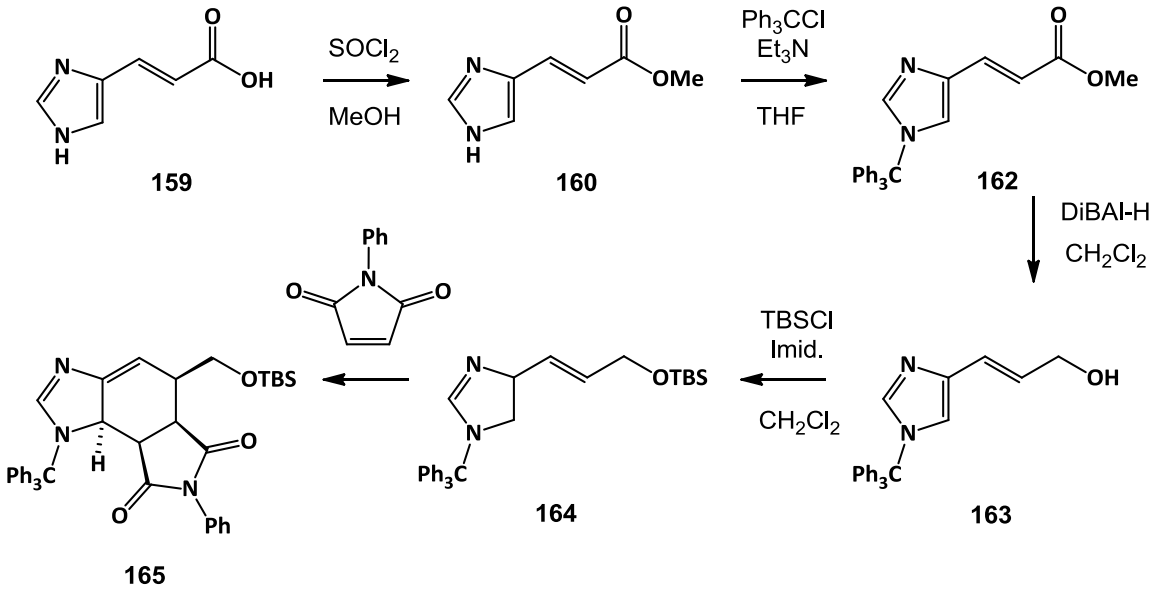
2.3.2 Conclusions

The [4+2] cycloaddition reaction of vinylthiophene **156** and NPM was successful, although the initial Diels-Alder adduct could not be isolated. The only isolable product was a 2:1 adduct **158**, having arisen from an ene reaction of the Diels-Alder cycloadduct with a second equivalent of NPM. This domino Diels-Alder/ene reaction is not uncommon for vinylthiophenes (see Chapter 1), although it is to our knowledge, the first example in which the ene adduct is the only product isolated.

2.4 Vinylimidazoles

2.4.1 Synthesis and Diels-Alder reaction of 1-trityl-4-((*E*)-3-(*tert*-butyldimethylsilyloxy)prop-1-enyl)-1*H*-imidazole (164)

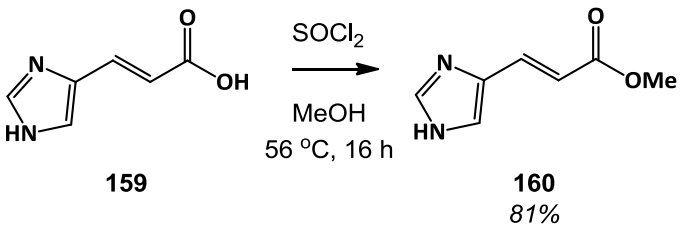
The substituted-vinylimidazole **164** was synthesised *via* methylation of urocanic acid (**159**), followed by tritylation of the least sterically hindered nitrogen, reduction to the primary alcohol and TBS protection. **164** was then submitted to Diels-Alder reaction with NPM (Scheme 2.17).



Scheme 2.17. Synthesis and Diels-Alder reaction of **164**.

2.4.1.1 Synthesis of methyl urocanate (160)

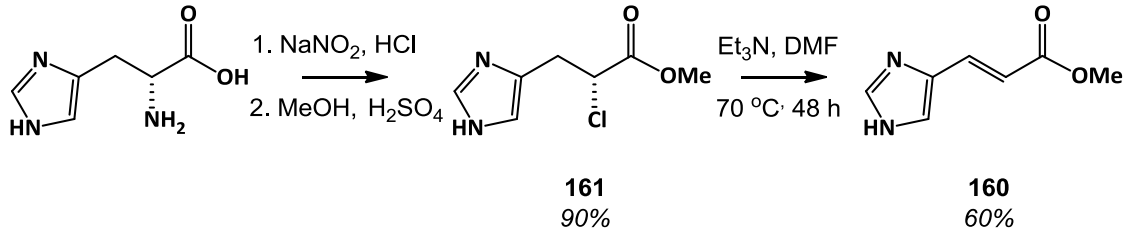
Methyl urocanate **160** was synthesised from the commercially available urocanic acid (**159**) following a literature procedure,[131] as shown in Scheme 2.18, providing **160** in good yield (81%).



Scheme 2.18. Esterification of urocanic acid.

This method of accessing methyl urocanate was suitable for our needs, although other groups have employed alternative methods, including Wittig and Horner-

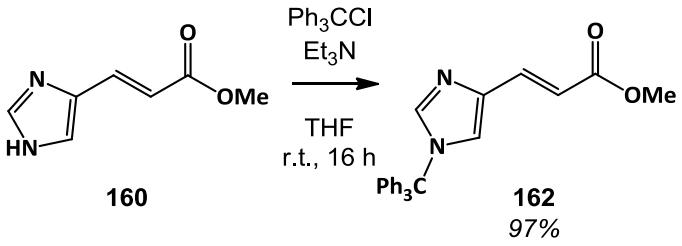
Wadsworth-Emmons reactions from imidazole-4-carboxaldehydes.[132] Lovely *et al*. developed a method to access methyl urocanate from histidine through diazotisation of the amino group to give the α-chloro acid **161**, followed by elimination of HCl to give alkene **160** (Scheme 2.19). These methods can be advantageous as the commercial supply of urocanic acid, synthesised *via* an enzymatic elimination of ammonia from histidine, is limited and variable.[133]



Scheme 2.19. Synthesis of methyl urocanate (**160**) from histidine.

2.4.1.2 Synthesis of (*E*)-methyl 3-(1-trityl-1*H*-imidazol-4-yl)acrylate (162)

With methyl urocanate in hand, trityl protection was carried out using triphenylmethyl chloride and triethylamine in THF. The trityl group was specifically chosen as the protecting group due to its bulky nature, allowing regioselective protection of the least sterically hindered N1 nitrogen over the more hindered N3. Analysis of the ^{1}H NMR spectrum showed the presence of a single regioisomer which was consistent with literature values,[134] indicating that the least sterically hindered nitrogen was protected in near quantitative yield (Scheme 2.20).



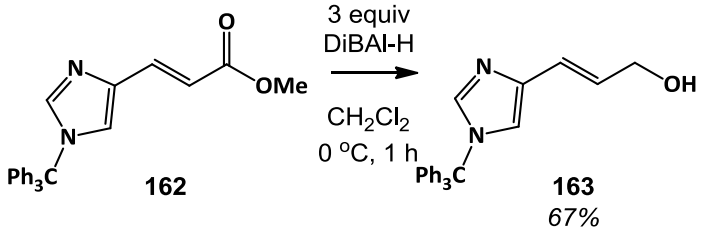
Scheme 2.20. Protection of **160** with triphenylmethyl chloride.

2.4.1.3 Synthesis of (*E*)-3-(1-trityl-1*H*-imidazol-4-yl)prop-2-en-1-ol (163)

Methyl ester **162** was then reduced to the terminal alcohol using DiBAl-H at 0 °C in CH_2Cl_2. The reaction was quenched by the slow addition into 1 M HCl/ice, basified with 1 M NaOH and extracted with ethyl acetate, according to a literature procedure.[135] The product could then purified by flash column chromatography to give **163** in moderate yield (67%, Scheme 2.21).

Analysis of the ^{1}H NMR spectrum indicated the formation of a new CH_2 signal as a doublet at 4.27 ppm, J = 4.1 Hz. It also showed the alkene double bond was still intact and over-reduction had not occurred, as in the case of substituted vinylfuran **142** and vinylthiophene **154**. This was evidenced by the overlapping signals at 6.44-6.46 ppm corresponding to the doublet and doublet of triplets of the vinylic HC=CH.

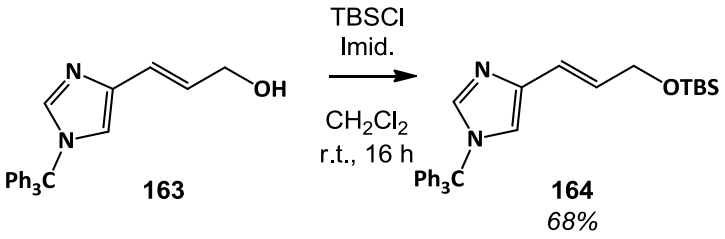
The reduced yield of this reaction can be related to loss of material during isolation of the product from aluminium salts generated in the aqueous work-up. Attempts were made to avoid this loss using standard DiBAl-H work-up methods, including acidic and basic work-up conditions, and quenching with a methanol/water mixture. Unfortunately, these attempts did not improve the yield.



Scheme 2.21. Reduction of **162** with DiBAl-H.

2.4.1.4 Synthesis of 1-trityl-4-((*E*)-3-(*tert*-butyldimethylsilyloxy)prop-1-enyl)-1*H*-imidazole (164)

Silyl protection of the allylic alcohol **163** was carried out with *tert*-butyldimethylsilyl chloride and imidazole in CH_2Cl_2 at r.t. overnight. The reaction proceeded smoothly and the expected product was isolated by flash column chromatography in reasonable yield (68%), and both ^{1}H and ^{13}C NMR spectra of the purified compound were consistent.



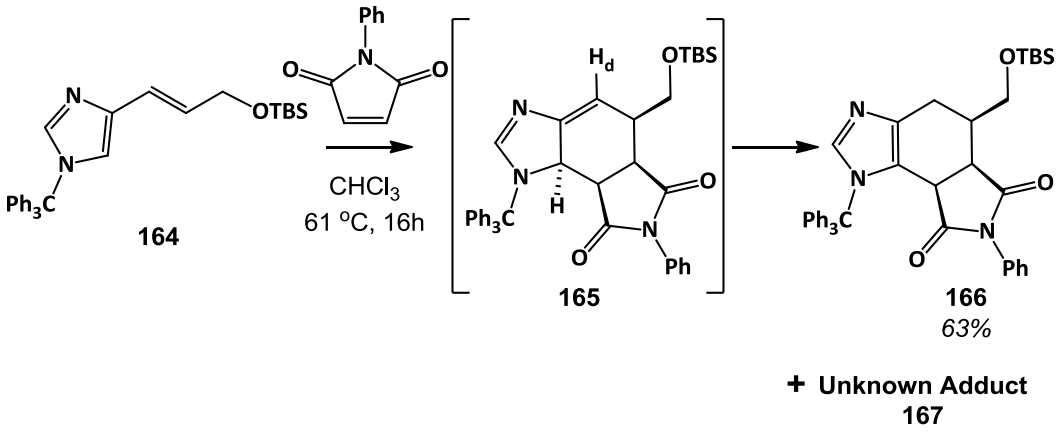
Scheme 2.22. Protection of **163** with *tert*-butyldimethylsilyl chloride.

2.4.1.5 Diels-Alder reaction of 1-trityl-4-((*E*)-3-(*tert*-butyldimethylsilyloxy)prop-1-enyl)-1*H*-imidazole (164) with NPM

With the trityl-protected substituted-vinylimidazole **164** in hand, its ability to

engage in Diels-Alder reactions was then investigated. Lovely *et al*. have previously reported successful thermal Diels-Alder reactions of methylene-OTBS substituted-vinylimidazoles with the reactive dienophile NPM,[44] and so this was the dienophile utilised initially. The reaction was performed with 2.5 equivalents of NPM, stirring at reflux in chloroform for 24 h, analogous to literature conditions. However, this was found to lead to a mixture of two compounds, characterised as **165** and **166**, and a large proportion of unchanged starting material.

The reaction was then repeated in toluene at 110 ^{o}C and after 16 h, examination of the crude reaction mixture by ^{1}H NMR spectroscopy indicated the disappearance of the vinylimidazole starting material, and the formation of two major adducts. These adducts were conveniently separated by flash column chromatography and analysed by ^{1}H NMR spectroscopy. The spectrum of the major adduct appeared to have 7 proton signals in the aliphatic region, which would be consistent with both the initial Diels-Alder enamine **165** and the rearomatised imidazole **166** (Scheme 2.23). However, the enamine would be expected to have a downfield proton signal corresponding to that of the exocyclic double bond (H_d), at around 5.0-6.0 ppm, which was noticeably absent.



Scheme 2.23. Diels-Alder reaction of **164** and NPM.

The purified compound was subjected to mass spectrometry which gave a parent ion of m/z 654.3145, consistent with a formula of $C_{41}H_{44}N_3O_3Si$. This molecular mass could correspond to either the initial Diels-Alder enamine or the isomeric rearomatised adduct.

Further NMR analysis by COSY and ^{13}C DEPT spectroscopy indicated the presence of two CH_2 groups, which would be inconsistent with **165**, which has a single CH_2 on the methylene OTBS. The rearomatised imidazole has an additional CH_2 α to the imidazole ring, and so the major adduct was assigned the structure corresponding to

rearomatised imidazole **166**. The minor compound was initially assigned unknown adduct **167** (Scheme 2.23).

To verify the structure of the major adduct, crystals were grown from slow diffusion of diethyl ether/pentane, and examined *via* single crystal X-ray crystallography. This analysis confirmed the occurrence of rearomatisation to reform the imidazole ring. In addition, the crystal structure revealed a hitherto unobserved trityl migration from N1→N3. We therefore found the major adduct to in fact be the N1→N3 trityl-migrated species **168** (Figure 2.2).

We attempted to confirm this assignment by NMR spectroscopy, using NOESY and ROESY experiments to elucidate the location of the trityl group, however these experiments proved inconclusive.

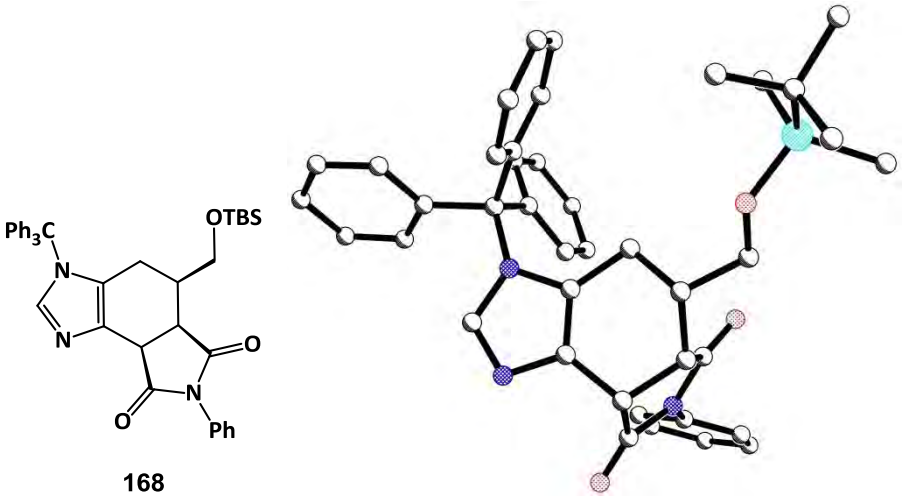
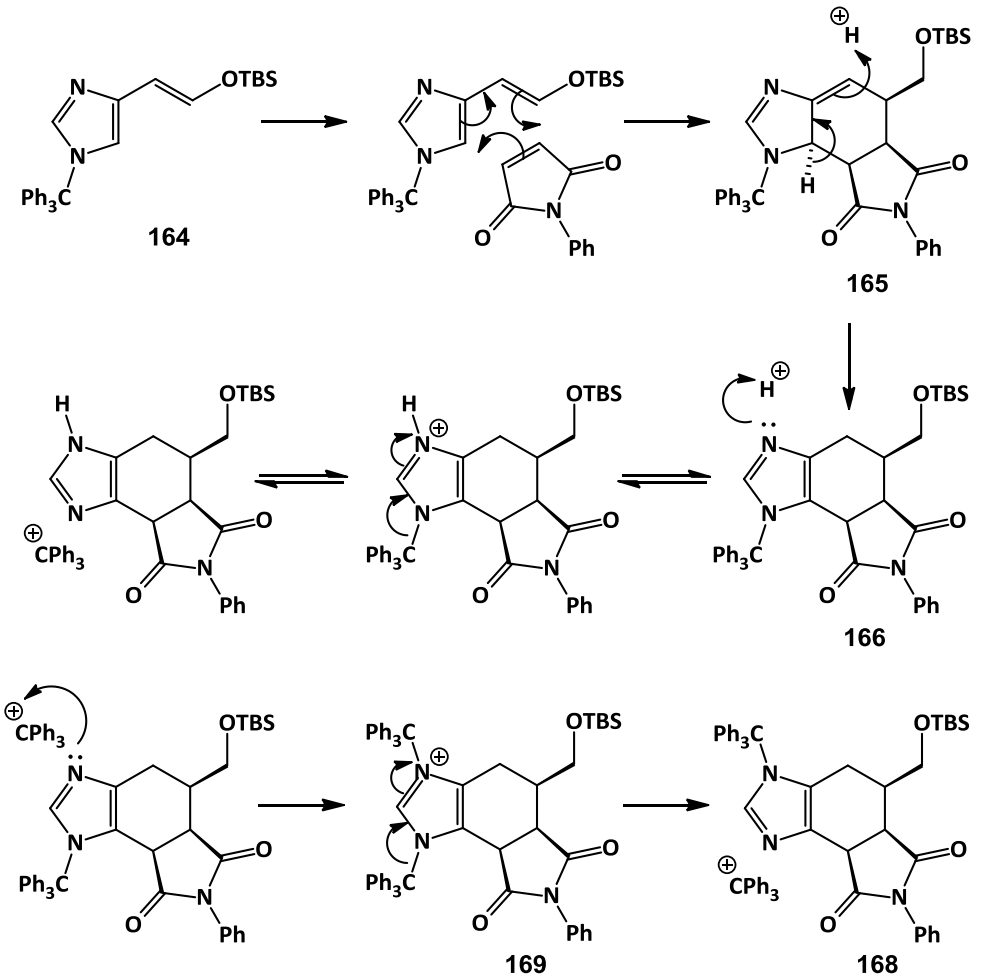


Figure 2.2. X-ray crystal structure of **168**. Hydrogens removed for clarity.

We believe that compound **164** undergoes a Diels-Alder reaction to give **165**, followed by a domino [1,3]-H migration to give **166**. The observed trityl migration may then arise through the addition of an electrophile/proton to the imidazole N lone pair of **166**, generating an imidazolium cation. Loss of a trityl cation followed by trapping by another molecule of **166** would result in a di-tritylated imidazolium cation **169**, which can in turn lose the most sterically hindered trityl to give **168** and propagate the reaction (Scheme 2.24). This mechanism is in agreement with that proposed previously by Bhagavatula[136] and Lovely[137] for the isomerisation of substituted imidazoles with the *N*-protecting groups Bn, SEM, MOM and DMAS, but has not previously been described for trityl protecting groups.



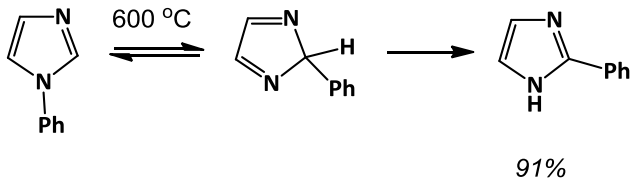
Scheme 2.24. Proposed mechanism for generation of a trityl cation and domino Diels-Alder/[1,3]-H shift/[1,3]-trityl migration.

2.4.2 Migrations

2.4.2.1 N1→C Migrations

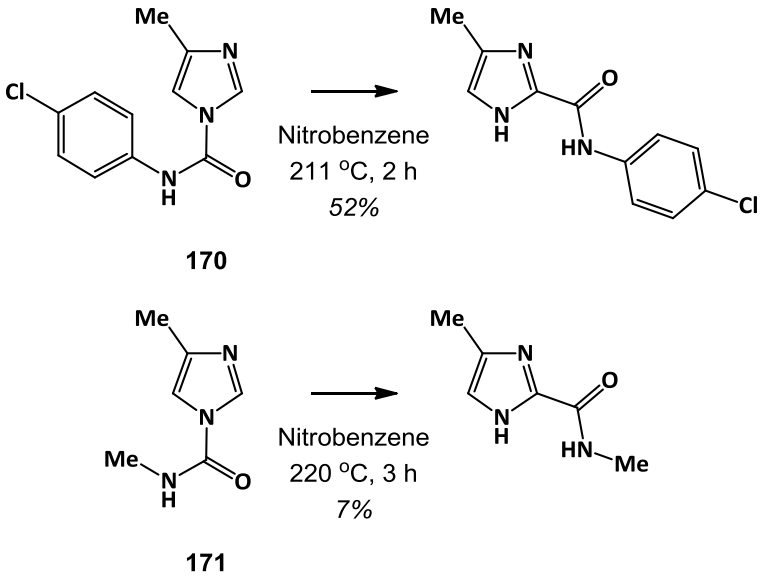
Migrations of alkyl groups on imidazole moieties have previously been reported under the conditions of flash vacuum pyrolysis *via* concerted [1,5]-sigmatropic rearrangements from the N1 to the C5 position.

Begg *et al.*[138] found that when passing through a silica tube at 530-600 ^{o}C, imidazoles substituted at the 1-position with a range of alkyl groups would rearrange to form mainly the 2-substituted isomers in good to excellent yields (60-100%), as shown in Scheme 2.25.



Scheme 2.25. N1→C2 migration of phenyl in 1-phenylimidazole.

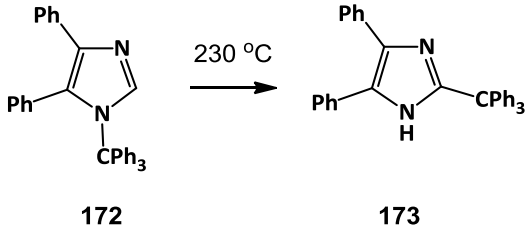
Mitsuhashi *et al.*[139] observed a similar migration from N1 to C2 with 1-carbamoyl-4-methylimidazoles. They found that when heating **170** in nitrobenzene at 211 °C for 2 h, or heating **171** in nitrobenzene in a sealed tube for 3 h at 220 °C, that migration to 2-carbamoyl-4-methylimidazoles would occur (Scheme 2.26).



Scheme 2.26. N1 to C2 migration of 1-carbamoyl-4-methylimidazoles.

2.4.2.2 N1→C2 migrations of trityl moiety

Giesemann and co-workers[140] found that on melting at 230 °C, 1-trityl-4,5-diphenylimidazole **172** would undergo a trityl migration from N1 to C2, to give 2-trityl-4,5-diphenylimidazole **173** (Scheme 2.27).

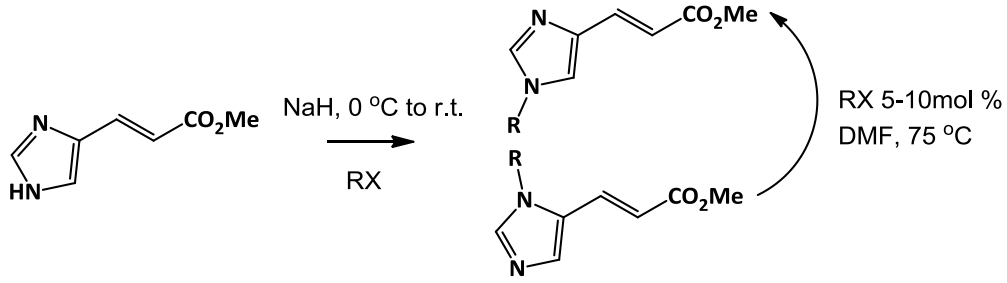


Scheme 2.27. Giesemann trityl migration from N1 to C2.

Evidently, all of the known examples of the migrations of alkyl groups in imidazoles from N1 to carbon require very high temperatures, in excess of 200 ^{o}C.

2.4.2.3 N1→N3 migrations

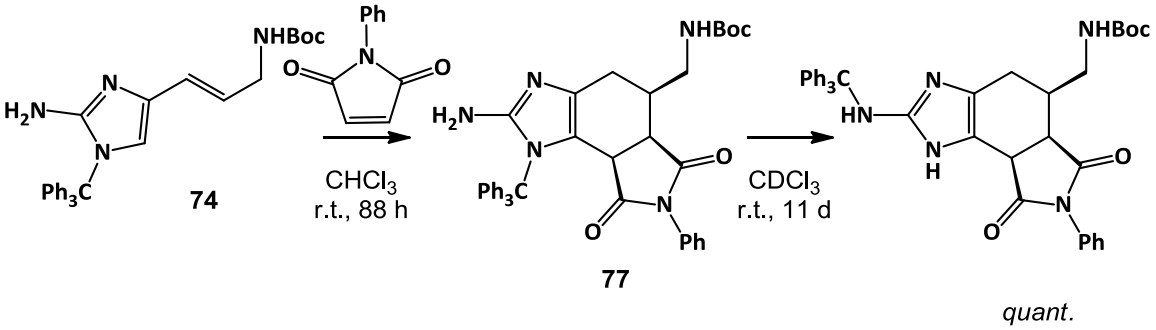
Lovely *et al*. have previously reported the N1→N3 migrations of Bn, SEM and MOM groups under more standard conditions, following the addition of catalytic BnCl, SEMCl or MOMCl respectively, to give the least sterically hindered thermodynamic products (Scheme 2.28).[44,137,141,142]



Scheme 2.28. Observed N1→N3 migrations of protecting groups.

2.4.2.4 N1→NX migrations of trityl

Poverlein *et al.*[45] have also previously noted that trityl-protected 2-aminoimidazole **74**, formed *via* a cycloaddition with NPM in chloroform (see Chapter 1), would undergo trityl-migration on prolonged standing at r.t. The trityl group would migrate from N1 to the terminal amino at C2 in quantitative yield (Scheme 2.29). It is possible that the slightly acidic nature of chloroform is encouraging the trityl lability.



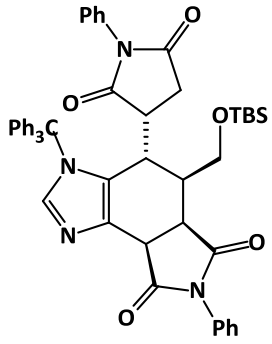
Scheme 2.29. N1→NX trityl migration of 1-trityl-4-vinylimidazole **74**.

2.4.3 Identification of Unknown Adduct 167

Analysis of the ^{1}H NMR spectrum of minor adduct **167** revealed 5 additional aromatic proton signals and 2 additional proton signals in the aliphatic region below 5.0

ppm, compared to rearomatised imidazole **168**. This indicated the presence of a second molecule of NPM, which suggested the occurrence of a 2:1 adduct. This was confirmed by high-resolution mass spectrometry, which gave a parent ion of m/z 849.3450 relating to a formula of $C_{51}H_{50}N_4O_5Si.Na$, indicating the presence of two molecules of NPM to one imidazole moiety.

Literature precedent would suggest this adduct would be the product of an ene reaction of the initial Diels-Alder adduct **165** with excess NPM, giving structure **174** (Figure 2.3).



174

Figure 2.3. Proposed structure of unknown cycloadduct **174**.

However, further NMR analysis using COSY, NOESY, and DEPT spectroscopy revealed the presence of three sp^3 CH_2 environments, which would be inconsistent with structure **174**. Therefore, to definitively identify the structure, crystals were grown for X-ray crystallographic analysis by slow diffusion from methanol/pentane and revealed the structure to be **175**, as shown in Figure 2.4.

The crystal structure also revealed the presence of a molecule of methanol in the unit cell, with a hydrogen-bonding interaction to N1 which is now free from the trityl protecting group. In addition, face-edge π-stacking is evident between a phenyl group from trityl and an adjacent phenyl from the NPM dienophile moiety.

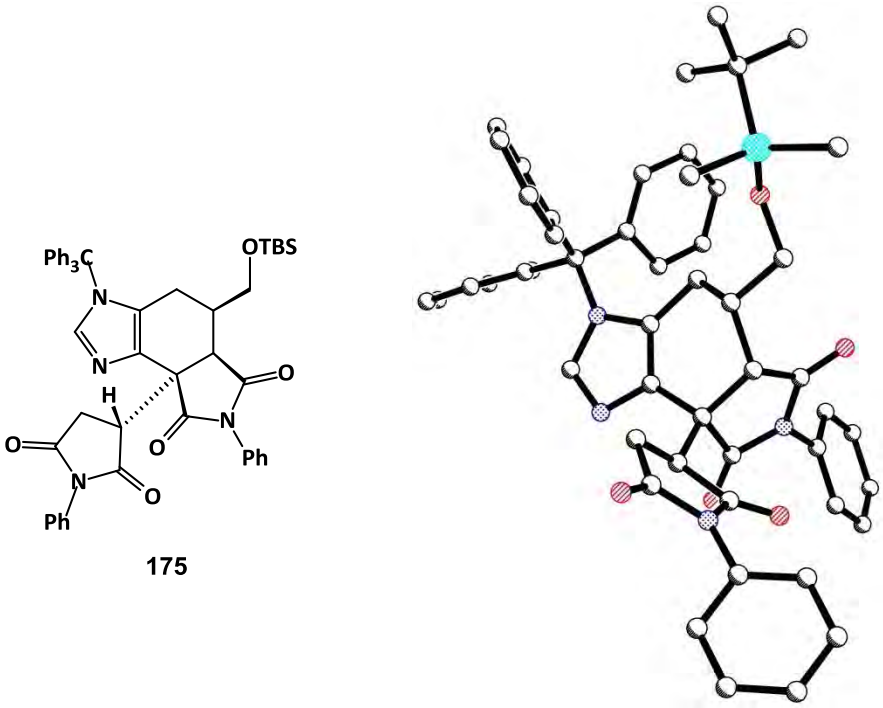
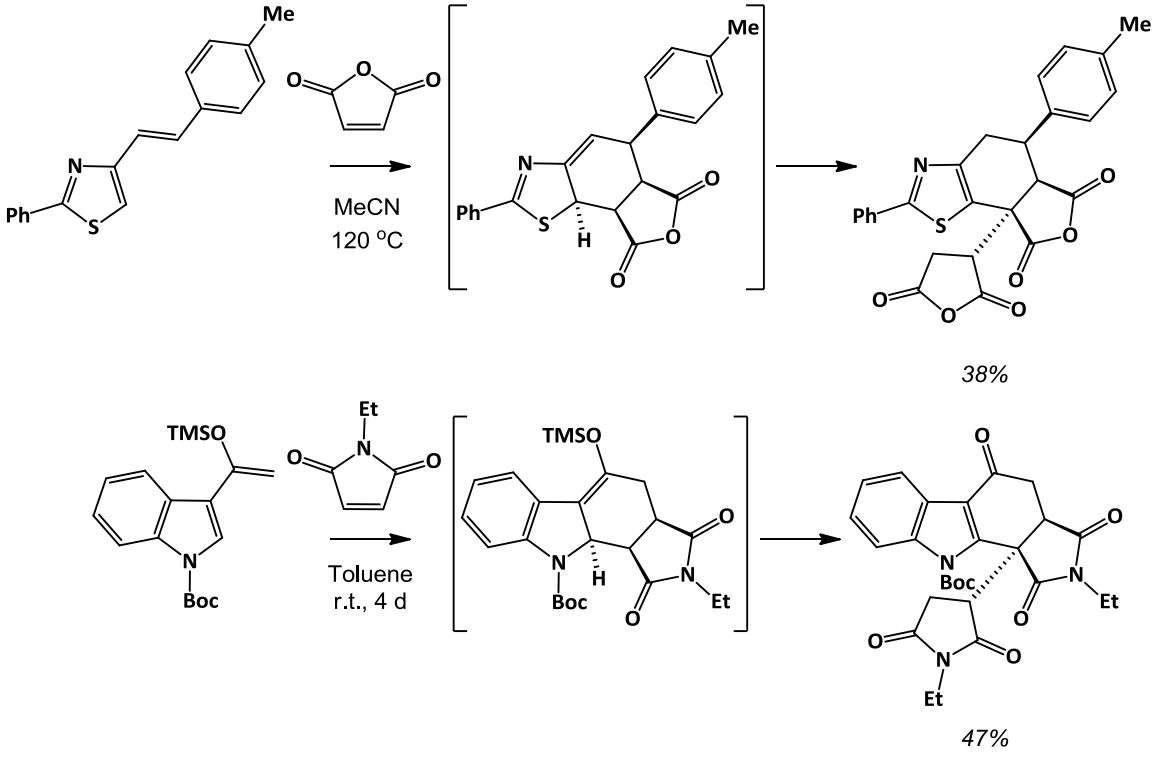


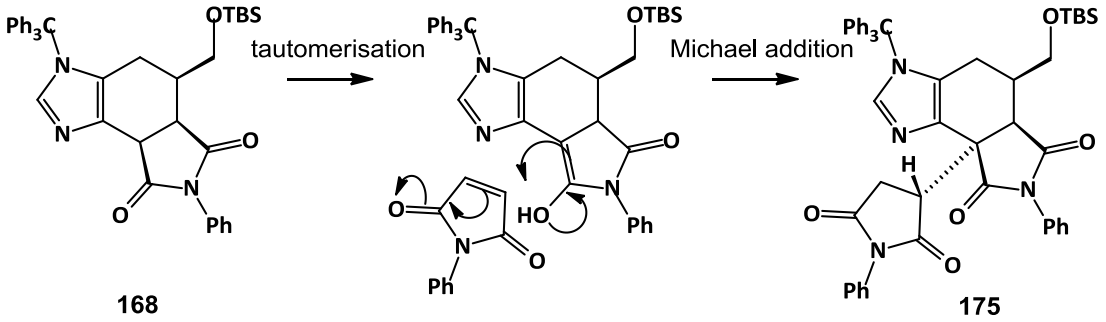
Figure 2.4. Confirmed structure of cycloadduct **175**, hydrogens of X-ray structure removed for clarity.

This structure is in agreement with that proposed by Cabrera *et al.*[143] in their work observing the Diels-Alder reactions of 4-alkenylthiazoles with maleic anhydride, which led to a 2:1 adduct following a Diels-Alder/Michael addition domino sequence, and with that of Bleile and co-workers,[52] in their studies of fused indole derivatives (Scheme 2.30).



Scheme 2.30. Domino Diels-Alder/Michael addition reactions.

The proposed mechanism for this reaction is given in Scheme 2.31 and shows tautomerisation of rearomatised imidazole **168** and subsequent Michael addition with a second equivalent of NPM, leading to Michael adduct **175**.



Scheme 2.31. Proposed mechanism for the formation of **175**.

On extended reaction times (see Table 2.1), it was possible to isolate the Michael adduct **175** as the major component, and indeed following refluxing of the reaction in toluene for 72 h, the Michael adduct could be obtained in 57% yield, along with 10% of the rearomatised adduct **168**. It was not possible, however, to isolate cleanly the initial Diels-Alder adduct **165**, as subsequent rearomatisation and trityl migration occurred so rapidly that all attempts at isolation provided only rearomatised imidazole **168**.

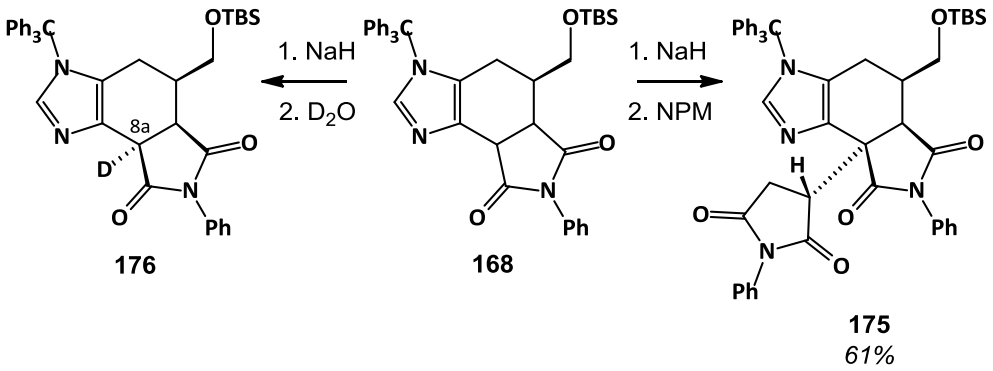
Solvent[a]	Temp/^{o}C	Time/h	Yield of 168[b]/%	Yield of 175[b]/%
Toluene	100	120	24	19
Toluene	110	16	63	9
Toluene	110	18	45	4
Toluene	110	21	30	21
Toluene[c]	110	48	15	35
Toluene	110	72	10	57

[a]Reaction conditions: 0.3 mmol **165**, 2.5 equiv of NPM. [b]Isolated yields. [c]Reaction performed under inert conditions.

Table 2.1. Yields of Diels-Alder reaction of **165** and NPM.

We were able to investigate our hypothesis that the reaction occurred *via* a Michael-type addition by dissolving purified **168** in toluene-d_8, deprotonating with 1 equivalent of NaH, then quenching with D_2O. This led to the selective deuteration of carbon 8a, α to the imidazole ring, which could be observed by the disappearance of the corresponding proton signal in the ^{1}H NMR spectrum of **176**. In a second experiment,

deprotonation of **168** with NaH as before and the subsequent addition of 1 equivalent of NPM led to the formation of **175**, which we were able to isolate in 61% yield (Scheme 2.32).

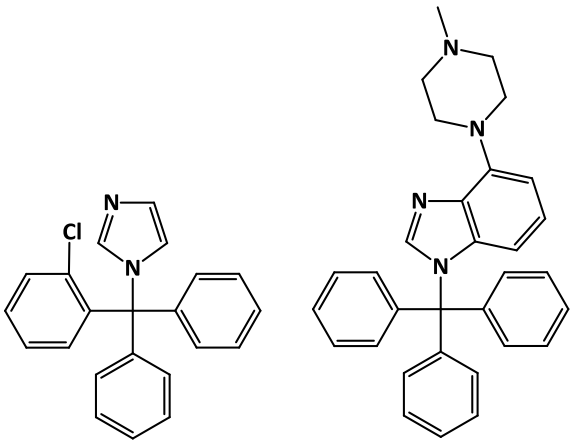


Scheme 2.32. Formation of **175** and **176** *via* Michael addition.

2.4.4 Conclusions

Diels-Alder [4+2] cycloadditions proceeded successfully for the substituted vinylimidazole **164**, however as in the case of methylene-OTBS substituted-vinylfuran **149** and thiophene **156**, more than one cycloadduct was produced and it was not possible to isolate the initial Diels-Alder enamine cleanly.

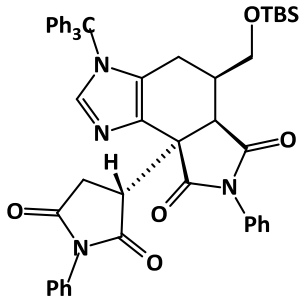
The rearomatised Diels-Alder adduct **168** was isolated in up to 63% yield and was observed to have undergone an unusual N1→N3 trityl-migration. It is our understanding that this is the first report of trityl N1→N3 migration under mild thermal conditions. This has important implications in medicinal chemistry due to the extensive use of trityl- and trityl-derived groups in imidazole-based medicinal compounds, for example, the imidazole antifungal agent clotrimazole (**177**) and the benzoimidazole 5-HT antagonist **178** (Scheme 2.33). The possibility of migration would also be of interest in the area of synthetic chemistry, particularly as the N→N trityl migration is difficult to observe by spectroscopic methods.



177 178

Scheme 2.33. Trityl-derived imidazole-based medicinal compounds.

In addition, the 2:1 adduct **175** was observed, and could be isolated as the major adduct on prolonged reaction times. This did not arise through an intermolecular ene reaction with additional NPM as the literature would suggest (see Chapter 1), but instead *via* a Michael addition of the enol form of **168** to an additional NPM moiety (Figure 2.5). This Diels-Alder/[1,3]-H shift/[1,3]-trityl migration/Michael domino reaction allows the formation of four contiguous stereocentres, including a quaternary centre, three new C-C bonds, and one C-N bond, and has only been observed in isolated literature examples,[35,52] but never explored.



175

Figure 2.5. Structure of cycloadduct **175**.

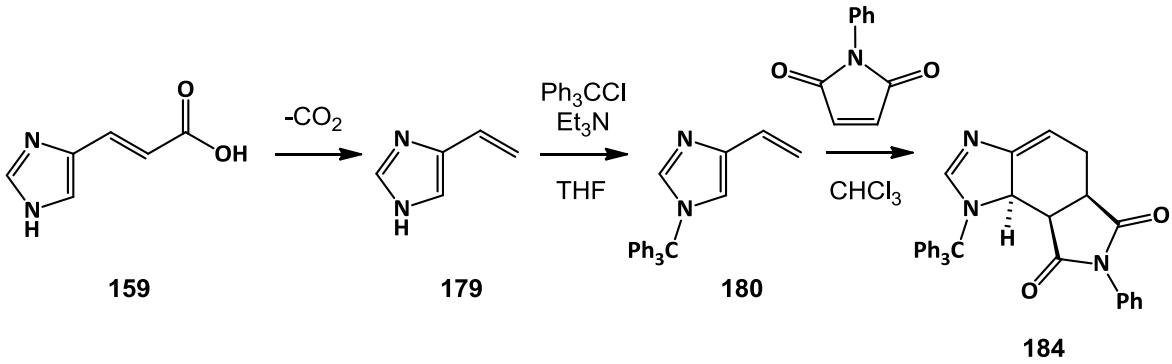
2.5 Unsubstituted Vinylimidazoles

Following the observation of these interesting domino reactions of substituted vinyl-heteroaromatics, we wished to explore the reaction conditions and product distribution in more detail. Therefore, we required a simplified substrate with which to test the system, and unsubstituted vinylimidazole **179** was selected.

2.5.1 Synthesis and Diels-Alder reaction of 1-trityl-4-vinyl-1*H*-imidazole (180)

In order to investigate the Diels-Alder reactivity of unsubstituted vinylimidazoles, an efficient, scalable, affordable route to *N*-protected unsubstituted-vinylimidazoles was required. Observations by Lovely *et al*.[44] have indicated that the electronics of the imidazole-N1 protecting group have a significant effect on the Diels-Alder reaction, and as our previous investigations have shown, the trityl-protecting group is subject to migration under facile thermal conditions. Therefore, it would beneficial for our needs if the synthetic route readily allowed for changes in the protecting group.

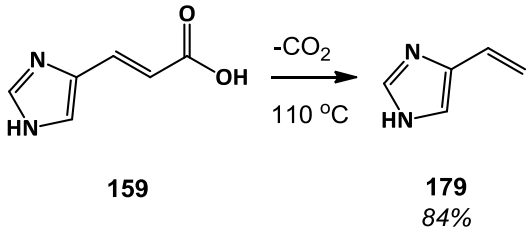
Our proposed route, shown in Scheme 2.34, was to effect a decarboxylation of urocanic acid (**159**) to yield the unprotected 4-vinyl-1*H*-imidazole **179**, and regioselectively protect the least hindered nitrogen with trityl chloride. The resulting 1-trityl-4-vinyl-1*H*-imidazole (**180**) will then be examined under Diels-Alder reaction conditions, and those results compared to literature data.[41,44,141]



Scheme 2.34. Proposed route to the Diels-Alder reactions of vinylimidazoles.

2.5.1.1 Synthesis of 4-vinyl-1*H*-imidazole (179)

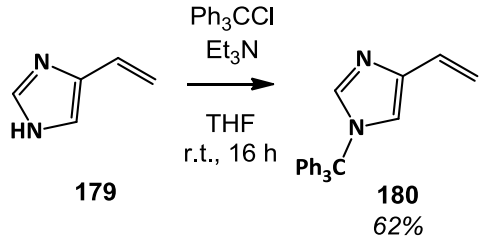
The preparation of **179** was adapted from a literature procedure by Overberger *et al*.[144,145] The thermal decarboxylation of the commercially available urocanic acid (**159**) was achieved by heating solid urocanic acid at 110 ^{o}C under reduced pressure. The resulting vapour was passed through a short-path distillation kit and collected 4-vinyl-1*H*-imidazole in 84% yield as a pale yellow oil, which solidified upon cooling (Scheme 2.35).



Scheme 2.35. Thermal decarboxylation of **159** to give **179**.

2.5.1.2 Synthesis of 1-trityl-4-vinyl-1*H*-imidazole (180)

Vinylimidazole **179** was then protected at N1 analogously to the substituted-vinylimidazole **162**, with trityl chloride and triethylamine in THF at r.t. overnight (Scheme 2.36). The resulting 1-trityl-4-vinylimidazole was obtained in moderate yield (62%) following purification by flash column chromatography.



Scheme 2.36. Trityl protection of **179**.

Examination of the ^{1}H NMR spectrum of this compound showed the formation of a single regioisomer. As migration of the trityl-group to imidazole-N3 was previously observed during the Diels-Alder reaction, we wished to unambiguously assign the regioselectivity of **180**. Crystals were grown from slow diffusion of diethyl ether/petroleum ether, and the structure was confirmed *via* single crystal X-ray analysis (Figure 2.6), revealing the trityl-protecting group to be on N1. This crystal structure is as expected, with no unusual features.

A number of other groups in the literature have previously synthesised trityl-protected 4-vinylimidazoles but most other methods rely on initial application of the protecting group to a substituted imidazole, followed by generation of the vinyl moiety.

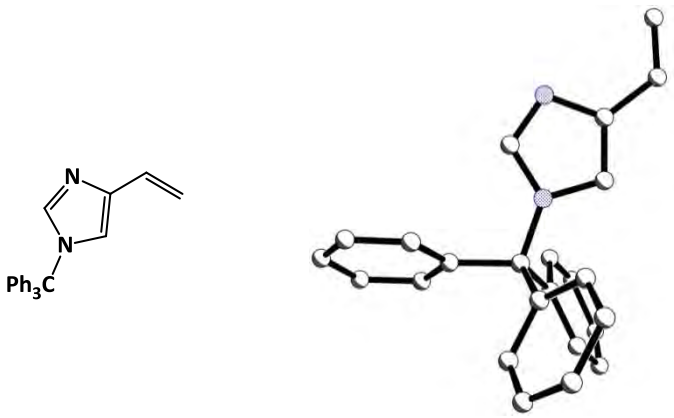
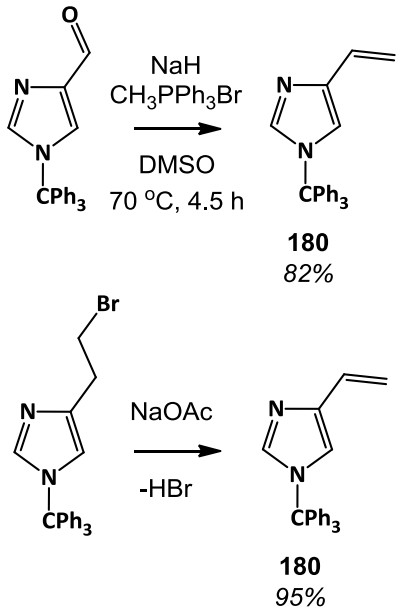


Figure 2.6. Structure of **180**. Non-essential hydrogen atoms omitted for clarity.

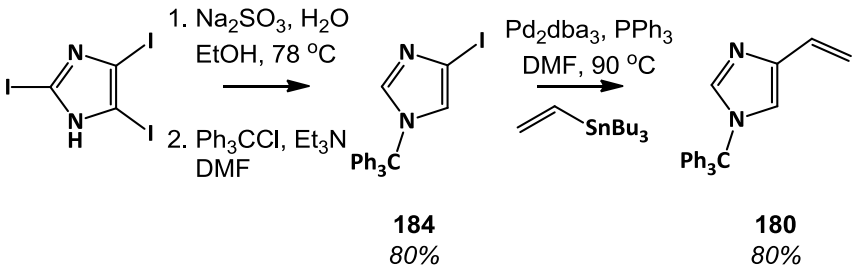
Kokosa *et al.*[146] performed a Wittig reaction on 1-(trityl)imidazole-4-carboxaldehyde **181** with sodium hydride and methyltriphenylphosphonium bromide to

give **180** in 82% yield (39% overall), whereas Altman and Wilchek[147] used sodium ethanoate to afford **180** by elimination of HBr from 4-(2-bromoethyl)-1-tritylimidazole **182** in 95% yield (30% overall, Scheme 2.37)



Scheme 2.37. Alternative synthetic routes to **180**.

Lovely *et al*.[41] adopted a different approach by polyiodinating imidazole through treatment with a solution of iodine in aqueous potassium iodide under basic conditions. Subsequent reductive deiodination with an aqueous ethanolic solution of sodium sulphite and regioselective protection on the least sterically hindered nitrogen gave 1-trityl-4-iodoimidazole (**183**), and this was subjected to a Stille cross-coupling with tributylvinylstannane to give **180** in 80% yield (30% overall, Scheme 2.38).



Scheme 2.38. Route to **180** *via* polyiodination of imidazole and Stille cross-coupling.

The thermal decarboxylation and subsequent protection was chosen in preference to these other methods as it avoids the removal of phosphonium salts, hydrogen bromide, or toxic tin by-products. In addition, by generating the unprotected vinylimidazole, the protecting group can be easily modified if required. Therefore, we were able to easily

scale this method and generate in excess of 15g of 1-trityl-4-vinylimidazole in only two steps, in 57% overall yield.

2.5.1.3 Diels-Alder reaction of trityl-vinyl-imidazole (180) with NPM

With 1-trityl-4-vinylimidazole in hand, its ability to engage in the Diels-Alder reaction was examined. **180** was heated in chloroform at 61 ^{o}C with 2.5 equivalents of NPM for 24 h, in conditions analogous to those previously reported in the literature.[41] Examination of the crude reaction mixture by ^{1}H NMR spectroscopy indicated the loss of the signals corresponding to the vinylic CH_2 protons at 5.69 and 5.16 ppm, and the formation of two major products. These compounds were conveniently separated by flash column chromatography and were initially assigned the structures corresponding to enamine **184** and imidazole **185**, arising from a Diels-Alder reaction and a Diels-Alder reaction/rearomatisation respectively, based on literature precedent (Figure 2.7).

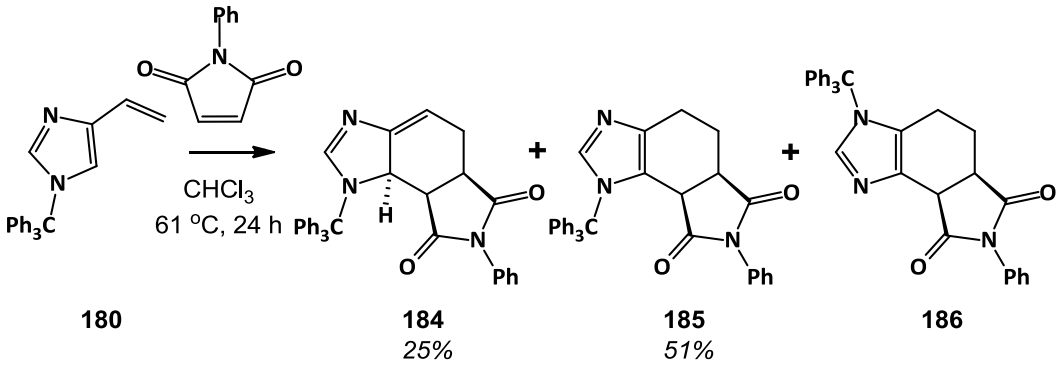
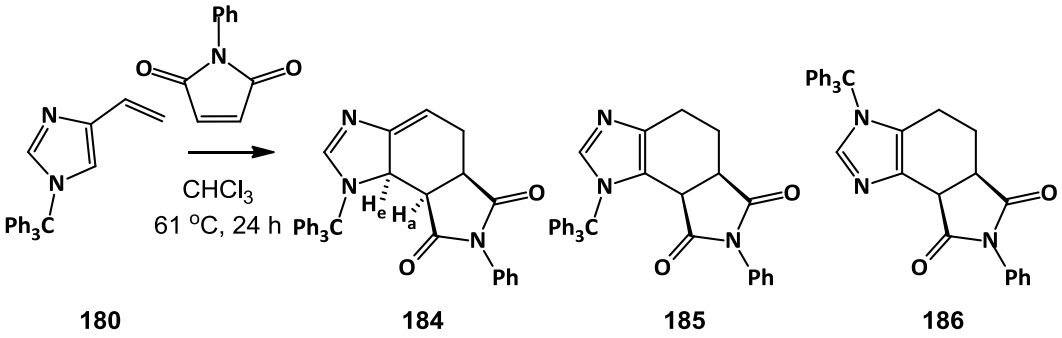


Figure 2.7. Cycloadducts resulting from Diels-Alder reaction of **180** with NPM.

However, upon closer examination of this reaction we found that the expected initial Diels-Alder cycloadduct **184** had indeed formed, but we found the major adduct to in fact be the N→N trityl-migrated species **186**, and only trace quantities of the rearomatised cycloadduct **185** could ever be isolated (Scheme 2.39).



Scheme 2.39. Cycloadducts arising from Diels-Alder reaction of **180** and NPM.

The structures are in agreement with those arising from extra-annular addition, and a small positive correlation between H_a and H_e in the NOE spectra of **184** suggests the stereochemistry is consistent with that resulting from an *endo* cycloaddition. Extra-annular cycloaddition occurring *via* an *endo* transition state is in good agreement with previous reports in the literature for the Diels-Alder reaction of vinylimidazoles and other vinyl-heteroaromatics (see Chapter 1).

Crystals of **185** were grown *via* slow diffusion of diethyl ether/ethanol, and of **186** by slow evaporation of methanol, and the structures were confirmed through single crystal X-ray analysis (Figure 2.8).

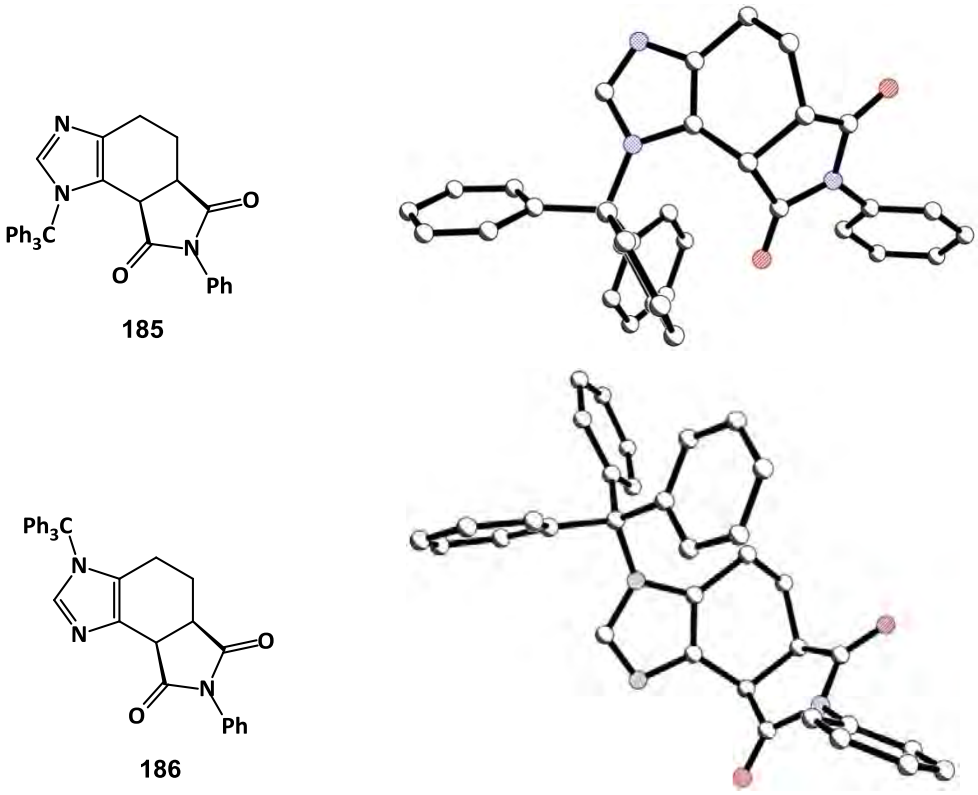
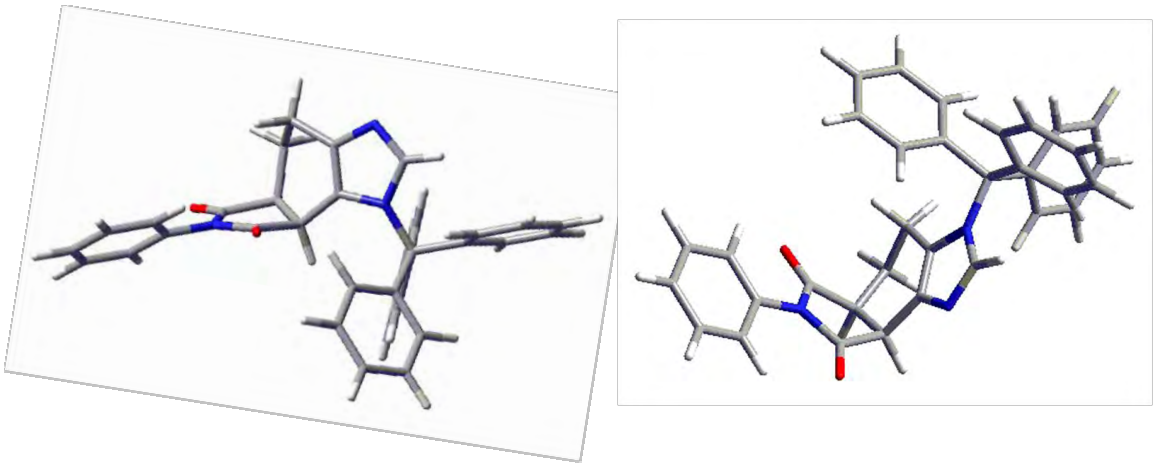


Figure 2.8. Structures of **185** and **186**. Hydrogens omitted for clarity.

The crystal structure of **186** showed both enantiomers were present together in the unit cell. It also revealed the trityl-groups of two adjacent molecules were arranged in a 6-fold phenyl embrace, by a cyclic arrangement of face-edge interactions between adjacent CPh_3 groups. The crystal structure of **185** contained a single enantiomer in its unit cell, and displayed no short contact interactions with adjacent molecules. Unfortunately, all attempts to grow crystals of **184** only resulted in isolation of the rearomatised material **185** and **186**.

On comparison with reported spectral data, we believe that rearomatised adduct **185** has been previously incorrectly assigned, due to the occurrence of a hitherto unobserved N1→N3 trityl migration. Furthermore, our spectral data for **186** matches data that have previously been erroneously attributed to a compound with structure **185**.[41,44,141]

Examination of the X-ray crystal structure of **185** shows significant steric crowding of the newly formed 1-phenylpyrrolidine-2,5-dione ring by the trityl group, whereas in **186**, the trityl group has migrated to give what appears to be a much less crowded molecule. We attempted to further rationalise this migration event by modelling structures **185** and **186** using a HF/3-21G* level of theory calculation with Spartan, carried out by our collaborator Dr. Beverly Stewart. The calculation showed that **186** is the thermodynamically favoured product, being approximately 19 kJ mol^{-1} more stable than **185** (Figure 2.9).



185 **186**

Figure 2.9. Hartree-Fock optimised structures for regioisomers **185** and **186**.

We examined this reaction in both chloroform and toluene and found that the product distribution can be skewed, to some extent, in favour of either the initial Diels-Alder enamine **184** or the rearomatised imidazole **186** (Table 2.2). The highest yields of enamine **184** could be obtained in toluene by keeping reaction times low, preferably less than 3 h, as rearomatisation of the enamine and decomposition within the reaction

mixture tends to occur on prolonged heating. Greater yields of the rearomatised adduct could be obtained by heating for 5 h in toluene, although this again led to decomposition on longer reaction times. It is likely that one of the leading causes of decomposition is loss of the labile trityl group on prolonged heating, as has been suggested previously in the literature.[41]

Solvent	Temp/^{o}C	Time/h	Yield of 184[b]/%	Yield of 185[b]/%	Yield of 186[b]/%
Toluene[a]	110	1	35	-	-
Toluene[a]	110	3	78	-	-
Toluene[c]	110	3	28	13	12
Toluene[c]	110	3	39	12	5
Toluene[a]	110	4	17	-	46
Toluene[a]	110	5	-	-	32
Toluene[a]	110	5	-	6	68
$CHCl_3$[a]	61	16	28	-	6
$CHCl_3$[a]	61	24	25	-	41

[a]Reaction conditions: 0.3 mmol **180**, 2.5 equiv of NPM. [b]Isolated yields. [c]Reaction conditions: 3.0 mmol **180**, 2.5 equiv of NPM.

Table 2.2. Yields of Diels-Alder reaction.

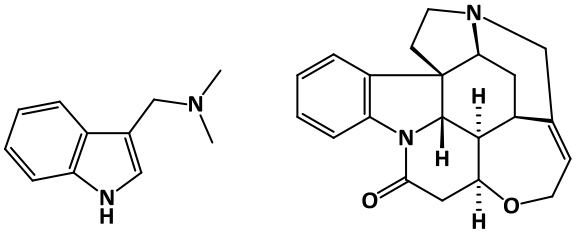
2.5.2 Conclusions

The Diels-Alder reaction of 1-trityl-4-vinyl-1*H*-imidazole (**180**) was successful with NPM, producing three cycloadducts. The initial Diels-Alder enamine **184** could be isolated exclusively in 78% yield when shorter reaction times were employed (toluene, 3 h), but as a mixture of cycloadducts with the rearomatised imidazole **186** following longer reaction times.

X-ray crystal structures were obtained of both rearomatised adducts to definitively assign the position of the trityl group. Analogously to the substituted-vinylimidazoles, the N1→N3 trityl-migrated species was the major product at longer reaction times. The rearomatised adduct **185** could only ever be isolated in low yields, and never free of the other cycloadducts.

2.6 Vinylindoles

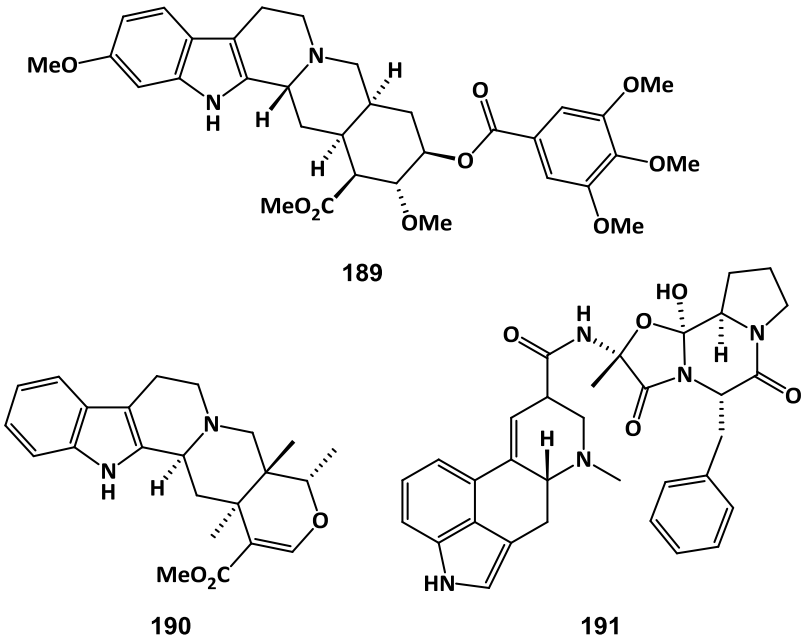
Indole-based heterocyclic compounds have attracted a great deal of attention from the synthetic community in the last 50 years. This is due to the vast examples of indole-containing natural products that have been isolated, both from terrestrial plants and animals, and from a wealth of marine species, many of which possess biological activities. While indole-alkaloids possess considerable structural diversity, they also vary widely in their structural complexity. They can range from the relatively simple gramine (**187**), to the structurally complex strychnine (**188**, Figure 2.10).



187 **188**

Figure 2.10. Example of the structural variation in indole-alkaloids.

A number of these indole-alkaloids have already been employed as lead compounds for the discovery of new pharmaceuticals. For example, the antihypertensive drug reserpine (**189**) was among the first of the indole-alkaloids to be employed commercially, and was originally prescribed as an antipsychotic.[148] Ajmalicine (**190**) is another indole alkaloid employed in the treatment of high blood pressure,[149] whilst ergotamine (**191**) is used as a vasoconstrictor.[150]



189

190 **191**

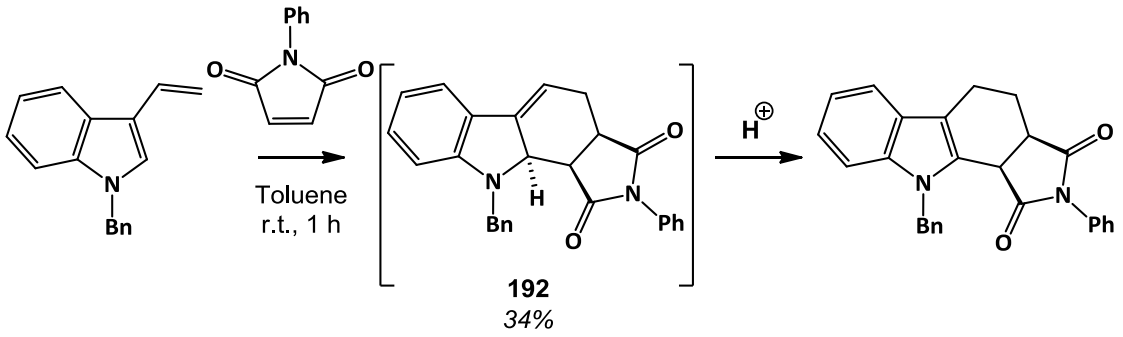
Figure 2.11. Selected biologically active indole-alkaloids.

Therefore, the development of rapid routes to structurally complex indole architectures would be of significant interest to the synthetic community and medicinal chemistry.

2.6.1 Synthesis of *N*-protected-3-vinyl-indole (197) and Diels-Alder reaction with NPM

Literature precedent suggests that the greater electron-density of indole, provided by conjugation, is a contributing factor in the increased rearomatisation observed in its Diels-Alder reactions compared to other heteroaromatics (see Chapter 1). It has been possible for some groups to overcome these challenges through the use of low reaction temperatures, although as our ultimate aim is to employ these compounds in one-pot reactions, we have chosen to tailor the electronics of the ring to access a system that would undergo successful, controllable Diels-Alder reactions under facile conditions.

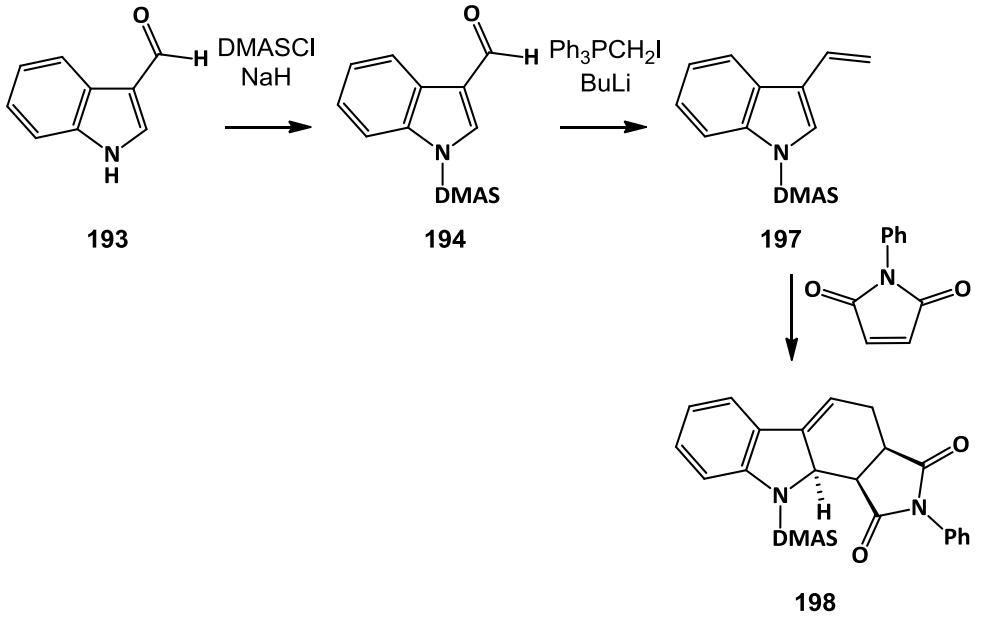
Previous work within our group has highlighted that as a protecting group for indole N1, benzyl is too electron-rich to be employed under standard conditions.[151] It was found that subsequent Diels-Alder reaction of benzyl-protected vinylindoles would lead to rapid rearomatisation and decomposition. In addition, the benzyl-protected cycloadduct **192** was found to rapidly rearomatise and decompose upon purification by flash column chromatography. It is thought that the slightly acidic nature of silica gel leads to acid-catalysed rearomatisation and decomposition.



192
34%

Scheme 2.40. Previous investigations with 1-benzyl-3-vinyl-1*H*-indole.

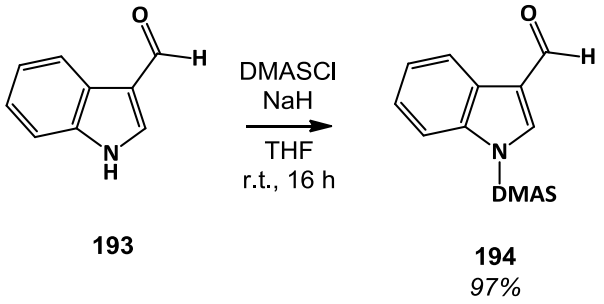
Studies are underway within the group to investigate the potential of the electron-poor tosyl protecting group, whilst this thesis will examine the suitability of protection of N1 with the DMAS group. 1*H*-indole-3-carboxaldehyde (**193**) will be *N*-protected with DMAS chloride, and subjected to a Wittig reaction to afford 3-vinylindole **197**, which will then be subjected to a Diels-Alder reaction (Scheme 2.41).



Scheme 2.41. Proposed route to the Diels-Alder reactions of vinylindoles.

2.6.1.1 DMAS protection of 1*H*-indole-3-carboxaldehyde (193)

The DMAS-protected indole carboxaldehyde **194** was synthesised from commercially available 1*H*-indole-3-carboxaldehyde (**193**) following an adapted literature procedure,[44] as shown in Scheme 2.42.



Scheme 2.42. DMAS protection of **193**.

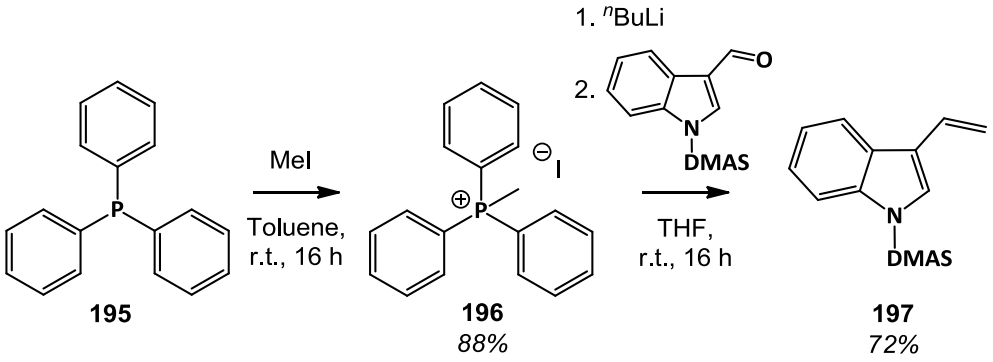
193 was dissolved in THF at 0 ^{o}C under N_2, and sodium hydride and DMAS chloride were added sequentially. The reaction was then stirred for 16 h at r.t., and the product isolated by extraction and purified by flash column chromatography in near quantitative yield (97%).

2.6.1.2 Synthesis of *N*,*N*-dimethyl-3-vinyl-1*H*-indole-1-sulfonamide (197)

The preparation of indole **197** was achieved *via* Wittig reaction of methyltriphenylphosphonium iodide (**196**) with carboxaldehyde **194**. **196** was synthesised

by the addition of methyl iodide to triphenylphosphine **195** in toluene, and recrystallised from toluene in excellent yield.

Subsequent deprotonation of **196** with ^{n}butyllithium led to formation of the phosphorane, which smoothly underwent Wittig reaction with carboxaldehyde **194**. Following careful quenching with water and extraction with CH_2Cl_2, **197** was isolated by flash column chromatography (Scheme 2.43).

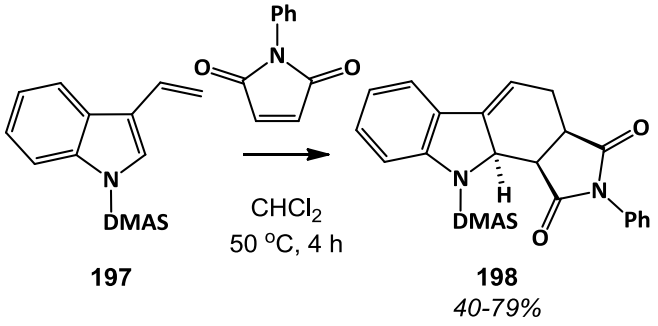


Scheme 2.43. Synthesis of methyltriphenylphosphonium iodide and Wittig reaction of carboxaldehyde **194**.

2.6.1.3 Diels-Alder reaction of 1-DMAS-3-vinylindole (197) with NPM

With the DMAS-protected vinylindole **197** in hand, we then examined its ability to engage in Diels-Alder reactions with NPM. The reaction was performed with 2.5 equivalents of NPM, stirring at 50 ^{o}C and monitoring by TLC and ^{1}H NMR spectroscopy. After 4 h, analysis of the crude ^{1}H NMR spectrum indicated full conversion to the initial Diels-Alder cycloadduct (**198**), with no evidence of starting material or the rearomatised adduct **199**.

However, upon isolation by flash column chromatography, only 40% of the Diels-Alder cycloadduct could be isolated. Previous work within our group has indicated that indole Diels-Alder cycloadducts can be unstable to chromatography due to facile rearomatisation on silica,[151] and so subsequently this compound was purified by recrystallisation from toluene in 79% yield.



Scheme 2.44. Diels-Alder reaction of **197** with NPM.

In order to definitively confirm the structure of **198**, crystals were grown for X-ray crystallographic analysis by slow diffusion from diethyl ether/petroleum ether. The structure of **198** is consistent with the Diels-Alder cycloadduct arising from extra-annular cycloaddition, *via* an *endo* transition state (Figure 2.12).

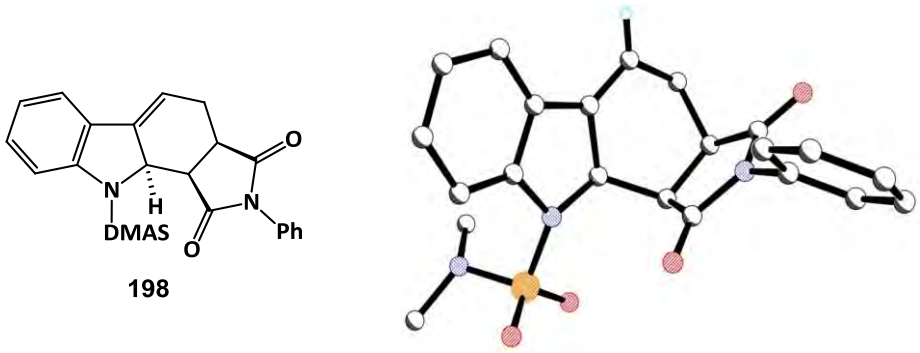


Figure 2.12. X-ray crystal structure of **198**. Non-essential hydrogens removed for clarity.

2.6.2 Conclusions

The primary focus of this aspect of the research programme was to find a suitable method for the synthesis of vinyl- and substituted vinyl-heteroaromatics, and to examine their behaviour in intermolecular Diels-Alder reactions.

Vinylfuran **149**, vinylthiophene **156**, vinylimidazoles **164** and **180**, and vinylindole **197** were synthesised successfully from either the corresponding heteroaromatic-carboxaldehyde, or in the imidazole cases, from urocanic acid.

The subsequent Diels-Alder cycloadditions of these dienes were then examined, with NPM as the dienophile. Diels-Alder reaction was found to occur readily with **156**, **164**, **180**, and **197**, with cycloadducts being observed by ^{1}H NMR spectroscopy. Reaction of **149** with NPM was not observed, and only degradation of the starting materials could be identified by ^{1}H NMR spectroscopy. This was attributed to the lower reactivity of vinylfurans necessitating longer reaction times, coupled with the instability of furan systems to prolonged heating.

The Diels-Alder cycloadduct arising from reaction of **197** with NPM was successful, and 100% conversion to **198** was observed by ^{1}H NMR spectroscopy after 4 h at 50 ^{o}C. However, a moderate yield (40%) was obtained following purification by column chromatography. This is consistent with previous work within the group, which indicated an instability of indole cycloadducts towards purification *via* silica gel. Therefore, further development of indole-based cycloadducts will utilise recrystallisation for purification.

The cycloadducts arising from reaction of vinylthiophene **156**, and vinylimidazoles **164** and **180** were subject to further *in situ* domino reactions, including rearomatisation, N1→N3 trityl migration, ene reaction and Michael addition. These results are consistent with examples in the literature in which cycloadducts undergo further reaction *via* domino Diels-Alder/Diels-Alder, Diels-Alder/ene reactions, and Diels-Alder/Michael-addition reaction sequences (see Chapter 1).

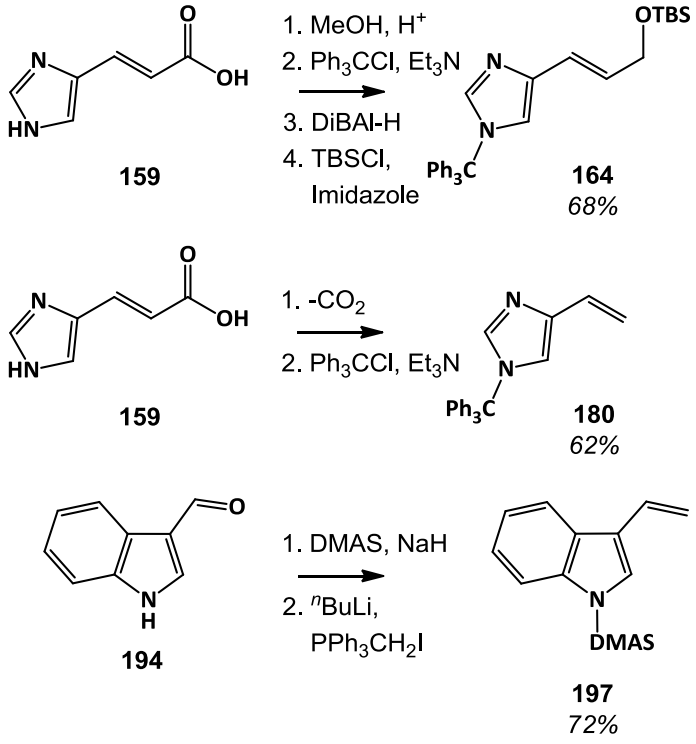
These *in situ* reactions are highly undesirable in terms of our research programme, as rearomatisation, Michael addition, and ene reaction with excess diene or dienophile would prevent the cycloadducts participating in ene reactions with the desired range of enophiles. In addition, the observed facile trityl migration may lead to the formation of a mixture of compounds which is undesirable.

Following the identification of these successful routes to vinyl-heteroaromatics and their corresponding cycloadducts, subsequent investigations will involve optimising the generation of the *N*-protected vinylimidazoles, and investigating variation of the dienophile.

Chapter 3. Optimisation Experiments

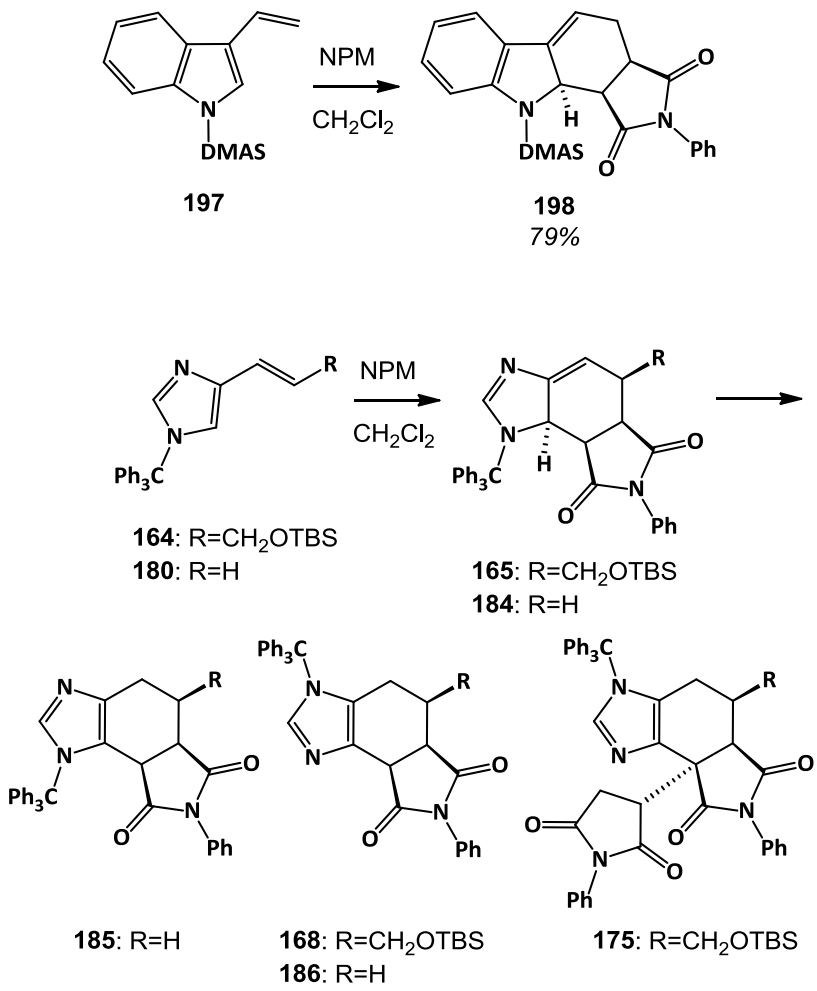
3.1 Introduction

The previous chapter has provided an introduction to the synthesis of *N*-protected vinyl-heteroaromatics, and shown the adopted synthetic route to be successful for the vinylimidazoles **164** and **180**, and vinylindole **197**. This route afforded the vinylimidazoles as single regioisomers, and all compounds were obtained in good yields (62-72%, Scheme 3.1).



Scheme 3.1. Synthetic route to vinyl-heteroaromatic dienes.

The Diels-Alder reactions of these dienes were also investigated, and were found to proceed readily with NPM under standard conditions. However, whilst the cycloadduct arising from vinylindole **197** led to the expected adduct (**198**) as a single diastereoisomer, those arising from vinylimidazoles underwent further *in situ* reactions. Cycloadducts **165** and **184** were shown to undergo hitherto unreported, facile, sterically driven N→N trityl migrations, which were a key step in several novel, highly diastereoselective domino reaction sequences, leading to a mixture of compounds (Scheme 3.2). This observed *in situ* rearomatisation is highly undesirable in terms of our research programme, as it would prevent further ene reaction, and in conjunction with the facile trityl migration, would lead to a number of products and potential side-reactions.

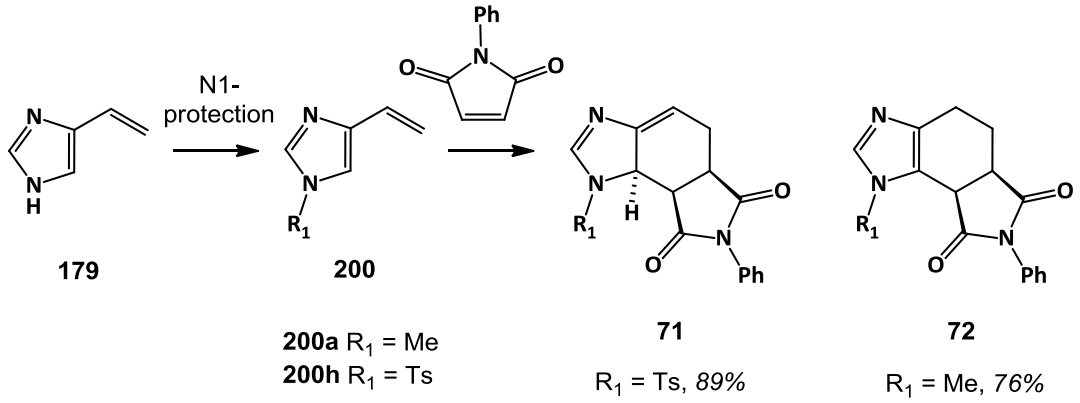


Scheme 3.2. Products arising from Diels-Alder cycloaddition with NPM.

With a view to synthesising suitable ene-substrates in high yields which do not succumb to these unwanted *in situ* domino reactions, a program of optimisation was undertaken. Initially, the synthetic ease with which various N1-protecting groups can be applied to the unsubstituted 4-vinyl-1*H*-imidazole (**179**) was evaluated, and their subsequent Diels-Alder reaction with NPM were studied. A high yielding N1-protected vinylimidazole **200e** was also selected to examine the reactivity and product distribution resulting from substituting NPM for a range of dienophiles in the Diels-Alder reaction.

3.2 N1-Protecting Group Optimisation

Previous studies in the literature have highlighted the influence of N1-protecting groups of 4-vinyl-1*H*-imidazole (**179**) upon product distribution in the Diels-Alder reaction with NPM.[39,43,44] Lovely *et al.* found that use of the electron-rich methyl protecting group led to a greater yield of the rearomatised adduct **72**, whilst the electron-poor tosyl group led to a higher yield of the initial Diels-Alder adduct **71** (Scheme 3.3).

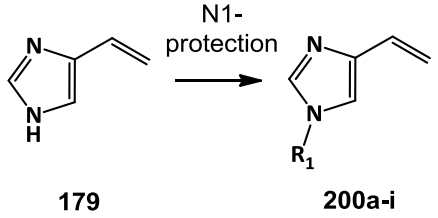


Scheme 3.3. Intermolecular Diels-Alder reaction of *N*-protected-4-vinylimidazole **200** and NPM.

Therefore, our initial work involved a program of investigation to optimise the N1-protecting group of vinylimidazole **179**. We required a facile, synthetic route that afforded the N-protected-4-vinyl-1*H*-imidazole as a single regioisomer, in good yield. In addition, the subsequent Diels-Alder reaction with NPM should afford the expected cycloadduct **71** exclusively, in high yield, under standard conditions.

3.2.1 N1-Protection of 4-Vinyl-1*H*-imidazole

4-Vinyl-1*H*-imidazole (**179**) was synthesised *via* a thermal decarboxylation of urocanic acid (**159**), as described previously. Compound **179** was then subjected to standard protection conditions with a range of protecting groups, the results of which are outlined in Table 3.1. Those results observed with trityl-protected imidazole **200b** (see Chapter 2) are also included for comparison.



Scheme 3.4. N1-protection of 4-vinyl-1*H*-imidazole.

Entry	R_1	Reagents	Temp/^oC	Time/h	200[a]/%
a	Me	MeI, NaH THF	20	3	**60 (2:1)[b]**
b	Trityl	TrCl, Et_3N THF	0→20	16	**62**
c	DMTr	DMTrCl, Et_3N THF	0→20	16	**75**
d	PMB	PMBCl, NaH DMF	50	16	**80**
e	Bn	BnBr, NaH CH_2Cl_2	50	16	**87**
f	PNB	PNBCl, NaH DMF	50	16	**0**
g	DMAS	DMASCl, NaH, THF	20	16	**90 (99:1)[b]**
h	Ns	NsCl, py	0→20	56	**50**
i	Ts	TsCl, Et_3N CH_2Cl_2	0→20	16	**81**

Table 3.1. N1-protection of **179**. [a]Isolated yields. [b]Ratio of regioisomers observed.

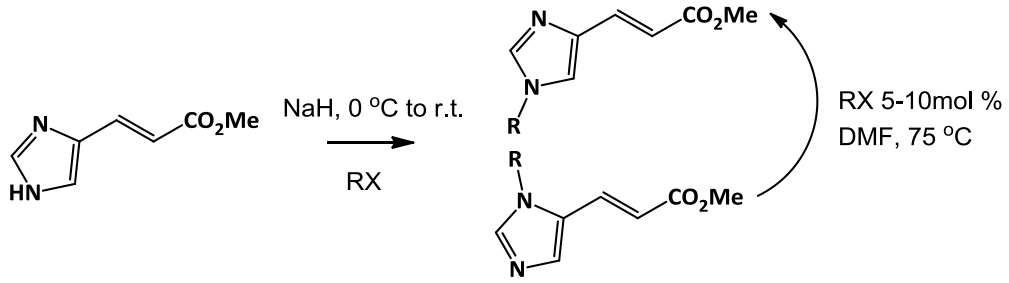
The vast majority of N1-protection conditions investigated led to the isolation of the desired imidazole, as a single regioisomer. However, a mixture of regioisomers was observed in reactions with the relatively small protecting groups, methyl and dimethylaminosulfonyl (entries **a** and **g**).

Following methyl protection, analysis of the crude reaction mixture by ^1H NMR spectroscopy revealed two regioisomers, appearing in a 2:1 ratio. The desired 1-methyl-4-vinyl isomer (**200a**) was identified as the major product on comparison with literature data.[44,152] Following an aqueous quench and purification, **200a** was isolated cleanly in 60% yield.

Similarly, when **179** was protected with dimethylaminosulfonyl (entry **g**) according to a literature procedure,[137] analysis of the crude reaction mixture revealed two regioisomers, in a 99:1 ratio. The major adduct was identified as the desired 4-vinyl regioisomer, on comparison with literature data.[41,44] The two regioisomers were readily

separated by flash column chromatography, and the desired compound was isolated in 90% yield.

Previous studies in the literature have indicated a lack of regioselectivity when applying protecting groups to 4-vinyl-imidazoles.[44,137,153] Lovely *et al*. observed that protection with benzyl, SEM, MOM and methyl would lead to formation of both the 4-vinyl and the unwanted 5-vinyl isomer in variable mixtures (1:0.3-0.7). However, they determined that further heating of the reaction mixture with an excess of the corresponding alkyl halide led to isomerisation of the unwanted 5-vinyl isomer, and the desired 4-vinyl isomer could then be isolated regioselectively (Scheme 3.5, Table 3.2). The authors attributed this isomerisation to equilibration of the initial kinetic distribution of products on heating to provide the thermodynamic distribution, giving almost exclusively the 4-vinyl isomer.



Scheme 3.5. Isomerisation from 4-vinylimidazole to 5-vinylimidazole.

RX	Initial Yield and Ratio (A:B)	Post-Heating Yield and Ratio (A:B)
BnBr	93 (**1**:0.3)	93 (**1**:0)
SEMCl	96 (**1**:0.3)	95 (**1**:0)
MOMCl	86 (**1**:0.5)	80 (**1**:0)
MeI	93 (**1**:0.7)	86 (**1**:0.3)

Table 3.2. Yields and ratio of isomers following protection and isomerisation.

Protection with the dimethoxytrityl group (entry **c**) was applied under analogous conditions to that of the trityl protection described previously (see Chapter 2), and the desired compound was isolated as a single regioisomer in a slightly higher yield following purification (75%). *p*-Methoxy-substituted trityl amines are known to have increased acid lability over quotidian trityl amines,[154] and as such may be more susceptible to N1→N3 trityl migration under our reaction conditions.

Crystals were grown of compound **200c** in order to definitively identify the

location of the DMTr group following protection and prior to cycloaddition. Suitable crystals were grown from slow evaporation of ethyl acetate/petroleum ether and were analysed by single crystal X-ray diffraction. The resulting structure confirmed the regiochemistry of the DMTr group to be on N1 (Figure 3.1). The structure obtained is as expected, with no unusual features present.

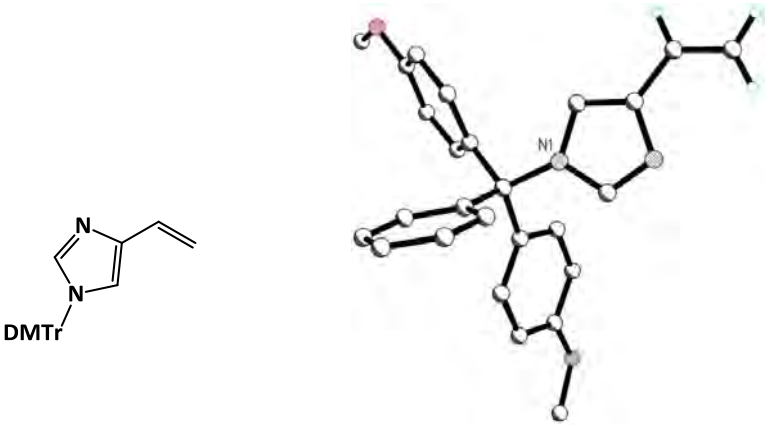


Figure 3.1. X-ray structure of **200c**. Non-essential hydrogens omitted for clarity.

The protection of **179** with each of the benzyl-related protecting groups (entries **d-f**) was carried out analogously, by stirring **179** with the corresponding benzyl halides and sodium hydride at 50 ^{o}C in DMF or CH_2Cl_2 for 16 h. Reaction of **179** with *p*-nitrobenzyl chloride and NaH (entry **f**) was unsuccessful, and no product was observed. However, both the desired *p*-methoxybenzyl and benzyl imidazoles were isolated in similarly high yields (~80%). These compounds were isolated as single regioisomers, with no observation of the 5-vinyl isomer. It is possible that the extended reaction times employed in our reaction conditions allow for formation of the thermodynamically more favourable 4-vinyl isomer preferentially.

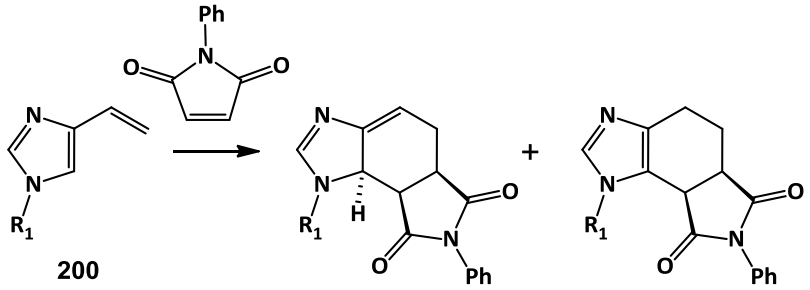
Benjes and Grimmett[153] also observed that N1-alkylation of 4(5)-substituted imidazoles leads to a mixture of isomeric products. They found that substitution with electron-withdrawing groups on the 4(5)-position led to the increased isolation of 1-alkyl-5-substituted imidazoles. They attributed this effect to N1 being deactivated towards reaction as the lone pair is conjugated with the electron-withdrawing group, which leads to increased reaction at N3.

3.2.2 Diels-Alder Reactions of 200 with NPM

Imidazoles **200a-e** and **200g-i** were then subjected to Diels-Alder reaction with NPM in both toluene and CH_2Cl_2. The general outcome of the reaction was consistent with those results observed previously in the literature. Cycloadducts possessing an

electron-poor protecting group on N1 (**71h-i**, Table 3.3) were formed as a single diastereoisomer when reacted in both toluene and CH_2Cl_2, although in relatively low yields. The rearomatised adduct was not observed in either case, even on extended reaction times.

The ^{1}H NMR spectra of these cycloadducts were compared with those of the trityl-protected cycloadduct (**184**) obtained previously, and were found to be broadly similar indicating these compounds share a common architecture.



Scheme 3.6. Intermolecular Diels-Alder reaction of *N*-protected-4-vinylimidazole **200** and NPM.

Imidazole	R	Solvent	Temp/^{o}C	Time/h	71[a]/%	72[a]/%
200a	Me	Toluene	110	3	**0**	**32**
		CH_2Cl_2	50	8	**5**	**95**
200b	Trityl	Toluene	110	5	**17**	**12**
		CH_2Cl_2	50	16	**66**	**0**
200c	DMTr	Toluene	110	30	**5**	**0**[b]
		CH_2Cl_2	50	48	**45**	**0**
200d	PMB	Toluene	110	3	**5**	**74**
		CH_2Cl_2	50	3	**79**	**0**
200e	Bn	Toluene	110	3	**0**	**73**
		CH_2Cl_2	50	6	**80**	**0**
200g	DMAS	Toluene	110	5	**60**	**5**
		CH_2Cl_2	50	16	**19**	**68**
200h	Ns	Toluene	110	5	**39**	**0**
		CH_2Cl_2	50	36	**10**	**0**
200i	Ts	Toluene	110	16	**34**	**0**
		CH_2Cl_2	50	36	**7**	**0**

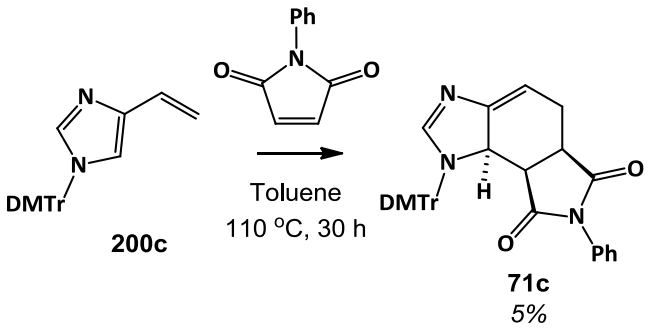
Table 3.3. Diels-Alder cycloaddition results. [a]Isolated yields. [b]Cycloadduct having undergone N1→N3 DMTr migration, **201c**, isolated in 17% yield.

The nosyl- and tosyl-protected cycloadducts **71h-i** appeared to be less reactive towards rearomatisation, even on prolonged heating in toluene or CH_2Cl_2. The inclination of these cycloadducts to undergo rearomatisation was examined by treating **71h-i** with 1 equivalent of HCl, stirring at r.t. in CH_2Cl_2 and monitoring the disappearance of the starting materials by ^1H NMR spectroscopy. After 6 h at r.t. the starting materials remained unchanged, and after long reaction times or when heating to 40 ^oC, only degradation was observed.

Those substrates possessing a more electron-rich protecting group on N1 (**200a-e**) afforded cycloadducts which were more likely to undergo rearomatisation at higher reaction temperatures, or after long reaction times. For example, investigations with the methyl- and benzyl-protected imidazoles **200a** and **200e** led to the exclusive isolation of the rearomatised cycloadducts **72a** and **72e** when reacted in refluxing toluene for 3 h.

Mixtures of both the Diels-Alder initial cycloadduct **71** and the rearomatised derivative **72** were obtained when the electron-rich imidazoles **200b-d** were reacted with NPM in refluxing toluene, although interestingly, when moving to CH_2Cl_2 as the solvent, the initial Diels-Alder adducts could be obtained exclusively in moderate to high yields. However, the DMAS-protected imidazole **200g** led to a mixture of both the Diels-Alder cycloadduct and the rearomatised adduct when reacted in both toluene and CH_2Cl_2.

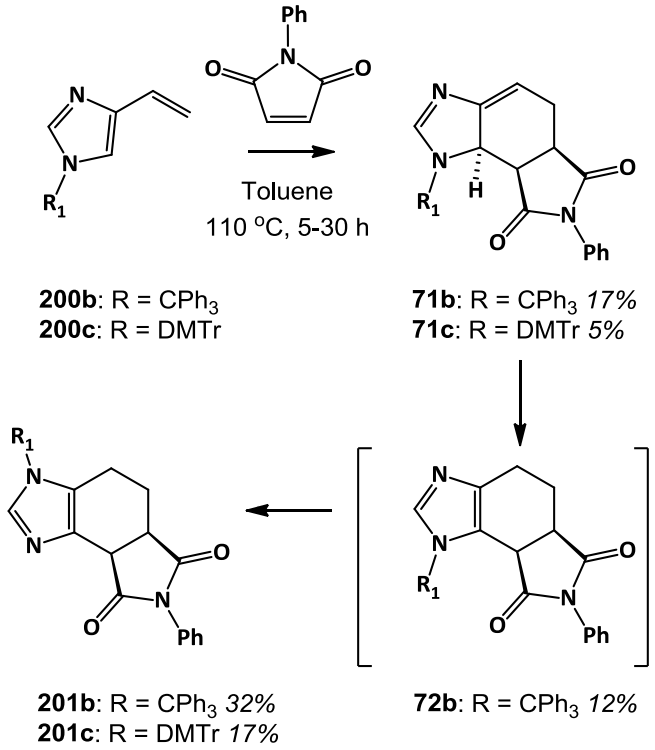
The cycloaddition of dimethoxytrityl-protected imidazole **200c** with NPM was found to lead to a similar product distribution to the closely-related trityl-protected imidazole (**200b**) discussed previously (see Chapter 2). A mixture of cycloadducts were obtained following reaction at 30 h in toluene at 110 ^oC, and on comparison with our data for the trityl-related species, the minor adduct appears to correspond to the initial Diels-Alder cycloadduct (**71c**, Scheme 3.7).



Scheme 3.7. Minor cycloadduct arising from cycloaddition of **200c** and NPM.

Dimethoxytrityl amines are well known to have enhanced lability in acidic conditions over quotidian trityl amines,[154] and therefore would be more likely to undergo

cleavage in the presence of catalytic acid. Indeed, on comparison with our data for reaction of the analogous trityl-protected imidazole (**200b**) with NPM, the major adduct arising from the reaction of dimethoxytrityl-protected imidazole (**200c**) is consistent with compound **201c**, having undergone a N1→N3 dimethoxytrityl migration (Scheme 3.8).



Scheme 3.8. Rearomatisation and N1→N3 protecting group migration of **71b/c**.

In conclusion, the desired Diels-Alder enamines can be isolated cleanly from reactions involving the electron-rich imidazoles **200b-e**, when carried out at 50 °C in CH_2Cl_2, and from **200h-i** when carried out in either toluene or CH_2Cl_2. However, the nosyl and tosyl-protected initial Diels-Alder cycloadducts (**71h-i**) are formed in comparatively low yields, and appear to be relatively stable to rearomatisation or further reaction.

The trityl and dimethoxytrityl-protected cycloadducts (**71b-c**) have proven to be unsuitable for our needs due to the inherent problems associated with N1→N3 protecting group migration, which would lead to mixtures of products and ambiguity with respect to the protecting group position.

Therefore, those cycloadducts arising from benzyl and *p*-methoxybenzyl protected imidazoles (**71d-e**) seem to be the most promising for examination in ene reactions; as they form in high yields as single diastereoisomers over short reaction times (3-6 h), and appear to be willing to undergo rearomatisation at higher temperatures which suggests

they may be susceptible to further reaction including ene reaction.

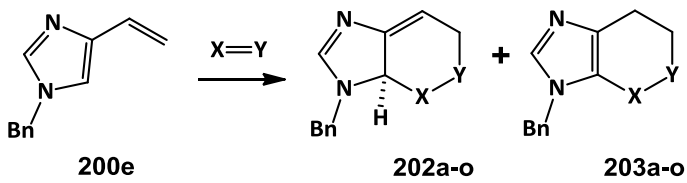
3.3 Dienophile Optimisation

Previous cycloadditions of 4-vinylimidazoles appearing in the literature have favoured the use of NPM as the dienophile, and there have been, to date, very few examples of the use of alternative dienophiles.[39,44]

Therefore, a program of study was undertaken to examine the effect on product distribution and yield through variation of the dienophile in the Diels-Alder reaction. The readily accessible 1-benzyl-4-vinyl-1*H*-imidazole (**200e**) was selected as the diene component.

3.3.1 Cycloadditions of 1-Benzyl-4-vinyl-1*H*-imidazole (200e)

Imidazole **200e** was subjected to Diels-Alder reaction with a range of dienophiles (see Table 3.3) in either toluene or CH_2Cl_2, and the progress of the reaction was assessed by monitoring the disappearance of the starting materials by ^{1}H NMR spectroscopy.



200e **202a-o** **203a-o**

Scheme 3.9. Intermolecular Diels-Alder reaction of **200e** with a range of dienophiles.

Entry	Dienophile	Solvent	Temp/^{o}C	Time/h	202[a]/%	203[a]/%
a	Nitrosobenzene	CH_2Cl_2	0	3	**0**	**0**
b	PTAD	CH_2Cl_2	-78	0.5	**63**	**0**
c	DEAD	CH_2Cl_2	20	24	**0**	**0**
d	Maleic Anhydride	CH_2Cl_2	50	4	**35**	**41**
e	Maleimide	CH_2Cl_2	50	8	**58**	**0**
f	NMM	CH_2Cl_2	50	8	**68**	**0**
g	NPM	CH_2Cl_2	50	6	**80**	**0**
h	Diethyl maleate	Toluene	110	168	**27**	**0**
i	Diethyl fumarate	Toluene	110	168	**39**	**0**
j	Dimethyl maleate	Toluene	110	168	**0**	**0**
k	Dimethyl fumarate	Toluene	110	168	**0**	**0**
l	1,4-Naphthaquionone	Toluene	110	168	**0**	**0**

m	Benzoquinone	Toluene	110	168	**0**	**0**
n	DMAD	CH_2Cl_2	20	6	**0**	**0**
o	Benzyne	CH_2Cl_2	40	4	**0**	**0**

Table 3.4. Diels-Alder cycloaddition results. [a]Isolated yields.

200e was reacted with the highly reactive hetero-dienophile nitrosobenzene (entry **a**), and examination of the crude ^{1}H NMR spectrum revealed a number of compounds, consistent with multiple highly coloured spots evident by TLC. However, all purification attempts were unsuccessful and resulted in isolation of unreacted starting material only.

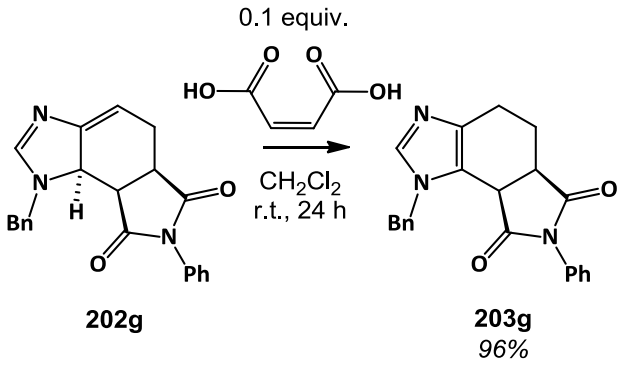
Reaction of the aza dienophile DEAD with **200e** was also unsuccessful when carried out between -78 and 0 ^{o}C in CH_2Cl_2, and the starting materials remained unchanged. Following longer reaction times or higher reaction temperatures, decomposition of the starting materials was observed and no cycloadducts could be isolated.

The aza dienophile PTAD was found to be highly reactive at r.t., with the distinctive vivid pink hue dissipating within a few seconds to give a dark yellow solution. Analysis of this crude solution by ^{1}H NMR spectroscopy revealed numerous compounds and evidence of decomposition. When repeated at -78 ^{o}C, the desired Diels-Alder cycloadduct, **202b**, could be isolated in 63% yield after 30 min. The ^{1}H NMR spectrum of the purified compound was found to be consistent.

The Diels-Alder reaction of **200e** was also investigated with a range of dienophiles containing α,β-unsaturated carbonyls (entries **d-m**), but only the most reactive were found to afford the desired Diels-Alder cycloadducts (**202d-g**). Diels-Alder reaction with the most reactive dienophile, maleic anhydride (entry **d**), led to an approximately 1:1 mixture of the desired cycloadduct **202d** and the rearomatised adduct **203d**. The rearomatisation to **203d** was observed to occur very rapidly following the formation of **202d**. It was thought that this rearomatisation may be promoted by small quantities of maleic acid present in maleic anhydride.

In order to assess whether maleic acid does indeed catalyse the rearomatisation of the initial Diels-Alder cycloadduct, **202g** was stirred in CH_2Cl_2 at r.t. for 24 h with 0.1 equivalents of maleic acid (Scheme 3.10). The solution was then concentrated and analysed by ^{1}H NMR spectroscopy, which revealed quantitative conversion of **202g** to the rearomatised **203g**. Analogous reactions without the presence of an acid catalyst did not lead to rearomatisation, and only the recovery of unreacted **202g** was observed after 7

days at r.t. in CH_2Cl_2.[50]



Scheme 3.10. Maleic acid catalysed rearomatisation of **202e**.

Reaction of vinylimidazole **200e** with the dienophiles maleimide, NMM and NPM (entries **e-g**) were conducted at 50 ^oC in CH_2Cl_2 until the complete disappearance of **200e**. The desired cycloadduct was isolated cleanly as a single diastereoisomer in each case. The dialkyl maleates and dialkyl fumarates **h-k** were found to be unreactive towards **200e** at 50 ^oC in CH_2Cl_2 even on extended reaction times. Following 168 h in toluene at 110 ^oC, only diethyl maleate and diethyl fumarate (entries **h** and **i**) were found to lead to the desired cycloadduct, in relatively low yields (27-39%).

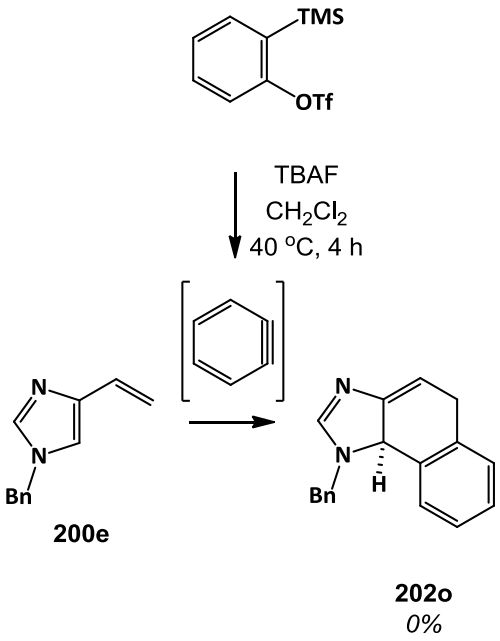
The quinones **l-m** were unreactive towards vinylimidazole **200e** in CH_2Cl_2 and toluene even on extended reaction times, and showed no conversion to cycloadducts after 7 days at 110 ^oC.

The alkyne and aryne dienophiles DMAD and benzyne (entries **n** and **o**) were also investigated, and both found to be unreactive towards Diels-Alder reaction with vinylimidazole **200e**. DMAD gave no reaction after 6 h at r.t., although the gradual degradation and disappearance of peaks relating to starting material was evident.

The highly reactive nature of benzyne necessitated its *in situ* generation, through modification of a literature preparation.[155] Vinylimidazole **200e** and trimethylsilylphenyl triflate **204** were stirred in CH_2Cl_2 at r.t., and cesium fluoride was added. The solution was then heated to 40 ^oC and monitored by ^1H NMR spectroscopy. Unfortunately, cesium fluoride appeared to be insoluble in the reaction conditions, and did not lead to the generation of benzyne.

A solution of *tetra*-butylammoniumfluoride in THF was then employed as an alternative fluoride source, and the reaction was heated to 40 ^oC. The disappearance of trimethylsilylphenyl triflate **204** was observed by ^{19}F NMR spectroscopy, although the

formation of no cycloadducts were observed (Scheme 3.11).



Scheme 3.11. *In-situ* generation of benzyne from trimethylsilylphenyl triflate **204**.

3.4 Conclusions

4-Vinyl-1*H*-imidazole **179** was protected with a series of protecting groups, with the vast majority proceeding in good to excellent yield. Both the 4- and 5-vinyl regioisomers were observed with the methyl (**200a**) and dimethylaminosulfonyl (**200g**) protecting groups, but these could be readily separated by chromatography.

Subsequent Diels-Alder reaction of these imidazoles with NPM led to the isolation of the desired initial Diels-Alder cycloadduct (**71**) in most cases, although the rearomatised adduct (**72**) could be observed on longer reaction times or at higher temperatures.

The N1-benzyl protected imidazole (**200e**) was formed in high yield as a single regioisomer, and was subsequently examined with a range of dienophiles to assess their viability in the formation of suitable cycloadduct ene substrates. NPM was found to be the most successful dienophile, forming the desired cycloadduct **202g** in 80% yield as a single diastereoisomer after 6 h at 50 °C in CH_2Cl_2. PTAD and NMM were also found to be successful dienophiles, leading to the desired cycloadducts in high yields following 0.5 h at -78 °C, and 8 h at 50 °C, respectively.

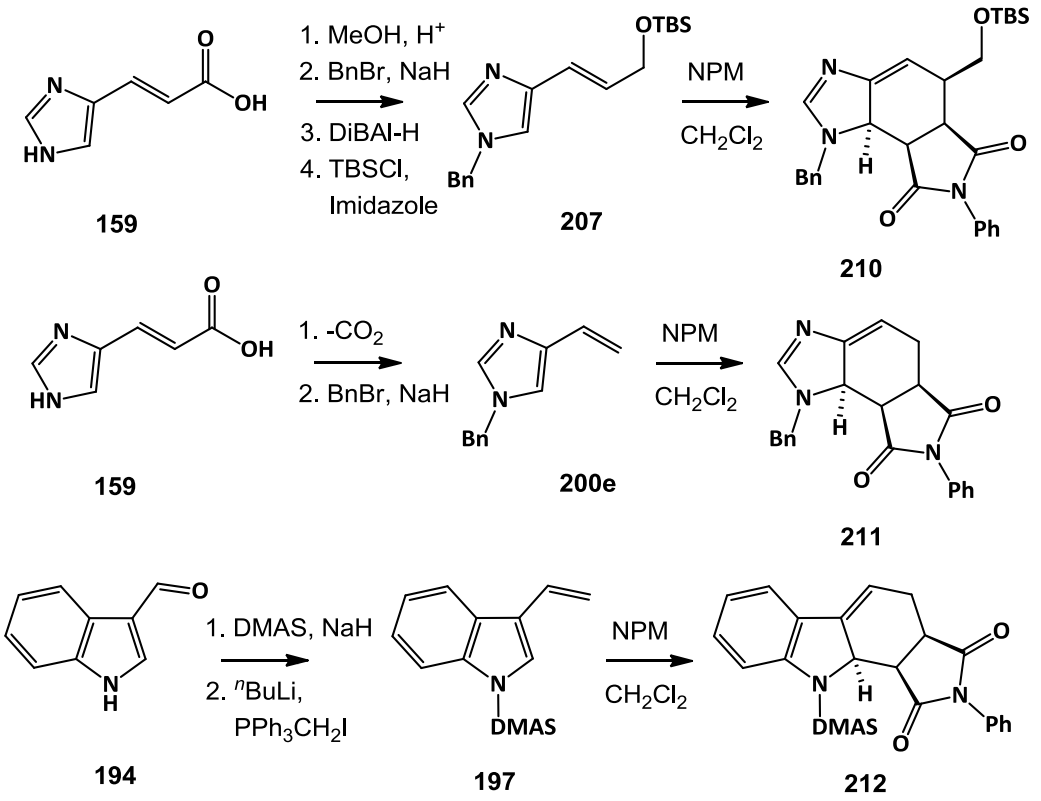
The benzyl-protecting group will now be applied to 4-vinylimidazoles **159** and **179**. These imidazoles and the DMAS protected 3-vinylindole **197** will be subjected to Diels-Alder reaction with NPM, as the dienophile of choice. It is hoped through the optimisation of the imidazole protecting group and Diels-Alder reaction that the potential

formation of unwanted regioisomers and the occurrence of side-reactions and undesirable *in situ* domino reactions has now been minimised. In the following chapter these cycloadducts will be subjected to sequential ene reactions with a range of enophiles, to create structurally complex molecules with a number of chiral centres.

Chapter 4. Ene Reactions

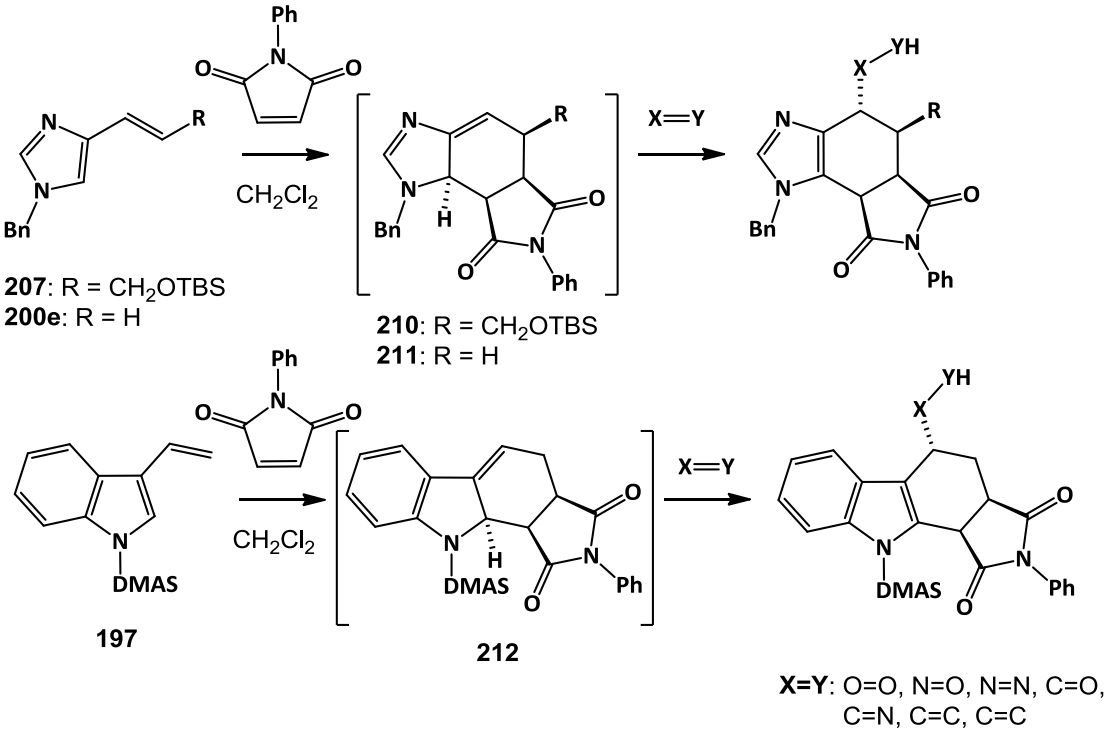
4.1 Introduction

The foregoing chapters have described a successful synthetic route to 1-benzyl-5,6,7,7a-tetrahydro-1*H*-benzo[*d*]imidazoles **210** and **211**, and *N*,*N*-dimethyl-2,3-dihydro-1*H*-carbazole-9(9a*H*)-sulfonamide **212** from simple achiral precursors, through the use of intermolecular Diels-Alder reactions with NPM (Scheme 4.1).



Scheme 4.1. Synthetic routes to Diels-Alder cycloadducts.

The next stage of our synthetic plan is to subject the Diels-Alder cycloadducts **210**, **211** and **212** to selective sequential ene reactions with a range of reactive enophiles to create rapid two-step routes to functionally diverse 4,5,6,7-tetrahydro-1*H*-benzo[*d*]imidazoles and 2,3,4,9-tetrahydro-1*H*-carbazoles. The adoption of this sequential approach to Diels-Alder/ene reactions will enable us to examine the susceptibility of our substrates to ene reaction, which would in turn allow us to select suitably reactive enophiles to trial in one-pot Diels-Alder/ene reactions (Scheme 4.2).



Scheme 4.2. Proposed synthetic route to ene adducts.

4.1.1 Intermolecular Ene Reactions

As discussed in Chapter 1, intermolecular ene reactions are highly useful tools in the generation of molecular complexity, allowing the controlled creation of up to two new stereocentres in a single step. The combination of an intermolecular Diels-Alder and an intermolecular ene reaction would allow, in two steps and from three simple starting materials, rapid access to complex unsaturated 4,5,6,7-tetrahydro-1*H*-benzo[*d*]imidazoles and 2,3,4,9-tetrahydro-1*H*-carbazole analogues, with 100% atom economy and high diastereomeric control in the formation of the multiple C-C and C-X bonds.

However, there are a number of potential problems that may be encountered when utilising the ene reaction, which must be considered.

4.1.1.1 Activation Energy Barrier

The activation energy for concerted intermolecular ene reactions is generally higher than for an analogous Diels-Alder reaction, with ene reactions typically occurring at very high temperatures. The use of elevated temperatures to facilitate the ene reaction with initial Diels-Alder adducts **210**, **211** and **212** is undesirable, and will ultimately lead to rearomatisation (see Chapter 1).

High reaction temperatures may be avoided through the addition of a Lewis acid

as a promoter or catalyst. Complexation of an enophile with a catalytic or stoichiometric quantity of Lewis acid would serve to lower the electron density of the enophile LUMO, making it more reactive, thus lowering reaction temperature. An additional advantage to this approach is the potential for ene reactions to be carried out with a chiral Lewis acid allowing for enantioselectivity.[156,157,158,159]

However, a major disadvantage in the use of Lewis acid catalysed ene reactions is the occurrence of Brønsted acid initiated side reactions. Protic acids may be present as an impurity in Lewis acids or be formed from reaction with traces of water, and can lead to polymerisation and rearomatisation of molecules such as **210**, **211** and **212**.[156] However, this can be circumvented to some extent by employing alkylaluminium halide Lewis acids (e.g. $AlMe_2Cl$), as these can scavenge any generated protons.[156]

An alternative approach to the use of Lewis acids would be to increase the reactivity of the ene or enophile. As the HOMO partner in the ene reaction, a more electron-rich ene would give greater reactivity. Equally, as the LUMO partner, the more electron-deficient an enophile, the more reactive.

A hetero-enophile, in which electronegative heteroatoms directly participate in the ene reaction, will serve to lower the energy of the LUMO and thus increase the reactivity (Figure 4.1). A similar enhancement in enophile reactivity is also observed when moving from alkenes to alkynes/arynes, and through the inclusion of electron-withdrawing substituents on the enophile.

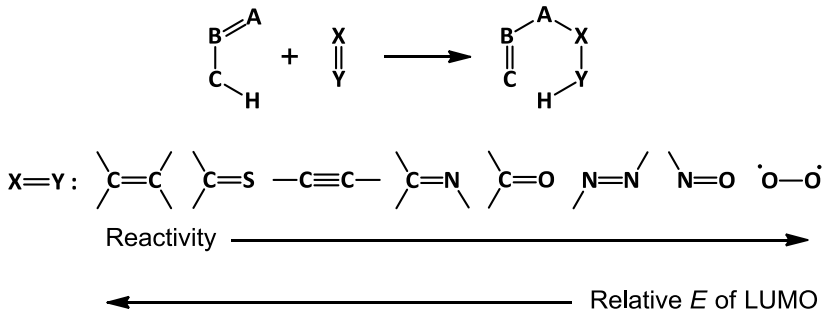
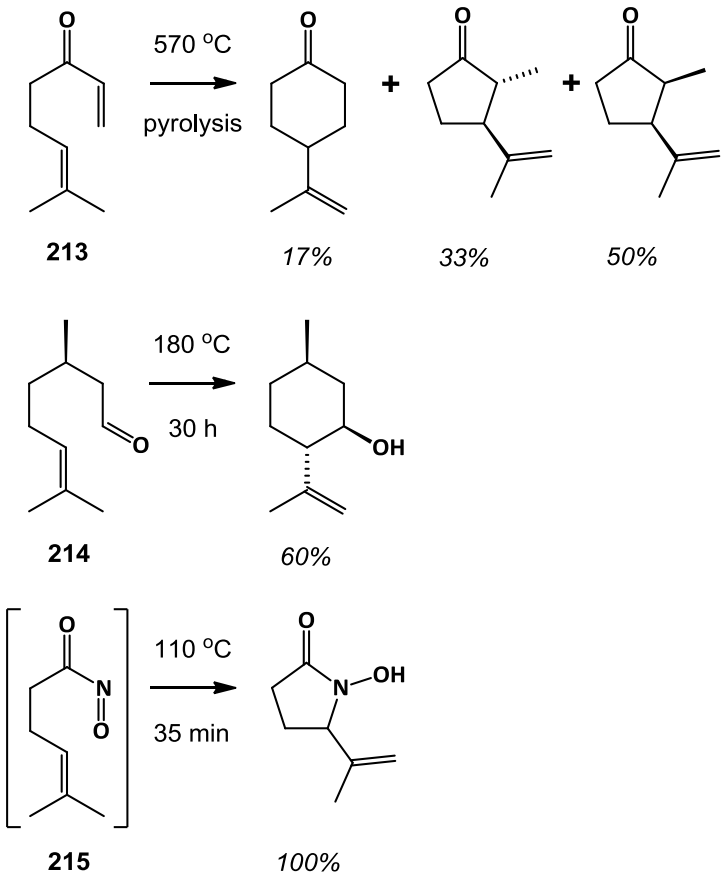


Figure 4.1. Enophile LUMO energy and reactivity.

An example of this increase in reactivity through the inclusion of heteroatoms in the enophile can be observed when comparing the reaction temperatures required for the all-carbon intramolecular ene reaction of **213**,[160] with those for the similar intramolecular hetero-ene reactions of **214**[89] and **215**[71] (Scheme 4.3). It is clear that all-carbon ene reactions require much greater reaction temperatures that their heteroatom equivalents.



Scheme 4.3. Comparison of all-carbon and hetero-ene reactions.

4.1.1.2 Regioselectivity

Thermal ene reactions can suffer from poor regioselectivity, with the steric accessibility of the double bond and allylic hydrogen being an important factor. It has been shown that methyl and methylene hydrogens are abstracted more easily than methine hydrogens, and a primary hydrogen is abstracted more readily than a secondary or tertiary hydrogen. However, the relative ease and resulting regioselectivity of hydrogen abstraction is largely dependent on the choice of enophile employed.[156]

This abstraction preference can be rationalised as a combination of the stabilisation provided through coordination to allylic hydrogens, and the minimisation of steric repulsion during the approach of the enophile. For example, singlet oxygen ($^1O_2$) will preferentially abstract from the more crowded side of the double bond, taking advantage of stabilising coordination with the allylic hydrogens, known as the *cis* effect. However, there is often little selectivity displayed between the *lone* and *twix* hydrogens. Triazolinediones (TAD) will generally prefer to abstract from the more crowded end of the alkene to minimise steric repulsion with the *twin* substituent (the *gem* effect), again with little selectivity for either *twin* or *twix*. Whereas arylnitroso compounds abstract

from both the more crowded *cis* side of the alkene, and the more crowded geminally substituted end. This combination of *cis* and *gem* effects leads it to preferentially abstract the *twix* hydrogen, *via* the so-called skew trajectory (Figure 4.2).[70]

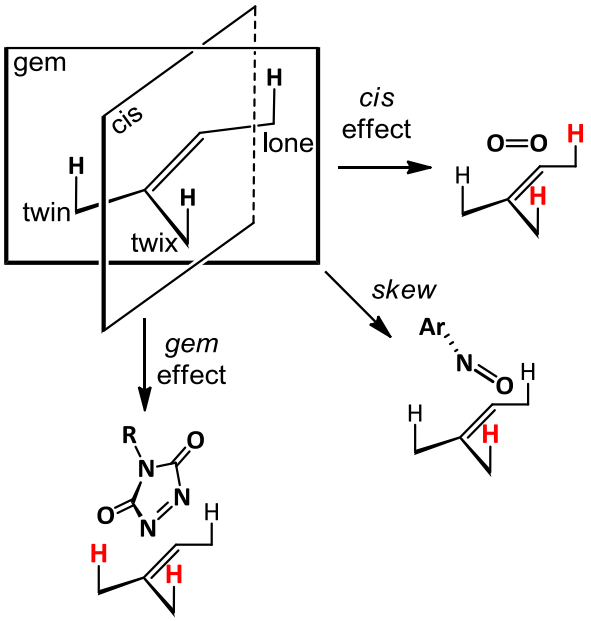
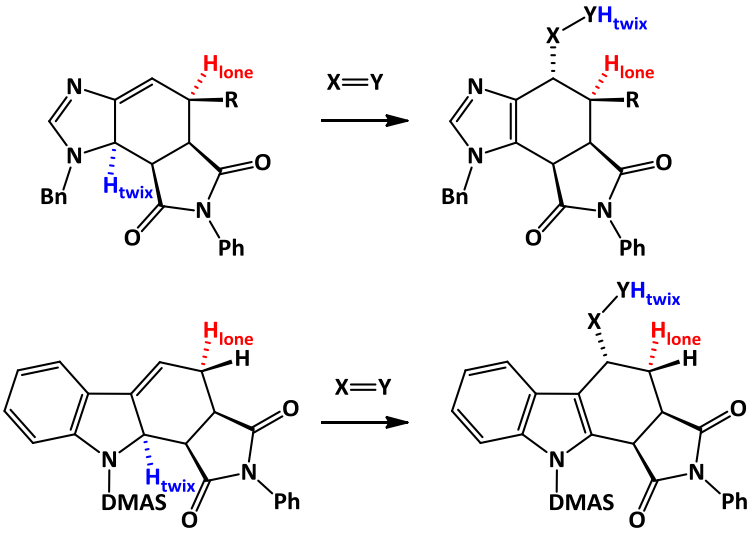


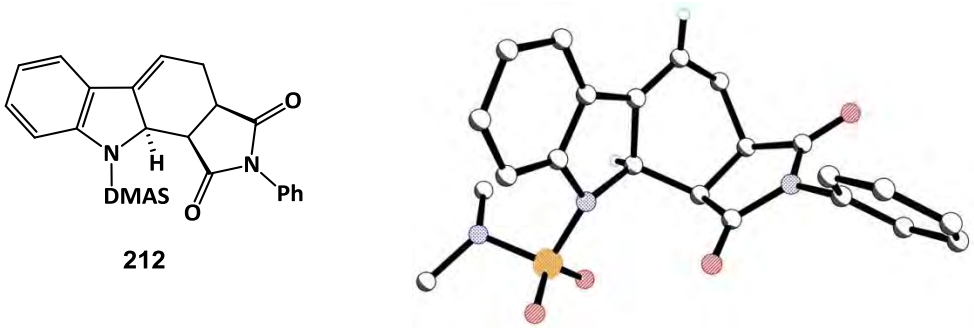
Figure 4.2. Regioselectivity in the ene reaction of ArNO, $^1O_2$ and TAD.[70]

Consideration of our ene substrates **210-212** reveals that abstraction of H_{twix} and H_{lone} are the only pathways possible for ene reaction, as neither substrate possesses a H_{twin}. A concerted ene reaction which abstracts the *twix* hydrogen would result in the installation of the enophile on the same face as the abstracted hydrogen, which would be more favourable sterically to avoid interaction with the NPM moiety. In addition, abstraction of H_{twix} would lead to rearomatisation of the imidazole or indole ring, providing highly favourable thermodynamics. (Scheme 4.4).



Scheme 4.4. Ene reaction involving abstraction of H_{twix}.

In addition, examination of the X-ray crystal structures of molecules such as **210**-**212** show that the *twix* C-H σ-bond is coplanar with the electron-rich cyclohexenyl C=C π-bond (Figure 4.3).[41,54,161] It is likely, therefore, that ene reactions with **210**-**212** would be regioselective, with preferential abstraction of the *twix* hydrogen.



212

Figure 4.3. X-ray crystal structure of **212**. Non-essential hydrogens removed for clarity.

4.1.1.3 Diastereoselectivity

The diastereoselectivity of the newly installed chiral centre observed in the ene reaction is controlled by the initial approach of the enophile, and whether this occurs in an *endo* or *exo* fashion. A number of studies in the literature have shown the ene reaction to have a slight *endo* preference.[162,163,164] Although this can be disrupted by steric effects,[157] through the use of a chiral enophile, steric/electronic shielding of one π face of the alkene, or by directing an enophile to a particular face through hydrogen bonding or coordination of enophile lone pairs.[70]

4.2 Evaluation of imidazole-based enes 210 and 211 in the ene reaction

4.2.1 Singlet Oxygen Ene Reactions

The singlet oxygen ene reaction has received the most synthetic attention of all intermolecular ene reactions appearing in the literature. Though numerous studies are in agreement that singlet-oxygen prefers to abstract hydrogen from the more congested side of the alkene *via* the *cis*-effect, its mechanistic detail remains in debate. Many theoretical and experimental results have been put forward to support both stepwise and concerted hypotheses.

The proposed concerted mechanism would involve a six-membered cyclic transition state in which the bonds are broken and formed concomitantly (pathway **a**, Figure 4.4). Alternatively, a range of stepwise pathways have also been suggested, including biradical (**b**), dipolar (**c**), perepoxide (**d**), exciplex (**e**) and 1,2-dioxetane (**f**) intermediates.[165]

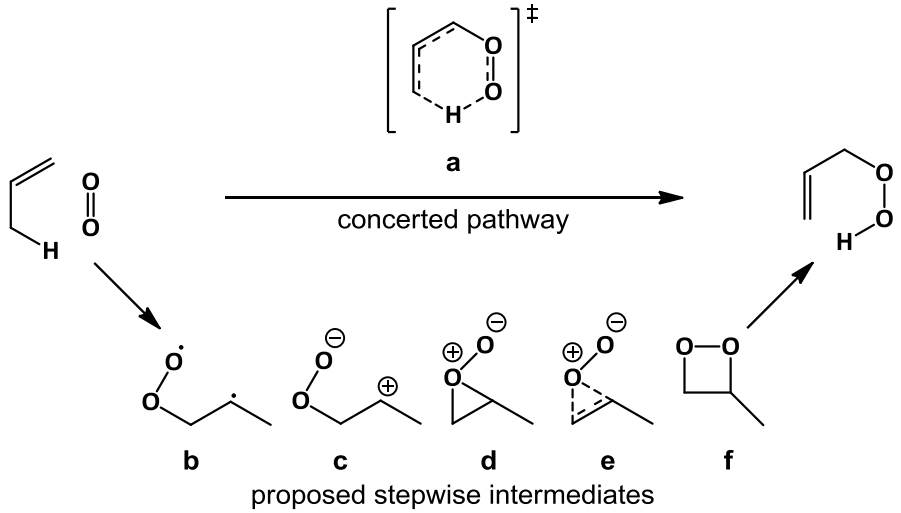


Figure 4.4. Proposed stepwise and concerted pathways for the $^1O_2$ ene reaction.[166]

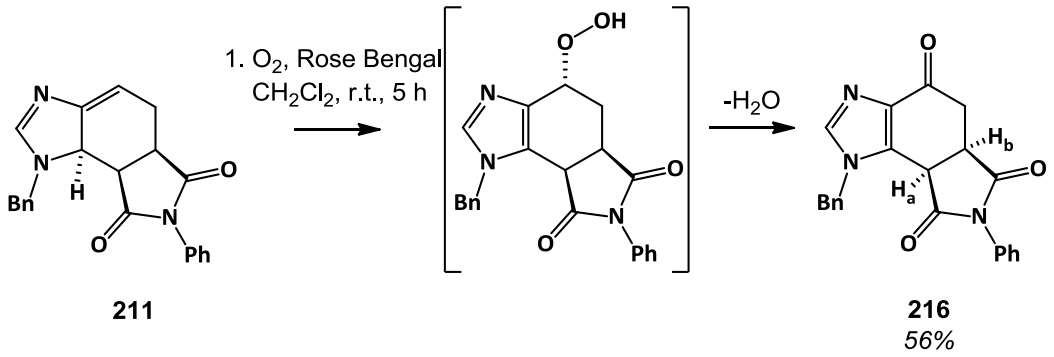
However, whilst experimental evidence exists to support each mechanism, the issue remains contentious.

4.2.1.1 Examination of the Singlet Oxygen Ene Reaction of 211

The Diels-Alder enamine **211** was dissolved in CH_2Cl_2 at r.t. and 0.01 equivalents of photosensitising dye (Rose Bengal) was added. The solution was then stirred vigorously while open to air under a constant source of light, monitoring by TLC. After 22 h, the starting material was no longer visible by TLC and a number of new spots had appeared. The reaction was then concentrated and purified by flash column chromatography to afford one major adduct in 56% yield.

Analysis of the purified compound by ^1H NMR spectroscopy revealed the new adduct displayed a downfield shift of the two doublets corresponding to the benzylic CH_2 protons from 4.77 and 4.90 ppm to 5.68 and 5.31 ppm. This downfield shift is consistent with the decreased nuclear-shielding that would be observed on rearomatisation through delocalisation with the re-formed imidazole ring.

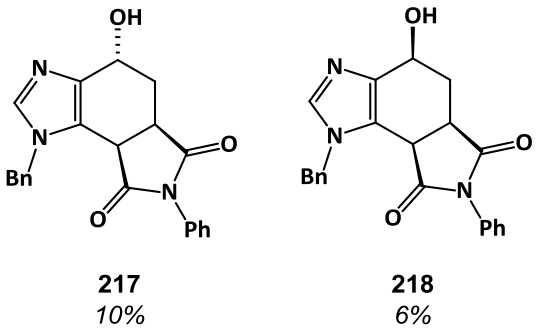
Also present in the aliphatic region was a doublet at 4.21 ppm corresponding to H_a and a doublet of doublets of doublets at 3.75 ppm corresponding to H_b. In addition, two doublets of doublets corresponding to a second CH_2, with a geminal coupling constant of 17.4 Hz appeared at 3.22 and 2.93 ppm. The proposed structure is shown below in Scheme 4.5, arising from singlet-oxygen ene reaction of **211**, followed by dehydration to afford ketone **216**.



Scheme 4.5. Singlet oxygen ene reaction of **211**.

Numerous literature examples are in agreement that singlet-oxygen preferentially abstracts a hydrogen from the more crowded side of the alkene during an ene reaction, from either the *lone* or *twix* position, due to favourable coordination with the allylic hydrogens. The observed regiochemistry indicates that abstraction of the *twix* hydrogen has occurred, leading to rearomatisation of the imidazole ring. However, the resulting reactive hydroperoxide has seemingly undergone dehydration to give ketone **216**.

It is not possible to determine the relative diastereoselectivity of the newly installed chiral centre, as we were unable to isolate the hydroperoxide before dehydration. However previously in the literature, Lovely *et al*. observed the formation of an epimeric mixture of alcohols **217** and **218** as a by-product of the Diels-Alder reaction of **211** and NPM (Scheme 4.6).[43,44,167] The authors attributed these by-products to oxidation of the initial Diels-Alder adduct **211** by oxygen dissolved in the reaction solvent. The major isomer observed by Lovely *et al*. is **217**, with the alcohol installed on the opposite face to the NPM moiety, on the same face from which H_{twix} was abstracted. This structure is likely favoured due to the reduction of steric interaction with NPM, and through favourable hydrogen-bonding interactions with the allylic hydrogens on the rear face.



Scheme 4.6. Epimeric by-products of the Diels-Alder reaction of **211** and NPM.

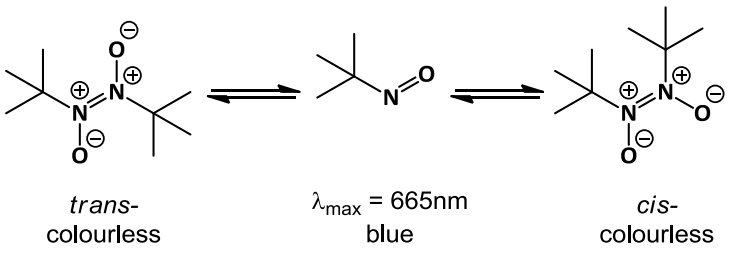
In our experiments, the reactive nature of singlet-oxygen also led to issues with by-products and degradation, as numerous compounds were visible by TLC and on analysis of the crude reaction mixture by ^{1}H NMR spectroscopy. Longer reaction times (22 h) led to greater degradation, which was observed by the disappearance of product peaks in the ^{1}H NMR spectrum, and the appearance of signals associated with several other molecules. Additionally, following longer reaction times, no products could be isolated in significant yield from purification attempts.

4.2.1.2 Conclusions

Following reaction of singlet oxygen with enamine **211**, the initial hydroperoxide ene adduct was not observed, and only the dehydrated ketone **216** could be isolated. In addition, the highly reactive nature of singlet oxygen led to the generation of numerous by-products and subsequent degradation. Therefore, it is unlikely that singlet oxygen would be a viable enophile for one-pot reactions under these conditions.

4.2.2 Nitroso Ene Reactions

Nitroso containing compounds are highly reactive and are known to participate in numerous reactions, including Grignard, nitroso-Aldol, and pericyclic reactions. The nature of this reactivity stems from their low energy LUMO, which make nitroso compounds powerful electrophiles. They are also known to readily dimerise, which can be observed as the loss of the typical vivid blue or green colouration arising from absorption in the λ_{max} ~700 nm region. These colourless dimers can exist in the *cis*- or *trans*- form (Scheme 4.7),[168] with the position of the equilibrium being largely dependent on the nature of the R-group.



Scheme 4.7. Dimerisation of nitroso compounds.

Nitroso compounds are commonly employed as enophiles in the nitroso-ene reaction, and represent a direct regioselective and stereoselective method of allylic nitrogen functionalisation of alkenes. The low energy LUMO caused by the polarisation

of the nitrogen-oxygen bond places them among the most reactive class of enophiles. However, this increased reactivity may also lead to a variety of *in-situ* side-reactions, including dimerisation, addition, oxidation and reduction.[70]

The number of readily available nitroso compounds is limited, as their high reactivity frequently leads to synthetic difficulties. In addition, the position of equilibrium between monomer and dimer often hinders the development of selective reactions involving nitroso compounds. However, a number of the more common nitroso compounds applied in ene reactions are shown in Figure 4.5.[70,169,170]

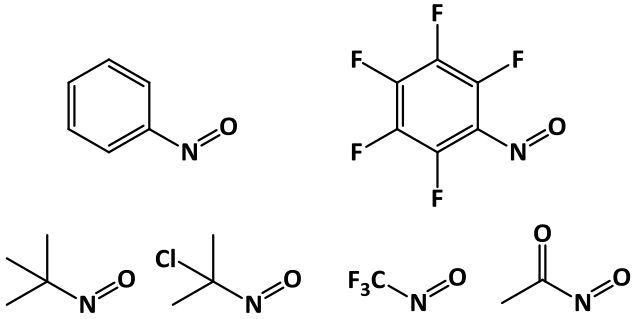


Figure 4.5. Common nitroso enophiles.

The regioselectivity of nitroso-ene reactions is often reliably predictable. Alkylation will occur at the electrophilic nitrogen rather than oxygen, and there is a clear preference for hydrogen abstraction at the more substituted (*geminal*) end of the alkene, choosing the *twix* hydrogen rather than the *twin*.[171] This regioselectivity minimises the steric repulsion of the enophile with substituents on the ene in the transition state.

In terms of our substrates **210**-**212**, *twin* hydrogen abstraction is not possible and so it would be expected that ene adducts would be formed from the regioselective abstraction of the sterically favourable twix hydrogen exclusively (Figure 4.6). In addition, this *twix* abstraction would lead to rearomatisation of the imidazole or indole ring, which would be thermodynamically favourable.

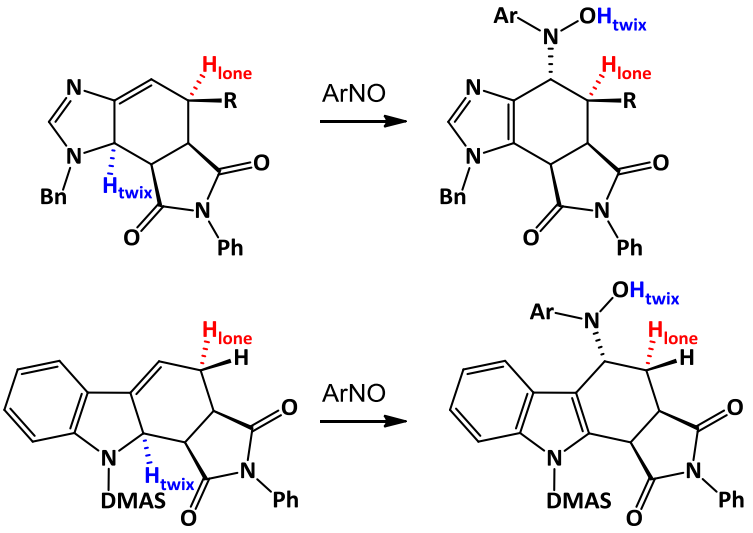
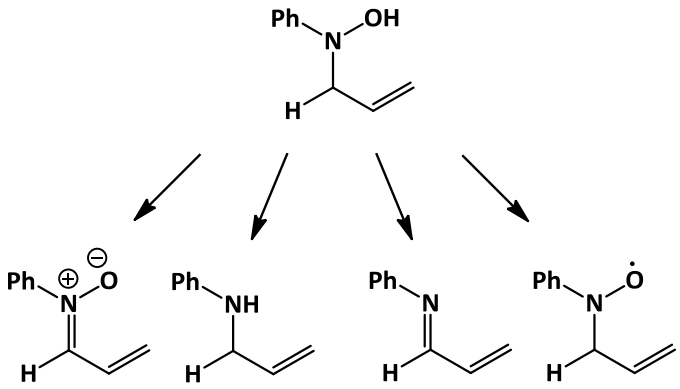


Figure 4.6. Predicted regioselectivity in the ene reaction of ArNO.

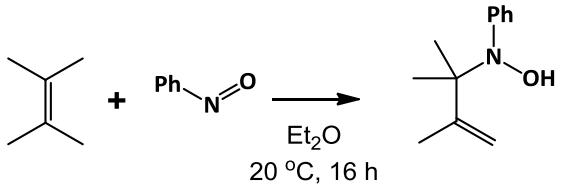
Whilst the regioselectivity of the nitroso-ene reaction is often predictable, the reactive nature of the resulting hydroxylamine products mean they may be subject to further *in situ* transformations to nitrones, imines, amines and nitroxides (Scheme 4.8), which can lead to poor yields.[70,168,169]



Scheme 4.8. *In-situ* transformations of hydroxylamine products of nitroso-ene reaction.

4.2.2.1 Examination of the Ene Reaction of 211 with Aryl-Nitroso Compounds

Historically, nitrosobenzene was one of the first nitroso compounds, and subsequently one of the most common, to be employed as an enophile. It was shown by Knight *et al.*[172] to react quantitatively with tetramethylene (**219**) at r.t. to give the corresponding hydroxylamine (**220**, Scheme 4.9).

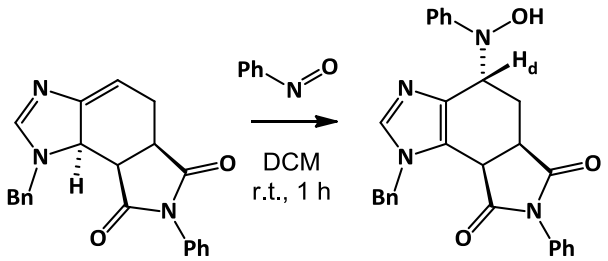


219 **220** *100%*

Scheme 4.9. Nitroso-ene reaction of tetramethylene and nitrosobenzene.

In our studies, the Diels-Alder enamine **211** was dissolved in CH_2Cl_2 at r.t. and nitrosobenzene added. The colourless solution turned a vivid green on the addition of nitrosobenzene, which dissipated after 15-30 s leaving a yellow solution. After stirring for 1 h a white precipitate formed, and the reaction was concentrated and purified by flash column chromatography, giving compound **221** in 95% yield.

Analysis of the purified compound by ^{1}H NMR spectroscopy revealed the characteristic downfield shift in the benzylic CH_2 protons following rearomatisation of the imidazole moiety. In addition, there was the appearance of a doublet of doublets at 4.75 ppm which would be consistent with the decreased shielding observed by H_d in the hydroxylamine adduct **221**, due to proximity to the electronegative N-OH (Scheme 4.10).



211 **221** *95%*

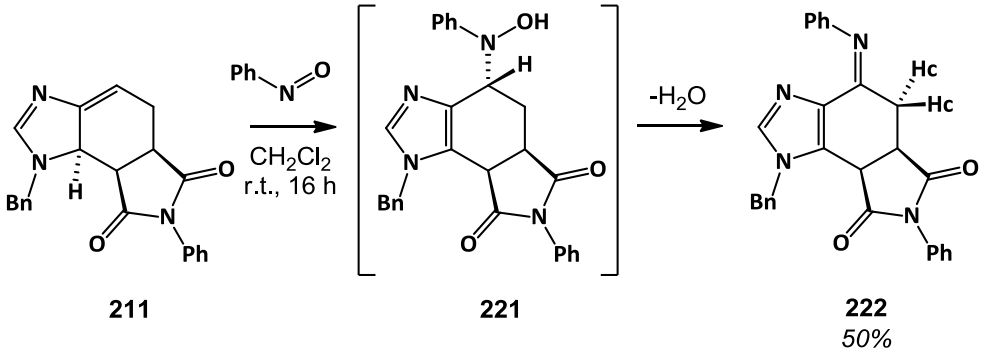
Scheme 4.10. Reaction of **211** with nitrosobenzene.

This structure indicates ene reaction has occurred with regioselective hydrogen abstraction from the *twix* position, as predicted. The newly installed enophile resides on the same face from which the abstracted hydrogen was lost, consistent with a concerted ene reaction.

During this 1 h reaction time, no by-products through *in-situ* transformations or degradation were observed. However, on longer reaction times, examination of the crude mixture by ^{1}H NMR spectroscopy revealed a number of additional compounds. Purification by flash column chromatography led to the isolation of imine **222** as the

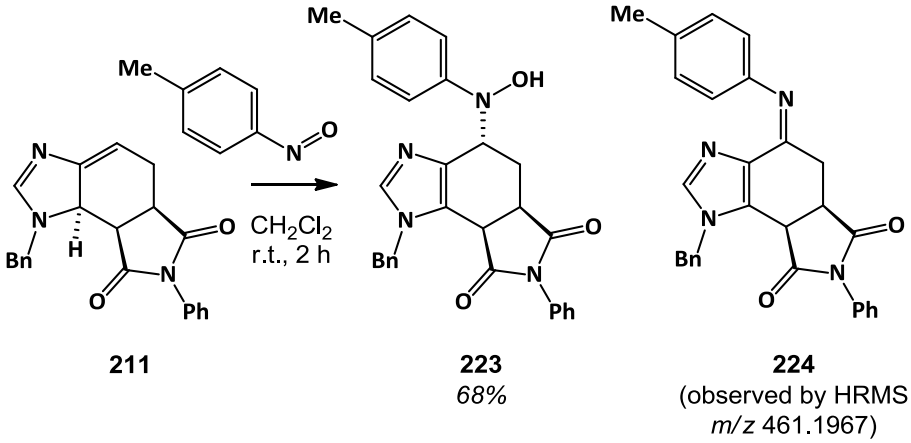
major component in 50% yield. Analysis of this compound by NOESY failed to show any positive correlation between the imino-phenyl and H_c which would suggest an *E*-configuration, therefore the structure has been assigned the *Z*-configuration (Scheme Scheme 4.11).

This dehydration to give imine **222** is often observed when ene products derived from electron-rich nitroso compounds are treated with acids or bases, or on heating.[70] No other compounds could be isolated cleanly.



Scheme 4.11. Ene reaction and subsequent dehydration to imine **222**.

Analogous results were observed in the reaction of 2-nitrosotoluene and **211**, which led to a single ene adduct, **223**, after 2 h at r.t. in CH_2Cl_2. Following purification by flash column chromatography, the ^{1}H NMR spectrum of the hydroxylamine ene adduct was similar to that of the nitrosobenzene adduct **221**, as expected. Analysis by HRMS was also consistent, with a parent ion of *m/z* 479.2065 giving a formula of $C_{29}H_{27}N_4O_3$. In addition, a peak was observed at *m/z* 461.1967, which is consistent with the formation of the imine **224**, although this was not observed by NMR analysis.



Scheme 4.12. Reaction of **211** with 2-nitrosotoluene.

To definitively assign the regiochemistry and stereochemistry at the ene chiral centre, crystals were grown by slow diffusion from diethyl ether/methanol for analysis by single crystal X-ray crystallography. The stereochemistry of the structure obtained indicated that ene reaction has occurred on the opposite face to the NPM moiety, on the same face of the molecule from which the allylic hydrogen is abstracted, which is consistent with concerted ene reaction (Figure 4.7).

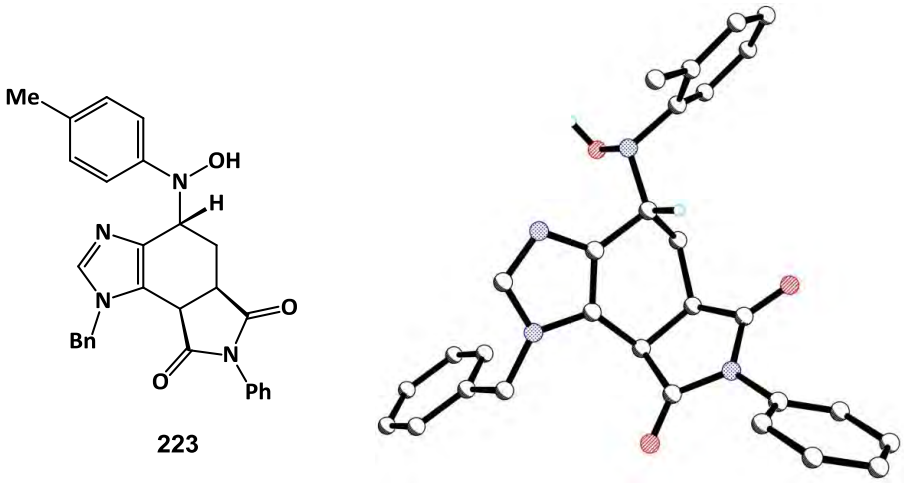
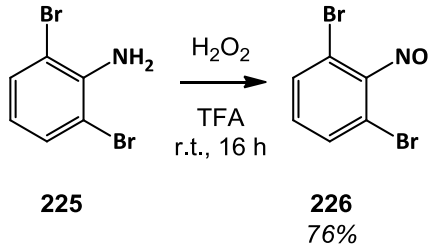


Figure 4.7. X-ray structure of **223**. Non-essential hydrogens omitted for clarity.

Ene reaction of **211** with 2,6-dibromonitrosobenzene (**226)** was then also examined. **226** was synthesised from direct oxidation of 2,6-dibromoaniline (**225**) with 35% hydrogen peroxide in trifluoroacetic acid, and recrystallised from *n*-hexane (Scheme 4.13).



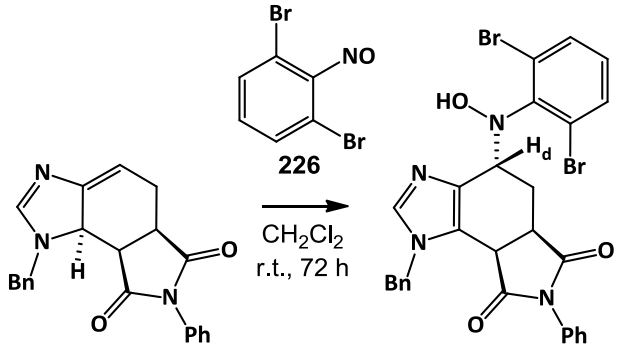
Scheme 4.13. Synthesis of **226** from 2,6-dibromoaniline.

226 was then stirred in CH_2Cl_2 at r.t. for 72 h with enamine **211** until there was no trace of starting materials visible. The crude material was then analysed by ^{1}H NMR spectroscopy and appeared to show the desired product, although the peaks were not well resolved.

Poor resolution in the NMR spectra is a commonly observed problem of nitroso-ene reactions, due to trace amounts of nitroxides that are very often formed, particularly

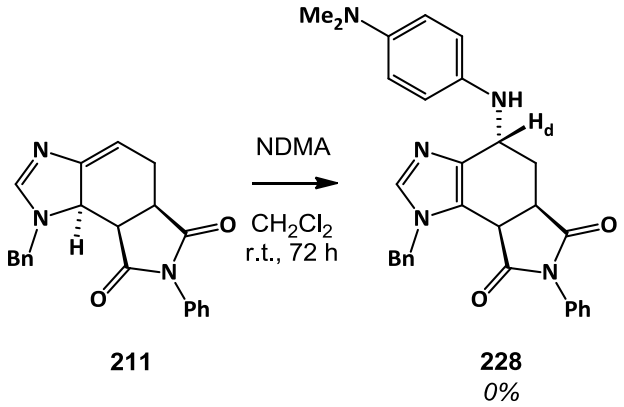
in those reactions of electron-rich substrates. These radicals can cause signal broadening in the NMR spectra which can hinder product analysis.[70] To resolve this problem, 5 mg of phenylhydrazine was added to the samples immediately before NMR analysis to remove the paramagnetic impurities.[173] This led to improved peak resolution, although the signals remained broader than those observed in **211** or analogous ene compounds.

The crude residue was then purified by flash column chromatography, and the major adduct (**227**) was isolated in 73% yield (Scheme 4.14). Analysis of the purified compound showed the characteristic downfield shift and separation of the benzylic CH_2 protons, and also a large downfield shift of the signal corresponding to H_d, to 5.34 ppm. This is a significant shift in comparison to the other nitroso-ene adducts (i.e. H_d in **221** = 4.75 ppm, and in **223** = 4.29 ppm). This effect is likely due to the increased electron-withdrawing nature of the dibromo-substituted phenyl.



Scheme 4.14. Ene reaction of **211** with 2,6-dibromonitrosobenzene.

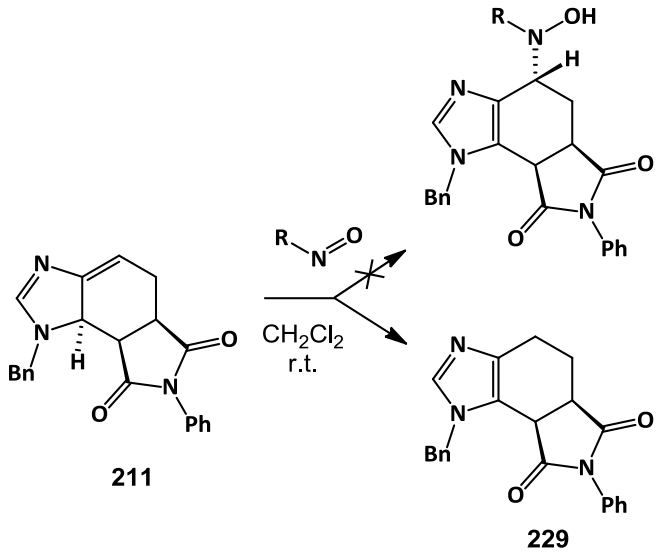
The Diels-Alder enamine **211** was also stirred with *N,N*-dimethyl-4-nitrosoaniline (NDMA) at r.t. for 72 h. Examination of the resulting crude mixture by ^{1}H NMR spectroscopy indicated a single adduct, which displayed the downfield shift of benzylic protons that is characteristic of rearomatisation and ene addition, and an apparent doublet of doublets at 4.45 ppm, consistent with H_d (Scheme 4.15). In addition, the aliphatic region has gained a singlet integrating to 6H at 2.85 ppm corresponding to $–NMe_2$, and a broad signal integrating to 1H at 2.99 ppm, which could be consistent with an N-H, as in structure **228** (Scheme 4.15). Unfortunately, all attempts to purify the reaction mixture by chromatography were unsuccessful, and adduct **228** was unobtainable.



Scheme 4.15. Unsuccessful ene reaction of **211** with NDMA.

4.2.2.2 Examination of the Ene Reaction of 211 with Alkyl-Nitroso and Nitrosamine Compounds

The nitroso compounds listed in Table 4.1 appeared to be too unreactive to undergo ene reaction with Diels-Alder cycloadduct **211** under these conditions, and failed to provide the expected ene adduct. Examination of the crude reaction mixtures by ^{1}H NMR spectroscopy revealed the major product to be rearomatised imidazole **229**. It appears that over extended reaction times, slow rearomatisation of the imidazole ring is competing with ene reaction (Scheme 4.16).



Scheme 4.16. Competing rearomatisation reaction.

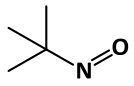
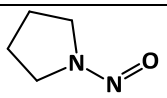
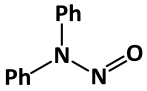
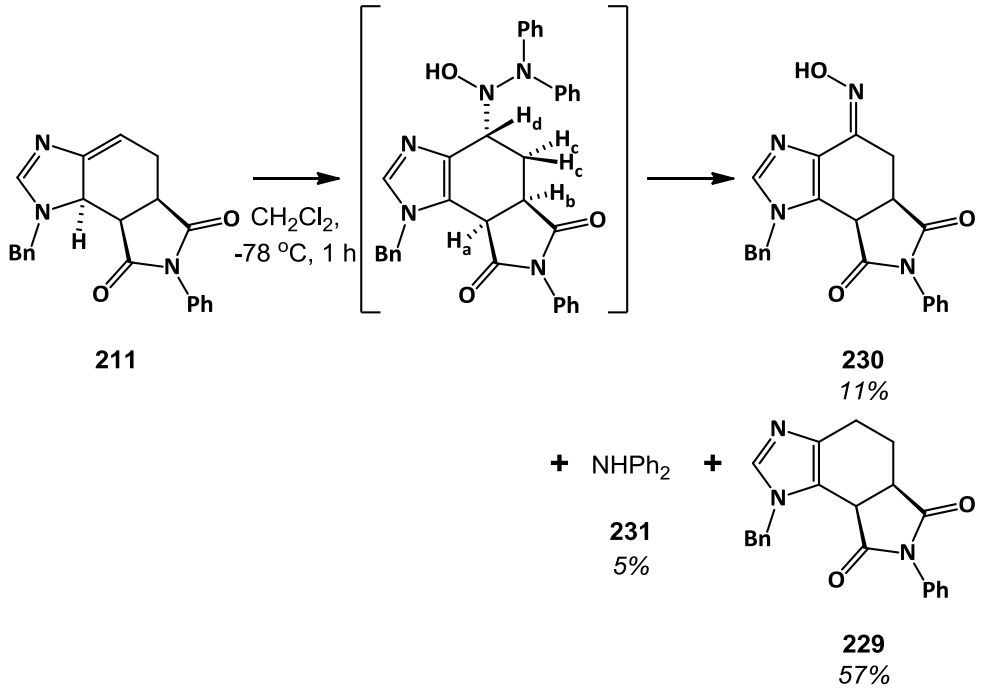
Entry	Nitroso Enophile	Reaction Conditions	Ene adduct (%)	Yield of by-products[a] (%)
a		CH_2Cl_2 0 °C→r.t., 16 h	0	**229** 18%
b		CH_2Cl_2 0 °C→r.t., 16 h	0	**229** 5%
c		CH_2Cl_2 0 °C→r.t., 72 h	0	**229** 57% **230** 11% **231** 5%

Table 4.1. Outcome of ene reactions with **211**. [a]Isolated yields.

The reaction of both the alkyl-nitroso compound 2-methyl-2-nitrosopropane (entry **a**) and the nitrosamine 1-nitrosopyrollidine (entry **b**) with enamine **211** led only to the isolation of the rearomatised Diels-Alder adduct **229** after 16 h at r.t. in CH_2Cl_2, in 18 and 5% yield respectively.

However, analysis of the reaction of **211** with *N*-nitrosodiphenylamine (entry **c**) by ^{1}H NMR spectroscopy revealed the appearance of two major adducts. These were consistent with the rearomatised imidazole **229** (57%), and a second adduct in low yield (11%). Analysis of the second adduct by ^{1}H NMR analysis indicated that it was comparatively similar to imidazole **229**, but appeared to be lacking the two protons corresponding to H_d (Scheme 4.17). Also, whilst the signals relating to protons H_a and H_b were essentially unchanged, those corresponding to H_c were simplified to two doublet of doublets, consistent with the loss of the additional splitting from the H_d protons. In addition, examination of the first fraction eluted indicated a highly non-polar compound with aromatic signals at 6.82-7.20 ppm integrating to 10 protons, and a broad singlet at 5.66 ppm integrating to 1 proton, which is consistent with literature values for diphenylamine (**231**).[174]

Examination of the aromatic region of the ^{1}H NMR spectrum does not reveal a gain in 10 aromatic protons which would be consistent with the addition of diphenylamine. It is likely therefore, that adduct **230** is an oxime, having lost the stable anion diphenylamine (Scheme 4.17). It was assigned the *Z*-configuration due to the lack of any positive correlation between the oxime and H_c when analysed by NOESY.



Scheme 4.17. Ene reaction of *N*-nitrosodiphenylamine leading to loss of diphenylamine.

4.2.2.3 Conclusions

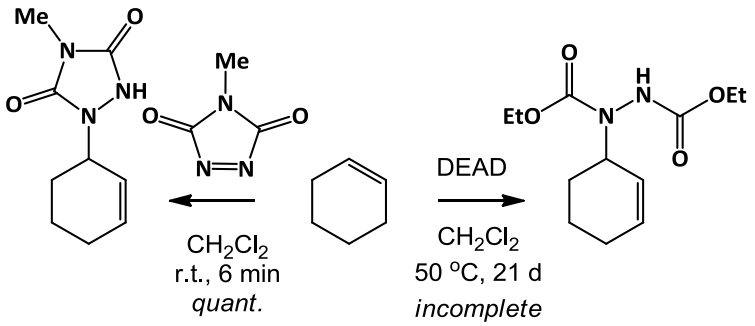
The nitroso-ene reactions of a number of aryl nitrosos with the ene substrate **211** were successful, with the desired hydroxylamines being isolable in excellent yield (68-95%). However, due to the high reactivity of these hydroxylamines, both those ene adducts arising from nitrosobenzene and 2-nitrosotoluene were subject to *in situ* dehydration to yield the respective imines on longer reaction times.

In addition, reaction with 1-methylnitrosopropane, 1-nitrosopyrrolidine and nitrosodiphenylamine led to the formation of a number of by-products including oxime **230**, and the rearomatised imidazole **229**. These results are consistent with those observed in the literature for highly electron-rich nitroso compounds such as *N,N*-dimethyl-4-nitrosoaniline, *N,N*-diphenyl-4-nitrosoaniline and 4-nitrosophenol, which have been shown to undergo almost entirely disproportionation to amines, nitrones and oximes when there is the possibility for stabilisation through conjugation.[70,175,176]

These *in situ* transformations, and the potential for side-reactions of the nitroso starting materials, are a limitation to the suitability of these compounds in ene reactions.

4.2.3 Aza Ene Reactions

Triazolinediones (TAD) are commonly employed as enophiles in the ene reaction due to the apparent similarities in their reactivity with that of singlet-oxygen.[170] The aza-ene reaction of TAD was first studied by Pirkle and Stickler,[79] who found that TAD would react rapidly with ene substrates and behaved as an excellent enophile in comparison to the rather sluggish, linear diethyl azodicarboxylate (DEAD). They showed that 4-methyl-1,2,4-triazoline-3,5-dione (MTAD) would fully react with cyclohexene in CH_2Cl_2 after 6 min at r.t., whilst the analogous reaction with DEAD was incomplete after 3 weeks at 50 ^oC (Scheme 4.18).



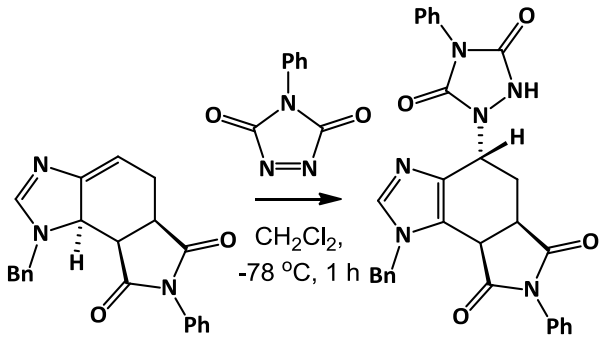
Scheme 4.18. Reaction of cyclohexene with MTAD and DEAD.

Aza-ene reactions of TAD have also been found to be highly regioselective. This can be attributed to the preference of TAD enophiles to abstract from the more crowded end of the ene, due to steric and electronic factors (*gem* effect).[171,177,178]

4.2.3.1 Ene reaction of 211 with PTAD

Following some reaction optimisation, **211** was reacted with PTAD in CH_2Cl_2 at -78 ^oC, giving an isolated 74% yield of a single product. Spectral data were in agreement with the expected ene reaction product (**232)**, with characteristic splitting of the benzylic CH_2 into two geminally coupled doublets, and a clean ^{13}C NMR spectrum and accurate mass (Scheme 4.19).

However, the ^1H NMR spectrum appeared to be subject to some degree of line broadening, which may be due to some restricted rotation around the newly formed N-C bond, possibly leading to rotamers in solution.



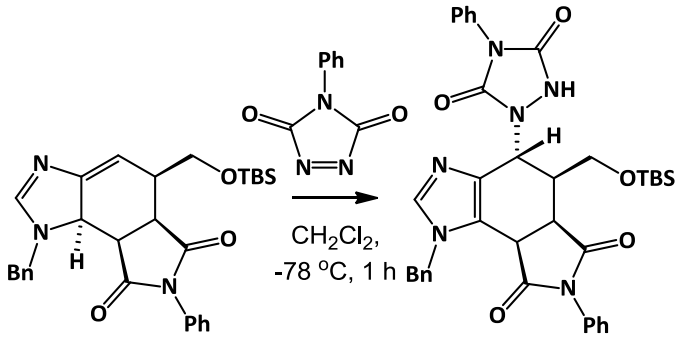
211 **232**
74%

Scheme 4.19. Reaction of **211** with PTAD to give **232**.

4.2.3.2 Ene reaction of 210 with PTAD

The methylene-OTBS substituted enamine **210** was also stirred with PTAD in CH_2Cl_2 at -78 °C for 1 h, and the corresponding ene adduct was obtained in 61% yield following purification by flash column chromatography (Scheme 4.20). Analysis by ^1H NMR spectroscopy was consistent with the desired ene adduct (**233**), and the typical downfield shift in the two doublets corresponding to the benzylic CH_2, to 5.27 and 5.56 ppm was also observed.

The reaction yield is slightly lowered in comparison to the non-substituted variant, which may be due to the reduced steric accessibility of the ene caused by the methylene-OTBS.



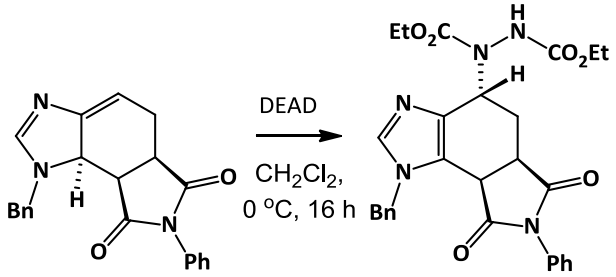
210 **233**
61%

Scheme 4.20. Ene reaction of **210** with PTAD.

4.2.3.3 Diethyl azodicarboxylate

211 was initially stirred with diethyl azodicarboxylate at -78 °C in CH_2Cl_2, and the crude reaction mixture was monitored by ^1H NMR spectroscopy. After 4 h, no

reaction was observed to have occurred and so the solution was warmed to 0 °C for 1 h. Following analysis by ^{1}H NMR spectroscopy, the observed peaks were consistent with the formation of a new cycloadduct which displayed the typical downfield shift of benzylic protons, characteristic of rearomatisation and ene addition. In addition, the multiplet at 4.38-3.94 ppm integrating to 4 protons corresponded to overlap of the two CH_2 groups of the ethyl esters, whilst the 6 proton multiplet at 1.23-1.15 ppm was consistent with overlap of the corresponding CH_3 groups of the ethyl esters (Scheme 4.21). However, all attempts to purify the reaction mixture by chromatography were unsuccessful, due to degradation on silica gel during chromatography and adduct **234** was unobtainable.



211 **234** *0%*

Scheme 4.21. Ene reaction of **211** with diethyl azodicarboxylate.

4.2.3.4 Conclusions

The aza-ene reaction of PTAD with enamines **210** and **211** was very rapid and led to decomposition when carried out at r.t. At -78 °C, the desired hydrazides (**232** and **233** were obtainable in good yields (61-74%).

The linear dienophile DEAD was less reactive, and required higher temperatures (0 °C) to facilitate reaction, although subsequent purification led to degradation on silica gel and no products could be isolated. Characterisation of crude **234** by ^{1}H NMR spectroscopy was difficult, due to the extent of line broadening evident in the spectrum, which may be due to the occurrence of rotamers caused by restricted rotation of the newly installed N-C bond. Line broadening was also observed in the examination of **232** and **233**, but to a lesser extent.

4.2.4 Carbonyl Ene Reactions

The carbonyl ene reaction represents an important carbon-carbon bond forming process, and is a useful method for the asymmetric synthesis of enantiomerically pure

acyclic molecules. One of the main drawbacks of the carbonyl ene reaction however, is the limited enophile scope. The majority of all successful reactions are limited to highly reactive carbonyl components (e.g. glyoxalates, formaldehyde or chloral), or highly activated ene components (e.g. 2-methylene-2,3-dihydrofuran).[157]

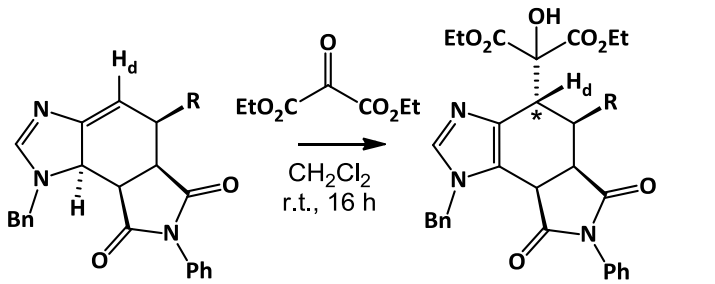
In addition, usually stoichiometric amounts of powerful Lewis acids are required, owing to the low nucleophilicity of the olefin and tight binding of the homoallylic alcohol to the catalyst, which can be detrimental to substrates and products.

4.2.4.1 Reaction of 210 and 211 with Diethyl Ketomalonate

Enamines **210** and **211** were both stirred with the achiral carbonyl enophile diethyl ketomalonate in CH_2Cl_2 at r.t. for 16 h, giving the ene adducts **235** and **236** in excellent yields (65% and 83 respectively) as single diastereoisomers (Scheme 4.22).

Analysis of **236** by ^{1}H NMR spectroscopy shows the two doublets corresponding to the benzylic CH_2 have shifted downfield from 4.77 and 4.90 ppm in **211**, to 5.28 and 5.61 ppm, which is a characteristic shift following the rearomatisation that occurs in ene reactions of this enamine. In addition, the signal corresponding to the sp^2 proton of the exocyclic ene in **211** (H_d) has shifted upfield from 5.62 ppm to 3.85ppm, as the sp^3 H_d in the product. Analogous results were observed with **235**, although the reaction yield was slightly lowered in comparison to the non-substituted variant, which may be due to the reduced steric accessibility of the ene caused by the methylene-OTBS.

The relative stereochemistry of the ene adducts at the chiral centre indicated was determined by comparison to crystal structures obtained for subsequent adducts (**237** and **242**).



210: R = CH_2OTBS
211: R = H

235: R = CH_2OTBS *65%*
236: R = H *83%*

Scheme 4.22. Reaction of **211** and **210** with diethyl ketomalonate.

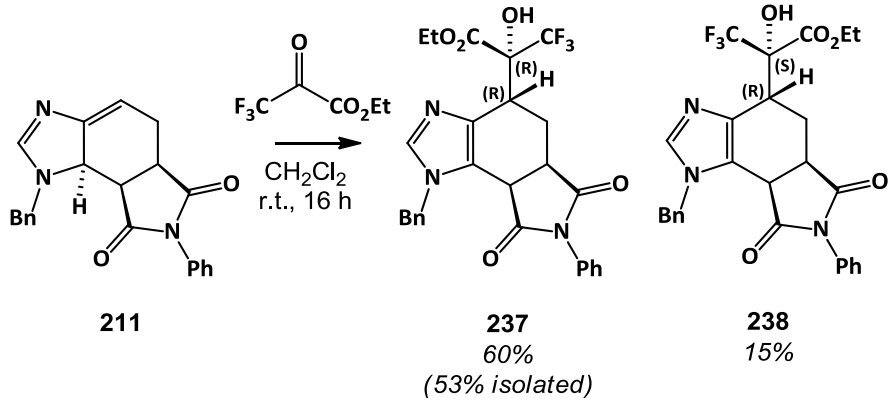
4.2.4.2 Reaction of 210 and 211 with Ethyl 3,3,3-trifluoro-2-oxopropanoate

Investigations of the ene reactions were extended to include a fifth exocyclic

stereocentre, through the employment of the reactive asymmetric carbonyl enophiles, ethyl 3,3,3-trifluoro-2-oxopropanoate and ethyl 2-oxoacetate.

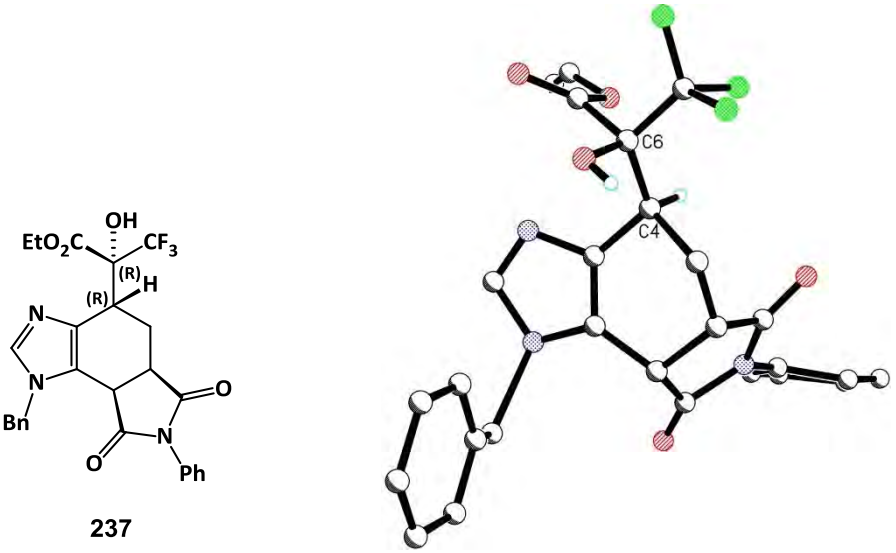
211 was stirred with ethyl 3,3,3-trifluoro-2-oxopropanoate in CH_2Cl_2 at r.t., and after 16 h, analysis of the crude material by ^1H NMR spectroscopy indicated the presence of two diastereoisomers in an approximately 3:1 ratio, which could clearly be observed by the downfield shifted doublets of the benzylic CH_2 protons. In addition, the ^{19}F NMR spectrum indicated two peaks at -73.37 and -74.61 ppm in a 3:1 ratio, and a third peak at -82.95 ppm relating to unreacted ethyl trifluoropyruvate.

Purification of the diastereoisomers was attempted by flash column chromatography and the major isomer (**237**) was successfully separated in 53% yield. Unfortunately, attempts to obtain a pure sample of the minor diastereomer (**238**) were unsuccessful (Scheme 4.23).



Scheme 4.23. Reaction of **211** with ethyl 3,3,3-trifluoro-2-oxopropanoate.

Crystals were grown of the major diastereoisomer (**237**) to assign the relative stereochemistry of both the ene centre (C4) and of the exocyclic chiral centre (C6). Analysis by single crystal X-ray crystallography revealed the major diastereoisomer has the configuration (*R*),(*R*) at these chiral centres, which is consistent with a concerted ene reaction in which hydrogen abstraction has occurred from the *twix* position, installing the enophile on the same face, and affording rearomatisation of the imidazole (Figure 4.8).

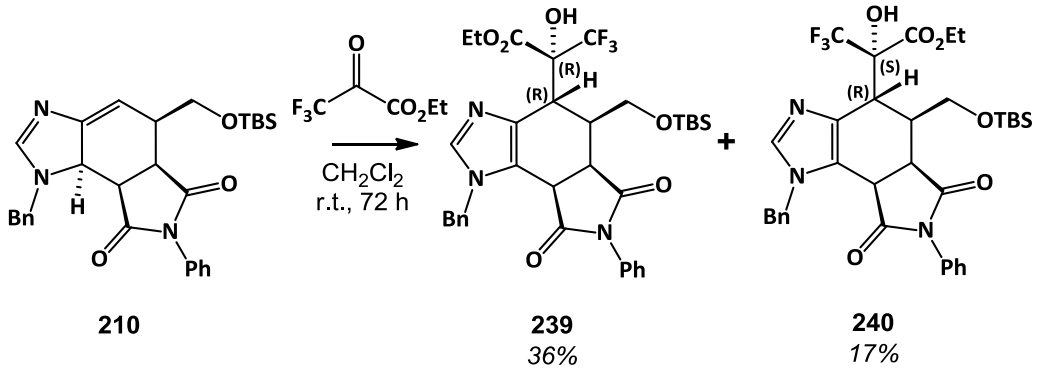


237

Figure 4.8. X-ray structure of major diastereoisomer **237**. Hydrogens omitted for clarity.

The configuration of the stereocentre at C6 of the major diastereoisomer indicates that **237** arises from an *endo*- transition state. This is consistent with the slight *endo*-preference observed for carbonyl-ene reactions in the literature.[157,162,163,164]

Enamine **210** was also stirred with ethyl trifluoropyruvate in CH_2Cl_2 at r.t. and after 72 h, two diastereoisomers (**239** and **240**) were evident in a 2:1 ratio. Fortunately, they could be conveniently separated by flash column chromatography (Scheme 4.24) and purified **239** and **240** were obtained in 36 and 17% yield respectively. The yield of this reaction is again lowered in comparison to the non-substituted variant, and required longer reaction times, which is most likely due to the increased steric bulk of the methylene-OTBS near the reaction centre.



210 **239** *36%* **240** *17%*

Scheme 4.24. Reaction of **210** with ethyl trifluoropyruvate.

Crystals were grown for single crystal X-ray analysis by recrystallisation from THF/pentane (Figure 4.9). The major diastereoisomer (**239**) has the same relative stereochemistry at both of the newly installed chiral centres as that of the major diastereoisomer of the non-substituted variant (**237**). This suggests both compounds have arisen *via* a concerted ene reaction, installing the enophile on the same face of the molecule as the abstracted hydrogen. In addition, the stereochemistry of the exocyclic stereocentre is consistent with having arisen from an *endo* transition state.

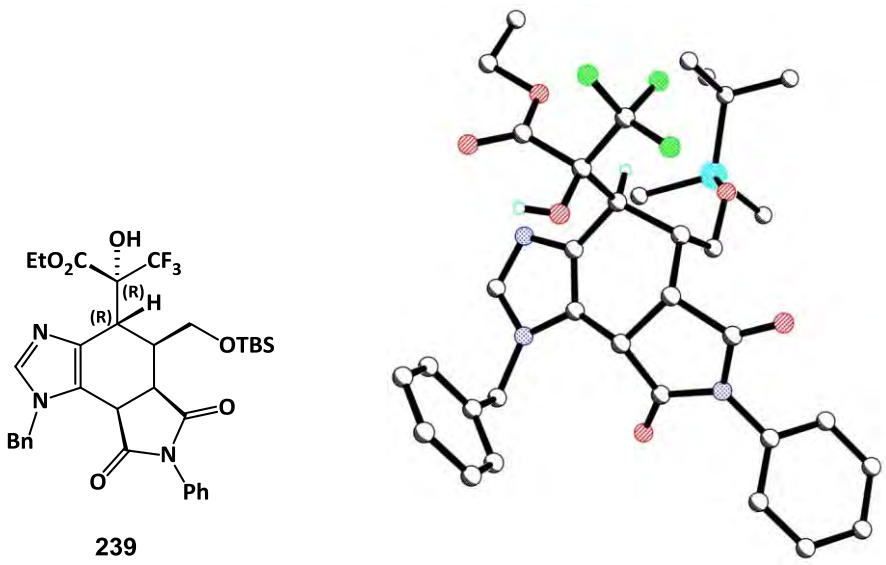
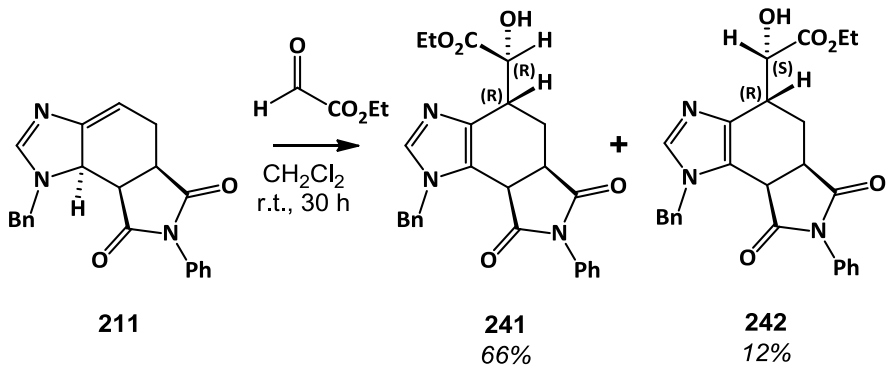


Figure 4.9. X-ray structure of major diastereoisomer **239**. Hydrogens omitted for clarity.

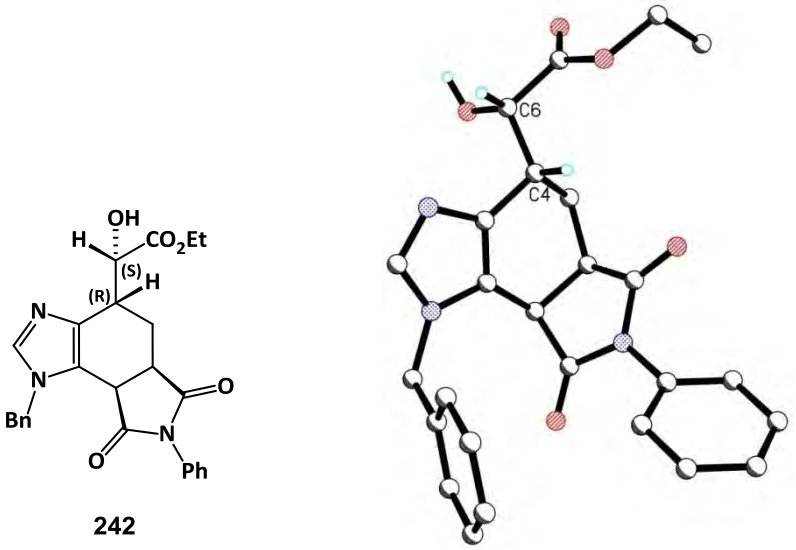
4.2.4.3 Reaction of 210 and 211 with Ethyl 2-oxoacetate

Enamine **211** was stirred with the unactivated aldehyde ethyl glyoxalate for 30 h in CH_2Cl_2. Following this time, two diastereoisomers were evident by ^1H NMR spectroscopy in a 5:1 ratio. Fortunately they could be conveniently separated by flash column chromatography, and it was possible to isolate the major diastereoisomer (**241**) in 66% yield and the minor diastereoisomer (**242**) in 12% yield (Scheme 4.25).



Scheme 4.25. Ene reaction of **211** with ethyl glyoxalate.

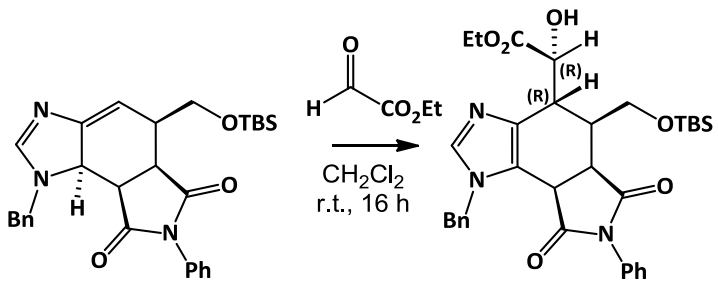
Crystals of the minor diastereoisomer **242** were grown *via* slow evaporation of diethyl ether/methanol (Figure 4.10). Analysis by single crystal X-ray crystallography indicated the stereochemistry at C4 to be consistent with the previous ene adducts observed, indicating a concerted ene reaction, with the enophile installed on the same face as the abstracted hydrogen. The exocyclic stereocentre, C6, displayed the opposite relative stereochemistry to the major adducts observed previously (**237** and **239**), indicating the minor isomer arises from an *exo* transition state.



242

Figure 4.10. X-ray structure of minor diastereoisomer **242**. Non-essential hydrogens omitted for clarity.

The methylene-OTBS substituted enamine **210** was also reacted with the unactivated aldehyde ethyl glyoxalate, and after 16 h in CH_2Cl_2 the ene adduct (**243**) was obtained in good yield (59%) as a single diastereoisomer (Scheme 4.26).



210 **243** *59%*

Scheme 4.26. Ene reaction of **210** with ethyl glyoxalate.

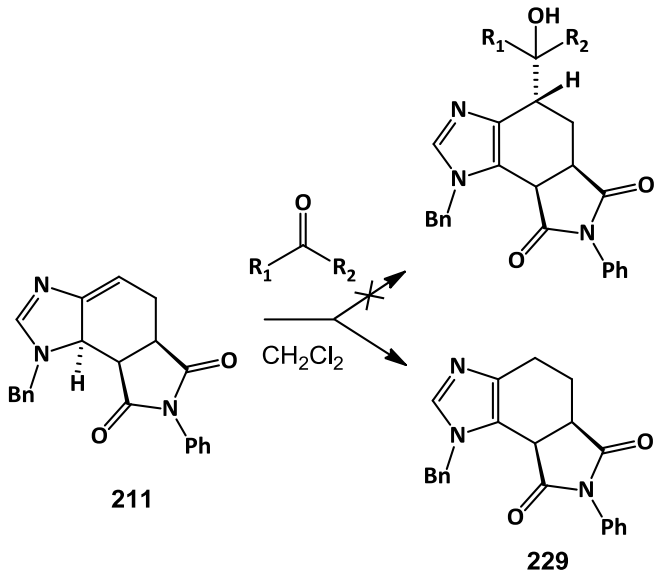
On analysis by ^{1}H NMR spectroscopy, the downfield shift and separation of the benzylic CH_2 protons was clearly evident, as were the diastereotopic protons of the newly

installed ethyl CH_2, which resolved into two doublets of quartets at 4.37 and 4.31 ppm.

The stereochemistry of the major adduct **243** was assigned by comparison with the crystal structure obtained for **237**, with an (*R*,*R*) configuration. The minor adduct was not observed.

4.2.4.4 Unsuccessful Carbonyl Ene Reactions

The ene reaction of **211** was also investigated with a number of other carbonyl enophiles under standard reaction conditions, detailed in Table 4.2. However, these compounds appeared to be too unreactive to undergo ene reaction with Diels-Alder cycloadduct **211** under these conditions, and failed to provide the expected ene adducts (Scheme 4.16).



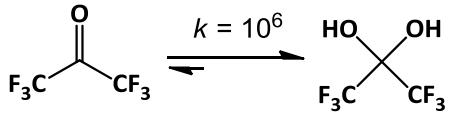
Scheme 4.27. Competing rearomatisation reaction observed during ene reaction.

Entry	Carbonyl Enophile	Recovered 211[a] (%)	229[a] (%)	Ene adduct[a] (%)
a	Acetone	81	0	0
b	Hexafluoroacetone	0	20	0
c	*p*-Nitrobenzaldehyde	10	10	0
d	2,4-Dinitrobenzaldehyde	40	20	0
e	Pentafluorobenzaldehyde	36	5	0
f	Ethyl pyruvate	90	0	0

Table 4.2. Unsuccessful carbonyl ene reactions. [a]Conversion observed by ^{1}H NMR spectroscopy.

Purification of the crude reaction mixture of the above reactions led to the recovery of unreacted starting material (**211**) in most cases, and the isolation of the rearomatised imidazole **229**. It appears that over extended reaction times, slow rearomatisation of the imidazole ring is competing with ene reaction

Hexafluoroacetone is known to be a highly reactive carbonyl enophile, as the six electronegative fluorines of hexafluoroacetone make the carbonyl highly activated.[85] This greater reactivity leads to the position of equilibrium sharply favouring the *gem*-diol in the presence of water. The gem-diol hydrate is then unreactive towards ene reaction (Scheme 4.28). In addition, the acidic nature of hexafluoroacetone is likely to have contributed to rearomatisation of **211**, which is known to be accelerated in catalytic acid.

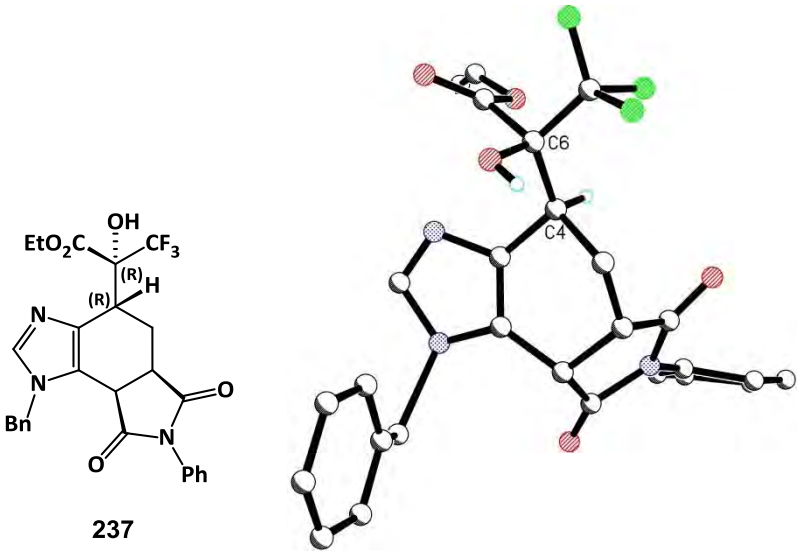


Scheme 4.28. Equilibrium of hexafluoroacetone.

4.2.4.5 Conclusions

The carbonyl ene reactions of enamines **211** and **210** were successful with a number of enophiles, and a single ene product was obtained in high yield with diethyl ketomalonate. Reactions with ethyl 3,3,3-trifluoro-2-oxopropanoate and ethyl 2-oxoacetate led to a mixture of diastereoisomers, and crystal structures were obtained for the major or minor diastereoisomers in each case.

The relative stereochemistry of chiral centre C4 was found to be consistent with that observed for the nitroso-ene adduct **223**, indicating the enophile is installed on the same face as the abstracted hydrogen *via* a concerted ene reaction. The relative stereochemistry at the exocyclic stereocentre C6 in the major diastereoisomers was found to occur *via* an *endo* transition state (Figure 4.11), and the opposite relative stereochemistry was observed with the minor diastereoisomers, indicating formation *via* an *exo* transition state .



237

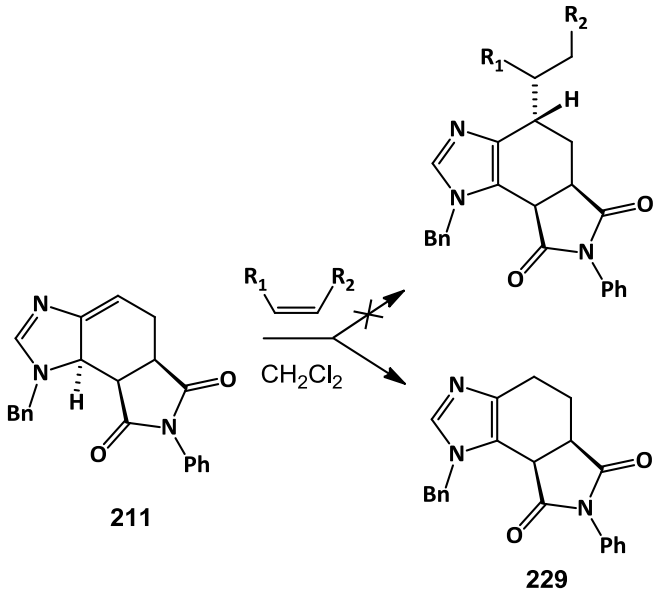
Figure 4.11. Structure and X-ray structure of **237**. Non-essential hydrogens omitted for clarity.

4.2.5 Carba-Ene Reactions

The carba-ene reaction is a very useful carbon-carbon bond forming reaction, although often requires higher temperatures than its heteroaromatic counterparts and suffers from poor regioselectivity. In recent years, the development of metal-catalysed carba-ene reactions, most notably by Trost *et al*.,[179] have increased their synthetic utility significantly.[180]

4.2.5.1 Examination of 211 in the Carba-Ene Reaction

The carba-ene reactions of enamine **211** with numerous all-carbon enophiles were investigated, and the results are tabulated in Table 4.3 below.



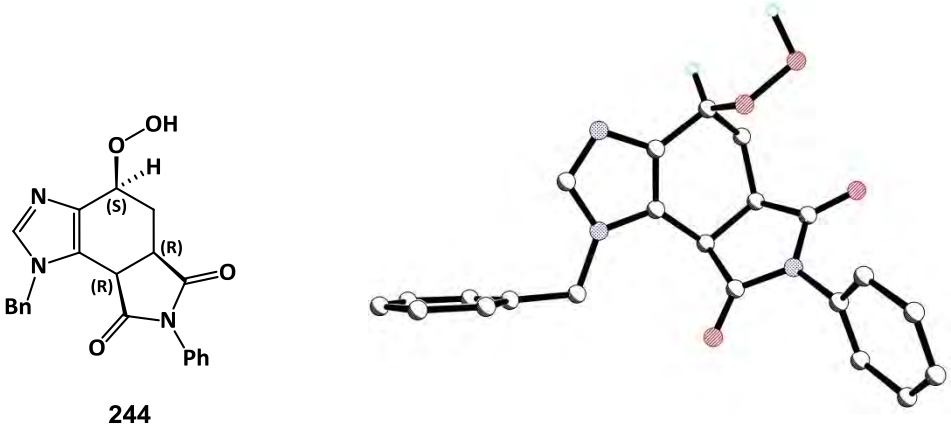
211 229

Scheme 4.29. Competing rearomatisation reaction.

Entry	Carba Enophile	Recovered 211[a] (%)	229[a] (%)	Ene adduct[a] (%)
a	Maleimide	0	22	0
b	*N*-Methylmaleimide	0	31	0
c	*N*-Phenylmaleimide	10	14	0
d	Maleic anhydride	0	100	0
e	Diethyl fumarate	25	45	0
f	Diethyl acetylenedicarboxylate	71	0	0

Table 4.3. Results of carba-ene reactions. [a]Isolated yields.

The carba-ene reaction with **211** was unsuccessful with all maleimide enophiles (entries **a**-**c**), even after extended reaction times (72 h), and instead led to the isolation of the rearomatised adduct **229** in all cases. In addition, in reactions of maleimide, NMM and NPM, a mixture of two additional compounds were evident by ^{1}H NMR spectroscopy in low yield, in a 1:1 ratio. Although insufficient quantities of these compounds could be isolated for full characterisation, crystals were grown from the crude reaction mixtures of entries **a** and **b** *via* slow evaporation of $CHCl_3$/pentane. Following analysis by single crystal X-ray crystallography, both structures were found to correspond to the hydroperoxide **244** (Figure 4.12).



244

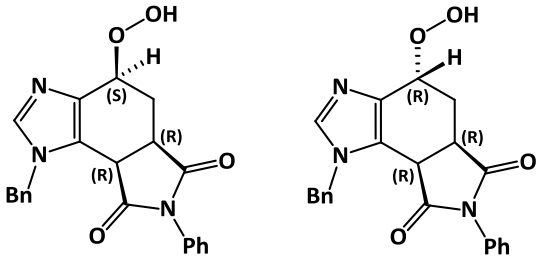
Figure 4.12. Structure isolated from reaction of **211** with maleimide and *N*-methylmaleimide.

Interestingly, the relative stereochemistry at the ene chiral centre in **244** from reaction with both maleimide and NMM displays the opposite relative stereochemistry to the previously observed ene reactions, with the hydroperoxide having installed on the

same face as the NPM moiety, and the opposite face to the abstracted hydrogen.

The observation of an epimeric mixture of alcohols has been reported previously by Lovely *et al*., as by-products from the Diels-Alder reaction of 1-benzyl-4-vinyl-1*H*-imidazole with NPM (see section 4.2.1.1). The authors attributed their formation to reaction of enamine **211** with dissolved oxygen.

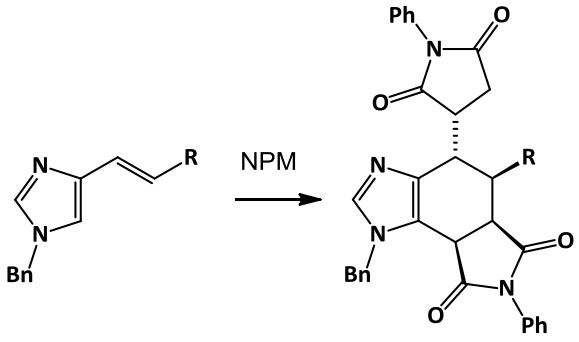
It is possible, therefore, that the two additional compounds observed by ^{1}H NMR spectroscopy for entries **a** and **b** were an epimeric mixture of hydroperoxides **244** and **245**, and that compound **244** preferentially crystallises in $CHCl_3$/pentane (Figure 4.13).



244 **245**

Figure 4.13. Proposed by-products of the ene reaction of **211** with maleimide and *N*-methylmaleimide.

The apparent unwillingness of NPM to react with **211** is somewhat surprising, as previous examples in the literature have highlighted the 2:1 ene adduct (**246** and **247**) as a by-product of the Diels-Alder reaction of **211** with NPM when heated in benzene at 90 ^{o}C (Scheme 4.30).[44] However, the lack of reactivity observed under our reaction conditions is encouraging, as it implies **211** will not be subject to side-reactions with excess NPM during one-pot reactions.



246: R = H (19%)
247: R = CH_2OTBS (10%)

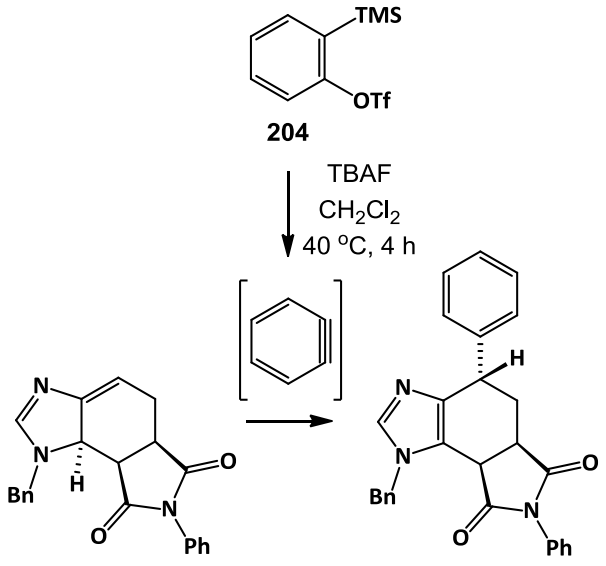
Scheme 4.30. Domino Diels-Alder/ene adducts.

Reaction of **211** with maleic anhydride rapidly led to the formation of the rearomatised adduct **229**, and following extended reaction times (29 h), the rearomatised adduct could be isolated in quantitative yield. The reaction was repeated with fresh reagents, but analogous results were obtained. It is likely that small quantities of maleic acid present in maleic anhydride have catalysed the rearomatisation of enamine **211** to **229**, as observed previously (see section 3.3.1)

Ene reaction was not observed to occur with diethyl fumarate and diethyl acetylenedicarboxylate (entries **e** and **f**), and only starting material and the rearomatised adduct **229** was recovered. It appears these carbonyls are too unreactive to undergo ene reaction with **211** under these conditions. This result is surprising, as the carbon-carbon triple bond of diethyl acetylenedicarboxylate and the electron-withdrawing groups of diethyl fumarate would be expected to lower the energy of the LUMO and increase the reactivity of these compounds.

4.2.5.2 Examination of 211 in the Carba-Ene Reaction with Benzyne

Following the unsuccessful ene reactions of **211** with alkene and alkyne enophiles (Table 4.3), the aryne enophile benzyne was then employed. The highly reactive nature of benzyne necessitated its *in situ* generation through modification of a literature procedure.[155] The Diels-Alder enamine **211** and trimethylsilylphenyl triflate **204** were stirred in CH_2Cl_2 at r.t., and benzyne generated through the addition of *tetra*-butylammoniumfluoride. The reaction was then heated to 40 ^oC for 2 h, and the desired ene adduct (**248**) was isolated in 68% yield (Scheme 4.31).



Scheme 4.31. Reaction of **211** with benzyne.

4.2.5.3 Conclusions

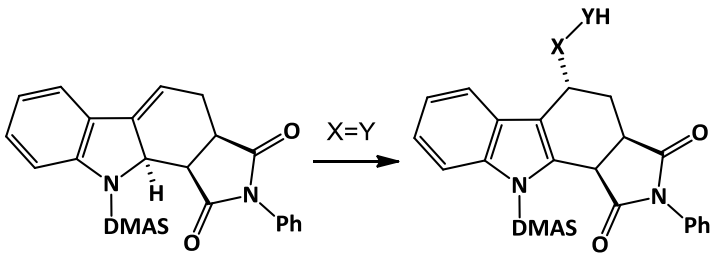
The carba-ene reactions of **211** were generally unsuccessful, with most reactions resulting in rearomatisation to **229** or air oxidation. However, enamine **211** smoothly underwent ene reaction with benzyne to give the expected adduct **248** in 68% yield, which resulted in a highly useful C-C bond forming reaction.

With the exception of benzyne, the carba-enophiles examined do not appear to be suitable for participation in one-pot Diels-Alder/ene reactions with our substrates. However, it is encouraging to observe that our current dienophile, NPM, is unreactive towards **211** under these conditions, as this suggests the formation of 2:1 adducts would not be observed as a by-product in one-pot reactions.

4.3 Evaluation of the indole-based ene 212 in the ene reaction

4.3.1 Reactions of 212 with reactive enophiles

Following the successful ene reactions of **210** and **211**, we then investigated ene reactions of the indole-based Diels-Alder cycloadduct *N*,*N*-dimethyl-2,3-dihydro-1*H*-carbazole-9(9a*H*)-sulfonamide, **212**, with a range of reactive enophiles (Scheme 4.32).



212

Scheme 4.32. Proposed ene reactions with **212**.

Numerous natural products and pharmaceutical agents are based on the indole scaffold (see Chapter 1), and therefore it would be beneficial to develop rapid synthetic routes to functionalised indoles. In particular, pyrrolo[3,4-α]carbazole-1,3-diones have been shown to selectively inhibit the serine/threonine-protein kinase Chk1,[181,182] in addition to antiproliferative[183] and antivascular activity (Figure 4.14).[184]

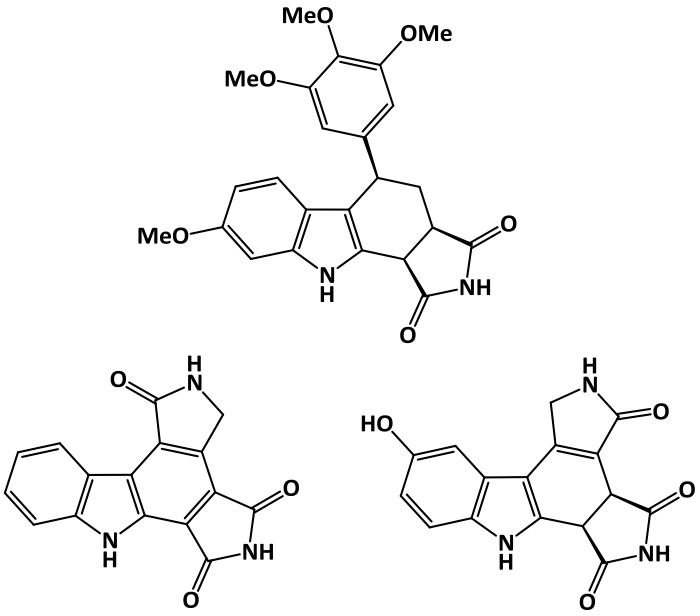
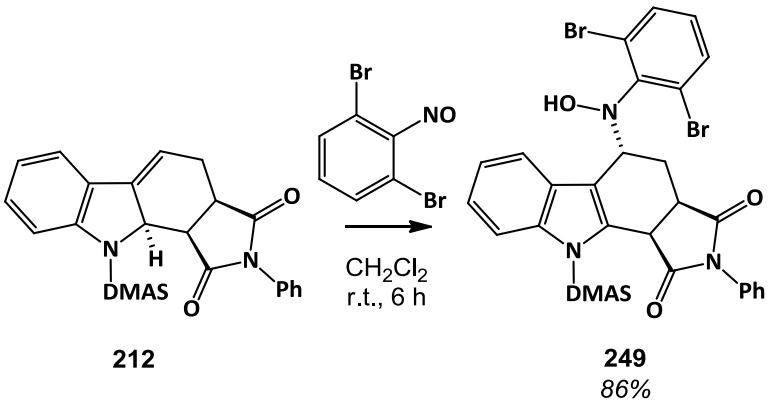


Figure 4.14. Bioactive pyrrolo[3,4-*a*]carbazole-1,3-diones.

The general conditions adopted for investigation of the reaction of **212** with an enophile was to stir both reagents in CH_2Cl_2 at r.t. until the disappearance of starting materials was observed by TLC and ^{1}H NMR spectroscopy. Under these conditions, **212** was examined with the arylnitroso compounds nitrosobenzene, 2-nitrosotoluene, 2,6-dibromonitrosobenzene (**226**) and *N*,*N*-dimethylnitrosoaniline.

Unfortunately, the only successful reaction observed with substrate **212** was with the 2,6-dibromonitrosobenzene (**226**). After stirring for 6 h in CH_2Cl_2 at r.t., the desired ene adduct **249** was observed and isolated in 86% yield following purification by flash column chromatography (Scheme 4.33).



Scheme 4.33. Reaction of **212** with 2,6-dibromonitrosobenzene.

To definitively assign the regiochemistry and stereochemistry at the ene chiral

centre, crystals were grown by slow evaporation from Et_2O/petroleum ether for analysis by single crystal X-ray crystallography. The structure obtained indicated that the stereochemistry is consistent with ene reaction occurring on the opposite face to the NPM moiety, on the same face of the molecule from which the allylic hydrogen is abstracted (Figure 4.15). In addition, the observed regiochemistry is consistent with the general rule for nitroso-ene reactions, in which the major adduct arises from *twix* hydrogen abstraction.

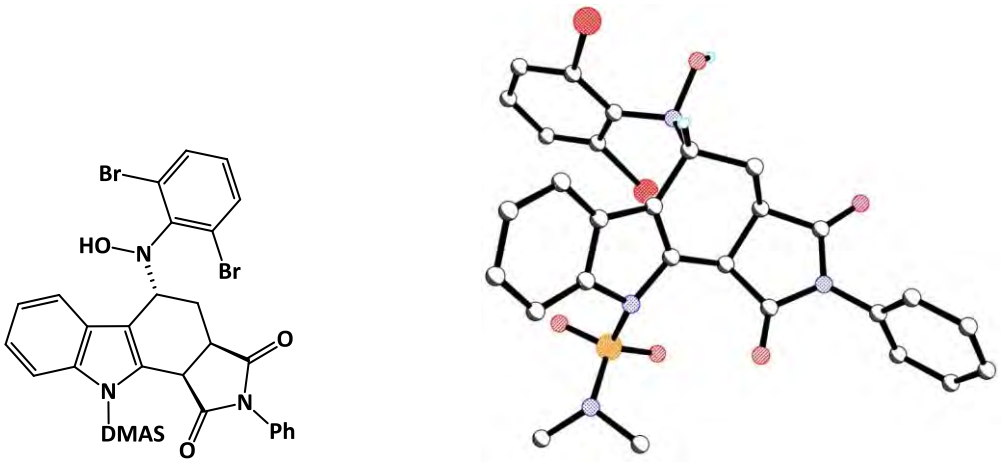


Figure 4.15. X-ray structure of **249**. Non-essential hydrogens removed for clarity.

212 was also reacted with the alkylnitroso 2-methyl-2-nitrosopropane, and the nitrosamine compounds 1-nitrosopyrrolidine and *N*-nitrosodiphenylamine, the aza compound PTAD, the activated carbonyl compound ethyl-3,3,3-trifluoro-2-oxopropanoate and the aryne benzyne, all of which proved unsuccessful.

Chapter 5. Conclusion and Future Work

The research described in this thesis aimed to develop efficient methods for the synthesis of molecularly diverse, structurally complex molecules inspired by bioactive alkaloid-like architectures based on vinyl-heteroaromatics, through a one-pot sequence. In view of this, it was necessary to explore the sequential intermolecular Diels-Alder reaction of vinyl- and substituted vinyl- heteroaromatics, and the sequential intermolecular ene reaction of these Diels-Alder cycloadducts with a range of enophiles.

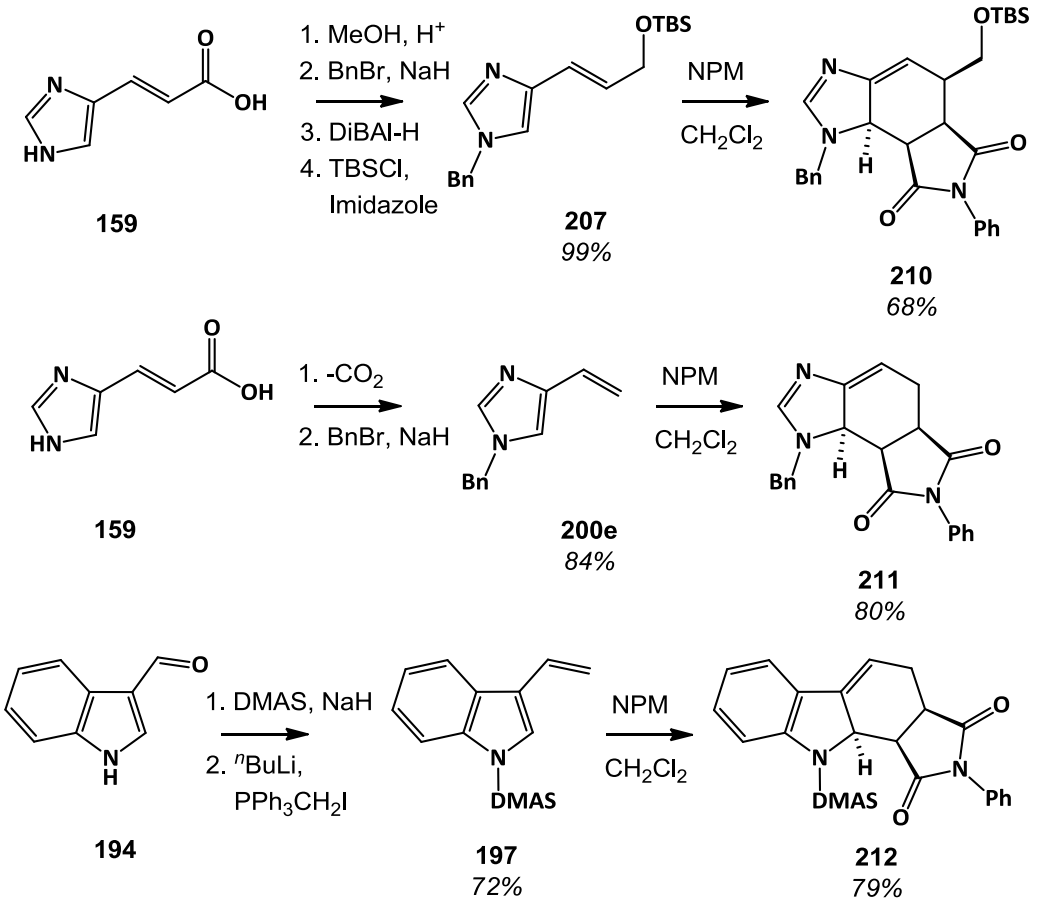
5.1 Sequential Intermolecular Diels-Alder Reactions of Vinyl- and Substituted Vinyl-Heteroaromatics

This aspect of the research programme aimed to find a suitable method for the synthesis of vinyl- and substituted vinyl-heteroaromatics, and to examine their behaviour in intermolecular Diels-Alder reactions. To this end, vinylfuran **149**, vinylthiophene **156**, vinylimidazoles **164** and **180**, and vinylindole **197** were synthesised and examined in Diels-Alder reactions with NPM. Extra-annular cycloaddition *via* an *endo* transition state was found to occur readily, although no cycloadducts could be isolated from reaction of **149** due to degradation.

Those cycloadducts arising from **156**, **164** and **180** were found to succumb to further *in situ* domino reactions, including rearomatisation, N1→N3 trityl migration, ene reaction and Michael addition, consistent with examples in the literature.

A study was then undertaken to synthesise suitable *N*-protected vinylimidazoles, and to optimise the conditions of the Diels-Alder reaction, in order to minimise these *in situ* domino reactions.

The N1-benzyl protected imidazole (**200e**) was found to form in high yield as a single regioisomer, and was subsequently examined in the Diels-Alder reaction with a range of dienophiles. NPM was found to be the most suitable dienophile for our research programme, forming the desired cycloadduct (**211**) in 80% yield as a single diastereoisomer after 6 h at 50 ^{o}C in CH_2Cl_2. The benzyl-protected 4-vinylimidazoles **207** and **200e**, and the DMAS protected 3-vinylindole **197** were then subjected to Diels-Alder reaction with NPM, as the dienophile of choice. In each case the desired Diels-Alder cycloadduct (**210**, **211** and **212**) could be obtained as a single diastereoisomer in high yield (68-80%, Scheme 5.1).



Scheme 5.1. Synthetic routes to Diels-Alder cycloadducts.

5.2 Sequential Intermolecular Ene Reactions of Diels-Alder Cycloadducts

The ene reactions of the imidazole-based enes **210** and **211** were largely successful, with numerous ene adducts being isolated in high yields (53-95%). The nitroso-ene reactions of a number of arylnitrosos with the ene substrate **211** led to isolation of the desired hydroxylamine, although due to their high reactivity, a number of other dehydration products and side-reactions were observed.

The aza-ene reaction of PTAD with enamines **210** and **211** was very rapid at -78 ^{o}C, although some line broadening was observed on examination of the ^{1}H NMR spectra, which is likely to due to the occurrence of restricted rotation in solution.

The carbonyl enophiles examined afforded the expected ene adducts when reacted with **210** and **211**, with the reactions of ethyl 3,3,3-trifluoro-2-oxopropanoate and ethyl 2-oxoacetate leading to a mixture of diastereoisomers. Crystal structures were obtained for the major or minor diastereoisomers in each case (Figure 5.1), and the relative stereochemistry indicated that the enophile is installed on the same face as the abstracted hydrogen, consistent with a concerted ene reaction. In addition, the relative stereochemistry of the major isomer was found to form *via* an *endo* transition state.

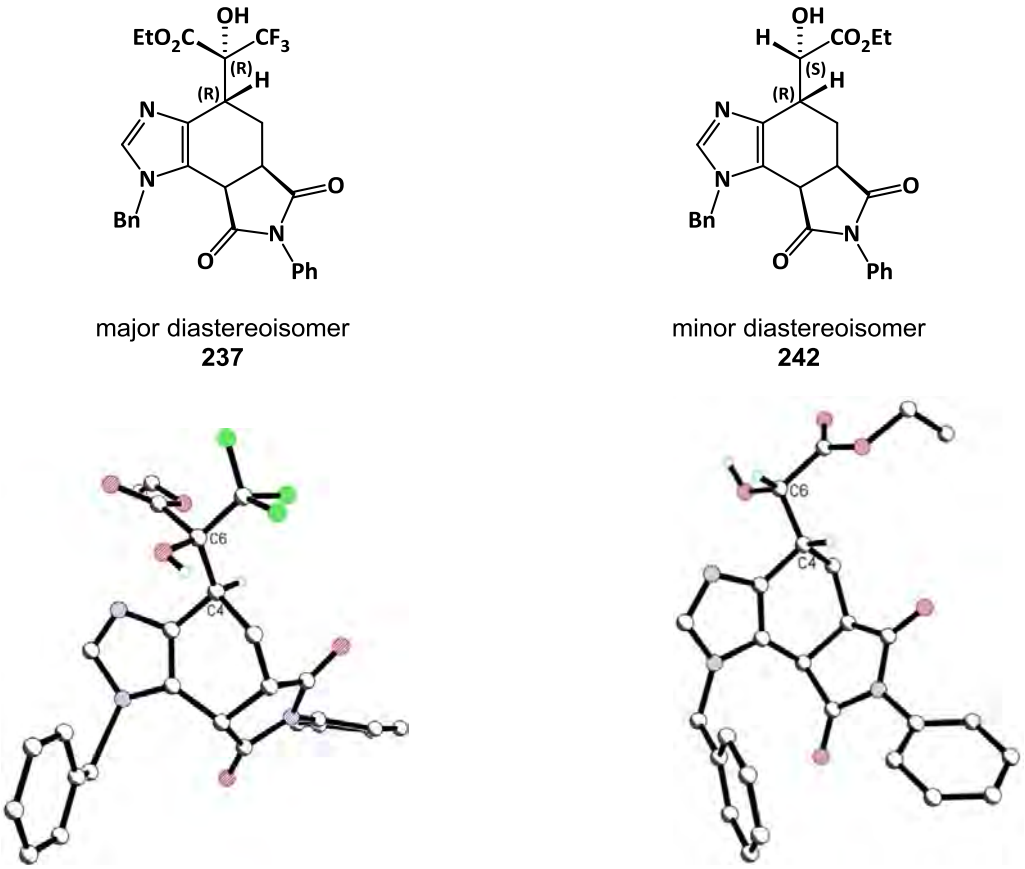
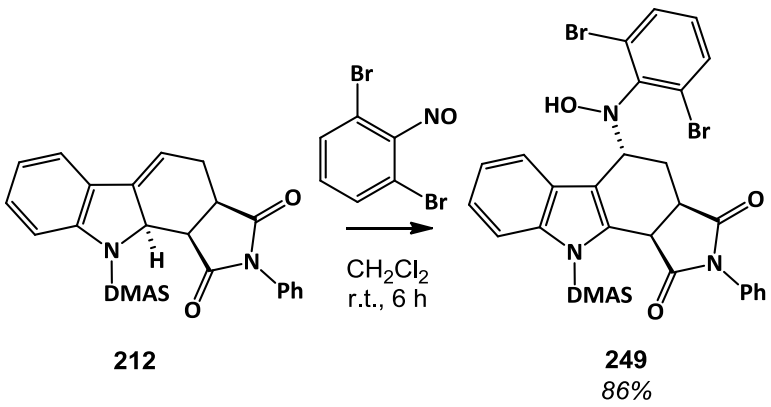


Figure 5.1. Structure and X-ray structures of major and minor diastereoisomers. Non-essential hydrogens omitted for clarity.

The carba-ene reactions were generally unsuccessful, with most reactions resulting in rearomatisation or air oxidation. However, successful ene reaction occurred with benzyne, resulting in a highly useful C-C bond forming reaction.

The indole-based ene **212** was only found to undergo successful ene reaction with 2,6-dibromonitrobenzene (Scheme 5.2), with all other reactions leading to the recovery of starting material only. It appears that the HOMO energy of the ene is too low to undergo reaction with anything other than very highly activated enes.

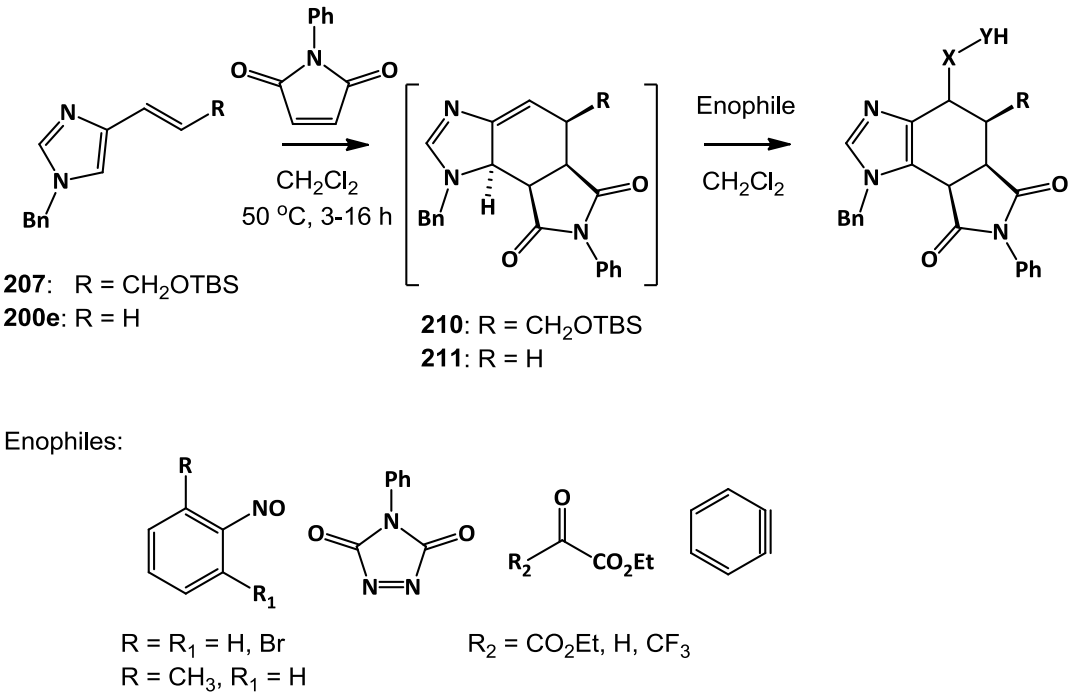


Scheme 5.2. Reaction of **212** with 2,6-dibromonitrosobenzene.

In conclusion, the sequential intermolecular Diels-Alder/intermolecular ene reactions of selected electron-rich vinyl-heteroaromatics have been investigated, as the basis for a new class of three component coupling reactions. This relatively unexplored reaction sequence has been shown to be successful, providing access to a number of 4,5,6,7-tetrahydro-1*H*-benzo[*d*]imidazoles and a 2,3,4,9-tetrahydro-1*H*-carbazole. The two-step reaction process proceeds with high atom economy and diastereocontrol of up to 5 new stereocentres.

5.3 Further Work

Having identified that this reaction process can be carried out successfully as a sequential process, further work would primarily focus on its employment as a one-pot domino procedure. In the first instance, the 1-benzyl-4-vinylimidazoles **200e** and **207** should be examined in one-pot sequential intermolecular Diels-Alder/intermolecular ene reactions. These reactions would employ NPM as the dienophile, and those enophiles which proved successful in the sequential ene reaction studies, namely nitrosobenzene, 2-nitrosotoluene, 2,6-dibromonitrosobenzene, PTAD, diethyl ketomalonate, ethyl 3,3,3-trifluoro-2-oxopropanoate, ethyl 2-oxoacetate and benzyne (Scheme 5.3).



Scheme 5.3. One-pot sequential Diels-Alder/ene reactions of 1-benzyl-4-vinylimidazoles.

Secondly, work that is currently on-going within the group, would be to investigate and optimise the Diels-Alder/ene reaction of 3-vinylindoles. This is likely to

involve tailoring the protecting group on N1 to generate Diels-Alder cycloadducts with sufficiently activated HOMOs that are then susceptible to ene reaction with less activated enophiles. However, the use of Lewis acid catalysis may also be an interesting route to explore, as there are a number of chiral Lewis acids available which would allow the reaction route to be carried out as an asymmetric process.

Chapter 6. Experimental

6.1 General Procedures

High resolution mass spectra were obtained with either a Waters Acquity ultra-performance LC instrument, or by the National Mass Spectrometry Service Centre on a Thermofisher LTQ Orbitrap XL. Melting points were determined on a hot stage and are uncorrected. Thin-layer chromatography (TLC) was carried out on EM reagent 0.25 mm silica gel 60F 254 plates and visualisations were accomplished with ultraviolet light and aqueous potassium permanganate (VII) solution. Flash column chromatography was performed using Merck Kieselgel 60 silica gel, eluting with the indicated solvent under forced flow. All manipulations involving air-sensitive materials were carried out using standard Schlenk-line techniques under an atmosphere of nitrogen in oven-dried glassware. Solvents were distilled under an atmosphere of nitrogen immediately prior to use; dichloromethane was distilled from calcium hydride, and THF and diethyl ether were distilled from sodium/benzophenone. All reagents were purchased from commercial suppliers and used as received.

6.2 NMR Spectroscopy and elemental analyses

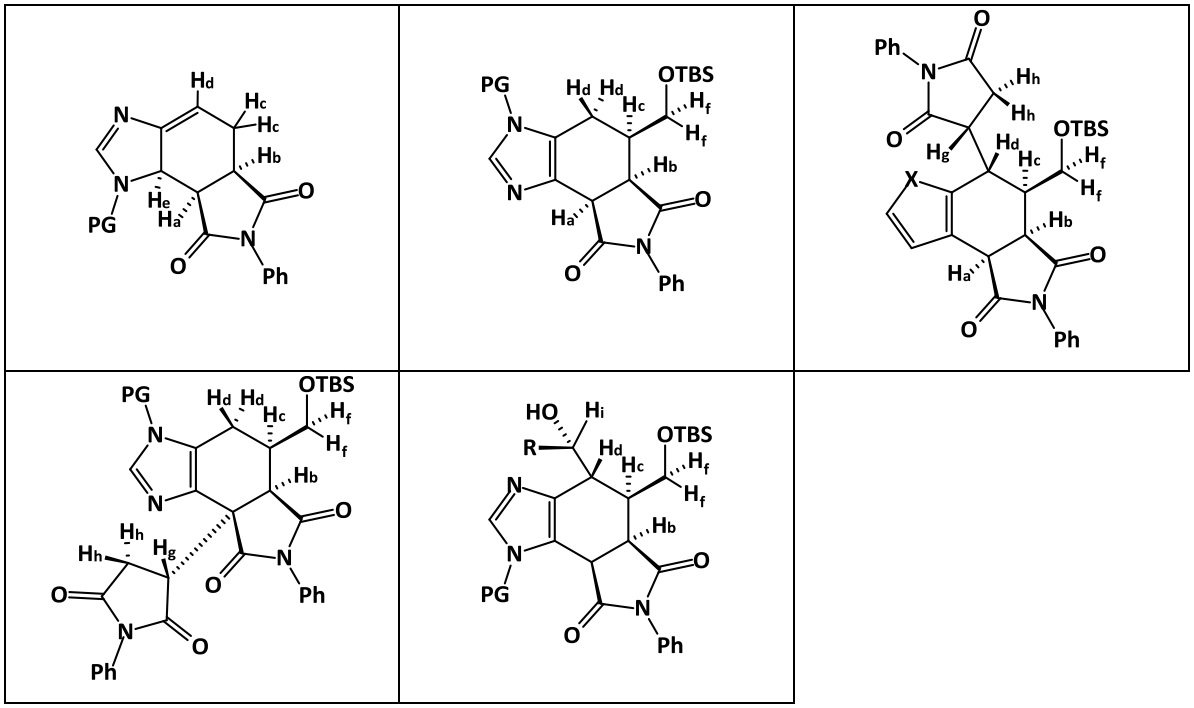
^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded on a JEOL Lambda500 spectrometer operating at 500.16 and 125.65 MHz, respectively, or a JEOL ECS400 spectrometer operating at 399.78 and 100.53 MHz, respectively, or a Brüker AMX 300 spectrometer operating at 300.13 and 75.47 MHz, respectively. $^{19}F\{^{1}H\}$ NMR spectra were recorded on a JEOL ECS400 spectrometer operating at 376.17 MHz; chemical shifts are quoted in ppm relative to TMS or $CFCl_3$ (positive for downfield shifts) as external standards. Elemental analyses were obtained by the Elemental Analysis Service of London Metropolitan University.

6.3 Crystal Structure Determination

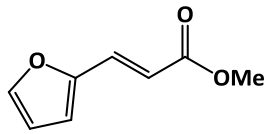
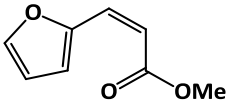
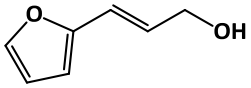
Measurements were made at 150 K on either a Brüker AXS SMART, a Nonius KappaCCD or an Oxford Diffraction Gemini A Ultra diffractometer using either graphite-monochromated MoKα or CuKα radiation (λ = 0.71073 and 1.54184 Å, respectively). Cell parameters were refined from the observed positions of all strong reflections. Intensities were corrected semi-empirically for absorption, based on symmetry-equivalent and repeated reflections. The structures were solved by direct methods and refined on F^2 values for all unique data. All non-hydrogen atoms were refined anisotropically, and H

atoms were constrained with a riding model; U(H) was set at 1.2 (1.5 for methyl groups) times U_{eq} for the parent atom. Programmes were Oxford Diffraction CrysAlisPro Brüker AXS SMART and SAINT or Nonius COLLECT and EvalCCD, and SHELXTL for structure solution, refinement and molecular graphics.

6.4 General Atom Labelling for the Assignment of Peaks in ^{1}H NMR spectra:



6.5 Table of Compounds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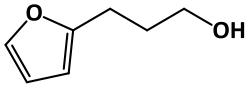	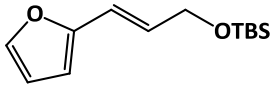	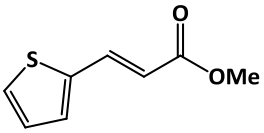
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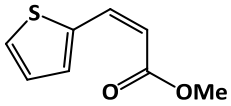	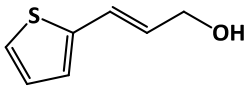	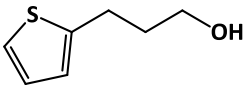
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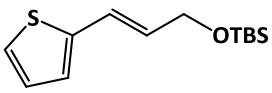	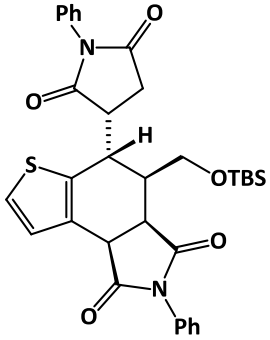	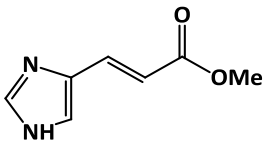
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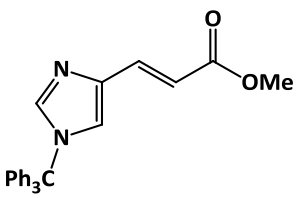	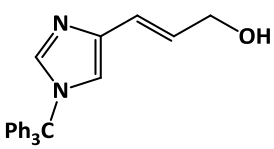	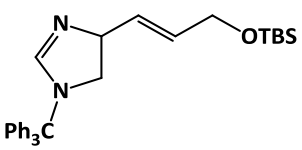
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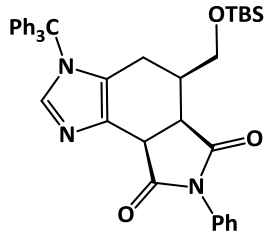	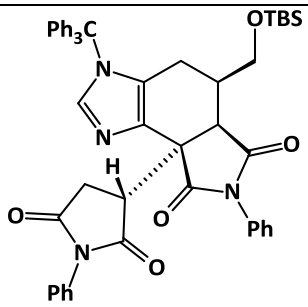	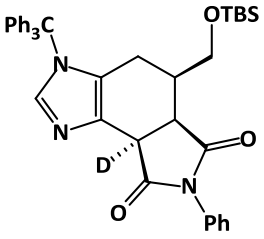
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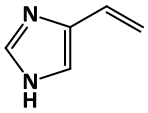	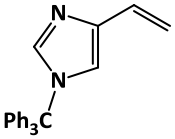	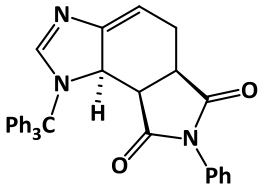
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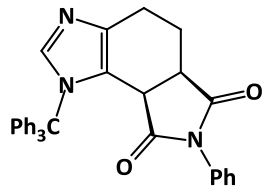	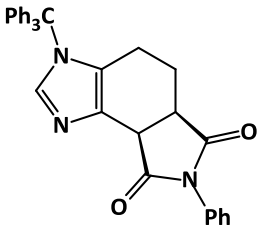	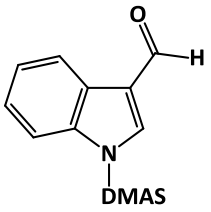
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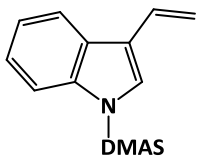
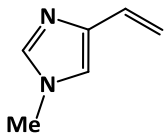
	**See 212**	
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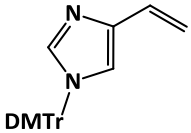
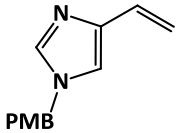
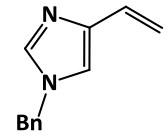
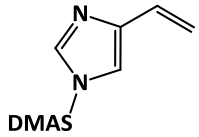
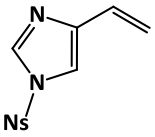
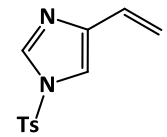
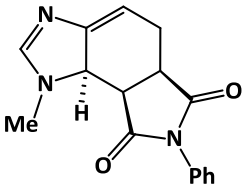
See 180		
200b	**200c**	**200d**

		
200e	**200g**	**200h**
		**See 184**
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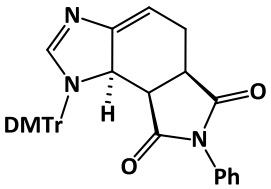
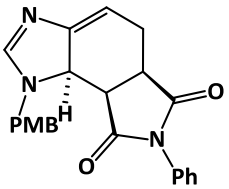
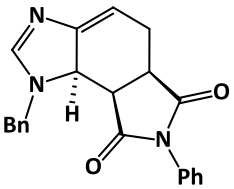
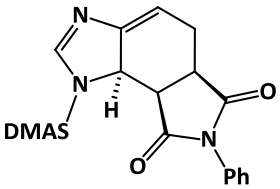
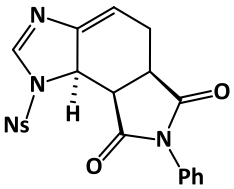
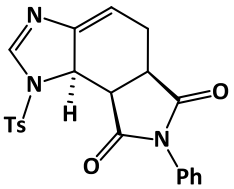
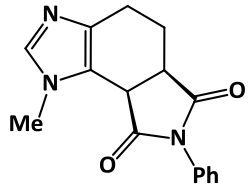
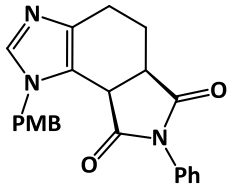
		
71c	**71d**	**71e**
		
71g	**71h**	**71i**
	**See 185**	
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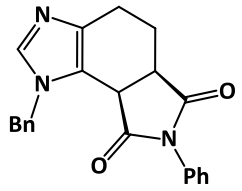	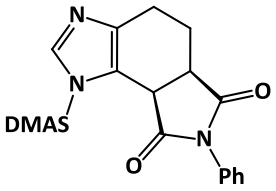	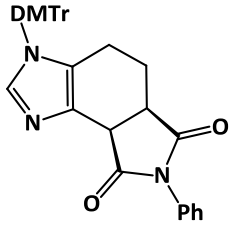
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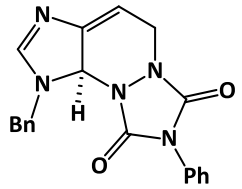
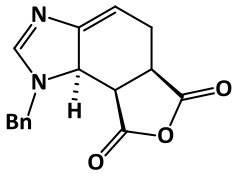
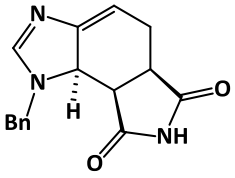
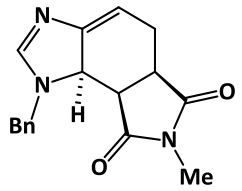
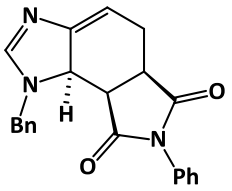
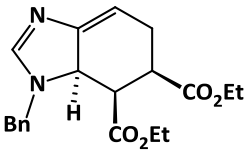
		
202b	**202d**	**202e**
		
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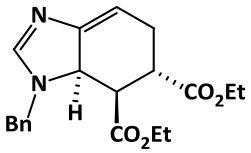	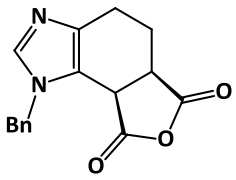	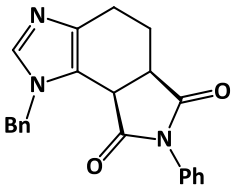
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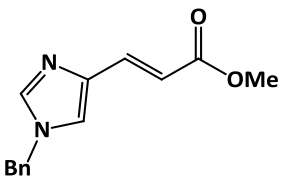	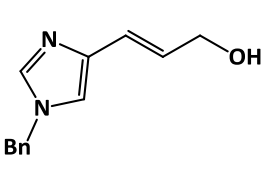	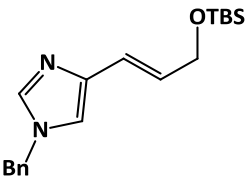
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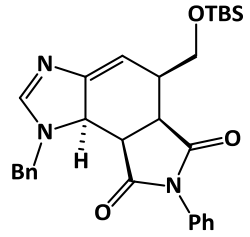
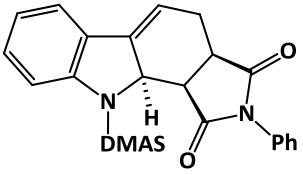
	**See 71e**	
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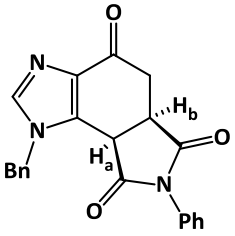	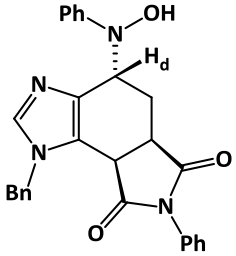	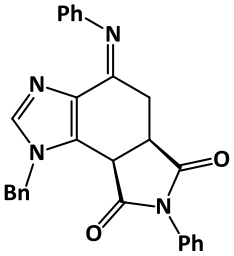
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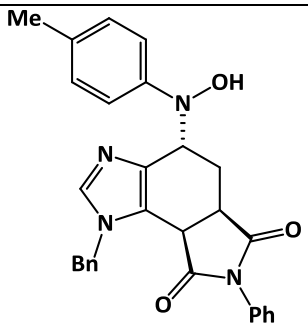	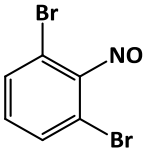	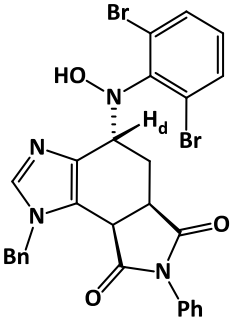
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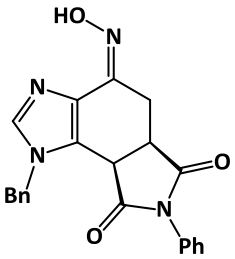	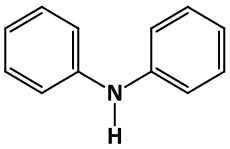	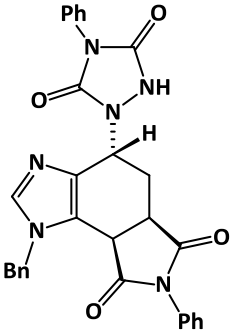
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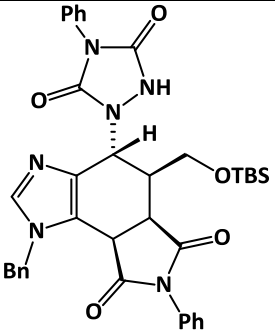	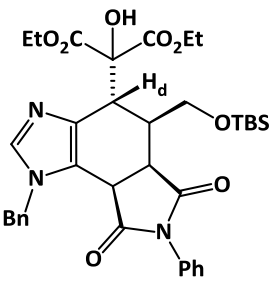	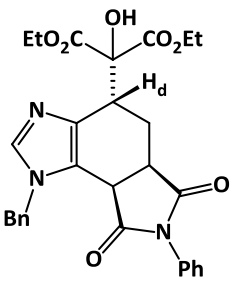
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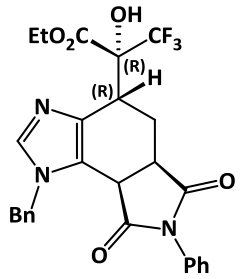	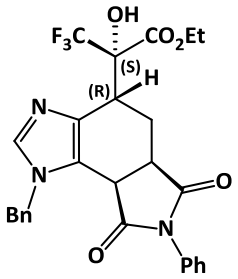	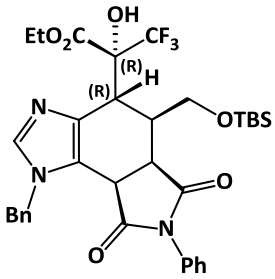
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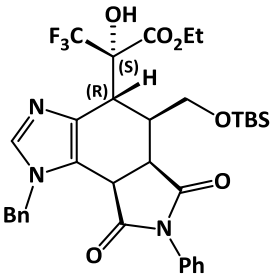	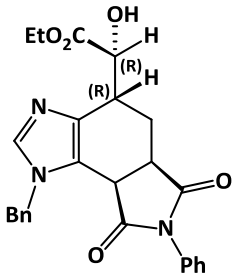	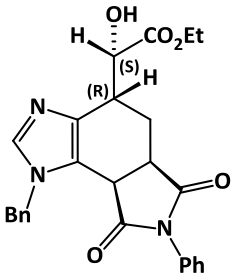
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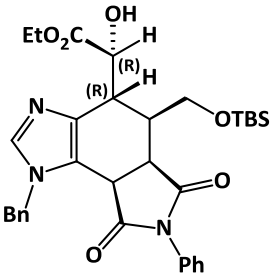	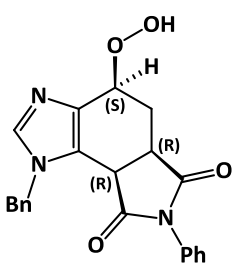	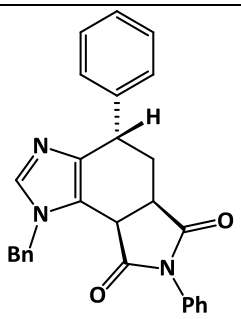
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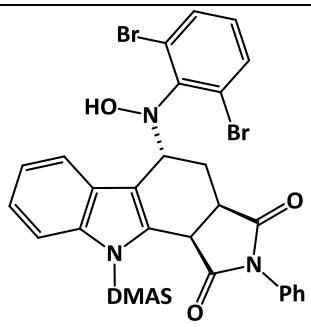
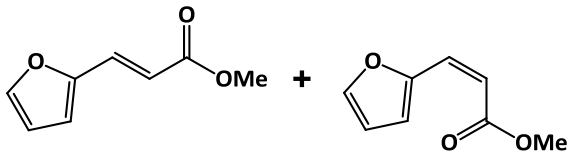
		
249		

6.6 Compound Experimental

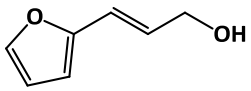


140 **141**

To a stirred suspension of sodium hydride (60% wt in oil, 1.0 g, 25.00 mmol) in THF (100 mL) at 0 ^{o}C was added trimethyl phosphonoacetate (5.3 g, 29.10 mmol, 4.2 mL). After 30 min, furan-2-carbaldehyde (2.0 g, 20.82 mmol) in THF (20 mL) was added dropwise. After stirring for an additional 30 min at r.t., the mixture was diluted with Et_2O (150 mL) and treated with water (100 mL). The organic layers were separated, washed with brine (50 mL) and dried ($MgSO_4$). After evaporation of the solvent, the residue was chromatographed on silica gel (eluting with Et_2O/petroleum ether 40-60, 1:20) obtaining **140** as a white solid, 2.62 g (83%) and a minor amount of the *Z*-isomer (**141**) as a pale yellow oil, 70 mg, (2%). R_f *E*-isomer 0.35, *Z*-isomer 0.48 (UV active, Et_2O:petroleum ether 40-60, 1:10), m.p.: *E*-isomer: 25-27 ^{o}C (lit.[185] 25-26 ^{o}C).

E-isomer: ^{1}H NMR, (300 MHz, $CDCl_3$): δ_H 7.49 (1H, d, *J* = 1.7 Hz, Furan–H), 7.45 (1H, d, *J* = 15.8 Hz, *H*C=CH), 6.62 (1H, d, *J* = 3.4 Hz, Furan–H), 6.48 (1H, dd, *J* = 3.4 Hz, 1.8 Hz, Furan–H), 6.33 (1H, d, *J* = 15.8 Hz, HC=C*H*), 3.80 (3H s, O–CH_3). ^{13}C NMR, (300 MHz, $CDCl_3$): δ_C 167.3 (C=O), 151.2 (Furan C), 144.6 (Furan C–H), 131.1 (H*C*=CH), 115.9 (HC=*C*H), 114.4 (Furan C–H), 112.2 (Furan C–H), 51.5 (O–CH_3). IR: ν_{max}/cm^{-1} 3124, 2952, 1703, 1637, 1260, 1015, 1161, 745.

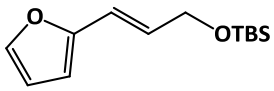
Z-isomer: ^{1}H NMR, (300 MHz, $CDCl_3$): δ_H 7.71 (1H, d, *J* = 3.6 Hz, Furan–H), 7.50 (1H, d, *J* = 1.8 Hz, Furan–H), 6.82 (1H, d, *J* = 12.9 Hz, *H*C=CH), 6.53 (1H, ddd, *J* = 3.6, 1.8, 0.6 Hz, Furan–H), 5.76 (1H, d, *J* = 12.9 Hz, HC=C*H*), 3.79 (3H, s, O–CH_3).



142

To (*E*)-methyl 3-(furan-2-yl)acrylate (**140**, 603 mg, 3.96 mmol) in CH_2Cl_2 (25 mL) under N_2 at -78 ^oC was added dropwise DiBAl-H (1M in CH_2Cl_2, 1.69 g, 11.88 mmol, 11.9 mL). The mixture was allowed to slowly warm to r.t. and then cooled to 0 ^oC. Water (3 mL) was cautiously added, followed by sodium hydroxide (1 M, 5 mL) and further water (3 mL). The mixture was then filtered through Celite and washed with CH_2Cl_2. The organic layer was separated and the aqueous extracted with further CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$) and after removal of the solvent under vacuum, the crude material was purified by chromatography with silica gel (eluting with Et_2O/petroleum ether 40-60, 10:90) to yield **142** as a pale yellow oil, 351 mg (71%). R_f 0.27 (UV active, Et_2O/petroleum ether 40-60, 30:70).

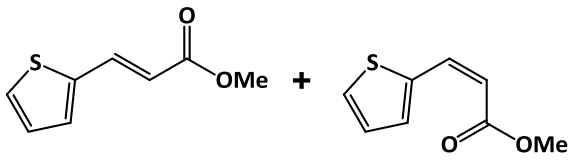
^1H NMR, (300 MHz, $CDCl_3$): δ_H 7.37 (1H, d, *J* = 1.7 Hz, Furan C–H), 6.47 (1H, dd, *J* = 15.9, 1.1 Hz, *H*C=CH), 6.39 (1H, dd, *J* = 3.3, 1.7 Hz, Furan-H), 6.30 (1H, dt, *J* = 15.9, 5.5, 5.5 Hz, HC=C*H*), 6.26 (1H, d, *J* = 3.3 Hz, Furan-H), 4.32 (2H, dd, *J* = 5.5, 1.1 O–CH_2), 1.60 (1H, br s, OH). ^{13}C NMR, (300 MHz, $CDCl_3$): δ_C 142.0 (Furan C), 127.6 (Furan C–H), 119.5 (HC=*C*H), 111.2 (H*C*=CH), 107.8 (Furan C–H), 99.7 (Furan C–H), 63.3 (O–CH_2).



149

To a solution of (*E*)-3-(furan-2-yl)prop-2-en-1-ol (**142**, 200 mg, 1.59 mmol) in CH_2Cl_2 (10 mL) was added imidazole (241 mg, 3.54 mmol) and *tert*-butylchlorodimethylsilane (267 mg, 1.77 mmol) at 0 ^oC and the mixture allowed to warm to r.t. and stirred for 16 h. The following day the reaction was washed with water (50 mL), brine (50 mL), dried ($MgSO_4$) and concentrated. The crude residue was chromatographed on silica gel (eluting with Et_2O/petroleum ether 40-60, 20:80) to yield **149** as a colourless oil, 370 mg (49%). R_f 0.94 (UV active, Et_2O/petroleum ether 40-60, 40:60).

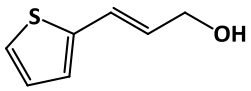
^1H NMR, (300 MHz, $CDCl_3$): δ_H 7.35 (1H, d, *J* = 1.8 Hz, Furan–H), 6.45 (1H, dt, *J* = 15.7, 1.8, 1.8 Hz, *H*C=CH), 6.38 (1H, *J* = 3.3, 1.8 Hz, Furan-H), 6.25 (1H, td, *J* = 15.7, 4.6, 4.6 Hz, HC=C*H*), 6.23 (1H, *J* = 4.6 Hz, Furan–H), 4.35 (2H, dd, *J* = 4.6, 1.8 Hz, O–CH_2), 0.95 (9H, s, CH_3 x 3), 0.12 (6H, s, CH_3 x 2). ^{13}C NMR, (75 MHz, $CDCl_3$): δ_C 153.2 (Furan C) 141.7 (Furan C–H), 128.3 (HC=*C*H), 118.0 (H*C*=CH), 111.1 (Furan C–H), 107.1 (Furan C–H), 63.4 (O–CH_2), 26.0 (CH_3 x 3), 18.4 (C–$(CH_3)_3$), –5.2 (CH_3 x 2).



152 **153**

To a stirred suspension of sodium hydride (60% in oil, 860 mg, 21.50 mmol) in THF (100 mL) at 0 ^{o}C was added trimethyl phosphonoacetate (4.5 g, 24.71 mmol, 3.6 mL). After 30 min, thiophene-2-carbaldehyde (2.0 g, 17.83 mmol, 1.6 mL) in THF (20 mL) was added dropwise. After stirring for an additional 30 min at r.t., the mixture was diluted with Et_2O (100 mL) and treated with water (100 mL). The organic layers were separated, washed with brine (50 mL) and dried ($MgSO_4$). After evaporation of the solvent, the residue was chromatographed on silica gel (eluting with Et_2O/petroleum ether 40-60, 1:20) obtaining **152** as a white solid, 2.30 g (77%), and a minor amount of the *Z*-isomer (**153**, 1%) as a yellow oil. R_f 0.46 (UV active, Et_2O/petroleum ether 40-60, 10:90), m.p.: *E*-isomer: 48-50 ^{o}C.

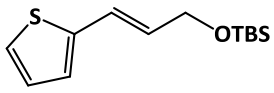
E-isomer: ^{1}H NMR, (300 MHz, $CDCl_3$): δ_H 7.81 (1H, ddd, J = 15.7, 1.1, 1.1 Hz, *H*C=CH), 7.39 (1H, dd, J = 5.1, 1.1 Hz, Thiophene C–H), 7.27 (1H, dd, J = 3.6, 1.1 Hz, Thiophene C–H), 7.07 (1H, dd, J = 5.1, 3.6 Hz, Thiophene C–H), 6.26 (1H, d, J = 15.7 Hz, HC=C*H*), 3.81 (3H, s, O–CH_3). ^{13}C NMR, (75 MHz, $CDCl_3$): δ_C 167.0 (C=O), 139.7 (Thiophene C–H), 137.1 (H*C*=CH), 130.4 (Thiophene C–H), 128.2 (Thiophene C–H), 128.0 (Thiophene C), 116.9 (HC=*C*H), 51.4 (O–CH_3). IR: ν_{max}/cm^{-1} 1704, 1621, 990, 1205, 1160, 702. HRMS: calcd for $C_8H_7O_2S$ $(M+H)^+$: 169.0318, found 169.0338. *Z*-isomer: ^{1}H NMR, (300 MHz, $CDCl_3$): δ_H 7.55 (1H, d, J = 5.0 Hz, Thiophene C–H), 7.47 (1H, dd, J = 3.9, 1.1 Hz, Thiophene C–H), 7.13 (1H, d, J = 11.9 Hz, *H*C=CH), 7.09 (1H, d, J = 5.0 Hz, Thiophene C–H), 5.78 (1H, d, J = 11.9 Hz, HC=C*H*), 3.81 (3H, s, O–CH_3).



154

To (*E*)-methyl 3-(thiophen-2-yl)acrylate (**152**, 1.0 g, 5.94 mmol) in CH_2Cl_2 (40 mL) under N_2 at -78 ^oC was added dropwise DiBAl-H (1M in CH_2Cl_2, 2.54 g, 17.82 mmol, 17.8 g mL). The mixture was allowed to slowly warm to r.t., then cooled to 0 ^oC and water (4 mL) was cautiously added, followed by NaOH (1 M, 6 mL) and further water (4 mL). The resulting slurry was filtered through Celite and washed with further CH_2Cl_2. The organic layer was then separated and the aqueous extracted with CH_2Cl_2 (3 x 30 mL) and the combined extracts dried ($MgSO_4$) and concentrated. The crude residue was purified by chromatography on silica gel (eluting with Et_2O/petroleum ether 40-60, 30:70) to yield **154** as a pale yellow oil, 813 mg (98%). R_f 0.31 (UV active, Et_2O/petroleum ether 40-60, 30:70).

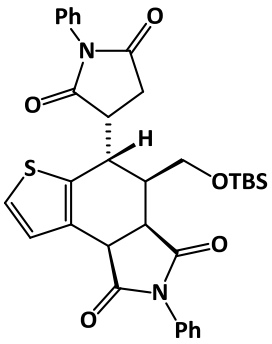
^1H NMR, (300 MHz, $CDCl_3$): δ_H 7.18 (1H, dd, *J* = 3.7, 2.9 Hz, Thiophene C–H), 6.98 (1H, d, *J* = 3.6 Hz, Thiophene C–H), 6.98 (1H, d, *J* = 3.6 Hz, Thiophene C–H), 6.77 (1H, dt, *J* = 15.8, 1.5 Hz, *H*C=CH), 6.22 (1H, dt, *J* = 15.7, 5.8 Hz, HC=C*H*), 4.30 (2H, ddd, *J* = 5.7, 1.4 Hz, O–CH_2), 1.66 (t, *J* = 5.8 Hz, OH). ^{13}C NMR, (75 MHz, $CDCl_3$): δ_C 142.2 (Thiophene C), 128.7 (Thiophene C–H), 127.6 (HC=*C*H), 125.9 (H*C*=CH), 124.6 (Thiophene C–H), 124.6 (Thiophene C–H), 63.6 (O–CH_2). IR: ν_{max}/cm^{-1} 3311, 2917, 2857, 1649, 953, 1432, 1240, 1000, 691. HRMS: calcd for C_7H_8OS $(M)^+$: 141.0290, found 141.0277.



156

To a solution of (*E*)-3-(thiophen-2-yl)prop-2-en-1-ol (**154**, 500 mg, 3.57 mmol) in CH_2Cl_2 (12.5 mL) was added imidazole (534 mg, 7.84 mmol) and *tert*-butylchlorodimethylsilane (591 mg, 3.92 mmol) at 0 ^oC and the mixture allowed to warm to r.t. and stirred for 16 h. The following day the reaction was washed with water (50 mL), brine (50 mL), dried ($MgSO_4$) and concentrated. The crude residue was chromatographed on silica gel (eluting with Et_2O/petroleum ether 40-60, 5:95) to yield **156** as a colourless oil, 783 mg (89%). R_f 0.84 (UV active, Et_2O/petroleum ether 40-60, 40:60).

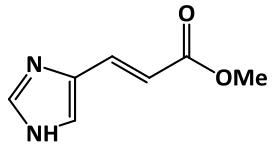
^1H NMR, (300 MHz, $CDCl_3$): δ_H 7.15 (1H, dd, J = 5.2, 1.3 Hz, Thiophene C–H), 7.00–6.94 (2H, m, Thiophene C–H x 2), 6.74 (1H, dt, J = 15.8, 1.3, 1.2 Hz, *H*C=CH), 6.15 (1H, dt, J = 15.8, 5.1, 5.1 Hz, HC=C*H*), 4.33 (2H, dd, J = 5.1, 1.2 Hz, O–CH_2), 0.96 (9H, s, CH_3 x 3), 0.13 (6H, s, CH_3 x 2). ^{13}C NMR, (75 MHz, $CDCl_3$): δ_C 142.5 (Thiophene C), 129.3 (Thiophene C–H), 127.3 (HC=*C*H), 125.1 (Thiophene C–H), 123.9 (H*C*=CH), 122.8 (Thiophene C–H), 63.5 (O–CH_2), 26.0 (CH_3 x 3), 18.5 (*C*–$(CH_3)_3$), –5.1 (CH_3 x 2).



158

To ((*E*)-3-thiophen-2-yl)allyloxy)(*tert*-butyl)dimethylsilane (**156**, 100 mg, 0.39 mmol) in toluene (5 mL) was added NPM (170 mg, 0.98 mmol) and the solution stirred at reflux for 16 h. The solvent was removed and the crude residue was chromatographed on silica gel (eluting with Et_2O/petroleum ether 40-60, 1% increasing to 20%) to yield **158** as a yellow solid, 65 mg (29%). R_f 0.51 (UV active, ethyl acetate/petroleum ether 40-60, 50:50), m.p.: 140-142 ^oC.

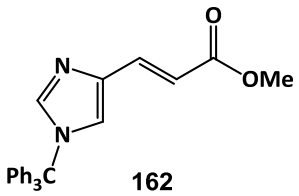
^1H NMR (400 MHz, $CDCl_3$): δ_H 7.52–7.37 (6H, m, Phenyl-H), 7.36-7.34 (2H, m, Phenyl-H), 7.34–7.33 (1H, m, Phenyl-H), 7.27-7.26 (1H, m, Phenyl-H), 7.24-7.21 (2H, m, Phenyl-H), 4.18 (1H, d, J = 10.7 Hz, H_a), 4.15 (1H, dd, J = 10.7, 6.0 Hz, H_b), 4.04 (1H, dd, J = 13.4, 10.1 Hz, H_h), 3.89 (1H, dd, J = 13.4, 6.9 Hz, H_h), 3.63 (1H, ddd, J = 10.1, 8.0, 6.9 Hz, H_g), 3.58 (1H, dd, J = 10.7, 8.0 Hz, H_d), 2.91 (1H, dd, J = 23.0, 8.0 Hz, H_f), 2.49 (1H, dddd, J = 10.7, 10.2, 8.0, 6.0, Hz, H_c), 2.46 (1H, dd, J = 23.0, 10.2 Hz, H_f), 0.85 (9H, s, $(CH_3)_3$), 0.01 and 0.00 (3H, s, CH_3). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 177.5 (NPM C=O), 175.9 (NPM C=O), 175.0 (NPM C=O), 174.7 (NPM C=O), 134.5 (Thiophene C), 132.0 (Phenyl C), 131.6 (Phenyl C), 130.6 (Thiophene C), 129.4 (Phenyl C–H), 129.2 (Phenyl C–H), 128.9 (Phenyl C–H), 128.8 (Phenyl C–H), 127.5 (Phenyl C–H), 126.5 (Phenyl C–H), 126.3 (Thiophene C–H), 125.4 (Thiophene C–H), 63.6 (C-H_h), 44.6 (C–H_a), 42.2 (C–H_d), 42.1 (C–H_b), 41.2 (C–H_g), 31.0 (C-H_f), 30.4 (C–H_c), 26.0 ($(CH_3)_3$), 18.4 ($C(CH_3)_3$), –5.4 and –5.5 (Si–CH_3). HRMS: calcd for $C_{33}H_{36}N_2O_5SSi$ $(M+Na)^+$: 623.2006, found 623.2022.



160

To methanol (150 mL) was added thionyl chloride (2.20 g, 18.49 mmol, 1.4 mL) dropwise, at r.t. and the solution stirred. To this was added urocanic acid (**159**, 2.50 g, 18.10 mmol) and the solution heated to reflux for 16 h. The solution was then allowed to cool and the methanol removed *in vacuo*. The solid residue was taken up in ethyl acetate (150 mL) and quenched with sat. aq. Na_2CO_3 (100 mL). The aqueous layer was extracted with further ethyl acetate (3 x 50 mL), dried ($MgSO_4$) and concentrated to give **160** as a white solid, 2.23 g (81%). R_f 0.87 (UV active, methanol/DCM, 1:9), m.p.: 90–92 ºC (lit.[186] 90-92 ^oC).

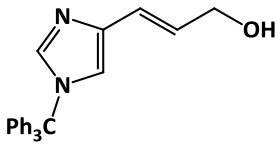
^1H NMR, (400 MHz, DMSO-d_6): δ_H 12.44 (1H, br s, N-H), 7.74 (1H, s, Imidazole-H), 7.50 (1H, d, J = 15.7 Hz, *H*C=CH), 7.49 (1H, s, Imidazole-H), 6.31 (1H, d, J = 15.7 Hz, HC=C*H*), 3.63 (s, 3H, O-CH_3). ^{13}C NMR, (75 MHz, DMSO–d_6): δ_C 167.7 (C=O), 136.7 (Imidazole C–H), 135.7 (Imidazole C), 134.8 (H*C*=CH), 121.6 (HC=*C*H), 116.3 (Imidazole C–H), 51.4 (O–CH_3). IR: ν_{max}/cm^{-1} 3136, 2928, 2869, 1707, 1645, 1431, 1259, 1096, 1148. HRMS: calcd for $C_7H_8N_2O_2$ $(M)^+$: 152.0580, found 152.0602.



162

To (*E*)-methyl 3-(1*H*-imidazol-4-yl)acrylate (**160**, 500 mg, 3.29 mmol) in THF (20 mL) at 0 °C was added triethylamine (831 mg, 8.21 mmol, 1.1 mL), followed by chlorotriphenylmethane (1.01 g, 3.62 mmol) in THF (60 mL) dropwise, and stirring continued at 0 °C for 1 h, then at r.t. for 16 h. The mixture was then concentrated and taken up in CH_2Cl_2 (100 mL), washed with water (3 x 100 mL), and dried (Na_2SO_4). After evaporation of the solvent the residue was chromatographed on silica gel (eluting with ethyl acetate/petroleum ether 40-60, 20:80) yielding **162** as a white solid, 1.26 g (97%). R_f 0.31 (UV active, ethyl acetate/petroleum ether 40-60, 20:80). m.p.: 192–195 °C.

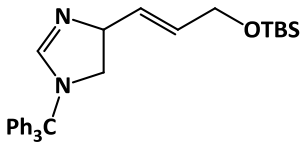
^{1}H NMR, (300 MHz, $CDCl_3$): δ_H 7.53 (1H, d, J = 15.7 Hz, *H*C=CH), 7.49 (1H, d, J = 0.9 Hz, Imidazole–H), 7.38–7.36 (9H, m, Phenyl–H), 7.16–7.13 (6H, m, Phenyl–H), 7.05 (1H, d, J = 0.9 Hz, Imidazole-H), 6.58 (1H, d, J = 15.7 Hz, HC=C*H*), 3.74 (3H, s, O–CH_3). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 167.9 (C=O), 141.9 (Phenyl C), 140.3 (Imidazole C), 137.0 (Imidazole C–H), 136.3 (H*C*=CH), 129.6 (Phenyl C–H), 128.3 (Phenyl C–H), 128.2 (Phenyl C–H), 124.0 (HC=*C*H), 115.7 (Imidazole C–H), 75.7 (C–Ph_3), 51.4 (O–CH_3). IR: ν_{max}/cm^{-1} 3056, 2947, 1707, 1640, 1490, 749, 700. HRMS: calcd for $C_{26}H_{22}N_2O_2$ $(M+Na)^+$: 417.1573, found 417.1574.



163

To (*E*)-methyl 3-(1-trityl-1*H*-imidazol-4-yl)acrylate (**162**, 500 mg, 1.27 mmol) in CH_2Cl_2 (100 mL) at -78 ^oC was added DiBAl-H (1 M solution in toluene, 541 mg, 3.81 mmol, 3.8 mL) dropwise over 10 min. After 1 h the reaction was quenched by slowly pouring into 1 M HCl/ice (150 mL) and stirring for 10 min. The solution was then basified with 1M $NaOH_{(aq)}$ and extracted with ethyl acetate (3 x 100 mL). The combined organics were washed with brine (100 mL) and dried (Na_2SO_4). After evaporation of the solvent, the residue was chromatographed on silica gel (eluting with ethyl acetate/petroleum ether 40-60/methanol, 40:58:2) affording **163** resulting in a white solid, 310 mg (67%). R_f 0.42 (UV active, ethyl acetate/petroleum ether 40-60/methanol, 50:40:10), m.p.: 200–203 ºC (lit.[187] 209-211 ^oC).

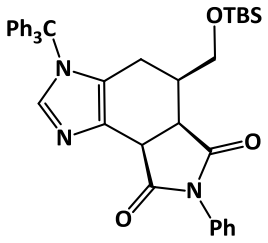
^1H NMR, (400 MHz, $CDCl_3$): δ_H 7.42 (1H, s, Imidazole-H), 7.37–7.33 (9H, m, Phenyl-H), 7.18–7.13 (6H, m, Phenyl-H), 6.77 (1H, s, Imidazole-H), 6.51–6.46 (2H, m, *H*C=CH and HC=C*H*), 4.27 (2H, d, J = 4.1 Hz, O-CH_2), 2.22 (1H, br s, OH). ^{13}C NMR, (75 MHz, $CDCl_3$): δ_C 142.3 (Phenyl C), 139.3 (Imidazole C-H), 138.7 (Imidazole C), 129.8 (Phenyl C-H), 128.2 (Phenyl C-H), 127.5 (H*C*=CH), 123.0 (HC=*C*H), 119.5 (Imidazole C-H), 75.4 (*C*-PH_3), 63.6 (O-CH_2). IR: ν_{max}/cm^{-1} 3660, 2981, 2889, 1474, 1382, 1156, 1085, 742, 696. HRMS: calcd for $C_{25}H_{22}N_2O$ $(M+H)^+$: 367.1805, found 367.1810.



164

To a solution of (*E*)-3-(1-trityl-1*H*-imidazol-4-yl)prop-2-en-1-ol (**163**, 400 mg, 1.09 mmol) in CH_2Cl_2 (10 mL) was added imidazole (163 mg, 2.39 mmol) and *tert*-butylchlorodimethylsilane (181 mg, 1.20 mmol) at 0 ^oC and the mixture allowed to warm to r.t. and stirred for 16 h. The following day the reaction was washed with water (30 mL), brine (30 mL), dried ($MgSO_4$) and concentrated. The crude residue was chromatographed on silica gel (eluting with Et_2O/petroleum ether 40-60, 40:60) to yield **164** as a white solid, 357 mg (68%). R_f 0.38 (UV active, Et_2O/petroleum ether 40-60, 50:50). m.p.: 134–136 ºC.

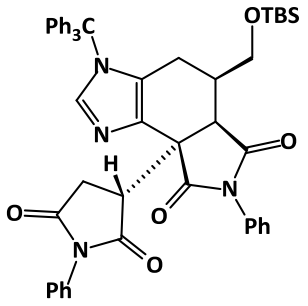
^1H NMR, (300 MHz, $CDCl_3$): δ_H 7.42 (1H, d, J = 1.1 Hz, Imidazole–H), 7.36–7.34 (9H, m, Phenyl–H), 7.18–7.15 (6H, m, Phenyl–H), 6.75 (1H, d, J = 1.1 Hz, Imidazole–H), 6.45–6.42 (2H, m, *H*C=CH and HC=C*H*), 4.33 (2H, d, J = 3.3 Hz, O–CH_2), 0.93 (9H, s, $(CH_3)_3$), 0.10 (6H, s, $Si(CH_3)_2$). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 142.4 (Phenyl C), 139.2 (Imidazole C–H), 129.9 (Phenyl C–H), 128.1 (Phenyl C–H), 128.0 (H*C*=CH), 127.2 (Imidazole C), 121.2 (HC=*C*H), 119.1 (Imidazole C–H), 75.3 (C–Ph_3), 63.8 (O–CH_2), 26.1 ($(CH_3)_3$), 18.5 ($C(CH_3)_3$), –5.1 ($Si(CH_3)_2$). IR: ν_{max}/cm^{-1} 2926, 2853, 1445, 1382, 1250, 1037, 833, 749, 700. HRMS: calcd for $C_{31}H_{36}N_2OSi$ $(M+H)^+$: 481.2670, found 481.2669.



168

To 1-trityl-4-((*E*)-3-(*tert*-butyldimethylsilyloxy)prop-1-enyl)-1*H*-imidazole (**164**, 600 mg, 1.25 mmol) in toluene (28 mL) was added NPM (520 mg, 3.00 mmol) and the solution stirred at reflux for 20 h. The solvent was removed and the crude residue was chromatographed on silica gel (eluting with ethyl acetate/petroleum ether 40-60, 60:40) to yield the product as a pale yellow solid, 496 mg (63%). R_f 0.48 (UV active, ethyl acetate/petroleum ether 40-60, 80:20), m.p.: 119–121 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.47–7.43 (2H, m, Phenyl–H), 7.39–7.37 (2H, m, Phenyl–H), 7.30–7.27 (9H, m, Phenyl–H), 7.12 (2H, d, J = 7.8, 1.3 Hz, Phenyl–H), 7.09–7.07 (6H, m, Phenyl–H + Imidazole–H), 4.27 (1H, d, J = 7.8 Hz, H_a), 3.93 (1H, dd, J = 9.8, 6.0 Hz, H_f), 3.65 (1H, dd, J = 9.8, 7.8 Hz, H_f), 3.50 (1H, dd, J = 7.8, 3.7 Hz, H_b), 2.12–2.08 (2H, m, H_c and H_d), 1.10 (1H, ddd, J = 14.7, 12.8, 1.4 Hz, H_d), 0.72 (9H, s, $(CH_3)_3$), –0.09 and –0.17 (3H, s, Si–CH_3). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 176.1 (NPM C=O), 174.5 (NPM C=O), 141.2 (Phenyl C), 139.1 (Imidazole C–H), 132.2 (Imidazole C), 131.9 (Imidazole C), 129.7 (Phenyl C–H), 129.3 (Phenyl C), 129.0 (Phenyl C–H), 128.4 (Phenyl C–H), 128.2 (Phenyl C–H), 128.1 (Phenyl C–H), 126.4 (Phenyl C–H), 75.0 (*C*–Ph_3), 64.1 (C-H_f), 42.8 (C–H_a), 41.4 (C–H_b), 38.9 (C–H_c), 25.8 ($(CH_3)_3$), 23.8 (C–H_d), 18.1 ($C(CH_3)_3$), –5.5 and –5.6 (Si–CH_3). IR: ν_{max}/cm^{-1} 2927, 2854, 1382, 1216, 1250, 1037, 832, 779, 700. HRMS: calcd for $C_{41}H_{44}N_3O_3Si$ $(M+H)^+$: 654.3146, found 654.3145.



175

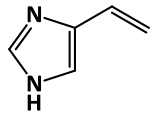
To 1-trityl-4-((*E*)-3-(*tert*-butyldimethylsilyloxy)prop-1-enyl)-1*H*-imidazole (**164**, 430 mg, 0.89 mmol) in toluene (20 mL) was added NPM (387 mg, 2.23 mmol) and the solution stirred at reflux for 72 h. The solvent was removed and the crude residue was chromatographed on silica gel (eluting with ethyl acetate/petroleum ether 40-60, 5% increasing to 60%) to yield **175** as a pale brown solid, 420 mg (57%). R_f 0.68 (UV active, ethyl acetate/petroleum ether 40-60, 35:65), m.p.: 185–188 ºC.

^{1}H NMR, (400 MHz, $CDCl_3$): δ_H 7.39 (6H, ddd, J = 9.6, 8.9, 1.6 Hz, Phenyl–H), 7.34–7.33 (1H, m, Phenyl–H), 7.31–7.30 (5H, m, Phenyl–H), 7.29–7.27 (3H, m, Phenyl–H), 7.26–7.23 (3H, m, Phenyl–H + Imidazole–H), 7.16–7.14 (2H, m, Phenyl–H), 7.04 (6H, ddd, J = 4.4, 1.6, 1.6 Hz, Phenyl–H), 4.83 (1H, dd, J = 9.8, 7.1 Hz, H_g), 3.93 (1H, dd, J = 10.2, 6.4 Hz, H_f), 3.58 (1H, dd, J = 10.2, 8.0 Hz, H_f), 3.22 (1H, d, J = 3.8 Hz, H_b), 3.11 (1H, dd, J = 18.4, 9.8 Hz, H_h), 2.79 (1H, dd, J = 18.4, 7.1 Hz, H_h), 2.13 (1H, dd, J = 16.3, 3.4 Hz, H_d), 2.03–1.95 (1H, m, H_c), 1.10 (1H, dd, J = 16.3, 12.1 Hz, H_d), 0.66 (9H, s, $(CH_3)_3$), –0.14 and –0.21 (3H, s, Si–CH_3). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 176.4 (NPM C=O), 175.3 (NPM C=O), 174.5 (NPM C=O), 174.5 (NPM C=O), 141.2 (Phenyl C), 139.9 (Imidazole C–H), 133.5 (Imidazole C), 132.0 (Phenyl C), 131.5 (Phenyl C), 131.0 (Imidazole C), 129.7 (Phenyl C–H), 129.3 (Phenyl C–H), 129.1 (Phenyl C–H), 128.9 (Phenyl C–H), 128.7 (Phenyl C–H), 128.5 (Phenyl C–H), 128.3 (Phenyl C–H), 126.8 (Phenyl C–H), 126.4 (Phenyl C–H), 75.3 (*C*–Ph_3), 63.9 (C-H_f), 49.3 (C_a), 44.8 (C–H_g), 44.2 (C–H_b), 40.6 (C–H_c), 32.0 (C-H_h), 25.9 ($(CH_3)_3$), 24.1 (C-H_d), 18.2 ($C(CH_3)_3$), –5.3 and –5.4 (Si–CH_3). IR: 2955, 2926, 1781, 1711, 1598, 1499, 1378, 1258, 1185, 837, 746, 691. HRMS: calcd for $C_{51}H_{50}N_4O_5Si$ $(M+Na)^+$: 849.3443, found 849.3450.

Alternative synthesis of **175** from **168**:

To (5*R*,5a*R*,8a*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-7-phenyl-3-trityl-5,5a,7,8a-tetrahydroimidazo[4,5-*e*]isoindole-6,8(3*H*,4*H*)-dione (**168**) (40 mg, 0.06 mmol) in toluene (2 mL) was added sodium hydride (60% wt in oil, 3 mg, 0.06 mmol) under N_2,

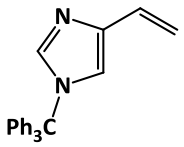
and the solution allowed to warm to r.t. and stirred for 1 h. *N*-phenylmaleimide (16 mg, 0.09 mmol) was then added and the solution stirred at reflux for 6 h. The solvent was removed and the crude residue was chromatographed on silica gel (eluting with methanol/diethyl ether, 2:98) to yield **175** as a pale brown solid, 31 mg (61%).



179

Short path distillation of urocanic acid (**159**, 10.00 g, 72.40 mmol) was carried out with heating under vacuum (0.18 mmHg). The stirred tan coloured powder began "frothing" at 110 ^{o}C, which subsided after 15 min. Heating of the resulting oily residue was continued and **179** distilled as a pale yellow oil. This oil was taken up in ethyl acetate (50 mL) and washed with sat. aq. Na_2CO_3 (25 mL). The layers were separated and the aqueous was re-extracted with further ethyl acetate (2 x 30 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give **179** as a pale yellow oil, which solidified on standing to give an off-white solid, 5.70 g (84%). R_f 0.67 (UV active, Et_2O/petroleum ether 40-60, 40:60), m.p.: 82–84 ºC (lit.[188] 82-84 ^{o}C).

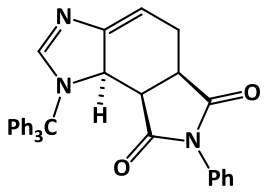
^{1}H NMR, (300 MHz, $CDCl_3$): δ_H 9.13 (1H, br s, N–H), 7.63 (1H, s, Imidazole–H), 7.06 (1H, s, Imidazole–H), 6.65 (1H, dd, *J* = 17.7, 11.2 Hz, Vinyl C–H), 5.69 (1H, dd, *J* = 17.7, 0.7 Hz, Vinyl CH_2 *trans* C–H), 5.16 (1H, dd, *J* = 11.2, 0.7 Hz, Vinyl CH_2 *cis* C–H). ^{13}C NMR, (75 MHz, $CDCl_3$): δ_C 136.0 (Imidazole C–H), 135.4 (Imidazole C–H), 126.7 (H*C*=CH_2), 119.4 (Imidazole C), 112.1 (HC=CH_2). IR: ν_{max}/cm^{-1} 3058, 3050, 2869, 2837, 1642. HRMS: calcd for $C_5H_6N_2$ $(M)^+$: 94.0531, found 94.0525.



180

To 4-vinyl-1*H*-imidazole (**179**, 500 mg, 5.31 mmol) in THF (20 mL) at 0 °C was added triethylamine (1.34 g, 13.24 mmol, 1.9 mL), followed by chlorotriphenylmethane (1.63 g, 5.85 mmol) in THF (20 mL) dropwise and stirring continued at 0 °C for 1 h, then at r.t. for 16 h. The mixture was then concentrated and taken up in CH_2Cl_2 (50 mL), washed with water (3 x 50 mL), and dried ($MgSO_4$). After evaporation of the solvent the residue was chromatographed on silica gel (eluting with Et_2O/petroleum ether 40-60, 50:50) yielding the product as a white solid, 1.11 g (62%). R_f 0.18 (UV active, Et_2O/petroleum ether 40-60, 40:60), m.p.: 208–211 °C (lit.[146] 205-207 °C).

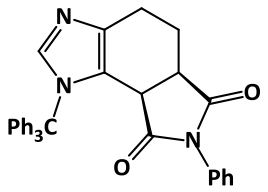
^{1}H NMR ($CDCl_3$, 300MHz): δ_H 7.43 (1H, d, J = 0.7 Hz, Imidazole–H), 7.38–7.32 (9H, m, 1H, Phenyl–H), 7.17 (6H, ddd, J = 5.5, 2.5, 1.3 Hz, Phenyl–H), 6.79 (1H, d, J = 0.8 Hz, Imidazole–H), 6.57 (1H, dd, J = 17.5, 11.0 Hz, Vinyl C–H), 5.85 (1H, dd, J = 17.5, 1.7 Hz, Vinyl CH_2 *trans* C–H), 5.14 (1H, dd, J = 11.0, 1.7 Hz, Vinyl CH_2 *cis* C–H). ^{13}C NMR, (75 MHz, $CDCl_3$): δ_C 142.7 (Phenyl C), 139.9 (Imidazole C), 139.3 (Imidazole C–H), 129.9 (Phenyl C–H), 128.9 (H*C*=CH_2), 128.1 (Phenyl C–H), 128.1 (Phenyl C-H), 119.1 (Imidazole C–H), 112.3 (HC=*C*H_2), 75.6 (C–Ph_3). IR: ν_{max}/cm^{-1} 3087, 3066, 3034, 1633, 1492, 1182, 1123, 750, 700. HRMS: calcd for $C_{24}H_{20}N_2$ $(M+H)^+$: 337.1699, found 337.1697.



184

To 1-trityl-4-vinyl-1*H*-imidazole (**180**, 264 mg, 0.52 mmol) in toluene (10 mL) was added NPM (224 mg, 1.30 mmol) and the solution stirred at reflux for 3 h. The solvent was removed, and the crude residue was chromatographed on silica gel (ethyl acetate/petroleum ether 40-60, 40:60) to yield **184** as a white solid, 207 mg (78%). R_f 0.42 (UV active, ethyl acetate/petroleum ether 40-60, 40:60), mp 208–211 ^{o}C.

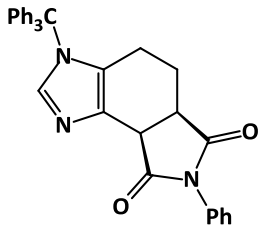
^{1}H NMR (300MHz, $CDCl_3$): δ_H 7.55–7.51 (6H, m, Phenyl–H + Imidazole–H), 7.47–7.34 (13H, m, Phenyl–H), 7.13 (2H, dd, *J* = 7.0, 1.6 Hz, Phenyl–H), 5.65 (1H, ddd, *J* = 5.4, 3.8, 3.8 Hz, H_d), 4.37 (1H, ddd, *J* = 6.0, 3.1, 3.1 Hz, H_a), 2.98 (1H, ddd, *J* = 15.4, 7.8, 1.1 Hz, H_c), 2.77 (1H, ddd, *J* = 8.2, 8.1, 0.7 Hz, H_b), 2.00 (2H, m, H_c and H_e). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 178.0 (NPM C=O), 174.0 (NPM C=O), 162.2 (Imidazole C–H), 155.5 (Phenyl C), 142.2 (Phenyl C), 131.6 (Imidazole C), 130.4 (Phenyl C–H), 129.1 (Phenyl C–H), 128.7 (Phenyl C–H), 128.1 (Phenyl C–H), 127.7 (Phenyl C–H), 126.6 (Phenyl C–H), 102.2 (C–H_d), 75.0 (C–Ph_3), 58.9 (C–H_a), 42.0 (C–H_e), 36.8 (C–H_b), 26.3 (C-H_c). IR: ν_{max}/cm^{-1} 3059, 2927, 2856, 1778, 1709, 1538, 1495, 749, 701. HRMS calcd for $C_{34}H_{27}N_3O_2$ $(M+Na)^+$: 532.1995, found 532.2007.



185

To 1-trityl-4-vinyl-1*H*-imidazole (**180**, 1.0 g, 2.97 mmol) in toluene (37 mL) was added NPM (1.29 g, 7.43 mmol) and the solution stirred at reflux for 3 h. The reaction mixture was concentrated to a low volume and cooled. The resulting crystals were filtered, yielding the product, 80mg (6%). R_f 0.29 (UV active, methanol/Et_2O, 2:98), m.p.: dec. >190 ^oC.

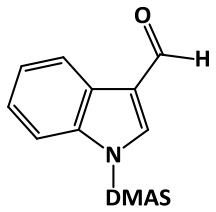
^1H NMR (400MHz, DMSO-d_6) δ_H 7.43-7.30 (12H, m, Phenyl-H), 7.29 (1H, s, Imidazole-H), 7.17-7.14 (6H, m, Phenyl-H), 7.09-7.07 (2H, m, Phenyl-H), 2.56 (1H, ddd, J = 19.2, 4.8, 4.8 Hz, H_d), 2.37 (1H, ddd, J = 19.7, 14.6, 5.4 Hz, H_d), 2.13 (1H, ddd, J = 12.0, 8.2, 4.2 Hz, H_c), 1.53-1.44 (3H, m, H_a, H_b, H_c). ^{13}C NMR, (101 MHz, CDCl3) δ_C 177.7 (C=O), 173.7 (C=O), 142.4 (Phenyl-C), 142.2 (Phenyl-C), 142.0 (Phenyl C-H), 141.8 (Imidazole C), 141.0 (Imidazole C), 130.8 (Phenyl C-H), 129.1 (Phenyl C-H), 128.5 (Phenyl C-H), 128.2 (Phenyl C-H), 127.9 (Imidazole C-H), 126.4 (Phenyl C-H), 77.3 (C-Ph_3), 42.4 (H_c), 40.8 (H_d), 24.9 (H_a), 23.0 (H_b). IR: ν_{max}/cm^{-1} 2970, 2360, 1716, 1379, 1174, 823, 751, 703. HRMS calcd for $C_{34}H_{27}N_3O_2$ $(M+Na)^+$: 532.1995, found 532.2006. Anal. Calcd for $C_{34}H_{27}N_3O_2$: C, 80.13; H, 5.34; N, 8.25. Found: C, 80.00; H, 5.26; N, 8.20.



186

To 1-trityl-4-vinyl-1*H*-imidazole (**180**, 500 mg, 0.98 mmol) in toluene (18.5 mL) was added NPM (425 mg, 2.45 mmol) and the solution stirred at reflux for 5 h. The solvent was removed and the crude residue was chromatographed on silica gel (eluting with ethyl acetate/petroleum ether 40-60, 60:40) to yield the product as a white solid, 240 mg (32%). R_f 0.10 (UV active, methanol/Et_2O, 2:98), m.p.: dec >232 ºC.

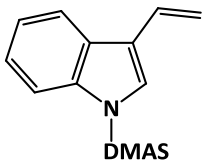
^{1}H NMR (400MHz, $CDCl_3$): δ_H 7.40–7.35 (2H, m, Phenyl–H), 7.31 (1H, s, Imidazole–H), 7.26 (10H, ddd, *J* = 10.4, 10.4, 6.0 Hz, Phenyl–H), 7.15–7.12 (2H, m, Phenyl–H), 7.05–7.02 (6H, m, Phenyl–H), 4.21 (1H, d, *J* = 8.2 Hz, H_a), 3.31 (1H, ddd, *J* = 9.2, 5.0, 4.1 Hz, H_b), 2.12–2.06 (1H, m, H_c), 1.72 (1H, ddd, *J* = 15.8, 4.1, 4.1 Hz, H_d), 1.67–1.59 (1H, m, H_c), 1.43 (1H, ddd, *J* = 15.8, 10.5, 4.6 Hz, H_d). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 177.6 (NPM C=O), 174.8 (NPM C=O), 141.5 (Imidazole C–H), 139.1 (Phenyl C), 132.1 (Imidazole C), 131.6 (Imidazole C), 129.9 (Phenyl C–H), 129.4 (Phenyl C), 129.1 (Phenyl C–H), 128.5 (Phenyl C–H), 128.3 (Phenyl C–H), 128.2 (Phenyl C–H), 126.5 (Phenyl C–H), 75.1 (C–Ph_3), 41.5 (C–H_a), 40.3 (C–H_b), 22.6 (C–H_c), 21.0 (C–H_d). IR: ν_{max}/cm^{-1} 3060, 2926, 1779, 1711, 1597, 1493, 756, 701. HRMS: calcd for $C_{34}H_{27}N_3O_2$ $(M+Na)^+$: 532.1995, found 532.2003. Anal. Calcd for $C_{34}H_{27}N_3O_2$: C: 80.13%, H: 5.34%, N: 8.25%, found C: 79.96%, H: 5.33%, N: 8.15%.



194

To 1*H*-indole-3-carboxaldehyde (2.0 g, 13.78 mmol) in THF (40 mL) at 0 ^{o}C under N_2 was added sodium hydride (60% wt in oil, 827 mg, 20.68 mmol) portionwise. The mixture was then allowed to warm to r.t. and stirred for 1.5 h, then cooled to 0 ^{o}C and DMAS-Cl (2.18 g, 15.18 mmol, 1.6 mL) was added dropwise. The mixture was allowed to warm to r.t. and stirred for 16 h. The reaction was then cooled to 0 ^{o}C and quenched slowly with ice/water (50 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organics were washed with brine (30 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure. Following chromatography on silica gel (eluting with ethyl acetate), **194** was obtained as a pale orange solid, 3.38 g (97%). R_f 0.63 (UV active, ethyl acetate), m.p.: 162-164 ^{o}C.

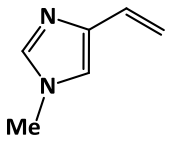
^{1}H NMR (400MHz, $CDCl_3$): δ_H 10.12 (1H, s, CHO), 8.36 (1H, ddd, J = 8.5, 3.0, 3.0 Hz, Phenyl-H), 8.12 (1H, s, C*H*-N), 7.94 (1H, ddd, J = 8.9, 3.0, 3.0 Hz, Phenyl-H), 7.49–7.39 (2H, m, Phenyl-H x 2), 2.95 (6H, s, CH_3 x 2). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 184.6 (C=O), 135.5 (Indole C), 127.1 (Indole C-H), 126.1 (Indole C), 124.8 (Indole C-H), 121.6 (Indole C-H), 119.8 (*C*-CHO), 118.3 (Indole C-H), 114.4 (Indole C-H), 39.9 (CH_3 x 2).



197

Methyltriphenylphosphonium iodide (4.68 g, 11.52 mmol) was dissolved in THF (50 mL) under N_2 at -78 ^oC and ^nBuLi (2.5 M, 10.50 mmol, 4.2 mL) added dropwise over 10 min. The solution was allowed to warm to 0 ^oC and 3-formyl-*N,N*-dimethyl-1*H*-indole-1-sulfolonamide (**194**, 2.5 g, 9.91 mmol) dissolved in THF (50 mL) was added *via* cannula, and the solution was allowed to warm to r.t. and stirred for 16 h. The reaction was then quenched by the careful addition of water (30 mL), and CH_2Cl_2 (100 mL). The aqueous was removed and re-extracted with further CH_2Cl_2 (3 x 50 mL). The combined organics were then washed with brine (50 mL) and dried ($MgSO_4$). The crude residue was purified by flash column chromatography (eluting with petroleum ether 40-60/Et_2O, 80:20) to give a white solid, 1.77 g (72%). R_f 0.63 (UV active, ethyl acetate).

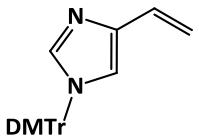
^1H NMR (400MHz, $CDCl_3$): δ_H 7.96 (1H, ddd, *J* = 6.0, 3.8, 2.7 Hz, Phenyl-H), 7.85 (1H, ddd, *J* = 7.6, 3.7, 3.0 Hz, Phenyl-H), 7.52 (1H, s, N-C*H*), 7.40-7.29 (2H, m, Phenyl-H x 2), 6.83 (1H ddd, *J* = 17.8, 11.3, 0.5 Hz, Vinyl C-H), 5.83 (1H, dd, *J* = 17.8, 1.0 Hz, Vinyl CH_2, *trans* C-H), 5.37 (1H, dd, *J* = 11.3, 1.0 Hz, Vinyl CH_2, *cis* C-H), 2.87 (5H, s, CH_3 x 2). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 134.6 (Indole C), 131.5 (H*C*=CH_2) 127.1 (Indole C-H), 125.9 (Indole C), 125.0 (Indole C-H), 123.3 (Indole C-H), 120.8 (Indole C-H), 118.5 (HC=*C*H_2), 114.4 (Indole C-H), 110.8 (*C*-CH=CH_2), 39.9 (CH_3 x 2).



200a

To 4-vinyl-1*H*-imidazole (**179**, 500 mg, 5.31 mmol) in THF (20 mL) at 0 ^{o}C under N_2 was added sodium hydride (60% wt in oil, 234 mg, 5.84 mmol) portionwise. The mixture was then allowed to warm to r.t. and stirred for 1.5 h, then cooled to 0 ^{o}C and methyl iodide (830 mg, 5.84 mmol, 0.4 mL) was added dropwise. The mixture was allowed to warm to r.t. and stirred for 3 h. The reaction was then cooled to 0 ^{o}C and quenched slowly with ice/water (30 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organics were washed with brine (30 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure. Following chromatography on silica gel (eluting with ethyl acetate), **200a** was obtained as a pale yellow liquid, 344 mg (60%). R_f 0.16 (UV active, ethyl acetate).

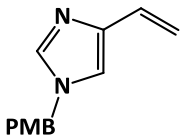
^{1}H NMR (400MHz, $CDCl_3$): δ_H 7.30 (1H, s, Imidazole C-H), 6.76 (1H, s, Imidazole C-H), 6.51 (1H, dd, *J* = 16.1, 10.9 Hz, CH), 5.74 (1H, dd, *J* = 16.1, 1.7 Hz, *trans*-CH), 5.03 (1H, dd, *J* = 10.9, 1.7 Hz, *cis*-CH), 3.56 (3H, s, CH_3). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 139.6 (Imidazole C), 137.5 (Imidazole C-H), 128.4 (CH), 117.6 (Imidazole C-H), 111.4 (CH_2), 33.1 (CH_3).



200c

To 4-vinyl-1*H*-imidazole (**179**, 95 mg, 1.01 mmol) in THF (2.5 mL) at 0 ^{o}C was added triethylamine (255 mg, 2.52 mmol, 0.4 mL), followed by 4,4'-dimethoxytrityl chloride (376 mg, 1.11 mmol) in THF (5 mL) dropwise and stirring continued at 0 ^{o}C for 1 h, then at r.t. for 16 h. The mixture was concentrated and taken up in CH_2Cl_2 (20 mL), washed with water (3 x 10 mL), and dried ($MgSO_4$). After evaporation of the solvent the residue was chromatographed on silica gel (eluting with Et_2O/petroleum ether 40-60, 50:50) yielding **200c** as a glassy yellow solid, 300 mg (75%). R_f 0.48 (UV active, ethyl acetate/petroleum ether 40-60, 40:60), m.p.: 162–164 ^{o}C.

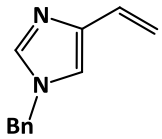
^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.41 (1H, s, Imidazole–H), 7.38–7.31 (3H, m, Phenyl–H), 7.16-7.10 (2H, m, Phenyl–H), 7.08-6.97 (4H, m, Phenyl–H), 6.88-6.78 (4H, m, Phenyl–H), 6.77 (1H, s, Imidazole–H), 6.57 (1H, dd, *J* = 17.1, 11.2 Hz, CH), 5.85 (1H, d, *J* = 17.1 Hz, *trans* CH), 5,14 (1H, d, *J* = 11.2 Hz, *cis* CH), 3.83 (6H, s, O–CH_3 x 2). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 159.3 (C-OMe), 143.1 (Phenyl-C), 139.6 (Imidazole C), 139.1 (Imidazole C-H), 134.9 (Phenyl C), 131.1 (Phenyl C-H), 129.6 (Phenyl C-H), 128.8 (C-H), 128.0 (Phenyl C-H), 127.9 (Phenyl C-H), 119.1 (Imidazole C-H), 113.4 (Phenyl C-H), 112.2 (CH_2), 74.8 (C-Ph_3), 55.3 (OMe). HRMS: calcd. for $C_{26}H_{24}N_2O_2$ $(2M + H)^+$ 793.3748, found 793.3749.



200d

To a solution of 4-vinyl-1*H*-imidazole (**179**, 500 mg, 5.31 mmol) in DMF (20 mL) under N_2 at 0 ^oC was added sodium hydride (60% wt in oil, 639 mg, 15.98 mmol). The mixture was allowed to warm to r.t. and stirred for 1 h before being cooled to 0 ^oC. 4-Methoxybenzyl chloride (953 mg, 5.97 mmol, 0.85 mL) was then added dropwise and the mixture heated to 50 ^oC for 16 h. The reaction was then allowed to cool and quenched with water (30 mL). Partitioned between water and ethyl acetate (20 mL). The aqueous was removed and the organic washed with water (2 x 15 mL), brine (30 mL) and dried ($MgSO_4$). After evaporation of the solvent, the crude material was purified by chromatography with silica gel (eluting with Et_2O/methanol, 99:1) to yield **200d** as a colourless oil, 908 mg (80%). R_f 0.47 (UV active, Et_2O/methanol, 99:1).

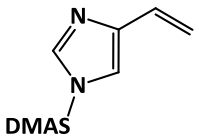
^1H NMR ($CDCl_3$, 400 MHz): δ 7.43 (1H, d, *J* = 1.6 Hz, Imidazole–H), 7.08–7.06 (2H, m, Phenyl–H), 6.85-6.82 (2H, m, Phenyl–H), 6.78-6.77 (1H, m, Phenyl–H), 6.90-6.82 (4H, m, Phenyl–H), 6.77 (1H, d, *J* = 1.6 Hz, Imidazole–H), 6.53 (1H, dd, *J* = 17.6, 11.2 Hz, CH), 5.77 (1H, dd, *J* = 17.6, 2.0 Hz, *trans*-CH), 5.07 (1H, dd, *J* = 11.2, 2.0 Hz, *cis*-CH), 4.95 (2H, s, $BnCH_2$), 3.76 (3H, s, CH_3). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 159.6 (C-OMe), 141.3 (Phenyl C), 137.4 (Imidazole C), 128.9 (Phenyl C-H), 128.7 (Imidazole C-H), 128.0 (Phenyl C-H), 116.9 (CH), 114.4 (Phenyl C-H), 112.1 (CH_2), 55.4 (CH_3), 50.4 ($BnCH_2$).



200e

To a solution of 4-vinyl-1*H*-imidazole (**179**, 2.00 g, 21.51 mmol) in DMF (20 mL) under N_2 at 0 ^oC was added sodium hydride (60% wt in oil, 1.02 g, 25.50 mmol). The mixture was allowed to warm to r.t. and stirred for 1.5 h before being cooled to 0 ^oC again. Benzyl bromide (4.43 g, 25.90 mmol, 2.9 mL) was then added dropwise and the mixture was heated to 50 ^oC for 16 h. The reaction was then allowed to cool and quenched with water (100 mL), and partitioned between water and ethyl acetate (100 mL). The aqueous was removed and the organic washed with water (2 x 50 mL), brine (50 mL) and dried ($MgSO_4$). After evaporation of the solvent, the crude material was purified by chromatography with silica gel (eluting with ethyl acetate/petroleum ether 40-60, 70:30) to yield the product as a white solid, 3.46 g (87%). R_f 0.22 (UV active, ethyl acetate/petroleum ether 40-60, 70:30), m.p.: 51–51 ^oC (lit.[44] 46-47 ^oC).

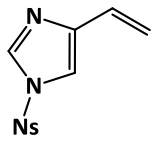
^1H NMR, (400 MHz, $CDCl_3$): δ_H 7.51 (1H, d, J = 0.7 Hz, Imidazole–H), 7.40–7.34 (3H, m, Phenyl–H), 7.21-7.15 (2H, m, Phenyl–H), 6.85 (1H, d, J = 0.7 Hz, Imidazole–H), 6.59 (1H, dd, J = 17.4, 11.0 Hz, CH), 5.84 (1H, dd, J = 17.4, 1.6 Hz, *trans*–CH), 5.13 (1H, dd, J = 11.0, 1.6 Hz, *cis*–CH), 5.09 (2H, s, $BnCH_2$). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 141.3 (Imidazole C), 137.5 (Imidazole C–H), 135.9 (Phenyl C), 129.0 (Phenyl C–H), 128.5 (Phenyl C–H), 128.3 (C-H), 127.3 (Phenyl C–H), 116.9 (Imidazole C–H), 112.1 (CH_2), 50.8 ($BnCH_2$). IR: ν_{max}/cm^{-1} 3092, 3025, 1492, 974, 906, 723, 695. HRMS: calcd. for $C_{12}H_{12}N_2$ $(M+H)^+$ 185.1073, found 185.1069.



200g

To 4-vinyl-1*H*-imidazole (**179**, 500 mg, 5.31 mmol) in THF (20 mL) at 0 ^{o}C under N_2 was added sodium hydride (60% wt in oil, 234 mg, 5.85 mmol) portionwise. The mixture was then allowed to warm to r.t. and stirred for 1.5 h, then cooled to 0 ^{o}C and *N*,*N*-dimethylaminosulfonyl chloride (840 mg, 5.85 mmol, 0.6 mL) was added dropwise. The mixture was allowed to warm to r.t. and stirred for 16 h. The reaction was then cooled to 0 ^{o}C and quenched slowly with ice/water (30 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organics were washed with brine (30 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure. Following chromatography on silica gel (eluting with ethyl acetate), **200g** was obtained as a white solid, 516 mg (90%). R_f 0.16 (UV active, ethyl acetate), m.p.: 77-79 ^{o}C (lit.[44] 76-77 ^{o}C).

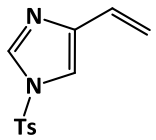
^{1}H NMR (400MHz, $CDCl_3$): δ_H 7.83 (1H, s, Imidazole-H), 7.13 (1H, d, J = 0.8 Hz, Imidazole-H), 6.55 (1H, dd, J = 17.6, 11.2 Hz, CH), 5.96 (1H, dd, J = 17.6, 0.8 Hz, *trans*-CH), 5.29 (1H, dd, J = 11.2, 0.8 Hz, *cis*-CH), 2.85 (6H, s, $N(CH_3)_2$). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 141.3 (Imidazole C), 136.7 (Imidazole C-H), 127.2 (CH), 115.7 (Imidazole C-H), 114.1 (CH_2), 38.4 ($N(CH_3)_2$).



200h

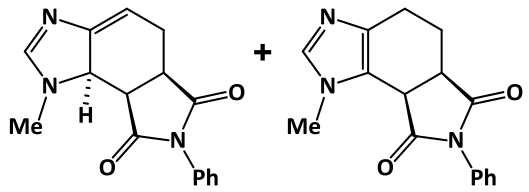
To a flask containing 4-vinyl-1*H*-imidazole (**179**, 750 mg, 7.97 mmol) under an atmosphere of N_2 was added anhydrous pyridine (30 mL) and the flask cooled to 0 ^oC for 30 min. 4-nitrobenzenesulfonyl chloride (2.59 g, 11.69 mmol) was then added portionwise over 5 min. The resulting solution was stirred at 0 ^oC for 8 h, then at r.t. for 48 h. The reaction mixture was then poured into ice-cold water (100 mL) and extracted with ethyl acetate (3 x 50 mL), washed with brine (50 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure. Following chromatography on silica gel (eluting with Et_2O:petroleum ether 40-60, 40:60), the product was obtained as a peach solid, 1.48 g (50%). R_f 0.20 (UV active, Et_2O/petroleum ether 40-60, 40:60), m.p.: 126–127 ^oC.

^1H NMR, (400 MHz, $CDCl_3$): δ_H 8.39 (2H, m, Phenyl–H), 8.11 (2H, m, Phenyl–H), 7.96 (1H, d, J = 1.2 Hz, Imidazole–H), 7.16 (1H, s, Imidazole–H), 6.45 (1H, dd, J = 17.6, 11.2 Hz, CH), 5.93 (1H, d, J = 17.6, 1.2 Hz, *trans*–CH), 5.30 (1H, d, J = 11.2, 1.2 Hz, *cis*–CH). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 143.8 (C–NO_2), 143.4 (C–SO_2), 136.9 (Imidazole C), 128.8 (Phenyl C–H), 126.5 (CH), 125.2 (Phenyl C–H), 117.1 (CH_2), 113.5 (Imidazole C–H). IR: ν_{max}/cm^{-1} 3106, 3058, 2980, 1504, 1543, 1375, 1351, 1175, 999, 922, 843. HRMS: calcd. for $C_{11}H_9N_3O_4S$ $(M+H)^+$ 280.0387, found 280.0388.



200i

To 4-vinyl-1*H*-imidazole (**179**, 500 mg, 5.31 mmol) in CH_2Cl_2 (20 mL) at 0 ^oC was added triethylamine (1.34 g, 13.24 mmol, 1.9 mL), followed by tosyl chloride (1.11 g, 5.82 mmol) in CH_2Cl_2 (10 mL) dropwise and stirring continued at 0 ^oC for 1 h, then at r.t. for 16 h. The mixture was then washed with water (3 x 10 mL), and dried ($MgSO_4$). After evaporation of the solvent the residue was chromatographed on silica gel (eluting with Et_2O/petroleum ether 40-60, 50:50) yielding **200i** as a glassy yellow solid, 324 mg (75%). R_f 0.48 (UV active, ethyl acetate/petroleum ether 40-60, 40:60), m.p.: 107–108 ^oC.
^1H NMR, (400 MHz, $CDCl_3$): δ_H 7.97 (1H, d, J = 0.8 Hz, Imidazole-H), 7.82 (2H, d, J = 8.5 Hz, Phenyl-H), 7.35 (2H, d, J = 8.5 Hz, Phenyl-H), 7.16 (1H, d, J = 0.8 Hz, Imidazole-H), 6.49 (1H, dd, J = 17.6, 11.2 Hz, CH), 5.93 (1H, d, J = 17.6, 1.2 Hz, *trans*–CH), 5.27 (1H, d, J = 11.2, 1.2 Hz, *cis*–CH), 2.45 (3H, s CH_3). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 146.5 (C–SO_2), 142.7 (Phenyl-C), 136.9 (Imidazole C), 134.8 (Phenyl C), 130.5 (Phenyl C-H), 127.4 (Phenyl C–H), 126.5 (CH), 116.1 (CH_2), 113.5 (Imidazole C–H), 21.8 (CH_3). IR: ν_{max}/cm^{-1} 3101, 2972, 1481, 1375, 1171, 851. HRMS: calcd. for $C_{12}H_{12}N_2O_2S$ $(M+H)^+$ 249.0692, found 249.0690.

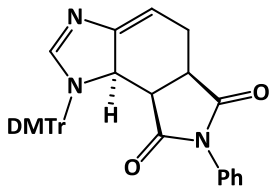


71a **72a**

To 1-methyl-4-vinyl-1*H*-imidazole (**200a**, 40 mg, 0.37 mmol) in CH_2Cl_2 (5 mL) was added NPM (160 mg, 0.92 mmol) and the mixture heated at 50 ºC for 8 h. The solution was concentrated and the crude residue purified by flash column chromatography (eluting with ethyl acetate/methanol, 99:1) to give **71a** as a white solid, 5.2 mg (5%). Further elution gave **72a** as an off-white solid, 99 mg (95%).

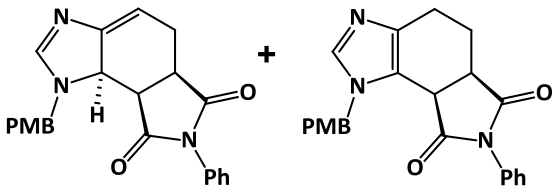
71a: R_f 0.41 (UV active, ethyl acetate/methanol, 99:1), m.p.: 181–183 ^oC. ^1H NMR (400MHz, $CDCl_3$): δ_H 7.41–7.22 (4H, m, Phenyl–H + Imidazole–H), 7.18-7.14 (2H, m, Phenyl–H), 5.61 (1H, ddd, J = 7.9, 3.8, 3.8 Hz, H_d), 4.00 (1H, ddd, J = 7.7, 3.8, 3.8 Hz, H_b), 3.80 (3H, s, CH_3), 3.64 (1H, dd, J = 8.9, 7.7 Hz, H_a), 3.11 (1H, ddd, J = 8.9, 6.7, 1.8 Hz, H_e), 3.09 (1H, ddd, J = 15.4, 7.9, 1.8 Hz, H_c), 1.95 (1H, dddd, J = 15.4, 6.7, 3.8, 3.8 H_c). IR: ν_{max}/cm^{-1} 2951, 2854, 1760, 1712, 1590, 1499. HRMS: calcd for $C_{34}H_{27}N_3O_2$ $(M+Na)^+$: 304.1056, found 304.1021.

72a: R_f 0.13 (UV active, ethyl acetate/methanol, 99:1), m.p.: 190–192 ^oC. ^1H NMR (400MHz, $CDCl_3$): δ_H 7.51-7.40 (3H, m, Phenyl-H), 7.43-7.39 (1H, m, Imidazole-H), 7.24-7.21 (2H, m, Phenyl-H), 4.25 (1H, d, J = 7.9 Hz, H_a), 3.86 (3H, s, CH_3), 3.52 (1H, ddd, J = 7.9, 5.0, 5.0 Hz, H_b), 2.76 (1H, ddd, J = 4.7, 4.7, 15.8 Hz, H_c), 2.69-2.63 (1H, m, H_c), 2.52 (1H, dd, J = 13.6, 4.8 Hz, H_d), 2.04-1.97 (1H, m, H_d). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 177.0 (NPM C=O), 174.2 (NPM C=O), 138.1 (Imidazole C), 137.9 (Imidazole C-H), 131.0 (Phenyl C), 128.7 (Phenyl C-H), 128.3 (Phenyl C-H), 125.3 (Phenyl C-H), 118.9 (Imidazole C), 40.5 (C-H_d), 38.4 (C-H_a), 32.3 (CH_3), 23.0 (C-H_b), 21.3 (C-H_c).



71c

To 1-(bis(4-methoxyphenyl)(phenyl)methyl)-4-vinyl-1*H*-imidazole (**200c**, 500 mg, 1.26 mmol) in CH_2Cl_2 (18 mL) was added NPM (546 mg, 3.15 mmol) and the mixture heated at 50 ºC for 48 h. The solution was concentrated and the crude residue purified by flash column chromatography (eluting with Et_2O/methanol, 99:1) to give **71c** as a pale yellow solid, 325 mg (45%). R_f 0.79 (UV active, Et_2O/methanol, 95:5), m.p.: 220–220 ^oC.
^1H NMR (400MHz, $CDCl_3$): δ_H 8.05–7.88 (12H, m, Phenyl–H + Imidazole–H), 7.35–7.31 (6H, m, Phenyl–H), 5.73 (1H, ddd, J = 5.4, 3.8, 3.8 Hz, H_d), 4.12 (1H, ddd, J = 6.0, 3.1, 3.1 Hz, H_a), 3.50 (6H, s, 2 x OCH_3), 2.42 (1H, ddd, J = 15.4, 7.8, 1.1 Hz, H_c), 2.20 (1H, ddd, J = 8.2, 8.1, 0.7 Hz, H_b), 1.30 (1H, ddd, J = 15.4, 7.8, 1.1 H_c), 1.17-1.13 (1H, m, H_e). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 178.1 (NPM C=O), 174.2 (NPM C=O), 162.3 (Imidazole C-H), 159.2 (Phenyl C-OMe), 156.1 (Phenyl C), 143.1 (Phenyl C), 134.8 (Imidazole C), 134.4 (Phenyl C-H), 130.2 (Phenyl C-H), 129.2 (Phenyl C-H), 128.8 (Phenyl C-H), 128.2 (Phenyl C-H), 128.1 (Phenyl C-H), 126.8 (Phenyl C-H), 113.4 (C-OMe), 113.3 (C-OMe), 102.1 (C-H_d), 74.1 (C-Ph_3), 59.0 (C-H_a), 42.1 (C-H_e), 37.0 (C-H_b), 26.4 (C-H_c). IR: ν_{max}/cm^{-1} 2978, 1786, 1705, 1554, 1502, 1251, 1030, 840. HRMS: calcd. for $C_{36}H_{31}N_3O_4$ (M+Na): 592.2212, found 592.2211.

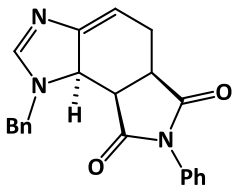


71d **72d**

To 1-(4-methoxybenzyl)-4-vinyl-1*H*-imidazole (**200d**, 353 mg, 1.65 mmol) in CH_2Cl_2 (7 mL) was added NPM (713 mg, 4.12 mmol) and the reaction stirred at 50 ^oC for 3 h. The solution was concentrated and purified by chromatography with silica gel (eluting with Et_2O/methanol, 98:2) to yield **71d** as an off-white solid, 32 mg (5%). R_f 0.13 (UV active, Et_2O/methanol, 98:2), m.p.: 201–203 ^oC. Further elution led to isolation of **72d** as a white solid, 478 mg (74%).

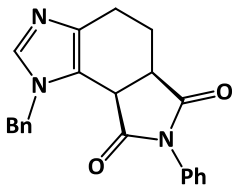
71d: ^1H NMR, (400 MHz, $CDCl_3$): δ_H 7.41–7.24 (8H, m, Phenyl–H + Imidazole–H), 7.14-7.18 (2H, m, Phenyl–H), 5.62 (1H, ddd, J = 7.9, 3.8, 3.8 Hz, H_d), 4.90 (1H, d, J = 15.1 Hz, Bn–CH_2), 4.77 (1H, d, J = 15.1 Hz, Bn–CH_2), 4.02 (1H, ddd, J = 7.7, 3.8, 3.8 Hz, H_b), 3.74 (3H, s, CH_3), 3.64 (1H, dd, J = 8.9, 7.7 Hz, H_a), 3.12 (1H, ddd, J = 8.9, 6.7, 1.8 Hz, H_e), 3.11 (1H, ddd, J = 15.4, 7.9, 1.8 Hz, H_c), 1.95 (1H, dddd, J = 15.4, 6.7, 3.8, 3.8 H_c). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 177.8 (C=O), 173.9 (C=O), 159.4 (Imidazole C–H), 154.6 (Imidazole C), 148.1 (C-OMe), 135.3 (Phenyl C), 131.6 (Phenyl C), 129.1 (Phenyl C-H), 129.2 (Phenyl C-H), 128.8 (Phenyl C-H), 128.3 (Phenyl C-H), 128.1 (Phenyl C-H), 126.5 (Phenyl C-H), 102.4 (C–H_d), 56.9 (C–H_a), 49.9 (Bn–CH_2), 42.5 (CH_3), 41.1 (C–H_b), 36.8 (C–H_e), 25.5 (C–H_c). IR: ν_{max}/cm^{-1} 3067, 3029, 2964, 2829, 1771, 1699, 1542, 1496, 758, 694.

72d: R_f 0.10 (UV active, Et_2O/methanol, 95:5), m.p.: 210–211 ^oC. ^1H NMR, (400 MHz, $CDCl_3$): δ_H 7.51 (1H, s, Imidazole C-H), 7.47-7.42 (2H, m, Phenyl-H), 7.40-7.31 (3H, m, Phenyl-H), 7.23-7.21 (2H, m, Phenyl-H), 7.17-7.15 (2H, m, Phenyl-H), 5.69 (1H, d, J = 15.5 Hz, $BnCH_2$), 5.27 (1H, d, J = 15.5 Hz, $BnCH_2$), 3.87 (1H, d, J = 8.2 Hz, H_a), 3.60 (3H, s, CH_3), 3.36 (1H, ddd, J = 8.2, 5.2, 5.2 Hz, H_b), 2.74 (1H, ddd, J = 16.1, 4.8, 4.8 Hz, H_c), 2.68-2.62 (1H, m, H_c), 2.46 (1H, ddd, J = 13.6, 9.4, 4.9 Hz, H_d), 2.0-1.93 (1H, m, H_d). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 177.1 (C=O), 175.1 (C=O), 139.6 (Imidazole C), 138.7 (Imidazole C-H), 136.1 (Phenyl-C), 131.6 (C-OMe), 129.3 (Phenyl C-H), 129.1 (Phenyl C-H), 128.9 (Phenyl C-H), 128.3 (Phenyl C-H), 127.5 (Phenyl C-H), 126.4 (Phenyl C-H), 119.0 (Imidazole C), 49.5 ($BnCH_2$), 51.4 (CH_3), 40.8 (C-H_b), 38.7 (C-H_a), 23.1 (C-H_c), 21.6 (C-H_d). IR: ν_{max}/cm^{-1} 2929, 2851, 1779, 1705, 1596, 1497, 832.



71e

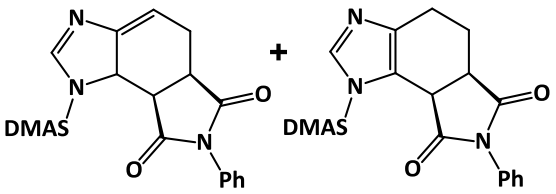
To 1-benzyl-4-vinyl-1*H*-imidazole (**200e**, 200 mg, 1.09 mmol) in CH_2Cl_2 (5 mL) was added NPM (470 mg, 2.71 mmol) and the reaction stirred at 50 ^oC for 6 h. The solution was concentrated to a low volume then cooled and filtered to give **71e** as a white solid, 200 mg (52%). The filtrate was concentrated and purified by chromatography with silica gel (eluting with Et_2O/methanol, 98:2) to yield further **71e** as a white solid, 113 mg (29%). R*f* 0.13 (UV active, Et_2O/methanol, 98:2), m.p.: 193–195 ^oC (lit.[44] 195-196 ^oC). ^1H NMR, (300 MHz, $CDCl_3$): δ_H 7.41–7.24 (9H, m, Phenyl–H + Imidazole–H), 7.14-7.18 (2H, m, Phenyl–H), 5.62 (1H, ddd, J = 7.9, 3.8, 3.8 Hz, H_d), 4.90 (1H, d, J = 15.1 Hz, Bn–CH_2), 4.77 (1H, d, J = 15.1 Hz, Bn–CH_2), 4.02 (1H, ddd, J = 7.7, 3.8, 3.8 Hz, H_b), 3.64 (1H, dd, J = 8.9, 7.7 Hz, H_a), 3.12 (1H, ddd, J = 8.9, 6.7, 1.8 Hz, H_e), 3.11 (1H, ddd, J = 15.4, 7.9, 1.8 Hz, H_c), 1.95 (1H, dddd, J = 15.4, 6.7, 3.8, 3.8 H_c). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 177.8 (C=O), 173.9 (C=O), 159.4 (Imidazole C–H), 154.6 (Imidazole C), 135.3 (Phenyl C), 131.6 (Phenyl C), 129.1 (Phenyl C-H), 129.2 (Phenyl C-H), 128.8 (Phenyl C-H), 128.3 (Phenyl C-H), 128.1 (Phenyl C-H), 126.5 (Phenyl C-H), 102.4 (C–H_d), 56.9 (C–H_a), 49.9 (Bn–CH_2), 41.1 (C–H_b), 36.8 (C–H_e), 25.5 (C–H_c). IR: ν_{max}/cm^{-1} 3067, 3029, 2964, 2829, 1771, 1699, 1542, 1496, 758, 694. HRMS: calcd. for $C_{22}H_{19}N_3O_2$ $(M+H)^+$ 358.1550, found 358.1554.



72e

To 1-benzyl-4-vinyl-1*H*-imidazole (**200e**, 200 mg, 1.09 mmol) in CH_2Cl_2 (5 mL) was added NPM (470 mg, 2.71 mmol) and the reaction stirred at 110 ^oC for 3 h. The solution was then concentrated and the crude residue was purified by chromatography with silica gel (eluting with Et_2O/methanol, 98:2) to yield **72e** as a white solid, 286 mg (73%). R_f 0.17 (UV active, Et_2O/methanol, 95:5), m.p.: 201–203 ^oC.

^1H NMR, (400 MHz, $CDCl_3$): δ_H 7.51 (1H, s, Imidazole-H), 7.47-7.43 (2H, m, Phenyl-H), 7.39-7.31 (4H, m, Phenyl-H), 7.25-7.21 (2H, m, Phenyl-H), 7.16-7.15 (2H, m, Phenyl-H), 5.69 (1H, d, J = 15.6 Hz, $BnCH_2$), 5.26 (1H, d, J = 15.6 Hz, $BnCH_2$), 3.87 (1H, d, J = 8.4 Hz, H_a), 3.36 (1H, ddd, J = 8.4, 5.2, 5.0 Hz, H_b), 2.73 (1H, ddd, J = 16.1, 5.2, 5.2 Hz, H_c), 2.26 (1H, ddd, J = 16.1, 10.1, 4.9 Hz, H_c), 2.45 (1H, dddd, J = 14.6, 5.0, 4.9 Hz, H_d), 1.95 (1H, ddd, J = 14.6, 10.1, 5.2 Hz, H_d). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 177.1 (C=O), 175.1 (C=O), 139.6 (Imidazole C), 138.7 (Imidazole C-H), 136.1 (Phenyl-C), 131.6 (Phenyl-C), 129.3 (Phenyl C-H), 129.1 (Phenyl C-H), 128.9 (Phenyl C-H), 128.3 (Phenyl C-H), 127.5 (Phenyl C-H), 126.4 (Phenyl C-H), 119.0 (Imidazole C), 49.5 ($BnCH_2$), 40.8 (C-H_b), 38.7 (C-H_a), 23.1 (C-H_c), 21.6 (C-H_d). IR: ν_{max}/cm^{-1} 2930, 2851, 1780, 1707, 1597, 1497, 732, 692. HRMS: calcd. for $C_{22}H_{19}N_3O_2$ $(M+Na)^+$ 380.1369, found 380.1357.

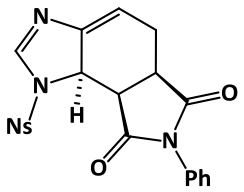


71g **72g**

To *N*,*N*-dimethyl-4-1*H*-imidazole-1-sulfonamide (**200g**, 40 mg, 0.20 mmol) in CH_2Cl_2 (5 mL) was added NPM (86 mg, 0.50 mmol) and the reaction stirred at 50 ^oC for 16 h. The solution was then concentrated and the crude residue purified by chromatography with silica gel (eluting with Et_2O/methanol, 95:5) to yield **71g** as an off-white solid, 15 mg (19%). R_f 0.24 (UV active, Et_2O/methanol, 95:5), m.p.: 197–198 ^oC. Further elution led to isolation of **72g** as an off-white solid, 51 mg (68%).

71g: ^1H NMR, (400 MHz, $CDCl_3$): δ_H 7.52 (1H, s, Imidazole-H), 7.44-7.35 (3H, m, Phenyl-H), 7.13-7.09 (2H, m, Phenyl-H), 5.87 (1H, ddd, J = 7.5, 3.6, 3.4 Hz, H_d), 4.62 (1H, ddd, J = 6.6, 3.5, 3.5 Hz, H_a), 3.80 (1H, dd, J = 8.7, 6.6 Hz, H_e), 3.27 (1H, ddd, J = 8.7, 7.2, 1.4 Hz, H_b), 3.09 (1H, ddd, J = 15.4, 7.5, 1.4 Hz, H_c), 2.95 (6H, s, $N(CH_3)_2$), 2.20 (1H, dddd, J = 15.4, 7.2, 3.7, 3.5 Hz, H_c). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 177.1 (C=O), 173.1 (C=O), 154.4 (Imidazole C-H), 152.5 (Imidazole C), 131.4 (Phenyl C), 129.3 (Phenyl C-H), 129.0 (Phenyl C-H), 126.6 (Phenyl C-H), 108.4 (C-H_d), 57.9 (C-H_a), 42.2 (C-H_b), 38.4 ($N(CH_3)_2$), 36.8 (C-H_e), 26.1 (C-H_c). IR: ν_{max}/cm^{-1} 3067, 2950, 2849, 1771, 1703, 1547, 1496, 758, 694.

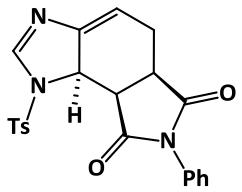
72g: ^1H NMR, (400 MHz, $CDCl_3$): δ_H 7.51 (1H, s, Imidazole-H), 7.47-7.41 (2H, m, Phenyl-H), 7.38-7.30 (2H, m, Phenyl-H), 4.60 (1H, ddd, J = 6.1, 3.5, 3.5 Hz, H_a), 3.95 (1H, dd, J = 8.2, 6.1 Hz, H_e), 3.30 (1H, ddd, J = 8.2, 7.2, 1.4 Hz, H_b), 3.15 (1H, ddd, J = 15.4, 7.5, 1.4 Hz, H_c), 3.00 (6H, s, $N(CH_3)_2$), 2.15 (1H, m, H_c).



71h

To 1-((4-nitrophenyl)sulfonyl)-4-vinyl-1*H*-imidazole (**200h**, 180 mg, 0.89 mmol) in toluene (7 mL) in a sealed pressure tube was added NPM (279 mg, 1.61 mmol) and the mixture heated at 110 ºC for 2 h. The solution was then allowed to cool and the subsequent precipitate collected by vacuum filtration and washed with ice-cold toluene to provide the product as an off-white solid, 113 mg (39%). R_f 0.33 (UV active, ethyl acetate/petroleum ether 40-60, 50:50), m.p.: 217–219 ^{o}C.

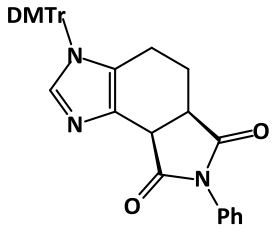
^{1}H NMR (400MHz, $CDCl_3$): δ_H 8.41 (2H, ddd, *J* = 8.7, 4.1, 2.3 Hz, Phenyl–H), 8.18 (2H, ddd, *J* = 8.7, 4.1, 2.3 Hz, Phenyl–H), 7.64 (1H, s, Imidazole C–H), 7.41–7.32 (3H, m, Phenyl–H), 7.06 (2H, ddd, 9.2, 4.2, 1.8 Hz, Phenyl–H), 5.92 (1H, ddd, *J* = 7.8, 7.8, 3.7 Hz, H_d), 4.44 (1H, ddd, *J* = 6.4, 6.4, 3.2 Hz, H_a), 3.85 (1H, dd, *J* = 8.7, 6.9 Hz, H_b), 3.26 (1H, ddd, *J* = 8.5, 7.4, 1.4 Hz, H_e), 3.10 (1H, ddd, *J* = 15.6, 7.8, 1.4 Hz, H_c), 2.19–2.12 (1H, m, H_c). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 177.0 (NPM C=O), 172.4 (NPM C=O), 151.6 (Imidazole C), 151.6 (Imidazole C–H), 151.0 (C–NO_2), 143.2 (C–SO_2), 131.3 (Phenyl C), 129.3 (Phenyl C–H), 129.1 (Phenyl C–H), 129.0 (Phenyl C–H), 126.4 (Phenyl C–H), 124.9 (Phenyl C–H), 110.8 (C–H_d), 56.9 (C–H_a), 41.7 (C–H_b), 36.4 (C–H_e), 26.0 (aliphatic C–H_c). IR: ν_{max}/cm^{-1} 3073, 1707, 1530, 1392, 1349, 1166, 860, 744, 681. HRMS: calcd. for $C_{21}H_{16}N_4O_6S$ $(M+H)^+$ 453.0863, found 453.0858.



71i

To 1-tosyl-4-vinyl-1*H*-imidazole (**200i**, 180 mg, 0.72 mmol) in toluene (7 mL) in a sealed pressure tube was added NPM (279 mg, 1.61 mmol) and the mixture heated at 110 ºC for 2 h. The solution was then allowed to cool and the subsequent precipitate collected by vacuum filtration, washing with ice-cold toluene, providing **71i** as an off-white solid, 86 mg (34%). R_f 0.23 (UV active, ethyl acetate/petroleum ether 40-60, 50:50), m.p.: 195–196 ^{o}C.

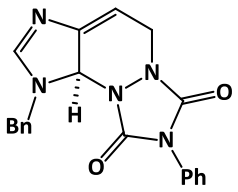
^{1}H NMR (400MHz, $CDCl_3$): δ_H 7.86 (2H, ddd, J = 8.7, 3.6, 1.8 Hz, Phenyl–H), 7.67 (1H, s, Imidazole C–H), 7.44–7.34 (5H, m, Phenyl–H), 7.14 (2H, ddd, 7.3, 3.6, 1.4 Hz, Phenyl–H), 5.87 (1H, ddd, J = 7.3, 3.6, 3.6 Hz, H_d), 4.29 (1H, ddd, J = 6.6, 3.2, 3.2 Hz, H_a), 3.94 (1H, dd, J = 8.7, 6.9 Hz, H_b), 3.26 (1H, ddd, J = 8.9, 7.3, 1.8 Hz, H_e), 3.12 (1H, ddd, J = 15.6, 7.8, 1.4 Hz, H_c), 2.47 (3H, s, Me), 2.18–2.10 (1H, m, H_c). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 177.4 (C=O), 172.5 (C=O), 152.9 (Imidazole C–H), 152.2 (Imidazole C), 145.5 (Phenyl C), 134.2 (C–SO_2), 131.5 (Phenyl–C), 130.5 (Phenyl C–H), 129.2 (Phenyl C–H), 128.9 (Phenyl C–H), 127.6 (Phenyl C-H), 126.5 (Phenyl C–H), 109.5 (C–H_d), 56.6 (C–H_a), 42.0 (C–H_b), 36.4 (C–H_e), 26.0 (C–H_c), 21.8 (CH_3). IR: ν_{max}/cm^{-1} 2970, 1708, 1555, 1500, 1354, 1157, 806, 752, 664. HRMS: calcd for $C_{22}H_{19}N_3O_4S$ $(M+H)^+$: 422.1169, found 422.1170.



201c

To 1-(bis(4-methoxyphenyl)(phenyl)methyl)-4-vinyl-1*H*-imidazole (**200c**, 500 mg, 1.26 mmol) in toluene (18 mL) was added NPM (546 mg, 3.15 mmol) and the mixture heated at 110 ºC for 30 h. The solution was concentrated and the crude residue purified by flash column chromatography (eluting with Et_2O/methanol, 99:1) to give **71c** as a white solid, 36 mg (5%). Further elution also provided **201c** as a white solid, 123 mg (17%). R_f 0.47 (UV active, Et_2O/methanol, 95:5), m.p.: dec. >231 ^oC.

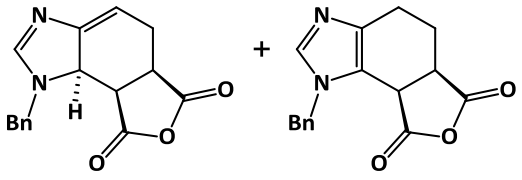
^1H NMR (400MHz, $CDCl_3$): δ_H 7.44–7.28 (2H, m, Phenyl–H), 7.24-7.19 (5H, m, Phenyl-H + Imidazole–H), 7.06-7.04 (4H, m, Phenyl–H), 6.99–6.96 (2H, m, Phenyl–H), 6.81–6.78 (5H, m, Phenyl–H), 4.24 (1H, d, J = 8.2 Hz, H_a), 3.79 (6H, s, 2 x OCH_3), 3.33 (1H, ddd, J = 9.2, 5.0, 4.1 Hz, H_b), 2.82–2.12 (1H, m, H_c), 1.79 (1H, ddd, J = 16.0, 4.1, 4.1 Hz, H_d), 1.73–1.65 (1H, m, H_c), 1.57-1.50 (1H, m, H_d). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 177.7 (NPM C=O), 174.9 (NPM C=O), 159.1 (C-OMe), 142.0 (Imidazole C–H), 139.0 (Phenyl C), 134.0 (Imidazole C), 133.9 (Imidazole C), 131.1 (Phenyl C), 130.0 (Phenyl C–H), 129.4 (Phenyl C-H), 129.1 (Phenyl C–H), 128.5 (Phenyl C–H), 128.3 (Phenyl C–H), 128.2 (Phenyl C–H), 126.5 (Phenyl C–H), 113.1 (Imidazole C), 74.2 (C–Ph_3), 41.5 (C–H_a), 40.3 (C–H_b), 22.6 (C–H_c), 20.9 (C–H_d). IR: ν_{max}/cm^{-1} 3060, 2926, 1779, 1711, 1597, 1493, 1254, 1041, 756, 701.



202b

To 1-benzyl-4-vinyl-1*H*-imidazole (**200e**, 40 mg, 0.22 mmol) in CH_2Cl_2 (2 mL) was added PTAD (38 mg, 0.22 mmol) in CH_2Cl_2 (1 mL) dropwise, and the reaction stirred at -78 ^oC for 30 min. Petroleum ether (40-60, 3 mL) was added to triturate and **202b** was filtered as a white solid and dried under vacuum, 45 mg (63%). R_f 0.11 (UV active, ethanol–ethyl acetate, 10:90), m.p.: dec 165 ^oC.

^1H NMR (400MHz, $CDCl_3$): δ_H 7.55-7.50 (4H, m, Phenyl-H), 7.47–7.27 (7H, m, Phenyl-H + Imidazole-H), 5.81 (1H, dd, J = 7.0, 3.2 Hz, H_d), 5.41 (1H, dd, J = 7.0, 3.2 Hz, H_e), 5.07 (1H, d, J = 14.8 Hz, $BnCH_2$), 4.87 (1H, d, J = 14.8 Hz, $BnCH_2$), 4.46 (1H, ddd, J = 16.9, 3.2, 3.2 Hz, H_c), 4.27 (1H, ddd, J = 16.9, 3.2, 3.2 Hz, H_c). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 161.7 (Imidazole C-H), 153.7 (C=O), 151.2 (C=O), 150.6 (Imidazole C), 135.0 (Phenyl C), 131.0 (Phenyl C), 129.4 (Phenyl C-H), 129.2 (Phenyl C-H), 129.0 (Phenyl C-H), 128.6 (Phenyl C-H), 128.4 (Phenyl C-H), 125.7 (Phenyl C-H), 105.1 (C-H_d), 73.8 (C-H_c), 51.9 ($BnCH_2$), 42.9 (C-H_e). IR: ν_{max}/cm^{-1} 1775, 1711, 1556, 1505, 860, 731, 700. HRMS: calcd for $C_{20}H_{17}N_5O_2$ $(M+H)^+$: 360.1455, found 360.1459.

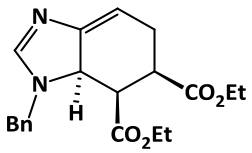


202d **203d**

To 1-benzyl-4-vinyl-1*H*-imidazole (**200e**, 55 mg, 0.30 mmol) in CH_2Cl_2 (3 mL) was added maleic anhydride (74 mg, 0.75 mmol), and the reaction stirred at 50 ^oC for 4 h. The reaction was then concentrated and the crude residue purified by flash column chromatography (eluting with Et_2O/methanol, 95:5) to give **202d** as a white solid, 29 mg (35%). Further elution also provided **203d** as a white solid, 35 mg (41%), and recovered **200e** (15 mg).

202b: R_f 0.38 (UV active, Et_2O/methanol, 95:5). ^1H NMR (400MHz, $CDCl_3$): δ_H 7.51 (1H, s, Imidazole C-H), 7.35-7.27 (3H, m, Phenyl-H), 7.15-7.09 (2H, m, Phenyl-H), 5.56 (1H, ddd, J = 7.3, 3.7, 3.4 Hz, H_d), 4.83 (1H, d, J = 15.0 Hz, $BnCH_2$), 4.59 (1H, d, J = 15.0 Hz, $BnCH_2$), 3.86-3.83 (1H, m, H_a), 3.63 (1H, dd, J = 9.5, 7.7 Hz, H_b), 3.42 (ddd, J = 15.6, 7.7, 1.4 Hz, H_c), 3.23 (ddd, J = 15.6, 9.5, 1.4 Hz, H_c), 2.69-2.61 (1H, m, H_e). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 161.7 (Imidazole C-H), 153.7 (C=O), 151.2 (C=O), 150.6 (Imidazole C), 135.0 (Phenyl C), 129.2 (Phenyl C-H), 128.6 (Phenyl C-H), 125.7 (Phenyl C-H), 105.1 (C-H_d), 73.8 (C-H_c), 51.9 ($BnCH_2$), 42.9 (C-H_e).

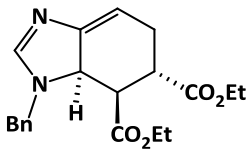
203d: R_f 0.11 (UV active, Et_2O/methanol, 95:5). ^1H NMR (400MHz, $CDCl_3$): 7.33-7.29 (4H, m, Phenyl-H + Imidazole-H), 7.14-7.09 (2H, m, Phenyl-H), 5.42 (1H, d, J = 15.5 Hz, $BnCH_2$), 5.21 (1H, d, J = 15.5 Hz, $BnCH_2$), 3.87 (1H, d, J = 8.4 Hz, H_a), 3.23 (1H, ddd, J = 8.4, 5.2, 5.0 Hz, H_b), 2.96 (1H, ddd, J = 16.1, 5.2, 5.2 Hz, H_c), 2.30 (1H, ddd, J = 16.1, 10.1, 4.9 Hz, H_c), 2.30 (1H, dddd, J = 14.6, 5.0, 4.9 Hz, H_d), 1.86 (1H, ddd, J = 14.6, 10.1, 5.2 Hz, H_d).



202h

To 1-benzyl-4-vinyl-1*H*-imidazole (**200e**, 200 mg, 1.09 mmol) in toluene (8 mL) was added diethyl maleate (467 mg, 2.71 mmol), and the reaction stirred at 110 ^{o}C in a sealed tube for 168 h. The reaction was then concentrated and the crude residue purified by chromatography with silica gel (eluting with ethyl acetate/petroleum ether 40-60, 50:50) to yield the product as an orange oil, 105 mg (27%). R_f 0.27 (UV active, ethyl acetate/petroleum ether 40-60, 50:50).

^{1}H NMR (400MHz, $CDCl_3$): δ_H δ_H 7.44 (1H, s, Imidazole-H), 7.38–7.29 (3H, m, Phenyl-H), 7.14–7.10 (2H, m, Phenyl-H), 5.15 (2H, s, $BnCH_2$), 4.12-4.08 (4H, m, CH_2 x 2), 4.11-4.07 (1H, m, H_a), 3.33 (1H, ddd, J = 5.8, 3.6, 3.6 Hz, H_b), 2.69 (1H, ddd, J = 9.7, 4.8, 4.8 Hz, H_d), 2.33–2.24 (1H, m, H_c), 2.15–2.04 (2H, m, H_c + H_e), 1.21 (6H, dt, 20.3, 7.1, 7.1 Hz, CH_2CH_3 x 2). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 172.5 (C=O), 171.6 (C=O), 137.8 (Imidazole C), 137.6 (Imidazole C-H), 136.0 (Phenyl C), 129.0 (Phenyl C-H), 128.2 (Phenyl C-H), 127.2 (Phenyl C-H), 121.7 (Imidazole C), 61.6 (CH_2CH_3), 61.1 (CH_2CH_3), 49.1 ($BnCH_2$), 42.6 (H_b), 40.0 (H_a), 23.2 (H_c), 21.8 (H_d), 14.2 (CH_2CH_3 x 2).

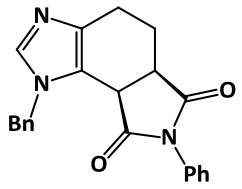


202i

To 1-benzyl-4-vinyl-1*H*-imidazole (**200e**, 200 mg, 1.09 mmol) in toluene (8 mL) was added diethyl fumarate (467 mg, 2.71 mmol), and the reaction stirred at 110 ^{o}C in a sealed tube for 168 h. The reaction was then concentrated and the crude residue purified by chromatography with silica gel (eluting with ethyl acetate/petroleum ether 40-60/methanol, 70:25:5) to yield the product as an orange oil, 150 mg (39%). R_f 0.17 (UV active, ethyl acetate/petroleum ether 40-60/methanol, 70:25:5).

^{1}H NMR (400MHz, $CDCl_3$): δ_H 7.42 (1H, s, Imidazole C-H), 7.34-7.31 (3H, m, Phenyl C-H), 7.25-7.22 (1H, m, Phenyl C-H), 7.12-7.08 (2H, m, Phenyl C-H), 5.12 (2H, s, $BnCH_2$), 4.06 (5H, m, CH_2 x 2 + H_a), 3.31 (1H, ddd, J = 7.2, 3.6, 3.6 Hz, H_b), 2.69-2.64 (2H, m, H_d + H_e), 2.31–2.21 (1H, m, H_c), 2.10–2.01 (1H, m, H_c), 1.18 (6H, dtd, J = 14.9, 6.9, 0.6 Hz, CH_3 x 2). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 172.5 (C=O), 171.4 (C=O), 137.5 (Imidazole C), 137.4 (Phenyl C), 135.8 (Imidazole C), 128.9 (Phenyl C-H), 128.1 (Phenyl C-H), 127.1 (Phenyl C-H), 121.7 (Imidazole C), 61.6 (CH_2CH_3), 61.0 (CH_2CH_3), 49.1 ($BnCH_2$), 42.5 (C-H_b), 39.9 (C-H_a), 23.1 (C-H_c), 21.6 (C-H_d), 14.1 (CH_2CH_3 x 2)

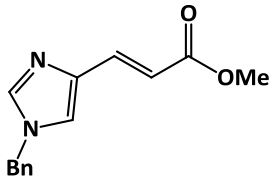
IR: ν_{max}/cm^{-1} 2934 (C-H), 1724 (C=O), 1591 (rearomatised C=C), 1497 (aromatic C=C), 1172 (C-O), 733 and 698 (mono-substituted phenyl)



203g

To (5a*S*,8a*S*)-1-benzyl-7-phenyl-1,5,5a,8b-tetrahydroimidazo[4,5-*e*]isoindole-6,8(7*H*,8a*H*)-dione (**202g**, 200 mg, 0.56 mmol) in CH_2Cl_2 (5 mL) was added maleic acid (60 mg, 0.62 mmol) and the reaction stirred at r.t. for 36 h. The solution was concentrated and purified by chromatography with silica gel (eluting with Et_2O/methanol, 95:5) to yield **203g** as a white solid, 193 mg (96%). R_f 0.17 (UV active, Et_2O/methanol, 95:5), m.p.: 201–203 ^oC (lit.[44] 203-204 ^oC).

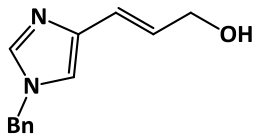
^1H NMR, (400 MHz, $CDCl_3$): δ_H 7.51 (1H, s, Imidazole -H), 7.47-7.43 (2H, m, Phenyl-H), 7.39-7.31 (4H, m, Phenyl-H), 7.25-7.21 (2H, m, Phenyl-H), 7.16-7.15 (2H, m, Phenyl-H), 5.69 (1H, d, J = 15.6 Hz, $BnCH_2$), 5.26 (1H, d, J = 15.6 Hz, $BnCH_2$), 3.87 (1H, d, J = 8.4 Hz, H_a), 3.36 (1H, ddd, J = 8.4, 5.2, 5.0 Hz, H_b), 2.73 (1H, ddd, J = 16.1, 5.2, 5.2 Hz, H_c), 2.26 (1H, ddd, J = 16.1, 10.1, 4.9 Hz, H_c), 2.45 (1H, dddd, J = 14.6, 5.0, 4.9 Hz, H_d), 1.95 (1H, ddd, J = 14.6, 10.1, 5.2 Hz, H_d). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 177.1 (C=O), 175.1 (C=O), 139.6 (Imidazole C), 138.7 (Imidazole C-H), 136.1 (Phenyl-C), 131.6 (Phenyl-C), 129.3 (Phenyl C-H), 129.1 (Phenyl C-H), 128.9 (Phenyl C-H), 128.3 (Phenyl C-H), 127.5 (Phenyl C-H), 126.4 (Phenyl C-H), 119.0 (Imidazole C), 49.5 ($BnCH_2$), 40.8 (C-H_b), 38.7 (C-H_a), 23.1 (C-H_c), 21.6 (C-H_d). IR: ν_{max}/cm^{-1} 2930, 2851, 1780, 1707, 1597, 1497, 732, 692. HRMS: calcd for $C_{22}H_{19}N_3O_2$ $(M+Na)^+$ 380.1369, found 380.1357.



205

To a solution of (*E*)-methyl 3-(1*H*-imidazol-4-yl)acrylate (**160**, 3.00 g, 19.72 mmol) in DMF (36 mL) at 0 ^{o}C under an atmosphere of N_2 was added sodium hydride (60% wt in oil, 870 mg, 21.69 mmol). The mixture was allowed to warm to r.t. and stirred for 1.5 h before being cooled to 0 ^{o}C again. Benzyl bromide (3.71 g, 21.69 mmol, 2.6 mL) was then added dropwise and the mixture was heated to 50 ^{o}C for 16 h. The reaction was then allowed to cool and quenched with water (50 mL) and partitioned between water and ethyl acetate (100 mL). The aqueous was removed and the organic washed with water (6 x 50 mL), brine (50 mL) and dried ($MgSO_4$). After evaporation of the solvent, **205** was obtained as an off-white solid, 3.35 g, (70%). R_f 0.11 (UV active, ethyl acetate/petroleum ether 40-60, 50:50), m.p.: 119–121 ^{o}C (lit.[44] 119-120 ^{o}C).

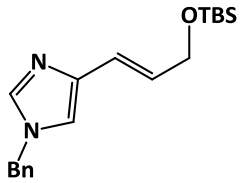
^{1}H NMR, (300 MHz, $CDCl_3$): δ_H 7.59 (1H, s, Imidazole–H), 7.55 (1H, d, J = 15.7 Hz, *H*C=CH), 7.43–7.35 (3H, m, Phenyl–H), 7.23–7.16 (2H, m, Phenyl–H), 7.10 (1H, s, Imidazole–H), 6.58 (1H, d, J = 15.7 Hz, HC=C*H*), 5.13 (2H, s, $BnCH_2$), 3.78 (3H, s, O–CH_3). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 167.8 (C=O), 138.6 (Phenyl C), 138.4 (Imidazole C), 136.1 (Imidazole C–H), 135.3 (H*C*=CH), 129.0 (Phenyl C–H), 128.4 (Phenyl C–H), 127.2 (Phenyl C–H), 121.7 (Imidazole C–H), 115.5 (HC=*C*H), 51.3 ($BnCH_2$), 50.9 (O–CH_3). IR: ν_{max}/cm^{-1} 3025, 2950, 1699, 1633, 1494, 1275, 1040, 1160, 715, 696. HRMS: calcd for $C_{14}H_{14}N_2O_2$ $(M+H)^+$: 243.1128, found 243.1134.



206

To (*E*)-methyl 3-(1-benzyl-1*H*-imidazol-4-yl)acrylate (**205**, 2.52 g, 10.40 mmol) in CH_2Cl_2 (100 mL) at –78 °C was added DiBAl-H (1 M solution in CH_2Cl_2, 4.44 g, 31.20 mmol, 31.2 mL) dropwise over 30 min. The mixture was allowed to slowly warm to r.t. and then cooled to 0 °C. Water (4.4 mL) was cautiously added, followed by sodium hydroxide (1 M, 4.4 mL) and further water (13.2 mL). The mixture was then filtered through Celite and washed with CH_2Cl_2. The organic layer was separated and the aqueous extracted with further CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$) and after removal of the solvent under vacuum, the crude material was purified by chromatography with silica gel (eluting with ethyl acetate–methanol, 25:1) to yield **206** as a yellow oil which solidified, 940 mg (42%). R_f 0.31 (UV active, ethyl acetate/methanol, 25:1), m.p.: 89–91 ºC (lit.[44] 89-90 °C).

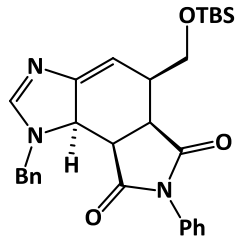
^{1}H NMR, (300 MHz, $CDCl_3$): δ_H 7.52 (1H, d, J = 1.1 Hz, Imidazole–H), 7.41–7.33 (3H, m, Phenyl–H), 7.21–7.14 (2H, m, Phenyl–H), 6.85 (1H, d, J = 1.1 Hz, Imidazole–H), 6.53–6.48 (2H, m, HC=CH), 5.09 (2H, s, $BnCH_2$), 4.30 (2H, dd, J = 2.9, 1.2 Hz, CH_2–OH), 1.6 (1H, br s, OH). ^{13}C NMR, (75 MHz, $CDCl_3$): δ_C 140.5 (Phenyl C), 137.7 (Imidazole C-H), 136.0 (Imidazole C), 129.1 (Phenyl C–H), 128.4 (Phenyl C–H), 127.6 (HC=*C*H), 127.4 (Phenyl C–H), 122.8 (Imidazole C-H), 117.0 (H*C*=CH), 63.6 (O-CH_2), 51.0 ($BnCH_2$). IR: ν_{max}/cm^{-1} 3387, 3025, 2951, 1633, 1380, 1134, 715, 694. HRMS: calcd for $C_{13}H_{14}N_2O$ $(M+H)^+$: 215.1179, found 215.1180.



207

To a solution of (*E*)-3-(1-benzyl-1*H*-imidazol-4-yl)prop-2-en-1-ol (**206**, 1.00 g, 4.67 mmol) in THF (20 mL) was added imidazole (700 mg, 10.28 mmol) and *tert*-butylchlorodimethylsilane (773 mg, 5.13 mmol) at 0 ^{o}C and the mixture allowed to warm to r.t. and stirred for 16 h. The reaction was then concentrated and taken up in ethyl acetate (35 mL), washed with water (30 mL), brine (30 mL), dried ($MgSO_4$) and concentrated. The crude residue was chromatographed on silica gel (eluting with ethyl acetate/petroleum ether 40-60, 50:50) to yield **207** as an off-white solid, 1.53 g (99%). R_f 0.71 (UV active, ethyl acetate/petroleum ether 40-60/methanol, 60:30:10), m.p.: 51–53 ºC (lit.[44] 63-64 ^{o}C).

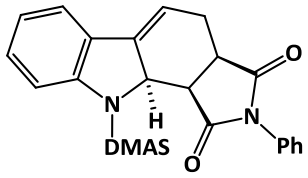
^{1}H NMR, (300 MHz, $CDCl_3$): δ_H 7.50 (1H, d, *J* = 0.9 Hz, Imidazole–H), 7.39–7.33 (3H, m, Phenyl–H), 7.21–7.14 (2H, m, Phenyl–H), 6.82 (1H, d, *J* = 0.9 Hz, Imidazole–H), 6.49 (1H, d, *J* = 15.7 Hz, H*C*=CH), 6.40 (1H, td, *J* = 15.7, 4.2, 4.2 Hz, HC=C*H*), 5.08 (2H, s, $BnCH_2$), 4.33 (1H, d, *J* = 4.2 Hz, CH_2–OH), 4.33 (1H, d, *J* = 4.2 Hz, CH_2-OH), 0.94 (9H, s, $(CH_3)_3$), 0.10 (6H, s, $(CH_3)_2$). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 140.8 (Phenyl C), 137.5 (Imidazole C–H), 136.0 (Imidazole C), 129.0 (Phenyl C–H), 128.2 (H*C*=CH), 127.6 (Phenyl C–H), 127.2 (Phenyl C–H), 121.0 (Imidazole C–H), 116.5 (HC=*C*H), 63.6 (O–CH_2), 50.8 ($BnCH_2$), 26.0 ($(CH_3)_3$), 18.4 ($C(CH_3)_3$), –5.2 ($(CH_3)_2$). IR: ν_{max}/cm^{-1} 3032, 2954, 2855, 1497, 1360, 1251, 1114, 834, 775, 707. HRMS: calcd for $C_{19}H_{28}N_2OSi$ $(M+H)^+$: 329.2044, found 329.2031.



210

To (*E*)-1-benzyl-4-(3-(*tert*-butyldimethylsilyloxy)prop-1-enyl)-1*H*-imidazole (**207**, 772 mg, 2.35 mmol) in CH_2Cl_2 (23.5 mL) was added NPM (1.02g, 5.87 mmol) and the solution stirred at 50 ^oC for 16 h. The solvent was removed and the crude residue was chromatographed on silica gel (eluting with petroleum ether 40-60/ethyl acetate, 25:75) to yield the product as a white solid, 802 mg (68%). R_f 0.32 (UV active, petroleum ether 40-60/ethyl acetate, 25:75), m.p.: 199-201^oC.

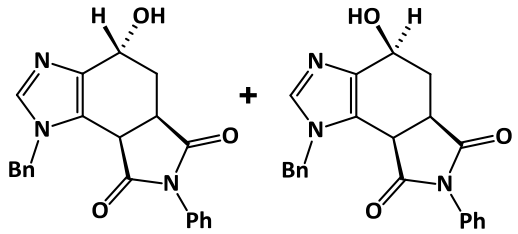
^1H NMR (400 MHz, $CDCl_3$) δ_H 7.46–7.35 (6H, m, Phenyl C-H), 7.34–7.29 (3H, m, Phenyl C-H + Imidazole C-H), 7.15–7.09 (2H, m, Phenyl C-H), 5.46 (1H, dd, *J* = 6.2, 4.6 Hz, H_e), 4.91 (1H, d, *J* = 15.2 Hz, $BnCH_2$), 4.80 (1H, d, *J* = 15.2 Hz, $BnCH_2$), 4.37 (1H, dd, *J* = 9.7, 8.9 Hz, H_f), 4.06 (1H, dd, *J* = 9.7, 7.0 Hz, H_f), 4.05 (1H, dd, *J* = 8.2, 6.3 Hz, H_b), 3.64 (1H, t, *J* = 8.2, 6.2 Hz, H_a), 3.37 (1H, dd, *J* = 8.5, 4.6 Hz, H_d), 2.26-2.17 (1H, m, H_c), 0.91 (9H, s), 0.11 (6H, s). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 175.6 (C=O), 173.7 (C=O), 159.7 (Imidazole C-H), 154.3 (Imidazole C), 135.4 (Phenyl C), 134.3 (Phenyl C), 131.7 (Phenyl C-H), 129.2 (Phenyl C-H), 128.8 (Phenyl C-H), 128.4 (Phenyl C-H), 128.2 (Phenyl C-H), 126.8 (Phenyl C-H),104.9 (C-H_e), 62.9 (C-H_d), 57.7 (C-H_f), 50.2 ($BnCH_2$), 41.7 (C-H_c), 41.7 (C-H_a), 38.0 (C-H_b), 26.1 (($CH_3)_3$), 18.4 ($C(CH_3)_3$), -5.2 and -5.3 (($CH_3)_2$). IR: ν_{max}/cm^{-1} 2951, 2927, 2855, 1772, 1703, 1541, 1498, 837, 777, 692. HRMS: calcd for $C_{29}H_{35}N_3O_3$ $(M+H)^+$: 502.2520, found 502.2517.



212

N,*N*-Dimethyl-3-vinyl-1*H*-indole-1-sulfonamide (**197**, 1.00 g, 3.99 mmol) and NPM (1.73 g, 9.99 mmol) were dissolved in CH_2Cl_2 (23 mL) and heated at 50 ^oC for 4 h. The solvent was removed and the crude residue was chromatographed on silica gel (eluting with Et_2O/petroleum ether/triethylamine, 90:9.9:0.1) to yield **212** as a white solid, 657 mg (40%). R_f 0.32 (UV active, Et_2O), m.p.: 202-203 ^oC.

^1H NMR (400MHz, $CDCl_3$): δ_H 7.45–7.26 (6H, m, Phenyl-H x 4 + Indole Phenyl-H x 2), 7.08–7.02 (3H, m, Indole Phenyl-H x 2 + Phenyl-H), 6.25 (1H, dt, J = 7.4, 3.7, 3.7 Hz, H_d), 4.94 (1H, ddd, J = 6.4, 3.3, 2.0 Hz, H_b), 4.11 (1H, dd, J = 8.9, 6.4 Hz, H_a), 3.37 (1H, ddd, J = 8.9, 7.4, 1.4 Hz, H_e), 3.16 (1H, ddd, J = 15.5, 7.4, 2.0 Hz, H_c), 3.08 (6H, s, CH_3 x 2), 2.35 (1H, dddd, J = 15.5, 3.7, 3.3, 1.4 Hz, H_c). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 178.0 (C=O), 173.9 (C=O), 145.7 (Indole C), 138.3 (Indole C), 131.7 (Phenyl C), 130.4 (Phenyl C-H), 129.1 (Phenyl C-H), 128.7 (Indole C), 126.5 (Phenyl C-H), 126.2 (Phenyl C-H), 123.5 (Phenyl C-H), 120.9 (Phenyl C-H), 115.0 (Phenyl C-H), 112.1 (C-H_d), 62.8 (C-H_b), 42.5 (C-H_a), 38.0 (CH_3 x 2), 37.6 (C-H_e), 26.1 (C-H_c). IR: ν_{max}/cm^{-1} 2978, 2887, 1781, 1705, 1599, 1499, 1462, 1359, 1155, 755, 694. HRMS: calcd for $C_{22}H_{21}N_3O_4S$ $(M+H)^+$: 424.1326, found 424.1326.

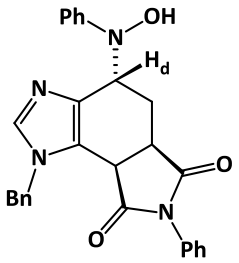


217 **218**

To (5a*S**,8a*S**)-1-benzyl-7-phenyl-1,5,5a,8b-tetrahydroimidazo-[4,5-*e*]isoindole-6,8(7*H*,8a*H*)-dione (**211**, 200 mg, 0.56 mmol) in CH_2Cl_2 (7 mL) was added Rose Bengal (5 mg) and the solution stirred vigorously under a constant light source at r.t. for 24 h. Triphenylphosphine (147 mg, 0.56 mmol) was then added and the reaction mixture stirred for a further 1 h. The solution was concentrated and purified by chromatography with silica gel (ethyl acetate/methanol, 95:5) to yield **217** and **218** as a 1:1 mixture of enantiomers, 120 mg (56%). R_f 0.13 (UV active, ethyl acetate/methanol, 95:5).

217: ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.53 (1H, s, Imidazole-H), 7.47-7.29 (12H, m, Phenyl-H), 7.22-7.16 (5H, m, Phenyl-H), 7.16-7.14 (4H, m, Phenyl-H), 5.64 (1H, d, J = 15.4 Hz, $BnCH_2$), 5.29 (1H, d, J = 15.4 Hz, $BnCH_2$), 4.88 (1H, dd, J = 4.7, 6.0 Hz, H_d), 3.88 (1H, d, J = 8.0 Hz, H_a), 3.54 (1H, ddd, J = 8.0, 8.0, 5.7 Hz, H_b), 2.45 (1H, ddd, J = 13.3, 8.0, 4.7 Hz, H_c), 2.16 (1H, ddd, J = 13.3, 6.0, 5.7 Hz, H_c). ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 177.9 (C=O), 177.0 (C=O), 175.0 (C=O), 174.4 (C=O), 142.1 (Phenyl C), 141.5 (Phenyl C), 139.3 (Imidazole C-H), 138.6 (Imidazole C-H), 135.6 (Phenyl C), 135.4 (Phenyl C), 131.9 (Phenyl C-H), 131.6 (Phenyl C-H), 129.3 (Phenyl C-H), 129.2 (Phenyl C-H), 129.1 (Phenyl C-H), 128.9 (Phenyl C-H), 128.8 (Phenyl C-H), 128.5 (Phenyl C-H), 128.4 (Phenyl C-H), 127.8 (Phenyl C-H), 127.6 (Phenyl C-H), 126.4 (Phenyl C-H), 120.4 (Imidazole C), 119.5 (Imidazole C), 62.5 (C-OH), 60.8 (C-OH), 50.0 ($BnCH_2$), 49.8 ($BnCH_2$), 38.8 (C-H_a), 38.4 (C-H_a), 38.0 (C-H_b), 37.7 (C-H_b), 32.4 (C-H_c), 31.8 (C-H_c).

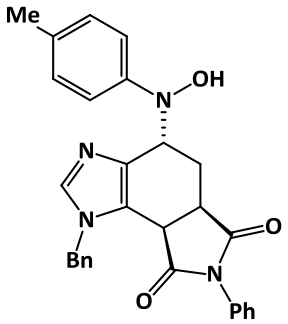
218: ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.53 (1H, s, Imidazole-H), 7.47-7.29 (12H, m, Phenyl-H), 7.22-7.16 (5H, m, Phenyl-H), 7.16-7.14 (4H, m, Phenyl-H), 5.68 (1H, d, J = 15.4 Hz, $BnCH_2$), 5.27 (1H, d, J = 15.4 Hz, $BnCH_2$), 5.03 (1H, dd, J = 3.2, 3.1 Hz, H_d), 3.96 (1H, d, J = 9.1 Hz, H_a), 3.33 (1H, ddd, J = 9.1, 6.8, 2.9 Hz, H_b), 2.78 (1H, ddd, J = 14.2, 3.2, 2.9 Hz, H_c), 2.02 (1H, ddd, J = 14.2, 6.8, 3.1 Hz, H_c).



221

To (5a*S**,8a*S**)-1-benzyl-7-phenyl-1,5,5a,8b-tetrahydroimidazo-[4,5-*e*]isoindole-6,8(7*H*,8a*H*)-dione (**211**, 200 mg, 0.56 mmol) in CH_2Cl_2 (15 mL) was added nitrosobenzene (60 mg, 0.56 mmol) and the solution stirred at r.t. for 1 h. The reaction was concentrated and purified by chromatography with silica gel (ethyl acetate–petroleum ether 40–60, 50:50) to yield **221** as an off-white solid, 248 mg (95%). R_f 0.33 (UV active, ethyl acetate–petroleum ether 40–60, 50:50); m.p.: 189–190 °C.

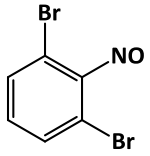
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.61 (1H, s, Imidazole-H), 7.47–7.44 (2H, m, Phenyl-H), 7.40–7.34 (4H, m, Phenyl-H), 7.28–7.18 (8H, m, Phenyl-H), 6.97-6.95 (1H, m, 5.67 (1H, d, J = 15.3 Hz, $BnCH_2$), 5.34 (1H, d, J = 15.3 Hz, $BnCH_2$), 4.75 (1H, dd, J = 7.8, 4.9 Hz, H_d), 3.94 (1H, d, J = 8.1 Hz, H_a), 3.55 (1H, dd, J = 13.1, 5.5 Hz, H_b), 2.38–2.32 (1H, m, H_c), 2.25–2.18 (1H, m, H_c); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 177.0 (NPM C=O), 174.7 (NPM C=O), 150.8 (Nitrosobenzene Phenyl C), 139.4 (Imidazole C-H), 138.7 (Imidazole C), 135.7 (Phenyl C), 131.5 (Phenyl C), 129.3 (Phenyl C-H), 129.2 (Phenyl C-H), 128.9 (Phenyl C-H), 128.8 (Phenyl C-H), 128.4 (Phenyl C-H), 127.6 (Phenyl C-H), 126.4 (Phenyl C-H), 122.0 (Phenyl C-H), 121.4 (Imidazole C), 117.2 (Phenyl C-H), 57.5 (H_d), 49.9 ($BnCH_2$), 39.4 (H_b), 38.7 (H_a), 23.4 (H_c). IR: ν_{max}/cm^{-1} 2980, 2884, 1773, 1715, 1597, 1496, 1377, 734, 690. HRMS: calcd for $C_{28}H_{23}N_4O_3$ $(M+H)^+$: 465.1921, found 465.1916.



223

To (5a*S*,8a*S*)-1-benzyl-7-phenyl-5,5a-7,8a-tetrahydroimidazo[4,5-*e*]isoindole-6,8(1*H*,4*H*)-dione (**211**, 200 mg, 0.56 mmol) in CH_2Cl_2 (5 mL) was added 2-nitrosotoluene (81 mg, 0.67 mmol) and the solution stirred at r.t. for 2 h. The solvent was removed and the crude residue was chromatographed on silica gel (eluting with Et_2O) to yield **223** as an off-white solid, 181 mg (68%). R_f 0.12 (UV active, Et_2O), m.p.: 202-204 ^oC.

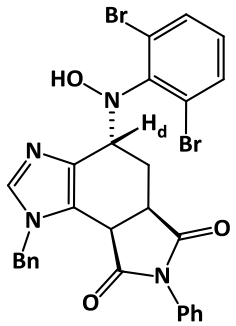
^1H NMR (400MHz, $CDCl_3$): δ_H 7.60 (1H, d, J = 7.3 Hz, Phenyl-H), 7.49 (1H, s, Imidazole C-H), 7.45-7.40 (2H, m, Phenyl-H), 7.36-7.32 (4H, m, Phenyl-H), 7.22-7.18 (5H, m, Phenyl-H), 7.12-7.10 (1H, m, Phenyl-H), 7.07-7.03 (1H, m, Phenyl-H), 6.82 (1H, br s, OH), 5.70 (1H, d, J = 15.6 Hz, $BnCH_2$), 5.30 (1H, d, J = 15.6 Hz, $BnCH_2$), 4.29 (1H, dd, J = 7.3, 5.0 Hz, H_d), 3.90 (1H, d, J = 6.9 Hz, H_a), 3.63 (1H, dd, J = 13.7, 6.9 Hz, H_b), 2.36 (1H, ddd, J = 13.7, 7.8, 5.5 Hz, H_c), 2.13 (1H, ddd, J = 14.1, 6.9, 5.0 Hz, H_c). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 176.9 (NPM C=O), 174.6 (NPM C=O), 149.0 (Imidazole C), 135.7 (Imidazole C-H), 131.5 (Phenyl-C), 131.3 (Phenyl-C), 130.8 (Phenyl C-H), 129.3 (Phenyl C-H), 129.2 (Phenyl C-H), 128.9 (Phenyl C-H), 128.4 (Phenyl C-H), 127.6 (Phenyl C-H), 126.4 (Phenyl C-H), 126.3 (Phenyl C-H), 125.2 (Phenyl C-H), 121.8 (Phenyl C-H), 121.1 (Imidazole C), 57.9 (C-H_d), 49.9 ($BnCH_2$), 39.5 (C-H_a), 38.7 (C-H_b), 24.8 (C-H_c), 18.1 (CH_3). IR: ν_{max}/cm^{-1} 3068, 3030, 2879, 1781, 1703, 1597, 1498, 1377, 730, 691. HRMS: calcd for $C_{29}H_{27}N_4O_3$ $(M+H)^+$: 479.2078, found 479.2065. Also visible in MS, imine: HRMS: calcd for $C_{29}H_{25}N_4O_2$ $(M+H)^+$: 461.1972, found 461.1967.



226

To 2,6-dibromoaniline (1.03 g, 4.09 mmol) in trifluoroacetic acid (7 mL) was added H_2O_2 (35% solution in water, 0.26 mol, 6.90 mL), and the mixture stirred at r.t. for 16 h. The reaction was then poured into ice-water (50 mL) and the orange/brown precipitate was filtered and recrystallised from *n*-hexane to give **226** as a beige solid, 824 mg (76%). R_f 0.60 (UV active, Et_2O/petroleum ether 40-60, 50:50), m.p.: 132-134 ^oC.

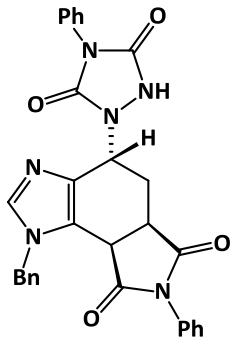
^1H NMR (300MHz, $CDCl_3$): δ_H 7.73 (2H, d, J = 7.4 Hz, H_a), 7.28 (1H, t, J = 7.9, 7.9 Hz, H_b). ^{13}C NMR, (75 MHz, $CDCl_3$): δ_C 182.6 (C-NO), 138.7 (Phenyl C-H), 136.1 (Phenyl C-H), 134.6 (C-Br). IR: ν_{max}/cm^{-1} 3069, 1563, 1437, 1279, 777, 733. HRMS: calcd for $C_6H_3NOBr_2$ $(M+H)^+$: 265.8633, found 265.8625.



227

To (5a*S*,8a*S*)-1-benzyl-7-phenyl-1,5,5a,8b-tetrahydroimidazo[4,5-*e*]isoindole-6,8(7*H*,8a*H*)-dione (**211**, 200 mg, 0.56 mmol) in CH_2Cl_2 (5 mL) was added 2,6-dibromonitrosobenzene (163 mg, 0.62 mmol), and the reaction stirred for at r.t. for 72 h. The solvent was removed and the crude residue was chromatographed on silica gel (eluting with Et_2O/petrol, 80:20) to yield **227** as a foamed oil, 256 mg (73%). R_f 0.22 (UV active, Et_2O/petrol, 80:20).

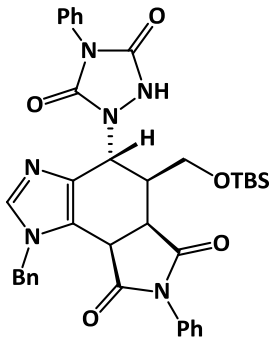
^{1}H NMR (400MHz, $CDCl_3$): δ_H 7.51–7.21 (11H, m, Phenyl-H x 10 + Imidazole-H), 6.98 (2H, d, J = 7.2 Phenyl-H), 6.91-6.90 (1H, m, Phenyl-H), 6.62 (1H, br s, OH), 5.82 (1H, d, J = 15.8 Hz, $BnCH_2$), 5.34 (1H, t, J = 3.2, 2.9 Hz, H_d), 5.18 (1H, d, J = 15.8 Hz, $BnCH_2$), 4.00 (1H, ddd, J = 12.9, 7.9, 4.6 Hz, H_b), 3.78 (1H, d, J = 7.9 Hz, H_a), 3.00 (1H, ddd, J = 13.5, 4.6, 3.2 Hz, H_c), 1.88 (ddd, J = 13.5, 12.9, 2.9 Hz, 1H). ^{13}C NMR, (101 MHz, $CDCl_3$): 178.0 (C=O), 174.2 (C=O), 144.3 (C-NOH), 139.2 (Imidazole C-H), 136.2 (Phenyl C), 135.8 (Phenyl C), 131.6 (Imidazole C), 129.5 (Phenyl C-H), 129.4 (Phenyl C-H), 129.0 (Phenyl C-H), 128.1 (Phenyl C-H), 127.3 (Phenyl C-H), 126.4 (Phenyl C-H), 122.3 (Imidazole C), 56.2 (C-H_d), 50.0 (Bn CH_2), 39.4 (C-H_a), 38.4 (C-H_b), 30.6 (C-H_c). IR: ν_{max}/cm^{-1} 2980, 2907, 2850, 1781, 1713, 1598, 1497, 1377, 748, 717, 691, 615. HRMS: calcd for $C_{28}H_{22}Br_2N_4O_3$ $(M+H)^+$: 621.0131, found 621.0130. Anal. calcd C: 54.04%, H: 3.56%, N: 9.00%, found C: 53.92%, H: 3.45%, N: 8.95%.



232

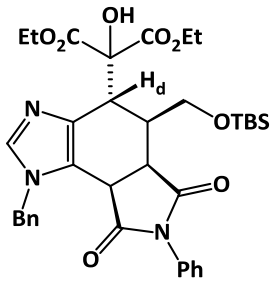
To (5a*S*,8a*S*)-1-benzyl-7-phenyl-1,5,5a,8b-tetrahydroimidazo[4,5-*e*]isoindole-6,8(7*H*,8a*H*)-dione (**211**, 200 mg, 0.56 mmol) in CH_2Cl_2 (7 mL) at -78 ^oC was added PTAD (98 mg, 0.56 mmol) in CH_2Cl_2 (3 mL) dropwise, and the reaction stirred for 1 h. The solvent was removed and the crude residue was chromatographed on silica gel (eluting with ethyl acetate 100%) to yield **232** as a white solid, 220 mg (74%). R_f 0.31 (UV active, ethyl acetate, 100%), m.p.: 173-174 ^oC.

^1H NMR, (400 MHz, $CDCl_3$): δ_H 7.42 (1H, s, Imidazole-H), 7.40-7.29 (7H, m, Phenyl C-H + N-H), 7.23-7.20 (5H, m, Phenyl C-H), 7.14 (2H, d, J = 7.4 Hz, Phenyl C-H), 7.05-7.03 (2H, m, Phenyl C-H), 5.44 (1H, d, J = 15.4 Hz, $BnCH_2$), 5.26 (1H, dd, J = 8.1, 5.4 Hz, H_d), 5.15 (1H, d, J = 15.4 Hz, $BnCH_2$), 3.90 (1H, d, J = 8.2 Hz, H_a), 3.47 (1H, dd, J = 13.4, 5.4 Hz, H_b), 2.59 (1H, ddd, J = 12.7, 4.7, 4.6 Hz, H_c), 2.13 (1H, ddd, 15.1, 9.6, 6.0 Hz, H_c). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 176.1 (NPM C=O), 174.0 (NPM C=O), 154.6 (PTAD C=O), 153.6 (PTAD C=O), 139.7 (Imidazole C-H), 135.3 (Imidazole C), 135.0 (Phenyl C), 131.4 (Phenyl C), 129.3 (C-H), 129.2 (Phenyl C), 129.2 (Phenyl C-H), 129.0 (Phenyl C-H), 128.5 (Phenyl C-H), 128.2 (Phenyl C-H), 127.6 (Phenyl C-H), 126.4 (Phenyl C-H), 125.9 (Phenyl C-H), 122.1 (Imidazole C), 49.8 ($BnCH_2$), 49.5 ($C\text{-}H_d$), 38.7 ($C\text{-}H_b$), 38.2 ($C\text{-}H_a$), 25.9 ($C\text{-}H_c$). IR: ν_{max}/cm^{-1} 3067, 1770, 1705, 1598, 1499, 862, 739, 692. HRMS: calcd for $C_{30}H_{24}N_6O_4$ $(M+H)^+$: 533.1932, found 533.1923. Anal. calcd C: 67.66%, H: 4.54%, N: 15.78%, found C: 67.73%, H: 4.58%, N: 15.59%.



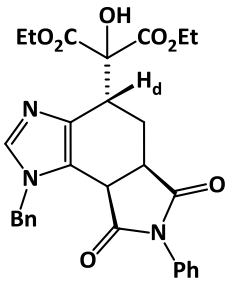
233

To 1-benzyl-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-7-phenyl-1,5,5a,8b-tetrahydroimidazo[4,5-*e*]isoindole-6,8(7*H*,8a*H*)-dione (**210**, 250 mg, 0.50 mmol) in CH_2Cl_2 (5 mL) at -78 ^oC, was added dropwise PTAD (87 mg, 0.50 mmol) in CH_2Cl_2 (5 mL), and the solution stirred for 1 h. The solvent was removed and the crude residue was chromatographed on silica gel (eluting with Et_2O/methanol, 98:2) to yield **233** as an orange solid, 206 mg (61%). R_f 0.37 (UV active, Et_2O/methanol, 95:5), m.p.: 147-148 ^oC. ^1H NMR (300MHz, CDCl3): δ_H 7.53–7.27 (10H, m , Phenyl C-H + Imidazole C-H), 7.14 (3H, ddd, J = 6.8, 3.7, 1.5 Hz, Phenyl C-H), 5.56 (1H, d, J = 15.7 Hz, $BnCH_2$), 5.27 (1H, dd, J = 12.3, 3.1 Hz, H_e), 5.23 (1H, d, J = 15.7 Hz, $BnCH_2$), 4.31 (1H, dd, J = 10.5, 6.2 Hz, H_d), 4.05 (1H, dd, J = 10.5, 6.2 Hz, H_d), 3.92 (1H, dd, J = 8.1, 1.4 Hz, H_a), 3.77 (1H, dd, J = 8.1, 4.5 Hz, H_b), 2.42 (1H, dt, J = 12.3, 6.2, 6.2 Hz, H_c). ^{13}C NMR, (101 MHz, $CDCl_3$): 174.9 (NPM C=O), 173.9 (NPM C=O), 154.7 (PTAD C=O), 153.8 (PTAD C=O), 140.0 (Imidazole C-H), 135.8 (Imidazole C), 135.3 (Phenyl C), 131.4 (Phenyl C), 131.3 (Phenyl C), 129.3 (Phenyl C-H), 129.2 (Phenyl C-H), 129.2 (Phenyl C-H), 129.0 (Phenyl C-H), 128.5 (Phenyl C-H), 128.3 (Phenyl C-H), 127.6 (Phenyl C-H), 126.3 (Phenyl C-H), 126.0 (Phenyl C-H), 122.3 (Imidazole C), 62.5 (H_d), 52.7 (H_e), 49.9 ($BnCH_2$), 42.2 (H_c), 40.6 (H_b), 39.3 (H_a), 26.0 (($CH_3)_3$), 18.4 ($C(CH_3)_3$), -5.4 (Si-CH_3), -5.4 (Si-CH_3). IR: ν_{max}/cm^{-1} 3067, 2930, 2857, 1771, 1712, 1600, 1500, 1380, 836, 778, 705, 766, 690. HRMS: calcd for $C_{37}H_{40}N_6O_5Si$ $(M+H)^+$: 677.2902, found 677.2899.



235

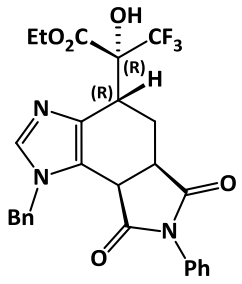
To 1-benzyl-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-7-phenyl-1,5,5a,8b-tetrahydroimidazo[4,5-*e*]isoindole-6,8(7*H*,8a*H*)-dione (**210**, 250 mg, 0.50 mmol) in CH_2Cl_2 (18 mL) was added diethyl ketomalonate (87 mg, 76 μL, 0.50 mmol) and the solution stirred at r.t. for 16 h. The solvent was removed and the crude residue was chromatographed on silica gel (eluting with Et_2O/petroleum ether 40-60, 60:40) to yield **235** as a white solid, 175 mg (65%). R_f 0.22 (UV active, Et_2O/petroleum ether, 25:75). ^{1}H NMR (400MHz, $CDCl_3$): δ_H 7.44 (2H, ddd, *J* = 7.2, 7.2, 1.6 Hz, Phenyl C-H), 7.39-7.35 (2H, m, Phenyl C-H), 7.35-7.24 (5H, m, Phenyl C-H + Imidazole C-H), 7.05 (2H, dd, *J* = 6.5, 1.3 Hz, Phenyl C-H), 5.70 (1H, d, *J* = 15.6 Hz, $BnCH_2$), 5.32 (1H, d, *J* = 15.6 Hz, $BnCH_2$), 4.40 (2H, dq, *J* = 7.2, 7.2, 7.2, 2.1 Hz, diastereotopic CH_2), 4.29 (2H, q, *J* = 7.2, 7.2, 7.2 Hz, diastereotopic CH_2), 4.03 (1H, s, H_a), 3.97 (1H, dd, *J* = 8.6, 6.5 Hz, H_b), 3.84 (1H, br s, OH), 3.89-3.61 (3H, m, H_d x 2 + H_e), 2.73 (1H, dd, *J* = 9.8, 4.9 Hz, H_c), 1.36 (3H, t, *J* = 7.2, 7.2 Hz, CH_3), 1.31 (3H, t, *J* = 7.2, 7.2 Hz, CH_3). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 176.6 (NPM C=O), 174.6 (NPM C=O), 170.3 (ester C=O), 169.3 (ester C=O), 138.3 (Imidazole C-H), 136.1 (Phenyl C), 135.5 (Phenyl C), 131.9 (Imidazole C), 129.1 (Phenyl C-H), 129.1 (Phenyl C-H), 128.6 (Phenyl C-H), 128.1 (Phenyl C-H), 127.3 (Phenyl C-H), 126.4 (Phenyl C-H), 122.0 (Imidazole C), 82.4 (C-OH), 64.7 (C-H_e), 63.4 (CH_2), 62.5 (CH_2), 49.8 ($BnCH_2$), 41.6 (C-H_a), 41.5 (C-H_b), 39.6 (C-H_c), 38.4 (C-H_d), 25.8 ((CH_3)$_3$), 18.4 (*C*(CH_3)), 14.1 (CH_2*C*H_3), 14.0 (CH_2*C*H_3), -5.7 and -5.7 (Si-CH_3). IR: ν_{max}/cm^{-1} 3474, 2988, 2941, 1711, 1597, 1498, 1381, 1284, 1225, 1248, 1029, 1185, 740, 691. HRMS: calcd for $C_{36}H_{45}N_3O_8Si$ $(M+H)^+$: 676.3049, found 676.3042. Anal. calcd C: 63.98%, H: 6.71%, N: 6.22%, found C: 63.99%, H: 6.65%, N: 6.12%.



236

To (5a*S*,8a*S*)-1-benzyl-7-phenyl-5,5a-7,8a-tetrahydroimidazo[4,5-*e*]isoindole-6,8(1*H*,4*H*)-dione (**211**, 230 mg, 0.64 mmol) in CH_2Cl_2 (6 mL) was added diethyl ketomalonate (134 mg, 0.77 mmol, 118 μL) and the solution stirred at r.t. for 16 h. The solvent was removed and the crude residue was chromatographed on silica gel (eluting with Et_2O) to yield **236** as a white solid, 283 mg (83%). R_f 0.16 (UV active, Et_2O), m.p.: 147-149 ^oC.

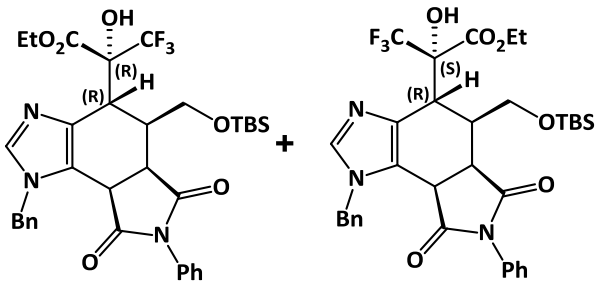
^1H NMR (400MHz, $CDCl_3$): δ_H 7.49–7.36 (4H, m), 7.36–7.28 (3H, m), 7.26–7.21 (2H, m), 7.18–7.10 (2H, m), 5.61 (1H, d, J = 15.5 Hz, $BnCH_2$), 5.28 (1H, d, J = 15.5 Hz, $BnCH_2$), 4.42 (1H, dq, J = 10.6, 7.1, 7.1, 6.9 Hz, diastereotopic CH_2 x 2), 4.38 (1H, dq, J = 10.8, 7.2, 7.0, 6.9 Hz, diastereotopic CH_2 x 2), 4.26 (1H, dq, J = 10.9, 7.2, 7.1, 7.1 Hz, diastereotopic CH_2 x 2), 4.32 (1H, dq, J = 10.7, 7.1, 7.1, 7.0 Hz, diastereotopic CH_2 x 2), 4.13 (1H, s, OH), 3.92 (1H, dd, J = 8.4, 1.3 Hz, H_a), 3.85 (1H, dd, J = 9.9, 4.5 Hz, H_d), 3.54 (1H, ddd, J = 10.5, 5.1, 5.1 Hz, H_b), 2.39 (1H, ddd, J = 13.4, 4.7, 4.7 Hz, H_c), 2.04 (1H, ddd, J = 13.4, 9.9, 5.6 Hz, H_c), 1.33 (6H, td, J = 7.3, 7.1, 1.1 Hz, CH_3 x 2). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 176.9 (NPM C=O), 174.9 (NPM C=O), 170.0 (C=O), 169.4 (C=O), 138.7 (Imidazole C-H), 137.7 (Imidazole C), 135.8 (Phenyl C), 131.6 (Phenyl C), 129.3 (Phenyl C-H), 129.2 (Phenyl C-H), 128.9 (Phenyl C-H), 128.3 (Phenyl C-H), 127.6 (Phenyl C-H), 126.4 (Phenyl C-H), 120.6 (Imidazole C), 80.6 (C(OH)(CO_2Et)$_2$), 63.0 (ethyl CH_2), 62.8 (ethyl CH_2), 49.7 (Bn CH_2), 39.9 (C-H_b), 38.5 (C-H_a), 37.2 (C-H_d), 24.1 (C-H_c), 14.2 (ethyl CH_3), 14.1 (ethyl CH_3). IR: ν_{max}/cm^{-1} 3481, 2982, 2967, 1783, 1711, 1734, 1597, 1499, 1380, 1249, 1029, 1185, 737, 690. HRMS: calcd for $C_{29}H_{29}N_3O_7$ $(M+H)^+$: 532.2078, found 532.2071.



237

To (5a*S*,8a*S*)-1-benzyl-7-phenyl-5,5a-7,8a-tetrahydroimidazo[4,5-*e*]isoindole-6,8(1*H*,4*H*)-dione (**211**, 90 mg, 0.25 mmol) in CH_2Cl_2 (2 mL) was added ethyl trifluoropyruvate (64 mg, 0.38 mmol, 50 μL) and the solution stirred at r.t. for 16 h. The solvent was removed and the crude residue was chromatographed on silica gel (eluting with Et_2O/petroleum ether 40-60, 60:40) to yield **237** as a white solid, 70 mg (53%). R_f 0.77 (UV active, ethyl acetate/petroleum ether 40-60, 2:1), m.p.: 174–175°C.

^{1}H NMR (400MHz, $CDCl_3$): δ_H 7.48–7.42 (2H, m, Phenyl C-H), 7.41–7.27 (5H, m, Phenyl C-H + Imidazole C-H), 7.26–7.22 (2H, m, Phenyl C-H), 7.12–7.11 (2H, m, Phenyl C-H), 5.65 (1H, d, J = 15.6 Hz, $BnCH_2$), 5.28 (1H, d, J = 15.6 Hz, $BnCH_2$), 4.53 (1H, dqd, J = 10.6, 7.3, 6.9, 6.9, 1.4 Hz, ethyl CH_2), 4.43 (1H, dqd, J = 10.6, 7.3, 6.9, 6.9, 1.4 Hz, ethyl CH_2), 4.02 (1H, d, J = 1.0 Hz, OH), 3.90 (1H, d, J = 8.2 Hz, H_a), 3.67 (1H, dd, J = 9.2, 5.0 Hz, H_d), 3.59 (1H, dddd, 8.2, 5.8, 5.0, 1.0 Hz, H_b), 2.61–2.55 (1H, m, H_c), 2.20 (1H, ddd, J = 13.3, 9.2, 5.8 Hz, H_c), 1.36 (3H, dt, J = 7.3, 6.9, 1.4 Hz, ethyl CH_3). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 176.7 (NPM C=O), 174.7 (NPM C=O), 169.7 (Pyruvate C=O), 138.7 (Imidazole C-H), 136.3 (Phenyl C), 135.7 (Phenyl C), 131.5 (Imidazole C), 129.3 (Phenyl C-H), 129.2 (Phenyl C-H), 128.9 (Phenyl C-H), 128.4 (Phenyl C-H), 127.5 (Phenyl C-H), 126.3 (Phenyl C-H), 123.6 (q, J = 287.8 Hz, CF_3), 121.3 (C-OH), 78.5 (q, J = 28.1 Hz, *C*-CF_3), 64.0 (CH_2), 49.8 (Bn CH_2), 39.6 (H_b), 38.4 (H_a), 35.1 (H_d), 23.6 (H_c), 13.9 (CH_3). ^{19}F NMR, (376 MHz, $CDCl_3$): δ_F -73.37 (CF_3). IR: ν_{max}/cm^{-1} 3651, 2982, 1705, 1596, 1497, 1375, 1172, 739, 694. HRMS: calcd for $C_{27}H_{24}F_3N_3O_5$ $(M+H)^+$: 528.1741, found 528.1731. Anal. calcd C: 61.48%, H: 4.59%, N: 7.97%, found C: 61.59%, H: 4.52%, N: 7.90%.



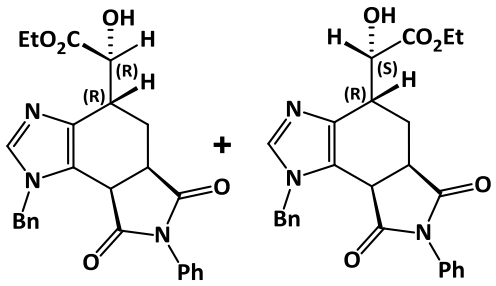
239 **240**

To (5a*S*,8a*S*)-1-benzyl-7-phenyl-1,5,5a,8b-tetrahydroimidazo[4,5-*e*]isoindole-6,8(7*H*,8a*H*)-dione (**210**, 400 mg, 0.80 mmol) in CH_2Cl_2 (6 mL) was added ethyl trifluoropyruvate (162 mg, 0.96 mmol, 0.12 mL) and the reaction stirred for at r.t. for 72 h. The solvent was removed and the crude residue was chromatographed on silica gel (eluting with Et_2O/petrol, 40:60) to yield the major diastereoisomer (**239**) as pale yellow crystals, 196 mg (36%), and the minor diastereoisomer (**240**) as a white solid, 92 mg (17%). **239**: R_f 0.30 (UV active, Et_2O/petrol, 50:50), m.p.: 176-178 ^oC.

^1H NMR, (400MHz, CDCl3): δ_H 7.49–7.41 (3H, m, Phenyl C-H), 7.41–7.36 (1H, m, Imidazole C-H), 7.36–7.26 (3H, m, Phenyl C-H), 7.22 (2H, ddd, *J* = 8.7, 2.5, 2.5 Hz, Phenyl C-H), 7.00 (2H, d, *J* = 7.8 Hz, Phenyl C-H), 5.79 (1H, d, *J* = 15.7 Hz, $BnCH_2$), 5.32 (1H, d, *J* = 15.7 Hz, $BnCH_2$), 4.55–4.43 (2H, m, CH_2CH_3), 4.02 (1H, s, H_e), 3.95 (1H, dd, *J* = 8.7, 6.1 Hz, H_b), 3.77 (1H, br s, OH), 3.69 (1H, d, *J* = 8.7 Hz, H_a), 3.59 (1H, dd, *J* = 10.0, 4.9 Hz, H_d), 3.44 (1H, dd, *J* = 10.0, 8.4 Hz, H_d), 3.07 (1H, ddd, *J* = 8.4, 6.1, 4.9 Hz, H_c), 1.43 (3H, t, *J* = 7.2, 7.2 Hz, CH_2CH_3), 0.78 (9H, s, $((CH_3)_3)$), -0.11 (6H, d, *J* = 3.1 Hz, CH_3 x 2). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 175.9 (NPM C=O), 174.6 (NPM C=O), 169.7 (Pyruvate C=O), 139.0 (Imidazole C-H), 136.1 (Imidazole C), 133.8 (Phenyl C), 131.7 (Phenyl C), 129.3 (Phenyl C-H), 129.1 (Phenyl C-H), 128.8 (Phenyl C-H), 128.2 (Phenyl C-H), 127.0 (Phenyl C-H), 126.3 (Phenyl C-H), 123.6 (q, *J* = 287.6 Hz, CF_3), 122.2 (Imidazole C), 80.2 (q, *J* = 27.9 Hz, *C*-CF_3), 64.3 (CH_2CH_3), 62.4 (H_d), 50.1 ($BnCH_2$), 41.2 (H_b), 38.7 (H_c), 38.6 (H_e), 37.9 (C-H_a), 25.8 ($(CH_3)_3$), 18.2 ($C(CH_3)_3$), 13.9 (CH_2CH_3), -5.6 (Si-CH_3), -5.7 (Si-CH_3). ^{19}F NMR, (376 MHz, $CDCl_3$): δ_F -72.62. IR: ν_{max}/cm^{-1} 3435, 2949, 2935, 2865, 1749, 1781, 1712, 1598, 1498, 1374, 1244, 1027, 1158, 1149, 1098, 836, 775, 689. HRMS: calcd for $C_{34}H_{41}F_3N_3O_6Si$ $(M+H)^+$: 672.2711, found 672.2705.

240: R_f 0.15 (UV active, Et_2O/petrol, 50:50), m.p.: 113-114 ^oC. ^1H NMR, (400MHz, CDCl3): δ_H 7.60 (1H, s, Imidazole C-H), 7.53–7.45 (2H, m, Phenyl C-H), 7.45–7.39 (1H, m, Phenyl C-H), 7.40–7.31 (3H, m, Phenyl C-H), 7.27–7.22 (2H, m, Phenyl C-H), 7.10–

7.04 (2H, m, Phenyl C-H), 5.88 (1H, d, *J* = 15.8 Hz, $BnCH_2$), 5.38 (1H, d, *J* = 15.8 Hz, $BnCH_2$), 4.65 (1H, s, H_e), 4.41 (1H, dq, *J* = 10.7, 7.2, 7.2, 7.2 Hz, CH_2CH_3), 4.32 (dq, *J* = 10.7, 7.2, 7.2, 7.2 Hz, CH_2CH_3), 3.95 (1H, s, OH), 3.89 (1H, dd, *J* = 8.7, 6.4 Hz, H_b), 3.76 (1H, d, *J* = 8.7 Hz, H_a), 3.60 (1H, dd, *J* = 10.2, 4.2 Hz, H_d), 3.50 (1H, dd, *J* = 10.2, 7.5 Hz, H_d), 2.67–2.59 (1H, m, H_c), 1.35 (3H, t, *J* = 7.2, 7.2 Hz, CH_2CH_3), 0.78 (9H, s, $(CH_3)_3$), -0.10 (6H, d, *J* = 15.8 Hz, $(CH_3)_2$). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 175.8 (NPM C=O), 174.3 (NPM C=O), 169.5 (ester C=O), 139.1 (Imidazole C-H), 136.1 (Imidazole C), 133.6 (Phenyl C), 131.6 (Phenyl C), 129.3 (Phenyl C-H), 129.2 (Phenyl C-H), 128.9 (Phenyl C-H), 128.2 (Phenyl C-H), 127.0 (Phenyl C-H), 126.3 (Phenyl C-H), 123.1 (q, *J* = 287.4 Hz, CF_3), 121.5 (Imidzole C), 80.4 (q, *J* = 28.2 Hz, *C*-CF_3), 63.9 (CH_2CH_3), 62.9 (C-H_d), 50.2 ($BnCH_2$), 41.3 (C-H_b), 39.7 (C-H_c), 38.2 (C-H_a), 38.0 (C-H_e), 25.8 ($(CH_3)_3$), 18.3 ($C(CH_3)_3$), 14.0 (CH_2CH_3), -5.6 (Si-CH_3), -5.7 (Si-CH_3). ^{19}F NMR, (376 MHz, $CDCl_3$): δ_F -73.26. IR: ν_{max}/cm^{-1} 3476, 3067, 2954, 2858, 1378, 1250, 1027, 1161, 1143, 836, 745, 692.



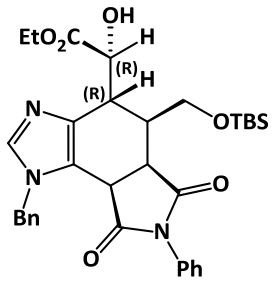
241 **242**

To (5a*S*,8a*S*)-1-benzyl-7-phenyl-5,5a-7,8a-tetrahydroimidazo[4,5-*e*]isoindole-6,8(1*H*,4*H*)-dione (**211**, 200 mg, 0.56 mmol) in CH_2Cl_2 (5 mL) was added ethyl glyoxalate (50% in toluene, 0.14 mmol, 0.7 mL) and the solution stirred at r.t. for 30 h. The solvent was removed and the crude residue was chromatographed on silica gel (eluting with Et_2O) to yield **241** as a white solid, 170 mg (66%). R_f 0.18 (UV active, ethyl acetate–methanol, 95:5), m.p.: 80–82°C.

^{1}H NMR (400MHz, $CDCl_3$): δ_H 7.47 (3H, m, Phenyl C-H + Imidazole C-H), 7.40-7.32 (4H, m, Phenyl C-H), 7.25-7.21 (2H, m, Phenyl C-H), 7.16-7.14 (2H, m, Phenyl C-H), 5.64 (1H, d, J = 15.5 Hz, $BnCH_2$), 5.28 (1H, d, J = 15.5 Hz, $BnCH_2$), 4.38 (1H, dq, J = 10.7, 7.1, ethyl CH_2), 4.33-4.20 (2H, m, ethyl CH_2 + H_e), 4.08 (1H, s, OH), 3.92 (1H, dd, J = 8.4, 1.0 Hz, H_a), 3.54 (1H, ddd, J = 8.6, 4.6, 4.0 Hz, H_d), 3.27 (1H, ddd, 9.0, 4.9, 4.1 Hz, H_b), 2.53 (1H, dt, J = 13.6, 4.6 Hz, H_c), 1.97 (1H, ddd, J = 13.7, 10.4, 5.6 Hz, H_c), 1.32 (3H, t, J = 7.2 Hz, ethyl CH_3). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 176.9 (NPM), 174.8 (NPM), 173.0 (ester C=O), 138.8 (Imidazole C-H), 138.7 (Imidazole C), 135.7 (Phenyl C), 131.5 (Phenyl C), 129.3 (Phenyl C-H), 129.2 (Phenyl C-H), 128.9 (Phenyl C-H), 128.4 (Phenyl C-H), 127.6 (Phenyl C-H), 126.4 (Phenyl C-H), 120.4 (Imidazole C), 73.4 (H_e), 61.9 (CH_2), 49.7 ($BnCH_2$), 40.0 (H_b), 38.5 (H_a), 35.4 (H_d), 26.0 (H_c), 14.3 (CH_3). IR: ν_{max}/cm^{-1} 2935, 1709, 1597, 1497, 1383, 1187, 724, 693. HRMS: calcd for $C_{26}H_{25}N_3O_5$ $(M+H)^+$: 460.1867, found 460.1862.

242 also obtained upon further elution, as a white solid, 32 mg (12%). R_f 0.10 (UV active, Et_2O/methanol, 95:5), m.p.: 198–199°C. ^{1}H NMR (400MHz, $CDCl_3$): δ_H 7.52 (1H, s, Imidazole C-H), 7.47-7.43 (2H, m, Phenyl C-H), 7.40-7.32 (4H, m, Phenyl C-H), 7.21-7.16 (4H, m, Phenyl C-H), 5.62 (1H, d, J = 15.4 Hz, $BnCH_2$), 5.31 (1H, d, J = 15.4 Hz, $BnCH_2$), 5.02 (1H, br s, OH), 4.33 (1H, dq, J = 10.6, 7.1 Hz, ethyl CH_2), 4.22 (1H, dq, J = 10.6, 7.1 Hz, ethyl CH_2), 3.95 (1H, d, J = 8.4 Hz, H_a), 3.51 (1H, ddd, J = 8.7, 4.6, 4.1 Hz, H_b), 3.27-3.25 (1H, m, H_d), 2.28 (1H, dt, J = 13.5, 4.2 Hz, H_c), 1.98 (1H, ddd, J = 13.5, 10.6, 5.5 Hz, H_c), 1.30 (3H, t, J = 7.1 Hz, ethyl CH_3). ^{13}C NMR, (101 MHz,

$CDCl_3$): δ_C 176.9 (NPM C=O), 174.9 (NPM C=O), 173.7 (ester C=O), 139.1 (Imidazole C-H), 138.9 (Imidazole C), 135.6 (Phenyl C), 131.6 (Phenyl C), 129.3 (Phenyl C-H), 129.2 (Phenyl C-H), 128.9 (Phenyl C-H), 128.4 (Phenyl C-H), 127.7 (Phenyl C-H), 126.4 (Phenyl C-H), 120.3 (Imidazole C), 70.6 (H_e), 61.9 (CH_2), 49.8 ($BnCH_2$), 39.9 (H_b), 38.7 (H_a), 35.5 (H_d), 22.4 (H_c), 14.4 (CH_3). IR: ν_{max}/cm^{-1} 2933, 1743, 1712, 1597, 1495, 1383, 1190, 726, 691. HRMS: calcd for $C_{26}H_{25}N_3O_5$ $(M+H)^+$: 460.1867, found 460.1865.



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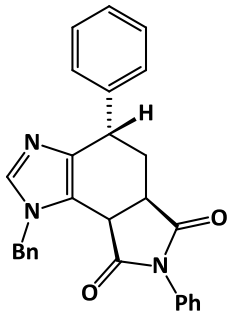
To (5*S*,5a*S*,8a*S*)-1-benzyl-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-7-phenyl-1,5,5a,8b-tetrahydroimidazo[4,5-*e*]isoindole-6,8(7H,8a*H*)-dione (**210**, 200 mg, 0.40 mmol) in CH_2Cl_2 (6 mL) was added ethyl glyoxalate (50% in toluene, 0.48 mmol, 98 μL) and the solution stirred at r.t. for 16 h. The solvent was removed and the crude residue was chromatographed on silica gel (eluting with Et_2O) to yield **243** as a white solid, 142 mg (59%). R_f 0.23 (UV active, Et_2O), m.p.: 76–78 ^oC.

^1H NMR (400MHz, $CDCl_3$): δ_H 7.52–7.44 (3H, m, Phenyl C-H + Imidazole C-H), 7.44–7.31 (4H, m, Phenyl C-H), 7.27–7.21 (2H, m, Phenyl C-H), 7.18–7.10 (2H, m, Phenyl C-H), 5.68 (1H, d, J = 15.5 Hz, $BnCH_2$), 5.29 (1H, d, J = 15.5 Hz, $BnCH_2$), 4.47 (1H, dd, J = 6.4, 2.5 Hz, H_f), 4.37 (1H, dq, J = 10.7, 7.1, 7.1, 7.1, 7.1 Hz, diastereotopic CH_2), 4.31 (1H, dq, J = 10.7, 7.1, 7.1, 7.1, 7.1 Hz, diastereotopic CH_2), 4.15 (1H, dd, J = 9.8, 7.3 Hz, H_d), 3.96 (1H, dd, J = 7.8 Hz, H_b), 3.95 (1H, dd, J = 14.7, 7.4 Hz, H_d), 3.87 (1H, d, J = 8.2 Hz, H_a), 3.52 (1H, d, J = 6.0 Hz, H_e), 3.00 (1H, d, J = 6.4 Hz, OH), 2.57 (1H, ddd, J = 14.7, 9.8, 6.0 Hz, H_c), 1.36 (3H, t, J = 7.1, 7.1 Hz, CH_3), 0.83 (9H, s, $(CH_3)_3$), -0.01 (6H, d, J = 8.7 Hz,$(CH_3)_2$). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 176.2 (NPM C=O), 174.8 (NPM C=O), 174.2 (C=O), 139.1 (Imidazole C-H), 137.4 (Imidazole C), 136.0 (Phenyl C), 131.6 (Phenyl C), 129.2 (Phenyl C-H), 129.2 (Phenyl C-H), 128.8 (Phenyl C-H), 128.3 (Phenyl C-H), 127.5 (Phenyl C-H), 126.4 (Phenyl C-H), 121.2 (Imidazole C), 71.3 (C-H_f), 62.6 (O-CH_2), 62.1 (diastereotopic CH_2), 49.8 (Bn CH_2), 41.1 (C-H_b), 40.9 (C-H_c), 39.3 (C-H_a), 39.1 (C-H_e), 26.0 (CH_3 x 3), 18.4 ($C(CH_3)$), 15.4 (CH_3), -5.4 (CH_3 x 2). IR: ν_{max}/cm^{-1} 2953, 2929, 2857, 1782, 1714, 1498, 1377, 1252, 1191, 1099, 836, 778, 691. HRMS: calcd for $C_{33}H_{41}N_3O_6$ $(M+H)^+$: 604.2837, found 604.2822.



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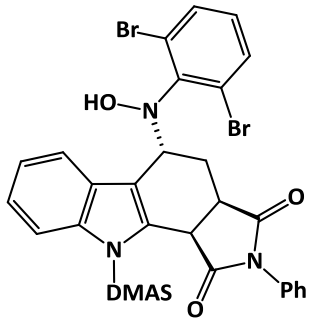
To (5a*S*,8a*S*)-1-benzyl-7-phenyl-5,5a-7,8a-tetrahydroimidazo[4,5-*e*]isoindole-6,8(1*H*,4*H*)-dione (**211**, 200 mg, 0.56 mmol) and trimethylsilylphenyl triflate (250 mg, 0.84 mmol, 204 μL) in CH_2Cl_2 (10 mL) was added *tetra*-butylammoniumfluoride (1M in THF, 219 mg, 0.84 mmol, 840 μL) and the solution heated at 40 ^oC for 2 h. The solvent was removed and the crude residue was chromatographed on silica gel (eluting with Et_2O/petroleum ether 40-60, 50:50→Et_2O) to yield the product as a white solid, 165 mg (68%). R_f 0.13 (UV active, Et_2O), m.p.: 228-229 ^oC.

^1H NMR (400MHz, $CDCl_3$): δ_H 7.59 (1H, s, Imidazole C-H), 7.55–7.47 (2H, m, Phenyl C-H), 7.46–7.31 (6H, m, Phenyl C-H), 7.31–7.20 (5H, m, Phenyl C-H), 7.19–7.13 (2H, m, Phenyl C-H), 5.81 (1H, d, J = 15.6 Hz, $BnCH_2$), 5.36 (1H, d, J = 15.6 Hz, $BnCH_2$), 4.11 (1H, dd, J = 8.1, 4.9 Hz, H_d), 3.98 (1H, d, J = 8.2 Hz, H_a), 3.39 (1H, ddd, J = 8.0, 6.3, 5.5 Hz, H_b), 2.66 (1H, ddd, J = 13.5, 6.3, 5.0 Hz, H_c), 2.17 (1H, ddd, J = 13.5, 8.4, 5.1 Hz, H_c). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 177.1 (C=O), 174.8 (C=O), 142.1 (Phenyl C), 141.7 (Imidazole C), 139.4 (Imidazole C-H), 136.2 (Phenyl C), 131.6 (Phenyl C), 129.3 (Phenyl C-H), 129.2 (Phenyl C-H), 128.9 (Phenyl C-H), 128.7 (Phenyl C-H), 128.4 (Phenyl C-H), 128.2 (Phenyl C-H), 128.1 (Phenyl C-H), 127.4 (Phenyl C-H), 127.2 (Phenyl C-H), 127.0 (Phenyl C-H), 126.4 (Phenyl C-H), 119.9 (Imidazole C-H), 49.8 ($BnCH_2$), 39.5 (C-H_b), 38.9 (C-H_d), 38.8 (C-H_a), 32.9 (C-H_c). IR: ν_{max}/cm^{-1} 3034, 2916, 2866, 1775, 1703, 1598, 1496, 734, 693. HRMS: calcd for $C_{28}H_{23}N_3O_2$ $(M+H)^+$: 434.1863, found 434.1862.



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(3a*R*, 10b*R*)-*N*,*N*-dimethyl-1,3-dioxo-2-phenyl-1,2,3,3a,4,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(10a*H*)-sulfonamide (**212**, 200 mg, 0.47 mmol) and 2,6-dibromonitrosobenzene (**226**, 125 mg, 0.47 mmol) were dissolved in CH_2Cl_2 and stirred together for 6 h at r.t.. The resulting solution was concentrated and the crude residue purified by chromatography on silica gel (eluting with Et_2O/petroleum ether, 40:60) to yield the product as a white solid, 189 mg (82%). R_f 0.43 (UV active, diethyl ether/petroleum ether 20:80), m.p.: 241-242 ^oC.

^1H NMR (400MHz, $CDCl_3$): δ_H 7.57 (2H, d, J = 8.5 Hz, Phenyl-H), 7.47 (3H, ddd, J = 7.6, 7.6 Hz, Phenyl-H), 7.39 (2H, ddd, J = 7.4, 7.4 Hz, Phenyl-H), 7.34 (2H, d, J = 7.6 Hz, Phenyl-H), 7.18 (1H, ddd, J = 7.8, 7.8, 7.8 Hz, Phenyl-H), 7.05 (1H, ddd, J = 7.6, 7.6, 7.6 Hz, Phenyl-H), 6.74 (1H, ddd, J = 8.0, 8.0, 8.0 Hz, Phenyl-H), 6.08 (1H, s, OH), 5.52 (1H, dd, J = 2.7, 2.7 Hz, H_d), 5.18 (1H, d, J = 7.4 Hz, H_a), 4.34 (1H, ddd, J = 12.2, 7.4, 4.6 Hz, H_b), 3.16 (1H, ddd, J = 17.0, 8.5, 4.9 Hz, H_c), 2.96 (3H, s, CH_3 x 2), 1.84 (1H, dddd, J = 13.3, 13.3, 2.7 Hz, H_c). ^{13}C NMR, (101 MHz, $CDCl_3$): δ_C 177.9 (C=O), 172.5 (C=O), 144.4 (Indole C), 136.2 (Phenyl C), 132.7 (Indole C), 131.9 (Phenyl C), 129.6 (Phenyl C-H), 129.2 (Phenyl C-H), 128.7 (Phenyl C-H), 128.1 (C-Br), 126.5 (Phenyl C-H), 124.2 (Phenyl C-H), 122.9 (Phenyl C-H), 119.1 (Phenyl C-H), 115.2 (Indole C), 113.7 (Phenyl C-H), 113.6 (Phenyl C-H), 54.8 (C-H_d), 42.6 (C-H_a), 39.0 (C-H_b), 38.1 (CH_3 x 2), 30.0 (C-H_c). IR: ν_{max}/cm^{-1} 3431, 2927, 1780, 1715, 1599, 1499, 1454, 1376, 1156, 747, 692, 630. HRMS: calcd for $C_{28}H_{24}Br_2N_4O_5S$ $(M+Na)^+$: 710.9713, found 710.9719.

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Appendix 1

JOC*Note*

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Thermal 1,3-Trityl Migrations in Diels−Alder Domino Reactions of 1-Trityl-4-vinyl-1*H*-imidazoles

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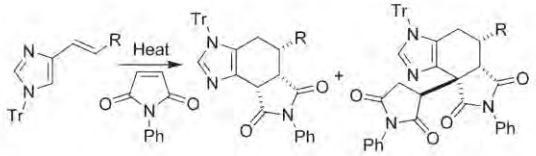

Under thermal conditions, tritylimidazoles have been shown to undergo sterically driven N→N trityl migrations, in disagreement with previously published reports. These migrations are a key step in several highly diastereoselective domino reaction sequences (Diels−Alder, [1,3]-H shift, [1,3]-trityl migration and Diels−Alder, [1,3]-H shift, [1,3]-trityl migration, Michael reaction) leading to architecturally complex molecules.

Diels−Alder (D−A) and hetero-Diels−Alder (h-D−A) reactions have long been used in both synthetic[1] and biosynthetic[2] approaches for the construction of complex natural product architectures. Within this field, vinyl-substituted heteroaromatics have been utilized extensively as dienes in inter- and intramolecular D−A and h-D−A reactions.[3−7]

D−A dimerization reactions of both vinylimidazoles and vinylindoles have been implicated in the biosynthesis of a number of marine alkaloids such as ageliferin (isolated from the sponge *Agelas coniferin*)[8] and cyclo-aplysinopsin A (isolated from an unidentified dendrophylliid coral from the Comoros islands).[9] These compounds may arise via head-to-head (ageliferin) or head-to-tail (cyclo-aplysinopsin A) D−A reactions followed by rearomatization of the heteroaromatic component (Figure 1).[10]

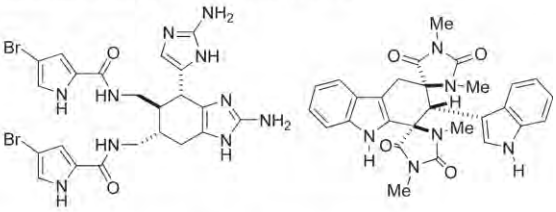

FIGURE 1. Ageliferin and cyclo-aplysinopsin A.

As part of an extensive investigation into the synthesis and biosynthesis of ageliferin (and related oroidin alkaloids), several research groups have examined the D−A reactions of a range of 3- and 4-vinyl-substituted imidazoles,[5] as well as the D−A reactions of imidazolones.[6]

These reports not only provided a valuable insight into alkaloid synthesis and biosynthesis but also contained discussion of a number of intriguing and unexpected byproducts arising from D−A initiated domino reactions.

Domino reactions are of increasing value in synthetic chemistry as they can allow the regio- and stereoselective construction of multiple C−C and C−X bonds in one reaction vessel. This leads to both highly efficient synthesis (through the minimization of isolation steps) and application through rapid library generation for use in medicinal chemistry and chemical biology.[11]

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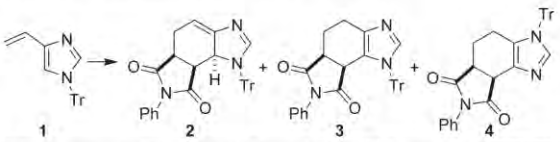
Thus inspired, we embarked upon an investigation of the D−A reactions of 4-vinyl-1*H*-imidazoles with a view to optimizing these reactions to selectively generate unusual domino reaction products in high yields.

Rapid routes to 4-vinylimidazoles from urocanic acid were based on the sterically controlled, selective trityl protection of 3-/4-substituted imidazoles. 1-Trityl-4-vinyl-1*H*-imidazole (**1**) was accessed via a literature approach involving thermal decarboxylation of urocanic acid and subsequent trityl protection of the 1 position (confirmation of the regiochemistry of **1** was achieved by single-crystal X-ray analysis, see the Supporting Information).[12,13]

Lovely et al. have previously reported the thermal D−A reaction of 1-trityl-4-vinyl-1*H*-imidazole (**1**) with *N*-phenylmaleimide (NPM).[5a,e,f] However, when we re-examined this reaction, under reaction conditions similar to those reported (heating in toluene or $CHCl_3$), we discovered that the reaction resulted in the formation of the expected D−A product **2** but only trace quantities of the rearomatized compound **3**. In addition, after prolonged reaction times we observed an unexpected N→N trityl migrated product **4** in moderate yield (Table 1).

TABLE 1. Reaction of 1 with NPM[a]



solvent	temp/°C	time/h	yield of **2**[b]/%	yield of **4**[b]/%
toluene	110	1	35	
toluene	110	3	78	
toluene	110	5		32
$CHCl_3$	61	16	28	6
$CHCl_3$	61	24	25	51

[a]Reaction conditions: 2.5 equiv of *N*-phenylmaleimide. [b]Isolated yields.

Confirmation of the structures of **3** and **4** was obtained through single-crystal X-ray analysis of the isolated compounds (see the Supporting Information). Unfortunately, all attempts to grow X-ray quality crystals of **2** only resulted in isolation of the rearomatized material **3**.[13]

On comparison with reported spectral data, we believe that the major compound **4** has been previously misassigned, due to the N→N trityl migration which has occurred. Thus, our spectral data for **4** matches data that have been erroneously attributed to a compound with structure **3**.[5a,e,f]

We submit that compound **1** undergoes a D−A reaction to give **2**, followed by a [1,3]-H migration to give **3**. Examination of the X-ray structure of **3** shows significant steric crowding of the newly formed 1-phenylpyrrolidine-2,5-dione ring by the trityl group, whereas in **4** the trityl group has migrated to give what appears to be a much less crowded molecule.

In an attempt to rationalize this migration event, structures **3** and **4** were modeled using a HF/3-21G* level of theory calculation, performed with Spartan.[14] The calculation showed that **4** is the thermodynamic product, being approximately 19 kJ mol^{-1} more stable than **3** (Figure 2).

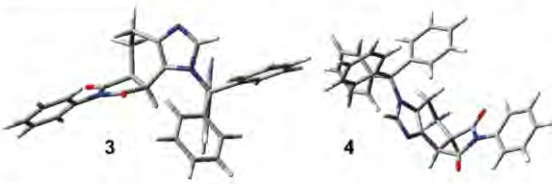


FIGURE 2. Hartree−Fock optimized structures for regioisomers **3** and **4**.

We hypothesized that the observed trityl migration might arise through addition of an electrophile/proton to the imidazole N lone pair of **3**, generating an imidazolium cation. Loss of a trityl cation followed by trapping by another molecule of **3** would result in a ditritylated imidazolium cation of **3**, which can in turn lose the most sterically hindered trityl to give **4** and propagate the reaction.

To explore this proposal, isolated **3** was heated to 45 °C in $CDCl_3$ and the reaction monitored by ^1H NMR. Clean conversion to **4** was observed after 14 h, along with the formation of protonated **4** arising from adventitious HCl. However, removal of HCl, via a $K_2CO_{3(aq)}$ wash of the reaction solvent, resulted in a considerable reduction in reaction rate.

N→C migrations in imidazole systems have previously been reported under flash vacuum pyrolysis conditions through concerted [1,5]-sigmatropic rearrangements of alkyl groups, from the N-1 to the C-5 position.[15] Under more standard reaction conditions, the N→N migrations of Bn, SEM, and MOM groups have recently been reported to occur with the addition of catalytic BnCl, SEMCl, or MOMCl, respectively, to give the least sterically hindered thermodynamic products.[16] However, this manuscript is, to our knowledge, the first report of trityl N→N migration under mild thermal conditions.

A common motif in the D−A chemistry of vinyl imidazoles involves the inclusion of a heteroatom-(N- or O-)-substituted methylene group at the vinyl terminus. These substrates have been examined in synthetic approaches to both ageliferin and several other related oroidin alkaloids.[5i] Thus, we decided to synthesize 4-((*E*)-3-((*tert*-butyl)dimethylsilyl)oxyprop-1-enyl)-1-trityl-1*H*-imidazole (**6**) to examine its potential for domino reactions under our conditions. Compound

(12) Synthesis of 4-vinyltritylimidazole: Faler, C. A.; Joullié, M. M. *Org. Lett.* **2007**, *9*, 1987–1990. Based on the original procedures: Overberger, C. G.; Glowaky, R. C.; Pacansky, T. J.; Sannes, K. N. *Macromol. Synth.* **1974**, *5*, 43–49. Burger, A.; Yost, W. L. *J. Am. Chem. Soc.* **1948**, *70*, 2198–2201. Data in agreement with: Kokosa, J. M.; Szafasz, R. A.; Tagupa, E. *J. Org. Chem.* **1983**, *48*, 3605–3607.

(13) The crystallographic coordinates of **1**, **3**, **4**, **7**, and **8** have been deposited with the Cambridge Crystallographic Data Centre, deposition nos. CCDC 768425, 768426, 768427, 768428, and 768429, respectively. These data can be obtained, free of charge, via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223−336−033; or deposit@ccdc.cam.ac.uk).

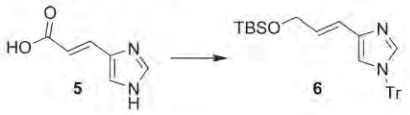
(14) Spartan '06 for Windows. Wavefunction, Inc.: Irvine, CA, 2006.

(15) N→C migrations: Begg, C. G.; Grimmett, M. R.; Wethey, P. D. *Aust. J. Chem.* **1973**, *26*, 2435–2446. Maquestiau, A.; Tommasetti, A.; Pedregal-Freire, C.; Elguero, J.; Flammang, R.; Wiersum, U. E.; Bender, H.; Wentrup, C. *J. Org. Chem.* **1986**, *51*, 306–309. Mitsuhashi, K.; Itho, E.-I.; Kawahara, T.; Tanaka, K. *J. Heterocycl. Chem.* **1983**, *20*, 1103–1105. N→C migrations of trityl: Giesemann, H.; Lettau, H.; Mannsfeldt, H.-G. *Chem. Ber.* **1960**, *93*, 570–576.

(16) N→N migrations: Kuroda, T.; Suzuki, F. *Tetrahedron Lett.* **1992**, *33*, 2027–2028. Moores, I. G.; Scriven, E. F. V.; Smalley, R. K.; Suschitzky, H. *J. Fluorine Chem.* **1988**, *41*, 277–288. He, Y.; Chen, Y.; Du, H.; Schmid, L. A.; Lovely, C. J. *Tetrahedron Lett.* **2004**, *45*, 5529–5532. Lovely, C. J.; Sivappa, R.; Mukherjee, S.; Doundoulakis, T.; Lima, H. M.; Yousufuddin, M. *Heterocycles* **2010**, *80*, 1353–1358.

6 was synthesized via methylation of urocanic acid (**5**), selective tritylation of the 1 position, DIBAL-H reduction to the primary alcohol, and TBS protection (Scheme 1).[17]

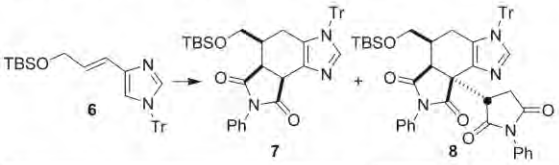
SCHEME 1. Synthesis of 6[a]



[a]Reaction conditions: (i) MeOH, $SOCl_2$, reflux, 16 h (81%); (ii) TrCl, Et_3N, THF, rt, 16 h (97%); (iii) 3 equiv of DIBAL-H, DCM, −78 °C, 1 h (67%); (iv) TBSCl, imidazole, DCM, 16 h (68%).

Under standard conditions, **6** reacts with NPM to give **7**, arising from an *endo*-D−A, [1,3]-H migration, [1,3]-Tr migration domino reaction sequence. However, with extended reaction times an additional compound **8** was also observed (Table 2). Again, confirmation of the structures of **7** and **8** was obtained through single-crystal X-ray analysis of the isolated compounds (see the Supporting Information).[13]

TABLE 2. Reaction of 6 with *N*-Phenylmaleimide[a]

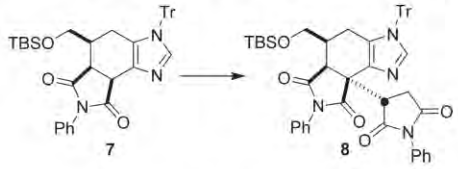


solvent	temp/°C	time/h	yield of **7**[b]/%	yield of **8**[b]/%
toluene	110	16	63	9
toluene	110	72	10	57

[a]Reaction conditions: 2.5 equiv of *N*-phenylmaleimide. [b]Isolated yields.

Unlike other reported 2:1 adducts, compound **8** did not arise through intermolecular ene reactions with additional NPM but instead through a previously unobserved Michael addition of the enol form of **7** to an NPM unit. We have demonstrated that compound **8** may be formed through such a Michael addition. Purified **7** was dissolved in $CDCl_3$, treated with 1 equiv of NaH, and quenched with D_2O. This led to selective deuteration of the tertiary carbon α to the imidazole ring. Thus, deprotonation of **7**, with NaH followed by addition of NPM, gave compound **8** in 61% isolated yield (Scheme 2).

SCHEME 2. Formation of 8 from 7 via Michael Addition[a]



[a]Reaction conditions: NaH, toluene, rt, 1 h, then NPM, reflux 6 h (61%).

(17) Dolensky, B.; Kirk, K. L. *J. Org. Chem.* **2002**, *67*, 3468–3473. Pirrung, M. C.; Pei, T. *J. Org. Chem.* **2000**, *65*, 2229–2230. Kosaka, K.; Maruyama, K.; Nakamura, H.; Ikeda, M. *J. Heterocycl. Chem.* **1991**, *28*, 1941–1944. Uenishi, J.; Motoyama, M.; Takahashi, K. *Tetrahedron: Asymmetry* **1994**, *5*, 101–110.

We have demonstrated a number of novel domino reaction routes for the rapid formation of complex molecules. For example, the formation of **8** generates four contiguous stereocenters, including a quaternary center, three new C−C bonds, and one C−N bond. Thus, this sets the scene for the construction of natural product scaffold libraries with potential medicinal chemistry application. We have also shown a facile, thermal N→N migration of trityl-protected imidazole systems to give the least sterically hindered thermodynamic product. The N→N trityl-migration is difficult to observe by NMR, our efforts to use NOESY and ROESY experiments to track the location of the trityl group proved inconclusive, thus X-ray crystallography has played a key role in this study. The observation of N→N trityl migrations has important implications on account of the extensive use of trityl and trityl-derived groups in imidazole-based medicinal compounds, such as the antifungal agents clotrimazole, fluotrimazole, and bifonazole, as well as in the field of synthetic chemistry.

Ongoing work in our group is aimed at optimizing and extending these domino reaction pathways to develop new, efficient routes to highly complex, natural product-inspired substrates.

Experimental Section

(±)-(5a*S*,8a*S*)-7-Phenyl-1-trityl-5,5a,7,8b-tetrahydroimidazo-[4,5-*e*]isoindole-6,8(7*H*,8a*H*)-dione (2). To 1-trityl-4-vinyl-1*H*-imidazole (**1**) (264 mg, 0.52 mmol) in toluene (10 mL) was added *N*-phenylmaleimide (224 mg, 1.30 mmol) and the solution stirred at reflux for 3 h. The solvent was removed, and the crude residue was chromatographed on silica gel (ethyl acetate−petroleum ether 40/60, 40:60) to yield the title compound as a white solid, 207 mg (78%): R_f 0.42 (UV active, ethyl acetate−petroleum ether 40/60, 40:60); mp 208−211 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.55−7.51 (6H, m), 7.47−7.34 (13H, m), 7.13 (2H, dd, J = 7.0, 1.6 Hz), 5.65 (1H, ddd, J = 5.4, 3.8, 3.8 Hz), 4.37 (1H, ddd, J = 6.0, 3.1, 3.1 Hz), 2.98 (1H, ddd, J = 15.4, 7.8, 1.1 Hz), 2.77 (1H, ddd, J = 8.2, 8.1, 0.7 Hz), 2.00 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 178.0, 174.0, 162.2, 155.5, 142.2, 131.6, 130.4, 129.1, 128.7, 128.1, 127.7, 126.6, 102.2, 75.0, 58.9, 42.0, 36.8, 26.3; IR 2362, 1709, 1381, 1160, 750, 701; HRMS calcd for $C_{34}H_{27}N_3O_2$ (M + Na)$^+$ 532.1995, found 532.2007.

(±)-(5a*S*,8a*S*)-5,5a-Dihydro-7-phenyl-1-tritylimidazo[4,5-*e*]-isoindole-6,8(1*H*,4*H*,7*H*,8a*H*)-dione (3). To 1-trityl-4-vinyl-1*H*-imidazole (**1**) (1.0 g, 2.97 mmol) in toluene (37 mL) was added *N*-phenylmaleimide (1.29 g, 7.43 mmol) and the solution stirred at reflux for 3 h. The reaction mixture was concentrated to a low volume and cooled. The resulting colorless crystals were filtered, yielding the title compound, 80 mg (5%): R_f 0.29 (UV active, methanol−diethyl ether, 2:98); mp 190 °C dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H 7.43−7.30 (12H, m), 7.29 (1H, s), 7.17−7.14 (6H, m), 7.09−7.07 (2H, m), 2.56 (1H, ddd, J = 19.2, 4.8, 4.8 Hz), 2.37 (1H, ddd, J = 19.7, 14.6, 5.4 Hz), 2.13 (1H, ddd, J = 12.0, 8.2, 4.2 Hz), 1.53−1.44 (2H, m); ^{13}C NMR, (101 MHz, $CDCl_3$) δ_C 177.7, 173.7, 142.4, 142.2, 142.0, 141.8, 141.0, 130.8, 129.1, 128.5, 128.2, 127.9, 126.4, 77.3, 42.4, 40.8, 24.9, 23.0; IR 2970, 2360, 1716, 1379, 1174, 823, 751, 703; HRMS calcd for $C_{34}H_{27}N_3O_2$ (M + Na)$^+$ 532.1995, found 532.2006. Anal. Calcd for $C_{34}H_{27}N_3O_2$: C, 80.13; H, 5.34; N, 8.25. Found: C, 80.00; H, 5.26; N, 8.20.

(±)-(5a*S*,8a*S*)-5,5a-Dihydro-7-phenyl-3-tritylimidazo[4,5-*e*]-isoindole-6,8(3*H*,4*H*,7*H*,8a*H*)-dione (4). To 1-trityl-4-vinyl-1*H*-imidazole (**1**) (500 mg, 0.98 mmol) in toluene (18.5 mL) was added *N*-phenylmaleimide (425 mg, 2.45 mmol) and the solution

stirred at reflux for 5 h. The solvent was removed, and the crude residue was chromatographed on silica gel (ethyl acetate−petroleum ether 40/60, 60:40) to yield the title compound as a white solid, 240 mg (32%): R_f 0.10 (UV active, methanol−diethyl ether, 2:98); mp >232 °C dec; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.40−7.35 (2H, m), 7.31 (1H, s), 7.27−7.23 (10H, m), 7.15−7.12 (2H, m), 7.05−7.02 (6H, m), 4.21 (1H, d, J = 10.4 Hz), 3.31 (1H, ddd, J = 10.4, 6.0, 6.0 Hz), 2.12−2.06 (1H, m), 1.72 (1H, ddd, J = 19.8, 5.3, 4.8 Hz), 1.67−1.59 (1H, m), 1.43 (1H, ddd, J = 19.6, 12.7, 5.3 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 177.6, 174.8, 141.5, 139.1, 132.1, 131.6, 129.9, 129.4, 129.1, 128.5, 128.3, 128.2, 126.5, 75.1, 41.5, 40.3, 22.6, 21.0; IR 2962, 2360, 1712, 1380, 1177, 701; HRMS calcd for $C_{34}H_{27}N_3O_2$ $(M + Na)^+$ 532.1995, found 532.2003. Anal. Calcd for $C_{34}H_{27}N_3O_2$: C, 80.13; H, 5.34; N, 8.25. Found: C, 79.96; H, 5.33; N, 8.15.

(±)-(5*S*,5a*S*,8a*S*)-5-((*tert*-Butyldimethylsilyloxy)methyl)-7-phenyl-3-trityl-5,5a,7,8-tetrahydroimidazo[4,5-*e*]isoindole-6,8-(3*H*,4*H*)-dione (7). To 1-trityl-4-((*E*)-3-(*tert*-butyldimethylsilyloxy)prop-1-enyl)-1*H*-imidazole (**6**) (600 mg, 1.2 mmol) in toluene (28 mL) was added *N*-phenylmaleimide (520 mg, 3.0 mmol) and the solution stirred at reflux for 20 h. The solvent was removed, and the crude residue was chromatographed on silica gel (ethyl acetate−petroleum ether 40/60, 60:40) to yield the title compound as a pale yellow solid, 496 mg (63%): R_f 0.48 (UV active, ethyl acetate−petroleum ether 40/60, 80:20); mp 119−121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.42 (2H, ddd, J = 9.6, 9.6, 0.7 Hz), 7.35 (2H, dd, J = 9.3, 0.7 Hz), 7.30−7.27 (9H, m), 7.12 (2H, dd, J = 9.4, 2.2 Hz), 7.09−7.07 (6H, m), 4.27 (1H, d, J = 9.6 Hz), 3.93 (1H, dd, J = 12.5, 7.8 Hz), 3.65 (1H, dd, J = 12.4, 9.9 Hz), 3.50 (1H, dd, J = 9.8, 4.8 Hz), 2.12−2.08 (2H, m), 1.10 (1H, ddd, J = 18.0, 16.0, 1.0 Hz), 0.72 (9H, s), −0.09, −0.17 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 176.1, 174.5, 141.2, 139.1, 132.2, 131.9, 129.7, 129.3, 129.0, 128.4, 128.2, 128.1, 126.4, 75.0, 64.1, 42.8, 41.4, 38.9, 25.8, 23.8, 18., −5.5, −5.6; IR 2925, 2316, 1710, 1384, 1085, 700; HRMS calcd for $C_{41}H_{43}N_3O_3Si$ $(M + H)^+$ 654.3146, found 654.3145. Anal. Calcd for $C_{41}H_{43}N_3O_3Si$: C, 75.31; H, 6.63; N, 6.43. Found: C, 75.21; H, 6.57; N, 6.37.

(±)-((5*S*,5a*S*,8a*S*)-5-((*tert*-Butyldimethylsilyloxy)methyl)-8a-((*R*)-2,5-dioxo-1-phenylpyrrolidin-3-yl)-7-phenyl-3-trityl-5,5a,7,8a-tetrahydroimidazo[4,5-*e*]isoindole-6,8(3*H*,4*H*)-dione (8). (See the Supporting Information for an alternative procedure from **7**.) To 1-trityl-4-((*E*)-3-(*tert*-butyldimethylsilyloxy)prop-1-enyl)-1*H*-imidazole (**6**) (430 mg, 0.9 mmol) in toluene (20 mL) was added *N*-phenylmaleimide (387 mg, 2.2 mmol) and the solution stirred at reflux for 72 h. The solvent was removed, and the crude residue was chromatographed on silica gel (ethyl acetate−petroleum ether 40/60, 5% increasing to 60%) to yield the title compound as a brown solid, 420 mg (57%), and a minor amount of **7**, as a yellow solid, 59 mg (10%): R_f 0.68 (UV active, ethyl acetate−petroleum ether 40/60, 35:65); mp 185−188 °C; ^{1}H NMR, (400 MHz, $CDCl_3$) δ_H 7.39 (6H, ddd, J = 9.6, 8.9, 1.6 Hz), 7.34−7.33 (1H, m), 7.31−7.30 (5H, m), 7.29−7.27 (3H, m), 7.26−7.23 (3H, m), 7.16−7.14 (2H, m), 7.04 (6H, ddd, J = 4.4, 1.6, 1.6 Hz), 4.83 (1H, dd, J = 12.1, 8.9 Hz), 3.93 (1H, dd, J = 12.9, 7.9 Hz), 3.58 (1H, dd, J = 12.6, 9.9 Hz), 3.22 (1H, d, J = 5.1 Hz), 3.11 (1H, dd, J = 23.0, 12.2 Hz,), 2.79 (1H, dd, J = 23.0, 8.9 Hz), 2.13 (1H, dd, J = 20.3, 4.3 Hz), 2.03−1.95 (1H, m), 1.10 (1H, dd, J = 20.3, 15.1 Hz), 0.66 (9H, s), −0.14 and −0.21 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 176.4, 175.3, 174.5, 174.5, 141.2, 139.9, 133.5, 132.0, 131.5, 131.0, 129.7, 129.3, 129.1, 128.9, 128.7, 128.5, 128.3, 126.8, 126.4, 75.3, 63.9, 49.3, 44.8, 44.2, 40.6, 32.0, 25.9, 24.1, 18.2, −5.3 and −5.4; IR 2325, 1781, 1711, 1498, 1378, 1185, 1089, 837, 747, 700; HRMS calcd for $C_{51}H_{50}N_4O_5Si$ $(M + Na)^+$ 849.3443, found 849.3450.

Acknowledgment. The authors would like to thank Newcastle University and the EPSRC for PhD funding (L.J.C.), EPSRC (EP/F03637X/1) for X-ray crystallography facilities, the EPSRC National Mass Spectrometry Service (University of Swansea), Prof. William McFarlane and Dr. Corinne Wills (Newcastle) for NMR studies, and Beverly Stewart (Newcastle) for computational studies.

Supporting Information Available: Experimental procedures for the synthesis of **1** and **6**. ^{1}H, ^{13}C spectra for compounds **1**−**4** and **6**−**8**. Crystallographic information files (CIFs) for compounds **1**, **3**, **4**, **7**, and **8**. Experimental details, optimized atomic coordinates, and final energies for Hartree−Fock model of **3** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

Appendix 2

Organic & Biomolecular Chemistry

Dynamic Article Links

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PAPER

Diastereoselective intermolecular ene reactions: synthesis of 4,5,6,7-tetrahydro-1*H*-benzo[*d*]imidazoles†

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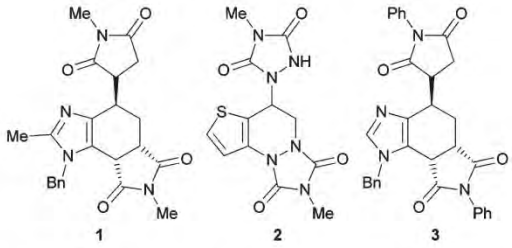
The Diels–Alder cycloadducts of 4-vinylimidazoles and *N*-phenylmaleimide are shown to undergo facile intermolecular ene reactions. Overall the reaction of three simple molecules (a diene, a dienophile and an enophile) in a two-step process gives 4,5,6,7-tetrahydro-1*H*-benzo[*d*]imidazoles with high yields, high atom economy and diastereocontrol of up to 5 new stereocentres.

Introduction

1*H*-Benzo[*d*]imidazoles are a core structure of many biologically active molecules, including drugs such as mebendazole and albendazole. However, despite the success of many aromatic compounds of this type, medicinal chemistry is moving from stereochemistry as "a source of problems" to stereochemistry as a vital tool for improving selectivity and efficacy.[1,2] Thus, there is an increasing interest in unsaturated, chiral 1*H*-benzo[*d*]imidazole analogues as medicinal leads.[3]

Recently we disclosed our investigations into the Diels–Alder (D–A) reactions of *N*-trityl-4-vinylimidazoles and *N*-phenylmaleimide. This resulted in the observation of novel domino reaction processes including D–A, [1,3]-H shift, [1,3]-trityl migrations and D–A, [1,3]-H shift, [1,3]-trityl migration, Michael reactions.[4]

These results prompted us to examine the reactivity of the D–A cycloadducts of 4-vinylimidazoles and maleimides in more detail.[5] During the study of D–A reactions of various vinyl-heteroaromatics with reactive dienophiles, a handful of research groups have reported the observation of an intriguing, if low-yielding, by-product formed from one molecule of vinyl-heteroaromatic and two molecules of the dienophile. It has been postulated that this occurs *via* an intermolecular Diels–Alder/intermolecular ene (IMDA/IME) reaction sequence, the products of which are shown (Scheme 1).[6] There are, however, no examples of this reaction sequence being carried out with the separation of the ene reaction from the other steps, allowing variation of the enophile.



Scheme 1 Observed by-products arising from postulated IMDA/IME reactions of vinyl-heteroaromatics.

Intermolecular pericyclic reactions are powerful tools in synthetic organic chemistry due to their ability to generate multiple covalent bonds and stereocentres in a single step.[7] Thus use of an intermolecular Diels–Alder and an intermolecular ene reaction would allow, in two steps and from three simple starting materials, rapid access to complex unsaturated 1*H*-benzo[*d*]-imidazole analogues with 100% atom economy and high diastereomeric control in the formation of the multiple C–C and C–X bonds.[7,8]

Through the introduction of different enophiles this reaction sequence would provide a hitherto unexplored synthetic approach for the diastereoselective generation of complex unsaturated 1*H*-benzo[*d*]imidazoles. Herein we discuss our investigations into the ability of the D–A cycloadducts of 4-vinyl-imidazoles and *N*-phenylmaleimide to undergo diastereoselective ene reactions with a broad range of enophiles (Scheme 2).[9]

Examination of the X-ray crystal structures of molecules such as **5** shows that the *twix* C–H σ-bond is coplanar with the electron-rich cyclohexenyl C=C π-bond.[10] In addition an ene reaction involving the *twix* C–H results in the rearomatisation of the imidazole ring providing highly favourable thermodynamics.[11] Thus we envisaged that ene reactions with molecules such as **5** would be both regio- and diastereoselective.

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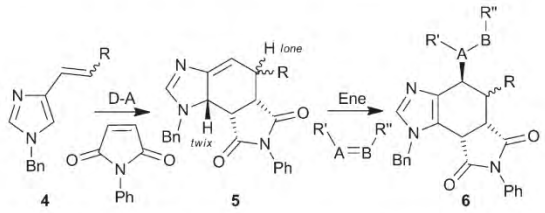
†Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra for all compounds, X-ray structures and .cif files for **6b**, **7c**, **7d**, **8a**. CCDC 860567–860571. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob26009c



Scheme 2 Planned IMDA/IME reaction sequence of vinylimidazoles.

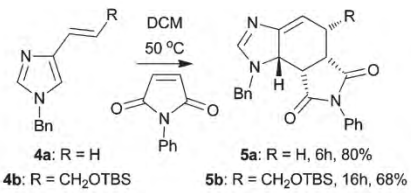
Results and discussion

The desired cycloadducts (**5a–b**) were prepared through the D–A reaction of *N*-phenylmaleimide (NPM) and the requisite vinylimidazole precursors (**4a–b**). 1-Benzyl-4-vinyl-1*H*-imidazole (**4a**) was synthesised *via* a thermal decarboxylation of urocanic acid followed by a benzyl protection of the sterically most accessible nitrogen atom. (*E*)-1-Benzyl-4-(3-((*tert*-butyldimethylsilyl)-oxy)prop-1-en-1-yl)-1*H*-imidazole (**4b**) was also synthesised starting from urocanic acid *via* an esterification, *N*-benzyl protection, DIBAL reduction and finally *O*-TBS protection. Vinylimidazoles (**4a–b**) were then reacted with NPM to give (**5a–b**) respectively (Scheme 3).[4,6b]

Reaction of **5a** was successful with a range of reactive enophiles including arylnitroso compounds (**6a–c**),[12] benzyne (**6d**, generated from trimethylsilylphenyl triflate and TBAF *in situ*),[13] PTAD (**6e**), and diethyl 2-oxomalonate (**6f**). These reactions gave good to excellent yields of the ene products as single diastereomers (Table 1). The ene reactions proved to be remarkably facile, requiring a few hours at moderate to low temperatures without the requirement of a Lewis acid catalyst. Relative stereochemistry of the ene products was determined through comparison with the results of single-crystal X-ray analysis of **6b** (see ESI†).[14]

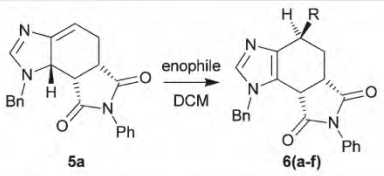
Interestingly, in the case of less reactive enophiles (*N*-phenyl- or *N*-methylmaleimide, maleic anhydride, *etc.*) even extended reaction times resulted in no observed ene products but only rearomatisation of the imidazole, and in some cases concurrent oxidation (potentially air oxidation) of the imidazolyl methylene.

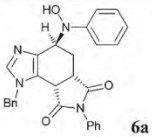
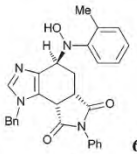
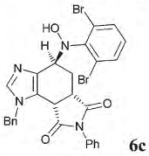
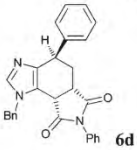
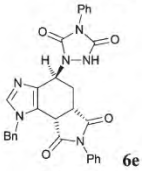
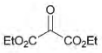
We then subjected **5b** to our previous ene reaction conditions. For **5b** ene reactions with arylnitroso compounds were not successful, but reactions with PTAD and diethyl 2-oxomalonate gave moderate yields of **6(g–h)** as single diastereomers, resulting in the generation, over two steps, of four contiguous stereocentres and three C–C/X bonds *via* the IMDA/IME three-component reaction sequence (Table 2).



Scheme 3 Synthesis of reactive cycloadducts **5a** and **5b**.

Table 1 Ene reactions of **5a**[a]

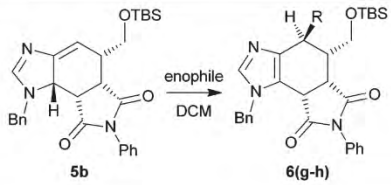


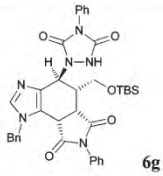
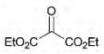
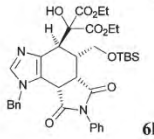
Enophile	Reaction conditions	Product	Yield[c]
	r.t., 1 h	 **6a**	95%
	r.t., 2 h	 **6b**[b]	68%
	r.t., 1 h	 **6c**	87%
 [d]	TBAF, 40 °C, 2 h	 **6d**	68%
	−78 °C, 1 h	 **6e**	74%
	r.t., 16 h	 **6f**	83%

[a] All compounds shown were isolated as single diastereomers. [b] Structure confirmed by single-crystal X-ray analysis. [c] Isolated yield of the ene reaction. [d] Benzyne precursor.

Both **5a** and **5b** were then reacted with the prochiral enophiles, ethyl 2-oxoacetate and ethyl 3,3,3-trifluoro-2-oxopropanoate, in order to introduce an additional exocyclic stereocentre, generating overall a total of five contiguous stereocentres (Table 3). In all cases reasonable yields were obtained with the *endo*-ene product as the major diastereomer.

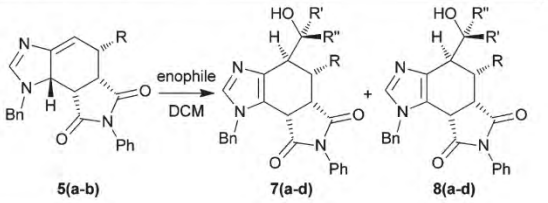
Table 2 Ene reactions of **5b**[a]

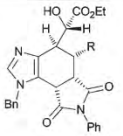
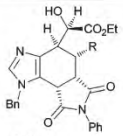
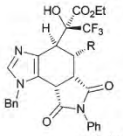
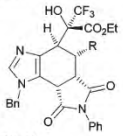


Enophile	Reaction conditions	Product	Yield[b]
	r.t., 1 h	 **6g**	61%
	r.t., 2 h	 **6h**	65%

[a] All compounds shown were isolated as single diastereomers. [b] Isolated yield of the ene reaction.

Table 3 Carbonyl ene reactions of **7(a–b)**[a]



Enophile	Substrate, conditions and yields[b]	Major diastereomer (*endo*-)	Minor diastereomer (*exo*-)
	R = H (**7a**/**8a**); r.t., 30 h, 72% R = CH_2OTBS (**7b**/**8b**); r.t., 16 h, 59%	 **7a**/**8a**[c] = 5:1 **7b**/**8b** ≥ 20:1[d]	
	R = H (**7c**/**8c**); r.t., 16 h, 53% R = CH_2OTBS (**7d**/**8d**); r.t., 72 h, 53%	 **7c**[c] /**8c** ≥ 20:1[e] **7d**[c] /**8d** = 2:1	

[a] All compounds shown were isolated as single diastereomers. [b] Isolated yields. [c] Structures confirmed by single-crystal X-ray analysis. [d] **8b** not observed. [e] **8c** not observed.

Relative stereochemistry of the products was determined through comparison with the results of single-crystal X-ray analysis of **7c**,[15] **7d** and **8a** (see ESI†).[14]

Conclusions

In summary, we have successfully demonstrated that the D–A cycloadducts of 4-vinylimidazoles are viable substrates for high-yielding and highly diastereoselective ene reactions with a wide range of enophiles. Our exemplified 2-step IMDA/IME process allows for the overall combination of three simple components (a vinylimidazole, a dienophile and an enophile) to generate, with 100% atom economy, complex 4,5,6,7-tetrahydro-1*H*-benzo[*d*]imidazoles containing up to 5 new stereocentres through the generation of C–C/X bonds. Current investigations are aimed towards enantioselective variants, extension to other vinyl-aromatic systems, and reaction telescoping.

Experimental section

(5a*S**,8a*S**)-1-Benzyl-7-phenyl-1,5,5a,8b-tetrahydroimidazo-[4,5-*e*]isoindole-6,8(7*H*,8a*H*)-dione (5a)

To 1-benzyl-4-vinyl-1*H*-imidazole (200 mg, 1.09 mmol) in dichloromethane (5 mL) was added *N*-phenylmaleimide (470 mg, 6.93 mmol) and the reaction mixture was stirred at 50 °C for 6 h. The solution was concentrated to a low volume then cooled and filtered to give a white solid. The filtrate was concentrated and purified by chromatography with silica gel (diethyl ether–methanol, 98 : 2) to yield the product as a white solid, 313 mg (80%).

R_f 0.13 (UV active, diethyl ether–methanol, 98 : 2); mp: 193–195 °C (lit.[6b] 195–196 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.45–7.28 (9H, m), 7.16–7.13 (2H, m), 5.62 (1H, ddd, J = 7.9, 3.8, 3.8 Hz), 4.90 (1H, d, J = 15.1 Hz), 4.77 (1H, d, J = 15.1 Hz), 4.02 (1H, ddd, J = 7.7, 3.8, 3.8 Hz), 3.64 (1H, dd, J = 8.9, 7.7 Hz), 3.12 (1H, ddd, J = 8.9, 6.7, 1.8 Hz), 3.11 (1H, ddd, J = 15.4, 7.9, 1.8 Hz), 1.95 (1H, dddd, J = 15.4, 6.7, 3.8, 3.8 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 177.8, 173.9, 159.4, 154.6, 135.3, 131.6, 129.1, 129.2, 128.8, 128.3, 128.1, 126.5, 102.4, 56.9, 49.9, 41.1, 36.8, 25.5; IR (neat): ν_{max}/cm^{-1} 3067, 3029, 2964, 2829, 1771, 1699, 1542, 1496, 758, 694; HRMS (ES-ToF): calcd for $C_{22}H_{19}N_3O_2$ $(M + H)^+$: 358.1550, found 358.1554.

1,3-Dibromo-2-nitrosobenzene[12]

To 2,6-dibromoaniline (0.52 g, 2.05 mmol) in trifluoroacetic acid (3.5 mL) was added H_2O_2 (35% solution in water, 0.15 mol, 4.67 mL), and the mixture stirred at r.t. for 16 h. The mixture was then poured into ice-water (20 mL) and the orange/brown precipitate was filtered and recrystallised from *n*-hexane to give the title compound as a beige solid, 339 mg (62%).

R_f 0.60 (UV active, diethyl ether–petroleum ether 40–60, 50 : 50); mp: 112–114 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.77

(2H, d, J = 7.7 Hz), 7.28 (1H, t, J = 7.7 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 172.5, 138.6, 134.5, 116.7; IR (neat): ν_{max}/cm^{-1} 3069, 1563, 1437, 1279, 777, 733; HRMS (ES-ToF): calcd for $C_6H_3NOBr_2$ $(M + H)^+$: 265.8633, found 265.8625.

(4*S,5a*S**,8a*S**)-1-Benzyl-4-(hydroxy(phenyl)amino)-7-phenyl-5,5a,7,8a-tetrahydroimidazo[4,5-*e*]isoindole-6,8(1*H*,4*H*)-dione (6a)**

To (5a*S**,8a*S**)-1-benzyl-7-phenyl-1,5,5a,8b-tetrahydroimidazo-[4,5-*e*]isoindole-6,8(7*H*,8a*H*)-dione (**5a**) (200 mg, 0.56 mmol) in dichloromethane (15 mL) was added nitrosobenzene (60 mg, 0.56 mmol) and the solution stirred at r.t. for 1 h. The reaction was concentrated and purified by chromatography with silica gel (ethyl acetate–petroleum ether 40–60, 50 : 50) to yield the product as an off-white solid, 248 mg (95%).

R_f 0.33 (UV active, ethyl acetate–petroleum ether 40–60, 50 : 50); mp: 189–190 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.61 (1H, s), 7.47–7.44 (2H, m), 7.40–7.34 (4H, m), 7.28–7.18 (8H, m), 6.96 (1H, t, J = 7.2 Hz, *N*-phenyl C–H), 5.67 (1H, d, J = 15.3 Hz), 5.34 (1H, d, J = 15.3 Hz), 4.75 (1H, dd, J = 7.8, 4.9 Hz), 3.94 (1H, d, J = 8.1 Hz), 3.55 (1H, dd, J = 13.1, 5.5 Hz), 2.38–2.32 (1H, m), 2.25–2.18 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 177.0, 174.7, 150.8, 139.4, 138.7, 135.7, 131.5, 129.3, 129.2, 128.9, 128.8, 128.4, 127.6, 126.4, 122.0, 121.4, 117.2, 57.5, 49.9, 39.4, 38.7, 23.4; IR (neat): ν_{max}/cm^{-1} 2980, 2884, 1773, 1715, 1597, 1496, 1377, 734, 690; HRMS (ES-ToF): calcd for $C_{28}H_{23}N_4O_3$ $(M + H)^+$: 465.1921, found 465.1916.

(4*S,5a*S**,8a*S**)-1-Benzyl-4-(hydroxy(*o*-tolyl)amino)-7-phenyl-5,5a,7,8a-tetrahydroimidazo[4,5-*e*]isoindole-6,8(1*H*,4*H*)-dione (6b)**

To (5a*S**,8a*S**)-1-benzyl-7-phenyl-1,5,5a,8b-tetrahydroimidazo-[4,5-*e*]isoindole-6,8(7*H*,8a*H*)-dione (**5a**) (200 mg, 0.56 mmol) in dichloromethane (5 mL) was added 2-nitrosotoluene (81 mg, 0.67 mmol) and the solution stirred at r.t. for 2 h. The solvent was removed and the crude residue was chromatographed on silica gel (diethyl ether) to yield the title compound as an off-white solid, 181 mg (68%).

R_f 0.12 (UV active, diethyl ether); mp: 202–204 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.60 (1H, d, J = 7.3 Hz), 7.49 (1H, s), 7.46–7.42 (2H, m), 7.39–7.33 (4H, m), 7.25–7.14 (5H, m), 7.12–7.10 (1H, m), 7.06–7.03 (1H, m), 6.82 (1H, br s), 5.70 (1H, d, J = 15.6 Hz), 5.30 (1H, d, J = 15.6 Hz), 4.29 (1H, dd, J = 7.3, 5.0 Hz), 3.90 (1H, d, J = 7.8 Hz), 3.64–3.59 (1H, m), 2.39–2.32 (1H, m), 2.26 (3H, s), 2.16–2.10 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 176.9, 174.6, 149.0, 139.2, 135.7, 131.5, 131.3, 130.8, 129.3, 129.2, 128.9, 128.4, 127.6, 126.4, 126.3, 125.2, 121.8, 121.1, 57.9, 49.9, 39.5, 38.7, 24.8, 18.1; IR (neat): ν_{max}/cm^{-1} 3068, 3030, 2879, 1781, 1703, 1597, 1498, 1377, 730, 691; HRMS (ES-ToF): calcd for $C_{29}H_{28}N_4O_3$ $(M + H)^+$: 479.2078, found 479.2065; HRMS (ES-ToF): calcd for $C_{29}H_{26}N_4O_3$ $([M - H_2O] + H)^+$: 461.1972, found 461.1967.

(4*S,5a*S**,8a*S**)-1-Benzyl-4-((2,6-dibromophenyl)(hydroxy)amino)-7-phenyl-5,5a,7,8a-tetrahydroimidazo[4,5-*e*]isoindole-6,8(1*H*,4*H*)-dione (6c)**

To (5a*S**,8a*S**)-1-benzyl-7-phenyl-1,5,5a,8b-tetrahydroimidazo-[4,5-*e*]isoindole-6,8(7*H*,8a*H*)-dione (**5a**) (200 mg, 0.56 mmol) in dichloromethane (5 mL) was added 1,3-dibromo-2-nitrosobenzene (163 mg, 0.62 mmol), and the solution stirred at r.t. for 72 h. The solvent was removed and the crude residue was chromatographed on silica gel (diethyl ether–petrol, 80 : 20) to yield the title compound as an oil, 256 mg (73%).

R_f 0.22 (UV active, diethyl ether–petrol, 80 : 20); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.49–7.23 (11H, m), 6.98 (2H, d, J = 6.3 Hz), 6.90 (1H, t, J = 8.0 Hz), 6.62 (1H, br s, OH), 5.82 (1H, d, J = 15.8 Hz), 5.34 (1H, t, J = 3.2, 2.9 Hz), 5.18 (1H, d, J = 15.8 Hz), 4.03–3.97 (1H, m), 3.78 (1H, d, J = 7.9 Hz), 3.03–2.97 (1H, m), 1.91–1.84 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$): 178.0, 174.2, 144.3, 139.2, 136.2, 135.8, 131.6, 129.5, 129.4, 129.0, 128.1, 127.3, 126.4, 122.3, 56.2, 50.0, 39.4, 38.4, 30.6; IR (neat): ν_{max}/cm^{-1} 2980, 2907, 2850, 1781, 1713, 1598, 1497, 1377, 748, 717, 691, 615; HRMS (ES-ToF): calcd for $C_{28}H_{22}Br_2N_4O_3$ $(M + H)^+$: 621.0131, found 621.0130; EA: calcd C: 54.04%, H: 3.56%, N: 9.00%, found C: 53.92%, H: 3.45%, N: 8.95%.

(4*R,5a*S**,8a*S**)-1-Benzyl-4,7-diphenyl-5,5a,7,8a-tetrahydroimidazo[4,5-*e*]isoindole-6,8(1*H*,4*H*)-dione (6d)**

To (5a*S**,8a*S**)-1-benzyl-7-phenyl-1,5,5a,8b-tetrahydroimidazo-[4,5-*e*]isoindole-6,8(7*H*,8a*H*)-dione (**5a**) (200 mg, 0.56 mmol) and trimethylsilylphenyl triflate (250 mg, 0.84 mmol, 204 μL) in dichloromethane (10 mL) was added tetra-butylammonium fluoride (1 M in THF, 219 mg, 0.84 mmol, 840 μL) and the solution heated at 40 °C for 2 h. The solvent was removed and the crude residue was chromatographed on silica gel (diethyl ether–petroleum ether 40–60, 50 : 50 → diethyl ether) to yield the title compound as a white solid, 165 mg (68%).

R_f 0.13 (UV active, diethyl ether); mp: 228–229 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.55 (1H, s), 7.47–7.45 (2H, m), 7.40–7.30 (6H, m), 7.29–7.19 (5H, m), 7.14–7.12 (2H, m), 5.77 (1H, d, J = 15.6 Hz), 5.32 (1H, d, J = 15.6 Hz), 4.08 (1H, dd, J = 8.1, 4.9 Hz), 3.94 (1H, d, J = 8.2 Hz), 3.38–3.33 (1H, m), 2.65–2.59 (1H, m), 2.17–2.10 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 177.1, 174.8, 142.1, 141.7, 139.4, 136.2, 131.6, 129.3, 129.2, 128.9, 128.7, 128.4, 128.2, 127.4, 127.0, 126.4, 119.9, 49.8, 39.5, 38.9, 38.8, 32.9; IR (neat): ν_{max}/cm^{-1} 3034, 2916, 2866, 1775, 1703, 1598, 1496, 734, 693; HRMS (ES-ToF): calcd for $C_{28}H_{23}N_3O_2$ $(M + H)^+$: 434.1863, found 434.1862.

(4*S,5a*S**,8a*S**)-1-Benzyl-4-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-7-phenyl-5,5a,7,8a-tetrahydroimidazo[4,5-*e*]isoindole-6,8-(1*H*,4*H*)-dione (6e)**

To (5a*S**,8a*S**)-1-benzyl-7-phenyl-1,5,5a,8b-tetrahydroimidazo-[4,5-*e*]isoindole-6,8(7*H*,8a*H*)-dione (**5a**) (200 mg, 0.56 mmol) in dichloromethane (7 mL) at −78 °C was added 4-phenyl-1,2,4-triazoline-3,5-dione (98 mg, 0.56 mmol) in dichloromethane (3 mL) dropwise, and the solution stirred for 1 h. The solvent was removed and the crude residue was chromatographed on silica gel (ethyl acetate 100%) to yield the title compound as a white solid, 220 mg (74%).

R_f 0.31 (UV active, ethyl acetate, 100%); mp: 173–174 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.44–7.26 (12H, m), 7.16 (2H, d,

J = 7.4 Hz), 7.07–7.05 (2H, m), 5.46 (1H, d, J = 15.4 Hz), 5.28 (1H, dd, J = 8.1, 5.4 Hz), 5.17 (1H, d, J = 15.4 Hz), 3.92 (1H, d, J = 8.2 Hz), 3.51–3.46 (1H, m), 2.63–2.57 (1H, m), 2.18–2.11 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 176.1, 174.1, 154.7, 153.6, 139.8, 135.4, 135.1, 131.4, 129.3, 129.3, 129.2, 129.0, 128.6, 128.3, 127.7, 126.5, 126.0, 122.2, 49.9, 49.6, 38.8, 38.3, 26.0; IR (neat): ν_{max}/cm^{-1} 3067, 1770, 1705, 1598, 1499, 862, 739, 692; HRMS (ES-ToF): calcd for $C_{30}H_{24}N_6O_4$ $(M + H)^+$: 533.1932, found 533.1923; EA: calcd C: 67.66%, H: 4.54%, N: 15.78%, found C: 67.73%, H: 4.58%, N: 15.59%.

Diethyl 2-((4*S,5a*S**,8a*S**)-1-benzyl-6,8-dioxo-7-phenyl-1,4,5,5a,6,7,8,8a-octahydroimidazo[4,5-*e*]isoindol-4-yl)-2-hydroxymalonate (6f)**

To (5a*S**,8a*S**)-1-benzyl-7-phenyl-1,5,5a,8b-tetrahydroimidazo-[4,5-*e*]isoindole-6,8(7*H*,8a*H*)-dione (**5a**) (230 mg, 0.64 mmol) in dichloromethane (6 mL) was added diethyl ketomalonate (134 mg, 0.77 mmol, 118 μL) and the solution stirred at r.t. for 16 h. The solvent was removed and the crude residue was chromatographed on silica gel (diethyl ether) to yield the title compound as a white solid, 283 mg (83%).

R_f 0.16 (UV active, diethyl ether); mp: 147–149 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.47–7.28 (7H, m), 7.24–7.23 (2H, m), 7.15–7.13 (2H, m), 5.61 (1H, d, J = 15.5 Hz), 5.28 (1H, d, J = 15.5 Hz), 4.46–4.22 (4H, m), 4.13 (1H, s, OH), 3.92 (1H, dd, J = 8.4, 1.3 Hz), 3.85 (1H, dd, J = 9.9, 4.5 Hz), 3.56–3.52 (1H, m), 2.39 (1H, dt, J = 13.4, 4.6 Hz), 2.08–2.00 (1H, m), 1.34–1.31 (6H, m); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 177.1, 175.1, 170.3, 169.6, 138.9, 137.9, 136.0, 131.8, 129.5, 129.4, 129.1, 128.5, 127.8, 126.6, 120.8, 80.8, 63.2, 63.1, 49.9, 40.1, 38.7, 37.4, 24.3, 14.4, 14.3; IR (neat): ν_{max}/cm^{-1} 3481, 2982, 2967, 1783, 1711, 1734, 1597, 1499, 1380, 1249, 1029, 1185, 737, 690; HRMS (ES-ToF): calcd for $C_{29}H_{29}N_3O_7$ $(M + H)^+$: 532.2078, found 532.2071.

(5*S,5a*S**,8a*S**)-1-Benzyl-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-7-phenyl-1,5,5a,8b-tetrahydroimidazo[4,5-*e*]isoindole-6,8(7*H*,8a*H*)-dione (5b)**

To (*E*)-1-benzyl-4-(3-(*tert*-butyldimethylsilyloxy)prop-1-enyl)-1*H*-imidazole (772 mg, 2.35 mmol) in dichloromethane (23.5 mL) was added *N*-phenylmaleimide (1.02 g, 5.87 mmol) and the solution stirred at 50 °C for 16 h. The solvent was removed and the crude residue was chromatographed on silica gel (petroleum ether 40–60–ethyl acetate, 25 : 75) to yield the title compound as a white solid, 802 mg (68%).

R_f 0.32 (UV active, petroleum ether 40–60–ethyl acetate, 25 : 75); mp: 199–201 °C (lit.[6b] mp: 203–204 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.46–7.33 (7H, m), 7.31–7.29 (2H, m), 7.12–7.10 (2H, m), 5.44 (1H, dd, J = 4.1, 4.1 Hz), 4.91 (1H, d, J = 15.2 Hz), 4.80 (1H, d, J = 15.2 Hz), 4.35 (1H, dd, J = 9.6, 8.9 Hz), 4.06–4.01 (2H, m), 3.62 (1H, t, J = 8.4 Hz), 3.35 (1H, dd, J = 8.5, 4.9 Hz), 2.24–2.15 (1H, m), 0.89 (9H, s), 0.09 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 175.8, 173.9, 159.9, 154.4, 135.5, 134.4, 131.8, 129.4, 129.0, 128.6, 128.3, 126.9, 105.1, 63.1, 57.8, 50.3, 41.9, 41.8, 38.2, 26.2, 18.6, −5.0, −5.1; IR (neat): ν_{max}/cm^{-1} 2951, 2927, 2855, 1772, 1703, 1541, 1498, 837, 777, 692; HRMS (ES-ToF): calcd for $C_{29}H_{35}N_3O_3Si$ $(M + H)^+$: 502.2520, found 502.2517.

(4*S,5*R**,5a*S**,8a*S**)-1-Benzyl-5-(((*tert*-butyldimethylsilyl)oxy)-methyl)-4-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-7-phenyl-5,5a,7,8a-tetrahydroimidazo[4,5-*e*]isoindole-6,8(1*H*,4*H*)-dione (6g)**

To (5*S**,5a*S**,8a*S**)-1-benzyl-5-(((*tert*-butyldimethylsilyl)oxy)-methyl)-7-phenyl-1,5,5a,8b-tetrahydroimidazo[4,5-*e*]isoindole-6,8-(7*H*,8a*H*)-dione (**5b**) (250 mg, 0.50 mmol) in dichloromethane (5 mL) at −78 °C was added dropwise 1,2,4-phenyltriazoline-3,5-dione (87 mg, 0.50 mmol) in dichloromethane (5 mL), and the solution stirred for 1 h. The solvent was removed and the crude residue was chromatographed on silica gel (eluting with diethyl ether–methanol, 98 : 2) to yield the major diastereoisomer as an orange solid, 206 mg (61%).

R_f 0.37 (UV active, diethyl ether–methanol, 95 : 5); mp: 147–148 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.57–7.37 (12H, m), 7.22–7.18 (3H, m), 5.63 (1H, d, J = 15.4 Hz), 5.35–5.32 (1H, m), 5.29 (1H, d, J = 15.4 Hz), 4.37 (1H, dd, J = 10.5, 6.2 Hz), 4.12 (1H, dd, J = 10.5, 6.2 Hz), 3.99 (1H, d, J = 8.1 Hz), 3.83 (1H, dd, J = 8.1, 4.5 Hz), 2.52–2.45 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$): 175.1, 174.0, 154.8, 154.0, 140.2, 136.0, 135.5, 131.6, 131.5, 129.4, 129.4 129.3, 129.1, 128.7, 128.5, 127.8, 126.5, 126.2, 122.5, 62.7, 52.9, 50.1, 42.4, 40.7, 39.5, 26.2, 18.6, −5.2, −5.3; IR: ν_{max}/cm^{-1} 3067, 2930, 2857, 1771, 1712, 1600, 1500, 1380, 836, 778, 705, 690; HRMS (ES-ToF): calcd for $C_{37}H_{40}N_6O_5Si$ $(M + H)^+$: 677.2902, found 677.2899.

(4*S,5*R**,5a*S**,8a*S**)-Diethyl 2-(1-benzyl-5-(((*tert*-butyldimethylsilyl)-oxy)methyl)-6,8-dioxo-7-phenyl-1,4,5,5a,6,7,8,8a-octahydroimidazo-[4,5-*e*]isoindol-4-yl)-2-hydroxymalonate (6h)**

To (5*S**,5a*S**,8a*S**)-1-benzyl-5-(((*tert*-butyldimethylsilyl)oxy)-methyl)-7-phenyl-1,5,5a,8b-tetrahydroimidazo[4,5-*e*]isoindole-6,8-(7*H*,8a*H*)-dione (**7b**) (250 mg, 0.50 mmol) in dichloromethane (18 mL) was added diethyl ketomalonate (87 mg, 76 μL, 0.50 mmol) and the solution stirred at r.t. for 16 h. The solvent was removed and the crude residue was chromatographed on silica gel (diethyl ether–petroleum ether 40–60, 60 : 40) to yield the title compound as a white solid, 175 mg (65%).

R_f 0.22 (UV active, diethyl ether–petroleum ether, 25 : 75); mp: 112–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.45–7.25 (9H, m), 7.06–7.04 (2H, m), 5.70 (1H, d, J = 15.6 Hz), 5.32 (1H, d, J = 15.6 Hz), 4.43–4.36 (2H, m), 4.29 (2H, q, J = 7.2 Hz), 4.03 (1H, s), 3.97 (1H, dd, J = 8.6, 6.5 Hz), 3.84 (1H, br s), 3.77–3.71 (3H, m), 2.75–2.71 (1H, m), 1.36 (3H, t, J = 7.2 Hz), 1.31 (3H, t, J = 7.2 Hz), 0.72 (9H, s), −0.10 (3H, s), −0.18 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$): 176.9, 174.9, 170.6, 169.5, 138.6, 136.4, 135.7, 132.2, 129.4, 129.3, 128.9, 128.4, 127.5, 126.7, 122.2, 82.6, 66.2, 64.9, 63.6, 62.8, 50.1, 41.9, 41.7, 39.9, 38.6, 26.1, 18.6, 15.6, 14.4, 14.3, −5.4; IR (neat): ν_{max}/cm^{-1} 3474, 2988, 2941, 1711, 1597, 1498, 1381, 1284, 1225, 1248, 1029, 1185, 740, 691; HRMS (ES-ToF): calcd for $C_{36}H_{45}N_3O_8Si$ $(M + H)^+$: 676.3049, found 676.3042; EA: calcd C: 63.98%, H: 6.71%, N: 6.22%, found C: 63.99%, H: 6.65%, N: 6.12%.

(*R)-Ethyl 2-((4*S**,5a*S**,8a*S**)-1-benzyl-6,8-dioxo-7-phenyl-1,4,5,5a,6,7,8,8a-octahydroimidazo[4,5-*e*]isoindol-4-yl)-2-hydroxyacetate (7a) and (*S**)-ethyl 2-((4*S**,5a*S**,8a*S**)-1-benzyl-6,8-dioxo-7-phenyl-1,4,5,5a,6,7,8,8a-octahydroimidazo[4,5-*e*]isoindol-4-yl)-2-hydroxyacetate (8a)**

To (5a*S**,8a*S**)-1-benzyl-7-phenyl-1,5,5a,8b-tetrahydroimidazo-[4,5-*e*]isoindole-6,8(7*H*,8a*H*)-dione (**5a**) (200 mg, 0.56 mmol) in dichloromethane (5 mL) was added ethyl glyoxalate (50% in toluene, 0.14 mmol, 0.67 mL) and the solution stirred at r.t. for 30 h. The solvent was removed and the crude residue was chromatographed on silica gel (ethyl acetate–methanol, 95 : 5) to yield the major diastereomer **7a** as a white solid, 154 mg (60%), and the minor diastereomer **8a** as a white solid, 32 mg (12%).

Major diastereomer

(*S)-Ethyl 2-((4*S**,5a*S**,8a*S**)-1-benzyl-6,8-dioxo-7-phenyl-1,4,5,5a,6,7,8,8a-octahydroimidazo[4,5-*e*]isoindol-4-yl)-2-hydroxyacetate (7a).** R_f 0.18 (UV active, ethyl acetate–methanol, 95 : 5); mp: 80–82 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.47–7.43 (3H, m), 7.40–7.32 (4H, m), 7.25–7.21 (2H, m), 7.16–7.14 (2H, m), 5.64 (1H, d, J = 15.5 Hz), 5.28 (1H, d, J = 15.5 Hz), 4.38 (1H, dq, J = 10.7, 7.1 Hz), 4.33–4.24 (2H, m), 4.08 (1H, br s), 3.92 (1H, dd, J = 8.4, 1.0 Hz), 3.56–3.52 (1H, m), 3.29–3.24 (1H, m), 2.53 (1H, dt, J = 13.6, 4.6 Hz), 1.97 (1H, ddd, J = 13.7, 10.4, 5.6 Hz), 1.32 (3H, t, J = 7.2 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 177.1, 175.1, 173.3, 139.1, 139.0, 136.0, 131.8, 129.5, 129.5, 129.2, 128.7, 127.8, 126.7, 120.6, 73.6, 62.1, 50.0, 40.2, 38.8, 35.6, 26.3, 14.6; IR: ν_{max}/cm^{-1} 2935, 1709, 1597, 1497, 1383, 1187, 724, 693; HRMS (ES-ToF): calcd for $C_{26}H_{24}N_3O_5$ $(M + H)^+$: 460.1867, found 460.1862.

Minor diastereomer

(*R)-Ethyl 2-((4*S**,5a*S**,8a*S**)-1-benzyl-6,8-dioxo-7-phenyl-1,4,5,5a,6,7,8,8a-octahydroimidazo[4,5-*e*]isoindol-4-yl)-2-hydroxyacetate (8a).** R_f 0.10 (UV active, ethyl acetate–methanol, 95 : 5); mp: 198–199 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.52 (1H, s), 7.47–7.43 (2H, m), 7.40–7.32 (4H, m), 7.21–7.16 (4H, m), 5.62 (1H, d, J = 15.4 Hz), 5.31 (1H, d, J = 15.4 Hz), 5.02 (1H, br s), 4.33 (1H, dq, J = 10.6, 7.1 Hz), 4.22 (1H, dq, J = 10.6, 7.1 Hz), 3.95 (1H, d, J = 8.4 Hz), 3.68 (1H, br s), 3.54–3.49 (1H, m), 3.28–3.25 (1H, m), 2.28 (1H, dt, J = 13.5, 4.2 Hz), 1.98 (1H, ddd, J = 13.5, 10.6, 5.5 Hz), 1.30 (3H, t, J = 7.1 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 177.1, 175.1, 174.0, 139.4, 139.2, 136.0, 131.8, 129.6, 129.4, 129.2, 128.6, 127.9, 126.7, 120.5, 70.9, 62.1, 50.0, 40.2, 38.9, 35.8, 22.6, 14.6; IR (neat): ν_{max}/cm^{-1} 2933, 1743, 1712, 1597, 1495, 1383, 1190, 726, 691; HRMS (ES-ToF): calcd for $C_{26}H_{26}N_3O_5$ $(M + H)^+$: 460.1867, found 460.1865.

Ethyl 2-((5*S,5a*S**,8a*S**)-1-benzyl-5-(((*tert*-butyldimethylsilyl)-oxy)methyl)-6,8-dioxo-7-phenyl-1,4,5,5a,6,7,8,8a-octahydroimidazo-[4,5-*e*]isoindol-4-yl)-2-hydroxyacetate (7b).** To (5*S**,5a*S**,8a*S**)-1-benzyl-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-7-phenyl-1,5,5a,8b-tetrahydroimidazo[4,5-*e*]isoindole-6,8(7*H*,8a*H*)-dione (**5b**) (200 mg, 0.40 mmol) in dichloromethane (6 mL) was added ethyl glyoxalate (50% in toluene, 0.48 mmol, 98 μL) and the solution stirred at r.t. for 16 h. The solvent was removed and the crude residue was chromatographed on silica gel (diethyl ether) to yield the title compound as a white solid, 142 mg (59%). *NB: only one diastereomer was observed.*

R_f 0.23 (UV active, diethyl ether); mp: 76–78 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.48–7.44 (3H, m), 7.40–7.29 (4H, m), 7.24–7.22 (2H, m), 7.13–7.11 (2H, m), 5.64 (1H, d, J = 15.5 Hz), 5.27 (1H, d, J = 15.5 Hz), 4.45 (1H, dd, J = 6.4, 2.5 Hz), 4.40 (1H, dq, J = 10.7, 7.1 Hz), 4.33 (1H, dq, J = 10.7, 7.1 Hz), 4.13 (1H, dd, J = 9.8, 7.3 Hz), 3.96–3.91 (2H, m), 3.85 (1H, d, J = 8.2 Hz), 3.51–3.49 (1H, m), 2.98 (1H, d, J = 6.4 Hz), 2.58–2.52 (1H, m), 1.34 (3H, t, J = 7.1 Hz), 0.84 (9H, s), 0.02 (3H, s), 0.00 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 176.2, 174.9, 174.1, 139.3, 136.3, 134.0, 131.9, 129.6, 129.4, 129.1, 128.5, 127.3, 126.6, 122.5, 64.6, 62.6, 50.3, 41.5, 39.0, 38.9, 38.1, 26.0, 18.5, 14.2, −5.3, −5.4; IR (neat): ν_{max}/cm^{-1} 2953, 2929, 2857, 1782, 1714, 1498, 1377, 1252, 1191, 1099, 836, 778, 691; HRMS (ES-ToF): calcd for $C_{33}H_{41}N_3O_6Si$ $(M + H)^+$: 604.2837, found 604.2822.

(*S)-Ethyl 2-((4*S**,5a*S**,8a*S**)-1-benzyl-6,8-dioxo-7-phenyl-1,4,5,5a,6,7,8,8a-octahydroimidazo[4,5-*e*]isoindol-4-yl)-3,3,3-trifluoro-2-hydroxypropanoate (7c).** To (5a*S**,8a*S**)-1-benzyl-7-phenyl-1,5,5a,8b-tetrahydroimidazo[4,5-*e*]isoindole-6,8(7*H*,8a*H*)-dione (**5a**) (90 mg, 0.25 mmol) in dichloromethane (2 mL) was added ethyl trifluoropyruvate (64 mg, 0.38 mmol, 50 μL) and the solution stirred at r.t. for 16 h. The solvent was removed and the crude residue was chromatographed on silica gel (diethyl ether–petroleum ether 40–60, 60 : 40) to yield the title compound as a white solid, 70 mg (53%). *NB: only one diastereomer was observed.*

R_f 0.77 (UV active, ethyl acetate–petroleum ether 40–60, 2 : 1); mp: 174–175 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.47–7.43 (2H, m), 7.40–7.31 (5H, m), 7.25–7.23 (2H, m), 7.12–7.11 (2H, m), 5.65 (1H, d, J = 15.5 Hz), 5.28 (1H, d, J = 15.5 Hz), 4.52 (1H, dqd, J = 10.6, 7.1, 1.4 Hz), 4.37 (1H, dqd, J = 10.6, 7.1, 1.4 Hz), 4.02 (1H, d, J = 1.0 Hz), 3.90 (1H, d, J = 8.2 Hz), 3.67 (1H, dd, J = 9.2, 5.0 Hz), 3.62–3.57 (1H, m), 2.61–2.55 (1H, m), 2.23–2.16 (1H, m), 1.36 (3H, dt, J = 7.1, 1.4 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 176.9, 174.9, 169.9, 138.9, 136.6, 136.0, 131.8, 129.5, 129.5, 129.1, 128.6, 127.8, 126.6, 125.0 (q, J = 287.8 Hz), 121.5, 78.7 (q, J = 28.1 Hz), 64.3, 50.0, 39.9, 38.7, 35.4, 23.9, 14.2; ^{19}F NMR (376 MHz, $CDCl_3$): δ_F −73.37; IR (neat): ν_{max}/cm^{-1} 3651, 2982, 1705, 1596, 1497, 1375, 1172, 739, 694; HRMS (ES-ToF): calcd for $C_{27}H_{24}F_3N_3O_5$ $(M + H)^+$: 528.1741, found 528.1731; EA: calcd C: 61.48%, H: 4.59%, N: 7.97%, found C: 61.59%, H: 4.52%, N: 7.90%.

(*S)-Ethyl 2-((4*S**,5*S**,5a*S**,8a*S**)-1-benzyl-5-(((*tert*-butyl-dimethylsilyl)oxy)methyl)-6,8-dioxo-7-phenyl-1,4,5,5a,6,7,8,8a-octa-hydroimidazo[4,5-*e*]isoindol-4-yl)-3,3,3-trifluoro-2-hydroxypropanoate (7d) and (2*R**)-ethyl 2-((5a*S**,8a*S**)-1-benzyl-5-(((*tert*-butyldi-methylsilyl)oxy)methyl)-6,8-dioxo-7-phenyl-1,4,5,5a,6,7,8,8a-octa-hydroimidazo[4,5-*e*]isoindol-4-yl)-3,3,3-trifluoro-2-hydroxy-propanoate (8d).** To (5*S**,5a*S**,8a*S**)-1-benzyl-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-7-phenyl-1,5,5a,8b-tetrahydro-imidazo[4,5-*e*]isoindole-6,8(7*H*,8a*H*)-dione (**5b**) (400 mg,

0.80 mmol) in dichloromethane (6 mL) was added ethyl trifluoropyruvate (162 mg, 0.12 mL, 0.96 mmol) and the solution stirred at r.t. for 72 h. The solvent was removed and the crude residue was chromatographed on silica gel (diethyl ether–petrol, 40 : 60) to yield the major diastereoisomer **7d** as pale yellow crystals, 196 mg (36%), and the minor diastereoisomer **8d** as a white solid, 92 mg (17%).

Major diastereomer

(*S)-Ethyl 2-((4*S**,5*S**,5a*S**,8a*S**)-1-benzyl-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-6,8-dioxo-7-phenyl-1,4,5,5a,6,7,8,8a-octahydroimidazo[4,5-*e*]isoindol-4-yl)-3,3,3-trifluoro-2-hydroxypropanoate (7d).** R_f 0.30 (UV active, diethyl ether–petrol, 50 : 50); mp: 176–178 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.49–7.31 (7H, m), 7.25–7.23 (2H, m), 7.03–7.01 (2H, m), 5.80 (1H, d, J = 15.7 Hz), 5.33 (1H, d, J = 15.7 Hz), 4.55–4.43 (2H, m), 4.04 (1H, s), 3.96 (1H, dd, J = 8.6, 6.1 Hz), 3.78 (1H, br s), 3.71 (1H, d, J = 8.6 Hz), 3.61 (1H, dd, J = 10.1, 4.5 Hz), 3.44 (1H, dd, J = 10.1, 8.4 Hz), 3.10–3.06 (1H, m), 1.45 (3H, t, J = 7.2 Hz), 0.80 (9H, s), −0.09 (3H, s), −0.10 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 176.2, 174.9, 169.9, 139.3, 136.3, 134.0, 131.9, 129.6, 129.4, 129.1, 128.5, 127.3, 126.6, 122.5, 64.6, 62.6, 50.3, 41.5, 39.0, 38.9, 38.1, 26.0, 18.5, 14.2, −5.3, −5.4; ^{19}F NMR (376 MHz, $CDCl_3$): δ_F −72.62; IR (neat): ν_{max}/cm^{-1} 3435, 2949, 2935, 2865, 1749, 1781, 1712, 1598, 1498, 1374, 1244, 1027, 1158, 1149, 1098, 836, 775, 689; HRMS (ES-ToF): calcd for $C_{34}H_{40}F_3N_3O_6Si$ $(M + H)^+$: 672.2711, found 672.2705.

Minor diastereomer

(*R)-Ethyl 2-((4*S**,5*S**,5a*S**,8a*S**)-1-benzyl-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-6,8-dioxo-7-phenyl-1,4,5,5a,6,7,8,8a-octahydroimidazo[4,5-*e*]isoindol-4-yl)-3,3,3-trifluoro-2-hydroxypropanoate (8d).** R_f 0.15 (UV active, diethyl ether–petrol, 50 : 50); mp: 113–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.57 (1H, s), 7.48–7.30 (6H, m), 7.23–7.21 (2H, m), 7.05–7.04 (2H, m), 5.85 (1H, d, J = 15.8 Hz), 5.36 (1H, d, J = 15.8 Hz), 4.69 (1H, s), 4.37 (1H, dq, J = 10.7, 7.2 Hz), 4.29 (dq, J = 10.7, 7.2 Hz), 3.92 (1H, s), 3.88 (1H, dd, J = 8.7, 6.4 Hz), 3.75 (1H, d, J = 8.7 Hz), 3.58 (1H, dd, J = 10.2, 4.2 Hz), 3.48 (1H, dd, J = 10.2, 7.5 Hz), 2.63–2.58 (1H, m), 1.32 (3H, t, J = 7.2 Hz), 0.76 (9H, s), −0.10 (3H, s), −0.14 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 176.0, 174.5, 169.7, 139.3, 136.3, 133.8, 131.8, 129.5, 129.4, 129.1, 128.4, 127.2, 126.5, 123.1 (q, J = 287.4 Hz), 121.7, 80.9 (q, J = 28.7 Hz), 64.1, 63.1, 50.4, 41.5, 39.9, 38.4, 38.2, 26.0, 18.5, 14.2, −5.4, −5.5; ^{19}F NMR (376 MHz, $CDCl_3$): δ_F −73.26; IR (neat): ν_{max}/cm^{-1} 3476, 3067, 2954, 2858, 1378, 1250, 1027, 1161, 1143, 836, 745, 692.

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15 Crystallographic data for **7c** are of low quality due to weak scattering and suspected but unresolved twinning; however, they are sufficient for the determination of the relative stereochemistry of the compound.

Appendix 3 – X-ray Crystallography Data

Compound 168

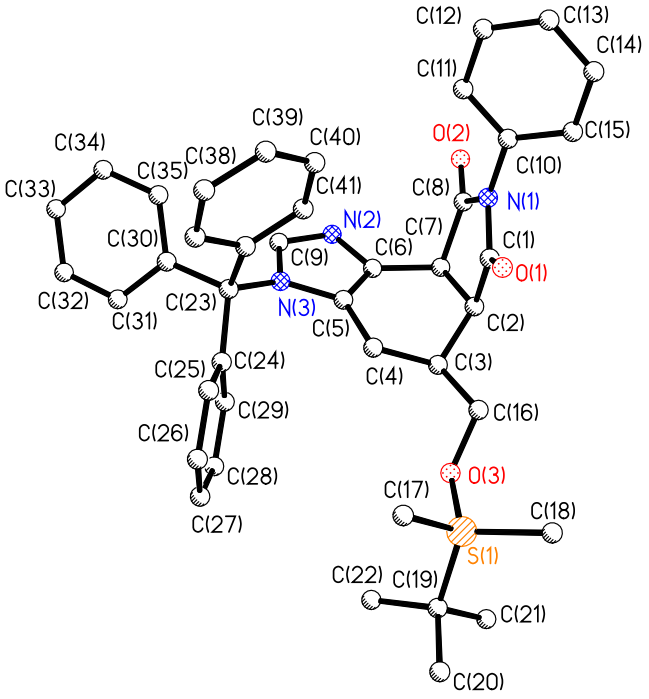

Table 1. Crystal data and structure refinement for **168**.

Identification code	**168**	
Chemical formula (moiety)	$C_{41}H_{43}N_3O_3Si \cdot C_4H_{10}O$	
Chemical formula (total)	$C_{45}H_{53}N_3O_4Si$	
Formula weight	727.99	
Temperature	293(2) K	
Radiation, wavelength	CuKα, 1.54184 Å	
Crystal system, space group	monoclinic, $P12_11$	
Unit cell parameters	a = 14.6807(3) Å	α = 90°
	b = 9.97200(13) Å	β = 113.381(3)°
	c = 15.8925(4) Å	γ = 90°
Cell volume	2135.56(7) $Å^3$	
Z	2	
Calculated density	1.132 g/cm^3	
Absorption coefficient μ	0.823 mm^{-1}	
F(000)	780	

Crystal colour and size	colourless, $0.32 \times 0.18 \times 0.04$ mm^3
Reflections for cell refinement	8935 (θ range 3.0 to 62.3°)
Data collection method	Xcalibur, Atlas, Gemini ultra thick-slice ω scans
θ range for data collection	3.0 to 62.4°
Index ranges	h −16 to 15, k −11 to 11, l −17 to 18
Completeness to θ = 62.4°	98.7 %
Reflections collected	15857
Independent reflections	6621 (R_{int} = 0.0332)
Reflections with $F^2>2\sigma$	5765
Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.7787 and 0.9678
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0947, 0.0000
Data / restraints / parameters	6621 / 5 / 484
Final R indices [$F^2>2\sigma$]	R1 = 0.0472, wR2 = 0.1264
R indices (all data)	R1 = 0.0554, wR2 = 0.1321
Goodness-of-fit on F^2	1.042
Absolute structure parameter	0.03(4)
Extinction coefficient	0.0016(3)
Largest and mean shift/su	0.012 and 0.001
Largest diff. peak and hole	0.70 and −0.19 e Å^{-3}

Compound 175

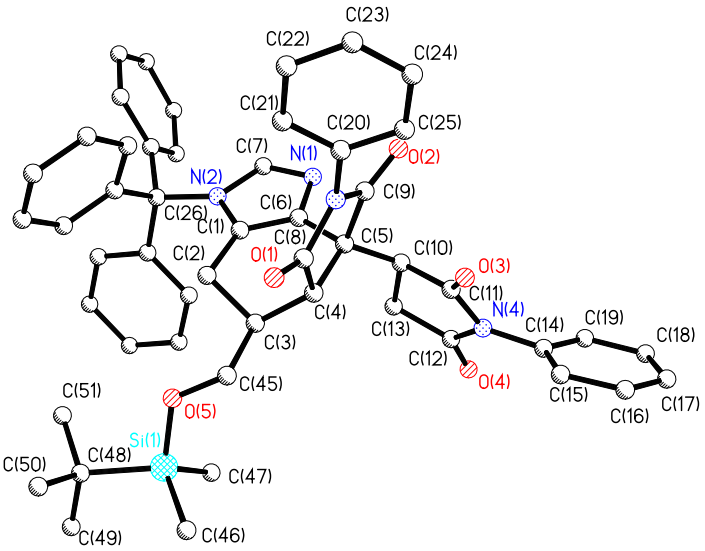

Table 1. Crystal data and structure refinement for **175**.

Identification code	**175**	
Chemical formula (moiety)	$C_{52}H_{54}N_4O_6Si$	
Chemical formula (total)	$C_{52}H_{54}N_4O_6Si$	
Formula weight	859.08	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	monoclinic, $P12_1/n1$	
Unit cell parameters	a = 10.3512(5) Å	α = 90°
	b = 13.8355(6) Å	β = 97.070(4)°
	c = 32.1240(16) Å	γ = 90°
Cell volume	4565.6(4) $Å^3$	
Z	4	
Calculated density	1.250 g/cm^3	
Absorption coefficient μ	0.106 mm^{-1}	
F(000)	1824	
Crystal colour and size	colourless, 0.22 × 0.18 × 0.18 mm^3	
Reflections for cell refinement	12710 (θ range 2.9 to 29.6°)	
Data collection method	Oxford Diffraction Gemini A Ultra diffractometer	
	thick-slice ω scans	
θ range for data collection	2.9 to 25.0°	
Index ranges	h –12 to 12, k –16 to 16, l –38 to 35	

Completeness to $\theta = 25.0°$	99.8 %
Reflections collected	41400
Independent reflections	8043 ($R_{int} = 0.0638$)
Reflections with $F^2>2\sigma$	5447
Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.9770 and 0.9811
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0600, 0.6088
Data / restraints / parameters	8043 / 0 / 578
Final R indices [$F^2>2\sigma$]	R1 = 0.0499, wR2 = 0.1165
R indices (all data)	R1 = 0.0796, wR2 = 0.1228
Goodness-of-fit on F^2	1.039
Largest and mean shift/su	0.001 and 0.000
Largest diff. peak and hole	0.35 and −0.31 e $Å^{-3}$

Compound 180

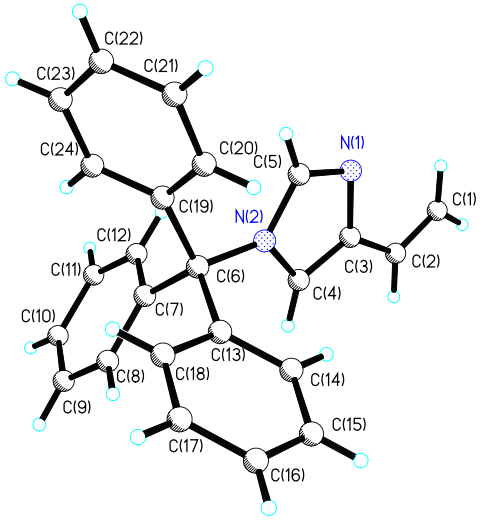

Table 1. Crystal data and structure refinement for **180**.

Identification code	**180**	
Chemical formula (moiety)	$C_{24}H_{20}N_2$	
Chemical formula (total)	$C_{24}H_{20}N_2$	
Formula weight	336.42	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	monoclinic, $P2_1$	
Unit cell parameters	a = 7.2450(4) Å	α = 90°
	b = 10.7383(7) Å	β = 98.399(6)°
	c = 11.5383(6) Å	γ = 90°
Cell volume	888.04(9) $Å^3$	
Z	2	
Calculated density	1.258 g/cm^3	
Absorption coefficient μ	0.074 mm^{-1}	
F(000)	356	
Crystal colour and size	colourless, 0.15 × 0.10 × 0.10 mm^3	
Reflections for cell refinement	3901 (θ range 2.8 to 28.4°)	
Data collection method	Oxford Diffraction Gemini A Ultra diffractometer	
	thick-slice ω scans	
θ range for data collection	2.8 to 28.5°	
Index ranges	h –9 to 9, k –13 to 13, l –14 to 15	
Completeness to θ = 26.0°	98.7 %	

Reflections collected	6989
Independent reflections	3192 (R_{int} = 0.0531)
Reflections with $F^2>2\sigma$	2532
Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.9890 and 0.9927
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.1008, 0.0000
Data / restraints / parameters	3192 / 1 / 235
Final R indices [$F^2>2\sigma$]	R1 = 0.0557, wR2 = 0.1571
R indices (all data)	R1 = 0.0690, wR2 = 0.1610
Goodness-of-fit on F^2	1.063
Absolute structure parameter	0(5)
Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	0.32 and −0.23 e $Å^{-3}$

Compound 186

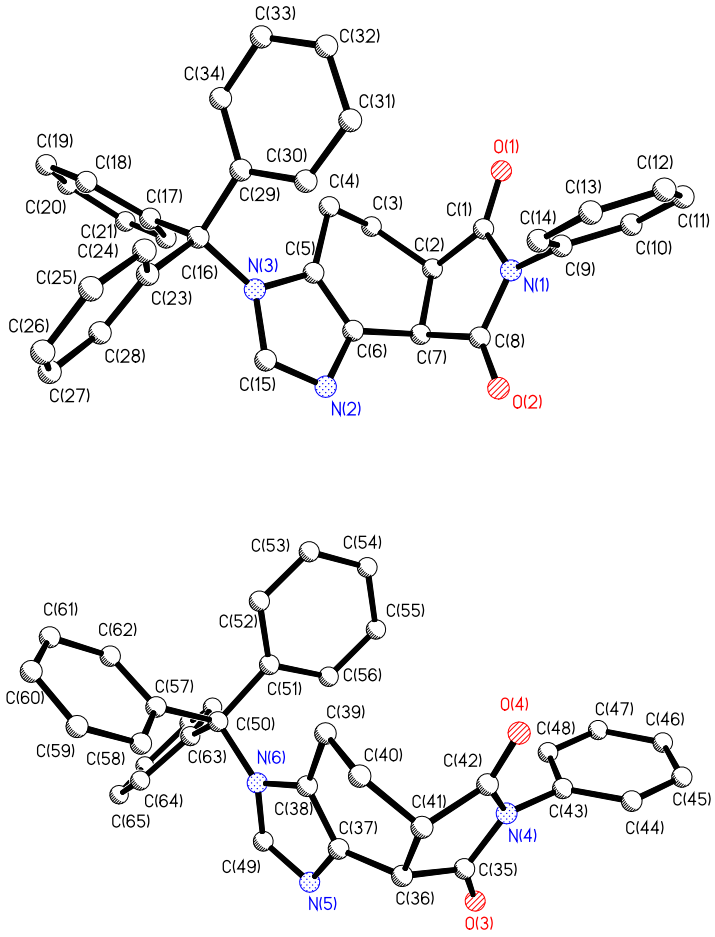

Table 1. Crystal data and structure refinement for **186**.

Identification code	**186**	
Chemical formula (moiety)	$C_{34}H_{27}N_3O_2$	
Chemical formula (total)	$C_{34}H_{27}N_3O_2$	
Formula weight	509.59	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	triclinic, $P\bar{1}$	
Unit cell parameters	a = 10.3238(5) Å	α = 91.145(4)°
	b = 15.5018(7) Å	β = 100.369(4)°
	c = 16.2068(8) Å	γ = 96.303(4)°
Cell volume	2533.8(2) $Å^3$	
Z	4	
Calculated density	1.336 g/cm^3	
Absorption coefficient μ	0.084 mm^{-1}	

F(000)	1072
Crystal colour and size	colourless, 0.34 × 0.30 × 0.30 mm^3
Reflections for cell refinement	6725 (θ range 2.8 to 28.5°)
Data collection method	Oxford Diffraction Gemini A Ultra diffractometer thick-slice ω scans
θ range for data collection	2.8 to 25.0°
Index ranges	h −11 to 12, k −17 to 18, l −19 to 19
Completeness to θ = 25.0°	99.8 %
Reflections collected	22724
Independent reflections	8906 (R_{int} = 0.0448)
Reflections with $F^2>2\sigma$	5341
Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.9720 and 0.9753
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0363, 0.0000
Data / restraints / parameters	8906 / 0 / 704
Final R indices [$F^2>2\sigma$]	R1 = 0.0392, wR2 = 0.0757
R indices (all data)	R1 = 0.0795, wR2 = 0.0819
Goodness-of-fit on F^2	0.845
Extinction coefficient	0.0055(4)
Largest and mean shift/su	0.001 and 0.000
Largest diff. peak and hole	0.24 and −0.18 e $Å^{-3}$

Compound 185

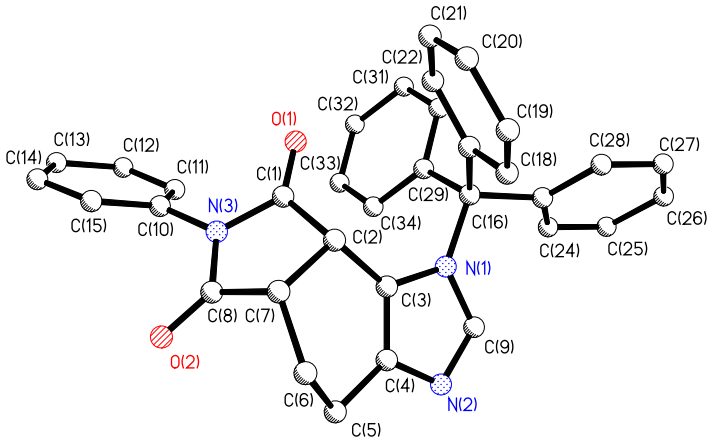

Table 1. Crystal data and structure refinement for **185**.

Identification code	**185**	
Chemical formula (moiety)	$C_{34}H_{27}N_3O_2$	
Chemical formula (total)	$C_{34}H_{27}N_3O_2$	
Formula weight	509.59	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	monoclinic, $P12_1/n1$	
Unit cell parameters	a = 10.8387(7) Å	α = 90°
	b = 13.4389(6) Å	β = 101.608(5)°
	c = 17.5331(9) Å	γ = 90°
Cell volume	2501.6(2) $Å^3$	
Z	4	
Calculated density	1.353 g/cm^3	
Absorption coefficient μ	0.085 mm^{-1}	
F(000)	1072	
Crystal colour and size	colourles, 0.12 × 0.10 × 0.10 mm^3	
Reflections for cell refinement	5320 (θ range 2.8 to 29.5°)	
Data collection method	Oxford Diffraction Gemini A Ultra diffractometer	
	thick-slice ω scans	
θ range for data collection	2.8 to 25.0°	
Index ranges	h –11 to 12, k –15 to 15, l –20 to 20	
Completeness to θ = 25.0°	99.9 %	
Reflections collected	24538	
Independent reflections	4401 (R_{int} = 0.0615)	

Reflections with $F^2>2\sigma$	2546
Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.9899 and 0.9915
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0280, 0.0000
Data / restraints / parameters	4401 / 0 / 353
Final R indices [$F^2>2\sigma$]	R1 = 0.0338, wR2 = 0.0590
R indices (all data)	R1 = 0.0756, wR2 = 0.0635
Goodness-of-fit on F^2	0.794
Extinction coefficient	0.0049(3)
Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	0.17 and –0.13 e $Å^{-3}$

Compound 186

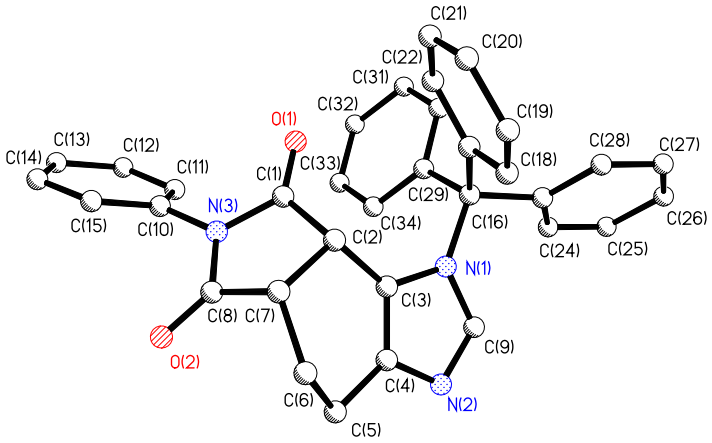

Table 1. Crystal data and structure refinement for **186**.

Identification code	**186**	
Chemical formula (moiety)	$C_{34}H_{27}N_3O_2$	
Chemical formula (total)	$C_{34}H_{27}N_3O_2$	
Formula weight	509.59	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	monoclinic, $P12_1/n1$	
Unit cell parameters	a = 10.8387(7) Å	α = 90°
	b = 13.4389(6) Å	β = 101.608(5)°
	c = 17.5331(9) Å	γ = 90°
Cell volume	2501.6(2) $Å^3$	
Z	4	
Calculated density	1.353 g/cm^3	
Absorption coefficient μ	0.085 mm^{-1}	
F(000)	1072	
Crystal colour and size	colourles, 0.12 × 0.10 × 0.10 mm^3	
Reflections for cell refinement	5320 (θ range 2.8 to 29.5°)	
Data collection method	Oxford Diffraction Gemini A Ultra diffractometer	
	thick-slice ω scans	
θ range for data collection	2.8 to 25.0°	
Index ranges	h –11 to 12, k –15 to 15, l –20 to 20	
Completeness to θ = 25.0°	99.9 %	
Reflections collected	24538	
Independent reflections	4401 (R_{int} = 0.0615)	

Reflections with $F^2>2\sigma$	2546
Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.9899 and 0.9915
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0280, 0.0000
Data / restraints / parameters	4401 / 0 / 353
Final R indices [$F^2>2\sigma$]	R1 = 0.0338, wR2 = 0.0590
R indices (all data)	R1 = 0.0756, wR2 = 0.0635
Goodness-of-fit on F^2	0.794
Extinction coefficient	0.0049(3)
Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	0.17 and –0.13 e $Å^{-3}$

Compound 200c

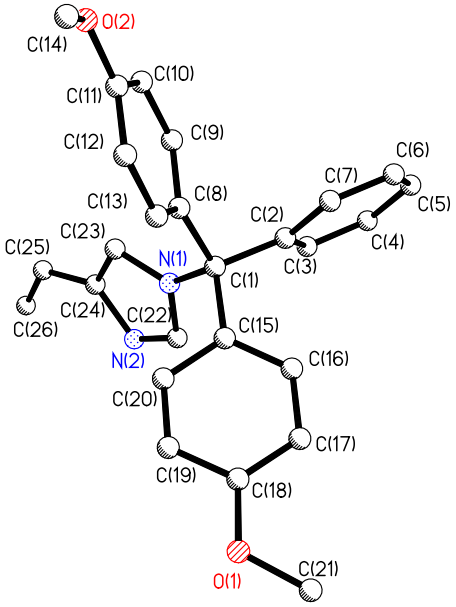

Table 1. Crystal data and structure refinement for **200c**.

Identification code	**200c**	
Chemical formula (moiety)	$C_{26}H_{24}N_2O_2$	
Chemical formula (total)	$C_{26}H_{24}N_2O_2$	
Formula weight	396.47	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	monoclinic, $P12_1/c1$	
Unit cell parameters	a = 10.0468(6) Å	α = 90°
	b = 17.9557(9) Å	β = 103.769(6)°
	c = 11.9078(6) Å	γ = 90°
Cell volume	2086.40(19) $Å^3$	
Z	4	
Calculated density	1.262 g/cm^3	
Absorption coefficient μ	0.080 mm^{-1}	
F(000)	840	
Reflections for cell refinement	2905 (θ range 2.9 to 29.7°)	
Data collection method	Xcalibur, Atlas, Gemini ultra	
	thick-slice ω scans	
θ range for data collection	2.9 to 29.7°	
Index ranges	h –13 to 12, k –25 to 23, l –11 to 16	

Completeness to $\theta = 26.0°$	99.9 %
Reflections collected	13058
Independent reflections	5094 ($R_{int} = 0.0528$)
Reflections with $F^2>2\sigma$	2265
Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.97621 and 1.00000
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0358, 0.0000
Data / restraints / parameters	5094 / 0 / 274
Final R indices [$F^2>2\sigma$]	R1 = 0.0441, wR2 = 0.0796
R indices (all data)	R1 = 0.1235, wR2 = 0.0910
Goodness-of-fit on F^2	0.777
Extinction coefficient	0.0058(6)
Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	0.34 and –0.16 e $Å^{-3}$

Compound 212

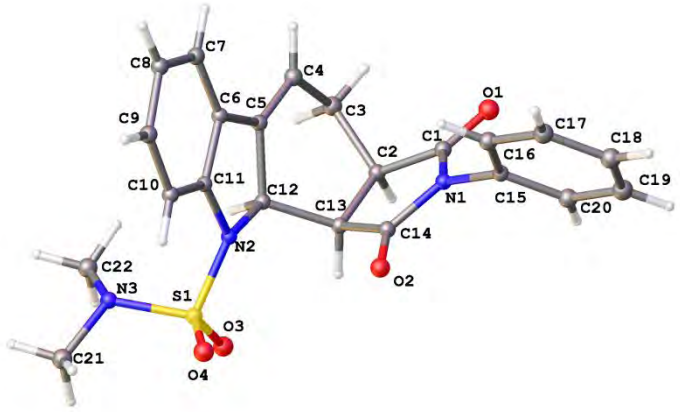

Table 1. Crystal data and structure refinement for **212**.

Identification code	**212**	
Chemical formula (moiety)	$C_{22}H_{21}N_3O_4S$	
Chemical formula (total)	$C_{22}H_{21}N_3O_4S$	
Formula weight	423.48	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	monoclinic, $P12_1/n1$	
Unit cell parameters	a = 12.7776(5) Å	α = 90°
	b = 12.1938(5) Å	β = 108.159(5)°
	c = 13.5282(7) Å	γ = 90°
Cell volume	2002.82(15) $Å^3$	
Z	4	
Calculated density	1.404 g/cm^3	
Absorption coefficient μ	0.197 mm^{-1}	
F(000)	888	
Reflections for cell refinement	5100 (θ range 3.1 to 28.5°)	
Data collection method	Xcalibur, Atlas, Gemini ultra	
	thick-slice ω scans	
θ range for data collection	3.1 to 28.6°	
Index ranges	h −16 to 16, k −12 to 16, l −15 to 17	
Completeness to θ = 26.0°	97.5 %	

Reflections collected	10268
Independent reflections	4276 (R_{int} = 0.0453)
Reflections with $F^2>2\sigma$	2809
Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.57876 and 1.00000
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0628, 0.0000
Data / restraints / parameters	4276 / 0 / 274
Final R indices [$F^2>2\sigma$]	R1 = 0.0426, wR2 = 0.1005
R indices (all data)	R1 = 0.0672, wR2 = 0.1060
Goodness-of-fit on F^2	0.910
Extinction coefficient	0.0004(7)
Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	0.27 and −0.45 e $Å^{-3}$

Compound 223

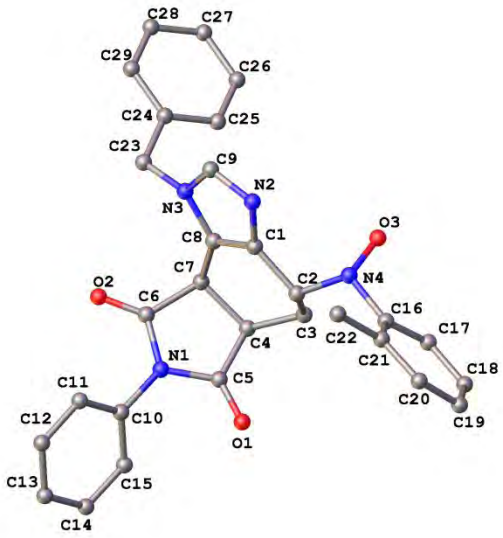

Table 1. Crystal data and structure refinement for **223**.

Identification code	**223**	
Chemical formula (moiety)	$C_{29}H_{26}N_4O_3$	
Chemical formula (total)	$C_{29}H_{26}N_4O_3$	
Formula weight	478.54	
Temperature	150(2) K	
Radiation, wavelength	synchrotron, 0.68890 Å	
Crystal system, space group	monoclinic, $P2_1/n$	
Unit cell parameters	a = 17.055(3) Å	α = 90°
	b = 7.5478(12) Å	β = 100.937(2)°
	c = 19.591(3) Å	γ = 90°
Cell volume	2476.1(7) $Å^3$	
Z	4	
Calculated density	1.284 g/cm^3	
Absorption coefficient μ	0.085 mm^{-1}	
F(000)	1008	
Crystal colour and size	yellow, 0.08 × 0.08 × 0.05 mm^3	
Reflections for cell refinement	9917 (θ range 2.3 to 27.5°)	
Data collection method	Rigaku Spider	
	thick-slice ω scans	
θ range for data collection	1.4 to 27.6°	
Index ranges	h –22 to 19, k –10 to 10, l –25 to 26	

Completeness to $\theta = 27.6°$	97.6 %
Reflections collected	24827
Independent reflections	6127 ($R_{int} = 0.0381$)
Reflections with $F^2>2\sigma$	4800
Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.9932 and 0.9958
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.1247, 2.3178
Data / restraints / parameters	6127 / 588 / 414
Final R indices [$F^2>2\sigma$]	R1 = 0.0853, wR2 = 0.2399
R indices (all data)	R1 = 0.0997, wR2 = 0.2519
Goodness-of-fit on F^2	1.039
Extinction coefficient	0.055(8)
Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	1.00 and –0.61 e $Å^{-3}$

Compound 239

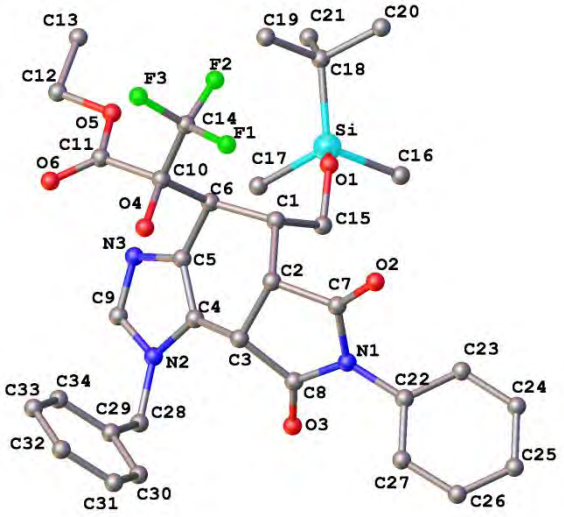

Table 1. Crystal data and structure refinement for **239**.

Identification code	**239**	
Chemical formula (moiety)	$C_{34}H_{40}F_3N_3O_6Si$	
Chemical formula (total)	$C_{34}H_{40}F_3N_3O_6Si$	
Formula weight	671.78	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	triclinic, $P\bar{1}$	
Unit cell parameters	a = 10.8328(6) Å	α = 72.909(5)°
	b = 12.7806(8) Å	β = 79.316(4)°
	c = 13.3203(6) Å	γ = 71.622(6)°
Cell volume	1664.08(16) $Å^3$	
Z	2	
Calculated density	1.341 g/cm^3	
Absorption coefficient μ	0.136 mm^{-1}	
F(000)	708	
Crystal colour and size	yellow, 0.34 × 0.30 × 0.30 mm^3	
Reflections for cell refinement	6507 (θ range 3.0 to 28.5°)	
Data collection method	Xcalibur, Atlas, Gemini ultra	
	thick-slice ω scans	

θ range for data collection	3.0 to 28.6°
Index ranges	h –13 to 14, k –17 to 15, l –17 to 17
Completeness to θ = 25.0°	99.8 %
Reflections collected	15021
Independent reflections	6980 (R_{int} = 0.0266)
Reflections with $F^2>2\sigma$	5675
Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.9551 and 0.9602
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0375, 0.8194
Data / restraints / parameters	6980 / 0 / 435
Final R indices [$F^2>2\sigma$]	R1 = 0.0410, wR2 = 0.0919
R indices (all data)	R1 = 0.0544, wR2 = 0.1012
Goodness-of-fit on F^2	1.031
Extinction coefficient	0.0030(8)
Largest and mean shift/su	0.001 and 0.000
Largest diff. peak and hole	0.34 and –0.31 e $Å^{-3}$

Compound 242

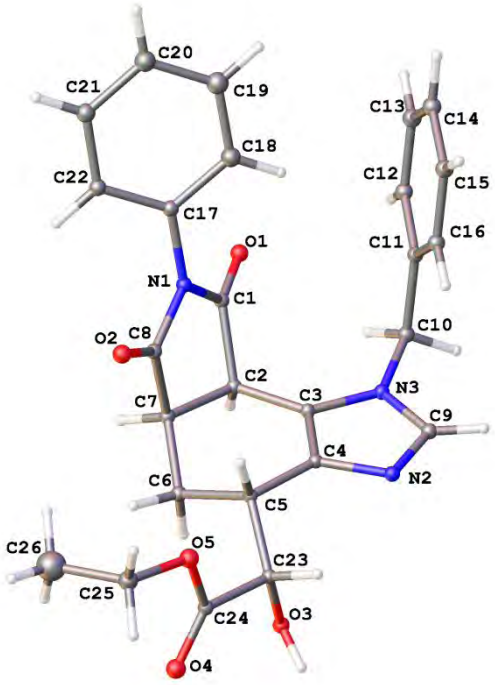

Table 1. Crystal data and structure refinement for **242**.

Identification code	**242**	
Chemical formula (moiety)	$C_{26}H_{25}N_3O_5$	
Chemical formula (total)	$C_{26}H_{25}N_3O_5$	
Formula weight	459.49	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	triclinic, $P\bar{1}$	
Unit cell parameters	a = 8.0807(3) Å	α = 79.423(3)°
	b = 11.5619(5) Å	β = 86.322(3)°
	c = 12.7860(5) Å	γ = 82.872(3)°
Cell volume	1164.15(8) $Å^3$	
Z	2	
Calculated density	1.311 g/cm^3	
Absorption coefficient μ	0.092 mm^{-1}	
F(000)	484	
Crystal colour and size	colourless, 0.34 × 0.30 × 0.30 mm^3	
Reflections for cell refinement	6804 (θ range 2.9 to 28.4°)	
Data collection method	Xcalibur, Atlas, Gemini ultra	
	thick-slice ω scans	

θ range for data collection	2.9 to 28.5°
Index ranges	h −9 to 10, k −11 to 15, l −14 to 16
Completeness to θ = 26.0°	97.5 %
Reflections collected	9971
Independent reflections	4854 (R_{int} = 0.0172)
Reflections with $F^2>2\sigma$	3963
Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.9694 and 0.9729
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0619, 0.0759
Data / restraints / parameters	4854 / 0 / 313
Final R indices [$F^2>2\sigma$]	R1 = 0.0348, wR2 = 0.0996
R indices (all data)	R1 = 0.0429, wR2 = 0.1020
Goodness-of-fit on F^2	1.122
Extinction coefficient	0.023(3)
Largest and mean shift/su	0.001 and 0.000
Largest diff. peak and hole	0.35 and −0.22 e $Å^{-3}$

Compound 244

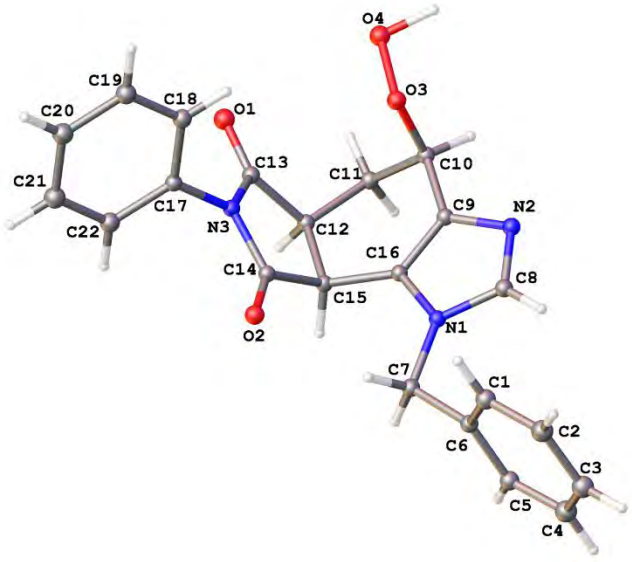

Table 1. Crystal data and structure refinement for **244**.

Identification code	**244**	
Chemical formula (moiety)	$C_{22}H_{19}N_3O_4$	
Chemical formula (total)	$C_{22}H_{19}N_3O_4$	
Formula weight	389.40	
Temperature	150(2) K	
Radiation, wavelength	CuKα, 1.54178 Å	
Crystal system, space group	monoclinic, $P12_1/n1$	
Unit cell parameters	a = 15.0141(2) Å	α = 90°
	b = 6.93930(10) Å	β = 93.228(2)°
	c = 18.3271(3) Å	γ = 90°
Cell volume	1906.42(5) $Å^3$	
Z	4	
Calculated density	1.357 g/cm^3	
Absorption coefficient μ	0.782 mm^{-1}	
F(000)	816	
Crystal colour and size	colourless, 0.08 × 0.02 × 0.01 mm^3	
Reflections for cell refinement	5835 (θ range 2.4 to 62.1°)	
Data collection method	Xcalibur, Atlas, Gemini ultra	
	thick-slice ω scans	
θ range for data collection	3.7 to 62.2°	

Index ranges	h −17 to 15, k −7 to 7, l −21 to 20
Completeness to θ = 26.0°	99.7 %
Reflections collected	10206
Independent reflections	2973 (R_{int} = 0.0253)
Reflections with $F^2>2\sigma$	2509
Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.9401 and 0.9922
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0422, 0.4501
Data / restraints / parameters	2973 / 0 / 267
Final R indices [$F^2>2\sigma$]	R1 = 0.0311, wR2 = 0.0799
R indices (all data)	R1 = 0.0387, wR2 = 0.0826
Goodness-of-fit on F^2	1.048
Extinction coefficient	0.00081(14)
Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	0.17 and −0.16 e $Å^{-3}$

Compound 249

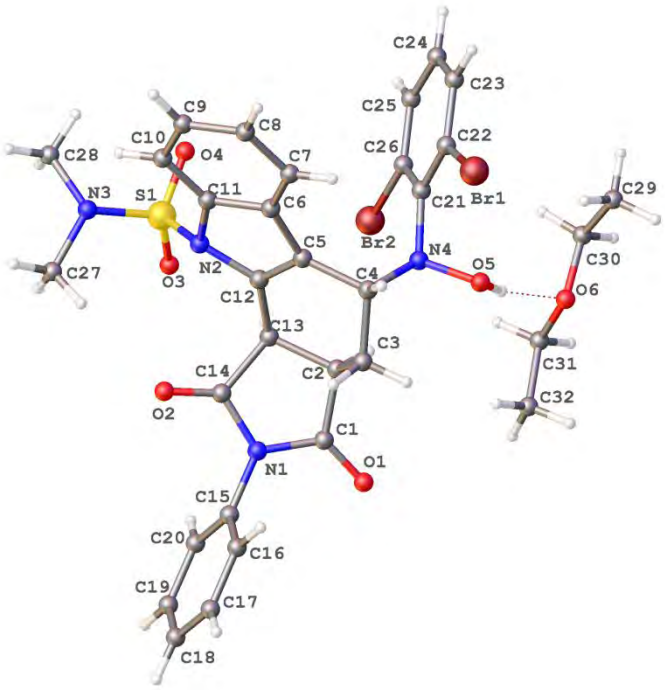

Table 1. Crystal data and structure refinement for **249**.

Identification code	**249**	
Chemical formula (moiety)	$C_{32}H_{34}Br_2N_4O_6S$	
Chemical formula (total)	$C_{32}H_{34}Br_2N_4O_6S$	
Formula weight	762.51	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	triclinic, $P\bar{1}$	
Unit cell parameters	a = 10.0526(9) Å	α = 87.382(8)°
	b = 12.4999(13) Å	β = 78.595(8)°
	c = 13.7721(13) Å	γ = 69.990(9)°
Cell volume	1593.5(3) $Å^3$	
Z	2	
Calculated density	1.589 g/cm^3	
Absorption coefficient μ	2.660 mm^{-1}	
F(000)	776	
Reflections for cell refinement	4815 (θ range 2.9 to 26.8°)	
Data collection method	Oxford Diffraction Gemini A Ultra diffractometer thick-slice ω scans	
θ range for data collection	2.9 to 26.0°	
Index ranges	h −12 to 12, k −15 to 8, l −16 to 15	

Completeness to $\theta = 26.0°$	95.3 %
Reflections collected	9887
Independent reflections	5958 ($R_{int} = 0.0303$)
Reflections with $F^2>2\sigma$	4827
Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.63826 and 1.00000
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0734, 7.8387
Data / restraints / parameters	5958 / 0 / 414
Final R indices [$F^2>2\sigma$]	R1 = 0.0619, wR2 = 0.1510
R indices (all data)	R1 = 0.0773, wR2 = 0.1664
Goodness-of-fit on F^2	1.025
Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	3.65 and −0.86 e $Å^{-3}$