Sustainable Approaches to Novel Heterocyclic Scaffolds for Medicinal Chemistry

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A thesis submitted in partial fulfilment of the requirement for the degree of Doctor of Philosophy (PhD).
Declaration

I, Robert William Foster, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Robert William Foster

13/07/2015
Abstract

This thesis investigates new methods for the environmentally sustainable synthesis of heterocyclic scaffolds for application in medicinal chemistry. Chapter I introduces general principles of sustainability in synthetic organic chemistry. This includes the characterization and application of sustainable solvents and the use of biomass feedstocks in synthesis.

Chapter II explores the synthesis of substituted isoindolinones via a ruthenium-catalyzed alkyne cyclotrimerization. The introduction details the synthesis and medicinal application of isoindolinones and describes previous research involving alkyne cyclotrimerizations. Following this, the development of a regioselective alkyne cyclotrimerization reaction in a sustainable solvent is reported. The optimized alkyne cyclotrimerization conditions are then used to synthesize a selection of isoindolinone products.

Chapter III describes the application of a kinetically-controlled furan-Diels–Alder reaction to the synthesis of heterocyclic scaffolds, including the \textit{endo}-cantharimide. The study and application of furan-Diels–Alder reactions are introduced. Following this, the Diels–Alder reaction of a 3-alkoxyfuran under sustainable reaction conditions is explored experimentally and applied to the diastereoselective synthesis of \textit{endo}-cantharimides. The potential application of \textit{endo}-cantharimides in medicinal chemistry is discussed with the aid of biological testing and the Diels–Alder reactions of 3-alkoxyfurans is probed with the aid of computational calculations.

Chapter IV concerns the cyclization of reducing sugars to prepare chiral tetrahydrofurans. The role of tetrahydrofurans in medicinal chemistry, the synthesis of tetrahydrofurans from sugar derivatives and the application of hydrazones in synthetic chemistry are introduced. Following this the development of a hydrazone-mediated cyclization of \textit{L}-arabinose under sustainable reaction conditions is reported. The optimized conditions are applied to prepare tetrahydrofurans from other sugars. The manipulation of the tetrahydrofuran products is also explored.

Chapter V draws some general conclusions from the thesis and describes potential future directions for the research. Chapter VI contains the details of experimental procedures and compound characterization for the results discussed in Chapters II–IV.
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I am indebted to my academic supervisors, Dr Tom Sheppard and Professor Helen Hailes. Over the past four years Tom and Helen have ensured that I have never been left short of ideas, inspiration or encouragement. I am grateful to them both for making the time I have spent at UCL a thoroughly enjoyable and engaging experience.

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## Summary of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,3-PDO</td>
<td>1,3-propane diol</td>
</tr>
<tr>
<td>2-MeTHF</td>
<td>2-methyltetrahydrofuran</td>
</tr>
<tr>
<td>3-HPA</td>
<td>3-hydroxypropanoic acid</td>
</tr>
<tr>
<td>9-BBN</td>
<td>9-borabicyclo[3.3.1]nonane</td>
</tr>
<tr>
<td>°C</td>
<td>degrees centigrade</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>ACS</td>
<td>American Chemical Society</td>
</tr>
<tr>
<td>Ar</td>
<td>generic aryl group</td>
</tr>
<tr>
<td>API</td>
<td>Active Pharmaceutical Ingredient</td>
</tr>
<tr>
<td>aq.</td>
<td>aqueous</td>
</tr>
<tr>
<td>AZT</td>
<td>Azidothymidine</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butyloxycarbonyl</td>
</tr>
<tr>
<td>b.p.</td>
<td>boiling point</td>
</tr>
<tr>
<td>br.</td>
<td>broad</td>
</tr>
<tr>
<td>BSTFA</td>
<td>bis(trimethylsilyl)trifluoroacetamide</td>
</tr>
<tr>
<td>BTX</td>
<td>benzene, toluene and xylenes</td>
</tr>
<tr>
<td>CED</td>
<td>cumulative energy demand</td>
</tr>
<tr>
<td>Cp</td>
<td>η-5 cyclopentadienyl</td>
</tr>
<tr>
<td>Cp*</td>
<td>η-5 pentamethyl cyclopentadienyl</td>
</tr>
<tr>
<td>CPME</td>
<td>cyclopentyl methyl ether</td>
</tr>
<tr>
<td>cPr</td>
<td>cyclopropyl</td>
</tr>
<tr>
<td>cod</td>
<td>1,5-cyclooctadiene</td>
</tr>
<tr>
<td>conc.</td>
<td>concentrated</td>
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<tr>
<td>CSA</td>
<td>(±)-camphorsulfonic acid</td>
</tr>
<tr>
<td>Cy</td>
<td>cyclohexyl</td>
</tr>
<tr>
<td>D-</td>
<td>dextrorotatory-</td>
</tr>
<tr>
<td>Da</td>
<td>dalton</td>
</tr>
<tr>
<td>DCE</td>
<td>1,2-dichloroethane</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>DIAD</td>
<td>diisopropyl azodicarboxylate</td>
</tr>
<tr>
<td>DIBAL</td>
<td>diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DIPEA</td>
<td>N,N-diisopropylethylamine</td>
</tr>
<tr>
<td>DMA</td>
<td>dimethylacetamide</td>
</tr>
</tbody>
</table>
DMAP  4-(dimethylamino)pyridine
DME  dimethoxyethane
DMF  dimethylformamide
DMSO  dimethyl sulfoxide
DPPE  1,2-bis(diphenylphosphino)ethane
DPPF  1,1′-bis(diphenylphosphino)ferrocene
d.r.  diastereoisomeric ratio
EC\textsubscript{50}  half maximal effective concentration
EDC  1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
e.e.  enantiomeric excess
Et  ethyl
ER  estrogen receptor
ESI  Electro-Spray Ionisation
FGI  functional group interconversion
GC  glycerol carbonate
GVL  $\gamma$-valerolactone
h  hour(s)
H\textsubscript{s}-BINAP  (S)-(−)-2,2′-Bis(diphenylphosphino)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl
HDAC  histone deacetylase
HIV  human immunodeficiency virus
HMDS  hexamethyldisilazide
HMF  hydroxymethylfurfural
hv  ultraviolet irradiation
HSQC  Heteronuclear Single Quantum Coherence
Hz  hertz
IC\textsubscript{50}  half maximal inhibitory concentration
J  joule
L  generic ligand
L-  levorotatory
i  iso
LDA  lithium diisopropylamide
M  molar
MDM2  mouse double minute 2 homolog
Me  methyl
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMPP</td>
<td>magnesium monoperxyphthalate</td>
</tr>
<tr>
<td>mol</td>
<td>mole(s)</td>
</tr>
<tr>
<td>Ms</td>
<td>methanesulfonyl</td>
</tr>
<tr>
<td>mw</td>
<td>molecular weight</td>
</tr>
<tr>
<td>n</td>
<td>norm</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>n.d.</td>
<td>not determined</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>P</td>
<td>partition-coefficient</td>
</tr>
<tr>
<td>p</td>
<td>para</td>
</tr>
<tr>
<td>PC</td>
<td>propylene carbonate</td>
</tr>
<tr>
<td>PEG</td>
<td>polyethylene glycol</td>
</tr>
<tr>
<td>petrol</td>
<td>petroleum ether</td>
</tr>
<tr>
<td>PMB</td>
<td>4-methoxybenzyl</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PPA</td>
<td>polyphosphoric acid</td>
</tr>
<tr>
<td>Ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>Pr</td>
<td>propyl</td>
</tr>
<tr>
<td>R</td>
<td>generic alkyl group</td>
</tr>
<tr>
<td>Rf</td>
<td>retention factor</td>
</tr>
<tr>
<td>ROE</td>
<td>Rotating-frame Overhauser Enhancement</td>
</tr>
<tr>
<td>RT</td>
<td>room temperature</td>
</tr>
<tr>
<td>SAMP</td>
<td>(S)-1-amino-2-methoxymethylpyrrolidine</td>
</tr>
<tr>
<td>SCX-2</td>
<td>Strong Cation eXchange cartridge</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butylidemethylsilyl</td>
</tr>
<tr>
<td>TEMPO</td>
<td>2,2,6,6-tetramethylpiperidinyloxy</td>
</tr>
<tr>
<td>t</td>
<td>tert</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethanesulfonyl</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>TFAA</td>
<td>trifluoroacetic anhydride</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin Layer Chromatography</td>
</tr>
<tr>
<td>Ts</td>
<td>para-toluenesulfonyl</td>
</tr>
</tbody>
</table>
# Table of Contents

**Chapter I. Introduction** ........................................................................................................ 17

1.1. Principles of Sustainable Synthetic Organic Chemistry........................................ 17

1.1.1. Economy in Synthesis .................................................................................... 17

1.1.2. Sustainable Solvents ................................................................................... 19

1.1.3. The Application of Biomass in Chemical Synthesis .................................... 24

1.2. Summary and Project Aims ............................................................................. 28

**Chapter II. Highly Regioselective Synthesis of Substituted Isoindolinones via Ruthenium-Catalyzed Alkyne Cyclotrimerizations** .............................................................. 31

2.1. Introduction ......................................................................................................... 31

2.1.1. The Application of Isoindolinones in Medicinal Chemistry ....................... 31

2.1.2 Synthetic Approaches to Substituted Isoindolinones ................................... 32

2.1.3. Synthesis of Aromatic Compounds via Alkyne Cyclotrimerization Reactions ........................................................................................................... 34

2.1.4. Synthesis of Isoindolinones via Alkyne Cyclotrimerizations .................... 38

2.1.5. Mechanisms for RuCpCl(cod)-Catalyzed Alkyne Cyclotrimerizations ...... 39

2.1.6. Chapter II Project Outline ....................................................................... 42

2.2. Results and Discussion ....................................................................................... 43

2.2.1. Starting Material Synthesis ......................................................................... 43

2.2.3. Preliminary Cyclizations ............................................................................ 44

2.2.4. Cyclization Optimization ........................................................................... 45

2.2.5. Monoyne Scope ......................................................................................... 50

2.2.6. Diyne Scope ............................................................................................... 56

2.2.7. Functional Group Manipulation of Cyclized Products ............................. 63

2.3. Chapter II Summary ......................................................................................... 67

**Chapter III. Irreversible endo-Selective Diels–Alder Reactions of Substituted Alkoxyfurans** .................................................................................................................. 69
3.1. Introduction .......................................................................................................... 69

3.1.1. The Application of Cantharimides and Related Heterocycles in Medicinal Chemistry .............................................................. 69

3.1.2. [4+2]-Cycloaddition Reactions of Furans and Dienophiles .................... 71

3.1.3. The Synthesis of Cantharimides and Other Oxabicyclo [2.2.1] heptane Derivatives ................................................................. 74

3.1.4. The Synthesis and Application of 3-Alkoxyfurans ............................... 76

3.1.5. Chapter III Project Outline ................................................................. 77

3.2. Results and Discussion ..................................................................................... 77

3.2.1. Starting Material Synthesis ..................................................................... 77

3.2.2. Synthesis of Cantharimides via the [4+2]-Cycloadditions of 3-Alkoxyfurans ......................................................... 82

3.2.3. Functional Group Manipulation of Cantharimide Products .................. 88

3.2.4. Physicochemical Properties ................................................................ 90

3.2.5. [4+2]-Cycloadditions with other Dienophiles ...................................... 91

3.2.6. Effect of a 3-Alkoxygroup on the [4+2]-Cycloaddition of Furans and N-Methylmaleimide: A Computational Study .................. 95

3.2.7. Aromatization of Cantharimide Products ........................................... 102

3.3. Chapter III Summary ......................................................................................... 109

Chapter IV. Synthesis of Chiral THFs via the Dehydration of Pentoses .......... 111

4.1. Introduction ........................................................................................................ 111

4.1.1. The Application of THFs in Medicinal Chemistry ............................... 111

4.1.2. The Synthesis of THFs from Sugars ..................................................... 112

4.1.3. The Application of N,N-Dialkylhydrazones in Organic Synthesis ....... 113

4.1.4. The Cyclization of Reducing Sugars using NH2NMe2 ......................... 116

4.1.5. Chapter IV Project Outline ................................................................. 116

4.2. Results and Discussion ..................................................................................... 117

4.2.1. Preliminary Studies ................................................................................. 117
4.2.2. Reaction Optimization ................................................................................. 119
4.2.3. Mechanistic Investigations .......................................................................... 122
4.2.4. Cyclization Scope ........................................................................................ 124
4.2.5. Functional Group Manipulation of Cyclized Products ................................ 127
4.3. Chapter IV Summary ....................................................................................... 136

Chapter V. Conclusions and Future Work ............................................................... 139
5.1. Conclusions ........................................................................................................ 139
5.2. Future Work ....................................................................................................... 140
  5.2.1. Alkyne Cyclotrimerizations ......................................................................... 140
  5.2.2. Furan-Diels–Alder Reactions ...................................................................... 142
  5.2.3. Hydrazone-Mediated Transformations of Reducing Sugars ....................... 143

Chapter VI. Experimental Details ............................................................................. 147
6.1. General Experimental ......................................................................................... 147
6.2. General Experimental Procedures ...................................................................... 148
6.3. Compound Synthesis: Experimental Details & Compound Characterisation.... 150
6.4. Crystallography Data ........................................................................................ 256

Chapter VII. References ............................................................................................. 261

Appendix ...................................................................................................................... 287
Chapter I. Introduction

The aim of this thesis is to explore the selective synthesis of novel heterocyclic scaffolds for medicinal chemistry using sustainable reaction conditions. This research is split into three independent areas: the synthesis of isoindolinones via ruthenium-catalyzed alkyne cyclotrimerizations, the synthesis of cantharimides from 3-alkoxyfurans and the transformation of reducing sugars into chiral tetrahydrofurans. This chapter will introduce the principles of sustainable organic synthesis, with a focus on the use of sustainable solvents and biomass-derived feedstocks.

1.1. Principles of Sustainable Synthetic Organic Chemistry

The twentieth century has witnessed rapid progress in the field of chemistry and a large expansion of materials and medicines that are in production. However, the manufacture of chemicals is heavily dependent on finite reserves of fossil fuels for both energy and feedstocks. Industry and governments are recognizing the importance of reducing this dependence in order to reduce the environmental damage caused by chemical processes.

A major consumer of fine chemicals and solvents, and ultimately fossil fuels, is the pharmaceutical industry. Reducing the environmental impact of drug manufacture is an important corporate goal of pharmaceutical companies. For example, GlaxoSmithKline have committed to a carbon-neutral value chain by the year 2050. In addition to drug manufacture, drug development is another significant source of environmental damage and addressing this is key to improving sustainability in the discovery of new medicines.

1.1.1. Economy in Synthesis

Twelve Principles of Green Chemistry

An important guide to sustainability in synthesis are the Twelve Principles of Green Chemistry, proposed by Anastas and Warner (Figure 1). In summary, they encourage the efficient use of renewable raw materials to selectively manufacture chemicals without the need for dangerous solvents, reagents and processes. This work has inspired other sustainability guides, including Winterton’s Twelve More Green Chemistry Principles, Anastas and Zimmerman’s principles of green engineering and Tang’s PRODUCTIVELY pneumonic.
1. It is better to prevent waste than to treat or clean up waste after it is formed.

2. Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.

3. Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.

4. Chemical products should be designed to preserve efficacy of function while reducing toxicity.

5. The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.

6. Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.

7. A raw material or feedstock should be renewable rather than depleting wherever technically and economically practicable.

8. Unnecessary derivatization (blocking group, protection/ deprotection, temporary modification) should be avoided whenever possible.

9. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

10. Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.

11. Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.

12. Substances and the form of a substance used in a chemical process should be chosen to minimize potential for chemical accidents, including releases, explosions, and fires.

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**Figure 1. Twelve Principles of Green Chemistry. Reproduced from Ref. 8 with permission from The Royal Society of Chemistry.**
Chapter I

**E Factor**

A useful measure of the economy of a chemical process is the E factor (Environmental Factor), as proposed by Sheldon. The E Factor is defined as the mass of the waste generated in a process divided by the mass of the product. As such, the E Factor of a process should be as close to zero as possible. In calculating a value all the raw material required to produce a product is considered, including all reagents, solvents and the fuel required. The only exception made is water (minus any organic or inorganic waste products in the aqueous extracts). While low E Factors can be achieved for petrochemical and bulk chemical processes, good economy in the pharmaceutical industry is a more challenging proposition (Table 1).

**Table 1. E Factors in chemical industries.**

<table>
<thead>
<tr>
<th>Industry</th>
<th>Product scale/tonnes</th>
<th>E Factor</th>
</tr>
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<tbody>
<tr>
<td>Oil refining</td>
<td>$10^6$–$10^8$</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Bulk chemicals</td>
<td>$10^4$–$10^6$</td>
<td>&lt;1–5</td>
</tr>
<tr>
<td>Fine chemicals</td>
<td>$10^2$–$10^4$</td>
<td>5–50</td>
</tr>
<tr>
<td>Pharmaceuticals</td>
<td>$10$–$10^3$</td>
<td>25–100</td>
</tr>
</tbody>
</table>

Reproduced from Ref. 10 with permission from The Royal Society of Chemistry.

**Atom Economy**

Another metric for sustainable chemistry is atom economy, as proposed by Trost. It is defined as the molecular weight of a product divided by the sum of the molecular weight of all substances formed for a reaction process. Atom Economy does not account for catalysts, solvent, excess reagent, reaction yield or the provenance of reagents but is a very straightforward method to quantify the efficiency of a process. Various other concepts have been proposed to quantify the economy of a synthesis, including process mass intensity, reaction mass efficiency and molar efficiency.

**1.1.2. Sustainable Solvents**

The biggest individual source of waste in the manufacture of active pharmaceutical ingredients (APIs) is solvent. A study by Henderson et al. of the waste generated by GlaxoSmithKline in the production of APIs concluded solvent was responsible for ca. 85% of the non-aqueous waste generated by mass (Figure 2). As such, the most effective way to reduce the environmental impact of a manufacturing process is very often to address the waste associated with the use of solvent.
Ideally reactions should be conducted without solvents or conducted in water to minimize the environmental waste. However, it is rarely possible to eliminate organic solvent from a synthesis and consideration must be given to which solvents should be used to minimize environmental impact. Other issues such as occupational health and safety, which are not directly related to environmental impact, are also often taken into consideration when rating solvents for their use in organic synthesis. A summary of these factors is given below.

**Manufacture**

The industrial production of solvent in an energy intensive process and is often dependent on the use of fossil fuels. Fischer *et al.* have calculated the cumulative energy demand (CED) for the manufacture of a series of common solvents, including those represented in Figure 3. It is notable that the energy required to manufacture THF is significantly greater than that required to manufacture a solvent like MeOH. This is in part because the synthesis of THF requires multiple steps, whereas MeOH can be prepared in a single step from synthesis gas.
Disposal and Recovery

Non-aqueous solvent is typically disposed by incineration and there are two important factors that determine how economical this is. Firstly, the disposal of chlorinated solvents is more expensive because they are typically non-flammable and so fuel must be consumed during incineration. In addition, if a solvent cannot be effectively separated from an aqueous extract then the aqueous extract must also be incinerated. This is a significant problem for solvents like THF that are only partly miscible with water.

One method to potentially improve the economy of a process is to recover the solvent at the end of a reaction through distillation and there are a number of factors that have an impact on how straightforward this may be. Ideally a solvent will not have a very high boiling point (to minimize energy use), not have a boiling point within 10 °C of many other solvents (to aid separation) and would not form an azeotrope with many other solvents. A low explosive/flammability risk is also important for safe solvent recovery, as is good solvent stability. Although solvent distillation can be an energy-intensive process, an analysis of twenty six common solvents by Fisher et al. concluded that distillation was generally environmentally superior to incineration.

Pollution

In addition to the carbon dioxide produced in the manufacture, recovery and disposal of solvent, there are also a number of other means by which the use of a solvent may result in environmental damage. Many organic solvents are classified as Volatile Organic Compounds (VOCs), which are known to reduce air quality when they evaporate. Solvents such as carbon tetrachloride and 1,1,1-trichloroethane pose a risk to the ozone
layer, and are subject to strict regulation. In addition, many solvents pose a risk to aquatic life. For example, solvents such as limonene, cyclohexane and dichlorobenzene are known to be very toxic to aquatic life and potential causes of long-term damage to the aquatic environment.

**Occupational Health**
A number of commonly used solvents possess an established or potential occupational health hazard. Solvents such as benzene and 1,2-dichloroethane (DCE) are known carcinogens while dimethylformamide (DMF), N-methyl-2-pyrrolidone (NMP) and 2-methoxyethanol are possible reproductive toxins.

**Patient Safety**
The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use have set limits on the presence of specific solvents in clinical medicines. While solvents such as EtOH, acetone and DMSO may be present at 5000 ppm the limit on benzene in 2 ppm. Consequently, the Food and Drug Administration recommend that benzene along with CCl₄, 1,1-dichloroethane and 1,2-dichloroethane are avoided in the synthesis of pharmaceutical agents on the grounds of patient safety.

**Occupational Safety**
There are numerous safety risks associated with the storage and use of organic solvents. The flammability risk is associated with physical properties such as the flash point, boiling point, autoignition temperature, electrical conductivity and vapor pressure. Rare solvents such as nitromethane pose an additional risk of explosions. Solvents such as THF are liable to form peroxides over time, which presents an additional explosive hazard unless special precautions are taken. Other solvents possess specific safety hazards. For example, AcOH can cause severe burns on contact with skin.

By considering these factors it is possible to assess solvents based on their environmental credentials. To date GlaxoSmithKline, AstraZeneca, Pfizer, Sanofi and the ACS Green Chemistry Institute Pharmaceutical Roundtable have all produced solvent guides to aid synthetic chemists. The summarized version of the GlaxoSmithKline Solvent Selection Guide is given in Figure 4 as a representative example. There are also solvent guides for specific transformations, which aim to replace traditional solvents with poor environmental profiles with more sustainable alternatives.
Figure 4. GlaxoSmithKline solvent selection guide. Reproduced from Ref. 23 with permission from The Royal Society of Chemistry.
With the need to find alternatives to many traditional solvents with poor environmental properties, a number of compounds have recently been publicized as alternative green solvents. Examples include 2-MeTHF, cyclopentyl methyl ether (CPME), dimethyl carbonate (DMC), propylene carbonate (PC), γ-valerolactone (GVL), glycerol, polyethylene glycol (PEG), piperylene sulfone and supercritical carbon dioxide. Ionic liquids have also been promoted as green solvents, although they can require significant resources to manufacture and exhibit acute toxicity to aquatic organisms. A particular challenge is to produce new sustainable solvents with similar properties to the established solvents which need to be avoided.

1.1.3. The Application of Biomass in Chemical Synthesis

The majority of carbon-based organic compounds manufactured by the chemical industry are derived directly from petroleum. With the supply of readily accessible oil dwindling, the scientific community has turned its attention to the use of biomass as an alternative feedstock for synthetic chemistry. It is estimated that annually the Earth produces $10^{11}$ tonnes of biomass, of which only 3% is harvested for human consumption. Human activity (such as agriculture and manufacturing) produces a significant quantity of biomass as waste and so it is a potentially ideal resource for the production of small molecules, materials and fuels. The majority of biomass (75%) is composed of carbohydrates such as cellulose, hemicellulose, chitin, starch, inulin and sucrose (Figure 5). Lignocellulose accounts for 20% of biomass, and comprises ca. 65% cellulose and hemicellulose and ca. 20% lignin. The remaining 5% of biomass is accounted for by proteins, terpenes and triglycerides.
Lignin is an abundant biopolymer that has been widely studied as a potential source of aromatic compounds. Lignin is typically extracted from lignocellulose by pre-treatment with water under high temperature and pressure followed by treatment with glycoside-degrading enzymes. However, the production of small molecules from lignin has proved extremely challenging and the majority of lignin produced as a by-product of the pulping industry is still burned as a fuel. There have been a number of recent advances in this area, including Westwood’s synthesis of small aromatic building blocks from birch lignin (Scheme 1).

Carbohydrates make up the greatest constituent of biomass and have also been investigated as a source for high-value small molecules. Agricultural biomass is typically 30–40% cellulose, a regular polysaccharide of D-glucose. An additional 20–30%
Introduction

is comprised of hemicellulose; an irregular carbohydrate formed from multiple polysaccharides. The composition of hemicellulose varies, but is mostly comprised of xylose, mannose, galactose, arabinose and rhamnose. Both cellulose and hemicellulose can be cleaved to give the component monosaccharides either under acidic conditions or using enzymes.48

There are multiple methods to transform the carbohydrates that can be sourced from cellulose and hemicellulose into valuable small molecules (Scheme 2).49 An industrially attractive method is fermentation and this has been used to access a series of platform chemicals that are traditionally prepared by the petrochemical industry. The fermentation of sugars to form EtOH is an age-old approach that has been adapted into an industrial process, with production reaching ca. 99 million tonnes in 2010.50 This process has been adapted for the formation of n-BuOH through the engineering of recombinant microorganisms.51 Dehydration of these compounds also allows access to bio-ethylene and bio-butene, both valuable intermediates in the bulk chemical industry.52 It is additionally possible to access olefins such as isobutene and butadiene directly through the fermentation of sugars.53 Other compounds which can be accessed through fermentation include 3-hydroxypropanoic acid (3-HPA) 105 (a precursor to acrylic acid),54 1,3-propane diol (1,3-PDO) 106 (a building block for the polyester polytrimethylene terephthalate)55 and adipic acid 107 (a component of nylon).56
Another valuable method for transforming carbohydrates is via chemical manipulation (Scheme 2). Reducing pentoses and hexoses using hydrogen gas and heterogeneous catalysts can yield a variety of hydrocarbons, such as benzene, PhMe and xylenes (BTX). A selective reduction of D-glucose gives sorbitol, which is used as a food sweetener and as an intermediate for the synthesis of fuels, materials and pharmaceutical agents. Dehydration of pentoses and hexoses under acidic conditions respectively yields furfural and hydroxymethylfurfural (HMF). These versatile intermediates have both been exploited for the synthesis of small-molecule building blocks, fuels, surfactants and bioactive compounds.

An important use for biomass-derived compounds is as organic solvents (Scheme 3). As described previously, solvent is typically the biggest input for the synthesis of pharmaceutical agents and therefore using renewably-sourced solvent is an effective way to improve the sustainability of a manufacturing process. For example, MeOH can be prepared from synthesis gas, which can in turn be prepared by gasification of lignocellulose. This can then be converted into dimethyl carbonate (DMC) through reaction with carbon monoxide and oxygen. As discussed above, higher alcohols such as EtOH and n-BuOH can be prepared by fermentation of carbohydrates. Carbohydrates can be converted into a variety of alcohols and hydrocarbons including some well-
established solvents. Carbohydrates can also be converted into furfural and HMF, which can be transformed into various solvents, including THF, 2-MeTHF, γ-valerolactone (GVL) and cyclopentyl methyl ether (CPME). Biomass feedstock is also a source of triglycerides, which can be hydrolyzed to give glycerol. Both glycerol and glycerol carbonate (GC) have been proposed as sustainable solvents.

Scheme 3. Preparing solvents from biomass.

1.2. Summary and Project Aims

The better management of natural resources and the reduction of environmental damage is critical to the future of the chemical industries. For the synthesis of pharmaceutical agents, the biggest cause of waste and environment damage is from the use, recovery and disposal of organic solvent. As such it is essential to expand the use of solvents with more sustainable properties and avoid those that are known to have serious environmental issues. It is also important to make better use of those resources that can be sourced sustainably from biomass, whether that be as solvents or molecular building blocks. This is essential not only for the sustainable manufacture of existing medicines but also for the sustainable discovery of new drugs.

The aim of this project is to develop sustainable methodologies for the synthesis of novel heterocyclic scaffolds for medicinal chemistry. Efficiency is key to a successful synthetic strategy, in terms of step-count, selectivity and yield. For medicinal chemistry it is important that methodologies are designed for the rapid preparation of compound libraries, using either convergent or divergent approaches. Substrate scope is also
essential in this regard. Finally, the principles of sustainable synthesis discussed in this chapter must be closely considered in developing new synthetic methods, in order to reduce the environmental impact.
Chapter II. Highly Regioselective Synthesis of Substituted Isoindolinones via Ruthenium-Catalyzed Alkyne Cyclotrimerizations

2.1. Introduction

2.1.1. The Application of Isoindolinones in Medicinal Chemistry

The isoindolinone skeleton has been applied widely within medicinal chemistry to develop compounds with activity against a range of biological targets, with examples given in Figure 6. Miyachia et al. developed hydroxamic acid 201 as a novel histone deacetylase (HDAC) inhibitor which exhibited improved activity over clinically used HDAC inhibitor Zolinza. Hardcastle et al. reported substituted isoindolinone 202 as a potent MDM2-p53 protein–protein interaction inhibitor (IC\textsubscript{50} = 44 ± 6 nM), with a potential application as an antitumor agent. In addition, isoindolinone 203 was developed by Kawanishi et al. and has been shown to be a selective inhibitor of cyclin-dependent kinase subtype 1 while Spicer et al. reported isoindolinone 204 as a cytolytic protein perforin inhibitor. Medicinal chemists have developed substituted isoindolinones with biological activity against a variety of other targets including the α1-adrenoceptor, DNA gyrase, dopamine D2 and D4 receptors, hypoxia-inducible factor-1α, metabotropic glutamate subtype 2 receptor and tumor necrosis factor-α. The isoindolinone motif also forms the core of a wide selection of natural products.
2.1.2 Synthetic Approaches to Substituted Isoindolinones

The regio- (and stereo-) selective synthesis of substituted isoindolinones has recently generated significant interest within the scientific community. This work has primarily focused on the generation of isoindolinones from a pre-formed aromatic ring with two adjacent substituent (X and Y, Scheme 4) that are transformed into a lactam. This general approach has been developed for a wide range of substrates to access different substituted isoindolinones products. A variety of catalysts have been used including copper, palladium, nickel, rhodium, KO\textsubscript{t}Bu, platinum nanowires, phase-transfer catalysts, chiral amines and NBu\textsubscript{4}OAc. A notable example is the Cu(I)-catalyzed alkynylation/lactamization cascade to convert benzaldehyde 207 into 3-alkynyl isoindolinone 210 with excellent stereocontrol, as reported by Singh et al. (Scheme 4).
Another important route to substituted isoindolinones is via C-H activation strategies (Scheme 5). This has been achieved using benzamide derivatives via palladium,\textsuperscript{95} rhodium,\textsuperscript{96} nickel\textsuperscript{97} and ruthenium catalysis.\textsuperscript{98} For example, Manoharan and Jeganmohan reported a ruthenium-catalyzed synthesis of isoindolinone \textsuperscript{215} from benzamide \textsuperscript{213} using a super-stoichiometric copper(II) oxidant and alcohol \textsuperscript{214} (Scheme 5).\textsuperscript{99} Additionally, Smith et al.\textsuperscript{100} have reported a similar approach to isoindolinones via directed lithiation of a substituted arene using stoichiometric ‘BuLi and Nakata et al.\textsuperscript{101} developed a synthesis of isoindolinones from isopropyl benzyl car bamates using a Bischler-Napieralski-type cyclization.

A much less explored route to isoindolinones is to prepare the heterocyclic core from aliphatic precursors.\textsuperscript{102} An example of such a strategy was reported by Ma et al. (Scheme 6).\textsuperscript{103} Their approach was based on a palladium/copper-catalyzed oxidative cyclization of enediyne \textsuperscript{217} and internal alkyne \textsuperscript{216} to give the highly substituted isoindolinone \textsuperscript{218},
although regioselectivity was generally poor when the alkyne was non-symmetrical. In general this approach of generating an aromatic core from linear precursors allows for a more convergent approach to substituted isoindolinone products.

Scheme 6. Synthesis of isoindolinones from enediyne 217 and alkyne 216 by Ma et al.\textsuperscript{103}

### 2.1.3. Synthesis of Aromatic Compounds via Alkyne Cyclotrimerization

**Reactions**

In 1948 Reppe et al.\textsuperscript{104} reported the first transition metal-catalyzed [2+2+2]-cyclotrimerization of alkynes to form substituted benzenes. Since then, alkyne cyclotrimerizations have been used to make densely functionalized aromatic compounds using a large range of transition metal catalysts (Scheme 7).\textsuperscript{105} Alkyne cyclotrimerizations offer a convergent and atom economical route to highly substituted unsaturated compounds from readily accessible starting materials. Traditionally, polysubstituted benzene rings are often prepared via electrophilic aromatic substitution, a synthetic strategy which typically requires multiple steps, the use of protecting groups, functional group interconversion and a careful choice of conditions to ensure good regioselectivity.\textsuperscript{106} Directed metalation is another widely used technique for aromatic substitution,\textsuperscript{107} but it is inherently limited by its nature.\textsuperscript{106} As such alkyne cyclotrimerization offers an attractive alternative to these more conventional techniques.

Scheme 7. Alkyne cyclotrimerization reaction.

The main synthetic challenge associated with alkyne cyclotrimerizations is that of regioselectivity. The homo-trimerization of a terminal alkyne will typically give a mixture of 1,2,4- and 1,3,5-trisubstituted benzenes, while attempting a 3-component heterotrimerization can yield over 30 different products.\textsuperscript{108} Examples of highly selective multicomponent [2+2+2]-cycloadditions have been reported but they are limited in
substrate scope.\textsuperscript{109} A more successful and general strategy for selective [2+2+2]-cyclization is to link 2 or 3 \pi-components with an organic linker (Scheme 8), as was pioneered by Vollhardt \textit{et al.}\textsuperscript{110} The strategy of tethering relies on the lower entropy of activation associated with intramolecular processes and has been applied to the synthesis of a wide range of products. However, it does not always eliminate side reactions as the intermolecular cyclization of tethered components is often observed.\textsuperscript{111}

![Scheme 8. Tethered alkyne cyclotrimerization.](image)

The cyclotrimerization of alkynes has been reported with an extensive number of organometallic catalysts, each with their own distinct reaction scope.\textsuperscript{105f} The metals which have been most widely studied in this field are cobalt, rhodium, iridium and ruthenium.\textsuperscript{105f}

**Cobalt Catalysis**

Much of the initial work on alkyne cyclotrimerizations was developed using CoCp(CO)\(_2\) under visible light irradiation. Vollhardt developed a lot of this early chemistry\textsuperscript{110} and applied it to the synthesis of B ring aromatic steroids.\textsuperscript{112} More recently, CoCp(CO)\(_2\) has been exploited by Malacria \textit{et al.}\textsuperscript{113} in the synthesis of the taxoid core, by Elwahy and Hafner in the synthesis of 1,2,4-tris(azulen-1-yl)benzenes\textsuperscript{114} and by Siebert \textit{et al.} in the cyclotrimerization of diborylacetylenes to give hexaborylbenzene derivatives.\textsuperscript{115} Although CoCp(CO)\(_2\) has proved popular for the cyclotrimerization of alkynes, its use typically requires heating of the reaction in xylene at reflux, the strict exclusion of oxygen and sometimes a stoichiometric amount of the metal complex.\textsuperscript{105f}

Cheaper catalytic systems based on cobalt halides have been developed.\textsuperscript{105f} In 2006, Okamoto \textit{et al.}\textsuperscript{116} reported a general synthesis of aromatic compounds using a low-cost cobalt catalyst and Zn dust in THF at 40 °C (Scheme 9). The reaction conditions were used to cyclize 1,6-diyynes with a wide range of monoynes in good yield and with good functional group tolerance to give highly substituted benzenes 222a. Additionally the reaction of a terminal monoyn with a mono-substituted diyne proceeded with good regioselectivity. Okamoto was also able to demonstrate the homo-trimerization of alkynes
and the intramolecular cyclization of triynes with some success. Okamoto later reported that adding a substoichiometric quantity of a silver salt to the catalytic system significantly improved reaction rate and substrate scope.\textsuperscript{117} This chemistry has since been applied to the synthesis of polymers\textsuperscript{118} and anthracenes.\textsuperscript{119}

Scheme 9. Okamoto’s alkyne cyclotrimerization using a low-cost cobalt complex.\textsuperscript{116}

**Rhodium Catalysis**

Rhodium-catalyzed alkyne cyclotrimerizations were pioneered by Muller,\textsuperscript{120} who used RhCl(PPh\textsubscript{3})\textsubscript{3} to form rhodacyclopentadienes from tethered diynes that formed substituted benzenes upon treatment with monoynes. In 1982 Griggs \textit{et al.}\textsuperscript{121} were the first to report the catalytic use of RhCl(PPh\textsubscript{3})\textsubscript{3} for cyclotrimerizations and since then it has been widely used in organic synthesis.\textsuperscript{105h} Recent examples of note include Sun’s alkyne cyclotrimerizations on a polymer support,\textsuperscript{122} Siegel’s synthesis of highly substituted fluoranthenes and indenocorannulenes\textsuperscript{123} and Ramana’s total synthesis of (–)-bruguierol A.\textsuperscript{124}

More recently cationic rhodium complexes have become popular catalysts for cyclotrimerizations.\textsuperscript{105h} Tanaka \textit{et al.}\textsuperscript{125} reported the first benzofuran synthesis \textit{via} an alkyne cyclotrimerization, using [Rh(cod):\textsubscript{2}]BF\textsubscript{4} in combination with H\textsubscript{8}-BINAP (Scheme 10). Although yields were generally reasonable it was limited by poor regioselectivity. It was also necessary to pre-activate the catalyst using hydrogen gas. Chiral cationic rhodium complexes have been widely used in the enantioselective synthesis of chiral aromatic compounds,\textsuperscript{105h} including axially chiral biaryls,\textsuperscript{126} \textit{P}-stereogenic alkynyl phosphine oxides\textsuperscript{127} and chiral aryl amides.\textsuperscript{128} Cationic rhodium catalysis has also been used in the synthesis of polyether cyclophanes and aryl boramides.\textsuperscript{129}
Chapter II

Scheme 10. Tanaka’s synthesis of benzofurans via rhodium-catalyzed alkyne cyclotrimerizations.\(^\text{125}\)

Iridium Catalysis

Kezuka et al.\(^\text{130}\) have established \([\text{Ir(cod)Cl}]_2/\text{DPPE}\) as a robust and efficient catalyst for tethered alkyne cyclotrimerizations. They reported the cyclizations of a broad range of monoynes with 1,6-diynes with good functional group tolerance. Most significantly, Kezuka reported reasonable regioselectivity for the reaction of a non-symmetrical diyne and a terminal monoyne, which could be reversed with the choice of ligand (Scheme 11). Iridium catalysis has been employed in a number of other alkyne cyclotrimerizations,\(^\text{131}\) which include Murakami’s synthesis of Silafluorenes\(^\text{132}\) and Shibata’s synthesis of axially chiral teraryl compounds.\(^\text{133}\)

Scheme 11. Kezuka’s ligand-controlled regioselective cyclotrimerization of a non-symmetrical diyne and a terminal monoyne.\(^\text{138}\)

Ruthenium Catalysis

Both Grubbs’ first generation catalyst\(^\text{134}\) and Hoveyda–Grubbs’ catalyst\(^\text{135}\) have been used to efficiently mediate alkyne cyclotrimerizations, albeit with limited substrate scope. Another ruthenium complex that can catalyze cyclotrimerizations is \(\text{RuCp}^*\text{Cl(cod)}\).\(^\text{136}\) Yamamoto and Itoh demonstrated the cyclization of a range of monoynes with different 1,6-diynes using \(\text{RuCp}^*\text{Cl(cod)}\) in DCE at RT (Scheme 12). Good regioselectivity was reported for the cycloaddition of terminal alkynes with non-symmetrical 1,6-diynes, especially when the diyne possessed a terminal trimethylsilyl substituent.
2.1.4. Synthesis of Isoindolinones via Alkyne Cyclotrimerizations

In 2004 Yamamoto et al. reported the first use of an amide tether for an alkyne cyclotrimerization to give an isoindolinone product (Scheme 13).\textsuperscript{137} The cyclization was effective with five different monoynes and it was additionally possible to introduce a methyl group at the propargylic position of the tether (i.e. $R^3 = \text{Me}$) without complication. The cycloaddition of amide-tethered diynes with ethyl cyanoformate and propyl isocyanate was later reported as a synthesis of pyridines and pyridones.\textsuperscript{136g}

Scheme 13. Synthesis of isoindolinones from amide-tethered diynes.\textsuperscript{137}

Yamamoto et al. demonstrated that a key challenge of using amide-tethered diynes for alkyne cyclotrimerization reactions was controlling the regioselectivity (Table 2).\textsuperscript{137} The authors observed that the cyclotrimerization of an amide-tethered diyne with $R^1 = \text{H}$ preferentially formed isoindolinone 229 over its regioisomer 229', in the ratio 2:1 (Entry 1). This regioselectivity was reinforced by a terminal methyl substituent $\beta$ to the carbonyl ($R^1 = \text{Me}$), with only isoindolinone 229 observed (Entry 2). Where the steric influence of a methyl substituent opposed the electronic influence of the amide ($R^1 = \text{H}$, $R^2 = \text{Me}$) the steric effect was dominant, with a product ratio 229:229' of 1:4 (Entry 3).
Table 2. Regioselectivity in the cyclotrimerization of amide-tethered diynes 227 and 1-hexyne 228.\textsuperscript{137}

\[
\begin{array}{ccccccc}
\text{Entry} & R^1 & R^2 & \text{RuCp*Cl(cod)/mol\%} & \text{Time/ h} & \text{Yield (229 and 229')/ \%} & 229:229' \\
1 & H & H & 1 & 0.5 & 76 & 2:1 \\
2 & Me & H & 1 & 0.5 & 81 & 229 only \\
3 & H & Me & 5 & 2 & 68 & 1:4 \\
\end{array}
\]

2.1.5. Mechanisms for RuCpCl(cod)-Catalyzed Alkyne Cyclotrimerizations

Alkyne cyclotrimerizations are believed to proceed via a number of distinct mechanisms, subject to the catalyst, ligands and substrate. One example that has been studied in detail with the aid of density functional calculations is the [RuCpCl]-catalyzed cyclotrimerization of acetylene (Scheme 14).\textsuperscript{136c, 138} The 1,5-cyclooctadiene (cod) ligand of RuCp(cod) is believed to be readily displaced by two molecules of acetylene. This gives intermediate complex 230a that can then undergo an oxidative cyclization to form ruthenacyclopentatriene 230b, in what is believed to be the rate determining step.\textsuperscript{138} X-ray crystal structures of analogous ruthenacycles have been acquired, and the C-C and Ru-C bond lengths are consistent with the aromatic biscarbene structure 230b, as opposed to its canonical structure 230b'.\textsuperscript{136b} Complex 230b is capable of coordinating with a third molecule of acetylene to form ruthenacyclopentadiene 230c. It has been calculated that complex 230c can isomerize to form ruthenabicyclo[3.2.0]heptatriene 230d with an activation energy of only 0.4 kJ mol\textsuperscript{-1}.\textsuperscript{136c} Intermediate 230d can then ring-open to form 7-membered ruthenacycle 230e, which on reductive elimination gives η\textsuperscript{2}-benzene complex 230f.\textsuperscript{138} Finally, displacement of benzene 230g and coordination of two new molecules of acetylene regenerates catalytically active complex 230a.
Scheme 14. Reaction mechanism for a [RuCpCl]-catalyzed alkyne cyclotrimerizations.\textsuperscript{136c, 138}

For the cyclization of non-symmetrical alkynes a question of regioselectivity may arise. Yamamoto \textit{et al.}\textsuperscript{137} reported the RuCp*Cl(cod)-catalyzed regioselective cyclization of an amide-tethered diyne and a monoyne (Scheme 15) and evaluated possible mechanistic pathways. They assumed that, mechanistically, [RuCp*Cl] would behave in a similar manner to [RuCpCl].

Scheme 15. Regioselective alkyne cyclotrimerization of amide-tethered diyne 231 and monoyne 232.\textsuperscript{137}

As previously discussed, the cod ligand of the RuCp*Cl(cod) precatalyst is readily displaced by two neutral electron donors, such as the alkyne units of the starting material (Scheme 16). The terminal alkyne of the diyne is a better ligand than the internal alkyne as it is sterically less hindered and it is not electronically deactivated by an adjacent carbonyl. Once the terminal alkyne reversibly coordinates to Ru, the internal alkyne can coordinate to the metal to form bidentate complex 234b. This can then undergo a
cyclization, which is presumed to be the rate determining step. In general, only the diyne will cyclize with the active catalyst to form ruthenacypentatetriene 234c as the amide tether holds the two alkynes in a reactive conformation, lowering the entropy of activation for the reaction.

Scheme 16. Formation of ruthenacycle 234c.

Once formed, the ruthenacypentatetriene 234c can undergo a [2+2]-addition with a third alkyne. If R² = H then the regioselectivity of this addition will be governed by electronic effects. Yamamoto et al.¹³⁷ used natural bond orbital calculations to determine natural charge for the ruthenacypentadiene 235 in Figure 7. A blue color indicates a decrease in the natural charge relative to an unsubstituted ruthenacycle while a red color indicates an increase. They demonstrated that the impact of the pyrrolidinone was to increase electron density of C-4 and decrease it at C-2. They proposed that an increase in charge at a carbon adjacent to the metal would accelerate the [2+2]-addition at that position, and this was consistent with experimental observation.

Figure 7. Pyrrolidinone ruthenacypentadiene 235 bearing calculated natural charges.¹³⁷

In cases where R² ≠ H, steric effects reinforce the electronic-based regioselectivity. If a [2+2]-addition occurs β to the carbonyl then the terminal alkyne substituent R² is forced above the plane of the pyrrolidinone (Scheme 17). This is sterically unfavorable as R² clashes with the bulky Cp* ligand. The alternative cycloaddition gives a sterically less
strained intermediate, such as complex 234e. Consequently, addition into the Ru=C bond that is distal to the R^3 substituent has a lower kinetic barrier.

Scheme 17. Selectivity for the addition of monoyne 232 to ruthenacyclopentatriene 234c.

Having established the metal-carbon bond over which the [2+2]-cycloaddition occurs, it is also necessary to consider the orientation in which the incoming alkyne reacts. As is shown in Scheme 18, the cycloaddition can occur to form either complex 234e or 234g. The steric clashing between the chloride ligand and R^3 means that formation of complex 234g is kinetically less favorable than the formation of its regioisomer 234e. Complex 234e isomerizes to form metallacycle 234f, which gives isoindolinone 233 upon elimination of the catalytic species.

Scheme 18. Regioselective addition of monoyne 232 to ruthenacyclopentatriene 234c.

2.1.6. Chapter II Project Outline

The aim of this part of the PhD was to develop a novel approach to highly-substituted isoindolinones based upon a regioselective alkyne cyclotrimerization (Scheme 19). This would allow for the rapid and convergent assembly of isoindolinone products from readily available alkyne precursors.
Scheme 19. Proposed synthetic route to highly-substituted isoindolinones.

It was identified that a key challenge of the above approach was controlling the regioselectivity of the cyclization.\(^{137}\) In order to address this, a trimethylsilyl group was selected as a potential regiodirecting group (Scheme 19).\(^{136a}\) Another important challenge to address was finding safe and sustainable reaction conditions for the alkyne cyclotrimerization. In particular, the DCE solvent used by Yamamoto et al. was something that had to be avoided.\(^{137}\) Having developed optimal cyclization conditions, it would then be necessary to prepare different isoindolinones, by exploring then substrate scope and manipulating the cyclization products. Finally, it would also be interesting to cleave the lactam of isoindolinone 240 to access monocyclic benzene derivatives. Such a “temporary tether” strategy has not been widely reported for [2+2+2]-cycloaddition reactions.\(^{113b, 136c, 136h}\)

2.2. Results and Discussion

2.2.1. Starting Material Synthesis

Initial efforts focused on the synthesis of amide-tethered diyne 245a via the coupling of carboxylic acid 242 and amine 244a (Scheme 20). Firstly, acid 242 was synthesized in 78% isolated yield by carboxylation of ethynyltrimethylsilane 241 according to the modified procedure of Fleming et al.\(^{139}\) Amine 244a was formed in 81% isolated yield from propargyl bromide, using 6.0 eq. of benzylamine, as previously reported by Burton and Hess.\(^{140}\) Using only 3.0 eq. of benzylamine resulted in a 48% yield of amine 244a due to significant over-alkylation. The coupling of carboxylic acid 242 and amine 244a in CH\(_2\)Cl\(_2\) via the corresponding acid chloride gave diyne 245a in 67% isolated yield. Substituting CH\(_2\)Cl\(_2\) with 2-MeTHF, a solvent noted for its sustainable properties,\(^{23}\) resulted in an improved 85% isolated yield of diyne 245a. Dyne 245a was found to be sensitive to desilylation on silica, so rapid purification by flash column chromatography was essential to attain a good yield.
Scheme 20. Starting material synthesis. Reagents and conditions: (i) EtMgBr, then CO$_2$(s); (ii) benzylamine; (iii) oxalyl chloride, DMF, 2-MeTHF then amine 244a, 2.5 eq. NEt$_3$, 2-MeTHF.

2.2.3. Preliminary Cyclizations

At the start of this study, the cyclotrimerization of diyne 245a with a selection of monoynes was briefly investigated. Following Yamamoto’s reported work on alkyne cyclotrimerizations, RuCp*Cl(cod) was chosen as a catalyst.$^{137}$ A significant disadvantage of Yamamoto’s cyclotrimerization protocol is the use of 1,2-dichloroethane (DCE) as solvent, which is potentially detrimental to human health and is generally avoided within industry. Consequently DCE was not used in the preliminary investigations and cyclopentyl methyl ether (CPME) was used as an alternative solvent because of its more environmentally sustainable properties.$^{23}$ The results of this study are summarized in Table 3.

Table 3. Synthesis of substituted isoindolinones using preliminary cyclization conditions.$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>R$^1$</th>
<th>Time/h</th>
<th>Isolated yield 247/$%$</th>
<th>Isolated yield 248/$%$</th>
<th>247:248$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$^a$Bu</td>
<td>0.5</td>
<td>61</td>
<td>16</td>
<td>2:1</td>
</tr>
<tr>
<td>2</td>
<td>$^t$Bu</td>
<td>0.5</td>
<td>22</td>
<td>43</td>
<td>1:3</td>
</tr>
<tr>
<td>3</td>
<td>4-MeC$_6$H$_4$</td>
<td>1.75</td>
<td>42</td>
<td>10</td>
<td>2:1</td>
</tr>
<tr>
<td>4</td>
<td>CH$_2$OMe</td>
<td>16</td>
<td>47</td>
<td>28</td>
<td>2:1</td>
</tr>
</tbody>
</table>

$^a$ A solution of 10 mol% RuCp*Cl(cod) and 4.0 eq. monoyne 246 in CPME was added dropwise over 15 minutes to a stirring solution of diyne 245a in CPME at RT. $^b$ As determined from $^a$H NMR spectrum of the crude product. $^c$ A co-spot prevented accurate determination of the reaction time by TLC.
Treating diyne \(245a\) with 4.0 eq. 1-hexyne \(246a\) and 10 mol% RuCp*Cl(cod) gave isoindolinone \(247a\), with complete conversion of diyne \(245a\) after 30 minutes (Table 3, Entry 1). The cyclization was highly regioselective, with no evidence of regioisomer \(249\) observed in the \(^1\)H NMR spectrum of the crude product. However, the \(^1\)H NMR spectrum of the crude product indicated the presence of a second isoindolinone \(248a\), formed from the homo-coupling of diyne \(245a\). Target isoindolinone \(247a\) was readily separated by flash column chromatography and was isolated in 61% yield. However, homo-coupled product \(248a\) underwent desilylation on silica gel to give isoindolinone \(248b\) in 16% yield.

Under the same conditions diyne \(245a\) readily cyclized with tert-butyl acetylene \(246b\) and 4-ethynyltoluene \(246c\) to give isoindolinones \(247b\) and \(247c\) respectively (Table 3, Entries 2 and 3). However, the cyclization with tert-butyl acetylene \(246b\) resulted in significant homo-coupling, with the desired isoindolinone \(247b\) isolated in only 22% yield. Methyl propargyl ether \(246d\) also cyclized with diyne \(245a\) (Entry 4), with isoindolinone \(247d\) isolated in 47% yield.

Isoindolinones \(247a, 247b\) and \(247d\) and homo-coupled isoindolinones \(248a\) and \(248b\) were found to decompose when dissolved in CDCl₃. These compounds were stable in DMSO, so from this point onwards DMSO-d₆ was used as a solvent for the acquisition of NMR data for all isoindolinone products.

### 2.2.4. Cyclization Optimization

The results of the preliminary cyclizations were promising, giving reasonable yields in a sustainable solvent under mild reaction conditions. In general the target isoindolinone was formed preferentially over the homo-coupled product. However, there was still significant room for improvement, especially in avoiding the high catalytic loading of RuCp*Cl(cod) and minimizing homo-coupling. To this end a range of reaction conditions were screened.

The reaction chosen to be optimized was the cyclotrimerization of amide-tethered diyne \(245a\) and 1-hexyne \(246a\) (Table 4). For the purpose of this optimization, all reactions were carried out over 16 h under an argon atmosphere and the unpurified product was analyzed by \(^1\)H NMR spectroscopy. For simplicity, the 15 minute dropwise addition of a solution of 1-hexyne \(246a\) and catalyst to a solution of diyne \(245a\) was avoided. Instead
a solution of diyne 245a was added dropwise to a stirring solution of monoyne 246a and catalyst over 1 minute (unless stated otherwise).

Table 4. Optimization of the cyclotrimerization of diyne 245a and monoyne 246a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Eq. 246a</th>
<th>Catalyst [loading/mol%]</th>
<th>Conversion 245a%</th>
<th>247a:248a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhMeb</td>
<td>4.0</td>
<td>Rh(PPh₃)₃Cl [10]</td>
<td>&lt;5</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>PhMeb</td>
<td>4.0</td>
<td>Co₂(CO)₈ [10]</td>
<td>&lt;5</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>DCEb</td>
<td>4.0</td>
<td>RuCp*Cl(cod) [1]</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>CH₂Cl₂b</td>
<td>4.0</td>
<td>Grubbs I [5]</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>neatc</td>
<td>4.0</td>
<td>RuCp*Cl(cod) [1]</td>
<td>50</td>
<td>3:2</td>
</tr>
<tr>
<td>6</td>
<td>neatc</td>
<td>4.0</td>
<td>RuCp*Cl(cod) [3]</td>
<td>100</td>
<td>3:1</td>
</tr>
<tr>
<td>7</td>
<td>CPME</td>
<td>4.0</td>
<td>RuCp*Cl(cod) [3]</td>
<td>100</td>
<td>5:1</td>
</tr>
<tr>
<td>8</td>
<td>CPME</td>
<td>4.0</td>
<td>RuCp*Cl(cod) [1]</td>
<td>60</td>
<td>4:1</td>
</tr>
<tr>
<td>9</td>
<td>CPME</td>
<td>2.0</td>
<td>RuCp*Cl(cod) [3]</td>
<td>100</td>
<td>2:1</td>
</tr>
<tr>
<td>10</td>
<td>CPME</td>
<td>4.0</td>
<td>RuCp*Cl(cod) [3]</td>
<td>100</td>
<td>8:1</td>
</tr>
<tr>
<td>11</td>
<td>CPME</td>
<td>2.0</td>
<td>RuCp*Cl(cod) [3]</td>
<td>100</td>
<td>9:1</td>
</tr>
<tr>
<td>12</td>
<td>CPME</td>
<td>1.1</td>
<td>RuCp*Cl(cod) [3]</td>
<td>100</td>
<td>2.5:1</td>
</tr>
<tr>
<td>13</td>
<td>MTBE</td>
<td>2.0</td>
<td>RuCp*Cl(cod) [3]</td>
<td>100</td>
<td>5:1</td>
</tr>
<tr>
<td>14</td>
<td>2-MeTHF</td>
<td>2.0</td>
<td>RuCp*Cl(cod) [3]</td>
<td>90</td>
<td>5:1</td>
</tr>
<tr>
<td>15</td>
<td>CPME/10% water</td>
<td>2.0</td>
<td>RuCp*Cl(cod) [3]</td>
<td>70</td>
<td>3:1</td>
</tr>
<tr>
<td>16</td>
<td>water/10% water</td>
<td>4.0</td>
<td>RuCp*Cl(cod) [3]</td>
<td>30</td>
<td>3:1</td>
</tr>
</tbody>
</table>

*a* Determined from the ¹H NMR spectrum of the crude product. *b* Solvent dried over activated 4 Å molecular sieves and degassed. *c* RuCp*Cl(cod) was added to the reaction mixture at 0 °C, which was then allowed to reach RT. *d* Diyne 245a in CPME was added dropwise over 3 h to a stirring solution of monoyne 246a and RuCp*Cl(cod).

Initially four different cyclotrimerization procedures reported in the literature were screened for the reaction of diyne 245a with 1-hexyne 246a (Table 4, Entries 1–4). Neither RhCl(PPh₃)₃¹⁴¹ nor Co₂(CO)₈¹⁴² were effective at catalyzing the reaction, with no measurable formation of isoindolinone 247a (Entries 1 and 2). Using 5 mol% of Grubbs’ I in anhydrous, degassed CH₂Cl₂ did generate the desired isoindolinone 247a, but with only 5% conversion of the diyne 245a (Entry 3).¹⁴³ Use of 1 mol% RuCp*Cl(cod) in anhydrous, degassed DCE also gave isoindolinone 247a, again with 5% conversion (Entry 4).¹³⁷

Given the poor conversion observed in Entry 4, alternatives to DCE as solvent were considered. When the reaction was conducted without any solvent a significant increase
in conversion of diyne 245a was observed (Table 4, Entry 5). With the higher conversion it was also possible to identify homo-coupled product 248a in the crude reaction mixture, with 247a and 248a formed in the ratio 3:2. Using 3 mol% of RuCp*Cl(cod) resulted in the complete consumption of diyne 245a within 16 h, with an improved selectivity for isoindolinone 247a over homo-coupled product 248a (Entry 6, 247a:248a = 5:1).

Using cyclopentyl methyl ether (CPME) as a solvent gave promising results in the preliminary cyclizations (Section 2.2.3.), so it was trialled as a solvent in the optimization study. As shown in Entries 7 and 8 of Table 4, the reaction proceeded in CPME and 3 mol% RuCp*Cl(cod) was sufficient to ensure 100% conversion of 245a within 16 h. In addition, the formation of homo-coupled product 248a was lower that was observed for the neat reactions. However, reducing the excess of monoyne 246a resulted in a significant increase in homo-coupling (Entry 9). It is important to note that, unlike previously reported methods for alkyne cyclotrimerizations, it was not necessary to dry or degas the solvent. This was important for both minimizing waste and improving the practicality of the reaction.

In an attempt to minimize formation of the homo-coupled product 248a, a 3 h dropwise addition of the diyne was considered. As shown in Entry 10 of Table 4, a 3 h dropwise addition resulted in reduced homo-coupling with no decrease in the conversion of diyne 245a. The 3 h addition also allowed the excess of monoyne 246a to be reduced from 4.0 eq. to 2.0 eq. with no increase in homo-coupling (Entry 11). As shown in Entry 12, using 1.1 eq. of monoyne 246a resulted in a significant increase in homo-coupling, but target isoindolinone 247a was still formed as the major product.

Alternative solvents to CPME were also considered. It was found that methyl tert-butyl ether (MTBE) and 2-MeTHF were both effective solvents for the cyclization (Table 4, Entries 13 and 14) but neither offered an improvement on CPME. The reaction was also found to be effective when CPME was used in combination with 10% water as a co-solvent (Entry 15), albeit with reduced conversion and increased homo-coupling. In fact, isoindolinone 247a was formed where water was exclusively used as solvent, with 30% conversion of diyne 245a (Entry 16). This is significant as it could enable the extension of the reaction to aqueous conditions for reactions involving water-soluble substrates.

The conditions described in Entry 11 of Table 4 were taken to be the optimized cyclization conditions, as they maximized conversion while minimizing catalyst loading.
and homo-coupling. However, before developing the reaction scope, two areas were investigated further. It was found that the reaction benefited from prolonged dropwise addition of diyne to a solution of monoyne and catalyst, but the effect of the addition time had not been fully explored. Secondly, all the experiments in Table 4 were conducted under an atmosphere of argon. If the reaction could be performed under an atmosphere of air with no detrimental outcome then this would allow for a more practical reaction. The results of the investigation are shown in Table 5.

Table 5. Further investigation of the cyclotrimerization of diyne 245a and 1-hexyne 246a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Addition time/h</th>
<th>Conversion 245a(^b)/%</th>
<th>247a:248a(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>100</td>
<td>10:1</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>100</td>
<td>9:1</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>100</td>
<td>4:1</td>
</tr>
<tr>
<td>4(^c)</td>
<td>3</td>
<td>80</td>
<td>3:1</td>
</tr>
<tr>
<td>5(^c)</td>
<td>1</td>
<td>100</td>
<td>4:1</td>
</tr>
</tbody>
</table>

\(^a\) Diyne 245a in CPME was added dropwise over the designated time period to a stirring solution of 2.0 eq. 1-hexyne 246a and 3 mol% RuCp*Cl(cod) in CPME. The reaction was stirred for a total of 16 h. \(^b\) Determined from the \(^1\)H NMR spectrum of the crude product. \(^c\) The reaction was conducted under air rather than argon.

As shown in Entries 1 and 2 of Table 5, adding a solution of the diyne dropwise to a solution of monoyne and catalyst over 6 h rather than 3 h did not significantly reduce formation of diyne homo-coupling product 248a. However, a shorter addition time resulted in increased diyne homo-coupling (Entry 3). This suggested that a 3 h dropwise addition was optimal.

Conducting the reaction with a 3 h dropwise addition under an atmosphere of air resulted in both reduced conversion of diyne 245a and an increase in diyne homo-coupling (Table 5, Entries 4 and 2). However, when the reaction was conducted under air using a 1 h dropwise addition the result was analogous to the corresponding reaction under argon (Entries 5 and 3). This suggested that the reaction was only sensitive to oxygen when the reaction was prolonged by a long (>1 h) dropwise addition.

The optimized reaction conditions are given below. These reaction conditions were used to convert diyne 245a (70 mg) and 1-hexyne 246a into isoindolinone 247a with an 81%
isolated yield (Scheme 21). This represented a significant improvement in terms of isolated yield compared to the preliminary cyclization conditions. In addition, both catalytic loading and the excess of monoyne had been reduced. Importantly the reaction was highly regioselective; regioisomer 249a was not observed at any point in this study. This reaction was also scaled up to use 500 mg of 245a and isoindolinone 247a was isolated in 66% yield.

A solution of diyne in CPME was added dropwise over 3 h to a stirring solution of 2.0 eq. monoyne and 3 mol% RuCp*Cl(cod) in CPME at RT under an atmosphere of argon. The reaction was stirred at RT for a total of 16 h. CPME was used without degassing or drying.

Scheme 21. Optimized cyclization of diyne 245a and 1-hexyne 246a.

To confirm that the trimethylsilyl group was responsible for controlling the regioselectivity of the alkyne cyclotrimerization rather than the reaction conditions, diyne 250 was treated with 1-hexyne 246a and RuCp*Cl(cod) under the optimized conditions described. As shown in Scheme 22, the regioselectivity of this cyclization was poor. This suggested that, as expected, the trimethylsilyl group of diyne 245a was acting as an effective regiodirecting group. The regioselectivity of this cyclization was comparable with the regioselectivity of the same reaction reported under Yamamoto’s conditions (Section 2.1.4., Table 2, Entry 1).137

Scheme 22. Cyclization of diyne 250 and 1-hexyne 246a under optimized conditions. Reagents and conditions: (i) K₂CO₃, MeOH; (ii) 3 mol% RuCp*Cl(cod), CPME, 16 h, RT.
2.2.5. Monoyne Scope

Having established optimized reaction conditions for the cyclotrimerization of amide-tethered diyne 245a with 1-hexyne 246a it was then important to explore the general applicability of the reaction by considering different monoynes.

Monoyne Synthesis

While the majority of the monoynes used in this section were sourced commercially, three monoynes were prepared in the laboratory (Scheme 23). Benzoate alkyne 246e was synthesized in 92% isolated yield over two steps via a Sonogashira coupling of aryl iodide 252 with ethynyltrimethylsilane, followed by desilylation and transesterification using K₂CO₃ in MeOH.¹⁴⁴ Carbamate 246f was prepared from propargylamine 254 and Boc₂O in 93% isolated yield.¹⁴⁵ Alkynyl boramide 246h was prepared over three steps from diol 255. Disilyl ether 256 was prepared from diol 255,¹⁴⁶ which was then treated with potassium ethynyl trifluoroborate 257 and Me₃SiCl to give aryl borate ester 258. The crude aryl borate ester 258 was then treated with naphthalene-1,8-diamine to yield boramide 246g, which was purified by flash column chromatography without special precautions.

Scheme 23. Monoyne synthesis. Reagents and conditions: (i) Pd(PPh₃)₄Cl₂, CuI, NEt₃, Me₃SiC≡CH; (ii) K₂CO₃, MeOH; (iii) (Boc)₂O; (iv) NH(SiMe₃)₂, Me₃SiCl; (v) Me₃SiCl; (vi) naphthalene-1,8-diamine.

Cyclizations with Different Monoynes

For the purpose of this study a series of monoynes were treated with N-Bn diyne 245a using the optimized reaction conditions (Scheme 24). Reactions that did not reach completion within 16 h were left for a total of 24 h. If this failed to result in 100% conversion of diyne 245a then catalyst loading was increased.
Scheme 24. Cyclization of diyne 245a with a selection of monoynes.

**Aliphatic Monoynes**

All the aliphatic monoynes explored in Table 6 cyclized with amide-tethered diyne 245a to give the corresponding isoindolinones 247 in 65–83% isolated yield without modification of the optimized reaction conditions. All five reactions were conducted in duplicate to demonstrate the reproducibility of the reaction. All of these cyclizations occurred with a low level of homo-coupling, except for the reaction to form isoindolinone 247b from tert-butylacetylene, where 247b:248a = 2:1 (Entries 3 and 4).

Table 6. Cyclization of diyne 245a with aliphatic monoynes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Time/ h</th>
<th>[Ru]/mol %</th>
<th>Conversion of 245a/%</th>
<th>Isolated yield 247/%</th>
<th>247: 248a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&quot;Bu</td>
<td>16</td>
<td>3</td>
<td>247a</td>
<td>100</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>&quot;Bu</td>
<td>16</td>
<td>3</td>
<td>247a</td>
<td>100</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>tBu</td>
<td>16</td>
<td>3</td>
<td>247b</td>
<td>100</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>tBu</td>
<td>16</td>
<td>3</td>
<td>247b</td>
<td>100</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>cPr</td>
<td>16</td>
<td>3</td>
<td>247h</td>
<td>100</td>
<td>78</td>
</tr>
<tr>
<td>6</td>
<td>cPr</td>
<td>16</td>
<td>3</td>
<td>247h</td>
<td>100</td>
<td>81</td>
</tr>
<tr>
<td>7</td>
<td>CH₂CH₂CH₂Cl</td>
<td>16</td>
<td>3</td>
<td>247i</td>
<td>100</td>
<td>83</td>
</tr>
<tr>
<td>8</td>
<td>CH₂CH₂CH₂Cl</td>
<td>16</td>
<td>3</td>
<td>247i</td>
<td>100</td>
<td>81</td>
</tr>
<tr>
<td>9</td>
<td>CH(CH₂CH₂)₂</td>
<td>16</td>
<td>3</td>
<td>247j</td>
<td>100</td>
<td>80</td>
</tr>
<tr>
<td>10</td>
<td>CH(CH₂CH₂)₂</td>
<td>16</td>
<td>3</td>
<td>247j</td>
<td>100</td>
<td>81</td>
</tr>
</tbody>
</table>

\[a\] Reagents and conditions: RuCp*Cl(cod), CPME, RT. The yields quoted with the structures are averaged over two experiments. \[b\] Determined from the \(^1\)H NMR spectrum of the crude product by the integration of peaks relating to compounds 245a, 247 and 248a.

**Aromatic Monoynes**

The reaction of a diyne 245a with a series of substituted phenyl acetylenes was explored, with the results summarized in Table 7. The reaction of diyne 245a with phenylacetylene
(Table 7, Entries 1–3) was slower than the corresponding reaction with 1-hexyne (Table 6, Entries 1 and 2) and the reaction required 4 mol% RuCp*Cl(cod) and 24 h to reach completion. Following this isoindolinone 247k was isolated in 83% yield (Table 7, Entry 3). In contrast, the reaction of diyne 245a with 2-tolylacetylene required only 3 mol% RuCp*Cl(cod) to reach completion within 16 h (Entries 4 and 5) The corresponding isoindolinone 247l was isolated in 93% yield, with negligible diyne homo-coupling observed in the crude $^1$H NMR spectrum. It is notable that 4-tolylacetylene behaved like phenylacetylene (Entries 6–8); 4 mol% RuCp*Cl(cod) and a 24 h reaction time resulted in 100% conversion of diyne 245a and a 83% isolated yield of 257n.
Table 7. Cyclization of diyne 245a with aromatic monoynes. a

![Diagram of cyclization reaction]

Entries | R | Time/ h | [Ru]/ mol % | Conversion 247 | Conversion 245a/% b | Isolated yield 247/

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th>247</th>
<th>245a (%)</th>
<th>248a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>16</td>
<td>3</td>
<td>247k</td>
<td>90</td>
<td>n.d.</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>24</td>
<td>3</td>
<td>247k</td>
<td>80</td>
<td>n.d.</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>24</td>
<td>4</td>
<td>247k</td>
<td>100</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>2-MeC₆H₄</td>
<td>16</td>
<td>3</td>
<td>247l</td>
<td>100</td>
<td>n.d.</td>
</tr>
<tr>
<td>5</td>
<td>2-MeC₆H₄</td>
<td>16</td>
<td>3</td>
<td>247l</td>
<td>100</td>
<td>93</td>
</tr>
<tr>
<td>6</td>
<td>4-MeC₆H₄</td>
<td>16</td>
<td>3</td>
<td>247c</td>
<td>80</td>
<td>n.d.</td>
</tr>
<tr>
<td>7</td>
<td>4-MeC₆H₄</td>
<td>24</td>
<td>3</td>
<td>247c</td>
<td>90</td>
<td>79</td>
</tr>
<tr>
<td>8</td>
<td>4-MeC₆H₄</td>
<td>24</td>
<td>4</td>
<td>247c</td>
<td>100</td>
<td>81</td>
</tr>
<tr>
<td>9</td>
<td>2-BrC₆H₄</td>
<td>16</td>
<td>3</td>
<td>247m</td>
<td>100</td>
<td>n.d.</td>
</tr>
<tr>
<td>10</td>
<td>2-BrC₆H₄</td>
<td>16</td>
<td>3</td>
<td>247m</td>
<td>100</td>
<td>80</td>
</tr>
<tr>
<td>11</td>
<td>4-BrC₆H₄</td>
<td>24</td>
<td>3</td>
<td>247n</td>
<td>100</td>
<td>83</td>
</tr>
<tr>
<td>12</td>
<td>4-BrC₆H₄</td>
<td>24</td>
<td>3</td>
<td>247n</td>
<td>100</td>
<td>78</td>
</tr>
<tr>
<td>13</td>
<td>4-(MeO₂C)C₆H₄</td>
<td>24</td>
<td>3</td>
<td>247e</td>
<td>100</td>
<td>79</td>
</tr>
<tr>
<td>14</td>
<td>4-(MeO)C₆H₄</td>
<td>24</td>
<td>4</td>
<td>247o</td>
<td>90</td>
<td>n.d.</td>
</tr>
<tr>
<td>15</td>
<td>4-(MeO)C₆H₄</td>
<td>24</td>
<td>5</td>
<td>247o</td>
<td>100</td>
<td>79</td>
</tr>
<tr>
<td>16</td>
<td>4-(Me₂N)C₆H₄</td>
<td>24</td>
<td>6</td>
<td>247p</td>
<td>80</td>
<td>n.d.</td>
</tr>
<tr>
<td>17</td>
<td>4-(Me₂N)C₆H₄</td>
<td>24</td>
<td>10</td>
<td>247p</td>
<td>90</td>
<td>79</td>
</tr>
</tbody>
</table>

a Reagents and conditions: RuCp*Cl(cod), CPME, RT. b Determined from the ¹H NMR spectrum of the crude product by the integration of peaks relating to compounds 245a, 247 and 248a.

The reaction of diyne 245a with 2-bromo and 4-bromophenylacetylene proceeded efficiently using 3 mol% RuCp*Cl(cod) to give isoindolinones 247m and 247n in 80% and 83% isolated yield respectively (Table 7, Entries 9–12). Using 4-(methoxycarbonyl)phenylacetylene as the monoyne similarly gave the desired isoindolinone 247e in 79% isolated yield, again with only 3 mol% of the catalyst required (Entry 13). The reaction of diyne 245a with 4-methoxyphenylacetylene required a higher
catalyst loading to reach completion (5 mol% RuCp*Cl(cod)), with isoindolinone \(247o\) isolated in 79% yield (Entries 14 and 15). The reaction of 4-(dimethylamino) phenylacetylene with diyne \(245a\) required a higher catalyst loading to achieve reasonable conversion of diyne \(245a\) (Entries 16 and 17). Using 10 mol% RuCp*Cl(cod) resulted in 90% conversion of diyne \(245a\), with isoindolinone \(247p\) isolated in 79% yield.

**Other Monoynes of Interest**

Ether \(247d\) and acetal \(247q\) were formed using 3 mol% RuCp*Cl(cod), but in low isolated yields (56% and 43% respectively) owing to significant diyne homo-coupling (Table 8, Entries 1–4). The methodology was extended to form aryl boramide \(247g\) using 5 mol% RuCp*Cl(cod) in 55% isolated yield (Entries 5 and 6). Gandon et al.\textsuperscript{129b} have reported that aryl boramides can be transformed to the analogous aryl boronic acid under strong acidic conditions, which can then be used for cross coupling. The reaction to form isoindolinone \(247e\) occurred with relatively high homo-coupling of diyne \(245a\), but isoindolinone \(247e\) was isolated in 63% yield (Entries 7 and 8). The corresponding reaction of 2-ethynylpyridine \(246r\) was comparatively slow and required 20 mol% RuCp*Cl(cod) to achieve 80% conversion of diyne \(245a\) (Entries 9–11). The reaction also occurred with significant diyne homo-coupling and isoindolinone \(247r\) was isolated in 50% yield.
Table 8. Cyclization of diyne 245a with other monoynes of interest.

![Diagram showing cyclization of diyne 245a with various monoynes](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Time/h</th>
<th>[Ru]/mol %</th>
<th>247</th>
<th>Conversion of 245a/%</th>
<th>Yield 247:248a%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂OMe</td>
<td>16</td>
<td>3</td>
<td>247d</td>
<td>100</td>
<td>56:3:2</td>
</tr>
<tr>
<td>2</td>
<td>CH₂OMe</td>
<td>16</td>
<td>3</td>
<td>247d</td>
<td>100</td>
<td>n.d.:3:2</td>
</tr>
<tr>
<td>3</td>
<td>CH(OEt)₂</td>
<td>16</td>
<td>3</td>
<td>247q</td>
<td>90</td>
<td>29:0.7:1</td>
</tr>
<tr>
<td>4</td>
<td>CH(OEt)₂</td>
<td>24</td>
<td>3</td>
<td>247q</td>
<td>100</td>
<td>43:0.8:1</td>
</tr>
<tr>
<td>5</td>
<td>B(C₁₀H₈N₂)</td>
<td>16</td>
<td>3</td>
<td>247g</td>
<td>70</td>
<td>n.d.:3:1</td>
</tr>
<tr>
<td>6</td>
<td>B(C₁₀H₈N₂)</td>
<td>24</td>
<td>5</td>
<td>247g</td>
<td>100</td>
<td>56:3:1</td>
</tr>
<tr>
<td>7</td>
<td>CH₂NHBoc</td>
<td>16</td>
<td>3</td>
<td>247f</td>
<td>80</td>
<td>n.d.:3:1</td>
</tr>
<tr>
<td>8</td>
<td>CH₂NHBoc</td>
<td>24</td>
<td>5</td>
<td>247f</td>
<td>100</td>
<td>63:2:1</td>
</tr>
<tr>
<td>9</td>
<td>pyridin-2-yl</td>
<td>24</td>
<td>3</td>
<td>247r</td>
<td>15</td>
<td>n.d.:3:2</td>
</tr>
<tr>
<td>10</td>
<td>pyridin-2-yl</td>
<td>24</td>
<td>10</td>
<td>247r</td>
<td>60</td>
<td>n.d.:3:2</td>
</tr>
<tr>
<td>11</td>
<td>pyridin-2-yl</td>
<td>24</td>
<td>20</td>
<td>247r</td>
<td>80</td>
<td>50:2:1</td>
</tr>
</tbody>
</table>

*Reagents and conditions: RuCp*Cl(cod), CPME, RT. b Determined from the ¹H NMR spectrum of the crude product by the integration of peaks relating to compounds 245a, 247 and 248a.

It is important to note that for all of the cyclizations in this section (Table 6, Table 7 and Table 8) that the target isoindolinone was formed with excellent regioselectivity (Scheme 25). Regioisomer 249 was not observed in the crude ¹H NMR spectra of any reaction in the above study. This suggested that the trimethylsilyl directing group of diyne 245a could effectively control regioselectivity for the reaction of 245a with a wide variety of monoynes under the optimized conditions.
Scheme 25. Highly regioselective cyclizations.

Failed Cyclizations

The monoynes depicted in Scheme 26 failed to cyclize with diyne 245a under the optimized reaction conditions to form an isoindolinone product. No reaction was observed when alkynes 246s and 246t were subjected to the cyclization conditions. The fact that not even homo-coupling was observed suggested that in both cases the monoyne deactivated the catalyst. The addition of propargyl alcohol 246u to a solution of RuCp*Cl(cod) resulted in the formation of a precipitate and again no cyclization occurred. Treating diyne 245a with benzonitrile 246v only resulted in the limited diyne homo-coupling. Diyne 245a was also treated with internal iodoalkyne 246w but again the only observed reaction was the homo-coupling of diyne 245a.

Scheme 26. Monoynes that failed to cyclize with diyne 245a under the optimized cyclization conditions.

2.2.6. Diyne Scope

In addition to demonstrating reaction scope with respect to monoyne, it was important to demonstrate the versatility of the reaction with different amide-tethered diynes (Scheme 27). The reaction was explored using a variety of amide-tethered diynes with different substituents at the N-position (R₁) and different alkynyl substituents (R² and R³).
Scheme 27. Probing the diyne scope of the optimized reaction.

**Diyne Synthesis**

In order to synthesize a range of new diyenes it was necessary to make four different propargylic amines (**Scheme 28**). The general approach to synthesize this group of compounds was to treat the corresponding primary amine with a propargyl halide. Amines \(244c\) and \(244d\) were both isolated in low yields following vacuum distillation. Amines \(244e\) and \(244f\) were isolated in 62% and 71% yields respectively following purification by flash column chromatography.

![Scheme 28. Amine synthesis. Reagents and conditions: (i) propargyl bromide; (ii) propargyl chloride; (iii) benzylamine.](image)

With the propargylic amines in hand, five amide-tethered diyenes were prepared in 66–83% isolated yield using the coupling procedure developed for \(N\)-Bn diyne \(245a\) (**Scheme 29**). This method was unsuited to the synthesis of diyne \(245g\), with little formation of the desired product. However, diyne \(245g\) was prepared in 71% isolated yield using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) as coupling reagent.
Scheme 29. Diyne synthesis. Reagents and conditions: (i) oxalyl chloride, DMF, 2-MeTHF then amine 244, NEt₃, 2-MeTHF; (ii) BnHNCH₂C≡CH 244a, EDC, DMAP, CH₂Cl₂.

In addition to the amide-tethered diynes above, N-Boc diyne 245h was identified as an interesting substrate for an alkyne cyclotrimerization. However, three different strategies failed to yield N-Boc diyne 245b (Scheme 30). Conversion of carboxylic acid 241 to the corresponding acid chloride followed by treatment with carbamate 246f failed to yield the desired diyne. N-H diyne 245b proved to be unstable in the presence of Boc₂O and DMAP in MeCN, with neither starting material nor product recovered from the reaction. Similarly, treating diyne 245b with Boc₂O and NEt₃ in CH₂Cl₂ was unsuccessful.

Scheme 30. Failed attempts at the synthesis of N-Boc diyne 245b. Reagents and conditions: (i) oxalyl chloride, DMF, 2-MeTHF then carbamate 246f, NEt₃, 2-MeTHF; (ii) (Boc)₂O, DMAP, MeCN; (iii) (Boc)₂O, NEt₃, CH₂Cl₂.

Cyclizations Involving Different N-Substitution of the Diyne

N-H Diyne

Under the optimized reaction conditions N-H diyne 245b cyclized with 1-hexyne 246a to form N-H isoindolinone 264a, but with only 50% conversion of diyne 245b and significant formation of homo-coupled product 265 (Table 9, Entry 1). A longer reaction time increased the conversion of 245b; but the reaction only reached 75% conversion after 5 days (Entry 2). Increasing the reaction temperature to 50 °C had no impact on either the conversion of 245b or the level of homo-coupling (Entry 3). The most effective method for maximizing conversion and selectivity was to use 10 mol% RuCp*Cl(cod) and a 24 h reaction time, which gave a 51% isolated yield of isoindolinone 264a (Entry 4). Under the same conditions 2-ethynyltoluene cyclized with N-H diyne 245b with a 62% isolated yield of isoindolinone 254b and 90% conversion of diyne 245b (Entry 5).
Table 9. Cyclization of N-H diyne 245b with monoynes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>[Ru]/mol%</th>
<th>Time</th>
<th>264</th>
<th>Conversion 245b/%</th>
<th>Isolated yield 264/%</th>
<th>264:265&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&quot;Bu</td>
<td>3</td>
<td>16 h</td>
<td>264a</td>
<td>50</td>
<td>-</td>
<td>3:2</td>
</tr>
<tr>
<td>2</td>
<td>&quot;Bu</td>
<td>3</td>
<td>5 days</td>
<td>264a</td>
<td>75</td>
<td>-</td>
<td>3:2</td>
</tr>
<tr>
<td>3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&quot;Bu</td>
<td>3</td>
<td>16 h</td>
<td>264a</td>
<td>50</td>
<td>-</td>
<td>3:2</td>
</tr>
<tr>
<td>4</td>
<td>&quot;Bu</td>
<td>10</td>
<td>24 h</td>
<td>264a</td>
<td>90</td>
<td>51</td>
<td>2:1</td>
</tr>
<tr>
<td>5</td>
<td>2-MeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>10</td>
<td>24 h</td>
<td>264b</td>
<td>90</td>
<td>62</td>
<td>7:1</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined from the <sup>1</sup>H NMR spectrum of the crude product. <sup>b</sup> Reaction conducted at 50 °C.

The observation that N-H diyne 245b was slower to cyclize with 1-hexyne that N-Bn diyne 245a was expected when the mechanism was considered (Scheme 31). The mechanism for RuCp*Cl(cod)-catalyzed alkyne cyclotrimerizations is believed to proceed through a bidentate complex of the diyne with RuCp*Cl (complex 266c). This is formed from monodentate complex 266b, where the two alkyne units are syn with respect to the amide bond. This, however, will be the minor rotamer in solution. It is sterically more favorable for the diyne to exist in an anti-conformation (complex 266a), where the propargyl group is pointing away from the internal alkyne, and this would retard the cyclization. N-Bn diyne 245a would also exist in an analogous rotamic equilibrium when in solution, but the sterically bulky benzyl substituent can shift the equilibrium further in favor of the reactive syn-conformation.

Scheme 31. Equilibrium between rotameric intermediates.

**N-"Bu Diyne**

The N-"Bu diyne 245c cyclized with 1-hexyne 246a under the optimized reaction conditions to give isoindolinone 267a in 84% yield and with little formation of homo-coupled product 268 (Table 10, Entry 1). The reaction of diyne 245c with
phenylacetylene was slower, requiring 24 h and 4 mol% RuCp*Cl(cod) to reach completion (Entry 2). However, isoindolinone 267b was formed in 89% yield and with almost no homo-coupled product 268. Finally, 2-ethynyltoluene also cyclized with diyne 245c to give isoindolinone 267c in 94% yield and very little homo-coupling was observed (Entry 3).

Table 10. Cyclization of N-tBu diyne 245c with monynes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>[Ru]/ mol%</th>
<th>Time/ h</th>
<th>267</th>
<th>Isolated yield 267/%</th>
<th>267:268&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-Bu</td>
<td>3</td>
<td>16</td>
<td>267a</td>
<td>84</td>
<td>10:1</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>4</td>
<td>24</td>
<td>267b</td>
<td>89</td>
<td>&gt;10:1</td>
</tr>
<tr>
<td>3</td>
<td>2-MeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>3</td>
<td>16</td>
<td>267c</td>
<td>94</td>
<td>&gt;10:1</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined from the <sup>1</sup>H NMR spectrum of the crude product.

**N-Allyl Diyne**

Subjecting N-allyl diyne 245d to the optimized reaction conditions with 1-hexyne 246a resulted in no reaction and the recovery of starting material (Scheme 32). Cyclization was also not observed when the reaction was conducted at 100 °C in a sealed tube with but-3-yn-1-ylbenzene 270 (chosen for its high boiling point).

Scheme 32. Failed cyclizations involving N-allyl diyne 245d. Reagents and conditions: 3 mol% RuCp*Cl(cod), CPME.

A possible conclusion from the failure to cyclize N-allyl diyne 245d is that the optimized reaction conditions are ineffective in the presence of a terminal alkene. To test this hypothesis, N-Bn diyne 245a was treated with 1-hexyne 246a under the optimized
conditions in the presence of 2.0 eq. of 1-hexene (Scheme 33). The alkene had no significant impact on the reaction, with only a slight drop in conversion after 16 h. This suggested that the optimized reaction conditions could tolerate the presence of alkenes in general and that a more subtle effect was hampering the reaction of diyne 245d with monoynes.

![Scheme 33](image)

Scheme 33. Reaction of diyne 245a and 1-hexyne 246a in the presence of 1-hexene. Reagents and conditions: 3 mol% RuCp*Cl(cod), CPME, 16 h, RT.

A potential explanation is depicted in Scheme 34. The key step in the cyclization of N-allyl diyne 245d would be the oxidative cyclization of bidentate complex 272. However, it is possible that the Ru centre complexes preferentially with the pendent alkene rather than the internal alkyne to form complex 272'. If the catalytic species remained in this unreactive complex 272' then no reaction could proceed.

![Scheme 34](image)

Scheme 34. Hypothetical complexation between the catalytic species and N-allyl diyne 245d.

Cyclizations Involving Different Alkyne-Substitution of the Diynes

A key strength of this methodology is its regioselectivity; minor regioisomer 274 was not observed in any cyclotrimerization reported to this point. To expand the reaction scope further and probe the question of regioselectivity a number of other cyclizations were examined (Scheme 35). Firstly, an extra substituent R¹ was incorporated into the diyne, weakening the diyne’s regiochemical bias. Secondly, a diyne where the regiodirecting group R³ was not SiMe₃ was examined, to see whether the high regioselectivity was maintained.
Scheme 35. Investigating the regioselectivity of alkyne cyclotrimerizations.

**Internal Diynes**

Preliminary cyclizations of diynes 245e and 245f with 1-hexyne 246a indicated that 10 mol% was a suitable level of catalyst loading to ensure complete conversion of the diyne within 24 h. They also showed that the internal diynes were not susceptible to homo-coupling. For this reason, the 3 h dropwise addition of diyne to monoyne and catalyst was omitted for simplicity. Four cyclizations were conducted and the results are given in **Table 11**.

**Table 11. Cyclization involving internal diynes.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diyne</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Isolated products</th>
<th>Yield (273 + 274)%&lt;sup&gt;b&lt;/sup&gt;</th>
<th>273:274&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>245e</td>
<td>Me</td>
<td>2-MeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>273/274a&lt;sup&gt;c&lt;/sup&gt;</td>
<td>69&lt;sup&gt;c&lt;/sup&gt;</td>
<td>9:1</td>
</tr>
<tr>
<td>2</td>
<td>245e</td>
<td>Me</td>
<td>2-MeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>273b</td>
<td>88&lt;sup&gt;d&lt;/sup&gt;</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>3</td>
<td>245f</td>
<td>Et</td>
<td>2-MeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>273c/274c&lt;sup&gt;c&lt;/sup&gt;</td>
<td>57&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2:1</td>
</tr>
<tr>
<td>4</td>
<td>245f</td>
<td>Et</td>
<td>2-MeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>273d/274d&lt;sup&gt;c&lt;/sup&gt;</td>
<td>73&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5:1</td>
</tr>
</tbody>
</table>

<sup>a</sup> A solution of diyne 245 in CPME was added to a stirring solution of 2.0 eq. monoyne 246 and 10 mol% RuCp*Cl(cod) in CPME over 1 minute. The reaction was stirred at RT for 24 h. Determined from the <sup>1</sup>H NMR spectrum of the crude product.  
<sup>b</sup> Isolated yield  
<sup>c</sup> Estimated from the <sup>1</sup>H NMR spectrum of the crude product by integration of peaks corresponding to isoindolinone 245e and those of impurities.

The cyclization of methyl-substituted diyne 245e with 1-hexyne 246a gave a 9:1 mixture of regioisomers 273a and 274a in 69% combined isolated yield (**Table 11**, Entry 1). The reaction of diyne 245e and 2-ethynyltoluene 246l was more regioselective, with no evidence of isoindolinone 274b in the crude <sup>1</sup>H NMR spectrum (Entry 2). Unfortunately, it was not possible to purify isoindolinone 273b as it was sensitive to degradation on silica gel to give an unidentified mixture of impurities. Ethyl-substituted diyne 245f also cyclized with 1-hexyne 246a and 2-ethynyltoluene 246l, but with reduced regioselectivity in both instances (Entries 3 and 4).
A Diyne with a Methyl Regiomedirecting Group

Using the optimized reaction condition for the cyclization of diyne 245g and 1-hexyne 246a gave isoindolinone 273e in 85% yield as a single regioisomer (Table 12, Entry 1). Evidence of limited homo-coupling of 245g was observed in the ¹H NMR spectrum of the crude product but these impurities were not isolated. Reducing the loading of RuCp*Cl(cod) to 1 mol% resulted in a lower conversion of diyne 245g (Entry 2). Diyne 245g also cyclized efficiently with 2-ethynyltoluene 246l to give isoindolinone 273f as the only product (Entry 3).

Table 12. Cyclization involving diyne 245g.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>[Ru]/*/mol%</th>
<th>Time/h</th>
<th>Isolated product</th>
<th>Conversion 245g/*%</th>
<th>Isolate yield 273/*%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>²Bu</td>
<td>3</td>
<td>16</td>
<td>273e</td>
<td>100</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>²Bu</td>
<td>1</td>
<td>16</td>
<td>273e</td>
<td>40</td>
<td>27</td>
</tr>
<tr>
<td>3</td>
<td>2-MeC₆H₄</td>
<td>3</td>
<td>16</td>
<td>273f</td>
<td>100</td>
<td>94</td>
</tr>
</tbody>
</table>

* A solution of diyne 245g in CPME was added to a stirring solution of 2.0 eq. monoyne 246 and RuCp*Cl(cod) in CPME over 3 h. The reaction was stirred at RT for 16 h. Determined from the ¹H NMR spectrum of the crude product.

2.2.7. Functional Group Manipulation of Cyclized Products

Transformation of the 2- and 7-Position.

In order to demonstrate the potential use of the developed methodology, functional group manipulation of the cyclotrimerization products was investigated to access novel isoindolinone products. Treatment of isoindolinone 247a with ICl or Br₂ in CH₂Cl₂ led to aryl iodide 275 and aryl bromide 276 respectively in good yields (Scheme 36). Replacing the CH₂Cl₂ solvent for the iodination of isoindolinone 247a with environmentally more benign 2-MeTHF resulted in no reaction. Treatment of N-²Bu isoindolinone 267a with TfOH resulted in a simultaneous deprotection of the lactam and protodesilylation within 30 minutes to give N-H isoindolinone 277 in 88% isolated yield. It was not possible to substitute TfOH with TFA; heating 267a in neat TFA at reflux for 48 h resulted in a complex mixture of products with no evidence of an N-H isoindolinone product by ¹H NMR spectroscopy. Treatment of 267a with ICl followed by deprotection with TfOH gave 7-iodo isoindolinone 278 in 84% isolated yield over two
steps. Thus, an N-Bu diyne can be used as an indirect method for the synthesis of N-H isoindolinones via this acid-mediated deprotection strategy.

A useful transformation for the N-Bn isoindolinone products would be their deprotection to make the corresponding N-H isoindolinones. Benzyl deprotection of amides is often carried out via a dissolving metal reduction, but such a reaction is unlikely to be selective for the benzyl aromatic ring. Hydrogenation was considered to be more amenable towards the isoindolinone core, but unfortunately resulted in no reaction (Scheme 37).\textsuperscript{152} Hydrogenation under elevated pressure may be more effective.

In 2005 Zhao and Snieckus reported a one-pot procedure for the ipso-borodesilylation of aryl silanes followed by a Suzuki-Miyaura cross-coupling with aryl halides to access biaryl products.\textsuperscript{153} Unfortunately, the application of their protocol to isoindolinone 247a did not result in any reaction (Scheme 38).

---

**Scheme 36. Functional group manipulation of isoindolinones 247a and 267a.** Reagents and conditions: (i) ICl, CH\textsubscript{2}Cl\textsubscript{2}; (ii) Br\textsubscript{2}, CH\textsubscript{2}Cl\textsubscript{2}; (iii) TfOH; (iv) ICl, CH\textsubscript{2}Cl\textsubscript{2}; (v) TfOH.

**Scheme 37. Failed deprotection of N-benzyl isoindolinone 247a.**

**Scheme 38. Failed synthesis of biaryl 279 by Snieckus' one-pot cross-coupling procedure.**\textsuperscript{153} Reagents and conditions: BBr\textsubscript{3}, CH\textsubscript{2}Cl\textsubscript{2}, 2 h 0 °C to RT, then concentrated and treated with PhI, Pd(PPh\textsubscript{3})\textsubscript{4}, DME, 2.0 M aq. Na\textsubscript{2}CO\textsubscript{3}, 5 h, reflux.
Lactam Ring-Opening

One of the aims of this project was to cleave the lactam of a cyclotrimerization product, in order to demonstrate that an amide can be used as a temporary tether to access a monocyclic benzene derivative (Section 2.1.6.). Initially the hydrolytic cleavage of isoindolinone 247a was investigated under different reaction conditions (Scheme 39).

Stirring isoindolinone 247a in 1.0 M aq. NaOH and either THF, 2-MeTHF or CPME at RT resulted in no reaction. Heating isoindolinone 247a in 1:1 1.0 M aq. NaOH:CPME at reflux over 3 days similarly resulted in no reaction. Heating isoindolinone 247a in 10:1 1.0 M aq. NaOH:MeOH at reflux for 3 days was just as ineffective. Heating isoindolinone 247a at reflux in either 6 M HCl or 1:1 4.5 M H$_2$SO$_4$:dioxane failed to give the hydrolyzed product in both cases. Finally, treating the isoindolinone 247a with H$_2$O$_2$/LiOH at RT also failed to hydrolyze the lactam.

Scheme 39. Failed attempts at the hydrolysis of isoindolinone 247a. Reagents and conditions: (i) 1.0 M aq. NaOH, THF, 16 h, RT; (ii) 1.0 M aq. NaOH, 2-MeTHF, 16 h, RT; (iii) 1.0 M aq. NaOH, CPME, 16 h, RT; (iv) 1.0 M aq. NaOH, CPME, reflux, 3 days; (v) 1.0 M aq. NaOH, MeOH, 3 days, reflux; (vi) 6.0 M aq. HCl, 16 h, reflux; (vii) 1:1 4.5 M aq. H$_2$SO$_4$:dioxane, 8 h, reflux; 35% H$_2$O$_2$ in H$_2$O, LiOH, THF, 16 h, 0°C to RT.

Although there was no literature precedent for lactam-cleavage of an N-Bn isoindolinone, there is limited precedent for the acid-mediated ring-opening of an N-H isoindolinone.$^{154}$ Heating N-H isoindolinone 277 at reflux in 6.0 M aq. HCl for 16 h resulted in the formation of a product consistent with ring-opened salt 281 [crude $^1$H NMR (400 MHz; DMSO-d$_6$); 4.28 (2H, q, $J = 8.8$, CH$_2$N)] (Scheme 40). Given the impracticalities associated with the purification, characterization and modification of hydrogen chloride salt 281 it was considered sensible to convert the compound in situ into an electronically neutral organic molecule. The reaction was repeated using 12 M aq. HCl and heated at reflux for 3 days. After this the volatile components were removed in vacuo and the crude product immediately treated with Ac$_2$O and NEt$_3$ in CH$_2$Cl$_2$. However, the major product of this reaction was N-Ac isoindolinone 282. Evidence of ring-opened compound 283 was observed [crude $^1$H NMR (400 MHz; DMSO-d$_6$); 8.20 (1H, t, $J = 5.8$, NHAc), 4.82 (2H, d, $J = 5.8$, CH$_2$N)] but this compound was not isolated. Starting material 277 was also present in the crude product. Given the forcing reaction conditions and the challenges
of functionalizing the ring-opened product, this line of inquiry was not pursued any further.

\[
\begin{align*}
\text{N-H lactam 277} & \xrightarrow{\text{(i) 12 M HCl, reflux, 3 days; (ii) Ac}_2\text{O, NEt}_3, \text{CH}_2\text{Cl}_2.}} \text{Scheme 40. Attempted cleavage of N-H lactam 277. Reagents and conditions: (i) 12 M HCl, reflux, 3 days; (ii) Ac}_2\text{O, NEt}_3, \text{CH}_2\text{Cl}_2.}
\end{align*}
\]

There is precedent for the hydrolytic ring-opening of an N-Boc isoindolinone\(^{155}\) so N-Boc isoindolinone 286 was prepared as a test substrate. Reduction of phthalimide 284 with metallic tin gave isoindolinone 285,\(^{156}\) which was treated with Boc\(_2\)O to form N-Boc isoindolinone 286 in 43\% isolated yield over two steps (Scheme 41).\(^{157}\)

\[
\begin{align*}
\text{O} & \xrightarrow{\text{(i) Sn, HCl, reflux, 2 h; (ii) (Boc)}_2\text{O, DMAP.}} \text{Scheme 41. Preparation of N-Boc isoindolinone 286. Reagents and conditions: (i) Sn, HCl, reflux, 2 h; (ii) (Boc)}_2\text{O, DMAP.}
\end{align*}
\]

The LiOH-mediated hydrolysis of N-Boc isoindolinone 286 proved to be ineffective, with no reaction observed (Scheme 42). However, with NaBH\(_4\) the N-Boc isoindolinone 286 was reduced to the corresponding alcohol 288 in 65\% isolated yield.\(^{158}\) This represented an effective means of cleaving an isoindolinone lactam bond under practical reaction conditions to access a ring-opened product.

\[
\begin{align*}
\text{OH} & \xrightarrow{\text{(i) aq. LiOH, THF; (ii) NaBH}_4, \text{H}_2\text{O, THF.}} \text{Scheme 42. Attempts to ring-open N-Boc isoindolinone 286. Reagents and conditions: (i) aq. LiOH, THF; (ii) NaBH}_4, \text{H}_2\text{O, THF.}
\end{align*}
\]

It was then necessary to apply the reductive cleavage conditions to a compound which had been prepared \textit{via} the cyclization methodology (Scheme 43). Protection of N-H isoindolinone 278 resulted in the formation of the corresponding N-Boc isoindolinone 289 in 91\% isolated yield. However, the conditions which were effective for the ring-
opening of test compound 286 were less effective on N-Boc isoindolinone 289. The major product of this reaction was hemiaminal 290, which was isolated in 50% yield. Target compound 291 was observed through analysis of the crude 1H NMR spectrum, in addition to starting material 278. When the reaction was repeated using LiBH₄ and MeOH in Et₂O the reaction reached completion and target alcohol 291 was formed in 53% yield.¹⁵⁹ A 1H NMR spectrum of the unpurified product indicated that hemiaminal 290 was also formed during this reaction, with 290:291 = 1:2.

![Scheme 43. Ring-opening of N-Boc isoindolinone 289. Reagents and conditions: (i) (Boc)₂O, DMAP; (ii) NaBH₄, H₂O, THF; (iii) LiBH₄, MeOH, Et₂O.](image)

**2.3. Chapter II Summary**

In conclusion, an efficient, selective and atom economical route to substituted isoindolinones via amide-tethered alkyne cyclotrimerizations has been established (Scheme 44). The key alkyne cyclotrimerization was conducted in CPME at RT with a commercial catalyst, so the reaction is readily transferable to a medicinal chemistry laboratory. Critically the solvent used for this reaction has a good environmental profile,²³ which is highly unusual for an alkyne cyclotrimerization.¹⁰⁵

![Scheme 44. Alkyne cyclotrimerization summary.](image)
This approach has been used access a wide selection of isoindolinone products from readily accessible alkyne starting materials. The alkyne cyclotrimerization was effective with a selection of monoynes, including those with aliphatic and aromatic substituents. The reaction was also effective with a selection of different diynes, with various substituents at R\(^1\) and R\(^2\) (Scheme 44). Crucially, where R\(^2\) = H, the reaction gave isoindolinone 240 as a single regioisomer.

It was also demonstrated that some of the cyclized products could be used as intermediates for the preparation of other synthetically interesting compounds (Scheme 45). It was shown that an aryl silane product could be converted to the corresponding aryl halide through ipso-substitution and that N-\(t\)-Bu isoindolinones could be converted in high yield to N-H isoindolinones through an acid-mediated deprotection. Finally it was demonstrated that this cyclization strategy could be used to access monocyclic benzene derivative 291 through reductive cleavage of the lactam.

Scheme 45. Functional group manipulation of cyclization producted 267a.
Chapter III. Irreversible endo-Selective Diels–Alder Reactions of Substituted Alkoxyfurans

3.1. Introduction

3.1.1. The Application of Cantharimides and Related Heterocycles in Medicinal Chemistry

Cantharidin

Cantharidin 301 (Figure 8) is a blister agent secreted as a defence by many species of blister beetle, including the Spanish fly (Lytta vesicatoria).\(^{160}\) The natural product has reportedly been exploited in Chinese medicine under the name of Mylabris for the treatment of boils and piles since before the Common Era. Physicians in ancient Greece prescribed cantharidin as an aphrodisiac and it was used in that capacity by both Louis XV of France and Ferdinand II of Aragon.\(^{161}\) Currently the only clinical application of the compound is as a 1% solution applied topically for the treatment of benign epithelial growths,\(^{161}\) but where this compound has generated most interest is in the development of anticancer agents.\(^{162}\) Cantharidin 301 has exhibited low \(\mu\)M activity against a selection of tumor cell lines, including cervical, colon, leukaemia, neuroblastoma and bone, although the cause of this cytotoxicity is not understood.\(^{163}\) Cantharidin 301 is also highly toxic to humans, with the fatal dose believed to be less than 60 mg.\(^{161}\)

![Figure 8. Cantharidin 301, norcantharidin 302 and cantharimide 303.](image)

The high toxicity of cantharidin 301 has prevented any clinical exploitation as an antitumor agent, but it has inspired a new generation of structural analogues. Removing the two methyl groups gives norcantharidin 302, which retains much of the antitumor activity with reduced renal and gastrointestinal toxicity (Figure 8).\(^{164}\) Replacing the anhydride in norcantharidin with an imide led to the cantharimide skeleton 303, which has been the focus of much interest within the medicinal chemistry community.
Cantharimides

Following on from the interest in cantharidin as an antitumor agent, substituted cantharimides have been investigated as potential cancer therapies (Figure 9).\textsuperscript{165} For example, cantharimide 303a was reported by Chan \textit{et al.} and was shown to inhibit the growth of hepatoma cell line SK-Hep-1.\textsuperscript{166} Cantharimide 303b was developed as an inhibitor of androgen receptor signalling for the treatment of prostate cancer,\textsuperscript{167} although it was abandoned following Phase I clinical trials. In addition, McCluskey \textit{et al.} recently reported cantharimide 303c with a GI\textsubscript{50} value of 14–28 µM against eight different human cancer cell lines.\textsuperscript{168} Substituted cantharimides have found applications outside of oncology,\textsuperscript{169} in the development of positive allosteric modulators of the metabotropic glutamate receptor 4 (mGlu4),\textsuperscript{170} as dynamin GTPase inhibitors\textsuperscript{171} and as nematicides.\textsuperscript{172}

![Figure 9. Cantharimides developed as an antitumor agents.](image)

Oxabicyclo[2.2.1]heptane derivatives

The cantharimide is based upon the oxabicyclo[2.2.1]heptane scaffold, and this scaffold has been used more widely within medicinal chemistry (Figure 10).\textsuperscript{162, 163, 173} For example, oxabicyclo[2.2.1]heptane 304a (a ring-opened derivative of a cantharimide) is an antiplasmodial agent that inhibits D6 and W2 \textit{Plasmodium falciparum} malarial strains with low µM activity.\textsuperscript{169b} Compound 304b was developed as an inhibitor of protein phosphatase 1 (IC\textsubscript{50} = 48 ± 9 µM) that is modestly selective over protein phosphatase 2a (IC\textsubscript{50} = 85 ± 3 µM).\textsuperscript{174} Sulfonate 304c was developed as a ligand for the estrogen receptor, which functioned as an antagonist for subtypes ER\textalpha{} and ER\textbeta{} with good affinity.\textsuperscript{175} Dhanapal \textit{et al.}\textsuperscript{176} have reported ketone 304d as a novel antibiotic. It has a MIC (minimum inhibitory concentration) of 0.004 mg mL\textsuperscript{-1} against \textit{Klebsiella pneumonia} (compared to MIC = 0.007 mg mL\textsuperscript{-1} for ciprofloxacin) but it lacked good activity against a broad spectrum of bacteria. In addition, 7-oxabicyclo[2.2.1]heptane derivatives are valuable intermediates for synthetic chemistry\textsuperscript{177} and the scaffold can be found in a number of natural products beyond cantharidin.\textsuperscript{178}
3.1.2. [4+2]-Cycloaddition Reactions of Furans and Dienophiles

The most exploited route to oxabicyclo[2.2.1]heptane derivatives is via the [4+2]-cycloaddition of furans and dienophiles. Following the pioneering work of Diels and Alder, the most widely studied example of a furan [4+2]-cycloaddition is the reaction of furan with maleic anhydride. This reaction is known to be thermodynamically controlled, ultimately giving exo-307 as a single diastereoisomer. (Scheme 46).

Svatoš et al. explored the reaction of furan 305 with maleic anhydride 306 computationally using MP2/6-31+G(d) equilibrium geometries. They calculated a small difference in activation energy for endo- and exo-cycloadditions but a significantly lower ΔG for the formation of exo-307 (Scheme 47). This, along with the small barrier to the retro-cycloaddition reaction, explains why any endo-307 formed under the reaction conditions readily isomerizes to give exclusively exo-307.

![Scheme 46: [4+2]-Cycloaddition of furan 305 and maleic anhydride 306.](image)
Scheme 47. Free energy diagram for the reaction of furan and maleic anhydride.\textsuperscript{182} Data calculated for reactions in MeCN at 25 °C using the MP2/6-31+G(d) level of theory. All values in kJ mol\textsuperscript{–1}.

The reaction of furan 305 with maleimide 308 was also explored experimentally and computationally by Svatoš et al. As part of their study, a purified sample of endo-309 was dissolved in MeCN-d\textsubscript{3} and it was observed to undergo a rapid decomposition at 65 °C to give furan 305, maleimide 308 and exo-309. This experiment suggested that the cycloaddition of furan 305 and maleimide 308 was reversible, with exo-309 the thermodynamic product. This hypothesis was supported by computational calculations, with the data illustrated in Scheme 48.

Scheme 48. Free energy diagram for the reaction of furan and maleimide.\textsuperscript{182} Data calculated for reactions in MeCN at 25 °C using the MP2/6-31+G(d) level of theory. All values in kJ mol\textsuperscript{–1}. 
The reversibility of furan-Diels–Alder reactions is in contrast with the corresponding reactions of cyclopentadiene, which undergoes a rapid and irreversible reaction with both maleic anhydride and maleimide. A reasonable justification for this is the loss of aromaticity that occurs when furan undergoes a cycloaddition reaction, which is not observed where cyclopentadiene is the dienophile. Svatoš explored this with use of two thermodynamic cycles detailed in Scheme 49. The total reaction free energy $\Delta E$ for the partial hydrogenation of furan 305 to give 2,5-dihydrofuran 310 was 72 kJ mol$^{-1}$ greater than the corresponding reaction of cyclopentadiene 305'. In contrast, the difference in $\Delta E$ for the second step of the two thermodynamic cycles was only 7.5 kJ mol$^{-1}$. This supported the theory that it is the dearomatization of furan 305 that reduces the thermodynamic driving force for the [4+2]-cycloaddition reaction with maleic anhydride 306, which contributes to the reversible nature of the reaction.

![Scheme 49](image)

**Scheme 49.** Thermodynamic cycle involving the hydrogenation of furan and cyclopentadiene.$^{182}$ Data calculated using DFT(B3LYP)/6-311++G(2d,p) level of theory.

In 2011 Boutelle and Northrop published computational and experimental work on the reaction between substituted furans and maleimide.$^{183}$ They demonstrated that different substituents at the 2- and 3-position had a dramatic impact on equilibrium position for the cycloaddition reaction (Scheme 50). The reaction of maleimide 308 and furan 305 was calculated to have a low thermodynamic driving force for both exo- and endo-diastereoisomers and it was shown experimentally that the reaction was reversible at 25 °C in MeCN. The reaction of furfural 311a with maleimide 308 was less favorable, with the equilibrium favoring the free furan. However, the reaction of 3-methoxyfuran 311b and maleimide 308 was calculated to have a significant thermodynamic driving
force and the authors suggested that this would be an irreversible cycloaddition reaction. This reaction was not attempted experimentally.

\[
\text{Scheme 50. The calculated effect of furan substituents on a furan Diels–Alder reaction. All values calculated for reactions in MeCN at 25 °C using the MP2/6-311+G(d,p) level of theory for single-point electronic energies and the the CBS-QB3 level of theory for vibrational frequency analysis.}
\]

3.1.3. The Synthesis of Cantharimides and Other Oxabicyclo [2.2.1] heptane Derivatives

The majority of cantharimides that have been prepared in medicinal chemistry programs have been accessed via the [4+2]-cycloaddition of furans and maleic anhydride.\textsuperscript{184} Reduction of the alkene unit followed by condensation with a primary amine gives the corresponding \textit{exo}-cantharimide as a single diastereoisomer (\textbf{Scheme 51}).

\[
\text{Scheme 51. Synthesis of cantharimide \textit{exo}-313 from anhydride \textit{exo}-307.}
\]

This approach has been applied to prepare large numbers of \textit{N}-substituted cantharimides, however the approach is not well suited to varying substitution about the carbon framework. There are relatively few examples of \textit{exo}-cantharimides being prepared from furans bearing substituents other than alkyl groups. A notable limitation is that there are
no reported examples of 2-aryl or 2-heteroarylfurans undergoing furan-Diels–Alder reactions with dienophiles of any type.

A less popular and more challenging route to cantharimides is via the [4+2]-cycloaddition of furans and maleimides (Scheme 52). As described in the previous section, this reaction is under thermodynamic control at RT, but equilibration is relatively slow and it is possible to isolate both endo- and exo-cantharimide 309 from a reaction mixture. However, cantharimide endo-309 was reported by Kwart and Burchuk to rapidly isomerize in either hot solvent or under visible light irradiation. As such there is no practical route to access endo-cantharimides through [4+2]-cycloaddition reactions and the scaffold has not been widely reported.

Scheme 52. [4+2]-cycloaddition of furan 305 and maleimide 308.

The [4+2]-cycloaddition of furan with dienophiles other than maleic anhydride and maleimides are known, although these reactions typically require either elevated pressures or Lewis acid catalysts. The most general set of conditions for the [4+2]-cycloaddition of furans with various dienophiles were developed by Hayashi et al. and relied upon HfCl₄ as a Lewis acid catalyst (Scheme 53). Under these conditions diethyl fumarate 314a and dimethyl maleate 314b could be converted into the corresponding furan adducts and in the latter case with excellent endo-selectivity. Furan 305 also underwent a [4+2]-cycloaddition with benzyl acrylate 314c to give oxabicyclo[2.2.1]heptene 315c in excellent yield. However, in order to achieve this 110 mol% HfCl₄ was required and furan 305 was used in twenty-fold excess. In some cases reactions were also conducted using only 20 mol% HfCl₄ but this resulted in reduced diastereoselectivity and/or reduced isolated yield. There was also a limited scope of furans used in this study, with only furan, 2-methylfuran and 2,5-dimethylfuran considered.
3.1.4. The Synthesis and Application of 3-Alkoxyfurans

Recent work within the Sheppard laboratory on the gold-catalyzed transformation of propargylic alcohols has led to an efficient synthesis of 3-alkoxyfurans, as summarized in Scheme 54.\textsuperscript{190} Treatment of propargylic alcohol 316 with 2.0 mol\% PPh$_3$AuNTf$_2$ in an alcohol solvent gave 3-alkoxyfuran 317 in 58–98\% yield. The reaction had a broad substrate scope both with regard to substituent R$^1$ and the alcohol solvent.

Prior to the above work there was no efficient route into 3-alkoxyfurans and so there is little reported precedent for these compounds being used as dienes in a cycloaddition reaction.\textsuperscript{191} It was shown that furan 318 underwent a [4+2]-cycloaddition reaction with N-methylmaleimide 319 at RT to give the corresponding adduct 320 as a mixture of diastereoisomers in 93\% combined isolated yield (Scheme 55).
3.1.5. Chapter III Project Outline
The cantharimide is a valuable scaffold for drug development but the preparation of highly substituted cantharimides presents a major synthetic challenge. The aim of this part of the PhD was to explore the reaction of 2-substitued 3-alkoxyfurans 317 and maleimides 321 as a novel route to substituted cantharimides (Scheme 56). The synthesis of endo-cantharimides was of particular interest given that this scaffold was broadly unexplored within medicinal chemistry. It was important that the conditions developed for the [4+2]-cycloaddition used sustainable solvents, in order to minimize the waste generated by the synthetic route.

Scheme 56. Proposed synthetic route to highly-substituted endo-cantharimides.

Another goal for this chapter was to prepare a more diverse range of heterocycles by using dienophiles other than maleimides, such as maleates, enones and acrylates (Figure 11). This would allow access to new classes of 7-oxabicyclo[2.2.1]heptane derivatives. It was also identified that aromatization of the furan-Diels–Alder products would generate highly substituted benzene-derivatives, such as phthalimides 323c.

Figure 11. Other heterocycles of interest.

3.2. Results and Discussion

3.2.1. Starting Material Synthesis
Preparation of Propargylic Alcohols
A number of propargylic alcohols 316 were prepared by a general procedure from commercial alkyne 324, as precursors to 3-alkoxyfurans. The general procedure is summarized in Scheme 57.
Initially four propargylic alcohols were prepared from aldehydes with adjacent sp³-centres in 71–86% yield (Figure 12). The reaction procedure was effective for preparing multi-gram quantities of product, with alcohol 316a synthesized from hydrocinnamaldehyde on a 60.0 mmol scale to give 12.8 g of product. The reaction tolerated both a cyclopropyl substituent and an N-Boc piperidine to give alcohols 316c and 316d respectively.

The general procedure was effective with a range of benzaldehyde derivatives to give propargylic alcohols bearing aromatic substituents in 78–96% yield (Figure 13). The reaction was again effective on a multi-gram scale; 10.5 g of alcohol 316e was prepared from benzaldehyde in 95% yield. The reaction tolerated electron-deficient (317f and 317j) and electron-rich arenes (316g) as well as an aryl bromide (316h) and a sterically encumbered arene (316i).

Figure 12. Propargylic alcohols prepared from aliphatic aldehydes.

Figure 13. Propargylic alcohols prepared from aromatic aldehydes.
Furthermore, it was possible to prepare propargylic alcohols bearing furan and thiophene substituents using the general procedure, as shown in Figure 14. While 3-pyridyl alcohol 316m was isolated in 70% yield by this approach, two separate attempts to access 2-pyridyl alcohol 316n gave only a complex mixture of unidentified products.

![Figure 14. Propargylic alcohols bearing heteroaromatic substituents prepared by the general procedure.](image)

### Preparation of 3-Alkoxyfurans

According to the method previously developed within the Sheppard Laboratory, 3-alkoxyfurans 317 were prepared from the corresponding propargylic alcohol 316 by a gold(I)-catalyzed cyclization (Scheme 58).\(^{190}\) The choice of alcohol solvent determined the alkoxy-substitution in the product.

![Scheme 58. General synthesis of 3-alkoxyfurans.](image)

In general, the 3-alkoxyfurans were found to be relatively volatile and this made isolating these compounds in good yield challenging. For this reason it was found generally best to avoid a work up and simply purify the reaction mixture (with solvent) directly by flash column chromatography. In order to avoid significant loss of product upon concentration the furans were purified using petroleum ether with a boiling point in the range 30–40 °C, along with TBME. The solvent was then removed using a rotary evaporator water bath at 0 °C at >100 mbar pressure.

Another challenge when isolating 3-alkoxyfurans was that they were liable to oxidize in the presence of atmospheric oxygen. This was a second reason for cooling the rotary evaporator water bath to 0 °C; furans were observed to oxidize on the rotary evaporator even at RT. It was generally necessary to use the furans as soon as they were prepared. In order to characterize the oxidation, furan 325e was heated in PhMe under an atmosphere of air and aldehyde 326 was isolated in 55% yield following purification (Scheme 59).
Scheme 59. Aerobic oxidation of furan 325e.

With the precautions described above, a selection of 3-ethoxyfurans 325 were isolated in 26–84% yield (Scheme 60). Both furans 325a and 325e were prepared using 2.00 g of the corresponding alcohol. The reaction was tolerant of a number of aliphatic substituents, most notably an N-Boc piperidine to give furan 325d in 77% yield. The reaction was also tolerant of a range of electron-rich, electron-poor and sterically encumbered aromatic substituents. Heteroaromatic substituents could also be accommodated, with bisfuran 325k and thiophene 325l prepared. The yields for bisfuran 325k and 2-cyclopropyl furan 325e were poor (26% and 29% respectively), which is likely due to their exceptionally high volatility.

Scheme 60. General synthesis of 3-ethoxyfurans 325.

In contrast to the above reactions, pyridine 316m underwent no reaction when it was treated with EtOH and 2.0 mol% PPh₃AuNTf₂ (Scheme 61). However, when 5.0 eq. of MsOH was added to the reaction mixture before the gold catalyst a reaction was observed, with furan 325m isolated in 73% yield.
Scheme 61. Synthesis of 2-pyridyl furan 325m.

The reaction was also conducted in other solvents to access furans with different alkoxy groups. Conducting the reaction at 0.50 M concentration in MeOH resulted in the formation of the desired 3-methoxyfuran 318 but with a small 3-ethoxyfuran impurity. However, this side product was avoided by diluting the reaction to 0.20 M (Scheme 62). These conditions could not be applied to the efficient synthesis of the analogous tert-butyl alkoxyfuran 327. Conducting the reaction in tBuOH gave the desired furan but in very low yield and with a 3-ethoxyfuran impurity.190

Scheme 62. Synthesis of 3-alkoxyfurans from different alcohols.

Synthesis of Dienophiles

The majority of dienophiles used in this work were purchased from commercial sources, but three compounds were prepared using literature procedures (Scheme 63). Imine 328 was prepared in 64% isolated yield by the condensation of ethyl 2-oxoacetate and (+)- tert-butyl sulfinamide.192 Maleimides 329a and 329b were made from maleic anhydride in poor yield (30% and 47% respectively) but on a gram scale.193
3.2.2. Synthesis of Cantharimides via the [4+2]-Cycloadditions of 3-Alkoxyfurans

The [4+2]-cycloaddition reaction of furan 325a and N-methylmaleimide 319 was found to proceed efficiently at RT in Et₂O, PhMe, EtOH and dimethyl carbonate (DMC) (Table 13, Entries 1–4). The endo- and exo-diastereoisomers of cantharimide 330a were identified by coupling constant analysis of the ¹H NMR spectra, as discussed in the following paragraph. DMC was selected as a solvent for further work as it resulted in the highest endo-selectivity (Entry 4) and because of its excellent environmental profile.²³ It was possible to remove the small excess of N-methylmaleimide 319 by flushing the reaction mixture through an aminopropyl cartridge, giving cantharimide 330a in 93% yield as a 70:30 mixture of endo- and exo-diastereoisomers (Entry 4). This reaction was scaled up to use 1.00 g of furan 325a with no significant impact on yield or selectivity (Entry 5). Cooling the reaction down to 0 °C had little effect on diastereoselectivity, with cantharimide 330a isolated as a 75:25 mixture of endo- and exo-diastereoisomers (Entry 6). Heating the reaction at 80 °C for 16 h reduced the diastereoselectivity, with cantharimide 330a isolated with an endo:exo ratio of 45:55 (Entry 7). Heating at the same temperature over 3 days gave cantharimide 330a with a small selectivity for exo-330a but in only 40% isolated yield (Entry 8). The conditions in Entry 4 were selected as the optimized reaction conditions for further studies into furan-Diels–Alder reactions.
Table 13. [4+2]-Cycloaddition of furan 325a and N-methylmaleimide 319.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature/°C</th>
<th>Time/h</th>
<th>Yield 330a/%</th>
<th>endo:exo&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>25</td>
<td>4</td>
<td>98&lt;sup&gt;b&lt;/sup&gt;</td>
<td>65:35</td>
</tr>
<tr>
<td>2</td>
<td>PhMe</td>
<td>25</td>
<td>4</td>
<td>100&lt;sup&gt;b&lt;/sup&gt;</td>
<td>65:35</td>
</tr>
<tr>
<td>3</td>
<td>EtOH</td>
<td>25</td>
<td>4</td>
<td>100&lt;sup&gt;b&lt;/sup&gt;</td>
<td>70:30</td>
</tr>
<tr>
<td>4&lt;sup&gt;d&lt;/sup&gt;</td>
<td>DMC</td>
<td>25</td>
<td>4</td>
<td>93&lt;sup&gt;c&lt;/sup&gt;</td>
<td>70:30</td>
</tr>
<tr>
<td>5&lt;sup&gt;e&lt;/sup&gt;</td>
<td>DMC</td>
<td>25</td>
<td>4</td>
<td>95&lt;sup&gt;c&lt;/sup&gt;</td>
<td>75:25</td>
</tr>
<tr>
<td>6</td>
<td>DMC</td>
<td>0</td>
<td>6</td>
<td>93&lt;sup&gt;c&lt;/sup&gt;</td>
<td>75:25</td>
</tr>
<tr>
<td>7</td>
<td>DMC</td>
<td>80</td>
<td>16</td>
<td>93&lt;sup&gt;c&lt;/sup&gt;</td>
<td>55:45</td>
</tr>
<tr>
<td>8</td>
<td>DMC</td>
<td>80</td>
<td>72</td>
<td>40&lt;sup&gt;c&lt;/sup&gt;</td>
<td>45:55</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by analysis of the crude <sup>1</sup>H NMR spectrum. 
<sup>b</sup> Yield determined by <sup>1</sup>H NMR spectroscopy using pentachlorobenzene as an internal standard. 
<sup>c</sup> Isolated yield. 
<sup>d</sup> Reaction conducted with 108 mg of furan 325a. 
<sup>e</sup> Reaction conducted with 1.00 g of furan 325a.

For the reactions in Table 13 the diastereoselectivity of the formation of cantharimide 330a was determined by analysis of the <sup>1</sup>H NMR spectra. It was observed that the coupling constant between the bridgehead proton H<sup>a</sup> and the adjacent proton H<sup>b</sup>, J<sub>(Ha-Hb)</sub> = 5.3 Hz (Figure 15). This was consistent with the endo-diastereomer, where the dihedral angle between H<sup>a</sup> and H<sup>b</sup> was calculated at 36.6°. In contrast, there was no measurable coupling measured between the corresponding protons for the minor diastereomer. This is consistent with exo-330a, where the dihedral angle between H<sup>a</sup> and H<sup>b</sup> was calculated as 80.6°. This coupling constant analysis was used to assign the diastereoselectivity of furan-Diels–Alder reactions throughout this study.

![Figure 15. Determining diastereoselectivity by coupling constant analysis.](image)
An important question regarding the \([4+2]\)-cycloaddition of 3-alkoxyfuran 325a and \(N\)-methylmaleimide 319 at RT was whether the reaction was under kinetic control. The endo- and exo-diastereoisomers of cantharimide 330a were separated by flash column chromatography and treating endo-330a under the replicated reaction conditions resulted in no isomerization (Scheme 64). This observation is consistent with a kinetically controlled Diels–Alder reaction.

**Scheme 64. Furan-Diels–Alder reversibility study.**

The optimized furan-Diels–Alder reaction conditions (Table 13, Entry 4) were applied to the reaction of 3-methoxyfuran 318 and \(N\)-methylmaleimide 319 (Scheme 65). Coupling constant analysis of the crude \(^1\text{H}\) NMR spectrum confirmed that the reaction was endo-selective (endosexo = 80:20). Following flash column chromatography the two diastereoisomers of cantharimide 320 were isolated separately in 89% combined yield.

**Scheme 65. \([4+2]\)-Cycloaddition of furan 318 and \(N\)-methylmaleimide 319.**

The optimized furan-Diels–Alder reaction conditions were applied to the reaction of \(N\)-methylmaleimide 319 and different 3-ethoxyfurans 325 (Table 14). The \([4+2]\)-cycloaddition reaction was found to be effective with a range 3-ethoxyfurans with aliphatic substituents (Entries 2–4). Cantharimides were isolated in 85–95% yield with reasonable endo-selectivity.
Table 14. [4+2]-Cycloadditions of different 3-ethoxyfurans 325 with N-methylmaleimide 319.

The reaction was also conducted with a range of aromatic substituents, giving the cantharimide product 330 in 75–90% isolated yield and with a consistent endo-diastereoselectivity (Table 14, Entries 5–10). As such these represent the first reported examples of furan-Diels–Alder reactions using 2-arylfurans. The reaction tolerated an electron rich aromatic substituent (Entry 7), an aryl bromide substituent (Entry 8), electron poor aromatic substituents (Entries 6 and 10) and a sterically hindered substituent (Entry 9). Isomerically pure samples of endo-330e and exo-330e were recrystallized from...
CH$_2$Cl$_2$/hexane and the relative stereochemistry of both diastereoisomers were confirmed by single crystal X-ray diffraction (Figure 16).\(^1\)

![Figure 16. Crystal structures of cantharimides endo-330e (left) and exo-330e (right). Ellipsoids are shown at 50% probability level. Only hydrogen atoms belonging to the cyclic core are shown for clarity.](image)

The furan-Diels–Alder reaction was also successful for furans with heteroaromatic substituents, as seen in Entries 11 to 13 of Table 14. The 2-furyl example shown in Entry 11 is an excellent demonstration of the strength of this strategy for accessing cantharimides, as the cycloaddition reaction occurred with high chemoselectivity for the 3-alkoxyfuran over the 3-H furan substituent.

Another substituent was incorporated into the cantharimide skeleton via substituent at the 5-position of the 3-alkoxyfuran (Scheme 66). Treating 3-alkoxyfuran 325a with Eschenmoser's salt 331 in MeCN resulted in the formation of furan 332 in 78% yield. Under the standard cyclization conditions cantharimide 333 was formed in 94% yield after 24 h as an 80:20 mixture of endo- and exo-diastereoisomers.

![Scheme 66. Preparation of a 5-substituted 3-alkoxyfuran and subsequent [4+2]-cycloaddition.](image)

The furan-Diels–Alder conditions could also be applied to reactions using other $N$-substituted maleimides, as shown in Table 15. The reaction was effective when the maleimide possessed a phenyl, benzylic or cyclopropyl substituent, with the

\(^1\) Dr Dejan-Krešimir Bučar and Dr Laure Benhamou are gratefully acknowledged for conducting and analyzing the single crystal X-ray diffraction experiment. Recrystallization was performed by the author.
cantharimides 334 isolated in 83–94% yield. Interestingly, while $N$-substitution had no notable effect on reaction time, substitution had a clear effect on diastereoselectivity. In particular, the reaction to form cantharimides 334b (Entry 2) lacks the clear endo-selectivity previously seen for the reaction of 3-alkoxyfurans 325 with $N$-methylmaleimide 319 (Table 14). This may be explained by the additional steric bulk at the $N$-terminus, which would increase unfavorable steric interactions in the endo-transition state.

Table 15. [4+2]-Cycloaddition of furan 325a with $N$-substituted maleimides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Isolated yield/%</th>
<th>endo:exo$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>334a</td>
<td>94</td>
<td>65:35</td>
</tr>
<tr>
<td>2</td>
<td>4-MeC$_6$H$_4$</td>
<td>334b</td>
<td>83</td>
<td>55:45</td>
</tr>
<tr>
<td>3</td>
<td>$^{t}$Pr</td>
<td>334c</td>
<td>87</td>
<td>60:40</td>
</tr>
</tbody>
</table>

$^a$ As determined from a $^1$H NMR spectrum of the crude product.

The cycloaddition reaction and the furan synthesis were combined into in a single step to generate a cantharimide directly from propargylic alcohol 316a (Scheme 67). However, rather than forming enol ether 330a as has been observed previously, the isolated product was diethyl acetal 335. This implied that the direct furan-Diels–Alder product 330a underwent a solvolysis reaction under the reaction conditions. However, enol ether 330a was formed in a one-pot procedure from propargylic alcohol 316a by: a) treating alcohol 316a with 2.0 mol% PPh$_3$AuNTf$_2$ in EtOH; b) addition of 2.5 mol% PPh$_3$ upon 100% conversion of alcohol 316a and; c) addition of $N$-methylmaleimide 319 after a further 1 h. By following this procedure acetal formation was avoided and enol ether was 330a isolated in 66% yield. This result suggested that the gold catalyst was responsible for the acetal formation and that the catalyst was deactivated using PPh$_3$. This rationale was tested by treating enol ether 330a with 2.0 mol% PPh$_3$AuNTf$_2$ in EtOH, which resulted in the efficient formation of diethyl acetal 335.
3.2.3. Functional Group Manipulation of Cantharimide Products

Enol ether *endo*-330e was readily hydrolyzed by loading the compound onto a Strong Cation eXchange cartridge (SCX-2); a silica column with a bound sulfonic acid residue (Scheme 68). Washing the column after 10 minutes with EtOAc gave the corresponding ketone 336 in 80% yield. Ketone 336 was then reduced to the corresponding secondary alcohol 337 using NaBH₄ in MeOH, with a 70% isolated yield and complete stereocontrol. Enol ether *endo*-330e was also reduced in a diastereoselective manner to give ethyl ether 338 in 76% isolated yield. Treatment of enol ether *endo*-330e with 9-borabicyclo[3.3.1]nonane (9-BBN) followed by an oxidative work up gave alcohol 339 in 52% isolated yield with excellent regio- and stereocontrol.
Scheme 68. Transformations of enol ether *endo*-330e. Reagents and conditions: (i) SCX-2; (ii) NaBH₄; (iii) H₂, 10% Pd/C; (iv) 9-BBN, then H₂O₂/NaOH.

The transformation of enol ether *endo*-330e into cantharimide 340 via a Heck arylation was investigated (Scheme 69). Treating *endo*-330e with 4-bromotoluene in the presence of N,N-diisopropylethylamine (DIPEA), PPh₃ and Pd(OAc)₂ in 85:15 DMF:water and heating the reaction to 110 °C resulted in the formation of furan 325e rather than cantharimide 340. This implied that enol ether *endo*-330e underwent a retro-cycloaddition reaction at elevated temperatures and that N-methylmaleimide 319 was unstable under the reaction conditions. The bromination of enol ether *endo*-330e was also explored. However treatment of enol ether *endo*-330e with N-bromosuccinimide (NBS) in 2-MeTHF resulted in the formation of a complex mixture of products.

Scheme 69. Failed transformations of enol ether *endo*-330e.
3.2.4. Physicochemical Properties

In order for a compound to succeed as a drug it must not only have a high and selective affinity for a target receptor but it must also have appropriate physicochemical properties to ensure favorable absorption and distribution, while minimizing undesired metabolism, elimination and toxicity. Various physicochemical properties are believed to be significant, including lipophilicity, molecular weight (mw) and polar surface area (PSA). It has also been noted that in optimizing the structure of a lead compound into a potential drug candidate that compounds typically become more lipophilic and increase in mw. As such, the physicochemical properties of a lead can have a direct impact on the physicochemical properties of a candidate, and its potential success as a drug. Churcher et al. proposed criteria for “Lead-like space”, where compounds are typically smaller and more lipophilic than would be typical for a successful drug (Table 16). They also emphasized the value of a highly three-dimensional structure, as this is associated with improved solubility, improved receptor affinity and reduced off-target effects.

<table>
<thead>
<tr>
<th>Lead-likeness guide</th>
<th>Preferred values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipophilicity guide</td>
<td>$-1 \leq \text{clog}P \leq 3$</td>
</tr>
<tr>
<td>Molecular size guide</td>
<td>$14 \leq \text{heavy atoms} \leq 26$</td>
</tr>
<tr>
<td></td>
<td>(mw = 200–350 Da)</td>
</tr>
</tbody>
</table>

Reproduced from Ref. 202 with permission from John Wiley and Sons.

In order to assess the value of the endo-cantharimide products that can be prepared using this methodology to medicinal chemistry, some physicochemical properties of three cantharimides were calculated (Figure 17). According to the criteria set down by Churcher et al., the values for clogP, mw and polar surface area (PSA) of cantharimides 337, 338 and 339 fall within the acceptable range of values for “lead-like” compounds. In addition, the structures only contain one aromatic ring and possess a high degree of 3D character. As such, molecules like these could be valuable additions to compound libraries for high throughput screening against biological targets.
Figure 17. Physicochemical properties of endo–cantharimides. Data calculated using ChemDraw 12.

Preliminary biological activity of alcohol 337 and ether 338 was explored using a screen of 40 medicinally important receptors. Unfortunately, this screen did not reveal any significant activity that could be a valuable starting point for further investigations. However, the screen did include the hERG receptor (which is responsible for common toxicity) and no measurable affinity was observed. Finally, the in vitro clearance of alcohol 337 in the presence of human microsomes was investigated. Pleasingly, no turnover was observed below the detectable limit of 0.53 mL min$^{-1}$ g$^{-1}$.

3.2.5. [4+2]-Cycloadditions with other Dienophiles

[4+2]-Cycloadditions without Lewis Acid Catalysis

Furan 325a underwent a reaction with 1.2 eq. of maleic anhydride 306 at RT, with 100% conversion of furan 325a within 1 h (Scheme 70). Although analysis of the crude $^1$H NMR spectrum indicated a product consistent with adduct 342 (endo:exo = 50:50), attempts to isolate the product by chromatography on silica, using an aminopropyl cartridge or using MgSiO$_3$ failed to give the target compound. It is known that adducts formed from furans and maleic anhydride are more liable to undergo a retro-cycloaddition reaction than the corresponding N-methylmaleimide adducts, which may explain the poor stability of adduct 342.$^{205}$

Scheme 70. Reaction of furan 325a with maleic anhydride.

$^{ii}$ IVC testing performed by Cyprotex®, 15 Beech Lane, Macclesfield, Cheshire, SK10 2DR, UK.
Treating furan 325a with 1.2 eq. of dimethyl maleate in DMC resulted in 100% conversion of furan 325a after 3 days at RT (Scheme 71). Enol ether 343 was formed with high endo-selectivity (endo:exo = 12:1), as determined by coupling constant analysis of the crude 1H NMR spectrum. Enol ether 343 was isolated in 69% yield following purification by flash column chromatography.

![Scheme 71](image)

Scheme 71. The reaction of furan 325a with dimethyl maleate.

Both dimethyl and diethyl fumarate reacted readily with furan 325a at RT to give the corresponding addition products 344, which were purified by flash column chromatography to give 77% and 89% isolated yields respectively (Scheme 72). The diastereoselectivity of the reactions were again determined by coupling constant analysis of 1H NMR spectra and in both cases there was a clear selectivity for the diastereoisomer that is exo with respect to the 3-position (3-exo-344). The reaction of a fumarate with a substituted furan was without literature precedent.

![Scheme 72](image)

Scheme 72. Reaction of furan 325a with dimethyl and diethyl fumarates.

Furan 325a underwent a slow reaction with ethyl vinyl ketone at RT, but at 80 °C the reaction reached completion within 16 h (Scheme 73). The direct cycloaddition product proved to be relatively unstable, but hydrolysis of the enol ether gave the corresponding ketone that was readily purified. Analysis of the crude 1H NMR spectrum indicated the presence of two regioisomers 345 and 345' in the ratio 95:5. The major regioisomers 345 was formed as 60:40 mixture of endo- and exo-diastereoisomers. Following column chromatography ketones 345 and 345' were isolated in a combined yield of 60%.
Scheme 73. [4+2]-Cycloaddition of furan 325a with ethyl vinyl ketone.

Furan 325a also reacted with dimethyl acetylenedicarboxylate 346, with 100% conversion of the furan observed after 5 h at RT (Scheme 74). However, analysis of the crude 1H NMR spectrum showed that the product was a complex mixture of products with no clear evidence for the expected adduct 347. A possible explanation was that the cycloaddition reaction occurred but that the immediate product was unstable and decomposed under the reaction conditions. The reaction of furan 325a with imide 328 proceeded in a similar manner; again the furan was consumed but only a complex mixture of unidentified products was isolated from the reaction.

Scheme 74. Failed cycloaddition reactions with furan 325a.

**Lewis-Acid Catalyzed [4+2]-Cycloadditions**

The reaction of furan 325a and ethyl acrylate was investigated under the standard reaction conditions but was found to proceed slowly at RT, with ca. 70% conversion of furan 325a observed after 24 h (Scheme 75). In light of this, the possibility of accelerating the reaction through use of a Lewis acid catalyst was investigated. It was found that enol ether 349 was unstable to purification by flash silica gel chromatography so it was not possible to isolate this compound.
Scheme 75. [4+2]-Cycloaddition of furan 325a and ethyl acrylate.

The reaction of furan 325a and 1.5 eq. of ethyl acrylate was explored at RT with a series of Lewis acids, with the results given in Table 17. Given the difficulty in isolating enol ether 349, the crude reaction mixtures were filtered through a SCX-2 plug to hydrolyze the cycloaddition product and form ketone 350. Both Yb(OTf)$_3$ and HfCl$_4$ were effective catalysts for the cycloaddition, with 100% conversion of furan 325a observed after 3 h and 6 h respectively (Entries 1 and 2). In contrast BF$_3$.THF and Cu(OTf)$_2$ were not effective catalysts for this transformation, with less than 100% conversion observed after 8 h (Entries 3 and 4). While Yb(OTf)$_3$ gave the shortest reaction time, HfCl$_4$ gave the best yield and, using 2.0 mol% HfCl$_4$ as catalyst, ketone 350 was isolated in 89% yield as a 65:35 mixture of endo- and exo-diastereoisomers (Entry 2).

Table 17. Catalyst screen for that reaction of furan 325a and ethyl acrylate.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Time/h</th>
<th>Yield 350/%$^a$</th>
<th>endo:exo$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yb(OTf)$_3$</td>
<td>3</td>
<td>70</td>
<td>65:35</td>
</tr>
<tr>
<td>2</td>
<td>HfCl$_4$</td>
<td>6</td>
<td>90 (89)$^b$</td>
<td>65:35</td>
</tr>
<tr>
<td>3</td>
<td>Cu(OTf)$_2$</td>
<td>8$^c$</td>
<td>30</td>
<td>85:15</td>
</tr>
<tr>
<td>4</td>
<td>BF$_3$.THF</td>
<td>8$^c$</td>
<td>30</td>
<td>85:15</td>
</tr>
</tbody>
</table>

$^a$ As determined from a $^1$H NMR spectrum of the crude product (using C$_6$HCl$_5$ as an internal standard). $^b$ Isolated yield; $^c$ Furan 325e still present.

Unfortunately, the substrate scope with regard to the furan was limited. Treating 2-Ph furan 325e with ethyl acrylate under the optimized conditions resulted in little conversion of the furan and no formation of the target product 351 (Scheme 76). A screen of alternative catalysts in DMC [Hf(OTf)$_4$, Yb(OTf)$_3$, Sc(OTf)$_3$, La(OTf)$_3$] did not yield any evidence for the formation of a cycloaddition product either. Finally the reaction was attempted under thermal conditions by heating the furan with 2.0 eq. of ethyl acrylate.
without solvent at 100 °C for 16 h, but no ketone 351 was formed as judged by analysis of the 1H NMR spectrum.

Scheme 76. Failed reaction of furan 325e and ethyl acrylate.

The dienophile scope was also evaluated. Unfortunately, none of the dienophiles in Scheme 77 underwent reaction with furan 325a to form a cycloaddition product that could be isolated. For enones 352a and 352b, 100% conversion of furan 325a was observed within 16 h but analysis of the crude 1H NMR spectrum revealed a complex mixture of products. For the case of cyclopentenone 352c, anhydride 352d and acrylamide 352e, no significant reaction was observed.

Scheme 77. Dienophiles that failed to cyclize with furan 325a.

3.2.6. Effect of a 3-Alkoxy group on the [4+2]-Cycloaddition of Furans and N-Methylmaleimide: A Computational Study

The aim of this computational study was to quantify the thermodynamic and kinetic effect of a 3-alkoxy group on the [4+2]-cycloaddition of 2-substituted furans with N-methylmaleimide 319. The reaction of ten furans 353 with N-methylmaleimide 319 were modelled using Gaussian09\textsuperscript{206} (Scheme 78). A 3-methoxy group was selected over a 3-ethoxy group in order to simplify structure optimizations.

Scheme 78. Model reactions for the computational study.
Structure Optimization
Before any reactions could be investigated it was first necessary to find the lowest energy conformation of starting materials and products. This was done using the M06-2X/6-31G(d) level of theory, which was chosen after preliminary calculations showed that it was able to reproduce reported calculated energies for related furans, dienophiles and adducts that had been published by Svatoš et al.182 The first question that was addressed was the favored rotamer of 3-methoxyfurans. It was energetically more favorable for the methoxy group of a 3-methoxyfuran to point away from the adjacent substituent at the 2-postion. For example, furan 353a was 13.3 kJ mol⁻¹ more stable than rotamer 353a’ (Figure 18). A similar effect was observed in the cantharimide products. For example, endo-354a was 11.6 kJ mol⁻¹ more stable than the corresponding rotamer endo-354a’.

Examing the geometries of 2-cyclopropylfuran 353b and cantharimides 354b revealed three rotamers for each compound (Scheme 79). For these examples, the lowest energy conformation for the starting material and product were used to calculate ΔH and ΔG, but all rotamers were considered to calculate minimum transition state geometries. Then the lowest energy transition state was used to calculate ΔH‡ and ΔG‡. The same approach was used for the corresponding 3-H furan.
Scheme 79. Energy and frequency minimized geometries for furan 353b and cantharimides 354b.

In contrast, where the 2-substituent was an aromatic ring there was a strong preference for a single conformation in both starting material and adduct. For the 2-aryl furans the two rings preferred to sit coplanar. For the cantharimides the preferred geometry saw the aromatic ring approximately coplanar with the ether bridge. The dihedral angle across the rotatable C-C bond for each isomer changed little as the aromatic ring was varied. The optimized geometries for furan 353e and cantharimides 354e are illustrated in Scheme 80.

Scheme 80. Energy and frequency minimized geometries for furan 353e and cantharimides 354e.
Free Energy and Enthalpy Calculation
By calculating minimum gas-phase energies for starting materials, cantharimides and transition states it was possible to calculate values for $\Delta H$ or $\Delta H^\ddagger$, $\Delta G$ and $\Delta G^\ddagger$ for each reaction, with the results given in Table 18. Transition state searches were conducted using the QST2 method at the M06-2X/6-31G(d) level of theory. The calculations were also performed for reactions in a series of solvents (hexane, Et$_2$O, CH$_2$Cl$_2$, PhMe, EtOH, MeCN and water), but this had little effect on $\Delta H$ or $\Delta H^\ddagger$, $\Delta G$ or $\Delta G^\ddagger$. Performing calculations in DMC was considered but this solvent was not an available option in Gaussian09 and so was thus not trivial to model.
Table 18. Calculated reaction and transition state enthalpies and free energies for the formation of cantharimides 354.\(^a\)

![Chemical structure](image)

<table>
<thead>
<tr>
<th>R</th>
<th>X</th>
<th>Product</th>
<th>(\Delta H)</th>
<th>(\Delta H^\ddagger)</th>
<th>(\Delta G)</th>
<th>(\Delta G^\ddagger)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>OMe</td>
<td>endo-354a</td>
<td>-106.4</td>
<td>18.8</td>
<td>-41.5</td>
<td>81.1</td>
</tr>
<tr>
<td>Me</td>
<td>OMe</td>
<td>exo-354a</td>
<td>-112.8</td>
<td>23.2</td>
<td>-47.7</td>
<td>82.1</td>
</tr>
<tr>
<td>(^c)Pr</td>
<td>OMe</td>
<td>endo-354b</td>
<td>-109.4</td>
<td>11.6</td>
<td>-44.1</td>
<td>75.0</td>
</tr>
<tr>
<td>(^c)Pr</td>
<td>OMe</td>
<td>exo-354b</td>
<td>-116.5</td>
<td>18.7</td>
<td>-53.2</td>
<td>78.6</td>
</tr>
<tr>
<td>4-MeOC(_6)H(_4)</td>
<td>OMe</td>
<td>endo-354c</td>
<td>-90.2</td>
<td>22.3</td>
<td>-32.5</td>
<td>76.8</td>
</tr>
<tr>
<td>4-MeOC(_6)H(_4)</td>
<td>OMe</td>
<td>exo-354c</td>
<td>-88.6</td>
<td>32.6</td>
<td>-30.1</td>
<td>85.3</td>
</tr>
<tr>
<td>Ph</td>
<td>OMe</td>
<td>endo-354d</td>
<td>-88.4</td>
<td>25.3</td>
<td>-34.0</td>
<td>83.6</td>
</tr>
<tr>
<td>Ph</td>
<td>OMe</td>
<td>exo-354d</td>
<td>-87.3</td>
<td>35.4</td>
<td>-28.2</td>
<td>91.3</td>
</tr>
<tr>
<td>4-F(_3)CC(_6)H(_4)</td>
<td>OMe</td>
<td>endo-354e</td>
<td>-89.2</td>
<td>28.2</td>
<td>-25.3</td>
<td>85.9</td>
</tr>
<tr>
<td>4-F(_3)CC(_6)H(_4)</td>
<td>OMe</td>
<td>exo-354e</td>
<td>-87.9</td>
<td>39.0</td>
<td>-23.8</td>
<td>96.8</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>endo-354f</td>
<td>-73.1</td>
<td>40.5</td>
<td>-11.8</td>
<td>97.9</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>exo-354f</td>
<td>-82.3</td>
<td>41.3</td>
<td>-16.8</td>
<td>96.2</td>
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<tr>
<td>(^c)Pr</td>
<td>H</td>
<td>endo-354g</td>
<td>-72.3</td>
<td>40.1</td>
<td>-12.5</td>
<td>92.2</td>
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<tr>
<td>(^c)Pr</td>
<td>H</td>
<td>exo-354g</td>
<td>-79.3</td>
<td>43.1</td>
<td>-10.3</td>
<td>92.8</td>
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<td>4-MeOC(_6)H(_4)</td>
<td>H</td>
<td>endo-354h</td>
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<td>44.1</td>
<td>-6.1</td>
<td>95.4</td>
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<td>4-MeOC(_6)H(_4)</td>
<td>H</td>
<td>exo-354h</td>
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<td>Ph</td>
<td>H</td>
<td>endo-354i</td>
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<td>-1.7</td>
<td>101.1</td>
</tr>
<tr>
<td>Ph</td>
<td>H</td>
<td>exo-354i</td>
<td>-60.0</td>
<td>48.8</td>
<td>0.7</td>
<td>105.5</td>
</tr>
<tr>
<td>4-F(_3)CC(_6)H(_4)</td>
<td>H</td>
<td>endo-354j</td>
<td>-60.6</td>
<td>45.7</td>
<td>-0.9</td>
<td>101.6</td>
</tr>
<tr>
<td>4-F(_3)CC(_6)H(_4)</td>
<td>H</td>
<td>exo-354j</td>
<td>-60.3</td>
<td>51.9</td>
<td>0.9</td>
<td>108.3</td>
</tr>
</tbody>
</table>

\(^a\)All values are in kJ mol\(^{-1}\). All data is calculated for species in the gas phase. The optimized geometries of all compounds and transition states can be found in appendix to this thesis.

Analysis of the data in Table 18 showed that the 3-alkoxy group has a dramatic impact on the thermodynamic driving force of the furan-Diels–Alder reaction. The introduction of a methoxy group at the designated position decreases the Gibbs free energy of reaction (\(\Delta G\)) by 24–34 kJ mol\(^{-1}\). This impact is most significant where the substituent is aromatic,
for example the 2-Ph furans illustrated in Scheme 81. For 2-phenylfuran 353i the reaction to form the thermodynamically more stable adduct endo-354i has a value of $\Delta G = -1.7 \text{ kJ mol}^{-1}$. Such a low thermodynamic driving force is not practical for an efficient synthesis of cantharimide 354i. By comparison, the reaction of 3-methoxyfuran 353d and N-methylmaleimide 319 has a significant thermodynamic driving force, which is consistent with kinetic control ($\Delta G_{exo} = -28.2 \text{ kJ mol}^{-1}$ and $\Delta G_{endo} = -34.0 \text{ kJ mol}^{-1}$). As would be expected for an electron rich diene, the 3-methoxy group also reduces the kinetic barrier for the Diels–Alder reaction. However, this effect was less pronounced, with a difference of 11–23 kJ mol$^{-1}$.

Scheme 81. Reaction and activation free energies for the [4+2]-cycloadditions of 2-phenylfurans and N-methylmaleimide 319. All values are in kJ mol$^{-1}$.

Transition State Geometries
The energy minimized structures for the endo- and exo-transition states for the formation of cantharimides 354d are shown in Figure 19. It is notable that in both cases the transition state geometries of the furan and maleimide components are relatively flat, as would be expected for an early transition state. The transition state geometries are also relatively symmetrical, with little difference in the length of the forming bonds.
Figure 19. Transition states for *endo*- and *exo*-cantharimides 354d.

**Hydrogenation Thermodynamic Cycle**

The reversibility of Diels–Alder reactions where the diene is a furan has been attributed to the loss of aromatic stabilization upon formation of the adduct, resulting in a facile retro-cycloaddition. In order to examine the effect of a 3-methoxy group on this phenomenon, thermodynamic cycles involving the partial hydrogenation of 3-methoxyfuran 355a and furan 358a to the corresponding 2,5-dihydrofurans 356a and 359a were considered (Scheme 82). It is notable that the free energy of hydrogenation for furan 355a is 25.9 kJ mol$^{-1}$ greater than for 3-methoxyfuran 358a. For the second step in the cycle to form adducts 357 and 360 no significant difference in ΔG was observed. In contrast, the analogous thermodynamic cycles for the corresponding cyclopentadienes 355b and 358b revealed little difference in ΔG for either Step A or Step B.

![Scheme 82. Hydrogenation Study.](image)

The observation that the addition of a methoxy group had little impact on ΔG for step B suggested that the formation of the two C-C bonds was not the determining factor in
explaining the difference in $\Delta G$ for the reactions of furan and 3-methoxyfuran with $N$-methylmaleimide. Rather this could be attributed to the change in conjugation associated with the cycloaddition reaction. These results suggest that the 3-methoxy group reduced the thermodynamic penalty associated with the loss of conjugation upon partial hydrogenation to the 2,5-dihydrofuran. The fact that a similar effect is not observed with the corresponding cyclopentadienes suggested that loss of aromaticity is the significant factor. In other words, a 3-methoxy group can reduce the energetic cost of losing aromaticity upon the cycloaddition of a furan with $N$-methylmaleimide.

3.2.7. Aromatization of Cantharimide Products

The dehydration of 7-oxabicyclo[2.2.1]heptanes under acidic or basic conditions was identified as a potentially valuable route to highly-substituted aromatic compounds, such as phthalimides (Scheme 83). In principle, this could be conducted using a mixture of endo- and exo-diastereoisomers as both would converge to the same product. Phthalimide is a privileged scaffold for drug discovery and forms the core of a number of existing and potential therapies.

Scheme 83. Proposed aromatization of cantharimides 361.

Base-Mediated Ring-Opening.

There is reasonable precedent for the aromatization of ether-bridged [4+2]-cycloaddition products using strong bases (Scheme 84). However, treating cantharimide endo-330e with lithium hexamethyldisilazide (LiHMDS) in anhydrous THF at $-78$ °C did not result in any evidence for cleavage of the ether bridge or formation of a phthalimide product. In addition to recovered starting material, 3-alkoxyfuran 325e was observed in the crude $^1$H NMR spectrum. This suggested that the reaction conditions induced a retro-[4+2]-cycloaddition of cantharimide endo-330e. No such reaction was observed when cantharimide endo-330e was treated with NaOMe in MeOH, but this only resulted in significant decomposition. Ketone 336 was also treated with LiHMDS in an attempt at inducing aromatization, but this too resulted in significant decomposition.
Scheme 84. Reaction of enol-ether endo-330e and ketone 336 with LiHMDS.

**Tf₂O-Mediated Ring-Opening**

The possibility of cleaving the ether bridge using Tf₂O was briefly considered. It was found that treating enol-ether exo-330a with Tf₂O in anhydrous CH₂Cl₂ gave a complex mixture of products. Following purification by flash column chromatography phthalimide 364 was isolated in 31% yield (Scheme 85). It was postulated that the formation of phthalimide 364 proceed through an acid-mediated electrophilic aromatic substitution of the pendent phenyl group, followed by aromatization of the resulting 7-oxabicyclo[2.2.1]heptane 366.

Scheme 85. Synthesis of phthalimide 364 from enol ether exo-330a.

In an attempt to convert cantharimide 330a into phenol ether 367, cantharimide 330a was treated with Tf₂O in the presence of 2,6-lutidine (Scheme 86). However, no reaction was observed and cantharimide 330a was recovered from the reaction. An interpretation of this result is that it was TfOH rather that Tf₂O that was responsible for the aromatization of intermediate cantharimide 366 in the formation of phthalimide 364 (Scheme 85).
Me₃SiOTf-Mediated Aromatization

The aromatization of enol ether endo-330e was considered under basic conditions using Me₃SiOTf as a dehydrating agent.²¹¹ After 24 h a 3:1 mixture of phthalimide 368 and starting material endo-330e were isolated. However, column chromatography failed to generate phthalimide 368 in sufficiently high purity and the yield was estimated at 50% (Scheme 87). Heating the reaction at reflux for 24 h resulted in 100% conversion of cantharimide endo-330e and approximately 40% yield of phthalimide 368, but again purification by silica gel column chromatography gave phthalimide 368 in only modest purity. Given the challenge of purifying this reaction, these conditions were not pursued further.

Acid-Mediated Ring-Opening

As an initial study, a solution of cantharimide endo-320 in CH₂Cl₂ was treated with TFA at RT (Scheme 88). This did not result in any formation of an aromatized product; rather ether 369 and ketone 370 were formed in the ratio 3:1. These two products were inseparable by silica gel chromatography so the mixture was treated with NaBH₄ in MeOH to give a separable mixture of ether 369 and alcohol 371. After purification, ether 369 was isolated in 69%.
Scheme 88. Acid-catalyzed rearrangement of cantharimide endo-320. Reagents and conditions: (i) TFA, CH₂Cl₂; (ii) NaBH₄, MeOH.

It was unclear whether ketone 370 was formed under the reaction conditions or whether it was only formed on work up. Repeating the reaction using anhydrous conditions and leaving the reaction for a further 8 h resulted in the same 3:1 mixture of products. A possible solution was to add HC(OMe)₃ to the reaction to regenerate starting material endo-320 from any ketone 370 formed in the reaction. However, after a 24 h reaction only ketone 370 was present in the crude product.

Given the complication of a pendent aromatic group and the apparent sensitivity of enol ethers to acidic conditions, diethyl acetal 335 was identified as a suitable substrate for investigating acid-mediated ring-opening (Scheme 89). Five different solvents were screened for the acid-mediated aromatization of acetal 335 using both 12 M aq. HCl and BF₃·THF as a potential catalyst. Acetal 335 was stirred in a 10:1 mixture of solvent:acid for 3 days at RT, but in all ten experiments no evidence of aromatization was observed. The only product formed in this solvent screen was the hydrolyzed product 336.

Scheme 89. Solvent screen for the acid-mediated rearrangement of acetal endo-335.
Given the difficulty in aromatizing acetal 335, more forcing acidic conditions were investigated. Stirring acetal endo-335 in neat TFA with 5.0 eq. of TFAA as a dehydrating agent at RT gave phthalimide 368 in 49% yield on a 10 mg scale (Scheme 90). Analysis of the crude 1H NMR spectrum suggested that phthalimide 368 was formed alongside ketone 336 in a 1:1 ratio.

Scheme 90. TFA-mediate aromatization of acetal endo-335.

This result suggested that the key to optimizing the aromatization reaction was reducing the rate of hydrolysis relative to that of aromatization. Given that forcing acidic conditions appeared to be beneficial, acetal endo-335 was stirred in MsOH at RT for 16 h. (Scheme 91). Pleasingly this resulted in formation of phthalimide 368 without the need for an additional dehydrating agent. However, these conditions offered no advantage in terms on minimizing the formation of ketone 336.

Scheme 91. Acid-mediated aromatization of acetal endo-335 using MsOH.

An attempt was made to convert propargylic alcohol 316e into phthalimide 368 without isolation of the cantharimide intermediates (Scheme 92). Alcohol 316e was converted to the corresponding cantharimide endo-335 using 2.0 mol% PPh3AuNTf2 and N-methylmaleimide 319 (Section 4.2.2., Scheme 67). This material was then concentrated and treated with MsOH along with 10% EtOH by volume, which was added in an attempt to minimize the formation of ketone 336. After 16 h the reaction was worked-up and the crude product again treated with MsOH and EtOH (10:1) in order to convert remaining ketone 336 into phthalimide 368. After this additional step phthalimide 368 was isolated in 47% yield from propargylic alcohol 316e.
Scheme 92. One-pot synthesis of phthalimide 368 from alcohol 316a.

A key limitation of MsOH as a reagent for the aromatization of cantharimides is the hydrolysis of diethylacetal 335 to the corresponding ketone 336. Adding EtOH to the reaction mixture had a limited effect at reducing this hydrolysis because of the autocatalytic reaction of EtOH and MsOH to form MsOEt. This was confirmed by treating MsOH with EtOH in the ratio 10:1; after 1 h analysis of the reaction by \(^1\)H NMR spectroscopy clearly showed that all the EtOH had been converted to MsOEt. A possible solution was to treat acetal 335 with MsOH and then add EtOH dropwise to the reaction mixture (Scheme 93). However, this proved to be detrimental to the reaction, with a reduced level of phthalimide 368 formed.

Scheme 93. Aromatization reaction of acetal 335 using MsOH and a dropwise addition of EtOH.

Given the problems associated with the aromatization of acetal 335 in MsOH, alternative catalysts were considered. Using AcOH, PTSA.H\(_2\)O, sulfuric acid and hydrochloric acid in combination with a HC(OEt)\(_3\) dehydrating agent did not result in aromatization of acetal 335. Polyphosphoric acid (PPA) was considered as an aromatization agent, with the results summarized in Table 19.
Table 19. Attempts to aromatize acetal 335 using polyphosphoric acid (PPA).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ratio PPA: HC(OEt)₃</th>
<th>Temperature/°C</th>
<th>368:336/%ₐ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10:1</td>
<td>RT</td>
<td>1:4</td>
</tr>
<tr>
<td>2</td>
<td>10:1</td>
<td>100</td>
<td>decomposition</td>
</tr>
<tr>
<td>3</td>
<td>1:1</td>
<td>100</td>
<td>1:4</td>
</tr>
<tr>
<td>4</td>
<td>1:1</td>
<td>120</td>
<td>3:2</td>
</tr>
<tr>
<td>5</td>
<td>1:1</td>
<td>150</td>
<td>3:1</td>
</tr>
<tr>
<td>6ᵇ</td>
<td>1:1</td>
<td>150</td>
<td>3:1ᶜ</td>
</tr>
</tbody>
</table>

ᵃ Determined from the ¹H NMR spectrum of the crude product.ᵇ Reaction heated for 24 h.ᶜ Phthalimide 368 isolated in 42% yield.

Stirring acetal 335 in a 10:1 mixture of polyphosphoric acid (PPA) and HC(OEt)₃ resulted in the formation of phthalimide 368 alongside ketone 336 in the ratio 1:4 (Table 19, Entry 1). Increasing the reaction temperature to 100 °C resulted in decomposition (Entry 2), however when the proportion of PPA used was decreased it was again possible to isolate phthalimide 368 alongside ketone 336 (Entry 3). Increasing the reaction temperature increased the ratio of phthalimide 368 to ketone 336 (Entries 4 and 5), with a 150 °C reaction temperature giving a ratio of 3:1. However, a longer reaction time of 24 h did not improve this ratio (Entry 6). Purification of this reaction gave phthalimide 368 in 42% isolated yield.

A one-pot synthesis of phthalimide 368 over two steps from furan 325e was attempted (Scheme 94). Furan 325e was treated with N-methylmaleimide 319 in HC(OEt)₃ and the reaction stirred at RT. After 6 h the reaction was treated with PPA and the resulting solution heated at 120 °C for 16 h. Following purification, phthalimide 368 was isolated in 33% yield.

![Scheme 94. One-pot synthesis of phthalimide 368 from furan 325a.](image-url)
Aromatization Conclusion

In conclusion, phthalimide 368 was prepared from the corresponding cantharimide under a variety of reaction conditions. However, the conditions required to achieve the aromatization reaction were always forcing and the best isolated yields were relatively low. While this route offers an interesting new approach into highly substituted phthalimides it was not pursued further due to these two limitations.

3.3. Chapter III Summary

Highly substituted endo-cantharimides 374 were prepared via the [4+2]-cycloaddition of 3-alkoxyfurans and maleimides under environmentally benign conditions (Scheme 95). The reaction was effective with a variety of 3-alkoxyfurans, including those bearing aromatic and heteroaromatic groups at the 2-position, giving cantharimide products in good yield and with reasonable endo-control. The reaction was also effective with a number of N-substituted maleimides, allowing cantharimides to be prepared in a highly convergent fashion. It was shown that the enol ethers formed by this approach could be efficiently converted into a number of endo-cantharimide products with promising lead-like properties. In addition, computational calculations were performed to quantify the effect that a 3-alkoxy group had on the thermodynamics and kinetics of furan-Diels–Alder reactions.

![Scheme 95. Summary of endo-cantharimide synthesis.](image)

In addition to cantharimide products, the methodology was extended to synthesize a variety of novel heterocycles from other dienophiles (Scheme 96). Finally, acid-mediated rearrangements of cantharimide products were used to make extended ring system 369 and phthalimide 368.
Scheme 96. Novel heterocycles prepared from 3-alkoxyfurans.
Chapter IV. Synthesis of Chiral THFs via the Dehydration of Pentoses

4.1. Introduction

4.1.1. The Application of THFs in Medicinal Chemistry

Nucleoside analogues are an important class of compounds in medicinal chemistry, which have been widely developed as antiviral agents, antibiotics and antitumor agents. Compounds of this class mimic the tetrahydrofuran (THF) ring of nucleosides and typically possess a nucleobase at the α-position (Figure 20). Examples include the chemotherapy agent Cytarabine 401, reverse transcriptase inhibitor Zalcitabine 402 and antiretroviral drug Azidothymidine (AZT) 403.

Figure 20. Nucleoside analogues in medicinal chemistry.

A structurally related class of drugs are based on a saturated THF scaffold, with examples illustrated in Figure 21. Alfuzosin 404 and structurally related Terazosin 405 are both α-1 antagonists and are used in the treatment of benign prostatic hyperplasia. Fosamprenavir 406a (a prodrug of protease inhibitor Amprenavir 406b) is used in the treatment of HIV. Naftidrofuryl 407 is a vasodilator and a treatment for cerebral vascular disorders while Mefruside 408 is a diuretic used for the treatment of edema.
Figure 21. Clinical drugs containing a THF.

A valuable drug bearing a fused bis-THF core is isosorbide 409, which is used as a diuretic to treat hydrocephalus (Figure 22). However, isosorbide has also been used more widely in drug development as a scaffold.221 Both isosorbide mononitrate 410 and isosorbide dinitrate 411 are used as vasodilators to treat angina.

Figure 22. Isosorbide and its derivatives in medicinal chemistry.

4.1.2. The Synthesis of THFs from Sugars

There has been significant interest in the preparation of isosorbide from sorbitol (which in turn is generated from carbohydrate feedstock) under acidic or basic conditions.222 For example, Rokicki et al. reported conditions for the preparation of isosorbide 409 from D-sorbitol 412 using K₂CO₃ as a base and DMC as an activating reagent (Scheme 97).223

Scheme 97. The preparation of isosorbide form D-sorbitol.

Another method for the cyclization of sugars is to selectively convert a primary alcohol into a leaving group followed by an intramolecular nucleophilic substitution.224, 225 This
was demonstrated by Smith et al.,²²⁶ who reported the cyclization of glycoside 413 in 26% yield through selective reaction of the primary alcohol with TsCl (Scheme 98, Part I). Lundt and Frank have reported a similar method for cyclizing lactone 416 in 39% yield over two steps (Scheme 98, Part II).²²⁷ A key limitation of this approach is the poor atom economy generally associated with converting a primary alcohol into a leaving group.

![Scheme 98. THF synthesis through activation of a primary alcohol as leaving groups.](image)

A more general route to THFs from sugar derivatives is via the reduction of a glycoside using Et₃SiH.²²⁸ This transformation can be high yielding, as exemplified by the work of Robins and Ewing (Scheme 99).²²⁹ However, this reduction has not been demonstrated on unprotected sugars, which limits its synthetic utility and results in low atom economy.

![Scheme 99. Reductive THF synthesis from a protected glycoside.](image)

### 4.1.3. The Application of N,N-Dialkylhydrazones in Organic Synthesis

N,N-Dialkylhydrazones are a valuable and versatile synthetic tool within organic chemistry (Figure 23).²³⁰ One of the main applications of N,N-dialkylhydrazones 421 is to increase the acidity of carbonyl compounds. Deprotonation at the α-position gives the conjugate base, which can then undergo a reaction with an electrophile.²³¹ The pKₐ of a hydrazone has been calculated to be ca. 10 units higher than the parent carbonyl compound and so the conjugate base of a hydrazone can exhibit greater reactivity towards electrophiles. Hydrazones can also undergo addition reactions with nucleophilic alkyl lithium reagents or free radicals to give hydrazine products.²³² Vinyl hydrazones 422 are also useful synthetic building blocks, acting as Michael acceptors with a variety of
nucleophiles. In addition, deprotonation at the γ-position generates a carbanion that can be trapped with electrophiles. Furthermore, vinyl hydrazones are effective dienes for heteronuclear Diels–Alder reactions owing to their electron-rich nature.\(^{233}\)

![Diels-Alder reaction diagram](image)

**Figure 23. Application of \(N,N\)-dialkylhydrazones.**\(^{230}\)

Hydrazone chemistry was developed most notably by Corey and Enders for the stereoselective α-alkylation of ketones using chiral \(N,N\)-dialkylhydrazones.\(^{234}\) An application of this approach was reported by Nicolaou \textit{et al.} as part of the total synthesis of Epothilones A and B (Scheme 100).\(^{235}\) Treating (S)-1-amino-2-methoxymethylpyrrolidine (SAMP) hydrazone with lithium diisopropylamide (LDA) and then alkyl iodide gave alkylated product as a single diastereoisomer in 70% yield. Numerous methods have been developed to liberate the original carbonyl functional group from \(N,N\)-dialkylhydrazones.\(^{236}\) Nicolaou \textit{et al.} converted hydrazone into aldehyde via an oxidative cleavage to give nitrile, which was then reduced using diisobutylaluminium hydride (DIBAL).

![Scheme 100](image)

**Scheme 100. Application of SAMP hydrazone 423 to the synthesis of Epothilones A and B.**\(^{238}\) Reagents and conditions: (i) 1.5 eq. 423, 1.5 eq. LDA, THF, 0 °C, 8 h; then 1.0 eq. 424, THF, –100 to –20 °C, 10 h, 70%; (ii) 2.5 eq. MMPP, MeOH:phosphate buffer pH 7 (1:1), 0 °C, 1 h, 80%; (iii) 2.0 eq. DIBAL, PhMe, –78 °C, 1 h, 82%.

\(N,N\)-Dialkylhydrazines have also been used to reverse the inherent reactivity of carbonyl compounds to generate an “acyl anion” equivalent, which can undergo reactions with
different electrophiles.\textsuperscript{237} This approach allows ketones to be generated from aldehydes, or for higher aldehydes to be prepared from formaldehyde. For example, Mayr \textit{et al.} explored the alkylation of \emph{N,N}-dialkylhydrazones with benzhydrylium ions, with an example given in Scheme 101.\textsuperscript{238}

A far less explored synthetic approach is to use a hydrazine to facilitate the elimination of a leaving group adjacent to a carbonyl.\textsuperscript{239} In 1953 Warnhoff and Johnson reported that 2,4-dinitrophenylhydrazone 430 underwent an acid mediated elimination of EtOH to give cyclohexene 431 (Scheme 102, Part I).\textsuperscript{240} Similarly, Behforouz \textit{et al.} reported that hydrazone 432 eliminated water in the presence of H\textsubscript{2}SO\textsubscript{4} to give alkene 433 in 82\% yield (Scheme 102, Part II).\textsuperscript{241} In addition, Lichtenthaler \textit{et al.} discovered that treatment of hydrazone 434 with pyridine resulted in ring-opening of the adjacent oxatane to give enol ether 436 in 94\% yield (Scheme 102, Part III).\textsuperscript{242} The authors suggested that the reaction proceeded via vinyl diazene intermediate 435.

\textbf{Scheme 101. Alkylation of \emph{N,N}-dialkylhydrazone 428.}\textsuperscript{238}

\textbf{Scheme 102. Elimination of a leaving group adjacent to a hydrazone.} \textit{Ar} = 2,4-dinitrophenyl.
4.1.4. The Cyclization of Reducing Sugars using NH₂NMe₂

Where an electron-rich aromatic group possesses a pendant sugar chain the aromatic ring can induce displacement of the adjacent hydroxyl group to give a resonance-stabilized cationic intermediate, which can be trapped by a pendent hydroxyl group to form a THF. This transformation has been used within synthetic chemistry and can be invoked in a proposed biosynthetic pathway for the formation of Saffloflavonesides B 439 (Scheme 103).

Scheme 103. Proposed biosynthetic pathway for the formation of Saffloflavoneside B 439.

A similar cyclization of a sugar chain to give a THF was reported by Koóš and Moscher (Scheme 104). Hydrazone 441a was prepared from the condensation reaction of L-arabinose and NH₂NMe₂. Hydrazone 441a was treated with 1.00 eq. of anhydrous p-toluenesulfonic acid (PTSA) and 4.0 eq. of (MeO)₂CMe₂ in anhydrous DMF, and THF 442 was isolated in 57% yield as a 65:35 mixture of diastereoisomers.

Scheme 104. Koóš and Moscher’s cyclization of hydrazone 441a.

4.1.5. Chapter IV Project Outline

The aim of this part of the PhD was to develop a hydrazone-based synthesis of THFs from biomass-derived reducing sugars using sustainable reaction conditions. This would allow for the synthesis of low-molecular weight chiral THFs with control over the absolute
stereochemistry. These products would potentially be valuable building-blocks for chiral sp³-rich molecular scaffolds.

The reported synthesis of THF 442 by Koóš and Moscher (Scheme 104) was a valuable start point for this work.²⁴⁵ A feature of this reaction is the simultaneous cyclization of the sugar chain and formation of an acetonide from (MeO)₂CMe₂. Protecting groups, although often a useful synthetic tool, typically have a detrimental impact on the step economy and atom economy of a synthesis.²⁴⁶ Therefore an attractive alternative reaction to develop was the cyclization of hydrazone 441a to give unprotected diol 443a (Scheme 105).

Scheme 105. Chapter IV project aim.

A significant drawback of Koóš and Moscher’s reaction conditions that needs to be addressed (Scheme 104) was the need for the vigorous exclusion of water, including the use of anhydrous PTSA. Also, DMF has a number of serious environmental drawbacks, so a more sustainable solvent would be advantageous. It would then be important to develop reaction scope with different sugars and to demonstrate the transformation of hydrazone products into a diverse selection of chiral THFs.

4.2. Results and Discussion

4.2.1. Preliminary Studies

Despite literature precedent, stirring L-arabinose 440a with NH₂NMe₂ in water at RT failed to afford hydrazone 441a.²⁴⁷ Following this, 20 mol% PTSA.H₂O and BF₃·THF were screened as catalysts in MeOH-d₄, CDCl₃, D₂O and DMSO-d₆, with PTSA.H₂O/MeOH-d₄ giving the greatest conversion of L-arabinose 440a after 24 h at RT. This reaction was scaled up using 5.0 mol% PTSA.H₂O in MeOH, which gave the desired hydrazone 441a in 79% yield. Replacing PTSA.H₂O with Amberlyst 15 acidic resin (0.100 g/mmol) gave hydrazone 441a in 99% yield on a 90.0 mmol scale, after removal of the resin by filtration (Scheme 106).
Scheme 106. Synthesis of hydrazone 441a.

As a starting point for the investigation, an attempt was made to reproduce Koós and Moscher’s reported synthesis of THF 442 (Scheme 104). Given that anhydrous PTSA is not readily available and difficult to prepare, (±)-camphorsulfonic acid (CSA) was used as an alternative acid (Scheme 107). This reaction yielded a complex mixture of products and analysis of the crude $^1$H NMR spectrum provided no clear evidence for the formation of known THF 442. Treating hydrazone 441a with 1.00 eq. of PTSA.H$_2$O and 4.0 eq. of (MeO)$_2$CMe$_2$ in MeOH-d$_4$, CDCl$_3$, D$_2$O or DMSO-d$_6$ similarly resulted in the 100% conversion of hydrazone 441a to give a complex mixture of products.

Scheme 107. Failed synthesis of THF 442.

Prior to investigating the acid-catalyzed cyclization of hydrazone 441a, an attempt was also made at preparing a reference sample of THF 443a using Mitsonobu conditions. Treating hydrazone 441a with 1.0 eq. of PPh$_3$ and 1.0 eq. of diisopropyl azodicarboxylate (DIAD) in either THF or MeCN resulted in the trace formation of cyclized product 443a (Scheme 108). Treating hydrazone 441a with TsCl in pyridine also resulted in the observation of THF 443a in a trace quantity. A possible explanation for the failure of this approach is the poor compatibility of the hydrazone functional group with the electrophilic species present under the reaction conditions.

Scheme 108. Attempted synthesis of hydrazone 443a through selective activation of the primary alcohol.
A series of Lewis acids were screened as catalysts for the cyclization of hydrazone 441a in MeOH at RT. It was observed that using 20 mol% [Cu(OTf)]$_2$PhMe and Cu(OTf)$_2$ both resulted in decomposition of the substrate after 8 h, while LiClO$_4$, MgBr$_2$ and Zn(OAc)$_2$ resulted in no reaction. However, 20 mol% BF$_3$.THF catalyzed the formation of THF 443a as a 65:35 mixture of diastereoisomers, with 90% conversion of 441a after 48 h at RT (Scheme 109).

The cyclization of hydrazone 441a in MeOH using 20 mol% BF$_3$.THF was repeated at 60 °C in order to drive the reaction to completion. The corresponding reaction with 20 mol% CSA was also conducted. Both reactions resulted in 100% conversion of hydrazone 441a within 16 h, with CSA resulting in fewer impurities (as determined by analysis of the crude $^1$H NMR spectra). The reaction with CSA was repeated on a 192 mg (1.00 mmol) scale and THF 443a isolated in 55% yield (Scheme 110). By crude $^1$H NMR spectroscopic analysis the diastereoisomeric ratio was measured as anti:syn = 75:25. Recrystallization of THF 443a from CH$_2$Cl$_2$ and hexane gave the major diastereoisomer anti-443a as a single stereoisomer, and the relative stereochemistry was confirmed by single crystal X-ray diffraction.iii

Scheme 109. Synthesis of THF 443a using BF$_3$.THF.

Scheme 110. Synthesis of THF 443a using CSA. Ellipsoids are shown at 50% probability level. Only hydrogen atoms belonging to the cyclic core are shown for clarity.

4.2.2. Reaction Optimization

The cyclization of hydrazone 441a using 20 mol% CSA over 16 h at RT was then investigated using a series of different solvents (Table 20). A screen of NMR solvents

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iii Dr Dejan-Krešimir Bučar and Dr Laure Benhamou are gratefully acknowledged for conducting and analyzing the single crystal X-ray diffraction experiment. Recrystallization was performed by the author.
revealed that no formation of THF 443a occurred in either D₂O or CDCl₃, while using DMSO-d₆ as solvent resulted in ca. 10% conversion of hydrazone 441a (Entries 1–3). The reaction was favored in alcohol solvents (Entries 4–8), with MeOH and nPrOH giving the highest yields as judged from ¹H NMR spectroscopic analysis. DMF, which was used in the cyclization reported by Kóóš and Moscher (Section 4.1.4., Scheme 104), did facilitate the formation of THF 443a (Entry 9) but in lower yield than for MeOH and nPrOH. No significant conversion of hydrazone 441a was observed where MeCN was used as solvent (Entry 10) and a slow reaction was observed in CPME (Entry 11).

Table 20. Solvent screen for the acid-catalyzed cyclization of hydrazone 443a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Conversion of 441a/%</th>
<th>Yield 443a/%</th>
<th>anti:syn 443a⁸</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>D₂O</td>
<td>-</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>CDCl₃</td>
<td>-</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>DMSO-d₆</td>
<td>-</td>
<td>10b</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>MeOH</td>
<td>50</td>
<td>50</td>
<td>65:35</td>
</tr>
<tr>
<td>5</td>
<td>EtOH</td>
<td>80</td>
<td>30</td>
<td>65:35</td>
</tr>
<tr>
<td>6</td>
<td>nPrOH</td>
<td>100</td>
<td>80</td>
<td>75:25</td>
</tr>
<tr>
<td>7</td>
<td>iPrOH</td>
<td>40</td>
<td>30</td>
<td>65:35</td>
</tr>
<tr>
<td>8</td>
<td>nBuOH</td>
<td>50</td>
<td>35</td>
<td>65:35</td>
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<tr>
<td>9</td>
<td>DMF</td>
<td>65</td>
<td>35</td>
<td>70:30</td>
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<tr>
<td>10</td>
<td>MeCN</td>
<td>20</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>CPME</td>
<td>25</td>
<td>15</td>
<td>50:50</td>
</tr>
</tbody>
</table>

⁸Determined by analysis of the crude ¹H NMR spectrum (using C₆HCl₅ as an internal standard). b Estimated without an internal standard.

A series of acids were screened as catalysts for the cyclization, using nPrOH as reaction solvent (Table 21). All the strong acids were effective at catalysing the cyclization (Entries 1–5) while AcOH resulted in no reaction (Entry 6). Both TFA and CSA were effective catalysts for the cyclization, with 80% yields of THF 443a calculated using ¹H NMR spectroscopy. CSA and TFA are of similar cost (ca. £200/kg of TFA compared to ca. £150/kg CSA) but the molecular weight of CSA is approximately twice that of TFA. On these grounds TFA was chosen as the more economical catalyst for further work.
Table 21. Cyclization catalyst screen.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Conversion 441a/%</th>
<th>Yield 443a/%</th>
<th>anti: syn 443a/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CSA</td>
<td>100</td>
<td>80</td>
<td>75:25</td>
</tr>
<tr>
<td>2</td>
<td>HCl (4 M in dioxane)</td>
<td>70</td>
<td>50</td>
<td>75:25</td>
</tr>
<tr>
<td>3</td>
<td>conc. H₂SO₄b</td>
<td>40</td>
<td>25</td>
<td>60:40</td>
</tr>
<tr>
<td>4</td>
<td>PTSA.H₂O</td>
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<td>5</td>
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<td>6</td>
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</tbody>
</table>

a Determined by analysis of the crude ¹H NMR spectrum (using C₆HCl₅ as an internal standard). b 10 mol%.

The reactions in Table 20 and Table 21 suggested that nPrOH was marginally the best solvent for the cyclization and TFA was the best catalyst. However, when these conditions were used on a 1.00 g scale two serious problems were observed. Firstly the reaction consistently took 72 h to reach completion, even when 4 Å molecular sieves were added as a dehydrating agent (Scheme 111). Secondly, the THF 443a could not be separated from an impurity by flash column chromatography, giving THF 443a in only 90% purity. While the impurity was not isolated or characterized, the ¹H NMR spectrum was consistent with solvolysis product 444.

Scheme 111. Cyclization of hydrazone 441a in nPrOH at RT.

Heating the reaction to 40 °C and increasing the reaction concentration to 0.50 M had a significant impact on the reaction time, with 100% conversion of hydrazone 441a observed after 16 h (Scheme 112). This reaction was conducted without 4 Å molecular sieves, with no detrimental impact on the yield of THF 443a. However, impurity 444 was still present following column chromatography and so these conditions required further optimization.
When the reaction solvent was switched to MeOH, THF 443a was isolated in 67% yield as a 75:25 mixture of diastereoisomers in excellent purity following flash column chromatography (Scheme 113). These reaction conditions were taken as the optimized reaction conditions for further investigation.

Recrystallization of THF 443a from hot CPME gave the major diastereoisomer anti-443a in high purity. The optimized cyclization conditions in Scheme 113 were replicated, but hydrazone 441a was substituted for an isomerically pure sample of THF anti-443a (Scheme 115). Analysis of the crude 1H NMR spectrum indicated that THF 443a had epimerized under the reaction conditions to give a 75:25 mixture of anti- and syn-diastereoisomers. This implied that the diastereoselectivity of the cyclization reaction was under thermodynamic control.
Scheme 115. Epimerization of anti-443a under the optimized cyclization conditions.

The epimerization of THF 443a could be explained by a reversible cyclization reaction, or alternatively via the formation of enamine intermediate 445 (Scheme 116, Part I). In order to gain insight, the optimized cyclization reaction of hydrazone 441a (Scheme 113) was replicated using MeOH-d₄ as solvent. This resulted in the formation of THF 443a as a 75:25 mixture of anti- and syn-diastereoisomers, which was isolated in 65% yield (Scheme 116, Part II). No measurable incorporation of deuterium was observed at the position adjacent to the hydrazone, which suggests that epimerization is not occurring via enamine 445.

Scheme 116. Potential enamine intermediate 445 and Cyclization of hydrazone 441a in MeOH-d₄.

As a final mechanistic experiment, the optimized cyclization reaction was replicated, but the reaction quenched after only 1 h. Analysis of the crude ¹H NMR spectrum implied ca. 30% conversion of hydrazone 441a and formation of THF 443a as a 70:30 mixture of anti- and syn-diastereoisomers (Scheme 117). This compares to a 75:25 d.r. when the same reaction was conducted over 16 h (Scheme 113). While the difference in d.r. at 1 h and 16 h was only small, the observation was consistent with a reaction where THF 443a was initially formed with a d.r. < 75:25, but equilibration over 16 h increased the proportion of the anti-diastereoisomer present.
Scheme 117. Cyclization of hydrazone 441a after 1 h.

A suggested mechanistic pathway is given in Scheme 118. The protonation of compound 441a to give intermediate 446 and subsequent elimination of water would result in the formation of a vinyldiazenium species 447. Cyclization of vinyldiazenium intermediate 447 could yield either anti- or syn-443a, depending on the conformation of the intermediate. The experiments detailed in Scheme 115 and Scheme 117 implied that this cyclization was reversible, ultimately giving the thermodynamic mixture of anti- and syn-diastereoisomers.

Scheme 118. Proposed mechanistic pathway for the formation of THF 443a.

4.2.4. Cyclization Scope

The optimized synthetic sequence was applied to a series of reducing sugars, with the results detailed in Table 22. As discussed previously, L-arabinose was efficiently converted to hydrazone 441a and this was converted to THF 443a in 67% yield as a 75:25 mixture of anti- and syn-diastereoisomers on a 1.26 g (6.60 mmol) scale (Entry 1). In addition, the cyclization step was scaled up to use 20.0 g (104 mmol) of hydrazone 441a with no notable drop in yield or stereoselectivity.
Table 22. Hydrazone-mediated cyclization of sugars 440.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sugar 440</th>
<th>Step 1 yield/%</th>
<th>THF 443&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Step 2 yield/ %</th>
<th>d.r.&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L-arabinose 440a</td>
<td>99</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;N=N-H</td>
<td>67 (66)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>75:25</td>
</tr>
<tr>
<td>2</td>
<td>D-ribose 440b</td>
<td>98</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;N=N-H</td>
<td>59</td>
<td>75:25</td>
</tr>
<tr>
<td>3</td>
<td>D-lyxose 440c</td>
<td>98</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;N=N-H</td>
<td>66</td>
<td>55:45</td>
</tr>
<tr>
<td>4</td>
<td>D-xylose 440d</td>
<td>not isolated</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;N=N-H</td>
<td>61&lt;sup&gt;e&lt;/sup&gt;</td>
<td>55:45</td>
</tr>
<tr>
<td>5</td>
<td>L-xylene ent 440d</td>
<td>not isolated</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;N=N-H</td>
<td>57&lt;sup&gt;e&lt;/sup&gt;</td>
<td>55:45</td>
</tr>
<tr>
<td>6</td>
<td>L-rhamnose 440e</td>
<td>99</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;N=N-H</td>
<td>69</td>
<td>60:40</td>
</tr>
</tbody>
</table>

<sup>a</sup> Step I reagents and conditions: 2.0 eq. NH<sub>2</sub>NMe<sub>2</sub>, Amberlyst 15, MeOH, 24 h, RT. <sup>b</sup> Step II conducted on a 6.00–6.70 mmol scale unless otherwise stated. <sup>c</sup> Determined by analysis of the crude <sup>1</sup>H NMR spectrum. <sup>d</sup> Reaction conducted using 20.0 g (104 mmol) of hydrazone 441a. <sup>e</sup> Yield over two steps from xylose.

D-Ribose 440b was converted into the corresponding hydrazone 441b in 98% yield and without need for purification (Table 22, Entry 2). Under the optimized cyclization conditions hydrazones 441b was converted into THF ent-443a in 59% yield as a 75:25 mixture of anti- and syn-diastereoisomers. According to the mechanism proposed in Scheme 118, the cyclization of arabinose- and ribose-derived hydrazones 441a and 441b proceed via enantiomeric vinyldiazenium intermediates (Scheme 119). The observation that both reactions resulted in the same ratio of anti- and syn-diastereoisomers is therefore consistent with the proposed mechanism.
Chiral THFs

Scheme 119. Cyclization of hydrazone 441a and 441b through enantiomeric vinyldiazenium intermediates.

The methodology was also extended to D-lyxose 440c, with the corresponding hydrazone prepared in 98% isolated yield (Table 22, Entry 3). The optimized cyclization step gave THF 443b in 66% isolated yield as a 55:45 mixture of diastereoisomers. Given the poor diastereoselectivity of this reaction, the relative stereochemistry of the major diastereoisomer was not examined.

The reaction of D-xylose 440d with NH$_2$NMe$_2$ under the optimized conditions resulted in 100% conversion of 440d within 24 h and analysis of the $^1$H NMR spectrum in DMSO-$d_6$ confirmed the formation of the corresponding hydrazone. However, the target hydrazone was not the only species observed by $^1$H NMR spectroscopy so it was not possible to calculate an isolated yield. Subjecting the crude hydrazone to the cyclization conditions gave THF 443b in 61% isolated yield over two steps (Table 22, Entry 4). Using the same approach, L-xylose ent-440c was converted into ent-443b with a comparable yield and diastereoselectivity (Entry 5).

The optimized synthetic pathway was also applied to deoxy sugar L-rhamnose 440e (Table 22, Entry 6). The corresponding hydrazone was accessed in 99% yield and this was cyclized to give THF 443c as a 60:40 mixture of diastereoisomers in 69% isolated yield without modification of the cyclization conditions.

The optimized conditions for hydrazone synthesis were also applied to D-galactose (Scheme 120). This reaction was slower than had been observed with the pentoses, but significant conversion of the starting material had occurred after 3 days at RT. It was necessary to purify the reaction by flash column chromatography, with hydrazone 441f
isolated in 31% yield. The optimized cyclization conditions gave a 60:40 mixture of THF 443d and tetrahydropyran 448 in 53% yield. Both compounds were formed as single stereoisomers and were separated by flash column chromatography.

Scheme 120. Cyclization of galactose-derived hydrazone 441f. Reagents and conditions: (i) 2.0 eq. NH₂NMe₂, Amberlyst 15, MeOH, 72 h, RT; (ii) 20 mol% TFA, MeOH, 16 h, 40 °C.

An attempt was made to extend the methodology to D-fructose 440g. Under the optimized condensation conditions very little conversion of D-fructose 440g was observed. Heating the reaction at reflux for 24 h improved the conversion of D-fructose 440g but yielded a complex mixture of products (Scheme 121).

Scheme 121. Unsuccessful reaction of d-fructose with NH₂NMe₂.

4.2.5. Functional Group Manipulation of Cyclized Products

Treatment of hydrazone 443a with an excess quantity of Amberlyst 15 acidic resin (1.00 g/mmol 443a) in water at RT resulted in rapid hydrolysis of the hydrazone. The resin was removed by filtration and the filtrate was then concentrated and lyophilized to yield a white gum. ¹H and ¹³C NMR data of the compound in D₂O suggested that the hydrolyzed product 449 existed as a hydrate 449a-d₄, as depicted in Scheme 124. The NMR data was consistent with an 85:15 mixture of diastereoisomers, without any impurities [¹³C NMR (150 MHz; D₂O) 90.4 (C(OD)₂ anti-449a-d₄), 89.2 (C(OD)₂ syn-449a-d₄); full characterization in Chapter VI]. However, analysis of the ¹H and ¹³C NMR spectra in MeOH-d₄ revealed a more complex mixture of compounds, with the majority of material existing as a compound consistent with hemiacetal 449b [¹³C NMR (150 MHz; MeOH-d₄) 98.9 (C(OD)(OCD₃)), 98.7 (C(OD)(OCD₃))]. Analysis of ¹H and ¹³C NMR spectra in DMSO-d₆ revealed an even more complex mixture of products, but
with evidence for aldehyde $449c$ [$^1H$ NMR (600 MHz; DMSO-$d_6$) 9.56 (1H, d, $J = 2.3$, C(O)H); $^{13}C$ NMR (150 MHz; DMSO-$d_6$) 201.9 (C(O)H)].

Scheme 122. Hydrolysis of 443a and the identity of hydrolyzed product 449 in NMR solvents.

A possible explanation for this observation is that compound 449 undergoes a reversible condensation when concentrated to form an oligomeric structure (Scheme 123). Given that hydrolyzed product 449 was formed in water, it is reasonable to assume it was formed as hydrate $449a$. If upon condensation hydrate $449a$ eliminated a molecule of water to give aldehyde $449c$, then this could react with a second molecule of $449a$ to give a dimer, such as compound $449d$. This could then undergo further dehydraion reactions to give a complex mixture of oligomers. An IR spectra of the neat gum only possessed one weak peak at 1720 cm$^{-1}$ in the region 1650–1750 cm$^{-1}$, suggesting that the solid state structure is not a monomeric aldehyde.

Scheme 123. Proposed reversible oligomerization of hydrolyzed product 449.

Without a definite structure of hydrolyzed product 449, it is not possible to definitively assign a yield for the hydrolysis reaction (Scheme 121). However, if it is assumed that during lyophilization one molecule of water is eliminated for every molecule of hydrate $449'$, then the isolated yield for compound 449 was 98%. For the remainder of Chapter IV, compound 449 is depicted as a free aldehyde (as in Scheme 124), however it is recognized that this is a simplification of its solid-state structure.
Scheme 124. Hydrolysis of hydrazone 443a.

It is also notable that the reaction proceeds with an increase in the diastereoisomeric ratio. Under the same reaction conditions isomerically pure anti-443a epimerized to give the same 85:15 mixture of diastereoisomers. It is therefore likely that the diastereoselectivity observed is due to thermodynamic control.

Compound 449 was reduced using NaBH₄ in MeOH to form triol 450, but isolation of the product was initially problematic. Flash column chromatography (using either silica or MgSiO₃) failed to yield pure product, in part because of the high polarity of triol 450. Amberlyst IRA743 boron scavenger was also trialled but this too failed to yield pure product. However, quenching the reaction with AcOH and subsequent treatment with a mixture of Amberlyst 15 acidic resin and Amberlyst A26 basic resin gave triol 450 in quantitative yield as an 85:15 mixture of diastereoisomers (Scheme 125, Part I). The major product has previously been prepared through the universal protection of D-ribose using bis(trimethylsilyl)trifluoroacetamide (BSTFA), reduction with TMSOTf/Et₃SiH and subsequent deprotection (Scheme 125, Part II). This allowed the relative stereochemistry of triol 450 (and, by implication, that of compound 449) to be confidently determined based on comparison with literature data.²⁵¹

Scheme 125. Reduction of compound 449 and previous approach to triol 450.²⁵⁶

Compound 449 was treated with a 1:1 mixture of Ac₂O in pyridine with the aim of universal acylation to give aldehyde 451 (Scheme 126). However, analysis of the crude
$^1$H NMR spectrum indicated 100% conversion of compound 449 to give a complex mixture of products, with no clear evidence for the target aldehyde 451.

![Scheme 126](image)

**Scheme 126. Failed acylation of compound 449.**

Compound 449 was also treated with 5.0 eq. of $^9$BuNH$_2$, 50 mol% AcOH and 10% Pd/C in MeOH in order to generate amine 452 (Scheme 127). This resulted in 100% conversion of compound 449 after 4 h, upon which the reaction mixture was filtered through Celite and concentrated. The crude amine 452 was too polar to purify directly by flash column chromatography, so it was dissolved in CPME and treated with Boc$_2$O. This generated carbamate 453 in 66% isolated yield as an 80:20 mixture of diastereoisomers.

![Scheme 127](image)

**Scheme 127. Reductive amination of compound 449.**

Treatment of compound 449 with Amberlyst 15 in MeOH resulted in the formation of dimethyl acetal 454 in 75% yield as a 65:35 mixture of diastereoisomers (Scheme 128). In order to assign the stereochemistry, acetal 454 was treated with 10 mol% K$_2$CO$_3$ in dimethyl carbonate (DMC) and the reaction heated at reflux for 16 h. This gave the corresponding carbonate 455 as a single anti-isomer in 87% yield following purification using a silica plug. The relative stereochemistry of carbonate 455 was determined from its $^1$H NMR spectrum by analysis of proton coupling constants, owing to the more rigid nature of the THF. Treatment of carbonate 455 with K$_2$CO$_3$ in MeOH-d$_4$ gave diol anti-454 as a single isomer, confirming the stereochemistry of the acetal formed. Repeating the carbonate formation step without the silica plug purification, followed by carbonate hydrolysis with K$_2$CO$_3$ in MeOH gave acetal 455 as a 65:35 mixture of diastereoisomers. This suggested that syn-455 may readily isomerize on silica to give the thermodynamically more stable anti-455.
Scheme 128. Dimethyl acetal formation.

Treatment of compound 449 with trimethylphosphonoacetate and K$_2$CO$_3$ in MeOH resulted in the formation of olefin 456 in 74% isolated yield (Scheme 129). The alkene was formed with excellent $E$-selectivity and the 85:15 mixture of diastereomers reflects that of compound 449. However, no reaction was observed when compound 449 was treated with diethyl benzylphosphonate under similar conditions, potentially due to the higher pK$_a$ or the phosphonate.

Scheme 129. Olefination of compound 449.

The hydrolysis/reduction sequence was also applied to the hydrazones 443b and 443c, derived from D-xylose and L-rhamnose respectively (Scheme 130). In both cases the hydrazones were transformed to the corresponding triols in good yield and with an increased diastereoisomeric ratio.
Scheme 130. Hydrolysis and reduction of hydrazones 458 and 459. Reagents and conditions: (i) Amberlyst 15, H₂O, 5 minutes, RT; (ii) NaBH₄, MeOH, 1 h, 0 °C.

It was possible to confirm the relative stereochemistry of triol 458 as the major isomer has previously been reported by Monrad and Madsen as a by-product from a rhodium-catalyzed decarbonylation of D-glucose (Scheme 131, Part I). The major isomer of triol 459 was prepared by Fleet et al. as part of the total synthesis of muscarine analogue 3R-3-hydroxymuscarine from L-rhamnose (Scheme 131, Part II), so again the relative stereochemistry was established.

Scheme 131. Madsen’s decarbonylation of D-glucose and Fleet’s total synthesis of 3R-3-hydroxymuscarine from L-rhamnose. Reagents and conditions: (i) Br₂; (ii) Tf₂O; (iii) pyridine, MeOH; (iv) LiAlH₄; (v) TsCl; (vi) NMe₃.

It is interesting to compare Fleet’s synthesis of triol 459 (Scheme 131) with the synthesis described in Scheme 130. Both approaches synthesise triol 459 over 4 steps without the use of protecting groups (Scheme 132). Fleet’s approach gives triol 459 as a single stereoisomer but in a lower overall yield. Perhaps the most significant advantages of the
new methodology for the synthesis of triol 459 is the improvement in atom economy and redox economy. The new methodology also avoids using water-sensitive Tf₂O and LiAlH₄, so it is potentially more amenable to large-scale synthesis.

As was mentioned previously, THF anti-443a was isolated as a single stereoisomer through recrystallization from hot CPME. The transformation of this product into (single isomer) THFs was investigated. The cyclization of diol anti-443a using 10 mol% K₂CO₃ in DMC gave carbonate 467 as a single isomer in quantitative yield (Scheme 133). Hydrolysis of the hydrazone with Amberlyst 15 in water gave a product which, in D₂O, was consistent with hydrate 468 by ¹H NMR spectroscopic analysis, in 87% yield as a single stereoisomer. However, this product was unstable over a period of approximately 24 h in D₂O and was not fully characterized.

Diol anti-443a was converted into acetonide 442 in good yield using acetone, (MeO)₂CM€ and 20 mol% PTSA.H₂O (Scheme 134). This reaction occurred with partial inversion of the epimerizable stereocentre, with acetonide 442 isolated as a 60:40 mixture of syn- and anti-diastereoisomers. The epimerization potentially occurred through acid-mediated reversible ring-opening of the THF under the reaction conditions. The 60:40
diastereoisomeric ratio of acetonide 442 is comparable with 65:35 ratio reported by Koóš and Moscher for the cyclization of arabinose hydrazone 441a in the presence of (MeO)₂CMe₂ in DMF (Section 4.1.4., Scheme 104).²⁴⁵

![Scheme 134. Synthesis of acetonide 442.](image)

Reduction of hydrazone anti-443a using hydrogen gas in the presence of Pd(OH)₂ in CPME in the presence of Boc₂O gave carbamate 469 in 60% yield as a single stereoisomer (Scheme 135).²⁵⁴ Conducting the reaction in the absence of Boc₂O resulted in the formation of two compounds consistent with amine 470 and hydrazine 471, with ca. 90% conversion of hydrazone anti-443a.

![Scheme 135. Reduction of hydrazone anti-443a.](image)

It is established that N,N-dialkylhydrazones can be converted to the corresponding nitrile through oxidation with magnesium monoperoxyphthalate (MMPP).²⁵⁵ Treating hydrazone anti-443a with 2.50 eq. of MMPP in MeOH at 0 °C resulted in 100% conversion of hydrazone anti-443a within 10 minutes (Scheme 136). Analysis of the crude product revealed a product consistent with nitrile 472 as a single isomer with only minor impurities. However, after a number of attempts it was not possible to isolate a purified sample of the compound. Why nitrile 472 was so difficult to isolate is unclear, but it could be due to poor stability on silica, volatility or simply a poor reaction yield. The reaction was also attempted using 1.20 eq. of MMPP, but this reaction failed to reach completion after 24 h.
The oxidation conditions were also applied to carbonate 467 (Scheme 137). This resulted in rapid conversion of the starting material but no product was isolated from this reaction. This result could be due to the instability of the cyclic carbonate group under the reaction conditions.

In an attempt to find a suitable substrate for the oxidative hydrazone cleavage, diol anti-443a was converted into cyclic silyl ether 474. Treating diol anti-443a with tBu₂Si(OTf)₂ in pyridine at 0 °C resulted in the formation of silyl ether 474 but with significant epimerization. However, the epimerization was avoided by using DMC as a solvent and 2,6-lutidine as a base, giving the desired silyl ether 474 in 48% yield as a single isomer (Scheme 138). Oxidation with MMPP gave a product consistent with nitrile 475 as a single diastereoisomer, but column chromatography failed to recover the target material.

A potentially useful transformation of the cis-diol anti-443a would be oxidation to give the corresponding dialdehyde 476 (Scheme 139). This could, for example, be condensed with an amine and reduced to access a chiral morpholine 477. However, treatment of diol anti-443a with NaIO₄ in D₂O resulted in the rapid conversion of diol anti-443a to give a complex mixture of products by TLC and ¹H NMR spectroscopic analysis. The reaction
in MeOH-d$_4$ took 8 h to achieve 100% conversion of diol *anti-443a* but resulted in an analogous outcome. A possible explanation is that the hydrazone group was unstable in the presence of NaIO$_4$.

![Scheme 139. Attempted oxidation of THF *anti-443a* using NaIO$_4$.](image)

Another potentially useful transformation of hydrazone *anti-443a* would be conversion to cyclic sulfate 478 (Scheme 140). In principle this could then react with an external nucleophile in a regioselective fashion to give THF 480. However, treatment of hydrazone *anti-443a* with SO$_2$Cl$_2$ and NEt$_3$ in CH$_2$Cl$_2$ resulted in the rapid decomposition of *anti-443a* with no evidence for the target sulfate 478. An alternative route to cyclic sulfates is via the corresponding cyclic sulfinate. Treatment of THF *anti-443a* with SOCl$_2$ and NEt$_3$ in CH$_2$Cl$_2$ gave a compound consistent with target sulfinate 479 in 23% yield with minor impurities. [1H NMR (600 MHz; CDCl$_3$) 5.80 (1H, d, $J = 6.0$, CH$_2$CHC$_3$H$_2$), 5.45 (1H, dd, $J = 6.0, 4.1$, CH$_2$CH$])$. However, sulfinate 479 decomposed overnight at RT in a solution of CDCl$_3$. The relative stereochemistry of sulfinate 479 was not established.

![Scheme 140. Attempted synthesis of a cyclic sulfate 478.](image)

### 4.3. Chapter IV Summary

In conclusion, a hydrazone-based methodology has been developed for the synthesis of chiral THFs from biomass feedstock under sustainable reaction conditions (Scheme 141). This approach was effective with different pentoses and *L*-rhamnose and was
demonstrated on a multi-gram scale. Furthermore, through reduction and hydrolysis of the hydrazone group, a diverse selection of chiral THFs were prepared without the use of protecting groups. This included a formal synthesis of 3R-3-hydroxymuscarnine.

Scheme 141. Chapter IV Summary.
Chapter V. Conclusions and Future Work

5.1. Conclusions

In summary, this project has led to the successful development of novel methods to access a diverse range of medicinally relevant heterocycles (Figure 24). In Chapter II, conditions were developed for the regioselective cyclotrimerization of amide-tethered diynes and monoynes, which was applied to the synthesis of highly substituted isoindolinone products.\textsuperscript{258} In Chapter III, the kinetically-controlled Diels–Alder reaction of 3-alkoxyfurans\textsuperscript{190} and maleimides was developed for the synthesis of endocantharimides.\textsuperscript{259} This Diels–Alder reaction was explored with the aid of computational calculations and the methodology extended to access a variety of sp\textsuperscript{3}-rich molecular scaffolds. In Chapter IV, a hydrazone-mediated cyclization of reducing sugars was developed for the synthesis of chiral THFs without the use of protecting groups.\textsuperscript{260} Crucially, the environmental impact of this research has been reduced by using sustainable solvents and chemicals from biomass-derived feedstocks.

Figure 24. Summary of heterocycles prepared in Chapters II–IV.
5.2. Future Work

5.2.1. Alkyne Cyclotrimerizations

In Chapter II, the regioselectivity of alkyne cyclotrimerizations was generally controlled through use for a SiMe₃ regiodirecting group, which could then be substituted to prepare aryl halides. By investigating different directing groups new isoindolinones could be synthesized. For example, a siletane directing group would give an isoindolinone that could in principle be oxidized to give phenol (Scheme 142). Aryl siletanes have also been used as the nucleophilic component of Hiyama-type cross-coupling reactions.

Scheme 142. Potential application of a siletanes directing group. Reagents and conditions: (i) H₂O₂, KF, KHCO₃; (ii) ArI, TBAF, [allylPdCl]₂, P(Bu)₃.

An alternative to an amide-tethered diyne would be ester-tethered diyne 506, which could be cyclized to form isobenzofuranone 508 (Scheme 143). With different monoynes, this could be used to prepare a selection of aromatic products. The approach could also be applied to the total synthesis of isopestacin 508, a racemic natural product with antifungal activity.

Scheme 143. Proposed cyclotrimerizations of ester-tethered diynes and monoynes.
The cyclization of ketone-tethered diynes would also be an interesting reaction to explore.\textsuperscript{137} This class of diyne could be prepared by the selective alkylation of commercially available methyl ketone \textbf{512 (Scheme 144)} and cyclized to generate different indanones \textbf{515}.\textsuperscript{266} Indanone \textbf{515} could then be used as a substrate for a whole cell-catalyzed Baeyer–Villiger oxidation to prepare chiral lactone \textbf{516}.\textsuperscript{267} If ketone \textbf{515} were racemized under the reaction conditions then lactone \textbf{516} could be prepared in an enantioconvergent fashion \textit{via} a dynamic kinetic resolution. Alternatively, a transaminase could be used to convert ketone \textbf{515} into amine \textbf{517}.\textsuperscript{268} If the transaminase was selective for the formation of one diastereoisomer over the other, this approach would also be an effective kinetic resolution strategy.

![Scheme 144](image)

\textbf{Scheme 144. Synthesizing substituted 1-indanones via an alkyne cyclotrimerization.} Reagents and conditions: (i) LDA, R\textsubscript{1}Br; (ii) LDA, propargyl bromide; (iii) cyclohexanone monooxygenase [see Ref 267], Lewatit MP62; (iv) (R)-\omega-transaminase [see Ref 268].

An interesting observation made in Chapter II was the unusual behaviour of 2-ethynyltoluene as a monoyne. The reaction of 2-ethynyltoluene and diyne \textbf{245a} occurred at a greater rate than the corresponding reaction of phenylacetylene and the reaction occurred with negligible diyne homo-coupling (\textbf{Scheme 145}). This reactivity could be explored further by considering the reaction of 2-ethynyltoluene with other diynes and by considering other 2-substituted phenylacetylenes. This phenomenon could also be explored with the aid of computational calculations.

![Scheme 145](image)

\textbf{Scheme 145. Unusual reactivity of 2-ethynyltoluene 246l.}
5.2.2. Furan-Diels–Alder Reactions

In Chapter III, endo-cantharimides were prepared from 2-substitued 3-alkoxyfurans. An alternative route to the endo-cantharimide could be via a fused bicyclic furan 525, prepared from a propargylic alcohol with a pendent nucleophile 524 (Scheme 146). In principle a furan could be prepared using a pendent oxygen or nitrogen nucleophile, with the example of a carbamate nucleophile illustrated below. The Diels–Alder reactions of 3-aminofurans have not been widely explored.269

Another direction for further studies could be an asymmetric cantharimide synthesis. Manna and Mukherjee reported the organocatalytic asymmetric vinylogous Michael addition of maleimides and deconjugated butenolides270 and a similar approach could be explored to prepare cantharimides (Scheme 147). Tautomerism of a substituted furanone271 530 would afford a 3-hydroxyfuran 533, which could form a hydrogen bond with a chiral amine catalyst. If the same catalyst activated the maleimide through hydrogen bonding with a thiourea then it could catalyze the Diels–Alder reaction in an asymmetric fashion. Such a constrained transition state may also improve the diastereoselectivity of the reaction. The product of the Diels–Alder reaction would be enol 535, which would tautomerize to give ketone product 532. The cyclization of 3-alkoxyfurans and dienophiles using chiral Lewis acid catalysts could also be explored.272
5.2.3. Hydrazone-Mediated Transformations of Reducing Sugars

An interesting extension of the research in Chapter IV would be to prepare THFs from ketoses. For example, fructose-derived hydrazone 441g may undergo a double condensation under acidic conditions to give isosorbide-derivative 537 (Scheme 148).

The stereochemistry of the reaction would in principle be controlled by the reversible nature of the cyclization and the strong thermodynamic preference for cis-fused [5,5]-ring systems. As discussed in Chapter IV (Section 4.2.4., Scheme 121), a key challenge with this approach was the synthesis of hydrazone 441g, which was not possible using the conditions used to prepare hydrazones from pentoses. This could potentially be addressed by exploring known literature conditions for related reactions, such as Reeves’ reported use of B(OCH$_2$CF$_3$)$_3$ to facilitate imine condensation.

The optimized cyclization has primarily been applied to the synthesis of THFs. If it were possible to incorporate an internal nitrogen-based nucleophile the methodology could
potentially be applied to the synthesis of $N$-heterocyclic compounds (Scheme 149). A potential route into these compounds would be via amine 538, formed from the reductive amination of L-arabinose. A selective oxidation of the primary alcohol would give amino sugar 539. This could then be condensed with NH$_2$NMe$_2$ to generate hydrazone 540 and cyclization would give pyrrolidinone 541. While a strong acid may be an inefficient catalyst for the cyclization of amines (given the propensity to form a salt in a polar solvent) the reaction could be more effective with a Lewis acid such as BF$_3$:THF. Using an electronically deactivated $N$-nucleophile (such as a carbamate) could also facilitate the cyclization. Another option would be to attempt a cyclization of hydrazone 540 under thermal conditions, without the use of a catalyst.

Scheme 149. Extending the methodology to $N$-heterocyclic compounds. Reagents and conditions: (i) RNH$_2$, NaBH$_3$CN, MeOH; (ii) TEMPO, trichloroisocyanuric acid, CH$_2$Cl$_2$; (iii) NH$_2$NMe$_2$, Amberlyst 15, MeOH.

Another potential area for further investigations would be the trapping of sugar-derived hydrazones with external nucleophiles. A potential method would be to transform arabinose-derived hydrazone 431a into acylated product 542 (Scheme 150). The acylation would simultaneously deactivate the primary hydroxyl group as a nucleophile and activate the hydroxyl group adjacent to the hydrazone as a leaving group. In principle, this could be trapped out with a variety of nucleophiles to access a substituted carbohydrate derivative 543. In a preliminary study, hydrazone 431a was converted to the acylated product 542. This compound was not stable enough to purify, but the crude product was concentrated and redissolved in MeOH before being treated with 4-chloroaniline. This gave a product consistent with hydrazone 543a in 85% isolated yield as a 60:40 mixture of diastereoisomers.
Scheme 150. Proposed substitution of acylated hydrazone derivative 542 with external nucleophiles.

The oxidative ring-opening of diol *anti*-433a was briefly explored in Chapter IV (Section 4.2.5., Scheme 139) but generated a complex mixture, potentially due to oxidation of the hydrazone group. An alternative approach would be to oxidize carbamate 458 (which has been prepared as a single stereoisomer) to the corresponding dialdehyde 544, and trap it out through a double-reductive amination to give chiral morpholine 545 (Scheme 151). An alternative approach would be to selectively oxidize ammonium salt 546, which could be potentially prepared through reduction of hydrazone *anti*-433a. The corresponding dialdehyde could then condense with the pendent amine to give imine 547, which could be selectively reduced to give morpholine 548. A key challenge of this approach would be to avoid epimerization of the remaining stereocentre following oxidation.

Scheme 151. Potential route to chiral morpholines 545 and 548.

Another potentially valuable transformation for *cis*-diols prepared in Chapter IV would be selective displacement of one hydroxyl group with a nucleophile. The transformation of hydrazone *anti*-433a into a cyclic sulfate was briefly explored (Section 4.2.5., Scheme 140) but proved challenging, potentially due to the instability of the hydrazone group.
under the reaction conditions. An alternative substrate could be carbamate 458, which could be converted into cyclic sulfate 549 (Scheme 152). The cyclic sulfate could then be displaced with an external nucleophile to access a variety of chiral THFs 550 as single stereoisomers. Ideally the regioselectivity of the cyclization would be controlled by the bulky carbamate sterically hindering attack of the proximal electrophilic centre. Alternatively, deprotonation of the carbamate using NaH would give an internal nucleophile, which could displace the cyclic sulfate to give ether 551. The regioselectivity of this reaction would, in principle, be control by the kinetic preference for the formation of five-membered rings over four-membered rings.

Scheme 152. Application of cyclic sulfates.

A drawback of the optimized acid-mediated cyclization reaction is the need to use a strong acid as a catalyst, which has associated safety implications and, as discussed above, potentially limits functional group compatibility. An attractive alternative would be to cyclize arabinose-derived hydrazone 401a under basic conditions (Scheme 153). This was achieved in a preliminary study by using ethylene carbonate as an activating reagent. This gave THF 443a with a preference for the syn-diastereoisomer, which is the opposite selectivity to that observed for the TFA-mediated cyclization.

Scheme 153. Proposed ethylene carbonate-mediated cyclization.
Chapter VI. Experimental Details

6.1. General Experimental

NMR spectra: $^1$H and $^{13}$C NMR spectra were recorded on Bruker AMX-300, Bruker AMX-400, Bruker Avance 400, Bruker Avance 500 or Brucker Avance 600 spectrometers. All chemical shifts are quoted in ppm relative to tetramethylsilane ($\delta = 0.00$ ppm) and referenced to residual protonated solvent unless otherwise stated. Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), combinations thereof or m (multiplet). All coupling constants ($J$) are quoted in Hz to 1 decimal place. The $^{13}$C NMR spectra of novel compounds were assigned with the aid of HSQC NMR spectra.

Mass spectra: Mass spectra were obtained using either a VG70-SE or MAT 900XP spectrometer at the Department of Chemistry, University College London. High resolution values are quoted in Daltons to 4 decimal places and are within 5 ppm of their theoretical values.

Other data: Infrared spectra were recorded on a Perkin-Elmer 1605 Fourier transform spectrometer or a Perkin-Elmer spectrum 100 FT-IR spectrometer as thin films. Absorption maxima ($\nu_{max}$) are quoted in wavenumbers ($\text{cm}^{-1}$) and are described as s (strong), m (medium) or w (weak) and where relevant br. (broad). Melting points were obtained using a Reichert hot-stage apparatus and are uncorrected. All optical rotation was measured on a Perkin-Elmer 343 polarimeter with a path length of 1 dm.

Chromatography: Analytical TLC was carried out using Merck Keiselgel aluminium-backed plates coated with silica gel, which were inspected under ultraviolet light and stained with basic potassium permanganate dip. Retention factors ($R_f$) are quoted with the solvent system in parentheses. Flash column chromatography was performed using BDH (40–60 μm) silica gel. Solvent systems are quoted in parentheses.

All experiments were conducted under an atmosphere of argon or nitrogen in oven-dried glassware. Solvent was used as commercially supplied unless otherwise stated.
6.2. General Experimental Procedures

General Amide Formation Procedure

Oxalyl chloride (1.1 eq.) was added dropwise to a stirring solution of acid 242 (1.2 eq.) and DMF (a few drops) in 2-MeTHF (0.85 mL/mmol of acid 242) at RT. The reaction was stirred for 1 h before the crude acid chloride solution was added dropwise to a stirring solution of amine 244 (1.0 eq.) and NEt₃ (2.5 eq.) in 2-MeTHF (4.5 mL/mmol of amine 244) at RT. The reaction was stirred for 1 h before being filtered through a silica plug, eluting with EtOAc. The filtrate was concentrated in vacuo to give the crude amide.

General Cyclization Procedure A- Cyclotrimerization of amide 245a and a Monoyne under Preliminary Conditions.

According to the modified procedure of Yamamoto et al.¹³⁷: A solution of monoyne 246 (2.0 mmol) and RuCp*Cl(cod) (19 mg, 0.050 mmol, 10 mol%) in degassed CPME (2.0 mL) was added dropwise over 15 minutes to a stirring solution of amide 245a (135 mg, 0.500 mmol) in degassed CPME (3.0 mL) at RT. The reaction was monitored by TLC and then the reaction mixture was filtered through a silica pad, eluting with EtOAc. The filtrate was concentrated in vacuo to give the crude isoindolinone product.

General Cyclization Procedure B- Cyclotrimerization of a Diyne and a Monoyne using a 3 h Dropwise Addition.

A solution of diyne (0.26 mmol) in CPME (1.6 mL) was added dropwise over 3 h to a stirring solution of monoyne (2.0 eq.) and RuCp*Cl(cod) in CPME (1.1 mL) at RT. The reaction was stirred for a specific period of time before the reaction mixture was filtered through a silica pad, eluting with EtOAc. The filtrate was concentrated in vacuo to give the crude isoindolinone product.

General Cyclization Procedure C- Cyclotrimerization of an Internal Diyne and a Monoyne using a 1 minute Dropwise Addition.

A solution of diyne (0.26 mmol) in CPME (1.6 mL) was added dropwise over 1 minute to a stirring solution of monoyne (2.0 eq.) and RuCp*Cl(cod) (10 mol%) in CPME (1.1 mL) at RT. The reaction was stirred for 24 h before the reaction mixture was filtered through a silica pad, eluting with EtOAc. The filtrate was concentrated in vacuo to give the crude isoindolinone product.
Chapter IV

General Alkynylation Procedure: Addition of 3,3-diethoxyprop-1-yne to Aldehydes

According to the procedure of Sheppard et al.\textsuperscript{190}: A solution of \textsuperscript{t}BuLi (1.1 eq., 1.6 M in hexanes) was added dropwise to a stirring solution of 3,3-diethoxyprop-1-yne (1.2 eq.) in anhydrous THF (2.0 mL/mmol of aldehyde) at \textasciitilde78 °C. The reaction mixture was stirred at \textasciitilde78 °C for 1 h before the aldehyde (1.0 eq.; neat unless otherwise indicated) was added dropwise. The reaction was stirred for 16 h, with the reaction allowed to slowly reach RT. The reaction was then cooled to 0 °C and was quenched by dropwise addition of aq. sat. NH\textsubscript{4}Cl (20 mL). The reaction mixture was diluted with EtOAc (20 mL) and the aq. extract washed with EtOAc (3 \times 20 mL). The combined organic extracts were dried (phase separator) and the filtrate was concentrated \textit{in vacuo} to give the crude product.

General Furan Procedure: Gold(I)-Catalyzed Cyclization of Propargylic Alcohols

According to the modified Procedure of Sheppard et al.\textsuperscript{190}: A solution of [PPh\textsubscript{3}AuNTf\textsubscript{2}]\textsubscript{2}PhMe (1 mol%, 2.0 mol% [Au]) in EtOH (50% of total volume) was added dropwise to a stirring solution of propargylic alcohol 316 in EtOH (50% of total volume) at RT to give a solution of the stated concentration. The resulting solution was stirred for 16 h before being purified by flash column chromatography (0 to 10% petrol 30–40 °C: TBME) to give the indicated 3-alkoxyfuran.

General Cycloaddition Procedure: Catalyst-Free [4+2]-Cycloaddition

A solution of dienophile (1.2 eq.) and 3-alkoxyfuran (1.0 eq.) in DMC (1.0 M with respect to the 3-alkoxyfuran) were stirred at RT until the reaction was judged to be complete by TLC or LC-MS analysis. The reaction was then diluted with EtOAc and loaded onto an aminopropyl cartridge. After 5 minutes the cartridge was then washed with EtOAc and the filtrate was concentrated \textit{in vacuo} to give the indicated product.

General Hydrazone Synthesis Procedure

A stirring mixture of sugar 440 in MeOH (2.0 M) was treated with NH\textsubscript{2}NMe\textsubscript{2} (2.0 eq.) and Amberlyst 15 (1.00 g/100 mmol sugar 440) at RT. The resulting mixture was stirred at RT for 24 h before the mixture was filtered and the filtrate concentrated \textit{in vacuo} to give the crude hydrazone.
General Acid-Catalyzed Cyclization Procedure

A stirring mixture of hydrazone 441 in MeOH (0.50 M) was treated with TFA (20 mol%) at RT and the reaction stirred at 40 °C for 16 h. The reaction was then quenched with aq. sat. NaHCO₃ and concentrated in vacuo to give the crude hydrazone.

6.3. Compound Synthesis: Experimental Details & Compound Characterisation

3-(Trimethylsilyl)propionic acid (242)

According to the modified procedure of Fleming et al.: A solution of ethynyltrimethylsilane (22 mL, 15 g, 150 mmol) in anhydrous THF (120 mL) was added slowly to a stirring solution of ethyl magnesium bromide (1.0 M in THF, 191 mL, 191 mmol) at 0 °C. The reaction mixture was stirred for 2 h at RT before being cooled to –20 °C. The solution was cautiously added to solid carbon dioxide (20 g, 450 mmol) and was stirred for 16 h, with the reaction allowed to slowly reach RT. The reaction was cooled to 0 °C and was quenched by dropwise addition of 1.0 M aq. HCl. The mixture was extracted with petrol 40–60 °C (4 × 100 mL), washed with brine (200 mL), dried (MgSO₄) and concentrated in vacuo to give the crude product, which was purified by vacuum distillation (b.p. 78–80 °C at 8 Torr) to the carboxylic acid 242 as a white crystalline solid (16.7 g, 117 mmol, 78%); m.p. 38–40 °C; b.p. 78–80 °C at 8 Torr (literature 108–100 °C at 10 Torr); Rf = 0.25 (1:1 petrol 40–60 °C:EtOAc); νmax (film/cm⁻¹) 3000m br. (O-H), 2965s (C-H), 2181w (C≡C), 1691s (C=O), 1402m, 1254s, 919s, 847s; ¹H NMR (400 MHz; CDCl₃) 10.28 (1H, br. s, C(O)OH), 0.28 (9H, s, Si(CH₃)₃); ¹³C NMR (100 MHz; CDCl₃) 157.5 (CO₂H), 97.5 (C≡C), 93.7 (C≡C), –1.0 (Si(CH₃)₃); data in accordance with the literature.

N-Benzylprop-2-yn-1-amine (244a)

According to the modified procedure of Burton and Hess: Propargyl bromide (6.7 mL, 8.8 g, 80 wt. % in PhMe, 60 mmol) was added dropwise to benzylamine (40 mL, 39 g,
360 mmol) with continuous stirring at RT. The reaction was stirred for 16 h and then partitioned between 2.0 M aq. NaOH (50 mL) and Et₂O (50 mL). The aq. extract was washed with Et₂O (2 × 50 mL) and the combined organic extracts were washed with brine (100 mL), dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (3:1 petrol 40–60 °C:EtOAc) to give the amine 244a as a yellow oil (7.05 g, 48.6 mmol, 81%); R$_f$ = 0.36 (3:1 petrol 40–60 °C:EtOAc); $\nu_{\text{max}}$ (film/cm$^{-1}$) 3292s (CC-H, N-H), 2838s (C-H), 1494s, 1453s; $^1$H NMR (400 MHz; CDCl$_3$) 7.39–7.26 (5H, m, ArH), 3.91 (2H, s, CH$_2$Ph), 3.46 (2H, d, J = 2.4, CH$_2$C≡C), 2.29 (1H, t, J = 2.4, C≡CH); $^{13}$C NMR (100 MHz; CDCl$_3$) 139.4 (Ar), 128.5 (Ar), 128.5 (Ar), 127.2 (Ar), 82.1 (C≡C), 71.6 (C≡C), 52.3 (CH$_2$N), 37.4 (CH$_2$N); data in accordance with the literature.$^{140}$

$\text{N-(\text{tert-Butyl})prop-2-yn-1-amine (244c)}^{147}$

\[
\text{CH}_2\text{N} \quad \equiv \\
\text{CH}_2\text{C≡CH}
\]

According to the modified procedure of Sulpizo *et al.*$^{147}$: Propargyl bromide (13 mL, 17 g, 80 wt. % in PhMe, 120 mmol) was added dropwise to a stirring solution of 2-methylpropan-2-amine (37 mL, 26 g, 350 mmol) in Et₂O (35 mL) at RT. The reaction was stirred at RT for 36 h before being concentrated *in vacuo*. The crude product was purified by distillation at atmospheric pressure (b.p. = 125–127 °C) to give the amine 244c as a colorless oil (4.10 g, 79 wt. % with PhMe, 29 mmol, 24%); $\nu_{\text{max}}$ (film/cm$^{-1}$) 3306s (CC-H), 3245m br. (N-H), 2963s (C-H), 1476s; $^1$H NMR (600 MHz; CDCl$_3$) 3.27 (2H, d, J = 2.3, CH$_2$N), 2.11 (1H, t, J = 2.3, CCH), 1.03 (9H, s, C(CH$_3$)$_3$); $^{13}$C NMR (150 MHz; CDCl$_3$) 83.4 (C≡CH), 70.8 (C≡CH), 50.9 (C(CH$_3$)$_3$), 32.0 (CH$_2$N), 28.8 (C(CH$_3$)$_3$); data in accordance with the literature.$^{147}$

$\text{N-(Prop-2-ynyl)prop-2-en-1-amine (244d)}^{280}$

\[
\text{CH}_2\text{N} \quad \equiv \\
\text{CH}_2\text{C≡CH}
\]

According to the modified procedure of Li and Marks$^{148}$: Propargyl chloride (6.8 mL, 7.0 g, 93 mmol) was added dropwise to allylamine (50 mL, 38 g, 660 mmol) with continuous stirring and the resulting solution was stirred at reflux for 48 h. The reaction mixture was allowed to cool to RT before being partitioned between water (300 mL) and Et₂O (300 mL). The aq. extract was washed with Et₂O (300 mL) and the combined
organic extracts were dried (MgSO$_4$) and concentrated in vacuo. The crude product was distilled at atmospheric pressure (b.p. 126–128 °C) to give the-amine 244d as a colorless oil (3.00 g, 31.5 mmol, 33%); b.p. 126–128 °C at atmospheric pressure (literature 44–46 °C at 0.22 Torr$^{280}$; $\nu_{\text{max}}$ (film/cm$^{-1}$) 3297s (CC-H) 3250m br. (N-H), 2832m (C-H), 1644s (C=C), 1452s; $^1$H NMR (500 MHz; CDCl$_3$) 5.80–5.72 (1H, m, C$_2$H$_2$N), 5.10 (1H, dq, $J$ = 17.3, 1.2, CH/H=CH), 5.00 (1H, dq, $J$ = 10.3, 1.2, CH/H=CH), 3.30 (2H, d, $J$ = 2.5, CH$_2$C=C)), 3.21 (2H, dt, $J$ = 6.1, 1.2, C=CHC$_2$H$_5$), 2.14 (1H, t, $J$ = 2.5, C≡CH); $^{13}$C NMR (125 MHz; CDCl$_3$) 135.9 (CH$_2$=C), 116.6 (CH$_2$=CH), 82.0 (C=C), 71.5 (C=C), 70.8 (CH$_2$CH), 37.2 (CH$_2$C=C); data in accordance with the literature.$^{280}$

**N-Benzylbut-2-yn-1-amine (244e)$^{281}$**

![Diagram](attachment:image.png)

According to the modified procedure of Burton and Hess$^{140}$: 1-Bromobut-2-yne (0.66 mL, 1.0 g, 7.5 mmol) was added dropwise to benzylamine (4.9 mL, 4.8 g, 45 mmol) with continuous stirring at 0 °C. The reaction was stirred for 16 h at RT and then partitioned between 1.0 M aq. NaOH (30 mL) and Et$_2$O (30 mL). The aq. extract was washed with Et$_2$O (2 × 30 mL) and the combined organic extracts were washed with brine (100 mL), dried (MgSO$_4$) and the concentrated in vacuo. The crude product was purified by flash column chromatography (5:1 petrol 40–60 °C:EtOAc) to give the amine 244e as a colorless oil (738 mg, 4.64 mmol, 62%); $R_f$ = 0.38 (2:1 petrol 40–60 °C:EtOAc); $\nu_{\text{max}}$ (film/cm$^{-1}$) 3319m (N-H), 2917s (C-H), 1495s, 1453s; $^1$H NMR (600 MHz; CDCl$_3$) 7.36–7.31 (4H, m, ArH), 7.27–7.23 (1H, m, ArH), 3.85 (2H, s, CH$_2$Ph), 3.38 (2H, q, $J$ = 2.3, CH$_2$C=C), 1.85 (3H, t, $J$ = 2.3, CH$_3$), 1.51 (1H, br. s, NH); $^{13}$C NMR (150 MHz; CDCl$_3$) 139.8 (Ar), 128.5 (Ar), 128.5 (Ar), 127.2 (Ar), 79.3 (C=C), 77.3 (C=C), 52.7 (PhCH$_2$), 38.0 (CH$_2$C=C), 3.7 (CH$_3$); data in accordance with the literature.$^{281}$

**N-Benzylpent-2-yn-1-amine (244f)$^{140}$**

![Diagram](attachment:image.png)

According to the modified procedure of Burton and Hess$^{140}$: 1-bromopent-2-yn (0.72 mL, 1.0 g, 7.0 mmol) was added dropwise to benzylamine (4.5 mL, 4.5 g, 42 mmol) with continuous stirring at 0 °C. The reaction was stirred for 16 h at RT and then partitioned between 1.0 M aq. NaOH (30 mL) and Et$_2$O (30 mL). The aq. extract was
washed with Et₂O (2 × 30 mL) and the combined organic extracts were washed with brine (100 mL), dried (MgSO₄) and the concentrated in vacuo. The crude product was purified by flash column chromatography (10:1 petrol 40–60 °C:EtOAc) to give the amine 244f as a pale yellow oil (858 mg, 4.96 mmol, 71%); R_f = 0.24 (5:1 petrol 40–60 °C:EtOAc); ν_max (film/cm⁻¹) 3313w br. (N-H), 2975s (C-H), 1639s, 1453s; ¹H NMR (400 MHz; CDCl₃) 7.38–7.32 (4H, m, ArH), 7.30–7.28 (1H, m, ArH), 3.88 (2H, s, C₂H₂Ph), 3.42 (2H, t, J = 2.2, NC≡C), 2.25 (2H, qt, J = 7.5, 2.2, C₂H₃), 1.53 (1H, br. s, NH), 1.17, (3H, t, J = 7.5, C₂H₃); ¹³C NMR (150 MHz; CDCl₃) 139.8 (Ar), 128.5 (Ar), 127.2 (Ar), 85.4 (C≡C), 77.4 (C≡C), 52.6 (CH₂Ph), 38.0 (NCH₂C≡C), 14.3 (CH₃), 12.6 (CH₂CH₃); data in accordance with the literature.¹⁴⁰

N-Benzyl-N-(prop-2-yn-1-yl)-3-(trimethylsilyl)propiolamide (245a)

Prepared from amine 244a (2.84 g, 19.6 mmol) according to the General Coupling Procedure and purified by flash column chromatography (9:1 petrol 40–60 °C:EtOAc) to give the amide 245a as a yellow oil (4.48 g, 16.6 mmol, 85%); R_f = 0.44 (6:1 petrol 40–60 °C:EtOAc); ν_max (film/cm⁻¹) 3292m (CC-H), 2962m (C-H), 1634s (C=O), 1417s; ¹H NMR (400 MHz; CDCl₃) a mixture of rotamers R₁ (major) and R₂ (minor); 7.40–7.28 (5H, m, ArH R₁; 5H, m, ArH R₂), 4.93 (2H, s, CH₂Ph R₁), 4.74 (2H, s, CH₂Ph R₂), 4.27 (2H, d, J = 2.5, CH₂C≡C R₂), 4.12 (2H, d, J = 2.5, CH₂C≡C R₁), 2.35 (1H, t, J = 2.5, C≡CH R₂), 2.25 (1H, t, J = 2.5, C≡CH R₁), 0.25 (9H, s, Si(CH₃)₃ R₂), 0.22 (9H, s, Si(CH₃)₃ R₁); ¹³C NMR (125 MHz; CDCl₃) a mixture of rotamers; 153.6 (C(O)), 153.5 (C(O)), 135.7 (Ar), 135.5 (Ar), 128.9 (Ar), 128.7 (Ar), 128.6 (Ar), 128.2 (Ar), 128.0 (Ar), 127.9 (Ar), 98.7 (C≡C), 98.5 (C≡C), 95.7 (C≡C), 95.3 (C≡C), 77.7 (C≡C), 77.6 (C≡C), 73.3 (C≡C), 72.6 (C≡C), 51.5 (CH₂N), 46.5 (CH₂N), 37.6 (CH₂C≡CH), 32.3 (CH₂C≡CH), –0.7 (Si(CH₃)₃), –0.8 (Si(CH₃)₃); HRMS (ESI⁺) found [M+H]⁺ 270.1308; C₁₆H₂₀NOSi requires 270.1314.
Experimental Details

*N-(Prop-2-ynyl)-3-(trimethylsilyl)propiolamide (245b)*

![Chemical Structure](image)

Prepared from propargylamine (0.34 mL, 0.29 g, 5.5 mmol) according to the General Coupling Procedure and purified by flash column chromatography (5:1 petrol 40–60 °C:EtOAc) to give the amide 245b as a white crystalline solid (789 mg, 4.40 mmol, 80%); m.p. 42–44 °C; R_f = 0.38 (5:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm\(^{-1}\)) 3275s (CC-H and N-H), 2963m (C-H), 1638s (C=O), 1526s; \(^1\)H NMR (600 MHz; DMSO-d\(_6\)) 9.15 (1H, t, J = 5.3, N\(_\text{H}\)), 3.85 (2H, dd, J = 5.3, 2.4, CH\(_2\)N), 3.13 (1H, t, J = 2.4, C≡CH), 0.21 (9H, s, Si(CH\(_3\))\(_3\)); \(^{13}\)C NMR (125 MHz; DMSO-d\(_6\)) 151.4 (C(O)), 98.3 (C≡C), 90.5 (C≡C), 80.1 (C≡C), 73.3 (C≡CH), 28.1 (CH\(_2\)N), –0.8 (Si(CH\(_3\))\(_3\)); HRMS (Cl\(^+\)) found [M+H]\(^+\) 180.0847; C\(_9\)H\(_{14}\)NOSi requires 180.0847.

*N-(tert-Butyl)-N-(prop-2-yn-1-yl)-3-(trimethylsilyl)propiolamide (245c)*

Prepared from amine 244c (0.500 mg, 87 wt. % in PhMe, 3.9 mmol) according to the General Coupling Procedure and purified by flash column chromatography (12:1 petrol 40–60 °C:EtOAc) to give the amide 245c as a white crystalline solid (612 mg, 2.6 mmol, 66%); m.p. 25–27 °C; R_f = 0.34 (12:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm\(^{-1}\)) 3252s (CC-H), 2965s (C-H), 1633s (C=O); \(^1\)H NMR (600 MHz; DMSO-d\(_6\)) a mixture of rotamers R\(_1\) (major) and R\(_2\) (minor); 4.44 (2H, d, J = 0.5, CH\(_2\)N R\(_1\)), 4.23 (2H, br. s, CH\(_2\)N R\(_2\)), 3.35 (1H, t, J = 0.5, CCH R\(_1\)), 3.32 (1H, br. s, CCH R\(_2\)), 1.60 (9H, s, C(CH\(_3\))\(_3\) R\(_2\)), 1.42 (9H, s, C(CH\(_3\))\(_3\) R\(_1\)), 0.22 (9H, s, Si(CH\(_3\))\(_3\) R\(_1\)), 9H, s, Si(CH\(_3\))\(_3\) R\(_2\)); \(^{13}\)C NMR (125 MHz; DMSO-d\(_6\)) 153.4 (C(O)), 97.9 (C≡C), 94.7 (C≡C), 80.9 (C≡C), 74.7 (HC≡C), 57.6 (C(CH\(_3\))\(_3\)), 29.8 (CH\(_2\)N), 27.6 (C(CH\(_3\))\(_3\)), –0.8 (Si(CH\(_3\))\(_3\)); HRMS (ES\(^+\)) found [M+Na]\(^+\) 258.1294; C\(_{13}\)H\(_{21}\)NNaOSi requires 258.1290.
**N-Allyl-N-(prop-2-ynyl)-3-(trimethylsilyl)propiolamide (245d)**

Prepared from amine 244d (300 mg, 3.15 mmol) according to the General Coupling Procedure and purified by flash column chromatography (10:1 petrol 40–60 °C:EtOAc) to give the amide 245d as a colorless oil (574 mg, 2.62 mmol, 83%); R_f = 0.43 (10:1 petrol 40–60 °C:EtOAc); ν_max (film/cm⁻¹) 3249m (CC-H), 2963m (C-H), 1632s (C=O), 1449s, 1411s; ¹H NMR (600 MHz; DMSO-d₆) a mixture of rotamers R₁ (major) and R₂ (minor); 5.90–5.83 (1H, m, C=CH₂ R₁), 5.76–5.70 (1H, m, C=CH₂ R₂), 4.32 (2H, d, J = 2.4, C=CH₂ C≡C R₂), 4.22 (2H, d, J = 5.7, NC=CH R₂), 4.11 (2H, d, J = 2.4, C=CH R₂), 3.99 (2H, d, J = 5.7, NC=CH R₃), 3.36 (1H, t, J = 2.4, C≡C H R₂), 0.24 (9H, s, Si(C₃H₃)₃ R₂), 0.22 (9H, s, Si(C₃H₃)₃ R₁); ¹³C NMR (125 MHz; DMSO-d₆) a mixture of rotamers 152.4 (C(O)), 152.3 (C(O)), 132.7 (CH=CH₂), 132.0 (CH=CH₂), 118.1 (CH=CH₂), 118.1 (CH=CH₂), 97.3 (C≡C), 96.9 (C≡C), 95.8 (C≡C), 95.7 (C≡C), 98.7 (C≡C), 98.6 (C≡C), 75.3 (C≡C), 74.5 (C≡C), 50.7 (NCH₂CH), 46.3 (NCH₂CH), 38.0 (CH₂C≡C), 33.2 (CH₂C≡C), –0.9 (Si(CH₃)₃), –0.9 (Si(CH₃)₃); HRMS (ES⁺) found [M+H]⁺ 220.1163; C₁₂H₁₈NOSi requires 220.1158.

**N-Benzyl-N-(but-2-yn-1-yl)-3-(trimethylsilyl)propiolamide (245e)**

Prepared from amine 244e (650 mg, 4.09 mmol) according to the General Coupling Procedure and purified by flash column chromatography (11:1 petrol 40–60 °C:EtOAc) to give the amide 245e as a colorless oil (826 mg, 2.92 mmol, 71%); R_f = 0.31 (11:1 petrol 40–60 °C:EtOAc); ν_max (film/cm⁻¹) 2961s (C-H), 1631s (C=O), 1496s; ¹H NMR (500 MHz; DMSO-d₆) a mixture of rotamers R₁ (major) and R₂ (minor); 7.40–7.21 (5H, m, ArH R₁; 5H, m, ArH R₂), 4.81 (2H, s, PhCH₂ R₁), 4.56 (2H, s, PhCH₂ R₂), 4.25 (2H, q, J = 2.3, CH₂C≡C R₂), 4.01 (2H, q, J = 2.3, CH₂C≡C R₁), 1.77 (3H, t, J = 2.3, CCH₃ R₂), 1.74 (3H, t, J = 2.3, CCH₃ R₁), 0.22 (9H, s, Si(CH₃)₃ R₂), 0.17 (9H, s, Si(CH₃)₃ R₁); ¹³C NMR (125 MHz; DMSO-d₆) a mixture of rotamers; 152.6 (C(O)), 152.5 (C(O)), 136.3 (Ar), 136.2 (Ar), 128.6 (Ar), 128.5 (Ar), 127.8 (Ar), 127.7 (Ar), 127.4 (Ar), 97.6
Experimental Details

(N≡C), 97.3 (C≡C), 96.2 (C≡C), 95.8 (C≡C), 80.9 (C≡C), 80.0 (C≡C), 73.7 (C≡C), 73.6 (C≡C), 51.3 (CH₂Ph), 46.9 (CH₂Ph), 38.5 (CH₂C≡C), 33.4 (CH₂C≡C), 3.0 (CCH₃), 3.0 (CCH₃), –0.9 (Si(CH₃)₃), –1.0 (Si(CH₃)₃); HRMS (CI⁺) found [M+H]⁺ 284.1459; C₁₇H₂₂NOSi requires 284.1465.

_N-Benzyln-(pent-2-yn-1-yl)-3-(trimethylsilyl)propiolamide (245f)_

Prepared from amine 244f (710 mg, 4.10 mmol) according to the General Coupling Procedure and purified by flash column chromatography (12:1 petrol 40–60 °C:EtOAc) to give the amide 245f as a colorless oil (823 mg, 2.95 mmol, 72%); Rf = 0.39 (12:1 petrol 40–60 °C:EtOAc); νmax (film/cm⁻¹) 2964s (C-H), 1632s (C=O), 1415s; ¹H NMR (600 MHz; DMSO-d₆) a mixture of rotamers R₁ (major) and R₂ (minor); 7.40–7.23 (5H, m, ArH R₁; 5H, m, ArH R₂), 4.82 (2H, s, PhCH₂ R₁), 4.57 (2H, s, PhCH₂ R₂), 4.28 (2H, t, J = 2.0, NCH₂C≡C R₂), 4.05 (2H, t, J = 2.0, NCH₂C≡C R₁), 2.18–2.11 (3H, m, CH₂CH₃ R₁; 3H, m, CH₂CH₃ R₂), 0.24 (9H, s, Si(CH₃)₃ R₂), 0.18 (9H, s, Si(CH₃)₃ R₁); ¹³C NMR (125 MHz; DMSO-d₆) a mixture of rotamers; 152.7 (C(O)), 152.5 (O), 136.4 (Ar), 136.3 (Ar), 128.7 (Ar), 128.5 (Ar), 127.9 (Ar), 127.7 (Ar), 127.5 (Ar), 127.5 (Ar), 97.6 (C≡C), 97.4 (C≡C), 96.2 (C≡C), 95.8 (C≡C), 86.4 (C≡C), 85.7 (C≡C), 74.0 (C≡C), 73.8 (C≡C), 51.4 (CH₂Ph), 47.1 (CH₂Ph), 38.6 (NCH₂C≡C), 33.5 (NCH₂C≡C), 13.6 (CH₂CH₃), 11.6 (CH₂CH₃), 11.6 (CH₂CH₃), –0.9 (Si(CH₃)₃), –1.0 (Si(CH₃)₃); HRMS (CI⁺) found [M+H]⁺ 298.1617; C₁₈H₂₄NOSi requires 298.1622.

_N-Benzyln-(prop-2-yn-1-yl)but-2-ynamide (245g)¹³⁷_

According to the modified procedure of Yamamoto _et al._: A solution of 2-butynoic acid (410 mg, 4.88 mmol) in anhydrous CH₂Cl₂ (3.0 mL) was added dropwise to a stirring solution of amine 244a (653 mg, 4.50 mmol), DMAP (62 mg, 0.51 mmol) and EDC (978 mg, 5.09 mmol) in anhydrous CH₂Cl₂ (8.6 mL) at 0 °C. The reaction was stirred for 16 h at RT before the reaction was partitioned between EtOAc (30 mL) and 1.0 M NaOH.
The aq. extract was washed with EtOAc (3 × 30 mL) and the combined organic extracts were washed with brine (100 mL), dried (MgSO₄) and concentrated in vacuo to give the crude product. This was dissolved in EtOAc (30 mL) and stirred with Amberlyst 15 (1.00 g) for 5 minutes. The mixture was then filtered and the resin washed with EtOAc (30 mL). The filtrate was concentrated in vacuo and purified by flash column chromatography (4:1 petrol 40–60 °C:EtOAc) to give the amide 245g as a colorless oil (678 mg, 3.21 mmol, 71%); Rf = 0.28 (4:1 petrol 40–60 °C:EtOAc); v_max (film/cm⁻¹) 3290s (CC-H), 2919w (C-H), 1624s (C=O), 1415s; ¹H NMR (600 MHz; DMSO-d₆) a mixture of rotamers R₁ (major) and R₂ (minor); 7.41–7.38 (2H, m, ArH R₁/R₂), 7.36–7.27 (6H, m, ArH, R₁/R₂), 4.82 (2H, s, PhCH₂ R₁), 4.57 (2H, s, PhCH₂ R₂), 4.30 (2H, d, J = 2.4, CH₂C≡C R₂), 4.29 (2H, d, J = 2.4, CH₂C≡C R₁), 3.37 (1H, t, J = 2.4, C≡CC≡C R₂), 3.22 (1H, t, J = 2.4, C≡CC≡C R₁); ¹³C NMR (125 MHz; DMSO-d₆) a mixture of rotamers; 153.5 (C(O)), 153.4 (C(O)), 136.3 (Ar), 136.2 (Ar), 128.8 (Ar), 128.6 (Ar), 127.8 (Ar), 127.5 (Ar), 90.7 (C≡C), 90.4 (C≡C), 78.7 (C≡C), 79.5 (C≡C), 75.6 (C≡CH), 74.7 (C≡CH), 72.8 (C≡C), 72.6 (C≡C), 51.2 (CH₂Ph), 46.8 (CH₂Ph), 38.0 (CH₂C≡C), 32.7 (CH₂C≡C), 3.5 (CH₃), 3.4 (CH₃); data in accordance with the literature.

N-Benzyl-N-(prop-2-yn-1-yl)propiolamide (250)

K₂CO₃ (14 mg, 0.10 mmol) was added to a stirring solution of amide 245a (40 mg, 0.15 mmol) in MeOH (2.0 mL) at RT. The reaction was stirred for 10 minutes before being filtered through a silica plug, eluting with EtOAc. The filtrate was concentrated in vacuo and the crude product purified by flash column chromatography (3:1 petrol 40–60 °C:EtOAc) to give the amide 250 as a colorless oil (26 mg, 0.13 mmol, 90%); Rf = 0.21 (4:1 petrol 40–60 °C:EtOAc); v_max (film/cm⁻¹) 3280s (CC-H), 2106s (C≡C), 1633s (C=O), 1449s, 1419s; ¹H NMR (600 MHz; DMSO-d₆) a mixture of rotamers R₁ (major) and R₂ (minor); 7.41–7.24 (5H, m, ArH R₁; 5H, m, ArH R₂), 4.85 (2H, s, PhCH₂ R₁), 4.72 (1H, s, HC≡CC(O) R₂), 4.67 (1H, s, HC≡CC(O) R₁), 4.59 (2H, s, PhCH₂ R₂), 4.32 (2H, d, J = 2.4, CH₂C≡C R₂), 4.06 (2H, d, J = 2.5, CH₂C≡C R₁), 3.19 (1H, t, J = 2.4, CH₂C≡CH R₂), 3.24 (1H, t, J = 2.5, CH₂C≡CH R₁); ¹³C NMR (150 MHz; DMSO-d₆) a mixture of rotamers; 152.7 (C(O)), 152.6 (C(O)), 136.0 (Ar), 135.9 (Ar), 128.8 (Ar), 128.6 (Ar),
Experimental Details

127.9 (Ar), 127.9 (Ar), 127.6 (Ar), 127.4 (Ar), 83.3 (C≡C), 83.0 (C≡C), 78.5 (C≡C), 78.2 (C≡C), 75.8 (C≡C), 75.5 (C≡C), 75.3 (C≡C), 74.9 (C≡C), 51.3 (CH=Ph), 47.2 (CH=Ph), 38.2 (CH=C), 33.1 (CH=C); data in agreement with the literature.²⁸²

**Ethyl 4-(((trimethylsilyl)ethynyl)benzoate (253)²⁸³**

\[
\text{EtO} \quad \text{SiMe}_3
\]

According to the modified procedure of Keana et al.¹⁴⁴: Ethyl 4-iodobenzolate (0.43 mL, 700 mg, 2.5 mmol), ethynyltrimethylsilane (0.43 mL, 300 mg, 3.0 mmol), Pd(PPh₃)₂Cl₂ (53 mg, 0.075 mmol, 3.0 mol%) and CuI (29 mg, 0.15 mmol, 6.0 mol%) were added to a stirring degassed solution of NEt₃ (1.3 mL, 0.94 g, 9.3 mmol) in THF (5.0 mL) in a sealed tube. The reaction mixture was stirred at 80 °C for 2 h before it was allowed to cool to RT. The reaction mixture was filtered and the residue washed with EtOAc. The filtrate was concentrated *in vacuo* and the crude product was purified by flash column chromatography (40:1 petrol 40–60 °C:EtOAc) to give the ester 253 as a white crystalline solid (615 mg, 3.00 mmol, 100%); m.p. 24–26 °C (literature 30 °C)²⁸³; R₉ = 0.29 (40:1 petrol 40–60 °C:EtOAc); *ν*ₘₐₓ (film/cm⁻¹) 2961s (C-H), 2159s (C≡C), 1718s (C=O), 1605s; ¹H NMR (600 MHz; DMSO-d₆) 7.98–7.95 (2H, m, ArH), 7.52–7.49 (2H, m, ArH), 4.36 (2H, q, J = 7.2, CH₂O), 1.38 (3H, t, J = 7.2, CH₃CH₂), 0.26 (9H, s, Si(CH₃)₃); ¹³C NMR (125 MHz; DMSO-d₆) 166.1 (C(O)), 131.9 (Ar), 130.1 (Ar), 129.4 (Ar), 127.7 (Ar), 104.2 (C≡C), 97.6 (C≡C), 61.2 (CH₂O), 14.4 (CH₃CH₂), −0.1 (Si(CH₃)₃); data in accordance with the literature.²⁸³

**Methyl 4-ethynylbenzoate (246e)²⁸⁴**

\[
\text{MeO}
\]

K₂CO₃ (345 mg, 0.250 mmol) was added to a stirring solution of ester 253 (615 mg, 2.50 mmol) in MeOH (5.0 mL) at RT. The suspension was stirred for 30 minutes before the reaction mixture was filtered through a silica plug, eluting with EtOAc. The filtrate was concentrated *in vacuo* and the crude product was purified by flash column
chromatography (40:1 petrol 40–60 °C:EtOAc) to give the ester 246e as a white crystalline solid (366 mg, 2.28 mmol, 92%); m.p. 80–82 °C (literature 87–88 °C); \( R_f = 0.26 \) (40:1 petrol 40–60 °C:EtOAc); \( \nu_{\text{max}} \) (film/cm\(^{-1}\)) 3242s (CC-H), 2952m (C-H), 1700s (C=O), 1607s, 1434s; \(^1\)H NMR (600 MHz; DMSO-\( \text{d}_6 \)) 7.94 (2H, d, \( J = 8.3 \), ArH), 7.61 (2H, d, \( J = 8.3 \), ArH), 4.49 (1H, s, CC\( \text{H} \)), 3.85 (3H, s, C\( \text{H}_3 \)O); \(^{13}\)C NMR (150 MHz; DMSO-\( \text{d}_6 \)) 165.6 (C\( \text{O} \)), 132.1 (Ar), 129.6 (Ar), 129.5 (Ar), 126.5 (Ar), 84.0 (C\( \text{CH}_2 \)), 82.6 (CCH), 52.4 (CH\( \text{O} \)); data in accordance with the literature.

**tert-Butyl prop-2-yn-1-ylcarbamate (246f)**

\[
\begin{array}{c}
\text{NHBoc}
\end{array}
\]

According to the modified procedure of Molander and Cadoret\(^{145}\): Boc\(_2\)O (7.50 g, 34.4 mmol) was added portionwise to a stirring solution of propargylamine (2.2 mL, 1.9 g, 34 mmol) in CH\(_2\)Cl\(_2\) (60 mL) at RT. The reaction mixture was stirred at RT for 1 h before it was concentrated \emph{in vacuo} to give the crude product, which was purified by recrystallization (Et\(_2\)O/hexane) to give the amine 246f as an off-white crystalline solid (4.98 g, 32.1 mmol, 93%); m.p. 32–34 °C (literature 41–42 °C); \( R_f = 0.29 \) (12:1 petrol 40–60 °C:EtOAc); \( \nu_{\text{max}} \) (film/cm\(^{-1}\)) 3306s (CC-H or N-H), 3281s (CC-H or N-H), 2980s (C-H), 1809m, 1682s (C=O); \(^1\)H NMR (500 MHz; CDCl\(_3\)) 4.85–4.69 (1H, br. s, NH), 3.92–3.81 (2H, br. s, C\( \text{H}_2 \)N), 2.20 (1H, t, \( J = 2.5 \), C≡C\( \text{H} \)), 1.43 (9H, s, N\( \text{H} \)), 3.92–3.81 (2H, br. s, CH\( \text{N} \)), 2.20 (1H, t, \( J = 2.5 \), C≡C\( \text{H} \)), 1.43 (9H, s, C(CH\(_3\))\(_3\)); \(^{13}\)C NMR (500 MHz; CDCl\(_3\)) 155 (C\( \text{O} \)), 80.2 (C\( \equiv \text{C} \)), 80.2 (CMe\(_3\)), 71.3 (C\( \equiv \text{C} \)), 30.4 (CH\(_2\)N), 28.4 (C(CH\(_3\))\(_3\)); data in accordance with the literature.\(^{145}\)

**2,2,5,5,8,8-Hexamethyl-3,7-dioxa-2,8-disilanonane (256)**

\[
\begin{array}{c}
\text{Me}_3\text{SiO} & \text{OSiMe}_3
\end{array}
\]

According to the procedure of Vaultier \emph{et al.}\(^{146}\): 2-dimethylpropane-1,3-diol (5.00 g, 48.0 mmol) was added portionwise to a stirring mixture of NH(SiMe\(_3\))\(_2\) (10 mL, 7.7 g, 48 mmol) and Me\(_3\)SiCl (1.2 mL, 1.0 g, 9.6 mmol) at RT. The reaction was heated to 70 °C for 2 h before being allowed to cool to RT. Water (50 mL) and Et\(_2\)O (50 mL) were added to the reaction mixture and the aq. layer was extracted with Et\(_2\)O (3 × 50 mL). The combined organic extracts were dried (MgSO\(_4\)) and concentrated \emph{in vacuo} to give the silyl ether 256 as a colorless oil (10.0 g, 40.7 mmol, 84%); \( R_f = 0.66 \) (100:1 petrol 40–60 °C:EtOAc); \( \nu_{\text{max}} \) (film/cm\(^{-1}\)) 2957s (C-H), 1476m; \(^1\)H NMR (500 MHz; CDCl\(_3\)) 3.28 (4H, s, CH\(_2\)O), 0.80 (6H, s, C(CH\(_3\))\(_2\)), 0.08 (18H, Si(CH\(_3\))\(_3\)); \(^{13}\)C NMR (125 MHz; CDCl\(_3\))
67.9 (CH₂O), 37.2 (C(CH₃)₂), 21.4 (C(CH₃)₂), –0.5 (Si(CH₃)₃); data in accordance with the literature.¹⁴⁶

2-Ethynyl-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (246g)¹²⁹b

According to the modified procedure of Gandon et al.¹²⁹b. Silyl ether 256 (4.46 g, 17.9 mmol) and Me₃SiCl (4.6 mL, 3.9 g, 36 mmol), were added dropwise to a stirring solution of potassium ethynyltrifluoroborate (2.50 g, 95% purity, 17.5 mmol) in anhydrous acetone (22 mL) at RT. The reaction was stirred at RT for 20 h before the reaction mixture was filtered and the filtrate concentrated in vacuo. The crude intermediate was dissolved in PhMe (300 mL) and 1,8-diaminonapthaline (2.06 g, 13.0 mmol) was added portionwise to the stirring solution at RT. The reaction was heated at reflux for 24 h before it was allowed to cool to RT. The reaction was concentrated in vacuo to give the crude product, which was purified by flash column chromatography (6:1 petrol 40–60 °C:EtOAc) to give the boramide 246g as a white crystalline solid (0.950 g, 4.95 mmol, 38%); m.p. 87–89 °C (literature 92 °C)¹²⁹b; Rf = 0.26 (40:1 petrol 40–60 °C:EtOAc); νmax (film/cm⁻¹) 3426s (N-H), 3405s (N-H), 3241s (CC-H), 2076s (C≡C), 1595s, 1500s, 1403s; ¹H NMR (600 MHz; DMSO-d₆) 8.30 (2H, s, NH), 7.03 (2H, t, J = 8.1, ArH), 6.88 (2H, d, J = 8.1, ArH), 6.42 (2H, d, J = 8.1, ArH), 3.42 (1H, s, C≡C); ¹³C NMR (150 MHz; DMSO-d₆) 141.7 (Ar), 135.9 (Ar), 127.6 (Ar), 119.9 (Ar), 116.7 (Ar), 105.5 (Ar), 94.1 (HC≡C), 85.4 (br., BC≡C); data in accordance with the literature.¹²⁹b

2-Benzyl-5-butyl-7-(trimethylsilyl)isoindolin-1-one (247a)

Prepared from amide 245a and 1-hexyne according to General Cyclization Procedure A (crude ratio 247a:8a = 2:1) and purified by flash column chromatography (16:1 petrol 40–60 °C:EtOAc) to give the isoindolinone 247a (107 mg, 0.304 mmol, 61%).
Prepared from amide 245a, 1-hexyne and RuCp*Cl(cod) (3 mg, 3 mol%) over 16 h according to General Cyclization Procedure B (crude ratio 247a:248a = 9:1) and purified by flash column chromatography (13:1 petrol 40–60 °C:EtOAc) to give the \textit{isoindolinone} 247a (75 mg, 0.21 mmol, 81%).

The \textit{isoindolinone} 247a was isolated as a colorless oil; \(R_f = 0.36\) (6:1 petrol 40–60 °C:EtOAc); \(\nu_{\text{max}}\) (film/cm\(^{-1}\)) 2955m (C-H), 2930m (C-H), 1688s (C=O), 1454m, 1409m; \(^1\)H NMR (600 MHz; DMSO-d\(_6\)) 7.34–7.21 (7H, m, ArH), 4.68 (2H, s, CH\(_2\)N), 4.24 (2H, s, CH\(_2\)N), 2.60 (2H, \(J = 7.7\), ArCH\(_2\)CH\(_2\)), 1.51 (2H, m, ArCH\(_2\)CH\(_2\)), 1.26 (2H, m, CH\(_2\)CH\(_3\)), 0.83 (3H, t, \(J = 7.4\), CH\(_2\)C\(_3\)), 0.34 (9H, s, Si(CH\(_3\))\(_3\)); \(^{13}\)C NMR (125 MHz; DMSO-d\(_6\)) 168.5 (\(C(O)\)), 144.8 (Ar), 142.1 (Ar), 137.7 (Ar), 136.9 (Ar), 134.3 (Ar), 134.0 (Ar), 128.6 (Ar), 127.6 (Ar), 127.2 (Ar), 123.7 (Ar), 48.9 (CH\(_2\)N), 45.4 (CH\(_2\)N), 35.1 (ArCH\(_2\)CH\(_2\)), 33.2 (ArCH\(_2\)CH\(_2\)), 21.8 (CH\(_2\)CH\(_3\)), 13.7 (CH\(_2\)CH\(_3\)), -0.4 (Si(CH\(_3\))\(_3\)); HRMS (El\(^+\)) found [M]+ 351.2011; C\(_{22}\)H\(_{29}\)NOSi requires 351.2013.

\[2\text{-Benzyl-5-(tert-butyl)-7-(trimethylsilyl)isoindolin-1-one (247b)}\]

Prepared from 3,3-dimethyl-1-butyne according to General Cyclization Procedure A (crude ratio 247b:258a = 1:3) and purified by flash column chromatography (12:1 petrol 40–60 °C:EtOAc) to give the \textit{isoindolinone} 247b (38 mg, 0.11 mmol, 22%).

Prepared from amide 245a, 3,3-dimethyl-1-butyne and RuCp*Cl(cod) (3 mg, 3 mol%) over 16 h according to General Cyclization Procedure B (crude ratio 247b:248a = 2:1) and purified by flash column chromatography (12:1 petrol 40–60 °C:EtOAc) to give the \textit{isoindolinone} 247b (60 mg, 0.17 mmol, 65%).

The \textit{isoindolinone} 247b was isolated as a white crystalline solid; m.p. 100–102 °C; \(R_f = 0.31\) (12:1 petrol 40–60 °C:EtOAc); \(\nu_{\text{max}}\) (film/cm\(^{-1}\)) 2958s (C-H), 1689s (C=O), 1698m, 1410s; \(^1\)H NMR (600 MHz; DMSO-d\(_6\)) 8.00 (1H, s, ArH), 7.97 (1H, s, ArH), 7.77–7.73 (2H, m, ArH), 7.69–7.66 (3H, m, ArH), 5.13 (2H, s, CH\(_2\)N), 4.72 (2H, s, CH\(_2\)N), 1.71 (9H, s, C(CH\(_3\))\(_3\)), 0.79 (9H, s, Si(CH\(_3\))\(_3\)); \(^{13}\)C NMR (125 MHz; DMSO-d\(_6\)) 168.8 (C(O)), 153.2 (Ar), 142.4 (Ar), 138.1 (Ar), 136.8 (Ar), 134.5 (Ar), 130.9 (Ar), 129.0 (Ar), 128.0 (Ar), 127.6 (Ar), 121.5 (Ar), 49.5 (CH\(_2\)N), 45.7 (CH\(_2\)N), 31.5 (CMe\(_3\)), 29.5...
Experimental Details

(C(H$_3$)$_3$)$_3$NOSi, 0.0 (Si(CH$_3$)$_3$); HRMS (Cl$^+$) found [M+H]$^+$ 352.2093; C$_{22}$H$_{30}$NOSi requires 352.2097.

**2-Benzyl-5-cyclopropyl-7-(trimethylsilyl)isoindolin-1-one (247h)**

Prepared from amide 245a, cyclopropyl acetylene and RuCp*Cl(cod) (3 mg, 3 mol%) over 16 h according to General Cyclization Procedure B (crude ratio 247h:248a = 10:1) and purified by flash column chromatography (13:1 petrol 40–60 °C:EtOAc) to give the isoindolinone 247h as a white crystalline solid (72 mg, 0.21 mmol, 81%); m.p. 66–68 °C; R$_f$ = 0.31 (13:1 petrol 40–60 °C:EtOAc); $\nu_{\text{max}}$ (film/cm$^{-1}$) 2951s (C-H), 1686s (C=O), 1600m, 1454s, 1410s; $^1$H NMR (600 MHz; DMSO-d$_6$) 7.35–7.23 (6H, m, ArH), 7.13 (1H, s, ArH), 4.69 (2H, s, C$_2$H$_2$N), 4.25 (2H, s, C$_2$H$_2$N), 2.03–1.98 (1H, m, C($\text{CH}_2$)$_2$), 1.00–0.97 (2H, m, CH($\text{CH}_2$)$_2$), 0.73–0.69 (2H, m, CH(CH$_2$)$_2$)$_2$, 0.35 (9H, s, Si(CH$_3$)$_3$); $^{13}$C NMR (150 MHz; DMSO-d$_6$) 168.5 (C(O)), 146.5 (Ar), 142.3 (Ar), 137.7 (Ar), 136.7 (Ar), 134.0 (Ar), 131.9 (Ar), 128.7 (Ar), 127.6 (Ar), 127.3 (Ar), 120.0 (Ar), 48.9 (CH$_2$N), 45.4 (CH$_2$N), 15.5 (CH(CH$_2$)$_2$), 10.1 (CH(CH$_2$)$_2$), −0.4 (Si(CH$_3$)$_3$); HRMS (Cl$^+$) found [M+H]$^+$ 336.1784; C$_{21}$H$_{26}$NOSi requires 336.1784.

**2-Benzyl-5-(3-chloropropyl)-7-(trimethylsilyl)isoindolin-1-one (247i)**

Prepared from amide 245a, 5-chloro-1-pentyne and RuCp*Cl(cod) (3 mg, 3 mol%) over 16 h according to General Cyclization Procedure B (crude ratio 247i:248a = 9:1) and purified by flash column chromatography (12:1 petrol 40–60 °C:EtOAc) to give the isoindolinone 247i as a colorless oil (81 mg, 0.22 mmol, 83%); R$_f$ = 0.31 (12:1 petrol 40–60 °C:EtOAc); $\nu_{\text{max}}$ (film/cm$^{-1}$) 2951s (C-H), 1684s (C=O), 1600m, 1453s, 1409s; $^1$H NMR (600 MHz; DMSO-d$_6$) 7.40 (1H, s, ArH), 7.36 (1H, s, ArH), 7.35–7.32 (2H, m, ArH), 7.30–7.24 (3H, m, ArH), 4.70 (2H, s, CH$_2$N), 4.29 (2H, s, CH$_2$N), 3.61 (2H, t, $J$ = 6.5, CH$_2$Cl), 2.78 (2H, t, $J$ = 7.6, CH$_2$CH$_2$CH$_2$Cl), 2.01 (2H, m, CH$_2$CH$_2$Cl), 0.36 (9H, s, Si(CH$_3$)$_3$); $^{13}$C NMR (150 MHz; DMSO-d$_6$) 168.4 (C(O)), 143.3 (Ar), 142.3 (Ar),
137.7 (Ar), 137.1 (Ar), 134.7 (Ar), 134.2 (Ar), 128.7 (Ar), 128.5 (Ar), 127.3 (Ar), 125.1 (Ar), 49.0 (CH₂N), 45.4 (CH₂N), 44.7 (CH₂Cl), 33.8 (CH₂CH₂Cl), 32.5 (CH₂CH₂CH₂Cl), −0.4 (Si(CH₃)₃); HRMS (CI⁺) found [M+H]⁺ 372.1548; C₂₁H₂₇ClNOSi requires 372.1550.

2-Benzyl-5-cyclopentyl-7-(trimethylsilyl)isoindolin-1-one (247j)

Prepared from amide 245a, cyclopentyl acetylene and RuCp*Cl(cod) (3 mg, 3 mol%) over 16 h according to General Cyclization Procedure B (crude ratio 247j:248a = 6:1) and purified by flash column chromatography (15:1 petrol 40–60 °C:EtOAc) to give the isoindolinone 247j as a colorless oil (78 mg, 0.21 mmol, 81%); Rₚ = 0.43 (15:1 petrol 40–60 °C:EtOAc); ν_max (film/cm⁻¹) 2951s (C-H), 1686s (C=O), 1599m, 1453s, 1409s; ¹H NMR (600 MHz; DMSO-d₆) 7.45–7.23 (7H, m, Ar_H), 4.70 (2H, s, CH₂N), 4.28 (2H, s, CH₂N), 3.06–3.00 (1H, m, CH(C₂H₅)), 2.03–1.98 (2H, m, CHCH₂H'), 1.78–1.72 (2H, m, CHCH₂CHH'), 1.66–1.59 (2H, m, CHCH₂CHH'), 1.56–1.49 (2H, m, CHCHH'), 0.35 (9H, s, Si(CH₃)₃); ¹³C NMR (150 MHz; DMSO-d₆) 168.5 (C(O)), 148.6 (Ar), 142.2 (Ar), 137.7 (Ar), 136.8 (Ar), 134.5 (Ar), 133.0 (Ar), 128.7 (Ar), 127.6 (Ar), 127.3 (Ar), 122.4 (Ar), 49.0 (CH₂N), 45.6 (CH(C₂H₅)), 45.4 (CH₂N), 34.5 (CH(C₂H₅)), 25.1 (CHCH₂CH₂), −0.4 (Si(CH₃)₃); HRMS (CI⁺) found [M+H]⁺ 364.2091; C₂₃H₃₀NOSi requires 364.2097.

2-Benzyl-5-phenyl-7-(trimethylsilyl)isoindolin-1-one (247k)

Prepared from amide 245a, phenylacetylene and RuCp*Cl(cod) (4 mg, 4 mol%) over 24 h according to General Cyclization Procedure B (crude ratio 247k:248a = 6:1) and purified by flash column chromatography (15:1 petrol 40–60 °C:EtOAc) to give the isoindolinone 247k as a white crystalline solid (81 mg, 0.22 mmol, 83%); Rₚ = 0.25 (15:1 petrol 40–60 °C:EtOAc); m.p. 117–119 °C; ν_max (film/cm⁻¹) 2950s (C-H), 1687s (C=O), 1597m, 1454s, 1409s; ¹H NMR (600 MHz; DMSO-d₆) 7.80 (1H, s, Ar_H), 7.75 (1H, d, J = 1.3, Ar_H), 7.69–7.66 (2H, m, Ar_H), 7.50 (2H, t, J = 4.8, Ar_H), 7.42–7.35 (3H, m, Ar_H), 7.30–
Experimental Details

7.27 (3H, m, ArH), 4.75 (2H, s, CH2N), 4.40 (2H, s, CH2N), 0.41 (9H, s, Si(CH3)3); 13C NMR (150 MHz; DMSO-d6) 168.3 (C(O)), 142.7 (Ar), 142.2 (Ar), 140.1 (Ar), 137.8 (Ar), 137.6 (Ar), 135.7 (Ar), 132.6 (Ar), 129.1 (Ar), 128.8 (Ar), 128.0 (Ar), 127.7 (Ar), 127.4 (Ar), 127.2 (Ar), 127.8 (Ar), 49.2 (CH2N), 45.5 (CH2N), −0.4 (Si(CH3)3); HRMS (Cl+) found [M+H]+ 372.1779; C24H26NOSi requires 372.1784.

2-Benzyl-5-\(o\)-tolyl-7-(trimethylsilyl)isoindolin-1-one (247l)

Prepared from amide 245a, 1-ethynyl-2-methylbenzene and RuCp*Cl(cod) (3 mg, 3 mol%) over 16 h according to General Cyclization Procedure B (crude ratio 247l:248a >10:1) and purified by flash column chromatography (17:1 petrol 40–60 °C:EtOAc) to give the isoindolinone 247l as a colorless oil (95 mg, 0.25 mmol, 93%); \(R_f = 0.28\) (17:1 petrol 40–60 °C:EtOAc); \(v_{\text{max}}\) (film/cm\(^{-1}\)) 2956s (C-H), 1689s (C=O), 1598m, 1454s, 1410s; \(^1\)H NMR (600 MHz; DMSO-d6) 7.52 (1H, s, ArH), 7.45 (1H, s, ArH), 7.38–7.21 (9H, m, ArH), 4.74 (2H, s, CH2N), 4.38 (2H, s, CH2N), 2.22 (3H, s, ArCH3), 0.38 (9H, s, Si(CH3)3); 13C NMR (150 MHz; DMSO-d6) 168.3 (C(O)), 143.1 (Ar), 142.0 (Ar), 140.9 (Ar), 137.6 (Ar), 136.9 (Ar), 135.3 (Ar), 134.7 (Ar), 134.6 (Ar), 130.5 (Ar), 129.6 (Ar), 128.8 (Ar), 127.8 (Ar), 127.7 (Ar), 127.4 (Ar), 126.1 (Ar), 124.8 (Ar), 49.2 (CH2N), 45.5 (CH2N), 20.2 (ArCH3), −0.4 (Si(CH3)3); HRMS (Cl+) found [M+H]− 386.1939; C25H28NOSi requires 386.1935.

2-Benzyl-5-\(p\)-tolyl-7-(trimethylsilyl)isoindolin-1-one (247c)

Prepared from 4-ethynyltoluene according to General Cyclization Procedure A (crude ratio 247c:248a = 2:1) and purified by flash column chromatography (6:1 petrol 40–60 °C:EtOAc) to give the isoindolinone 247c (82 mg, 0.21 mmol, 42%).
Prepared from amide 245a, 4-ethynyltoluene and RuCp*Cl(cod) (4 mg, 4 mol%) over 24 h according to General Cyclization Procedure B (crude ratio 247c:248a = 6:1) and purified by flash column chromatography (15:1 petrol 40–60 °C:EtOAc) to give the isoindolinone 247c (82 mg, 0.22 mmol, 81%).

The isoindolinone 247c was isolated as a white crystalline solid; Rf = 0.50 (6:1 petrol 40–60 °C:EtOAc); m.p. 78–80 °C; νmax (film/cm$^{-1}$) 2950s (C-H), 1686s (C=O), 1453s, 1409s; $^1$H NMR (600 MHz; DMSO-d$_6$) 7.76 (1H, s, ArH), 7.73–7.72 (1H, m, ArH), 7.58–7.56 (2H, m, ArH), 7.38–7.34 (2H, m, ArH), 7.30–7.27 (5H, m, ArH), 4.74 (2H, s, CH$_2$N), 4.38 (2H, s, CH$_2$N), 2.34 (3H, s, ArCH$_3$), 0.40 (9H, s, Si(CH$_3$)$_3$); $^{13}$C NMR (150 MHz; DMSO-d$_6$) 168.3 (C(O)), 142.7 (Ar), 142.1 (Ar), 137.7 (Ar), 137.6 (Ar), 137.4 (Ar), 137.1 (Ar), 135.4 (Ar), 132.3 (Ar), 129.7 (Ar), 128.8 (Ar), 127.7 (Ar), 127.3 (Ar), 127.0 (Ar), 122.4 (Ar), 49.2 (CH$_2$N), 45.5 (CH$_2$N), 20.7 (ArCH$_3$), −0.4 (Si(CH$_3$)$_3$); HRMS (ESI$^+$) found [M-Me]$^+$ 370.1620; C$_{24}$H$_{24}$NOSi requires 370.1627.

2-Benzyl-5-(2-bromophenyl)-7-(trimethylsilyl)isoindolin-1-one (247m)

Prepared from amide 245a, 1-ethynyl-2-methylbenzene and RuCp*Cl(cod) (3 mg, 3 mol%) over 16 h according to General Cyclization Procedure B (crude ratio 247m:248a = 8:1) and purified by flash column chromatography (20:1 petrol 40–60 °C:EtOAc) to give the isoindolinone 247m as a colorless oil (95 mg, 0.21 mmol, 80%); Rf = 0.37 (15:1 petrol 40–60 °C:EtOAc); νmax (film/cm$^{-1}$) 2974s (C-H), 1688s (C=O), 1602m, 1452s, 1409s; $^1$H NMR (600 MHz; DMSO-d$_6$) 7.74 (1H, dd, $J = 8.0$, 0.8, ArH), 7.56 (2H, d, $J = 2.9$, ArH), 7.47–7.45 (1H, m, ArH), 7.42–7.40 (1H, m, ArH), 7.37–7.26 (6H, m, ArH), 4.75 (2H, s, CH$_2$N), 4.38 (2H, s, CH$_2$N), 0.38 (9H, s, Si(CH$_3$)$_3$); $^{13}$C NMR (150 MHz; DMSO-d$_6$) 168.2 (C(O)), 142.1 (Ar), 141.8 (Ar), 141.4 (Ar), 137.6 (Ar), 136.7 (Ar), 135.9 (Ar), 134.9 (Ar), 133.2, (Ar), 131.5 (Ar), 129.8 (Ar), 128.7 (Ar), 128.2 (Ar), 127.8 (Ar), 127.4 (Ar), 125.0 (Ar), 121.6 (Ar), 49.2 (CH$_2$N), 45.5 (CH$_2$N), −0.4 (Si(CH$_3$)$_3$); HRMS (Cl$^-$) found [M+H]$^+$ 450.0870; C$_{24}$H$_{25}$BrNOSi requires 450.0889.
2-benzyl-5-(4-bromophenyl)-7-(trimethylsilyl)isoindolin-1-one (247n)

Prepared from amide 245a, 1-ethynyl-2-methylbenzene and RuCp*Cl(cod) (3 mg, 3 mol%) over 24 h according to General Cyclization Procedure B (crude ratio 247n:248a = 5:1) and purified by flash column chromatography (12:1 petrol 40–60 °C:EtOAc) to give the isoindolinone 247n as a colorless oil (98 mg, 0.22 mmol, 83%); Rf = 0.20 (15:1 petrol 40–60 °C:EtOAc); νmax (film/cm–1) 2950s (C-H), 1684s (C=O), 1600s, 1495s, 1453s, 1409s; 1H NMR (600 MHz; DMSO-d6) 7.77 (1H, s, ArH), 7.72 (1H, s, ArH), 7.29–7.26 (3H, m, ArH), 7.37–7.33 (2H, m, ArH), 7.66–7.60 (4H, m, ArH), 4.74 (2H, s, CH2N), 4.37 (2H, s, CH2N), 0.40 (9H, s, Si(CH3)3); 13C NMR (150 MHz; DMSO-d6) 168.2 (C(O)), 142.7 (Ar), 140.8 (Ar), 139.2 (Ar), 137.9 (Ar), 136.9 (Ar), 136.0 (Ar), 132.4 (Ar), 132.0 (Ar), 129.3 (Ar), 128.7 (Ar), 127.7 (Ar), 127.4 (Ar), 122.6 (Ar), 121.6 (Ar), 49.2 (CH2N), 46.2 (CH2N), -0.4 (Si(CH3)3); HRMS (Cl+) found [M+H]+ 450.0877; C24H25BrNOSi requires 450.0889.

Methyl 4-(2-benzyl-1-oxo-7-(trimethylsilyl)isoindolin-5-yl)benzoate (247e)

Prepared from amide 245a, methyl 4-ethynylbenzoate 246e and RuCp*Cl(cod) (3 mg, 3 mol%) over 24 h according to General Cyclization Procedure B (crude ratio 247e:248a = 5:1) and purified by flash column chromatography (15:1 petrol 40–60 °C:EtOAc) to give the isoindolinone 247e as a colorless oil (89 mg, 0.21 mmol, 79%); Rf = 0.29 (9:1 petrol 40–60 °C:EtOAc); νmax (film/cm–1) 2951s (C-H), 1686s (lactam C=O), 1608s, 1434s, 1410s; 1H NMR (600 MHz; DMSO-d6) 8.05 (1H, s, ArH), 8.03 (1H, s, ArH), 7.83–7.77 (4H, m, ArH), 7.36–7.32 (2H, m, ArH), 7.29–7.26 (3H, m, ArH), 4.73 (2H, s, CH2N), 4.37 (2H, s, CH2N), 3.89 (3H, s, OCH3)), 0.41 (9H, s, Si(CH3)3); 13C NMR (150 MHz; DMSO-d6) 168.1 (C(O)), 166.0 (C(O)), 144.5 (Ar), 142.7 (Ar), 140.8 (Ar), 138.0 (Ar), 137.5 (Ar), 136.5 (Ar), 132.7 (Ar), 129.9 (Ar), 128.9
(Ar), 128.7 (Ar), 127.7 (Ar), 127.5 (Ar), 127.4 (Ar), 123.1 (Ar), 52.2 (OCH₃), 49.2 (CH₂N), 45.5 (CH₂N), –0.4 (Si(CH₃)₃); HRMS (ES⁺) found [M+Na]⁺ 452.1642; C₂₆H₂₇NNaO₃Si requires 452.1658.

2-Benzyl-5-(4-methoxyphenyl)-7-(trimethylsilyl)isoindolin-1-one (247o)

Prepared from amide 245a, 1-ethynyl-4-methoxybenzene and RuCp*Cl(cod) (5 mg, 5 mol%) over 24 h according to General Cyclization Procedure B (crude ratio 247o:248a = 6:1) and purified by flash column chromatography (12:1 petrol 40–60 °C:EtOAc) to give the isoindolinone 247o (83 mg, 0.21 mmol, 79%) as a colorless oil; Rf = 0.28 (15:1 petrol 40–60 °C:EtOAc); νmax (film/cm⁻¹) 2952s (C-H), 1685s (C=O), 1606s 1516s, 1454s, 1409s; ¹H NMR (600 MHz; DMSO-d₆) 7.73 (1H, s, ArH), 7.71 (1H, s, ArH), 7.61 (2H, d, J = 8.7, ArH), 7.36–7.33 (2H, m, ArH), 7.28–7.26 (3H, m, ArH), 7.04 (2H, d, J = 8.7 ArH), 4.72 (2H, s, CH₂N), 4.35 (2H, s, CH₂N), 3.78 (3H, s, OCH₃), 0.40 (9H, s, Si(CH₃)₃); ¹³C NMR (150 MHz; DMSO-d₆) 168.4 (C(O)), 159.3 (Ar), 142.7 (Ar), 141.8 (Ar), 137.6 (Ar), 137.6 (Ar), 135.0 (Ar), 132.3 (Ar), 132.1 (Ar), 128.7 (Ar), 128.3 (Ar), 127.7 (Ar), 127.4 (Ar), 122.1 (Ar), 114.5 (Ar), 55.2 (OCH₃), 49.1 (CH₂N), 45.5 (CH₂N), –0.4 (Si(CH₃)₃); HRMS (ES⁺) found [M+Na]⁺ 424.1694; C₂₅H₂₇NNaO₂Si requires 424.1709.

2-Benzyl-5-(4-(dimethylamino)phenyl)-7-(trimethylsilyl)isoindolin-1-one (247p)

Prepared from amide 245a, 4-ethynyl-N,N-dimethylaniline and RuCp*Cl(cod) (10 mg, 10 mol%) over 24 h according to General Cyclization Procedure B (crude ratio 247p:248a = 7:1) and purified by flash column chromatography (10:1 petrol 40–60 °C:EtOAc) to give the isoindolinone 247p (86 mg, 0.21 mmol, 79%) as a colorless oil; Rf = 0.27 (10:1 petrol 40–60 °C:EtOAc); νmax (film/cm⁻¹) 2897s (C-H), 1682s (C=O),
Experimental Details

1609s, 1592s 1526s, 1452s, 1409s; $^1$H NMR (600 MHz; DMSO-d$_6$) 7.70 (2H, s, ArH), 7.53 (2H, d, $J$ = 8.8, ArH), 7.37–7.34 (2H, m, ArH), 7.30–7.26 (3H, m, ArH), 6.81 (2H, d, $J$ = 8.8, ArH), 4.72 (2H, s, CH$_2$N), 4.35 (2H, s, CH$_2$N), 2.93 (6H, s, N(CH$_3$)$_2$), 0.40 (9H, s, Si(CH$_3$)$_3$); $^{13}$C NMR (150 MHz; DMSO-d$_6$) 168.5 (C(O)), 150.2 (Ar), 142.7 (Ar), 142.3 (Ar), 137.7 (Ar), 137.4 (Ar), 134.2 (Ar), 131.4 (Ar), 128.7 (Ar), 127.7 (Ar), 127.4 (Ar), 127.1 (Ar), 121.2 (Ar), 112.7 (Ar), 49.2 (CH$_2$N), 45.5 (CH$_2$N), 39.9 (N(CH$_3$)$_2$), −0.3 (Si(CH$_3$)$_3$); HRMS (ES$^+$) found [M+H]$^+$ 415.2219; C$_{26}$H$_{31}$N$_2$OSi requires 415.2206.

2-Benzyl-5-(methoxymethyl)-7-(trimethylsilyl)isoindolin-1-one (247d)

Prepared from 3-methoxy-1-propyne according to General Cyclization Procedure A (crude ratio 247d:248a = 2:1) and purified by flash column chromatography (6:1 petrol 40–60 °C:EtOAc) to give the isoindolinone 247d (79 mg, 0.23 mmol, 47%).

Prepared from amide 245a, 3-methoxy-1-propyne and RuCp*Cl(cod) (3 mg, 3 mol%) over 16 h according to General Cyclization Procedure B (crude ratio 247d:248a = 3:2) and purified by flash column chromatography (12:1 petrol 40–60 °C:EtOAc) to give the isoindolinone 247d (50 mg, 0.15 mmol, 56%).

The isoindolinone 247d was isolated as a white crystalline solid; m.p. 57–59 °C; R$_f$ = 0.26 (12:1 petrol 40–60 °C:EtOAc); $\nu_{max}$ (film/cm$^{-1}$) 2896s(C-H), 1684s(C=O), 1453s, 1409s; $^1$H NMR (600 MHz; DMSO-d$_6$) 7.48 (s, 2H, ArH), 7.37–7.33 (2H, m, ArH), 7.29–7.26 (3H, m, ArH), 4.71 (2H, s, CH$_2$N), 4.49 (2H, s, CH$_2$O), 4.33 (2H, s, CH$_2$N), 3.31 (3H, s, OCH$_3$), 0.36 (9H, s, Si(CH$_3$)$_3$); $^{13}$C NMR (150 MHz; DMSO-d$_6$) 168.4 (C(O)), 142.1 (Ar), 140.7 (Ar), 137.6 (Ar), 137.0 (Ar), 135.9 (Ar), 132.9 (Ar), 128.7 (Ar), 127.7 (Ar), 127.4 (Ar), 123.1 (Ar), 73.5 (CH$_2$O), 57.8 (OCH$_3$), 49.1 (CH$_2$N), 45.5 (CH$_2$N), −0.4 Si(CH$_3$)$_3$; HRMS (ESI$^+$) found [M]$^+$ 339.1647; C$_{20}$H$_{25}$NO$_2$Si requires 339.1649.
2-Benzyl-5-(diethoxymethyl)-7-(trimethylsilyl)isoindolin-1-one (247q)

Prepared from amide 245a, 3,3-diethoxyprop-1-yn and RuCp*Cl(cod) (3 mg, 3 mol%) over 24 h according to General Cyclization Procedure B (crude ratio 247q:248a = 0.8:1) and purified by flash column chromatography (17:1 petrol 40–60 °C:EtOAc) to give the isoindolinone 247q (45 mg, 0.11 mmol, 43%) as a colorless oil; Rf = 0.27 (17:1 petrol 40–60 °C:EtOAc); νmax (film/cm−1) 2874s (C-H), 1689s (C=O), 1454s, 1409s; 1H NMR (600 MHz; DMSO-d6) 7.59 (1H, s, ArH), 7.57 (1H, s, ArH), 7.37–7.26 (5H, m, ArH), 5.56 (1H, s, CH(OEt)2), 4.72 (2H, s, CH2N), 4.36 (2H, s, CH2N), 3.59–3.53 (2H, m, OCHH'), 3.32–3.46 (2H, m, OCHH'), 1.14 (6H, t, J = 7.0, CH2CH3), 0.36 (9H, s, Si(CH3)3); 13C NMR (150 MHz; DMSO-d6) 168.3 (C(O)), 141.9 (Ar), 141.3 (Ar), 137.6 (Ar), 136.8 (Ar), 136.6 (Ar), 132.0 (Ar), 128.7 (Ar), 127.7 (Ar), 127.4 (Ar), 122.4 (Ar), 100.9 (CH(OEt)2), 61.1 (OCH2), 49.2 (CH2N), 45.5 (CH2N), 15.2 (CH2CH3), −0.4 (Si(CH3)3); HRMS (ES+) found [M+Na]+ 420.1970; C23H31NNaO3Si requires 420.1971.

2-Benzyl-5-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)-7-(trimethylsilyl)isoindolin-1-one (247g)

Prepared from amide 245a, boramide 246g and RuCp*Cl(cod) (5 mg, 5 mol%) over 24 h according to General Cyclization Procedure B (crude ratio 247g:248a = 3:1) and purified by flash column chromatography (3:1 petrol 40–60 °C: Et2O) to give the isoindolinone 247g as a white crystalline solid (67 mg, 0.15 mmol, 55%); m.p. 96–98 °C; Rf = 0.56 (2:3 petrol 40–60 °C: Et2O); νmax (film/cm−1) 3333s (N-H), 2952s (C-H), 1672s (C=O), 1599s, 1512s, 1405s; 1H NMR (600 MHz; DMSO-d6) 8.35 (2H, s, NH), 8.02 (1H, s, ArH), 7.96 (1H, s, ArH), 7.39–7.36 (2H, m, ArH), 7.31–7.28 (3H, m, ArH), 7.09 (2H, t, J = 8.0, ArH), 6.91 (2H, d, J = 8.0, ArH) 6.59 (2H, d, J = 7.2, ArH), 4.76 (2H, s, CH2N), 4.42
(2H, s, CH$_2$N), 0.44 (9H, s, Si(CH$_3$)$_3$); $^{13}$C NMR (150 MHz; DMSO-$d_6$) 168.6 (C(O)), 142.3 (Ar), 140.8 (Ar), 138.0 (Ar), 137.9 (Ar), 137.7 (Ar), 136.0 (Ar), 136.0 (Ar), 128.8 (Ar), 128.4 (Ar), 127.7 (Ar), 127.7 (Ar), 127.4 (Ar), 119.8 (Ar), 116.4 (Ar), 105.8 (Ar), 49.2 (CH$_2$N), 45.5 (CH$_2$N), –0.1 (Si(CH$_3$)$_3$), N$_2$BC not observed; HRMS (EI$^+$) found [M]$^+$ 461.2089; C$_{28}$H$_{28}$BN$_3$OSi requires 461.2089.

tert-Butyl ((2-benzyl-1-oxo-7-(trimethylsilyl)isoindolin-5-yl)methyl)carbamate (247f)

Prepared from amide 245a, carbamate 246f and RuCp*Cl(cod) (5 mg, 5 mol%) over 24 h according to General Cyclization Procedure B (crude ratio 247f:248a = 2:1) and purified by flash column chromatography (8:1 petrol 40–60 °C:EtOAc) to give the isoindolinone 247f as a white crystalline solid (71 mg, 0.17 mmol, 63%); m.p. 124–126 °C; R$_f$ = 0.44 (4:1 petrol 40–60 °C: Et$_2$O); $\nu_{max}$ (film/cm$^{-1}$) 3334s (N-H), 2975s (C-H), 1685s (lactam and carbamate C=O), 1516s, 1454s, 1411s; $^1$H NMR (600 MHz; DMSO-$d_6$) a mixture of rotamers R$_1$ (major) and R$_2$ (minor) 7.51–7.45 (2H, m, ArH, NH R$_1$; 2H, m, ArH, NH R$_2$), 7.38–7.34 (3H, m, ArH R$_1$; 3H, m, ArH R$_2$), 4.71 (2H, s, CH$_2$NCH$_2$ R$_1$; 2H, s, CH$_2$NCH$_2$ R$_2$), 4.32 (2H, s, CH$_2$NCH$_2$ R$_1$; 2H, s, CH$_2$NCH$_2$ R$_2$), 4.20 (2H, s, J = 6.2, CH$_2$NH R$_1$) 4.13 (2H, br. s, CH$_2$NH R$_2$) 1.39 (9H, s, C(CH$_3$)$_3$ R$_1$), 1.29 (9H, s, C(CH$_3$)$_3$ R$_2$), 0.35 (9H, s, Si(CH$_3$)$_3$ R$_1$; 9H, s, Si(CH$_3$)$_3$ R$_2$); $^{13}$C NMR (150 MHz; DMSO-$d_6$) 168.4 (lactam C(O)), 155.9 (carbamate C(O)), 142.7 (Ar), 142.1 (Ar), 137.7 (Ar), 136.9 (Ar), 135.2 (Ar), 132.6 (Ar), 128.7 (Ar), 127.7 (Ar), 127.3 (Ar), 122.6 (Ar), 77.9 (C(CH$_3$)$_3$), 49.1 (CH$_2$NCH$_2$), 45.5 (CH$_2$NCH$_2$), 43.5 (CH$_2$NH), 28.3 (CMe$_3$), –0.4 (Si(CH$_3$)$_3$); HRMS (ES$^+$) found [M+H]$^+$ 425.2274; C$_{24}$H$_{33}$N$_2$O$_3$Si requires 425.2260.
2-Benzyl-5-(pyridin-2-yl)-7-(trimethylsilyl)isoindolin-1-one (247r)

Prepared from amide 245a, 2-ethynylpyridine and RuCp*Cl(cod) (20 mg, 20 mol%) over 24 h according to General Cyclization Procedure B (crude ratio 247r:248a = 2:1) and purified by flash column chromatography (3:1 petrol 40–60 °C:Et₂O) to give the isoindolinone 247r as a colorless oil (49 mg, 0.13 mmol, 50%); R_f = 0.40 (1:1 petrol 40–60 °C:Et₂O); ν_max (film/cm⁻¹) 2973s (C-H), 1686s (C=O), 1587s, 1409s; _1H NMR (600 MHz; DMSO-d₆) 8.71–8.70 (1H, m, ArH), 8.26–8.25 (1H, m, ArH), 8.20–8.20 (1H, m, ArH), 7.99–7.98 (1H, m, ArH), 7.93–7.89 (1H, m, ArH), 7.40–7.35 (3H, m, ArH), 7.31–7.27 (3H, m, ArH), 4.75 (2H, s, C₂H₂N), 4.42 (2H, s, C₂H₂N), 0.42 (9H, s, Si(C₃H₃)₃); _13C NMR (150 MHz; DMSO-d₆) 168.2 (C(O)), 155.7 (Ar), 149.8 (Ar), 142.5 (Ar), 140.3 (Ar), 137.6 (Ar), 137.5 (Ar), 137.5 (Ar), 137.1 (Ar), 132.3 (Ar), 128.8 (Ar), 127.7 (Ar), 127.4 (Ar), 123.1 (Ar), 122.5 (Ar), 121.0 (Ar), 49.3 (CH₂N), 45.6 (CH₂N), –0.3 (Si(CH₃)₃). HRMS (CI⁺) found [M+H]⁺ 371.1708; C₂₃H₂₅N₂OSi requires 373.1731.

5-Butyl-7-(trimethylsilyl)isoindolin-1-one (264a)

Prepared from amide 245b, 1-hexyne and Cp*RuCl(cod) (10 mg, 10 mol%) over 24 h according to the General Cyclization Procedure B (crude ratio 264a:265 = 2:1) and purified by flash column chromatography (5:1 petrol 40–60 °C:EtOAc) to give the isoindolinone 264a as a white crystalline solid (35 mg, 0.13 mmol, 51%); m.p. 140–142 °C; R_f = 0.57 (2:1 petrol 40–60 °C:EtOAc); ν_max (film/cm⁻¹) 3307m (N-H), 2968s (C-H), 1690s (C=O); _1H NMR (600 MHz; DMSO-d₆) 8.37 (1H, s, NH), 7.36 (1H, s, ArH), 7.33 (1H, s, ArH), 4.30 (2H, s, CH₂N), 2.66 (2H, t, J = 7.7, CH₂CH₂), 1.59–1.53 (2H, m, ArCH₂CH₂), 1.32 (2H, sextet, J = 7.4, CH₂CH₂), 0.90 (3H, t, J = 7.4, CH₂CH₃), 0.32 (9H, s, Si(CH₃)₃); _13C NMR (150 MHz; DMSO-d₆) 171.2 (C(O)), 144.7 (Ar), 144.6 (Ar), 136.6 (Ar), 134.9 (Ar), 133.9 (Ar), 124.1 (Ar), 44.7 (CH₂N), 35.1 (ArCH₂CH₂), 33.3
(ArCH₂CH₂), 21.9 (CH₂CH₃), 13.8 (CH₂CH₃), −0.3 (Si(CH₃)₃); HRMS (ES⁺) found [M-Me]⁺ 246.1302; C₁₄H₂₀NOSi requires 246.1314.

5-(o-Tolyl)-7-(trimethylsilyl)isoindolin-1-one (264b)

Prepared from amide 245b, 2-ethynyltoluene and RuCp*Cl(cod) (10 mg, 10 mol%) over 24 h according to the General Cyclization Procedure B (crude ratio 264b:265 = 7:1) and purified by flash column chromatography (2:1 petrol 40–60 °C:EtOAc) to give the isoindolinone 264b as a white crystalline solid (48 mg, 0.16 mmol, 62%); m.p. 133–135 °C; Rf = 0.30 (2:1 EtOAc: petrol 40–60 °C); νmax (film/cm⁻¹) 3190 (N-H), 2947s (C-H), 1690s (C=O), 1450s; ¹H NMR (600 MHz; DMSO-d₆) 8.53 (1H, s, NH), 7.53 (1H, s, ArH), 7.43 (1H, s, ArH), 7.33–7.24 (4H, m, ArH), 4.40 (2H, s, CH₂N), 2.24 (3H, s, ArCH₃), 0.32 (9H, s, Si(CH₃)₃); ¹³C NMR (150 MHz; DMSO-d₆) 171.0 (C(O)), 144.4 (Ar), 143.0 (Ar), 141.0 (Ar), 136.7 (Ar), 135.9 (Ar), 134.7 (Ar), 134.4 (Ar), 130.5 (Ar), 129.6 (Ar), 127.7 (Ar), 126.1 (Ar), 125.0 (Ar), 45.0 (CH₂N), 20.2 (ArCH₃), −0.3 (Si(CH₃)₃); HRMS (CI⁺) found [M+H]+ 296.1458; C₁₈H₂₂NOSi requires 296.1470.

2-(tert-Butyl)-5-butyl-7-(trimethylsilyl)isoindolin-1-one (267a)

Prepared from amide 245c, 1-hexyne and RuCp*Cl(cod) (3 mg, 3 mol%) over 16 h according to General Cyclization Procedure B (crude ratio 267a:268 = 10:1) and purified by flash column chromatography (30:1 petrol 40–60 °C:EtOAc) to give the isoindolinone 267a (70 mg, 0.22 mmol, 84%); Rf = 0.36 (30:1 EtOAc:petrol 40–60 °C); νmax (film/cm⁻¹) 2957s (C-H), 1681s (C=O), 1455s; ¹H NMR (600 MHz; DMSO-d₆) 7.32 (1H, s, ArH), 7.31 (1H, s, ArH), 4.48 (2H, s, CH₂N), 2.65 (2H, t, J = 7.7 ArCH₂CH₂), 1.54 (2H, m, ArCH₂CH₂), 1.47 (9H, s, C(CH₃)₃), 1.30 (2H, sextet, J = 7.3, CH₂CH₃), 0.89 (3H, t, J = 7.3, CH₂CH₃), 0.31 (9H, s, Si(CH₃)₃); ¹³C NMR (150 MHz; DMSO-d₆) 168.9 (C(O)), 144.3 (Ar), 141.7 (Ar), 136.3 (Ar), 136.0 (Ar), 134.0 (Ar), 123.4 (Ar), 53.5 (CMe₃), 47.8
(CH₂N), 35.1 (ArCH₂CH₂), 33.4 (ArCH₂CH₂), 27.5 (C(CH₃)₃), 21.8 (CH₂CH₃), 13.8 (CH₂CH₃), −0.2 (Si(CH₃)₃); HRMS (Cl⁺) found [M+H]⁺ 318.2252; C₁₉H₃₂NOSi requires 318.2248.

2-(tert-Butyl)-5-phenyl-7-(trimethylsilyl)isoindolin-1-one (267b)

Prepared from amide 245c, phenylacetylene and RuCp*Cl(cod) (4 mg, 4 mol%) over 24 h according to General Cyclization Procedure B (crude ratio 267b:268 > 10:1) and purified by flash column chromatography (35:1 petrol 40–60 °C:EtOAc) to give the isoindolinone 267b as a white crystalline solid (79 mg, 0.23 mmol, 89%); m.p. 73–75 °C; Rᵣ = 0.36 (30:1 EtOAc: petrol 40–60 °C); νmax (film/cm⁻¹) 2963s (C-H), 1677s (C=O), 1448s; ¹H NMR (600 MHz; DMSO-d₆) 7.78 (1H, s, ArH), 7.72–7.70 (1H, m, ArH), 7.69–7.67 (2H, m, ArH), 7.50 (2H, t, J = 9.3, ArH), 7.43–7.39 (1H, m, ArH), 4.60 (2H, s, CH₂N), 1.51 (9H, s, C(CH₃)₃), 0.37 (9H, s, Si(CH₃)₃); ¹³C NMR (150 MHz; DMSO-d₆) 168.6 (C(O)), 142.2 (Ar), 141.8 (Ar), 140.2 (Ar), 137.7 (Ar), 137.0 (Ar), 132.4 (Ar), 129.1 (Ar), 127.9 (Ar), 127.2 (Ar), 122.2 (Ar), 53.7 (CMe₃), 48.1 (CH₂N), 27.5 (C(CH₃)₃), −0.3 (Si(CH₃)₃); HRMS (ES⁺) found [M+H]⁺ 338.1940; C₂₁H₂₈NOSi requires 338.1940.

2-(tert-Butyl)-5-(α-tolyl)-7-(trimethylsilyl)isoindolin-1-one (267c)

Prepared from amide 245c, 2-ethynyltoluene and RuCp*Cl(cod) (3 mg, 3 mol%) over 16 h according to the General Cyclization Procedure B (crude ratio 267c:268 > 10:1) and purified by flash column chromatography (20:1 petrol 40–60 °C:EtOAc) to give the isoindolinone 267c as a yellow oil (87 mg, 0.25 mmol, 94%); Rᵣ = 0.31 (20:1 EtOAc: petrol 40–60 °C); νmax (film/cm⁻¹) 2973s (C-H), 1680s (C=O), 1452s; ¹H NMR (600 MHz; DMSO-d₆) 7.48 (1H, s, ArH), 7.40 (1H, s, ArH), 7.31–7.21 (3H, m, ArH), 7.21–7.18 (1H, m, ArH), 4.58 (2H, s, CH₂N), 2.21 (3H, s, ArCH₃), 1.49 (9H, s, C(CH₃)₃), 0.33 (9H, s, Si(CH₃)₃); ¹³C NMR (150 MHz; DMSO-d₆) 168.6 (C(O)), 142.9 (Ar), 141.5 (Ar), 141.1 (Ar), 137.3 (Ar), 136.1 (Ar), 134.7 (Ar), 134.4 (Ar), 130.5 (Ar), 129.6 (Ar),
127.6 (Ar), 126.0 (Ar), 124.3 (Ar), 53.6 (CMe₃), 48.0 (CH₂N), 27.4 (C(CH₃)₃), 20.2 (ArCH₃), –0.3 (Si(CH₃)₃); HRMS (Cl⁺) found [M+H]⁺ 352.2088; C₂₂H₃₀NOSi requires 352.2097.

2-Benzyl-5-butyl-4-methyl-7-(trimethylsilyl)isoindolin-1-one (273a) and 2-Benzyl-6-butyl-4-methyl-7-(trimethylsilyl)isoindolin-1-one (274a)

Prepared from amide 245e and 1-hexyne according to the General Cyclization Procedure C (crude ratio 273a:274a = 9:1) and purified by flash column chromatography (15:1 petrol 40–60 °C:EtOAc) to give a mixture of the isoindolinone 273a and the isoindolinone 274a as a colorless oil (10 mg, 0.027 mmol, 11%; 273a:274a = 3:1). Further elution of the column gave more of the isoindolinone 273a as a colorless oil (55 mg, 0.15 mmol, 58%).

**Isoindolinone 273a:** Rₓ = 0.75 (9:1 petrol 40–60 °C:EtOAc); vₓ (film/cm⁻¹) 2956s (C-H), 1688s (C=O), 1454s, 1409s; ¹H NMR (600 MHz; DMSO-d₆) 7.37–7.34 (2H, m, ArH), 7.31 (1H, s, ArH), 7.29–7.26 (3H, m, ArH), 4.71 (2H, s, NCH₂), 4.27 (2H, s, NCH₂), 2.65 (2H, t, J = 7.8, ArCH₂CH₂), 2.17 (3H, s, ArCH₃), 1.50–1.45 (2H, m, ArCH₂CH₂), 1.35 (2H, sextet, J = 7.3, CH₂CH₃), 0.91 (3H, t, J = 7.3, CH₂CMe₃), 0.34 (9H, s, Si(CH₃)₃); ¹³C NMR (150 MHz; DMSO-d₆) 169.0 (C(O)), 143.0 (Ar), 141.6 (Ar), 137.8 (Ar), 135.0 (Ar), 134.2 (Ar), 133.6 (Ar), 128.7 (Ar), 127.7 (Ar), 123.3 (Ar), 48.6 (CH₂N), 45.5 (CH₂N), 32.5 (ArCH₂CH₂), 32.4 (ArCH₂CH₂), 22.1 (CH₂CH₃), 13.8 (CH₃), 13.7 (CH₃), –0.3 (Si(CH₃)₃); HRMS (Cl⁺) found [M+H]⁺ 366.2246; C₂₃H₃₂NOSi requires 366.2248. A NOESY experiment showed an NOE between; 2.65 (ArCH₂CH₂) and 2.17 (ArCH₃); 7.31 (ArH) and 2.65 (ArCH₂CH₂); 7.31 (ArH) and 0.34 (Si(CH₃)₃).

**Isoindolinone 274a:** Rₓ = 0.77 (9:1 petrol 40–60 °C:EtOAc); ¹H NMR (600 MHz; DMSO-d₆) 7.37–7.34 (2H, m, ArH), 7.30–7.26 (3H, m, ArH), 7.13 (1H, s, ArH), 4.70 (2H, s, NCH₂), 4.22 (2H, s, NCH₂), 2.73 (2H, t, J = 7.7, ArCH₂CH₂), 2.20 (3H, s, ArCH₃), 1.44–1.40 (2H, m, ArCH₂CH₂), 1.32 (2H, sextet, J = 7.4, CH₂CH₃), 0.89 (3H, t, J = 7.4, CH₂CH₃), 0.40 (9H, s, Si(CH₃)₃); ¹³C NMR (150 MHz; DMSO-d₆) 168.9 (C(O)), 149.1
(Ar), 139.1 (Ar), 137.4 (Ar), 133.7 (Ar), 133.3 (Ar), 132.4 (Ar), 128.5 (Ar), 127.7 (Ar), 47.7 (CH2N), 45.6 (CH2N), 36.4 (ArCH2CH2), 35.7 (ArCH2CH2), 22.1 (CH2CH3), 16.9 (ArCH3), 14.0 (CH2CH3), 3.4 (Si(CH3)3). Two aromatic 13C resonances were obscured by compound 273a.

2-Benzyl-4-methyl-5-(o-tolyl)-7-(trimethylsilyl)isoindolin-1-one (273b)

Prepared from amide 245e and 2-ethynyltoluene according to the General Cyclization Procedure C to give the isoindolinone 273b as a yellow oil (114 mg, approximately 90% pure by 1H NMR, 0.23 mmol, 88%); Rf = 0.22 (18:1 petrol 40–60 °C:EtOAc); νmax (film/cm−1) 3950s (C-H), 1688s (C=O), 1410s; 1H NMR (600 MHz; DMSO-d6) 7.37–7.21 (9H, m, ArH), 7.06 (1H, d, J = 7.2, ArH), 4.78 (1H, d, J = 15.4, CH2N), 4.74 (1H, d, J = 15.4, CH2N), 4.39 (1H, d, J = 17.4, CH'H), 4.34 (1H, d, J = 17.4, CH'H'), 1.98 (3H, s, ArCH3), 1.92 (3H, s, ArCH3), 0.34 (9H, s, Si(CH3)3); 13C NMR (150 MHz; DMSO-d6) 168.8 (C(O)), 143.1 (Ar), 141.6 (Ar), 140.1 (Ar), 137.3 (Ar), 135.4 (Ar), 135.2 (Ar), 134.9 (Ar), 133.8 (Ar), 131.6 (Ar), 130.0 (Ar), 129.1 (Ar), 128.7 (Ar), 127.8 (Ar), 127.6 (Ar), 127.1 (Ar), 125.8 (Ar), 48.7 (CH2N), 45.6 (CH2N), 19.6 (ArCH3), 14.7(ArCH3), –0.3 (Si(CH3)3); HRMS (CI+) found [M+H]+ 400.2106; C26H30NOSi requires 400.2091. This compound was unstable to flash column chromatography.

2-Benzyl-5-butyl-4-ethyl-7-(trimethylsilyl)isoindolin-1-one (273c) and 2-Benzyl-6-butyl-4-ethyl-7-(trimethylsilyl)isoindolin-1-one (274c)

Prepared from amide 245f and 1-hexyne according to the General Cyclization Procedure C (crude ratio 273c:274c = 2:1) and purified by flash column chromatography (18:1 petrol 40–60 °C:EtOAc) to give a mixture of the isoindolinone 273c and the isoindolinone 274c as a colorless oil (40 mg, 0.11 mmol, 40%, 273c:274c = 2:3). Further elution of the
column gave more of the isoindolinone 273c as a colorless oil (17 mg, 0.045 mmol, 17%); ν\textsubscript{max} (film/cm\textsuperscript{-1}) 2957s (C-H), 1690s (C=O), 1409s; HRMS (Cl\textsuperscript{+}) found [M+H]\textsuperscript{+} 380.2410; C\textsubscript{24}H\textsubscript{34}NOSi requires 380.2404.

**Isoindolinone 273c:** R\textsubscript{f} = 0.25 (18:1 petrol 40–60 °C:EtOAc); \textsuperscript{1}H NMR (600 MHz; DMSO-d\textsubscript{6}) 7.36–7.33 (3H, m, ArH), 7.29–7.26 (3H, m, ArH), 4.71 (2H, s, CH\textsubscript{2}N), 4.33 (2H, s, CH\textsubscript{2}N), 2.65 (2H, t, J = 7.9, ArCH\textsubscript{2}CH\textsubscript{2}), 2.58 (2H, q, J = 7.6, ArCH\textsubscript{2}CH\textsubscript{3}), 1.52–1.47 (2H, m, ArCH\textsubscript{2}CH\textsubscript{2}), 1.37 (2H, sextet, J = 7.4, CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 1.06 (3H, t, J = 7.6, ArCH\textsubscript{2}CH\textsubscript{3}), 0.91 (3H, t, J = 7.4, CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 0.34 (9H, s, Si(CH\textsubscript{3})\textsubscript{3}).

**Isoindolinone 274c:** R\textsubscript{f} = 0.31 (18:1 petrol 40–60 °C:EtOAc); \textsuperscript{1}H NMR (600 MHz; DMSO-d\textsubscript{6}) 7.36–7.32 (2H, m, ArH), 7.29–7.25 (3H, m, ArH), 7.14 (1H, s, ArH), 4.69 (2H, s, CH\textsubscript{2}N), 4.25 (2H, s, CH\textsubscript{2}N), 2.74 (2H, t, J = 7.9, ArCH\textsubscript{2}CH\textsubscript{2}), 2.52 (2H, q, J = 7.6, ArCH\textsubscript{2}CH\textsubscript{3}), 1.45–1.40 (2H, m, ArCH\textsubscript{2}CH\textsubscript{2}), 1.31 (2H, sextet, J = 7.2, CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 1.13 (3H, t, J = 7.6, ArCH\textsubscript{2}CH\textsubscript{3}), 0.87 (3H, t, J = 7.2, CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 0.40 (9H, s, Si(CH\textsubscript{3})\textsubscript{3}); \textsuperscript{13}C NMR (150 MHz; DMSO-d\textsubscript{6}) 169.0 (C(O)), 149.3 (Ar), 139.0 (Ar), 138.3 (Ar), 137.5 (Ar), 135.5 (Ar), 132.6 (Ar), 131.9 (Ar), 127.7 (Ar), 47.4 (CH\textsubscript{2}N), 45.6 (CH\textsubscript{2}N), 36.5 (ArCH\textsubscript{2}CH\textsubscript{2}), 35.9 (ArCH\textsubscript{2}CH\textsubscript{2}), 23.9 (ArCH\textsubscript{2}CH\textsubscript{3}), 22.1 (ArCH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}), 14.0 (CH\textsubscript{2}CH\textsubscript{3}), 13.8 (CH\textsubscript{2}CH\textsubscript{3}), 0.3 (Si(CH\textsubscript{3})\textsubscript{3}). Two aromatic \textsuperscript{13}C resonances were obscured by compound 273c.

2-Benzyl-4-ethyl-5-(o-tolyl)-7-(trimethylsilyl)isoindolin-1-one (273d) and 2-benzyl-4-Ethyl-6-(o-tolyl)-7-(trimethylsilyl)isoindolin-1-one (274d)

\[
\begin{align*}
\text{273d} & \quad + \quad \text{274d}
\end{align*}
\]

Prepared from amide \textbf{245f} and 2-ethyltoluene according to the General Cyclization Procedure C (crude ratio 273d:274d = 5:1). This was purified by flash column
chromatography (18:1 petrol 40–60 °C:EtOAc) to give a mixture of the isoindolinone 273d and the isoindolinone 274d as a colorless oil (80 mg, 0.19 mmol, 73%; 273d:274d = 5:1); Rf = 0.33 (18:1 petrol 40–60 °C:EtOAc); νmax (film/cm⁻¹) 2964s (C-H), 1690s (C=O), 1410s; ¹H NMR (600 MHz; DMSO-d₆) 7.39–7.23 (8H, m, ArH 273d; 8H, m, ArH 274d), 7.19 (1H, s, ArH 273d), 7.11 (1H, d, J = 7.6, ArH 273d), 7.04 (1H, m, CH₂N, 274d), 4.48–4.40 (2H, m, CH₂N, 274d), 2.60 (2H, q, J = 7.8, CH₂CH₃ 274d), 2.50–2.42 (1H, m, CHH'CH₃ 273d), 2.27–2.19 (1H, m, CHH'CH₃ 273d), 2.05 (3H, s, ArC₃H₃ 274d), 1.98 (3H, s, ArCH₃ 273d), 1.15 (3H, t, J = 7.6, CH₂C₂H₅ 274d), 0.82 (3H, t, J = 7.7, CH₂CH₃ 273d), 0.34 (9H, s, Si(CH₃)₃ 273d), –0.06 (9H, s, Si(CH₃)₃ 274d); ¹³C NMR (150 MHz; DMSO-d₆) 168.8 (C(O)), 168.7 (C(O)), 148.4 (Ar), 144.0 (Ar), 142.6 (Ar), 141.0 (Ar), 140.0 (Ar), 139.4 (Ar), 138.8 (Ar), 137.8 (Ar), 137.7 (Ar), 137.4 (Ar), 135.9 (Ar), 135.4 (Ar), 135.2 (Ar), 135.1 (Ar), 134.1 (Ar), 133.1 (Ar), 131.5 (Ar), 130.0 (Ar), 129.7 (Ar), 129.2 (Ar), 128.7 (Ar), 127.8 (Ar), 127.7 (Ar), 127.5 (Ar), 127.4 (Ar), 125.6 (Ar), 125.3 (Ar), 48.4 (CH₂N), 47.7 (CH₂N), 45.7 (CH₂N), 45.6 (CH₂N), 23.8 (CH₂CH₃), 22.2 (CH₂CH₃), 20.2 (ArCH₃), 19.9 (ArCH₃), 13.6 (CH₂CH₃), 1.6 (Si(CH₃)₃), −0.3 (Si(CH₃)₃); HRMS (Cl⁺) found [M+H]+ 414.2245; C₂₇H₃₂NOSi requires 414.2248.

2-Benzyl-5-butyl-7-methylisoindolin-1-one (273a)¹³⁷

Prepared from amide 245g, 1-hexyne and RuCp*Cl(cod) (3 mg, 3 mol%) over 16 h according to the General Cyclization Procedure B and purified by flash column chromatography (7:1 petrol 40–60 °C:EtOAc) to give the isoindolinone 273a as a colorless oil (65 mg, 0.22 mmol, 85%); Rf = 0.31 (7:1 petrol 40–60 °C:EtOAc); νmax (film/cm⁻¹) 2927s (C-H), 1681s (C=O), 1615s, 1453s, 1407s; ¹H NMR (600 MHz; DMSO-d₆) 7.36–7.32 (2H, m, ArH), 7.28–7.24 (3H, m, ArH), 7.13 (1H, s, ArH), 7.04 (1H, s, ArH), 4.67 (2H, s, CH₂N), 4.24 (2H, s, CH₂N), 2.61–2.57 (5H, m, ArCH₃; ArCH₂CH₂), 1.53 (2H, quintet, J = 7.5, ArCH₂CH₂), 1.28 (2H, sextet, J = 7.5, CH₂CH₃), 0.87 (3H, t, J = 7.5, CH₂CH₃); ¹³C NMR (150 MHz; DMSO-d₆) 168.2 (C(O)), 145.9 (Ar), 142.6 (Ar), 137.7 (Ar), 136.0 (Ar), 129.9 (Ar), 128.7 (Ar), 127.7 (Ar), 127.3 (Ar), 126.8
Experimental Details

\[(\text{Ar}), 120.6 (\text{Ar}), 48.5 (\text{CH}_2\text{N}), 45.1 (\text{CH}_2\text{N}), 34.9 (\text{ArCH}_2\text{CH}_2), 33.1 (\text{ArCH}_2\text{CH}_2), 21.8 (\text{CH}_2\text{CH}_3), 16.7 (\text{ArCH}_3), 13.8 (\text{CH}_2\text{CH}_3)\]; data in accordance with the literature.\(^{137}\)

**2-Benzyl-7-methyl-5-(o-tolyl)isoindolin-1-one (273b)**

Prepared from amide 245g, 2-ethynyltoluene and RuCp*Cl(cod) (3 mg, 3 mol%) over 16 h according to the General Cyclization Procedure B to give the **isoindolinone 273b** as a yellow oil (80 mg, 0.24 mmol, 94%); \(R_f = 0.31\) (5:1 petrol 40–60 °C:EtOAc); \(\nu_{\text{max}}\) (film/cm\(^{-1}\)) 2923s (C-H), 1684s (C=O), 1614s, 1495s, 1453s; \(^1\)H NMR (600 MHz; DMSO-d\(_6\)) \(7.37–7.34\) (2H, m, ArH), \(7.30–7.22\) (7H, m, ArH), \(7.19–7.17\) (2H, m, ArH), 4.71 (2H, s, C\(_2\)H\(_2\)N), 4.31 (2H, s, C\(_2\)H\(_2\)N), 2.63 (3H, s, ArC\(_3\)H), 2.21 (3H, s, ArC\(_3\)H); \(^{13}\)C NMR (150 MHz; DMSO-d\(_6\)) 168.0 (C(O), 144.1 (Ar), 142.4 (Ar), 140.7 (Ar), 137.7 (Ar), 136.1 (Ar), 134.7 (Ar), 130.5 (Ar), 130.4 (Ar), 129.5 (Ar), 128.7 (Ar), 127.7 (Ar), 127.5 (Ar), 126.0 (Ar), 121.5 (Ar), 48.7 (CH\(_2\)N), 45.3 (CH\(_2\)N), 20.2 (ArCH\(_3\)), 16.8 (ArCH\(_3\)); HRMS (Cl\(^+\)) found [M+H]\(^+\) 328.1688; C\(_{23}\)H\(_{22}\)NO requires 328.1696.

**N-Benzyl-N-((2-benzyl-1-oxo-7-(trimethylsilyl)isoindolin-5-yl)methyl)-3-(trimethylsilyl)propiolamide (248a)**

Isolated from the certain alkyne cyclotrimerization reaction involving amide 245a.

The **isoindolinone 248a** was isolated as a colorless oil; \(R_f = 0.24\) (6:1 petrol 40–60 °C:EtOAc); \(\nu_{\text{max}}\) (film/cm\(^{-1}\)) 3279s (CC-H), 2960w (C-H), 2108w (C≡C), 1630s (C=O), 1415s; \(^1\)H NMR (600 MHz; DMSO-d\(_6\)) a 1:1 mixture of rotamers; 7.46–7.17 (12H, m, ArH), 12H, m, ArH), 4.79 (2H, s, CH\(_2\)N), 4.73 (2H, s, CH\(_2\)N), 4.72 (2H, s, CH\(_2\)N), 4.71 (2H, s, CH\(_2\)N), 4.55 (2H, s, CH\(_2\)N), 4.47 (2H, s, CH\(_2\)N), 4.32 (2H, s, CH\(_2\)N), 4.30 (2H, s, CH\(_2\)N), 0.34 (9H, s, Si(CH\(_3\))\(_3\)), 0.33 (9H, s, Si(CH\(_3\))\(_3\)), 0.17 (9H, s, Si(CH\(_3\))\(_3\)), 0.13 (9H, s, Si(CH\(_3\))\(_3\)); \(^{13}\)C NMR (125 MHz; DMSO-d\(_6\)) a mixture of rotamers; 168.2 (C(O)), 168.2
N-Benzyl-N-((2-benzyl-1-oxo-7-(trimethylsilyl)isoindolin-5-yl)methyl)propiolamide (248b)

\[
\begin{align*}
\text{O} & \quad \text{SiMe}_3 \\
\text{BnN} & \quad \text{CH}_2 & \quad \text{Bn} & \quad \text{O} \\
& \quad \text{C} & \quad \text{Si} & \quad \text{H}_3 \\
& \quad \text{Si} & \quad \text{H}_3 & \quad \text{Si} & \quad \text{H}_3
\end{align*}
\]

Isolated from the specific alkyne cyclotrimerization reaction involving amide 248b.

The *isoindolinone* 248b was isolated as a colorless oil; 
\[ R_f = 0.10 \] (6:1 petrol 40–60 °C:EtOAc); 
\[ \nu_{\text{max}} \text{ (film/cm}^{-1} \text{) } 3288s \text{ (CC-H), 2932s (C-H), 2104w (C≡C), 1653s (C=O), 1601, 1453s; } \]
\[ ^1\text{H NMR (600 MHz; CDCl}_3 \text{)} a 1:1 mixture of rotamers; 7.44–7.14 (12 H, m, ArH; 12H, m, ArH), 4.80 (2H, s, CH$_2$N), 4.73 (2H, s, CH$_2$N), 4.71 (2H, s, CH$_2$N), 4.70 (2H, s, CH$_2$N), 4.64 (1H, s, HC≡C), 4.63 (1H, s, HC≡C), 4.53 (2H, s, CH$_2$N), 4.45 (2H, s, CH$_2$N), 4.32 (2H, s, CH$_2$N), 4.29 (2H, s, CH$_2$N), 0.34 (9H, s, Si(CH$_3$)$_3$), 0.32 (9H, s, Si(CH$_3$)$_3$); 
\[ ^13\text{C NMR (125 MHz; DMSO-d}_6 \text{)} a mixture of rotamers; 168.2 (C(O)), 168.1 (C(O)), 153.3 (Ar), 153.3 (Ar), 142.3 (Ar), 142.2 (Ar), 138.6 (Ar), 138.6 (Ar), 138.6 (Ar), 137.6 (Ar), 137.6 (Ar), 137.6 (Ar), 136.3 (Ar), 136.2 (Ar), 136.0 (Ar), 135.7 (Ar), 133.5 (Ar), 133.0 (Ar), 133.1 (Ar), 128.7 (Ar), 128.4 (Ar), 127.8 (Ar), 127.7 (Ar), 127.6 (Ar), 127.4 (Ar), 127.4 (Ar), 123.4 (Ar), 123.1 (Ar), 82.9 (C≡C), 75.9 (C≡C), 51.6 (CH$_2$N), 51.6 (CH$_2$N), 49.0 (CH$_2$N), 49.0 (CH$_2$N), 47.1 (CH$_2$N), 47.0 (CH$_2$N), 45.4 (CH$_2$N), –0.5 (Si(CH$_3$)$_3$).
A solution of RuCp*Cl(cod) (10 mg, 0.026 mmol, 10 mol%) in CPME (1.1 mL) was added dropwise to a stirring solution of amide 245b (47 mg, 0.26 mmol) in CPME (1.6 mL) at RT. The reaction was stirred for 16 h before the reaction mixture was filtered through a silica pad, eluting with EtOAc. The filtrate was concentrated in vacuo to give the crude product, which was purified by flash column chromatography (2:1 EtOAc:petrol 40–60 °C) to give the isoindolinone 265 as a white crystalline solid (47 mg, 0.10 mmol, 79%); m.p. 104–106 °C; Rf = 0.36 (2:1 EtOAc:petrol 40–60 °C); νmax (film/cm⁻¹) 3321m (N-H), 3208m (N-H), 2957m (C-H), 1674s (C=O), 1655s (C=O), 1601m; ¹H NMR (600 MHz; DMSO-d₆) 9.30 (1H, t, J = 5.7, NH straight chain amide), 8.46 (1H, s, NH lactam), 7.42 (1H, s, ArH), 7.40 (1H, s, ArH), 4.38–4.31 (4H, m, C₂H₂N, C₂H₂N), 0.32 (9H, s, Si(CH₃)₃), 0.30 (9H, s, Si(CH₃)₃); ¹³C NMR (150 MHz; DMSO-d₆) 171.0 (C(O) lactam), 151.8 (C(O) straight chain amide), 144.6 (Ar), 140.7 (Ar), 136.9 (Ar), 136.1 (Ar), 133.1 (Ar), 123.3 (Ar), 98.8 (C≡C), 90.1 (C≡C), 44.8 (CH₂N), 42.5 (CH₂N), –0.4 (Si(CH₃)₃), –0.7 (Si(CH₃)₃); HRMS (Cl⁺) found [M+H]⁺ 359.1617; C₁₈H₂₇N₂O₂Si₂ requires 359.1611.

N-(tert-Butyl)-N-((2-(tert-butyl)-1-oxo-7-(trimethylsilyl)isoindolin-5-yl)methyl)-3-(trimethylsilyl)propiolamide (268)

RuCp*Cl(cod) (8 mg, 0.011 mmol, 10 mol%) was added dropwise to a stirring solution of amide 245c (50 mg, 0.11 mmol) in CPME (2.2 mL) at RT. The reaction was stirred for 16 h before the reaction mixture was filtered through a silica pad, eluting with EtOAc. The filtrate was concentrated in vacuo to give the crude product, which was purified by flash column chromatography (10:1 EtOAc:petrol 40–60 °C) to give the isoindolinone
268 as a colorless oil (50 mg, 0.11 mmol, 100%); \( \nu_{\text{max}} \) (film/cm\(^{-1}\)) 2963s (C-H), 1680s (C=O), 1631s (C=O); \(^1\)H NMR (400 MHz; DMSO-d\(_6\)) 7.47 (1H, s, ArH) 7.41 (1H, s, ArH), 5.00 (2H, s, CH\(_2\)N), 4.54 (2H, s, CH\(_2\)N), 1.47 (9H, s, C(CH\(_3\))\(_3\)), 1.31 (9H, s, C(CH\(_3\))\(_3\)), 0.31 (9H, s, Si(CH\(_3\))\(_3\)), 0.00 (9H, s, Si(CH\(_3\))\(_3\)); \(^{13}\)C NMR (125 MHz; DMSO-d\(_6\)) 168.5 (C(O) lactam), 154.4 (C(O) straight chain amide), 141.8 (Ar), 141.1 (Ar), 137.5 (Ar), 136.2 (Ar), 131.6 (Ar), 121.4 (Ar), 98.6 (C≡C), 93.6 (C≡C), 57.7 (CMe\(_3\)), 53.6 (CMe\(_3\)), 50.4 (CH\(_2\)N), 47.9 (CH\(_2\)N), –0.4 (Si(CH\(_3\))\(_3\)), –1.1 (Si(CH\(_3\))\(_3\)); HRMS (CI\(^+\)) found [M]\(^+\) 470.2791; C\(_{26}\)H\(_{42}\)N\(_2\)O\(_2\)Si\(_2\) requires 470.2779.

2-Benzyl-5-butyl-7-iodoisooindolin-1-one (275)

According to the modified procedure of Clayden et al.\(^{149}\): A solution of ICl (93 mg, 0.57 mmol) in CH\(_2\)Cl\(_2\) (0.57 mL) was added dropwise to a stirring solution of isoindolinone 247a (26 mg, 0.074 mmol) in CH\(_2\)Cl\(_2\) (17 mL) at RT. The reaction was stirred for 3.5 h and aq. sat. Na\(_2\)S\(_2\)O\(_3\) was added to afford a colorless solution. The reaction was extracted with CH\(_2\)Cl\(_2\) (2 × 20 mL), dried (MgSO\(_4\)), and concentrated in vacuo. The crude product was purified by flash column chromatography (5:1 petrol 40–60 °C:EtOAc) to give the isoindolinone 275 as a colorless oil (27 mg, 0.067 mmol, 90%); \( R_f \) = 0.20 (6:1 petrol 40–60 °C:EtOAc); \( \nu_{\text{max}} \) (film/cm\(^{-1}\)) 2929s (C-H), 1690s (C=O), 1609s, 1453s, 1408s; \(^1\)H NMR (600 MHz; DMSO-d\(_6\)) 7.74 (1H, s, ArH), 7.38 (1H, s, ArH), 7.36–7.33 (2H, m, ArH), 7.29–7.25 (3H, m, ArH), 4.69 (2H, s, CH\(_2\)N), 4.23 (2H, s, CH\(_2\)N), 2.60 (2H, t, \( J = 7.7 \), ArCH\(_2\)CH\(_2\)), 1.53 (2H, m, ArCH\(_2\)CH\(_2\)), 1.27 (2H, sextet, \( J = 7.4 \), CH\(_2\)CH\(_3\)), 0.87 (3H, t, \( J = 7.4 \), CH\(_3\)); \(^{13}\)C NMR (150 MHz; DMSO-d\(_6\)) 165.9 (C(O)), 148.1 (Ar), 144.6 (Ar), 139.0 (Ar), 137.4 (Ar), 129.4 (Ar), 127.7 (Ar), 127.4 (Ar), 123.4 (Ar), 89.9 (Cl), 47.7 (CH\(_2\)N), 45.6 (CH\(_2\)N), 34.2 (ArCH\(_2\)CH\(_2\)), 32.9 (ArCH\(_2\)CH\(_2\)), 21.7 (CH\(_2\)CH\(_3\)), 13.8 (CH\(_3\)); HRMS (ES\(^+\)) found [M+H]\(^+\) 406.0663; C\(_{19}\)H\(_{21}\)INO requires 406.0668.
2-Benzyl-7-bromo-5-butylisoindolin-1-one (276)

According to the modified procedure of Snieckus et al.\textsuperscript{150}: A solution of Br\textsubscript{2} (118 mg, 0.738 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (0.36 mL) was added dropwise to a stirring solution of the isoindolinone 247a (26 mg, 0.074 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (0.36 mL) at RT. The reaction was stirred for 16 h and aq. sat. Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} was added to afford a colorless solution. The reaction was extracted with CH\textsubscript{2}Cl\textsubscript{2} (2 \times 20 mL), dried (MgSO\textsubscript{4}), and concentrated \textit{in vacuo}. The crude product was purified by flash column chromatography (10:1 petrol 40–60 °C:EtOAc) to give the isoindolinone 276 as a colorless oil (21 mg, 0.058 mmol, 78%); \(R_f = 0.50\) (5:1 petrol 40–60 °C:EtOAc); \(\nu_{\text{max}}\) (film/cm\textsuperscript{-1}) 2928s (C-H), 1692s (C=O), 1615s, 1453s, 1408s; \(^1^H\) NMR (600 MHz; DMSO-d\textsubscript{6}) 7.49 (1H, s, ArH), 7.37–7.33 (3H, m, ArH), 7.29–7.26 (3H, m, ArH), 4.69 (2H, s, CH\textsubscript{2}N), 4.28 (2H, s, CH\textsubscript{2}N), 2.64 (2H, t, \(J = 7.7\), ArCH\textsubscript{2}CH\textsubscript{2}), 1.54 (2H, m, ArCH\textsubscript{2}CH\textsubscript{2}), 1.28 (2H, sextet, \(J = 7.4\), CH\textsubscript{2}CH\textsubscript{3}), 0.87 (3H, t, \(J = 7.4\), CH\textsubscript{3}); \(^{13}C\) NMR (150 MHz; DMSO-d\textsubscript{6}) 165.3 (C(O)), 148.3 (Ar), 145.0 (Ar), 137.4 (Ar), 132.4 (Ar), 128.7 (Ar), 127.7 (Ar), 127.4 (Ar), 126.9 (Ar), 122.9 (Ar), 117.2 (Ar), 48.1 (CH\textsubscript{2}N), 45.4 (CH\textsubscript{2}N), 34.4 (ArCH\textsubscript{2}CH\textsubscript{2}), 32.9 (ArCH\textsubscript{2}CH\textsubscript{2}), 21.7 (CH\textsubscript{2}CH\textsubscript{3}), 13.8 (CH\textsubscript{3}); HRMS (ESI\textsuperscript{+}) found [M+H]\textsuperscript{+} 358.0807; C\textsubscript{19}H\textsubscript{21}BrNO requires 358.0807.

5-Butylisoindolin-1-one (277)

According to the modified procedure of Miranda \textit{et al.}\textsuperscript{151}: TfOH (0.50 mL) was added to the isoindolinone 267a. (50 mg, 0.16 mmol). The resulting solution was stirred at RT for 30 minutes before being partitioned between EtOAc (20 mL) and water (20 mL). The aq. extract was washed with EtOAc (2 \times 20 mL) and the combined organic extracts were washed with aq. sat. Na\textsubscript{2}CO\textsubscript{3} (50 mL) and brine (50 mL), dried (MgSO\textsubscript{4}) and concentrated \textit{in vacuo} to give the crude product. This was purified by flash column chromatography (3:1 EtOAc:petrol 40–60 °C) to give the isoindolinone 277 as a white crystalline solid (26 mg, 0.014 mmol, 88%); m.p. 145–147 °C; \(R_f = 0.57\) (2:1 petrol 40–60 °C:EtOAc);
According to the modified procedure of Clayden et al.\textsuperscript{149}: A solution of ICl (400 mg, 2.49 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (5.0 mL) was added dropwise to a stirring solution of isoindolinone \textbf{267a} (158 mg, 0.498 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (5.0 mL) at RT. The reaction was stirred for 2 h and the reaction mixture was diluted with sat. aq. NaHCO\textsubscript{3}, before sat. aq. NaN\textsubscript{2}SO\textsubscript{3} was added dropwise to afford a colorless solution. The reaction was extracted with CH\textsubscript{2}Cl\textsubscript{2} (2 × 20 mL), dried (MgSO\textsubscript{4}), and concentrated \textit{in vacuo} to give the isoindolinone as a yellow oil (183 mg, 0.492 mmol, 99%); \(R_f = 0.31\) (6:1 petrol 40–60 °C:EtOAc); \(\nu_{\text{max}}\) (film/cm\textsuperscript{-1}) 2957s (C-H), 2928s (C-H), 1678s (C=O), 1607s, 1455s; \(^1\text{H} \text{NMR}\) (600 MHz; DMSO-d\textsubscript{6}) 7.67 (1H, s, Ar\textit{H}), 7.33 (1H, s, Ar\textit{H}), 4.39 (2H, s, CH\textsubscript{2}N), 2.57 (2H, t, \(J = 7.6\), ArCH\textsubscript{2}CH\textsubscript{2}), 1.44 (9H, s, C(CH\textsubscript{3})\textsubscript{3}), 1.25 (2H, sextet, \(J = 7.4\), CH\textsubscript{2}CH\textsubscript{3}), 0.85 (3H, t, \(J = 7.4\), CH\textsubscript{2}CH\textsubscript{3}); \(^{13}\text{C} \text{NMR}\) (150 MHz; DMSO-d\textsubscript{6}) 165.8 (C(O)), 147.4 (Ar), 144.1 (Ar), 138.8 (Ar), 130.5 (Ar), 122.9 (Ar), 89.0 (Cl), 53.8 (CMe\textsubscript{3}), 46.3 (CH\textsubscript{2}N), 34.3 (ArCH\textsubscript{2}CH\textsubscript{2}), 33.0 (ArCH\textsubscript{2}CH\textsubscript{2}), 27.4 (C(CH\textsubscript{3})\textsubscript{3}), 21.7 (CH\textsubscript{2}CH\textsubscript{3}), 13.8 (CH\textsubscript{2}CH\textsubscript{3}); HRMS (Cl\textsuperscript{+}) found [M+H]\textsuperscript{+} 372.0837; C\textsubscript{19}H\textsubscript{23}INO requires 372.0824.

\textbf{5-Butyl-7-idoisoindolin-1-one (278)}

TfOH (0.75 mL) was added to 2-(\textit{tert}-butyl)-5-butyl-7-idoisoindolin-1-one (156 mg, 0.420 mmol). The resulting solution was stirred at RT for 2 days before being partitioned
between EtOAc (20 mL) and water (20 mL). The aq. extract was washed with EtOAc (2 × 20 mL) and the combined organic extracts were washed with aq. sat. Na₂CO₃ (50 mL) and brine (50 mL), dried (MgSO₄) and concentrated in vacuo to give the crude product. This was purified by flash column chromatography (1:1 EtOAc:petrol 40–60 °C) to give the isoindolinone 278 as a white crystalline solid (112 mg, 0.355, 85%); m.p. 137–139 °C; Rᵣ = 0.37 (2:1 EtOAc:petrol 40–60 °C); νₘₐₓ (film/cm⁻¹) 3171s (N-H), 3073s (C-H), 2928s (C-H), 1702s (C=O), 1607s, 1457s; ¹H NMR (600 MHz; DMSO-d₆): 8.64 (1H, s, N-H), 7.73 (1H, s, ArH), 7.41 (1H, s, ArH), 4.23 (2H, s, CH₂N), 2.63 (2H, t, J = 7.7, ArCH₂CH₂), 1.59–1.53 (2H, m, ArCH₂CH₂), 1.29 (2H, sextet, J = 7.4, CH₂CH₃), 0.88 (3H, t, J = 7.4, CH₃); ¹³C NMR (150 MHz; DMSO-d₆); 168.5 (C(O)), 147.9 (Ar), 146.8 (Ar), 138.8 (Ar), 129.7 (Ar), 123.6 (Ar), 89.7 (Cl), 43.0 (CH₂N), 34.2 (ArCH₂CH₂), 33.0 (ArCH₂CH₂), 21.7 (CH₂CH₃), 13.8 (CH₃); HRMS (ES⁺) found [M]⁺ 315.0108; C₁₂H₁₄INO requires 315.0120.

2-Acetyl-5-butylisoindolin-1-one (282)

According to the modified procedure of Clift and Silverman¹⁵⁴: aq. HCl (8.0 mL, 12 M) was added to isoindolinone 277 (37 mg, 0.20 mmol). The reaction mixture was heated at reflux for 3 days before it was allowed to cool to RT. The reaction mixture was concentrated in vacuo and then it was dissolved in CH₂Cl₂ (5.0 mL). The resulting solution was stirred at RT and treated with NEt₃ (0.14 mL, 100 mg, 1.0 mmol) and Ac₂O (95 μl, 100 mg, 1.0 mmol). The reaction was stirred at RT for 16 h, quenched with water (1.0 mL) and filtered through a silica plug, eluting with EtOAc. The filtrate was concentrated in vacuo to give the crude product, which was purified by flash column chromatography (10:1 EtOAc:petrol 40–60 °C) to give the isoindolinone 282 as a white crystalline solid (26 mg, 0.11 mmol, 56%); m.p. = 69–71 °C; Rᵣ = 0.29 (10:1 petrol 40–60 °C:EtOAc); νₘₐₓ (film/cm⁻¹) 2930s (C-H), 1712s (C=O ester), 1693s (C=O lactam), 1589s, 1439s; ¹H NMR (600 MHz; DMSO-d₆): 7.73 (1H, d, J = 7.9, ArH), 7.48 (1H, s, ArH), 7.39 (1H, d, J = 7.9, ArH), 4.74 (2H, s, CH₂N), 2.71 (2H, t, J = 7.7 ArCH₂CH₂), 2.53 (3H, s, CH₃C(O)), 1.61–1.56 (2H, m, ArCH₂CH₂), 1.31 2H, sextet, J = 7.4, CH₂CH₃), 0.90 (3H, t, J = 7.4, CH₂CH₃); ¹³C NMR (150 MHz; DMSO-d₆); 170.2 (C(O)), 167.7 (C(O)), 149.6 (Ar), 142.1 (Ar), 129.0 (Ar), 128.5 (Ar), 124.3 (Ar), 123.6 (Ar), 47.9...
(CH₂N), 35.2 (ArCH₂CH₂), 33.0 (ArCH₂CH₂), 24.6 (CH₃C(O)), 21.8 (CH₂CH₃), 13.8 (CH₂CH₃); HRMS (EI⁺) found [M⁺] 231.1252; C₁₄H₁₇NO₂ requires 231.1259.

**tert-Butyl 1-oxoisooindoline-2-carboxylate (286)**

According to the procedure of Motherwell *et al.*[156]: Tin (41.7 g, 351 mmol) was added portionwise to a vigorously stirring suspension of phthalimide (20.0 g, 136 mmol) in AcOH (100 mL) and aq. HCl (50 mL, concentrated). The resultant suspension was heated at reflux for 2 h before being allowed to cool to RT. The reaction mixture was diluted with chloroform (100 mL) and the aq. extract washed with chloroform (2 × 100 mL). The combined organic extracts were dried (MgSO₄) and concentrated *in vacuo* to give the crude product, which was washed with hot ether and recrystallized (hot EtOAc/ether) to give an impure sample isoindolin-1-one **285** as a yellow solid (13.0 g, *ca.* 80% purity by ¹H NMR). Then according to the modified procedure of Cativiela *et al.*[157]: Boc₂O (3.04 g, 13.9 mmol) and DMAP (68 mg, 0.56 mmol) were added to a stirring solution of isoindolin-1-one (800 mg, *ca.* 80% purity, *ca.* 4.8 mmol) in THF (45 mL) at RT. The reaction was stirred at RT for 16 h before the volatile components were removed *in vacuo* to give the crude product. This was purified by flash column chromatography (4:1 petrol 40–60 °C: EtOAc) to give the *isoindolinone 286* as a white crystalline solid (832 mg, 3.57 mmol, 43% over 2 steps); m.p. 110–112 °C (literature 117–119 °C[157]); R₇ = 0.25 (4:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm⁻¹); 2980s (C-H), 1777s, 1742s, 1714s, 1618s, 1470s, 1454s; ¹H NMR (600 MHz; DMSO-d₆); 7.76 (1H, d, J = 7.6, ArH), 7.72 (1H, t, J = 7.6, ArH), 7.64 (1H, d, J = 7.6, ArH), 7.53 (1H, t, J = 7.6, ArH), 4.79 (2H, s, CH₂N), 1.52 (9H, s, C(CH₃)₃); ¹³C NMR (150 MHz; DMSO-d₆) 165.9 (C(O)C), 149.7 (C(O)O), 141.5 (Ar), 133.7 (Ar), 130.8 (Ar), 128.4 (Ar), 124.0 (Ar), 123.9 (Ar), 81.9 (CMes), 49.1 (CH₂N), 27.8 (C(CH₃)₃); data in agreement with the literature.[157]
Experimental Details

**tert-Butyl 2-(hydroxymethyl)benzylcarbamate (288)**

According to the modified procedure of Murata et al.\textsuperscript{158}: A solution of NaBH\textsubscript{4} (105 mg, 2.78 mmol) in water (1.2 mL) was added dropwise to a stirring solution of isoindolinone 286 (100 mg, 0.429 mmol) in THF (4.0 mL) at 0 °C over 1 minute. The resulting mixture was stirred vigorously for 24 h with the reaction allowed to slowly reach RT. Amberlyst A-26 was added and the resulting mixture filtered. The filtrate was concentrated \textit{in vacuo} to give the crude product, which was purified by flash column chromatography (5:1 petrol 40–60 °C:EtOAc) to give the isoindolinone 288 as a white crystalline solid (66 mg, 0.28 mmol, 65%); m.p. 90–92 °C; R\textsubscript{f} = 0.33 (2:1 petrol 40–60 °C:EtOAc); ν\textsubscript{max} (film/cm\textsuperscript{-1}) 3352s (O-H), 2977s (C-H), 1686s (C=O), 1519s, 1454s; \textsuperscript{1}H NMR (600 MHz; DMSO-d\textsubscript{6}) a mixture of rotamers R\textsubscript{1} (major) and R\textsubscript{2} (minor) 7.37–7.35 (1H, m, Ar\textsubscript{H} R\textsubscript{1}; 1H, t, J = 6.0, NH R\textsubscript{1}); 1H, t, J = 6.0, NH R\textsubscript{2}), 7.26–7.20 (3H, m, ArH R\textsubscript{1}; 3H, m, ArH R\textsubscript{2}), 5.13 (1H, t, J = 5.4, OH R\textsubscript{1}; 1H, t, J = 5.4, OH R\textsubscript{2}), 4.54 (2H, d, J = 5.4, CH\textsubscript{2}OH R\textsubscript{1}; 2H, d, J = 5.4, CH\textsubscript{2}OH R\textsubscript{2}), 4.16 (2H, d, J = 6.0, CH\textsubscript{2}N R\textsubscript{1}; 2H, d, J = 6.0, CH\textsubscript{2}N R\textsubscript{2}) 3.36 (9H, s, C(CH\textsubscript{3})\textsubscript{3} R\textsubscript{1}) 3.33 (9H, s, C(CH\textsubscript{3})\textsubscript{3} R\textsubscript{2}); \textsuperscript{13}C NMR (150 MHz; DMSO-d\textsubscript{6}) 155.7 (C(O)), 139.4 (Ar), 137.1 (Ar), 127.1 (Ar), 126.9 (Ar), 126.8 (Ar), 126.5 (Ar), 77.8 (CMe), 60.6 (CH\textsubscript{2}OH), 40.3 (CH\textsubscript{2}N), 28.3 (C(CH\textsubscript{3})\textsubscript{3}); HRMS (Cl\textsuperscript{+}) found [M+H]\textsuperscript{+} 238.1438; C\textsubscript{13}H\textsubscript{20}NO\textsubscript{3} requires 238.1443.

**tert-Butyl 5-butyl-7-iodo-1-oxoisoindoline-2-carboxylate (289)**

Boc\textsubscript{2}O (55 mg, 0.25 mmol) and DMAP (1.5 mg, 0.012 mmol) were added to a stirring solution of isoindolinone 278 (40 mg, 0.13 mmol) in THF (2.0 mL) at RT. The resulting solution was stirred at RT for 16 h, after which a further quantity of Boc\textsubscript{2}O (55 mg, 0.25 mmol) and DMAP (1.5 mg, 0.012 mmol) were added. After a further 3 h the reaction mixture was concentrated \textit{in vacuo} to give the crude product, which was purified by flash column chromatography (10:1 petrol 40–60 °C:EtOAc) to give the isoindolinone 289 as
a colorless oil (48 mg, 0.12 mmol, 91%); $R_f = 0.24$ (10:1 petrol 40–60 °C:EtOAc); $\nu_{\text{max}}$ (film/cm$^{-1}$) 2930s (C-H), 1777s (C=O), 1747s (C=O), 1712s (C=O), 1605s, 1456s; $^1$H NMR (600 MHz; DMSO-d$_6$): 7.82 (1H, s, ArH), 7.47 (1H, s, ArH), 4.63 (2H, s, CH$_2$N), 2.64 (2H, t, $J = 7.7$, ArCH$_2$CH$_2$), 1.59–1.53 (2H, m, ArCH$_2$CH$_2$), 1.52 (9H, s, C(C$_3$H$_9$)$_3$), 1.30 (2H, sextet, $J = 7.4$, C$_2$H$_5$CH$_3$), 0.89 (3H, t, $J = 7.4$, CH$_2$C$_3$H$_3$); $^{13}$C NMR (150 MHz; DMSO-d$_6$): 164.1 (C(O)C), 150.2 (C(O)O), 149.8 (Ar), 144.5 (Ar), 139.7 (Ar), 128.0 (Ar), 123.5 (Ar), 91.3 (Cl), 82.0 (CMe$_3$), 47.3 (CH$_3$N), 34.4 (ArCH$_2$CH$_2$), 32.7 (ArCH$_2$CH$_2$), 27.7 (C(CH$_3$)$_3$), 21.8 (CH$_2$CH$_3$), 13.7 (CH$_2$CH$_3$); HRMS (CI$^+$) found [M+H]$^+$ 416.0717; $C_{17}H_{23}$INO$_3$ requires 416.0723.

**tert-Butyl 5-butyl-1-hydroxy-7-iodoisoiindoline-2-carboxylate (290)**

According to the modified procedure of Murata et al.$^{158}$: A solution of NaBH$_4$ (19 mg, 0.49 mmol) in water (0.22 mL) was added dropwise to a stirring solution of isoindolinone 289 (32 mg, 0.077 mmol) in THF (0.70 mL) at 0 °C over 1 minute. The resulting mixture was stirred vigorously for 16 h with the reaction allowed to slowly reach RT. A further portion of NaBH$_4$ (19 mg, 0.49 mmol) was added to the reaction mixture at RT and the reaction was stirred vigorously of a further 24 h. Amberlyst A-26 was added and the resulting mixture filtered. The filtrate was concentrated in vacuo to give the crude product, which was purified by flash column chromatography (10:1 petrol 40–60 °C:EtOAc) to give hemiaminal 290 as a colorless oil (16 mg, 0.038 mmol, 50%); $R_f = 0.20$ (10:1 petrol 40–60 °C:EtOAc); $\nu_{\text{max}}$ (film/cm$^{-1}$) 2974s (C-H), 1755s, 1707s (C=O), 1456s; $^1$H NMR (600 MHz; DMSO-d$_6$) a 50:50 mixture of rotamers R$_1$ and R$_2$; 7.55 (1H, s, ArH R$_1$), 7.20 (1H, s, ArH R$_2$), 7.18 (1H, s, ArH R$_1$ or R$_2$), 6.39 (1H, d, $J = 8.0$, O$_2$H R$_1$), 6.22 (1H, d, $J = 8.3$, O$_2$H R$_2$), 6.03 (1H, d, $J = 8.0$, CHO R$_1$), 5.94 (1H, d, $J = 8.3$, CHO R$_2$), 4.59–4.45 (2H, m, CH$_2$N R$_1$), 2H, m, CH$_2$N R$_2$), 2.56 (2H, t, $J = 7.7$, ArCH$_2$CH$_2$ R$_1$), 2H, t, $J = 7.7$, ArCH$_2$CH$_2$ R$_2$), 1.54–1.50 (2H, m, ArCH$_2$CH$_2$ R$_1$), 2H, m, ArCH$_2$CH$_2$ R$_2$), 1.47 (9H, s, C(CH$_3$)$_3$ R$_1$ or R$_2$), 1.46 (9H, s, C(CH$_3$)$_3$ R$_1$ or R$_2$), 1.28 (2H, sextet, $J = 7.3$, CH$_2$CH$_3$ R$_1$), 2H, sextet, $J = 7.3$, CH$_2$CH$_3$ R$_2$), 0.88 (3H, d, $J = 7.3$, CH$_2$CH$_3$ R$_1$), 3H, d, $J = 7.3$, CH$_2$CH$_3$ R$_2$); $^{13}$C NMR (150 MHz; DMSO-d$_6$) a mixture of rotamers; 153.1 (C(O)), 153.0 (C(O)), 145.4 (Ar), 140.7 (Ar),
Experimental Details

140.2 (Ar), 138.7 (Ar), 138.4 (Ar), 136.9 (Ar), 136.9 (Ar), 122.6 (Ar), 122.5 (Ar), 91.7 (Cl), 85.6 (CHO), 85.6 (CHO), 79.4 (CMe₃), 79.2 (CMe₃), 50.7 (CH₂N), 50.4 (CH₂N), 34.1 (ArCH₂CH₂), 33.1 (ArCH₂CH₂), 28.1 (C(CH₃)₃), 21.7 (CH₂CH₃), 13.8 (CH₂CH₃); HRMS (Cl⁺) found [M+H]⁺ 418.0870; C₁₇H₂₅INO₃ requires 418.0874.

**tert-Butyl 5-butyl-2-(hydroxymethyl)-3-iodobenzylcarbamate (291)**

According to the modified procedure of Ohno et al.¹⁵⁹: LiBH₄ (4.2 mg, 0.19 mmol) was added to a solution of isoindolinone 289 (32 mg, 0.077 mmol) and MeOH (3.7 mg, 0.12 mmol) in Et₂O (1.0 mL) at 0 °C. The resulting solution was stirred at RT for 90 minutes, after which a further portion of LiBH₄ (42 mg, 0.19 mmol) was added. The reaction was stirred at RT for a further 16 h before the reaction was diluted with aq. sat. NH₄Cl (10 mL) and Et₂O (10 mL). The aq. extract was washed with Et₂O (3 × 10 mL) and the combined organic extracts were washed with water (10 mL) and brine (10 mL), dried (MgSO₄) and concentrated *in vacuo* to give the crude product. This was purified by flash column chromatography (8:1 petrol 40–60 °C:EtOAc) to give the carbamate 291 as a white crystalline solid (17 mg, 0.041 mmol, 53%); m.p. 78–76 °C; Rᵢ= 0.11 (5:1 petrol 40–60 °C:EtOAc); ν_max (film/cm⁻¹), 3353s (O-H, N-H), 2958s (C-H), 2925s (C-H), 2856s (C-H), 1687s (C=O) 1601s, 1507s, 1458s; ¹H NMR (600 MHz; DMSO-d₆) 7.47 (1H, s, ArH), 7.26 (1H, t, J = 5.9, NH), 7.09 (1H, s, ArH), 5.01 (1H, t, J = 5.0, CH₂OH), 4.62 (2H, d, J = 5.0, CH₂OH), 4.28 (2H, d, J = 5.9, CH₂N), 2.51–2.48 (2H, m, ArCH₂CH₂ and solvent peak), 1.49 (2H, quintet, J = 7.4, ArCH₂CH₂), 1.39 (9H, s, C(CH₃)₃), 1.27 (2H, sextet, J = 7.4, CH₂CH₂), 0.87 (3H, t, J = 7.4, CH₂CH₃); ¹³C NMR (150 MHz; DMSO-d₆); 155.7 (C(O)), 143.8 (Ar), 140.4 (Ar), 137.7 (Ar), 137.4 (Ar), 127.8 (Ar), 102.5 (Cl), 78.0 (CMe₃), 64.8 (CH₂OH), 42.7 (CH₂N), 33.9 (ArCH₂CH₂), 32.9 (ArCH₂CH₂), 28.2 (C(CH₃)₃), 21.6 (CH₂CH₃), 13.8 (CH₂CH₃); HRMS (Cl⁺) found [M+H]⁺ 420.1027; C₁₇H₂₇INO₃ requires 420.1030.
6,6-Diethoxy-1-phenylhex-4-yn-3-ol (316a)<sup>190</sup>

![Chemical structure](image)

Prepared from 3-phenylpropanal (8.8 mL, 9.0 g, 90% purity by weight, 60 mmol) according to the General Alkynylation Procedure and purified by flash column chromatography (4:1 petrol 40–60 °C:EtOAc) to give the propargylic alcohol 316a as a colorless oil (12.8 g, 48.8 mmol, 81%); \( R_f = 0.33 \) (4:1 petrol 40–60 °C:EtOAc); \( \nu_{\text{max}} \) (film/cm\(^{-1}\)) 3426s (O-H), 2976s (C-H), 1454s; \(^1\)H NMR (500 MHz; CDCl\(_3\)); 7.30–7.25 (2H, m, Ar\( H \)), 7.21–7.18 (3H, m, Ar\( H \)), 5.31 (1H, s, C\( H(OEt)_2 \)), 4.45–4.40 (1H, m, \( CH(OH) \)), 3.78–3.71 (2H, m, C(OCH\( H' \))\(_2 \)), 3.68–3.57 (2H, m, C(OCH\( H' \))\(_2 \)), 2.80 (2H, t, \( J = 7.8, \) PhCH\(_2 \)), 2.08–2.01 (2H, m, CH\(_2\)COH), 1.89 (1H, d, \( J = 5.1, \) OH), 1.24 (6H, t, \( J = 7.1, \) CH\(_3 \)); \(^{13}\)C NMR (125 MHz; CDCl\(_3\)) 141.3 (Ar), 128.6 (Ar), 128.5 (Ar), 126.1 (Ar), 91.4 (C(OEt)\(_2 \)), 86.7 (C=C), 80.3 (C=C), 61.3 (COH), 61.1 (OCH\(_2 \)), 61.0 (OCH\(_2 \)), 39.1 (PhCH\(_2 \)), 31.5 (CH\(_2\)COH), 15.2 (CH\(_2\)CH\(_3 \)); data in accordance with the literature.<sup>190</sup>

1-Cyclohexyl-4,4-diethoxybut-2-yn-1-ol (316b)<sup>190</sup>

![Chemical structure](image)

Prepared from cyclohexanecarbaldehyde (2.0 mL, 1.3 g, 14.0 mmol) according to the General Alkynylation Procedure and purified by flash column chromatography (0 to 50% EtOAc:cyclohexane) to give the propargylic alcohol 316b as a colorless oil (2.39 g, 9.94 mmol, 86%); \( R_f = 0.29 \) (10:1 petrol 40–60 °C:EtOAc); \( \nu_{\text{max}} \) (film/cm\(^{-1}\)) 3416s br. (O-H), 2925s (C-H), 1450s; \(^1\)H NMR (600 MHz; CDCl\(_3\)) 5.28 (1H, s, CH(OEt)\(_2 \)), 4.18 (1H, d, \( J = 6.0, \) CH\(_2\)OH), 3.74–3.68 (2H, m, OCH\(_2\)H\(_'\)), 3.59–3.53 (2H, m, OCH\(_2\)H\(_'\)), 2.20 (br. s, CHO\(_H\)), 1.89–1.79 (2H, m, CHCH\(_2\)H\(_'\)), 1.76–1.72 (2H, m, CHCH\(_2\)C\(_H\)H\(_'\)), 1.67–1.62 (1H, m, CHCH\(_2\)C\(_H\)H\(_'\)), 1.57–1.51 (1H, m, CHCH\(_2\)), 1.26–1.18 (8H, m, CH\(_3\), 2 \( \times \) CH\(_2\)CH\(_2\)CH\(_2\)H\(_'\)), 1.16–0.99 (3H, m, 2 \( \times \) CH\(_2\)CH\(_2\)CH\(_2\)H\(_'\)), \(^{13}\)C NMR (150 MHz; CDCl\(_3\)) 91.3 (CH(OEt)\(_2 \)), 85.7 (C=C), 80.9 (C=C), 67.0 (COH), 61.0 (OCH\(_2 \)), 60.9 (OCH\(_2 \)), 43.9 (CHCH\(_2\)), 28.6 (CHCH\(_2\)), 28.2 (CHCH\(_2\)), 26.4
Experimental Details

(\text{CHCH}_2\text{CH}_2\text{CH}_2), 25.9 (\text{CHCH}_2\text{CH}_2), 25.9 (\text{CHCH}_2\text{CH}_2), 15.2 (\text{CH}_2\text{CH}_3); \text{data in accordance with the literature.}^{190}

\begin{center}
1-Cyclopropyl-4,4-diethoxybut-2-yn-1-ol (316c)\textsuperscript{190}
\end{center}

\begin{center}
\begin{tikzpicture}
  \node[shape=circle,draw,inner sep=1pt,fill=black] (a) at (0,0) {OEt};
  \node[shape=circle,draw,inner sep=1pt,fill=black] (b) at (0,1) {OEt};
  \node[shape=circle,draw,inner sep=1pt,fill=black] (c) at (0,2) {OH};
  \node[shape=circle,draw,inner sep=1pt,fill=black] (d) at (-1,1) {C\equiv C};
  \node[shape=circle,draw,inner sep=1pt,fill=black] (e) at (-1,0) {CH(CH\_2)\_2};
  \node[shape=circle,draw,inner sep=1pt,fill=black] (f) at (-1,-1) {CH(CH\_3)};
  \draw [thick] (a) -- (b);
  \draw [thick] (b) -- (c);
  \draw [thick] (c) -- (d);
  \draw [thick] (d) -- (e);
  \draw [thick] (e) -- (f);
\end{tikzpicture}
\end{center}

Prepared from cyclopropenecarbaldehyde (0.90 mL, 0.84 g, 12 mmol) according to the General Alkynylation Procedure and purified by flash column chromatography (0 to 50% EtOAc:cyclohexane) to give the propargylic alcohol 316c as a colorless oil (1.97 g, 9.94 mmol, 83%); \(R_f = 0.29\) (3:1 cyclohexane:EtOAc); \(\nu_{\text{max}}\) (film/cm\(^{-1}\)) 3403 s br. (O-H), 2977 s (C-H), 1444 m; \(^1\)H NMR (400 MHz; CDCl\(_3\)) 5.32–5.29 (1H, m, \(\text{C}\text{H(OEt)}_2\)), 4.27–4.21 (1H, m, \(\text{C}\text{HOH}\)), 3.78–3.69 (2H, m, \(\text{OCHH'}\)), 3.64–3.54 (2H, m, \(\text{OCHH'}\)), 2.40–1.93 (1H, m, \(\text{OH}\)); 1.31–1.21 (7H, m, \(\text{CH}_2\text{CH}_3\), \(\text{CH(CH}_2\text{)}_2\)), 0.63–0.42 (4H, m, \(\text{CH(CH}_2\text{)}_2\)); \(^{13}\)C NMR (100 MHz; CDCl\(_3\)) 89.6 (\(\text{C}\text{H(OEt)}_2\)), 82.7 (\(\text{C}\equiv\text{C}\)), 78.7 (\(\text{C}\equiv\text{C}\)), 63.9 (\(\text{CHOH}\)), 59.3 (\(\text{OCH}_2\)), 59.2 (\(\text{OCH}_2\)), 15.3 (\(\text{CH}_2\text{CH}_3\)), 13.4 (\(\text{CH(CH}_2\text{)}_2\)), 1.6 (\(\text{CH(CH}_2\text{)}_2\)); \text{data in accordance with the literature.}^{190}

\begin{center}
tert-Butyl 4-(5,5-diethoxy-2-hydroxypent-3-yn-1-yl)piperidine-1-carboxylate (316d)
\end{center}

\begin{center}
\begin{tikzpicture}
  \node[shape=circle,draw,inner sep=1pt,fill=black] (a) at (0,0) {OEt};
  \node[shape=circle,draw,inner sep=1pt,fill=black] (b) at (0,1) {OEt};
  \node[shape=circle,draw,inner sep=1pt,fill=black] (c) at (0,2) {OH};
  \node[shape=circle,draw,inner sep=1pt,fill=black] (d) at (-1,1) {C\equiv C};
  \node[shape=circle,draw,inner sep=1pt,fill=black] (e) at (-1,0) {CH(CH\_2)\_2};
  \node[shape=circle,draw,inner sep=1pt,fill=black] (f) at (-1,-1) {CH(CH\_3)};
  \node[shape=circle,draw,inner sep=1pt,fill=black] (g) at (-2,-2) {O'Bu};
  \draw [thick] (a) -- (b);
  \draw [thick] (b) -- (c);
  \draw [thick] (c) -- (d);
  \draw [thick] (d) -- (e);
  \draw [thick] (e) -- (f);
  \draw [thick] (f) -- (g);
\end{tikzpicture}
\end{center}

Prepared from a solution of tert-butyl 4-(2-oxoethyl)piperidine-1-carboxylate (1.50 g, 6.60 mmol) in anhydrous THF (4.0 mL) according to the General Alkynylation Procedure and purified by flash column chromatography (0 to 100% heptane:TBME) to the propargylic alcohol 316d as a colorless oil (1.67 g, 4.70 mmol, 71%); \(R_f = 0.47\) (1:1 40–60 °C:EtOAc); \(\nu_{\text{max}}\) (film/cm\(^{-1}\)) 3417 s br. (O-H), 2929 s (C-H), 1693 s (C=O), 1669 s (C=O), 1424 s; \(^1\)H NMR (400 MHz; CDCl\(_3\)) 5.31 (1H, s, (\(\text{C}\text{H(OEt)}_2\)), 4.54 (1H, q, \(J = 5.9\), \(\text{CHOH}\)), 4.10 (2H, br. s, \(\text{NCHH'}\)), 3.79–3.71 (2H, m, \(\text{OCHH'}\)), 3.64–3.57 (2H, m, \(\text{OCHH'}\)), 2.71 (2H, br. t, \(\text{NCHH'}\)), 1.89 (1H, m, \(\text{OH}\)), 1.76–1.62 (5H, m, \(\text{OCHCH}_2\text{CH(CHH'}_2\)), 1.47 (9H, s, C(CH\(_3\))\(_3\)), 1.26 (6H, t, \(\text{CH}_2\text{CH}_3\)), 1.20–1.12 (2H, m,
OCHCH$_2$CH(CHR')$_2$; $^{13}$C NMR (100 MHz; CDCl$_3$) 154.8 (C(O)), 91.3 (CH(OEt)$_2$), 86.3 (C=O), 80.4 (C=O), 79.3 (C(CH$_3$)$_3$), 61.0 (OCH$_2$), 60.9 (OCH$_2$), 60.0 (CH(OH)), 43.05 (NCH$_2$, OCHCH$_2$), 32.5 (OCHCH$_2$CH), 32.3 (OCHCH$_2$CH(CHR)(CH$_3$)$_2$), 31.8 (OCHCH$_2$CH(CHR)(CH$_3$)$_2$), 28.5 (C(CH$_3$)$_3$), 15.1 (CH$_2$CH$_3$); HRMS (ESI$^+$) found [M+Na]$^+$ 378.2202; C$_{19}$H$_{33}$NNaO$_5$ requires 378.2256.

4,4-Diethoxy-1-phenylbut-2-yn-1-ol (316e)$^{190}$

![Image of 4,4-Diethoxy-1-phenylbut-2-yn-1-ol](image)

Prepared from benzaldehyde (4.9 mL, 5.0 g, 47 mmol) according to the General Alkynylation Procedure and purified by flash column chromatography (7:1 40–60 °C:EtOAc) to give the propargylic alcohol 316e as a colorless oil (10.5 g, 44.6 mmol, 95%); $R_f = 0.33$ (5:1 petrol 40–60 °C:EtOAc); $\nu_{\text{max}}$ (film/cm$^{-1}$) 3317s br. (O-H), 2977s (C-H), 1493m, 1455s; $^1$H NMR (400 MHz; CDCl$_3$) 7.57–7.54 (2H, m, ArH), 7.43–7.33 (3H, m, ArH), 5.83 (1H, s, C(OEt)$_2$), 5.55 (1H, d, $J = 6.2$, CH(OH)), 3.81–3.73 (2H, m, OCHH'), 3.67–3.58 (2H, m, OCHH'), 2.43 (1H, d, $J = 6.2$, OH), 1.25 (6H, t, $J = 7.1$, CH$_2$CH$_3$); $^{13}$C NMR (125 MHz; CDCl$_3$) 140.1 (Ar), 128.7 (Ar), 128.5 (Ar), 126.7 (Ar), 91.4 (CH(OEt)$_2$), 85.2 (C=C), 82.0 (C=C), 64.5 (CHOH), 61.1 (OCH$_2$), 61.0 (OCH$_2$), 15.1 (CH$_2$CH$_3$); data in accordance with the literature.$^{190}$

4,4-Diethoxy-1-(4-(trifluoromethyl)phenyl)but-2-yn-1-ol (316f)$^{190}$

![Image of 4,4-Diethoxy-1-(4-(trifluoromethyl)phenyl)but-2-yn-1-ol](image)

Prepared from 4-(trifluoromethyl)benzaldehyde (1.6 mL, 2.0 g, 12 mmol) according to the General Alkynylation Procedure and purified by flash column chromatography (0 to 50% EtOAc:cyclohexane) to give the propargylic alcohol 316f as a colorless oil (2.88 g, 9.94 mmol, 79%); $R_f = 0.22$ (3:1 cyclohexane:EtOAc); $\nu_{\text{max}}$ (film/cm$^{-1}$) 3408s br. (O-H), 2981s (C-H), 1620s, 1416s; $^1$H NMR (400 MHz; CDCl$_3$) 7.69–7.64 (4H, m, ArH), 5.60 (1H, d, $J = 5.9$, CH(OH)), 5.37 (1H, s, CH(OEt)$_2$), 3.80–3.72 (2H, m, OCHH'), 3.66–3.58 (2H, m, OCHH'), 2.66–1.63 (1H, m, COH), 1.26 (6H, t, $J = 7.0$, CH$_2$CH$_3$); $^{13}$C NMR
Experimental Details

(100 MHz; CDCl\textsubscript{3}) 143.7 (Ar), 130.6 (q, J\textsubscript{C-F} = 30.0, Ar), 126.9 (Ar), 125.6 (q, J\textsubscript{C-F} = 3.5, Ar), 124.0 (q, J\textsubscript{C-F} = 272.2, CF\textsubscript{3}), 91.2 (CH(OEt)\textsubscript{2}), 84.2 (C≡C), 82.6 (C≡C), 63.7 (CHOH), 61.1 (OCH\textsubscript{2}), 61.1 (OCH\textsubscript{2}), 15.0 (CH\textsubscript{2}CH\textsubscript{3}); data in accordance with the literature.\textsuperscript{190}

4,4-Diethoxy-1-(4-methoxyphenyl)but-2-yn-1-ol (316g)\textsuperscript{190}

Prepared from 4-methoxybenzaldehyde (1.4 mL, 1.6 g, 11 mmol) according to the General Alkynylation Procedure and purified by flash column chromatography (0 to 50% EtOAc:cyclohexane) to give the propargylic alcohol 316g as a yellow oil (2.92 g, 11.1 mmol, 96%); R\textsubscript{f} = 0.18 (3:1 cyclohexane:EtOAc); \nu\textsubscript{max} (film/cm\textsuperscript{-1}) 3423s br. (O-H), 2976s (C-H), 1611s, 1511s; \textsuperscript{1}H NMR (400 MHz; DMSO-d\textsubscript{6}) 7.43–7.33 (2H, m, Ar\textsubscript{H}), 6.96–9.88 (2H, m, Ar\textsubscript{H}), 5.97 (1H, br. s, CHO\textsubscript{H}), 5.37 (1H, br. s, CHOH), 5.37 (1H, s, CH(OEt)\textsubscript{2}), 3.75 (3H, s, OC\textsubscript{H}\textsubscript{3}), 3.67–3.56 (2H, m, OCH\textsubscript{H}'), 3.55–3.45 (2H, m, OCH\textsubscript{H}'), 1.13 (6H, t, J = 7.1, CH\textsubscript{2}CH\textsubscript{3}); \textsuperscript{13}C NMR (100 MHz; DMSO-d\textsubscript{6}) 159.2 (Ar), 134.3 (Ar), 128.1 (Ar), 114.1 (Ar), 91.2 (CH(OEt)\textsubscript{2}), 87.2 (C≡C), 80.7 (C≡C), 62.3 (CHOH), 60.6 (OCH\textsubscript{2}), 55.6 (OCH\textsubscript{3}), 15.4 (CH\textsubscript{2}CH\textsubscript{3}); data in accordance with the literature.\textsuperscript{190}

1-(4-Bromophenyl)-4,4-diethoxybut-2-yn-1-ol (316h)\textsuperscript{190}

Prepared from a solution of 4-bromobenzaldehyde (2.15 g, 11.9 mmol) in anhydrous THF (12 mL) according to the General Alkynylation Procedure and purified by flash column chromatography (0 to 100% EtOAc:cyclohexane) to give the propargylic alcohol 316h as a colorless oil (3.01 g, 9.61 mmol, 83%); R\textsubscript{f} = 0.69 (1:1 cyclohexane:EtOAc); \nu\textsubscript{max} (film/cm\textsuperscript{-1}) 3410s br. (O-H), 2978s (C-H), 1486s; \textsuperscript{1}H NMR (400 MHz; CDCl\textsubscript{3}) 7.55–7.51 (2H, m, Ar\textsubscript{H}), 7.45–7.41 (2H, m, Ar\textsubscript{H}), 5.51 (1H, d, J = 6.0, CHOH), 5.36 (1H, s, CH(OEt)\textsubscript{2}), 3.80–3.71 (2H, m, OCH\textsubscript{H}'), 3.66–3.58 (2H, m, OCH\textsubscript{H}'), 2.40 (1H, d, J = 6.0, COH), 1.26 (3H, t, J = 7.1, CH\textsubscript{2}CH\textsubscript{3}), 1.26 (3H, t, J = 7.1, CH\textsubscript{2}CH\textsubscript{3}); \textsuperscript{13}C NMR (100 MHz;
CDCl$_3$) 138.4 (Ar), 131.7 (Ar), 128.3 (Ar), 122.5 (Ar), 91.3 (CH(OEt)$_2$), 84.4 (C=C), 82.4 (C=C), 63.8 (CHOH), 61.1 (OCH$_2$), 61.0 (OCH$_2$), 15.1 (CH$_2$CH$_3$); data in accordance with the literature.$^{190}$

4,4-Diethoxy-1-(o-tolyl)but-2-yn-1-ol (316i)

Prepared from 2-methylbenzaldehyde (1.3 mL, 1.4 g, 11 mmol) according to the General Alkynylation Procedure and purified by flash column chromatography (0 to 100% EtOAc:cyclohexane) to give the propargylic alcohol 316i as a colorless oil (2.58 g, 10.4 mmol, 92%); R$_f$ = 0.24 (3:1 cyclohexane:EtOAc); $\nu_{\text{max}}$ (film/cm$^{-1}$) 3422s br. (O-H), 2977s (C-H), 1487s, 1460s; $^1$H NMR (400 MHz; CDCl$_3$) 7.68–7.63 (1H, m, ArH), 7.28–7.18 (3H, m, ArH), 5.70 (1H, dd, $J$ = 6.0, 1.2, CHOH), 5.37 (1H, d, $J$ = 1.2, CH(OEt)$_2$), 3.81–3.72 (2H, m, OCHH$'$), 3.67–3.58 (2H, m, OCHH$'$), 2.46 (3H, s, ArCH$_3$), 2.20 (1H, d, $J$ = 6.0, OH), 2.26 (3H, t, $J$ = 7.1, CH$_2$CH$_3$), 2.25 (3H, t, $J$ = 7.1, CH$_2$CH$_3$); $^{13}$C NMR (100 MHz; CDCl$_3$) 137.0 (Ar), 136.0 (Ar), 130.8 (Ar), 128.6 (Ar), 126.6 (Ar), 126.2 (Ar), 91.4 (CH(OEt)$_2$), 84.7 (C=C), 82.0 (C=C), 62.3 (CHOH), 61.0 (OCH$_2$), 61.0 (OCH$_2$), 18.9 (ArCH$_3$), 15.1 (CH$_2$CH$_3$); HRMS (Cl$^+$) found [M]$^+$ 248.1409; C$_{15}$H$_{20}$O$_3$ requires 248.1412.

Methyl 3-(4,4-diethoxy-1-hydroxybut-2-yn-1-yl)benzoate (316j)$^{190}$

Prepared from a solution of methyl 3-formylbenzoate (1.31 g, 7.98 mmol) in anhydrous THF (8.0 mL) according to the General Alkynylation Procedure and purified by flash column chromatography (0 to 100% TBME:cyclohexane) to give the propargylic alcohol 316j as a colorless oil (1.83 g, 6.26 mmol, 78%); R$_f$ = 0.71 (3:1 cyclohexane:EtOAc); $\nu_{\text{max}}$ (film/cm$^{-1}$) 3433s br. (O-H), 2887s (C-H), 1721s (C=O), 1481s; $^1$H NMR (400 MHz; MeOH-d$_4$) 8.22 (1H, s, ArH), 7.98 (1H, d, $J$ = 7.8, ArH), 7.77 (1H, d, $J$ = 7.8, ArH), 7.51 (1H, t, $J$ = 7.8, ArH), 5.56 (1H, s, CHOH), 5.37 (1H, s, CH(OEt)$_2$), 3.93 (3H, s, OCH$_3$), 3.80–3.70 (2H, m, OCHH$'$), 3.67–3.56 (2H, m, OCHH$'$), 1.21 (6H, t, $J$ = 7.1 CH$_2$CH$_3$);
$^{13}$C NMR (100 MHz; MeOH-d$_4$) 166.8 (C(O)), 141.8 (Ar), 131.0 (Ar), 130.2 (Ar), 128.8 (Ar), 128.4 (Ar), 127.3 (Ar), 91.3 (CH(OEt)$_2$), 85.0 (C≡C), 81.1 (C≡C), 62.8 (CHOH), 60.7 (OCH$_2$), 60.7 (OCH$_2$), 51.3 (OCH$_3$), 14.0 (CH$_2$CH$_3$); data in accordance with the literature.$^{190}$

**4,4-Diethoxy-1-(furan-2-yl)but-2-yn-1-ol (316k)$^{190}$**

![Structural diagram]

Prepared from furfural (0.96 mL, 1.1 g, 12 mmol) according to the General Alkynylation Procedure and purified by flash column chromatography (0 to 50% EtOAc:cyclohexane) to give the propargylic alcohol 316k as a yellow oil (2.23 g, 9.96 mmol, 86%); $R_f = 0.30$ (3:1 cyclohexane:EtOAc); $\nu_{\text{max}}$ (film/cm$^{-1}$) 3411s br. (O-H), 2978s (C-H); $^1$H NMR (400 MHz; CDCl$_3$) 7.43–7.42 (1H, m, ArH), 6.47 (1H, d, $J = 3.2$, ArH), 6.38–6.36 (1H, m, ArH), 5.53 (1H, d, $J = 6.9$, CHO), 5.37–5.36 (1H, m, CH(OEt)$_2$), 3.82–3.73 (2H, m, OCHH$'$), 3.68–3.60 (2H, m, OCHH$'$), 2.69–1.50 (1H, m, OHHH), 1.25 (6H, t, $J = 6.8$, CH$_3$); $^{13}$C NMR (100 MHz; CDCl$_3$) 152.4 (Ar), 143.1 (Ar), 110.4 (Ar), 108.0 (Ar), 91.2 (CH(OEt)$_2$), 82.6 (C≡C), 81.2 (C≡C), 61.1 (OCH$_2$), 61.0 (OCH$_2$), 58.0 (CHOH), 15.0 (CH$_2$CH$_3$); data in accordance with the literature.$^{190}$

**4,4-Diethoxy-1-(thiophen-2-yl)but-2-yn-1-ol (316l)$^{190}$**

![Structural diagram]

Prepared from thiophene-2-carbaldehyde (1.6 mL, 1.9 g, 17 mmol) according to the General Alkynylation Procedure and purified by flash column chromatography (0 to 100% TBME:cyclohexane) to give the propargylic alcohol 316l as a yellow oil (2.00 g, 8.32 mmol, 49%); $R_f = 0.61$ (1:1 cyclohexane:EtOAc); $\nu_{\text{max}}$ (film/cm$^{-1}$) 3403s br. (O-H), 2926s (C-H); $^1$H NMR (400 MHz; CDCl$_3$) 7.33–7.31 (1H, m, ArH), 7.21–7.17 (1H, m, ArH), 7.00–6.98 (1H, m ArH), 5.74 (1H, d, $J = 6.9$, CHO), 5.37 (1H, s, CH(OEt)$_2$), 3.83–3.74 (2H, m, OCHH$'$), 3.67–3.58 (2H, m, OCHH$'$), 2.69 (1H, d, $J = 6.9$, OHH), 1.26 (6H, t, $J = 7.1$, CH$_2$CH$_3$); $^{13}$C NMR (100 MHz; CDCl$_3$) 143.9 (Ar), 126.8 (Ar), 126.2 (Ar),
125.7 (Ar), 91.2 (CH(OEt)$_2$), 84.3 (C≡C), 81.4 (C≡C), 61.1 (OCH$_2$), 61.0 (OCH$_2$), 60.1 (CHOH), 15.1 (CH$_2$CH$_3$); data in accordance with the literature.$^{190}$

**4,4-Diethoxy-1-(pyridin-3-yl)but-2-yn-1-ol (316m)**

![Propargylic Alcohol Structure](image)

Prepared from nicotinaldehyde (1.1 mL, 1.3 g, 12 mmol) according to the General Alkynylation Procedure and purified by flash column chromatography (0 to 100% cyclohexane: EtOAc) to give the *propargylic alcohol* 316m as a yellow oil (1.93 g, 8.20 mmol, 70%); $R_f = 0.40$ (40:1 cyclohexane:EtOAc); $\nu_{\max}$ (film/cm$^{-1}$) 3160 s br. (O-H), 2977 s (C-H), 1427 s; $^1$H NMR (400 MHz; DMSO-d$_6$) 8.65 (1H, d, $J = 1.8$, ArH), 8.53 (1H, dd, $J = 4.9$, 1.8, ArH), 8.42 (1H, dt, 7.8, 1.8, ArH), 7.42 (1H, dd, $J = 7.8$, 4.9, ArH), 6.31 (1H, d, $J = 6.1$, CHOH), 5.55 (1H, d, $J = 6.1$, CH(OEt)$_2$), 3.66–3.58 (2H, m, OCH$_2$), 1.13 (6H, t, $J = 7.1$, CH$_2$CH$_3$); $^{13}$C NMR (100 MHz; DMSO-d$_6$) 148.9 (Ar), 147.8 (Ar), 137.1 (Ar), 134.0 (Ar), 123.5 (Ar), 90.7 (CH(OEt)$_2$), 85.6 (C≡C), 81.0 (C≡C), 60.8 (CHOH), 60.3 (OCH$_2$), 60.2 (OCH$_2$), 14.9 (CH$_2$CH$_3$); HRMS (CI$^+$) found [M+H]$^+$ 236.1281; C$_{14}$H$_{17}$NO$_3$ requires 236.1287.

**3-Methoxy-2-phenethylfuran (318)$^{190}$**

![Furan Structure](image)

A solution of [PPh$_3$AuNTf$_2$]$_2$PhMe (30 mg, 0.019 mmol, 1.0 mol%, 2.0 mol% [Au]) in MeOH (4.8 mL) was added dropwise to a stirring solution of propargylic alcohol 316a (500 mg, 1.91 mmol) in MeOH (4.8 mL) at RT. The resulting solution was stirred for 16 h before being filtered through a silica plug, eluting with TBME. The filtrate was concentrated in vacuo to give the crude product, which was purified by flash column chromatography (0 to 10% petrol 30–40 °C: TBME) to give the furan 318 as a colorless oil (266 mg, 1.32 mmol, 69%); $R_f = 0.29$ (40:1 petrol 40–60 °C:EtoAc); $\nu_{\max}$ (film/cm$^{-1}$) 2935 s (C-H), 1637 s, 1496 s, 1454 s 1410 s; $^1$H NMR (600 MHz; CDCl$_3$) 7.28–7.26 (2H, m, ArH), 7.20–7.16 (3H, m, ArH), 7.14 (1H, d, $J = 2.1$, ArH), 6.26 (1H, d, $J = 2.1$, ArH), 3.59 (3H, s, OCH$_3$), 2.94–2.86 (4H, m, PhCH$_2$CH$_2$); $^{13}$C NMR (150 MHz; CDCl$_3$) 143.7
Experimental Details

(Ar), 141.6 (Ar), 139.2 (Ar), 139.2 (Ar), 128.6 (Ar), 128.4 (Ar), 126.0 (Ar), 103.3 (Ar), 59.6 (OCH₃), 34.4 (CH₂) 27.2 (CH₂); data in accordance with the literature.¹⁹⁰

3-Ethoxy-2-phenethylfuran (325a)¹⁹⁰

![Structure of 3-Ethoxy-2-phenethylfuran (325a)]

Prepared according to the General Furan Procedure from propargylic alcohol 316a (500 mg, 1.91 mmol) in EtOH (0.50 M) to give the furan 325a as a colorless oil (737 mg, 3.41 mmol, 45%); Rₖ = 0.72 (10:1 cyclohexane:EtOAc); v_max (film/cm⁻¹) 2927s (C-H), 1635s, 1495s, 1453s, 1420s; ¹H NMR (400 MHz; MeOH-d₄) 7.27–7.09 (6H, m, ArH), 6.28 (1H, d, J = 2.0, ArH), 3.74 (2H, q, J = 7.1, OCH₂), 2.93–2.81 (4H, m, CH₂CH₂Ph), 1.19 (3H, t, J = 7.1, CH₂CH₃); ¹³C NMR (125 MHz; CDCl₃) 142.4 (Ar), 141.3 (Ar), 139.3 (Ar), 139.0 (Ar), 128.1 (Ar), 127.8 (Ar), 125.5 (Ar), 103.6 (Ar), 67.4 (OCH₂), 33.9 (CH₂), 26.6 (CH₂), 14.0 (CH₂CH₃); data in accordance with the literature.¹⁹⁰

2-Cyclohexyl-3-ethoxyfuran (325b)

![Structure of 2-Cyclohexyl-3-ethoxyfuran (325b)]

Prepared according to the General Furan Procedure from propargylic alcohol 316b (0.500 g, 2.08 mmol) in EtOH (2.0 M) to give the furan 425b as a colorless oil (273 mg, 1.41 mmol, 68%); Rₖ = 0.33 (40:1 petrol 40–60 °C:EtOAc); v_max (film/cm⁻¹) 2927s (C-H), 1627s; ¹H NMR (600 MHz; CDCl₃) 7.09 (1H, s, ArH), 7.08 (1H, s, ArH), 3.91 (2H, q, J = 7.0, OCH₂), 2.70 (1H, tt, J = 11.7, 3.2, ArCH), 1.84–1.76 (4H, m, 2 × CHCHHH', 2 × CHCH₂CHH'), 1.71–1.66 (1H, m, CHH'CH₂CH₂CH), 1.58–1.51 (2H, m, CHCHHH'), 1.37–1.29 (5H, m, CH₂CH₃); 2 × CHCH₂CHH'); 1.28–1.23 (1H, m, CHH'CH₂CH₂CH); ¹³C NMR (150 MHz; CDCl₃) 145.0 (Ar), 140.6 (Ar), 138.6 (Ar), 140.2 (Ar), 68.1 (OCH₂), 35.3 (CHCH₂), 31.3 (CHCH₂), 26.5 (CHCH₂CH₂), 26.1 (CHCH₂CH₂CH₂), 15.4 (CH₂CH₃); HRMS (CI⁺) found [M+H]⁺ 195.1389; C₁₂H₁₉O₂ requires 195.1385.
2-Cyclopropyl-3-ethoxyfuran (325c)⁹⁰

Prepared according to the General Furan Procedure from propargylic alcohol 316c (250 mg, 1.26 mmol) in EtOH (2.0 M) to give the furan 325c as a colorless oil (56 mg, 0.368 mmol, 29%); R_f = 0.78 (10:1 cyclohexane:EtOAc); ν_max (film/cm⁻¹) 2991s (C-H), 1666s, 1600s, 1432s; ¹H NMR (400 MHz; DMSO-d₆) 7.24 (1H, d, J = 2.0, ArH), 6.41 (1H, d, J = 2.0, ArH), 3.91 (2H, q, J = 7.1, OC₂H₂), 1.86–1.79 (1H, m, CH(CH₂)₂), 1.24 (3H, t, J = 7.1, CH₂C₃H₇), 0.84–0.80 (2H, m, CH(CHH’₂), 0.73–0.69 (2H, m, CH(CHH’₂)); ¹³C NMR (100 MHz; DMSO-d₆) 142.0 (Ar), 139.1 (Ar), 128.6 (Ar), 104.5 (Ar), 66.8 (OCH₂), 14.9 (CH₂CH₃), 6.3 (CH(CH₂)₂), 5.3 (CH(CH₂)₂); data in accordance with the literature.⁹⁰

tert-Butyl 4-((3-ethoxyfuran-2-yl)methyl)piperidine-1-carboxylate (325d)

Prepared according to the General Furan Procedure from propargylic alcohol 316d (500 mg, 1.41 mmol) in EtOH (1.0 M) to give the furan 325d as a colorless oil (335 mg, 1.08 mmol, 77%); R_f = 0.34 (10:1 cyclohexane:EtOAc); ν_max (film/cm⁻¹) 2930s (C-H), 1693s (C=O), 1422m; ¹H NMR (400 MHz; DMSO-d₆) 7.20 (1H, d, J = 2.0, ArH), 6.35 (1H, d, J = 2.0, ArH), 4.07–4.01 (2H, m, NCHH’), 3.95 (2H, q, J = 7.1, OCH₂), 2.83–2.68 (2H, m, NCHH’), 2.53 (2H, d, J = 6.9, ArCH₂), 1.86–1.75 (1H, m, ArCH₂CH), 1.67–1.61 (2H, m, CH(CHH’₂), 1.47 (9H, s, C(CH₃)₃), 1.31 (3H, t, J = 7.1, CH₂CH₃), 1.19–1.07 (2H, m, CH(CHH’₂); ¹³C NMR (100 MHz; DMSO-d₆) 156.6 (C(O)), 144.4 (Ar), 140.6 (Ar), 139.7 (Ar), 104.6 (Ar), 80.9 (CMs), 68.6 (OCH₂), 36.9 (ArCH₂CH), 33.0 (CH(CH₂)₂), 32.5 (ArCH₂), 28.7 (C(CH₃)₃), 15.5 (CH₂CH₃); HRMS (Cl⁺) found [M+H]⁺ 310.2012; C₁₇H₂₇NO₄ requires 310.2018.
3-Ethoxy-2-phenylfuran (325e)\(^{190}\)

Prepared according to the General Furan Procedure from propargylic alcohol 316e (2.00 g, 8.54 mmol) in EtOH (2.0 M) to give the furan 325e as a colorless oil (910 mg, 4.83 mmol, 57%); \(R_f = 0.33\) (40:1 petrol 40–60 °C:EtOAc); \(\nu_{\text{max}}\) (film/cm\(^{-1}\)) 2980s (C-H), 1612s, 1510s, 1427s; \(^1\)H NMR (600 MHz; CDCl\(_3\)) 7.81 (2H, d, \(J = 7.7\), ArH), 7.37 (2H, t, \(J = 7.7\), ArH), 7.27 (1H, d, \(J = 1.6\), ArH), 7.17 (1H, t, \(J = 7.7\), ArH), 4.10 (2H, q, \(J = 7.0\), OC\(_2\)H\(_2\)), 1.44 (3H, t, \(J = 7.0\), CH\(_2\)C\(_6\)H\(_5\)); \(^{13}\)C NMR (150 MHz; CDCl\(_3\)) 144.4 (Ar), 140.2 (Ar), 136.9 (Ar), 131.1 (Ar), 128.5 (Ar), 125.8 (Ar), 123.1 (Ar), 104.1 (Ar), 67.3 (OCH\(_2\)), 15.4 (CH\(_2\)CH\(_3\)); data in accordance with the literature.\(^{190}\)

3-Ethoxy-2-(4-(trifluoromethyl)phenyl)furan (325f)\(^{190}\)

Prepared according to the General Furan Procedure from propargylic alcohol 316f (500 mg, 1.65 mmol) in EtOH (2.0 M) to give the furan 325f as a colorless oil (357 mg, 1.39 mmol, 84%); \(R_f = 0.50\) (10:1 cyclohexane:EtOAc); \(\nu_{\text{max}}\) (film/cm\(^{-1}\)) 2985s (C-H), 1614s; \(^1\)H NMR (600 MHz; MeOH-d\(_4\)) 7.92 (2H, d, \(J = 8.3\), ArH), 7.34 (2H, d, \(J = 8.3\), ArH), 7.47 (1H, d, \(J = 2.1\), ArH), 6.62 (1H, d, \(J = 2.1\), ArH), 4.19 (2H, q, \(J = 7.1\), OCH\(_2\)), 1.46 (3H, t, \(J = 7.1\), CH\(_2\)CH\(_3\)); \(^{13}\)C NMR (150 MHz; MeOH-d\(_4\)) 146.5 (Ar), 141.7 (Ar), 134.8 (Ar), 134.4 (q, \(J_{\text{C-F}} = 1.3\), Ar), 126.5 (q, \(J_{\text{C-F}} = 32.3\), Ar), 124.9 (q, \(J_{\text{C-F}} = 3.9\), Ar), 124.5 (q, \(J_{\text{C-F}} = 271.0\), CF\(_3\)), 122.3 (Ar), 103.6 (Ar), 66.9 (OCH\(_2\)), 14.0 (CH\(_2\)CH\(_3\)); data in accordance with the literature.\(^{190}\)
3-Ethoxy-2-(4-methoxyphenyl)furan (325g)\textsuperscript{190}

![Chemical Structure](image)

Prepared according to the General Furan Procedure from propargylic alcohol 316g (500 mg, 1.89 mmol) in EtOH (0.50 M) to give the furan 325g as a colorless oil (334 mg, 1.53 mmol, 81%); $R_f = 0.48$ (10:1 cyclohexane:EtOAc); $\nu_{\text{max}}$ (film/cm\textsuperscript{-1}) 2980s (C-H), 1606s, 1520s, 1431s; $^1$H NMR (400 MHz; MeOH-d\textsubscript{4}) 7.72–7.69 (2H, m, ArH), 7.30 (1H, d, $J = 2.2$, ArH), 7.95–7.91 (2H, m, ArH), 6.51 (1H, d, $J = 2.2$, ArH), 4.08 (2H, q, $J = 7.0$, OCH\textsubscript{2}), 3.90 (3H, s, OCH\textsubscript{3}), 1.40 (3H, t, $J = 7.0$, CH\textsubscript{2}CH\textsubscript{3}); $^{13}$C NMR (100 MHz; MeOH-d\textsubscript{4}) 157.9 (Ar), 142.7 (Ar), 139.3 (Ar), 136.9 (Ar), 128.5 (Ar), 124.0 (Ar), 113.5 (Ar), 103.8 (Ar), 66.8 (OCH\textsubscript{2}), 54.3 (OCH\textsubscript{3}), 14.2 (CH\textsubscript{2}CH\textsubscript{3}); data in accordance with the literature.\textsuperscript{190}

2-(4-Bromophenyl)-3-ethoxyfuran (325h)

Prepare according to the General Furan Procedure from propargylic alcohol 316h (500 mg, 1.60 mmol) in EtOH (2.0 M) to give the furan 325h as a colorless oil (334 mg, 1.25 mmol, 78%); $R_f = 0.57$ (10:1 cyclohexane:EtOAc); $\nu_{\text{max}}$ (film/cm\textsuperscript{-1}) 2980s (C-H), 1669m, 1612s, 1504s, 1431s; $^1$H NMR (400 MHz; DMSO-d\textsubscript{6}) 7.67–7.65 (5H, m, ArH), 6.75 (1H, d, $J = 2.0$, ArH), 4.10 (2H, q, $J = 6.8$, OCH\textsubscript{2}), 1.35 (3H, t, $J = 6.8$, CH\textsubscript{2}CH\textsubscript{3}); $^{13}$C NMR (100 MHz; DMSO-d\textsubscript{6}) 145.1 (Ar), 141.9 (Ar), 134.2 (Ar), 131.6 (Ar), 129.6 (Ar), 124.0 (Ar), 118.1 (Ar), 104.8 (Ar), 66.8 (OCH\textsubscript{2}), 14.9 (CH\textsubscript{2}CH\textsubscript{3}); HRMS (Cl\textsuperscript{+}) found [M+H]\textsuperscript{+} 265.9942; C\textsubscript{12}H\textsubscript{12}BrO\textsubscript{2} requires 265.9945.
3-Ethoxy-2-(o-tolyl)furan (325i)

Prepared according to the General Furan Procedure from propargylic alcohol 316i (500 mg, 2.01 mmol) in EtOH (2.0 M) to give the furan 325i as a colorless oil (177 mg, 0.875 mmol, 44%); R_f = 0.64 (10:1 cyclohexane:EtOAc); \( \nu_{\text{max}} \) (film/cm\(^{-1}\)) 2979s (C-H), 1618s; \(^1\)H NMR (400 MHz; MeOH-d\(_4\)) 7.52–7.48 (1H, m, ArH), 7.41 (1H, d, J = 2.0, ArH), 7.24–7.17 (3H, m, ArH), 6.53 (1H, d, J = 2.0, ArH), 4.02 (2H, q, J = 7.1, OCH\(_2\)), 2.39 (3H, s, ArCH\(_3\)), 1.32 (3H, t, J = 7.1, CH\(_2\)C\(_3\)H\(_3\)); \(^{13}\)C NMR (100 MHz; MeOH-d\(_4\)) 145.1 (Ar), 141.7 (Ar), 139.2 (Ar), 137.0 (Ar), 131.6 (Ar), 131.3 (Ar), 129.5 (Ar), 128.4 (Ar), 126.4 (Ar), 104.9 (Ar), 68.2 (OCH\(_2\)), 21.1 (ArCH\(_3\)), 15.5 (CH\(_2\)CH\(_3\)); HRMS (CI\(^{-}\)) found [M+H\(^+\)] 203.1075; C\(_{13}\)H\(_{15}\)O\(_2\) requires 203.1072.

**Methyl 3-(3-ethoxyfuran-2-yl)benzoate (325j)**

Prepared according to the General Furan Procedure from propargylic alcohol 316j (500 mg, 1.71 mmol) in EtOH (0.50 M) to give the furan 325j as a pale wax (302 mg, 1.23 mmol, 72%); R_f = 0.47 (10:1 cyclohexane:EtOAc); \( \nu_{\text{max}} \) (film/cm\(^{-1}\)) 2981s (C-H), 1720s (C=O), 1667s, 1431s; \(^1\)H NMR (400 MHz; MeOH-d\(_4\)) 8.43 (1H, t, J = 1.4, ArH), 8.00 (1H, dt, J = 7.8, 1.4, ArH), 7.80 (1H, dt, J = 7.8, 1.4, ArH), 7.47 (1H, t, J = 7.8, ArH), 7.43 (1H, d, J = 2.1, ArH), 6.61 (1H, d, J = 2.1, ArH), 4.17 (2H, q, J = 7.0, OCH\(_2\)), 3.94 (3H, s, OCH\(_3\)), 1.46 (3H, t, J = 7.0, CH\(_2\)CH\(_3\)); \(^{13}\)C NMR (100 MHz; MeOH-d\(_4\)) 167.2 (C(O)), 145.3 (Ar), 140.9 (Ar), 135.4 (Ar), 131.4 (Ar), 130.2 (Ar), 128.3 (Ar), 126.7 (Ar), 125.9 (Ar), 123.3 (Ar), 103.7 (Ar), 66.9 (OCH\(_2\)), 51.2 (OCH\(_3\)), 14.1 (CH\(_2\)CH\(_3\)); HRMS (Cl\(^{-}\)) found [M+H\(^+\)] 247.0971; C\(_{14}\)H\(_{15}\)O\(_4\) requires 247.0970.
3-Ethoxy-2,2'-bifuran (325k)

![3-Ethoxy-2,2'-bifuran](image)

Prepared according to the General Furan Procedure from propargylic alcohol 316k (500 mg, 2.23 mmol) in EtOH (0.50 M) to give the furan 325k as a colorless oil (102 mg, 0.572 mmol, 26%); R<sub>f</sub> = 0.50 (10:1 cyclohexane:EtOAc); ν<sub>max</sub> (film/cm<sup>-1</sup>) 3150m, 2981s (C-H), 1629s, 1575s, 1415s; <sup>1</sup>H NMR (400 MHz; MeOH-d<sub>4</sub>) 7.47 (1H, d, J = 2.0, ArH), 7.35 (1H, d, J = 2.2, ArH), 6.53 (1H, d, J = 2.2, ArH), 6.50 (1H, dd, J = 3.4, 2.0, ArH), 6.45 (1H, d, J = 3.4, ArH), 4.10 (2H, q, J = 6.9, OCH<sub>2</sub>), 1.39 (3H, t, J = 6.9, CH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz; MeOH-d<sub>4</sub>) 145.5 (Ar), 143.2 (Ar), 140.6 (Ar), 140.5 (Ar), 112.0 (Ar), 110.7 (Ar), 103.9 (Ar), 103.6 (Ar), 67.01 (OCH<sub>2</sub>), 14.0 (CH<sub>2</sub>CH<sub>3</sub>); HRMS (CI<sup>+</sup>) found [M+H]<sup>+</sup> 179.070; C<sub>10</sub>H<sub>10</sub>O<sub>3</sub> requires 179.0708.

3-Ethoxy-2-(thiophen-2-yl)furan (325l)

![3-Ethoxy-2-(thiophen-2-yl)furan](image)

Prepared according to the General Furan Procedure from propargylic alcohol 316l (500 mg, 2.23 mmol) in EtOH (0.50 M) to give the furan 325l as a colorless oil (328 mg, 1.69 mmol, 78%); R<sub>f</sub> = 0.52 (10:1 cyclohexane:EtOAc); ν<sub>max</sub> (film/cm<sup>-1</sup>) 2980s (C-H), 1620s; <sup>1</sup>H NMR (400 MHz; MeOH-d<sub>4</sub>) 7.32 (1H, d, J = 2.2, ArH), 7.27–7.22 (2H, m, ArH), 7.05–7.02 (1H, m, ArH), 6.52 (1H, d, J = 2.2, ArH), 4.12 (2H, q, J = 7.1, OCH<sub>2</sub>), 1.42 (3H, t, J = 7.1, CH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz; MeOH-d<sub>4</sub>) 142.6 (Ar), 139.9 (Ar), 134.6 (Ar), 132.3 (Ar), 126.6 (Ar), 122.1 (Ar), 120.0 (Ar), 103.7 (Ar), 67.1 (OCH<sub>2</sub>), 14.1 (CH<sub>2</sub>CH<sub>3</sub>); HRMS (CI<sup>+</sup>) found [M+H]<sup>+</sup> 195.0473; C<sub>10</sub>H<sub>11</sub>O<sub>2</sub>S requires 195.0473.

3-(3-Ethoxyfuran-2-yl)pyridine (325m)

![3-(3-Ethoxyfuran-2-yl)pyridine](image)

Subjecting propargylic alcohol 316m to the General Furan Procedure in EtOH (0.50 M) resulted in no reaction.
A stirring solution of propargylic alcohol 316m (200 mg, 0.851 mmol) and MsOH (0.28 mL, 0.48 g, 4.3 mmol) in EtOH (4.2 mL) was treated with [PPh₃AuNTf₂]₂PhMe (33 mg, 0.021 mmol, 2.5 mol%, 5.0 mol% [Au]) at RT. The resulting solution was stirred for 2 h at RT before it was treated with water (5.0 mL) and stirred for a further 1 h. The reaction was then cooled to 0 °C, diluted with Et₂O (20 mL) and quenched with aq. sat. NaHCO₃ (20 mL). The aq. extract was washed with Et₂O (3 × 20 mL) and the combined organic extracts were dried (phase separator) and concentrated in vacuo to give the crude product, which was purified by flash column chromatography (0 to 10% petrol 30–40 °C: TBME) to give the furan 325m as a colorless oil (117 mg, 0.619 mmol, 73%); R_f = 0.23 (10:1 cyclohexane:EtOAc); ν_max (film/cm⁻¹) 2959w (C-H), 1659s, 1678s, 1440s; ¹H NMR (400 MHz; MeOH-d₄) 8.94 (1H, d, J = 1.7, ArH), 8.31 (1H, dd, J = 4.9, 1.7, ArH), 8.14 (1H, d, J = 8.1, ArH), 7.49 (1H, d, J = 2.2, ArH), 7.44 (1H, dd, J = 8.1, 4.9, ArH), 6.64 (1H, d, J = 2.2, ArH), 4.19 (2H, q, J = 7.0, OC₂H₂), 1.45 (3H, t, J = 7.0, CH₂C₃H₃); ¹³C NMR (100 MHz; MeOH-d₄) 146.5 (Ar), 145.0 (Ar), 142.9 (Ar), 132.9 (Ar), 129.9 (Ar), 127.8 (Ar), 123.8 (Ar), 103.6 (Ar), 67.0 (OCH₂), 14.0 (CH₂C₃H₃); HRMS (Cl⁻) found [M+H]+ 190.0863; C₁₁H₁₂NO₂ requires 190.0868.

(E)-3-Ethoxy-4-oxo-4-phenylbut-2-enal (326)

A solution of furan 325e (103 mg, 0.548 mmol) in PhMe (2.0 mL) was heated at reflux under an atmosphere of air for 24 h. The reaction was then allowed to cool to RT before it was concentrated in vacuo to give the crude product. This was purified by flash column chromatography (4:1 petrol 40–60 °C:EtOAc) to give the aldehyde 326 as a white crystalline solid (61 mg, 0.30 mmol, 55%); m.p. 52–54 °C; R_f = 0.50 (1:1 petrol 40–60 °C:EtOAc); ν_max (film/cm⁻¹) 2981s (C-H), 1757s (C=O), 1675s (C=O), 1630s, 1597s, 1451s; ¹H NMR (600 MHz; CDCl₃) 9.51 (1H, d, J = 7.8, C(O)H), 7.93 (2H, t, J = 7.6, ArH), 7.66 (1H, t, J = 7.6, ArH), 7.52 (2H, t, J = 7.6), 5.73 (1H, d, J = 7.8, EtOCC₃H₃), 4.12 (2H, q, J = 7.1, OCH₂), 1.44 (3H, t, J = 7.1, CH₂CH₃); ¹³C NMR (150 MHz; CDCl₃) 189.8 (C(O)H), 189.6 (C(O)Ph), 172.0 (EtOCC), 134.9 (Ar), 134.7 (Ar), 130.1 (Ar), 129.1 (Ar), 107.8 (C(O)CH), 66.3 (OCH₂), 14.1 (CH₂CH₃); HRMS (Cl⁻) found [M+H]^+ 205.0859; C₁₂H₁₃O₃ requires 205.0859.
(E)-Ethyl 2-((tert-butylsulfinyl)imino)acetate (328)\textsuperscript{192}

According to the modified procedure of Fei et al.\textsuperscript{192}: 2-Methylpropane-2-sulfinamide (3.00 g, 24.8 mmol) was added to a stirring mixture of ethyl 2-oxoacetate (50% in PhMe, 4.9 mL, 25 mmol) and activated 4 Å molecular sieves (16.0 g) in PhMe (50 mL). The reaction mixture was stirred at 50 °C for 24 h before it was allowed to reach room temperature. The reaction was filtered and the volatile components were removed in vacuo to give imine 328 as a yellow oil (3.24 g, 15.8 mmol, 64%); R\textsubscript{f} = 0.27 (5:1 cyclohexane:EtOAc); ν\textsubscript{max} (film/cm\textsuperscript{-1}) 2982\textsuperscript{s} (C-H), 1744\textsuperscript{s}, 1724\textsuperscript{s}, 1695\textsuperscript{s}, 1606\textsuperscript{s}, 1470\textsuperscript{s}; \textsuperscript{1}H NMR (400 MHz; CDCl\textsubscript{3}) 8.01 (1H, s, N=C\textsubscript{H}), 4.39 (2H, q, J = 7.1, CH\textsubscript{2}C\textsubscript{H}\textsubscript{3}), 1.39 (3H, t, J = 7.1, CH\textsubscript{2}CH\textsubscript{3}), 1.28 (9H, s, C(CH\textsubscript{3})\textsubscript{3}); \textsuperscript{13}C NMR (125 MHz; CDCl\textsubscript{3}) 161.1 (C(O)), 155.6 (C=N), 62.4 (CH\textsubscript{2}CH\textsubscript{3}), 58.9 (C(CH\textsubscript{3})\textsubscript{3}), 22.7 (C(CH\textsubscript{3})\textsubscript{3}), 14.1 (CH\textsubscript{2}CH\textsubscript{3}); data in accordance with the literature.\textsuperscript{192}

1-(4-Methylbenzyl)-1H-pyrrole-2,5-dione (329a)

According to the modified procedure of Ordónez et al.\textsuperscript{193}: p-Tolylmethanamine (2.6 mL, 2.4 g, 20 mmol) was added to a stirring solution of maleic anhydride (2.00 g, 20.4 mmol) in AcOH (40 mL) at RT and the resulting solution was heated at reflux for 3 h. The reaction was then allowed to cool to RT and concentrated in vacuo before being redissolved in EtOAc (50 mL) and washed with aq. sat. NH\textsubscript{4}Cl. The aq. extract was washed with EtOAc (3 × 50 mL) and the combined organic extracts were dried (phase separator) and concentrated in vacuo to give the crude product. This was purified by flash column chromatography (0 to 100% cyclohexane: EtOAc) to give imide 329a as a white crystalline solid (1.23 g, 6.11 mmol, 30%); m.p. = 100–102 °C; R\textsubscript{f} = 0.62 (1:1 cyclohexane:EtOAc); ν\textsubscript{max} (film/cm\textsuperscript{-1}) 3097\textsuperscript{m} (C-H), 2941\textsuperscript{m} (C-H), 1696\textsuperscript{s} (C=O), 1515\textsuperscript{s}, 1443\textsuperscript{s}; \textsuperscript{1}H NMR (400 MHz; MeOH-d\textsubscript{4}) 7.15–7.10 (4H, m, ArH), 7.06 (2H, s, H=C=CH), 4.55 (2H, s, NCH\textsubscript{2}), 2.27 (3H, s, ArCH\textsubscript{3}); \textsuperscript{13}C NMR (100 MHz; MeOH-d\textsubscript{4}) 170.8 (C(O)),
136.6 (Ar), 134.6 (CH=CH), 133.7 (Ar), 129.1 (Ar), 127.2 (Ar), 40.7 (NCH₂), 20.6 (ArCH₃); HRMS (Cl⁺) found [M+H]⁺ 202.0860; C₁₂H₁₂NO₂ requires 200.0868.

1-Cyclopropyl-1H-pyrrole-2,5-dione (329b)

According to the modified procedure of Ordónez et al.¹⁹³: Cyclopropanamine (1.4 mL, 1.1 g, 20 mmol) was added to a stirring solution of maleic anhydride (2.00 g, 20.4 mmol) in AcOH (40 mL) at RT and the resulting solution was heated at reflux for 2 h. The reaction was then allowed to cool to RT and concentrated in vacuo before being dissolved in EtOAc (50 mL) and washed with aq. sat. NaHCO₃. The aq. extract was washed with EtOAc (3 × 50 mL) and the combined organic extracts were dried (phase separator) and concentrated in vacuo to give the crude product. This was purified by flash column chromatography (0 to 100% TBME:cyclohexane) to give imide 329b as a white crystalline solid (1.30 g, 9.48 mmol, 47%); m.p. = 57–59 °C; Rf = 0.55 (1:1 cyclohexane:EtOAc); νmax (film/cm⁻¹) 2977s (C-H), 1775m, 1757s (C=O), 1400s;

¹H NMR (400 MHz; DMSO-d₆) 6.93 (2H, s, H₃C=CH), 2.52–2.45 (1H, m, NCH(CH₂)₂), 0.85–0.79 (2H, m, CH(CHH′)₂) 0.78–0.72 (2H, m, CH(CHH′)₂); ¹³C NMR (100 MHz; DMSO-d₆) 171.4 (C(O)), 134.2 (CH=CH), 19.7 (NCH), 4.4 (NCH(CH₂)₂); HRMS (Cl⁺) found [M+H]⁺ 138.0555; C₇H₈NO₂ requires 138.0555.
(3aS,4R,7R,7aR)-5-Ethoxy-2-methyl-4-phenethyl-3a,4,7,7a-tetrahydro-1H-4,7-
epoxyisoindole-1,3(2H)-dione (endo-330a) and (3aR,4R,7R,7aS)-5-Ethoxy-2-
methyl-4-phenethyl-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione
(exo-330a)

**Method A (0.500 mmol):** Prepared from furan 225a (108 mg, 0.500 mmol) and N-
methylmaleimide according to the General Cycloaddition Procedure to give a mixture of
the cantharimides 330a as a colorless oil (153 mg, 0.467 mmol, 93%; endo:exo = 70:30).

**Method A (4.62 mmol):** Prepared from furan 225a (1.00 g, 4.62 mmol) and N-
methylmaleimide according to the General Cycloaddition Procedure to give the crude
product (endo:exo = 75:25). Purification by flash column chromatography (0 to 100%
TBME:cyclohexane) gave the cantharimide endo-330a (906 mg, 2.77 mmol, 60%).
Further elution of the column gave a mixture of the cantharimide endo-330a and the
cantharimide exo-330a (202 mg, 0.618 mmol, 13%). Further elution of the column gave
the cantharimide exo-330a (310 mg, 0.948 mmol, 21%).

**Method B:** A solution of N-methylmaleimide (67 mg, 0.60 mmol) and furan 225a
(108 mg, 0.500 mmol) in DMC (0.50 mL) was stirred at 80 °C for 16 h. The reaction was
then allowed to cool to RT before it was diluted with EtOAc and loaded onto an
aminopropyl cartridge. After 5 minutes the cartridge was then washed with EtOAc and
the filtrate was concentrated in vacuo to give a mixture of the cantharimides 330a as a
colorless oil (153 mg, 0.467 mmol, 93%; endo:exo = 55:45).

**Method C:** A solution of [PPh₃AuNTf₂]₂PhMe (60 mg, 1.0 mol%, 2.0 mol% [Au]) in
EtOH (1.9 mL) was added dropwise to a stirring solution of propargylic alcohol 325a
(1.00 g, 3.81 mmol) in EtOH (1.9 mL) at RT. The resulting solution was stirred for 3 h
before it was treated with PPh₃ (25 mg, 2.5 mol%). After a further 1 h the reaction was
treated with N-methylmaleimide (508 mg, 4.57 mmol) and stirred for 16 h at RT. The
reaction mixture was then loaded onto an aminopropyl cartridge and, after 5 minutes,
eluted with EtOAc. The filtrate was concentrated *in vacuo* to give the crude product (*endo*:*exo* = 70:30), which was purified by flash column chromatography (0 to 100% TBME:cyclohexane) to give a mixture of the *cantharimides* **330a** as a colorless oil (828 mg, 2.53 mmol, 66%; *endo*:*exo* = 70:30).

**Cantharimide endo-330a**: Isolated a white crystalline solid. m.p. 90–92 °C; R<sub>f</sub> = 0.62 (2:1 petrol 40–60 °C:EtOAc); v<sub>max</sub> (film/cm<sup>−1</sup>) 2981s (C-H), 1774m (C=O), 1710s (C=O), 1623s, 1432s; <sup>1</sup>H NMR (600 MHz; CDCl<sub>3</sub>) 7.29 (2H, t, <i>J</i> = 7.3, ArH), 7.23 (2H, d, <i>J</i> = 7.3, ArH), 7.19 (1H, t, <i>J</i> = 7.3, ArH), 5.18 (1H, dd, <i>J</i> = 5.3, 1.4, COCH), 4.96 (1H, d, <i>J</i> = 1.4, C=CH), 3.85–3.80 (1H, m, OCCHH'<sup>′</sup>), 3.67 (1H, dd, <i>J</i> = 7.6, 5.3, OCHCCH), 3.57–3.51 (1H, m, OCHCH'<sup>′</sup>), 3.19 (1H, d, <i>J</i> = 7.6, OCHCHCH), 2.83–2.79 (5H, m, NCH<sub>3</sub>; PhCH<sub>2</sub>), 2.62–2.55 (1H, m, PhCH<sub>2</sub>CHH'<sup>′</sup>), 2.28–2.22 (1H, m, PhCH<sub>2</sub>CHH'<sup>′</sup>), 1.27 (3H, t, <i>J</i> = 7.0, CH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR (150 MHz; CDCl<sub>3</sub>) 175.7 (C(O)), 174.2 (C(O)), 164.1 (EO<sub>C</sub>), 141.7 (Ar), 128.5 (Ar), 128.5 (Ar), 126.1 (Ar), 96.6 (C=CH), 89.6 (COCH), 78.2 (COCH), 66.9 (OCH<sub>2</sub>), 51.4 (OCHCHCH), 49.8 (OCHCHCH), 31.9 (PhCH<sub>2</sub>CH<sub>2</sub>), 30.5 (PhCH<sub>2</sub>), 24.5 (NCH<sub>3</sub>), 14.2 (CH<sub>2</sub>CH<sub>3</sub>); HRMS (CI<sup>+</sup>) found [M+H]<sup>+</sup> 328.1544; C<sub>19</sub>H<sub>22</sub>NO<sub>4</sub> requires 328.1543.

**Cantharimide exo-330a**: Isolated as a pale wax. R<sub>f</sub> = 0.50 (1:1 cyclohexane:EtOAc); <sup>1</sup>H NMR (400 MHz; MeOH-d<sub>4</sub>) 7.36–7.16 (5H, m, ArH), 5.20 (1H, d, <i>J</i> = 2.0, C=CH), 5.13 (1H, d, <i>J</i> = 2.0, COCH), 3.94–3.76 (2H, m, OCH<sub>2</sub>), 3.15 (1H, d, <i>J</i> = 6.4, CHC(O)), 2.95 (1H, d, <i>J</i> = 6.4, CHC(O)), 2.90–2.74 (2H, m, PhCH<sub>2</sub>), 2.44–2.36 (1H, m, PhCH<sub>2</sub>CHH'<sup>′</sup>), 2.31–2.22 (1H, m, PhCH<sub>2</sub>CHH'<sup>′</sup>), 1.39 (3H, t, <i>J</i> = 7.1, CH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR (150 MHz; MeOH-d<sub>4</sub>) 177.1 (C(O)), 175.6 (C(O)), 166.6 (COEt), 142.1 (Ar), 128.0 (Ar), 127.9 (Ar), 125.5 (Ar), 99.5 (C=CH), 88.8 (COCH), 79.9 (COCH), 66.5 (OCH<sub>2</sub>), 54.3 (CHC(O)), 49.1 (CHC(O)), 30.4 (CH<sub>2</sub>), 29.7 (CH<sub>2</sub>), 23.4 (NCH<sub>3</sub>), 13.2 (CH<sub>2</sub>CH<sub>3</sub>).
Prepared from furan 318 (101 mg, 0.500 mmol) and N-methylmaleimide according to the General Cycloaddition Procedure over 4 h to give the crude product (endo:exo = 80:20). This was purified by flash column chromatography (0 to 100% TBME:cyclohexane) to give the cantharimide endo-320 as a white crystalline solid (105 mg, 0.335 mmol, 67%). Further elution of the column gave the cantharimide exo-320 as a white crystalline solid (34 mg, 0.11 mmol, 22%).

**Cantharimide endo-320**: m.p. 94–96 °C; R_f = 0.40 (1:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^−1) 2931 s (C-H), 1774 s, 1699 s (C=O), 1625 s, 1433 s; 1H NMR (600 MHz; CDCl_3) 7.27 (2H, t, J = 7.5, ArH), 7.24 (2H, d, J = 7.5, ArH), 7.19 (1H, t, J = 7.5, ArH), 5.20 (1H, dd, J = 5.2, 1.3, COC_H), 5.02 (1H, d, J = 1.3, C=CH), 3.70 (1H, dd, J = 7.5, 5.2, OCHCHCH), 3.53 (3H, s, OCH_3), 3.21 (1H, d, J = 7.5, OCHCH), 2.85 (3H, s, NCH_3), 2.83–2.78 (2H, m, PhCH_2), 2.62–2.56 (1H, m, PhCH_2CH'H'), 2.28–2.22 (1H, m, PhCH_2CH'H'); 13C NMR (150 MHz; CDCl_3) 175.6 (C(O)), 174.3 (C(O)), 165.4 (MeOC), 141.6 (Ar), 128.5 (Ar), 128.5 (Ar), 126.1 (Ar), 96.9 (C=CH), 89.7 (COCH), 78.2 (COCH), 58.2 (OCH_3), 51.3 (OCHCHCH), 49.8 (OCHCHCH), 31.9 (PhCH_2CH_2), 30.5 (PhCH_2), 24.6 (NCH_3); data in accordance with the literature.190

**Cantharimide exo-320**: m.p. 149–151 °C; R_f = 0.50 (1:2 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^−1) 2922 s (C-H), 1764 s, 1698 s (C=O), 1633 s, 1440 s; 1H NMR (600 MHz; CDCl_3) 7.29–7.25 (2H, m, ArH), 7.24–7.21 (2H, m, ArH), 7.17 (1H, t, J = 7.2, ArH), 5.18 (1H, s, C=CH), 5.16 (1H, s, COCH), 3.66 (3H, s, OCH_3), 3.14 (1H, d, J = 6.4, CHC(O)), 2.96 (3H, s, NCH_3), 2.93 (1H, d, J = 6.4, CHC(O)), 2.85–2.73 (2H, m, PhCH_2), 2.39–2.33 (1H, m, PhCH_2CH'H'), 2.30–2.20 (1H, m, PhCH_2CH'H'); 13C NMR (150 MHz; CDCl_3)
176.4 (C(O)), 174.9 (C(O)), 168.4 (MeO), 141.9 (Ar), 128.5 (Ar), 128.4 (Ar), 126.0 (Ar), 99.6 (C=CH), 89500 M.3 (COCH), 79.9 (COCH), 58.3 (OCH), 54.4 (CHC(O)), 49.2 (CH(O)), 30.8 (PhCH), 25.0 (PhCH₂CH₂), 25.0 (NCH₃); data in accordance with the literature.¹⁹⁰

(3aS,4R,7R,7aR)-4-Cyclohexyl-5-ethoxy-2-methyl-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (endo-330b) and (3aR,4R,7R,7aS)-4-Cyclohexyl-5-ethoxy-2-methyl-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (exo-330b)

Prepared from furan 325b (97 mg, 0.50 mmol) and N-methylmaleimide according to the General Cycloaddition Procedure over 4 h to give a mixture of the cantharimides 330b as a colorless oil (145 mg, 0.475 mmol, 95%, endo:exo = 85:15); R_f = 0.51 (1:1 cyclohexane:EtOAc); ν_max (film/cm⁻¹) 2983s (C-H), 1773m, 1702s (C=O), 1624s, 1433s; ¹H NMR (400 MHz; MeOH-d₄) 5.21 (1H, dd, J = 2.1, 1.0, C=C_H exo-330b), 5.06 (1H, dd, J = 5.0, 2.1, COC_H endo-330b), 5.00 (1H, d, J = 2.1, C=C_H endo-330b), 4.96 (1H, d, J = 2.1, COC_H exo-330b), 3.88–3.75 (1H, m, OCH_H_H’ endo-330b; 2H, m, OCH₂ exo-330b), 3.63 (1H, dd, J = 7.4, 5.0, OCHC_HCH endo-330b), 3.58–3.51 (1H, m, OCH_H_H’ endo-330b), 3.51 (1H, d, J = 7.4, CyCCH endo-330b), 3.18–3.13 (2H, m, 2 × CHC(O) exo-330b), 2.91 (3H, s, NCH₃ exo-330b), 2.79 (3H, s, NCH₃ endo-330b), 2.36–2.29 (1H, m, CHH’ exo-330b), 2.14–1.91 (3H, m, 3 × CHH’ endo-330b), 1.91–1.66 (4H, m, 4 × CHH’ endo-330b), 1.44–1.14 (3H, m, CH₂CH₃ endo-330b; 3H, m, CH₂CH₃ exo-330b; 3H, 3 × CHH’ endo-330b) [9 × CHH’ protons of exo-330b cannot be assigned with confidence]; ¹³C NMR (100 MHz; MeOH-d₄) 177.1 (C(O)), 176.3 (C(O)), 175.3 (C(O)), 175.1 (C(O)), 167.4 (COEt), 164.3 (COEt), 100.6 (C=CH exo-330b), 96.6 (C=CH endo-330b), 92.3 (CyC), 91.8 (CyC), 79.3 (COCH exo-330b), 77.3 (COCH endo-330b), 66.4 (OCH₂), 66.2 (OCH₂), 54.3 (CHC(O) exo-330b), 51.3 (OCHC_HCH endo-330b), 47.9 (CHC(O) exo-330b), 46.2 (CyCCH endo-330b), 39.2 (CH(CH₂)₂ exo-330b), 37.0 (CH(CH₂)₂ endo-330b), 27.8 (CH₂), 27.5 (CH₂), 26.7 (CH₂), 26.4 (CH₂), 26.3 (CH₂), 26.3 (CH₂), 26.2 (CH₂), 26.1 (CH₂), 26.1 (CH₂), 26.0 (CH₂), 23.5 (NCH₃), 23.2 (NCH₃), 13.3
(3aS,4R,7R,7aR)-4-Cyclopropyl-5-ethoxy-2-methyl-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (endo-330c) and (3aR,4R,7R,7aS)-4-Cyclopropyl-5-ethoxy-2-methyl-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (exo-330c)

Prepared from furan 325c (76 mg, 0.50 mmol) and N-methylmaleimide according to the General Cycloaddition Procedure over 4 h to give a mixture of the cantharimides 330c as a colorless oil (118 mg, 0.448 mmol, 90%, endo:exo = 80:20); Rf = 0.48 (1:1 cyclohexane:EtOAc); νmax (film/cm⁻¹) 2980s (C-H), 1702s (C=O), 1624m; ¹H NMR (400 MHz; MeOH-d₄) 5.15 (1H, d, J = 2.0, C=C endo-330c), 5.04 (1H, dd, J = 5.1, 2.0, COC endo-330c), 5.00 (1H, d, J = 2.0, C=C endo-330c), 4.96 (1H, d, J = 2.0, COC exo-330c), 3.93–3.76 (1H, m, OCH₂ endo-330c; 2H, m, OCH₂ exo-330c), 3.67 (1H, dd, J = 7.6, 4.1, OCH₂CH₂ endo-330c), 3.62–3.54 (1H, d, J = 7.6, OCH₂CH₂ exo-330c), 3.24–3.20 (1H, d, J = 7.6, OCH₂CH₂CH₂ endo-330c; 1H, m, CH(C=O) exo-330c), 3.00 (1H, d, J = 6.4, CH(C=O) exo-330c), 2.93 (3H, s, NCH₃ exo-330c), 2.81 (3H, s, NCH₃ endo-330c), 1.57–1.47 (1H, m, CH(CH₂)₂ exo-330c), 1.44–1.38 (1H, m, CH(CH₂)₂ endo-330c), 1.34 (3H, t, J = 7.0, CH₂CH₂ exo-330c), 1.26 (3H, t, J = 7.1, CH₂CH₂ endo-330c), 0.79–0.49 (4H, m, CH(CH₂)₂ endo-330c; 3H, m, CH(CH₂)₂(CHH’)(CHH’) endo-330c), 0.34–0.30 (1H, m, CH(CH₂)₂(CHH’)(CHH’) exo-330c); ¹³C NMR (100 MHz; CDCl₃) 177.2 (C=O), 176.2 (C=O), 175.6 (C=O), 174.9 (C=O), 167.5 (COEt), 164.7 (COEt), 98.6 (C=CH exo-330c), 95.9 (C=CH endo-330c), 89.1 (PrC), 88.4 (PrC), 79.1 (COCH exo-330c), 77.3 (COCH endo-330c), 66.4 (OCH₂), 66.4 (OCH₂), 54.6 (CH(C=O) exo-330c), 51.2 (OCH₂CH₂ endo-330c), 49.5 (CH(C=O) exo-330c), 48.8 (OCH₂CH₂CH₂ endo-330c), 23.4 (NCH₃), 23.3 (NCH₃), 13.2 (CH₂CH₃), 13.1 (CH₂CH₃), 9.5 (CH(CH₂)₂), 7.9 (CH(CH₂)₂), 0.9 (CH(CH₂)₂), 0.5 (CH(CH₂)₂), 0.3 (CH(CH₂)₂); HRMS (CI⁺) found [M+H]⁺ 264.1239; C₁₄H₁₈NO₄ requires 264.1236.
**Experimental Details**

*tert-Butyl 4-((3aS,4R,7R,7aR)-5-ethoxy-2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1H-4,7-epoxyisoindol-4-yl)methyl)piperidine-1-carboxylate (endo-330d) and tert-Butyl 4-((3aR,4R,7R,7aS)-5-ethoxy-2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1H-4,7-epoxyisoindol-4-yl)methyl)piperidine-1-carboxylate (exo-330d)*

Prepared from furan 325d (44 mg, 0.14 mmol) and N-methylmaleimide according to the General Cycloaddition Procedure over 4 h to give a mixture of the cantharimides 330d as a colorless oil (51 mg, 0.12 mmol, endo:exo = 75:25); Rf = 0.50 (1:1 cyclohexane:EtOAc); v_max (film/cm⁻¹) 2929s (C-H), 1701s (C=O), 1428m; ¹H NMR (600 MHz; CDCl₃) 5.19–5.16 (1H, m, COC_H endo-330d; 1H, m, COC_H exo-330d), 5.05 (1H, s, C=C_H exo-330d), 4.94 (1H, s, C=C_H endo-330d), 4.04 (2H, br. s, NCH_H endo-330d; 2H, br. s, NCH_H exo-330d), 3.89–3.75 (1H, m, OC_H H' endo-330d; 2H, m, OC_H H' exo-330d), 3.64 (1H, dd, J = 7.7, J = 5.0, OCH_H' endo-330d), 3.58–3.52 (1H, m, OCH endo-330d), 3.17 (1H, d, J = 7.7, OCHCH endo-330d), 3.08 (1H, d, J = 6.2, C_H C(O) exo-330d), 2.98 (3H, s, NCH₃, exo-330d), 2.84 (3H, s, NCH₃ endo-330d), 2.83 (1H, d, J = 6.2, CHC(O) exo-330d), 2.76–2.63 (2H, m, NCH_H' exo-330d; 2H, br. s, NCH_H' exo-330d), 2.30 (1H, dd, J = 15.0, 5.5, COCCH_H' endo-330d), 2.09 (1H, dd, J = 15.4, 5.5, CHOCC_H' exo-330d), 1.91–1.65 (1H, m, COCCH_H' endo-330d; 2H, m, N(CH₂CHH')₂ endo-330d; 1H, m, N(CH₂CH₂)₂CH endo-330d; 2H, m, COCH_H' exo-330d; 2H, m, N(CH₂CH₂H')₂ exo-330d; 1H, m, N(CH₂CH₂)₂CH exo-330d; 1H, m, N(CH₂CH₂)₂CH exo-330d), 1.59 (9H, s, C(CH₃)₃ exo-330d), 1.46 (9H, s, C(CH₃)₃ endo-330d), 1.35 (3H, t, J = 7.0, CH₂CH₃ exo-330d), 1.28 (3H, t, J = 7.0, CH₂CH₃ endo-330d), 1.25–1.11 (1H, m, N(CH₂CHH')₂ exo-330d; 2H, m, N(CH₂CHH')₂ exo-330d); ¹³C NMR (150 MHz; CDCl₃) 176.4 (C(O)N), 175.5 (C(O)N), 175.0 (C(O)N), 174.1 (C(O)N), 166.9 (EtO), 164.1 (EtO), 154.9 (CO'Bu), 98.8 (C=CH exo-330d), 96.1 (C=CH endo-330d), 89.6 (COCH), 89.2 (COCH), 79.9 (COCH), 79.2 (CMe₂), 79.1 (CMe₂), 78.1 (COCH), 66.8 (OCH₂), 66.6 (OCH₂), 54.2 (CH), 51.0 (CH), 50.8 (CH), 49.8 (CH), 43.9 (br. NCH₂ endo-330d; NCH₂ exo-330d), 36.1 (CH₂), 33.1 (br. NCH₂CH₂), 32.9 (N(CH₂CH₂)₂CH), 32.6 (N(CH₂CH₂)₂CH), 32.5
(br. NCH₂CH₂), 28.5 (C(CH₃)₃ \text{endo-330d}); C(CH₃)₃ \text{exo-330d}) 24.8 (NCH₃), 24.4
(NCH₃), 14.2 (CH₂CH₃), 14.1 (CH₂CH₃); HRMS (Cl⁺) found [M+H]⁺ 421.2333;
C₂₂H₃₃N₂O₆ requires 421.2339; Strong ROE between OCHCH \text{endo-330d} and COCH
\text{endo-330d}; Weak ROE between OCHCH \text{exo-330d} and COCH \text{exo-330d}.

(3aS,4S,7R,7aR)-5-Ethoxy-2-methyl-4-phenyl-3a,4,7,7a-tetrahydro-1H-4,7-
epoxyisoindole-1,3(2H)-dione (\text{endo-330e}) and (3aR,4S,7R,7aS)-5-Ethoxy-2-methyl-
4-phenyl-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (\text{exo-330e})

\text{endo-330e} + \text{exo-330e}

Experiment A (0.428 mmol scale): Prepared from furan 325e (94 mg, 0.50 mmol) and
N-methylmaleimide according to the General Cycloaddition Procedure over 6 h to give a
mixture of the cantharimides 330e as a white crystalline solid (128 mg, 0.428 mmol, 86%,
\text{endo:exo} = 80:20).

Experiment B (5.32 mmol scale): Prepared from furan 325e (1.00 g, 5.32 mmol) and N-
methylmaleimide according to the General Cycloaddition Procedure over 24 h to give the
 crude product, which was purified by flash column chromatography (0 to 70%
TBME:cyclohexane) to give cantharimide \text{endo-330e} as a white crystalline solid (1.04 g,
3.47 mmol, 65%). Further elution of the column gave the cantharimide \text{exo-330e} as a
white crystalline solid (334 mg, 1.12 mmol, 21%).

Cantharimide \text{endo-330e}: m.p. 96–98 °C; Rₐ = 0.45 (3:1 petrol 40–60 °C:EtOAc); νₘₐₓ
(film/cm⁻¹) 2982 (C-H), 1774s, 1700s (C=O), 1623s, 1500s, 1432s; ¹H NMR (600 MHz;
CDCl₃) 7.89–7.79 (2H, m, ArH), 7.47–7.38 (3H, m, ArH), 5.32 (1H, dd, J = 5.2, 2.1,
COCH), 5.02 (1H, d, J = 2.1, C=CH), 3.84–3.78 (2H, m, OCHCH); OCHCHCH), 3.58–
3.52 (2H, m, OCHH⁺; PhCHCH), 2.91 (3H, s, NCH₃), 1.18 (3H, t, J = 7.1, CH₂CH₃);
¹³C NMR (150 MHz; CDCl₃) 175.4 (C(O)), 174.3 (C(O)), 164.9 (COEt), 134.7 (Ar),
128.7 (Ar), 128.4 (Ar), 127.2 (Ar), 95.5 (C=CH), 90.3 (CPh), 77.9 (COCH), 67.1 (OCH₂),
51.8 (OCHCHCH), 51.0 (PhCHCH), 24.6 (NCH₃), 13.9 (CH₂CH₃); HRMS (Cl⁻) found
[M+H]⁻ 300.1239; C₁₇H₁₈NO₄ requires 300.1230.
Cantharimide exo-330e: m.p. 119–121 °C; R<sub>f</sub> = 0.38 (3:1 petrol 40–60 °C:EtOAc); <sup>1</sup>H NMR (400 MHz; MeOH-d<sub>4</sub>) 7.51–7.45 (2H, m, Ar<sub>H</sub>), 7.39–7.29 (3H, m, Ar<sub>H</sub>), 5.28 (1H, d, J = 2.2, C=CH), 5.22 (1H, d, J = 2.2, COC), 3.83 (2H, q, J = 7.1, OCH2), 3.46 (1H, d, J = 6.4, C=CH), 3.38–3.34 (1H, m, C=CH), 2.80 (3H, s, NCH3), 1.28 (3H, t, J = 7.1, CH<sub>2</sub>C<sub>3</sub>H<sub>3</sub>); <sup>13</sup>C NMR (400 MHz; MeOH-d<sub>4</sub>) 177.0 (C(O)), 174.5 (C(O)), 167.1 (COEt), 132.6 (Ar), 127.5 (Ar), 127.1 (Ar), 98.1 (C=CH), 90.2 (CPh), 79.8 (COCH), 66.6 (OCH2), 54.6 (CHC(O)), 23.3 (NCH3), 13.0 (CH2CH3).

(3aS,4S,7R,7aR)-5-Ethoxy-2-methyl-4-(4-(trifluoromethyl)phenyl)-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (endo-330f) and (3aR,4S,7R,7aS)-5-Ethoxy-2-methyl-4-(4-(trifluoromethyl)phenyl)-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (exo-330f)

Prepared from furan 325f (64 mg, 0.25 mmol) and N-methylmaleimide according to the General Cycloaddition Procedure over 24 h to give a mixture of the cantharimides 330f as a white crystalline solid (69 mg, 0.18 mmol, 75%, endo:exo = 80:20); m.p. = 243–245 °C; R<sub>f</sub> = 0.55 and 0.75 (1:1 cyclohexane:EtOAc); ν<sub>max</sub> (film/cm<sup>–1</sup>) 2986m (C-H), 1776m, 1702s (C=O), 1625s; <sup>1</sup>H NMR (400 MHz; MeOH-d<sub>4</sub>) 7.98 (2H, d, J = 7.7, Ar<sub>H</sub> endo-330f), 7.71 (2H, d, J = 7.7, Ar<sub>H</sub> exo-330f), 7.66–7.65 (4H, m, Ar<sub>H</sub> endo-330f), 5.31–5.30 (1H, dd, J = 5.1, 2.2, COC endo-330f), 5.14 (1H, d, J = 2.2, C=CH endo-330f), 3.87 (1H, dd, J = 5.1, 7.6, OCHCHCH endo-330f), 3.86–3.77 (1H, m, OCHH′ endo-330f), 3.60 (1H, d, J = 7.6, OCHCHCH endo-330f), 3.60–3.55 (1H, m, OCHH′ endo-330f), 3.51 (1H, d, J = 6.4, CHC(O) exo-330f), 3.36 (1H, d, J = 6.4, CHC(O) exo-330f), 2.87 (3H, s, NCH3 endo-330f), 2.78 (3H, s, NCH3 exo-330f), 1.26 (3H, t, J = 7.1, CH2CH3 exo-330f), 1.15 (3H, t, J = 7.1, CH2CH3 endo-330f); <sup>13</sup>C NMR (150 MHz; MeOH-d<sub>4</sub>) 176.7 (C(O)), 175.6 (C(O)), 174.5 (C(O)), 174.3 (C(O)), 166.4 (COEt), 164.3 (COEt), 139.6 (Ar), 137.1 (Ar), 130.1 (q, J<sub>C-F</sub> = 33.2, Ar), 129.9 (q, J<sub>C-F</sub> = 32.4, Ar), 127.7 (Ar),
127.2 (Ar), 124.4 (q, J_C-F = 4.4, Ar), 124.0 (q, J_C-F = 4.4, Ar), 124.4 (q, J_C-F = 270.9, CF_3), 124.3 (q, J_C-F = 270.9, CF_3), 98.4 (C=CH exo-330f), 95.6 (C=CH endo-330f), 89.6 (COCH), 89.3 (COCH), 80.1 (COCH exo-330f), 77.9 (COCH endo-330f), 66.9 (OCH_2), 54.4 (CHC(O) exo-330f), 51.5 (OCHCHCH endo-330f), 49.9 (CHC(O) exo-330f), 23.4 (NCH_3), 23.3 (NCH_3), 13.0 (CH_2CH_3), 12.9 (CH_2CH_3); HRMS (CI') found [M+H]^+ 368.1111; C_{18}H_{17}F_3NO_4 requires 368.1110.

(3aS,4S,7R,7aR)-5-Ethoxy-4-(4-methoxyphenyl)-2-methyl-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (endo-330g) and (3aR,4S,7R,7aS)-5-Ethoxy-4-(4-methoxyphenyl)-2-Methyl-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (exo-330g)

Prepared from furan 325g (55 mg, 0.25 mmol) and N-methylmaleimide according to the General Cycloaddition Procedure over 4 h to give a mixture of the cantharimides 330g as a colorless oil (74 mg, 0.23 mmol, 90%, endo:exo = 80:20); R_f = 0.15 and 0.08 (3:1 cyclohexane:EtOAc); \( \nu_{\text{max}} \) (film/cm\(-1\)) 2981s (C-H), 1773m, 1702s (C=O), 1622s, 1519s; \( ^1H \) NMR (400 MHz; CDCl_3) 7.76–7.71 (2H, m, ArH endo-330g), 7.46–7.43 (2H, m, ArH exo-330g), 7.01–6.94 (2H, m, ArH endo-330g; 2H, m, ArH exo-330g), 5.33–5.30 (1H, dd, J = 2.0, 5.1, COCH endo-330g; 1H, m, COCH exo-330g), 5.15 (1H, d, J = 2.2, C=CH exo-330g), 5.04 (1H, d, J = 2.0, C=CH endo-330g), 3.87–3.76 (3H, m, OC\_H\_3 endo-330g, 1H, m, OCHH' endo-330g; 3H, m, OCH\_3 exo-330g, 1H, m, OCH\_3 exo-330g), 3.30 (1H, d, J = 6.3, C(O)CH exo-330g), 2.92 (1H, d, J = 6.3, C(O)CH exo-330g), 2.92 (3H, m, NCH\_3 endo-330g), 2.88 (3H, m, NCH\_3 exo-330g), 1.30 (3H, t, J = 7.1, CH\_2CH\_3 endo-330g), 1.20 (3H, t, J = 7.1, CH\_2CH\_3 exo-330g); \( ^13C \) NMR (100 MHz; CDCl_3) 176.2 (C(O)), 175.3 (C(O)), 174.2 (C(O)), 173.9 (C(O)), 167.5 (EtOC), 164.9 (EtOC), 159.8 (Ar), 159.3 (Ar), 128.5 (Ar), 127.7 (Ar), 126.8 (Ar), 124.1 (Ar), 113.7 (Ar), 113.2 (Ar), 97.9 (C=CH exo-330g), 95.4 (C=CH endo-330g), 90.2 (COCH), 90.1 (COCH), 79.8
Experimental Details

(COH exo-330g), 77.7 (COH endo-330g), 66.9 (OCH2 endo-330g; OCH2 exo-330g), 55.3 (OCH3), 55.1 (OCH3), 54.7 (CH), 51.8 (CH), 50.9 (CH), 50.0 (CH), 24.8 (NCH3), 24.6 (NCH3), 14.8 (CH2CH3), 13.8 (CH2CH3); HRMS (CI+) found [M+H]+ 330.1347; C18H20NO5 requires 330.1342.

(3aS,4S,7R,7aR)-4-(4-Bromophenyl)-5-ethoxy-2-methyl-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (endo-330h) and (3aR,4S,7R,7aS)-4-(4-Bromophenyl)-5-ethoxy-2-methyl-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (exo-330h)

Prepared from furan 325h (134 mg, 0.500 mmol) and N-methylmaleimide according to the General Cycloaddition Procedure over 24 to give the crude product (endo:exo = 80:20), which was purified by flash column chromatography (0 to 100% TBME:cyclohexane) to give a mixture of the cantharimides 330h as a colorless oil (149 mg, 0.392 mmol, 78%; endo:exo = 20:1); Rf = 0.28 and 0.49 (1:1 cyclohexane:EtOAc); νmax (film/cm⁻¹) 2981 s (C-H), 1775 w, 1702 s (C=O), 1624 s, 1491 s; 1³H NMR (400 MHz; MeOH-d₄, endo-330h) 7.75–7.61 (2H, m, ArH), 7.61–7.55 (2H, m, ArH), 5.29 (1H, dd, J = 5.1, 2.1, COCH), 5.13 (1H, d, J = 2.1, C=CH), 3.87 (1H, dd, J = 5.1, 7.8, OCHCHCH), 3.84–3.77 (1H, m, OCHH'), 3.60 (1H, d, J = 7.8, OCHCHCH), 3.60–3.53 (1H, m, OCHH'), 2.88 (3H, s, NCH₃), 1.17 (3H, t, J = 7.1, CH₂CH₃); 1³C NMR (100 MHz; MeOH-d₄, endo-330h), 175.7 (C(O)), 174.6 (C(O)), 164.4 (COEt), 134.5 (Ar), 130.7 (Ar), 129.0 (Ar), 122.1 (Ar), 95.5 (C=CH), 89.4 (COCH), 77.7 (COCH), 66.8 (OCH₂), 51.5 (CHC(O)), 50.7 (CHC(O)), 23.4 (NCH₃), 12.9 (CH₂CH₃); HRMS (CI+) found [M+H]+ 378.0340; C17H177²⁹BrNO4 requires 378.0341.
(3aS,4S,7R,7aR)-4-(o-Tolyl)-5-ethoxy-2-methyl-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (endo-330i) and (3aR,4S,7R,7aS)-4-(o-Tolyl)-5-ethoxy-2-methyl-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (exo-330i)

Prepared from furan 325i (101 mg, 0.500 mmol) and N-methylmaleimide according to the General Cycloaddition Procedure over 24 h to give a mixture of the cantharimides 330i as a colorless oil (135 mg, 0.431 mmol, 86%, endo:exo = 80:20); \( R_f = 0.63 \) and 0.59 (1:1 cyclohexane:EtOAc); \( \nu_{\text{max}} \) (film/cm\(^{-1}\)) 2981 s (C-H), 1773 m, 1700 s (C=O), 1625 s, 1433 s; \( ^1H \) NMR (400 MHz; DMSO\( -d_6 \)) 8.01–7.97 (1H, m, Ar\( H \) endo-330i), 7.36–7.28 (2H, m, Ar\( H \) endo-330i; 1H, m, Ar\( H \) exo-330i), 7.23–7.17 (1H, m, Ar\( H \) endo-330i; 2H, m, Ar\( H \) exo-330i), 7.13–7.08 (1H, m, Ar\( H \) exo-330i), 5.36 (1H, d, \( J = 2.2 \), C=C\( H \) exo-330i), 5.31 (1H, dd, \( J = 5.1, 2.0 \), COC\( H \) endo-330i), 5.19–5.16 (1H, m, C=C\( H \) endo-330i; 1H, m, COCH\( H \) endo-330i), 4.07 (1H, d, \( J = 7.8 \), OCHCHC\( H \) endo-330i), 3.83–3.73 (1H, m, OC\( H \)H' endo-330i; 1H, m, OCHC\( H \)CH\( H \) endo-330i; 1H, m, OC\( H \)2 exo-330i), 3.60–3.52 (1H, m, OCH\( H \)' exo-330i), 3.34–3.31 (1H, m, C\( H \)C(O) exo-330i; HOD), 2.76 (3H, s, NCH\( 3 \) endo-330i), 2.69 (3H, s, NCH\( 3 \) exo-330i), 2.59 (3H, s, ArCH\( 3 \) exo-330i), 2.31 (3H, s, ArCH\( 3 \) endo-330i), 1.66 (3H, t, \( J = 7.0 \), CH\( 2 \)CH\( 3 \) endo-330i), 1.02 (3H, t, \( J = 7.0 \), CH\( 2 \)CH\( 3 \) exo-330i); \( ^{13}C \) NMR (100 MHz; CDCl\( 3 \)) 176.7 (C(O)), 175.5 (C(O)), 174.5 (C(O)), 174.3 (C(O)), 166.9 (COEt), 164.3 (COEt), 139.3 (Ar), 137.3 (Ar), 132.4 (Ar), 132.4 (Ar), 131.4 (Ar), 131.2 (Ar), 130.4 (Ar), 129.4 (Ar), 128.2 (Ar), 125.9 (Ar), 125.5 (Ar), 100.0 (C=CH exo-330i), 96.0 (C=CH endo-330i), 91.3 (COCH), 90.8 (COCH), 78.8 (COCH exo-330i), 77.9 (COCH endo-330i), 67.0 (OCH\( 2 \)), 66.8 (OCH\( 2 \)), 53.7 (CHC(O) exo-330i), 51.0 (OCHCHCH exo-330i), 49.3 (CHC(O) exo-330i), 49.0 (OCHCHCH endo-330i), 24.7 (NCH\( 3 \)), 24.7 (NCH\( 3 \)), 22.3 (ArCH\( 3 \)), 20.8 (ArCH\( 3 \)), 14.4 (CH\( 2 \)CH\( 3 \)), 14.2 (CH\( 2 \)CH\( 3 \)); HRMS (CI\(^+\)) found [M+H]\(^+\) 314.1399; C\(_{18}\)H\(_{20}\)NO\(_{4}\) requires 314.1392.
Experimental Details

Methyl 3-((3aS,4S,7R,7aR)-5-ethoxy-2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1H-4,7-epoxyisoindol-4-yl)benzoate (endo-330j) and Methyl 3-((3aR,4S,7R,7aS)-5-ethoxy-2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1H-4,7-epoxyisoindol-4-yl)benzoate (exo-330j)

Prepared from furan 325j (123 mg, 0.500 mmol) and N-methylmaleimide according to the General Cycloaddition Procedure over 24 h to give the crude product (endo:exo = 75:25). This was purified by flash column chromatography (0 to 100% TBME:cyclohexane) to give the cantharimide endo-330j (107 mg, 0.300 mmol, 60%). Further elution of the column gave the cantharimide exo-330j (41 mg, 0.12 mmol, 23%).

Cantharimide endo-330j: Isolated as a white crystalline solid; m.p. = 126–128 °C; R_f = 0.44 (1:1 cyclohexane:EtOAc); ν_max (film/cm⁻¹) 2980s (C-H), 1775m, 1720s (C=O ester and imide), 1624s, 1433s; _1H NMR (400 MHz; DMSO-d_6) 8.30 (1H, t, _J_ = 1.6, ArH), 8.06–7.96 (2H, m, ArH), 7.63 (1H, t, _J_ = 7.7, ArH), 5.36 (1H, dd, _J_ = 5.1, 2.0, COCH), 5.22 (1H, d, _J_ = 2.0, C=CH), 3.92–3.85 (4H, m, CO_2CH_3; OCHC_HCH), 3.83–3.74 (1H, m, OC_HH'), 3.68 (1H, d, _J_ = 7.6, OCHCHC_H), 3.59–3.50 (1H, m, OCH_H'), 2.78 (3H, s, NCH_3), 1.05 (3H, t, _J_ = 7.0, CH_2CH_3); _13C NMR (100 MHz; DMSO-d_6) 175.3 (C(O)N), 174.5 (C(O)N), 166.5 (C(O)Ome or COEt), 164.0 (C(O)Ome or COEt), 136.4 (Ar), 132.5 (Ar), 130.0 (Ar), 129.6 (Ar), 129.2 (Ar), 128.2 (Ar), 97.0 (C=CH), 89.3 (COCH), 77.7 (COCH), 67.1 (OCH), 52.7 (OCH_3 or OCHCHCH), 51.7 (OCH_3 or OCHCHCH), 50.9 (OCHCHCH), 24.8 (NCH_3), 14.1 (CH_2CH_3); HRMS (Cl⁺) found [M+H]^+ 358.1294; C_{10}H_{20}NO_6 requires 358.1291.

Cantharimide exo-330j: Isolated as a white crystalline solid; m.p. = 118–120 °C; R_f = 0.27 (1:1 cyclohexane:EtOAc); _1H NMR (400 MHz; DMSO-d_6) 7.99 (1H, t, _J_ = 1.4, ArH), 7.93 (1H, dd, _J_ = 7.7, 1.4, ArH), 7.75–7.69 (1H, m, ArH), 7.58–7.52 (1H, m, ArH), 5.37 (1H, d, _J_ = 2.2, C=CH), 5.24 (1H, d, _J_ = 2.2, COCH), 3.87 (3H, s, OCH_3), 3.80 (2H, q, _J_ = 7.0, OCH_2), 3.56 (1H, d, _J_ = 6.4, CHC(O)), 3.37 (1H, d, _J_ = 6.4, CHC(O)), 2.69
(3H, s, NCH$_3$), 1.18 (3H, t, $J = 7.0$, CH$_2$CH$_3$); $^{13}$C NMR (100 MHz; DMSO-d$_6$) 176.4 (C(O)N), 174.2 (C(O)N), 166.6 (C(O)OMe or COEt), 165.9 (C(O)OMe or COEt), 133.9 (Ar), 132.2 (Ar), 129.5 (Ar), 129.1 (Ar), 128.5 (Ar), 99.7 (C=CH), 89.7 (COCH), 80.0 (COCH), 54.5 (CHC(O)), 52.7 (OCH$_3$), 50.0 (CHC(O)), 24.7 (NCH$_3$), 14.3 (CH$_2$CH$_3$).

(3aS,4S,7R,7aR)-4-(Furan-2-yl)-5-ethoxy-2-methyl-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (endo-330k) and (3aR,4S,7R,7aS)-4-(Furan-2-yl)-5-ethoxy-2-methyl-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (exo-330k)

Prepared from furan 325k (104 mg, 0.584 mmol) and N-methylmaleimide according to the General Cycloaddition Procedure over 24 h to give the crude product (endo:exo = 90:10). This was purified by flash column chromatography (0 to 100% EtOAc:cyclohexane) to give the a mixture of the cantharimides 330k as a white crystalline solid (143 mg, 0.494 mmol, 85%, endo:exo = 95:5); m.p. = 122–124 °C; R$_f$ = 0.16 (2:1 cyclohexane:EtOAc); $\nu$$_{max}$ (film/cm$^{-1}$) 2982s (C-H), 1775m, 1701s (C=O), 1631s 1434s; $^1$H NMR (400 MHz; DMSO-d$_6$, endo-330k) 7.83–7.73 (1H, m, ArH), 6.84 (1H, d, $J = 3.4$, ArH), 6.57 (1H, dd, $J = 3.4$, 2.0, ArH), 5.31–5.21 (2H, m, C=CCH; COCHH), 3.92 (1H, d, $J = 7.6$, OCHCHCH), 3.88–3.81 (2H, m, OCHH'); OCHCHCH), 3.59–3.51 (1H, m, OCHH'), 2.72 (3H, s, NCH$_3$), 1.10 (3H, t, $J = 7.1$, CH$_2$CH$_3$); $^1$H NMR (400 MHz; DMSO-d$_6$, exo-330k) 7.72–7.71 (1H, m, ArH), 6.70 (1H, d, $J = 3.2$, ArH), 6.46 (1H, dd, $J = 2.0$, 3.4, ArH), 5.36 (1H, d, $J = 2.0$, C=CH or COCH), 5.16 (1H, d, $J = 2.0$, C=CH or COCH), 2.78 (3H, s, NCH$_3$), 1.21 (3H, t, $J = 6.9$, CH$_2$CH$_3$), remaining resonances obscured by the major diastereoisomer; $^{13}$C NMR (100 MHz; DMSO-d$_6$, endo-330k), 175.4 (C(O)), 173.6 (C(O)), 162.5 (COEt), 147.6 (Ar), 144.9 (Ar), 112.8 (Ar), 111.2 (Ar), 97.9 (C=CH), 84.4 (COCH), 76.0 (COCH), 67.2 (OCH$_2$), 51.0 (CHC(O)), 48.9 (CHC(O)), 24.6 (NCH$_3$), 14.3 (CH$_2$CH$_3$); HRMS (Cl$^+$) found [M+H]$^+$ 290.1028; C$_{15}$H$_{16}$NO$_5$ requires 290.1029.
(3aS,4R,7R,7aR)-5-Ethoxy-2-methyl-4-(thiophen-2-yl)-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (endo-330l) and (3aR,4R,7R,7aS)-5-Ethoxy-2-methyl-4-(thiophen-2-yl)-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (exo-330l)

Prepared from furan 325l (97 mg, 0.50 mmol) and N-methylmaleimide according to the General Cycloaddition Procedure over 24 h to give a mixture of the cantharinides 330l as a colorless oil (147 mg, 0.481 mmol, 96%, endo: exo = 70:30); Rf = 0.42 and 0.63 (1:1 cyclohexane:EtOAc); ν\text{max} (film/cm\textsuperscript{-1}) 2982s (C-H), 1774m, 1700s (C=O), 1626s, 1433s; 1H NMR (400 MHz; DMSO-d\textsubscript{6}) 7.63 (1H, dd, J = 5.0, 1.1, Ar\textit{H} endo-330l), 7.57–7.48 (1H, m, Ar\textit{H} endo-330l; 1H, m, Ar\textit{H} exo-330l), 7.25 (1H, dd, J = 3.5, 1.1, Ar\textit{H} exo-330l), 7.14 (1H, dd, J = 5.0, 3.7, Ar\textit{H} endo-330l), 7.07 (1H, dd, J = 5.1, 3.5, Ar\textit{H} exo-330l), 5.34 (1H, d, J = 2.0, C=CH exo-330l), 5.27 (2H, dd, J = 5.1, 2.2, COCH endo-330l), 5.21 (1H, d, J = 2.2, C=CH endo-330l), 5.18 (1H, d, J = 2.0, COCH exo-330l), 3.90–3.77 (1H, m, OCHCH\textit{H} endo-330l; 1H, m, OCHCH\textit{H}′ endo-330l; 1H, m, OCH\textit{H} endo-330l; 1H, m, OCH\textit{H}′ exo-330l), 3.74 (1H, d, J = 6.6, CHC(O) exo-330l), 3.33–3.32 (1H, m, CHC(O) exo-330l; HOD), 2.75 (3H, s, NCH\textsubscript{3} endo-330l; 3H, s, NCH\textsubscript{3} exo-330l), 1.22 (3H, t, J = 7.1, CH\textsubscript{2}CH\textsubscript{3} exo-330l), 1.09 (3H, t, J = 7.0, CH\textsubscript{2}CH\textsubscript{3} endo-330l); 13C NMR (100 MHz; DMSO-d\textsubscript{6}) 176.3 (C(O)), 175.4 (C(O)), 173.9 (C(O)), 173.7 (C(O)), 165.7 (EtOC), 163.4 (EtOC), 137.2 (Ar), 134.5 (Ar), 128.4 (Ar), 127.7 (Ar), 127.4 (Ar), 127.2 (Ar), 127.0 (Ar), 126.4 (Ar), 99.4 (C=CH exo-330l), 97.2 (C=CH endo-330l), 88.2 (COCH), 87.2 (COCH), 80.2 (COCH exo-330l), 77.9 (COCH endo-330l), 67.2 (OCH\textsubscript{2}), 67.2 (OCH\textsubscript{2}), 55.0 (CH), 51.7 (CH), 51.6 (CH), 51.0 (CH), 24.8 (NCH\textsubscript{3}), 24.7 (NCH\textsubscript{3}), 14.4 (CH\textsubscript{2}CH\textsubscript{3}), 14.2 (CH\textsubscript{2}CH\textsubscript{3}); HRMS (Cl\textsuperscript{+}) found [M+H]\textsuperscript{+} 306.0795; C\textsubscript{15}H\textsubscript{16}NO\textsubscript{4}S requires 306.0800.
(3aS,4S,7R,7aR)-5-Ethoxy-2-methyl-4-(pyridin-3-yl)-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (endo-330m) and (3aR,4S,7R,7aS)-5-Ethoxy-2-methyl-4-(pyridin-3-yl)-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (exo-330m)

Prepared from furan 325m (25 mg, 0.015 mmol) and N-methylmaleimide according to the General Cycloaddition Procedure over 24 h to give a mixture of the cantharimides 330m as a colorless oil (37 mg, 0.12 mmol, 92%, endo: exo = 70:30); Rf = 0.28 and 0.16 (1:1 cyclohexane:EtOAc); νmax (film/cm⁻¹) 2980s (C-H), 1774s, 1695s (C=O), 1623s, 1480s; 1H NMR (400 MHz; DMSO-d6) 8.93 (1H, m, ArH endo-330m), 8.66 (1H, m, ArH exo-330m), 8.58 (1H, d, J = 5.0, ArH endo-330m), 8.52 (1H, d, J = 5.0, ArH exo-330m), 8.26 (1H, d, J = 8.2, ArH endo-330m), 7.95 (1H, d, J = 8.3, ArH exo-330m), 7.52 (1H, dd, J = 8.2, 5.0, ArH endo-330m), 7.47 (1H, dd, J = 8.3, 5.0, ArH exo-330m), 5.36–5.35 (1H, m, COC_H endo-330m; 1H, m, C=CH exo-330m), 5.29 (1H, d, J = 2.0, COCH exo-330m), 5.19 (1H, d, J = 2.2, C=CH endo-330m), 3.92–3.79 (1H, m, OCHC_H CH endo-330m; 1H, m, OC_H H' endo-330m; 2H, m, OC_H2 exo-330m), 3.67 (1H, d, J = 7.6, OCHCHCH endo-330m), 3.64–3.56 (1H, m, OCHH' endo-330m; 2H, m, OCH2 exo-330m), 3.59 (1H, d, J = 6.4, CHC(O) exo-330m), 2.89 (3H, s, NCH3 endo-330m), 2.81 (3H, s, NCH3 exo-330m), 1.28 (3H, t, J = 7.1, CH2CH3 exo-330m), 1.18 (3H, t, J = 7.1, CH2CH3 endo-330m); 13C NMR (100 MHz; MeOH-d4) 176.6 (C(O)), 175.5 (C(O)), 174.4 (C(O)), 174.3 (C(O)), 166.2 (COEt), 163.9 (COEt), 148.6 (Ar), 148.0 (Ar), 147.5 (Ar), 147.0 (Ar), 135.8 (Ar), 135.3 (Ar), 132.0 (Ar), 129.7 (Ar), 123.3 (Ar), 123.0 (Ar), 98.5 (C=CH exo-330m), 95.8 (C=CH endo-330m), 88.3 (COCH), 87.9 (COCH), 80.4 (COCH exo-330m), 78.2 (COCH endo-330m), 67.0 (OCH2), 67.0 (OCH2), 54.3 (CHC(O) exo-330m), 51.3 (OCHCHCH endo-330m), 50.8 (OCHCHCH endo-330m), 49.7 (COCH exo-330m), 23.4 (NCH3), 23.4 (NCH3), 13.0 (CH2CH3), 12.9 (CH2CH3); HRMS (Cl+) found [M+H]+ 301.1189; C16H17N2O4 requires 301.1188.
Experimental Details

1-(4-Ethoxy-5-phenethylfuran-2-yl)-N,N-dimethylmethanamine (332)

Prepared according to the modified procedure of Sheppard et al.190: A stirring solution of furan 325a (50 mg, 0.23 mmol) in MeCN (2.3 mL) was treated with dimethylmethylideneammonium iodide (85 mg, 0.46 mmol) and the resulting mixture was stirred at RT for 16 h before it was concentrated in vacuo to give the crude product. This was purified by flash column chromatography (1:1 petrol 40–60 °C: Et₂O with 1% NEt₃) to give the furan 332 as a colorless oil (49 mg, 0.18 mmol, 78%); Rₓ = 0.30 (1:1 petrol 40–60 °C: EtOAc); νₓ (film/cm⁻¹) 2927s (C-H), 1635s, 1495s, 1453s, 1420s; ¹H NMR (600 MHz; MeOH-d₄) 7.22–7.18 (2H, m, ArH), 7.14–7.10 (3H, m, ArH), 6.19 (1H, s, ArH), 3.71 (2H, q, J = 7.1, OC₃H₂), 3.39 (2H, s, CH₂N), 2.90–2.82 (4H, m, CH₂CH₂Ph), 2.22 (6H, s, N(C₃H₃)₂), 1.17 (3H, t, J = 7.1, CH₂C₃H₃); ¹³C NMR (150 MHz; MeOH-d₄) 148.6 (Ar), 144.1 (Ar), 142.7 (Ar), 140.6 (Ar), 129.5 (Ar), 129.2 (Ar), 126.9 (Ar), 104.8 (Ar), 68.7 (OCH₂), 56.6 (NCH₂), 44.7 (N(CH₃)₂), 35.3 (CH₂), 28.0 (CH₂), 15.4 (CH₃); HRMS (ESI⁺) found [M+H]+ 274.1818; C₁₇H₂₄N₂O₂ requires 274.1807.

(3aS,4R,7R,7aR)-5-Ethoxy-2-methyl-4-phenethyl-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (endo-333) and (3aR,4R,7R,7aS)-5-Ethoxy-2-methyl-4-phenethyl-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (exo-333)

Prepared from furan 332 (88 mg, 0.32 mmol) and N-methylmaleimide according to the General Cycloaddition Procedure over 24 h to give a mixture of the cantharimides 333 as a colorless oil (116 mg, 0.302 mmol, 94%; endo:exo = 20:80); Rₓ = 0.35 (Et₂O); νₓ (film/cm⁻¹) 2938s (C-H), 1772m, 1698s (C=O), 1626s, 1454s; ¹H NMR (600 MHz; MeOH-d₄) 7.29–7.12 (5H, m, ArH endo-333; 5H, m, ArH exo-333), 5.28 (1H, s, C=CH exo-333), 5.01 (1H, s, C=CH endo-333), 3.97–3.91 (1H, m, OCHH’ exo-333), 3.88–3.82 (1H, m, OCHH’ endo-333; 1H, m, OCHH’ exo-333), 3.59–3.51 (1H, m, OCHH’ endo-333; 1H, m, OCHH’ exo-333).
3.47 (1H, d, J = 7.5, Me₂NCH₂CCH(O endo-333), 3.37 (1H, d, J = 14.7, Me₂NCHH’ exo-333), 3.33 (1H, d, J = 7.5, EtOCCC(O endo-333), 3.22 (1H, d, J = 14.3, Me₂NCHH’ endo-333), 3.15 (1H, d, J = 6.4, Me₂NCH₂CCH(O exo-333), 3.02 (1H, d, J = 6.4, EtOCCC(O exo-333), 2.89 (3H, s, C(O)NCH₃ exo-333), 2.82–2.68 (3H, m, C(O)NCH₃ endo-333; 2H, m, CH₂CH₂ endo-333; 3H, m, C(O)NCH₃ endo-333; 2H, m, CH₂CH₂ exo-333), 2.74 (1H, d, J = 14.3, Me₂NCHH’ endo-333), 2.55 (1H, d, J = 14.7, Me₂NCHH’ exo-333), 2.48–2.43 (1H, m, CH₂CHH’ endo-333), 2.34 (6H, s, N(CH₃)₂ endo-333; 6H, s, N(CH₃)₂ exo-333), 2.33–2.06 (1H, m, CH₂CHH’ endo-333; 1H, m, CH₂CH₂ exo-333), 1.37 (3H, t, J = 7.1, CH₂CH₃ exo-333), 1.25 (3H, t, J = 7.1, CH₂CH₃ endo-333); 13C NMR (150 MHz; MeOH-d₄) 177.4 (C(O)), 176.6 (C(O)), 176.5 (C(O)), 176.3 (C(O)), 167.3 (COEt), 165.0 (COEt), 143.4 (Ar), 143.1 (Ar), 129.5 (Ar), 129.4 (Ar), 129.3 (Ar), 127.0 (Ar), 127.0 (Ar), 102.6 (C=CH exo-333), 99.1 (C=CH endo-333), 91.2 (COC), 90.9 (COC), 90.8 (COC), 90.2 (COC), 68.0 (OCH₂ endo-333), 67.9 (OCH₂ exo-333), 61.7 (NCH₂ endo-333), 60.3 (NCH₂ exo-333), 57.7 (Me₂NCH₂CCH(O exo-333), 54.6 (Me₂NCH₂CCH(O endo-333), 52.7 (EtOCCC(O endo-333), 52.6 (EtOCCC(O exo-333), 47.3 (N(CH₃)₂ endo-333), 47.2 (N(CH₃)₂ exo-333), 33.2 (CH₂CH₂ endo-333), 32.1 (CH₂CH₂ exo-333), 31.6 (CH₂CH₂ endo-333), 31.1 (CH₂CH₂ exo-333), 24.9 (NCH₃ imide exo-333), 24.7 (NCH₃ imide endo-333), 14.7 (CH₂CH₃ exo-333), 14.6 (CH₂CH₃ endo-333); Significant NOE between Me₂NCH₂CCH(O) and Me₂NCH₂ for endo-333; No Significant NOE between Me₂NCH₂CCH(O) and Me₂NCH₂ for exo-333; HRMS (Cl⁺) found [M+H]⁺ 385.2127; C₂₂H₂₉N₂O₄ requires 385.2127.

(3aS,4R,7R,7aR)-5-Ethoxy-2-phenyl-4-phenethyl-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (endo-334a) and (3aR,4R,7R,7aS)-5-Ethoxy-2-phenyl-4-phenethyl-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (exo-334a)

Prepared from furan 325a (108 mg, 0.500 mmol) and 1-phenyl-1H-pyrrole-2,5-dione according to the General Cycloaddition Procedure over 4 h to give a mixture of the
cantharimides 334a as a pale wax (183 mg, 0.470 mmol, 94%, endo:exo = 65:35); 
Rf = 0.64 (1:1 cyclohexane:EtOAc); νmax (film/cm⁻¹) 2977s (C–H), 1713s (C=O), 1624s, 1498s; ¹H NMR (400 MHz; CDCl₃) 7.51–7.17 (10H, m, ArH, endo-334a; 10H, m, ArH, exo-334a), 5.32 (1H, t, J = 2.0, COC–H endo-334a), 5.31 (1H, d, J = 2.0, COC–H exo-334a), 5.19 (1H, d, J = 2.0, C=C–H exo-334a), 5.15 (1H, d, J = 2.0, C=C–H endo-334a), 3.96–3.80 (1H, m, OCH–C=HCH–CH–H exo-334a; 1H, m, OCH–C=HCH–CH–H endo-334a; 2H, m, OCH₂ exo-334a), 3.76–3.68 (1H, m, OCH′–C=HCH–CH–H endo-334a), 3.38 (1H, d, J = 7.8, OCHCH₃ endo-334a), 3.32 (1H, d, J = 7.8, OCHCH₃ exo-334a), 2.95–2.82 (2H, m, PhCH₂ endo-334a; 2H, m, PhCH₂ exo-334a), 2.73–2.63 (1H, m, PhCH₂CHH′ endo-334a), 2.50–2.42 (1H, m, PhCH₂CHH′ exo-334a), 2.41–2.28 (1H, m, PhCH₂CHH′ exo-334a; 1H, m, PhCH₂CHH′ endo-334a), 1.40 (3H, t, J = 7.1, CH₃ exo-334a), 1.33 (3H, t, J = 7.1, CH₂CH₃ endo-334a); ¹³C NMR (100 MHz; CDCl₃) 175.3 (C(O)), 174.3 (C(O)), 173.8 (C(O)), 172.8 (C(O)), 167.2 (COEt), 164.4 (COEt), 142.0 (Ar), 141.6 (Ar), 131.8 (Ar), 131.7 (Ar), 129.1 (Ar), 129.1 (Ar), 128.7 (Ar), 128.4 (Ar), 128.3 (Ar), 126.6 (Ar), 126.0 (Ar), 125.9 (Ar), 125.8 (Ar), 99.6 (C=CH exo-334a), 97.0 (C=CH endo-334a), 90.0 (COCH), 89.7 (COCH), 80.5 (COCH), 78.5 (COCH), 66.9 (OCH₂), 66.8 (OCH₂), 54.3 (CHC(O) exo-334a), 51.2 (OCHCHCH endo-334a), 49.5 (OCHCHCH endo-334a), 49.2 (CHC(O) exo-334a), 31.9 (CH₂), 30.7 (CH₂), 30.4 (CH₂), 29.5 (CH₂), 14.3 (CH₂CH₃), 14.3 (CH₂CH₃); HRMS (Cl⁺) found [M+H]⁺ 390.1708; C₂₄H₂₄NO₄ requires 390.1705.
(3aS,4R,7R,7aR)-5-Ethoxy-2-(4-methylbenzyl)-4-phenethyl-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (endo-334b) and (3aR,4R,7R,7aS)-5-Ethoxy-2-(4-methylbenzyl)-4-phenethyl-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (exo-334b)

Prepared from furan 325a (108 mg, 0.500 mmol) and imide 329a according to the General Cycloaddition Procedure over 4 h to give a mixture of the cantharimides 334b as a pale wax (173 mg, 0.414 mmol, 83%, endo:exo = 55:45); R_f = 0.51 (1:1 cyclohexane:EtOAc); ν_max (film/cm\(^{-1}\)) 2977s (C-H), 1771m, 1701s (C=O), 1623m, 1513m, 1430m; \(^1\)H NMR (600 MHz; CDCl_3) 7.32–7.11 (9H, m, ArH endo-334b; 9H, m, ArH exo-334b), 5.22 (1H, d, J = 1.8, COC_H exo-334b), 5.18 (1H, dd, J = 5.1, 1.5, COC_H endo-334b), 5.12 (1H, d, J = 1.8, C=C_H exo-334b), 4.75 (1H, d, J = 1.5, C=C_H endo-334b), 4.62 (1H, d, J = 1.5, C=CH endo-334b), 4.57 (1H, d, J = 14.0, NHCH\(_2\) endo-334b), 4.53 (1H, d, J = 14.0, NHCH\(_2\) exo-334b), 4.39 (1H, d, J = 14.0, NHCH\(_2\) endo-334b), 3.91–3.89 (1H, m, OCH\(_2\) endo-334b), 3.83–3.78 (1H, m, OCH\(_2\) exo-334b), 3.69 (1H, d, J = 7.7, 5.1, OCHCHCH endo-334b), 3.33–3.28 (1H, m, OCHCH exo-334b), 3.21 (1H, d, J = 7.7, OCHCHCH endo-334b), 3.14 (1H, d, J = 6.4, C(O)CH endo-334b), 2.92 (1H, d, J = 6.4, C(O)CH exo-334b), 2.86–2.75 (2H, m, CH\(_2\)Ph endo-334b; 2H, m, CH\(_2\)Ph exo-334b), 2.58–2.51 (1H, m, CHH’CH\(_2\)Ph endo-334b), 2.51–2.46 (1H, m, CHH’CH\(_2\)Ph exo-334b), 2.40–2.32 (1H, m, CHH’CH\(_2\)Ph endo-334b), 2.17–2.09 (1H, m, CHH’CH\(_2\)Ph endo-334b; 3H, m, ArCH\(_3\) endo-334b), 2.17–2.09 (1H, m, CHH’CH\(_2\)Ph endo-334b; 3H, m, ArCH\(_3\) endo-334b), 2.17–2.09 (1H, m, CHH’CH\(_2\)Ph endo-334b; 3H, m, ArCH\(_3\) endo-334b), 1.38 (3H, t, J = 7.0, exo-334b CH\(_2\)CH\(_3\)), 1.06 (3H, t, J = 7.0, CH\(_2\)CH\(_3\) endo-334b); \(^13\)C NMR (150 MHz; CDCl_3) 175.8 (C(O)), 175.0 (C(O)), 174.5 (C(O)), 173.6 (C(O)), 167.1 (COEt), 164.2 (COEt), 142.0 (Ar), 141.6 (Ar), 137.7 (Ar), 137.4 (Ar), 133.1 (Ar), 132.7 (Ar), 129.6 (Ar), 129.2 (Ar), 128.4 (Ar), 128.4 (Ar), 128.3 (Ar), 128.2 (Ar), 125.9 (Ar), 125.8 (Ar), 99.3 (C=CH exo-334b), 95.9 (C=CH endo-334b), 89.3 (COCH), 89.3 (COCH), 79.9 (COCH exo-334b), 78.2 (COCH endo-334b), 66.7 (OCH\(_2\) exo-334b), 65.8 (OCH\(_2\) endo-334b), 54.3 (CHC(O) exo-334b), 51.0 (OCHCHCH endo-334b), 49.5 (OCHCHCH endo-334b),
Experimental Details

49.1 (CHC(O) exo-334b), 42.1 (NCH2), 41.9 (NCH2), 31.9 (CH2), 30.6 (CH2), 30.3 (CH2), 29.3 (CH2), 21.1 (ArCH3), 21.1 (ArCH3), 14.3 (CH2CH3), 14.2 (CH2CH3); HRMS (CI⁻) found [M+H]+ 418.2020; C26H28NO4 requires 418.2018.

(3aS,4R,7R,7aR)-2-Cyclopropyl-5-ethoxy-4-phenethyl-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (endo-334c) and (3aR,4R,7R,7aS)-2-Cyclopropyl-5-ethoxy-4-phenethyl-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (exo-334c)

Prepared from furan 325a (108 mg, 0.500 mmol) and imide 329b according to the General Cycloaddition Procedure over 4 h to give a mixture of the cantharimides 334c as a pale wax (153 mg, 0.433 mmol, 87%; endo:exo = 60:40); Rf = 0.69 (1:1 cyclohexane:EtOAc); \( \nu_{\text{max}} \) (film/cm\(^{-1}\)) 2977s (C-H), 1775m, 1707s (C=O), 1401s; \(^1\)H NMR (600 MHz; CDCl\(_3\)) 7.34–7.18 (5H, m, ArH, endo-334c; 5H, m, ArH, exo-334c), 5.19 (1H, dd, \( J = 5.4, 2.0 \), COC\( H_{\text{endo}-334c} \)), 5.17 (1H, d, \( J = 2.0 \), COC\( H_{\text{exo}-334c} \)), 5.11 (1H, d, \( J = 2.0 \), C=C\( H_{\text{exo}-334c} \)), 5.00 (1H, dd, \( J = 5.4, 2.0 \), COCH endo-334c), 5.17 (1H, d, \( J = 2.0 \), COCH exo-334c), 3.92–3.75 (1H, m, OCH\( H'_{\text{endo}-334c} \); 1H, m, OCH\( H'_{\text{exo}-334c} \)), 3.65–3.58 (1H, m, OCHC\( H_{\text{endo}-334c} \)), 3.15 (1H, d, \( J = 7.8 \), OCHCH\( H_{\text{exo}-334c} \)), 3.07 (1H, d, \( J = 7.8 \), CHC(O) exo-334c), 2.89–2.74 (2H, m, CH\(_2\)Ph endo-334c; 1H, m, OCH\( H'_{\text{endo}-334c} \); 2H, m, CH\(_2\)Ph exo-334c; 1H, m, CHC(O) exo-334c), 2.63–2.55 (1H, m, NCH exo-334c; 1H, m, CH\(_2\)'CH\(_2\)Ph endo-334c), 2.50–2.46 (1H, m, NCH endo-334c), 2.42–2.34 (1H, m, CH\(_2\)'CH\(_2\)Ph exo-334c), 2.31–2.17 (1H, m, CH\(_2\)'CH\(_2\)Ph endo-334c; 1H, m, CH\(_2\)'CH\(_2\)Ph exo-334c), 1.37 (3H, t, \( J = 7.1 \), CH\(_2\)CH\(_3\) exo-334c), 1.34 (3H, t, \( J = 7.1 \), CH\(_2\)CH\(_3\) endo-334c), 0.98–0.85 (2H, m, CH(CH\(_2\))\(_2\) endo-334c; 4H, m, CH(CH\(_2\))\(_2\)' exo-334c), 0.82–0.78 (2H, m, CH(CH\(_2\))\(_2\) exo-334c); \(^{13}\)C NMR (150 MHz; CDCl\(_3\)) 176.7 (C(O)), 175.9 (C(O)), 175.4 (C(O)), 174.4 (C(O)), 167.0 (COEt), 164.1 (COEt), 142.0 (Ar), 141.6 (Ar), 128.4 (Ar), 128.4 (Ar), 128.3 (Ar), 126.0 (Ar), 125.8 (Ar), 99.4 (C=CH exo-334c), 96.5 (C=CH endo-334c), 89.6 (COCH), 89.3 (COCH), 80.1 (COCH), 78.2 (COCH), 66.7 (OCH\(_2\)), 66.6 (OCH\(_2\)), 53.8 (CHC(O) exo-334c), 50.6
(OCHCHCH endo-334c), 49.0 (OCHCHCH endo-334c), 48.5 (CHC(O) exo-334c), 31.8 (CH2), 30.7 (CH2), 30.3 (CH2), 29.3 (CH2), 22.2 (NCH), 21.9 (NCH), 14.3 (CH2CH3), 14.3 (CH2CH3), 5.0 (NCHCH2), 5.0 (NCHCH2), 4.9 (NCHCH2), 4.6 (NCHCH2); HRMS (Cl+) found [M+H]’ 354.1708; C21H24NO4 requires 354.1705.

(3aS,4R,7R,7aR)-5,5-Diethoxy-2-methyl-4-phenethylhexahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (endo-335) and (3aR,4R,7R,7aS)-5,5-Diethoxy-2-methyl-4-phenethylhexahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (exo-335)

A solution of [PPh3AuNTf2]2PhMe (60 mg, 1.0 mol%, 2.0 mol% [Au]) in EtOH (1.9 mL) was added dropwise to a stirring solution of propargylic alcohol 316a (1.00 g, 3.81 mmol) and N-methylmaleimide (0.508 g, 4.57 mmol) in EtOH (5.7 mL) at RT. The resulting solution was stirred for 16 h before being filtered through an aminopropyl cartridge, eluting with EtOAc. The filtrate was concentrated in vacuo to give the crude product (endo:exo = 70:30), which was purified by flash column chromatography (0 to 100% TBME:cyclohexane) to give the cantharimide endo-335 (276 mg, 0.740 mmol, 19%). Further elution of the column gave a mixture of the cantharimides endo-335 and exo-335 (528mg, 1.41 mmol, 37%). Further elution of the column gave the cantharimide exo-335 (228 mg 0.605 mmol, 16%).

Cantharimide endo-335: Isolated as a white crystalline solid. m.p. = 123–125 °C; Rf = 0.61 (1:1 cyclohexane:EtOAc); νmax (film/cm−1) 2973s (C-H), 1772w, 1697s (C=O), 1431s; 1H NMR (400 MHz; CDCl3) 7.34–7.28 (2H, m, ArH), 7.26–7.18 (3H, m, ArH), 4.75 (1H, t, J = 6.3, COCH), 3.67–3.62 (1H, m, OCHC(CH3)), 3.50–3.42 (2H, m, OCHCH2; OCH2), 2.87–2.79 (4H, m, NCH3; PhCH2H'), 2.75–2.66 (1H, m, PhCHH'), 2.48–2.40 (1H, m, PhCH2CHH'), 2.37–2.31 (1H, m, CHH'(OEt)2), 2.08–1.99 (1H, m, PhCH2CHH'), 1.41 (1H, d, J = 13.7, CHH'(OEt)2), 1.12 (3H, t, J= 7.1, CH3CH3), 0.95 (3H, t, J= 7.1, CH3CH3); 13C NMR (100 MHz; CDCl3) 175.8 (C(O)), 174.8 (C(O)), 142.4 (Ar), 128.9 (Ar), 128.6 (Ar), 126.3 (Ar), 107.6
(C(OEt)₂, 92.9 (COCH), 75.4 (COCH), 58.3 (OCH₂), 55.9 (OCH₂), 52.4 (OCHCHCH),
49.8 (OCHCHCH), 38.9 (CH₂C(OEt)₂), 31.9 (CH₂), 30.1 (CH₂), 24.8 (NCH₃), 15.3 (CH₂CH₃), 15.2 (CH₂CH₃); HRMS (Cl⁺) found [M+H]+ 374.1971; C₁₂H₂₈NO₅ requires 374.1968.

**Cantharimide exo-335**: Isolated as a colorless oil. R_{f} = 0.48 (1:1 cyclohexane:EtOAc);
^{1}H NMR (400 MHz; CDCl₃); 7.38–7.16 (5H, m, ArH), 4.82 (1H, d, J = 5.9, COCH), 3.29 (1H, d, J = 7.1, CHC(O)), 3.10 (1H, d, J = 7.1, CHC(O)), 3.03 (3H, s, NCH₃), 2.89–2.76 (1H, m, CH'H'CH₂Ph), 2.63–2.44 (2H, m, CH'H'CH'H'Ph), 2.44–2.31 (1H, m, CH'H'Ph; 1H, m, CH'H'(OEt)₂), 1.71 (1H, d, J = 13.0, CH'H'(OEt)₂), 1.27 (3H, t, J = 7.0, CH₂CH₃), 1.18 (3H, t, J = 7.1, CH₂CH₃); ^{13}C NMR (100 MHz; CDCl₃) 177.1 (C(O) ketone), 177.0 (C(O) imide), 142.7 (Ar), 128.5 (Ar), 128.3 (Ar), 125.8 (Ar), 108.0 (C(OEt)₂), 91.4 (COCH), 77.2 (COCH), 58.5 (OCH₂), 57.5 (OCH₂), 51.2 (CHC(O)), 46.8 (CHC(O)), 41.4 (CH₂C(OEt)₂), 30.6 (CH₂), 29.4 (CH₂), 25.1 (NCH₃), 15.3 (CH₂CH₃), 15.1 (CH₂CH₃).

(3aS,4S,7R,7aR)-2-Methyl-4-phenyltetrahydro-1H-4,7-epoxyisoindole-
1,3,5(2H,6H)-trione (336)

A solution of cantharimide endo-330e (290 mg, 0.970 mmol) in EtOAc (5.0 mL) was
loaded onto silica plug (SCX-2, 20 g), which was then washed with EtOAc after
10 minutes. The filtrate was concentrated in vacuo to give the crude product, which was
treated with cyclohexane (5.0 mL), sonicated and filtered to give the cantharimide 336 as
a white crystalline solid (210 mg, 0.775 mmol, 80%); m.p. 171–173 °C; R_{f} = 0.45 (2:1
petrol 40–60 °C:EtOAc); ν_{max} (film/cm⁻¹) 2988s (C-H), 1765s (C=O), 1694s (C=O),
1500s; ^{1}H NMR (400 MHz; CDCl₃) 7.76–7.72 (2H, m, ArH), 7.47–7.38 (3H, m, ArH),
5.31 (1H, t, J = 6.0, OCH), 3.95 (1H, dd, J = 9.1, 6.0, OCHCHCH), 3.66 (1H, d, J = 9.1,
PhCCH), 3.00 (3H, s, NCH₃), 2.85 (1H, dd, J = 18.3, 6.0, Ha), 4.32 (1H, d, J = 18.3, Hb);
^{13}C NMR (100 MHz; CDCl₃) 204.7 (C(O) ketone), 173.8 (C(O) imide), 172.3 (C(O) imide),
132.3 (Ar), 128.9 (Ar), 128.5 (Ar), 126.5 (Ar), 90.6 (PhCO), 74.7 (COCH), 53.2 (PhCCH), 51.5 (OCHCH), 41.7 (CH₂), 25.2 (NCH₃); HRMS (Cl⁺) found [M+H]+ 272.0920; C₁₅H₁₄NO₄ requires 272.0923.
(3aS,4S,5R,7R,7aR)-5-Hydroxy-2-methyl-4-phenylhexahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (337)

NaBH₄ (35 mg, 0.92 mmol) was added portionwise to a stirring solution of cantharimide 336 (50 mg, 0.18 mmol) in MeOH (1.8 mL) at 0 °C. The resulting solution was stirred at 0 °C for 1 h, before being filtered through a silica plug, eluting with EtOAc. The solvent was removed in vacuo to give the crude product, which was purified by flash column chromatography (0 to 100% TBME:cyclohexane) to give the cantharimide 337 as a white crystalline solid (35 mg, 0.13 mmol, 70%); m.p. = 185–187 °C; Rᵢ = 0.43 (1:1 cyclohexane:EtOAc); νₘₐₓ (film/cm⁻¹) 3388s br. (O-H), 2943w (C-H), 1763m, 1685s (C=O); 1492s; ¹H NMR (400 MHz; CDCl₃) 7.88–7.80 (2H, m, ArH), 7.51–7.42 (2H, m, ArH), 7.42–7.35 (1H, m, ArH), 4.98 (1H, t, J = 6.1, COC₄H), 4.28 (1H, dd, J = 9.7, 3.0, CHO), 3.77 (1H, dd, J = 10.0, 6.1, 1.8, COCH₃CH₃), 3.50 (1H, d, J = 10.0, PhCCH₃C(O)), 3.06 (3H, s, NCH₃), 2.57 (1H, dddd, J = 13.8, 9.7, 6.1, 1.8, Hₐ), 1.96 (1H, br. s, OHH), 1.63 (1H, dd, J = 13.8, 3.0 Hₐ); ¹³C NMR (100 MHz; CDCl₃) 175.4 (C (O)), 175.1 (C (O)), 138.3 (Ar), 128.8 (Ar), 128.4 (Ar), 125.7 (Ar), 91.8 (PhC), 79.5 (COH), 77.7 (COCH), 53.0 (COCH₃), 36.1 (CH₃), 25.0 (NCH₃); HRMS (CI⁺) found [M+H]⁺ 274.1075; C₁₅H₁₆NO₄ requires 274.1079.

(3aS,4S,5R,7R,7aR)-5-Ethoxy-2-methyl-4-phenylhexahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (338)

A solution of cantharimide endo-325e (52 mg, 0.17 mmol) in EtOH (3.5 mL) was added to a flask primed with 10% Pd/C (30 mg, 0.28 mmol) at RT. The flask was placed under an atmosphere of hydrogen gas (1 atm.) and stirred at RT for 16 h, before the reaction mixture was filtered through Celite and the filtrate concentrated in vacuo to give the cantharimide 338 as a white crystalline solid (39 mg, 0.13 mmol, 76%); m.p. = 152–154 °C; Rᵢ = 0.65 (1:1 cyclohexane:EtOAc); νₘₐₓ (film/cm⁻¹) 2977s (C-H), 1775m, 1699s
(C=O), 1433s; $^1$H NMR (400 MHz; CDCl$_3$) 7.83 (2H, d, $J = 7.3$, ArH), 7.47–7.40 (2H, m, ArH), 7.40–7.34 (1H, m, ArH), 4.96 (1H, t, $J = 6.1$, COCH), 3.95 (1H, dd, $J = 9.8$, 3.2, CHOEt), 3.80–3.72 (1H, m, COCHCHCH), 3.52 (1H, d, $J = 9.8$, PhCCHC(O)), 3.38–3.31 (1H, m, OCHH$^+$), 3.12–3.11 (1H, m, OCHH$^+$), 3.04 (3H, s, NCH$_3$), 2.55–2.46 (1H, m, $H_a$), 1.66 (1H, dd, $J = 13.7$, 3.2, $H_b$), 1.04 (3H, t, $J = 7.0$, CH$_2$C$H_3$); $^{13}$C NMR (100 MHz; CDCl$_3$) 175.3 (C(O)), 174.5 (C(O)), 139.3 (Ar), 128.5 (Ar), 128.1 (Ar), 126.0 (Ar), 91.4 (PhC), 85.9 (CHOEt), 77.4 (COCH), 66.8 (OCH$_2$), 53.0 (CHC(O)), 52.9 (CHC(O)), 35.6 (CH$_3$), 24.9 (NCH$_3$), 15.1 (CH$_2$C$H_3$); HRMS (Cl$^+$) found [M+H]$^+$ 302.1399; C$_{17}$H$_{20}$NO$_4$ requires 302.1392.

(3a$S$,4$S$,5$R$,6$S$,7$S$,7$aR$)-5-Ethoxy-6-hydroxy-2-methyl-4-phenylhexahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (339)

A solution of 9-BBN (0.50 M in THF, 1.7 mL, 0.85 mmol) was added dropwise to a stirring solution of cantharimide endo-330e (50 mg, 0.17 mmol) in anhydrous THF (0.85 mL) at 0 °C. The resulting reaction mixture was stirred at 0 °C for 5 h before the reaction was treated with 2.0 M aq. NaOH (2.0 mL) and hydrogen peroxide (30% in water, 1.0 mL) at 0 °C. The resulting mixture was stirred at RT for 16 h before the reaction was quenched with 10% aq. Na$_2$S$_2$O$_3$ (10 mL) and extracted with EtOAc (3 × 20mL). The combined organic fractions were dried (phase separator) and concentrated in vacuo to give the crude product, which was purified by flash column chromatography (0 to 100% TBME:cyclohexane) to give the cantharimide 339 as a white crystalline solid (28 mg 0.088 mmol, 52%); m.p. = 216–218 °C; $R_f$ = 0.65 (1:1 petrol 40–60 °C:EtOAc); $\nu_{max}$ (film/cm$^{-1}$) 3447m br. (O-H), 2973w (C-H), 1774w, 1695s (C=O), 1434; $^1$H NMR (400 MHz; DMSO-d$_6$) 7.77–7.70 (2H, m, ArH), 7.47–7.41 (2H, m, ArH), 7.40–7.34 (1H, m, ArH), 5.65 (1H, d, $J = 4.6$, COH), 4.61 (1H, dd, $J = 7.0$, 1.5, COCH), 3.78 (1H, dd, $J = 9.7$, 1.5, OCHH(O)), 3.67 (1H, dd, $J = 4.6$, 1.5, CHOH), 3.59–3.56 (1H, m, CHOEt), 3.39 (1H, d, $J = 9.7$, PhCCHC(O)), 3.27–3.19 (2H, m, OCH$_2$), 2.84 (3H, s, NCH$_3$), 0.95 (3H, t, $J = 7.0$, CH$_2$C$H_3$); $^{13}$C NMR (100 MHz DMSO-d$_6$) 175.2 (C(O)), 174.3 (C(O)), 139.6 (Ar), 128.7 (Ar), 128.5 (Ar), 126.4 (Ar), 95.8 (COEt), 90.3 (PhC), 83.4 (PhCOCH), 76.1 (CHOH), 66.4 (OCH$_2$), 52.1 (PhCCHC(O)), 50.1 (OCHCHC(O)), 41.1 (PhCOH), 38.8 (PhH), 30.2 (PhH), 24.9 (NCH$_3$), 15.1 (CH$_2$C$H_3$);
24.9 (NCH₃), 15.3 (CH₂CH₃); HRMS (CI⁺) found [M+H]⁺ 318.1342; C₁₇H₂₀NO₅ requires 318.1342; Weak (but real) ROE between CHO and NCH₃; No significant ROE between CHOEt and NCH₃.

(1R,2S,3R,4R)-Dimethyl 6-ethoxy-1-phenethyl-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (endo-343a) and Dimethyl (1R,2R,3S,4R)-6-ethoxy-1-phenethyl-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (exo-343)

Prepared from furan 325a (108 mg, 0.500 mmol) and dimethyl maleate according to the General Cycloaddition Procedure over 3 days to give the crude product (endo:exo = 12:1), which was purified by flash column chromatography (0 to 100% TBME:cyclohexane) to give a mixture of the enol ethers 343 as a colorless oil (125 mg, 0.347 mmol, 69%, endo:exo = 12:1); Rᵢ = 0.32 (3:1 cyclohexane:EtOAc); νmax (film/cm⁻¹) 2951s (C-H), 1739s (C=O), 1630s, 1435s; ¹H NMR (400 MHz; CDCl₃, endo-343) 7.35–7.19 (5H, m, ArH), 5.34 (1H, d, J = 2.0, C=C₃H), 5.03 (1H, dd, J = 2.0, 3.9, COCH), 3.91–3.84 (1H, m, OCH₂H'), 3.78–3.72 (1H, m, OCH₂H'), 3.65 (3H, s, OCH₃), 3.64 (3H, s, OCH₃), 3.49 (1H, dd, J = 9.8, 3.9, CH₃), 3.31 (1H, dd, J = 9.8, CH₃), 2.88–2.74 (2H, m, CH₂Ph), 2.46–2.38 (1H, m, CHH'CH₂Ph), 2.20–2.12 (1H, m, CHH'CH₂Ph), 1.30 (3H, t, J = 7.1, CH₂CH₃); ¹H NMR (400 MHz; CDCl₃, exo-343) the following peaks in the ¹H NMR spectra indicate the presence of exo-343; 5.19 (1H, d, J = 2.0, COCH), 5.11 (1H, d, J = 2.0, C=CH). The remaining resonances were obscured by the major diastereoisomers and could not be full assigned; ¹³C NMR (100 MHz; CDCl₃, endo-343) 171.2 (C(O)), 170.1 (C(O)), 163.0 (COEt), 142.1 (Ar), 128.4 (Ar), 125.9 (Ar), 99.2 (C=CH), 90.4 (COCH), 78.3 (COCH), 66.0 (OCH₂), 51.8 (CH or CH₃), 51.6 (CH or CH₃), 51.5 (CH or CH₃), 50.9 (CH or CH₃), 31.4 (CH₂), 30.6 (CH₂), 14.4 (CH₂CH₃); HRMS (CI⁺) found [M+H]⁺ 361.1654; C₂₀H₂₅O₆ requires 361.1651.
(1R,2R,3R,4R)-Dimethyl 6-oxo-1-phenethyl-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylate (3-endo-344a) and (1R,2S,3S,4R)-Dimethyl 6-oxo-1-phenethyl-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylate (3-exo-344a)

Prepared from furan 325a (108 mg, 0.500 mmol) and dimethyl fumarate according to the General Cycloaddition Procedure over 4 h to give the crude product (3-endo-344a: 3-exo-344a = 20:80), which was purified by flash column chromatography (0 to 100% TBME:cyclohexane) to give a mixture of the enol ethers 344a as a colorless oil (139 mg, 0.386 mmol, 77%; 3-endo-344a: 3-exo-344a = 20:80); Rf = 0.39 (2:1 cyclohexane:EtOAc); νmax (film/cm$^{-1}$) 2952s (C-H), 1736s (C=O), 1630s, 1436s; $^1$H NMR (400 MHz; DMSO-d$_6$) 7.35–7.18 (5H, m, ArH 3-endo-344a; 5H, m, ArH 3-exo-344a), 5.20 (1H, dd, J = 4.5, 2.0, COC$_2$H$_3$ 3-endo-344a), 5.18 (1H, d, J = 2.0, COC$_2$H$_3$ 3-exo-344a), 5.11 (1H, d, J = 2.0, C=C$_3$H$_7$ 3-endo-344a), 5.01 (1H, br. s, C=C$_3$H$_7$ 3-exo-344a), 3.94–3.55 (6H, m, 2 × CO$_2$CH$_3$ 3-endo-344a; 6H, m, 2 × CO$_2$CH$_3$ 3-exo-344a; 2H, m, OCHCHCH 3-endo-344a; 2H, m, OCH$_2$ 3-endo-344a; 2H, m, OCH$_2$ 3-exo-344a), 3.20 (1H, d, J = 3.9, CHCO$_2$Me 3-exo-344a), 3.06 (1H, d, J = 3.9, CHCO$_2$Me 3-exo-344a), 2.78–2.69 (1H, m, PhCH' 3-exo-344a), 2.66–2.54 (2H, m, PhCH$_2$ 3-endo-344a; 1H, m, PhCH' 3-exo-344a), 2.35–2.26 (1H, m, CHH'CH$_2$Ph 3-exo-344a), 2.20–2.08 (1H, m, CHH'CH$_2$Ph 3-endo-344a; 1H, m, CHH'CH$_2$Ph 3-exo-344a), 1.78–1.69 (1H, m, CHH'CH$_2$Ph 3-endo-344a), 1.25 (3H, t, J = 7.0, CH$_2$CH$_3$ 3-endo-344a), 1.19 (3H, t, J = 7.1, CH$_2$CH$_3$ 3-exo-344a);$^{13}$C NMR (100 MHz; DMSO-d$_6$) 172.7 (C(O)), 172.1 (C(O)), 171.3 (C(O)), 170.8 (C(O)), 165.6 (COEt), 163.4 (COEt), 142.1 (Ar), 142.0 (Ar), 128.9 (Ar), 128.8 (Ar), 128.6 (Ar), 128.5 (Ar), 126.4 (Ar), 126.3 (Ar), 100.3 (C=CH), 99.3 (C=CH), 90.7 (COCH), 89.4 (COCH), 80.6 (COCH), 78.4 (COCH), 66.9 (OCH$_2$), 66.4 (OCH$_2$), 54.2 (CH or CH$_3$), 52.6 (CH or CH$_3$), 52.5 (CH or CH$_3$), 52.4 (CH or CH$_3$), 50.6 (CH), 50.4 (CH), 31.2 (CH$_2$), 31.0 (CH$_2$), 30.6 (CH$_2$), 30.0 (CH$_2$), 14.6 (CH$_2$CH$_3$), 14.3 (CH$_2$CH$_3$); HRMS (CI') found [M+H]$^+$ 361.1658; C$_{20}$H$_{25}$O$_6$ requires 361.1651.
(1R,2R,3R,4R)-Diethyl 6-oxo-1-phenethyl-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylate (3-endo-344b) and (1R,2S,3S,4R)-Diethyl 6-oxo-1-phenethyl-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylate (3-exo-344b)

Prepared from furan 325a (108 mg, 0.500 mmol) and diethyl fumarate according to the General Cycloaddition Procedure over 4 h to give the crude product (3-endo-344b: 3-exo-344b = 15:85), which was purified by flash column chromatography (0 to 100% TBME:cyclohexane) to give a mixture of the enol ethers 344b as a colorless oil (172 mg, 0.443 mmol, 89%, 3-endo-344b: 3-exo-344b = 15:85); Rf = 0.83 (1:1 cyclohexane:EtOAc); v_max (film/cm⁻¹) 2981s (C-H), 1731s (C=O), 1629s; ¹H NMR (400 MHz; MeOH-d₄) 7.31–7.14 (5H, m, ArH 3-endo-344b; 5H, m, ArH 3-exo-344b), 5.18 (1H, d, J = 2.0, C=C 3-exo-344b), 5.14 (1H, dd, J = 4.4, 2.0, COC 3-endo-344b), 5.11–5.08 (1H, m, C=C 3-endo-344b; 1H, m, COC 3-exo-344b), 4.25–4.03 (4H, m, CO₂C₉H₉ 3-endo-344b; 4H, m, CO₂C₉H₉ 3-exo-344b), 3.87–3.76 (1H, m, OCHC₉H₉ 3-endo-344b; 2H, m, C=COC₉H₂ 3-endo-344b; 2H, m, C=COC₉H₂ 3-exo-344b), 3.29 (1H, d, J = 3.7, C₉H₉C(O) 3-exo-344b), 3.14 (1H, d, J = 3.7, C₉H₉C(O) 3-exo-344b), 2.92 (1H, d, J = 4.4, OCHCHCH₃ 3-endo-344b), 2.86–2.65 (2H, m, CH₂Ph 3-endo-344b; 2H, m, CH₂Ph 3-exo-344b), 2.46–2.39 (1H, m, CHH’CH₂Ph 3-exo-344b), 2.29–2.17 (1H, m, CHH’CH₂Ph 3-endo-344b; CHH’CH₂Ph 3-exo-344b), 1.86–1.78 (1H, m, CHH’CH₂Ph 3-endo-344b), 1.38–1.20 (9H, m, CH₂CH₃ 3-endo-344b; 9H, m, CH₂CH₃ 3-exo-344b); ¹³C NMR (100 MHz; CDCl₃) 172.6 (C(O)), 172.2 (C(O)), 171.0 (C(O)), 170.5 (C(O)), 165.9 (COEt), 162.8 (COEt), 142.0 (Ar), 141.9 (Ar), 128.1 (Ar), 128.0 (Ar), 127.9 (Ar), 127.8 (Ar), 125.6 (Ar), 125.5 (Ar), 99.2 (C=CH), 98.2 (C=CH), 90.9 (COCH), 89.4 (COCH), 80.9 (COCH), 78.5 (COCH), 66.4 (OCH₂), 65.9 (OCH₂), 60.8 (OCH₂), 60.8 (OCH₂), 60.7 (OCH₂), 60.6 (OCH₂), 54.3 (CHC(O)), 52.6 (CHC(O)), 50.2 (CHC(O)), 50.1 (CHC(O)), 31.2 (CH₂), 30.6 (CH₂), 30.2 (CH₂), 30.0 (CH₂), 13.3 (CH₂CH₃), 13.2 (CH₂CH₃), 13.2 (CH₂CH₃); HRMS (CI⁺) found [M+H]+ 389.1967; C₂₂H₂₉O₆ requires 389.1964.
Experimental Details

(1R,4R,5R)-1-Phenethyl-5-propionyl-7-oxabicyclo[2.2.1]heptan-2-one (endo-345), (1R,4R,5S)-1-Phenethyl-5-propionyl-7-oxabicyclo[2.2.1]heptan-2-one (exo-345) and (1R,4S)-1-Phenethyl-6-propionyl-7-oxabicyclo[2.2.1]heptan-2-one (345’)

Pent-1-en-3-one (49 μl, 0.50 mmol) was added to a stirring solution of furan 325a (54 mg, 0.25 mmol) in DMC (0.25 mL) in a sealed tube at RT. The resulting reaction mixture was stirred at 80 °C for 16 h before the reaction was allowed to cool to RT. The reaction mixture was filtered through a silica plug (SCX-2, 10 g) with EtOAc and the filtrate concentrated in vacuo to give the crude product (endo-345: exo-345: 345’ = 60:40:5), which was purified by flash column chromatography (0 to 100% TBME:cyclohexane) to give a mixture of the ketones 13 as a colorless oil (22 mg, 0.081 mmol, 32%, endo-345: exo-345: 345’ = 10:3:1, fraction A). Further elution of the column gave a second fraction of the ketones 13 as a colorless oil (19 mg, 0.070 mmol, 28%, endo-345: exo-345: 345’ = 1:12:1, fraction B); Rf = 0.47 (4:1 hexane:EtOAc); νmax (film/cm–1) 2939s (C-H), 1756s (C=O), 1715s (C=O), 1456s; HRMS (CI+) found [M+H]+ 273.1493; C17H21O3 requires 273.1491.

The three title compounds were not fully separated from each other. The following NMR assignments are based upon analysis of fractions A and B.

Ketone endo-345:

1H NMR (600 MHz; DMSO-d6) 7.30–7.26 (2H, m, ArH), 7.22–7.16 (3H, m, ArH), 5.13 (1H, t, J = 5.1, COCH), 3.60–3.57 (1H, m, CH(C(O)), 2.76–2.70 (1H, m, PhCHH’), 2.60–
2.45 (3H, m, CH₂CH₃; PhCH₂CH₂), 2.48 (1H, dd, J = 17.7, 5.1, H₆), 2.09–1.96 (2H, m, PhCH₂CH₂), 1.96 (1H, d, J = 17.7, H₆), 1.93 (1H, dd, J = 13.2, 4.9, H₈), 1.86 (1H, dd, J = 13.2, 10.5, H₇), 0.93 (3H, t, J = 7.2, CH₂CH₃); ¹³C NMR (150 MHz; DMSO-d₆) 211.0 (C(O)), 208.7 (C(O)), 141.6 (Ar), 128.4 (Ar), 128.1 (Ar), 125.9 (Ar), 88.5 (COCH), 74.9 (COCH), 53.9 (CH₃(O)Et), 40.9 (CH₆), 35.5 (CH₂CH₃), 30.8 (CH₆), 30.5 (PhCH₂CH₂), 29.8 (PhCH₂), 7.4 (CH₂CH₃).

Ketone exo-345:

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¹H NMR (400 MHz; MeOH-d₄) 7.34–7.11 (5H, m, ArH), 5.02 (1H, d, J = 6.1, COCH), 3.15 (1H, dd, J = 9.0, 4.9, CHC(O)), 2.81 (1H, ddd, J = 13.6, 11.7, 5.5, PhCH₂), 2.74–2.49 (4H, m, CH₂CH₃; PhCH₂CH₂); H₈, 2.30 (1H, d, J = 17.6, H₆), 2.20–2.02 (3H, m, PhCH₂CH₂; H₇), 1.80 (1H, dd, J = 13.2, 9.0, H₈), 1.08 (3H, t, J = 7.2, CH₂CH₃); ¹³C NMR (150 MHz; MeOH-d₄) 212.0 (C(O)), 209.6 (C(O)), 141.8 (Ar), 128.0 (Ar), 127.9 (Ar), 125.6 (Ar), 87.7 (COCH), 76.3 (COCH), 54.2 (CH(O)C), 43.7 (CH₆), 33.5 (CH₂CH₃), 30.8 (CH₆), 30.5 (PhCH₂CH₂), 30.0 (PhCH₂), 6.7 (CH₂CH₃).

Ketone exo-345⁺:

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¹H NMR (600 MHz; DMSO-d₆) 4.94 (1H, t, J = 5.7, COCH), 2.90 (1H, dd, J = 8.7, 5.3, CHC(O)), 2.50 (1H, dd, J = 17.7, 5.7, H₆), 2.29 (1H, d, J = 17.7, H₈), 2.21–2.17 (1H, m, H₇), 1.96 (1H, dd, J = 12.4, 8.7, H₈), 0.87 (3H, t, J = 7.2, CH₂CH₃); remaining peaks obscured by the major products.
Experimental Details

**Ethyl (1R,2R,4R)-5-oxo-4-phenethyl-7-oxabicyclo[2.2.1]heptane-2-carboxylate (endo-352) and Ethyl (1R,2S,4R)-5-oxo-4-phenethyl-7-oxabicyclo[2.2.1]heptane-2-carboxylate (exo-352)**

A solution of HfCl₄ (1.6 mg, 2.0 mol%) in DMC (0.06 mL) was added dropwise to a stirring solution of ethyl acrylate (41 µL, 38 mg, 0.38 mmol) and furan 325a (54 mg, 0.25 mmol) in DMC (0.18 mL). The resulting solution was stirred at RT for 6 h before it was filtered through a silica plug (SCX-2, 10 g) with EtOAc and the filtrate concentrated in vacuo to give a mixture of the enol ethers 352 as a colorless oil (64 mg, 0.22 mmol, 89%, endo:exo = 70:30; no evidence for a minor regioisomer); Rₓ = 0.73 (1:1 cyclohexane:EtOAc); νₓ (film/cm⁻¹) 2938s (C-H), 1762s (C=O), 1730s (C=O), 1604m, 1493m, 1454s; HRMS (ESI⁺) found [M+H]⁺ 289.1437; C₁₇H₂₁O₄ requires 289.1434. In order to aid characterisation a sample of the mixed product was separated by Mass Directed Automated Purification to give the two diastereoisomers.

**Ketone endo-352**: ¹H NMR (600 MHz; CDCl₃) 7.35–7.21 (2H, m, ArH), 7.26 (2H, d, J = 7.0, ArH), 7.25–7.22 (1H, m, ArH), 5.01 (1H, t, J = 5.4, COCH), 4.22 (2H, q, J = 7.2, OCH₂), 3.40 (1H, dt, J = 11.2, 5.4, CHCO₂Et), 2.85 (1H, td, J = 12.9, 5.0, PhCHH'), 2.71 (1H, td, J = 12.9, 5.0, PhCHH'), 2.57 (1H, dd, J = 17.8, 5.4, Hα), 2.38 (1H, d, J = 17.8, Hb), 2.29 (1H, ddd, J = 14.4, 12.9, 5.0, PhCH₂CH/H'), 2.18–2.12 (2H, m, PhCH₂CHH', CHH'CHCO₂Et), 2.08–2.02 (1H, m, CHH'CHCO₂Et), 1.32 (3H, t, J = 7.2, CH₂CH₃); ¹³C NMR (150 MHz; CDCl₃) 210.2 (CO₂Et), 171.3 (C(O)), 141.6 (Ar), 128.4 (Ar), 128.3 (Ar), 126.0 (Ar), 88.9 (COCH), 75.6 (COCH), 61.2 (OCH₂), 47.3 (CHCO₂Et), 41.4 (C(O)CH₂), 32.8 (CH₂CHCO₂Et), 30.9 (CH₂CH₂Ph), 30.2 (CH₂Ph), 14.2 (CH₂CH₃); No ROE between Hₗ and CHCO₂Et.

**Ketone exo-352**: ¹H NMR (600 MHz; CDCl₃) 7.31–7.27 (2H, m, ArH), 7.24–7.21 (2H, m, ArH), 7.21–7.17 (1H, m, ArH), 5.10 (1H, d, J = 6.1, COCH), 4.23 (2H, q, J = 7.2, OCH₂), 2.88 (1H, dd, J = 9.2, 4.8, CHCO₂Et), 2.83 (1H, td, J = 12.9, 5.0, PhCHH'), 2.67
(1H, td, J = 12.9, 5.0, PhCH'H'), 2.59 (1H, dd, J = 17.2, 6.1, Hb), 2.28–2.14 (4H, m, PhCH₂CH₂', Hb, CHH'CHCO₂Et), 1.90 (1H, dd, J = 13.6, 9.2, CHH'CHCO₂Et), 1.31 (3H, t, J = 7.2, CH₃); (150 MHz; CDCl₃) 211.2 (C(O)), 172.3 (C(O)), 141.6 (Ar), 128.4 (Ar), 128.4 (Ar), 126.0 (Ar), 88.0 (COCH), 77.3 (COCH), 61.4 (OCH₂), 47.9 (CHCO₂Et), 44.2 (C(O)CH₂), 32.4 (CH₂CHCO₂Et), 30.6 (PhCH₂CH₂), 30.3 (PhCH₂), 14.2 (CH₂CH₃); ROE between Hb and CHCO₂Et.

2-Methyl-4,5-dihydro-1H-naphtho[2,1-e]isoindole-1,3(2H)-dione (364)

A solution of Tf₂O (43 µL, 73 mg, 0.43 mmol) in CH₂Cl₂ (0.25 mL) was added to a stirring solution of cantharimide endo-330a (28 mg, 0.086 mmol) in CH₂Cl₂ (0.25 mL). The reaction was stirred for 16 h before the reaction was cooled to 0 °C and quenched with aq. sat. NaHCO₃ (10 mL) and diluted with CH₂Cl₂ (10 mL). The aq. extract was washed with CH₂Cl₂ (3 × 10 mL) and the combined organic extracts washed with brine (20 mL), dried (MgSO₄) and concentrated in vacuo to give the crude product. This was purified by flash column chromatography (2:1 petrol 40–60 °C:EtOAc) to give phthalimide 364 as a white crystalline solid (7 mg, 0.027 mmol, 31%); m.p. 160–162 °C; Rf = 0.40 (8:1 petrol 40–60 °C:EtOAc); vmax (film/cm⁻¹) 2942s (C-H), 1765s, 1705s (C=O), 1479s; ¹H NMR (600 MHz; CDCl₃) 8.02 (1H, d, J = 7.9, ArH), 7.78–7.75 (2H, m, ArH), 7.37–7.32 (2H, m, ArH), 7.31–7.29 (1H, m, ArH), 3.44 (2H, t, J = 7.2, CH₂), 3.18 (3H, s, CH₃), 2.91 (2H, t, J = 7.2, CH₂); ¹³C NMR (150 MHz; CDCl₃) 169.5 (C(O)), 168.4 (C(O)), 141.3 (Ar), 138.0 (Ar), 137.3 (Ar), 132.8 (Ar), 131.1 (Ar), 129.3 (Ar), 128.6 (Ar), 128.5 (Ar), 127.5 (Ar), 124.7 (Ar), 121.8 (Ar), 27.9 (CH₂), 24.0 (CH₃), 23.1 (CH₂); HRMS (CI⁺) found [M]+ 263.0949; C₁₇H₁₃NO₂ requires 263.0946.
Experimental Details

(3aS,3bR,9bS,11R,11aR)-9b-Methoxy-2-methyl-4,5,9b,10,11,11a-hexahydro-3b,11-epoxynaphtho[2,1-e]isoindole-1,3(2H,3aH)-dione (369) and (3aS,4R,5R,7R,7aR)-5-Hydroxy-2-methyl-4-phenethylhexahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (371)

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\text{TFA (0.50 mL) was added to a stirring solution of cantharimide endo-320 (46 mg, 0.15 mmol) in CH}_2\text{Cl}_2 (1.0 mL) at -78^\circ\text{C. The reaction was allowed to reach RT and stirred for 16 h before the reaction was quenched with aq. sat. NaHCO}_3 (10 mL) and diluted with CH}_2\text{Cl}_2 (10 mL). The aq. extract was washed with CH}_2\text{Cl}_2 (3 × 10 mL) and the combined organic extracts washed with brine (20 mL), dried (MgSO}_4) and concentrated in vacuo to give the crude product (369:370 = 3:1). This was partially purified by flash column chromatography (2:1 petrol 40–60 °C:EtOAc) to give a mixture of 369 and 370 (3:1). The mixture of products was then dissolved in hot MeOH (2.0 mL), cooled to 0 °C and treated with NaBH}_4 (10 mg, 0.31 mmol). The resulting suspension was stirred at 0 °C for 4 h before the reaction was diluted with CH}_2\text{Cl}_2 (10 mL) and treated with Amberlyst IRA743 boron scavenger (ca. 100 mg). The mixture was filtered and the solution concentrated in vacuo to give the crude product, which was purified by flash column chromatography (2:1 petrol 40–60 °C:EtOAc) to give the cantharimide 369 as a white crystalline solid (32 mg, 0.10 mmol, 69%); m.p. 174–176 °C; R}_f = 0.55 (1:1 petrol 40–60 °C:EtOAc); ν_max (film/cm^{-1}) 2934s (C-H), 1771s, 1693s (C=O), 1434s; ^1\text{H NMR (600 MHz; CDCl}_3) 7.27–7.22 (2H, m, ArH), 7.19 (1H, t, J = 7.1, ArH), 7.10 (1H, d, J = 7.7, ArH), 4.77 (1H, t, J = 6.2, OCH), 3.71 (1H, dd, J = 9.8, 6.2, OCHCH), 3.16 (1H, d, J = 9.8, OCHCHCH), 3.02–2.96 (4H, m, NCH}_3; ArCHH')}.
ArCHH'), 2.76 (3H, s, OCH3), 2.53 (1H, dd, J = 13.8, 6.2, Hα), 2.43 (1H, td, J = 14.2, 6.0, ArCH2CHH'), 2.34 (1H, dd, J = 14.2, 6.0, ArCH2CHH'), 2.25 (1H, d, J = 13.8, Hb); 13C NMR (150 MHz; CDCl3) 175.5 (C(=O)), 174.7 (C(=O)), 138.3 (C1), 135.8 (Ar), 128.5 (Ar), 127.6 (Ar), 127.5 (Ar), 91.2 (COCH), 82.7 (MeO), 76.9 (COCH), 54.6 (OCHCH), 54.3 (OCHCHCH), 53.1 (OCH3), 46.7 (CHa), 28.4 (ArCH2C), 26.0 (ArCH2CH2), 25.0 (NCH3); HRMS (CI+) found [M+H]+ 314.1382; C18H20NO4 requires 314.1387. A HMBC experiment measured JCH (C1, Hα) = 5.0 Hz (torsion angle ca. 0°); JCH (C1, Hb) = 1.0 Hz (torsion angle ca. 120°).

Further elution of the column gave the cantharimide 371 as a colorless oil (8 mg, 0.027 mmol, 18%); Rf = 0.23 (1:1 petrol 40–60 °C:EtOAc); νmax (film/cm–1) 3445s (O-H), 2927s (C-H), 1771s, 1691s (C=O), 1434s; 1H NMR (600 MHz; CDCl3) 7.31 (2H, t, J = 7.4, ArH), 7.27 (2H, d, J = 7.4, ArH), 7.22 (1H, t, J = 7.2, ArH), 4.77 (1H, t, J = 6.1, OCH), 4.23 (1H, m, CHOH), 3.64 (1H, dd, J = 9.7, 6.1, OCHCH), 3.20 (1H, d, J = 9.7, OCHCHCH), 3.00–2.88 (4H, m, NCH3; PhCHH'), 2.42–2.27 (3H, m, BnCH2; Hα), 1.98–1.95 (1H, m, OH), 1.49 (1H, dd, J = 13.8, 3.0, Hb), 1.25 (1H, m, PhCHH'); 13C NMR (150 MHz; CDCl3) 175.8 (C(=O)), 175.7 (C(=O)), 141.2 (Ar), 128.8 (Ar), 128.4 (Ar), 126.4 (Ar), 90.8 (BnCH2C), 77.7 (OCHCH), 75.5 (COH), 52.8 (OCHCH), 51.9 (OCHCHCH), 36.8 (HOCHCH2), 35.0 (BnCH2), 30.0 (PhCH2), 24.9 (NCH3); HRMS (CI+) found [M+H]+ 302.1385; C17H20NO4 requires 302.1387.

5-Ethoxy-2-methyl-4-phenylisoindoline-1,3-dione (368)

A solution of propargylic alcohol 316e (100 mg, 0.427 mmol) in EtOH (1.0 mL) was treated with N-methylmaleimide (57 mg, 0.51 mmol) and [PPh3AuNTf2]2PhMe (7 mg, 0.043 mmol, 2.0 mol% [Au]) at RT. The resulting solution was stirred at RT for 9 h before it was filtered through a silica plug, eluting with EtOAc, and the filtrate concentrated in vacuo to give the crude intermediate. This was then treated with EtOH (0.20 mL) and MsOH (2.0 mL) at RT and stirred for 16 h. The reaction was then diluted with water (30 mL) and EtOAc (30 mL) and the aq. extract washed EtOAc (3 × 20 mL). The combined organic extracts were then washed with 10% aq. K2CO3 (50 mL) and brine.
Experimental Details

(50 mL), dried (MgSO₄) and concentrated. The concentrated material was then treated with EtOH (0.20 mL) and MsOH (2.0 mL) at RT and stirred for 16 h. The reaction was then diluted with water (30 mL) and EtOAc (30 mL) and the a. extract washed EtOAc (3 × 20 mL). The combined organic extracts were then washed with 10% aq. K₂CO₃ (50 mL) and brine (50 mL), dried (MgSO₄) and concentrated in vacuo to give the crude product. This was purified by flash column chromatography (7:1 petrol 40–60 °C: EtOAc) to give the phthalimide 368 as a white crystalline solid (55 mg, 0.20 mmol, 47%); m.p. 93–95 °C; Rᵋ = 0.31 (7:1 petrol 40–60 °C:EtOAc); νₑₓₑₘₐₓ (film/cm⁻¹) 2922s (C-H), 1764m (C=O), 1709s (C=O), 1466s; ¹H NMR (600 MHz; CDCl₃) 7.80 (1H, d, J = 8.2, ArH), 7.46–7.40 (3H, m, ArH), 7.38–7.36 (2H, m, ArH), 7.15 (1H, d, J = 8.2, ArH), 4.09 (2H, q, J = 6.8, OCH₂), 3.07 (3H, s, NH₃); ¹³C NMR (150 MHz; CDCl₃) 168.2 (C=O), 167.8 (C=O), 161.2 (Ar), 132.0 (Ar), 130.5 (Ar), 130.3 (Ar), 130.2 (Ar), 128.3 (Ar), 127.7 (Ar), 124.3 (Ar), 124.0 (Ar), 115.5 (Ar), 65.1 (OCH₂), 23.9 (NCH₃), 14.5 (CH₂CH₃); HRMS (Cl⁺) found [M⁺] 281.1047; C₁₇H₁₅NO₃ requires 281.1052.

(2S,3R,4S,E)-5-(2,2-Dimethylhydrazono)pentane-1,2,3,4-tetraol (441a)²⁴⁷

Prepared from L-arabinose (13.5 g, 90.0 mmol) according to the General Hydrazine Synthesis Procedure to give the hydrazone 441a as a white crystalline solid (17.1 g, 89.5 mmol, 99%); m.p. = 93–95 °C (lit. m.p. = 88–90 °C)²⁴⁷; Rᵋ = 0.24 (acetone); νₑₓₑₘₐₓ (film/cm⁻¹) 3420s (O-H), 3264s (O-H), 2938s (C-H), 1470s; ¹H NMR (600 MHz; DMSO-d₆) 6.61 (1H, d, J = 6.2, HC=N), 4.61 (1H, d, J = 5.8, CHO), 4.53 (1H, d, J = 5.7, CHO), 4.42 (1H, d, J = 7.2, CHO), 4.33 (1H, t, J = 5.6, CH₂OH), 4.23–4.19 (1H, m, N=CHCH), 3.66–3.55 (1H, m, CHH'=OH), 3.51–3.46 (1H, m, CHCH₂OH), 3.41–3.33 (1H, m, CHH'OH; HOD), 3.31–3.27 (1H, m, N=CHCHCH), 2.67 (6H, s, N(CH₃)₂); ¹³C NMR (150 MHz; DMSO-d₆) 138.5 (C=N), 73.8 (CHCH₂OH), 71.2 (N=CHCHCH), 70.5 (N=CHCH), 63.5 (CH₂OH), 42.6 (N(CH₃)₂); [α]D (20 °C) = −44.0 (MeOH, C = 1.0); data in accordance with the literature.²⁴⁷
(2R,3S,4S,E)-5-(2,2-Dimethylhydrazono)pentane-1,2,3,4-tetraol (441b)

Prepared from d-ribose (1.00 g, 6.67 mmol) according to the General Hydrazone Synthesis Procedure to give the hydrazone 441b as a white crystalline solid (1.26 g, 6.56 mmol, 98%); m.p. = 70–72 °C; Rf = 0.24 (acetone); \( \nu_{\text{max}} \) (film/cm\(^{-1}\)) 3335s br. (O-H), 2992s (C-H), 1597s, 1469s, 1444s; \(^1\)H NMR (600 MHz; DMSO-d\(_6\)) 6.56 (1H, d, \( J = 6.4, \text{N} = \text{CH} \)), 4.85 (1H, d, \( J = 5.1, \text{CHOH} \)), 4.63 (1H, d, \( J = 5.3, \text{CHOH} \)), 4.48 (1H, d, \( J = 4.9, \text{CHOH} \)), 4.31 (1H, t, \( J = 5.7, \text{CH}_2\text{OH} \)), 4.12–4.09 (1H, m, N=CHCH), 3.57–3.54 (1H, m, CH\(_2\)OH), 3.46–3.35 (3H, m, CH\(_2\)OH), 2.67 (6H, s, N(CH\(_3\))\(_2\)); \(^{13}\)C NMR (150 MHz; DMSO-d\(_6\)) 137.4 (N=CH), 74.4 (CH), 72.3 (CH), 72.2 (CH), 63.2 (CH\(_2\)), 42.6 (N(CH\(_3\))\(_2\)); HRMS (ESI\(^{+}\)) found [M+H]\(^+\) 193.1180; C\(_7\)H\(_{17}\)N\(_2\)O\(_4\) requires 193.1188; \([\alpha]_D^{(20 \degree C)} = -22.6 \text{ (MeOH, C = 1.0)}.\)

(2R,3R,4R,E)-5-(2,2-Dimethylhydrazono)pentane-1,2,3,4-tetraol (441c)

Prepared from d-lyxose (1.00 g, 6.67 mmol) according to the General Hydrazone Synthesis Procedure to give the hydrazone 441c as a white crystalline solid (1.26 g, 6.56 mmol, 98%); m.p. = 73–75 °C; Rf = 0.14 (acetone); \( \nu_{\text{max}} \) (film/cm\(^{-1}\)) 3336s br. (O-H), 2865s (C-H), 1599s, 1468s, 1443s; \(^1\)H NMR (600 MHz; DMSO-d\(_6\)) 6.56 (1H, d, \( J = 6.2, \text{N} = \text{CH} \)), 4.84 (1H, d, \( J = 5.3, \text{CHOH} \)), 4.45 (1H, t, \( J = 5.6, \text{CH}_2\text{OH} \)), 4.22 (1H, d, \( J = 6.6, \text{CHOH} \)), 4.19 (1H, d, \( J = 7.2, \text{CHOH} \)), 4.01–3.96 (1H, m, N=CHCH), 3.66–3.62 (1H, m, CH\(_2\)OH), 3.43–3.38 (2H, m, N=CHCHCH, CHH\(^{\text{I}}\)OH), 3.37–3.33 (1H, m, CH\(_2\)OH; HOD), 2.68 (6H, s, N(CH\(_3\))\(_2\)); \(^{13}\)C NMR (150 MHz; DMSO-d\(_6\)) 138.5 (N=C), 72.8 (N=CHCHCH), 71.0 (N=CHCH), 70.3 (CH\(_2\)OH), 62.8 (CH\(_2\)OH), 42.6 (N(CH\(_3\))\(_2\)); HRMS (ESI\(^{+}\)) found [M+H]\(^+\) 193.1196; C\(_7\)H\(_{17}\)N\(_2\)O\(_4\) requires 193.1188; \([\alpha]_D^{(20 \degree C)} = +16.4 \text{ (MeOH, C = 0.58)}.\)
Experimental Details

(2S,3S,4S,5S,E)-1-(2,2-Dimethylhydrazono)hexane-2,3,4,5-tetraol (441e)

Prepared from l-rhamnose monohydrate (2.58 g, 14.2 mmol) according to the General Hydrazine Synthesis Procedure to give the hydrazone 441e as a white crystalline solid (2.90 g, 14.1 mmol, 99%); m.p. = 101–103 °C; R<sub>f</sub> = 0.30 (acetone); ν<sub>max</sub> (film/cm<sup>-1</sup>) 3347 s (O-H), 2920 w (C-H), 1611 m, 1444 s; <sup>1</sup>H NMR (600 MHz; DMSO-d<sub>6</sub>) 6.57 (1H, d, J = 6.0, N=C<sub>H</sub>), 4.82 (1H, d, J = 5.3, CHO<sub>H</sub>), 4.41 (1H, d, J = 5.6, CHO<sub>H</sub>), 4.12 (1H, d, J = 7.7, CHO<sub>H</sub>), 4.08 (1H, d, J = 7.2, CHO<sub>H</sub>), 3.98–3.93 (1H, m, N=CHC<sub>H</sub>), 3.64–3.60 (1H, m, N=CHCHC<sub>H</sub>), 3.59–3.53 (1H, m, CH<sub>2</sub>O<sub>H</sub>), 3.44–3.36 (3H, m, CH<sub>2</sub>O<sub>H</sub>, CH<sub>3</sub>OH), 2.67 (6H, s, N(C<sub>H</sub><sub>3</sub>)<sub>2</sub>); <sup>13</sup>C NMR (150 MHz; DMSO-d<sub>6</sub>) 138.8 (N=C), 73.5 (CH), 71.1 (CH), 66.3 (CH), 42.6 (N(CH<sub>3</sub>)<sub>2</sub>), 20.8 (CH<sub>3</sub>); HRMS (ESI<sup>+</sup>) found [M+H]<sup>+</sup> 207.1347; C<sub>8</sub>H<sub>19</sub>N<sub>2</sub>O<sub>4</sub> requires 207.1345; [α]<sub>D</sub> (20 °C) = +4.1 (MeOH, C = 1.3).

(2R,3S,4R,5S,E)-6-(2,2-Dimethylhydrazono)hexane-1,2,3,4,5-pentaol (441f)<sup>247</sup>

A stirring solution of d-galactose (1.80 g, 10.0 mmol) in MeOH (20 mL, 0.50 M) was treated with NH<sub>2</sub>NMe<sub>2</sub> (1.5 mL, 1.2 g, 20 mmol) and Amberlyst 15 (2.00 g) at RT and the reaction stirred at RT for 3 days. The reaction was then filtered and the filtrate concentrated in vacuo to give the crude product, which was purified by flash column chromatography (acetone) to give the hydrazone 441f as a yellow crystalline solid (680 mg, 3.06 mmol, 31%); m.p. = 106–108 °C (lit. m.p. = 96–100 °C)<sup>247</sup>; R<sub>f</sub> = 0.20 (1:5 MeOH:acetone); ν<sub>max</sub> (film/cm<sup>-1</sup>) 3362 s (O-H), 2931 s (C-H), 1593 s, 1469 s, 1412 s; <sup>1</sup>H NMR (600 MHz; DMSO-d<sub>6</sub>) 6.65 (1H, d, J = 6.0, N=CH), 4.53 (1H, d, J = 6.0, N=CH), 4.08 (1H, d, J = 7.2, CHO), 3.98–3.93 (1H, m, N=CHCH), 3.59–3.53 (1H, m, CHCH<sub>3</sub>), 3.32–3.29 (1H, m, CHCHCH<sub>3</sub>), 2.66 (6H, s, N(CH<sub>3</sub>)<sub>2</sub>), 1.10 (3H, d, J = 6.2, CHCH<sub>3</sub>); <sup>13</sup>C NMR (150 MHz; DMSO-d<sub>6</sub>) 138.8 (N=C), 73.5 (CH), 71.1 (CH), 66.3 (CH), 42.6 (N(CH<sub>3</sub>)<sub>2</sub>), 20.8 (CH<sub>3</sub>); HRMS (ESI<sup>+</sup>) found [M+H]<sup>+</sup> 207.1347; C<sub>8</sub>H<sub>19</sub>N<sub>2</sub>O<sub>4</sub> requires 207.1345; [α]<sub>D</sub> (20 °C) = +4.1 (MeOH, C = 1.3).
(CH$_2$)$_2$, 42.7 (N(CH$_3$)$_2$); [α]$_D$ (20 °C) = −30.0 (MeOH, C = 1.0); Data in accordance with the literature.

(2R,3S,4S)-2-((E)-(2,2-Dimethylhydrazono)methyl)tetrahydrofuran-3,4-diol (anti-443a) and (2S,3S,4S)-2-((E)-(2,2-Dimethylhydrazono)methyl)tetrahydrofuran-3,4-diol (syn-443a)

Experiment A (6.60 mmol scale): Prepared from hydrazone 441a (1.26 g, 6.60 mmol) according to the General Acid-Catalyzed Cyclization Procedure, to give the crude product (anti: syn = 75:25). This was purified by flash column chromatography (80:100 hexane:acetone) to give the tetrahydrofuran 443a (772 mg, 4.44 mmol, 67%, anti: syn = 75:25).

Experiment B (104 mmol scale): Prepared from hydrazone 441a (20.0 g, 104 mmol) according to the General Acid-Catalyzed Cyclization Procedure, to give the crude product (anti: syn = 75:25). This was purified by flash column chromatography (80:100 hexane:acetone) to give a mixture of the tetrahydrofuran anti-443a and the tetrahydrofuran syn-443a (11.9 g, 68.3 mmol, 66%, anti: syn = 75:25).

**Tetrahydrofuran anti-443a:** Isolated as a single stereoisomer following recrystallization from boiling CPME. Isolated as a white crystalline solid; m.p. = 65–67 °C; R$_f$ = 0.33 (1:1 acetone:hexane); $\nu_{\text{max}}$ (film/cm$^{-1}$) 3415s br. (O-H), 2875s (C-H), 1586s, 1467s, 1445s; $^1$H NMR (600 MHz; MeOH-d$_4$) 6.51 (1H, d, $J$ = 6.6, N=C=CH), 4.23–4.18 (2H, m, N=CHC=CH, CH$_2$CH), 4.08 (1H, dd, $J$ = 9.6, 4.9, OCH$H'$), 4.02 (1H, dd, $J$ = 7.3, 5.1, N=CHCH$H$), 3.76–3.72 (1H, m, OCH$_2$H), 2.79 (6H, s, N(CH$_3$)$_2$); $^{13}$C NMR (150 MHz; MeOH-d$_4$) 135.6 (C=N), 82.5 (CHCH$_2$), 76.5 (N=CHCHCH), 73.9 (OCH$_2$), 72.4 (CH$_2$CHCH), 42.8 (N(CH$_3$)$_2$); HRMS (EI$^+$) found [M]$^+$ 174.0979; C$_7$H$_{14}$N$_2$O$_3$ requires 174.0999; [α]$_D$ (20 °C) = +85.8 (anti-443a, MeOH, C = 1.4).

**Tetrahydrofuran syn-443a:** $^1$H NMR (600 MHz; MeOH-d$_4$) 6.71 (1H, d, $J$ = 7.2, N=CH), 4.36–4.31 (2H, m, N=CHCH; CH$_2$CH), 4.15 (1H, t, $J$ = 4.8, CHCHCH$_2$), 3.91 (1H, dd, $J$ = 8.7, 6.2, OCH$H'$), 3.76–3.72 (1H, m, OCH$H'$), 2.79 (6H, s, N(CH$_3$)$_2$); $^{13}$C NMR
(150 MHz; MeOH-d$_4$) 135.6 (C=N), 83.1 (CHCH$_2$), 74.3 (N=CHCHCH), 73.2 (N=CHCH), 72.5 (OCH$_2$), 42.8 (N(CH$_3$)$_2$).

**(2S,3R,4R)-2-**((E)-(2,2-Dimethylhydrazono)methyl)tetrahydrofuran-3,4-diol (*ent-syn*-443a) and **(2R,3R,4R)-2-**((E)-(2,2-Dimethylhydrazono)methyl)tetrahydrofuran-3,4-diol (*ent-syn*-443a)

Prepared from hydrazone 441b (1.16 g, 6.03 mmol) according to General Acid-Catalyzed Cyclization Procedure to give the crude product (*anti*: *syn* = 75:25). This was purified by flash column chromatography (80:100 hexane:acetone) the tetrahydrofuran 433a as a yellow oil (620 mg, 3.56 mmol, 59%, *anti*: *syn* = 75:25); $^1$H NMR consistent with 433a; $[\alpha]$D (20 °C) = –24.2 (*ent-syn* 433a, MeOH, C = 1.1).

**(2R,3R,4S)-2-**((E)-(2,2-Dimethylhydrazono)methyl)tetrahydrofuran-3,4-diol (**anti**-433b) and **((2S,3R,4S)-2-**((E)-(2,2-Dimethylhydrazono)methyl)tetrahydrofuran-3,4-diol (**syn**-433b)

**Method A:** Prepared from hydrazone 441c (1.22 g, 6.35 mmol) according to the General Acid-Catalyzed Cyclization Procedure to give the crude product (*d.r.* = 55:45). This was purified by flash column chromatography (80:100 hexane:acetone) to give the tetrahydrofuran 433b (731 mg, 4.20 mmol, 66%, *d.r.* = 55:45).

**Method B:** Prepared according to the General Hydrazone Synthesis Procedure from D-xylose (1.00 g, 6.67 mmol) to give a crude hydrazone, which was subjected to the General Acid-Catalyzed Cyclization Procedure to give the crude product (*d.r.* = 55:45). This was purified by flash column chromatography (80:100 hexane:acetone) to give a mixture of the tetrahydrofurans 433b as a yellow oil (711 mg, 4.09 mmol, 61% over 2 steps from D-xylose, *d.r.* = 55:45).
Isolated as a yellow oil; R_f = 0.20 (1:1 acetone:hexane); ν_max (film/cm^{-1}) 3360s br. (O-H), 2875s (C-H), 1595s, 1470s, 1445s; ^1H NMR (600 MHz; D_2O) 6.92 (1H, d, J = 6.6, N=CH major), 6.88 (1H, d, J = 6.4, N=CH minor), 4.60 (1H, d, J = 6.4, 3.6, N=CHCH minor), 4.40–4.38 (1H, m, CHCH_2 minor), 4.35–4.33 (2H, m, CHCH_2, N=CHCH major), 4.26–4.23 (2H, m, CHCHCHH’ minor), 4.20–4.19 (1H, m, CHCHCH_2 major), 4.10 (1H, dd, J = 10.0, 4.1, CHH’ major), 3.98 (1H, dd, J = 10.0, 2.0, CHHF’ major), 3.83 (1H, dd, J = 10.0, 1.1, CHHF’ minor), 2.80 (6H, s, N(CH_3)_2 minor), 2.78 (6H, s, N(CH_3)_2 major); ^13C NMR (150 MHz; D_2O, with a MeOH standard) 140.6 (C=N), 138.1 (C=N), 85.3 (CH), 81.0 (CH), 80.9 (CH), 78.1 (CH), 77.2 (CH), 77.1 (CH), 73.8 (CH_2), 73.7 (CH_2), 43.0 (N(CH_3)_2); HRMS (EI^+ ) found [M]+ 174.0969; C_7H_14N_2O_3 requires 174.0999; [α]D (20 °C) = +45.6 (MeOH, C = 1.1).

(2R,3S,4R)-2-((E)-(2,2-Dimethylhydrazono)methyl)tetrahydrofuran-3,4-diol (ent-anti-433b) and ((2S,3S,4R)-2-((E)-(2,2-Dimethylhydrazono)methyl)tetrahydrofuran-3,4-diol (ent-syn-433b)

 Prepared according to the General Hydrazone Synthesis Procedure from L-xylose (1.00 g, 6.67 mmol) to give a crude hydrazone, which was subjected to the General Acid-Catalyzed Cyclization Procedure to give the crude product (d.r. = 55:45). This was purified by flash column chromatography (90:100 petroleum ether 40–60 °C:acetone) to give the tetrahydrofuran ent-433b as a yellow oil (656 mg, 3.77 mmol, 57% over 2 steps from L-xylose, d.r. = 55:45); ^1H NMR consistent with 443b; [α]D (20 °C) = −45.3 (MeOH C = 1.2).
Experimental Details

\((2S,3R,4R,5S)-2-((E)-(2,2-Dimethylhydrazono)methyl)-5-methyltetrahydrofuran-3,4-diol\) (\textit{anti}-433c) and \((2R,3S,4R,5S)-2-((E)-(2,2-Dimethylhydrazono)methyl)-5-methyltetrahydrofuran-3,4-diol\) (\textit{syn}-433c)

\[
\begin{align*}
\text{anti-433c} & \quad \text{syn-433c}
\end{align*}
\]

Prepared from hydrazone 431e (1.37 g, 6.65 mmol) according General Acid-Catalyzed Cyclization Procedure to give the crude product (\textit{d.r.} = 60:40). This was purified by flash column chromatography (80:100 hexane:acetone) to give the tetrahydrofuran 433c as a yellow oil (866 mg, 4.61 mmol, \textit{d.r.} = 60:40); \(R_f = 0.38\) (1:1 acetone:hexane); \(\nu_{\text{max}}\) (film/cm\(^{-1}\)) 3377 s br. (O-H), 2921 s (C-H), 1642 s, 1445 s; \(^1\)H NMR (600 MHz; MeOH-d\(_4\)) 6.64 (1H, d, \(J = 7.0\), N=C\(_{\text{H}}\) minor), 6.61 (1H, d, \(J = 6.4\), N=C\(_{\text{H}}\) major), 4.41 (1H, dd, \(J = 7.0\), 4.6, N=CHCH minor), 4.25 (1H, t, \(J = 6.4\), N=CHCH major), 4.03 (1H, t, \(J = 6.4\), N=CHCHCH minor), 4.01–3.98 (1H, m, N=CHCHCH minor), 3.88 (1H, quintet, \(J = 6.4\), CHCH\(_3\) major), 3.79–3.74 (2H, m, CHCHCH\(_3\) minor), 3.69 (1H, t, \(J = 6.4\), CHCHCH\(_3\) major), 2.81 (6H, s, N(CH\(_3\))\(_2\) minor), 2.79 (6H, s, N(CH\(_3\))\(_2\) major), 1.34 (3H, d, \(J = 6.0\), CHCH\(_3\) minor), 1.28 (3H, d, \(J = 6.4\), CHCH\(_3\) major); \(^{13}\)C NMR (150 MHz; MeOH-d\(_4\)) 136.1 (C=N major), 134.3 (C=N minor), 84.8 (CH minor), 84.1 (CH major), 83.7 (CH major), 82.7 (CH minor), 82.5 (CH minor), 81.8 (CH major), 80.9 (CH minor), 80.2 (CH major), 42.9 (N(CH\(_3\))\(_2\) major), 42.8 (N(CH\(_3\))\(_2\) minor), 19.6 (CHCH\(_3\) minor), 19.3 (CHCH\(_3\) major); HRMS (ESI\(^+\)) found [M+H]\(^+\) 189.1235; \(C_8H_{17}N_2O_3\) requires 189.1239; \([\alpha]_D^0\) (20 °C) = –33.2 (MeOH, C = 3.3).

\((2R,3S,4R,5R)-2-((E)-(2,2-Dimethylhydrazono)methyl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol\) (443d) and \((2S,3S,4S,5R)-2-((E)-(2,2-Dimethylhydrazono)methyl)tetrahydro-2H-pyran-3,4,5-triol\) (448)

\[
\begin{align*}
\text{443d} & \quad \text{448}
\end{align*}
\]

Prepared from hydrazone 441f (222 mg, 1.00 mmol) according to the General Acid-Catalyzed Cyclization Procedure to give the crude product (443d:448 = 60:40). This was
purified by flash column chromatography (30:70 hexane:acetone) to give the tetrahydrofuran 443d as a colorless oil (59 mg, 0.29 mmol, 29%). Further elution of the column gave the tetrahydropyran 436 as a colorless oil (49 mg, 0.24 mmol, 24%, 20% impurity of 433d).

**Tetrahydrofuran 443d:** R_f = 0.43 (70:30 acetone:hexane); ν_{max} (film/cm\(^{-1}\)) 3372s br. (O-H), 2898s (C-H), 1599w, 1444m, 1406m; \(^1\)H NMR (600 MHz; D\(_2\)O) 6.93 (1H, d, J = 6.0, N=CH), 4.22 (1H, dd, J = 9.4, 6.0, N=CHCH), 4.15–4.12 (1H, m, CHCHCH\(_2\)), 4.04 (1H, dd, J = 9.4, 3.2, N=CHCHCH), 4.01–3.98 (2H, m, CHH’), 2.89 (6H, s, N(CH\(_3\))\(_2\)); \(^1^3\)C NMR (150 MHz; D\(_2\)O with MeOH standard) 139.0 (C=N), 75.8 (CH), 70.0 (CH), 69.8 (CH), 67.6 (CH), 66.7 (CH\(_2\)), 43.0 (N(CH\(_3\))\(_2\)); HRMS (ES\(^+\)) found [M+H]\(^+\) 205.1181; C\(_8\)H\(_{17}\)N\(_2\)O\(_4\) requires 205.1188; [\(\alpha\)]\(_D\) (20 °C) = +1.2 (MeOH, C = 0.5).

**Tetrahydropyran 448:** Isolated with a 20% impurity of 443d; R_f = 0.28 (1:1 acetone:hexane); \(^1\)H NMR (600 MHz; D\(_2\)O) 6.97 (1H, d, J = 5.1, N=CH), 4.24 (1H, d, J = 5.1, N=CHCH), 4.16–4.11 (2H, m, CHH’, N=CHCHCH), 3.98–3.94 (1H, m, CHCH\(_2\)), 3.74 (1H, dd, J = 9.6, 3.4, CHCHCH\(_2\)), 3.37 (1H, t, J = 10.9, CHH’), 2.86 (6H, s, N(CH\(_3\))\(_2\)); \(^1^3\)C NMR (150 MHz; D\(_2\)O with MeOH standard) 139.1 (C=N), 79.1 (CH), 74.4 (CH), 71.4 (CH), 69.6 (CH\(_2\)), 66.9 (CH), 43.1 (N(CH\(_3\))\(_2\)).

(2S,3S,4S)-2-(Dihydroxymethyl)tetrahydrofuran-3,4-diol (anti-449a) and (2R,3S,4S)-2-(Dihydroxymethyl)tetrahydrofuran-3,4-diol (syn-449a)

Amberlyst 15 (6.90 g) was added to as stirring solution of hydrazone 443a (1.20 g, 6.90 mmol) in water (34 mL) at RT. After 5 minutes the reaction was filtered and concentrated in vacuo and lyophilized to give the hydrolyzed product as a white gum (894 mg); R_f = 0.42 (acetone); ν_{max} (film/cm\(^{-1}\)) 3345s br. (O-H), 2945s (C-H), 1720w, 1441m; [\(\alpha\)]\(_D\) (20 °C) = +36.9 (MeOH, C = 1.0).

Analysis of the \(^1\)H NMR in H\(_2\)O, D\(_2\)O, DMSO-d\(_6\) and MeOH-d\(_4\) suggested that the structure of the hydrolyzed product 449 was dependent on the solvent. In H\(_2\)O and D\(_2\)O
Experimental Details

(accounting for deuterium exchange) the NMR data was consistent with a mixture of (2S,3S,4S)-2-(dihydroxymethyl)tetrahydrofuran-3,4-diol \textit{anti-449}a and (2R,3S,4S)-2-(dihydroxymethyl)tetrahydrofuran-3,4-diol \textit{syn-449}a (\textit{anti:syn} = 85:15). In DMSO-d$_6$ and MeOH-d$_4$ the NMR data was consistent with a more complex composition [see Section 4.2.5. for further discussion].

(2S,3S,4S)-2-(Dihydroxymethyl)tetrahydrofuran-3,4-diol \textit{anti-449}a and (2R,3S,4S)-2-(Dihydroxymethyl)tetrahydrofuran-3,4-diol \textit{syn-449}a:

\[
\text{H} \quad \text{NMR (600 MHz; D}_2\text{O)} \quad 5.16 (1H, d, J = 7.2, \text{CH(OD)}_2 \text{syn-449a}), 5.04 (1H, d, J = 5.1, \text{CH(OD)}_2 \text{anti-449a}), 4.49 (1H, td, J = 7.2, 4.0, \text{CHCH}_2 \text{syn-449a}), 4.31–4.27 (1H, m, \text{CHCH}_2 \text{anti-449a}); 1H, m, \text{CHCHCH}_2 \text{syn-449a}), 4.24 (1H, t, J = 5.1, \text{CHCHCH}_2 \text{anti-449a}), 4.06–4.02 (1H, dd, J = 10.0, 3.0, \text{CHH'} \text{anti-449a}); 1H, m, \text{CHH'} \text{syn-449a}), 3.82 (1H, dd, J = 10.0, 3.0, \text{CHH'} \text{anti-449a}), 3.79 (1H, dd, J = 7.2, 4.0, \text{CHCH(OD)}_2 \text{syn-449a}), 3.75 (1H, t, J = 5.1, \text{CHCH(OD)}_2 \text{anti-449a}), 3.71 (1H, t, J = 7.2, \text{CHH'} \text{syn-449a}); \text{C} \text{NMR (150 MHz; D}_2\text{O with MeOH standard)} 90.4 (\text{C}\text{H(OD)}_2 \text{anti-449a}), 89.2 (\text{C}\text{H(OD)}_2 \text{syn-449a}), 84.2 (\text{CHCH(OD)}_2 \text{anti-449a}), 83.3 (\text{CHCH(OD)}_2 \text{syn-449a}), 73.0 (\text{CHCH}_2 \text{anti-449a}), 72.7 (\text{OCH}_2 \text{anti-449a}), 71.9 (\text{CHCHCH}_2 \text{anti-449a}), 71.8 (\text{CHCH}_2 \text{CH}_2 \text{syn-449a}), 71.5 (\text{CHCH}_2 \text{syn-449a}), 70.8 (\text{OCH}_2 \text{syn-449a}).
\]

(2S,3R,4S)-2-((E)-(2,2-Dimethylhydrazono)methyl)tetrahydrofuran-3,4-diol (\textit{anti-450})\textsuperscript{251} and (2R,3R,4S)-2-((E)-(2,2-Dimethylhydrazono)methyl)tetrahydrofuran-3,4-diol (\textit{syn-450})

A stirring solution of hydrolyzed product 449 (103 mg, 0.780 mmol, \textit{anti:syn} = 85:15) in MeOH (3.9 mL) was treated with NaBH$_4$ (43 mg, 1.2 mmol) portionwise at 0 °C. The reaction was stirred at 0 °C for 1 h before the reaction was quenched with AcOH (1 drop) and treated with Amberlyst 15 (1.60 g) and Amberlyst A26 (1.60 g). The mixture was then stirred at RT for 30 minutes before it was filtered the filtrate concentrated \textit{in vacuo} to give the triol 450 as a white crystalline solid (104 mg, 0.776 mmol, 100%, \textit{anti:syn} = 85:15); m.p. = 83–85 °C; R$_f$ = 0.57 (acetone); $\nu_{max}$ (film/cm$^{-1}$) 3342s br. (O-H), 2930s (C-H), 1683s, 1411m; $^1$H NMR (600 MHz; D$_2$O) 4.44 (1H, q, J = 5.8, CHCH$_2$
**Chapter IV**

**syn-450**, 4.33 (1H, t, J = 4.8, CHCHCH₂ syn-450), 4.31–4.29 (1H, m, CHCH₂ anti-450), 4.13 (1H, dd, J = 7.3, 4.9, CHCHCH₂ anti-450), 4.09 (1H, dd, J = 10.2, 4.3, CHH’ anti-450), 4.08–4.06 (1H, m, CHCH₂ syn-450), 3.99 (1H, dd, J = 7.3, 4.9, CHH’ anti-450), 3.90–3.86 (1H, m, CHCH₂ syn-450), 3.85–3.81 (2H, m, CH₃H’ anti-450), 3.77–3.73 (2H, m, CH₃H’, CHH’ syn-450), 3.70 (1H, m, CH₃H’ syn-450); ¹³C NMR (150 MHz; D₂O with MeOH reference) δ 2.1 (CH anti-450), 81.4 (CH syn-450), 72.8 (CH₂ anti-450), 72.2 (CH anti-450), 71.8 (CH syn-450), 71.7 (CH anti-450), 71.0 (CH₂ syn-450), 61.9 (CH₂ anti-450), 61.0 (CH₂ syn-450); HRMS (CI+) found [M+H]+ 135.0652; C₅H₁₁O₄ requires 135.0652; [α]D (20 °C) = +50.9 (MeOH, C = 2.0); data in accordance with the literature.

**tert-Butyl butyl(((2R,3S,4S)-3,4-dihydroxytetrahydrofuran-2-yl)methyl)carbamate (anti-453)** and **tert-Butyl butyl(((2S,3S,4S)-3,4-dihydroxytetrahydrofuran-2-yl)methyl)carbamate (syn-453)**

A stirring solution of hydrolyzed product 449 (124 mg, 0.939 mmol, anti:syn = 85:15) in MeOH (4.7 mL) was treated with AcOH (27 µL, 28 mg, 0.47 mmol), n-BuNH₂ (0.47 mL, 640 mg, 8.7 mmol) and 10% Pd/C (124 mg) at RT before the reaction was placed under an atmosphere of hydrogen gas. The reaction was stirred at RT for 4 h before it was filtered through Celite and the filtrate concentrated in vacuo. The crude product was then dissolved in CPME (2.0 mL) and stirred at RT. The reaction was treated with a solution of Boc₂O (308 mg, 1.44 mmol) in CPME (3.0 mL) and resulting mixture stirred at RT for 16 h. The reaction was then concentrated in vacuo to give the crude product, which was purified by flash column chromatography (70:30 hexane:acetone) to give the carbamate 453 as a white gum (179 mg, 0.619 mmol, 66%, anti:syn = 80:20); Rf = 0.38 (30:70 acetone:hexane); νmax (film/cm⁻¹) 3406s br. (O-H), 2931s (C-H), 1690s, 1665s, 1479s, 1416s; ¹H NMR (400 MHz; DMSO-d₆, 80 °C) 4.90–4.06 (2H, br. m, 2 × O₃H anti-453; 3H, br. m, 2 × OH syn-453, CH syn-453), 4.05–4.00 (1H, m, CH anti-453), 3.94–3.88 (1H, m, H syn-453), 3.91 (1H, dd, J = 9.3, 5.3, CHH’ anti-453), 3.88–3.83 (1H, m, CH syn-453), 3.76–3.70 (1H, m, CH anti-453, 1H, m, H syn-453), 3.66 (1H, dd, J = 6.0, 5.3, CH anti-453), 3.54–3.47 (2H, m, H syn-453), 3.51 (1H, dd, J = 9.3, 4.0, CHH’ anti-
Experimental Details

453), 3.44 (1H, dd, J = 14.3, 4.0, CHH’ anti-453), 3.27–3.15 (2H, m, CH2Pr anti-453; 3H, m, CH2Pr syn-453, H syn-453), 3.11 (1H, dd, J = 14.3, 7.3, CHH’ anti-453), 1.52–1.44 (2H, m, CH2CH2CH3 anti-453; 2H, m, CH2CH2CH3 syn-453), 1.42 (9H, s, C(CH3)3 anti-453), 1.41 (9H, s, C(CH3)3 syn-453), 1.31–1.21 (2H, m, CH2CH3 anti-453; 2H, m, CH2CH3 syn-453), 0.90 (3H, t, J = 7.3, CH2CH3 anti-453; 3H, t, J = 7.3, CH2CH3 syn-453); 13C NMR (150 MHz; DMSO-d6) 154.9 (C(O)), 81.2 (CH), 80.8 (CH), 78.3 (CO’Bu), 73.5 (CH), 72.2 (CH2), 71.3 (CH), 70.9 (CH), 70.5 (CH2), 70.1 (CH), 49.1 (CH2), 48.8 (CH2), 47.0 (CH2), 46.5 (CH2), 30.0 (CH2), 29.5 (CH2), 28.1 (C(CH3)3), 19.5 (CH3), 13.8 (CH2CH3)); HRMS (ESI+) found [M+H]+ 290.1979; C14H28NO5 requires 290.1967; [α]D (20 °C) = +25.0 (MeOH, C = 1.0).

(2S,3S,4S)-2-(Dimethoxymethyl)tetrahydrofuran-3,4-diol (anti-454) and (2R,3S,4S)-2-(Dimethoxymethyl)tetrahydrofuran-3,4-diol (syn-454)

Amberlyst 15 (83 mg) was added to a stirring solution of hydrolyzed product 449 (109 mg, 0.820 mmol, anti:syn = 85:15) in MeOH (4.1 mL) RT. The reaction was stirred at RT for 48 h before the reaction mixture was filtered and the filtrate concentrated in vacuo to give the crude product (anti:syn = 65:35). This was purified by flash column chromatography (80:100 hexane:acetone) to give the acetal-454 as a colorless oil (111 mg, 0.624 mmol, 76%, anti:syn = 75:25); Rf = 0.34 (1:1 hexane:acetone); νmax (film/cm–1) 3443s br. (O-H), 2947s (C-H); 1H NMR (600 MHz; MeOH-d4) 4.59 (1H, d, J = 7.5, CH(OMe)2 syn-454), 4.33–4.29 (1H, m, CHCH2 syn-454), 4.31 (1H, d, J = 4.7, CH(OMe)2 anti-454), 4.13 (1H, q, J = 4.7, CHCH2 anti-454), 4.10–4.06 (1H, m, CHCHCH(OMe)2 syn-454), 4.09 (1H, t, J = 4.7, CHCHCH(OMe)2 anti-454), 3.93 (1H, dd, J = 9.2, 4.7, CHH’ anti-454), 3.89 (1H, t, J = 7.9, CHH’ syn-454), 3.83 (1H, t, J = 4.7, CHCH(OMe)2 anti-454), 3.79 (1H, dd, J = 7.5, 3.4, CHCH(OMe)2 syn-454), 3.68 (1H, dd, J = 9.2, 4.7, CHH’ anti-454), 3.65 (1H, t, J = 7.9, CHH’ syn-454), 3.44 (3H, s, OCH3 syn-454), 3.43 (3H, s, OCH3 anti-454), 3.42 (3H, s, OCH3 anti-454), 3.39 (3H, s, OCH3 syn-454); 13C NMR (150 MHz; MeOH-d4) 106.3 (C(OMe)2 anti-454), 104.2 (C(OMe)2 syn-454), 84.1 (CHCH(OMe)2 anti-454), 81.5 (CHCH(OMe)2 syn-454), 73.6 (CHCHCH2
K₂CO₃ (7 mg, 10 mol%) was added to a stirring solution of acetal 454 (90 mg, 0.51 mmol, anti:syn = 75:25) in DMC (2.5 mL) at RT. The reaction was heated at reflux for 16 h before the reaction was allowed to cool to RT, filtered through a silica plug (eluting with Et₂O) and the filtrate concentrated in vacuo to give the carbonate 455 as a colorless oil (90 mg, 0.44 mmol, 87%, single diastereoisomer); Rᶠ = 0.35 (80:20 hexane:acetone); v_max (film/cm⁻¹); 2942s (C-H), 1797s (C=O), 1459s; ¹H NMR (600 MHz; CDCl₃) 5.26 (1H, d, J = 7.0, CHCH₂), 5.18–5.16 (1H, m, CH₂), 4.33 (1H, d, J = 2.7, CH(OMe)₂), 4.25 (1H, d, J = 2.7, CHCH(OMe)₂), 4.14–4.12 (2H, m, OCH₃), 3.46 (3H, s, OCH₃), 2.43 (3H, s, OCH₃); ¹³C NMR (150 MHz; CDCl₃) 154.5 (C(O)), 105.6 (C(OMe)₂), 84.0 (CHCH(OMe)₂), 81.3 (CHCH₂), 80.9 (CH₂), 73.9 (OCH₃), 56.9 (OCH₃), 56.5 (OCH₃); HRMS (Cl⁺) found [M+H⁺] 205.0708; C₈H₁₃O₆ requires 205.0707; [α]D (20 °C) = +25.0 (MeOH, C = 0.45).

Methyl (E)-3-((2R,3S,4S)-3,4-dihydroxytetrahydrofuran-2-yl)acrylate (anti-456) and Methyl (E)-3-((2S,3S,4S)-3,4-dihydroxytetrahydrofuran-2-yl)acrylate (syn-456)

K₂CO₃ (78 mg, 0.57 mmol) and trimethyl phosphonoacetate (74 µL, 82 mg, 0.43 mmol) were added to a stirring solution of hydrolyzed product 449 (50 mg, 0.38 mmol, anti:syn = 85:15) in MeOH (1.9 mL) at 0 °C. The reaction was stirred at 0 °C for 4 h before the
reaction mixture was filtered through a silica plug (eluting with EtOAc) and the filtrate concentrated in vacuo to give the crude product (anti:syn = 85:15). This was purified by flash column chromatography (CH₂Cl₂) to give the alkene **456** as a colorless oil (53 mg, 0.28 mmol, 74%, anti:syn = 85:15; R₂ = 0.58 (1:1 acetone:hexane); νmax (film/cm⁻¹) 3400 s br. (O-H), 2944 s (C-H), 1715 s (C=O), 1649 s, 1319 s; ¹H NMR (600 MHz; MeOH-d₄) 7.02 (1H, dd, J = 15.6, 4.7, MeO₂CCH=CH anti-456), 6.98 (1H, dd, J = 15.8, 1.7, MeO₂CCH syn-456), 6.08 (1H, dd, J = 15.8, 1.7, MeO₂CCH anti-456), 6.07–6.04 (1H, m, MeO₂CCH syn-456), 4.50 (1H, td, J = 4.7, 1.7, CH=CHC₃H syn-456), 4.34–4.31 (1H, m, C₂HCH₂ syn-456), 4.30–4.27 (1H, m, CH=CHC₃H anti-456), 4.19 (1H, t, J = 4.7, C₂HCH₂ syn-456), 3.96–3.93 (1H, m, C₂HCH₂ syn-456), 3.76–3.74 (1H, m, C₂HCH₂ syn-456), 3.72 (3H, s, OCH₃ anti-456), 3.71 (3H, s, OCH₃ syn-456); ¹³C NMR (150 MHz; MeOH-d₄) 168.3 (C(=O), anti-456), 148.1 (MeO₂CCH=CH syn-456), 146.7 (MeO₂CCH=CH syn-456), 122.5 (MeO₂CCH=CH syn-456), 121.5 (MeO₂CCH=CH anti-456), 81.6 (CH=CHCH syn-456), 81.5 (CH=CHCH anti-456), 77.7 (CH₂CHCHCH anti-456), 74.3 (CH₂ anti-456), 74.2 (CHOD syn-456), 73.1 (CHOD syn-456), 72.6 (CH₂ syn-456), 72.4 (CH₂CH anti-456), 52.1 (OCH₃ anti-456), 52.1 (OCH₃ syn-456); HRMS (EI⁺) found [M]+ 188.0680; C₈H₁₂O₅ requires 188.0679; [α]D (20 °C) = +40.5 (MeOH, C = 0.45).

**(2R,3S,4R)-2-(Hydroxymethyl)tetrahydrofuran-3,4-diol (anti-458)**[252] and **(2S,3S,4R)-2-(Hydroxymethyl)tetrahydrofuran-3,4-diol (syn-458)**

Amberlyst 15 (701 mg) was added to a stirring solution of hydrazone **443b** (122 mg, 0.701 mmol, 55:45 d.r.) in water (3.5 mL) at RT. After 5 minutes the reaction mixture was filtered and the filtrate concentrated in vacuo and lyophilized to give a white gum. The intermediate was then dissolved in MeOH (3.5 mL) and treated with NaBH₄ (40 mg, 1.1 mmol) portionwise at 0 °C and the reaction stirred at 0 °C for 1 h. The reaction was then quenched with AcOH (1 drop) and treated with Amberlyst 15 (1.40 g) and Amberlyst A26 (1.40 g). The mixture was then stirred at RT for 30 minutes before it was filtered the filtrate concentrated in vacuo to give tritol **458** as a colorless oil (85 mg, 0.63 mmol, 90%,
anti:syn = 65:35; R_f = 0.57 (acetone); ν_{max} (film/cm^{-1}) 3330s br. (O-H), 2939s (C-H), 1655s, 1414s; ^{1}H NMR (600 MHz; D_{2}O) 4.33–4.29 (1H, m, CH syn-458), 4.27–4.25 (1H, m, CH anti-458), 4.23 (1H, dd, J = 3.6, 1.3, CH syn-458), 4.18 (1H, dd, J = 10.3, 4.2, CHH' syn-458), 4.05–4.02 (2H, m, CH, CHH' anti-458), 3.86–3.79 (2H, m, C'H syn-458; 2H, m, CH syn-458), 3.80–3.71 (2H, m, CHH2 syn-458), 62.2 (CHH2 anti-458), 60.5 (CH syn-458); HRMS (ESI^+) found [M+H]^+ 135.0658; C_{5}H_{11}O_{4} requires 135.0652; [α]D (20 °C) = +69.6 (MeOH, C = 0.17); Data for anti-458 in accordance with the literature.\(^{252}\)

(2R,3R,4R,5S)-2-(Hydroxymethyl)-5-methyltetrahydrofuran-3,4-diol (syn-459)\(^{253}\) and (2S,3R,4R,5S)-2-(Hydroxymethyl)-5-methyltetrahydrofuran-3,4-diol (anti-459)

Amberlyst 15 (888 mg) was added to a stirring solution of hydrazone 433c (167 mg, 0.888 mmol, 60:40 d.r.) in water (4.4 mL) at RT. After 5 minutes the reaction mixture was filtered and the filtrate concentrated in vacuo and lyophilized to give a white gum. The intermediate was then dissolved in MeOH (4.4 mL) and treated with NaBH\(_{4}\) (49 mg, 1.3 mmol) portionwise at 0 °C and the reaction stirred at 0 °C for 1 h. The reaction was then quenched with AcOH (1 drop) and treated with Amberlyst 15 (1.80 g) and Amberlyst A26 (1.80 g). The mixture was then stirred at RT for 30 minutes before it was filtered and the filtrate concentrated in vacuo to give the triol 459 as a colorless oil (122 mg, 0.824 mmol, 93%, syn:anti = 70:30); R_f = 0.26 (1:1 acetone:hexane); ν_{max} (film/cm^{-1}) 3317s (O-H), 2930s (C-H), 1450s; ^{1}H NMR (600 MHz; D_{2}O) 4.21–4.19 (1H, m, CH anti-459), 4.09–4.06 (1H, m, CHH OH syn-459), 4.04 (1H, t, J = 6.4, CHOD syn-459), 3.96–3.91 (2H, m, CH syn-459), 3.86–3.80 (1H, m, CHOD syn-459; 3H, m, CHCH₃, CHH', CHH' syn-459), 3.78–3.73 (1H, m, CHH' syn-459; 1H, m, CHH' anti-459), 3.72–3.69 (1H, dd, J = 12.4, 5.8, CHH syn-459), 1.37–1.35 (3H, m, CHCH₃ anti-459), 1.32 (3H, d, J = 6.4, CHCH₃ syn-459); ^{13}C NMR (150 MHz; D₂O with MeOH standard) 83.4...
(CH anti-459), 82.5 (CH syn-459), 82.3 (CH syn-459), 81.3 (CH anti-459), 80.9 (CH anti-459), 78.6 (CH syn-459), 78.2 (CH anti-459), 77.2 (CH syn-459), 61.9 (CH2 syn-459), 60.7 (CH2 anti-459), 18.7 (CH3 anti-459), 18.3 (CH3 syn-459); HRMS (Cl+) found [M+H]+ 149.0821; C6H13O4 requires 149.0808; [α]D (20 °C) = –28.7 (MeOH, C = 3.3); Data for syn-459 accordance with the literature.253

(3aR,4R,6aS)-4-((E)-(2,2-Dimethylhydrazono)methyl)tetrahydrofuro[3,4-d][1,3]dioxol-2-one (467)

A solution of tetrahydrofuran anti-433a (316 mg, 1.82 mmol) in DMC (9.1 mL) was treated with K2CO3 (25 mg, 10 mol%) and the reaction mixture heated at reflux for 16 h. The reaction mixture was then allowed to cool to RT before it was filtered through a silica plug (elution with Et2O) and the filtrate concentrated in vacuo to give the carbonate 467 as a colorless oil (364 mg, 1.82 mmol, 100%); Rf = 0.71 (1:1 acetone:hexane); νmax (film/cm–1) 2863m (C-H), 1798s (C=O), 1587s, 1468s, 1444s; 1H NMR (600 MHz; CDCl3) 6.35 (1H, d, J = 2.6, N=C), 5.63 (1H, d, J = 6.8, CHCH2), 5.18 (1H, d, J = 6.8, 3.8, CHH2), 4.90 (1H, d, J = 2.6, N=CHH), 4.12 (1H, d, J = 11.5, CHH′), 3.76 (1H, dd, J = 11.5, 3.8, CHF), 2.82 (6H, s, N(CH3)2); 13C NMR (150 MHz; CDCl3) 154.8 (C(O)), 127.0 (N=CH), 82.2 (N=CHCH), 81.4 (CHCHCH2), 80.9 (CHCH2), 70.5 (CH2O), 42.5 (N(CH3)2); HRMS (EI+) found [M]+ 200.0796; C8H12N2O4 requires 200.0792; [α]D (20 °C) = +122.2 (MeOH, C = 1.0).
Chapter IV

\((E)-2-(((3aR,4S,6aS)-2,2\text{-Dimethyltetrahydrofuro}[3,4-d][1,3]\text{-dioxol-4-yl})\text{-methylene})-1,1\text{-dimethylhydrazine (syn-442) and (E)-2-(((3aR,4R,6aS)-2,2-}
\text{-Dimethyltetrahydrofuro}[3,4-d][1,3]\text{-dioxol-4-yl})\text{-methylene}-1,1\text{-dimethylhydrazine (anti-442)}^{245}\)

A stirring solution of tetrahydrofuran anti-443a (154 mg, 0.885 mmol) in acetone (4.4 mL) was treated with (MeO)$_2$CMe$_2$ (0.89 mL) and PTSA.H$_2$O (34 mg, 0.18 mmol, 20 mol%) at RT and the reaction stirred at RT for 24 h. The reaction was then quenched with aq. sat. NaHCO$_3$ and filtered through a silica plug, eluting with acetone. The filtrate was concentrated in vacuo to give acetonide 442 as a colorless oil (182 mg, 0.850 mmol, 96%; syn:anti = 60:40); R$_f$ = 0.45 and 0.35 (1:4 acetone:hexane); ν$_{\text{max}}$ (film/cm$^{-1}$) 2934s (C-H), 1689s, 1597s, 1470s; HRMS (ESI$^+$) found [M+H]$^+$ 215.1398; C$_{10}$H$_{19}$N$_2$O$_3$ requires 215.1396; [α]$^D$ (20 °C) = +103.0 (MeOH, C = 1.0); data in accordance with the literature.$^{245}$

**Acetonide syn-442:** $^1$H NMR (600 MHz; MeOH-d$_4$) 6.57 (1H, d, J = 6.8, N=CH), 4.86–4.82 (1H, m, CHCH$_2$), 4.71–4.66 (1H, m, CHCHCH$_2$), 4.00 (1H, dd, J = 6.8, 3.9, N=CHCH), 3.94 (1H, d, J = 10.5, OCHH$^+$), 3.53 (dd, J = 10.5, 3.7, OCHH$^+$), 2.81 (6H, s, N(CH$_3$)$_2$), 1.46 (3H, s, C(CH$_3$)), 1.31 (3H, s, C(CH$_3$)); $^{13}$C NMR (150 MHz; MeOH-d$_4$) 132.1 (C=N), 113.2 (C(CH$_3$)$_2$), 83.7 (N=CHCH), 83.3 (CHCHCH$_2$), 82.7 (CHCH$_2$), 73.6 (OCH$_2$), 42.8 (N(CH$_3$)$_2$), 26.3 (CCH$_3$), 24.7 (CCH$_3$); data in accordance with the literature.$^{245}$

**Acetonide anti-442:** $^1$H NMR (600 MHz; MeOH-d$_4$) 6.50 (1H, d, J = 4.3, N=CH), 4.97 (1H, d, J = 6.0, CHCHCH$_2$), 4.81 (1H, dd, J = 6.0, 4.3, CHCH$_2$), 4.54 (1H, d, J = 4.3, N=CHCH), 3.86 (1H, d, J = 10.5, CHH$^+$), 3.75 (1H, d, J = 10.5, 4.3, CHH$^+$), 2.77 (6H, s, N(CH$_3$)$_2$), 1.46 (3H, s, C(CH$_3$)), 1.32 (3H, s, C(CH$_3$)); $^{13}$C NMR (150 MHz; MeOH-d$_4$) 132.5 (C=N), 113.4 (C(CH$_3$)$_2$), 85.1 (CH), 84.4 (CH), 82.4 (CH), 73.0 (OCH$_2$), 42.8 (N(CH$_3$)$_2$), 26.7 (CCH$_3$), 25.0 (CCH$_3$); data in accordance with the literature.$^{245}$
**Experimental Details**

**tert-Butyl (((2R,3S,4S)-3,4-dihydroxytetrahydrofuran-2-yl)methyl)carbamate (469)**

A stirring solution of tetrahydrofuran *anti-443a* (100 mg, 0.57 mmol) in CPME (2.9 mL) was treated with a solution of Boc₂O (313 mg, 1.44 mmol) in CPME (2.9 mL) at RT. The resulting solution was then treated with Pd(OH)₂ (20% on carbon, 163 mg) and the reaction was placed under an atmosphere of hydrogen gas (1 atm). The reaction was stirred at RT for 24 h before it was filtered through Celite and the filtrate concentrated *in vacuo* to give the crude product, which was purified by flash column chromatography (100:90 hexane:acetone) to give *carbamate 469* as a colorless oil (80 mg, 0.34 mmol, 60%); Rₚ = 0.40 (100:90 hexane:acetone); ν_max (film/cm⁻¹) 3362s br. (O-H, N-H), 2977s (C-H), 1688s (C=O), 1523s, 1367s, 1251s; ¹H NMR (600 MHz; CDCl₃) 5.21–5.17 (1H, m, NH), 4.22–4.19 (1H, m, OCH₂C₃H), 4.05 (1H, dd, J = 10.2, 4.9, OCHH'), 3.84–3.80 (1H, m, NCH₂CHC₃H), 3.78–3.75 (2H, m, OCHH', NCH₂CH), 3.42–3.36 (1H, m, NCH₂CHCH), 3.31–3.26 (1H, m, NCHH'), 1.41 (9H, s, C(CH₃)₃); ¹³C NMR (150 MHz; CDCl₃) 157.0 (C(O)), 80.6 (NCH₂CH), 80.2 (CMe₃), 73.2 (OCH₂), 73.1 (NCH₂CHCH), 71.2 (OCH₂CH), 42.0 (NCH₂), 28.5 (C(CH₃)₃); HRMS (ES⁺) found [M+H]⁺ 234.1339; C₁₀H₂₀N₂O₅ requires 234.1341; [α]D²⁰ (20 °C) = +32.9 (MeOH, C = 1.0).

**(E)-2-(((3aR,4R,6aS)-2,2-Di-tert-butyltetrahydrofuro[3,4-d][1,3,2]dioxasilol-4-yl)methylene)-1,1-dimethylhydrazine (474)**

A solution of tetrahydrofuran *anti-443a* (312 mg, 1.79 mmol) in DMC (18 mL) at 0 °C was treated with 2,6-lutidine (0.63 mL, 580 mg, 5.4 mmol) and di-tert-butylsilyl bis(trifluoromethanesulfonate) (0.64 mL, 870 mg, 2.0 mmol). The resulting mixture was stirred at 0 °C for 1 h before the reaction was quenched with water (1 drop) and filtered through a silica plug, eluting with Et₂O. The filtrate was concentrated *in vacuo* to give *silyl ether 474* as a colorless oil (269 mg, 0.857 mmol, 48%); Rₚ = 0.44 (20:80 EtOAc:hexane); ν_max (film/cm⁻¹) 2930s (C-H), 2856s (C-H), 1594w,
$\text{\textsuperscript{1}}$H NMR (600 MHz; CDCl$_3$) 6.44 (1H, d, $J = 4.0$, N=CH), 4.87 (1H, dd, $J = 6.6$, 2.6, CHCHCH$_2$), 4.75–4.70 (1H, m, CHCH$_2$), 4.51–5.49 (1H, m, N=CHCH), 3.94 (1H, dd, $J = 10.4$, 5.3, CHH'), 3.84 (1H, dd, $J = 10.4$, 3.0, CHH'), 2.80 (6H, s, N(C$\text{\textsubscript{3}}$H$_2$)$_2$), 1.09 (9H, s, C(C$\text{\textsubscript{3}}$H$_3$)$_3$), 1.04 (9H, s, C(C$\text{\textsubscript{3}}$H$_3$)$_3$); $\text{\textsuperscript{13}}$C NMR (150 MHz; CDCl$_3$) 131.3 (C=N), 85.2 (CH), 81.4 (CH), 79.3 (CH), 73.9 (CH$_2$), 42.7 (N(CH$_3$)$_2$), 27.4 (C(CH$_3$)$_3$), 26.9 (C(CH$_3$)$_3$), 21.9 (C(CH$_3$)$_3$), 20.1 (C(CH$_3$)$_3$); HRMS (El$^+$) found [M]$^+$ 314.2022; C$_{15}$H$_{30}$N$_2$O$_3$Si requires 314.2020; [$\alpha$]$_D$ (20 °C) = +78.0 (MeOH, C = 1.0).
6.4. Crystallography Data

All the information in the section was provided by Dr Dejan-Krešimir Bučar and Dr Laure Benhamou.

General Experimental Procedure: Single X-ray diffraction data were collected using an *Agilent SuperNova (Dual Source)* single crystal X-ray diffractometer equipped with an *Atlas CCD Detector*. The diffraction experiment was conducted at 150 K using CuK$_\alpha$ radiation ($\lambda = 1.54184$ Å). Data collection and processing was accomplished using the *CrysAlisPro* program. Empirical absorption correction was performed using spherical harmonics implemented in the *SCALE3 ABSPACK* scaling algorithm. Structure solution and refinement were accomplished using *SHELXS-97* and *SHELXL-97*, respectively. The structure was solved using direct methods. All non-hydrogen atoms were refined anisotropically, while hydrogen atoms associated with carbon and oxygen atoms were refined isotropically in geometrically constrained positions.
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<td><em>b</em> / Å</td>
<td>17.8742(3)</td>
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<tr>
<td><em>c</em> / Å</td>
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<td><em>β</em> / °</td>
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<td><em>γ</em> / °</td>
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<td><em>Z</em></td>
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<td><em>ρ&lt;sub&gt;calc&lt;/sub&gt;</em> / g cm&lt;sup&gt;-3&lt;/sup&gt;</td>
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<td>Crystal size / mm&lt;sup&gt;3&lt;/sup&gt;</td>
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<tr>
<td>Radiation</td>
<td>CuKα (λ = 1.5418 Å)</td>
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<td>Unique reflections</td>
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<td>Reflections with <em>I</em> ≥ 2σ(<em>I</em>)</td>
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<td>Number of parameters</td>
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<tr>
<td>Final <em>R</em> indexes [<em>I</em> ≥ 2σ(<em>I</em>)]</td>
<td><em>R</em>₁ = 0.0281, <em>wR</em>₂ = 0.0659</td>
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<tr>
<td>Final <em>R</em> indexes [all data]</td>
<td><em>R</em>₁ = 0.0309, <em>wR</em>₂ = 0.0677</td>
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<td>Largest diff. peak/hole / e Å&lt;sup&gt;3&lt;/sup&gt;</td>
<td>0.160 / -0.138</td>
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<td>CCDC deposition number</td>
<td>1411520</td>
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</table>
Chapter VII. References


24 http://www.acs.org/content/dam/acsorg/greenchemistry/industriainnovation/roundtable/solvent-selection-guide.pdf


27 http://www.acs.org/content/dam/acsorg/greenchemistry/industriainnovation/roundtable/acs-gci-pr-solvent-selection-guide.pdf


References


Chapter VII


Chapter VII


194 Dihedral angles were calculated using ChemBio3D Ultra® following an MM2 structure optimization.


References


http://www.sigmaaldrich.com. Based on prices quoted on 03/05/2015.


Appendix

The following manuscripts are included in the appendix to this thesis:


The following files are included in the electronic appendix to this thesis, which can be found on a CD in the inside of the back cover;

1. Computational Supporting Information.

2. The.cif file for *endo-330e*.

3. The.cif file for *exo-330e*.

4. The.cif file for *anti-443e*. 
Highly Regioselective Synthesis of Substituted Isoindolinones via Ruthenium-Catalyzed Alkyne Cyclotrimerizations

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Abstract: (Cyclooctadiene)(pentamethylcyclopentadiene)ruthenium chloride [Cp*RuCl(ACTUNG TRENNUNG)2 (cod)] has been used to catalyze the regioselective cyclization of amide-tethered diynes with monosubstituted alkynes to give polysubstituted isoindolinones. Notably, the presence of a trimethylsilyl group on the diyne generally led to complete control over the regioselectivity of the alkyne cyclotrimerization. The cyclization reaction worked well in a sustainable non-chlorinated solvent and was tolerant of moisture. The optimized conditions were effective with a diverse range of alkynes and diynes. The 7-silylisoindolinone products could be halogenated, protodesilylated or ring opened to access a range of usefully functionalized products.

Keywords: alkyne; amide tether; cyclotrimerization; isoindolinones; ruthenium; trimethylsilyl group

Introduction

Substituted isoindolinones have recently generated considerable interest because of their diverse biological activities, including the inhibition of angiogenesis,[1] tumour necrosis factor production,[2] MDM2-p53 protein-protein interactions,[3] hypoxia-inducible factor-1α[4] and histone deacetylase.[5] The majority of existing protocols for isoindoline synthesis require the construction of a γ-lactam adjacent to a preformed aromatic core.[6] Recent examples include the one-pot transformation of 2-halobenzaldimines into chiral 3-substituted isoindolinones and the Ni-mediated cyclization of N-benzoyl aminals in the presence of a stoichiometric Lewis acid.[7-8] However, the inevitable limitation of these approaches is the accessibility of the arene starting material itself. The synthesis of polysubstituted arenes is often non-trivial, frequently requiring numerous steps, the use of protecting group strategies and/or functional group interconversions.

The transition metal-catalyzed [2+2+2]cyclotrimerization of alkynes is emerging as an elegant, atom efficient and convergent approach to the synthesis of highly substituted arenes.[9] The strategy allows for the regioselective synthesis of compounds that would be extremely difficult to make via traditional aromatic chemistry. The regioselectivity of a cyclotrimerization is normally controlled by tethering two or three of the alkyne components together, so this strategy is best suited to the synthesis of bicyclic and tricyclic ring systems. This allows for the assembly of substituted multiple-ring aromatic compounds from alkyne precursors in a single step.

Yamamoto and co-workers have previously recognized the potential of alkyne cyclotrimerizations for the synthesis of isoindolinones bearing substituents on the aromatic ring.[10] They reported the cyclization of amide-tethered diynes 1 with monoynes 2 using Cp*RuCl(cod) 3 as the catalyst to give regioisomeric isoindolinones 4 and 5 (Scheme 1). In general the regioselectivity of the cyclotrimerization was poor to moderate, with the exception of a single example bearing a methyl group at R1. In addition, a significant limitation of this method is the use of 1,2-dichloroethane (DCE) as solvent, a substance which is potentially detrimental to human health and is generally avoided within industry.[11]
The aim of this study was to explore the regioselective synthesis of polysubstituted isoindolinones using more industrially viable reaction conditions, to establish the general applicability of the reaction, and to develop the synthetic potential of the cyclized products. On the basis of previously reported cyclizations we envisaged that the introduction of a trimethylsilyl group at R1 in diyne 1 would direct the regioselectivity of the cyclisation reaction effectively with a broad range of monoynes. The arylsilane unit present in the isoindolinone product could then be transformed using standard chemical techniques to access a variety of 7-substituted derivatives.

### Results and Discussion

#### Diyne Synthesis

Initially several amide-tethered diynes 6 were prepared by the coupling of propargylic amines 7 with 3-(trimethylsilyl)propionic acid 8, via the corresponding acid chloride (Scheme 2). Where necessary the corresponding amines were prepared using literature procedures.

#### Optimization

Various conditions were screened for the cyclotrimerization of diyne 6a with 1-hexyne 9a to form isoindolinone 10a, and the results are summarized in Table 1. All reactions were conducted for 16 h at which point

### Table 1. Optimization of the cyclotrimerization of 6a and 9a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Equivalents of 9a</th>
<th>Catalyst</th>
<th>Catalyst loading [mol%]</th>
<th>Conversion [%]</th>
<th>Ratio 10a:11</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhMe[c]</td>
<td>4</td>
<td>RhCl(PPh3)3</td>
<td>5</td>
<td>&lt;5</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>PhMe[c]</td>
<td>4</td>
<td>Co2(CO)8</td>
<td>10</td>
<td>&lt;5</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>CH2Cl2[c]</td>
<td>4</td>
<td>Grubbs I</td>
<td>5</td>
<td>5</td>
<td>n.d.</td>
</tr>
<tr>
<td>4</td>
<td>DCE[c]</td>
<td>4</td>
<td>Cp*RuCl(cod)</td>
<td>1</td>
<td>5</td>
<td>n.d.</td>
</tr>
<tr>
<td>5</td>
<td>neat[d]</td>
<td>4</td>
<td>Cp*RuCl(cod)</td>
<td>1</td>
<td>50</td>
<td>3:2</td>
</tr>
<tr>
<td>6</td>
<td>neat[d]</td>
<td>4</td>
<td>Cp*RuCl(cod)</td>
<td>3</td>
<td>100</td>
<td>3:1</td>
</tr>
<tr>
<td>7</td>
<td>CPME</td>
<td>4</td>
<td>Cp*RuCl(cod)</td>
<td>3</td>
<td>100</td>
<td>5:1</td>
</tr>
<tr>
<td>8</td>
<td>CPME</td>
<td>4</td>
<td>Cp*RuCl(cod)</td>
<td>3</td>
<td>60</td>
<td>4:1</td>
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<td>9</td>
<td>CPME</td>
<td>2</td>
<td>Cp*RuCl(cod)</td>
<td>3</td>
<td>100</td>
<td>2:1</td>
</tr>
<tr>
<td>10[e]</td>
<td>CPME</td>
<td>3</td>
<td>Cp*RuCl(cod)</td>
<td>3</td>
<td>100</td>
<td>8:1</td>
</tr>
<tr>
<td>11[e]</td>
<td>CPME</td>
<td>3</td>
<td>Cp*RuCl(cod)</td>
<td>3</td>
<td>100</td>
<td>9:1</td>
</tr>
<tr>
<td>12[e]</td>
<td>CPME</td>
<td>1.1</td>
<td>Cp*RuCl(cod)</td>
<td>3</td>
<td>100</td>
<td>5:2</td>
</tr>
<tr>
<td>13[e]</td>
<td>MTBE</td>
<td>2</td>
<td>Cp*RuCl(cod)</td>
<td>3</td>
<td>100</td>
<td>5:1</td>
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<td>14[e]</td>
<td>2-MeTHF</td>
<td>2</td>
<td>Cp*RuCl(cod)</td>
<td>3</td>
<td>90</td>
<td>5:1</td>
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<tr>
<td>15[e]</td>
<td>CPME/10% water</td>
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<td>3</td>
<td>70</td>
<td>3:1</td>
</tr>
<tr>
<td>16[e]</td>
<td>water</td>
<td>4</td>
<td>Cp*RuCl(cod)</td>
<td>3</td>
<td>30</td>
<td>3:1</td>
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</table>

[a] Determined by analysis of the crude 1H NMR spectrum.
[b] Conversion of 6a into 10a and 11 (determined by crude 1H NMR without the use of an internal standard).
[c] Solvent dried over activated 4 Å molecular sieves and degassed.
[d] Cp*RuCl(cod) 3 was added to the reaction mixture at 0 °C, which was then allowed to reach room temperature.
[e] Diyne 6a in CPME was added dropwise over 3 h to a stirring solution of 9a and 3 in CPME.
conversion and selectivity were determined by analysis of the crude $^1$H NMR spectrum.

The cyclotrimerization of diyne 6a and alkyne 9a was examined using four different literature procedures. Neither RhCl(PPh$_3$)$_3$ nor Co$_2$(CO)$_6$ were effective in catalyzing the alkyne cyclotrimerization, with no measurable conversion of diyne 6a (entries 1 and 2).[16] Treating diyne 6a with 5 mol% Grubbs’ first generation catalyst and 4 equivalents of 1-hexyne 9a in dried, degassed CH$_2$Cl$_2$ resulted in formation of the target isoindolinone 10a with only 5% conversion (entry 3).[17] Treating diyne 6a with 1-hexyne 9a and 1 mol% Cp*RuCl(cod) in dried, degassed DCE also gave isoindolinone 10a, again with 5% conversion of 6a (entry 4).[10] Given that the latter procedure gave a similar conversion with a lower catalyst loading, Cp*RuCl(cod) was selected for subsequent optimization.

Interestingly, treating diyne 6a with 1-hexyne 9a and 1 mol% Cp*RuCl(cod) with no solvent (neat) at 0°C gave isoindolinone 10a with a 50% conversion (entry 5). This suggests that using DCE as a solvent for this reaction is actually detrimental. In addition to the desired isoindolinone 10a, dimer 11 was also formed as a significant by-product.[12]

Crucially, regioisomeric cyclotrimerization product 12 was not observed at all in the crude $^1$H NMR spectrum. The reaction under neat conditions reached completion within 16 h when 3 mol% of catalyst 3 was used, and with a significant reduction in the proportion of homo-coupled product 11 produced (entry 6).

We were interested in using cyclopentyl methyl ether (CPME) as a solvent for this cyclization as it has been recently established as a safer and more environmentally benign alternative to many traditional organic solvents.[18] As shown in entry 7, when the reaction was conducted in CPME with 3 mol% of catalyst 3, diyne 6a was completely consumed within 16 h and an improved selectivity for the cross-coupled product 10a was observed. By comparison, the same reaction using only 1 mol% catalyst resulted in a comparable level of selectivity, but a lower conversion (entry 8). Reducing the number of equivalents of 1-hexyne 9a to two resulted in the complete consumption of diyne 6a but also a significantly increased level of homo-coupling.

In an attempt to minimise the formation of dimer 11, diyne 6a was added dropwise over 3 h to a stirring solution of monoyne 9a and catalyst 3[19] and this proved to be highly effective (entry 10). When using the 3-hour dropwise addition it was possible to reduce the number of equivalents of 1-hexyne 9a from four to two with no increase in homo-coupling (entry 11). A further reduction to 1.1 equivalents of 1-hexyne 9a did result in increased homo-coupling, but target isoindolinone 10a was still the major product (entry 12).

The cyclization of 6a and 9a was also effective when 2-MeTHF or MTBE were used as solvents, but in both cases a greater degree of homo-coupling of 6a was observed than with CPME (entries 13 and 14). The reaction proved to be relatively water tolerant, with a significant conversion and a reasonable selectivity observed when the reaction was conducted in the presence of 10% water (entry 15). Cyclization was even observed when the reaction was conducted in water as solvent (entry 16). This is important as it could enable the extension of the reaction to aqueous conditions for reactions of water-soluble substrates.

Following the optimization study the conditions described in entry 11 were taken as the “optimized” cyclization conditions as they required a reduced excess of monoyne and minimized the formation of dimer 11. Crucially this protocol did not require the CPME solvent to be either degassed or dried. This, together with the environmental benefits of CPME, makes this reaction a very practical method for the synthesis of isoindolinones. Dimer 11 could be readily separated from the desired product by flash column chromatography, and the optimized conditions described in entry 11 gave the target isoindolinone 10a in 81% isolated yield (Table 2, entry 1). This reaction was also scaled up to a 500-mg scale and isoindolinone 10a was isolated in 66% yield (428 mg product).

**Monoyne Scope**

The cyclization of 6a was then examined with a variety of monynes using the optimized conditions described above to determine how robust the reaction was for a range of different substrates. Diyne 6a cyclized with a wide range of monynes 9 as detailed in Table 2. Crucially, no evidence for the formation of regioisomeric isoindolinones was observed in any of the cyclization reactions. Alkyl monynes 9a–e cyclized efficiently with 6a to give the corresponding isoindolinones 10a–e in good isolated yield (entries 1–5, 66–83%). Little formation of the undesired dimer 11 was observed, except in the reaction of tert-butylacetylene 9b, presumably due to high steric crowding about the monoalkyne. Carbamate 9f cyclized with 6a to give 10f in reasonable yield and with modest levels of homo-coupling (entry 6).

Ether 9g and acetal 9h both underwent cyclotrimerization with 6a, but with the formation of significant quantities of dimer 11. Propargylic alcohol 9i and methoxyacetylene 9j both failed to cyclize with diyne 6a, with only starting material being recovered in both cases. In addition to aliphatic monynes, diyne 6a cyclized effectively with a broad range of aromatic monynes. Electron-rich (entries 12, 13, 17 and 18), electron-poor (entry 16) and sterically hindered substrates (entries 12 and 14) could all be tolerated and products
Table 2. Reaction of diyne 6a with a selection of monoynes 9.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkyne 9</th>
<th>3 [mol%]</th>
<th>Time [h]</th>
<th>Product 10</th>
<th>Yield of 10 [%][b]</th>
<th>Ratio 10:11[c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-Bu</td>
<td>9a</td>
<td>3</td>
<td>10a</td>
<td>81</td>
<td>9:1</td>
</tr>
<tr>
<td>2</td>
<td>t-Bu</td>
<td>9b</td>
<td>3</td>
<td>10b</td>
<td>66</td>
<td>2:1</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>9c</td>
<td>3</td>
<td>10c</td>
<td>81</td>
<td>9:1</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>9d</td>
<td>3</td>
<td>10d</td>
<td>81</td>
<td>6:1</td>
</tr>
<tr>
<td>5</td>
<td>(CH₂Cl)</td>
<td>9e</td>
<td>3</td>
<td>10e</td>
<td>83</td>
<td>8:1</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>9f</td>
<td>5</td>
<td>10f</td>
<td>63</td>
<td>2:1</td>
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<tr>
<td>7</td>
<td></td>
<td>9g</td>
<td>3</td>
<td>10g</td>
<td>56</td>
<td>3:2</td>
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<tr>
<td>8</td>
<td></td>
<td>9h</td>
<td>3</td>
<td>10h</td>
<td>43</td>
<td>4:5</td>
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<tr>
<td>9</td>
<td></td>
<td>9i</td>
<td>3</td>
<td></td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>9j</td>
<td>3</td>
<td></td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>9k</td>
<td>4</td>
<td>10k</td>
<td>83</td>
<td>6:1</td>
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<tr>
<td>12</td>
<td></td>
<td>9l</td>
<td>3</td>
<td>10l</td>
<td>93</td>
<td>&gt;10:1</td>
</tr>
<tr>
<td>13</td>
<td></td>
<td>9m</td>
<td>4</td>
<td>10m</td>
<td>83</td>
<td>6:1</td>
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<tr>
<td>14</td>
<td></td>
<td>9n</td>
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<td>15</td>
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<td>9o</td>
<td>3</td>
<td>10o</td>
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<td>9p</td>
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<td>17</td>
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<td>9q</td>
<td>5</td>
<td>10q</td>
<td>79</td>
<td>6:1</td>
</tr>
<tr>
<td>18</td>
<td></td>
<td>9r</td>
<td>10</td>
<td>10r</td>
<td>79</td>
<td>7:1</td>
</tr>
<tr>
<td>19</td>
<td></td>
<td>9s</td>
<td>3</td>
<td></td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>20</td>
<td></td>
<td>9t</td>
<td>20</td>
<td>10t</td>
<td>50</td>
<td>2:1</td>
</tr>
<tr>
<td>21</td>
<td></td>
<td>9u</td>
<td>3</td>
<td>10u</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>22</td>
<td></td>
<td>9v</td>
<td>5</td>
<td>10v</td>
<td>55</td>
<td>3:1</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: A solution of 6a in CPME was added dropwise to a stirring solution of 9 and 3 in CPME over 3 h at room temperature.
[b] Isolated yield.
[c] Determined by the analysis of crude ¹H NMR spectra.

were isolated in good yields (79–93%) with low levels of diyne homo-coupling. For most of these examples longer reaction times (up to 24 h), and in some cases higher catalyst loadings, were required to drive the reaction to completion. However, the reactions with ortho-substituted arylacetylenes 9l and 9n reached...
Highly Regioselective Synthesis of Substituted Isoindolinones

Table 3. Cyclizations involving diynes with different N-substituents[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R₁</th>
<th>R₂</th>
<th>3 [mol%]</th>
<th>Time [h]</th>
<th>Product 13</th>
<th>Yield of 13 [%][b]</th>
<th>Ratio of 13:14[c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>t-Bu 6b</td>
<td>n-Bu 9a</td>
<td>3</td>
<td>16</td>
<td>13a</td>
<td>84</td>
<td>10:1</td>
</tr>
<tr>
<td>2</td>
<td>t-Bu 6b</td>
<td>Ph 9k</td>
<td>4</td>
<td>24</td>
<td>13b</td>
<td>89</td>
<td>&gt;10:1</td>
</tr>
<tr>
<td>3</td>
<td>t-Bu 6b</td>
<td>o-tolyl 9l</td>
<td>3</td>
<td>16</td>
<td>13c</td>
<td>94</td>
<td>&gt;10:1</td>
</tr>
<tr>
<td>4</td>
<td>H 6c</td>
<td>n-Bu 9a</td>
<td>10</td>
<td>24</td>
<td>13d</td>
<td>51 (90%[d])</td>
<td>2:1</td>
</tr>
<tr>
<td>5</td>
<td>H 6c</td>
<td>o-tolyl 9l</td>
<td>10</td>
<td>24</td>
<td>13e</td>
<td>62 (90%[d])</td>
<td>7:1</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: a solution of 6 in CPME was added dropwise to a stirring solution of 9 and 3 in CPME over 3 h at room temperature.
[b] Isolated yield.
[c] Determined by the analysis of crude 1H NMR spectra.
[d] Conversion of diyne 6 to 13/14 (determined by crude 1H NMR without the use of an internal standard).

completion within 16 h with only 3 mol% of catalyst 3 (entries 12 and 14). Monoyne 9l also cyclized with exceptionally high selectivity for the cross-coupled product 10l over dimer 11, whereas ortho-bromo alkyne 9a gave a slightly lower selectivity. Although Yamamoto et al. have reported the [2+2+2]-cycloaddition of an electron-deficient nitrile and an amide-tethered diyne to give a pyridine,[20] in our reaction nitrile 9s failed to cyclize with 6a to form any product via reaction of either the alkyne or the nitrile (entry 19). Only a limited quantity of 11 (~10%) was formed in this reaction suggesting that 9s may inhibit the catalyst. Heterocycle-containing alkyne 9t cyclized effectively with 6a to give the corresponding 2-pyridyl derivative 10t in a moderate 50% yield (entry 20). In contrast N-methylimidazole 9u failed to cyclize with 6a, with unreacted starting material being recovered (entry 21). Alkyne 9v cyclized with 6a to give bora-mide 10v in reasonable yield (entry 22).[21]

Diyne Scope

The cyclization of amide-tethered diynes bearing different N-substituents was examined and the results are summarized in Table 3. N-t-Bu diyne 6b proved to be an excellent substrate for the synthesis of 5,7-substituted isoindolinones. Treatment of 6b with 1-hexyne 9a under the optimized reaction conditions gave isoindolone 13a in 84% yield with little formation of the dimer 14a (entry 1). The cyclization of 6b with 9k required 4 mol% 3 and 24 h to reach completion, giving isoindolone 13b in 89% yield (entry 2). The reaction of 6b with 2-ethynyltoluene 9i proceeded in 94% yield without an elevated reaction time or an increased loading of catalyst 3, and also occurred with very little formation of dimer 14a (entry 3).

The N-H diyne 6c proved less effective for the synthesis of isoindolinones, with the cyclization of 6c and 1-hexyne 9a requiring 10 mol% Cp*RuCl(cod) 3 and 24 h to achieve a 90% conversion of diyne 6c (entry 4). Isoindolone 13d was only formed in modest yield (51%) and significant formation of dimer 14b was observed. Under the same conditions the cyclization of 2-tolylacetylene 9l and N-H diyne 6c gave the desired isoindolone 13e in a slightly higher yield with 90% conversion. Again, the reaction with 2-ethynyltoluene 9i proved to be unusually selective, with 13e and 14b formed in the ratio 7:1 (entry 5). The lack of a sterically bulky N-substituent is presumably responsible for both the reduced reactivity of N-H diyne 6c with monoynes and the high level of diyne homo-coupling observed in these reactions.

The cyclization of amide-tethered diynes bearing different alkyn substituents was also explored (Table 4). With doubly substituted diynes 6d and 6e, no homo-coupling of the diyne was observed and dropwise addition of the diyne to the reaction was unnecessary (entries 1–3). With 10 mol% of Cp*RuCl(cod), methyl-substituted diyne 6d cyclized with 1-hexyne 9a to form a 9:1 mixture of regioisomeric isoindolinones 15a and 16a (entry 1).

Ethyl-substituted diyne 6e reacted with 1-hexyne 11a with lower regioselectivity, giving a 2:1 mixture of isoindolinones 15b and 16b (entry 2). However, diyne 6e cyclized with 2-ethynyltoluene 9l, to give a 5:1 mixture of isoindolinones 15c and 16c (entry 3). Interestingly, the presence of diastereotopic benzylic protons in the 'H NMR spectrum suggests that isoindolinone
15c is a chiral molecule, presumably due to restricted rotation about the hindered biaryl unit.

The dependence of the cyclotrimerization on an SiMe3 regiodirecting group was also investigated. Diyne 6f with a terminal methyl substituent reacted with 1-hexyne 9a under the optimized cyclization conditions to give isoindolinone 15d in 85% yield (entry 4). Crucially, there was no trace of the regioisomeric isoindolinone 16d by crude 1H NMR. Similarly, diyne 6f cyclized with 2-ethynyl toluene 9l to give isoindolinone 15e in 94% yield, with no evidence for the formation of regioisomer 16e (entry 5).

Functional Group Manipulation of Cyclized Products

Conversion of the cyclized isoindolinone products into a number of synthetically interesting motifs was examined. Isoindolinone 10a was converted to aryl halides 17 and 18, in 79% and 90% yields, respectively, via an ipso substitution of the silyl group (Scheme 3).[22] Treatment of N-t-butylisoindolinone 13a with triflic acid resulted in a simultaneous deprotection of the lactam and protodesilylation within 30 min to give N-H isoindolinone 20 in good yield.[23] Alternatively, treatment of 13a with iodine monochloride followed by depredtection with triflic acid gave 7-iodoisoindolinone 19 in 83% yield. Thus, an N-t-Bu diyne can be used as an indirect method for the synthesis of N-H isoindolinones via this acid-mediated deprotection.

It was also possible to access a tetrasubstituted monocyclic benzene. Treatment of N-H isoindolinone 19 with di-tert-butyl dicarbonate gave N-Boc isoindolinone 21, which could be reduced with lithium borohydride to form N-Boc protected amino alcohol 22.

Table 4. Cyclizations involving diynes with different alkyne substituents.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diyne 6</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>Time [h]</th>
<th>Isolated products</th>
<th>Yield of (15 + 16) [%] [b]</th>
<th>Ratio of 15:16[c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6d</td>
<td>SiMe3</td>
<td>Me</td>
<td>n-Bu 9a</td>
<td>10</td>
<td>24</td>
<td>15a/16a</td>
<td>69</td>
</tr>
<tr>
<td>2</td>
<td>6e</td>
<td>SiMe3</td>
<td>Et</td>
<td>n-Bu 9a</td>
<td>10</td>
<td>24</td>
<td>15b/16b</td>
<td>57</td>
</tr>
<tr>
<td>3</td>
<td>6e</td>
<td>SiMe3</td>
<td>o-toly 9l</td>
<td>10</td>
<td>24</td>
<td>15c/16c</td>
<td>73</td>
<td>5:1</td>
</tr>
<tr>
<td>4[e]</td>
<td>6f</td>
<td>Me</td>
<td>H</td>
<td>n-Bu 9a</td>
<td>3</td>
<td>16</td>
<td>15d[f]</td>
<td>85</td>
</tr>
<tr>
<td>5[f]</td>
<td>6f</td>
<td>Me</td>
<td>H</td>
<td>o-toly 9l</td>
<td>3</td>
<td>16</td>
<td>15e</td>
<td>94</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: A solution of 6 in CPME was added to a stirring solution of 9 and 3 in CPME over 1 min at room temperature.
[b] Isolated yield.
[c] Determined by the analysis of crude 1H NMR spectra.
[d] Diyne 6f in CPME was added dropwise over 3 h to a solution of 9 and 3 in CPME.
[e] Evidence of limited homo-coupling of 6f was observed in the crude 1H NMR spectrum.
Highly Regioselective Synthesis of Substituted Isoindolinones

A solution of 6a (500 mg, 1.86 mmol) in CPME (11 mL) was added dropwise over 3 h to a stirring solution of 1-hexyne 9a (0.43 mL, 300 mg, 3.7 mmol) and Cp*RuCl (21 mg, 3 mol%) in CPME (7.7 mL) at room temperature. The reaction mixture was stirred for a further 13 h before being filtered through a silica pad, eluting with ethyl acetate. The solvent was removed under vacuum to give the crude product 10a; yield: 428 mg (1.22 mmol, 66%). IR (film): νmax = 2955 (m, C–H), 2930 (m, C=C), 1688 (s, C=O), 1454 (m), 1409 cm⁻¹ (m); ¹H NMR (600 MHz, DMSO-d₆): δ = 7.34–7.21 (7 H, m, ArH), 4.68 (2H, s, C=CH₂), 1.51 (2H, m, CH₂CH₂CH₂), 1.26 (2H, m, CH₂CH₂CH₂), 0.83 (3H, t, J = 7.4, CH₃CH₂), 0.34 [9H, s, Si(CH₃)]; ¹³C NMR (125 MHz, DMSO-d₆): δ = 168.5, 144.8, 142.1, 137.7, 136.9, 134.3, 134.0, 128.6, 127.6, 127.2, 123.7, 48.9, 45.4, 35.1, 33.2, 21.8, 13.7, –0.4; HR-MS (EI⁺): m/z = 351.0111 [M⁺], C₁₂H₁₄ON requires 351.0123.

Conclusions

In summary, we have demonstrated the regioselective synthesis of polysubstituted isoindolinones via the Cp*RuCl(cod)-catalyzed cyclotrimerization of amide-tethered dynes and monoynes. This cyclization is effective with a wide range of structurally diverse monoynes and was demonstrated to work with a variety of different dynes. We have also demonstrated that the cyclization products could be converted into a range of functionalized isoindolinones and a tetrasubstituted benzene derivative.

Experimental Section

Full experimental details are provided in the Supporting Information.

Cp*RuCl(cod)-Catalyzed Cyclization of a Diyne and a Monoyne

This work was supported by the Engineering and Physical Sciences Research Council (Advanced Research Fellowship EP/E052789/1), together with GlaxoSmithKline (Industrial CASE Award) and the UCL PhD program in Drug Discover-ery. We would also like to acknowledge Simon Peace (GSK) for helpful discussions.

Acknowledgements

References

Gold catalysed synthesis of 3-alkoxyfurans at room temperature†

Matthew N. Pennell,a Robert W. Foster,a Peter G. Turner,b Helen C. Hailes,a Christopher J. Tamea and Tom D. Sheppard*a

We have recently reported that the gold-catalysed rearrangement of propargylic alcohols to enones (the Meyer–Schuster rearrangement) proceeds at room temperature in toluene, in the presence of a small amount of alcohol additive (MeOH or EtOH).¹⁶ During the course of our study into the scope of this reaction, we observed that attempted rearrangement of acetal-containing propargylic alcohol 1a (Scheme 1, R¹ = 4-CF₃C₆H₄)

Synthetically important 3-alkoxyfurans can be prepared efficiently via treatment of acetal-containing propargylic alcohols (obtained from the addition of 3,3-diethoxypropyne to aldehydes) with 2 mol% gold catalyst in an alcohol solvent at room temperature. The resulting furans show useful reactivity in a variety of subsequent transformations.

Furans are important structural motifs which appear in a wide array of natural products, biologically active compounds and pharmaceuticals.¹ They also have potential uses in the construction of conjugated polymers for applications such as organic electronics.² As a consequence, the synthesis of polysubstituted furans has attracted considerable interest. Recent synthetic approaches have included a number of transition-metal catalysed cyclisation reactions³ mediated by a variety of catalysts⁴–⁸ including systems based on palladium,⁴ rhodium,⁵ ruthenium⁶ and silver.⁷ Over the past few years, the use of homogeneous gold catalysts for facilitating the addition of nucleophiles to carbon–carbon multiple bonds has emerged as a very powerful synthetic method⁹ and a number of gold-catalysed approaches to the synthesis of heterocyclic aromatic rings,¹⁰ including simple furans,¹¹ have been reported. Simple 3-alkoxyfurans such as 3-methoxyfuran are highly electron rich systems which show useful reactivity,¹² and have found application in natural product synthesis¹³ as well as in the construction of polysubstituted tetrahydrofurans.¹⁴ However, the chemistry of more complex 3-alkoxyfurans has not been widely explored, largely as a consequence of their synthetic inaccessibility.¹⁵ Herein, we describe a gold-catalysed method for the synthesis of a wide variety of 3-alkoxyfurans from readily available propargylic alcohols, via a process that allows straightforward variation of substituents both on the furan ring and the alkoxy group.

![Scheme 1 Gold-catalysed synthesis of 3-ethoxyfurans and 3-methoxyfurans. a 600 mg scale reaction. b Clean conversion of the aldehyde in propargylic alcohol 1o into the dimethylacetal occurred under the reaction conditions.](image)

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† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data for all compounds and ¹H and ¹³C NMR spectra for novel compounds. See DOI: 10.1039/c3cc48290a
gave a mixture of the expected enone 2a and 3-ethoxyfuran 3a, where the alcohol additive had become incorporated.17 Given the importance of polysubstituted furans in a wide variety of applications, we sought to optimise this transformation.18 Pleasingly in ethanol furan 3a was formed in 89% yield with complete selectivity. With these optimised conditions in hand, the synthesis of a wide range of 3-ethoxyfurans and 3-methoxyfurans was then explored. High yields (68–98%) of the corresponding furans 3 and 4 were obtained with a selection of propargylic alcohols 1a–1o. A wide range of aromatic groups can be incorporated at the 2-position of the furan ring, including electron deficient (1a, 1b, 1m), electron rich (1c, 1n) and sterically encumbered (1f) benzene rings, as well as thiophene (1j) and furan (1i) rings. Propargylic alcohols containing aliphatic groups were also smoothly converted into the corresponding 2-alkyl furans (1b, 1d, 1g, 1k). When methanol was used as the reaction solvent, direct solvolysis to generate the 3-methoxyfurans 4 occurred selectively over formation of the corresponding dimethoxymethane 4o. Many functional groups including an alkene (1g), a nitrile (1h), a halide (1i), an ester (1m), and even a free phenol (1n) were compatible with the reaction. In the case of the aldehyde containing substrate 1o, concomitant formation of the corresponding dimethoxymethane 4o was observed. The synthesis of furan 3b was performed on a 600 mg scale without difficulty to give the alkyl furan in 85% yield.

The synthesis of more complex 3-alkoxyfurans was then explored, by incorporation of other alcohols in the furan formation reaction (Scheme 2). Primary (5b, 6b, 7b), secondary (8b) and tertiary (9b) alcohols were incorporated efficiently, including functionalised examples such as allyl alcohol (6b) and ethylene glycol (7b).

It was also possible to construct a conjugated bis-(3-alkoxy-2-furyl)benzene 4p in excellent yield by gold-catalysed reaction of bis-propargylic alcohol 1p with MeOH (Scheme 3). The conjugated triaryl unit in 4p is reminiscent of the oligofuran systems currently being investigated for a variety of applications in organic electronics.2 Interestingly, propargylic alcohol 1q containing a nearby alkenne unit underwent tandem alcohol addition/ene-yne cyclisation to give fused cyclohexylfurans 10 in excellent yield, with incorporation of the alcohol on the cyclohexane ring. This provides a rapid assembly of the fused furan-cyclohexane motif present in the terpene natural product furadysin.19

Appropriate control experiments18 were performed to demonstrate that the gold catalyst was required for the furan formation, and that the reaction was unlikely to be catalysed by Brønsted acid (Tf$_2$NH)$_2$20 or silver salts [AgNTf$_2$].16,21 The furan formation reaction potentially proceeds via regioselective gold-catalysed addition of the alcohol to the alkyne to generate a vinyl gold intermediate 11 (Scheme 4). Loss of ethanol can then lead to allenyl ether 12 which can undergo further activation by gold to give oxonium ion 13. Oxonium ion 13 can then be attacked by the nearby alcohol to generate dihydrofurane intermediate 14 which will evolve to the furan 3 after protodeauration and loss of ethanol. An alternative pathway which proceeds via Lewis-acid activation of the acetal to generate oxonium ion 15, followed by conjugate addition of the alcohol to give 12, can also be envisaged. However, this seems less likely given the fact that the furan formation does not readily occur in the presence of a simple Brønsted acid catalyst.18

The electron-rich 3-alkoxyfurans are highly reactive, and care should be taken during the isolation of these compounds in order to prevent decomposition of the products via atmospheric oxidation.18 The reactivity of these furan systems can nevertheless be readily harnessed in a variety of other useful transformations (Scheme 5). Furans 4b readily underwent a Diels–Alder reaction with N-methylmaleimide at room temperature to generate the cycloaduct 16 as a 2:1 mixture of separable stereoisomers in excellent overall yield (94%). Treatment of the major diastereoisomer with TFA led to stereoselective cyclisation to give the polycyclic ether 17 in 69% yield. Cyclohexyl fused furan 10b gave tertiary amine 18 in 92% yield upon reaction with Eschenmoser’s salt.12c We were also able to promote Claisen rearrangement12 of the alkoxyfuran 6b by heating at reflux in toluene to generate 2,2-disubstituted 3-furanone 19 in 80% yield. Electrophilic bromination23 of furan 3e proceeded in 75% yield.

![Scheme 2](image1)

Scheme 2 Incorporation of different alcohols in the 3-alkoxyfuran formation reaction with 1b.
to give bromide 20, providing a useful building block for cross-coupling reactions.

In summary, we have developed a mild gold-catalysed method for the formation of synthetically useful 3-alkoxyfurans which enables these versatile molecules to be prepared in two steps from readily available aldehydes, alcohols and 3,3-dithioisopropylene. The reaction gives access to a wide range of 3-alkoxyfurans in good to excellent yield, and the products can be used in subsequent transformations to access more complex structures.

We would like to acknowledge the Engineering and Physical Sciences Research Council (EP/E052789/1 and EP/G040680/1) and GlaxoSmithKline (CASE award, PhD studentship support and supply of selected aldehydes) for supporting this work.

Notes and references

9 See ESi† for further details.
Organic Synthesis

Irreversible endo-Selective Diels–Alder Reactions of Substituted Alkoxyfurans: A General Synthesis of endo-Cantharimides


Abstract: The [4+2] cycloaddition of 3-alkoxyfurans with N-substituted maleimides provides the first general route for preparing endo-cantharimides. Unlike the corresponding reaction with 3H furans, the reaction can tolerate a broad range of 2-substituted furans including alkyl, aromatic, and heteroaromatic groups. The cycloaddition products were converted into a range of cantharimide products with promising lead-like properties for medicinal chemistry programs. Furthermore, the electron-rich furans are shown to react with a variety of alternative dienophiles to generate 7-oxabicyclo[2.2.1]heptane derivatives under mild conditions. DFT calculations have been performed to rationalize the activation effect of the 3-alkoxy group on a furan Diels–Alder reaction.

Introduction

To access new areas of chemical space, medicinal chemistry programs are increasingly focusing on fragments and scaffolds with rigid 3D structures that contain a significant proportion of sp3 carbon atoms.[1] This in turn presents a considerable synthetic challenge as these molecules are generally not straightforward to synthesize, and late-stage derivatization is often far from trivial. Further challenges reside in the control of relative and absolute stereochemistry due to the presence of numerous chiral centres. Current structural scaffolds of interest include strained small-ring molecules (cyclopropanes, oxetanes, azetidines),[2] as well as fused (dihydrobenzofurans, indolines, tetrahydroquinolines)[3] and bridged bicyclic and polycyclic compounds (bicyclopentanes, cubanes, etc).[4] Natural products have also traditionally provided chemists with inspiration, as they include bioactive molecules with complex 3D architectures.[5] Many of these compounds, however, have high molecular weights or are too structurally complex to be suitable for use as scaffolds for medicinal chemistry applications. Nevertheless, smaller natural products contain ring systems that are potentially ideal scaffolds for use in medicinal chemistry, provided that efficient synthetic routes can be developed with appropriate functional groups at positions on the central core.

The endo-cantharimide skeleton (Figure 1, derived from cantharidin, a natural product secreted by many species of blister beetle with well-established cytotoxic activity)[6] has been exploited in a wide range of molecules with useful biological properties. The motif is present in several cytotoxic compounds,[7] antiplasmodial agents,[8] androgen receptor antagonists[9] and in a positive allosteric modulator of the metabotropic glutamate receptor 4 (mGlu4).[10] More generally, the 7-oxabicyclo[2.2.1]heptan skeleton is found in a number of other important natural products[11–13] and it has proved to be a valuable intermediate for synthetic chemists.[14–17] The properties of the endo-cantharimide skeleton have been extensively explored with a range of N-substituted derivatives showing useful biological properties. However, there are few methods for the introduction of substituents around the 7-oxabicyclo[2.2.1]heptan ring system.[18] Furthermore, the corresponding endo-cantharimide scaffold has rarely been reported at all.[19]

The endo-cantharimide skeleton is typically prepared by the [4+2] cycloaddition of furans and maleic anhydride, followed by alkene reduction and condensation with an amine (Scheme 1).[20] A curious feature of the cycloaddition reaction is...
the high stereoselectivity for theexo diastereomer observed, believed to be the result of a highly reversible cycloaddition process which is operating under thermodynamic control.\cite{21,22} It is possible to access the corresponding endo-cantharimide by a Diels–Alder reaction of furan with maleimide.\cite{23} However, experimental and computational studies have shown that this reaction is under thermodynamic control with the exo-cantharimide being the thermodynamic product.\cite{24} As a consequence, the endo-adduct of maleimide and furan is known to rapidly isomerize either in hot solvent or when exposed to visible light, which impedes both the isolation and application of these compounds.\cite{25} Another serious limitation of furan Diels–Alder reactions is that any deactivating substituents on the furan have a profound effect on the equilibrium position of the cyclization. For example, there are no reported examples of the [4+2] cycloaddition of 2-aryl or 2-heteroaryl furans with dienophiles of any type.

There is a long tradition of activating dienes for Diels–Alder reactions through the use of electron-donating substituents, which are known to reduce the activation energy for the cycloaddition reaction.\cite{26} However, this is generally a kinetic effect and reducing the kinetic barriers to a thermodynamically controlled reaction would only increase the rate at which isomerization occurs. To access stable endo-cantharimides it is therefore necessary to develop reactions with a significantly improved thermodynamic driving force.\cite{27}

We have recently developed a straightforward approach to 2-substituted-3-alkoxyfurans by gold-catalysed solvolytic cyclisation of suitably functionalised propargylic alcohols (Scheme 2).\cite{27} Preliminary studies indicated that 3-alkoxyfurans underwent rapid and endo-selective reactions with N-methylmaleimide to generate kinetically stable cantharimide products. The distinct 3D structure of the endo-cantharimide motif, coupled with its physical properties, should make it a valuable new scaffold for medicinal chemistry applications. Such an approach should enable control of substituents at a variety of positions on the tricyclic ring system.

## Results and Discussion

The reaction of 3-ethoxyfuran 2a with 1.2 equivalents of N-methylmaleimide proceed in a variety of solvents at room temperature to give cantharimide 3a in near quantitative yield (Table 1, entries 1 to 4). Crucially the cantharimide was formed with a clear preference for the endo diastereomer and the two isomers could be readily separated by flash column chromatography. The identity of the solvent had little impact on yield or diastereoselectivity, so dimethyl carbonate (DMC) was selected on the grounds of its excellent environmental profile.\cite{28} The reaction could also be scaled up to use 1 g of furan 2a, giving cantharimide 3a in 95% yield (entry 5, endo/exo ratio of 75:25). A purified sample of endo-3a was treated under the same reaction conditions and no isomerization was observed, suggesting the reaction proceeds under kinetic control. However, it was possible to increase the proportion of exo-3a by heating the reaction at 80 °C for 16 h (entry 6). The cyclization was equally effective when 3-methoxyfuran 2b was used as a diene, giving the corresponding adduct in excellent yield as an 80:20 mixture of endo and exo diastereomers (entry 7). These reaction conditions were applied to a wide range of 3-ethoxyfurans with different substituents at the 2-position.

### Table 1. \([4+2]\) cycloaddition of 3-alkoxyfurans 2 with N-methylmaleimide.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Solvent</th>
<th>T [°C]</th>
<th>Reaction t [h]</th>
<th>Product</th>
<th>Yield [%]</th>
<th>endo/exo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et</td>
<td>EtO</td>
<td>25</td>
<td>4</td>
<td>3a</td>
<td>98</td>
<td>65:35</td>
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<tr>
<td>2</td>
<td>Et</td>
<td>PhMe</td>
<td>25</td>
<td>4</td>
<td>3a</td>
<td>100</td>
<td>65:35</td>
</tr>
<tr>
<td>3</td>
<td>Et</td>
<td>EtOH</td>
<td>25</td>
<td>4</td>
<td>3a</td>
<td>100</td>
<td>70:30</td>
</tr>
<tr>
<td>4</td>
<td>Et</td>
<td>DMC</td>
<td>25</td>
<td>4</td>
<td>3a</td>
<td>93</td>
<td>70:30</td>
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<td>5</td>
<td>Et</td>
<td>DMC</td>
<td>25</td>
<td>4</td>
<td>3a</td>
<td>95</td>
<td>75:25</td>
</tr>
<tr>
<td>6</td>
<td>Et</td>
<td>DMC</td>
<td>80</td>
<td>16</td>
<td>3a</td>
<td>93</td>
<td>55:45</td>
</tr>
<tr>
<td>7</td>
<td>Me</td>
<td>DMC</td>
<td>25</td>
<td>4</td>
<td>3b</td>
<td>89</td>
<td>80:20</td>
</tr>
</tbody>
</table>

[a] DMC refers to dimethyl carbonate. [b] Determined by analysis of the crude \(^1\)H NMR spectrum. [c] Yield determined by \(^1\)H NMR spectroscopy using penta-chlorobenzene as an internal standard. [d] Isolated yield. [e] Reaction conducted with 1.0 g of furan 2a.
with the results summarized in Table 2. The reaction tolerated furans with primary and secondary aliphatic substituents (Table 2, entries 2 and 3). It was also possible to incorporate a tert-butoxycarbonyl (N-Boc) piperidine, as shown in entry 4. The reaction was very effective with an aromatic group at the 2-position, giving the first reported examples of 4-arylcantharimides (entries 5 to 10). The reaction of 2-phenylfuran 2f gave an 80:20 mixture of endo and exo diastereomers in good yield. This reaction could also be conducted on a 1.0 g scale, giving the two diastereomers 3f in a combined yield of 86%, and with complete isomeric separation following chromatography on silica gel. The relative stereochemistry of the two diastereomers was confirmed by X-ray crystallography (Figure 2).

The reaction was tolerant of electron-poor aromatic substituents (Table 2, entries 6 and 9), an electron-rich aromatic substituent (entry 8) and an aryl bromide substituent (entry 7). It was also possible to use a sterically encumbered 2-tolyl substituent to give cantharimide 3k in 86% yield. Furthermore, the reaction was effective when the 3-alkoxyfuran possessed a heteroaromatic substituent, as can be seen in entries 11 to 13 (85–96% yields). The chemoselective reaction of bis-furan 2l with N-methylmaleimide to give exclusively the enol ether adduct is an interesting demonstration of the high reactivity of the 3-alkoxyfuran unit in a [4+2] cycloaddition reaction. It was also possible to functionalize a 3-alkoxyfuran at the 5-position prior to the cycloaddition reaction, in order to introduce a substituent at the 7-position of the endo-cantharimide scaffold (Scheme 3).

The cycloaddition of 3-alkoxyfuran 2a was effective with a number of alternative N-substituted maleimides, as illustrated in Table 3. Sterically more challenging N-substituents could be incorporated in high yield and without an extended reaction time.

Additionally, it was possible to combine the gold-mediated furan synthesis with the cycloaddition reaction in a single step (Scheme 4, conditions i). Treating propargylic alcohol 1a with gold catalyst and N-methylmaleimide gave diethyl acetal 6 in good yield. It appeared that the gold catalyst was responsible for the in situ conversion of enol ether 3a into the corresponding diethyl acetal, as the interconversion can be avoided by poisoning the catalyst with 2.5 mol% PPh3 prior to addition of

Table 2. [4+2] cycloaddition of 3-alkoxyfurans 2 with N-methylmaleimide.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Isolated yield [%]</th>
<th>endo/endo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>93</td>
<td>70:30</td>
</tr>
<tr>
<td>2</td>
<td>cyclohexane</td>
<td>95</td>
<td>85:15</td>
</tr>
<tr>
<td>3</td>
<td>cyclopropane</td>
<td>90</td>
<td>80:20</td>
</tr>
<tr>
<td>4</td>
<td>N-Boc</td>
<td>85</td>
<td>75:25</td>
</tr>
<tr>
<td>5</td>
<td>3f</td>
<td>86 (86)</td>
<td>80:20</td>
</tr>
<tr>
<td>6</td>
<td>CF3</td>
<td>75</td>
<td>80:20</td>
</tr>
<tr>
<td>7</td>
<td>Br</td>
<td>78</td>
<td>80:20</td>
</tr>
<tr>
<td>8</td>
<td>OMe</td>
<td>95</td>
<td>80:20</td>
</tr>
<tr>
<td>9</td>
<td>CO2Me</td>
<td>84</td>
<td>75:25</td>
</tr>
<tr>
<td>10</td>
<td>3k</td>
<td>86</td>
<td>80:20</td>
</tr>
<tr>
<td>11</td>
<td>3l</td>
<td>85</td>
<td>90:10</td>
</tr>
<tr>
<td>12</td>
<td>3m</td>
<td>96</td>
<td>70:30</td>
</tr>
<tr>
<td>13</td>
<td>3n</td>
<td>92</td>
<td>70:30</td>
</tr>
</tbody>
</table>

[a] Combined isolated yield of endo-3 and exo-3. [b] Determined by analysis of the 1H NMR spectrum of the crude product. [c] Reaction conducted with 1.0 g of furan 2f.

Figure 2. Crystal structures of cantharimides 3f. Ellipsoids are shown at the 50% probability level. Only hydrogen atoms belonging to the cyclic core are shown for clarity.

Scheme 3. Synthesis of a 7-substituted endo-cantharimide: i) (H,C==NMe2)2I (2 equiv), MeCN, 16 h, RT; ii) N-methylmaleimide (1.2 equiv), DMC, 24 h, RT.

The reaction was tolerant of electron-poor aromatic substituents (Table 2, entries 6 and 9), an electron-rich aromatic substituent (entry 8) and an aryl bromide substituent (entry 7). It was also possible to use a sterically encumbered 2-tolyl substituent to give cantharimide 3k in 86% yield. Furthermore, the reaction was effective when the 3-alkoxyfuran possessed a heteroaromatic substituent, as can be seen in entries 11 to 13 (85–96% yields). The chemoselective reaction of bis-furan 2l with N-methylmaleimide to give exclusively the enol ether adduct is an interesting demonstration of the high reactivity of the 3-alkoxyfuran unit in a [4+2] cycloaddition reaction. It was also possible to functionalize a 3-alkoxyfuran at the 5-position prior to the cycloaddition reaction, in order to introduce a substituent at the 7-position of the endo-cantharimide scaffold (Scheme 3).
Table 3. [4+2] cycloaddition of 3-alkoxyfuran 2a with maleimides 4.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield 5 [%]</th>
<th>endo/exo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph 4a</td>
<td>94</td>
<td>65:35</td>
</tr>
<tr>
<td>2</td>
<td>4-MeC₆H₄ 4b</td>
<td>83</td>
<td>55:35</td>
</tr>
<tr>
<td>3</td>
<td>c-Pr 4c</td>
<td>67</td>
<td>60:40</td>
</tr>
</tbody>
</table>

[a] Determined by analysis of the ¹H NMR spectrum of the crude product.

Scheme 4. One-pot cantharimide synthesis from propargylic alcohol 1a. i) N-methylmaleimide, 2 mol % PPh₃AuNTf₂, EtOH; ii) 2 mol % PPh₃AuNTf₂, EtOH then 2.5 mol % PPh₃ then N-methylmaleimide.

Scheme 5. Functional-group interconversion of enol ether endo-3f: i) H₂, 10% Pd/C; ii) 9-BBN then H₂O₂/NaOH; iii) SCX-2 cartridge; iv) NaBH₄, MeOH. 9-BBN = 9-borabicyclo[3.3.1]nonane.

The enol ether also underwent hydroboration and oxidation to give alcohol 8, with complete regio- and stereocontrol. Enol ether endo-3f could be hydrolysed to give ketone 9 in good yield by passing it through a strong cation exchange (SCX-2) cartridge. Treating ketone 9 with NaBH₄ afforded alcohol 10, again with high stereocontrol.

The acid-mediated aromatization of 7-oxabicyclo[2.2.1]heptane derivatives has been previously applied to the synthesis of aromatic rings, and this approach could be used to prepare substituted phthalimide 11. The one-pot cantharimide synthesis described in Scheme 4 was used to convert alcohol 1f into the crude cantharimide, which could be converted into phthalimide 11 by acid-mediated ring-opening and aromatization (Scheme 6).

Physicochemical properties

An important challenge for drug development is the generation of novel heterocyclic building blocks with suitable properties for use in screening and medicinal chemistry programs. The cantharimides accessed using this methodology have appropriate physicochemical properties for lead-like compounds, including lipophilicity, molecular weight and polar surface area (Figure 3). Another attractive feature of these scaffolds is the high proportion of sp³-hybridized carbon atoms, which is typically associated with improved protein binding selectivity and frequency, better solubility and a reduced chance of off-target effects. Indeed, cantharimides 7, 10, endo-3f and exo-3f were screened against the hERG receptor (IC₅₀ > 50 μM) and the aryl hydrocarbon receptor (EC₅₀ > 100 μM), which are responsible for common off target effects, and no affinity was observed. In addition the in vitro clearance of alcohol 10 in the presence of human microsomes was determined and only a low level of turnover was observed (< 0.53 mL min⁻¹ g⁻¹).
[4+2] cycloadditions with other dienophiles

The [4+2] cycloaddition of furans with maleate esters is known but was reported to require either forcing pressure\(^\text{[41]}\) or high catalyst loadings of a Lewis acid.\(^\text{[41]}\) In contrast, the catalyst-free reaction of dimethyl maleate \(\text{12a}\) and furan \(\text{2a}\) proceeded at room temperature to give adduct \(\text{13a}\) in a good yield and with excellent \(\text{endo}\) selectivity (Table 4, entry 1). The reactions of dimethyl and diethyl fumarate (\(\text{12b}\) and \(\text{12c}\)) with furan \(\text{2a}\) proceeded more rapidly, giving the corresponding adducts in 77–89% yield after 4 h (entries 2 and 3). There is a clear selectivity in both examples for the product which possessed stereochemistry with respect to the 3-position (\(\text{3-endo}\) with excellent regiocontrol (95:5) after 6 h at room temperature (Table 4, entry 5). The catalyst loading for this reaction is much lower than the high (some-times stoichiometric) loading reported for the Lewis acid-catalyzed reactions of 3\(H\) furans and acrylates.\(^\text{[41, 43]}\)

### Computational study

The reactions of five 3-alkoxyfurans and \(N\)-methylymaleimide were explored with the M06-2X exchange–correlation function of Truhlar et al.,\(^\text{[44]}\) a density functional that has been successfully used to model the reaction and activation energies of different cycloaddition processes.\(^\text{[44]}\) 2-Substituted-3-methoxyfurans were chosen as suitable models for our 3-alkoxyfurans and these were compared to the corresponding 3\(H\) furans.

The 3-alkoxy group has a dramatic effect on the thermodynamics of the cycloaddition reaction, as is evident in Table 5. All five reactions of 3-alkoxyfurans have a clear thermodynamic driving force for the formation of both \(\text{endo}\)- and \(\text{exo}\)-addition products (Figure 5) and the data is consistent with a reaction that is likely to be kinetically controlled. In contrast, the values of \(\Delta G\) for the corresponding reactions of 3\(H\) furans are all greater by 24–34 kJ mol\(^{-1}\).

### Table 4. [4+2] cycloaddition of 3-alkoxyfuran 2a with different dienophiles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dienophile 12</th>
<th>Reaction t [h]</th>
<th>Product 13</th>
<th>Isolated yield [%]</th>
<th>Product ratio(^\text{[41]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeO(\text{CCH}_{2})(\text{COOMe})(\text{12a})</td>
<td>72</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>MeO(\text{CCH}_{2})(\text{COOMe})(\text{12b})</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>EtO(\text{CCH}_{2})(\text{COEt})(\text{12c})</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Et(\text{COCH}_{3})(\text{12d})</td>
<td>16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Me(\text{COOMe})(\text{12e})</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\([a]\) Determined by analysis of the \(^1\text{H}\) NMR spectrum of the crude product. \([b]\) Reaction conducted at 80 °C. \([c]\) Crude product flushed through a SCX-2 cartridge. \([d]\) Reaction conducted with 2 mol % HFCl\(_2\).\(^\text{[41]}\)

### Table 5. Calculated \(\Delta G\) and \(\Delta G^\text{\textit{a}}\) for the reactions of furans 14 and \(N\)-methylymaleimide 15.\(^\text{[50]}\)

<table>
<thead>
<tr>
<th>14</th>
<th>15</th>
<th>endo-16</th>
<th>exo-16</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 14a | Me | OMe | \(-41.5\) | \(-47.7\) | \(82.1\) |
| 14b | 'Pr | OMe | \(-44.1\) | \(-53.2\) | \(78.6\) |
| 14c | 4-MeOC\(\text{CCH}_3\) | OMe | \(-32.5\) | \(-30.1\) | \(85.3\) |
| 14d | Ph | OMe | \(-34.0\) | \(-28.2\) | \(91.4\) |
| 14e | 4-F\(\text{CCH}_3\) | OMe | \(-25.3\) | \(-23.8\) | \(96.8\) |
| 14f | Me | H | \(-11.8\) | \(-16.8\) | \(96.2\) |
| 14g | 'Pr | H | \(-12.5\) | \(-10.3\) | \(92.8\) |
| 14h | 4-MeOC\(\text{CCH}_3\) | H | \(-6.1\) | \(-3.6\) | \(98.8\) |
| 14i | Ph | H | \(-1.7\) | \(0.7\) | \(105.5\) |
| 14j | 4-F\(\text{CCH}_3\) | H | \(-0.9\) | \(0.9\) | \(108.3\) |

\([a]\) All values in kJ mol\(^{-1}\). All data is calculated for species in the gas phase.
This effect is most significant when the 2-substituent is aromatic, as this results in a value of $\Delta G$ close to zero for the furans. As expected, the 3-alkoxy group also has a significant effect on the free energy of activation for the cycloaddition reaction, with the kinetic barrier reduced by 11–23 kJ mol$^{-1}$. The effect of solvation on these reactions was also considered but was found to have little effect (see Supporting Information).

The reversibility of most furan Diels–Alder reactions has been attributed to the loss of aromatic stabilization upon formation of an adduct, which results in a facile retro-cycloaddition. In order to examine the effect of a 3-methoxy group on this phenomenon, thermodynamic cycles involving the partial hydrogenation of 3-methoxyfuran and furan to the corresponding 2,5-dihydrofurans were considered (Scheme 7). It is notable that the free energy of hydrogenation for furan was 25.9 kJ mol$^{-1}$ greater than for 3-methoxyfuran. The corresponding reaction free energies for cyclopentadienes and were also calculated but no significant difference was observed. The implications of these calculations are that 1) the difference in behaviour between 3H and 3-methoxy furans in cycloaddition reactions can be attributed to differences associated with loss of aromaticity rather than with C–C bond formation and 2) a 3-methoxy group can reduce the energetic penalty associated with the loss of aromaticity upon the Diels–Alder reaction of a furan, increasing the thermodynamic stability of the cycloaddition product.

**Figure 4.** Calculated $\Delta G$ and $\Delta G^*$ values for the reactions of 2-phenylfurans 14d and 14i and N-methylmaleimide 15 in kJ mol$^{-1}$.

(Figure 4). This effect is most significant when the 2-substituent is aromatic, as this results in a value of $\Delta G$ close to zero for the furans 14h–j. As expected, the 3-alkoxy group also has a significant effect on the free energy of activation for the cycloaddition reaction, with the kinetic barrier reduced by 11–23 kJ mol$^{-1}$. The effect of solvation on these reactions was also considered but was found to have little effect (see Supporting Information).

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**Figure 5.** M06-2X/6-31G(d)-optimized endo and exo transition states for the reaction of furan 14d and N-methylmaleimide 15$^{[29]}$. Distances in Å.

**Scheme 7.** Thermodynamic cycle involving the hydrogenation of dienes 17 and 20.

**Conclusions**

We have demonstrated that 3-alkoxyfurans are excellent dienes for [4+2] cycloadditions with a wide variety of maleimides and other dienophiles. This methodology significantly expands the nature of cantharimides that can be readily prepared with high endo selectivity. The reaction tolerates alkyl, aryl and heteroaryl substituents and the enol ether cycloaddition product can be transformed into a diverse collection of drug-like compounds. Finally, DFT calculations have confirmed that a 3-alkoxy group has a significant effect on both the thermodynamic driving-force and the activation energy of the Diels–Alder reaction of 2-substituted furans with N-methylmaleimides. The former effect can potentially be attributed to the 3-alkoxy group leading to a reduced energetic penalty associated with the loss of furan aromaticity that occurs during the cycloaddition reaction.

**Experimental Section**

**General cycloaddition procedure**

A solution of the maleimide (1.2 equiv) in dimethyl carbonate (3.6 mL) was added to a stirring solution of 3-alkoxyfuran (1.0 equiv) in dimethyl carbonate (1.5 mL) at room temperature and the reaction stirred at room temperature for 4–24 h. The reaction was then diluted with ethyl acetate and loaded onto an aminopropyl cartridge. After 5 min the cartridge was then flushed with ethyl acetate and the solvent removed in vacuo to give the crude cycloaddition product. Experimental procedures, $^1$H and $^{13}$C NMR spectra, characterization data of all compounds, compound screening data, details of computational studies including energy minimized geometries and XRD crystallography files are available in the Supporting Information.

**Acknowledgements**

This work was supported by GlaxoSmithKline and the Engineering and Physical Sciences Research Council (EPSRC Industrial CASE Award) and the UCL Ph.D. program in Drug Discovery.
Polar Surface Area and \( \text{clog P} \) were calculated using ChemBioDraw Ultra 14.0, CambridgeSoft.


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Sustainable Synthesis of Chiral Tetrahydrofurans via the Selective Dehydration of Pentoses

Robert W. Foster,[a] Christopher J. Tame,[b] Dejan-Krešimir Bučar,[a] Helen C. Hailes,[a] and Tom D. Sheppard[a]

Abstract: L-Arabinose is an abundant resource available as a waste product of the sugar beet industry. Through use of a hydrazone-based umpolung strategy, L-arabinose was selectively dehydrated to form a chiral tetrahydrofururan on a multi-gram scale without the need for protecting groups. This approach was extended to other biomass-derived reducing sugars and the mechanism of the key cyclization investigated. This methodology was applied to the synthesis of chiral tetrahydrofurans, including a formal synthesis of 3R,3-hydroxymuscarine.

The more effective use of biomass, and in particular that generated as waste,[1] is essential to reduce the global dependence on petrochemical resources for the manufacture of valuable compounds, fuels and materials.[2] The majority of biomass is made up of carbohydrates, which are an abundant source of pentoses and hexoses.[3] For example, the refinement of sugar beet generates beet pulp as a major waste product, and this is a rich source of L-arabinose.[4] A variety of techniques have been developed to convert these biomass resources into valuable small molecules, such as the dehydration of pentoses under forcing acidic conditions to give furfural (Scheme 1), which can then be converted into various alcohols, alkynes and heterocycles.[5] However, the majority of compounds prepared from pentoses and hexoses in this fashion are either achiral[6] or racemic mixtures where the stereochemistry of the chiral precursors is lost.[7] Therefore using these products as intermediates in the synthesis of more complex targets may require the reintroduction or single-isomeric stereocentres using asymmetric catalysis[8] or resolutions.[9]

The tetrahydrofuran (THF) is a privileged scaffold within medicinal chemistry[10] and the stereoselective synthesis of chiral THFs has been an area of recent research.[11] An attractive approach is to utilize the inherent chirality present in single isomer biomass-derived carbohydrates.[12] However, existing methods often require the selective conversion of a primary alcohol into an alkyl sulfonate or halide[13] and/or the use of protecting groups.[14] Both of which are detrimental to the economy of a synthetic route.[15] Herein we describe the application of N,N-dimethylhydrazine[16] for the selective dehydration of biomass-derived reducing sugars to prepare chiral THFs under mildly acidic conditions (Scheme 1).[17]

Treating L-arabinose 1a with N,N-dimethylhydrazine and Amberlyst® 15 acidic resin in methanol at room temperature gave hydrazone 2a in 99% yield (Table 1). Stirring hydrazone 2a in methanol at 40 °C for 16 h with 20 mol% TFA resulted in 100% conversion of 2a. Analysis of the crude 1H NMR indicated the formation of THF 3a as a 75:25 mixture of diastereoisomers and purification by flash column chromatography gave a mixture of the two stereoisomers in 67% yield. The reaction was scaled up from a 6.7 mmol scale to a 104 mmol scale without any significant drop in yield, giving 11.9 g of THF 3a. The major diastereoisomer was isolated by recrystallization and the stereochemistry was confirmed by single crystal X-ray diffraction (Figure 1). Both steps were conducted in a sustainable solvent[18] (methanol) without the need for either pre-drying or for a drying agent to be present. The same reaction conditions were used to prepare the enantiomeric THF ent-3a from D-ribose (Table 1, entry 2) in a 59% yield over two steps. It is notable that the diastereoselectivity of this reaction was comparable with that observed for the cyclization of arabinose-derived hydrazone 2a.

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Supporting information for this article is given via a link at the end of the document.
Table 1. Two-step synthesis of THFs 3 from sugars 1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sugar 1</th>
<th>Step 1 yield/%</th>
<th>THF 3[b]</th>
<th>Step 2 yield%</th>
<th>d.r.[c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L-arabinose 1a</td>
<td>99</td>
<td>Me₂NN=N-OH</td>
<td>67 (66)[d]</td>
<td>75:25</td>
</tr>
<tr>
<td>2</td>
<td>D-ribose 1b</td>
<td>98</td>
<td>Me₂NN=N-OH</td>
<td>59</td>
<td>75:25</td>
</tr>
<tr>
<td>3</td>
<td>D-lyxose 1c</td>
<td>98</td>
<td>Me₂NN=N-OH</td>
<td>66</td>
<td>55:45</td>
</tr>
<tr>
<td>4</td>
<td>D-xylene 1d</td>
<td>not isolated</td>
<td>Me₂NN=N-OH</td>
<td>61[e]</td>
<td>55:45</td>
</tr>
<tr>
<td>5</td>
<td>L-xylene ent-1d</td>
<td>not isolated</td>
<td>Me₂NN=N-OH</td>
<td>57[e]</td>
<td>55:45</td>
</tr>
<tr>
<td>6</td>
<td>L-rhamnose 1e</td>
<td>99</td>
<td>Me₂NN=N-OH</td>
<td>69</td>
<td>60:40</td>
</tr>
</tbody>
</table>

[a] Reagents and Conditions: NH₂·NHMe (2 equiv.), Amberlyst® 15, MeOH, 24 h, RT. [b] Reaction conducted on a 0.00–0.70 mmol scale unless otherwise stated. [c] Determined by analysis of the crude ¹H NMR spectra. [d] Reaction conducted using 20.0 g (104 mmol) of hydrazone 2a. [e] Yield over two steps from xylose.

The methodology was also extended to D-lyxose (Table 1, entry 3), with the corresponding hydrazone prepared in good yield. The TFA-mediated cyclization step gave THF 3b in 66% yield as a 55:45 mixture of diastereoisomers. THF 3b could also be prepared from D-xylene in 61% yield over two steps, again as a 55:45 mixture of diastereoisomers (entry 4). This is a particularly important result as D-xylene is one of the major components of biomass.[9] Xylose is naturally available in both enantiomers and using L-xylene it was possible to access ent-3b in a comparable yield (entry 5). The methodology was extended to deoxy sugar L-rhamnose, another constituent of sugar beet pulp, to give THF 3c in 69% yield as a 60:40 mixture of diastereoisomers (entry 6).

Recrystallization of hydrazone 3a yielded the major anti-diastereoisomer in high purity. Reducing hydrazone anti-3a using hydrogen, a palladium catalyst and Boc₂O gave carbamate 4 in 60% yield as a single stereoisomer (Scheme 2).

Treatment of THF 3a (d.r. = 75:25) with Amberlyst® 15 acidic resin in water at room temperature resulted in rapid hydrolysis of the hydrazone to give hydrolyzed product 5 (Scheme 3).[20] Reduction of compound 5 with NaBH₄ in methanol gave triol 6 as an 85:15 mixture of diastereoisomers in 98% yield over two steps from hydrazone 3a. Reductive amination of intermediate 5 using n-butylamine, acetic acid and hydrogen/palladium, followed by trapping of the intermediate amine with Boc₂O, gave carbamate 7 in 65% yield from hydrazone 3a as an 80:20 mixture of diastereoisomers. Compound 5 was also converted to alkene 8 using trimethyl phosphonoacetate in 73% yield over two steps with excellent E-selectivity. Finally, treating compound 6 with Amberlyst® 15 in methanol resulted in the formation of dimethyl acetal 9 in 74% yield over two steps from 3a as a 65:35 mixture of stereoisomers.

The hydrolysis/reduction sequence was also applied to the hydrazones 3b and 3c, gave the corresponding triols 10 and 11 in 90% and 93% yield respectively. L-Rhamnose-derived triol 11 is a late-stage intermediate in Fleet’s synthesis of...
3R-3-hydroxymuscariine 12 was previously prepared from L-rhamnose using stoichiometric bromine, trifluoromethanesulfonic anhydride and lithium aluminium hydride, so our route represents a less hazardous and more sustainable alternative.

Scheme 4. Hydrolysis of hydrazones 3 and transformation into a range of tetrahydrofuran products. Reagents and conditions: (i) Amberlyst® 15, H₂O, 5 minutes, RT; (ii) NaBH₄, MeOH, 1 h, 0 °C; (iii) n-BuNH₂, AcOH, H₂ (1 atmosphere), 10% Pd/C, CPMe, 16 h, RT; (iv) trimethyl phosphonoacetate, K₂CO₃, MeOH, 4 h 0 °C; (v) Amberlyst® 15, MeOH, 48 h, RT.

A plausible reaction mechanism for the cyclization of hydrazone 2a is proposed in Scheme 4. The N,N-dialkyldiazonium group of 2a could promote the acid-mediated elimination of the adjacent hydroxyl to give vinylidazinium intermediate 13. Cyclization of this intermediate would give THF 3a as either an anti- or syn-diastereoisomer. Resubmission of an isomerically pure sample of anti-3a to the reaction conditions resulted in the same 75:25 mixture of anti- and syn-diastereoisomers that is observed in the original reaction, which suggests that the diastereoselectivity is under thermodynamic control. Conducting the reaction in MeOH-d₄ did not result in the measurable incorporation of deuterium adjacent to the hydrazone, indicating that epimerization occurs through a reversible ring closure rather than via a vinylhydrazine intermediate. The proposed mechanism is also consistent with the observation that hydrazones 2a and 2b converge to THF 3a and ent-3a with the same diastereoselectivity (Table 1, entries 1 and 2), as the two reactions would proceed through enantiomeric vinylidazinium intermediates. Without TFA present no reaction was observed.

Postulated Mechanism

Reversibility Study

Deuteration Study

Scheme 5. Postulated mechanism and mechanistic studies.

In a preliminary study, the extension of this approach to hexoses was explored. Hydrazone 14, formed from D-galactose, was treated was subjected to the TFA-mediated cyclization conditions. This gave a 60:40 mixture of THF 15 and tetrahydropyran 16 in 53% isolated yield, with both heterocycles formed as single stereoisomers.

Scheme 2. Extending the methodology to D-galactose. Reagents and conditions; 20 mol% TFA.

In summary, we have developed an efficient multi-gram approach to low-molecular weight chiral molecules from biomass feedstock. This route allows access to a range of THF products without the need for protecting groups, including a formal synthesis of 3R-3-hydroxymuscariine. On the basis of experimental evidence, we have also proposed a reaction mechanism for the key cyclization which is based on an unusual vinylhydrazine intermediate.
Experimental Section

Experimental procedures, $^1$H and $^{13}$C NMR spectra, characterization data of all compounds and XRD crystallography files are available in the supporting information.

A stirring mixture of hydrazone 2a (20.0 g, 104 mmol) in methanol (210 mL, 0.5 M) was treated with TFA (1.5 mL, 2.4 g, 20 mol%) at room temperature and the reaction stirred at 40 °C for 16 h. The reaction was then quenched withaq. sat. NaHCO$_3$ and concentrated in vacuo to give the crude hydrazone (anti: syn = 75:25). This was purified by flash column chromatography (80:100 hexane:aceton) to give THF 3a (11.9 g, 88.3 mmol, 66%).

**THF anti-3a:** Isolated as a single stereoisomer following recrystallization from boiling CPME. Isolated as a white crystalline solid; m.p. = 65–67 °C; $R_f$ = 0.33 (1:1 acetone:hexane); $\nu_{max}$ (film/cm$^{-1}$) 3415s br, 2875s, 1586s, 1467s, 1445s; $^1$H NMR (600 MHz; MeOH-d$_4$) 6.51 (1H, d, $J$ = 6.6, N=CH), 4.23–4.18 (2H, m, N=CH$_2$CH$_2$), 4.08 (1H, dd, $J$ = 9.6, 4.9, OCH$_3$), 0.02 (1H, dd, $J$ = 7.3, 5.1, CH$_2$CH$_2$), 3.76–3.72 (1H, m, OCH$_3$), 2.79 (6H, s, N(CH$_3$_)$_3$) $^{13}$C NMR (150 MHz; MeOH-d$_4$) 135.6 (C=N), 82.5 (CH$_3$), 76.5 (N=CH$_2$), 73.9 (OCH$_3$), 72.4 (CH$_2$CH$_2$), 42.8 (N(CH$_3$_)$_3$); HRMS (EI) found [M]+ 174.0979; $\delta$$_D$ (20 °C) = +85.8 (anti-3a, MeOH, C = 1.4).

**THF syn-3a:** $^1$H NMR (600 MHz; MeOH-d$_4$) 6.71 (1H, d, $J$ = 7.2, N=CH), 4.36–4.31 (2H, m, N=CH$_2$CH$_2$), 4.15 (1H, d, $J$ = 4.8, CH$_2$CH$_2$), 3.91 (1H, dd, $J$ = 8.7, 6.2, OCH$_3$), 3.76–3.72 (1H, m, OCH$_3$), 2.79 (6H, s, N(CH$_3$_)$_3$) $^{13}$C NMR (150 MHz; MeOH-d$_4$) 135.6 (C=N), 83.1 (CH$_3$), 74.3 (N=CH$_2$CH$_2$), 73.2 (N=CH$_2$), 72.5 (OCH$_3$), 42.8 (N(CH$_3$_)$_3$).

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Keywords: Biomass, Tetrahydrofuran, Hydrazone, Arabinose

COMMUNICATION

Entry for the Table of Contents

COMMUNICATION

Sweet pickings. L-Arabinose, a major component of sugar beet pulp, was converted into a chiral tetrahydrofuran through use of an unusual hydrazone-mediated cyclization. This approach was developed for the stereoselective synthesis of diverse small-molecule tetrahydrofurans from biomass feedstock sources, without the use of protecting groups.