The Synthesis of Novel Analogues of the Antitumour Antibiotic Pyrrolobenzodiazepines.

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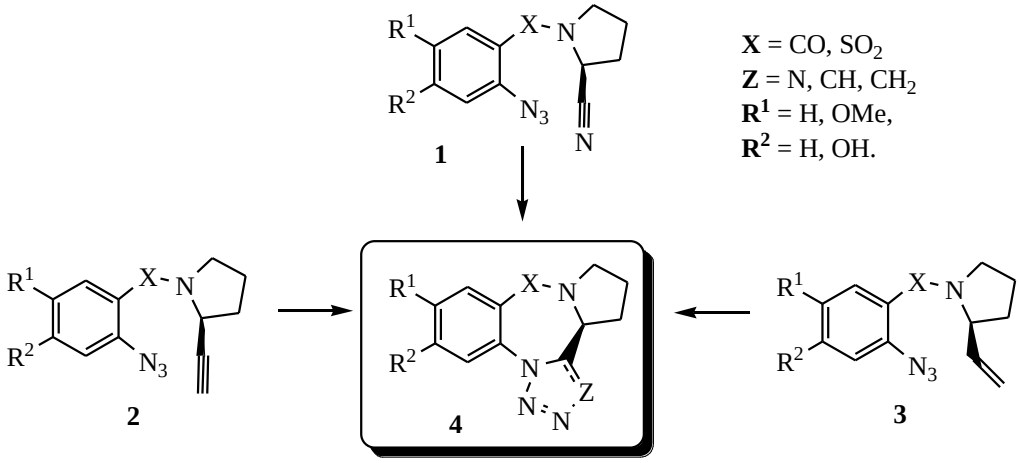
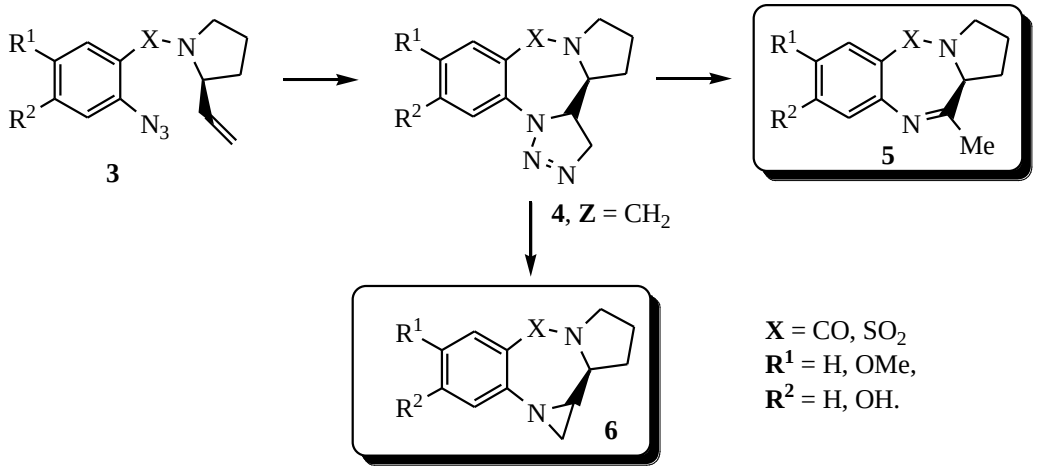
Abstract.

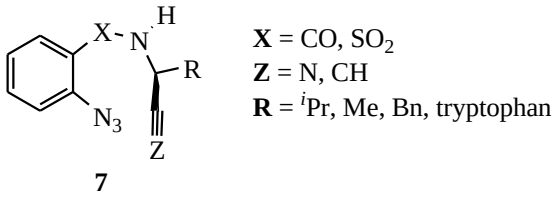
In this thesis, the novel synthesis of tetra- and triazolo-analogues of the pyrrolobenzodiazepines, pyrrolobenzothiadiazepines, benzodiazepines and benzothiadiazepines are described. These compounds are of great interest as synthetic targets due to their potential medical properties. The key processes are the intramolecular 1,3-dipolar cycloaddition between the azide and the nitrile present in compound (**1**), the azide and the alkyne present in compound (**2**) the azide and the alkene present in compound (**3**), to form the novel final compounds of type (**4**). The synthesis of these precursors from readily available starting materials is discussed.



The intramolecular 1,3-dipolar cycloaddition of the alkene with the azide (**3**) afforded the triazoline (**4**, Z = CH_2) which upon nitrogen extrusion formed either the methyl imine (**5**) or an aziridine (**6**) as shown in the Scheme on the next page. Reactions of other alkenes, more highly substituted than compound (**3**) are also described.



This thesis will also describe a general route to triazolobenzodiazepines and triazolobenzothiadiazepines (**7**, X = CO, SO_2; Z = CH). The reactions of the corresponding nitriles (**7**, X = CO, SO_2; Z = N) will also be described, as with other approaches to the pyrrolobenzodiazepines.



Abbreviations.

~	Approximately
°C	Degrees Celcius (Temperature)
υ_{max}	Frequency of vibration (used in infrared spectra)
$[M+Na]^+$	Molecular ion and sodium (MS)
µl	Microlitres i.e. 1 x 10^{-6} litres
ABD	Azetidino[2,1-*c*][1,4]benzodiazepine
AcOH	Acetic acid
bd	Broad doublet
bm	Broad multiplet
Boc	Tert-butyloxycarbonyl
BOP	(Benzotriazol-1-yloxy) tris(dimethylamino)phosphonium
br	Broad (IR and NMR)
bs	Broad singlet (NMR)
CNS	Central Nervous System
COSY	Correlation Spectroscopy (NMR)
CSI	Chlorosulfonylisocyanate
d	Doublet (NMR)
DBU	(1,8-Diazabicyclo[5.4.0]undec-7-ene)
DCC	*N*,*N*′-Dicyclohexylcarbodiimide
DCM	Dichloromethane
dd	Doublet of doublets (NMR)
ddd	doublet of doublets of doublets (NMR)
DEA	*N*,*N*-Diethylaniline
Dept	Distortionless Enhancement by Polarization Transfer
DIBAL-H	Diisobutylaluminium hydride
DIPEA	Diisopropylethylamine
DMA	*N*,*N*-Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
DPP	Diphenylcyclopropenone
DPPE	1,2-Bis(diphenylphosphino)-ethane
dsept	Doublet of septet (NMR)
dt	Doublet of triplets (NMR)
eq	Equivalents
EDC	(1-Ethyl-3-[3-dimethylamino propyl] carbodiimide hydro-chloride
ESI^+	Electron spray ionisation
Fmoc	9-Fluorenylmethyloxycarbonyl
H	Proton (NMR)
HIV	Human Immunodeficiency Virus

HMBC	Heteronuclear Multiple Bond Correlation
HRMS	High Resolution Mass Spectrometry
HSQC	Heteronuclear Single Quantum Coherence
IAAC	Intramolecular Alkyne-Azide Cycloaddition
IBX	2-Iodoxybenzoic acid
IR	Infrared
J	Coupling constant (NMR)
LHMDS	Lithium Hexamethyldisilazide
LRMS	Low Resolution Mass Spectrum
M	Molar (i.e. a unit of concentration moles per litre)
***m*-CPBA**	*meta*-Chloroperoxybenzoic acid
mg	Milligrams (i.e. 1 x 10^{-3} grams)
MHz	Mega Hertz frequency measurement
mins.	Minutes
mmol	Millimole i.e 1 x 10^{-3} moles
mp	Melting point
MS	Mass spectrum
NMR	Nuclear magnetic resonance
o.n.	Overnight
oct	Octet (NMR)
PBD	Pyrrolobenzodiazepine
PBTD	Pyrrolobenzothiadiazepine
PCC	Pyridinium chlorochromate
Pd/C	Palladium on charcoal
PNZ	*para*-Nitrobenzyloxycarbonyl
ppm	Parts per million (NMR)
Py	Pyridine
q	Quaternary carbon (^{13}C NMR), Quartet (^{1}H NMR)
QCS	Quinolinium camphorsulfonate
r.t.	Room temperature
s	Sharp (IR); Singlet (NMR)
TBTU	2-(1*H*-Benzotriazole-1-yl)-1, 1, 3, 3-tetramethyluronium-tetrafluoroborate
^{t}BuOK	Potassium *tert*-butoxide
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMSCl	Trimethylsilyl chloride
TosMIC	(Tosylmethyl isocyanide)
TPAP	Tetrapropylammonium perruthenate
Troc	2,2,2-Trichloroethoxycarbonyl
TsOH	*para*-Toluene sulfonic acid
vs	Very strong (IR)
w	Weak (IR)
δ	Chemical shift (unit in NMR)

1 Introduction

1.1 Benzodiazepines.

The benzodiazepine nucleus is a well studied pharmocophoric scaffold that has emerged as a core structural fragment of various muscle relaxant, antistaminic, anxiolytic and anticonvulsant agents.[1-6] The most well studied examples are the 1,4-benzodiazep-2-ones (**1**) and the 1,4-benzodiazep-2,5-ones (**2**) but less is known about 1,4-benzodiazep-5-ones (**3**), which, as will been seen later, form the heterocyclic core of our target molecules.

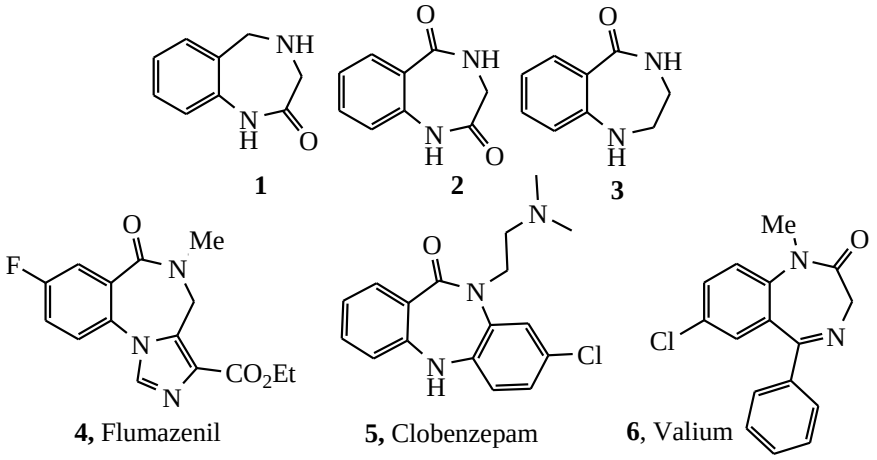


Figure 1-1

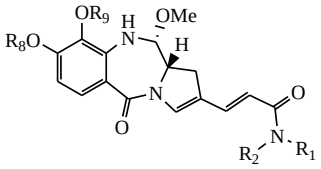
Nonetheless, 1,4-benzodiazepin-5-one nucleus has proved to be a major synthon for the development of new drugs,[7,8] such as the antidepressant Flumazenil (**4**), antistaminic Clobenzepam (**5**)[2,3,8] and the anxiety drug Valium (**6**).[5,9]

The major developments in the synthesis of 1,4-benzodiazepin-5-one (**3**) are modified Strecker-type reaction,[1] Ugi four component condensation,[2,10] the Schmidt rearrangements,[3,11-14] aryne nucleophilic substitution,[3,15] hetero Diels-Alder[4] and 1,3 dipolar cycloaddition.[8]

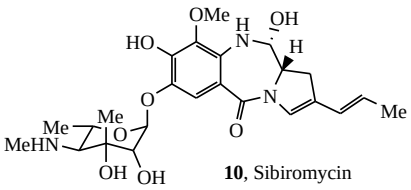
Due to the fact that this thesis will focus on tri- and tetracyclic systems, approaches to the simple bicyclic systems will not be reviewed further. This introduction will look at the synthesis of tricyclic pyrrolo-benzodiazepines and -thiadiazepine analogues, tricyclic systems of relevance and also tetracyclic systems which have a benzodiazepine/thiadiazepine core.

1.2 Pyrrolobenzodiazepines.

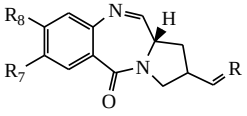
Pyrrolobenzodiazepines (PBDs) are a family of DNA interacting antitumour-antibiotics known as the "anthramycins". They were first discovered in 1965 when Lei mgruber and co-workers isolated anthramycin from *Streptomyces refuineus.*[16,17] Other compounds were later isolated from other various *Streptomyces species*[18-28] and some well known examples are anthramycin (**7**),[17,22,23,29-33] mazethramycin (**8**),[32] porothramycin (**9**),[34] sibiromycin (**10**),[22,23,30,32] tomaymycin(**11**),[20-23,30,32,33,35] prothracarin (**12**),[36] sibanomycin (**13**) (DC-102),[34,37] neothramycins A (**14a**) and B (**14b**),[20,23,32,38] DC-81 (**15**),[20-22,24,29-33] chicamycin A (**16**)[20,32,33,39] and abbeymycin (**17**)[34-36] as shown in the Figure1-2.



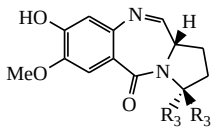
7, Anthramycin (R_8 = Me, R_9 = R_1= R_2 = H)
8, Mazethramycin (R_8 = R_1 = Me, R_9 = R_2 = H)
9, Porothramycin (R_8 = H, R_9 = R_1 = R_2 = Me)



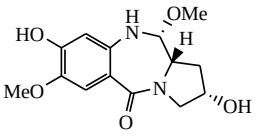
10, Sibiromycin



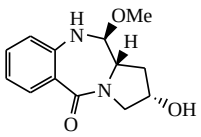
11, Tomaymycin (R_7 = OMe, R_8 = OH, R = Me)
12, Prothracarcin (R_7 = R_8 = H, R = CH_3)
13, Sibanomicin (R_8 = H, R_7 = sibirosamine pyranoside as in 5, R = Et)



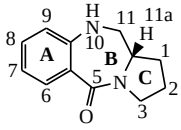
14a, Neothramycin A (R_3 = H, R_3 = OH)
14b, Neothramycin A (R_3 = OH, R_3 = H)
15, DC-81 (R_3 = R_3 = H)



16, Chicamycin A



17, Abbeymycin



18, PBD core structure

Figure 1-2

The DNA-interactive ability and consequential biological effects are a result of the covalent bond formation between the *N*10 and *C*11 (carbinolamine/imine) moiety in the central B ring of the PBD structure, as shown in the Figure 1.3 below,[34,40] and *N*2 of the guanine residue in the minor groove of DNA.[16,23,24,26,29-32,35,41-43] The molecules have a right handed twist provided by the *S* configuration at *C*11a in compound (**18**) and it is of note that this feature allows this structure to follow the curvature of the minor groove of the DNA double helix,[16,19,20,44-47]an essential factor in the biological activity of these compounds.

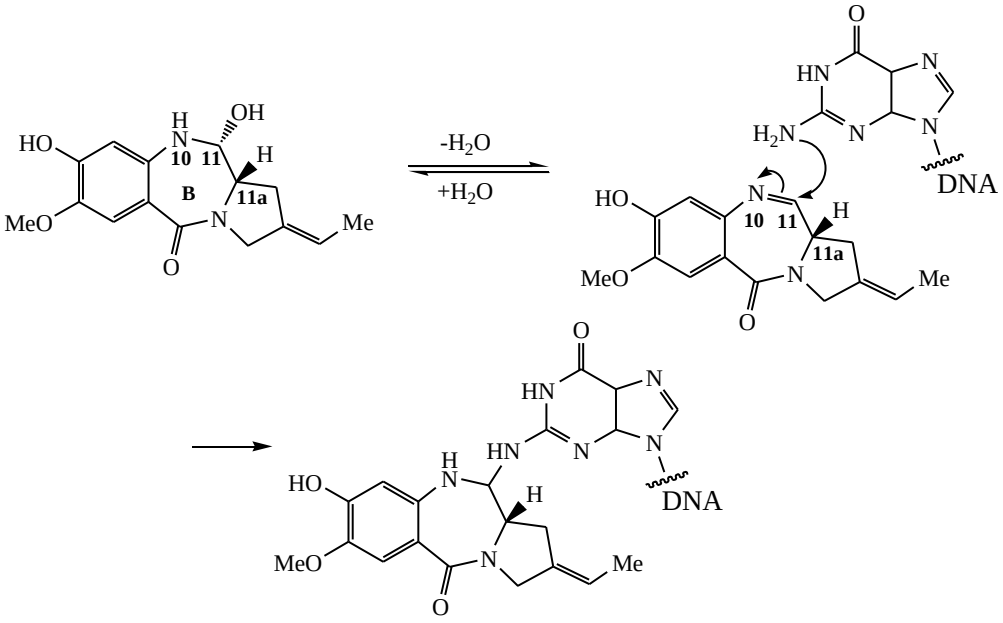


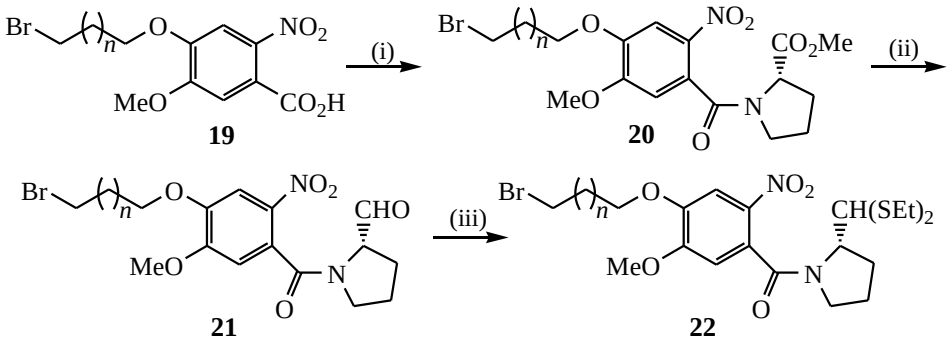
Figure 1-3

The main synthetic approaches to the PBD structure involve either ring closure between an amino group and a thioacetal (Section 1.2.1), protected-NH ring closures (Section 1.2.2), cyclisation between an azide and aldehyde (Section 1.2.3) and cyclisations involving nitro reductions (Section 1.2.4). Typical examples of each method will be detailed below. This section will limit itself to methods developed post 1994 as before this time Thurston and Bose have reviewed[34] this area. Only ring formation processes will be considered, and side chain manipulations and the synthesis of so called "conjugates" by side chain manipulation will not be considered.

1.2.1 Amino-thioacetal ring closure.

One approach for the synthesis of analogues of the PBD pharmacophore involves the formation of the *N*10-*C*11 bond formation by B ring closure between a thioacetal and an amine moiety. This process appeared in Thurston's original review, but has now been extended to include access to "conjugate" systems (examples of conjugate systems are shown in scheme 2-1 compounds **26-30**)[19,23-25,27,29-31,33,35,37,48]

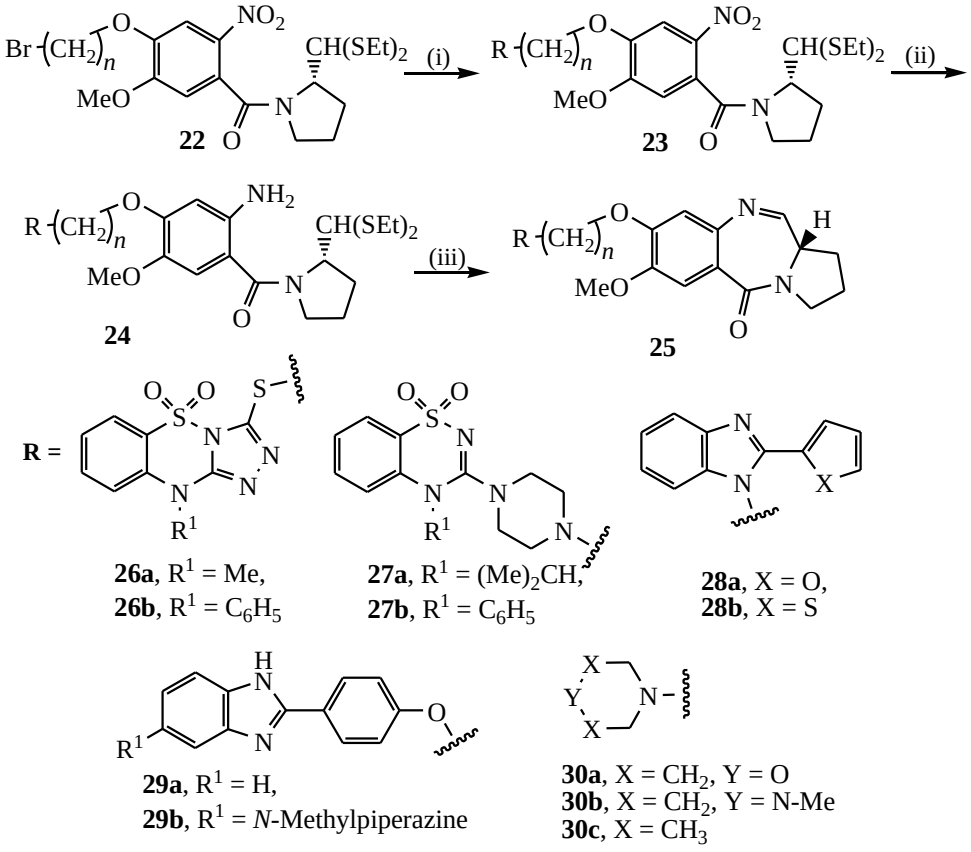
One of the key intermediates in the synthesis of conjugated analogues of the PBD pharmacophore are the carboxylic acids (**19**).[30] Coupling, in the presence of triethylamine, of (*S*)-(+)-pyrrolidine methyl ester hydrochloride with the activated acid of compound (**19**) afforded compound (**20**) which was reduced with DIBAL-H to the corresponding aldehyde (**21**), and protected with the diethylthioacetal group by using TMSCl-EtSH to give the key intermediate (**22**), as shown in Scheme 1-1.



Scheme 1-1 (i) $SOCl_2$, *L*-pyrrolidine methyl ester hydrochloride, Et_3N, H_2O, 0°C, 3 hrs, 80% (ii) DIBAL-H, DCM, -78°C, 45mins, 65% (iii) EtSH-TMSCl, $CHCl_3$, rt, 18 hrs, 82%.

The formation of the conjugate systems was achieved by the linking of the R groups (**26-30**) (which are shown in the Scheme 1-2) to the intermediate compound (**22**) to afford the linked compounds (**23**) (also shown in the Scheme 1-2). These were reduced to afford the amino-diethylthioacetal

precursors (**24**), which in turn were cyclised by the deprotection of the diethylthioacetal to form the conjugate systems (**25**) of the DC-81 structure.



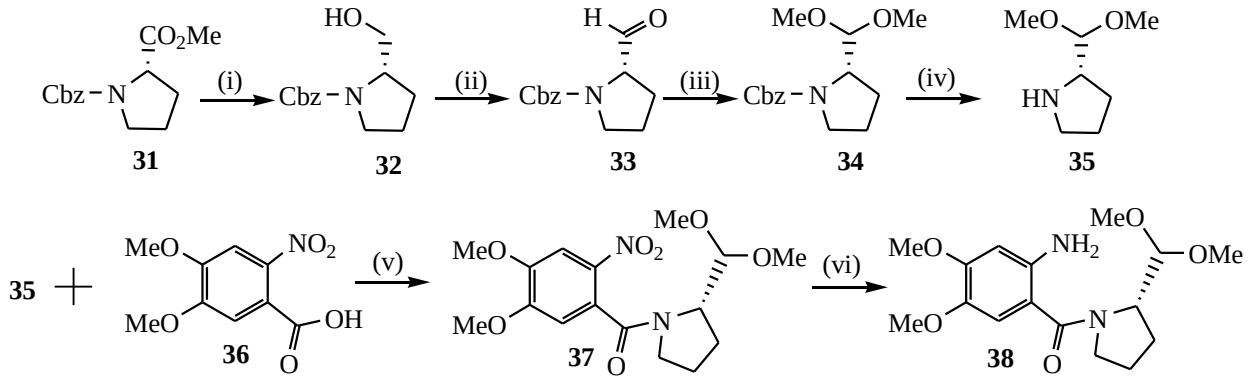
Scheme 1-2 (i) **26-30**, K_2CO_3, acetone or DMF, reflux, 24-48hrs (ii) $SnCl_2.2H_2O$, MeOH, reflux, 24-48hrs (iii) $HgCl_2/CaCO_3$, MeCN:H_2O (4:1), 8-12 hrs.

Similar diethylthiocetal approaches to the PBD nucleus have also been reported,[23,24,29,31-33,37,49-53] including other conjugates and also PBD dimers[20,54-57] which are useful DNA cross linking agents.

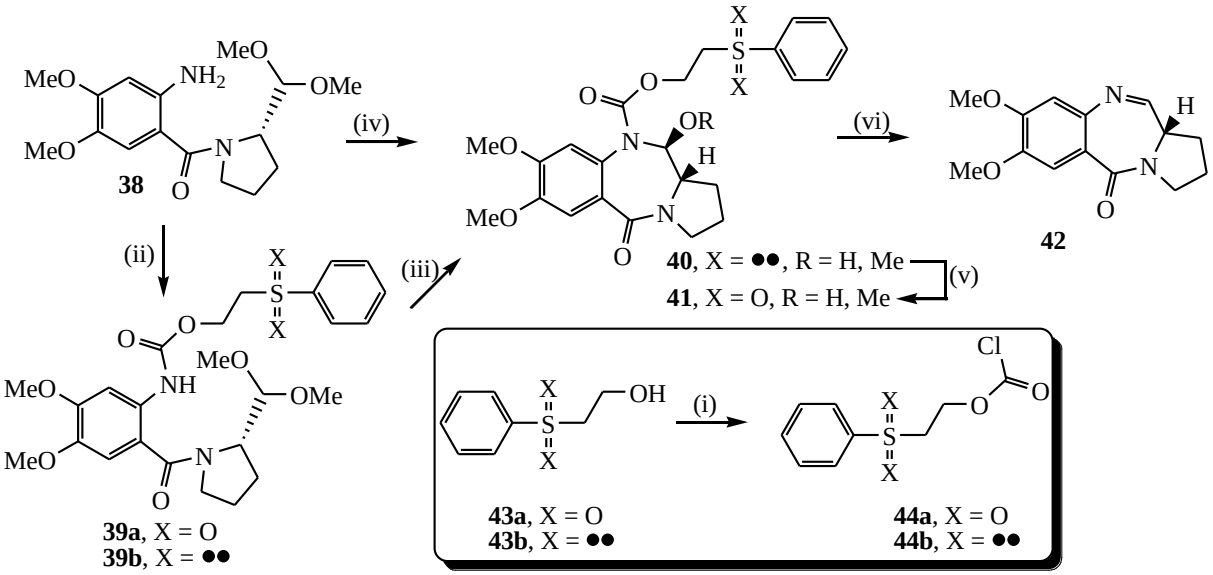
1.2.2 Ring closure involving *N*-protected amines.

*N*10 protected PBDs have been shown to be unable to interact with DNA and are therefore devoid of cytoactivity[58] (biological activity with in the cytoplasm of the cell). However, these molecules can sometimes act as prodrugs in that enzymatic removal of the protecting group will form the active *N*10-*C*11 imine bond, carbinolamine or methyl forms which may then interact with the DNA strand.[46] In this section of the introduction the synthesis of one such analogue by this approach is illustrative and will be detailed, drawing on a paper by Berry and Howard.[46]

The first stage in the synthesis was to produce the C-ring acetal (**35**), which was synthesised in four steps from the commericially available *N*-carbobenzyloxy-*L*-proline methyl ester (**31**), as shown in scheme 1-3. Amine (**35**) was joined with 4, 5-dimethoxy-2-nitrobenzoic acid (**36**) by the standard coupling procedure employing an equimolar amount of 2-(1*H*-benzotriazole-1-yl)-1, 1, 3, 3-tetra-methyluronium tetrafluoroborate (TBTU) and diisopropylethylamine (DIPEA) in DMF to afford (**37**) in 51% yield. The subsequent reduction of the nitro moiety utilising 10% palladium on carbon with hydrogen afforded the aniline (**38**).



Scheme 1-3 (i) $LiBH_4$, THF, 0ºC (ii) SO_3·pyridine, Et_3N, DMSO/DCM (4:5), -10ºC (iii) $SOCl_2$, $HC(OMe)_3$, MeOH, 60ºC (iv) Raney-Ni, EtOH or H_2, 10% Pd/C, EtOH (v) TBTU, DIPEA, DMF (vi) H_2, 10% Pd/C, EtOH



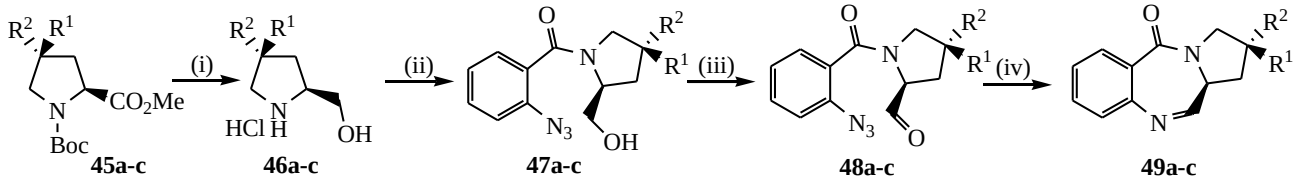
Scheme 1-4 (i) **43a-b**, triphosgene, pyridine, DCM, 0ºC (ii) **44a**, pyridine, DCM, 0ºC (iii) $(MeCN)_2PdCl_2$, acetone (iv) **44b**, pyridine, DCM, 0ºC (v) **40**, *m*-CPBA, DCM, 0ºC (vi) **41**, DBU, benzene, 5ºC.

At this stage in the synthesis, an attempt to protect the amine as either the sulfone (**39a**) or the sulfide (**39b**) carbamate, using the corresponding chloroformates (**44a,b**), which were prepared freshly (as seen in the box in the Scheme 1-4) from 2-(phenylsulfonyl)ethanol (**43a**) or 2-(phenylthio)ethanol (**43b**) and triphosgene. However, on attempting to synthesise the Ptec-protected PBD (**39b**) from (**38**) utilising this strategy, intramolecular cyclisation to the PBD sulfide (**40**) occured, and therefore (**39b**) could not be isolated. This is likely to be due to the HCl liberated during the protection reaction causing premature hydrolysis of the acetal leading to the ring closure. Interestingly, this was not the case for the sulfone Psec intermediate (**39a**), which could be isolated. Acetal deprotection by treatment with trans-bis(acetonitrile)palladium(II) chloride in acetone afforded the cyclised compound (**41**). The sulfone (**41**) was also obtained in 87% yield by the oxidation of the sulfide (**40**) with *m*-CPBA (3-chloroperoxybenzoic acid) in DCM. The deprotection of (**41**) with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in benzene yielded the PBD pharmacophore (**42**) in 77% yield. This approach is quite general, and similar approaches using Troc and Boc protected amines[48,59-61] have also appeared, as well as PNZ[58] and Alloc.[62-65]

1.2.3 Azide based cyclisations.

Due to the incorporation of the azide group into many of the molecules used later in this thesis, these routes are particularly relevant. Staudinger/aza-Wittig methodology[66-71] and azide reduction routes have been exploited in the synthesis of many PBDs. In this subsection a brief overview will be described.

One analogue was described by O'Neil[36] who produced fluoropyrrolo analogues (as shown in the Scheme 1-5). Thus, reduction of the fluoro substituted prolines (**45**)[72] with DIBAL-H followed by deprotection with 4M HCl in 1,4-dioxane afforded the cis-4-fluoro- (**46a**), trans-4-fluoro- (**46b**), and 4,4'-difluoroprolinol (**46c**) hydrochlorides in good yields. The coupling of 2-azidobenzoyl chloride with (**46a-c**) afforded the compounds (**47a-c**) which upon oxidation with Dess-Martin periodinane furnished the PBD precursors (**48a-c**). Staudinger/aza-Wittig cyclisation with DPPE in THF gave the fluoro-substituted PBDs, (**49a-c)** in 71, 80, 62% yields, respectively.



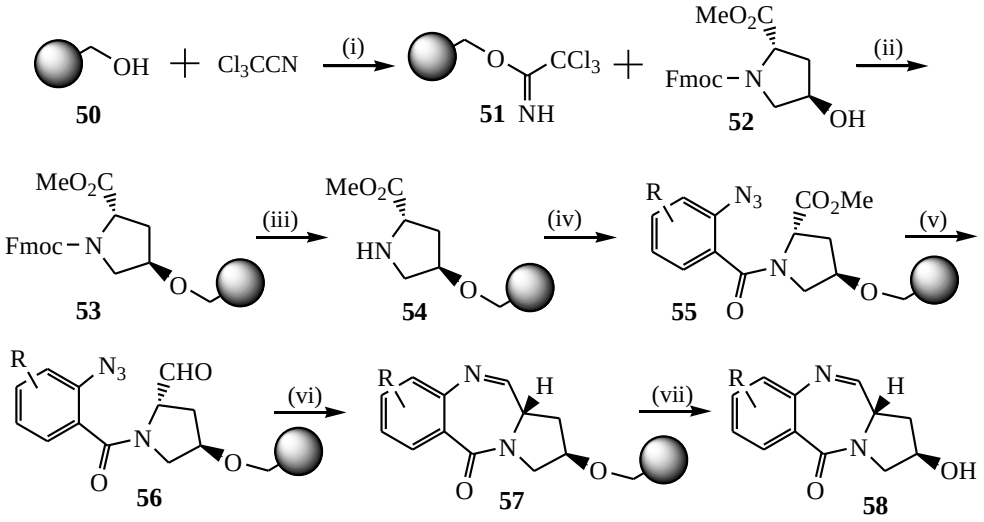
45a-c **46a-c** **47a-c** **48a-c** **49a-c**

a, R^1 = F, R^2 = H; **b**, R^1 = H, R^2 = F; **c**, R^1 = F, R^2 = F

Scheme 1-5 (i) DIBAL-H, THF, -78°C to r.t., o.n., then 4M HCl in 1,4-dioxane, o.n. (ii) 2-azidobenzoyl chloride, Et_3N, DCM, -78°C to r.t., o.n. (iii) Dess-Martin periodinane, DCM, r.t., o.n. (iv) DPPE, THF, 2hrs.

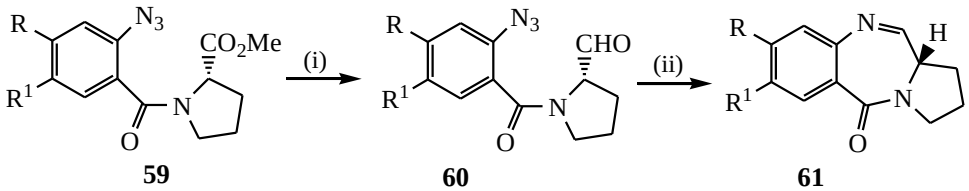
Kamal *et al*,[39] have utilised solid phase synthesis for the synthesis of hydroxyl derivatives of the PBDs (see Scheme 1-6). The synthesis started from the Wang trichloroacetamidate resin (**51**) which was prepared by the Hanessian protocol and then coupled with Fmoc-protected 4-hydroxyproline-methyl ester (**52**). The product (**53**) was deprotected (**54**) and coupled with 2-azidobenzoic acid in the presence of DCC and DMAP to afford the amide (**55**). The reduction of the ester moiety to the

aldehyde (**56**) was achieved by treatment with DIBAL-H at -78°C. The Staudinger/aza-Wittig cyclisation process on compound (**56**) and the subsequent cleavage of the Wang resin gave the final compounds of type (**58**).



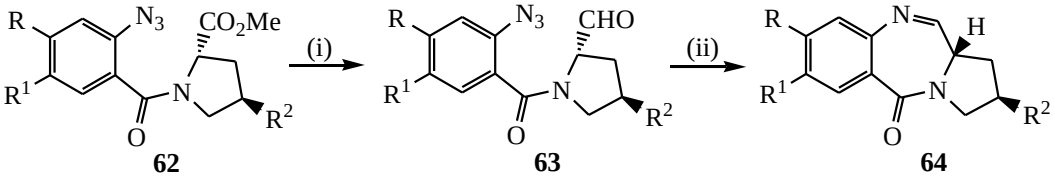
Scheme 1-6 (i) DBU, DCM (ii) BF_3OEt_2 or CF_3SO_3H, DCM (iii) 20% piperidine/DMF (iv) 2-azidobenzoic acid, DCC, DMAP, DCM, 0°C (v) DIBAL-H, DCM, -78°C, 2 hrs (vi) PPh_3, toluene (vii) TFA/DCM (1:3).

An example of a reductive cyclisation was studied by Kamal *et al*,[73] (shown in Scheme 1-7) in which they used HI in the ring closure to bring about reduction of the aromatic azide (**60**) to the aromatic amine which underwent intramolecular cyclisation with the aldehyde to yield the PBD pharmacophore (**61**) in 70-75% yields.



Scheme 1-7 (i) DIBAL-H, DCM, -78°C, 45mins, 80-85% (ii) HI, r.t., 70-75%.

Azides can also give the pyrrolobenzodiazepines via other reductive cyclisations[27,39,73-77] and many such methods have been studied in the Kamal group.[24,30,31,33,37,42,43,56,78] Thus, for example, the use of $Al/NiCl_2.6H_2O$ or Al/NH_4Cl have been reported to give efficient and effective routes to PBDs via azide reduction and cyclisation (as shown in Scheme 1-8). A very simple azide reduction involved employing $FeSO_4.7H_2O/NH_3$ as the reducing system[79] as shown in the Scheme 1-8. Compound (**64**) was produced in yields of 68-72%.



62 **63** **64**

a) R = R^1 = R^2= H, **b**) R = OH, R^1 = OMe, R^2 = H,
c) R = R^2 = H, R^1 = CH_3 **d**) R = R^1 = H, R^2 = OH

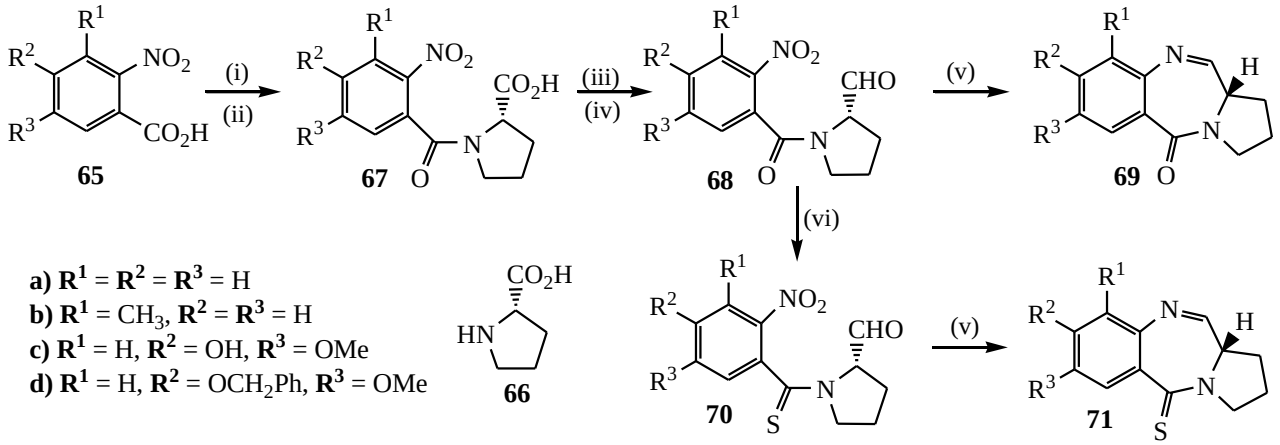
Scheme 1-8 (i) DIBAL-H, DCM, -78°C, 45 min, 72%-75% (ii) $FeSO_4.7H_2O/NH_3$, DCM, 4 hrs, r.t.

1.2.4 Nitro based reductive cyclisations.

The formation of the *N*10-*C*11 imine bond can also be achieved from reductive cyclisations involving the nitro group, and this constitutes the last of the methods commonly used for PBD synthesis that will be presented in this thesis.

As an example, Kamal and Reddy[80] have synthesised compound (**69**), and the thione derivative (**71**), as shown in the Scheme 1-9. The synthesis started from the coupling of proline (**66**) with the activated 3,4,5-substituted-2-nitrobenzoic acid (**65**) to give the coupled product (**67**). Esterification followed by reduction with DIBAL-H yielded the (2*S*)-*N*-(2-nitrobenzoyl)-pyrrolidine-2-carboxaldehydes (**68**). Intramolecular cyclisation in the presence of iron and a mixture of acetic acid/THF as solvent yielded the DC-81 analogue (**69**) in 65-75% yields. The synthesis of the thione derivative from compound (**68**) was achieved by treatment with Lawesson's reagent to yield

compound (**70**), which underwent intramolecular cyclisation in the presence of iron, acetic acid/THF to afford the thione derivatives (**71**).



a) $\mathbf{R^1} = \mathbf{R^2} = \mathbf{R^3} = H$
b) $\mathbf{R^1} = CH_3$, $\mathbf{R^2} = \mathbf{R^3} = H$
c) $\mathbf{R^1} = H$, $\mathbf{R^2} = OH$, $\mathbf{R^3} = OMe$
d) $\mathbf{R^1} = H$, $\mathbf{R^2} = OCH_2Ph$, $\mathbf{R^3} = OMe$

Scheme 1-9 (i) $SOCl_2$, benzene, r.t., 3-4 hrs (ii) **66**, Et_3N, THF, 0ºC, 1 hr (iii) H^+, MeOH, reflux, 2-3hrs (iv) DIBAL-H, DCM, -78ºC, 45 mins (v) Fe, AcOH, THF, r.t., 3-6 hrs (vi) Lawesson's reagent, toluene, 80ºC, 2-3 hrs.

It is notable that earlier studies by Thurston[81] led to the discovery that the balance of AcOH:THF was important in order to prevent the over reduction of the newly formed imine bond of compound (**73**) which would yield the undesired secondary amine (**74**) as shown in Figure 1-4:

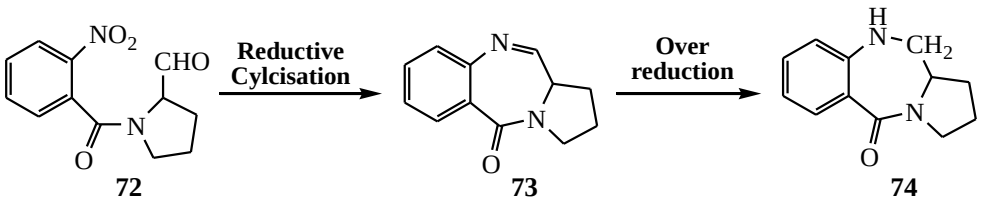
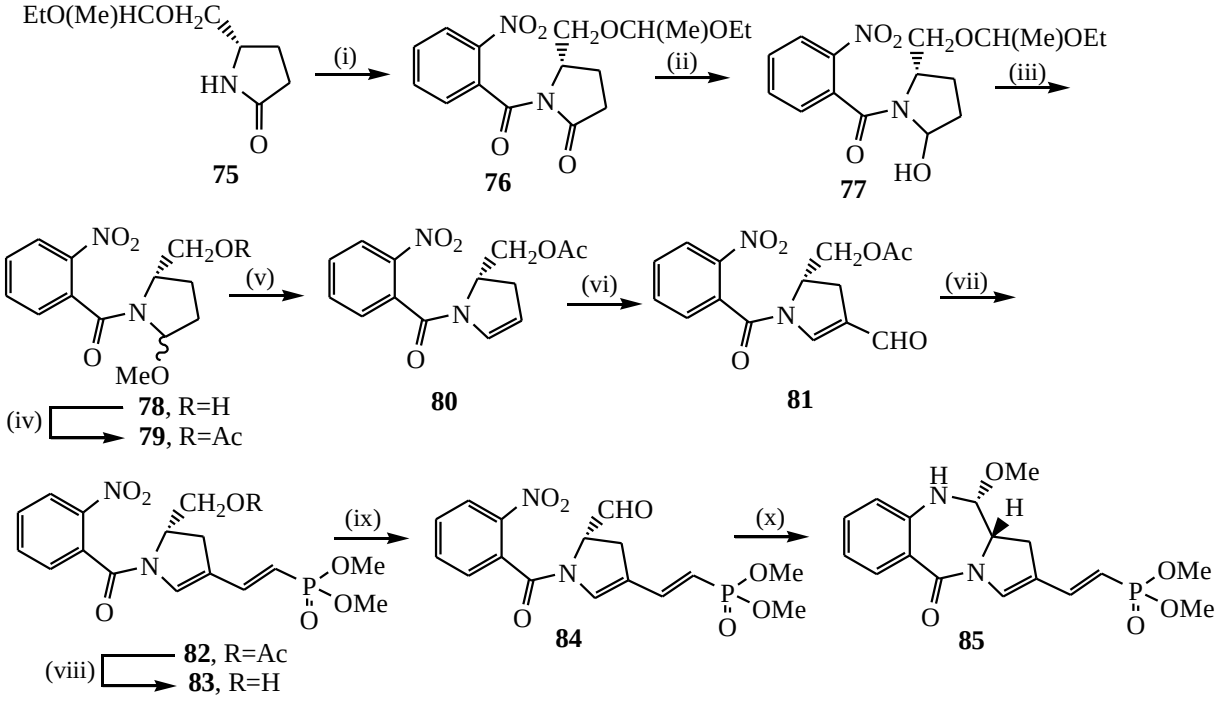


Figure 1-4

Rojas-Rousseau *et al*,[82] have reported the synthesis of an analogue (**85**) of porothramycin (see Scheme 1-10) which utilises Raney-Ni nitro reduction. The first step was the formation of (5*S*)-5-(ethoxy-ethoxymethyl)pyrrolidin-2-one (**75**) as per literature methods.[83] After deprotonation, this

compound was treated with 2-nitrobenzoyl chloride yielding the imide (**76**) in 95% yield. The unstable α-hydroxy-2-nitrobenzamides (**77**) were generated by reduction with DIBAL-H at -78°C in toluene, and were quantitatively converted to the more stable α-methoxy-2-nitrobenzamides (**78**). The primary alcohol was reprotected with an acetyl group to afford compound (**79**) and the methoxy group was eliminated to form the enamide (**80**) in high yield by heating in toluene in the presence of quinolinium camphorsulfonate [QCS] as a catalyst. The enamide (**80**) was converted into a highly versatile unsaturated aldehyde (**81**) moiety quantitatively via a Vilsmeier-Haack reaction.

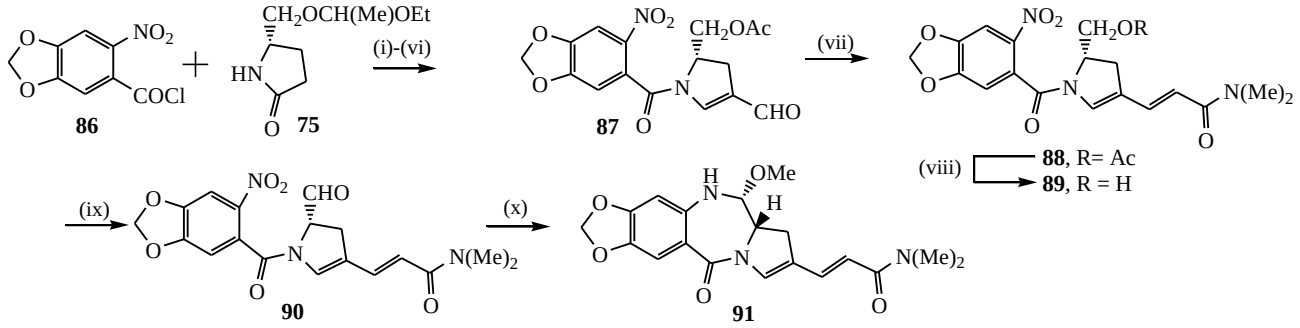


Scheme 1-10 (i) NaH, KI, 2-nitrobenzoyl chloride (95%) (ii) DIBAL-H, Toluene (80%) (iii) MeOH, TsOH (100%) (iv) Ac_2O, Py (98%) (v) 15 mol% QCS, Toluene (94%) (vi) $POCl_3$, DMF (100%) (vii) $CH_2[P(O)(OMe)_2]_2$, ^{n}BuLi (87%) (viii) $Ba(OH)_2$, then CO_2 (86%) (ix) DMSO, $COCl_2$, $^{i}Pr_2NEt$ (99%) (x) Raney-Ni, then MeOH, TFA.

Treatment of the aldehyde (**81**) with tetramethyl-methylenediphosphonate in the presence of one equivalent of ^{n}BuLi at 0°C provided compound (**82**) as a single diastereoisomer in 87% yield.

Saponification of the acetate (**82**) with barium hydroxide afforded to the primary alcohol (**83**), which upon Swern oxidation with $^{i}Pr_2NEt$ as base led to the aldehyde (**84**) in almost quantitative yields (99%). Reductive cyclisation employing Raney-Ni followed by treatment with methanol and small amounts of TFA afforded the porothramycin analogue (**85**).

Langois *et al*,[84] reported a similar approach to a different analogue in which the A ring contains a methylenedioxy group (see below for Scheme 1-11). This was coupled with the (5*S*)-5-(ethoxy-ethoxymethyl) pyrrolidin-2-one (**75**), and proceeded to the nitro acetylated aldehyde (**87**) in much the same manner as described above. The aldehyde (**87**) was condensed with the lithiated anion of diethyl-[2-(dimethylamino)-2-oxoethyl]phosphonate to provide the derivative (**88**).



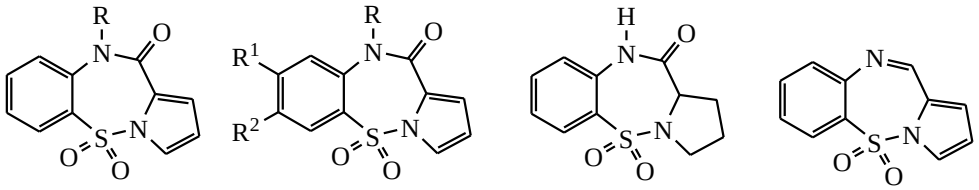
Scheme 1-11 (i) NaH-KI, THF, r.t. (86%) (ii) DIBAL-H, toluene -78°C (97%) (iii) MeOH, H^+ (94%) (iv) Ac_2O-Py (100%) (v) QCS, toluene, reflux, (89%) (vi) DMF, $POCl_3$, DCM (84%) (vii) $^{n}BuLi$, $(EtO)_2$-$P(O)CH_2CONMe_2$ (viii) $Ba(OH)_2$, dioxane, r.t. (99% for two steps) (ix) DMSO, $(COCl)_2$, $^{i}Pr_2NEt$ (99%) (x) Raney-Ni then MeOH, H^+ (68%).

The acyl protection of the primary alcohol was removed by alkaline hydrolysis to afford (**89**), followed by oxidation under Swern conditions using Hünig's base yielded the PBD precursor (**90**) without any racemisation. Reduction of the aromatic nitro moiety with Raney-Ni gave rise to the PBD imine, which was not purified at this stage but was converted to the crystalline carbinolamine methyl ether (**91**) by weak acid-MeOH treatment.

1.3 Pyrrolobenzothiadiazepines.

Whilst the biological aspects and synthesis of 1,4-benzodiazepine and pyrrolobenzodiazepine pharmocophores have been well studied, the pyrrolo[1,2-*b*][1,2,5]benzothiadiazepine 5,5-dioxide (**95**) nucleus has attracted less interest.[85] Pyrrolo[1,2-*b*][1,2,5]benzothiadiazepines are pyrrolo[2,1,-*c*][1,4]benzodiazepines possessing a sulfonyl moiety at position 5 in the 7-membered 1,4-diazepine ring, and have gained interest as analogues of the benzodiazepines due to their possible activity against leukaemia,[86,87] and as non-nucleoside reverse transcriptase inhibitors,[67,88-90] with some activity against HIV.[86,87,89,91-93]

For these reasons, pyrrolo[1,2-*b*][1,2,5]benzothiadiazepines (PBTDs) (**92-95**, shown in Figure 1-5) have been synthesised. A brief overview of the methods used to make them follows.



92 **93** **94** **95**

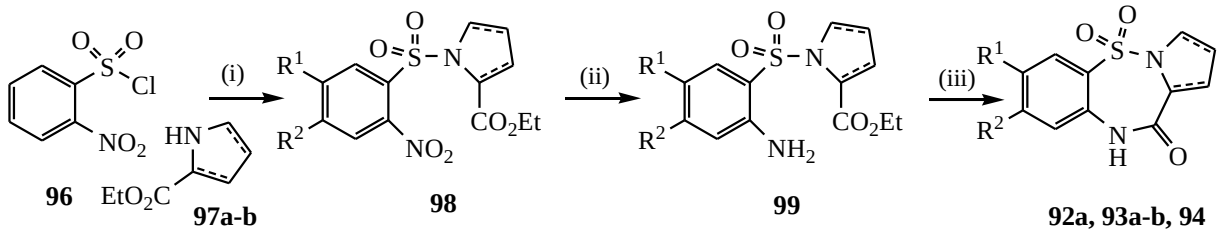
Figure 1-5

The synthesis of the analogues (**92-94**), shown in the Scheme 1-12, was achieved by coupling of sulfonyl chloride (**96**) with the fully saturated (**97a**) or unsaturated pyrrolo ester (**97b**) derivatives, followed by the reduction with iron and acetic acid to give the corresponding amino ester (**99**).

Intramolecular cyclisation occured by heating in the presence of 2-hydroxypyridine as a bifunctional catalyst (a catalyst which contains two functional groups, i.e. the basic lone pair on the nitrogen and the acidic proton on the hydroxyl group) to afford the analogues (**92a**, unsaturated pyrrole ring), (**93a-b,** unsaturated pyrrole ring), (**94**, fully saturated pyrrole ring) (the R groups are shown in table 1-1).[89]

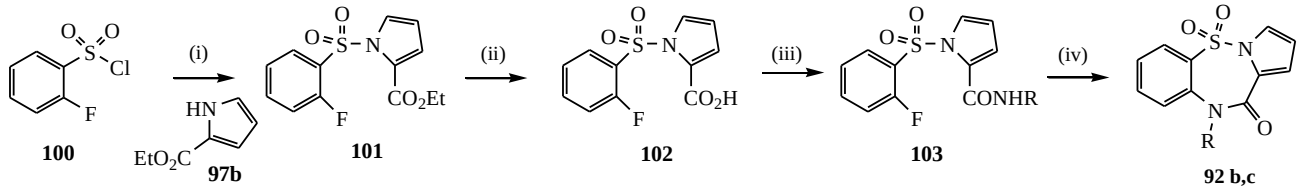
Table 1-1

Compound	R^1	R^2
92a	H	H
93a	Cl	H
93b	H	Cl
94a	H	H



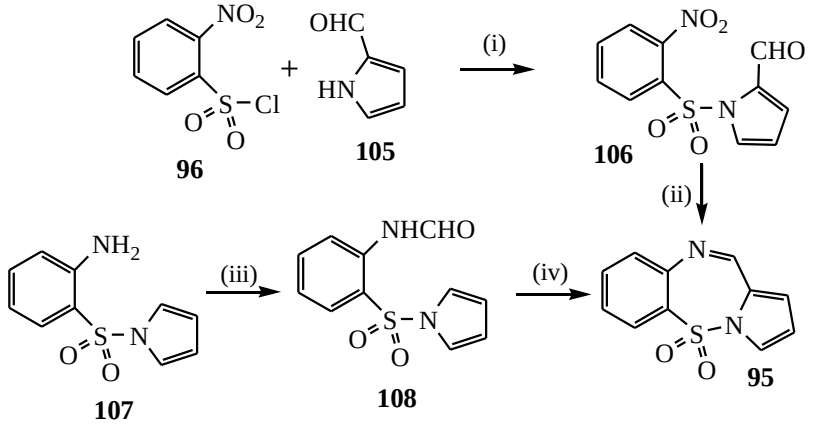
Scheme 1-12 (i) ^{t}BuOK, 18-crown-6 (ii) Fe, acetic acid (iii) 2-hydroxypyridine

The cyclopropyl analogue (**92b-c**) was obtained by the intramolecular cyclisation of the 1-(2-fluorobenzene-1-sulfonyl)-1*H*-pyrrole-2-(*N*-cyclopropyl)carboxyamide (**103**) in the presence of sodium hydride and cuprous iodide. The amide derivative (**103**) was synthesised by treatment of the carboxylic acid in the presence of the amine, EDC and DMAP, whereby the acid in turn was synthesised via the coupling of the 2-fluorobenzene-1-sulfonyl chloride (**100**) with the unsaturated pyrrolo ester (**97b**) in the presence of 18-crown-6 and potassium tert-butoxide followed by the alkaline hydrolysis of the ester.[89](as shown in Scheme 1-13)



Scheme 1-13 (i) ^{t}BuOK, 18-crown-6 (ii) KOH (iii) R-NH_2, EDC, DMAP (iv) NaH, CuI. R= cyclopropyl or benzyl

The synthesis of compound (**95**) was carried out by Silvestri *et al*,[94] by two different routes. The first of these was the coupling of pyrrole-2-carboxaldehyde (**105**) to 2-nitrobenzenesulfonyl chloride (**104**) in the presence of ^{t}BuOK and 18-crown-6 as a condensing agent followed by the intramolecular cyclisation via reduction of the nitro group of compound (**106**) to the amine with iron and acetic acid. The second route employed treatment with acetic-formic anhydride to compound (**107**) to afford 1-(2-foramidobenzenesufonyl)pyrrole (**108**) which was cyclised with phosphorus oxychloride via a Bischler-Napieralski reaction as seen in the Scheme 1-14.



Scheme 1-14 (i) ^{t}BuOK, 18-crown-6 (ii) Fe, acetic acid (iii) Formic acid, acetic anhydride (iv) $POCl_3$

1.4 Tetracyclic PBDs and PBTDs.

One of the aims of this work was to make tetracyclic analogues of the pyrrolobenzodiazepines.[69,96] The specific targets that were intended were those formed by intramolecular azide 1,3-cycloadditions as shown in the Figure 1-6:

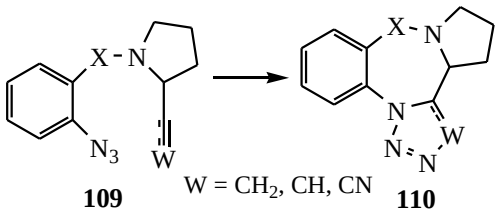
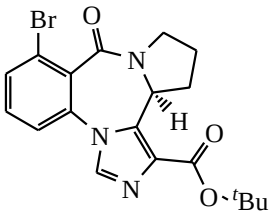


Figure 1-6

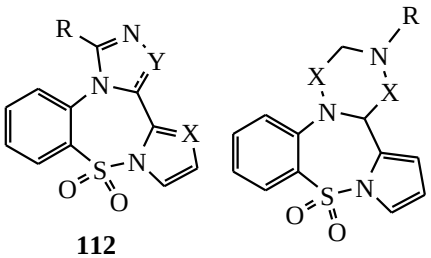
There were two reasons for this, firstly, the possibility that (**110**) (W = CH_2) would collapse to an imine or aziridine, both of interest in potential DNA interaction processes and, secondly, to produce analogues of tetracyclic PBDs such as the CNS active bretazenil (**111**, structure shown in Figure 1-7). For this reason a brief review of the approaches to tetracyclic PBDs follows.



111, bretazenil

Figure 1-7

The main workers in this area are Silvestri *et al*, and the table below and next three Schemes show their approaches to compounds of general structure (**112**)[89,94] and (**113**)[97] (as shown in Figure 1-8 and substituent groups in table 1-2).



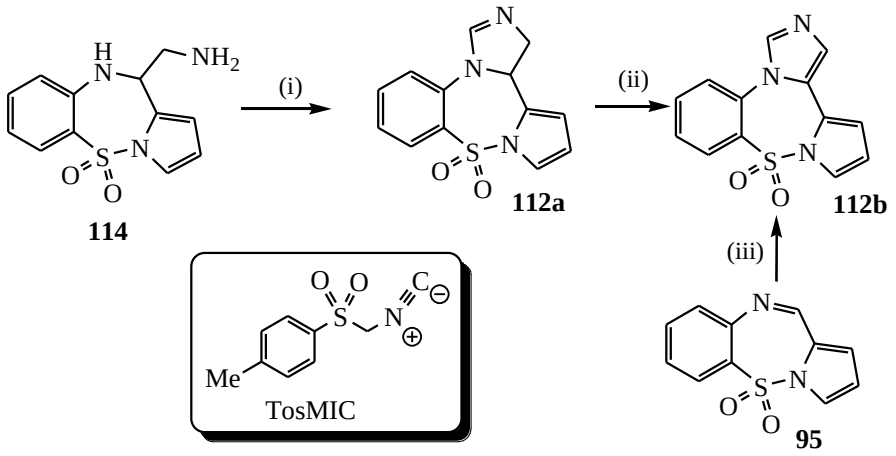
112 **113**

Figure 1-8

Table 1-2

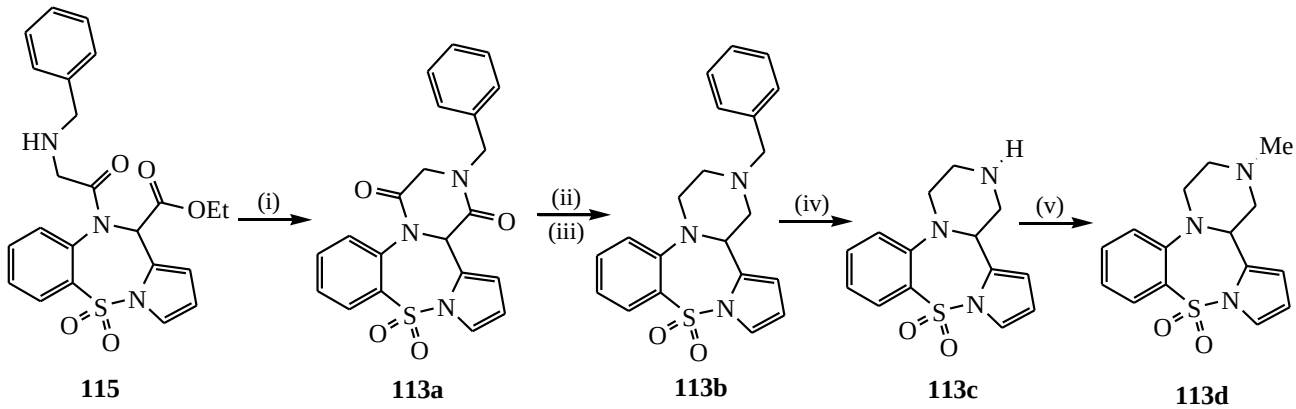
Compound	*X*	*Y*	*R*
112a	CH	N	H
112b	CH	CH	H
113a	CO	-	CH_2Ph
113b	CH_2	-	CH_2Ph
113c	CH_2	-	H
113d	CH_2	-	CH_3

The formation of imidazo[5,1-*d*]pyrrolo[1,2-*b*][1,2,5]benzothiadiazepine 5,5-dioxide (**112b**, Y = X = CH) was acheived by two different synthetic routes,[94] as shown in Scheme 1-15. The first of these was the direct route from compound (**95**) using tosylmethyl isocyanide (TosMIC) and ^{n}BuLi resulting in cycloaddition across the azomethine double bond. The second route was a two step synthesis starting from compound (**114**), and treatment with triethyl orthoformate to form the tetracyclic system which was oxidised with MnO_2 to form compound (**112b**).



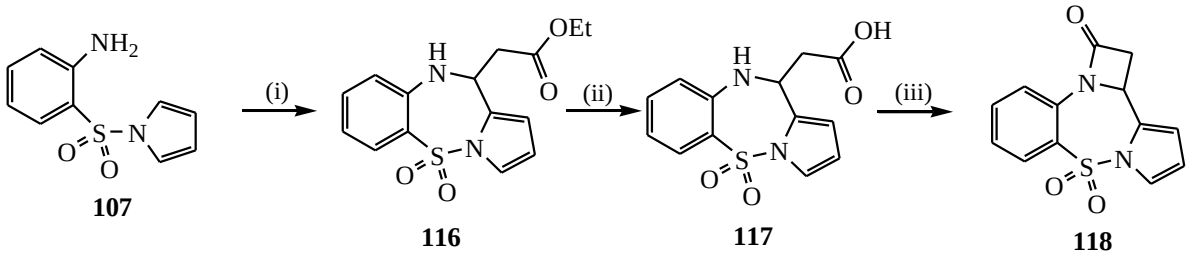
Scheme 1-15 (i) $CH(OEt)_3$ (triethyl orthoformate) (ii) MnO_2 (iii) TosMIC, ^{n}BuLi.

The synthesis of the aptazepine analogue (**113d**) started from the synthesis of the readily available compound (**115**, as shown in Scheme 1-16)[86] which underwent thermal cyclisation in toluene to afford the tetracyclic PBTD dioxopiperazinyl derivative (**113a**). Reduction using a mixture of lithium aluminium hydride and sulfuric acid gave pyrazinopyrrolo[1,2-*b*][1,2,5]benzothiadiazepine (**113b**) a further example of a tetracyclic PBTD. Compound (**113b**) was debenzylated using hydrogen in the presence of 10% palladium on charcoal as the catalyst to yield (**113c**) which was reductively methylated with formaldehyde in the presence of hydrogen to give the methyl derivative (**113d**) in 70% yield.[97]



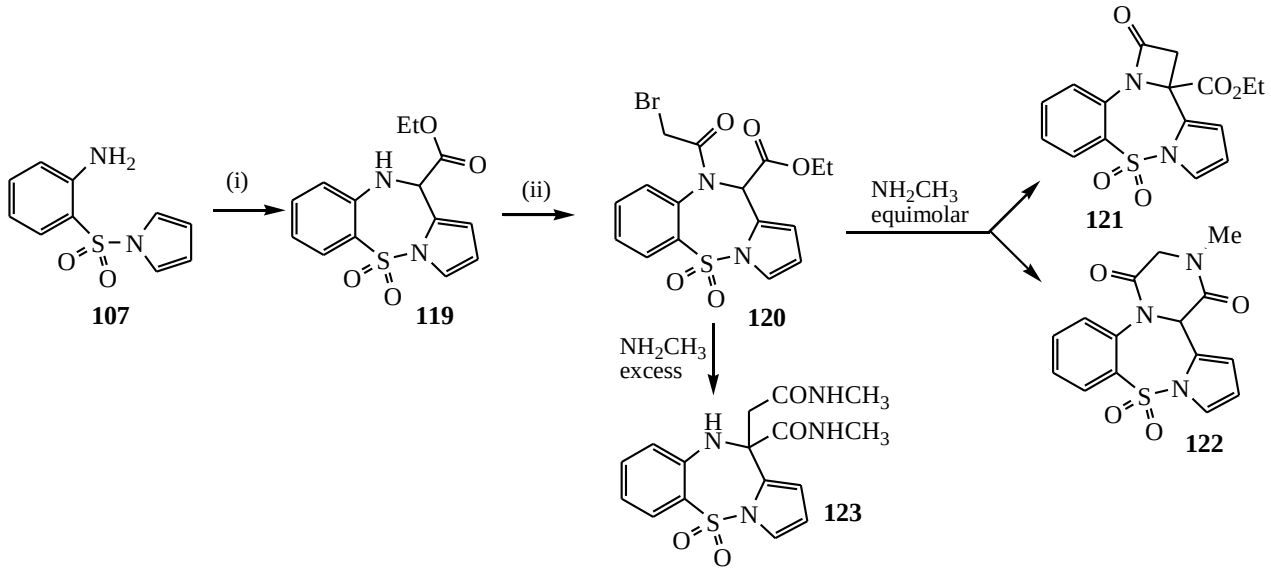
Scheme 1-16 (i) Toluene, heat (ii) $LiAlH_4$ (iii) H_2SO_4 (iv) H_2, Pd/C (v) $(CH_2O)_n$, H_2, Pd/C

The PBTD (**116**),[86,90] easily obtained from the substituted pyrrole (**107**), was hydrolysed with potassium hydroxide, after which TFA-induced ring closure afforded the azetidino pyrrolobenzothiadiazepine (**118,** as shown in Scheme 1-17).



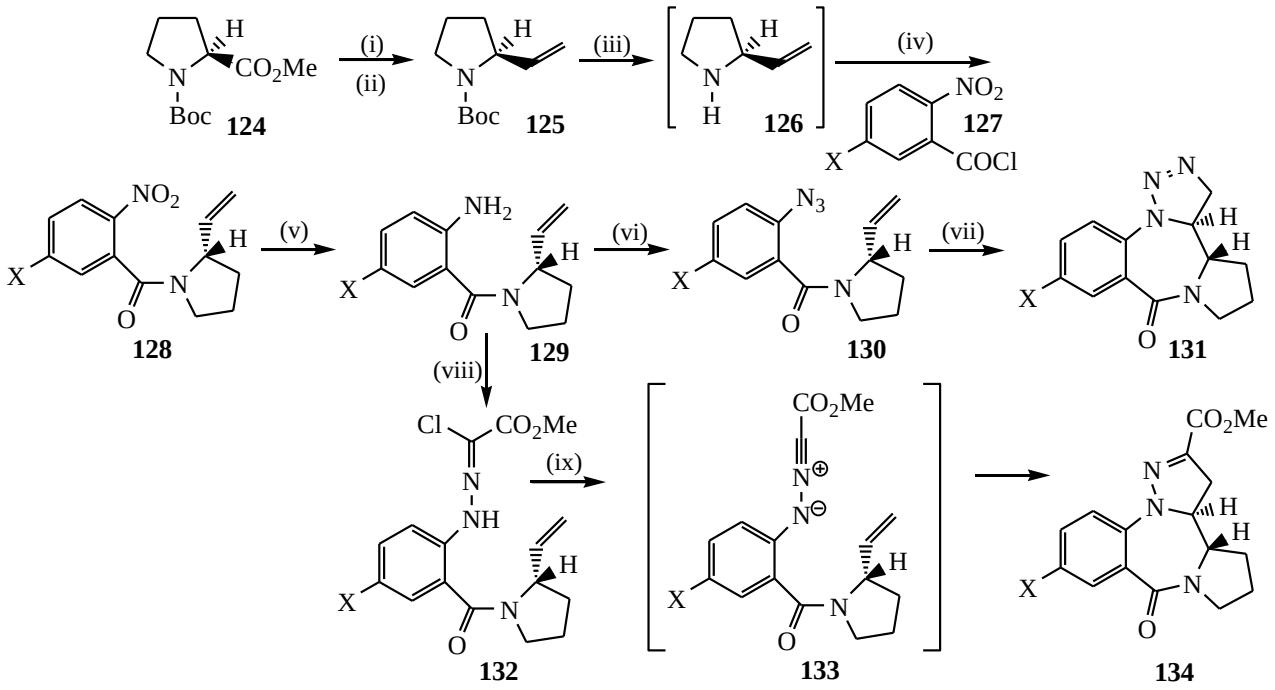
Scheme 1-17 (i) $(EtO)_2CHCH_2CO_2Et$, acetic acid/H_2O (ii) KOH (iii) Trifluoroacetic acid

The reaction of the substituted pyrrole (**107**, as shown in Scheme 1-18) with ethyl glyoxylate dimethoxy-acetal followed by bromoacetyl-bromide gave the PBTD (**120**). Treatment of compound (**120**) with an equimolar amount of aqueous methylamine in the presence of triethylamine in a sealed tube furnished a mixture of the lactam derivative (**121**) and the aptazepine derivative (**122**). Excess treatment of the methylamine under the same conditions yielded the compound (**123**).



Scheme 1-18 (i) ethyl glyoxylate dimethoxyacetal, TsOH, absolute EtOH, reflux, o.n. (ii) $BrCOCH_2Br$, $NaHCO_3$

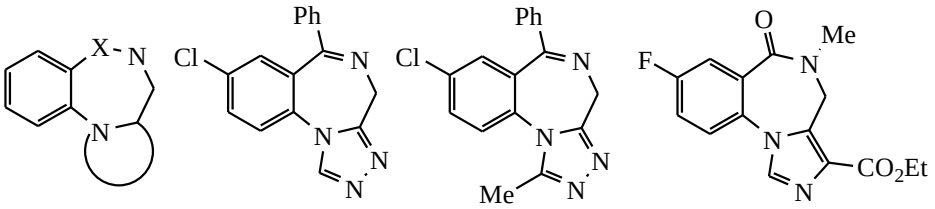
Broggini *et al*,[98,99] have published two routes to bretazenil analogues both of which started from the (*S*)-*N*-Boc protected proline derivative (**124**, as shown in Scheme 1-19), which was reduced in the presence of DIBAL-H and subjected to Wittig olefination to afford compound (**125**). Deprotection gave the intermediate (**126**). Coupling to the substituted 2-nitrobenzoyl chloride (**127**) afforded the 8-substituted 2-nitro derivatives, (**128**), which after reductive treatment with iron and acetic acid afforded the compounds (**129**). Diazotisation with sodium nitrite and hydrochloric acid followed by treatment with sodium azide gave compound (**130**), whilst coupling with methyl-2-chloroacetoacetate afforded the hydrazonyl derivative (**132**). Subsequent treatment of the azido derivative (**130**) by heating in carbon tetrachloride, or heating the hydrazonyl derivatives (**133**) with triethylamine and toluene yielded the [1,2,3]triazolo[1,5-*a*]pyrrolobenzodiazepine and pyrazolo[1,5-*a*]pyrrolobenzodiazepine derivatives (**131**) and (**134**), respectively, via 1,3-dipolar intramolecular cyclisation.



Scheme 1-19 (i) DIBAL-H, dry toluene, N_2 atmosphere, -60°C (ii) $Ph_3PMe^+I^-$, ^tBuOK, dry THF, N_2 atmosphere, 0°C (iii) TFA, N_2 atmosphere, 1hr (iv) K_2CO_3, dry toluene, reflux, 4hrs (v) Fe, AcOH, EtOH, reflux, 2hr (vi) $NaNO_2$, HCl, Et_2O, 0°C, 30 mins then NaN_3, r.t., 40min (vii) CCl_4, reflux, 5hrs (viii) $NaNO_2/H^+$ then $MeCOCHClCO_2Me$ (ix) Et_3N, toluene, reflux.

1.5 Other Tricyclic 1,4-Benzodiazepines.

In this thesis (see discussion) some of the target molecules were the "a" fused tricyclic benzodiazepine analogues represented by the general structure (**135**), shown below. A review of the published syntheses of such systems now follows. Examples of compounds in this class include Alprazolam (**136**), Estazolam (**137**) and Flumazenil (**4**), as shown in Figure 1-9. Alprazolam and Estazolam are common anxiolytic agents,[100,101] Flumazenil[100] is a cognitition enhancer and all are common anxiolytic agents and all have found both clinical and commercial success.



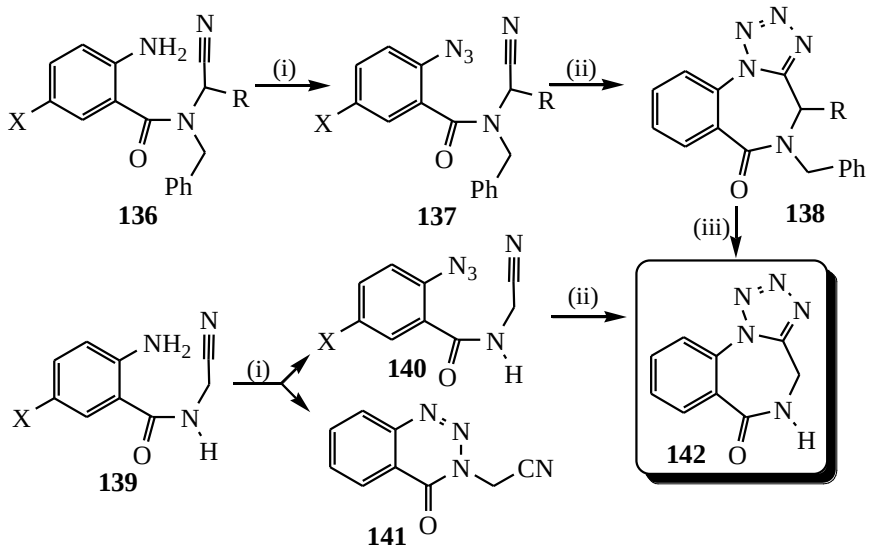
135 **136**, Alprazolam **137**, Estazolam **4**, Flumazenil

Figure 1-9

1,3-Dipolar cycloadditions of nitriles, alkenes and alkynes with azides will form the main part of this section (1.5.1) as they will become important later in this thesis. Also discussed are the Ugi four component reaction (1.5.2), the imidazolo formation approach (1.5.3) and the Harvey reaction (1.5.4) which are all important as they contain the triazole or tetrazole annulated ring on the "a" face. Finally, an approach to azetidinobenzodiazepines will be detailed (1.5.5), as this system will be of some importance later on in this thesis.

1.5.1 The 1,3-dipolar cycloaddition of azides with nitriles, alkynes and alkenes.

Broggini *et al*,[102] have explored the cyclisation of the dipolarophilic nitrile moiety with a dipolar azide (see reaction Scheme 1-20).



Scheme 1-20 (i) $NaNO_2$, HCl then NaN_3 (ii) Toluene, reflux (iii) 95% formic acid

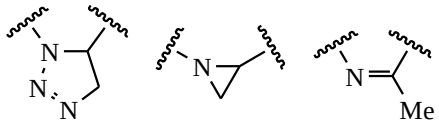
Starting from 2-aminocarbonylanilines (**136**), treatment with sodium azide gave the 2-substituted aryl azides (**137**), which could not be isolated in analytically pure form due to side cyclisation products. The intramolecular cyclisations of the crude compound (**137**), containing various R and X groups (shown in the table 1-3) were carried out by heating to reflux in dry toluene to afford compound (**138**).

Table 1-3

Entry	***X***	***R***	***Time***	***Products and yields***		
			(hrs)	**138**	**141**	**142**
137a	H	H	33	75	-	-
137b	Cl	H	77	95	-	-
137c	H	Me	64	30	-	-
137d	H	Ph	15	57	-	-
137e	H	4-Me-C_6H_6	16	56	-	-
137f	H	4-Me-C_6H_6	15	47	-	-
137g	H	4-Me-C_6H_6	16	65	-	-
140	-	-	480	-	5	6

The parent 4,5,7-unsubstituted product (**142**) was also seen as a valuable target and hence the starting material 2-amino-*N*-cyanomethylbenzamide (**139**) was converted to the corresponding azide derivative (**140**) as before. Unfortunately the yield of this reaction was low due to the formation of the undesired 3-cyanomethylbenzotriazin-4-one (**141**) (20% after purification). The 1,3-dipolar cycloaddition between the nitrile and the azide of compound (**140**) proved to be troublesome since a very long reaction time was required and extensive decomposition occurred at high temperatures. In addition compound (**140**) lost molecular nitrogen, generating the corresponding nitrene which resulted in the re-formation of compound (**139**). Due to this, compound (**142**) was best synthesised in 37% yield by benzyl group cleavage of compound (**138a**) with 95% formic acid.

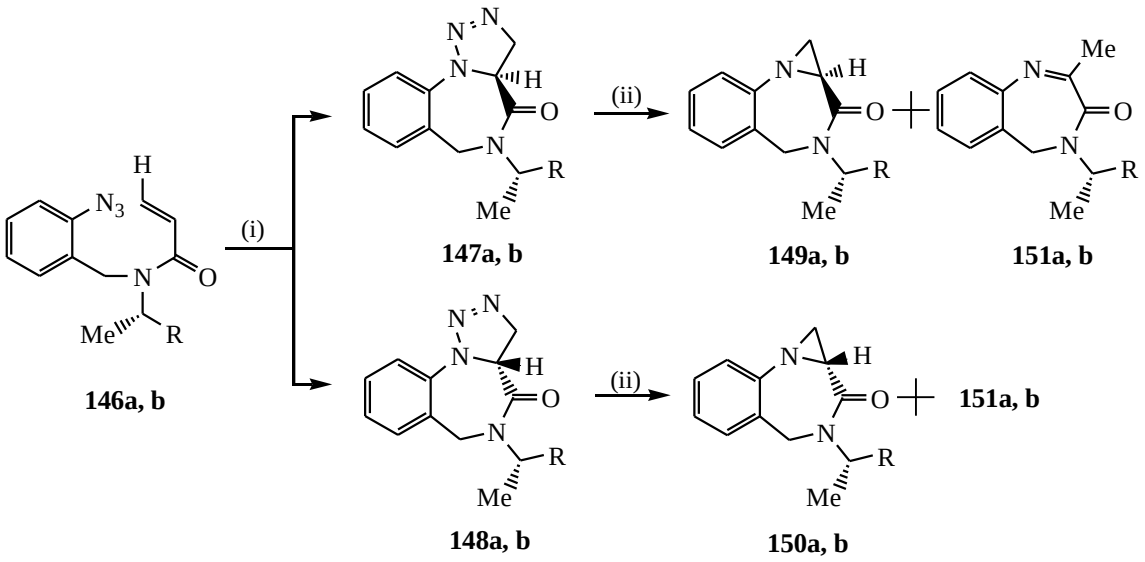
The intramolecular cycloaddition between an alkene and an azide can result in the formation of a triazolidine (**143**) which can spontaneously lose molecular nitrogen to form either an aziridine (**144**) or a methylimine (**145**) as shown in the Figure 1-10.[9,103]



143 **144** **145**

Figure 1-10

Broggini *et al*,[103] investigated these processes by the synthesis of compounds (**146a-d**) (see Schemes 1-21). The unsubstituted compounds (**146a-b**) were not fully characterised due to their ability at room temperature to undergo intramolecular cycloaddition to give a crude mixture of diastereoisomeric 1,2,3-triazolo[1,5-*a*][1,4]benzodiazepinones (**147a-b**) and (**148a-b**) on reaction work-up. Complete conversion into these compounds was accomplished by stirring a 0.02M ethereal solution of the crude azides at room temperature to give the yields shown in the table. Further treatment of the triazole derivatives (**147a-b**) and (**148a-b**) in toluene at reflux gave the corresponding diastereoisomeric aziridines (**149a-b**) and (**150a-b**) or the methyl imines (**151a-b**) via the extrusion of nitrogen from the triazole ring.



Scheme 1-21 (i) Et_2O, r.t. (ii) toluene, reflux

Table 1-4

Compound	*Time*	*Products and yields (%)*			
	(hrs)	**147**	**148**	**149**	**150**
146a	0.75[a]	61	28	-	-
146b	0.5[a]	57	18	-	-
146c	7.5[b]	-	-	58	33
146d	6.5[b]	-	-	47	31

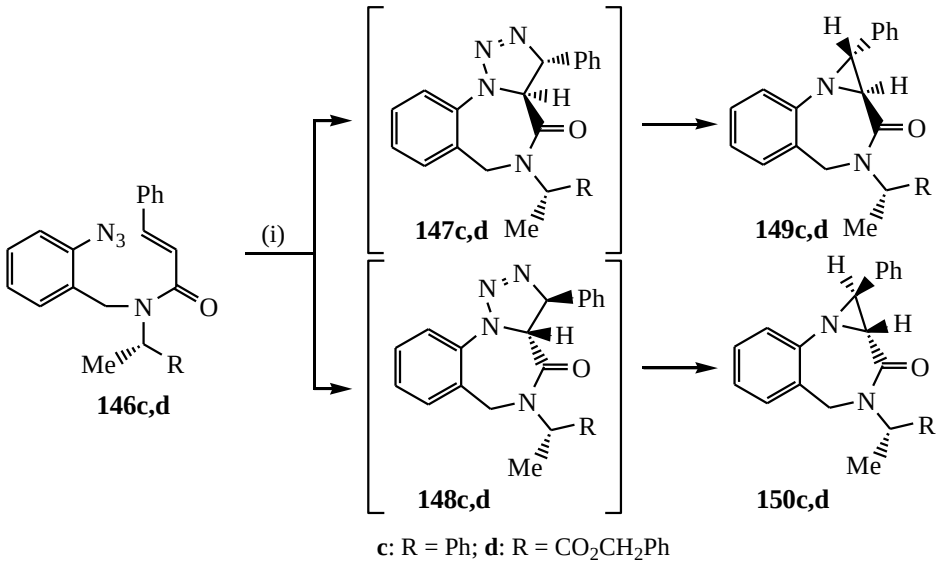
Intramolecular cycloadditions of N-alkenoyl aryl azides (**146**)

[a] in dry Et_2O, r.t.

[b] in refluxing toluene

In contrast, the phenyl-substituted azides (**146c-d**) (shown in the Scheme 1-22)[103] were more stable and were obtained as crystalline solids. The intramolecular cycloaddition was accomplished by heating at reflux in toluene and 1% triethylamine giving the diastereoisomeric aziridino-[2,1-

c][1,4]benzodiazepinones (**149c-d**) and (**150c-d**) via the intermediate triazoles with thermal expulsion of molecular nitrogen in the yields shown in the table 1-5.



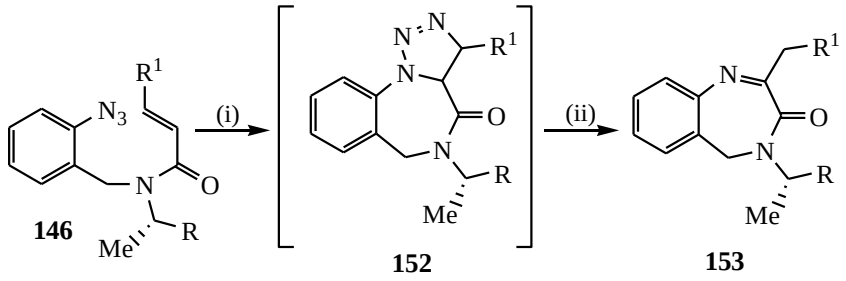
c: R = Ph; **d**: R = CO_2CH_2Ph

Scheme 1-22 (i) toluene reflux

Table 1-5

Compound	***Time***	***Products and yields (%)***					
	(hrs)	**149a**	**149b**	**150a**	**150b**	**151a**	**151b**
147a	1	43	-	-	-	44	-
147b	1	-	48	-	-	44	-
148a	6	-	-	30	-	-	42
148b	8	-	-	-	53	-	43

When the same reaction was carried out in a study by Molteni *et al*,[104] the homochiral azides (**146a-f**) when heated in toluene with 2% TsOH gave pure imines (**153a-f**) with high yields (92-98%) after recrystallisation from diisopropyl ether. It is noteworthy that the homochiral azides (**146a-f**) were stable at room temperature and did not undergo room temperature intramolecular cyclisation to the intermediate (**152a-f**).



Scheme 1-23 (i) TsOH (2% mol), toluene, reflux (ii) $-N_2$

A list of the different R and R^1 groups in compound (**153**) are listed in the table 1-6:

Table 1-6

Entry	***a***	***b***	***c***	***d***	***e***	***f***
R	CO_2Bn	CO_2Bn	CO_2Bn	Ph	Ph	Ph
R^1	H	Me	Ph	H	Me	Ph

The loss of molecular nitrogen from intermediate (**152**) to form product (**153**) can occur via two different routes.[104]

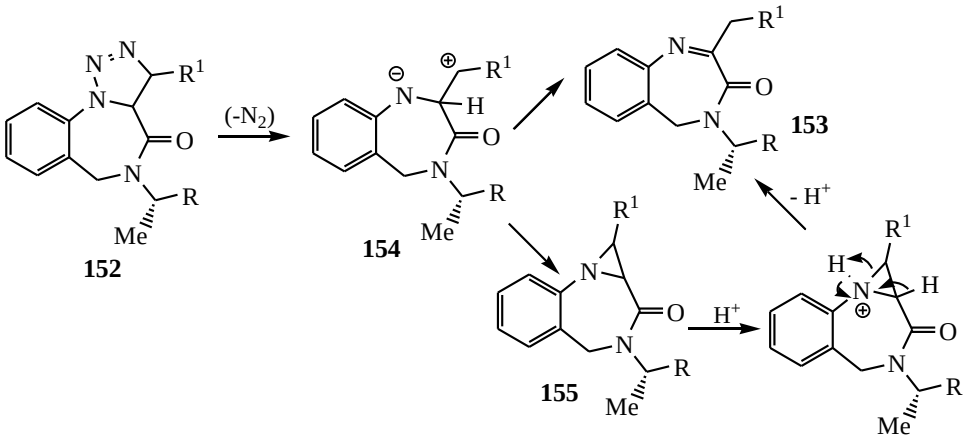
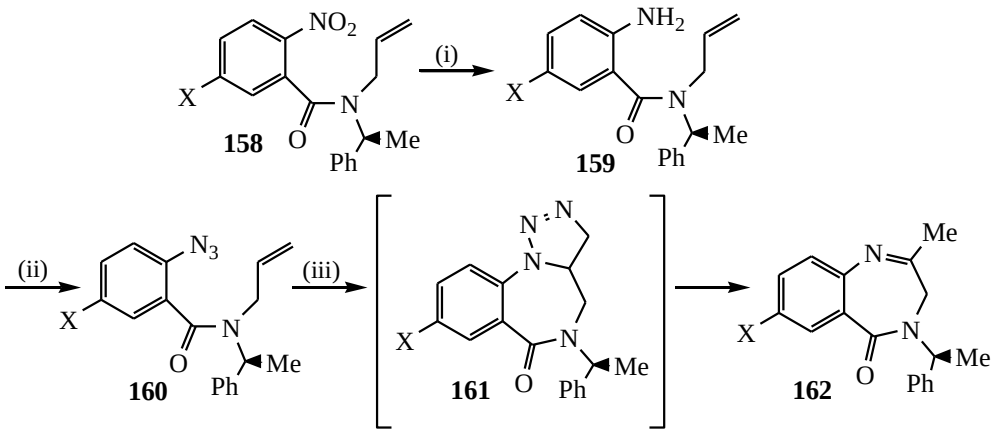


Figure 1-11

The first route requires prototropic migration on compound (**154**) after the loss of nitrogen from compound (**152**) to give compound (**153**). Alternatively, ring closure gives the aziridino[2,1-

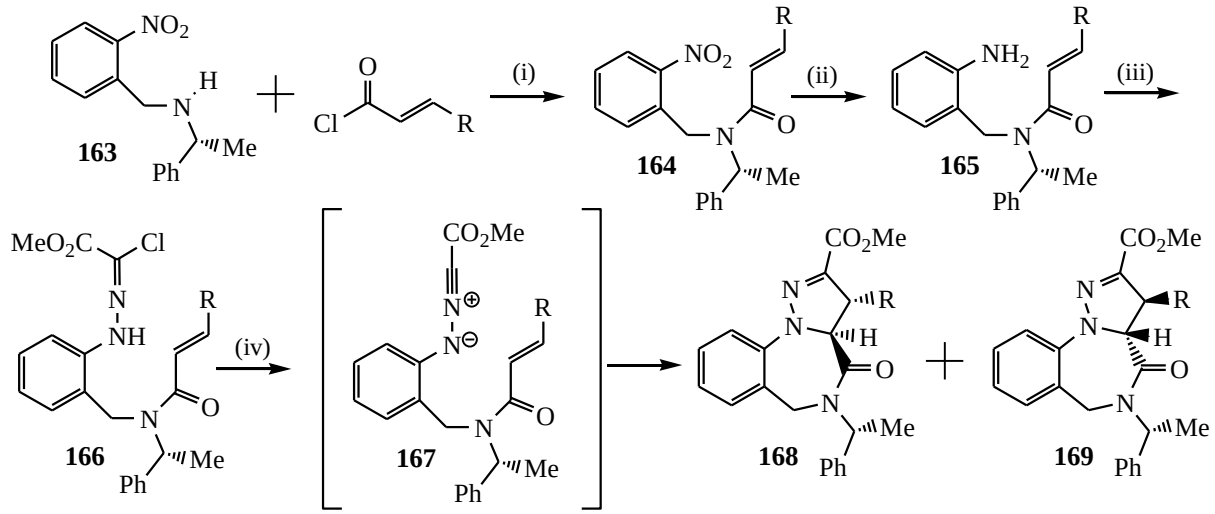
c][1,4]benzodiazepinones (**155**), which in the presence of a catalystic amount of TsOH yielded product (**153**) through the mechanism shown in Figure 1-11.

Broggini and Baccalli *et al*,[9] have also utilised intramolecular cycloaddition between an alkene and azide to yield imines directly as shown in the Scheme 1-24. Reduction of the readily available compound (**158**) afforded compound (**159**). The diazotisation of (**159**) followed by treatment with sodium azide led to the derivatives (**160**) which could be isolated before intramolecular cyclisation between the alkene and the azide. The conversion of (**160**) to (**162**) via the intermediate triazoline (**161**) was achieved by heating to reflux in toluene, which proceeded in good yields (54-72%).



Scheme 1-24 (i) Fe, EtOH, AcOH, (ii) $NaNO_2$, HCl then NaN_3 (iii) toluene, reflux. X : **a** = H, **b** = Cl, **c** = F

A further example of the formation of a seven membered ring utilised a different type of intramolecular 1,3-dipolar cycloaddition between an alkene and a nitrilimine in the intermediate compound (**167**) to make diastereoisomers of pyrazolo[1,5-*a*][1,4] benzodiazepine-4-ones (**168**) and (**169**) (the yields are shown in the table 1-7) which were isolated via column chromatography as pure diastereoisomeric cycloadducts.[105] The nitrilimine precursor (**166**) was easily constructed from precursor (**163**) as shown Scheme 1-25.

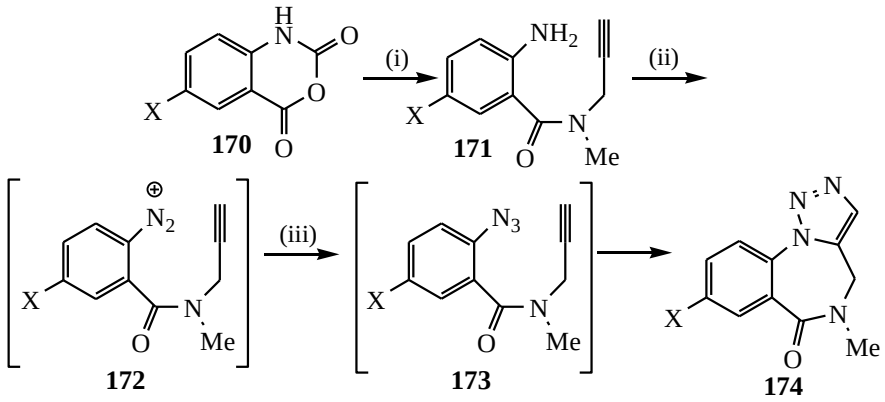


Scheme 1-25 (i) K_2CO_3, toluene, reflux (ii) Fe, EtOH, 20% AcOH (iii) $NaNO_2$, HCl then $MeCOCHClCO_2Me$ (iv) Ag_2CO_3, dioxane or Et_3N, dioxane. R= **a**: H, **b**: Me, **c**: Ph

Table 1-7

Entry	Compound	Base (*Eq.*)	Time (*hrs*)	Products and Yields (%)	
				168	**169**
a	**166a**	Ag_2CO_3 (2)	52	75	21
b	**166b**	Ag_2CO_3 (2)	140	61	33
c	**166c**	Ag_2CO_3 (2)	140	69	27
d	**166a**	Et_3N (5)	24	52	20

The final example in this section involves a 1,3-dipolar cycloaddition between an azide and an alkyne. The synthesis of these two functional groups involved the reaction of 5-substituted isatoic anhydrides (**170**) with methylpropargylamine as shown in the reaction Scheme 1-26.[100]

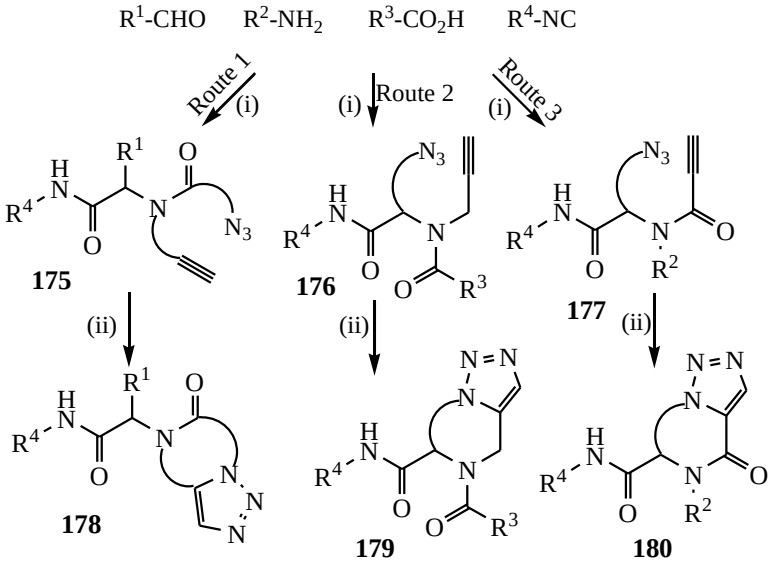


Scheme 1-26 (i) *N*-Methylpropargylamine (ii) $NaNO_2$, HCl (iii) NaN_3, X = H, Cl, F, NO_2, NH_2

The reaction was carried out in boiling dioxane in the case of (**170**) (where X = H) and for the less reactive substrates (where X ≠ H) in boiling DMF to give the anthranilamides (**171**) in moderate yields (44-54%). These compounds were all treated with sodium nitrite and acid to form the diazonium salts (**172**) followed by sodium azide to form the azides (**173**). As before the azides could not be isolated as they underwent *in situ* 1,3-dipolar cycloaddition with the terminal alkyne to yield the [1,2,3]triazolo[1,5-*a*][1,4]benzodiazepin-5-one derivatives (**174**) in 41-55%.

1.5.2 Reactions involving multi-component Ugi processes.

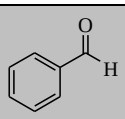
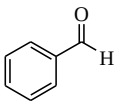
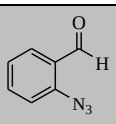
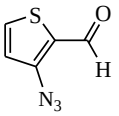
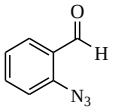
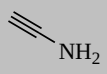
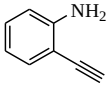
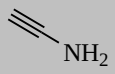
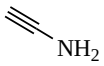
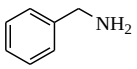
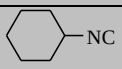
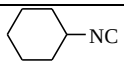
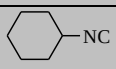
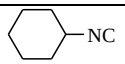
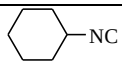
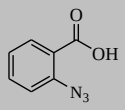
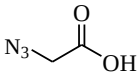
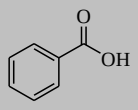
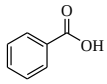
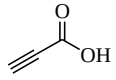
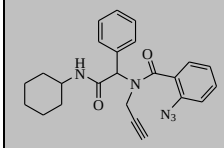
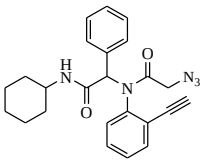
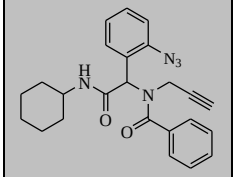
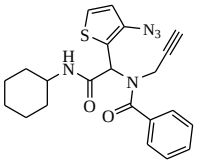
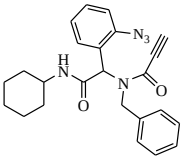
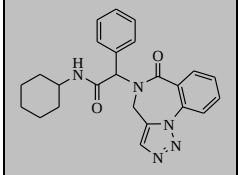
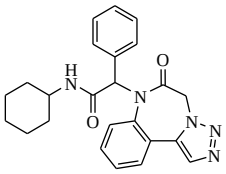
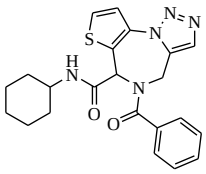
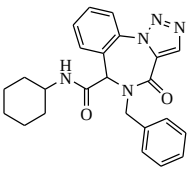
Another route to provide the terminal alkyne and the azide that allow access to triazolobenzodiazepines has been achieved by Akritopoulou-Zanze *et al*,[106] who utilized the Ugi multi-component reaction with components containing a terminal alkyne and an azide. The synthesis is shown in the Scheme 1-27, and a variety of seven membered rings fused with the triazoles have been successfully synthesised using coupling partners containing the azide functionality on the carboxylic acid (route 1) or aldehyde inputs (route 2 and 3) and the acetylenic functionality on the amine (routes 1 and 2) or carboxylic acid (route 3).



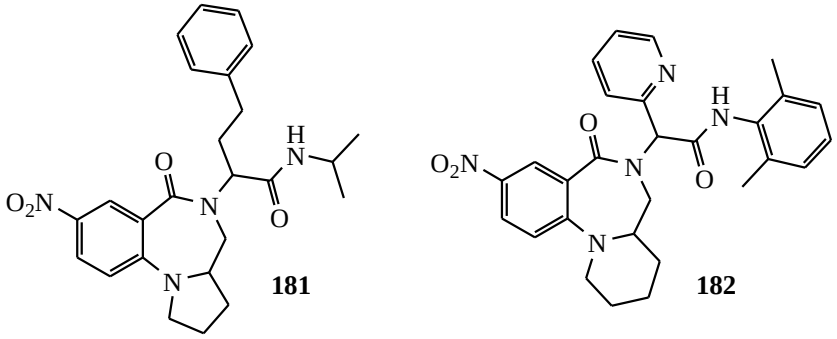
Scheme 1-27 (i) MeOH, 24-48 hours, r.t. (ii) benzene, reflux, 4-18hrs.
(R groups are shown in table 1-8)

The Ugi reactions proceeded smoothly to provide the intermediates in moderate to high yields as shown in the table 1-8. Heating these intermediates to reflux in benzene afforded the cyclised products in excellent yields, via intramolecular alkyne-azide cycloaddition (IAAC).

Table 1-8

Aldehyde					
Amine					
Isocyanide					
Acid					
Ugi Product					
Ugi Yield (%)	81	71	51	33	50
IAAC Product					
IAAC Yield (%)	96	97	96	97	86

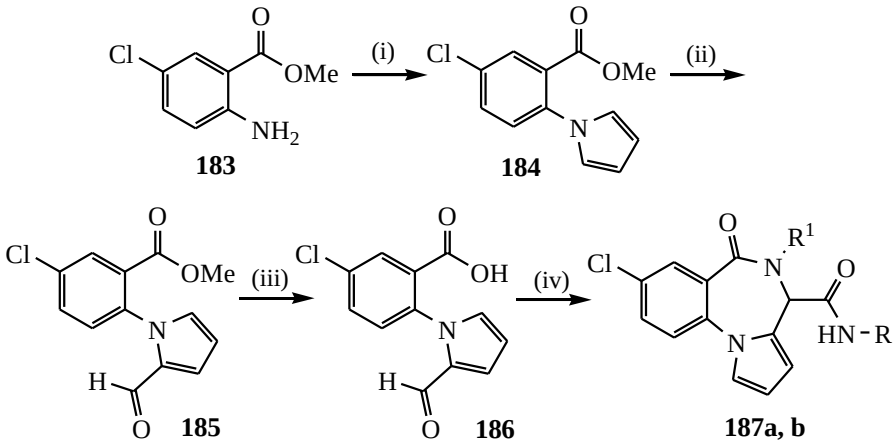
The four pot Ugi condensation reaction has proven to be a simple and effective route through to other 1,4-benzodiazepin-5-ones. Thus, Tempest *et al*,[10] have successfully synthesised the compounds (**181**-**182**) in the Figure 1-12.



181 **182**

Figure 1-12

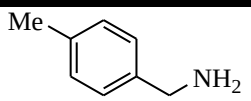
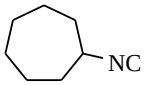
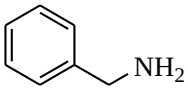
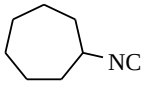
A four pot condensation in which a variety of substituents could be added in the final multi-component Ugi-type step (shown in Scheme 1-28) started from the commercially available aminocarboxylate (**183**) which was treated with 2,5-dimethoxytetrahydrofuran in acetic acid to form the 1*H*-pyrrol-1-yl derivative (**184**). The aldehyde moiety of compound (**185**) was introduced using $POCl_3$ in DMF in good yields (64-77%) and the precursor (**186**) was synthesised by hydrolysis of the ester with sodium hydroxide solution to provide the carboxylic acid and the aldehyde moieties (two of the four parts of the Ugi four pot condensation reaction). The final part of the synthesis introduced the other two components, the isocyanate and the amide (shown in the table 1-9), to provide the analogues (**187a-b**) in 75-85% yield.[107]



183 **184** **185** **186** **187a, b**

Scheme 1-28 (i) 2,5-dimethoxytetrahydrofuran, AcOH, 4hrs (ii) DMF, $POCl_3$ (iii) 1% aq. NaOH, 40°C, 8hrs (iv) R-NC, R^1-NH_2, MeOH, 40°C, 4-18hrs. (See table 1-9 for R groups and yields)

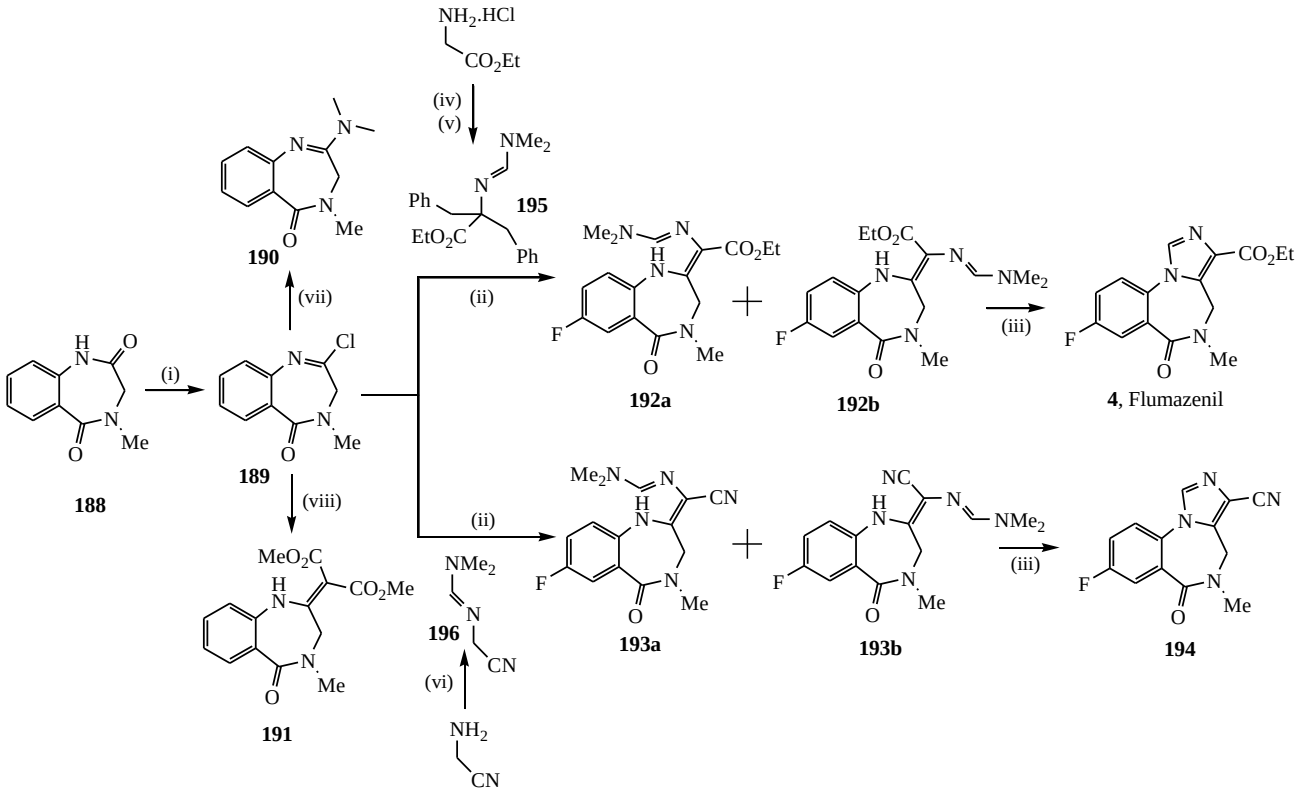
Table 1-9

Entry	Amine	Isonitrile	Yield (%)
R			**75**
R[1]			**85**

1.5.3 Imidazolo ring formation: imidazolobenzodiazepines.

Flumazenil (structure **4** shown in the Scheme 1-29) blocks the central effects of the classical benzodiazepines and has been used in the treatment of benzodiazepine overdosing and sedation as well as being evaluated for the improvement of cognitive function in Alzhiemer's patients.[108]

The synthesis (shown in the Scheme 1-29)[108] starts from the iminochloride (**189**) which was prepared by the dropwise addition of a slight excess of $POCl_3$ to a hot toluene solution of the amine (**188**) in the presence of *N,N*-dimethyl-*p*-toluidine. The treatment of the iminochloride (**189**) with 2 eq of the lithiated (**195**) at -35°C gave rise to a mixture of the uncyclised intermediate (**192a**) and Flumazenil (**4**) (approx 20:1) on aqueous work up. A non-aqueous workup procedure allowed the isolation of the intermediate (**192a**), isomerisation to compound (**192b**), and intramolecular cyclisation and elimination of dimethylamine to produce Flumazenil (**4**) in isolated yields of upto 98%.

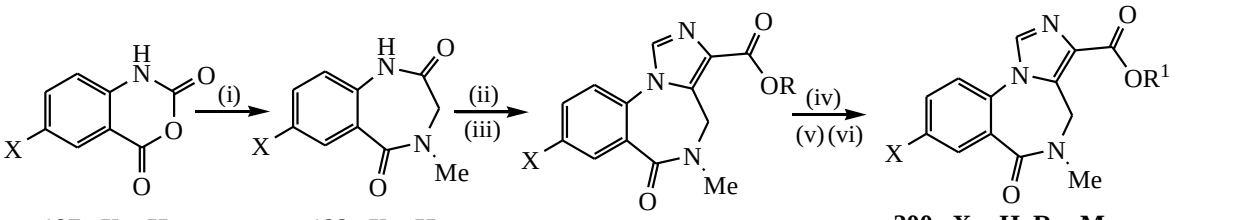


Scheme 1-29 (i) $POCl_3$, *N*,*N*-dimethyl-*p*-toluidine toluene, 100°C, 2hrs, 86% (ii) LHMDS, THF, -30°C, 2hrs, *N*,*N*-dimethyl-*p*-toluidine (iii) AcOH, reflux (iv) DMF-DMA, Et_3N, DCM, r.t., 1hr (v) BnzCl (vi) DMF-DEA, reflux, 5 hrs (vii) Me_2NH, EtOH, 30mins (viii) $CH_2(CO_2Me)_2$, LHMDS, THF, -30°C, 16hrs.

This method was further exploited in the synthesis of compound (**194**) by the treatment of the iminochloride (**189**) with the amidine (**196**) as the building block to give the intermediates (**193a** and **b**) as a 1:1 mixture. The isomer (**193a**) was converted to the more stable isomer (**193b**) which could then be heated in the presence of acetic acid to give, in quantitative yields, the nitrile derivative (**194**).

The synthesis of imidazo[1,5-*a*][1,4] benzodiazepines has been explored by Gu *et al*,[109] by employing the reactions as shown in the Scheme 1-30. The synthesis started from commercially

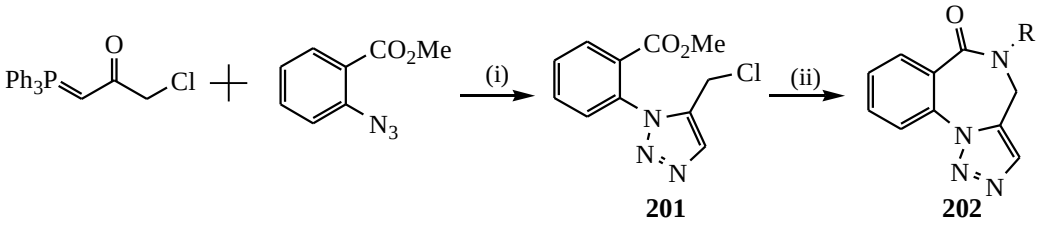
available isatoic anhydride (**197a**) or 5-chloroisatoic anhydride (**197b**) which was heated in the presence of *N*-methylglycine in dimethyl sulfoxide to afford the the corresponding di-lactams (**198a-b**). Deprotonation with sodium hydride in THF and DMF, followed by the treatment with diethylphosphorochloridate, formed the intermediate enol-phosphates (not shown). These were subsequently reacted with a solution of ethyl or tert-butylisocyanoacetate and sodium hydride in DMF to afford compounds (**199a-d**). Further side chain manipulation of (**199a-b**) yielded examples (**200a-h**).



Scheme 1-30 (i) *N*-Methylglycine, DMSO, 140°C (ii) NaH, THF, DMF, $(EtO)_2POCl$ (iii) NaH, DMF, $CNCH_2CO_2R$ (iv) 10% KOH in MeOH, H_2O, HCl (v) $SOCl_2$, toluene (vi) R^1OH.

1.5.4 The Harvey approach.

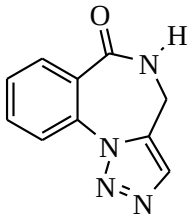
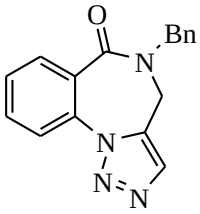
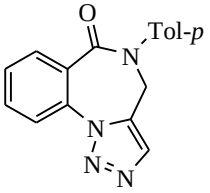
This synthesis (shown in Scheme 1-31) started with methyl 2-azidobenzoate and its thermal cycloaddition to (3-chloro-acetonylidene)triphenylphosphorane via a Harvey approach which is visualised as a 1,3-dipolar cycloaddition of the azide group to the C=C bond of the resonance phosphorane structure with spontaneous elimination of the stable phosphine oxide to give the intermediate compound (**201**). The treatment of compound (**201**) with ammonia, benzylamine or *p*-toludine gave the 1,2,3-triazolo[1,5-*a*][1,4]benzodiazepine derivatives (**202**) in the yields shown in the table 1-10.[101]



201 **202**

Scheme 1-31 (i) toluene, reflux (ii) see table 1-10.

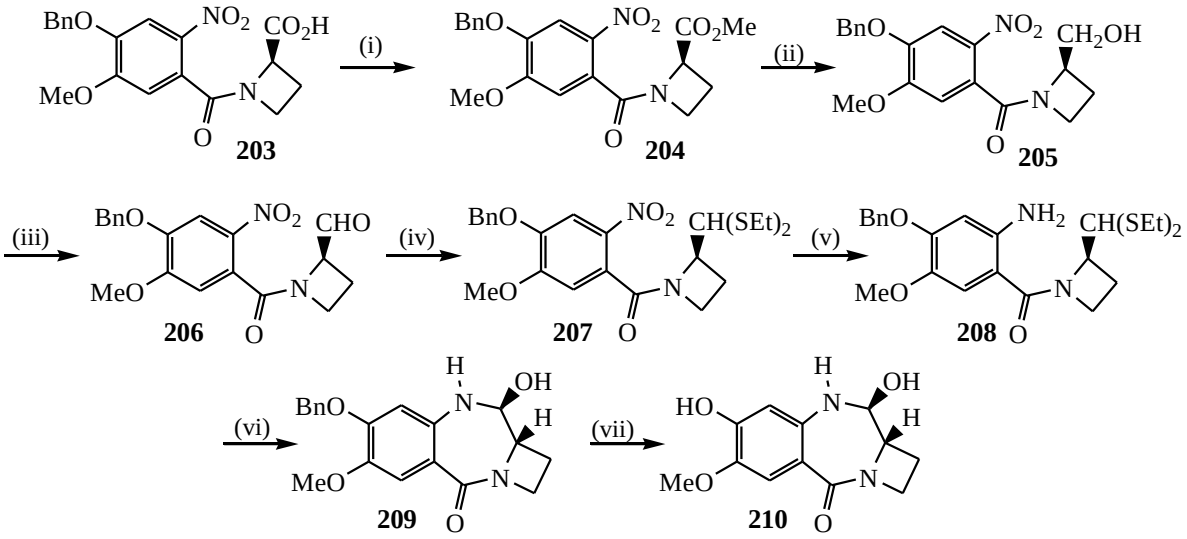
Table 1-10

Reaction conditions	***Product***	***Yield (%)***
NH_3, CH_3CN, 80°C, 12hrs, NOTE Et_3N was not needed		87
$BnNH_2$, Et_3N, toluene, reflux, 5 days		80
p-toluidine, Et_3N, toluene, 140°C, 14 days		52

1.5.5 Thioacetal-amine ring closure to form an azetidinobenzodiazepine.

Bose and Srinivas[110] have replaced the C ring pyrrole of the PBD structure with an azetidine ring, to produce an azetidino[2,1-*c*][1,4]benzodiazepine ring system (ABD). This synthetic approach, shown in the Scheme 1-32, involved the initial preparation of the 4-benzyloxy-5-methoxy-benzoic acid of the A ring fragment. This fragment was converted into the corresponding acid chloride under the

usual conditions and coupled to (*S*)-azetidine-2-carboxylic acid in the presence of triethylamine, to afford the corresponding amide (**203**) which was used without purification and converted to the methyl ester by treatment with thionyl chloride and methanol. Formation of the aldehyde (**206**) was achieved with lithium borohydride to afford the alcohol in 78% yield, followed by subsequent oxidation. The aldehyde (**206**) proved to be unstable, so was converted to the diethyl thioacetal (**207**) which was further reduced with tin(II)chloride dihydrate to afford the uncyclised intermediate precursor (**208**). The deprotection of the diethyl thioacetal, using $HgCl/CaCO_3$ led to the B-ring closure to afford the carbinolamine (**209**), which upon debenzylation yielded the azetidine ring system (**210**).



Scheme 1-32 (i) $SOCl_2$, MeOH (ii) $LiBH_4$, THF, 0°C, r.t. (iii) IBX, DMSO, r.t., 30mins (iv) EtSH, TMSCl, r.t., 12hrs (v) $SnCl_2.2H_2O$, MeOH. reflux, 40mins (vi) HgCl, $CaCO_3$, $MeCN:H_2O$ (4:1), 2.5hrs (vii) 10% Pd/C, cyclohexadiene, EtOH, 45 mins.

1.6 Tricyclic Benzothiadiazepines.

In this the final part of the introduction the synthesis of tricyclic derivatives of the 1,2,5-benzothiadiazepines will be discussed. These structures have attracted interest as novel inhibitors of human immunodeficiency virus type 1 (HIV-1),[88,111] and examples are shown in the Figure 1-13:

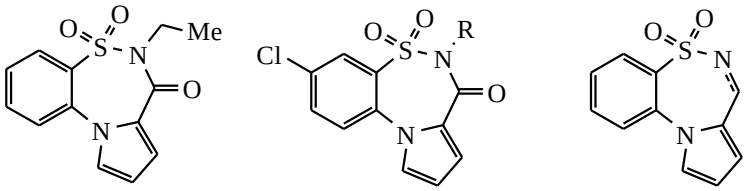
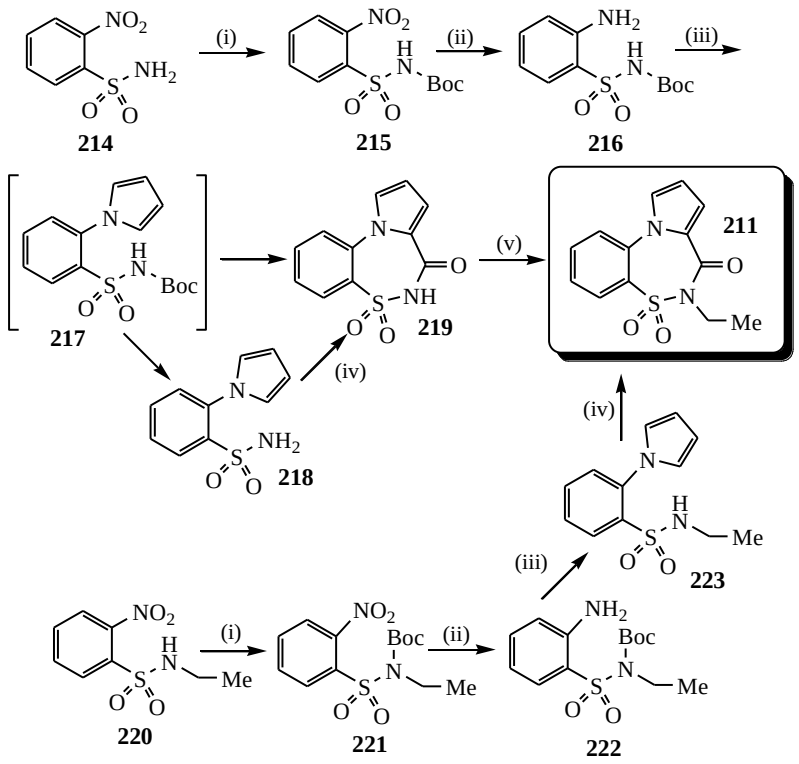


Figure 1-13

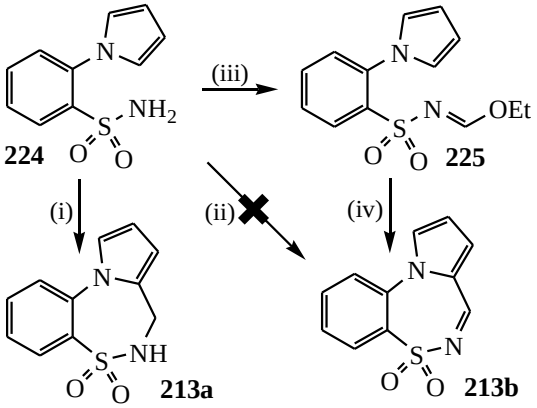
Di Santo *et al*,[111] have synthesised analogues of compound (**211**), shown in the Figure 1-13. Hence, the reaction of 2-nitrobenzensulfonamide with tert-butoxycarbonic anhydride in the presence of DMAP afforded the protected 2-nitrobenzenesulfonamide (**215**). Reduction in the presence of iron and hot acetic acid at 60°C gave compound (**216**), which was further treated with 2,5-dimethoxytetrahydrofuran in hot acetic acid to undergo the Clauson-Kaas reaction to form the pyrrole ring system of compound (**217**). The formation of the pyrrole ring system occurred easily and was accompanied by deprotection of the amide moiety with formation of the required pyrrole sulfonamide (**218**). Also, isolated as a side product of the reaction was the tricyclic pyrrolobenzothiazepinone (**219**), due to acid catalysed intramolecular cyclisation of the intermediate (**217**), with elimination of tert-butylalcohol. Further transformation of 2-(1*H*-pyrrol-1-yl) benzenesulfonamide (**218**) to (**219**) was accomplished by treatment with triphosgene. The final stage was the alkylation of compound (**219**) with iodoethane to yield the analogue (**211**) in 72% (as shown in the Scheme 1-33).



Scheme 1-33 (i) $(Boc)_2O$, DMAP (ii) Fe, AcOH (iii) 2,5-dimethoxytetrahydrofuran, AcOH (iv) triphosgene (v) C_2H_5I, K_2CO_3.

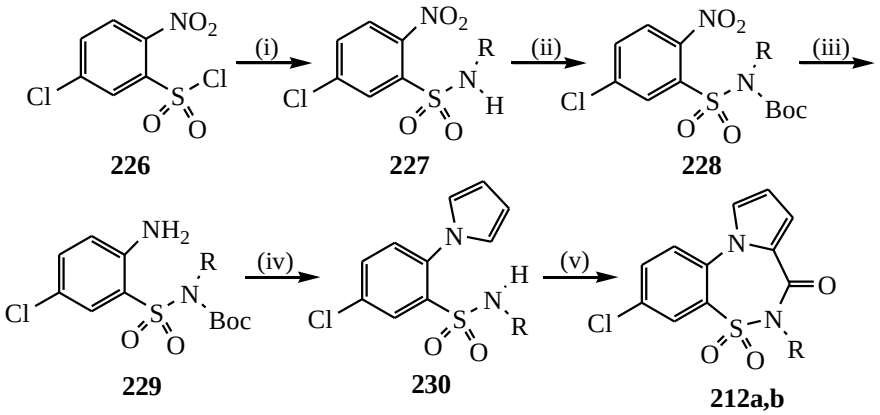
The second route started from the 2-nitrobenzenesulfonamide derivative (**220**) which was Boc-protected and reduced, as carried out for the first route. The Clauson-Kaas reaction yielded the *N*-ethyl-2-pyrrolo system (**223**), which was treated with triphosgene to give the analogue (**211**) in 62% yield (as shown in the Scheme 1-33).

Disanto *et al*,[111] also synthesised the analogue (**213a**) (shown in the Scheme 1-34) by the treatment of 2-(1*H*-pyrrol-1-yl)benzenesulfonamide (**224**) with paraformaldehyde in refluxing ethanol. Intramolecular cyclisation with formic acid as a reagent did not yield the compound (**213b**) and so the treatment of (**224**) in the presence of triethyl orthoformate to yield (**225**), and subsequent intramolecular cyclisation was used to access compound (**213b**).



Scheme 1-34 (i) $(CH_2O)_n$, EtOH (ii) Formic acid (iii) H^+, $HC(OEt)_3$ (iv) H^+

The 3-chloro-pyrrolo[2,1-*d*]1,2,5]benzothiadiazep-7(6*H*)-one 5,5-dioxide derivatives (shown in the Scheme 1-35) were synthesised starting from 5-chloro-2-nitrobenzenesulfonyl chloride (**226**) which was successfully coupled to secondary amines. The *N*-protection of the sulfonamide was achieved with $(Boc)_2O$ in the presence of 4-dimethylaminopyridine (DMAP) to afford *N*-tert-butoxycarbonyl-5-chloro-2-nitrobenzenesulfonamide derivatives (**228**). Reduction with iron in hot acetic acid to afford (**229**) followed by treatment with dimethoxytetrahydrofuran in acetic acid at reflux via the Clauson-Kaas method yielded the 5-chloro-(1*H*-pyrrol-1-yl)benzenesulfonamides (**230**). Finally, the cyclised compounds (**212a-b**) were obtained by treatment with triphosgene.[88]



Scheme 1-35 (i) R-NH_2 (ii) $(Boc)_2O$, DMAP (iii) Fe, AcOH (iv) 2,5-dimethoxytetrahydrofuran, AcOH (v) triphosgene R = H, Et.

2 Discussion: Synthesis of the tetrazolopyrrolobenzodiazepines and tetrazolopyrrolobenzothiadiazepines.

In this research project the aim, summarised in Figure 2-1, is to synthesise tetra- and triazolo-analogues of the pyrrolobenzodiazepines, pyrrolobenzothiadiazepines, benzodiazepines and benzothiadiazepines. As discussed in the introduction, these compounds are of great interest as synthetic targets due to their potential medical properties. In the first part of the discussion, the synthesis of triazolo/tetrazolo pyrrolobenzodiazepines and pyrrolobenzothiadiazepines will be discussed (Sections 2.1 & 2.2), followed by the synthesis of other triazolo/tetrazolo benzodiazepines (Section 3), alkene cycloaddition (Section 4), and the further developments towards benzodiazepine analogues (Sections 5 & 6).

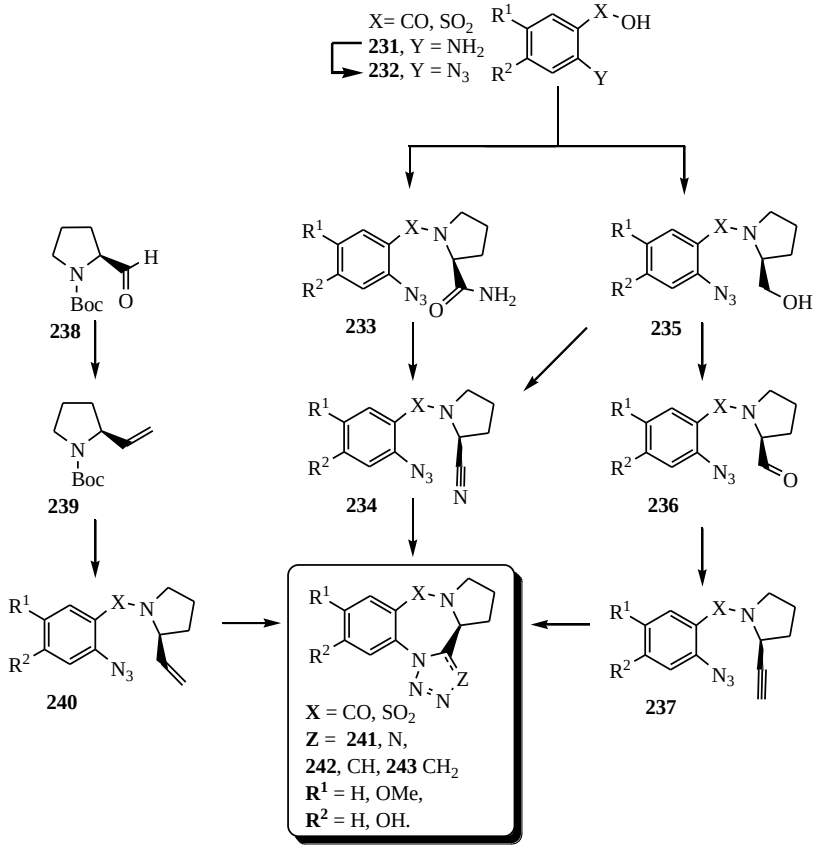
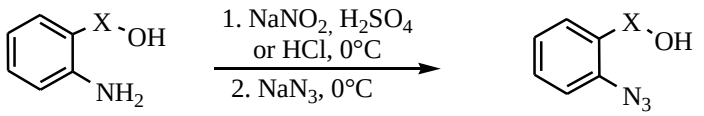


Figure 2-1

2.1 Synthesis of Tetrazolopyrrolobenzodiazepines and Tetrazolopyrrolobenzothiadiazepines.

2.1.1 Synthesis of 2-azidobenzoic and sulfonic acids (**232**).



231a, X = CO
231b, X = SO_2

232a, X = CO
232b, X = SO_2

Scheme 2-1

The chemistry shown in Scheme 2-1 relies upon the use of 2–azidobenzoic acid (**232a**, X = CO) and 2-azidobenzenesulfonic acid (**232b**, X = SO_2) as starting materials. The synthesis[69] of both the azido products started from the commercially available corresponding anilines [(**231** X = CO, SO_2) Aldrich]. Straightforward diazonium formation followed by the displacement of nitrogen by the nucleophilic azide anion gave the products, and probably proceeds via the mechanism shown in Figure 2-2 to give the azides in high yields, 95%.

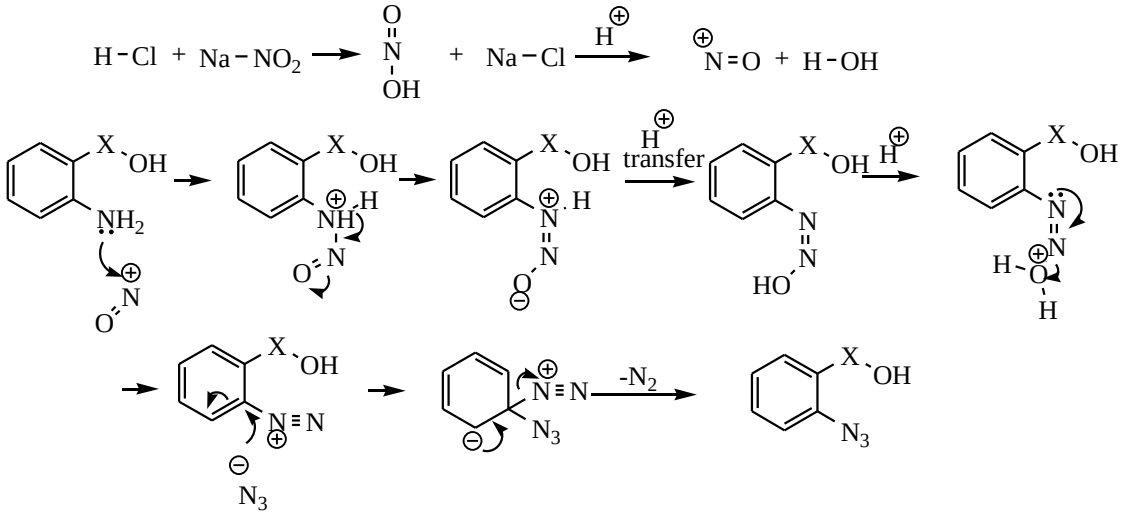
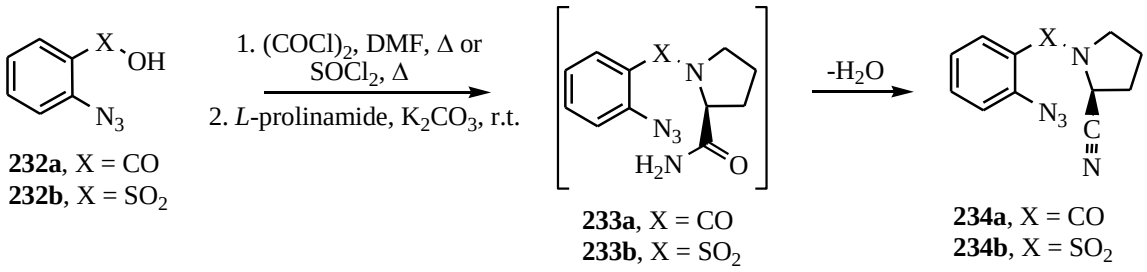


Figure 2-2

The ^{1}H NMR spectrum (500 MHz) was consistent with the structure of 2-azidobenzoic acid (**232a**, X = CO) which showed four aromatic protons with a 1,2-substitution pattern i.e. two doublets at 7.20 ppm, 7.67 ppm and two pseudo triplets at 7.15 and 7.49 ppm, respectively. The appearance of a sharp peak at υ_{max} 2124 cm^{-1} in the IR spectrum is consistent with an azide group being present, which along with the correct mass of 186.0 $[M+Na]^+$ supports the structural assignment.

The structural assignment of the 2-azidobenzenesulfonic acid (**232b**, X = SO_2) was consistent with the 1,2-substitution pattern present in the aromatic region of the ^{1}H NMR (400 MHz) spectrum with triplets at 7.15 ppm, 7.45 ppm and the doublets being at 7.28 and 7.70 ppm. The IR spectrum of the product showed the diagnostic azide absorption peak at υ_{max} 2122 cm^{-1} and confirmed the formation of the product.

2.1.2 Coupling of the acid chlorides with prolinamide.



232a, X = CO
232b, X = SO_2

233a, X = CO
233b, X = SO_2

234a, X = CO
234b, X = SO_2

Scheme 2-2

With the azide group in place, the next step was the coupling of the corresponding acid chloride to prolinamide with a view to subsequent dehydration to put in place the nitrile group. The carboxylic acid was refluxed in $SOCl_2$ to give the acid chloride which was coupled up with the prolinamide in a mixed phase reaction pot containing K_2CO_3 as the base. The *N*-aryl prolinamide (**233a**, X = CO) was not isolated from the mixture but instead underwent *in situ* dehydration to give the nitrile (**234a**, X = CO) as a mixture of rotamers in 33% yield. This may have been due to an excess of the acid chloride in solution which initiated the dehydration as shown in the Figure 2-3.

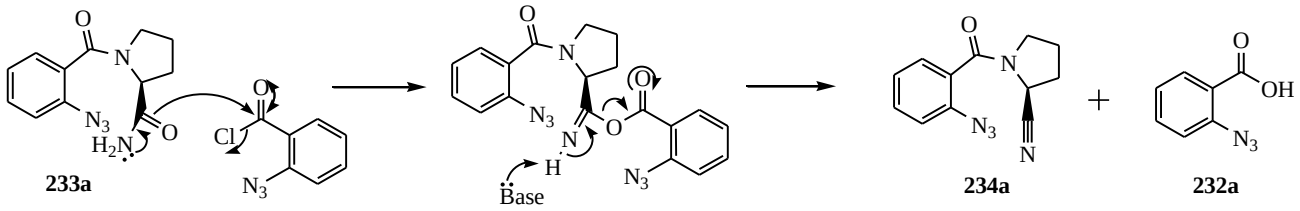


Figure 2-3

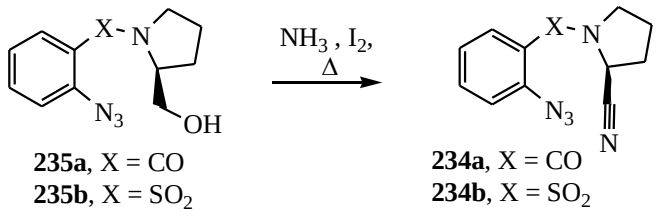
The structure of (**234a**) was confirmed by the ^{1}H (400 MHz) NMR spectrum which showed loss of the amide protons. The aliphatic CH_2 protons of the pyrrolidine ring structure were found at 2.01-2.10 (1H), 2.11-2.25 (1H), 2.27-2.41 (1H), 3.27-3.34 (1H), 3.37-3.45 (1H), 3.72-3.83 (1H) ppm with the single CH in the ring at 4.92 ppm. The aromatic protons were located downfield at 7.23 (2H), 7.34 and 7.48 ppm. The ^{13}C Dept-135 (100 MHz) NMR spectrum showed doubling up of the three proline CH_2 signals and the CH showing that the product was a mixture of rotamers. The presence of a quaternary carbon at 117.4/117.6 ppm showed the presence of the (C≡N), further proof of which came from the IR spectrum with a υ_{max} 2241 cm^{-1} (C≡N) and a correct mass at 259.1304 $[M+NH_4]^+$ in the high resolution mass spectrum.

The 2-azidobenzenesulfonic acid (**232b**, X = SO_2) was converted into the acid chloride by heating at reflux as a suspension in 2M $(COCl)_2$ in DCM and DMF. Coupling the acid chloride to prolinamide in a mixed phase process with K_2CO_3 as the base was successful. This time the isolated product was the amide (**233b**, X = SO_2) in 62% yield, the structure of which was confirmed by the ^{1}H (400 MHz) NMR spectrum which gave two broad singlets at 5.72 and 6.90 ppm in addition to the expected pyrrolidine and aromatic protons. The ^{13}C (100 MHz) NMR spectra showed a quaternary carbon at 174.2 ppm which confirmed the presence of the ($CONH_2$). The IR spectrumgave a peak at υ_{max} 3250- 3700 cm^{-1} for the N-H stretches and a carbonyl amide stretch at υ_{max} 1670 cm^{-1} which along with the correct accurate mass of 313.1077 for $[M+NH_4]^+$ gave further evidence for the structural assignment.

The amide (**233b**, X = SO_2) was dehydrated by treatment with tosyl chloride and pyridine[112] at reflux under nitrogen to yield the nitrile (**234b**, X = SO_2) in 37% yield. The structure was confirmed by the

^{1}H (400 MHz) NMR spectrum which showed the disappearance of the two broad amide NH_2 singlets and the ^{13}C NMR (100 MHz) which showed a new quaternary carbon at 118.3 ppm and the loss of the amide carbonyl at 174 ppm. The IR spectrum with a new peak at υ_{max} 2305 cm^{-1} (C≡N) and the loss of the amide carbonyl and N-H peaks, along with the confirmation of the mass of 295.0972 for the measured ion $[M+NH_4]^+$ in the mass spectrum gave further evidence for the structural assignment. The mechanism of the dehydration is similar to that in the Figure 2-3 with tosyl chloride in place of the acid chloride.

2.1.3 An alternative synthesis of the azido nitrile (**234**).



235a, X = CO
235b, X = SO_2

234a, X = CO
234b, X = SO_2

Scheme 2-3

An alternative route to the nitrile (**234**) was to utilise the prolinol derived alcohol (**235**), the synthesis[113] of which is described later in section 2.2.2.1, and to treat it with a mixture of concentrated ammonia and water (7:3) and freshly ground iodine, and heating to reflux. The process was inconsistent and always gave lower yields than the dehydration route. The proposed mechanism is shown in Figure 2-4.[113]

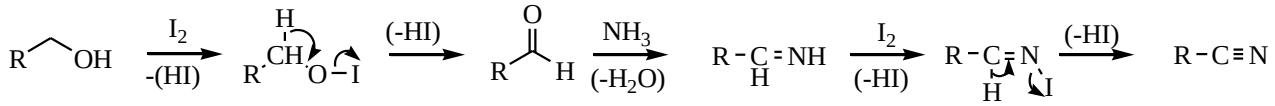
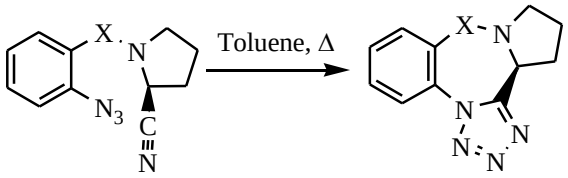


Figure 2-4

2.1.4 Synthesis of tetrazolopyrrolobenzodiazepine & tetrazolopyrrolobenzothiadiazepine.



234a, X = CO
234b, X = SO_2

241a, X = CO
241b, X = SO_2

Scheme 2-4

The next stage utilises a Huisgen 1,3-dipolar cycloaddition between the nitrile and the azide to make a tetrazolo ring[101,114-116] as shown in Figure 2-5.

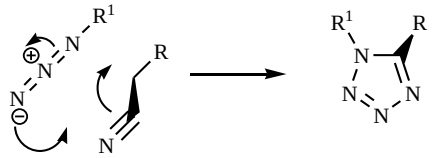


Figure 2-5

Successful cyclisation proceeded by heating to reflux in toluene for both examples. The PBD (**241a**, X = CO) reacting in 40 % yield in 6 hours and the PBTD (**241b**, X = SO_2) reacting in quantitative yield in 72 hours. The lack of the azide and nitrile peaks in the IR spectrum at υ_{max} ~2100 cm^{-1} and 2305 cm^{-1} implies that these groups were not present.

The ^{1}H (400 MHz) NMR spectrum for the PBD (**241a**), showed the six upfield aliphatic protons between 2.16-3.91 ppm and the single CH in the pyrrolidine ring system at 4.83 ppm. The four aromatic protons were downfield at 7.64, 7.76, 7.94 and 8.18 ppm giving a pattern of dt, dt, dd and dd consistent with a 1,2-disubstituted benzene ring system. The ^{13}C (100 MHz) NMR spectra showed the presence of the three CH_2 and the CH of the pyrrolidine ring system downfield and the four CH of the benzene ring along with three quaternary carbons and the imine bond quaternary carbon at

154.5 ppm. Further evidence was given by the correct measured mass of 242.1034 for the ion $[M+H]^+$.

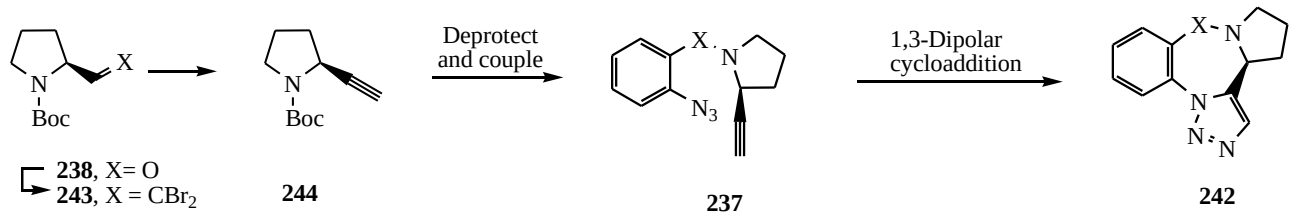
Evidence for the formation of the PBTD (**241b**, X = SO_2) was given by the ^1H (500 MHz) NMR which showed the six aliphatic CH_2 protons between 1.80-3.64 ppm and the single CH at 5.59 ppm showing the pyrrolidine ring is still intact. The four aromatic protons at 7.65, 7.83, 8.12, 8.16 with the multiplicity of dt, dt, dd, dd, showed the 1,2-substitution pattern of the benzene ring. The ^{13}C-Dept (100 MHz) NMR spectrum showed the three CH_2 and the CH upfield for the aliphatic ring system and the presence of four aromatic CH signals. The 3 quaternary carbons appeared in the ^{13}C (100 MHz) spectrum, the key one being the imine bond at 155.4 ppm, a feature that is consistent with the assigned structure. The measured mass of 278.0707 for the ion $[M+H]^+$ is further proof of the structural assignment.

2.2 Synthesis of the triazolopyrrolobenzodiazepine and triazolopyrrolobenzo-thiadiazepine (242).

Access to the triazolo systems required the synthesis of the azido alkyne system shown in Figure 2.1. Two routes to the azido alkyne precursors were explored, one of which involved conversion of prolinol into the alkyne and then coupling (discussed in section 2.2.1), whilst the other involved coupling up to prolinol and then producing the alkyne (discussed in section 2.2.2).

2.2.1 Synthesis via alkyne formation then coupling (the Corey Fuchs route).

The key here was to convert a proline derivative (**238**) into the alkyne (**244**), couple up the alkyne to the relevant acid chloride and then investigate the intramolecular 1,3-dipolar cycloaddition as shown in the Scheme 2-5.



Scheme 2-5

The Corey-Fuchs method converted the commercially available *N*-Boc protected prolinal (**238**) to the terminal dibromo alkene (**243**) using the ylide shown in Figure 2-6. This ylide was synthesised by Wolkoff's method[117] using triphenylphosphine and carbon tetrabromide[118] to form a stable intermediate which was used as crude in the next step. The dibromo Boc-protected proline derivative (**243**) gave fully consistent spectroscopic data.

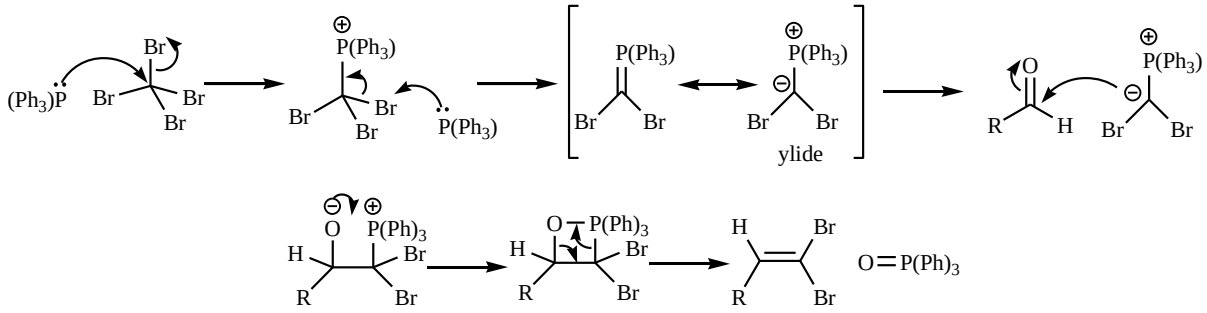
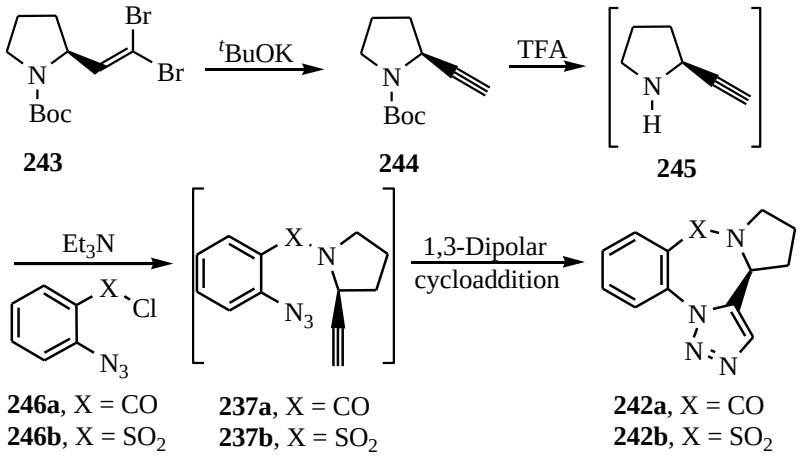


Figure 2-6

2.2.1.1 Conversion of the dibromo prolinal derivative (**243**) into the alkyne (**245**) and subsequent coupling to the acid chlorides (**246**).

The Scheme 2-6 shows the sequence of the reactions that were carried out in the synthesis of the desired compounds (**242**, X = CO, SO_2).



Scheme 2-6

Thus, the dibromo species (**243**) was converted into the terminal alkyne (**244**) by treatment with potassium tert-butoxide in dry THF.[119] The alkyne (**244**) was isolated after treatment of the intermediate potassium salt with aqueous acid according to the mechanism outlined in Figure 2-7:

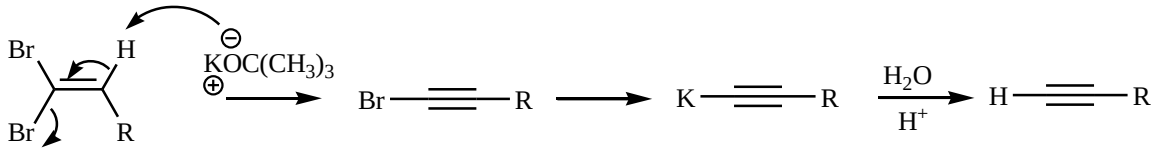
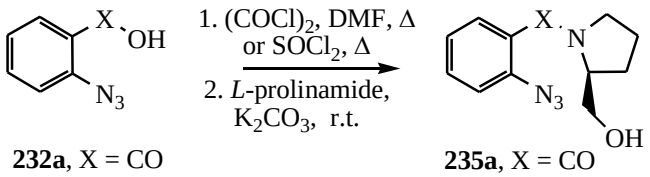


Figure 2-7

The alkyne (**244,** in Scheme 2-6) was found to be air sensitive[119] so had to be used directly in the next step in which the Boc group was removed by treatment with TFA.[120] The crude, deprotected, proline-derived alkyne (**245**) was coupled to either 2-azidobenzoyl chloride (**246a**, X = CO) or 2-azidobenzenesufonyl chloride (**246b**, X = SO_2) in the presence of base to give, after intramolecular 1,3-dipolar cycloaddition, the triazolo-PBD (**242a**, X = CO) and triazolo-PBTD (**242b**, X = SO_2) in low overall yields (3% and 14% from the commercially available prolinal, respectively). Due to the low overall yields and extremely difficult nature of this route it was not explored any further, particularly in light of the ease of the highly successful nature of the route described in the next section.

2.2.2 Synthesis via coupling then alkyne formation.

2.2.2.1 Prolinol coupling reaction.



232a, X = CO
232b, X = SO_2

235a, X = CO
235b, X = SO_2

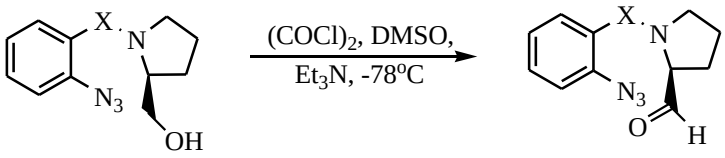
Scheme 2-7

This route started with the coupling of *L*-prolinol to the corresponding acid chlorides (as shown in Scheme 2-7).[69] The *L*-isomer was chosen in order to produce analogues with the same stereochemistry as the natural products discussed in the introduction. In both cases the acids (**232**, X = CO, SO_2) were converted to the acid chlorides and coupled up to prolinol in an aqueous solution of potassium carbonate giving the alcohol (**235**, X = CO, SO_2) in good to excellent yields (63% for X = CO, and 96% for X = SO_2).

Evidence for the successful coupling (**235a**, X = CO) was given by ^{1}H NMR (400 MHz) spectrum which showed the seven protons on the pyrrolidine ring at 1.60-1.84 (3H), 2.04-2.14 (1H), 3.15-3.26 (2H) and 3.66 ppm (1H). The two protons of the alkanol chain where located at 3.75-3.78 (1H) and 4.28-4.31 ppm (1H) and the alcohol hydrogen appeared as a broad singlet at 4.67 ppm. The four aromatic protons where found at 7.10-7.15 (2H), 7.24 (1H) and 7.37 ppm (1H). The ^{13}C-Dept 135 (100 MHz) NMR spectrum showed the four CH_2 for the pyrrolidine ring system at 24.5, 28.6, 49.6 and the alkyl chain at 66.5 ppm. The four aromatic carbons were present at 118.5, 125.3, 127.8 and 130.7 ppm. The ^{13}C (100 MHz) NMR spectra showed the three quaternary carbons at 129.3, 136.0 and 169.0 ppm, the latter being the carbonyl. The IR spectrum contained the expected azide peak, plus a broad peak between υ_{max} 3000-3500 cm^{-1} for O-H stretching, and the measured mass of 269.1008 for the ion $[M+Na]^+$ gives further evidence for the structure.

Confirmation of the second successful coupling (**235b**, X = SO_2) was given by the ^1H (400 MHz) NMR spectrum with the pyrrolidine ring CH_2 system protons being downfield at 1.67-1.78 (1H), 1.79-1.99 (3H), 3.38 (1H), 3.49-3.56 (1H) and the CH of the pyrrolidine ring being at 4.02-4.08 ppm (1H). The alkyl chain protons were found at 3.62 (1H) and 3.70 ppm. The ^{13}C-Dept 135 (100 MHz) NMR spectrum showed the four CH_2 signals, three for the ring system and one for the alkanol chain. The single CH of the pyrrolidine ring system was downfield and the four aromatic carbons upfield. The two quaternary carbons were clear in the ^{13}C (100 MHz) NMR spectrum and were found at 129.0 and 138.2 ppm. The IR spectrum showed a broad peak at υ_{max} 3172-3693 cm^{-1} and gave further strong evidence for the proposed structure, together with consistent mass spectral data.

2.2.2.2 Oxidation of the alcohols (**235**).



235a, X = CO
235b, X = SO_2

236a, X = CO
236b, X = SO_2

Scheme 2-8

Oxidation of the alkyl alcohol (**235**, X = CO, SO_2) to the aldehyde (**236**, X = CO, SO_2) was the next step. The first method for the attempted oxidation used pyridinium chlorochromate (PCC).[69] Unfortunately, after several attempted oxidations the yield was still low (<15%), even using freshly prepared PCC. The next conditions tried were those of the Swern oxidation[121] which uses $COCl_2$ and DMSO, for which the mechanism is shown in Figure 2-8.[122]

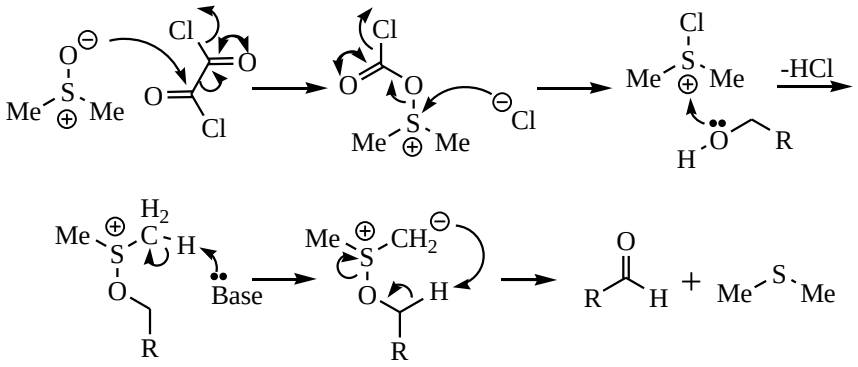
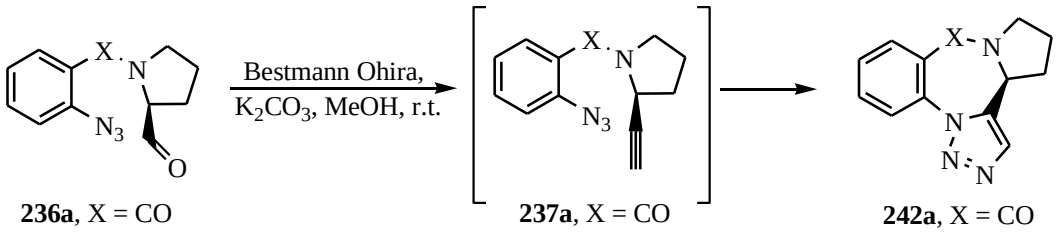


Figure 2-8

This proved to be successful giving yields of 73% and 72% for (**236**, X = CO and SO_2), respectively. The carbonyl compound (**236a**, X = CO) gave a mixture of rotamers shown by the appearance of the aldehyde CH as two singlets at 9.22 and 9.62 ppm in the ^{1}H (400 MHz) NMR spectrum. Further proof was given by the disappearance of both the alkanol chain protons and the broad singlet of the $CH_2O\mathit{H}$. The ^{13}C-Dept 135 (100 MHz) NMR spectrum showed doubling up of the three CH_2 units, a CH downfield, four aromatic CHs, together with the distinctive CHO signals at 198.0 and 199.3 ppm. The ^{13}C (100 MHz) NMR spectrum showed 3 quaternary carbons. The disappearance of the broad peak υ_{max} ~3000-3500 cm^{-1} in the IR spectrum showed the O-H stretching was not present which, along with the presence of a new peak at 1732 cm^{-1} for the CHO stretch, gave further evidence for the formation of the aldehyde. The measured mass of 245.1032 for the ion $[M+H]^{+}$ showed the correct mass for the molecule.

The ^{1}H (400 MHz) NMR spectrum for the sulfonyl analogue (**236b**, X = SO_2) showed the formation of the product with the disappearance of the alkanol chain signals and the appearance of the aldehyde signal downfield at 9.72 ppm. Further evidence came from the ^{13}C-Dept 135 (100 MHz) NMR spectrum with the appearance of the distinctive aldehyde signal upfield at 200.5 ppm. The disappearance of the broad OH stretch in the IR spectrum υ_{max} 3000-3500 cm^{-1} and the appearance of a carbonyl stretch at 1730 cm^{-1} gave further evidence for the aldehyde.

2.2.2.3 Conversion of the aldehydes (**236**) into alkynes (**237**) and subsequent triazole formation (**242**).



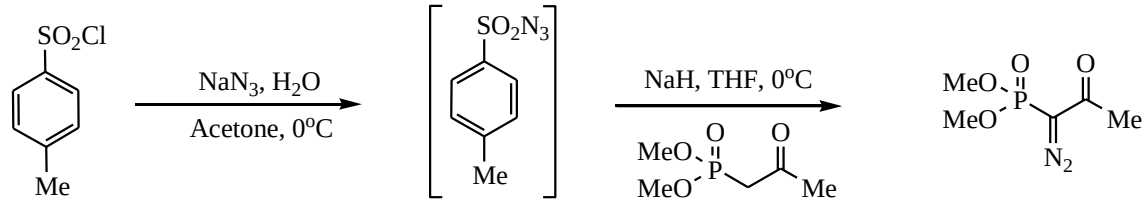
236a, X = CO
236b, X = SO_2

237a, X = CO
237b, X = SO_2

242a, X = CO
242b, X = SO_2

Scheme 2-9

The next step in the synthesis was to convert the aldehyde moiety of compound (**236**) into the terminal alkyne (**237**). This was proceeded by using the Bestmann-Ohira reagent which was synthesied[123] in a two step synthesis procedure. The azidation of tosyl chloride formed tosyl azide *in situ* which was reacted with dimethyl (2-oxopropyl)phosphonate to give the Bestmann Ohira reagent. All spectroscopic data agreed with the literature.[123]



Scheme 2-10

With the reagent in hand, the aldehydes were converted to the alkynes by reaction in a basic solution of K_2CO_3 in MeOH. The proposed mechanism[124] for the formation of the alkyne moiety is shown in Figure 2-9.

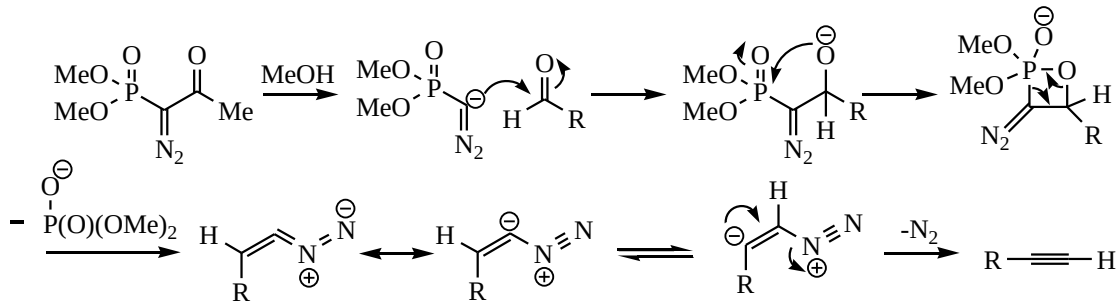
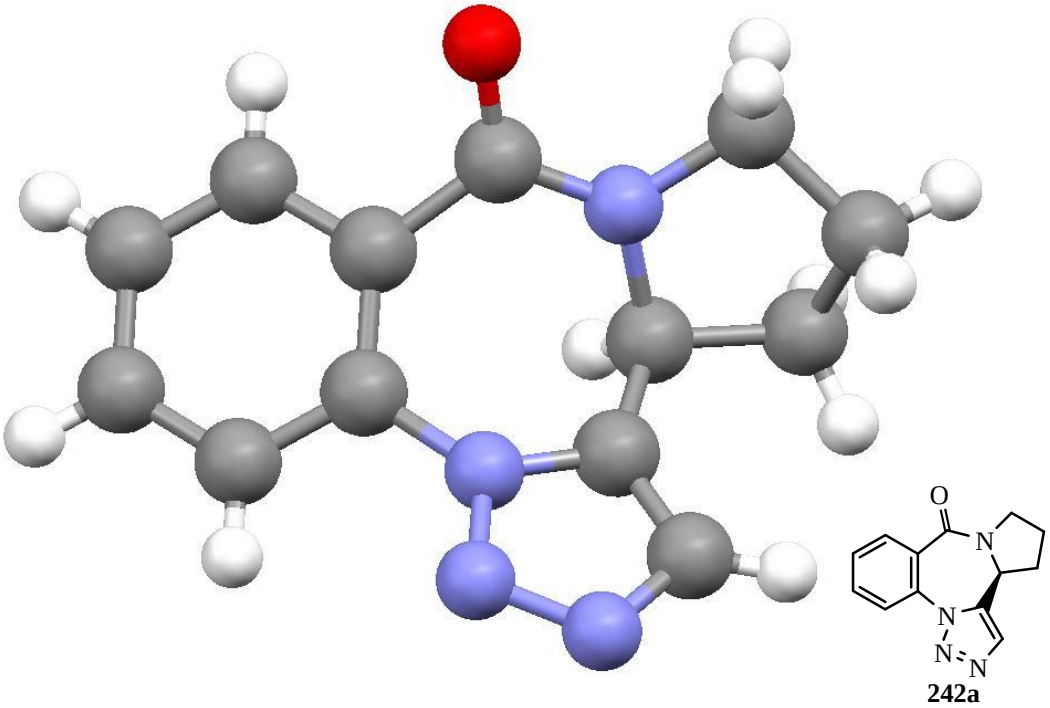


Figure 2-9

In both cases, the alkyne product (**237**, X = CO, SO_2) was not isolated, as the alkyne and the azide moiety underwent a 1,3-dipolar cycloaddition to form the desired triazole product (**242**, X = CO, SO_2). The formation of the triazolopyrrolobenzodiazepine (**242a**, X = CO) occurred in 83% yield. The ^{1}H NMR (400 MHz) spectrum showed a singlet downfield at 7.57 ppm, which showed that the product had an extra aromatic proton, over that which was expected for the alkyne. The aliphatic protons of the pyrrolidine ring where found upfield at 2.03-3.78 ppm and the CH of the pyrrolidine ring at 4.70 ppm. The four aromatic protons of the benzene ring were found downfield at 7.49, 7.62, 7.92, 8.04 ppm in the 1,2-substitution pattern of dt, dt, dd, and dd. The ^{13}C-Dept 135 (100 MHz) NMR spectrum showed the presence of five CH signals downfield for the benzene and triazole carbons as well as three CH_2 signals and a single CH for the pyrrolidine ring system upfield. Further proof of the cyclisation came from the IR spectrum which showed no peak for the azide at υ_{max} ~ 2100 cm^{-1} and no peaks for the alkyne. The correct accurate mass of 241.1083 for the ion $[M+H]^+$ in the mass spectrum supported the structural assignment. It is noteworthy that this process allowed the formation of the triazolo- PBD directly from the aldehyde, a nice example of a domino style "click" reaction (a series of intramolecular reactions which proceed through highly reactive intermediates, of which one is the click reaction between the alkyne and the azide). The structure of the final product was confirmed by a single crystal X-ray diffraction (see Figure 2-10), which showed clearly the tetracyclic ring system.

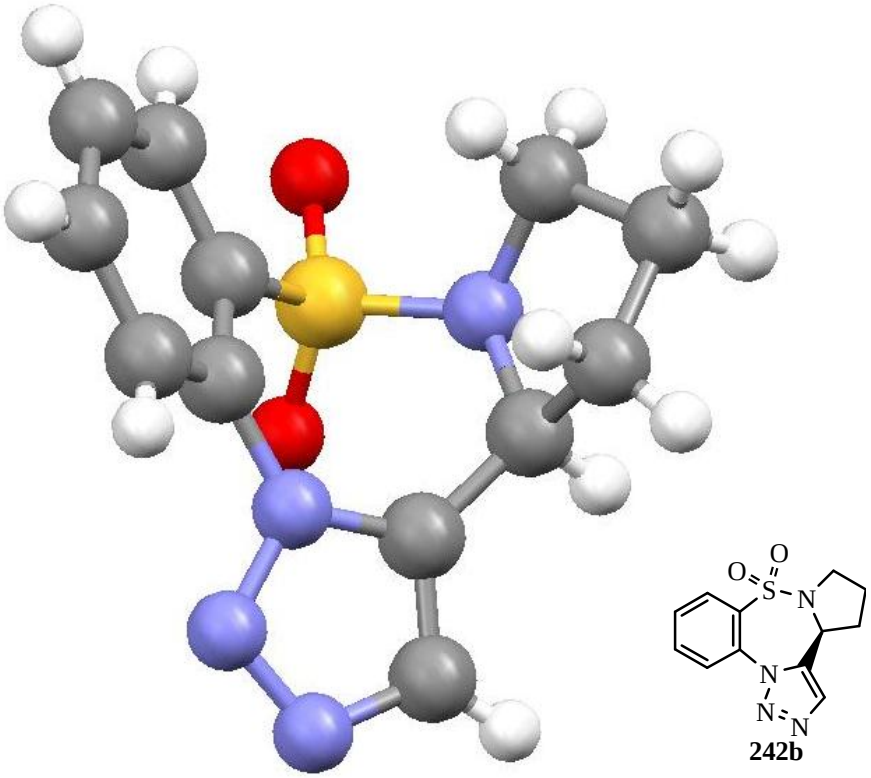


242a

Figure 2-10

The structure of the triazolopyrrolobenzothiadiazepine (**242b**, X = SO_2) was assigned on the basis of the ^{1}H NMR (400 MHz) spectra which showed a singlet downfield at 7.79 ppm for the new aromatic proton in the triazole ring moiety. The pyrrolidine ring CH_2 protons were upfield between 1.63-3.68 and the single CH of the pyrrolidine ring was at 5.19 ppm. The four aromatic protons of the benzene ring were found in the usual 1,2-substitution pattern at 7.62 (dt), 7.83 (dt), 8.10 (dd), 8.15 (dd) ppm. The appearance of five CH signals downfield in the ^{13}C Dept-135 (100 MHz) at 125.4, 128.7, 129.3, 134.1, 134.4 ppm confirmed an extra aromatic carbon from the newly formed triazole ring. Further evidence for the structure was given by the IR spectrum which showed the lack of the distinctive azide absorbance peak at υ_{max} ~ 2100 cm^{-1} together with an absence of the alkyne peaks. The accurate mass for the measured ion $[M+H]^+$ was consistent at 277.0752. X-Ray crystallographic analysis, shown in Figure 2-11, confirmed the structural assignment as the triazolopyrrolo-

benzothiadiazepine. Once more this product was formed directly from the aldehyde via an intermediate alkyne which could not be isolated but gave instead the 1,2,3-triazole product directly. On this occasion the yield of the triazolo-PBTD from the aldehyde was quantitative.



242b

Figure 2-11

Due to the success of this Bestmann-Ohira derived methodology, it was decided to investigate the synthesis and reactivity of other amino acid derived alkynes (i.e. other than proline). This, together with the synthesis and reactivity of the corresponding nitriles is described in the next section.

3 Discussion: Synthesis of Other Tetrazolo- and Triazolo- Benzodiazepines and Benzothiadiazepines.

As described above, the success of the Bestmann-Ohira route as a method for making triazolo PBDs and PBTDs prompted the examination of the suitability of the route for making triazolo benzodiazepines and benzothiadiazepines from amino acids other than proline. The same short series of amino acids would also be used to make the nitrile precursors for the synthesis of tetrazolo benzodiazepines and benzothiadiazepines using the route that was applied above to the successful synthesis of tetrazolo PBDs and PBTDs. The proposed routes are outlined in the Figure 3-1.

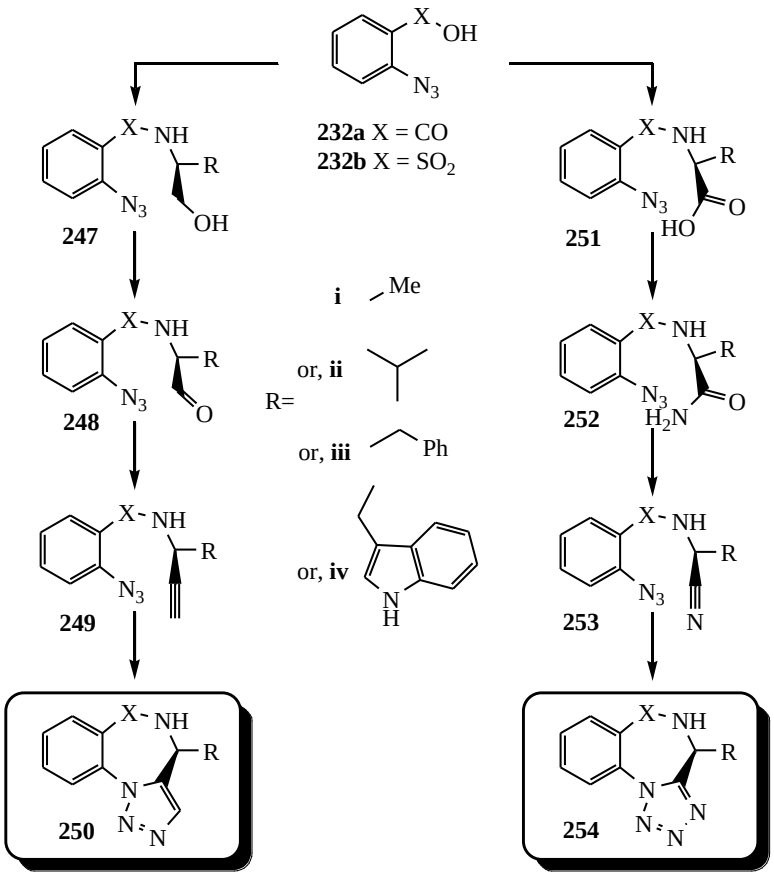
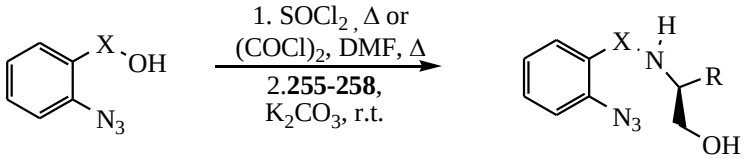


Figure 3-1

3.1 Synthesis of Triazolo-benzodiazepines and benzothiadiazepines.

3.1.1 Triazolo Systems Part 1: Synthesis of the alcohols (**247**).



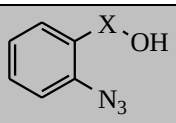
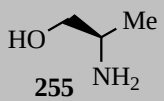
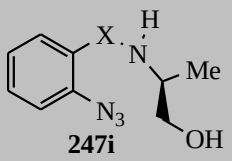
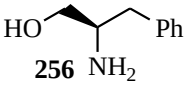
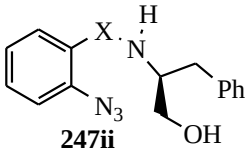
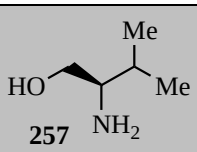
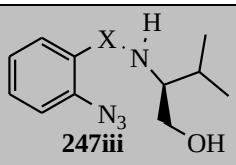
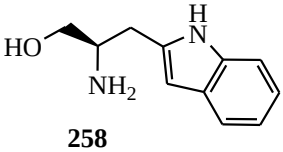
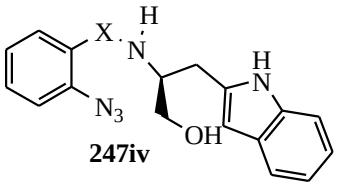
232a, X = CO
232b, X = SO_2

247a, X = CO
247b, X = SO_2

Scheme 3-1

The acid chlorides were made in the usual way and were coupled to a variety of amino acid alcohol derivatives (**255-258**). The different amino acid alcohols chosen were alaninol (**255**), phenylalaninol (**256**), valinol (**257**) and tryptophanol (**258**). Each example was successful apart from the coupling of the acid chloride (**246b**, X = SO_2) with tryptophanol. Each acid chloride was added to a basic mixture of K_2CO_3 in water with the amino acid derivative in an organic phase of DCM. Yields are shown in the table 3-1:

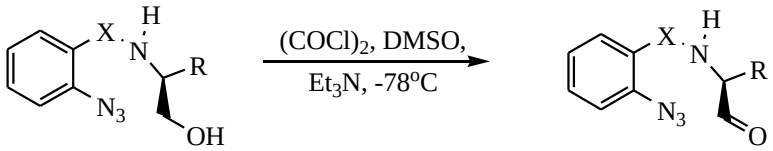
Table 3-1

	Amino acid derivative	**Yield**		**Product**
		 **232a** X = CO **232b** X = SO_2		
		a X=CO	**b** X= SO_2	
i	 **255**	38%	81%	 **247i**
ii	 **256**	93%	81%	 **247ii**
iii	 **257**	88%	55%	 **247iii**
iv	 **258**	90%	Unsuccessful	 **247iv**

All compounds gave consistent spectroscopic data. The structure of compound (**247ai**), for example, was confirmed by ^{1}H NMR (400 MHz) spectroscopy which showed (3H, d, *J* 6.8) upfield at 1.22 for the methyl and a broad singlet at 3.18 ppm for the alcohol unit. The methyl was coupled to the CH signal which appeared at 4.16-4.26 (1H, tq, *J* 6.8, 3.74), the aromatic protons were downfield at 7.11

(1H, d), 7.16 (1H, t), 7.42 (1H, dt), 8.03 (1H, dd), and the N-H was found downfield at 7.55 ppm (1H, bd, *J* 5.8). The ^{13}C (100 MHz) NMR spectrum showed a methyl carbon at 17.1 ppm, a CH at 48.5 ppm and the CH_2 at 67.2 ppm. The four aromatic CH carbons were seen at 118.4, 125.2, 132.2, 132.5 ppm. The quaternary carbons in the ^{13}C NMR (100 MHz) spectrum were detected at 124.8 and 137.1 for the quaternary carbons in the benzene ring and for the carbonyl at 165.3 ppm. The secondary amide NH was shown at υ_{max} 3018 cm^{-1} in the IR spectrum and the broad peak of the O-H stretch was present between υ_{max} 3310-3495 cm^{-1}. The correct mass of 243.0854 for the ion $[M+Na]^+$ provided further evidence for the structural assignment.

3.1.2 Triazolo Synthesis Part 2: Synthesis of the aldehydes (**248**).



247a, X = CO
247b, X = SO_2

248a, X = CO
248b, X = SO_2

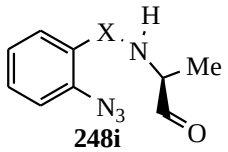
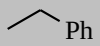
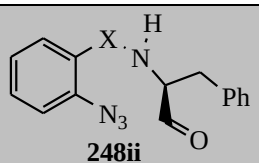
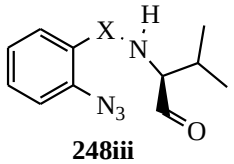
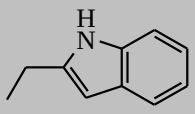
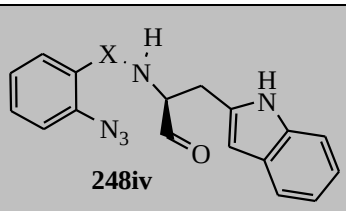
Scheme 3-2

With the coupling reactions mostly being successful, attention turned to the oxidation of the alcohols to give the aldehyde moiety. In cases (**248ai**) and (**248bi**) oxidation by the Swern method[121] and other methods (Dess-Martin,[4,85,95,125] PCC, TPAP[44] etc.) did not yield the aldehyde. The phenylalaninol (**247aii** & **247bii**) and valinol adducts (**247aiii**, & **247biii**) gave the four expected aldehydes in good yield under Swern conditions, whilst the benzoyl (**247aiv**) tryptophan adduct gave the aldehyde in below 10% yield under all conditions of oxidation. All spectroscopic data were fully consistent with the assigned structure. For example, with the oxidation to the aldehyde (**248aii**), the ^1H NMR (400 MHz) spectrum showed the presence of a signal at 9.61 (1H, s) for the aldehyde moiety. Along with the absence of the CH_2 signal on the primary alcohol chain at 3.60-3.71 ppm, this gave strong evidence for the success of the oxidation. The ^{13}C Dept-135 (100 MHz) spectrum showed a deshielded CH at 198.6 ppm and the disappearance of an aliphatic CH_2. Similarly, infra-red spectroscopy showed the loss of the alcohol OH and appearance of the aldehyde carbonyl, which

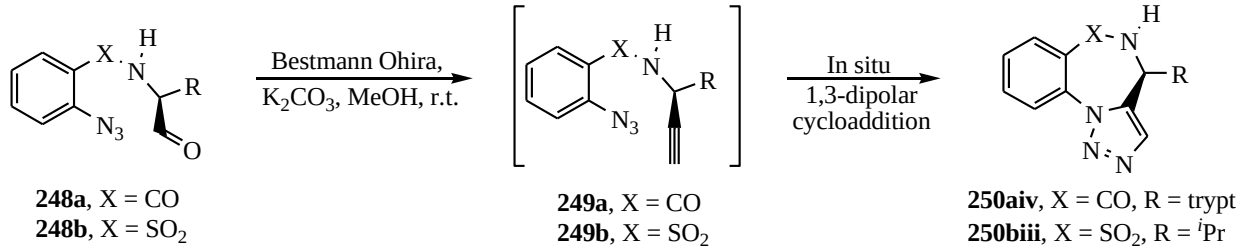
together with the correct measured mass of 319.1150 for the $[M+Na]^+$ ion further supported the structure.

The structures of the other examples were confirmed in the same manner with ^1H (400 MHz) NMR spectroscopy showing the disappearance of the primary alcohol chain and the appearance of the deshielded CHO proton downfield above 9 ppm. All of the ^{13}C (100 MHz) NMR spectra showed the presence of an extra CHO downfield close to 200 ppm and the disappearance of an aliphatic CH_2 upfield for the primary alcohol alkyl chain. The correct accurate masses were observed by high resolution mass spectrometry for all the examples, apart from (**248bii**), as this was found to be extremely unstable and was used directly in the next step, decomposing before accurate mass could be obtained. Table 3-2 summaries the yields of the different analogues.

Table 3-2

	R group	**Yield**		**Product**
		a, X=CO	**b**, X= SO_2	
i		0%	0%	 **248i**
ii		72%	65%	 **248ii**
iii		50%	75%	 **248iii**
iv		<10%	N/A	 **248iv**

3.1.3 Triazolo Synthesis Part 3: Reaction of the aldehydes (**248**) with the Bestmann-Ohira reagent.



248a, X = CO
248b, X = SO_2

249a, X = CO
249b, X = SO_2

250aiv, X = CO, R = trypt
250biii, X = SO_2, R = ^{i}Pr

Scheme 3-3

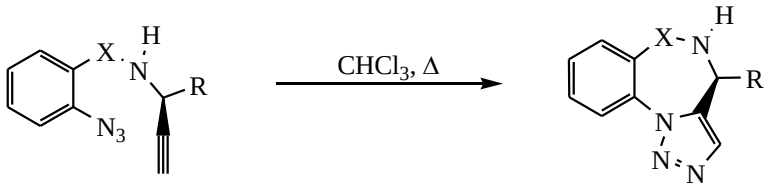
With the aldehydes in hand, the next step was to take advantage of the previously utilised Bestmann-Ohira methodology[124,126] to make the terminal alkyne. The evidence for successful reactions came from the disappearance of the aldehyde peak around 9 ppm in the ^{1}H (400 MHz) NMR spectra and the loss of the deshielded carbon in the ^{13}C (100 MHz) NMR spectra characteristic of the aldehyde moiety at over 190 ppm.

For the examples, where [X = CO, R = tryptophan, **250aiii**, and X = SO_2, R = $CH(CH_3)_2$, **250biv**] the Bestmann-Ohira process proceeded as per the proline systems described previously i.e. the alkyne intermediate could not be isolated and the reaction gave the tricyclic system directly in yields of 54% and 33%, respectively. Spectroscopic data was consistent with the expected structures. For example, [**248biii**, when X = SO_2, R = $CH(CH_3)_2$] the ^{1}H (400 MHz) NMR spectrum showed a signal at 7.77 (1H, s) for the new aromatic proton of the triazole ring system as well as the four aromatic protons at 7.62 (1H, dt), 7.80 (1H, dt), 8.05 (1H, dd) and 8.10 ppm(1H, dd). A signal at 5.35 ppm (1H, bs), was consistent with the N-H, and the presence of signals at 0.90 (3H, d), 1.04 (3H, d), 2.18 (1H, dsept) and 4.58 ppm (1H, m) for the CH-isopropyl linkage confirmed the assignment. The ^{13}C (100 MHz) NMR spectra showed five aromatic CHs at 125.4, 126.7, 129.2, 134.2, 134.4 ppm [four for the benzene ring & one for the new triazole ring system], the presence of three quaternary carbons at 133.5, 133.9, 135.1 ppm and the presence of signals at 17.7 (Me), 18.9 (Me), 32.8 (CH), 54.5 ppm (CH) ppm for the CH-isopropyl linkage. Further evidence for the

cyclisation was the disappearance of the azide peak in the IR spectrum and the correct mass of 301.0717 for the ion $[M+Na]^+$ in the high resolution mass spectrum.

The remaining examples in this series (X = CO, R = ^{i}Pr, X = CO or SO_2, R = CH_2Ph) did not cyclise directly and are discussed in the next section.

3.1.4 Isolation of alkynes (**249**) and subsequent cyclisation.



249a, X = CO
249b, X = SO_2

250a, X = CO
250b, X = SO_2

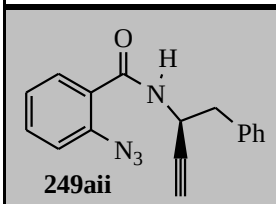
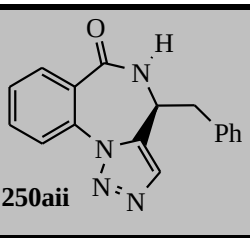
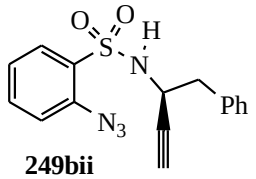
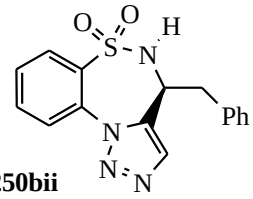
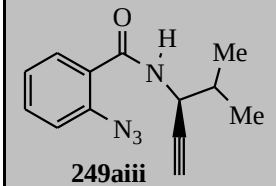
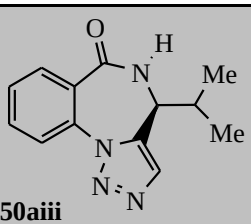
Scheme 3-4

As discussed above, three of the alkynes from the Bestmann-Ohira reaction did not undergo in-situ 1,3-dipolar cyclisation and could be isolated, which was confirmed by IR and NMR spectroscopy. For example, for compound (**249ai,** when X= CO and R= $[CH(CH_3)_2]$), there was a sharp peak for the azide in the IR spectrum at υ_{max} 2129 cm^{-1} and the terminal CH of the alkyne was found in the ^1H (400 MHz) NMR spectrum at 2.22 ppm (1H, d, *J* 2.4, HC≡C), and at 72.0 ppm in the ^{13}C (100 MHz) NMR spectrum.

The compounds were heated to reflux in $CHCl_3$ and monitored by TLC. In all cases, TLC showed the complete disappearance of the starting material after 72 hours and the appearance of a single new spot. In all cases spectroscopic analysis confirmed that intramolecular 1,3-dipolar cyclisation had occurred with the disappearance of the azide and alkyne groups (shown in the IR spectrum), loss of the alkyne HC≡C and the gaining of the new triazole CH (shown in the ^1H and ^{13}C NMR spectra). For example, compound (**250ai**, X = CO, R = $CH[CH_3]_2$), showed the disappearance of the azide and alkyne peaks in the IR spectrum and also the movement of the terminal alkyne proton downfield to

7.68 ppm (1H, s) in the ^{1}H (400 MHz) NMR spectrum and the presence of 5 aromatic CH carbons in the ^{13}C (100 MHz) NMR spectra at 123.0 (CH) 129.1 (CH), 130.6 (CH), 131.7 (CH), 133.3 ppm (CH) [four for the benzene ring system and one for the new triazole ring]. The correct mass of 265.1064 for the measured ion $[M+Na]^{+}$ further supports the structural assignment. The yields of the different analogues are logged in the table 3-3

Table 3-3

Starting Material	time (*hrs*)	yield (%)	Product
 **249aii**	72hours	99%	 **250aii**
 **249bii**	72 hours	99%	 **250bii**
 **249aiii**	72 hours	98%	 **250aiii**

For compound (**250aii**, X = CO, R = CH_2Ph) further structural evidence was given by the X-Ray crystal structure which is shown in Figure 3-2.

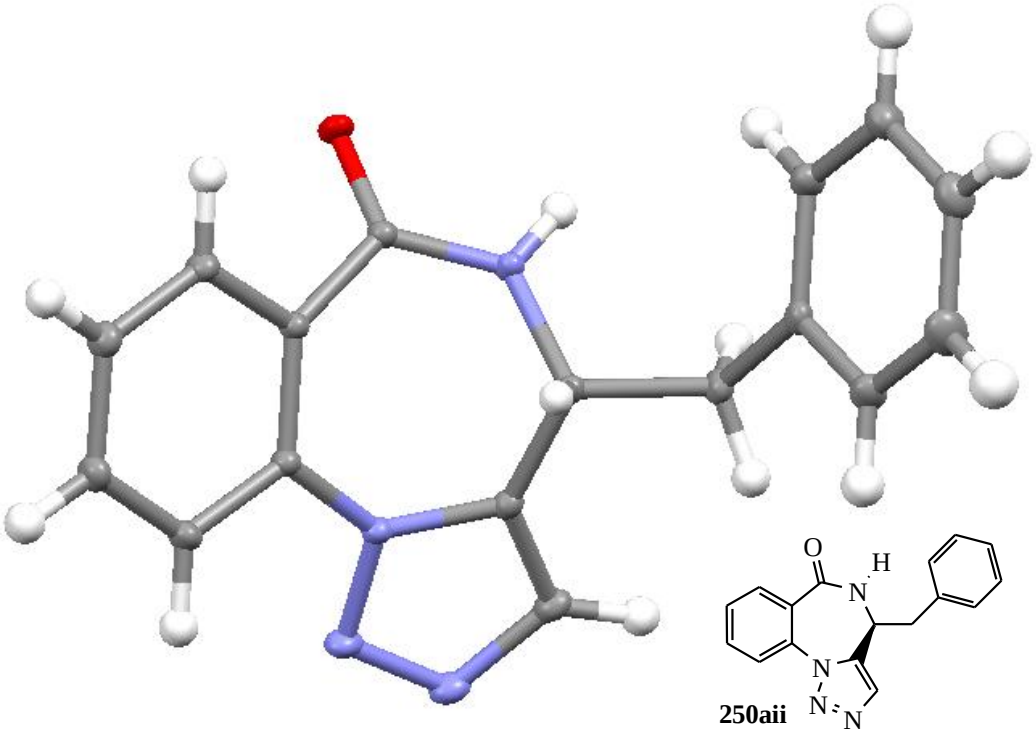


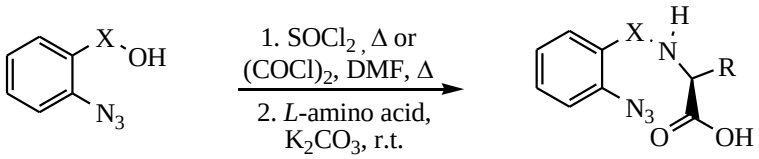
Figure 3-2

3.2 Attempted Synthesis of Tetrazolobenzodiazepines and Tetrazolobenzothiadiazepines.

The success of the prolinamide based synthesis of the tetrazolo-pyrrolobenzodiazepine and benzothiadiazepine, described previously in this thesis, prompted the exploration of the use of some other amino acids as precursors for the synthesis of tetrazolobenzodiazepines and tetrazolobenzothiadiazepines. Time restrictions meant that the study was limited to valine and phenylalanine.

3.2.1 The coupling of the amino acids to the different acid chlorides.

The first step in this process was the coupling up of the amino acid to the corresponding acid chloride (**246**, X= CO, SO_2), derived by the treatment of the acids (**232**) with $SOCl_2$ as shown in Scheme 3-5:



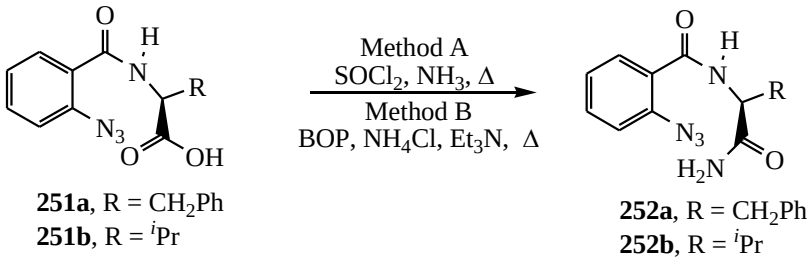
232a, X = CO
232b, X = SO_2

251a, R = CH_2Ph
251b, R = ^{i}Pr

Scheme 3-5

The coupling of the acid (**232**, X = CO, SO_2) via the acid chloride with both valine and phenylalanine proceeded with excellent yields (95% and 83%, respectively) but coupling up to the sulfonyl chloride failed in both instances, despite repeated attempts. The structures of the products were confirmed by ^{1}H NMR spectroscopy. For example, compound (**251a**, X = CO, R = CH_2Ph) which showed the presence of the five aromatic phenylalanine protons downfield in the region of 7.27-7.38 ppm as well as the two benzylic protons upfield at 3.30 (1H, dd, *J* 14.0, 6.3) and 3.37 (1H, dd, *J* 14.0, 5.6) with the methine resonating at 5.10 (1H, dt, *J* 6.3, 5.6), which along with the single proton for the secondary amide at 8.06 ppm (1H, bd, 6.9) gave strong evidence for the structural assignment. The ^{13}C Dept-135 (125MHz) NMR spectrum showed the presence of the CH_2 of the alkyl chain at 37.1 and the CH at 54.3 ppm. The presence of a total of seven types of aromatic CH carbons, four from the di-substituted azido benzene ring and three from the mono-substituted benzene ring, together with the five quaternary carbons in the ^{13}C (125MHz) NMR spectra, two of which are carbonyls, confirmed the assignment. The correct mass of 333.0944 for the measured ion $[M+Na]^{+}$ in the HRMS provided further evidence.

3.2.2 Conversion of the carboxylic acids into amides.



251a, R = CH_2Ph
251b, R = ^{i}Pr

252a, R = CH_2Ph
252b, R = ^{i}Pr

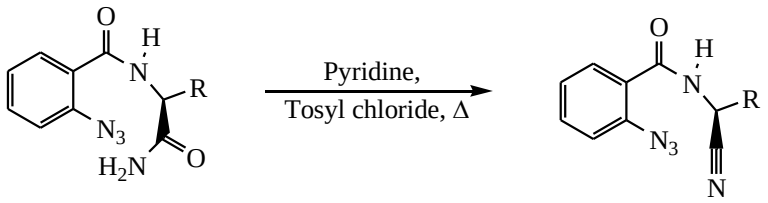
Scheme 3-6

The next stage in the synthesis was to convert the carboxylic acid (**251**) into the primary amide (**252**). Unfortunately, the usual coupling method, conversion to the acid chloride and reaction with ammonia, was unsuccessful so an activation method utilising (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium (BOP) was used to give the desired products in 72% and 91% yields, starting from phenylalanine and valine, respectively.

Proof for the presence of the amide in the phenylalanine derivative (**252a**) was given by the ^{1}H (400 MHz) NMR spectrum which showed the presence of two broad singlets at 5.98 ppm (1H, bs) and 6.61 ppm (1H, bs). The IR spectrum showed the a clear NH stretch, which along with the correct measured mass of 332.1110 for the ion $[M+Na]^{+}$ in the mass spectrum, confirmed that the reaction was successful.

The valine analogue (**252b**) showed similarly consistent data, for example, the amide $CONH_2$ protons were present in the ^{1}H (400 MHz) NMR spectrum at 5.83 (1H, bs) and 6.67 ppm (1H, bs), and the high resolution mass spectrum gave the correct accurate measurement of 284.1111 for the ion $[M+Na]^{+}$.

3.2.3 Conversion of the amides into the nitriles.



252a, R = CH_2Ph
252b, R = ^{i}Pr

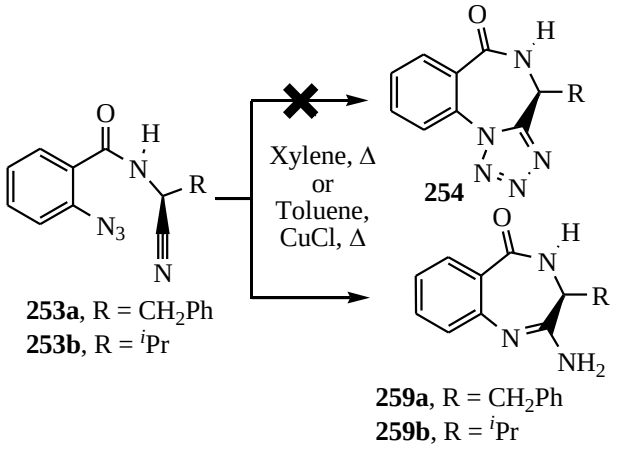
253a, R = CH_2Ph
253b, R = ^{i}Pr

Scheme 3-7

The penultimate step (the step prior to cyclisation) was the dehydration of the two primary amides (**252a-b**) to the nitriles (**253a-b**). This was carried out by using tosyl chloride and pyridine[112] and heating to 60°C. Evidence for the successful dehydration in the case of the phenylalanine derivative was given in the ^{1}H (400 MHz) NMR spectrum which showed the disappearance of the two broad signals for the primary amide of the starting material. The ^{13}C (100 MHz) NMR spectrum showed the disappearance of the carbonyl signal down field at 173.3 ppm and the appearance of a new peak at 118.2 ppm which is consistent with the loss of C=O unit and the formation of a nitrile. The IR spectrum showed the presence of a new peak at υ_{max} 2089 cm^{-1} for the nitrile with a further peak at υ_{max} 2128 cm^{-1} which showed that the azide was still intact. Along with the disappearance of the primary amide NH stretches in the infra red spectrum and the correct accurate mass of 314.1017 for the measured ion $[M+Na]^{+}$, the data all supported the structural assignment for the compound (**253a**).

The valine derived system (**253b**) showed the same set of diagnostic signals (the loss of the NH_2, appearance of the nitrile) together with a consistent high resolution mass measurement.

3.2.4 Attempted synthesis of tetrazolobenzodiazepines (**254**).



Scheme 3-8

With the nitriles (**253**) synthesised, the next step was to perform the intramolecular 1,3-dipolar cycloaddition. After heating the phenylalanine analogue for 72 hours at reflux in $CHCl_3$, no reaction had occurred, so the solvent was replaced with xylene and the mixture heated at reflux for 96 hours after which time a new product had formed.

The isolated product was not the expected tetrazole (**254**) and showed a high resolution mass measurement of 266.1270 for the ion $[M+H]^+$, which was consistent with the loss of nitrogen and the gain of two protons. The ^1H (400 MHz) NMR spectrum showed a signal at 5.58 integrating to two protons (broad singlet) and the IR spectrum showed new peaks at υ_{max} 3357, 3474 cm^{-1} consistent with the formation of an amine. This inferred that the structure of the new product was that of compound (**259a**). The presence of the $CHCH_2Ph$ was shown by signals at 3.17 (1H, dd), 3.23 (1H, dd) and 5.21-5.24 ppm (1H, m) in the ^1H (400 MHz) NMR spectrum, as well as the single amide proton at 6.48 (1H, bd) and consistent signals at 6.63 (1H, t), 6.69 (1H, d) and 7.19-7.45 ppm (7H, m) for the disubstituted and monosubstitued benzene ring systems. The ^{13}C (100 MHz) NMR spectra was also consistent with the assigned structure. The product was obtained in 18% yield.

A possible mechanistic pathway, shown in Figure 3-3, can be proposed whereby nitrene (**260**) formation occurs rather than 1,3-dipolar cycloaddition, and is followed by proton abstraction from the solvent to give the amine (**261**), a reduction process that is not uncommon with azides. Intramolecular attack of the nitrile by the amine and subsequent proton transfer (**262**) and tautomerism then yields the observed product (**259**). Alternatively, ring closure of the nitrene (**260**) by intramolecular reaction with the nitrile to compound (**263**) followed by proton abstraction to compound (**264**) from the solvent could also lead to the observed product.

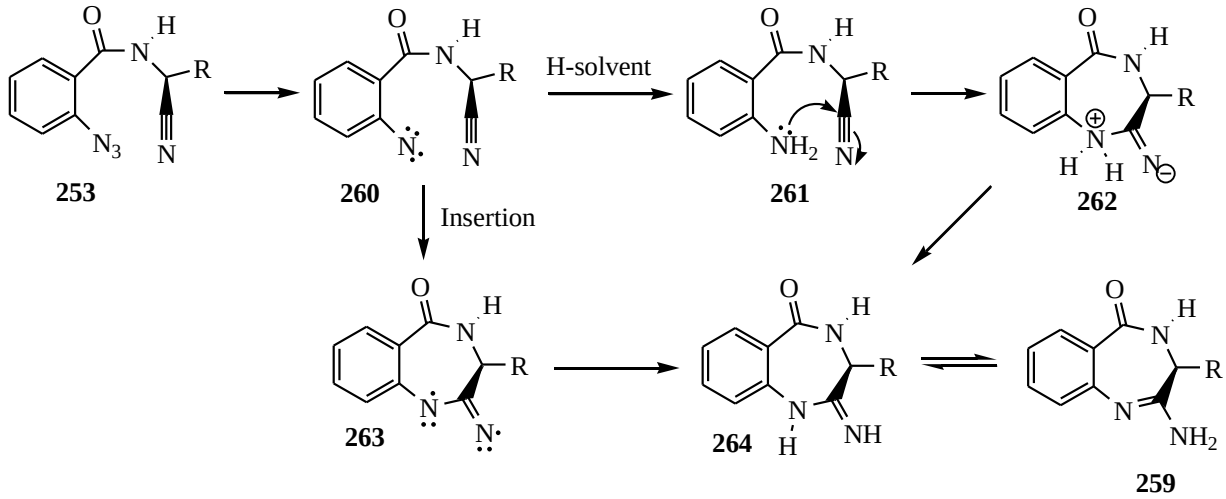
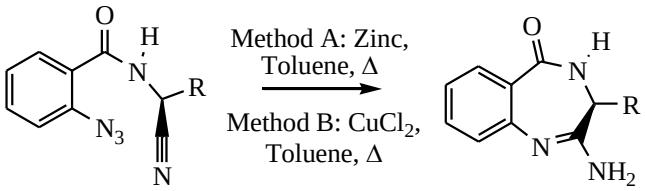


Figure 3-3

The same type of product was formed by heating in xylene at reflux for 36 hours and also after shorter periods in the same solvents in the presence of zinc[17] and copper[116,127-130] catalysts. Pleasingly, the isopropyl analogue behaved in the same manner to furnish the corresponding 2-amino-1,4-benzodiazepine (**259b**, R = ^{i}Pr) in 50% yield.



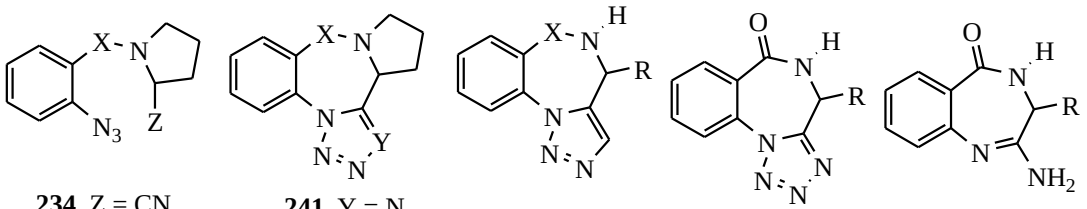
253a, R = CH_2Ph
253b, R = ^{i}Pr

259a, R = CH_2Ph
259b, R = ^{i}Pr

Scheme 3-9

Conclusion.

As discussed in section 2, the synthesis of the proline derived nitriles and alkynes (**234** and **237**) allowed access to the tetrazolo and triazolo PBD and PBTD analogues (**241** and **242**). With other amino acids, the triazolo systems (**250**) could be accessed, but the tetrazolo systems (**254**) could not be formed, due to the formation of the benzodiazepines (**259**) instead. The structures of which are shown are shown in the Figure 3-4 below.



234, Z = CN
237, Z= CCH

241, Y = N
242, Y= CH

250

254

259

Figure 3-4

4 Discussion: Use of Intramolecular Azide to Alkene Cycloadditions to Produce PBD Derivatives.

As described in the previous chapters, the intramolecular reactions between an azide group and an alkyne or nitrile allows the synthesis of triazolo- and tetrazolobenzodiazepines and benzothiadiazepines including some tetracyclic pyrrolobenzodiazepine analogues. In this section the intramolecular reaction between alkenes and azides as a route to pyrrolobenzodiazepine analogues will be investigated. The Figure 4-1 shows the plan whereby a proline derived alkene is to be coupled to ortho-azidobenzoic or sulfonic, acid. The possible outcomes of the reaction are the triazoline (**243**), aziridine (**270**) or the cyclic imine (**271**), where the latter two products form via nitrogen extrusion reactions.[131] Each of the products (**270**) and (**271**) (the aziridine and imine) have functionality which may interact with nucleophilic residues in DNA.

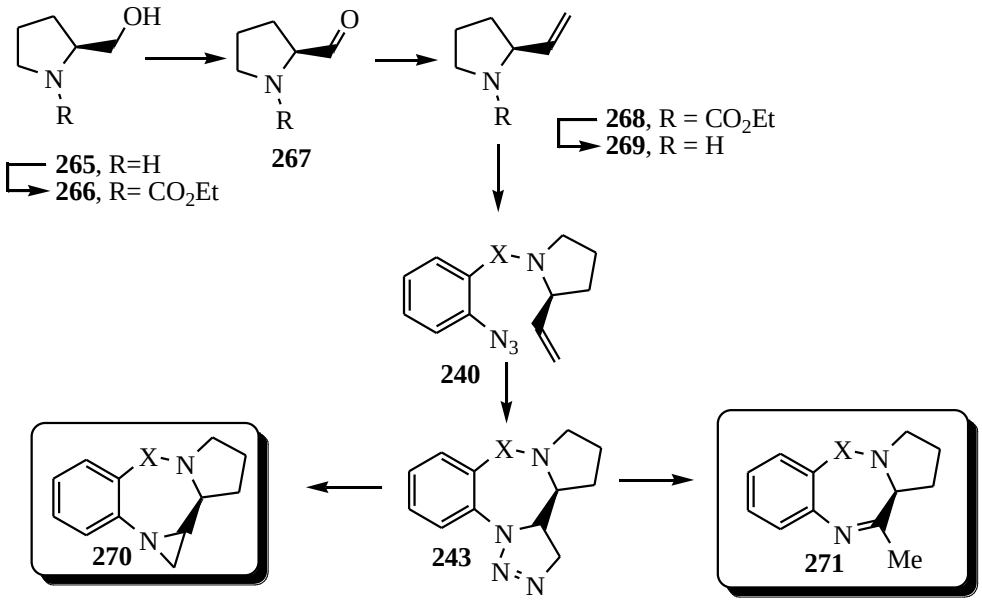
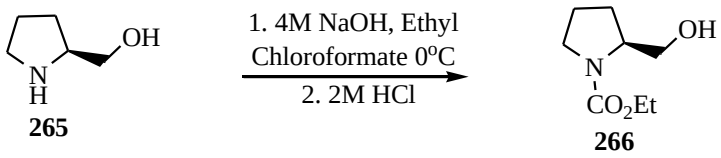


Figure 4-1

The literature details the use of an *N*-(ethoxycarbonyl) group (R = CO_2Et) as a precursor for the synthesis[132] of the *N*-unsubstituted proline derived alkene (**268**).

4.1.1 Synthesis of the alkenyl pyrrolidine derivative (**266**, R = CO_2Et).

Step 1:

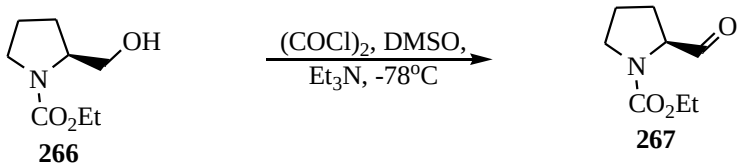


265 **266**

Scheme 4-1

The first step of the synthesis was to protect commercially available prolinol (**265**) with the carbethoxy group prior to the oxidation of the primary alcohol (**266**). This was done by treating the prolinol with chloroformate in the presence of aqueous sodium hydroxide. Neutralisation with 2M HCl gave the product in 96% yield. Spectroscopic analysis confirmed the inclusion of the carbethoxy group.

Step 2:



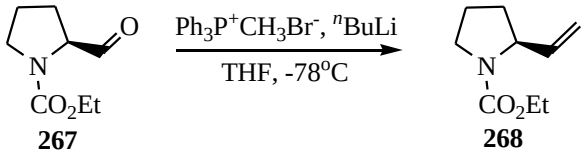
266 **267**

Scheme 4-2

With the successful protection of the amine, the next stage was the oxidation of the alcohol (**266**) to the aldehyde (**267**). Swern oxidation was used to give the product in 89% yield as a mixture of rotamers. ^{1}H (400 MHz) NMR spectroscopy showed two rotameric signals at 9.48 & 9.56 ppm for the aldehyde. No broad peak for the OH of the alcohol and also the loss of the signals between 3.59-3.69 ppm for the CH_2 next to the alcohol in the spectrum supported the assignment. The ^{13}C NMR (100 MHz) spectrum showed a signal downfield at 200.2/200.3 ppm (rotamers) for the carbon of the

aldehyde moiety together with the loss of the primary alcohol CH_2. The IR spectrum showed the loss of the broad OH stretch and a new peak for the carbonyl stretch of the aldehyde moiety.

Step 3:

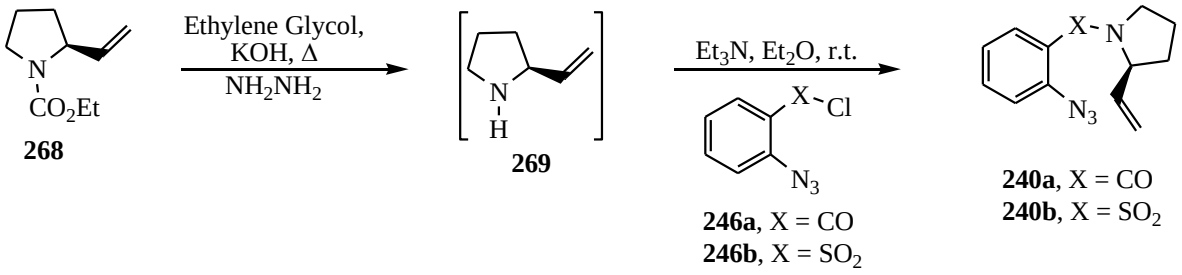


267 **268**

Scheme 4-3

With the aldehyde (**267**) successfully synthesised the next step was to use the Wittig reaction to convert the aldehyde moiety into a terminal alkene. The reaction proceded using ^{n}BuLi and methyltriphenylphosphonium bromide to make the ylide which reacted with the aldehyde to form the alkene (**268**) as a mixture of air sensitive rotamers in 45% yield. The key evidence for the formation of the correct structure was given by the ^{13}C NMR (100 MHz) spectrum which showed signals at 113.8/138.5 for the new vinylic CH_2 and 138.2/138.5 for the CH of the new alkene, as well as the loss of the diagnostic aldehyde CH.

4.1.2 The coupling of the pyrrolidinyl alkene (**269**) to the acid chlorides (**246**).



268

269

246a, X = CO
246b, X = SO_2

240a, X = CO
240b, X = SO_2

Scheme 4-4

The next step was to couple up the alkene (**269**) with the acid chlorides (**246a-b**, X = CO, SO_2). The deprotection to create the free amine was carried out using potassium hydroxide and hydrazine

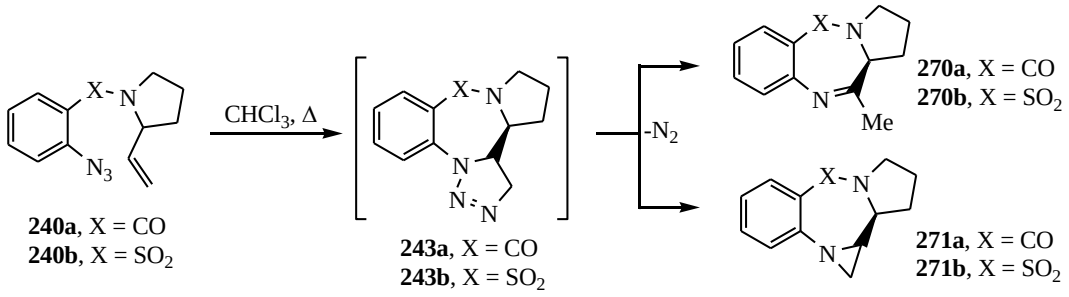
hydrate in ethylene glycol as described in the literature.[132] The acid chloride (**246a-b**) was coupled to the resultant amine in an ethereal solution of triethylamine. This procedure gave the product (**240a**, X = CO) in 32% yield as a mixture of rotamers. The structure of the product was confirmed by the ^{1}H (400 MHz) NMR spectrum which showed the presence of signals at 4.89 & 5.20 (1H, 2 x d), 4.89 & 5.20 (1H, 2 x d) and 5.56 & 5.90 (1H, 2 x dd) for the terminal alkene. The ^{13}C (100 MHz) NMR spectrum was also fully consistent showing (as a mixture of rotamers) the three pyrrolidine ring CH_2 signals, the terminal alkene CH_2 (114.5/114.9), the alkene CH (118.4/118.5) and the pyrrolidine ring CH (58.4/61.1 ppm) together with four aromatic CH signals and the carbonyl and two quaternary carbons. The IR spectrumgave a sharp peak at υ_{max} 2128 cm^{-1} which showed the presence of the azide group which is consistent with the uncyclised product. Further proof was given by the correct mass of 265.1064 for the measured ion $[M+Na]^+$.

With the successful synthesis of compound (**240a**, X = CO) achieved, attention was turned to the coupling of the sulfonyl derivative (**240b**, X = SO_2). The same method was used to give the correct product in 20% yield, which showed fully consistent spectroscopic data for the assigned structure. In the ^{1}H (400 MHz) NMR spectrum, for example, signals at 4.37-4.40 (1H, m, CH=C*H*H), 4.54 (1H, dd, CH=CH*H*) and 5.30-5.37 (1H, m, C*H*=CH_2) showed the presence of the terminal alkene. The ^{1}H (400 MHz) NMR spectrum also showed the expected four aromatic signals for the four aromatic protons of the benzene ring. The IR spectrum showed the azide at υ_{max} 2137 cm^{-1}, which, with the correct mass of 301.0722 for the measured ion $[M+Na]^+$ further supported the structural assignment.

4.1.3 Cycloaddition of the alkene and the azide.

With the alkene in hand the final step was to study the 1,3-dipolar cycloaddition between the alkene and the azide. Both examples (**240a-b**, X = CO, SO_2) were treated by heating to reflux in chloroform and monitoring by TLC. The first example in this discussion will be compound (**240a**, X = CO).

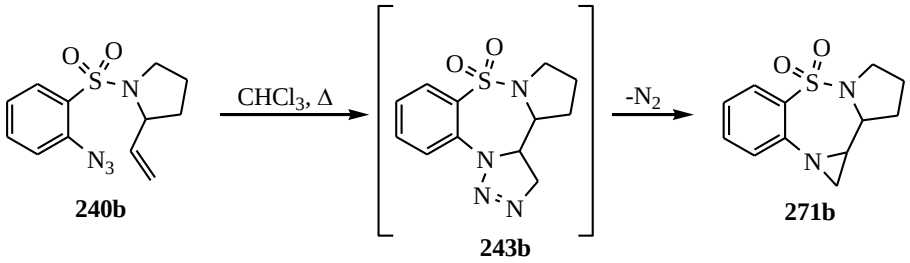
After 16 hours this reaction was deemed complete and was concentrated and purified to give an inseperable mixture of two compounds, in a ratio of 1:1. Spectroscopic analysis confirmed that the starting material was not present as the sharp azide peak was not present in the IR spectrum, and ^{1}H (400 MHz) NMR spectroscopy showed that the protons of the alkene were not present. Mass spectroscopic analysis showed that the starting material had lost 28 mass units and hence the triazoline (**243a**) intermediate could be discounted. The ^{1}H NMR (400 MHz) spectrum showed the presence of a total of eight aromatic protons which is consistent for two aromatic benzene ring systems, a feature confirmed in the ^{13}C (100 MHz) NMR spectra which showed eight aromatic CHs and four aromatic quaternary carbons together with two carbonyl signals. The methyl imine (**270a**) was inferred from an extra quaternary carbon at 165.5 ppm in the ^{13}C (100 MHz) NMR spectrum and a clear methyl signal at 22.4 ppm in the ^{13}C (100 MHz) NMR spectrum, which appeared at 2.27 ppm (3H, s) in the ^{1}H (400 MHz) NMR spectrum. Evidence for the aziridine (**271a**) was given by the presence of an extra CH_2 (seven in total) in the ^{13}C (100 MHz) NMR spectra and the presence of the extremely distinctive CH_2CH of the aziridine in the ^{1}H (400 MHz) NMR spectrum.



Scheme 4-5

In contrast to the amide system (**240a**, X = CO), the sulfonamide (**240b**, X = SO_2) gave a much cleaner reaction yielding only a single product which was identified as the aziridino-pyrrolobenzothiadiazepine (**271b**, X = SO_2) presumably formed as shown below. Thus, the ^{13}C (125MHz) NMR spectra showed the expected four CH_2 signals, two aliphatic CHs and the expected aromatic carbons (4 CHs and 2 quaternary). Mass spectrometric analysis confirmed the loss of 28 mass units so the intermediate triazoline (**243b**, X = SO_2) could be discounted. The ^{1}H (500 MHz) NMR spectrum showed the aziridine CH_2 protons coupled to the aziridine CH which was in turn

coupled to the pyrrolidine CH, confirming the connectivity of the aziridinopyrrolo system (**271b**, X = SO_2).



Scheme 4-6

The mechanism for the nitrogen extrusion to form the aziridine or the cyclic imine is also shown in Figure 4-2.

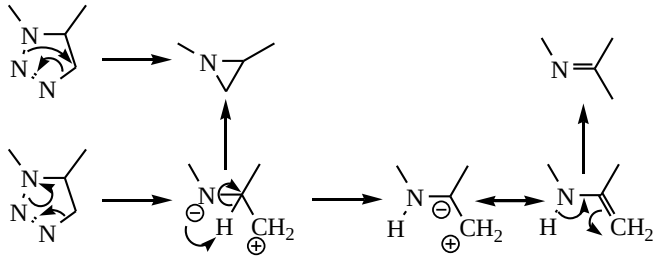
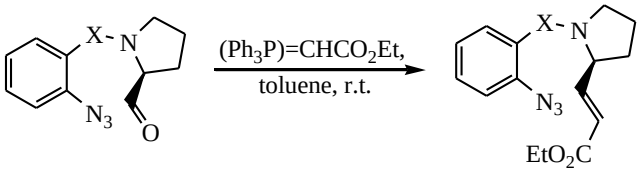


Figure 4-2

4.1.4 Formation and subsequent cycloaddition of a substituted alkene and the azide.



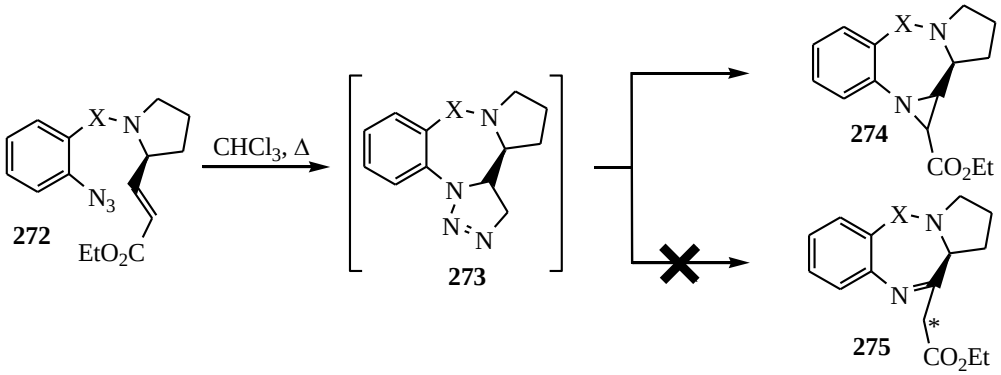
236a, X = CO
236b, X = SO_2

272a, X = CO
272b, X = SO_2

Scheme 4-7

A substituted alkene was synthesised from the aldehydes (**236a-b**, discussed previously) in order to perform further studies of the above cycloaddition between the alkene and the azide. The aldehyde (**236a**, X = CO) was treated with (carbethoxymethyl)triphenylphosphorane in toluene at room

temperature to afford the ethylcarbothoxy substituted alkene (**272a**, X = CO). ^{1}H (400 MHz) NMR spectroscopy showed the disappearence of the characteristic deshielded aldehyde peak and also the inclusion of signals at 1.29 & 1.31 (3H, t) and 4.13 & 4.21 (2H, q) for the presence of the carbethoxy unit (the product exists in rotameric form). The IR spectrum showed that the azide was still intact at υ_{max} 2130 cm^{-1} showing the product had not undergone cycloaddition. Further evidence was provided by the accurate mass measurement.



Scheme 4-8

The precursor (**272a**, X = CO) was heated at reflux in $CHCl_3$ for 48 hours before being purified and analysed. IR analysis showed the lack of a peak in the region υ_{max} 2130 cm^{-1} showing that the azide had reacted. The ^{1}H (400 MHz) spectrum showed that the product was a 1:1 mixture of isomers. The shifting of the former alkene peaks upfield to 2.77 (1H, d), 3.08 (1H, dd) and 3.37 ppm (1H, dt) provided evidence that the aziridine (**274a**, X = CO, see Scheme 4-8) or triazoline (**273a**, X = CO) had formed. The accurate mass confirmed that the mass of the starting material had decreased by 28 mass units inferring that the aziridine (**274**, X = CO) was the product. The formation the cyclic imine (**275a**) could be discounted due to the lack of the extra CH_2* group (see Scheme 4-8) in the ^{13}C (100 MHz) spectrum.

This method was further examined with the sulfonyl (**236b**, X=SO_2) which was treated under the same conditions but this time the intermediate alkene (**272b**, X = SO_2) was not isolated but the azide and the alkene underwent *in situ* cycloaddition to form the aziridine (**274b**, X = SO_2) as a single isomer in 17% yield, from the aldehyde (**236b**)

4.2 Attempted Synthesis of Other Aziridinobenzodiazepines.

In view of the formation of the aziridino PBDs and PBTDs detailed above, it was decided to look at some other intramolecular azide to alkene cycloadditions that might give access to some other aziridino-fused benzodiazepine derivatives. The 4-vinyl-azetidinones (**277** & **282**) where chosen for this study to provide a potential route to azetidinobenzodiazepines as analogues of the potent antibiotic pyrrolobenzodiazepines which contain both the β-lactam ring and the electrophilic imine (or aziridine) of the PBD (or PBTD) which is the feature that provides the PBDs (or PBTDs) with their antibiotic activity.[133-135] The β-lactams are a well known class of antibiotics, so the synthesis of azetidinobenzodiazepine fused lactams is of interest. The proposed route to azetidinobenzodiazepines is shown in the Figure 4-3 and is discussed in the rest of this section.

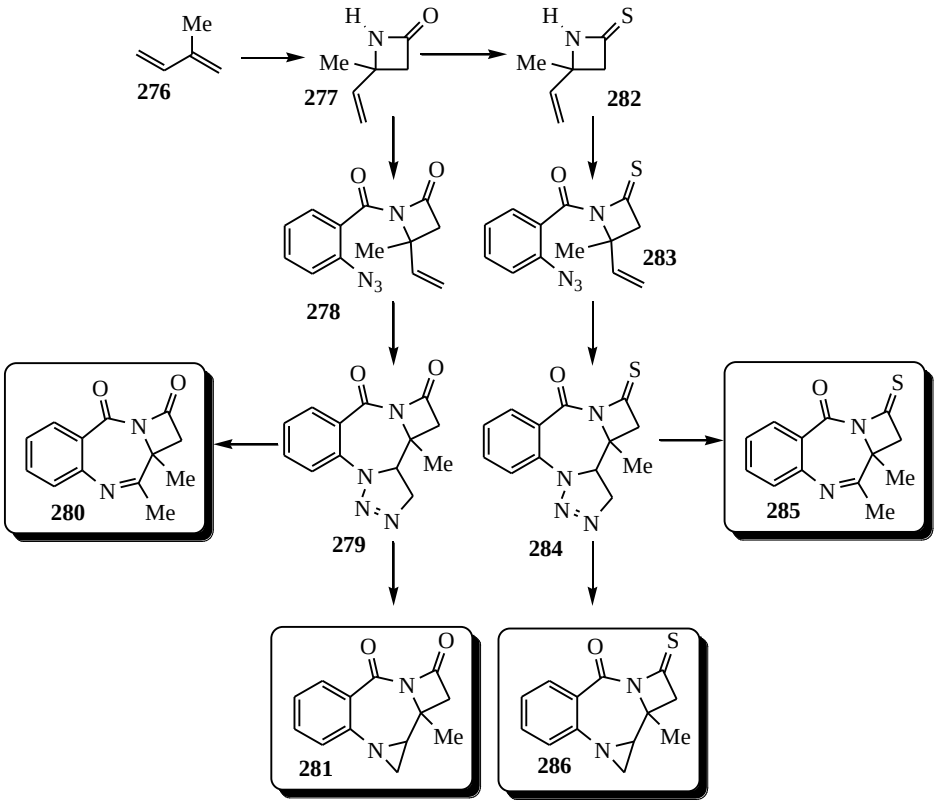
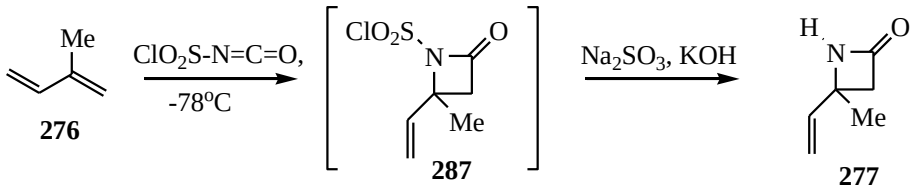


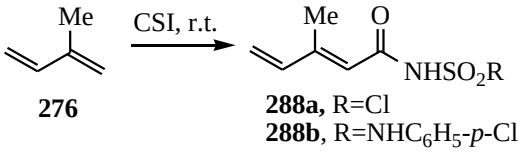
Figure 4-3

4.2.1 Synthesis of the 4-vinyl-azetidinone (**277**).



Scheme 4-9

The synthesis started from isoprene (**276**) which was cooled to -78°C in ether before slow addition of chlorosulfonylisocyanate (CSI). It was important to keep the reaction at low temperature to eliminate possible side reactions which have been noted by Moriconi and Meyer[136] who showed that reaction at room temperature led to the structure (**288a**, as shown in Scheme 4-10), the presence of which was shown upon workup with *p*-anisidine to give the structure (**288b**).



Scheme 4-10

To add more complications to the reaction sequence, it was noted that if the β-lactam (**287**) was warmed to room temperature the four membered ring would undergo ring opening to form the 6-membered ring lactam (**289**), which undergoes further transformations as shown in Figure 4-4.

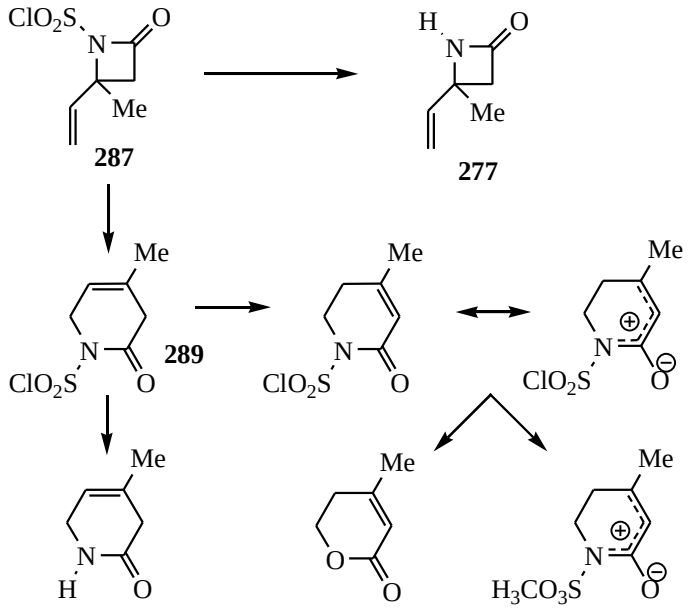
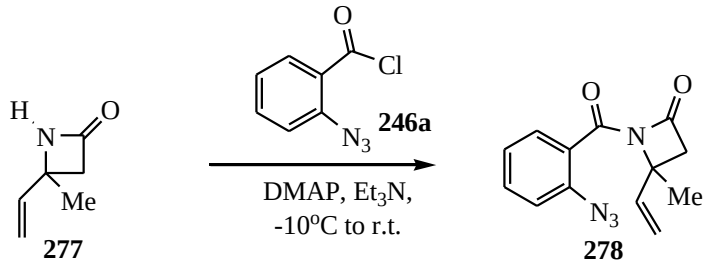


Figure 4-4

In the event, when the reaction was carried out at -78°C with an excess of isoprene and allowed to reach a temperature no higher than -10°C, the desired β-lactam (**277**) was isolated in 44% yield after the removal of the *N*-sulfonyl group *in situ*. The spectroscopic analysis was consistent with the literature data[136] for the expected structure. For example, the ^{13}C NMR spectra showed the presence of the alkene with the CH at 113.8 ppm and the CH_2 at 141.1 ppm which supports the structure of the desired β-lactam rather than other possible side products.

4.2.2 Synthesis of the 1-(2-azidobenzoyl)-4-vinyl-azetidin-2-one.

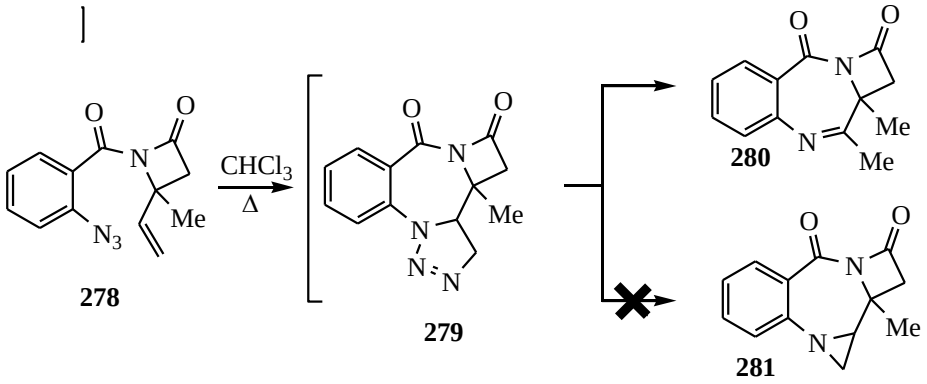


Scheme 4-11

With the *N*-unsubstituted β-lactam (**277**) to hand, the next stage was coupling to the corresponding acid chloride (**246a**) using DMAP and Et_3N. Coupling up to the acid chloride (**246a**) gave the expected alkene (**278**), the structure of which was confirmed by the ^1H (400 MHz) NMR spectrum which showed signals at 5.35 (1H, d, *J* 10.7), 5.45 (1H, d, *J* 17.3) and 6.24 ppm (1H, dd, *J* 10.7, 17.3) for the alkene. The aromatic ring system was shown to be present due to the signals at 7.22 (1H, t), 7.23 (1H, d), 7.42 (1H, dd) and 7.52 ppm (1H, dt, ArH). The ^{13}C (100 MHz) NMR spectrum showed the presence of the alkene 114.9 (CH_2) and 117.5 ppm (CH) plus all other expected signals. The presence of the sharp azide peak [at υ_{max} 2131 cm]$^{-1}$ in the IR spectrum showed that the azide was intact and the product had not undergone a 1,3-dipolar cycloaddition.

4.2.3 Attempted cyclisation by the reaction of the alkene and azide.

The following potential outcomes were considered with a view to discovering which of the cyclised products, if any, would form:



Scheme 4-12

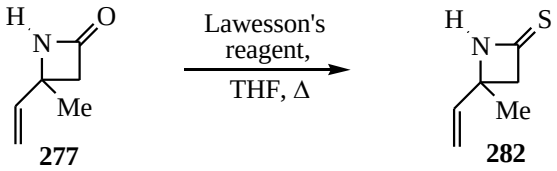
The 1-(2'-azidobenzoyl)-4-vinyl-azetidin-2-one (**278**) was dissolved in $CHCl_3$ and heated at reflux temperature. After 72 hours, TLC analysis indicated that the product had been consumed. Analysis of the purified product by ^{13}C (125MHz) NMR spectroscopy revealed the presence of two methyl groups and inferred the formation of the methyl imine product (**280**). The ^{13}C NMR spectrum showed a CH_2 at 43.6 ppm, and a quaternary carbon for the imine C=N at 155.2 ppm. The

quaternary carbon bearing the second methyl appeared at 73.3 ppm. The four CHs of the benzene ring appeared at 126.5 to 134.3 ppm and the two carbonyl signals at 158.1 and 204.2 ppm. The presence of two methyls in the ^{1}H (500 MHz) NMR spectrum at 2.00 (3H, s), 2.49 (1H, s), the single CH_2 giving two signals coupled together at 3.42 (1H, d, *J* 16.0), 3.77 ppm (1H, d, *J* 16.0) and the four aromatic signals was consistent with the structural assignment of the methyl imine product (**280**) which was formed in 22% yield. Accurate mass measurement was consistent with the desired $[M+H]^+$ at 229.0978 and also confirmed that the product had lost nitrogen discounting the formation of structure (**279**, in Scheme 4-12).

4.3 The synthesis of the thiolactam derivatives.

The *N*-(2-azidobenzoyl)-4-vinyl-azetidin-2-one (**278**) discussed above gave the cyclic imine (**280**) rather than the aziridine (**281**). In order to explore this chemistry fully, it was decided to investigate if the azetidine-2-thione would behave in the same manner.

4.3.1 Synthesis of 4-vinyl-azetidinethione (**282**).



277 **282**

Scheme 4-13

The first stage in this process was the synthesis of the thiolactam (**282**), which was easily prepared using Lawesson's reagent,[137] a reaction believed to proceed via the mechanism, shown in the Figure 4-5. Successful reaction was shown by the ^{13}C (100 MHz) NMR spectra which showed the loss of the quaternary carbon 167.6 ppm and the appearance of a peak at 202.2 ppm which is consistent with the new (C=S). Further proof came from the IR spectrum which showed the loss of the amide C=O signal at υ_{max} 1720 cm^{-1}.

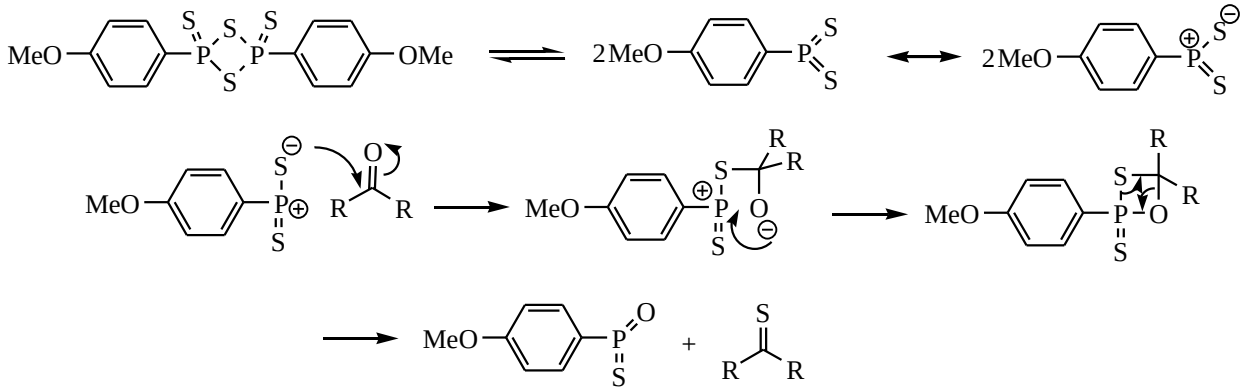
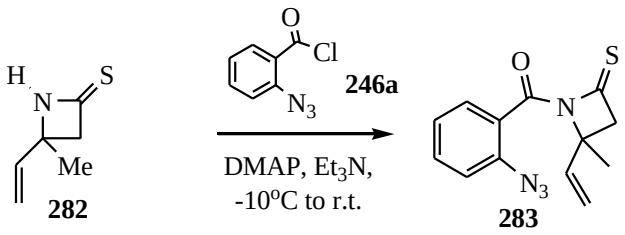


Figure 4-5

4.3.2 Synthesis of the 2-(2'-azidobenzoyl)-4-vinyl-azetidin-2-thione (**283**).

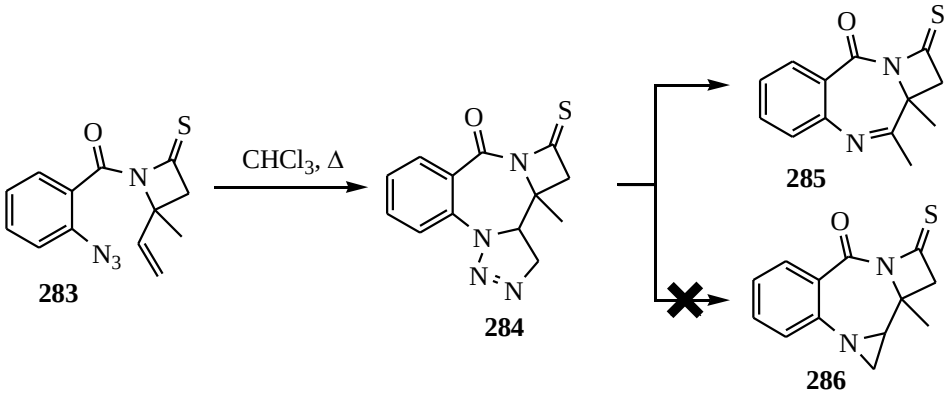


Scheme 4-14

The next stage in the synthesis was the coupling of the thiolactam (**282**) to the acid chloride (**246**). The acid chloride (**246**) was made in the usual way and was coupled up to the thiolactam (**282**) using DMAP and Et_3N to yield the coupled product in 84% yield. The ^1H (400 MHz) NMR spectrum showed the disappearance of the broad peak for the azetidine NH around 8.78 ppm and the appearance of the aromatic carbons of the benzene ring at 7.20 (1H, d), 7.24 (1H, dt), 7.36 (1H, dd) and 7.54 ppm (1H, dt). The ^{13}C (100 MHz) NMR spectrum showed the presence of four aromatic CH carbons at 125.1, 128.9, 132.1 and 137.7 ppm as well as the characteristic signals of the alkene downfield at 116.4 (CH_2) and 118.5 ppm (CH). The IR spectrum confirmed the presence of the azide peak at υ_{max} 2131 cm^{-1}. The correct high resolution mass spectrum peak of 295.0623 for the ion $[M+Na]^+$ supported the structural assignment.

4.3.3 The cyclisation of the thiolactam alkene with the azide.

The intramolecular 1,3-dipolar cycloaddition between the alkene and azide groups was the next step in the synthesis and was carried out by heating compound (**283**) in $CHCl_3$ at reflux. The anticipated possible structural outcomes of this reaction are shown in Scheme 4-15:



Scheme 4-15

After 36 hours a major new spot had appeared on TLC and the starting material has disappeared so the reaction products were purified and analysed. At first glance the main change to note was in the ^1H (500 MHz) spectrum which showed that there was only one methyl peak, a feature which was confirmed by ^{13}C (125MHz) NMR spectroscopy. This discounted the dimethyl structure (**285**). The analysis of the product by HRMS showed the mass of the ion $[M+Na]^+$ to be 295.0622 which was the same as the mass as starting compound (**283**), showing no loss of nitrogen. The IR spectrum showed no azide peak at υ_{max} 2131 cm^{-1} which showed the azide had reacted and confirmed that the product was not the starting material (**283**). The ^1H (400 MHz) NMR spectrum showed signals for the CH_2 of the triazoline ring at 4.37 (1H, dd, *J* 6.1, 17.7), 4.71 (1H, dd, *J* 12.2, 17.7) and a CH at 4.27 ppm (1H, dd, *J* 6.1, 12.2) which was also confirmed in the ^{13}C (100 MHz) NMR spectra with peaks at 59.6 (CH) and 70.4 ppm (CH_2). This led to the identification of the product as the triazolinoazetidobenzodiazepine (**284**) which was formed in 61% yield.

Further exposure of compound (**284**) to boiling in chloroform gave solely the azetidino-benzodiazepine (**285**) in a yield of 32%, the structure of which was determined by the loss of 28 mass giving the mass 267.0551 along with an extra methyl in both the ^{1}H (400 MHz) at 2.47 ppm and 26.3 ppm in the ^{13}C (100 MHz) NMR spectra.

In conclusion, 4-vinyl-azetidinones proved to be useful substrates for the synthesis of some novel azetidinoaziridinobenzodiazepines and their non-aziridino (methyl imine) analogues.

5 Discussion: Intramolecular Azide Cycloadditions Using Highly Substituted Benzene Rings.

In this, the penultimate part of the discussion, the synthesis discussed in the previous chapters will be exploited to make direct analogues of DC-81. This functionality has been explored vastly in the literature (as discussed in the Section 1.2), both in order to produce DC-81 itself and to produce natural & synthetic analogues of DC-81.

The transformations that will be discussed in this section are summarised in the Figure 5-1 and broadly parallels the processes discussed above i.e. eventual intramolecular 1,3-dipolar cycloaddition between an azide and a nitrile, alkyne and alkene. Due to the fact that these routes require the synthesis of the 2-azidobenzoic acid (**294**), this section is detailed separately to the routes described previously in this thesis, although some of the later steps will be seen to be similar.

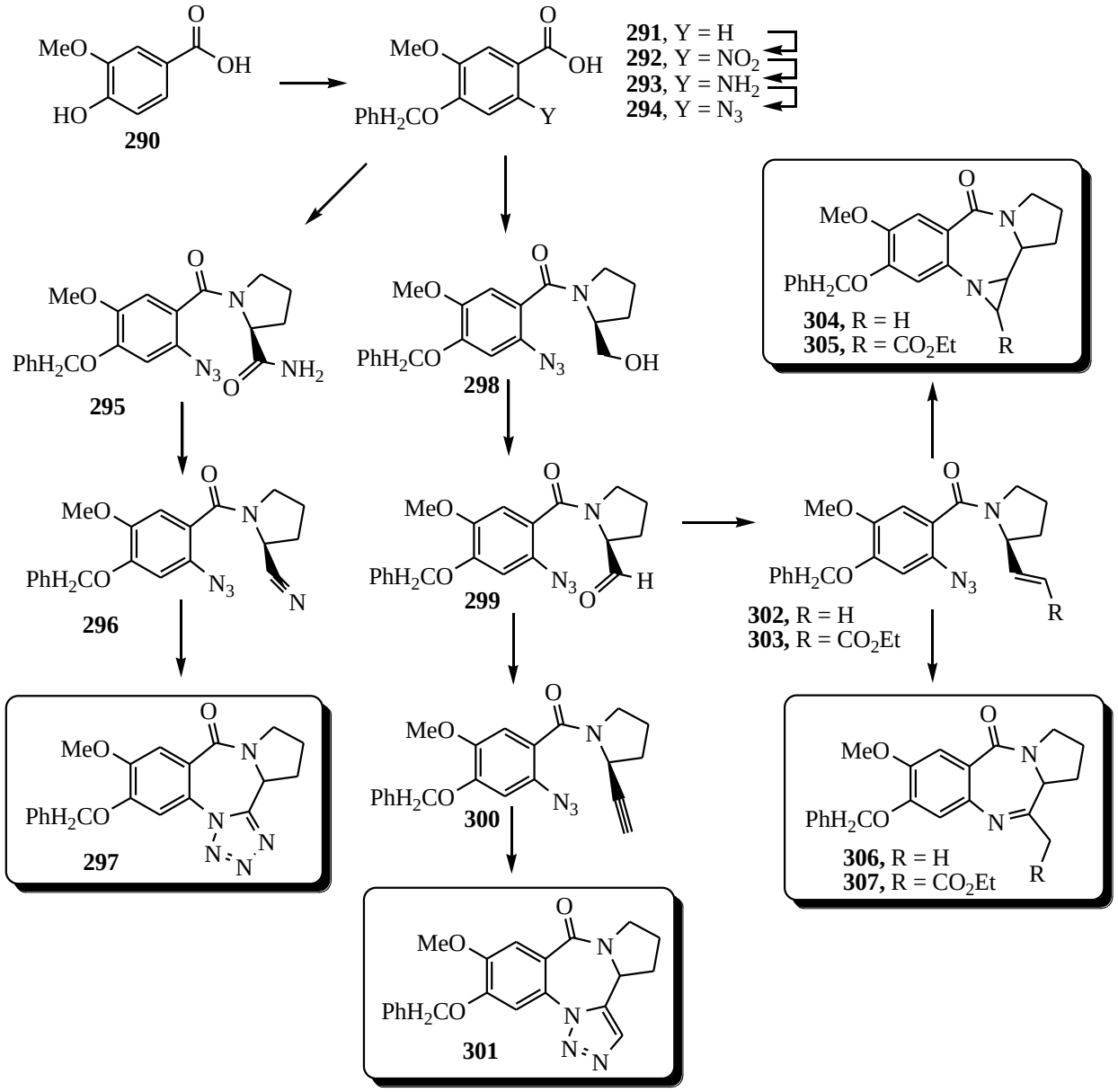
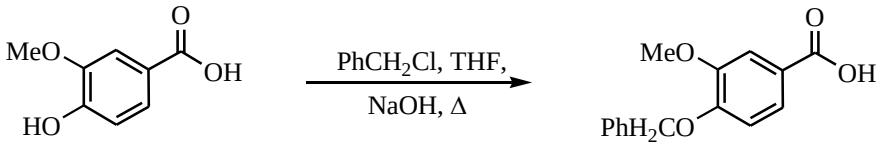

MeO
OH
HO
O
290
PhH2CO
Y
291, Y = H
292, Y = NO2
293, Y = NH2
294, Y = N3
N
N3
NH2
295
OH
298
296
299
H
297
300
301
304, R = H
305, R = CO2Et
302, R = H
303, R = CO2Et
306, R = H
307, R = CO2Et
R

Figure 5-1

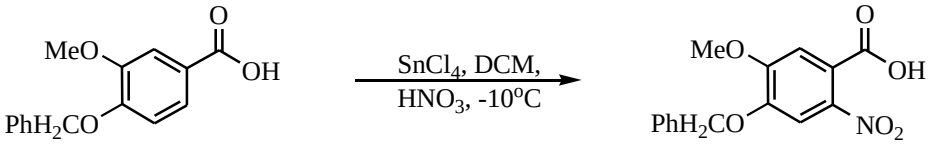
5.1.1 Synthesis of 4-benzyloxy-5-methoxy-2-azidobenzoic acid (**294**): Step 1 – Benzyl protection and nitration of vanillic acid.



290 **291**

Scheme 5-1

The synthesis started by the protection of the hydroxyl group of vanillic acid as this needs to be protected for the coupling procedure later in the synthesis. Thurston *et al*,[96] provided a quick two step synthesis to the nitro derivative (**292**); starting from vanillic acid (**290**). Benzyl chloride was added slowly to vanillic acid in 2M NaOH and the whole was heated at reflux. The product (**291**) was isolated by acidification with HCl to form the product from the sodium salt. Spectroscopic analysis was consistent with the literature and with the expected structure.



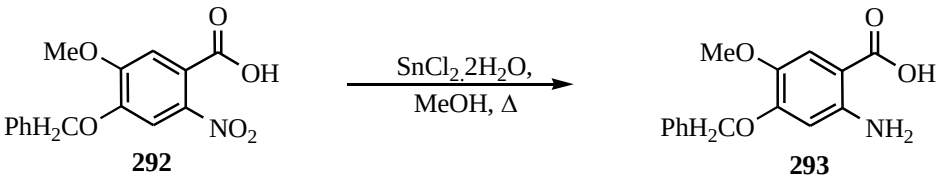
291 **292**

Scheme 5-2

Nitration of the benzene ring system with a tin(IV)chloride-nitric acid[96] complex afforded the product (**292**) in 63% yield which was characterised by comparison to the literature values and by ^{1}H (500 MHz) NMR spectroscopy which showed two singlets downfield at 7.31 (1H, s) and 7.70 ppm (1H, s) showing the 1, 2, 4, 5-substitution pattern of the central benzene ring. The ^{13}C (125MHz) NMR spectrum showed one less aromatic carbon downfield compared to the starting material. The IR spectrum showed peaks at υ_{max} 1351 and 1537 cm^{-1} giving strong evidence for the N-O stretches.

The correct mass of 326.1 for the measured ion $[M+Na]^+$ provided further strong evidence that the correct product was formed.

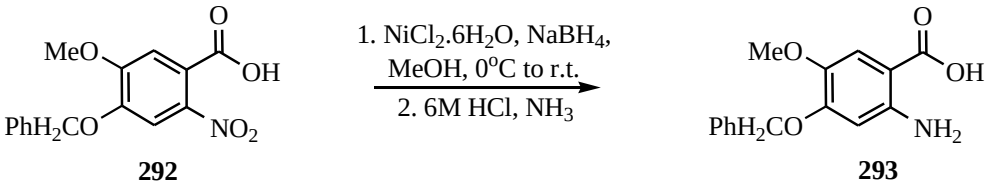
5.1.2 Synthesis of the 4-benzyloxy-5-methoxy-2-azidobenzoic acid (**294**): Step 2 - nitro reduction.



292 **293**

Scheme 5-3

The synthesis of the amine (**293**) was the next step in the process. Results were variable and methods capricious with some reactions working to give the amine in excellent yield and other reactions failing. A solution was not found to this capriciousness, but a variety of methods where examined over a long period. A method by Eguchi *et al*,[138] which used tin(II)chloride dehydrate worked best to give a white solid in 88% yield, but this method was unreliable, and had to be performed numerous times to enable access to the desired product.

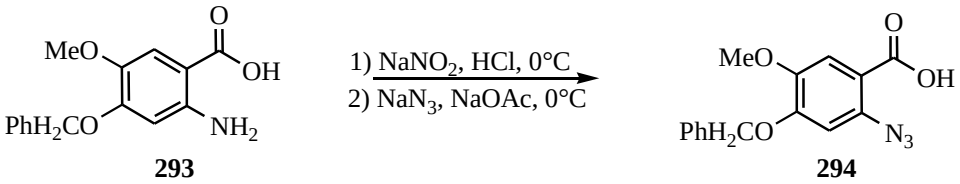


292 **293**

Scheme 5-4

The next method attempted was also from the group of Eguchi and utilised $NiCl_2.6H_2O$ and sodium borohydride as the reducing agent which gave impure product in around 25% yield. Other reactions were carried out using iron dust and acetic acid[99] which proved to be unsuccessful. Analysis was carried by ^1H, ^{13}C NMR and IR spectroscopy which, together with mass spectrometry, confirmed the structural assignment. It should be pointed out that this apparently simple transformation proved extremely troublesome and took up a significant amount of time and effort.

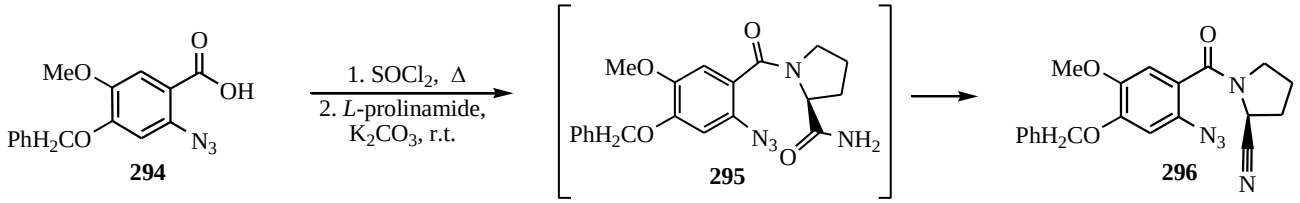
5.1.3 Synthesis of the 4-benzyloxy-5-methoxy-2-azidobenzoic acid (**294**): Step 3 - azidation.



Scheme 5-5

With the amine (**293**) in hand the next stage was to convert the amine to the azide moiety. This was carried out by literature methods[69,138] to give the azide in 47% yield. Analysis by IR spectroscopy showed the successful azidation by the loss of the aryl NH_2 peaks at υ_{max} 3354 and 3530 cm^{-1} and the appearance of the azide peak at υ_{max} 2099 cm^{-1}. Further proof was given by the correct mass of 322.0789 for the measured ion $[M+Na]^+$ which was consistent with the assigned structure of the azide (**294**).

5.1.4 Coupling to Prolinamide and Subsequent Nitrile Formation.

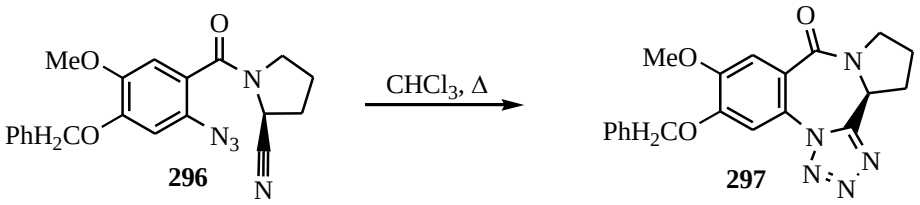


Scheme 5-6

The next stage was to couple the azide (**294**) to *L*-prolinamide. Coupling was achieved by converting the acid into the acid chloride using thionyl chloride. The acid chloride was added slowly to a basic solution of potassium carbonate and the *L*-prolinamide. The coupled product was not isolated as the primary amide (**295**) but, as with a previous example, dehydration occurred spontaneously to give the nitrile product (**296**) in 56% yield. The successful coupling and dehydration was shown by ^1H (400 MHz) NMR spectroscopy which showed the inclusion of the pyrrolidine ring system with signals upfield at 2.17-2.44 (3H), 3.39-3.52 (2H), 3.75-3.82 (1H) and 4.92 ppm (1H). The aromatic

protons were found downfield at 6.72 (1H, s), 6.92 (1H, s) and 7.37-7.51 (5H) with the methoxy at 3.94 ppm (3H, s, OC*H*$_3$), and the benzyl CH_2 at 5.24 ppm (2H, s, OCH_2). The absence of no broad signals in the spectrum inferred that there were no OH or NH groups present in the structure. The ^{13}C-Dept 135 (100 MHz) NMR spectrum showed the presence of the methylene carbons at 25.0, 30.5, 47.7 ppm for the pyrrolidine ring system with the pyrrolidine CH at 46.4 ppm. The more deshielded methoxy and OCH_2 were found at 56.5 and 71.4 ppm respectively. The ^{13}C (100 MHz) NMR spectra also showed the presence of seven quaternary carbons with only one quaternary carbon in the carbonyl region of 167.0 ppm which is consistent with the dehydration of the molecule. The IR spectrum showed the presence of the azide at υ_{max} 2114 cm^{-1} and also the presence of the nitrile at υ_{max} 2253 cm^{-1}. The correct accurate mass of 378.1566 for the measured ion $[M+H]^+$ was consistent with the assignment of the structure.

5.1.5 Synthesis of the DC-81 Tetrazolo analogue (**297**).



Scheme 5-7

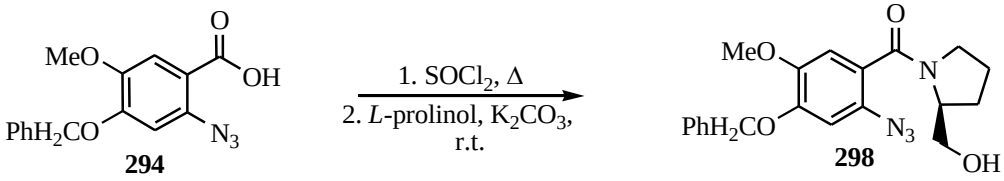
With the successful coupling and dehydration achieved, the final step in the synthesis of this analogue of DC-81 was carried out by heating the nitrile (**296**) at reflux in $CHCl_3$ for 72 hours to yield the product (**297**) in 58% yield. Analysis by ^{1}H (400 MHz) showed the pyrrolidine ring system was present with the signals at 2.04 - 2.18 (2H), 2.42 - 2.52 (1H), 3.06 - 3.13 (1H), 3.61 - 3.68 (1H), 3.73 - 3.79 (1H) and 4.68 ppm (1H). The benzene ring systems and substituents were shown by the signals at 3.93 (3H, s), 5.15 (1H, d), 5.26 (1H, d), 7.19 (1H, s), 7.25 - 7.41 (5H) and 7.53 ppm (1H, s). The ^{13}C (100 MHz) NMR spectra confirmed the presence of the three methylenes of the pyrrolidine ring and the OCH_2 with signals at 23.5, 28.2, 48.2 and 71.3 ppm, the methoxy at 56.4 ppm, one CH at 49.8 ppm along with the five aromatic CH's downfield and seven quaternary

carbons. Key information was provided by the IR spectrum which showed the lack of the azide peak at υ_{max} 2131 cm^{-1}, the disappearance of the nitrile signal at 2253 cm^{-1} and the correct mass of 378.1564 for the measured ion $[M+H]^+$ in the high resolution mass spectrum.

5.2 Synthesis of the DC-81 Triazole Analogue.

With the synthesis of the tetrazole example completed the next task was the synthesis of the triazole analogue. As described previously the triazole unit would be synthesised by the cyclisation between the alkyne and azide functional groups. Molina *et al*,[69] have already shown how prolinol can be coupled to the DC-81 carboxylic acid, and hence no problems were anticipated with this reaction. Once the prolinol coupled product was synthesised, the next step would be conversion into the alkyne.

5.2.1 Synthesis of DC-81 prolinol derivative (**298**).



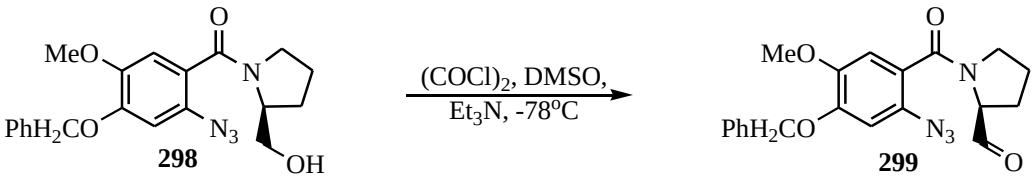
Scheme 5-8

The coupling of *S*-prolinol to the acid chloride was achieved by heating the carboxylic acid in a solution of $SOCl_2$ and toluene. The acid chloride was used directly by addition to a mixed phase basic solution of K_2CO_3 and prolinol. After purification of this reaction mixture, the desired product (**298**) was isolated in 87% yield, the structure of which was confirmed by the ^1H (400 MHz) NMR spectrum which was consistent with that of Molina.[69]

The ^{13}C (100 MHz) NMR spectra showed the five CH_2 signals at 24.5, 28.5, 49.6, 66.6 and 71.2 ppm for the pyrrolidine ring, alkyl chain and the OCH_2 as well a signal for the methoxy at 56.3 ppm. A

single CH for the pyrrolidine ring system at 61.2 ppm with five aromatic CH signals at 104.2, 110.7, 127.3, 128.2 and 128.7 ppm. The presence of six quaternary carbons was consistent with the structural assignment. The IR spectrum showed the broad peak between υ_{max} 3145-3593 cm^{-1} for the O-H stretch and also the azide intact with a sharp peak at υ_{max} 2109 cm^{-1}. The correct mass of 383.1708 for the ion $[M+H]^+$ gave further evidence for the structural assignment.

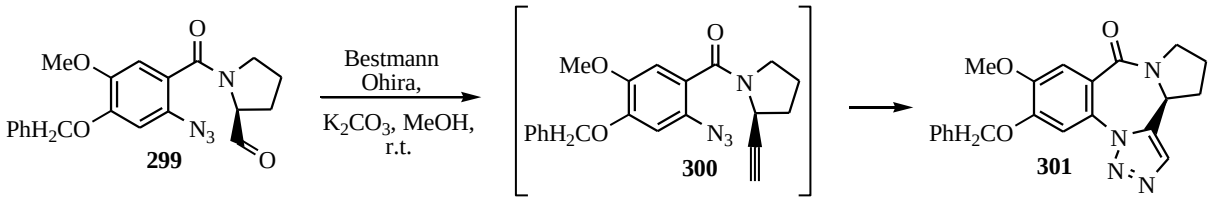
5.2.2 The Swern Oxidation of the DC-81 alcohol derivative.



Scheme 5-9

As previously, the next step was the conversion of the alcohol group to the aldehyde, under the Swern conditions. The product (**299**) was isolated as a mixture of rotamers in 65% yield as was shown by the presence of two doublets at 9.22 & 9.62 ppm as well as the disappearance of the alkyl chain protons in the ^1H (400 MHz) NMR spectrum. The ^{13}C (100 MHz) NMR spectrum showed a new peak at 198.0/199.4 ppm and the loss of the CH_2 at 71.2 ppm confirming the presence of the aldehyde moiety. The presence of peaks at υ_{max} 1731 cm^{-1} for the carbonyl of the aldehyde and the lack of the broad peak at υ_{max} ~ 3330 cm^{-1} in the IR spectrum and the correct mass of 403.1375 for the measured ion $[M+Na]^+$ supported the structural assignment.

5.2.3 Formation of the triazolo DC-81 derivative (**301**).



Scheme 5-10

With the aldehyde (**299**) in hand the next stage was the conversion of the aldehyde moiety to the terminal alkyne utilising the Bestmann-Ohira reagent as discussed previously. In this case the terminal alkyne (**300**) could not be isolated as 1,3-dipolar cycloaddition between the terminal alkyne and the azide occurred spontaneously to give the triazole (**301**) in 84% yield.

The formation of the cyclised product (**301**) was confirmed by ^{1}H (400 MHz) NMR spectroscopy which gave three aromatic singlets at 7.47, 7.50 and 7.52 ppm for the benzene ring and the new CH of the aromatic triazole ring. The signals at 1.98-2.09 (2H), 2.41-2.50 (2H), 3.63-3.73 (2H) and 4.63 ppm (1H) showed that the pyrrolidine ring system was still intact. The presence of signals at 5.12 (1H) and 5.24 (1H) with the aromatic protons at 7.23-7.28 (1H, m, ArH), 7.27-7.33 (2H, m, ArH) and 7.38-7.40 ppm (2H, m, ArH) showed the presence of the benzyl group. The methoxy appeared at 3.91 (3H, s). The ^{13}C (100 MHz) NMR spectrum showed the disappearance of the distinctive aldehyde CH above 190 ppm. The presence of six aromatic CH signals [for the two benzene rings and one for the new triazole] as well at the expected seven quaternary carbons [one in the newly formed triazole] gave evidence for the cyclisation. The IR spectrum showed the disappearance of the sharp peak for the azide at υ_{max} 2109 cm^{-1}, which together with the correct mass of 377.1600 for the ion $[M+H]^{+}$ in the high resolution mass spectrum supported the structural assignment.

5.3 Investigations of DC-81 Analogue Synthesis from Alkene Cycloadditions.

In this part of the discussion the aim was to analyse intramolecular 1,3-dipolar cycloadditions between alkene derived analogues of the DC-81 systems discussed thus far in this chapter. The first system that was explored was the synthesis of the alkene (**302a**) and its potential cyclisation to give the aziridino DC-81 analogue (**304**) or the DC-81 methyl imine (**306**) (as shown in the Figure 5-2 below). In the event, all attempts to synthesise the alkene (**302**) were unsuccessful, and hence other routes to alkenes (**303**) were explored. These routes are described in the preceeding sections.

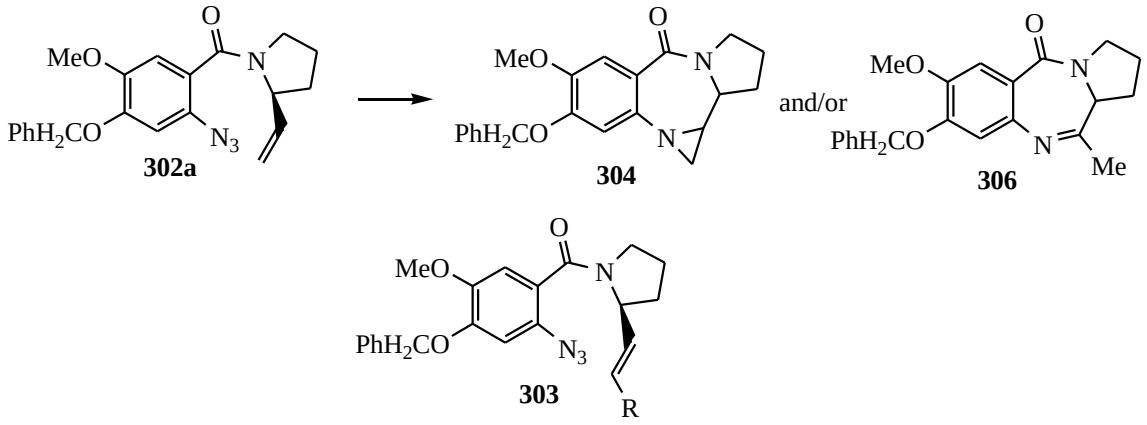
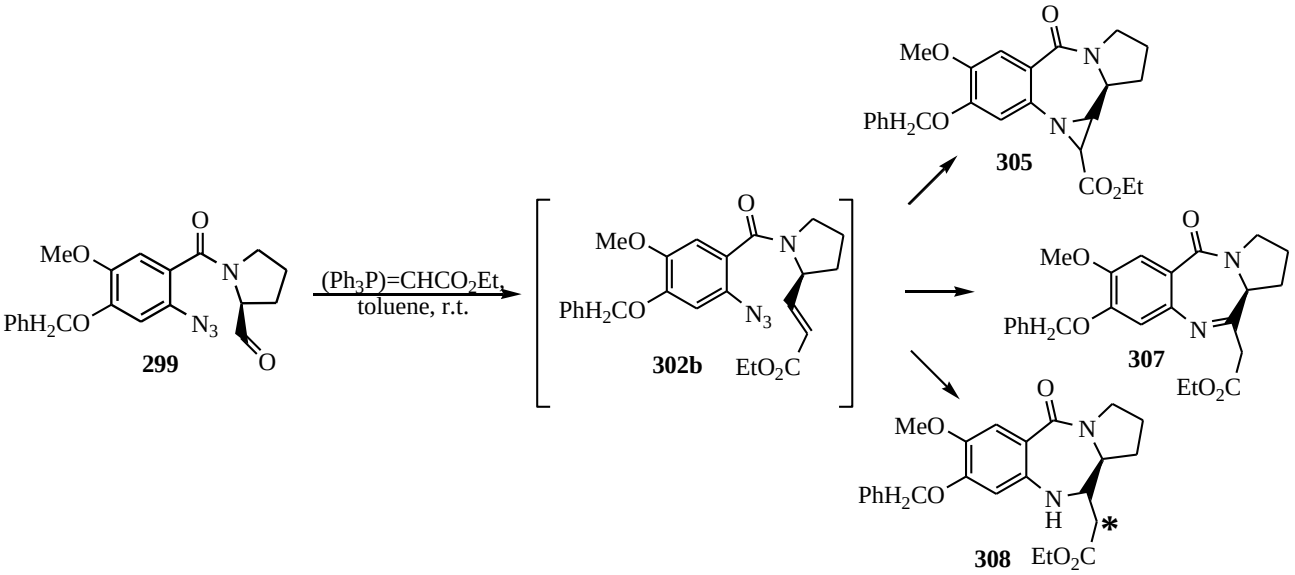


Figure 5-2

5.3.1 The synthesis of other alkene based systems.

For ease of synthesis, the analogue that was chosen for exploration was the ethyl carboxylate (**302b**) which was anticipated to be readily available from the aldehyde (**299**), which has been synthesised before, see section 5.2.2.



Scheme 5-11

Compound (**302b**) was formed from the Wittig reaction of (carbethoxymethylene)-triphenylphosphorane with the aldehyde (**299**) in toluene at room temperature. The expected product (**302b**, shown in the Scheme 5-11) was not isolated.

The IR spectrum confirmed that there was no azide present which, with the lack of a sharp peak at υ_{max} 2109 cm^{-1} discounted the uncyclised product (**302b**). Also, peaks were present which were consistent with the presence of a N-H stretch. The ^{13}C (125MHz) NMR spectra showed the presence of two CH signals at 50.1 and 62.7 ppm upfield of five types of aromatic CH carbons at 108.1, 113.1, 127.4, 128.0 and 128.4 ppm. Also, a total of six CH_2 signals were present, three for the proline ring, one for the benzyl protection group, one for the ethyl group and the $*CH_2$ (shown in Scheme 5-11).

Interestingly, mass spectroscopy showed a molecular ion 447.1895 $[M+Na]^+$ which is two mass units higher than either compounds (**305**) and (**307**). This, combined with the extra CH and CH_2 led to the assignment of structure (**308**) as the product. ^1H (500 MHz) NMR spectroscopy was fully consistent

with an extra CH_2 at 2.31–2.34 and an extra CH at 3.43–3.47. 2D NMR (HMBC, HSQC and COSY) confirmed the connectivity.

The Figure 5-3 shows a possible mechanism whereby 1,3-dipolar cycloaddition is followed by facile extrusion of N_2 and subsequent proton abstraction by the resultant diradical.

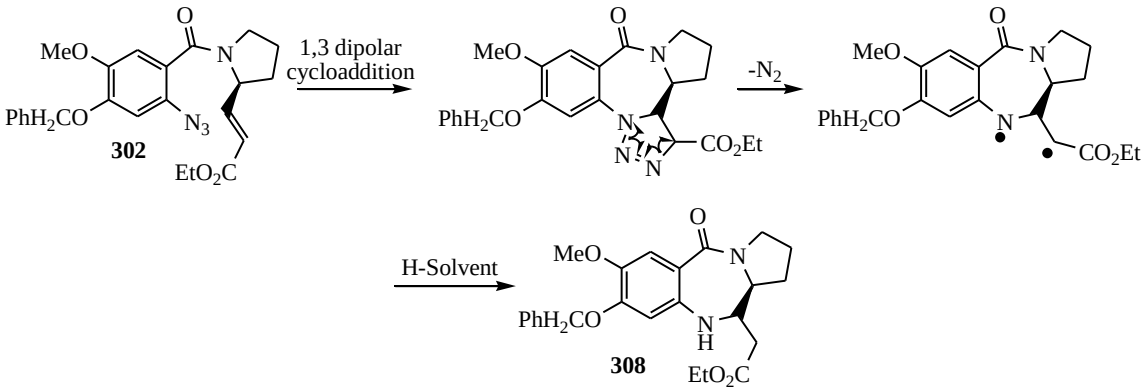


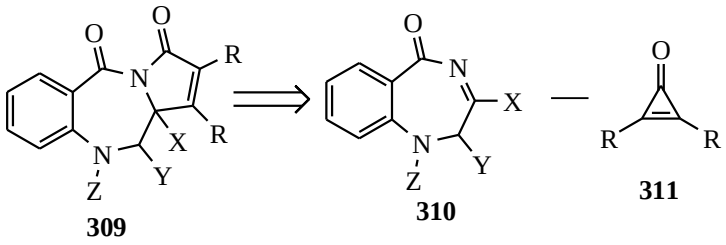
Figure 5-3

Conclusion

This section shows that the azide to nitrile, alkyne and alkene cycloaddition processes are applicable to the benzene substitution pattern present in DC-81.

6 Discussion: The Attempted Synthesis of PBDs via Cyclopropenone Additions.

In this final section, the following route to the PBD nucleus will be explored. This route relies upon the fact that electron rich imines (imidates) are known to react with cyclopropenones[139] (**311**) to form pyrrolidinones as shown in the Figure 6-1.

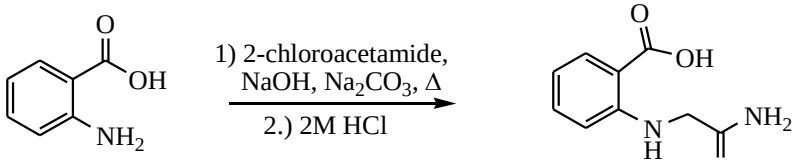


309 **310** **311**

Figure 6-1

In order to explore this as a potential route to PBDs a rapid access to the cyclic amine (**310**) was required. Wiklund *et al*,[140] have synthesised 1,4-benzodiazepin-3,5-diones which could allow the introduction of the imine bond which upon addition of DPP could potentially give rise to a unique route to novel PBDs.

6.1.1 Synthesis of the 1,4-benzodiazepin-3,5-dione (**310**): Step 1

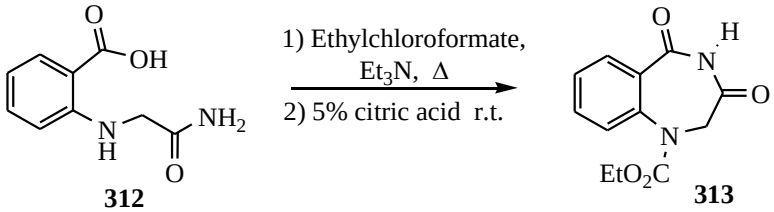


231 **312**

Scheme 6-1

The first stage in the synthesis was to repeat the literature coupling of 2-chloroacetamide with anthranilamide in the presence of sodium hydroxide and sodium carbonate.[140] After heating to reflux the product was isolated from the sodium salt by acidification with hydrochloric acid to give the product (**312**) in 53% yield after vacuum filtration. Analysis showed the presence of signals at 3.78 (2H, s), 7.19 (1H, bs) and 7.53 ppm (1H, bs) for the CH_2 and the amide protons in the ^1H (400 MHz) NMR spectrum. The secondary amine and the acid proton were present at 8.15 (1H, bs) and 12.60 (1H, bs) respectively along with the expected four signals for the aromatic protons at 6.50 (1H, d), 6.57 (1H, t), 7.36 (1H, dt) and 7.79 ppm (1H, dd). The ^{13}C (100 MHz) NMR spectrum showed signals at 45.9, 170.1 and 171.4 ppm for the presence of the CH_2 and the two carbonyls. The further presence of the two quaternary carbons of the benzene ring at 111.1 and 150.5 and the four aromatic CHs at 111.8, 115.0 132.1 and 134.9 ppm was consistent with the structure. The IR spectrum showed peaks at υ_{max} 1604, 1661, 3170, 3451 cm^{-1} which was consistent with two carbonyls, the amine and amide stretches, respectively. Further evidence was given by the correct mass measurement of 217.0582 for the ion $[M+Na]^+$ in the mass spectrum. Careful analysis of the spectroscopic data was necessary in order to clarify some ambiguity in the literature.[140]

6.1.2 Synthesis of the 1,4-benzodiazepin-3,5-dione (**310**): Step 2



312 **313**

Scheme 6-2

The next stage was a literature[140] precedented ring closure by heating (**312**) to reflux in MeCN in the presence of ethyl chloroformate and triethylamine with simultaneous protection of the secondary amine with the ethyl chloroformate by further heating to reflux. After workup in citric acid and cooling, the solid product was collected by vacuum filtration in 48% yield. The disappearance of the broad singlet for the acidic proton in the ^1H (500 MHz) NMR spectrum and the loss of one NH, plus

the inclusion of the ester group in the ^{1}H and ^{13}C NMR spectra indicated that the reaction was successful. The accurate mass measurement of 271.0687 for the ion $[M+Na]^{+}$ in the mass spectrum confirmed the structural assignment. Cyclopropenones react with imidates/thio imidates and hence the next step was to convert compound (**313**) into either the imidate (**314**) or thioimidate (**315**) (shown in Figure 6-2):

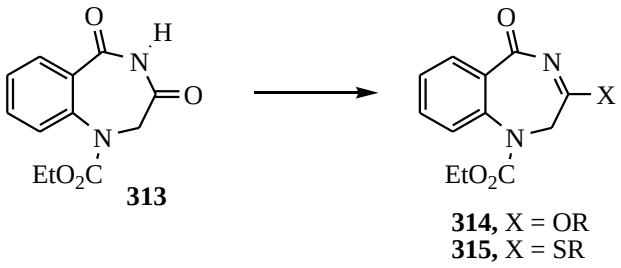
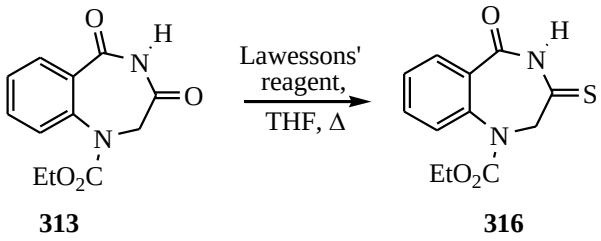


Figure 6-2

All attempts at *O*-alkylation failed to give compound (**314**). In order to access the thioimidate (**315**), conversion of the 1,4-benzodiazepin-3,5-dione (**313**) into the 3-thione compound was required.

6.1.3 Synthesis of 1,4-benzodiazepin-5-on-3-thione (**316**).

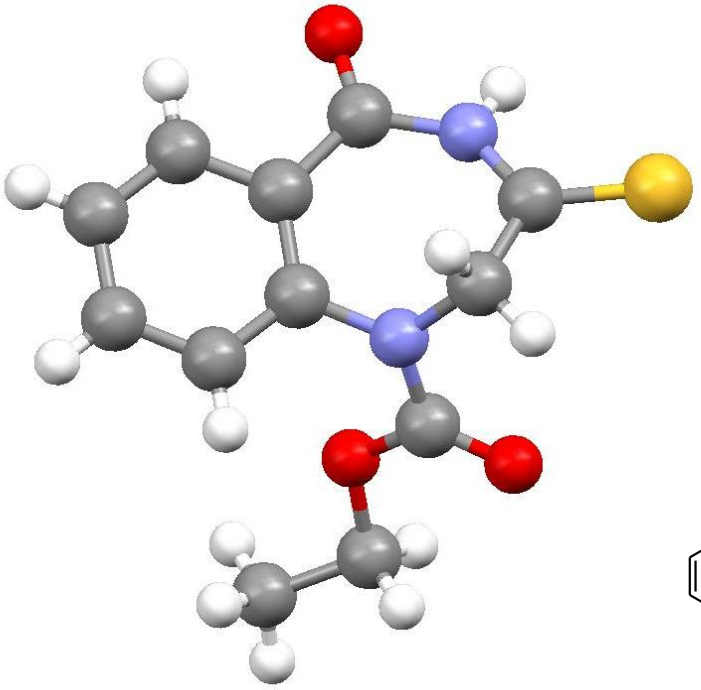


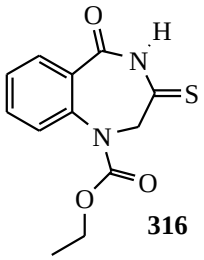
Scheme 6-3

The thionation of the carbonyl at the 3-position was the next step in the synthesis. As there was a possibility of the thionation of three different carbonyls, the reaction was carefully monitored by TLC. After treatment with 0.5 equivalents of Lawsseson's reagent and heating to reflux for 2 hours

in THF only one major spot was observed, so the reaction was stopped, purified and analysed. The ^{1}H (500 MHz) NMR spectrum showed a major shift downfield of the amide proton from 8.75 ppm to 10.08 ppm which is consistent with the NH environment having changed. The ^{13}C (125MHz) NMR spectrum showed only one peak at 204.6 ppm which was consistent with the conversion of only one carbonyl to the thiocarbonyl. The presence of one CH_3 and two CH_2 signals at 14.3, 59.8 and 63.0 ppm, and the observation of quaternary carbonyls at 162.7 and 153.5 ppm showed that the diazepine ring was intact. The expected four CH signals for the benzene ring were present at 127.1, 127.4, 133.4 and 134.2 ppm. The IR spectrum showed absorbances at υ_{max} 1154, 1313, 1648 and 1716 cm^{-1} which was consistent for the C=S plus two carbonyls.

In order to confirm the regiochemistry of the thionation reaction, the solid product was recrystallised and X-Ray crystallographic analysis was carried out (structure shown in Figure 6-3). This confirmed that thiation had occurred exclusively at the desired position.

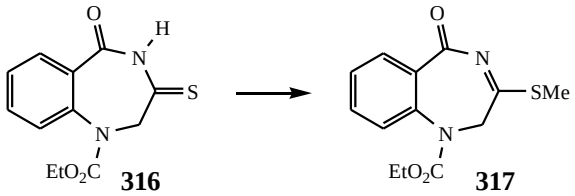




316

Figure 6-3

6.1.4 Attempted *S*-alkylation of the thioamide.



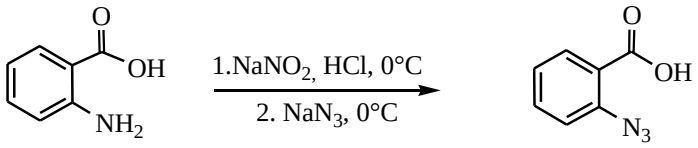
Scheme 6-4

Alkylation of the thioamide utilising dimethyl sulfate or Meerwein's reagent was the next step in the synthesis. Unfortunately the alkylation methods attempted all proved to be unsuccessful and time restrictions prevented a more comprehensive study in this thesis. However, the successful production of the 1,4-benzodiazepin-3-thione discussed above is currently underway to discover a successful *S*-alkylation procedure, and it can be concluded that this route to the PBD nucleus may well turn out to be successful.

7 Experimental: Section 1 Tetrazolo & Triazolo- PBDs and PBTDs.

7.1 Tetrazolo PBDs and PBTDs.

7.1.1 Synthesis of 2-azidobenzoic acid.



231a **232a**

Scheme 7-1

Anthranilic acid (2.00 g, 14.6 mmol, 1.0 eq) was suspended in 6M HCl (22 mL), $NaNO_2$ (1.24 g, 17.5 mmol, 1.2 eq) in water (6 mL) was added dropwise and the mixture was stirred at 0°C for 30 minutes. The resultant solution was added dropwise to a solution of NaOAc (15 g, 183 mmol, 12.5 eq), NaN_3 (1.17 g, 17.5 mmol, 1.2 eq) in water (22 mL) and stirred for 2 hours at 0°C. The precipitate was collected by vacuum filtration, washed with ice cooled water (2 x 40 mL) and dried in an oven overnight at 80-100°C to afford the product as a peachy solid (1.77 g, 95%) mp = 156-160°C, identical to that reported in the literature.[141]

δ_H (500 MHz, d_6-DMSO): 7.15 (1H, t, *J* 8.2, ArH), 7.20 (1H, d, *J* 8.2, ArH), 7.49 (1H, t, *J* 7.7, ArH), 7.67 (1H, d, *J* 7.7, ArH).

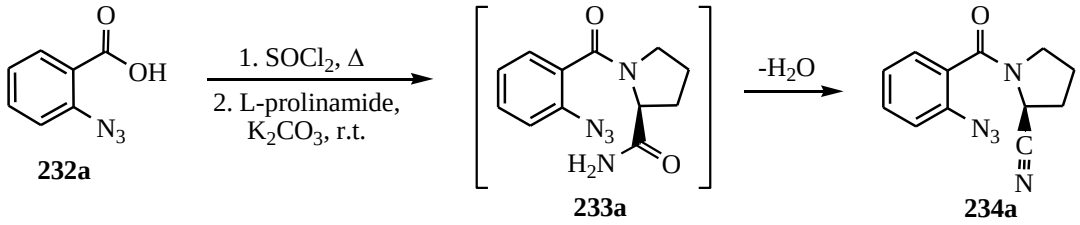
δ_C (125MHz, d_6-DMSO): 121.4 (CH), 124.2 (q), 125.9 (CH), 132.2 (CH), 134.4 (CH), 139.9 (q), 168.4 (q).

υ_{max} (thin film cm^{-1}): 1078 (m), 1172 (m), 1264 (s), 1303 (m), 1406 (m), 1445 (s), 1459 (s), 1484 (s), 1576 (s), 1596 (s), 1668 (s), 2123 (s), 2623-2920 (br).

LRMS (ESI+): Found 186.0 $[M+Na]^+$.

HRMS (ESI+): Found 186.0274 $[M+Na]^+$, $C_7H_5N_3NaO_2$ requires 186.0280.

7.1.2 Synthesis of (2*S*)-*N*-(2'-azidobenzoyl)-pyrrolidine-2-carbonitrile.



Scheme 7-2

A solution of 2-azidobenzoic acid (710 mg, 4.36 mmol, 2.49 eq) in thionyl chloride (5 mL) was heated at reflux under a nitrogen atmosphere at 85°C for 3 hours. The reaction mixture was allowed to reach room temperature before the excess thionyl chloride was removed *in vacuo*. Washing with DCM (2 x 10 mL) afforded the crude 2-azidobenzoyl chloride as a brown-black solid.

Potassium carbonate (1.00 g, 7.25 mmol, 4.14 eq) dissolved in water (5 mL) was added in one portion to a stirring solution of *L*-prolinamide (200 mg, 1.75 mmol, 1.0 eq) in DCM (5 mL). After stirring for 5 minutes, 2-azidobenzoyl chloride (~0.7 g, 2.5 eq) in DCM (5 mL) was added to the reaction mixture dropwise and the mixture was stirred for 20 hours. The organic phase was separated and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to yield the crude product. Purification by silica column chromatography (EtOAc:Hex; 1:1) yielded (2*S*)-*N*-(2'-azidobenzoyl)-pyrrolidine-2-carbonitrile as a mixture of rotamers in the form of a yellow oil (140 mg, 33%).

δ_H (400 MHz, $CDCl_3$): 2.01-2.10 (1H, m, C*H*H), 2.11-2.25 (1H, m, CH*H*), 2.27-2.41 (1H, m, C*H*H), 3.27-3.34 (1H, m, CH*H*), 3.37-3.45 (1H, m, NC*H*H), 3.72-3.83 (1H, m, NCH*H*), 4.92 (1H, dd, *J* 3.8, 7.5, C*H*CN), 7.23 (2H, m, Ar*H*), 7.34 (1H, dd, *J* 7.8, 1.6, Ar*H*), 7.48 (1H, dt, *J* 7.8, 1.6, Ar*H*).

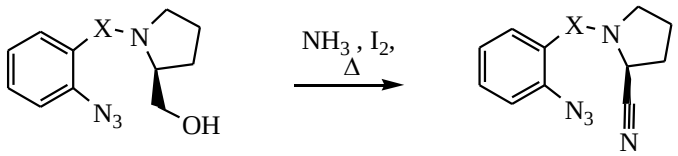
δ_C (100 MHz, $CDCl_3$): 22.6/24.3 (CH_2), 29.8/31.6 (CH_2), 45.1/47.0 (CH_2), 45.5/48.2 (CH), 117.4/117.6 (q), 117.9/118.0 (CH), 124.6/124.8 (CH), 127.2/127.5 (q), 127.4 (CH), 130.5/130.7 (CH), 135.8 (q), 166.5 (q).

υ_{max} (thin film cm^{-1}): 1094 (w), 1125 (m), 1151 (w), 1200 (w), 1292 (m), 1342 (m), 1410 (vs), 1450 (s), 1489 (s), 1578 (m), 1642 (vs), 2112 (s), 2131 (vs).

LRMS (ESI+): Found 264.1 $[M+Na]^+$, 288.3 $[M+2Na]^+$, 505.1 $[2M+Na]^+$.

HRMS (ESI+): Found $[M+NH_4]^+$ 259.1304, $C_{12}H_{15}N_6O$ requires 259.1302.

7.1.3 An alternative synthesis of the nitriles.



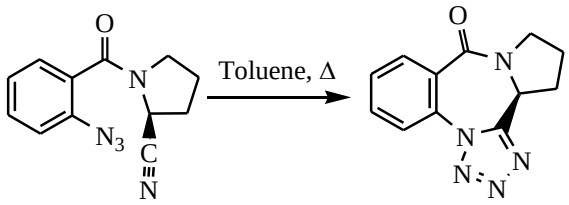
235a, X = CO
235b, X = SO_2

234a, X = CO
234b, X = SO_2

Scheme 7-3

To the nitrile (**235**) (580 mg, 2.37 mmol, 1 eq) in a mixture of conc. ammonia:water ; 7:3 (60ml) was added freshly ground iodine (6.01 g, 46.7 mmol, 10 eq) in small portions. The whole was heated to reflux at 85°C for 68 hours whilst being monitored by TLC. After several attempts at this reaction only minor amounts of product was present by TLC so the route was abandoned.

7.1.4 Synthesis of tetrazolo[1,5-*a*] pyrrolo[2,1-*c*][1,4] benzodiazepine-5-one.



234a **241a**

Scheme 7-4

A solution of (2*S*)-*N*-(2'-azidobenzoyl)-pyrrolidine-2-carbonitrile (100 mg, 0.415 mmol) in anhydrous toluene (5 mL) was heated to reflux for 6 hours under a dry nitrogen atmosphere. The reaction mixture was allowed to cool to ambient temperature and the solvent removed *in vacuo* to yield a pale yellow oil, which was purified by silica chromatography (EtOAc:Hex; 3:1) to yield the tetrazolo pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one as a white solid (40 mg, 40%).

δ_H (400 MHz, $CDCl_3$): 2.16-2.40 (2H, m, NCH_2CH_2), 2.53-2.63 (1H, m, C*H*H), 3.16-3.23 (1H, m, CHCH*H*), 3.70-3.77 (1H, m, NC*H*H), 3.85-3.91 (1H, m, NCH*H*), 4.83 (1H, dd, *J* 8.4, 3.2, C*H*CN), 7.64 (1H, dt, *J* 7.8, 0.9, Ar*H*), 7.76 (1H, dt, *J* 7.8, 1.4 Ar*H*), 7.94 (1H, dd, *J* 8.0, 0.9, Ar*H*), 8.18 (1H, dd, *J* 8.0, 1.4 Ar*H*).

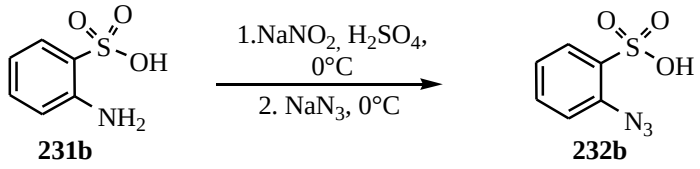
δ_C (100 MHz, $CDCl_3$): 23.5 (CH_2), 28.2 (CH_2), 48.2 (CH_2), 49.7 (CH), 122.5 (CH), 127.2 (q), 129.8 (CH), 130.3 (q), 132.3 (CH), 133.1 (CH), 154.5 (q), 163.4 (q).

υ_{max} (thin film cm^{-1}): 832 (m), 1023 (m), 1095 (m), 1125 (m), 1151 (m), 1241 (m), 1409 (s), 1470 (s), 1489 (s), 1605 (s), 1635 (s), 1735 (m), 2893 (m), 2923 (m).

LRMS (ESI+): Found 264.1 $[M+Na]^+$, 505.2 $[2M+Na]^+$.

HRMS (ESI+): Found 242.1034 $[M+H]^+$, $C_{12}H_{12}N_5O$ requires 242.1036.

7.1.5 Synthesis of 2-azidobenzenesulfonic acid.



231b **232b**

Scheme 7-5

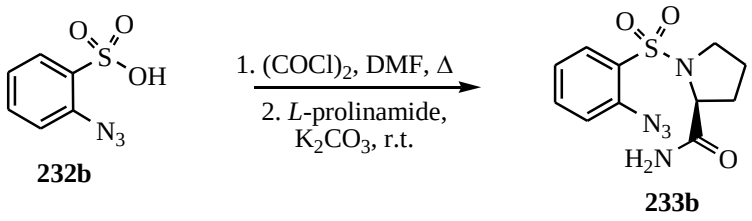
To a suspension of aniline-2-sulfonic acid (5.79 g, 33.4 mmol, 1 eq) in water (22 mL) at 0°C, was added cooled conc. H_2SO_4 (7.5 mL) dropwise. A solution of $NaNO_2$ (3.0 g, 43.4 mmol, 1.3 eq) in water (15 mL) cooled to 0°C was added to the suspension dropwise and the whole stirred for 30mins before a cooled solution of NaN_3 (4.34 g, 66.8 mmol, 2 eq) in water (15 mL) was added dropwise and the reaction was allowed to warm to room temperature. The resulting solution was crash cooled in an ice bath to afford the 2-azidobenzenesulfonic acid as a precipitate which was collected by vacuum filtration and dried in the oven at 80-100°C to give the product as a pale grey solid (4.91 g, 74%).

δ_H (400 MHz, d_6-DMSO): 7.15 (1H, t, *J* 7.6, ArH), 7.28 (1H, d, *J* 8.0, ArH), 7.45 (1H, dt, *J* 7.8, 1.5, ArH), 7.7 (1H, dd, *J* 7.8, 1.5, ArH).

δ_C (100 MHz, d_6-DMSO): 121.1 (CH), 125.4 (CH), 129.4 (CH), 132.7 (CH), 136.7 (q), 137.7 (q).

υ_{max} (thin film cm^{-1}): 665 (s), 740 (m), 765 (s), 1024 (s), 1087 (s), 1133 (m), 1145 (m), 1161 (m), 1199 (s), 1213 (s), 1237 (m), 1261 (m), 1279 (s), 1439 (m), 1472 (m), 1574 (w), 2122 (s).

7.1.6 Synthesis of 2(*S*)-*N*-(2'-azidobenzenesulfonyl)-2-prolinamide.



232b **233b**

Scheme 7-6

To 2-azidobenzenesulfonic acid (900 mg, 4.52 mmol, 2.6 eq) was added a 2M solution of oxalyl chloride in DCM (6 mL, 12.00 mmol, 6.85 eq) followed by the addition of DMF (50µl). The resultant mixture was heated to reflux for 15 hours under nitrogen at 80°C. The excess oxalyl chloride was removed *in vacuo* and the residue was washed with DCM (2 x 10 mL) to give the crude sulfonyl chloride as an orange solid.

A solution of potassium carbonate (1.32 g, 9.57 mmol, 5.5 eq) in water (10 mL) was added in one portion to *L*-prolinamide (200 mg, 1.75 mmol, 1 eq) in DCM (10 mL). The sulfonyl chloride was dissolved in DCM (5 mL) and was added dropwise to this solution. The reaction was allowed to stir at room temperature for 20 hours before the organic layer was separated and the aqueous layer washed with DCM (2 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, concentrated and purified by silica column chromatography (EtOAc: Hex; 10:1) to yield the product as a brown oil (330 mg, 62%).

δ_H (400 MHz, $CDCl_3$): 1.74-1.99 (3H, m, CH_2+CH*H*), 2.31-2.40 (1H, m, C*H*H), 3.26-3.38 (1H, m, NCH*H*), 3.43-3.53 (1H, m, NC*H*H), 4.64-4.67 (1H, m, NC*H*), 5.72 (1H, bs, N*H*), 6.90 (1H, bs, N*H*), 7.29 (1H, t, *J* 7.7, Ar*H*), 7.34 (1H, d, *J* 8.0, Ar*H*), 7.64 (1H, t, *J* 7.7, Ar*H*), 8.03 (1H, d, *J* 8.0, Ar*H*).

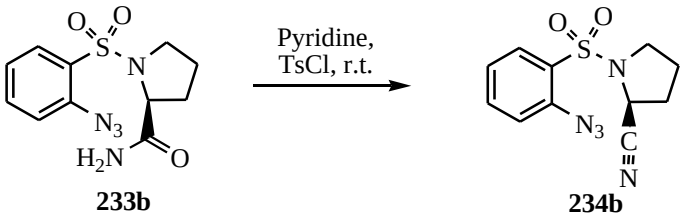
δ_C (100 MHz, $CDCl_3$): 24.6 (CH_2), 29.7 (CH_2), 49.1 (CH_2), 62.3 (CH), 119.9 (CH), 124.9 (CH), 127.8 (q), 133.0 (CH), 134.7 (CH), 138.4 (q), 174.2 (q).

υ_{max} (thin film cm^{-1}): 759 (m), 1157 (s), 1198 (s), 1334 (m), 1574 (m), 1670 (s), 2122 (m), 2132 (s), 3145 (m), 3476 (m).

LRMS (ESI+): Found 318.1 $[M+Na]^+$.

HRMS (ESI+): Found 313.1077 $[M+NH_4]^+$ $C_{11}H_{17}N_6O_3S$ requires 313.1077.

7.1.7 Synthesis of 2(*S*)-*N*-(2'-azidobenzenesulfonyl)-pyrrolidine-2-carbonitrile.



233b **234b**

Scheme 7-7

To a solution of the 2(*S*)-*N*-(2'-azidobenzenesulfonyl)-2-prolinamide (300 mg, 1.02 mmol, 1 eq) in DCM (5 mL) at room temperature was added pyridine (620 mg, 0.63 mL, 7.84 mmol, 7.7 eq) followed by neat tosyl chloride (1.27 g, 6.67 mmol, 6.5 eq). The resultant mixture was heated to reflux under a nitrogen atmosphere for 6 hours at 50°C. The solvent was removed *in vacuo* and the crude product was purified by silica chromatography (EtOAc: Hex; 1:1) to yield the product as a brown oil (90 mg, 37%).

δ_H (500 MHz, $CDCl_3$): 2.06-2.34 (4H, m, 2 x CH_2), 3.41-3.47 (1H, m, NC*H*H), 3.59 (1H, ddd, *J* 3.6, 7.6, 9.5, NCH*H*), 4.95 (1H, dd, *J* 2.8, 7.2, C*H*), 7.28 (1H, t, *J* 7.7, Ar*H*), 7.33 (1H, d, *J* 8.1, Ar*H*), 7.64 (1H, dt, *J* 7.7, 1.5, Ar*H*), 8.02 (1H, d, *J* 8.1, 1.5, Ar*H*).

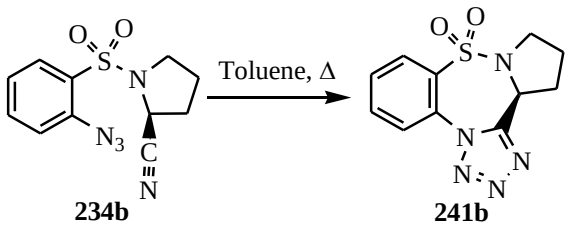
δ_C (125MHz, $CDCl_3$): 24.8 (CH_2), 32.2 (CH_2), 47.7 (CH_2), 48.8 (CH), 118.3 (q), 119.8 (CH), 124.7 (CH), 129.0 (q), 131.7 (CH), 134.6 (CH), 138.4 (q).

υ_{max} (thin film cm^{-1}): 896 (s), 1164 (m), 1265 (vs), 1347 (m), 1422 (m), 1473 (m), 2122 (m), 2134 (s), 2987 (m), 3054 (s).

LRMS (ESI+): Found 300.1 $[M+Na]^+$.

HRMS (ESI+): Found 295.0972 $[M+NH_4]^+$ $C_{11}H_{15}N_6O_2S$ requires 295.0972.

7.1.8 Synthesis of tetrazolo[1,5-*d*]-pyrrolo[1,2-*b*][1,2,5]benzothiadiazepin-9,9-dioxide.



234b **241b**

Scheme 7-8

(*S*)-*N*-(2'-azidobenzenesulfonyl)-pyrrolidine-2-carbonitrile (90 mg, 0.325 mmol) was heated to reflux temperature in dry toluene (8 mL) under a nitrogen atmosphere for 72 hours. The solvent was removed *in vacuo* and the crude product was purified by silica chromatography (EtOAc: Hex; 2:1) to yield the product as a white solid (90 mg, 100%).

δ_H (500 MHz, $CDCl_3$): 1.80 (1H, m, C*H*H), 1.94 (1H, m, CH*H*), 2.08 (1H, m, C*H*H), 2.61 (1H, m, CH*H*), 3.04 (1H, ddd, *J* 9.8, 7.5, 7.4, C*H*H), 3.64 (1H, ddd, *J* 4.7, 7.2, 9.8, CH*H*), 5.59 (1H, dd, *J* 7.2, 7.4, NCC*H*N), 7.65 (1H, dt, *J* 7.8, 0.8, Ar*H*), 7.83 (1H, dt, *J* 7.8, 1.4, Ar*H*), 8.12 (1H, dd, *J* 8.0, 1.4, Ar*H*), 8.16 (1H, dd, *J* 8.0, 0.8, Ar*H*).

δ_C (125MHz, $CDCl_3$): 24.5 (CH_2), 34.5 (CH_2), 49.3 (CH_2), 56.1 (CH), 125.1 (CH), 129.4 (CH), 129.7 (CH), 130.7 (q), 131.1 (q), 134.6 (CH), 155.4 (q).

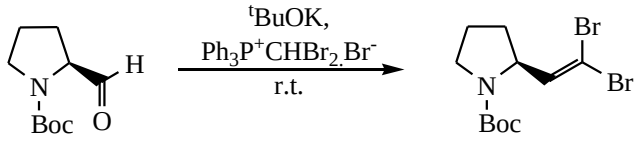
υ_{max} (thin film cm^{-1}): 895 (m), 1174 (s), 1265 (s), 1363 (m), 1421 (m), 1482 (m), 1590 (w), 2986 (m), 3054 (m).

LRMS (ESI+): Found 278.1 $[M+H]^+$, 577.1 $[2M+Na]^+$, 854.2 $[3M+Na]^+$.

HRMS (ESI+): Found 278.0707 $[M+H]^+$, $C_{11}H_{12}N_5O_2S$ requires 278.0706.

7.2 Triazolo- PBDs and PBTDs.

7.2.1 Synthesis of *N*-Boc-dibromoethenyl pyrrolidine.

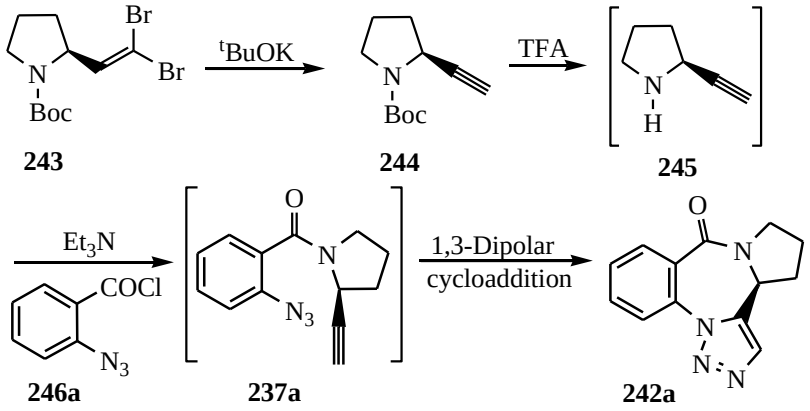


238 **243**

Scheme 7-9

To dibromo-methyltriphenylphosphonium bromide (1.3 g, 2.52 mmol, 3 eq) in anhydrous THF (20 mL) was added a solution of 1M ^{t}BuOK in methyl-2-propanol (2.8 mL, 2.62 eq) dropwise and the whole stirred for 5 minutes under nitrogen at room temperature. A solution of the *N*-protected aldehyde (**238**, 0.20 mL, 213 mg, 1.07 mmol, 1 eq) in THF (5 mL) was injected into the first solution dropwise over 10 minutes. After 1 hour the reaction was quenched with water (20 mL) and the organic layer was collected. The aqueous layer was extracted with EtOAc (3 x 20 mL), the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a brown solid. Purification by silica chromatography (30 g) (EtOAc: Hex; 3:2) yielded the product as a yellow oil (355 mg, 94%) which was used immediately in the next step.

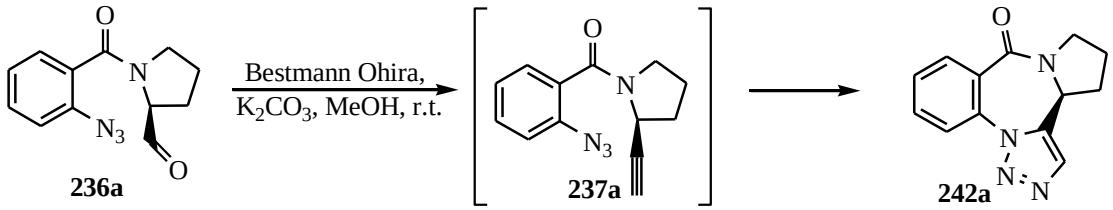
7.2.2 Synthesis of 1,2,3-triazolo-[1,5-*a*]-pyrrolo-[2,1-*c*] benzodiazepine-5-one (**242**).



Scheme 7-10

N-Boc-dibromoethenyl pyrrolidine (350 mg, 0.985 mmol) was dissolved in THF (10 mL) and 1M ^{t}BuOK in 2-methyl-2-propanol (2.5 mL, 2.5 mmol) was added under nitrogen. The reaction was quenched after stirring for 45 minutes with water (20 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (2 x 10 mL) and the combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo*. The crude product was purified by silica column chromatography (30 g) (EtOAc: Hex; 3:2) to yield the air sensitive *N*-Boc protected alkyne (top spot, 255 mg, 1.39 mmol, 1 eq). The alkyne was dissolved in DCM (6 mL); TFA (0.46 mL, 710 mg, 6.23 mmol, 4.5 eq) was added dropwise and the mixture was stirred under nitrogen at r.t. for 3 hours. The reaction was quenched with 2M NaOH (6 mL) and the pH was adjusted to 7 using 2M HCl. The organic layer was separated and the aqueous layer extracted with DCM (3 x 10 mL). The combined organic layers were washed with saturated brine solution (1 x 10ml), dried ($MgSO_4$) and the volume was reduced *in vacuo* to approximately 15 mL. To this solution, Et_3N (0.3 mL, 280 mg, 2.78 mmol, 2 eq) and the acid chloride* (**246a**, 249 mg, 1.39 mmol, 1 eq) were added dropwise under nitrogen at 0°C. The whole reaction was stirred under nitrogen for 48 hours; the reaction was diluted with water (20 mL). The organic layer was separated, the aqueous layer was extracted with DCM (2 x 10 mL), the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by silica column chromatography (40 g) (EtOAc: Hex; 10:1) to yield the product as a white solid (10 mg, 3%).

*Note : The carboxylic acid chloride was prepared by heating the 2-azidobenzoic acid (225 mg, 1.39 mmol, 1 eq) at reflux in $SOCl_2$ (2 mL) under nitrogen at 85°C for 3 hours. The excess $SOCl_2$ was removed *in vacuo* and the brown/black solid was redissolved in fresh DCM (2 x 10 mL), which was evaporated to remove excess $SOCl_2$.



236a **237a** **242a**

Scheme 7-11

Method B: The aldehyde [See part 7.2.6] (672 mg, 2.75 mmol, 1 eq) was dissolved in dry methanol (5 mL); K_2CO_3 (760 mg, 5.51 mmol, 2.0 eq) and the Bestmann-Ohira reagent (635 mg, 3.30 mmol, 1.2 eq) were added and the whole was stirred for 5 hours under nitrogen at room temperature. The reaction was quenched with saturated aqueous solution of NH_4Cl (10 mL), the organic phase was separated and the aqueous phase was extracted with DCM (3 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a yellow solid (632 mg, 96%). Purification by silica chromatography (40 g) (EtOAc:Hex; 9:1) yielded the product as a white solid (550 mg, 83%).

δ_H (400 MHz, $CDCl_3$): 2.03-2.12 (2H, m, CH_2), 2.44-2.56 (2H, m, CH_2), 3.64-3.78 (2H, m, NCH_2), 4.70 (1H, dd, *J* 7.2, 4.9, NC*H*), 7.49 (1H, dt, *J* 7.6, 1.1, ArH), 7.57 (1H, s, C*H*NN), 7.62 (1H, dt, *J* 7.6, 1.5, ArH), 7.92 (1H, dd, *J* 8.1, 1.1, ArH), 8.04 (1H, dd, *J* 7.9, 1.5, ArH).

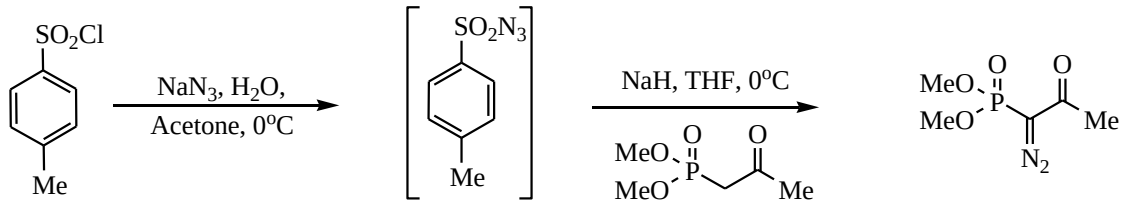
δ_C (100 MHz, $CDCl_3$): 23.7 (CH_2), 29.4 (CH_2), 47.7 (CH_2), 49.6 (CH), 123.0 (CH), 127.2 (q), 128.8 (CH), 129.0 (CH), 131.8 (CH), 132.8 (CH), 133.1 (q), 138.9 (q), 164.0 (q).

υ_{max} (thin film cm^{-1}): 986 (m), 1127 (m), 1245 (m), 1412 (s), 1434 (s), 1473 (s), 1579 (m), 1634 (s), 2963(m), 2981(m).

LRMS (ESI+): Found 241.1 $[M+H]^+$.

HRMS (ESI+): Found 241.1083 $[M+H]^+$, $C_{13}H_{13}N_4O$ requires 241.1084.

7.2.3 Synthesis of the Bestmann-Ohira Reagent.



Scheme 7-12

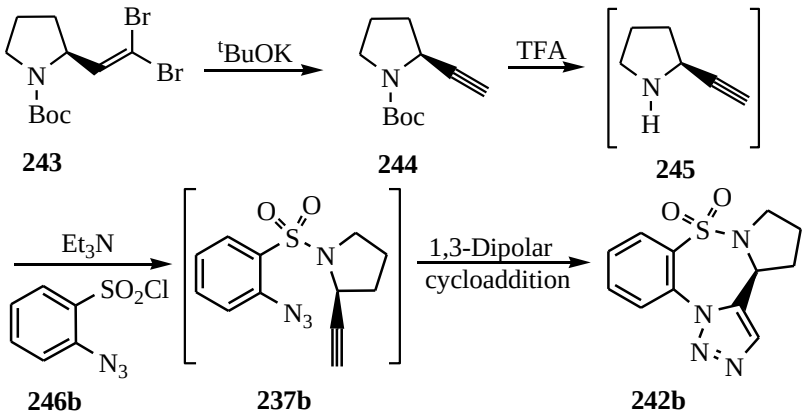
A solution of tosylchloride (8.00 g, 42 mmol) in acetone (120ml) was added to NaN_3 (2.73 g, 42.0 mmol) in water (120ml) and the whole was stirred at 0°C for 2 hours. The reaction mixture was concentrated *in vacuo* to approximately 20ml and the mixture was extracted with Et_2O (3 x 120ml). The combined organics were dried ($MgSO_4$), filtered and concentrated to approximately 20ml to yield an ethereal solution of the tosyl azide.

A solution of NaH (1.65g of 60% dispersion in oil) was washed with hexane (3 x 10ml) to give oil free NaH (0.99 g, 41.5 mmol) which was suspended in THF (100ml) and cooled to 0°C. Dimethyl (2-oxopropyl)phosphonate (6.26 g, 37.7 mmol) in THF (100ml) was added dropwise and the whole was stirred at 0°C for an hour before the tosyl azide was added in three portions and stirred at 0°C for 10mins. The mixture was concentrated and purified by silica chromatography (100 g) (neat EtOAc) to yield the product as pale yellow oil (4.27 g, 59%).

δ_H (400 MHz, $CDCl_3$): 2.19 (3H, s, $COCH_3$), 3.76 (3H, s, OCH_3), 3.79 (3H, s, OCH_3).

δ_C (100 MHz, $CDCl_3$): 27.2 (CH_3), 53.6 (CH_3), 53.7 (CH_3), 126.4 (q), 189.9 (q).

7.2.4 Synthesis of 1,2,3-triazolo[1,5-*d*]-pyrrolo[1,2-*b*][1,2,5]benzothiadiazepin-9,9-dioxide.

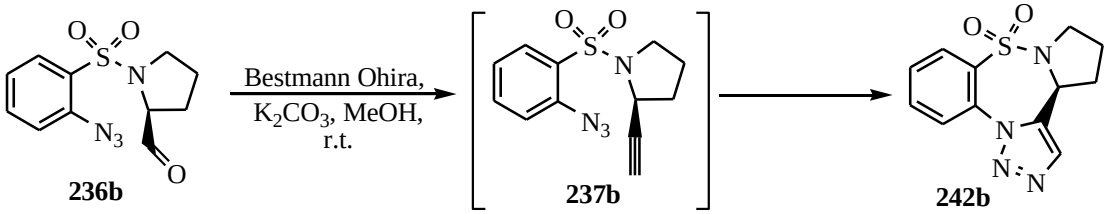


Scheme 7-13

Method A: *N*-Boc-dibromoethenyl pyrrolidine (355 mg, 1.00 mmol) was dissolved in THF (10 mL); 1M ^{t}BuOK in 2-methyl-2-propanol (2.5 mL, 2.5 mmol) was added under nitrogen. The reaction was quenched after stirring for 45 minutes by the addition of water (20 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo* to give an orange oil. The crude product was purified by silica chromatography (30 g) (EtOAc: Hex; 3:2) to yield the air sensitive alkyne (top spot, 110 mg, 0.564 mmol, 1.3 eq). The alkyne was dissolved in anhydrous DCM (6 mL); TFA (0.15 mL, 220 mg, 1.93 mmol, 4.6 eq) was added dropwise and the mixture was stirred under nitrogen at r.t. for 3 hours. The reaction was quenched with 2M aqueous NaOH (2 mL, 4.0 mmol, 9.5 eq) and the pH was adjusted to 7 using 2M HCl. The organic layer was separated and the aqueous layer extracted with DCM (3 x 10 mL). The combined organic layers were washed with saturated brine solution (1 x 10ml), dried ($MgSO_4$), filtered and reduced *in vacuo* to 15 mL. To this solution Et_3N (0.12 mL, 87 mg, 0.86 mmol, 1.95 eq) and the sulfonyl chloride (**246b**)* (approx 1 eq) were added dropwise under nitrogen at 0°C. The whole reaction was allowed to warm slowly to

room temperature over 2 hours and stirred under nitrogen for 48 hours before being diluted with water (20 mL). The organic layer was separated and the aqueous layer was extracted with DCM (2 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by silica chromatography (20 g) (EtOAc: Hex; 2:1) to yield the product as an orange solid (bottom spot, 23 mg, 14%).

*Note : The 2-azidobenzenesulfonyl chloride was prepared using 2-azidobenzenesulfonic acid (84 mg, 0.422 mmol, 1.0 eq) suspended in dry DCM (3 mL), to which was added 2M oxalyl chloride in DCM (0.6 mL), followed by DMF (50µl). The mixture was heated to reflux under nitrogen at 85°C for 3 hours. The reaction was allowed to cool to room temperature before the excess oxalyl chloride was removed *in vacuo* to give 2-benzenesulfonyl chloride as an orange solid after washing with DCM (2 x 5 mL).



236b **237b** **242b**

Scheme 7-14

Method B: The aldehyde (300 mg, 1.07 mmol, 1 eq) was dissolved in dry methanol (5 mL); K_2CO_3 (296 mg, 2.14 mmol, 2.0 eq) and the Bestmann-Ohira reagent (247 mg, 1.29 mmol, 1.2 eq) were added and the whole was stirred for 22 hours under nitrogen. The reaction was quenched with saturated aqueous NH_4Cl (10 mL), the organic phase was separated and the aqueous phase was extracted with DCM (3 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield an orange solid. Purification by silica chromatography (20 g) (EtOAc:Hex;3:1) yielded the product as a pale yellow solid (295 mg, 100%).

δ_H (400 MHz, $CDCl_3$): 1.63-1.73 (1H, m, C*H*H), 1.88-2.09 (2H, m, CH_2), 2.27 (1H, dddd, *J* 2.8, 6.6, 6.2, 12.4, CH*H*), 3.12 (1H, ddd, *J* 6.6, 9.9, 9.9, CH*H*N), 3.68 (1H, ddd, *J* 2.4, 7.5, 9.9, C*H*HN), 5.19

(1H, dd, *J* 6.2, 10.2, NCHCN), 7.62 (1H, dt, *J* 1.0, 7.7, Ar*H*), 7.79 (1H, s, NCC*H*N), 7.83 (1H, dt, *J* 1.5, 7.8, Ar*H*), 8.10 (1H, dd, *J* 1.5, 7.8, Ar*H*), 8.15 (1H, dd, *J* 1.0, 8.0, Ar*H*).

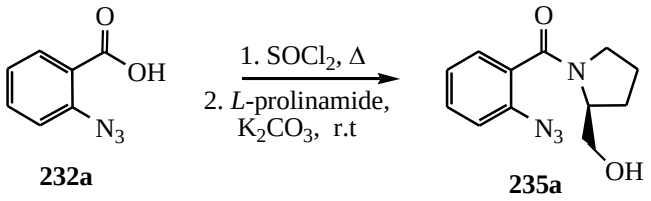
δ_C (100 MHz, $CDCl_3$): 24.4 (CH_2), 35.4 (CH_2), 50.0 (CH_2), 55.1 (CH), 125.4 (CH), 128.7 (CH), 129.3 (CH), 130.9 (q), 133.5 (q), 134.1 (CH), 134.4 (CH), 136.8 (q).

υ_{max} (thin film cm^{-1}): 1119 (m), 1170 (s), 1265 (m), 1356 (m), 1457 (w), 1485 (w), 1541 (w), 1558 (w), 1654 (s), 2924 (w).

LRMS (ESI+): Found 299.1 $[M+Na]^+$, 575.2 $[2M+Na]^+$.

HRMS (ESI+): Found 277.0752 $[M+H]^+$, $C_{12}H_{13}N_4O_2S$ r equires 277.0754.

7.2.5 Synthesis of (2*S*)-*N*-(2'-azidobenzoyl)-2-(hydroxymethyl) pyrrolidine.



232a **235a**

Scheme 7-15

A solution of 2-azidobenzoic acid (770 mg, 4.72 mmol, 1 eq) in thionyl chloride (5 mL) was heated to reflux under a nitrogen atmosphere at 85°C for 3 hours. The reaction mixture was cooled to room temperature before the excess thionyl chloride was removed *in vacuo*, and washed with DCM (2 x 10 mL) to yield the crude 2-azidobenzoyl chloride as a dark brown solid.

A solution of potassium carbonate (2.07 g, 15 mmol, 3.2 eq) dissolved in water (5 mL) was added in one portion to a stirring solution of *S*-prolinol (780 mg, 7.71 mmol, 1.63 eq) in DCM (15 mL). After stirring for 15 minutes the 2-azidobenzoyl chloride in DCM (10 mL) was added to the reaction

mixture dropwise and the whole was stirred at room temperature for 20 hours. The organic phase was separated and the aqueous phase extracted with DCM (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated to yield the crude product as a black oil. Purification by silica chromatography (EtOAc:Hex; 2:1) yielded the product as a yellow solid (720 mg, 62%) mp = 99-103°C. [lit 98-100°C].[69]

δ_H (400 MHz, $CDCl_3$): 1.60-1.84 (3H, m, C*H*H+CH_2), 2.04-2.14 (1H, m, CH*H*), 3.15-3.26 (2H, m, NCH_2), 3.66 (1H, dd, *J* 7.1, 11.5, NC*H*CH_2), 3.75-3.78 (1H, m, C*H*HOH), 4.28-4.31 (1H, m, CH*H*OH), 4.67 (1H, brs, O*H*), 7.10-7.15 (2H, m, Ar*H*), 7.24 (1H, dd, *J* 1.5, 8.0, Ar*H*), 7.37 (1H, dt, *J* 1.5, 8.0, Ar*H*).

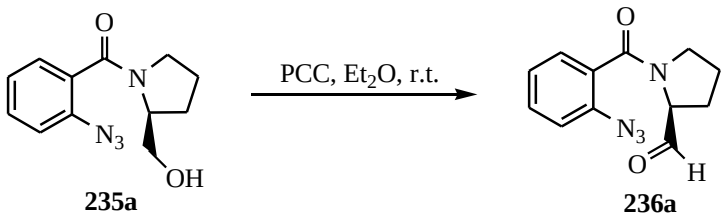
δ_C (100 MHz, $CDCl_3$): 24.5 (CH_2), 28.6 (CH_2), 49.6 (CH_2), 61.3 (CH), 66.5 (CH_2), 118.5 (CH), 125.3 (CH), 127.8 (CH), 129.3 (q), 130.7 (CH), 136.0 (q), 169.0 (q).

υ_{max} (thin film cm^{-1}): 1217 (m), 1265 (s), 1294 (m), 1428 (s), 1454 (s), 1614 (s), 2130 (s), 2882 (w), 2983 (w), 3019 (w), 3053 (w), 3100-3500 (br).

LRMS (ESI+): Found 269.1 $[M+Na]^+$, 512.2 $[2M+Na]^+$.

HRMS (ESI+): Found 269.1008 $[M+Na]^+$, $C_{12}H_{14}N_4NaO_2$ requires 269.1009.

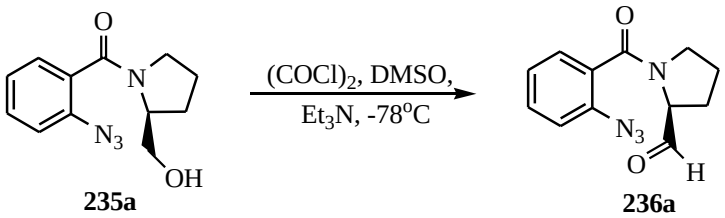
7.2.6 Synthesis of (2*S*)-*N*-(2'-azidobenzoyl)-2-methylpyrrolidinal.



235a **236a**

Scheme 7-16

Method A: The alcohol (540 mg, 2.20 mmol, 1 eq) was dissolved in dry DCM (10 mL) and pyridinium chlorochromate (946 mg, 4.40 mmol, 2 eq) was added and the mixture stirred at room temperature under nitrogen for 18 hours. The reaction was quenched with Et_2O (1 x 20 mL) and the organic supernatant was decanted off. The resultant black tar was washed with EtOAc (5 x 20 mL) in an ultrasound bath. The combined organic layers were collected, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield a brown/black oil (482 mg). Purification by silica chromatography (40 g) (EtOAc:Hex; 3:1) yielded the aldehyde as a yellow oil (80 mg, 15%).



235a **236a**

Scheme 7-17

Method B: A solution of 2M oxalyl chloride in DCM (1.8 mL, 3.66 mmol, 1.2 eq) was cooled to -78°C and diluted with dry DCM (4 mL). To this, DMSO (0.63 mL, 693 mg, 8.87 mmol, 2.9 eq) in dry DCM (5 mL) and the alcohol (750 mg, 3.05 mmol, 1 eq) in dry DCM (5 mL) were added dropwise over 15 minutes. After 10 minutes stirring at -78°C, Et_3N (1.12 mL, 813 mg, 8.04 mmol, 2.64 eq) was added dropwise and the reaction was allowed to reach room temperature over an hour. The reaction was quenched with a mixture of Et_2O (10 mL) and H_2O (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the crude product as brown oil. Purification by silica chromatography (50 g) (EtOAc:Hex; 3:1) yielded the product as a mixture of rotamers in the form of a yellow oil (544 mg, 73%).

δ_H (400 MHz, $CDCl_3$) rotamers: 1.80-1.93 (2H, m, CH_2), 1.95-2.05 (1H, m, C*H*H), 2.09-2.20 (1H, m, CH*H*), 3.25-3.38 & 3.64-3.81 (2H, m, CH_2), 4.10-4.12 & 4.52-4.56 (1H, m & ddd, *J* 8.0, 1.9, 5.7, C*H*CHO), 7.05-7.17 (2H, m, ArH), 7.20 & 7.29 (1H, dd, *J* 7.5, 1.3 & 7.4, 1.2, ArH), 7.34 & 7.39 (1H, dt, *J* 7.8, 1.5 & 7.8, 1.5), 9.22 & 9.62 (1H, d, *J* 1.9, CHO).

δ_C (100 MHz, $CDCl_3$) rotamers: 22.8/24.8 (CH_2), 26.4/27.8 (CH_2), 46.6/48.6 (CH_2), 64.7/66.4 (CH), 118.6 (CH), 125.1/125.2 (CH), 127.5/128.0 (CH), 128.48/128.51 (q), 130.9/131.0 (CH), 136.0/136.2 (q), 167.3/167.6 (q), 198.0/199.3 (CH).

υ_{max} (thin film cm^{-1}): 896 (m), 1265 (s), 1422 (m), 1453 (m), 1633 (s), 1732 (m), 2131 (s), 2986 (m), 3054 (m).

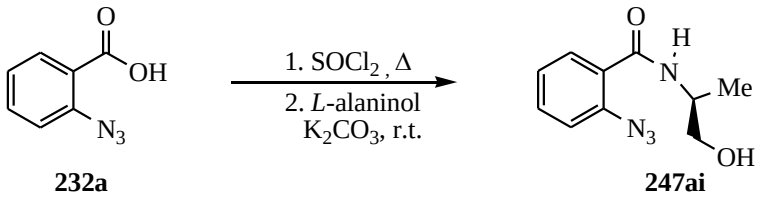
LRMS (ESI+): Found 245.1 $[M+H]^+$.

HRMS (ESI+): Found 245.1032 $[M+H]^+$, $C_{12}H_{13}N_4O_2$ requires 245.1033.

8 Experimental:The Synthesis of Triazolo and Tetrazolo Benzodiazepines and Benzothiadiazepines.

8.1 The Synthesis of the Triazolo-Benzodiazepine and Benzothiadiazepines.

8.1.1 Synthesis of (*S*)-*N*-(2'-azidobenzoyl)alaninol.



232a **247ai**

Scheme 8-1

2-Azidobenzoic acid (596 mg, 3.65 mmol, 1 eq) was heated at reflux under nitrogen in $SOCl_2$ (5 mL). The excess thionyl chloride was removed under reduced pressure to yield the acid chloride as a crude oil which was washed with fresh DCM (2 x 10 mL) and concentrated under reduced pressure.

To a stirring solution of *S*-alaninol (0.50 mL, 482 mg, 6.40 mmol, 1.8 eq) in DCM (15 mL) was added K_2CO_3 (2.01 g, 14.6 mmol, 4 eq) in water (5 mL) in one portion. After 5 mins of stirring at room temperature, the acid chloride in fresh DCM (10ml) was added dropwise. The whole was stirred for 18 hours before the organic layer was separated. The aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to yield the crude product as a peachy brown solid (917 mg). Purification by silica chromatography (80 g) (EtOAc:Hex;3:1) yielded the product as a peachy solid (306 mg, 38%).

δ_H (400 MHz, $CDCl_3$): 1.22 (3H, d, *J* 6.8, C*H*$_3$), 3.18 (1H, bs, O*H*), 3.55-3.60 (1H, m, C*H*HOH), 3.48-3.72 (1H, m, CH*H*OH), 4.16-4.26 (1H, dsextet, *J* 6.8, 3.7, C*H*CH_3), 7.11 (1H, d, *J* 8.0, Ar*H*), 7.16 (1H, t, *J* 7.6, Ar*H*), 7.42 (1H, dt, *J* 7.6, 1.6 Ar*H*), 7.55 (1H, bd, *J* 5.4, N*H*), 8.03 (1H, dd, *J* 8.0, 1.6, Ar*H*).

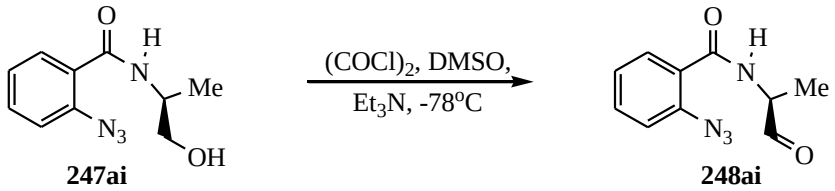
δ_C (100 MHz, $CDCl_3$): 17.1 (CH_3), 48.5 (CH), 67.2 (CH_2), 118.4 (CH), 124.8 (q), 125.2 (CH), 132.2 (CH), 132.5 (CH), 137.1 (q), 165.3 (q).

υ_{max} (thin film cm^{-1}): 1046 (m), 1163 (m), 1311 (s), 1480 (m), 1541 (s), 1597 (m), 1635 (s), 2133 (s), 2976 (m), 3317 (s).

LRMS (ESI+): Found 243.1 $[M+Na]^+$, 463.2 $[2M+Na]^+$.

HRMS (ESI+): Found 243.0854 $[M+Na]^+$, $C_{10}H_{12}N_4NaO_2$ requires 243.0852.

8.1.2 Synthesis of (*S*)-*N*-(2'-azidobenzoyl)alaninol.

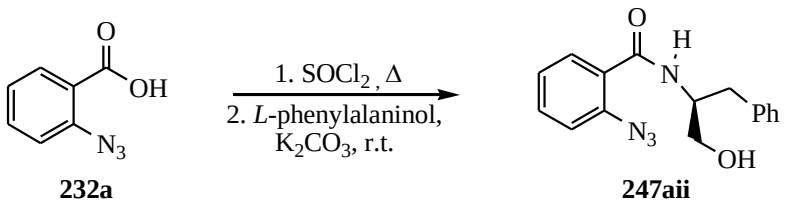


247ai **248ai**

Scheme 8-2

A 2M solution of oxalyl chloride in DCM (0.84 mL, 1.67 mmol, 1.2 eq) was diluted with dry DCM (1 mL) and cooled to -78°C. DMSO (0.24 mL, 264 mg, 3.39 mmol, 2.4 eq) in dry DCM (1 mL) and the alcohol (306 mg, 1.39 mmol, 1 eq) in dry DCM (5 mL) were added dropwise over 15 mins to the cooled solution. Et_3N (0.969 mL, 703 mg, 6.95 mmol, 2 eq) was added dropwise after 10 mins of stirring at -78°C and the reaction was allowed to reach ambient temperature over an hour. The reaction was quenched with a mixture of Et_2O (10 mL) and H_2O (10 mL). The organic phase was separated and the aqueous phase was extracted with DCM (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated *in vacuo* to give a purple solid (396 mg). Purification by silica chromatography and repeated attempts gave no identifiable product.

8.1.3 Synthesis of (*S*)-*N*-(2'-azidobenzoyl)phenylalaninol.



232a **247aii**

Scheme 8-3

2-Azidobenzoic acid (317 mg, 1.95 mmol, 1 eq) was heated at reflux under nitrogen at 80°C in $SOCl_2$ (5 mL). The excess thionyl chloride was removed under reduced pressure to yield the acid chloride as a crude oil which was washed with fresh DCM (2 x 10 mL) and concentrated under reduced pressure.

To a stirring solution of *L*-phenylalaninol (500 mg, 3.31 mmol, 1.7 eq) in DCM (10 mL) was added K_2CO_3 (1.83 g, 13.2 mmol, 6.8 eq) in water (5 mL) in one portion and after 5 mins of stirring the acid chloride in fresh DCM (10ml) was added. The whole was stirred for 6 hours before the organic layer was separated. The aqueous layer was extracted with DCM (3 x 10 mL) and the combined organic layers were dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to yield the crude product as a brown solid. Purification by silica chromatography (50 g) (EtOAc:Hex; 3:1) yielded the product as a pale yellow solid (538 mg, 93%).

δ_H (400 MHz, $CDCl_3$): 2.88 (1H, dd, *J* 7.4, 13.8, C*H*HPh), 2.95 (1H, dd, *J* 6.9, 13.8, C*H*HPh), 3.44 (1H, bs, OH), 3.60 (1H, dd, *J* 11.0, 5.2, C*H*HOH), 3.68-3.71 (1H, m, CH*H*OH), 4.23-4.37 (1H, m, NHC*H*), 7.04 (1H, d, *J* 8.0, ArH), 7.08-7.27 (6H, m, ArH), 7.38 (1H, t, *J* 8.0, ArH), 7.65 (1H, bs, N*H*), 7.99 (1H, d, *J* 8.0, ArH).

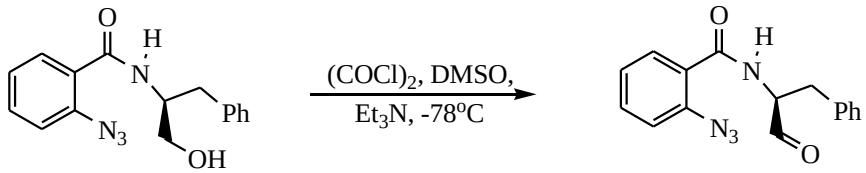
δ_C (100 MHz, $CDCl_3$): 37.0 (CH_2), 54.1 (CH), 64.5 (CH_2), 118.4 (CH), 124.6 (q), 125.2 (CH), 126.8 (CH), 128.6 (CH), 129.5 (CH), 132.2 (CH), 132.5 (CH), 137.1 (q), 137.5 (q), 165.3 (q).

υ_{max} (thin film cm^{-1}): 1039 (m), 1287 (s), 1445 (m), 1480 (m), 1496 (m), 1532 (s), 1597 (m), 1636 (s), 2130 (s), 2930 (w), 3027 (w), 3063 (w), 3250-3550 (br).

LRMS (ESI+): Found 319.1 $[M+Na]^+$, 615.2 $[2M+Na]^+$.

HRMS (ESI+): Found 319.1150 $[M+Na]^+$, $C_{16}H_{16}N_4NaO_2$ requires 319.1165.

8.1.4 Synthesis of (*S*)-*N*-(2'-azidobenzoyl)phenylalaninal.



247aii **248aii**

Scheme 8-4

A 2M solution of oxalyl chloride in DCM (1.00 mL, 2.06 mmol, 1.2 eq) was diluted with dry DCM (2 mL) and cooled to -78°C. DMSO (0.29 mL, 322 mg, 4.12 mmol, 2.4 eq) in dry DCM (2 mL) and (*S*)-*N*-(2'-azidobenzoyl)phenylalaninol (508 mg, 1.72 mmol, 1 eq) in dry DCM (5 mL) were added dropwise, over 15 minutes. The reaction was maintained at -78°C for 10 mins before Et_3N (1.20 mL, 871 mg, 8.61 mmol, 5 eq) was added dropwise. The reaction was allowed to reach room temperature over an hour before being quenched with a mixture of Et_2O (10 mL) and H_2O (10 mL). The organic phase was separated and the aqueous phase was extracted with DCM (4 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by silica chromatography (52 g) (EtOAc:Hex;1:1) to yield the product as a yellow oil (365 mg, 72%).

δ_H (400 MHz, $CDCl_3$): 3.14 (1H, dd, *J* 14.1, 6.5, C*H*HPh), 3.19 (1H, dd, *J* 14.1, 6.6, CH*H*Ph), 4.76 (1H, dt, *J* 6.6, 6.5, C*H*CH_2Ph), 7.07 (1H, d, *J* 8.0, ArH), 7.13-7.27 (6H, m, ArH), 7.42 (1H, dt, *J* 7.9, 1.6, ArH), 7.98 (1H, bs, NH), 8.06 (1H, dd, *J* 7.9, 1.6 ArH), 9.61 (1H, s, CHO).

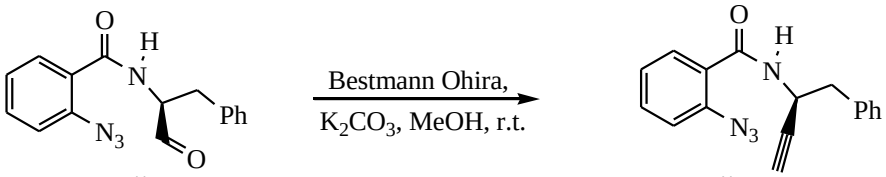
δ_C (100 MHz, $CDCl_3$): 34.2 (CH_2), 60.1 (CH), 117.9 (CH), 123.0 (q), 124.5 (CH), 126.6 (CH), 128.1 (CH), 128.8 (CH), 131.7 (CH), 132.2 (CH), 135.1 (q), 136.7 (q), 164.0 (q), 198.6 (CH).

υ_{max} (thin film cm^{-1}): 1266 (s), 1447 (m), 1480 (m), 1524 (m), 1598 (s), 1645 (s), 2131 (s), 2848 (w), 2917 (w).

LRMS (ESI+): Found 295.1 $[M+H]^+$, 611.2 $[2M+Na]^+$.

HRMS (ESI+): Found 295.1190 $[M+H]^+$, $C_{16}H_{15}N_4O_2$ requires 295.1190.

8.1.5 Synthesis of (*S*)-*N*-(2'-azidobenzoyl)-3-amino-4-phenylbut-1-yne.



248aii **249aii**

Scheme 8-5

The aldehyde (266 mg, 0.905 mmol) was dissolved in dry methanol (10 mL); K_2CO_3 (250 mg, 1.81 mmol, 2 eq) and the Bestmann-Ohira reagent (208 mg, 1.09 mmol, 1.2 eq) were added. The whole was stirred and monitored by TLC (EtOAc:Hex; 3:1) for 6 hours. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) solution and the organic layer was separated. The aqueous layer was extracted with DCM (3 x 10 mL) and the combined organics were dried ($MgSO_4$), filtered, concentrated *in vacuo* to yield a brown oil. Purification by silica chromatography (50 g) (EtOAc:Hex; 3:1) yielded the alkyne (212 mg, 81%) as a unstable yellow oil.

δ_H (400 MHz, $CDCl_3$): 2.26 (1H, d, *J* 2.4, *H*CCCH), 2.99 (1H, dd, *J* 13.4, 7.2, PhC*H*H), 3.07 (1H, dd, *J* 13.4, 5.0, PhCH*H*), 5.13-5.20 (1H, m, HNC*H*CH_2Ph), 7.07 (1H, dd, *J* 8.0, 0.7, ArH), 7.15 (1H,

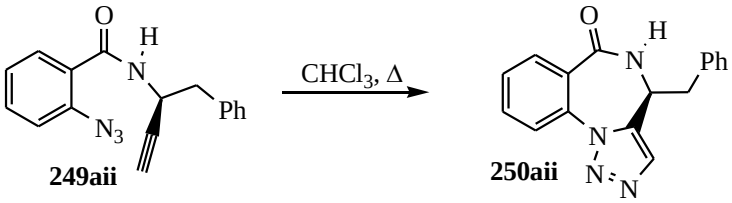
dt, *J* 7.6, 1.0, ArH), 7.17-7.31 (5H, m, Ph), 7.40 (1H, dt, *J* 8.0, 1.6, ArH), 7.68 (1H, bd, *J* 7.8, N*H*), 8.08 (1H, dd, *J* 7.8, 1.6 ArH).

δ_C (100 MHz, $CDCl_3$): 40.8 (CH_2), 42.9 (CH), 72.3 (q), 82.5 (CH), 118.4 (CH), 124.0 (q), 125.1 (CH), 127.1 (CH), 128.1 (CH), 130.0 (CH), 132.4 (CH), 132.6 (CH), 136.1 (q), 137.0 (q), 163.4 (q).

υ_{max} (thin film cm^{-1}): 1088 (w), 1165 (m), 1216 (m), 1295 (s), 1445 (m), 1480 (s), 1518 (s), 1597 (m), 1651 (s), 2131 (s), 2926 (w), 3010 (m), 3303 (s).

MS product decomposed before analysis.

8.1.6 Synthesis of (*S*)-3-benzyl-1,2,3-triazolo[1,5-*a*][1,4]benzodiazepine-5-one.



249aii **250aii**

Scheme 8-6

The alkyne (212 mg, 0.731 mmol) was heated to reflux under an atmosphere of nitrogen in $CHCl_3$ and monitored by TLC (EtOAc:Hex;1:1). After 72 hours the solvent was removed *in vacuo* and the crude was purified by silica chromatography (23 g) (EtOAc:Hex;1:1) to yield the product as a pale grey solid (208 mg, 98%).

δ_H (400 MHz, $CDCl_3$): 3.25-3.33 (2H, m, CH_2Ph), 4.70-4.75 (1H, dt, *J* 6.2, 8.6, C*H*CH_2Ph), 7.19-7.30 (5H, m, CH_2*Ph*), 7.58 (1H, dt, *J* 7.7, 1.1, ArH), 7.62 (1H, s, N_3CH), 7.73 (1H, dt, *J* 7.7, 1.5, ArH), 8.02 (1H, d, *J* 8.1, ArH), 8.07 (2H, m, Ar*H* + N*H*).

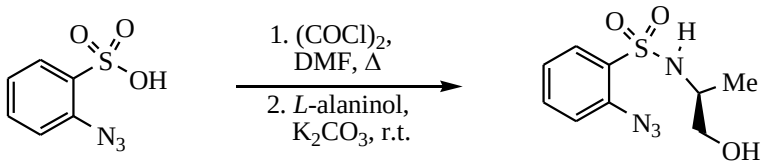
δ_C (100 MHz, $CDCl_3$): 46.7 (CH), 60.3 (CH_2), 122.9 (CH), 126.4 (q), 127.4 (CH), 128.9 (CH), 129.1 (CH), 129.8 (CH), 131.8 (CH), 133.2 (CH), 135.5 (q), 139.1 (q) 167.6 (q).

υ_{max} (thin film cm^{-1}): 1215 (s), 1391 (m), 1473 (m), 1487 (m), 1605 (m), 1660 (s), 2925 (w), 3019 (m), 3188 (m).

LRMS (ESI+): Found 313.1 $[M+Na]^+$, 603.2 $[2M+Na]^+$, 893.3 $[3M+Na]^+$.

HRMS (ESI+): Found 313.1059 $[M+Na]^+$ $C_{17}H_{14}N_4NaO$ requires 313.1060.

8.1.7 Synthesis of (*S*)-*N*-(2'-azidobenzenesulfonyl)-alaninol.



232b **247bi**

Scheme 8-7

2-Azidobenzenesulfonyl acid (2.55 g, 12.8 mmol, 3.3 eq) was suspended in 2M solution of $(COCl)_2$ in DCM (12 mL, 24 mmol, 6.2 eq). DMF (50µl) was added and the whole was heated at reflux under nitrogen at 80°C for 5 hours. The crude product was concentrated under reduced pressure to yield the acid chloride as a crude oil which was re-dissolved in fresh DCM (2 x 10 mL), concentrated under reduced pressure and finally dissolved in fresh DCM (10 mL) and added to the following reaction mixture dropwise.

To a stirring solution of (*S*)-alaninol (0.30 mL, 289 mg, 3.85 mmol, 1.0 eq) in DCM (10 mL) was added K_2CO_3 (2.08 g, 15.1 mmol, 3.9 eq) in water (5 mL) in one portion and the whole stirred for 5 mins before the acid chloride solution from above was added. The whole was stirred for 18 hours before the organic layer was separated and the aqueous layer was extracted with DCM (3 x 10 mL).

The combined organic layers were dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to yield the crude product as a yellow solid. Purification by silica chromatography (50 g) (EtOAc:Hex;1:1) yielded the product as a pale yellow solid (802 mg, 81%).

δ_H (400 MHz, $CDCl_3$): 0.96 (3H, d, *J* 6.6, CH_3), 2.50 (1H, bs, OH), 3.26 (1H, m, NC*H*CH_3), 3.37 (1H, dd, *J* 6.0, 11.1, C*H*HOH), 3.46 (1H, dd, *J* 4.1, 11.1, CH*H*OH), 5.41-5.43 (1H, bd, *J* 6.0, SO_2N*H*), 7.18 (1H, t, *J* 7.7, ArH), 7.23 (1H, d, *J* 7.7, ArH), 7.52 (1H, t, *J* 7.8, ArH), 7.89 (1H, d, *J* 7.8, ArH).

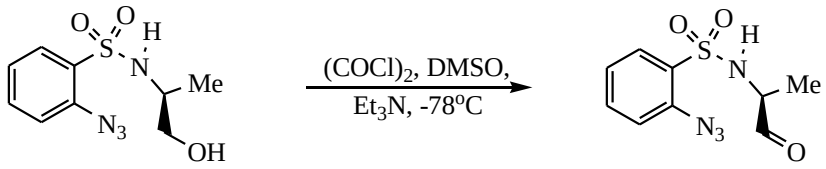
δ_C (100 MHz, $CDCl_3$): 17.4 (CH_3), 51.9 (CH), 66.0 (CH_2), 119.6 (CH), 124.8 (CH), 130.4 (CH), 130.45 (q), 134.1 (CH), 137.8 (q).

υ_{max} (thin film cm^{-1}): 1146 (m), 1165 (s), 1215 (s), 1289 (m), 1333 (m), 1473 (s), 1578 (m), 1637 (s), 2134 (s), 3250-3450 (br).

LRMS (ESI+): Found 279.1 $[M+Na]^+$, 535.1 $[2M+Na]^+$.

HRMS (ESI+): Found 279.0521 $[M+Na]^+$, $C_9H_{12}N_4NaO_3S$ requires 279.0522.

8.1.8 Attempted synthesis of (*S*)-*N*-(2-azidobenzenesulfonyl)-alaninal.

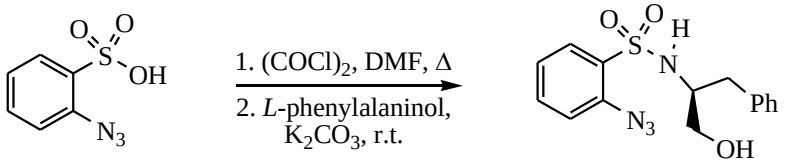


247bi **248bi**

Scheme 8-8

A 2M solution of oxalyl chloride in DCM (1.23 mL, 2.45 mmol, 1.2 eq) was diluted with dry DCM (2 mL) and cooled to -78°C. DMSO (0.348 mL, 383 mg, 4.90 mmol, 2.4 eq) in dry DCM (3 mL) and the alcohol (523 mg, 2.04 mmol, 1 eq) in dry DCM (5 mL) were added respectively dropwise over 15 mins to the cooled solution. Et_3N (1.42 mL, 1.03 g, 10.2 mmol, 5 eq) was added dropwise after 10 mins of stirring at -78°C and the whole was allowed to reach room temperature, over a period of 2 hours. The reaction was quenched with a mixture of Et_2O (10 mL) and H_2O (10 mL) and the organic phase was separated. The aqueous phase was extracted with DCM (3 x 10 mL), the combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification by silica chromatography gave no identifiable products and all subsequent efforts at oxidation failed.

8.1.9 Synthesis of (*S*)-*N*-(2'-azidobenzenesulfonyl)phenylalaninol.



232b **247bii**

Scheme 8-9

2-Azidobenzenesulfonic acid (1.48 g, 7.45 mmol, 2.5 eq) was suspended in 2M solution of $(COCl)_2$ in DCM (7.5 mL, 14.9 mmol, 5.0 eq). DMF (50µl) was added and the whole heated at reflux under nitrogen at 80°C for 4 hours. The crude product was concentrated under reduced pressure to yield the acid chloride as a crude oil which was re-dissolved in fresh DCM (2 x 10 mL), concentrated under reduced pressure and finally dissolved in fresh DCM (10 mL) and added to the following reaction mixture dropwise.

To a stirring solution of (*S*)-phenylalaninol (450 mg, 2.98 mmol, 1 eq) in DCM (15 mL) was added K_2CO_3 (1.64 g, 11.9 mmol, 4 eq) in water (10 mL) in one portion. After 10mins of stirring the acid chloride solution from above was added. The whole was stirred for 18 hours before the organic layer was separated and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. Purification by silica chromatography (25 g) (EtOAc:Hex;1:1) yielded the product as a pale yellow solid (769 mg, 81%).

δ_H (400 MHz, $CDCl_3$): 2.28 (1H, bs, OH), 2.66 (1H, dd, *J* 8.6, 14.1, PhC*H*H), 2.82 (1H, dd, *J* 6.0, 14.1, PhCH*H*), 3.35-3.43 (1H, m, NHC*H*CH_2OH), 3.54 (1H, bd, *J* 10.8, C*H*HOH), 3.64 (1H, bd *J* 10.8, CH*H*OH), 5.21 (1H, d, *J* 6.0, N*H*), 6.91-6.94 (2H, m, CH_2Ph*H*), 6.98 (1H, d, *J* 8.0, ArH), 7.08-7.11 (3H, m, CH_2Ph*H*), 7.13 (1H, t, *J* 7.8, ArH), 7.45 (1H, dt, *J* 7.8, 1.5, ArH), 7.84 (1H, dd, *J* 8.0, 1.5, ArH).

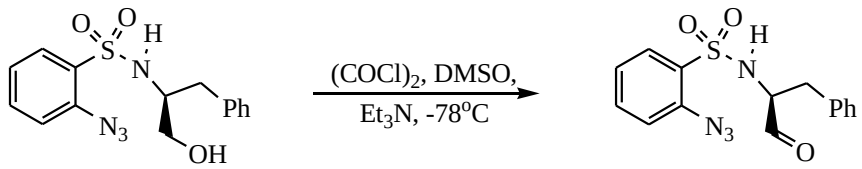
δ_C (100 MHz, $CDCl_3$): 37.7 (CH_2), 57.3 (CH), 64.6 (CH_2), 119.4 (CH), 124.4 (CH), 126.8 (CH), 128.5 (2 x CH), 128.9 (2 x CH), 129.5 (q), 130.1 (CH), 133.7 (CH), 136.6 (q), 137.6 (q).

υ_{max} (thin film cm^{-1}): 1024 (s), 1050 (m), 1147 (s), 1161 (s), 1224 (w), 1327 (s), 1427 (m), 1471 (s), 1583 (s), 2138 (s), 3225-3497 (br).

LRMS (ESI+): Found 355.1 $[M+Na]^+$, 687.2 $[2M+Na]^+$.

HRMS (ESI+): Found 355.0819 $[M+Na]^+$, $C_{15}H_{16}N_4NaO_3S$ requires 355.0835.

8.1.10 Synthesis of (*S*)-*N*-(2'-azidobenzenesulfonyl)phenylalaninal.

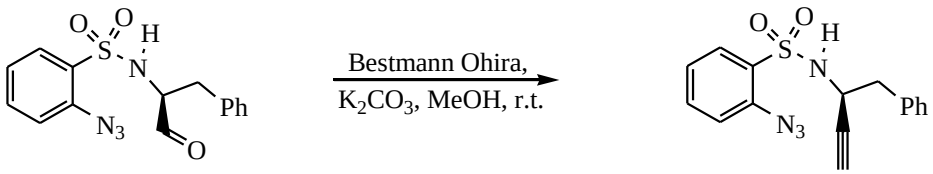


247bii **248bii**

Scheme 8-10

A 2M solution of oxalyl chloride in DCM (0.82 mL, 1.64 mmol, 1.2 eq) was diluted with dry DCM (3 mL) and cooled to -78°C. DMSO (0.23 mL, 256 mg, 3.28 mmol, 2.4 eq) in dry DCM (3 mL) and (*S*)-*N*-(2'-azidobenzenesulfonyl)phenylalaninol (440 mg, 1.32 mmol, 1 eq) in dry DCM (5 mL) were added dropwise, over 15 mins and the whole was stirred for 10 mins at -78°C. Et_3N (0.950 mL, 690 mg, 6.83 mmol, 5 eq) was added dropwise at -78°C and the reaction was allowed to reach room temperature over 2 hours. The reaction was quenched with a mixture of Et_2O (10 mL) and H_2O (10 mL) and the organic phase was separated. The aqueous phase was extracted with DCM (4 x 10 mL), the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil (820 mg) which was purified by silica chromatography (80 g) (EtOAc:Hex;1:2) to give the aldehyde (296 mg, 65%) which was used directly in the next step.

8.1.11 Synthesis of (*S*)-*N*-(2'-azidobenzenesulfonyl)-3-amino-4-phenylbut-1-yne.



248bii **249bii**

Scheme 8-11

The aldehyde (296 mg, 0.897 mmol, 1 eq) was dissolved in dry methanol (10 mL); K_2CO_3 (248 mg, 1.79 mmol, 2 eq) and the Bestmann-Ohira reagent (207 mg, 1.08 mmol, 1.2 eq) were added and the whole was stirred for 6 hours. The reaction was quenched with saturated aqueous NH_4Cl (10 mL),

the organic layer was separated and the aqueous layer was extracted with DCM (4 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by silica chromatography (30 g) (EtOAc:Hex;1:1) yielding the terminal alkyne (92 mg, 31%) together with the cyclised product (48 mg, 16%).

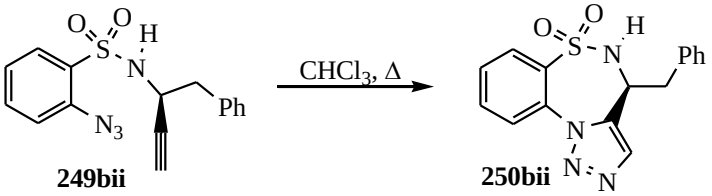
δ_H (400 MHz, $CDCl_3$): 2.08 (1H, s, *H*C≡C), 3.05 (1H, dd, *J* 7.0, 13.5, PhC*H*H), 3.10 (1H, dd, *J* 5.7, 13.5, PhCH*H*), 4.32-4.39 (1H, m, $PhCH_2CH$), 5.37 (1H, bs, NH), 7.23-7.38 (7H, m, ArH), 7.61 (1H, dt, *J* 7.9, 1.4, ArH), 8.00 (1H, dd, *J* 7.9, 1.4, ArH).

δ_C (100 MHz, $CDCl_3$): 42.0 (CH_2), 46.5 (CH), 73.5 (CH), 80.7 (q), 119.2 (CH), 127.4 (CH), 128.5 (2 x CH), 129.8 (2 x CH), 130.0 (q), 130.3 (CH), 134.1 (CH), 135.2 (q), 138.0 (q).

LRMS (ESI+): Found 349.1 $[M+Na]^+$, 675.2 $[2M+Na]^+$.

HRMS (ESI+): Found 349.0720 $[M+Na]^+$, $C_{16}H_{14}N_4NaO_2S$ requires 349.0730.

8.1.12 Synthesis of 3-benzyl-1,2,3 triazolo[1,5-*d*][1,2,5]benzodiazepin-5,5-dioxide.



249bii **250bii**

Scheme 8-12

The terminal alkyne (92 mg, 0.282 mmol) was heated at reflux under nitrogen in $CHCl_3$ (10 mL) and monitored by TLC (EtOAc:Hex;1:1). After 72 hours the solvent was removed under reduced pressure and purified by silica chromatography (10 g) (EtOAc:Hex;1:1) to yield the product as a pale grey solid (91 mg, 99%).

δ_H (400 MHz, $CDCl_3$): 3.03 (1H, dd, *J* 6.8, 13.8, PhC*H*H), 3.06 (1H, dd, *J* 6.9, 13.8, PhCH*H*), 4.76 (1H, dd, *J* 6.9, 6.8, C*H*CH_2Ph), 6.90-6.94 (2H, m, CH_2Ph*H*), 7.02-7.10 (3H, m, CH_2Ph*H*), 7.44 (1H, dt, *J* 7.7, 1.0, ArH), 7.50 (1H, s, N_3CHC), 7.60 (1H, dt, *J* 7.8, 1.4, ArH), 7.78 (1H, d, *J* 7.8, 1.0, ArH), 7.85 (1H, dd, *J* 7.7, 1.4, ArH), 8.00 (1H, bs, NH).

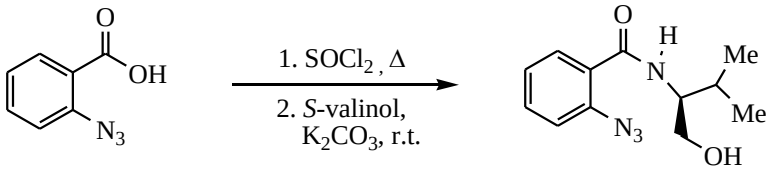
δ_C (100 MHz, $CDCl_3$): 45.8 (CH_2), 54.3 (CH), 129.8 (CH), 131.0 (CH), 132.0 (CH), 133.3 (2 x CH), 133.8 (CH), 134.2 (2 x CH), 137.9 (q), 138.5 (CH), 138.7 (CH), 139.1 (q), 140.0 (q), 140.7 (q).

υ_{max} (thin film cm^{-1}): 1171 (m), 1215 (s), 1380 (m), 1337 (m), 1486 (m), 2922 (w), 3019 (s), 3143 (w), 3260 (s).

LRMS (ESI+): Found 327.1 $[M+H]^+$.

HRMS (ESI+): Found 327.0910 $[M+H]^+$, $C_{16}H_{15}N_4O_2S$ requires 327.0910.

8.1.13 Synthesis of (*S*)-*N*-(2'-azidobenzoyl)valinol.



232a **247aiii**

Scheme 8-13

2-azidobenzoic acid (295 mg, 1.81 mmol, 1 eq) was heated at reflux under nitrogen in $SOCl_2$ (5 mL) at 85°C for 3 hours. The excess $SOCl_2$ was removed under reduced pressure to yield the acid chloride as a crude oil which was re-dissolved in fresh DCM (2 x 10 mL), concentrated under reduced pressure and finally dissolved in fresh DCM (5 mL) and added to the following reaction mixture dropwise.

(*S*)-Valinol (400 mg, 3.88 mmol, 2.15 eq) was dissolved in DCM (10 mL) and to this K_2CO_3 (1.00 g, 7.23 mmol, 4 eq) in water (5 mL) was added in one portion. The acid chloride in DCM (5 mL) was added dropwise and the whole was stirred overnight. The organic phase was separated and the aqueous phase extracted with DCM (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated under reduced pressure and purified by silica chromatography (30 g) (EtOAc:Hex; 3:2) to give the product as a black oil (394 mg, 88%).

δ_H (400 MHz, $CDCl_3$): 0.92 (3H, d, *J* 6.8, C*H*$_3$CHCH$_3$), 0.93 (3H, d, *J* 6.8, CH$_3$CHC*H*$_3$), 1.93 (1H, oct, *J* 6.8, C*H*(CH$_3$)$_2$), 3.53 (1H, bs, OH), 3.61-3.69 (2H, m, C*H*$_2$OH), 3.84-3.91 (1H, m, NHC*H*), 7.06 (1H, d, *J* 8.1, ArH), 7.11 (1H, t, *J* 7.9, ArH), 7.38 (1H, dt, *J* 8.1, 1.5, ArH), 7.55 (1H, bd, *J* 8.0, NH), 7.95 (1H, dd, *J* 7.9, 1.4, ArH).

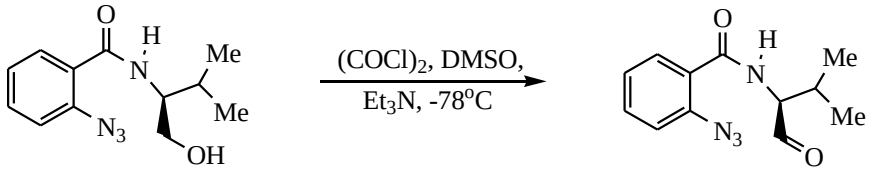
δ_C (100 MHz, $CDCl_3$): 18.7 (CH_3), 19.7 (CH_3), 29.0 (CH), 57.9 (CH), 63.8 (CH_2), 118.4 (CH), 125.0 (q), 125.1 (CH), 132.1 (CH), 132.4 (CH), 137.0 (q), 165.6 (q).

υ_{max} (thin film cm^{-1}): 755 (s), 908 (s), 1216 (m), 1277 (m), 1480 (s), 1536 (s), 1598 (m), 1641 (s), 2130 (s), 2875 (m), 2964 (s), 3010 (m), 3200-3500 (br).

LRMS (ESI+): Found 271.1 $[M+Na]^+$, 519.2 $[2M+Na]^+$.

HRMS (ESI+): Found 271.1154 $[M+Na]^+$, $C_{12}H_{16}N_4NaO_2$ requires 271.1165.

8.1.14 Synthesis of (*S*)-*N*-(2'-azidobenzoyl)valinol.



247aiii **248aiii**

Scheme 8-14

2M oxalyl chloride in DCM (0.86 mL, 1.73 mmol, 1.2 eq) was diluted with DCM (3 mL) and cooled to -78°C. DMSO (0.245 mL, 270 mg, 3.45 mmol, 2.4 eq) in dry DCM (3 mL) and the alcohol (357 mg, 1.44 mmol, 1 eq) in dry DCM (5 mL) were added dropwise, over 15 mins and the whole was stirred for 10 mins. Et_3N (1.00 mL, 726 mg, 7.20 mmol, 5.0 eq) was added dropwise and the whole was allowed to reach room temperature over an hour before being quenched with a mixture of Et_2O (10 mL) and H_2O (10 mL). The organic layer was separated and the aqueous phase was extracted with DCM (4 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated under reduced pressure and purified by silica chromatography (50 g) (EtOAc:Hex; 1:1) to yield the product as a yellow oil (177 mg, 50%).

δ_H (400 MHz, $CDCl_3$): 0.99 (3H, d, *J* 7.0, C*H*$_3$CHCH$_3$), 1.01 (3H, d, *J* 7.0, CH$_3$CHC*H*$_3$), 2.37 (1H, dsept, *J* 7.0, 4.5, (CH$_3$)$_2$C*H*), 4.67 (1H, dd, *J* 7.4, 4.5, NHC*H*), 7.15 (1H, d, *J* 7.9, ArH), 7.17 (1H, t, *J* 7.6, ArH), 7.44 (1H, dt, *J* 7.6, ArH), 7.97 (1H, bd, *J* 6.5, NH), 8.06 (1H, d, *J* 7.9, ArH), 9.64 (1H, s, CHO).

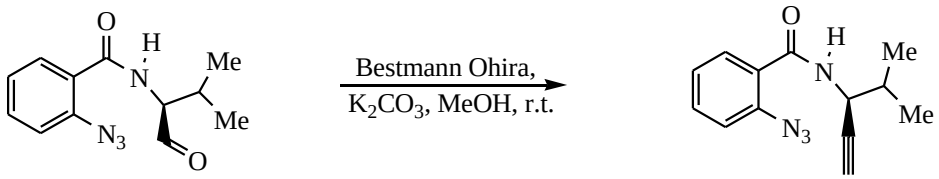
δ_C (100 MHz, $CDCl_3$): 17.3 (CH_3), 18.5 (CH_3), 28.4 (CH), 63.5 (CH), 117.7 (CH), 123.6 (q), 124.5 (CH), 131.6 (CH), 132.0 (CH), 136.3 (q), 164.1 (q), 199.3 (CH).

υ_{max} (thin film cm^{-1}): 909 (s), 1277 (m), 1481 (m), 1526 (s), 1598 (s), 1651 (s), 1732 (s), 2131 (s), 2967 (m), 3379 (m).

LRMS (ESI+): Found 515.2 $[2M+Na]^+$.

HRMS (ESI+): 515.2127 $[2M+Na]^+$, $C_{24}H_{28}N_8NaO_4$ requires 515.2126.

8.1.15 Synthesis of (*S*)-*N*-(2'-azidobenzoyl)-3-amino-4-methylpent-1-yne.



248aiii **249aiii**

Scheme 8-15

The aldehyde (118 mg, 0.480 mmol, 1 eq) was dissolved in dry MeOH (6 mL) to which K_2CO_3 (132 mg, 0.959 mmol, 2 eq) and the Bestmann-Ohira reagent (111 mg, 0.576 mmol, 1.2 eq) were added. After 4 hours the reaction was quenched with saturated aqueous NH_4Cl (10 mL), the organic layer was separated and the aqueous phase was extracted with DCM (4 x 10 mL). The combined organic phases were dried, filtered, concentrated under reduced pressure and purified by silica chromatography (20 g) (EtOAc:Hex;1:3) yielding the alkyne as a yellow solid (90 mg, 78%).

δ_H (400 MHz, $CDCl_3$): 0.99 (6H, d, *J* 6.8, $(CH_3)_2CH$), 1.99 (1H, dsept, *J* 6.8, 5.6, $CH(CH_3)_2$), 2.22 (1H, d, *J* 2.4, *HC*≡C), 4.79 (1H, ddd, *J* 2.4, 5.6, 8.1, NHC*H*), 7.10 (1H, dd, *J* 8.0, 0.9, ArH), 7.14 (1H, dt, *J* 7.9, 0.9, ArH), 7.41 (1H, dt, *J* 8.0, 1.6, ArH), 7.66 (1H, bd, *J* 8.1, NH), 8.05 (1H, dd, *J* 7.9, 1.6, ArH).

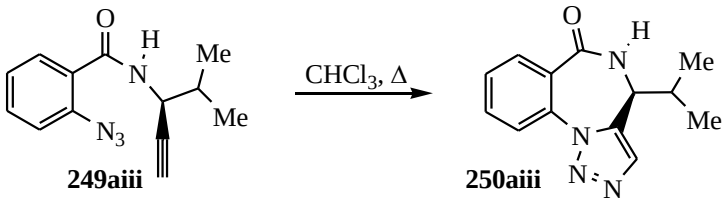
δ_C (100 MHz, $CDCl_3$): 17.7 (CH_3), 18.9 (CH_3), 32.6 (CH), 47.5 (CH), 72.0 (CH), 81.7 (q), 118.4 (CH), 124.5 (q), 125.2 (CH), 132.4 (CH), 132.6 (CH), 137.0 (q), 163.6 (q).

υ_{max} (thin film cm^{-1}): 1060 (m), 1087 (m), 1153 (m), 1369 (m), 1445 (m), 1481 (s), 1525 (s), 1598 (s), 1650 (s), 2129 (s), 2417 (w), 2873 (m), 2930 (m), 2963 (s), 3067 (w).

LRMS (ESI+): Found 265.1 $[M+Na]^+$, 507.2 $[2M+Na]^+$.

HRMS (ESI+): Found 265.1053 $[M+Na]^+$ requires $C_{13}H_{14}N_4NaO$ 265.1060.

8.1.16 Synthesis of 3-isoproyl-1,2,3-triazolo[1,5-*a*][1,4]benzodiazepine-5-one.



249aiii **250aiii**

Scheme 8-16

The alkyne (73 mg, 0.30 mmol) was heated at reflux at 75°C in $CHCl_3$ (10 mL) under a dry atmosphere of nitrogen for 72 hours. The reaction was cooled to room temperature and the solvent was removed *in vacuo*. Purification by silica chromatography (10 g) (EtOAc:Hex; 1:1) yielded the cyclised product as a pale yellow solid (72 mg, 99%).

δ_H (400 MHz, $CDCl_3$): 1.00 (3H, d, *J* 6.0, C*H*$_3$CHCH$_3$), 1.18 (3H, d, *J* 6.6, CH$_3$CHC*H*$_3$), 2.23 (1H, bm, CH$_3$C*H*CH$_3$), 4.13 (1H, dd, *J* 6.4, 8.9, NHC*H*), 7.59 (1H, dt, *J* 7.7, 1.1, ArH), 7.68 (1H, s, C*H*N$_3$), 7.74 (1H, dt, *J* 8.0, 1.5, ArH), 8.05 (1H, dd, *J* 8.0, 0.8, ArH), 8.11 (2H, dd + brs, *J* 7.7, 1.5, ArH + CHN*H*).

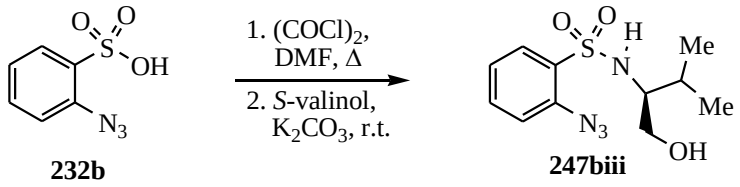
δ_C (100 MHz, $CDCl_3$): 19.2 (CH_3), 20.3 (CH_3), 29.3 (CH), 52.2 (CH), 123.0 (CH), 126.2 (q), 129.1 (CH), 130.6 (CH), 131.7 (CH), 133.3 (CH), 133.5 (q), 138.4 (q), 168.1 (q).

υ_{max} (thin film cm^{-1}): 754 (s), 842 (m), 990 (m), 1245 (m), 1350 (m), 1395 (s), 1469 (s), 1580 (m), 1605 (m), 1651 (s), 2860 (w), 2958 (w), 3047 (m), 3174 (m).

LRMS (ESI+): Found 265.1 $[M+Na]^+$, 507.2 $[2M+Na]^+$.

HRMS (ESI+): Found 265.1064 $[M+Na]^+$, $C_{13}H_{14}N_4NaO$ requires 265.1060.

8.1.17 Synthesis of (*S*)-*N*-(2'-azidobenzenesulfonyl)valinol.



232b **247biii**

Scheme 8-17

2-Azidobenzenesulfonic acid (1.24 g, 6.25 mmol, 2.5 eq) was suspended in 2M oxalyl chloride in DCM (6.25 mL, 12.5 mmol, 5.0 eq) and a drop of DMF was added. The whole was heated at reflux under nitrogen for 4 hours before the excess oxalyl chloride was removed under reduced pressure to yield the acid chloride as a crude oil which was re-dissolved in fresh DCM (2 x 10 mL), concentrated under reduced pressure and finally dissolved in fresh DCM (10 mL) and added to the following reaction mixture dropwise.

To a stirring solution of (*S*)-valinol (258 mg, 2.5 mmol, 1.0 eq) in DCM (15 mL), K_2CO_3 (1.38 g, 10 mmol, 4 eq) in water (10 mL) was added in one portion and the acid chloride in DCM (10 mL) was added dropwise. The whole was stirred overnight before the organic layer was separated and the aqueous phase was extracted with DCM (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated under reduced pressure and purified by silica chromatography (50 g) (EtOAc:Hex; 1:2) giving the alcohol as a yellow-orange solid (384 mg, 55%).

δ_H (400 MHz, $CDCl_3$): 0.76 (3H, d, *J* 6.9, CHC*H*$_3$CH$_3$), 0.79 (3H, d, *J* 6.9, CHCH$_3$C*H*$_3$), 1.76 (1H, oct, *J* 6.9, C*H*[CH$_3$]$_2$,) 2.20 (1H, bs, CH$_2$O*H*), 2.94-3.00 (1H, m, NHC*H*), 3.35-3.42 (1H, m, C*H*HOH), 3.48-3.52 (1H, m, CH*H*OH), 5.37 (1H, bd, *J* 8.2, SO$_2$N*H*), 7.16 (1H, dt, *J* 7.6, 0.9, ArH), 7.22 (1H, dd, *J* 8.0, 0.9, ArH), 7.51 (1H, dt, *J* 7.6, 1.4, ArH), 7.87 (1H, dd, *J* 8.0, 1.4, ArH).

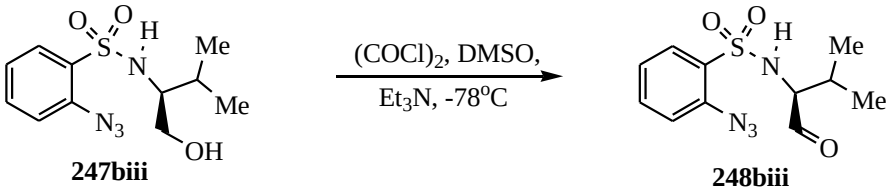
δ_C (100 MHz, $CDCl_3$): 18.6 (CH_3), 19.0 (CH_3), 29.5 (CH), 61.5 (CH), 62.5 (CH_2), 119.6 (CH), 124.7 (CH), 130.0 (CH), 130.9 (q), 133.9 (CH), 137.8 (q).

υ_{max} (thin film cm^{-1}): 909 (s), 1042 (m), 1067 (m), 1216 (m), 1324 (m), 1472 (s), 1575 (s), 2101 (s), 2926 (m), 2965 (m), 3021 (m), 3163 (w), 3400-3600 (br).

LRMS (ESI+): Found 307.1 $[M+Na]^+$, 591.2 $[2M+Na]^+$.

HRMS (ESI+): Found 307.0821 $[M+Na]^+$, $C_{11}H_{16}N_4NaO_3S$ requires 307.0835.

8.1.18 Synthesis of (*S*)-*N*-(2'-azidobenzenesulfonyl)valinal.



247biii **248biii**

Scheme 8-18

2M oxalyl chloride in DCM (0.81 mL, 1.62 mmol, 1.2 eq) was diluted with DCM (3 mL) and cooled to -78°C. DMSO (0.23 mL, 253 mg, 3.24 mmol, 2.4 eq) in dry DCM (3 mL) and the alcohol (384 mg, 1.35 mmol, 1 eq) in dry DCM (5 mL) were added dropwise, over 15 minutes and the whole was stirred for 10 mins. Et_3N (0.94 mL, 684 mg, 6.76 mmol, 5.0 eq) was added and the reaction was allowed to reach room temperature before being quenched with a mixture of Et_2O (10 mL) and H_2O

(10 mL). The organic layer was separated and the aqueous phase was extracted with DCM (4 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated under reduced pressure and purified by silica chromatography (50 g) (EtOAc:Hex; 1:1) to yield the product as an unstable white solid (284 mg, 75%).

δ_H (400 MHz, $CDCl_3$): 0.86 (3H, d, *J* 6.9, CH_3), 0.99 (3H, d, *J* 6.9, CH_3), 2.20 (1H, dsept, *J* 6.9, 4.0, C*H*[CH_3]$_2$), 3.75 (1H, dd, *J* 4.0, 7.3, C*H*CHO), 5.83 (1H, bd, *J* 7.3, NH), 7.14 (1H, dt, *J* 7.7, 1.0, ArH), 7.22 (1H, dd, *J* 8.0, 1.0, ArH), 7.51 (1H, t, *J* 7.7, 1.5, ArH), 7.81 (1H, d, *J* 8.0, 1.5, ArH), 9.38 (1H, s, C*H*O).

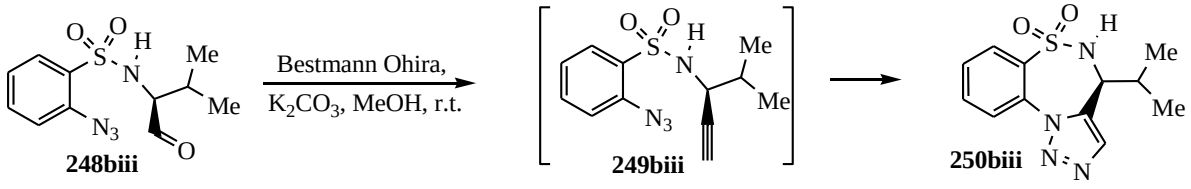
δ_C (100 MHz, $CDCl_3$): 17.3 (CH_3), 18.9 (CH_3), 29.5 (CH), 67.3 (CH), 119.6 (CH), 124.5 (CH), 129.7 (q), 130.1 (CH), 134.2 (CH), 138.2 (q), 198.4 (CH).

υ_{max} (thin film cm^{-1}): 759 (s), 1170 (s), 1290 (m), 1348 (m), 1472 (s), 1586 (m), 1730 (s), 2135 (s), 2968 (m), 3020 (s), 3310 (w).

LRMS (ESI+): Found 305.1 $[M+Na]^+$, 587.1 $[2M+Na]^+$, $C_{11}H_{14}N_4NaO_3$ requires 305.1.

HRMS: decomposed before analysis was possible.

8.1.19 Synthesis of 3-isoproyl-1,2,3-triazolo [1,5-d][1,2,5]benzothiadiazepin-5,5-dioxide.



248biii **249biii** **250biii**

Scheme 8-19

The aldehyde (244 mg, 0.865 mmol, 1.0 eq) was dissolved in MeOH (10 mL), K_2CO_3 (239 mg, 1.73 mmol, 2.0 eq) and the Bestmann-Ohira reagent (200 mg, 1.04 mmol, 1.2 eq) were added and the whole was stirred at room temp for 6 hours. The reaction was quenched with saturated aqueous NH_4Cl (10 mL). The organic phase was separated and the aqueous phase was extracted with DCM (4 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated and purified by silica chromatography (30 g) (EtOAc:Hex; 1:1) giving the cyclised product as a white solid (131 mg, 54%).

δ_H (400 MHz, $CDCl_3$): 0.90 (3H, d, *J* 6.7, CH_3), 1.04 (3H, d, *J* 6.7, CH_3), 2.18 (1H, dsept, *J* 5.3, 6.7, C*H*[CH_3]$_2$), 4.58 (1H, m, NHC*H*), 5.35 (1H, bs, NH), 7.62 (1H, dt, *J* 7.8, 1.4, ArH), 7.77 (1H, s, C*H*N_3), 7.80 (1H, dt, *J* 7.8, 1.4, ArH), 8.05 (1H, dd, *J* 8.0, 1.2, ArH), 8.10 (1H, dd, *J* 8.0, 1.2, ArH).

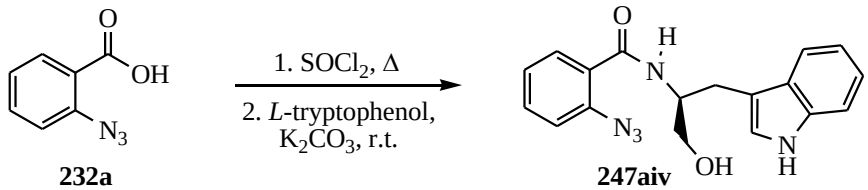
δ_C (100 MHz, $CDCl_3$): 17.7 (CH_3), 18.9 (CH_3), 32.8 (CH), 54.5 (CH), 125.4 (CH), 126.7 (CH), 129.2 (CH), 133.5 (q), 133.9 (q), 134.2 (CH), 134.4 (CH), 135.1 (q).

υ_{max} (thin film cm^{-1}): 734 (s), 760 (s), 908 (s), 1101 (w), 1172 (m), 1215 (s), 1337 (m), 1370 (m), 1483 (w), 1590 (w), 2876 (w), 3019 (m).

LRMS (ESI+): Found 301.1 $[M+Na]^+$, 579.2 $[2M+Na]^+$.

HRMS (ESI+): Found 301.0717 $[M+Na]^+$, $C_{12}H_{14}N_4NaO_2S$ requires 301.0730.

8.1.20 Synthesis of (*S*)-*N*-(2'-azidobenzoyl)tryptophanol.



232a **247aiv**

Scheme 8-20

Azidobenzoic acid (252 mg, 1.55 mmol, 1 eq) was heated at reflux under nitrogen at 85°C in $SOCl_2$ (5 mL) for 3 hours. The excess $SOCl_2$ was removed under reduced pressure to yield the acid chloride as a crude oil which was re-dissolved in fresh DCM (2 x 10 mL), concentrated under reduced pressure and finally dissolved in fresh DCM (5 mL).

K_2CO_3 (854 mg, 6.2 mmol, 4 eq) in water (5 mL) was added in one portion to a stirring solution of *L*-tryptophanol (500 mg, 2.63 mmol, 1.7 eq) in DCM (10 mL). The crude acid chloride in DCM (5 mL) was added dropwise and the whole was stirred overnight. The organic layer was separated and the aqueous phase was extracted with DCM (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated under reduced pressure and purified by silica chromatography (40 g) (EtOAc: Hex; 4:1) yielding the product as a fluffy yellow solid (497 mg, 90%).

δ_H (400 MHz, $CDCl_3$): 3.13 (1H, dd, *J* 6.9, 15.0, C*H*HCHNH), 3.17 (1H, dd, *J* 6.9, 15.0, CH*H*CHNH), 3.56 (1H, bs, OH), 3.75-3.85 (2H, m, CH_2OH), 4.49-4.57 (1H, m, NHC*H*CH_2OH), 7.08 (1H, d, *J* 7.8, ArH), 7.10 (1H, s, ArH), 7.14 (1H, t, *J* 7.0, ArH), 7.19 (1H, t, *J* 7.8, ArH), 7.20 (1H, t, *J* 7.0, ArH), 7.37 (1H, d, *J* 8.0, ArH), 7.45 (1H, dt, *J* 8.0, 1.5, ArH), 7.72 (1H, d, *J* 7.8, ArH), 7.83 (1H, bd, *J* 6.9, CON*H*CH), 8.11 (1H, dd, *J* 7.8, 1.5, ArH), 8.47 (1H, bs, ArNH).

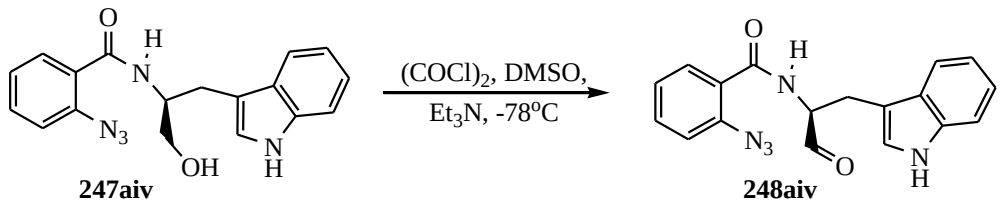
δ_C (100 MHz, $CDCl_3$): 26.5 (CH_2), 53.3 (CH), 64.9 (CH_2), 111.2 (CH), 111.3 (q), 118.3 (CH), 118.7 (CH), 119.5 (CH), 122.1 (CH), 123.0 (CH), 124.5 (q), 125.0 (CH), 127.6 (q), 132.0 (CH), 132.4 (CH), 136.2 (q), 137.0 (q), 165.5 (q).

υ_{max} (thin film cm^{-1}): 1215 (s), 1281 (m), 1457 (m), 1480 (m), 1529 (s), 1598 (m), 1636 (s), 2131 (s), 2928 (w), 3019 (m), 3200-3500 (br).

LRMS (ESI+): Found 358.1 $[M+Na]^+$, 693.3 $[2M+Na]^+$.

HRMS (ESI+): Found 358.1273 $[M+Na]^+$, $C_{18}H_{17}N_5NaO_2$ requires 358.1274.

8.1.21 Synthesis of (*S*)-*N*-(2'-azidobenzoyl)tryptophanal.



247aiv **248aiv**

Scheme 8-21

2M oxalyl chloride in DCM (0.86 mL, 1.73 mmol, 1.2 eq) was diluted with DCM (3 mL) and cooled to -78°C. DMSO (0.24 mL, 269 mg, 3.44 mmol, 2.4 eq) in dry DCM (3 mL) and the alcohol (481 mg, 1.44 mmol, 1 eq) in DCM (5 mL) were added respectively dropwise over 15 minutes. Et_3N (1.00 mL, 726 mg, 7.18 mmol, 5 eq) was added after 10 mins stirring at -78°C. The whole was allowed to reach room temperature over an hour, before being quenched with a mixture of Et_2O (10 mL) and H_2O (10 mL). The organic layer was separated and the aqueous phase was extracted with DCM (4 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by silica chromatography (50 g) (EtOAc:Hex;1:2) yielded the product as a yellow solid (33 mg, 7%) which was highly unstable and so was used quickly in the next step.

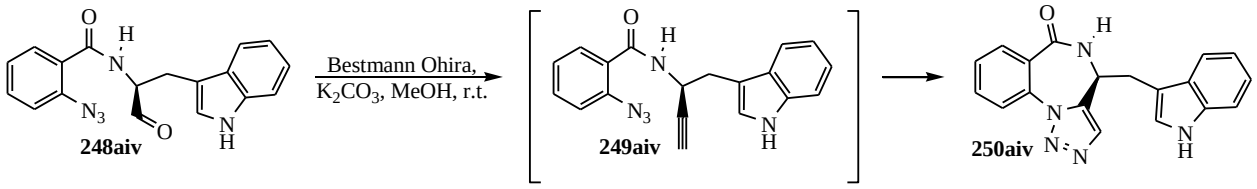
δ_H (400 MHz, $CDCl_3$): 3.36 (1H, dd, *J* 6.4, 14.9, C*H*HCHNHCO), 3.49 (1H, dd, *J* 6.4, 14.9, CH*H*CHNHCO), 4.95 (1H, q, *J* 6.4, CH_2C*H*NHCO), 7.10 (1H, s, ArH indole), 7.11 (1H, d, *J* 8.2, ArH), 7.14 (1H, t, *J* 8.1, ArH), 7.21 (1H, t, *J* 8.1, ArH), 7.23 (1H, t, *J* 7.8, ArH), 7.37 (1H, d, *J* 8.0 ArH), 7.49 (1H, dt, *J* 7.7, 1.6, ArH), 7.66 (1H, d, *J* 7.9, ArH), 8.17 (1H, dd, *J* 7.9, 1.6, ArH), 8.20 (1H, bs, NH), 8.42 (1H, bs, ArNH), 9.71 (1H, s, CHO).

δ_C (100 MHz, $CDCl_3$): 24.8 (CH_2), 60.2 (CH), 109.8 (q), 111.4 (CH), 118.4 (CH), 118.7 (CH), 119.9 (CH), 122.5 (CH), 123.2 (CH), 123.8 (q), 125.1 (CH), 127.3 (q), 132.3 (CH), 132.9 (CH), 136.2 (q), 137.5 (q), 164.8 (q), 200.3 (CH).

υ_{max} (thin film cm^{-1}): 1215 (s), 1278 (m), 1480 (m), 1525 (m), 1598 (m), 1643 (s), 2131 (s), 3019 (m).

MS: Product decomposed before analysis was possible.

8.1.22 Synthesis of 3-(3'-methyltryptophano)-1,2,3-triazolo[1,5-*d*][1,4]benzodiazepin-5-one.



Scheme 8-22

The aldehyde (33 mg, 0.1 mmol, 1 eq) was dissolved in dry MeOH (5 mL), and K_2CO_3 (27 mg, 0.2 mmol, 2 eq) and the Bestmann-Ohira reagent (23 mg, 0.12 mmol, 1.2 eq) were added. After 24 hours of stirring at room temperature, the reaction was quenched with saturated aqueous NH_4Cl (5 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 x 5ml). The combined organic layers were dried ($MgSO_4$), filtered, concentrated under reduced pressure and purified by silica chromatography (15 g) (EtOAc:Hex; 1:2) to yield the cyclised product as an orange solid (11 mg, 33%).

δ_H (400 MHz, $CDCl_3$): 3.35 (1H, dd, *J* 9.9, 14.9, C*H*HCH), 3.60 (1H, dd, *J* 4.8, 14.9, CH*H*CH), 4.77 (1H, dt, *J* 4.8, 9.9, C*H*CH_2), 6.67 (1H, bs, CONH), 7.05 (1H, dt, *J* 7.9, 0.8, ArH), 7.07 (1H, s, ArH indole), 7.17 (1H, dt, *J* 7.6, 0.8, ArH), 7.33 (1H, d, *J* 8.2, ArH), 7.43 (1H, d, *J* 8.2, ArH), 7.49 (1H, dt, *J* 7.6, 1.0 ArH), 7.66 (1H, dt, *J* 7.9, 1.5, ArH), 7.70 (1H, s, N_3C*H*), 7.97 (1H, dd, *J* 7.9, 1.5, ArH), 8.00 (1H, dd, *J* 8.2, 1.0, ArH), 8.23 (1H, bs, ArNH).

δ_C (100 MHz, $CDCl_3$): 29.7 (CH_2), 53.1 (CH), 108.9 (q), 111.7 (CH), 118.0 (CH), 120.0 (CH), 122.8 (CH), 123.1 (CH), 123.4 (CH), 125.7 (q), 126.6 (q), 129.1 (CH), 129.6 (CH), 132.1 (CH), 133.3 (q), 133.4 (CH), 136.5 (q), 139.3 (q), 167.5 (q).

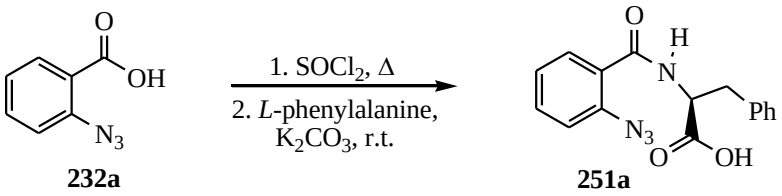
υ_{max} (thin film cm^{-1}): 1041(m), 1215 (s), 1458 (w), 1656 (s), 2854 (w), 2927 (m).

LRMS (ESI+): Found 330.1 $[M+H]^+$.

HRMS (ESI+): Found 330.1348 $[M+H]^+$, $C_{19}H_{16}N_5O$ requires 330.1349.

8.2 Cycloaddition Reactions involving nitriles.

8.2.1 Synthesis of *N*-(2'-azidobenzoyl)phenylalanine.



232a **251a**

Scheme 8-23

2-Azidobenzoic acid (560 mg, 3.43 mmol, 1.0 eq) was heated at reflux under nitrogen in $SOCl_2$ (8 mL) for 4 hours. The reaction was allowed to reach room temperature before the excess $SOCl_2$ was removed under reduced pressure to yield the acid chloride as a crude oil which was re-dissolved in fresh DCM (2 x 10 mL), concentrated under reduced pressure and finally dissolved in fresh DCM (5 mL).

K_2CO_3 (1.90 g, 13.7 mmol, 4 eq) in water (5 mL) was added in one portion to *L*-phenylalanine (963 mg, 5.83 mmol, 1.7 eq) in DCM (10 mL). The acid chloride in DCM (5 mL) was added dropwise and the whole was stirred overnight before the mixture was acidified to pH 2 with 2M HCl. The organic phase was separated and the aqueous phase was extracted with DCM (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated under reduced pressure to give a black oil (1.01 g, 95%) which was not purified any further.

δ_H (500 MHz, $CDCl_3$): 3.30 (1H, dd, *J* 14.0, 6.3, PhC*H*HCH), 3.37 (1H, dd, *J* 14.0, 5.6, PhCH*H*CH), 5.10 (1H, dt, *J* 6.3, 5.6, $PhCH_2CHNH$), 7.16 (1H, d, *J* 8.0, ArH), 7.25 (1H, t, *J* 7.7, ArH), 7.27-7.38 (5H, m, CH_2ArH), 7.51 (1H, dt, *J* 7.7, 1.5, ArH), 8.06 (1H, bd, *J* 6.9, N*H*), 8.16 (1H, dd, *J* 8.0, 1.5, ArH), 10.26 (1H, bs, COOH).

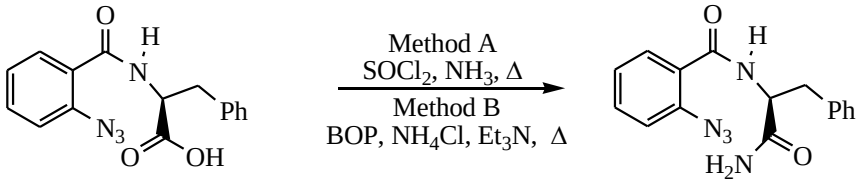
δ_C (125MHz, $CDCl_3$): 37.1 (CH_2), 54.3 (CH), 118.5 (CH), 123.5 (q), 125.2 (CH), 127.4 (CH), 128.6 (CH), 129.5 (CH), 132.4 (CH), 132.9 (CH), 135.7 (q), 137.4 (q), 164.8 (q), 175.5 (q).

υ_{max} (thin film cm^{-1}): 733 (s), 908 (s), 1217 (m), 1279 (s), 1481 (m), 1532 (s), 1597 (m), 1642 (s), 1724 (s), 2132 (s), 2929 (m), 3030 (m), 3351 (bm).

LRMS (ESI+): Found 333.1 $[M+Na]^+$, 643.2 $[2M+Na]^+$.

HRMS (ESI+): Found 333.0944 $[M+Na]^+$, $C_{16}H_{14}N_4NaO_3$ requires 333.0958.

8.2.2 Synthesis of *N*-(2'-azidobenzoyl)phenylalanamide.



251a **252a**

Scheme 8-24

Method A: The phenylalanine coupled product (380 mg, 1.23 mmol, 1 eq) was heated at reflux in $SOCl_2$ (4 mL) under nitrogen for 4 hours. The excess $SOCl_2$ was removed under reduced pressure and the crude acid chloride was dissolved in DCM and re-concentrated (3 x 10 mL). Concentrated ammonia solution (2 mL) was added dropwise to the crude acid chloride in dry THF (~10 mL) and the whole was stirred overnight before saturated aqueous NH_4Cl solution (20 mL) was added. The

organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organics where dried ($MgSO_4$), filtered, concentrated and purification by silica chromatography (23 g) (EtOAc:Hex; 4:1) afforded a yellow solid (146 mg) from which no products could be identified.

Method B: The carboxylic acid (325 mg, 1.05 mmol, 1 eq) was dissolved in dry DCM (5 mL), followed by the addition of Et_3N (0.146 mL, 106 mg, 1.05 mmol, 1 eq) and BOP (464 mg, 1.05 mmol, 1 eq). The whole was stirred for 5 mins before NH_4Cl (solid) (84 mg, 1.58 mmol, 1.5 eq) and Et_3N (0.22 mL, 160 mg, 1.58 mmol, 1.5 eq) were added. After 3 hours of stirring at ambient temperature, the reaction was diluted with DCM (15 mL), washed with 3M HCl (3 x 10 mL), saturated sodium carbonate solution (3 x 10 mL) and brine (3 x 10 mL). The organic phase was dried ($MgSO_4$), filtered, concentrated under reduced pressure and purified by silica chromatography (20 g) (EtOAc:Hex; 3:1) to yield the product as a yellow solid (232 mg, 72%).

δ_H (400 MHz, $CDCl_3$): 2.96-3.05 (2H, m, PhC*H*$_2$CH), 4.71 (1H, dt, *J* 6.7, 7.2, PhCH$_2$C*H*), 5.98 (1H, bs, CON*H*H), 6.61 (1H, bs, CONH*H*), 6.90-7.10 (7H, m, ArH), 7.28 (1H, dt, *J* 7.8, 1.6, ArH), 7.75 (1H, dd, *J* 7.8, 1.6, ArH), 7.82 (1H, bd, *J* 7.3, N*H*CHCH$_2$Ph).

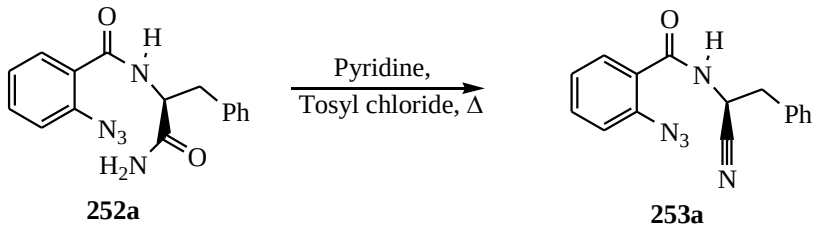
δ_C (100 MHz, $CDCl_3$): 37.9 (CH_2), 54.8 (CH), 118.5 (CH), 124.7 (q), 125.0 (CH), 126.9 (CH), 128.4 (CH), 129.5 (CH), 131.7 (CH), 132.4 (CH), 136.7 (q), 137.3 (q), 164.6 (q), 173.3 (q).

υ_{max} (thin film cm^{-1}): 909 (s), 988 (s), 1199 (s), 1249 (s), 1299 (s), 1479 (s), 1523 (m), 1642 (s), 1696 (s), 1731 (s), 2132 (s), 2930 (s), 2999 (m), 3190 (m), 3365 (m).

LRMS (ESI+): Found 332.1 $[M+Na]^+$.

HRMS (ESI+): Found 332.1110 $[M+Na]^+$, $C_{16}H_{15}N_5NaO$ requires 322.1118.

8.2.3 Synthesis of *N*-(2'-azidobenzoyl)-2-amino-3-phenylpropionitrile.



252a **253a**

Scheme 8-25

To the amide (563 mg, 1.82 mmol, 1 eq) in dry DCM (12 mL) at room temp was added pyridine (0.737 mL, 721 mg, 9.1 mmol, 5 eq) followed by neat tosyl chloride (694 mg, 3.64 mmol, 2 eq) and the reaction was heated at reflux under nitrogen for 48 hours. The reaction was allowed to cool to room temperature before being quenched with saturated aqueous NH_4Cl (30 mL). The organic layer was separated and the aqueous phase was extracted with DCM (3 x 10 mL). The combined organics were dried ($MgSO_4$), filtered, concentrated and purified by silica chromatography (24 g) (EtOAc:Hex; 2:1) yielding a yellow solid (345 mg, 65%).

δ_H (400 MHz, $CDCl_3$): 3.19 (1H, dd, *J* 6.9, 13.8, PhC*H*H), 3.29 (1H, dd, *J* 5.2, 13.8, PhCH*H*), 5.37 (1H, ddd, *J* 5.2, 6.9, 7.8, $PhCH_2CH$), 7.19 (1H, dd, *J* 8.0, 0.8, ArH), 7.28 (1H, dt, *J* 7.7, 1.0, ArH), 7.37-7.46 (5H, m, ArH), 7.56 (1H, dt, *J* 7.7, 1.6, ArH), 8.04 (1H, bd, *J* 7.8, CONH), 8.23 (1H, dd, *J* 8.0, 1.6, ArH).

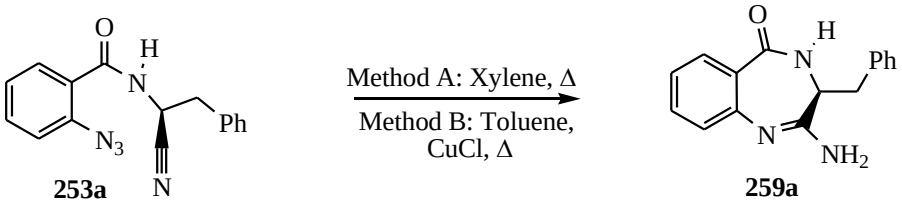
δ_C (100 MHz, $CDCl_3$): 38.5 (CH_2), 42.1 (CH), 118.2 (q), 118.5 (CH), 122.7 (q), 125.4 (CH), 128.2 (CH), 128.9 (CH), 129.8 (CH), 132.8 (CH), 133.4 (CH), 134.0 (q), 137.3 (q), 163.8 (q).

υ_{max} (thin film cm^{-1}): 1266 (s), 1296 (s), 1483 (m), 1520 (s), 1578 (w), 1597 (s), 1658 (s), 3058 (w), 3272 (m).

LRMS (ESI+): Found 314.1 $[M+Na]^+$, 605.2 $[2M+Na]^+$.

HRMS (ESI+): Found 314.1017 $[M+Na]^+$, $C_{16}H_{13}N_5NaO$ requires 314.1012.

8.2.4 Synthesis of 2-amino-3-benzyl-1,4-benzodiazepin-5-one.



Scheme 8-26

Method A: The nitrile (141 mg, 0.485 mmol) was heated at reflux in xylene (10 mL) under nitrogen at 175°C for 36 hours. The reaction was allowed to reach room temperature before being concentrated and purified by silica chromatography (20 g) (EtOAc:Hex; 1:3) giving the product as a yellow oil (18 mg, 14%).

Method B: The nitrile (204 mg, 0.7 mmol) was heated at reflux under nitrogen in toluene for 5 days with the addition of copper (I) chloride (10 mg). The reaction was concentrated and purified by silica chromatography (22 g) (EtOAc:Hex;1:3) to yield the product as a yellow oil (14 mg, 8%).

δ_H (400 MHz, $CDCl_3$): 3.17 (1H, dd, *J* 7.2, 13.8, PhC*H*H), 3.23 (1H, dd, *J* 5.8, 13.8, PhCH*H*), 5.21-5.24 (1H, m, $PhCH_2CH$), 5.58 (2H, bs, $NCNH_2$), 6.48 (1H, bd, *J* 8.2, CON*H*CH), 6.63 (1H, t, *J* 7.1, ArH), 6.69 (1H, d, *J* 8.2, ArH), 7.19-7.45 (7H, m, ArH).

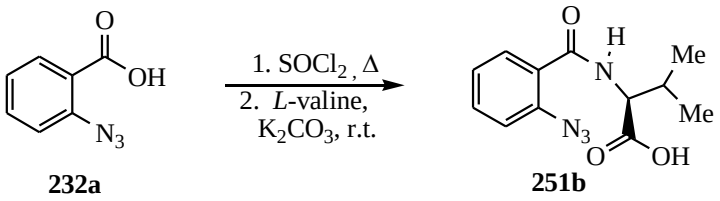
δ_C (100 MHz, $CDCl_3$): 38.8 (CH_2), 41.7 (CH), 113.5 (q), 114.8 (CH), 116.7 (CH), 117.6 (q), 127.2 (CH), 128.0 (CH), 128.9 (CH), 129.5 (CH), 133.3 (CH), 134.0 (q), 149.3 (q), 168.3 (q).

υ_{max} (thin film cm^{-1}): 698 (s), 747 (s), 1159 (m), 1256 (s), 1295 (m), 1454 (m), 1496 (s), 1514 (s), 1586 (s), 1612 (s), 1650 (s), 2853 (w), 2923 (s), 3025 (w), 3357 (m), 3474 (w).

LRMS (ESI+): Found 266.1 $[M+H]^+$, 531.3 $[2M+H]^+$.

HRMS (ESI+): Found 266.1270 $[M+H]^+$, $C_{16}H_{16}N_5O$ requires 266.1288.

8.2.5 Synthesis of *N*-(2'-azidobenzoyl)-valine.



232a **251b**

Scheme 8-27

2-Azidobenzoic acid (396 mg, 2.43 mmol, 1 eq) was heated at reflux under nitrogen for 5 hours in $SOCl_2$ (5 mL). The excess $SOCl_2$ was removed under reduced pressure to yield the acid chloride as a crude oil which was re-dissolved in fresh DCM (2 x 10 mL), concentrated under reduced pressure and finally dissolved in fresh DCM (5 mL).

K_2CO_3 (1.34 g, 9.72 mmol, 4 eq) in water (5 mL) was added in one portion to *L*-valine (711 mg, 6.07 mmol, 2.5 eq) in DCM (10 mL). The acid chloride in DCM (5 mL) prepared above was added dropwise and the whole was stirred overnight. The reaction mixture was acidified with 2M HCl to pH 2-3 and the organic layer was separated. The aqueous phase was extracted with EtOAc (3 x 10 mL), the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a black oil (528 mg, 83%), which was in the next step used without further purification.

δ_H (400 MHz, $CDCl_3$): 1.06 (3H, d, *J* 6.8, C*H*$_3$CHCH$_3$), 1.07 (3H, d, *J* 6.8, CH$_3$CHC*H*$_3$), 2.38 (1H, dsept, *J* 6.8, 4.6, [CH$_3$]$_2$C*H*), 4.81 (1H, dd, *J* 8.3, 4.6, NHC*H*COOH), 7.22 (1H, t, *J* 8.4, ArH), 7.25 (1H, d, *J* 8.4, ArH), 7.52 (1H, dt, *J* 7.9, 1.5, ArH), 8.11 (1H, bd, *J* 8.3, CONH), 8.14 (1H, dd, *J* 7.9, 1.5, ArH).

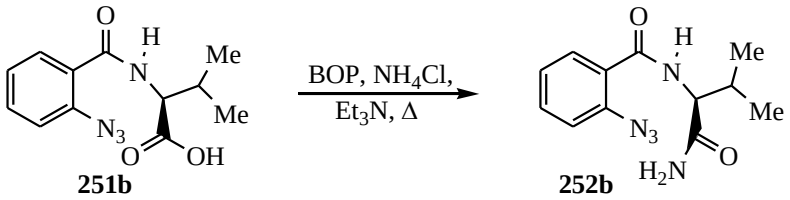
δ_C (100 MHz, $CDCl_3$): 17.9 (CH_3), 19.2 (CH_3), 31.1 (CH), 58.0 (CH), 118.4 (CH), 124.1 (q), 125.2 (CH), 132.4 (CH), 132.8 (CH), 137.4 (q), 165.0 (q), 176.0 (q).

υ_{max} (thin film cm^{-1}): 909 (s), 1216 (m), 1276 (s), 1553 (s), 1598 (s), 1643 (s), 1719 (s), 2131 (s), 2252 (m), 2967 (s), 3365 (s).

LRMS (ESI+): Found 285.1 $[M+Na]^+$, 547.2 $[2M+Na]^+$.

HRMS (ESI+): Found 285.0945 $[M+Na]^+$, $C_{12}H_{14}N_4NaO_3$ requires 285.0958.

8.2.6 Synthesis of *N*-(2'-azidobenzoyl)-valinamide.



251b **252b**

Scheme 8-28

The valine derived starting material (322 mg, 1.23 mmol, 1 eq) was dissolved in dry DCM (5 mL). BOP (544 mg, 1.23 mmol, 1 eq) and Et_3N (0.171 mL, 124 mg, 1.23 mmol, 1 eq) were added respectively and the whole was stirred for 10 mins. Saturated aqueous NH_4Cl (solid) (99 mg, 1.85 mmol, 1.5 eq) and Et_3N (0.258 mL, 187 mg, 1.85 mmol, 1.5 eq) were added and the whole was stirred overnight. The reaction was diluted with DCM (15 mL) and washed successively with 3M HCl (3 x 10 mL), saturated $NaHCO_3$ solution (3 x 10 mL) and saturated brine (3 x 10 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated under reduced pressure and purified by silica chromatography (23 g) (EtOAc:Hex;2:1) to yield the amide as a yellow solid (293 mg, 91%).

δ_H (400 MHz, $CDCl_3$): 1.08 (3H, d, *J* 6.8, C*H*$_3$CHCH$_3$), 1.09 (3H, d, *J* 6.8, CH$_3$CHCH$_3$), 2.35 (1H, oct, *J* 6.8, [CH$_3$]$_2$C*H*), 4.60 (1H, dd, *J* 6.2, 8.3, NHC*H*CONH$_2$), 5.83 (1H, bs, CON*H*H), 6.67 (1H, bs, CONH*H*), 7.25 (1H, dd, *J* 7.8, 0.9, ArH), 7.27 (1H, dt, *J* 7.8, 0.9, ArH), 7.55 (1H, dt, *J* 7.9, 1.6, ArH), 8.00 (1H, bd, *J* 8.3, CONH), 8.11 (1H, dd, *J* 7.9, 1.6, ArH).

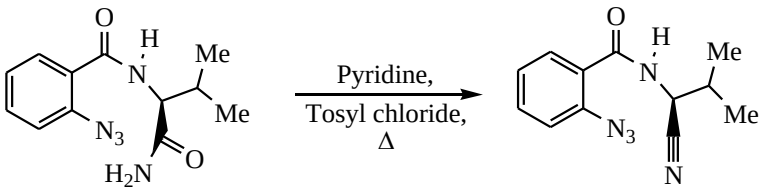
δ_C (100 MHz, $CDCl_3$): 18.2 (CH_3), 19.4 (CH_3), 30.7 (CH), 58.8 (CH), 118.4 (CH), 124.6 (q), 125.2 (CH), 132.1 (CH), 132.6 (CH), 137.3 (q), 164.9 (q), 173.4 (q).

υ_{max} (thin film cm^{-1}): 747 (s), 984 (s), 1067 (s), 1197 (s), 1297 (s), 1460 (s), 1656 (s), 2129 (s), 2806 (m), 2848 (m), 2894 (m), 2923 (s), 2997 (s).

LRMS (ESI+): Found 284.1 $[M+Na]^+$, 545.2 $[2M+Na]^+$.

HRMS (ESI+): Found 284.1111 $[M+Na]^+$, $C_{12}H_{15}N_5NaO_2$ requires 284.1118.

8.2.7 Synthesis of *N*-(2'-azidobenzoyl)-2-amino-3-methyl-butanonitrile.



252b **253b**

Scheme 8-29

The valine derived amide (533 mg, 2.04 mmol, 1 eq) was dissolved in dry DCM (10 mL). Pyridine (0.83 mL, 808 mg, 10.2 mmol, 5 eq) and tosyl chloride (779 mg, 4.08 mmol, 2 eq) were added and the whole was heated at reflux under nitrogen for 24 hours. The reaction was quenched with saturated aqueous NH_4Cl (20 mL) and the organic layer was separated. The aqueous phase was extracted with EtOAc (3 x 30 mL), the combined organic layers were dried ($MgSO_4$), filtered,

concentrated under reduced pressure and purified by silica chromatography (40 g) (EtOAc:Hex;1:3) to yield the product as a yellow solid (199 mg, 40%).

δ_H (400 MHz, $CDCl_3$): 1.07 (3H, d, *J* 6.8, C*H*$_3$CHCH$_3$), 1.10 (3H, d, *J* 6.8, CH$_3$CHCH$_3$), 2.11 (1H, oct, *J* 6.8, [CH$_3$]$_2$C*H*), 4.92 (1H, dd, *J* 6.8, 8.4, NHC*H*CN), 7.14 (1H, d, *J* 8.0, ArH), 7.18 (1H, t, *J* 7.7, ArH), 7.48 (1H, dt, *J* 7.7, 1.5, ArH), 7.97 (1H, bd, *J* 8.4, CONH), 8.07 (1H, dd, *J* 8.0, 1.5, ArH).

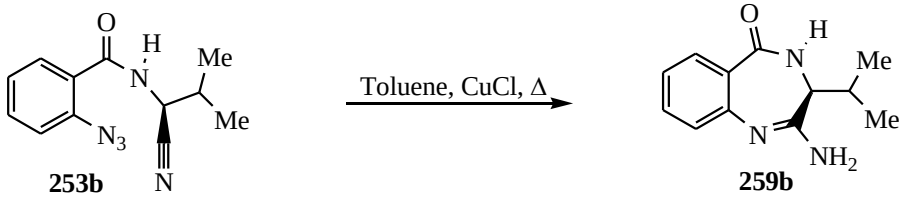
δ_C (100 MHz, $CDCl_3$): 18.2 (CH_3), 18.8 (CH_3), 31.6 (CH), 47.1 (CH), 117.8 (q), 118.5 (CH), 123.2 (q), 125.4 (CH), 132.6 (CH), 133.3 (CH), 137.3 (q), 164.1 (q).

υ_{max} (thin film cm^{-1}): 754 (s), 1165 (m), 1216 (s), 1277 (s), 1447 (m), 1481 (s), 1522 (s), 1577 (s), 1598 (s), 1658 (s), 2131 (s), 2244 (w), 2854 (m), 2876 (m), 2928 (s), 2967 (s).

LRMS (ESI+): Found 266.1 $[M+Na]^+$, 509.2 $[2M+Na]^+$, $C_{12}H_{13}N_5NaO$ requires 266.1

HRMS (ESI+): Found 266.1001 $[M+Na]^+$, $C_{12}H_{13}N_5NaO$ requires 266.1012.

8.2.8 Synthesis of 2-amino-3-(^{i}propyl)-4-amino-1,4-benzodiazepin-5-one.



Scheme 8-30

The nitrile (36 mg, 0.148 mmol) was heated at reflux in toluene (10 mL) with the addition of copper (I) chloride (10 mg) under nitrogen at 120°C for 3 days. The toluene was removed under reduced pressure and the crude product was purified by silica chromatography (22 g) (EtOAc:Hex;1:4) to yield the product as an orange solid (16 mg, 50%).

δ_H (400 MHz, $CDCl_3$): 1.15 (3H, d, *J* 6.7, C*H*$_3$CHCH$_3$), 1.18 (3H, d, *J* 6.7, CH$_3$CHC*H*$_3$), 2.16 (1H, oct, *J* 6.7, C*H*[CH$_3$]$_2$), 4.98 (1H, dd, *J* 6.3, 8.6, NHC*H*), 5.56 (2H, bs, NH_2), 6.39 (1H, bd, *J* 8.6, C*H*NH), 6.70 (1H, dt, *J* 8.1, 0.9, ArH), 6.72 (1H, dd, *J* 8.1, 0.9, ArH), 7.27 (1H, dt, *J* 7.8, 1.4, ArH), 7.35 (1H, dd, *J* 7.8, 1.4, ArH).

δ_C (100 MHz, $CDCl_3$): 18.1 (CH_3), 18.8 (CH_3), 31.8 (CH), 46.6 (CH), 113.8 (q), 116.7 (CH), 117.6 (CH), 118.0 (q), 127.1 (CH), 133.3 (CH), 149.2 (q), 168.4 (q).

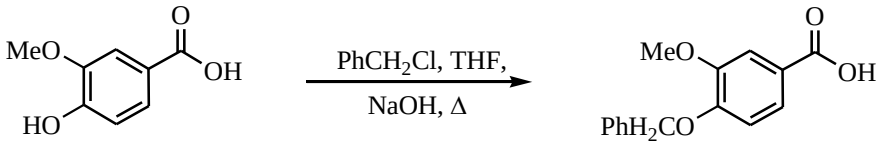
υ_{max} (thin film cm^{-1}): 1155 (m), 1260 (s), 1299 (s), 1352 (m), 1488 (s), 1539 (s), 1584 (s), 1635 (s), 2245 (w), 2875 (m), 2962 (m), 3301 (s), 3382 (s), 3483 (s).

LRMS (ESI+): Found 218.1 $[M+H]^+$.

HRMS (ESI+): Found 218.1283 $[M+H]^+$, $C_{12}H_{16}N_3O$ requires 218.1288.

9 Experimental: Synthesis of benzene ring with the DC-81 substitution pattern.

9.1.1 Synthesis of 4-(benzyloxy)-3-methoxybenzoic acid.



290 **291**

Scheme 9-1

4-Hydroxy-3-methoxybenzoic acid (30 g, 178 mmol, 1 eq) was dissolved in a mixture of THF (90 mL) and 2M aqueous NaOH (250 mL). Benzyl chloride (25 mL, 217 mmol, 1.22 eq) in THF (90 mL) was added to the ice cooled solution over 15 minutes. The mixture was allowed to reach room temperature before heating at reflux for 48 hours. The aqueous phase was separated and washed with hexane (2 x 150 mL). Some remaining THF in the aqueous phase was removed *in vacuo* and the aqueous solution was acidified to pH 1 with HCl (36% ~80 mL). The pale peach precipitate was collected by vacuum filtration on a sinter glass. Recrystallisation from EtOAc afforded a pale peach solid which was collected by vacuum filtration on a sinter (32.87 g, 74%) mp=169-173°C [lit 171-173°C].[96]

δ_H (500 MHz, d_6-DMSO): 3.78 (3H, s, OMe), 5.12 (2H, s, OCH_2), 7.10 (1H, d, *J* 8.4, Ar*H*), 7.32 (1H, t, *J* 7.3, Ar*H*), 7.38 (2H, t, *J* 7.3, Ar*H*), 7.43 (2H, d, *J* 7.3, Ar*H*), 7.45 (1H, s, Ar*H*), 7.54 (1H, d, *J* 8.4, Ar*H*), 12.58 (1H, bs, CO_2H).

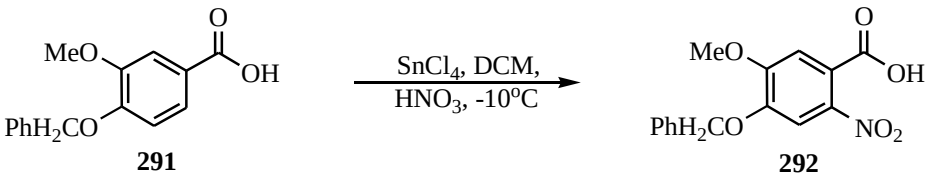
δ_C (125MHz, d_6-DMSO): 55.8 (CH_3), 70.2 (CH_2), 112.4 (CH), 112.7 (CH), 123.5 (CH), 128.3 (CH), 128.4 (CH), 128.9 (CH), 136.8 (q), 148.9 (q), 151.9 (q), 167.6 (q).

υ_{max} (thin film cm^{-1}): 996 (m), 1023 (s), 1227 (s), 1270 (s), 1303 (m), 1348 (m), 1425 (s), 1452 (m), 1517 (m), 1584 (m), 1671 (s).

LRMS (ESI+): Found 281.1 $[M+Na]^+$.

HRMS (ESI+): Found 281.0772 $[M+Na]^+$, $C_{15}H_{14}NaO_4$ requires 281.0784.

9.1.2 Synthesis of 4-(benzyloxy)-5-methoxy-2-nitrobenzoic acid.



291 **292**

Scheme 9-2

4-(Benzyloxy)-3-methoxybenzoic acid (8.70 g, 28.7 mmol, 1 eq) in DCM (120 mL) was cooled to -10°C before a mixture of $SnCl_4$ (10.02 g, 4.5 mL, 39 mmol, 1.33 eq) and conc. HNO_3 (2.39 mL, 3.34 g, 57 mmol, 1.98 eq) in DCM (34 mL) was added dropwise. The reaction was maintained at -10°C for 30mins before being quenched with water (200 mL) and allowed to reach room temperature. Some solid product formed in the reaction was retained by vacuum filtration. The organic phase was separated and the aqueous layer was extracted with EtOAc (2 x 150 mL). The combined organic layers were dried ($MgSO_4$), filtered and solvent removed *in vacuo* to afford crude 4-(benzyloxy)-5-methoxy-2-nitrobenzoic acid (10.5 g). Recrystallisation from EtOAc/Hexane yielded a yellow solid (6.53g combined, 63%) which was collected through vacuum filtration, mp=178-182°C [lit 180-183°C].[96]

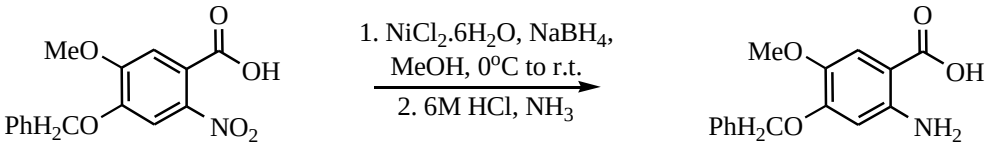
δ_H (500 MHz, d_6-DMSO): 3.90 (3H, s, CH_3), 5.23 (2H, s, CH_2), 7.31 (1H, s, Ar*H*), 7.32-7.48 (5H, m, Ar*H*), 7.70 (1H, s, Ar*H*), 13.62 (1H, bs, CO_2H).

δ_C (125MHz, d_6-DMSO): 56.5 (CH_3), 70.6 (CH_2), 108.4 (CH), 111.4 (CH), 121.5 (q), 128.2 (CH), 128.3 (CH), 128.6 (CH), 135.9 (q), 141.2 (q), 149.0 (q), 152.1 (q), 166.0 (q).

υ_{max} (thin film cm^{-1}): 975 (m), 1010 (m), 1048 (s), 1185 (s), 1212 (s), 1275 (s), 1351 (s), 1415 (s), 1454 (m), 1537 (m), 1583 (m), 1603 (s), 1683 (s), 2838 (w).

LRMS (ESI+): Found 326.1 $[M+Na]^+$, $C_{15}H_{13}NNaO_6$ requires 326.1.

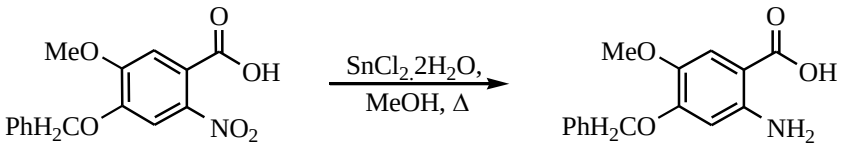
9.1.3 Synthesis of 2-amino-4-(benzyloxy)-5-methoxybenzoic acid.



292 **293**

Scheme 9-3

Method A: To a stirring solution of 4-(benzyloxy)-5-methoxy-2-nitrobenzoic acid (1.00 g, 3.3 mmol, 1 eq) and $NiCl_2.6H_2O$ (1.57 g, 6.6 mmol, 2 eq) in MeOH (8 mL) at 0°C was added portionwise $NaBH_4$ (500 mg, 13.2 mmol, 4 eq). The solvent was removed *in vacuo* after 30mins of stirring at room temperature. The residue was dissolved in 6M HCl, and adjusted to pH8 with 2M ammonia solution. The organic layer was separated and the aqueous layer was extracted with EtOAc (6 x 40 mL). The combined organic phases were dried (Na_2SO_4), filtered and the solvent removed *in vacuo* to yield a black solid (360 mg). Purification by silica chromatography (EtOAc:Hex; 1:1) yielded the product as a white solid (200 mg, 25%).



292 **293**

Scheme 9-4

Method B: A mixture of 4-(benzyloxy)-5-methoxy-2-nitrobenzoic acid (2.4 g, 8 mmol, 1 eq) and $SnCl_2.H_2O$ (7.2 g, 32 mmol, 4 eq) was heated at reflux for 3 hours in MeOH (24 mL). The solvent was removed *in vacuo* and the yellow syrup was redissolved in EtOAc (25 mL). A solution of 5% $NaHCO_3$ (25 mL) was added and the mixture was stirred overnight at room temperature. The precipitate was collected by filtration under vacuum to yield a white solid (1.92 g, 88%) which needed no further purification.

δ_H (500 MHz, d_6-DMSO): 3.73 (3H, s, C*H*$_3$), 5.09 (2H, s, CH_2), 6.99 (1H, s, Ar*H*), 7.32-7.45 (8H, m, N*H*$_2$+ 6 x Ar*H*), 11.48 (1H, bs, CO_2H).

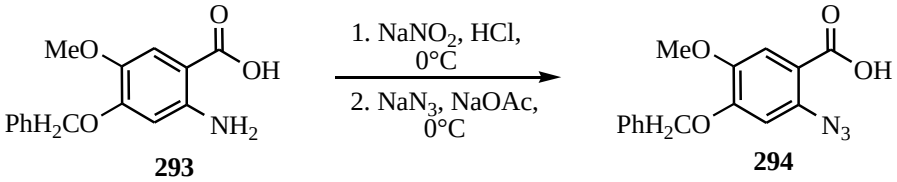
δ_C (125MHz, d_6-DMSO): 56.3 (CH_3), 70.3 (CH_2), 106.0 (CH), 113.7 (CH), 128.3 (q), 128.4 (2 x CH), 128.6 (CH), 128.9 (2 x CH), 136.3 (2 x q), 144.7 (q), 152.7 (q), 167.9 (q).

υ_{max} (thin film cm^{-1}): 881 (m), 981 (m), 1069 (m), 1170 (s), 1211 (s), 1254 (m), 1280 (s), 1505 (s), 1526 (m), 1701 (s), 2200-3250 (OH-br), 3354 (N-H), 3530 (N-H).

LRMS (ESI+): Found 274.1 $[M+H]^+$, 296.1 $[M+Na]^+$.

HRMS (ESI+): Found 274.1076 $[M+H]^+$, $C_{15}H_{16}NO_4$ requires 274.1074.

9.1.4 Synthesis of 2-azido-4-(benzyloxy)-5-methoxybenzoic acid.



293 **294**

Scheme 9-5

To a stirred ice cooled solution of the amine (1.15 g, 4.21 mmol, 1 eq) in 6M HCl (20 mL) was added portionwise $NaNO_2$ (420 mg, 6.09 mmol, 1.45 eq) in water (5 mL) and the mixture stirred for 30 minutes. This solution was added dropwise to a stirred solution of NaOAc (9.43 g, 115 mmol, 27.3 eq) and NaN_3 (340 mg, 5.23 mmol, 1.24 eq) in water (20 mL). After stirring for a further 90 minutes, the precipitates were filtered, washed with water, and redissolved in $CHCl_3$. The solution was dried (Na_2SO_4) stripped of solvent *in vacuo* to yield (990 mg, 78%) of crude product. Recrystallisation from toluene gave the product as a black solid (600 mg, 47%). mp= 138-141°C [lit 139-141°C].[138]

δ_H (400 MHz, $CDCl_3$): 3.82 (3H, s, CH_3), 5.14 (2H, s, CH_2), 6.60 (1H, s, ArH), 7.24-7.37 (5H, m, ArH), 7.51 (1H, s, ArH), 10.82 (1H, bs, CO_2H).

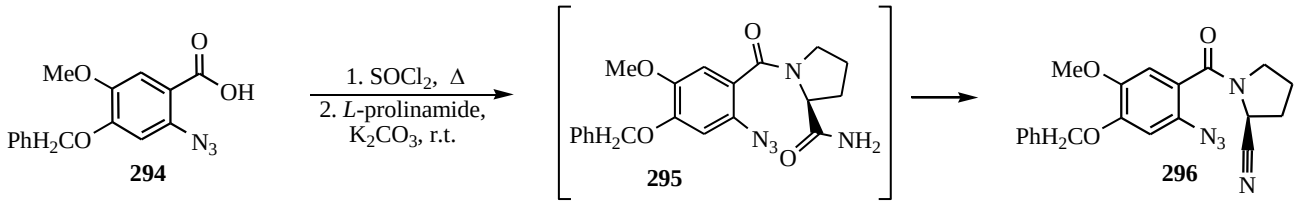
δ_C (100 MHz, $CDCl_3$): 55.2 (CH_3), 70.2 (CH_2), 104.5 (CH), 112.6 (q), 114.8 (CH), 127.3 (CH), 128.1 (CH), 128.5 (CH), 134.1 (q), 135.4 (q), 146.6 (q), 153.0 (q), 168.1 (q).

υ_{max} (thin film cm^{-1}): 820 (m), 874 (m), 923 (m), 1179 (s), 1205 (s), 1250 (s), 1415 (m), 1463 (m), 1513 (s), 1573 (m), 1602 (m), 1666 (s), 2103 (s), 2614-2940 (br).

LRMS (ESI+): Found 322.1 $[M+Na]^+$, 621.2 $[2M+Na]^+$.

HRMS (ESI+): Found 322.0789 $[M+Na]^+$, $C_{15}H_{13}N_3NaO_4$ requires 322.0798.

9.1.5 Synthesis of 2-cyano-1-[2'-azido-4-(benzyloxy)-5-methoxybenzoyl]pyrrolidine.



Scheme 9-6

The azide (250 mg, 0.836 mmol, 2.4 eq) was dissolved in toluene (5 mL) and $SOCl_2$ (1.5 mL) was added. The whole was heated to reflux under nitrogen for 3 hours. The reaction mixture was concentrated *in vacuo*, and the residue was dissolved in DCM (2 x 10 mL) to remove excess $SOCl_2$, to yield the crude acid chloride.

K_2CO_3 (193 mg, 1.4 mmol, 4 eq) dissolved in water (3 mL) was added in one portion to a stirring solution of *L*-prolinamide (40 mg, 0.35 mmol, 1 eq) in DCM (3 mL). After stirring for 30mins at ambient temperature the acid chloride redissolved in DCM (5 mL) was added dropwise and the mixture was stirred overnight. The organic layer was separated and the aqueous layer extracted from DCM (2 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a black-brown oil (460 mg). Purification by silica chromatography (40 g) (EtOAc: Hex; 3:1) yielded the product as a grey solid (74 mg, 56%).

δ_H (400 MHz, $CDCl_3$): 2.17-2.44 (3H, m, CH_2+CH*H*), 3.39-3.52 (2H, m, CH_2), 3.75-3.82 (1H, m, C*H*H), 3.94 (3H, s, OCH_3), 4.92 (1H, dd, *J* 3.8, 7.5, NCC*H*N), 5.24 (2H, s, OCH_2), 6.72 (1H, s, Ar*H*), 6.92 (1H, s, Ar*H*), 7.37-7.51 (5H, m, Ar*H*).

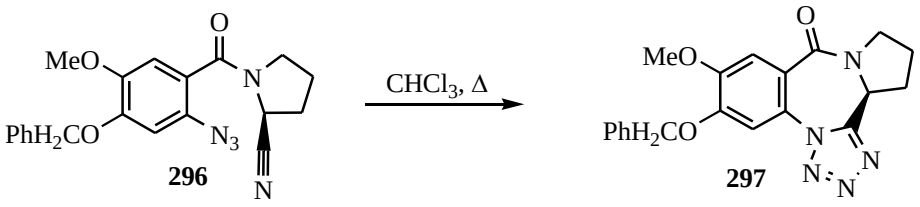
δ_C (100 MHz, $CDCl_3$): 25.0 (CH_2), 30.5 (CH_2), 46.4 (CH), 47.7 (CH_2), 56.5 (CH_3), 71.4 (CH_2), 104.4 (CH), 111.3 (CH), 118.4 (q), 120.0 (q), 127.4 (2 x CH), 128.4 (CH), 128.8 (2 x CH), 135.9 (2 x q), 147.4 (q), 150.3 (q), 167.0 (q).

υ_{max} (thin film cm^{-1}): 910 (s), 1181 (m), 1211 (m), 1245 (s), 1386 (m), 1425 (s), 1453 (m), 1512 (s), 1606 (m), 1638 (s), 2114 (s), 2253 (s), 2937 (w).

LRMS (ESI+): Found 377.2 $[M]^+$, 378.2 $[M+H]^+$.

HRMS (ESI+): Found 378.1566 $[M+H]^+$, $C_{20}H_{20}N_5O_3$ requires 378.1561.

9.1.6 Synthesis of tetrazolo[1,5-*a*]-4-(benzyloxy)-5-methoxy-pyrrolo[2,1-*c*][1,4]benzodiazepine.



Scheme 9-7

The starting material (50 mg, 0.133 mmol) was heated at reflux under nitrogen in $CHCl_3$ (10 mL) for 72 hours. The solvent was removed *in vacuo* and the crude was purified by silica chromatography (20 g) (EtOAc: Hex; 3:1) to yield the product as a white solid (29 mg, 58%).

δ_H (400 MHz, $CDCl_3$): 2.04-2.18 (2H, m, CH_2), 2.42-2.52 (1H, m, C*H*H), 3.06-3.13 (1H, m, CH*H*), 3.61-3.68 (1H, m, C*H*H) , 3.73-3.79 (1H, m, CH*H*), 3.93 (3H, s, OCH_3), 4.68 (1H, dd, *J* 3.2, 8.4, NCC*H*N), 5.15 (1H, d, *J* 12.0, OC*H*H), 5.26 (1H, d, *J* 12.0, OCH*H*) 7.19 (1H, s, Ar*H*), 7.25- 7.41 (5H, m, Ar*H*), 7.53 (1H, s, Ar*H*).

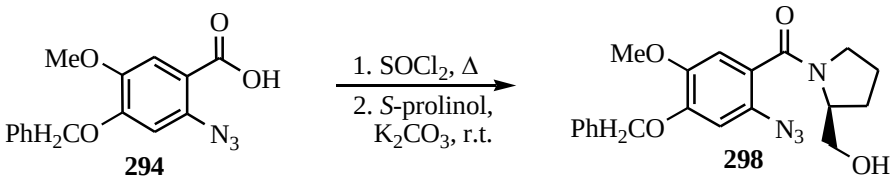
δ_C (100 MHz, $CDCl_3$): 23.5 (CH_2), 28.2 (CH_2), 48.2 (CH_2), 49.8 (CH), 56.4 (CH_3), 71.3 (CH_2), 106.5 (CH), 113.3 (CH), 119.8 (q), 124.2 (q), 127.6 (CH), 128.5 (CH), 128.8 (CH), 135.3 (q), 150.3 (q), 151.7 (q), 154.1 (q), 163.4 (q).

υ_{max} (thin film cm^{-1}): 1242 (m), 1269 (s), 1374 (s), 1429 (s), 1453 (m), 1517 (s), 1606 (s), 1631 (s), 2853 (s), 2924 (s).

LRMS (ESI+): Found 377.2 $[M]^+$, 378.2 $[M+H]^+$.

HRMS (ESI+): Found 378.1564 $[M+H]^+$, $C_{20}H_{20}N_5O_3$ requires 378.1561.

9.1.7 Synthesis of 1-[2'-azido-4-(benzyloxy)-5-methoxybenzoyl]prolinol.



Scheme 9-8

The protected azidobenzoic acid (236 mg, 0.789 mmol, 1.0 eq) was dissolved in dry toluene (5 mL) and $SOCl_2$ (1.5 mL) was added. The solution was placed in a preheated oil bath at 85°C for 3 hours. The reaction was cooled to ambient temperature, concentrated *in vacuo*, dissolved in fresh DCM (3 x 10 mL) and concentrated *in vacuo*, to remove the excess $SOCl_2$.

K_2CO_3 (218 mg, 1.58 mmol, 2 eq) in water (2 mL) was added in one portion to a stirring solution of *S*-prolinol (0.162 mL, 168 mg, 1.66 mmol, 2.1 eq) in DCM (2 mL) and the whole was stirred for 10 minutes. The acid chloride in DCM (5 mL) was added dropwise and the whole was stirred at ambient temperature overnight before the organic layer was separated. The aqueous phase was extracted with DCM (3 x 10 mL) and the combined organic layers were dried ($MgSO_4$), filtered, concentrated and purified by silica chromatography (20 mg) (EtOAc:Hex; 3:1) to yield the product as an orange oil (262 mg, 87%).

δ_H (400 MHz, $CDCl_3$): 1.56-1.84 (3H, m, CH_2 +C*H*H), 2.06-2.13 (1H, m, CH*H*), 3.20-3.30 (2H, m, CH_2), 3.62-3.67 (1H, m, C*H*HOH), 3.73-3.77 (1H, m, CH*H*OH), 3.80 (3H, s, OMe), 4.23-4.29 (1H,

m, C*H*CH_2OH), 4.69 (1H, bs, CH_2O*H*), 5.10 (2H, s, OCH_2), 6.59 (1H, s, ArH), 6.76 (1H, s, ArH), 7.24-7.38 (5H, m, ArH).

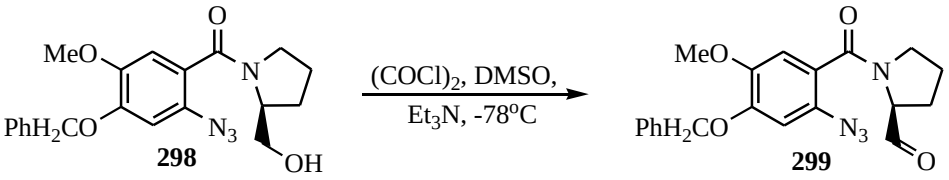
δ_C (100 MHz, $CDCl_3$): 24.5 (CH_2), 28.5 (CH_2), 49.6 (CH_2), 56.3 (CH_3), 61.2 (CH), 66.6 (CH_2), 71.2 (CH_2), 104.2 (CH), 110.7 (CH), 121.4 (q), 127.3 (CH), 128.2 (CH), 128.7 (CH), 135.9 (q), 147.2 (q), 149.8 (q), 168.8 (q).

υ_{max} (thin film cm^{-1}): 742 (s), 1004 (m), 1048 (m), 1077 (m), 1178 (s), 1214 (s), 1242 (s), 1433 (s), 1511 (s), 1603 (s), 2109 (s), 2882 (w), 2937 (w), 3145-3593 (br).

LRMS (ESI+): Found 383.2 [M+H]+, 765.3 $[2M+H]^+$, 787.3 $[2M+Na]^+$.

HRMS (ESI+): Found 383.1708 $[M+H]^+$, $C_{20}H_{23}N_4O_4$ requires 383.1714.

9.1.8 Synthesis of 1-[2'-azido-4-(benzyloxy)-5-methoxybenzoyl]prolinal.



Scheme 9-9

DMSO (0.14 mL, 154 mg, 1.97 mmol, 3.01 eq) in DCM (1 mL) and the alcohol (250 mg, 0.654 mmol, 1 eq) in DCM (2 mL) where added dropwise respectively, over 15 minutes, to a solution of 2M oxalyl chloride (0.39 mL, 0.785 mmol, 1.2 eq) at -78°C in DCM (1 mL). After 10 mins, Et_3N (0.24 mL, 174 mg, 1.72 mmol, 2.63 eq) was added dropwise to the mixture at -78ºC. The whole was allowed to reach room temperature over two hours before being quenched with a mixture of Et_2O (10 mL) and H_2O (10 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organics were dried ($MgSO_4$), filtered, concentrated and

purified by silica chromatography (20 g) (EtOAc:Hex; 3:1) to give the product as a mixture of rotamers in the form of an orange oil (161 mg, 65%).

δ_H (400 MHz, $CDCl_3$): 1.79-1.89 (2H, m, CH_2), 1.97-2.04 (1H, m, C*H*H), 2.07-2.20 (1H, m, CH*H*), 3.28-3.34 & 3.35-3.41 (2H, m, NCH_2), 3.76 & 3.81 (3H, 2 x s, OCH_3), 4.12-4.17 & 4.52-4.57 (1H, m, NC*H*CHO), 5.08 & 5.12 (2H, 2 x s, OCH_2), 6.53 & 6.61 (1H, 2 x s, ArH), 6.72 & 6.80 (1H, 2 x s, ArH), 7.24-7.39 (5H, m, ArH), 9.22 & 9.62 (1H, 2 x d, *J* 1.4 & 1.8, CHO).

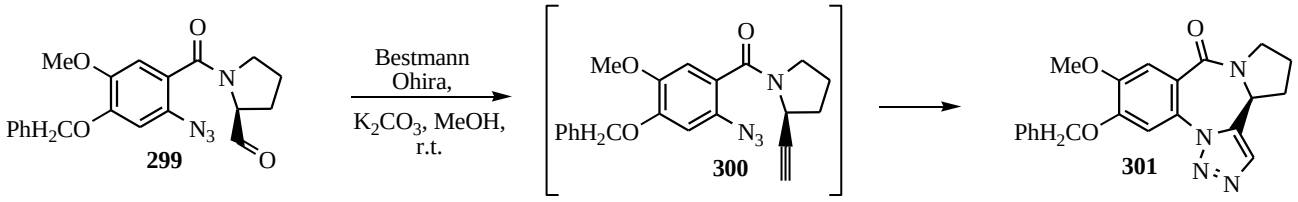
δ_C (100 MHz, $CDCl_3$): 24.9/26.4 (CH_2), 46.8/48.6 (CH_2), 56.3/56.4 (CH_3), 60.4 (CH_2), 64.8/66.5 (CH), 71.3/71.3 (CH_2), 104.2/104.4 (CH), 111.2/111.5 (CH), 120.7/120.8 (q), 127.4 (CH), 128.3 (CH), 128.8 (CH), 135.9/136.0 (q), 147.3/147.3 (q), 150.0/150.1 (q), 167.2/167.4 (q), 198.0/199.4 (CH).

υ_{max} (thin film cm^{-1}): 1245 (s), 1430 (s), 1454 (s), 1512 (s), 1604 (s), 1622 (s), 1731 (m), 2110 (s), 2942 (m).

LRMS (ESI+): Found 381.2 $[M+H]^+$, 403.1 $[M+Na]^+$, 783.3 $[2M+Na]^+$.

HRMS (ESI+): Found 403.1375 $[M+Na]^+$, $C_{20}H_{20}N_4NaO_4$ requires 403.1377.

9.1.9 Synthesis of 3-benzyloxy-4-methoxy-1,2,3-triazolo[1,5-*a*][1,4]pyrrolo[2,1-*c*]benzodiazepin-5-one.



Scheme 9-10

The aldehyde (113 mg, 0.30 mmol, 1 eq) was dissolved in dry MeOH (3 mL). K_2CO_3 (82 mg, 0.60 mmol, 2 eq) and Bestmann Ohira reagent (68 mg, 0.36 mmol, 1.2 eq) were added and the whole was stirred for 6 hours. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and the organic layer was separated. The aqueous phase was extracted with DCM (3 x 10 mL) and the combined organics were dried ($MgSO_4$), filtered, concentrated and purified by silica chromatography (22 g) (EtOAc:Hex; 9:1) to yield the cyclised product as a white solid (95 mg, 84%).

δ_H (400 MHz, $CDCl_3$): 1.98-2.09 (2H, m, CH_2), 2.41-2.50 (2H, m, CH_2), 3.63-3.73 (2H, m, CH_2), 3.91 (3H, s, OMe), 4.63 (1H, t, *J* 5.2 C*H*CH_2), 5.12 (1H, d, *J* 11.9, PhC*H*HO), 5.24 (1H, d, *J* 11.9, PhCH*H*O), 7.23-7.28 (1H, m, ArH), 7.27-7.33 (2H, m, ArH), 7.38-7.40 (2H, m, ArH), 7.47 (1H, s, ArH), 7.50 (1H, s, ArH), 7.52 (1H, s, ArH).

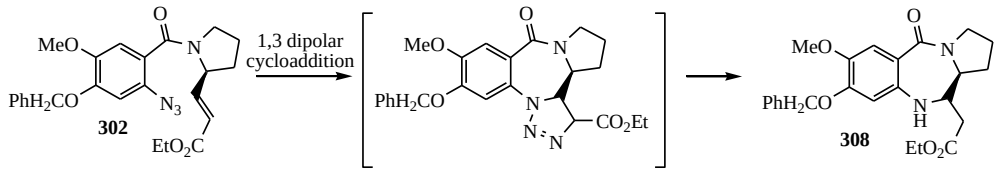
δ_C (100 MHz, $CDCl_3$): 23.0 (CH_2), 28.7 (CH_2), 47.0 (CH_2), 49.0 (CH), 55.6 (CH_3), 70.4 (CH_2), 106.3 (CH), 112.4 (CH), 119.0 (q), 126.5 (q), 126.9 (CH), 127.7 (CH), 127.9 (CH), 128.1 (CH), 134.9 (q), 137.9 (q), 148.9 (q), 150.7 (q), 163.2 (q).

υ_{max} (thin film cm^{-1}): 1135 (m), 1269 (s), 1366 (m), 1430 (s), 1453 (m), 1516 (s), 1584 (m), 1629 (s), 2927 (m).

LRMS (ESI+): Found 377.2 $[M+H]^+$.

HRMS (ESI+): Found 377.1600 $[M+H]^+$, $C_{21}H_{21}N_4O_3$ requires 377.1608.

9.1.10 Synthesis of 3-benzyloxy-4-methoxy-11-ethyl-ethanoyl-[1,4]-pyrrolo[2,1-*c*] benzodiazepin-5-one.



Scheme 9-11

The aldehyde (198 mg, 0.581 mmol, 1.0 eq) was dissolved in toluene (10 mL) and (carbethoxymethylene)-triphenylphosphorane (180 mg, 0.521 mmol, 1 eq) was added in one portion and the whole was stirred for 18 hours. The reaction was concentrated *in vacuo* and purified by silica chromatography (30 g) (EtOAc:Hex; 4:1) to yield the product as a yellow oil (52 mg, 21%).

δ_H (500 MHz, $CDCl_3$): 1.32 (3H, t, *J* 7.2, $CO_2CH_2CH_3$), 1.74-1.80 (1H, m, C*H*H), 1.93-2.19 (3H, m, CH*H* + CH_2), 2.31-2.24 (2H, m, CH_2CO_2Et), 3.43-3.47 (1H, m, NHC*H*), 3.62-3.66 (1H, m, NC*H*CH), 3.68-3.73 (1H, m, NC*H*H), 3.76-3.80 (1H, m, NCH*H*), 3.89 (3H, s, OMe), 4.22 (2H, quartet, *J* 7.2, $CO_2CH_2CH_3$), 5.13 (1H, d, J 12.3, PhC*H*HO), 5.18 (1H, d, *J* 12.3, PhCH*H*O), 6.34 (1H, s, ArH), 7.31-7.50 (7H, m, 6 x ArH +NH).

δ_C (125MHz, $CDCl_3$): 14.2 (CH_3), 23.2 (CH_2), 29.9 (CH_2), 37.3 (CH_2), 46.9 (CH_2), 56.3 (CH_3), 60.1 (CH), 61.0 (CH_2), 62.7 (CH), 70.9 (CH_2), 108.1 (CH), 113.1 (CH), 120.0 (q), 127.4 (CH), 128.0 (CH), 128.4 (CH), 136.5 (q), 137.8 (q), 145.0 (q), 150.9 (q), 168.3 (q), 171.9 (q).

υ_{max} (thin film cm^{-1}): 723 (m), 1025 (s), 1119 (s), 1178 (s), 1218 (s), 1260 (s), 1373 (m), 1432 (s), 1453 (m), 1503 (m), 1602 (s), 1623 (m), 1726 (m), 2860 (m), 2924 (s), 2953 (m).

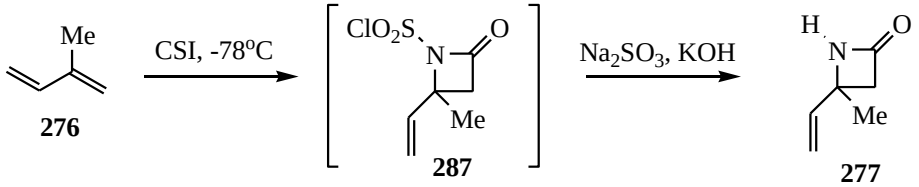
LRMS (ESI+): Found 447.2 $[M+Na]^+$.

HRMS (ESI+): Found 447.1895 $[M+Na]^+$ requires $C_{24}H_{28}N_2NaO_5$ requires 447.1890.

10 Experimental: Intramolecular Cycloadditon of Azides onto Alkenes: Triazolino-, Aziridino- and Azetindinobenzodiazepines.

10.1 Synthesis of the Azetidinobenzodiazepines.

10.1.1 Synthesis of 4-methyl-4-vinylazetidin-2-one.



276 **287** **277**

Scheme 10-1

Isoprene (8.82 mL, 6.00 g, 88.2 mmol, 2 eq) in dry ether (20 mL) was cooled to -78°C before dropwise addition of CSI (3.84 mL, 6.24 g, 44.1 mmol, 1 eq) in dry ether (20 mL) over 30 minutes. The whole was allowed to reach -10°C and the temperature was maintained for a further 4 hours. A solution of 25% aqueous Na_2SO_3: ether; 2:1 (21 mL) was cooled to -10°C and the initial solution was added keeping the whole slightly basic with 10% aqueous KOH. The organic layer was separated and the aqueous phase was extracted with ether (1 x 20 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated to give a colourless oil (2.15 g, 44%) which needed no further purification.

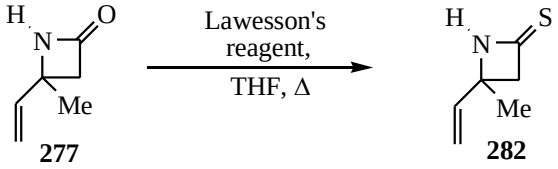
δ_H (400 MHz, $CDCl_3$): 1.50 (3H, s, Me), 2.79 (2H, s, C*H*$_2$), 5.10 (1H, dd, *J* 10.6, 0.7, CH=C*H*H), 5.22 (1H, dd, *J* 17.2, 0.7, CH=CH*H*), 6.02 (1H, dd, *J* 10.6, 17.2, C*H*=CH_2), 6.83 (1H, br, NH).

δ_C (100 MHz, $CDCl_3$): 24.8 (CH_2), 50.7 (CH_3), 54.5 (q), 113.8 (CH), 141.1 (CH_2), 167.6 (q).

υ_{max} (thin film cm^{-1}): 923 (m), 1153 (m), 1186 (m), 1226 (m), 1274 (w), 1304 (m), 1372 (m), 1412 (m), 1643 (m), 1720 (s), 2970 (w), 3235 (m).

LRMS (ESI+): Found 134.1 $[M+Na]^+$, 291.2 $[2M+3Na]^+$.

10.1.2 Synthesis of 4-methyl-4-vinylazetidin-2-thione.



277 **282**

Scheme 10-2

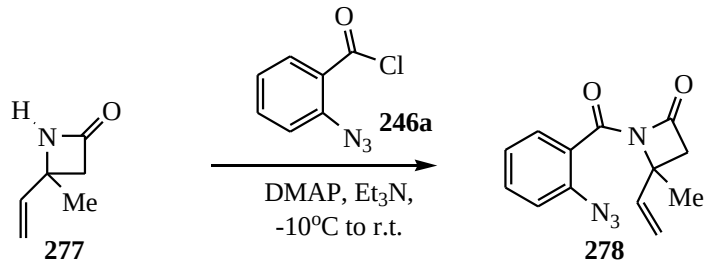
To the azetidin-2-one (1.49 g, 13.4 mmol, 1.0 eq) in dry THF (18 mL) was added Lawesson's reagent (3.26 g, 8.06 mmol, 0.6 eq) and the whole was stirred at room temperature for an hour before being heated to reflux for a further hour. The reaction was allowed to reach ambient temperature before being concentrated and purified by silica chromatography (200 g) (EtOAc:Hex; 1:4) to give the product as a pale red oil (1.32 g, 77%).

δ_H (400 MHz, $CDCl_3$): 1.60 (3H, s, Me), 2.98 (2H, s, $CSCH_2$), 5.21 (1H, d, *J* 10.6, CH=C*H*H), 5.28 (1H, d, *J* 17.2, CH=CH*H*), 6.05 (1H, dd, *J* 10.6, 17.2 C*H*=CH_2), 8.78 (1H, bs, NH).

δ_C (100 MHz, $CDCl_3$): 23.8 (CH_3), 54.6 (CH_2), 63.7 (q), 115.1 (CH_2), 139.0 (CH), 202.2 (q).

υ_{max} (thin film cm^{-1}): 924 (s), 989 (m), 1016 (m), 1081 (s), 1217 (m), 1288 (m), 1374 (m), 1404 (s), 1466 (s), 1640 (w), 2971 (w), 3147 (m).

10.1.3 Synthesis of 1-(2'-azidobenzoyl)-4-methyl-4-vinylazetidin-2-one.



Scheme 10-3

The azidobenzoic acid (508 mg, 3.02 mmol, 1.0 eq) was heated to reflux in $SOCl_2$ (4 mL) for 3 hours under nitrogen. The excess $SOCl_2$ was removed *in vacuo* and the crude acid chloride was redissolved in DCM (3 x 5 mL) which was removed in vacuo to yield the crude benzoyl chloride.

The β-lactam (457 mg, 4.12 mmol, 1.36 eq) in DCM (25 mL) and DMAP (100 mg) were chilled to -10°C. The crude acid chloride in DCM (5 mL) was added dropwise to the solution over 10 mins. The whole was maintained at -10°C for 30 mins before the addition of Et_3N (0.89 mL, 646 mg, 6.40 mmol, 2.12 eq) and the whole was allowed to reach room temperature overnight. The reaction was concentrated and purified by silica chromatography (70 g) (EtOAc:Hex;1:4) to give the coupled product in rotermeric form as a dark yellow oil (498 mg, 65%).

δ_H (400 MHz, $CDCl_3$) *rotamer 1*: 1.87 (3H, s, Me), 2.98 (1H, d, *J* 16.2, COC*H*H), 3.08 (1H, d, *J* 16.2, COCH*H*), 5.35 (1H, d, *J* 10.7, C*H*H=CH), 5.45 (1H, d, *J* 17.3, CH*H*=CH), 6.24 (1H, dd, *J* 10.7, 17.3, C*H*=CH_2), 7.22 (1H, t, *J* 7.6, ArH), 7.23 (1H, d, *J* 8.3, ArH), 7.42 (1H, dd, *J* 7.6, 1.3, ArH), 7.52 (1H, dt, *J* 8.3, 1.4, ArH).

δ_H (400 MHz, $CDCl_3$) *rotamer 2*: 1.51 (3H, s, Me), 2.68 (1H, d, *J* 15.8, COC*H*H), 2.82 (1H, d, *J* 15.8, COCH*H*), 5.20 (1H, d, *J* 10.6, C*H*HCH), 5.32 (1H, d, *J* 17.2, CH*H*CH), 5.91 (1H, dd, *J* 10.6, 17.2, C*H*CH_2), 7.21 (1H, dt, *J* 7.6, 0.9, ArH), 7.24 (1H, d, *J* 7.6, ArH), 7.51 (1H, dt, *J* 7.8, 1.5, ArH), 7.67 (1H, dd, *J* 7.8, 1.5, ArH).

δ_C (100 MHz, $CDCl_3$) *rotamer 1*: 21.7 (CH_3), 49.2 (CH_2), 58.9 (q), 114.9 (CH_2), 117.5 (CH), 123.7 (CH), 125.8 (q), 128.1 (CH), 131.2 (CH), 137.1 (q), 137.2 (CH), 162.4 (q), 162.5 (q).

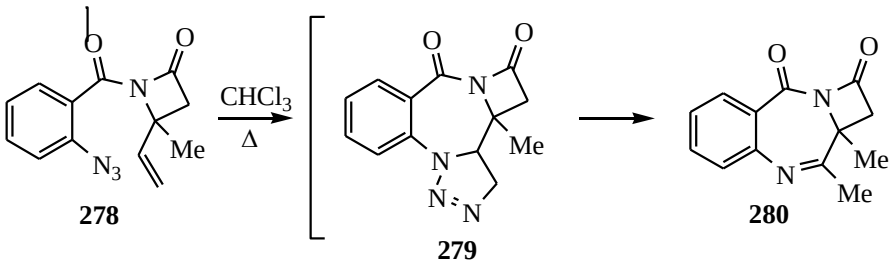
δ_C (100 MHz, $CDCl_3$) *rotamer 2*: 27.6 (CH_3), 39.5 (CH_2), 58.6 (q), 114.3 (CH_2), 119.9 (CH), 123.5 (q), 124.7 (CH), 130.8 (CH), 132.1 (CH), 138.9 (q), 139.9 (CH), 151.5 (q), 165.3 (q).

υ_{max} (thin film cm^{-1}): 1084 (m), 1216 (s), 1329 (s), 1391 (s), 1451 (m), 1478 (m), 1519 (s), 1604 (m), 1656 (m), 1682 (m), 1721 (w), 1801 (s), 2131 (s), 2853 (m), 2925 (m).

LRMS (ESI+): 279.1 $[M+Na]^+$, 535.2 $[2M+Na]^+$. $C_{13}H_{12}N_4NaO_2$ requires 279.1.

HRMS (ESI+): 279.0862 $[M+Na]^+$, $C_{13}H_{12}N_4NaO_2$ requires 279.0852.

10.1.4 Synthesis of 8,9-dimethylazetidino [2,1-a] [1,4] benzodiazepin-2,11-dione.



278 **279** **280**

Scheme 10-4

The azetidinone (372 mg, 1.45 mmol) was heated to reflux in $CHCl_3$ (10 mL) nitrogen and monitored by NMR every 24 hours. After 72 hours, the reaction was concentrated and purified by silica chromatography (22 g) using graduated elutation (EtOAc:Hex; 1:4-3:1) to give the imine as a yellow solid (74 mg, 22%).

δ_H (500 MHz, $CDCl_3$): 2.00 (3H, s, Me), 2.49 (1H, s, Me), 3.42 (1H, d, *J* 16.0, COCH*H*), 3.77 (1H, d, *J* 16.0, COCH*H*), 7.52 (1H, dt, *J* 7.7, 1.0, Ar*H*), 7.70 (1H, dd, *J* 8.0, 1.0, Ar*H*), 7.78 (1H, dt, *J* 7.7, 1.6, Ar*H*), 8.32 (1H, dd, *J* 8.0, 1.6, Ar*H*).

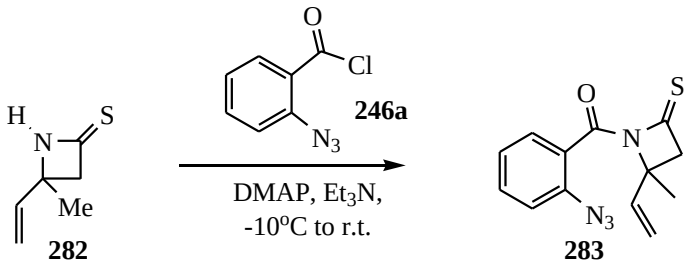
δ_C (125MHz, $CDCl_3$): 20.1 (CH_3), 26.2 (CH_3), 43.6 (CH_2), 73.3 (q), 123.7 (q), 126.5 (CH), 126.7 (CH), 127.4 (CH), 134.3 (CH), 149.7 (q), 155.2 (q), 158.1(q), 204.2 (q)

υ_{max} (thin film cm^{-1}): 702 (s), 730 (s), 1264 (s), 1421 (m), 1463 (m), 1609 (m), 1657 (m), 1686 (m), 1721 (s), 1799 (w), 2928 (w).

LRMS (ESI+): Found 229.1 $[M+H]^+$, 251.1 $[M+Na]^+$, 479.2 $[2M+Na]^+$.

HRMS (ESI+): Found 229.0978 $[M+H]^+$, 479.1703 [2M+Na], $C_{13}H_{12}N_2NaO_2$ requires 229.0972 and $C_{23}H_{24}N_4NaO_4$ requires 479.1690.

10.1.5 Synthesis of 1-(2'-azidobenzoyl)-4-methyl-4-vinyl-1-azetidin-2-thione.



Scheme 10-5

The azidobenzoic acid (214 mg, 1.3 mmol, 1.0 eq) was heated to reflux under nitrogen in $SOCl_2$ (4 mL) for 4 hours. The excess thionyl chloride was removed *in vacuo* and the product dissolved in DCM (3 x 5 mL) and concentrated *in vacuo* to give the crude acid chloride.

The methylthiolactam (250 mg, 1.97 mmol, 1.5 eq) in DCM (25 mL) and DMAP (100 mg) was chilled to -10°C. The crude acid chloride in DCM (5 mL) was added dropwise over 10mins and the whole was maintained at -10°C for 30mins before dropwise addition of Et_3N (0.41 mL, 299 mg, 2.95 mmol, 2.25 eq). The whole was allowed to reach room temperature overnight and the reaction was concentrated and purified by silica chromatography (22 g) (EtOAc:Hex;1:4) to give the product as an orange oil (296 mg, 84%).

δ_H (400 MHz, $CDCl_3$): 1.92 (3H, s, Me), 2.93 (1H, d, *J* 16.9, CSC*H*H), 3.04 (1H, d, *J* 16.9, CSCH*H*), 5.38 (1H, d, *J* 10.8, C*H*HCH), 5.45 (1H, d, *J* 17.3, CH*H*CH), 6.31 (1H, dd, *J* 17.3, 10.8 CHHC*H*), 7.20 (1H, dd, *J* 8.2, 0.8, ArH), 7.24 (1H, dt, *J* 7.6, 0.8, ArH), 7.36 (1H, dd, *J* 7.6, 1.5, ArH), 7.54 (1H, dt, *J* 8.2, 1.5, ArH).

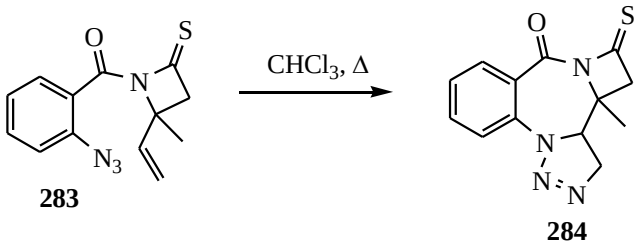
δ_C (100 MHz, $CDCl_3$): 22.3 (CH_3), 54.5 (CH_2), 67.5 (q), 116.4 (CH_2), 118.5 (CH), 125.1 (CH), 126.6 (q), 128.9 (CH), 132.1 (CH), 137.7 (CH), 138.3 (q), 164.2 (q), 201.7 (q).

υ_{max} (thin film cm^{-1}): 909 (s), 931 (m), 1215 (s), 1322 (s), 1358 (m), 1448 (w), 1478 (m), 1674 (s), 2131 (s).

LRMS (ESI+): Found 295.1 $[M+Na]^+$, 567.1 $[2M+Na]^+$.

HRMS (ESI+): Found 295.0623 $[M+Na]^+$, $C_{13}H_{12}N_4NaOS$ requires 295.0624.

10.1.6 Synthesis of 12-methyl-1,2,3-triazolino[1,5-a]azetidino[1,4-c][1,4]benzodiazepin-2-on-14-thione.



283 **284**

Scheme 10-6

The *N*-(2'-azidobenzoyl)-azetidine (295 mg, 1.08 mmol) was heated at reflux in $CHCl_3$ (10 mL) under nitrogen for 36 hours before being concentrated and purified by silica chromatography (22 g) (EtOAc:Hex;1:1) to give the triazolino product as a yellow solid (180 mg, 61%).

δ_H (500 MHz, $CDCl_3$): 1.22 (3H, s, Me), 2.89 (1H, d, *J* 16.8, SCC*H*H), 2.94 (1H, d, *J* 16.8, SCCH*H*), 4.27 (1H, dd, *J* 6.1, 12.2, CH_3C*H*N), 4.37 (1H, dd, *J* 6.1, 17.7, N_3CHH), 4.71 (1H, dd, *J* 12.2, 17.7, N_3CHH), 7.14 (1H, dt, *J* 7.1, 1.0, ArH), 7.52 (1H, dt, *J* 7.2, 1.6, ArH), 8.04 (1H, dd, *J* 8.4, 0.9, ArH), 8.2 (1H, d, *J* 8.3, 1.5, ArH).

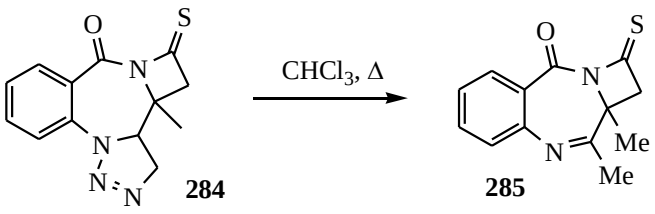
δ_C (125MHz, $CDCl_3$): 16.8 (CH_3), 50.5 (CH_2), 59.6 (CH), 65.0 (q), 70.4 (CH_2), 115.9 (q), 118.6 (CH), 123.4 (CH), 134.2 (CH), 134.5 (CH), 138.3 (q), 161.8 (q), 198.1 (q).

υ_{max} (thin film cm^{-1}): 745 (s), 1103 (m), 1162 (m), 1211 (m), 1251 (m), 1322 (s), 1461 (s), 1483 (s), 1607 (s), 1651 (s), 1678 (s), 1720 (m), 2921 (w), 3000 (w).

LRMS (ESI+): Found 295.1 $[M+Na]^+$, 567.1 $[2M+Na]^+$.

HRMS (ESI+): Found 295.0622 $[M+Na]^+$, $C_{13}H_{12}N_4NaOS$ requires 295.0624.

10.1.7 Synthesis of 11-thioxo-8,9-dimethyl-azetidino[2,1-c][1,4]benzodiazepin-2-one.



284 **285**

Scheme 10-7

A sample of the triazolo compound from above (87 mg, 0.319 mmol) was heated at reflux in $CHCl_3$ (10 mL) under nitrogen for a week before being concentrated and purified by silica chromatography (15 g) (EtOAc:Hex;3:2) to give the methyl imine product as a yellow solid (25 mg, 32%).

δ_H (400 MHz, $CDCl_3$): 1.98 (3H, s, Me), 2.47 (3H, s, Me), 3.40 (1H, d, *J* 16.0, CSC*H*H), 3.77 (1H, d, *J* 16.0, CSCH*H*), 7.50 (1H dt, *J* 7.7, 1.0, ArH), 7.68 (1H, d, *J* 8.1, ArH), 7.77 (1H, dt, *J* 7.7, 1.5, ArH), 8.30 (1H, dd, *J* 8.1, 1.3, ArH).

δ_C (100 MHz, $CDCl_3$): 20.1 (CH_3), 26.3 (CH_3), 43.6 (CH_2), 73.3 (q), 123.6 (q), 126.6 (CH), 126.7 (CH), 127.3 (CH), 134.3 (CH), 149.6 (q), 155.2 (q), 158.0 (q), 204.4 (q).

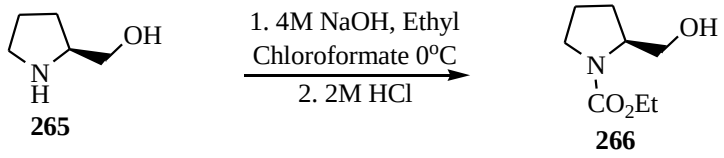
υ_{max} (thin film cm^{-1}): 647 (s), 770 (s), 1103 (m), 1115 (m), 1132 (m), 1300 (m), 1323 (s), 1346 (s), 1460 (s), 1606 (s), 1651 (s), 1676 (s), 1719 (m), 2928 (w), 2975 (w).

LRMS (ESI+): Found 267.1 $[M+Na]^+$.

HRMS (ESI+): Found 267.0551 $[M+Na]^+$, $C_{13}H_{12}N_2NaOS$ requires 267.0563.

10.2 Intramolecular Cycloadditon of Azides onto Alkenes: Aziridinopyrrolo-benzodiazepines

10.2.1 Synthesis of (*S*)-*N*-(ethoxycarbonyl)-prolinol.



265 **266**

Scheme 10-8

To a stirring solution of *S*-prolinol (1.0 g, 9.89 mmol, 1.0 eq) in 4M NaOH (7 mL) was added ethyl chloroformate (1.13 mL, 1.287 g, 11.9 mmol, 1.2 eq) over 10mins at 0°C. The reaction was maintained at 0°C for 30mins followed by 30mins at ambient temperature. The reaction solution was neutralised with 2M HCl, the aqueous phase was separated and extracted with DCM (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated to give the crude product (1.64 g, 96%) as a yellow oil which was used as crude in the following reaction.

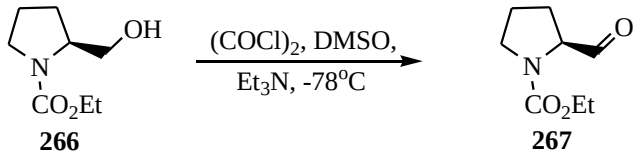
δ_H (400 MHz, $CDCl_3$): 1.27 (3H, t, *J* 7.1, $COCH_2CH_3$), 1.57 (1H, m, C*H*H), 1.74-1.91 (2H, m, CH*H* + C*H*H), 1.99-2.08 (1H, m, CH*H*), 3.31-3.78 (1H, m, NC*H*H), 3.49-3.54 (1H, m, NCH*H*), 3.59-3.69 (2H, m, CH_2OH), 3.97-4.03 (1H, m, CH_2OH), 4.14 (2H, quartet, *J* 7.1, $COCH_2CH_3$), 4.61 (1H, dd, *J* 7.6, 2.6, NC*H*CH_2).

δ_C (100 MHz, $CDCl_3$): 14.7 (CH_3), 24.1 (CH_2), 28.6 (CH_2), 47.3 (CH_2), 60.6 (CH), 61.6 (CH_2), 67.3 (CH_2), 157.6 (q).

υ_{max} (thin film cm^{-1}): 770 (s), 906 (m), 1046 (s), 1106 (s), 1333 (s), 1379 (s), 1414 (s), 1667 (s), 2876 (w), 2975 (w), 3400-3500 (br).

LRMS (ESI+): Found 196.1 $[M+Na]^+$, $C_8H_{15}N_4NaO_3$ requires 196.1.

10.2.2 Synthesis of (*S*)-*N*-(ethoxycarbonyl)-prolinal.



266 **267**

Scheme 10-9

2M $(COCl)_2$ in DCM (4.72 mL, 9.43 mmol, 1.2 eq) was diluted with dry DCM (12 mL) and cooled to -78°C under N_2. DMSO (1.34 mL, 1.474 g, 18.9 mmol, 2.4 eq) in DCM (5 mL) followed by the alcohol (1.36 g, 7.86 mmol, 1 eq) in DCM (5 mL) were added respectively, over 15mins. The whole was maintained at -78°C for 30mins before dropwise addition of Et_3N (5.48 mL, 3.98 g, 39.3 mmol, 5 eq) over 10mins. The whole was allowed to reach room temperature over an hour before being quenched with a mixture of Et_2O (12.5 mL) and H_2O (12.5 mL). The organic layer was separated and the aqueous phase was extracted with DCM (3 x 10 mL). The combined organics were dried ($MgSO_4$), filtered, concentrated and purified by silica chromatography (20 g) (EtOAc:Hex;2:3) to yield the aldehyde in rotameric form as a yellow oil (1.19 g, 89%).

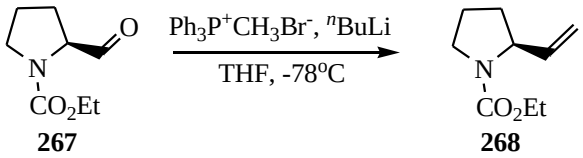
δ_H (400 MHz, $CDCl_3$): 1.17 & 1.24 (3H, 2 x t, *J* 7.1 & 7.1, $COCH_2CH_3$), 1.76-1.92 (2H, m, CH_2), 1.93-2.09 (2H, m, CH_2), 3.40-3.57 (2H, m, NCH_2), 4.02-4.14 & 4.17-4.22 (3H, m, $CO_2CH_2CH_3$ & NC*H*CHO), 9.48 & 9.56 (1H, 2 x d, *J* 2.5, 1.7, CHO).

δ_C (100 MHz, $CDCl_3$): 14.5/14.7 (CH_3), 23.8/24.5 (CH_2), 26.6/27.8 (CH_2), 46.6/47.1 (CH_2), 61.5 (2 x CH_2), 64.8/65.1 (CH), 154.7/155.6 (q), 200.2/200.3 (CHO).

υ_{max} (thin film cm^{-1}): 729 (s), 771 (s), 914 (m), 1021 (m), 1102 (s), 1172 (m), 1341 (s), 1380 (s), 1416 (s), 1466 (s), 1687 (s), 1733 (s), 2872 (m), 2980 (m).

LRMS (ESI+): Found 194.1 $[M+Na]^+$, $C_8H_{13}NNaO_3$ requires 194.1.

10.2.3 Synthesis of (*S*)-*N*-2-ethenyl-1-ethoxycarbonylpyrrolidine.



267 **268**

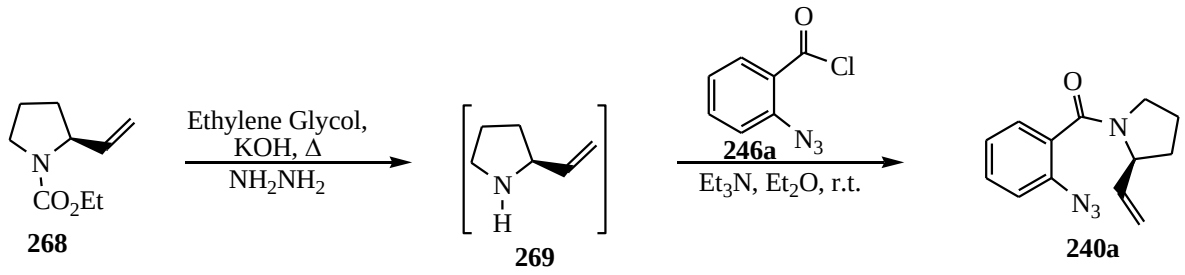
Scheme 10-10

1.6M ^{n}BuLi in hexanes (10.5 mL, 16.8 mmol, 2.4 eq) was added dropwise over 30mins to a stirring suspension of methyltriphenylphosphonium bromide (5.52 g, 15.4 mmol, 2.2 eq) in anhydrous THF (30 mL) at -78°C under an inert atmosphere of nitrogen. The whole was allowed to reach -10°C and kept at that temperature for 30mins before being cooled back to -78°C. The aldehyde (1.20 g, 7.02 mmol, 1.0 eq) in anhydrous THF (5 mL) was added dropwise over 10 mins. The whole was allowed to warm to -10°C, where the temperature was maintained for 2 hours and then the mixture was allowed to reach room temperature overnight. The mixture was quenched with saturated aqueous NH_4Cl (20 mL) and the aqueous layer was separated and extracted with EtOAc (3 x 10 mL). The combined organics were dried ($MgSO_4$), filtered, concentrated and purified by silica chromatography (50 g) (EtOAc:Hex;3:2) yielding an air sensitive product as a mixture of rotamers in the form of a pale orange oil (536 mg, 45%).

δ_H (400 MHz, $CDCl_3$): 1.22-1.27 (3H, br, m, CH_3), 1.71 (1H, bs, $CH_2CH\mathit{H}CH_2$), 1.81 (2H, br, m, $NCHCH_2$), 1.97 (1H, m, br, $CH_2C\mathit{H}HCH_2$), 3.43 (2H, s, br, NCH_2), 4.13 (2H, br, m, OCH_2), 4.33 (1H, br, m, NCH), 5.04-5.12 (2H, br, m, $CH=CH_2$), 5.72 (1H, br, m, $CH=CH_2$).

δ_C (100 MHz, $CDCl_3$): 14.2/14.8 (CH_3), 22.6/23.4 (CH_2), 31.2/31.9 (CH_2), 46.3/46.5 (CH_2), 58.9/59.3 (CH), 60.4/60.8 (CH_2), 113.8/114.1(CH_2), 138.2/138.5 (CH), 155.1/155.4 (q).

10.2.4 Synthesis of (*S*)-*N*-(2'-azidobenzoyl)-2-ethenyl-pyrrolidine.



Scheme 10-11

To a vigorously stirred suspension of finely ground KOH (2.31 g, 41.2 mmol, 26 eq) in ethylene glycol (7.2 mL) was added hydrazine hydrate (0.25 mL, 7.92 mmol, 5 eq) and (*S*)-(-)-2-ethenyl-1-ethoxycarbonylpyrrolidine (268 mg, 1.58 mmol, 1.0 eq) and the whole was heated to reflux (195°C) for 4hours. The reaction was allowed to reach ambient temperature before being diluted with a mixture of Et_2O (4 mL) and H_2O (4 mL). The thick syrup was extracted with Et_2O (3 x 5 mL) and dried with finely ground NaOH. Et_3N (0.331 mL, 2.37 mmol, 1.5 eq) was added to the ethereal solution containing the amine at 0°C under an inert atmosphere and was stirred for 10 mins before freshly prepared acid chloride (~480 mg, 1.5 eq) in Et_2O (5 mL) was added dropwise over 10mins and the whole was allowed to reach ambient temperature overnight. The reaction was diluted with water (20 mL), the ethereal layer was separated and the aqueous phase was extracted with ether (3 x 10 mL). The combined organics were dried ($MgSO_4$), filtered, concentrated and purified by silica chromatography (21 g) (EtOAc:Hex; 2:3) to yield the product as a mixture of rotamers (123 mg, 32%) in the form of a yellow oil.

δ_H (400 MHz, $CDCl_3$): 1.73-2.15 (4H, m, 2 x CH_2), 3.17-3.23 & 3.30- 3.36 (1H, m, C*H*HCH_2), 3.64-3.71 & 3.74-3.82 (1H, m, CH*H*CH_2), 4.11-4.15 & 4.84-4.87 (1H, br, m, C*H*CH_2), 4.70 & 5.35 (1H, 2 x d, *J* 16.9, 17.1, C*H*HCH), 4.89 & 5.20 (1H, 2 x d, *J* 10.3 & 10.4, CHCH*H*), 4.89 & 5.20 (1H, 2 x d, *J* 10.3 & 10.4, CHC*H*H), 5.56 & 5.90 (1H, 2 x ddd, *J* 6.2, 10.4, 16.9 & 4.8, 10.4, 17.1, C*H*CH_2) 7.10-7.24 (3H, m, ArH), 7.32-7.45 (1H, m, ArH).

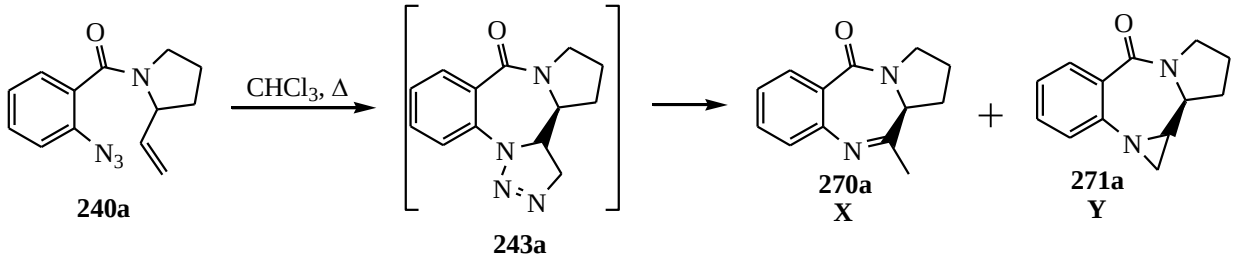
δ_C (100 MHz, $CDCl_3$): 22.1/23.6 (CH_2), 30.9/32.3 (CH_2), 45.9/48.2 (CH_2), 58.4/61.1 (CH), 114.5/114.9 (CH_2), 118.4/118.5 (CH), 124.6/125.2 (CH), 127.9/128.3 (CH), 129.6/130.1 (q), 130.2/130.3 (CH), 136.1 (q), 136.9/137.6 (CH), 166.8/167.4 (q).

υ_{max} (thin film cm^{-1}): 750 (s), 932 (s), 1083 (m), 1149 (m), 1292 (s), 1415 (s), 1449 (s), 1479 (s), 1598 (s), 1631 (s), 2128 (s), 2878 (m), 2973 (m), 3078 (w).

LRMS (ESI+): Found 265.1 $[M+Na]^+$, 507.2 $[2M+Na]^+$.

HRMS (ESI+): Found 265.1064 $[M+Na]^+$, $C_{13}H_{14}N_4NaO$ requires 265.1060.

10.2.5 Synthesis of pyrrolobenzodiazepine (**270a**) and aziridinopyrrolobenzodiazepine (**271a**).



240a **243a** **270a** **X** **271a** **Y**

Scheme 10-12

The alkene (78 mg, 0.322 mmol) was dissolved in $CHCl_3$ (10 mL) and heated at reflux under an inert atmosphere of nitrogen for 16 hours whilst being monitored by TLC (EtOAc:Hex;3:2). The reaction mixture was concentrated and purified by silica chromatography (20 g) (EtOAc:Hex; 3:2-4:1) to yield two spots on TLC which were purified by chromatography to give an inseparable mixture of the aziridine (**271a**) and the methyl imine (**270a**) products (**271a**:**270a**;X:Y;1:1) (43 mg, 55%).

δ_H (400 MHz, $CDCl_3$): 1.84-1.96 (2H, m, Y-CH_2), 1.93 (1H, d, *J* 3.4, X-NC*H*HCH), 1.96-2.06 (3H, m, X-CH_2 + Y-C*H*H), 2.09-2.22 (2H, m, X-C*H*H + Y-CH*H*), 2.27 (3H, s, X-$NCCH_3$), 2.29-2.37 (1H, m, X-CHH), 2.45 (1H, d, *J* 4.5, X-NCH*H*CH), 2.69-2.73 (1H, m, Y-CH), 3.24-3.30 (1H, m, Y-

CH), 3.45-3.52 (1H, m, Y-CHH), 3.56-3.63 (1H, m, Y-CHH), 3.64-3.72 (1H, m, X-CH), 3.74-3.84 (2H, m, Y-CHH +Y-CHH), 6.94 (1H, dt, *J* 7.5, 1.1, Y-ArH), 7.04 (1H, dd, *J* 8.0, 0.9, Y-ArH), 7.14-7.18 (2H, m, X-ArH+X-ArH), 7.25 (1H, dt, *J* 7.7, 1.6, Y-ArH), 7.40 (1H, dt, *J* 7.6, 1.6, X-ArH), 7.66 (1H, dd, *J* 7.8, 1.5, Y-ArH), 7.93 (1H, dd, *J* 7.8, 1.5, X-ArH).

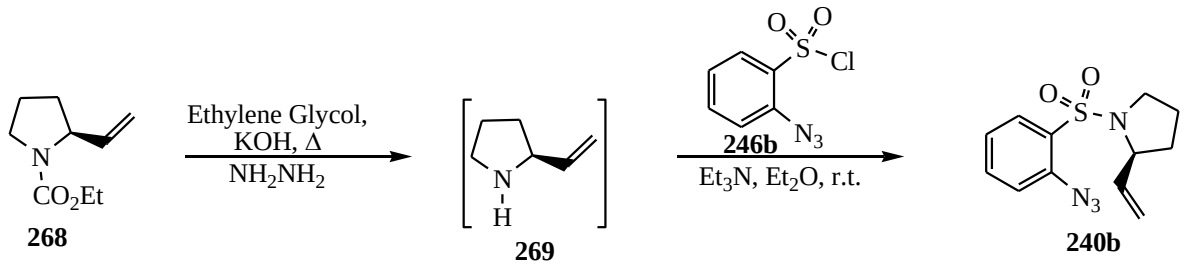
δ_C (100 MHz, $CDCl_3$): 22.4 (X-CH_3), 23.2 (Y-CH_2), 24.2 (X-CH_2), 27.9 (X-CH_2), 30.0 (Y-CH_2), 32.9 (X-CH_2), 45.0 (Y-CH), 46.3 (Y-CH_2), 46.4 (Y-CH_2), 55.6 (X-CH), 58.3 (Y-CH), 122.2 (Y-CH), 123.1 (Y-CH), 125.4 (Y-q), 125.5 (X-CH), 126.4 (X-CH), 127.0 (X-q), 129.8 (X-CH), 130.8 (Y-CH), 131.4 (X-CH), 131.8 (Y-CH), 145.7 (X-q), 150.4 (Y-q), 165.5 (X-q), 166.9 (Y-q), 169.9 (X-q).

υ_{max} (thin film cm^{-1}): 907 (s), 1244 (m), 1320 (m), 1403 (m), 1454 (s), 1614 (s), 1681 (m), 1743 (m), 2876 (w), 2924 (m), 2970 (w).

LRMS (ESI+): Found 215.1 $[M+H]^+$, 237.1 $[M+Na]^+$, 451.2 $[2M+Na]^+$, 665.3 $[3M+Na]^+$.

HRMS (ESI+): Found 215.1179 $[M+H]^+$, $C_{13}H_{15}N_2O$ requires 215.1179.

10.2.6 Synthesis of *N*-(2'-azidobenzenesulfonyl)-2-ethenyl-pyrrolidine.



Scheme 10-13

To a stirring suspension of KOH (4.28 g, 76.5 mmol, 26 eq) in ethylene glycol (15 mL), hydrazine hydrate (0.457 mL, 471 mg, 14.7 mmol, 5 eq) was added under nitrogen followed by the ester protected alkene (497 mg, 2.94 mmol, 1.0 eq), and the whole was heated at reflux (195°C) for 4.5

hours. The reaction mixture was cooled to ambient temperature and was diluted with Et_2O (9 mL) and water H_2O (9 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 5 mL) and dried over NaOH. Et_3N (0.62 mL, 4.41 mmol, 1.5 eq) was added to the ethereal solution containing the amine at 0°C and was stirred for 10 mins under an inert atmosphere of nitrogen before addition of the sulfonic acid chloride in Et_2O, [which was prepared by heating at reflux 2-azidobenzenesulfonic acid (900 mg, 4.41 mmol, 1.5 eq) in 2M solution of oxalyl chloride in DCM (4.4 mL, 8.82 mmol, 3.0 eq) which was concentrated in vacuo and suspended in Et_2O (3 x 10ml)]. The whole was allowed to reach room temperature overnight. The reaction was diluted with water (30ml), the ethereal layer was separated and the aqueous layer was extracted with Et_2O (3 x 10ml). The combined organics were dried ($MgSO_4$), filtered, concentrated in vacuo and purified by silica chromatography (20 g) (EtOAc:Hex;1:4) to yield the product as a yellow oil (163 mg, 20%).

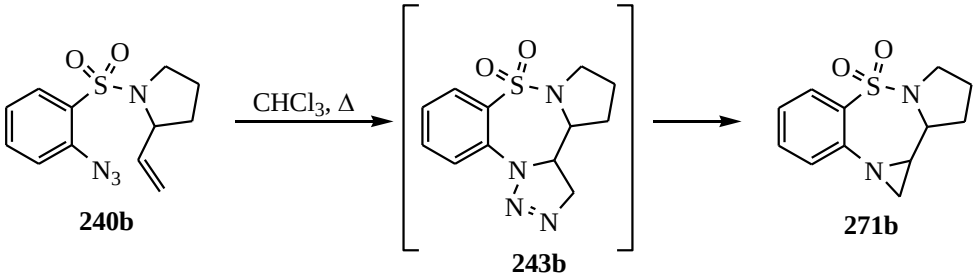
δ_H (400 MHz, $CDCl_3$): 1.30-1.40 (1H, m, C*H*H), 1.83-1.92 (2H, m, CH_2), 2.07-2.10 (1H, m, CH*H*), 2.92-2.99 (1H, m, C*H*H), 3.54-3.57 (1H, m, CH*H*), 3.93-3.98 (1H, m, NCH), 4.37-4.40 (1H, m, CH=C*H*H), 4.54 (1H, dd, *J* 12.6, 17.8, CH=CH*H*), 5.30-5.37 (1H, m, C*H*=CH_2), 7.16 (1H, t, *J* 8.0, ArH), 7.45 (1H, t, *J* 8.4, ArH), 7.83 (1H, d, *J* 8.4, ArH), 7.91 (1H, d, *J* 8.0, ArH).

υ_{max} (thin film cm^{-1}): 926 (m), 1026 (s), 1099 (m), 1157 (m), 1182 (s), 1296 (m), 1330 (m), 1445 (m), 1471 (s), 1518 (m), 1592 (s), 1714 (m), 2137 (s), 2871 (m), 2977 (m).

LRMS (ESI+): Found 301.1 $[M+Na]^+$.

HRMS (ESI+): Found 301.0722 $[M+Na]^+$ requires 301.0730.

10.2.7 Synthesis of Aziridinopyrrolobenzothiadiazepine (**271b**).



240b **243b** **271b**

Scheme 10-14

The *N*-(2'-azidobenzenesulfonyl)-2-ethenyl-pyrrolidine (143 mg, 0.514 mmol) was heated at reflux under nitrogen in $CHCl_3$ (10 mL) for 4 days. The crude product was concentrated and analysed by NMR to show little reaction. The crude product was dissolved in toluene (10 mL) and heated to reflux for 24 hours. The reaction was allowed to reach room temperature before the solvent was removed and the crude was purified by silica chromatography (20 g) (EtOAc:Hex;1:2) to yield the aziridine product (23 mg, 18%).

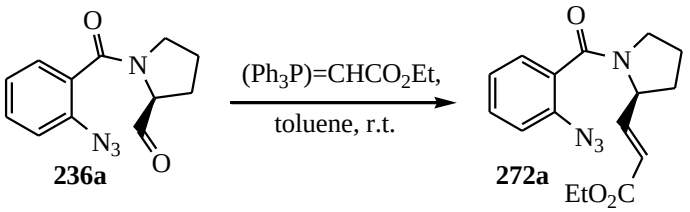
δ_H (500 MHz, $CDCl_3$): 1.81-2.07 (4H, m, 2 x CH_2), 2.91-2.95 (1H, m, C*H*H), 3.32 (1H, dd, *J* 9.9, 11.7, CHCHC*H*H), 3.50 (1H, apparent t, *J* 7.7, CH*H*), 3.57 (1H, dd, *J* 3.9, 11.7, CHCHCH*H*), 3.89 (1H, apparent dt, *J* 2.9, 7.9, SO_2NCH), 4.84-4.87 (1H, NCH_2CH), 6.70 (1H, d, *J* 8.1, ArH), 6.84 (1H, t, *J* 7.8, ArH), 7.20 (1H, dt, *J* 7.8, 1.3, ArH), 7.70 (1H, dd, *J* 8.1, 1.2, ArH).

δ_C (125MHz, $CDCl_3$): 24.5 (CH_2), 25.8 (CH_2), 43.4 (CH_2), 49.2 (CH_2), 59.3 (CH), 62.9 (CH), 118.6 (CH), 119.9 (CH), 125.7 (q), 129.2 (CH), 132.7 (CH), 144.6 (q).

υ_{max} (thin film cm^{-1}): 759 (s), 1009 (m), 1037 (m), 1081 (s), 1127 (s), 1274 (m), 1333 (s), 1482 (s), 1520 (m), 1591 (s), 2926 (m), 2970 (w), 3066 (m), 3362 (w).

LRMS (ESI+): Found 273.1 $[M+Na]^+$, 523.1 $[2M+Na]^+$, $C_{12}H_{14}N_2NaO_2S$ requires 273.1 .

10.2.8 Synthesis of (*S*)-*N*-(2'-azidobenzoyl)-2-(carbethoxy-1"-ethenyl)-pyrrolidine.



236a **272a**

Scheme 10-15

The aldehyde (273 mg, 1.12 mmol, 1.0 eq) was dissolved in toluene (10 mL). (Carbethoxymethylene) triphenylphosphorane (390 mg, 1.12 mmol, 1.0 eq) was added in one portion and the whole was stirred at room temperature in an inert atmosphere of nitrogen for 12 hours before being concentrated and purified by silica chromatography (40 g) (EtOAc:Hex; 3:2) to yield the product as a yellow oil as a mixture of rotamers (a:b;2:3;178 mg, 51%).

δ_H (400 MHz, $CDCl_3$): 1.29 & 1.31 (3H, t, *J* 7.1, 2 x $COCH_2CH_3$), 1.80-1.99 & 2.01-2.43 (4H, m, CH_2), 3.21-3.28 & 3.78-3.86 (1H, m, C*H*H), 3.34-3.40 & 3.69-3.75 (1H, m, CH*H*), 4.13 & 4.21 (2H, quartet, *J* 7.1 & 7.1, $COCH_2CH_3$), 4.24-4.30 & 4.96-5.00 (1H, m, $NCHCH_2$), 5.46 & 6.15 (1H, dd & d, *J* 15.6, 1.1 & 15.6, $CHCHCO_2Et$), 6.59 & 6.94 (1H, dd & dd, *J* 15.6, 6.4 & 15.6, 4.9, $CHCHCO_2Et$), 7.12 (1H, t, *J* 7.5, ArH), 7.14 (1H, d, *J* 7.3, ArH), 7.19-7.25 (1H, m, ArH), 7.40 & 7.45 (2H, 2 x dt, *J* 7.8, 1.6, & 7.8, 1.6, ArH).

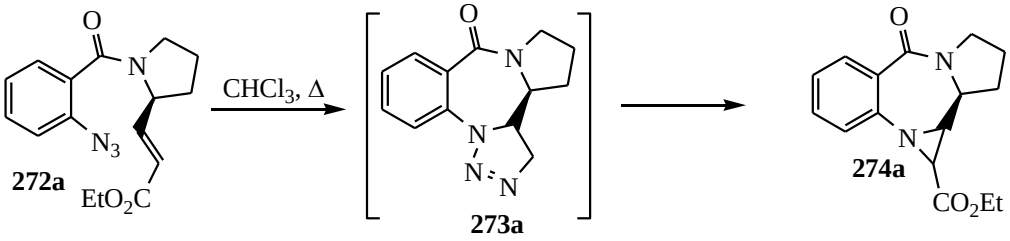
δ_C (100 MHz, $CDCl_3$): 14.2/14.3 (CH_3), 22.3/23.8 (CH_2), 30.5/32.1 (CH_2), 46.1/48.2 (CH_2), 57.2 (CH), 60.4/60.6 (CH_2), 118.5 (CH), 121.2/121.3 (CH), 124.9/125.2 (CH), 127.9 (CH), 129.1/129.5 (q), 130.6 (CH), 133.7/136.2 (q), 146.5 (CH), 165.8/166.5 (q), 167.1/167.4 (q).

υ_{max} (thin film cm^{-1}): 753 (s), 1043 (m), 1093 (m), 1180 (s), 1301 (s), 1369 (m), 1414 (s), 1451 (s), 1475 (m), 1633 (s), 1716 (s), 2130 (s), 2238 (w), 2880 (m), 2979 (m).

LRMS (ESI+): Found 315.1 $[M+H]^+$, 337.1 $[M+Na]^+$, 651.3 $[2M+Na]^+$.

HRMS (ESI+): Found 315.1451 $[M+H]^+$, $C_{16}H_{19}N_4O_3$ requires 315.1452.

10.2.9 Synthesis of Aziridinopyrrolobenzodiazepine (**274**).



Scheme 10-16

The substituted alkene (178 mg, 0.567 mmol) was heated at reflux under nitrogen in $CHCl_3$ (10 mL) for 48 hours before being concentrated and purified by silica chromatography (20 g) (EtOAc:Hex ;3:2) to yield the product as a mixture of diastereoisomers (a:b;1:1) in the form of a yellow oil (47 mg, 30%).

δ_H (400 MHz, $CDCl_3$)[mixture of isomers]: 1.23 (3H, t, *J* 7.1, $COCH_2CH_3$, isomer "a"), 1.29 (3H, t, *J* 7.1, $COCH_2CH_3$, isomer "b"), 1.74-1.80 (2H, m, CH_2),1.81-2.27 (4H, m, 2 x CH_2), 2.77 (1H, d, *J* 2.6, $CHCO_2Et$), 3.08 (1H, dd, *J* 9.6, 2.6, NCH), 3.37 (1H, dt, *J* 8.7, 2.7, NCH),3.57 (1H, dt, *J* 7.3, 12.0, CHH), 3.66-3.73 (4H, m, 2 x CH_2), 3.74-3.79 (1H, m, CH), 3.78-3.87 (1H, m, CHH), 4.20 (2H, quartet, *J* 7.1, $COCH_2CH_3$, isomer "a"), 4.23 (2H, quartet, *J* 7.1, $COCH_2CH_3$, isomer "b"), 4.38 (1H, d, *J* 10.8, CH), 6.69 (1H, d, *J* 7.4, ArH), 6.94 (1H, dt, *J* 7.5, 0.9, ArH), 7.01 (1H, dt, *J* 7.5, 1.0, ArH), 7.07 (1H, d, *J* 8.0, ArH), 7.19 (1H, dt, *J* 7.6, 1.6, ArH), 7.28 (1H, dt, *J* 7.7, 1.6, ArH), 7.70 (2H, dd, *J* 7.8, 1.8, ArH).

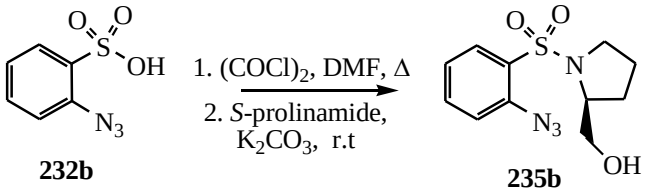
δ_C (100 MHz, $CDCl_3$): 14.2 (CH_3), 14.5 (CH_3), 23.1 (CH_2), 25.6 (CH_2), 29.5 (2 x CH_2), 42.6 (CH), 46.4 (CH_2), 47.0 (CH), 50.4 (CH), 56.6 (CH), 57.2 (CH), 60.1 (CH), 61.4 (CH_2), 62.0 (CH_2), 68.0 (CH_2), 121.3 (CH), 122.0 (CH), 123.1 (CH), 123.3 (CH), 125.3 (q), 126.6 (q), 130.7 (CH), 131.0 (CH), 132.0 (CH), 132.2 (CH), 142.9 (q), 148.1 (q), 166.0 (q), 166.3 (q), 167.9 (q), 168.8 (q).

υ_{max} (thin film cm^{-1}): 752 (m), 1024 (s), 1178 (s), 1217 (s), 1260 (s), 1372 (m), 1454 (m), 1503 (m), 1602 (s), 1622 (s), 1725 (s), 2871 (m), 2926 (m), 2977 (m).

LRMS (ESI+): Found. 309.1 $[M+Na]^+$.

HRMS (ESI+): Found 309.1206 $[M+Na]^+$, $C_{16}H_{18}N_2NaO_3$ requires 309.1210.

10.2.10 Synthesis of *N*-(2'-azidobenzenesulfonyl)prolinol.



232b **235b**

Scheme 10-17

2-Azido-benzenesulfonic acid (2.95 g, 14.83 mmol, 2.5 eq) was heated at reflux in a 2M solution of $(COCl)_2$ in DCM (14.8 mL, 29.6 mmol, 5 eq) with a drop of DMF under an inert atmosphere of nitrogen for 5 hours. The reaction was allowed to reach room temperature before the crude acid chloride was concentrated in vacuo and redissolved in DCM (3 x 10 mL) to yield the crude sulfonyl chloride.

K_2CO_3 (3.3 g, 23.7 mmol, 4 eq) in water (10 mL) was added in one portion to a stirring solution of *S*-prolinol (600 mg, 5.93 mmol, 1 eq) in DCM (15 mL). The crude acid chloride suspended in DCM (10 mL) was added slowly and the whole was stirred for 18 hours. The organic layer was separated and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organics were dried ($MgSO_4$), filtered, concentrated to give the product as a pure orange oil (1.61 g, 96%).

δ_H (400 MHz, $CDCl_3$): 1.67-1.78 (1H, m, C*H*H), 1.79-1.99 (3H, m, CH*H* + CH_2), 2.79 (1H, bs, CH_2O*H*), 3.38 (1H, dt, *J* 6.3, 10.2, NCH*H*), 3.49-3.56 (1H, m, NC*H*H), 3.62 (1H, dd, *J* 5.6, 11.5,

C*H*HOH), 3.70 (1H, dd, *J* 4.2, 11.5, CH*H*OH), 4.02-4.08 (1H, m, C*H*CH_2OH), 7.27 (1H, dt, *J* 1.0, 7.8, ArH), 7.32 (1H, dd, *J* 0.9, 8.0, ArH), 7.62 (1H, dt, *J* 1.5, 7.8, ArH), 8.02 (1H, dd, *J* 1.4, 8.0, ArH).

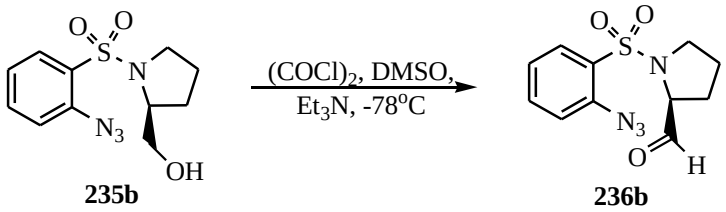
δ_C (100 MHz, $CDCl_3$): 24.7 (CH_2), 29.0 (CH_2), 49.5 (CH_2), 61.8 (CH), 65.5 (CH_2), 119.9 (CH), 124.8 (CH), 129.0 (q), 132.6 (CH), 134.2 (CH), 138.2 (q).

υ_{max} (thin film cm^{-1}): 759 (s), 819 (m), 1043 (s), 1069 (s), 1146 (s), 1199 (m), 1264 (m), 1287 (s), 1323 (s), 1439 (m), 1471 (s), 1583 (m), 2120 (s), 2876 (w), 2953 (w), 3172-3593 (mbr).

LRMS (ESI+): Found 305.1 $[M+Na]^+$, 587.1 $[2M+Na]^+$.

HRMS (ESI+): Found 305.0676 $[M+Na]^+$, $C_{11}H_{14}N_4NaO_3S$ requires 305.0679.

10.2.11 Synthesis of *N*-(2'-azidobenzenesulfonyl)prolinal.



235b **236b**

Scheme 10-18

A 2M solution of oxalyl chloride in DCM (1.88 mL, 3.75 mmol, 1.2 eq) was diluted with DCM (10 mL) and cooled to -78°C under nitrogen. DMSO (0.532 mL, 586 mg, 7.5 mmol, 2.4 eq) in DCM (10 mL) and the alcohol (800 mg, 3.125 mmol, 1 eq) in DCM (5 mL) were added respectively over 10mins. The whole was maintained at -78°C for 30 mins before dropwise addition of Et_3N (2.18 mL, 1.581 g, 15.6 mmol, 5 eq) and the whole was allowed to reach room temp. The reaction was quenched with a mixture of Et_2O (10 mL) and H_2O (10 mL). The organic layer was separated and

the aqueous phase was extracted with DCM (3 x 10 mL). The combined organics were dried ($MgSO_4$), filtered, concentrated and purified by silica chromatography (20 g) (EtOAc:Hex; 2:3) to yield the product as a white solid (572 mg, 72%), which degraded rapidly and needed to be used quickly in subsequent reaction.

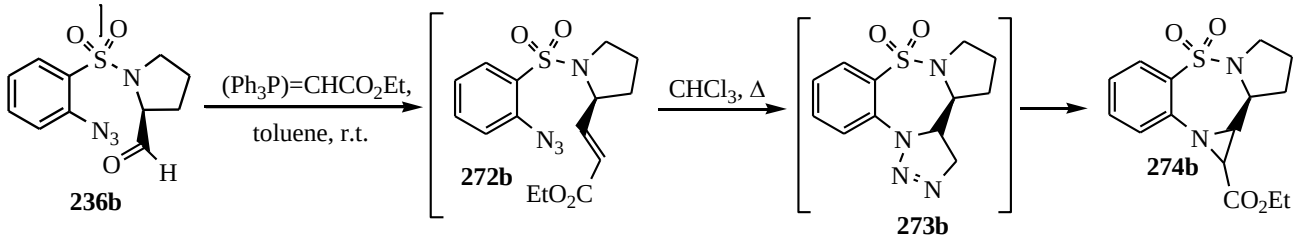
δ_H (400 MHz, $CDCl_3$): 1.83-1.95 (2H, m, CH_2), 1.98-2.09 (1H, m, C*H*H), 2.15-2.23 (1H, m, CH*H*), 3.40 (1H, dt, *J* 9.7, 7.2, NC*H*H), 3.57 (1H, ddd, *J* 5.5, 6.8, 9.7, CH*H*), 4.47 (1H, ddd, *J* 1.9, 4.5, 8.5, C*H*CHO), 7.28 (1H, dt, *J* 7.8, 1.0, ArH), 7.34 (1H, dd, *J* 8.0, 0.9, ArH), 7.64 (1H, dt, *J* 7.8, 1.6, ArH), 8.03 (1H, dd, *J* 8.0, 1.5, ArH), 9.72 (1H, d, *J* 1.9, CHO).

δ_C (100 MHz, $CDCl_3$): 25.0 (CH_2), 27.7 (CH_2), 48.8 (CH_2), 67.1 (CH), 119.9 (CH), 124.9 (CH), 128.9 (q), 132.5 (CH), 134.4 (CH), 138.2 (q), 200.5 (CH).

υ_{max} (thin film cm^{-1}): 820 (m), 999 (m), 1080 (s), 1122 (s), 1156 (s), 1265 (m), 1287 (s), 1332 (s), 1439 (m), 1471 (s), 1603 (m), 1730 (s), 2122 (s), 2953 (w).

MS: Product decomposed before analysis was possible.

10.2.12 Synthesis of aziridinopyrrolobenzothiadiazepine (**274b**).



Scheme 10-19

The aldehyde (572 mg, 2.25 mmol, 1.0 eq) was dissolved in toluene (12 mL) and (carbethoxymethylene) triphenylphosphorane (785 mg, 2.25 mmol, 1 eq) was added in one portion

and the whole was stirred at room temperature for 18 hours. The reaction was concentrated and purified by silica chromatography (40 g) (EtOAc:Hex; 3:2) to yield, as a single isomer, the aziridine as a yellow oil (123 mg, 17%).

δ_H (500 MHz, $CDCl_3$): 1.41 (3H, t, *J* 7.1, $COCH_2CH_3$), 1.75-1.80 (1H, m, C*H*H), 1.87-2.01 (1H, m, CH*H*), 2.09-2.16 (1H, m, C*H*H), 2.27-2.35 (1H, m, CH*H*), 3.19 (1H, ddd, *J* 5.0, 9.6, 9.6, C*H*H), 3.67-3.73 (2H, m, CH*H* + CHC*H*CH), 4.08 (1H, ddd, *J* 2.1, 7.4, 9.8, SO_2NCH), 4.33-4.40 (2H, m, $COCH_2CH_3$), 4.94 (1H, d, *J* 10.7, C*H*CO_2Et), 7.43 (1H, dt, *J* 7.7, 1.1, ArH), 7.55 (1H, dd, *J* 8.0, 1.1, ArH), 7.60 (1H, dt, *J* 7.7, 1.5, ArH), 8.04 (1H, dd, *J* 8.0, 1.5, ArH).

δ_C (125MHz, $CDCl_3$): 14.1 (CH_3), 22.7 (CH_2), 28.9 (CH_2), 46.4 (CH_2), 60.7 (CH), 61.8 (CH), 63.0 (CH_2), 85.4 (CH), 123.8 (CH), 126.6 (CH), 128.5 (CH), 131.6 (q), 133.6 (CH), 138.4 (q), 167.3 (q).

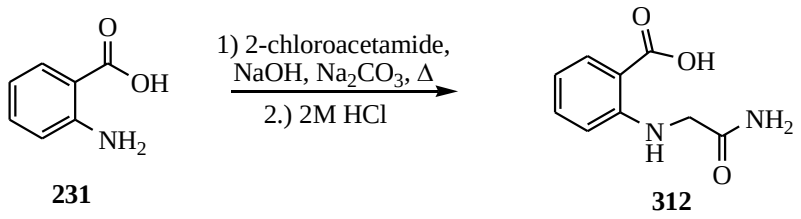
υ_{max} (thin film cm^{-1}): 1035 (m), 1066 (m), 1092 (s), 1135 (m), 1167 (s), 1205 (m), 1247 (m), 1271 (m), 1344 (s), 1469 (s), 1503 (m), 1589 (m), 1738 (s), 2981 (m).

LRMS (ESI+): Found 345.1 $[M+Na]^+$, 723.2 $[2M+Na]^+$.

HRMS (ESI+): Found 345.0875 $[M+Na]^+$, $C_{15}H_{18}N_2NaO_4S$ requires 345.0879.

11 Experimental: Synthesis of other BDs via the cycloaddition of DPP.

11.1.1 Synthesis of 2-(Carbamoylmethylamino)benzoic acid.



231 **312**

Scheme 11-1

Anthranilic acid (2.74 g, 20.0 mmol, 1 eq) was dissolved in water (20 mL) and NaOH (800 mg, 20.0 mmol, 1 eq) was added. A solution of Na_2CO_3 (2.12 g, 20.0 mmol, 1 eq) in water (20 mL) was added in one portion followed by dropwise addition of 2-chloroacetamide (3.80 g, 40.6 mmol, 2.03 eq) and the whole was heated at reflux for 18 hours. The reaction was allowed to reach ambient temperature before being acidified with 2M HCl until a white precipitate persisted at around pH4. The reaction was stored in the fridge overnight and the solid was collected by vacuum filtration to give the product as a pale pink solid (2.05 g, 53%).

δ_H (400 MHz, d_6-DMSO): 3.78 (2H, s, C*H*$_2$CONH$_2$), 6.50 (1H, d, *J* 8.3, ArH), 6.57 (1H, t, *J* 7.2, ArH), 7.19 (1H, bs, CON*H*H), 7.36 (1H, dt, *J* 7.2, 1.6, ArH), 7.53 (1H, bs, CONH*H*), 7.79 (1H, dd, *J* 7.9, 1.6, ArH), 8.15 (1H, bs, N*H*CH$_2$), 12.60 (1H, bs, CO$_2$H).

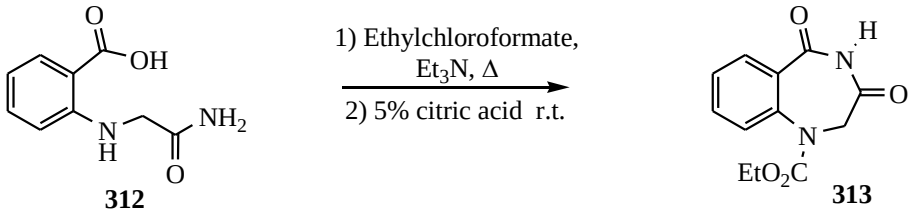
δ_C (100 MHz, d_6-DMSO): 45.9 (CH$_2$), 111.1 (q), 111.8 (CH), 115.0 (CH), 132.1 (CH), 134.9 (CH), 150.5 (q), 170.1 (q), 171.4 (q).

υ_{max} (thin film cm^{-1}): 1114 (m), 1152 (s), 1167 (m), 1220 (s), 1271 (m), 1505 (m), 1557 (m), 1581 (m), 1604 (s), 1661 (s), 3400-3450 (bw).

LRMS (ESI+): Found 217.1 $[M+Na]^+$.

HRMS (ESI+): Found 217.0582 $[M+Na]^+$, $C_9H_{10}N_2NaO_3$ requires 217.0584.

11.1.2 Synthesis of 1-Ethoxycarbonyl-1*H*-1,4-benzodiazepin-3,5-dione.



Scheme 11-2

2-(Carbamoylmethylamino)-benzoic acid (2.0 g, 10.3 mmol, 1 eq) was heated at reflux in MeCN (20 mL) with Et_3N (5.0 mL, 36 mmol, 3.53 eq) for 15mins. The reaction was allowed to reach ambient temperature before ethylchloroformate (2.0 mL, 21 mmol, 2.04 eq) was added dropwise and the whole was brought back to reflux for 75 mins. The reaction was allowed to reach ambient temperature before being poured directly into 5% citric acid (2.5g in 50 mL of water) and diluted with ice to a total volume of 100 mL (i.e. 30g of ice) and the whole was stirred for 1 hour. The precipitate was collected via vacuum filtration and washed with water to give the product as a pale brown solid (1.22 g, 48%).

δ_H (500 MHz, $CDCl_3$): 1.18 (3H, bm, $COCH_2CH_3$), 3.83 (1H, bs, COC*H*H), 4.17 (2H, bm, $COCH_2CH_3$), 5.08 (1H, bs, COCH*H*), 7.23-7.36 (1H, m, ArH), 7.38 (1H, t, *J* 7.9, ArH), 7.55 (1H, t, *J* 7.4, ArH), 8.07 (1H, d, *J* 7.5, ArH), 8.47 (1H, bs, NH).

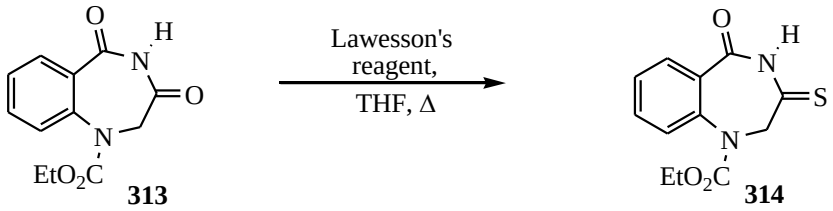
δ_C (125MHz, $CDCl_3$): 14.4 (CH_3), 53.0 (CH_2), 63.1 (CH_2), 127.4 (q), 127.6 (CH), 127.8 (CH), 133.0 (CH), 134.0 (CH), 140.5 (q), 153.9 (q), 164.2 (q), 171.0 (q).

υ_{max} (thin film cm^{-1}): 1037 (m), 1098 (m), 1134 (m), 1212 (s), 1240 (m), 1348 (s), 1380 (m), 1456 (m), 1487 (m), 1653 (m), 1707 (s), 2895 (w), 3064 (w), 3139 (w).

LRMS (ESI+): Found 271.1 $[M+Na]^+$, 519.2 $[2M+Na]^+$.

HRMS (ESI+): Found 271.0687 $[M+Na]^+$, $C_{12}H_{12}N_2NaO_4$ requires 271.0689.

11.1.3 Synthesis of 1-Ethoxycarbonyl-1*H*-1,4-benzodiazepin-5-on-3-thione.



Scheme 11-3

The diketone (610 mg, 2.46 mmol, 1 eq) was dissolved in dry THF (10 mL), Lawesson's reagent (497 mg, 1.23 mmol, 0.5 eq) was added in one portion and the whole was stirred at room temperature for 1 hour before being heated at reflux for 2 hours. The reaction mixture was concentrated and purified by silica chromatography (70 g) (EtOAc:Hex; 1:3) to yield the product as a yellow solid (162 mg, 25%).

δ_H (500 MHz, $CDCl_3$): 1.27 (3H, bs, $COCH_2CH_3$), 4.11-4.30 (3H, bm, $COCH_2CH_3$ + COCHH), 5.56 (1H, bs, COCHH), 7.43 (1H, t, *J* 7.8, ArH), 7.44 (1H, d, *J* 7.8, ArH), 7.63 (1H, t, *J* 8.0, ArH), 8.18 (1H, d, *J* 8.0, ArH), 10.08 (1H, bs, NH).

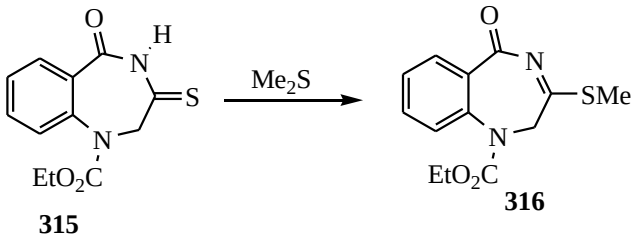
δ_C (125MHz, $CDCl_3$): 14.3 (CH_3), 59.8 (CH_2), 63.0 (CH_2), 126.5 (q), 127.1 (CH), 127.4 (CH), 133.4 (CH), 134.2 (CH), 141.3 (q), 153.5 (q), 162.7 (q), 204.6 (q).

υ_{max} (thin film cm^{-1}): 885 (m), 1049 (s), 1154 (s), 1223 (s), 1272 (s), 1313 (s), 1353 (s), 1379 (s), 1421 (m), 1453 (m), 1498 (m), 1597 (m), 1648 (s), 1716 (s), 2964 (w), 3105 (m), 3173 (m).

LRMS (ESI+): Found 265.1 $[M+H]^+$, 287.0 $[M+Na]^+$, 551.1 $[2M+Na]^+$, $C_{12}H_{13}N_2O_3S$ requires 265.1.

Structure confirmed by X-Ray crystallographic analysis (see discussion).

11.1.4 Attempted S-Methylation of the 1,4-benzodiazepin-5-on-3-thione.



315 **316**

Scheme 11-4

The thione (572 mg, 2.16 mmol, 1 eq) was suspended in dimethyl sulfate (0.822 mL, 1.093 g, 8.67 mmol, 4 eq) and stirred overnight. The suspension was dissolved ih DCM (4 mL) and heated in an oil bath at 40°C for 6 hours. More dimethyl sulfate (0.45 mL) was added and the whole was stirred overnight at 40°C. The reaction was concentrated and suspended in ether (10 mL). The reaction was quenched with 10% K_2CO_3 (20 mL) and the ether layer was separated. The aqueous phase was extracted with DCM (3 x 10 mL). The combined organics were dried, filtered and concentrated. Purification by silica chromatography (30 g) (EtOAc:Hex;2:3) gave no identifiable product.

To conclude this thesis, this page will give a brief personal overview of the project. It has been a great project and the main success was the cyclisations of the alkynes and the azides using the Bestmann-Ohira reagent (discussed in section 3.1). This could be expanded to include other amino acids derivatives (for example cystine, methionine etc..). The chemistry of the nitrile systems (discussed in section 3.2) could be further explored to establish if the amino-1,4-benzodiazepines or the tetrazolo-1,4-benzodiazepines are synthesised.

The synthesis of the PBDs via a cyclopropenone addition (Chapter 6), could be further explored by the successful *S*-alkylation of the thioamide and then the addition of DPP.

The chirality of the products are assumed throughout and have not been established during the synthesis of the compounds. Further work could be to establish the stereochemistry of the major products in this thesis.

Further work could be carried out to establish the problem that I had in the nitro reduction to the amine discussed in Chapter 5. This would then lead onto a variety of avenues, firstly the work with the alkene and azides could be further explored. Also the chemistry that is established could be used to synthesis dimers via linking though the the OH on the benzene ring. The chemistry of section 3.1 and then 3.2 could also be applied to afford a vast array of compounds.

Other further work could include a variety of different substituted alkenes discussed in Chapter 4 could be synthesied i.e. starting from a variety of 1,3 dienes for an example 1,3-butidiene and the compounds could be tested for their biological activity

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