Certain Polyhydroxylated Amines in the Genesis of Dendritic Molecules an
as Potential Inhibitors

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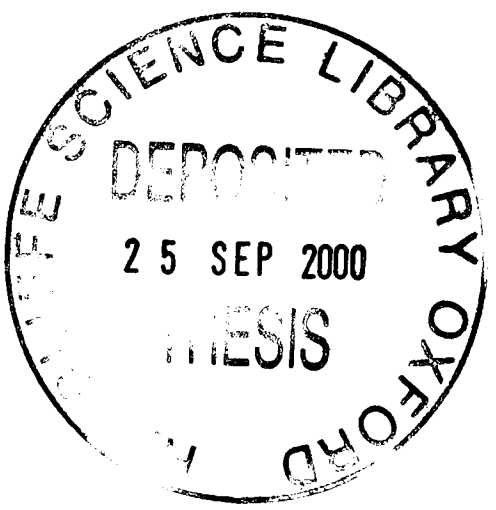
for the degree of Doctor of Philosophy (D. Phil.)



Abstract: Certain Polyhydroxylated Amines in the Genesis of Dendritic Molecules and as Potential Inhibitors

Malcolm Finn, Wolfson College, University of Oxford

D. Phil. Thesis, 1999

This thesis describes investigations into the synthesis and properties of novel cyclic and acyclic polyhydroxylated amines arising from carbohydrate derivatives or from the union of simpler, achiral molecules by bespoke *de novo* construction strategies. These compounds were contrived on the premise of being potential inhibitors of sugar processing enzymes. The highly branched and symmetrical polyhydroxylated amines have found utility in the construction of novel dendritic structures.

In studies directed towards the production of acyclic equivalents of nitrogen analogues of monosaccharides it was found that a reductive amination of dihydroxyacetone by ammonium salts with sodium cyanoborohydride gave *bis*(1,3-dihydroxy-*iso*propyl)amine [BDI] in good yield and high purity. BDI and its diacetonide are hindered nucleophiles but may be further reductively alkylated to form *N*-alkyl derivatives. BDI is an open chain equivalent of DMDP [2,5-dideoxy-2,5-imino-D-mannitol] but neither BDI nor its *N*-alkyl derivatives showed inhibition of any glycosidase or transferase assayed. BDI may provide an example of an AB_4 dendritic monomer and initial investigation into the chemistry of this novel branching unit and its expedient origins are addressed.

The diacetonide of BDI is a hindered nucleophile with masked hydroxyl groups on the periphery. Various symmetrically and non-symmetrically trisubstituted *s*-triazines have been synthesised embodying *bis*(1,3-dihydroxy-*iso*propyl)amine as a dendritic monomer to furnish highly branched structures with an array of peripheral primary hydroxyl groups. Controlled stepwise 2,4,6-trifunctionalisation of cyanuric chloride with a series of amines including the novel BDI branching unit has genertated a series of dendritic molecules. The variable temperature proton NMR experiments of such molecules showed them to exhibit restricted rotation in solution. The syntheses of these rotationally restricted tri-functionalised *s*-triazines and the observation of the variable temperature NMR experiments are presented. In studies towards a three-directional molecule incorporating BDI and based on a triazine nucleus a number of dendrimer prototypes were constructed from novel AB_4 building blocks.

The synthesis of a range of eight carbon, nitrogen containing derivatives utilising carbohydrate lactone starting materials is described. Manipulation of the eight carbon lactone derivatives of protected α-D-glucoheptono-1,4-lactone generated by a Wittig homologation produces a range of novel, highly functionalised precursors containing an α,β-unsaturated ester functionality and a free hydroxyl at C-2. An unsuccessful approach that was anticipated to allow access to eight carbon homologues of α- and β-HNJ from such precursors is described. Formation of the piperidine ring was envisaged to result from the intramolecular 1,3-dipolar cycloaddition of the C-2 azide or from the intramolecular conjugate addition of the tethered nitrogen at C-2 to the α,β-unsaturated ester functionality. It is found that displacement of the 2,3,4-all *cis* 2-*O*-triflate derived from aforementioned protected α-D-glucoheptono-1,4-lactone derivatives with sodium azide in DMF gives rise to a kinetic C-2 inverted azide, and a thermodynamic azide *cis* to the side chain, in which the stereochemistry at C-2 is retained. Additionally an inversion of the C-2 alcohol is described, thus allowing complete control of the stereochemistry at C-2 and consequent tailoring of the desired stereochemistry in the piperidine analogues.

Acknowledgements

MF wishes to thank the following, who have made the work and the consequent production of this thesis possible:

Over the last three years my supervisor, Prof. George Fleet has been a fervent and yet non-stifling supervisor who has allowed me to explore some viable and interesting chemistry without being over-bearing in the overall direction. His constant enthusiasm and passion for the projects, his guidance, and indeed his incredible capacity to keep a track of the slightest details of everyone's work on a day to day basis has certainly driven me through the two projects I have undertaken.

'Results! Why man, I have gotten a lot of results. I know several thousand things that won't work.'*

The group has been in constant change in my time here and its varied members, both past and present have been a good resource of experience, assistance, friendship and (constructive) criticism. My contemporaries Becky and Dave, the Dan, Mart, John (and Mark) league, the eclectic post-docs, part II's and the D. Phils that I have known in my time in the Perkin lab have been a superb bunch, "good guys" one and all! I particularly thank Dave Scott for being a partner in initiating the dendrimer project and I greatly admire his endurance, tenacity, and continuing belief in the success of the project. I wonder what applications will be found for our beautiful molecules and what the future of the project will be.

I am particularly grateful to Tim Claridge for his help in some of the NMR studies, and of course Elizabeth McGuinness who I hope will enjoy a happy and healthy retirement. I am also grateful to other members of the NMR and technical staff for their assistance. Thanks to my expert panel of proof readers Dr. Martin Smith for the most part, Dr. Thomas Krülle, and Dr. Tim Claridge, and in some parts David Scott. The blame will rest with me for any mistakes remaining. Thanks also to Dr. Andrew Shipway for his help with some of the diagrams in the introduction and Chris Newman for being very helpful with my crystal structure. I also acknowledge the funding I have received from the EPSRC.

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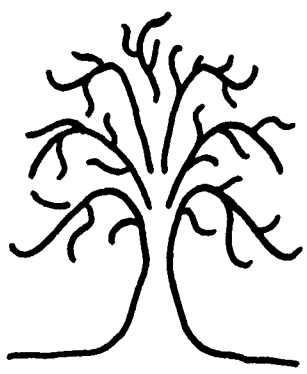
I should also like to thank my family for their support particularly my mum, to whom this thesis is dedicated.

* T. A. Edison, 1847 – 1931.

Apologia Pro Vita Contemplativa

This tree, whose forking branches bare
Criss-cross the chilly winter air
Stands fruitless, and no shelter forms
For pilgrims weary of the storm.
Its fragile branching symmetries
Can satisfy no human need:
Yet fascinate the passer-by
With patterns to ensnare the eye.
If he should fritter hours away
With idle hands and avid gaze
Be not too quick to criticise
This seeming waste of precious time.
Not worthless, though of worth unknown
The seeds of such abstraction, sown
On barren land, in wintertime
May reach the soil of fertile minds,
Where implications ramify,
Cross-pollinate, and fructify:
Whose consequences, yet undreamed
May benefit futurity.

E.C.A., 1999



To Mum

for her unbounded and constant love, support, reassurance and encouragement which have allowed me to pursue my academic interests and studies thus far

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Declaration

The work described in this thesis is my own and has not been published elsewhere, although certain aspects may be described in the journal articles listed below:

1. Andrew A. Bell, Lea Pickering, Malcolm Finn, Carmen de la Fuente, Thomas M. Krülle, Ben G. Davis, George W.J. Fleet. – 'Caesium Trifluoroacetate Displacement of Triflates in the Inversion of Alcohols'. Synlett, 1997, **9**, 1077-1078

2. David A. Scott, Thomas M. Krülle, Malcolm Finn, George W.J. Fleet. – 'Synthesis of a Novel AB_4 Monomer and its Incorporation into Highly Branched Dendritic Structures'. *Abstracts of papers of the American Chemical Society*, 1999, **217**, No. Pt2, pp. 87-orgn.

3. Malcolm Finn, Thomas M. Krülle, David A. Scott, George W.J. Fleet. – 'Highly Branched Polyhydroxylated Dendritic Molecules Based on a Triazine Skeleton'. *Abstracts of papers of the American Chemical Society*, 1999, **217**, No. Pt2, pp. 88-orgn.

4. David A. Scott, Thomas M. Krülle, Malcolm Finn, Robert. J. Nash, Ana. L. Winters, Naoki. Asano, Terry D. Butters and George W.J. Fleet. – 'Synthesis of *bis*(1,3-Dihydroxy-*iso*propyl)amine by Reductive Amination of Dihydroxyacetone: Open Chain Equivalent of DMDP and a Potential AB_4 Dendritic Monomer'. *Tetrahedron Lett.*, 1999, **40**, 7581-7584.

5. Andrew Jackson, David A. Scott, Malcolm Finn, George W.J. Fleet, Robert K. Thomas. – 'New Non-Ionic Surfactants Based on the *bis*(1,3-Dihydroxy-*iso*propyl)amine Head Group'. *Langmuir*, in preparation.

6. Malcolm Finn, Timothy D.W. Claridge, David A. Scott, David J. Watkins, Christopher J. Newman, George W.J. Fleet. – 'Dendrimeric and Amphiphilically Equipped Triazines: Syntheses and Restricted Rotation Phenomena'. *J. Chem. Soc., Perkin Trans. 2,* in preparation.

7. Timothy D.W. Claridge, Malcolm Finn, George W.J. Fleet. – 'NMR Analysis of Restricted Dynamics in a 4,6-Dichloro-2-amino-1,3,5-triazine'. *J. Chem. Soc., Perkin Trans. 2,* in preparation.

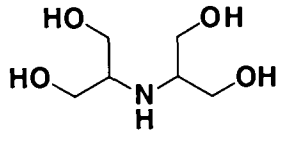
Abbreviations

The following abbreviations are used in this thesis:

App.	Apparent
Ac	Acetyl
APCI	Atmospheric pressure chemical ionisation
aq.	Aqueous
Ar	Aryl
br	Broad
Bn	Benzyl
BOC	*t*-Butoxycarbonyl
Bu	Butyl
CI	Chemical ionisation
d	Doublet
dd	Double doublet
DCM	Dichloromethane
DEPT	Distortionless enhancement by polarisation transfer
DIBAL	Diisobutylaluminium hydride
DIPEA	*N,N*-Diisopropylethylamine
DMAP	4-*N,N*-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMP	Dimethoxypropane
DMSO	Dimethylsulfoxide
eq.	Equivalents
ES	Electrospray
Et	Ethyl
Glc	Glucose
h	Hours
HMQC	Heteronuclear multiple quantum correlation
HRMS	High resolution mass spectrometry
KJ	Kilojoule
Lit.	Literature value
m	Multiplet
M	Molar
MALDI	Matrix assisted laser desorption ionisation
Me	Methyl
mol	mole
m.p.	Melting point
Ms	Methanesulfonyl
NMR	Nuclear magnetic resonance
PCC	Pyridinium chlorochromate
Ph	Phenyl
ppm.	Parts per million
PPTS	Pyridinium toluene-*p*-sulfonate
Pr	Propyl
R	Alkyl
q	Quartet
R_f	Retention factor
r.t.	Room temperature
s	Singlet
t	Triplet
TBDMS	*tert*-Butyldimethylsilyl
TBTU	*O*-(1H-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate
TES	Triethylsilyl
TMS	Trimethylsilyl
Tf	Trifluoromethanesulfonic
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
t.l.c.	Thin layer chromatography
Ts	*p*-Toluenesulfonic
Z	Benzoyloxycarbonyl
Δ	Heat

Note Concerning Nomenclature

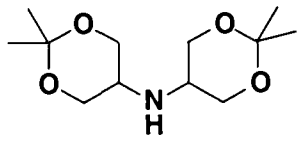
The pivotal molecules in the construction of the dendritic molecules presented in this thesis are the polyhydroxylated amine (a) and its diacetonide (b). Throughout the discursive parts of this thesis these units are referred to their trivial names and abbreviations as outlined below. The use of these trivial names is less cumbersome than using their systematic names, especially in the highly functionalised derivatives.



(a)

bis-(1,3-dihydroxy-isopropyl)amine
This is abbreviated as BDI.

Systematic name:
2-(2-Hydroxy-1-hydroxymethyl-ethylamino)-propane-1,3-diol

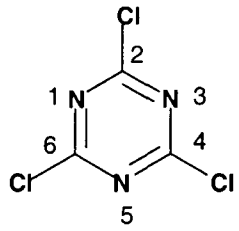


(b)

bis-(1,3-dihydroxy-*iso*propyl)amine diacetonide or
bis-(1,3-*O*-*iso*propylidene-1,3-dihydroxy-*iso*propyl)amine.
This is abbreviated as BDI diacetonide.

Systematic name:
bis-(2,2-dimethyl-[1,3]dioxan-5-yl)-amine

A number of *s*-triazine derivatives have been prepared and the numbering in the *s*-triazine ring is as follows:

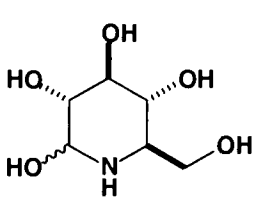


2,4,6,-Trichloro-1,3,5-triazene

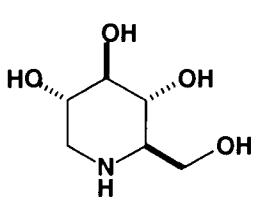
For the carbohydrate derivatives presented in this thesis, both trivial and systematic nomenclature is used.

1. Trivial Names

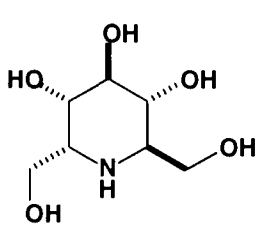
Azasugars are referred to by widely accepted trivial names or abbreviated trivial names. Commonly, azapyranoses are referred to as parent sugar derivatives of nojirimycin (abbreviated to NJ).



Nojirimycin
NJ



Deoxynojirimycin
DNJ

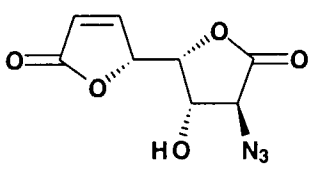


α–Homonojirimycin
α–HNJ

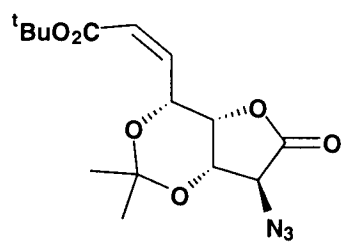
1-Deoxyazapyranoses are the homologous iminoaldoheptitols and are referred to as parent sugar derivatives of homonojirimycin (HNJ). The α- and β-prefixes refer to the configuration at the pseudoanomeric carbon equivalent to that of the anomeric carbon in the parent α- or β-aldopyranose, e.g. α-homonojirimycin (α-NHJ).

2. Systematic Names

The spectroscopic data of compounds is assigned based upon a numbering scheme derived from the systematic naming of materials according to IUPAC recommendations on carbohydrate nomenclature.§ Examples are given below:

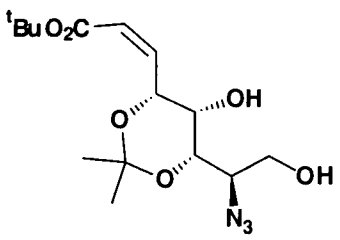


(Z)-2-Azido
2,6,7-trideoxy-3,5-*O*-isopropylidene-D-*ido*-octaro-6-eno-1,4:5,8-dilactone

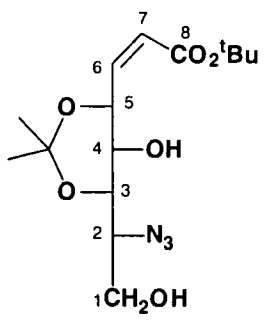


(Z)-(*tert*-Butyl
2-azido-2,6,7-trideoxy-3,5-*O*-isopropylidene-D-*ido*-octar-6-enoate)-1,4-lactone

On reducing the lactone functionality in such octarates and leaving the ester group intact the resulting compounds have the numbering of the carbons remaining the same for the purposes of consistency in the treatment of the spectroscopic data. This results in the C-8 label remaining at the ester carbonyl. However, in terms of naming them systematically the C-1 carbon is sited at the ester carbonyl, so for example the systematic and labelling for spectroscopic assignments for one such compound would be as follows:



tert-Butyl
7-azido-2,3,7-trideoxy-4,6
-*O*-isopropylidene-D-*ido*-o
ct-2-enosonate



§ A.D. McNaught, *Pure Appl. Chem.*, 1996, **68**, 1919.

1. Dendritic Molecules

1.1 New Macromolecular Architectures

Introduction

Over the last two decades a new macromolecular architecture has been outlined which mimics the dendritic branching of trees. These three-dimensional dendritic polymers can be sub-divided into two classes: dendrimers and hyperbranched polymers. Both are built up from bifunctional AB_n dendritic branching units, by constructing branches upon branches.* These two classes are distinct in their degree of polydispersity as a consequence of the processes by which they are synthesised.

◆ Stepwise growth procedures, involving protection/deprotection protocols at every step, lead to structurally well-defined, monodisperse *dendrimers*, albeit with the requirement of extensive purification steps.

◆ A one-step procedure leads to polydisperse, *hyperbranched polymers* that display dendrimer-like properties but are not as structurally well-defined. Such macromolecules can be prepared in 'one-pot' by melt polymerisation routes.[1]

Dendrimers are a relatively new class of macromolecule having a highly ramified structure and are greatly functionalised, but are distinct from normal polymers in two ways. Firstly, they are constructed from bifunctional AB_n branching units (where $n > 1$, usually 2 or 3; $n = 1$ for linear polymers). Secondly, dendrimers are synthesised in an iterative fashion whereby the molecular weight is increased by adding further branching sites with an identical microenvironment to each and every surface group. Coupling these features leads to a non-linear stepwise growth. Each successive iteration adds another layer of branches - called a generation - to the pre-existing dendrimer framework, leading to highly branched and regularly repeating molecular architectures.

* Branching units are compounds with at least three reactive sites of two types (AB_n), from which a dendrimer can be constructed. Note that not all dendrimers are built from branching units – branching can be generated in the growth reaction.

For one-step preparations it is clear that near perfect branching in AB_n systems does not imply the formation of materials with dendritic topology. **Figure 1.1** considers an AB_2 monomer, where (b) represents one possible topology in the spectrum between the linear structure (a) and the perfect dendritic wedge (c).

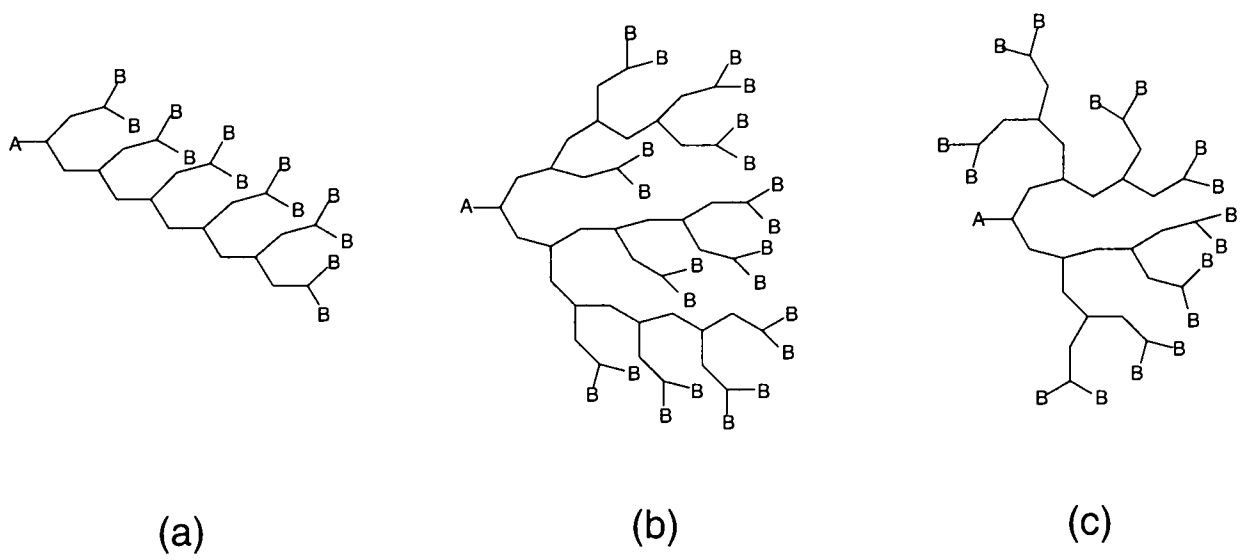


Figure 1.1. Possible structures of an AB_2 hyperbranched polymer with a branching factor of one.[†]

Although the one-step preparation is simple, there is loss of control in molecular weight, accompanied by a broad molecular weight distribution. These highly branched, untangled and globular structures have received much interest in recent years. Dendrimers have been studied extensively for their size, shape, and surface functional group related properties. Their large-scale synthesis has been limited to only a few structures because of the inherent difficulties in the stepwise growth process. The one-step approach leading to hyperbranched polymers has potential for large-scale syntheses but lacks well-defined and monodisperse properties associated with dendrimers.

The term "dendrimer" is now used almost universally to describe highly branched, monodisperse macromolecular compounds, and is synonymous with both *arborol* and cascade which will be discussed later. However for larger, divergently grown (see below) dendrimers, polydispersity is often a consequence of incomplete reactions. The use of the term is attributed

[†] Branching factor is defined here as the fraction of non-peripheral branching units which have reacted at all their surface functions (a peripheral branching unit is one which has reacted at none of its surface functions). A perfect dendrimer has a value of 1. The important difference between dendrimers and hyperbranched polymers is the degree of polydispersity.

to A. J. Vogel[2] and it is derived from *dendra* – the Greek word for 'trees'. To date, a rigorous definition of the term "dendrimer" has not emerged.

The iterative synthetic method is the quintessential macromolecular construction technique. Dendrimer synthesis leads to high molecular weight molecules in a controlled manner within a short sequence of synthetic steps. In the infancy of dendrimer research, the main driving force was the synthesis of large dendrimers for their own sake. The creation of esthetical, highly symmetrical molecular objects has long motivated hard-earned synthetic achievements.[3]

Structurally perfect dendrimers are highly pure, and have defined molecular weight, three-dimensional size, shape and topology which imparts interesting characteristics and features. Diverse arrays of dendrimers with organic, organometallic, and inorganic architectures are now available for studies of their structure-property relationships. This offers an unlimited potential for fundamental discoveries and practical applications.

Dendrimers possess unusual chemical and physical properties which are not displayed by smaller molecules, and dendritic molecules with novel physical, material, electrochemical, optical, photophysical/photochemical, biological and catalytic properties are beginning to emerge.[4] The research in this field has recently switched to the practical uses of these molecules and is expected to yield applications in many areas, such as catalysis, pharmacology and materials science.[5]

Origins of Dendritic Molecules

Here, and elsewhere in this chapter it is not intended to present a comprehensive overview on reported dendrimers. Rather, the aim is to highlight pioneering studies which contribute to a better understanding of the properties of dendrimers, and their potential applications and limitations. Use is made of specific examples of reported syntheses to illustrate some concepts of macromolecular construction. There are some excellent books and reviews that have been

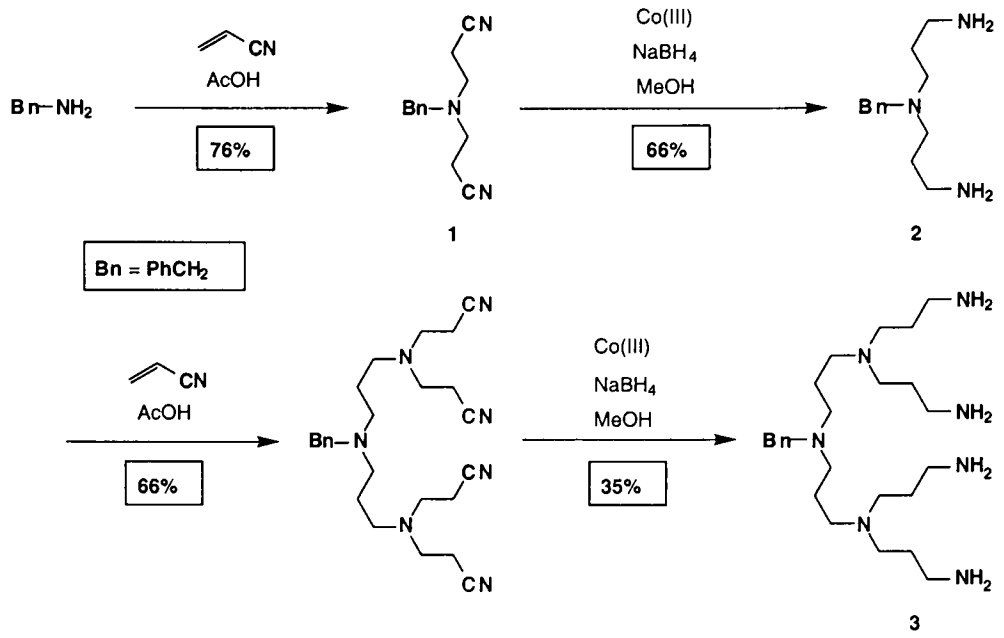
published by various experts in the field which discuss the intriguing properties of dendrimers as well as their syntheses and possible applications.[6]

The polymerisation of an AB_2 type monomer was suggested and carried out in the 1950's by a polymer chemist, Flory, who published theoretical and experimental evidence of such a hyperbranched polymer.[7] Flory considered the classical branching pattern of the polymerisation - an 'infinite network theory' - evolving in the form of Cayley trees,[‡] rooted on an 'A' group. At each step, 'A' of one molecule reacts with 'B' on another, tending towards an infinitely high molecular weight.

However, an unrealistic assumption is made in that intramolecular reactions are considered not to take place even if the monomer is sufficiently flexible i.e. several flexible bonds between functional groups. This consideration is addressed in a recent communication[8] where small ring formation is competing with step growth. Such a '3D lattice model' of step growth allows proper competition in 3D space between fractal growth and cyclisation. In 1987 Kim patented the first intentional preparation of a hyperbranched polymer.[9]

The first attempted dendrimer synthesis was reported by Vögtle and co-workers in the 1970's.[10] A "cascade" synthesis was described (**Scheme 1.1.1**) invoking an exhaustive Michael – type addition of an amine to acrylonitrile (e.g. benzylamine, to give the bisnitrile **1**), followed by reduction of the nitrile groups to primary amines (e.g. to give bisamine **2**). Such iterative steps could theoretically be repeated *ad infinitum,* however technical problems were encountered in the reduction step.

[‡] Cayley trees are mathematically described branching networks.



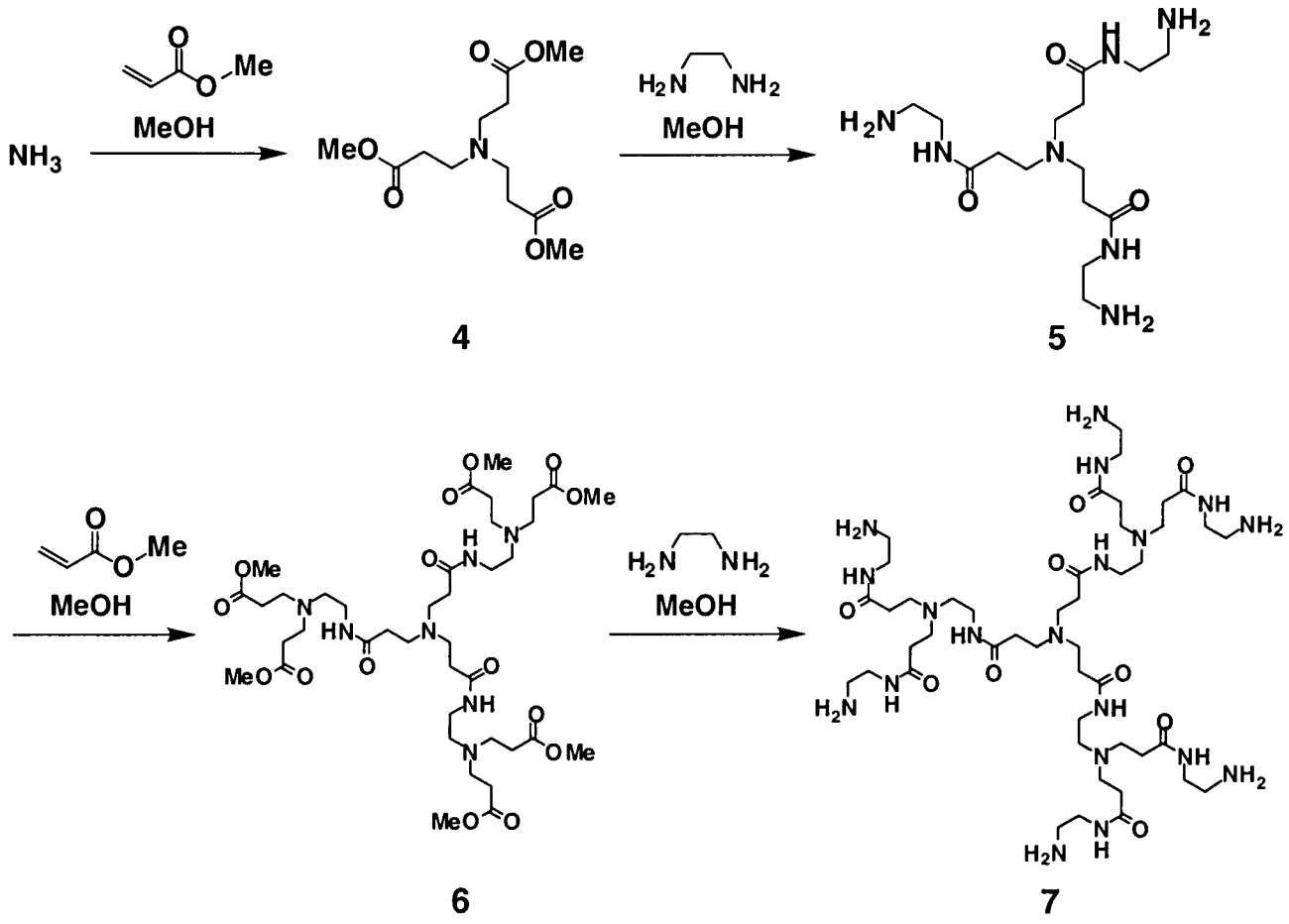
Scheme 1.1.1. Vögtle's cascade synthesis of "poly(propylene imine)" dendrimers.

The process was only repeated twice affording the doubly branched polyamine **3** – before the metal complexing ability of the substrate made work-up of the reduction step problematic and low yields ensued. The problem was resolved later by use of different catalysts which allows the synthesis of "poly(propylene imine)" dendrimers to be achieved on a commercial scale.[11] It can be envisaged that side reactions lead to the formation of defect structures going from one amine generation to the next. Although the perfect structure might be the dominant species, there will be structures corresponding to "missed" Michael additions arising from incomplete cyanoethylations or retro-Michael additions.

A few years later, in the early 1980's, Denkewalter[12] patented the synthesis of L-lysine-based dendrimers. The patents describe structures up to high generations, however, except for size exclusion chromatography data,[13] no detailed characteristics of the materials are given.

In the 1980's Tomalia's group[14] devised a synthetic strategy whereby a "stepwise polymerization" led to highly branched polymers with narrow polydispersity. The polyamidoamine (PAMAM) series ("Starburst™ dendrimers") illustrates this iterative stepwise growth (**Scheme 1.1.2**) – the first two generations of dendritic growth from an ammonia core is shown.

Exhaustive Michael addition of ammonia to methyl acrylate affords triester **4** which is amidated with a large excess (15 – 250 molar eq.) of ethylenediamine to yield the trisbranched compound **5**. Iteration of this sequence leads to next generation analogues **6** and **7**. The yields are high at every step (*ca.* 98 – 100%) and the synthesis of polymers up to 10 generations has been reported. These are the most studied dendrimers, and are commercially available.[15] The high generation dendrimers have a small but unavoidable polydispersity.



Scheme 1.1.2. PAMAM dendrimer synthesis.

There are some unwanted side reactions in the PAMAM dendrimer series. Retro-Michael reactions and intramolecular lactam formations can produce defect structures in the series. ESI-MS studies on PAMAM dendrimers indicate defect structures arising from these side reactions.[16]

Newkome and co-workers[17] developed compact "arborol" structures[§] with densely packed surface hydroxyl groups (**Figure 1.3**). These globular dendritic polyalcohols exhibit micellular

[§] The term "arborol" is derived from the Latin, *arbor*, meaning tree.

behaviour and a series of such highly branched compounds were developed and investigated as micelle analogues and supramolecular building blocks.

Newkome used the term "directionality" to define the number of branched arms attached to the initiator core. These are shown schematically in **Figure 1.2**. Thus a one-directional cascade would describe the mushroom structure (b) and three-directional cascade would describe the structure (a) in **Figure 1.3**. Similarly two-directional structures akin to a dumbbell structure, and four-directional structures have been prepared.

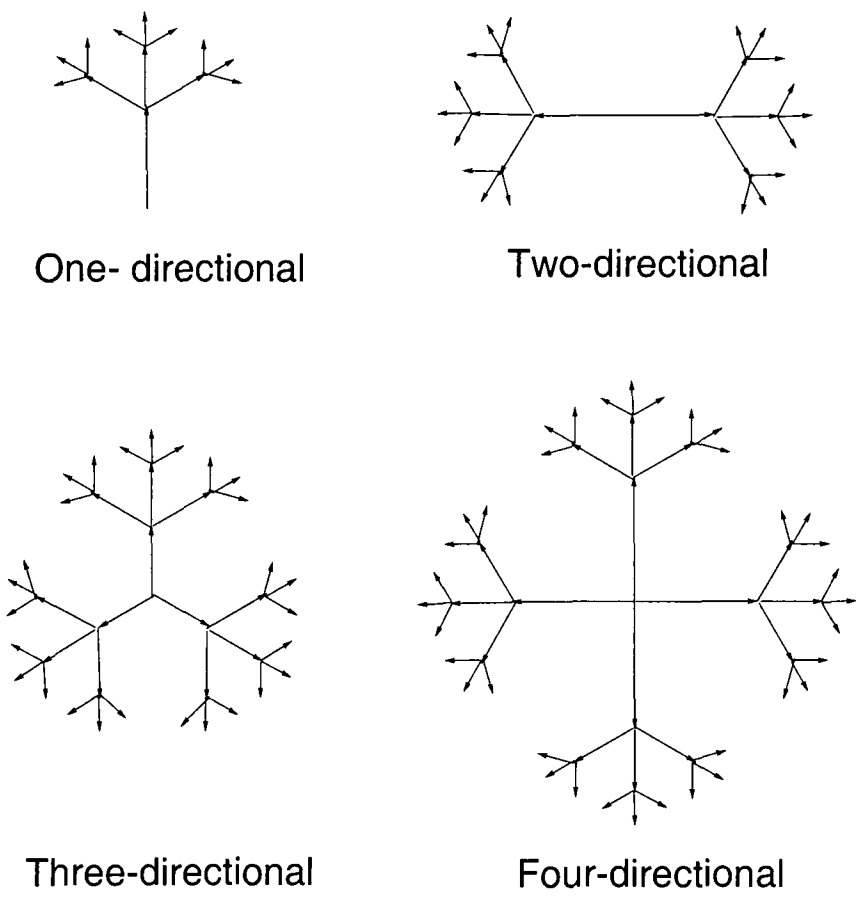


Figure 1.2. "Directionality" in Newkome's "aborols".

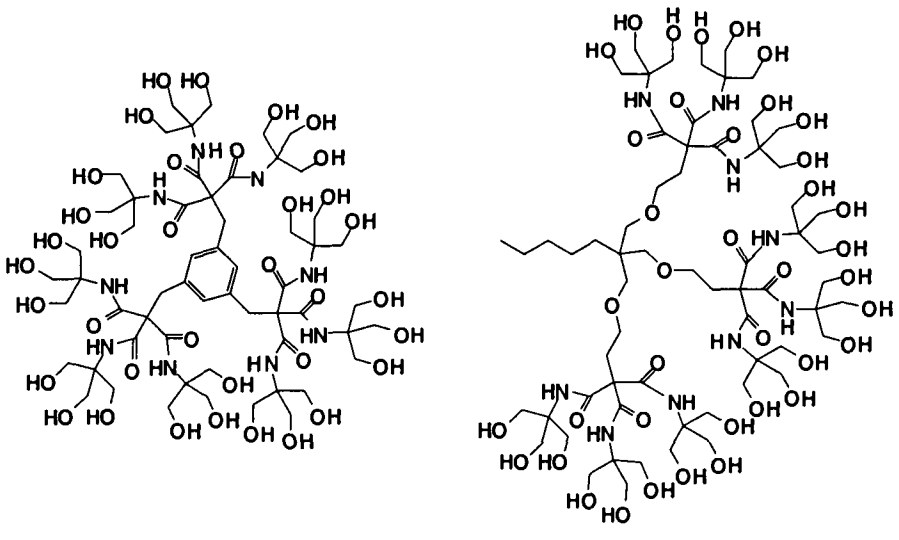
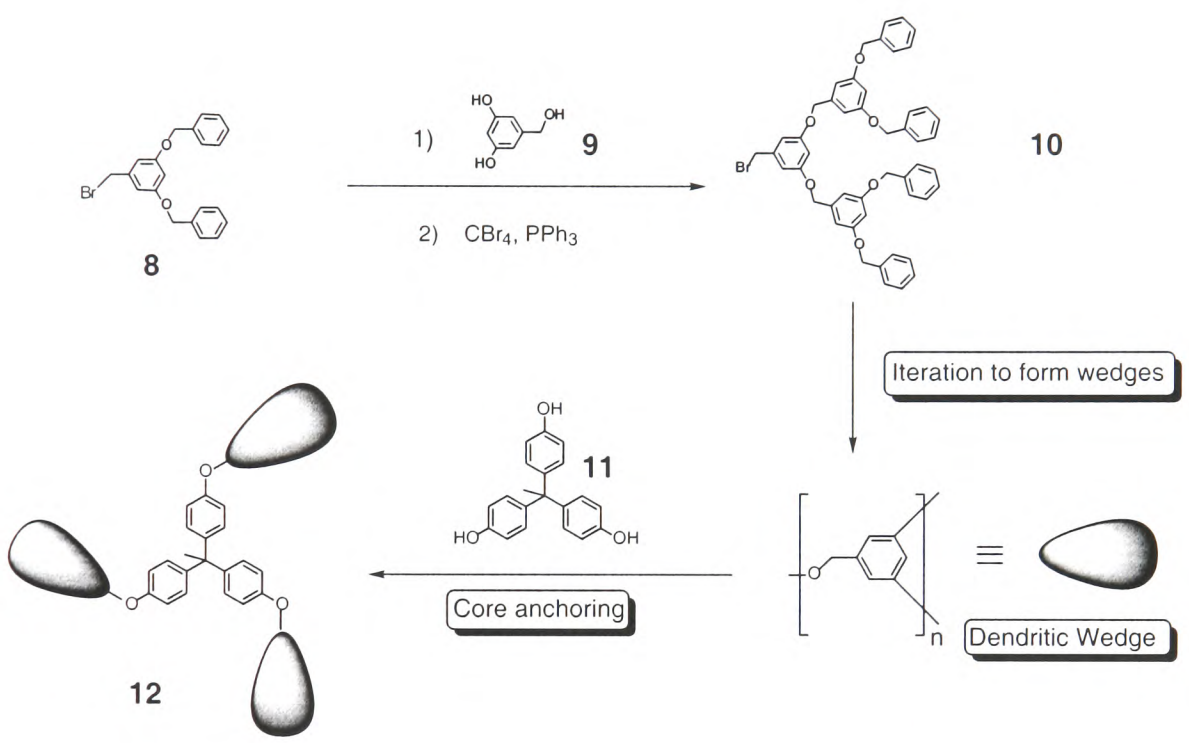


Figure 1.3. Newkome's "aborols".

In the early 1990's Hawker and Fréchet[18] utilised the reactions of a resorcinol derivative **9** with a benzylic bromide **8,** and subsequent and bromination of the benzylic alcohol (with PPh_3 and CBr_4) to produce wedge **10**. Such an iterative strategy (**Scheme 1.1.3**) allowed the synthesis of a bifurcating polyether structure **12** on coupling to core **11**. This was the first 'convergent' synthesis (see below) and the series has been studied thoroughly up to the sixth generation. Dendrimer synthesis developed by Fréchet will also be discussed below.



Scheme 1.1.3. Convergent synthesis of Fréchet's polyether dendrimer.

Both the convergent and the divergent methods consist of the reiteration of a sequence of reactions, which allows generative growth of the dendrimers. The divergent methods of Newkome and Tomalia have a notable and general difference rooted in the formation and introduction of the branching centres of the growing molecule or polymer. Tomalia's procedure produces branching centres during dendritic construction at the periphery of the growing polymer *via* attachment of linear (AB type) monomers to the dendritic surface. In contrast, Newkome used monomers possessing preconstructed branching sites for subsequent attachment to a molecular surface.

Structure of Dendritic Molecules

Such monodisperse molecules have an unusual architecture possessing unique structural features and properties. The structural components of the dendritic structure include a core unit, peripheral groups and multiple branching units that span the two. A fifth-generation dendritic structure is shown in **Figure 1.4**.

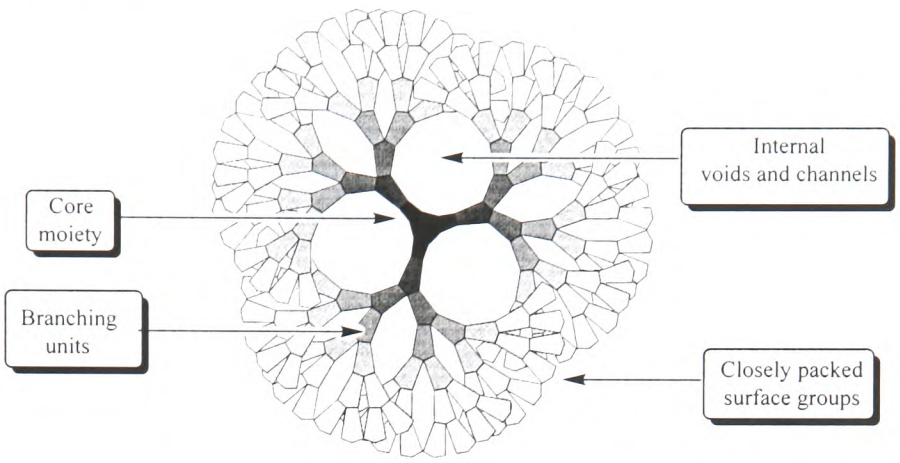


Figure 1.4. Schematic fifth generation dendritic structure

Classically, the surface of the dendrimer has a large number of functional groups, which confer properties such as solubility, viscosity, and thermal behaviours different from those of more classical polymers. The internal cavities arise from branch multiplicities and the directionality of the core confers the overall shape and dimensions of the dendrimer. It can be predicted that as the number of monomer units in a dendrimer is increased by generative growth, there will be a limit when growth is prohibited as a consequence of a lack of space. This led to the concept of the "starburst limit".[19] At the surface of higher generation molecules the branching units are closely packed and the molecule adopts a globular conformation.[20] The formation of dynamic channels and cavities in the dendritic structure has been predicted by computer modelling experiments[21] and provides a microenvironment for the entrapment of guest molecules[22] and other applications (see below).

On paper, dendrimers are often drawn in such a highly symmetrical fashion, a spherical entity with all branches pointing radially outward and the end groups invariably being located at the surface. However, some theoretical and experimental results over the last decade have revealed the true nature of dendrimers in terms of both their three-dimensional shape and their

properties. These studies have revealed unexpected conformational features of dendritic molecules, most notably the degree of backfolding of flexible branches.[23]

Many theoretical predictions such as starburst limits and the conformational space available to a dendrimer can be modelled mathematically.[24] A host of abstract terms and equations have evolved but these will not be addressed here. Perhaps it would be appropriate however, to clarify some of the terms used in the pragmatic treatment of dendritic structures.

Nomenclature and Features of Dendrimers

Some terms have been used already in this introduction which might need further amplification and others need to be presented before proceeding any further. The dendritic structure has already been discussed in terms of cores, branching units, surface units and generations, **Figure 1.5** describes some of these terms.[5] Some definitions of the terms used in the pragmatic treatment of dendritic structures are also listed.

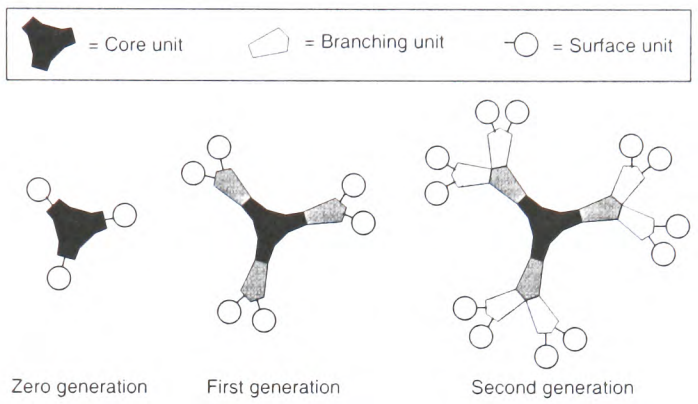


Figure 1.5. A pictorial definition of some terms.

Branching Multiplicity	The number of branches emanating from a branching point or monomer
Branching Unit	A compound with at least three reactive sites of two types (AB_n), from which a dendrimer can be constructed. Note that not all dendrimers are built from branching units – branching can be generated in the growth reaction
Core Multiplicity	1. The number of reactive sites on a core; 2. The number of branches emanating from a core
Dendron	A wedge or dendritic oligomer
Dendritic Monomer	See branching unit
Dendritic Oligomer	A discrete molecular species composed of more than one branching unit
Directionality	The core multiplicity of a dendrimer
Focal Point	The single functional group in a dendritic monomer or oligomer from which branching emanates
Generation	The number of branching points encountered in the molecular skeleton when tracing a path from the core to the surface. The branching in the core is not included
Microenvironment	The local environment on the micro- or nanoscale, as opposed to the macroscopic properties of a material
Starburst Limit	The point (usually measured in generations) at which unblemished dendrimer growth can no longer take place as a consequence of steric interactions
Surface	The functional groups at the ends of the branches in a dendrimer, dendritic oligomer or monomer
Wedge	A dendritic species with reactive functionality at the focal point

The representation of dendrimers on paper and by name is made difficult by the size and complexity of these molecules. Systematic nomenclatures can be invoked when each generation is made up from one particular monomer type - such as "cascade"[25] or "fractal"[26] macromolecules - this system is, however, not in widespread use. Current nomenclature rules do not easily accommodate dendritic structures and there are a number of shortcomings using such rules. Firstly the names rapidly increase in length and complexity with successive generations and important structural features such as the core, branch multiplicity and terminal functionality are not obvious. In addition, such a system requires tremendous patience and effort to name even an initial generation dendritic molecule.

Structural formulae can often be drawn using bent or elongated bonds, which is not ideal and becomes unacceptable for high generations. Advantage can be taken of the high symmetry and repetitious nature of a dendrimer and schematic "cartoons" can be used. This is illustrated in **Figure 1.6.**

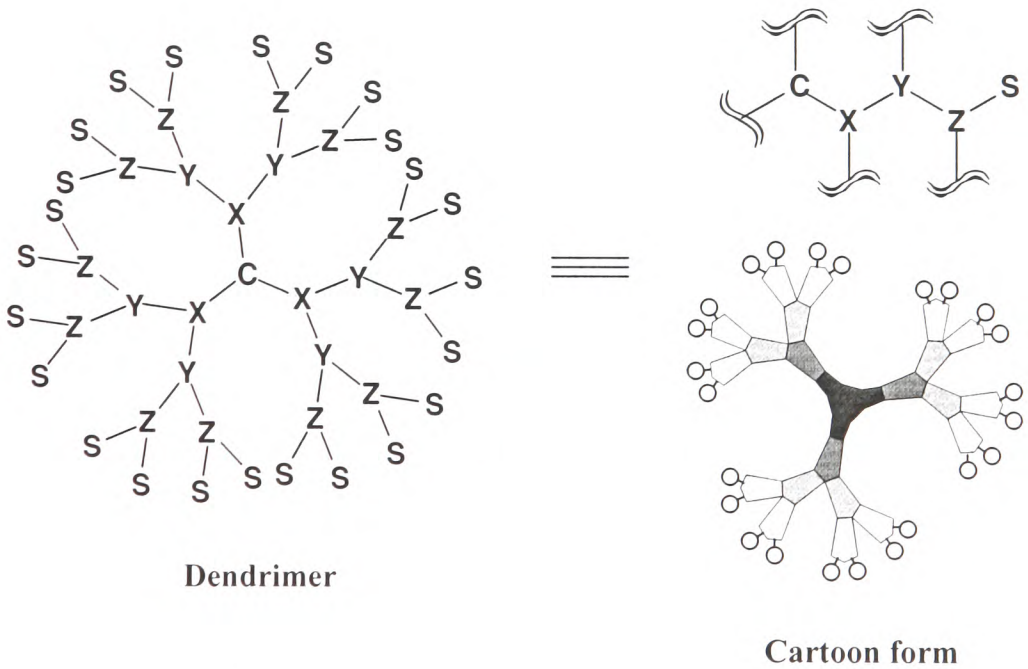


Figure 1.6. Representations of the dendritic structure.

Core (C/dark), surface (S/circles) and branching (X,Y,Z/wedge) units.

1.2 The Construction of Dendrimers

Introduction

Any methodologies applied to the synthesis of dendrimers must present control over the architecture of the molecule in terms of parameters such as size, shape, topology, flexibility and surface chemistry.

The choice of the branched monomer unit will impart control over the molecular cavities - by varying the nature of the branching structure. The choice of the growth reaction dictates the way in which branching is introduced into the dendrimer. Branching can either be present in the building blocks, in which case each branch end only has to undergo a single reaction with the focal point of another branching unit. Alternatively branching may be created as a function of the growth reaction [as in the case of PAMAMs and the poly(propylene imines)]. This approach requires at least two reactions (such as the double Michael addition of a primary amine to methyl acrylate in the PAMAMs) to be performed at a single chain end.

Some pioneering methodologies and dendrimer growth strategies will be illustrated below. Further details of the chemistry employed and many other dendrimer growth strategies are presented in several comprehensive works.[27] Interest in dendrimers has been prolific in the last ten years or so, with a great many structures being reported in the literature. The study of dendrimers has also become inextricably linked with many other fields, leaving the comprehensive reviewer of the subject a near impossible task to fulfil.

Most syntheses involve repetitious alternation of a growth/activation reaction sequence at the periphery of the molecule. Consequently, as the generations are increased, such reactions have to be performed on many sites on the same molecule simultaneously. This iterative approach demands that the reactions be clean and high yielding and a proper selection of the peripheral functionality must be made in order to present reactive groups for further growth, and to convey the surface properties of the dendrimer.

On the other hand, one step preparations of dendritic molecules based on the polymerisation of monomer units are also known. Despite such approaches being synthetically more efficient and less time consuming, they invariably produce dendrimers of high polydispersity and with considerable skeletal defects. Thus, structurally perfect dendrimers are usually prepared using iterative synthetic procedures. The construction of dendrimers has been dominated by two antithetical philosophies; 'divergent' and 'convergent' approaches.

'Divergent' Synthetic Methods

The divergent approach was developed in the late seventies and early eighties with pioneers and key contributors including Vögtle,[28] Denkewalter,[29] Tomalia,[30] and Newkome.[31] Growth is shell-like from a central core to the periphery and branching is encouraged *via* a series of repetitive addition and activation steps. Thus, by starting construction from the 'root' of the molecular trees generative growth can result.

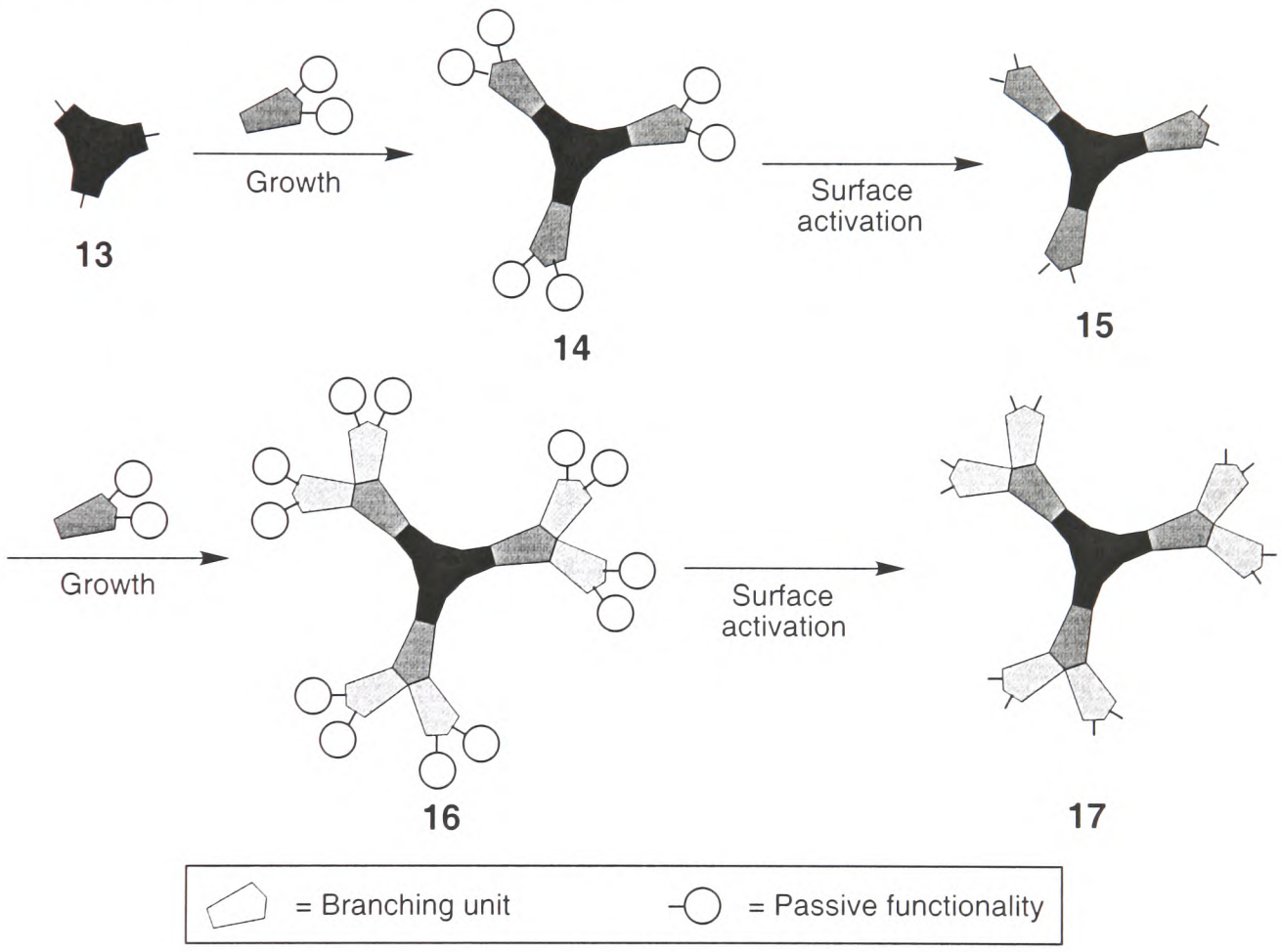
This radial iteration sequence results in rapid geometric growth in the number of surface groups while the radius of the dendrimer increases in an arithmetic fashion. The generations are thus concentric layers around the central core and a self-limiting size (generation) will occur for a dendrimer series when the surface groups are too congested for further growth without creating structural defects.

The divergent approach is a fast and efficient procedure to produce high generation dendrimers and is indeed the preferred industrial route. It is successful at producing large quantities of dendrimers. This method is characterised by reactions at an ever increasing number of sites and the process requires a large excess of reagents. This limitation, coupled with the problem of incomplete growth steps and side reactions, leads to the isolation and characterisation of slightly impure samples.**

** Dendrimers grown this way have very similar structures to their by-products.

It is not possible to achieve selective conversion of only one or several of the reactive groups of the reactive surface using the divergent procedure – it does not allow for the selective functionalisation of only part of the surface sector. This and other weaknesses of the divergent approach were resolved several years later by the development of the convergent approach (see below).

The preparation of the polyamidoamine (PAMAM) series (**Scheme 1.1.2**) is an example of a dendrimer prepared by the divergent approach.



Scheme 1.2.1. Schematic representation of the divergent approach.

Scheme 1.2.1 shows a schematic representation of divergent growth. From a reactive core **13**, a generation is grown by reaction of the core's functionalities with monomer units to give **14** which is then activated to yield the first generation analogue **15**. The unmasked 'active' groups on the periphery of **15** can now be reacted with further monomer units to give the second generation analogue **17** *via* **16** as shown.

'Convergent' Synthetic Methods

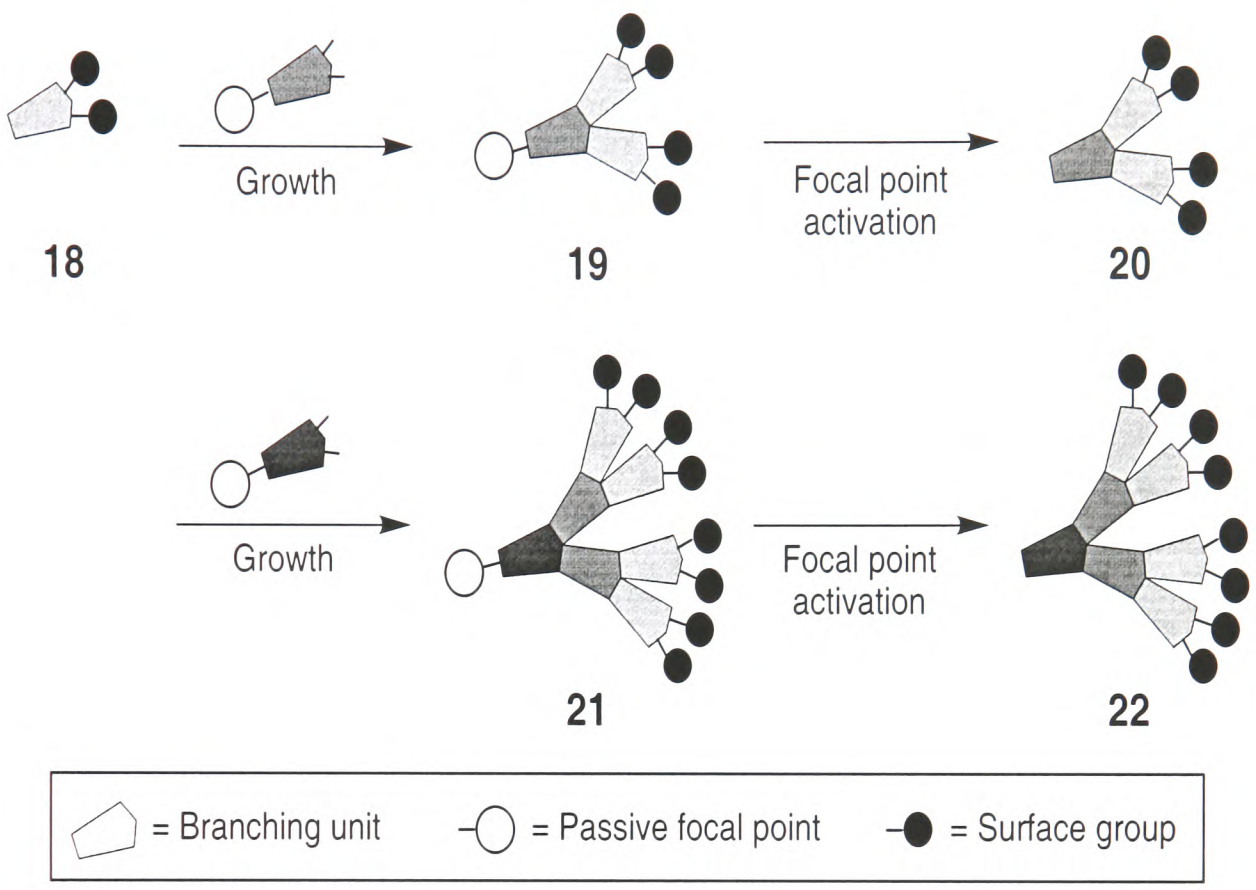
Starting growth from the leaves of the molecular trees and anchoring of these to a central core through a focal point also produces dendritic structures. These leaves are fashioned by the synthetic union of branching units to form dendrons (dendritic wedges) and subsequent attachment of these dendrons to a core *via* some reactive focal point leads to the dendrimer. Thus the convergent approach works inwards from what ultimately becomes the surface of the dendrimer by linking surface units together with more monomer, propagating toward the central core. Such a process was introduced and developed independently by Fréchet [32] and Miller. [33]

The convergent approach presents the potentiality of producing unsymmetrical dendrimers by coupling different dendron sectors to the core. This allows for the introduction of subtle engineering into the dendrimer as the approach confers control over the number and placement of dendritic wedges and functional groups (at the periphery as well as the interior regions of the macromolecule). Straightforward preparation of novel dendritic layer-block[††] and segment block copolymers[34] as well as specific surface functionalised dendrimers[35] is thus possible. Examples of how the synthesis of a dendrimer can be controlled using the convergent approach are outlined below.

Additionally, in contrast to the divergent approach, the number of possible side reactions is low and the synthesis of monodispersed dendritic molecules with a high degree of control is achievable. This approach is not amenable to large-scale production but is ideal for the production of laboratory quantities of ideally branched dendrimers since, separation from defective counterparts is feasible. Fewer molecules are required in each reaction and there is no longer a need for a massive excess of reagents to quench each and every functional group on the surface.

[††] A "layer-block" copolymer is a term used to describe dendrimers where layers (generations) are of different constitutions. A "segment-block copolymer" is a term used to describe dendrimers where segments are of different constitutions.

The convergent approach may suffer from steric inhibition at the focal point, particularly for the higher generation dendritic wedges which can lower yields. This can be overcome to some degree by using more flexible monomers *i.e.* extension of the linking units or circumvented by using hypercores (both will be discussed below).



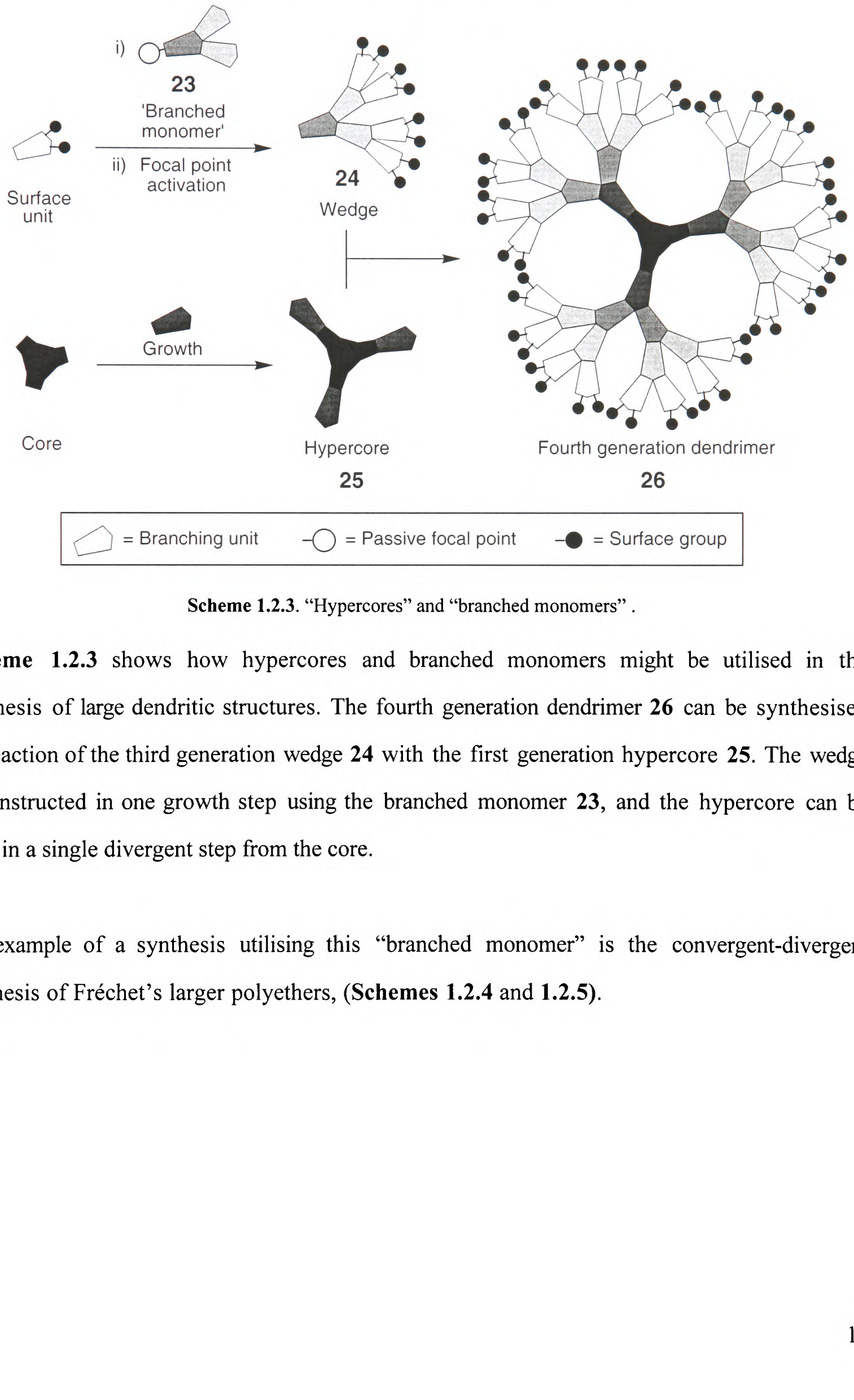
Scheme 1.2.2. Schematic representation of the convergent growth of dendritic wedges.

Scheme 1.2.2 shows the schematic convergent growth of a dendritic wedge. Reaction of two or more surface units (e.g. **18** or **20**) with monomer gives a product (e.g. **19** or **21**) with an unreactive "focal point". A second reaction activates this focal point (e.g. to give **20** or **22**) for reaction with further monomer or, when the wedges are large enough, attachment to a suitable core to give a dendrimer.

Accelerated Approaches and Solid Supported Synthesis

After the development of the convergent synthesis, the Fréchet group focused their efforts on the more subtle aspects of dendrimer synthesis. The outcome of this research was the demonstration of "hypercores"[36] (pre-branched core-analogues) and "branched monomers",[37] (pre-branched monomer analogues). These methods involve the preassembly of oligomeric

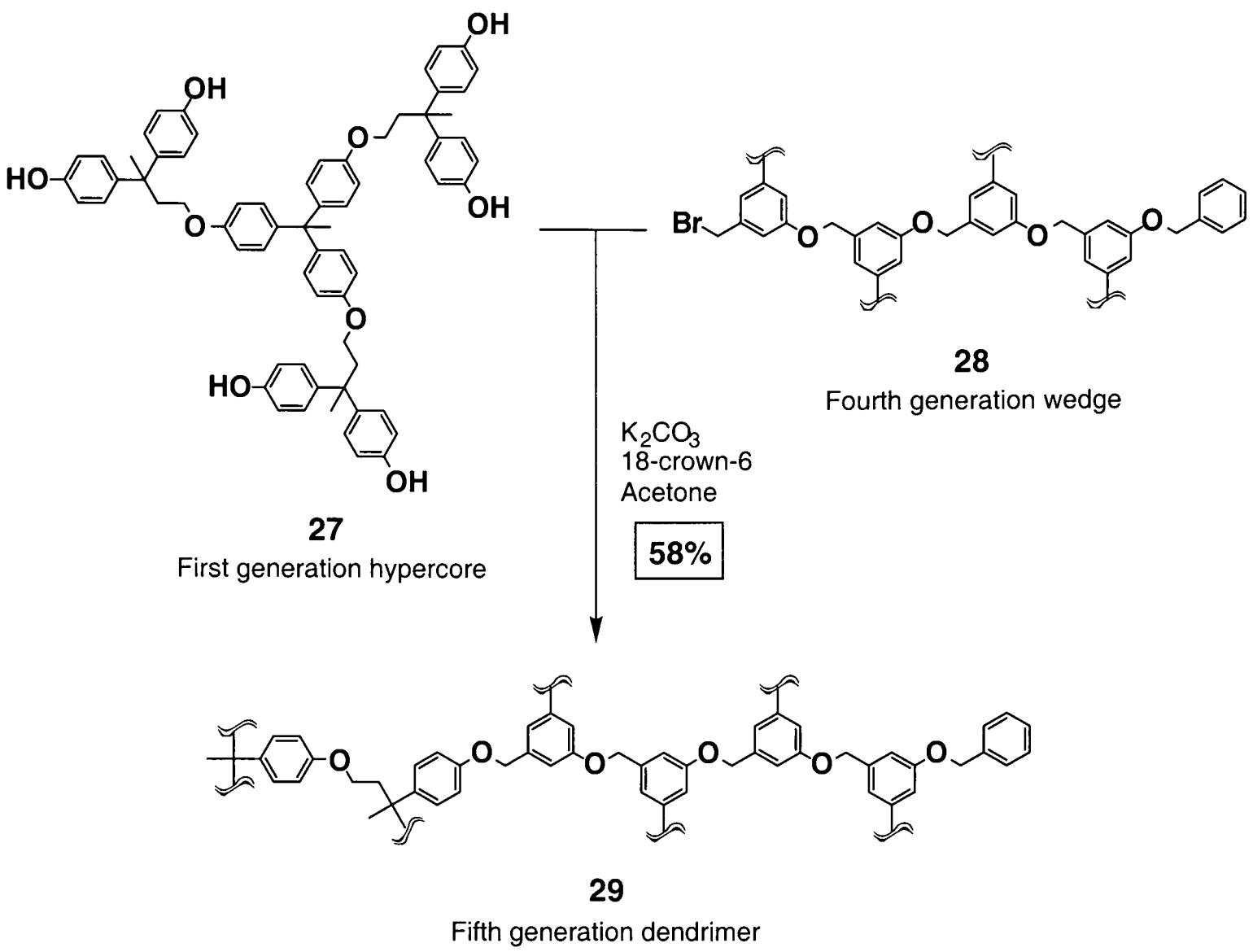
species, which can then be linked together to give dendrimers in fewer steps and higher yields – taking advantage of the best points of convergent and divergent strategies.



Scheme 1.2.3. "Hypercores" and "branched monomers" .

Scheme 1.2.3 shows how hypercores and branched monomers might be utilised in the synthesis of large dendritic structures. The fourth generation dendrimer **26** can be synthesised by reaction of the third generation wedge **24** with the first generation hypercore **25**. The wedge is constructed in one growth step using the branched monomer **23**, and the hypercore can be built in a single divergent step from the core.

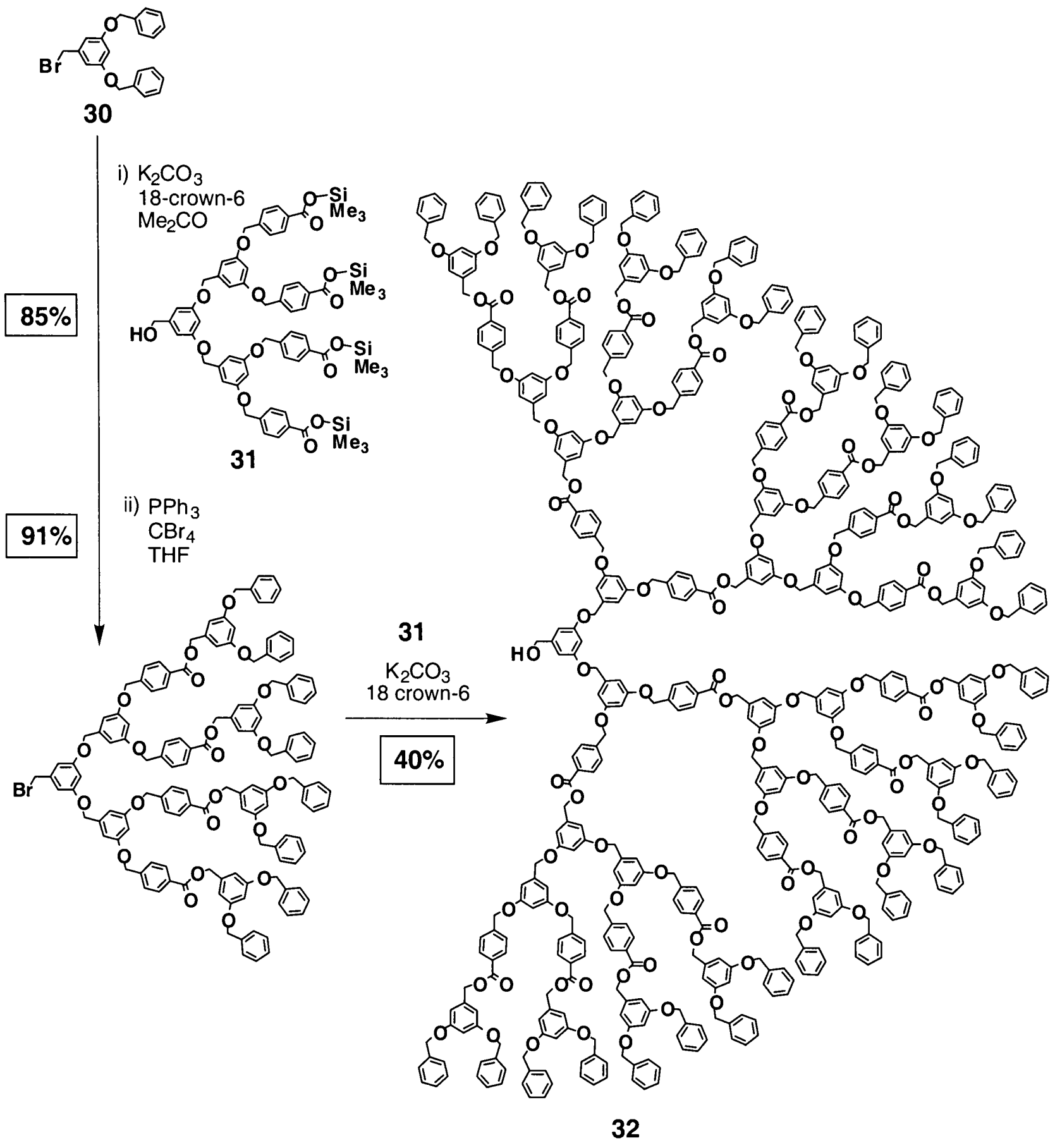
An example of a synthesis utilising this "branched monomer" is the convergent-divergent synthesis of Fréchet's larger polyethers, (**Schemes 1.2.4** and **1.2.5**).



Scheme 1.2.4. Convergent-divergent synthesis of polyethers.

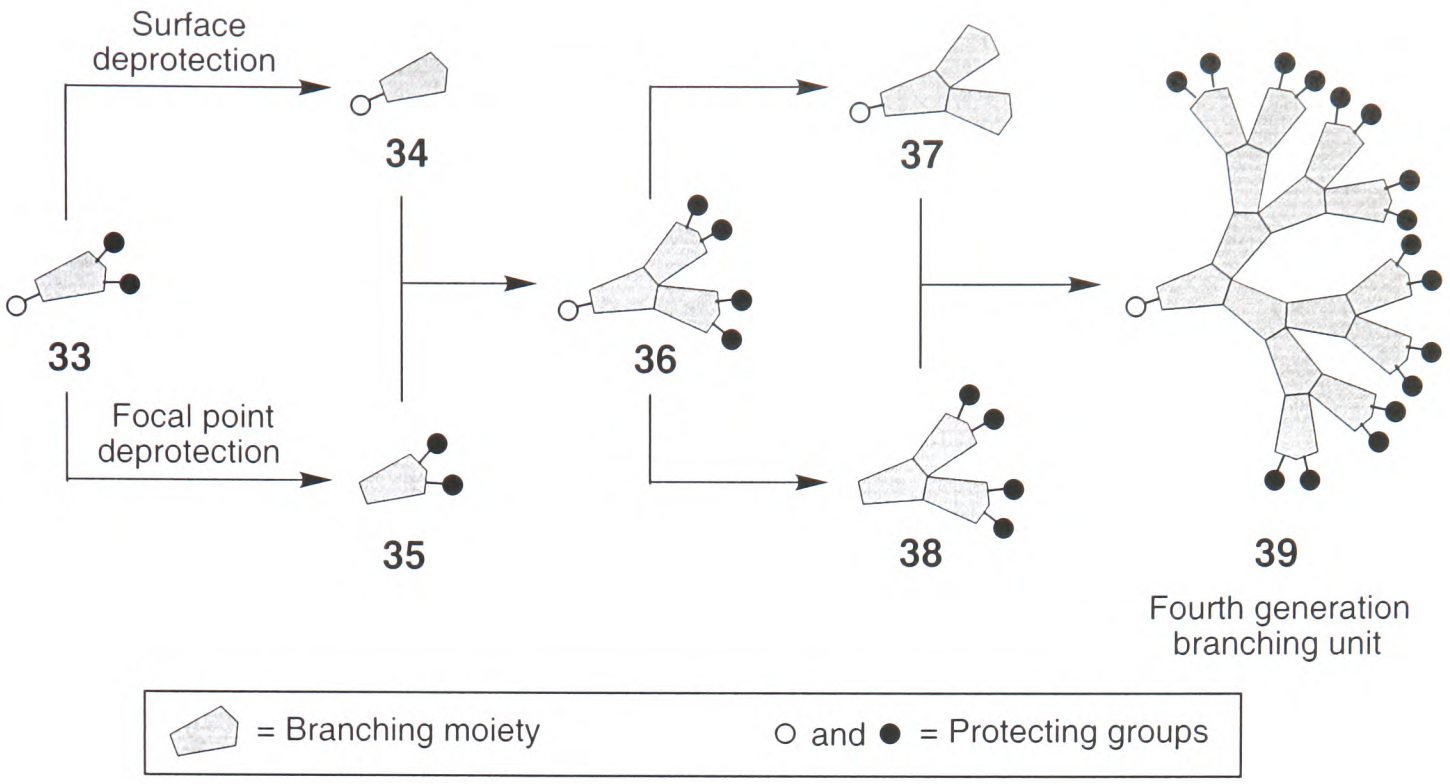
The dendrimer-forming step (the reaction of wedge **28** with hypercore **27** to give dendrimer **29**) suffered much less steric hindrance than the analogous step using a zero-generation core with a fifth generation wedge. This is the working assumption of the technique *i.e.* the surface functionality of the hypercore is less sterically hindered than those of a simple non-dendritic core molecule used in the conventional convergent methodology.

The "branched monomer" **31** was used in the preparation of the fifth-generation wedge **32, (Scheme 1.2.5)**. This is in contrast to the fact that four growth steps would be needed if a first-generation monomer were used.

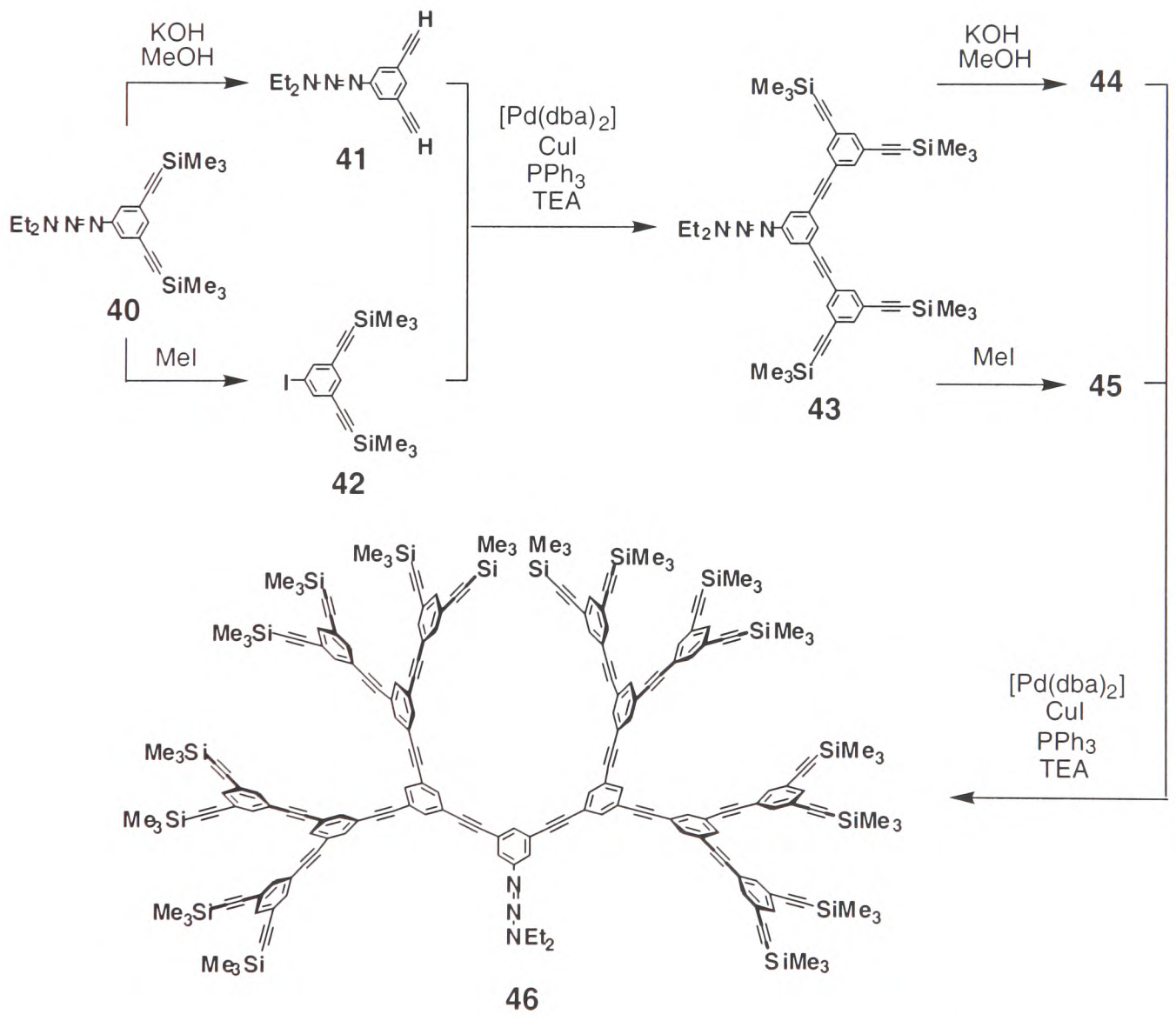


Scheme 1.2.5. Preparation of fifth generation dendritic wedge.

Another fundamental breakthrough (**Scheme 1.2.6**) was the concept and implications of "double exponential" growth.[38]



Scheme 1.2.6. Schematic representation of "double exponential" growth.



Scheme 1.2.7. Synthesis of a fourth generation phenylacetylene dendrimer.

In this strategy, a higher generation hyperbranched dendritic wedge, instead of a simple lower generation dendritic sector, is used to anchor to a hypercore. Double exponential growth

employs a bifunctional AB_2 monomer where A and B are both protected (orthogonally). Selective deprotection (**Scheme 1.2.6**) of the fully protected monomer **33** at the surface and at the focal point in separate reactions gives monomers **34** and **35**. Reaction of these two products gives an orthogonally protected trimer **36** which may be used to repeat the growth process again. Moore's synthesis is shown (**Scheme 1.2.7**); the fourth generation phenylacetylene dendrimer **46** was prepared from the monomer **40** *via* the second-generation oligomer **43**. Use was made of TMS protection chemistry, 1-aryl – 3,3 – dialkyltriazine masking of the aryl iodide, and palladium-catalysed cross-coupling reaction of the terminal acetylenes with aryl halides.

Such dendrimers are the largest hydrocarbon dendrimers ever isolated. Using this strategy, a seventh generation phenylacetylene dendritic fragment of 40kDa could be prepared in 9 steps, while a convergent growth scheme would require 15 synthetic operations.

Since the synthesis of dendrimers requires a repetitive, stepwise reaction procedure in which large excesses of reagents are used, it is amenable to solid phase synthesis. In 1991, Fréchet reported the first use of polystyrene supports for the synthesis of polyamide dendrimers.[39] The purification procedure for each generation is simplified as the excess reagents used to ensure complete reaction of the surface functional groups can be removed easily by washing the polymer bound dendrimer. The desired dendritic polymer is then isolated by cleavage of the macromolecule from the solid support. However, yields of the coupling reactions tend to be rather poor and higher generation dendritic fragments prepared by this method have severe structural defects.[40]

1.3 The Characterisation of Dendrimers

The characterisation of dendrimers is rather complex due to the size of, and symmetry in these macromolecules. This can be divided into the elucidation of structure, and characterisation of the microenvironment. The ultimate determination of dendritic structures would be a crystal structure. However, due to the lack of long-range order[41] in the solid state structures this

technique has so far been of little use. There are a few examples of crystalline[42] dendrimers and powder and single crystal X-ray studies of dendrimers, but these examples are confined to low generations and to rigid, hindered molecules.

NMR spectroscopy and MS have been invaluable techniques for the characterisation of dendrimers. Due to the structural regularity of dendrimers, their proton and carbon NMR spectra are surprisingly simple and can reveal defects in dendritic structures. NMR spectroscopy, especially of ^{13}C and heteronuclei, has been extremely useful in assessing dendrimer purity since any defects will lead to an unsymmetrical structure and result in more ^{13}C signals.

With the advent of modern techniques in mass spectroscopy (soft ionisation techniques), it has now become possible to ionise dendritic molecules and to determine their molecular mass with high precision. Many results have been obtained by the use of MALDI – TOF (Matrix- assisted laser desorption ionisation – time of flight)[43], and ESI (electrospray ionisation) MS methods.[44]

Often MS is the best evidence for dendritic structures particularly for example, when NMR is ambiguous. Also they can reveal small amounts of impurities, especially in higher generation dendrimers. Microanalysis is usually of limited use since the elemental compositions of dendrimers vary very little within any dendritic family.

Dendrimers are also characterised by standard polymer characterisation techniques such as size exclusion chromatography (SEC), viscosity and light scattering measurements.

The dendritic microenvironment (such as cavities and voids) is of great importance in the study of dendrimers and in relation to potential applications. In order to understand, engineer, and utilise the microenvironment it is necessary to characterise this space and determine how it is affected by dendrimer size, constitution and solvent.

Functional probes can either be attached covalently to the dendritic structure, or introduced as guest species. An example is a solvatochromic[45] chromophore that has been attached to the focal points of a series of Fréchet's polyether wedges in order to examine the effects of solvent and dendrimer size on the microenvironment. In non-polar solvents, a dramatic change in absorbance wavelength was observed at the transition from the third- to the fourth- generation species. This change was attributed to a change in the conformation of the dendrimer from an extended to a globular shape. Spectroscopic methods have also been used such as the observation of decreased ^{13}C relaxation times for internal generations of PAMAM dendrimers, suggesting that these moieties are less mobile than the surface groups.

Computer modelling can provide insight into dendrimer behaviour but care must be exercised in the interpretation of the results.

1.4 Dendritic Architectures

Control of Dendritic Shape and Functionality

Exploitation of the unique properties of dendrimers is necessary to utilise any potential application. Control of size is easily achievable by growth strategies - there is an increase in size from generation to generation. The overall shape can be manipulated to produce macromolecules from spheres to ellipsoids to rods. The question of how to control dendritic size and shape is briefly addressed here.

The functionalisation of dendrimers after their synthesis has been completed – post-synthesis modification – has had some degree of success. Perhaps the most striking example is the "dendritic box" (**Figure 1.7**) by Meijer and co-workers[46] and Newkome *et al.*[47]

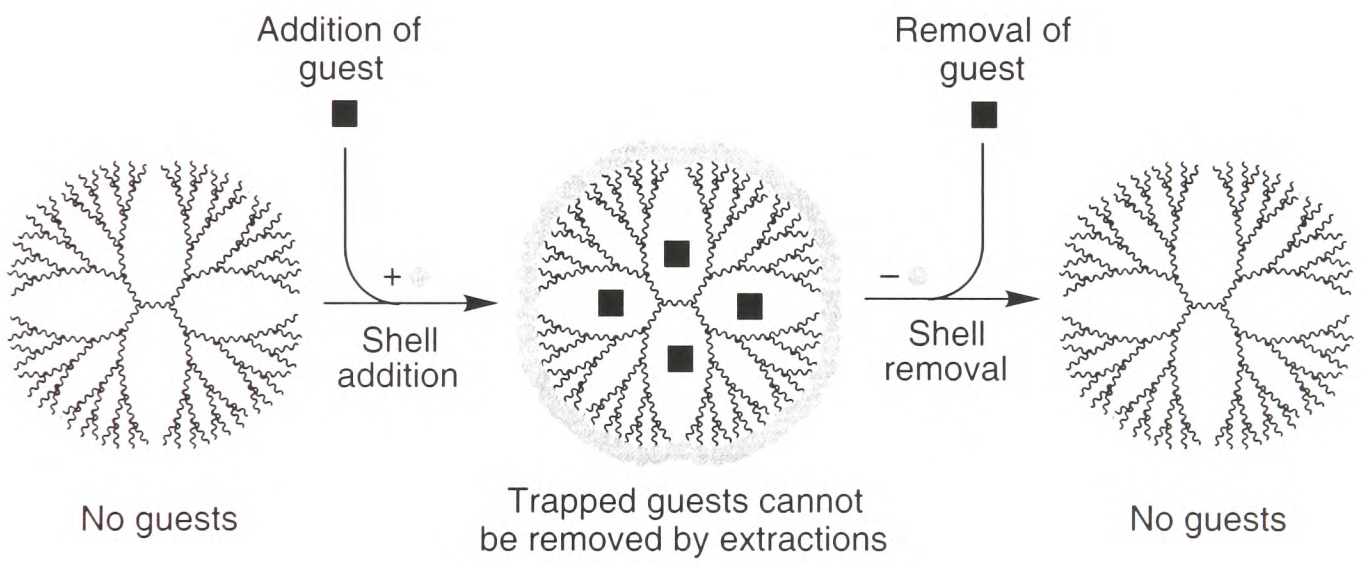


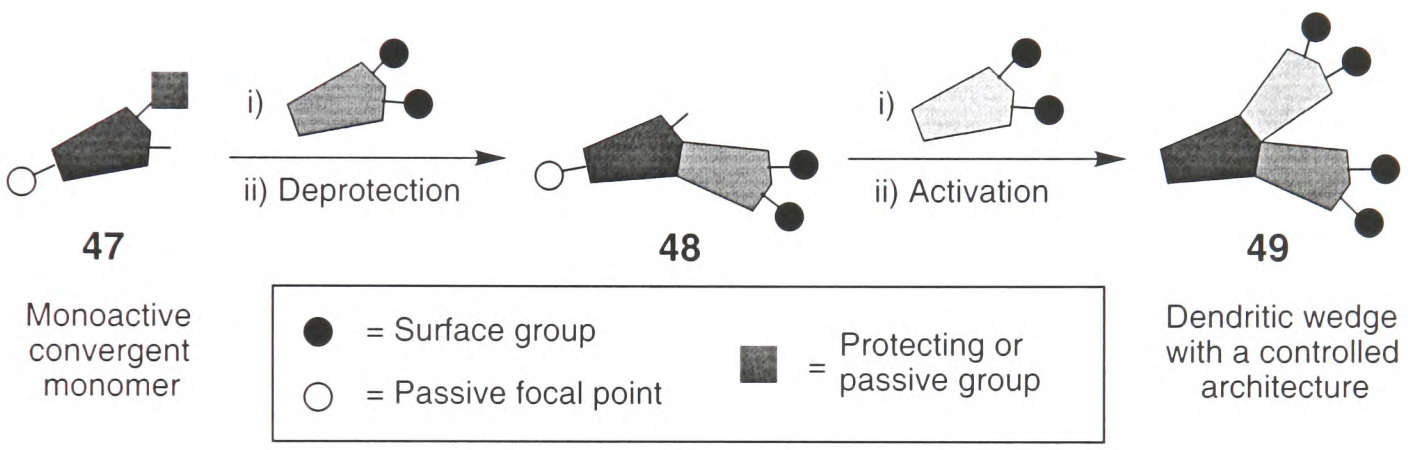
Figure 1.7. Principle of the dendritic box.

It was found that a shell could be formed around the surface of a poly(propylene imine) dendrimer by reaction of the terminal amines with BOC-protected amino acids. When the shell is added in the presence of guest molecules, those that are encapsulated in the dendritic voids are trapped sterically. Hydrolysis of the shell releases the trapped guests.

Although such modifications of known dendrimers has attractions, a more versatile approach is needed for the synthesis of more complicated dendritic architectures. In order to synthesise

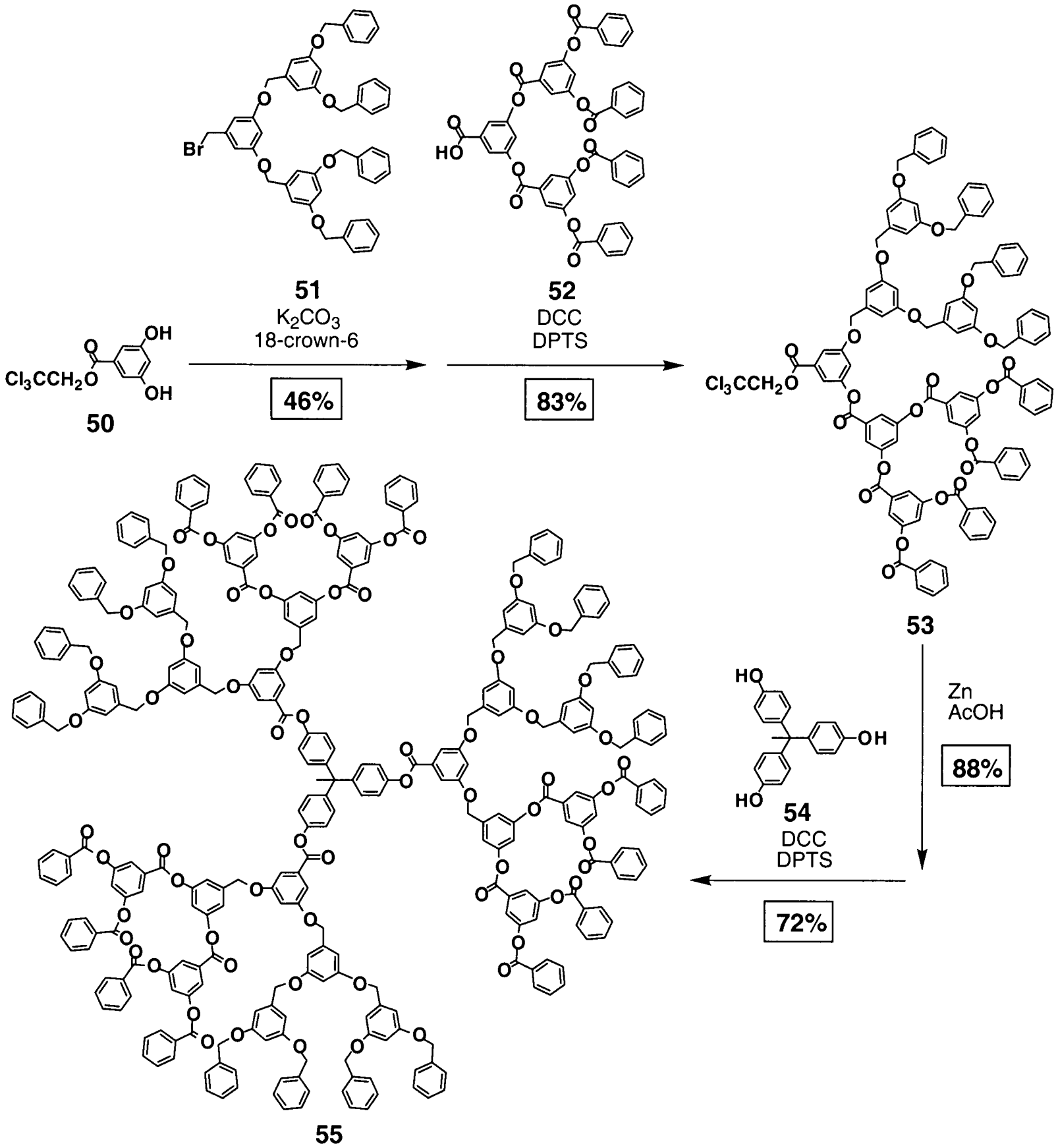
structures by design, methodologies must allow the selective incorporation of functionality at given positions within the dendritic structure.

Fréchet and colleagues have shown (**Scheme 1.4.1**) how the convergent approach can be utilised to control surface[48] and internal[49] functionalities. Reaction of wedge **47** with a large excess of monomer or with a mono-protected monomer generates a half-reacted branching unit **48**. Another wedge is then attached to the other branch in a further step, giving yet another branching unit **49** with different functionalities on each branch.



Scheme 1.4.1

A dendrimer composed of a controlled mixture of ether and ester linkages has been synthesised by Hawker and Fréchet[42] (**Scheme 1.4.2**).



Scheme 1.4.2

The monomer **50** was linked in turn to the convergently grown wedges **51** and **52**. The composite product **53** was deprotected at the focal point and then coupled with the three-directional core **54** to yield the "dendritic segment-block copolymer" **55**. In order to control the construction of dendrimers, one must have a highly developed methodology as well as a variety of compatible building blocks. The lack of compatibility[42] has so far been the biggest stumbling block to the production of a range of "segment-block" and "layer-block" architectures.

Dendritic properties: Potential Applications

As alluded to previously, dendrimers possess unique structural features imparting novel properties not displayed by smaller molecules. From this excitement, many potential applications for dendrimers have been proposed in the many articles and reviews of the scientific literature as well as in the popular press. It is probably apt to review some of the properties of dendrimers that have resulted in – or are most likely to result in – 'real' applications.

Especially at high molecular weight, certain properties of dendrimers deviate from those of linear molecules. The intrinsic viscosity is a physical parameter for which such a deviation has been measured. A characterising feature of dendritic polymers is that past a critical point, the intrinsic viscosity of a polymer solution decreases with increasing molecular weight giving the bell-shaped relationship, (**Figure 1.8**).[50] This is contrary to the behaviour observed for linear polymers. This effect is believed to result from the globular shapes of high generation dendrimers, leaving them unable to "tangle" with one another in the manner of linear polymers.

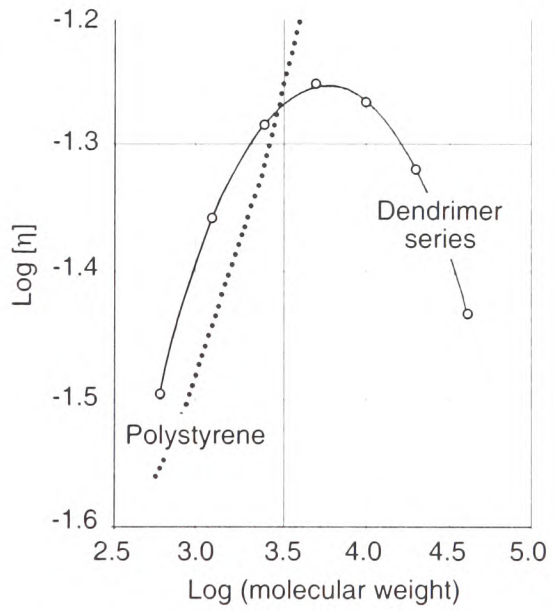


Figure 1.8. A log-log plot of the intrinsic viscosity ([η]) against molecular weight for a dendrimer and polystyrene.[51]

Hyperbranched polymers obtained in a single-step polycondensation of an AB_2 monomer (see earlier) are thought to possess an intermediate structure, somewhere between dendrimers and linear polymers. Considerations of other physical properties have led to similar conclusions.

Additionally, the comparison of solubility between dendrimers and their linear analogues have been carried out by a number of groups.[52] The solubility of a polyether dendrimer in THF was found to be approximately 50 times that of its linear analogue, which indicates that shape has a pronounced effect on solubility. These solubility effects are attributed to the globular architecture displayed by higher order dendrimers. The physical behaviour of dendrimers is different from that of linear polymers, and equally importantly, dendrimers need to have a certain size to display significantly different physical behaviour.

Among the potential uses of dendritic structures are rheology modifiers, adhesives, components for reactive injection moulding, coatings and foams, surface-modifying agents, demulsifiers of oil/water emulsions, electrolytes, lubricants, plasticisers, wet strength agents in the manufacture of paper and agents for modifying the viscosity in aqueous formulations such as paints.[5]

Generally, possible applications of practical interest might include:

◆Water solubilising of hydrophobic molecules

◆Metal ion binders

◆Drug delivery systems

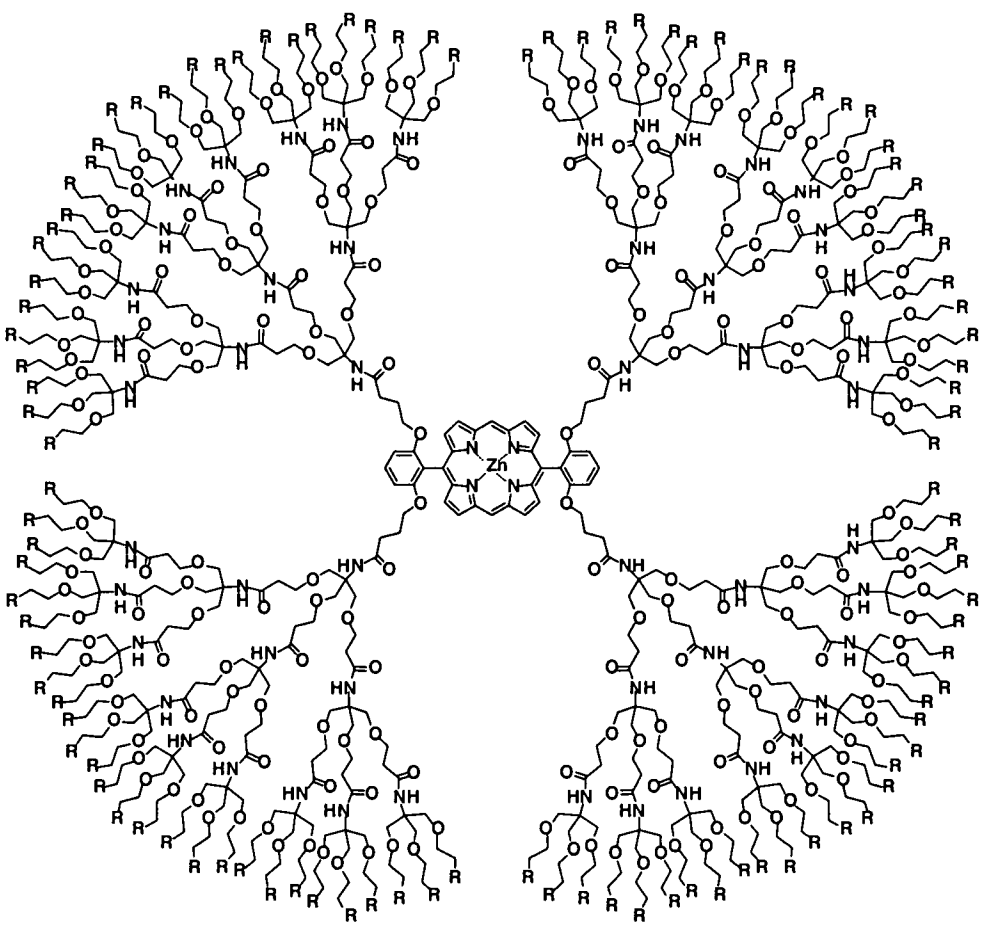
◆Removal of toxic pollutants from the environment

◆Development of effective guest sensors

◆Slow release of cosmetics and agrochemicals.

In the design of an application-based dendrimer, certain moieties are required within the structure. The incorporation of desired functionality into a dendrimer can be achieved with the use of "application-based monomers"[53] or functional cores. There are many examples of dendrimers whose constitutions have been designed with a purpose in mind. Application oriented groups can also be built in as surface groups at the beginning of convergent syntheses or at the end of a divergent one. Such techniques allow control of dendrimer- solvent interactions without changing the nature of the internal regions of the dendrimer.

Figure 1.9 shows a porphyrin core dendrimer, synthesised by Diederich[54] as a model of cytochrome c. Porphyrins are of interest because of their redox and binding properties and their extensive involvement in natural processes.



R = COOMe

Figure 1.9

Due to their 'caged' structures, dendrimers may function as host molecules and encapsulate guest molecules. The reversible host-guest interactions of such molecules has been illustrated by the 'dendritic box'. The various kinds of functional groups within a dendrimer may function as receptors *via endo-* or *exo-* recognition sites. An example of the former would be the preparation of novel encapsulating agents, and an example of the latter would be the attachment of boronic acid groups to the surface of Shinkai and co-workers' sugar-binding dendrimer to facilitate the complexation of a variety of saccharides.[55] These designed receptors enhanced binding of saccharides (when compared to a flexible diboronic or monoboronic acid) is probably attributable to a high local concentration effect. Thus, following the interaction of the sugar with one boronic acid, it may intramolecularly bind to any of the several different boronic acids.

Chiral dendrimers have also been synthesised.[56] The introduction of chiral elements into a dendritic structure should result in the formation of non-symmetrical, non-spherical molecules having a chiral surface and chiral cavities. Again these may function as chiral *exo* or chiral *endo* receptors. Chiral dendrimers are therefore potentially useful materials for chiral recognition and enantioselective binding of guest molecules.

For applications such as chiral chromatography materials, catalysts in asymmetric synthesis or similar, we need to know how the molecular chirality of the dendritic building blocks and the macroscopic chirality of the compound are related to each other.

The idea of dendrimers having applications in catalysis or as biocatalytic mimics has yet to be realised. In order to produce an effective catalyst it is advantageous to have some insight into the binding properties of the active site of the catalyst. Many examples of catalytic dendrimers have taken a known catalytic site and attempted to use dendrimers as an auxiliary for enhancement of rate or selectivity. One example is "dendrizyme" – i.e. diphenylphosphine ligands substituted with chiral- surfaced dendritic wedges – which has been designed to act as an enantioselective transition-metal catalyst, **Figure 1.10**.

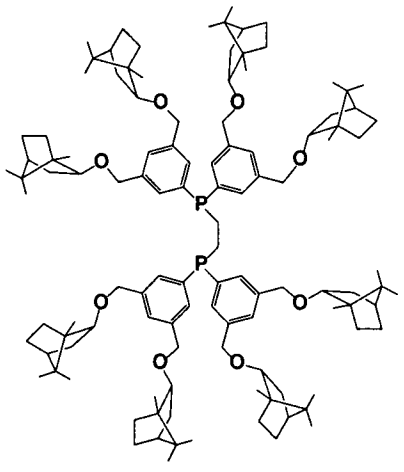


Figure 1.10. An example of a chiral 'dendrizyme' which, as its Rh(I) complex, catalyses the hydrogenation of acetamidocinnamic acid.[57]

It is known that transition-metal-co-ordinated chiral diphenylphosphine ligands function as enantioselective catalysts – in the case of "dendrizyme" the intention of the dendritic substituents was to afford enantio- and size selective catalysts. However, extremely low

enantioselectivities have been reported for several dendrizyme-catalysed reactions, probably reflecting the high flexibility of the dendritic substituents.

Metal complexes (either Zn(II) or Ti(IV) of TADDOL (**Figure 1.11**)) terminated dendrimers have been used as homogeneous, enantioselective catalysts by Seebach *et al.*[58] The observed catalytic activity was similar to the non-dendrimeric parent TADDOLate complex and the catalyst was reclaimed in high yield. Due to the cooperativity effect, it might be expected that dendritic catalysts with multiple catalytic centres may offer superior reactivity than their monomeric analogues, although most often the effectiveness of dendritic catalysts varies according to the intricate interactions amongst the catalytic functionalities, the nature of the environment and the substrate itself.

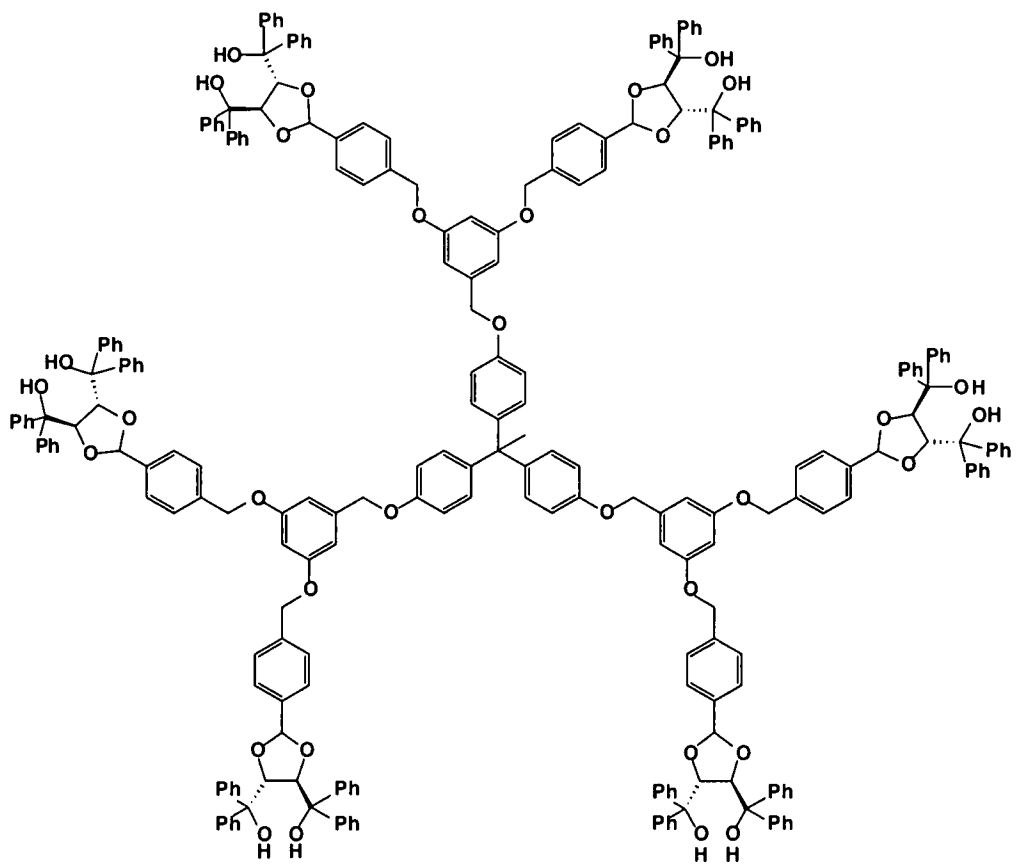


Figure 1.11. TADDOL (α,α,α,′α′ - tetraaryl- 1,3-dioxolane-4,5-dimethanol) terminated dendrimer which forms catalytic Ti (IV) and Zn (II) complexes.

Depending on its functional constituent, a dendrimer may possess electrochemical, photochemical, liquid crystalline, magnetic, and/or plastic properties which could offer a wealth of potential applications. With developments in rapid and efficient syntheses of dendrimers affording large amounts of dendritic macromolecules it is surely only a matter of time for the properties of these novel molecules to be realised in genuine applications.

There is vast potential for dendrimer chemistry to meld with the more mature chemistries. This ease of integration into inorganic and organometallic arenas, for example, has been emphasised in a number of copious, recent reviews.[59] The molecular diversity of such molecules is immense and should lead to compounds with novel and interesting properties and indeed potential applications.

The fractal molecular architecture challenges the creativity and inventiveness of chemists of all branches. The dendrimer architecture offers structural benefits for potential applications not available in other substance classes. However, there is great effort associated with multi-step syntheses leading to structurally perfect macromolecules. Compounds of lower structural perfection can display similar effects and might be of use where exact definition of the structure is not crucial.

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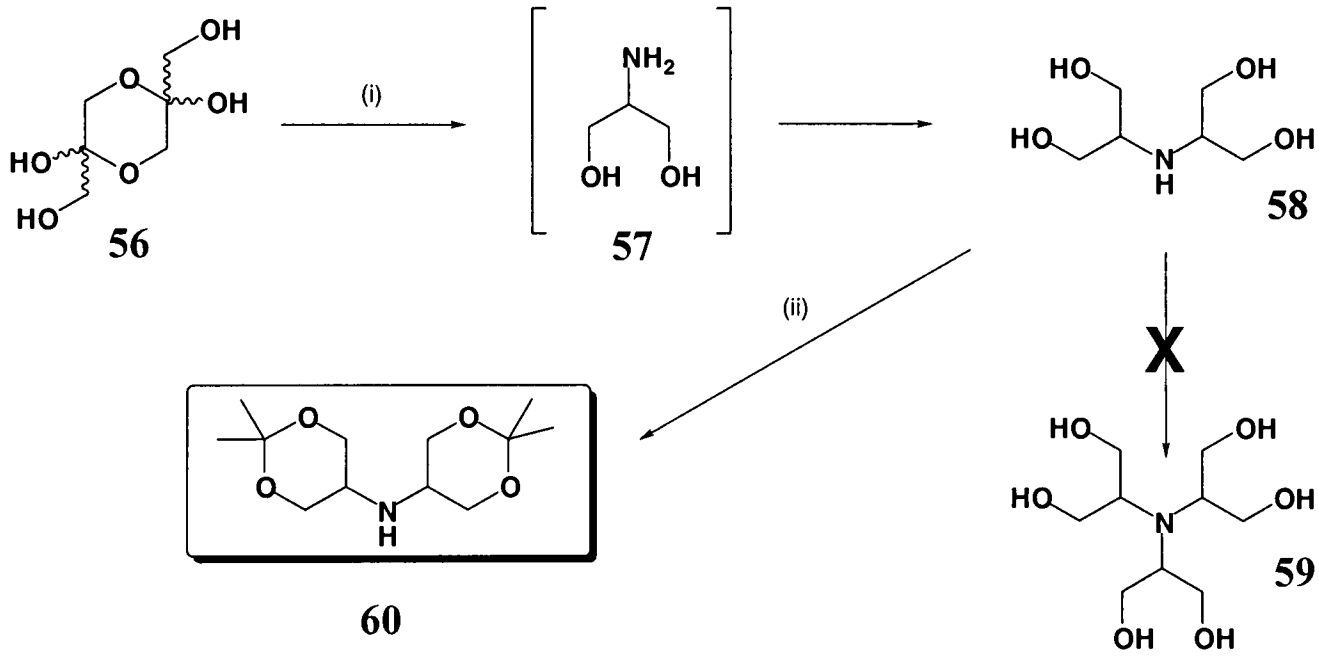
2. Development of a Novel AB_4 Dendritic Unit

2.1 Introduction

The Origin of *bis*(1,3-dihydroxy-*iso*propyl)amine [BDI]: A Biorational Motivation.

In studies directed towards the production of acyclic analogues of naturally occurring and synthetic nitrogen analogues of monosaccharides, an efficient synthesis of *bis*(1,3-dihydroxy-*iso*propyl)amine [BDI] **58**, was developed. The reductive amination of dihydroxyacetone **56** by ammonium salts with sodium cyanoborohydride gives BDI **58**, in good yield (*ca.* 85 – 90%) and high purity (**Scheme 2.1.1**). It was possible to find conditions where two units of dihydroxyacetone are condensed to afford BDI as the exclusive product. A study into the rather surprising product distribution and optimisation of this reaction is presented, together with some initial chemistry of this novel polyhydroxylated amine.



Reagents and Conditions: (i) NH_4Cl, $NaCNBH_3$, MeOH, AcOH, (ii) Acetone, 2,2-dimethoxypropane, DMF, c. H_2SO_4.

Scheme 2.1.1

All the alcohol functions in BDI **58** were protected as the diacetonide **60** by treatment with acetone and dimethoxypropane in DMF in the presence of an acid catalyst. Thus **60** provides a suitable derivative of BDI for elaboration of the nitrogen e.g. by nucleophilic attack by the amine function. No trimeric product **59** has been evidenced.

BDI is an open chain equivalent of DMDP [2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine], **62**, which mimics β-D-Fructose in the furanose configuration. Deoxynojirimycin (DNJ) **61(a)** (mimics glucose in the pyranose configuration) and DMDP **62** are naturally occurring, nitrogen analogues of monosaccharides with a range of biological activities, the best known of which is their specific inhibition of glycosidases (see chapter 5 for an account of such inhibition).[1] DMDP is a five-membered polyhydroxylated pyrrolidine with four contiguous chiral centres and resembles sugars in the furanose configuration.

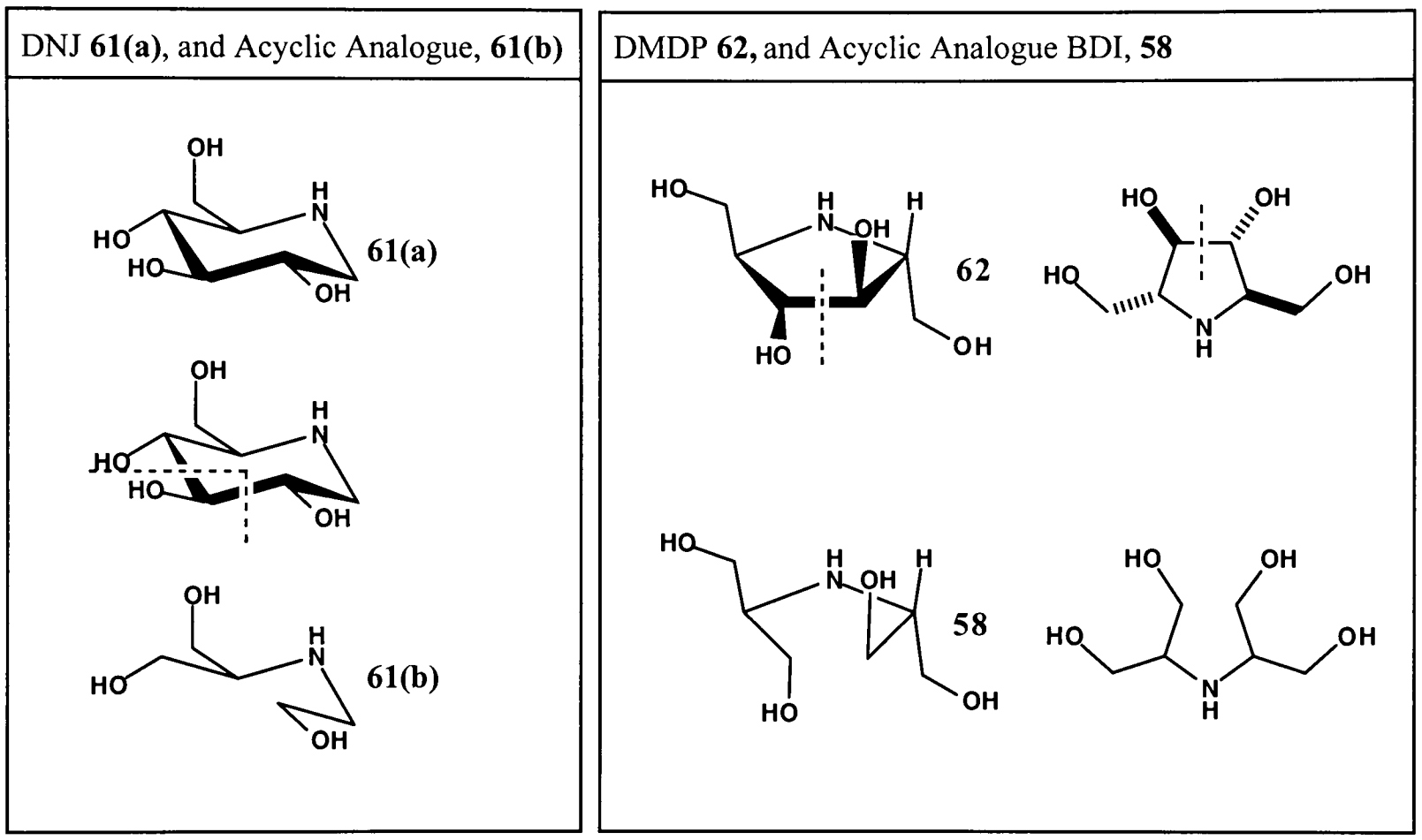


Figure 2.1. DNJ and DMDP together with their acyclic analogues.

It has been demonstrated that *N*-Alkylation of these amines changes their biological activities and the more lipophilic *N*-butyl derivatives show antiviral properties,[2] probably by modification of *N*-linked glycoprotein processing by the inhibition of glucosidases. Furthermore, such modifications may increase lipid solubility, and thus intracellular bioavailability. Enzymes other than hydrolases are also affected. *N*-Butyl DNJ and *N*-butyl DMDP have been shown to inhibit UDP-glucose-ceramide transferase,[3] a key enzyme involved in the biosynthesis of glycosphingolipids; inhibition of this biosynthetic pathway may provide a strategy for the treatment of a number of genetic storage diseases, including Tay-Sachs and Gauchers diseases.[4]

In the search for a compound which is specific for the UDP-Glu-ceramide transferase, a large number of *N*-alkylated analogues of various azafuranose and azapyranose sugars have been evaluated. The structure activity relationship of such materials is not easy to rationalise; inhibition of UDP-glucose-ceramide transferase is not dependent on UDP-glucose concentration, so it appears that the inhibitors mimic ceramide rather than the sugar.[5]

With this in mind, there was a focus to synthesise an easily obtainable analogue of the sugar moiety. There are 10 stereoisomers of DMDP **62**, but conceptual hydrogenolytic cleavage of the C3-C4 bond would give rise to BDI **58** with no stereogenic centres. Some less symmetrical truncated acyclic analogues of DNJ have been shown to be moderate inhibitors of glucosidases.[6,7] Some of the biological activity of the parent cyclic systems might be retained in the simpler compounds by mimicking smaller structural units present in these parent systems. Haines *et al.*[6] found this to be true of the 2-hydroxyethylamino propane 1,3-diol **61(b)**.

The structural representation of the acyclic analogue **61(b)** is drawn in such a way so as to emphasize its structural analogy with DNJ. The triol **61(b)**, was prepared by Haines *et al.* as its hydrochloride by reaction of commercially available serinol **57**, with 1-bromo-2-trityloxyethane, and the resulting ether was then subjected to de-*O*-tritylation through treatment with methanol containing a molar equivalent of hydrochloric acid.

The polyhydroxylated amine **61(b)**, has been made by other routes. In the search for anticancer agents, Williamson *et al.*[8] have synthesised amine **61(b)** by reacting together serinol and oxirane, in aqueous solution. More recently, Ashry *et al.*[5] have synthesised amine **61(b)** in three steps from 1,3-di-*O*-benzylglycerol. Using the reductive amination technology described above in the synthesis of BDI, the polyhydroxylated amine **61(b)** was made in one step from ethanolamine and excess dihydroxyacetone and isolated in 63% yield using ion-exchange chromatography. Again no trimeric products corresponding to a condensation of the secondary amine **61(b)** with a second unit of dihydroxyacetone were isolated and the polyhydroxylated amine **61(b)**, was the only isolable product.

N-Butyl BDI **94** was prepared by a reductive amination (**Scheme 2.1.1**) in the hope that it might, as a potential ceramide analogue, inhibit UDP-Glu-ceramide transferase significantly. The open chain DMDP analogues **58** and **94** were tested at a concentration of 1 mM against a number of glycosidases but there was no significant inhibition of any hydrolase.[9] *N*-Butyl BDI **94** was also assayed for potential inhibition of UDP-glucosyl ceramide transferase but again no effect on the enzyme was observed.[10] Derivatives of BDI are therefore not likely to be of interest as specific enzyme inhibitors, possibly on entropic grounds given that there will be conformational requirements for the flexible BDI to bind in the active site.

Another motivation for the development of the reductive amination technology was to chemically modify imino-sugars. Imino sugars are a general family of glycosidase inhibitors and inhibitors of other enzymes involving the processing of sugars.[11] Thus, new classes of imino-sugars could be made which might inhibit sugar-processing enzymes and offer therapy for a number of conditions. Examples of these putative novel modified analogues are shown (**Figure 2.2**); **64** (glucose), **65** (fucose), **66** (mannose), together with Miglitol **63,** which is marketed by Bayer Company as a chemotherapeutic agent for the treatment of diabetes.* However, as yet no secondary amines have undergone reductive amination with dihydroxyacetone using this reductive amination technology to afford the ensuing tertiary amines.

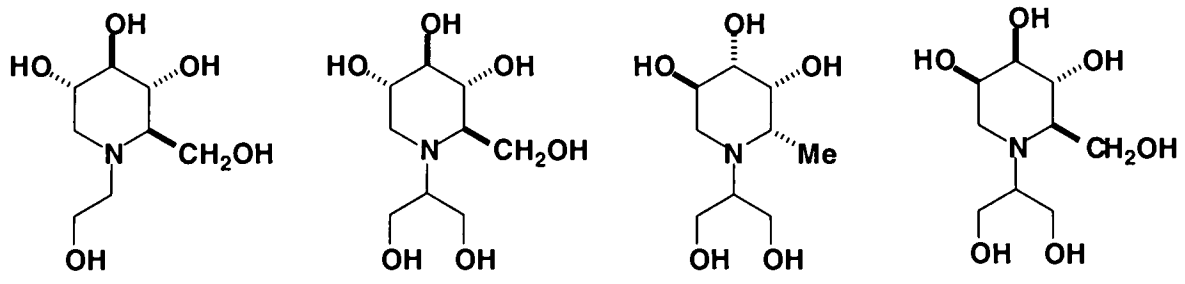


Figure 2.2. Some modified imino-sugars.

The successful protection chemistry and facile *N*-alkylation chemistry of BDI incited further consideration and investigation of this highly branched and functionalised material.

* Miglitol (BAY m1099)

Potential as a Dendritic AB_4 monomer

Although neither the polyhydroxlated amine BDI, nor its *N*-alkyl derivatives displayed any activity as glycosidase inhibitors it did seem to be a winsome and prepossessing molecule. There has been some work on the syntheses and the evaluations of the biological activities of a number of carbohydrate containing dendritic molecules - *'glycodendrimers'* by Roy,[12] Stoddart,[13] and Lindhorst.[14]

These non-carbohydrate dendritic arrays with sugars on the periphery exhibit the concept of the multivalent or cluster effect in their properties.[15] The synthesis of several saccharide residues attached at the periphery of preformed PAMAM dendritic cores has been reported by Aoi *et al.*[16] These fully sugar-persubstituted dendrimers - called 'sugar balls' - demonstrate increased binding affinity with certain proteins when compared with the individual monomeric sugar unit. This massively improved co-operative binding and consequent increased activity can be attributed to the 'cluster effect'.

Such work provided the impetus to conceptualise spherically symmetrical macromolecules incorporating BDI on the periphery for multipresentation to the active site of various glycosidases. Of course this idea pre-dated the discovery that BDI did not show glycosidase activity, but it did point to the production of esthetical molecules with high symmetry.

Thus the somewhat biorationally motivated but worthy discovery of the one-step synthesis of this symmetrical, highly branched, bifunctional molecule might be consequential in the arena of dendrimer construction. BDI is thus doubly significant as it can be considered as an AB_n monomer i.e. a bifunctional dendritic building block. Such AB_n compounds, where n represents the degree of branching are used as dendritic building blocks and for nearly all reported dendritic compounds, n = 2 or 3. BDI **58** is a very rare example of an AB_4 monomer (**Figure 2.3**) - this multiplicity has only been achieved previously by moieties based on heteroatoms.[17]

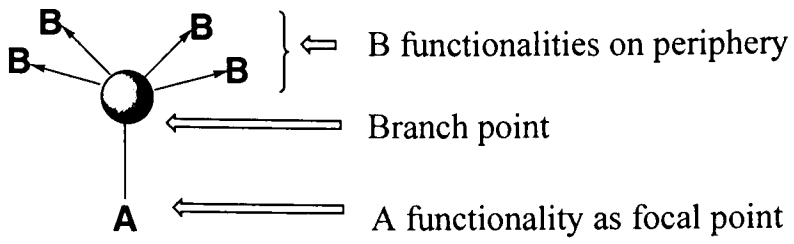
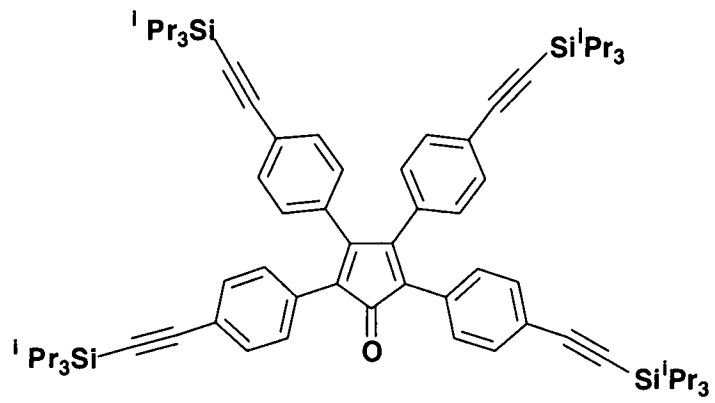


Figure 2.3. A generic AB_4 dendritic monomer.

There are other instances of such a highly branched monomer in the literature but these are rather more cumbersome and less densely dendritic structures. An example is the cyclopentadione derivative **67**, which has a tetravalent branch juncture.[18] By invoking Diels-Alder chemistry, the AB_4 building block **67**, undergoes [2+4] cycloadditions with 3,3′,5,5′-tetraethynylbiphenyl allowing for the rapid synthesis of a spherical polyphenylene dendrimer with 102 benzene rings.



67

Additionally, Fréchet *et al.* have reported on AB_2, AB_4, and AB_6 monomers in the preparation of hyperbranched poly(siloxysilanes).[19] Stefanescu and Wooley have reported on hyperbranched polyfluorinated polymers from AB_4 monomers with a single benzylic alcohol at the focal point and four pentafluorophenyl groups at the chain ends.[20] The polymerisation involves deprotonation of the hydroxyl group followed by nucleophilic displacement of the *para*-fluorine atoms resulting in polyethers.

BDI may provide the opportunity for the development of very highly branched structures with a large array of primary hydroxyl groups. In addition, the high branching multiplicity *per* dendritic monomer will translate to a large number of chain ends *per* macromolecule. Such a macromolecule will have more surface functionality and will tend to a more globular topology for a given generation when compared to their n = 2,3 counterparts.

2.2 Results and Discussion

Reductive Amination of Dihydroxyacetone: Investigation of Product Distribution

The pivotal molecule for our work in the field of dendrimer construction was BDI **58**, which may be efficiently prepared by the simple reductive amination of ammonium salts and dihydroxyacetone by sodium cyanoborohydride. No such reductive amination products were apparent using an ammonium salt and dihydroxyacetone under catalytic hydrogenation conditions.

However, it seems fortuitous that with the plethora of possible reductive amination products the only basic product is BDI when the dihydroxyacetone is in excess. The BDI is readily obtained in a pure form by ion exchange chromatography in 85-90% yields based on the ammonium salt, potentially on a large scale. Other products such as the amine produced by one condensation with dihydroxyacetone **57** and the amine produced by the condensation of three dihydroxyacetone units **59** are either excluded or avoided. No basic products were isolated which correspond to the mono, di or tri- condensation of the isomer of dihydroxyacetone, glyceraldehyde, with the ammonium salt. The Lobry de Bruyn-Alberda van Eckestein rearrangement, which interconverts dihydroxyacetone and glyceraldehyde, seems to be avoided. The slightly basic conditions needed for such an isomerisation are present for some time before the addition of acetic acid.

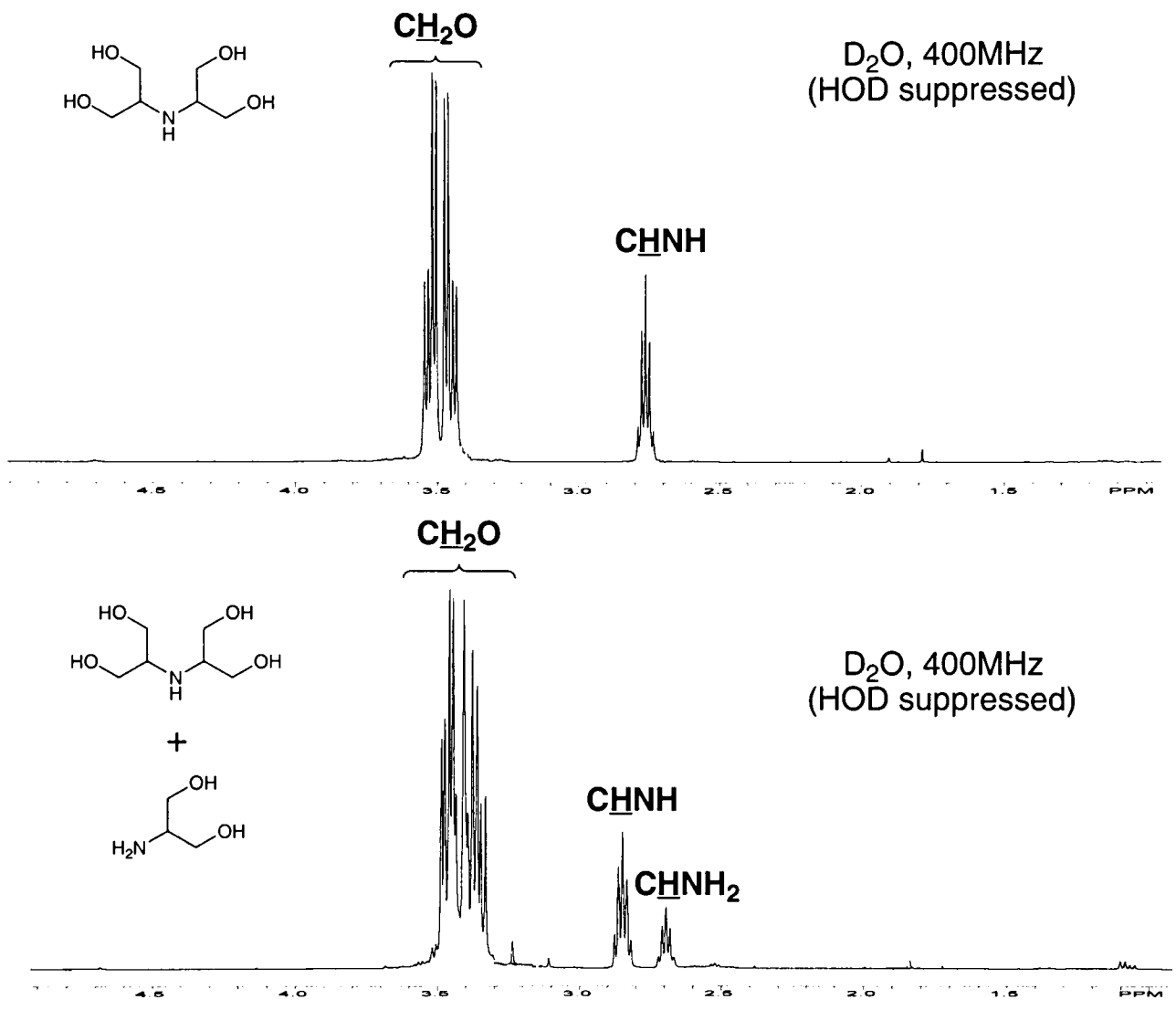
In an effort to clarify this, some attention was given to the optimisation of the procedure and the synthesis of expected reductive amination products by unambiguous pathways. From such work it is evident that the reductive amination takes place sequentially, but there is a greater predisposition for the first product **57** to undergo a second reductive amination step than for its initial formation.

In an attempt to synthesise the monomeric reductive amination product **57** (**Scheme 2.1.1, p38**) six equivalents of ammonium ions to one equivalent of dihydroxyacetone **56** were reacted

with sodium cyanoborohydride under standard conditions. The ratio of BDI **58** to serinol **57** thus formed was approximately 1.8 to 1 as judged by ^{1}H NMR. The monomeric reductive amination product **57** is distinct from BDI **58** in its ^{1}H NMR (**Figure 2.4**). This is compelling evidence to show the greater propensity of BDI formation, even in conditions where one might expect the monomeric product **57** to be more abundant. GCMS analysis of the trimethylsilyl derivatives of mixtures of serinol **57** and BDI **58** allowed quantitative analysis of the proportions of the two products formed in these reductions.[21] No trace of **57** was found when dihydroxyacetone **56** was used in a two-fold molar excess to the ammonium salt. No conditions have yet been found which result in a third reductive amination, potentially to give **59**; no trace of this trimeric product was detected by GCMS or otherwise.

Serinol has been synthesised from dihydroxyacetone in high yield using reductive amination strategies. Hiroshi has prepared serinol by the reductive amination of dihydroxyacetone with aqueous ammonia in the presence of supported catalysts containing rhodium on carbon with heating at elevated temperature and pressure to afford serinol, in 91% yield.[22] Another process, developed and patented by Merck, involves similar chemistry: catalytic hydrogenation using Raney nickel at elevated temperature and pressure afforded serinol in 99% when the ammonia was in a six fold excess compared to the dihydroxyacetone. The stoichiometry is comparable to the experiment described above which was thought to favour serinol **57**. However the product distribution is not comparable. Using the sodium cyanoborohydride reductive amination conditions, BDI is still the major product whereas the Merck patent reports serinol as the exclusive product.

The reductive amination experiments afforded a distribution of polyhydroxylated amine products which were analysed by GCMS and ^{1}H NMR. The proton spectra are shown (**Figure 2.4**).



Conditions: Dihydroxyacetone, NH_4Cl, $NaCNBH_3$, MeOH, AcOH

Stoichiometry:		Stoichiometry:	
NH4Cl	1eq.	NH4Cl	6eq.
Dihydroxyacetone	3eq.	Dihydroxyacetone	1eq.
Product: 100% dimer One compound by GCMS		Product: 64% dimer, 36% monomer. (as estimated by 1 H nmr.) Two compounds by GCMS.	

Figure 2.4. HOD suppressed ^{1}H NMR of BDI **58** (upper plot), and a mixture of BDI **58** together with serinol **57** (lower plot).

The proton NMR was performed in D_2O and shows two sets of roofed double doublets which are close on the δ_H scale. These correspond to the protons on the methylene carbons and are not as simple as might expect for such a symmetrical molecule. The two sets of protons are diastereotopic (**Figure 2.5**) and are always in different environments no matter how fast the bond rotation is – they never interchange environments.

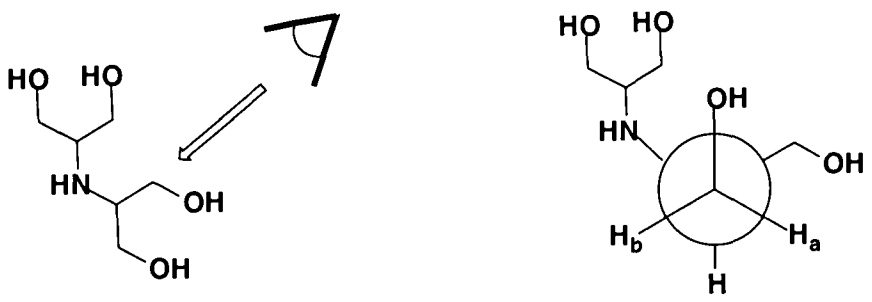


Figure 2.5. Newman projection showing that H_a and H_b are diastereotopic.

The non-equivalence within the methylene pair is also evident in the non-chiral molecule serinol **57** which analogously has diastereotopic protons giving rise to a similar spectrum.

On acetonation of the BDI unit the proton NMR is much the same in that there are the two sets of double doublets from the methylene protons but in this case it is because they are in axial and equatorial environments on the dioxane ring (**Figure 2.6**).

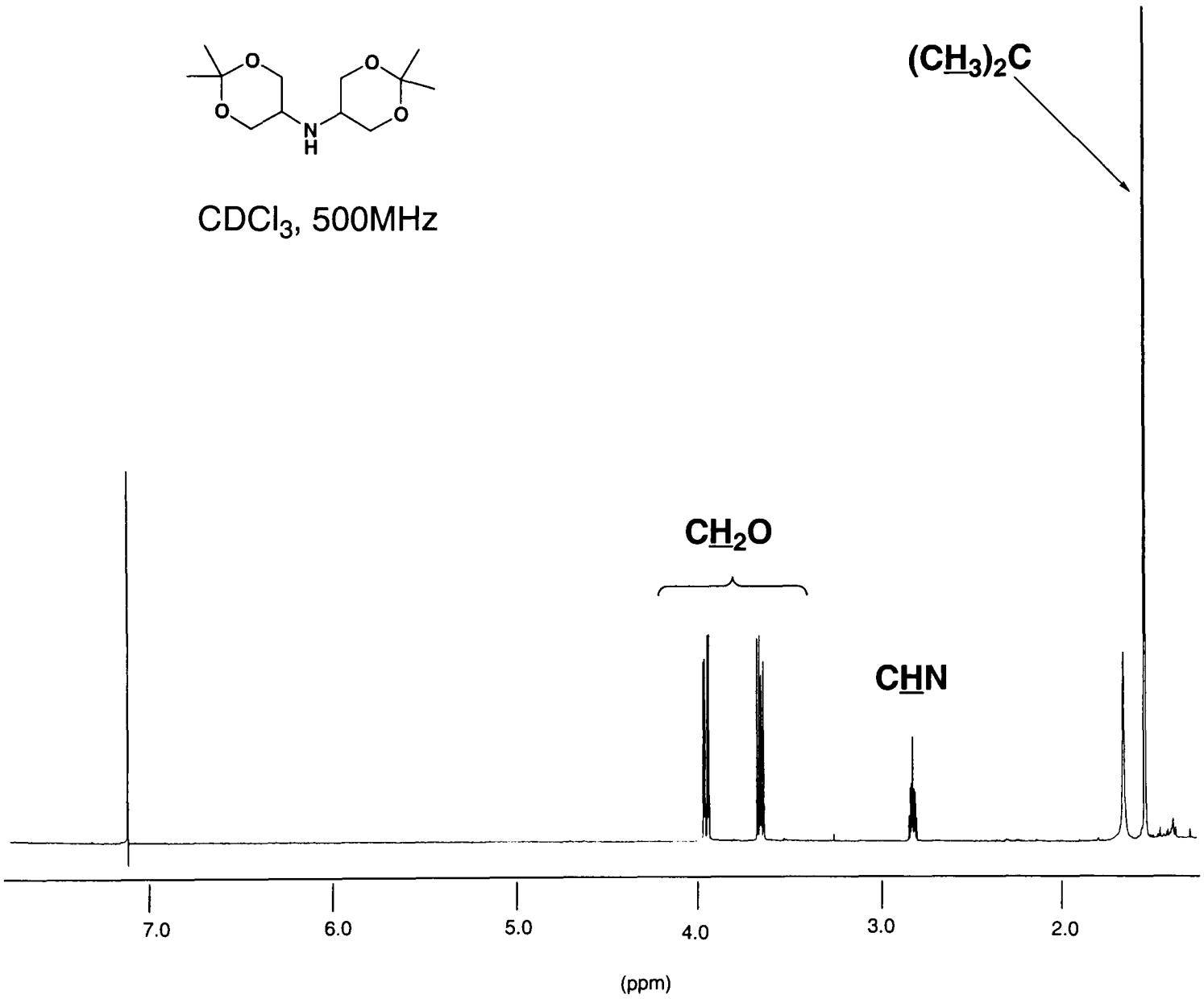


Figure 2.6. ^{1}H NMR of diisopropylidene derivative of BDI, **60**.

Towards a Trimeric Polyhydroxylated Amine

There is a great utility in the reaction of dihydroxyacetone and ammonium salts using the sodium cyanoborohydride reductive amination technology to produce the non-vitiated BDI product in good yield. However, a trimeric polyhydroxylated amine would be quite desirable as a three directional core could be elaborated into a three fold symmetric dendritic structure of the type shown (**Figure 2.7**). Some attempts to synthesise the trimeric polyhydroxylated amine **59** or its protected equivalent **81** are presented.

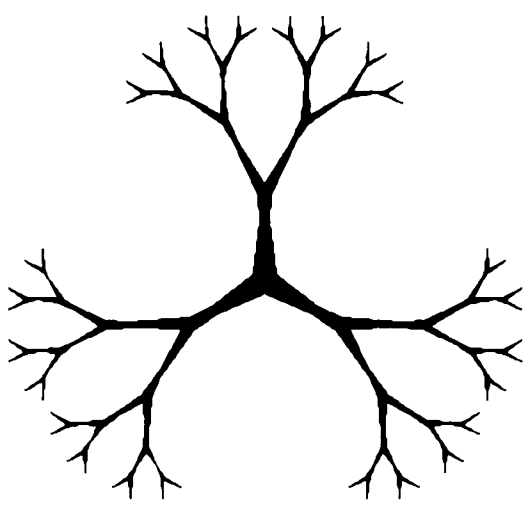


Figure 2.7. A schematic three fold symmetric dendritic structure.

The preferred approach to the synthesis of triisopropylamines involves addition to iminium intermediates, with yields generally around 40%.[23] This method avoids elimination reactions but makes it difficult to control the stereochemistry of the new stereogenic centre in the case of homochiral C_3 triisopropylamines. Alkylation of α-halo esters is generally an efficient process because the π system facilitates S_N2 attack. Effenberger has demonstrated α-halo esters to be inferior to the corresponding triflates in additions to amines.[24] An extension of his synthesis[25] of dialkylamines to trialkylamines could not be applied here as no precursor to the suitably functionalised triflate could be found. Instead a displacement of the triflate **80**, derived from the dihydroxyacetone equivalent **70** was attempted (**Scheme 2.2.1**).

In order to effect elaboration of the nitrogen in BDI **58**, its diacetonide derivative **60**, (with masked hydroxyl groups), was used in much of the chemistry directed towards a trimeric isopropylamine. Additionally, the high polarity of BDI, and its poor solubility in organic

solvents, limited its use to reactions that did not require protection of the hydroxyl groups such as the reductive aminations which can be performed on unprotected BDI. Difficulties in the monitoring of reactions by t.l.c. and the subsequent purification of derivatives and separation from non-derivatised counterparts by flash column chromatography arise. Ion exchange chromatography is not suitable if acid labile groups are present, and in any case the derivatives cannot be separated from any unreacted BDI by these means.

Likewise, a masked analogue of dihydroxyacetone was used – the acetonide, **70**, which could also serve as a precursor for the triflate, **80**. The retrosynthesis of **70** is considered (**Figure 2.8**).

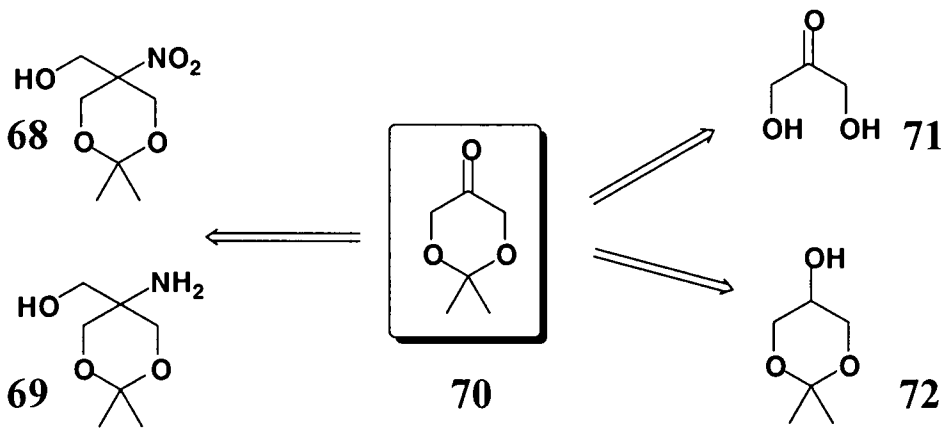


Figure 2.8. Retrosynthesis of dihydroxyacetone equivalent, **70**.

The acetonide, **70** is not simply prepared by the reaction of acetone under acidic conditions with commercially available dihydroxyacetone dimer **56** which produces compounds such as **74**, **75** (major), and **76**,[26] nor by the acetonation of glycerol **71** (**Figure 2.9**) followed by oxidation of the alcohol at C-2 in **72**.

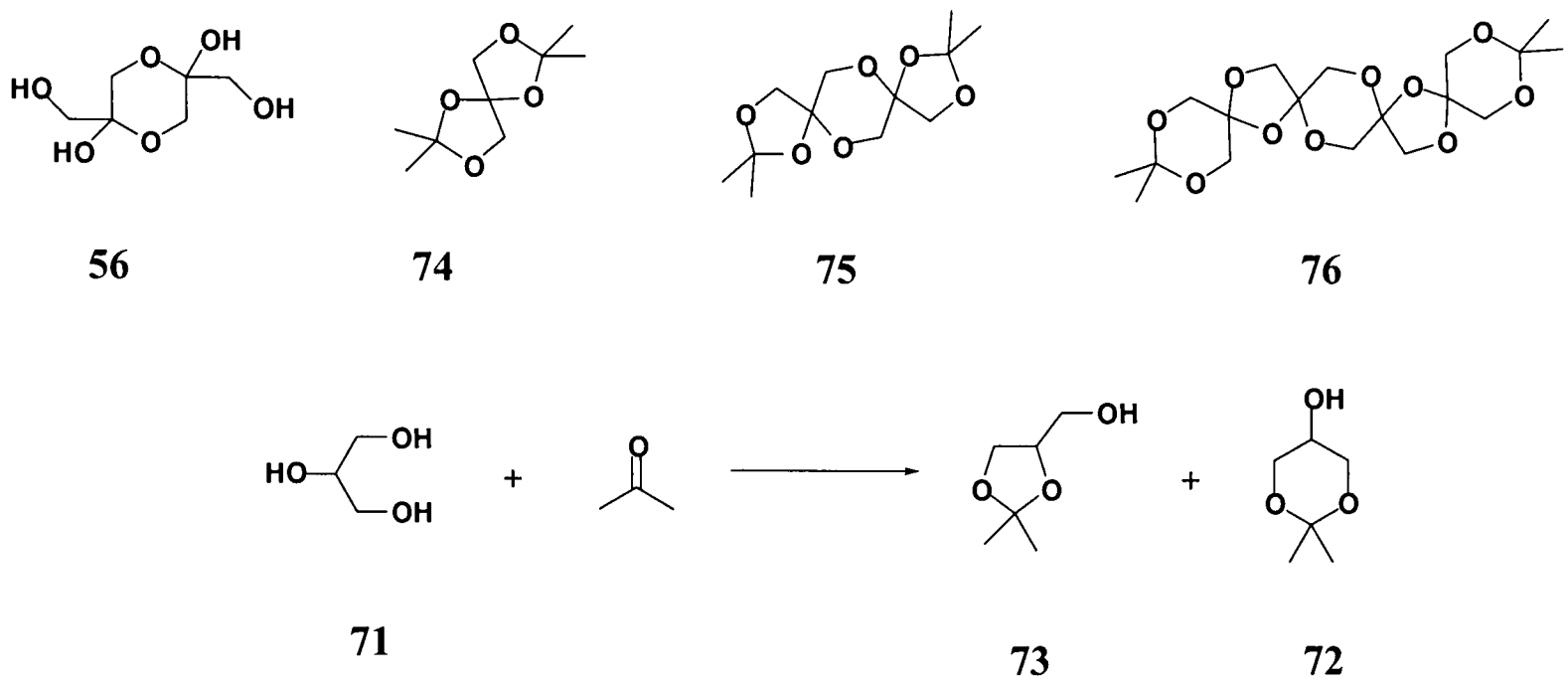
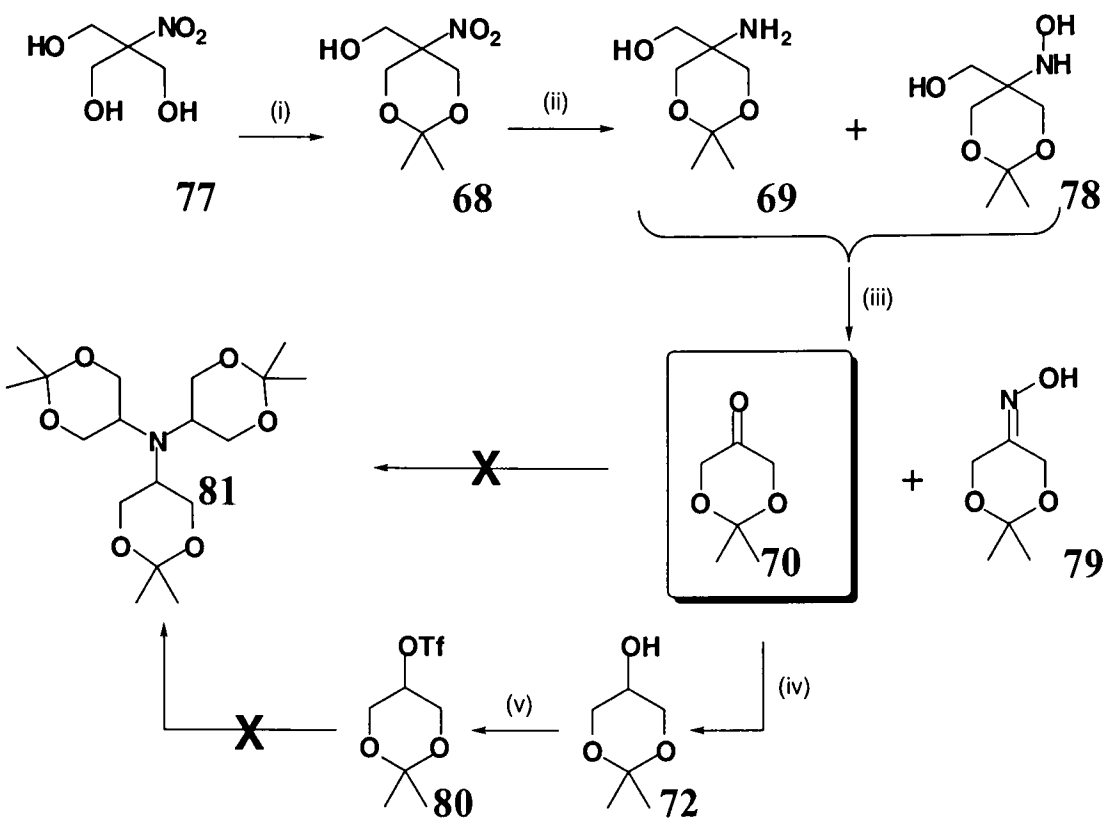


Figure 2.9. Possible products from the acetonation of dihydroxyacetone **56** and glycerol **71**.

The acetalization of glycerol affords the 1,2 dioxolane product **73** virtually exclusively.[27] In the acetalization an equilibrium is established and the composition of the product mixture is determined by the relative free energies of the various cyclic acetals that can be formed.[28] The 1,2 dioxolane product is preferred as the five membered ring is stabilised by a small *gem*-dimethyl effect that allows greater puckering of the ring, thereby reducing the torsional strain. In contrast the high non-bonded interactions associated with an axial alkyl group on C-2 of a 1,3-dioxane ring explains the reluctance of polyhydric alcohols to yield six-membered cyclic ketals.

The 5-hydroxy-1,3-dioxanes such as **72** are produced in low yield but require labour-intensive separation schemes for their isolation[29]. Even with recently reported transacetalization /recrystallisation[30] and chemoselective derivatisation methodologies[31], low isolated product yields result. The dihydroxyacetone equivalent **70** is also commercially available.[32]

Recognising the general limitations of producing the dihydroxyacetone equivalent, **70**, from glycerol or dihydroxyacetone itself, the commercially available nitro compound **77** was selected as the starting material (**Scheme 2.2.1**).Acetonation of trihydroxymethylnitromethane **77** under standard conditions followed by reduction of the nitro group and oxidative cleavage of the amino alcohol should afford the ketone **70**, (**Scheme 2.2.1**).



Reagents and Conditions: (i) Acetone, $CuSO_4$, c. H_2SO_4, (ii) HCO_2NH_4, 10% Pd/C, MeOH, (iii) $NaIO_4$, MeOH/H_2O (1:1), (iv) $NaBH_4$, MeOH, (v)Tf_2O, py, DCM.

Scheme 2.2.1

Although starting from the nitro compound **77** is one extra step than starting from the TRIS compound with a primary amine (commercially available as the hydrochloride), it is reported to be better for the incorporation of sterically demanding residues. It would be desirable to incorporate benzaldehyde protected subunits onto BDI to afford differentially protected sectors (**Figure 2.10**). Functionalisation of these dendron sectors sequentially can give rise to non-symmetrical dendrimers.

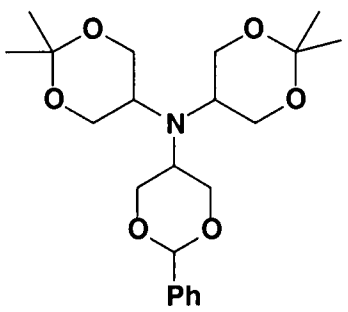


Figure 2.10. Differentially protected trimeric amine.

Reduction of the nitro group in **68** by hydrogenation has been effected by Majewski *et al.*[25] at high pressure (1400psi) and at an elevated temperature (85°C) using Raney nickel. This facility was not available and so alternative methods to effect this reduction were sought. Other attempts to reduce the nitro group in **68** included catalytic hydrogenation with palladium black,

Adam's catalyst in a variety of solvents and transfer hydrogenation with palladium black and cyclohexadiene in refluxing ethyl acetate, but these all failed. Although catalytic hydrogenations usually require longer times than chemical reductions, no product formation was observed even after reacting for several days and the starting material was recovered in all cases.

However, catalytic transfer hydrogenation using ammonium formate (HCO_2NH_4) as the hydrogen source in place of cyclohexadiene, and 10% palladium on carbon as the catalyst worked well. There is literature precedent for such transformations and generally all reductions of alkyl nitro compounds proceed readily to afford the amine.[33] The reaction was performed in methanol at room temperature and was complete after 30 minutes even on multigram scales. The reaction was monitored by t.l.c. analysis and mass spectroscopy and yields a complex mixture thought to comprise hydroxylamine **78**, and primary amine **69**, and was not amenable to separation. This mixture was subjected to oxidative cleavage using sodium metaperiodate in methanol/water to afford a mixture of the oxime **79** (27%), and the ketone **70** (19%). Both these products are useful for further studies but a more efficient procedure for the preparation of the ketone **70**, with the sterically undemanding diacetonide protecting group, would be to start from TRIS **69**[34] and subject solely the amine to oxidative cleavage.

It has been reported that certain appropriately substituted nitro compounds do not give amines under the transfer hydrogenation conditions. Examples include α,β-unsaturated nitroalkenes which give oximes, [35] γ-nitro ketones which give cyclic nitrones,[36] and 2-nitro-β-nitrostyrenes which give indoles.[37] The oxime product is further evidence for the existence of the hydroxylamine in the previous step from which it must be derived. In any case the route generated the dihydroxyacetone equivalent and allowed for the exclusive formation of the dioxane and not the dioxalane ring system.

All attempts to form the trimeric amine **81**, using the ketone **70** and the protected BDI **60** under reductive amination conditions were unsuccessful. Sodium triacetoxyborohydride was tried as the reducing agent and catalytic hydrogenation conditions using 10% palladium on charcoal were

also tried. A similar reaction is reported in the literature where an attempted reductive amination of cycloheptanone with diisopropylamine undergoes no reaction even after 4 days.[52]

The ketone **70** was reduced using sodium borohydride and the resulting alcohol **72** was subsequently esterified with trifluoromethanesulfonic anhydride to form the unstable triflate **80.** The triflate **80** was not isolated but reacted in situ with the protected BDI **60** in DMF.[38] None of the anticipated product derived from the S_N2 displacement was apparent.

The trimeric amine **81** has been elusive probably as a consequence of its sterically encumbered focal point coupled with the deactivated carbonyl group in **70** (due to the β oxygens). Iminium ion formation with the ketone **70**, or S_N2 displacement at the secondary triflate in **80** does not proceed. The attempted reductive amination of cycloheptanone and diisopropylamine using sodium triacetoxyborohydride did not undergo any reaction even after 4 days.[52] Indeed triisopropylamine derivatives are difficult to make by any route due to the steric congestion around the central nitrogen atom. The nitrogen atom of triisopropylamine itself is so hindered that it adopts a ground state geometry that is close to planar.[39] Chiral C_3 triisopropylamines with substituents α to the central nitrogen are rare and to date the only type reported has been the *N,N,N*,-tris-aminal derivative (**Figure 2.11(c)**),[40] and the homochiral triethanolamine derivative, (**Figure 2.11(b)**), prepared by the displacement of an activated triflate by a diamine.[41]

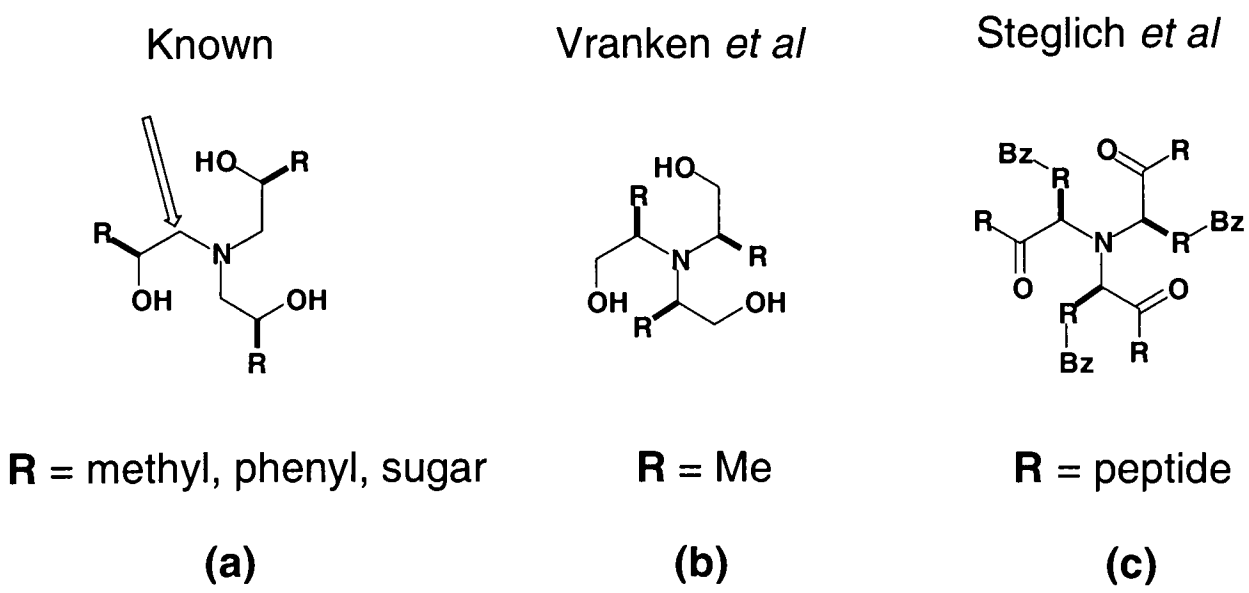
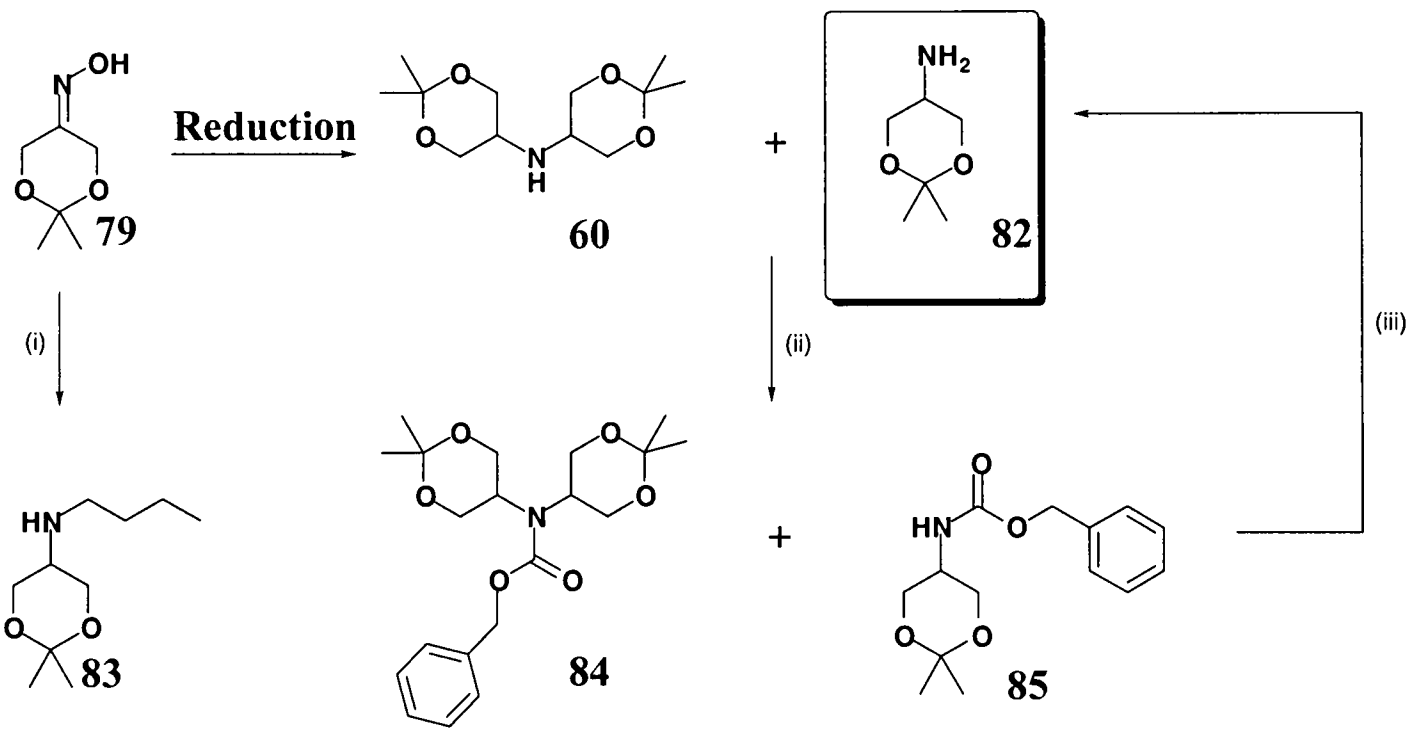


Figure 2.11. Homochiral C_3 trialkylamine derivatives.

Further Reductive Amination Attempts and the Synthesis of Acetonated Monomer

Another target in the study of these novel amines was the unambiguous synthesis of the protected amine **82** (**Scheme 2.2.2**). Initially it was thought that this could simply be obtained by the reduction of the oxime, **79**. Catalytic hydrogenation of this oxime using 10% palladium on carbon in methanol afforded the dimeric amine **60** and no starting oxime **79** as judged by proton NMR of the crude product mixture. Filtering this crude mixture through Celite and eluting with methanol afforded the pure dimeric amine **60** in 59% yield. The oxime **79** might thus provide a preferred route to the protected unit **60**. Alternatively, reductive amination of the dihydroxyacetone equivalent **70** with ammonium salts under non-acidic conditions might lead to the protected dimer **60** directly.



Reagents and Conditions: (i) $^{n}BuNH_2$, H_2/Pd black, MeOH, (ii) $PhCH_2OCOCl$, aq. $NaHCO_3$, ether (iii) H_2/Pd black, EtOAc.

Scheme 2.2.2

It was thought that the oxime **79** was being reduced to the monomeric amine **82** and that the ensuing primary amine is then reacting with the highly polarised double bond of further oxime to form the dimer **60** as a competing reaction. The demonstration of the feasibility of such a transformation was carried out. Treatment of the oxime **79** and excess ^{n}butylamine in methanol with palladium black under a positive pressure of hydrogen afforded the monoalkylated product **83** in 40% yield after flash column chromatography. Mass spectrometry and t.l.c. analysis of

the reaction leading to the formation of amine **83** showed a concomitant reduction of the oxime to the monomer and a trace of dimer being formed. Although these techniques revealed the trace products they were not isolated. Reductive amination of the ketone **70** under the same conditions afforded the identical monoalkylated product **83** in 70% yield after flash column chromatography. The amine **83** could not be further reductively alkylated under these conditions to give the tertiary amine **93**. No reduction of the oxime **79**, or reductive alkylation of the oxime **79**, could be effected using sodium triacetoxyborohydride as the reducing agent.

Treatment of the oxime **79** with a ten-fold excess of ammonium formate allowed reduction to the monomer **82**, with less dimer formation. The product ratio was greatly enriched in favour of the monomer as evidenced by proton NMR. The monomeric amine was difficult to separate from the dimer by flash column chromatography - no solvent system was found which could elute the monomeric product off the baseline. However, the isolation and/or crystallisation of amines is often facilitated by benzyloxycarbonyl derivatisation of the crude amine generated in another reaction.[42]

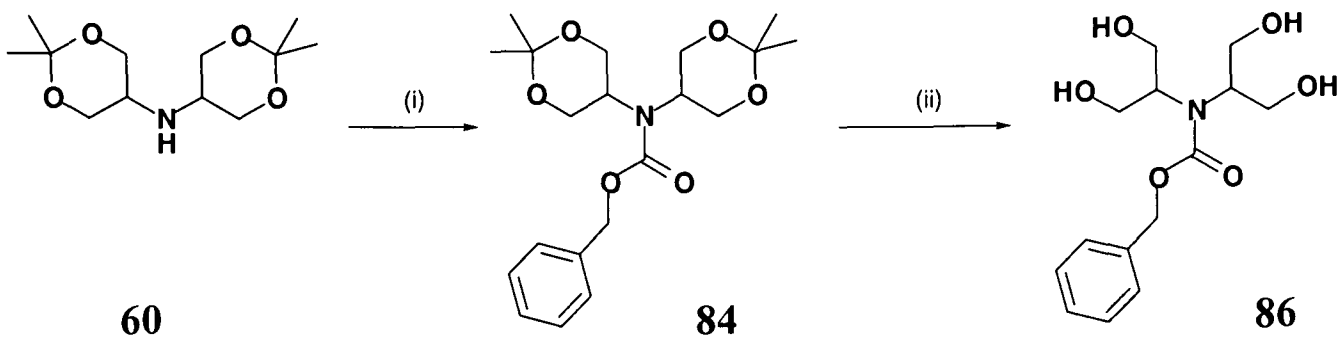
Benzyloxycarbonyl derivatisation of the mixture of amines **82** and **60** produced from the ammonium formate reaction was effected using benzyl chloroformate dichloromethane in the presence of triethylamine.[43] These conditions were found to be superior to the Schotten-Baumann conditions using aqueous sodium hydrogencarbonate in an organic solvent.[44] Such acylations afforded mainly the Z-monomer **85** which was very difficult to purify and separate from the Z-dimer **84** by flash column chromatography. However the monomeric Z-derivative **85** was a solid and could be crystallised in the presence of the Z-dimer **84**. Repeated recrystallisation afforded pure Z-monomer **85** in 66% yield based on the oxime over the two steps. Hydrogenolysis of this Z-monomer **85**, with palladium black in ethyl acetate afforded the pure monomeric amine **82** in quantitative yield. The protected monomer **82** is distinct from the protected BDI **60** in the proton NMR, again confirming the lack of monomeric amine **57** in the basic products of the reductive amination of dihydroxyacetone.

Some Basic Chemical Manipulations of BDI

By making use of reliable, well known protecting group manipulations, BDI **58** may be functionalised at the hydroxyls or at the secondary amine. As the diacetonide **60**, the nucleophilic oxygens are masked allowing manipulation at the nucleophilic nitrogen. Alternatively the hydroxyl groups in the Z-derivative **84** may be transformed. The nitrogen in BDI and its protected derivatives is probably quite hindered. Additionally, as a result of the high branch multiplicity, the scope for further reaction is quite limited. It should be possible to transform both the hydroxyls and the nitrogen into electrophilic or nucleophilic functional groups with much less steric crowding.

The Z-group is stable to a variety of weakly acidic and basic conditions and is thus orthogonal to the acid labile acetonides.[45] Benzyl carbamates are commonly cleaved to the free amine by catalytic hydrogenolysis[46] although a profusion of alternative reductive (e.g. transfer hydrogenolysis[47], Li/liquid NH_3[48]), strongly acidic (e.g. HBr/HOAc[49]), and neutral conditions have been employed. The Z-derivative **84**, is the simplest orthogonally protected unit and allows for growth in the convergent and divergent directions and can thus be considered as a double exponential building block.

Either the 'A' or 'B' functional groups can be generated with mutual exclusion of the other, and the integrity of the other protecting group is maintained. These types of structures are ideal candidates for the stepwise synthesis of dendrimers. The synthesis of the Z-derivative **84** from the BDI derivative **60** was effected using standard acylation conditions, and the derivative **86** could be prepared from **84** in quantitative yield using 70% AcOH/ H_2O (**Scheme 2.2.3**). The derivative **86** is an amphiphilic molecule of the type which will be discussed in chapter 4.



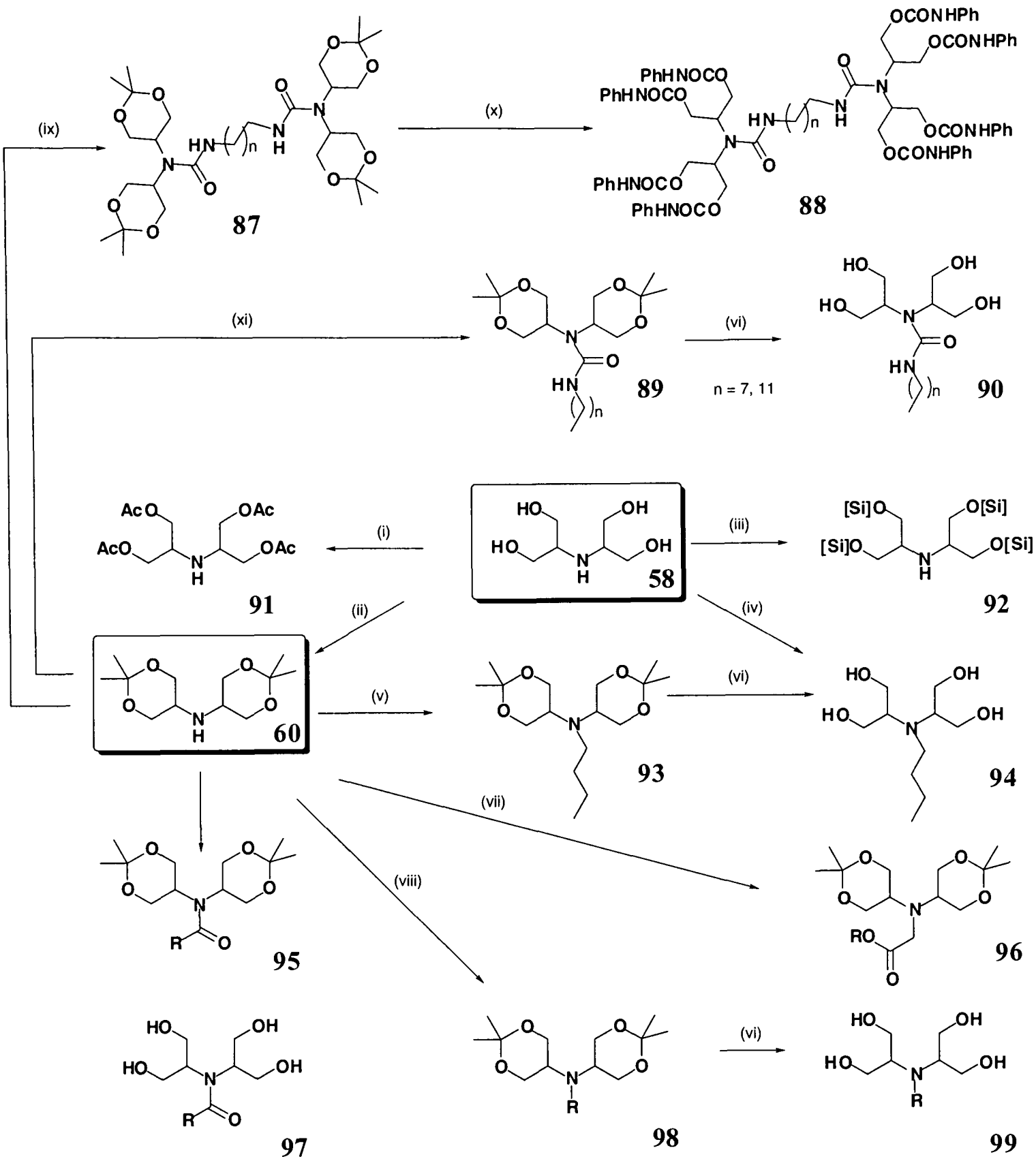
60 **84** **86**

Reagents and Conditions: (i) $PhCH_2OCOCl$, DIPEA, DCM, (ii) 70% aq. AcOH.

Scheme 2.2.3

Concurrent Studies on BDI: An Eclectic Chemical Tool Kit[50]

With the BDI unit **58**, its diacetonide derivative **60** and *N*-alkyl derivatives in hand, work was begun on investigating the reactivity of the focal point and the peripheral hydroxyls towards a variety of electrophilic reagents. Some representative results of this work are summarised and presented here to put consequent notions and strategies into context (**Scheme 2.2.4**).



Reagents and Conditions: (i) Ac_2O, py, (ii) Acetone, 2,2-dimethoxypropane, DMF, c. H_2SO_4, (iii) TBDMSCl, imid, DMF,(iv) $Me(CH_2)_2CHO$, H_2/Pd black, H_2O, (v) $Me(CH_2)_2CHO$, $NaBH(OAc)_3$, 1,2-DCE, (vi)TFA/H_2O (1:1), (vii) $BrCH_2CO_2R$, Toluene, DIPEA, cat. Bu_4NI, (viii) RBr (neat), reflux ,(ix) $OCN(CH_2)_nNCO$, THF, (n=7,11), (x) AcOH/H_2O, then PhNCO, THF.

Scheme 2.2.4

The nitrogen in BDI **58** is not very nucleophilic and the major product isolated from acetylation of **58** by acetic anhydride is the tetraacetate ester **91** (60% yield), resulting from acylation of the alcohols rather than of the amine. The carbonyl stretch at 1740 cm^{-1} and a highly symmetrical ^{13}C NMR spectrum provide strong support for **91** as the structure of the acetylated compound. Reaction of **58** with TBDMS chloride in the presence of imidazole gave the symmetrical tetrasilyl ether **92**, in 78% yield.

Thus reductive alkylation of the diacetonide **60** with *n*-butyraldehyde by sodium triacetoxyborohydride in dichloroethane[51] gave the *N*-butyl derivative **93** in 79% yield. This was by far the superior method to effect the reductive alkylation of the sterically hindered amine **60**. Removal of the acetonide protecting groups in **93** by aqueous trifluoroacetic acid gave the *N*-butyltetraol **94** as a potential ceramide mimic, in quantitative yield. Alternatively, *N*-butylBDI **94** may be obtained in 81% yield by direct reductive alkylation of unprotected BDI **58** by hydrogenation in the presence of palladium black.

The nitrogen in the BDI derivative **60** can react in excellent yield with isocyanates and indeed diisocyanates in refluxing toluene to form ureas such as **89** and **87**, which can be deprotected in quantitative yield using aqueous acid to reveal the hydroxyl functionality. These nucleophilic hydroxyls can also react with isocyanates, e.g. phenyl isocyanate to produce carbamates such as **88** in good yield, on refluxing in dry THF. Reaction of the diacetonide **60**, with acid chlorides in pyridine and catalytic DMAP at 70°C afforded amides of the type **95**, which can be similarly deprotected to form the generic tetraol amide **97**. The diacetonide **60** is very unreactive towards simple alkyl halides and the ^{n}butyl compound **93** was formed in only 25% by reaction with BuI under quite forcing conditions. The method of choice to effect such alkylations is thus the reductive amination of aldehydes using sodium acetoxyborohydride which proceeds smoothly and in high yield. Alkylations with alpha- haloesters in the presence of *N,N*-diisopropylethylamine and catalytic tetrabutylammmonium iodide in refluxing toluene proceed in good yield. The ester group at the focal point in **96** can undergo further manipulation.

Conclusion and Outlook

The reductive amination of dihydroxyacetone by ammonium salts with sodium cyanoborohydride gives BDI **58** in good yield and high purity. The choice of sodium cyanoborohydride for the reductive amination of dihydroxyacetone **56** with ammonium salts was necessary in spite of the highly toxic nature of the reagent and the production of toxic by-products such as hydrogen cyanide and sodium cyanide upon work-up. Dihydroxyacetone **56** and the polyhydroxylated amine **58** are readily soluble in methanol and the successful use of sodium cyanoborohydride is due to its solubility and indeed stability, in this hydroxylic solvent.

For reductive aminations of the BDI derivative **60**, with aldehydes the reagent of choice is sodium triacetoxyborohydride which is a mild reagent due to the steric and electron withdrawing effects of the three acetoxy groups which stabilise the B-H bond. Additionally it eliminates the risk of residual cyanide in the product and in the work-up waste stream. Improved yields, faster reaction times and fewer side reactions are seen for some hindered and weakly basic amines, compared to sodium cyanoborohydride which is sluggish and inefficient using the same substrates.

The study into the synthesis and the initial chemistry described herein present the development of a building block for dendrimer construction offering a high degree of versatility. The AB_4 dendritic unit has a number of desirable features which invite its exploitation in the synthesis of dendrimers.

The bifunctional molecule **58** has a high branching multiplicity with branching in four directions giving a large number of chain ends per macromolecule. The array of hydroxyl functionalities allows iterative coupling and also ultimately constitute the periphery of the molecule - affecting properties such as viscosity and solubility characteristics. The branching is incorporated into the dendritic building block and so the units can be linked by non-branching reactions allowing a wider choice of reactions.

The unit possesses an amine focal point which is probably quite hindered but presents a point for attachment to a central core and for iterative coupling reactions. The low nucleophilicity at the focal point may be problematic and may limit possible coupling reactions. Orthogonal protection of the focal point and the peripheral groups can easily be performed using known reactions. Growth in the convergent and divergent direction can be envisaged and so the AB_4 dendritic unit can be considered as a double exponential building block. Very fast growth should be achievable thus countering one of the much cited weaknesses of many dendrimer syntheses.[52]

A convergent growth strategy is usually tried in the first instance as this allows for the purification and isolation of intermediates from defective counterparts making it easier to study and optimise candidate reactions for the linking and core anchoring of units. The next step would be to transfer the discovered reliable and high yielding reactions to a divergent pathway which is amenable to large scale work.

The high branch multiplicity might be limiting however in terms of finding reactions that can be used iteratively and result in generative growth. The highly branched monomer will lead to a more precise spherical assembly even for low generation dendrimers. Apart from the molecular shape other properties may be consequential such as internal and external rigidity, lipophilicity and hydrophilicity, degrees of void volume and excluded volume, density gradients, complimentary functionalities and even environmental co-operativity. Thus, unique molecules with novel properties should be accessible which may lead to some diverse applications. Derivatives of the water soluble, symmetrical polyhydroxylated amine **58**, should have an environmentally acceptable profile.

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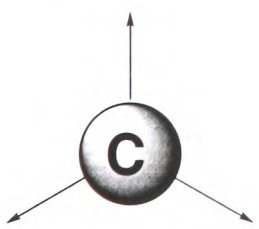
3. Dendrimeric and Amphiphilically Equipped Triazines: C_3 Symmetry

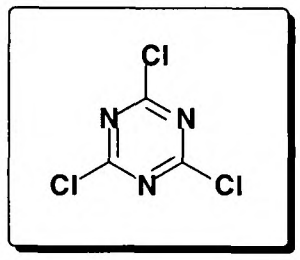
3.1 Introduction

A Three Directional Core

The synthesis of *bis*(1,3-dihydroxy-*iso*propyl)amine (BDI) **58** and its subsequent protection as the diacetonide **60** is an expedient sequence to obtain a masked AB_4 dendritic monomer. The peripheral groups in this building block are protected and 'tied back' from the nitrogen at the focal point allowing elaboration of the amine function, for example by nucleophilic attack. This would ultimately lead to dendritic structures with many free hydroxyl units on the periphery. Through investigations into the chemistry of the BDI diacetonide, **60**, a small number of reliable, and reproducible reactions have been ascertained which have been addressed in the previous chapter.

As alluded to in the previous chapter, BDI does not undergo a third reductive amination with dihydroxyacetone to give the tertiary amine, **59**. This led to the notion of linking the BDI units around a core unit. It was envisaged that the commercially available and inexpensive[1] trifunctional scaffold, 2,4,6-trichloro-1,3,5–triazine, **100**, would be a suitable three directional linker for BDI (**Figure 3.1**).*





100

Figure 3.1. Three directional core.

2,4,6-Trichloro–1,3,5–triazine (*s*-trichlorotriazine, cyanuric chloride) **100** is a heteroaromatic compound which is known to react with carbon, oxygen and nitrogen nucleophiles to give a range of substituted 1,3,5-triazines accessible *via* displacement of the chlorine atoms.[2] A

* The class of compounds containing the 1,3,5-triazine moiety are also referred to as *s-*/*sym*-triazines because of the symmetrical substitution.

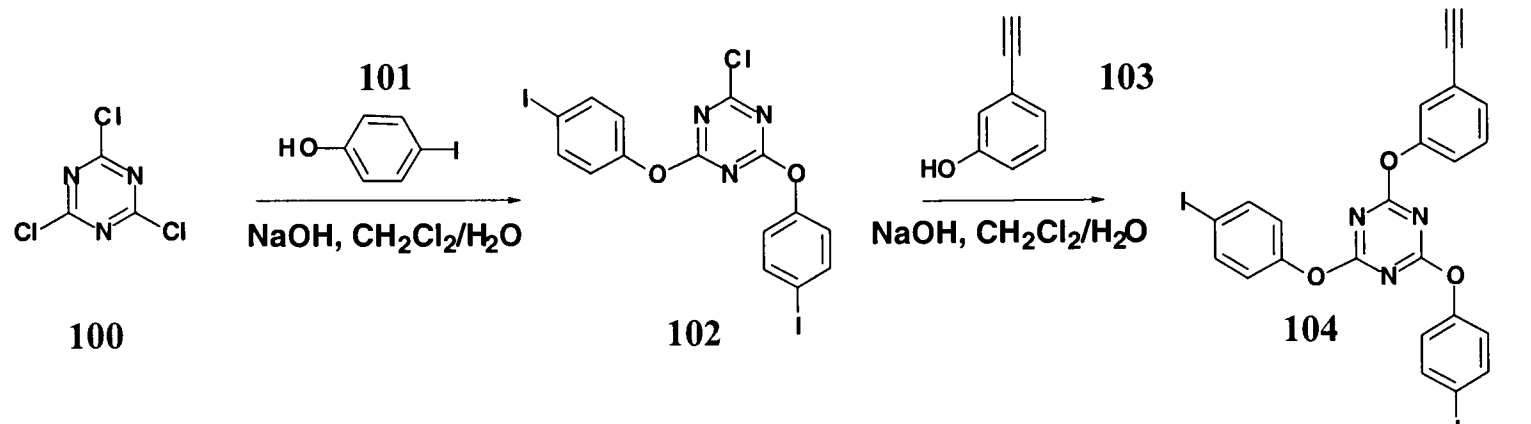
number of *s*-triazine derivatives have been synthesised employing such strategies and have found uses as drugs,[3] agrochemicals,[4] dyes,[5] and synthetic receptors.[6]

More recently, trifunctionalisation of the *s*-triazine moiety with optically active 1-(1-napthyl)ethylamine has produced derivatives which function as versatile chiral solvating agents in the NMR determination of the enantiomeric composition of chiral compounds.[7] An analogous ethylamino derivative, optically active 1-(9-anthryl)ethylamine has had its absolute configuration determined by attachment of the *s*-triazine chromophore.[8]

Katritzky has reported on a range of alkylamino-*s*-triazines which exhibit restricted rotations at low temperatures as evidenced by dynamic NMR studies and x-ray crystal structures.[9] Moreover, Clayden has reported on the ability to control stereoselectivity of a number of reactions with rotationally restricted amides of diisopropylamine.[10] Although studies into the applications of the novel *s*-triazines presented here have been limited, they may serve as stereo-directing templates akin to those of Clayden by virtue of the large barriers to rotation that exist in such hindered molecules.

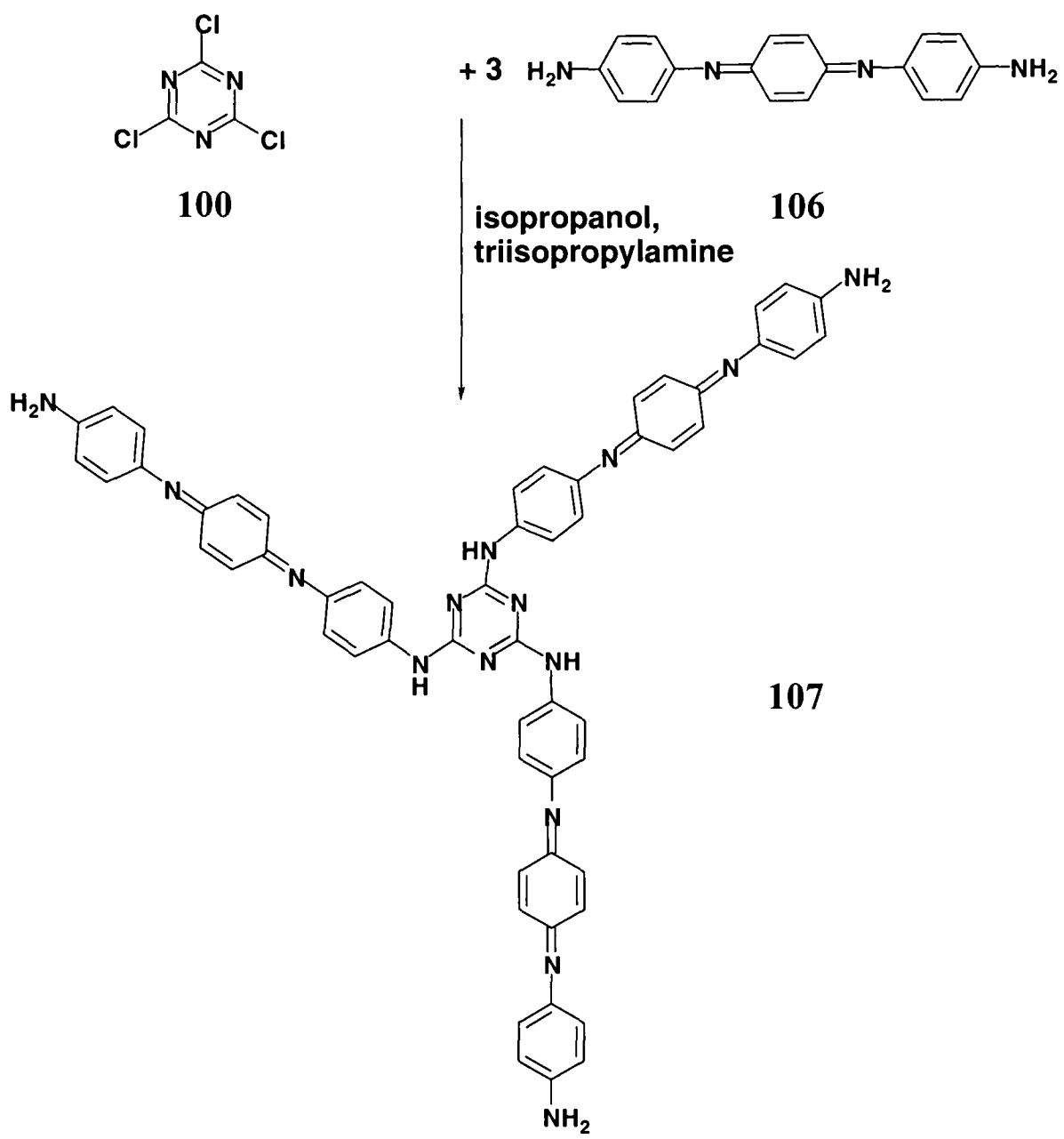
The triazine scaffolds incorporating BDI have large barriers to rotation and are rotationally restricted at temperatures above room temperature. Possible approaches to rigid, directing templates might involve the anchoring of chiral auxiliaries to the triazines which do not display inherent axial chirality. Such a rigid core molecule with functional groups of well defined stereochemistry, stereo-orientation and spatial arrangement might serve as rigid directing templates. Although these systems have not been designed with specific functions in mind again it is the interesting properties that may give rise to applications. Additionally, Taddei *et al.* have recently reported on solid-supported chloro 1,3,5-triazine derivatives as auxiliaries in amide synthesis.[11]

To date, a very small number of reported dendritic molecules incorporate the *s*-triazine nucleus.[12] The work of Kim *et al.* has resulted in dendritic hyperbranched polyethynylenes integrating the 1,3,5-*s*-triazine moiety. Kim[12(b)] made use of the selective reactivities of the three chlorine atoms on cyanuric chloride to construct AB_2 type 1,3,5-*s*-triazine molecules, **104**. These have a 3-ethynylphenoxy substituent as A and a 4-iodophenoxy substituent as B. The polymerisation is based on the Heck coupling reaction of aryl ethynyl and aryl iodide units to yield ethynylene branching moieties[13] and a portion of this hyperbranched polymer **105** is shown, which of course has structural irregularity. (**Scheme 3.1.1**)



Scheme 3.1.1. Kim's hyperbranched polymers based on AB_2 units incorporating the 1,3,5-triazine system.

Viswanathan *et al.*[12(c)] have reported on the synthesis of 'dendrimer' **107**, made by reacting the diamine telechelic **106** with cyanuric chloride **100** in a 3:1 ratio (**Scheme 3.1.2**); yield is not reported.



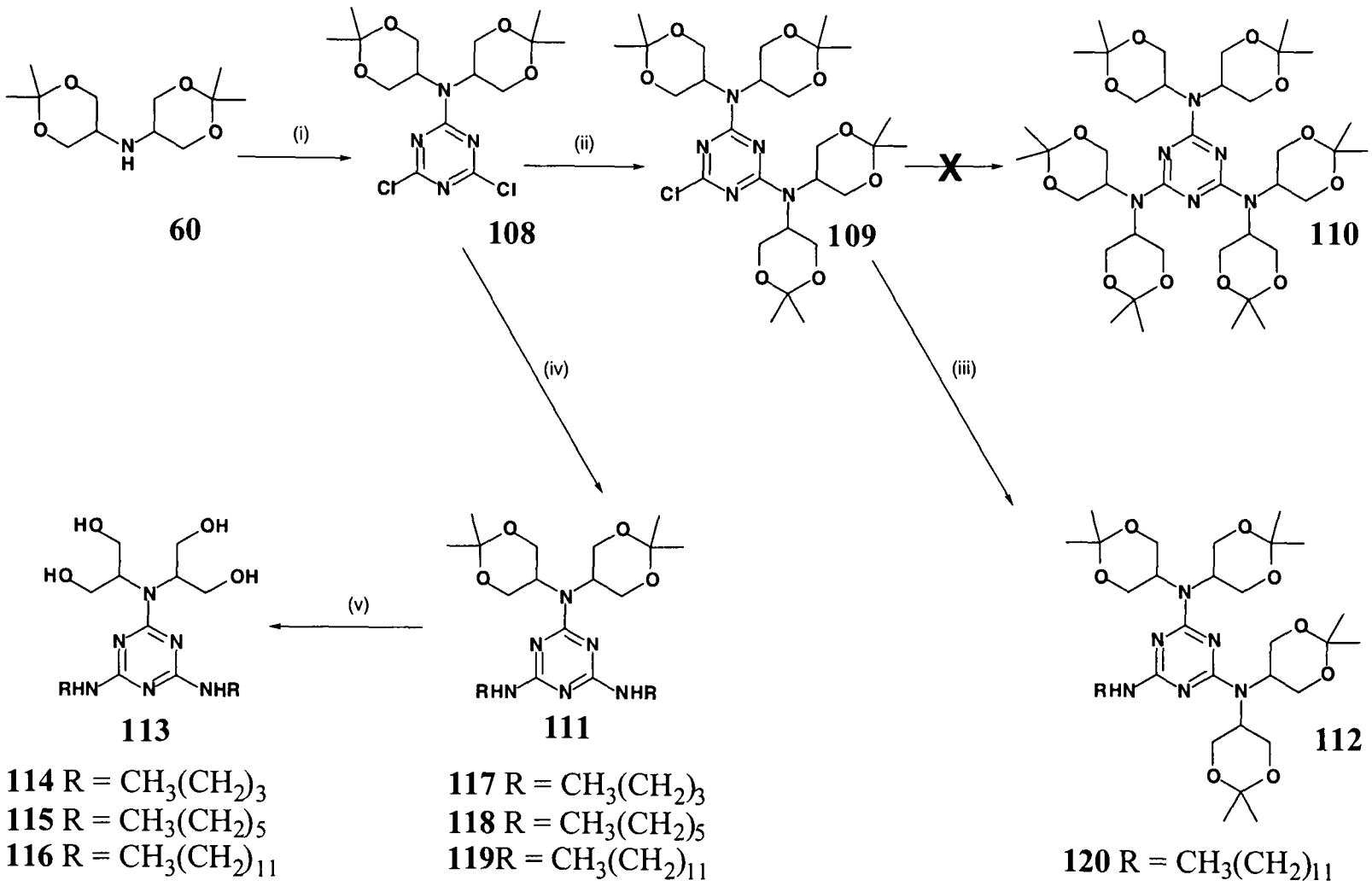
Scheme 3.1.2

3.2 Results and Discussion

Towards a Three Directional Structure

The selective reactivities of three chlorine atoms on cyanuric chloride toward a variety of nucleophiles provides versatility for the synthesis of dendrimers containing a 1,3,5-*s*-triazine moiety. Such a feature would allow for the potentiality of producing symmetric and non-symmetric dendrimers by coupling different dendron sectors to the core in a stepwise, convergent approach. This stepwise replacement of chlorine atoms in the reactive nitrogen analogue of an acid chloride, makes it a valuable core unit.

It was anticipated that such a core (**100**) could react with the amine focal points of three BDI diacetonide branching units and form C-N bonds. The attempted synthesis of a three directional dendritic molecule, incorporating BDI and based on a 1,3,5-triazine skeleton is presented (**Scheme 3.2.1**). It emerged that BDI could displace the chlorine atoms in 2,4,6-Trichloro-1,3,5–triazine to afford various *N*-alkylamino derivatives (**Scheme 3.2.1**).



114 R = $CH_3(CH_2)_3$ **117** R = $CH_3(CH_2)_3$
115 R = $CH_3(CH_2)_5$ **118** R = $CH_3(CH_2)_5$
116 R = $CH_3(CH_2)_{11}$ **119**R = $CH_3(CH_2)_{11}$
120 R = $CH_3(CH_2)_{11}$

Reagents and Conditions: (i) Cyanuric chloride, DIPEA, toluene, Δ, (ii) BDI, DIPEA, toluene, Δ, (iii) RNH_2 (2 equiv.), toluene, Δ, (iv) RNH_2 (4 equiv.), toluene, Δ ,(v) 70% aq. AcOH.

Scheme 3.2.1

Reactions leading to C-N bond formation, and requiring selective, sequential derivatisation were accomplished using *N,N*-diisopropylethylamine as a base and dry toluene as solvent. In the reaction of the disubstituted triazine **109** with dodecylamine, an excess of the nucleophilic amine was used so that the reaction is self buffered.

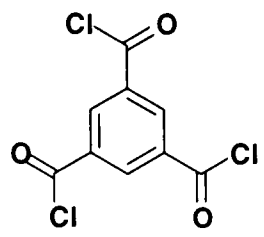
Thus by employing the appropriate number of equivalents of the nucleophilic amine, stepwise substitution of the chlorine atoms in cyanuric chloride and various mono- and di-chloro-*s*-triazines can be effected. Normally stepwise substitution is controlled by invoking strict temperature regimes[14] - the mono-substitution usually requiring depressed reaction

temperatures. However, owing to the poor nucleophilicity of the nitrogen in BDI, elevated temperatures were necessary for even the mono-substitution.

Due to the very reactive nature of cyanuric chloride, the first displacement with BDI to afford the *s*-triazine **108** proceeds in excellent yield (96%) whilst the second substitution proceeds in moderate to good yield (60%) to afford **109**. The differing reactivity of the chlorides with respect to displacement is attested by the reaction times for these transformations. The monosubstituted triazine **108** is formed by refluxing in toluene for 1 hour whereas the formation of the disubstituted triazine **109** from **108** is incomplete even after refluxing for 2 days in toluene. The conversion of the monosubstituted triazine **108** to disubstituted triazine **109** was not facilitated by the more polar, aprotic solvent DMF,[15] and refluxing in xylene at higher temperatures was not accompanied by an increase in yield. Indeed, there was no improvement in yield in making use of other, more polar solvents such as THF, acetonitrile or acetone where in fact lower yields were observed possibly due to the lower temperature regimes.

Furthermore, the monosubstituted triazine **108** is unstable with respect to the ease of hydrolytic cleavage of the C-Cl bond. No conditions have yet been found in which the third position in triazine **109** could be substituted by BDI to give **110**. However, this position is still active towards displacement by less sterically encumbered nitrogen nucleophiles, such as dodecylamine to give structures such as **112**. Thus the principal impediment to the third BDI displacement to potentially form **110** from **109** seems simply to be steric approach rather than electronic deactivation of subsequent positions as the chlorine atoms are replaced by electron donating nitrogen atoms. Likewise, reaction of the monosubstituted triazine **108** with excess amine results in the formation of the tri-functionalised *s*-triazinic structures **111, 117, 118** and **119**. These will be addressed in the next chapter.

No reaction of BDI was observed with the commercially available three directional core, 1,3,5-benzene tricarbonyl chloride, **121**, to form tertiary amides.[16]



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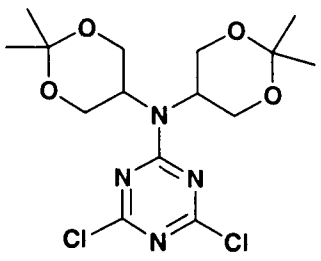
Restricted Rotation Phenomena

Interestingly, all the resulting *N*-alkylamino triazines exhibited variable temperature NMR characteristics. These properties are consistent with the comments reported by Katritzky *et al.*[9] and have prompted an elaborate study with the rationale of producing a three-fold directional structure involving various dendrimer prototypes. It was hoped that such unique dendritic molecules would display novel and attractive properties which might lead to viable applications.

In this chapter, the syntheses of a range of novel dendrimer prototypes which embody BDI as the branching unit and the observation of the interesting dynamic phenomena of such molecules will be presented. A detailed and elegant NMR investigation into the dynamic processes giving rise to observations reported here has been carried out on the triazine **108**, for which a crystal structure has been obtained. These extensive findings will also be discussed.[17]

The proton NMR spectrum of the triazine **108** shows broadening of the axial CH_2 protons on the dioxane ring at room temperature in both $CDCl_3$ and toluene d_8 (**Figures 3.2** and **3.3**). The CH on the α carbon is resolved at room temperature in $CDCl_3$ and only resolved at 90°C when toluene d_8 is used as the NMR solvent. The equatorial protons are clearly resolved at both temperatures in toluene d_8 and at room temperature in $CDCl_3$. Aside from the broadening of some signals there is also a great amount of deshielding of the protons in **108** (**Figure 3.2**) when compared to their counterparts in **60** (**Figure 2.6**). Most notably a large downfield shift is observed for the protons on the α carbon of the amine, attributable to the electron withdrawing triazine ring. A comprehensive proton NMR study has been performed on this compound.[17]



$CDCl_3$, 500MHz

Figure 3.2. ^{1}H NMR spectrum of triazine **108** in $CDCl_3$ at room temperature.

At elevated temperature the proton spectrum of **108** exhibits five well resolved resonances which can be attributed to the five distinct sites within each dioxane ring, and enables the differentiation of the axial and equatorial protons on the basis of their vicinal coupling constants with the $C_\alpha H$ proton (^3J= 7.1 and 5.2 Hz respectively).

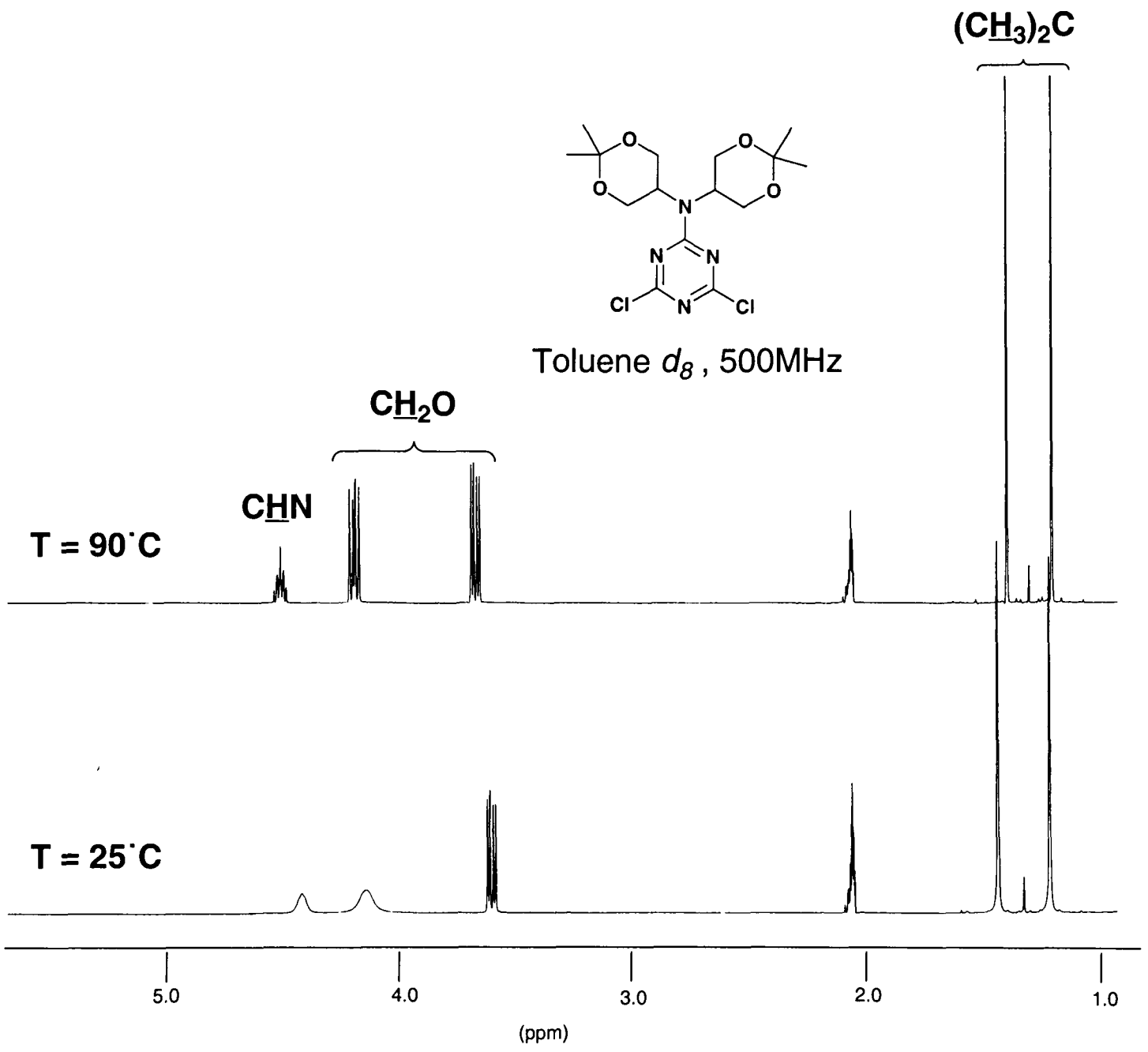


Figure 3.3. ^{1}H NMR spectrum of triazine **108** in toluene d_8 at variable temperature.

The proton NMR for the triazine **109** shows a similar spectrum at high temperature but it is still broad and though is recognisably simplified, it has yet to coalesce even at 90°C (**Figure 3.4**). Clearly this is a very hindered, rotationally restricted compound with very bulky groups in close proximity.

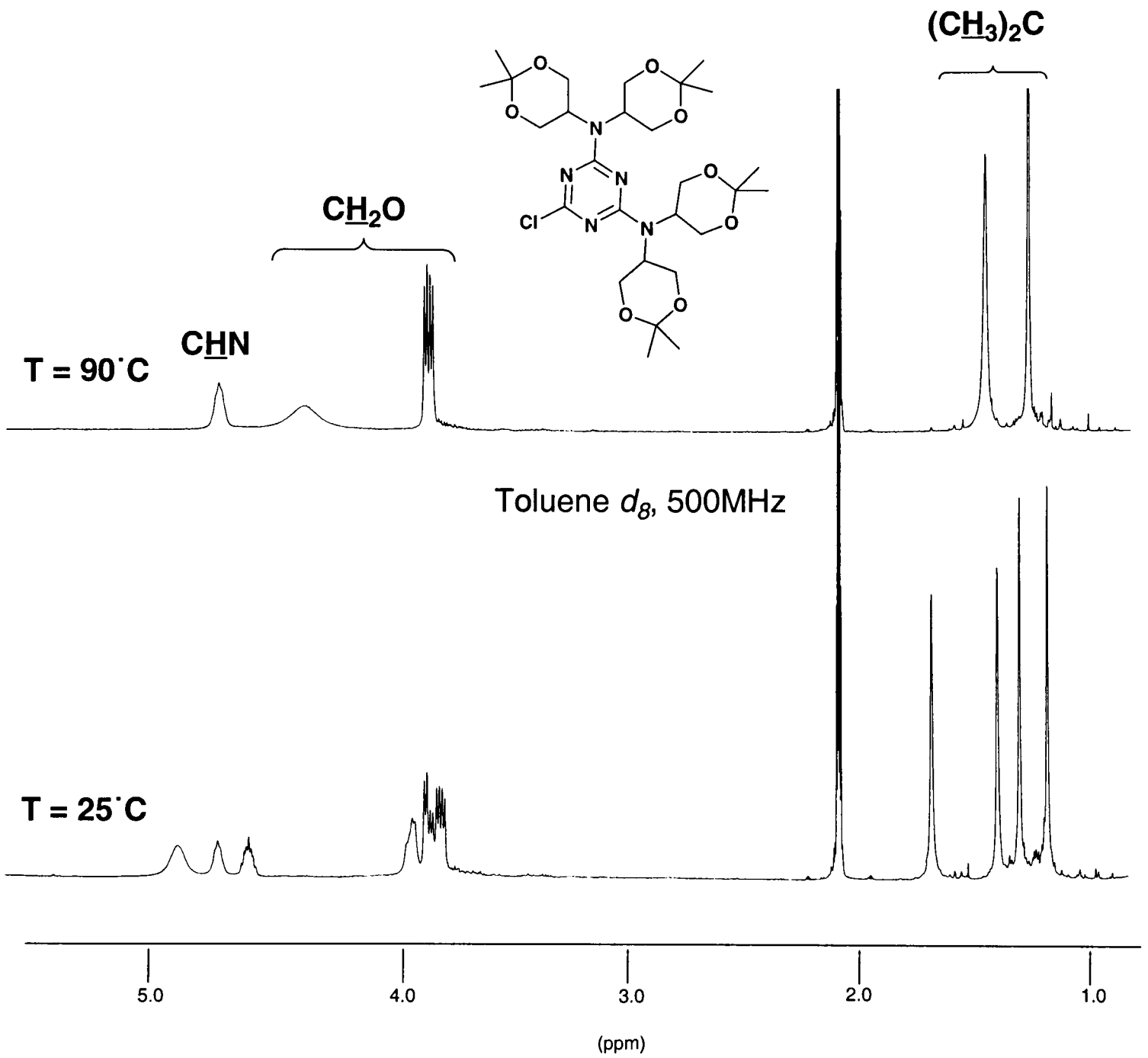


Figure 3.4. ^{1}H NMR spectrum of triazine **109** in toluene d_8 at variable temperature.

The mono- and di-chloro-*s*-triazines **108** and **109** are thus useful reactive intermediates in the preparation of non-symmetrical tri-functionalised *s*-triazines incorporating BDI. The X-ray crystal structure of the di-chloro-*s*-triazine **108** has been obtained and shows some interesting features (**Figure 3.5**).

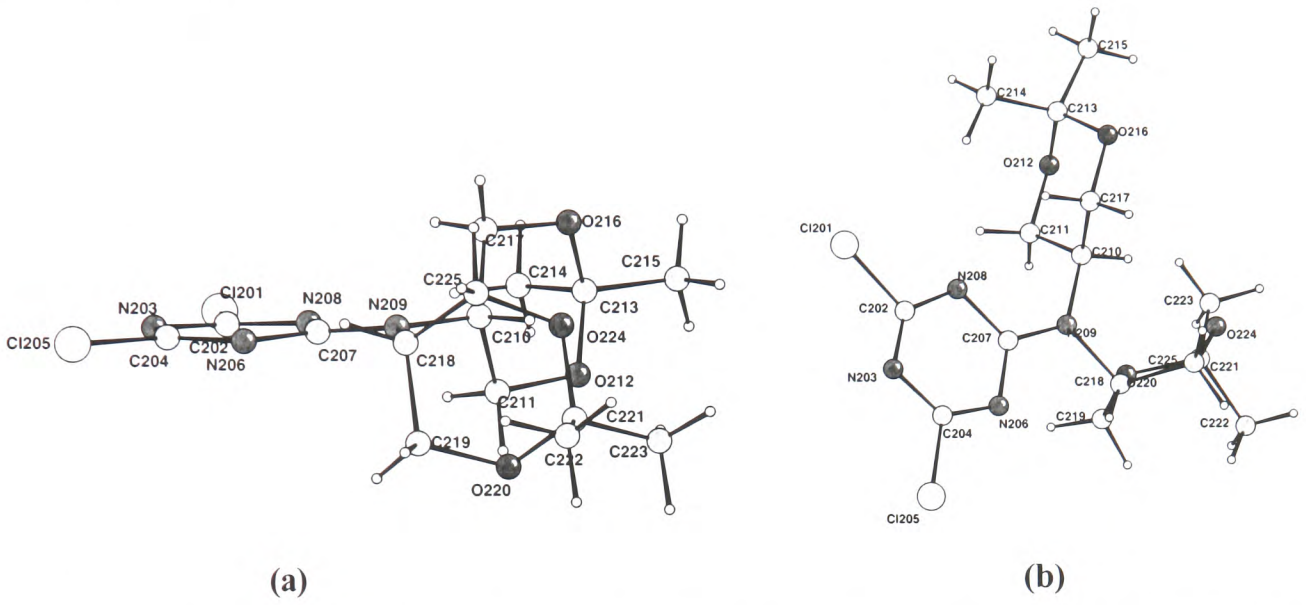


Figure 3.5. Two perspective views of the crystal structure of **108** showing atom labelling. (a) has the plane of the triazine ring orthogonal to the plane of the paper and (b) has the plane of the triazine ring in the plane of the paper.

The triazine **108** crystallises in the monoclinic system, space group P 2_1/c with a = 12.51, b = 17.64, and c = 17.05Å; β = 93.54°, and Z = 8 asymmetric units: 16 molecules per unit cell. The triazine ring is close to planar and the attached amino substituent shows clear evidence of partial double bond character in the exocyclic N-C(Ar) bond. The mean value for this C (207) – N (209) bond is 1.316Å which equates to a value between that of a C-N single bond (1.472Å) and a C=N double bond (1.29Å).[18] Clearly there is delocalisation of the nitrogen lone pair into the electron withdrawing triazine ring. This is further evidenced by the planar geometry around the amino nitrogen, with bond angles close to 120° (120.47°, 119.08°, and 120.30°). Consequently, all attached α carbons lie approximately in the plane of the triazine ring.

The solid state structure of **108** has the isopropylidene groups bisected by the central plane of the triazine ring. Both rings are in the chair conformation but they are not related by a 'tongue and groove' (statistically geared) conformation as is the case with isopropyl groups attached to a planar skeleton (e.g. hexaisopropylbenzene and tetraisopropylethylene).[19] The isopropylidenes are not oriented in the same direction, indeed the ring systems have inverted conformations relative to each other, so that one has the C-N bond equatorial and one axial.

In the unit cell the acetonide groups are exquisitely interlocked as shown below (**Figure 3.6**) and it could be that crystal packing forces lead to the chair inversion of one dioxane ring with respect to the other. However, this has no bearing on the solution structures and the low-energy conformers exist in the so-called "tongue and groove" orientation as previously observed for diisopropyl substituted *s*-triazines and hexaisopropylbenzene.[19]

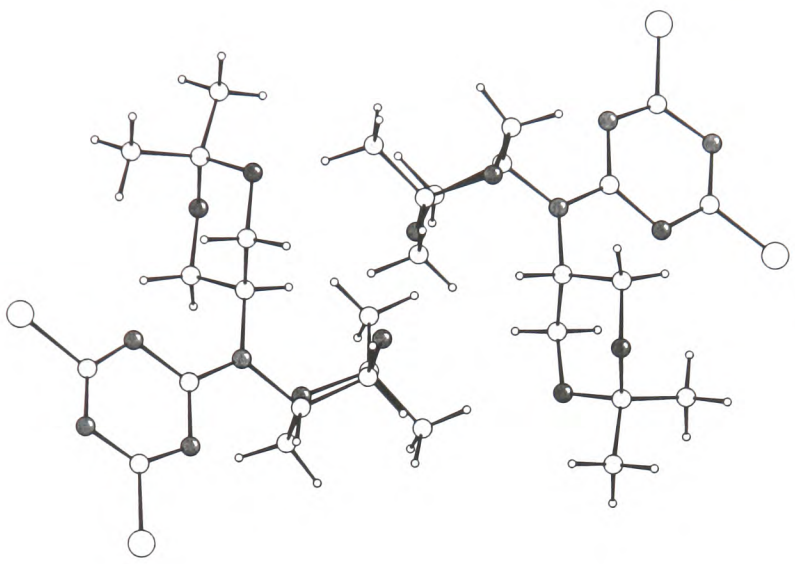


Figure 3.6. Representation of the asymmetric unit of the crystal structure of triazine **108**.

A detailed NMR investigation has been performed on triazine **108** (Appendix II). It seems the broadening of the proton NMR at room temperature is not simply explained by arguments of restricted rotation about the C(Ar)-N bond but also restricted rotation about the C_α-N bond.

There are at least three dynamic processes in such a molecule which give rise to the observed variable temperature NMR experiments. Two of the three processes have been investigated in detail as these occurred at temperatures above the freezing point of toluene. Restricted rotation about the C(Ar)-N bond (**Figure 3.7(a)**) is evidenced at low temperature, and is consistent with the x-ray crystal structure observations of a partial double bond (**Figure 3.7(b)**). Additionally there is simultaneous restricted rotation about the C-N single bond at room temperature (**Figure 3.7(b)**) and a process by which the interplay between the three ring systems in close proximity in the rotationally restricted system undergo a symmetrical exchange, probably by a concerted pathway. It is possible to explain the observable NMR effects by the C_α-N rotations, however **(a)** in **Figure 3.7** may occur simultaneously although the data is insensitive to this rotation

since the resulting chemical shifts brought about by rotation of the triazine are identical by virtue of the C_2 symmetry of this ring.

Of the two possible mechanisms for such a symmetrical exchange, method **(e)** in **Figure 3.7** seems unreasonable due to steric compression when the rings have the up-up orientation and can be largely discounted on this basis. Furthermore, the precise 1:1 ratio of the exchanging sites in both ^{1}H and ^{13}C spectra would require the down-down and up-up conformers to similarly exist in precise 1:1 ratios, which seems highly unlikely for similar reasons. This ratio is exactly as expected for mechanism **(d)** where the exchange follows a concerted rotation of both dioxane rings about the C_{α}-N bond. The exchanging equatorial sites are separated by only 0.4 ppm and thus at ambient temperature have already coalesced, whilst the exchanging axial and methine $C_{\alpha}H$ sites differ by substantially greater shifts, 1.6 ppm and 1.5 ppm respectively, and thus still appear broadened in the ambient temperature proton spectrum. In $CDCl_3$ - a non-aromatic solvent- the $C_{\alpha}H$ signal has coalesced at room temperature, **Figure 3.2**.

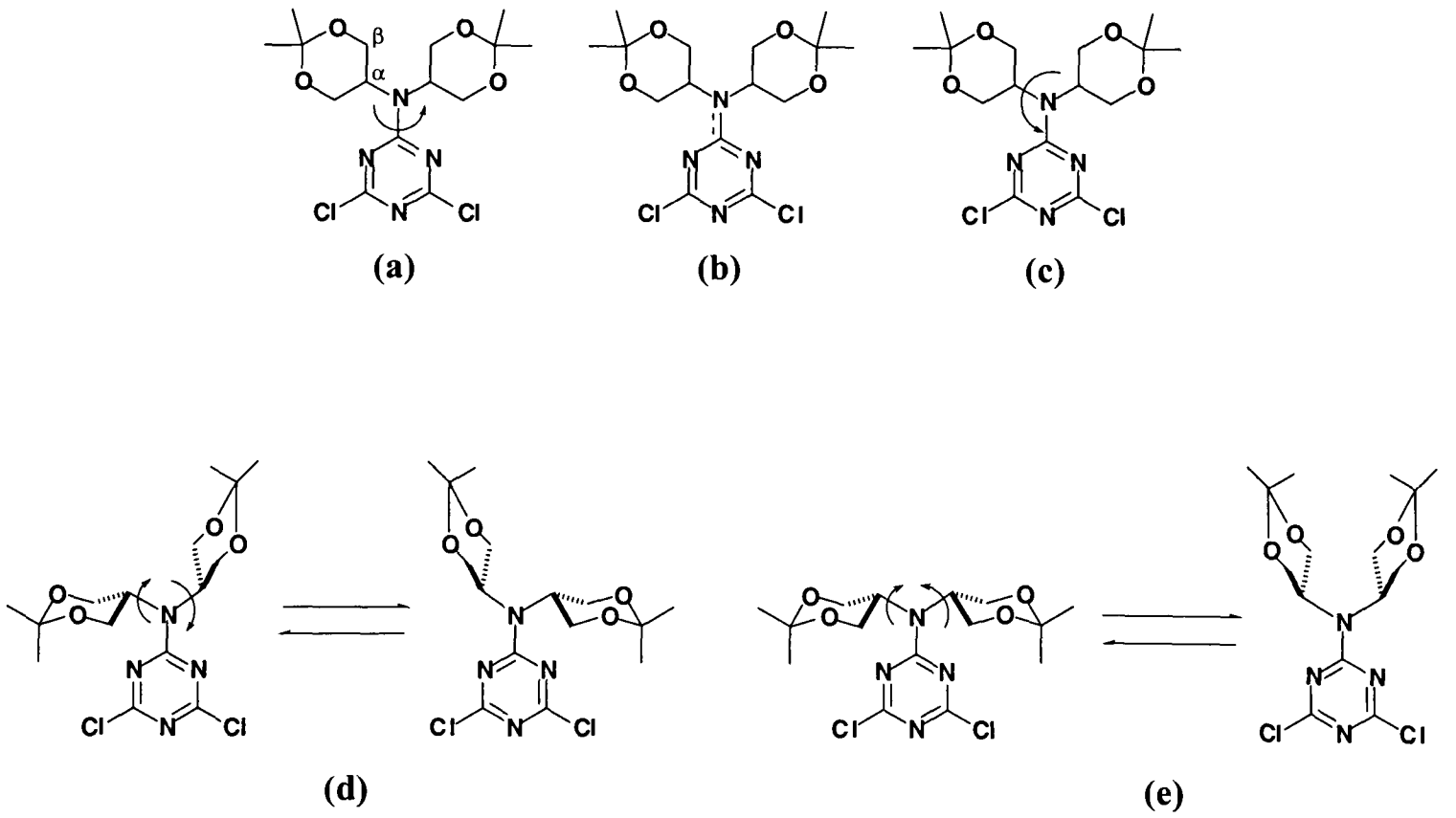


Figure 3.7

At temperatures below 213K further broadening of resonances in both ^{1}H and ^{13}C spectra occurs (Appendix II), indicating the presence of an additional conformational exchange process.

Restrictions imposed by the freezing point of the solvent have precluded a complete investigation of this, but it seems likely that this relates to conformational rearrangement within the dioxane ring itself.

The Syntheses of a New Family of Dendrimers and a Projected Growth Strategy

The preparation of a three fold symmetrical triazine structure could not be effected using BDI as the AB_4 dendritic monomer and cyanuric chloride as the reactive nucleus. However it was thought that the more reactive cyanuric fluoride might afford the trisubstituted triazine **110** or at least the disubstituted triazine **109** in greater yield.

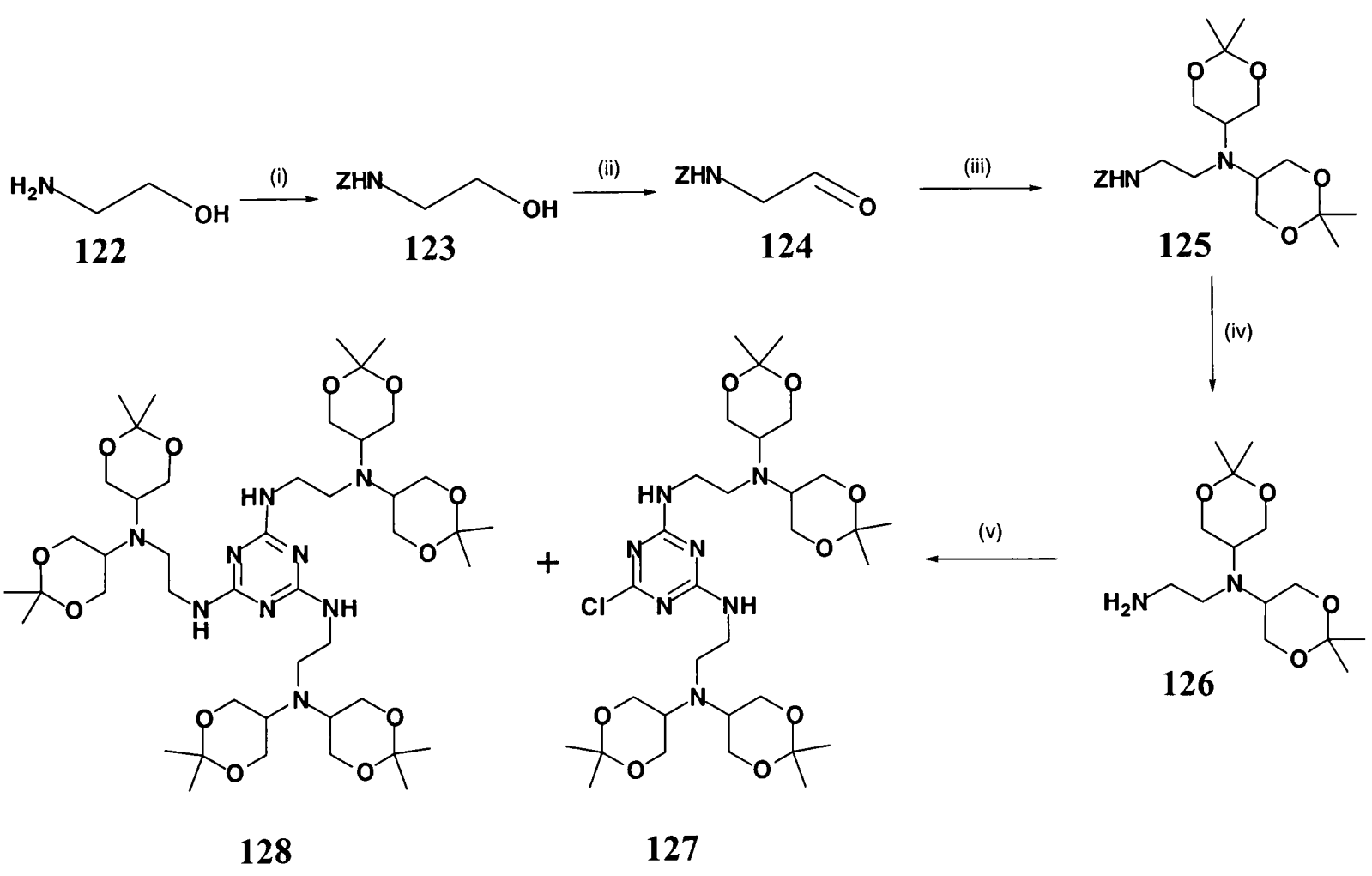
Normally there is a greater reactivity of carbon-fluorine bonds over carbon-chlorine bonds in nucleophilic aromatic substitution, $S_N(Ar)$. Nucleophilic aromatic substitution is a stepwise process involving addition of the nucleophile to form an intermediate which then eliminates. It is the first step that is rate limiting and so with the greater polar effect of the fluorine over chlorine the addition step is more favoured and the overall rate is increased. However, using cyanuric fluoride instead of the chloride under the same conditions did not increase the yield for the monosubstituted triazine **108** or disubstituted triazine **109** and there was no trace of the trisubstituted triazine **110**. Another strategy that was not tried but might be effective here is that of palladium catalysed C-N bond forming reactions.[20]

Refluxing cyanuric chloride with a six fold excess of the amine **60** in a sealed tube afforded the disubstituted triazine **109** in comparable yield to its formation by the stepwise route under standard conditions, and no monosubstituted triazine **108** was isolated. Again no trace of the trisubstituted triazine **110** was detected. However the seminal structures shown in **Scheme 3.2.1** have highlighted the reactivity of the third chlorine position in **109** towards primary amines and have led to the development of the more nucleophilic AB_4 dendritic monomer **126** (**Scheme 3.2.2**). It was thought that the poor nucleophilicity of the BDI derivative **60** could be circumvented by installing a C_2 linker with a primary amine functionality at the focal point.

There are two possible routes to vicinial diamines. They can be derived from β-amino alcohols where the hydroxyl group is transformed into a leaving group and substituted by a nucleophilic nitrogen or by reductive alkylation of an amine with a suitably protected α-amino aldehyde. Both strategies were tried using precursors derived from ethanolamine **122**.

Ideally, just one reaction is employed for linking branching units in a dendritic system and if further reactions are necessary they should be reliable and high yielding and not compromise the output of valuable dendritic intermediates. Thus in developing a new building block, additional reactions should be reliable and facile. The aldehyde **124** formed from the alcohol in **123** was reactive in reductive alkylations of the BDI derivative **60** (**Scheme 3.2.2**).

The choice of a C_2 chain was two-fold - firstly ethanolamine is a cheap and readily available starting material and the sequence allows installation of BDI at a late stage in the synthesis.



Reagents and Conditions: (i) Benzylchloroformate, Na_2CO_3, dioxane/water (1:1), (ii) PCC, DCM, molecular sieve, (iii) $Na(OAc)_3BH$, 1,2-dichloroethane, BDI, (iv) H_2/Pd black, EtOAc ,(v) Cyanuric chloride, toluene, DIPEA, Δ.

Scheme 3.2.2

PCC oxidation of the primary alcohol in the ethanolamine derivative **123** leads to the preparation of aldehyde **124**, which undergoes smooth reductive amination with BDI using sodium triacetoxyborohydride in dichloroethane to afford the orthogonally protected AB_4 unit **125**. Focal point activation by hydrogenolysis proceeds quantitatively, and reaction of the resulting diamine **126** with cyanuric chloride under the standard conditions affords the desired trisubstituted *s*-triazine **128**, together with the disubstituted *s*-triazine **127.** No conditions were found which effected the complete conversion from the disubstituted to the trisubstituted product. However, this may not be a serious drawback as these could be separated by flash column chromatography. Additionally the product distribution might indicate that the disubstituted product is adopting an interesting topology as steric effects may be playing a significant role and hindering the core anchoring of the third amine unit. The ratio of the trisubstituted product **128** to the disubstituted product **127** is about 7:3 based on isolated yields. The steric inhibition to dendritic growth is not unexpected for molecules prepared by the convergent approach.

Happily, some of the three-directional first generation dendrimer **128** was obtained to complete the family of dendrimers. Its variable temperature proton NMR is shown below (**Figure 3.8**). In the trisubstituted triazine **128** the planarity extends out to the α carbons, giving rise to a sterically and rotationally restricted molecule which again clearly exhibits dynamic NMR properties. This is clearly a similar structure to **108** but the behaviour is more complicated due to more degrees of rotational freedom between the BDI unit and the triazine core. There has been no detailed analysis on this molecule.

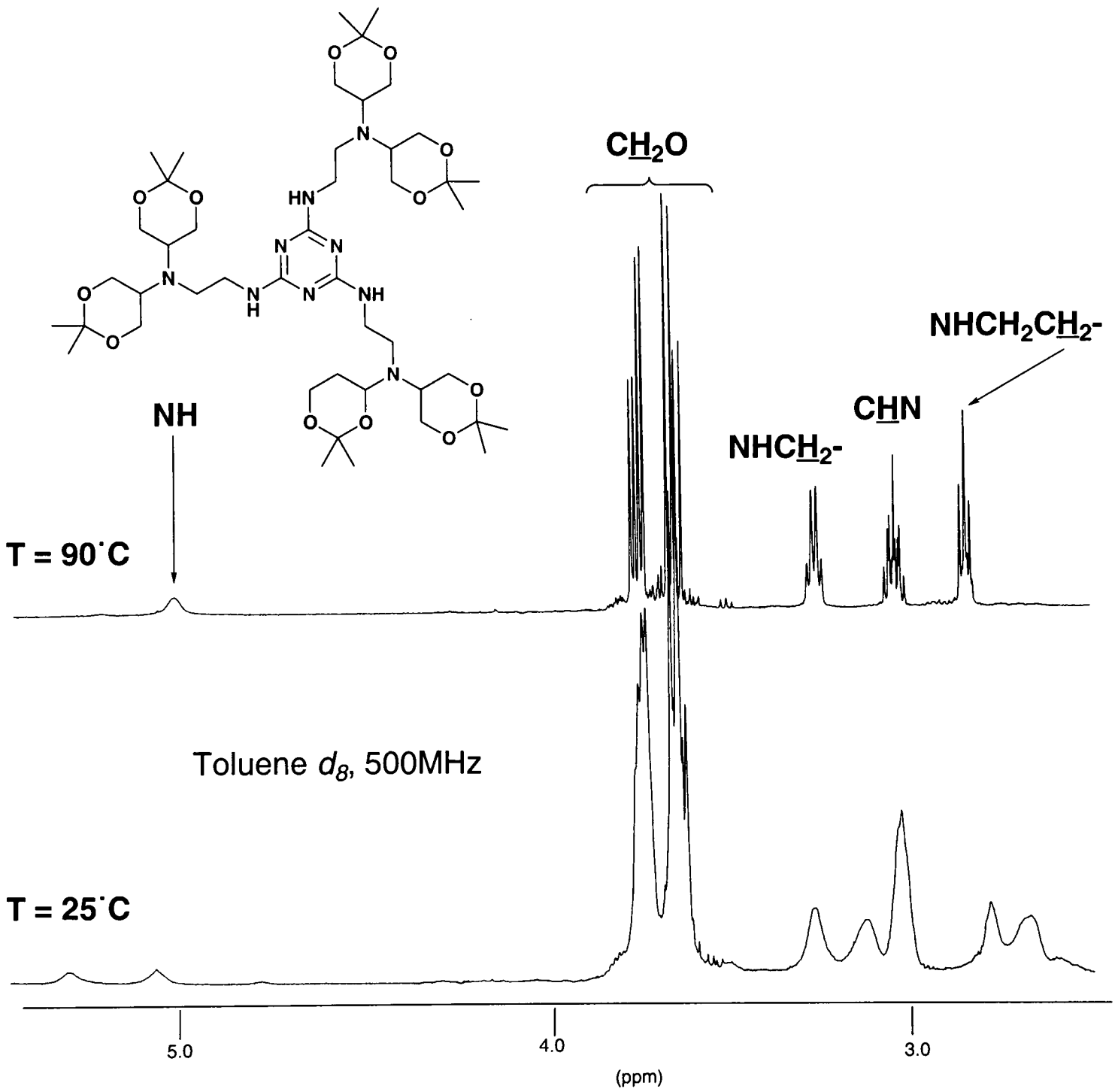
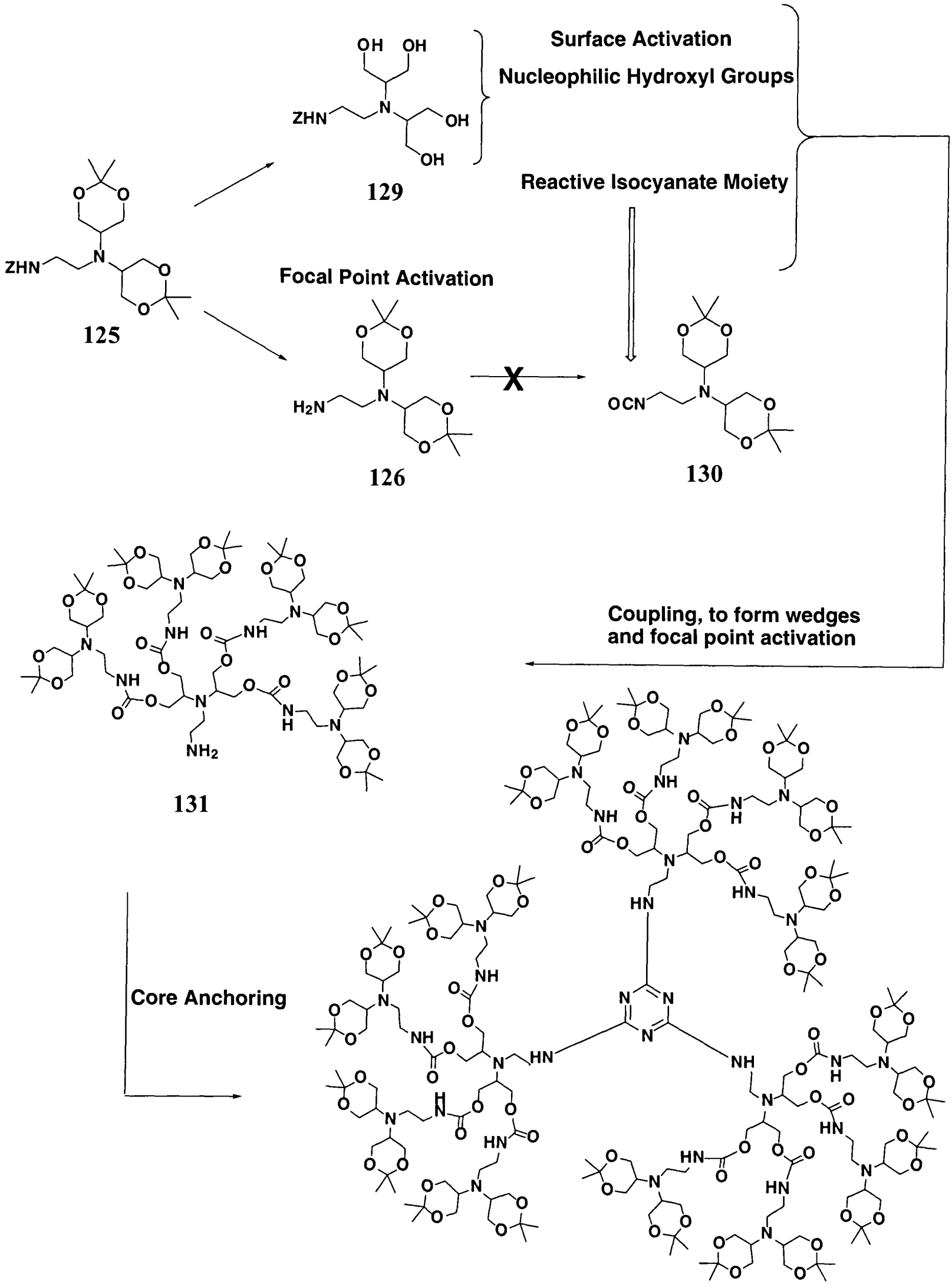


Figure 3.8. Expansion of part of the ^{1}H NMR spectrum of triazine **128** in toluene d_8 at variable temperature.

Orthogonally protected branching units such as **125** are ideal candidates for the stepwise synthesis of dendrimers and are amenable to both divergent and convergent growth strategies. A convergent synthesis leading to clean, isolable products should be tried in the first instance and then projected to a larger scale divergent synthesis once it has been established that all the reactions are reliable and high yielding.

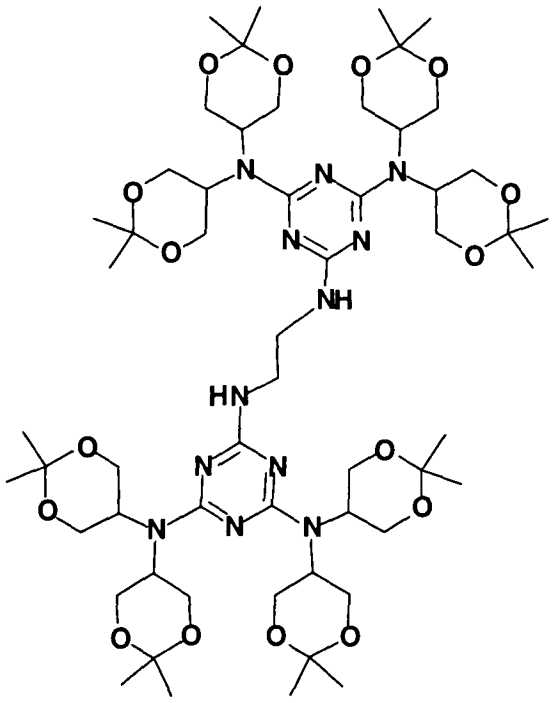
A projected, highly convergent strategy (**Scheme 3.2.3**) is presented. The diamine **126** could potentially be converted to the reactive isocyanate **130** which could then couple to the primary hydroxyls on the BDI head unit of **129** generating wedges which can be anchored to the core to give the putative second generation dendrimer **132**. Iteration of this could then lead to higher generation dendrimers. The concept of this isocyanate coupling was demonstrated in the previous chapter. Additionally, a number of other research groups have used the reactive isocyanate moiety in their dendritic building blocks.[21]

However, attempts to make the isocyanate **130** from diamine **126** by reaction with triphosgene in the presence of triethylamine and dichloromethane as solvent[22] were unsuccessful. A recently reported method for the synthesis of isocyanates from carbamate esters employing boron trichloride[23] could not be applied here. The known strong Lewis acid character of boron trihalides and their ability to cleave a wide variety of acetals (also ethers and esters) under relatively mild conditions makes their use incompatible with the acetal protecting groups. In any case the low yields of the synthesis leading to the trisubstituted triazine **128** meant that it was difficult to produce meaningful amounts of this compound for further study.

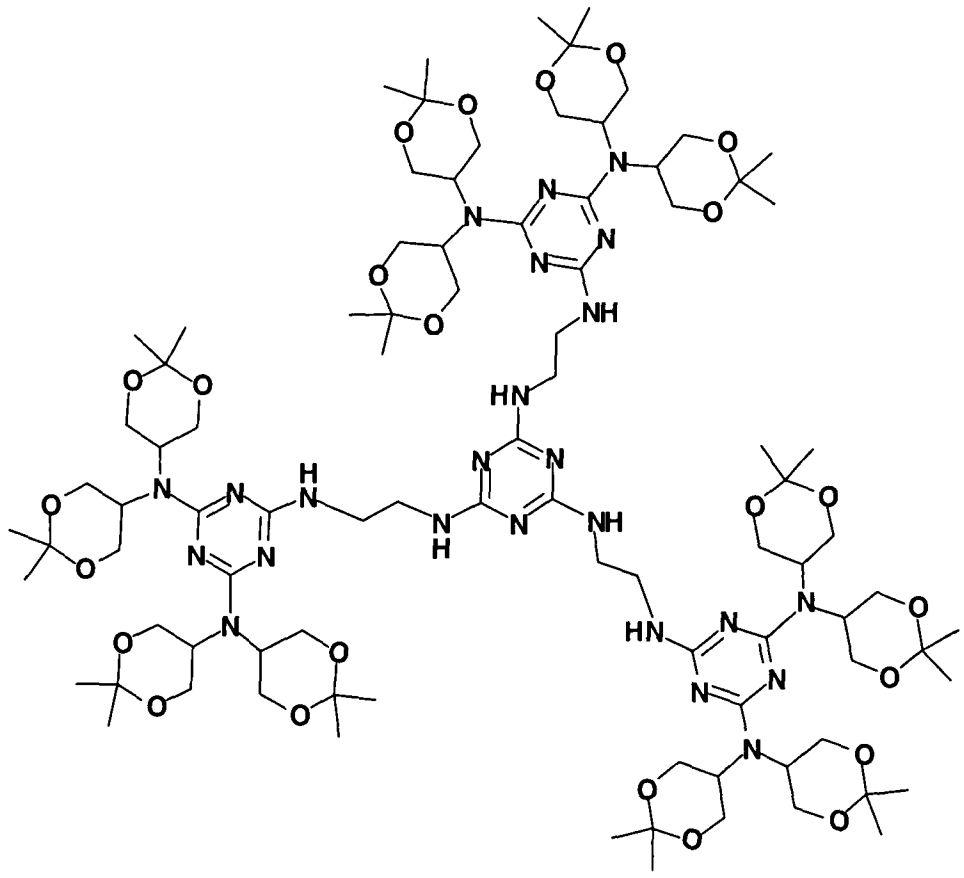

Surface Activation
Nucleophilic Hydroxyl Groups
Reactive Isocyanate Moiety
Focal Point Activation
Coupling, to form wedges and focal point activation
Core Anchoring
125
129
126
130
131
132

Scheme 3.2.3

It has been demonstrated that the third position in the disubstituted triazine **109** is still active to displacement by primary alkyl amines, such as dodecylamine, to give the trisubstituted triazine **112**. Thus it can be envisaged reaction of the disubstituted triazine **109** with diamines might feasibly result in rod shaped dendritic structures and even more highly branched first generation structures on anchoring to cyanuric chloride. For example, using 1,2 diaminoethane it can be postulated that reaction with **109** would afford a highly branched AB_2 unit with a reactive primary amine at the focal point (A) and two BDI diacetonide units as the 'B' moieties. This AB_2 unit can be reacted with a further equivalent of the disubstituted triazine **109** or with cyanuric chloride to give the plausible structures **133** and **134**.



133



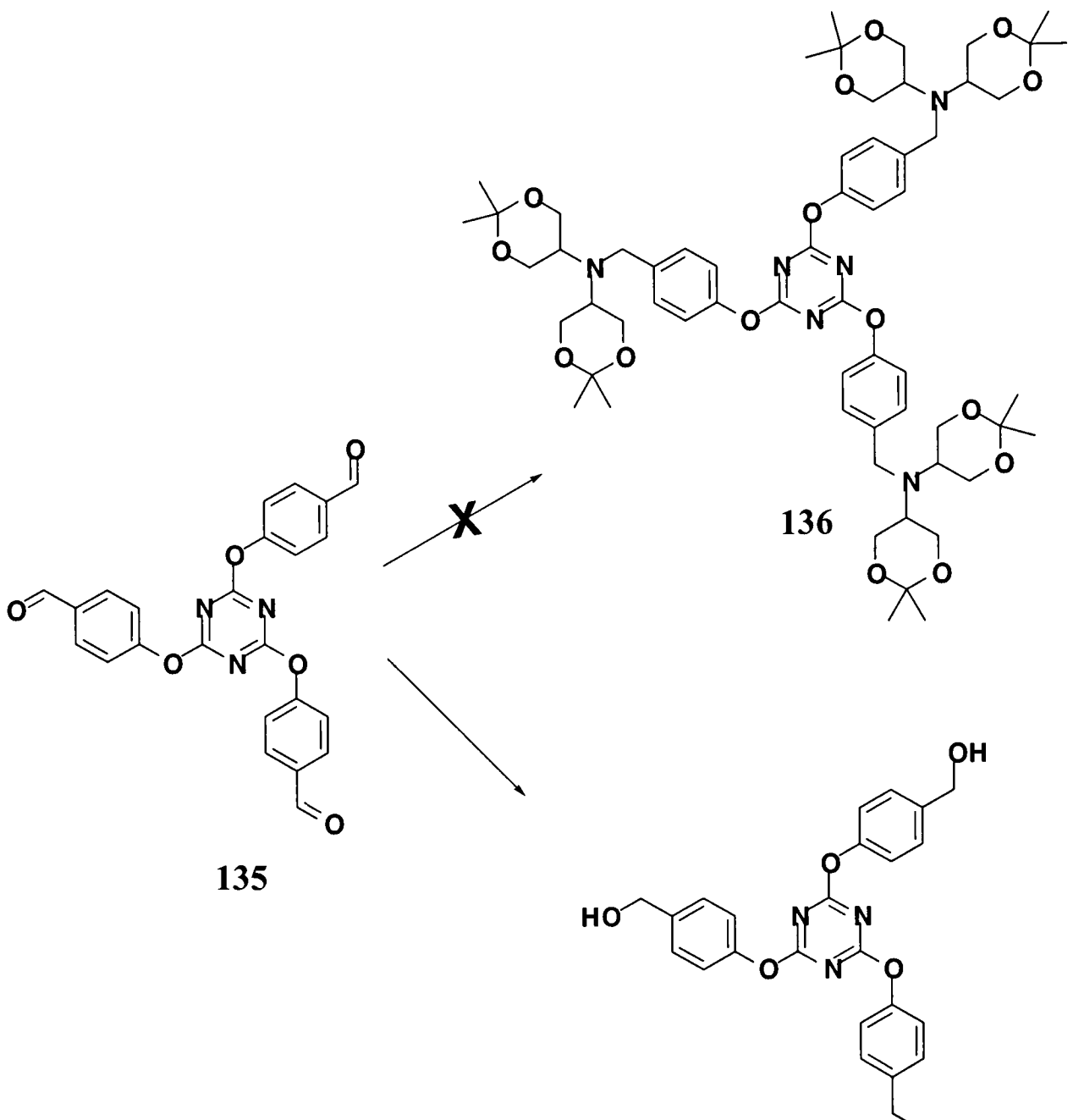
134

It might be that a longer diamine chain is necessary to overcome steric issues as seen with the less branched analogues incorporating a C_2 spacer. It can be predicted that reaction of the commercially available triamine core, tris(2-aminoethyl)amine, with the disubstituted triazine **109** might afford similar structures with less steric hindrance and possibly simplified NMR spectra.

Hypercores Based on the Triazine Nucleus

A contrasting approach to that of extending the nucleophilic branching unit is to extend the core unit. The trisubstituted triazine **135**, is a trialdehyde template prepared in a single step by the reaction of cyanuric chloride with three equivalents of *p*-hydroxybenzaldehyde in refluxing toluene[24]. Dubbed 'TRIPOD' it was designed as a template for the synthesis of a three helix bundle protein. It has also been shown to form a variety of stable Schiff bases with certain amines and has been shown to undergo reductive aminations with a variety of amines using sodium cyanoborohydride as the reducing agent in methanol/ acetonitrile (1:1).[25] Sasaki *et al.* have also showed that acid hydrolysis of these Schiff bases regenerates the trialdehyde, **135** demonstrating the robustness of the phenoxy linkage to acids – the integrity of the recovered trialdehyde being confirmed by t.l.c. and HPLC. Additionally no *p*-hydroxybenzaldehyde product was detected in the hydrolysis products.

With the trialdehyde **135**, in hand, it was anticipated that reaction of this with the diacetonide of BDI, **60** under reductive amination conditions would afford the three-directional structure **136** (**Figure 3.9**). This would be a two step synthesis from the amine **60** which would be installed late in the synthesis. It might be possible that BDI itself **58** would undergo reductive amination with 'TRIPOD' **135** thus negating the protection/deprotection steps. With the knowledge that the phenoxy ether linkages are acid stable, global deprotection of **136** with aqueous acid would lead to a polyhydroxylated first generation dendrimer. The mono- and di- reductive amination products might also be prepared giving access to dendritic structures with an intact aldehyde functionality.



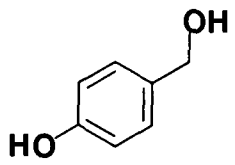
135 **136** **137**

Figure 3.9. Anticipated (**136**) and fated (**137**) products of treating 'TRIPOD' with BDI derivative **60** under catalytic hydrogenation conditions or other reducing conditions.

However all attempts to effect this reductive amination including catalytic hydrogenation with 10% palladium on carbon, sodium cyanoborohydride, and finally sodium triacetoxyborohydride were unsuccessful. The boron reducing agents gave no reaction whilst catalytic hydrogenation for 3 days afforded the reduction product, **137** as the major product.

The tri-benzylic alcohol **137** was the major product isolated under catalytic hydrogenation conditions, however other products were observed by t.l.c. The reaction was carried out again under the same conditions using *p*-hydroxybenzaldehyde instead of the trialdehyde **135**. This should allow the detection and isolation of the reduction product and any concomitant reductive amination products. The only isolated product was the diol **138** in 83% yield and no reductive

amination products (or their hydrogenolysed counterparts were detected). Additionally there was no evidence for degradation caused by the attack on the ether linkage by the amine.



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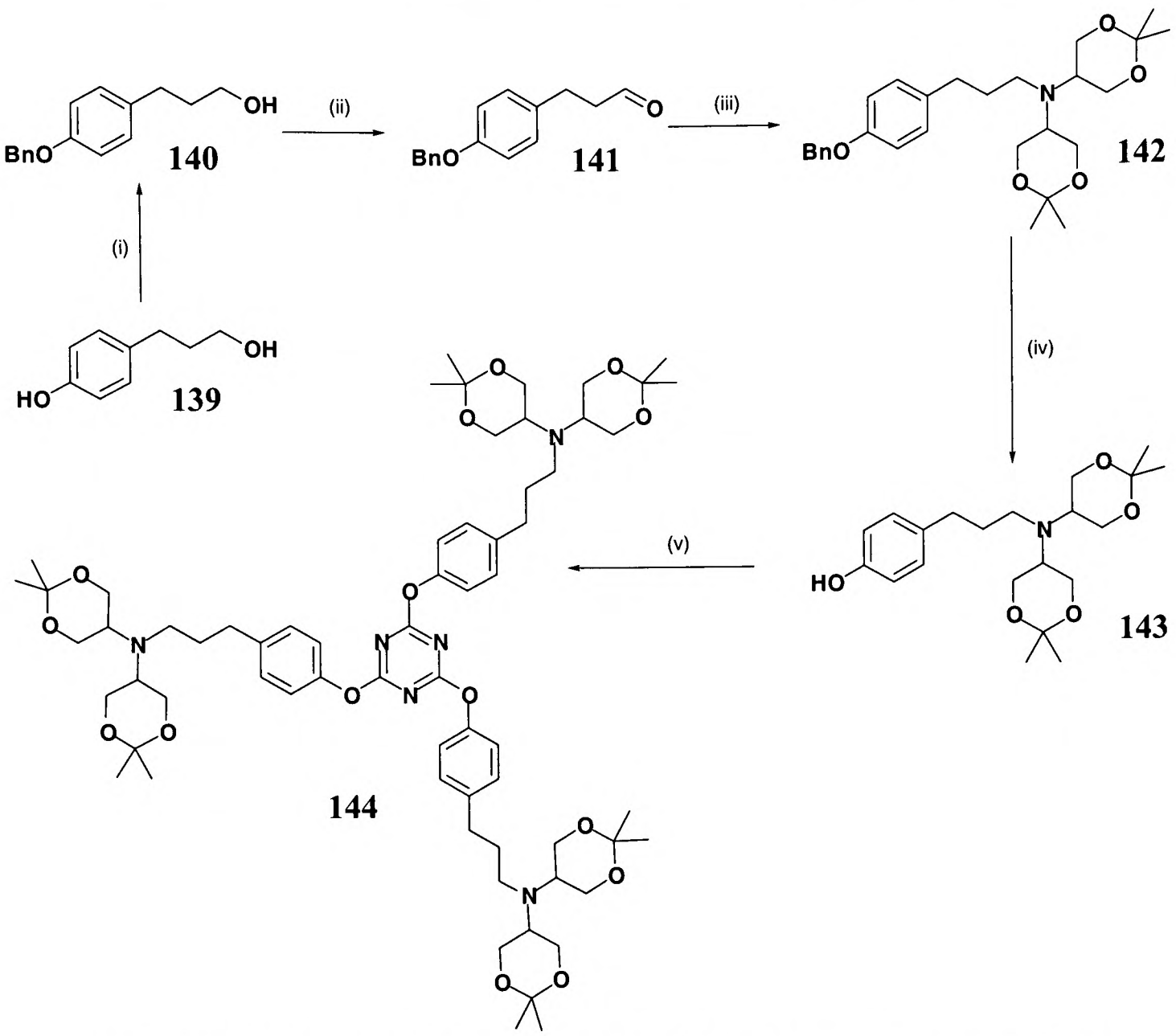
This was compelling enough to demonstrate that a reductive amination by this route could not be effected. This was not an obvious outcome to predict given the observation that the BDI derivative **60** undergoes smooth reductive amination with aldehydes. However with hindsight it might be easy to rationalise. The sterically encumbered iminium ion that would have to form transiently between the BDI derivative, **60** and the aldehyde (with a large α-substituent) in order to be reduced and form the amine might be disfavoured on steric and entropic grounds.

An AB_4 Unit with a Phenolic Focal Point: The Production of a Small Dendrimer

The next logical step was to extend the aldehyde portion out from the phenol moiety to see whether an aldehyde with a less bulky α substituent might undergo reaction. Starting from the commercially available diol **139**, a chemoselective benzylation affords **140**, in 95% yield (**Scheme 3.2.4**). The free hydroxyl group in **140** can now be oxidised by PDC to form the aldehyde **141**. BDI diacetonide **60** does indeed undergo smooth reductive amination with this aldehyde to afford the orthogonally protected AB_4 dendritic monomer, **142**. Focal point activation by hydrogenolysis proceeds quantitatively to afford the phenol, **143**. This can be anchored to the *s*-triazine core to give the first generation dendrimer, **144**.



Reagents and Conditions: (i) BnBr, NaH, DMF, (ii) PDC, DCM, (iii) $Na(OAc)_3BH$, amine **60** , 1,2-DCE, (iv) H_2/Pd black, MeOH, (v) Cyanuric chloride, acetone, K_2CO_3.

Scheme 3.2.4

Although this is a longer sequence than the trialdehyde hypercore it does allow access to the orthogonally protected AB_4 branching unit, **142**. This should allow rapid dendritic growth by invoking the double exponential growth strategy (chapter 1 and **Figure 3.10**) and lead to dendrimers with high branch multiplicity and consequently a large array of peripheral hydroxyl groups in even the lower generation structures.

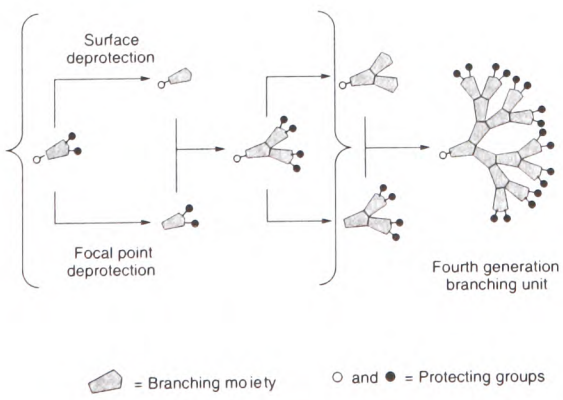
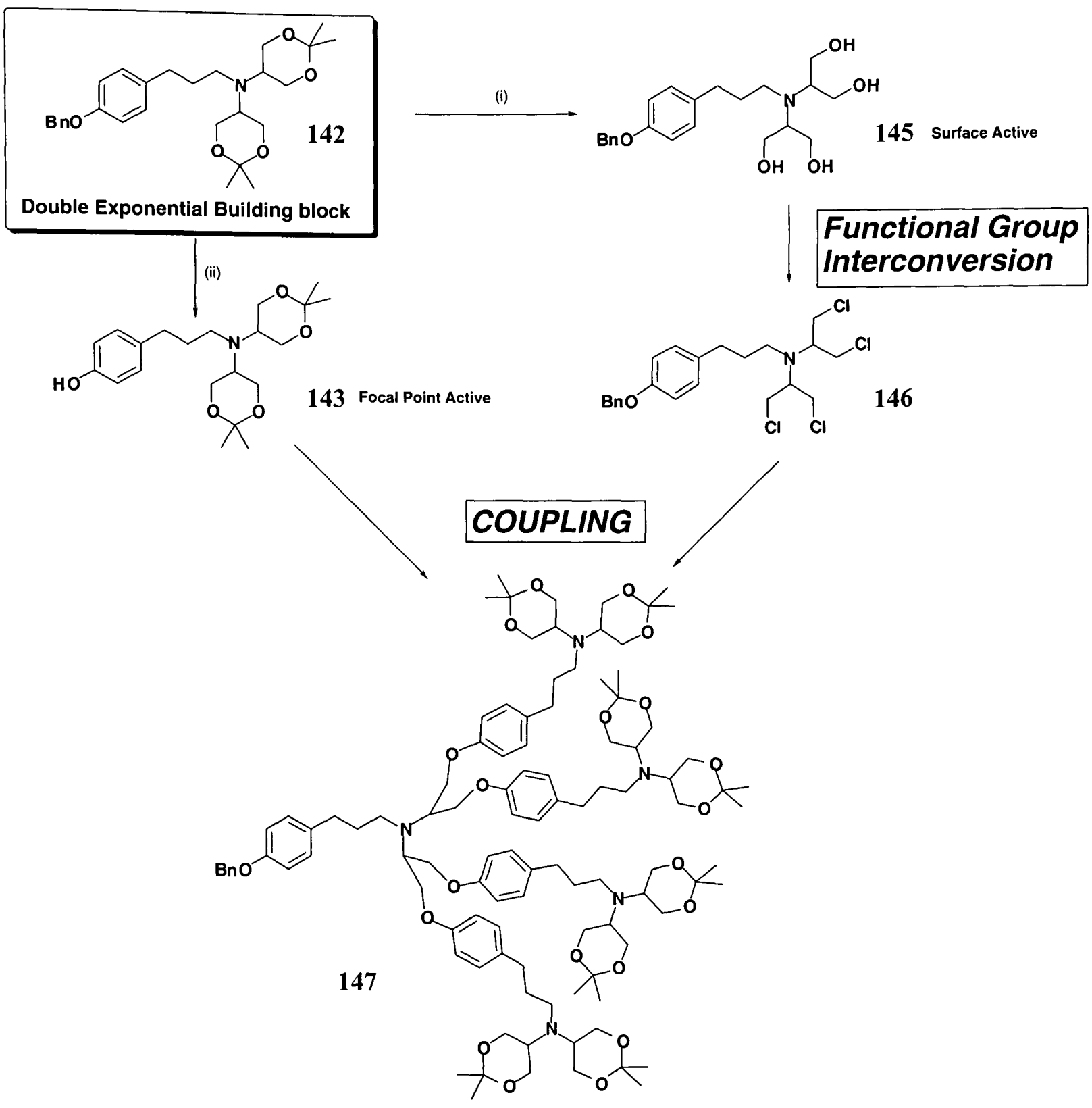


Figure 3.10. Double exponential growth strategy (also chapter 1). Construction of a second generation wedge in parentheses.

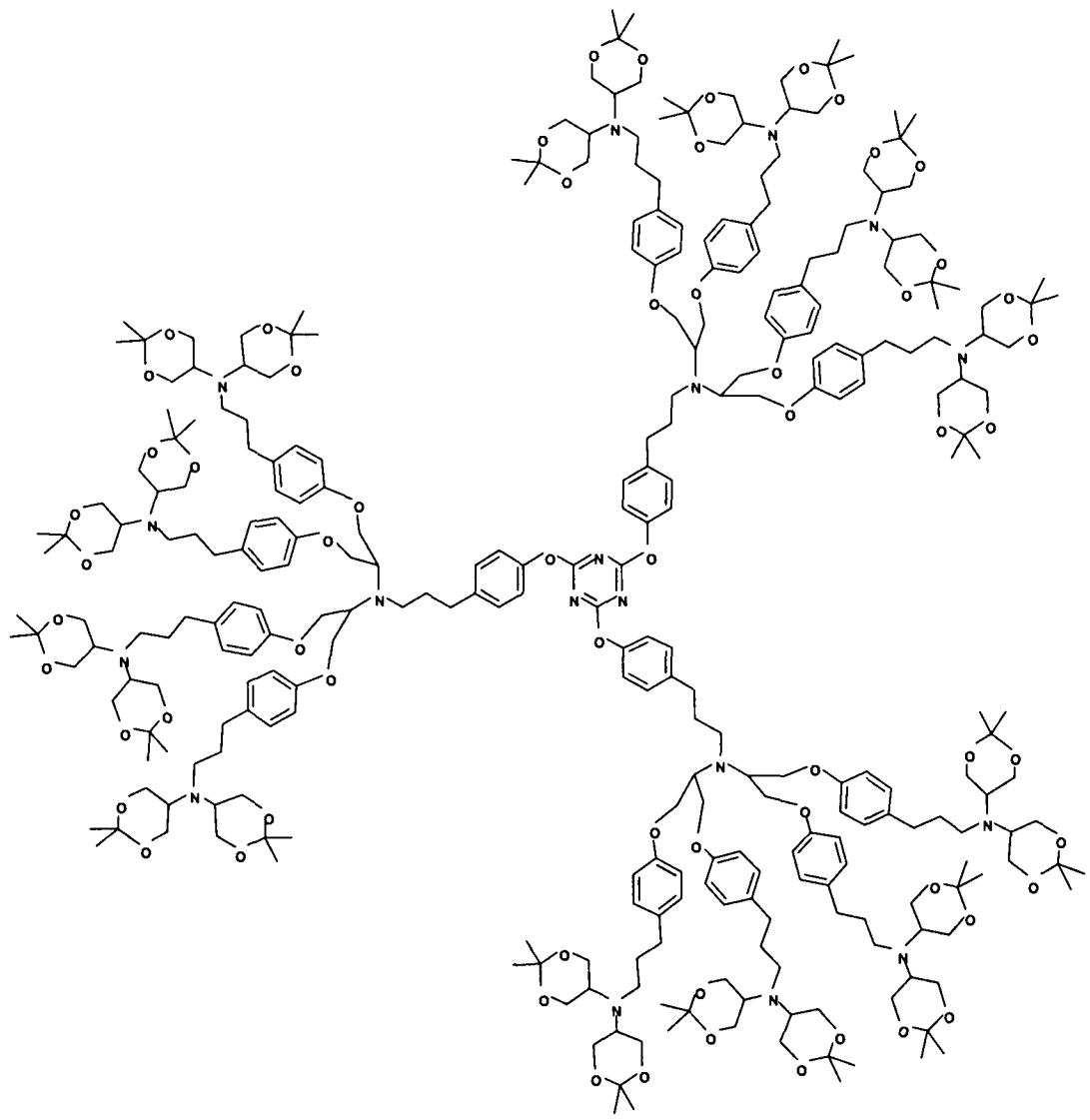
A possible growth strategy is illustrated (**Scheme 3.2.5**) and the putative second generation structure **148** is shown.



Reagents and Conditions: (i) TFA/H_2O (1:1), (ii) H_2/Pd black, MeOH.

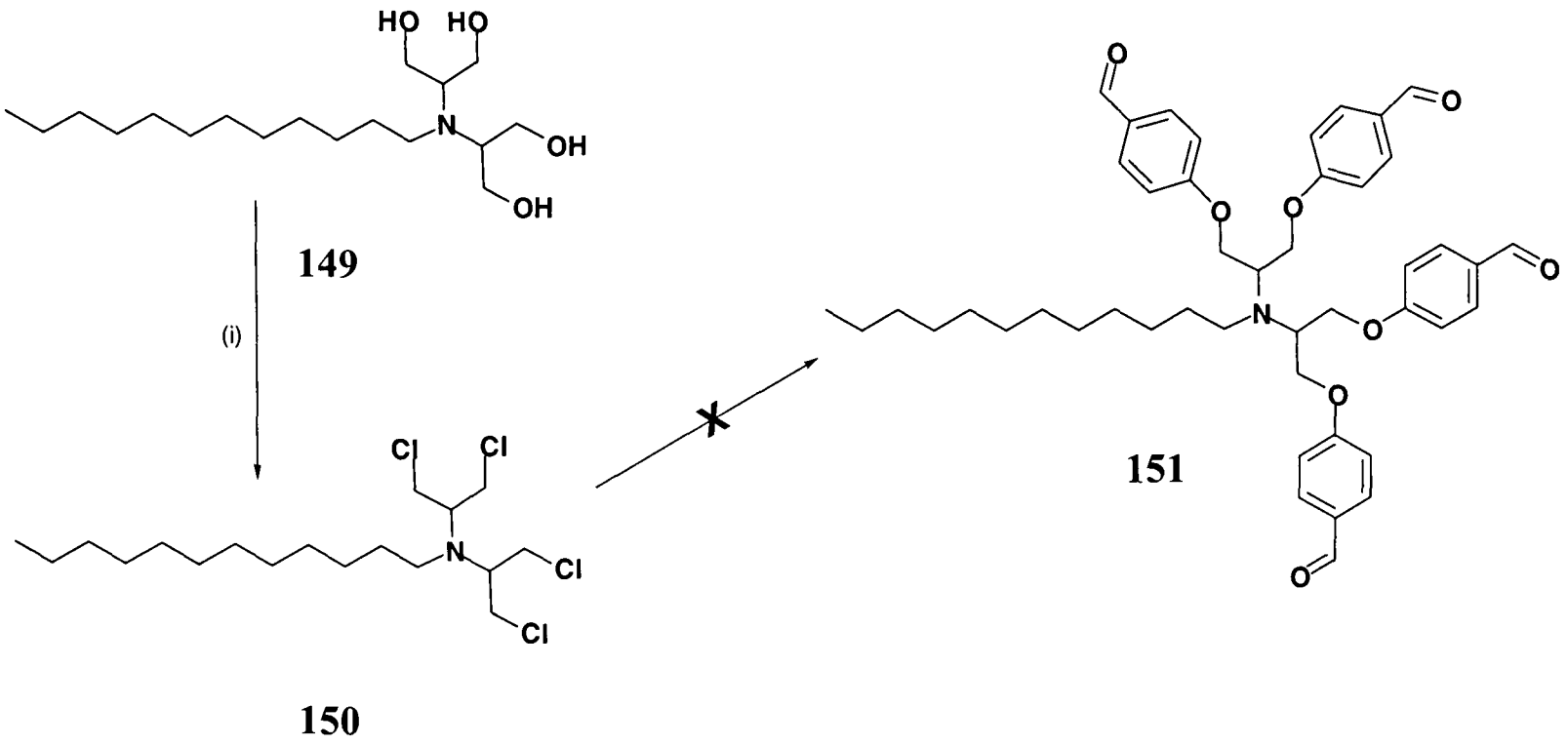
Scheme 3.2.5

Focal point activation of **147** by hydrogenolysis followed by core anchoring to cyanuric chloride **100**, would afford the three directional second generation dendrimer **148**. This would have 48 free hydroxyl groups on global deprotection.



148

So far, the concept has been demonstrated using the simpler analogue **149** prepared from the reductive alkylation of BDI **58** with dodecanal.[26] With this tetraol in hand, the tetrachloro derivative **150** could be quantitatively generated by treatment of **149** with thionyl chloride and catalytic DMF (**Scheme 3.2.6**).



Reagents and Conditions: (i) $SOCl_2$, cat. DMF, (ii) **150**, K_2CO_3, acetone, Δ.

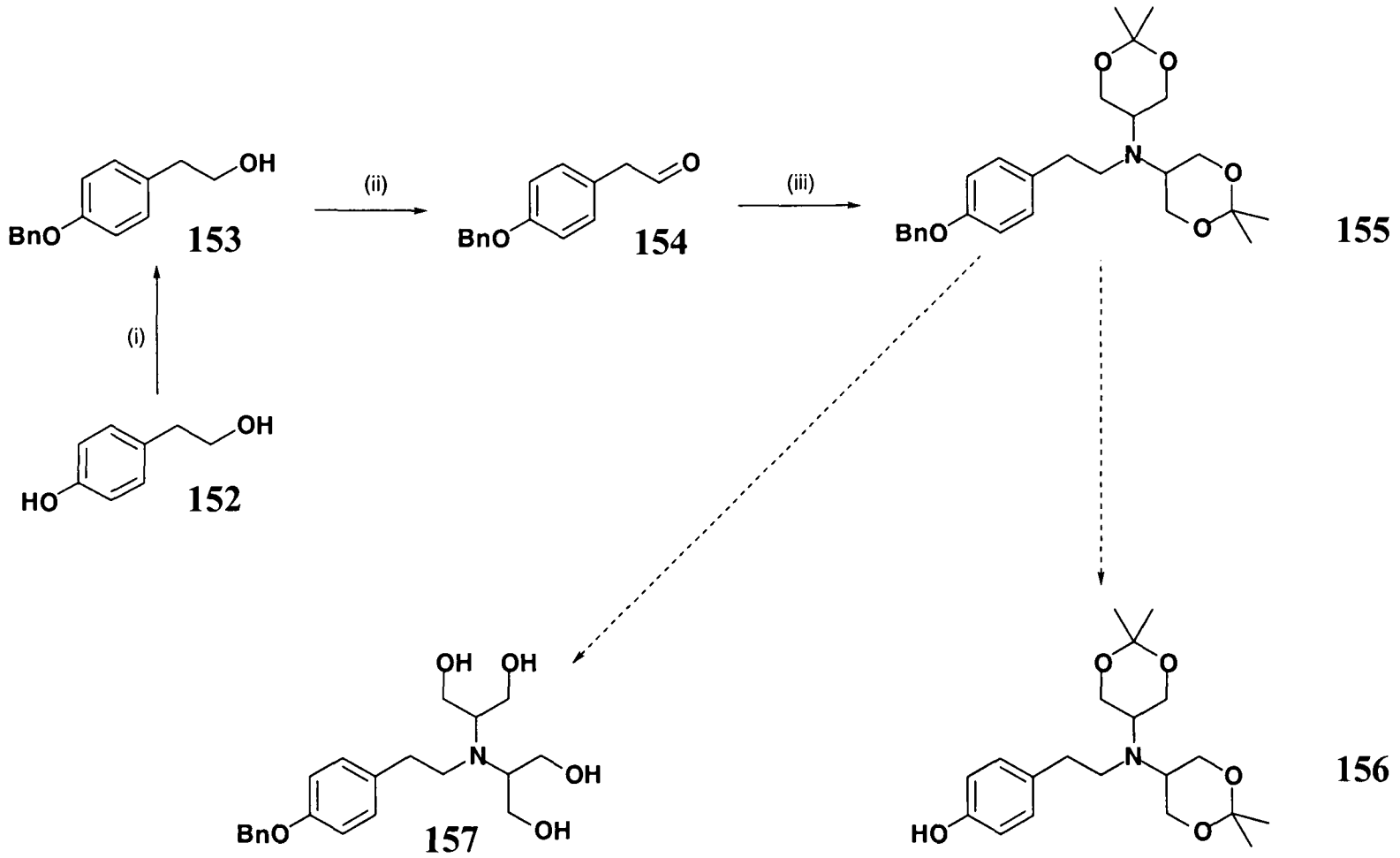
Scheme 3.2.6

The derivative **150** was treated with a variety of nitrogen and oxygen nucleophiles including *p*-hydroxybenzaldehyde but no direct displacements were observed. *p*-Hydroxybenzaldehyde was chosen as a chain-end moiety both for its structural similarity to the nucleophilic portion of the AB_4 branching unit, **143**, and for its ability to serve as an NMR 'tag' for the characterisation of the growing molecule. The aldehydic protons are distinct and should not overlap with any of the other proton signals. This then serves as a reliable handle to assist in characterising the resulting dendrons. Additionally – it incorporates a UV active chromophore facilitating the monitoring of the reaction by t.l.c. It is possible that such displacements might be effected by invoking nucleophilic catalysis with sodium iodide in the presence of base to deprotonate the phenol.[27] However such a derivative may still exhibit a neopentyl-type inertness to sterically encumbered nucleophiles.[28] Such problems have been overcome by extending these groups with linkers (see below).

The derivative **149** was chosen to pilot such an iterative scheme as it was deemed to be large enough to render the derivative **150** non-volatile. It should be noted that such structures resemble mustard gases. The tetrachloro derivative **150** was not isolated and characterised but

its formation was convincingly inferred from mass spectrometry studies including an assessment of the isotopic distribution envelope.

Analogous chemistry was performed on the truncated phenol **152** to generate the exponential building block **155** in good yield. Deprotection strategies would afford the singly protected analogues **156** and **157** (**Scheme 3.2.7**).



Reagents and Conditions: (i) BnBr, NaH, DMF, (ii) PDC, DCM, (iii) $Na(OAc)_3BH$, amine **60** ,1,2-DCE.

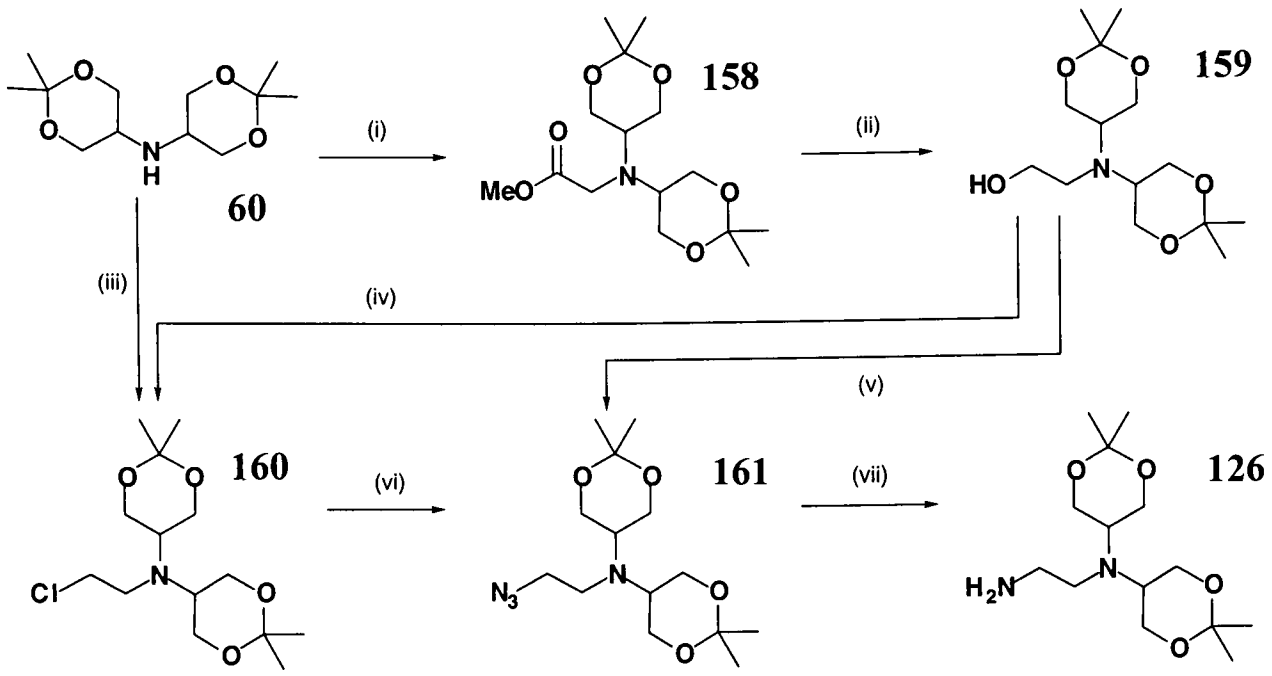
Scheme 3.2.7

Extension of the BDI Unit – New Dendritic Building Blocks[26]

To circumvent the inertness of derivatives such as **150,** with respect to nucleophilic displacement, and delay the onset of dense packing, a number of building blocks have been constructed which extend the highly directional BDI unit.

Recognising the low reactivity of the sterically hindered amine functionality in BDI **58** and its diacetonide **60**, attention was directed to the extension of the nitrogen focal point using linkers. A number of such linkers have been presented in this chapter. The C_2 ethylamine compound

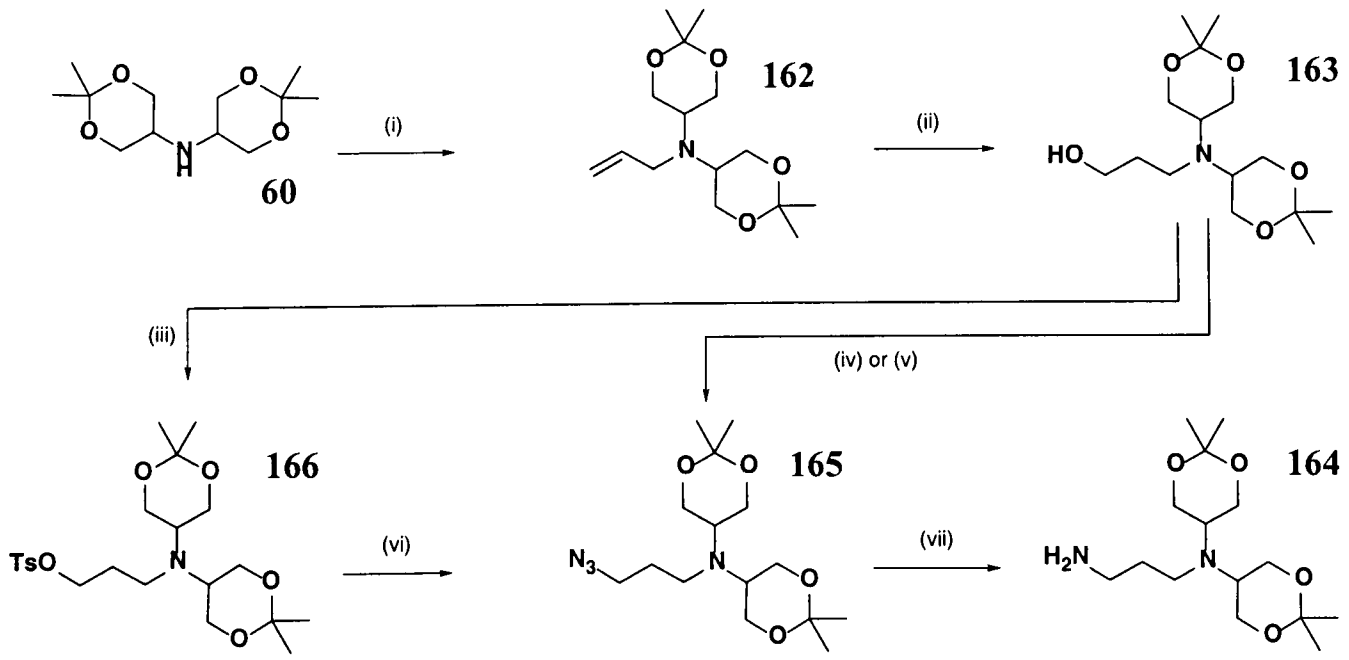
126 has also been prepared by a longer route which installs an azide as the latent primary amine functionality (**Scheme 3.2.8**).



Reagents and Conditions: (i) $BrCH_2CO_2Me$, toluene, DIPEA, cat. Bu_4NI, 110°C, (ii) $LiBH_4$, THF, (iii) $ClCH_2CHO$, $Na(OAc)_3BH$, DCE, (iv) MsCl, py, (v) $(PhO)_2PON_3$, DBU, DMF, 60°C, (vi) NaN_3, DMF, (vii) H_2/Pd black, EtOAc.

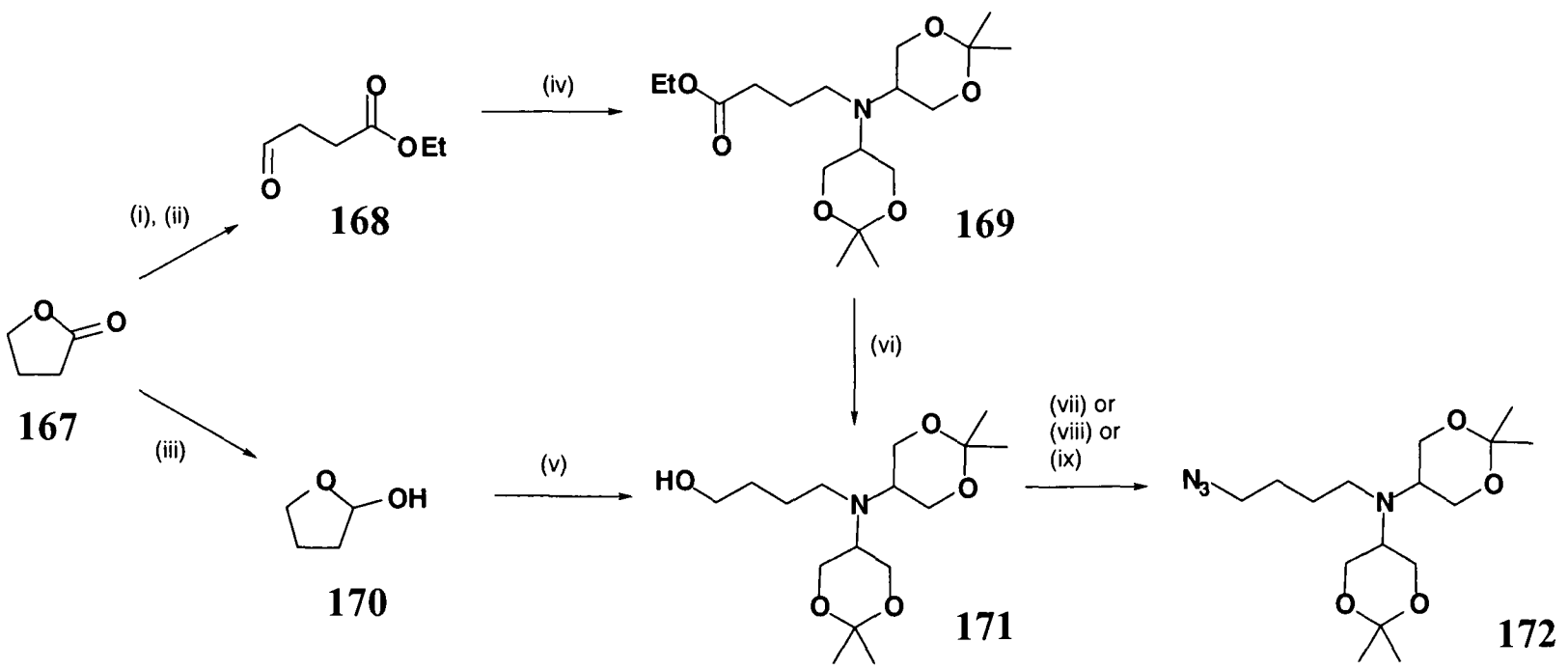
Scheme 3.2.8

Additionally, a C_3 diamine **164** and a C_4 azide **172** were synthesised (**Schemes 3.2.9** and **3.2.10**) and using these building blocks a number of first generation dendrimers and have been constructed based on the 1,3,5-benzene tricarbonyl chloride core **121**. For example, the C_2 diamine **126** affords triamide dendritic structures such as **173**, and on global deprotection **174**.



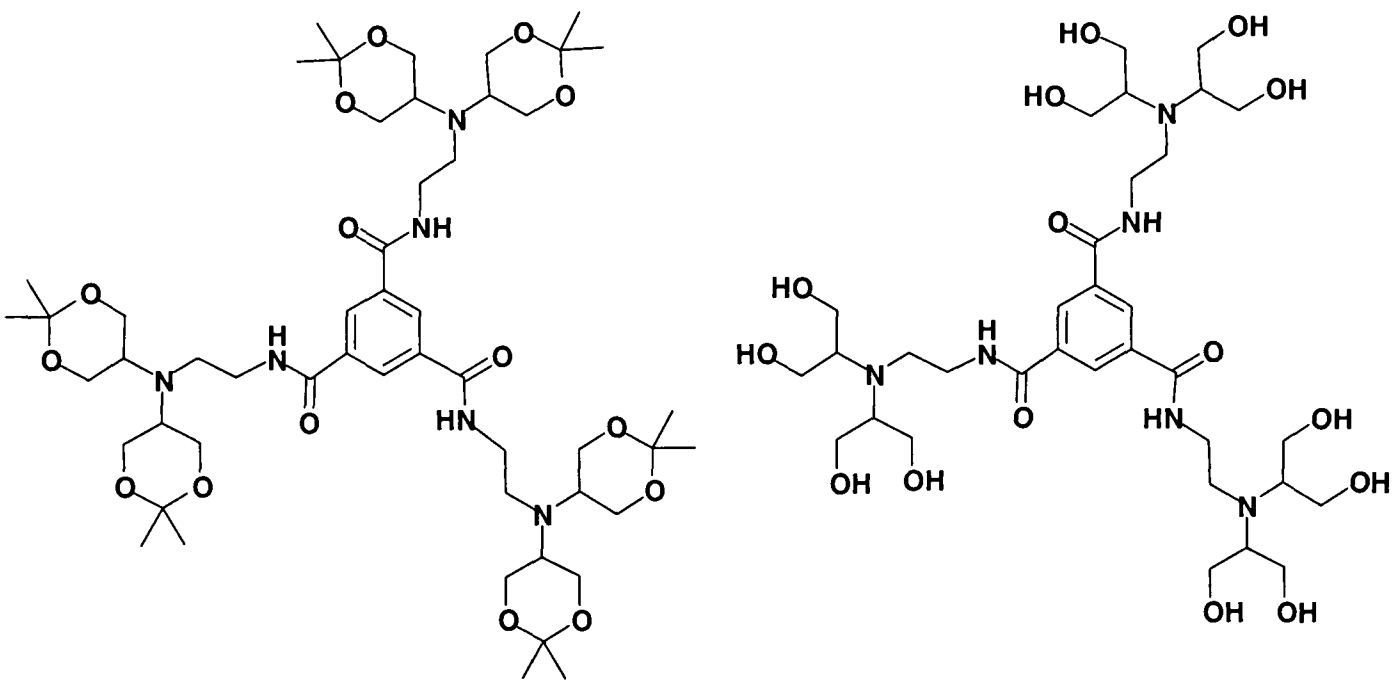
Reagents and Conditions: (i) CH_2=$CHCH_2I$, DMF, K_2CO_3, 70°C, (ii) (a) 9-BBN, THF, (b) H_2O_2, NaOH, 60°C, (iii) Ts_2O, py, sieve, (iv) $(PhO)_2PON_3$, DBU, DMF, 60°C, (v) MsCl, DIPEA, DMF, 0°C then NaN_3, r.t., (vi) NaN_3, DMF, (vii) H_2/Pd black, EtOAc.

Scheme 3.2.9



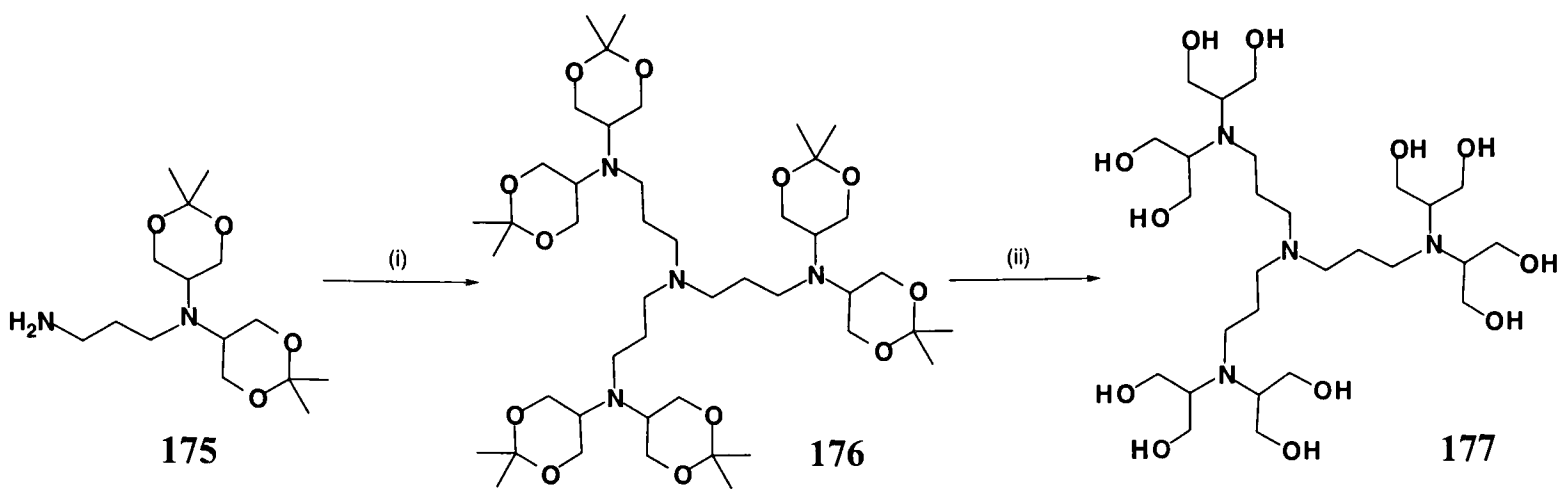
Reagents and Conditions: (i)EtOH, c. H_2SO_4, (ii) PCC, DCM, sieves, (iii) DIBALH, toluene, -78°C, (iv) $Na(OAc)_3BH$, DCE, BDI, (v) $Na(OAc)_3BH$, DCE, BDI, (vi) $LiBH_4$, THF, (vii) MsCl, py, 0°C then NaN_3, DMF, (viii) Ts_2O, py, sieve then NaN_3, DMF, (ix) $(PhO)_2PON_3$, DBU, DMF, 60°C.

Scheme 3.2.10



173 **174**

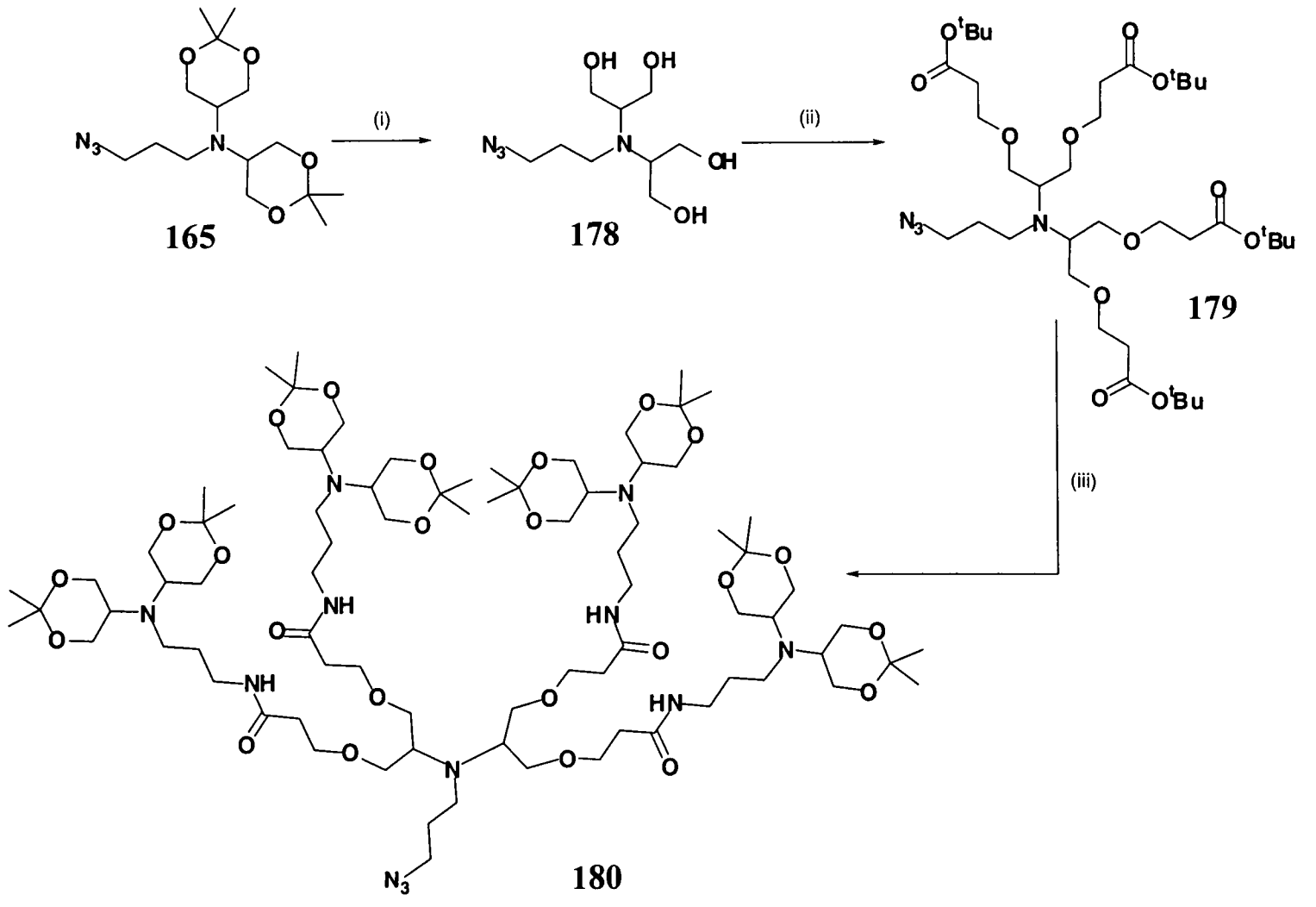
By coupling two equivalents of the tosylate **166** with diamine **175** the three fold symmetric structure **176** is generated which has branching from a trigonal nitrogen centre and three methylenes between the centre and the trigonal nitrogen branching points (**Scheme 3.2.11**).



Reagents and Conditions: (i) Tosylate **166**, DCM, DIPEA, (ii) TFA/H_2O (1:1).

Scheme 3.2.11

Additionally, the steric retardation of S_N2-type chemical transformation caused by the neopentyl type hydroxymethyls in the BDI unit can be circumvented by extension of the primary hydroxyl arms. At least a three atom distance is needed between the branch point and the reactive chemical centre. A successful strategy is outlined below (**Scheme 3.2.12**) which affords the second generation wedge **180** in 90% yield over two steps from **179**.



Reagents and Conditions: (i) AcOH/H_2O (1:1), (ii) Acrylic acid *tert*-butyl ester, aq. NaOH, $^nBuNHSO_4$, (iii) TFA/ H_2O (1:1) then amine **126**, TBTU, DIPEA.

Scheme 3.2.12

Thus, the problems associated with the conversion of terminal, neopentyl-type hydroxymethyl groups were bypassed by the introduction of spacer groups. Although these steps proved successful they added several steps to the iterative process.

Conclusion

In time, oak trees are produced from acorns and likewise the design of a novel orthogonally protected AB_4 dendritic building block has been established which seeds further work in this area. The synthesis was effected by a series of logical developments and modified notions involving the construction of various dendrimer prototypes. The incorporation of a range of AB_4 dendritic building blocks embodying BDI into dendritic structures based on a triazine nucleus has been demonstrated as a versatile approach to symmetrical and non-symmetrical dendrimers, either by convergent or divergent routes. Non-symmetrical dendritic molecules of C_2 symmetry will be discussed (chapter 4).

The ready availability of novel branched building blocks and suitable initiator cores is critical to the development and advancement of new dendritic macromolecules. The utilisation of novel dendritic monomers together with the structural features of the ensuing dendritic molecules has been presented.

As yet, little attention has been directed to the chemical and physical properties of these molecules. Potential applications may be thwarted by the low yields of synthesis using triazine linkers and the limitation of not being able to produce meaningful amounts.

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4. Dendrimeric and Amphiphilically Equipped Triazines II: C_2 Symmetry

4.1 Introduction

Amphiphilic Molecules

Substances which are strongly adsorbed at an interface and hence cause a substantial lowering of the surface tension are termed surfactants, or surface active agents.[1] These substances include naturally occurring and synthetic units, and have a wide range of applications. An interesting property of surfactants is that they can spontaneously self-assemble into micellar structures, or association colloids, (**Figure 4.1**) and such structures are limited to a finite size by both geometric and energy factors. A feature common to such surface active substances is that they are amphiphilic, possessing distinct hydrophobic and hydrophilic portions. However, micellisation is not confined to water as a solvent and can occur in many non-polar media.

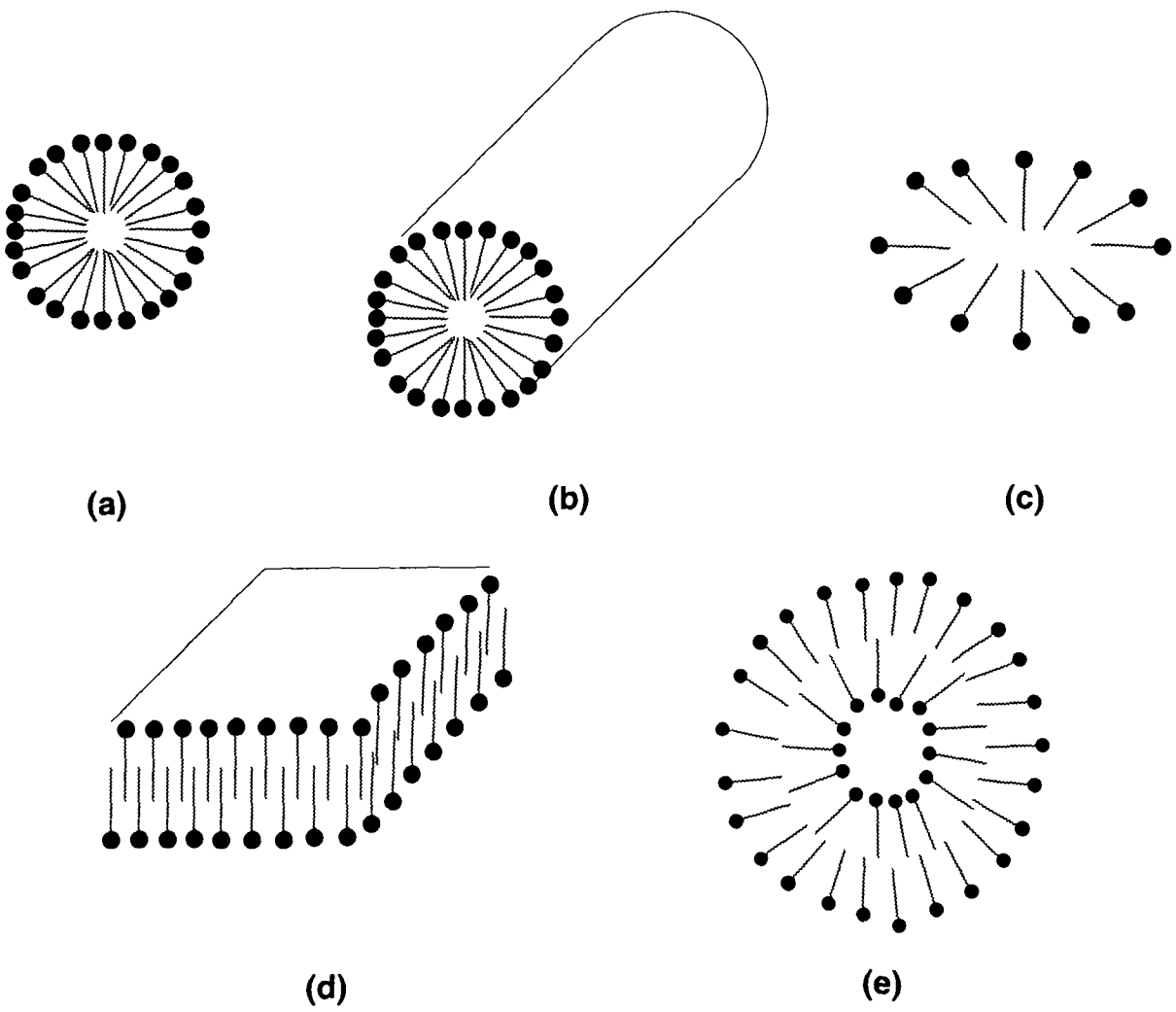


Figure 4.1. Some types of micellar structure:- (a) spherical, (b) cylindrical, (c) disc like, (d) lamella, (e) spherical vesicle. The head groups are represented as filled circles.

In chapter 1 there was allusion to the divergent syntheses of 'arborols' by Newkome and co-workers.[2] These micellar dendrimers, with both hydrophilic and hydrophobic portions were

described in terms of 'directionality' (**Figure 1.2**). It is the one (mushroom shaped) and two-directional (dumbbell shaped) type structures that are of relevance here as they both have C_2 rotation axes, (**Figure 4.2**). Molecules of both types, incorporating BDI together with other amines, to form non-symmetrical *s*-triazines will be addressed here.

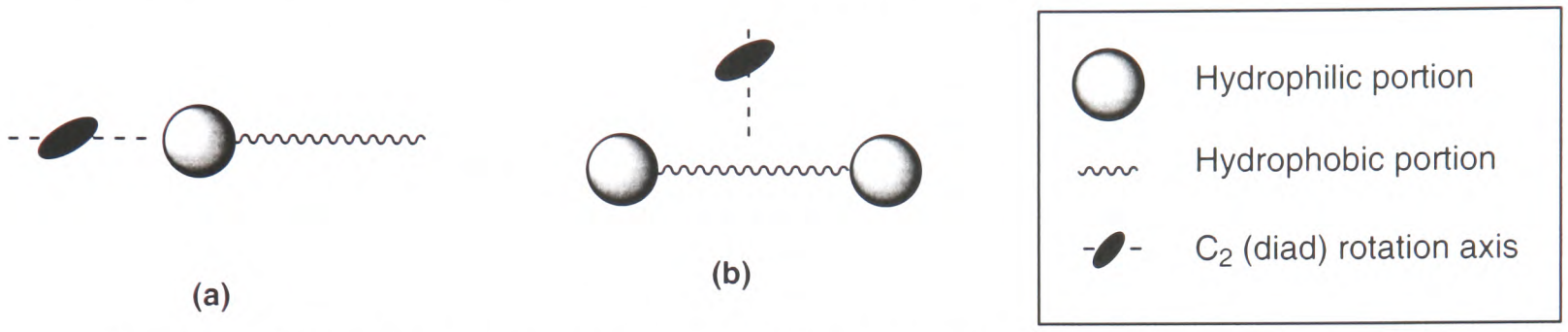


Figure 4.2. Schematic one and two-directional amphiphilic molecules showing the C_2 rotaion axes.

Amphiphilic molecules spontaneously self-organise and there is no nucleation step - the driving force for this process being the hydrophobic effect. The molecules self-assemble to create a microphase in which the hydrophobic portions sequester themselves inside the aggregate and the polar head groups orient themselves toward the aqueous phase. Historically, amphiphilic molecules have comprised of surfactants of low molecular weight with a compact polar head group, or amphiphilic block copolymers with linear, extendable polar chains.

There is a well defined surfactant concentration when the molecules in a monolayer adsorbed at an interface form spherical micelles – this point being the critical micelle concentration (CMC), (**Figures 4.3** and **4.4**). At the CMC the micelles are approximately spherical in shape and at increased concentrations they can assume disc like, cylindrical, ellipsoidal, or laminar structures.

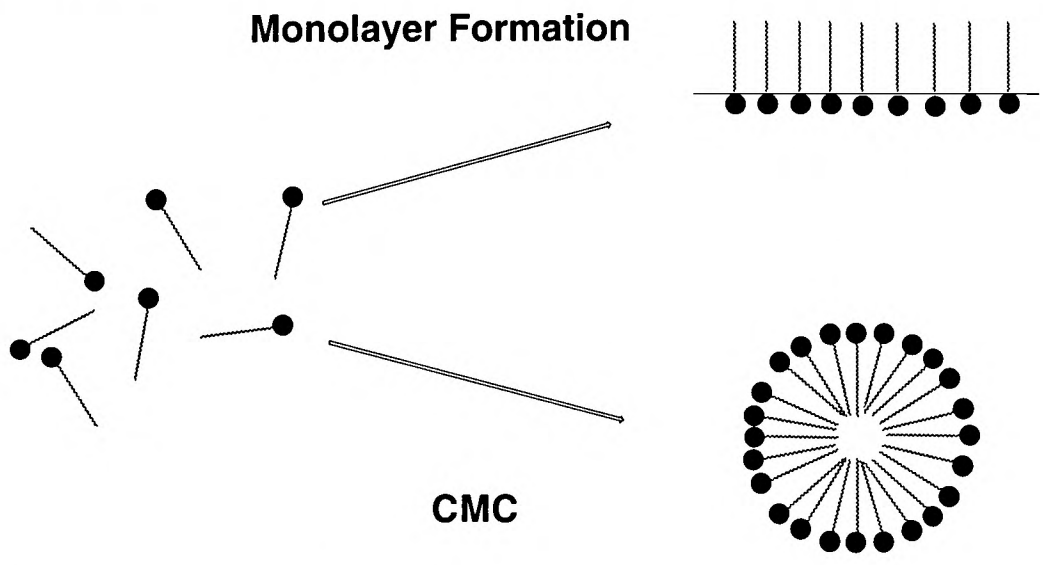


Figure 4.3. Amphiphillic molecules aggregate as a monolayer when adsorbed at an interface and at the CMC form micelles.

The occurrence of a CMC is the result of the two opposing factors of the hydrophobic effect and the repulsion between the head groups as they come close together. Thus under these conditions the growth process has specific limits, and aggregates cease to grow once they reach a certain size.

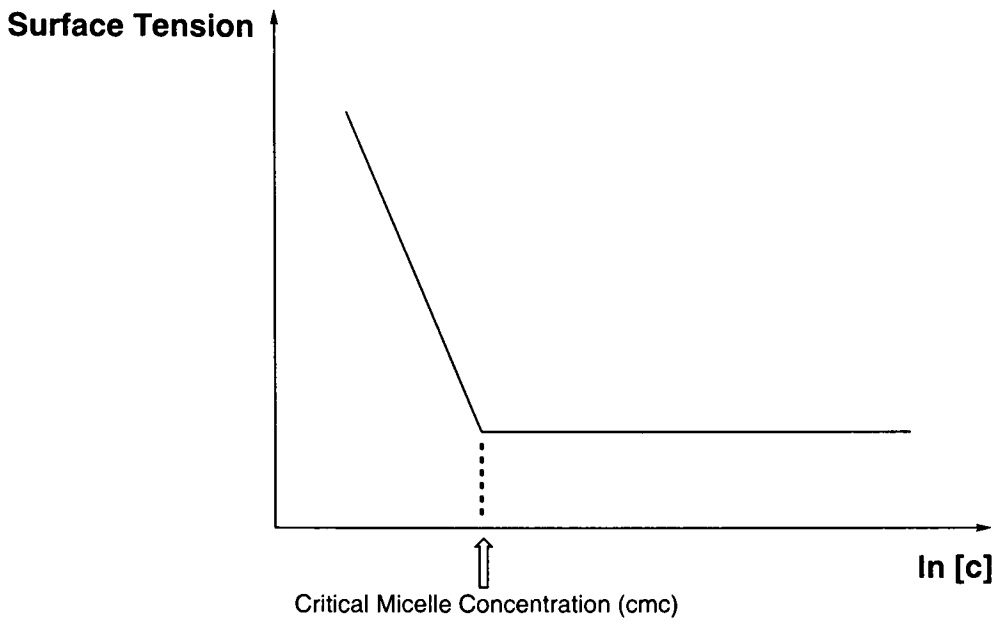


Figure 4.4. Plot for a layer of surfactant molecules adsorbed at an interface showing decrease in surface tension as concentration is increased and micelle formation at the CMC with no further decrease in surface tension.

Above the CMC, adding more surfactant simply produces more micelles over a considerable concentration range rather than further growth of existing micelles. Micelles are the simplest and best understood of all amphiphilic self-organising structures. The structure and stability of the aggregate is dependent on both internal conditions such as the critical packing parameter, *i.e.* the relative size of the hydrophilic to hydrophobic portions, and external conditions such as temperature and concentration. Such amphiphilic molecules may act as non-ionic surfactants.

Surfactant types are generally classified according to the charge on their head groups and therefore divide into three main groups, anionic, non-ionic and cationic surfactants, although there are other important groups for example, zwitterionic and polymeric surfactants. Non-ionic surfactants are widely used in many detergent and personal care products and are valued for several characteristics, some of which are that they are generally milder than ionic surfactants in terms of their effects on materials (particularly skin). They are usually more surface active than their ionic equivalents, they are not affected by the presence of Ca^{2+} and Mg^{2+} in water and they are often effective in stabilising foams.[3] Surfactants play an important role in a variety of

technological processes. Detergents, emulsification, coatings, lubrication, mineral flotation, and oil recovery are just a few examples.[4]

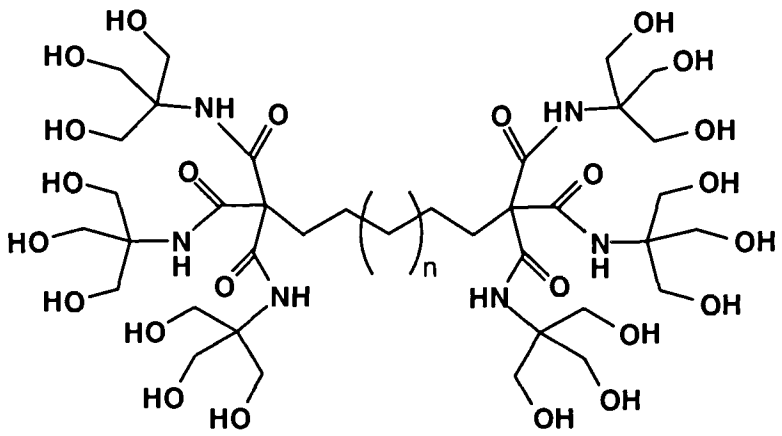
The main impetus for the synthesis of C_2 symmetric structures of the type shown in **Figure 4.2** was the production of amphiphilic molecules with potential use in micelle studies, surfactants (detergents/soaps), and the solubilising of derived organic compounds in water. Studies into further applications have involved enzyme inhibition studies (chapter 2) and even anti-viral testing with any biological activity presumably being attributable to the structural analogy of the acyclic BDI unit to natural products with known properties and not to the topology or physical characteristics of the whole molecule. Surfactant molecules containing multiple hydrophobic tails and hydrophilic heads have lately attracted considerable attention.[5]

Dumbbell-shaped amphiphiles are comprised of two hydrophilic groups connected by a hydrophobic linkage. Thus they fit the definition of a bolaamphiphile - a term derived from 'bolaform amphiphile', originally introduced in 1891 by Fuoss and Edleson.[6] Fuoss and Edleson's molecules have a structurally similar architecture although the hydrophilic groups were ionic. The synthesis and self-assembly of several bolaamphiphiles was initially reported by Fuhrhop and Mathieu.[7]

A bolaamphiphile is simply defined as a molecule in which two or more hydrophilic groups are connected by hydrophobic functionalities and such molecules have recently been highlighted[8] and reviewed.[9] They are also known as bolaform surfactants, bolaphiles, or α,ω-type surfactants. Compared to the case for the single-headed amphiphiles, the introduction of a second head group generally induces a higher solubility in water, an increase in the CMC, and a decrease in the aggregation number.[10]

Newkome's dumbbell shaped 'arborols' are two-directional surfactant-like macromolecules and were ideal for the study of aggregation. They were observed to stack in an organized manner so that the lipophilic alkyl chain moieties are orthogonally juxtaposed. The ability of these

compounds to induce gel formation when added to an aqueous environment in low concentration was shown to be affected both by the length and rigidity of the spacer groups. In the case of **181**, gelation occurred readily and the resultant gel could be characterised by a number of techniques including viscometry, optical microscopy, transmission electron microscopy (TEM), and light scattering.[11] The model proposed to explain this is based on an orthogonal stacking of the dumbbell shaped arborols to form a long, thin aggregate.



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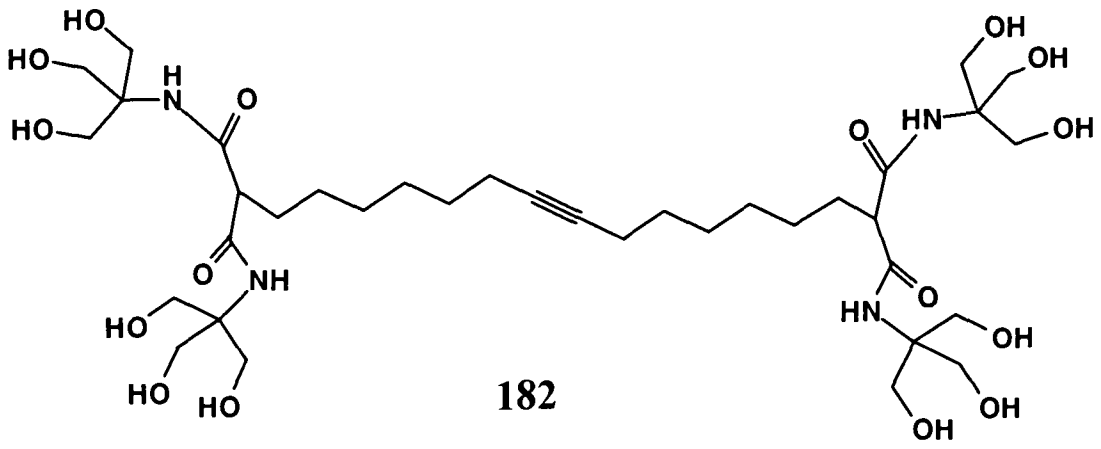

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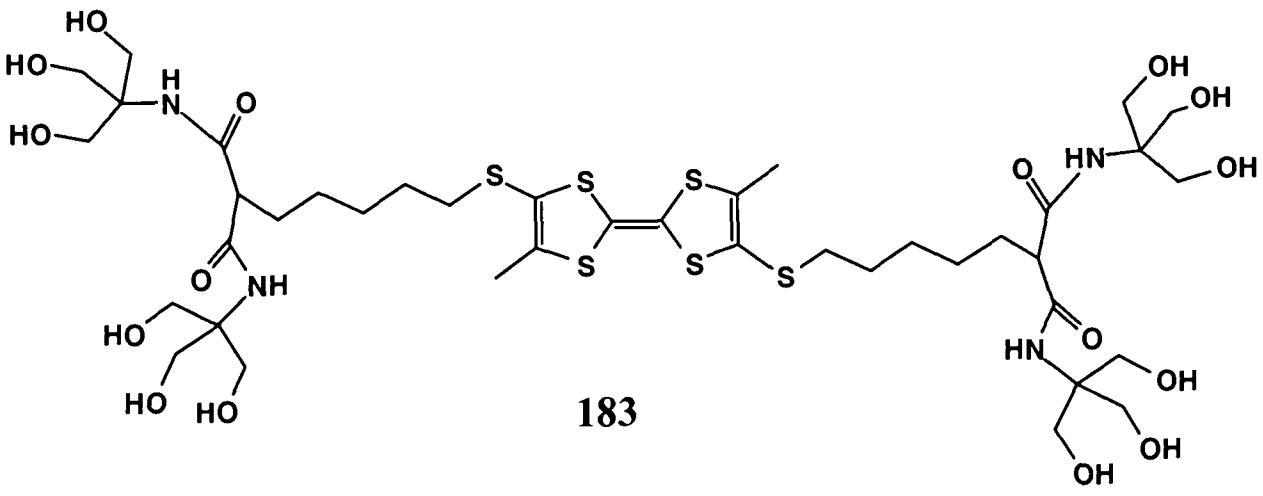


183

Thus hydrophobic groups associate in the interior and hydroxy groups project outward of the rod-shaped aggregate and interact with each other or water through hydrogen-bonding

interactions. It is possible that hydrogen-bonding interactions between amide groups along the rod axis further stabilise the aggregate.

The central alkyne bond functionality on the lipophilic linkage preorganises the unit **182** for subsequent interactions. In an analogous way to the alkane bridged bolaamphiphile, the alkyne formed a gel on dissolution in water. However, electron microscopy shows that due to the presence of the rigid, linear central alkyne moiety a less orthogonal chain alignment results, giving rise to helices rather than a stacked, linear aggregate.[12] Jorgensen and co-workers[13] synthesised bolaamphiphile **183** with a tetrathiafulvene (TTF) spacer. The resultant gel was made up of string-like assemblages with lengths in the order of tens of microns and diameters in the order of *ca.* 100nm.

Generally, the minimisation of lipophilic-hydrophilic interactions as well as the maximisation of hydrogen bonding and packing effects leads to gel formation. A number of structural features can also help to pre-organise and stabilise the gels once formed. Dispersions in which the attractive interactions between the elements of the disperse phase are so strong that the whole system develops a rigid network structure and under small stresses behaves elastically are termed gels.[14]

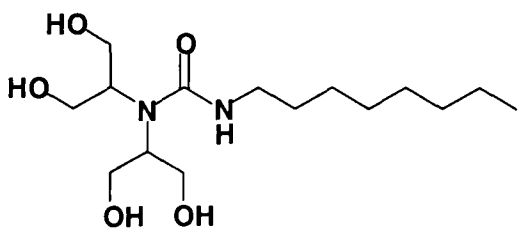
The aggregate morphologies of bolaamphiphiles include spheres, large cylinders, small and large discs, and vesicles.[10] Bolaamphiphiles have gained increasing attention since they may offer insight into micellular systems that can mimic enzymes, act as therapeutic agents, or serve as tools in the investigation of molecular recognition and assemblages.

4.2 Results and Discussion

BDI as a Polar Head Group: An Overview

Recently, several research groups have studied the aggregation behaviour of surfactants with unusual structural features in order to further understand the relationship between the structure of the amphiphile and the type of aggregates it forms. The literature is replete with publications in this area. Examples include surfactants with hyperextended[15] and spiro[16] hydrocarbon chains, gemini surfactants[17] and super surfactants, e.g. block copolymers of polystyrene and poly(propyleneimine) dendrimers.[18]

In the previous chapter, some attempts at synthesising three-fold symmetric dendritic molecules based on a triazine nucleus were presented. By making use of the stepwise substitution of the chlorine atoms in cyanuric chloride **100**, by BDI diacetonide **60**, it was demonstrated that unsymmetrical dendritic structures such as **112** could be synthesised in good yield. This observation, coupled with the knowledge that the polyhydroxylated head unit of BDI **58** has been incorporated into a range of *N*-alkylated derivatives, including **184**, **185**, and **186** (which already show potential as novel non-ionic surfactants[19]) led to studies into similar amphiphilic structures based on the triazine nucleus.



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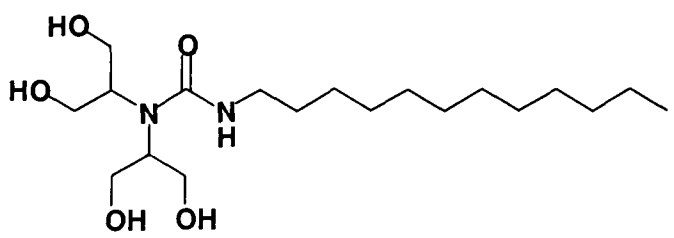

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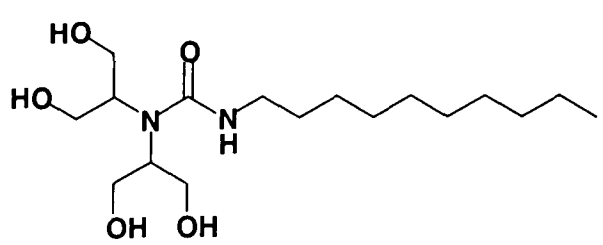


186

The molecules **184**, **185**, and **186**, were synthesised by reacting the appropriate alkyl isocyanate with the BDI derivative **60** in refluxing toluene followed by hydrolysis of the acetonides in the resulting urea.* These derivatives have undergone studies of their micellar properties.

Surfactant	*CMC (mM)*	*Limiting Surface Tension (mN/cm)*
C_8 urea **184**	5.9	36.9
C_{10} urea **185**	1.5	33.3
C_{12} urea **186**	0.092	32.2

Table 4.2.1

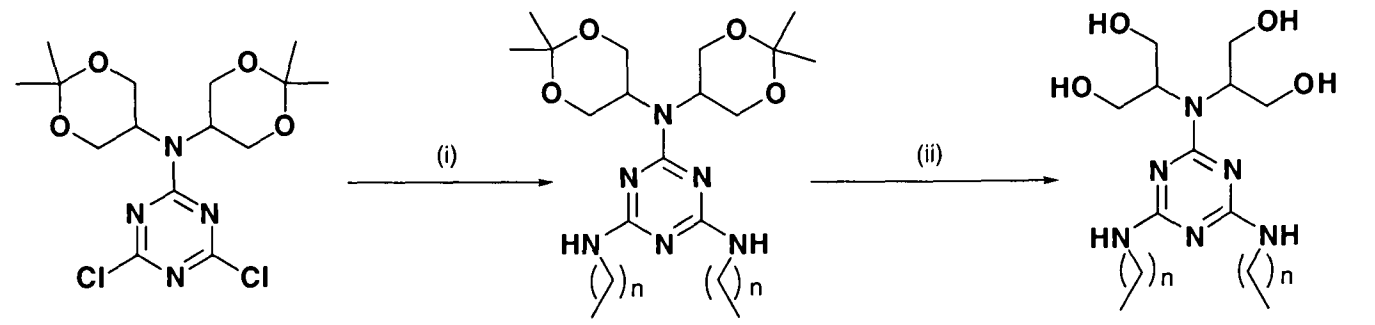
There are a number of trends that can be seen in the above data (**Table 4.2.1**). Firstly, a decrease in CMC with increasing chain length which can be anticipated from a consideration of the hydrophobic effect. An increase in chain length increases unfavourable interactions with the solvent and drives micellisation at a lower concentration. Secondly, there is a decrease in the limiting surface tension with increasing chain length. The limiting surface tension *(mN/cm)* is that above the CMC (**Figure 4.4**).

Potential Non-Ionic Surfactants and Bolaamphiphiles

Some two-fold symmetric structures based on a triazine nucleus and incorporating BDI as the polar head group have been prepared and are undergoing examination for their micellar properties. It should be possible to study the structure-property relationships of these molecules by the synthesis and characterisation of a range of novel amphiphiles incorporating BDI as the head group. An array of unsymmetrical dendritic molecules **117** - **119** was constructed as it was hoped that on global deprotection they would function as non-ionic surfactants (**Scheme 4.2.1**).

* Decylisocyanate was prepared *in situ* from decylamine with triphosgene in dichloromethane in the presence of N,N-diisopropylethylamine.

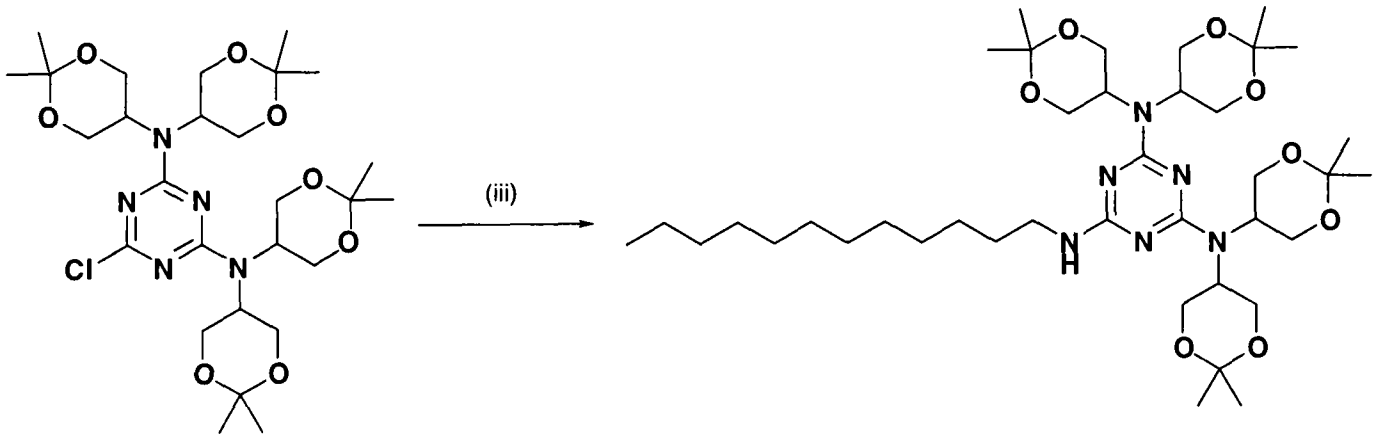
Molecules of the type shown in **Scheme 4.2.1** have two-fold symmetry by virtue of a C_2 rotation axis in the plane of the triazine ring and dendrimers derived thus are amphiphilic in that they possess both a hydrophilic and a hydrophobic portion. Here the polar head group is a dendritic polyol (BDI) and the hydrophobic portions are simply alkyl amines linked by the triazine nucleus. Such an amphiphilic arrangement is as yet an unknown class of surfactants.



108

117 n = 3
118 n = 5
119 n = 11

114 n = 3
115 n = 5
116 n = 11



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112

Reagents and Conditions: (i) RNH_2, toluene, Δ, (ii) 70% aq. AcOH, (iii) $CH_3(CH_2)_{11}NH_2$ (2eq.), toluene, Δ.

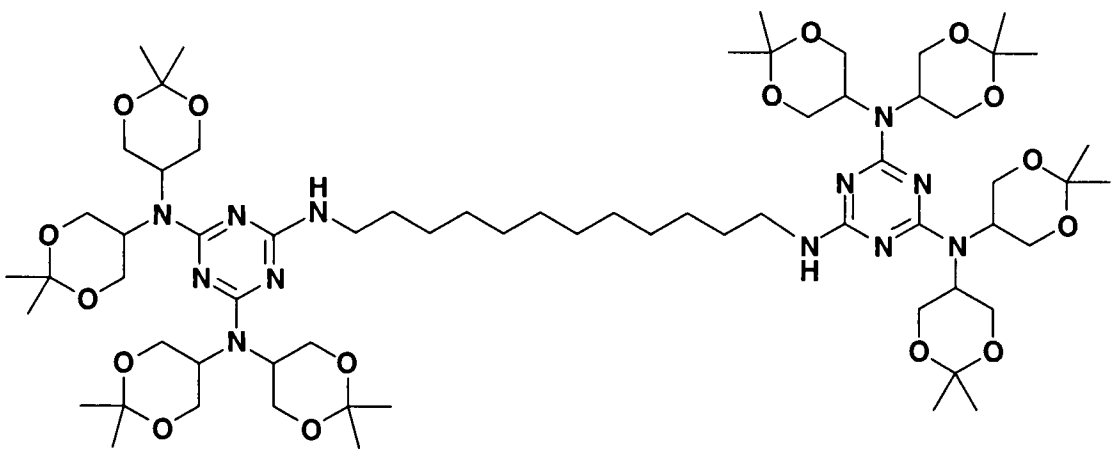
Scheme 4.2.1

It is easy to see how to vary the critical packing parameter in terms of the alcohol surface density of head group and the length and relative size of hydrophobic chains. Initial measurements suggest CMC values of 6.1×10^{-3} (**114**) and 2.2×10^{-3} (**115**).

The trisubstituted triazine **114**, where n = 3, displays amphiphilic behaviour and resembles a gemini surfactant which formally consists of two hydrophobic chains and two hydrophilic headgroups linked by a relatively short (rigid or flexible) spacer. For all but a few exceptions

gemini surfactants reported thus far possess ionic head groups.[20] **114** has interesting solubility properties in which it is most soluble in protic organic solvents such as methanol whilst only being partially soluble in chloroform and water, however this has yet to be quantified.

A different arrangement would be one in which there is a C_2 rotation axis perpendicular to the plane of the triazine ring in order to give rod shaped dendrimers. These are 'bolaamphiphiles' might also display interesting aggregation behaviour in solution. Again such novel molecules are hoped to exhibit properties not displayed by smaller molecules or more 'classical' polymers.



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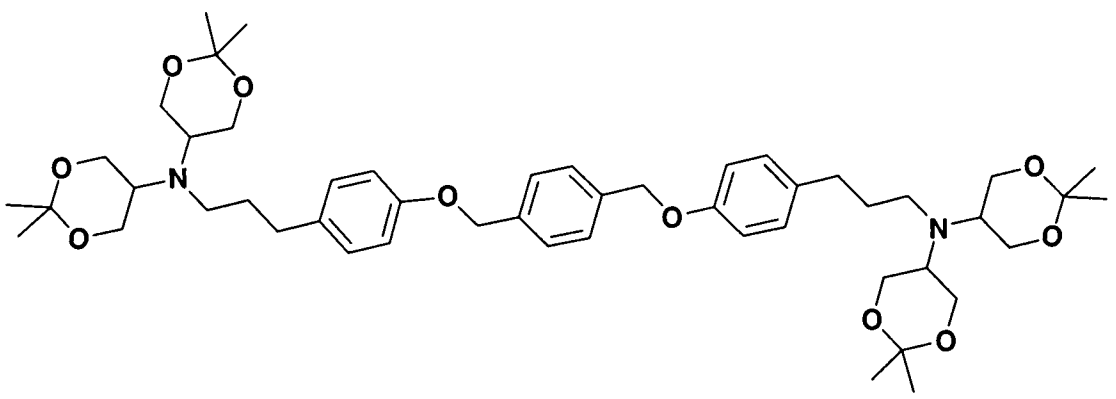

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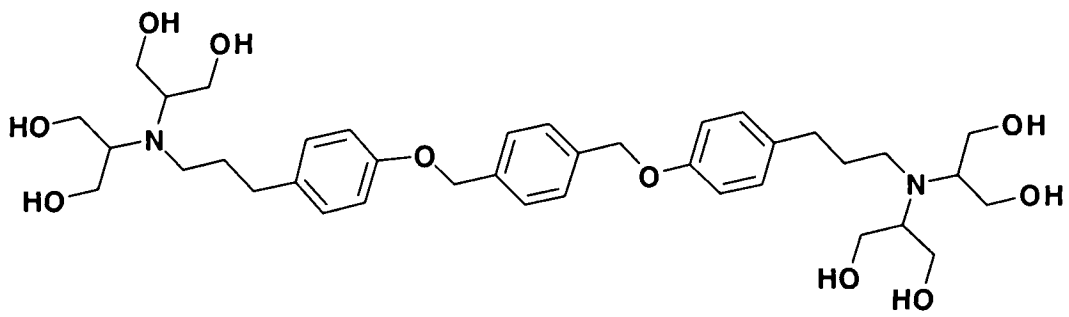
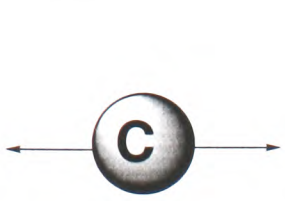
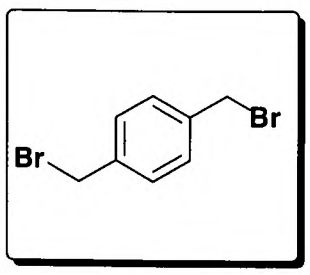


189

A C_2 symmetric dumbbell shaped molecule with a diaminododecane core coupled to two units of the monochloro-triazine derivative can be envisaged **187**. The bolaamphiphile **189** can be synthesised from the precursor **188** in an approach that invokes the use of the two directional aromatic core **190**.





190

Figure 4.5. Two directional core.

Face to face π-π stacking interactions may exist to help generate linear arrays by offering a degree of preorganisation and then stabilising the resulting aggregates.[21] With the AB_4 unit **143** in hand, displacement of the active benzyl bromides in **190** was effected to form the structure **188**. This is similar to the polyether chemistry of Fréchet.[22]

The ^1H NMR of **188** in $CDCl_3$ shows the high symmetry of the molecule in that it is simpler than expected. ^1H NMR also shows the double-doublets of the BDI diacetonide moiety have been simplified due to the dynamic unmbrella inversion of the nitrogen. This has been observed in other N-alkyl derivatives of the BDI diacetonide where the expected AB system of the methylene protons is not observed due to the rapid inversion of the nitrogen. At room temperature the signals are seen to degenerate into singlets.

Restricted Rotation Phenomena

Akin to the alkylamino triazines discussed earlier (chapter 3), these structures display restricted rotation properties. Taking the simplest triazine **117** and its deprotected counterpart **114** as a case study, it is possible to see the signals from each and every proton in the fully resolved, high temperature NMR in the variable temperature ^1H NMR experiments (**Figures 4.6,4.7** and **4.8**).

The fully protected derivative, **117**, is well resolved at 90°C in toluene d_8, but is clearly broadened at room temperature. The methylene protons in the dioxane ring appear as two sets of double-doublets corresponding to the axial and equatorial environments which is also manifested in the coupling constants.

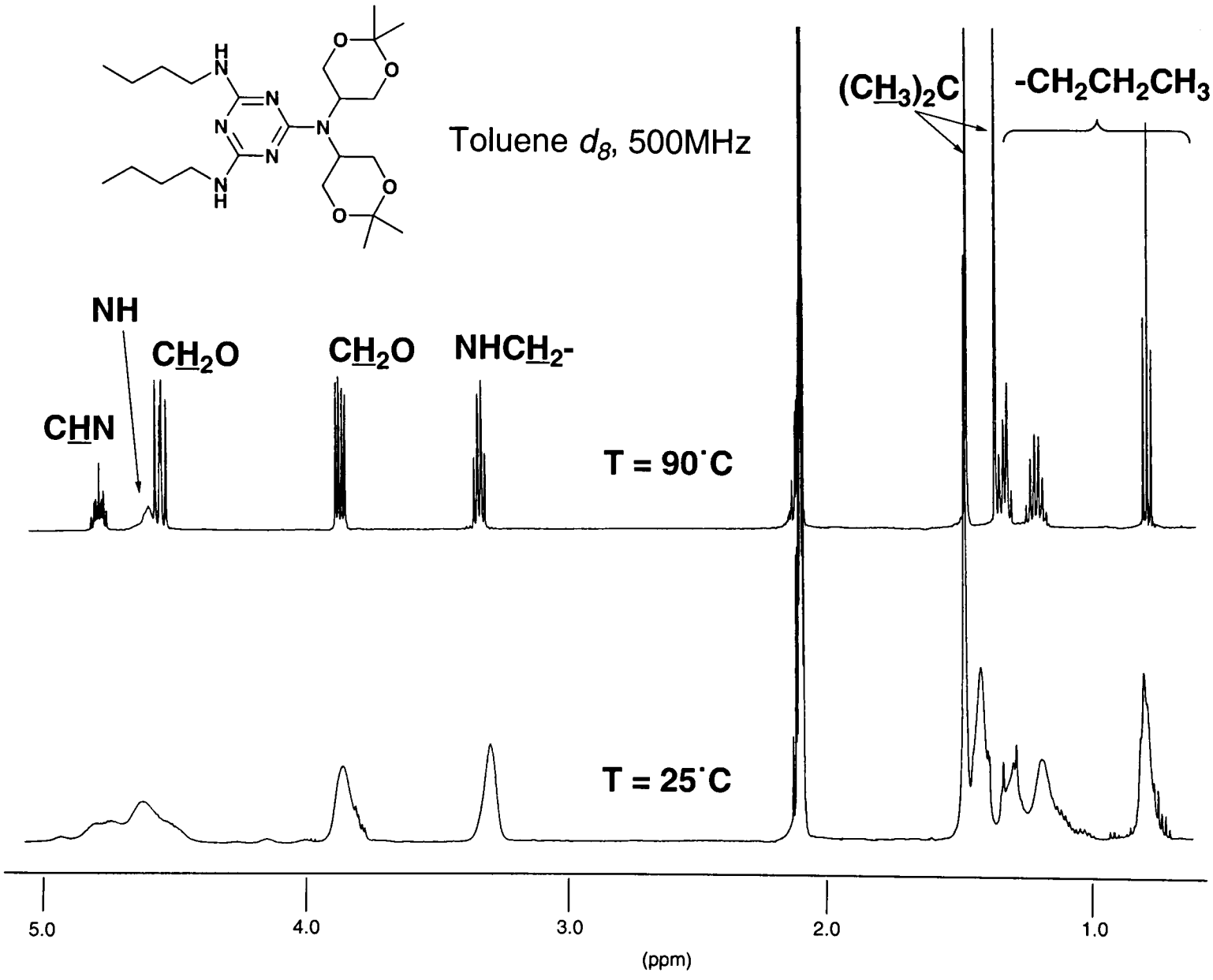


Figure 4.6. ^{1}H NMR spectrum of triazine **117** in toluene d_8 at variable temperature.

Acid hydrolysis of the acetonide protecting groups in **117** affords **114**. The hydroxymethylene protons appear as two double-doublets as they are diastereotopic. At high temperature the hydroxyl protons are broadened massively even though there is a suggestion of their presence at room temperature.

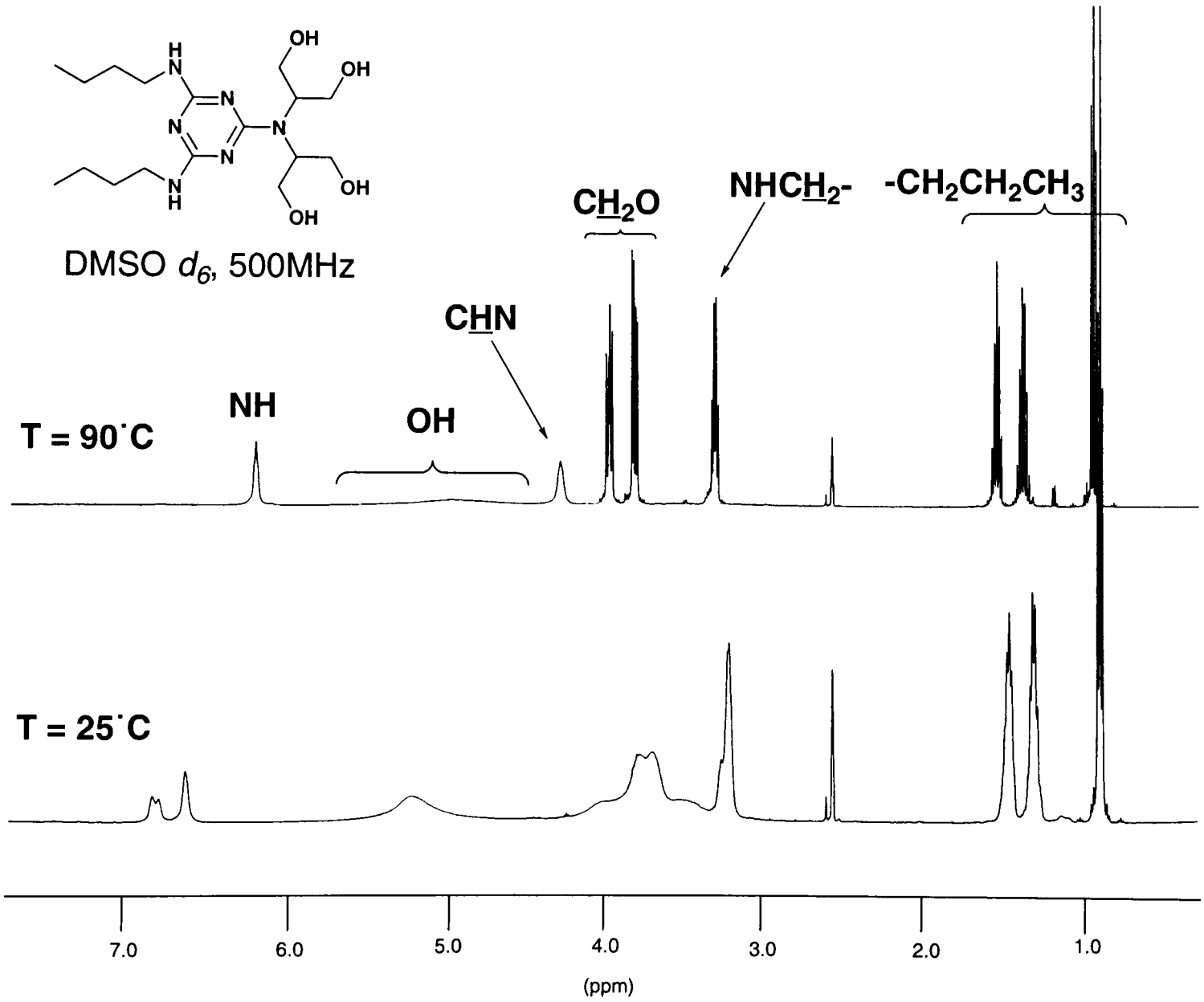


Figure 4.7. ^{1}H NMR spectrum of triazine **114** in DMSO d_6 at variable temperature.

Irradiation of the highly deshielded NH signal at 6.0ppm simplifies its coupling partner, the α-CH_2NH signal, confirming the previous assignments (**Figure 4.7**).

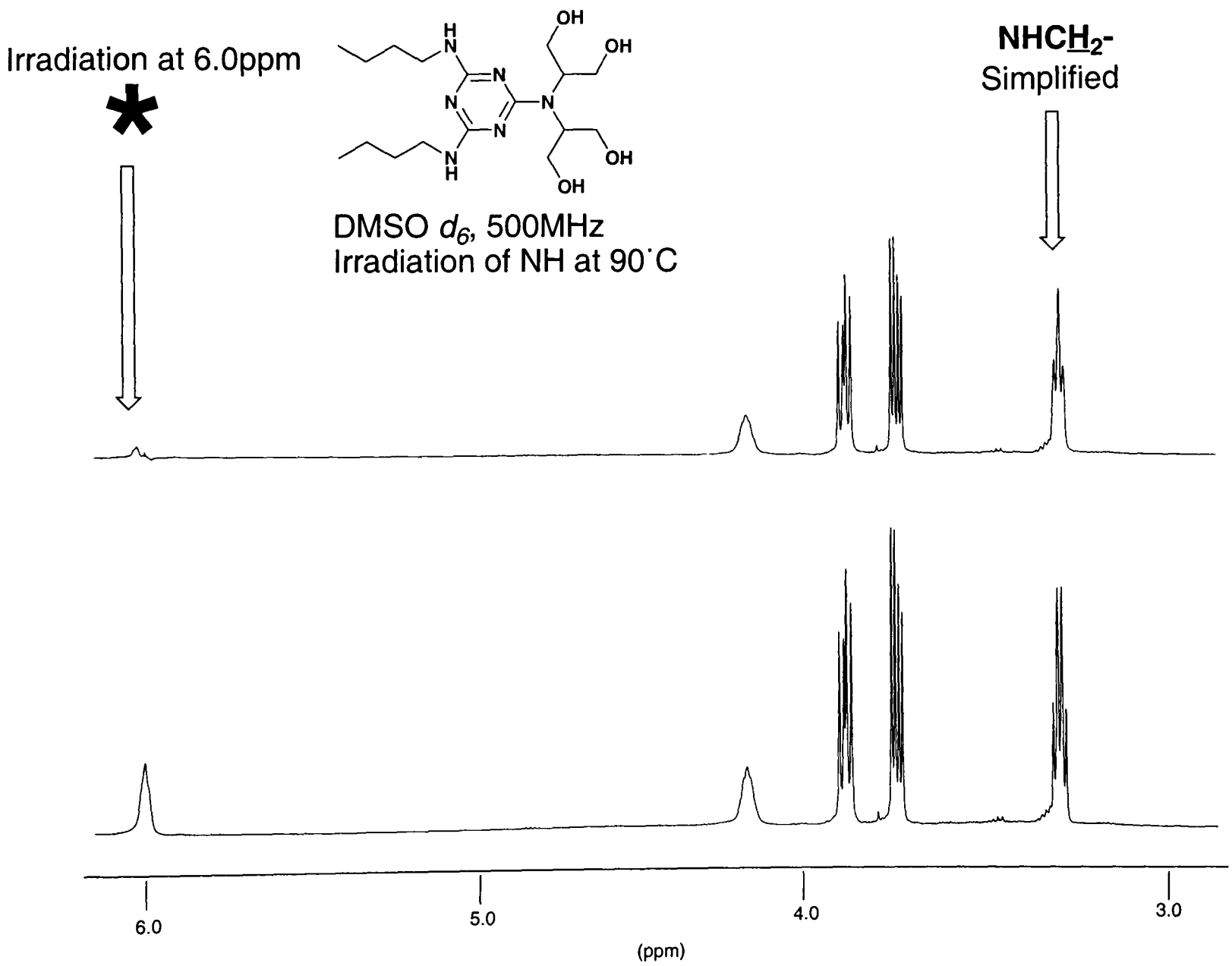


Figure 4.8. ^1H NMR spectrum of triazine **114** in toluene d_8 at 90°C with irradiation of the NH proton.

Conclusion

'*In the beginning beauty is enough but then one wonders: what's it good for?*'.[23]

A range of trisubstituted alkylamino *s*-triazines which display amphiphilic character have been synthesised in the hope that they may serve as non-ionic surfactants. The hydrophilic head group is furnished by the dendritic polyol BDI structure. Variation in the surface density of the head group versus the length and relative size of the hydrophobic portion has been addressed to a small degree in the preparation of potential surfactants. Such molecules again display variable temperature NMR characteristics.

Such surface active groups can spontaneously form aggregates in an aqueous environment. Bolaamphiphilic structures embodying BDI and based on a triazine nucleus can be envisaged and would be expected to display similar aggregation phenomena. The synthesis of bolaamphile precursor **188** has been demonstrated using the two directional core **190**. As well as potentially being of interest as a bolaamphiphilic molecule, it can also be viewed as a rod-shaped first generation, two-fold symmetric dendrimer. A change in directionality and overall shape might precipitate interesting properties and consequent applications.

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5. Potential Inhibitors of Carbohydrate Processing Enzymes

5.1 Introduction

Biological Provenance of Carbohydrate Based Therapeutics

Carbohydrates play an important role in a vast array of biological processes including the intricate workings of the immune system, the means by which bacteria, viruses and cancer cells interact within their hosts and the mechanism of tissue growth and repair.[1] Thus there is great potential for the application of this insight to carbohydrate based therapeutics and indeed a number of drug candidates are in development or undergoing trials in patients.[2] Such therapeutics include anti-inflammatories, cancer chemotherapy, anti-thrombotics, diabetes therapy, anti-infectives, aminoglycoside antibiotics, anti-virals, immunostimulants, and neurological therapeutics.[3] All these applications have their origin in the biological roles of carbohydrates.

A number of nitrogen-containing carbohydrate analogues (imino sugars, commonly named azasugars[4]) can inhibit the glycosidases that are responsible for the degradation of poly- and oligosaccharides. Various powerful sugar-shaped polyhydroxylated nitrogen heterocycles with trivalent, basic nitrogen instead of oxygen in the ring have been found as natural products or have been synthesised by chemical as well as enzymatic methods. These sugar mimics are metabolically inert but the retention of functional groups with the stereochemistry of the parent sugar allows recognition with moderate specificity and low toxicity and provides a powerful group of glycosidase inhibitors.[5] Inhibitors of such enzymes are potential therapeutic agents and could be powerful investigative tools for glycobiology.

Glycosidases (glycosylhydrolases) are ubiquitous enzymes that are involved not only in the degradation of carbohydrate foodstuffs[6] but also in the processing of eukaryotic glycoproteins[7] and glycolipids.[8] These enzymes are essential for normal cellular development of all organisms. Glycosidases can be classified in various ways: according to their function, by their location in the

organism, or by their mechanistic characteristics.[9] Inhibitors of glycosylhydrolases can provide mechanistic insight into the biocatalytical aspects of these enzymes and have proven to be important tools for the elucidation of metabolic pathways to the various glycoforms of glycoproteins and glycolipids.

Mechanism of Action of Glycosidases

Glycosidases catalyse the specific hydrolysis of the glycosidic bond between a sugar residue and its anomeric substituent (aglycon).[10] They can be divided into inverting and retaining glycosidases according to the stereochemical outcome at the anomeric centre upon glycosidic bond cleavage.[11] The mechanism of action of retaining glycosidases is accepted to proceed through an oxonium-type transition state *via* a double inversion process[12], **Figure 5.1**.

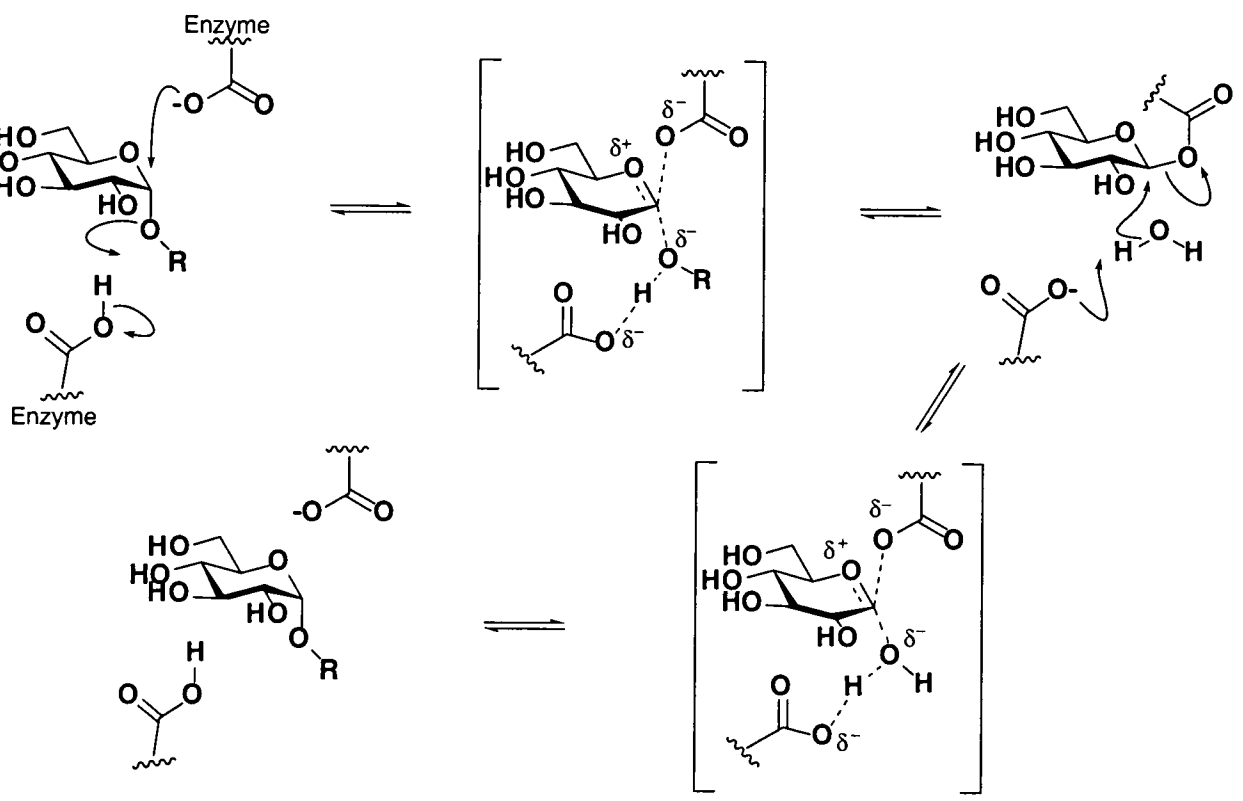


Figure 5.1. Schematic representation of the mechanism of retaining glycosidases.

Initial protonation of the exocyclic oxygen by a carboxylic acid is accompanied by nucleophilic attack of a carboxylate group from the opposite face *via* an oxonium-like transition state. This nucleophilic attack cleaves the exocyclic bond with inversion of configuration at the anomeric centre, to give a glycosyl-enzyme bound species. Subsequent hydrolysis, again *via* an oxonium-like transition state, proceeds with inversion to give the free monosaccharide with overall retention of configuration. Inverting glycosidases operate in a mechanistically similar fashion, although the hydrolysis proceeds in a single inversion step *via* a similar transition state.

Design of Specific Inhibitors of Glycosidases

Polyhydroxylated piperidines display the same stereochemical information as the common hexoses but contain an NH in place of the pyranose ring oxygen. The mechanism of inhibition of glycosidases by azasugars is believed to be a result of the protonation of the nitrogen in the piperidine ring at physiological pH, thus providing an electronic mimic of the transition state oxonium ion involved in enzymatic glycosidase modification. When protonated, the azasugar can interact ionically with a negatively charged carboxylate ion in the active site. Carbohydrate mimetics have a number of advantages over their parent structures as therapeutic agents. They can be designed such that they:

- Are more stable toward endogenous degradative enzymes
- Have improved bioavailability and reduced clearance rates,
- Have a higher affinity and selectivity for their cognate receptors by taking advantage of interactions that the natural saccharide does not.

Initially the inhibition displayed by such molecules was attributed to their resemblance to the parent sugars, however imitation of the transition states rather than ground states result in greater inhibition of the enzymes than simple substrate analogues. A recent review highlights some important interactions which can be built into the rational design of enzyme inhibitors.[13] A number of features of basic sugar analogues are of importance for their inhibitory potency:

- Position of the basic (cationic) centre
- Basicity
- Geometry and charge distribution at the anomeric position
- Hydroxylation pattern, ring size and flexibility as determinants of specificity
- Interactions with the aglycon binding site
- Hydrogen bond formation with the catalytic acid. [14]

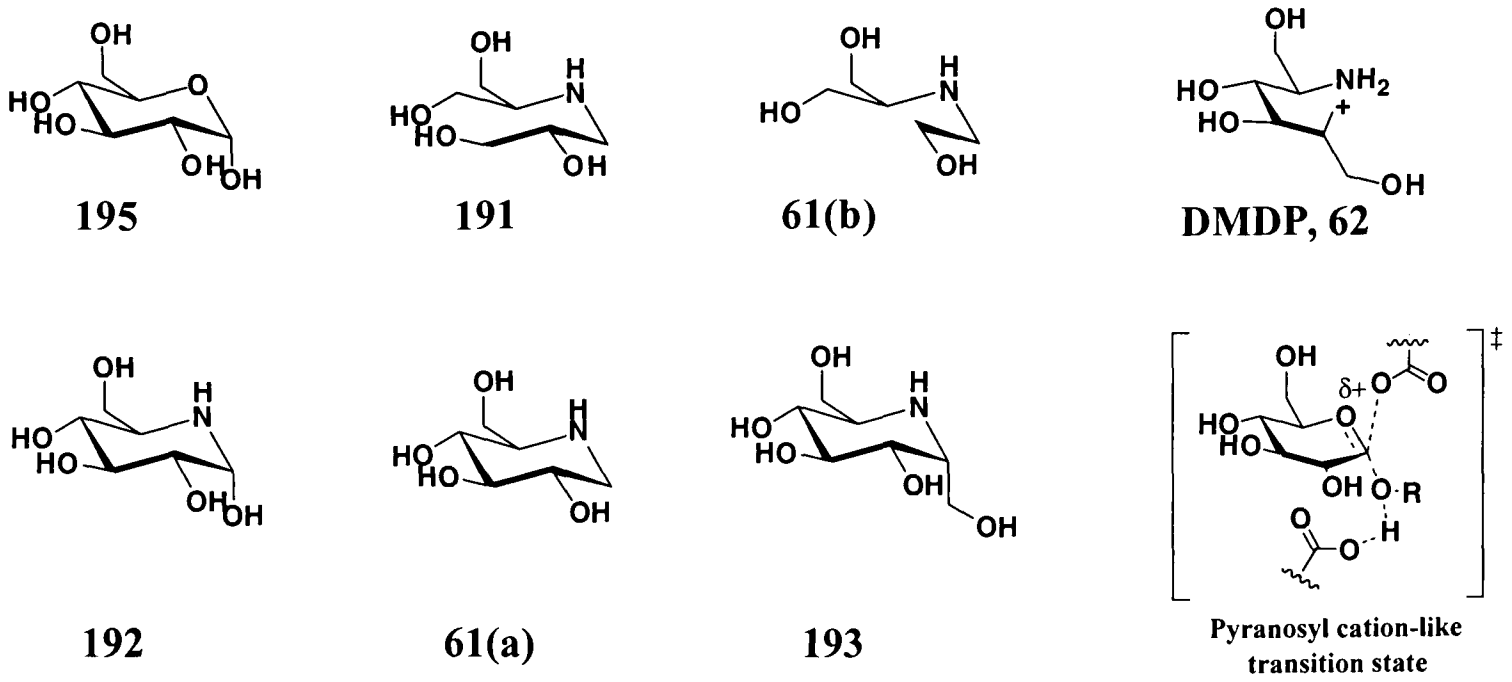


Figure 5.2. Structures of α-D-glucose, iminosugar piperidines (nojirimycins) and truncated analogues

The first reported five-membered azasugar, DMDP **62**, was isolated from a leguminous plant in 1916[15] but the wide inhibitory potential of this class of compounds was recognised only in 1925.[16] It appears that structure **62** bears less structural resemblance with the pyranosyl cation-like transition state (**Figure 5.1**) than the corresponding inhibitors with a hexapyranose-like structure. However **62** inhibits many glucosidases more than 100-fold better than 1-deoxynojirimycin **61(a)**, (1-deoxynojirimycin is a more stable piperidine than α-nojirimycin **192**). This is quite pronounced with α-glucosidase from yeast and DNJ **61(a)** where DMDP* has $K_i \approx$ 1.6μM[16] and DNJ has K_i = 13μM.[17] As proposed by Sinott[18] this can be explained by the better resemblance of hydroxy group orientation in the half-chair furanose structures with the transition state than in the chair conformation of the DNJ inhibitor, (**Figure 5.2**). The importance of the conformation is shown by the truncated analogues **191** and **61(b)** with similar or up to 4-fold better inhibition of α-glucosidase from yeast than DNJ **61(a)**. Homoazapyranoses such as **193** will be addressed below.

In order to appreciate these results the large entropy loss from freezing out four or five rotational degrees of freedom should be taken into account when these flexible inhibitors bind to the enzyme, which puts them at a disadvantage over their cyclic analogues. According to Page and Jencks[19] the entropy loss per degree of freedom amounts to about 5 cal/Kmol, corresponding to

* Approximate K_i (≈) estimated from IC_{50} assuming competitive inhibition and [S] = K_m.

an increase of the binding energy of 6-7 kcal/mol. Thus, if these open-chain amino alcohols could be fixed in the conformation they adopt in the active site they would inhibit with K_i values in the subnanomolar range. It remains to be tested if other glycosidases respond in the same way to open-chain azasugars of appropriate structure. The acyclic analogue of DMDP, BDI **58** reported in the earlier chapters of this thesis has six degrees of rotational freedom and so is greatly disadvantaged in terms of entropy loss.

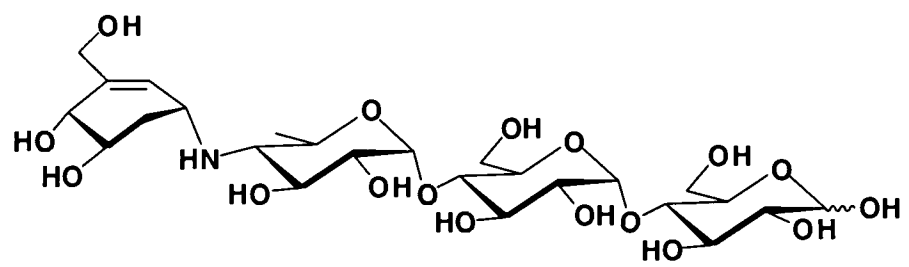
A Case Study: Diabetes Therapy

An important area for the application of carbohydrate therapeutics is for the treatment of diabetes. To understand this, an appreciation of the biological roles of carbohydrates in energy and metabolism is needed. Carbohydrates are classically attributed to being the medium for energy storage and transport. Ingestion of substances such as starch, lactose and sucrose results in the absorption of their constituent monosaccharides (simple sugars, mainly glucose) into the bloodstream as a result of the action of enzymes present in the digestive system. Glucose is stored as a highly branched polymer, glycogen, in tissues such as muscle and liver, and released back into the bloodstream when there is a demand for energy – the catabolic process again involving enzyme catalysis. Following transport across the cell membranes of target tissues, glucose is converted by the enzyme hexokinase into its 6-phosphate derivative, a reactant in several cellular pathways including the production of ATP (adenosine triphosphate) and acetyl-CoA, both essential metabolic intermediates. Diabetes is the condition of having unregulated blood glucose levels.

In diabetes therapy, there are a number of opportunities to intercept the biological processes controlling blood glucose levels by interfering with certain enzymes. The controlled inhibition of the digestion and absorption of dietary carbohydrates in the small intestine (digestive glucosidases) has therapeutic potential in the treatment of diabetes and even obesity. A number of nitrogen containing carbohydrate analogues can inhibit the glycosidases which are responsible for the degradation of poly- and oligosaccharides. Inhibiting intestinal sucrase and amylase in this way prevents the production of glucose, and therefore its absorption into the bloodstream, after the

ingestion of carbohydrates. As such compounds of this sort are currently used in diabetes therapy in combination with conventional agents which aid either the release or effect of insulin.

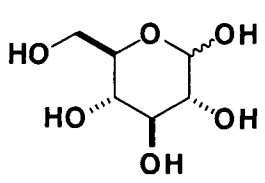
α-D-glucosidase inhibitors such as the carba-tetrasaccharide acarbose (BAY g5421) **194**, and Miglitol ((N-hydroxyethyl)-1-deoxynojirimycin, BAY m1099) **63** are in clinical use or undergoing clinical trials for the treatment of non-insulin dependent (type II) and insulin dependent (type I) diabetes mellitus.[20] Acarbose, unlike Miglitol, is not absorbed appreciably into the bloodstream and therefore its action is largely confined to the intestine. Its main side effect is moderate diarrhoea and associated flatulence.



5.2 Results and Discussion

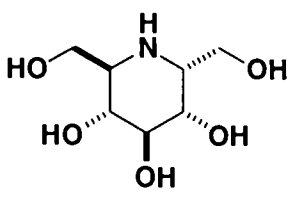
An Eight Carbon Skeleton

Homoazasugars, are homologues of 1-deoxyazapyranoses, bearing an additional hydroxymethyl group at the pseudoanomeric centre providing the opportunity for α- and β- epimers. The target molecules were the eight carbon derivatives **198** and **199** which are based on the homoazasugars α- and β-HNJ and have chemical modifications at C-6 in that they possess an hydroxyethyl side chain and stereochemical modifications at C-2, the pseudoanomeric carbon (**Figure 5.3**). It should be possible to access both epimers at C-6 for each anomeric analogue giving rise to four possible targets, **198** and **199**, where both epimers at C-6 are implied.



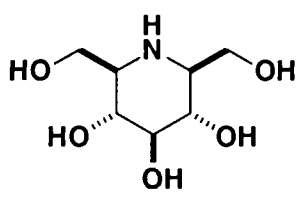
α–D-Glucopyranose

195



α–Homonojirimycin

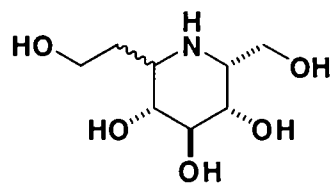
α–HNJ **196**



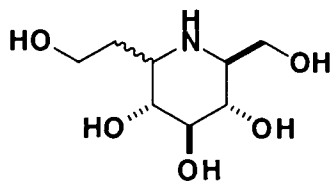
β–Homonojirimycin

β–HNJ **197**

FOUR TARGET MOLECULES



198



199

Figure 5.3

These C-glycosides are eight carbon homologues of HNJ and may serve as glycosidase inhibitors by virtue of being fortuitous inhibitors rather than transition state analogues. The production of a family of epimers at C-2 and C-6 with the conservation of the stereochemical integrity of the hydroxyl groups on the piperidine ring should allow for the study of structure-activity relationships and investigation of the contribution of the different chiral centres on the specificity and potency of the inhibitor. Additionally kinetic measurements can be compared to known standards and the eight carbon analogues may provide a new class of bioactive pyranose mimics. The hydroxyethyl group could be used as a tether for linking other moieties and provide a linker

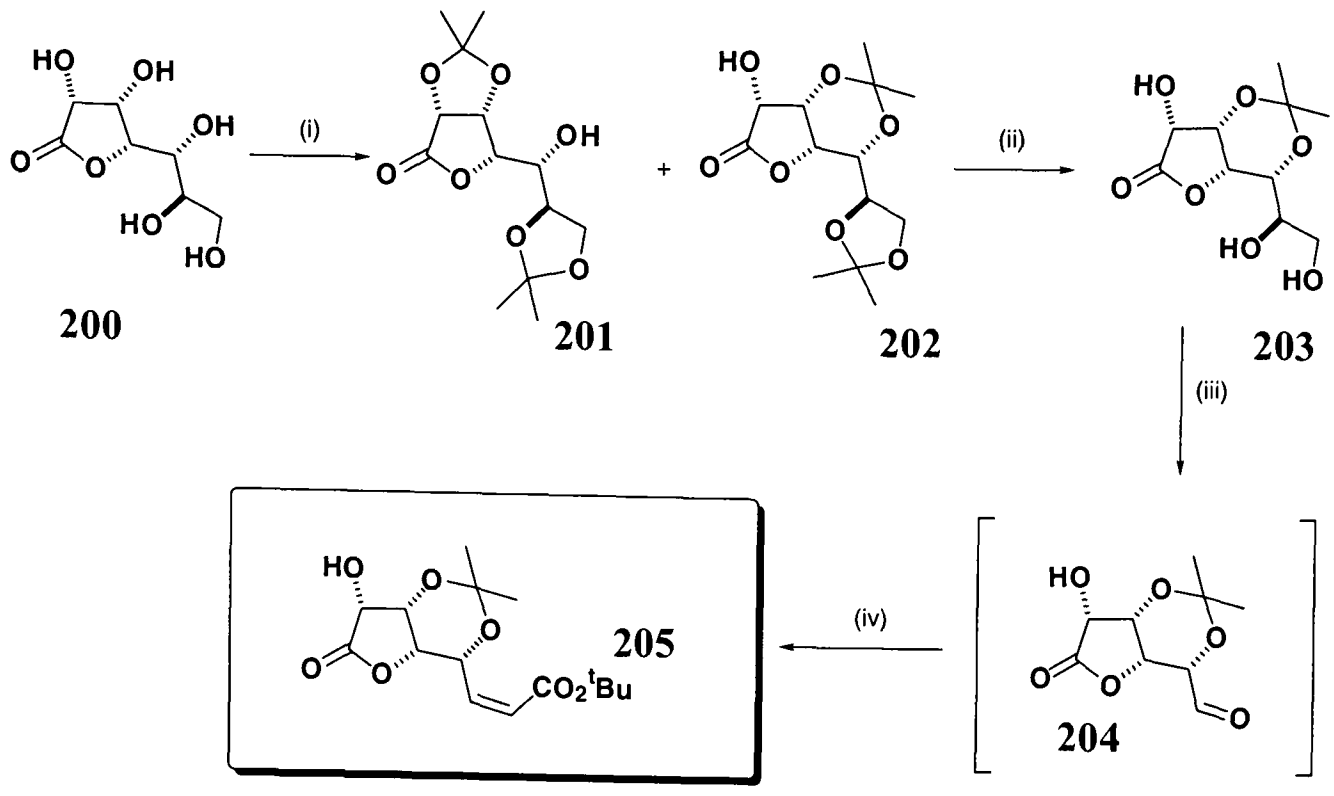
for incorporation into larger structures in the search for more potent and selective inhibitors of carbohydrate processing enzymes.

Hydroxyethyl azasugars have been prepared by other routes, most noticeably the production of D-mannose analogues by previous workers in the group.[21]

Suitable starting materials for the synthesis of such eight carbon iminosugars are *via* azidolactones. Traditionally the most popular nitrogen source for iminosugar synthesis has been the azido group. This can easily be reduced to an amine by many different methods and although it does add extra steps to the synthesis the azide intermediates are far less polar and therefore easier to handle. Using carbohydrate starting materials confers the advantage of the close structural relation to the target but does involve a number of protection/ deprotection strategies. Sugar lactones are versatile starting materials for a wide range of complex targets by routes which require little or no protection.[22]

The aldonolactones provide a chiral pool of readily available starting materials. The commercially available and inexpensive[23] seven carbon aldonolactone **200** presents a number of contiguous chiral centres with well-defined relative and absolute stereochemistry. It is suitable for the application of a range of protecting group strategies allowing faster manipulation of specific hydroxyl groups. Additionally a major attraction of such carbohydrate lactones is the absence of anomeric substituents. The acidic cleavage of a glycosidic bond in corresponding glycosides can be difficult and is quite often not compatible with the protecting group strategy in multistep synthesis.

The eight carbon lactone **205** is derived from D-*glycero*-D-*gulo*-heptono-γ-lactone (D-glucoheptonic lactone) **200** which has a seven carbon atom chain. Thus a single carbon extension of D-glucoheptonic lactone should afford the required eight carbon framework. This prescribed carbon framework was established by excision of a terminal carbon and then extension of the carbon chain by two carbons in one step in a predictable way (**Scheme 5.2.1**).



Reagents and Conditions: (i) Acetone, 2,2-dimethoxypropane, TsOH, (ii) 70% aq. AcOH, (iii) $NaIO_4$, MeOH, H_2O, (iv) $Ph_3PCH_2CO_2{}^tBu$, THF.

Scheme 5.2.1

The known diacetonide of D-glucoheptonic lactone **202** was formed by thermodynamically controlled acetonation using the conditions of Brimacombe and Tucker.[24] This afforded an approximate 1:13 mixture of the diacetonides **201** : **202** which can be readily separated (purification by recrystallisation). The diacetonide **201** can be obtained in greater relative yield by using different conditions for the acetonation.[25] The diacetonide **202** then underwent selective hydrolysis at the terminal isopropylidene group using aqueous acetic acid to give the triol, **203**. The selectivity was evident from the ^{13}C NMR spectral analysis. The quaternary carbons of the dioxane ring and the dioxolane ring in **203** showed different resonances[26] and removal of the terminal acetonide was indicated by the absence of the resonance of the dioxolane and the continued existence of the dioxane ring ketal carbon in the ^{13}C spectrum of **203**.

Glycol cleavage oxidation of the newly revealed terminal vicinial diol in **203** with sodium metaperiodate afforded the aldehyde **204** which was not isolated. Crude ^1H NMR (200MHz, $CDCl_3$) of this aldehyde showed that it possessed one aldehydic proton at δ_H 9.61 indicating only one aldehyde product **204** is afforded and there is no epimerisation of the α-carbon due to the 1,3 dioxane ring locking the conformation and rendering the α-proton effectively non-

enolisable. In my hands the conditions for the glycol oxidative cleavage using sodium metaperiodate were superior to those using periodic acid as the former was cleaner, higher yielding and gave the crude product as a reassuring white solid rather than a yellow oil.

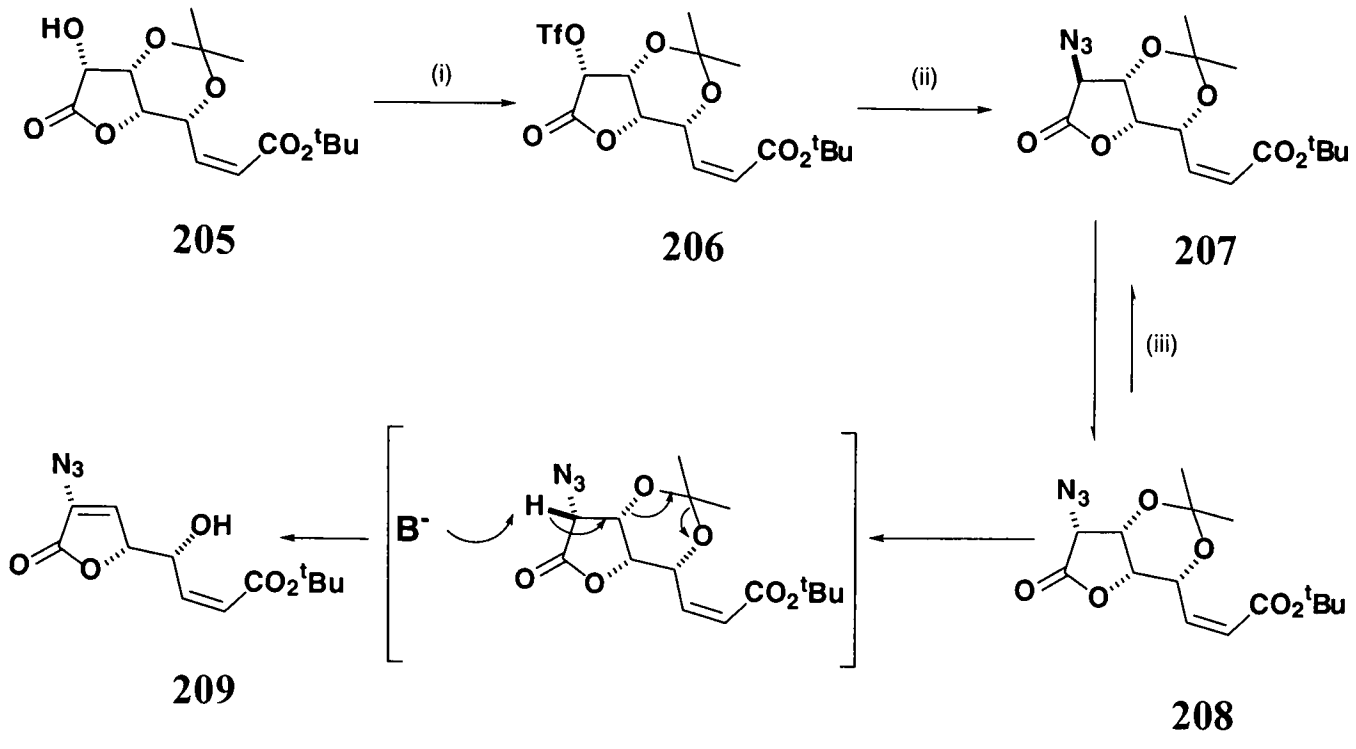
Treatment of this crude, unstable aldehyde with an excess of *tert*-butoxycarbonylmethylenetriphenylphosphorane resulted in Z-selective Wittig homologation furnishing the Z-alkene **205** in very good yield (81%). Additionally the carbon extension is occurring at the non-reducing end of the sugar and the glycol cleavage followed by a Wittig homologation is an attractive protocol for effecting this. None of the E-alkene was isolated, either because it was excluded or it co-ran with the triphenylphosphine oxide side product.

It is perhaps a peculiar result that the carbonyl stabilised ylide affords the non-anticipated Z-alkene product in high yield. However structural details in the aldehyde component are also important especially when heteroatom substituents are present. α-Oxygenated aldehydes reverse normal selectivity with stabilised ylides and it is important that the α-oxygenated functionality be protected as an ether. Precise rules for the prediction of E- and Z-selectivity with α-oxygenated substrates are difficult to formulate. It is probable that the presence of an electron lone-pair in the adequate position inhibits the reversion of the kinetic *erythro*-betaine, allowing formation of the Z-isomer.[27]

Introduction of Nitrogen with Stereochemical Control in Eight Carbon Precursors

The free hydroxyl group in **205** allows for the introduction of an azide at C-2 by displacement of the corresponding triflate ester with sodium azide in DMF, (**Scheme 5.2.2**). Additionally the enhanced reactivity of the 2-position in aldonolactones means that such a molecule is perfectly set up for displacement chemistry α- to the carbonyl group.[†]

[†] Electronic and steric effects account for this, the C-2 is α- to a carbonyl group which is electron withdrawing and also planar.



Reagents and Conditions: (i) Tf_2O, py, DCM, -30°C, (ii) NaN_3, DMF, (iii) NaN_3, PPTS, DMF.

Scheme 5.2.2

Esterification of **205** with trifluoromethanesulfonic anhydride in the presence of pyridine afforded the stable triflate **206** in excellent yield (97%). Treatment of the triflate **206** with sodium azide in DMF for 30 minutes gave a mixture of two separable epimeric azido lactones **207** and **208** in a ratio 12:1 (D-*ido*:D-*gulo*) and a combined yield of 87%. Leaving the reaction under the same conditions for 45 minutes resulted in an erosion of the product ratio based on isolated yields and an erosion of the overall isolated yield. Further investigation revealed that the 'inverted' D-*ido* azide epimerises to the apparently more crowded although thermodynamically more stable D-*gulo* azide.

A pure sample of the 'inverted' D-*ido* azide **207** was treated with an excess of sodium azide in DMF in the presence of PPTS.[‡] This lead to epimerisation of the 'inverted' D-*ido* azide **207** to the thermodynamically more stable D-*gulo* azide **208**. However some elimination product tentatively assigned to be the tetrahydrofuranic lactone **209** was also isolated in significant quantities suggesting that the D-*gulo* azide is unstable under the reaction conditions. The epimerisation and ensuing degradation of newly formed D-*gulo* azide in the reaction mixture explains the erosion of product distribution and isolated combined yields with increasing

[‡] It is thought that the PPTS acts to suppress the elimination by buffering the basicity of the azide.

reaction time. The lactone **203** could be formed from the *gulo* azide **202** by azide induced elimination of the acetonide group.

Given that the epimeric azide **208** can be derived from the pure azide **207** under the reaction conditions described, the epimerisation can proceed via two possible mechanisms, **Figure 5.4**.

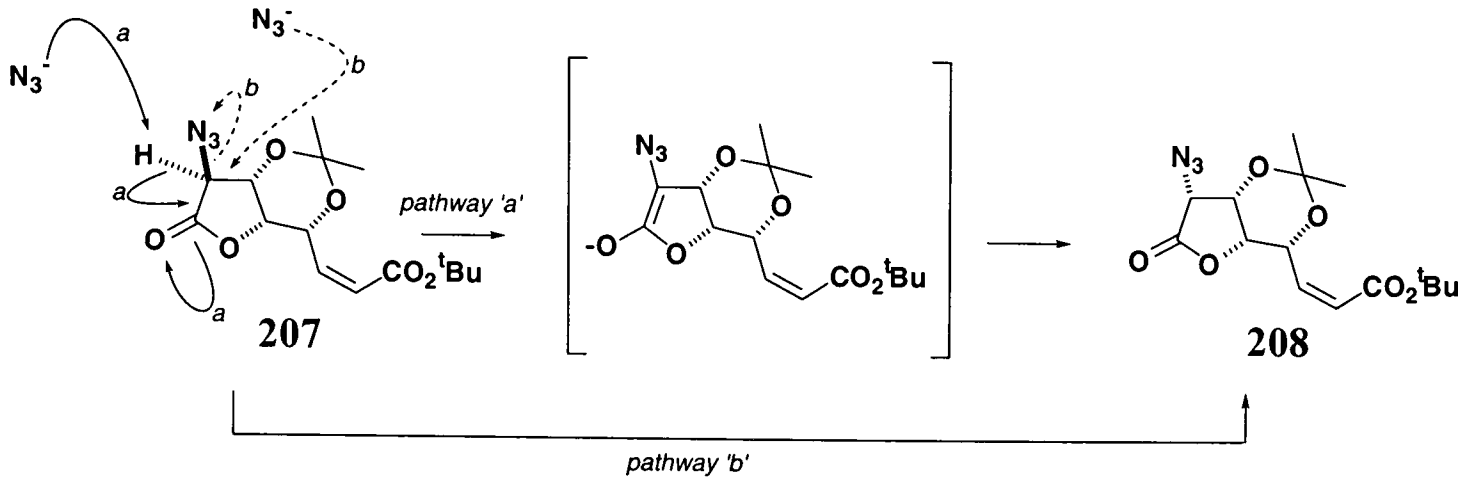


Figure 5.4. Representation of the two possible mechanistic pathways by which epimerisation may occur.

An enolisation/reprotonation type mechanism with azide ion acting as a base (pathway 'a') seems to be the most likely although a direct Finkelstein-type displacement (pathway 'b') is also plausible. However, the poor leaving group ability of azide ion makes epimerisation *via* the enolate intermediate more likely. Enolisation of the triflate **206** in the original displacement could also play a part. Previous work has shown that the epimerisation of D-*ido* triflate to the D-*gulo* triflate can occur in similar systems.[28] Thus there is a great propensity for these systems to epimerise under basic conditions to what appears to be the more crowded all *cis* configuration. This has been observed in a number of related systems,[29] although the driving force for this epimerisation is not clear. Analysis of the ^{13}C data for both epimeric azides **207** and **208** allows for relatively accurate prediction of their conformations, **Figure 5.5**.

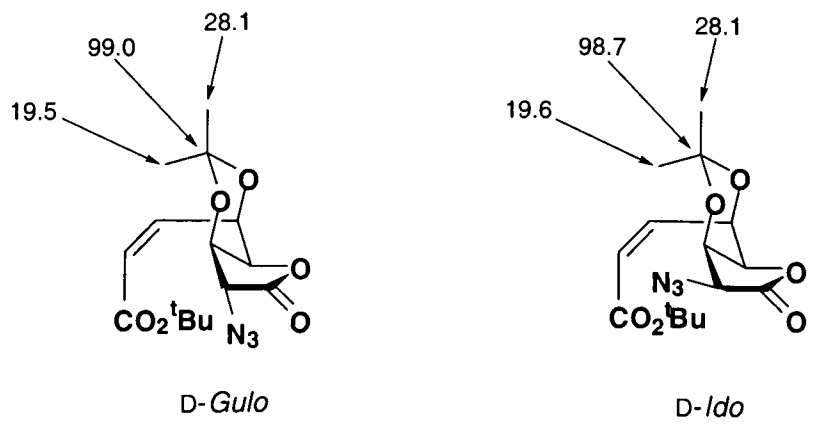
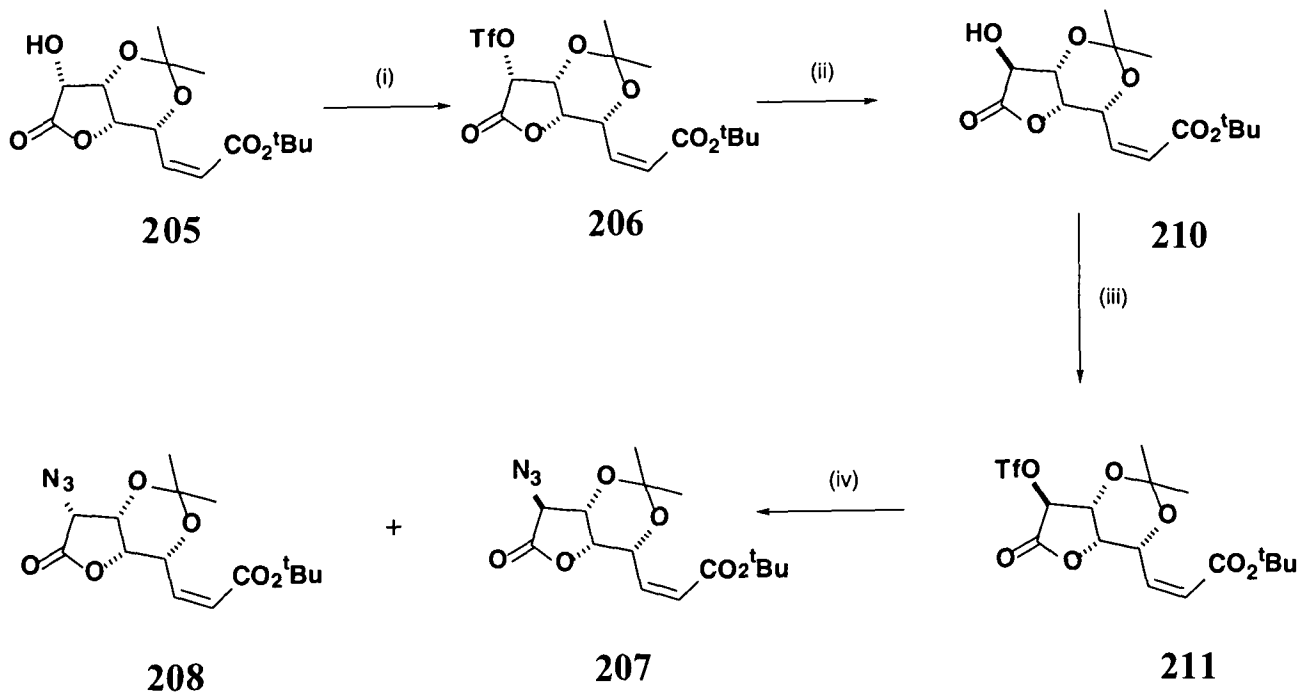


Figure 5.5. ^{13}C Chemical shifts of isopropylidene carbons for the D-*ido* **207** and D-*gulo* **208** azides.

Examination of the ^{13}C NMR chemical shifts of isopropylidene derivatives of diols is a valuable method for stereochemical assignment.[30] This technique was originally applied to carbohydrates by Buchanan[31] and has recently been used by Rychnovsky[32] and Evans[33] in their investigations into polyol conformations. Application of these principles to the azido-lactones **207** and **208** reveal that both the six-ring isopropylidene groups are in a chair conformation. This is based upon observation of one of the isopropylidene methyl group resonances at approximately 28 ppm, whilst the other appears at 9 ppm higher field, indicating that they are in significantly different environments. Also, the quaternary isopropylidene carbons both resonate below 99 ppm, consistent only with a chair conformation (quaternary range: 97.1-99.9); the quaternary carbons of twist boat conformations typically resonate in the range 100.6-101.1.[34] Thus with the conformations being the same in both the azides **207** and **208** it is easy to see the difference in the configuration at C-2 in the coupling constants – azide **208**, $J_{2,3}$ is 3.9 Hz and in azide **207** $J_{2,3}$ is 0 Hz.

Such facile control of the configuration at the C-2 stereocentre can be utilised in tailoring the desired stereochemistry in the final product. It was thought that the D-*gulo* azide **208** could be obtained by inverting the alcohol **205** at C-2 and displacing the corresponding *ido*-triflate **211** with sodium azide in DMF (**Scheme 5.2.3**).



205 **206** **210** **208** **207** **211**

Reagents and Conditions: (i) Tf_2O, py, DCM, -30°C, (ii) CF_3COOCs, butanone, Δ, (iii) Tf_2O, py, DCM, -30°C, (iv) NaN_3, DMF.

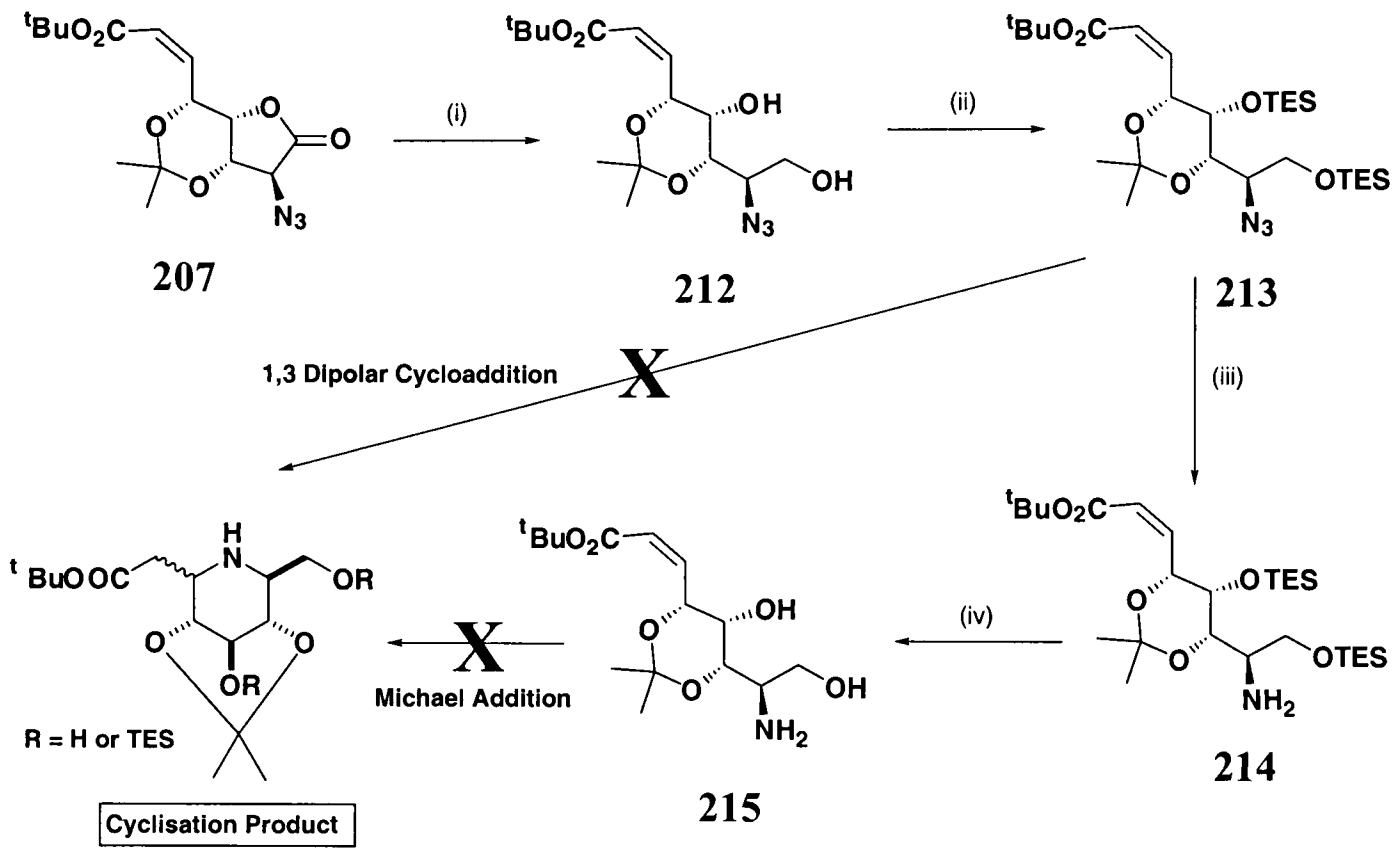
Scheme 5.2.3

In the presence of the lactone and ester functionalities the replacement of a triflate with an oxygen nucleophile may present problems due to the high susceptibility of these functionalities to nucleophilic attack. The use of caesium trifluoroacetate[35] in butanone as the nucleophile led to high yields of conversion generating the D-*ido* alcohol **210**. Efficient inversion for the hydroxyl group α- to the carbonyl lactone occurred with an overall yield of 95%. Neither the solvent nor the caesium trifluoroacetate were dried, so that there is enough water to complete the hydrolysis of the intermediate trifluoroacetate esters *in situ*.

Treatment of the D-*ido* triflate **211** with sodium azide in DMF afforded a mixture of epimers and the thermodynamically more stable D-*gulo* azide obtained in only low yields (combined yield 45%, D-*gulo*:D-*ido,* 1:3). This result can be understood if we assume the epimerisation of the triflate (D-*ido* to D-*gulo*) occurs prior to the azide displacement in a S_N2 fashion (D-*gulo* to D-*ido*) . The only practical way of obtaining the D-*gulo* azide **208** is the epimerisation of the D-*ido* azide **207** under short reaction times. Although azide **208** is sensitive to azide induced elimination a moderately effective equilibration of **207** with PPTS and sodium azide allows isolation of a moderate amount of the D-*gulo* azide **208** with some of the D-*ido* azide **207** remaining.

Approaches to Novel Piperidine Nitrogen Heterocycles

With a facile route to large quantities of the D-*ido* azide **207** a chemoselective reduction of the γ-lactone in **207** was attempted in the first instance (**Scheme 5.2.4**). By invoking the use of lithium borohydride in THF it has been possible to effect the chemoselective reduction of the lactone **207** to afford the azido diol **212**. This transformation proceeds in reasonable yield (64%, colourless oil) in the presence of an ester functionality and is cleaner, with less possibility of side reactions than sodium borohydride (37%, yellow oil). There is precedent for the lithium borohydride mediated reduction of lactones in the literature.[36]



Reagents and Conditions: (i) $LiBH_4$, THF, -10°C, (ii) TESCl, imid, DMF, (iii) NaTeH, $EtOH/Et_2O$, (iv) NH_4F, DMF.

Scheme 5.2.4

Protection of the azido diol **212** as its persilylated derivative affords an easy to handle oil which is suitably protected for further study. The functional groups are orchestrated to allow an intramolecular 1,3 dipolar cycloaddition or a Michael addition to access the piperidine ring in the eight carbon analogues. With azido diol **212** in hand it was decided to investigate the thermal reaction between the azido group and the unsaturated system which should undergo an intramolecular 1,3 dipolar cycloaddition reaction ultimately producing a vinylogous urethane, **Figure 5.6** shows this with a methyl ester.[37] More importantly this should result in the synthesis of an eight carbon piperidine azasugar mimic using an azide-cycloaddition reaction to form the piperidine ring.

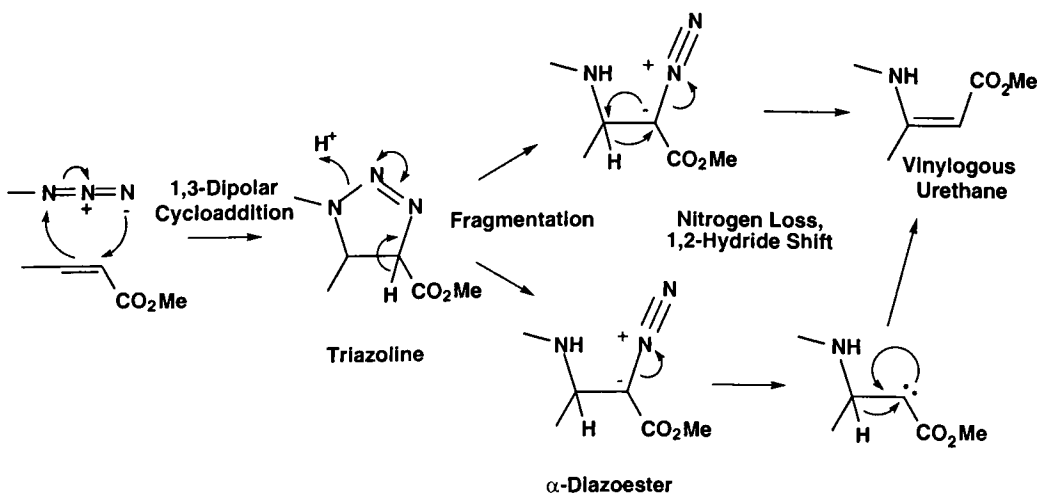


Figure 5.6

Such an α,β-unsaturated ester is expected to undergo reduction to the β-amino ester using sodium cyanoborohydride at low pH proceeding via hydride delivery to the tautomeric iminium ion, **Figure 5.7**.

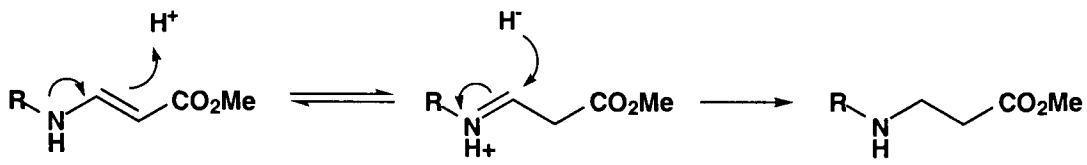
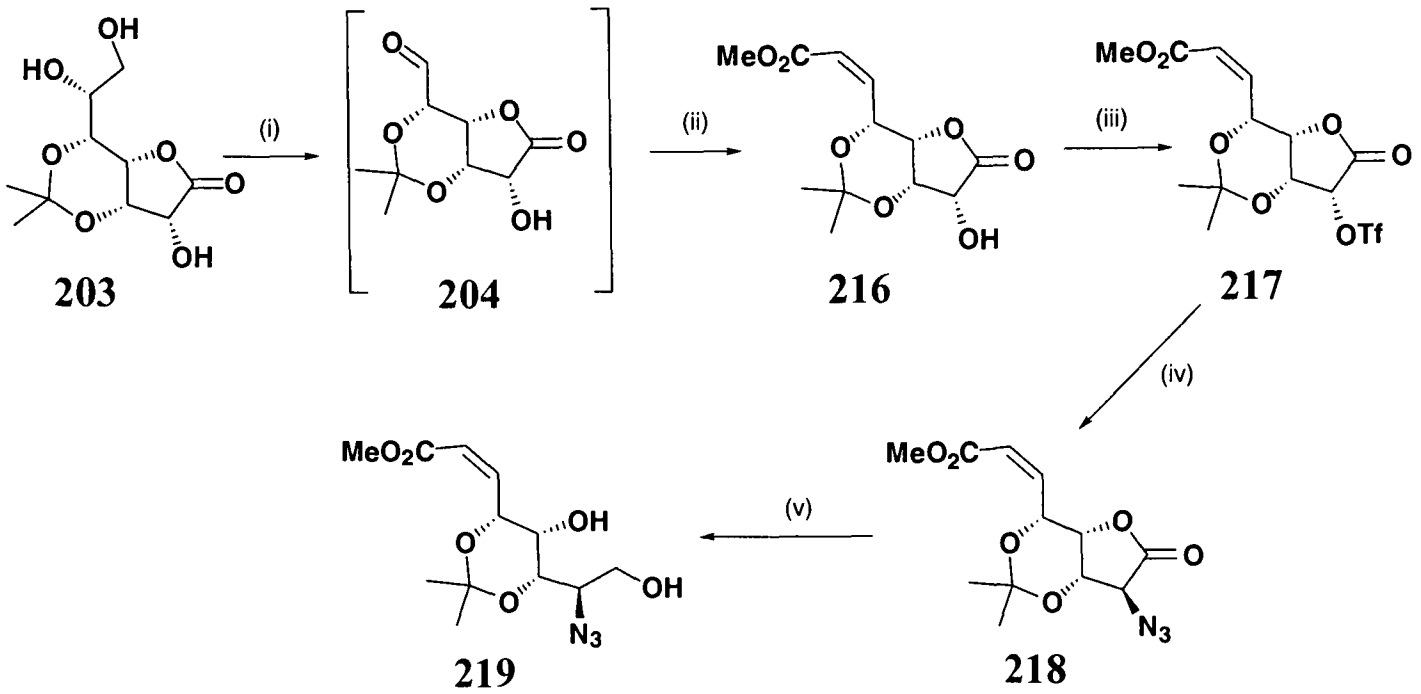


Figure 5.7

However, in an NMR experiment, in which the azido compound **213** was heated at reflux in toluene d_8 (additionally monitored by t.l.c. analysis) - no apparent transformation ensued. Perhaps the use of a solvent with a higher boiling point for a long period of time would effect the desired transformation in this highly protected substrate.

The same azido compound **213** was also envisaged to undergo a chemoselective reduction to the free amine **214** which could then be capable of an intramolecular Michael addition to form the piperidine ring. This will give access to eight carbon polyhydroxylated nitrogen heterocycles in a short and unique way. Treatment of azide **213** with sodium hydrogentelluride[38] in ethanol/ether accomplished the chemoselective reduction of the azide to the amine **214** in moderate yield (58%). It should be possible to effect a Michael type addition on removal of the silyl protecting groups using ammonium fluoride. Additionally the basic fluoride anion should act as a catalyst for the Michael type addition.[39] However the amino-diol **215** was the only product isolated from the reaction mixture and it would appear that the acetonide would need to be removed to allow sufficient degrees of freedom for the reactive groups to come into close enough proximity for reaction.

To this end the corresponding methyl ester series has also been synthesised which would allow the removal of the acetonide in methanolic hydrochloric acid without complications of competing concomitant transesterification, (**Scheme 5.2.5**).



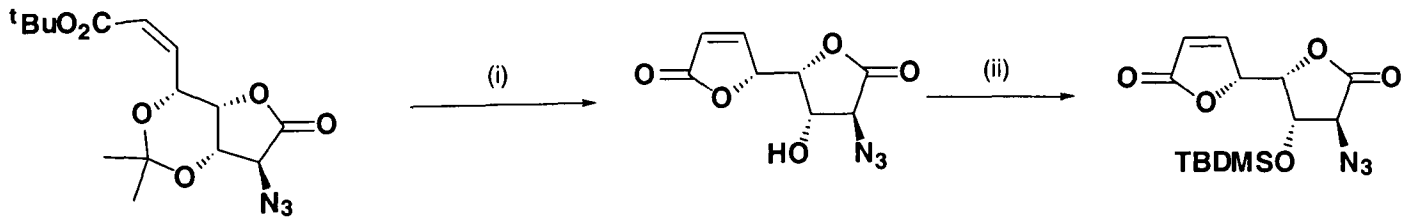
203 204 216 217 218 219

Reagents and Conditions: (i) $NaIO_4$, MeOH, H_2O, (ii) $Ph_3PCH_2CO_2Me$, THF, (iii) Tf_2O, py, DCM, -30°C, (iv) NaN_3, DMF, (v) $LiBH_4$, THF, -10°C.

Scheme 5.2.5

This scheme proceeded smoothly but was thwarted by the lithium borohydride reduction of the lactone **218** which advanced in low yield to afford azido diol **219** and a number of side products. It would appear that the methyl ester is less hindered than the *tert*-butyl ester group in **207** and does not allow for a chemoselective reduction of the lactone group in the same molecule.

Treatment of the azido lactone **207** with aqueous TFA afforded the rather polar dilactone **220** in quantitative yield and the remaining hydroxyl group could be silylated using *tert*-butyldimethylsilyltriflate in good yield (**Scheme 5.2.6**). Attempts to chemoselectively reduce the azide in the silyl protected dilactone **221** using dithiothreitol[40] did not seem to result in any apparent transformation.



207 220 221

Reagents and Conditions: (i) TFA/H_2O (1:1), (ii) TBDMSTf, DMF.

Scheme 5.2.6

Conclusion and Outlook

The synthesis of a variety of highly functionalised eight carbon molecules based on the aldonolactone **200** have been carried out with the aim of producing eight carbon homologues (**198** and **199**) of homonojirimycin. The approach to such homologues invoked the installation of nitrogen as an azide at the C-2 position. The stereochemistry of this position could be controlled easily allowing the tailoring of the stereochemistry in the eight carbon homologue target products. The stereochemistry of the products also depends on the stereochemical outcome of the reaction leading to the formation of the six membered piperidine ring.

Strategies to these homologues included a thermal 1,3-dipolar intramolecular cycloaddition. Additionally chemoselective reduction of the azide affords a tethered nitrogen nucleophile which can potentially undergo an intramolecular conjugate addition. Both of these approaches were unsuccessful. However a simple synthesis of multifarious eight carbon intermediates with high functionality has been established.

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6. Experimental

1. General Experimental

1.1 Solvents

Tetrahydrofuran was distilled under an atmosphere of dry nitrogen from sodium benzophenone ketyl or purchased dry from the Aldrich chemical company in sure-seal™ bottles; dichloromethane was distilled from calcium hydride; pyridine was distilled from calcium hydride and stored over dried 4 Å molecular sieve; hexane refers to the fraction of petroleum ether which boils in the range 60-80°C and was redistilled before use; water was distilled. *N*, *N*-Dimethylformamide and toluene were purchased dry from the Aldrich chemical company in sure-seal™ bottles. All other solvents were used as supplied (Analytical or HPLC grade), without prior purification.

1.2 Reagents

Reactions performed under an atmosphere of nitrogen, argon or hydrogen gas were maintained by an inflated balloon. pH7 Buffer was prepared by dissolving KH_2PO_4 (85 g) and NaOH (14.5 g) in distilled water (950 ml). Imidazole was crystallised from dichloromethane. All other reagents were used as supplied, without prior purification.

1.3 Chromatography

Thin layer chromatography (t.l.c.) was performed on aluminium or plastic sheets coated with 60 F_{254} silica. Sheets were visualised using a spray of 0.2% w/v cerium (IV) sulphate and 5% ammonium molybdate in 2M sulphuric acid or 0.5% ninhydrin in methanol (particularly for amines). Flash chromatography was performed on Sorbsil C60 40/60 silica and ion-exchange chromatography was performed on Amberlite IR-120 (H^+).

1.4 Melting Points

Melting points were recorded on a Kofler hot block and are corrected.

1.5 Nuclear Magnetic Resonance Spectroscopy

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AM 500 or AMX 500 (^{1}H: 500 MHz and ^{13}C: 125.3 MHz) or where stated on a Bruker AC 200 (^{1}H: 200 MHz and ^{13}C: 50.3 MHz) or Bruker DPX 400 (^{1}H: 400 MHz and ^{13}C: 100.6 MHz) spectrometer in the deuterated solvent stated. All chemical shifts (δ) are quoted in ppm and coupling constants (J) in Hz. Coupling constants are quoted twice, each being recorded as observed in the spectrum without averaging. Residual signals from the solvents were used as an internal reference and ^{13}C NMR spectra in D_2O were referenced to 1,4-dioxane (δ_C 67.4). ^{13}C multiplicities were assigned using a DEPT sequence. All spectra are recorded at room temperature unless otherwise stated.

1.6 Infrared Spectroscopy

Infrared spectra were recorded on a Perkin-Elmer 1750 IR Fourier Transform spectrophotometer using either thin films on NaCl plates (film) or KBr discs (KBr) as stated. Only the characteristic peaks are quoted.

1.7 Mass Spectrometry

Low resolution mass spectra (*m/z*) were recorded on VG MassLab 20-250, Micromass BIOQ-II, Micromass Platform 1, Micromass TofSpec 2E, or Micromass Autospec 500 OAT spectrometers and high resolution mass spectra (HRMS) on a Micromass Autospec 500 OAT spectrometer. Techniques used were electrospray (ES), chemical ionisation (CI, NH_3), or atmospheric pressure chemical ionisation (APCI) using partial purification by HPLC with methanol:acetonitrile:water (40:40:20) as eluent, as stated.

1.8 Polarimetry

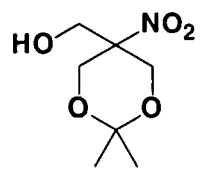
Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a path length of 1 dm. Concentrations are quoted in g/100 ml.

1.9 Elemental Analysis

Elemental analyses were performed by the microanalysis service of the Dyson Perrins Laboratory, Oxford, or the Inorganic Chemistry Laboratory, Oxford.

6. Experimental (Chapter 2)

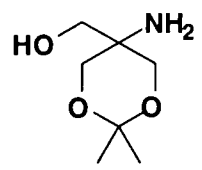
(5-Nitro-2,2-dimethyl-[1,3]dioxan-5-yl)-methanol 68



68

This compound was prepared according to a modified literature procedure.[1] Tris(hydroxymethyl)nitromethane **77** (2 g, 16.5 mmol) was dissolved in acetone (200 ml) and solid copper sulfate (4 g) was added in one portion. To this vigorously stirred suspension was added concentrated sulfuric acid (0.5 ml) dropwise. The reaction mixture was stirred at r.t. for 16 hours and the reaction monitored by t.l.c. (ethyl acetate/ hexane, 1:1) which indicated formation of a new product (R_f 0.30). The reaction mixture was neutralised with solid sodium hydrogen carbonate with stirring for a further 2 hours. The reaction mixture was concentrated *in vacuo* and filtered through a pad of silica, eluting with ethyl acetate. The filtrate was partitioned with brine (200 ml) and the aqueous phase extracted with ethyl acetate (200 ml, in two portions). The organic phases were combined, dried ($MgSO_4$) and filtered and the filtrate concentrated *in vacuo* to afford the title compound as an off-white solid (2.28 g, 90%). m.p. 121 - 123°C (ethyl acetate), [Lit.[1] 123 - 125°C]. ν_{max} (KBr): 3429 (br, OH), 1542, 1352 (NO_2). δ_H ($CDCl_3$, 500 MHz): 1.43, 1.45 (2 x 3H, 2 x s, $C(CH_3)_2$), 2.14 (1H, br s, $CH_2\underline{OH}$), 4.06 (2H, d, J 12.6, CH_2O), 4.09 (2H, s, $\underline{CH_2}OH$), 4.40 (2H, d, J 12.6, CH_2O).

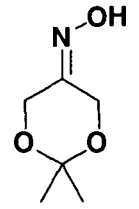
(5-Amino-2,2-dimethyl-[1,3]dioxan-5-yl)-methanol 69



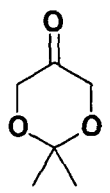
69

This compound was prepared according to a modified literature procedure.[2] A solution of the nitro compound **68** (1.0 g, 5.2 mmol) in methanol (15 ml) plus 10% palladium on carbon (350 mg) was stirred at r.t. and solid ammonium formate (1.71 g, 27 mmol) was added in one portion. The resulting heterogeneous reaction mixture was stirred at r.t. under argon for 30 minutes. T.l.c. (ethyl acetate) indicated complete conversion of starting material (R_f 0.70) into a major product (R_f 0.26) and baseline material. Diethyl ether (20 ml) was added to the reaction mixture and the catalyst was removed by filtration. The filtrate was concentrated *in vacuo* to remove the solvent and the residue was partitioned with ethyl acetate (50 ml) and brine (30 ml). The aqueous phase was extracted with further ethyl acetate (2 x 50 ml) and the organic phases were combined, dried (Na_2SO_4) and filtered. Evaporation of the filtrate *in vacuo* afforded the crude, unstable title compound which was immediately submitted to oxidative cleavage conditions without further purification.

2,2-Dimethyl-[1,3]dioxan-5-one oxime 79 and 2,2-Dimethyl-[1,3]dioxan-5-one 70



79



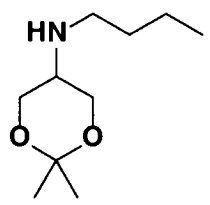
70

These compounds were prepared according to a modified literature procedure.[1] Sodium metaperiodate (3.99 g, 18.7 mmol) as a solution in water (63 ml) was added in one portion to a cold solution (ice-bath, 0°C), of the amino alcohol **69** in methanol/water (1:1, 75 ml) with vigorous stirring. The reaction mixture was stirred at 0°C for 55 minutes and then filtered eluting with dichloromethane (20 ml). The whole filtrate was transferred to a separating funnel and the aqueous phase was extracted with further dichloromethane (60 ml in two portions). The organic phases were combined, dried ($MgSO_4$) and filtered. Concentration of the filtrate *in vacuo* followed by purification by flash column chromatography (ethyl acetate/ hexane, 1:4) afforded the title compounds, oxime **79** (R_f 0.29) as a yellow oil (611 mg, 27%) and the known ketone **70** (R_f 0.57) as a colourless oil (371 mg, 19%).

Data for oxime **79**: ν_{max} (KBr): 3368 (br, OH), 1654 (C=NOH). δ_H ($CDCl_3$, 200 MHz): 1.42 (6H, s, $C(CH_3)_2$), 4.27 (2H, s, CH_2O), 4.60 (2H, s, CH_2O), 8.07 (1H, s, NOH). δ_C ($CDCl_3$, 50 MHz): 24.0 (q, $C(CH_3)_2$), 57.8 (t, CH_2O), 59.5 (t, CH_2O), 100.4 (s, $C(CH_3)_2$), 156.6 (C=NOH). *m/z* (APCI+): 146 ($M+H^+$, 100%), 128 ($M+H^+$-18, 100%). Found: C 49.64, H 7.75, N 9.70%; $C_6H_{11}NO_3$ requires: C 49.65, H 7.64, N 9.65%.

Data for ketone **70**: ν_{max} (film): 1727 (C=O). δ_H ($CDCl_3$, 200 MHz): 1.44 (6H, s, $C(CH_3)_2$), 4.15 (4H, s, CH_2O).

^{n}Butyl-(2,2-dimethyl-[1,3]dioxan-5-yl)-amine 83



83

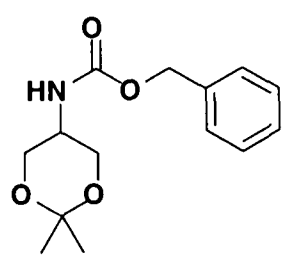
Method 1.

A solution of the oxime **79** (100 mg, 0.69 mmol) in methanol (5 ml) plus palladium black (40 mg) was hydrogenated at r.t. and pressure for 17 hours. T.l.c. (10% methanol/ ethyl acetate) formation of a major product (R_f 0.36). The reaction mixture was filtered through a pad of Celite, eluting with ethyl acetate (10 ml). The solvent was removed from the filtrate *in vacuo* and the residue was dissolved in ethyl acetate, preadsorbed onto silica gel and purified by flash column chromatography to afford the title compound as a brown oil (52 mg, 40%). δ_H ($CDCl_3$, 500 MHz): 0.92 (3H, t, J 7.3), 1.25 – 1.53 (4H, m, 2 x $C\underline{H}_2$), 1.42, 1.44 (2 x 3H, 2 x s, $C(CH_3)_2$), 2.62 – 2.70 (3H, m, -$C\underline{H}_2$NH, C$\underline{H}$NH), 2.84 (1H, br s, NH), 3.73 (2H, dd, J 11.8, 5.4, CH_2O), 3.99 (2H, dd, J 11.8, 3.6, CH_2O). δ_C ($CDCl_3$, 50 MHz): 13.9 (q, -CH_2CH_3), 20.4 (t, CH_2), 23.0, 24.4 (2 x q, $C(CH_3)_2$), 32.4 (t, CH_2), 46.5 (t, CH_2NH), 51.0 (d, CHNH), 63.6 (t, CH_2O), 98.1 (s, $C(CH_3)_2$). *m/z* (APCI+): 188 ($M+H^+$, 3%), 130 ($M+H^+$-58, 100%). HRMS (CI+): Found 188.1646; $C_{10}H_{22}NO_2$ requires 188.1651.

Method 2.

A solution of the ketone **70** (90 mg, 0.7 mmol) in methanol (5 ml) plus palladium black (36 mg) was hydrogenated at room temperature and pressure for 17 hours. T.l.c. (10% methanol/ ethyl acetate) formation of a major product (R_f 0.36). The reaction mixture was filtered through a pad of Celite, eluting with ethyl acetate (10 ml). The solvent was removed from the filtrate *in vacuo* and the residue was dissolved in ethyl acetate, preadsorbed onto silica gel and purified by flash column chromatography to afford the title compound as a brown oil (92 mg, 70%).

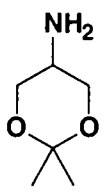
(2,2-Dimethyl-[1,3]dioxan-5-yl)-carbamic acid benzyl ester 85



A solution of ammonium formate (574 mg, 9.1 mmol) in methanol (10 ml) was added to the oxime **79** (132 mg, 0.91 mmol) and 10% Pd/C (53 mg) under argon. The resulting mixture was stirred at r.t. for 21 hours when t.l.c. (ethyl acetate/hexane, 1:2) indicated no oxime remained (R_f 0.46). Reaction mixture was filtered (eluting with methanol, 30 ml) and the resulting filtrate was concentrated *in vacuo* to *ca.* 10 ml in volume. To the filtrate was added diethyl ether (100 ml) and the ensuing precipitate was filtered off. Analysis of the precipitate showed no desired products were present. The filtrate was concentrated *in vacuo* to afford a white solid to which was added saturated aqueous sodium hydrogencarbonate (2 ml) and diethyl ether (5 ml). The resulting mixture was cooled to 0°C and benzyl chloroformate (220 µl, 1.55 mmol) was added dropwise to the vigorously stirred mixture and allowed to stir at 0°C for a further 4 hours. T.l.c. (ethyl acetate/hexane, 1:2) showed formation of a new product (R_f 0.32). The reaction mixture was partitioned between diethyl ether and water, and aqueous phase was extracted with further diethyl ether (2 x 15 ml). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* and the resulting residue dissolved in ethyl acetate. Preadsorption onto

silica gel followed by purification by flash column chromatography (ethyl acetate/ hexane, 1:2) afforded the title compound as a white solid (148 mg, 62% over two steps). m.p. (ethyl acetate/hexane) 75 - 77°C. ν_{max} (KBr, cm^{-1}): 3329 (NH), 1716 (C=O). δ_H (400 MHz, $CDCl_3$) : 1.40, 1.48 (2 x 3H, 2 x s, $C(CH_3)_2$), 3.63 (1H, dt, J 9.0, 2.3, HCN), 3.74 (2H, br d, J 12.1, CH_2O), 4.12 (2H, br d, J 12.4, CH_2O), 5.12 (2H, s, $ArCH_2$), 7.31 – 7.39 (5H, m ArH). δ_C (100 MHz, $CDCl_3$) : 18.7, 28.5 (2 x q, 2 x $C(CH_3)_2$), 45.2 (d, CHNH), 63.7 (t, CH_2O), 66.8 (t, $ArCH_2$), 98.5 (s, $C(CH_3)_2$), 127.0 (d, Ar), 128.2 (d, Ar), 128.6 (d, Ar), 136.3 (s, Ar), 155.8 (C=O). *m/z* (APCI+): 266 ($M+H^+$, 10%), 208 ($M+H^+$ - 58, 30%). Found: C 63.40, H 7.10, N 5.28 %; $C_{14}H_{19}NO_4$ requires: C 63.38, H 7.22, N 5.28 %.

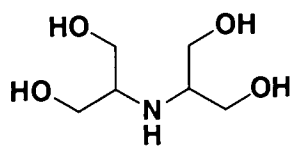
2,2-Dimethyl-[1,3]dioxan-5-ylamine 82



82

A solution of the Z-amine **85** (46 mg, 0.17 mmol) in ethyl acetate (3 ml) plus palladium black (30 mg) was hydrogenated at r.t. and pressure for 17 hours. T.l.c. (ethyl acetate/ hexane, 1:2) showed complete consumption of starting material (R_f 0.32) to baseline material. The reaction mixture was filtered through Celite, eluting with ethyl acetate (10 ml). The solvent was removed from the filtrate *in vacuo* to afford the known[3] title compound as a brown oil (22 mg, 100%). ν_{max} (film): 3358 (br NH_2). δ_H (500 MHz, $CDCl_3$): 1.43 (6H, s, $C(CH_3)_2$), 2.16 (2H, br s, NH_2), 2.85 (1H, m, CHN), 3.57 (2H, dd, J 11.8, 5.4, CH_2O), 4.02 (2H, dd, J 11.8, 3.8, CH_2O).

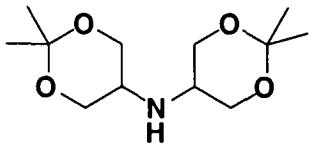
2-(2-Hydroxy-1-hydroxymethyl-ethylamino)-propane-1,3-diol 58



58

Sodium cyanoborohydride (10.0 g, 159 mmol) was added to a solution of dihydroxyacetone dimer (28.67 g, 159 mmol) and ammonium chloride (2.84 g, 53 mmol) in methanol (400 ml) and acetic acid (40 ml). After stirring for 20 hours, aqueous hydrochloric acid (2M, 100 ml) was added, and after stirring for 4 hours the reaction was concentrated *in vacuo*, dissolved in methanol (100 ml), filtered and concentrated once more. The viscous residue was dissolved in water and applied to an ion-exchange column (Amberlite, IR-120, H^+), which was eluted first with water, and then a solution of aqueous ammonia (1M). The solvent was removed to afford the title compound as a hygroscopic oil (7.49 g, 85%). δ_H (200 MHz, D_2O): 2.85 (2H, m, CHN), 3.53 (4H, dd, J 5.5, 11.5, CH_2O), 3.61 (4 H, dd, J 5.5, 11.5, CH_2O). δ_C (50 MHz, D_2O): 58.1 (d, CHN), 61.8 (t, OCH_2). *m/z* (APCI+): 165.8 ($M+H^+$, 15%), 147.9 ($M+H^+-H_2O$), 129.9 ($M+H^+-2H_2O$); 103.7 (100%). HRMS (CI+): Found 166.1076; $C_6H_{16}NO_4$ requires 166.1079.

***Bis*-(2,2-dimethyl-[1,3]dioxan-5-yl)-amine 60**



60

Method 1.

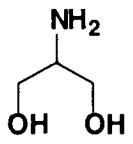
Acetone (30 ml), 2,2-dimethoxypropane (10 ml) and concentrated sulfuric acid (1 ml) were added to a solution of BDI **58** (1.71 g, 10.35 mmol) in DMF (10 ml) at r.t. An initially formed precipitate gradually dissolved. The reaction mixture was stirred for 4 hours, after which solid sodium hydrogencarbonate (5 g) was added until the pH had risen to 7. The solvents were removed *in vacuo* and the residue was partitioned between ethyl acetate (100 ml) and water (50 ml). The aqueous layer was extracted with ethyl acetate (2 x 50ml), and the combined organic extracts were washed with brine (50 ml), dried ($MgSO_4$), filtered and concentrated to give the title compound as a light orange solid (1.89 g, 74%), sufficiently pure for further elaboration. A sample of **60** was crystallised from hexane/diethyl ether for analysis. m. p. 64 - 66°C (hexane/diethyl ether). δ_H (200 MHz, $CDCl_3$) 1.42 (12H, s, $C(C\underline{H}_3)_2$), 2.74 (2 H, m, CHN), 3.63

(4H, dd, J 6.7, 11.5, CH_2O), 3.86 (4 H, dd, J 4.0, 11.5, CH_2O). δ_C (50 MHz, acetone d_6): 21.9, 26.1 (2 x q, 2 x $C(CH_3)_2$), 49.5 (d, CHN), 65.1 (t, CH_2O), 98.0 (s, $C(CH_3)_2$). *m/z* (APCI+): 284 ($M+K^+$, 5%), 268 ($M+Na^+$, 25%), 246 ($M+H^+$, 100%). Found: C 58.89, H 9.57; N, 5.64%, $C_{12}H_{23}NO_4$ requires: C 58.75, H 9.45, N 5.71%.

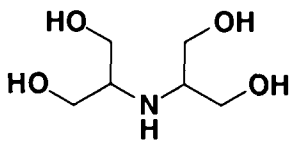
Method 2.

A solution of the oxime **79** (70 mg, 0.48 mmol) in methanol (4 ml) containing 10% Pd/C (30 mg) was hydrogenated at r.t. and pressure for 17 hours after which time t.l.c. (ethyl acetate/ hexane 1:2) indicated complete conversion of starting material (R_f 0.46) to baseline. The reaction mixture was filtered through Celite eluting with further methanol and the filtrate was concentrated *in vacuo* to afford an analytically pure sample of the title compound as a white solid (34 mg, 58%).

2-Amino-propane-1,3-diol (Serinol) 57 and 2-(2-Hydroxy-1-hydroxymethyl-ethylamino)-propane-1,3-diol 58



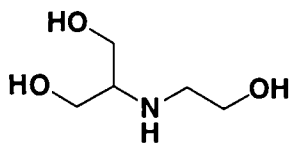
57



58

To a solution of dihydroxyacetone dimer (2.0 g, 11.1 mmol) and ammonium fluoride (2.41 g, 66.6 mmol) in methanol (100 ml) was added sodium cyanoborohydride (1.74 g, 27.8 mmol) and acetic acid (10 ml). After stirring for 19 hours, 2M hydrochloric acid (25 ml) was added, and after stirring with suction for 4 hours the reaction was concentrated *in vacuo*, dissolved in methanol (100 ml), filtered and concentrated once more. The viscous residue was dissolved in water and applied to an ion-exchange column (Amberlite, IR-120, H^+), which was eluted first with water, and then ammonia solution (1M). The basic washings were concentrated to give 750 mg of a mixture of amines as an orange oil, characterised as a mixture of amines serinol **57** :BDI **58** (1:1.8) as judged by ^1H NMR.

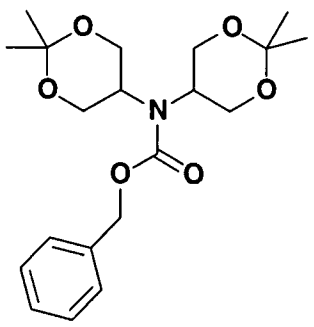
2-(2-Hydroxy-ethylamino)-propane-1,3-diol 61(b)



61(b)

Sodium cyanoborohydride (1.55 g, 24.6 mmol) was added to a solution of dihydroxyacetone dimer (4.43 g, 24.6 mmol) and ammonium chloride (2.84 g, 53 mmol) in methanol (50 ml) and acetic acid (5 ml). After stirring for 20 hours, aqueous hydrochloric acid (2M, 12 ml) was added, and after stirring for 4 hours the reaction was concentrated *in vacuo*, dissolved in methanol (50 ml), filtered and concentrated once more. The viscous residue was dissolved in water and applied to an ion-exchange column (Amberlite, IR-120, H^+), which was eluted first with water, and then a solution of aqueous ammonia (1M). The solvent was removed to give the known[4] title compound as a hygroscopic oil, (4.19 g, 63%). δ_H (200 MHz, D_2O): 2.87 (1H, m, CHN), 3.33 - 3.53 (8H, m, 4 x CH_2).

***Bis*-(2,2-dimethyl-[1,3]dioxan-5-yl)-carbamic acid benzyl ester 84**

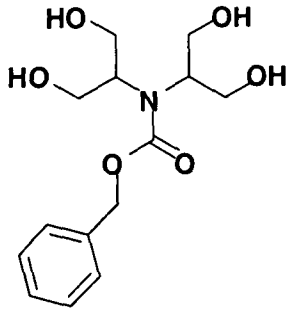


84

The diacetonide **60** (200 mg, 0.82 mmol) was dissolved in dichloromethane (2 ml) and cooled to *ca.* 0°C under an atmosphere of argon. DIPEA (137 µl, 1.06 mmol) was then added, followed by benzylchloroformate (dropwise over 5 minutes) (151 µl, 1.06 mmol). Reaction mixture was stirred for 30 minutes at 0°C and then warmed to r.t. and stirred for a further 19 hours. T.l.c. (ethyl acetate/ hexane, 1:2) showed formation of a new product (R_f 0.26). The reaction mixture was diluted with diethyl ether (20 ml) and the whole was transferred to a separating funnel,

washed with 1M sodium hydrogencarbonate, and the aqueous phase extracted with ethyl acetate (20 ml in two portions). The organic phases were combined and dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate/ hexane, 1:2) to afford the title compound as a colourless oil (202 mg, 65%). ν_{max} (film): 1694 (C=O). δ_H (toluene d_8, 500 MHz, 90°C): 1.28, 1.33 (2 x 6H, 2 x s, $C(CH_3)_2$), 3.65 – 3.67 (4H, m, CH_2O), 4.03 – 4.10 (6H, m, CH_2O and 2 x CHN), 4.97 (2H, s, $ArCH_2$), 7.02 – 7.16 (5H, ArH). δ_C ($CDCl_3$, 125 MHz): 22.7, 25.8 (2 x q, $C(CH_3)_2$), 51.4 (d, CHN), 62.1 (t, CH_2O), 67.9 (t, $ArCH_2$), 98.5 (s, $C(CH_3)_2$), 128.3, 128.5, 129.2, (3 x d, 3 x Ar), 139.3 (s, Ar), 154.8 (s, C=O). *m/z* (APCI+): 402 ($M+Na^+$, 1%), 322 ($M+H^+$ - 58, 5%), 264 ($M+H^+$ - 2(58), 100%). Found: C 63.31, H 7.39, N 3.36%, $C_{20}H_{29}NO_6$ requires: C 63.31, H 7.70, N 3.69%.

***Bis*-(2-hydroxy-1-hydroxymethyl-ethyl)-carbamic acid benzyl ester 86**



86

The z derivative **84** (200 mg, 0.53 mmol) was dissolved in trifluoroacetic acid (1 ml) and water (1 ml) was added to the stirred solution. The reaction mixture was allowed to stir at r.t. for 17 hours. T.l.c. (ethyl acetate/hexane, 1:2) showed complete consumption of starting material (R_f 0.26) to baseline. The reaction mixture was concentrated *in vacuo,* and co-evaporated with toluene (2 x 2ml) to afford the product as a colourless oil (157mg, 100%). ν_{max} (film): 3350 (br OH), 1674 (C=O). δ_H (DMSO d_6, 500 MHz, 90°C): 3.44 – 3.82 (4H, m, CH_2O), 4.41 – 4.68 (6H, m, CH_2O and 2 x CHN), 5.08 (2H, s, $ArCH_2$), 7.02 – 7.16 (5H, ArH). δ_C (D_2O, 50 MHz): 60.1 (d, CHN), 60.6 (t, CH_2O), 68.4 (t, $ArCH_2$), 128.6, 129.2, 129.5, (3 x d, 3 x Ar), 136.9 (s,

Ar) 158.6 (s, C=O). *m/z* (APCI+): 338 ($M+K^+$, 7%), 300 ($M+H^+$, 28%), 282 (MH^+ - 18, 13%), 192 (100%). HRMS (CI+): Found 300.1441; $C_{14}H_{22}NO_6$ requires 300.1448.

References and Notes

[1] Majewski,M., Gleave, D.M., Nowak, P.; *Can. J. Chem.*; 1995, **73**, 1616.

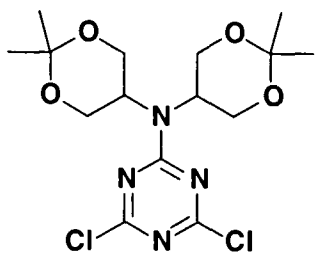
[2] Barrett, A.G.M., Spilling, C.D.; *Tetrahedron Lett.*, 1988, **29**, 5733.

[3] Harada, H., Morie, T., Hirokawa, Y., Kato, S.; *Chem. Pharm. Bull.*, 1996, **44**, 2205.

[4] El Ashry, E. S. H., Abdel-Rahman, A. A.-H., El Kilany, Y., Schmidt, R. R.; *Tetrahedron*, 1999, **55**, 2381.

6. Experimental (Chapter 3)

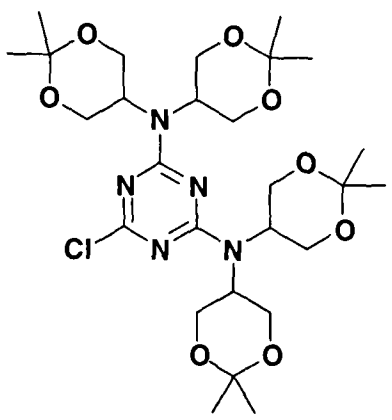
4,6-Dichloro-2-*bis*-(2,2-dimethyl-[1,3]dioxan-5-yl)-amino-1,3,5-triazine 108



108

To a solution of 2,4,6-trichloro-1,3,5-triazine (500 mg, 2.7 mmol) in dry toluene (12 ml) were added DIPEA (472 μl) and a solution of *bis*-(2,2-dimethyl-[1,3]dioxan-5-yl)-amine **60** (664 mg, 2.7 mmol) in toluene (6 ml). The reaction mixture was heated at reflux with stirring for 50 minutes under argon. T.l.c. (ethyl acetate/ hexane, 1:3) showed complete consumption of starting material (R_f 0.03) and formation of a single product (R_f 0.19). The reaction mixture was concentrated *in vacuo* and the residue dissolved in ethyl acetate, preadsorbed onto silica gel and purified by flash column chromatography (ethyl acetate/ hexane, 1:3) to afford the title compound as a yellow solid (1025 mg, 96%). m.p. 127 - 130°C (toluene). δ_H (toluene d_8, 500 MHz, 90°C): 1.28, 1.46 (2 x 6H, 2 x s, $C(CH_3)_2$), 3.61 (4H, dd, J 5.2, 11.8 CH_2O), 4.10 (4H, dd, J 7.1, 11.8, CH_2O), 4.40 (2H, m, 2 x CHN). δ_C ($CDCl_3$, 125 MHz): 22.8, 24.8 (2 x q, $C(CH_3)_2$), 50.6 (d, CHN), 60.2 (t, CH_2O), 98.5 (s, $C(CH_3)_2$), 164.9, 169.8 (2 x s, Ar, triazinics). *m/z* (APCI+): 393 ($M+H^+$, 20%), 335 ($M+H^+$ - 58, 85%). HRMS (CI+): Found 393.1096; $C_{15}H_{23}N_4O_4Cl_2$ requires 393.1088.

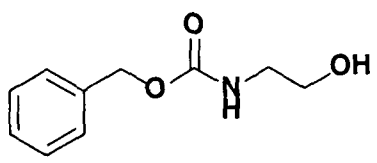
2-Chloro-4,6-*bis*[*bis*-(2,2-dimethyl-[1,3]dioxan-5-yl)-amino]-1,3,5-triazine 109



109

To a solution of 4,6-dichloro-2-*bis*-(2,2-dimethyl-[1,3]dioxan-5-yl)-amino-1,3,5-triazine **108** (221 mg, 0.56 mmol) in dry toluene (1 ml) were added DIPEA (98 µl, 0.56 mmol) and a solution of *bis*-(2,2-dimethyl-[1,3]dioxan-5-yl)-amine **60** (140 mg, 0.56 mmol) in toluene (1 ml). The reaction mixture was heated at reflux with stirring for 50 hours under argon. T.l.c. (ethyl acetate/ hexane, 1:2) indicated formation of a single product (R_f 0.27) and a trace of starting material (R_f 0.50). The reaction mixture was concentrated *in vacuo* and the residue dissolved in ethyl acetate, preadsorbed onto silica gel and purified by flash column chromatography (ethyl acetate/ hexane, 1:3) to afford the title compound as a yellow solid (109 mg, 53% - over recovered starting material). m.p. 133 - 135°C (toluene). δ_H (toluene d_8, 500 MHz, 90°C): 1.33, 1.50 (2 x 12H, 2 x s, $C(CH_3)_2$), 3.74 (8H, dd, J 5.4, 11.5, CH_2O), 4.23 (8H, br m, CH_2O), 4.58 (4H, m, 4 x CHN). δ_C ($CDCl_3$, 125 MHz): 20.5, 23.5, 24.5, 27.5 (4 x q, $C(CH_3)_2$), 49.8, 50.3 (2 x d, 2 x CHN), 60.6, 61.1 (2 x t, 2 x CH_2O), 98.1, 98.6 (2 x s, 2 x $C(CH_3)_2$), 164.9, 167.4 (2 x s, 2 x Ar, triazinics). *m/z* (APCI+): 602 ($M+H^+$, 17%), 544 ($M+H^+$ - 58, 100%). HRMS (CI+): Found 602.2957; $C_{27}H_{45}N_5O_8Cl$ requires 602.2940.

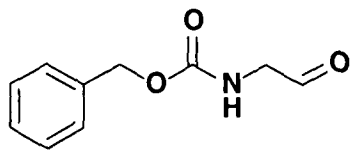
2-Benzyloxycarbonylaminoethanol 123



123

This compound was prepared according to a literature procedure.[1] δ_H ($CDCl_3$, 200 MHz): 2.20 (1H, br s, OH), 3.36 (2H, q_{app}, CH_2N), 3.72 (2H, m, $\underline{CH_2}OH$), 5.11 (2H, s, $ArCH_2$), 5.26 (1H, br s, NH), 7.35 – 7.46 (5H, m, ArH).

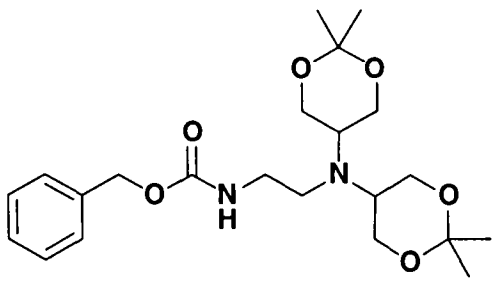
2-Benzyloxycarbonylaminoethanal 124



124

This compound was prepared according to a modified literature procedure.[2] Under an atmosphere of argon, dry dichloromethane (30 ml) was added to powdered (3Å) molecular sieves (2.13 g) which were previously dried for 2 hours. Solid pyridinium chlorochromate (5.50 g, 25.5 mmol) was then added and the mixture stirred at r.t. under argon for 10 minutes. A solution of the alcohol **123** (1.42 g, 7.28 mmol) in dry dichloromethane (30 ml) was added dropwise to the stirred mixture. After 2.5 hours t.l.c. (ethyl acetate/ hexane 1:1) indicated complete conversion of the starting material (R_f 0.26) to product (R_f 0.61). The reaction mixture was diluted with diethyl ether (80 ml) and stirred for 10 minutes. The solution was then filtered through a silica plug, eluting with diethyl ether. The residual molecular sieves and pyridinium chlorochromate were collected and crushed in a mortar and pestle with diethyl ether and the resulting solution was filtered through the plug eluting with further diethyl ether. The resulting filtrate was concentrated *in vacuo* and the ensuing oil purified by flash column chromatography (ethyl acetate/ hexane 1:1) to afford the title compound as a colourless oil (777 mg, 55%). ν_{max} (film): 3350 (NH), 1730, 1710 (carbamate and aldehyde). δ_H ($CDCl_3$, 200 MHz): 4.16 (2H, d, J 5.0, $\underline{CH_2}CHO$), 5.05 – 5.19 (3H, m, $ArCH_2$, NH), 7.30 – 7.48 (5H, m, ArH), 9.68 (1H, s, CHO).

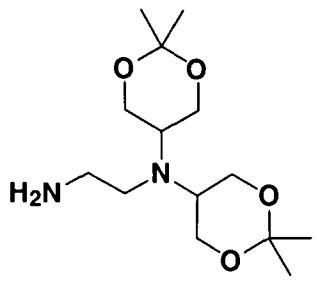
Bis-(2,2-dimethyl-[1,3]dioxan-5-yl)-amino]-ethyl-carbamic acid benzyl ester 125



125

The aldehyde **124** (472 mg, 2.4 mmol) was dissolved in dichloroethane (6 ml) and to this was added a solution of the amine **60** (628mg, 2.6mmol) in dichloroethane (4 ml) under an atmosphere of argon, followed by solid sodium triacetoxyborohydride (762 mg, 3.6 mmol) in one portion. The reaction mixture was stirred for 2 hours at r.t. after which time t.l.c. (ethyl acetate/ hexane, 1:1) indicated the appearance of a new product (R_f 0.43) and a trace of starting material (R_f 0.51). An aqueous solution of sodium hydroxide (1M, 20ml) was added to the reaction mixture and stirred for a further 10 minutes. The reaction mixture was partitioned with ethyl acetate (100ml) and the aqueous phase was extracted with further ethyl acetate (50ml in two portions). The organic phases were combined and dried ($MgSO_4$) , filtered and the filtrate concentrated *in vacuo* to give a residue which was purified by flash column chromatography (ethyl acetate/ hexane, 1:1) to afford the title compound as a yellow oil (821 mg, 81%). ν_{max} (film): 3338 (br NH), 1716 (C=O). δ_H (toluene d_8, 500 MHz, 90°C): 1.28 (12H, s, 2 x $C(CH_3)_2$), 2.67 (2H, t, J 6.6, CH_2N), 2.85 – 2.90 (4H, m, $\underline{CH_2}NH$, 2 x CHN), 3.53 (4H, dd, J 5.7, 11.8, CH_2O), 4.10 (4H, dd, J 7.3, 11.8, CH_2O), 4.97 (1H,s, NH), 5.02 (2H, s, $PhCH_2$), 7.02 – 7.22 (5H, m, ArH). δ_C ($CDCl_3$, 125 MHz): 22.3, 26.4 (2 x q, 2 x $C(CH_3)_2$), 40.9 (t, CH_2N), 46.9 (t, CH_2NH), 52.8 (d, CHN), 62.9 (t, CH_2O), 98.7 (s, $C(CH_3)_2$), 128.7, 129.1, (2 x d, 2 x ArH) 137.05 (s, Ar), 156.97 (s, C=O). *m/z* (APCI+): 423 ($M+H^+$, 100%), 365 ($M+H^+$ - 58, 15%). HRMS (CI+): Found 423.2489; $C_{22}H_{35}N_2O_6$ requires 423.2496.

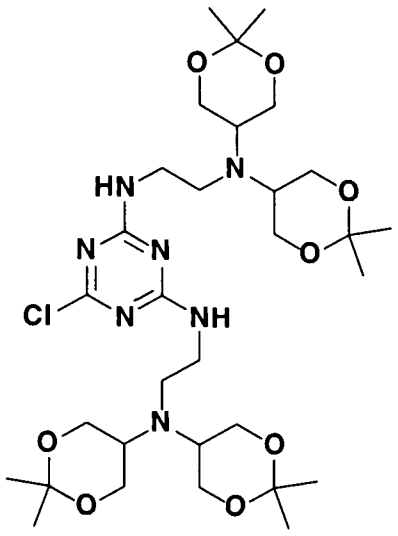
Bis-(2,2-dimethyl-[1,3]dioxan-5-yl)-ethane-1,2-diamine 126



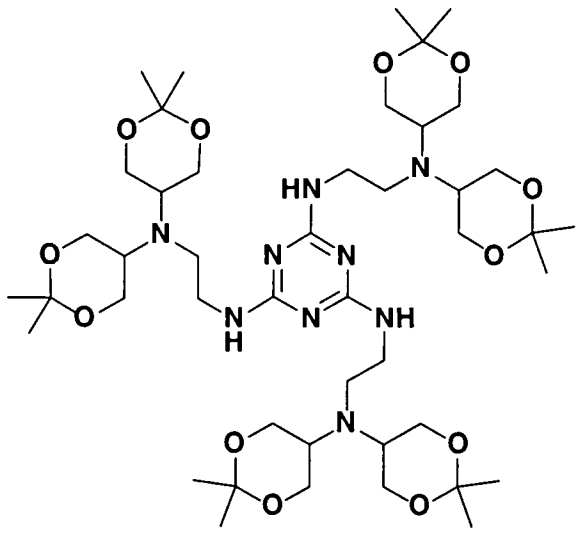
126

A solution of the Z-diamine **125** (580 mg, 1.4 mmol) in ethanol (6 ml) plus palladium black (80 mg) was hydrogenated at r.t. and pressure for 19 hours. T.l.c. analysis (ethyl acetate/ hexane, 1:1) indicated the appearance of some baseline product and no starting material (R_f 0.43). The reaction mixture was filtered through a small pad of Celite eluting with ethyl acetate. The solvent was removed from the filtrate *in vacuo* to afford the title compound as a colourless oil (395 mg, 100%). ν_{max} (film): 3360 (br NH_2). δ_H ($CDCl_3$, 400 MHz): 1.38, 1.44 (2 x 6H, 2 x s, $C(CH_3)_2$), 2.74 (2H, t, J 6.0, CH_2), 2.88 (2H, t, J 6.0 Hz, CH_2), 3.09 (2H, m, 2 x CHN), 3.79 (8H, d_{app}, J_{app} 6.7, CH_2O). δ_C ($CDCl_3$, 50 MHz): 21.3, 26.3 (2 x q, $C(CH_3)_2$), 40.6 (t, CH_2N), 48.8 (t, CH_2NH_2), 52.2 (d, CHN), 62.3 (t, CH_2O), 98.1 (s, $C(CH_3)_2$). *m/z* (APCI+): 289 ($M+H^+$, 100%), 231 ($M+H^+$ - 58, 24%). HRMS (CI+): Found 289.2125; $C_{14}H_{29}N_2O_4$ requires 289.2127.

2-Chloro-4,6-*bis*(*bis*-(2,2-dimethyl-[1,3]dioxan-5-yl)-ethane-1,2-diamino)-1,3,5-triazine 127 and 2,4,6-*tris*(*bis*-(2,2-dimethyl-[1,3]dioxan-5-yl)-ethane-1,2-diamino)-1,3,5-triazine 128



127



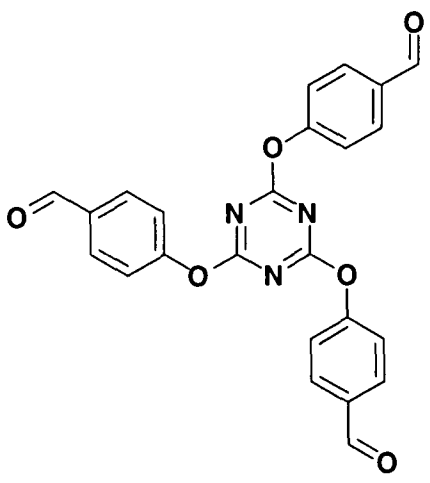
128

To a solution of 2,4,6-trichloro-1,3,5-triazine (22 mg, 0.12 mmol) in dry toluene (2 ml) were added DIPEA (75 µl, 0.43 mmol) and a solution of the diamine **126** (120 mg, 0.43 mmol) in toluene (1.5 ml). The reaction mixture was heated at reflux with stirring for 16 hours under argon. T.l.c. (ethyl acetate/ methanol, 19:1) showed formation of two products (R_f 0.43, 0.51). The reaction mixture was concentrated *in vacuo* and the residue dissolved in ethyl acetate, preadsorbed onto silica gel and purified by flash column chromatography (ethyl acetate/ methanol, 19:1) to afford the title compounds, both as yellow oils, the disubstituted triazine **127** (58mg, 71%, eluted first), and the trisubstituted triazine **128** (33mg, 29%, eluted second).

Data for disubstituted triazine **127**: ν_{max} (film): 3268 (br NH). δ_H (toluene d_8, 500 MHz, 90°C): 1.29, 1.30 (2 x 12H, 2 x s, $C(CH_3)_2$), 2.78 (4H, t, J 6.0, CH_2N), 2.94 (4H, m, 4 x CHN). 3.14 (4H, br m, CH_2NH), 3.57 (8H, dd, J 5.6, 11.8, CH_2O), 3.69 (4H, dd, J 7.4, 11.7, CH_2O), 5.37 (2H, br s, 2 x NH). δ_C (toluene d_8, 125 MHz, 60°C): 22.5, 25.7 (2 x q, $C(CH_3)_2$), 41.3 (t, CH_2N), 46.5 (t, CH_2NH), 52.6 (d, CHN), 62.8 (t, CH_2O), 98.4 (s, $C(CH_3)_2$), 166.8 (br s, Ar, triazinics). *m/z* (APCI+): 689 ($M+H^+$, 100%). HRMS (CI+): Found 688.3801; $C_{31}H_{55}N_7O_8Cl$ requires 688.3797.

Data for trisubstituted triazine **128**: ν_{max} (film): 3270 (br, NH). δ_H (toluene d_8, 500 MHz, 90°C): 1.30, 1.31 (2 x 18H, 2 x s, $C(CH_3)_2$), 2.84 (6H, t, J 6.7, CH_2N), 3.03 (6H, m, 6 x CHN). 3.24 (6H, q_{app}, CH_2NH), 3.62 (12H, dd, J 5.7, 11.7, CH_2O), 3.72 (12H, dd, J, 7.7, 11.7, CH_2O), 4.97 (3H, br s, 3 x NH). δ_C (toluene d_8, 125 MHz, 25°C): 22.9, 25.1 (2 x q, $C(CH_3)_2$), 46.6 (t, CH_2N), 49.2 (d, CHN), 62.6 (t, CH_2NH), 64.7 (t, CH_2O), 97.9 (s, $C(CH_3)_2$), 159.5 (s, Ar, triazinics). *m/z* (APCI+): 963 ($M+Na^+$, 18%), 941 ($M+H^+$, 100%). HRMS (CI+): Found 940.6083; $C_{45}H_{82}N_9O_{12}$ requires 940.6077.

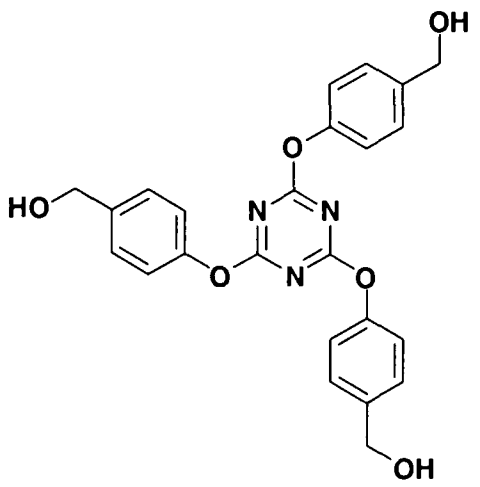
2,4,6-*Tris*(4-Hydroxy-benzaldehyde)-1,3,5-triazine 135



135

This compound was prepared according to a literature procedure.[3] δ_H ($CDCl_3$, 200 MHz): 7.32 (6H, d, J 8.5, ArH), 7.92 (6H, d, J 8.5, ArH), 10.00 (3H,s, C<u>H</u>O).

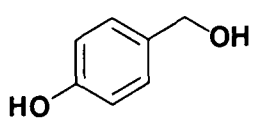
2,4,6-*Tris*(4-Hydroxymethyl-phenoxy)-1,3,5-triazine 137



137

A solution of the trialdehyde **135** (100 mg, 0.23 mmol) and amine **60** (169 mg, 0.69 mmol) in ethyl acetate (6 ml) plus 10% palladium on carbon (20 mg) was hydrogenated at r.t. and pressure for 80 hours. T.l.c. analysis (ethyl acetate) indicated the appearance of a three new products (R_f 0.36 (major), 0.52, 0.67) and starting amine (R_f 0.26). The reaction mixture was filtered through Celite eluting with ethyl acetate. The solvent was removed from the filtrate *in vacuo* and the resulting mixture was purified by flash column chromatography (ethyl acetate) to give the title compound as the fated product as a white solid (69 mg, 67%) . ν_{max} (KBr): 3442 (br OH). δ_H (acetonitrile d_3, 500 MHz): 3.38 (3H, br s, D_2O exch., 3 x OH) 4.60 (6H, s, 3 x $ArCH_2$), 7.14 (6H, d, J 8.5, ArH), 7.39 (6H, d, J 8.5Hz, ArH). δ_C (acetonitrile d_3, 50 MHz): 62.4 (t, $ArCH_2$), 121.1 (d, Ar), 127.6 (d, Ar), 140.4 (s, Ar), 150.1 (s, Ar), 173.2 (s, Ar, triazinics). *m/z* (APCI+): 448 ($M+H^+$, 100%). HRMS (CI+): Found 448.1516; $C_{24}H_{22}N_3O_6$ requires 448.1509.

4-Hydroxymethyl-phenol 138

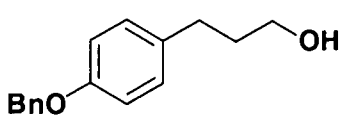


138

A solution of the *p*-hydroxy benzaldehyde (50 mg, 0.41 mmol) and amine **60** (100 mg, 0.41 mmol) in ethyl acetate (2 ml) plus 10% palladium on carbon (20 mg) was hydrogenated at r.t. and pressure for 80 hours. T.l.c. (ethyl acetate/ hexane, 1:1) indicated the appearance of a new product

(R_f 0.18). The reaction mixture was filtered through Celite eluting with ethyl acetate. The solvent was removed from the filtrate *in vacuo* and the resulting mixture was purified by flash column chromatography (ethyl acetate : hexane, 1:1) to give the title compound as a pale orange solid (42 mg, 83%). δ_H (acetonitrile d_3, 200 MHz): 3.03 (1H, t, J 5.8, $CH_2\underline{OH}$) 4.46 (2H, d, J 5.8, $ArCH_2$), 6.77 (2H, d, J 8.5, ArH), 6.94 (1H, s, Ar$\underline{OH}$), 7.17 (2H, d, J 8.5, ArH).

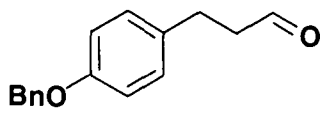
3-(4-Benzyloxy-phenyl)-propan-1-ol 140



140

This compound was prepared according to a modified literature procedure.[4] To a stirred suspension of sodium hydride (212 mg, 60% by mass, 5.3 mmol) in DMF (4 ml) at r.t. was added a solution of 3-(*p*-hydroxyphenyl)-1-ethanol **139** (800 mg, 5.3 mmol) in DMF (2 ml) dropwise over 20 minutes. The solution was stirred until gas evolution had ceased and then benzyl bromide (0.63 ml, 5.3 mmol) was added in one portion. The reaction mixture was stirred at r.t. for 17 hours when t.l.c. analysis (ethyl acetate/ hexane, 1:1) indicated formation of a single product (R_f 0.46) and a trace of starting material (R_f 0.34). The reaction mixture was then poured into water (30 ml) and extracted with diethyl ether (60ml) in three portions. The combined organic phases were washed with 3M sodium hydroxide (10ml), and brine (10ml), dried ($MgSO_4$), filtered, and the filtrate evaporated to give crude crystalline material. Recrystallization from diethyl ether/ petroleum ether provided analytically pure title compound (1.21 g, 95%). δ_H ($CDCl_3$, 200 MHz): 1.25 (1H, br m., D_2O exch., -OH), 1.84 – 1.94 (2H, m, -CH_2 $\underline{CH_2}$ CH_2OH), 2.66 (2H, t, J 7.7, Ar$\underline{CH_2}$), 3.68 (2H, dd_{app}, J_{app} 11.4, 6.2, t J 11.1 on D_2O exch., $\underline{CH_2}OH$), 5.05 (2H, s, $ArCH_2$), 6.92 (2H, d, J 8.7, ArH), 7.13 (2H, d, J 8.7, ArH), 7.30 – 7.46 (5H, m, ArH).

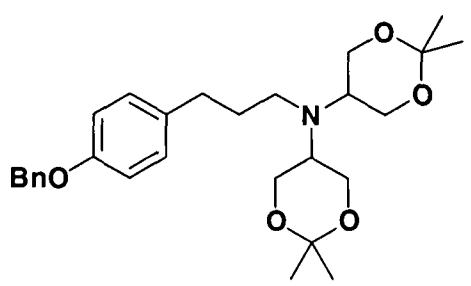
3-(4-Benzyloxy-phenyl)-propan-1-al 141



141

This compound was prepared according to a literature procedure[4]. δ_H ($CDCl_3$, 200 MHz): 2.55 – 2.98 (4H, m , 2 x CH_2), 5.05 (2H, s, $ArCH_2$), 6.92 (2H, d, J 8.7, ArH), 7.13 (2H, d, J 8.7, ArH), 7.29 – 7.53 (5H, m, ArH), 9.85 (1H, s, CHO).

[3-(4-Benzyloxy-phenyl)-propyl]-*bis*-(2,2-dimethyl-[1,3]dioxan-5-yl)amine 142

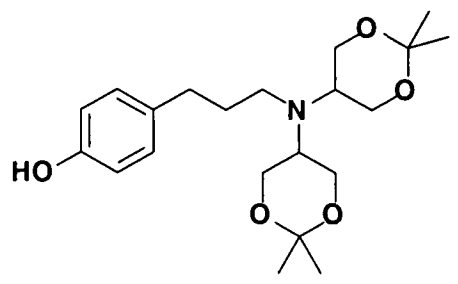


142

The aldehyde **141** (372 mg, 1.5 mmol) was dissolved in dichloroethane (6 ml) and to this was added a solution of the amine **60** (379 mg, 1.5 mmol) in dichloroethane (4 ml) under an atmosphere of argon, followed by solid sodium triacetoxyborohydride (413 mg, 2.0 mmol) in one portion. The reaction mixture was stirred for 3 hours at r.t. after which time t.l.c. (ethyl acetate/ hexane, 1:2) indicated the appearance of a new product (R_f 0.4) and no starting material (R_f 0.6). An aqueous solution of sodium hydroxide (1M, 10ml) was added to the reaction mixture and stirred for a further 10 minutes. The reaction mixture was partitioned with ethyl acetate (25ml) and the aqueous phase was extracted with a further ethyl acetate (50ml in two portions). The organic phases were combined and dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo* to give a residue which was purified by flash column chromatography (ethyl acetate/ hexane, 1:3) to afford the title compound as a colourless oil (539 mg, 77%). δ_H ($CDCl_3$, 400 MHz): 1.37, 1.39 (2 x 3H, 2 x s, $C(CH_3)_2$), 1.64 - 1.71 (2H, m, CH_2), 2.53 (2H, t, J 7.5, CH_2), 2.71 (2H, t, J 7.4), 3.03-3.10 (2H, m , 2 x CHN), 3.71 (8H, d_{app}, J_{app} 10.6, CH_2O),

5.05 (2H, s, $ArCH_2$), 6.91 (2H, d, J 8.6, ArH), 7.09 (2H, d, J 8.6, ArH), 7.31 – 7.45 (5H, m, ArH). δ_C ($CDCl_3$, 50 MHz): 20.6, 27.0 (2 x q, $C(CH_3)_2$), 32.1 (t, CH_2), 46.5 (t, CH_2), 52.3 (d, CHN), 62.5 (t, CH_2O), 70.0 (t, CH_2N), 97.8 (s, $C(CH_3)_2$), 114.8, 127.4, 127.9, 128.5, 129.2 (5 x d, Ar), 134.1 (s, Ar), 137.2 (s, Ar), 157.0 (s, Ar) . *m/z* (APCI+): 492 ($M+Na^+$, 7%), 470 ($M+H^+$, 100%), 412 ($M+H^+$-58, 71%). HRMS (CI+): Found 470.2912; $C_{28}H_{40}NO_5$ requires 470.2907.

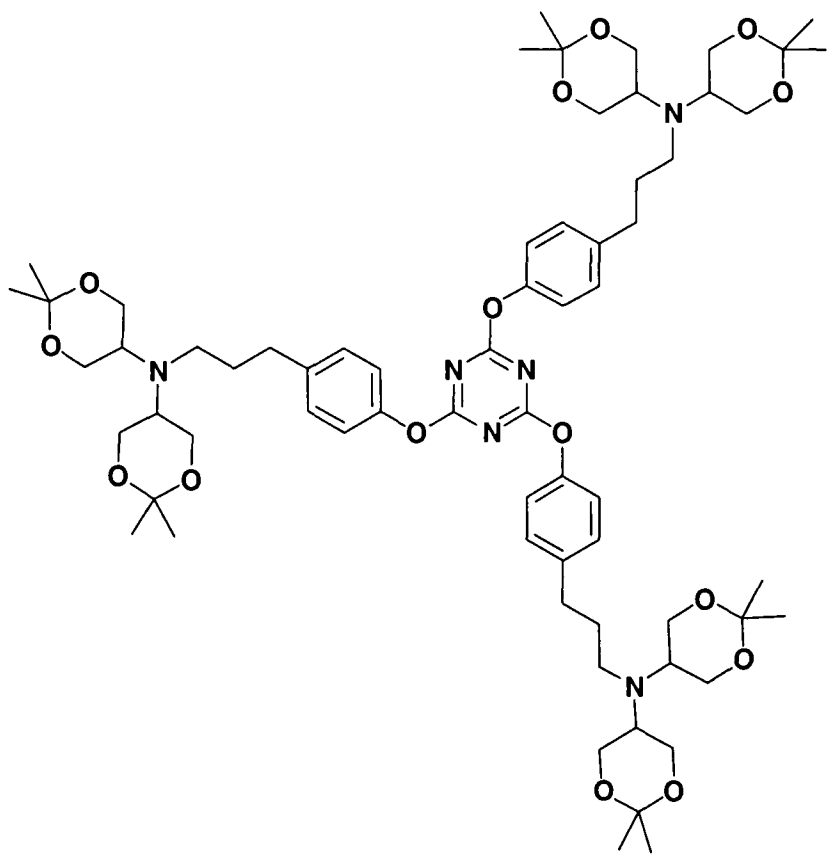
[3-(4-hydroxy-phenyl)-propyl]-*bis*-(2,2-dimethyl-[1,3]dioxan-5-yl)amine 143



143

A solution of the benzyloxy-phenyl amine **142** (206 mg, 0.44 mmol) in dry methanol (5 ml) plus palladium black (20 mg) was hydrogenated at r.t. and pressure for 20 hours. T.l.c. analysis (ethyl acetate/ hexane, 1:2) indicated the appearance of a new product (R_f 0.3) and no starting material (R_f 0.5). The reaction mixture was filtered through Celite eluting with ethyl acetate. The solvent was removed from the filtrate *in vacuo* to afford the title compound as a colourless oil (single component on t.l.c., 167mg, 100%). ν_{max} (film): 3351 (br OH). δ_H ($CDCl_3$, 400 MHz): 1.37, 1.39 (2 x 3H, 2 x s, $C(CH_3)_2$), 1.65 - 1.70 (2H, m, CH_2), 2.51 (2H, t, J 7.4, CH_2), 2.71 (2H, t, J 7.2, CH_2N), 3.05-3.10 (2H, m, 2 x CHN), 3.71 (8H, d_{app}, J_{app} 8.8, CH_2), 4.86 (1H, br s, ArOH), 6.76 (2H, d, J 8.4, ArH), 7.04 (2H, d, J 8.4, ArH). δ_C ($CDCl_3$, 50 MHz): 20.9, 26.7 (2 x q, $C(CH_3)_2$), 32.1 (t, CH_2), 46.7 (t, CH_2), 52.2 (d, CHN), 62.2 (t, CH_2O), 98.1 (s, $C(CH_3)_2$), 115.3 (d, Ar), 129.3 (d, Ar), 133.1 (s, Ar), 154.3 (s, Ar). *m/z* (APCI+): 380 ($M+H^+$, 100%), 322 ($M+H^+$-58, 56%). HRMS (CI+): Found 380.2444; $C_{21}H_{34}NO_5$ requires 380.2438.

2,4,6-*Tris*-([3-(4-hydroxy-phenyl)-propyl]-*bis*-(2,2-dimethyl-[1,3]dioxan-5-yl)amino)-1,3,5-triazine 144

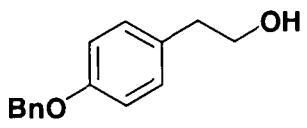


144

To a solution of the phenol **143** (78 mg, 0.21 mmol) in acetone (0.5 ml) was added potassium carbonate (150 mg) followed by 2,4,6-trichloro-1,3,5-triazine (9.5 mg, 0.05 mmol). A catalytic quantity of 18-crown-6 was added and the reaction mixture was heated at reflux with stirring for 70 hours. T.l.c. (ethyl acetate/ hexane, 1:1) indicated formation of a new product (R_f 0.14) and a trace of starting material (R_f 0.39). The reaction mixture was concentrated *in vacuo* and the resulting residue was dissolved in ethyl acetate (10 ml) and partitioned with brine (10 ml). The aqueous phase was further extracted with ethyl acetate (30 ml in three portions). The organics were combined, dried ($MgSO_4$), filtered and the filtrate concetrated *in vacuo*. The resulting residue was purified by flash column chromatography (ethyl acetate/ hexane, 1:1) to afford the title compound as a colourless oil (27 mg, 44%). δ_H ($CDCl_3$, 500 MHz): 1.36, 1.38 (2 x 18H, 2 x s, $C(CH_3)_2$), 1.65 – 1.78 (6H, m, CH_2), 2.59 (6H, t, J 7.4, CH_2), 2.77 (6H, t, J 7.2, CH_2N), 3.05-3.19 (6H, m, 6 x CHN), 3.71 (24H, m, CH_2), 7.08 (6H, d, J 8.4, ArH), 7.20 (6H, d, J 8.4, ArH). δ_C ($CDCl_3$, 125 MHz): 21.2, 27.2 (2 x q, $C(CH_3)_2$), 32.9 (t, CH_2), 45.6 (t, CH_2), 52.8 (d, CHN),

62.8 (t, CH_2O), 98.5 (s, $C(CH_3)_2$), 121.7 (d, Ar), 129.8 (d, Ar), 150.2 (s, Ar), 174.2 (s, Ar), 201.7 (s, Ar, triazinic). *m/z* (APCI+): 1156 (MH^+ - 58, 100%).

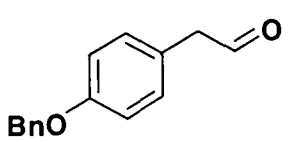
2-(4-benzyloxyphenyl)ethanol 153



153

This compound was prepared according to a modified literature procedure.[5] To a stirred suspension of sodium hydride (440 g, 60% by mass, 11.0 mmol) in DMF (7 ml) at r.t. was added a solution of 3-(*p*-hydroxyphenyl)-1-ethanol **152** (1.5 g, 11.0 mmol) in DMF (7 ml) dropwise over 20 minutes. The solution was stirred until gas evolution had ceased and then benzyl bromide (1.31 ml, 11.0 mmol) was added in one portion. The reaction mixture was stirred at r.t. for 17 hours when t.l.c. analysis (ethyl acetate/ hexane, 1:1) indicated formation of a single product (R_f 0.42) and a trace of starting material (R_f 0.26). The reaction mixture was then poured into water (50 ml) and extracted with diethyl ether (100 ml in three portions). The combined organic phases were washed with 3M sodium hydroxide (30 ml), and brine (30 ml), dried ($MgSO_4$), filtered, and the filtrate evaporated to give crude crystalline material. Recrystallization from ethyl acetate provided analytically pure title compound (2.23 g, 89%). δ_H ($CDCl_3$, 200 MHz): 1.36 (1H, t, J 5.9, OH), 2.82 (2H, t, J 6.5, CH_2), 3.84 (2H, q_{app}, CH_2), 5.06 (2H, s, $ArCH_2$), 6.96 (2H, d, J 8.6, ArH), 7.15 (2H, d, J 8.6, ArH), 7.29 – 7.79 (5H, m, ArH).

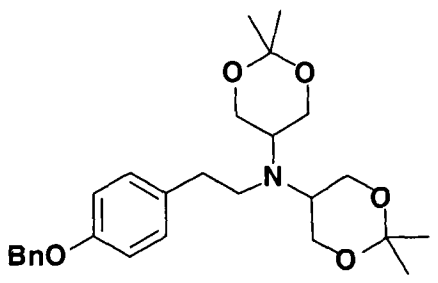
2-(4-benzyloxyphenyl)ethanal 154



154

This compound was prepared according to a modified literature procedure.[5] To a stirred suspension of pyridinium dichromate (3.61 g, 9.6 mmol) in dichloromethane (30 ml) at r.t. was added the alcohol **153** (1.46 g, 6.4 mmol) as a solid in one portion. The reaction mixture was stirred for 22 hours under argon. The volume was then reduced *in vacuo* by approximately a half, diethyl ether (30 ml) was added and the slurry filtered through Celite, eluting with further diethyl ether. The filtrate was washed sequentially with dilute cupric sulfate (30 ml) in two portions, saturated sodium hydrogencarbonate (30 ml) and finally brine (30 ml) and then dried ($MgSO_4$), and filtered. Evaporation of the filtrate *in vacuo* gave a light brown oil which was passed through a silica plug eluting with dichloromethane to afford the title compound as a colourless oil (1.01 g, 71%) on concentrating *in vacuo*. δ_H ($CDCl_3$, 200 MHz): 3.84 (2H, d, J 7.3 CH_2), 5.07 (2H, s, $ArCH_2$), 6.95 (2H, d, J 8.6, ArH), 7.11 (2H, d, J 8.6, ArH), 7.29 – 7.79 (5H, m, ArH), 9.73 (1H, t J 7.3, CHO).

[2-(4-Benzyloxy-phenyl)-ethyl]-*bis*-(2,2-dimethyl-[1,3]dioxan-5-yl)amine 155



155

The aldehyde **154** (200 mg, 0.88 mmol) was dissolved in dichloroethane (2 ml) and to this was added a solution of the amine **60** (216 mg, 0.88 mmol) in dichloroethane (2 ml) under an atmosphere of argon, followed by solid sodium triacetoxyborohydride (244 mg, 1.15 mmol) in one portion. The reaction mixture was stirred for 1 hour at r.t. after which time t.l.c. (ethyl acetate/ hexane, 1:2) indicated the complete conversion of starting material to a new product (R_f 0.30). An aqueous solution of sodium hydroxide (1M, 10ml) was added to the reaction mixture and stirred for a further 10 minutes. The reaction mixture was partitioned with ethyl acetate (25 ml) and the aqueous phase was extracted with a further ethyl acetate (50 ml in two portions).

The organic phases were combined and dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo* to give a residue which was purified by flash column chromatography (ethyl acetate/ hexane, 1:2) to afford the title compound as a colourless oil (290 mg, 73%). δ_H ($CDCl_3$, 400 MHz): 1.42, 1.44 (2 x 6H, 2 x s, $C(CH_3)_2$), 2.60 (2H, t, J 7.1, CH_2), 2.92 (2H, t, J 7.4, CH_2), 3.07-3.14 (2H, m , 2 x CHN), 3.66 – 3.76 (8H, m, CH_2O), 5.05 (2H, s, $ArCH_2$), 6.93 (2H, d, J 8.6, ArH), 7.07 (2H, d, J 8.6, ArH), 7.31 – 7.46 (5H, m, ArH, $ArCH_2$). δ_C ($CDCl_3$, 50 MHz): 20.7, 26.9 (2 x q, $C(CH_3)_2$), 37.0 (t, CH_2), 49.7 (t, CH_2), 52.4 (d, CHN), 62.5 (t, CH_2O), 70.0 (t, CH_2N), 97.9 (s, $C(CH_3)_2$), 114.7, 127.4, 127.9, 128.5, 129.7 (5 x d, Ar), 132.1 (s, Ar), 137.1 (s, Ar), 157.2 (s, Ar) . *m/z* (APCI+): 478 ($M+Na^+$, 7%), 456 ($M+H^+$, 100%), 398 ($M+H^+$-58, 98%). HRMS (CI+): Found 456.2746; $C_{27}H_{38}NO_5$ requires 456.2751.

References and Notes

[1] Townsend, C.A., Basak, A., *Tetrahedron*, 1991, **47**, 2591.

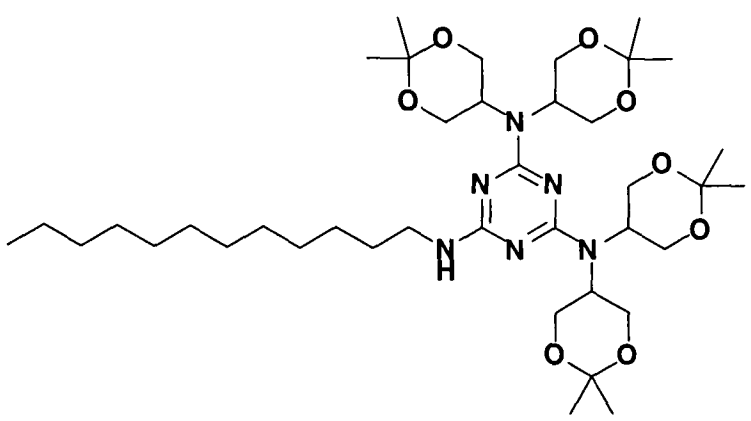
[2] Hamada, Y., Kohda, K., Shioiri, T.; *Tetrahedron Lett.*, 1984, **25**, 5303.

[3] Tahmassebi, D.C., Sasaki, T.; *J.Org. Chem.*, 1994, **59**, 680.

[4] Ronald, C.R., Wheeler, C.J.; *J.Org. Chem.*, 1984, **49**, 1658.

[5] Takaoka, E., Yoshikawa, N., Yamada, Y.M.A., Sasai, H., Shibasaki, M.; *Heterocycles*, 1997, **46**, 157.

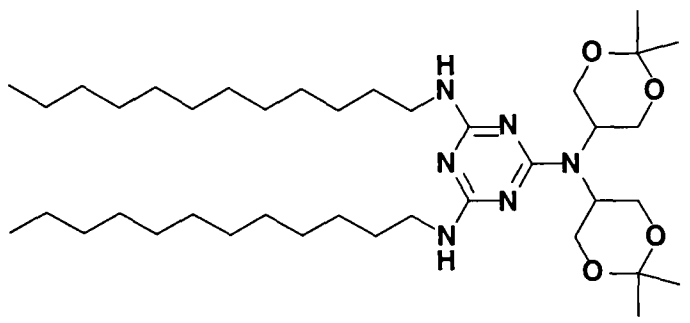
2,4-*Bis*[*bis*-(2,2-dimethyl-[1,3]dioxan-5-yl)-amino],6-[dodecylamino]-1,3,5-triazine 112



112

To a solution of the monochloro triazine **109** (54 mg, 0.10 mmol) in dry toluene (1 ml) was added a solution of dodecylamine (68 mg, 0.40 mmol) in toluene (1 ml). The reaction mixture was heated at reflux with stirring for 16 hours under argon. T.l.c. (ethyl acetate/ hexane, 1:2) indicated formation of a single product (R_f 0.27) and complete consumption of starting material (R_f 0.41). The reaction mixture was concentrated *in vacuo* and the residue dissolved in ethyl acetate, preadsorbed onto silica gel and purified by flash column chromatography (ethyl acetate/ hexane, 1:3) to afford the title compound as a yellow oil (54mg, 76%). ν_{max} (film): 3366 (br NH). δ_H (toluene d_8, 500 MHz, 90°C): 0.87 (3H, t, J 6.9, $\underline{CH_3}(CH_2)_{11}NH$), 1.28 (20H, m, $CH_3(\underline{CH_2})_{10}CH_2NH$), 1.36, 1.49 (2 x 12H, 2 x s, $C(CH_3)_2$), 3.36 (2H, q_{app} J_{app} 6.9, 13.1 $CH_3(CH_2)_{10}\underline{CH_2}NH$), 3.82 (8H, dd, J 5.5, 11.4, CH_2O), 4.33 (8H, dd, J 8.1, 11.1, CH_2O), 4.45 (1H, m, $CH_2\underline{NH}$), 4.70 (4H, m, 2 x CHN). δ_C (toluene d_8, 125 MHz, 50°C): 14.1 (q, $\underline{CH_3}(CH_2)_{11}NH$), 20.6, 22.9, 23.7, 27.2, (4 x q, 2 x $C(CH_3)_2$), 26.9, 28.9, 29.3, 29.4, 29.5, 29.6, 29.6, 30.3, 31.9 (10 x t, $CH_3(\underline{CH_2})_{10}CH_2NH$), 41.1 (t, CH_2NH), 49.5 (d, CHN), 61.7 (t, CH_2O), 98.1 (s, $C(CH_3)_2$), 164.9 (br s, Ar, triazinics). *m/z* (APCI+): 752 ($M+H^+$, 100%), 694 ($M+H^+$ - 58, 25%). HRMS (CI+): Found 751.5333; $C_{39}H_{71}N_6O_8$ requires 751.5335.

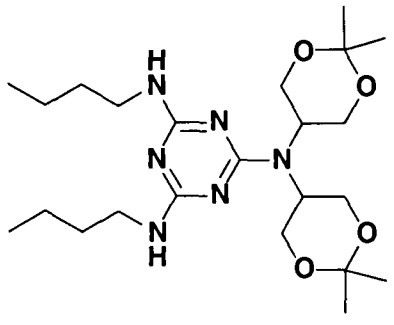
2,4-*Bis*[dodecylamino],6-[*bis*-(2,2-dimethyl-[1,3]dioxan-5-yl)-amino]-1,3,5-triazine 119



119

To a solution of the dichloro triazine **108** (150 mg, 0.38 mmol) in dry toluene (1 ml) was added a solution of dodecylamine (283 mg, 1.53 mmol) in toluene (3 ml). The reaction mixture was heated at reflux with stirring for 13 hours under argon. T.l.c. (ethyl acetate/ hexane, 1:3) indicated formation of a single product (R_f 0.19) and complete consumption of starting material (R_f 0.34). The reaction mixture was concentrated *in vacuo* and the residue dissolved in ethyl acetate, preadsorbed onto silica gel and purified by flash column chromatography (ethyl acetate/ hexane, 1:3) to afford the title compound as a yellow oil (217 mg, 95%). ν_{max} (film): 3360 (br NH). δ_H (toluene d_8, 500 MHz, 90°C): 0.87 (6H, t, J 6.9, 2 x $\underline{CH_3}(CH_2)_{11}NH$), 1.29 (36H, m, $CH_3(\underline{CH_2})_{10}CH_2NH$), 1.37 (6H, s, $C(CH_3)_2$), 1.43 (4H, m, $CH_3(\underline{CH_2})_{10}CH_2NH$), 1.49 (6H, s, $C(CH_3)_2$), 3.30 (4H, q_{app}, $CH_3(CH_2)_{10}\underline{CH_2}NH$), 3.78 (4H, dd, J 5.5, 11.3, CH_2O), 4.43 (4H, dd, J 8.4, 11.3, CH_2O), 4.49 (2H, br m, $CH_2\underline{NH}$), 4.65 (2H, m, 2 x CHN). δ_C ($CDCl_3$, 125 MHz): 14.1 (q, 2 x $\underline{CH_3}(CH_2)_{11}NH$), 21.7, 26.6 (2 x q, $C(CH_3)_2$) 22.6, 26.9, 29.3, 29.4, 29.6, 29.5, 29.8, 31.9 (8 x t, $CH_3(\underline{CH_2})_{10}CH_2NH$), 40.8 (t, CH_2NH), 50.0 (d, CHN), 61.7 (t, CH_2O), 97.9 (s, $C(CH_3)_2$), 165.8 (br s, Ar, triazinics). *m/z* (APCI+): 692 ($M+H^+$, 100%), 634 ($M+H^+$ - 58, 20%). Found C 67.68, H 10.81, N 11.91%; $C_{39}H_{71}N_6O_8$ requires: C 67.78, H 10.79, N 12.16%.

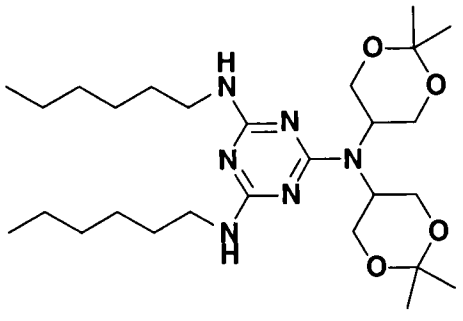
2,4-*Bis*[butylamino],6-[*bis*-(2,2-dimethyl-[1,3]dioxan-5-yl)-amino]-1,3,5-triazine 117



117

To a solution of the dichloro triazine **108** (200 mg, 0.50 mmol) in dry toluene (1 ml) was added a solution of ^{n}butylamine (201 µl, 2.0 mmol) in toluene (3 ml). The reaction mixture was heated at reflux with stirring for 13 hours under argon. T.l.c. (ethyl acetate/ hexane, 1:2) indicated formation of a single product (R_f 0.45) and complete consumption of starting material (R_f 0.31). The reaction mixture was concentrated *in vacuo* and the residue dissolved in ethyl acetate, preadsorbed onto silica gel and purified by flash column chromatography (ethyl acetate/ hexane, 1:2) to afford the title compound as a yellow oil (182 mg, 78%). ν_{max} (film): 3359 (br NH). δ_H (toluene d_8, 500 MHz, 90°C): 0.82 (6H, t, J 7.3, 2 x $\underline{CH_3}(CH_2)_3NH$), 1.24 (4H, m, $CH_3(\underline{CH_2})_2CH_2NH$), 1.34 (4H, m, $CH_3(\underline{CH_2})_2CH_2NH$), 1.38, 1.49 (2 x 6H, 2 x s, $C(CH_3)_2$), 3.27 (4H, q_{app},, $CH_3(CH_2)_2\underline{CH_2}NH$), 3.78 (4H, dd, J 5.5, 11.4, CH_2O), 4.43 (4H, dd, J 8.4, 11.4, CH_2O), 4.47 (2H, br m, 2 x $CH_2\underline{NH}$), 4.64 (2H, m, 2 x CHN). δ_C ($CDCl_3$, 50 MHz): 13.8 (q, $\underline{CH_3}(CH_2)_3NH$), 20.0, 31.9 (2 x t, $CH_3(\underline{CH_2})_2CH_2NH$), 21.7, 26.5 (2 x q, $C(CH_3)_2$), 40.5 (t, CH_2NH), 49.9 (d, CHN), 61.6 (t, CH_2O), 98.0 (s, $C(CH_3)_2$), 164.4, 165.7 (2 x s, 2 x Ar, triazinics). *m/z* (APCI+): 467 ($M+H^+$, 100%), 409 ($M+H^+$ - 58, 48%). HRMS (CI+): Found 467.3346; $C_{23}H_{42}N_6O_4$ requires 467.3346.

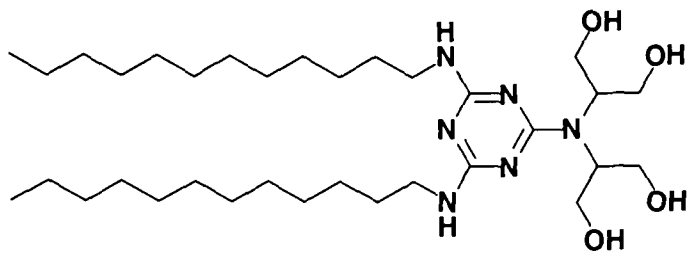
2,4-*Bis*[hexylamino],6-[*bis*-(2,2-dimethyl-[1,3]dioxan-5-yl)-amino]-1,3,5-triazine 118



118

To a solution of the dichloro triazine **108** (141 mg, 0.36 mmol) in dry toluene (1 ml) was added a solution of ^{n}hexylamine (190 µl, 1.43 mmol) in toluene (2 ml). The reaction mixture was heated at reflux with stirring for 12 hours under argon. T.l.c. (ethyl acetate/ hexane, 1:3) indicated formation of a single product (R_f 0.19) and complete consumption of starting material (R_f 0.34). The reaction mixture was concentrated *in vacuo* and the residue dissolved in ethyl acetate, preadsorbed onto silica gel and purified by flash column chromatography (ethyl acetate/ hexane, 1:3) to afford the title compound as a yellow oil (164 mg, 89%). ν_{max} (film): 3358 (br NH). δ_H (toluene d_8, 500 MHz, 90°C): 0.84 (6H, t, J 6.9, 2 x $\underline{CH_3}(CH_2)_3NH$), 1.27 (12H, m, $CH_3(\underline{CH_2})_4CH_2NH$), 1.38, 1.49 (2 x 6H, 2 x s, $C(CH_3)_2$), 1.42 (4H, m, $CH_3(\underline{CH_2})_4CH_2NH$), 3.29 (4H, q_{app}, $CH_3(CH_2)_4\underline{CH_2}NH$), 3.78 (4H, dd, J 5.4, 11.3, CH_2O), 4.43 (4H, dd, J 8.4, 11.3, CH_2O), 4.46 (2H, br m, 2 x $CH_2\underline{NH}$), 4.65 (2H, m, 2 x CHN). δ_C (toluene d_8, 125 MHz): 14.2 (q, $\underline{CH_3}(CH_2)_3NH$), 22.4 (q, $C(CH_3)_2$), 23.0, 27.1, 30.5, 32.1 (4 x t, $CH_3(\underline{CH_2})_4CH_2NH$), 26.7 (q, $C(CH_3)_2$), 41.3 (t, CH_2NH), 50.8 (d, CHN), 62.1 (t, CH_2O), 98.2 (s, $C(CH_3)_2$), 167.8, 169.0 (2 x s, 2 x Ar, triazinics). *m/z* (APCI+): 523 ($M+H^+$, 100%), 465 ($M+H^+$ - 58, 26%). HRMS (CI+): Found 523.3972; $C_{27}H_{51}N_6O_4$ requires 523.3972.

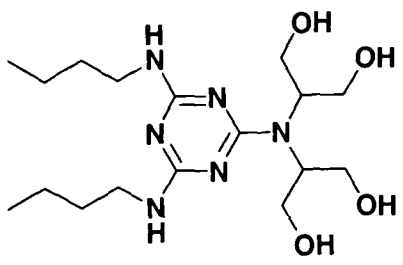
2,4-*Bis*[dodecylamino],6-[*bis*-(1,3-dihydroxy-*iso*propyl)-amino]-1,3,5-triazine 116



116

To the 2,4,6-trialkylamino triazine **119** (215 mg, 0.3 mmol) was added 70% aqueous acetic acid (3 ml) and the reaction mixture was stirred at r.t. for 11 hours. The reaction mixture was concentrated *in vacuo* and coevaporated with toluene (2 x 2 ml) to afford the title compound as a white solid (188 mg, quantitative). ν_{max} (KBr): 3317 (br NH/OH). δ_H (DMSO d_6, 500 MHz, 90°C): 0.88 (6H, t, J 7.0, 2 x $\underline{CH_3}(CH_2)_{11}NH$), 1.31 (36H, m, $CH_3(\underline{CH_2})_{10}CH_2NH$), 1.51 (4H, m, $CH_3(\underline{CH_2})_{10}CH_2NH$), 3.20 (4H, q_{app}, $CH_3(CH_2)_{10}\underline{CH_2}NH$), 3.71 (4H, dd, J 5.3, 11.0, CH_2O), 3.86 (4H, dd, J 7.1, 11.0, CH_2O), 4.16 (2H, m, 2 x CHN), 4.56 (4H, br s, 4 x OH), 5.98 (2H, br m, 2 x NH). δ_C (DMSO d_6, 125 MHz, 50°C): 13.8 (q, $\underline{CH_3}(CH_2)_{11}NH$), 22.0, 26.5, 28.6, 29.0, 29.5, 31.2 (6 x t, $CH_3(\underline{CH_2})_{10}CH_2NH$), 40.8 (t, CH_2NH), 50.0 (d, CHN), 60.5 (t, CH_2O), 165.1, 165.8 (2 x s, 2 x Ar, triazinics). *m/z* (APCI+): 612 ($M+H^+$, 100%), 593 ($M+H^+$ - 18, 18%). HRMS (CI+): Found 611.5218; $C_{33}H_{67}N_6O_4$ requires 611.5225.

2,4-*Bis*[butylamino],6-[*bis*-(1,3-dihydroxy-*iso*propyl)-amino]-1,3,5-triazine 114

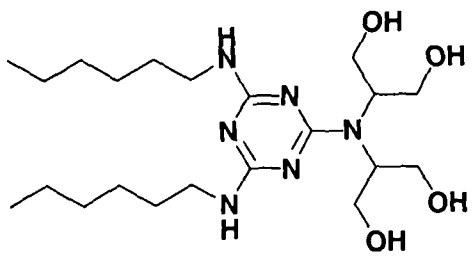


114

To the 2,4,6-trialkylamino triazine **117** (77 mg, 0.17 mmol) was added 70% aqueous acetic acid (3 ml) and the reaction mixture was stirred at r.t. for 13 hours. The reaction mixture was concentrated *in vacuo* and coevaporated with toluene (2 x 2 ml) to afford the title compound as a white solid (64 mg, quantitative). ν_{max} (KBr): 3293 (br NH/OH). δ_H (DMSO d_6, 500 MHz,

90°C): 0.91 (6H, t, J 7.4, 2 x $\underline{CH_3}(CH_2)_3NH$), 1.34 (4H, m, $CH_3(\underline{CH_2})_2CH_2NH$), 1.50 (4H, m, $CH_3(\underline{CH_2})_2CH_2NH$), 3.22 (4H, q_{app},, $CH_3(CH_2)_2\underline{CH_2}NH$), 3.71 (4H, dd, J 5.4, 11.0, CH_2O), 3.87 (4H, dd, J 7.2, 11.0, CH_2O), 4.17 (2H, m, 2 x CHN), 6.02 (2H, m, 2 x $CH_2\underline{NH}$). δ_C (DMSO d_6, 125 MHz): 14.2 (q, $\underline{CH_3}(CH_2)_3NH$), 21.1, 32.9 (2 x t, $CH_3(\underline{CH_2})_2CH_2NH$), 41.4 (t, CH_2NH), 49.9 (d, CHN), 61.9 (t, CH_2O), 162.9, 167.0 (2 x s, 2 x Ar, triazinics). *m/z* (APCI+): 387 ($M+H^+$, 100%), 369 ($M+H^+$ - 18, 22%). HRMS (CI+): Found 387.2720; $C_{17}H_{35}N_6O_4$ requires 387.2709.

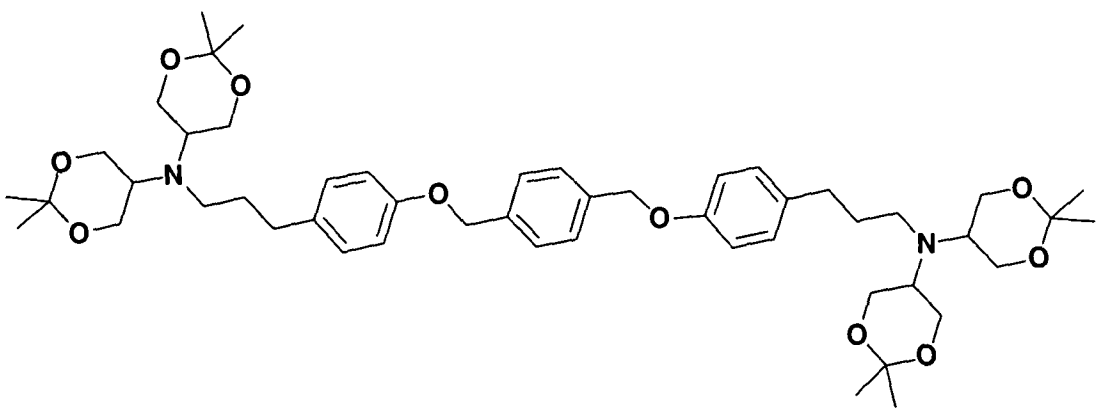
2,4-*Bis*[hexylamino],6-[*bis*-(1,3-dihydroxy-*iso*propyl)-amino]-1,3,5-triazine 115



115

To the 2,4,6-trialkylamino triazine **118** (150 mg, 0.29 mmol) was added 70% aqueous acetic acid (3 ml) and the reaction mixture was stirred at room temperature for 13 hours. The reaction mixture was concentrated *in vacuo* and coevaporated with toluene (2 x 2 ml) to afford the title compound as a white solid (126 mg, quantitative). ν_{max} (KBr): 3340 (br NH/OH). δ_H (DMSO d_6, 500 MHz, 90°C): 0.89 (6H, t, J 6.9, 2 x $\underline{CH_3}(CH_2)_3NH$), 1.31 (12H, m, $CH_3(\underline{CH_2})_4CH_2NH$), 1.51 (4H, m, $CH_3(\underline{CH_2})_4CH_2NH$), 3.21 (4H, q_{app}, $CH_3(CH_2)_4\underline{CH_2}NH$), 3.71 (4H, dd, J 5.4, 11.0, CH_2O), 3.86 (4H, dd, J 7.1, 11.0, CH_2O), 4.16 (2H, br m, 2 x CHN), 6.00 (2H, br m, 2 x $CH_2\underline{NH}$). δ_C (DMSO d_6, 125 MHz): 13.7 (q, $\underline{CH_3}(CH_2)_4NH$), 21.9, 26.0, 29.4, 31.0 (4 x t, $CH_3(\underline{CH_2})_4CH_2NH$), 41.7 (t, 2 x CH_2NH), 49.9 (d, 2 x CHN), 60.5 (t, CH_2O), 165.1, 165.7 (2 x s, 2 x Ar, triazinics). *m/z* (APCI+): 443 ($M+H^+$, 100%), 425 ($M+H^+$ - 18, 23%). HRMS (CI+): Found 443.3342; $C_{27}H_{51}N_6O_4$ requires 443.3347.

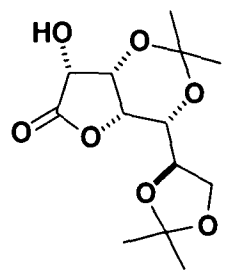
[3-(4-Benzyloxy-phenyl-4-Benzyloxy-phenyl-propyl-bis-(2,2-dimethyl-[1,3]dioxan-5-yl)amine)-propyl]-bis-(2,2-dimethyl-[1,3]dioxan-5-yl)amine 188



188

To a solution of the phenol **143** (105 mg, 0.28 mmol) in acetone (3 ml) was added potassium carbonate (77 mg) followed by *p*-xylene dibromide (36 mg, 0.14 mmol). A catalytic quantity of 18-crown-6 was added and the reaction mixture was heated at reflux with stirring for 38 hours. T.l.c. (ethyl acetate/ hexane 1:2) indicated formation of a new product (R_f 0.13) and a trace of starting material (R_f 0.28). The reaction mixture was concentrated *in vacuo* and the resulting residue was dissolved in ethyl acetate (10ml) and partitioned with brine (10ml). The aqueous phase was extracted with further ethyl acetate (30ml in three portions). The organics were combined, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (ethyl acetate/ hexane 1:2) to afford the title compound as a colourless oil (34 mg, 29**%**). δ_H ($CDCl_3$, 500 MHz): 1.37, 1.39 (2 x 12H, 2 x s, $C(CH_3)_2$), 1.64-1.71 (4H, m, CH_2), 2.53 (4H, t_{app}, J 7.5, CH_2), 2.71 (4H, t_{app}, J 7.2, CH_2), 3.02-3.10 (4H, m, 4 x CHN), 3.62 – 3.76 (16H, m, CH_2), 5.05 (4H, s, 2 x $PhCH_2$), 6.90 (4H, d, J 8.4, 4 x ArH), 7.09 (4H, d, J 8.4, 4 x ArH), 7.45 (4H, s, 4 x ArH). δ_C ($CDCl_3$, 125 MHz): 20.5, 27.0 (2 x q, $C(CH_3)_2$), 32.7, 32.1, 46.5 (3 x t, 3 x CH_2), 52.2 (d, CHN), 62.5 (t, CH_2O), 69.7 ($ArCH_2$), 97.8 (s, $C(CH_3)_2$), 114.8, 129.3, 131.8 (3 x d, Ar), 134.2, 136.2, 156.9 (3 x s, Ar). *m/z* (APCI+): 862 (MH^+, 100%), 804.4 (MH^+ - 58, 23%). HRMS (CI+): Found 861.5261; $C_{50}H_{73}N2O_{10}$ requires 861.5266.

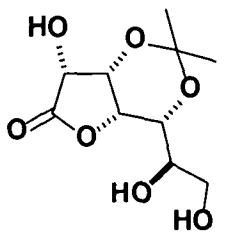
3,5:6,7-Di-*O*-isopropylidene-D-*glycero*-D-*gulo*-heptono-1,4-lactone 202



202

This compound was prepared according to a literature procedure.[1] m.p. 149 - 151°C (chloroform/hexane) [Lit.[1] 153 - 154°C (chloroform/hexane)]. $[\alpha]_D^{23}$ = -62.5 (c, 1.0 in $CHCl_3$) [Lit.[1] $[\alpha]_D^{30}$ = -76.0 (c, 2.0 in $CHCl_3$). δ_H ($CDCl_3$, 500 MHz): 1.35, 1.41, 1.44, 1.51 (4 x 3H, 4 x s, 2 x $C(CH_3)_2$), 2.83 (1H, d, $J_{OH,2}$ 10.1, OH), 3.84 (1H, dd, $J_{5,6}$ 8.6, $J_{5,4}$ 2.1, H-5), 3.94 (1H, dd, $J_{7,7'}$ 8.9, $J_{7,6}$ 4.0, H-7), 4.11 (1H, dd, $J_{7',7}$ 9.0, $J_{7',6}$ 6.2, H-7'), 4.32 – 4.34 (1H, m, H-6), 4.35 (1H, t $J_{4,3}$ 2.1, H-4), 4.49 (1H, dd, $J_{2,OH}$ 10.1, $J_{2,3}$ 4.1, H-2), 4.62 (1H, dd, $J_{3,2}$ 4.1, $J_{3,4}$ 2.2, H-3).

3,5-*O*-Isopropylidene-D-*glycero*-D-*gulo*-heptono-1,4-lactone 203



203

This compound was prepared according to a literature procedure.[2] δ_H ($CDCl_3$, 500 MHz): 1.37, 1.51 (2 x 3H, 2 x s, $C(CH_3)_2$), 3.58 (1H, dd, J 4.8, J 11.4, H-7), 3.70 – 3.82 (2H, m, H-7', H-6), 4.05 (1H, dd, J 1.5, J 9.0, H-5), 4.44 (1H, br t, J 1.5, H-4) 4.61 – 4.66 (2H, m, H-2, H-3).

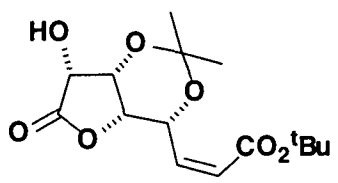
tert-Butoxycarbonylmethylenetriphenylphosphonium bromide

This compound was prepared according to a literature procedure.[3] δ_H ($CDCl_3$, 200 MHz): 1.21 (9H, s, $C(CH_3)_3$), 5.44 (2H, d, J 14.1, CH_2), 7.52 – 7.97 (15H, m, Ar).

tert-Butoxycarbonylmethylenetriphenylphosphorane

This compound was prepared according to a literature procedure.[3] δ_H ($CDCl_3$, 200 MHz): 1.22 (9H, s, $C(CH_3)_3$), 2.69 (1H, br s, CH), 7.41 – 7.70 (15H, m, Ar).

(Z)-(_tert_-Butyl 6,7-dideoxy-3,5-_O-iso_propylidene-D-_gulo_-octar-6-enoate)-1,4-lactone 205

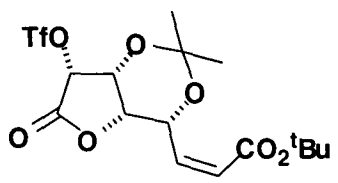


205

To a stirred solution of the triol **203** (5.0 g, 20.1 mmol) in methanol (250 ml) and water (20 ml) was added solid sodium periodate (5.18 g, 24.2 mmol) in one portion. The reaction mixture was stirred at r.t for a further 30 minutes. The reaction mixture was filtered through Celite eluting with further ethyl acetate. Evaporation of the filtrate *in vacuo* afforded the crude aldehyde **204** as a white solid which was dried by coevaporating with toluene (3 x 20 ml). The crude aldehyde **204** was then dissolved in freshly distilled THF (140 ml) with no further purification. The solid *tert*-butoxycarbonylmethylenetriphenylphosphorane (8.7 g, 23.1 mmol) was added in one portion to this solution and the resulting mixture was stirred at r.t. for 20 hours. T.l.c. analysis (2:1, hexane/ethyl acetate) indicated formation of a new product (R_f 0.43) and no starting material (R_f 0.05). The reaction mixture was concentrated *in vacuo* and the residue dissolved in ethyl acetate, preadsobed onto silica gel and purified by flash column chromatography (2:1, hexane/ethyl acetate) then (1:1, hexane/ethyl acetate) to afford the title compound as a white crystalline solid

(5.11 g, 81%). m.p. (ethyl acetate/hexane) 120 - 122°C. ν_{max} (KBr): 3464 (br OH), 1794 (C=O, lactone), 1702 (C=O, ester), 1655 (C=C). $[\alpha]_D^{23}$ = -21.4 (c, 1.0 in $CHCl_3$). δ_H ($CDCl_3$, 500 MHz): 1.45, 1.48 (2 x 3H 2 x s, $C(CH_3)_2$), 1.57 (9H, s, $C(CH_3)_3$), 2.87 (1H, d, $J_{OH,2}$ 10.2, D_2O exch., OH), 4.46 (1H, dd, $J_{2,OH}$ 10.2, $J_{2,3}$ 4.1, d on D_2O shake, H-2), 4.54 (1H, t_{app}, J_{app} 2.2, H-4), 4.68 (1H, dd, $J_{3,2}$ 4.1, $J_{3,4}$ 2.2, H-3), 5.68 (1H, dt_{app}, H-5), 5.89 (1H, dd, $J_{7,6}$ 11.7, $J_{7,5}$ 1.6, H-7), 6.20 (1H, dd, $J_{6,7}$ 11.7, $J_{6,5}$ 6.5, H-6). δ_C ($CDCl_3$, 125 MHz) : 19.6, 29.1 (2 x q, 2x $(CH_3)_2C$), 28.1 ($(CH_3)_3C$), 65.8, 67.8, 70.4, 71.4 (4 x d, C-2, C-3, C-4, C-5), 81.2 (s, $(CH_3)_3C$), 98.9 (s, $(CH_3)_2C$), 123.1 (d, C-7), 144.1 (d, C-6), 165.3 (s, C-8) 174.7 (s, C-1). *m/z* (APCI+): 315.1 ($M+H^+$, 8%), 259.1 ($M+H^+$ - 56, 100%). Found C 56.96, H 7.16%; $C_{15}H_{22}O_7$ requires C 57.32, H 7.05%.

(Z)-(*tert*-Butyl 6,7-dideoxy-3,5-*O*-*iso*propylidene-2-*O*-trifluoromethanesulfonyl-D-*gulo*-octar-6-enoate)-1,4-lactone 206

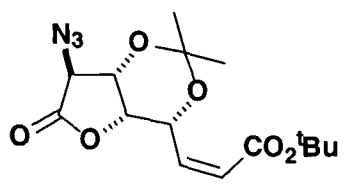


206

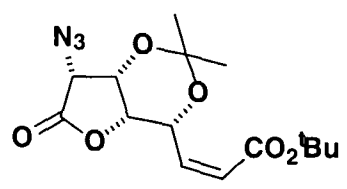
Trifluoromethanesulfonic anhydride (81 µl, 0.48 mmol) was added dropwise to a stirred solution of the lactone **205** (100 mg, 0.32 mmol) in freshly distilled dichloromethane (4 ml) and dry pyridine (78 µl, 0.96 mmol) at -30°C under an atmosphere of nitrogen. The reaction mixture was stirred at -30°C for 30 minutes after which time t.l.c. analysis (ethyl acetate/ hexane, 2:1) indicated complete conversion of the starting material (R_f 0.5) to a single product (R_f 0.75). The reaction mixture was diluted with dichloromethane (20 ml) and washed sequentially with 2M hydrochloric acid (10ml) and pH7 buffer (25ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was preadsorbed onto silica gel and purified by flash column chromatography (ethyl acetate/ hexane 1:4) to afford the title compound as a white solid (138mg, 97%). m.p. 133 – 136°C. ν_{max} (KBr): 1815 (C=O, lactone), 1709 (C=O, ester), 1645 (C=C). $[\alpha]_D^{23}$ = -16.2 (c, 1.0 in $CHCl_3$). δ_H ($CDCl_3$, 500 MHz,): 1.48, 1.56 (2 x 3H, 2 x s,

$(CH_3)_2C$), 1.49 (9H, s, $C(CH_3)_3$), 4.65 (1H, t, $J_{4,3}$ 2.1Hz, H-4), 4.90 (1H, dd, $J_{3,2}$ 4.0, $J_{3,4}$ 2.1 H-3), 5.33 (1H, d, $J_{2,3}$ 4.0, H-2), 5.68 (1H, dt_{app}, H-5), 5.91 (1H, dd, $J_{7,6}$ 11.6Hz, $J_{7,5}$ 1.7Hz H-7), 6.19 (1H, dd, $J_{6,7}$ 11.6, $J_{6,5}$ 6.3, H-6). δ_C ($CDCl_3$, 125 MHz): 19.4 ($(CH_3)_2C$), 28.1 ($(CH_3)_3C$), 28.1 ($(CH_3)_2C$), 65.6, 67.3, 70.4, 78.9 (C-2, C-3, C-4, C-5), 81.5 ($(CH_3)_3C$), 99.2 ($(CH_3)_2C$), 123.6 (C-7), 143.5 (C-6), 165.3 (C-8) 166.64 (C-1). *m/z* (APCI+): 447.5 ($M+H^+$, 20%), 391.0 ($M+H^+$ - 57, 57%). Found C 42.95, H 4.63%; $C_{16}H_{21}O_9F_3S$ requires C 43.05, H 4.74%.

(Z)-(*tert*-Butyl 2-azido-2,6,7-trideoxy-3,5-*O*-*iso*propylidene-D-*ido*-octar-6-enoate)-1,4-lactone 207 (Z)-(*tert*-Butyl 2-azido-2,6,7-trideoxy-3,5-*O*-*iso*propylidene-D- *gulo*-octar-6-enoate)-1,4-lactone 208



207



208

Method 1.

The D-*gulo* triflate **206** (100 mg, 0.22 mmol) was dissolved in anhydrous DMF (2 ml) and solid sodium azide (19 mg, 0.29 mmol) was added in one portion. The reaction mixture was stirred at r.t. under an atmosphere of nitrogen for 45 minutes. T.l.c. analysis (ethyl acetate/hexane, 1:5) indicated formation of two new products (R_f 0.4 (major) and R_f 0.2 (minor)) and complete consumption of starting material (R_f 0.3). The reaction mixture was concentrated *in vacuo* and the residue was washed sequentially with brine (3 x 10 ml) extracting with ethyl acetate. The organics were combined, dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography (ethyl acetate/hexane 1:5) to afford the D-*gulo* azide **208** (17 mg, 23%) and the D-*ido* azide **207** (40 mg, 54%).

Data for D-*ido* azide **207**: ν_{max} (KBr): 2124 (N_3), 1781 (C=O, lactone), 1707 (C=O, ester), 1641 (C=C). δ_H ($CDCl_3$, 500 MHz) : 1.41, 1.52 (2 x 3H, 2 x s, $C(CH_3)_2$), 1.49 (9H, s, $C(CH_3)_3$), 4.06 (1H, s, H-2), 4.54 (1H, t_{app}, J_{app} 2.2, H-4), 4.38 (1H, d, $J_{3,4}$ 2.5 H-3), 4.67 (1H, dt_{app}, H-5),

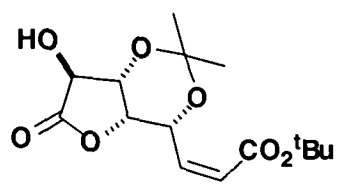
5.89 (1H, dd, $J_{7,6}$ 11.7, $J_{7,5}$ 1.6, H-7), 6.18 (1H, dd, $J_{6,7}$ 11.7, $J_{6,5}$ 6.7, H-6). δ_C ($CDCl_3$, 125 MHz) : 19.6 ($(CH_3)_2C$), 28.1 ($(CH_3)_3C$), 29.0 ($(CH_3)_2C$), 63.4, 65.5, 70.6, 74.0 (C-2, C-3, C-4, C-5), 81.2 ($(CH_3)_3C$), 98.7 ($(CH_3)_2C$), 123.2 (C-7), 143.8 (C-6), 165.2 (C-8) 171.1 (C-1). *m/z* (APCI+): 362.1 ($M+Na^+$, 12%), 334.1 ($M+Na^+$ - 28, 15%), 256.2 (100%). Found C 53.27, H 6.26, N 12.35%; $C_{15}H_{21}O_6N_3$ requires C 53.09, H 6.24, N 12.38%.

Data for D-*gulo* azide **208**: ν_{max} (KBr): 2121 (N_3), 1802 (C=O, lactone), 1706 (C=O, ester), 1659 (C=C). δ_H ($CDCl_3$, 500 MHz) : 1.57, 1.58 (2 x 3H, 2 x s, $C(CH_3)_2$), 1.48 (9H, s, $C(CH_3)_3$), 3.91 (1H, d, $J_{2,3}$ 3.9, H-2), 4.59 (1H, t_{app}, J_{app} 2.2, H-4), 4.77 (1H, dd, $J_{3,2}$ 4.0, $J_{3,4}$ 2.2, H-3), 5.69 (1H, dt_{app}, H-5), 5.90 (1H, dd, $J_{7,6}$ 11.7, $J_{7,5}$ 1.7, H-7), 6.21 (1H, dd, $J_{6,5}$ 11.7, $J_{6,7}$ 6.5, H-6). δ_C ($CDCl_3$, 125 MHz) : 19.5 ($(CH_3)_2C$), 28.1 ($(CH_3)_3C$), 28.9 ($(CH_3)_2C$), 61.4, 65.8, 69.7, 71.7 (C-2, C-3, C-4, C-5), 81.3 ($(CH_3)_3C$), 99.0 ($(CH_3)_2C$), 123.3 (C-7), 144.0 (C-6), 165.4 (C-8) 170.6 (C-1). *m/z* (APCI+): 362.1 ($M+Na^+$, 12%), 334.1 ($M+Na^+$ - 28, 15%), 256.2 (100%). Found C 53.15, H 6.22, N 12.27%; $C_{15}H_{21}O_6N_3$ requires C 53.09, H 6.24, N 12.38.

Method 2.

The D-*ido* azide **207** (200 mg, 0.59 mmol) was dissolved in anhydrous DMF (10 ml) and PPTS (148 mg, 0.59 mmol) followed by sodium azide (61 mg, 0.94 mmol) was added to the solution. The reaction mixture was stirred at r.t. under an atmosphere of nitrogen for six days. T.l.c. analysis (ethyl acetate/ hexane, 1:5) indicated the formation of two new products (R_f 0.2 and R_f 0.07) and starting material (R_f 0.4). The reaction mixture was concentrated *in vacuo* and the residue washed with brine (40 ml in three portions) extracting with ethyl acetate (3 x 20ml). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Preadsorption onto silica gel followed by purification by flash column chromatography (ethyl acetate/ hexane, 1:5) afforded the D-*gulo* azide **208** (94 mg, 47%) identical to the product previously described, D-*ido* azide **xx** (4mg, 2%) identical to the product previously described.

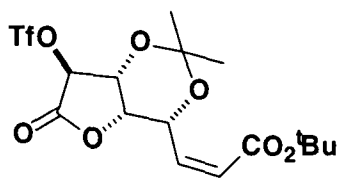
(Z)-(*tert*-Butyl 6,7-dideoxy-3,5-*O*-*iso*propylidene-D-*ido*-octar-6-enoate)-1,4-lactone 210



210

Butanone (2 ml) was added to a mixture of caesium trifluoroacetate (55 mg, 0.22 mmol) and the triflate **206** (50 mg, 0.11 mmol) under an atmosphere of nitrogen. The resulting solution was heated at reflux for 24 hours when t.l.c. (ethyl acetate/ hexane, 1:4) indicated formation of a single product (R_f 0.2) and a trace of starting material (R_f 0.5). The reaction mixture was concentrated *in vacuo* and the resulting residue dissolved in ethyl acetate. Preadsorption onto silica gel followed by purification by flash column chromatography (ethyl acetate/ hexane, 1:4) afforded the title compound as a white solid (34 mg, 98%). m.p. (ethyl acetate/hexane) 143 - 146°C. $[\alpha]_D^{23}$ = -26.5 (c 0.7, $CHCl_3$). ν_{max} (KBr): 3351 (OH), 1779 (C=O, lactone), 1707 (C=O, ester), 1656 (C=C). δ_H ($CDCl_3$, 500 MHz): 1.40, 1.54 (6H, 2 x 3H 2 x s, $(CH_3)_2C$), 1.49 (9H, s, $C(CH_3)_3$), 3.20 (1H, d, $J_{OH,2}$ 3.1, D_2O exch., OH), 4.17 (1H, d, $J_{2,OH}$ 2.7, s on D_2O shake, H-2), 4.50 (1H, d, $J_{3,4}$ 2.5, H-3), 4.81 (1H, t_{app}, J_{app} 2.3, H-4), 5.75 (1H, dt_{app}, H-5), 5.88 (1H, dd, $J_{7,6}$ 11.7, $J_{7,5}$ 1.6, H-7), 6.21 (1H, dd, $J_{6,7}$ 11.7, $J_{6,5}$ 6.8, H-6). δ_C ($CDCl_3$, 125 MHz): 19.6 ($(CH_3)_2C$), 28.1 ($(CH_3)_3C$), 29.1 ($(CH_3)_2C$), 65.5, 71.6, 73.7, 74.4 (C-2, C-3, C-4, C-5), 81.2 ($(CH_3)_3C$), 98.4 ($(CH_3)_2C$), 123.1 (C-7), 144.1 (C-6), 165.2 (C-8), 175.3 (C-1). *m/z* (APCI+): 259.2 ($M+H^+$ - 56, 100%). Found C 57.16, H 7.09%; $C_{15}H_{22}O_7$ requires C 57.32, H 7.05%.

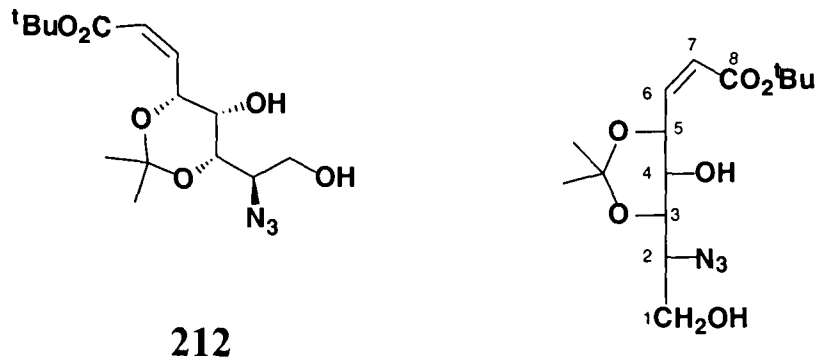
(Z)-(*tert*-Butyl 6,7-dideoxy-3,5-*O*-*iso*propylidene-2-*O*-trifluoromethanesulfonyl-D-*ido*-octar-6-enoate)-1,4-lactone 211



211

Trifluoromethanesulfonic anhydride (73 μl, 0.43 mmol) was added dropwise to a stirred solution of the lactone **210** (85 mg, 0.27 mmol) in freshly distilled dichloromethane (7 ml) and dry pyridine (70 μl, 0.86 mmol) at -30°C under an atmosphere of nitrogen. The reaction mixture was stirred at -30°C for 30 minutes after which time t.l.c. analysis (ethyl acetate/ hexane, 1:4) indicated complete conversion of the starting material (R_f 0.13) to a single product (R_f 0.57). The reaction mixture was diluted with dichloromethane (15 ml) and washed sequentially with 2M hydrochloric acid (15 ml) and pH7 buffer (40 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was preadsorbed onto silica gel and purified by flash column chromatography (ethyl acetate/ hexane 1:4) to afford the title compound as a white solid (106 mg, 88%). ν_{max} (KBr): 1801 (C=O, lactone), 1714 (C=O, ester), 1648 (C=C). $[\alpha]_D^{24}$ = -14.4 (c, 0.75 in $CHCl_3$). δ_H ($CDCl_3$, 500 MHz): 1.43, 1.57 (2 x 3H, 2 x s, $(CH_3)_2C$), 1.50 (9H, s, $C(CH_3)_3$), 4.73 (1H, d, $J_{3,4}$ 2.1, H-3), 4.86 (1H, t_{app}, J_{app} 2.4, H-4), 4.98 (1H, s, H-2), 5.76 (1H, dt_{app}, H-5), 5.92 (1H, dd, $J_{7,6}$ 11.6, $J_{7,5}$ 1.7, H-7), 6.19 (1H, dd, $J_{6,7}$ 11.6, $J_{6,5}$ 6.5, H-6). δ_C ($CDCl_3$, 125 MHz): 19.7 ($(CH_3)_2C$), 28.1 ($(CH_3)_3C$), 28.9 ($(CH_3)_2C$), 65.3, 69.9, 74.0, 80.8 (C-2, C-3, C-4, C-5), 81.5 ($(CH_3)_3C$), 99.4 ($(CH_3)_2C$), 123.5 (C-7), 143.3 (C-6), 165.2 (C-8) 166.8 (C-1). *m/z* (APCI+): 469.0 ($M+Na^+$, 10%). Found C 43.24, H 4.62%; $C_{16}H_{21}O_9F_3S$ requires C 43.05, H 4.74%.

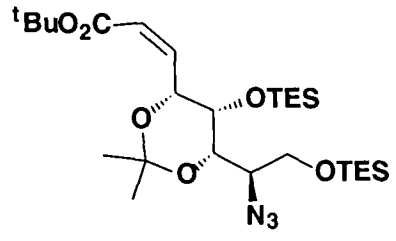
tert-Butyl 7-azido-2,3,7-trideoxy-4,6-*O*-*iso*propylidene-D-*ido*-oct-2-enosonate) 212



212

The D-*ido* azido lactone **207** (500 mg, 1.47 mmol), was dissolved in anhydrous THF (20 ml) and cooled to -10°C with stirring under an atmosphere of nitrogen. Solid lithium borohydride (74 mg, 3.39 mmol) was added portionwise over 5 minutes and the reaction mixture was stirred at -10°C for 25 minutes. T.l.c. analysis (ethyl acetate/hexane, 1:2) showed formation of a new product (R_f 0.19) and a trace of starting material (R_f 0.78). To the reaction mixture was added saturated aqueous ammonium chloride solution (1 ml) dropwise and the reaction mixture was stirred at r.t. for a further 5 minutes. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in ethyl acetate, preadsorbed onto silica gel and purified by flash column chromatography (ethyl acetate/hexane, 1:2) to afford the title compound as a colourless oil (321 mg, 64%). ν_{max} (film): 3448 (br OH), 2117 (N_3), 1718 (C=O, ester), 1653 (C=C). δ_H ($CDCl_3$, 500 MHz): 1.50, 1.56 (2 x 3H, 2 x s, $(CH_3)_2C$), 1.47 (9H, s, $C(CH_3)_3$), 2.23 (1H, br s, D_2O exch., OH), 2.69 (1H, d, $J_{OH,4}$ 11.5 D_2O exch., OH), 3.66 – 3.79 (4H, m, H-1,1′, H-2, H-4), 4.18 (1H, d, $J_{3,4}$ 7.9, H-3), 5.47 (1H, dt_{app}, $J_{5,6}$ 6.9, H-5), 5.92 (1H, dd, $J_{7,6}$ 11.8, $J_{7,5}$ 1.4, H-7), 6.15 (1H, dd, $J_{6,7}$ 11.8, $J_{6,5}$ 6.9, H-6). δ_C ($CDCl_3$, 125MHz): 19.1 ($(CH_3)_2C$), 28.1 ($(CH_3)_3C$), 29.6 ($(CH_3)_2C$), 60.79 (C-1), 63.77, 65.87, 70.35, 73.76, (C-2, C-3, C-4, C-5), 81.04 ($(CH_3)_3C$), 100.05 ($(CH_3)_2C$), 122.88 (C-7), 144.66 (C-6), 165.01 (C-8). *m/z* (APCI+): 366.1 ($M+Na^+$, 5%), 260.2 (100%). Found C 52.32, H 7.26, N 12.13%; $C_{15}H_{25}O_6N_3$ requires C 52.47, H 7.34, N 12.24%.

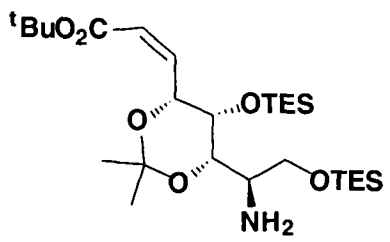
tert-Butyl 7-azido-2,3,7-trideoxy-4,6-*O*-_iso_propylidene-5,8-di-O-triethylsilyl-D-_ido_-oct-2-enosonate) 213



213

Anhydrous DMF (0.7 ml) was added to a mixture of the azido diol **212** (240 mg, 0.72 mmol) and imidazole (439 mg, 6.45 mmol) under an atmosphere of nitrogen. Triethylsilylchloride (324 mg, 360 µl, 2.15 mmol) was added to the reaction mixture which was allowed to stir for 3 hours at r.t. T.l.c. analysis (ethyl acetate/ hexane ,1:3) showed no starting material (R_f 0.17) remained and the formation of a new product (R_f 0.46). The mixture was diluted with dichloromethane (20 ml) and partitioned with pH7 buffer (20 ml). The aqueous phase was extracted with further dichloromethane (3 x 20 ml). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was preadsorbed onto silica gel and purified by flash column chromatography (ethyl acetate/ hexane ,1:3) to afford the title compound as a yellow oil (400 mg, 97%). ν_{max} (film): 2101 (N_3), 1713 (C=O, ester), 1652 (C=C). δ_H ($CDCl_3$, 500 MHz): 0.51 – 0.70 (12H, m ($Si(\underline{CH_2}CH_3)_3$), 0.89 – 1.01 (18H, m ($Si(CH_2\underline{CH_3})_3$), 1.49, 1.51 (2 x 3H, 2 x s, $(CH_3)_2C$), 1.48 (9H, s, $C(CH_3)_3$), 3.41 – 3.44 (1H, m, H-2), 3.70 (1H, dd $J_{1,1'}$ 10.7, $J_{1,2}$ 4.2, H-1), 3.79 (1H, dd $J_{1',1}$ 10.7, $J_{1',2}$ 2.7, H-1'), 3.96 (1H, br s, H-3), 4.15 (1H, m, H-4), 5.35 (1H, d, $J_{5,6}$ 6.7, H-5), 5.83 (1H, dd, $J_{7,6}$ 11.9, $J_{7,5}$ 1.5, H-7), 6.13 (1H, dd, $J_{6,7}$ 11.9, $J_{6,5}$ 6.7, H-6). δ_C ($CDCl_3$, 125 MHz): 4.3 ($Si(\underline{CH_2}CH_3)_3$, 5.6 ($Si(\underline{CH_2}CH_3)_3$, 6.7 ($Si(CH_2\underline{CH_3})_3$, 6.9 ($Si(CH_2\underline{CH_3})_3$, 19.2 ($(CH_3)_2C$), 28.1 ($(CH_3)_3C$), 29.6 ($(CH_3)_2C$), 61.9 (C-1), 62.5, 66.4, 71.14, 71.47, (C-2, C-3, C-4, C-5), 80.70 ($(CH_3)_3C$), 99.05 ($(CH_3)_2C$), 122.51 (C-7), 147.52 (C-6), 164.83 (C-8). *m/z* (APCI+): 594.2 ($M+Na^+$, 65%), 566.3 (28%). Found C 56.55, H 9.32, N 7.10; $C_{27}H_{53}O_6N_3Si_2$ requires C 56.70, H 9.34, N 7.35.

tert-Butyl 7-amino-2,3,7-trideoxy-4,6-*O*-_iso_propylidene-5,8-di-O-triethylsilyl-D-_ido_-oct-2-enosonate) 214

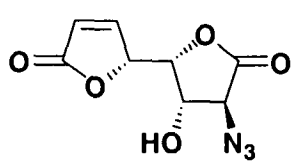


214

A round bottomed flask charged with powdered telleurium (118mg, 0.93mmol) and sodium borohydride (84mg, 2.22mmol) was dried under vacuum for 1 hour and then flushed with nitrogen and a condenser and septum were fitted. Under an atmosphere of nitrogen, degassed ethanol (3ml) was transferred to the flask by means of a cannular and the resulting mixture was refluxed for 1 hour after which time a dark red solution formed. This was allowed to cool to r.t. under nitrogen and then a solution of the azido compound **213** (210mg, 0.37mmol) in ether (3ml) was introduced to the flask containing the red solution. This was accompanied by the immediate formation of a black precipitate and the mixture was allowed to stir for a further 5 minutes before being opened to the air and allowed to stir for a further 10 minutes. T.l.c analysis (ethyl acetate/ hexane 1:2) showed a trace of starting material (R_f 0.01) and the formation of a new product (R_f 0.71). The reaction mixture was filtered through a small pad of Celite eluting with ethyl acetate and the residue was concentrated *in vacuo* and purified by flash column chromatography (ethyl acetate/ hexane 1:1.5 + 1% TEA) to afford the title compound as a yellow oil (117 mg, 58%). ν_{max} (film): 3392 (br OH), 1713 (C=O, ester), 1652 (C=C). δ_H ($CDCl_3$, 500 MHz): 0.53 – 0.65 (12H, m ($Si(\underline{CH_2}CH_3)_3$), 0.92 – 1.01 (18H, m ($Si(CH_2\underline{CH_3})_3$), 1.46, 1.47 (2 x 3H, 2 x s, $(CH_3)_2C$), 1.48 (9H, s, $C(CH_3)_3$), 1.88 (2H, br. s, D_2O exch., NH_2), 2.99 – 3.02 (1H, m, H-2), 3.61 (1H, dd $J_{1,1'}$ 9.8, $J_{1,2}$ 4.6, H-1), 3.69 (1H, dd $J_{1',1}$ 9.8, $J_{1',2}$ 4.8, H-1'), 3.79 (1H, d, $J_{??}$ 7.7 H-4), 3.90 ((1H, br. s, H-3), 5.32 (1H, m, H-5), 5.81 (1H, dd, $J_{7,6}$ 11.9, $J_{7,5}$ 1.4, H-7), 6.13 (1H, dd, $J_{6,7}$ 11.9, $J_{6,5}$ 6.8, H-6). δ_C ($CDCl_3$, 125 MHz): 4.3 ($Si(\underline{CH_2}CH_3)_3$, 5.5 ($Si(\underline{CH_2}CH_3)_3$, 6.8 ($Si(CH_2\underline{CH_3})_3$, 6.9 ($Si(CH_2\underline{CH_3})_3$, 19.5 ($(CH_3)_2C$), 28.1 ($(CH_3)_3C$), 29.8 ($(CH_3)_2C$), 62.65 (C-1), 52.6, 67.0, 71.0.

72.9 (C-2, C-3, C-4, C-5), 80.7 ($(CH_3)_3C$), 98.8 ($(CH_3)_2C$), 122.4 (C-7), 147.6 (C-6), 164.89 (C-8). *m/z* (APCI+): 568.0 ($M+Na^+$, 50%), 546.7 ($M+H^+$, 100%). Found C 59.12, H 9.96, N 2.28; $C_{27}H_{55}O_6NSi_2$ requires C 59.41, H 10.15, N 2.57.

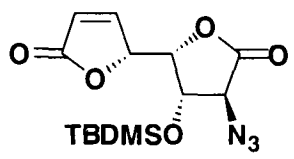
(Z)-2-Azido 2,6,7-trideoxy-3,5-*O*-*iso*propylidene-D-*ido*-octar-6-eno-1,4:5,8-dilactone 220



220

The azido lactone **207** was stirred in TFA/H_2O (1:1) at r.t for 20 minutes. T.l.c. analysis (ethyl acetate/ hexane, 5:1) showed no starting material (R_f 0.5) and the formation of a new product (R_f 0.05). The reaction mixture was concentrated *in vacuo* and co-evaporated with toluene (3 x 2 ml) to afford an off-white solid (137 mg, quantitative). ν_{max} (KBr): 3392 (br OH), 2122 (N_3), 1796 (C=O, lactone, α, β-unsaturated), 1743 (C=O, lacone). δ_H (acetonitrile d_3, 500 MHz): 4.58 (1H, m, H-3), 4.65 (1H, d, $J_{2,3}$ 2.4, H-2), 4.82 (1H, dd, $J_{4,3}$ 7.7, $J_{4,5}$ 1.7, H-4), 5.51 (1H, m, H-5), 6.20 (1H, dd, $J_{7,6}$ 5.8, $J_{7,5}$ 2.2, H-7), 7.65 (1H, dd, $J_{6,7}$ 5.8, $J_{6,5}$ 1.6, H-6). δ_C (acetonitrile d_3, 125 MHz): 62.7, 72.1, 77.3, 80.4 (C-2, C-3, C-4, C-5), 123.0 (C-7), 155.2 (C-6), 171.8 (C-8) 173.0 (C-1). *m/z* (APCI+): 248 ($M+Na^+$ 248, 100%). HRMS (CI+): Found 226.0458; $C_8H_7N_3O_5$ requires 226.0465.

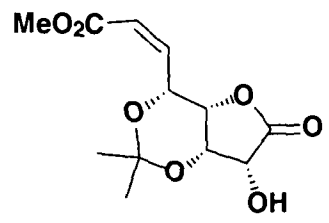
(Z)-2-Azido 2,6,7-trideoxy-3,5-*O*-*iso*propylidene-3-*O*-*tert*-butyldimethylsilyl-D-*ido*-octar-6-eno-1,4:5,8-dilactone 221



221

The azido dilactone **220** (60 mg, 0.27 mmol) was dissolved in dry pyridine (0.4 ml) with stirring at r.t. under an atmosphere of nitrogen and the resulting solution was cooled to 0°C. *tert*-Butyldimethylsilyltriflate (0.1 ml, 0.40 mmol) was added dropwise to the cooled solution and the solution was allowed to stir for 30 minutes. T.l.c. analysis (ethyl acetate/ hexane, 1:2) showed a trace of starting material (R_f 0.02) and the formation of a new product (R_f 0.32). Ethanol (1.5 ml) was added to the reaction mixture and the solvents were removed *in vacuo*. The resulting residue was dissolved in ethyl acetate and preadsorbed onto silica gel and purified by flash column chromatography (ethyl acetate/ hexane, 1:2) to afford the title compound as a yellow solid (62 mg, 68%). ν_{max} (KBr): 2123 (N_3), 1811 (C=O, lactone, α, β-unsaturated), 1761 (C=O, lacone). δ_H (acetonitrile d_3, 500 MHz): 0.19, 0.22 (2 x 3H, 2 x s, $Si(\underline{CH_3})_2C(CH_3)_3$), 0.96 (9H, s, $Si(CH_3)_2C(\underline{CH_3})_3$), 4.67 (2H, m, H-3, H-2), 4.84 (1H, dd, $J_{4,3}$ 7.7, $J_{4,5}$ 1.2, H-4), 5.46 (1H, m, H-5), 6.20 (1H, dd, $J_{7,6}$ 5.8, $J_{7,5}$ 2.2, H-7), 7.65 (1H, dd, $J_{6,7}$ 5.8, $J_{6,5}$ 1.7, H-6). δ_C (acetonitrile d_3, 125 MHz): 1.2, 1.4 ($Si(\underline{CH_3})_2C(CH_3)_3$), 25.8 ($Si(CH_3)_2C(\underline{CH_3})_3$), 63.0, 73.6, 76.9, 80.5 (C-2, C-3, C-4, C-5), 122.9 (C-7), 155.4 (C-6), 171.9 (C-8) 173.1 (C-1). *m/z* (APCI+): 340.8 (MH^+, 5%), 312.1 (MH^+ - 28, 25%). HRMS (CI+): Found 340.1333; $C_{14}H_{22}N_3O_5Si$ requires 340.1329.

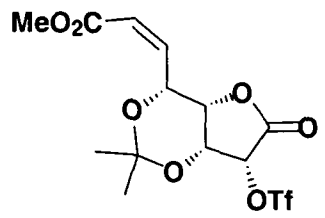
(Z)-(Methyl 6,7-dideoxy-3,5-*O*-*iso*propylidene-D-*gulo*-octar-6-enoate)-1,4-lactone 216



216

To a stirred solution of the triol **203** (1.0 g, 4.02 mmol) in methanol (50 ml) and water (4 ml) was added solid sodium periodate (1.03 g, 4.83 mmol) in one portion. The reaction mixture was stirred at r.t for a further 30 minutes. The reaction mixture was filtered through Celite eluting with further ethyl acetate. Evaporation of the filtrate *in vacuo* afforded the crude aldehyde **204** as a white solid which was dried by coevaporating with toluene (3 x 20 ml). The crude aldehyde **204** was then dissolved in freshly distilled THF (30 ml) with no further purification. The solid methoxycarbonylmethylenetriphenylphosphorane (1.54 g, 4.62 mmol) was added in one portion to this solution and the resulting mixture was stirred at r.t. for 17 hours. T.l.c. analysis (2:1, hexane/ethyl acetate) indicated formation of a new product (R_f 0.65) and no starting material (R_f 0.05). The reaction mixture was concentrated *in vacuo* and the residue dissolved in ethyl acetate, preadsobed onto silica gel and purified by flash column chromatography (2:1, hexane/ethyl acetate) then (1:1, hexane/ethyl acetate) to afford the title compound as a white crystalline solid (0.47 g, 43%). ν_{max} (KBr): 3416 (br OH), 1793 (C=O, lactone), 1703 (C=O, ester), 1648 (C=C). δ_H ($CDCl_3$, 500 MHz) : 1.45, 1.56 (2 x 3H 2 x s, $C(CH_3)_2$), 2.93 (1H, d, $J_{OH,2}$ 9.7, D_2O exch., OH), 3.74 (3H, s, OCH_3), 4.46 (1H, m, d $J_{2,3}$ 4.1on D_2O shake, H-2), 4.53 (1H, t_{app}, J_{app} 2.2, H-4), 4.68 (1H, dd, $J_{3,2}$ 4.1, $J_{3,4}$ 2.2 H-3), 5.70 (1H, dt_{app}, J 6.6, H-5), 5.99 (1H, dd, $J_{7,6}$ 11.6, $J_{7,5}$ 1.6 H-7), 6.32 (1H, dd, $J_{6,7}$ 11.6, $J_{6,5}$ 6.6, H-6). δ_C ($CDCl_3$, 125 MHz) : 19.6 ($(CH_3)_2C$), 29.0 ($(CH_3)_2C$), 51.7 (OCH_3), 65.9, 67.8, 70.3, 71.4 (C-2, C-3, C-4, C-5), 99.0 ($(CH_3)_2C$), 120.3 (C-7), 145.7 (C-6), 166.4 (C-8) 174.7 (C-1). *m/z* (APCI+): 295.1 ($M+Na^+$, 37%), 215.0 (100%). Found C 52.72, H 5.92%; $C_{12}H_{16}O_7$ requires C 52.94, H 5.92%.

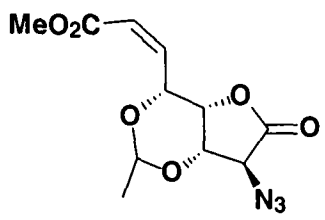
(Z)-(Methyl 6,7-dideoxy-3,5-*O*-*iso*propylidene-2-*O*-trifluoromethanesulfonyl-D-*gulo*-octar-6-enoate)-1,4-lactone 217



217

Trifluoromethanesulfonic anhydride (0.72 ml, 4.30 mmol) was added dropwise to a stirred solution of the lactone **216** (900 mg, 3.31 mmol) in freshly distilled dichloromethane (36 ml) and dry pyridine (0.80 ml, 9.92 mmol) at -30°C under an atmosphere of nitrogen. The reaction mixture was stirred at -30°C for 40 minutes after which time t.l.c. analysis (ethyl acetate/ hexane, 1:1) indicated complete conversion of the starting material (R_f 0.15) to a single product (R_f 0.63). The reaction mixture was diluted with dichloromethane (40 ml) and washed sequentially with 2M hydrochloric acid (80 ml) and pH7 buffer (150 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was preadsorbed onto silica gel and purified by flash column chromatography (ethyl acetate/ hexane 1:1) to afford the title compound as a white solid (1.24 g, 93%). ν_{max} (KBr): 1806 (C=O, lactone), 1720 (C=O, ester), 1652 (C=C). δ_H ($CDCl_3$, 500MHz) : 1.48, 1.56 (2 x 3H 2 x s, $C(CH_3)_2$), 3.75 (3H, s, CH_3), , 4.63 (1H, t_{app}, J_{app} 2.2, H-4), 4.89 (1H, dd, $J_{3,2}$ 4.1, $J_{3,4}$ 2.2 H-3), 5.33 (1H, d $J_{2,3}$ 4.0 H-2), 5.70 (1H, dt_{app}, J 6.3, H-5), 6.02 (1H, dd, $J_{7,6}$ 11.6, $J_{7,5}$ 1.6 H-7), 6.30 (1H, dd, $J_{6,7}$ 11.6, $J_{6,5}$ 6.6, H-6). δ_C ($CDCl_3$, 125MHz) : 19.3 ($(CH_3)_2C$), 28.9 ($(CH_3)_2C$), 51.8 (OCH_3), 65.7, 67.3, 70.2, 78.8 (C-2, C-3, C-4, C-5), 99.3 ($(CH_3)_2C$), 121.3 (C-7), 145.0 (C-6), 166.3 (C-8) 166.6 (C-1). *m/z* (APCI+): 427.5 ($M+Na^+$, 26%). Found C 38.85, H 3.60%; $C_{13}H_{15}O_9F_3S$ requires C 38.62, H 3.74%.

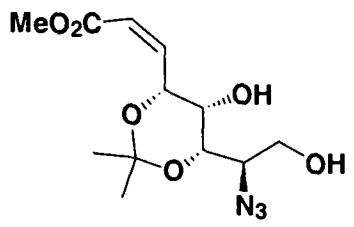
(Z)- (Methyl 2-azido-2,6,7-trideoxy-3,5-*O-iso*propylidene-D-*ido*-octar-6-enoate)-1,4-lactone 218



218

The D-*gulo* triflate **217** (1241 mg, 3.07 mmol) was dissolved in anhydrous DMF (15) and solid sodium azide (259 mg, 3.99 mmol) was added in one portion. The reaction mixture was stirred at r.t. under an atmosphere of nitrogen for 40 minutes. T.l.c. analysis (ethyl acetate/hexane 1:5) indicated formation of a new product (R_f 0.3) and complete consumption of starting material (R_f 0.19). The reaction mixture was concentrated *in vacuo* and the residue was washed sequentially with brine (3 x 10ml) extracting with ethyl acetate. The organics were combined, dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography (ethyl acetate/hexane 1:5) to afford the D-*ido* azide **218** as a colourless oil (815 mg, 89%). ν_{max} (KBr): 2116 (N_3), 1789 (C=O, lactone), 1718 (C=O, ester), 1654 (C=C). δ_H ($CDCl_3$, 500 MHz): 1.40, 1.52 (2 x 3H 2 x s, $C(CH_3)_2$), 3.75 (3H, s, OCH_3), 4.07 (1H, s, H-2), 4.38 (1H, d, $J_{3,4}$ 2.5, H-3), 4.67 (1H, t_{app}, J_{app} 2.3 H-4), 5.71 (1H, dt_{app}, J 6.6, H-5), 5.99 (1H, dd, $J_{7,6}$ 11.6, $J_{7,5}$ 1.5 H-7), 6.30 (1H, dd, $J_{6,7}$ 11.6, $J_{6,5}$ 6.6, H-6). δ_C ($CDCl_3$, 125 MHz) : 19.5 ($(CH_3)_2C$), 29.0 ($(CH_3)_2C$), 51.7 (OCH_3), 63.3, 65.6, 70.6 73.8 (C-2, C-3, C-4, C-5), 98.8 ($(CH_3)_2C$), 120.9 (C-7), 145.5 (C-6), 166.2 (C-8), 171.1 (C-1). Found C 48.35, H 4.89, N 13.95; $C_{12}H_{15}O_6N_3$ requires C 48.49, H 5.09, N 14.14.

Methyl 7-azido-2,3,7-trideoxy-4,6-*O*-*iso*propylidene-5,8-di-O-triethylsilyl-D-*ido*-oct-2-enosonate) 219



219

The D-*ido* azido lactone **218** (79 mg, 0.27 mmol), was dissolved in anhydrous THF (2 ml) and cooled to -10°C with stirring under an atmosphere of nitrogen. Solid lithium borohydride (13 mg, 0.61 mmol) was added portionwise over 5 minutes and the reaction mixture was stirred at -10°C for 1 hour. T.l.c. analysis (ethyl acetate/hexane, 1:1) showed formation of a major product (R_f 0.23) and a trace of starting material (R_f 0.82). To the reaction mixture was added saturated aqueous ammonium chloride solution (1 ml) dropwise and the reaction mixture was stirred at room temperature for a further 5 minutes. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in ethyl acetate, preadsorbed onto silica gel and purified by flash column chromatography (ethyl acetate/hexane, 1:2) to afford the title compound as a colourless oil (17 mg, 21%). ν_{max} (film): 3421 (br OH), 2106 (N_3), 1717 (C=O, ester), 1653 (C=C). δ_H ($CDCl_3$, 500MHz): 1.51, 1.57 (2 x 3H, 2 x s, $(CH_3)_2C$), 1.73 (1H, br s, D_2O exch., OH), 2.67 (1H, d, $J_{OH,4}$ 11.8 D_2O exch., OH), 3.67 – 3.79 (4H, m, H-1,1′, H-2, H-4), 3.74 (3H, s, CH_3), 4.18 (1H, d $J_{3,4}$ 7.1, H-3), 5.51 (1H, d, $J_{5,6}$ 6.9, H-5), 5.95 (1H, dd, $J_{7,6}$ 11.7, $J_{7,5}$ 1.5, H-7), 6.28 (1H, dd, $J_{6,7}$ 11.7, $J_{6,5}$ 6.9, H-6). δ_C ($CDCl_3$, 125MHz): 19.02 ($(CH_3)_2C$), 29.55 ($(CH_3)_2C$), 51.59 (OCH_3), 60.80 (C-1), 63.68 (C-2, C-3, C-4, C-5), 65.80 (C-2, C-3, C-4, C-5), 70.53 (C-2, C-3, C-4, C-5), 73.80 (C-2, C-3, C-4, C-5), 100.12 ($(CH_3)_2C$), 120.43 (C-7), 146.80 (C-6), 166.13 (C-8). *m/z* (APCI+): 302 ($M+H^+$, 5%), 274 ($M+H^+$ - 28, 100%). HRMS (CI+): Found 302.1346; $C_{12}H_{20}N_3O_6$ requires 302.1353.

References and Notes

[1] Brimacombe, J.S., Tucker, L.C.N.; *Carbohydrate Res.*, 1965, **1**, 332.

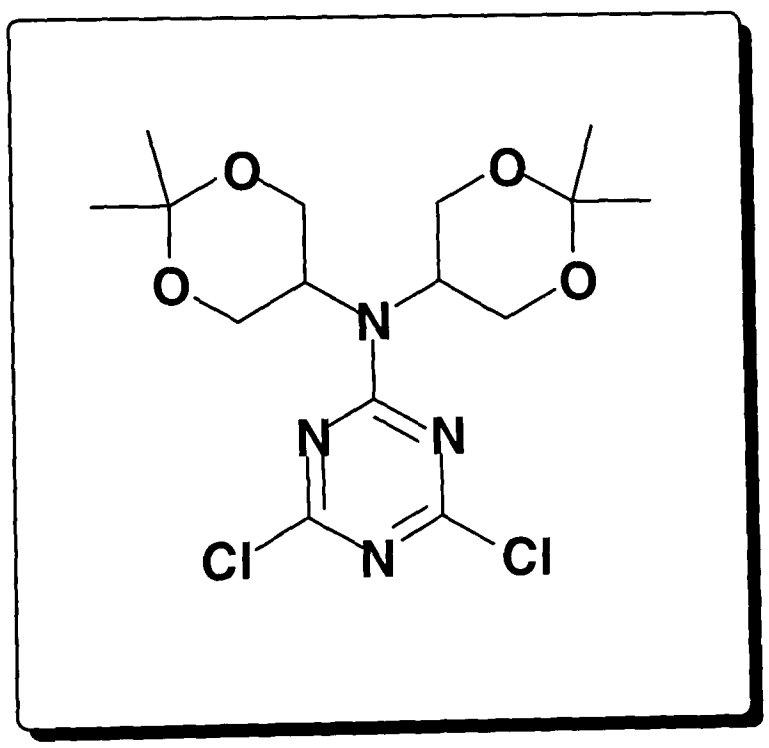
[2] Shing, T.K.M., Tsui, H.-C., Zhou, Z.-H.; *J. Org. Chem.*, 1995, **60**, 3121.

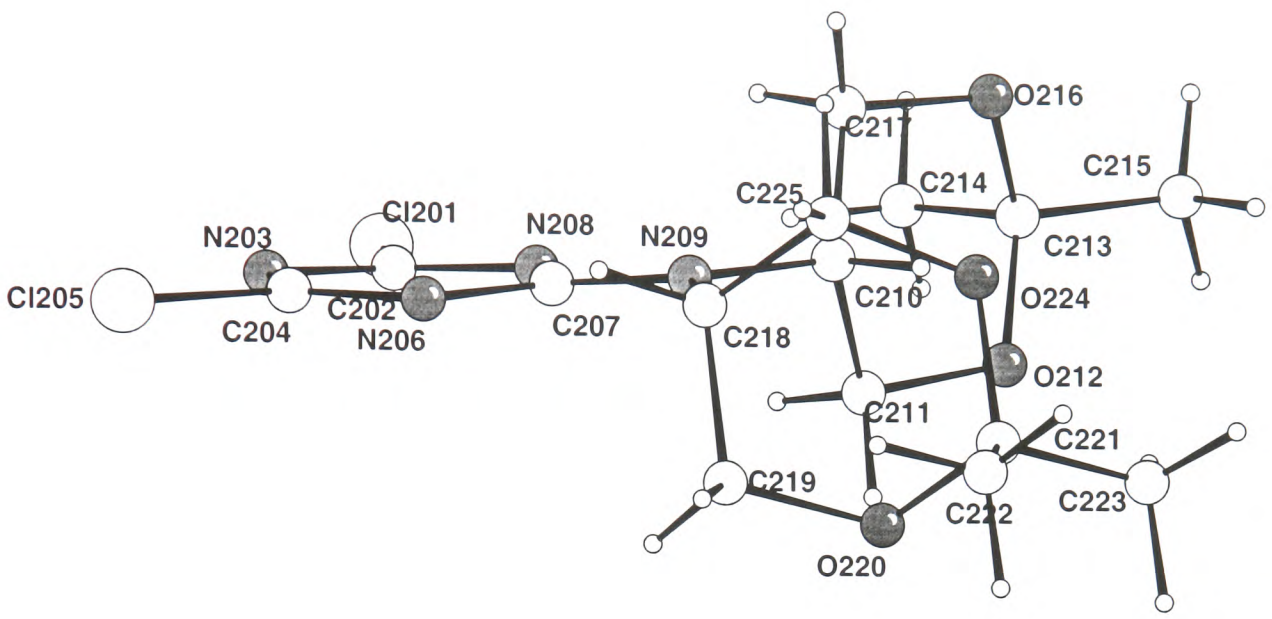
[3] Griffiths, G.F., Kenner, G.W., McCombie, S.W., Smith, K., Sutton, M.J.; *Tetrahedron*, 1976, **32**, 275.

Appendix I - X-Ray Crystal Structure

X-Ray Crystal Structure:

(4,6-Dichloro-[1,3,5]triazin-2-yl)-bis-(2,2-dimethyl-[1,3]dioxan-5-yl)-amine **108**





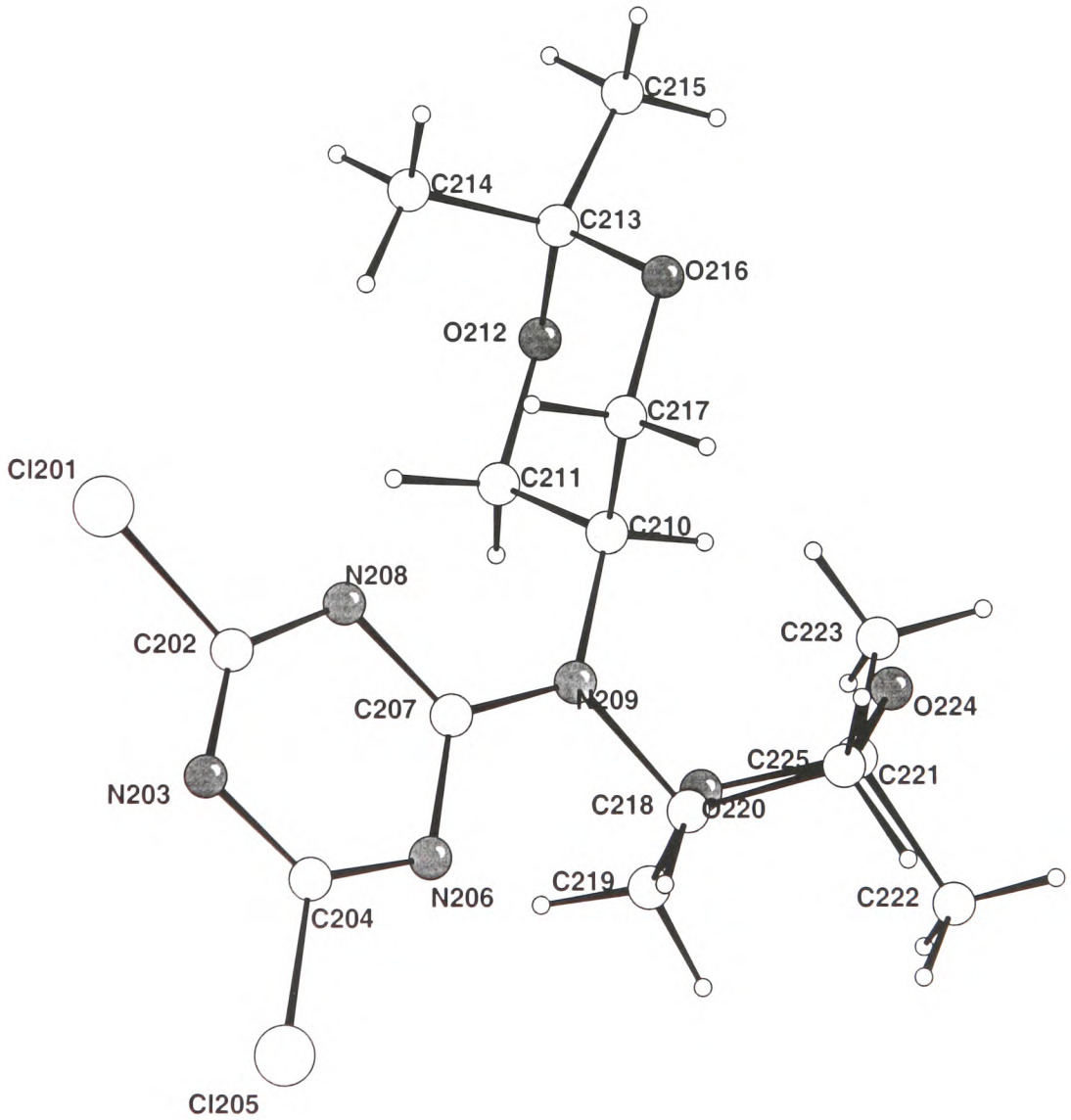


Figure I. Representations of the crystal structure of (4,6-Dichloro-[1,3,5]triazin-2-yl)-bis-(2,2-dimethyl-[1,3]dioxan-5-yl)-amine **108** showing atom labelling.

X-Ray Crystal Structure Data:

(4,6-Dichloro-[1,3,5]triazin-2-yl)-bis-(2,2-dimethyl-[1,3]dioxan-5-yl)-amine

Crystal Data

Molecular Formula: $C_{15}H_{22}Cl_2N_4O_4$
2 molecules per asymmetic unit
Crystal System: Monoclinic
a (Å) 12.5148(16)
b (Å) 17.641(4)
c (Å) 17.051(3)
V (Å^3) 3757.2
Z = 16
μ 0.37mm^{-1}
Crystal size (mm) 0.4 x 0.5 x 0.6

M_r 393.269 g mol^{-1}
786.538 g mol^{-1}
Space Group: $P\,2_1/c$
α (°) 90
β (°) 93.545(13)
γ (°) 90
D_m (Mg m^{-3}) not measured
D_x (Mg m^{-3}) 1.39

Data Collection and Processing

Spectrometer: Enraf-nonius CAD-4 diffractometer
Scan mode: 2θ/ω
X-radiation: Mo $K\alpha$ λ (Å) 0.71073
No. reflections for lattice parameters: 24
No. reflections used: 8186
No. independent reflections: 7650
No. observed relections: 3385 [I≥3σ(I)]
R_{int} 0.0511
No. standard reflections: 3
Intensity decay: 90.50% (Note: all three standard reflection decayed monotonically)
Interval (count): 200

θ_{min}, θ_{max} (°) 0, 74
T (K) 293
h range -15 15
k range 0 22
l range 0 21

Refinement

Refinement on *F Squared*

R 0.0837
wR 0.0956
S 1.0702
No. reflections: 3385
No. parameters: 452

Weighting scheme: Chebychev polynomial with 3 parameters
$\Delta\rho_{max}$ (e Å^{-3}) 0.58
$\Delta\rho_{min}$ (e Å^{-3}) -0.37
$(\Delta/\sigma)_{max}$ 0.004060
Extinction coefficient: none
Extinction correction: none

Crystal structure determination was kindly performed by C. J. Newman and D. J. Watkin, Chemical Crystallography, Parks Road, Oxford, UK.

Scattering factors from *International Tables for X-ray Crystallography* (Vol. IV)[1]

Structure refinement software: CRYSTALS[2]

1. *International Tables for Crystallography*, Vol IV, Kluwer Academic Publishers, Dordrecht, 1992.
2. D.J. Watkin, C.K. Prout, J.R. Carruthers, and P.W. Betteridge, *CRYSTALS Issue 10*, Chemical Crystallography Laboratory, University of Oxford, 1996.

Table 1:
Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2)
(e.s.d. in parentheses)

Atom	*x/a*	*y/b*	*z/c*	*U(iso)*
Cl(101)	-0.34671(12)	0.2226(1)	0.27202(11)	0.0565
Cl(105)	-0.22474(14)	0.03072(9)	0.4893(1)	0.0530
Cl(201)	0.85308(13)	0.02189(12)	0.19268(12)	0.0627
Cl(205)	0.7291(2)	0.22094(15)	-0.01642(16)	0.1005
O(116)	0.0534(3)	0.2811(2)	0.1531(2)	0.0464
O(112)	0.0452(3)	0.3689(2)	0.2539(2)	0.0444
O(124)	0.2834(3)	0.1700(2)	0.3262(2)	0.0395
O(120)	0.2349(3)	0.2442(2)	0.4306(2)	0.0413
O(212)	0.4419(3)	-0.1020(2)	0.2415(2)	0.0473
O(216)	0.4472(3)	-0.0036(2)	0.3315(2)	0.0445
O(220)	0.2836(3)	0.0114(2)	0.0405(2)	0.0457
O(224)	0.2224(3)	0.0827(3)	0.1436(2)	0.0463
N(108)	-0.1497(4)	0.1947(3)	0.3101(3)	0.0381
N(109)	0.0311(4)	0.1766(3)	0.3422(3)	0.0372
N(106)	-0.0924(4)	0.1089(3)	0.4115(3)	0.0367
N(103)	-0.2764(4)	0.1246(3)	0.3775(3)	0.0435
N(208)	0.6558(4)	0.0546(3)	0.1594(3)	0.0393
N(209)	0.4762(4)	0.0801(3)	0.1339(3)	0.0376
N(206)	0.5980(4)	0.1429(3)	0.0618(3)	0.0490
N(203)	0.7839(4)	0.1219(3)	0.0907(3)	0.0555
C(102)	-0.2454(5)	0.1751(3)	0.3253(4)	0.0394
C(107)	-0.0708(4)	0.1600(3)	0.3549(3)	0.0334
C(110)	0.0586(5)	0.2371(3)	0.2868(4)	0.0389
C(117)	0.0247(5)	0.2192(3)	0.2010(4)	0.0429
C(113)	0.0085(5)	0.3515(3)	0.1762(4)	0.0424
C(111)	0.0197(5)	0.3148(4)	0.3104(4)	0.0441
C(114)	-0.1131(6)	0.3501(4)	0.1668(4)	0.0588
C(115)	0.0554(7)	0.4111(4)	0.1246(4)	0.0642
C(118)	0.1188(5)	0.1395(3)	0.3912(4)	0.0401
C(125)	0.2103(5)	0.1122(3)	0.3441(4)	0.0442
C(121)	0.3221(5)	0.2133(4)	0.3916(4)	0.0412
C(119)	0.1635(5)	0.1884(4)	0.4574(4)	0.0473
C(123)	0.3798(6)	0.2798(4)	0.3582(5)	0.0622
C(122)	0.3980(6)	0.1681(4)	0.4469(4)	0.0572
C(104)	-0.1934(5)	0.0957(3)	0.4171(4)	0.0398
C(202)	0.7521(5)	0.0719(4)	0.1414(4)	0.0437
C(207)	0.5761(4)	0.0925(3)	0.1176(3)	0.0338
C(210)	0.4456(4)	0.0261(3)	0.1956(3)	0.0363
C(211)	0.4753(5)	-0.0556(3)	0.1793(4)	0.0400
C(213)	0.4792(5)	-0.0788(3)	0.3179(4)	0.0419
C(217)	0.4854(5)	0.0490(3)	0.2769(4)	0.0423
C(215)	0.4225(6)	-0.1277(4)	0.3745(4)	0.0579
C(214)	0.6000(5)	-0.0885(4)	0.3299(4)	0.0534
C(218)	0.3894(5)	0.1191(3)	0.0848(4)	0.0427
C(219)	0.3501(5)	0.0710(4)	0.0166(4)	0.0512
C(221)	0.1918(5)	0.0368(4)	0.0775(4)	0.0492
C(225)	0.2929(5)	0.1432(4)	0.1282(4)	0.0492
C(223)	0.1424(6)	-0.0336(5)	0.1103(5)	0.0703

C(222)	0.1145(6)	0.0787(5)	0.0211(4)	0.0619
C(204)	0.6995(6)	0.1537(4)	0.0536(4)	0.0543
H(61)	0.1387	0.2391	0.2915	0.0541
H(71)	-0.0547	0.2110	0.1945	0.0578
H(72)	0.0620	0.1723	0.1835	0.0578
H(111)	0.0536	0.3301	0.3626	0.0630
H(112)	-0.0607	0.3138	0.3141	0.0630
H(121)	-0.1450	0.3993	0.1830	0.0775
H(122)	-0.1432	0.3084	0.2011	0.0775
H(123)	-0.1398	0.3388	0.1108	0.0775
H(131)	0.0258	0.4626	0.1403	0.0860
H(132)	0.1348	0.4132	0.1317	0.0860
H(133)	0.0327	0.4019	0.0684	0.0860
H(141)	0.0820	0.0938	0.4145	0.0549
H(151)	0.2503	0.0690	0.3735	0.0582
H(152)	0.1797	0.0886	0.2923	0.0582
H(191)	0.2047	0.1557	0.4987	0.0622
H(192)	0.1039	0.2139	0.4846	0.0622
H(201)	0.4096	0.3134	0.4042	0.0864
H(202)	0.4415	0.2635	0.3284	0.0864
H(203)	0.3299	0.3118	0.3246	0.0864
H(211)	0.4239	0.1989	0.4930	0.0732
H(212)	0.4604	0.1478	0.4194	0.0732
H(213)	0.3577	0.1220	0.4677	0.0732
H(311)	0.3653	0.0271	0.1945	0.0471
H(321)	0.5560	-0.0606	0.1757	0.0577
H(322)	0.4403	-0.0738	0.1280	0.0577
H(361)	0.5650	0.0512	0.2809	0.0584
H(362)	0.4567	0.1016	0.2887	0.0584
H(371)	0.4463	-0.1123	0.4300	0.0768
H(372)	0.4443	-0.1822	0.3671	0.0768
H(373)	0.3437	-0.1232	0.3670	0.0768
H(381)	0.6274	-0.0731	0.3839	0.0681
H(382)	0.6218	-0.1431	0.3212	0.0681
H(383)	0.6377	-0.0565	0.2904	0.0681
H(391)	0.4245	0.1667	0.0660	0.0652
H(401)	0.4138	0.0488	-0.0104	0.0641
H(402)	0.3091	0.1035	-0.0249	0.0641
H(441)	0.3186	0.1670	0.1810	0.0672
H(442)	0.2519	0.1845	0.0976	0.0672
H(451)	0.0784	-0.0227	0.1394	0.0908
H(452)	0.1974	-0.0609	0.1477	0.0908
H(453)	0.1229	-0.0707	0.0663	0.0908
H(461)	0.0507	0.0972	0.0469	0.0776
H(462)	0.1528	0.1241	-0.0014	0.0776
H(463)	0.0912	0.0449	-0.0245	0.0776

Table 2:
Interatomic distances (Å)
(e.s.d. in parentheses)

Cl(101)- C(102)	1.730(6)
Cl(105)- C(104)	1.744(6)
Cl(201)- C(202)	1.733(7)
Cl(205)- C(204)	1.738(7)
O(116)- C(117)	1.423(7)
O(116)- C(113)	1.428(7)
O(112)- C(113)	1.408(8)
O(112)- C(111)	1.407(7)
O(124)- C(125)	1.417(7)
O(124)- C(121)	1.412(7)
O(120)- C(121)	1.420(7)
O(120)- C(119)	1.424(8)
O(212)- C(211)	1.423(7)
O(212)- C(213)	1.417(7)
O(216)- C(213)	1.409(7)
O(216)- C(217)	1.418(7)
O(220)- C(219)	1.416(8)
O(220)- C(221)	1.418(8)
O(224)- C(221)	1.421(8)
O(224)- C(225)	1.419(8)
N(108)- C(102)	1.288(7)
N(108)- C(107)	1.355(7)
N(109)- C(107)	1.339(7)
N(109)- C(110)	1.481(7)
N(109)- C(118)	1.489(7)
N(106)- C(107)	1.360(7)
N(106)- C(104)	1.295(7)
N(103)- C(102)	1.333(8)
N(103)- C(104)	1.307(8)
N(208)- C(202)	1.297(8)
N(208)- C(207)	1.365(7)
N(209)- C(207)	1.316(7)
N(209)- C(210)	1.486(7)
N(209)- C(218)	1.497(8)
N(206)- C(207)	1.342(7)
N(206)- C(204)	1.301(9)
N(203)- C(202)	1.314(8)
N(203)- C(204)	1.323(9)
C(110)- C(117)	1.531(9)
C(110)- C(111)	1.517(9)
C(113)- C(114)	1.521(9)
C(113)- C(115)	1.513(9)
C(118)- C(125)	1.517(8)
C(118)- C(119)	1.500(9)
C(121)- C(123)	1.507(9)
C(121)- C(122)	1.522(9)
C(210)- C(211)	1.518(8)
C(210)- C(217)	1.499(9)
C(213)- C(215)	1.505(9)
C(213)- C(214)	1.522(9)
C(218)- C(219)	1.497(9)
C(218)- C(225)	1.517(9)
C(221)- C(223)	1.51(1)
C(221)- C(222)	1.51(1)

Table 3:
Interatomic angles (°)
(e.s.d. in parentheses)

C(117)- O(116)- C(113)	113.0(4)
C(113)- O(112)- C(111)	114.9(4)
C(125)- O(124)- C(121)	114.4(4)
C(121)- O(120)- C(119)	113.6(5)
C(211)- O(212)- C(213)	115.0(4)
C(213)- O(216)- C(217)	113.3(4)
C(219)- O(220)- C(221)	113.6(5)
C(221)- O(224)- C(225)	115.0(5)
C(102)- N(108)- C(107)	114.8(5)
C(107)- N(109)- C(110)	121.4(5)
C(107)- N(109)- C(118)	119.4(5)
C(110)- N(109)- C(118)	118.8(4)
C(107)- N(106)- C(104)	114.2(5)
C(102)- N(103)- C(104)	110.6(5)
C(202)- N(208)- C(207)	114.9(5)
C(207)- N(209)- C(210)	123.1(5)
C(207)- N(209)- C(218)	118.1(5)
C(210)- N(209)- C(218)	118.7(4)
C(207)- N(206)- C(204)	114.7(6)
C(202)- N(203)- C(204)	109.5(5)
Cl(101)- C(102)- N(108)	115.2(5)
Cl(101)- C(102)- N(103)	116.1(4)
N(108)- C(102)- N(103)	128.7(6)
N(108)- C(107)- N(109)	118.6(5)
N(108)- C(107)- N(106)	122.0(5)
N(109)- C(107)- N(106)	119.4(5)
N(109)- C(110)- C(117)	113.6(5)
N(109)- C(110)- C(111)	113.0(5)
C(117)- C(110)- C(111)	111.4(5)
O(116)- C(117)- C(110)	109.0(5)
O(116)- C(113)- O(112)	109.8(5)
O(116)- C(113)- C(114)	111.4(5)
O(112)- C(113)- C(114)	111.7(5)
O(116)- C(113)- C(115)	105.7(5)
O(112)- C(113)- C(115)	106.3(5)
C(114)- C(113)- C(115)	111.8(6)
O(112)- C(111)- C(110)	109.9(5)
N(109)- C(118)- C(125)	113.4(5)
N(109)- C(118)- C(119)	113.4(5)
C(125)- C(118)- C(119)	108.8(5)
O(124)- C(125)- C(118)	113.8(5)
O(124)- C(121)- O(120)	110.0(5)
O(124)- C(121)- C(123)	105.7(5)
O(120)- C(121)- C(123)	106.2(5)
O(124)- C(121)- C(122)	112.1(5)
O(120)- C(121)- C(122)	112.2(5)
C(123)- C(121)- C(122)	110.3(6)
O(120)- C(119)- C(118)	111.6(5)
Cl(105)- C(104)- N(106)	115.7(5)
Cl(105)- C(104)- N(103)	114.6(4)
N(106)- C(104)- N(103)	129.7(6)
Cl(201)- C(202)- N(208)	114.9(5)
Cl(201)- C(202)- N(203)	115.6(5)
N(208)- C(202)- N(203)	129.6(6)
N(208)- C(207)- N(209)	118.8(5)
N(208)- C(207)- N(206)	121.3(5)
N(209)- C(207)- N(206)	119.9(5)
N(209)- C(210)- C(211)	113.7(5)
N(209)- C(210)- C(217)	113.3(5)
C(211)- C(210)- C(217)	110.7(5)
O(212)- C(211)- C(210)	108.9(5)

O(212)- C(213)- O(216)	110.1(5)
O(212)- C(213)- C(215)	106.4(5)
O(216)- C(213)- C(215)	106.4(5)
O(212)- C(213)- C(214)	111.1(5)
O(216)- C(213)- C(214)	112.0(5)
C(215)- C(213)- C(214)	110.6(5)
O(216)- C(217)- C(210)	109.0(5)
N(209)- C(218)- C(219)	111.5(5)
N(209)- C(218)- C(225)	115.4(5)
C(219)- C(218)- C(225)	107.7(5)
O(220)- C(219)- C(218)	111.6(5)
O(220)- C(221)- O(224)	110.3(5)
O(220)- C(221)- C(223)	105.4(6)
O(224)- C(221)- C(223)	105.8(6)
O(220)- C(221)- C(222)	112.0(5)
O(224)- C(221)- C(222)	110.8(6)
C(223)- C(221)- C(222)	112.2(6)
O(224)- C(225)- C(218)	113.7(5)
Cl(205)- C(204)- N(206)	115.2(5)
Cl(205)- C(204)- N(203)	114.9(5)
N(206)- C(204)- N(203)	129.9(6)

Table 4:
Final anisotropic temperature factors
(e.s.d. in parenthesis)

Atom	*u(11)*	*u(22)*	*u(33)*	*u(23)*	*u(13)*	*u(12)*
Cl101	0.0381(9)	0.057(1)	0.0740(12)	0.0138(9)	-0.0028(8)	0.0068(7)
Cl105	0.064(1)	0.0474(9)	0.0487(9)	0.0086(8)	0.0120(8)	-0.0126(7)
Cl201	0.0409(9)	0.0773(13)	0.0697(11)	0.006(1)	0.0013(8)	0.0141(8)
Cl205	0.0926(17)	0.110(2)	0.1001(18)	0.0595(16)	0.0155(14)	-0.0281(14)
O116	0.055(3)	0.042(2)	0.044(2)	0.008(2)	0.012(2)	0.002(2)
O112	0.059(3)	0.031(2)	0.042(2)	0.0034(19)	-0.006(2)	-0.0072(18)
O124	0.043(2)	0.044(2)	0.032(2)	0.0002(19)	0.0028(17)	0.0072(19)
O120	0.046(2)	0.043(2)	0.036(2)	0.0012(19)	0.0056(18)	0.0014(19)
O212	0.059(3)	0.036(2)	0.046(3)	0.008(2)	-0.004(2)	-0.011(2)
O216	0.050(2)	0.049(3)	0.035(2)	0.002(2)	0.0055(19)	0.004(2)
O220	0.045(2)	0.049(3)	0.042(2)	-0.006(2)	-0.0007(19)	-0.0034(19)
O224	0.038(2)	0.060(3)	0.041(2)	-0.002(2)	0.0008(18)	0.006(2)
N108	0.040(3)	0.030(3)	0.044(3)	0.004(2)	-0.001(2)	0.002(2)
N109	0.033(3)	0.032(2)	0.047(3)	0.006(2)	0.000(2)	-0.002(2)
N106	0.049(3)	0.026(2)	0.035(3)	0.003(2)	0.003(2)	0.003(2)
N103	0.040(3)	0.038(3)	0.053(3)	-0.007(3)	0.009(3)	-0.008(2)
N208	0.044(3)	0.037(3)	0.037(3)	0.004(2)	0.004(2)	0.004(2)
N209	0.037(3)	0.035(3)	0.040(3)	0.004(2)	-0.001(2)	0.000(2)
N206	0.055(3)	0.046(3)	0.046(3)	0.013(3)	0.001(2)	-0.005(3)
N203	0.045(3)	0.067(4)	0.056(4)	-0.003(3)	0.011(3)	-0.017(3)
C102	0.040(3)	0.032(3)	0.048(4)	-0.014(3)	0.007(3)	-0.004(3)
C107	0.045(3)	0.021(3)	0.035(3)	-0.004(3)	0.008(3)	0.001(2)
C110	0.036(3)	0.041(3)	0.040(3)	0.009(3)	0.001(2)	0.001(3)
C117	0.051(4)	0.035(3)	0.044(4)	0.000(3)	0.012(3)	0.006(3)
C113	0.051(4)	0.034(3)	0.043(4)	0.009(3)	0.003(3)	-0.001(3)
C111	0.057(4)	0.039(3)	0.035(3)	0.007(3)	-0.003(3)	-0.010(3)
C114	0.058(4)	0.057(4)	0.060(4)	0.010(4)	-0.005(3)	0.007(3)
C115	0.087(5)	0.052(4)	0.054(4)	0.022(4)	0.010(4)	0.003(4)
C118	0.041(3)	0.030(3)	0.049(4)	0.013(3)	0.002(3)	0.002(2)
C125	0.043(3)	0.036(3)	0.053(4)	-0.003(3)	-0.004(3)	-0.004(3)
C121	0.037(3)	0.045(4)	0.042(4)	0.001(3)	0.004(3)	0.002(3)

C119	0.042(3)	0.062(4)	0.039(3)	0.010(3)	0.010(3)	0.008(3)
C123	0.057(4)	0.060(5)	0.072(5)	-0.000(4)	0.021(4)	-0.012(4)
C122	0.051(4)	0.072(5)	0.048(4)	-0.002(4)	-0.011(3)	0.008(4)
C104	0.040(3)	0.035(3)	0.045(3)	-0.019(3)	0.004(3)	-0.003(3)
C202	0.043(4)	0.048(4)	0.040(3)	-0.004(3)	0.006(3)	0.001(3)
C207	0.041(3)	0.030(3)	0.031(3)	0.001(3)	0.002(2)	-0.000(3)
C210	0.030(3)	0.038(3)	0.039(3)	0.010(3)	-0.007(2)	0.004(2)
C211	0.049(3)	0.035(3)	0.035(3)	-0.001(3)	-0.004(3)	-0.005(3)
C213	0.052(4)	0.038(3)	0.034(3)	0.004(3)	-0.006(3)	-0.003(3)
C217	0.050(4)	0.038(3)	0.039(3)	0.002(3)	0.005(3)	0.009(3)
C215	0.061(4)	0.062(4)	0.051(4)	0.022(4)	-0.001(3)	-0.006(3)
C214	0.051(4)	0.054(4)	0.053(4)	0.005(3)	-0.011(3)	0.003(3)
C218	0.046(3)	0.040(3)	0.042(3)	0.011(3)	0.000(3)	-0.003(3)
C219	0.053(4)	0.071(5)	0.030(3)	-0.000(3)	0.002(3)	0.000(3)
C221	0.044(4)	0.058(4)	0.045(4)	-0.000(3)	-0.000(3)	-0.002(3)
C225	0.048(4)	0.043(4)	0.054(4)	0.000(3)	-0.015(3)	0.014(3)
C223	0.052(4)	0.084(6)	0.075(5)	0.015(5)	-0.003(4)	-0.010(4)
C222	0.054(4)	0.074(5)	0.055(4)	-0.010(4)	-0.015(3)	0.000(4)
C204	0.052(4)	0.056(4)	0.055(4)	0.007(4)	0.001(3)	-0.009(3)

Appendix II – Further ^{1}H NMR Studies on Triazine 108

NMR spectra were recorded of a 50 mg sample of **108** in toluene d_8 on a Bruker AMX500 spectrometer equipped with a 5 mm inverse broadband z-gradient probehead. Probe temperature calibrations were carried out with a sample of neat MeOH (+ trace HCl). Saturation transfer experiments were performed by presaturating a target resonance for a period of 1 second and then recording the 1D proton spectrum. Once exchange partners had been identified by this method, exchanging (protonated) carbon sites were readily identified with a gradient-selected ^{1}H-^{13}C correlation (HMQC) recorded at 203 K.

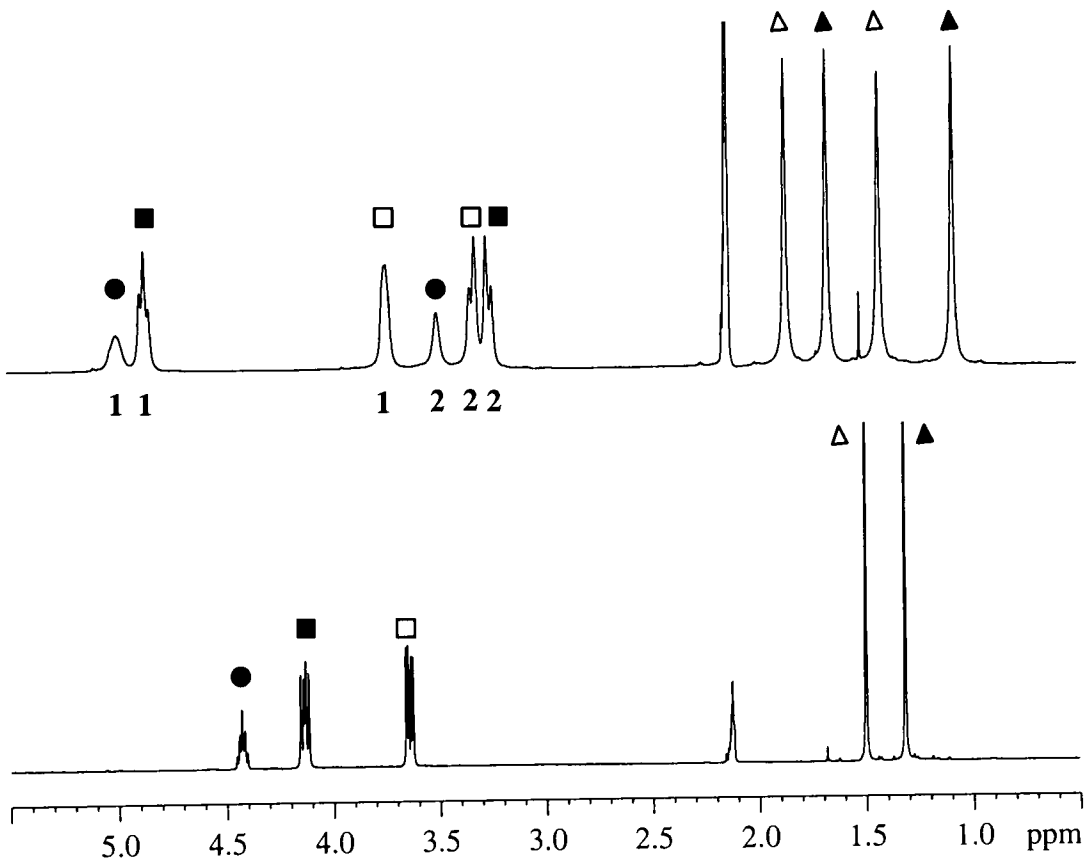


Figure I. Summary of saturation transfer experiments showing mutually exchanging sites.

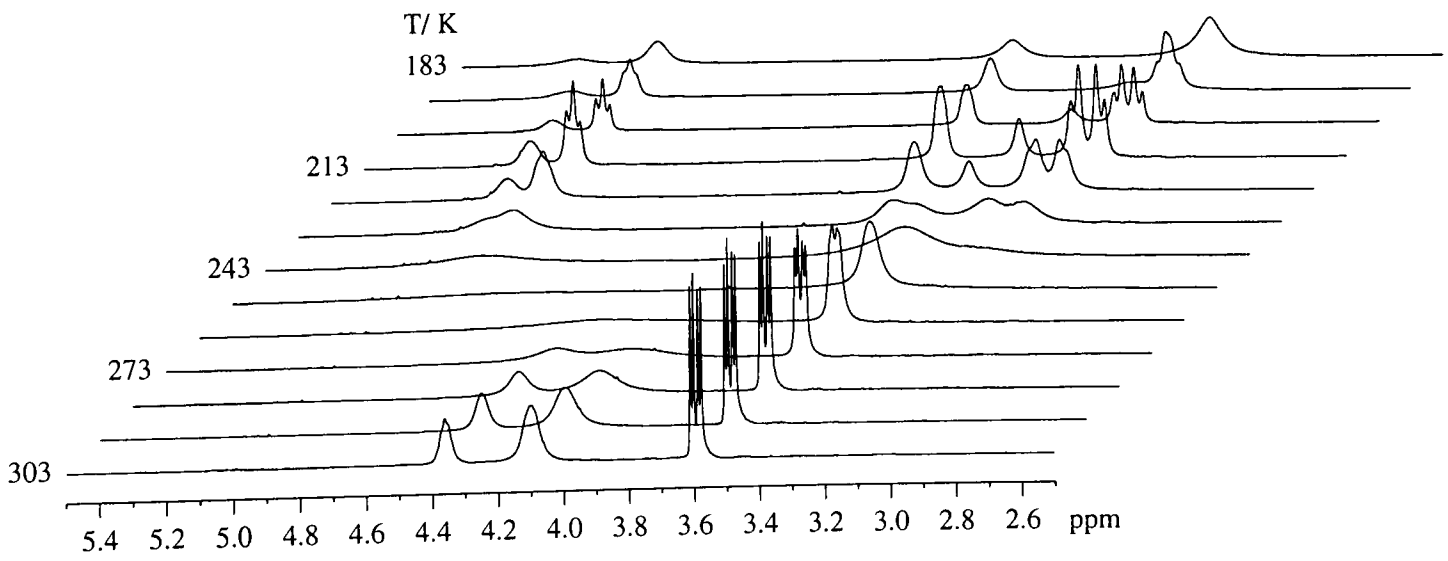


Figure II. Stack plots of variable temperature ^{1}H NMR experiments.

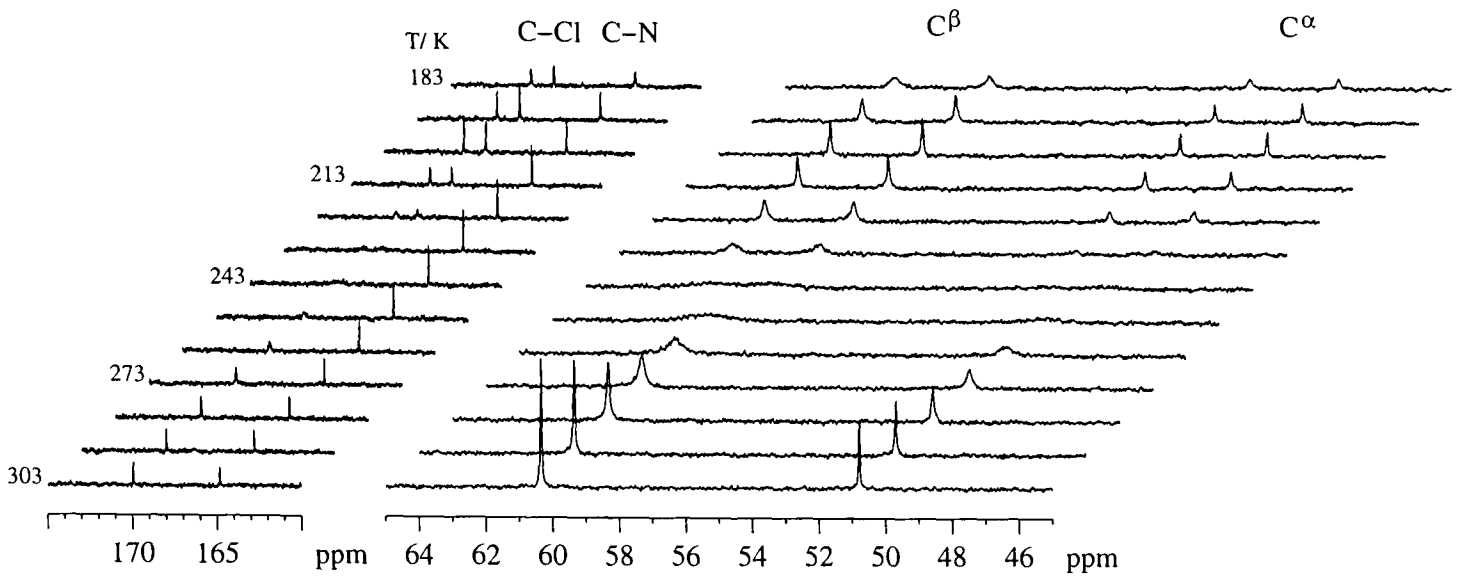


Figure III. Stack plots of variable temperature ^{13}C NMR experiments.