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ORCHESTRATION OF REACTIONS ON GLYCOLURIL TEMPLATES

By

CHRISTOPHER N. COW, B.Sc.E.

A Thesis

Submitted to the School of Graduate Studies

in Partial Fulfillment of the Requirements

for the Degree

Doctor of Philosophy

Department of Chemistry

McMaster University

ORCHESTRATION OF REACTIONS ON GLYCOLURIL TEMPLATES

DOCTOR OF PHILOSOPHY (1997) **McMaster University**

(Chemistry) **Hamilton, Ontario**

TITLE: Orchestration of Reactions on Glycoluril Templates

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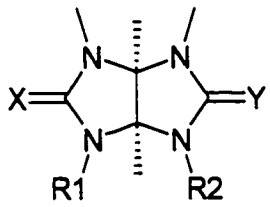
SUPERVISOR: Dr. Paul Harrison

NUMBER OF PAGES: xxii, 227

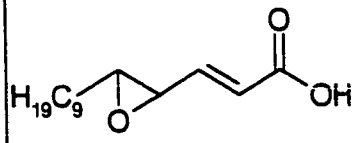
ABSTRACT

Glycoluril **1** has been shown to act as a template, facilitating intramolecular Claisen-type condensations between bound acyl units. Repetitive acylations, condensations, and functional group manipulations allow the synthesis of complex structures from simple starting materials. Thus, the natural product tetradec-2-enoic acid-4,5-epoxide **2** was prepared by condensation on **1** of decanoic acid with two units of acetate. The 1-(3'-oxododecanoyl) glycoluril **3** was prepared from **1** via **4**. Conversion to the dodecenoyl derivative **5** (2 steps), followed by a second cycle of acetylation, condensation, reduction and dehydration provided tetradeca-2,4-dienoyl glycoluril **6**. Direct cleavage to the carboxylic acid, followed by epoxidation gave **2**.



1, 3 - 19

1. X = Y = O, R1 = R2 = H
3. X = Y = O, R1 = $C(O)CH_2C(O)C_9H_{19}$, R2 = H
4. X = Y = O, R1 = $C(O)CH_3$, R2 = $C(O)C_9H_{19}$
5. X = Y = O, R1 = $C(O)CH{=}CH\text{-}C_9H_{19}$, R2 = H
6. X = Y = O, R1 = $C(O)CH{=}CH\text{-}CH{=}CH\text{-}C_9H_{19}$, R2 = H
7. X = S, Y = O, R1 = R2 = H
8. X = Y = S, R1 = R2 = H
9. X = O, Y = S, R1 = $C(O)CH_2R3$, R2 = H, R3 = H or Et
10. X = S, Y = O, R1 = $C(O)CH_3$, R2 = H
11. X = S, Y = O, R1 = R2 = $C(O)CH_3$
12. X = S, Y = O, R1 = H, R2 = $C(O)CH_2C(O)CH_3$
13. X = S, Y = O, R1 = $C(O)CH_2C(O)CH_3$, R2 = H
14. X = S, Y = O, R1 = $C(O)C_3H_7$, R2 = $C(O)CH_3$
15. X = S, Y = O, R1 = $C(O)CH_3$, R2 = $C(O)C_3H_7$
16. X = S, Y = O, R1 = H, R2 = $C(O)CH_2C(O)C_3H_7$
17. X = S, Y = O, R1 = C(O)CH(Et)C(O)CH_3, R2 = H
18. X = S, Y = O, R1 = $C(O)CH_2C(O)C_3H_7$, R2 = H
19. X = S, Y = O, R1 = H, R2 = C(O)CH(Et)C(O)CH_3



2

Mono- (**7**) and di-thio (**8**) analogues of **1** are readily prepared using Lawesson's reagent; this novel application of Lawesson's reagent can be extended to N-acylglycolurils, leading to monoacylmonothio derivatives (**9**) in which thionation occurs at the least hindered urea carbonyl. The thio analogues **7** and **8** are more readily acylated than **1**; acylation of **7** occurs exclusively on the NH site adjacent to sulfur to give **10**. All diacetylthioglycolurils underwent the Claisen-like condensation reaction to give acetoacetyl thioglycoluril derivatives; **11** undergoes selective deprotonation of the acetyl group adjacent to oxygen to give a mixture of **12** and **13** (2.2:1). Crossed-Claisen condensations of both isomers of acetyl-butanoyl monothioglycoluril (**14**, **15**) afforded 3-ketohexanoyl and 2-ethyl-3-ketobutanoyl thioglycolurils (**16** and **17**, **18** and **19**, respectively). Condensation of **14** led to a highly selective crossed-Claisen condensation (**16:17** 6:1); while condensation of **15** led to a reversal of regioselectivity (**18:19** 0.75:1).

The x-ray crystallographic structures of key compounds in the glycoluril cycle were compared in order to improve understanding of geometrical factors involved in the condensation reaction. Additionally, several reactions in the cycle, including the first acylation, the condensation, the reduction, and the cleavage reactions were investigated to find conditions which lead to improved yields.

ACKNOWLEDGEMENTS

I would like to thank my supervisor, Dr. Paul Harrison, for his support and encouragement over the last five years, as well as for many interesting and relevant discussions. I thank Dr. Russell Bell and Dr. William Leigh for taking the time to discuss my research, and for a number of helpful suggestions along the way. Special thanks go to my predecessor, Dr. Sengen Sun, for his help and guidance early in my project, and to the other group members, both past and present, for their input and suggestions; Dr. Louise Edwards, Dr. Endang Saepudin, Bill Riddoch and Steve Jenkins. Dr. Donald Hughes, Dr. Brian Sayer and George Timmins deserve thanks for their help in use of nmr and infrared spectrometers. Dr. Jim Britten and Cherif Matta are thanked for their contribution to this work, specifically, for determination of the x-ray crystal structures.

NSERC and McMaster University are acknowledged for financial support of this research.

To my wife Anne, without whom I'd be nothing, and my father, Dr. David Cow, who taught me how to learn and to live.

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LIST OF ABBREVIATIONS

Ac	Acetyl
Anal.	Analysis
Bn	Benzyl
Bu	Butyl
Calcd.	Calculated
CIMS	Chemical Ionization Mass Spectrometry
cm	Centimetre
d	Doublet
DCC	1,3-Dicyclohexylcarbodiimide
dd	Doublet of Doublets
dq	Doublet of Quartets
dt	Doublet of Triplets
EIMS	Electron Impact Ionization Mass Spectrometry
eq.	Equivalent(s)
Et	Ethyl
EtOAc	Ethyl Acetate
FAS	Fatty Acid Synthase
FTIR	Fourier Transform Infrared Spectroscopy
h	Hour(s)
HRMS	High Resolution Electron Impact Mass Spectrometry

IR	Infrared Spectroscopy
LDA	Lithium Diisopropylamide
LiO^{t}Am	Lithium *tert*-amylate [Lithium 1,1-dimethylpropoxide]
M	Molarity
M^+	Molecular Ion
Me	Methyl
m/z	Mass / Charge Ratio
mL	Millilitre
mmol	Millimole
mp	Melting Point
MS	Mass Spectrometry
□L	Microlitre
nm	Nanometre
nmr	Nuclear Magnetic Resonance
PKS	Polyketide Synthase
ppm	Parts Per Million
q	Quartet
s	Singlet
s.m.	Starting Material
t	Triplet
TBDMS	*tert*-Butyldimethylsilyl
THF	Tetrahydrofuran

TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
UV	Ultraviolet

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CHAPTER 1: Introduction

1.1 Enzyme Mimics and Models

1.1.1 How Enzymes Work

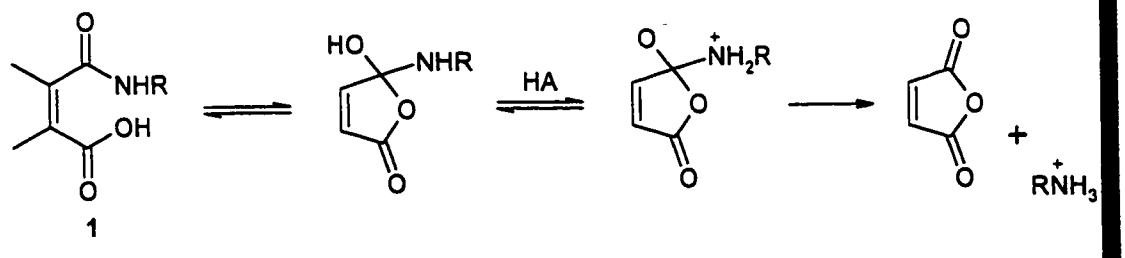
Enzymes are special proteins which act as catalysts in living systems to allow chemical reactions to proceed swiftly and selectively. They facilitate a number of reactions which would otherwise not occur, or occur far too slowly to be of practical use. Enzyme-catalysed reactions exhibit a high degree of specificity and efficiency; properties which have elicited interest by synthetic organic chemists. Enzyme efficiency results from binding and stabilization of the transition state of the reaction, and enzymes can provide multiple catalytic functionalities which operate simultaneously to greatly enhance the reactivity. Almost all enzymes exist at physiological *p*H, but the enzyme active sites can have acidic or basic residues, thus influencing the local *p*H significantly and allowing for acid-base type chemistry to occur. In addition, enzymes recognize and respond to molecules other than their specific substrates and products, which act as molecular switches for the cell and allow for biofeedback.

An understanding of how enzymes work can lead to the production of synthetic catalysts which are frequently more robust than proteins, and can easily be produced in a

pure form. Additionally, these artificial enzymes could be tailor made for almost any organic reaction of interest.

1.1.2 Enzyme Models [1]

Enzyme models, unlike real enzymes, need only confine themselves to optimizing the catalytic efficiency for the reaction of interest; they do not generally need to consider specificity for the substrate. This stems from the fact that enzymes experience a great variety of different chemicals, whereas enzyme models will normally only be exposed to the compounds of interest. Additionally, enzymes provide catalysis for each individual step in the reaction including binding of the substrate and release of the product, while enzyme models typically only catalyze the slowest chemical step in the reaction. The best models of enzymes are simple reactions which can rival the rates of their enzyme-catalyzed counterparts such as cyclizations. In particular, intramolecular nucleophilic reactions have been observed to occur very rapidly. An example of this is shown in Scheme 1.1, the cyclization of an aliphatic amide **1** with the COOH group which is held in close proximity[2].

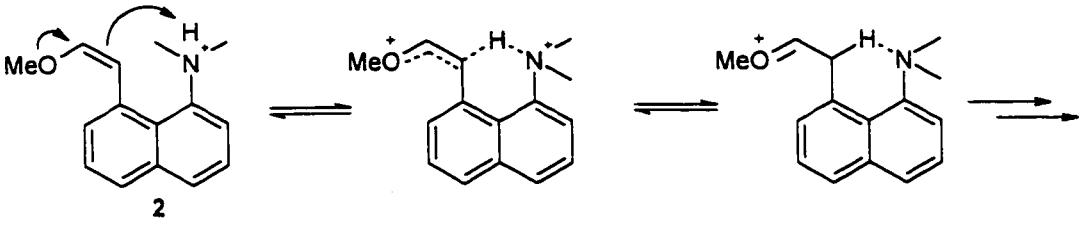


Scheme 1.1: Example of an Intramolecular Cyclization

Effective molarity (EM) is often used to measure the efficiency of intramolecular catalysis; it is the ratio of the first order rate constant for the intramolecular reaction to the second order rate constant for the intermolecular reaction that proceeds by the same mechanism under identical conditions. Essentially, the effective molarity indicates how catalytic efficiency relates to structure in systems that are designed to bring the functional groups into close proximity in a manner analogous to that which occurs in an enzyme-substrate complex.

A number of studies have led to the following generalizations; that catalysis is highly efficient in cyclization reactions which involve formation of bonds between heavy atoms. Typical EM's of $10^8 - 10^9$ M have been observed in flexible systems; in systems which have been designed to relieve ground state strain in the reaction, effective molarities of up to 10^{13} M have been reported. Also, intramolecular reactions which involve rate determining proton transfer (general acid / general base catalysis) are far less efficient (EM's ~ 10 M). However, some systems, which have been specially designed to have strong intramolecular hydrogen bonds have effective molarities of up to 10^6 M. This situation is analogous to the hydrogen bonds which are frequently formed in enzymes to facilitate similar reactions, since general acid or base catalysis forms the majority of enzyme-mediated mechanisms, and thus must occur very efficiently. In particular, enolizations are key steps in enzyme-catalyzed aldol condensations. The key requirement for efficient proton transfer catalysis is dynamic binding of the proton in a strong transition state hydrogen bond. Kirby and O'Carroll[3] have shown that even C-H protons can become acidic enough to be involved in strong hydrogen bonding in

enolization reactions. Thus, the enol ether **2** exhibits strong hydrogen bonding between the α-hydrogen and the dimethylammonium group (Scheme 1.2).



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Scheme 1.2: Example of Intramolecular C-H Hydrogen Bond

The E.M. of the dimethylammonium group in this reaction is on the order of 10^6, and compound **2** has a half-life of only 10 s at 39 °C.

1.1.3 Enzyme Mimics

Enzyme mimics resemble enzymes much more than the models, since they generally exhibit some of the binding effects, as well as the catalysis observed in the intramolecular models. One of the most popular and enduring enzyme mimics is represented by the cyclodextrin class of compounds, which have been very well studied[1]. Cyclodextrins are cyclic oligomers of α-D-glucose, and have a central hydrophobic pocket with functional hydroxyl groups on both rims. One of these rims is slightly larger than the other since the secondary OH groups are all aligned on one face. Furthermore, cyclodextrins are readily available in 3 sizes: the α-cyclodextrin has a cavity diameter of ~ 5 Å, the β-cyclodextrin of ~ 7 Å, and the □-cyclodextrin has a cavity diameter of ~ 9

Å; thus, the cyclodextrin can be chosen appropriately to best fit the guest molecule of choice.

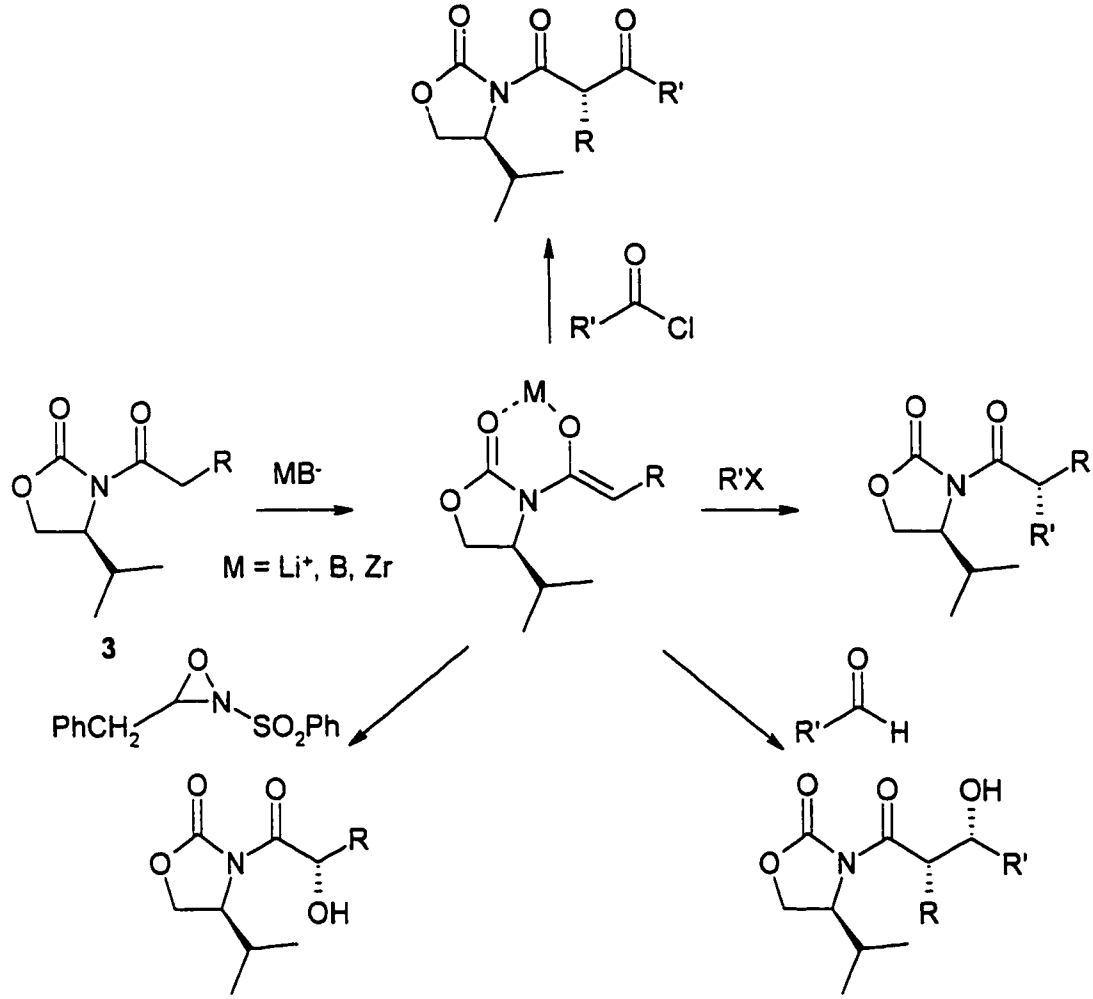
Unmodified cyclodextrins catalyze a number of rapid reactions, such as the hydrolysis of nitrophenyl esters[4]. Chemical modifications of the cyclodextrin rim have also been successful; Breslow *et al.*[5] have used a β-cyclodextrin moiety carrying 2 imidazole groups, both of which are involved in a push-pull type mechanism in the hydrolysis of a cyclic phosphodiester. This result is quite analogous to similar reactions in the active sites of a number of enzymes. Breslow has also used the same modified cyclodextrin to catalyze the enolization of a bound ketone: *p-tert*-butylacetophenone[6] and for catalysis of an intramolecular aldol condensation[7] which cyclized a keto aldehyde into a *trans*-keto alcohol, although with only minimal enantiomeric induction (<10% ee).

In addition to the cyclodextrins, a wide variety of synthetic hosts have also been used as enzyme mimics, including cucurbituril, a molecule derived from glycoluril.

1.2 Evans' Oxazolidinones

Evans' oxazolidinone compounds have been used for many years as chiral auxiliaries for a number of intermolecular reactions which exhibit excellent enantio- and diastereoselectivity. The oxazolidinones are derived from (*S*)-valinol (**3**) or (1*S*, 2*R*)-norephedrine and either phosgene or diethyl carbonate. These two chiral auxiliaries are complementary, leading to opposite enantiomers. A wide variety of chemistry has been

performed on the acyl oxazolidinone adducts (eg. **3**) (Scheme 1.3), including alkylations[8], acylations[9], aldol reactions[10] and α-hydroxylation reactions using Davis' reagent[11].



Scheme 1.3: Summary of Evans' Oxazolidinone Chemistry

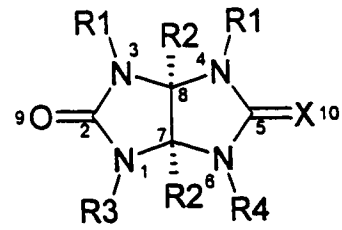
All of the above reactions exhibit excellent diastereoselection, frequently in excess of 95 %, and in the case of the aldol condensation reaction, this selectivity exceeds 400 : 1. The oxazolidinone chiral auxiliaries work by using the base to hold the two

carbonyl groups together in the enolate; the substituent at the chiral centre then blocks one face of the enolate from attack. An additional selectivity is observed since, in the case of aldehydes, the base also chelates with the incoming aldehyde, leading to the extremely high selectivity observed in these cases.

The other key factor in this system is the facile removal of the chiral auxiliaries, either to carboxylic acid derivatives by alkoxides, or directly to the alcohols under reductive conditions with $LiAlH_4$.

This methodology has been used and its utility illustrated in the total synthesis of a variety of natural products, including (+)-Calyculin A[12] and Cytovaricin[13], among others[14]. These oxazolidinone chiral auxiliaries have since been used by many other groups, and have become recognized synthons in general organic synthesis.

1.3 Glycolurils



4: R1 - R4 = H, X = O
5: R1 = R2 = Me, R3 = R4 = H, X = O
6: R1 = R2 = Me, R3 = $COCH_3$, R4 = H, X = S

Figure 1.1: Structure of Glycolurils

Glycolurils are small, rigid *cis*-fused bicyclic compounds which contain a number of functional sites (Figure 1.1). The parent compound, glycoluril **4**, has four hydrogen bond donors (NH groups) and two hydrogen bond acceptors in the form of carbonyl groups. It is very polar, and is insoluble in most organic solvents, although it does exhibit some solubility in methanol and DMSO. Using various synthetic methods, starting with either the glycoluril or by modifying its building blocks, urea and glyoxal, it is possible to obtain a wide variety of different structures, with different substitution patterns. The chemistry available for use with glycolurils is quite varied, and does not always follow the chemistry used for amides or even for ureas, making this a very interesting and challenging building block in a wide variety of systems.

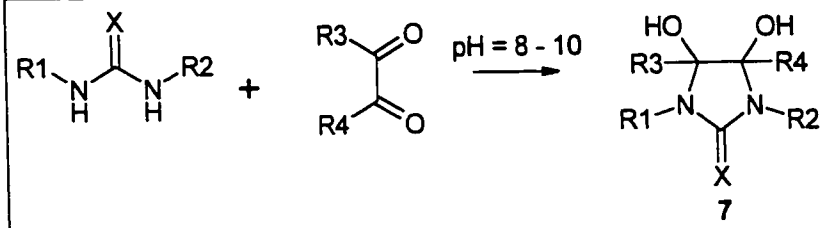
1.3.1 Nomenclature Conventions

There are several different conventions which are typically used to name glycoluril structures; this ambiguity can easily cause confusion. The IUPAC nomenclature for glycoluril **5** is 1,4,5,6-tetramethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione. Glycolurils have also been named as derivatives of perhydroimidazo[4,5-*d*]imidazol-2,5-dione. To complicate things further, there are three different numbering conventions associated with the glycoluril trivial name; compound **5** is thus either 3,3a,4,6a-tetramethylglycoluril, 1,6,7,8-tetramethylglycoluril, or 3,4,7,8-tetramethylglycoluril, depending on the numbering system chosen. To maintain consistency with the acyl derivatives of **5**, whose numbering is unambiguous, and to

avoid unnecessary confusion, the latter system will be used throughout this document. In the case of thioglycoluril derivatives, the nomenclature becomes even more confusing, since the thione takes precedence over the carbonyl, but the nitrogen substitution frequently, in our work at least, contradicts this. For simplicity's sake and to maintain consistency, substitution at the nitrogen in these compounds will take priority, followed by the presence of a thione. Thus, compound **6** is 1-acetyl-3,4,7,8-tetramethyl-5-thioglycoluril.

1.3.2 Synthesis of Glycolurils and Related Compounds

The first reported synthesis of glycolurils was by Schiff in 1877[15]; in spite of this, a number of more recent reports have illustrated that the synthesis is not always straightforward. Addition of 2 equivalents of urea to 1 equivalent of glyoxal in an acidic medium does lead to compound **4**, but simple modifications of either the urea or the α-dicarbonyl compound can have dramatic effects on the chemistry. The situation becomes even more complex when a thiourea is utilized instead of a urea. All reported ureas and thioureas proceed via the same intermediate, a diol (**7**) which arises from addition of one unit of urea (thiourea) with the dione (Scheme 1.4). This diol is isolable for many of these reactions at neutral or slightly alkaline *p*H[16], and an x-ray crystal structure has been obtained for **7a**[17]. The results show this compound to be a *trans*-diol; presumably the same stereochemistry also applies for intermediates **7b-l**.



X = O or S

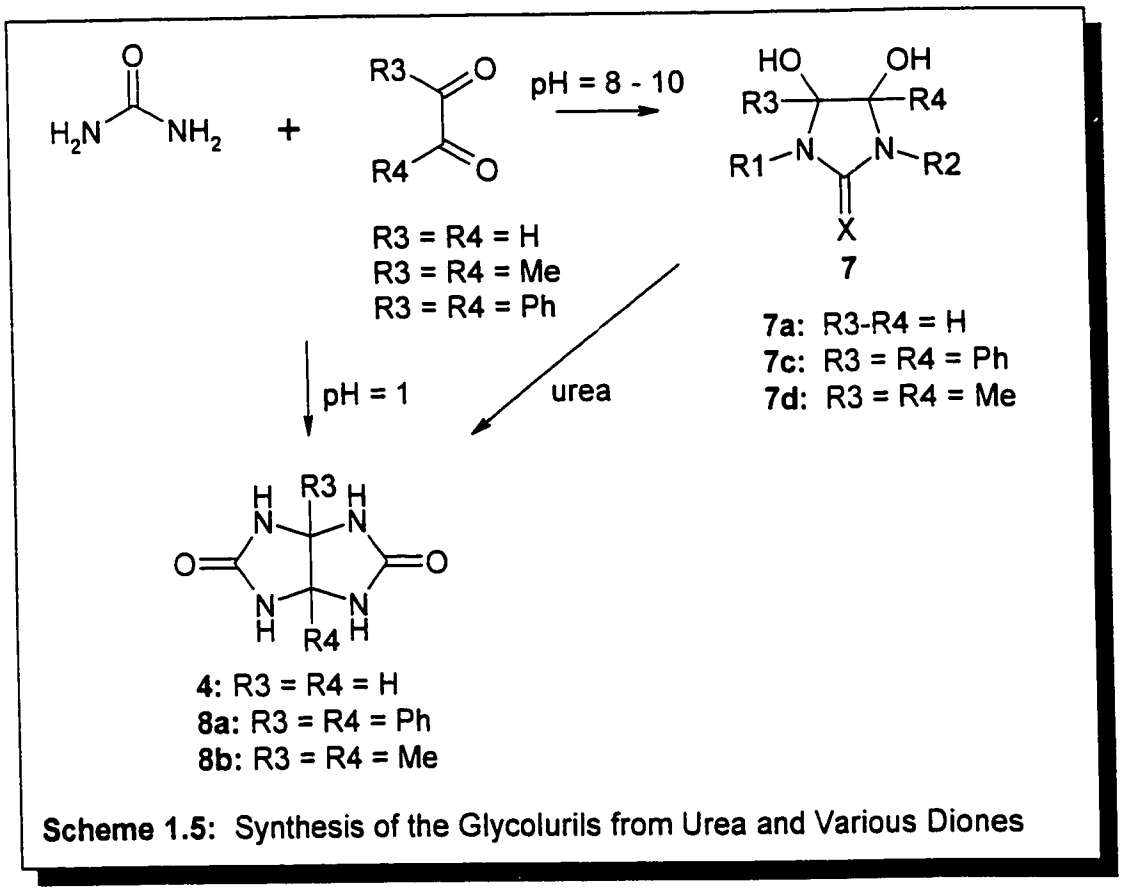
R1 = R2 = H
R1 = H, R2 = Me
R1 = R2 = Me

R3 = R4 = H
R3 = R4 = Me
R3 = R4 = Ph
R3 = H, R4 = Ph
R3 = Me, R4 = Ph

7a: X = O, R1-R4 = H
7b: X = O, R1-R3 = H, R4 = Ph
7c: X = O, R1 = R2 = H, R3 = R4 = Ph
7d: X = O, R1 = R2 = H, R3 = R4 = Me
7e: X = O, R1 = H, R2-R4 = Me
7f: X = O, R1-R4 = Me
7g: X = O, R1 = H, R2 = Me, R3 = R4 = Ph
7h: X = O, R1 = R2 = Me, R3 = R4 = Ph
7i: X = S, R1-R4 = H
7j: X = S, R1 = R2 = H, R3 = R4 = Ph
7k: X = S, R1 = H, R2 = Me, R3 = R4 = Ph
7l: X = S, R1 = R2 = Me, R3 = R4 = Ph

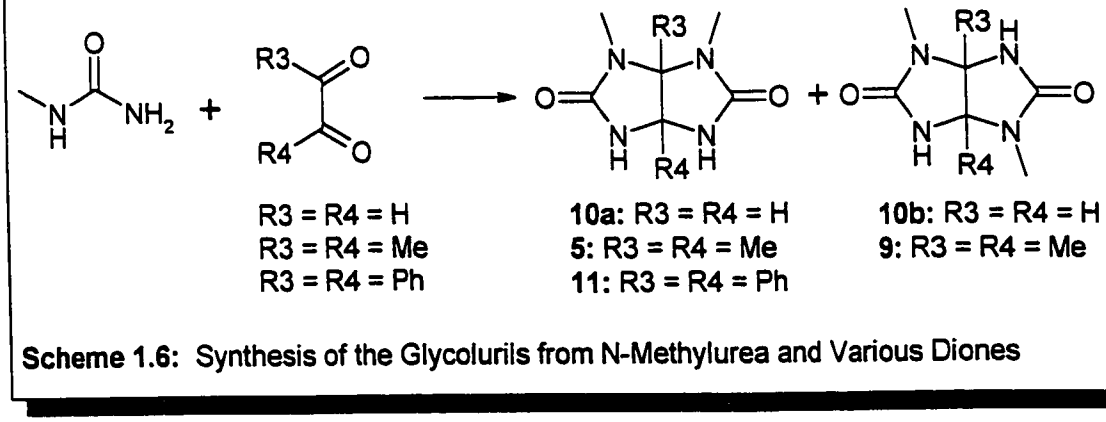
Scheme 1.4: Synthesis of the Intermediate Diol **7** on the Route to Glycolurils

In the case of the ureas, addition of an identical urea to that used in the synthesis of **7** leads to the glycoluril structures in most cases, or the reaction can be performed in one step via the addition of an excess of urea to the dione in an acidic medium. These conditions lead directly to the glycoluril structures for unsubstituted or monosubstituted ureas. In particular, 2 equivalents of urea + glyoxal leads to intermediate **7a** on the way to glycoluril **4**. This reaction leads to analogous products (**8a**, **8b**) if the dione is changed to benzil or butane-2,3-dione[18,19] (Scheme 1.5).



Scheme 1.5: Synthesis of the Glycolurils from Urea and Various Diones

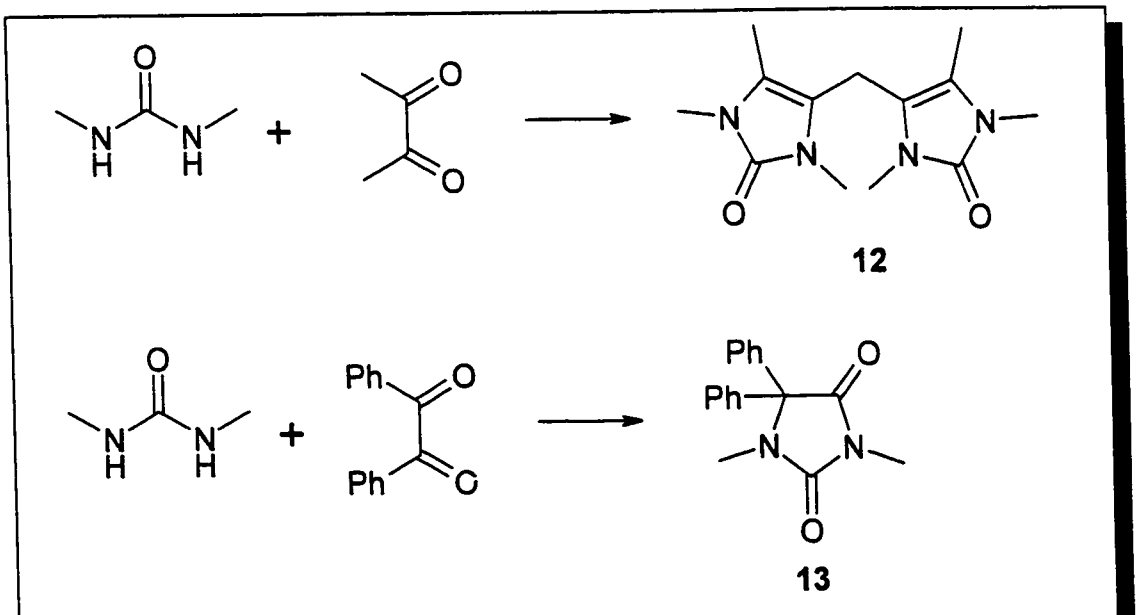
Reaction of *N*-Methylurea[18,19] with the same diones under acidic conditions leads to analogous glycoluril products (Scheme 1.6).



Scheme 1.6: Synthesis of the Glycolurils from N-Methylurea and Various Diones

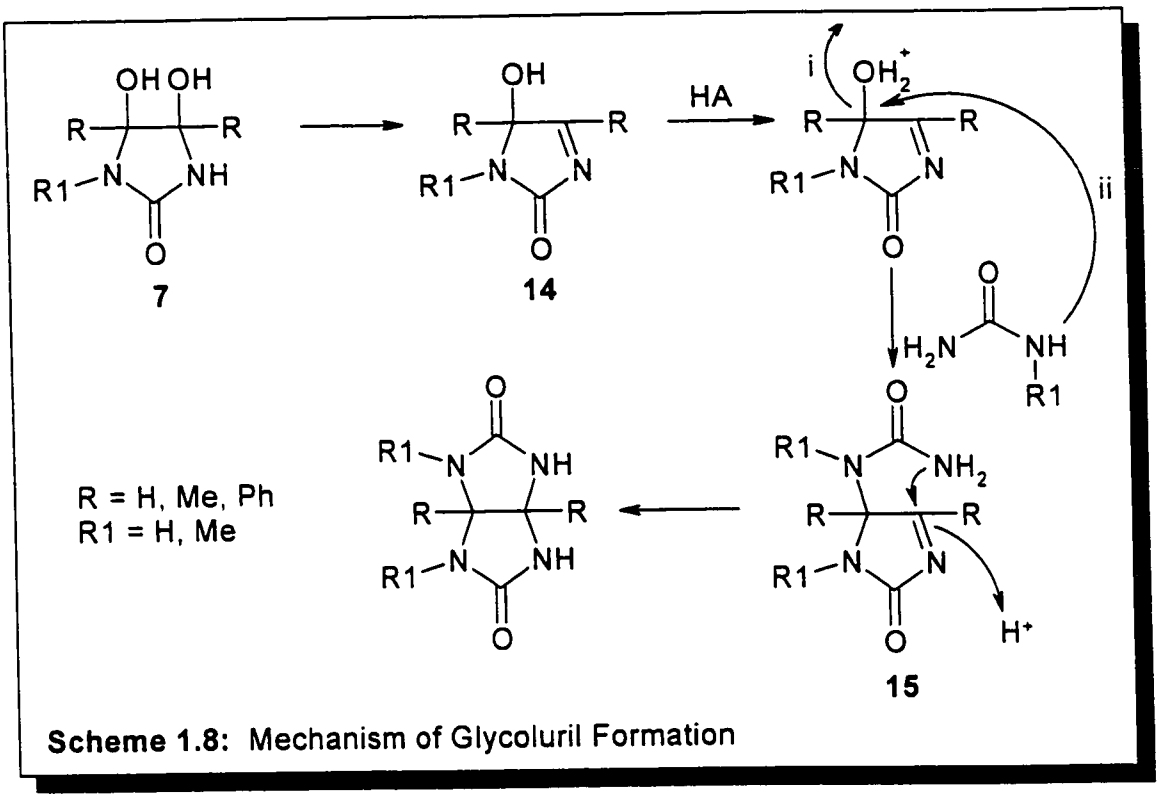
N-Methylurea reacts with butane-2,3-dione to give a mixture of the two possible products, the *syn*-compound 3,4,7,8-tetramethylglycoluril **5** and the *anti*-compound 3,6,7,8-tetramethylglycoluril **9**, in approximately equal amounts. Reaction of *N*-methylurea with glyoxal similarly results in the production of the two regioisomers **10a** and **10b**; however, reaction of *N*-methylurea with benzil results in the production of only the *syn*-isomer **11**.

Reactions with *N,N'*-dimethylurea[18,19] do not lead to glycoluril structures on addition of either butane-2,3-dione or benzil. Instead, the condensation of *N,N'*-dimethylurea and butane-2,3-dione leads to a complex product **12** (Scheme 1.7). The condensation of *N,N'*-dimethylurea and benzil, on the other hand, leads to the hydantoin **13** as the only isolable product. The hydantoin arises from a phenyl migration, and both products have been explained through an examination of the mechanism of formation of the glycolurils.



Scheme 1.7: Products of Condensation of 1,3-Dimethylurea with Diones.

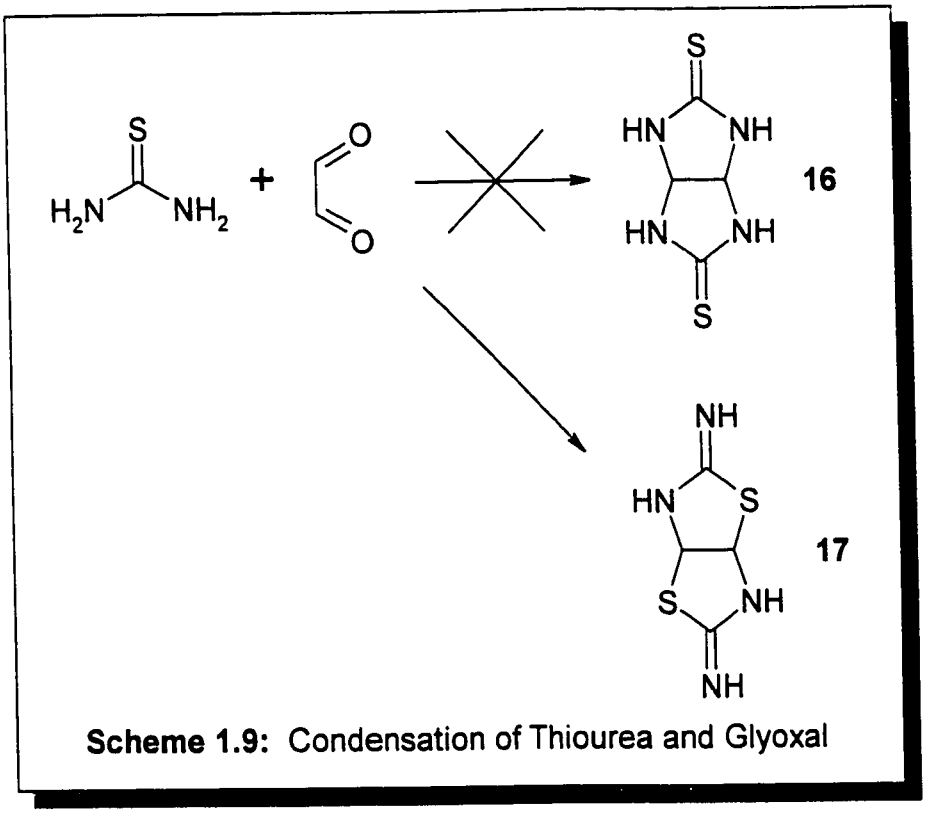
The mechanism of glycoluril formation is postulated to occur as follows from the intermediate **7** (Scheme 1.8). Diol **7** eliminates water to give compound **14**, which



Scheme 1.8: Mechanism of Glycoluril Formation

contains a double bond to one of the ring nitrogens. S_N1 displacement of water by a nitrogen on the incoming urea forms intermediate **15**, which then closes rapidly to the glycolurils (Scheme 1.8). In general, the more substituted nitrogen of the urea is more nucleophilic, depending on the structure of R1, but it is also more hindered, which is why both **5** and **9** are produced in the reaction of *N*-methylurea and butanedione. This mechanism also explains why *N,N'*-dimethylurea does not give glycoluril products, since the *N*-methyl group prevents the double bond in compound **14** from forming, thus leading to other products.

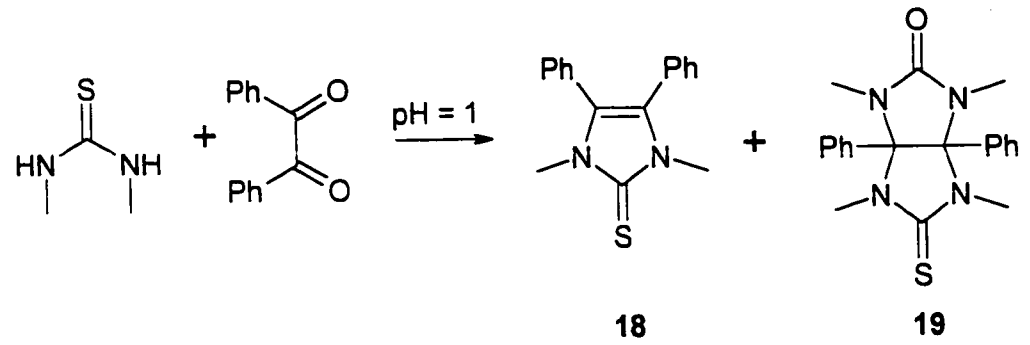
In 1930, Pauly[20] reported that thiourea and glyoxal react to give the dithioglycoluril **16**; however, this has been disputed, since Long *et al.* reported in 1982[21] that the compound formed was in fact the diiminodithiadiazabicyclooctane **17** (Scheme 1.9).



Scheme 1.9: Condensation of Thiourea and Glyoxal

Broan and Butler have investigated the reactions of thioureas with benzil in both alkaline[22] and acidic[23] conditions, and have shown that quite different products are obtained. Under acidic conditions, very small amounts of thioglycoluril compounds are formed. Reaction of *N,N'*-dimethylthiourea with benzil leads to the unsaturated compound **18**, via reductive loss of 2 water molecules from **71**, as the major product, along with a small amount of a mixed glycoluril **19** (Scheme 1.10). The mixed glycoluril

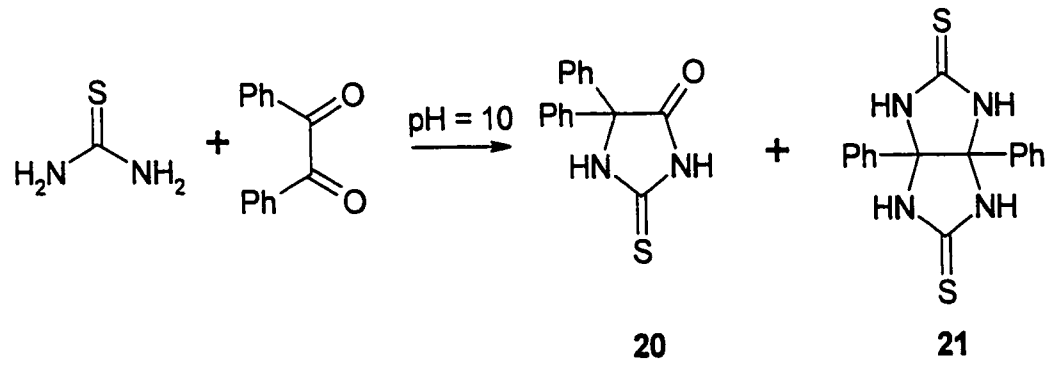
arises from condensation of **71** with *N,N'*-dimethylurea, which is formed through an oxygen-sulfur exchange between thiourea and one of the hydroxyl groups on the diol.



18 **19**

Scheme 1.10: 1,3-Dimethylthiourea and Benzil Condensation in Acidic Conditions

N-Methylthiourea and thiourea both react with benzil in acidic conditions to give small amounts of the analogues of **19** (minus appropriate methyl groups), along with formation of a disulfide derived from **18** by oxidation as the major product.



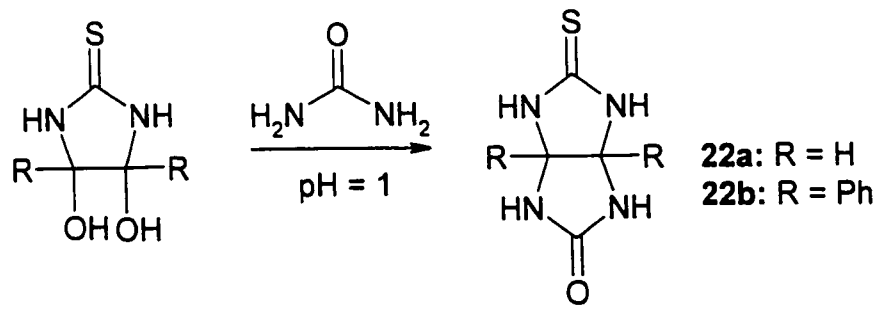
20 **21**

Scheme 1.11: Thiourea and Benzil Condensation under Alkaline Conditions

In contrast, reaction of *N,N'*-dimethylthiourea with benzil under alkaline conditions leads to formation of the diol **71** as the only isolable product. Condensation of

N-methylurea with benzil under identical conditions leads to thiohydantoins as the only products, while thiourea itself condenses with benzil to give a mixture of the thiohydantoin **20** and the desired dithioglycoluril **21** (Scheme 1.11).

In addition to these studies, Murray and Whelan[13] have reported the synthesis of mixed O-S glycolurils (**22a**, **22b**), starting from compounds **7i** or **7j** by addition of a urea under acidic conditions (Scheme 1.12). It is interesting, although not surprising, to find that the opposite strategy, making oxygen analogs of **7**, then reacting with thioureas, did not lead to glycoluril structures.

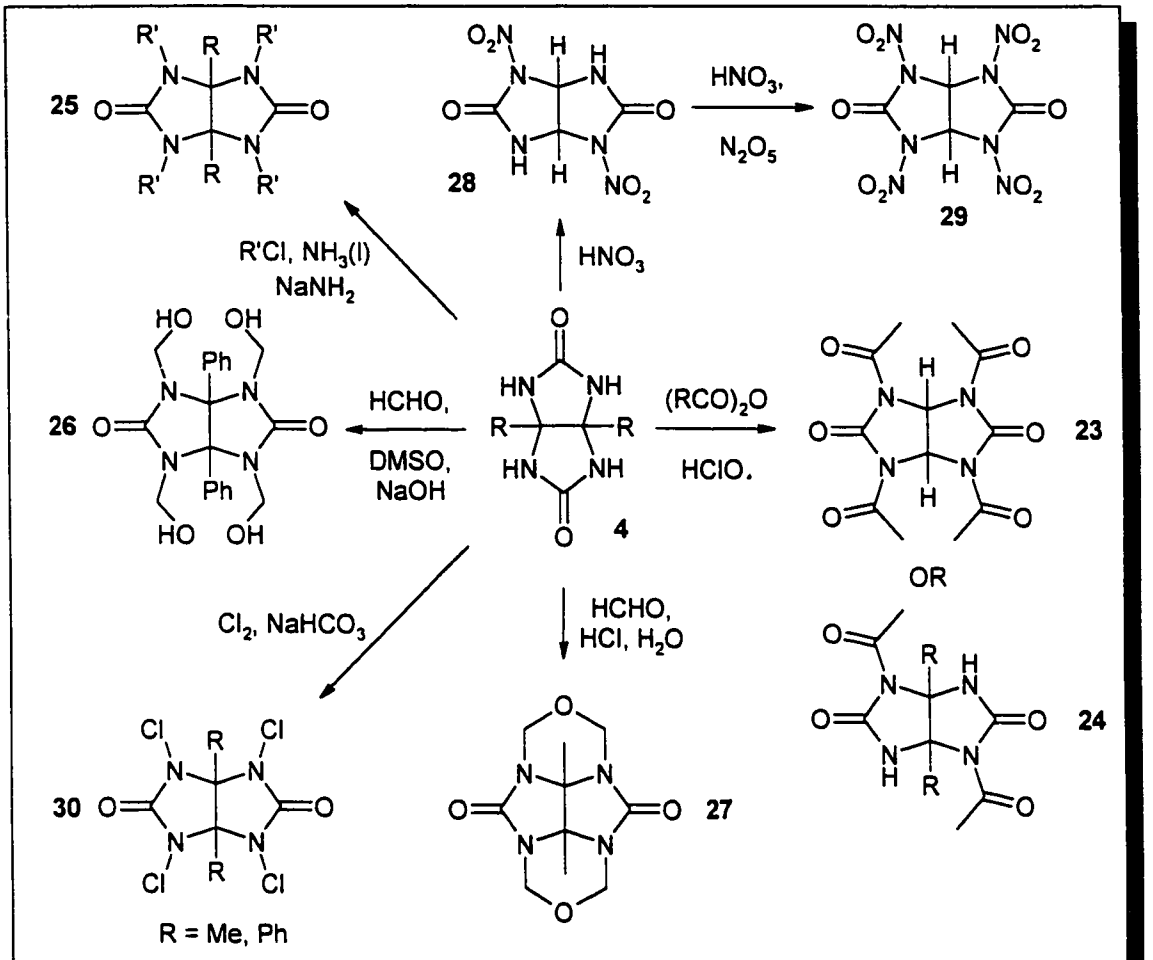


Scheme 1.12: Formation of Mixed O-S glycolurils

Eres'ko *et al.*[24] report that the condensation of **7a** with thiourea does lead to the mixed O-S glycoluril, but only in very low (5-6 %) yield. Toray Industries have a Japanese patent[25] on a method of synthesizing a dithioglycoluril which contains a cyclohexane bridge in good yields (71 %) from 2-aminocyclohexanone oxime and thiocyanates in acetic acid. Finally, Takahashi and Myadai[26] describe a synthesis of 1,4-diaryl dithioglycolurils by the addition of diimines to TMS-protected thiocyanates.

1.3.3 Chemistry of Glycolurils

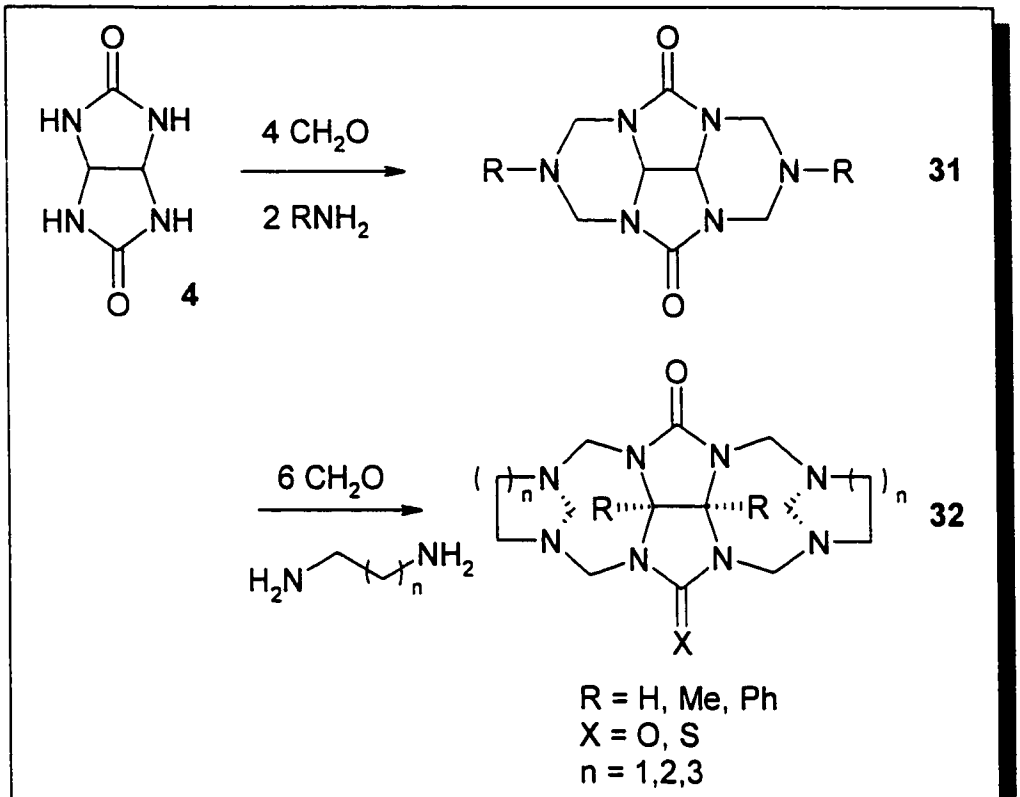
Glycolurils can be exposed to a number of different conditions to give a wide variety of compounds. Reaction of glycoluril **4** with an acyl anhydride such as acetic anhydride under acidic conditions gives the tetraacetylglycoluril adduct **23**, or the diacetylglycoluril adduct **24** in good yield if the anhydride is limited to ~2.5 equivalents (Scheme 1.13)[27]. *N*-Alkylation of **4** can be accomplished by the use of an alkyl chloride in liquid ammonia under basic conditions to give the tetra-*N*-alkyl derivative **25**[28]. Another general reaction of glycoluril involves addition of paraformaldehyde in DMSO and NaOH to give the tetraalcohol structure **26**[29], which can then be further functionalized. Reaction with formaldehyde and HCl in water leads to the tetracyclic structure **27**[30]. Exposure of glycoluril **4** to HNO_3 at 20 – 60 °C leads to the dinitro compound **28**[31], which can then be reacted further with HNO_3/N_2O_5 at 15 °C to give the tetranitro compound **29**. Reaction of glycoluril **4** with chlorine and $NaHCO_3$ leads to the *N*-tetrachloro glycoluril **30**.



Scheme 1.13: General reactions of glycolurils

Glycolurils are also versatile progenitors of polycyclic ring systems. Reaction of **4** with formaldehyde under strongly acidic conditions leads to the nonadecacyclic cage structure of cucurbituril[32]; use of 7,8-dimethylglycoluril leads to the corresponding decamethylcucurbit[5]uril[33], so this is a somewhat general reaction. Under less stringent conditions, **4** condenses with formaldehyde in the presence of aliphatic amines to give tetracyclic derivatives **31**[34] (Scheme 1.14). Similar conditions with diamines leads to a

number of products which incorporate 6 formaldehyde and 2 diamine units per glycoluril to give compounds of type **32**[35].



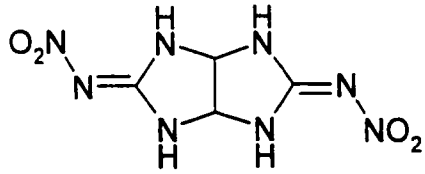
Scheme 1.14: Construction of Polycyclics Using Glycoluril

1.3.4 Uses of Glycolurils

Glycolurils have been used for a wide variety of applications, which has, in part, led to the great interest in these compounds in the literature. Glycoluril **4** has itself found industrial use as a slow release fertilizer[36], and has been observed to be a biotin analog[37]. Glycoluril is a bicyclic, *cis*-fused ring compound, each ring of which resembles the ureido ring of biotin. Additionally, all of the chemistry of biotin is thought to occur on

the ureido ring, specifically at the $N^{1'}$ nitrogen atom[38], while the remainder of the biotin structure is involved in binding to the enzymes which biotin serves. Recently, glycoluril has been shown to bind to Streptavidin[39], a tetrameric protein from *Streptomyces avidinii*, with micromolar affinity ($K_d = 2.5 \times 10^{-6}$ M). Streptavidin shows remarkable binding to biotin, with a K_d of about 10^{-14} M; crystal structures of the bound substrates show that the two molecules are bound in a similar manner, and studies by Katz *et al.* [40] concluded that the weaker binding of glycoluril compared with biotin results from the missing valerate group.

Derivatives of glycoluril **4** have been shown to have many interesting properties as well. Nitro derivatives are very powerful explosives[41]; the tetra N-nitro compound **29** is, in fact, one of the most powerful modern explosives. Another nitramine explosive (**33**)[42] has an obviously related structure (Figure 1.2), and shows remarkable thermal stability.



33

Figure 1.2: Structure of Nitramine Explosive

Alkylated glycolurils exhibit varying degrees of psychotropic behaviour[43]. The type and degree of the pharmacological activity of these alkyl glycolurils depends on the nature and the number of substituents on the glycoluril structure; tetra-*N*-alkylated

compounds (**25**) are the most active, and activity decreases rapidly with a decrease in the number of alkyl substituents. Tetraacetylglycoluril has been used as a bleaching activator[44,45], in a similar manner to other N- and O- acetyl species. This process occurs by reaction of hydrogen peroxide with the acetyl group to make peroxyacetic acid, which has greatly improved bleaching efficiency compared to hydrogen peroxide. Tetraacetylglycoluril also acts as an acetyl donor[46], transferring four acyl groups in two stages when reacting with nucleophiles. The first stage transfers two acyl groups, and can involve nucleophiles such as amines, phenols, and thiols, and occurs under mild conditions. The second stage transfers the last two acyl groups, and requires harsher conditions. A tetra *N*-chloro glycoluril **30** forms the basis for the IodoGen method of radio-iodination of biomolecules[47]. It acts as a mild, solid-phase reagent for protein iodination, and is more efficient than chloramine-T, one of the standard reagents for this labeling. Specifically, Iodogen produces a 3- to 17-fold greater specific reactivity without sacrificing viral or cellular integrity, is simpler to use, and unlike the use of lactoperoxidase-catalysed iodination, does not require the presence of extraneous proteins to initiate the reaction[48].

1.3.5 Glycolurils as Molecular Clips and Cages

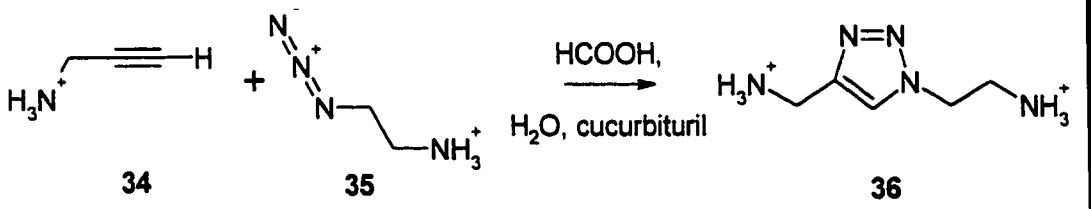
1.3.5.1 Cucurbituril

As mentioned in section 1.3.3, glycoluril can form a self-assembled macrocyclic molecule called cucurbituril when reacted with formaldehyde in acidic conditions. Cucurbituril is composed of six units of glycoluril bound in a macrocyclic cage by methylene bridges, and has a hydrophobic cavity measuring 5.5 Å in diameter and a 4 Å diameter hydrophilic portal at each end, composed of polar carbonyl groups. In contrast, decamethylcucurbit[5]uril has a slightly larger inner cavity (6 Å), but much smaller carbonyl portals, at only 2.5 Å diameter. This may limit its utility as a host, since larger molecules may not fit through the portals. The unique aspect of cucurbiturils compared with cyclodextrins and other macrocycles is their structural rigidity; this leads to exceptional specificity of complexation and high association constants. The cavity of cucurbituril is of comparable size to that of α-cyclodextrin (5.7 Å), and has been used as a host to bind alkylammonium ions[49], alkali metal cations, and NH_4^+ in acidic aqueous solutions[50]. For *N*-alkylammonium ions, the best binding was observed for *n*-butylammonium ions; 1,6-hexanediammonium ion exhibits the best binding for diammonium salts, and exhibits the strongest binding of the compounds studied (K_d = 3.6 × 10^{-7} M). Small cyclic hydrocarbons fit into the cavity, with optimal complexation for the 5-membered ring of cyclopentanemethylammonium ion, and *p*-disubstituted benzene

rings can also be encapsulated, although *m*- and *o*- disubstituted compounds are too sterically bulky to fit.

Alkali metals, on the other hand, are not encapsulated, but rather bind to sites in the planes of the carbonyl groups. Cucurbituril binds most strongly to Na^+, exhibiting weaker binding to both larger and smaller cations, and binds cations in a 1 : 2 ratio, indicating that the two rings bounded by carbonyl groups are located far enough apart not to interact significantly. In this way, cucurbituril acts in a manner similar to the crown ethers, although the more polar carbonyl groups increase the strength of the binding, leading to stronger interactions with cations than occurs in 18-crown-6.

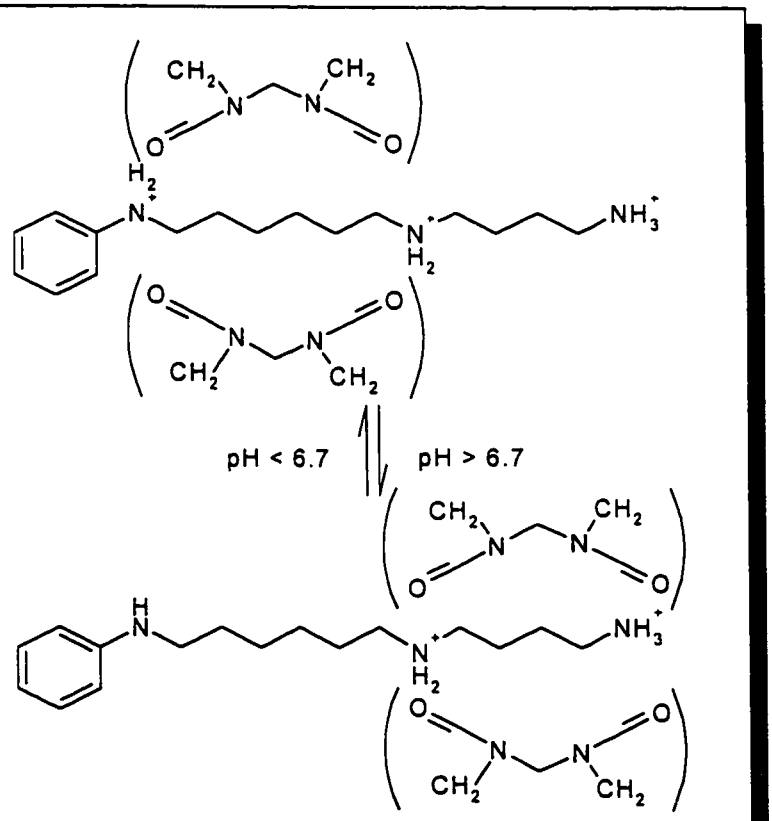
Recently, an X-ray crystal structure was obtained of a rotaxane of cucurbituril threaded with a dinitrophenyl substituted spermine unit[51]. Rotaxanes are supramolecular species in which a cyclic bead is threaded by a linear chain having bulky end groups. While cyclodextrins have been used as beads for rotaxanes[52], no crystal structures have yet been obtained, primarily because of the difficulty in obtaining X-ray quality crystals of cyclodextrins.



34 35 36

Scheme 1.15: Catalysis of a 1,3-Dipolar Cyclization by Cucurbituril

Cucurbituril has also been shown by Mock *et al.*[53] to be capable of catalytic activity in a 1,3-dipolar cyclization (Scheme 1.15). Thus, **34** and **35** react to give **36**. In the absence of cucurbituril, the reaction proceeds very slowly, and leads to a mixture of the two possible regioisomers. When a catalytic amount of cucurbituril is added, the rate experiences a 10^5-fold acceleration, and the reaction is rendered regiospecific leading to **36** as the only observed product. Interestingly, this system follows enzyme-like kinetics, including catalytic saturation, substrate inhibition, and slow product release, making this a very good enzyme mimic.



Scheme 1.16: Use of Cucurbituril as a Molecular Switch

Further work by Mock and Pierpont[54] has shown that cucurbituril can also be used as a molecular switch that uses *p*H as the trigger (Scheme 1.16). The triamine ligand $PhNH(CH_2)_6NH(CH_2)_4NH_2$ was specifically designed to be able to bind in two distinct ways to cucurbituril. The nitrogen atoms which are not adjacent to the benzene ring are estimated to be 10^6-fold more basic that the nitrogen attached to the benzene ring. Furthermore, the hexanediammonium ion binds ~100-fold more tightly than the butanediammonium ion, so simply changing *p*H changes the binding site of the cucurbituril to the triamine.

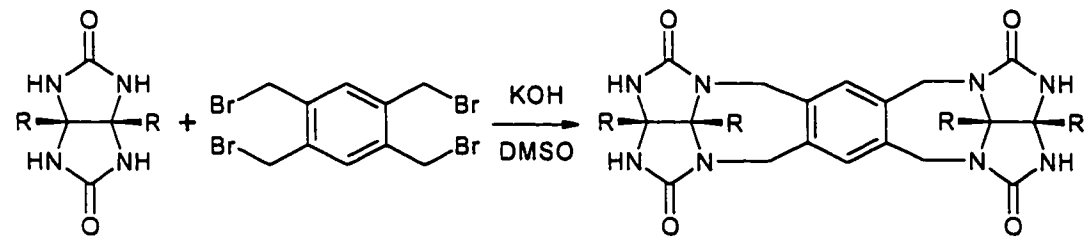
1.3.5.2 Rebek's Molecular Cages

Rebek has used glycoluril structures as the sites responsible for the self-assembly of a number of cage-like structures[55,56,57]. Many biological molecules exhibit self-assembly behaviour, including a number of enzymes. Chemists have been interested in molecular cages for a number of years now, since they can be used to encapsulate appropriate guest molecules and can even be used as enzyme mimics to promote several reactions by holding starting materials in appropriate configurations. Indeed, self-assembly of a number of systems has been shown to be accelerated by the addition of a guest molecule of the correct size and shape.

Almost all biological molecules capable of self-assembly such as allosteric enzymes, palindromic nucleic acids and viral capsids consist of interlocking, identical subunits held together by weak intermolecular forces such as hydrogen bonding and Van

der Waals interactions. Complementarity of shape, size, and chemical surface is the driving force for molecular recognition.

Rebek's molecular cage structures consist of two glycoluril units separated by a rigid spacer group. These compounds undergo a reversible dimerization to form a closed–shell cavity, the surface of which resembles a tennis ball. The glycoluril units provide self-complementary hydrogen bond donors and acceptors capable of forming eight intermolecular hydrogen bonds between monomer subunits.



R = Ph, 4-Me_2NPh CO_2Et

37: R = CO_2Et
38: R = Ph
39: R = 4-Me_2NPh

Scheme 1.17: Synthesis of Rebek's Molecular Cages

The monomeric species are synthesized by addition of the appropriate glycoluril to tetrabromodurene in KOH and DMSO (Scheme 1.17). Examination of a number of these compounds has illustrated that the formation of the dimer unit is dependent on solvent; in hydrophobic solvents such as benzene or $CDCl_3$, the dimer forms readily, whereas in DMSO, which can disrupt the hydrogen bonding array in the dimer, the monomeric form predominates. In addition, simple modifications of the side chains at the C7 and C8 positions can greatly modify the solubility of both the monomers and the dimers. Compound **37** is much more soluble in organic solvents, such as $CHCl_3$, THF,

and DMF, than compounds **38** or **39**. The dimer of this series of compounds when the spacer group is a benzene ring has a very small cavity; nonetheless, encapsulation of small molecules, such as CH_4, ethene, and xenon has been demonstrated. The x-ray crystal structure of **38** was obtained, and confirmed that the compound exists as the spherical dimer in the solid state.

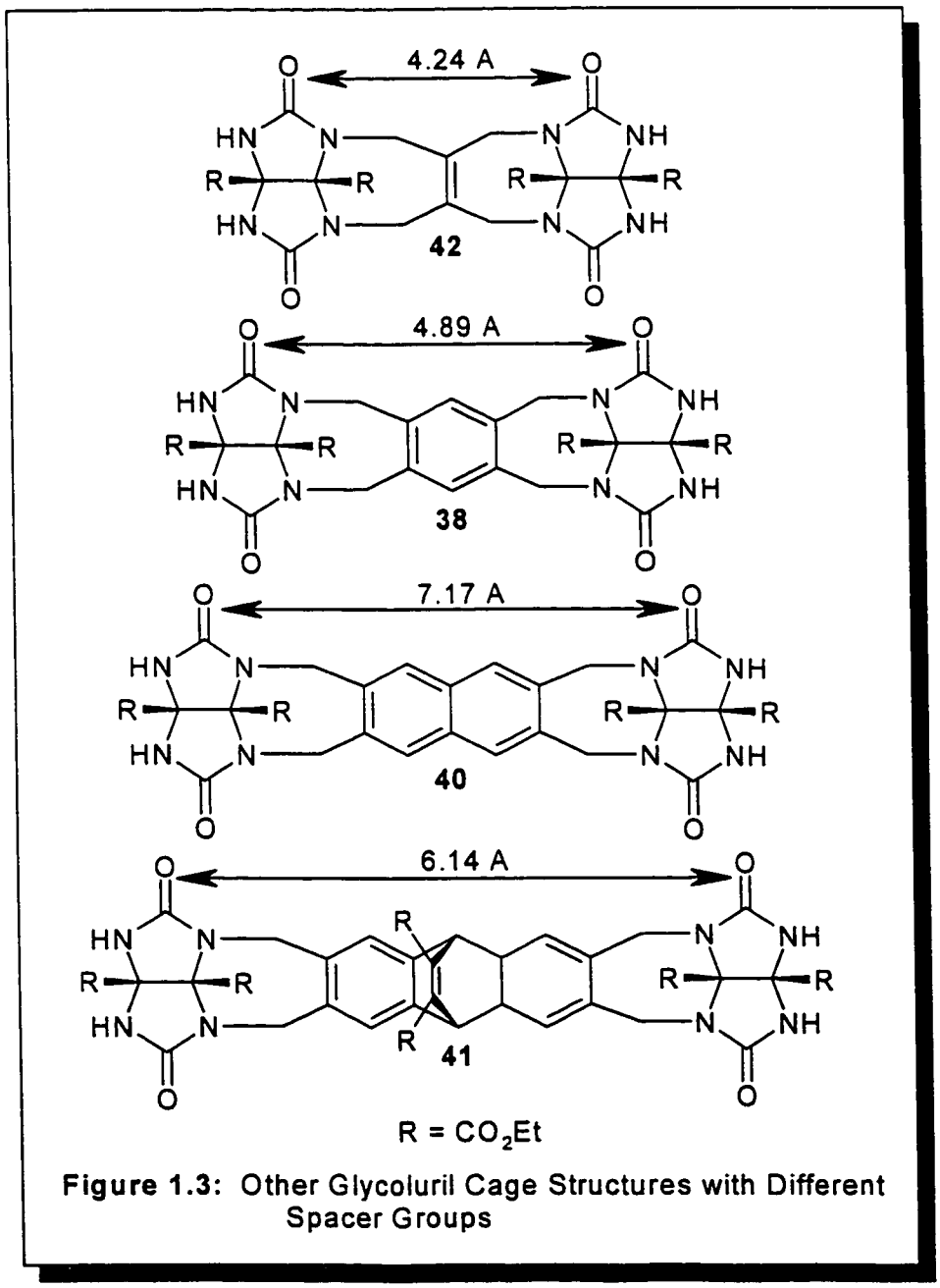


Figure 1.3: Other Glycoluril Cage Structures with Different Spacer Groups

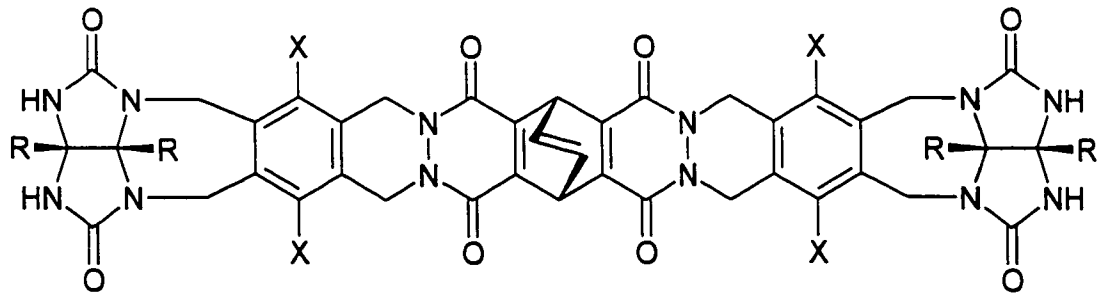
Changing the size of the spacer group changes the size of the cavity, and also influences the ability of the compound to form dimeric units. Rebek *et al.*[57] designed compounds (Figure 1.3) with ethylene, benzene, naphthalene and dibenzobarrelene spacer groups, which have quite different distances through space between the carbonyl groups. All of these analogues lead to the usual pseudo-spherical structures with cavities that are either larger or smaller than **38**.

Compound **40**, separated by the naphthalene spacer group, is the least suitable for dimerization, since if all 8 possible hydrogen bonds were to form, the π-surface of the naphthalene would have to bend significantly. In order to maintain the planarity of the naphthalene ring, only 4 hydrogen bonds can be formed between the monomer units, leading to very weak dimer formation. In contrast, **41**, with the larger dibenzobarrelene spacer group displays good geometry for dimerization, since the ethylene bridge in the compound provides a "crease" in the structure. Compound **41** dimerizes readily to provide a much larger cavity than **38**, so large that the solvent molecules are able to move freely in and out of the cavity, and direct detection of guest molecules was not possible.

One of the other very interesting results from this work was that in mixtures of 2 different dimers in the same solution, heterodimers are formed. This indicated that structurally related molecules which are self-complementary can also show complementarity to each other. It was also observed that the recombination of dimers could be controlled by the addition of suitable guests, a phenomenon which is known as nucleation. Thus, hybrid dimers **38:42**, **38:41**, and **40:41** were formed, relating to the compounds which were close enough in size to effectively dimerize. Dimer **38:42**

encapsulates CH_4 nicely, while **38:41** and **40:41** are relatively weak dimers, having six hydrogen bonds, and 4 strong, 2 weak (elongated) hydrogen bonds, respectively.

Rebek *et al.* have also designed a much larger system, based on similar architecture with glycoluril units at both ends[58,59], but with a much larger, rigid spacer group consisting of 13 fused rings (Figure 1.4). For these structures, additional hydrogen bonding sites in the middle of the molecule were added to get the same sort of "tennis ball" dimers. These dimers have a much larger cavity, suitable for larger guest molecules, such as adamantane derivatives and ferrocenes. The best binding for **43a** was observed for 1-adamantanecarboxylic acid; 1-adamantanecarboxamide and 1-ferrocenecarboxylic acid were also quite good guest molecules.



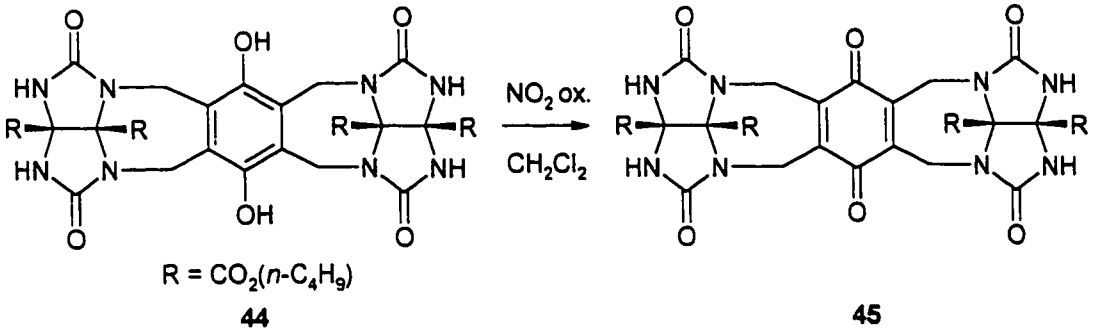
43a: R = Ph, X = H
43b: R = CO_2isopentyl, X = H
43c: R = 4-*n*-heptylphenyl, X = OH

Figure 1.4: Structure of Larger Molecular Cages Based on Glycoluril

For compounds **43a** and **43b**, the presence of a solvent ill-suited for encapsulation such as $CHCl_3$ or *p*-xylene led to a low-ordered aggregate of the monomer. Addition of a complementary guest favours the formation of the spherical dimer, and led to its

formation. Guests which were capable of hydrogen bonding also led to increased formation of the dimer.

In contrast, **43c** which has additional hydrogen bonding sites prefers dimers over other possible assemblies. This compound also encapsulates adamantyl and ferrocene derivatives. It was noted with some surprise that guest encapsulation increased with increasing temperature. This is surprising, since molecular assembly formation involves a competition between favourable binding forces (enthalpy) and the decreased freedom of the individual subunits (entropy). In this case, a favourable entropy term for encapsulation was observed, and it was theorized that the encapsulation of a single molecular guest of complementary size and shape by this host is more entropically favourable than the encapsulation of a number of solvent molecules.



Scheme 1.18: A Molecular Cage with Two Possible Oxidation States

Rebek *et al.*[60] have also designed a host molecule which can be readily converted between two different oxidation states, the hydroquinone **44** and the quinone **45** (Scheme 1.18). These structures have been shown to encapsulate CH_4, ethane, CH_3F, and CF_4. While these hosts are quite small, an integration of this technology with the larger hosts

above (eg. compound **43c**) could lead to a catalytic effect, such as those observed with other enzyme mimics.

Finally, their group has also recently designed another monomer **46** which consists of 3 glycoluril units arrayed in a triangular fashion[61] (Figure 1.5). This structure forms a dimer held together by 12 strong hydrogen bonds, which is suitable for encapsulating disc-shaped guests such as benzene, xylene, or most efficiently, cyclohexane. In contrast to many of Rebek's other host molecules, competitive encapsulation (for example, between xylene, a poor guest, and cyclohexane, an excellent guest) occurs very slowly, reflecting that a sizable fraction of the hydrogen bonds in this complex must be broken to permit entry and exit of guests.

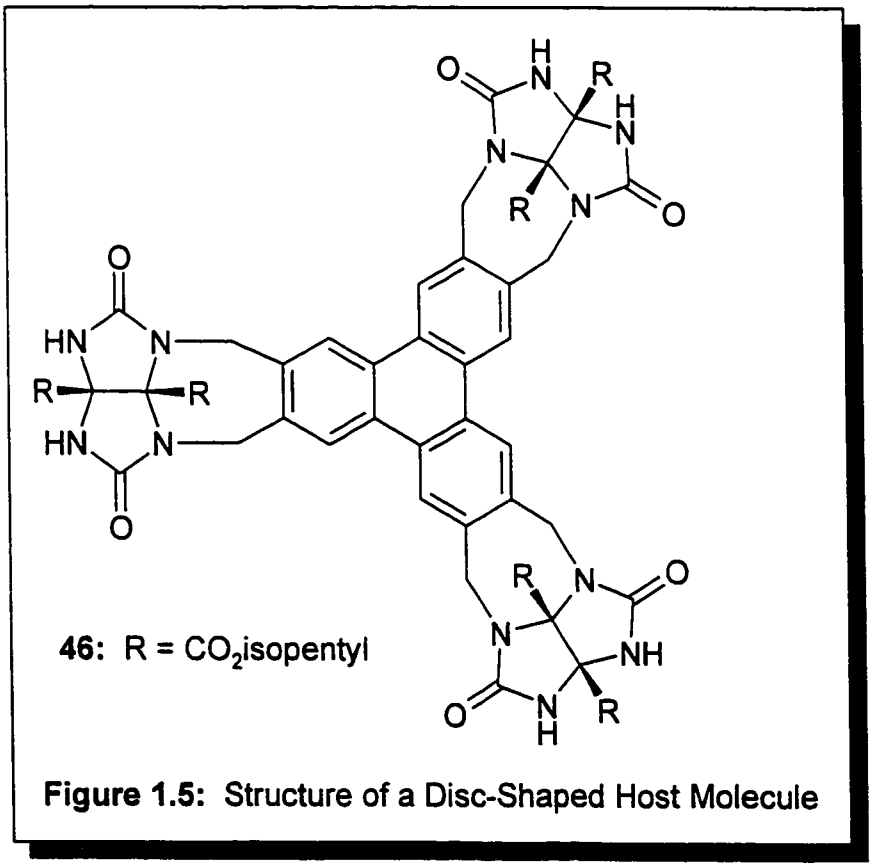
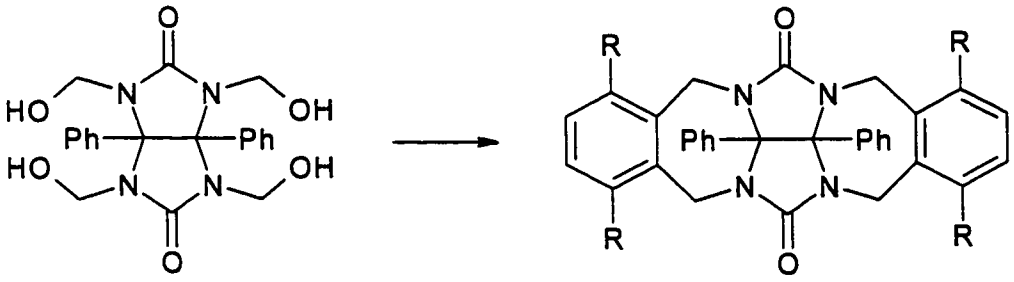


Figure 1.5: Structure of a Disc-Shaped Host Molecule

1.3.5.3 Nolte's Molecular Clips

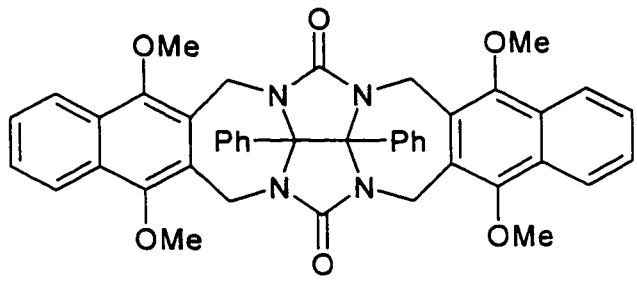
Enzymes and other natural hosts often contain a cleft or cavity whose inner concave surface matches the convex surface of a specific guest molecule. Enzymes also contain one or more catalytic centers, often metals, held in close proximity to this cavity. For the last several years, Nolte *et al.* have investigated the binding properties and catalytic activity of a number of molecular clips and baskets based on 7,8-diphenylglycoluril as a building block. The simplest of these are compounds containing 2 *o*-xylylene side walls separated by the diphenylglycoluril moiety, such as in compounds **47a-c** (Scheme 1.19). These compounds are derived from tetraalcohol **26** or the tetracyclic ether **27** by an electrophilic aromatic substitution reaction[62,63]. An alternative synthesis involves use of a tetra(chloromethyl)glycoluril derivative with Lewis acid catalysis and the aromatic component, and is reported to give better yields in shorter reaction times, as well as being more versatile, allowing the synthesis of a wide variety of side walls[64].



Scheme 1.19: Synthesis of Nolte's Clips

In these compounds, the glycoluril moiety provides a rigid geometrical structure, with the two bridgehead phenyl groups blocking the convex side of the template, thus the *o*-xylylene side walls are forced to orient themselves on the same side of the molecule, providing a cleft which is able to form stacking π-π interactions with aromatic guest molecules. In particular, an x-ray crystal structure[65] of **47b** has shown that the *o*-xylylene side walls are held at an angle of 27°, and the distance between the centers of the walls is 5.8 Å. In addition to the π-π interactions, compounds of type **47** are also capable of forming strong hydrogen bonds through the carbonyl moieties, which are oriented into the cleft. These compounds have been shown to be reasonably good hosts for dihydroxybenzene molecules, especially catechol and resorcinol. Resorcinol is bound to host **47b** with an association constant K_a of 2600 M^{-1}.

In an attempt to get better binding with dihydroxybenzene compounds, a compound with 1,4-dimethoxynaphthalene walls **48** was synthesized[66] (Figure 1.6). Surprisingly, this compound failed to exhibit any binding whatsoever to the dihydroxybenzenes. An x-ray crystal structure of compound **48** shows that unlike the obviously related compound **47c**, the methyl groups in this molecule preferentially point into the cavity, thus blocking the hydrogen-bond acceptor carbonyl sites and making it very difficult for guest molecules to fit into the cleft. This result supports the observation that small conformational changes can completely change the complexation behaviour of an otherwise rigid host molecule.



48

Figure 1.6: Structure of an Unsuccessful Molecular Clip

A more successful strategy[67,68] involved the use of 2,7-dimethoxynaphthalene walls as in **49**, which has a larger aromatic pocket, and is able to bind guests on the basis of π-π interactions alone. In this case, the molecular clip exists as a mixture of three conformers, the *ss* (*syn-,syn-*), where the phenyl groups are all oriented in the same direction, *sa* (*syn-, anti-*), which has one side wall oriented in the same direction as the glycoluril phenyl groups and the other pointing away, and the *aa* (*anti-, anti-*) conformer, where the side walls of the cleft are on the opposite side of the glycoluril phenyl groups, forming an appropriate cleft to accommodate a guest molecule (Figure 1.7).

Compound **49c**, for example, exists as 66% *sa*, 29% *aa*, and 5% *ss* at room temperature by ^{1}H nmr experiments. However, on addition of excess resorcinol, all of these molecules undergo complete conversion to the *aa* conformer, which is the only one which can bind the guest molecule effectively. Compound **49c** also behaves as a thermotropic liquid crystal, with several distinct phases available. The *aa* conformer of **49b** has an angle of 22° between the naphthalene walls, which are 6.5 Å apart. This corresponds to the optimal distance for sandwiching an aromatic guest. 1,3-

dinitrobenzene and 1,4-dicyanobenzene were both bound strongly to the host molecule through π-π interactions alone (K_a's ~ 100-200 M^{-1}).

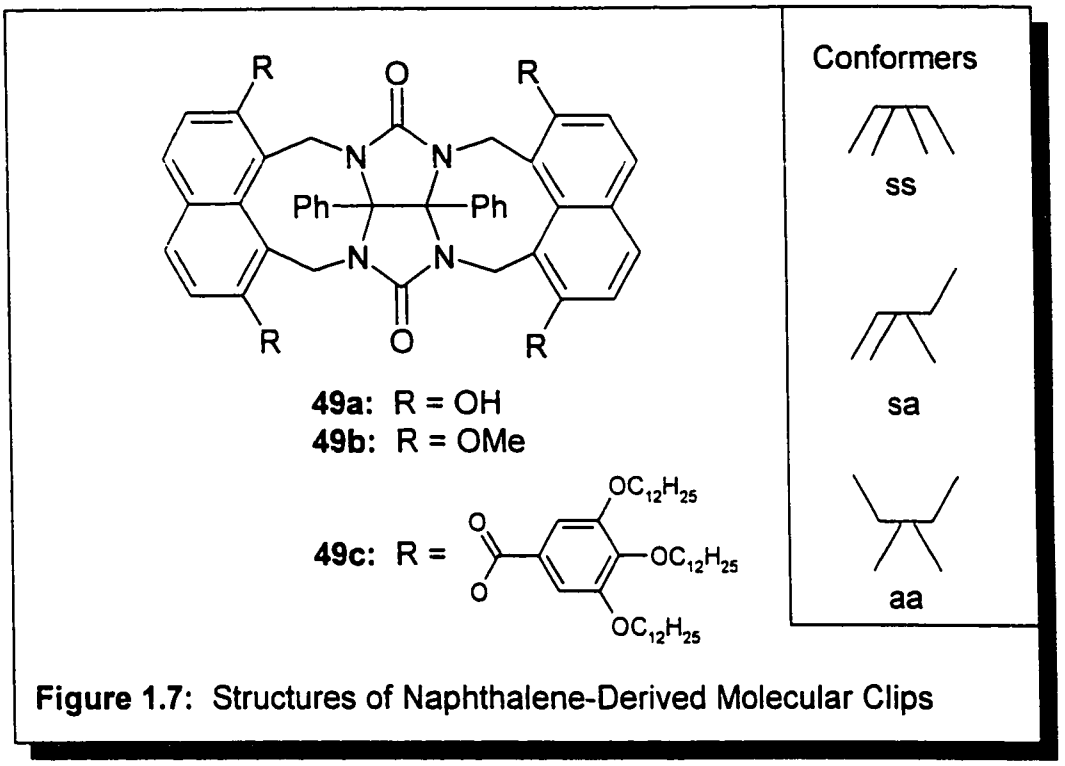
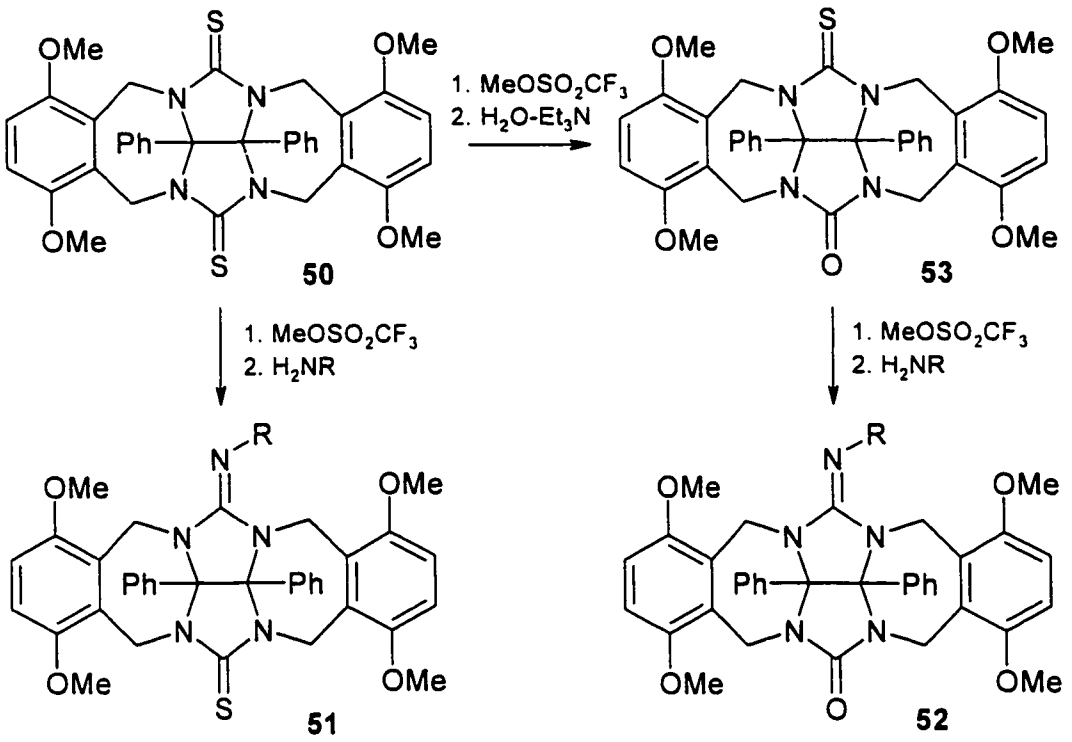


Figure 1.7: Structures of Naphthalene-Derived Molecular Clips

Hosts of this type were found to select their guests on the basis of size, rather than acceptor strength, so these clips operate by an induced-fit mechanism. Compound **49b** also binds silver ions, which act to change the conformation of the molecular clips towards both the aa and the ss conformers[69].

Another modification of the molecular clips involved replacing the urea functionality on the 7,8-diphenylglycoluril portion with thiourea or guanidine groups[70]. These compounds were prepared from the diphenyldithioglycoluril **21**, since attempts to convert molecular clips **47** directly to the thio-derivatives using P_2S_5 and other reagents were unsuccessful.



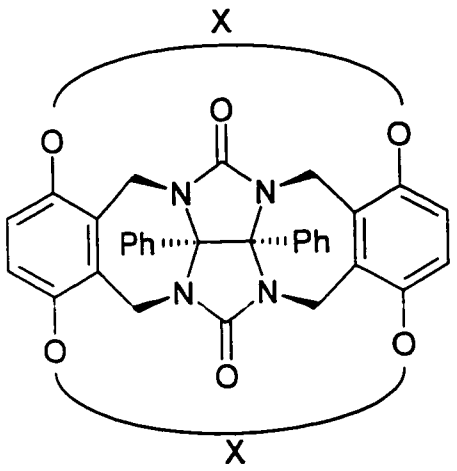
Scheme 1.20: Modification of the Urea Functionality to Guanidines

The strategy employed was addition of one equivalent of an alkylating agent, such as methyl triflate, to compound **50** followed by a primary amine to give the guanidine structures **51** and **52** (Scheme 1.20). The guanidine derivative **52** displayed very high binding affinity to resorcinol guests, with a K_a of 25000 M^{-1}. This is a 10-fold increase relative to the binding of **47b**. In contrast, the thiourea derivatives **50** and **53** both showed poor binding characteristics compared to **47b**. The mixed thiourea/guanidine structure **52** exhibited a moderate increase in the association constant of resorcinol relative to **47b** (4700 M^{-1} compared to 2600 M^{-1} for **47b**). This indicates that a guanidine

functionality can more than make up for the loss of hydrogen bonding properties observed going from a urea to a thiourea.

Nolte *et al.* have recently published a new general synthetic method to get to molecular clips of type **47** which possess two different side walls, in moderate-to-good yields[71]. A number of these new compounds also display very interesting binding characteristics.

In addition to their work on molecular clips, Nolte *et al.* have also further functionalized a number of their clips with crown ether or aza-crown ether moieties[72], thus forming molecular "baskets" (**54**), cavitands which have a much deeper cleft and which can also bind molecules or ions through their ether links (Figure 1.8). These linker bridges have the additional advantage that they force the compounds into an aa-type conformer. Compound **54c** was observed to contain two binding sites ringed with crown ether and carbonyl oxygens which are capable of binding alkali metals; binding affinities peak for K^+ at $K_a = 4.2 \times 10^8\ M^{-1}$. Much like cucurbituril itself, this molecule is also an excellent host for aliphatic protonated diamines, containing 3 to 9 $-CH_2-$ group spacers. Aromatic diammonium salts are also good guest molecules, and have very high association constants (up to $10^{10}\ M^{-1}$).

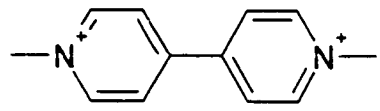


54a: X = -$(CH_2)_6$-
54b: X = -$(CH_2CH_2O)_2CH_2CH_2$-
54c: X = -$(CH_2CH_2O)_3CH_2CH_2$-
54d: X = -$(CH_2CH_2O)_4CH_2CH_2$-
54e: X = -$CH_2CH_2OCH_2CH_2$-NR-$CH_2CH_2OCH_2CH_2$-, R = Benzyl
54f: X = -$CH_2CH_2OCH_2CH_2$-NR-$CH_2CH_2OCH_2CH_2$-, R = H
54g: X = -$(CH_2)_2$-NR-$(CH_2)_2$-, R = Benzyl
54h: X = -$(CH_2)_2$-NR-$(CH_2)_2$-, R = H

Figure 1.8: Structures of Some Molecular Baskets

Compounds **54b** and **54c** form 1:1 complexes with K^+ ions, enfolding the ion in a "clamshell"-like complex, while compound **54d** forms either a 1:1 or a 1:2 complex with K^+ and Cs^+, depending on the ion concentration. It is very interesting to note that in the synthesis of the crown ether compounds, K_2CO_3 is used as the base; here, the K^+ ions act as a template promoting ring closure by forcing the oxyethylene chains to adopt an appropriate conformation for the ring closure. It is also interesting to note that for these compounds, the second spacer chain closes faster than the first, probably by adding rigidity to the system and freezing the compound in the correct conformation.

The crown ether derivative **54c** has also been shown to bind paraquat (**55**) (Figure 1.9), and polymeric paraquat derivatives[73]. In fact, it is an exceptional host for paraquat, with a binding constant to the $(PF_6)_2$ salt in acetonitrile of 57000 M^{-1}.



55

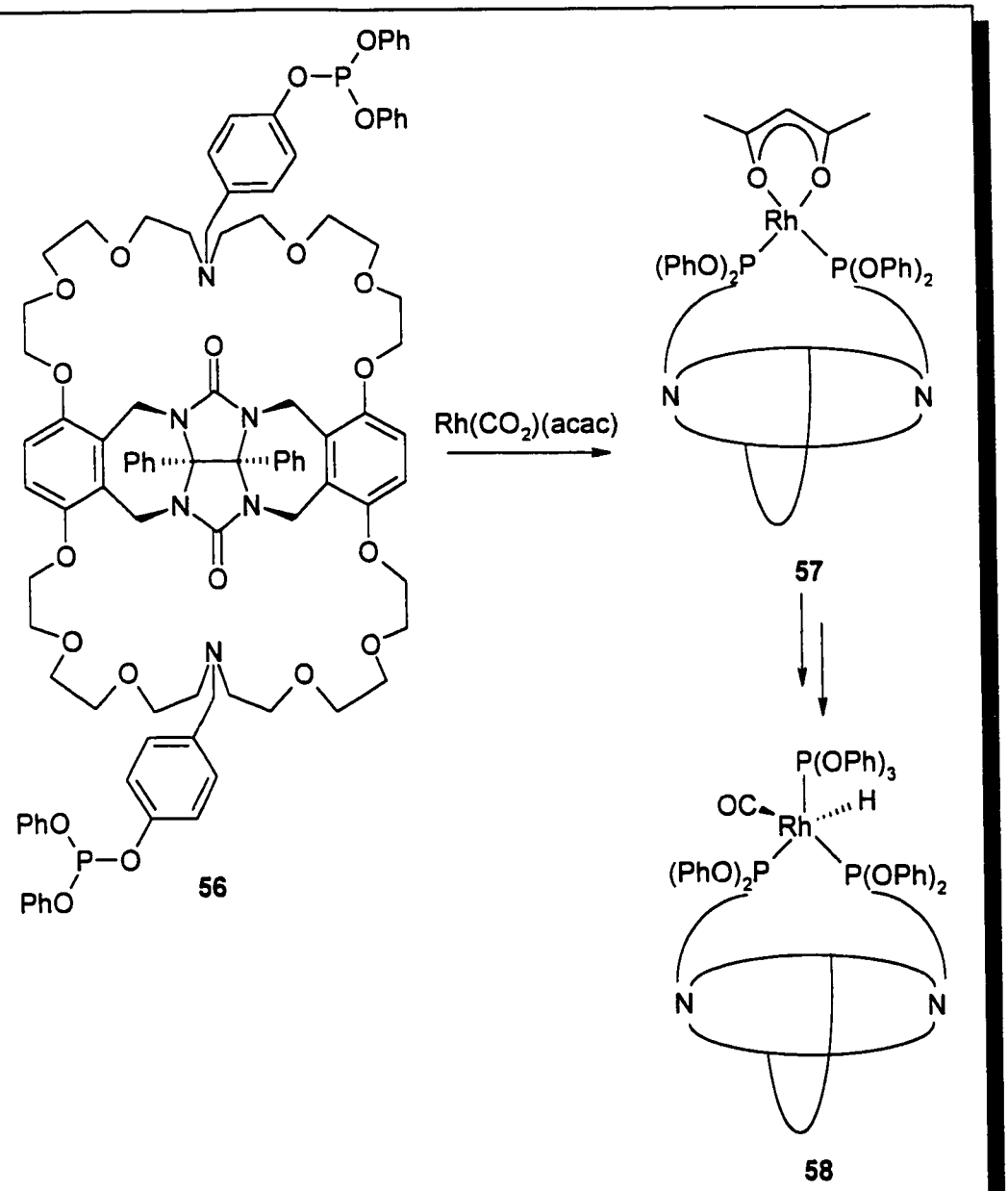
Figure 1.9: Structure of Paraquat

The nitrogens of the aza-crown ether tethered compounds, **54e-h**, are capable of forming hydrogen bonds to the phenol functionalities on dihydroxybenzenes (DHB's), and these compounds exhibit good binding characteristics to dihydroxybenzenes as well, with the exception of compound **54g**, which shows very poor binding to DHB's. Examination of the crystal structure of **54g**[74] shows that the *N*-benzyl groups are positioned directly above the cleft, and thus block entry to the cleft by guest molecules. The other aza-crown ethers show excellent binding for resorcinol and for hydroquinone, and moderate binding to catechol, which can be explained by taking into account the fact that catechol has a strong intramolecular hydrogen bond which must be broken for it to bind with the receptor. Receptor **54e** has a very high association constant with 2,3-dicyanohydroquinone ($K_a \sim 3 \times 10^5$ M^{-1}); in fact, this is one of the highest binding constants reported for a complex between a synthetic receptor and a neutral guest in an organic solvent.

The molecular clip **49** which has the 2,7-dihydroxynaphthalene walls was also linked by aza-crown ether links, with a side chain equivalent to that in **54e**. This receptor binds 1,3-dinitrobenzene well, and the binding is promoted by the addition of K^+ ions through an allosteric effect.

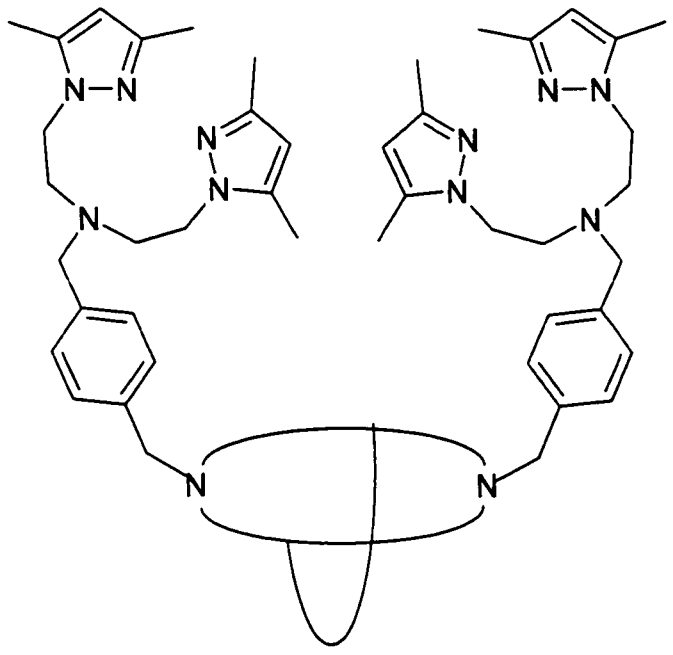
A derivative of the molecular clip **47b** with R = $(O\text{-}CH_2CH_2)_2SNa$ was used to encapsulate an iron-sulfur Fe_4S_4 cluster[75]. These clusters are quite interesting, and have been examined in other cavitand and macrocyclic systems, which coordinate the Fe_4S_4 core to try to design models of iron-sulfur type proteins. This molecular basket forms a 1:1 complex with the Fe_4S_4 cluster; this cluster is semi-encapsulated by the basket, and displays electronic behaviour which has previously only been encountered in metalloproteins.

Another derivative of **54e**, which has a phenyl phosphite chain attached to nitrogen (**56**), has been reacted with $[Rh(CO)_2(acac)]$ to give the metallohost **57** (Scheme 1.21). This compound can be converted to **58** (**57** and **58** shown in a schematic representation), which has catalytic activity[76,77]. Specifically, **58** selectively hydrogenates and isomerizes allyl-substituted dihydroxyarene substrates that are bound in its cavity. Moreover, compound **58** mimics a number of other enzyme properties, such as following Michaelis-Menten-like kinetics, and demonstrating an ~10-fold rate increase (from 3.4 to 29.8 □M/s) on addition of resorcinol as a cofactor.



Scheme 1.21: Synthesis of a Rhodium Metallohost

Compound **54f** was also derivatized at nitrogen with *bis*-pyrazole ligands that bind copper(II) and copper(I)[78] to give compound **59** (Figure 1.10).

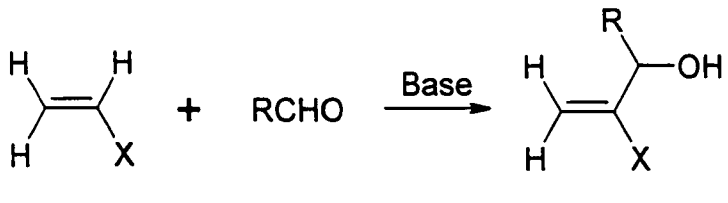


59

Figure 1.10: Structure of a Receptor That Binds Copper

Compound **59** coordinates to two copper centers, giving a dinuclear metallohost. The reduction of Cu(II) to Cu(I) occurs readily in the presence of easily oxidizable compounds, such as alcohols. Thus, benzyl alcohol, 3-hydroxybenzyl alcohol, and 3,5-dihydroxybenzyl alcohol were all oxidized to their respective aldehydes by the metallohost. 3-Hydroxybenzyl alcohol and 3,5-dihydroxybenzyl alcohol both exhibited much faster rates than that for oxidation of benzyl alcohol; this has been attributed to efficient binding of the first two guests within the cavity of the basket through hydrogen bonds as well as π-π interactions. Substrates with a complementary shape to the binding site are oxidized at least 4 orders of magnitude faster than substrates which do not possess a complementary shape.

A number of chiral aza-crown ether rings were synthesized, with the goal of achieving asymmetric induction in reactions catalysed in the clefts of these compounds[79]. These molecular baskets proved to catalyze the addition of benzenethiols to cyclohexenones; however, only very low values of optical purity were obtained[80]. Derivatives of compound **54h**, where R = (*R*)-$CH_2CH_2CH(OH)CH_3$ were also used to catalyze the Bayliss-Hillman reaction (Scheme 1.22), which proceeds via dipolar intermediates and is accelerated by pressure.



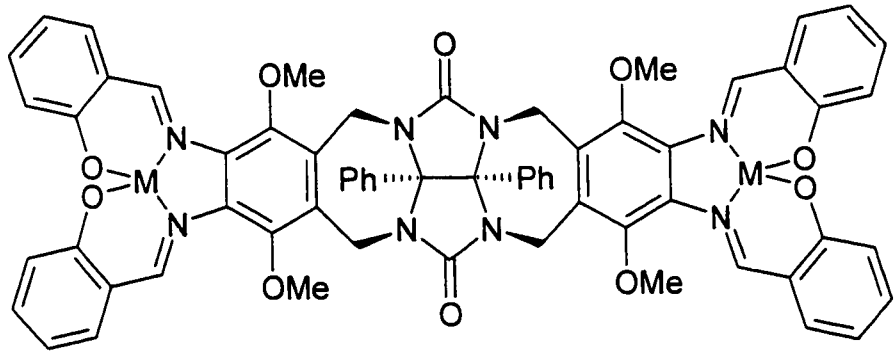
X = CHO, CO_2R, COR, CN

Scheme 1.22: The Bayliss-Hillman Reaction

This derivative of **54h** catalysed the reaction of benzaldehyde and acrylonitrile in $CDCl_3$ at 50 °C to give 95% conversion to products. Again, as in the previous case, only very low levels of asymmetric induction (e.e. < 5%) were observed. In contrast, 3,5-dihydroxybenzaldehyde showed very little conversion to products at all, in spite of its proven better fit into the cavity of these molecules.

A different catalytic effect was investigated[81] by functionalizing the side walls of the molecular clip **47c** with nickel binding sites to give **60** (Figure 1.11). This compound was used as a catalyst for the epoxidation of non-functionalized alkenes such as α-pinene, allylbenzene, styrene, and *trans*-stilbene in the presence of sodium hypochlorite

to give the epoxidized compounds in low yields (4 – 40%). Against expectations, **60** did not achieve selective epoxidation of benzenediol derivatives (eg: 5-allyl-1,3-benzenediol). Investigation of the x-ray crystal structure of **60** shows that this is likely due to a twist in the molecule, which places two of the methoxy groups inside the cleft, blocking interaction with the carbonyl H-bond acceptors.



60: M = Ni^{2+}

Figure 1.11: Structure of a Clip with Metal Binding Sites

A recent publication by Nolte *et al.* describes a number of molecular clips which were modified to contain a porphyrin ring[82]. These porphyrins contain a substrate binding pocket in the form of the molecular clip, and either a donor (**61**) or an acceptor (**62**) group (Figure 1.12). These compounds were made in order to study the role of intervening aromatic molecules which are complexed between the donor and acceptor in electron transfer processes. Compounds **61** and **62** do exhibit reasonable binding to dihydroxybenzene molecules, and it was shown that electron transfer does occur between

the excited porphyrin ring and the quinone acceptor **62**, although details have not yet been published.

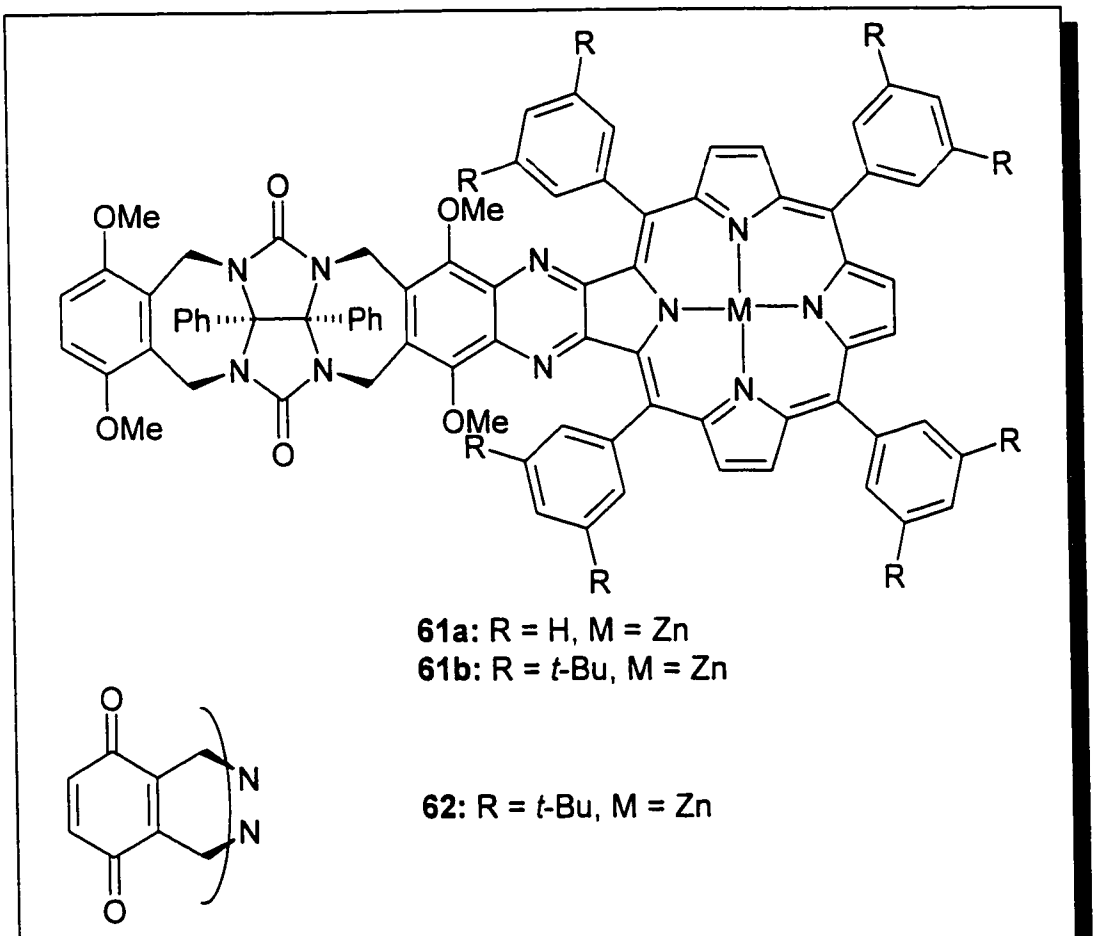


Figure 1.12: Structures of Porphyrin Rings Attached to a Molecular Clip

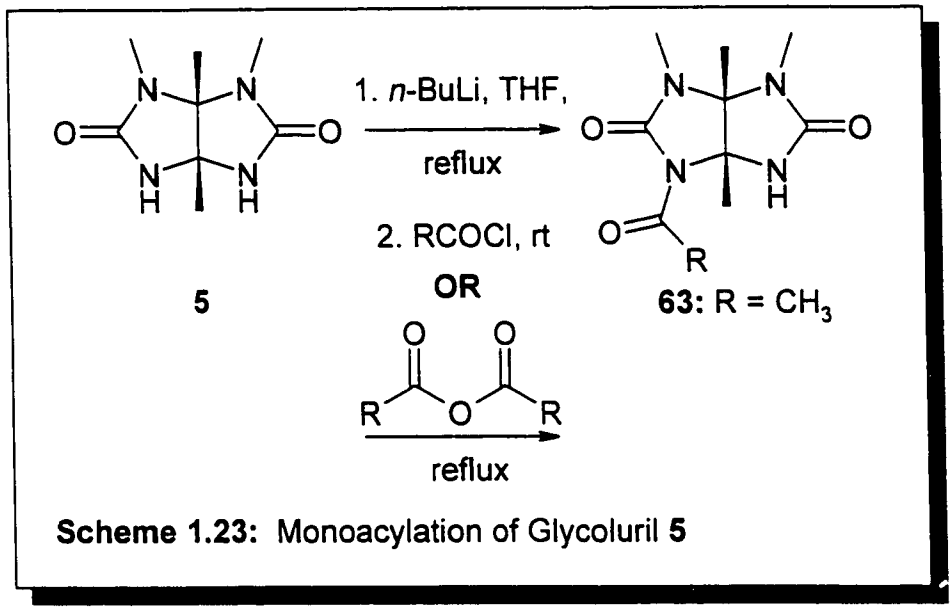
Murray and Whelan[83] have also investigated a number of molecular clip structures, several of them identical to those used by Nolte *et al.*, regarding their binding of dihydroxybenzenes. They found that the host molecules were able to catalyze the transport of resorcinol from water to chloroform.

1.3.6 3,4,7,8-Tetramethylglycoluril as a Template for Intramolecular Claisen Condensations

The design and use of the enzyme model 3,4,7,8-tetramethylglycoluril **5** as a biomimetic template in the condensation of acetyl units is described in detail in Dr. Sengen Sun's Ph.D. thesis[84]. The glycoluril was designed as a bifunctional template which mimics some features of the fatty acid (FAS) and polyketide synthases (PKS). It may also be thought of as an intramolecular version of Evans' oxazolidinone compounds, holding and orienting both reactive groups. Thus, 2 NH groups of **5** are used to hold and orient the two acyl groups in a similar manner to the thiol groups on FAS / PKS. Nitrogen is substituted for the thiol groups to give a stable model in which the binding sites are held rigidly in place with respect to each other. Once the template was designed, it was tested by building up short polyketide and fatty acid chains using conventional organic chemistry techniques. A brief summary of the results of these studies will be detailed below; for a more complete treatment, the reader is referred to the original literature[85,86].

The glycoluril **5** was synthesized by the condensation of 2,3-butanedione with two equivalents of N-methylurea (Scheme 1.6). This product was separated from the undesired isomer **9** by recrystallization from absolute ethanol. Crystals of **5** are very stable to most organic solvents and to temperatures as high as 300 °C as a result of each glycoluril molecule being hydrogen bonded to four others in the crystal structure, as has been shown by x-ray diffraction.

The first acylation reaction can be carried out by two methods (Scheme 1.23). In the first method, the purified glycoluril template is reacted first with *n*-BuLi in THF at reflux, then cooled to room temperature and reacted with an acyl chloride. This provides excellent yields, up to 89 % for acetyl chloride (**63**).

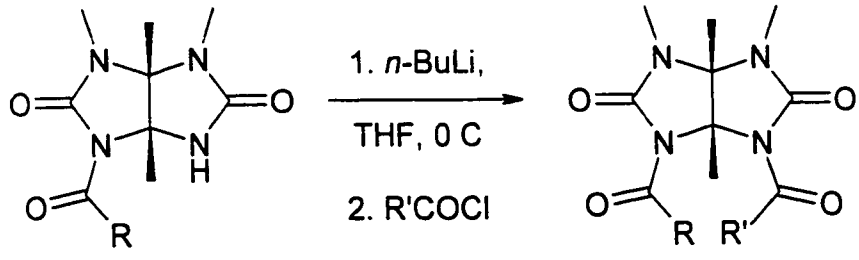


Scheme 1.23: Monoacylation of Glycoluril **5**

The second method of producing an acyl glycoluril adduct is to heat the crude glycoluril (**5** and **9**) at reflux in neat acyl anhydride. Yields of this reaction are somewhat reduced (ca. 78 %), but this method has the advantage of not requiring separation of the isomers produced in formation of **5**; compound **9** does not react with the anhydride under these conditions, and can be removed easily by filtration after this step.

Adding a second acyl group to the acetyl glycoluril **63** is much easier because of the dramatically increased solubility of the monoacyl glycoluril over the parent glycoluril **5**, presumably due to the decreased hydrogen bonding ability in the crystals of **63**. For

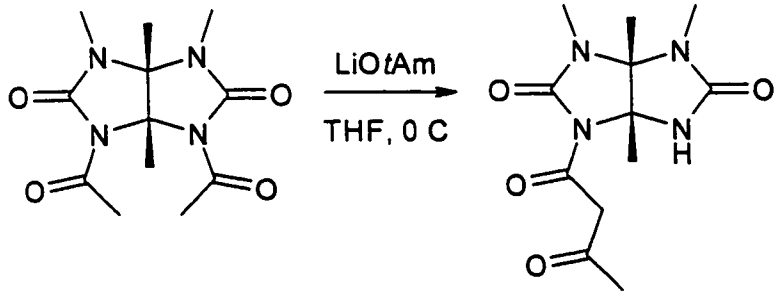
this reaction, 1 equivalent of LDA or *n*-BuLi at 0 °C, followed by an acyl chloride is sufficient to give the desired products in good yields (Scheme 1.24).



63: R = CH_3 **64:** R = R' = CH_3

Scheme 1.24: Second Acylation Reaction

Intramolecular condensation of the diacyl derivatives proceeds very quickly (total reaction time = 20 min) in good yields with a moderate, hindered base. When LiO^{t}Am was used as a base on the 1,6-diacetyl glycoluril derivative **64**, a yield of 93 % of acetoacetyl derivative **65** was obtained after purification (Scheme 1.25).

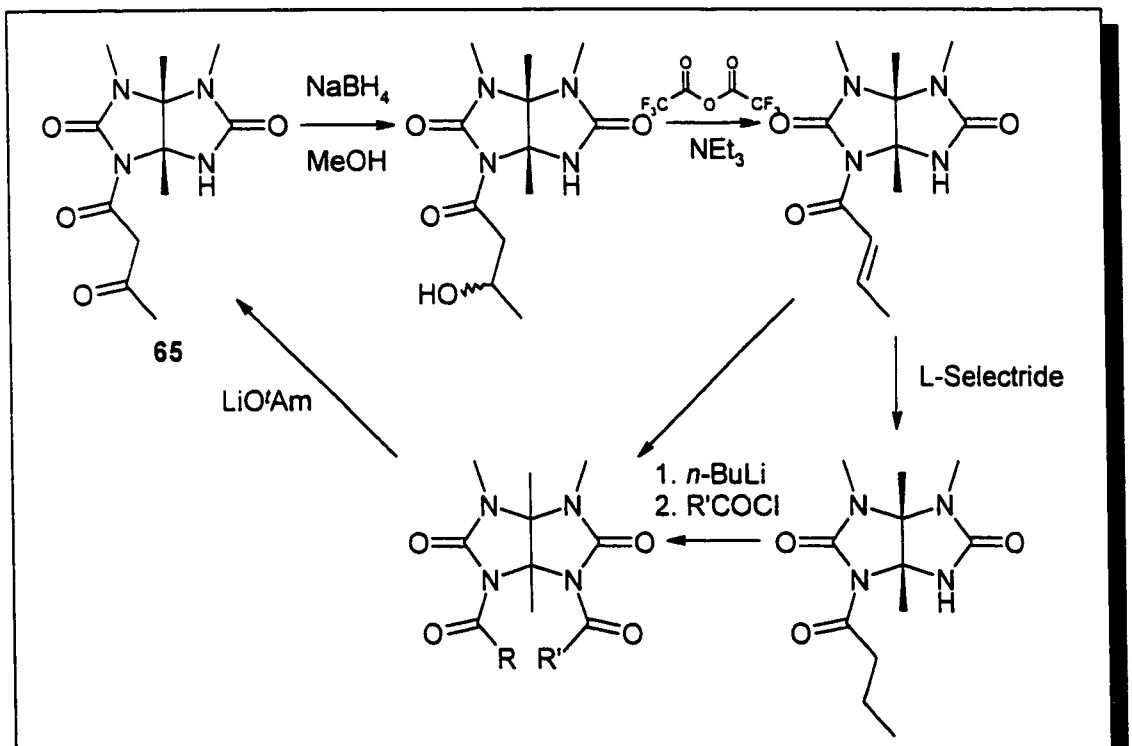


64 **65**

Scheme 1.25: Condensation of 1,6-Diacetyl Glycoluril **64**

This condensation reaction is quite general, and similar behaviour is observed for a number of different diacyl derivatives.

Subsequent reactions which can be performed readily on the acetoacetate side chain include reduction with $NaBH_4$ in MeOH, elimination of water with trifluoroacetic anhydride and triethylamine, and hydride conjugate addition to give a saturated chain (Scheme 1.26). These processes mimic the sequence of events that occur on polyketide synthase. Further rounds of acylation and functional group transformations were carried out, proceeding to the fourth round of condensations with little difficulty.



Scheme 1.26: Functional Group Manipulations of the Glycoluril Template

Removal of a synthesized carbon chain from the glycoluril was accomplished using LiOBn, to give high yields for saturated chains (83 % for butanoyl glycoluril), and

more modest yields for unsaturated chains (55 % for crotonyl glycoluril) due to formation of a side product (benzyl β-benzyloxybutyrate, 15 %) which results from 1,4-addition of the benzalkoxide to the double bond.

1.4 Objectives of this Thesis

While Sun examined the mechanism of the Claisen-like condensation reaction in some detail, showing by various labelling studies that the reaction was entirely intramolecular in nature, and that proton abstraction is involved in the rate determining step of the reaction, the precise mechanism of this reaction is still undetermined. The X-ray crystal structures of a number of key compounds will be investigated in Chapter 2, in order to determine whether a comparison of several of the solid-state structures leads to any insights into the mechanism of the condensation reaction.

Although many studies were performed on the mechanism of the Claisen-like condensation, the rate of this reaction has yet to be determined. For this purpose, and to investigate the reaction on aromatic side chains, an acetyl benzoyl adduct was synthesized and condensed. This work is described in Section 3.1.

Although the condensation reaction generally gives very high yields and good product ratios, a number of other reactions in the biomimetic cycle have proved more problematic. In particular, the first acylation reaction requires extremely harsh conditions, and for more complicated acyl halides, frequently gives quite unsatisfactory yields. An investigation into alternative methods for the first acylation reaction was

undertaken, and is described in section 3.2.1, and this consideration also played a major role in the decision to investigate sulfur derivatives of the glycoluril template which is reported in Chapter 4.

Additionally, the role of the six-membered transition state in the Claisen condensation reaction is unclear; is it a major or a minor contributor to the observed rate enhancement? An investigation of this question involved the synthesis of acetyl pyruvoyl glycoluril, followed by treatment of this compound under conditions which effect the condensation reaction in simpler systems. This work is described in Section 3.2.2.1.

Sun showed that 3,4,7,8-tetramethylglycoluril can be used as a template for the intramolecular Claisen-like condensation of acyl side chains via generation of an enolate intermediate. This enolate was generated by direct addition of a moderate, hindered base such as KO^{t}Bu, or by conjugate addition of L-Selectride to an α,β-unsaturated side chain. These represent only two possible methods of generating an enolate; another method, involving a Reformatsky-like reaction has been investigated for its utility with this system. This aspect is described in Section 3.2.2.2.

The reduction of β-ketoadducts works well for simple side chains, but units of unsaturation lead to drastically reduced yields in this reaction. Thus, other methods to accomplish this reaction were investigated in some detail; this work is described in Section 3.2.3.

Finally, in Sun's work cleavage of acyl groups from the glycoluril template were effected by addition of LiOBn; an alternative method which leads directly to the free

acid, thus reducing the number of steps and eliminating side products is described in Section 3.2.4.

Starting from a diacetyl glycoluril adduct, Sun went through one round of condensation, reduction, and elimination to obtain a crotonyl side chain. A second round of condensation with an acetyl group, followed by reduction and elimination led to the production of a sorboyl side chain. These results led to an interest in attaching both a crotonyl and a sorboyl side chain to the glycoluril, and subjecting this compound to Diels-Alder type conditions; this work is discussed in Section 3.3.

As well as the possibility of facilitating the first acylation reaction, it was postulated that sulfur analogs of the glycoluril template, particularly an asymmetrical S-O derivative, could result in altered selectivity in the Claisen condensation reaction. To date, as shown in Section 1.3.2, no satisfactory, general method of synthesizing thioglycolurils has been published, so Chapter 4 examines both a novel, reasonably general method of synthesizing *mono-* and *di*-thioglycoluril compounds, and investigates the utility of these sulfur analogues as templates for the Claisen condensation reaction.

Finally, although the glycoluril **5** has been used to build up a number of structures of varying complexity, previously, all of the molecules made were derivatives of commercially available acyl compounds. Thus, a synthesis of a more complex natural product, the fatty acid of pramanicin, was investigated in order to judge the synthetic utility of our system, as is described in Chapter 5.

Although a greater understanding of this methodology has been obtained, and a number of very interesting compounds have been investigated, represented by both the

work presented in this thesis and that which has gone before, much work still remains to be done. There remain a number of very interesting possibilities to explore, including the use of the *mono*-thioglycoluril template to effect a decarboxylative condensation reaction, and the attachment of a template-like molecule to a solid support for solid-phase synthesis. These and other ideas will be investigated in Chapter 6 (Future Work).

CHAPTER 2: Structures of Glycoluril Template and Derivatives

A critical examination of the structures of the compounds involved in the Claisen-like condensation reaction, and their precursors, was thought likely to provide insight into the characteristics of this template system. Most critically, a concrete picture of the relative geometries of the two acyl side chains, which are presumably controlled by the glycoluril template, might help to explain the high reactivity of these compounds, as well as help to answer some mechanistic questions.

The systematic analysis of structural data has been recognized as a legitimate research technique in organic chemistry[87]. Thus, a systematic study of a number of critical compounds was undertaken[‡,†]. In addition to mechanistic insights, these compounds also display a number of features on an individual basis which are quite interesting. Each of these structures will be discussed briefly, then comparisons between them will be made. At this point, details of the crystal packing of these molecules will be omitted; these will be published in due course.

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‡ Crystals of **2-1** and **2-3** grown by S. Sun, all others grown by C. Cow

† X-Ray crystal structures were solved by J. Britten for **2-1 – 2-3**, and by C. Matta for **2-4 – 2-6**.

2.1 X-Ray Crystal Structure of 3,4,7,8-Tetramethylglycoluril (2-1*)

In order to undertake a comparison of the acetyl adducts, it is very helpful to know the structure of the starting compound (**2-1**). Crystals of this compound were prepared by slow cooling from a dilute solution in ethanol. ORTEP drawings of three orthogonal views of the molecule are shown in Figures 2.1 and 2.2; bond lengths and angles are shown in Table 2.1. This work has recently been submitted for publication[88].

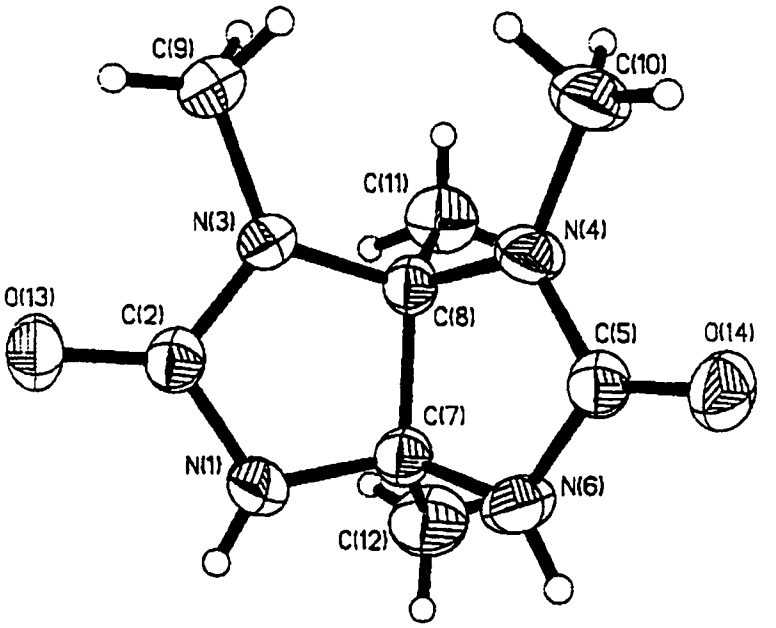


Figure 2.1: X-Ray Crystal Structure of 3,4,7,8-Tetramethylglycoluril (Top)

* Compounds throughout the remainder of this document have been numbered such that the prefix (e.g.: 2-, 3-, etc.) refers to the chapter wherein the experimental for the compound may be found.

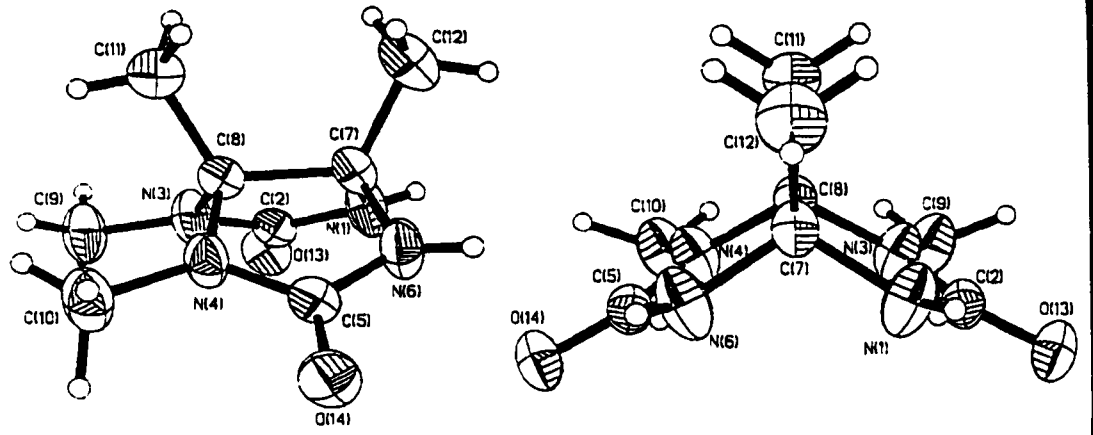


Figure 2.2: X-Ray Crystal Structure of 3,4,7,8-Tetramethylglycoluril (Other Views)

Bond Lengths (Å)		**Bond Angles (°)**		**Dihedral Angles (°)**	
N1-C2	1.358 (3)	C2-N1-C7	113.3 (2)	C12-C7-C8-C11	0.0
N1-C7	1.450 (3)	O13-C2-N3	125.4 (2)	C7-N1-C2-O13	177.3 (3)
C2-O13	1.228 (3)	O13-C2-N1	126.3 (2)	C7-N1-C2-N3	-4.1 (3)
C2-N3	1.346 (3)	N3-C2-N1	108.4 (2)	O13-C2-N3-C9	-2.0 (4)
N3-C9	1.447 (4)	C2-N3-C9	121.5 (2)	N1-C2-N3-C9	179.4 (3)
N3-C8	1.456 (3)	C2-N3-C8	113.7 (2)	O13-C2-N3-C8	-177.3 (2)
C7-C12	1.512 (6)	C9-N3-C8	124.7 (3)	N1-C2-N3-C8	4.1 (3)
C7-C8	1.575 (5)	N6-C7-N1	111.7 (3)	C2-N1-C7-N6	111.6 (3)
C8-C11	1.516 (6)	N1-C7-C12	111.3 (2)	C2-N1-C7-C12	-123.3 (4)
		N1-C7-C8	102.5 (2)	C2-N1-C7-C8	2.5 (3)
		C12-C7-C8	116.9 (4)	C2-N3-C8-N4	-110.8 (3)
		N3-C8-N4	112.2 (3)	C9-N3-C8-N4	74.0 (4)
		N3-C8-C11	111.5 (2)	C2-N3-C8-C11	123.3 (3)
		N3-C8-C7	102.0 (2)	C9-N3-C8-C11	-51.9 (4)
		C11-C8-C7	117.0 (3)	C2-N3-C8-C7	-2.4 (3)
				C9-N3-C8-C7	-177.5 (3)
				N1-C7-C8-N4	116.0 (2)
				N1-C7-C8-N3	-0.0 (3)
				C12-C7-C8-N3	122.0 (2)
				N1-C7-C8-C11	-122.0 (2)

Table 2.1: Selected Bond Lengths and Angles for Tetramethylglycoluril **2-1**.

As observed for other glycoluril molecules, **2-1** posseses a *cis*-fused bicyclic structure, with the five-membered rings both very close to planar (mean deviation 0.017Å). The angle between the mean planes is 118.0°, compared with 121.4° for glycoluril **4**, and 115° for 7,8-diphenylglycoluril. This change is almost exactly what is expected from added steric bulk of the *C*-methyl groups compared to hydrogen. Glycoluril **2-1** possesses a mirror plane through the two bridgehead carbons (C7 and C8) and the two attached methyl groups (C11 and C12), making the dihedral angle C11-C8-C7-C12 = 0°.

2.2 X-Ray Crystal Structure of 1-Acetyl-3,4,7,8-tetramethylglycoluril (2-2)

Acetyl glycoluril **2-2** was crystallized by slow diffusion of ethyl acetate into a solution of **2-2** in chloroform. ORTEP drawings of orthogonal views of the molecule are shown in Figures 2.3, and 2.4; bond lengths and angles are given in Table 2.2.

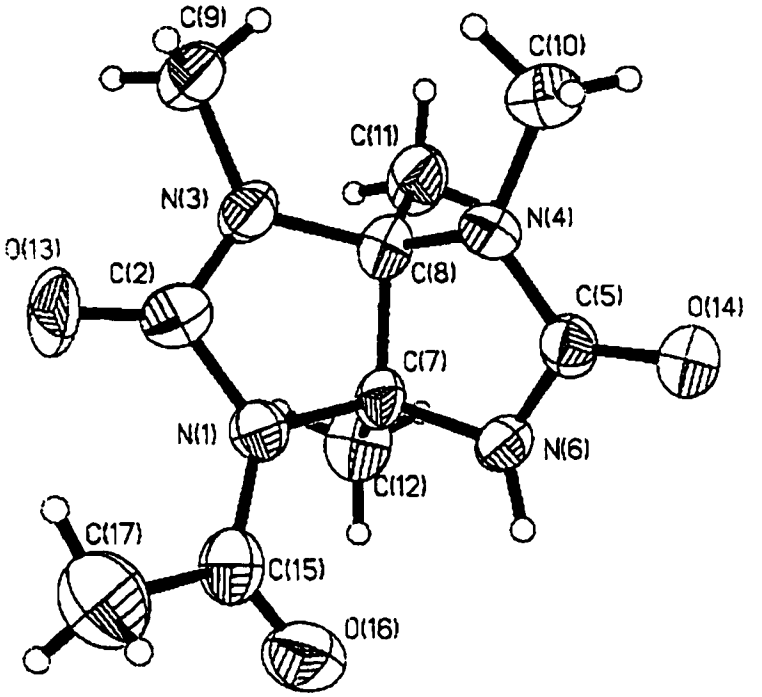


Figure 2.3: X-Ray Crystal Structure of Acetyl Glycoluril **2-2**: "Top" View

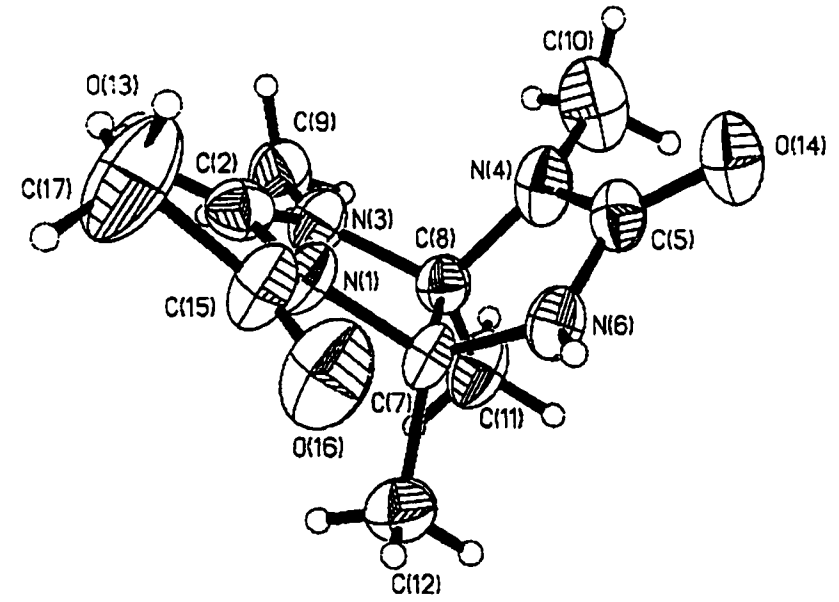


Figure 2.4: X-Ray Crystal Structure of Acetyl Glycoluril **2-3**: "Front" View.

Bond Lengths (Å)		Bond Angles (°)	
N1-C15	1.375 (10)	C15-N1-C2	127.8 (6)
N1-C2	1.397 (9)	C15-N1-C7	120.3 (6)
N1-C7	1.493 (9)	C2-N1-C7	111.9 (6)
C2-O13	1.221 (9)	O13-C2-N3	126.0 (7)
C2-N3	1.335 (9)	O13-C2-N1	126.3 (8)
N3-C9	1.455 (8)	N3-C2-N1	107.7 (7)
N3-C8	1.472 (9)	C2-N3-C9	122.6 (7)
N4-C5	1.354 (9)	C2-N3-C8	113.5 (6)
N4-C10	1.451 (9)	C9-N3-C8	123.8 (7)
N4-C8	1.467 (10)	C5-N4-C10	120.9 (6)
C5-O14	1.239 (9)	C5-N4-C8	111.5 (6)
C5-N6	1.353 (10)	C10-N4-C8	123.7 (6)
N6-C7	1.426 (9)	O14-C5-N6	125.0 (7)
C7-C12	1.510 (10)	O14-C5-N4	126.3 (7)
C7-C8	1.565 (10)	N6-C5-N4	108.8 (7)
C8-C11	1.502 (10)	C5-N6-C7	112.1 (6)
C15-O16	1.205 (9)	N6-C7-N1	113.3 (6)
C15-C17	1.528 (12)	N6-C7-C12	113.9 (6)
		N1-C7-C12	110.0 (6)
		N6-C7-C8	102.8 (6)
		N1-C7-C8	100.5 (6)
		C12-C7-C8	115.5 (6)
		N4-C8-N3	112.1 (6)
		N4-C8-C11	112.6 (7)
		N3-C8-C11	112.1 (6)
		N4-C8-C7	100.3 (6)
		N3-C8-C7	102.5 (6)
		C11-C8-C7	116.3 (6)
		O16-C15-N1	120.5 (7)
		O16-C15-C17	121.9 (8)
		N1-C15-C17	117.5 (8)

Table 2.2: Selected Bond Lengths and Angles for Acetyl Glycoluril **2-2**

The most striking feature in this molecule, unlike glycoluril **2-1**, is the lack of symmetry in the ring systems, accompanied by a large C11-C8-C7-C12 dihedral angle

(23.1°). Although several glycoluril structures have a dihedral angle of 0°, such as **2-1** and glycoluril **4**, other structures[89,90] have been reported to have quite significant twists, up to 24°. The acetyl group is oriented in the crystal structure with the oxygen pointing in toward the centre of the molecule. The angle between the plane of the ring and that of the acetyl unit is 8.7°, indicating that there is significant overlap of the N1 lone pair with the carbonyl group of the acetyl unit.

2.3 X-Ray Crystal Structure of 1,6-Diacetyl-3,4,7,8-tetramethylglycoluril (2-3)

Diacetyl glycoluril **2-3** was crystallized by slow diffusion of hexanes into a solution of **2-3** in chloroform. ORTEP drawings of orthogonal views of the molecule are shown in Figure 2.5, and 2.6; bond lengths and angles are given in Table 2.3.

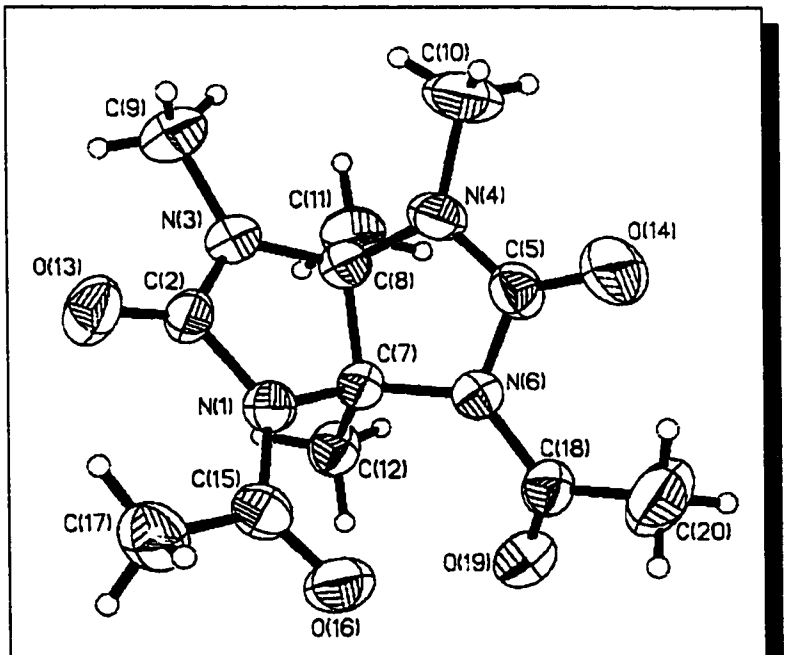


Figure 2.5: X-Ray Crystal Structure of Diacetyl Glycoluril **2-3**: "Top" View

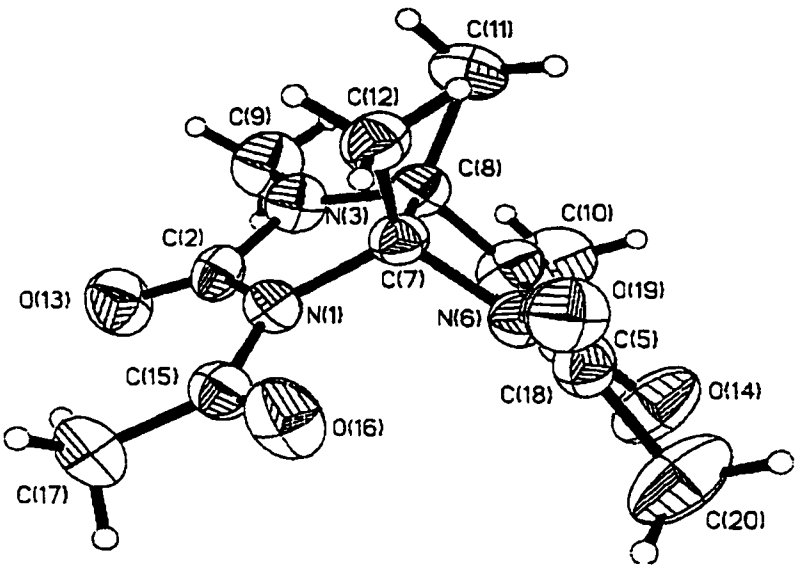


Figure 2.6: X-Ray Crystal Structure of Diacetyl Glycoluril **2-3**: "Front" View

Bond Lengths (Å)		**Bond Angles (°)**	
N3-C8	1.449 (6)	N3-C8-N4	111.2 (4)
N4-C8	1.456 (6)	N3-C8-C11	112.2 (4)
C8-C11	1.521 (7)	N4-C8-C11	111.7 (4)
C7-C8	1.558 (6)	N3-C8-C7	103.2 (4)
C2-N3	1.346 (6)	N4-C8-C7	102.0 (3)
N3-C11	1.452 (6)	C7-C8-C11	115.9 (4)
C2-O13	1.211 (6)	C2-N3-C8	113.7 (4)
N1-C2	1.409 (6)	C2-N3-C9	120.6 (4)
N1-C15	1.384 (6)	C8-N3-C9	125.0 (4)
N1-C7	1.491 (6)	O13-C2-N3	126.0 (4)
N6-C7	1.462 (6)	O13-C2-N1	126.6 (5)
C7-C12	1.521 (7)	N3-C2-N1	107.4 (4)
N6-C18	1.397 (6)	C15-N1-C2	126.6 (4)
C5-N6	1.406 (6)	C15-N1-C7	122.0 (4)
C5-O14	1.217 (6)	C2-N1-C7	111.3 (4)
N4-C5	1.343 (6)	N1-C7-N6	111.4 (4)
N4-C10	1.462 (6)	N6-C7-C12	117.3 (4)
C15-O16	1.217 (6)	N1-C7-C12	109.4 (4)
C15-C17	1.487 (7)	N6-C7-C8	103.1 (3)
C18-O19	1.207 (6)	N1-C7-C8	101.3 (3)

C18-C20	1.496 (8)	C12-C7-C8	113.4 (4)
		C18-N6-C5	123.5 (4)
		C18-N6-C7	126.3 (4)
		C5-N6-C7	109.8 (4)
		O14-C5-N4	125.7 (5)
		O14-C5-N6	125.6 (5)
		N4-C5-N6	108.7 (4)
		C5-N4-C8	113.1 (4)
		C5-N4-C10	120.4 (4)
		C8-N4-C10	125.6 (4)
		O16-C15-N1	119.4 (4)
		O16-C15-C17	121.0 (5)
		N1-C15-C17	119.5 (5)
		O19-C18-N6	121.7 (5)
		O19-C18-C20	120.7 (5)
		N6-C18-C20	117.6 (5)

Table 2.3: Selected Bond Lengths and Angles for Diacetyl Glycoluril **2-3**.

The x-ray crystal structure of 1,6-diacetyl-3,4,7,8-tetramethylglycoluril **2-3** revealed that two distinct molecules were present in the crystal lattice; comparison of the two structures indicates that they contain identical bond lengths and angles within a 95% confidence limit.

The ureido rings of the diacetyl template also had a significant twist relative to each other, illustrated by the C12-C7-C8-C11 dihedral angle, which was 24° for this compound. In this structure, both of the acetyl groups are oriented with the oxygens pointing inward; one of the acetyl groups is coplanar with the adjacent ring of the glycoluril, while the other is twisted out of the plane by 21.0°.

2.4 X-Ray Crystal Structure of 1-Benzoyl-6-acetyl-3,4,7,8-tetramethylglycoluril (2-4)

Acetyl benzoyl template **2-4** was crystallized by slow diffusion of hexanes into a solution of **2-4** in $CHCl_3$. An ORTEP drawing of the molecule is shown in Figure 2.7; bond lengths and angles are given in Table 2.4.

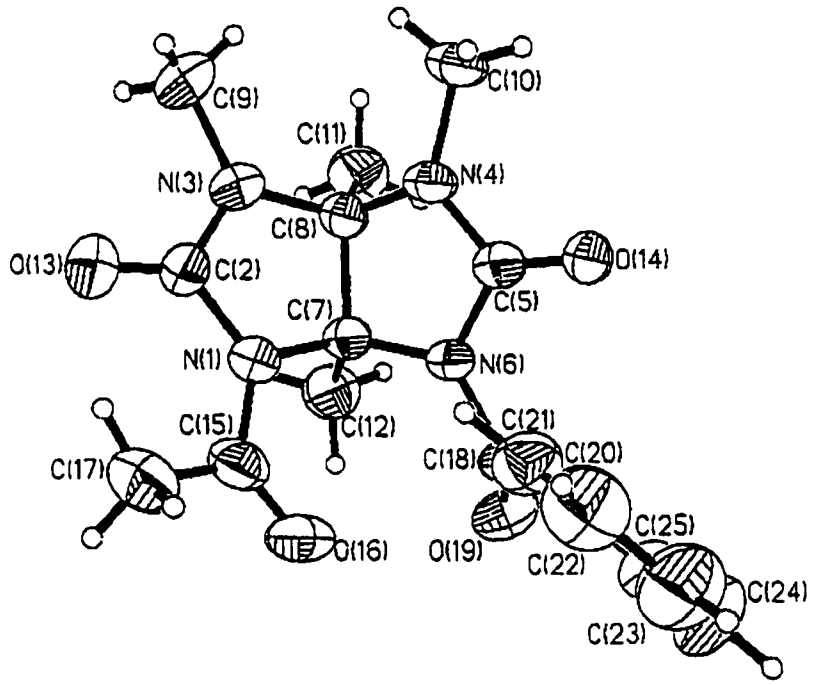


Figure 2.7: X-Ray Crystal Structure of Acetyl Benzoyl Template **2-4**: "Top" View

Bond Lengths (Å)		Bond Angles (°)	
N1-C2	1.403 (6)	C2-N1-C15	126.9 (4)
N1-C15	1.404 (6)	C2-N1-C7	111.1 (4)
N1-C7	1.490 (6)	C15-N1-C7	122.0 (4)
N6-C5	1.400 (5)	C5-N6-C18	121.6 (4)
N6-C18	1.425 (5)	C5-N6-C7	111.8 (3)
N6-C7	1.465 (5)	C18-N6-C7	126.4 (3)
O14-C5	1.202 (5)	C5-N4-C8	114.0 (3)
N4-C5	1.355 (6)	C5-N4-C10	121.4 (4)
N4-C8	1.447 (5)	C8-N4-C10	124.1 (4)
N4-C10	1.463 (5)	O13-C2-N3	126.5 (5)
O19-C18	1.201 (5)	O13-C2-N1	125.7 (5)
C2-O13	1.205 (6)	N3-C2-N1	107.8 (4)
C2-N3	1.344 (6)	O14-C5-N4	127.1 (4)
O16-C15	1.196 (6)	O14-C5-N6	125.6 (4)
N3-C8	1.450 (6)	N4-C5-N6	107.3 (4)
N3-C9	1.455 (6)	C2-N3-C8	114.0 (4)
C7-C12	1.513 (6)	C2-N3-C9	121.6 (4)
C7-C8	1.570 (6)	C8-N3-C9	124.4 (4)
C8-C11	1.521 (7)	N6-C7-N1	110.2 (3)
C15-C17	1.493 (7)	N6-C7-C12	115.1 (4)
C18-C20	1.483 (7)	N1-C7-C12	110.8 (4)
C20-C21	1.386 (7)	N6-C7-C8	102.7 (3)
C20-C25	1.384 (7)	N1-C7-C8	101.1 (3)
C25-C24	1.375 (9)	C12-C7-C8	115.7 (4)
C21-C22	1.383 (8)	N4-C8-N3	112.6 (4)
C24-C23	1.357 (10)	N4-C8-C11	111.5 (4)
C22-C23	1.357 (10)	N3-C8-C11	111.3 (4)
		N4-C8-C7	102.0 (3)
		N3-C8-C7	102.9 (3)
		C11-C8-C7	115.9 (4)
		O16-C15-N1	119.3 (5)
		O16-C15-C17	122.5 (5)
		N1-C15-C17	118.2 (5)
		O19-C18-N6	121.1 (4)
		O19-C18-20	122.5 (4)
		N6-C18-C20	116.4 (4)

Table 2.4: Selected Bond Lengths and Angles for Acetyl Benzoyl Glycoluril **2-4**

Acetyl benzoyl glycoluril **2-4** crystallized in a 1:1 ratio with chloroform, which forms a reasonably strong hydrogen bond (d{O14-$C_{Chloroform}$} = 3.091Å), significantly shorter than 3.22 Å, the sum of the Van der Waals radii of oxygen and carbon) between the hydrogen of chloroform and the O14 atom of the acetyl benzoyl template. Aromatic π-stacking appears to separate the sheets in the crystal lattice.

Acetyl benzoyl glycoluril **2-4** possesses a dihedral angle C12-C7-C8-C11 of 18.4°. Similar to **2-3**, the acyl oxygens point in towards each other. In this case, the acetyl group is nearly coplanar with the adjacent ureido group (twist of 8.0° out of plane), while the benzoyl group displays a significant twist of 45.2° out of the plane of the adjacent ring, indicating significantly less overlap of the N6 lone pair into the benzoyl carbonyl group. This is reflected by greater pyramidalization of N4 and N6 relative to N3 and N1, and by increased puckering of the N4, N6 ring. Additionally, the benzoyl carbonyl is twisted out of plane of the phenyl ring as well; the dihedral angle O19-C18-C20-C21 is 26.6°. This may be due to reduced π overlap of the carbonyl group into the phenyl ring, or possibly more likely, an artifact of the crystal packing that allows for more efficient π-π stacking between phenyl groups on adjacent molecules.

2.5 X-Ray Crystal Structure of 1-Benzoylacetyl-3,4,7,8-tetramethylglycoluril (2-5)

Benzoylacetyl template **2-5** was crystallized by slow evaporation of a solution of **2-5** in $CDCl_3$. An ORTEP drawing of the molecule is shown in Figure 2.8; bond lengths and angles are given in Table 2.5.

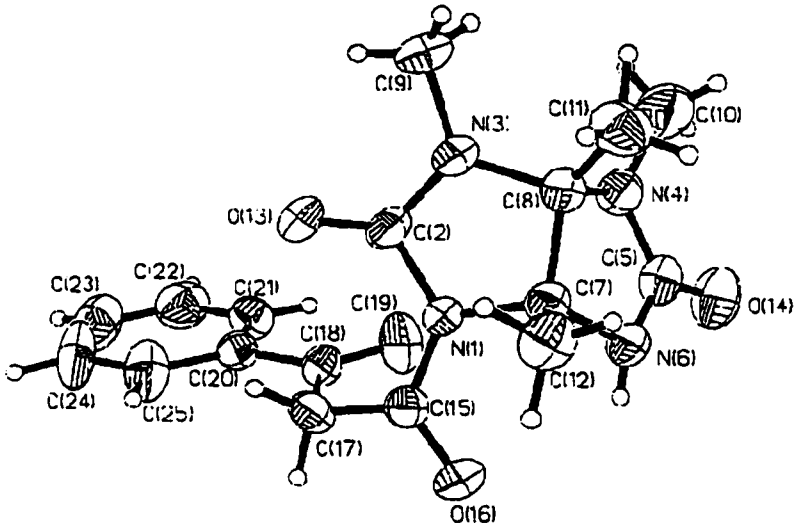


Figure 2.8: X-Ray Crystal Structure of Benzoylacetyl Glycoluril **2-5**: "Top" View

Bond Lengths (Å)		**Bond Angles (°)**	
N1-C15	1.384 (5)	C15-N1-C2	127.2 (3)
N1-C2	1.403 (4)	C15-N1-C7	121.4 (3)
N1-C7	1.479 (4)	C2-N1-C7	111.3 (3)
C2-O13	1.209 (4)	O13-C2-N3	126.9 (3)
C2-N3	1.347 (5)	O13-C2-N1	126.2 (4)
N3-C8	1.453 (4)	N3-C2-N1	106.9 (3)
N3-C9	1.460 (5)	C2-N3-C8	113.5 (3)
N4-C5	1.377 (5)	C2-N3-C9	121.1 (4)
N4-C10	1.439 (6)	C8-N3-C9	124.8 (4)
N4-C8	1.457 (5)	C5-N4-C10	118.9 (4)
C5-O14	1.214 (4)	C5-N4-C8	111.2 (3)
C5-N6	1.366 (5)	C10-N4-C8	124.6 (4)
N6-C7	1.437 (4)	O14-C5-N6	126.0 (4)
C7-C12	1.502 (5)	O14-C5-N4	125.9 (4)
C7-C8	1.550 (5)	N6-C5-N4	108.1 (3)
C8-C11	1.508 (6)	C5-N6-C7	111.7 (3)
C15-O16	1.217 (4)	N6-C7-N1	112.6 (3)
C15-C17	1.494 (5)	N6-C7-C12	113.4 (3)
C17-C18	1.497 (6)	N1-C7-C12	109.9 (3)
C18-O19	1.216 (4)	N6-C7-C8	102.7 (3)
C18-C20	1.488 (5)	N1-C7-C8	101.2 (3)
C20-C21	1.378 (6)	C12-C7-C8	116.5 (3)

C20-C25	1.381 (5)	N3-C8-N4	112.7 (3)
C21-C22	1.370 (7)	N3-C8-C11	112.2 (4)
C22-C23	1.364 (7)	N4-C8-C11	110.8 (4)
C23-C24	1.370 (8)	N3-C8-C7	102.4 (3)
C24-C25	1.386 (7)	N4-C8-C7	101.8 (3)
		C11-C8-C7	116.3 (4)
		O16-C15-N1	117.9 (3)
		O16-C15-C17	123.5 (4)
		N1-C15-C17	118.6 (3)
		C15-C17-C18	113.7 (3)
		O19-C18-C20	120.4 (4)
		O19-C18-C17	120.5 (4)

Table 2.5: Selected Bond Lengths and Angles for Benzoylacetyl Glycoluril **2-5**.

Benzoylacetyl template is the only example of a condensation reaction product examined in this series. It displays significant π-π interactions in the crystal lattice.

The dihedral angle C12-C7-C8-C11 is 24.1°, and the acyl chain extends away from the glycoluril group, probably to optimize π-π interactions in the crystal.

2.6 X-Ray Crystal Structure of 1,6-Diacetyl-3,4,7,8-tetramethyl-2,5-dithioglycoluril (2-6)

Diacetyl dithioglycoluril **2-6** was crystallized by slow evaporation of a solution of **2-6** in CH_2Cl_2. ORTEP drawings of orthogonal views of the molecule, as well as Hyperchem diagrams, are given in Figures 2.9 and 2.10; bond lengths and angles are given in Table 2.6.

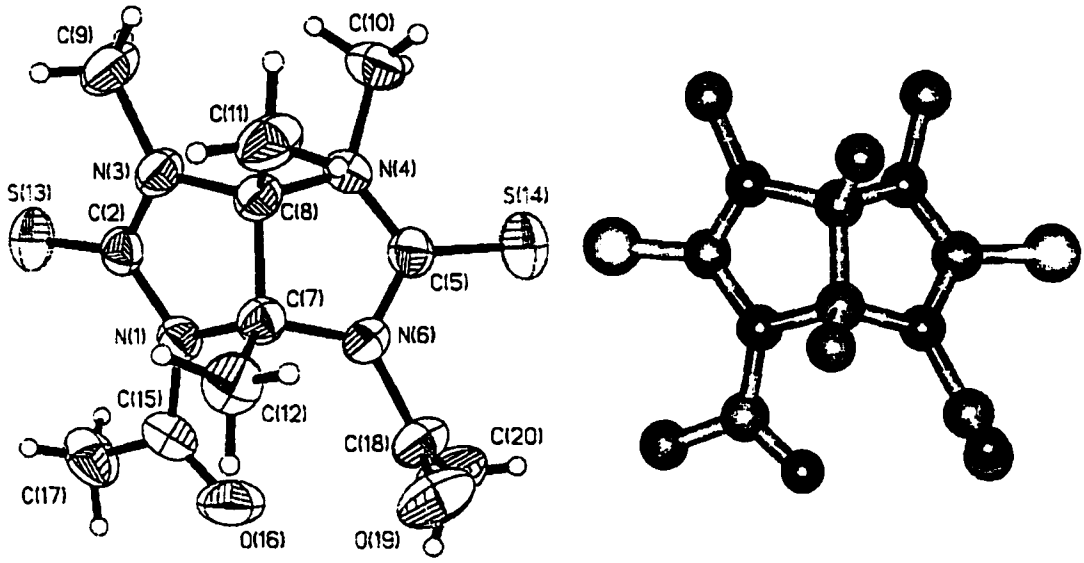


Figure 2.9: X-Ray Crystal Structure of Diacetyl Dithioglycoluril **2-6**: ORTEP Drawing (left) and Hyperchem Representation (right): "Top" View

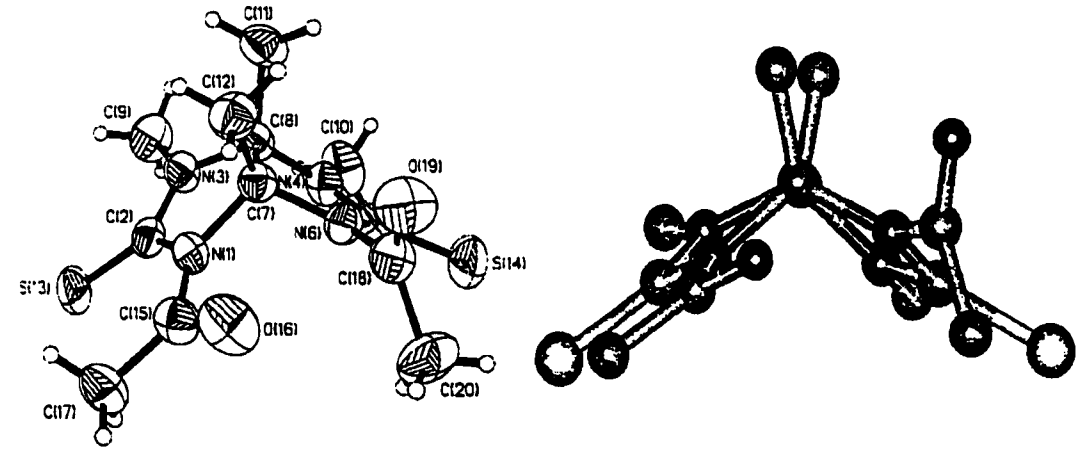


Figure 2.10: X-Ray Crystal Structure of Diacetyl Dithioglycoluril **2-6**: ORTEP Drawing (left) and Hyperchem Representation (right): "Front" View

Bond Lengths (Å)		Bond Angles (°)	
N1-C2	1.397 (3)	C2-N1-C15	130.0 (2)
N1-C15	1.399 (3)	C2-N1-C7	111.3 (2)
N1-C7	1.508 (3)	C15-N1-C7	118.6 (2)
C2-N3	1.342 (3)	N3-C2-N1	107.6 (2)
C2-S13	1.653 (2)	N3-C2-S13	124.1 (2)
N3-C9	1.457 (3)	N1-C2-S13	128.3 (2)
N3-C8	1.460 (3)	C2-N3-C9	122.9 (2)
N4-C5	1.348 (3)	C2-N3-C8	113.9 (2)
N4-C10	1.452 (3)	C9-N3-C8	123.2 (2)
N4-C8	1.475 (3)	C5-N4-C10	123.0 (2)
C5-N6	1.370 (3)	C5-N4-C8	112.6 (2)
C5-S14	1.663 (2)	C10-N4-C8	122.7 (2)
N6-C18	1.450 (3)	N4-C5-N6	108.3 (2)
N6-C7	1.463 (3)	N4-C5-S14	125.2 (2)
C7-C12	1.519 (4)	N6-C5-S14	126.5 (2)
C7-C8	1.547 (3)	C5-N6-C18	122.6 (2)
C8-C11	1.520 (4)	C5-N6-C7	111.9 (2)
C15-O16	1.214 (3)	C18-N6-C7	125.3 (2)
C15-C17	1.485 (4)	N6-C7-N1	110.8 (2)
C18-O19	1.192 (3)	N6-C7-C12	116.1 (2)
C18-C20	1.494 (4)	N1-C7-C12	109.9 (2)
		N6-C7-C8	102.9 (2)
		N1-C7-C8	101.3 (2)
		C12-C7-C8	114.7 (2)
		N3-C8-N4	111.1 (2)
		N3-C8-C11	112.7 (2)
		N4-C8-C11	111.6 (2)
		N3-C8-C7	103.0 (2)
		N4-C8-C7	101.6 (2)
		C11-C8-C7	116.1 (2)
		O16-C15-N1	117.3 (2)
		O16-C15-C17	121.3 (3)
		N1-C15-C17	121.4 (3)
		O19-C18-N6	119.2 (2)
		O19-C18-C20	123.3 (3)
		N6-C18-C20	117.4 (2)

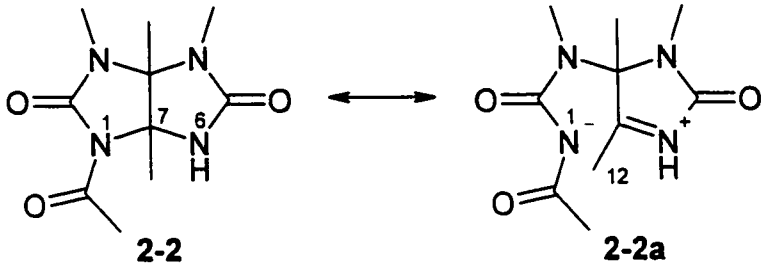
Table 2.6: Selected Bond Lengths and Angles for Diacetyl Dithioglycoluril **2-6**.

This structure also has a significant twist in the thioureido rings, and the dihedral angle C12-C7-C8-C11 is 21.2°. One of the acetyl groups is coplanar with the adjacent five-membered ring, while the other experiences a severe twist out of plane, of 54.4°; again, both oxygens point generally inwards. This twist of an acetyl group is the largest yet observed in this series. The thioureido ring attached to the coplanar acetyl group is quite planar, with N1 and N3 both displaying a trigonal planar geometry. In contrast, N4 and N6 are both pyramidalized to a significant extent (C7-N6-C5-C18 = 174°, C8-N4-C5-C10 = 165°).

2.7 Comparisons and Conclusions

2.7.1 Effects of the First Acylation Reaction

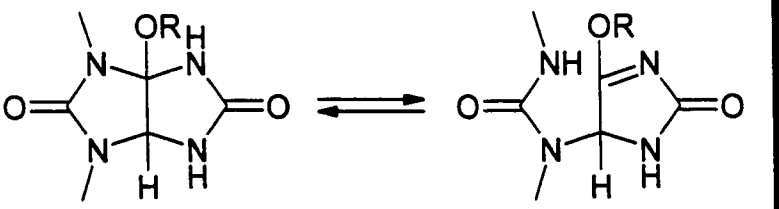
Interestingly, C12 in **2-2** moves toward the substituted nitrogen N1, rather than away from it, implying that this effect is not primarily due to steric interaction between C12 and the acetyl group. Rather, lengthening of the N1-C7 bond (by 0.046 Å), and corresponding shortening of the N6-N7 bond (by 0.021 Å) in **2-2** compared with **2-1** reflects the greater ability of N1 to accept negative charge. This can also be represented as an increased contribution of the open ring resonance form **2-2a** (Figure 2.11), in which the methyl group C12 points towards N1.



2-2 **2-2a**

Figure 2.11: Resonance Contributors of **2-2**

The structure of **2-2a** as a significant contributor is quite reasonable, since the negative charge at N1 is resonance-stabilized through overlap with the two carbonyl groups adjacent to it. Additionally, a related structure **2-7** (Scheme 2.1) has been observed to undergo a 5-*Exo-Trig* process to give the open chain tautomer **2-8**, which is in equilibrium with **2-7**[91].



R = menthyl

2-7 **2-8**

Scheme 2.1: Ring-Chain Tautomeric Equilibrium

As N1 is acylated to give **2-2**, conjugation between the lone pair on N1 and the carbonyl group C2-O13 is diminished due to developing overlap of this lone pair with the C15-O17 carbonyl group, an effect which is illustrated by the observed lengthening of the

N1-C2 bond by 0.039 Å as **2-1** is converted to **2-2**. Most of the other bond lengths and angles do not experience a significant change in going from **2-1** to **2-2**.

Similar observations can be made by comparison of **2-1** to the Benzoylacetyl condensation product **2-5**, which also possesses only one acyl substituent; here, the N1-C7 bond has lengthened by 0.029 Å, with a corresponding shortening of the N6-C7 bond length by 0.013 Å. This, presumably, again indicates a contribution from the open chain resonance form of the molecule. Additionally, the N1-C2 bond in **2-5** has lengthened significantly (0.045 Å) relative to the parent template **2-1**, demonstrating a substantial overlap of the N1 lone pair into the carbonyl of the acyl group, thus diminishing the π-character of the N1-C2 bond.

2.7.2 Effects of the Second Acylation Reaction

Comparison of the monoacetyl template **2-2** to the diacetyl template **2-3** or the acetyl benzoyl template **2-4** reveal some of the effects of the second acylation reaction on the structure of the glycoluril rings. It is very interesting to note that the addition of a second acyl unit does not restore any symmetry to the glycoluril ring: both **2-3** and **2-4** still have quite significant twists across the bridgehead methyl groups, giving dihedral angles of 24° and 18° respectively.

While the N1-C7 bond does not change to any significant extent in going from **2-2** to **2-3** or **2-4**, the N6-C7 bond does lengthen, by 0.036Å for diacetyl glycoluril, and by 0.039Å for acetyl benzoyl glycoluril. This reflects the fact that the addition of an acyl

group lowers the bond order, i.e. that there is significantly less double-bond character between N6 and C7. Similarly, the N6-C5 bond is also lengthened significantly, by 0.109 Å for diacetyl glycoluril and by 0.047Å for acetyl benzoyl glycoluril, reflecting greatly reduced overlap of the N6 lone pair of electrons into the π-system of the ureido carbonyl. Presumably, this occurs because these electrons can now overlap efficiently with the acyl carbonyl. This difference is larger for diacetyl glycoluril than for the acetyl benzoyl adduct because the twist of the acyl groups allows for better overlap in the diacetyl case (see section 2.7.3). Interestingly, in these systems the N4-C5 bond length does not change much, indicating that the bond order, and hence the amount of overlap of the N4 lone pair into the ureido carbonyl, is relatively constant regardless of the substituent on N6 (H or acyl).

2.7.3 Comparison of Diacyl Glycolurils: Reactivity to the Condensation Reaction

The diacetyl glycoluril **2-3**, the acetyl benzoyl glycoluril **2-4**, and the diacetyl dithioglycoluril **2-6** allow a direct comparison of the reactivity of these compounds towards the Claisen-like condensation reaction with the geometry of the acyl groups. Although the rate of the condensation reaction has not yet been measured with confidence, an examination of the products of the reaction provides an imprecise picture of these compounds' reactivity. Diacetyl template **2-3** rearranges to give the condensation product acetoacetyl glycoluril as the only product in an optimized yield of 93%. The acetyl benzoyl template **2-4** rearranges in the presence of a hindered base to

give benzoylacetyl template in quantitative yield as the only product. In contrast, the diacetyl dithioglycoluril template **2-6** condenses to the acetoacetyl adduct in an unoptimized yield of 62%, as well as generating a trace amount of the acetyl dithioglycoluril **4-4**. This result implies that the acetyl group in **2-6** is more reactive than that in **2-3**, since it is presumably cleaved through nucleophilic attack by lithium *tert*-amylate.

Normal amides possess planar geometry, as a result of the partial double bond character of the N-C(O) bond due to resonance. Twisted amides have received interest from a number of groups over the past 20 years, since they display unusually high reactivity towards nucleophiles, and have also been described as models for activated peptide units[92]. Recently, Shinji Yamada[93] reported on the properties of 3-pivaloyl-1,3-thiazolidine-2-thione as an extremely twisted amide. This compound has a twist of τ = 74.3°, which is the highest twist reported. The twist angle $\tau = \frac{1}{2}(\omega_1 + \omega_2)$, where ω_1 and ω_2 are the O-C-N-C dihedral angles, as defined by F.K. Winkler and J.D. Dunitz[94], with the alteration suggested by Yamada. Thus, the maximum twist angle τ would be 90°.

Previous to Yamada's report, no twisted amides were reported with a twist angle > 40°. Yamada's compound was extremely reactive to alcohols, even at neutral *p*H, and was 100-1000 times more reactive than the isopropyl derivative, in spite of the added steric bulk of the *tert*-butyl group. The bond length of the N-C(O) bond was very long (1.448Å) compared with a related compound with a much smaller twist angle (1.413Å, 20.1° twist).

One probable reason for the Claisen-like condensation reactivity is the existence of these twisted amides in the structures **2-3**, **2-4**, and **2-6** (Table 2.7).

Compound	N6-Acetyl Twist[a]	N6-C18 Bond Length (Å)
Diacetyl Glycoluril **2-3**	21.0°	1.397 (6)
Acetyl Benzoyl **2-4**	45.2°	1.425 (5)
Diacetyl Dithio **2-6**	54.4°	1.450 (3)

[a] "Acetyl twist" defined by $\tau = \frac{1}{2}(\omega_1 + \omega_2)$

Table 2.7: Comparison of Twisted Amide Character of Diacyl Glycolurils

The diacetyl glycoluril **2-3** has the smallest twist angle ($\tau = 21.0°$) in the crystal structure, and the corresponding shortest bond length (1.397Å), indicating that there is still significant overlap of the N6 lone pair of electrons into the acyl carbonyl group. The observed geometry of the acetyl benzoyl template **2-4** implies that the twist occurs in the acceptor amide ($\tau = 45.2°$), which makes sense in terms of reactivity, since the twisted acyl group will have a much more electrophilic carbonyl than the coplanar acyl group. The diacetyl dithioglycoluril **2-6** has a very large twist angle ($\tau = 54.4°$), approaching that observed by Yamada, and an extremely long amide N-C(O) bond (1.450Å), even longer than the bond length reported by Yamada. This result is quite interesting, since the two diacetyl compounds **2-3** and **2-6** are very similar in terms of steric bulk. Therefore the twist of the acyl group must result from electronic effects. It should be

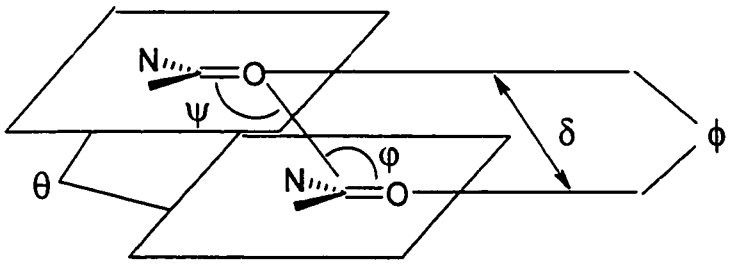
mentioned that the bond length N1-C15 for the coplanar acetyl units in all three compounds is effectively constant, at ~ 1.39 - 1.40Å.

2.7.4 Examination of Putative Condensation Reaction Transition State

In solution, the acyl groups must rotate about the amide bond in order to undergo the Claisen condensation reaction, since this reaction has been shown to occur solely in an intramolecular manner. This rotation is hindered, since amide bonds have considerable double bond character, especially for those acyl groups which are coplanar with the adjacent ureido rings. The precise barrier to rotation is unknown, but should lie between 22 kcal/mol, the barrier for rotation of N,N-dimethylacetamide[95], and 11.5 kcal/mol for pivaloyl dimethylamine. This is a significant barrier, and implies that free rotation is unlikely in these systems. Although solvent effects may lower the barrier to rotation significantly, it is likely that the counterion of the base aids in the rotation through chelation between the acyl oxygen and the urea oxygen.

The assumption was made that the reactive carbon of the enolate formed in the transition state occupies the same space as the oxygen in the x-ray crystal structure as a result of rotation about the amide bond by 180°, possibly through a chelation effect. A series of parameters can then be assigned which define the geometry of the nucleophilic enolate and the electrophilic carbonyl relative to each other (Figure 2.12). These parameters can then be compared with the ideal distances and angles for this type of

reaction to occur, and a rough picture of the transition state of the condensation reaction can be obtained.



	Diacetyl	Acetyl Benzoyl	Diacetyl Dithio
δ	2.83 A	2.75 A	2.63 A
ψ	113	110	118
φ	78	89	98
ϕ	130	138	132
θ	90	61	62

Figure 2-12: Observed Geometry for Diacylglycolurils

Important parameters have been determined to be: the distance between the oxygen of one acyl group (or putative enolate carbon) and the acceptor carbonyl carbon of the other: δ, the angle ψ between the C=O of the donor and the carbon of the acceptor, the angle φ between the oxygen (putative carbon) of the donor and the C=O of the acceptor, the angle ϕ between the two carbonyl groups, and the angle θ between the two N-C(O)-C planes.

In an ideal system, δ should be within < 3.4 Å, which is twice the Van der Waals radius of carbon, ψ should lie between about 90-110° for efficient overlap of the π-electrons of the donor HOMO with the acceptor LUMO, φ should correspond to the

Burgi-Dunitz angle of attack of a nucleophile on a carbonyl of ~105°[96], the dihedral angle C=O-C=O between the carbonyl of the donor and of the acceptor ϕ, which should be approximately 180°, and θ, the angle between the planes defined by C15(O16)-C17 and C18(O19)-C20 which should be 0° to optimize the overlap.

The x-ray crystal structures show that these compounds are not set up ideally for the condensation reaction to occur, although the δ and ψ values are reasonably close to the ideal. The value for φ is also not too bad, but the angle ϕ is about 40 - 50° away from the ideal, and θ is nearly orthogonal in all of these systems, indicating that significant rotation does need to occur before the reaction is likely to happen.

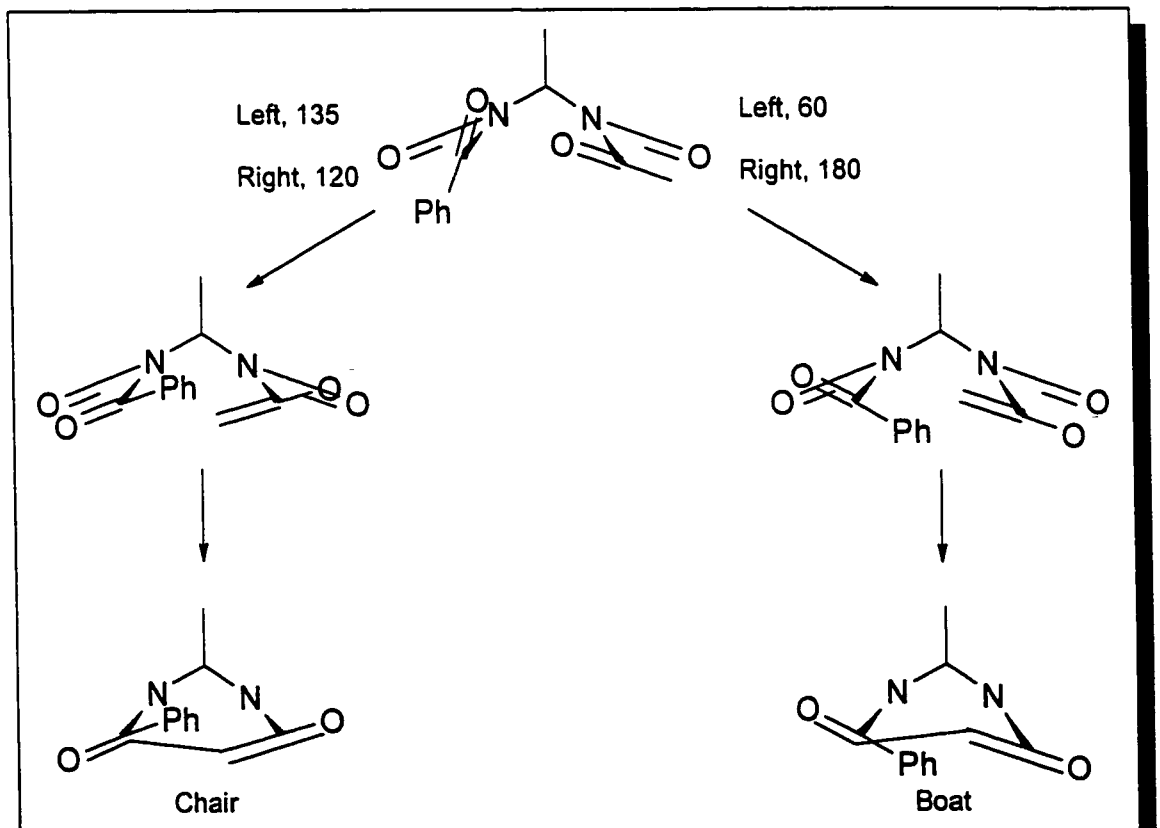


Figure 2-13: Transition-States During Condensation of Acetyl Benzoyl Glycoluril **2-4**

There are two likely ways to get near-optimum geometry from these systems, involving rotations of the two acyl groups. Examining acetyl benzoyl template as an example (Figure 2.13) since the two acyl groups are easily distinguished, the optimal geometry can be obtained by rotating the benzoyl group by 135° and the acetyl group by 60° to get the transition state shown on the left, which adopts a chair-like conformation.

Conversely, rotating the acetyl by 180° and the benzoyl by 120° leads to the transition state shown on the right, which adopts a boat-like conformation. Although in other systems, the chair conformer is preferred, here this seems unlikely, since twisting the acetyl group out of the plane of the ureido ring puts more positive charge on the carbonyl carbon, while allowing the benzoyl group to be coplanar with the ureido ring will decrease the electrophilic character of the carbonyl on this acceptor site by allowing better overlap with the nitrogen lone pair. In the boat conformation, on the other hand, the enolate carbon should be more electronegative, thus enhancing its nucleophilicity, while the benzoyl group is still twisted out of the plane, leading to a more electrophilic carbonyl and a longer, weaker N-C(O) bond. Both of these factors should work together in this system to facilitate the condensation reaction. Thus, it seems quite likely from this analysis that the transition state passes through a boat-like, rather than a chair-like, conformation. Similar analyses of the other two compounds support this result.

2.8 Summary

The crystal structures of compounds **2-1** to **2-6** reveal a number of interesting features, such as large twist angles in the amide bonds of some of the diacyl glycolurils (eg. **2-4** and **2-5**) which may help to explain the high reactivity of these systems. However, the ground-state configurations of these compounds do not correspond to the conformations required for the intramolecular Claisen-like condensation reaction. Instead, rotation of the acyl groups must occur around the amide bonds, and an analysis shows that this rotation is likely to lead to a boat-like transition state for this reaction.

2.9 Experimental

General

All reactions were performed in flame-dried glassware, under a positive pressure of nitrogen, unless otherwise noted. Air- and moisture-sensitive compounds were transferred by syringe. Melting points are uncorrected. Proton and carbon-13 nmr spectra were obtained on a Bruker AC-200 spectrometer. The reference for nmr chemical shifts was TMS. Data are given as chemical shift (integral, multiplicity [s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet], coupling constant(s) (Hz), assignment). Fourier transform infrared (FTIR) spectra were recorded on a Bio-Rad SPC 3200 spectrophotometer. Mass spectra were recorded on a VG analytical ZAB-E machine using electron impact (EIMS). High resolution mass spectra were also recorded on the same spectrometer. Flash column chromatography was performed with Kieselgel 60 (230-400 mesh ASTM) according to the method of Still[97]. THF was freshly distilled

under nitrogen protection from potassium/benzophenone. *n*-Butyllithium (*n*-BuLi) was titrated using 2,5-dimethoxybenzyl alcohol in THF[98].

General Preparation of Monoacylglycolurils

Method a) One equivalent of *n*-BuLi was added to a stirred suspension of glycoluril **2-1** in dry THF (60 mL / g) under nitrogen, and the mixture was heated at reflux for 1 h, during which time the suspension changed colour from white to orange, and its viscosity increased dramatically. The suspension was cooled to room temperature, then a 20 % excess of acyl chloride was added and the mixture was stirred for 1 h.

Method b) Glycoluril **2-1** was heated at reflux for 20 h in neat acyl anhydride.

For both a) and b), the mixture was quenched with ammonium bicarbonate for 12 h, then filtered to remove solid material. Unreacted **2-1** was recovered by washing the solid residue thoroughly with MeOH. The filtrate was concentrated, then the components were separated by flash column chromatography on silica gel using EtOAc as the eluent.

General Preparation of Diacylglycoluril

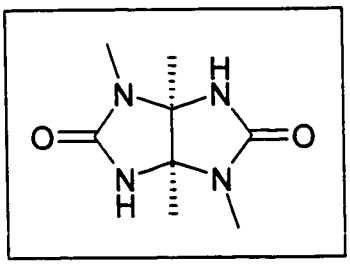
One equivalent of *n*-BuLi in hexane or freshly prepared LDA in THF was added to a stirred solution of monoacylated template in THF (60 mL/g starting material) at 0 °C. After stirring for 30 min, acyl chloride was added in 20-50 % mole excess. After being stirred for another hour at room temperature, the solution was quenched with either NH_4HCO_3 powder, or with 1 M $NaHSO_4$ solution. The product was then either filtered to remove NH_4HCO_3, or extracted into chloroform (from $NaHSO_4$ solution). The

remaining solvent was removed at reduced pressure, and the product was separated from residual starting material by flash column chromatography in EtOAc.

3,4,7,8-Tetramethylglycoluril (2-1). To a stirred suspension of *N*-methylurea (38 g, 0.514 mol) in absolute ethanol (65 mL) was added concentrated hydrochloric acid (15 drops) and 2,3-butanedione (22.5 mL, 22.5 g, 0.260 mol). The solution clarified as the exothermic reaction proceeded. Product appeared as a precipitate after *ca.* 15 min. The mixture was stirred for a further 30 min, then cooled to 0 °C for 1 h. The solid product was collected by vacuum filtration to give 26 g (51 %) of a mixture of two regioisomers **2-1** and **2-1a** in a ratio of 1 : 1. The crude product was recrystallized twice from ethanol (60 mL ethanol/1 g solid). The desired isomer **2-1** was obtained as colourless crystals (21%). Mp: (EtOH) >300 °C; ^{1}H nmr (CD_3OD, 200 MHz) δ 2.77 (6H, s, NC*H*$_3$), 1.48(3H, s, *CH*$_3$), 1.39 (3H s, C*H*$_3$); ^{13}C nmr (CD_3OD, 50 MHz) δ 161.0 (*C*=O), 83.1 (*C*NN), 74.7 (*C*NN), 26.8 (N*C*H$_3$), 22.1 (*C*H$_3$), 15.9 (*C*H$_3$); FTIR (KBr pellet, cm^{-1}) 3282 (NH), 2920 (C-H), 1693 (C=O), 1506, 1441, 1414, 1389, 1263, 1230, 1120, 1087, 1003, 963, 768, 721; EIMS *m/z* 198 [M]$^+$, 183, 140, 126, 125, 111, 85, 65 (base); HRMS calcd. for $C_8H_{14}N_4O_2$ 198.1117, found 198.1121.

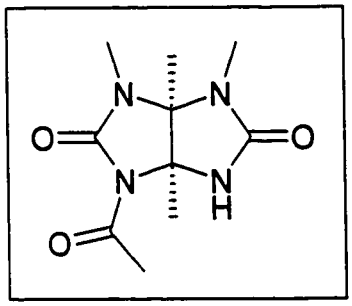
1,4,7,8-Tetramethylglycoluril (2-1a). A mixture of **2-1** and **2-1a** (2 g, 1:1 ratio) was heated at reflux in acetic anhydride (20 mL) for 20 h. Compound **2-1** was completely

converted and dissolved. After cooling to room temperature, the solid material was



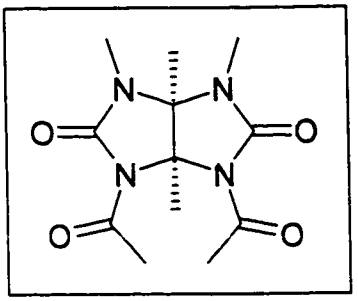
collected and washed with $CHCl_3$, THF, and cooled ethanol. Compound **2-1a** was obtained in a yield of 810 mg (81% based on the true quantity of **2-1** in the starting material). ^1H nmr (CD_3OD, 200 MHz) δ 2.61 (6H, s, NC*H*$_3$), 1.40 (6H, s, C*H*$_3$); HRMS calcd. for $C_9H_{14}N_4O_2$ 198.1117, found 198.1111.

1-Acetyl-3,4,7,8-tetramethylglycoluril (2-2). Glycoluril **2-1** (2 g, 10 mmol) was heated

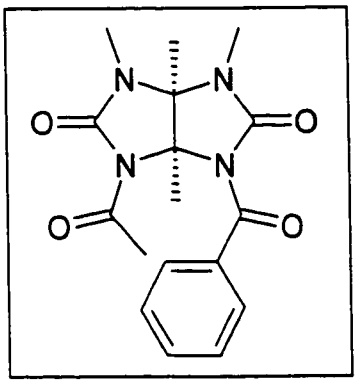


with acetic anhydride (20 mL) to give **2-2** (1.89 g, 78%) as a white powder by method b). Mp: 178-180 °C; ^1H nmr ($CDCl_3$, 200 MHz) δ 6.00 (1 H, s, N*H*), 3.02 (3H, s, NC*H*$_3$), 2.87 (3H, s, NC*H*$_3$), 2.48 (3H, s, COC*H*$_3$),1.69 (3H, s, C*H*$_3$), 1.56 (3H, s, C*H*$_3$); ^{13}C nmr ($CDCl_3$, 50 MHz) δ 171.0 (Me*C*=O), 157.2 (NN*C*=O), 153.0 (NN*C*=O), 78.5 (*C*NN), 76.4 (*C*NN), 27.0, 26.3, 24.8, 19.5, 15.6; FTIR (KBr pellet, cm^{-1}) 3250 (NH), 2980 (CH), 2940 (CH), 1723 (C=O), 1689 (C=O), 1487, 1416, 1326, 1117, 943; EIMS *mlz* 240 $[M]^+$, 225, 210, 198, 183, 168, 156, 140, 125 (base); HRMS calcd for $C_{10}H_{16}N_4O_3$ 240.1222, found 240.1231; Anal. calcd for $C_{10}H_{16}N_4O_3$ C, 49.99; H 6.71; N, 23.32, found C, 50.27; H 6.85; N, 23.16.

1,6-Diacetyl-3,4,7,8-tetramethylglycoluril (2-3). Observed as a side product in the intramolecular Reformatsky reaction (see section 3.2.2.2); identical by proton nmr to authentic material synthesized by Sengen Sun. ^{1}H nmr ($CDCl_3$, 200 MHz) δ 2.97 (6H, s, NCH_3), 2.48 (3H, s, O=C-CH_3), 1.95 (3H, s, CH_3), 1.51 (3H, s, CH_3).



1-Benzoyl-6-acetyl-3,4,7,8-tetramethylglycoluril (2-4). Acetyl glycoluril **2-2** (708 mg, 2.95 mmol) was charged to a flask along with 50 mL THF and cooled to 0 °C. *n*-Butyl lithium (1.05 eq., 2 mL of 1.6 M solution in hexanes) was added dropwise, and the mixture was stirred for 15 min. Benzoyl chloride (1.2 eq., 410 □L) was added and the stirring was continued for 1 h. The reaction mixture was quenched with $NaHSO_4$ (10 mL of 1 M aqueous solution), extracted into $CHCl_3$ (3 × 20 mL), washed with water (20 mL) and brine (20 mL), then dried over anhydrous sodium sulfate (2 g). The mixture was filtered, and the solvent was removed from the filtrate by rotary evaporation to give a yellowish oil which foamed on exposure to vacuum. The product (855 mg, 92%) was recrystallized from $CHCl_3$/Hexanes, and determined to be a 9:1 mixture of the expected product and a compound identified as 1,6-dibenzoyl-3,4,7,8-tetramethylglycoluril. ^{1}H nmr (200 MHz, $CDCl_3$) δ 7.51 - 7.42 (3H, m, *m*-, *p*- C_6H_5), 7.37 – 7.24 (2H, m, *o*- C_6H_5), 3.00 (3H, s, N-CH_3), 2.82 (3H, s, N-CH_3),

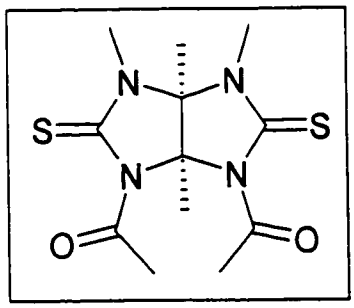


2.47 (3H, s, O=C-CH_3), 2.03 (3H, s, CH_3), 1.53 (3H, s, CH_3); ^{13}C nmr (50 MHz, $CDCl_3$) δ 170.99 (O=*C*-C), 170.18 (O=*C*-C), 153.29 (*C*=O), 152.79 (*C*=O), 135.07, 132.19, 131.94, 129.21, 128.59, 127.67 (Ph), 80.20, 78.15 (*C* bridgehead), 27.04, 25.18, 20.92, 19.29, 15.21, 14.08; IR (NaCl disks, cm^{-1}) 3020 (C-H str.), 1728 (C=O), 1408, 1333, 1216, 1114; UV (THF): λ_{max} = 242 nm (ε =6300); EIMS 344 [M^+], 301, 229, 126, 105 (base), 77, 56; HRMS calcd. for $C_{17}H_{20}N_4O_4$: 344.1484, found: 344.1492; Anal. calcd. for $C_{17}H_{20}N_4O_4$: C: 59.24, H: 5.85, N: 16.27; found C: 60.21, H: 5.87, N: 15.91.

1-(3'-Phenyl-3'-oxopropanoyl)-3,4,7,8-tetramethylglycoluril (2-5). Acetyl benzoyl glycoluril **2-4** (100 mg, 2.9×10^{-4} mol) was dissolved in THF (10 mL) and cooled to 0 °C. Potassium *tert*-butoxide (1.3 eq., 43 mg) was added and the mixture was stirred for ½ h. The reaction mixture was quenched over 3 h with ammonium bicarbonate, then filtered through Celite. Solvent was removed on the rotary evaporator to give a clear oil which foamed on exposure to high vacuum to give the product (98 mg, 98%) as a 2.6:1 mixture of keto : enol tautomers. ^{1}H nmr (200 MHz, $CDCl_3$) δ 8.1 – 7.40 (5 H, m, C_6H_5), 6.11 (1H, s, N*H* enol),6.09 (1H, s, N*H*), 4.94 (1H, d, O=C-C*H*H, ^{2}J = 16.3 Hz), 4.05 (1H, d, O=CH*H*, ^{2}J = 16.3 Hz), 3.02 (3H, s, N-CH_3 enol), 2.92 (3H, s, N-CH_3), 2.86 (3H, s, N-CH_3 enol), 2.84 (3H, s, N-CH_3), 2.14 (3H, s, O=C-CH_2, O*H* enol), 1.79 (3H, s, CH_3), 1.76 (3H, s, CH_3 enol), 1.56 (3H, s, CH_3 enol), 1.55 (3H, s, CH_3); ^{13}C nmr (125 MHz, $CDCl_3$) δ 193.67

O=*C*-Ph), 167.91 (*C*=O), 167.23 (*C*=O), 152.79 (*C*=O), 136.06, 133.73, 131.58, 128.73, 128.16, 126.48, 88.24, 78.80, 48.15, 28.10, 26.44, 20.05, 199.32, 15.71; IR (NaCl disks, cm^{-1}) 3020 (C-H str.), 1728 (C=O), 1408, 1333, 1216, 1114; UV (THF) $\square_{max}$ = 325.0 nm ($\square$ = 4400), $\square$ = 280.2 nm ($\square$ = 6300); EIMS *m/z* 344 [M^+], 272, 198, 125, 105 (base), 77, 56; HRMS calcd. for $C_{17}H_{20}N_4O_4$: 344.1484, found: 344.1492; Anal. calcd. for $C_{17}H_{20}N_4O_4$: C: 59.24, H: 5.85, N: 16.27; found C: 59.16, H: 6.05, N: 16.58.

1,6-Diacetyl-3,4,7,8-tetramethyl-2,5-dithioglycoluril (2-6). Method 1: (See Chapter 4). A flask was charged with 1-acetyl-3,4,7,8-tetramethyl-2,5-dithioglycoluril **4-4** (52 mg, 0.19 mmol) and THF (10 mL) and cooled to 0 °C, then *n*-BuLi (1.1 eq, 137 $\square$L of 1.4 M solution) was added and the mixture was stirred for 10 min. Acetyl chloride (1.2 eq., 16 $\square$L) was added and the mixture was stirred for a further 2 h. The reaction was then quenched with 2 mL of 1 M $NaHSO_4$, and the product was extracted into $CHCl_3$ (3 × 10 mL), washed with water (10 mL) and dried over anhydrous sodium sulfate. The mixture was filtered and the solvent was removed on the rotary evaporator. The product (50.4 mg, 84%) was isolated as a white powder after flash column chromatography on silica gel in 70% EtOAc/Hexanes. **Method 2:** This compound was prepared in one step from 3,4,7,8-tetramethyl-2,5-dithioglycoluril **4-2** (504.9 mg, 2.36 mmol) by heating at reflux in neat acetic anhydride for 16 h. The acetic anhydride was removed by distillation, then the products were purified by flash column chromatography



on silica gel in 70 % EtOAc/Hexanes. The product (158 mg, 24%) was isolated as a white powder. Mp: 172-178 °C, decomposes; ^{1}H nmr ($CDCl_3$, 500 MHz) δ 3.22 (6H, s, S=C-N-C*H*$_3$), 2.72 (6H, s, O=C-C*H*$_3$), 1.86 (3H, s, C*H*$_3$), 1.53 (3H, s, C*H*$_3$); ^{13}C nmr ($CDCl_3$, 125 MHz) δ 177.93 (*C*=S), 172.84 (*C*=O), 87.03, 85.19, 31.17, 29.02, 18.71, 15.10; EIMS *m/z* 314 [M^+], 273, 184, 142 (base), 109, 56; HRMS calcd. for $C_{12}H_{18}N_4O_2S_2$: 314.0871, found: 314.0870; Anal. calcd. for $C_{12}H_{18}N_4O_2S_2$: C: 45.80, H: 5.77, N: 17.82; found: C: 46.13, H: 5.87, N: 17.87.

CHAPTER 3: Mechanistic Aspects of the Glycoluril Template

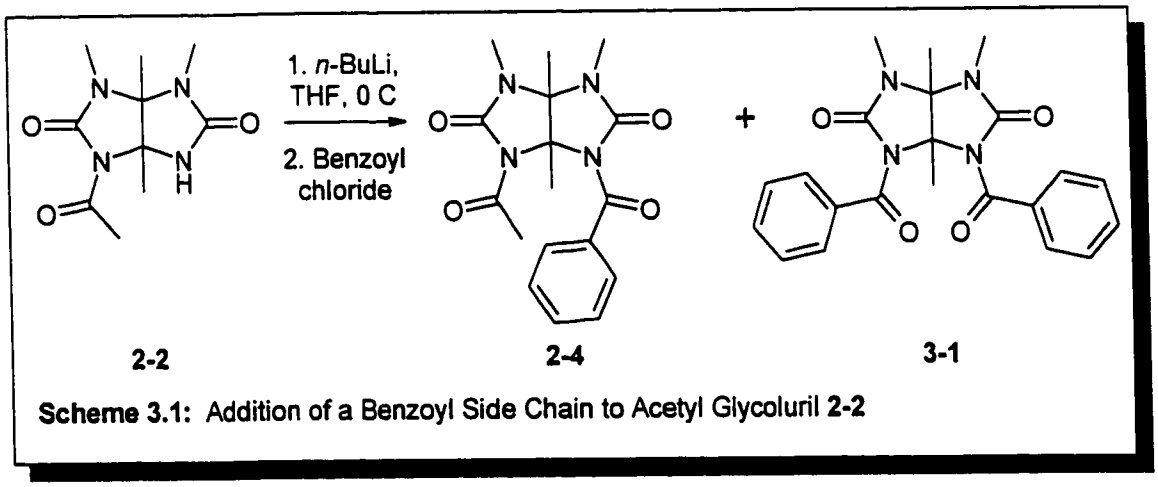
3.1 From Acyl to Aroyl

Although a number of acyl adducts of the glycoluril template have been synthesized and studied, to this point no attempt to use aroyl moieties as substrates for the intramolecular Claisen-like condensation reaction had been examined. There was some question as to whether an acyl-aroyl glycoluril compound could be made, and more critically, whether this compound would undergo the intramolecular condensation reaction. Thus, the simplest compound, 1-benzoyl-6-acetyl-3,4,7,8-tetramethylglycoluril was synthesized and examined. It was also noted that this could be a convenient compound to study the kinetics of the condensation reaction, since it can only rearrange in one fashion, thus simplifying the observable products, and also since it should be strongly absorbing in the UV.

3.1.1 Synthesis of Acetyl Benzoyl Glycoluril

The synthesis of acetyl-benzoyl glycoluril adduct **2-4** was undertaken in one step from acetyl glycoluril **2-2** (Scheme 3.1). Thus, the acetylated compound **2-2** was dissolved in THF at 0 °C, then 1.1 equivalents *n*-BuLi was added, followed by 1.2 equivalents of

benzoyl chloride to provide **2-4** in 86% yield. The benzoylation reaction provides as a side product about 10% of a *bis*-benzoyl adduct (**3-1**), whose formation remains unexplained but may be related to extended times of reaction, since it has only been observed in reactions that were allowed to stir overnight. A similar product was observed by Sun[84] in the acetylation of acetyl glycoluril **2-2** with ^{13}C-labelled acetyl chloride. Separation of this side-product has proven difficult since they have similar physical properties including polarity and solubility, so the mixture was used as is in further steps, although the amount of **3-1** present was minimised by shorter reaction times.



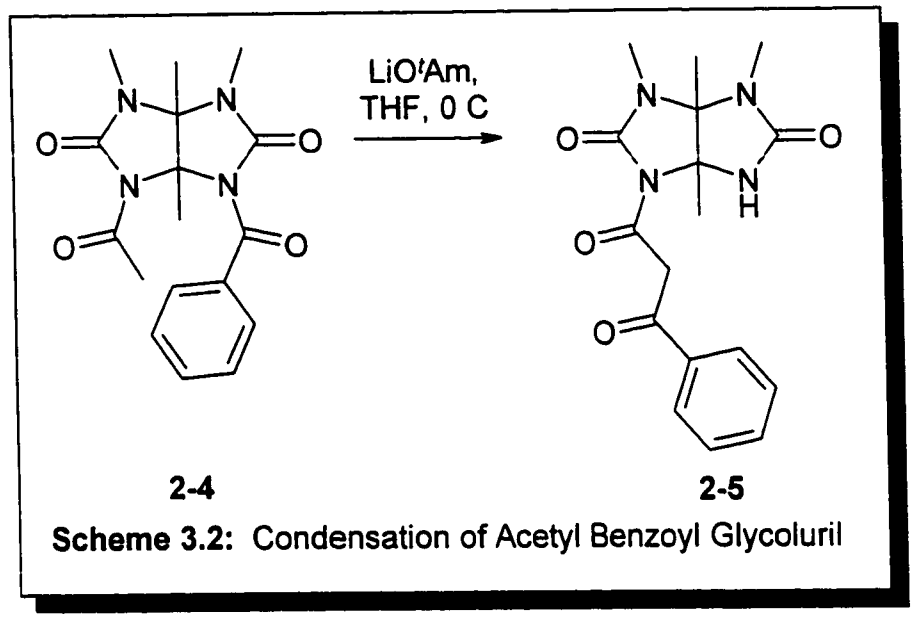
2-2 **2-4** **3-1**

Scheme 3.1: Addition of a Benzoyl Side Chain to Acetyl Glycoluril **2-2**

3.1.2 Condensation of Acetyl-Benzoyl Template

The condensation reaction to produce the benzoylacetyl adduct **2-5** proceeds smoothly and in near quantitative yields (crude product contains only **2-5** by ^{1}H nmr) under standard conditions (LiO^{t}Am, THF, 0 °C, 20 minutes) (Scheme 3.2). As expected,

the condensation of **2-4** provides only product **2-5** rather than a mixture, since the benzoyl moiety does not possess any acidic protons α to the carbonyl group.



2-4 **2-5**

Scheme 3.2: Condensation of Acetyl Benzoyl Glycoluril

3.1.3 Kinetic Studies on Acetyl-Benzoyl Condensation Reaction

Initial kinetic studies of the condensation reaction were undertaken with the help of Monica Joch, a co-op student working in our laboratory, and were very promising. Although both **2-4** and **2-5** absorb strongly at 280 nm, the enol tautomer of the product also absorbs at 325 nm. By dissolving the compound in an 0.1 M K_2CO_3 buffer at pH 10.3 the equilibrium is shifted in favour of the enolate form, which also absorbs at 325 nm. Early studies involved manipulating the temperature and solvent mixture to get a usable system, where the kinetics can be observed. The reaction was carried out at -20 °C in THF, and aliquots were removed every 30 s and quenched into the buffer. Dioxane

was added to keep the compounds soluble, and UV spectra were recorded as a function of reaction time.

These preliminary results showed that the reaction occurred very rapidly under these conditions; no additional product formation was observed after 5 min. In contrast, no reaction occurred at –78 °C. However, the results obtained were not sufficiently reproducible to extract a reliable rate constant for the reaction; different runs gave quite different results. This is, perhaps, not entirely surprising, given the uncertainty involved in the timing of the quenches, and in the complexity of the solution being analysed.

With this in mind, kinetic aspects of this project were taken over by Dr. Bob MacDonald (Mount St. Vincent University). A different approach, monitoring the reaction directly in the UV cell, was envisioned as the solution for the problems that had been observed. His student, Verna MacKinnon, has encountered other difficulties, including problems relating to keeping the mixture homogeneous, and complete removal of water from the system, since any water present will immediately quench an equivalent amount of potassium *tert*-butoxide. In order to obtain an observable rate, the reaction must be run at extreme dilution; therefore, any water in the solvent is quite significant. A recent report from his student indicated that one experimental run provided evidence that the reaction follows first-order kinetics in substrate, giving an apparent rate constant k_{obs} = 7.7×10^{-3} s^{-1}, corresponding to a half-life of 90 seconds under very dilute condtions ([substrate] = 1.0×10^{-4} mol/L, [base] = 1.7×10^{-3} mol/L). If one assumes that the reaction is first order in base, which has not yet been proven, then this corresponds to a bimolecular rate constant k_2 = 4.5 $Lmol^{-1}s^{-1}$. Dr. MacDonald has theorized that the

of the other possible products were observed, this would indicate that the six-membered transition state was not the most important factor in the condensation reaction.

Treatment of **3-5** with a hindered base under standard conditions did not lead to any of the expected products; instead, the reaction conditions led solely to degradation of the acetyl pyruvoyl template to the acetyl glycoluril adduct (**2-2**). Several variations in

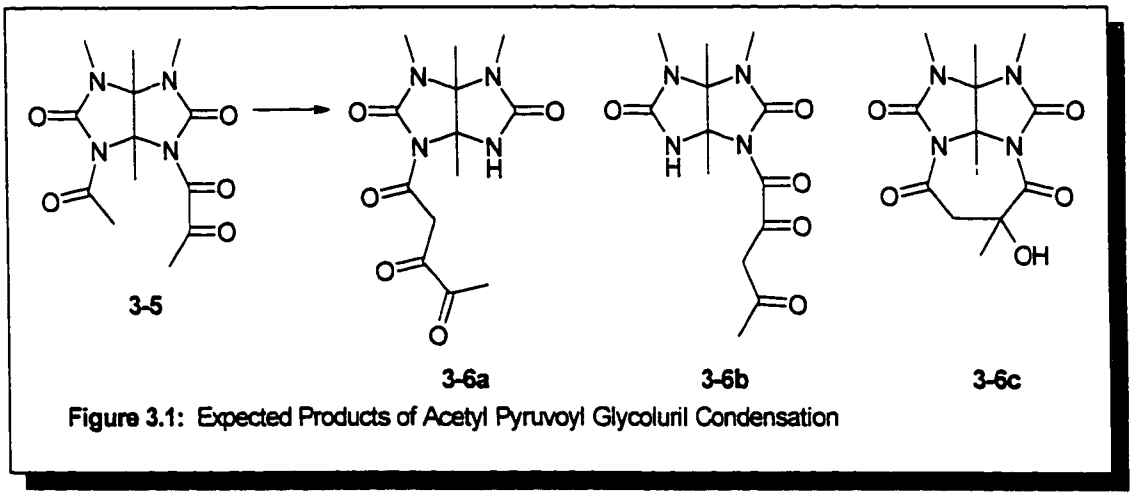


Figure 3.1: Expected Products of Acetyl Pyruvoyl Glycoluril Condensation

the reaction conditions were investigated, including lowering the temperature to –78 °C, and using a variety of bases, but the results were the same. Thus, the only conclusion that can be drawn from this study is that glycoluril compounds with a pyruvoyl side-chain are very unstable to basic conditions. This is perhaps not surprising when one considers that a number of other α-keto carbonyl compounds also display low stability to harsh conditions.

problems with reproducibility that they have observed stem from the lowering of base concentration by trace water in the solvents and from the atmosphere, and that the actual rate constants are likely higher than those reported above.

3.2 Closer Investigation of Important Reactions

3.2.1 Other Methods to Acylate Glycoluril 2-1

The conversion of 3,4,7,8-tetramethylglycoluril **2-1** to an acyl glycoluril adduct proceeds very readily and with high yields for a number of simple acyl units. More complicated substrates, however, frequently exhibit poor reactivity to the standard conditions used for the first acylation reaction. The first method, which involves heating the glycoluril template in neat acyl anhydride is often impractical, either because of the expense of the anhydride in question, or because of the high volatility of some acyl anhydrides. The second method, which is more commonly used with complex acyl side chains, involves abstraction of a proton from the glycoluril NH site with *n*-BuLi in THF at reflux to give the amide anion, followed by addition of an acyl chloride at room temperature. The high temperature required for this reaction stems from the extremely low solubility of glycoluril **2-1** in organic solvents. This requirement to form the anion before reacting with the acyl chloride is very limiting; extreme care must be taken to remove even trace amounts of HCl from the acyl halide, since it will rapidly quench the anion.

In many cases where the anion must be generated, and the acid chloride is synthesized from the acid, very low yields (10 – 40%) have been observed. This is attributed to residual HCl in the acid chloride, which can be present even after distillation.

These observations led to the following study, wherein a variety of non-anionic reaction conditions were investigated for their utility in leading to acyl glycoluril adducts. Another aspect of this investigation was to find other, more suitable solvents for the glycoluril template, which previously had been shown to be soluble in H_2O, somewhat soluble in MeOH, and soluble in boiling EtOH, none of which are suitable reaction solvents for the acylation reaction.

Preliminary studies have tested a wide variety of solvents for solubility of glycoluril **2-1**, both at room temperature and at elevated temperatures. One experiment involved reacting the glycoluril **2-1** with *n*-BuLi at room temperature, followed by addition of excess acetyl chloride; another involved stirring glycoluril **2-1** in boiling solvent to test solubility, followed by addition of excess Ac-Cl while the solution was hot as a preliminary test of reactivity (Table 3.1). Production of the acetyl glycoluril adduct was monitored by comparison of TLC plates with authentic material.

Solvent Added[a]	Solubility[b] Cold or Hot	Base Added	Production of 2-3 (by TLC)
THF	Insoluble	*n*-BuLi	N.D.[c]
THF/20% TMEDA	Moderate at R.T.	*n*-BuLi	Yes
THF/20% DMSO	Insoluble	*n*-BuLi	N.D.
THF/20% HMPA	Slight at R.T.	*n*-BuLi	Trace
Pyridine	Insoluble	None	N.D.[d]
1,2-Dimethoxyethane	Slight at Reflux	None	Some
Dimethoxydigol	Insoluble	None	N.D.
DMSO	Soluble at Reflux	None	Some

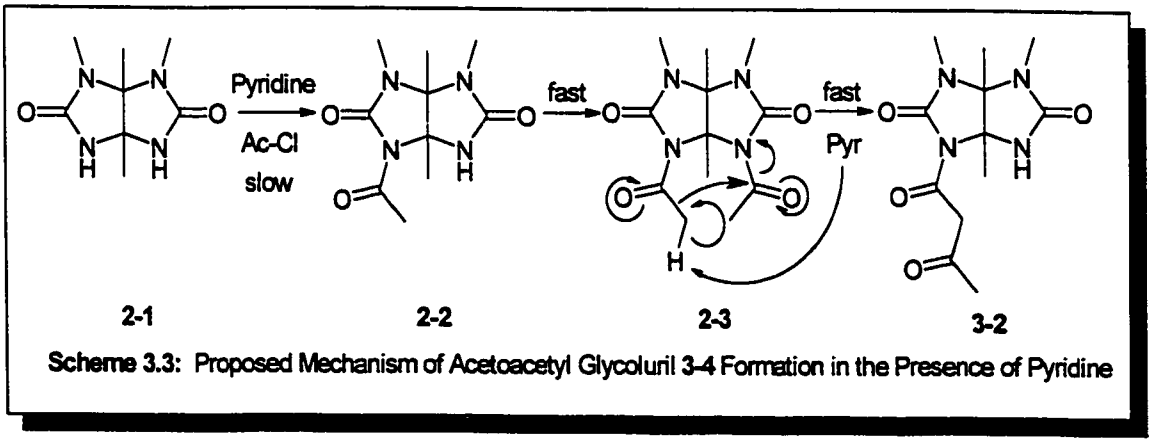
[a] Approximately 2 mL of solvent added / 50 mg glycoluril
[b] "Soluble" refers to complete disappearance of crystals
[c] N.D. = none detected
[d] trace acetoacetyl glycoluril **3-2** production observed

Table 3.1: Solubility and Reactivity Studies on Glycoluril **2-1**

The best combination investigated thus far for the acetylation of glycoluril **2-1** is the tetramethylethylenediamine / THF combination using a base, which gave good conversion of **2-1** to **2-2** using acetyl chloride, as determined by both TLC and proton nmr analyses. Presumably, the TMEDA serves as a polar cosolvent, aiding in the solubilization of glycoluril **2-1**, and thus allowing the reaction to occur at room temperature. Strangely, when the identical reaction was performed with decanoyl chloride, the presence of TMEDA inhibited the reaction compared to a flask treated

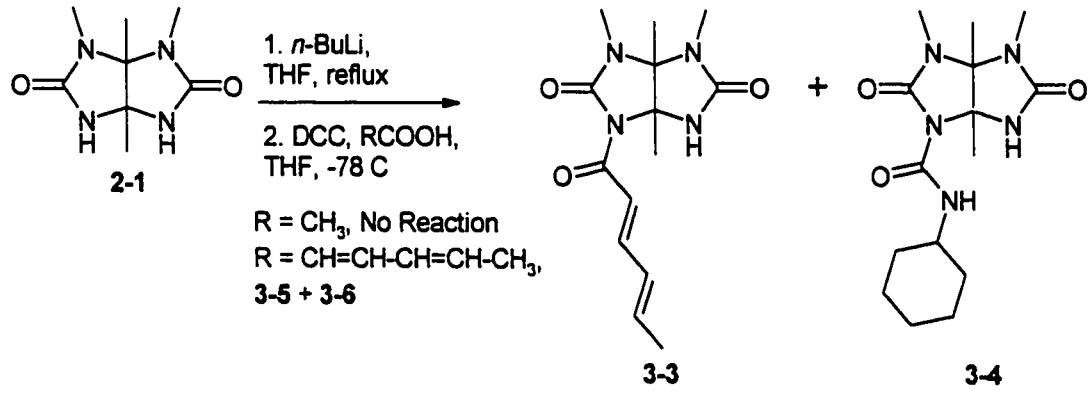
identically that lacked the TMEDA (12.2% with TMEDA, 52.5% yield without), possibly through stabilization of the anion. This incongruity means that the use of TMEDA must be evaluated separately for each reaction attempted.

Production of acetoacetyl glycoluril **3-2** in the pyridine system was unexpected, but can be easily explained. Pyridine is a moderate base, but the template is only slightly soluble in pyridine, even at reflux. Thus, it is likely that the first acylation occurs on only a small amount of material (Scheme 3.3). Since the product, acetyl glycoluril **2-2** is more soluble than the reactant, it is subjected to a large excess of both base and acetyl chloride (actually present as an acetyl pyridinium species, which is also a highly activated acid derivative that is frequently used instead of acid chlorides). Effectively, the second acetylation in this system has a lower barrier than solubilizing more of the parent glycoluril; once the diacetyl glycoluril **2-3** is produced, pyridine is sufficiently basic to cause a spontaneous condensation reaction in the usual manner, so one observes production of a small amount of acetoacetyl glycoluril **3-2**, along with unreacted starting material. Neither acetyl glycoluril **2-2** nor diacetyl glycoluril **2-3** was directly observed in this case.



Scheme 3.3: Proposed Mechanism of Acetoacetyl Glycoluril **3-4** Formation in the Presence of Pyridine

A DCC-promoted coupling reaction was attempted between the anion of glycoluril **2-1** (prepared by addition of *n*-BuLi and heating to reflux) and both acetic acid and sorbic acid. No formation of acetyl glycoluril **2-2** or diacetyl glycoluril **2-3** was detected; however addition of sorbic acid under identical conditions did lead to formation of the expected sorboyl template **3-3** in an ~1:1 mixture with a product which has been tentatively identified as the urea adduct **3-4** (Scheme 3.4) in a combined yield of 18%.



Scheme 3.4: DCC - Promoted Coupling of an Acid with Glycoluril Template **2-1**

This result is quite interesting, since **3-4** represents a direct attack by the template anion on the DCC itself, an event which does not normally occur. Attempts to aid in this reaction by heating the mixture above room temperature resulted in reversion, giving back the starting material **2-1**.

Additionally, the procedure of Barstow and Hruby[99] for the synthesis of amides from amines and acid chlorides formed in neutral conditions from triphenylphosphine and $CBrCl_3$ was attempted with the glycoluril **2-1** as the "amine", and acetic acid as the

acid component. The reaction mixture was heated at reflux in THF overnight, but no acetyl template was detected; this may be attributed to either the considerably lower reactivity of **2-1** compared with an amine, or to the insolubility of **2-1** in THF, or a combination of both of these factors. In order to test this, the more soluble acetyl glycoluril **2-2** was treated under identical conditions. In spite of the enhanced solubility of **2-2**, no diacetyl glycoluril **2-3** was detected. This supports the hypothesis that the glycoluril nitrogens are simply not reactive enough to undergo this reaction, although **2-2** also has more steric hindrance than glycoluril **2-1**.

A recent reaction of 3,4,7,8-tetramethyl-2,5-dithioglycoluril (**4-2**, see Chapter 4) with carbon tetrachloride, triethylamine, acetic acid and triphenylphosphine resulted in the isolation of acetyl dithioglycoluril **4-4** in a yield of 12%. While the yield of this reaction was quite low, it clearly demonstrates the enhanced reactivity of these compounds, and may be optimized by the substitution of $CBrCl_3$ for the less reactive carbon tetrachloride, as well as heating in higher boiling solvents, such as dioxane. This result represents the first successful attempt to react a glycoluril template with an acid under non-anionic conditions, and should be investigated further.

One possibility for optimization of this first acylation reaction for complex acyl groups involves using the acyl chloride as the limiting reagent, and adding an excess of the glycoluril anion; after work-up, **2-1** could be easily recovered by simple filtration, and recycled. This methodology would mop up excess HCl by quenching the glycoluril anion, while still allowing enough to react with the acyl chloride.

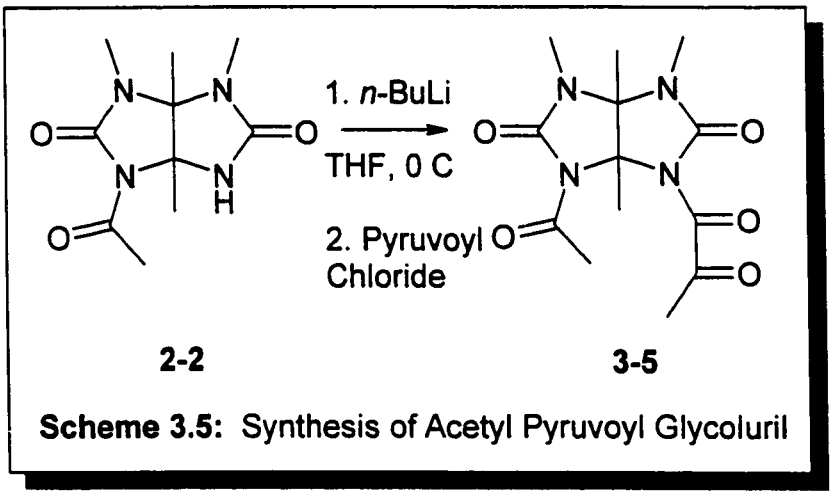
Recently, unpublished results presented by Dr. R.D. Singer from St. Mary's University at the 80th annual CSC Conference in Windsor illustrated the possibility of using ionic liquids as solvents for acylation reactions. He examined the Friedel-Crafts acylation of ferrocenes in an ethylmethylimidazole^{+} / $AlCl_4^{-}$ ionic liquid. Ionic liquids are classified as very polar, aprotic solvents. This salt is a liquid at room temperature, and provided excellent yields of acylated ferrocenes by reaction with stoichiometric amounts of acetic anhydride at 0 °C. This result contrasts with standard Friedel-Crafts acylation conditions, which require boiling in neat acetic anhydride. The latter conditions are very reminiscent of those used in our system for the first acylation of glycoluril **2-1**, which is insoluble in organic solvents; thus, ionic liquids such as the one mentioned above may prove ideal for the first acylation reaction on the template, and allow the reaction to occur at or below room temperature, and in a neutral environment. This possibility is being investigated.

3.2.2 Investigating the Condensation Reaction

3.2.2.1 Synthesis and Reactivity of Acetyl Pyruvoyl Glycoluril

One area of interest regarding the intramolecular crossed Claisen-like condensation reaction is the relative contributions from different aspects of the system to the high rate observed for this reaction. In particular, it would be very interesting to investigate the relative importance of the six-membered cyclic transition state that occurs

in the Claisen-like condensation. Typical reaction conditions for intermolecular Claisen condensations require 8h to 3 days under reflux for good yields[100]; however, intramolecular glycoluril-mediated condensations are complete in about 5 min or less at 0 °C. Part of this rate enhancement is due simply to the intramolecular nature of the reaction, but it is expected that a large contribution would result from the favourable geometry of the system in a six-membered transition state.



Scheme 3.5: Synthesis of Acetyl Pyruvoyl Glycoluril

In order to probe the influence of the six-membered cyclic transition state on the condensation reaction, an acetyl pyruvoyl glycoluril adduct **3-5** was synthesized in one step from acetyl glycoluril **2-2** by addition of *n*-BuLi in THF at 0 °C, followed by addition of pyruvoyl chloride to provide **3-5** in 40% yield (Scheme 3.5). The pyruvoyl chloride was prepared by standard procedures[101]: addition of pyruvic acid to α,α-dichloromethyl methyl ether in CH_2Cl_2.

The condensation of **3-5** could lead to three possible products **3-6a**, **3-6b**, or **3-6c** (Figure 3.1); if the six-membered transition state was of paramount importance in the reaction, the only observable product should be **3-6a**. If, on the other hand, one or both

of the other possible products were observed, this would indicate that the six-membered transition state was not the most important factor in the condensation reaction.

Treatment of **3-5** with a hindered base under standard conditions did not lead to any of the expected products; instead, the reaction conditions led solely to degradation of the acetyl pyruvoyl template to the acetyl glycoluril adduct (**2-2**). Several variations in

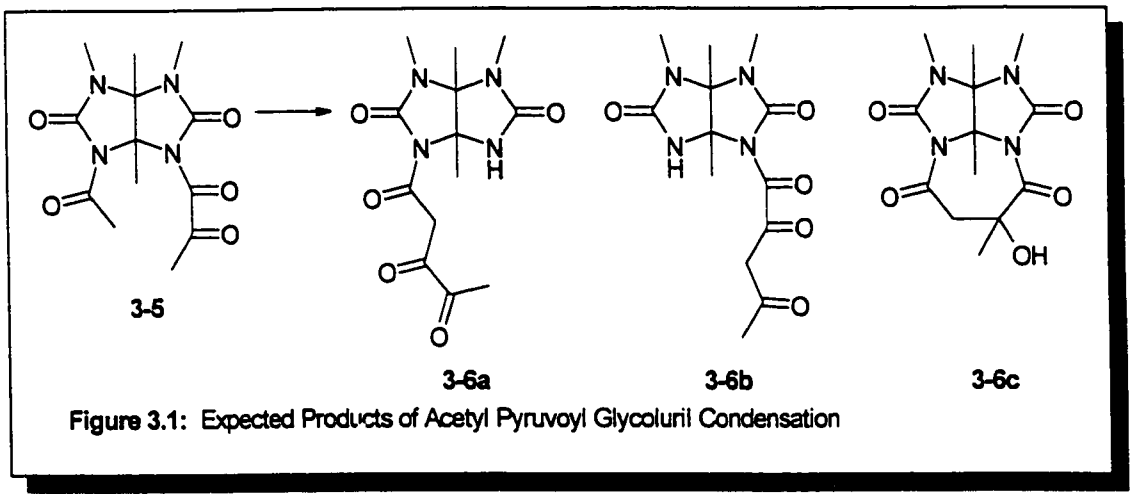
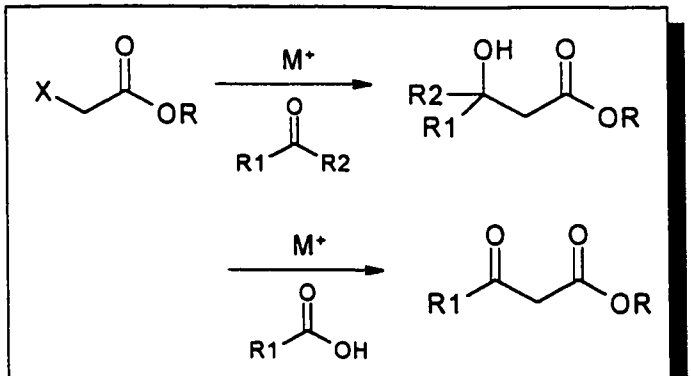


Figure 3.1: Expected Products of Acetyl Pyruvoyl Glycoluril Condensation

the reaction conditions were investigated, including lowering the temperature to –78 °C, and using a variety of bases, but the results were the same. Thus, the only conclusion that can be drawn from this study is that glycoluril compounds with a pyruvoyl side-chain are very unstable to basic conditions. This is perhaps not surprising when one considers that a number of other α-keto carbonyl compounds also display low stability to harsh conditions.

3.2.2.2 Enolate Production By Dehalogenation of α-Haloacylglycolurils

Since a number of possible substrates for the condensation reaction, such as compound **3-5** in section 3.2.2.1, are quite base sensitive, other methods of enolate production were investigated for their utility in the condensation reaction on the

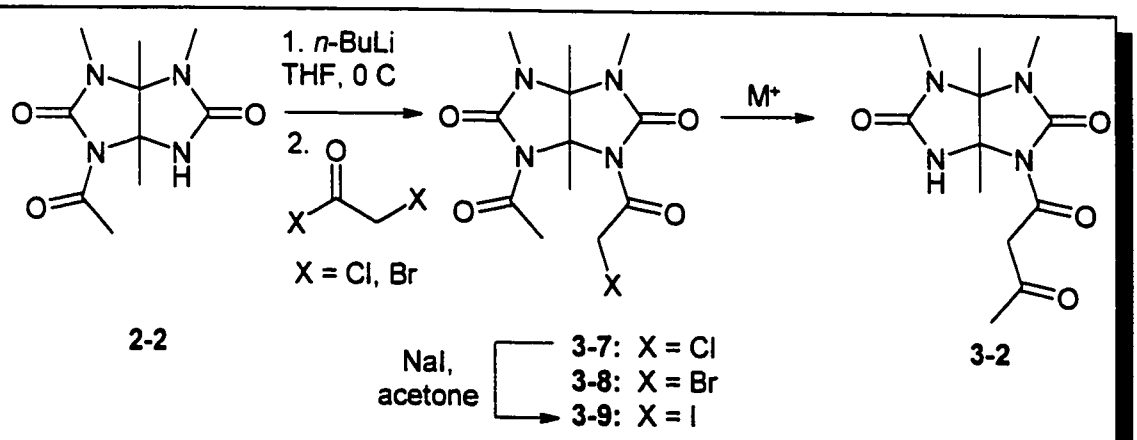


Scheme 3.6: General Reformatsky Reaction

glycoluril template. Additionally, greater selectivity for the condensation reaction was desired; in the crossed Claisen-like condensation reaction, unless one of the acyl groups was very bulky or had no hydrogens α to the carbonyl group, a mixture of products was obtained. A different approach to this problem of selectivity involves incorporating a functional group on one of the side chains, thus forcing the condensation reaction to proceed in only one manner. A reported reaction of this type is the Reformatsky reaction[102]; one of the most general methods for the preparations of β-hydroxyesters[103]. If a carboxylic acid derivative is used as a substrate rather than a ketone, the result is a β-ketoester; which is the desired target in our study (Scheme 3.6). Many publications exist

on this topic and on ways to optimise the yield of the reaction, notably by the use of activated metals[104] and sonication[105].

A Reformatsky-like reaction on the glycoluril template would involve generation of an enolate by metal-mediated removal of a halogen from a haloacetyl side chain on one active site of the glycoluril. This enolate should condense rapidly with an acetyl group on the other active site of the glycoluril in a manner similar to the standard condensation reaction (Scheme 3.7).



Scheme 3.7: Reformatsky-like Reaction: Preparation of Substrates and Condensation Reaction

Chloroacetyl acetyl glycoluril **3-7** was synthesized by reacting acetyl glycoluril **2-2** with *n*-BuLi, then with chloroacetyl chloride (42% yield) under standard conditions. No side reactions, such as S_N2 substitution by the glycoluril anion on the α-position of the acid chloride, were observed, and the remaining material was unreacted starting material **2-2** (49%), which was recycled.

Bromoacetyl acetyl glycoluril **3-8** was prepared in a similar manner to **3-7** using bromoacetyl bromide as a reactant. This reaction also provided the desired product (44%) and unreacted starting material (52%) as the only observable products.

Iodoacetyl acetyl glycoluril **3-9** was formed directly from **3-7** by reaction with NaI in acetone[106]. This equilibrium reaction is pushed in the forward direction by the insolubility of NaCl, which precipitates during the reaction. Compound **3-7** was converted quantitatively (95% after chromatography) to **3-9** by this method.

Activated Zn, In, and Mg metals were prepared following several literature procedures[107,108], which are reported to give much smaller metal particles than are found in normal powders. This increases the surface area for the reaction by several orders of magnitude, and results in greatly increased reactivity, as seen in the literature results. Sonication was also used in some cases to increase the reaction rate.

The results of the Reformatsky-like reaction between the metals and **3-7**, **3-8**, or **3-9** are summarized in Table 3.2.

S.M.	Metal	Solvent	Reflux/ Sonication	Yield of 2-2 (%)[a]	Yield of 2-3 (%)	Yield of 3-2 (%)
3-7	Zn pd [c]	THF	Sonic	N/D[d]	75	25
3-7	In	THF	Sonic	N/D	N/D	N/D
3-7	Mg	THF	Sonic	66	N/D	33 [b]
3-7	Mg* [e]	THF	Reflux	N/D	90	10
3-8	In*	Xylene	Sonic	100	N/D	N/D
3-8	Zn*	Dioxane	Sonic	N/D	N/D	N/D
3-8	Mg*	THF	Sonic	20	N/D	N/D
3-8	Mg pd	THF	Reflux	30	50	20 [b]
3-8	Mg*	THF	Reflux	40	N/D	N/D
3-8	Zn*	THF	Reflux	15	85	N/D
3-9	Mg*	THF	Reflux	N/D[f]	N/D	N/D
3-9	Zn*	THF	Reflux	11	79	10
3-9	Zn	Dioxane	Reflux	20	80	N/D
3-9	Mg*	THF	Reflux	20	80	N/D
3-9	Zn	THF	Reflux	20	80	N/D
3-9	Li	THF	Reflux	20	80	N/D

[a] Yields, unless otherwise noted, were estimated from crude proton nmr
[b] Yield reported is isolated yield
[c] pd = powder [d] N/D = product not detected [e] * indicates activated metal
[f] product was formed, but did not contain glycoluril moiety; was not investigated further

Table 3.2: Results of Reformatsky-like Condensation Reactions of α-Haloacetyl-acetyl Glycolurils

On examination, the results are quite varied, and it is difficult to find any trends or draw conclusions. Most of the product observed was diacetyl glycoluril **2-3**, produced by metal-mediated loss of the halide without further reaction. This result indicates that either the enolate is not being formed, or is quenched very rapidly (faster than the intramolecular condensation reaction), or is held in a conformation which cannot undergo the condensation reaction. One way that the latter could occur is by complexation of both the glycoluril carbonyl and the haloacetyl carbonyl to the metal ion, rather than having the metal form a complex between the two acetyl carbonyls, which occurs in the case of the intermolecular Reformatsky reaction.

To investigate these possibilities, the iodoacetyl acetyl template was reacted first with Zn powder in THF, then with excess methyl iodide. No methylated product was observed by ^{1}H nmr. In a separate reaction, the same starting material was reacted first with Zn powder, then with D_2O/CH_3COOD. Again, no uptake of deuterium was observed into the diacetyl compound **2-3** by ^{1}H nmr. These results suggest that either the enolate is not being formed and that the halide is replaced by hydrogen without significant enolate formation, or that the enolate which is formed is being quenched very rapidly, probably with aid of the metal.

Many of the iodoacetyl compounds proved very unstable, and underwent a deacylation reaction under the reaction conditions to produce mainly the acetyl glycoluril **2-2**. The highest yields of the desired acetoacetate adduct **3-2** were observed with the combination of unactivated Mg or Zn powder with either the chloroacetyl or bromoacetyl adduct. In this study, the yields were quite unsatisfactory (maximum of 33%), indicating

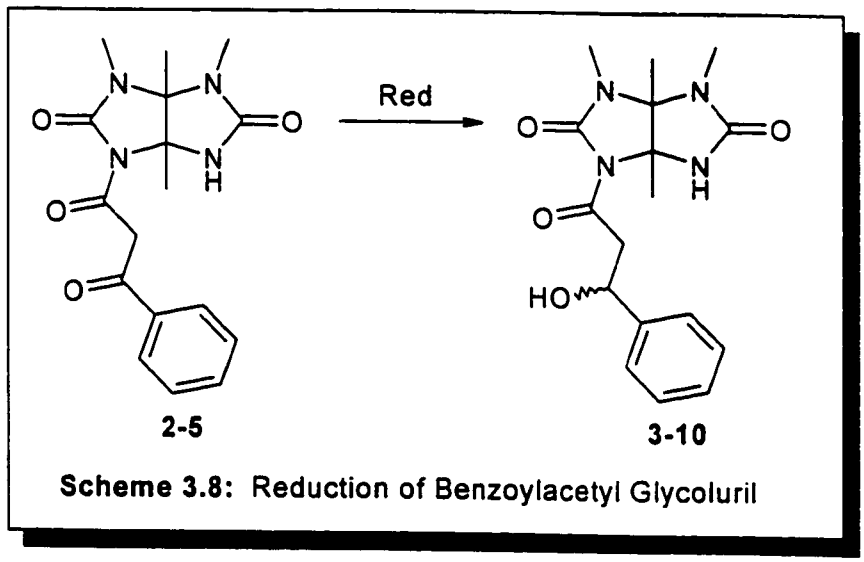
that this method of enolate formation is not very favourable for our system. Since the Reformatsky reaction relies on coordination of the metal to the reactant carbonyl groups, it seems likely that the inefficiency of the reaction stems at least in part from poor selectivity of the metal to the reactant carbonyl groups, rather than the carbonyl groups of the glycoluril itself.

One way to make this methodology work would be to change the system; in particular, production of 1-chloroacetyl-6-acetyl-3,4,7,8-tetramethyl-2,5-dithioglycoluril (see Chapter 4), followed by a Reformatsky reaction utilizing a small metal which shows high selectivity for oxygen over sulfur might promote the Reformatsky reaction to give more satisfactory results.

3.2.3 Investigation of the Reduction Reaction

The reduction of β-keto compounds on the glycoluril skeleton to the corresponding β-hydroxy adducts works well with a number of substrates. The conditions used involve stirring the β-keto adduct with $NaBH_4$ in methanol[109]; however, the reaction must occur rapidly, since quenching with acid is done within 10 minutes. Sun[84] observed that longer reaction times lead to cleavage products, presumably through the generation of methoxide by $NaBH_4$. Thus, many compounds which are less reactive to the reduction conditions exhibit poor yields; in particular, conjugated β-keto compounds frequently exhibit low yields in this reaction (eg. 24% for reduction of

acetododecenoyl glycoluril **5-9**) while the mass balance is comprised exclusively of unreacted starting material. This result may stem from the presence of larger amounts of the enol form of the compounds; enolization extends the conjugation resulting in greater stability, but this component must be converted to the keto form before the desired reduction can occur. If this keto/enol conversion is slow, it may be the limiting factor in this reaction.



Scheme 3.8: Reduction of Benzoylacetyl Glycoluril

The reduction of benzoylacetyl template **2-5** to the racemic β-alcohol **3-10** (Scheme 3.8) was investigated as a model for other β-keto adduct reductions on the template. Increasing the reaction time is not possible, since after 10 minutes, methoxide production becomes a problem: methoxide begins cleaving the acyl side chains from the glycoluril template. Other conditions were attempted, including use of $CeCl_3$ with $NaBH_4$, which has been reported to promote reduction of α-β unsaturated carbonyl compounds[110]; $LiAlH_4$; $LiAl[OC(CH_3)_3]H$; $NaB(CN)H_3$, which can be used under acidic conditions (pH = 4.5)[111]; $Zn(BH_4)_2$, which has been reported by D.A. Evans to reduce β-

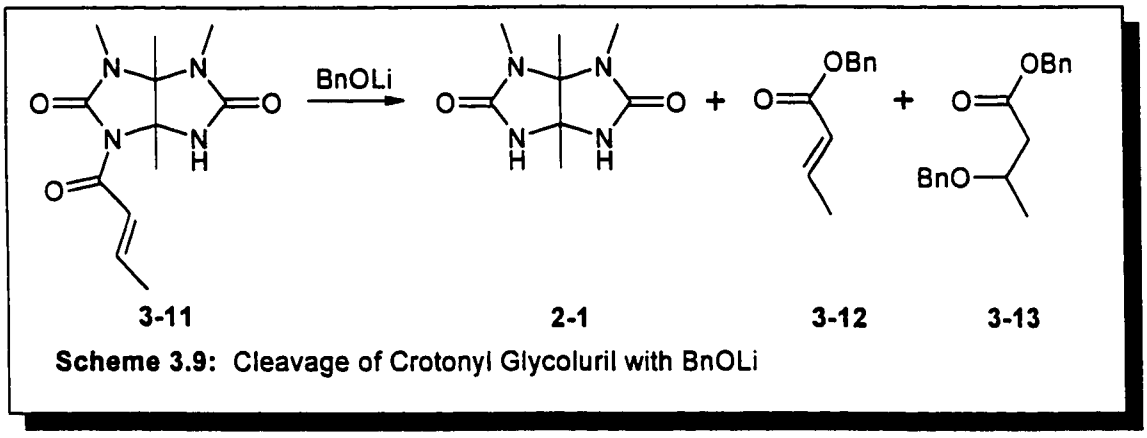
keto amides on his oxazolidinones[112] and has also been used for the reduction of β-ketoesters[113]; and the combination of yeast alcohol dehydrogenase and α-nicotinamide adenine dinucleotide (reduced form) (YADH / NADH)[114]. In all of the above cases, very little or no product formation was observed by ^{1}H nmr or TLC. Controls of easily reduced compounds were used for several of these reactions to verify that the reagents were active. In the case of the lithium aluminum hydrides, which are stronger reducing compounds than the borohydrides, it is postulated that the reagents are too basic and convert the starting material entirely to the enolate. No further reduction occurs from this state. The zinc borohydride case is more interesting, since it has been used on closely related molecules. Zn^{2+} coordinates between the two doubly bonded oxygens and delivers the borohydride directly to the site of action[113]. One possible reason for the lack of product formation in this reaction may be that the zinc is coordinating between two other oxygen (or possibly nitrogen) atoms within the glycoluril carbonyl group, and the coordinated borohydride is thus not being held in proximity to the ketone.

3.2.4: Alternative Methods for Cleavage of Acyl Chains from the Glycoluril Template

Sun effected cleavage of the acyl side chains by addition of lithium benzyloxide; the resulting benzyl esters could then be deprotected to give the free acid. In particular, for a saturated butyryl side chain, this first reaction gave a yield of 83% benzyl butyrate with 92% recovery of the glycoluril template **2-1**. Use of the same conditions on an

unsaturated crotonyl glycoluril **3-11** led to the production of benzyl crotonate (**3-12**, 55% yield) and benzyl β-benzyloxybutyrate (**3-13**, 15% yield), along with recovered glycoluril template **2-1** (80% yield) (Scheme 3.9).

As well as the lower yield for this compound, the deprotection of benzyl crotonate may prove difficult, since hydrogenation conditions are likely to lead to reduction of the double bond as well as deprotection. However, a milder alternative deprotection of a benzyl group has been reported using aluminum trichloride[115]; this method could provide a valid deprotection without affecting the double bond in the compound, but still adds an additional step in any proposed synthesis.



3-11 **2-1** **3-12** **3-13**

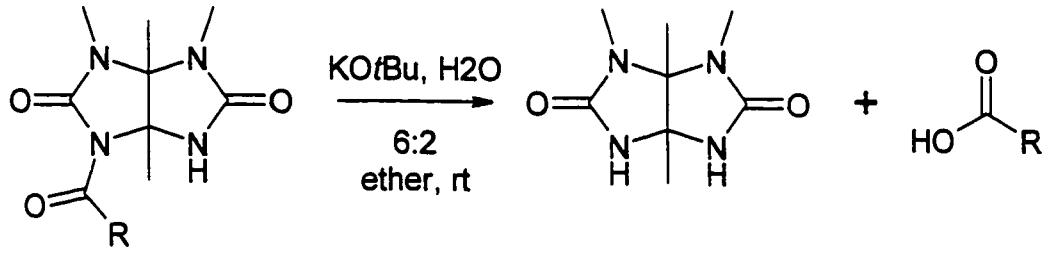
Scheme 3.9: Cleavage of Crotonyl Glycoluril with BnOLi

Because of the poor utility of lithium benzyloxide for cleavage of compounds of this type, alternative methods of cleavage were investigated. Stirring of sorboyl glycoluril **3-3** with 1 equivalent of NaOH in methanol for three hours produced no sorbic acid; instead, starting materials were recovered quantitatively. More prolonged reaction times (overnight) still did not result in the production of sorbic acid, but instead produced crotonic acid. These results suggest that the degradation of the sorboyl moiety occurs on

the glycoluril template, with removal of the side chain occurring after it is transformed into a crotonyl unit.

NaOMe in MeOH should react with the acyl side chain to remove the acyl unit from the glycoluril template as the methyl ester, but stirring with **3-3** overnight resulted only in the recovery of starting material. LiOOH is used as a gentle way to remove acids from Evans' oxazolidinone systems[116], and similarities between the oxazolidinone and the glycoluril systems prompted investigation into this reagent. Prolonged reaction of **3-3** with LiOOH showed no reaction by TLC or ^{1}H nmr.

Reaction of 1-acetyl-3,4,7,8-tetramethyl-5-thioglycoluril **4-6** with excess sodium ethoxide in EtOH resulted in quantitative cleavage to the *mono*-thioglycoluril **4-1** (see Chapter 4).



3-3: R = CH=CH-CH=CH-CH_3
5-11: R = CH=CH-CH=CH-C_9H_{19}
5-3: R = C_9H_{19}
5-6: R = $CH_2C(OH)C_9H_{19}$ ⟶ N.R.
2-5: R = $CH_2COC_6H_5$ ⟶ N.R.

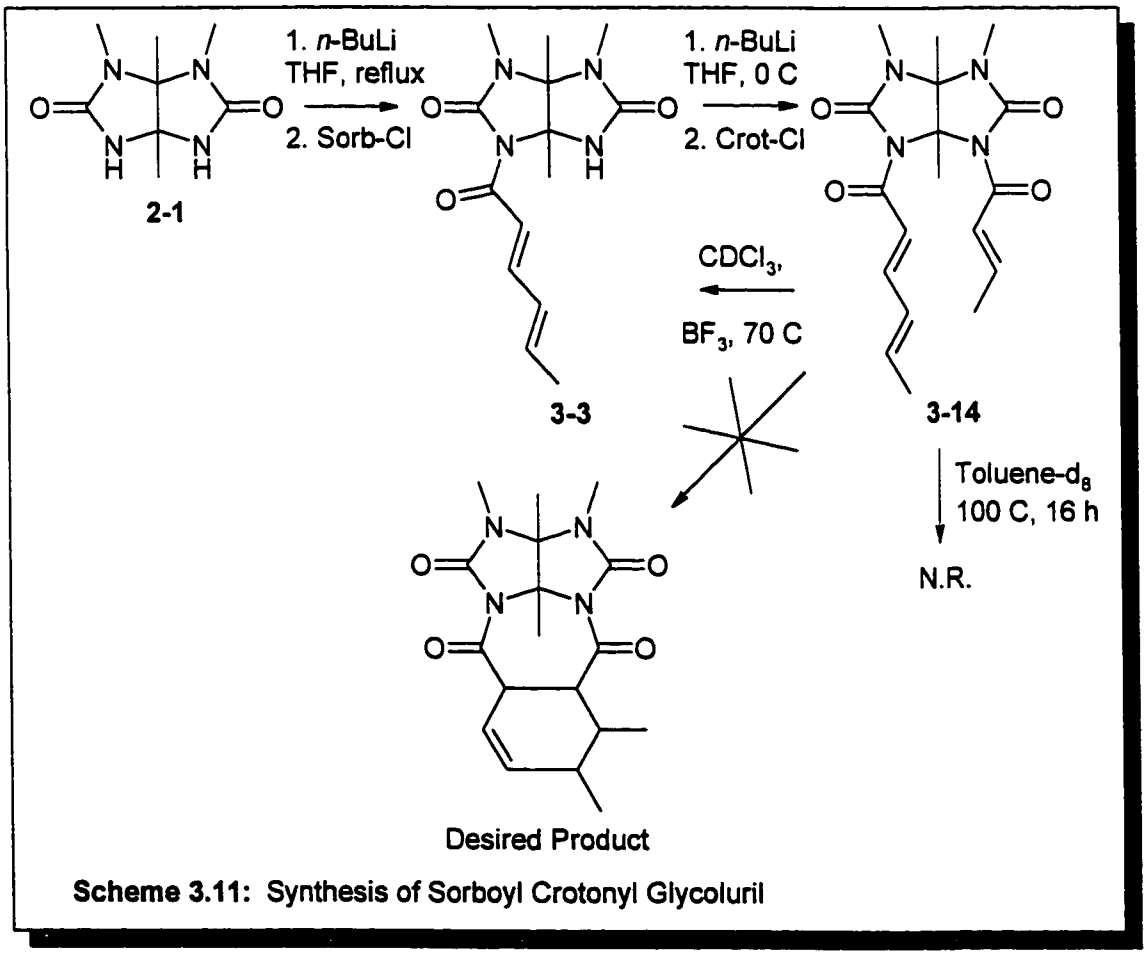
Scheme 3.10: Cleavage of Acyl Side Chains by Anhydrous Hydroxide

Treatment of sorboyl glycoluril **3-3** with 6 equivalents of potassium *tert*-butoxide and 2 equivalents of water in ether, according to the procedure of Gassman *et al.*[117] for the cleavage of amides, resulted in isolation of sorbic acid as the only observed product (46% yield), along with recovered starting material (Scheme 3.10). These reagents lead to *in situ* production of hydroxide in an anhydrous environment, which is known to increase its reactivity. Treatment of tetradecadienoyl template **5-11** (see Chapter 5) under identical conditions led to isolation of the acid in 68% yield, and exposure of decanoyl template **5-3** to these conditions led to isolation of decanoic acid in 40% yield. It should be noted that these yields are not optimized, so manipulation of conditions should lead to further improvements. Initial attempts to cleave a β-alcohol adduct (specifically 1-(3'-hydroxydodecanoyl)-3,4,7,8-tetramethylglycoluril **5-6**) and a β-keto adduct (benzoylacetyl glycoluril **2-5**) were unsuccessful; it is likely that these compounds need to be protected before such a cleavage is attempted, although this has not been undertaken.

3.3 Intramolecular Diels-Alder Reactions

Sun's work has shown that the bifunctional glycoluril is an effective and efficient template for the intramolecular Claisen condensation, and that functional group manipulations on the acyl glycolurils which are necessary to build up fatty acids and polyketides can be achieved. In order to expand the library of compounds which can be created on this template, and thus its use in synthetic methodology, it would be advantageous to use the same scaffold to facilitate other types of intramolecular

reactions. One reaction which was investigated in depth was the possibility of using the glycoluril **2-1** as a template for intramolecular Diels-Alder reactions. The Diels-Alder reaction is a $4\pi + 2\pi$ cycloaddition[118], which has been used in tandem intramolecular reactions to build up very complex ring systems in only a few steps. Additionally, the Diels-Alder reaction shows excellent regiochemical[119] and in some cases, stereochemical[120] control. Evans[121] has used a crotonyl oxazolidinone adduct as the dienophile in an intermolecular Diels-Alder reaction with cyclopentadiene.



Scheme 3.11: Synthesis of Sorboyl Crotonyl Glycoluril

It was hypothesized that the glycoluril **2-1** could be used to hold two appropriately unsaturated acyl units, one acting as the diene, the other as the dienophile in close proximity, thus promoting the intramolecular Diels-Alder cyclization. In addition, it was thought that if this reaction did occur, the endo/exo selectivity would be moderated directly by the presence of the glycoluril moiety. This cyclized product could then be removed from the glycoluril template, or reacted further to give more complex products. In order to examine such a process, 1-crotonyl-6-sorboyl-3,4,7,8-tetramethyl glycoluril **3-14** was synthesized according to Scheme 3.11. Thus, treatment of glycoluril **2-1** with *n*-BuLi in THF at reflux, followed by addition of sorboyl chloride gave sorboyl glycoluril **3-3** in 14% yield. Compound **3-3** was then reacted with *n*-BuLi in THF at 0 °C, followed by addition of crotonyl chloride to give **3-14** in 32% yield.

It was discovered that heating compound **3-14** in either $CDCl_3$ or toluene-d_8 did not provide the desired Diels-Alder product. Use of a Lewis acid catalyst, BF_3-etherate, resulted in selective removal of the crotonyl group. These reactions were performed in deuterated solvents for direct nmr analysis, due to the small amount of starting material available. Proton nmr spectra taken several times during the course of the "reaction" showed that **3-14** was stable under these conditions.

Simplistic molecular modelling of the expected product in Hyperchem 3.0 showed that the desired product was a reasonable structure, so the geometry of the starting material is not likely the cause of the lack of reactivity observed. An investigation of the rotamers of **3-14** in Hyperchem indicated that there were only two

likely conformations of the acyl side chains that could lead to the Diels-Alder product (Figure 3.2).

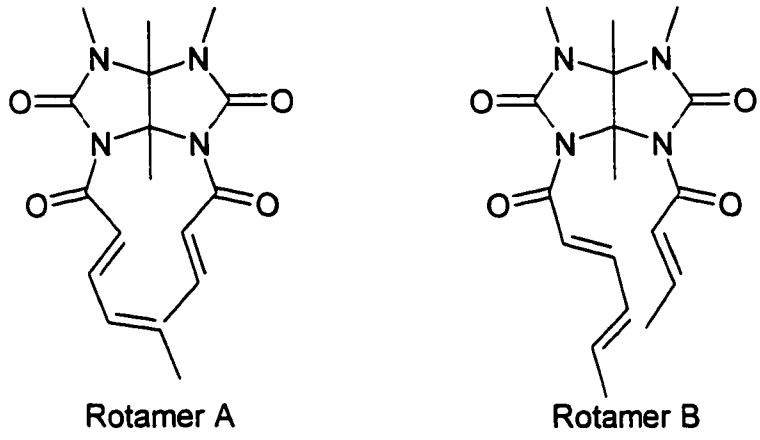


Figure 3.2: Accessible Rotamers of 3-14 for Intramolecular Diels-Alder Reaction

Conformers A and B are both quite accessible by MNDO calculations, and give reasonable distances between the reactive carbons of the double bonds (for A, 2.44 Å and 1.87 Å; for B, 2.38 Å and 2.51 Å); however, in both structures, the minimum geometry had the two planes of the acyl groups nearly orthogonal to one another (101-115° for A, 75-85° for B). This geometry results from the desire of **3-14** to maintain conjugated π-orbital overlap in both side chains. The barrier to rotation of these chains is unknown, but may be high enough tc contribute somewhat to the lack of reactivity observed for this system.

The primary contributor to the unreactive nature of this compound is most likely a result of the compound investigated. In this system, the dienophile (crotonyl side chain) is activated by the presence of the carbonyl group next to the double bond, but the diene

is deactivated by the presence of the carbonyl group on the sorboyl chain. This combination of deactivated diene and activated dienophile is far from ideal for this reaction, and has been observed to be unreactive. The combination of the two factors discussed above makes the Diels-Alder reaction of this compound improbable, so the project was halted at this point.

It is believed that a crotonyl glycoluril adduct should undergo intermolecular reaction with an activated diene, in a manner analogous to that observed for Evan's oxazolidinone system; however, such reactions are not in line with our current objectives, and were not investigated. Furthermore, a glycoluril which contains a crotonyl side chain on one side and an activated diene attached to an appropriate tether on the other side could lead to intramolecular Diels-Alder products. The problem, depending on the type of tether used, would then involve the cleavage of this side chain from the glycoluril to get to the final product desired.

3.4 Summary

A number of reactions were investigated in some detail either for their utility on the glycoluril template, or in an effort to find optimal conditions for known reactions. The synthesis and condensation of the acetyl benzoyl template **2-4** indicates that simple phenyl groups α to the carbonyl make excellent substrates in the condensation reaction; the phenyl ring does not cause significant steric hindrance in either of these reactions.

The use of the acetyl benzoyl adduct for kinetic studies of the condensation reaction is still ongoing.

A critical factor in expanding the use of the glycoluril template from simple acyl groups to more complex ones involves finding simpler methods of acylation, preferably from the acid, using non-anionic conditions. Although many different conditions were investigated, the use of the sulfur template **4-2** with $CBrCl_3$, PPh_3, Et_3N, in THF (or dioxane) at reflux holds the most promise for the realization of this goal, which should allow the addition of complex acyl groups in high yields.

The Claisen-like condensation reaction, for which the glycoluril template was designed, works very well. However, as observed for the acetyl pyruvoyl template, other reactions can compete quite favourably if the starting material is unstable. The investigation of the generation of enolates through a Reformatsky-like reaction illustrated that α-haloacyl adducts were formed quite readily, with no formation of alkylation products which would result from S_N2 attack of the anion on the α-halo carbon. However, generation of enolates via this method did not produce a satisfactory yield of the desired product; instead, competitive loss of the α-halogen or deacylation of the α-haloacetyl side chain predominated.

Investigations of the reduction of β-keto compounds showed that this class of substrates was unreactive to a wide variety of reduction conditions, although there remain a number of interesting possibilities to examine, including catalytic hydrogenation conditions, and reduction of the β-carbonyl with Et_3SiH, or similar mild reagents.

Cleavage of the acyl side chains from the template was found to occur readily using hydroxide in anhydrous conditions, via the method of Gassman *et al.*[117] to give the free acids in good yields for saturated and unsaturated acyl chains; protection of the oxo- or hydroxy- groups in the β-keto or β-hydroxy adducts is expected to allow similar conditions for the cleavage of these more reactive groups, although this has not yet been attempted.

Finally, attempts to force an intramolecular Diels-Alder reaction between a sorboyl side chain and a crotonyl side chain were unsuccessful. This result is not surprising since the glycoluril template was not designed with this type of reaction in mind; thus the geometry may not allow easy access to appropriate conformations of the side chains relative to one another. Additionally, the system consists of an activated dienophile and a deactivated diene, which may prevent efficient overlap of the π-orbitals, thus leading to no observable reaction.

3.5 Experimental

Reformatsky-Like Condensation Reaction. 30 - 200 mg of compound **3-7, 3-8,** or **3-9** was dissolved in a minimum of the solvent used (usually THF). Excess metal powder or activated metal complex, which had been dried with stirring under N_2, was added to the reaction and the reaction mixture was either sonicated or heated at reflux overnight with

monitoring by TLC. The mixture was quenched by pouring into 1 N HCl, then product(s) were extracted into chloroform and washed with water. The chloroform layers were dried (Na_2SO_4), filtered and concentrated prior to analysis of composition by nmr.

Pyruvoyl Chloride. Pyruvoyl chloride was synthesized from pyruvic acid and α-α-dichloromethyl methyl ether according to the procedure by Ottenheijm and Tijhuis[101]. After distillation, the product was found by ^{1}H NMR to contain 80 % pyruvoyl chloride, 15 % methyl formate, and 5 % acetyl chloride resulting from an impurity in the starting material.

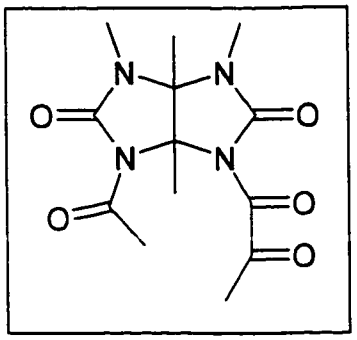
Sorboyl Choride. Sorboyl chloride was synthesized from sorbic acid by several methods. **Method 1:** Sorbic acid (7 g) was mixed dry with PCl_5 (14 g) until the mixture liquified. The mixture was distilled in vacuo (13 mm Hg). The first fraction distilled at 35-39 °C and was discarded. The second fraction distilled at 59-68 °C and was shown to be sorboyl chloride by ^{1}H NMR. **Method 2:** Sorbic acid (2 g) was dissolved in 10 mL CH_2Cl_2, then 1.6 mL of oxalyl chloride was added slowly. Initiation of reaction was carried out by addition of 1 drop of DMF. The solution was stirred for 2 h, then solvent was removed on the rotary evaporator. A small flow of N_2 into the rotary evaporator was maintained when the mixture became nearly dry to remove dissolved HCl. The residue was washed twice with benzene, which was then removed on the rotary evaporator. The acid chloride was then dissolved in a known amount of ether, and stored over NaH.

1-(3'-Oxobutanoyl)-3,4,7,8-tetramethylglycoluril (3-2). Method 1: Glycoluril **2-1** (2-3 mg) was charged to a test tube containing 2 mL pyridine and heated to reflux. Excess acetyl chloride was added, and the mixture was stirred for an additional 10 min. at reflux, then cooled. The reaction mixture was extracted into chloroform (3 × 4 mL), washed with copper sulfate (2 × 5 mL) to remove pyridine and water (3 mL), then dried over anhydrous sodium sulfate. Solvent was stripped on the rotary evaporator to give a mixture of **3-2** (10%) and starting material **2-1** (90%). **Method 2:** Compound **3-2** was formed as a minor product in the Reformatsky-like reaction of metals with haloacetyl acetyl glycolurils (**3-7**, **3-8**, or **3-9**). Thus, for example, chloroacetyl acetyl glycoluril **3-7** (31 mg, 0.11 mmol) was dissolved in 10 mL THF. One crystal of iodine and excess magnesium metal powder were added, and the reaction was stirred by an ultrasonic bath for 1 h, then the mixture was filtered to remove magnesium, and solvent was removed on the rotary evaporator. The residue was redissolved in chloroform and water, extracted into chloroform (3 × 5 mL), and dried over anhydrous sodium sulfate (2 g). The mixture was filtered, and the filtrate was concentrated on the rotary evaporator. The product (9.0 mg, 33% yield) was separated from diacetyl glycoluril **2-3** (17.8 mg, 66% yield) by flash column chromatography on silica gel in EtOAc. This product was identical by ^{1}H nmr to authentic material prepared by Sun.

1-*trans,trans*-Hexa-2',4'-dienoyl-3,4,7,8-tetramethylglycoluril (sorboyl glycoluril 3-3). Glycoluril **2-1** (500 mg, 0.5 mmol) was treated with 1.74 mL of a 1.6 M solution of *n*-BuLi in hexanes and 40 mL THF, and heated at reflux for 1h. The suspension was cooled to room temperature and 2 eq. of freshly prepared sorboyl chloride (540 μL) was added and the mixture was stirred for 30 min. The reaction mixture was quenched with solid ammonium bicarbonate, filtered through celite and the residue was washed with chloroform (20 mL). The filtrate was concentrated, and the product (109 mg, 14 %) was purified by flash column chromatography in 1% MeOH/EtOAc. ^{1}H nmr ($CDCl_3$, 200 MHz) δ 7.50 (1H dd, O=C-CH=C*H*, ^{3}J = 1 5.3, 5.5 Hz), 7.22 (1H, d, O=C-C*H*, ^{3}J = 15.2 Hz), 6.23 (2H, m, C*H*=CH-CH_3), 6.11 (1H, s, N*H*), 3.02 (3H, s, NCH_3), 2.92 (3H, s, NCH_3), 1.85 (3H, d, CH=CH-CH_3, ^{3}J = 5.6 Hz), 1.63 (3H, s, CH_3), 1.56 (3H, s, CH_3); ^{13}C nmr ($CDCl_3$, 50 MHz) δ 166.1 (*C*=O), 157.2 (NN*C*=O), 153.0 (NN*C*=O), 78.5 (*C*NN), 77.4 (*C*NN), 27.0, 26.3, 19.7, 18.6, 15.6; EIMS *m/z* 292 $[M]^+$ 216, 168, 125 (base); HRMS calcd. for $C_{14}H_{20}N_4O_3$: 292.1535, found: 292.1535.

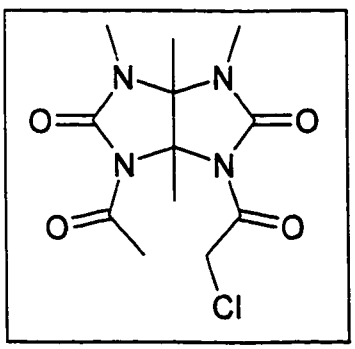
1-Acetyl-6-pyruvoyl-3,4,7,8-tetramethylglycoluryl (3-5). Acetyl glycoluril **2-2** (2.11 g, 8.4 mmol) was stirred with 1.1 eq *n*-BuLi (6.0 mL of 1.6 M solution in hexanes) in 60 mL of THF at 0 ° C for ½ h, then 1.3 eq freshly prepared pyruvoyl chloride was added,

and the mixture was stirred for 30 min. The reaction mixture was quenched with



$NaHSO_4$, and extracted into chloroform (3 × 50 mL), washed with water (50 mL), and dried over anhydrous sodium sulfate (5 g). The mixture was filtered, and the filtrate was concentrated on the rotary evaporator. The resulting residue was purified by flash column chromatography (1% MeOH/EtOAc) to give **3-5** (1.29 g, 49%). ^1H nmr ($CDCl_3$, 200 MHz) δ 3.05 (3H, s, NCH_3), 2.93 (3H, s, NCH_3), 2.51 (3H, s, $O{=}CCH_3$), 2.39 (3H, s, $COCOCH_3$), 2.00 (3H, s, CH_3), 1.58 (3H, s, CH_3); ^{13}C nmr ($CDCl_3$, 50MHz) δ 194.1 (*C*=O), 169.6 (*C*=O), 166.4 (*C*=O), 152.5 (*C*=O), 152.4 (*C*=O), 79.15 (*C*), 27.1 (CH_3), 26.3 (CH_3), 26.2 (CH_3), 25.4 (CH_3), 17.6 (CH_3), 14.8 (CH_3); FTIR (KBr pellet, cm^{-1}) 2990 (CH), 2940 (CH), 1740 (C=O); HRMS calcd. for $C_{13}H_{18}N_4O_5$: 311.1355, found 311.1339; Anal. calcd. for $C_{13}H_{18}N_4O_5$ C: 50.27, H: 5.85, N: 18.05; found: C: 50.34, H: 5.90, N: 17.87.

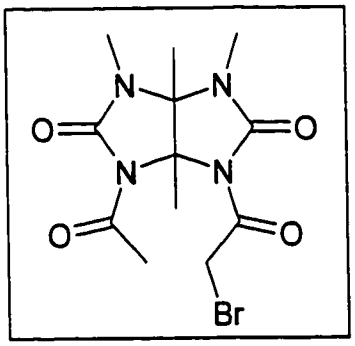
1-Acetyl-6-chloroacetyl-3,4,7,8-tetramethylglycoluril (3-7) . Acetyl glycoluril **2-2**



(1.07 g, 4.5 mmol) was treated first with 1.1 eq. *n*-BuLi (2.80 mL) in 30 mL THF at 0 °C for 1 h, then 1.2 eq. (5.3mmol, 0.60 g, 416 μL) chloroacetyl chloride was added and the mixture was stirred for 30 min at RT. The reaction was quenched with $NaHSO_4$,

and the mixture was extracted into chloroform (3 × 20 mL), washed with water (40 mL), and dried over anhydrous sodium sulfate (2 g). The mixture was filtered, and concentrated on the rotary evaporator. The product (590 mg, 42%) was separated from the unreacted starting material (525 mg, 49 %) by flash column chromatography in 1% MeOH/EtOAc. ^{1}H nmr ($CDCl_3$, 200 MHz) δ 4.88 (1H, d, O=C-C*H*$_2$-Cl, ^{2}J = 15.9 Hz), 4.52 (1H, d, O=C-C*H*$_2$-Cl, ^{2}J = 15.9 Hz), 3.00 (3H, s, NC*H*$_3$), 2.97 (3H, s, NC*H*$_3$), 2.49 (3H, s, O=C-C*H*$_3$), 1.97 (3H, s, C*H*$_3$), 1.54 (3H, s, C*H*$_3$); ^{13}C nmr ($CDCl_3$, 50 MHz) δ 170.2 (O=*C*), 166.3 (O=*C*), 152.8 (O=*C*), 152.5 (O=*C*), 80.5, 78.3, 45.4, 26.9, 26.7, 25.8, 18.8, 14.6; EIMS *m/z* = 318 [M$^+$, ^{37}Cl] 316 [M$^+$, ^{35}Cl], 274, 200, 168, 141, 125 (base); HRMS calcd. for $C_{12}H_{17}N_4O_4Cl$ 316.0938, found: 316.0935.

1-Acetyl-6-bromoacetyl-3,4,7,8-tetramethylglycoluril (3-8). Acetyl glycoluril **2-2**



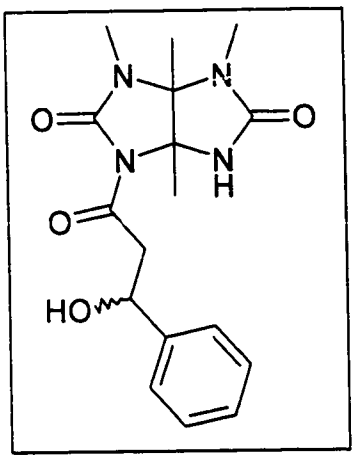
(1.05 g, 4.4 mmol) was treated first with 1.1 eq. *n*-BuLi (2.75 mL) in 30 mL of THF at 0 °C, then 1.05 eq. (4.6mmol, 0.93 g, 400 μL) bromoacetyl bromide was added, and the mixture was stirred for 30 min at room temperature. The reaction was quenched with $NaHSO_4$, and the mixture was extracted into chloroform (3 × 30 mL), washed with water (40 mL) and dried over anhydrous sodium sulfate (2g). The mixture was filtered, and the filtrate was concentrated on the rotary evaporator. The product (691 mg, 44%) was separated from the unreacted starting material (520 mg, 52%) by flash column chromatography in EtOAc. ^{1}H nmr ($CDCl_3$, 200 MHz) δ 4.68 (1H, d, O=C*H*$_2$-Br, ^{2}J =

12.8 Hz), 4.38 (1H, d, O=CH_2-Br, ^{2}J = 12.8 Hz), 3.00 (3H, s, NCH_3), 2.99 (3H, s, NCH_3), 2.49 (3H, s, O=CCH_3), 1.96 (3H, s, CH_3), 1.55 (3H, s, CH_3); EIMS *m/z* = 362 [M$^+$, ^{81}Br], 360 [M$^+$, ^{79}Br], 318, 240, 168, 140, 125(base); HRMS calcd. for $C_{12}H_{17}N_4O_4Br$: 360.0483, found: 360.0417.

1-Acetyl-6-iodoacetyl-3-4-7-8-tetramethylglycoluril (3-9). Chloroacetyl acetyl glycoluril **3-7** (100 mg, 0.31 mmol) was dissolved in acetone, then 1.1 eq. NaI (52mg) was added and the mixture was stirred for 3 h. The solution was filtered to remove solid NaCl, then acetone was removed on the rotary evaporator. The residue was extracted with water and chloroform to remove excess NaI, and the organic layers were collected, concentrated, and dried in a vacuum desiccator to give the desired product (124 mg, 95%). ^{1}H nmr ($CDCl_3$, 200 MHz) δ 4.42 (1H, d, O=C-CH_2-I, ^{2}J = 6.5 Hz), 4.29 (1H, d, O=C-CH_2-I, ^{2}J = 6.5 Hz), 2.94 (3H, s, NCH_3), 2.92 (3H, s, NCH_3), 2.41 (3H, s, O=C-CH_3), 1.87 (3H, s, CH_3), 1.47 (3H, s, CH_3); CIMS *m/z* = 328 [M]$^+$ 334, 317(base), 283, 241, 125.

1-(3'-Hydroxy-3'-phenylpropanoyl)-3,4,7,8-tetramethylglycoluril (3-10). Benzoylacetyl glycoluril **2-5** (31.9 mg, 9.3 × 10^{-5} mol) was dissolved in 2 mL methanol at room temperature, then 1.8 eq. (6.3 mg) sodium borohydride was added and the mixture was stirred for 10 min. The reaction was quenched with acetic acid (1 mL), and the

mixture was extracted into chloroform (3 × 5 mL), washed with water (5 mL), and dried

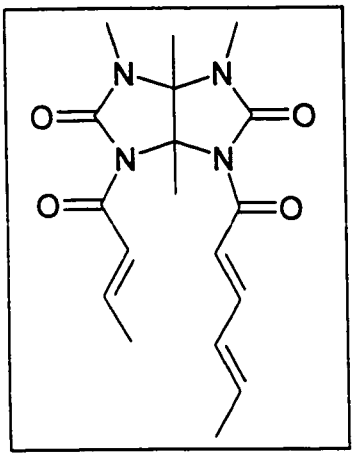


over anhydrous sodium sulfate. The mixture was filtered and the filtrate was concentrated on the rotary evaporator. The product (22.1 mg, 69% yield) was purified by flash column chromatography on silica gel in EtOAc as a 1:1 mixture of two diastereomers. ^{1}H nmr ($CDCl_3$, 200 MHz) δ 7.34 (10H, m, C_6H_5 and C'_6H_5), 6.30 (1H, s, N*H*), 6.27 (1H, s, N'*H*) 5.15 (2H, m, C*H*OH and C'*H*O'H), 3.75 (1H, d, CHO*H*), 3.64 (1H, d, C'HO'*H*), 3.30 (4 H, m, O=C-CH_2 and O'=C'-C'H_2), 2.96 (6H, s, N-CH_3 and N'-C'H_3), 2.83 (6H, s, N-CH_3 and N'-C'H_3), 1.68 (6H, s, CH_3 and C'H_3), 1.54 (6H, s, CH_3 and C'H_3).

General Acyl Group Cleavage Reaction. A slurry of 2 equivalents ultrapure H_2O, 6 equivalents of potassium *tert*-butoxide, and 10 mL anhydrous ether was prepared and stirred for 10 min, then substrate was added and stirred for 3 h. The reaction mixture was quenched with 1 mL glacial acetic acid, then filtered to remove the insoluble glycoluril **2-1**. The filtrate was concentrated on the rotary evaporator, and the product was purified by flash column chromatography on silica gel using 10% EtOAc / 0.1% AcOH / hexanes as the eluent.

1-(*trans*-But-2-enoyl)-6-(*trans,trans*-hexa-2,4-dienoyl)-3-4-7-8-tetramethylglycoluril (crotonyl sorboyl glycoluril 3-14). Sorboyl glycoluril **3-3** (130 mg, 0.44 mmol) was

treated first with 1.1 eq *n*-BuLi in 10 mL THF at -78 °C, then was stirred with 1.2 eq (50



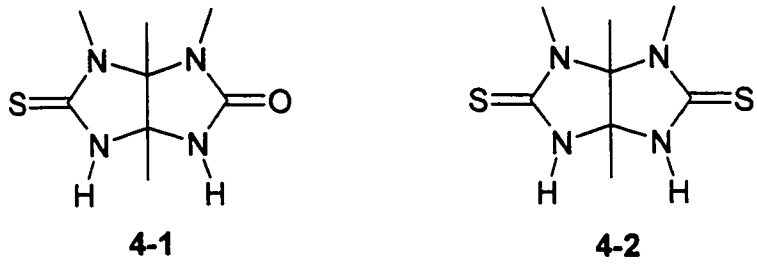
μL) crotonyl chloride for 30 min. The mixture was quenched with solid ammonium bicarbonate, then filtered through celite to give crude product. Solvent was removed on the rotary evaporator, and the product (52 mg, 32 %) was purified by flash column chromatography in 2:1 EtOAc/Hexanes. ^{1}H nmr ($CDCl_3$, 200 MHz) δ 7.35 (1H, dd, O=C-CH=C*H*, ^{3}J=15.0, 10.1 Hz), 6.98 (3H, m, O=C-C*H*, ^{3}J=15.2 Hz, O=C-C*H*=C*H*-CH_3), 6.18 (2H, m, C*H*=C*H*-CH_3), 2.95 (6H, s, NCH_3), 1.99 (3H, s, CH_3),1.88 (3H, d, CH=CH-CH_3, ^{3}J = 5.4 Hz), 1.81 (3H, d, CH=CH-CH_3, ^{3}J = 5.9 Hz), 1.49 (3H s, CH_3).

CHAPTER 4: Sulfur Analogs of the Glycoluril Template

4.1 Synthesis of Sulfur Analogs of 3,4,7,8-Tetramethylglycoluril

There are a number of very interesting reasons for making derivatives of the glycoluril template developed by S. Sun. The acylation reactions on the 3,4,7,8-tetramethylglycoluril template require harsh conditions, especially the first acylation reaction, which requires either boiling in the acyl anhydride overnight, or reacting with *n*-BuLi in THF at reflux, followed by addition of the acyl chloride. This latter reaction requires such harsh conditions primarily because of the nearly total insolubility of the template crystals in any useful organic solvents. By examining analogs of the parent template, milder conditions may be found for this reaction, as well as for the subsequent acylation.

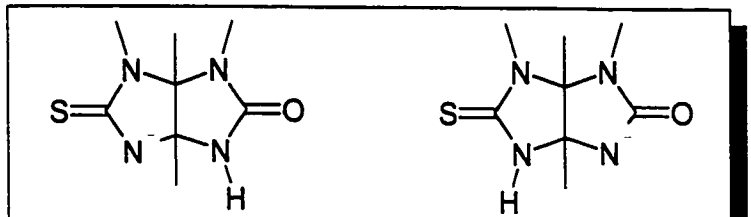
Another reason to examine derivatives of the parent template is to create asymmetry in the molecule. This will make the two NH sites non-equivalent, and should lead to interesting selectivity both in the acylation reactions, and in the Claisen-like condensation reaction. If significant selectivity can be observed in the condensation reaction, these compounds could aid in the synthesis of novel chemical compounds which are either unavailable or produced in very low yield on the parent template.



4-1 4-2

Figure 4.1: Sulfur Derivatives of the Glycoluril Template

A logical class of derivatives to make is the sulfur derivatives, formed by replacing one or both (Figure **4.1**: **4-1** and **4-2** respectively) oxygens on the glycoluril structure with sulfur. This substitution was envisioned to change the reactivity primarily through electronic effects, specifically by dropping the pK_a of the glycoluril hydrogens, while leaving the geometry of the molecule basically the same. There is an observed drop in pK_a of about 6 pK_a units when going from ureas to thioureas[122]; a comparable drop should be observed in the glycoluril/thioglycoluril series. Molecular modeling on the thioamide vs. amide anions (**4-1a**, **4-1b**; Figure 4.2) at the PM3† level gave a ΔH_f of –65.81 kcal/mol for the thioamide anion **4-1a**, and a ΔH_f of –58.93 kcal/mol for the amide anion **4-1b**.



4-1a 4-1b

Figure 4.2: Monothioglycoluril Anions

† Molecular Modeling studies were undertaken by Bill Riddoch as a project for Chem 720a.

Since the change in geometry going from the thioglycoluril template to the anions was found to be nearly identical for each compound by PM3 calculations ($\Delta\Delta S = 0$), the ΔpK_a can be calculated from the modeling. This is estimated using the relationship

$$-\Delta\Delta G/RT = \ln K_1 - \ln K_2.$$

$$= -11.62 \text{ at } T = 273 \text{ K}$$

Therefore: $K_1/K_2 = e^{-11.62}$

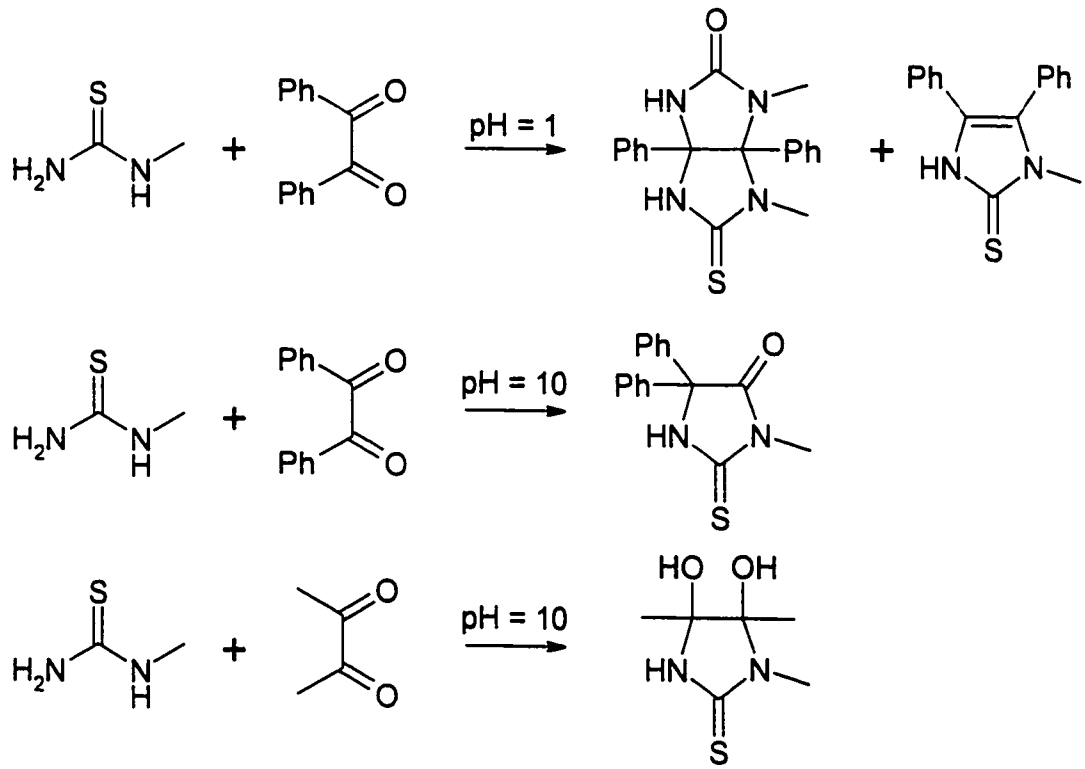
$$= 8.98 \times 10^{-6}$$

$$-\log (K_1/K_2) = \Delta pK_a \cong 5$$

Thus, the pK_a difference for the glycoluril protons in substituting sulfur for oxygen is estimated to be 5, a very significant change. Additionally, the crystal lattice energies of these compounds should be lower than that of the oxygen template because the thiocarbonyl group is expected to be much less susceptible to intermolecular hydrogen bond formation.

As stated in section 1.3.2, synthesis of thioglycoluril compounds is not a trivial matter. Broan and Butler[23] report the synthesis of 7,8-diphenyldithioglycoluril from thiourea and benzil, but state that *N*-methylthiourea reacts with benzil under acidic conditions to yield a small amount of a mixed O-S glycoluril, along with a disulfide compound. In alkaline conditions[22], the same reagents lead to the thiohydantoin compounds preferentially to the thioglycolurils. To date, however, no attempt at this synthesis using butanedione rather than benzil as the dione has been reported. Attempts to make compounds **4-1** and **4-2** by addition of 2 equivalents of *N*-methylthiourea to 1 equivalent of butanedione by Candace Webb, as a senior thesis project, were

unsuccessful, but, since benzil does not lead to the glycoluril products, this result is not surprising.

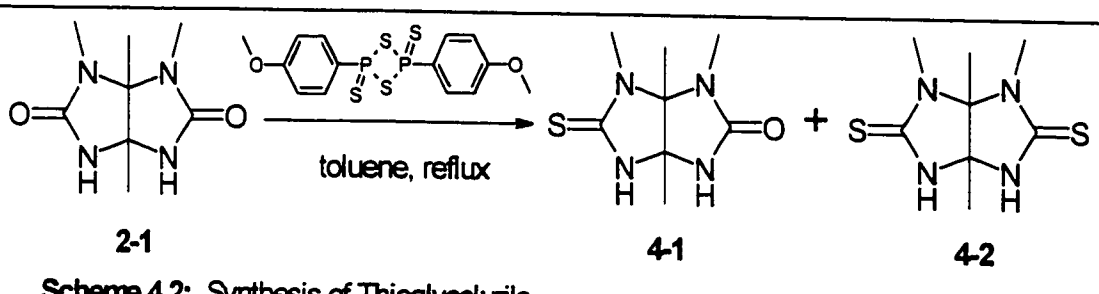


Scheme 4-1: Reaction of *N*-Methylthiourea with Diones

When *N*-methylthiourea was added to a variety of diones, including 2,3-butanedione and benzil, no glycoluril-type products were observed; the nmr spectra of the products indicate that the first imidazoline ring closes, but the second does not[123]. Instead, the diol formed is insoluble, and precipitates out of solution.

Another strategy to prepare the sulfur derivatives involves introducing sulfur into the parent template. One way of doing this involves reacting the template with Lawesson's reagent under conditions that have been reported to work for amides[124].

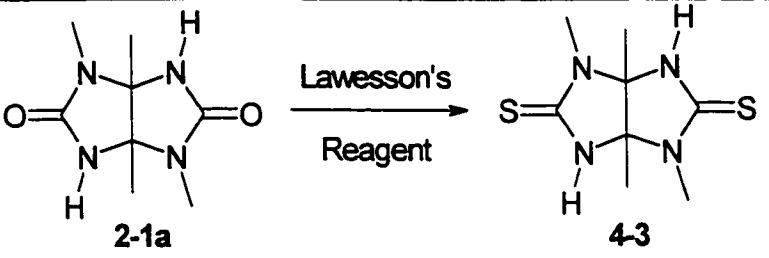
[125](toluene, heat at reflux overnight). This is, to our knowledge, the first use of Lawesson's reagent on glycoluril structures. El-Barbary and Lawesson reported in 1984[126] the use of Lawesson's reagent on ureas and urea derivatives, and observed that urea, *N*-methylurea, *N,N*-dimethylurea, and *N,N'*-dimethylurea reacted with Lawesson's reagent to give a complex mixture of products with no thio-analogues being obtained. Tetrasubstituted ureas gave quantitative conversion to the thio-analogues, and trisubstituted ureas gave a mixture of thio-analogues and other products.



2-1 **4-1** **4-2**

Scheme 4.2: Synthesis of Thioglycolurils

In the case of 3,4,7,8-tetramethylglycoluril **2-1**, the reaction proceeded smoothly with an excess of Lawesson's reagent to give a mixture of products which was rich in the dithiolated product **4-2** (Scheme 4.2). If a single equivalent of Lawesson's reagent was used, the reaction gave a mixture rich in the monothiolated product **4-1**. Both of these mixtures also contain about 10% of a compound (**4-3**) which results from the reaction of Lawesson's reagent with the *anti-* isomer of the parent template (**2-1a**) (Figure 4.3), traces of which were present in the starting glycoluril **2-1**. This product is exclusively dithiolated; no monothiolated compound corresponding to this starting material impurity



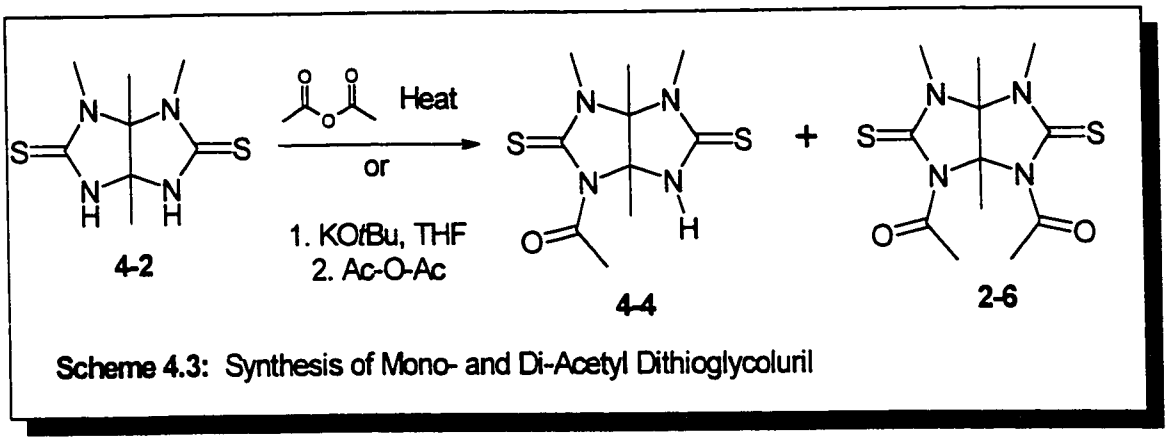
2-1a 4-3

Figure 4.3: Source of Additional Impurity in Lawesson's Reaction

2-1a was observed. The compounds at this stage are very polar and difficult to separate; instead, they underwent the first acylation reaction without further purification. Pure samples were subsequently prepared as described below, in Section 4.3.2. The generality of this reaction of Lawesson's reagent with glycolurils is questionable, since treatment of glycoluril **4** with Lawesson's reagent under identical conditions did not result in the production of thioglycoluril. It should be noted, however, that the poor reactivity of glycoluril may result from its insolubility (even more so than tetramethylglycoluril **2-1**) in organic solvents.

4.2 First Acylation Reaction

4.2.1 Acylation of Dithioglycoluril Template



Scheme 4.3: Synthesis of Mono- and Di-Acetyl Dithioglycoluril

Acylation of the dithioglycoluril template was initially performed under similar conditions to those used for acylation of the oxygen template; that is, heating in neat acetic anhydride (Scheme 4.3).

This reaction was found to occur more easily than on the oxygen template, giving a significant amount of the diacetyl compound **2-6** (which is not observed under identical conditions for the oxygen template[84]). In addition, the degree of acylation can be modulated by adjusting the temperature of the reaction. Heating at 80 °C leads to the monoacetylated product **4-4** in a yield of 63% (11% diacetylated) from the 3,4,7,8-tetramethylglycoluril template **2-1**. In contrast, heating at reflux (120 °C) led primarily to the diacetylated product (24%) with only minor formation of the monoacetyl adduct (13%). In fact, the sulfur template is much more reactive towards acylation than the oxygen template, as can be observed by the reaction with the same reagents at room temperature, which proceeded to give the monoacetyl adduct **4-4** in 23% yield after 24 h.

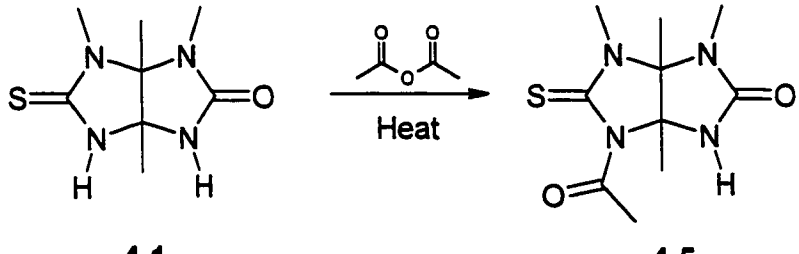
An alternative route to the monoacyl adduct **4-4** for this sulfur template involves reacting the template with KO^{t}Bu in THF at room temperature in a stoichiometric

fashion, followed by addition of the acyl chloride or anhydride. In the case of acetic anhydride, the monoacetyl adduct **4-4** was isolated in 67% yield, with no diacetylated products observed. It should be noted that the oxygen analogue is unreactive to these conditions, and no acyl adducts are observed. This methodology should be applicable for a variety of the thioglycoluril templates, for acylation on the same side as sulfur.

A recent experiment involved addition of triphenylphosphine, triethylamine, and carbon tetrachloride with acetic acid and **4-2** in THF at reflux, and resulted in production of the monoacetyl derivative in 12% yield (see Section 3.2.1). Again, this illustrates the enhanced reactivity of the NH groups on the thioglycolurils, since the equivalent reaction does not occur on the oxygen template **2-1**.

4.2.2 Acylation of Monothioglycoluril Template

Acetylation of the monothioglycoluril template **4-1** occurs readily in neat acetic anhydride at reflux; addition occurs exclusively on the sulfur side of the molecule to give **4-5** in 11% yield from the parent template (Scheme 4.4). This yield is low at least in part



4-1 **4-5**

Scheme 4.4: Acetylation of Monothioglycoluril

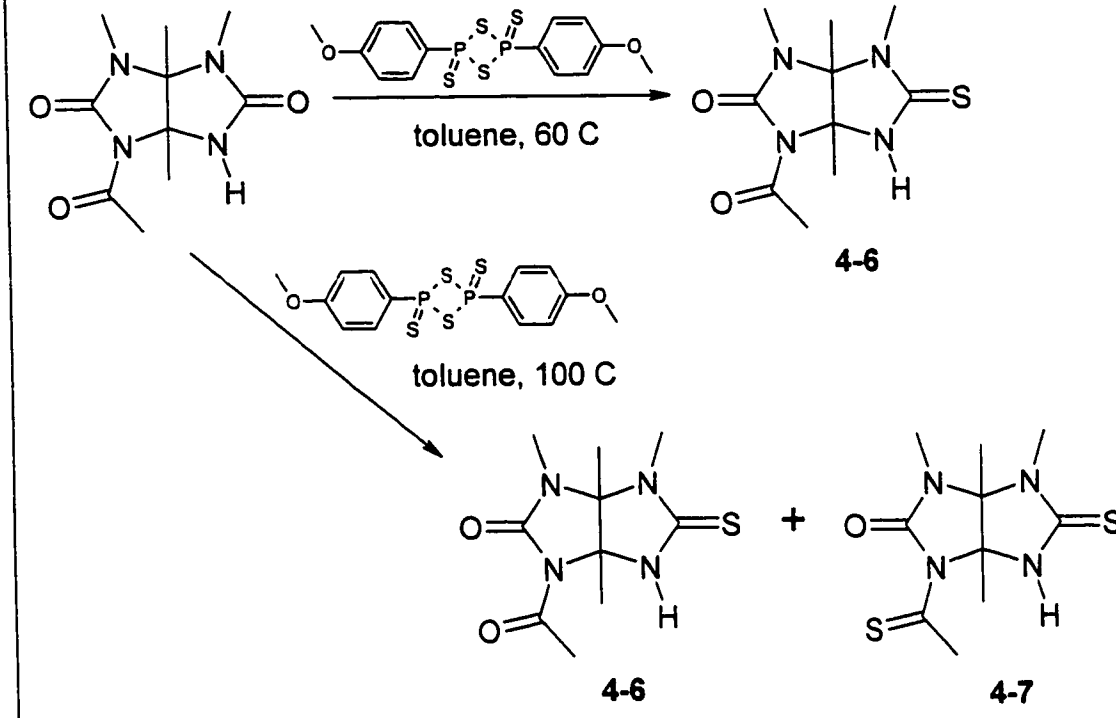
because of the impurity of the starting material; other starting materials such as **4-2** and **4-3** in the mixture lead to other products, which are easily separated at this stage by flash column chromatography.

4.2.3 More Efficient Route to Acetyl Monothioglycoluril

The synthetic route discussed in Schemes 4.1 and 4.4 to obtain the acetyl monothioglycoluril template is very inefficient, since it involves a statistical distribution of products from the reaction with Lawesson's reagent, followed by an acylation step which generates a number of products from the mixture. Separation at this stage is quite tedious, and only small amounts of the desired products were obtained. In summary, a better route to these compounds was essential to make this a viable method for synthesis.

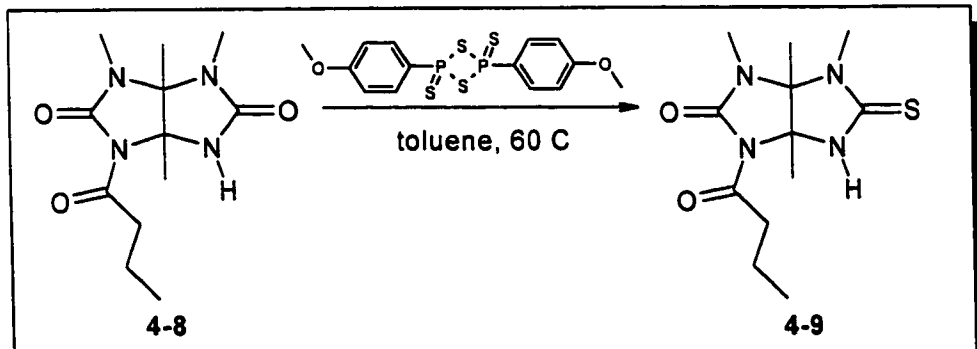
Reaction of Lawesson's reagent with 1-Acetyl-3,4,7,8-tetramethylglycoluril **2-2** in toluene at 60 °C gave a respectable yield (47%) of **4-6** as the only product (Scheme 4.5).

Product **4-6** has the sulfur on the opposite side from the acetyl group (*anti*-), compared with the acetyl monothioglycoluril **4-5** made by acetylation of the monothioglycoluril (*syn*-). Reaction of Lawesson's reagent occurs first on the side opposite the acetyl group, presumably because of steric hindrance. However, if the temperature for this reaction is raised to 100 °C, while still only adding 1 equivalent of Lawesson's reagent, the thioacetyl compound **4-7** is the primary product, produced in 22% yield.



Scheme 4.5: Reaction of Lawesson's Reagent with Acetyl Glycoluril.

In order to illustrate the general nature of this reaction, as well as to make a precursor of one of the compounds which will be used to investigate the selectivity of the condensation reaction, Lawesson's reagent was also reacted with 1-butanoyl-3,4,7,8-tetramethylglycoluril **4-8** in toluene at 60 °C to give compound **4-9** in 74% yield (Scheme 4.6).



Scheme 4-6: Reaction of Lawesson's Reagent with Butanoyl Glycoluril.

4.2.4 Stuctural Assignments of Acyl Thioglycoluril Adducts

Since this entire project relies heavily on the correct assignment of proton and carbon nmr spectra for a series of compounds that differ only by the number and relative position of sulfur(s) in the glycoluril structure, a detailed analysis of these compounds would be helpful. In the proton nmr spectra, the diagnostic signals are the N-*H* proton, which is somewhat unreliable since it may undergo exchange, and thus the chemical shift may be concentration dependent; and the acetyl protons, or protons α- to the acyl carbonyl group in the case of longer chains. For the ^{13}C nmr spectra, the chemical shift of each of the carbonyl/thiocarbonyl carbons is, of course, quite diagnostic as well.

Compound	Proton nmr Chemical Shifts (ppm) ($CDCl_3$)		^{13}C nmr Chemical Shifts (ppm) ($CDCl_3$)	
	N-*H*	α-acyl *H*'s	*C*=X, *C*=Y	*C*=X, acyl
Monoacetyl **2-2**	6.00	2.45	157.2, 153.0	171.0
Monoacetyl dithio **4-4**	7.30	2.76	180.8, 177.1	172.2
Monoacetyl thio **4-5**	6.30	2.72	N/A	N/A
Monoacetyl thio **4-6**	7.14	2.45	181.2, 153.1	170.9
Thioacetyl thio **4-7**	8.09	3.05	180.9, 151.8	206.8

Table 4.1: Characteristic ^{1}H and ^{13}C nmr Shifts in Monoacetyl Compounds

These diagnostic shifts are shown in Table 4.1 for the compounds described above. From these results, it can easily be seen that when an acetyl group is next to sulfur, the α-proton signal shifts ~0.3 ppm downfield; when an N-H site is adjacent to the thiocarbonyl group, the N-H signal shifts ~1 ppm downfield. In the ^{13}C nmr spectra, replacement of a carbonyl by a thiocarbonyl results in a downfield shift of ~30 ppm, while the other urea-like or acetyl carbons remain at approximately the same chemical shift. Although the chemical shifts of the acetyl compounds have been shown for illustrative purposes, similar chemical shifts have also been observed for the equivalent α sites of the longer chain acyl adducts (Table 4.2).

Compound[a]	δ(N*H*)[b]	Side[c]	δ(CH_2CON)-a[d]	Side[c]	δ(CH_2CON)-b[d]	Side[c]
4-15	7.26	S	5.05	S	3.90	S
4-16	7.08	S	4.34	O	3.52	O
4-17	6.12	O	4.98	S	4.00	S
4-21	7.10	S	4.36	O	3.47	O
4-22	6.09	O	5.54 (C*H*)[e]	S	-	-
4-24	7.11	S	4.38 (C*H*)[e]	O	-	-

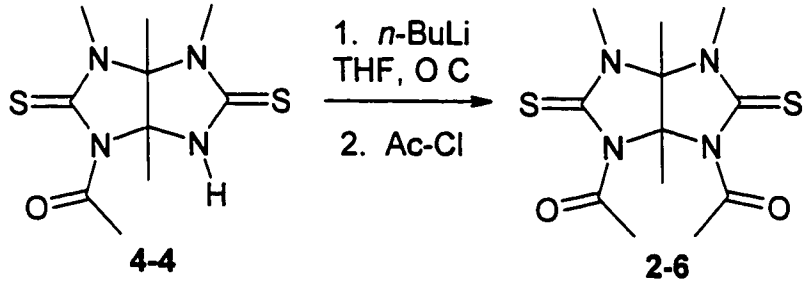
[a] Compounds are described later in the text. [b] All chemical shifts reported in ppm, and determined in $CDCl_3$ [c] "Side" refers to the side of the thioglycoluril on which the group is located [d] Two values refer to chemical shifts of two diastereotopic α-methylene protons [e] Single proton α to carbonyl

Table 4.2: "Fingerprint" Chemical Shifts of Diacylthioglycolurils and their Condensation Products.

4.3 2nd Acylation Reaction on Sulfur Analogs

4.3.1 2nd Acylation Reaction of Acetyl Dithioglycoluril Template

A second acyl group can be added to the acetyl dithioglycoluril template **4-4** under identical conditions to the equivalent reaction on the parent template; that is, by addition of *n*-BuLi in THF at 0 °C, followed by addition of an acyl chloride to give the *bis*-acyl adducts. In the case of acetyl chloride, the diacetyl dithioglycoluril adduct **2-6** was obtained in 84% yield (Scheme 4.7).



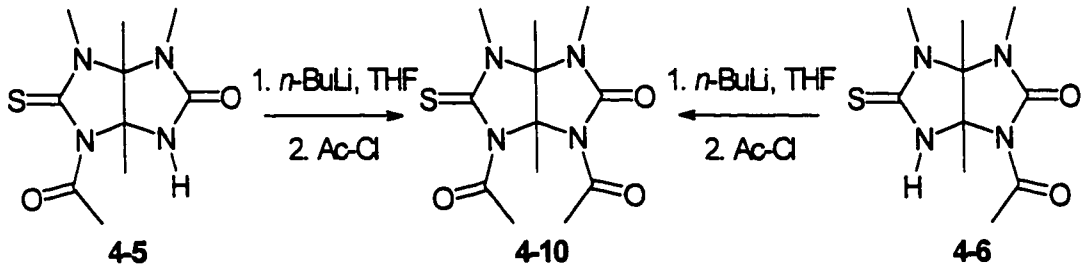
4-4 **2-6**

Scheme 4.7: Acetylation of Acetyl Dithioglycoluril.

Symmetrical *bis*-acyl products can also be reached in a single step from **4-2** by refluxing in the acyl anhydride for at least 24 h (Scheme 4.3). Other symmetrical diacyl products should be formed just as easily by the same methods.

4.3.2 2nd Acylation of Acetyl Monothioglycoluril Template

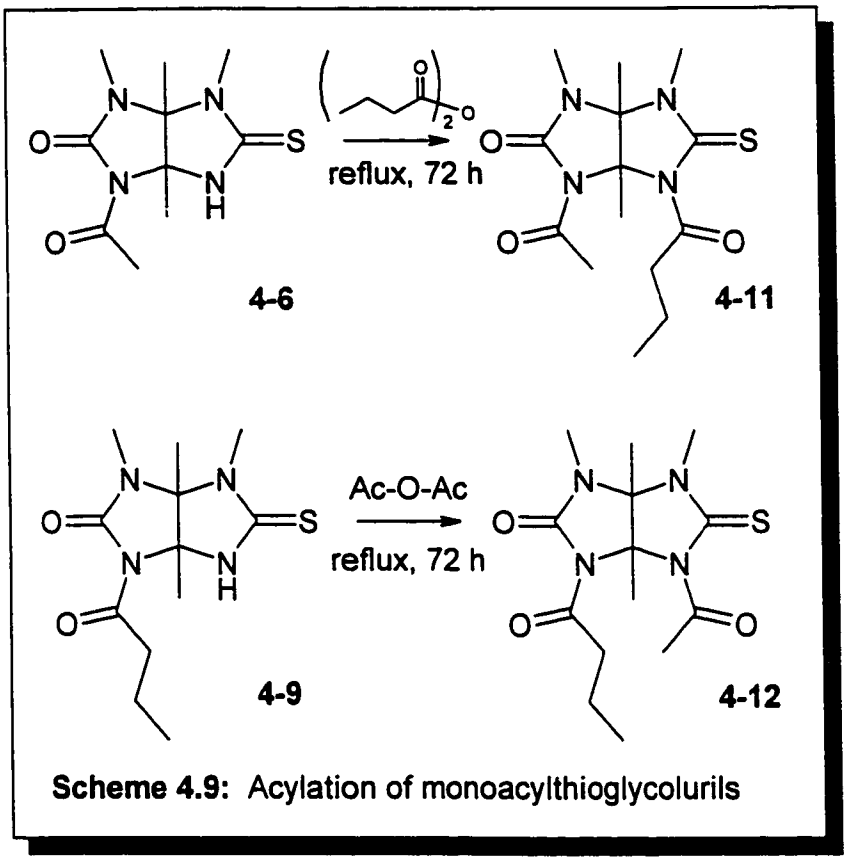
Diacetyl monothioglycoluril **4-10** can be synthesised from either of the monoacyl adducts **4-5** or **4-6** by addition of *n*-BuLi in THF at 0 °C, followed by addition of acetyl chloride under standard conditions giving yields of 23% and 58% respectively (Scheme 4.8). These yields are not optimised, so direct comparison is not possible at this time.



4-5 **4-10** **4-6**

Scheme 4.8: Acetylation of Monoacylthioglycolurils

Acetyl-butanoyl adducts of the monothioglycoluril template were also made, in order to test the selectivity of the condensation reaction. These were made in a slightly different manner, taking advantage of the enhanced reactivity of the N-H site adjacent to sulfur. Thus, compounds **4-6** and **4-9** were reacted with butyric anhydride and acetic anhydride respectively for three days at reflux to give the acetyl-butanoyl adducts **4-11** and **4-12** in good yields (69% and 68%, respectively) (Scheme 4.9). These compounds differ only with respect to the relative position of the sulfur and the acetyl group (same side or opposite), and thus should provide a useful model of the effect of sulfur on the condensation reaction.

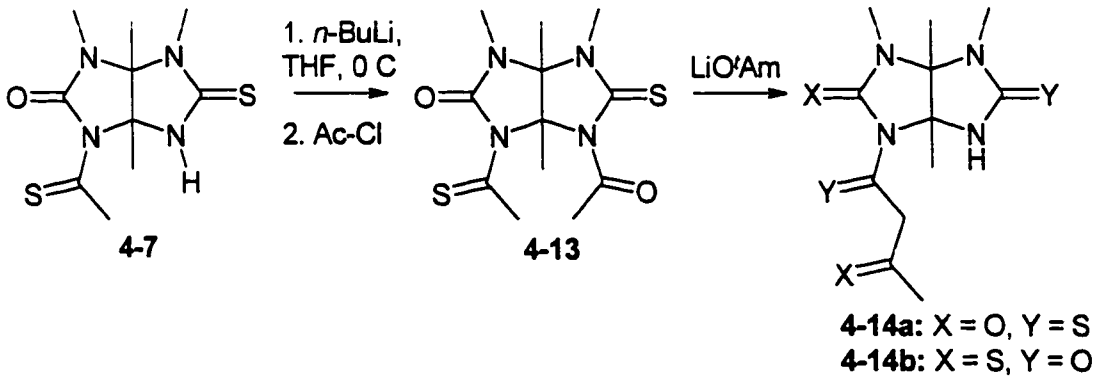


Scheme 4.9: Acylation of monoacylthioglycolurils

An attempt to remove the thioamide proton in **4-6** using sodium ethoxide, followed by addition of acetic anhydride, resulted not in the formation of the diacetyl species **4-10**, but instead resulted in quantitative cleavage of the acetyl group to give the thioglycoluril structure **4-1** in a highly pure form. This cleavage reaction is also expected to be quite general.

4.3.3 Acetylation and Condensation of Thioacetylthioglycoluril

Thioacetylthioglycoluril **4-7**, which was formed as the major product of reaction of 1-acetyl-3,4,7,8-tetramethylglycoluril with Lawesson's reagent at elevated temperatures (100 °C), was acetylated using standard conditions (*n*-BuLi, THF, 0 °C,



Scheme 4.10: Acetylation and Condensation of Thioacetylthioglycoluril

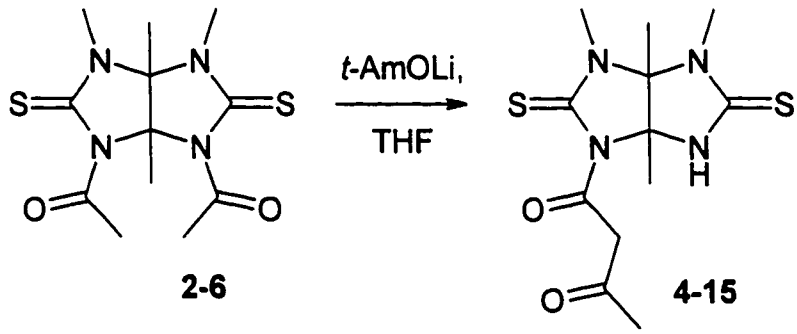
then acetyl chloride) to give the 1-thioacetyl-6-acetyl-3,4,7,8-tetramethyl-5-thioglycoluril **4-13** in 67% yield (Scheme 4-10). This compound was expected to show high selectivity for deprotonation on the thioacetyl group to give **4-14a** as the major product, from an analogous argument to that made for the urea vs. thiourea anions; that is, that the pK_a of the protons on the thioacetyl group should be several units lower than the pK_a of the acetyl hydrogens. Compound **4-13** also represents the first condensation reaction undertaken with a thioacetyl moiety as one of the side chains. Treatment of **4-13** with a hindered base under standard conditions resulted in a complex mixture of products, one of which was the expected product **4-14a**, isolated in 26% yield, along with several products that do not contain the glycoluril moiety. These non-glycoluril products have

not been fully characterized or identified. This less than satisfying result terminated this particular investigation in favour of more interesting compounds.

4.4 The Condensation Reaction: Selectivity

4.4.1 Condensation of Diacetyldithioglycoluril

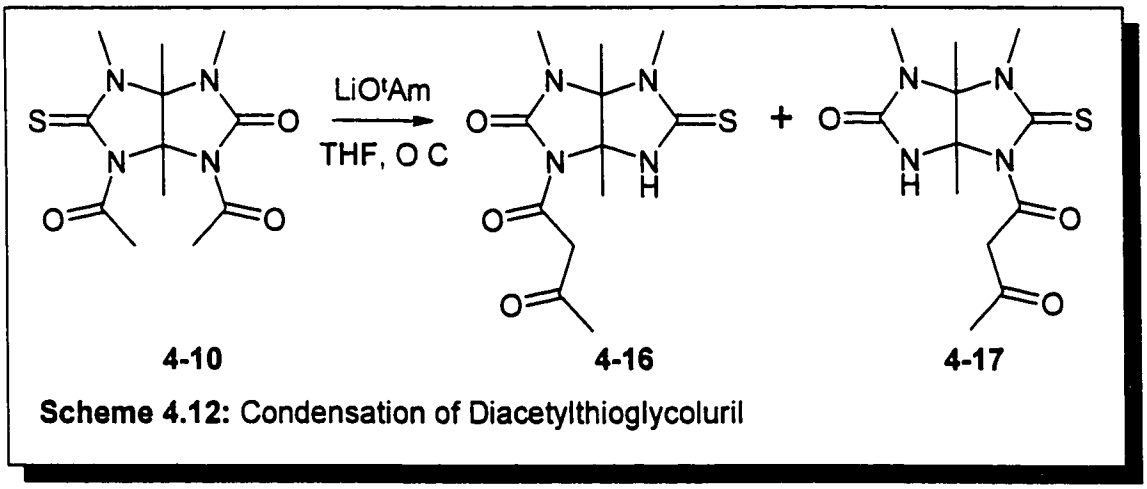
Condensation of the diacetyldithioglycoluril **2-6** proceeded smoothly under standard conditions with LiO^{t}Am in THF to give the acetoacetyl adduct **4-15** in 62% yield, with unreacted starting material as the only other product (Scheme 4.11).



Scheme 4.11: Condensation of Diacetyldithioglycoluril

4.4.2 Condensation of Diacylthioglycolurils

Condensation of the asymmetrical diacylthioglycolurils was expected to show some interesting selectivity relating to the sulfur in the template, when reacted under standard conditions. The condensation of the diacetyl adduct **4-10** with LiO^{t}Am in THF at 0 °C produced a mixture of **4-16** and **4-17** in a 2.2 : 1 ratio (Scheme 4.12).



Scheme 4.12: Condensation of Diacetylthioglycoluril

This result is very important, because it demonstrates that the sulfur does have an effect on the selectivity of the condensation reaction. There are a number of possible reasons for this result. The sulfur could be affecting the pK_a of the acetyl hydrogens, although the site is quite remote to the sulfur. Molecular modelling of this possibility, measuring the relative stabilities of the enolate anions using PM3 calculations, found a difference in pK_a's of only 0.2, favouring deprotonation on the sulfur side. This is contrary to what is observed, and the pK_a difference is indistinguishable from the error by this method. Another possibility is that the selectivity depends on the stability of the

leaving group, a thioamide versus an amide anion. As previously discussed, the thioamide anion is much more stable, and is thus a better leaving group. The implication of this interpretation is that breaking of the amide bond is part of the rate limiting step of the reaction, since otherwise a 1:1 distribution would be expected.

From mechanistic studies using deuterium labelling on 1,6-diacetyl-3,4,7,8-tetramethylglycoluril **2-3**, it has previously been shown that the mechanism of the condensation reaction involves rate limiting hydrogen abstraction[84]. These facts imply that there has either been a change in the rate determining step of the reaction in going from the glycoluril to the thioglycoluril templates, or that the reaction involves concerted hydrogen abstraction, new bond formation, and amide bond cleavage. Both of these possibilities need to be investigated further.

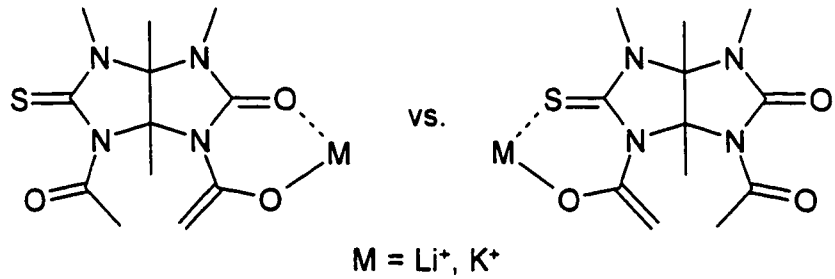


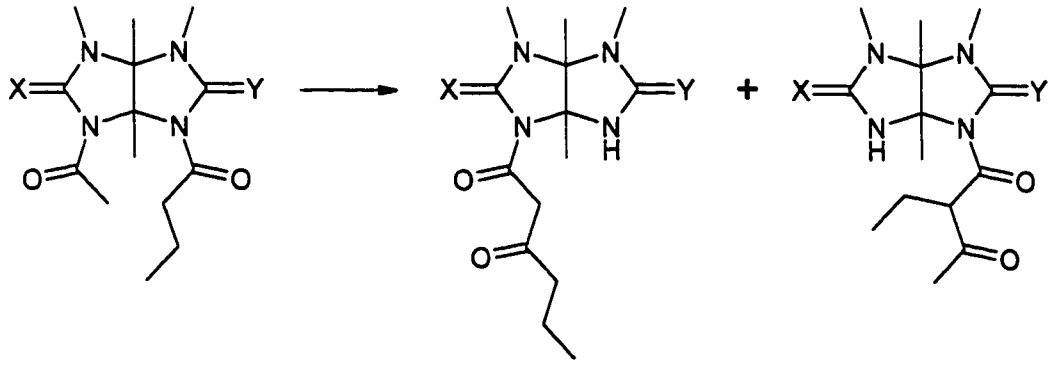
Figure 4.4: Possible Contribution of Chelation to Condensation Selectivity

The final and perhaps most likely possibility for the observed product ratio is that chelation of the lithium cation is a deciding factor in the selectivity. Lithium or potassium, the counterions generally used in this reaction, will bind much more strongly to oxygen than to sulfur (Figure 4.4), thus forming a bridge between the two oxygens

preferentially over the oxygen and sulfur on the other side of the molecule. Although previous studies of the chelation effect in the condensation reaction of the parent glycoluril compound have been inconclusive in showing a clear role for chelation in this reaction, in this system, this possibility cannot be overlooked. If this proves to be the major contributor to the observed selectivity, the possibility of reversing the selectivity simply by changing the counterion to a metal with a higher affinity to sulfur than oxygen exists.

Although the reaction in Scheme 4.12 does show selectivity, after removal of the side chain, one obtains identical products. Therefore, in order to further investigate the selectivity of the condensation reaction and to obtain some more interesting condensation products, the acetyl-butanoyl adducts **4-11** and **4-12** were subjected to identical reaction conditions (Scheme 4.13).

The oxygen analogue **4-18** of these compounds has been very well characterized in other studies, and gives an 88% yield of products **4-19** and **4-20** in a ratio of 81:19.



4-18: X = Y = O
4-11: X = O, Y = S
4-12: X = S, Y = O

4-19: X = Y = O
4-21: X = O, Y = S
4-23: X = S, Y = O

4-20: X = Y = O
4-22: X = O, Y = S
4-24: X = S, Y = O

Scheme 4.13: Condensation of Acetyl-Butanoyl Thioglycolurils

The acetyl-butanoyl adduct **4-11**, which has the thioglycoluril oxygen on the same side as the acetyl group is set up even better for this reaction; a 97% yield of products **4-21** and **4-22** was isolated, with a product ratio of 86 : 14. This may represent a slightly better ratio, but is still very close to that observed on the oxygen template. In contrast, compound **4-12**, in which the oxygen is on the opposite side of the thioglycoluril to the acetyl group, exhibits a reversal in selectivity. The products **4-23** and **4-24** were isolated in a total yield of 57%, with a product ratio of 43 : 57. It should be noted that these reactions were performed under identical conditions, simultaneously, in order to get a comparable result; further experiments to optimise yields, such as adding two equivalents or more of base (to abstract the labile proton on the product, making it inert), and to obtain a better product ratio, such as reducing the temperature of the reaction, should make this a viable synthetic route.

4.5 Summary

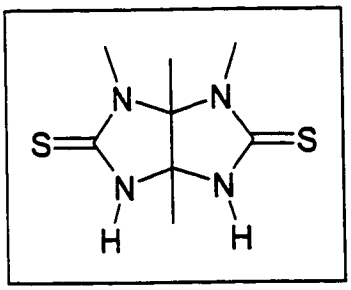
Use of Lawesson's reagent under conditions suitable for amides provides a viable, novel route to a number of thioglycoluril compounds in good yields. The full generality of this reaction has not yet been investigated.

The observed selectivity of the condensation reaction illustrates the possibility of using this system to deliberately obtain a series of compounds that would be equivalent to polyketide synthase using butanoyl groups in the biosynthetic pathway; which, while less common than adding acetyl groups, is not uncommon. The same strategy could be used

to assemble natural products based on the condensation of propionyl chains, which are encountered very frequently. One example of a natural product which is assembled from the condensation of propionyl units is erythromycin, whose biosynthesis results from the condensation of seven propionyl units[127]. The observed selectivity in this condensation reaction makes this methodology suitable for a number of substituted natural products which were previously, for all practical purposes, unattainable on the glycoluril template by direct methods†.

4.6 Experimental

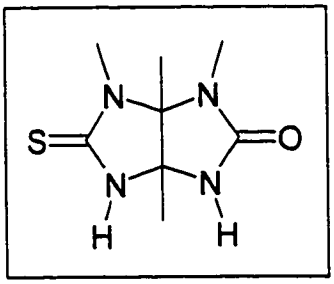
3,4,7,8-Tetramethyl-2,5-dithioglycoluril (4-2). A flask was charged with 3,4,7,8-tetramethylglycoluril **2-1** (2.03 g, 10.2 mmol) and toluene (20 mL). Three equivalents (12.4 g, 30.7 mmol) of Lawesson's reagent was added, and the mixture was heated at reflux for 16 h. The mixture was cooled, quenched with 5% HCl (10 mL), then partitioned between methanol (50 mL) and hexanes (50 mL). The methanol fraction was evaporated, and the resulting residue was recrystallized from 95% ethanol. The product (1.39 g, 60% yield) was isolated as a white powder. Mp: >260 °C; ^{1}H nmr (CD_3OD, 200 MHz) δ 3.14 (6H, s, N-CH_3), 1.58 (3H, s, CH_3), 1.45 (3H, s, CH_3); IR ($CHCl_3$, NaCl



† Compounds of this substitution pattern are available via conjugate addition of *L*-selectride to enoyl-acyl glycolurils; however, this involves use of a more complicated and expensive substrate.

disks, cm^{-1}) 3439 (NH), 3154, 2931, 1490, 1442, 1289 (C=S), 1085, 547; EIMS *m/z* 230 [M^+], 142 (base), 109, 56.

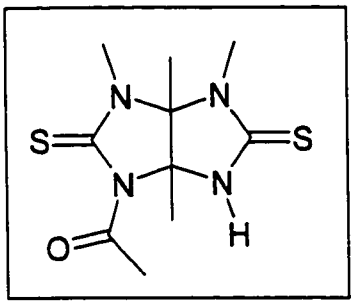
3,4,7,8-Tetramethyl-2-thioglycoluril (4-1). Method 1: This compound was prepared



from 3,4,7,8-tetramethylglycoluril **5** (2.03 g, 10.3 mmol) identically to 3,4,7,8-tetramethyl-2,5-dithioglycoluril **4-2**, except that only 1.0 equivalents (4.16 g) of Lawesson's reagent was used. The product was isolated as a white powder (1.83 g, 83% yield) as a (2:1) mixture of **4-1** to **4-2**, and was used in the next step without further purification. **Method 2:** A flask was charged with 1-acetyl-3,4,7,8-tetramethyl-5-thioglycoluril (**4-6**) (100 mg, 4.1×10^{-4} mol), and THF (5 mL). Sodium ethoxide (1.2 eq., 0.5 mL of 1 M solution) was added and the mixture was stirred for ½ h, then excess acetic anhydride was added and stirring was continued for 2 h. The reaction mixture was extracted into $CHCl_3$ (3 × 10 mL), washed with water (10 mL), and dried over anhydrous sodium sulfate. The mixture was filtered, and the solvent was removed on the rotary evaporator. The product (86 mg, 98% yield) was isolated as a white powder. Mp: 222-225 °C, decomposes; ^1H nmr (CD_3OD + dash $CDCl_3$, 500 MHz) δ 3.16 (3H, s, S=C-N-C*H*$_3$), 2.88 (3H, s, O=C-N-C*H*$_3$), 1.58 (3H, s, C*H*$_3$), 1.48 (3H, s, C*H*$_3$); ^{13}C nmr (CD_3OD + dash $CDCl_3$, 125 MHz) δ 182.05 (*C*=S), 160.04 (*C*=O), 86.13, 77.13, 30.70, 26.81, 21.41, 15.91; IR ($CHCl_3$, NaCl disks, cm^{-1}) 3439 (NH), 3020, 2400, 1686 (C=O), 1503, 1215 (C=S), 1082; EIMS *m/z* 214 [M^+], 143, 126 (base), 56, 44; HRMS calcd. for

$C_8H_{14}N_4OS$: 214.0884, found: 214.0888; Anal. calcd. for $C_8H_{14}N_4OS$: C: 44.80, H: 6.58, N: 26.14; found C: 44.85, H: 6.50, N: 24.67.

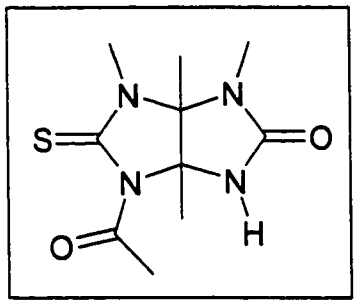
1-Acetyl-3,4,7,8-tetramethyldithioglycoluril (4-4). Method 1: This compound was



produced by adding 3,4,7,8-tetramethyl-2,5-dithioglycoluril (**4-2**) (200 mg, 8.7×10^{-4} mol) to neat acetic anhydride (50 mL) and heating to 80 °C for 16 h. The acetic anhydride was then evaporated on a rotary evaporator to give a solid residue, which was purified by flash column chromatography on silica gel using $CHCl_3$ as the eluent. The product was collected (R_f = 0.15) and the solvent was removed to obtain a white powder (135 mg, 63% yield from **1**). **Method 2:** This compound was synthesized by reacting 3,4,7,8-tetramethyl-2,5-dithioglycoluril (**4-2**) (100 mg, 4.3×10^{-4} mol) with 1.2 eq. KO^{t}Bu (58 mg) in THF (10 mL) for ½ h, followed by addition of excess acetic anhydride. The mixture was stirred for an additional 2 h, then the solvent was removed on the rotary evaporator to give a solid white residue. The product was purified by flash column chromatography on silica gel using $CHCl_3$ as the eluent to give a white solid (94 mg, 85% yield). Mp: 214–217 °C; ^{1}H nmr ($CDCl_3$, 200 MHz) δ 7.32 (1H, s, N*H*), 3.27 (3H, s, N-CH_3), 3.10 (3H, s, N-CH_3), 2.75 (3H, s, O=C-CH_3), 1.68 (3H, s, CH_3), 1.57 (3H, s, CH_3); ^{13}C nmr ($CDCl_3$, 50 MHz) δ 180.76 (*C*=S), 177.12 (*C*=S), 172.16 (*C*=O), 85.56, 82.92, 31.77, 29.93, 27.87, 18.83, 15.82; IR ($CHCl_3$, NaCl disks, cm^{-1}) 3431 (NH), 3020,

1681 (C=O), 1477, 1306, 1216 (C=S), 1081, 928; EIMS *m/z* 272 [M^+], 184, 142 (base), 109, 84, 56; Anal. calcd. for $C_{10}H_{16}N_4OS_2$: C: 44.06, H: 5.92, N: 20.57; found C: 44.65, H: 5.78, N: 20.30.

1-Acetyl-3,4,7,8-tetramethyl-2-thioglycoluril (4-5). This compound was produced by adding 3,4,7,8-tetramethyl-2-thioglycoluril (**4-1**) (505 mg, 2.4 mmol) to neat acetic anhydride (30 mL) and heating to reflux for 16 h. The majority of the acetic anhydride was removed by distillation, then 30 mL $CHCl_3$ was added and evaporated on the rotary evaporator to obtain a solid residue. The product was purified by flash column chromatography using 50% EtOAc/Hexanes, and was isolated from the most polar fraction as a white powder (199 mg, 36% from **4-1**). Mp: 145-147 °C; ^{1}H nmr ($CDCl_3$, 200 MHz) δ 6.09 (1H, s, N*H*), 3.29 (3H, s, S=C-N-C*H*$_3$), 2.83 (3H, s, O=C-N-C*H*$_3$), 2.78 (3H, s, O=C-C*H*$_3$), 1.67 (3H, s, C*H*$_3$), 1.56 (3H, s, C*H*$_3$); IR ($CHCl_3$, NaCl disks, cm^{-1}) 3439 (NH), 3019, 1718 (C=O), 1682 (C=O), 1485, 1379, 1296, 1215 (C=S), 1107; EIMS *m/z* 256 [M^+], 126 (base), 84, 56, 49; Anal. calcd. for $C_{10}H_{16}N_4O_2S$: C: 46.82, H: 6.29, N: 21.86; found C: 47.27, H: 6.32, N: 21.55.



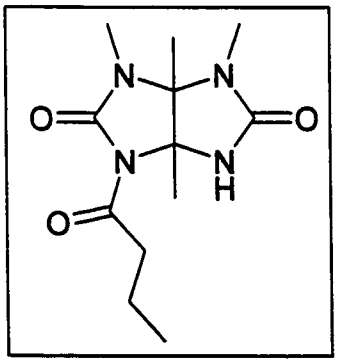
1-Acetyl-3,4,7,8-tetramethyl-5-thioglycoluril (4-6). 1-Acetyl-3,4,7,8-tetramethylglycoluril (**2-2**) (5.4 g, 23 mol) was dissolved in toluene (100 mL), then 1.3

equivalents of Lawesson's reagent (11.9 g, 30 mmol) was added and the mixture was heated at 60 °C for 16 h. The reaction was quenched with 5% HCl (10 mL) and the mixture was filtered to give a yellowish solid. This residue was dissolved in a small amount of $CHCl_3$, and the product was purified by elution through a silica gel plug with 70% EtOAc/Hexanes. The solvent was removed on the rotary evaporator to give a white solid (2.7 g, 47% yield). Mp: 181-182 °C; ^{1}H nmr ($CDCl_3$, 200 MHz) δ 7.14 (1H, s, N*H*), 3.15 (3H, s, S=C-N-C*H*$_3$), 3.01 (3H, s, O=C-N-C*H*$_3$), 2.45 (O=C-C*H*$_3$), 1.69 (3H, s, C*H*$_3$), 1.56 (3H, s, C*H*$_3$); ^{13}C nmr ($CDCl_3$, 50 MHz) δ 181.18 (NN*C*=S), 170.87 (*C*=O), 153.08 (NN*C*=O), 82.69, 78.58, 30.30, 27.16, 24.74, 19.23, 15.79; IR ($CHCl_3$, NaCl disks, cm^{-1}) 3440 (NH), 2994, 2946, 1738 (C=O), 1665 (C=O), 1490, 1329 (C=S) , 1284, 1098, 753; EIMS *m/z* 256 [M$^+$], 168, 127, 58, 43 (base); HRMS calcd. for $C_{10}H_{16}N_4O_2S$: 256.0944, found: 256.1000; Anal. calcd. for $C_{10}H_{16}N_4O_2S$: C: 46.82, H: 6.29, N: 21.86, S: 12.51; found: C: 46.95, H: 6.31, N: 21.51, S: 12.10.

1-Thioacetyl-3,4,7,8-tetramethyl-5-thioglycoluril (4-7). This compound was formed as a byproduct of the reaction of 1-acetyl-3,4,7,8-tetramethylglycoluril (**2-2**) with Lawesson's reagent to give 1-acetyl-3,4,7,8-tetramethyl-5-thioglycoluril (**4-6**) at temperatures in excess of 80 °C. Therefore, 1-acetyl-3,4,7,8-tetramethylglycoluril **2-2** (5.03 g,

20.8 mmol) was dissolved in 100 mL of toluene, and 1.3 equivalents of Lawesson's reagent (10.9 g) was added. The mixture was heated at reflux for 16 h, then was cooled to room temperature and quenched with 5% HCl (10 mL) and extracted into $CHCl_3$ (3 × 100 mL). The organic fraction was washed with water (80 mL), dried over anhydrous sodium sulfate, and filtered. Solvent was removed on the rotary evaporator to produce a bright yellow solid, which was recrystallized from $CHCl_3$/EtOAc. The product (1.22 g, 22% yield) was isolated as a yellow solid from 1-acetyl-3,4,7,8-tetramethyl-5-thioglycoluril by flash column chromatography on silica gel using 70% EtOAc/Hexanes. Mp: 173-174 °C; ^{1}H nmr ($CDCl_3$, 200 MHz) δ 8.09 (1H, s, N*H*), 3.11 (3H, s, S=C-N-C*H*$_3$), 3.05 (3H, s, S=C-C*H*$_3$), 2.97 (3H, s, O=C-N-C*H*$_3$), 1.86 (3H, s, C*H*$_3$), 1.55 (3H, s, C*H*$_3$); ^{13}C nmr ($CDCl_3$, 50 MHz) δ 206.77 (CH_3C=S), 180.86 (*C*=S), 151.75 (*C*=O), 82.78, 82.31, 31.12, 29.90, 27.47, 17.47, 15.38; IR ($CHCl_3$, NaCl disks, cm^{-1}) 3384 (NH), 3020, 2988, 1746 (C=O), 1417, 1331 (C=S), 1216 (C=S), 1079; EIMS *m/z* 314 [M$^+$], 272, 184, 126, 43 (base); Anal. calcd. for $C_{10}H_{16}N_4OS_2$: C: 44.06, H: 5.92, N: 20.57; found: C: 43.83, H: 5.92, N: 20.40.

1-Butanoyl-3,4,7,8-tetramethylglycoluril (4-8). Glycoluril **2-1** (2 g, 10 mmol) was added to 100 mL THF, then 1.0 eq. *n*-BuLi (6.3 mL) was added slowly, then the mixture was refluxed for 1 h. The suspension was cooled to room temperature, and butyric anhydride (2 mL, 12 mmol) was added and stirred for ½ h. The reaction was quenched with

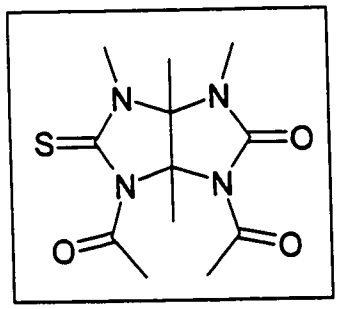


20 mL of 1 M $NaHSO_4$, and the mixture was extracted into chloroform (3 × 100 mL), washed with water (50 mL), and dried over anhydrous sodium sulfate. The solvent was removed on the rotary evaporator, and the product was recrystallized from $CHCl_3$ and hexanes (527 mg, 20% yield). The product was identical by ^1H nmr to material synthesized by Sun.

1-Butanoyl-3,4,7,8-tetramethyl-5-thioglycoluril (4-9). 1-Butanoyl-3,4,7,8-tetramethylglycoluril **4-8** (500 mg, 1.8 mmol) was dissolved in toluene (10 mL), then 1.2 equivalents of Lawesson's reagent (0.9 g) was added and the mixture was heated at 60 °C for 16 h. The reaction was quenched with 5% HCl (5 mL), then filtered. The filtrate was extracted into $CHCl_3$ (20 mL) and washed with 0.5 N NaOH (2 × 20 mL), then with water (20 mL) and brine (20 mL). The organic fraction was dried over anhydrous sodium sulfate, then filtered and the solvent was removed on the rotary evaporator to give a yellow oil, which foamed under vacuum (388 mg, 74%). Mp: 124 °C; ^1H nmr ($CDCl_3$, 200 MHz) δ 7.17 (1H, s, N*H*), 3.12 (3H, s, S=C-N-C*H*$_3$), 2.98 (3H, s, O=C-N-C*H*$_3$), 2.79 (2H, m, O=C-C*H*$_2$), 1.66 (3H, s, C*H*$_3$), 1.57 (2H, m, O=C-CH$_2$-C*H*$_2$), 1.54 (3H, s, C*H*$_3$), 0.89 (3H, t, ^3J = 7.34 Hz, O=CH$_2$-CH$_2$-C*H*$_3$); ^{13}C nmr ($CDCl_3$, 50 MHz) δ 181.01 (*C*=S), 173.79 (CH$_2$-*C*=O), 152.42 (*C*=O), 82.60, 78.54, 38.07, 30.20, 27.03, 19.17, 17.57, 15.72, 13.52; IR ($CHCl_3$, NaCl disks, cm^{-1}) 3435 (NH), 3020, 2972, 1738 (C=O), 1685 (C=O), 1463,

1215 (C=S), 1083; EIMS *m/z* 284 [M^+], 196, 127 (base), 56; HRMS calcd. for $C_{12}H_{20}N_4O_2S$: 284.1307, found: 284.1296; Anal. calcd. for $C_{12}H_{20}N_4O_2S$: C: 51.37, H: 7.19, N: 19.98; found: C: 51.50, H: 7.31, N: 19.72.

1,6-Diacetyl-3,4,7,8-tetramethyl-2-thioglycoluril (4-10). Method 1: A flask was

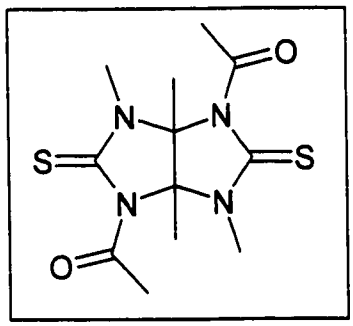


charged with 1-acetyl-3,4,7,8-tetramethyl-2-thioglycoluril (**4-5**) (60 mg, 2.3 × 10^{-4} mol) and THF (10 mL) and cooled to 0 °C, then *n*-BuLi (1.1 eq., 172 □L of 1.5 M solution in hexanes) was added dropwise and the mixture was stirred for 10 minutes. Acetyl chloride (1.2 eq., 20 □L) was added and the stirring continued for 2 h. The reaction was quenched with 2 mL of 1 M $NaHSO_4$, then the product was extracted into $CHCl_3$ (3 × 10 mL), washed with water (10 mL) and dried over anhydrous sodium sulfate. The mixture was filtered, and the solvent was removed on the rotary evaporator. The product was isolated as a white powder after flash column chromatography on silica gel in $CHCl_3$ (2^{nd} fraction, 15.8 mg, 23% yield). **Method 2:** A flask was charged with 1-acetyl-3,4,7,8-tetramethyl-5-thioglycoluril (**4-6**) (75 mg, 2.9 × 10^{-4} mol), and THF (5 mL) and cooled to 0 °C. *n*-BuLi (1.05 eq., 205 □L) was added and the mixture was stirred for 10 min. Acetyl chloride (1.2 eq., 25 □L) was added and the stirring was continued for 2 h. Work up as for Method 1 gave product which was isolated as a white powder (51 mg, 58% yield). Mp: 177-180 °C, decomposes; ^{1}H nmr ($CDCl_3$, 500 MHz) δ 3.20 (3H, s, S=C-N-C*H*$_3$), 2.98 (3H, s, O=C-N-C*H*$_3$), 2.72, (3H, s, O=C-C*H*$_3$), 2.47 (3H, s, O=C-C*H*$_3$), 1.89 (3H, s,

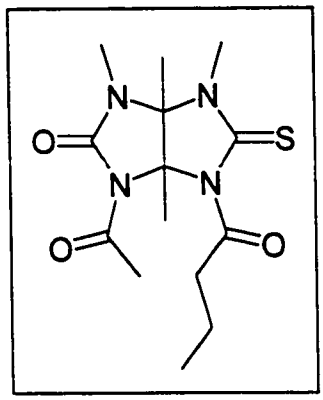
C*H*$_3$), 1.52 (3H, s, C*H*$_3$); ^{13}C nmr ($CDCl_3$, 125 MHz) δ 178.34 (*C*=S), 173.27 (*C*=O, acetyl), 170.62 (*C*=O, acetyl), 152.66 (*C*=O), 83.29, 81.92, 31.08, 29.40, 26.92, 25.65, 19.02, 14.94; EIMS *m/z* 298 [M$^+$], 257, 168, 126 (base), 56, 43; HRMS calcd. for $C_{12}H_{18}N_4O_3S$: 298.1090, found: 298.1099; Anal. calcd. for $C_{12}H_{18}N_4O_3S$: C: 48.26, H: 6.08, N: 18.78; found: C: 46.79, H: 6.24, N: 16.27.

1,6-Diacetyl-3,4,7,8-tetramethyl-2,5-dithioglycoluril (2-6). Described in Section 2.8.

1,4-Diacetyl-3,6,7,8-tetramethyl-2,5-dithioglycoluril. This compound was observed as a byproduct of the reaction of the mixture of sulfur template isomers with acetic anhydride at reflux. This product arises from the *anti*-isomer (3,6,7,8-tetramethylglycoluril **2-1a**) of the parent oxygen template which is present in the Lawesson's reaction and carries over to this step. The product was isolated as the least polar fraction by flash column chromatography on silica gel using 50% EtOAc/Hexanes as a white powder (115.3 mg (597 mg starting material), 17% yield). Mp: 189 °C; ^{1}H nmr ($CDCl_3$, 200 MHz) δ 3.33 (6H, s, 2 × N-C*H*$_3$), 2.72 (6H, s, 2 × O=C-C*H*$_3$), 1.68 (6H, s, 2 × C*H*$_3$); ^{13}C nmr (50 MHz) δ 178.47 (2 × *C*=S), 172.67 (2 × *C*=O), 87.24 (2 × *C* bridgehead), 33.98, 28.05, 15.95; IR ($CHCl_3$, NaCl disks, cm^{-1}) 3020, 2994, 1697 (C=O), 1385, 1319, 1218 (C=S), 1121, 1028; EIMS *m/z* 314 [M$^+$], 184, 142 (base), 83; Anal. calcd. for $C_{12}H_{18}N_4O_2S_2$: C: 45.80, H: 5.77, N: 17.82; found: C: 45.58, H: 5.80, N: 17.51.



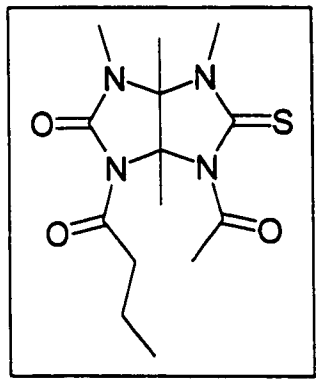
1-Butanoyl-6-acetyl-3,4,7,8-tetramethyl-2-thioglycoluril (4-11). Method 1: A flask



was charged with 1-acetyl-3,4,7,8-tetramethyl-5-thioglycoluril (**4-6**) (100 mg, 0.39 mmol) and THF (20 mL) and cooled to 0 °C, then *n*-BuLi (1.1 eq., 268 □L of 1.5 M) was added and the mixture was stirred for 30 minutes. Butyric anhydride (1.2 eq., 76 □L) was added and stirring was continued for 2 h, then the reaction mixture was quenched with $NaHSO_4$ (2 mL of 1 M) and extracted into $CHCl_3$. The organic fraction was washed with water (20 mL), dried over anhydrous sodium sulfate, then was filtered and the solvent was removed on the rotary evaporator. The product was isolated as a white powder after flash column chromatography (81.3 mg, 64%; remainder was 18% starting material, and 18% *bis*-butanoyl adduct). **Method 2:** A flask was charged with 1-acetyl-3,4,7,8-tetramethyl-5-thioglycoluril **4-6** (125 mg, 0.48 mmol) and butyric anhydride (5 mL) and heated at reflux for 72 h. The butyric anhydride was then removed by distillation, and the product was isolated by flash column chromatography on silica gel with 50% EtOAc/Hexanes (110 mg, 69% yield; remainder was starting material). Mp: 114 °C; ^{1}H nmr ($CDCl_3$, 200 MHz) δ 3.43 (1 H, dq, ^2J = 17.0, ^3J = 6.8 Hz, O=C-C*H*H-CH_2), 3.17 (3H, s, S=C-N-CH_3), 2.94 (3H, s, O=C-N-CH_3), 2.78 (1H, dq, ^2J = 16.9, ^3J = 6.8 Hz, O=C-CH*H*-CH_2), 2.43 (3H, s, O=C-CH_3), 1.86 (3H, s, CH_3), 1.69 (2H, app. septet, ^3J = 7.4 Hz, CH_2), 1.49 (3H, s, CH_3), 0.91 (3H, t, ^3J = 7.4 Hz, CH_2-CH_3); ^{13}C nmr ($CDCl_3$, 50 MHz) δ 178.26 (*C*=S), 176.46 (*C*=O), 170.57 (*C*=O),

152.55 (*C*=O), 83.37, 81.74, 42.60, 31.06, 26.77, 25.66, 18.96, 18.22, 15.03, 13.52; IR ($CHCl_3$, NaCl disks, cm^{-1}) 3020, 2971, 1740 (C=O), 1695 (C=O), 1476, 1403, 1330, 1215 (C=S); EIMS *m/z* 326 [M^+], 257, 181, 168, 127, 84, 43 (base); HRMS calcd. for $C_{14}H_{22}N_4O_3S$: 326.1413, found: 326.1400; Anal. calcd. for $C_{14}H_{22}N_4O_3S$: C: 51.47, H: 6.79, N: 17.16; found: C: 51.49, H: 6.98, N: 17.00.

1-Acetyl-6-butanoyl-3,4,7,8-tetramethyl-2-thioglycoluril (4-12). 1-Butanoyl-3,4,7,8-tetramethyl-5-thioglycoluril **4-9** (300 mg 1.1 mmol) was dissolved in acetic anhydride (20 mL) and heated at reflux for 72 h. The acetic anhydride was removed by distillation, then the product was isolated as a white powder by flash column chromatography on silica gel with 70%EtOAc/Hexanes (233 mg, 68%; 18% starting material was also isolated). Mp: 133-135 °C; ^1H nmr ($CDCl_3$, 200 MHz) δ 3.18 (3H, s, S=C-N-C*H*$_3$), 2.97 (3H, s, O=C-N-C*H*$_3$), 2.82 (2H, app. quintet, ^3J = 7.2 Hz, O=C-C*H*$_2$), 2.67 (3H, s, O=C-C*H*$_3$), 1.86 (3H, s, C*H*$_3$), 1.63 (2H, app. q, ^3J = 7.3 Hz, O=C-CH$_2$-C*H*$_2$), 1.50 (3H, s, C*H*$_3$), 0.89 (3H, t, ^3J = 7.3 Hz, CH$_2$-C*H*$_3$); ^{13}C nmr ($CDCl_3$, 50 MHz) δ 178.21 (*C*=S), 173.65 (*C*=O), 173.29 (*C*=O), 152.54 (*C*=O), 83.25, 81.98, 38.99, 31.00, 29.43, 26.89, 19.02, 17.75, 14.93, 13.40; IR ($CHCl_3$, NaCl disks, cm^{-1}) 3020, 2972, 1738 (C=O), 1698 (C=O), 1475, 1324, 1215 (C=S), 1094, 1024, 928; EIMS *m/z* 326 [M^+], 285, 196, 127 (base), 56, 43; HRMS calcd. for $C_{14}H_{22}N_4O_3S$: 326.1413,

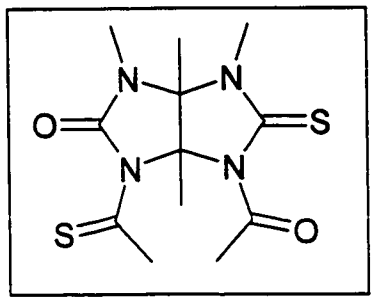


found 326.1423; Anal. calcd. for $C_{14}H_{22}N_4O_3S$: C: 51.47, H: 6.79, N: 17.16; found: C: 51.37, H: 7.00, N: 16.90.

1,6-Dibutanoyl-3,4,7,8-tetramethyl-2-thioglycoluril. A flask was charged with 1-acetyl-3,4,7,8-tetramethyl-5-thioglycoluril **4-6** (100 mg, 0.39 mmol) and 10 mL THF and cooled to 0 °C in an ice bath. *n*-BuLi (1.1 eq, 268 □L of 1.5 M solution) was added and stirred for 30 minutes, then butyric anhydride (1.2 eq, 76 □L) was added and stirring was continued for 2 h. The reaction mixture was quenched with $NaHSO_4$ (2 mL of 1 M solution), extracted into $CHCl_3$ (3 × 10 mL), washed with water (20 mL) and dried over anhydrous sodium sulfate. After filtering, the solvent was removed on the rotary evaporator, and the product was isolated as a white powder (28.4 mg, 20.5% yield) by flash column chromatography on silica gel with 70% EtOAc/Hexanes. ^{1}H nmr ($CDCl_3$, 200 MHz) δ 3.46 (1H, m, O=C-C*H*H-CH_2), 3.19 (3H, s, S=C-N-CH_3), 2.96 (3H, s, O=C-N-CH_3), 2.76 (3H, m, O=C-CH*H*-CH_2, O=C-CH_2), 1.89 (3H, s, CH_3), 1.72 (4H, m, 2 × O=C-CH_2-CH_2), 1.51 (3H, s, CH_3), 0.94 (3H, t, ^{3}J = 7.4 Hz, CH_2- CH_3), 0.92 (3H, t, ^{3}J = 7.4 Hz, CH_2-CH_3); EIMS *m/z* 354 [M^+], 326, 285, 257, 196 (base), 181, 159, 41.

1-Thioacetyl-6-acetyl-3,4,7,8-tetramethyl-5-thioglycoluril (4-13). A flask was charged with 1-thioacetyl-3,4,7,8-tetramethyl-5-thioglycoluril **4-7** (100 mg, 0.37 mmol)

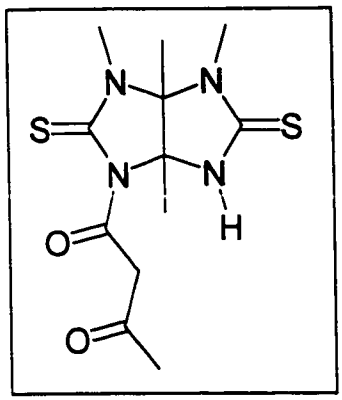
and 10 mL THF and cooled to 0 °C in an ice bath. *n*-BuLi (1.1 eq, 252 □L of 1.5 M



solution) was added dropwise and the mixture was stirred for 15 minutes, then acetyl chloride (1.2 eq, 31.5 □L) was added and stirring was continued for 2 hours. The reaction mixture was quenched with $NaHSO_4$ (3 mL of 1 M solution), extracted into $CHCl_3$ (3 × 10 mL), washed with water (20 mL), and dried over anhydrous sodium sulfate. The solution was filtered, and the solvent was removed on the rotary evaporator to give a yellow solid. Product (77.5 mg, 67% yield; rest (30 mg, 30%) was s.m.) was purified by flash column chromatography on silica gel in 50% EtOAc/Hexanes. Mp: 138 °C; ^{1}H nmr ($CDCl_3$, 500 MHz) δ 3.21 (3H, s, S=C-N-C*H*$_3$), 2.95 (3H, s, S=C-C*H*$_3$), 2.74 (3H, s, O=C-N-C*H*$_3$), 2.31 (3H, s, O=C-C*H*$_3$), 1.78 (3H, s, C*H*$_3$), 1.49 (3H, s, C*H*$_3$); ^{13}C nmr ($CDCl_3$, 125 MHz) δ 191.94 (S=*C*-CH$_3$), 177.84 (*C*=S), 172.75 (O=*C*-CH$_3$), 154.52 (*C*=O), 84.25, 82.21, 31.20, 30.45, 28.46, 27.03, 18.13, 15.51; EIMS *m/z* 314 [M$^+$], 271, 240, 214, 182, 142, 126, 56, 43 (base); Anal. calcd. for $C_{12}H_{18}N_4O_2S_2$: C: 45.80, H: 5.77, N: 17.82; found: C: 46.71, H: 5.67, N: 15.94.

1-(3'-Oxobutanoyl)-3,4,7,8-tetramethyl-2,5-dithioglycoluril (4-15). A flask was charged with 1,6-diacetyl-3,4,7,8-tetramethyl-2,5-dithioglycoluril **2-6** (20 mg, 6.4 × 10^{-5} mol) and 5 mL THF and cooled to 0 °C in an ice bath. A solution of LiO^{t}Am (1.2 eq., 15 □L of distilled *t*-amyl alcohol was added to 2.5 mL THF, then *n*-BuLi (50 □L of 1.6 M solution) was added slowly at 0 °C and the mixture was stirred for 30 minutes)

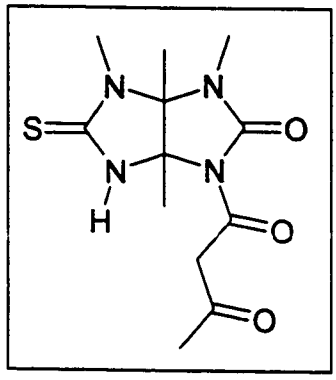
was added and the mixture was stirred for 2 h. The reaction mixture was quenched with



$NaHSO_4$ (1 mL of 1 M), extracted into $CHCl_3$ (3 × 10 mL), washed with water (10 mL) and dried over anhydrous sodium sulfate. The mixture was filtered and the solvent was removed on the rotary evaporator to give a white product. The product (12.4 mg, 62% yield) was separated from unreacted starting material (5 mg, 20%) and trace amounts of acetyl dithioglycoluril **4-4** by flash column chromatography on silica gel with 50% EtOAc/Hexanes. Mp: >260 °C, decomposes; ^{1}H nmr ($CDCl_3$, 500 MHz) δ 7.26 (1H, s, N*H*), 5.05 (1H, d, ^2J = 16.8 Hz, O=C-C*H*H-C=O), 3.90 (1H, d, ^2J = 16.8 Hz, O=C-CH*H*-C=O), 3.27 (3H, s, N-CH_3), 3.14 (3H, s, N-CH_3), 2.24 (3H, s, O=C-CH_3), 1.76 (3H, s, CH_3), 1.60 (3H, s, CH_3); ^{13}C nmr ($CDCl_3$, 125 MHz) δ 200.71 (*C*=S), 181.05 (*C*=S), 177.56 (*C*=O), 168.56 (*C*=O), 85.77, 83.40, 53.90, 49.67, 31.87, 30.10, 18.71, 15.96; EIMS *m/z* 230, 168, 142 (base), 109, 85; CIMS (NH_3) *m/z* 315 $[M+H]^+$, 231 (base), 142, 81, 56.

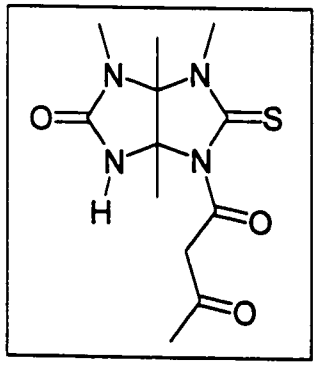
1-(3'-Oxobutanoyl)-3,4,7,8-tetramethyl-5-thioglycoluril (4-16). A flask was charged with 1,6-diacetyl-3,4,7,8-tetramethyl-5-thioglycoluril **4-10** (15.5 mg, 5.2 × 10^{-5} mol) and 5 mL THF and cooled to 0 °C, then LiO^tAm (1.2 eq, 700 □L of 0.09 M solution in THF) was added and the mixture was stirred for 1 h. The reaction mixture was quenched with $NaHSO_4$ (1 mL of 1 M), extracted into $CHCl_3$ (3 × 10 mL), washed with water (10 mL)

and dried over anhydrous sodium sulfate. The mixture was filtered and the solvent was



removed on the rotary evaporator to give a white product. This product (4 mg, 26% yield) was separated from the other condensation product (1-(3'-oxobutanoyl)-3,4,7,8-tetramethyl-2-thioglycoluril **4-17**) by flash column chromatography on silica gel with EtOAc as eluent. ^{1}H nmr ($CDCl_3$, 200 MHz) δ 7.08 (1 H, s, N*H*), 4.34 (1H, d, ^{2}J = 16.4 Hz, O=C-C*H*H-C=O), 3.52 (1H, d, ^{2}J = 16.5 Hz, O=CH*H*-C=O), 3.16 (3H, s, S=C-N-CH_3), 2.98 (3H, s, O=C-N-CH_3), 2.23 (3H, s, O=C-CH_3), 1.76 (3H, s, CH_3), 1.58 (3H, s, CH_3).

1-(3'-Oxobutanoyl)-3,4,7,8-tetramethyl-2-thioglycoluril (4-17). To 1,6-diacetyl-3,4,7,8-tetramethyl-5-thioglycoluril **4-10** (15.5 mg, 5.2 × 10^{-5} mol) dissolved in 5 mL THF and cooled to 0 °C, LiO^{t}Am (1.2 eq, 700 □L of 0.09 M solution in THF) was added and the mixture was stirred for 1 h. The reaction mixture was quenched with $NaHSO_4$ (1 mL of 1 M), extracted into $CHCl_3$ (3 × 10 mL), washed with water (10 mL) and dried over anhydrous sodium sulfate. The mixture was filtered and the solvent was removed on the rotary evaporator to give a white product. This product (2.95 mg, 20% yield) was separated from the other condensation product (1-(3'-oxobutanoyl)-3,4,7,8-tetramethyl-5-thioglycoluril **4-16**) by flash column



chromatography on silica gel with EtOAc as eluent. ^{1}H nmr ($CDCl_3$, 200 MHz) δ 6.12 (1H, s, N*H*), 4.98 (1H, d, ^{2}J = 16.9 Hz, O=C-C*H*H-C=O), 4.00 (1H, d, ^{2}J = 16.7 Hz, O=C-CH*H*-C=O), 3.26 (3H, s, S=C-N-CH_3), 2.84 (3H, s, O=C-N-CH_3), 2.24 (3H, s, O=C-CH_3), 1.73 (3H, s, CH_3), 1.58 (3H, s, CH_3).

1-(3'-Oxohexanoyl)-3,4,7,8-tetramethyl-5-thioglycoluril (4-21). To 1-Acetyl-6-butanoyl-3,4,7,8-tetramethyl-5-thioglycoluril **4-11** (55.4 mg, 0.17 mmol) dissolved in 10 mL THF and cooled to 0 °C, LiO^{t}Am (1.2 eq, 5 mL of 0.05 M solution in THF) was added and the mixture was stirred for 1 h. The reaction mixture was quenched with $NaHSO_4$ (1 mL of 1 M), extracted into $CHCl_3$ (3 × 10 mL), washed with water (10 mL) and dried over anhydrous sodium sulfate. The mixture was filtered and the solvent was removed on the rotary evaporator to give a white product. The product (42.3 mg, 79% yield) was separated from the other condensation product (6-(3'-oxo-2-ethylbutyryl)-3,4,7,8-tetramethyl-5-hioglycoluril **4-22**) and unreacted starting material by flash column chromatography on silica gel with 70% EtOAc/Hexanes as eluent. ^{1}H nmr ($CDCl_3$, 200 MHz) δ 7.10 (1H, s, N*H*), 4.36 (1H, d, ^{2}J = 16.4 Hz, O=C-C*H*H-C=O), 3.47 (1H, d, ^{2}J = 16.4 Hz, O=C-CH*H*-C=O), 3.15 (3H, s, S=C-N-CH_3), 2.98 (3H, s, O=C-N-CH_3), 2.47 (2H, m, O=C-CH_2), 1.76 (3H, s, CH_3), 1.57 (3H, s, CH_3), 1.54 (2H, m, O=C-CH$_2$-CH_2), 0.91 (3H, t, ^{3}J = 7.4 Hz, CH$_2$-CH_3).

1-(3'-Oxo-2-ethylbutyryl)-3,4,7,8-tetramethyl-2-thioglycoluril (4-22). To 6-acetyl-1-butanoyl-3,4,7,8-tetramethyl-5-thioglycoluril **4-11** (55.4 mg, 0.17 mmol) dissolved in 10 mL THF and cooled to 0 °C, LiO^{t}Am (1.2 eq, 5 mL of 0.05 M solution in THF) was added and the mixture was stirred for 1 h. The reaction mixture was quenched with $NaHSO_4$ (1 mL of 1 M), extracted into $CHCl_3$ (3 × 10 mL), washed with water (10 mL) and dried over anhydrous sodium sulfate. The mixture was filtered and the solvent was removed on the rotary evaporator to give a white product. The two diastereomeric products (11.4 mg, 19% yield) were separated from the other condensation product (1-(3'-oxohexanoyl)-3,4,7,8-tetramethyl-5-thioglycoluril **4-21**) and unreacted starting material by flash column chromatography on silica gel with 70% EtOAc/Hexanes as the eluent. The product exists as two diastereomers in a ratio of 1.5 : 1, which were not readily separable. ^{1}H nmr ($CDCl_3$, 500 MHz) δ 6.09 (1H, s, N*H*), 6.08 (1H, s, N'*H*), 5.78 (1H, dd, ^{3}J = 7.3, 5.7 Hz, O'=C'-C'*H*), 5.54 (1H, dd, ^{3}J = 3.9, 9.2 Hz, O=C-C*H*), 3.28 (3H, s, S'=C'-N'-C'H_3), 3.25 (3H, s, S=C-N-CH_3), 2.86 (3H, s, O'=C'-N'-C'H_3), 2.84 (3H, s, O=C-N-CH_3), 2.28 (3H, s, O=C-CH_3), 2.18 (3H, s, O'=C'-C'H_3), 1.94 (4H, br. m, CH_2 and C'H_2), 1.73 (3H, s, CH_3), 1.69 (3H, s, C'H_3), 1.58 (3H, s, C'H_3), 1.57 (3H, s, CH_3), 0.96 (6H, m, CH_2-CH_3 and C'H_2-C'H_3); ^{13}C nmr ($CDCl_3$, 125 MHz.) δ 204.33 (*C*=S), 181.30 (*C*=O), 169.63 (*C*=O), 153.50 (*C*=O), 81.83 , 77.25, 62.17, 61.28, 31.76, 29.20, 26.31, 26.23, 21.94, 21.72, 19.72, 19.46, 19.10, 16.01, 15.93,

13.58, 12.55, 12.21; EIMS: 326 [M^+], 284, 253, 226, 159, 126 (base), 84, 43; HRMS calcd. for $C_{14}H_{22}N_4O_3S$: 326.1413, found: 326.1439.

1-(3'-Oxo-2-ethylbutyryl)-3,4,7,8-tetramethyl-5-thioglycoluril (4-24). To 6-acetyl-1-butanoyl-3,4,7,8-tetramethyl-5-thioglycoluril **4-12** (51.5 mg, 0.16 mmol) dissolved in 10 mL THF and cooled to 0 °C, LiO^{t}Am (1.5 eq, 5 mL of 0.05 M solution in THF) was added and the mixture was stirred for 1 h. The reaction mixture was quenched with $NaHSO_4$ (1 mL of 1 M), extracted into $CHCl_3$ (3 × 10 mL), washed with water (10 mL) and dried over anhydrous sodium sulfate. The mixture was filtered and the solvent was removed on the rotary evaporator to give a white product. The two diastereomeric products (17.3 mg, 33% yield) were separated from the other condensation product (6-(3'-oxohexanoyl)-3,4,7,8-tetramethyl-5-thioglycoluril **4-23**) and unreacted starting material by flash column chromatography on silica gel with 70% EtOAc/Hexanes as eluent. Partial separation of the diastereomers was also achieved. **Less Polar Diastereomer:** ^{1}H nmr ($CDCl_3$, 500 MHz) δ 7.11 (1H, s, N*H*), 4.38 (1H, dd, ^3J = 3.8, 9.0 Hz, O=C-C*H*), 3.15 (3H, s, S=C-N-CH_3), 2.96 (3H, s, O=C-N-CH_3), 2.27 (O=C-CH_3), 1.97 (2H, m, CH_2), 1.74 (3H, s, CH_3), 1.55 (3H, s, CH_3), 0.96 (3H, t, ^3J = 7.2 Hz, CH_2-CHC_3); ^{13}C nmr ($CDCl_3$, 125 MHz) δ 205.21 (*C*=S), 181.30 (*C*=O), 169.64 (*C*=O), 152.68 (*C*=O), 82.83, 79.08, 60.71, 30.29, 28.97, 27.06, 20.54, 18.62, 15.73, 12.58. **More Polar Diastereomer:** ^{1}H nmr ($CDCl_3$, 500 MHz) δ 7.15 (1H,

s, N*H*), 4.52 (1H, dd, ^{3}J = 2.85, 8.13 Hz, O=C-C*H*), 3.17 (3H, s, S=C-N-CH_3), 3.00 (3H, s, O=C-N-CH_3), 2.17 (O=C-CH_3), 1.88 (2H, m, CH_2), 1.71 (3H, s, CH_3), 1.58 (3H, s, CH_3), 0.94 (3H, t, ^{3}J = 7.3 Hz, CH_2-CH_3); ^{13}C nmr ($CDCl_3$, 125 MHz) δ 202.97 (*C*=S), 181.40 (*C*=O), 170.48 (*C*=O), 152.47 (*C*=O), 82.63, 78.92, 60.71, 30.42, 28.87, 27.17, 21.41, 19.37, 15.89, 12.32; EIMS: 326 [M$^+$], 238, 126 (base), 84, 43; HRMS calcd. for $C_{14}H_{22}N_4O_3S$: 326.1413, found: 326.1419.

1-(3'-Oxohexanoyl)-3,4,7,8-tetramethyl-2-thioglycoluril (4-23). To 6-acetyl-1-butanoyl-3,4,7,8-tetramethyl-5-thioglycoluril **4-12** (51.5 mg, 0.16 mmol) dissolved in 10 mL THF and cooled to 0 °C, LiO^{t}Am (1.2 eq, 5 mL of 0.05 M solution in THF) was added and the mixture was stirred for 1 h. The reaction mixture was quenched with $NaHSO_4$ (1 mL of 1 M), extracted into $CHCl_3$ (3 × 10 mL), washed with water (10 mL) and dried over anhydrous sodium sulfate. The mixture was filtered and the solvent was removed on the rotary evaporator to give a white product. The product (12.4 mg, 15% yield) was separated from the other condensation product (1-(3'-oxo-2-ethylbutyryl)-3,4,7,8-tetramethyl-5-thioglycoluril **4-24**) and unreacted starting material by flash column chromatography on silica gel with 70% EtOAc/Hexanes as eluent. Mp: 126-127 °C; ^{1}H nmr ($CDCl_3$, 500 MHz) δ 6.10 (1H, s, N*H*), 5.01 (1H, d, ^{2}J = 16.6 Hz, O=C-C*H*H-C=O), 3.94 (1H, d, ^{2}J = 16.6 Hz, O=C-CH*H*-C=O), 3.25 (3H, s,

S=C-N-C*H*$_3$), 2.83 (3H, s, O=C-N-C*H*$_3$), 2.55 (1H, dt, ^{2}J = 17.2, ^{3}J = 7.4 Hz, O=C-C*H*H-CH$_2$), 2.45 (1H, dt, ^{2}J = 17.3, ^{3}J = 7.2 Hz, O=C-CH*H*-CH$_2$), 1.73 (3H, s, C*H*$_3$), 1.60 (2H, app. q, ^{3}J = 7.3 Hz, O=C-CH$_2$-C*H*$_2$), 1.57 (3H, s, C*H*$_3$), 0.91 (3H, t, CH$_2$-C*H*$_3$, ^{3}J = 7.4 Hz); ^{13}C nmr ($CDCl_3$, 125 MHz) δ 203.13 (*C*=S), 177.83 (*C*=O), 169.10 (*C*=O), 156.62 (*C*=O), 81.91, 81.18, 53.24, 44.79, 31.85, 26.24, 19.25, 16.81, 15.98, 13.67; EIMS: 326 [M$^+$], 214, 126 (base), 56, 43; HRMS calcd. for $C_{14}H_{22}N_4O_3S$: 326.1413, found: 326.1412; Anal. calcd for $C_{14}H_{22}N_4O_3S$: C: 51.47, H: 6.79, N: 17.16; found: C: 51.44, H: 7.17, N: 16.77.

CHAPTER 5: Towards the Synthesis of the Antibiotic Pramanicin

5.1 Structure, Properties and Likely Biosynthesis of Pramanicin

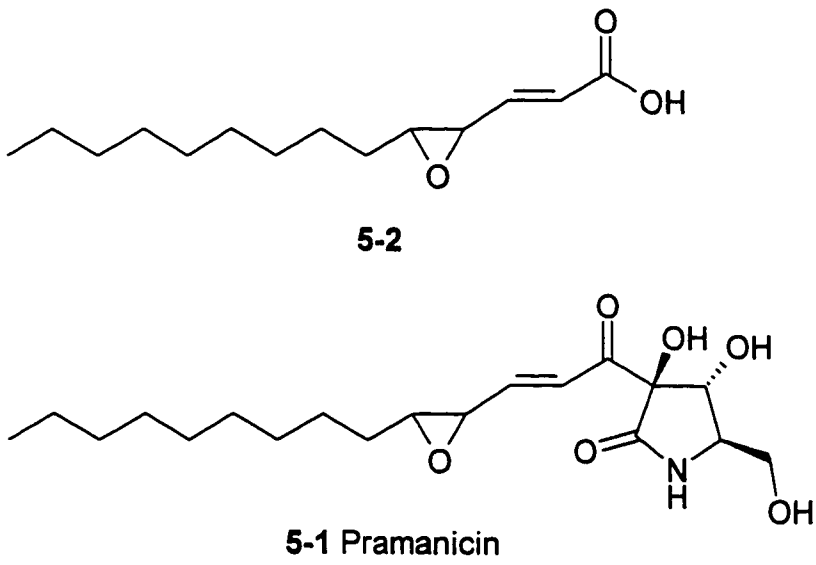


Figure 5-1: Structure of Pramanicin (**5-1**) and Related Fatty Acid (**5-2**)

Pramanicin (**5-1**) and the related fatty acid (**5-2**) (Figure 5.1) are natural products which were first isolated by Schwartz *et al.*[128] from a fermentation of an unidentified fungal species (MF5868) growing on grass. Pramanicin consists of a polar head group attached to a 14-carbon fatty acid chain. Pramanicin displays significant antifungal activity versus *Cryptococcus neoformans*, the causative agent of meningitis in AIDS patients, at a minimum inhibitory concentration (MIC) of 20 μM. It is also a potent agent

against *Candida* spp., with MIC's in the range of 4 to > 100 μM[128]. These properties make it an interesting synthetic target. Synthesis of pramanicin should allow for determination of the absolute stereochemistry of the epoxide, since this has not yet been reported for this compound, as well as for simple preparation of analogues for structure-activity correlations.

The biosynthesis of pramanicin has not yet been fully studied, but it is likely that the molecule is assembled through the head-to-tail addition of seven acetate units by a polyketide synthase type enzyme. This would generate a 14-membered fatty acid, which could be epoxidized to give **5-2**, which was also isolated from the fermentation mixture. Addition of the polar head group probably occurs later, and may come from a variety of sources. Recent investigations of ^{13}C-labelled acetate incorporation in the biosynthesis of pramanicin[†] have revealed that it is indeed generated by the head-to-tail addition of seven acetate units; another acetate unit was incorporated into the pyrrolidinone head group. These results are consistent with incorporation of the labelled acetate into glutamate and/or proline, or else direct chain extension of **5-2** followed by cyclization with serine. The determination of the origin of the polar head group thus awaits further biosynthetic investigation.

5.2 Retrosynthetic Analysis of Pramanicin

[†] Biosynthetic experiments carried out by Dr. P. Harrison (unpublished).

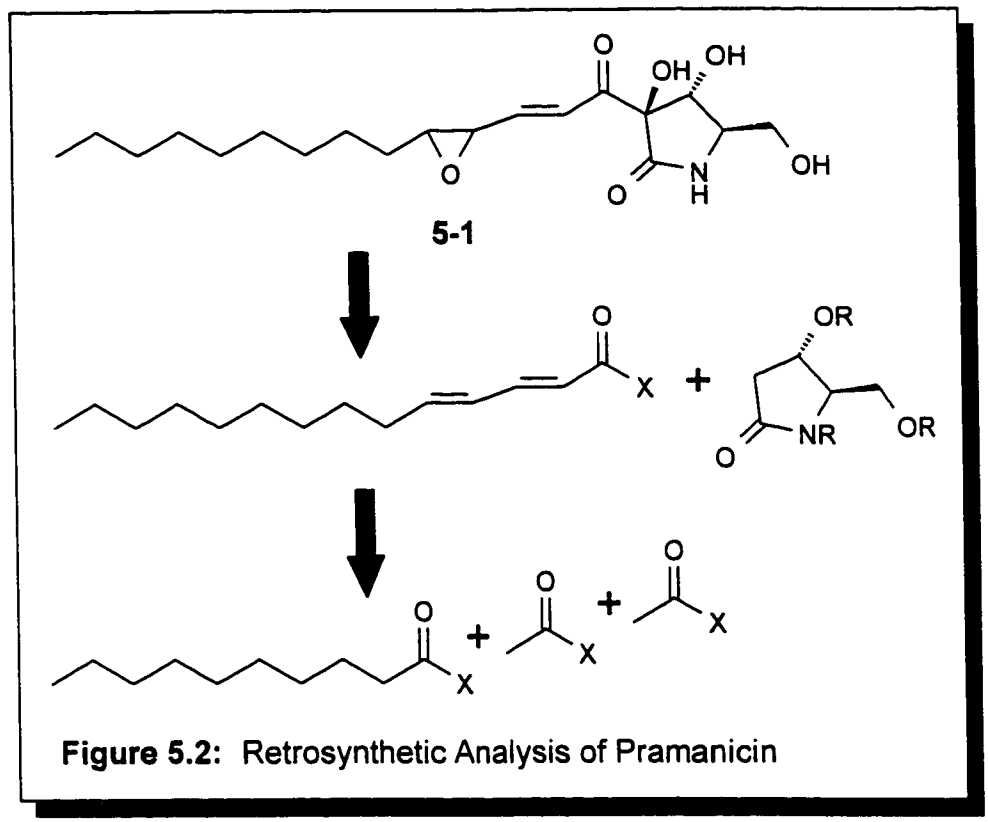


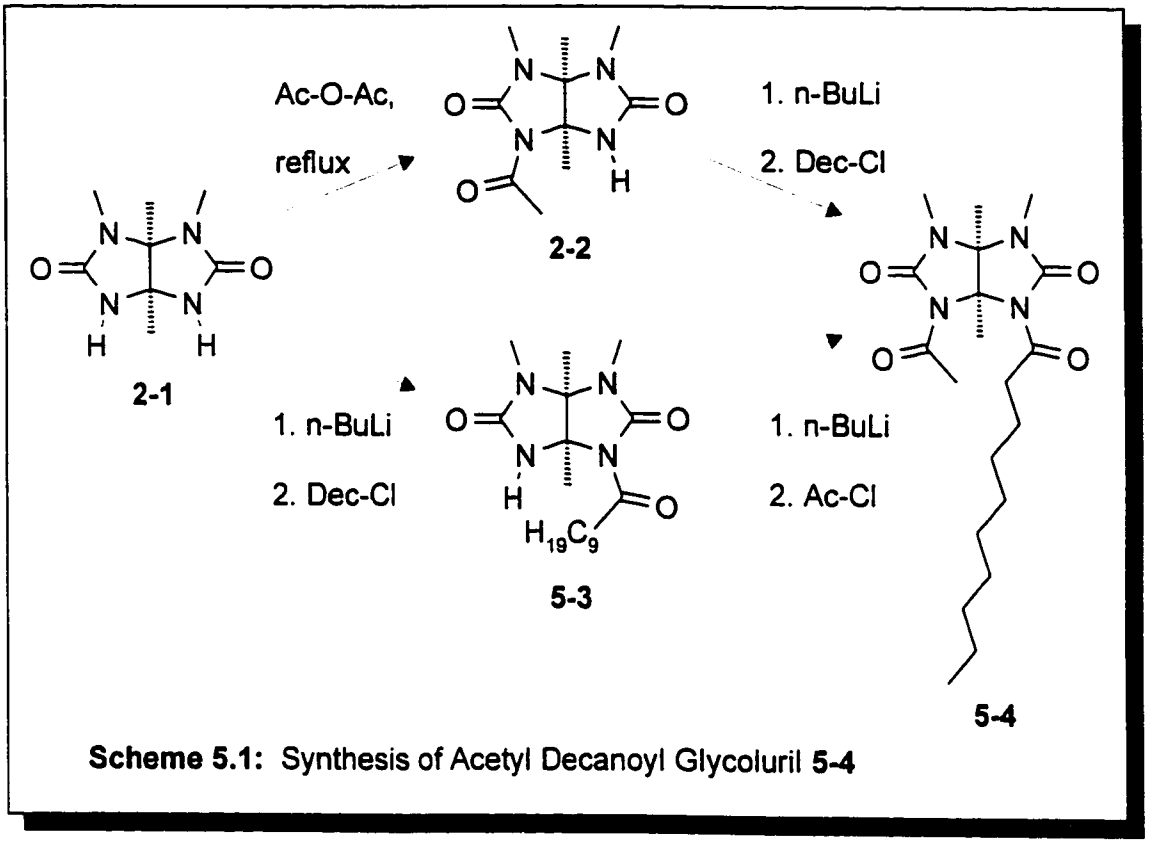
Figure 5.2: Retrosynthetic Analysis of Pramanicin

A retrosynthetic analysis of pramanicin leads to the condensation of the fatty acid side chain with the head group as one of the last steps in the synthesis. This allows for a somewhat convergent synthesis in which most of the functionality of the head group and the side chain is established before they are attached to each other. This chain of events corresponds to that which is assumed to occur in the biosynthesis of **5-1**. Furthermore, the fatty acid side chain is an ideal target for a glycoluril template-directed synthesis, mimicking the events which occur on the polyketide synthase enzyme. This fatty acid can be broken down retrosynthetically into a decanoyl unit and two acetate units. Although in principle, the decanoyl unit could arise from the template-directed condensation of five acetate units, this process would be quite expensive and tedious, so a

decision was made to start from decanoyl chloride, the last commercially available activated acid derivative on the reaction pathway.

5.3 Template-Directed Synthesis of the Fatty Acid of Pramanicin[129]

The fatty acid of pramanicin makes an ideal target for a template-directed synthesis using methods previously developed in our laboratory. It was also deemed to be a good test for the applicability of the template methodology to the synthesis of interesting and biologically relevant compounds. Although similar functionality has been created on the glycoluril template, the effect of long fatty acid chains on the reactions had not been investigated. Small linear carbon chains, up to 6 carbons, tend to adopt linear conformations in organic solvents, but long chains display a tendency to coil; therefore, they may possess significantly more steric bulk than shorter chains, thus altering their reactivity in some reactions[130].

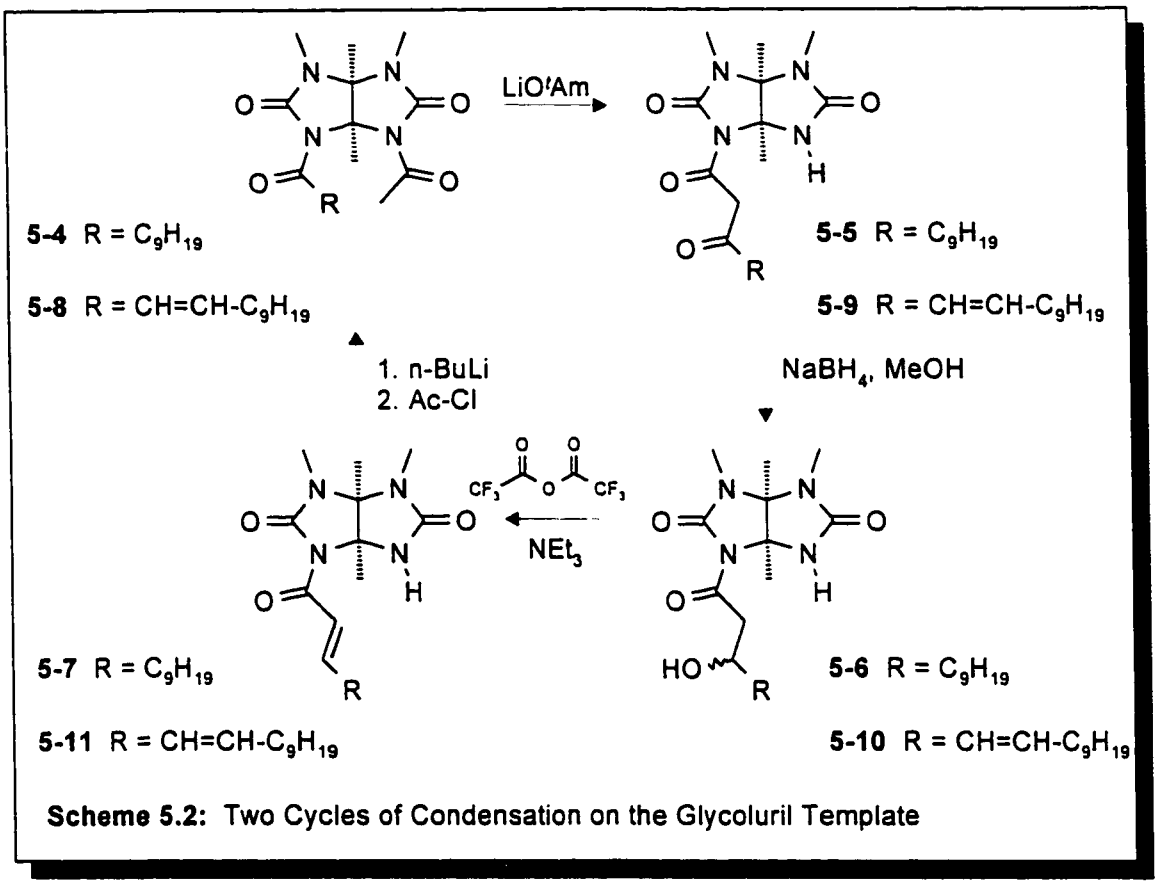


Scheme 5.1: Synthesis of Acetyl Decanoyl Glycoluril **5-4**

Synthesis of the fatty acid of pramanicin started by treatment of the glycoluril **2-1** with *n*-BuLi in THF at reflux followed by decanoyl chloride to afford the decanoyl derivative **5-3** in a yield of 65%‡ (Scheme 5.1). Addition of an acetyl group by treatment of **5-3** with *n*-BuLi, then acetyl chloride, led to the formation of the acetyl decanoyl adduct **5-4** in a yield of 38%. This reaction proceeded rather poorly, and this may be explained by the coiling of the decanoyl chain in solution, which could significantly block the NH site of the glycoluril to attack. An improved yield was obtained by reacting glycoluril **2-1** first under standard conditions to give acetyl glycoluril **2-2**, followed by

‡ Unless otherwise noted, all yields in this chapter are unoptimised.

reaction with *n*-BuLi, then decanoyl chloride to give **5-4** in a yield of 68% from the parent glycoluril **2-1**.



Scheme 5.2: Two Cycles of Condensation on the Glycoluril Template

The intramolecular Claisen-like condensation between the acetyl and decanoyl groups of **5-4** was effected with lithium *tert*-amylate in THF at 0 °C, providing the 3'-oxododecanoyl glycoluril **5-5** in 65% yield as the sole detectable product (Scheme 5-2). Interestingly, the other possible condensation product, afforded by generation of the enolate on the decanoyl chain followed by a condensation with the acetyl chain, was not observed. Again, this may be caused by coiling of the decanoyl chain in solution, thus

reducing or even eliminating access of the hindered base to the α-hydrogens of the decanoyl side chain.

Reduction of **5-5** with $NaBH_4$ in methanol provided the alcohol **5-6** in 79% yield, along with recovered starting material (18%) as the only other product. Elimination of water with trifluoroacetic anhydride and triethylamine proceeded smoothly to give the unsaturated chain **5-7**, which was > 99% *trans* by ^1H nmr in a yield of 76%.

A second acetylation reaction with *n*-BuLi and acetyl chloride provided the acetyl dodecenoyl adduct **5-8** in 61% yield (along with 24% recovered starting material). Condensation of this compound with LiO^tAm under standard conditions afforded the ketone **5-9** in 50% yield. This reduced yield likely results from the lower reactivity of the α,β-unsaturated carbonyl moiety present in **5-8**.

Reduction of the α,β-unsaturated carbonyl in **5-9** using the conditions developed by Sun ($NaBH_4$, MeOH, 10 minutes) resulted in formation of the alcohol **5-10** in a yield of 24%. This result was not very satisfactory, and prompted the examination of reduction conditions undertaken in section 3.2.3. The low yield of this reaction is likely due to the tautomerization of compound **5-9** between the keto- and enol forms (Figure 5.3) (58:42 ratio by ^1H nmr). These tautomers were not interconvertible on the nmr timescale, since all peaks were well-defined and did not exhibit significant broadening, as would be expected for rapid interconversion. Thus, it is likely that only the keto-form of the compound is reactive to these reduction conditions, leading to a reduced overall yield due to the limited duration of the reduction reaction under these conditions (since reaction times > 10 minutes begin to give cleavage products).

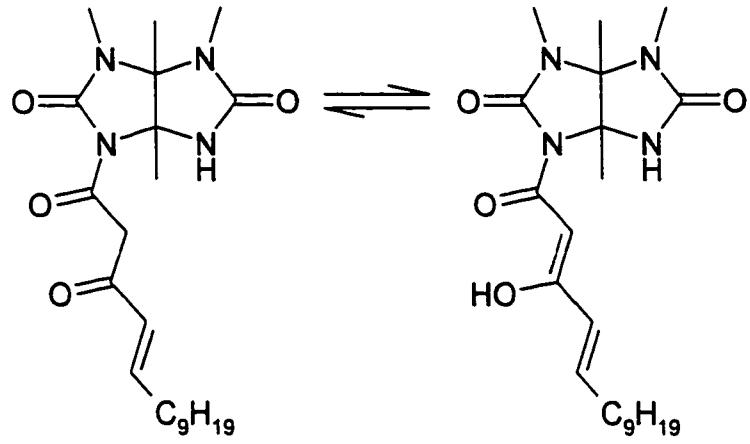
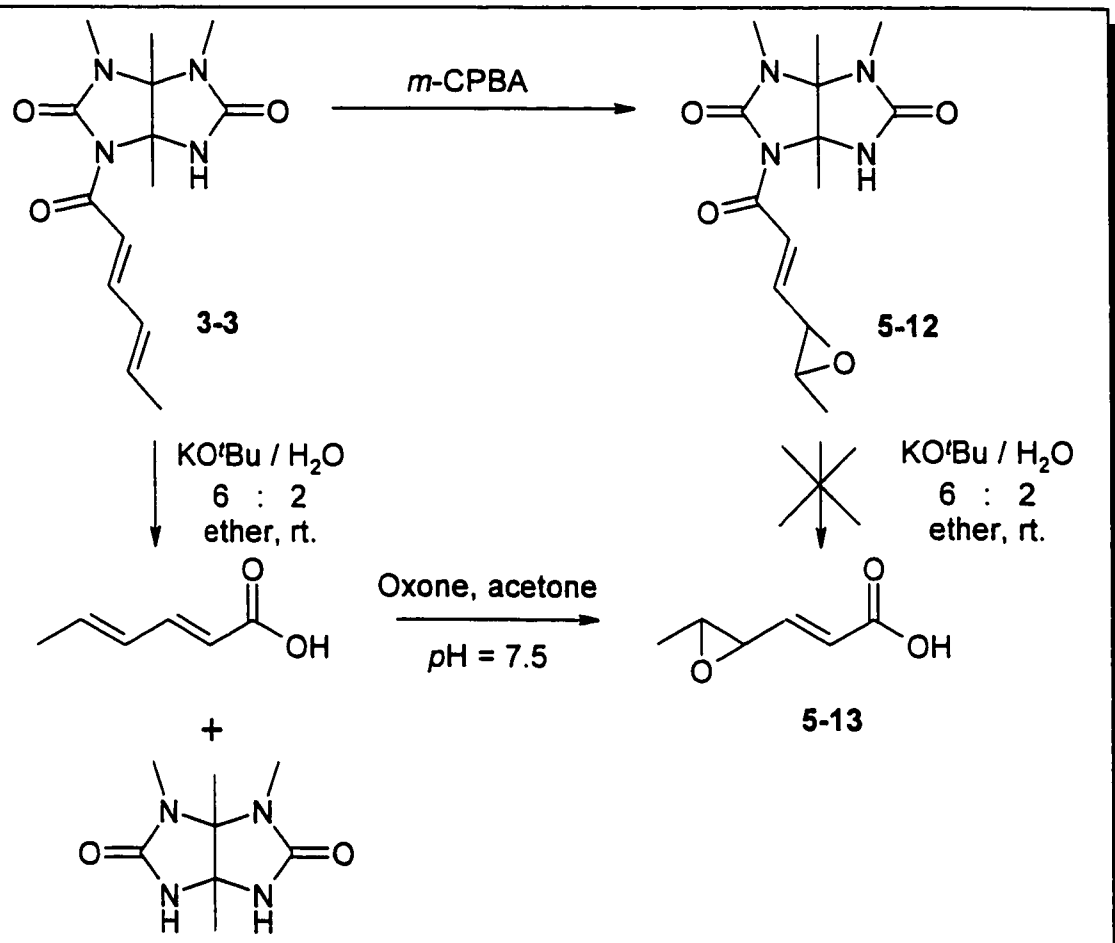


Figure 5.3: Tautomerization of 3'-Oxotetradecenoyl Glycoluril **5-9**

Elimination of water from **5-10** provided exclusively the *trans*, *trans* isomer of tetradeca-2-4-dienoyl glycoluril **5-11** in an isolated yield of 93%.

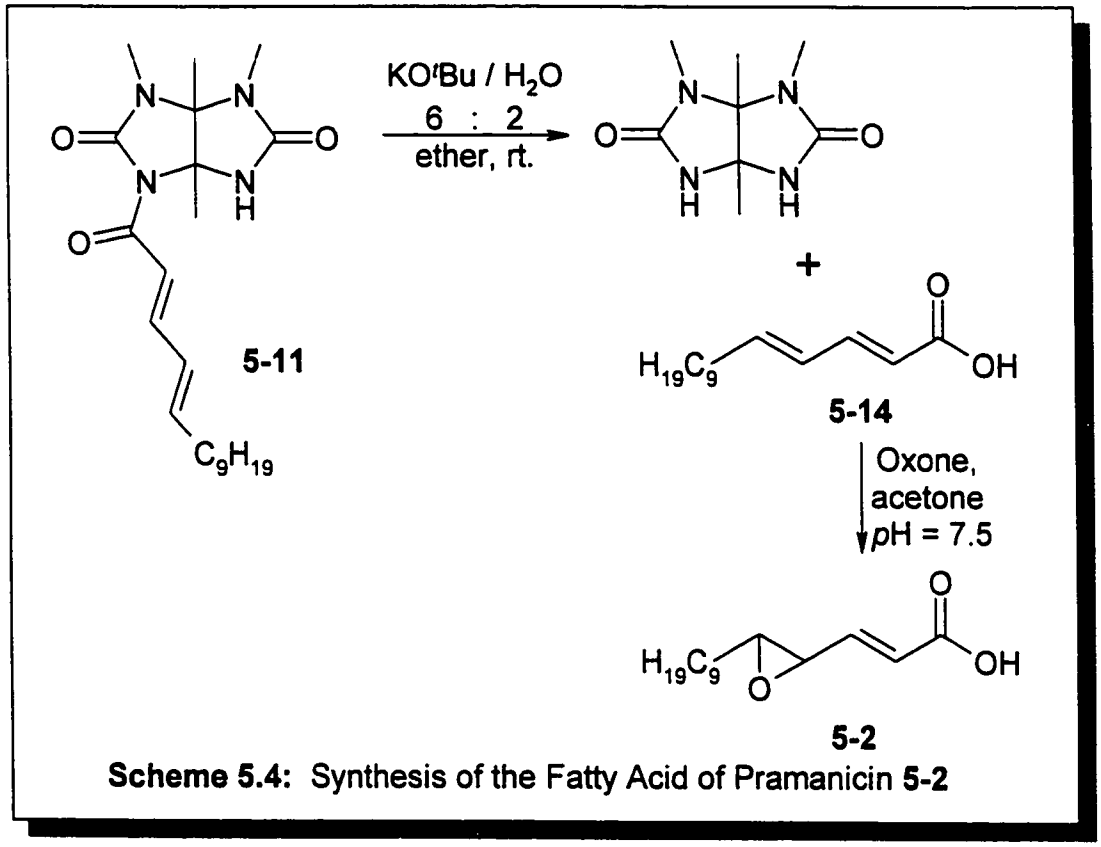
All that remained in the synthesis of the fatty acid portion of pramanicin was to epoxidize the □,δ-double bond and to cleave the acid from the template. The order in which these reactions should be undertaken was, however, unclear. Thus, both possible routes were explored using sorboyl glycoluril **3-3** as a model compound (Scheme 5.3). Epoxidation of **3-3** by *m*-CPBA proceeded readily to give the desired epoxide **5-12** in good yield (60%) and with high selectivity for the 4,5 over the 2,3 double bond. However, all attempts to cleave this product from the glycoluril template (NaOH, NaOMe, LiOOH, LiOBn, KO^{t}Bu/H_2O) were unsuccessful, resulting either in recovery of the starting material, or degradation of the epoxide.



Scheme 5.3: Epoxidation and Cleavage of Sorboyl Glycoluril **3-3** as a Model Compound for Tetradecadienoyl Glycoluril **5-11**

In contrast, the sorboyl glycoluril was found to be readily cleaved from the glycoluril template by treatment with potassium *tert*-butoxide and water under conditions described by Gassman *et al.*[117] (see Section 3.2.4) to give sorbic acid in a yield of 48%. Epoxidation of the acid with oxone[131] furnished the epoxide **5-13** in 83% yield. These epoxidation conditions were chosen since it was a known reaction with sorbic acid, and since the use of oxone rather than *m*-CPBA leads to a much simpler purification of the

product (everything else is in an aqueous layer). Oxone (nominally K_2SO_5) generates a dioxirane intermediate[132] on reaction with acetone, which is the active species in the epoxidation reaction.



Scheme 5.4: Synthesis of the Fatty Acid of Pramanicin **5-2**

These studies on the model compound showed that the preferred route is to cleave the chain from the template first, then to epoxidize the resulting carboxylic acid. Cleavage of the tetradeca-2,4-dienoyl adduct under identical conditions to those used for the sorboyl adduct led to the free tetradecadienoic acid **5-14** in 68% yield (Scheme 5.4). Epoxidation of the tetradeca-2,4-dienoic acid required the use of a biphasic mixture of

oxone, benzene, 18-crown-6, phosphate buffer, and acetone in order to solubilize the acid, and resulted in the fatty acid of pramanicin (**5-2**) in a yield of 35%.

Tetradeca-2,4-dienoic acid was also prepared according to the method of Burden and Crombie[133]; by addition of decanal to triethyl 4-phosphonocrotonate to give the ethyl ester in 28% yield, followed by hydrolysis in KOH / methanol to give the acid in a yield of 37%. Material was prepared by this method for comparison of the nmr spectra, as well as for comparison of the overall yields of the two methods. Although the overall yield for the second method is higher (7.8% after corrected yield of epoxidation), the template-directed synthesis has the advantage that preparation of labelled analogues of the fatty acid for biosynthetic incorporation experiments is quite simple. Preparation of labelled analogues by Burden and Crombie's method would be both expensive and inefficient.

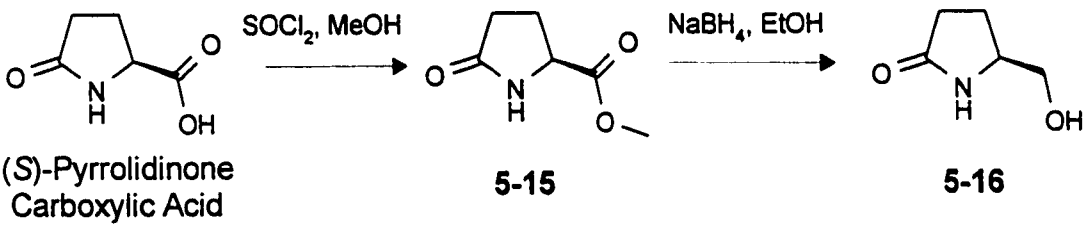
This successful synthesis represents the first application of the glycoluril template methodology to the synthesis of a natural product which is not readily available, and illustrates the potential of this method for the syntheses of a number of other fatty acid and polyketide derived natural products.

5.4 Construction of the Pyrrolidinone Head Group of Pramanicin

In order to complete the synthesis of the antibiotic pramanicin, it was necessary to construct the pyrrolidinone head group, then attach the fatty acid to it, and finish the synthesis with a number of functional group manipulations and deprotections. The simplest route to the desired pyrrolidinone ring involved starting with (*S*)-pyrrolidinone

carboxylic acid. A considerable amount of research has been undertaken by various groups on related compounds, for example, using pyrrolidines as chiral auxiliaries[134], as aza-analogs of nucleosides[135], as glycosidase inhibitors[136], in the synthesis of swainsonine and its derivatives[137], and in a number of other systems[138].

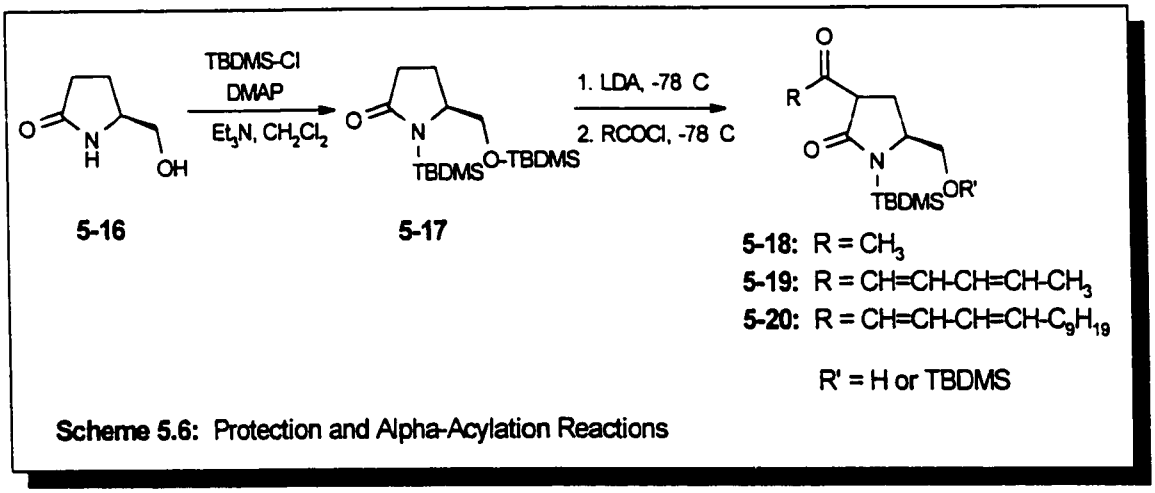
The synthesis of the head group started by converting (*S*)-pyrrolidinone carboxylic acid to the methyl ester (**5-15**) in 80% yield, followed by reduction with $NaBH_4$ to the alcohol **5-16** in a yield of 50% according to literature procedures[139] (Scheme 5.5). Although distillation of the alcohol is reported, it proved unnecessary, and in fact, the alcohol does appear to undergo some decomposition at the temperatures required for the distillation (~140 °C, 0.2 mm Hg).



Scheme 5.5: Conversion of S-Pyrrolidinone Carboxylic Acid to Alcohol **5-16**

bis-Protection of the hydroxymethyl pyrrolidinone **5-16** was accomplished in a single step by addition of triethylamine, *tert*-butyldimethylsilyl chloride (TBDMS-Cl), dimethylformamide (DMF), and dimethylaminopyridine (DMAP) in dichloromethane to give the *bis*-TBDMS protected compound **5-17**[140] in a yield of 60%. In this reaction, a comparison was made between reaction of the alcohol **5-16** which was distilled, and that

which was not. Surprisingly, the distilled alcohol produced the product **5-17** in lower yield and purity than the crude alcohol.



Scheme 5.6: Protection and Alpha-Acylation Reactions

Although α-alkylation of a protected analogue of **5-16** is known[141], the equivalent acylation reaction has not been reported.

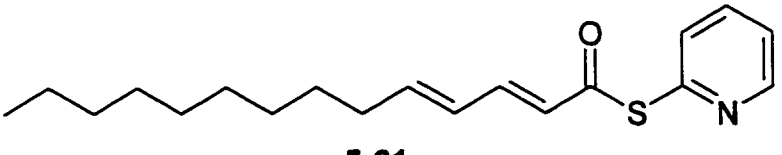
Acylation of **5-17** at the α-position has proved to be a very non-trivial reaction. Initial studies, investigating the addition of acetyl chloride to the anion of **5-17** showed that the reaction did occur, albeit in very low yields (6%) to give product **5-18**, where R' = TBDMS. Rather than attempting to optimise this reaction, addition of the sorboyl chloride was attempted instead, since it should be a much better model of the tetradeca-2,4-dienoyl chloride.

Addition of sorboyl chloride to the anion of **5-17** initially resulted in very low yields (15%) of a product **5-19** which had lost one of the TBDMS protecting groups. Use of two equivalents of LDA rather than 1 significantly increased the yield of this product, up to 87%. This presumably occurs by stabilization of the product by removal of the

very acidic α-proton, which otherwise will quench an equivalent of the anion of **5-17**, resulting in a maximum possible yield of 50%.

The remaining TBDMS group on **5-19** is thought to be attached to the amide nitrogen for two reasons: firstly, Greene[142] reports that harsher conditions are required for the cleavage of an amide TBDMS group than for a primary alcohol, and secondly, the proton nmr of the starting material **5-17** indicates that one of the TBDMS groups possesses diastereotopic methyl groups, while the other does not. Since the silicon of the amide-protecting group is one bond closer to the chiral centre than the silicon of the alcohol-protecting group, the diastereotopic methyls are assigned to the amide protecting group. In the product **5-19**, the diastereotopic methyl groups of the TBDMS protecting group have remained, while signals due to the other TBDMS protecting group have disappeared.

The cause of loss of the TBDMS protecting group is less clear; possibly, it results from attack of Cl^- on the silicon of the protecting group, although this does not occur in most systems. In order to prevent this, a number of different acid derivatives were investigated, including the acyl imidazolide and the acid iodide, but both of these compounds proved ineffective in the α-acylation reaction.



5-21

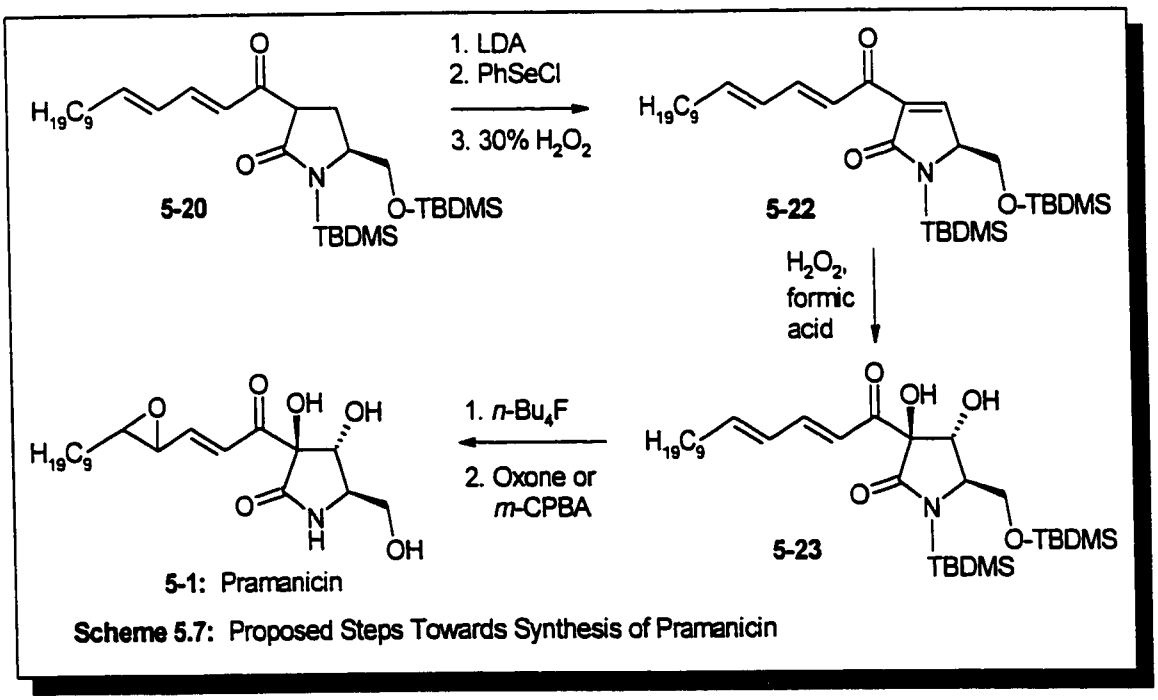
Figure 5.4: Structure of Mercapto-pyridine Acid Derivative

Addition of tetradeca-2,4-dienoyl chloride to the anion of **5-17** results in product **5-20**, where R' is H in 17% yield, as well as a small amount of material which looks like it has retained the TBDMS group (~ 10%). Since this reaction presented several problems, reaction with a different acid derivative was attempted; namely the mercapto-pyridine derivative **5-21** (Figure 5.4). This compound has the benefit that it can be easily purified by flash column chromatography, while the acid chloride of **5-2** is very difficult to purify, since it decomposes on distillation and will react readily with silica gel. At the same time, compounds similar to **5-21** are still very reactive to anions[143], and this derivative can be used in an analogous fashion in one of the simpler ways of preparing strained β-lactone rings. Reaction of **5-21** with the anion of **5-17** resulted in a complex mixture of products which have not been fully characterized; at least some appear to contain the mercapto-pyridine moiety attached to the pyrrolidinone ring.

The original plan for the synthesis of pramanicin involved the sequence of events shown in Scheme 5.7. Thus, compound **5-20** would be subjected to phenyl selenium chloride followed by peroxide to generate the unsaturated compound **5-22**, which would then be epoxidized and opened to the diol **5-23**, followed by a final deprotection and epoxidation of the side chain to give pramanicin.

There are a number of steps in this proposed synthesis which could present problems, so these steps were investigated briefly. The production of a double bond to give an α,β-unsaturated amide is well known[135, 144] for analogs of **5-17**, but the addition of an acyl group at the α-position may cause a number of problems; the α-proton is much

more acidic, and therefore the anion generated is less reactive, and the proposed reaction involves generation of a quaternary carbon centre, which are notoriously difficult to make. If the α,β-unsaturated compound **5-22** can be made, it may prove very reactive and difficult to isolate. The epoxidation reaction to get to the diol may in fact epoxidize at the □,δ-position of the fatty acid side chain as well as at the more reactive double bond, but this is not expected to pose a very significant problem, although opening only the desired epoxide to the diol may prove difficult. The stereochemistry of the diol should be relatively easy to manipulate, since many methods of manipulating the stereochemistry of epoxides[145] are known; in fact, Sharpless[146] conditions may prove useful if the primary alcohol is free; since these reactions have been shown to exhibit stereoselection on homoallylic and *bis*-homoallylic alcohols.



Scheme 5.7: Proposed Steps Towards Synthesis of Pramanicin

In order to examine the feasibility of the remaining reactions, the model sorboyl compound **5-19** was reacted with phenyl selenium chloride as shown above, but on examination by ^{1}H nmr, no product consistent with a structure like **5-22** was observed.

However, due to the difficulties experienced in this proposed reaction pathway, with the relatively unprecedented acylation reaction, and with production of the reactive double bond in **5-22**, this project was halted at this point in order to reevaluate the synthetic pathway. A revised proposal for the synthesis of pramanicin can be found in section 6.2.2, which addresses a number of the observed problems, and attempts to find a viable way around them.

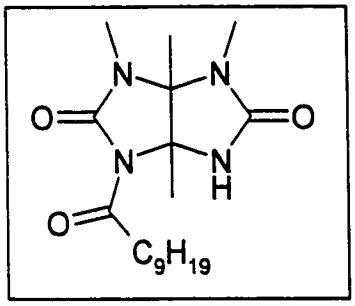
5.5 Summary

The fatty acid of pramanicin **5-2** was synthesized from simple starting materials by the template-directed condensation of a decanoyl side chain with two sequential acetate units and functional group manipulations to provide the desired units of unsaturation. The acyl chain was then cleaved from the template and epoxidized to give **5-2** in an overall yield of 0.5% from the acetyl glycoluril **2-2** in 10 steps. Many of the reactions on this pathway were unoptimised, and starting material was often recovered from the mixture, frequently as the only other reaction product. Thus, if the yields of the individual reactions are corrected to account for recovered starting material, the corrected overall yield is 6.8%. By comparison, synthesis of the tetradecadienoic acid by Burden and Crombie's method[133], followed by our epoxidation method would give the same fatty

acid **5-2** in an overall yield of 7.8%, assuming the same optimal conditions for the epoxidation based on recovered starting material as were used for the corrected yield by our method. This illustrates the synthetic utility of the template, since even though many more steps were undertaken, a comparable corrected yield was observed to literature preparations. The template-directed synthetic method is also much more versatile, since it leads readily to production of analogues and isotopically labelled material for biosynthetic studies.

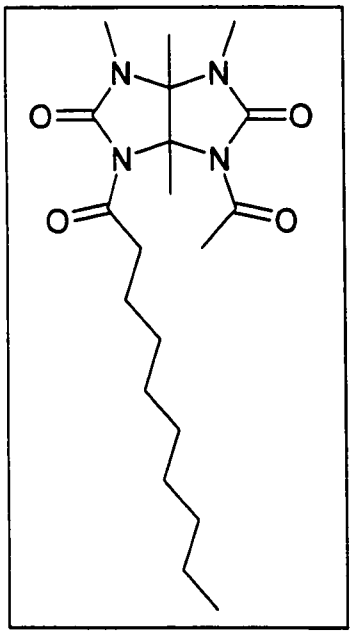
5.6 Experimental

1-Decanoyl-3,4,7,8-tetramethylglycoluril (5-3). To a suspension of glycoluril **2-1** (1 g, 5.1 mmol) in THF (60 mL) at reflux was added *n*-BuLi (3.45 mL of a 1.6 M solution in hexane, 5.5 mmol). The mixture was cooled to room temperature and decanoyl chloride (1.3 mL, 1.2 g, 6.3 mmol) was added. After stirring for 1 h, solid ammonium bicarbonate (2 g) was added. The mixture was filtered, and the residue was washed with chloroform (2 X 30 mL). The filtrate was evaporated, and the product was purified by flash column chromatography in EtOAc to give 1.17 g (3.3 mmol, 65 %) of **5-3** as white crystals. ^{1}H nmr ($CDCl_3$, 200 MHz) δ 6.09 (1H, br s, N*H*), 2.98 (3H, s, NC*H*$_3$), 2.84 (3H, s, NC*H*$_3$), 2.81 (2H, m, O=C-C*H*$_2$), 1.65 (3H, s, C*H*$_3$), 1.56 (2H, pent, J = 7.3 Hz, O=C-CH$_2$C*H*$_2$), 1.52 (3H, s, C*H*$_3$), 1.24 (12 H, br. s, C*H*$_2$), 0.83 (3H, t, J = 6.6 Hz, CH$_2$C*H*$_3$); ^{13}C nmr ($CDCl_3$, 50



MHz) δ 174.28 (*C*=O), 157.20 (NN*C*=O), 152.94 (NN*C*=O), 78.53 (*C*NN), 77.63 (*C*NN), 36.36, 31.78, 29.33, 29.18 (2C), 29.07, 27.00, 26.34, 24.23, 22.58, 19.60, 15.67, 14.02; EIMS m/z 352 $[M]^+$, 253, 240 (base), 199, 156, 141, 125; HRMS calcd. for $C_{18}H_{32}N_4O_3$: 352.2474, found 352.2482.

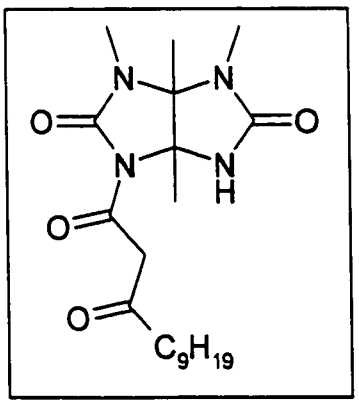
1-Decanoyl-6-acetyl-3,4,7,8-tetramethylglycoluril (5-4). Method 1. A solution of



decanoylglycoluril **5-3** (500 g, 1.4 mmol) in THF (30 mL) at 0 °C was treated with *n*-BuLi (0.88 mL of a 1.6 M solution in hexane, 1.4 mmol). The mixture was stirred for 10 min, then acetyl chloride (0.12 mL, 0.13 g, 1.7 mmol) was added and stirring continued for 1 h, during which time the mixture warmed slowly to room temperature. Aqueous $NaHSO_4$ (5 mL, 1 M) was added, and the mixture was extracted with chloroform (3 X 30 mL). The chloroform layers were combined, washed with water, dried over Na_2SO_4, and concentrated. Flash column chromatography of the residue in EtOAc gave white crystals of **5-4** (214 mg, 38%) and unreacted **5-3** (159 mg, 32%). **Method 2.** A solution of acetyl glycoluril **2-2** (2.57 g, 10.7 mmol) in THF (120 mL) was treated with *n*-BuLi (7.4 mL of a 1.6 M solution in hexane, 11.8 mmol) at 0 °C for 30 min. Decanoyl chloride (2.7 mL, 12.8 mmol) was added and the solution was stirred for 1 h, during which time the mixture warmed slowly to room temperature. Aqueous $NaHSO_4$ (25 mL, 1 M) was added, and the mixture was extracted with chloroform (3 X 60 mL). The

chloroform layers were combined, washed with water, dried over Na_2SO_4, and concentrated. Flash column chromatography of the residue in EtOAc gave product **5-4** (3.17 mg, 75.2%) and unreacted **2-2** (600 mg, 23.3%). ^{1}H nmr ($CDCl_3$, 200 MHz) δ 2.92 (6H, s, NC*H*$_3$), 2.81 (2H, m, O=CC*H*$_2$), 2.44 (3H, s, O=CC*H*$_3$), 1.90 (3H, s, C*H*$_3$), 1.56 (4H, m, O=CCH$_2$C*H*$_2$ and O=CH$_2$CH$_2$C*H*$_2$), 1.45 (3H, s, C*H*$_3$), 1.22 (10 H, br. m, C*H*$_2$), 0.83 (3H, t, J = 7 Hz, CH$_2$C*H*$_3$); ^{13}C nmr ($CDCl_3$, 50 MHz) δ 173.73 (*C*=O), 170.50 (*C*=O), 153.06 (2 NNC=O), 80.48 (*C*NN), 77.63 (*C*NN), 37.61, 31.80, 29.37 - 29.05 (5 C overlapping), 26.70, 26.14, 24.31, 22.60, 19.06, 14.51, 14.04; IR (KBr pellet) 2921, 2853 (C-H str.), 1684-1749 (br. C=O str.), 1332, 1092, 759, 607; EIMS m/z 394 [M]$^+$, 353, 295, 282, 253, 241 (base), 199, 168, 141, 125.

1-(3'-Oxododecanoyl)-3,4,7,8-tetramethylglycoluril (5-5). Acetyl decanoyl glycoluril **5-4**



(4.7 g, 12 mmol) was dissolved in THF (200 mL). Separately, *n*-BuLi (9.4 mL of a 1.6 M solution in hexane, 15 mmol) was added to *tert*-amyl alcohol (2.6 mL, 24 mmol) in THF (10 mL) at 0 °C, and the mixture was stirred for 10 min. The amylate solution was cannulated into the glycoluril solution at 0 °C, and the mixture was stirred for 2 h at 0 °C. Aqueous $NaHSO_4$ (20 mL, 1 M) was added, and the mixture was extracted into chloroform. The chloroform layers were combined, washed with water, dried over Na_2SO_4, and concentrated. Flash column chromatography of the residue in EtOAc gave **5-5** (3.0 g, 65 %) as white crystals and unreacted **5-4** (0.92 g, 17 %). ^{1}H nmr

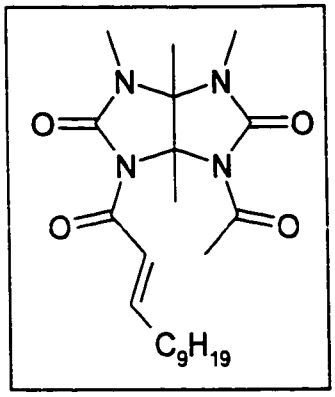
($CDCl_3$, 200 MHz) δ 6.05 (1H, s, N*H*), 4.29 (1H, d, J = 16.3 Hz, O=C-C*H*$_a$H-C=O), 3.52 (1H, d, J = 16.3 Hz, O=C-CH*H*$_b$-C=O), 2.93 (3H, s, NC*H*$_3$), 2.83 (3H, s, NC*H*$_3$), 2.48 (2H, m, O=CC*H*$_2$CH$_2$), 1.71 (3H, s, C*H*$_3$),1.65 (2H, m, O=CCH$_2$C*H*$_2$),1.53 (3H, s, C*H*$_3$), 1.22 (12 H, br. m, C*H*$_2$), 0.84 (3H, t, J = 6.0 Hz, C*H*$_3$); ^{13}C nmr ($CDCl_3$, 50 MHz) δ 203.66 (*C*=O), 167.42 (*C*=O), 157.14 (*C*=O), 152.73 (*C*=O), 76.71, 76.60, 51.48, 42.06, 31.80, 29.34 (2C), 29.20, 28.99, 27.06, 26.40, 23.28, 22.60, 19.23, 15.68, 14.04; IR (KBr pellet) 3337 (N-H str.), 2925, 2854 (C-H str.), 1724 (br. C=O str.), 1411, 1111, 760; EIMS m/z 394 $[M]^+$ 352, 295, 282, 253, 240, 199, 183, 138, 125 (base); HRMS calcd. for $C_{20}H_{34}N_4O_4$: 394.2851, found 394.2859.

1-(3'-Hydroxydodecanoyl)-3,4,7,8-tetramethylglycoluril (5-6). Oxododecanoyl glycoluril **5-5** (45 mg, 0. 11 mmol) was dissolved in MeOH (7 mL) at 0 °C. $NaBH_4$ (5 mg, 0.16 mmol) was added and the mixture was stirred for 10 min. Glacial acetic acid (1 mL) was added, then solvents were removed on the rotary evaporator. Flash column chromatography of the residue in EtOAc gave **5-6** (36 mg, 79 %) as a white crystalline solid. ^{1}H nmr ($CDCl_3$, 200 MHz) δ 6.04 (1H, br m, N*H*), 4.00 (1H, m, C*H*OH), 3.21 (1H, dd, J = 17. 0, 2.6 Hz,O=CC*H*$_a$H$_b$), 2.98 (3H, s, NC*H*$_3$), 2.84 (3H, s, NC*H*$_3$), 2.84 (1H, m, O=CC*H*$_b$H$_a$), 1.67 (3H, s, C*H*$_3$), 1.60 (3H, s, C*H*$_3$), 1.44 (2H, m, HOCHC*H*$_2$), 1.23 (15 H, br. s, C*H*$_2$ and O*H*), 0.85 (3H, t, J = 6.0 Hz, C*H*$_3$); ^{13}C nmr ($CDCl_3$, 50 MHz) δ 167.42 (*C*=O), 157.14 (*C*=O), 152.73 (*C*=O), 77.63, 76.50, 67.95,

43.34, 31.86, 29.55 - 29.28 (6C), 27.13, 26.41, 22.60, 19.23, 15.68, 14.04; EIMS m/z 396 $[M]^+$ 378, 269, 240, 199, 156, 138, 125 (base).

1-(*trans*-Dodec-2'-enoyl)-3,4,7,8-tetramethylglycoluril (5-7). Compound **5-6** (720 mg, 1.8mmol) was dissolved in CH_2Cl_2 (10 mL), then trifluoroacetic anhydride (0.77 mL, 5.4 mmol) was added and the mixture was stirred for 1 h. Triethylamine (0.33 mL, 3.6 mmol) in CH_2Cl_2 (5 mL) was added dropwise. After 10 min, further Et_3N (2 mL) was added and the mixture was heated at reflux for 20 min. Evaporation and flash column chromatography of the residue in EtOAc gave **5-7** (520 mg, 76 %) as a white crystalline solid. ^1H nmr ($CDCl_3$, 200 MHz) δ 7.28 (1H, dd, J = 15.3, 3.2 Hz, O=CC*H*=CH), 7.09 (1H, dt, J = 15.3, 6.6 Hz, O=C-CH=C*H*), 6.09 (1H, s, N*H*), 3.04 (3H, s, NCH_3), 2.89 (3H, s, NCH_3), 2.27 (2H, dt, J = 6.9, 6.9 Hz, O=CCH=CHCH_2), 1.74 (3H, s, CH_3), 1.59 (3H, s, CH_3), 1.49 (2H, m, CH=CHCH$_2$-CH_2), 1.29 (12H, br. s, CH_2), 0.90 (3H, t, J = 6.7 Hz, CH_3); ^{13}C nmr ($CDCl_3$, 50 MHz) δ 165.90 (*C*=O), 157.25 (*C*=O), 153.02 (*C*=O), 150.60 (*C*=O), 121.74, 78.54, 76.68, 32.60, 31.80, 29.40 - 29.17 (4C), 28.07, 27.06, 26.33, 22.60, 19.70, 15.71, 14.05; IR (KBr pellet) 3337 (N-H str.) 2925, 2854 (C-H str.), 1702-1736 (br. C=O str.), 1630 (C=C str.), 1468, 1089, 761; EIMS m/z 378 $[M]^+$, 251, 199, 125 (base). HRMS calcd. for $C_{20}H_{34}N_4O_3$: 378.2632, found 378.2618.

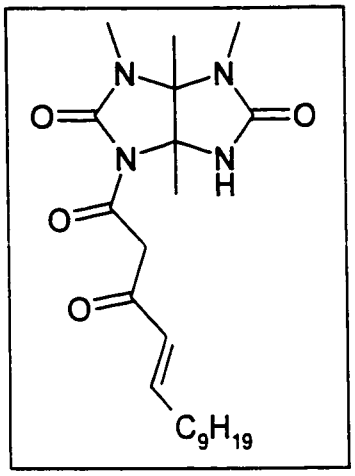
1-(*trans*-Dodec-2'-enoyl)-6-acetyl-3,4,7,8-tetramethylglycoluril (5-8).



Dodecenoylglycoluril **5-7** (416 mg, 1.1 mmol) was dissolved in THF (10 mL). *n*-BuLi (0.73 mL of a 1.6 M solution in hexane, 1.1 mmol) was added at 0 °C, the mixture was stirred (10 min) and acetyl chloride (86 □L, 1.2 mmol) was added. After 1 h, aqueous $NaHSO_4$ (1 mL, 1 M) was added, and the mixture was extracted with chloroform (3 X 10 mL). The chloroform layers were combined, washed with water (2 X 10 mL), dried over Na_2SO_4, and concentrated. Flash column chromatography in EtOAc afforded **5-8** as a white solid (282 mg, 61%) and recovered **5-7** (98 mg, 24 %). ^{1}H nmr ($CDCl_3$, 200 MHz)δ6.8 - 7.1 (2H, m, C*H*=C*H*), 2.90 (3H, s, NCH_3), 2.89 (3H, s, NCH_3), 2.39 (3H, s, O=CCH_3), 2.14 (2H, dt, J = 6.9, 6.9 Hz, O=CCH=CHCH_2), 1.89 (3H, s, CH_3), 1.44 (3H, s, CH_3), 1.44 (2H, m, CH=CHCH$_2$CH_2), 1.17 (12H, br. s, CH_2), 0.79 (3H, t, J = 6.7 Hz, CH_3); EIMS m/z 420 $[M]^+$, 336, 293, 282, 241, 225, 199, 168, 125 (base).

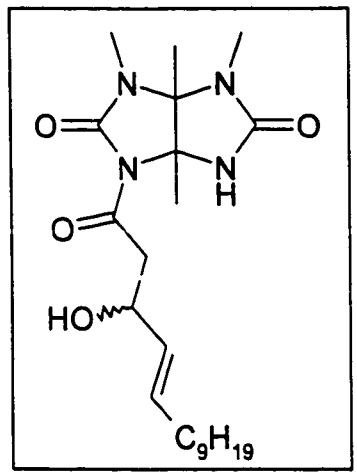
1-(3'-Oxo-*trans*-tetradec-4'-enoyl)-3,4,7,8-tetramethylglycoluril (5-9). Acetyl dodecenoyl glycoluril **5-8** (395 mg, 0.94 mmol) was dissolved in THF (20 mL). Separately, *n*-BuLi (0.69 mL of a 1.6 M solution in hexane, 1.1 mmol) was added to *tert*-amyl alcohol (0.21 mL, 2.2 mmol) in 5 mL THF and the mixture was stirred for 10 min at 0 °C. The *tert*-amylate solution was cannulated into the glycoluril solution, and the mixture was stirred at 0 °C for 2 h. Aqueous $NaHSO_4$ (2 mL, 1 M) was added and the mixture was extracted into

chloroform (3 X 20 mL). The chloroform layers were combined, washed with water, dried



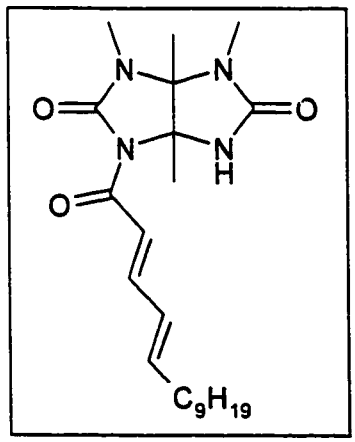
over Na_2SO_4, and concentrated. Flash column chromatography of the residue in EtOAc gave **5-9** (197 mg, 50 %) as a white, crystalline solid and recovered **5-8** (140 mg, 35 %). ^{1}H nmr ($CDCl_3$, 200 MHz) δ Keto form: 7.03 (1H, m, O=C-C*H*=CH), 6.26 (1H, s, N*H*), 6.05 (1H, d, J = 15.8 Hz, O=CCH=C*H*), 4.46 (1H, d, J = 16.2 Hz, O=C-C*H*H-C=O), 3.69 (1H, d, J = 16.2 Hz, O=C-CH*H*-C=O), 2.97 (3H, s, NCH_3), 2.82 (3H, s, NCH_3), 2.17 (2H, m, O=CCH=CHCH_2), 1.72 (3H, s, CH_3), 1.52 (3H, s, CH_3), 1.42 (2H, br. m, CH=CHCH$_2$CH_2), 1.22 (12H, br. m, CH_2), 0.84 (3H, t, CH_3); enol form: 13.17 (1H, s, O*H*), 6.72 (1H, m, HOC-C*H*=CH), 6.47 (1H, s, O=C-C*H*=COH), 6.20 (lH s, N*H*), 5.84 (1H, dd, J = 12.3,1.6 Hz, HOC-CH=C*H*), 2.92 (3H, s, NCH_3), 2.82 (3H, s, NCH_3), 2.17 (2H, m, O=C-CH=CH-CH_2), 1.69 (3H, s, CH_3), 1.52 (3H, s, CH_3), 1.42 (2H, br. m, CH=CH-CH$_2$-CH_2), 1.22 (12H, br. m, CH_2), 0.84 (3H, t, J = 7.0 Hz, CH_3); ^{13}C nmr ($CDCl_3$, 50 MHz) δ 193.23, 172.67, 171.29, 170.01, 167.76, 165.84, 157.34, 152.70, 151.19, 150.60, 149.30, 129.36, 125.01, 121.70, 120.81, 90.90, 78.69, 78.52, 76.70, 76.35, 48.93, 32.57, 32.45, 32.18, 31.78, 29.39, 29.30, 29.20, 28.31, 28.02, 27.84, 27.04, 26.37, 22.58, 19.97, 19.67, 19.23, 15.67, 14.02; IR (KBr pellet) 3237 (N-H str.), 2914, 2851 (C-H str.), 1690-1722 (br. C=O str.), 1466, 1412, 1090, 759; EIMS m/z 420 $[M]^+$ 378, 240, 141, 125 (base); HRMS calcd. for $C_{22}H_{36}N_4O_4$: 420.2737, found: 420.2732.

1-(3'-Hydroxy-*trans*-tetradec-4'-enoyl)-3,4,7,8-tetramethylglycoluril (5-10). 3-



Oxotetradecenoyl glycoluril **5-9** (84 mg, 0.20 mmol) was dissolved in MeOH at 0 °C. $NaBH_4$ (11.3 mg, 0.30 mmol) was added and the mixture was stirred for 10 min. Excess glacial acetic acid (0.5 mL) was added, and solvents were removed on the rotary evaporator. Flash column chromatography of the residue in EtOAc gave **5-10** (20 mg, 24 %). ^{1}H nmr ($CDCl_3$, 200 MHz) δ 6.04 (1H, s, N*H*), 5.70 (1H, td, J = 6.5, 15.5 Hz, HOCH-CH=C*H*), 5.47 (1H, dd, J = 15.5, 5.0 Hz, HOCH-C*H*=CH), 4.51 (1H, m, C*H*OH), 3.23 (1H, m, OCCH_aH$_b$), 3.01 (1H, m, O=CCH_bH$_a$), 2.98 (3H, s, NCH_3), 2.84 (3H, s, NCH_3), 1.96 (2H, m, CH=CH-CH_2), 1.70 (3H, s, CH_3), 1.54 (3H, s, CH_3), 1.23 (15H, br. s, CH_2 and O*H*), 0.85 (3H, t, J = 6.7 Hz, CH_3); EIMS m/z 422 $[M]^+$ 406, 348, 295, 282, 240, 206, 199, 125 (base); HRMS calcd. for $C_{22}H_{38}N_4O_4$: 422.2893, found: 422.2889.

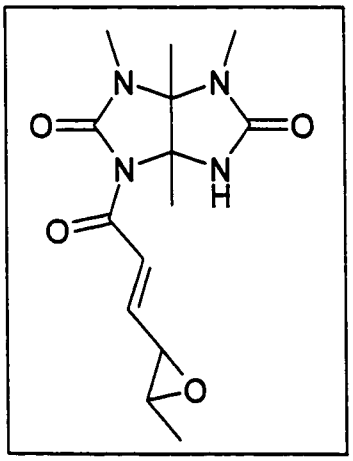
1-(*trans, trans*-Tetradeca-2',4'-dienoyl)-3,4,7,8-tetramethylglycoluril (5-11). Alcohol **5-**



10 (5.5 mg, 0.013 mmol) was dissolved in CH_2Cl_2 (2 mL), and trifluoroacetic anhydride (5.5 □L, 0.039 mmol) was added. The mixture was stirred for 1 h, then Et_3N (1.8 □L, 0.026 mmol) dissolved in CH_2Cl_2 (1 mL) was added dropwise. After 10 min, an additional 0.5 mL Et_3N was added and the mixture was heated at

reflux for 20 min. Evaporation followed by flash column chromatography of the residue in EtOAc afforded **5-11** (4.9 mg, 94 %) as a white crystalline solid. ^{1}H nmr ($CDCl_3$, 200 MHz) δ 7.40 (1H, dd, J = 15.3, 9.2 Hz, O=CCH=C*H*), 7.22 (1H, d, J = 15.2 Hz, O=C-C*H*), 6.20 (2H, m, C*H*=C*H*CH$_2$), 6.09 (1H, s, N*H*), 3.02 (3H, s, NC*H*$_3$), 2.86 (3H, s, NC*H*$_3$), 2.17 (2H, q, J = 6.6 Hz, CH=CHC*H*$_2$), 1.71 (3H, s, C*H*$_3$), 1.56 (3H, s, C*H*$_3$), 1.37 (2H, br. m, CH=CHCH$_2$C*H*$_2$), 1.26 (12H, br. m, C*H*$_2$), 0.87 (3H, t, J = 6.8 Hz, C*H*$_3$); ^{13}C nmr ($CDCl_3$, 125 MHz) δ 166.22 (CH*C*=O), 157.29 (*C*=O), 153.02 (*C*=O), 145.90 (*C*=C), 145.78 (C=*C*), 128.97 (*C*=C), 119.73 (C=*C*), 78.53, 33.00, 31.81, 29.44, 29.36, 29.22, 29.10, 28.60, 27.04, 26.36, 22.59, 19.76, 16.94, 15.71, 14.02; EIMS m/z 404 $[M]^+$, 277, 236, 220, 206, 199, 153, 125 (base), 94, 84, 56, 49; HRMS calcd. for $C_{22}H_{36}N_4O_3$: 404.2789, found: 404.2795.

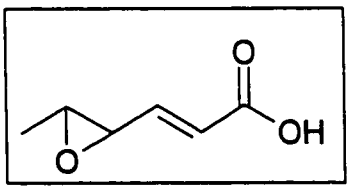
(*trans,trans*-Hex-2'-enoyl)-3,4,7,8-tetramethylglycoluril-4',5' epoxide (5-12). Sorboyl glycoluril (50 mg, 0.17 mmol) **3-3** was dissolved in 5 mL dichloromethane at 0 °C, then 73 mg (0.42 mmol) *m*-CPBA (50% pure) was added and stirred for 3 h. The reaction was quenched with 10 mL of 1 M aqueous sodium carbonate, then the mixture was extracted into CH_2Cl_2 (3 × 10 mL), washed with water (10 mL), and dried over anhydrous sodium sulfate.



The solvent was removed on the rotary evaporator, and the product (31.7 mg, 60.2% yield) was isolated by flash column chromatography on silica gel in 3% methanol / $CHCl_3$ as the eluent. ^{1}H nmr ($CDCl_3$, 200 MHz) δ 7.56 (1H, dd, 4.7, ^{3}J = 4.7, 15.6 Hz,

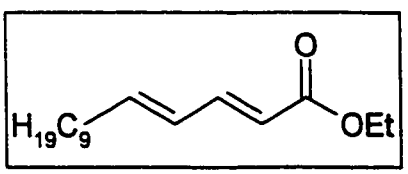
O=C-C*H*=CH), 6.67 (1H, m, O=C-CH=C*H*), 6.06 (1H, s, N*H*), 3.22 (1H, dd, ^{3}J = 1.9, 7.7 Hz), 3.00 (3H, s, N-CH_3), 2.84 (3H, s, N-CH_3), 1.70 (3H, s, CH_3), 1.54 (3H, s, CH_3), 1.35 (3H, d, ^{3}J = 5.15 Hz), O-CH-CH_3).

***trans,trans*-Hex-2-enoic acid 4,5-epoxide (5-13).** Sorbic acid (110 mg, 0.98 mmol) was



dissolved in a mixture of acetone (90 □L, 1.3 mmol), and 10 mL of water at *p*H 7.5. A freshly prepared solution of 0.04 M (2.8 g) potassium peroxomonosulfate was prepared with 4 × 10^{-4} M EDTANa_2 (14.8 mg) in 100 mL distilled water. 60 mL of this solution was added slowly to the substrate over 2h, while the *p*H was maintained at 7.5 by addition of 0.5 N KOH solution as necessary. The reaction was quenched with 5% HCl to *p*H 3, and the mixture was extracted into chloroform (3 × 20 mL), and dried over anhydrous magnesium sulfate (2 g). The solvent was removed on the rotary evaporator, giving the product (104.5 mg, 83.2% yield) without further purification. ^{1}H nmr ($CDCl_3$, 200 MHz) δ 6.76 (1H, dd, ^{3}J = 6.9, 15.6 Hz, O=C-CH=C*H*), 6.09 (1H, d, ^{3}J = 15.6 Hz), 3.18 (1H, dd, ^{3}J = 1.8, 6.9 Hz, CH=CH-C*H*(O)-CH), 2.96 (1H, dq, ^{3}J = 1.9, 5.1 Hz, CH(O)C*H*-CH_3), 1.37 (3H, d, ^{3}J = 5.1 Hz).

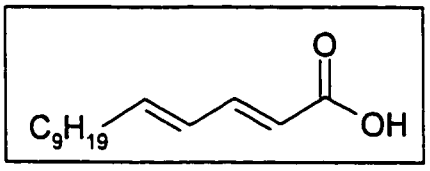
Ethyl *trans,trans*-Tetradeca-2,4-dienoate. This compound was prepared by the method of



Burden and Crombie[133]; thus triethyl 4-phosphonocrotonate (14 g, 12.6 mL) and decanal (9.2 g, 11.1 mL) was stirred vigorously in 30 mL of

dimethylformamide. Sodium ethoxide (1.1 eq, 140 mL of 0.44 M solution in EtOH) was added dropwise over 1 h, then the mixture was stirred for an additional ½ h. The reaction was quenched with an excess of water and the mixture was extracted into hexanes (6 × 100 mL), then washed with water (100 mL) and brine (100 mL). The solvent was removed on the rotary evaporator, and the product (3.89 g, 28%) was purified by distillation (109 – 117 °C, 0.13 mm Hg). ^{1}H nmr ($CDCl_3$, 200 MHz) δ 7.27 (1H, m, O=C-CH=C*H*), 6.13 (2H, m, O=C-CH=CH-C*H*=C*H*), 5.76 (1H, d, ^{3}J = 15.4 Hz, O=C-C*H*=CH), 4.20 (2H, q, ^{3}J = 7.1 Hz, O-C*H*$_2$-CH$_3$), 2.16 (2H, m, CH=CH-C*H*$_2$), 1.37 (2H, m, CH=CH-CH$_2$-C*H*$_2$), 1.29 (3H, t, ^{3}J = 7.1 Hz, O-CH$_2$-C*H*$_3$), 1.27 (12H, s, -C*H*$_2$-), 0.88 (3H, t, ^{3}J = 6.7 Hz, CH$_2$-CH$_2$-C*H*$_3$); ^{13}C nmr ($CDCl_3$, 50 MHz) δ 167.20 (*C*=O), 145.00 (*C*H=CH), 144.61 (CH=C*H*), 128.26 (*C*H=CH), 119.09 (CH=*C*H), 60.03, 32.92, 31.83, 29.46, 29.37, 29.23, 29.12, 28.67, 22.60, 14.23, 14.02.

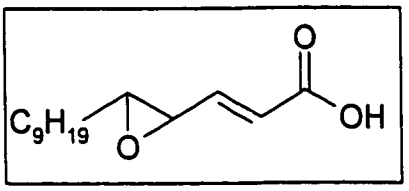
***trans, trans*-Tetradeca-2,4-dienoic acid (5-14). Method 1:** The tetradecadienoyl adduct



5-11 (22.7 mg, 0.056 mmol) was added to a slurry of H_2O (2.1 □L, 0.11 mmol) and *t*-BuOK (38 mg, 0.33 mmol) in ether (10 mL). The mixture was stirred at room temperature overnight, then 5 % HCl (1 mL) was added and the mixture was extracted with chloroform (3 X 10 mL). The combined extracts were washed with water (10 mL) and brine (10 mL), then dried over Na_2SO_4 and filtered. Concentration of the filtrate gave the title acid as a solid white powder (8.9 mg, 71 %). **Method 2:** Tetradecadienoic acid was prepared via the method of Burden and Crombie[133]; thus, ethyl *trans,trans*-tetradeca-2,4-

dienoate (3.89 g, 15.4 mmol) was heated at reflux with potassium hydroxide (1.5 g, 27 mmol) in 10 mL methanol for 1.5 hr. The reaction mixture was cooled, then conc. HCl was added to *p*H = 2-3, and the mixture was filtered to give the acid as waxy crystals. Recrystallization from hexanes provided pure **5-14** (1.27 g, 36.8% yield) ^{1}H nmr ($CDCl_3$, 200 MHz) δ 7.34 (1H, m, C*H*=CH), 6.20 (2H, m, 2 C*H*=CH), 5.78 (1H, d, J = 15.22 Hz, O=CC*H*=CH), 2.18 (2H, m, CH=CHCH_2), 1.42 (2H, m, CH=CHCH$_2$-CH_2), 1.26 (12 H, m, CH_2), 0.88 (3H, t, J = 6.12 Hz, CH_3); ^{13}C nmr ($CDCl_3$, 125 MHz) δ 171.36 (C=O), 147.49 (C=C), 146.23 (C=C), 128.22 (C=C), 117.94 (C=C), 33.05, 31.87, 29.50, 29.41, 29.28, 29.18, 28.64, 22.66, 14.07; IR (KBr pellet) 3423 (O-H str.), 2924, 2854 (C-H str.), 1686 (C=O str.), 1638 (C=C str.), 1617 (C=C str.), 1466, 1307, 1007, 698; EIMS m/z 225 $[MH]^+$, 224 $[M]^+$, 216, 195, 181, 164, 153, 142, 125, 109, 97, 84, 49, 45 (base), 43; HRMS calcd. for $C_{14}H_{25}O_2$ (MH^+): 225.1856, found: 225.1864.

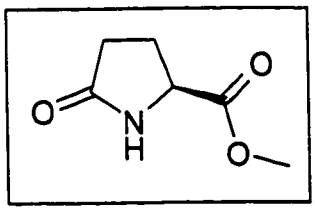
***trans, trans*-Tetradec-2-enoic acid 4,5-epoxide (5-2).** Tetradeca-2,4-dienoic acid (**5-14**)



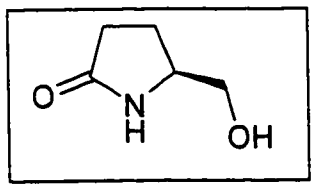
(100 mg, 0.45 mmol) was added to a well-stirred biphasic mixture of benzene (30 mL) and phosphate buffer (15 mL, *p*H 7.5, 0.5 M) containing acetone (2 mL) and 18-crown-6 (100 mg, 0.38 mmol) as the phase transfer catalyst. A freshly prepared solution of potassium peroxomonosulfate (Oxone) (0.04 M, 20 mL) with $EDTANa_2$ (4 X 10^{-4} M) was added dropwise over 30 min. at 6 - 8 °C. During addition, the *p*H was maintained at 7.5 by addition of 0.5 N KOH. The mixture was stirred for 3 h at r.t., then extracted with benzene (3 X 30 mL) and dried over $MgSO_4$. The combined extracts were

concentrated, then purified by flash column chromatography using 30 % EtOAc in hexanes as eluant. Evaporation gave a white powder (35 %, 37.5 mg) which was identical to that reported in the literature[128]. Mp: 81 - 81.5 °C; ^{1}H nmr (CD_3OD, 200 MHz) δ 6.62 (1H, dd, ^{3}J = 7.2, 15.7 Hz, O=C-CH=C*H*), 6.11 (1H, d, ^{3}J = 15.6 Hz, O=C-C*H*=CH), 3.21 (1H, dd, ^{3}J = 1.6, 7.0 Hz, CH=CH-C*H*-O), 2.90 (1H, dt, ^{3}J = 5.9, 2.0 Hz, CH=CH-CH-O-C*H*), 1.58 (2H, m, O-CH-CH_2), 1.44 (2H, m, O-CH-CH$_2$-CH_2), 1.29 (12 H, br. s, CH_2), 0.89 (3H, t, ^{3}J = 6.7 Hz, CH_3); ^{13}C nmr ($CDCl_3$, 125 MHz) δ 169.89 (C=O), 147.34 (C=C), 122.56 (C=C), 61.72 (C-O-C), 56.13 (C-O-C), 31.90, 31.86, 29.46, 29.33, 29.26, 25.78, 25.65, 22.65, 14.06 (CH_3); IR (KBr pellet) 3420 (O-H str.), 2916, 2851 (C-H str.), 1730 (C=O str.), 1696 (C=C str.), 1308, 857 (epoxide). EIMS m/z 241 $[MH]^+$ (v. weak), 240 $[M]^+$ (v. weak), 195, 84 (base).

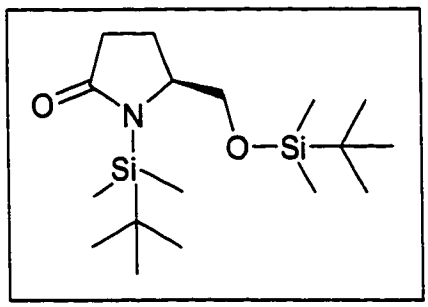
***(S)*-Pyrrolidinone-5-methyl ester (5-15).** Thionyl chloride (17.8 g, 150 mmol, 10.9 mL) was slowly added to a stirred solution of (*S*)-pyrrolidinone carboxylic acid (25.4 g, 200 mmol) in 250 mL methanol at – 20 °C. The mixture was stirred for 3 h, as the temperature was allowed to rise to room temperature. Removal of the solvent by rotary evaporation, followed by distillation (145 – 148 °C, 0.6 mm Hg) provided the product (22.4 g, 79.5% yield) as a yellowish oil. ^{1}H nmr ($CDCl_3$, 200 MHz) δ 7.49 (1H, br. s, N*H*), 4.0 – 4.2 (1H, m, HN-C*H*), 3.58 (3H, s, CH_3), 1.97 – 2.34 (4H, m, O=C-CH_2-CH_2); ^{13}C nmr ($CDCl_3$, 50 MHz) δ 178.26 (*C*=O), 172.40 (*C*=O), 55.19, 52.07, 28.97, 24.38; identical to authentic material[141].



(*S*)-5-Hydroxymethyl-2-pyrrolidinone (5-16). Sodium borohydride (1.33 g, 35.1 mmol) was added to a stirred solution of (*S*)-pyrrolidinone methyl ester **5-15** (5.03 g, 35.1 mmol) in 100 mL of absolute ethanol. The mixture was stirred overnight, then quenched with conc. HCl (5 mL). The ethanol was removed on the rotary evaporator, then the residue was extracted into chloroform (4 × 30 mL), washed with water (30 mL), and dried over anhydrous sodium sulfate. The solvent was removed on the rotary evaporator, giving an oil (2.03 g, 50.2% yield) which was used without further purification. ^{1}H nmr ($CDCl_3$, 200 MHz) δ 7.50 (1H, br. s, N*H*), 4.50 (1H, br. s, O*H*), 3.75 (1H, br. m, HN-C*H*), 3.63 (1H, dd, ^2J = 7.2, ^3J = 3.1 Hz, HO-C*H*H), 3.41 (1H, dd, ^2J = 11.4, ^3J = 6.9 Hz, HO-CH*H*), 1.70 - 2.37 (4H, m, O=C-CH_2-CH_2); identical to authentic material[141].



1-*tert*-Butyldimethylsilyl-5-*tert*-butyldimethylsilyloxymethyl-2-pyrrolidinone (5-17). Alcohol **5-16** (295 mg, 2.6 mmol) was dissolved in 5 mL dimethylformamide, then 3 eq (1.07 mL) triethylamine was added, followed by 2.5 eq (0.96 g) *tert*-butyldimethylsilyl chloride and CH_2Cl_2 (4 mL). A catalytic amount (trace) of dimethylaminopyridine (DMAP) was added, and the reaction was stirred in the dark for 24 h. The reaction was quenched with 5% HCl (2 mL), then the mixture was extracted into CH_2Cl_2 (5 mL), and



washed with water (2 × 100 mL) and brine (50 mL). The organic layers were dried over anhydrous sodium sulfate, then the mixture was filtered, and the solvent was removed on the rotary evaporator to give an oil. The product (712 mg, 80% yield) was isolated as a yellowish oil by flash column chromatography in 5% EtOAc / Hexanes. ^{1}H nmr ($CDCl_3$, 200 MHz) δ 3.38 – 3.62 (3H, m, O-CH_2-CH), 2.00 – 2.53 (4H, m, O=C-CH_2CH_2), 0.93 (9H, s, N-Si-C-CH_3), 0.87 (9H, s, O-Si-C-CH_3), 0.25 (3H, s, N-Si-CH_3), 0.23 (3H, s, N-Si-C'H_3), 0.03 (6H, s, O-Si-CH_3); ^{13}C nmr ($CDCl_3$, 50 MHz) δ 184.15 (*C*=O), 65.70, 59.93, 31.27, 27.09, 25.79, 25.85, 24.88, 19.18, 18.13, 18.96, -3.63, -4.55, -5.51; IR (NaCl disks, cm^{-1}) 3355, 2960, 2854 (C-H str.), 1697 (C=O str.), 1469, 1389, 1363, 1257, 1122; CIMS 344 $[M+H]^+$, 286, 230 (base), 172, 73; Anal calcd. for $C_{17}H_{37}NO_2Si_2$ C: 59.36, H: 10.85, N: 4.08; found: C: 56.78, H: 10.70, N: 5.30.

3-Acetyl-1-*tert*-butyldimethylsilyl-5-*tert*-butyldimethylsilyloxymethyl-2-pyrrolidinone (5-18). The *bis*-TBDMS protected compound **5-17** (104 mg, 0.3 mmol) was dissolved in 5 mL THF, then 1.05 eq. LDA (42 □L diisopropylamine, 210 □L *n*-BuLi, 1.5 M in hexanes, dissolved in 5 mL THF at 0 °C and stirred for 5 min) was prepared, and cooled to – 78 °C. The solution of substrate **5-17** was added dropwise to the solution of LDA, and the mixture was stirred at – 78 °C for ½ h, then 1.2 eq. (25 □L) acetyl chloride was added and the reaction mixture was stirred for 2 h as the temperature was allowed to rise slowly to room temperature.

The reaction was quenched with solid ammonium bicarbonate, then the mixture was filtered and the solvent was removed on the rotary evaporator. The residue was purified by flash column chromatography on silica gel using 7% EtOAc / Hexanes as the eluent, giving product in the first fraction (7.7 mg, 6% yield). ^{1}H nmr ($CDCl_3$, 200 MHz) δ 3.41 – 3.78 (3H, m, O-C*H*$_2$-C*H*), 1.98 – 2.48 (3H, m, O=C-C*H*-C*H*$_2$), 1.57 (3H, s, C*H*$_3$), 0.94 (9H, s, N-Si-C-C*H*$_3$), 0.87 (9H, s, O-Si-C-C*H*$_3$), 0.26 (3H, s, N-Si-C*H*$_3$), 0.22 (3H, s, N-Si-C'*H*$_3$), 0.03 (6H, s, O-Si-C*H*$_3$).

3-(Hexa-2',4'-dienoyl)-1-*tert*-butyldimethylsilyl-5-hydroxymethyl-2-pyrrolidinone (5-19). The *bis*-TBDMS protected compound **5-17** (100 mg, 0.29 mmol) was dissolved in 5 mL THF, then 2.1 eq. LDA (4 mL of solution of 200 □L diisopropylamine and 840 □L *n*-BuLi (1.5 M in hexanes) in 10 mL THF, prepared at 0 °C) was added dropwise and the mixture was stirred for 1 h. Sorboyl chloride (1.2 eq., 67 mg) was added, and the mixture was stirred for 2 h, then the reaction was quenched with solid ammonium bicarbonate (1 g). The mixture was filtered and the solvent was removed on the rotary evaporator. The product (77.4 mg, 86.7% yield) was isolated by flash column chromatography on silica gel using 7% EtOAc / Hexanes as the eluent. ^{1}H nmr ($CDCl_3$, 200 MHz) δ 7.19 – 7.45 (2H, m, O=C-CH=C*H*-CH=C*H*), 5.95 – 6.37 (2H, m, O=C-C*H*=CH-C*H*=CH), 4.46 (1H, m, O=C-C*H*), 3.94 (1H, dd, ^{2}J = 10.4, ^{3}J = 3.5 Hz, O-C*H*H), 3.67 (1H, dt, ^{2}J = 10.4, ^{3}J = 2.7 Hz,

O-CH*H*), 2.82 (1H, m, O-CH_2-C*H*), 2.40 (1H, m, O-CH_2-CH-C*H*H), 2.08 (2H, m, HO-CH_2-CH-CH*H*), 1.84 (3H, d, ^3J = 6.1 Hz, O*H*), 0.83 (9H, s, N-Si-C-CH_3), -0.01 (3H, s, N-Si-CH_3), -0.04 (3H, s, N-Si-C'H_3).

3-(Tetradeca-2,4-dienoyl)-1-*tert*-butyldimethylsilyl-5-hydroxymethyl-2-pyrrolidinone (5-20). The *bis*-TBDMS protected compound **5-17** (120 mg, 0.34 mmol) was dissolved in 10 mL THF and cooled to – 78 °C, then 2.2 eq. LDA (106 □L diisopropylamine, 480 □L *n*-BuLi (1.5 M solution in hexanes) in 5 mL THF, prepared at 0 °C) was added dropwise and stirred for 1h. Tetradecadienoyl chloride (100 mg) was added dropwise and the solution was stirred for 2 h with gradual warming to room temperature. The reaction was quenched with solid ammonium bicarbonate (1 g), then the mixture was filtered and the solvent was removed on the rotary evaporator. The product (25.7 mg, 17.0% yield) was isolated by flash column chromatography with 7% EtOAc / Hexanes as the eluent. ^{1}H nmr ($CDCl_3$, 200 MHz) δ 7.15 (1H, dd, ^3J = 9.9, 15.0 Hz, O=C-CH=C*H*), 6.07 (2H, m, O=C-CH=CH-C*H*=C*H*), 5.69 (1H, d, ^3J = 15.0 Hz, O=C-C*H*), 4.05 (1H, m, O=C-C*H*-C=O), 3.61 (2H, m, O-CH_2), 2.35 (2H, m, *H*O-CH_2-C*H*), 2.11 (2H, m, CH=CH-CH_2), 1.86 (2H, m, O-CH_2-CH-CH_2), 1.23 (14H, br. s, CH_2), 0.87 (9H, s, Si-C-CH_3), 0.85 (3H, t, ^3J = 6.9 Hz, CH_2-CH_3), 0.03 (6H, s, Si-CH_3).

Tetradeca-2,4-dienoyl-(2'-pyridyl) sulfide (5-21). Tetradecadienoic acid **5-14** (400 mg, 1.8 mmol) was dissolved in 10 mL anhydrous $CHCl_3$, and this solution was added slowly to a stirred solution of 2,2'-dipyridyl disulfide (590 mg, 2.7 mmol) and triphenylphosphine (787 mg, 3 mmol) in 20 mL anhydrous $CHCl_3$ at room temperature. The mixture was stirred for 1 h, then quenched with H_2O (10 mL) and the mixture was extracted into $CHCl_3$ (3 × 20 mL), washed with water (20 mL), and dried over anhydrous sodium sulfate (1 g). The mixture was filtered and the solvent was removed on the rotary evaporator. The product (328 mg, 60% yield) was isolated by flash column chromatography on silica gel using $CHCl_3$ as the eluent. ^1H nmr ($CDCl_3$, 200 MHz) δ 8.51 (1H, m, pyr), 7.59 (2H, m, pyr), 7.16 (2H, m, pyr, O=C-CH=C*H*), 5.98 – 6.15 (3H, m, O=C-C*H*=CH-C*H*=C*H*), 2.07 (2H, m, CH=CH-CH_2), 1.28 (2H, m, CH=CH-CH_2-CH_2), 1.15 (12H, br. s, -CH_2-), 0.76 (3H, t, ^3J = 5.9 Hz, CH_2-CH_3).

CHAPTER 6: Conclusions and Future Work

6.1 Conclusions

Examination of the x-ray crystal structures of several key compounds in the glycoluril template series has shown that the ground state of the diacyl compounds does not possess optimal geometry for the Claisen-like condensation reaction; instead, a rotation of each acyl group around the amide bond is required to undergo the reaction. This rotation may be aided by chelation of the counterion between the acyl oxygen and the adjacent oxygen (or sulfur) of the glycoluril. From an analysis of the structures, along with what is known about electronic effects in donor and acceptor sites, it seems likely that the transition state for this reaction involves a boat-like conformation rather than the frequently more stable chair-like conformation.

Examination of several reactions in detail has led to the conclusions that aromatic groups are excellent substrates for the acylation and condensation reactions; that non-anionic acylation conditions are possible, although the more reactive sulfur templates may be required to achieve this; and that the condensation reaction is general, but has definite limits in the stability of the substrates. Additionally, it was found that enolate production through the use of Reformatsky conditions is quite inefficient for this system, and enolate formation by reaction with a strong, hindered base is far superior. The

weakest link in the template methodology is the reduction of β-keto adducts, especially for β-keto side chains which contain conjugated double bonds. Although a variety of conditions was investigated, none were found that gave better yields of product than the $NaBH_4$ / methanol combination. Not all reagents have been investigated, and a solution to this problem would make this methodology considerably more suitable for the synthesis of natural products.

A facile method for cleavage of acyl groups from the template to the free acid has been discovered and investigated; this method provides good yields of the free acids, and allows recycling of the glycoluril template after use.

A new method for the synthesis of *mono-* and *di*-thioglycolurils by addition of Lawesson's reagent to the parent glycoluril template, or more efficiently, to the monoacyl adduct leads to a variety of interesting new structures, which are acylated more readily than their oxygen analogues. At least one of these new acylation conditions allows the use of non-anionic conditions and the direct addition of the acid, thus bypassing synthesis and purification of the acyl halides which are normally used.

The investigation of several thioglycoluril compounds as templates for the intramolecular Claisen-like condensation reaction has proven successful, and these compounds have exhibited interesting selectivities in the condensation reaction, even to the point of reversing the major product formed in the reaction.

The glycoluril **2-1** was used as a template on which to build up tetradeca-2,4-dienoic acid, which was then cleaved from the template and epoxidized to give the fatty acid of pramanicin. This synthesis gave a comparable corrected overall yield compared

with literature procedures[133], although it took several more steps; however, this methodology lends itself well to the synthesis of analogues, including isotopically labelled compounds which could be used for biosynthetic incorporation experiments.

The synthesis of the head group of pramanicin proved quite difficult due to several unprecedented reactions, and it became necessary to re-evaluate the synthetic pathway chosen.

In brief, the glycoluril template **2-1** was designed for the intramolecular Claisen-like condensation reaction, and the geometry of the acyl groups facilitates this reaction, by means of a six-membered boat-like transition state, and chelation of the counterion between the donor acyl group oxygen and the adjacent oxygen of the glycoluril template. This reaction occurs very quickly, although reliable, precise kinetic data have not been obtained yet. Since the design of the glycoluril template was based on this condensation reaction, it is not surprising that several other reactions do not give quantitative results.

The glycoluril **2-1** is an excellent template for the condensation of simple acyl and aroyl groups, but the *mono*- or *di*-thioglycoluril templates should prove to be better for the condensation of more complex side chains, since acylation of these templates occurs under milder conditions. Additionally, the *mono*-thioglycoluril **4-1** is a good choice if the goal is either to slightly improve the product ratio in the Claisen-condensation reaction, or to reverse the selectivity of the condensation reaction to get the more substituted product.

The *mono*-thioglycoluril template may not be suitable for extended syntheses; since in the second or third round of condensations, the preferred thioamide leaving

group must compete with extraction of a proton at a primary or secondary versus a tertiary centre. This competition may lead to another reversal of selectivity of the reaction, or to very low yields of product.

6.2 Future Work

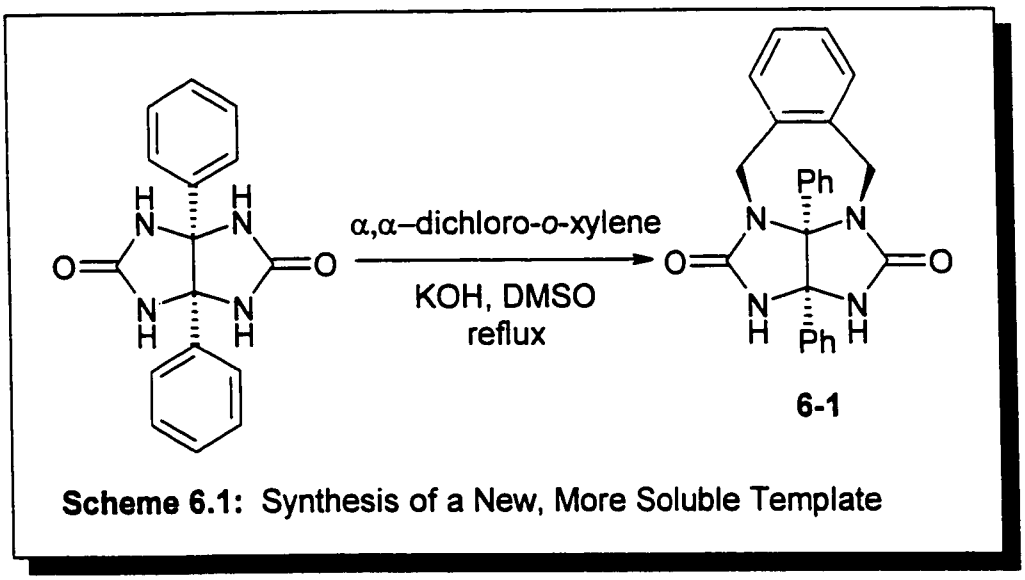
While there remain a nearly limitless number of interesting ideas to explore regarding various aspects and analogues of the glycoluril template, a few of these deserve special attention, and will be discussed below.

6.2.1 Other Glycoluril Structures as Templates for the Claisen Condensation

As mentioned, the glycoluril **2-1** is not an ideal template for the biomimetic cycle. In particular, the low solubility of this compound in most organic solvents has led to the use of very harsh conditions in the first acylation reaction. One interesting possibility is the use of other glycoluril derivatives, such as **6-1**, since two closely related compounds have been synthesized by Rebek[55, 57] (Scheme 6.1) for comparison of the nmr with his molecular clips.

This synthesis has the advantage that the reaction of urea and benzil results in a single, symmetrical product, eliminating the production of an *anti*-adduct, such as **2-1a**, which should result in considerably higher yields. Compound **6-1** should be much more soluble in organic solvents than the more polar tetramethylglycoluril **2-1**. This enhanced

solubility should lead to milder conditions in the first acylation reaction, since the NH groups are not expected to be much more sterically blocked than they are in **2-1**. Exploration of this compound for its utility in the biomimetic glycoluril pathway should be undertaken as soon as possible.



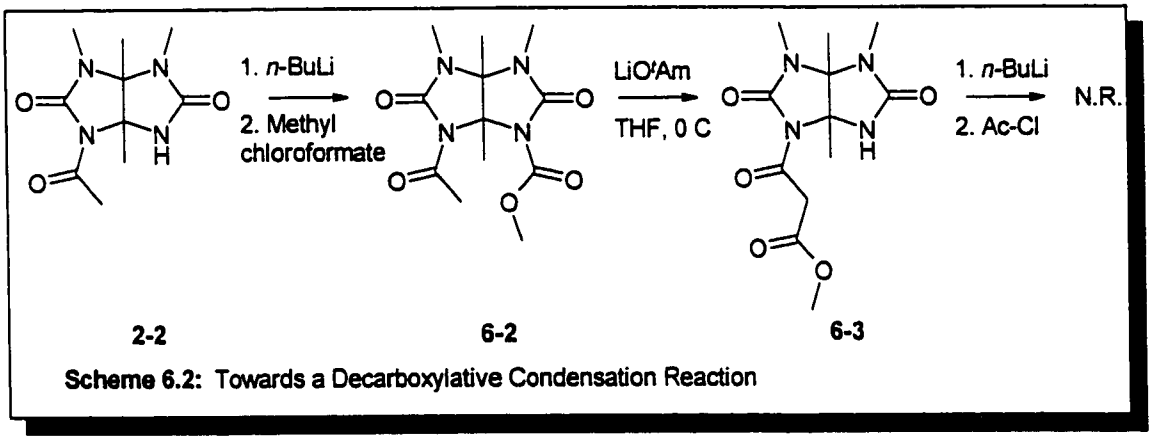
Scheme 6.1: Synthesis of a New, More Soluble Template

6.2.2 Decarboxylative Enolate Generation for the Condensation Reaction: A Better Model of Polyketide Synthase

Although the glycoluril **2-1** has been used as a template for an intramolecular Claisen condensation reaction, and displays some of the characteristics of a polyketide synthase enzyme, it utilizes a different substrate to get to the same product. The glycoluril template reacts by generation of an enolate on one of the acyl side chains by addition of a hindered base, followed by a rapid condensation reaction. This leads to a

mixture of products, predominating in the compound resulting from deprotonation at the less hindered acyl group. In contrast, PKS generates an enolate by enzyme assisted decarboxylation of a malonyl group, thus leading to only one regioisomer.

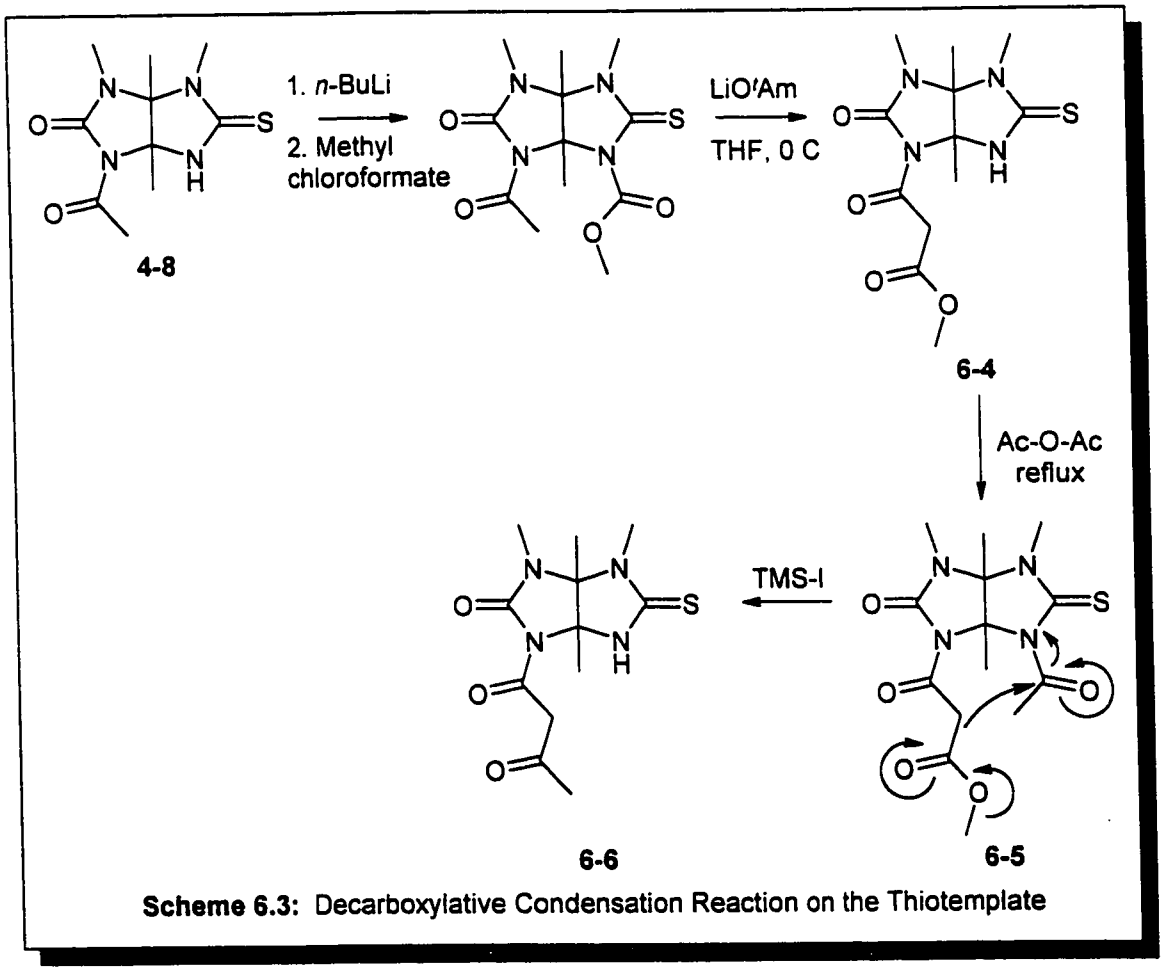
Previous attempts to prepare a compound bearing both acetyl and malonyl side chains on the glycoluril template have proved unsuccessful. It is possible to react acetyl glycoluril **2-2** with methyl chloroformate to give the acetyl carbomethoxy adduct **6-2** in good yields (Scheme 6.2). Subsequent condensation of this compound proceeds smoothly to give **6-3**; however, addition of another unit of acetate at this point has proven very difficult, due to the acidity of the malonate α-protons.



Scheme 6.2: Towards a Decarboxylative Condensation Reaction

As seen in Chapter 4, the sulfur templates are much more reactive at nitrogen, and the second acylation reaction can be accomplished by heating in an acyl anhydride, which provides a neutral or slightly acidic environment. Thus, a thio derivative of **6-3** (**6-4**) should be acetylated readily to give **6-5**, which is now set up for the decarboxylative condensation reaction (Scheme 6.3). Removal of the methoxy group by TMS-I or a similar reagent should lead to decarboxylation to give the acetoacetate adduct **6-6**,

although mediation of an appropriate metal may be required to assist in this reaction. If this proceeds smoothly, it will represent one of the first truly biomimetic reactions of this nature. The only other example of this type in the literature was by Scott *et al.*[147] in 1975, who made an acetoacetyl adduct on a catechol template by decarboxylation of a malonyl group followed by condensation with an acetyl group on the other site in 30% yield.



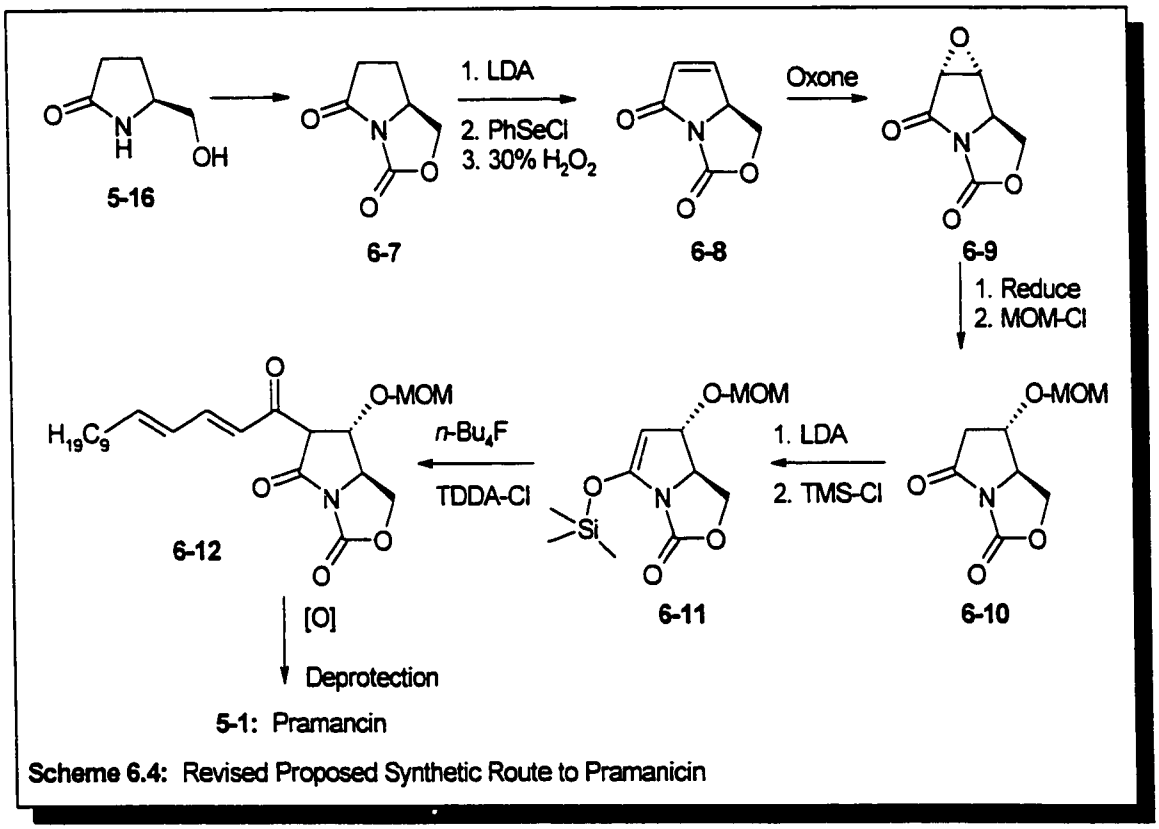
Scheme 6.3: Decarboxylative Condensation Reaction on the Thiotemplate

6.2.3 Synthesis of Pramanicin

The synthesis of pramanicin should be pursued, although an altered pathway to the pyrrolidinone head group is strongly recommended because of the difficulties observed in the attempted synthesis (see Section 5.3). There are a number of alterations that can be attempted in order to obtain improved yields and product distributions on the route to pramanicin. In particular, since one of the observed difficulties involves loss of one of the *tert*-butyldimethylsilyl protecting groups, a different protection scheme is necessary. A good choice would be either protection of the alcohol with a methoxymethyl (MOM) group and the amide with a modified benzyl protecting group, both of which have been used in related syntheses[135] using pyrrolidinones, or more elegantly, protection of both the amide and the alcohol in an oxazolidinone ring[10, 148].

Another alteration involves modification of the order of reaction; performing the acylation reaction later in the synthesis may prove quite beneficial. Starting from the alcohol **5-16**, protection of the alcohol and the amide in an oxazolidinone ring should give **6-7** in good yields. The conversion of **6-7** to the α,β-unsaturated amide **6-8**, while it is a new reaction for this substrate, is nonetheless well precedented[135, 137, 139]. Epoxidation of the double bond, by Oxone or *m*-CPBA should give epoxide **6-9**, with the stereochemistry shown; a related compound has been used in the synthesis of the natural product (2*R*, 3*R*, 4*R*)-2-Hydroxymethyl-3,4-dihydroxypyrrolidine, which displays the same stereochemistry as our target molecule[134]. Reduction of the epoxide **6-9** by one of several available reagents should produce the alcohol, which could then be protected as

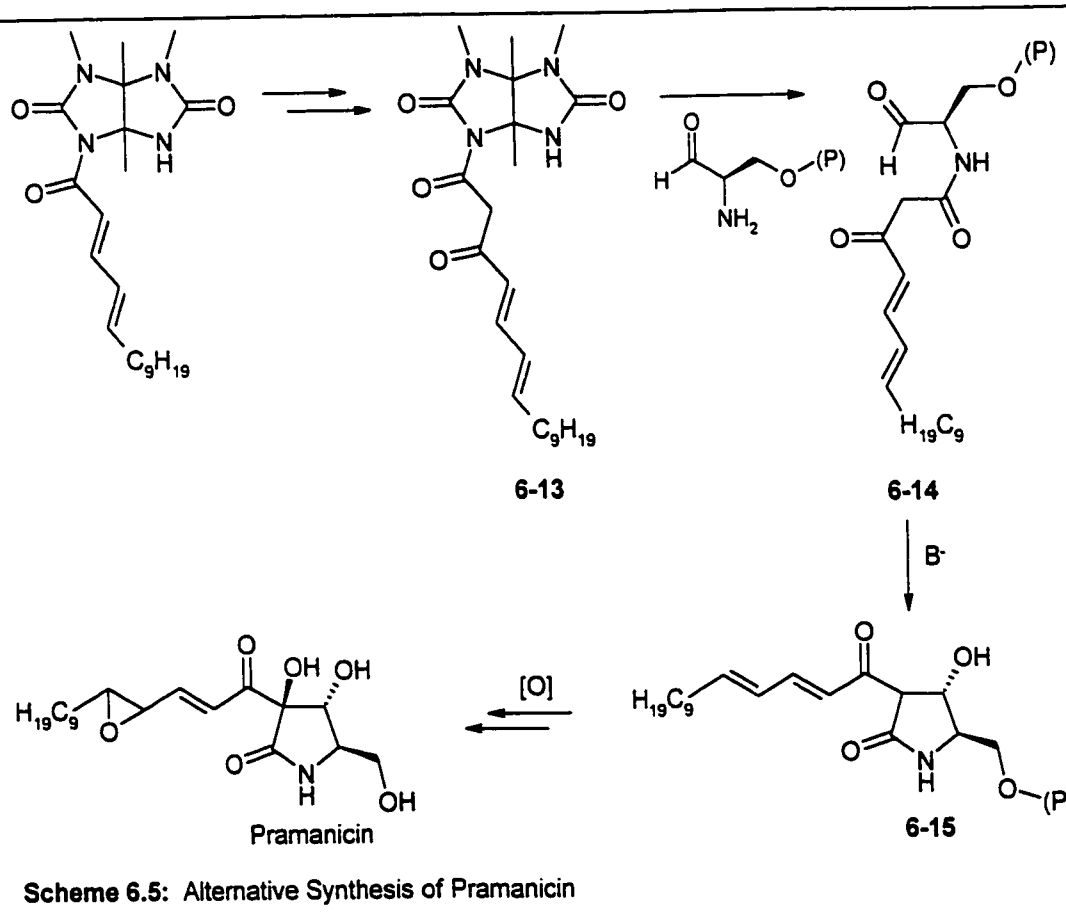
the methoxymethyl (MOM) ether to give **6-10**. The use of a strong base should deprotonate α to the carbonyl, leading to formation of the enolate which could be trapped with 1 equivalent of TMS-Cl to give **6-11**, followed by reaction of the silyl enol ether with F^- and tetradecadienoyl chloride should lead to compound **6-12**. This approach uses a milder method of generating the enolate *in situ*, in the presence of the acyl chloride, and should lead to better yields of the acylation product.



Scheme 6.4: Revised Proposed Synthetic Route to Pramanicin

Oxidation of **6-12** at the α-position may be accomplished by several methods. Although MoOPh[149] and Davis' reagent[150] have often been used for α-hydroxylation reactions, neither have been effectively used on methylenes of β-ketoesters or related compounds. For example, MoOPh complexes with ethyl benzoylacetate and fails to react[151]. Methods

that do work for β-ketoesters include the use of dibenzyl peroxydicarbonate by Vederas *et al.*[152] and treatment of the silyl enol ether directly with *m*-CPBA[153]. Thus, either of the latter methods should lead to an α-hydroxylated compound, which can then be deprotected and epoxidized to give pramanicin.



Scheme 6.5: Alternative Synthesis of Pramanicin

An alternative method, which is quite attractive from a biomimetic standpoint, involves extending the acyl chain on the template by another acetyl unit to give the β-keto compound **6-13**, then cleaving the protected product directly with a protected serine derivative, producing compound **6-14** (Scheme 6.5). This is not unprecedented, since

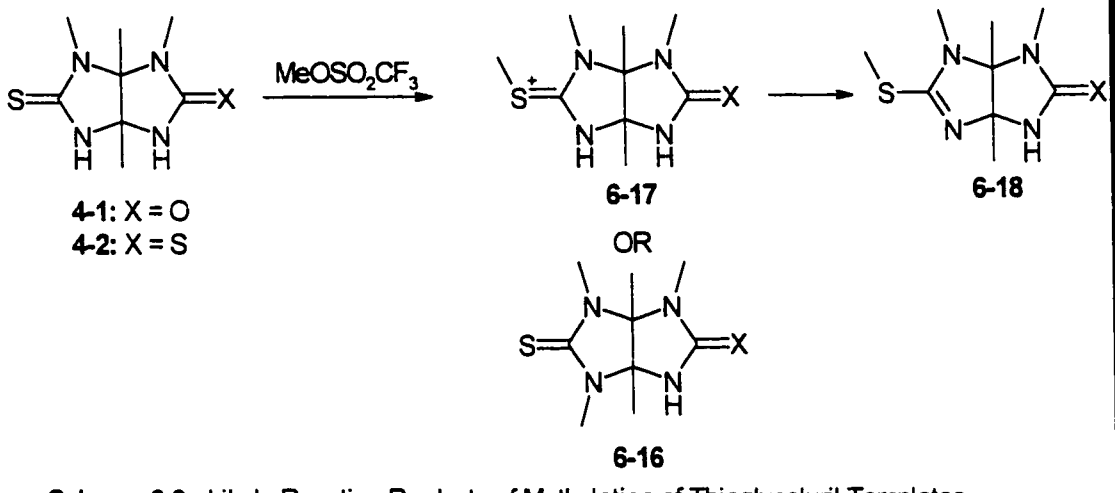
Kuhling[27] has used tetraacetylglycoluril as an acetylating agent for amines. Compound **6-14** could then be cyclized to give the pyrrolidinone **6-15**, which only requires hydoxylation at the α-carbon, deprotection, and epoxidation to give pramanicin.

This latter method is very attractive from a biomimetic point of view, since the carbonyl carbon of the ring has been shown to originate from acetate. Whether this is directly incorporated by polyketide synthase, or whether the acetate is incorporated into a glutamate or proline unit separately, remains unclear at this time. Additionally, this method bypassed the need for an enolate condensation of the pyrrolidinone ring with an activated acid, which has been identified, at least in the case studied, as a problem reaction.

6.2.4 Further Reactions on the Thiotemplates

Although the thioglycoluril analogs **4-1** and **4-2** have been shown to readily undergo acylation at nitrogen, and are capable of the Claisen-like condensation reaction, no attempt has been made to carry the compounds through the remainder of the glycoluril cycle; that is, the reduction, elimination, conjugate addition of hydride and cleavage of a growing chain from the template. Although no difficulties are anticipated with these reactions, future work should definitely include verifying that these processes can occur on the thiotemplates, and investigation of any differences in reactivity between these compounds and the oxygen template.

6.2.5 Nitrogen Analogs of the Glycoluril Template



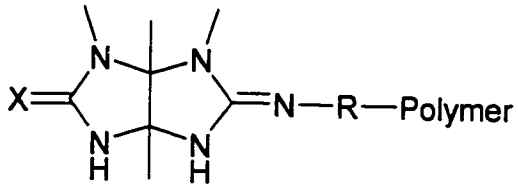
Scheme 6.6: Likely Reaction Products of Methylation of Thioglycoluril Templates

Sulfur analogs of the glycoluril template have exhibited very interesting properties in terms of reactivity and selectivity, and can also lead to the production of other analogues, including compounds where one oxygen, or one sulfur, is replaced with nitrogen, leading to guanidine in place of the urea or thiourea. Nolte *et al.*[154] have described an alkylation of the thiourea moiety with methyl triflate, followed by reaction with a primary amine to give the guanidine analogue of one of his molecular clips. The same reaction on either the monothioglycoluril **4-1** or the dithioglycoluril **4-2** is not likely to lead to the guanidine analogues, since alkylation will probably occur on the nitrogen preferentially to the sulfur to give the alkylated product **6-16** (Scheme 6.6). Even if methylation does occur on sulfur to give compound **6-17**, this product is likely to lose a proton readily to produce **6-18**, which is expected to be quite a stable compound.

Other methods to produce the guanidine analogue should be explored, and if no better methods can be found, then the reaction is expected to work with the acetylated compounds, although this at least partially defeats the purpose, since selectivity and ease of acylation are of great interest. However, diacyl thioglycolurils or diacyl dithioglycolurils should react as in Nolte's case, to give the guanidine analogues, which could then be explored in terms of the selectivity of the condensation reaction. This reaction may also work for 1-acetyl-3,4,7,8-tetramethyl-2-thioglycoluril **4-7**, since the acetyl group is on the sulfur side in this compound, providing that *S*-alkylation occurs preferentially to *N*-alkylation in this case.

6.2.6 Template Condensations on the Solid Phase

A long-time goal of this project has been to develop a system for the construction of fatty acid and polyketide molecules on the solid phase. Although a number of strategies have been theorized for the attachment of the glycoluril template to a solid phase support, one of the most attractive involves the use of the guanidine derivatives described in section 6.2.5. This strategy would involve reaction of the guanidine moiety with a spacer group, which could then be reacted with an appropriately functionalized polymer surface. This system should result in simpler reaction and purification methods for a number of the reactions in the glycoluril template cycle.



X = O, S
R = spacer group

Figure 6.1: Attachment of Template to a Solid Support

6.3 Experimental

1-Acetyl-6-carboxymethyl-3,4,7,8-tetramethylglycoluril (6-2). Acetyl glycoluril **2-2** (1 g, 4.2 mmol) was dissolved in 60 mL of THF and cooled to 0 °C, then *n*-BuLi (1.05 eq., 2.9 mL of 1.5 M solution in hexanes) was added and the mixture was stirred for 20 min. Methyl chloroformate (1.2 eq., 385 □L) was added, and stirring was continued for 2 h. The reaction was quenched with aqueous $NaHSO_4$ (10 mL, 1M), and the mixture was extracted into chloroform (3 × 60 mL), washed with water (60 mL), then dried over anhydrous sodium sulfate. The solvent was removed on the rotary evaporator, and the solid residue was recrystallized from chloroform / EtOAc to give product (821 mg, 66% yield) as white crystals. ^{1}H nmr ($CDCl_3$, 200 MHz) δ 3.84 (3H, s, O=C-O-CH_3), 2.96 (3H, s, N-CH_3), 2.87 (3H, s, N-CH_3), 2.41 (3H, s, O=C-CH_3), 1.86 (3H, s, CH_3), 1.48

(3H, s, CH_3); ^{13}C nmr ($CDCl_3$, 50 MHz) δ 170.33 (*C*=O), 152.63 (2 × *C*=O), 151.53 (*C*=O), 79.68, 77.57, 53.32, 26.85, 26.50, 25.27, 18.85, 14.58.

1-(3'-oxo-3'-methoxypropanoyl)-3,4,7,8-tetramethylglycoluril (6-3). 1-Acetyl-6-carboxymethyl-3,4,7,8-tetramethylglycoluril **(6-2)** (100 mg, 0.34 mmol) was dissolved in 5 mL of THF and cooled to 0 °C, then lithium *tert*-amylate (1.2 eq., 4.5 mL of 0.09 M solution in THF) was added and the mixture was stirred for 1 h. The reaction was quenched with aqueous $NaHSO_4$ (1 mL, 1M), then the mixture was extracted into chloroform (3 × 10 mL), washed with water (10 mL), and dried over anhydrous sodium sulfate (1 g). The solvent was removed on the rotary evaporator, then the product (65 mg, 65%) was purified by flash column chromatography on silica gel using EtOAc as the eluent. ^{1}H nmr ($CDCl_3$, 200 MHz) δ 5.97 (1H, br. s, N*H*), 4.06 (1H, d, ^{2}J = 16.4 Hz, O=C-C*H*H), 3.69 (3H, s, O=C-O-CH_3), 3.68 (1H, d, ^{2}J = 16.4 Hz, O=C-CH*H*), 2.98 (3H, s, N-CH_3), 2.83 (3H, s, N-CH_3), 1.70 (3H, s, CH_3), 1.54 (3H, s, CH_3).

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