UNIVERSITY OF SOUTHAMPTON

Approaches to functionalised amine-based ligands for radiopharmaceutical delivery systems.

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A thesis submitted for the degree of Doctor of Philosophy

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ABSTRACT

FACULTY OF SCIENCE

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Approaches to functionalised amine-based ligands for radiopharmaceutical delivery systems

by Paul Michael Bergin

This thesis describes the results of an investigation into the synthesis and behaviour of tetra-aza ligands intended for use as novel diagnostic radiopharmaceutical agents through technetium complexation and attachment to bioactive targeting groups. The literature concerning radiopharmaceutical imaging agents is reviewed. The main body of the thesis concerns a study focussed on two ligand classes, the 1,4,8,11-tetraazaundecanes (TAs) and 3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioximes (propylene amine oximes; PnAOs), in which a single arylmethyl substituent is attached at the apical position (C-6), either directly or via an ether-linkage. A number of routes have been explored to TA-derivatives bearing a benzyl or 4-bromobenzyl group and bis-oxo-TA derivatives have been successfully prepared. However, conversion of these into their saturated analogues has proved difficult.

Methods for the attachment of sulfonamide substituents to the arylmethyl side-arm have also been developed.

In a parallel study, three novel oxotechnetium(V) complexes of analogous apically substituted PnAO derivatives have been prepared and characterised by single-crystal X-ray diffraction. Comparison of the structures of these complexes with literature data and the results of recent structural studies of other transition metal-ion complexes with such ligands gives useful insight into both the effect of apical substitution and the ability of other metal ions to 'mimic' the Tc=O core.

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I would firstly like to thank my supervisor, Dr Martin Grossel, without whose patience, encouragement and enthusiasm I could not have submitted this work.

I also thank the current and past members of the Grossel group for making our lab the friendliest in Southampton. My thanks go to those there at the beginning: Paul (for understanding the woes brought by amine chemistry and radioactivity), Enrique (for his infectious Venezuelan humour), Simon (for a calmness epitomised by managing to juggle ether inches from my free-flame distillation), Andrew (for introducing me to the wonders of the Web) and, in particular, Robert (for many helpful synthetic discussions over the bar at The Crown). Those who have arrived since have continued the fine tradition: Fred (for turning a blind eye to disappearing glassware), John (for being the only teetotaller to be first in the queue for a pub crawl), Peter (for his undoubted skills as a crystallographer), Dan (for his sympathetic depression and insomnia), Chris (for making me believe that *I* have a sane attitude towards women), Sam (for introducing me to Reef and a new level of hangover), Muhanna and Mustafa (for jointly providing a formidable strike force on the football pitch) and Jaesun (for proving that you don't need a Y-chromosome to work in the group).

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Finally, and most importantly, I thank my mum, dad and brother, whose continuous encouragement and support have allowed me to stumble on this far.

Abbreviations and Nomenclature

APCI	Atmospheric Pressure Chemical Ionisation
Bn	Benzyl [$PhCH_2$-]
Boc	*tert*-Butoxycarbonyl
b.p.	Boiling point
CI	Chemical ionisation
COSY	Correlated SpectroscopY
CPK	Corey-Pauling-Koltun
DCC	*N,N'*-Dicyclohexylcarbodiimide
DEPT	Distortionless Enhancement by Polarisation Transfer
DCM	Dichloromethane
Diethyl malonate	Diethyl propanedioate
DMF	*N,N'*-Dimethyl formamide
DMSO	Dimethyl sulfoxide
EI	Electron ionisation
ES	Electrospray (Mass Spectrometry)
Et	Ethyl
Ethylenediamine	1,2-Ethanediamine
Fmoc	9-Fluorenylmethoxycarbonyl
FSF	Fibrin Stabilising Factor
FTIR	Fourier Transform Infra-red spectroscopy
GP	Glycoprotein
i-Pr	*iso*-Propyl [$(CH_3)_2CH$-]
Me	Methyl
m.p.	Melting point
NMR	Nuclear Magnetic Resonance

(P)	Protecting Group (unspecified)
PET	Positron Emission Tomography
Ph	Phenyl
PnAO	Propylene amine oxime [3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioxime]
RCP	Radiochemical purity
SPECT	Single Photon Emission Computed Tomography
TA	1,4,8,11-Tetraazaundecane
Tf	Trifluoromethanesulfonyl [CF_3SO_2-]
TFA	Trifluoroacetic acid [CF_3CO_2H]
THF	Tetrahydrofuran
Tr	Trityl [Ph_3C-]
Ts	*p*-Toluenesulfonyl [*p*-CH_3-C_6H_4-SO_2-]
Z	Benzyloxycarbonyl [$C_6H_5CH_2OCO$-]

Nitrogen is the element of faction neatly dividing organic chemists into camps. Those who have mastered its vagaries, are undaunted by the prospect of its reactivity. Then there are those in the minority antipodal camp (like the author) who suspect that nitrogen is best confined to a cylinder and used to shield precious reactions and reagents from the ravages of air and moisture!

P.J. Kocienski

1 Introduction

1.1 Nuclear Medicine

Techniques such as X-ray, ultrasound and magnetic resonance imaging (MRI) are invaluable tools for the diagnosis of disease, providing detailed images of anatomical features. However, they provide only limited information about biochemical and physiological function.[1] Such data may be obtained through nuclear medicine, where the distribution of a radionuclide within the body is monitored to give information about the structure and function of a target organ or system. The radionuclide may be present simply as an atom (*e.g.* ^{133}Xe), an ion (*e.g.* $^{201}Tl^{+}$) or, more commonly, it may be incorporated into a larger molecule or complex, to form a radiopharmaceutical. The radiopharmaceutical is introduced into the body, where either perfusion (blood-flow) or a specific receptor-binding interaction causes it to localise in the tissue or organ under investigation. For imaging (diagnostic) purposes, minimum interaction with tissues should occur, in order to facilitate the external detection of the emission and to minimise the radioactive dose delivered to the patient. For this reason, gamma (γ) and positron (β^{+}) emitting nuclei are employed and the detection of the resulting radiation leads to the techniques of Single Photon Emission Computed Tomography (SPECT)[2] and Positron Emission Tomography (PET),[3] respectively.

1.1.1 Gamma-Emitting Isotopes

Gamma radiation, which is electromagnetic in nature, results from the relaxation of an excited nuclear state, with the observed photon corresponding to the energy difference between the two states. It is highly penetrating and interacts only weakly with body tissues. For the purpose of medical imaging, gamma radiation of energy 80 – 300 keV is required, with the range 100 – 200 keV being considered optimal for the instrumentation currently available in Nuclear Medicine departments. The most frequently used detector, the Anger camera, consists of an array of sodium iodide

crystals activated with thallium. Incident gamma radiation causes the ejection of a core electron, which imparts its kinetic energy to the crystal matrix, resulting in the emission of photons. A photomultiplier tube or photodiode converts the light into an electrical pulse, which may then be converted into a graphical display for diagnosis (Figure 1.1).[4] The resolution obtained using a conventional camera (*ca.* 10 mm) may be enhanced by the use of tomographic methods.[5]

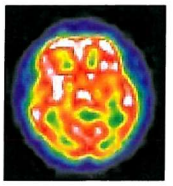


Figure 1.1: Ceretec brain scan

1.1.2 Positron-Emitting Isotopes

A positron (positively charged electron) may be viewed as the charged particle ejected from the nucleus upon the conversion of a proton to a neutron. The mass numbers of the parent and daughter isotope are the same, while the atomic number decreases by one. An emitted positron rapidly encounters an electron in the environment, resulting in the annihilation of the two particles and the production of two, collinear gamma photons each with an energy of 511 keV. Although specialised equipment is required for the coincidence detection of the two photons, this unique feature gives rise to the high resolution of PET scans (*ca.* 3mm).[5]

$$ {}^{1}_{1}p^{+} \rightarrow {}^{1}_{0}n + {}^{0}_{1}\beta^{+} $$

$$ {}^{11}_{6}C \rightarrow {}^{11}_{5}B + \beta^{+} $$

1.1.3 Radionuclides

Since the vast majority of pharmaceuticals are organic molecules, a suitable isotope of carbon might be considered as the ideal radionuclide for incorporation into a radiopharmaceutical. However, while carbon-11 is a positron emitter, its short half-life (20.3 min) and the requirement of a proximate cyclotron for production of the isotope have precluded the general clinical application of ^{11}C-based radiopharmaceuticals. Similar problems have also prevented the widespread use of positron-emitting isotopes of other elements that are common constituents of organic molecules, *e.g.* ^{13}N, $t_{½}$ = 9.97 min and ^{15}O, $t_{½}$ = 2.03 min. The use of such isotopes has largely been confined to research applications but, as isotopes of atoms naturally occurring in biologically-active molecules, they have been valuable tools in the investigation of small molecule-receptor interactions. The univalent halogen isotopes ^{18}F (β^+, $t_{½}$ = 109.7 min) and ^{123}I (γ, $t_{½}$ = 13 h) have also been incorporated covalently into bioactive small molecules to allow the probing of interactions with receptors.[6,7] While such a modification may be expected not to alter significantly the biodistribution of the labelled compound relative to that of the unlabelled molecule,[1] the rapid and efficient covalent incorporation of the radionuclide immediately prior to administration to the patient provides a considerable synthetic challenge.

1.1.3.1 Desirable Properties

A diverse range of properties would be required from the "ideal" radionuclide for SPECT. The isotope should be readily available from an on-site generator and should decay to a long-lived daughter isotope by γ-emission with an energy of 100 – 200 keV that is not accompanied by any particulate radiation. The half-life should be between a few hours and one day, in order to allow sufficient time for the necessary chemical preparation and the imaging procedure itself while minimising the radioactive dose to the patient. In practice, the radionuclides most closely approaching this ideal are metals, and the field of radiopharmaceuticals has been dominated by the design and preparation of ligands to bind radioactive metal ions, producing complexes that may be administered to the patient.

1.1.4 Radiopharmaceuticals

Metal-based radiopharmaceuticals may be broadly divided into two categories: metal-essential and metal-tagged. In the former case, the biological properties of the complex as a whole (*e.g.* charge, lipophilicity, stability) determine its distribution within the body, while in the latter system, the metal-chelating group is covalently attached to a carrier molecule (*e.g.* a receptor-specific small molecule or a monoclonal antibody), which directs localisation within the body. In such a compound the metal may be regarded as being "simply along for the ride".[1] However, the need to append a chelating moiety may produce a compound of significantly increased molecular weight, hindering transport across cell membranes.[8] The attachment site must also be carefully chosen to be in a region where the receptor will tolerate the increased steric bulk. Such problems with the conjugate approach have lead to recent investigations into an integrated approach, where the immediate co-ordination sphere around the metal has been designed to mimic a biologically active molecule (Figure 1.2).

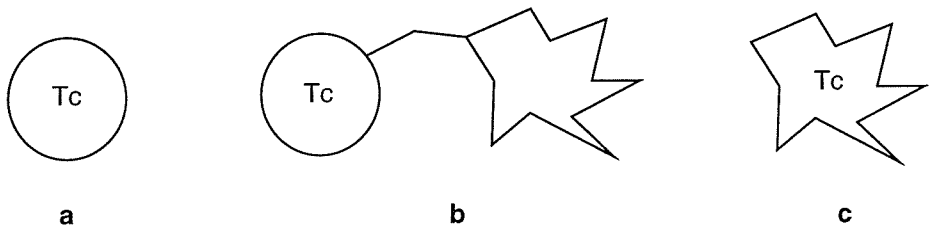


Figure 1.2: Schematic representations of a) technetium-essential, b) technetium-tagged (conjugate) and c) integrated radiopharmaceuticals.

1.1.5 Therapy

More recently, investigations have begun into potential therapeutic applications of nuclear medicine. These demand the accurate delivery of a sterilising dose of ionising radiation to the site of a disease (*e.g.* a tumour). Since the objective in this case is cell destruction, particulate emissions are employed. An alpha-particle (α) generally results from the decay of a heavy element and consists of two protons and two neutrons, *i.e.* a helium nucleus, ${}^{4}_{2}He^{2+}$. α-Particles are highly energetic due to their large mass but are weakly penetrating. A beta-particle (β^-) is an electron expelled from the nucleus as a

result of the conversion of a neutron to a proton. This process results in an increase of one in the atomic number of the isotope while the mass number remains unchanged.

$$^{1}_{0}n \rightarrow {}^{1}_{1}p^{+} + {}^{0}_{-1}\beta^{-}$$

$$^{186}_{75}Re \rightarrow {}^{186}_{76}Os + {}^{0}_{-1}\beta^{-}$$

1.2 Technetium

1.2.1 Discovery

Mendeleev predicted the existence of further elements in the manganese group in his early periodic tables of 1870, naming the missing elements *eka-manganese* and *dwi-manganese*. The later concept of atomic number identified these missing components of the periodic table as elements 43 and 75. Although Noddack *et al.* published details[9] of the isolation of these elements in 1925, naming them *masurium* and *rhenium* respectively, their claim to the discovery of the lighter element could not be substantiated. It is generally agreed that the first sample of element 43 was isolated by Perrier and Segrè in 1937, from a molybdenum target which had been bombarded with deuterons at the Berkeley cyclotron.[10] The new element was named *technetium* after the Greek *τεχνητός* (*technetos*), meaning artificial.[11] There are now twenty known isotopes of technetium (^{91}Tc – ^{110}Tc) and seven metastable nuclear isomers (excited states with a measurable lifetime). All of the isotopes of technetium are radioactive and, although technetium-99 is a product of the natural decay of uranium-235, the amounts of the element that may be found in the environment are negligible. However, it has been estimated that, as a result of the use of uranium for nuclear fuel, the quantity of artificially-produced technetium in existence may now exceed that of rhenium, its naturally occurring congener.[12]

1.2.2 Chemistry

Technetium can exist in oxidation states ranging from –I to +VII and, since it is a transition metal, there is much interest in its co-ordination chemistry. The metastable isotope technetium-99m is used in approximately 90 % of the diagnostic scans carried out in nuclear medicine departments[13] and this application has fuelled an explosion of research into the chemical behaviour of the element over the past twenty years.

1.2.3 Application in Nuclear Medicine

Although technetium-99m features almost ideal nuclear properties for imaging purposes ($t_{½}$ = 6.02 h, E_γ = 140 keV),[14] two other factors have led to the widespread use of technetium radiopharmaceuticals.[15] The first is the development of the $^{99}Mo/^{99m}Tc$ generator by Tucker and Greene in the 1950s and 1960s, which allowed the production of technetium-based radiopharmaceuticals at locations without a nearby cyclotron.[16] The generator consists of $^{99}MoO_4^{2-}$ adsorbed onto an alumina column. The 66 h half-life decay of the radioactive molybdenum species by β^--emission leads to the production of $^{99m}TcO_4^-$ (Figure 1.3), which may be eluted from the column daily with physiological saline solution; the more highly charged molybdenum species remains bound to the column. The half-life of the molybdenum species permits the weekly replacement of the generator.

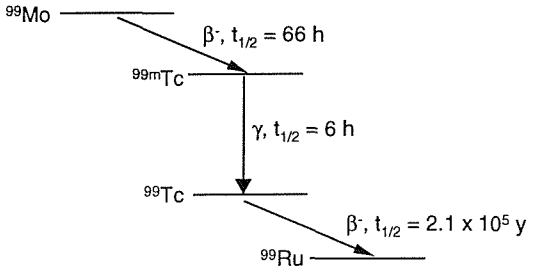


Figure 1.3: Schematic diagram of the decay of ^{99}Mo.

The second factor is the development of single-vial kits, allowing the rapid preparation of the radiopharmaceutical from the eluted pertechnetate solution.[17] The kits consist chiefly of suitable reducing and chelating agents so that the desired radiopharmaceutical may be prepared "instantly" in a high radiochemical purity (RCP) of > 90 %.[15]

The intensely radioactive nature of ^{99m}Tc means it is unsuitable for the characterisation of technetium complexes. Instead, its daughter isotope, ^{99}Tc, is employed. It is a β^--emitter ($t_{½} = 2 \times 10^5$ y, $E_\beta = 293$ keV) which may be handled safely in milligram quantities if the appropriate safety precautions are employed.[4] The β-particle is of sufficiently low energy to be adequately shielded by standard laboratory glassware.

1.3 Technetium Radiopharmaceuticals

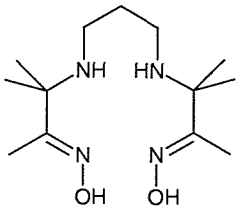
The first application of technetium for medical imaging was the use of the pertechnetate ion itself ($^{99m}TcO_4^-$) for the imaging of the thyroid gland.[18] This was based on the principle that the charge and size of pertechnetate would cause it to behave similarly *in vivo* to the iodide ion.

The utility of technetium has since been extended by the development of the co-ordination chemistry of its ions. Investigations into the preparation of ligands and their technetium complexes have formed the basis of Nuclear Medicine to date and are likely to continue to do so for the near future. Ligands may be designed to produce complexes of particular stability, lipophilicity, charge and/or structure in order that they localise in the desired biological target. Of the technetium radiopharmaceuticals currently in widespread use for imaging, while some of the more recent examples have been characterised crystallographically, there persists some controversy as to the precise nature of several of the early technetium diagnostic agents.

1.3.1 Technetium-Based Imaging Agents

1.3.1.1 Brain Imaging

The commercial radiopharmaceutical Ceretec™ (Nycomed Amersham) was developed from studies of the complex (**1**) between technetium and the ligand 3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioxime (propylene amine oxime, PnAO, **2**).[19] Structural variants of the PnAO ligand were prepared and the bio-distribution of their technetium complexes was investigated. The lipophilic complexes were found to cross the blood-brain barrier, potentially allowing cerebral blood-flow to be imaged.[20,21] However, only the technetium complex (**3**) of *dl*-3,6,6,9-tetramethyl-4,8-diazaundecane-2,10-dione dioxime (**4**) was found to be retained in the brain for a sufficient time for imaging to take place. It is believed that, having crossed into the brain, the *dl*-isomer is metabolised to a more hydrophilic species, preventing diffusion back into the blood. The mechanism of this transformation and the structure of the hydrophilic species remain unknown.



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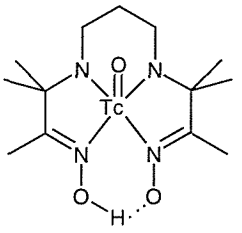

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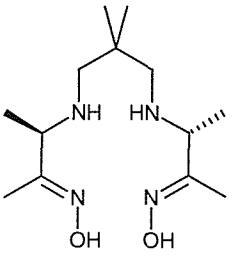

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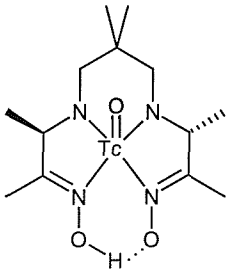

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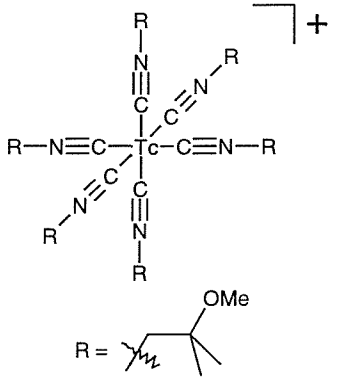
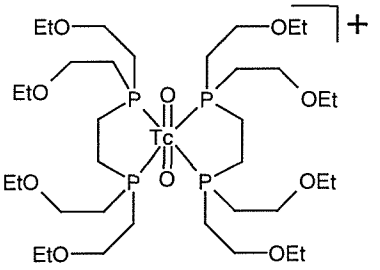
1.3.1.2 Heart Imaging

The potential for cationic, lipophilic complexes to allow imaging of myocardial perfusion was first illustrated by Deutsch *et al.*[22] The original hypothesis upon which the work was carried out was that unipositively charged complexes would concentrate in the muscle of the heart (myocardium) in a similar way to K^+, Rb^+ and Tl^+. A number of commercially available imaging agents are currently in use for the imaging of the heart, including Cardiolite® (DuPont-Merck) and Myoview® (Nycomed Amersham). Cardiolite (**5**) features an octahedral array of six isonitrile ligands surrounding the central Tc(I) ion. Myoview (**6**) features a dioxotechnetium (V) core (TcO_2^+) bound by two neutral diphosphine ligands.



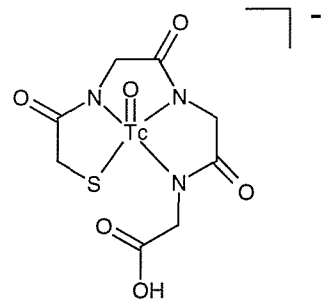
Cardiolite, **5**



Myoview, **6**

1.3.1.3 Kidney Imaging

The technetium complex of mercaptoacetyltriglycine (TcO-MAG_3, **7**) was developed for renal imaging, particularly for testing the function of the renal tubuli.[23] The complex features an oxotechnetium (V) core and an N_3S donor set, in a distorted square pyramid arrangement. The carboxylate group is not associated even weakly with the metal centre, and its presence is thought necessary for efficient renal excretion.



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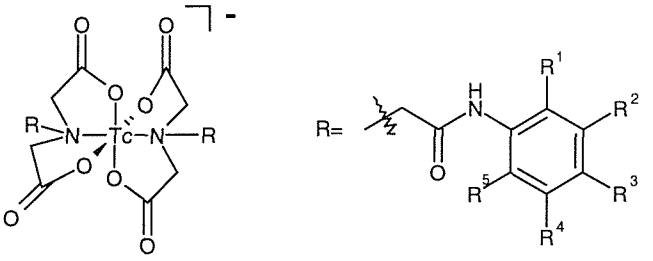
1.3.1.4 Liver Imaging

Three derivatives of iminodiacetic acid (HIDA, **8a-c**) have been approved for the imaging of the hepatobiliary systems. The technetium complexes of the ligands are extracted efficiently from the blood by the liver and excreted into the bile, thus allowing the diagnosis of a variety of diseases of the liver, hepatic duct, gall bladder and intestine. The structures of the complexes and the oxidation state of the technetium ion present remain unknown and several possible structures have been postulated. The structure illustrated shows a Tc(III) ion bound octahedrally by two, tridentate ligands, each binding through the amine nitrogen and two oxygen atoms of the deprotonated carboxylate groups.

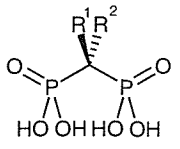


8

Name (Trade Name, Manufacturer)	**Substituents**
Mebrofenin (Choletec™, Bristol-Myers Squib)	**8a**, $R^1 = R^3 = R^5 = Me$, $R^2 = Br$, $R^4 = H$.
Disofenin (Hepatolite™, duPont-NEN)	**8b**, $R^1 = R^5 = i\text{-Pr}$, $R^2 = R^3 = R^4 = H$.
Lidofenin (TechneScan HIDA™, Mallinckrodt)	**8c**, $R^1 = R^5 = Me$, $R^2 = R^3 = R^4 = H$.

1.3.1.5 Skeletal Imaging

Complexes of technetium with phosphonate ligands (**9a-c**) give rise to agents suitable for the skeletal imaging because of the affinity of the co-ordinated ligand for calcium ions, which are present in higher concentration in stressed and growing bone. The preparation of the radiopharmaceutical forms a number of oligomeric and polymeric species; concentration, pH and the reductant used all affect the resulting mixture. One example of a polymeric Tc-MDP structure has been characterised crystallographically.[24] Each technetium ion is bound by two ligands and each diphosphonate coordinates to two Tc centres. The dominant oxidation state in such mixtures appears to be Tc(IV).

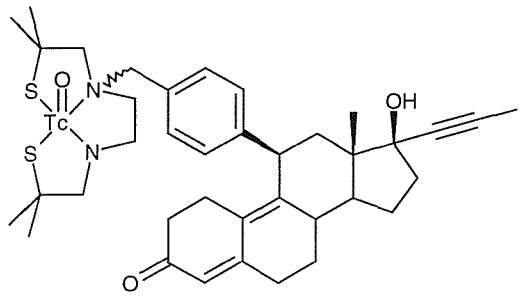


9a (MDP): $R^1 = R^2 = H$
9b (HMDP): $R^1 = OH$, $R^2 = H$
9c (HEDP): $R^1 = OH$, $R^2 = Me$

1.3.2 Recent Approaches

The examples discussed above may be categorised as metal-essential radiopharmaceuticals. However, a great deal of effort is currently being directed towards the development of metal-tagged agents for use as the next generation of radiopharmaceuticals. By attaching the radio-metal to a bioactive compound with a known affinity for a receptor site, it is hoped that the localisation of the resulting agent *in vivo* could be directed, rather than relying on serendipity. This may allow the development of agents for the diagnosis of particular conditions, rather than for the visualisation of the wider function of an organ or system.[8]

Much work has been carried out on the preparation of antibodies bearing a chelating group capable of binding a metallic radionuclide. However, such an approach has proved problematic with technetium as a result of the non-specific binding of the metal ion to the peptide chain of the protein rather than to the incorporated ligand.[5] There has been considerable interest in the conjugation of technetium ligands to small molecules,[8] in particular steroids. For example, oestrogen and progesterone receptors are frequently over-expressed by cancer cells during the early stages of the disease and a suitable radiopharmaceutical might greatly aid early diagnosis. The affinity towards the progesterone receptor of **10,** a progestin bearing a conjugated technetium chelator, was investigated. Although the receptor affinity was found to be high, problems with low target-tissue uptake and high non-specific binding to other organs prevented the further development of this compound.[25]



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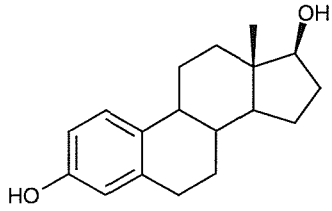
More recently, the use of an integrated approach has been explored, where a portion of the steroidal backbone is replaced by a technetium ligand. Katzenellenbogen *et al.* have investigated the preparation of metal-centred oestradiol (**11**) mimics.[26] While a stable, lipophilic, tetradentate complex of non-radioactive rhenium was produced (**12**), it exhibited only weak binding to the target oestrogen receptor and was unsuitable for further development with radioactive technetium. Nevertheless, the work represents an important early stage in the challenging field of developing metal-centred steroidal radiopharmaceuticals.



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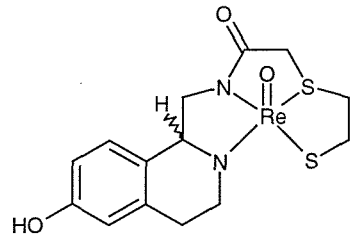


12

1.4 Mimics

The absence of any stable isotopes of technetium means that preliminary studies must be carried out using alternative ions that mimic particular features of this radionuclide. Rhenium would seem to be the obvious choice as a technetium mimic, being the next member of group 7, because of the general similarities in the chemistries of second- and third-row transition metals within the same group. In particular, the ionic radii of technetium and rhenium in identical oxidation states are very similar (Table 1.1), as a result of the lanthanide contraction.[27] However, some anomalous cases exist – for example, while the technetium and rhenium complexes of the ligand MAG_3 adopt analogous structures (*e.g.* **7**), each featuring the mono-oxo core (MO^{3+}), the rhenium complex of PnAO, which may also be expected to feature an oxorhenium(V) core, has yet to be isolated. This has led both Engelhardt *et al.*[28] and Walker[29] to explore the

utility of alternative ions (*e.g.* Co^{3+}, Cu^{2+}) for the initial investigation of the complexing behaviour of PnAO and related ligands.

Ion	Co-ordination number	Ionic radius / pm
Co^{3+} (High spin)	6	75
Co^{3+} (Low spin)	6	68.5
Cu^{2+}	6	87
Tc^{5+}	6	74
Re^{5+}	6	72

Table 1.1: Ionic radii for selected metal ions.[30 31]

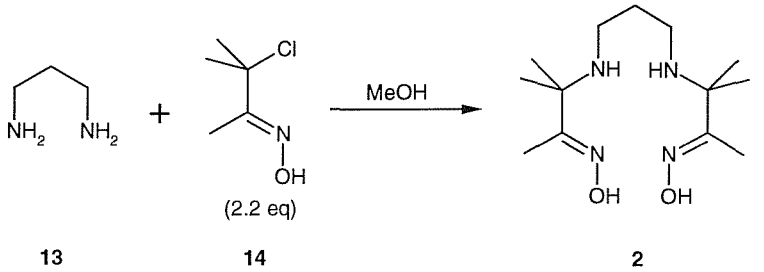
Clearly, ionic radius is only one of a number of factors which would determine the ability of an ion to successfully mimic technetium. The electronic and co-ordination requirements of the ion must also be considered if an appropriate mimic is to be found.

1.5 Ligand Systems

1.5.1 Propylene Amine Oxime Ligands

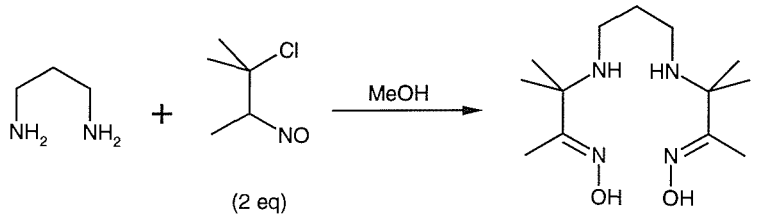
1.5.1.1 Synthesis

The tetradentate ligand PnAO (**2**) was first prepared by Murmann *et al.* as one of a series of α-amino oxime ligands, by the direct reaction of 1,3-propanediamine (**13**) and oxime **14** (Scheme 1.1).[32]



Scheme 1.1: Preparation of PnAO by the method of Murmann *et al.*[32]

The route was later improved by Troutner and co-workers by the use of nitroso-compound **15** for the *N*-alkylation step (Scheme 1.2).[33] Under the reaction conditions, the nitroso groups spontaneously tautomerise to yield the isolated dioxime product.



13 15 2

Scheme 1.2: Preparation of PnAO by the method of Troutner *et al.*[33]

1.5.1.2 X-Ray Crystallographic Studies

Metal complexes of the PnAO ligand (**2**) have been studied extensively to probe the intramolecular hydrogen bond generally formed between the oxime oxygen atoms upon complexation. Such complexes are known with a variety of transition metal ions, *e.g.* Ni(II),[32,34] Cu(II),[35] Co(III),[36] Pt(II).[37] An investigation of the complex between ^{99m}Tc and the PnAO ligand at tracer levels indicated, by radiochemical methods, that a neutral, lipid-soluble complex (**2**) had been formed.[19] The structure was elucidated by scaling-up the procedure to milligram quantities using the long-lived isomer ^{99}Tc, whereupon crystals suitable for single-crystal X-ray crystallography were obtained. The structure consists of an oxotechnetium (V) core (TcO^{3+}) sitting slightly above the plane of the four nitrogen donors, with the oxo (O^{2-}) ligand in an apical position (Figure 1.4).[38] The complex is neutral, as a result of deprotonation of both of the amine nitrogens and of one of the oxime groups. The former process allows the stabilisation of the high formal charge of the Tc (V) ion by π-donation while the latter facilitates hydrogen bonding between the oxime groups resulting in a *pseudo*-macrocyclic character for the complex.

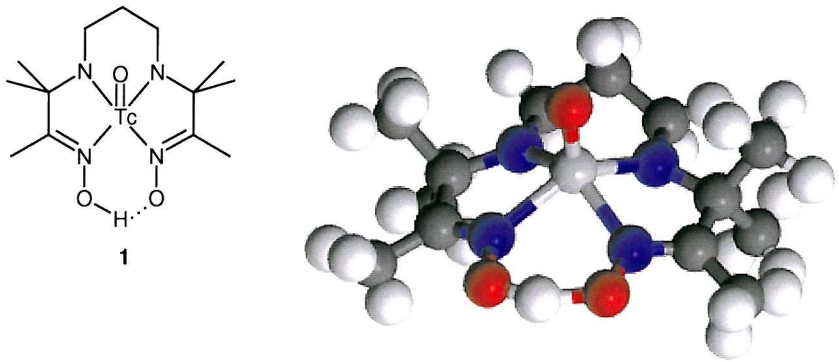


Figure 1.4: Crystal structure of the TcO-PnAO complex (**1**).

The commercially available radiopharmaceutical Ceretec™ (**3**), which was developed from PnAO by Amersham International, has been shown to adopt an analogous structure in the crystalline state (Figure 1.5).[39]

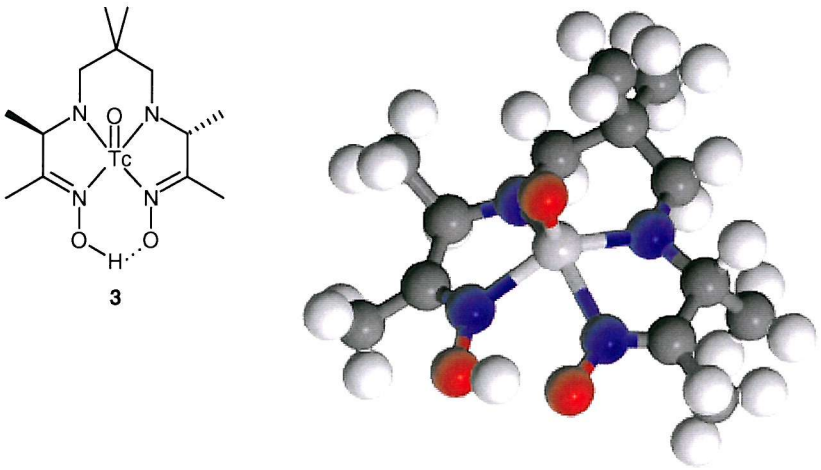
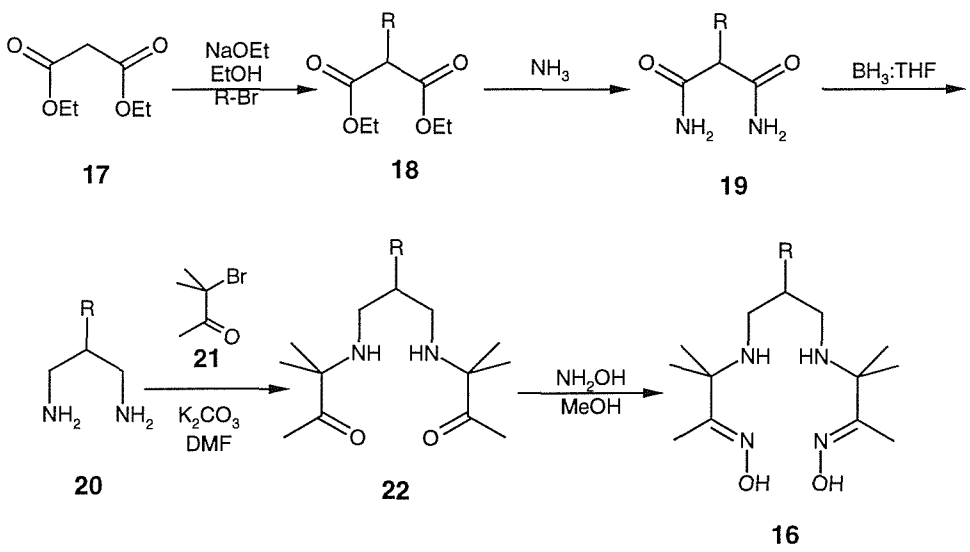


Figure 1.5: Crystal Structure of Ceretec™ (**3**).

1.5.1.3 Synthesis of Derivatives

Given the high stability of the complex formed between technetium and PnAO, attention was then turned to the possibility of attaching the ligand to a bioactive

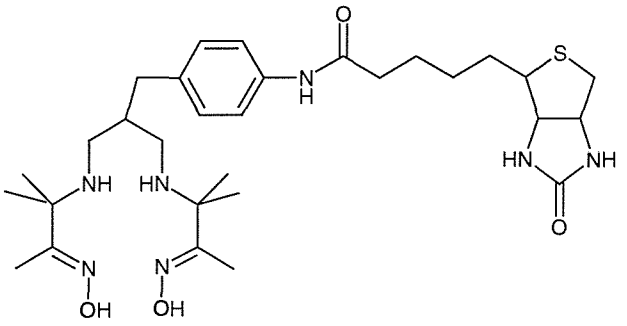
targeting group to form a metal-tagged radiopharmaceutical. Nanjappan *et al.* devised an alternative route to 6-substitued PnAO ligands (**16**) in order to investigate the attachment of a nitroimidazole group which would make possible the imaging of hypoxic (oxygen-deficient) tissues (Scheme 1.3).[40,41] This route allowed for a substituent at the 6-position to be introduced by the alkylation of diethyl malonate (**17**). Reaction of the substituted malonates (**18**) with ammonia gave diamides (**19**) which were then reduced with borane-tetrahydrofuran, to give 2-alkylpropane-1,3-diamines (**20**). Nanjappan *et al.* found that superior yields of the final PnAO derivatives were obtained using a two-step alkylation-oximation procedure rather than Troutner's method of direct reaction with nitroso-compound **15**. Alkylation at nitrogen using bromoketone **21** gives the diamine-dione (**22**), which may then be converted to the dioxime derivative (**16**) by reaction with excess hydroxylamine.



Scheme 1.3: Preparation of alkyl-PnAO ligands.[40,41]

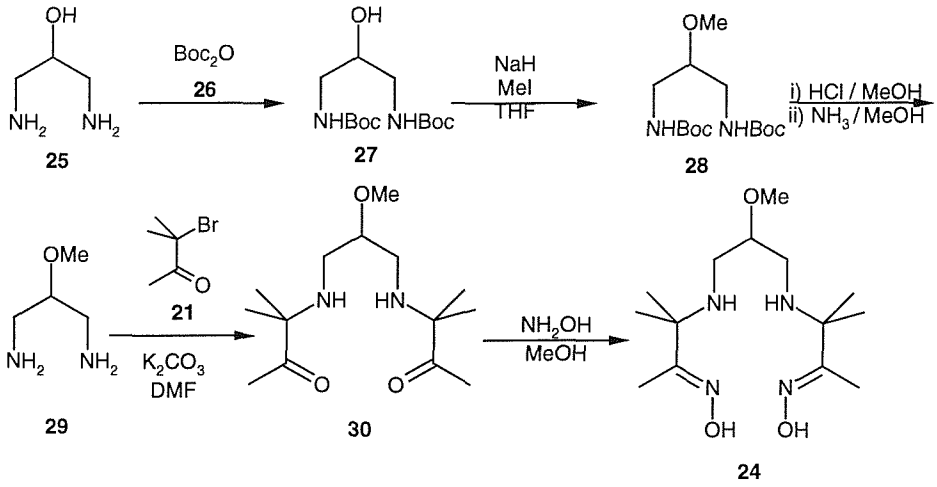
Walker developed this approach for the production of a series of 6-substituted PnAO derivatives with substituents ranging from simple alkyl groups to potentially co-ordinating pyridyl moieties.[29]

PnAO has also been used as the technetium-binding ligand conjugated to biologically-active targeting groups such as a somatostatin analogue and biotin[42] (*e.g.* **23**), although the lipophilic nature of the TcO-PnAO complex led to high liver uptake and slow blood clearance.



23

Ramalingam *et al.* have also prepared one example of an alkoxy-substituted PnAO ligand, bearing a simple methoxy substituent at the 6-position (**24**). Such a modification required an alternative synthetic route (Scheme 1.4)[41] to that which had been developed for the preparation of 6-alkyl PnAO ligands. Diaminoalcohol **25** was protected at nitrogen with di-*tert*-butyl dicarbonate (**26**), to give alcohol **27** which was then alkylated at oxygen to give protected ether **28**. Deprotection with methanolic HCl afforded a 2-alkoxy diamine (**29**), which could then be elaborated to a PnAO ligand in a manner similar to that used for the 2-alkyl diamines (**16**).

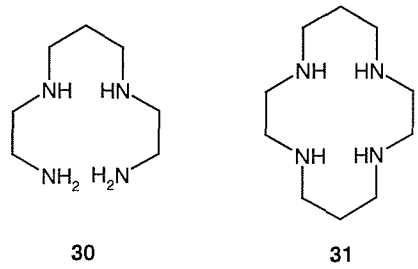


Scheme 1.4: Preparation of alkoxy-PnAO ligands.

1.5.2 1,4,8,11-Tetraazaundecane Ligands

1.5.2.1 Preparation

The ligand 1,4,8,11-tetraazaundecane (**30**) was first prepared by van Alphen as part of a complex mixture of products from the reaction of ethylenediamine with 1,3-dibromopropane.[43] The ligand may be viewed as an acyclic analogue of cyclam (1,4,8,11-tetraazacyclotetradecane, **31**) and comparative binding studies of TA and cyclam have been used to illustrate the "macrocyclic effect".[44] The complexes formed by TA with a variety of transition metals have been studied (*e.g.* Cr(III), Rh(III), Cu(II), Ni(II) and Co(III)[45,46]).



1.5.2.2 X-Ray Crystallography

While a simple, monomeric complex between technetium and **30** has yet to be characterised crystallographically,[47] Mantegazzi *et al.* have determined the structure of the polymeric compound $\{Li[TcO_2(C_7H_{20}N_4)](CF_3SO_3)_2\}_n$ (**32**) which features the Tc-TA unit. Unlike the technetium complex of PnAO there is no deprotonation of the amine nitrogen atoms; instead the high formal charge of the Tc (V) ion is stabilised by a second oxo ligand giving a dioxotechnetium (V) core (TcO_2^+).[48]

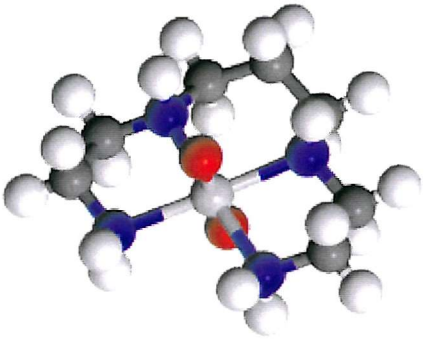


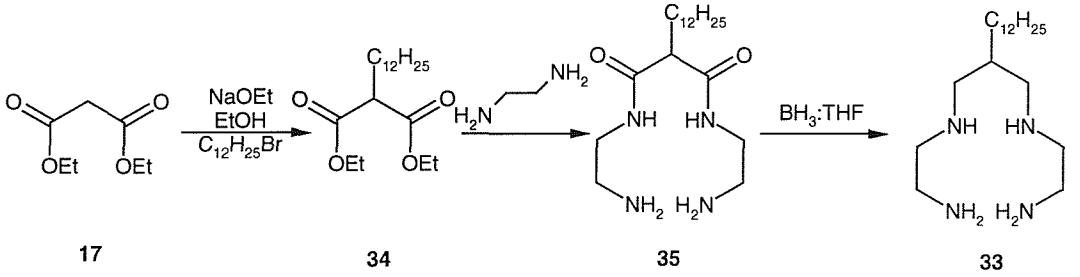
Figure 1.6: Crystal structure of the $[TcO_2\text{-}TA]^+$ Unit (**32**).

The binding of rhenium by TA (**30**) has also been evaluated. The resulting complex is very similar to its technetium analogue. It features a *trans*-dioxo core (ReO_2^+)[47] and has been investigated as a means of incorporating a radionuclide for targeted radiotherapy (^{186}Re, β^-, $t_{½}$ = 90.64 h).[49] Chelation of rhenium by TA proceeded in an acceptable yield (87%) under aqueous conditions in a single step. It is noteworthy that synthesis of the corresponding cyclam (**31**) complex required a more involved procedure, including the use of an organic solvent. This is undesirable for a practical nuclear medicine application.[49]

1.5.2.3 Derivatives of the TA Ligand

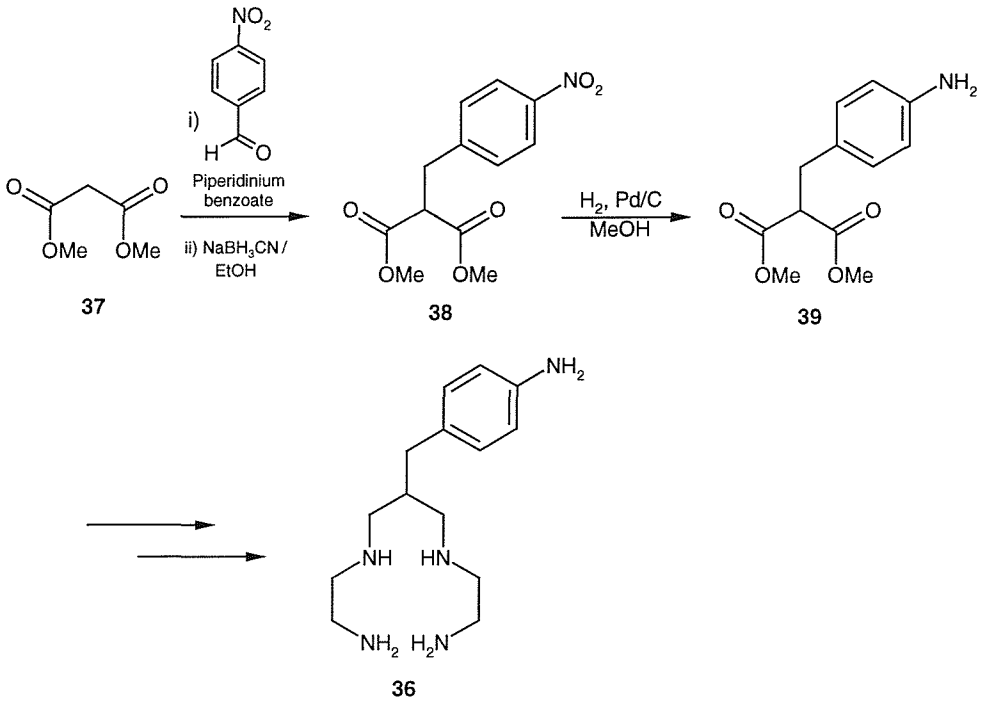
Simon *et al.* prepared substituted TA derivatives as novel amphiphilic ligands for the investigation of assemblies of transition metal ions, using the route outlined in Scheme 1.5.[50] 6-Dodecyl-1,4,8,11-tetraazaundecane (**33**) was prepared by the alkylation of

diethyl malonate (**17**) with 1-bromododecane to give **34**, followed by amidation with excess ethylenediamine. The target was prepared by the reduction of diamine-diamide **35** using borane-tetrahydrofuran solution.



Scheme 1.5: Preparation of alkyl-TA ligands.[50]

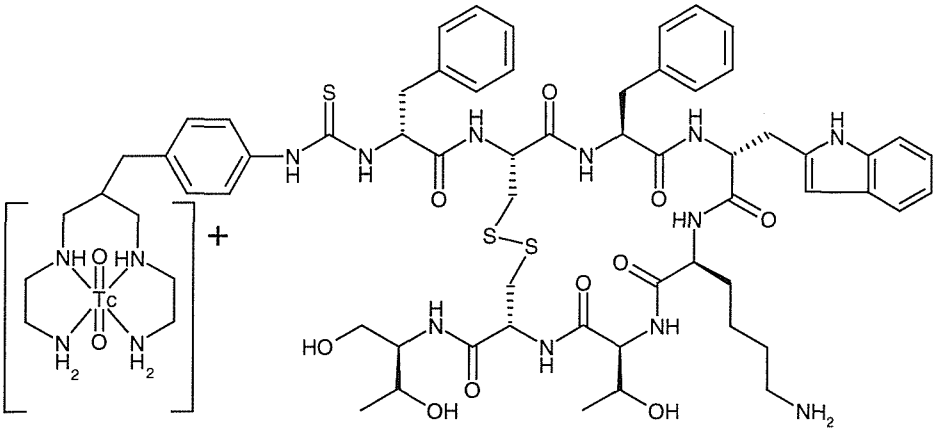
A similar approach was employed by Kruper *et al.* for the preparation of bifunctional chelating agent **36**, designed to allow the binding of radioactive rhodium-105 and the attachment of an antibody *via* the aromatic amine function.[51] Alkylation of dimethyl malonate (**37**) was in this case accomplished in two steps by a Knoevenagel condensation followed by reduction with sodium cyanoborohydride to give **38** (Scheme 1.6). Catalytic hydrogenation afforded the amine derivative **39**, which was elaborated to the target in an analogous fashion to Scheme 1.5.



Scheme 1.6: Alternative preparation of an alkyl-TA ligand.[51]

1.5.3 Conjugated Systems Featuring TA Ligands

The neutral, lipophilic nature of the TcO-PnAO complex has led to problems of high liver uptake and slow blood clearance (see 1.5.1.3 above). Accordingly, the use of TA binding groups, giving a more hydrophilic complex with technetium,[15] has been investigated, leading Maina *et al.* to prepare octreotide derivative **40**. The complex was found to have a high affinity for the somatostatin receptors often expressed by gastroenteropancreatic tumours.[52]



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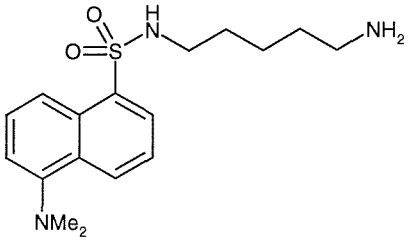
1.6 Thrombosis

Monodansyl cadaverine (*N*-(5-aminopentyl)-5-dimethylamino-1-naphthalenesulfonamide, **41**) and related compounds have been shown to be potent inhibitors of the fibrin stabilising factor (FSF).[53] This factor catalyses the cross-linking of monomeric fibrin molecules *via* intermolecular amide bonds, forming insoluble coagulums which produce a thrombus (blood clot) by trapping blood cells in the growing matrix. While such compounds have the potential for use against diseases that cause the blood to clot, the introduction of a radioactive atom into an FSF-inhibitor may allow the determination of the location of forming thrombi. Such knowledge is of vital importance during the treatment of patients prone to the formation of potentially fatal blood clots.



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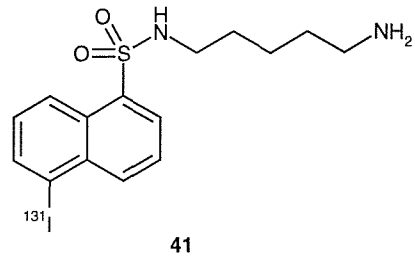
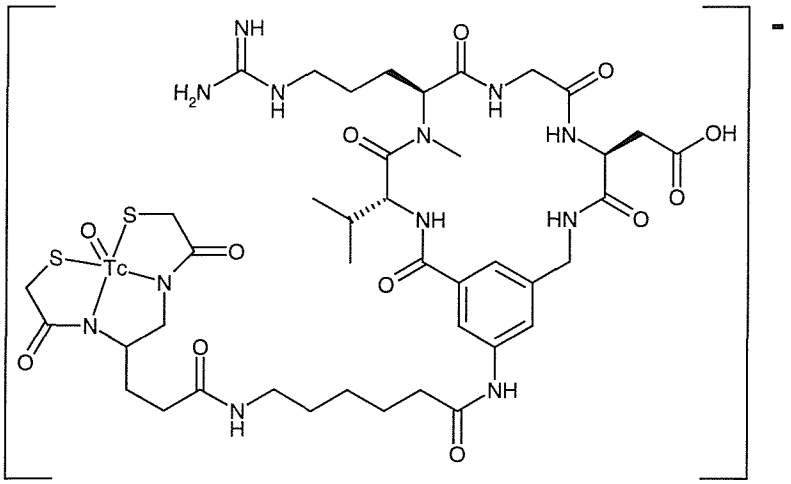
De Jong *et al.* prepared a series of compounds labelled with iodine-125 and iodine-131 (*e.g.* **41**) and demonstrated *in vitro* that the radiolabelled species were efficiently incorporated into fibrin clots.[54]



41

While ^{131}I (E_γ = 364 keV, $t_{½}$ = 8.05 d) has found some application in nuclear medicine, it features undesirable properties such as the emission of photons of a relatively high-energy, an accompanying particulate emission (β^-, E_β = 188 keV) and the requirement of a reactor for its production. Iodine-123 (E_γ = 159 keV, $t_{½}$ = 13.2 h) radiopharmaceuticals are available, but a cyclotron is required for the production of the isotope and, given its relatively short half-life, commercial exploitation is somewhat problematic. A more general difficulty with the use of iodine isotopes is the lability of C-I bonds *in vivo*, which frequently leads to a build up of the isotope in the thyroid gland. This may require suppression by the administration of excess sodium iodide.[13]

Such difficulties with radio-iodine, together with the ready availability of technetium in Nuclear Medicine departments throughout the world, have led researchers to investigate the development of technetium-based agents for the imaging of thrombi. Fibrinogen, which mediates the aggregation process, binds to the GP IIb/IIIa receptor by an Arg-Gly-Asp motif. Cyclic peptides incorporating this unit were found to be antagonists of the receptor and were themselves adapted to allow for the incorporation of a technetium-chelator.[55] For example, compound **42** demonstrated good contrast in SPECT images of deep vein thrombosis *in vivo*.[56]



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1.7 Varying the Nature of the Side-Arm Linker

CPK (Corey-Pauling-Koltun) and computer modelling studies of 6-substituted PnAO ligands have revealed the possibility of a steric clash when the ligand adopts a suitable conformation for the chelation of the fifth co-ordinating group.[29] Under these circumstances, the protons of the first methylene unit of the pendent group and those α to the 6-position on the ligand backbone are brought into close proximity (Figure 1.7).

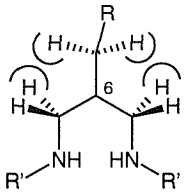
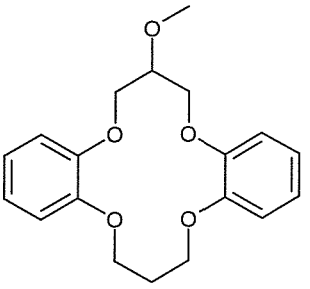


Figure 1.7: Steric clash

The replacement of this methylene unit with an oxygen atom was postulated as a means to relieve the steric congestion. Such a substitution may also bring with it a conformational advantage to favour binding of the additional coordinating group by a preference for a pseudo-axial orientation of the side arm. Lariat substituents linked by an ether oxygen atom to derivatives of dibenzo-14-crown-4 (**43**) have been shown by

solution NMR experiments to favour a pseudo-axial conformation even in the free ligand.[57] However, X-ray crystallographic studies of related compounds have revealed the adoption of both pseudo-axial and pseudo-equatorial orientations. Whether or not this would be true for the PnAO skeleton, the use of this linker would at least facilitate the adoption of an axial conformation, thereby allowing possible scorpionate complexation.[58]



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1.8 Aims of the Research Project

Development of a route to alkoxy-PnAO ligands which allows the attachment of potentially co-ordinating substituents.

Development of a route to alkoxy-TA ligands.

An investigation of potential methods for the attachment of biologically active targeting groups to ligands known to bind technetium.

Structural characterisation of the technetium complexes of selected ligands.

2 Results and Discussion

The target structure of the present study is illustrated schematically in Figure 2.1. It was decided that initial investigations would concern the development of a reliable synthetic route to the technetium-binding ligand fragment. Attention could then be turned to the incorporation of the bioactive targeting group into this structure.

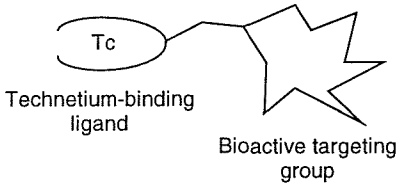


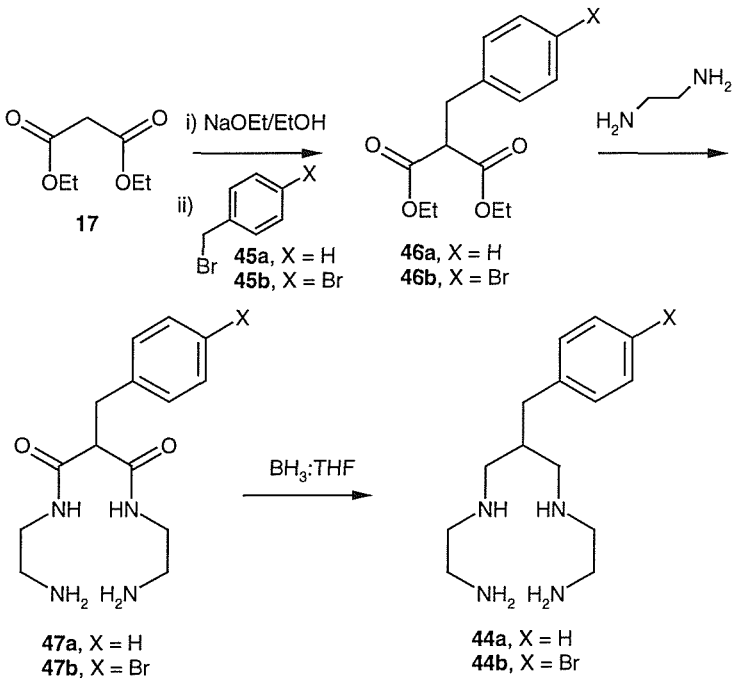
Figure 2.1: Schematic diagram of target molecule.

2.1 Alkyl-Substituted 1,4,8,11-Tetraazaundecane Ligands

2.1.1 Overview

After consultation with Amersham International, the technetium-binding ligand chosen for the focus of the current work was 1,4,8,11-tetraazaundecane (**30**). A particular advantage to the use of the TA ligand was its formation of a cationic complex with dioxotechnetium(V) (TcO_2^+), which would be expected to enhance the solubility of the complex in aqueous medium of the blood.[15]

The initial synthetic targets were **44a-b**. Whilst compound **44a** bears a simple benzyl group and represents the "base" structure, **44b** features a 4-bromobenzyl substituent, which should allow the exploration of further functionalisation of the side chain. The route proposed for the preparation of simple model compounds was based on published work for the preparation of 6-substituted TA[50,51] and cyclam[59,60] derivatives and is illustrated in Scheme 2.1.

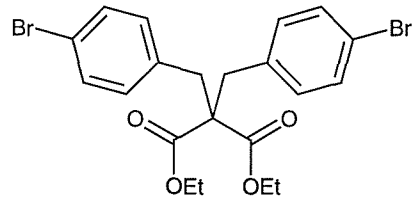


Scheme 2.1: Route to alkyl-TA targets.

2.1.2 Alkylation of Diethyl Malonate

Preparation of diethyl 2-(phenylmethyl)propanedioate (**46a**) by the reaction of stoichiometric quantities of sodium metal, diethyl malonate (**17**) and benzyl bromide (**45a**) in ethanol proceeded in reasonable yield (56 %, lit.[61] 51-57 %). However, when the same method was applied to the preparation of malonate **46b**, the desired product was isolated in a rather poorer yield (38 %). Analysis of the residue from the distillation revealed its chief component to be di-substituted malonate **48**. While the use of an alternative base such as sodium hydride was considered as a means of ensuring irreversible formation of the malonate anion, a survey of the literature revealed that the problem was not unprecedented. Adamczyk *et al.*[62] achieved the preparation of the desired compound in a more satisfactory yield simply by using an excess of diethyl propanedioate to favour the formation of the mono-substituted product. Following this procedure, the excess diethyl malonate was readily separated from the desired product by distillation and malonate **46b** was subsequently prepared in a reasonable yield

(60 %). Both mono-substituted malonates (**46a** and **46b**) were satisfactorily characterised in good agreement with literature data.[61,62]

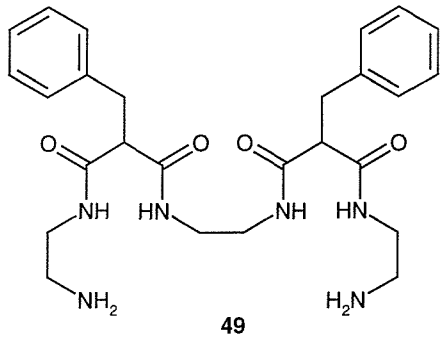


48

2.1.3 Reaction With Ethylenediamine

The simplest way to prepare diamine-diamides **47a** and **47b** from malonates **46a** and **46b** respectively seemed to be by direct reaction of the diesters with ethylenediamine. Such an approach has been taken by both Simon *et al.*[50] and Kruper *et al.*[51] Similarly, this reaction has been exploited extensively for the preparation of dendritic macromolecules,[63,64] a process which demands high efficiency with little "cross-linking" (*i.e.* difunctionalisation of the diamine). However, optimum results require long reaction times (*ca.* 7 days) and the use of a large excess of diamine, although both Betts *et al.*[65] and Walker[29] have reported that the rate of reaction between ethyl esters and amines can be enhanced by the use of a catalytic quantity of sodium methoxide.

Initial attempts to produce 6-(phenylmethyl)-1,4,8,11-tetraazaundecane-5,7-dione (**47a**) by the reaction of malonate **46a** with ten equivalents of 1,2-ethanediamine led to the isolation of the dimeric ("cross-linked") product, tetra-amide **49**. While the ^{1}H-NMR spectrum was broad, both the mass spectrum (*m/z* = 497.2, M+H^{+}) and ^{13}C-NMR (ten carbon environments rather than the expected nine, the additional signal being a secondary centre by DEPT-135) proved valuable for the identification of **49**.



49

In order to favour production of the desired compound, a greater (twenty-five fold) excess of ethylenediamine was used in subsequent preparations. It should be noted, however, that the use of such a large excess of 1,2-ethanediamine does not make the production of the diamine-diamides uneconomical as the excess may be recovered by distillation (at reduced pressure) of the product mixture.

In an effort to monitor the efficiency of the reaction, an attempt was made to use mass spectrometry to estimate the relative proportions of diamine-diamide **47a** and tetra-amide **49** when the reaction was performed with and without anhydrous methanol as solvent. The intensity of the peaks for $(\mathbf{47a}+H)^+$ and $(\mathbf{49}+H)^+$ in positive electrospray mass spectra were compared (Table 2.1). The method was considered justifiable as it was used only to gauge the relative amounts of products **47a** and **49**, under identical conditions. The presence of methanol as solvent was not found to greatly affect the ratio of products. For convenience, subsequent preparations were carried out in neat ethylenediamine.

Molar excess of ethylenediamine	**Volume of methanol / ml**	**Intensity of $(47a+H)^+$ peak / %**	**Intensity of $(49+H)^+$ peak / %**	**Ratio of 47a:49**
25	100	57	10	5.7
25	0	44	6	7.3

Table 2.1: Effect of methanol as solvent on the amidation of malonate esters.

After the removal of excess ethylenediamine, the electrospray mass spectrum of the crude isolated material showed the expected peak at $m/z = 279$ ([**47a**+H]$^+$) but purification of diamide-diamine **47a** proved difficult. Attempts to isolate **47a** from a variety of solvents proved unsuccessful. White needles which crystallised from toluene subsequently collapsed to a light brown semi-solid upon filtration, although previous work by Hill *et al.* does not suggest that this class of compounds is notably air-sensitive.[66,67] Purification at this stage was deemed necessary otherwise any residual impurities would have to be separated from the highly polar tetra-amine final product. However, further attempts to isolate **47a** as its dihydrochloride salt by the treatment of a solution of the diamine-diamide with gaseous hydrogen chloride did not result in the formation of a filterable solid. Given the extremely poor combustion analysis data obtained for the crude product, it was decided not to attempt the reduction of this compound.

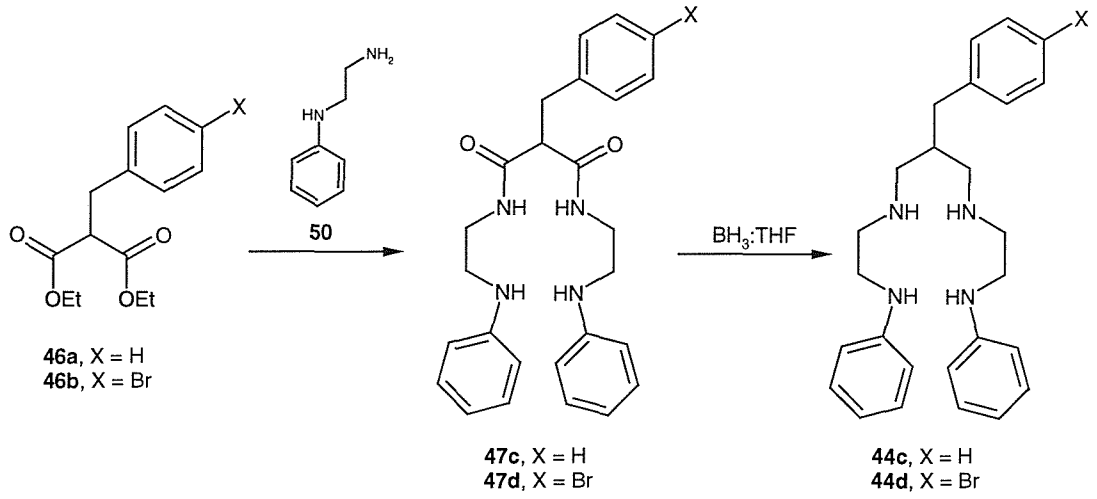
Following a similar procedure, bromophenyl diamine-diamide **47b** was successfully prepared by the reaction of malonate **46b** with twenty-five equivalents of 1,2-ethanediamine. In this case the crude product crystallised satisfactorily from toluene.

2.1.4 Terminal *N*-Substituted Diamines

In view of the comparative success of the amidation process described above, and in an attempt to circumvent the inconvenience of "cross-linking" reactions of a symmetrical diamine, it was decided to explore the use of unsymmetrical diamines.

Accordingly, a parallel study was begun into the preparation of ligands derived from the condensation of malonate esters **46a** and **46b** with *N*-phenyl-1,2-ethanediamine (**50**). In this case the primary amine function may be expected to be significantly more reactive towards malonate esters than the secondary nitrogen, the lone pair of which is conjugated with the adjacent aromatic ring. The production of oligomeric by-products,

seen previously with ethylenediamine, should therefore be avoided and it was hoped that in this case the use of a large excess of diamine might be circumvented.



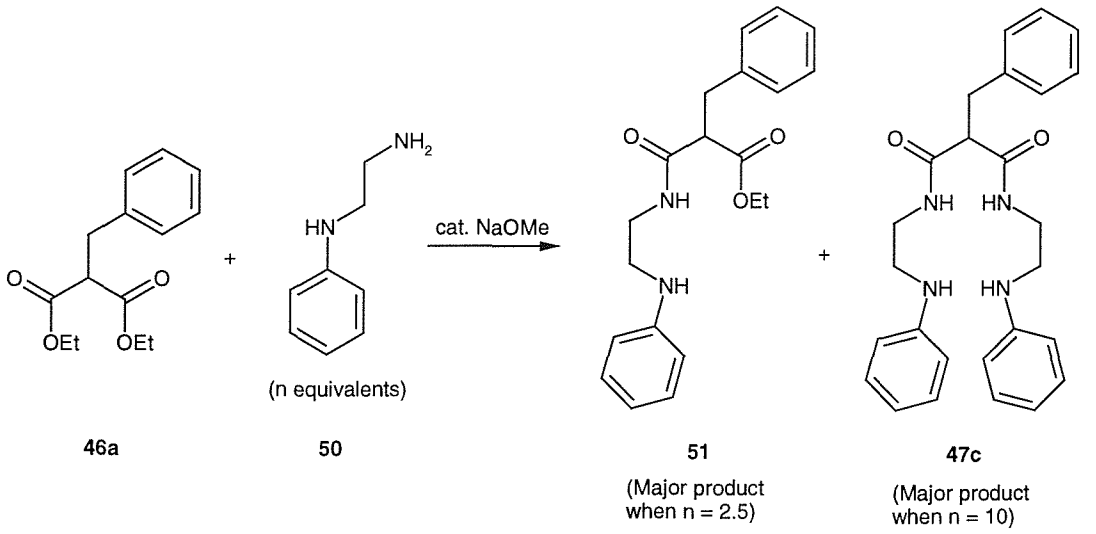
46a, X = H
46b, X = Br

47c, X = H
47d, X = Br

44c, X = H
44d, X = Br

Whilst the large phenyl rings would ultimately have to be brought into relatively close proximity in order for the complexation of a metal ion to occur, such ligands would also offer distinct advantages for the possibility of determining binding constants by UV titration, since binding of a metal ion by **44c** or **44d** should result in the removal of the nitrogen lone-pair from conjugation with the aromatic π-system. Thus the ligand possesses a chromophore which could facilitate measurement of the association constant, K_a.

The initial attempt to synthesise diamine-diamide **47c** by the condensation of malonate **46a** with a small excess of diamine **50** (2½-equivalents) in the presence of sodium methoxide as catalyst resulted in the isolation of the mono-substituted amide **51** as the major product. It is noteworthy that the stepwise amidation of the malonate would allow the preparation of unsymmetrical ligands. However, the desired target intermediate of the current work, *N*-phenyl diamine-diamide (**44c**), was subsequently obtained by the use of ten equivalents of diamine **50**.



46a **50** **51** **47c**

(Major product when n = 2.5)

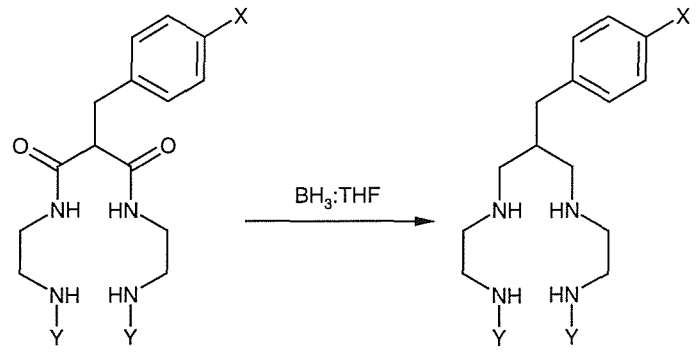
(Major product when n = 10)

The use of a large excess of the diamine gave rise to problems with the isolation of the desired compound. *N*-Phenyl-1,2-ethanediamine (**50**) is more expensive than ethylenediamine while being significantly less volatile, hence efficient recovery of the excess reagent is desirable and at the same time more difficult. Distillation of the reaction mixture at reduced pressure required prolonged heating (b.p. 100 °C / 0.8 mmHg) to remove excess diamine, while the product diamine-diamide **47c** was obtained after trituration of the distillation residue with ethanol in moderate yield (47 %).

The *N*-phenyl diamine-diamide **47d** was subsequently prepared from malonate **46b** in very good yield (82 %). This may be attributed to improvements in the work-up procedure since distillation of the crude reaction mixture was found to be unnecessary if ether, rather than ethanol, was used as solvent for the trituration.

2.1.5 Reduction

The final step in the preparation of tetra-amine ligands requires the reduction of the diamine-diamide intermediates **47a-d**. Similar transformations have previously been accomplished by reaction of such compounds with borane in tetrahydrofuran.[50,59]



47a, X = H, Y = H
47b, X = Br, Y = H
47c, X = H, Y = Ph
47d, X = Br, Y = Ph

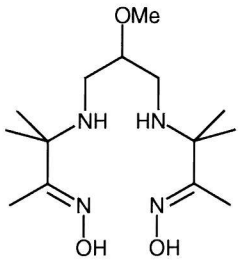
44a, X = H, Y = H
44b, X = Br, Y = H
44c, X = H, Y = Ph
44d, X = Br, Y = Ph

N-Phenyl diamine-diamides **47c** and **47d** were chosen for the initial investigations into this reduction, since they were expected, when reduced, to present fewer difficulties during chromatographic purification than the tetra-amines derived from the reduction of **47a** and **47b**, which feature primary amine functions. Reduction of **47d** proceeded smoothly in refluxing borane-tetrahydrofuran and the tetra-amine **44d** was obtained in a moderate yield of 63 % after purification by column chromatography (silica gel, eluant ether/methanol/"880" ammonia (30:2:1)). This tetra-amine was satisfactorily characterised by ^{1}H-NMR, ^{13}C-NMR, MS and IR.

An alternative, more convenient purification procedure was investigated for future reductions, based on methods employed for the preparation of aza-crown ethers, utilising a series of simple acid/base separations to effect efficient purification.[59] Such a protocol was applied to the purification of the product derived from the reduction of diamine-diamide **47c**, the corresponding tetra-amine **44c** being obtained in an excellent yield of 91 % and satisfactorily characterised by ^{1}H-NMR, ^{13}C-NMR, MS and IR.

2.2 Alkoxy-PnAO

In addition to the development of routes to substituted TA ligands, it was decided to continue with the preliminary studies into the preparation of 6-alkoxy PnAO ligands carried out previously by Walker.[29] While Nanjappan *et al.* had previously prepared a single example of this ligand class (**24**), it bore only a methoxy substituent.[41]



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2.2.1 Introduction of the Ether Linkage

Application of the Williamson ether synthesis to this unsymmetrical system leaves the choice of which component is employed as the nucleophile and which as the electrophile (Figure 2.2).

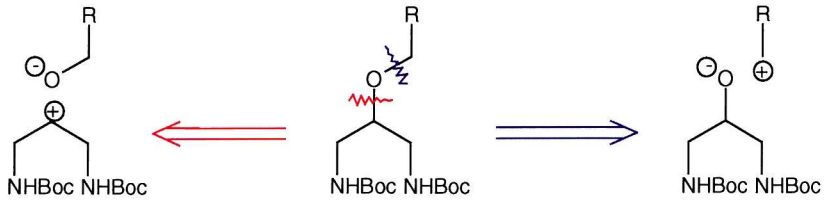


Figure 2.2: Alternative disconnections leading to protected ethers.

Previous attempts by Nanjappan[41] and Walker[29] to introduce the ether group by the method shown in Figure 2.3 had proved unsuccessful, as a result of the displacement of the leaving group by the neighbouring nitrogen atom, which may be deprotonated under the reaction conditions. Subsequent opening of the resulting aziridine by another

nucleophile is favoured at the less hindered position (Scheme 2.2), resulting in the introduction of a terminal alkoxy group.

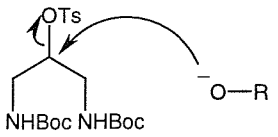
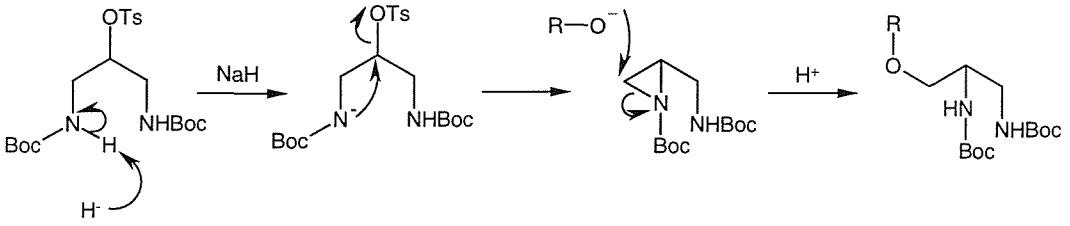


Figure 2.3: Protected diamine as electrophile.



Scheme 2.2: Aziridine ring-opening.

However, this problem should be avoided if the roles of nucleophile and electrophile are reversed, as depicted in Figure 2.4. A second potential advantage of such an approach is that it involves attack by the secondary alkoxide (from deprotonation of **27**) on the less-hindered primary alkyl halide.

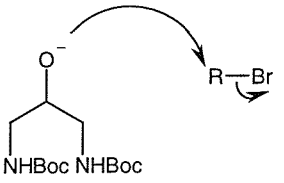
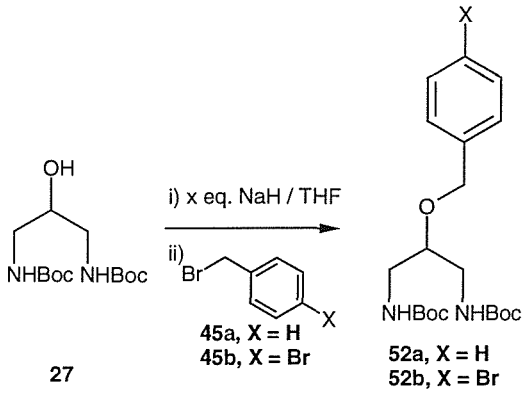


Figure 2.4: Protected diamine as nucleophile.

2.2.2 Alkylation at Oxygen

Reaction of compound **27** with one equivalent of sodium hydride and benzyl bromide afforded ether **52a** in a moderate yield of 51 %, based on consumed **27**. While the percentage of alcohol **27** converted to ether **52a** was only 22 %, the recovery of the majority of the unreacted starting material was easily accomplished during the chromatographic separation of the desired compound. Since the Boc-protected nitrogen

atoms also possess a relatively acidic proton, which may compete for the available base, the proportion of base used was increased in an attempt to make the process more efficient (Table 2.2).



Experiment	x (equivalents of NaH)	Percentage Yield of 52a	Percentage Conversion of 27
1	1	51	22
2	1½	50	21
3	3	0	0

Table 2.2: Effect of varying the amount of base on *O*-alkylation.

However, the presence of excess base did not encourage greater conversion of alcohol **27** to the desired ether **52a**. Indeed, experiments 2 and 3 were less efficient than the method originally employed (experiment 1). The large excess of base used in experiment 3 appears to result in the destruction of alcohol **27**, as neither the starting material nor the desired product could be recovered.

The diastereotopic nature of the protons on carbon atoms 1 and 3 is clearly evident in the ^{1}H-NMR spectrum of ether **52a**. These could not be unambiguously assigned by direct measurement of coupling constants because of the broadness of the signals for the protons on carbons 1-3. A ^{1}H-^{13}C COSY experiment was therefore performed which

clearly resolved the signals due to the non-equivalent protons on C-1 and C-3 (Figure 2.5) from that for the methine proton on C-2.

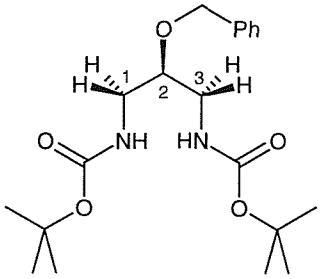
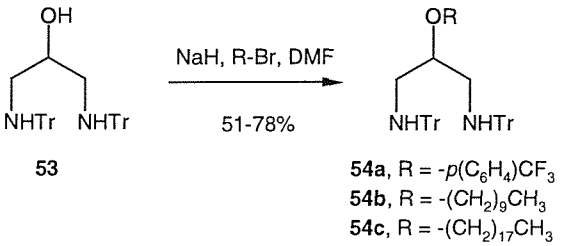


Figure 2.5: Diastereotopic centres in **52a**.

2.2.3 Preparation of Further Members of the Series

Preparation of ether **52b** was accomplished using one equivalent of sodium hydride, by a procedure analogous to experiment 1 above. Both the yield (71 %) and the percentage conversion of **27** (33 %) were superior to those observed for the preparation of ether **52a**. Subsequent preparations of both **52a** and **52b** resulted in enhancements to both the yield and the percentage conversion.

Very recently, Bonnet *et al.* have further explored Nanjappan's method for the alkylation of alcohol **27** to form diamine building blocks for combinatorial chemistry.[68] They concluded that the generally poor yields of the ether products could be improved if the trityl group was employed, in place of the Boc protecting group, to give alcohol **53**.

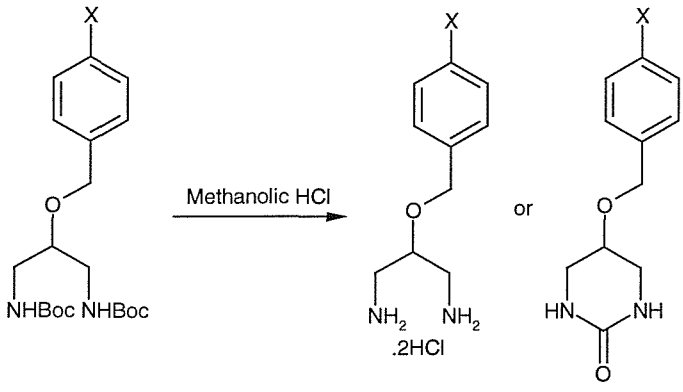


53

54a, R = -*p*(C_6H_4)CF_3
54b, R = -$(CH_2)_9CH_3$
54c, R = -$(CH_2)_{17}CH_3$

2.2.4 Removal of Boc Protecting Groups

Removal of the *tert*-butoxycarbonyl (Boc) protecting groups from intermediate **52a** initially appeared to be problematic, the "standard" deprotection conditions of 10 % trifluoroacetic acid in dichloromethane or methanolic HCl both resulting in the formation of a product with an apparent mass of 206 Da by electrospray mass spectrometry, whereas the desired product, **55a**, has a mass of 180 Da. The addition of D_2O resulted in a mass spectrum consistent with a structure having two exchangeable protons, *e.g.* urea **56a**, which had previously been formed from **52a** upon treatment with strong *bases*.[69] Other data for urea **56a** could not be compared since, unfortunately, Fordon *et al.* have published no characterisation data for either ether **52a** or urea **56a**.



52a, X = H
52b, X = Br

55a, X = H
55b, X = Br

56a, X = H
56b, X = Br

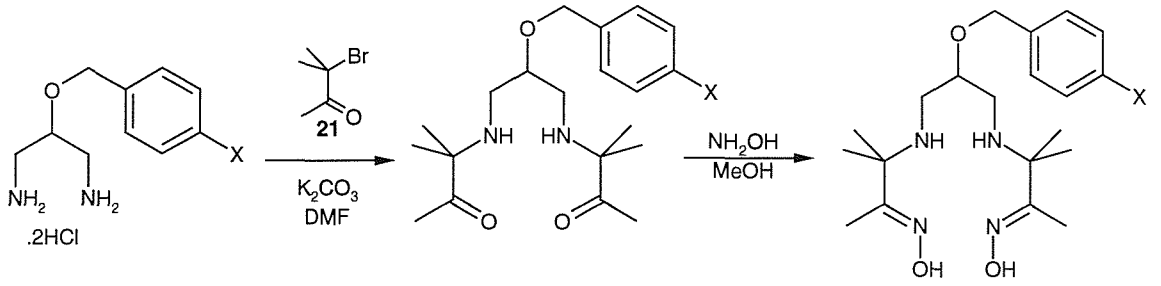
The infra-red spectrum of the product did not indicate the presence of a urea carbonyl, the expected absorption[70] for a six-membered ring urea at *ca.* 1640 cm^{-1} not being observed. The ^{1}H-NMR spectrum could not be used to unambiguously assign the structure and the ^{13}C-NMR spectrum did not contain a resonance in the carbonyl region. However, the possibility of the urea carbon nucleus being slow to relax as a result of the two adjacent nitrogen atoms, and therefore difficult to observe, was considered and so a ^{13}C-NMR spectrum was obtained again using a greater (two-second) delay in the pulse sequence, but once again, no signals were observed in the carbonyl region of the spectrum.

It was decided to employ chemical tests for the presence of amine functions. The ninhydrin test proved ambiguous, while the appearance of a dark blue colour upon treatment with a dilute solution of copper (II) sulfate indicated the presence of amines, the distinctive colour being a result of complexation of the metal ion. It was decided to attempt the reaction of the deprotected product with bromoketone **21** in order to definitively elucidate its structure.

Diamine **55b** was deprotected by treatment with methanolic HCl in an excellent yield of 94 %. While giving a similarly anomalous result in the electrospray mass spectrum, the resulting dihydrochloride salt has been satisfactorily characterised by ^{1}H-NMR, ^{13}C-NMR, IR and elemental analysis.

2.2.5 *N*-Alkylation

N-Alkylation of diamine **55a** with 3-bromo-3-methyl-2-butanone (**21**) afforded diketone **58a** in 58 % yield. Prior neutralisation of the dihydrochloride salt[40] was found to be unnecessary if the appropriate additional quantity of potassium carbonate was present in the reaction mixture. The difficulties reported by Walker[29] regarding the purification of similar alkyl-substituted diketones by column chromatography were not encountered in the alkoxy-substituted case investigated here. However, even after an extended period of warming under high vacuum it did not prove possible to entirely remove residual DMF from the viscous product. Alkylation of diamine **55b** with bromoketone **21**, in the presence of K_2CO_3 afforded diketone **58b**. However the alkylating agent was erroneously present in only 1.5 molar equivalents whereas previously an excess of the ketone (2.5 equivalents) had been employed.[40,41] Nevertheless, whilst the yield of the reaction was inevitably reduced (60 %, based on the ketone as the limiting reagent), this novel PnAO precursor was characterised by ^{1}H-NMR, ^{13}C-NMR, MS and IR after purification by column chromatography. Once again, some residual DMF was still present in the product oil.



55a, X = H
55b, X = Br

58a, X = H
58b, X = Br

59a, X = H
59b, X = Br

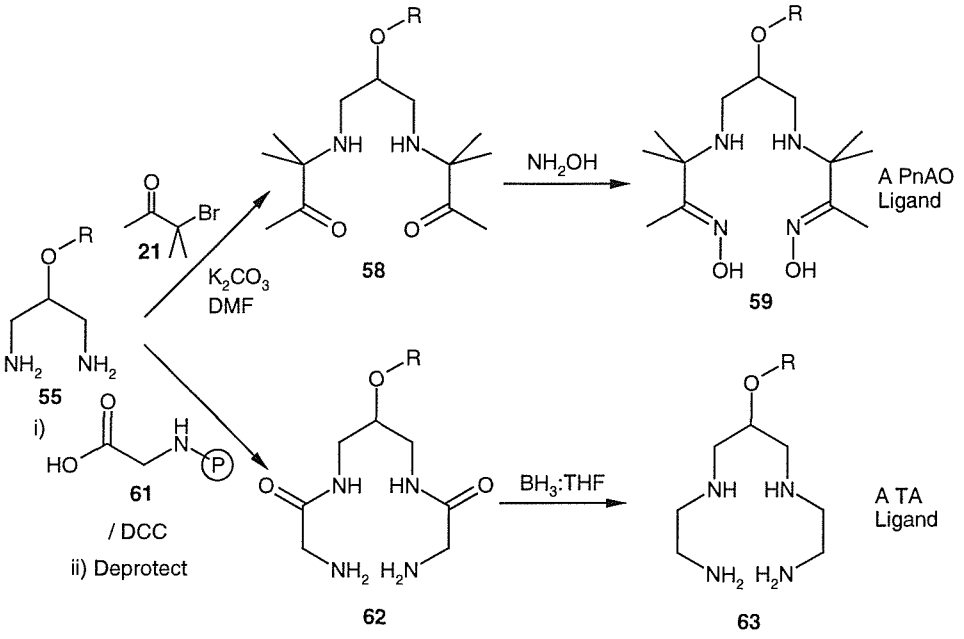
2.2.6 Oxime Formation

The reaction of **58a** with excess hydroxylamine to form dioxime **59a** was attempted following literature methods which have previously been used for the preparation of analogous alkyl-substituted PnAO ligands.[40,41] The oil isolated from the reaction mixture did not yield a solid when triturated with water, as has been previously reported for similar compounds,[40,41] while trituration with methanol resulted in the isolation of excess hydroxylamine hydrochloride. Disappointingly, a similar result was observed in the case of diketone **58b**.

2.3 Alkoxy-TA Ligands

2.3.1 Overview

It was initially envisaged that the route to 6-alkoxy substituted TA ligands would exploit the 2-alkoxy-1,3-diamine intermediates already prepared on the route to alkoxy-PnAO ligands. The development of divergent pathways from common intermediates leading to two ligand classes was attractive (Scheme 2.3). Given the success of amide reduction in the routes to alkyl-PnAO ligands (Scheme 1.3) and alkyl-TA ligands (Scheme 2.1), a similar approach was explored for the preparation of alkoxy-TA ligands. In order to deliver the desired TA skeleton, the required acyl component was a derivative of glycine. This approach also gave rise to the possibility of the development of the route using alternative amino-acids to introduce further functionality.

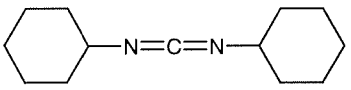


Scheme 2.3: Divergent routes to PnAO and TA ligands.

2.3.2 DCC Coupling

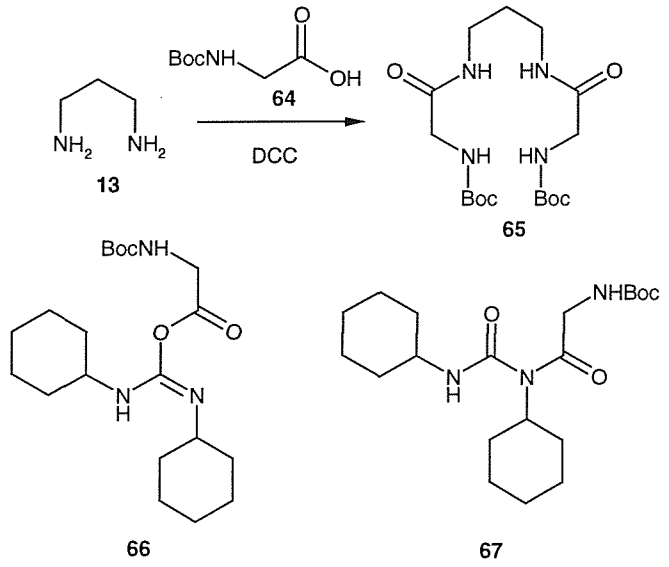
N,N'-Dicyclohexylcarbodiimide (DCC, **60**) has frequently been employed as a coupling agent for the preparation of amides from carboxylic acid and amine components.[71] The application of this method to the synthesis of 6-alkoxy 1,4,8,11-tetraazaundecanes was therefore investigated. The coupling of a diamine compound (**55**) with a suitably protected glycine derivative (**61**) would produce a diamide (**62**) which could be deprotected and then reduced to give the desired tetra-amine target (**63**).

t-Butoxycarbonyl- (Boc-) protection[72] was the first to be studied, *N*-Boc glycine (**64**) being prepared by the method of Fiakpui *et al.*,[73] with minor amendments, in excellent yield (90 %).

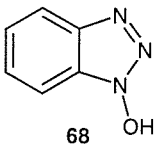


60

This synthetic approach was modelled using 1,3-propanediamine (**13**). An initial attempt at the preparation of diamide **65**, with dichloromethane as solvent,[74] was unsuccessful. Analysis of the reaction mixture by electrospray mass spectrometry indicated the presence of the desired product (m/z = 389, $M+H^+$), although purification by column chromatography afforded only a product with an apparent mass of 381. This mass corresponds to that of the activated ester (**66**) formed by reaction of the carboxylic acid with DCC, but is more likely to be urea **67** since intramolecular acyl-transfer has been observed to be a competitive side-reaction in acid – amine coupling reactions.[75]



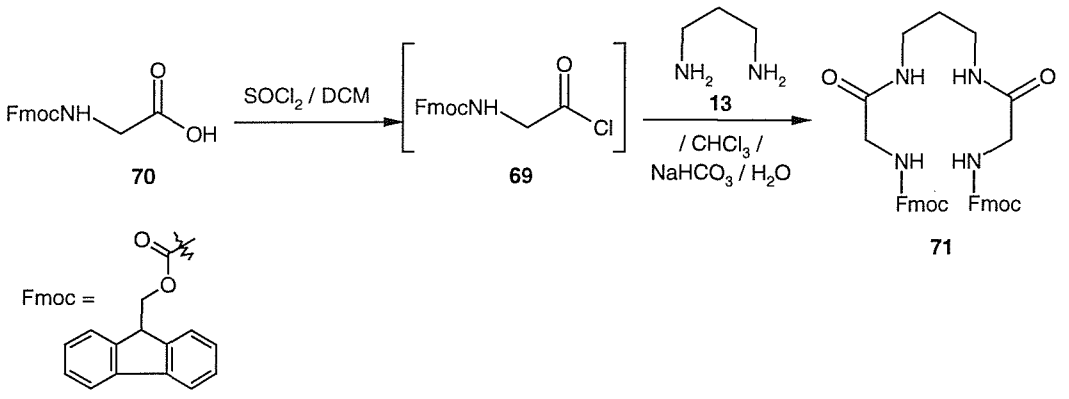
The use of alternative, more polar solvents, which have been shown to favour the desired coupling reaction,[75] was then investigated but when the reaction was carried out in both acetonitrile and methanol the desired product was not isolated. While the use of an α-nucleophile,[75] such as 1-hydroxybenzotriazole (HOBt, **68**), was also considered, the more direct approach of using a more reactive derivative of the protected amino-acid was favoured.



68

2.3.3 Acid Chloride – Amine Condensation

The condensation of a diamine with two equivalents of an acid chloride appeared to provide an alternative method for accomplishing the desired transformation. This route requires an amine-protecting group that is stable to the strongly acidic conditions needed for acid chloride formation. The previously employed Boc protecting group is labile under moderately acidic conditions hence the (9-fluorenylmethyloxy)carbonyl (Fmoc) group[72] was chosen. Fmoc-glycyl chloride (**69**) was successfully prepared from Fmoc-glycine (**70**) by the method of Carpino *et al.*[76] The reactive acid chloride intermediate was not isolated but analysis of the carbonyl region of the IR spectrum of Fmoc-glycyl chloride confirmed that conversion of the acid ($\nu_{C=O}$ = 1736 cm^{-1}) to the acid chloride ($\nu_{C=O}$ = 1799 cm^{-1}) had occurred.

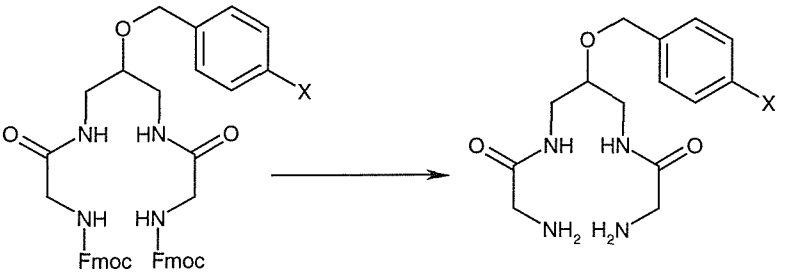


70 69 71

The method of Carpino[76] was also found to be a convenient method for the formation of the amide bond. A two-phase system of chloroform and water was employed, allowing the use of the mild base sodium hydrogen carbonate. This minimises the possibility of premature removal of the Fmoc group, which is labile to base by virtue of the readily

accessible $E1_{CB}$ pathway available for its elimination.[72] The method also allows for the *in situ* neutralisation of the dihydrochloride salts isolated in the previous step.

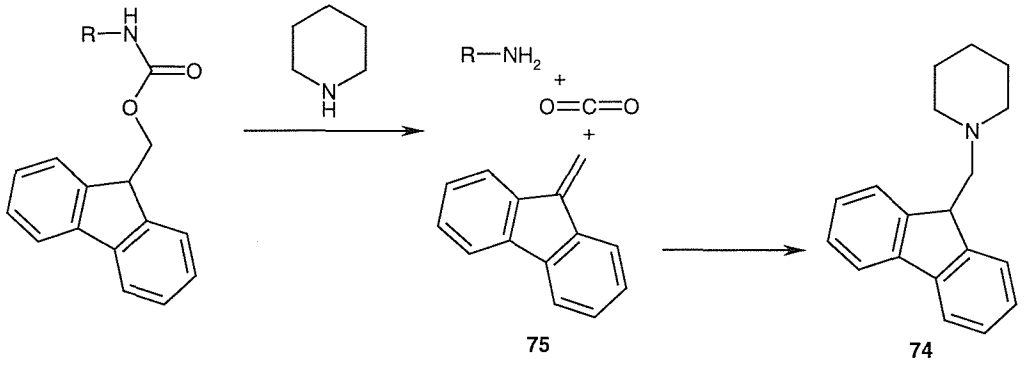
The reaction was initially modelled using 1,3-propanediamine (**13**), and the successful preparation of protected diamide **71** suggested that the method was worthy of application to substituted diamines **55a-b**. While electrospray mass spectrometry and IR spectroscopy indicated the successful formation of the desired protect amides **72a** and **72b**, the purification and full characterisation of these materials proved troublesome as a result of their insolubility in a wide variety of solvents. Similar problems have previously been reported for Fmoc-protected oligopeptides.[75] It was therefore decided to attempt the deprotection of **72a-b** without further purification and to fully characterise the deprotected diamine-diamides **73a-b** at the next step.



72a, R = H
72b, R = Br

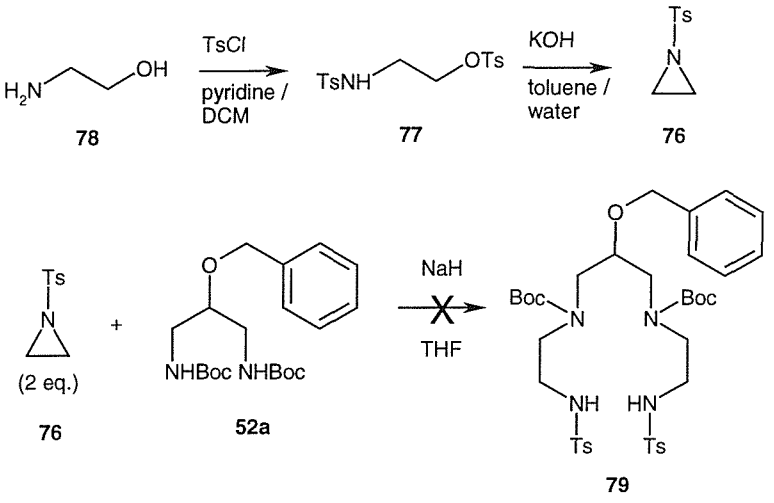
73a, R = H
73b, R = Br

Removal of the Fmoc protecting group is routinely accomplished by reaction with an amine base. However, attempts to deprotect compound **72a** under the normal, relatively mild conditions of ammonia in acetonitrile failed as a result of the poor solubility of the starting material. Attempted deprotection with piperidine resulted in the formation of an intractable mixture. The piperidine adduct (**74**) of dibenzofulvene (**75**) is widely reported to be formed as a side product of Fmoc deprotection[77] and separation of this from the desired product did not prove to be possible.



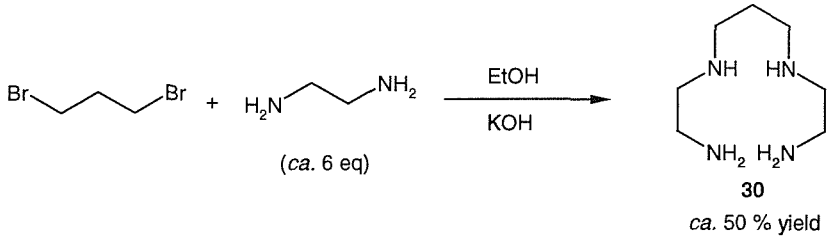
2.3.4 Alkylation of Boc-Protected Diamines

In view of the problems with the route to TA ligands *via* protected amides, alkylation of the Boc-protected diamine **52a** was also explored as a possible route to the desired tetra-amines. Boc-protected primary amines have been methylated by treatment with sodium hydride and methyl iodide.[78] A similar approach was considered, using *N*-tosyl aziridine (**76**) as the alkylating agent.[79] Readily available and inexpensive starting materials may be used to produce **77** in one step, by the simultaneous protection of the nitrogen atom and conversion of the alcohol function of 2-aminoethanol (**78**) into a good leaving group. Preparation of the material was accomplished satisfactorily following literature procedures.[79,80] However, recrystallisation by the methods previously employed proved unsatisfactory as a result of the poor recovery from methanol[80] and the toxicity of tetrachloromethane.[79] Recrystallisation from a large volume of aqueous ethanol provided material of high purity (m.p. 87-88 °C, lit.[79] 87 °C) in very good yield (73 %). Ditosyl compound **77** gave aziridine **76** upon treatment with potassium hydroxide in a two-phase system of water and toluene.[81] However, subsequent attempted reaction with ether **52a** and sodium hydride resulted in the recovery of unchanged **52a**.

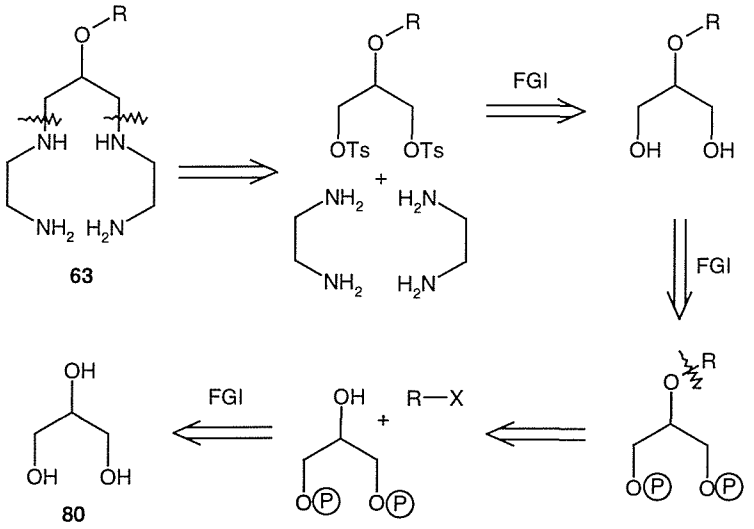


2.3.5 Dioxolane Route

The difficulties experienced with the elaboration of diamine intermediates to alkoxy-TA ligands resulted in the consideration of alternative strategies towards these targets. Symmetrical tetra-amines are, in general, prepared by the reaction of an α,ω-dibromide with in excess of two equivalents of diamine in ethanol.[82] For example, 1,4,8,11-tetraazaundecane (**30**) may be prepared by the reaction of 1,3-dibromopropane with an excess of ethylenediamine.[43,83]



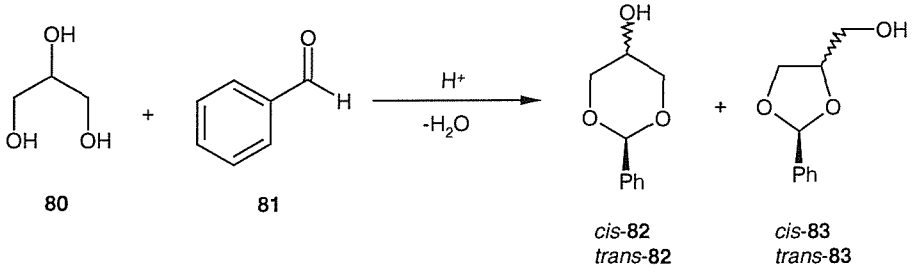
The possibility that a similar approach may be applied to the preparation of alkoxy-TA ligands was therefore investigated. Retrosynthetic analysis of the target molecule of the present study, **63**, leads to glycerol (**80**) (Scheme 2.4).



Scheme 2.4: Retrosynthetic analysis of alkoxy-TA ligands

2.3.6 Protection of the 1,3-Hydroxy Functions of Glycerol

Selective protection of the primary alcohol functions of glycerol (**80**) was required and their 1,3 disposition suggested that this might best be achieved by condensation with benzaldehyde (**81**). Benzaldehyde is well known to favour formation of the six-membered acetal (a 1,3-dioxane), rather than the five-membered isomer (a 1,3-dioxolane), upon reaction with 1,2,3-triols, *e.g.* carbohydrates.[84] However, its reaction with glycerol appears to be an anomalous case, being reported to give a mixture of the four possible products with benzaldehyde.[85,86,87]



Preparation of acetal **82** was attempted under Dean-Stark conditions in toluene in the presence of a catalytic quantity of *p*-toluenesulfonic acid. Abraham *et al.* had reported[88]

that the equilibrium mixture derived from the analogous condensation of glycerol and 2-methylpropanal could be altered to favour the 1,3-dioxane components by allowing the reaction mixture to stand in a refrigerator. Accordingly, the present reaction mixture was left to stand at 4 °C for five days, the progress of the equilibration being monitored by ^{1}H-NMR spectroscopy since Carlsen *et al.* had identified the signal of the benzylic proton for each of the four isomers.[86] The relative proportions of each of the structural and geometric isomers could be readily ascertained by integration of the appropriate one-proton singlet, each of which is well-resolved from the remainder of the spectrum (Table 2.3).

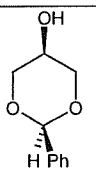
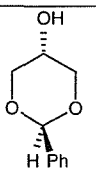
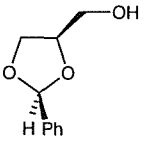
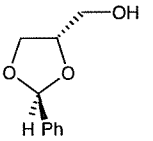
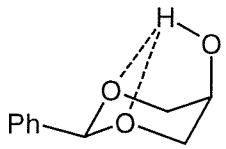
				
Designation	*cis*-**82**	*trans*-**82**	*cis*-**83**	*trans*-**83**
δ/ppm of benzylic proton	5.54	5.39	5.95	5.81
4 °C, 0 h (%)	39	19	19	23
4 °C, 48 h (%)	46	20	16	18
4 °C, 120 h (%)	50	22	12	16

Table 2.3: Percentage composition (by NMR), *after reflux*, 4 h.

The data confirm the increase in the proportion of the 1,3-dioxane components and a corresponding decrease in the relative amounts of the 1,3-dioxalanes with extended chilling of the sample. Abrahams *et al.* have argued that the 1,3-dioxanes were favoured at low temperatures because the more rigid six-membered ring is favoured enthalpically but disfavoured entropically.[88] The predominance of *cis*-**82** may be explained by the potential for intramolecular hydrogen bonding within that structure.

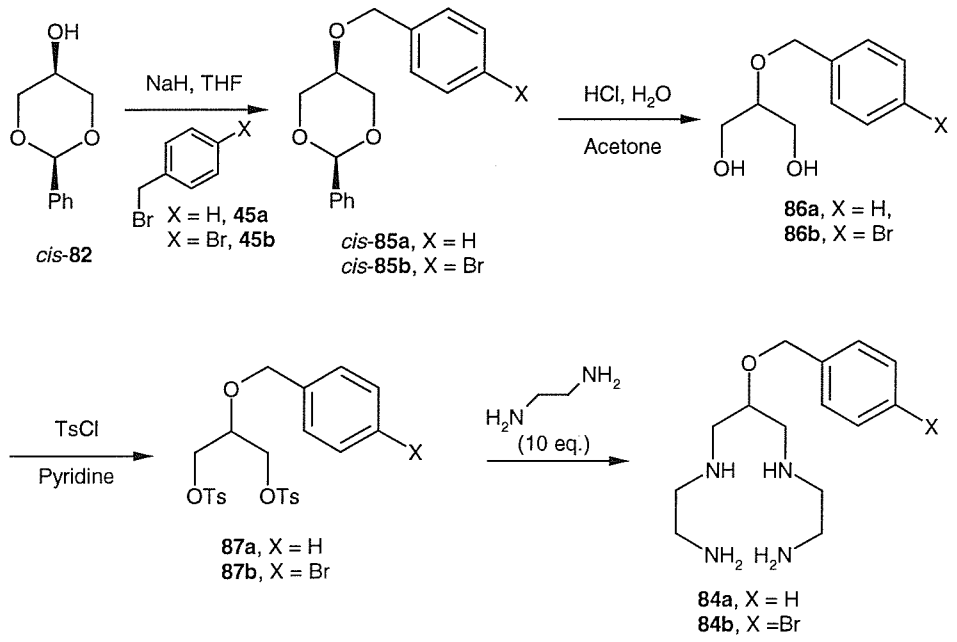


cis-**82**

In the present work, acetal *cis*-**82** was readily isolated by crystallisation of the mixture from ether at –20 °C, and is pure after recrystallisation from toluene / petroleum ether (40:60).

2.3.7 Elaboration Towards Alkoxy-TA Ligands

Attention was then turned to the method by which acetal *cis*-**82** could be elaborated to alkoxy-TA ligands (*e.g.* **84a-b**). The proposed route was alkylation at oxygen, giving ethers **85a-b**, which may be deprotected under acidic conditions to give diols **86a-b**. Conversion of the primary alcohol functions to good leaving groups (*e.g.* ditosylates **87a-b**) should allow the preparation of tetra-amine targets **84a-b** by reaction with ethylenediamine.



Scheme 2.5: Planned route to alkoxy-TA ligands.

2.3.8 Alkylation at Oxygen

Reaction of alcohol *cis*-**82** with sodium hydride and benzyl bromide (**45a**) in tetrahydrofuran gave *cis*-**85a** in almost quantitative crude yield (85 % yield after recrystallisation from ether). The product was characterised satisfactorily in agreement with the literature.[89] Ether *cis*-**85b**, the product of the reaction with *p*-bromobenzyl bromide (**45b**), required purification by column chromatography to separate it from unreacted starting materials, and was obtained in 85 % yield (based on consumed *cis*-**82**). Further attempts to prepare ether *cis*-**85b** from alcohol *cis*-**82** under identical conditions unexpectedly gave a mixture of *cis*- and *trans*-**85b**, in spite of the basic reaction conditions. NMR studies were carried out in deuterochloroform stored over potassium carbonate in order to remove any acidic impurities to which the acetal may be sensitive. Integration of the well-defined singlets assigned to the benzylic protons indicated a *cis*- : *trans*- composition of 2:1. However, since the removal of the benzaldehyde protecting group from either isomer leads to the same product, the presence of stereoisomers in no way detracted from the utility of this synthetic route.

2.3.9 Deprotection

Removal of the benzaldehyde protecting group from *cis*-**85a** was initially achieved in hydrochloric acid / acetone / water, in a very poor 26 % yield. Whilst diol **86a** had previously been reported as a low-melting solid (lit.[89] m.p. 37-39 °C), it did not prove possible to satisfactorily purify the oil that was obtained and it was decided to form the ditosylate in the next step without further purification. Tosylates are in general highly crystalline and therefore may be readily purified by recrystallisation. Diol **86b** was obtained after deprotection under identical conditions in a moderate yield (55 %), after recrystallisation from ether – petroleum ether (40:60), whether the starting material used was pure ether *cis*-**85b** or a mixture of diastereoisomers.

The poor yield of diol **86a** gave considerable scope for optimisation of the hydrolysis reaction. The substitution of ethanol for acetone as the solvent for the hydrolysis was found to be beneficial. Although ethers **85a** and **85b** were only sparingly soluble in cold ethanol, dissolution was complete at reflux. Considerable enhancement of the yield of diol **86a** was also noted (71 % compared to 26 % obtained previously) resulting in part from more efficient extraction of the product from the aqueous phase. The diol was also now obtained as a low-melting solid (m.p. 36-39 °C (toluene), lit.[89] m.p. 37-39 °C (benzene)) rather than an oil, possibly due to the avoidance of the formation of involatile impurities from the self-condensation of acetone.

Similar improvements to the procedure for the hydrolysis of **85b** afforded diol **86b** in a somewhat improved yield (68 %). Toluene was preferred as recrystallisation solvent for diol **86b**.

2.3.10 Introduction of Tosylate Groups

The alcohol functions of bromophenyl diol **86b** were converted into leaving groups by reaction with *p*-toluenesulfonyl chloride in pyridine / dichloromethane in good yield (79 %). Conversion of the parent diol **86a** was less satisfactory (37 %) as a result of poor recovery of the recrystallised product from toluene – petroleum ether (40:60). The use of dichloromethane – petroleum ether (40:60) as recrystallisation solvent allowed the isolation of pure tosylate **87a** in an improved yield (52 %).

2.3.11 Reaction With Ethylene Diamine

Initial attempts to react ditosylate **87a** with an excess of ethylenediamine unexpectedly resulted in the recovery of unchanged starting material. The solvent used for this reaction was dichloromethane and possibility that the displacement was unfavourable in the relatively non-polar solvent was considered, since the use of uncharged reactants gives rise to a charge-separated transition state (Figure 2.6).[90]

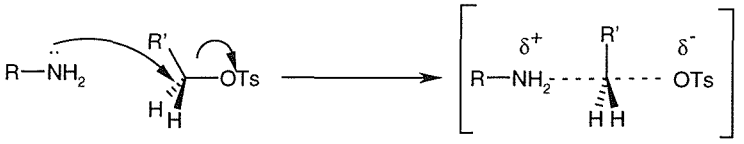
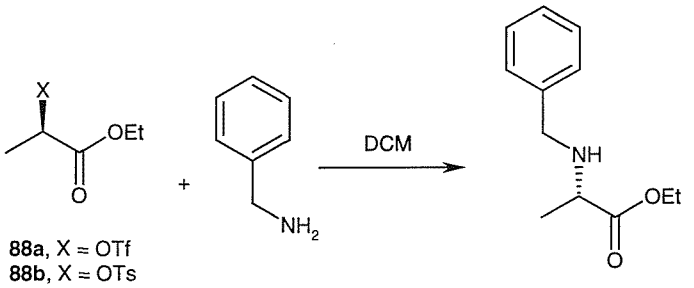


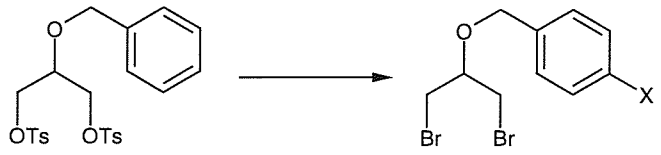
Figure 2.6: The development of a charge-separated transition state.

Accordingly, the reaction was also attempted using the more polar solvents dimethoxyethane and acetonitrile but once again, in both cases, only unchanged starting material was recovered.

A further examination of the literature revealed that Effenberger *et al.* had studied[91] the reaction of chiral propanoate esters (**88a-e**) with benzylamine (**89**). They found that leaving group ability decreased in the order TfO >>Br > MsO > TsO > Cl. Only 45 % conversion of tosylate (**88b**) was reported after 250 h at reflux in dichloromethane, in contrast to 100 % conversion of the triflate (**88a**) in the same solvent after 30 min at 0 °C.



Accordingly, a portion of ditosylate **87a** was converted to dibromide **91a** by reaction with lithium bromide in acetone. The successful displacement of the tosylate indicated that steric hindrance was unlikely to be the cause of the low reactivity of **87a**, a possibility which had also been considered. It is noteworthy that, in the case of dibromide **91**, the methylene protons were resolved as a 4H doublet, in contrast to the precursor compounds, for which, in each case, the diastereotopic protons had been observed as two, 2H signals.

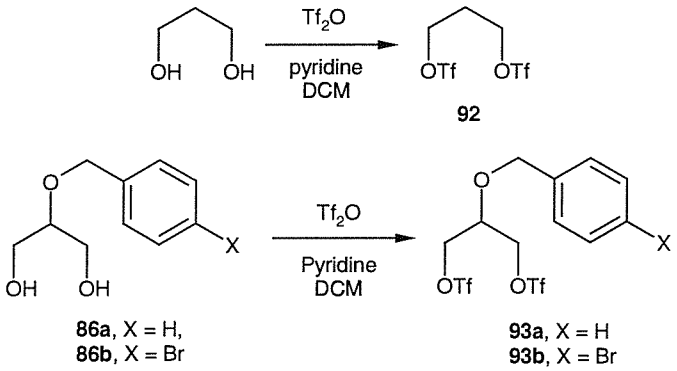


87a **91**

The reaction between dibromide **91** and ethylenediamine was subsequently attempted at reflux in DCM, but after 24 h the desired product was not observed.

2.3.12 Preparation of Triflates

In view of the low yields of the sulfonate esters and the inertness of the tosylates **87a** and **87b** towards substitution by 1,2-ethanediamine, and the relative success reported for alternative leaving groups, the use of the trifluoromethanesulfonate (triflate) leaving group was investigated.



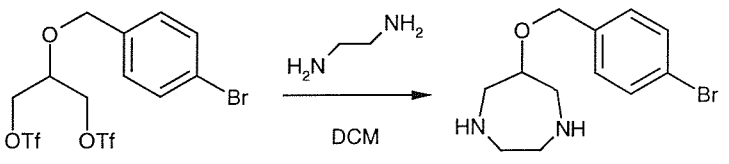
The procedure of Salomon *et al.*[92] for the preparation of **92** was adapted to the preparation of triflates **93a** and **93b**. Small-scale reaction of diol **86a** with trifluoromethanesulfonic anhydride (triflic anhydride) in anhydrous dichloromethane in the presence of dry pyridine afforded triflate **93a** in a very good 79 % yield, as an oil which solidified on standing. Similarly, triflate **93b** was obtained in excellent yield (99 %). Complete removal of pyridine from the crude product was best accomplished by washing the organic phase with a weak solution of hydrochloric acid (1 % w/w) rather than the aqueous wash described in the original work. Attempts to prepare an

analytical sample of **93a** by recrystallisation from pentane produced a black tar so, following Salomon's procedure, both triflates were subsequently stored in the freezer at –18 °C and were used in subsequent steps without further purification.

The signal for the triflate carbon ($\underline{C}F_3SO_2$-) was not observed in the ^{13}C-NMR spectrum of either product as it may be predicted to resonate at extremely low field (*ca.* 250 ppm[93]), beyond the usual chemical shift range of the spectrometer. A comparison of the ^{1}H-NMR spectra of diol **86b** and bistriflate **93b** reveals a significant downfield shift of *ca.* 1 ppm for the signal of the protons on the carbons bearing the alcohol functions upon reaction with triflic anhydride. The chemical shifts are also consistent with those previously reported for the analogous protons in **92**. Examination of the infra-red spectra of **93b** and its precursor **86b** show the disappearance of the broad O-H absorption at 3167 cm^{-1} and the appearance of characteristic bands for SO_2-O and C-F bonds at 1145 cm^{-1} and 1205 cm^{-1}, respectively.[93]

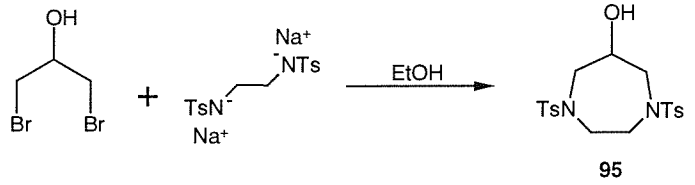
2.3.13 Reaction of Triflates

An initial, small-scale investigation into the reaction of a twenty-fold excess of 1,2-ethanediamine with triflate **93a** led only to the isolation of the dihydrochloride salt of the diamine after treatment with gaseous hydrogen chloride. A second experiment, using a similar reagent stoichiometry with triflate **93b**, resulted unexpectedly in the isolation of the cyclic diamine **94b** as the sole product in 92 % yield. In spite of the large (twenty-fold) excess of 1,2-ethanediamine, after displacement of the first triflate group, reaction of the second leaving group with the intramolecular amine nucleophile is clearly favoured over intermolecular attack.



93b **94b**

While such problems have not previously been reported with the preparation of acyclic tetra-amine ligands from α,ω-dibromides,[82] an examination of literature methods for the synthesis of 1,4-diazepines (*e.g.* **95**) reveals similar reactions with 1,2-diamines[94] or their derivatives[95] (Scheme 2.6) have previously been exploited to form a route to compounds of this class.



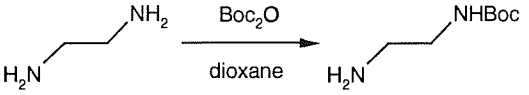
95

Scheme 2.6: 1,4-Diazepine synthesis.[95]

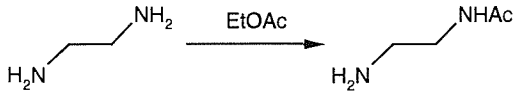
2.3.14 *N*-Protection

The most obvious solution to the problem appeared to be to reduce the nucleophilicity of one of the amine functions in ethylenediamine by the use of a suitable protecting group. The disadvantage of this approach is that the diamine component is required in large (ten- to twenty-fold) excess to circumvent the possibility of multiple *N*-alkylation. This requires a separation protocol allowing for the efficient recovery of excess protected diamine, which, unlike ethylenediamine itself, will not be volatile and which may, by virtue of the chosen protecting group, be sensitive to the acidic and basic extractions frequently employed for the isolation of amines.

Accordingly, *N*-(*t*-butoxycarbonyl)-1,2-ethanediamine (**96**) was prepared by the method of Krapcho *et al.*[96] in 73 % yield. *N*-Acetyl-1,2-ethanediamine (**97**) was also prepared, bearing a more robust protecting group for the initial investigation of this nuclephilic substitution reaction.

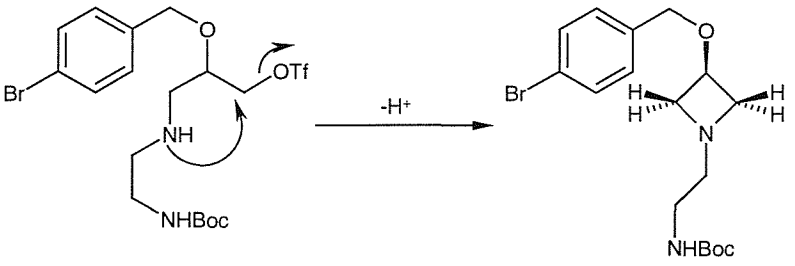


96



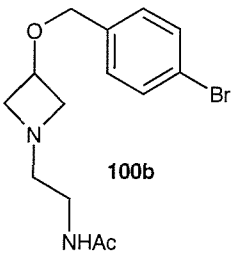
97

The reaction of a ten-fold excess of protected diamine **96** with triflate **93b** was attempted. Surprisingly, the isolated product was azetidine **98b**, arising from intramolecular reaction of the mono-substituted intermediate (**99**) rather than reaction with a second molecule of the diamine from solution. Azetidine **98b** was initially distinguished from the expected tetra-amine **84b** by its ^{1}H-NMR spectrum, particularly the integration of the signals for the protons of the ethylene chain, and their lack of diastereotopicity, together with the diastereotopic ring protons.



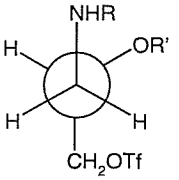
99 **98b**

A similar result was obtained using the acetyl-protected diamine (**97**), giving azetidine **100b**.

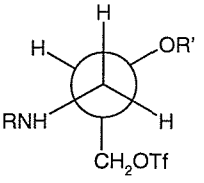


100b

An examination of the literature revealed that such reactions are not unprecedented for related 1,3-dihalopropanes. Cromwell and Phillips have argued that the steric bulk of the amine and ether groups determines the conformation of intermediate **99**, with staggered conformation **99s** (favouring intermolecular reaction) preferred when both groups are small.[97] Larger groups favour conformation **99e**, which resembles the eclipsed transition state required for intramolecular reaction.

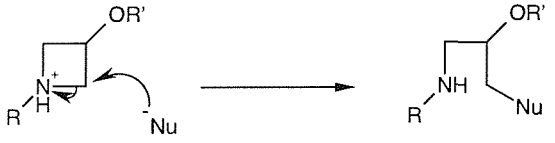


99s

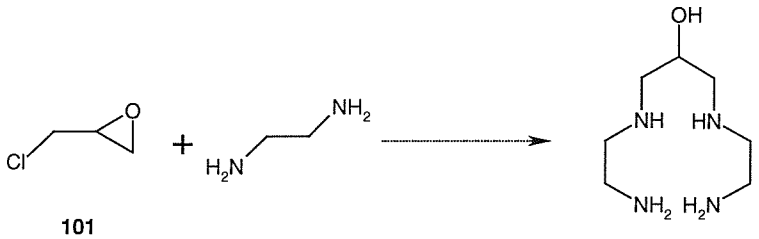


99e

The possibility of employing a ring-opening reaction using a further equivalent of the protected diamine as nucleophile was considered. However, unlike the facile ring-opening reactions of aziridines, which leads them to be potent alkylating agents, azetidines are significantly less reactive towards nucleophiles.[98] Ring-opening reactions have been shown to require acid catalysis and heating to 125 °C in a bomb.[99] Unfortunately, such forcing conditions were considered impractical for application to the current study.



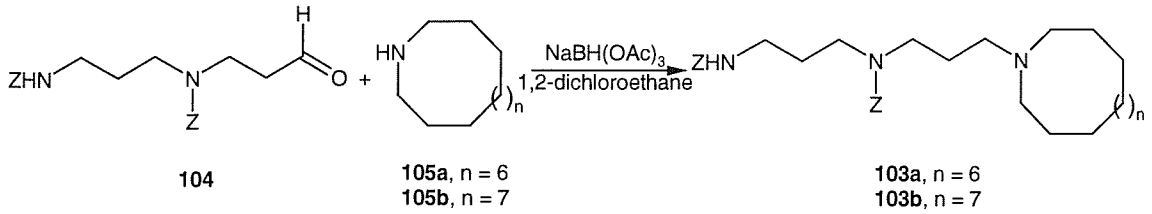
While the reaction of epichlorohydrin (2-(chloromethyl)oxirane, **101**) with excess ethylenediamine to form tetra-amine **102** had also been considered as a means of entry to this ligand class, literature precedent for the reaction with other amines suggested that, in this case too, azetidine formation would result.[100] Tetra-amine **102** was an attractive target as it might have allowed an investigation into the possibility of protecting the amine functions by complexation to a metal ion (*e.g.* Cu(II)[42]), thereby potentially allowing selective functionalisation by *O*-alkylation.



101 **102**

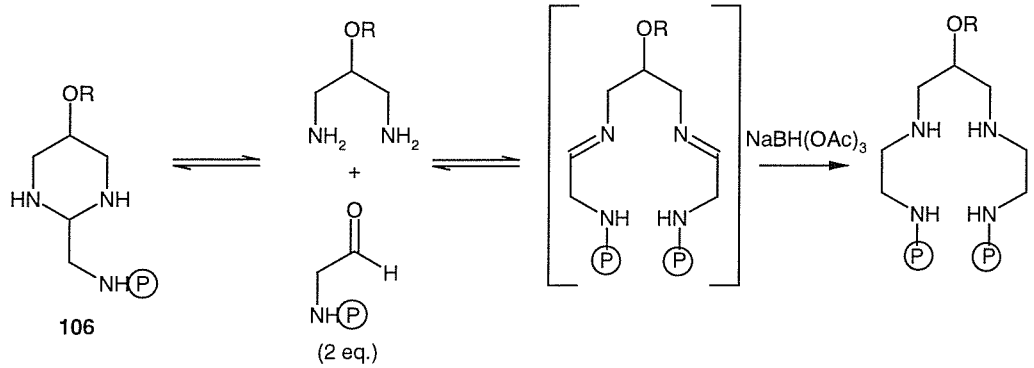
2.3.15 Reductive Alkylation

The failure of the dioxolane route to deliver the desired tetra-amine targets prompted a further re-examination of the utility of 2-alkoxy-1,3-diamines such as **55a-b**. While attempts had been made to form the desired skeleton by a two-step amidation/reduction strategy, the possibility of a single-step reductive alkylation of the diamines had not been considered. The condensation of an aldehyde with an amine results in the formation of an imine which, under the reaction conditions, is protonated to form an iminium ion which can then be reduced *in situ* by a suitable reducing agent. A similar approach has recently been employed for the preparation of sponge alkaloid precursors **103a** and **103b**.[101] The key step involves the reductive amination of an aldehyde function using sodium triacetoxyborohydride.[102] This reagent has gained popularity over sodium cyanoborohydride[103] as the latter produces toxic by-products on workup.



104 **105a**, n = 6 **105b**, n = 7 **103a**, n = 6 **103b**, n = 7

A possible problem of this approach was recognised to be the potential formation of the six-membered ring aminal (**106**), given the 1,3-relationship of the diamine functions. However, since aminal formation is a reversible process while imine reduction is irreversible, it was envisaged that the equilibrium would be altered to favour the desired product (Scheme 2.7).

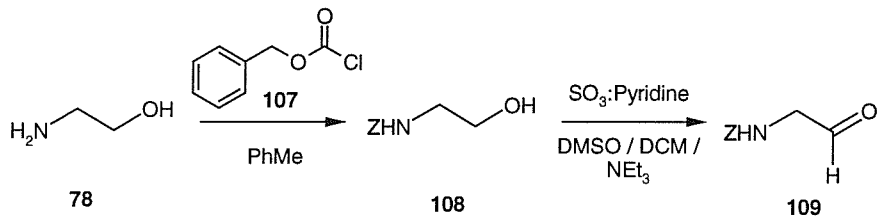


Scheme 2.7: Aminal formation *versus* reductive alkylation.

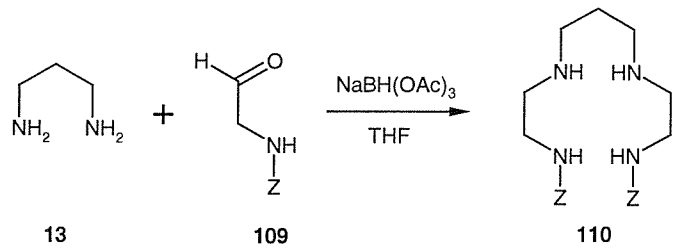
2.3.15.1 Benzyloxycarbonyl Protecting Group

The required aldehyde may be prepared from 2-aminoethanol by *N*-protection and then oxidation. In order to model the process, the benzyloxycarbonyl (Z) protecting group was introduced and subsequent oxidation was carried out with DMSO / sulfur trioxide-pyridine complex / triethylamine, according to the method of Shioiri.[104] *N*-protection of the amino alcohol **78** with benzyl chloroformate (**107**) proceeded smoothly, however repeated attempts to reproduce the oxidation of alcohol **108** to aldehyde **109** were met with little success. While in the original work the product was used without further purification after extraction from the reaction mixture, the crude product isolated in the

present work contained several components by TLC and required purification by column chromatography. The desired product was eventually isolated in a very poor yield of *ca.* 25 %.



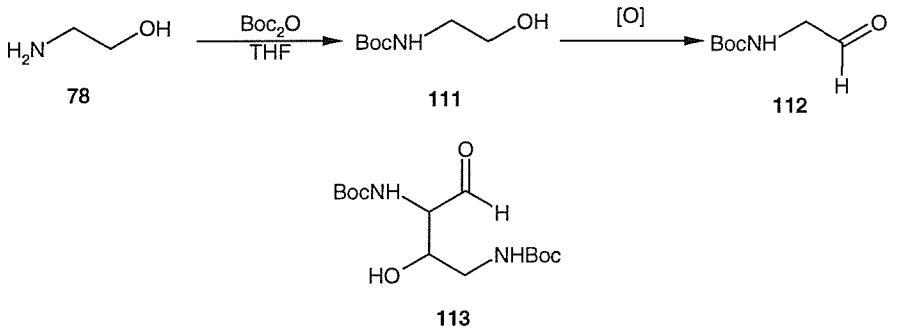
While the yield of aldehyde **109** was disappointing, the reaction nonetheless gave material which allowed the preliminary investigation of the reductive alkylation strategy. Once again, 1,3-propanediamine (**13**) was used to initially model the process, which was based on established methodologies for the reductive alkylation of mono-amines.[102]



Reaction of diamine **13** with aldehyde **109** in the presence of sodium triacetoxyborohydride gave encouraging results. After attempted purification of the product as its oxalate salt, both the mass spectrum and the IR spectrum indicated the presence of **110**, although the ^{1}H-NMR spectrum was poorly defined, and could not be unambiguously assigned to **110**. Rather than attempting to purify and optimise the reaction of Z-protected aldehyde **109** with the diamine, it was decided to concentrate on the development of the procedure using a protecting group compatible with the benzyl ethers present in diamines **55a-b**, in the short time that remained.

2.3.15.2 Boc Protecting Group

In order to apply the reaction to precursors **55a** and **55b**, an alternative nitrogen protecting group was required, the conditions for the removal of which were compatible with the presence of benzyl ethers. Once again, the acid-labile Boc group was chosen for initial investigation. The *N*-protection of amino-alcohol **78** by the method of Mayor and co-workers[105] proved facile, but the oxidation of protected alcohol **111** to aldehyde **112** proved problematic. Both the method of DeVita and co-workers,[106] using DMSO / sulfur trioxide-pyridine complex / triethylamine, and the method of de Napoli *et al.*,[107] using pyridinium chlorochromate (PCC),[108] were unsatisfactory, leading to a close-running impurity by TLC. Separation of the components by column chromatography did not prove possible; indeed exposure to silica gel appeared to increase the relative proportion (by TLC) of the impurity, which was identified as aldol **113**, from the self-condensation of the desired aldehyde.



Since aldol formation is known to be catalysed by basic or acidic conditions, the oxidation was attempted using pyridinium dichromate (PDC), an oxidising agent which has been shown to be essentially neutral.[109] Surprisingly, the alcohol was recovered unchanged after attempted reaction with a suspension of PDC in DCM.

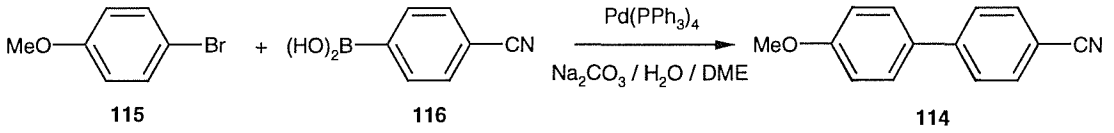
In an attempt to avoid chromatographic separation, the distillation at reduced pressure of the crude product of PCC oxidation was attempted. However, decomposition was

observed due to the thermal instability of the Boc group, resulting in the formation of a black tar in the distillation flask. In the light of these results this route was abandoned.

2.4 Introduction of a Bioactive Targeting Group

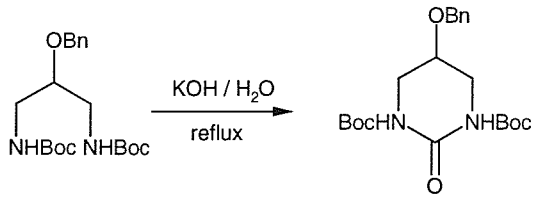
2.4.1 Biaryl Coupling

The Suzuki coupling reaction between an areneboronic acid and an aryl bromide in the presence of a palladium catalyst has become an important method for the formation of biaryl compounds.[110] In this procedure, the areneboronic acid and aryl bromide are heated under reflux in 1,2-dimethoxyethane (DME) with two equivalents of aqueous sodium carbonate, in the presence of tetrakis(triphenylphosphine) palladium (0). The reaction is of interest as a means by which a bioactive targeting group might be attached to a technetium-chelating ligand. Accordingly, an investigation into the application of the Suzuki coupling for the preparation of biaryl functionalised TA derivatives was begun. Simple biphenyl **114**, a well-characterised liquid crystalline material, was prepared[111] from 4-bromoanisole (1-bromo-4-methoxybenzene, **115**) and 4-cyanobenzeneboronic acid (**116**) in order to gain experience of the reaction. It was obtained in a reasonable yield of 42 % (lit.[111] 51 %).



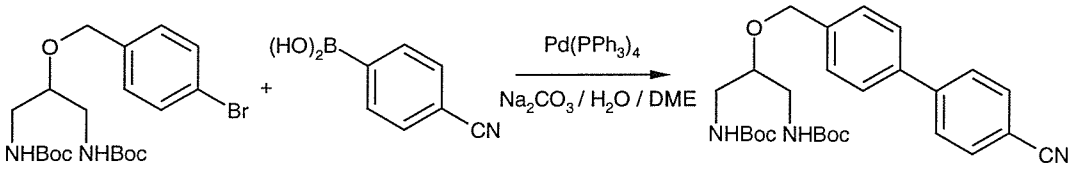
115 **116** **114**

The suitability of compound **52b** as component for the coupling reaction was initially investigated, since it has been reported that Boc-protected 1,3-propanediamines undergo a cyclisation to form a 6-membered cyclic urea (**56**) when heated under reflux in aqueous alkali (see 2.2.4 above).[69]



52a **56**

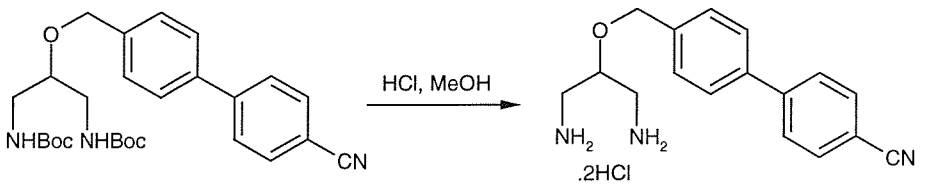
As a further model reaction, the coupling of bromoether **52b** with boronic acid **116** was attempted. Biphenyl **117** was obtained in a moderate yield of 41 % and has been satisfactorily characterised. This result demonstrated the tolerance of the fuctionality present in compound **52b** for the reaction conditions and gave encouragement that, with suitable refinements to the protocol, the Suzuki reaction should allow the efficient incorporation of biaryl groups into TA ligands.



52b **116** **117**

2.4.1.1 Removal of Boc-Protecting Groups

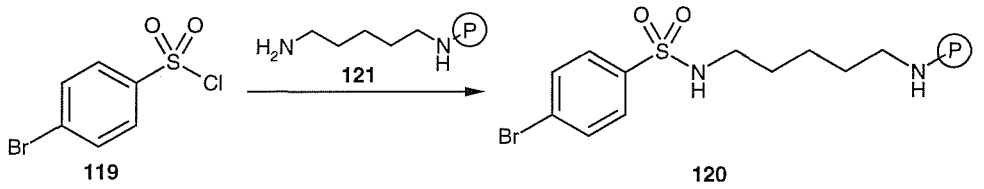
Biphenyl **117** was deprotected using methanolic HCl. However, in this case, the yield was poor (54 %) by comparison with those previously observed for compounds **52a** and **52b** (92 % and 94 % respectively). This may simply be due to the increased solubility of the product in organic solvents.



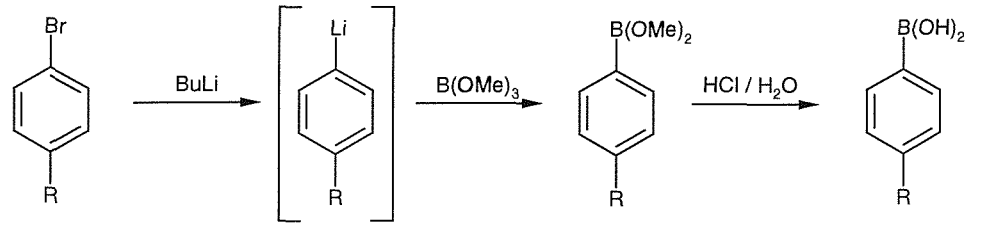
117 **118**

2.4.1.2 Application to the Current Work

In spite of the promising initial model results, the problems associated with applying the Suzuki coupling to the current work soon became apparent, namely the preparation of suitable precursors. It was envisaged that commercially available sulfonyl chloride **119** could be exploited to form the bioactive sulfonamide portion of the target molecule (**120**) by reaction with mono-protected cadaverine (**121**). This fragment could then be coupled to a precursor of the desired technetium-binding ligand, *e.g.* bromoether **52a**.



However, neither component appeared tolerant of the conditions required for the conversion of the aryl bromide function to the requisite boronic acid (Scheme 2.8). Sulfonamide **120** bears an acidic proton attached to the sulfonamide nitrogen, which might be expected to interfere with the exchange of lithium for bromine, while the Boc protecting groups in bromoether **52b** were expected to be sensitive to the acidic conditions required to hydrolyse the intermediate boronic ester, if not the strongly basic alkyl lithium reagent.



Scheme 2.8: Preparation of boronic acids.

2.4.2 Direct Introduction of a Sulfonamide Functional Group

In parallel with the Suzuki coupling, investigations were also made into the direct incorporation of an aromatic sulfonamide function (Figure 2.7). Direct chlorosulfonation of an alkyl-substituted aromatic ring (*e.g.* methylbenzene (**122**), Scheme 2.9) has been shown to occur predominantly in the *ortho*-position (**124**).[112] However, since it is desirable for the technetium-binding and bioactive targeting functions to act independently of each other, the *para*-substituted isomer is the preferred target.

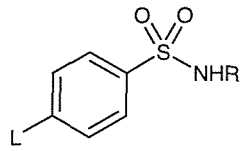
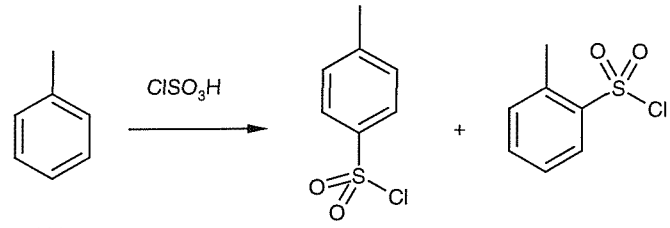


Figure 2.7: *Para* disposition of binding group - L indicates the point of attachment of a technetium-binding ligand.

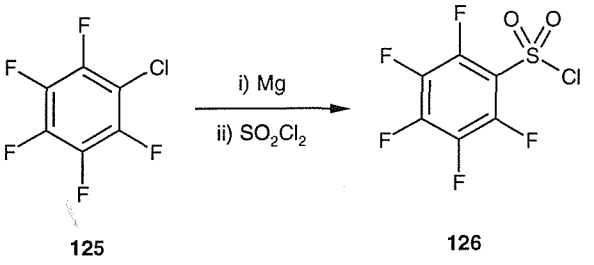


Scheme 2.9: Direct chlorosulfonation.

Since compounds **46b**, **47b**, **52b**, **55b**, *etc.*, featuring a *p*-bromophenyl substituent, had been successfully prepared, attention was then turned to the development of a method by which such compounds might be converted regioselectively into the corresponding *para*-sulfonamide.

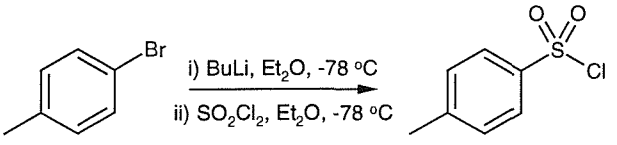
The reaction of pentafluorophenyl magnesium chloride (**125**) with sulfuryl chloride has previously been employed to prepare pentafluorobenzenesulfonyl chloride (**126**) in

good yield.[113] While the use of a Grignard reagent appears to be incompatible with the current synthesis, the exchange of bromine for lithium (upon treatment of an aryl bromide with an alkyl lithium[114]) produces a species which may be expected to demonstrate similar reactivity. This exchange has been shown, at low temperatures, to be faster than both nucleophilic addition[115] and the removal of acidic protons[116] by the alkyl lithium.



125 126

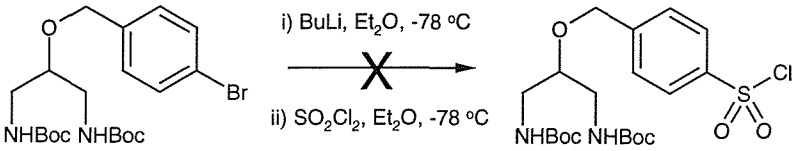
Although alkanesulfonyl chlorides have been prepared from the appropriate alkyl lithium and sulfuryl chloride,[117] the application of the procedure to an aryl system appears to be novel. Accordingly, a model reaction was carried out and 4-methylbenzenesulfonyl chloride (tosyl chloride, **123**) was prepared in a moderate yield of 63 % from 1-bromo-4-methylbenzene (**127**) and sulfuryl chloride.



127 123

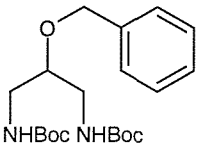
Initial attempts to extend the protocol to a compound of direct interest to the current work proved unsuccessful. While the potential problem of the acidity of the carbamate protons was appreciated, the reported rapidity of the bromine-lithium exchange reaction ensured that the method was worthy of investigation. Treatment of aryl bromide **52b** with one equivalent of butyl lithium, followed by quenching with sulfuryl chloride,

resulted in the recovery of unchanged starting material, suggesting that the relative acidity of the carbamate protons would indeed present a problem here.



52b **128**

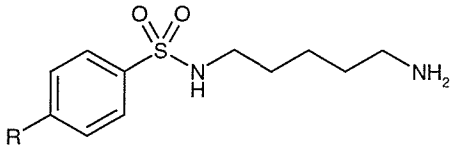
The reaction was repeated using three equivalents of base. Analysis of the products again failed to reveal the presence of the desired compound, although in addition to the recovery of some starting material, compound **52a** was isolated, presumably from protonation of the intermediate carbanion. This may suggest that bromine-lithium exchange occurs more rapidly than deprotonation by the alkyl lithium but that the aryl carbanion deprotonates the carbamate nitrogen atom. Since reaction temperature has been shown to be of crucial importance to the preference for halogen-metal exchange over competing processes,[115] the experiment was repeated with the internal temperature of the reaction being monitored to ensure that the mixture remained cold (*ca.* –100 °C) throughout the procedure, without success. Whilst the use of an alternative base (*e.g.* sodium hydride) to deprotonate the carbamate functions prior to the addition of butyl lithium was also considered, the results already obtained indicated that compound **52b** was unsuitable for accomplishing the desired transformation.



52a

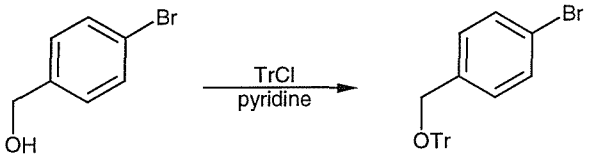
2.4.3 Alternative Routes

Whilst the trapping of an aryl-lithium species with sulfuryl chloride appeared to offer a means by which a sulfonamide could be introduced, the problems associated with applying the reaction to aryl bromide **52b** led to the exploration of alternative routes to the desired product. The sulfonamide could be introduced at a much earlier stage in the synthesis, since analogous *p*-toluenesulfonamide derivatives of amines are themselves used as robust *N*-protecting groups. This would also require protection of the primary amine function of the cadaverine moiety with a group orthogonal to the required sulfonamide.



129

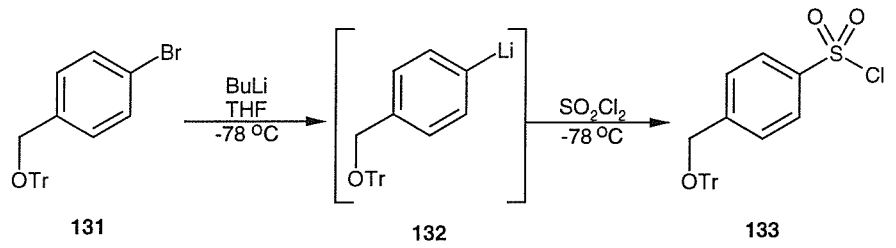
Accordingly, it was decided to develop an alkylating agent bearing the aromatic cadaverine sulfonamide (**129**). 4-Bromobenzyl alcohol (**130**) was chosen as the basis for the route, the alcohol function being protected with the base-stable trityl group to give **131** in 76 % yield.[72]



130 **131**

Halogen-metal exchange proceeded rapidly in THF at –78 °C and the lithiated species (**132**) was trapped efficiently with sulfuryl chloride, two equivalents of which were used to reduce the possibility of sulfone formation. The product was found to be unstable, most probably due to hydrolysis of the sulfonyl chloride function, which in turn leads to the formation of acidic impurities to which the trityl group is sensitive. It should be

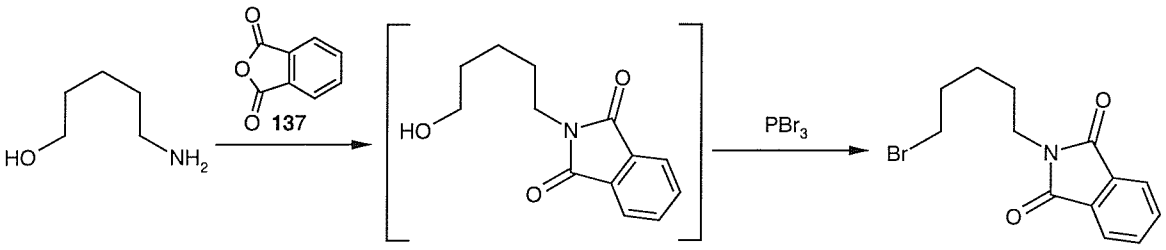
noted that some decomposition was observed even after storage overnight in a desiccator. Nevertheless, sulfonyl chloride **133** proved a useful reagent if used immediately after its preparation.



131 **132** **133**

Direct trapping of sulfonyl chloride **133** with a cadaverine derivative would required the preparation of a mono-protected α,ω-diamine in good yield, a procedure which has previously proved challenging.[96] An alternative approach was therefore initially investigated, namely the alkylation of simple sulfonamide **134**, derived from ammonia. Reaction of sulfonyl chloride **133** with ammonia solution in ethanol afforded sulfonamide **134** in excellent yield (85 %).

A robust protecting group was required for the *N*-protection of amino-alcohol **135** and the phthalimide protecting group was chosen for this purpose. The alkylating agent required (**136**) was prepared by the reaction of amino-alcohol **135** with phthalic anhydride (**137**) followed by treatment by phosphorus tribromide.



135 **138** **136**

Regrettably, there was insufficient time for further investigation of the alkylation reaction.

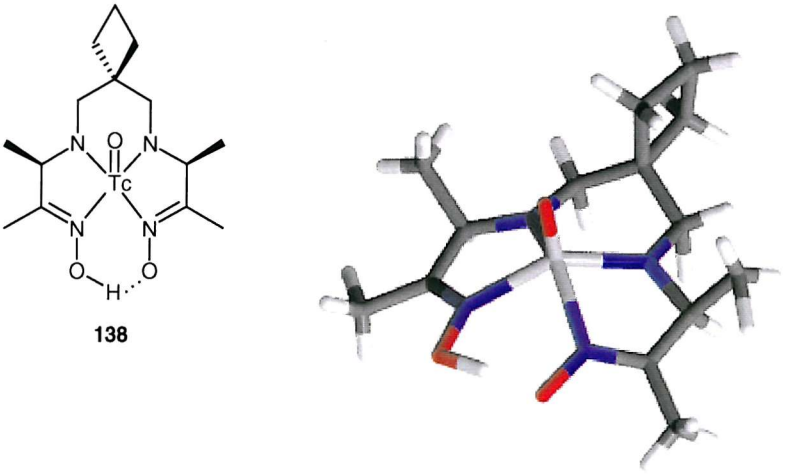
3 X-Ray Crystallographic Studies

This was found pretty soon, drawing on good inorganic chemistry, that distant Cartesian island, a lost paradise, for us organic chemists, bunglers, "students of gunk"…

Primo Levi

3.1 Introduction

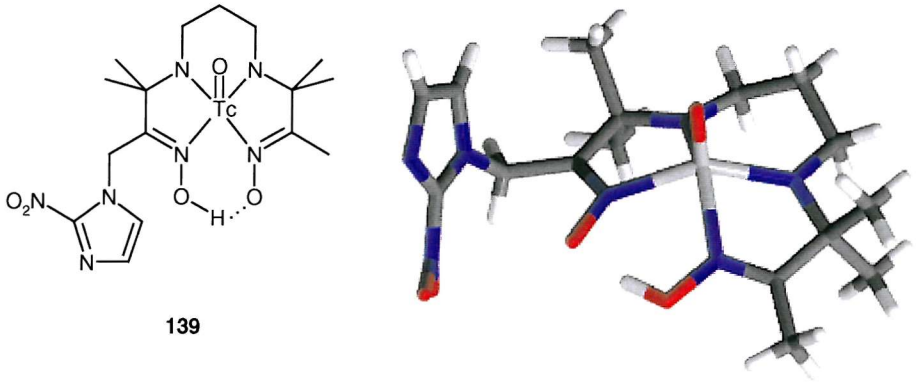
While several examples of PnAO ligands substituted unsymmetrically at the 6-position have been prepared,[29,40,41] a survey of the Cambridge Crystallographic Database[118] has revealed no crystallographic characterisation of the complexes of such ligands with technetium. The technetium-PnAO complexes reported to date bear two identical substituents at the six-position, most frequently two hydrogen atoms or *gem*-dimethyl groups but also including spiro cyclobutane derivative[119] **138** (Figure 3.1).



138

Figure 3.1: Crystal structure of $TcO(C_{14}H_{25}N_4O_2)$ [**138**].[119]

An example featuring a bioactive targeting group has also been characterised crystallographically (**139**),[120] although in this case the nitroimidazole group was introduced at the 1-position (Figure 3.2). Such an unsymmetrical substitution brings with it the synthetic challenge of the stepwise mono-alkylation of the intermediate diamine[41] and, upon complexation with oxotechnetium (V), gives rise to enantiomeric products.



139

Figure 3.2: Crystal structure of $TcO(C_{16}H_{26}N_7O_4)$ [**139**].[120]

3.2 Complexation Behaviour of 6-Monosubstituted PnAO Ligands

The investigation of the complexation behaviour of symmetrical, 6-monosubstituted ligands utilised a model series of PnAO ligands previously prepared by Walker.[29] While crystals suitable for single crystal X-ray diffraction had previously been obtained by complexing representative ligands with cobalt (III) and copper (II), the preparation of the corresponding technetium complexes had not been attempted by Walker.

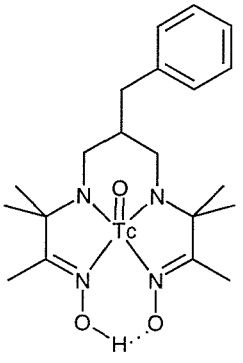
The spectroscopic characterisation of radioactive samples must be carried out on designated NMR and Mass Spectrometers. This meant that the primary characterisation method available on site for the current work was single crystal X-ray crystallography.

Good radiochemical practice requires that procedures be initially modelled using non-radioactive isotopes. However, since no stable isotopes of technetium exist, the

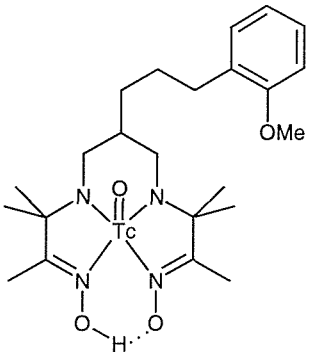
procedure had to be initially studied using non-radioactive rhenium. It has not previously proved possible to isolate a rhenium complex of PnAO or one of its derivatives and, while here too no product could be isolated, the experiment provided a valuable practice for the safe handling of the technetium complexes.

3.2.1.1 Complexation Protocol

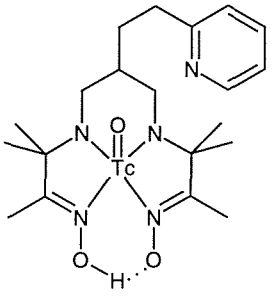
The procedure for the complexation of technetium with the PnAO ligands was based on that of Troutner *et al.*,[39] with minor amendments. The ligand and ammonium pertechnetate were mixed in a two-phase system of water and ether, in the presence of tin(II) chloride as reducing agent and tartaric acid to stabilise the reduced technetium species before complexation by the PnAO ligand. The lipophilic nature of the resulting complexes was clear in each case as a result of the rapid appearance of a distinctive yellow-orange colour in the organic phase. Chromatographic separation of the complex from excess ligand followed by dissolution of the resulting orange powder in a minimum of ether or methanol-ether and then chilling of the solution in the refrigerator or freezer resulted in each case in the preparation of single crystals suitable for X-ray crystallographic study. Three complexes **140a-c** have been successfully characterised.



140a



140b



140c

3.2.2 ORTEP Diagrams of Complexes 140a-c

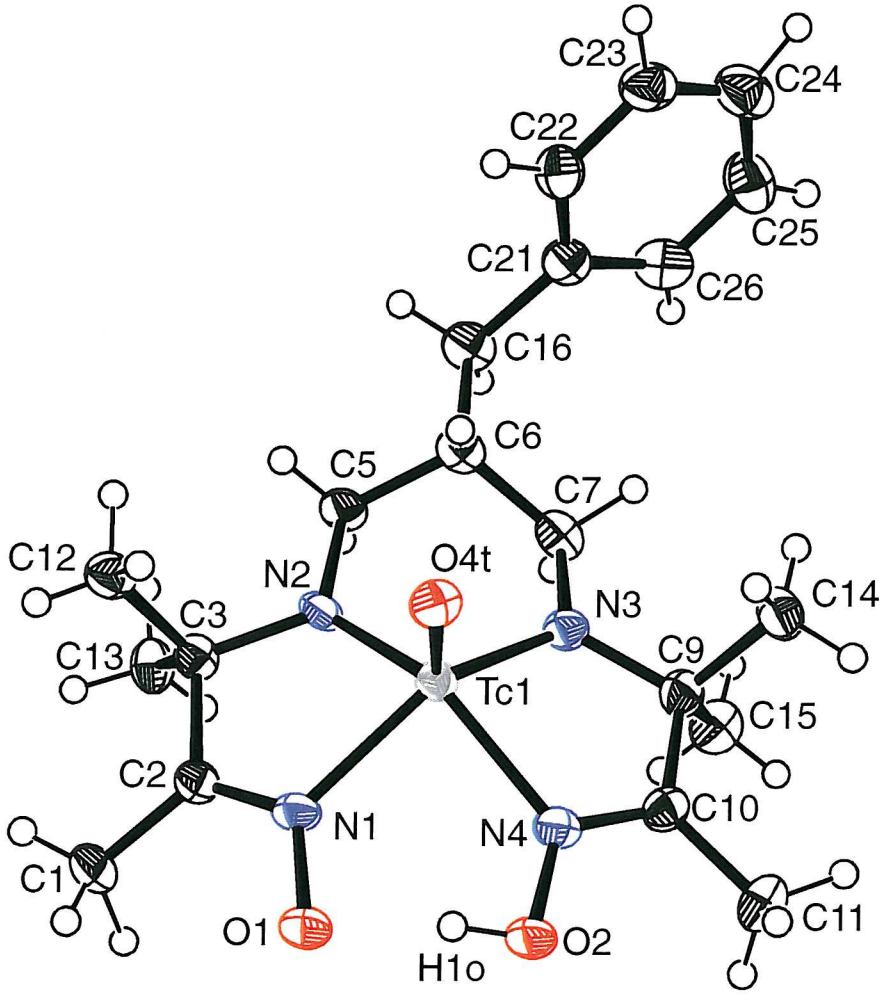


Figure 3.3: ORTEP diagram of $TcO(C_{20}H_{31}N_4O_2)$ [**140a**]. Thermal ellipsoids are shown at 50 % probability.

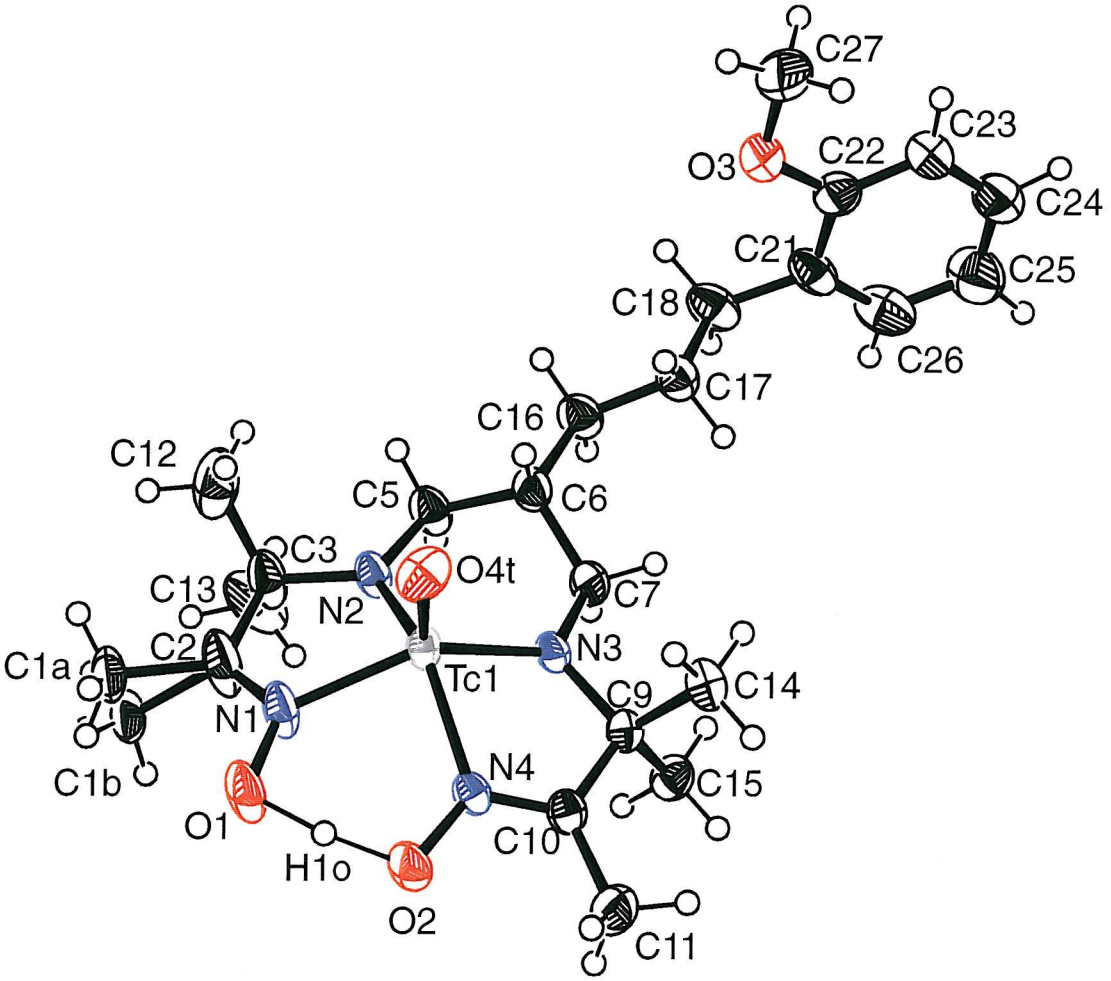


Figure 3.4: ORTEP diagram of $TcO(C_{23}H_{37}N_4O_3)$ [**140b**]. Thermal ellipsoids are shown at 50 % probability.

The C1 atom was found to be disordered over two sites (C1a and C1b).

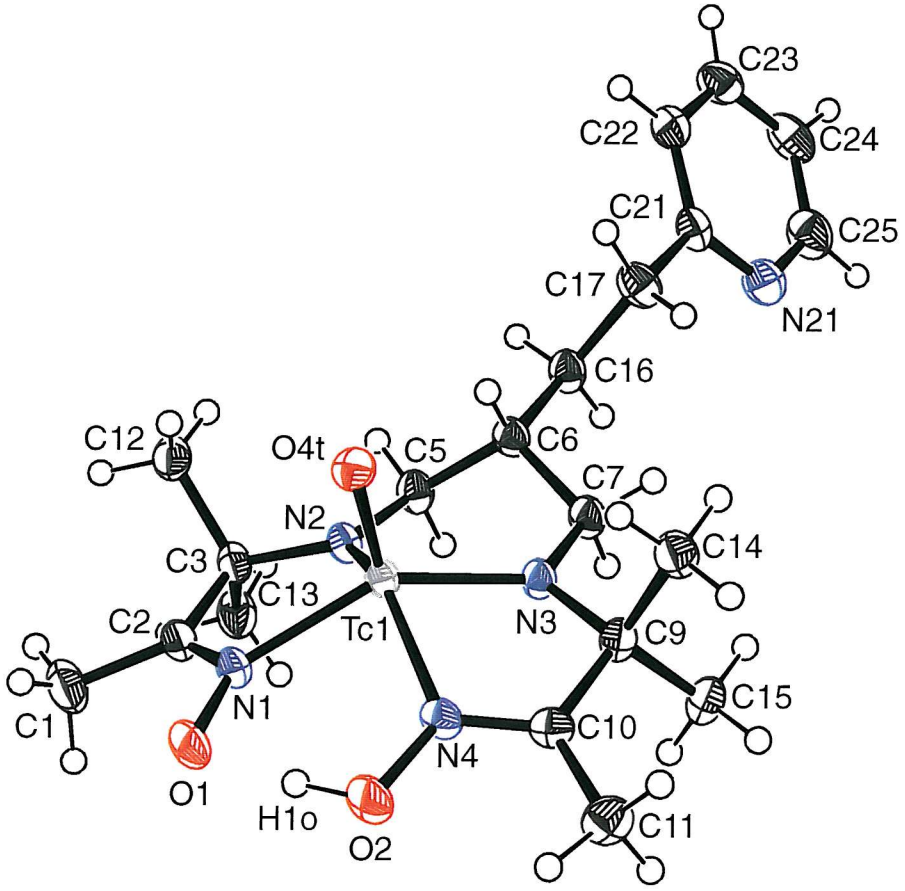


Figure 3.5: ORTEP diagram of $TcO(C_{20}H_{32}N_5O_2)$ [**140c**]. Thermal ellipsoids are shown at 50 % probability.

In all three cases, the observed structure is analogous to that of the parent TcO-PnAO complex (**1**). The technetium complex adopts a square pyramidal geometry, with the base defined by the plane of the four nitrogen donors and the oxo ligand occupying the apical position. The technetium ion sits approximately 0.67 Å above the plane of the nitrogen atoms. The ligand is deprotonated at both of the amine functions (to give amides in the Inorganic Chemistry sense) and at one of the oxime hydroxyl groups, thereby resulting in an overall neutral complex with oxotechnetium (V) [TcO^{3+}]. The shorter N(amide) – Tc bond lengths (*ca.* 1.91 Å) compared to the N(oxime) – Tc distance (*ca.* 2.08 Å) reflect the multiple bond character of the former bonds caused by π-donation to stabilise the high formal charge on the technetium core. This in turn leads to a slight weakening, and hence lengthening, of the Tc=O bond (*ca.* 1.68 Å), a value

which lies at the upper end of the range observed for oxotechnetium(V) complexes (1.610 – 1.672 Å),[38] in common with the complexes previously observed with this ligand class.[39]

	140a [Benzyl]	**140b** [Anisyl]	**140c** [Pyridyl]	**1** [Parent PnAO][38]
Tc(1) – O(4t)	1.679(3)	1.6758(13)	1.6722(17)	1.679(3)
Tc(1) – N(1)	2.084(4)	2.0672(15)	2.0848(19)	2.086(3)
Tc(1) – N(2)	1.905(4)	1.9190(14)	1.910(2)	1.917(3)
Tc(1) – N(3)	1.911(4)	1.9121(13)	1.9213(19)	1.908(3)
Tc(1) – N(4)	2.081(4)	2.0770(15)	2.079(2)	2.093(4)
Tc(1) – N_4 plane	0.667(22)	0.667(9)	0.664(20)	0.678(1)

Table 3.1: Comparison of selected bond lengths and distances (Å).

In each case, the substituent occupies a pseudo-equatorial orientation, which places the pendent group at the greatest distance from the metal-binding site. Such a conformation is desirable for the application of a PnAO ligand as a metal-chelator attached to a bioactive targeting group.

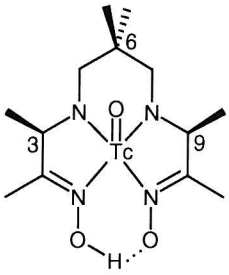
In the three structures, all non-methyl hydrogen atoms were located from a difference map, particularly the proton of the O···H – O hydrogen bond which has previously proved somewhat difficult to detect in similar complexes.[38,39] The disorder of the methyl hydrogen atoms suggests that intra- or intermolecular hydrogen-bonding type CH···X interactions to the methyl groups are unimportant in these structures.[121] Further

evidence for this comes from the examination of the tables of inter- and intramolecular close-contacts for each structure.

The three complexes prepared above clearly illustrate that the TcO-PnAO complex is a robust *pseudo*-crown which is insensitive to the nature of the side-arm. In particular, since the TcO-PnAO complex can be regarded as an 18-electron species, the absence of co-ordination from the additional pyridyl group in complex **140c** is not surprising. Such a co-ordination would also require a some distortion of the geometry of the complex, since the pyridine ring is linked to the PnAO skeleton by an ethyl chain.

3.2.3 Conformation of the Six-Membered Chelate Ring.

In all cases, the six-membered chelate ring adopts a pseudo-boat conformation, in common with the majority of TcO-PnAO complexes. Indeed a pseudo-chair conformation has only been observed in the case of complex **141**, where the asymmetric unit contains one molecule of the complex in a chair conformation (Figure 3.6) and a second, independent molecule in a boat conformation (Figure 3.7).[39] This example appears to be the only case in which the relative energies of the two conformations are close enough for the chair conformation to compete with the boat, leading to the presence of both conformers. The most obvious explanation for the adoption of a chair conformation in this *meso*-substituted case would appear to be the absence of any steric clash between the axial methyl group on C6 and substituents anti to the oxo ligand, since C3 and C9 each bear only a single methyl substituent orientated syn to the oxo ligand. Such a conformation might therefore have been predicted for the complexes in the current study, since the adoption of a chair conformation would require only that an axial hydrogen on C6 be located syn to the methyl substituents of C3 and C9.



141

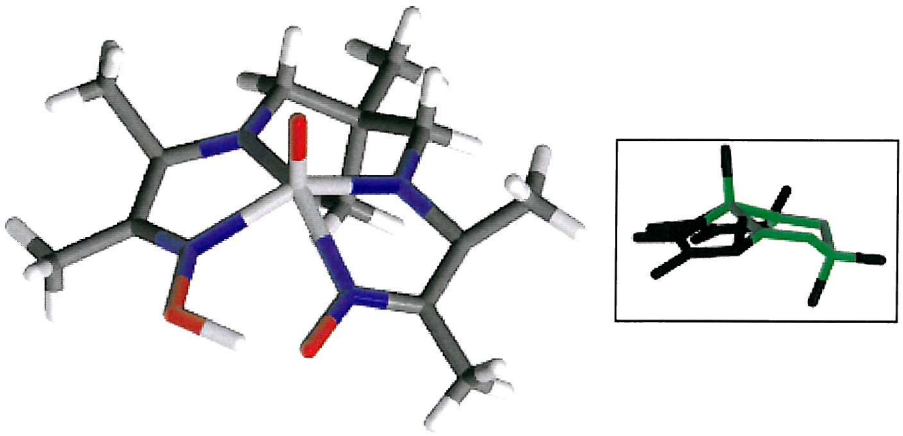


Figure 3.6: Chair conformation of **141** (highlighted inset).

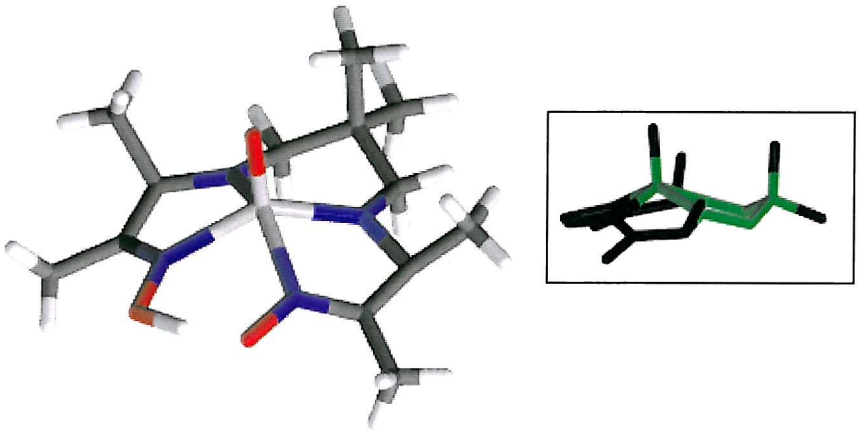


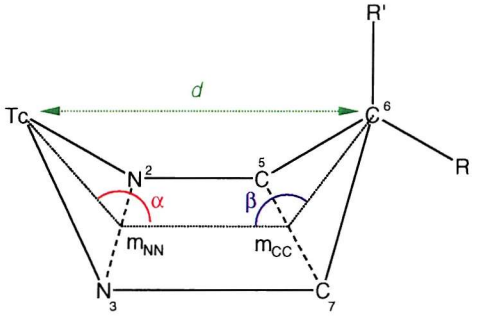
Figure 3.7: Boat conformation of **141** (highlighted inset).

Closer examination of the precise geometry of the six-membered chelate ring in the structures presented here and in representative examples of technetium-PnAO

complexes reported previously reveals a sensitivity to the nature of substituents at the 6-position. It appears that the "flattening" of the boat conformation can be quantified (Table 3.2) by the measurement of the angles of fold α and β and the distance *d* (Figure 3.8). The smallest values of α and β are observed with R=R'=H, while the introduction of bulkier methyl groups produces the greatest flattening of the ring, with α increasing by 10.3° and β by 6.5°, leading to a significant increase in the distance, *d*, from the technetium to C6 (*ca.* 3.34 Å *versus* 3.13 Å). While care must be taken with the data for the cyclobutane derivative **138**, since in this case C3 and C6 each bear only a single methyl group, the geometry of that structure shows intermediate values as might be predicted for groups smaller than methyl substituents by virtue of their restricted conformation.

R	R'	α / °	β / °	*d* / Å	Source of structural data
-H	-H	158.61	121.48	3.134	38
$-(CH_2)_3-$		165.78	123.48	3.249	39
-Me	-Me	168.90	128.01	3.341	119
$-CH_2Ph$	-H	159.64	123.87	3.179	Present work
$-(CH_2)_3$-*o*-C_6H_4-OMe	-H	158.68	123.44	3.171	Present work
$-(CH_2)_2$-*o*-C_5H_4N	-H	159.53	123.52	3.169	Present work

Table 3.2: 6-Membered chelate ring conformational data (α, β and *d* being defined in Figure 3.8).



$\alpha = Tc\text{-}m_{NN}\text{-}m_{CC}$

$\beta = C6 - m_{CC} - m_{NN}$

$d = Tc - C6$

where

m_{CC} is the midpoint of C5 and C7

m_{NN} is the midpoint of N2 and N3

Figure 3.8: Definitions of α, β and *d*.

The data for the complexes bearing a single substituent at C6 show values for the angles α and β and the distance *d* very close to those found in the complex unsubstituted at C6 (*i.e.* R=R'=H), as would be expected for a ligand bearing only a hydrogen in the axial position on C6.

3.2.4 PnAO Complexes With Other Metal Ions

A review of the behaviour of the complexes of PnAO derivatives with metal ions other than technetium reported in the Cambridge Crystallographic Database[118] and those recently prepared by Walker[29] has been carried out. This reveals that in all cases the ligand is not deprotonated at the amine nitrogens. The six-membered chelate ring is

also observed to adopt a chair conformation in each case, which is in contrast with the interpretation of these other structures by Jurisson *et al.*, who stated that "the boat conformation [is] observed for other metal complexes of this ligand type".[39] Both deprotonation and the adoption of a boat geometry are unique structural features of the TcO-PnAO family of complexes, hence the use of alternative metal ions for the initial screening of potential radiopharmaceuticals does not seem to be justifiable.

4 Conclusions

Several conclusions can be drawn from the work reported in this thesis:

1. A number of routes to apically substituted TA-ligands have been explored. Whilst terminal *N*-phenyl TA analogues have been successfully prepared, the parent ligands have proved less accessible. Nonetheless, their diamine-diamide precursors have been obtained in good yield. However, reduction of these latter to their tetra-amine analogues has to date proved unsatisfactory, partly due to the problems associated with the isolation and satisfactory purification of these highly polar products.

2. In the course of the investigation of the addition of the ethylenediamine units into 1,3-disubstituted propane derivatives, the formation of both four- and seven-membered heterocyclic derivatives was observed, a process which may have some more general synthetic utility.

3. Methodology has been developed for the preparation of aryl sulfonamides from the corresponding aryl bromides *via* the quenching of an aryl lithium species with sulfuryl chloride.

4. Preparation and characterisation of three novel Tc=O complexes with PnAO ligands has demonstrated that (i) apical substituents do not significantly perturb the complexation properties of the PnAO core; (ii) the presence of functionality in this side chain also has little effect on complex formation; (iii) a single substituent placed at C-6 (the apical site) of the PnAO core adopts a pseudo-equatorial position in the complex; and (iv) other transition metal ions are poor mimics for such technetium complexes.

5 Experimental

Laughter and tears are both responses to frustration and exhaustion... I myself prefer to laugh, since there is less cleaning up to do afterward.

Kurt Vonnegut, Jr.

5.1 General

5.1.1 Instrumentation

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AC 300 spectrometer. Chemical shifts (δ) are quoted relative to tetramethylsilane at 0 ppm or to residual solvent peaks. Carbon assignments were supported by DEPT experiments.

Infra-red spectra were obtained using sodium chloride plates on a Perkin-Elmer 1600 Series FTIR or using a Golden Gate sampling attachment on a Mattson Satellite 3000 FTIR.

Electrospray mass spectra were recorded on a Micromass Platform II single quadrupole mass spectrometer. The instrument is calibrated with a mixture of sodium and caesium iodide, the operating conditions were capillary 3.50 kV, HV lens 0.5 kV, cone voltage 20V, source temperature 110 °C, ES eluant: 100 % acetonitrile at 100 µl min^{-1}, nitrogen drying gas 300 l h^{-1} and nebulising gas 20 l h^{-1}. 10 µl injections of ≈1-10 µl ml^{-1} solutions were made using a Hewlett-Packard HP1050 autosampler. Negative ion data were recorded under identical conditions except for different polarity voltages and capillary voltages of –3.0 kV. Atmospheric Pressure Chemical Ionisation mass spectrometry operating conditions were capillary 3.5 kV, HV lens 0 kV, cone voltage 20 V, source temperature 150 °C, probe temperature 450 °C, eluant: 100 % acetonitrile at 200 µl min^{-1}, nitrogen drying gas 250 l h^{-1} and APCI sheath gas 50 l h^{-1}.

Negative ion data were recorded under identical conditions except for different polarity voltages and capillary voltages of –3.0 kV. Electron Ionisation (EI) and Chemical Ionisation (CI) mass spectrometry was carried out on a ThermoQuest TraceMS gas chromatography mass spectrometer configured for open access operation.

Elemental analyses were performed by the Microanalytical Service, Department of Chemistry, University College London.

Melting points were measured on an Electrothermal melting point apparatus or a Kyowa Optical Model SDZ-PL heated-stage microscope, and are uncorrected.

Thin layer chromatography was carried out on Machery-Nagel Alugram® Sil G/UV_{254}. Preparative scale column chromatography was carried out on Sorbsil C60 40/60 H.

5.1.2 Chemicals

Unless otherwise stated, all chemicals were reagent grade and were used as supplied by Aldrich Chemical Company, Lancaster or Avocado. Ammonium pertechnetate was kindly provided as a gift by Nycomed Amersham.

Anhydrous methanol and anhydrous ethanol were dried by distillation from magnesium and iodine.[122] Anhydrous dichloromethane was distilled from calcium hydride. Anhydrous ether was dried over sodium wire.[122] Anhydrous tetrahydrofuran was distilled from sodium wire using benzophenone ketyl indicator.[122] Anhydrous pyridine was decanted from either potassium hydroxide or calcium hydride.[122] Anhydrous DMF was distilled from calcium sulphate.[122]

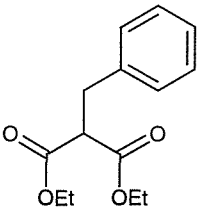
3-Bromo-3-methyl-2-butanone (**21**) and *N,N'*-Bis(*t*-butoxy)-2-hydroxy-1,3-propanediamine (**27**) were prepared by Walker.[29] 4-Cyanobenzeneboronic acid (**116**) was prepared by Parker.[111] Pyridinium chlorochromate (PCC) and pyridinium dichromate (PDC) were prepared by the methods of Harwood and Moody[123] and

Corey,[109] respectively. Methanolic HCl was prepared by bubbling a stream of HCl gas (from the reaction of NaCl with c.H_2SO_4) through anhydrous methanol.

5.2 Methods of Synthesis

5.2.1 Diethyl 2-(phenylmethyl)propanedioate (46a)

Prepared by the method of Marvel,[61] *with minor amendments.*



To anhydrous ethanol (200 ml) was added slowly with stirring sodium metal (1.11 g; 48mmol). When the sodium had dissolved (*ca.* 1 hr), diethyl propanedioate (7.71 g, 48 mmol) was added dropwise followed by (bromomethyl)benzene (8.21 g, 48 mmol). The mixture was heated to reflux for 18 hours after which it was concentrated *in vacuo*, diluted with water (20 ml) and extracted with ether (2 x 20 ml). The ether was removed *in vacuo* and the resulting pale yellow oil was distilled at reduced pressure (b.p. 150-180 °C / 18 mmHg; lit.[61] 145-155 °C / 5 mmHg) to yield the title compound as a colourless oil (6.67 g, 27 mmol, 56 %). δ_H(300 MHz; $CDCl_3$) 7.28-7.20 (5H, m, Ar-H), 4.16 (4H, m, -OC<u>H</u>$_2$CH$_3$), 3.66 (1H, t, J = 7.7 Hz, -C<u>H</u><), 3.23 (2H, d, J = 7.7, -C<u>H</u>$_2$Ph), 1.21 (6H, t, J = 7.3, -OCH$_2$C<u>H</u>$_3$); δ_C(75 MHz; $CDCl_3$) 169.02 (-<u>C</u>O$_2$Et), 138.03 (Ar), 128.99 (Ar), 128.64 (Ar), 126.87 (Ar), 61.61 (-O<u>C</u>H$_2$CH$_3$), 54.00 (-<u>C</u>H(CO$_2$Et)$_2$), 34.83 (-<u>C</u>H$_2$Ph), 14.15 (-OCH$_2$<u>C</u>H$_3$); *m/z* (APCI$^-$; MeCN) 249 (M-H)$^-$; ν(film)/cm^{-1}: 3064 (w), 3030 (w), 2983 (m), 2938 (m), 1732 (s), 1605 (w), 1496 (m), 1455 (m).

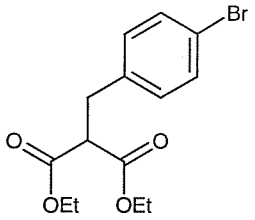
5.2.2 Diethyl 2-((4-bromophenyl)methyl)propanedioate (46b) *and* diethyl 2,2-bis((4-bromophenyl)methyl)propanedioate (48)

Method 1

To anhydrous ethanol (200 ml) was added slowly with stirring sodium metal (1.13 g, 48mmol). When the sodium had dissolved (*ca.* 1 hr), diethyl propanedioate (7.69 g, 48 mmol) was added dropwise. 1-Bromo-4-(bromomethyl)benzene (12.02 g, 48 mmol) was then added in portions (*ca.* 1 g min^{-1}) before the mixture was heated to reflux for 18 hours. The mixture was concentrated *in vacuo* then diluted with water (20 ml) and

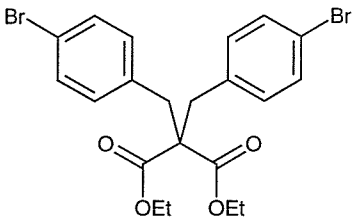
extracted with ether (2 x 20 ml). The organic portion was dried ($MgSO_4$) and the ether was then removed *in vacuo*. The resulting pale yellow oil was distilled at reduced pressure to yield **46b** as a colourless oil (6.08 g, 18 mmol, 38 %; b.p. 170-204 °C / 18 mmHg, lit.[62] 176 °C / 4 mmHg). The residue from the distillation was crystallised from ethanol to give **48** as a white crystalline solid (4.01 g, 8.1 mmol, 34 %; m.p. 105-106 °C).

Data for 46b



δ_H(300 MHz; $CDCl_3$) 7.40 (2H, AA'BB', J_{AB} = 8.5 Hz, $J_{AB'}$ = 2.2 Hz, Ar-H), 7.09 (2H, AA'BB', J_{BA} = 8.5 Hz, $J_{BA'}$ = 2.2 Hz, Ar-H), 4.15 (4H, q, J = 7.0 Hz, -OC<u>H</u>$_2$CH$_3$), 3.60 (1H, t, J = 7.7 Hz, -C<u>H</u>(CO_2Et)$_2$), 3.16 (2H, d, J = 7.7 Hz, ArC<u>H</u>$_2$-), 1.22 (6H, t, J = 7.0 Hz, -OCH$_2$C<u>H</u>$_3$); δ_C(75 MHz; $CDCl_3$) 168.75 (-<u>C</u>O_2Et), 137.02 (Ar), 131.72 (Ar), 130.79 (Ar), 120.79 (Ar), 61.73 (-OCH_2CH_3), 53.72 (-<u>C</u>H(CO_2Et)$_2$), 34.17 (-<u>C</u>H_2Ph), 14.16 (-OCH$_2$<u>C</u>H_3); *m/z* (APCI$^-$; MeCN) 327 $(M-H)^-$; ν_{max}(film)/cm^{-1}: 2982 (s), 2938 (m), 2906 (m), 2872 (w), 1738 (s), 1732 (s), 1593 (w), 1489 (s), 1464 (m), 1446 (m).

Data for 48



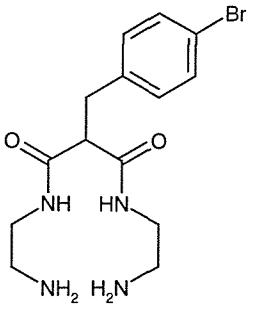
Found: C, 50.6; H, 4.4; Br, 31.8. $C_{21}H_{22}Br_2O_4$ requires C, 50.6; H, 4.45; Br, 32.1 %. δ_H(300 MHz; $CDCl_3$) 7.39 (4H, AA'BB', J_{AB} = 8.5 Hz, $J_{AB'}$ = 2.2Hz, Ar-H), 7.02 (4H, AA'BB', J_{BA} = 8.5 Hz, $J_{BA'}$ = 2.2 Hz, Ar-H), 4.10 (4H, q, J = 7.0 Hz, -OC<u>H</u>$_2$CH$_3$), 3.14 (4H, s, -CH_2Ar), 1.16 (6H, t, J =7.0 Hz, -OCH$_2$C<u>H</u>$_3$); δ_C(75 MHz; $CDCl_3$) 171.12 (C=O), 135.70 (Ar), 132.35 (Ar), 131.92 (Ar), 121.62 (Ar), 62.04 (-CH_2-), 60.43 (>C<), 39.51 (-CH_2-), 14.45 (-CH_3); ν_{max}(Nujol mull)/cm^{-1}: 1731 (s), 1488 (s), 1265 (m); *m/z* (EI) 327 (41 %), 281 (99), 191 (20), 169 (100), 90 (36).

5.2.3 Diethyl 2-((4-bromophenyl)methyl)propanedioate (46b)

Method 2 - Adamczyk et al.,[62] *with minor amendments.*

To anhydrous ethanol (60 ml) was added slowly with stirring sodium metal (1.95 g, 85 mmol). When the sodium had dissolved (*ca.* 1 hr), diethyl propanedioate (26.08 g, 163 mmol) was added dropwise. 1-Bromo-4-(bromomethyl)benzene (12.48 g, 50 mmol) was then added in portions (*ca.* 1 g min^{-1}) before the mixture was heated to reflux for 20 hours. The mixture was concentrated *in vacuo* then diluted with water (30 ml) and extracted with ether (3 x 30 ml). The combined organic portions were dried ($MgSO_4$) then the ether was removed *in vacuo*. The resulting orange oil was distilled at reduced pressure (bp 195-210 °C / 18 mmHg; lit.[62] 176 °C / 4 mmHg) to yield the title compound as a colourless oil (9.83 g, 30 mmol, 60 %), giving data as above (section 5.2.2).

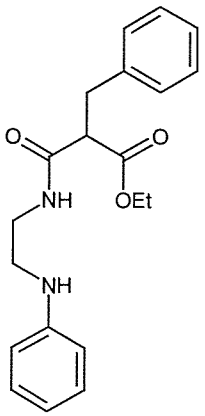
5.2.4 6-((4-Bromophenyl)methyl)-1,4,8,11-tetraazaundecane-5,7-dione (47b)



To 1,2-ethanediamine (15.30 g, 255 mmol, 25 eq.) in anhydrous methanol (20 ml) was added diethyl 2-((4-bromophenyl)methyl)-propanedioate (3.35 g, 10.0 mmol, 1 eq.) with stirring. Sodium methoxide (37 mg, 0.69 mmol, 0.07 eq.) was then added and the mixture was stirred at room temperature for seven days. Excess 1,2-ethanediamine was then removed *in vacuo* to yield a yellow oil which solidified on standing. The solid was crystallised from toluene to yield the title compound as a white micro-crystalline solid (2.95 g, 8.26 mmol, 83 %; m.p. 148-152 °C;). δ_H(300 MHz; D_2O / CF_3CO_2H) 7.99 (br t, J = 6.1 Hz, -CONHR), 7.70 (br s, $-CH_2NH_2$), 7.40 (2H, d, J = 8.3 Hz, Ar-H), 7.04 (2H, d, J = 8.3 Hz, Ar-H), 3.67-3.42 (5H, m, $-CONHCH_2-$ + $-CH(CONHR)_2$), 3.21-3.07 (6H, m, $-CH_2Ar$ + $-CH_2NH_2$); δ_C(75 MHz; DMSO-d_6) 168.80 (-CONHR), 138.88 (Ar), 131.11 (Ar), 131.01 (Ar), 119.28 (Ar), 54.65 ($-CH(CONHR)_2$), 42.06 ($-CONHCH_2-$), 41.02 ($-CH_2NH_2$), 34.33 ($-CH_2Ar$); ν_{max}(Nujol mull)/cm^{-1} 3300 (s, br), 1660 (s), 1538 (m), 1298 (w); *m/z* (ES^+; MeCN /

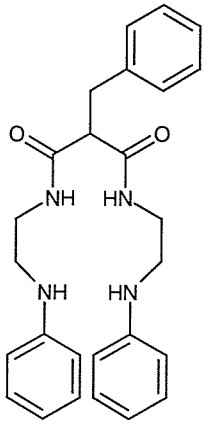
MeOH / HCO_2H) 357 $(M+H)^+$; 379 $(M+Na)^+$; 420 $(M+H+MeCN)^+$; 715 $(2M+H)^+$; 737 $(2M+Na)^+$.

5.2.5 Ethyl 3-oxo-3-((2-(phenylamino)ethyl)amino)-2-(phenylmethyl)propanoate (51)



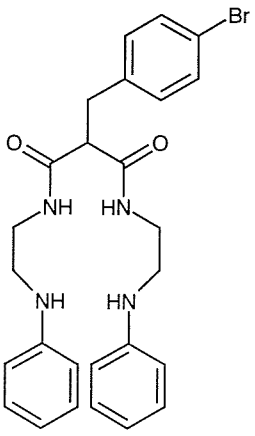
Anhydrous ethanol (10 ml) and *N*-phenyl-1,2-ethanediamine (1.36 g, 10 mmol, 2.5 eq.) were mixed and to the resulting solution was added diethyl 2-(phenylmethyl)propanedioate (1.00 g, 4 mmol, 1 eq.). After stirring for 13 days, the ethanol was removed *in vacuo* to leave a viscous oil (2.10 g) which was chromatographed over silica gel (84.3 g) with petroleum ether (40:60): ethyl acetate (2:1 v/v) as eluant. The title compound was isolated as white micro-crystalline solid (0.68 g, 2.0 mmol, 50 %; m.p. 80-82 °C). Found: C, 70.3; H, 7.2; N, 8.1. $C_{20}H_{24}N_2O_3$ requires C, 70.6; H, 7.1; N, 8.2 %. δ_H(300 MHz; $CDCl_3$) 7.22-7.04 (7H, m, Ar-H), 6.65-6.56 (2H, m, aromatic H + -CONHR), 6.50-6.44 (2H, m, Ar-H), 4.09-3.92 (2H, m, $-OC\underline{H}_2CH_3$), 3.71 (1H, br s, $-CH_2N\underline{H}Ph$), 3.44-3.25 (2H, m, $-C\underline{H}_2-$), 3.23-3.02 (3H, m, $-C\underline{H}_2-$ + $-C\underline{H}(CO_2Et)(CONHR)$), 1.07 (3H, t, J = 7.0 Hz, $-OCH_2C\underline{H}_3$); δ_C(75 MHz; $CDCl_3$) 171.14 (-CONHR), 168.72 ($-\underline{C}O_2Et$), 147.90 (Ar), 137.95 (Ar), 129.47 (Ar), 129.13 (Ar), 128.70 (Ar), 127.03 (Ar), 117.71 (Ar), 112.88 (Ar), 61.75 ($-O\underline{C}H_2CH_3$), 54.88 ($-\underline{C}H(CO_2Et)(CONHR)$), 43.69 ($-CH_2-$), 39.24 ($-CH_2-$), 36.52 ($-CH_2-$), 14.13 ($-OCH_2\underline{C}H_3$); ν_{max}(Nujol mull)/cm^{-1} 3374 (s), 3322 (s), 3322 (s), 1722 (s), 1657 (s), 1607 (w), 1542 (m), 1526 (m), 1500 (w); *m/z* (ES^+; MeCN) 341.3 $(M+H)^+$.

5.2.6 1,11-Diphenyl-6-(phenylmethyl)-1,4,8,11-tetraazaundecane-5,7-dione (47c)



To *N*-phenyl-1,2-ethanediamine (8.32 g, 61mmol, 10 eq.) in dry methanol (10 ml) was added diethyl 2-(phenylmethyl)propanedioate (1.53 g, 6 mmol, 1eq.) with stirring. Sodium methoxide (0.019 g, 0.35 mmol, 0.05 eq.) was then added and the mixture was stirred at room temperature for eight days. The solvent was removed *in vacuo* to leave a red, viscous oil. Excess *N*-phenyl-1,2-ethanediamine was removed by distillation (100 °C / 0.8 mmHg) to leave a viscous, dark red oil from which a white solid precipitated on standing. The mixture was triturated with ethanol (30ml) at 0 °C to give the title compound as a white crystalline solid (1.22 g, 2.84 mmol, 47 %; m.p. 133-135 °C). δ_H(300 MHz; $CDCl_3$) 8.13 (2H, br t, J =5.1 Hz, -CONHR), 7.26-7.11 (5H, m, Ar-H), 7.06 (4H, t, J =7.8 Hz, Ar-H), 6.62-6.46 (6H, m, Ar-H), 5.55 (2H, br t, J =5.8 Hz, -NHPh), 3.43-3.37 (1H, m, -CH(CONHR)$_2$), 3.20 (4H, dt, J = 5.8, 6.4 Hz, -CH_2NHPh), 3.07-2.91 (6H, m, -CH_2Ph + -CH_2NHPh); δ_C(75 MHz; $CDCl_3$) 169.17 (-CONHR), 148.66 (Ar), 139.16 (Ar), 129.00 (Ar), 128.81(Ar) , 128.19 (Ar), 126.21 (Ar), 115.84 (Ar), 112.07 (Ar), 55.16 (-CH(CONHR)$_2$), 42.39 (-CONHCH_2-), 38.27 (-CH_2NH_2), 35.38 (-CH_2Ph); ν_{max}(Nujol mull)/cm^{-1} 3332 (m), 1638 (s), 1607 (w), 1535 (w), 1518 (w); *m/z* (ES^+; MeCN / MeOH) 431.3 $(M+H)^+$; 453.3 $(M+Na)^+$.

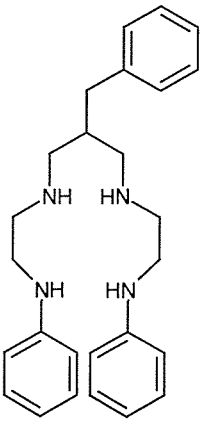
5.2.7 6-((4-Bromophenyl)methyl)-1,11-diphenyl-1,4,8,11-tetraazaundecane-5,7-dione (47d)



To anhydrous methanol (10 ml) was added *N*-phenyl-1,2-ethanediamine (5.44 g, 40 mmol, 10 eq) followed by diethyl 2-((4-bromophenyl)methyl)propanedioate (1.32 g, 4.0 mmol, 1 eq.). Sodium methoxide (11 mg, 0.2 mmol, 5 mol %) was then added and the resulting mixture was stirred at room temperature for ten days. Ether (20 ml) was added, the mixture was stirred

for ten minutes and was then filtered under suction to give the title compound as a white solid (1.67 g, 3.28 mmol, 82 %; m.p. 157-160 °C). Found: C, 61.1; H, 5.5; N, 10.9; Br, 15.4. $C_{26}H_{29}BrN_4O_2$ requires C, 61.3; H, 5.7; N, 11.0; Br, 15.7 %. δ_H(300 MHz; DMSO-d_6) 8.12 (2H, t, J = 5.5 Hz, -CONHR), 7.37 (2H, d, J = 8.1 Hz, Ar-H), 7.14 (2H, d, J = 8.1 Hz, Ar-H), 7.12-7.00 (m, 4H, Ar-H), 6.60-6.50 (m, 6H, Ar-H), 5.53 (2H, t, J = 5.5 Hz, -NHPh), 3.36 (1H, t, J = 7.7 Hz, -CH(CONHR)$_2$), 3.27-3.15 (4H, m, -CH$_2$-), 3.08-2.93 (6H, m, -CH$_2$- + -CH$_2$Ar); δ_C(75 MHz; DMSO-d_6) 169.00 (C=O), 148.65 (Ar), 138.52 (Ar), 131.16 (Ar), 131.04 (Ar), 129.02 (Ar), 119.41 (Ar), 115.86 (Ar), 112.06 (Ar), 54.94 (-CH<), 42.41 (-CONHCH$_2$-), 38.30 (-CH$_2$NHPh), 34.76 (-CH$_2$Ar); ν_{max}(Nujol mull)/cm^{-1}: 3394 (m), 3326 (m), 1636 (s), 1606 (m), 1585 (w), 1536 (m), 1514 (m); *m/z* (ES$^+$, MeCN) 509.3 (M+H)$^+$.

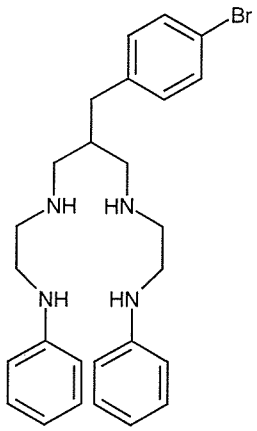
5.2.8 1,11-Diphenyl-6-(phenylmethyl)-1,4,8,11-tetraazaundecane (44c)



Under a nitrogen atmosphere, to 1,11-diphenyl-6-(phenylmethyl)-1,4,8,11-tetraazaundecane-5,7-dione (0.180 g, 0.45 mmol) was added borane-THF (1M; 16 ml; 16 mmol). The solution was heated under reflux for 48 hours and then cooled before methanol (5 ml) was added cautiously. When the effervescence had ceased, hydrochloric acid (2M; 10 ml) was added before the solvent was removed *in vacuo*. The residue was repeatedly co-evaporated with methanol (4 x 20 ml) to give a whitish solid which was suspended in water. The mixture was then adjusted to pH>11 (UI paper) with solid potassium hydroxide. The aqueous phase was extracted with DCM (3 x 10 ml) and the combined organic portions were dried (Na_2SO_4). Gaseous hydrogen chloride was bubbled through the organic solution, which was then extracted with water (4 x 20 ml). To the combined aqueous phases was added solid potassium hydroxide to attain pH>11 (UI paper) before the alkaline solution was extracted with DCM (4 x 30 ml). The organic portions were combined and dried (Na_2SO_4) and the solvent was then removed *in vacuo* to give the title compound as a reddish oil (0.162 g, 0.40 mmol, 91 %). δ_H(300 MHz; $CDCl_3$) 7.40-7.14 (9H, m, Ar-H), 6.74 (2H, t, J = 7.4 Hz, Ar-H),

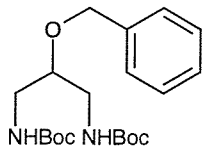
6.64 (4H, t, J = 8.5 Hz, Ar-H), 4.02 (2H, br s, -NHPh), 3.17 (2H, t, J = 5.5 Hz, -CH_2NHPh), 2.95-2.75 (4H, m, -CH_2NH-), 2.75-2.55 (6H, m, -CH_2NH- + -CH_2Ph), 2.10-1.98 (1H, m, -CH<); δ_C(75 MHz; $CDCl_3$) 148.71 (Ar), 140.63 (Ar), 129.48 (Ar), 129.27 (Ar), 128.61 (Ar), 126.26 (Ar), 117.56 (Ar), 113.16 (Ar), 52.86 (-CH_2-), 49.03 (-CH_2-), 43.57 (-CH_2-), 40.69 (-CH_2-), 38.13 (-CH<); ν_{max}(Liquid film)/cm^{-1}: 3346 (m), 2923 (s), 2853 (s), 1602 (s), 1504 (s); *m/z* (ES^+, MeCN) 403.5 $(M+H)^+$.

5.2.9 1,11-Diphenyl-6-((4-bromophenyl)methyl)-1,4,8,11-tetraazaundecane (44d)



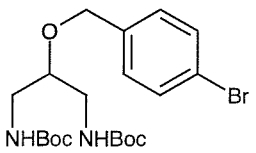
Under a nitrogen atmosphere, to 1,11-diphenyl-6-((4-bromophenyl)methyl)-1,4,8,11-tetraazaundecane-5,7-dione (0.50 g, 0.98 mmol) was added borane-THF (1M; 10 ml; 10 mmol). The solution was heated under reflux for 24 hours and then cooled before HCl (6M; 20 ml) was added cautiously. The solvent was removed *in vacuo* to leave a semi-solid residue which was repeatedly co-evaporated with methanol (5 x 20 ml). The resulting oil was taken to pH>11 (UI paper) with aqueous sodium hydroxide (10 % w/w) then the mixture was extracted with DCM (4 x 10 ml). The combined organic extracts were dried (Na_2SO_4) and the solvent was then removed *in vacuo*. The resulting viscous yellow oil was chromatographed over silica gel (eluant ether/methanol/ammonia ("880"); 30:2:1) to give the title compound as an orange oil (0.31 g, 0.64 mmol, 63 %). δ_H(300 MHz; $CDCl_3$) 7.44 (2H, d, J = 8.1 Hz, Ar-H), 7.27 (4H, t, J = 7.4 Hz, Ar-H), 7.08 (2H, d, J = 8.1 Hz, Ar-H), 6.81 (2H, t, J = 7.4 Hz, Ar-H), 6.70 (4H, d, J = 7.4 Hz, Ar-H), 4.23 (2H, br s, -NHPh), 3.23 (2H, t, J = 5.3 Hz, -CH_2NHPh), 2.98-2.78 (4H, m, -CH_2NH-), 2.78-2.56 (6H, m, -CH_2NH- + -CH_2Ph), 2.07-1.95 (1H, m, -CH<); δ_C(75 MHz; $CDCl_3$) 148.73 (Ar), 139.67 (Ar), 131.66 (Ar), 131.12 (Ar), 129.56 (Ar), 120.01 (Ar), 117.63(Ar), 113.21(Ar), 52.64 (-CH_2-), 49.05 (-CH_2-), 43.57 (-CH_2-), 40.57 (-CH_2-), 37.32 (-CH<); ν_{max}(film)/cm^{-1}: 3363 (m), 2923 (s), 2853 (s), 1603 (s), 1504 (s); *m/z* (ES^+, MeCN) 481.5 $(M+H)^+$.

5.2.10 *N,N'*-Bis(*t*-butoxycarbonyl)-2-(phenylmethoxy)-1,3-propanediamine (52a)



Under a nitrogen atmosphere, *N,N'*-bis(*t*-butoxycarbonyl)-2-hydroxy-1,3-propanediamine (3.02 g, 10.3 mmol) was dissolved in anhydrous tetrahydrofuran (20 ml). Sodium hydride (60 % dispersion in mineral oil; 0.4 g, equivalent to 0.24 g, 10 mmol NaH) was added and the resulting mixture was stirred at room temperature for one hour. (Bromomethyl)benzene (1.22 ml; 1.76 g, 10.3 mmol) was added and the mixture was stirred at room temperature for 48 hours. The solvent was removed *in vacuo* and the resulting white paste was dissolved in methanol (20 ml), treated with silica (2.5 g) and concentrated *in vacuo* to give a silica pad. Chromatography over silica gel (eluant petroleum ether (40:60) / ethyl acetate (3:1 v/v)) gave unreacted *N,N'*-bis(*t*-butoxycarbonyl)-2-hydroxy-1,3-propanediamine (1.81 g, 6.24 mmol) and the title compound (0.99 g, 2.61 mmol, 62 %; m.p. 101-103 °C (hexane)). Found: C, 63.1; H, 8.6; N, 7.3; $C_{20}H_{32}N_2O_5$ requires C, 63.1; H, 8.5; N, 7.4. δ_H(300 MHz; $CDCl_3$) 7.27-7.16 (5H, m, Ar-H), 5.15-5.06 (2H, m, -CONHR), 4.50 (2H, s, -$C\underline{H}_2$Ph), 3.50-3.38 (1H, m, -$C\underline{H}(CH_2NHBoc)_2$), 3.38-2.98 (4H, m, -$C\underline{H}_2$NHBoc), 1.35 (18H, s, -$C(C\underline{H}_3)_3$); δ_C(75 MHz; $CDCl_3$) 155.41 ($\underline{C}$=O), 137.04 (Ar), 127.32 (Ar), 126.81 (Ar), 78.34 (-$\underline{C}(CH_3)_3$), 75.63 (-$\underline{C}H(CH_2NHBoc)_2$), 70.50 (-$\underline{C}H_2$Ph), 39.39 (-$\underline{C}H_2$NHBoc), 27.36 (-$C(\underline{C}H_3)_3$); ν_{max}(Nujol mull)/cm^{-1} 3356 (m, br), 2978 (m), 2932 (m), 1698 (s), 1514 (s), 1455 (m), 1392 (m), 1366 (s), 1273 (s), 1252 (s), 1169 (s); *m/z* (ES^+; MeCN) 381.2 $(M+H)^+$, 398.2 $(M+NH_4)^+$, 403.2 $(M+Na)^+$.

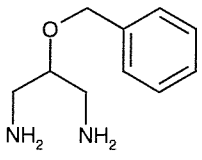
5.2.11 *N,N'*-Bis(*t*-butoxycarbonyl)-2-((4-bromophenyl)methoxy)-1,3-propanediamine (52b)



Under a nitrogen atmosphere, *N,N'*-bis(*t*-butoxycarbonyl)-2-hydroxy-1,3-propanediamine (3.0 g, 10.3 mmol) was dissolved in anhydrous tetrahydrofuran (20 ml). Sodium hydride (60 % dispersion in mineral oil; 0.4 g, equivalent to 0.24 g, 10 mmol NaH) was added and the resulting mixture was stirred at room temperature for two hours. 1-Bromo-4-

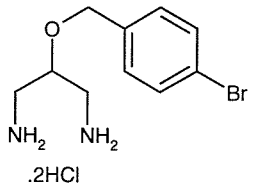
(bromomethyl)benzene (2.60 g, 10.3 mmol) in anhydrous tetrahydrofuran (10 ml) was added and the mixture was stirred at room temperature for 48 hours. The solvent was removed *in vacuo* and the resulting white paste was dissolved in methanol (50 ml), treated with silica (1.5 g) and concentrated *in vacuo* to give a silica pad which was chromatographed over silica gel (eluant petroleum ether (40:60) / ethyl acetate (2:1 v/v)). Crystallisation from hexane afforded the title compound as a white crystalline solid (1.52 g, 3.31 mmol, 70 %; m.p. 77-79 °C). Found: C, 52.5; H, 6.7; N, 6.1; Br, 17.1. $C_{20}H_{31}BrN_2O_5$ requires C, 52.3; H, 6.8; N, 6.1; Br, 17.4 %. δ_H(300 MHz; $CDCl_3$) 7.47 (2H, d, J = 8.5 Hz, Ar-H), 7.21 (2H, d, J = 8.5 Hz, Ar-H), 5.06 (2H, br t, J = 6.0 Hz, -NHBoc), 4.55 (2H, s, -CH_2Ar), 3.51 (1H, quintet, J = 5.1 Hz, -CH<), 3.47-3.33 (2H, m, -CH_aH_bNHBoc), 3.13 (2H, dt, J = 14.3, 5.1 Hz, -CH_aH_bNHBoc), 1.44 (18H, s, C(CH_3)$_3$); δ_C(75 MHz; $CDCl_3$) 156.53 (C=O), 137.72 (Ar), 131.72 (Ar), 129.59 (Ar), 121.85 (Ar), 79.63 (-C(CH_3)$_3$), 76.90 (-OCH<), 70.85 (-OCH_2Ar), 40.46 (-CH_2NHBoc), 28.53 (-C(CH_3)$_3$); ν_{max}(mull)/cm^{-1}: 3382 (m), 3324 (m), 1698 (s), 1685 (s), 1541 (s), 1514 (s); *m/z* (ES$^+$, MeCN) 459.1 $(M+H)^+$, 476.1 $(M+NH_4)^+$.

5.2.12 2-(Phenylmethoxy)-1,3-propanediamine, dihydrochloride salt (55a)



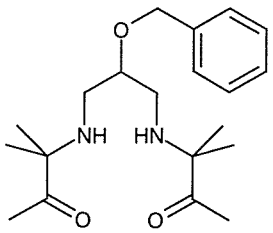
To *N,N'*-bis(*t*-butoxycarbonyl)-2-(phenylmethoxy)-1,3-propanediamine (0.81g, 2.13 mmol) was added methanolic HCl (25 ml). The resulting mixture was stirred at room temperature for three hours. The title compound was precipitated by the addition of anhydrous ether (75 ml) to give a white crystalline solid (0.50 g, 1.98 mmol, 93 %; m.p. 181-184 °C). Found: C, 47.25; H, 6.9; N, 10.9; Cl, 27.9. $C_{10}H_{16}N_2O.2HCl$ requires C, 47.4; H, 7.2; N, 11.1; Cl, 28.0 %. δ_H(300 MHz; D_2O) 7.40 (5H, m, Ar-H), 4.64 (2H, s, -CH_2Ph), 4.06 (1H, tt, J = 6.6, 4.1 Hz, -CH(CH_2NH_2)$_2$), 3.26 (2H, dd, J = 13.8, 4.1 Hz, -$CH_aH_b$$NH_2$), 3.09 (2H, dd, J = 13.8, 6.8, -$CH_aH_b$$NH_2$); δ_C(75 MHz; D_2O) 139.08 (Ar), 131.66 (Ar), 131.48 (Ar), 131.42 (Ar), 74.51 (-OCH_2-), 73.49 (-OCH<), 42.22 (-CH_2NH_2); ν_{max}(KBr disc)/cm^{-1}: 3417 (br, s), 2999 (br, s), 2882 (s), 1594 (s), 1558 (m).

5.2.13 2-((4-Bromophenyl)methoxy)-1,3-propanediamine, dihydrochloride salt (55b)



To *N,N'*-bis(*t*-butoxycarbonyl)-2-((4-bromophenyl)methoxy)-1,3-propanediamine (0.411 g, 0.89 mmol) was added methanolic HCl (5 ml) and the resulting mixture was stirred at room temperature for 30 minutes. The title compound was precipitated by the addition of anhydrous ether (20 ml) as a white micro-crystalline solid (0.280 g, 0.84 mmol, 94 %; m.p. 237-239 °C). Found: C, 36.7; H, 5.2; N, 8.1; Br, 24.0; Cl, 21.0. $C_{10}H_{15}BrN_2O.2HCl$ requires C, 36.2; H, 5.2; N, 8.4; Br, 24.1; Cl, 21.35 %. δ_H(300 MHz; D_2O) 7.54 (2H, d, J = 8.5 Hz, Ar-H), 7.31 (2H, d, J = 8.5 Hz, Ar-H), 4.14 (2H, s, -CH_2Ar), 4.08 (1H, tt, J = 7.0, 4.1 Hz, -CH(CH_2NH_2)$_2$), 3.29 (2H, dd, J = 13.6, 4.1 Hz, -C$H_aH_bNH_2$), 3.09 (2H, dd, J = 13.6, 7.0, -$CH_aH_bNH_2$); δ_C(75 MHz; D_2O) 138.17 (Ar), 134.48 (Ar), 133.04 (Ar), 124.67 (Ar), 73.71 (-OCH_2-), 73.71 (-OCH<), 42.16 (-CH_2NH_2); ν_{max}(KBr disc) /cm^{-1}: 3417 (br, s), 2999 (br, s), 2882 (s), 1594 (s), 1558 (m).

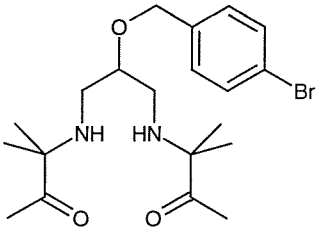
5.2.14 6-(Phenylmethoxy)-3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione (58a)



To dry *N,N*-dimethylformamide (10 ml) was added 2-(phenylmethoxy)-1,3-propanediamine, dihydrochloride salt (0.40 g, 1.58 mmol) followed by potassium carbonate (1.00 g, 7.24 mmol). The mixture was stirred for ten minutes before 3-bromo-3-methyl-2-butanone (0.65 g, 3.95 mmol) was added. The resulting mixture was stirred overnight at room temperature before DCM (10 ml) was added and the organic solution was washed with aqueous sodium bicarbonate solution (5% w/w; 2 x 10ml) and then dried (Na_2SO_4). The solvent was removed *in vacuo* to give a dark red oil, which was chromatographed over silica gel (eluant DCM – methanol 19:1). The title compound was isolated as a yellow oil (0.32 g, 0.92 mmol, 58 %). δ_H(300 MHz; $CDCl_3$) 7.40-7.20 (5H, m, Ar-H), 4.60 (2H, s, -OCH_2-), 3.57 (1H, dd, J = 5.5, 5.1 Hz, -OCH<), 2.70-2.44 (4H, m, CH_aH_b), 2.15 (6H, s, -$COCH_3$), 1.21 (12H, s, -CH_3); δ_C(75 MHz; $CDCl_3$) 213.51

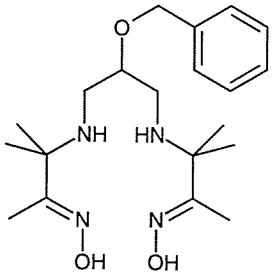
(>C=O), 130.70 (Ar), 129.85 (Ar), 129.55 (Ar), 121.66 (Ar), 79.23 (-OCH<), 70.91 (-OCH_2Ph), 62.83 (-$C(CH_3)_2$-), 45.40 (-CH_2NHR), 24.79 (-CH_3), 24.55 (-CH_3), 24.43 (-CH_3); ν_{max}(film)/cm^{-1}: 3327 (m), 2976 (s), 2925 (s), 1704 (s), 1454 (m); *m/z* (ES^+, MeCN) 349.3 $(M+H)^+$.

5.2.15 6-((4-Bromophenyl)methoxy)-3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione (58b)



To 2-((4-bromophenyl)methoxy)-1,3-propanediamine, dihydrochloride salt (0.102 g, 0.31 mmol) was added anhydrous *N,N*-dimethylformamide (5 ml) followed by potassium carbonate (0.119 g, 0.864 mmol). The resulting mixture was stirred for five minutes before 3-bromo-3-methyl-2-butanone (0.079 g, 0.48 mmol) in dry *N,N*-dimethylformamide (5 ml) was added. The mixture was stirred at room temperature for six days before DCM (20 ml) was added. The solution was washed with water (20 ml) and saturated aqueous sodium bicarbonate (20 ml) then the aqueous layers were combined and extracted with DCM (20 ml). The combined organic portions were dried (Na_2SO_4) and the solvent was then removed *in vacuo* to give a yellow oil which was chromatographed over silica gel (eluant DCM / methanol (19:1 v/v)) to yield the title compound as a pale yellow oil (0.061g, 0.143 mmol, 60 %). δ_H(300 MHz; $CDCl_3$) 7.45 (2H, AA'BB', J_{app} = 8.3 Hz, Ar-H), 7.23 (2H, AA'BB', J_{app} = 8.3 Hz, Ar-H), 4.53 (2H, s, -CH_2Ph), 3.52 (1H, quintet, J = 5.2 Hz, -OCH<), 2.64-2.50 (4H, m, -CH_2NHR), 2.13 (6H, s, -$COCH_3$), 1.20 (12H, s, -CH_3); δ_C(75 MHz; $CDCl_3$) 213.51 (>C=O), 137.70 (Ar), 131.65 (Ar), 129.55 (Ar), 121.66 (Ar), 79.23 (-OCH<), 70.91 (-OCH_2Ph), 62.83 (-$C(CH_3)_2$-), 45.40 (-CH_2NHR), 24.79 (-CH_3), 24.55 (-CH_3), 24.43 (-CH_3); ν_{max}(film)/cm^{-1}: 3327 (m), 2926 (s), 2855 (s), 1706 (s), 1592 (w); *m/z* (ES^+, MeCN): 427.6 $(M+H)^+$, 449.6 $(M+Na)^+$.

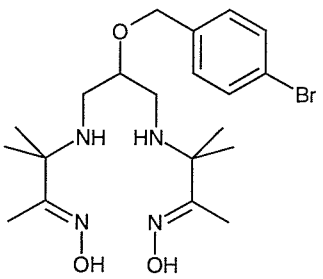
5.2.16 Attempted preparation of 6-(phenylmethoxy)-3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioxime (59a)



To hydroxylamine hydrochloride (0.24 g, 3.5 mmol) in anhydrous methanol (5 ml) was added solid sodium hydroxide (0.13g, 3.25 mmol) at 0 °C and the resulting mixture was stirred for two hours. The solution was filtered to remove sodium chloride and the filtrate was added to 6-(phenylmethoxy)-3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione (200 mg, 0.57 mmol). The resulting mixture was stirred overnight before the solvent was removed *in vacuo* to give a brown gum.

Attempted trituration of the gum with water (2 ml) failed, while trituration with methanol (5 ml) resulted in the isolation of a small quantity of excess hydroxylamine hydrochloride (20 mg, 0.29 mmol). To date, further attempts to isolate the title compound have failed.

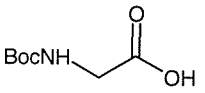
5.2.17 Attempted preparation of 6-((4-bromophenyl)methoxy)-3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioxime (59a)



At 0 °C, to hydroxylamine hydrochloride (0.22 g, 3.1 mmol) in anhydrous methanol (5 ml) was added solid sodium hydroxide (0.11g, 2.8 mmol) and the resulting mixture was stirred for two hours. The solution was filtered to remove sodium chloride and the filtrate was added to 6-(phenylmethoxy)-3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione (60 mg, 0.14 mmol). The resulting mixture was stirred overnight before the solvent was removed *in vacuo* to give a brown solid. Attempted trituration of the solid with water (2 ml) produced an oily residue. To date, further attempts to isolate the title compound have failed.

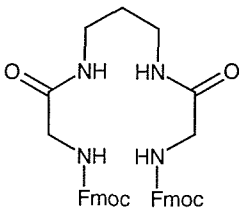
5.2.18 *N*-(*t*-Butoxycarbonyl)-2-aminoethanoic acid (Boc-glycine, 64)

Prepared by the method of Fiakpui et al.[73]



To water (5 ml) was added triethylamine (2.02 g, 20 mmol) and glycine (1.01 g, 13.5 mmol) and the resulting mixture was cooled to 0 °C. Di-*tert*-butyl dicarbonate (3.10 g, 14.2 mmol) in tetrahydrofuran (10 ml) was added slowly to the aqueous solution before the mixture was allowed to warm to room temperature and was then stirred overnight. Water (20 ml) was added and the resulting solution was acidified to pH 3 (UI paper) with aqueous citric acid (10 % w/w) then extracted with ethyl acetate (4 x 40 ml). The organic phases were combined, washed with brine (60 ml) and then dried (Na_2SO_4). The solvent was removed *in vacuo* to leave a viscous oil which solidified on standing. The solid was recrystallised from petroleum ether (40:60) – ethyl acetate to give the title compound as white needles (2.13 g, 12.2 mmol, 90 %; m.p. 85-88 ° C (lit.[124] 88-90 °C)). δ_H(300 MHz; DMSO-d_6) 7.06 (1H, t, J = 6.1 Hz, -NH-), 3.56 (2H, d, J = 6.1 Hz, -CH_2-), 1.37 (9H, s, -C(CH_3)$_3$); δ_C(75 MHz; DMSO-d_6) 171.88 (C=O), 155.90 (C=O), 78.10 (-C(CH_3)$_3$), 41.85 (-CH_2-), 28.24 (-C(CH_3)$_3$); ν_{max}(Nujol mull)/cm^{-1}: 3405 (m), 3341 (m), 1748 (s), 1670 (s), 1535 (s); *m/z* (ES$^-$, MeCN) 287.9 (M+TFA-H)$^-$, 349.1 (2M-H)$^-$.

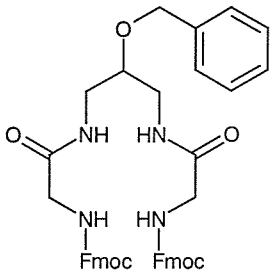
5.2.19 1,11-Bis((9-fluorenylmethoxy)carbonyl)-1,4,8,11-tetraazaundecane-3,9-dione (71)



To anhydrous DCM (5 ml) was added Fmoc-glycine (0.25g, 0.84 mmol) followed by thionyl chloride (0.61 ml; 1.0 g, 8.4 mmol). The mixture was heated under reflux for two hours before the solvent and excess thionyl chloride were removed *in vacuo* to leave a white solid. The solid was immediately dissolved in DCM (5 ml) and to the resulting solution were added 1,3-propanediamine (20 µl; 0.030 g, 0.4 mmol) and aqueous sodium hydrogen carbonate (10 % w/w; 10 ml). The mixture was stirred overnight at room temperature before the organic phase was separated, washed with saturated brine solution (2 x 5 ml) and dried (Na_2SO_4).

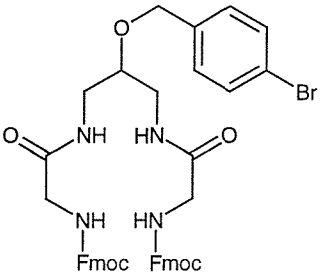
Removal of the solvent gave a white semi-solid which was triturated with acetone (5 ml) at 0 °C. The title compound was isolated as a white solid (0.190 g, 0.30 mmol, 75 %; m.p. 120-126 °C). δ_H(300 MHz; $CDCl_3$) 7.73 (4H, d, J = 7.7 Hz, Ar-H), 7.62 (4H, d, J = 7.7 Hz, Ar-H), 7.38 (4H, t, J = 7.7 Hz, Ar-H), 7.28 (4H, t, J = 7.7 Hz, Ar-H), 6.72-6.63 (2H, m, -CONH-), 4.37 (4H, d, J = 7.0 Hz, CH_2CH<), 4.20 (2H, t, J = 7.0Hz, -CH_2CH<), 3.80 (4H, d, J = 5.5 Hz, -CH_2CONH-), 3.26 (4H, m, $CH_2(CH_2NHR)_2$), 1.65 (2H, quintet, J = 6.3 Hz, $CH_2(CH_2NHR)_2$); δ_C(75 MHz; $CDCl_3$) 174.67 (-CH_2CONH-), 161.73 (-OCONH-), 148.73 (Ar), 146.04 (Ar), 132.59 (Ar), 131.96 (Ar), 130.7 (Ar), 124.81 (Ar), 71.56 (-CH_2-), 51.97 (-CH_2-), 49.28 (>CH-), 41.21 (-CH_2-), 34.02 (-CH_2-); ν_{max}(Nujol mull)/cm^{-1} 3315 (s), 1691 (s), 1656 (s), 1535 (m); *m/z* (ES^+, MeCN) 633.4 $(M+H)^+$, 655.4 $(M+Na)^+$, 671.3 $(M+K)^+$.

5.2.20 1,11-Bis((9-fluorenylmethoxy)carbonyl)-6-(phenylmethyl)-1,4,8,11-tetraazaundecane-3,9-dione (72a)



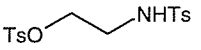
To anhydrous DCM (5 ml) was added Fmoc-glycine (0.30 g, 1.0 mmol) followed by thionyl chloride (0.65 ml; 1.07 g, 9.0 mmol). The mixture was heated under reflux for two hours before the solvent and excess thionyl chloride were removed *in vacuo* to leave a white solid. The solid was immediately dissolved in chloroform (5 ml) and to the resulting solution was added 2-(phenylmethyl)-1,3-propanediamine, dihydrochloride salt (0.114 g, 0.45 mmol) and aqueous sodium hydrogen carbonate (10 % w/w; 10 ml). The mixture was stirred overnight at room temperature before the reaction mixture was filtered under suction. The resulting solid was triturated with acetone (5 ml) and the title compound was isolated as a white solid (0.236 g, 0.32 mmol, 71 %; m.p. 138-148 °C). ν_{max}(Nujol mull)/cm^{-1} 3310 (s), 1696 (s), 1658 (s), 1530 (s); *m/z* (ES^+, MeCN) 739.5 $(M+H)^+$, 761.4 $(M+Na)^+$. The compound was insoluble in $CDCl_3$, DMSO-d_6, CD_3OD and CD_3CN.

5.2.21 1,11-Bis((9-fluorenylmethoxy)carbonyl)-6-((4-bromophenyl)methyl)-1,4,8,11-tetraazaundecane-3,9-dione (72b)



To anhydrous DCM (5 ml) was added Fmoc-glycine (0.25 g, 0.84 mmol) followed by thionyl chloride (0.61 ml; 1.0 g, 8.4 mmol). The mixture was heated under reflux for two hours before the solvent and excess thionyl chloride were removed *in vacuo* to leave a white solid. The solid was immediately dissolved in chloroform (5 ml) and to the resulting solution were added 2-((4-bromophenyl)methyl)-1,3-propanediamine, dihydrochloride salt (0.133 g, 4.0 mmol) and aqueous sodium hydrogen carbonate (10 % w/w; 10 ml). The mixture was stirred overnight at room temperature before the reaction mixture was filtered under suction. The resulting solid was triturated with acetone (5 ml) and the title compound was isolated as a white solid (0.226 g, 0.276 mmol, 69 %; m.p. > 300 °C). ν_{max}(Nujol mull)/cm^{-1} 3367 (m), 3301 (m), 1694 (s), 1665 (s); *m/z* (ES$^+$, MeCN): 819.4 $(M+H)^+$, 841.4 $(M+Na)^+$. The compound was insoluble in $CDCl_3$, DMSO-d_6, CD_3OD and CD_3CN.

5.2.22 2-((4-Methylphenyl)sulfonylamino)ethyl 4-methylbenzenesulfonate (77)



Prepared by the method of Chandrasekhar et al.,[79] *with minor amendments.*

2-Aminoethanol (1.71 g, 28 mmol) and pyridine (7 ml) were dissolved in DCM (30 ml) and cooled to 0 °C. 4-Methylbenzenesulfonyl chloride (16.00 g, 84 mmol) was added in portions (*ca.* 2 g min^{-1}) with magnetic stirring. The mixture was allowed to warm to room temperature and was stirred overnight. The DCM was removed *in vacuo* before the resulting viscous brown oil was poured into ice-water (60 ml) and triturated to give an off-white solid which was filtered under suction and then washed with water (3 x 10 ml), hydrochloric acid (2M; 3 x 10 ml) and water (3 x 10 ml). The solid was recrystallised from aqueous ethanol to give the title compound as a white crystalline solid (m.p. 87-88 °C (lit.[79] 87 °C); 7.75 g, 21 mmol, 75 %). δ_H(300 MHz; $CDCl_3$) 7.74

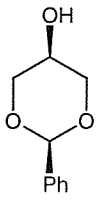
(2H, d, J = 8.3 Hz, Ar-H), 7.70 (2H, d, J = 8.3 Hz, Ar-H), 7.34 (2H, d, J = 8.3 Hz, Ar-H), 7.29 (2H, d, J = 8.3 Hz, Ar-H), 5.08 (1H, t, J = 6.4 Hz, -NH-), 4.05 (2H, t, J = 5.5 Hz, -CH_2O-), 3.21 (2H, dt, J = 6.4, 5.5, -CH_2NH-), 2.45 (3H, s, -CH_3), 2.42 (3H, s, -CH_3); δ_C(75 MHz; $CDCl_3$) 145.53 (Ar), 143.96 (Ar), 136.69 (Ar), 132.33 (Ar), 130.21 (Ar), 130.01 (Ar), 128.11 (Ar), 127.18 (Ar), 68.90 (-CH_2O-), 42.25 (-CH_2NH-), 21.85 (-CH_3), 21.70 (-CH_3); ν_{max}(Nujol mull)/cm^{-1} 3290 (s), 1599 (m), 1495 (w), 1364 (s), 1328 (m); *m/z* (ES^+, MeCN) 370.0 $(M+H)^+$, 387.1 $(M+NH_4)^+$.

5.2.23 1-(4-Methylphenylsulfonyl)aziridine (76)

Prepared by the method of Martin et al.[81]

To 2-((4-methylphenyl)sulfonylamino)ethyl 4-methylbenzenesulfonate (4.53 g, 12.3 mmol) in toluene (100 ml) was added rapidly with stirring aqueous potassium hydroxide (20 % w/w; 20 ml). After two hours, water (50 ml) was added and the organic phase was separated, washed with water (50 ml) and dried (Na_2SO_4). The solvent was removed *in vacuo* to give a pale yellow oil which solidified on standing and this material was crystallised from petroleum ether (40:60) to give a white crystalline solid (2.03 g, 10.3 mmol, 84 %; m.p. 52-54 °C (lit.[125] 52 °C)). δ_H(300 MHz; $CDCl_3$) 7.80 (2H, d, J = 8.1 Hz, Ar-H), 7.32 (2H, d, J = 8.1 Hz, Ar-H), 2.42 (3H, s, -CH_3), 2.37 (4H, br s, -CH_2-); δ_C(75 MHz; $CDCl_3$) 144.85 (Ar), 134.89 (Ar), 129.91 (Ar), 128.12 (Ar), 27.57 (-CH_2-), 21.78 (-CH_3).

5.2.24 *cis*-2-Phenyl-1,3-dioxan-5-ol (*cis*-82)

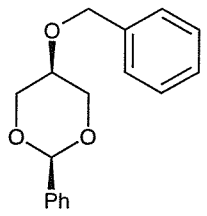


Benzaldehyde (20.67 g, 195 mmol) and glycerol (17.94 g, 195 mmol) were mixed and dissolved in toluene (90 ml). *p*-Toluenesulfonic acid (0.14 g, 0.7 mmol, cat.) was added and the mixture was then heated under reflux for 4 hours in a Dean-Stark apparatus. The mixture was allowed to cool before being stored at 4 °C for 5 days. The solution was then washed with saturated aqueous sodium hydrogen carbonate (50 ml) and the organic phase was dried ($MgSO_4$). Removal of the solvent *in vacuo* gave a reddish oil which was dissolved in ether (80 ml) and stored at –20 °C for 4 days. The resulting white solid was filtered under suction

then crystallised from toluene – petroleum ether (40:60) to give a white crystalline solid (14.04 g, 78 mmol, 40 %; m.p. 82-84 °C (lit.[86] 82-83 °C)). δ_H(300 MHz; $CDCl_3$) 7.56-7.48 (2H, m, Ar-H), 7.45-7.33 (3H, m, Ar-H), 5.55 (1H, s, >CH-Ph), 4.17 (2H, dd, J = 11.8, 1.1 Hz, -C$\underline{H}_a$H$_b$-), 4.10 (2H, d, J = 11.8 Hz, -CH$_a\underline{H}_b$-), 3.61 (1H, br m, >CH-OH), 3.31 (1H, br s, -OH); δ_C(75 MHz; $CDCl_3$) 138.02 (Ar), 129.25 (Ar), 128.48 (Ar), 126.07 (Ar), 101.76 (>CH-Ph), 72.41 (-CH_2-), 64.10 (>CH-OH).

5.2.24.1 Procedure For The Monitoring of the Composition of the Reaction Mixture
An aliquot of the reaction mixture (1 ml) was withdrawn and shaken with aqueous sodium hydroxide solution (2M; 1 ml). The organic phase was separated and the solvent was removed *in vacuo*. The residue was dissolved in $CDCl_3$ and the ^{1}H-NMR spectrum was recorded. The relative proportions of the isomeric acetals were determined by integration of the signal of the acetal proton for each of the four components.[86]

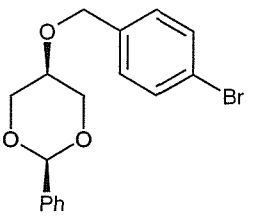
5.2.25 *cis*-2-Phenyl-5-(phenylmethoxy)-1,3-dioxane (*cis*-85a)



Under a nitrogen atmosphere, to anhydrous tetrahydrofuran (10 ml) was added *cis*-2-phenyl-1,3-dioxan-5-ol (1.01 g, 5.61 mmol) followed by (bromomethyl)benzene (0.96 g, 5.61 mmol). Sodium hydride (60 % dispersion in mineral oil; 0.25 g; equivalent to 0.15 g, 6.25 mmol NaH) was then added in portions and the mixture was stirred at room temperature for 3 days. The solvent was removed *in vacuo* before water (15 ml) was added and the resulting suspension was extracted with DCM (4 x 10 ml). The combined organic phases were dried ($MgSO_4$) then the solvent was removed *in vacuo*, to give a white solid which was recrystallised from ether to give the title compound (1.29 g, 4.77 mmol, 85 %; m.p. 75-78 °C (lit.[89] 77-78 °C)). δ_H(300 MHz; $CDCl_3$) 7.60-7.54 (2H, m, Ar-H), 7.47-7.29 (8H, m, Ar-H), 5.59 (1H, s, >CH-Ph), 4.73 (2H, s, -CH_2Ph), 4.39 (2H, dd, J = 12.9, 1.5 Hz, -C$\underline{H}_a$H$_b$-), 4.06 (2H, dd, J = 12.9, 1.8 Hz, -CH$_a\underline{H}_b$-), 3.36 (1H, tt, J = 1.8, 1.5 Hz, >CH-O-); δ_C(75 MHz; $CDCl_3$) 138.30 (Ar), 129.09 (Ar), 128.64 (Ar), 128.39 (Ar), 127.93 (Ar), 127.90 (Ar), 126.39 (Ar),

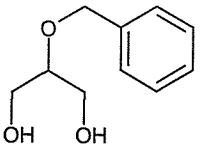
126.36 (Ar), 101.55 (>CH-Ph), 70.48 (-CH_2-), 69.39 (>CH-OH), 69.18 (-CH_2-); *m/z* (ES^+, MeCN) 271.3 $(M+H)^+$, 288.3 $(M+NH_4)^+$.

5.2.26 *cis*-2-Phenyl-5-(4-bromophenyl)methoxy-1,3-dioxane (*cis*-85b)



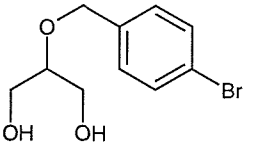
Under a nitrogen atmosphere, to anhydrous tetrahydrofuran (20 ml) was added *cis*-2-phenyl-1,3-dioxan-5-ol (0.250 g, 1.38 mmol) followed by 1-bromo-4-(bromomethyl)benzene (0.351 g, 1.40 mmol). Sodium hydride (60 % dispersion in mineral oil; 0.056 g; equivalent to 0.0336 g, 1.38 mmol NaH) was then added in portions then the mixture was stirred at room temperature for one day. Examination of the reaction mixture by TLC showed that unreacted starting material remained and a further portion of sodium hydride (60 % dispersion in mineral oil; 0.030 g; equivalent to 0.018 g, 0.75 mmol) was added. The reaction mixture was stirred for a further day before the solvent was removed *in vacuo*. To the residue was added water (10 ml) and the resulting mixture was extracted with DCM (3 x 10 ml). The organic phases were combined, washed with water (10 ml) and then dried ($MgSO_4$). Removal of the solvent *in vacuo* gave a white solid, to which was added DCM (10 ml) and silica gel (0.4 g). Evaporation of the solvent gave a silica pad which was chromatographed over silica gel (18 g; eluant petroleum ether (40:60) / diethyl ether, 1:1) to give unreacted 1-bromo-4-(bromomethyl)benzene (0.13 g, 0.5 mmol) and the title compound as a white crystalline solid (0.26 g, 0.75 mmol, 85 %, based on consumed **82**; m.p. 122-124 °C). Found: C, 58.4; H, 4.8; Br, 22.65; $C_{17}H_{17}BrO_3$ requires C, 58.5; H, 4.9; Br, 22.9 %; δ_H(300 MHz; $CDCl_3$) 7.57-7.52 (2H, m, Ar-H), 7.49 (2H, d, J = 8.5 Hz, Ar-H), 7.41-7.33 (3H, m, Ar-H), 7.30 (2H, d, J = 8.5 Hz, Ar-H), 5.58 (1H, s, >CH-Ph), 4.66 (2H, s, -CH_2Ar), 4.37 (2H, dd, J = 12.5, 1.5 Hz, -$C\underline{H}_aH_b$-), 4.07 (2H, dd, J = 12.5, 1.5 Hz, -$CH_a\underline{H}_b$-), 3.35 (1H, quintet, J = 1.5 Hz); δ_C(75 MHz; $CDCl_3$) 138.19 (Ar), 137.38 (Ar), 131.70 (Ar), 129.47 (Ar), 129.13 (Ar), 128.40 (Ar), 126.32 (Ar), 121.68 (Ar), 101.54 (>CH-Ph), 77.44 (-CH_2-), 69.81 (-CH_2-), 69.10 (>CH-Ar); ν_{max}(Nujol mull)/cm^{-1}: 1593 (w), 1487 (s), 1338 (s), 1317 (w), 1296 (m), 1279 (m), 1239 (m), 1218 (w); *m/z* (ES^+, MeCN): 349.3 $(M+H)^+$, 356.3 $(M+NH_4)^+$.

5.2.27 2-Phenylmethoxy-1,3-propanediol (86a)



cis-2-Phenyl-5-(phenylmethoxy)-1,3-dioxane (1.00 g, 3.70 mmol) was dissolved in hot ethanol (10 ml) then water (2 ml) and concentrated hydrochloric acid (2 ml) were added. The mixture was heated under reflux for 4 hours before the solvent was removed *in vacuo* to give a residue, to which was added saturated aqueous sodium chloride (10 ml). The aqueous phase was extracted with ether (4 x 10 ml) then the combined organic phases were dried (Na_2SO_4) before the solvent was removed *in vacuo* to give a white solid. Recrystallisation from hot (not boiling) toluene gave the title compound as a white crystalline solid (0.47 g, 2.6 mmol, 71 %; m.p. 36-39 °C (lit.[89] 37-39 °C)). δ_H(300 MHz; $CDCl_3$) 7.39-7.29 (5H, m, Ar-H), 4.66 (2H, s, $-CH_2-$), 3.85-3.66 (4H, br m, $-C\underline{H}_a\underline{H}_b-$), 3.59 (1H, quintet, J = 4.8 Hz, >CH-O-), 2.31 (2H, br m, -OH); δ_C(75 MHz; $CDCl_3$) 138.14 (Ar), 128.72 (Ar), 128.14 (Ar), 128.04 (Ar), 79.35 (-OCH<), 72.03 ($-CH_2-$), 62.11 ($-CH_2-$); ν_{max}(Golden Gate)/cm^{-1} 3286 (br s), 3064 (w), 2885 (m), 1469 (m), 1450 (s).

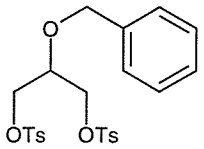
5.2.28 2-(4-Bromophenyl)methoxy-1,3-propanediol (86b)



To a mixture of *cis*- and *trans*-5-(4-bromophenyl)methoxy-2-phenyl-1,3-dioxane (1.00 g, 2.85 mmol) was added hot ethanol (9 ml), water (2 ml) and concentrated hydrochloric acid (1 ml). The mixture was heated under reflux for 4 hours before the solvent was removed *in vacuo*. Saturated aqueous sodium chloride (10 ml) was added to the residue and the resulting suspension was extracted with ether (4 x 10 ml). The organic phases were combined and dried (Na_2SO_4) before the solvent was removed to give a white solid, which was crystallised from toluene to give the title compound as a white crystalline solid (0.51g, 1.95 mmol, 68 %; m.p. 82-85 °C). Found: C, 46.0; H, 4.95; Br, 30.8; $C_{10}H_{13}BrO_3$ requires C, 46.0; H, 5.0; Br, 30.6 %; δ_H(300 MHz; $CDCl_3$) 7.49 (2H, d, J = 8.3 Hz, Ar-H), 7.24 (2H, d, J = 8.3 Hz, Ar-H), 4.62 (2H, s, $-CH_2Ph$), 3.81 (2H, dd, J = 11.8, 4.6, $-C\underline{H}_aH_b-$), 3.73 (2H, dd, J = 11.8, 4.6 Hz, $-CH_a\underline{H}_b-$), 3.58

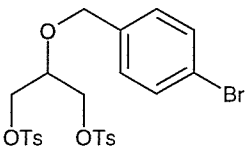
(1H, quintet, J = 4.8 Hz, >CH-O-), 2.05 (2H, br s, -OH); δ_C(75 MHz; $CDCl_3$) 137.15 (Ar), 131.81 (Ar), 129.59 (Ar), 122.00 (Ar), 79.40 (-CH_2-), 71.26 (>CH-), 62.31 (-CH_2-); ν_{max}(Nujol mull)/cm^{-1}: 3178 (br s), 1590 (w), 1341 (w), 1119 (s), 1070 (s); *m/z* (ES^-, 0.1 % NH_3 / MeCN): 373.2 $[M+TFA-H]^-$.

5.2.29 2-Phenylmethoxy-1,3-propanediyl bis(4-methylbenzenesulfonate) (87a)



2-Phenylmethoxy-1,3-propanediol (0.250 g, 1.37 mmol) and dry pyridine (0.27 g, 3.43 mmol) were mixed and dissolved in anhydrous DCM (5 ml). *p*-Toluenesulfonyl chloride (0.65 g, 3.43 mmol) was added in portions with magnetic stirring and the resulting mixture was then stirred at room temperature overnight. The solvent was removed *in vacuo* to give a pale orange oil which was triturated with water (10 ml). The resulting off-white solid was filtered under suction, washed with hydrochloric acid (2M, 2 x 2 ml) and water (2 x 2 ml) and then crystallised from DCM – petroleum ether (40:60) to give a white crystalline solid (m.p. 111-112 °C (lit.[126] 109.5-110.5 °C), 0.350 g, 0.71 mmol, 52 %). δ_H(300 MHz; $CDCl_3$) 7.74 (4H, d, J = 8.4 Hz, Ar-H), 7.32 (4H, d, J = 8.4 Hz, Ar-H), 7.31-7.28 (3H, m, Ar-H), 7.21-7.15 (2H, m, Ar-H), 4.48 (2H, s, -CH_2-), 4.10-3.99 (4H, m, -$\underline{H}_a\underline{H}_b$-), 3.80 (1H, quintet, J = 5.2 Hz, >CH-O-), 2.45 (6H, s, -CH_3); δ_C(75 MHz; $CDCl_3$) 145.35 (Ar), 137.12 (Ar), 132.47 (Ar), 130.13 (Ar), 128.60 (Ar), 128.19 (Ar), 128.11 (Ar), 127.94 (Ar), 73.96 (>CH-), 72.65 (-CH_2-), 67.86 (-CH_2-), 21.85 (-CH_3).

5.2.30 2-((4-Bromophenyl)methoxy)-1,3-propanediyl bis(4-methylbenzenesulfonate) (87b)



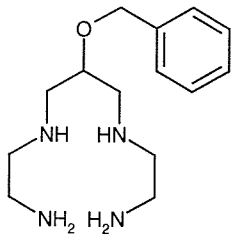
2-((4-Bromophenyl)methoxy)-1,3-propanediol (0.030 g, 0.123 mmol) was dissolved in pyridine (1 ml) and *p*-toluenesulfonyl chloride (0.064 g, 0.33 mmol) was added with magnetic stirring. The resulting mixture was stirred at room temperature overnight before the solvent was removed *in vacuo* to give an orange oil, which was triturated with water (2 ml). Filtration under suction gave an off-white solid (0.055 g, 9.7 x 10^{-5}

mol, 79 %; m.p. 87-90 °C (toluene – petroleum ether (40:60))). δ_H(300 MHz; $CDCl_3$) 7.74 (4H, d, J = 7.9 Hz, Ar-H), 7.42 (2H, d, J = 8.1 Hz, Ar-H), 7.33 (4H, d, J = 7.9 Hz, Ar-H), 7.06 (2H, d, J = 8.1 Hz, Ar-H), 4.45 (2H, s, -CH_2Ar), 4.10-3.95 (4H, m, -$C\underline{H_a}\underline{H_b}$-), 3.80 (1H, br quintet, $J \approx 7$ Hz, >CH-), 2.46 (6H, s, -CH_3); δ_C(75 MHz; $CDCl_3$) 145.10 (Ar), 136.20 (Ar), 132.45 (Ar), 131.68 (Ar), 130.14 (Ar), 129.50 (Ar), 128.09 (Ar), 122.06 (Ar), 74.31 (>CH-), 71.93 (-CH_2-), 67.87 (-CH_2-), 21.86 (-CH_3); ν_{max}(Golden Gate)/cm^{-1} 1597 (w), 1488 (w), 1456 (w), 1356 (m), 1176 (s).

5.2.31 Attempted Preparations of 6-(Phenylmethoxy)-1,4,8,11-tetraazaundecane (84a)

5.2.31.1 Method 1 (Solvent: dichloromethane)

To a stirred solution of ethylenediamine (200 mg, 3.33 mmol) in anhydrous DCM (5 ml) was added 2-phenylmethoxy-1,3-propanediyl bis(4-methylbenzenesulfonate) (100 mg, 0.20 mmol) in anhydrous DCM (4 ml). The resulting mixture was stirred at room temperature overnight before the solvent and excess ethylenediamine were removed *in vacuo*. Aqueous sodium hydroxide (10 % w/w; 5 ml) was added to the residue and the aqueous phase was extracted with DCM (4 x 5 ml). The organic portions were combined, dried (K_2CO_3) and the solvent was removed *in vacuo* to give an oil which solidified on standing. Recrystallisation from methanol gave a white crystalline solid with identical m.p. and ^{1}H-NMR to that of the ditosylate **87a**.



5.2.31.2 Method 2 (Solvent: 1,2-dimethoxyethane)

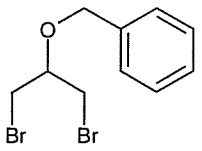
To a stirred solution of ethylenediamine (0.10 g, 1.67 mmol) in 1,2-dimethoxyethane (5 ml) was added 2-phenylmethoxy-1,3-propanediyl bis(4-methylbenzenesulfonate) (0.045 g, 9.2 x 10^{-5} mol) in 1,2-dimethoxyethane (4 ml), followed by sodium carbonate (0.10 g, 0.94 mmol). The resulting mixture was stirred at room temperature overnight before the solvent and excess ethylenediamine were removed *in vacuo*. Aqueous sodium

hydroxide (10 % w/w; 5 ml) was added to the residue and the aqueous phase was extracted with DCM (4 x 5 ml). The organic portions were combined, dried (K_2CO_3) and the solvent was removed *in vacuo* to give an oil which solidified on standing. The solid gave identical ^{1}H-NMR to that for the ditosylate 87**a**.

5.2.31.3 Method 3 (Solvent: acetonitrile)

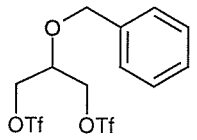
To a stirred solution of ethylenediamine (0.12 g, 2.0 mmol) in acetonitrile (5 ml) was added 2-phenylmethoxy-1,3-propanediyl bis(4-methylbenzenesulfonate) (43 mg, 8.8 x 10^{-5} mol) in acetonitrile (4 ml), followed by sodium iodide (5 mg, cat.). The resulting mixture was stirred at room temperature overnight before the solvent and excess ethylenediamine were removed *in vacuo*. Aqueous sodium hydroxide (10 % w/w; 5 ml) was added to the residue and the aqueous phase was extracted with DCM (4 x 5 ml). The organic portions were combined, dried (K_2CO_3) and the solvent was removed *in vacuo* to give an oil which solidified on standing. The solid gave identical ^{1}H-NMR to ditosylate **87a**.

5.2.32 1,3-Dibromo-2-(phenylmethoxy)propane (91)



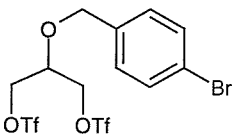
2-Phenylmethoxy-1,3-propanediyl bis(4-methylbenzenesulfonate) (53 mg, 0.108 mmol) was dissolved in acetone (10 ml) and to the resulting solution was added lithium bromide (0.50g, 5.7 mmol). The resulting mixture was heated under reflux overnight before the solvent was removed *in vacuo*. To the residue was added ether (10 ml) and the resulting solution was washed with saturated aqueous sodium hydrogen carbonate (5 ml) and then dried (Na_2SO_4). The solvent was removed *in vacuo* to give the title compound[127] as a yellow oil (29 mg, 9.4 x 10^{-5} mol, 87 %). δ_H(300 MHz; $CDCl_3$) 7.43-7.29 (5H, m, Ar-H), 4.68 (2H, s, -CH_2Ph), 3.82 (1H, quintet, J = 5.2 Hz, >CH-O-), 3.59 (4H, d, J = 5.2 Hz, -CH_2-); δ_C(75 MHz; $CDCl_3$) 137.35 (Ar), 128.74 (Ar), 128.33 (Ar), 128.11 (Ar), 77.21 (>CH-), 72.50 (-CH_2-), 32.69 (-CH_2-).

5.2.33 2-(Phenylmethoxy)-1,3-propanediyl bis(trifluoromethanesulfonate) (93a)



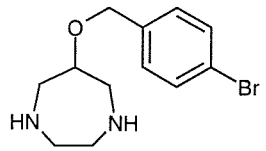
At 0 °C, to trifluoromethanesulfonic anhydride (0.51 g, 1.81 mmol) in dry DCM (4 ml) was added dropwise over 20 minutes a mixture of 2-phenylmethoxy-1,3-propanediol (0.150 g, 8.24 x 10^{-4} mol) and dry pyridine (0.143 g, 1.81 mmol) in dry DCM (6 ml). The mixture was stirred at 0 °C for 1 hour before the solution was rapidly washed with water (10 ml), then dried ($MgSO_4$). Removal of the solvent *in vacuo* gave the title compound as a reddish oil, which solidified on standing (0.290 g, 6.50 x 10^{-4} mol, 79 %) and which was used without further purification. δ_H(300 MHz; $CDCl_3$) 7.45-7.30 (5H, m, Ar-H), 4.71 (2H, s, -OCH_2-), 4.60 (2H, dd, J = 11.0, 4.8 Hz, -$C\underline{H}_aH_b$-), 4.53 (2H, dd, J = 11.0, 4.8 Hz, -$CH_a\underline{H}_b$-), 4.00 (1H, quintet, J = 4.8 Hz, -OCH<); δ_C(75 MHz; $CDCl_3$) 136.04 (Ar), 128.96(Ar), 128.85 (Ar), 128.32 (Ar), 73.21 (-CH_2-), 72.85 (-OCH<), 72.49 (-CH_2-); ν_{max}(Golden Gate)/cm^{-1} 1410 (m), 1244 (m), 1199 (s), 1138 (s), 943 (s), 812 (m).

5.2.34 2-((4-Bromophenyl)methoxy)-1,3-propanediyl bis(trifluoromethanesulfonate) (93b)



At 0 °C, to trifluoromethanesulfonic anhydride (0.48 g, 1.68 mmol) in dry DCM (5 ml) was added dropwise over 20 minutes a mixture of 2-((4-bromophenyl)methoxy)-1,3-propanediol (0.200 g, 7.66 x 10^{-4} mol) and anhydrous pyridine (0.13 g, 1.68 mmol) in dry DCM (5 ml). The mixture was stirred at 0 °C for 1 hour before the solution was rapidly washed with dilute hydrochloric acid (1 % w/w; 10 ml), then dried ($MgSO_4$). Removal of the solvent *in vacuo* gave the title compound as a pinkish solid (m.p. 57-59 °C; 0.402 g, 7.62 x 10^{-4} mol, 99 %) which was used without further purification. δ_H(300 MHz; $CDCl_3$) 7.52 (2H, d, J = 8.3 Hz, Ar-H), 7.23 (2H, d, J = 8.3 Hz, Ar-H), 4.61 (2H, dd, J = 11.0, 4.9 Hz), 4.55 (2H, dd, J = 11.0, 4.9 Hz), 4.01 (1H, quintet, J = 4.9 Hz, -OCH<); δ_C(75 MHz; $CDCl_3$) 135.05 (Ar), 132.05 (Ar), 129.79 (Ar), 122.78 (Ar), 73.28 (-OCH<), 72.42 (-CH_2-), 72.33 (-CH_2-); ν_{max}(Nujol mull)/cm^{-1}: 1594 (w), 1247 (s), 1205 (s), 1145 (s), 1070 (m), 1046 (m).

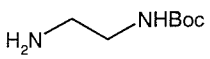
5.2.35 6-(4-Bromophenylmethoxy)-1,4-diazacycloheptane (94)



Under a nitrogen atmosphere, 1,2-ethanediamine (0.46 g, 7.6 mmol) and dry DCM (3.5 ml) were mixed and cooled to 0 °C before 2-((4-bromophenyl)methoxy)-1,3-propanediyl bis(trifluoromethanesulfonate) (200 mg, 3.8 x 10^{-4} mol) was added dropwise with magnetic stirring over 20 minutes. The resulting mixture was stirred at 0 °C for a further 1 hour before being washed with aqueous sodium hydroxide (10 % w/w; 10 ml) then dried (K_2CO_3). The solvent was removed *in vacuo* to give a pale yellow oil (101 mg, 3.51 x 10^{-4} mol, 92 %). δ_H(300 MHz; $CDCl_3$) 7.46 (2H, d, J = 8.3 Hz, Ar-H), 7.20 (2H, d, J = 8.3 Hz, Ar-H), 4.38 (2H, s, -OCH_2-), 4.19 (1H, quintet, J = 5.9 Hz), 3.65-3.55 (2H, m, -OCH(C$\underline{H}_a$$H_b$-)$_2$, 2.95-2.86 (2H, m, -OCH($CH_a\underline{H}_b$-)$_2$), 2.70-2.48 (4H, m, -NHC$\underline{H}_2$-), 1.71 (2H, br s, -NH-); δ_C(75 MHz; $CDCl_3$) 137.64 (Ar), 131.22 (Ar), 129.94 (Ar), 120.69 (Ar), 69.13 (-CH<), 68.26 (-OCH_2-), 61.48 (-CH_2-), 40.00 (-CH_2-); ν_{max}(Liquid film)/cm^{-1} 3364 (br s), 2938 (s), 2845 (s), 1592 (m), 1488 (s); *m/z* (ES^+, MeCN) 285.2 $(M+H)^+$.

5.2.36 *N*-(*t*-Butoxycarbonyl)-1,2-ethanediamine (96)

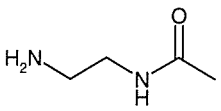
Prepared by the method of Krapcho and Kuell.[96]



To 1,2-ethanediamine (5.25 g, 87 mmol) in dioxane (30 ml) was added dropwise over 2 hours a solution of di-*tert*-butyl dicarbonate (2.45g, 11 mmol) in dioxane (30 ml). The resulting mixture was stirred at room temperature for 24 hours before the solvent was removed *in vacuo* to leave a residue to which was added water (50 ml). The mixture was filtered under suction and the filtrate was then extracted with DCM (3 x 50 ml). Removal of the solvent gave an oil, which solidified on standing to give the title compound as a white solid (1.28 g, 8.03 mmol, 73 %; m.p. 107-109 °C (lit.[96] 108-110 °C)). δ_H(300 MHz; $CDCl_3$) 5.22 (1H, br s, -NHBoc), 3.15 (2H, q, J = 6.9 Hz, -C$\underline{H}_2$NHBoc), 2.80 (2H, t, J = 6.9 Hz, -C$\underline{H}_2$$NH_2$), 1.82 (2H, br s, -$NH_2$), 1.35 (9H, s, -$C(CH_3)_3$); ν_{max}(Golden Gate)/cm^{-1} 3353 (w), 2973 (m), 1687 (s), 1517 (s), 1453 (m).

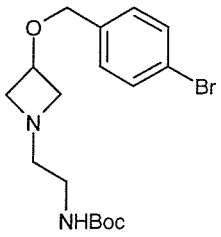
5.2.37 *N*-Acetyl-1,2-ethanediamine (97)

Prepared by the method of Dugenet et al.[128]



To ethylenediamine (18.00 g, 0.30 mol) was added ethyl acetate (8.80 g, 0.10 mol) and the resulting mixture was stirred at room temperature for 6 days. The mixture was then concentrated *in vacuo* to give a white semi-solid, which was distilled at reduced pressure to give the title compound as a colourless liquid (5.92 g, 58 mmol, 58 %; b.p. 145-155 °C / 10 mmHg (lit.[128] 125-130 °C / 5 mmHg)). δ_H(300 MHz; $CDCl_3$) 6.30 (1H, br s, -NHAc), 3.26 (2H, dt, J = 5.5, 5.9 Hz, -C$\underline{H}_2$NHAc), 2.81 (2H, t, J = 5.9 Hz, $NH_2C\underline{H}_2$-), 1.98 (3H, s, -CH_3), 1.45 (2H, s, -NH_2); ν_{max}(Golden Gate)/cm^{-1} 3276 (br m), 3072 (w), 2930 (w), 2865 (w), 1632 (s), 1548 (s), 1433 (m), 1371 (m).

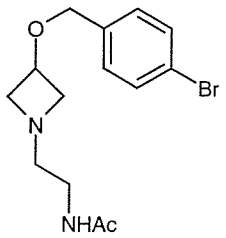
5.2.38 *N*-(2-(*t*-Butoxycarbonylamino)ethyl)-3-(4-bromophenylmethoxy)-1-azacyclobutane (98b)



N-(*t*-Butoxycarbonyl)-1,2-ethanediamine (0.46 g, 2.86 mmol, 10 eq.) was dissolved in anhydrous DCM (3.5 ml) and cooled to 0 °C. A solution of 2-((4-bromophenyl)methoxy-1,3-propanediyl bis(trifluoromethanesulfonate) (0.150 g, 0.286 mmol) in dry DCM (3 ml) was added dropwise and the resulting mixture was stirred at 0 °C for 1 hour. The organic solution was then washed with aqueous sodium hydroxide (10 % w/w; 2 x 10 ml) and dried (K_2CO_3) before the solvent was removed *in vacuo* to give a colourless oil (77 mg, 0.20 mmol, 70 %). δ_H(300 MHz; $CDCl_3$) 7.46 (2H, d, J = 8.1 Hz, Ar-H), 7.19 (2H, d, J = 8.1 Hz, Ar-H), 4.93 (1H, s, NH), 4.38 (2H, s, -CH_2Ar), 4.19 (1H, quintet, J = 5.9 Hz, >CH-), 3.65-3.59 (2H, m, -C$\underline{H}_a\underline{H}_b$-), 3.11 (2H, dt, J = 5.3, 5.7 Hz, -C$\underline{H}_2$NH-), 2.97 (2H, t, J = 6.8 Hz, -$CH_a\underline{H}_b$-), 2.59 (2H, t, J = 5.7 Hz, -CH_2N<), 1.43 (9H, s, -C(CH_3)$_3$); δ_C(75 MHz; $CDCl_3$) 156.38 (C=O), 136.65 (Ar), 131.51 (Ar), 129.49 (Ar), 121.71 (Ar), 79.28 (-$\underline{C}$(CH_3)$_3$), 70.30 (-CH_2O-), 68.50 (>CH-), 61.61 (-CH_2-), 58.74 (-CH_2-), 40.99 (-CH_2-), 28.38 (-CH_3); ν_{max}(Golden Gate)/cm^{-1} 3354 (m),

2983 (w), 2934 (w), 2871 (w), 1682 (s), 1638 (m), 1590 (m), 1527 (s), 1162 (s); *m/z* (ES^+/MeCN) 385.3 $(M+H)^+$.

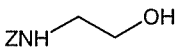
5.2.39 *N*-(2-(Acetylamino)ethyl)-3-(4-bromophenylmethoxy)-1-azacyclobutane (100b)



N-Acetyl-1,2-ethanediamine (0.29 g, 2.86 mmol, 10 eq.) was dissolved in anhydrous DCM (5 ml) and cooled to 0 °C. A solution of 2-((4-bromophenyl)methoxy-1,3-propanediyl bis(trifluoromethanesulfonate) (0.150 g, 0.286 mmol) in dry DCM (3 ml) was added dropwise and the resulting mixture was stirred at 0 °C for 3 hours. The organic solution was then washed with aqueous sodium hydroxide (10 % w/w; 2 x 10 ml) and dried (K_2CO_3), before the solvent was removed *in vacuo* to give a colourless oil (76 mg, 0.27 mmol, 82 %). δ_H(300 MHz; $CDCl_3$) 7.47 (2H, d, J = 8.2 Hz, Ar-H), 7.20 (2H, d, J = 8.2 Hz, Ar-H), 6.02 (1H, br s, NH), 4.38 (2H, s, $-CH_2-$), 4.18 (1H, quintet, J = 5.9 Hz), 3.61-3.52 (2H, m, $-C\underline{H}_aH_b-$), 3.21 (2H, dt, J = 5.1, 5.5 Hz, $-C\underline{H}_2NHAc$), 2.99-2.92 (2H, m, $-CH_a\underline{H}_b-$), 2.57 (2H, t, J = 5.5 Hz, $-CH_2N<$); δ_C(75 MHz; $CDCl_3$) 170.43 (C=O), 136.76 (Ar), 131.73 (Ar), 129.67 (Ar), 121.96 (Ar), 70.51 (>CH-), 68.57 ($-CH_2-$), 61.65 ($-CH_2-$), 58.44 ($-CH_2-$), 37.67 ($-CH_2-$), 23.40 ($-CH_3$); ν_{max}(Golden Gate)/cm^{-1} 3268 (m), 3087 (w), 2930 (m), 2826 (m), 2794 (m), 1637 (s), 1554 (s), 1485 (s); *m/z* (ES^+, MeCN) 327.2 $(M+H)^+$, 349 $(M+Na)^+$.

5.2.40 *N*-Benzyloxycarbonyl-2-aminoethanol (108)

Prepared by the method of Hamada et al.[104]

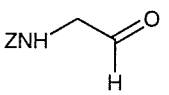


To 2-aminoethanol (7.2 ml; 0.12 mol) in toluene (20 ml) at 0 °C was added over 20 minutes benzyl chloroformate (7.14 ml; 0.05 mol) in toluene (40 ml). The resulting mixture was stirred at room temperature for 30 minutes before being washed with water (2 x 50 ml) and then saturated brine (50 ml). The organic phase was dried (Na_2SO_4) then the solvent was removed *in vacuo* to give the title compound as a white crystalline solid which was recrystallised from ethyl acetate – petroleum ether (60:80) (8.32 g, 42.8 mmol, 85 %; m.p. 60-61 °C (lit.[104] 60-62 °C)). δ_H(300 MHz;

$CDCl_3$) 7.40-7.30 (5H, m, Ar-H), 5.26 (1H, br s, NH), 5.11 (2H, s, $-CH_2Ph$), 3.71 (2H, t, J = 5.0 Hz, $-CH_2O-$), 3.35 (2H, dt, J = 5.5, 5.0 Hz, $-CH_2N-$), 2.19 (1H, br s, -OH); ν_{max}(Golden Gate)/cm^{-1} 3314 (s), 3062 (w), 2940 (w), 2885 (w), 1690 (s), 1536 (s), 1452 (s).

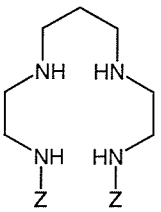
5.2.41 *N*-Benzyloxycarbonyl-2-aminoethanal (109)

Prepared by the method of Hamada et al., with amendments.[104]



N-Benzyloxycarbonyl-2-aminoethanol (1.95 g , 10 mmol) and triethylamine (3.04 g, 30 mmol) were dissolved in dry DCM (30 ml) and cooled to –10 °C. Sulfur trioxide-pyridine complex (4.77 g, 30 mmol) in DMSO (30 ml) was added in one portion and the resulting mixture was stirred at –10 °C for 5 minutes before being allowed to warm to room temperature over 15 minutes. The reaction mixture was poured onto ice-saturated brine (90 ml) and extracted with ether (1 x 40 ml, 2 x 20 ml). The combined organic phases were combined, washed with aqueous citric acid (10 % w/w; 20 ml) followed by saturated brine (2 x 20 ml) and then dried (Na_2SO_4). Removal of the solvent gave a yellow oil, which was chromatographed over silica gel (eluant ether – ethyl acetate, 9:1) to give the title compound as a colourless oil (0.52 g, 2.71 mmol, 27 %). δ_H(300 MHz; $CDCl_3$) 9.63 (1H, s, CHO), 7.40-7.28 (5H, m, Ar-H), 5.61 (1H, br s, NH), 5.12 (2H, s, $-CH_2Ph$), 4.10 (2H, d, J = 5.4 Hz, $-NCH_2-$).

5.2.42 Attempted Preparation of 1,11-Bis(benzyloxycarbonyl)-1,4,8,11-tetraazaundecane (110)

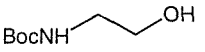


Under a nitrogen atmosphere, 1,3-propanediamine (0.11 g, 1.48 mmol) and *N*-benzyloxycarbonyl-2-aminoethanal (0.56 g, 2.96 mmol) were mixed in dry THF (20 ml) and then sodium triacetoxyborohydride (0.80 g, 3.79 mmol, 2.6 eq.) was added. The resulting cloudy mixture was stirred at room temperature for 24 hours. Aqueous sodium hydroxide (10 % w/w; 20 ml) was then added and the phases were then separated. The aqueous phase was extracted with ether (3 x 10 ml) and the organic portions were then combined, dried ($MgSO_4$) and concentrated *in vacuo* to give a viscous yellow oil (*ca.*

0.6 g). The oil was dissolved in methanol (3 ml) and then a solution of oxalic acid (0.134 g, 1.48 mmol) in methanol (3 ml) was added. The white precipitate which formed instantly was filtered under suction and dried *in vacuo*. The solid was found to be insoluble in D_2O and DMSO-d_6, so a portion (200 mg) was dissolved in aqueous sodium hydroxide (2M; 5 ml) and extracted with DCM (3 x 5 ml). The combined organic solutions were dried (K_2CO_3) and then concentrated in vacuo to give a viscous, colourless oil (90 mg) which gave δ_H(300 MHz; $CDCl_3$) 7.40-7.11 (10H, m, Ar-H), 5.02 (4H, s, -CH_2-), 3.25-3.01 (4H, m, -CH_2-), 2.75-2.50 (8H, m, 2 x -CH_2-), 1.61 (4H, br s, NH?), 1.60-1.40 (2H, m, -CH_2-); ν_{max}(Golden Gate)/cm^{-1} 3293 (m), 2936 (m), 2836 (w), 1691 (s), 1527 (s), 1454 (s), 1249 (s); *m/z* (ES^+, MeCN) 427.4 $(M+H)^+$.

5.2.43 *N*-(*t*-Butoxycarbonyl)-2-aminoethanol (111)

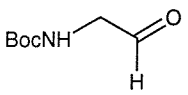
Prepared by the method of Mayor et al.[105]



Di-*tert*-butyl dicarbonate (5.01 g, 22.9 mmol) was dissolved in dry THF (20 ml) and cooled to 0 °C before a solution of 2-aminoethanol (1.41 g, 23.1 mmol) in dry THF (10 ml) was added over 10 minutes. The mixture was stirred overnight at room temperature and then the solvent was removed *in vacuo* to give the title compound as a colourless oil (2.70 g, 16.8 mmol, 73 %). δ_H(300 MHz; $CDCl_3$) 5.03 (1H, br s, NH), 3.70 (2H, t, J = 5.1 Hz, -CH_2O-), 3.28 (2H, dt, J = 4.8, 5.1 Hz, -NCH_2-); ν_{max}(Golden Gate)/cm^{-1} 3332 (br m), 2975 (m), 2933 (m), 1679 (s), 1516 (s), 1453 (m).

5.2.44 Attempted Preparations of *N*-(*t*-Butoxycarbonyl)-2-aminoethanal (112)

5.2.44.1 Method 1 – DeVita et al.[106]



To *N*-(*t*-butoxycarbonyl)-2-aminoethanol (700 mg, 4.34 mmol) in dry DCM (35 ml) was added DMSO (4 ml) and triethylamine (4.8 ml; 3.5 g, 35 mmol). Sulfur trioxide-pyridine complex (2.8 g, 17 mmol) was then added in portions over 10 minutes and the resulting brown mixture was stirred at room temperature for 3 hours. The mixture was diluted with dry ether (500 ml), washed with dilute hydrochloric acid (1M; 2 x 50 ml), saturated aqueous sodium bicarbonate (100 ml) and brine (100 ml) and then dried ($MgSO_4$). Removal of the solvent *in vacuo* gave a yellow-brown oil (*ca.* 510 mg), which by TLC (ether-petroleum ether (40:60) (4:1)) was a mixture of the starting alcohol and two close-running components. ^{1}H-NMR and MS indicated aldol formation from the desired aldehyde. Attempted purification by column chromatography (silica gel; eluant ether-petroleum ether (40:60) (4:1)) was unsuccessful, the aldol and aldehyde co-eluting.

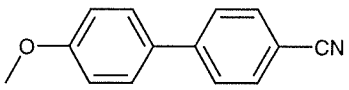
5.2.44.2 *Method 2 – De Napoli et al.*[107]

To a solution of *N*-(*t*-butoxycarbonyl)-2-aminoethanol (0.81 g, 5 mmol) in dry DCM (100 ml) was added PCC (5 g, 23 mmol). The mixture rapidly turned from orange to black, and was stirred at room temperature for 3½ hours before dry ether (100 ml) was added. The solvent was concentrated *in vacuo* to *ca.* 30 ml and filtered through a short column of silica gel, before the solvent was removed at reduced pressure to give a slightly yellow oil (0.53 g). TLC (ether-petroleum ether (40:60) (4:1)) indicated a mixture of the aldehyde and aldol.

5.2.44.3 Method 3

To a solution of *N*-(*t*-butoxycarbonyl)-2-aminoethanol (0.50 g, 3.11 mmol) in dry DCM (10 ml) was added PDC (2.40 g, 6.21 mmol, 2 eq.) with magnetic stirring. After 24 hours at room temperature, the mixture was diluted with dry ether (40 ml) and filtered through a short column of silica. Examination of the filtrate by TLC (ether-petroleum ether (40:60) (4:1)) indicated solely the presence of unreacted alcohol.

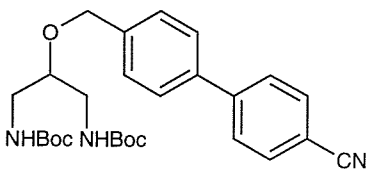
5.2.45 4-Methoxy-4'-cyanobiphenyl (114)



Prepared by the method of Parker.[111]

Under a nitrogen atmosphere, to degassed 1,2-dimethoxyethane (15 ml) were added 4-cyanobenzeneboronic acid (0.147 g, 1 mmol), 1-bromo-4-methoxybenzene (0.191 g, 1 mmol) and degassed aqueous sodium carbonate (2M; 1.5 ml, 3 mmol). The mixture was then stirred for 40 minutes before tetrakis(triphenylphosphine) palladium (0.04 g, 35 μmol, 3.5 mol %) was added. The mixture was heated under reflux for 18 hours and then allowed to cool before DCM (30 ml) was added. The organic phase was separated, washed with water (2 x 20 ml), followed by saturated sodium hydrogen carbonate solution (20 ml) and then dried (Na_2SO_4). The solvent was removed *in vacuo* to give a yellow oil, which was dissolved in DCM (5 ml) then concentrated with silica gel (0.18 g) to form a silica pad which was chromatographed over silica gel (10.3 g, eluant petroleum ether (40:60) / diethyl ether, 19:1). The title compound was isolated as a white crystalline solid (0.058 g, 0.42 mmol, 42 %; m.p. 103-104 °C (lit.[129] 104 °C)). δ_H(300 MHz; $CDCl_3$) 7.75 (2H, AA'BB', J_{app} = 8.6 Hz, Ar-H), 7.67 (2H, AA'BB', J_{app} = 8.6 Hz, Ar-H), 7.56 (2H, d, J = 8.6 Hz, Ar-H) 7.01 (2H, d, J = 8.6 Hz, Ar-H), 3.87 (3H, s, -OCH_3).

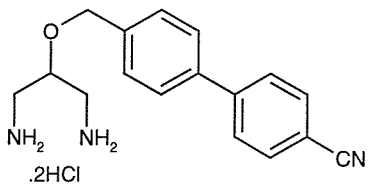
5.2.46 *N,N'*-Bis((*t*-butoxycarbonyl)-2-((4-(cyanophenyl)phenyl)methoxy)-1,3-propanediamine (117)



Under a nitrogen atmosphere, to degassed 1,2-dimethoxyethane (15 ml) was added 4-cyanobenzeneboronic acid (0.130 g, 0.88 mmol), 6-((4-bromophenyl)methyl)-1,11-diphenyl-1,4,8,11-tetraazaundecane-5,7-dione (0.402 g, 0.88 mmol) and degassed aqueous sodium carbonate (2M; 1.5 ml, 3 mmol). The mixture was then stirred for 60 minutes before tetrakis(triphenylphosphine) palladium (0.03 g, 26 μmol, 3 mol %) was added. The mixture was heated under reflux for 18 hours then allowed to cool before DCM (30 ml)

was added. The organic phase was successively washed with water (2 x 20 ml) and saturated sodium hydrogen carbonate solution (20 ml) and then dried (Na_2SO_4). The solvent was removed *in vacuo* to give a dark orange oil, which was dissolved in DCM (10 ml) then concentrated with silica gel (0.18 g) to form a silica pad which was chromatographed over silica gel (10.4 g, eluent petroleum ether (40:60) / ethyl acetate, 2:1). The title compound was isolated as a white solid (0.172 g, 0.358 mmol, 41%; m.p. 134-136 °C). Found: C, 66.9; H, 7.4; N, 8.5. $C_{27}H_{35}N_3O_5$ requires C, 67.3; H, 7.3; N, 8.7 %. δ_H(300 MHz; $CDCl_3$) 7.73 (2H, AA'BB', J_{app} = 8.5 Hz, Ar-H), 7.67 (2H, AA'BB', J_{app} = 8.5 Hz, Ar-H), 7.58 (2H, d, J = 8.5 Hz, Ar-H), 7.46 (2H, d, J = 8.5 Hz, Ar-H), 5.11 (2H, br t, J = 6.0 Hz, -NHBoc), 4.67 (2H, s, $-CH_2Ar$), 3.58 (1H, quintet, J = 5.5 Hz, -CH<), 3.53-3.38 (2H, m, $-CH_aH_bNHBoc$), 3.13 (2H, dt, J = 14.3, 5.5 Hz, $-CH_aH_bNHBoc$), 1.45 (18H, s, $C(CH_3)_3$); δ_C(75 MHz; $CDCl_3$) 156.58 (C=O), 145.41 (Ar), 138.89 (Ar), 138.81 (Ar), 132.77 (Ar), 128.64 (Ar), 127.81 (Ar), 127.49 (-C≡N), 119.07 (Ar), 111.08 (Ar), 79.65 ($-C(CH_3)_3$), 76.99 (-OCH<), 71.14 ($-OCH_2Ar$), 40.46 ($-CH_2NHBoc$), 28.53 ($-C(CH_3)_3$); ν_{max}(Nujol mull)/cm^{-1} 3369 (s), 2226 (w), 1684 (s), 1606 (w), 1527 (s); *m/z* (ES^+, MeCN) 482.2 $(M+H)^+$, 504.2 $(M+Na)^+$.

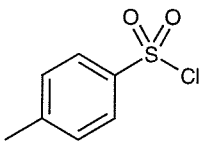
5.2.47 2-((4-(4-Cyanophenyl)phenyl)methoxy)-1,3-propanediamine, dihydrochloride salt (118)



To *N,N'*-bis(*t*-butoxycarbonyl)-2-((4-(4-cyanophenyl)phenyl)methoxy)-1,3-propanediamine (0.085 g, 0.175 mmol) was added methanolic HCl (5 ml) and the resulting mixture was stirred at room temperature for 60 minutes. The title compound was precipitated by the addition of anhydrous ether (20 ml) as a white micro-crystalline solid (m.p. > 240 °C; 0.034 g, 0.096 mmol, 54 %). δ_H(300 MHz; D_2O) 7.60-7.32 (8H, m, Ar-H), 4.68 (2H, s, $-CH_2Ph$), 4.12 (1H, tt, J = 6.8, 4.1 Hz, $-CH(CH_2NH_2)_2$), 3.30 (2H, dd, J = 13.9, 4.1 Hz, $-CH_aH_bNH_2$), 3.09 (2H, dd, J = 13.9, 6.8 Hz, $-CH_aH_bNH_2$); δ_C(75 MHz; D_2O) 146.85 (Ar), 141.07 (Ar), 139.55 (Ar), 135.37 (Ar), 131.81 (Ar), 129.99 (Ar), 129.74 (Ar),

122.24 (Ar), 112.00 (-<u>C</u>N), 74.04 (-O<u>C</u>H_2-), 73.84 (-O<u>C</u>H<), 42.21 (-<u>C</u>H_2NH_2); ν_{max}(Nujol mull)/cm^{-1} 3374 (s), 2225 (w), 1606 (m), 1530 (m).

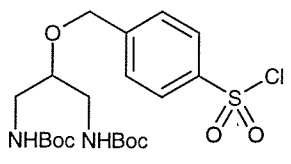
5.2.48 4-Methylbenzenesulfonyl Chloride (123)



Under a nitrogen atmosphere at –78 °C, to 1-bromo-4-methylbenzene (1.01 g, 5.85 mmol) in anhydrous ether (10 ml) was added n-butyl lithium (1.5 M; 3.9 ml; 5.85 mmol). The resulting solution was stirred at –78 °C for 3 hours before being added *via* canula to sulfuryl chloride (0.95 ml; 1.58 g, 11.7 mmol) in anhydrous ether (20 ml). The resulting mixture was stirred at –78 °C for two hours before being allowed to warm to room temperature. The mixture was stirred overnight and was then poured onto ice-water (60 ml). The organic phase was separated and the aqueous layer was extracted with ether (2 x 30 ml). The combined organic portions were washed successively with saturated aqueous sodium sulfite (30 ml), saturated aqueous sodium hydrogen carbonate (30 ml), water (30 ml) and were then dried ($MgSO_4$). The solvent was removed *in vacuo* to give a dark brown solid which was chromatographed over silica gel (eluant petroleum ether (40:60)/ ether (2:1)). Recrystallisation from petroleum ether (40:60) gave the title compound as a white crystalline solid (0.701 g, 3.68 mmol, 63 %; m.p. 68 – 69 °C (lit.[112] 69 °C)). δ_H(300 MHz; $CDCl_3$) 7.93 (2H, d, J = 8.4 Hz, Ar-H), 7.42 (2H, d, J = 8.4 Hz, Ar-H), 2.50 (3H, s, -C<u>H</u>$_3$).

5.2.49 Attempted Preparations of *N,N'*-Bis(*t*-butoxycarbonyl)-2-((4-(chlorosulfonyl)phenyl)methoxy)-1,3-propanediamine (128)

5.2.49.1 Method 1



Under a nitrogen atmosphere at –78 °C, *N,N'*-bis(*t*-butoxycarbonyl)-2-((4-bromophenyl)methoxy)-1,3-propanediamine (0.25 g, 0.54 mmol) in anhydrous ether (10 ml) was added n-butyl lithium (1.5 M; 0.36 ml; 0.54 mmol). The resulting solution was stirred at –78 °C for 30 minutes before being added

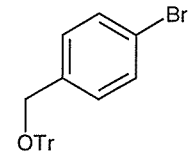
via a canula to sulfuryl chloride (0.15 g, 1.08 mmol) in anhydrous ether (10 ml). The resulting mixture was stirred at –78 °C for one hour before being allowed to warm to room temperature. The mixture was stirred for a further two hours and then poured onto ice-water (30 ml). The organic layer was separated and the aqueous layer was extracted with ether (2 x 20 ml). The organic phases were combined and washed successively with saturated aqueous sodium sulfite (20 ml), saturated aqueous sodium hydrogen carbonate (20 ml) and water (20 ml) and were then dried (Na_2SO_4). The solvent was removed *in vacuo* to leave a white solid, which was crystallised from hexane and found by ^{1}H-NMR, MS and melting point to be unchanged starting material (0.207 g, 0.41 mmol recovered).

5.2.49.2 Method 2

Under a nitrogen atmosphere at –100 °C, to *N,N'*-bis(*t*-butoxycarbonyl)-2-((4-bromophenyl)methoxy)-1,3-propanediamine (0.20 g, 0.44 mmol) in anhydrous ether (10 ml) was added n-butyl lithium (1.85 M; 0.75 ml; 1.39 mmol). The resulting solution was stirred at –100 °C for 40 minutes before being added *via* a canula to sulfuryl chloride (0.04 ml; 0.067 g, 0.49 mmol) in anhydrous ether (10 ml). The resulting mixture was stirred at –78 °C for one hour and then allowed to warm to room temperature. The mixture was stirred for a further two days and then poured onto ice-water (30 ml). The organic layer was separated and the aqueous layer was extracted with ether (2 x 20 ml). The organic phases were combined and washed successively with saturated aqueous sodium hydrogen carbonate (20 ml) and water (20 ml) and then dried (Na_2SO_4). The solvent was removed *in vacuo* to leave a white semi-solid, which was dissolved in methanol, treated with silica and concentrated *in vacuo* to give a silica pad which was chromatographed over silica gel (eluant petroleum ether / ethyl acetate (3:1)). Unchanged starting material (0.05 g, 0.01 mmol) was recovered together with material which was found to have identical ^{1}H-NMR, MS and melting point to *N,N'*-bis(*t*-butoxycarbonyl)-2-(phenylmethoxy)-1,3-propanediamine (**52a**) (0.10 g, 0.026 mmol).

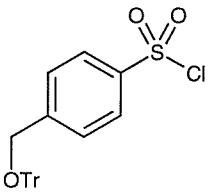
5.2.50 4-Bromo-1-(triphenylmethoxymethyl)benzene (131)

Prepared by the method of Doyle and Siegfried,[130] *with minor amendments.*



To 4-bromobenzyl alcohol (2.52 g, 13.5 mmol) in dry pyridine (10 ml) was added triphenylmethyl chloride (3.76 g, 13.5 mmol) in one portion. The resulting mixture was heated under reflux for 24 hours, before the pyridine was removed *in vacuo* to leave a brownish solid. Water (30 ml) was added and the aqueous phase was extracted with DCM (3 x 20 ml). The combined organic phases were washed with dilute hydrochloric acid (2 M; 30 ml) and then water (30 ml) and were finally dried (Na_2SO_4). Removal of the solvent *in vacuo* gave a buff-coloured solid, which was crystallised from chloroform-ethanol to give the title compound as a white crystalline solid (4.42 g, 10.3 mmol, 76 %; m.p. 152-153 °C (lit.[130] 150.5-152.5 °C). Found: C, 72.7; H, 4.9; Br, 18.5. $C_{26}H_{21}BrO$ requires C, 72.7; H, 4.9; Br, 18.6 %. δ_H(300 MHz; $CDCl_3$) 7.54-7.45 (8H, m, Ar-H), 7.38-7.23 (11H, m, Ar-H), 4.15 (2H, s, $-CH_2-$); δ_C(75 MHz; $CDCl_3$) 144.77 (Ar), 138.97 (Ar), 132.20 (Ar), 129.51 (Ar), 129.50 (Ar), 128.77 (Ar), 127.99 (Ar), 121.72 (Ar), 87.98 ($-O\underline{C}Ph_3$), 65.97 ($-CH_2-$); ν_{max}(Golden Gate)/cm^{-1} 3026 (w), 2887 (w), 2858 (w), 1597 (w), 1486 (s), 1146 (s), 1074 (s); *m/z* (EI) 244 (68 %), 183 (31), 165 (100), 77 (35), 50 (40).

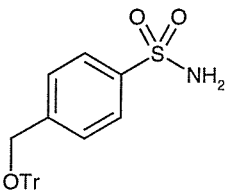
5.2.51 4-(Triphenylmethoxymethyl)-1-benzenesulfonyl chloride (133)



4-Bromo-1-(triphenylmethoxymethyl)benzene (1.00 g, 2.33 mmol) was dissolved in anhydrous THF (20 ml) under a dry nitrogen atmosphere and cooled to –78 °C. Butyl lithium (1.5 M solution in hexanes; 1.55 ml, 2.33 mmol) was then added and the mixture was stirred at –78 °C for 30 minutes. A white precipitate was observed, which redissolved immediately upon the rapid addition of sulfuryl chloride (0.40 ml; 0.68 g, 5.0 mmol). The resulting mixture was stirred at –78 °C for 30 minutes before being allowed to warm to room temperature (*ca.* 1 hour). The mixture was poured onto saturated sodium hydrogen carbonate (20 ml) and the organic phase was separated. The aqueous phase was extracted with ether (5 x 10 ml) and the organic phases were combined and then

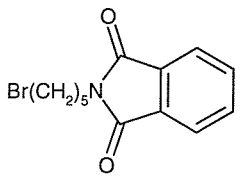
dried ($MgSO_4$). Removal of the solvent *in vacuo* gave a viscous oil which solidified on standing and was crystallised from DCM – petroleum ether (40:60) to give the title compound as a white crystalline solid (0.85 g, 1.89 mmol, 81 %). δ_H(300 MHz; $CDCl_3$) 8.02 (2H, d, J = 8.5 Hz, Ar-H), 7.63 (2H, d, J = 8.5 Hz, Ar-H), 7.58-7.45 (6H, m, Ar-H), 7.43-7.32 (9H, m, Ar-H), 4.35 (2H, s, -CH_2-). As the compound was found to be unstable, it was characterised as its sulfonamide derivative.

5.2.52 4-(Triphenylmethoxymethyl)-1-benzenesulfonamide (134)



To freshly prepared 4-(triphenylmethoxymethyl)-1-benzenesulfonyl chloride (0.30 g, 0.68 mmol) was added ammonia solution ("880"; 5 ml) then ethanol (5 ml). The mixture was heated under reflux for 2 hours then allowed to cool before being poured onto crushed ice (*ca.* 30 g). In the absence of a filterable solid, the solvent was removed *in vacuo* to leave a white residue, which was crystallised from ethanol to give the title compound as a white solid (0.25 g, 0.58 mmol, 85 %; m.p. 198-200 °C). δ_H(300 MHz; DMSO-d_6) 7.82 (2H, d, J = 8.5 Hz, Ar-H), 7.58 (2H, d, J = 8.5 Hz, Ar-H), 7.49-7.25 (15H, m, Ar-H), 4.16 (2H, s, -CH_2-); δ_C(75 MHz; DMSO-d_6) 143.62 (Ar), 143.00 (Ar), 142.59 (Ar), 128.25 (Ar), 128.22 (Ar), 127.35 (Ar), 127.06 (Ar), 125.86 (Ar), 86.79 (-CPh_3), 64.68 (-CH_2-); ν_{max}(Golden Gate)/cm^{-1} 3412 (w), 3272 (m), 3069 (w), 1598 (w), 1490 (m), 1449 (m), 1337 (s), 1164 (s), 1075 (s).

5.2.53 *N*-(5-Bromopentyl)phthalimide (136)

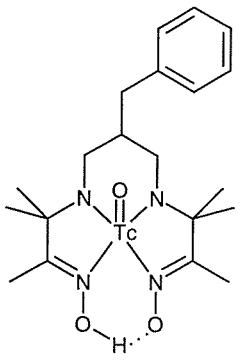


Prepared by the method of Payne and Boger.[131]

A solution of 5-amino-1-pentanol (1.03 g, 10 mmol) and phthalic anhydride (1.48 g, 10 mmol) in toluene (100 ml) was heated under reflux for 5 hours in a flask fitted with a Dean-Stark trap. The mixture was allowed to cool slightly before phosphorus tribromide (0.6 ml; 1.71 g, 6.3 mmol) in toluene (4 ml) was added. The mixture was stirred at 100 °C for two hours then allowed to cool before the solvent was removed *in vacuo* to give a brownish oil, which was dissolved in DCM (20 ml) and filtered through a short pad of silica to give a

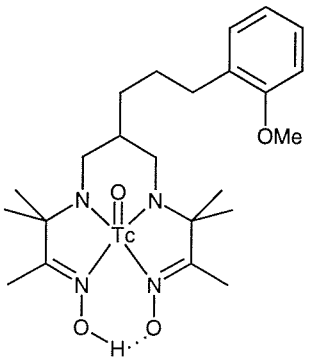
colourless oil. The title compound was obtained as a white crystalline solid after crystallisation from ethanol (25 ml) at –20 °C (1.81 g, 6.1 mmol, 61 %; m.p. 58-59 °C (lit.[131] 59.5-60.0 °C). δ_H(300 MHz; $CDCl_3$) 7.89-7.82 (2H, AA'BB', J_{app} = 5.2, 3.1 Hz, Ar-H), 7.76-7.69 (2H, AA'BB', J_{app} = 5.1, 3.1 Hz, Ar-H), 3.71 (2H, t, J = 7.2 Hz, $-CH_2-$), 3.41 (2H, t, J = 6.8 Hz, $-CH_2-$), 1.92 (2H, tt, J = 7.0, 7.4 Hz, $-CH_2-$), 1.72 (2H, quintet, J = 7.4 Hz, $-CH_2-$), 1.57-1.44 (2H, m, $-CH_2-$).

5.2.54 Oxo[6-benzyl-3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioximato(3-)-*N,N',N'',N'''*]technetium(V) (140a)



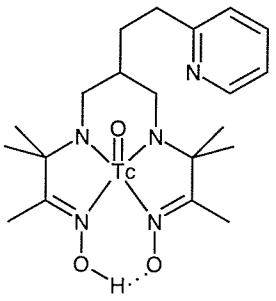
6-Benzyl-3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioxime (20.3 mg, 55.2 μmol) was dissolved in saline (0.9 %; 5 ml) and hydrochloric acid (5 M; 2 drops). Ammonium pertechnetate (4.98 mg; 27.6 μmol) was added followed by aqueous sodium hydrogen carbonate (1 M; 3 ml) and ether (20 ml). Tartaric acid (9.06 mg; 60 μmol) in saline (0.9 %; 1ml) was then added, followed by tin (II) chloride, dihydrate (13.5 mg, 60 μmol) in saline (0.9 %; 1ml), whereupon the aqueous phase changed from colourless to yellow. The mixture was stirred at room temperature for 20 minutes, during which time the yellow colour was observed to move from the aqueous phase into the organic phase. The phases were then separated and the aqueous phase was extracted with ether until no yellow coloration was observed in the extract (3 x 10 ml). The combined organic phases were dried (Na_2SO_4) then concentrated *in vacuo* to *ca.* 2 ml. The solution was introduced to a silica gel (5 g) column prepared with ether, and initially eluted with ether (10 ml). The orange fraction was then displaced with methanol, the coloured fractions were collected and taken to dryness *in vacuo*. The resulting orange powder, which exhibited a high count-rate (>500 Bq), was dissolved in the minimum volume of ether and was then allowed to stand at -20 °C overnight. The title compound was isolated as an orange crystalline solid. This was characterised by a single crystal X-ray structural study.

5.2.55 Oxo[6-(3-(2-methoxyphenyl)propyl)-3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioximato(3-)-*N,N',N'',N'''*]technetium(V) (140b)



6-(3-(2-Methoxyphenyl)propyl)-3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioxime (23.2 mg, 55.2 μmol) was dissolved in saline (0.9 %; 5 ml) and hydrochloric acid (5 M; 2 drops). Ammonium pertechnetate (5.00 mg; 27.6 μmol) was added followed by aqueous sodium hydrogen carbonate (1 M; 2 ml) and ether (10 ml). Tartaric acid (9.07 mg; 60 μmol) in saline (0.9 %; 1ml) and tin (II) chloride dihydrate (13.4 mg, 60 μmol) in saline (0.9 %; 1ml) were then added sequentially, whereupon the aqueous phase changed from colourless to yellow. The mixture was stirred at room temperature for 30 minutes, during which time the yellow colour was observed to move from the aqueous phase into the organic phase. The phases were then separated and the aqueous phase was extracted with ether until no yellow coloration was observed in the extract (3 x 10 ml). The combined organic phases were briefly dried (Na_2SO_4) and then concentrated *in vacuo* to *ca.* 1 ml. The solution was introduced to a silica gel (5 g) column prepared with ether, and initially washed with ether (10 ml), before the orange fraction was eluted with methanol. The combined orange fractions were taken to dryness *in vacuo*. The resulting orange powder was dissolved in the minimum volume of ether and was then allowed to stand at -20 °C for 14 days. The title compound was isolated as an orange crystalline solid characterised by single crystal X-ray structural study.

5.2.56 Oxo[6-(2-(2-pyridyl)ethyl)-3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioximato(3-)-*N,N',N'',N'''*]technetium(V) (140c)



6-(2-(2-Pyridyl)ethyl)-3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioxime (20.8 mg, 55.2 μmol) was dissolved in saline (0.9 %; 5 ml) and hydrochloric acid (5 M; 2 drops). Ammonium pertechnetate (5.01 mg; 27.6 μmol) was added followed by aqueous sodium hydrogen carbonate (1 M; 2 ml) and ether (10 ml). Tartaric acid (9.07 mg; 60 μmol) in saline (0.9 %; 1ml) was then added, followed by tin (II) chloride, dihydrate (13.5 mg, 60 μmol) in saline (0.9 %; 1ml), whereupon the aqueous phase changed from colourless to yellow. The mixture was stirred at room temperature for 25 minutes, during which time the yellow colour was observed to move from the aqueous phase into the organic phase. The phases were then separated and the aqueous phase was extracted with ether until no yellow coloration was observed in the extract (3 x 10 ml). The combined organic phases were dried (Na_2SO_4) and were then concentrated *in vacuo* to *ca.* 2 ml. The solution was introduced to a silica gel column prepared with ether, and initially eluted with ether (10 ml), before the orange fraction was displaced with methanol. The combined orange fractions were taken to dryness *in vacuo*. The resulting orange powder was dissolved in the minimum volume of methanol-ether then allowed to stand at -20 °C for 3 days. The title compound was isolated as an orange crystalline solid and was characterised by a single crystal X-ray structural study

Appendix A

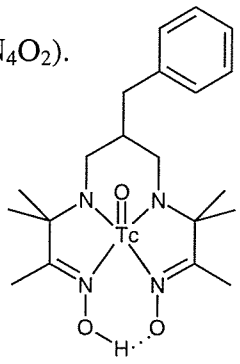


Table A1. Crystal data and structure refinement for $TcO(C_{20}H_{31}N_4O_2)$.

Identification code	$TcO(C_{20}H_{31}N_4O_2)$	
Empirical formula	C20 H31 N4 O3 Tc	
Formula weight	473.49	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic P	
Space group	$P2_1/c$	
Unit cell dimensions	a = 7.957(2) Å	α= 90°.
	b = 11.979(2) Å	β= 91.00(3)°.
	c = 22.914(5) Å	γ = 90°.
Volume	2183.8(8) $Å^3$	
Z	4	
Density (calculated)	1.440 Mg/m^3	
Absorption coefficient	0.686 mm^{-1}	
F(000)	984	
Crystal size	0.15 x 0.1 x 0.05 mm^3	
Theta range for data collection	3.07 to 25.03°.	
Index ranges	-9<=h<=9, -14<=k<=14, -27<=l<=27	
Reflections collected	28423	
Independent reflections	3854 [R(int) = 0.1585]	
Completeness to theta = 25.03°	99.7 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3854 / 0 / 359	
Goodness-of-fit on F^2	1.051	
Final R indices [I>2sigma(I)]	R1 = 0.0548, wR2 = 0.1250	

R indices (all data)	R1 = 0.0803, wR2 = 0.1366
Largest diff. peak and hole	1.242 and -1.352 e.Å^{-3}

Table A2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for $TcO(C_{20}H_{31}N_4O_2)$. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Tc(1)	4071(1)	960(1)	8584(1)	22(1)
O(2)	1106(5)	239(3)	9316(2)	32(1)
O(4T)	3147(4)	1791(3)	8084(1)	26(1)
O(1)	1886(5)	-1132(3)	8585(2)	33(1)
N(4)	2523(5)	869(3)	9305(2)	25(1)
N(2)	6070(5)	346(3)	8271(2)	25(1)
N(3)	5303(5)	1799(4)	9157(2)	25(1)
N(1)	3371(5)	-687(4)	8416(2)	26(1)
C(10)	2819(6)	1550(4)	9730(2)	26(1)
C(9)	4458(7)	2164(5)	9701(2)	28(1)
C(16)	9448(7)	2579(5)	8457(3)	34(1)
C(24)	9906(8)	6148(6)	8632(3)	45(2)
C(23)	9306(8)	5678(5)	8115(3)	40(2)
C(6)	7690(7)	2073(5)	8501(2)	28(1)
C(26)	10101(7)	4314(5)	9046(3)	39(1)
C(2)	4396(7)	-1293(4)	8125(2)	25(1)
C(3)	5999(6)	-725(4)	7948(2)	25(1)
C(22)	9130(7)	4536(5)	8065(3)	34(1)
C(5)	7726(6)	887(5)	8277(3)	29(1)
C(7)	7069(7)	2113(5)	9122(3)	32(1)
C(25)	10272(8)	5461(6)	9095(3)	45(2)
C(21)	9552(7)	3825(5)	8528(2)	31(1)
C(15)	5520(9)	1851(6)	10246(3)	39(1)

C(12)	5903(8)	-503(5)	7285(2)	30(1)
C(14)	4156(9)	3431(5)	9685(3)	37(1)
C(11)	1608(9)	1660(6)	10217(3)	44(2)
C(1)	3976(9)	-2461(5)	7981(3)	36(1)
C(13)	7482(8)	-1483(5)	8094(3)	31(1)

Table A3. Bond lengths [Å] and angles [°] for $TcO(C_{20}H_{31}N_4O_2)$.

Tc(1)-O(4T)	1.679(3)	C(3)-C(13)	1.521(7)
Tc(1)-N(2)	1.905(4)	C(3)-C(12)	1.545(7)
Tc(1)-N(3)	1.911(4)	C(22)-C(21)	1.397(8)
Tc(1)-N(4)	2.081(4)		
Tc(1)-N(1)	2.084(4)	O(4T)-Tc(1)-N(2)	109.26(17)
O(2)-N(4)	1.358(5)	O(4T)-Tc(1)-N(3)	111.78(19)
O(1)-N(1)	1.359(5)	N(2)-Tc(1)-N(3)	92.32(17)
N(4)-C(10)	1.290(7)	O(4T)-Tc(1)-N(4)	108.40(16)
N(2)-C(5)	1.469(6)	N(2)-Tc(1)-N(4)	142.10(17)
N(2)-C(3)	1.480(6)	N(3)-Tc(1)-N(4)	77.63(17)
N(3)-C(7)	1.458(7)	O(4T)-Tc(1)-N(1)	108.81(17)
N(3)-C(9)	1.493(7)	N(2)-Tc(1)-N(1)	77.68(17)
N(1)-C(2)	1.287(7)	N(3)-Tc(1)-N(1)	139.24(17)
C(10)-C(11)	1.492(8)	N(4)-Tc(1)-N(1)	86.41(16)
C(10)-C(9)	1.500(7)	C(10)-N(4)-O(2)	118.6(4)
C(9)-C(14)	1.537(8)	C(10)-N(4)-Tc(1)	117.7(4)
C(9)-C(15)	1.541(8)	O(2)-N(4)-Tc(1)	123.1(3)
C(16)-C(21)	1.504(8)	C(5)-N(2)-C(3)	114.5(4)
C(16)-C(6)	1.530(7)	C(5)-N(2)-Tc(1)	125.5(3)
C(24)-C(25)	1.371(10)	C(3)-N(2)-Tc(1)	119.9(3)
C(24)-C(23)	1.388(10)	C(7)-N(3)-C(9)	114.8(4)
C(23)-C(22)	1.380(9)	C(7)-N(3)-Tc(1)	125.6(3)
C(6)-C(5)	1.511(8)	C(9)-N(3)-Tc(1)	119.7(3)
C(6)-C(7)	1.515(8)	C(2)-N(1)-O(1)	119.2(4)
C(26)-C(21)	1.387(8)	C(2)-N(1)-Tc(1)	117.4(3)
C(26)-C(25)	1.385(9)	O(1)-N(1)-Tc(1)	123.3(3)
C(2)-C(1)	1.474(7)	N(4)-C(10)-C(11)	120.6(5)
C(2)-C(3)	1.507(7)	N(4)-C(10)-C(9)	115.1(5)

C(11)-C(10)-C(9)	124.3(5)
N(3)-C(9)-C(10)	107.4(4)
N(3)-C(9)-C(14)	109.9(5)
C(10)-C(9)-C(14)	110.4(5)
N(3)-C(9)-C(15)	110.9(5)
C(10)-C(9)-C(15)	108.1(5)
C(14)-C(9)-C(15)	110.1(5)
C(21)-C(16)-C(6)	115.8(5)
C(25)-C(24)-C(23)	118.8(6)
C(22)-C(23)-C(24)	120.5(6)
C(5)-C(6)-C(7)	110.9(5)
C(5)-C(6)-C(16)	109.1(5)
C(7)-C(6)-C(16)	111.3(5)
C(21)-C(26)-C(25)	121.2(6)
N(1)-C(2)-C(1)	120.6(5)
N(1)-C(2)-C(3)	115.5(4)
C(1)-C(2)-C(3)	123.9(5)
N(2)-C(3)-C(2)	106.4(4)
N(2)-C(3)-C(13)	112.6(4)
C(2)-C(3)-C(13)	109.2(4)
N(2)-C(3)-C(12)	110.0(4)
C(2)-C(3)-C(12)	108.3(4)
C(13)-C(3)-C(12)	110.1(4)
C(23)-C(22)-C(21)	121.1(6)
N(2)-C(5)-C(6)	113.3(4)
N(3)-C(7)-C(6)	112.0(4)
C(24)-C(25)-C(26)	120.8(6)
C(26)-C(21)-C(22)	117.5(6)
C(26)-C(21)-C(16)	121.8(5)
C(22)-C(21)-C(16)	120.7(5)

Table A4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for $TcO(C_{20}H_{31}N_4O_2)$. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Tc(1)	20(1)	19(1)	25(1)	1(1)	2(1)	1(1)
O(2)	24(2)	29(2)	42(2)	-3(2)	10(2)	-9(2)
O(4T)	23(2)	25(2)	32(2)	6(2)	3(2)	9(2)
O(1)	27(2)	32(2)	40(2)	-4(2)	8(2)	-11(2)
N(4)	22(2)	23(2)	31(2)	3(2)	2(2)	0(2)
N(2)	25(2)	16(2)	34(2)	-1(2)	3(2)	-4(2)
N(3)	20(2)	26(2)	30(2)	0(2)	4(2)	-3(2)
N(1)	22(2)	25(2)	32(2)	1(2)	4(2)	-7(2)
C(10)	23(3)	29(3)	27(3)	2(2)	3(2)	2(2)
C(9)	26(3)	27(3)	32(3)	-3(2)	3(2)	1(2)
C(16)	21(3)	32(3)	49(4)	1(3)	3(3)	2(2)
C(24)	37(4)	31(4)	69(5)	3(3)	11(3)	3(3)
C(23)	36(3)	34(3)	51(4)	9(3)	13(3)	5(3)
C(6)	18(3)	26(3)	39(3)	-1(2)	0(2)	0(2)
C(26)	32(3)	42(4)	42(4)	8(3)	-5(3)	-3(3)
C(2)	29(3)	21(3)	26(3)	1(2)	1(2)	0(2)
C(3)	23(3)	22(3)	31(3)	-1(2)	1(2)	3(2)
C(22)	34(3)	33(3)	36(3)	-2(3)	1(3)	4(3)
C(5)	16(3)	28(3)	41(3)	-4(3)	5(2)	-6(2)
C(7)	31(3)	25(3)	38(3)	-2(3)	-3(2)	-2(3)
C(25)	46(4)	39(4)	51(4)	-11(3)	-5(3)	-5(3)
C(21)	20(3)	30(3)	42(3)	-2(2)	6(2)	-1(2)
C(15)	38(4)	41(4)	37(3)	1(3)	1(3)	3(3)

C(12)	30(3)	25(3)	36(3)	2(2)	3(2)	1(3)
C(14)	38(4)	26(3)	47(4)	-8(3)	8(3)	-2(3)
C(11)	51(4)	48(4)	34(3)	-8(3)	16(3)	-4(3)
C(1)	50(4)	20(3)	37(3)	-2(2)	4(3)	-5(3)
C(13)	33(3)	26(3)	36(3)	-5(3)	0(3)	10(3)

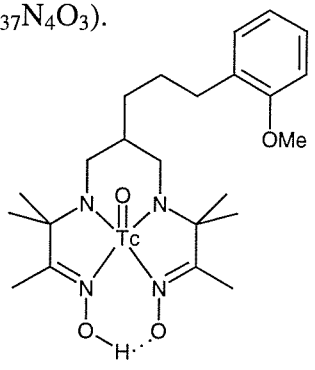
Table A5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for $TcO(C_{20}H_{31}N_4O_2)$.

	x	y	z	U(eq)
H(15A)	5670(90)	1110(60)	10250(30)	58
H(15B)	4920(90)	1970(60)	10570(30)	58
H(15C)	6540(90)	2220(60)	10280(30)	58
H(12B)	4890(80)	10(50)	7170(20)	46
H(12A)	5890(80)	-1140(60)	7100(30)	46
H(12C)	6850(80)	-90(50)	7160(20)	46
H(14B)	5160(90)	3830(60)	9700(30)	56
H(14C)	3530(90)	3640(60)	10010(30)	56
H(14A)	3580(90)	3610(60)	9340(30)	56
H(11A)	450(100)	1900(60)	10050(30)	66
H(11B)	1940(90)	2270(60)	10510(30)	66
H(11C)	1570(90)	980(60)	10440(30)	66
H(1B)	3960(80)	-2930(60)	8390(30)	53
H(1A)	4680(90)	-2770(60)	7700(30)	53
H(1C)	2800(90)	-2660(50)	7840(30)	53
H(13B)	8670(90)	-1190(50)	7980(30)	47
H(13C)	7540(80)	-2160(60)	7880(30)	47
H(13A)	7610(80)	-1590(50)	8500(30)	47
H(25)	10550(70)	5700(50)	9430(30)	32(16)
H(26)	10510(70)	3930(50)	9360(30)	36(16)
H(24)	10070(80)	6920(60)	8620(20)	46(18)
H(5A)	8090(60)	850(40)	7900(20)	20(13)
H(22)	8790(70)	4270(50)	7720(30)	36(17)

H(5B)	8450(70)	450(50)	8530(20)	23(13)
H(16A)	9890(60)	2410(40)	8090(20)	9(12)
H(16B)	10110(70)	2240(40)	8770(20)	24(14)
H(23)	8960(110)	6130(70)	7760(40)	90(30)
H(7A)	7300(70)	2890(50)	9280(20)	36(15)
H(7B)	7670(60)	1660(40)	9360(20)	13(12)
H(6)	6940(80)	2410(50)	8270(30)	50(19)
H(1o)	1360(100)	-170(70)	9030(30)	80(30)

Appendix B

Table B1. Crystal data and structure refinement for $TcO(C_{23}H_{37}N_4O_3)$.



Identification code	$TcO(C_{23}H_{37}N_4O_3)$	
Empirical formula	C23 H37 N4 O4 Tc	
Formula weight	531.57	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic P	
Space group	$P2_1/n$	
Unit cell dimensions	a = 12.963(3) Å	α= 90°.
	b = 7.577(2) Å	β= 91.89(3)°.
	c = 25.431(5) Å	γ = 90°.
Volume	2496.5(10) $Å^3$	
Z	4	
Density (calculated)	1.414 Mg/m^3	
Absorption coefficient	0.611 mm^{-1}	
F(000)	1112	
Crystal size	0.5 x 0.15 x 0.1 mm^3	
Theta range for data collection	2.92 to 30.00°.	
Index ranges	-15<=h<=17, -9<=k<=10, -33<=l<=24	
Reflections collected	14941	
Independent reflections	6036 [R(int) = 0.0672]	
Completeness to theta = 30.00°	82.9 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6036 / 0 / 370	
Goodness-of-fit on F^2	1.037	
Final R indices [I>2sigma(I)]	R1 = 0.0462, wR2 = 0.1026	

R indices (all data)	R1 = 0.0839, wR2 = 0.1176
Largest diff. peak and hole	0.834 and -1.022 e.Å^{-3}

Table B2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for $TcO(C_{23}H_{37}N_4O_3)$. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Tc(1)	7085(1)	563(1)	6078(1)	28(1)
O(4T)	8062(1)	1787(2)	6326(1)	45(1)
O(2)	5235(1)	2081(1)	6626(1)	40(1)
O(1)	5511(1)	3344(2)	5764(1)	57(1)
O(3)	12288(1)	-5411(2)	6344(1)	56(1)
N(4)	5884(1)	673(2)	6598(1)	29(1)
N(2)	7401(1)	-337(2)	5397(1)	33(1)
N(3)	7101(1)	-1752(2)	6377(1)	29(1)
C(22)	11985(2)	-7040(3)	6518(1)	42(1)
C(17)	9796(2)	-5089(3)	6099(1)	39(1)
C(9)	6557(1)	-2071(2)	6875(1)	29(1)
C(6)	8478(2)	-2728(2)	5798(1)	36(1)
C(10)	5841(1)	-551(2)	6947(1)	31(1)
C(16)	9148(2)	-4296(2)	5656(1)	42(1)
N(1)	6186(1)	2141(2)	5583(1)	43(1)
C(18)	10445(2)	-6605(3)	5903(1)	48(1)
C(5)	7976(2)	-1952(2)	5299(1)	41(1)
C(7)	7653(2)	-3247(2)	6180(1)	37(1)
C(21)	11032(2)	-7631(3)	6317(1)	44(1)
C(23)	12565(2)	-8078(3)	6862(1)	51(1)
C(3)	7103(2)	677(2)	4919(1)	51(1)
C(25)	11244(2)	-10246(3)	6855(1)	70(1)
C(24)	12178(2)	-9677(3)	7026(1)	59(1)

C(26)	10680(2)	-9246(3)	6497(1)	57(1)
C(2)	6364(2)	2085(3)	5089(1)	68(1)
C(27)	13244(2)	-4749(3)	6550(1)	71(1)
C(11)	5116(2)	-462(2)	7385(1)	45(1)
C(14)	7350(2)	-2133(2)	7339(1)	38(1)
C(15)	5917(1)	-3770(2)	6842(1)	37(1)
C(12)	8040(2)	1562(3)	4687(1)	71(1)
C(13)	6546(2)	-503(3)	4510(1)	76(1)
C(1A)	6104(4)	3678(5)	4732(1)	59(1)
C(1B)	5582(3)	2964(6)	4701(1)	56(1)

Table B3. Bond lengths [Å] and angles [°] for $TcO(C_{23}H_{37}N_4O_3)$.

Tc(1)-O(4T)	1.6758(13)	C(23)-C(24)	1.381(3)
Tc(1)-N(3)	1.9121(13)	C(3)-C(2)	1.506(3)
Tc(1)-N(2)	1.9190(14)	C(3)-C(12)	1.523(3)
Tc(1)-N(1)	2.0672(15)	C(3)-C(13)	1.533(3)
Tc(1)-N(4)	2.0770(15)	C(25)-C(24)	1.344(4)
O(2)-N(4)	1.3619(17)	C(25)-C(26)	1.376(3)
O(1)-N(1)	1.3541(19)	C(2)-C(1A)	1.541(4)
O(3)-C(22)	1.373(2)	C(2)-C(1B)	1.542(4)
O(3)-C(27)	1.422(3)		
N(4)-C(10)	1.286(2)	O(4T)-Tc(1)-N(3)	111.10(6)
N(2)-C(5)	1.458(2)	O(4T)-Tc(1)-N(2)	110.76(7)
N(2)-C(3)	1.479(2)	N(3)-Tc(1)-N(2)	91.90(6)
N(3)-C(7)	1.439(2)	O(4T)-Tc(1)-N(1)	108.23(7)
N(3)-C(9)	1.489(2)	N(3)-Tc(1)-N(1)	140.47(6)
C(22)-C(23)	1.380(3)	N(2)-Tc(1)-N(1)	77.81(6)
C(22)-C(21)	1.396(3)	O(4T)-Tc(1)-N(4)	108.16(6)
C(17)-C(16)	1.509(3)	N(3)-Tc(1)-N(4)	77.42(5)
C(17)-C(18)	1.518(3)	N(2)-Tc(1)-N(4)	140.91(6)
C(9)-C(10)	1.494(2)	N(1)-Tc(1)-N(4)	86.87(6)
C(9)-C(15)	1.533(2)	C(22)-O(3)-C(27)	116.91(16)
C(9)-C(14)	1.539(2)	C(10)-N(4)-O(2)	119.27(14)
C(6)-C(7)	1.520(3)	C(10)-N(4)-Tc(1)	117.43(12)
C(6)-C(16)	1.522(3)	O(2)-N(4)-Tc(1)	122.76(9)
C(6)-C(5)	1.525(2)	C(5)-N(2)-C(3)	114.64(13)
C(10)-C(11)	1.484(3)	C(5)-N(2)-Tc(1)	125.31(10)
N(1)-C(2)	1.286(2)	C(3)-N(2)-Tc(1)	119.98(11)
C(18)-C(21)	1.496(3)	C(7)-N(3)-C(9)	115.11(12)
C(21)-C(26)	1.388(3)	C(7)-N(3)-Tc(1)	125.60(11)

C(9)-N(3)-Tc(1)	119.19(10)	C(2)-C(3)-C(12)	108.78(17)
O(3)-C(22)-C(23)	124.15(18)	N(2)-C(3)-C(13)	111.00(16)
O(3)-C(22)-C(21)	115.38(16)	C(2)-C(3)-C(13)	108.6(2)
C(23)-C(22)-C(21)	120.46(18)	C(12)-C(3)-C(13)	111.03(17)
C(16)-C(17)-C(18)	110.90(15)	C(24)-C(25)-C(26)	119.4(2)
N(3)-C(9)-C(10)	107.00(12)	C(25)-C(24)-C(23)	121.1(2)
N(3)-C(9)-C(15)	111.10(12)	C(25)-C(26)-C(21)	122.1(2)
C(10)-C(9)-C(15)	108.45(15)	N(1)-C(2)-C(3)	116.15(17)
N(3)-C(9)-C(14)	109.50(14)	N(1)-C(2)-C(1A)	120.5(2)
C(10)-C(9)-C(14)	109.37(13)	C(3)-C(2)-C(1A)	120.9(2)
C(15)-C(9)-C(14)	111.29(13)	N(1)-C(2)-C(1B)	118.4(2)
C(7)-C(6)-C(16)	111.66(14)	C(3)-C(2)-C(1B)	122.2(2)
C(7)-C(6)-C(5)	109.95(15)	C(1A)-C(2)-C(1B)	32.7(2)
C(16)-C(6)-C(5)	109.57(14)		
N(4)-C(10)-C(11)	121.91(15)		
N(4)-C(10)-C(9)	115.50(15)		
C(11)-C(10)-C(9)	122.58(14)		
C(17)-C(16)-C(6)	116.20(15)		
C(2)-N(1)-O(1)	119.46(15)		
C(2)-N(1)-Tc(1)	117.40(14)		
O(1)-N(1)-Tc(1)	122.74(9)		
C(21)-C(18)-C(17)	115.85(15)		
N(2)-C(5)-C(6)	112.86(13)		
N(3)-C(7)-C(6)	112.84(14)		
C(26)-C(21)-C(22)	117.24(18)		
C(26)-C(21)-C(18)	121.70(19)		
C(22)-C(21)-C(18)	120.98(18)		
C(22)-C(23)-C(24)	119.7(2)		
N(2)-C(3)-C(2)	106.43(14)		
N(2)-C(3)-C(12)	110.86(18)		

Table B4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for $TcO(C_{23}H_{37}N_4O_3)$. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Tc(1)	35(1)	22(1)	25(1)	1(1)	-1(1)	2(1)
O(4T)	50(1)	44(1)	42(1)	-4(1)	1(1)	-17(1)
O(2)	51(1)	31(1)	39(1)	0(1)	7(1)	18(1)
O(1)	89(1)	42(1)	39(1)	6(1)	12(1)	42(1)
O(3)	41(1)	68(1)	59(1)	22(1)	-2(1)	1(1)
N(4)	33(1)	22(1)	31(1)	-3(1)	-2(1)	5(1)
N(2)	44(1)	29(1)	26(1)	0(1)	-1(1)	14(1)
N(3)	31(1)	21(1)	36(1)	4(1)	0(1)	6(1)
C(22)	40(1)	49(1)	38(1)	-1(1)	7(1)	4(1)
C(17)	41(1)	38(1)	38(1)	0(1)	0(1)	6(1)
C(9)	32(1)	25(1)	29(1)	2(1)	-1(1)	0(1)
C(6)	41(1)	31(1)	37(1)	4(1)	4(1)	9(1)
C(10)	34(1)	27(1)	31(1)	0(1)	-2(1)	1(1)
C(16)	42(1)	42(1)	42(1)	-3(1)	3(1)	11(1)
N(1)	67(1)	32(1)	30(1)	3(1)	2(1)	24(1)
C(18)	43(1)	54(1)	48(1)	-14(1)	-4(1)	14(1)
C(5)	51(1)	39(1)	34(1)	-3(1)	1(1)	19(1)
C(7)	41(1)	26(1)	44(1)	5(1)	6(1)	8(1)
C(21)	42(1)	46(1)	44(1)	-10(1)	-3(1)	19(1)
C(23)	41(1)	57(1)	55(1)	9(1)	0(1)	8(1)
C(3)	77(2)	51(1)	26(1)	5(1)	5(1)	32(1)
C(25)	63(2)	47(1)	100(2)	11(1)	-3(2)	1(1)
C(24)	45(1)	57(1)	74(2)	13(1)	-1(1)	8(1)

C(26)	44(1)	46(1)	82(2)	-14(1)	-8(1)	-1(1)
C(2)	108(2)	61(1)	36(1)	12(1)	13(1)	56(1)
C(27)	47(1)	86(2)	78(2)	25(1)	-4(1)	-20(1)
C(11)	52(1)	44(1)	40(1)	3(1)	11(1)	4(1)
C(14)	44(1)	33(1)	38(1)	3(1)	-7(1)	4(1)
C(15)	41(1)	30(1)	40(1)	1(1)	4(1)	-4(1)
C(12)	117(2)	51(1)	47(1)	10(1)	28(1)	26(1)
C(13)	79(2)	112(2)	36(1)	-21(1)	-18(1)	47(1)
C(1A)	75(3)	57(2)	47(2)	32(2)	21(2)	35(2)
C(1B)	66(3)	66(3)	36(2)	29(2)	14(2)	29(2)

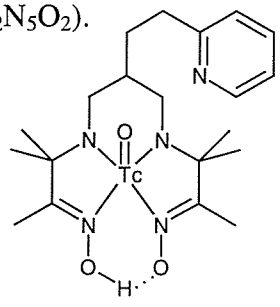
Table B5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for $TcO(C_{23}H_{37}N_4O_3)$.

	x	y	z	U(eq)
H(27A)	13254	-4816	6927	106
H(27B)	13324	-3542	6444	106
H(27C)	13799	-5441	6419	106
H(11A)	5135	700	7536	68
H(11B)	5314	-1312	7650	68
H(11C)	4429	-716	7254	68
H(14A)	7736	-1052	7351	58
H(14B)	7812	-3107	7293	58
H(14C)	6996	-2279	7662	58
H(15A)	5570	-3939	7166	55
H(15B)	6364	-4755	6783	55
H(15C)	5416	-3679	6557	55
H(12A)	8384	2272	4952	106
H(12B)	7821	2297	4397	106
H(12C)	8506	676	4567	106
H(13A)	7032	-1309	4365	114
H(13B)	6247	217	4235	114
H(13C)	6012	-1156	4676	114
H(17A)	9296(14)	-5515(19)	6382(6)	32(5)
H(5A)	7528(11)	-2836(18)	5132(5)	17(4)
H(16A)	8670(14)	-5220(20)	5515(6)	32(5)
H(16B)	9642(15)	-3980(20)	5392(7)	60(6)
H(17B)	10070(11)	-4067(17)	6239(5)	10(3)

H(1O)	5339(16)	2800(30)	6202(7)	68(6)
H(23)	13212(15)	-7650(20)	6958(6)	57(6)
H(25)	10880(20)	-11370(40)	6984(9)	119(9)
H(5B)	8497(14)	-1800(20)	5027(6)	47(5)
H(7A)	7219(10)	-4045(19)	6016(5)	9(4)
H(18A)	10943(17)	-5980(30)	5651(7)	67(6)
H(6)	8958(13)	-1840(20)	5932(6)	40(5)
H(24)	12620(20)	-10350(30)	7248(10)	100(9)
H(7B)	8007(13)	-3840(20)	6460(6)	39(5)
H(18B)	9943(14)	-7370(20)	5743(6)	44(5)
H(26)	10109(19)	-9440(30)	6405(8)	70(7)
H(1A1)	5421	3540	4580	89
H(1A2)	6592	3744	4457	89
H(1A3)	6136	4742	4937	89
H(1B1)	4919	2417	4732	84
H(1B2)	5811	2823	4349	84
H(1B3)	5531	4198	4782	84

Appendix C

Table C1. Crystal data and structure refinement for $TcO(C_{20}H_{32}N_5O_2)$.



Identification code	$TcO(C_{20}H_{32}N_5O_2)$	
Empirical formula	C20 H32 N5 O3 Tc	
Formula weight	488.51	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 10.678(2) Å	α = 92.05(3)°.
	b = 10.852(2) Å	β = 113.21(3)°.
	c = 11.052(2) Å	γ = 109.55(3)°.
Volume	1088.2(3) $Å^3$	
Z	2	
Density (calculated)	1.491 Mg/m^3	
Absorption coefficient	0.692 mm^{-1}	
F(000)	508	
Crystal size	0.25 x 0.15 x 0.05 mm^3	
Theta range for data collection	3.15 to 30.56°.	
Index ranges	-13<=h<=11, -15<=k<=13, -13<=l<=14	
Reflections collected	12741	
Independent reflections	5467 [R(int) = 0.0419]	
Completeness to theta = 30.56°	81.9 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5467 / 0 / 324	
Goodness-of-fit on F^2	1.051	
Final R indices [I>2sigma(I)]	R1 = 0.0367, wR2 = 0.0790	

R indices (all data)	R1 = 0.0541, wR2 = 0.0858
Largest diff. peak and hole	1.037 and -0.906 e.Å^{-3}

Table C2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for $TcO(C_{20}H_{32}N_5O_2)$. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Tc(1)	3467(1)	4855(1)	1537(1)	20(1)
O(4T)	5269(2)	5419(2)	1935(2)	26(1)
O(2)	3275(2)	5571(2)	4152(2)	33(1)
O(1)	3202(2)	7261(2)	2742(2)	35(1)
N(3)	2703(2)	2948(2)	1327(2)	22(1)
N(21)	1485(3)	-1233(2)	-3387(2)	37(1)
N(2)	2337(2)	4781(2)	-321(2)	23(1)
N(1)	2906(2)	6516(2)	1580(2)	26(1)
C(6)	2514(3)	2671(2)	-979(2)	24(1)
C(17)	3151(3)	924(3)	-1960(3)	33(1)
N(4)	3147(2)	4570(2)	3259(2)	23(1)
C(22)	3446(3)	23(3)	-3923(3)	32(1)
C(21)	2669(3)	-143(2)	-3143(2)	28(1)
C(23)	2973(3)	-966(3)	-5001(3)	35(1)
C(9)	2797(3)	2364(2)	2532(2)	24(1)
C(7)	2175(3)	2006(2)	100(2)	26(1)
C(2)	2409(3)	6902(2)	466(3)	28(1)
C(25)	1060(3)	-2180(3)	-4434(3)	41(1)
C(16)	2085(3)	1632(2)	-2198(3)	27(1)
C(3)	2080(3)	5987(2)	-762(2)	24(1)
C(24)	1756(3)	-2097(3)	-5253(3)	38(1)
C(10)	2957(2)	3413(2)	3576(2)	24(1)
C(5)	1765(3)	3643(2)	-1402(2)	26(1)

C(14)	4191(3)	2024(3)	3097(3)	30(1)
C(12)	3118(3)	6683(2)	-1387(3)	30(1)
C(11)	2909(3)	3129(3)	4862(2)	33(1)
C(15)	1424(3)	1122(2)	2252(3)	29(1)
C(1)	2176(4)	8186(3)	424(3)	42(1)
C(13)	467(3)	5641(2)	-1770(3)	34(1)

Table C3. Bond lengths [Å] and angles [°] for $TcO(C_{20}H_{32}N_5O_2)$.

Tc(1)-O(4T)	1.6722(17)	C(25)-C(24)	1.368(4)
Tc(1)-N(2)	1.910(2)	C(3)-C(12)	1.536(3)
Tc(1)-N(3)	1.9213(19)	C(3)-C(13)	1.541(3)
Tc(1)-N(4)	2.079(2)	C(10)-C(11)	1.482(3)
Tc(1)-N(1)	2.0848(19)		
O(2)-N(4)	1.375(2)	O(4T)-Tc(1)-N(2)	111.36(9)
O(1)-N(1)	1.355(3)	O(4T)-Tc(1)-N(3)	109.71(9)
N(3)-C(7)	1.454(3)	N(2)-Tc(1)-N(3)	92.39(9)
N(3)-C(9)	1.478(3)	O(4T)-Tc(1)-N(4)	109.49(8)
N(21)-C(21)	1.333(3)	N(2)-Tc(1)-N(4)	138.97(8)
N(21)-C(25)	1.337(4)	N(3)-Tc(1)-N(4)	77.33(8)
N(2)-C(5)	1.463(3)	O(4T)-Tc(1)-N(1)	107.14(8)
N(2)-C(3)	1.485(3)	N(2)-Tc(1)-N(1)	77.54(8)
N(1)-C(2)	1.283(3)	N(3)-Tc(1)-N(1)	142.96(8)
C(6)-C(5)	1.509(3)	N(4)-Tc(1)-N(1)	87.15(8)
C(6)-C(7)	1.518(3)	C(7)-N(3)-C(9)	115.74(18)
C(6)-C(16)	1.535(3)	C(7)-N(3)-Tc(1)	125.57(15)
C(17)-C(21)	1.508(4)	C(9)-N(3)-Tc(1)	118.33(15)
C(17)-C(16)	1.522(4)	C(21)-N(21)-C(25)	116.8(3)
N(4)-C(10)	1.287(3)	C(5)-N(2)-C(3)	115.16(18)
C(22)-C(23)	1.377(4)	C(5)-N(2)-Tc(1)	125.41(15)
C(22)-C(21)	1.393(4)	C(3)-N(2)-Tc(1)	119.28(15)
C(23)-C(24)	1.377(4)	C(2)-N(1)-O(1)	120.06(19)
C(9)-C(10)	1.509(3)	C(2)-N(1)-Tc(1)	117.07(17)
C(9)-C(15)	1.534(3)	O(1)-N(1)-Tc(1)	122.44(15)
C(9)-C(14)	1.546(3)	C(5)-C(6)-C(7)	111.6(2)
C(2)-C(1)	1.493(3)	C(5)-C(6)-C(16)	110.5(2)
C(2)-C(3)	1.499(3)	C(7)-C(6)-C(16)	111.05(19)

C(21)-C(17)-C(16)	112.6(2)	C(11)-C(10)-C(9)	122.5(2)
C(10)-N(4)-O(2)	117.75(19)	N(2)-C(5)-C(6)	112.22(19)
C(10)-N(4)-Tc(1)	117.82(16)		
O(2)-N(4)-Tc(1)	124.08(14)		
C(23)-C(22)-C(21)	119.2(3)		
N(21)-C(21)-C(22)	122.6(2)		
N(21)-C(21)-C(17)	116.8(2)		
C(22)-C(21)-C(17)	120.6(2)		
C(22)-C(23)-C(24)	118.4(3)		
N(3)-C(9)-C(10)	107.42(18)		
N(3)-C(9)-C(15)	112.50(19)		
C(10)-C(9)-C(15)	108.9(2)		
N(3)-C(9)-C(14)	109.6(2)		
C(10)-C(9)-C(14)	108.00(19)		
C(15)-C(9)-C(14)	110.2(2)		
N(3)-C(7)-C(6)	112.80(19)		
N(1)-C(2)-C(1)	121.1(2)		
N(1)-C(2)-C(3)	115.8(2)		
C(1)-C(2)-C(3)	123.2(2)		
N(21)-C(25)-C(24)	124.4(3)		
C(17)-C(16)-C(6)	113.4(2)		
N(2)-C(3)-C(2)	106.92(19)		
N(2)-C(3)-C(12)	110.23(19)		
C(2)-C(3)-C(12)	109.4(2)		
N(2)-C(3)-C(13)	111.49(18)		
C(2)-C(3)-C(13)	108.7(2)		
C(12)-C(3)-C(13)	110.0(2)		
C(25)-C(24)-C(23)	118.6(3)		
N(4)-C(10)-C(11)	123.1(2)		
N(4)-C(10)-C(9)	114.5(2)		

Table C4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for $TcO(C_{20}H_{32}N_5O_2)$. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Tc(1)	22(1)	16(1)	21(1)	0(1)	9(1)	6(1)
O(4T)	23(1)	25(1)	26(1)	1(1)	9(1)	6(1)
O(2)	47(1)	26(1)	26(1)	-3(1)	17(1)	13(1)
O(1)	52(1)	21(1)	34(1)	-3(1)	23(1)	13(1)
N(3)	28(1)	17(1)	19(1)	2(1)	10(1)	8(1)
N(21)	42(1)	29(1)	41(1)	0(1)	20(1)	12(1)
N(2)	25(1)	18(1)	23(1)	2(1)	9(1)	9(1)
N(1)	29(1)	17(1)	31(1)	-1(1)	15(1)	7(1)
C(6)	27(1)	20(1)	23(1)	1(1)	10(1)	8(1)
C(17)	40(2)	32(1)	26(1)	-1(1)	13(1)	17(1)
N(4)	24(1)	20(1)	20(1)	-4(1)	8(1)	6(1)
C(22)	37(2)	26(1)	35(2)	4(1)	17(1)	13(1)
C(21)	35(1)	23(1)	26(1)	4(1)	11(1)	15(1)
C(23)	44(2)	41(2)	30(2)	5(1)	18(1)	22(1)
C(9)	28(1)	21(1)	22(1)	4(1)	10(1)	8(1)
C(7)	33(1)	19(1)	24(1)	0(1)	12(1)	8(1)
C(2)	29(1)	19(1)	39(2)	5(1)	17(1)	10(1)
C(25)	38(2)	30(2)	47(2)	-3(1)	13(1)	10(1)
C(16)	34(1)	23(1)	24(1)	2(1)	12(1)	10(1)
C(3)	24(1)	19(1)	30(1)	5(1)	10(1)	9(1)
C(24)	40(2)	36(2)	31(2)	-8(1)	4(1)	20(1)
C(10)	22(1)	27(1)	22(1)	1(1)	9(1)	8(1)
C(5)	32(1)	21(1)	21(1)	2(1)	8(1)	10(1)

C(14)	36(1)	29(1)	28(1)	7(1)	14(1)	16(1)
C(12)	32(1)	25(1)	33(1)	9(1)	14(1)	11(1)
C(11)	37(2)	36(2)	24(1)	4(1)	13(1)	11(1)
C(15)	35(1)	23(1)	27(1)	7(1)	14(1)	7(1)
C(1)	61(2)	29(1)	49(2)	11(1)	28(2)	26(1)
C(13)	27(1)	28(1)	43(2)	8(1)	9(1)	12(1)

Table C5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for $TcO(C_{20}H_{32}N_5O_2)$.

	x	y	z	U(eq)
H(14A)	4119	1365	2443	45
H(14B)	4272	1681	3902	45
H(14C)	5045	2814	3296	45
H(12A)	4121	6900	-751	44
H(12B)	2979	7486	-1625	44
H(12C)	2905	6100	-2177	44
H(11A)	3112	3940	5413	49
H(11B)	3635	2766	5319	49
H(11C)	1949	2498	4687	49
H(15A)	573	1354	1944	44
H(15B)	1537	779	3061	44
H(15C)	1304	455	1576	44
H(1A)	1335	8094	590	64
H(1B)	2012	8408	-444	64
H(1C)	3033	8880	1099	64
H(13A)	266	5115	-2590	51
H(13B)	306	6448	-1948	51
H(13C)	-177	5144	-1398	51
H(5B)	620(30)	3120(20)	-1760(20)	27(7)
H(25)	170(30)	-2960(30)	-4580(30)	38(8)
H(22)	4310(30)	810(30)	-3720(20)	28(7)
H(5A)	1930(30)	3950(20)	-2130(30)	28(7)
H(16A)	1120(30)	1020(20)	-2460(20)	23(6)
H(7A)	2580(30)	1320(20)	300(20)	20(6)

H(7B)	1120(30)	1550(30)	-260(30)	33(7)
H(16B)	2070(30)	2060(30)	-2960(30)	40(8)
H(6)	3490(30)	3140(30)	-640(30)	25(7)
H(24)	1430(30)	-2830(30)	-5940(30)	44(8)
H(17A)	3260(30)	610(30)	-1190(30)	32(8)
H(17B)	4170(30)	1510(30)	-1710(30)	40(8)
H(23)	3480(40)	-930(30)	-5500(30)	54(10)
H(1O)	3240(40)	6270(40)	3650(40)	68(11)

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