# Photocatalytic Generation of Free Radicals from Furan







A thesis submitted to the Board of the Faculty of Physical Sciences in partial fulfilment of the requirements for the degree of Doctor of Philosophy of the University of Oxford

**Wilfred Lewis**

**Lady Margaret Hall**

**Trinity Term 2019**

# Summary

This thesis concerns the development of a stannane-free method for generating reactive free radicals adjacent to a 2,5-disubstituted furan, the development of a furan oxidation method, and the total synthesis of the legonmycins, bacterial pyrrolizidine alkaloids.

The synthetic utility of free radicals, and the effectiveness of organotin compounds in generating them, are discussed in Chapter 1, as are the reasons for avoiding organotin contamination of synthetic compounds, established means for doing so, and photoredox catalysis. The synthesis of model substrates for photoredox-mediated hydrogen abstraction from 2,5-disubstituted furans is described in Chapter 2. Visible light-mediated cyclisation did not occur as intended, but the use of a polyoxometalate cluster and ultraviolet light to effect the same transformation is also described. Chapter 3 concerns the synthesis of precursors to tin-mediated generation of free radicals adjacent to furan, the behaviour of those radicals once formed, and the implications for the work described in Chapter 4. A side reaction was observed when carrying out the work described in Chapter 2; Chapter 4 describes the development of this into a method for complete and efficient conversion of furans into 2-ene-1,4-dicarbonyls, complementing existing methods for the same transformation. Chapter 5 describes abortive routes for the total synthesis of legonmycin A, *via* the methodology described in Chapter 4 and *via* nitrile activation upon acylation, and a successful route based on an existing synthesis of the jenamidines, incorporating an iodine-catalysed hydroxylation with $O_2$ as the terminal oxidant. This transformation proved problematic in previous syntheses of similar structures.

# Table of Contents

**Acknowledgements** ..... **v**
**Abbreviations** ..... **vii**
**1 Introduction** ..... **1**
Free Radical Chemistry and Stannanes ..... 1
Why (the Right) Chemical Reactions Don't Happen ..... 1
The Kinetic Case for Free Radical Chemistry in Synthesis ..... 4
Evolution of Synthetic Radical Chemistry and the Utility of Stannanes ..... 9
Mitigating Stannane Toxicity: Alternative Reductants ..... 17
Transition Metal and Group 13 Hydrides ..... 18
Group 14 Hydrides ..... 19
Phosphorus-based H-donors ..... 27
Thiols ..... 30
Mitigating Stannane Toxicity: Reducing Sn Contamination ..... 31
Catalytic Use of Tin ..... 31
Modified Tin Hydrides ..... 32
Stannanes on Polymeric or Insoluble Supports ..... 36
Reaction Additives and Modified Workup Techniques ..... 40
Open-Shell Species From Excited Electronic States ..... 43
**2 Photocatalytic Generation of α-Furfuryl Radicals** ..... **57**
Initial Proposal ..... 57
Substrate and Catalyst Syntheses ..... 59
Attempted Photoredox Cyclisation ..... 63
An Alternative Photocatalyst ..... 65
Synthesis of TBADT ..... 67
Confirming the Viability of TBADT and Reaction Setup ..... 68
Cycloisomerisation with TBADT ..... 69
Studies of Polarity Effects ..... 70
Conclusions ..... 72
Further Work ..... 74
**3 Behaviour of α-Furfuryl and Related Radicals** ..... **77**
Rationale for Stannane-mediated Formation of α-Furfuryl Radicals ..... 77
Synthesis of Precursors to Radicals of Interest ..... 78
Radical Cyclisations ..... 84

Conclusions ..... 90
Further Work ..... 91
**4 Development of Conditions for Oxidation of Furans to Enediones ..... 95**
Existing Methods for Furan Oxidation ..... 95
Optimisation Studies ..... 95
Synthesis of Substrates ..... 101
Evaluation of Reaction Scope ..... 104
Mechanism of Oxidation and the Role of Pyridine ..... 110
Cyclisation *in situ* via Conjugate Addition of Tethered Nucleophiles ..... 115
Conclusions ..... 117
Further Work ..... 118
**5 A Short Total Synthesis ..... 123**
Bacterial Pyrrolizidine Alkaloids ..... 123
Legonmycins from a Furan-derived Enedione ..... 130
Attempted Synthesis *via* Cyclisation of *N*-Acylnitrilium Ion ..... 132
A Less Ambitious Route ..... 138
Conclusions ..... 144
Further Work ..... 145
**6 Experimental Section ..... 147**
General Remarks ..... 147
Index of Compounds by Systematic Name ..... 149
Index of Compounds by Number ..... 153
Chapter 1 ..... 157
Chapter 2 ..... 158
Chapter 3 ..... 181
Chapter 4 ..... 204
General Procedure for Oxidation of Furan Mediated by 2.8 ..... 204
Chapter 5 ..... 234
Other Compounds ..... 252
**7 References ..... 255**
**8 Appendices ..... 273**
Appendix 1: Details of Visible Light- and UV-mediated Photocatalytic Runs ..... 273
Appendix 2: Nuclear Overhauser Effect Analysis of Compound 2.9 ..... 276
Appendix 3: Nuclear Overhauser Effect Analysis of Compound 3.22 ..... 277
Appendix 4: Nuclear Overhauser Effect Analysis of Compound 3.23 ..... 278

Appendix 5: Explanation of Formulae for Conversion and Polymerisation of Furan in Oxidation Reactions .....279
Appendix 6: Details of Optimisation of Conditions for Furan Oxidation.....286

# Acknowledgements

This whole enterprise has been surprisingly good fun for a surprising proportion of the time. The greatest factor in this has been my supervisor, Prof. Robertson. Jeremy, I'd like to thank you for your boundless patience, and for your understanding on the (many) occasions when I pushed the bounds of human fallibility and questionable decision-making.

To the EPSRC and DSTL, the taxpayers who fund them, and the private sector industrial partners of the SBM CDT, thank you for paying for all of this; Martin, Darren, Lara, Laura and Maitane, thank you for your hard work organising everything, and for looking after us so well. Thank you to everyone at Vertex Pharmaceuticals (but particularly Dave) for looking after me so well on my placement and helping me make compound *cis*-**3.23** in helpful quantities. I'm sorry that the saga of arriving at the right conditions didn't make it into the final draft. I would also like to thank the workshops and the analytical departments within the Chemistry Department for the analytical support offered, which I understand students working elsewhere can only dream of.

I thank Drs. Stephen Bell and Iain Fowlis, and most of all Dr. Arnold Fairless, for their concern, support and commiseration during a long and sometimes painful writing-up process. To my small army of proofreaders, thank you for performing an unenviable task: not because you had to, but because you are kind. To Sky, Nut, Jack, Patri and Leonidas, thank you for looking after the new guy, and then continuing to do so when it emerged that a certain degree of husbandry was necessary even when I wasn't the new guy any more. Cat, Kat, Joe, Helena, Marty, Stuart, Rob, Dave, Sam, Morgan, Linden, Jess, Xinlan, and Jack, our time working together was short, but I hope you enjoyed it as

much as I did. Victoria, Lucy, Xinxin, Jonny, and Alethea: it's been a pleasure working with you; for heaven's sake don't write your thesis like I did.

Finally, I'd like to thank my parents for getting me this far, for giving me a roof over my head and food while I wrote up, and for their understanding surrounding the duration of this mooching!

# Abbreviations

| | |
|---|---|
| $\lambda_{max,abs}$ | wavelength of maximum absorption |
| $\lambda_{max,irr}$ | wavelength of maximum emission in the context of UV light sources |
| ACVA | 4,4'-azobis(4-cyano-4-methylvaleric acid) |
| atm. | atmosphere or atmospheric |
| BDE | bond dissociation enthalpy |
| bpy | 2,2'-bipyridine |
| bpz | 2,2'-bipyrazine |
| br | broad |
| Cnp | indicates NMR assignment refers to 2-cyanopropanoyl functional group |
| DAST | diethylaminosulfur trifluoride |
| DBE | 1,2-dibromoethane |
| DMDHF | 2,5-dihydro-2,5-dimethoxyfuran (mixture of stereoisomers) |
| dtbbp | 4,4'-di-*tert*-butylbiphenyl |
| Dth | dithian-2-yl |
| EPHP | 1-ethylpiperidinium hypophosphite |
| eq. | molar equivalent(s) |
| FDMO | flavin-dependent monooxygenase |
| Fn | 5-methylfuran-2-yl as an abbreviation in structures, indicates NMR assignment refers to any furan in the context of spectroscopic assignment |
| FPTC | freeze/pump/thaw cycle |
| FT | Fourier transform |
| HAT | hydrogen atom transfer |
| H-G II | [1,3-Bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene]di-chloro(*o*-isopropoxyphenylmethylene)ruthenium, *alias* Hoveyda-Grubbs catalyst™ 2$^{nd}$ generation |

| | |
|---|---|
| HMDS | bis(trimethylsilyl)amide anion; refers to bis(trimethylsilyl)amine where cation (L = lithium, Na = sodium, K = potassium) not specified |
| Hx | indicates NMR assignment refers to *n*-hexyl functional group |
| Ic | isocaproyl (4-methylpentanoyl) |
| ICP-AES | inductively coupled plasma atomic emission spectroscopy |
| ICP-MS | inductively-coupled plasma mass spectrometry |
| Im | 1-imidazolyl |
| Iv | isovaleryl (3-methylbutanoyl) |
| m | multiplet in the context of NMR resonances, medium intensity in the context of IR absorptions |
| NBS | *N*-Bromosuccinimide |
| n.i. | not isolated |
| NRPS | non-ribosomal peptide synthetase |
| OSP | photoredox cycle in which the excited state of the catalyst is **o**xidatively quenched by the **s**ubstrate, and single-electron oxidation of the second **p**artner in an overall radical-radical coupling reaction returns the oxidised photocatalyst to the ground state |
| Oxp | indicates NMR assignment refers to 2-oxopropyl group |
| $P_{irr}$ | Luminosity of light source at specified wavelength |
| PCET | proton-coupled electron transfer |
| PE | light petroleum, bp 30 – 40 °C |
| PG | protecting group |
| Pld | indicates NMR assignment refers to pyrrolidine |
| ppy | 2-(2-pyridyl)phenyl |
| Pz | indicates NMR assignment refers to (dihydro- or tetrahydro)pyrrolizine core |
| RAFT | reversible addition-fragmentation chain-transfer |

| | |
|---|---|
| RSI | photoredox cycle in which the excited state of the catalyst is **r**eductively quenched by the **s**ubstrate, and a reactive **i**ntermediate thus derived reoxidises the photocatalyst to the ground state |
| rt | room temperature |
| rxn | reaction |
| sat. | a saturated solution of |
| sat. aq. | a saturated aqueous solution of |
| SET | single-electron transfer |
| sh. | Indicates shoulder on another UV absorption peak |
| SM | starting material |
| SOMO | singly-occupied molecular orbital |
| sp. | species (biological) |
| TBADT | tetra-*n*-butylammonium decatungstate |
| TBT | tri-*n*-butyltin |
| TBTCl | tri-*n*-butyltin chloride |
| TBTH | tri-*n*-butylstannane |
| TBTH-*d* | tri-*n*-butyl(deuterio)stannane |
| TCDI | 1,1'-(thiocarbonyl)diimidazole |
| $T_{max}$ | Temperature of maximum heat capacity in the context of DSC |
| TMP | 2,2,6,6-tetramethylpiperidide anion |
| wrt | with respect to |
| w/u | workup, work up or worked up |

# 1 Introduction

*"是故勝兵先勝而後求戰，敗兵先戰而後求勝."*
(Victorious warriors win first and then go to war, while defeated warriors go to war first and then seek to win.)
Sun Tzu (544 – 496 B.C.E.), philosopher and military strategist

## Free Radical Chemistry and Stannanes

### Why (the Right) Chemical Reactions Don't Happen

Because of the diversity of possible reactivity in the field of synthetic organic chemistry, and the instability of organic compounds with respect to combustion or fragmentation, attaining selectivity for desired transformations (other than high-temperature pyrolysis or combustion) inevitably involves some degree of kinetic control.[i] The Eyring equation (Equation 1.1) shows that the rate constant $k$ of any elementary reaction is a function of temperature $T$ and the standard Gibbs' energy of activation $\Delta^{\ddagger}G^{\ominus}$; all other elements of this equation are constants.[ii]

$$k = \frac{\kappa k_B}{h} \cdot T \cdot e^{-\frac{\Delta^{\ddagger}G^{\ominus}}{N_{Av} \cdot k_B T}} \qquad 1.1$$

Where a desired reaction occurs unacceptably slowly, warming the mixture may cause the reaction to proceed at an acceptable rate. If competing processes exist with a slightly higher associated $\Delta^{\ddagger}G^{\ominus}$-value, however, then warming will also cause these processes to occur, at the expense of the yield and purity of the target material. In general, carrying out reactions at low temperatures (necessitating a reaction pathway with a low-

[i] The term "thermodynamic control" is often usefully applied to reactions where the dominant product is the most stable one that is observed under conditions commonly imposed during organic synthesis (in contrast to "kinetic control", where the dominant product is the one that is formed fastest, other more stable products not being formed in the same quantity). If a product forms under thermodynamic control as described in this footnote, but under prolonged heating at (*e.g.*) hundreds or thousands of °C, the SM is converted to other compounds, then arguably that product is not truly the thermodynamic one.
[ii] The transmission coefficient $\kappa$ is the proportion of complexes passing through an energy maximum that do not revert to reactants.

energy transition state if a reasonable reaction rate is to be attained) is beneficial to selectivity. Unfortunately, synthetic chemists are impatient and ambitious; reactions that appear desirable to a synthetic chemist typically involve major rearrangement of the atoms and bonds constituting the reactant(s) and go to completion in minutes or hours. Such attributes indicate a high-energy transition state and elevated reaction temperatures, in direct contrast to factors engendering reaction selectivity. This impasse is resolved by use of transformations that convert SMs to products *via* interconversion with intermediate species through multiple, simpler, rearrangements.

Consider a product **P**, which can be formed directly from starting material(s) $\mathbf{SM_1}$ in a single transformation whose rate is determined by associated activation energy $\Delta^{\ddagger}G_{\text{direct,1}}^{\ominus}$ (Figure 1.1). If the reaction can be catalysed, or otherwise promoted by addition of other chemical species, then an alternative pathway *via* intermediate(s) $\mathbf{Int_{cat}}$ becomes possible, and the reaction proceeds at a rate limited by the elementary step with the highest associated activation energy $\Delta^{\ddagger}G_{\text{cat}}^{\ominus}$ (portrayed in Figure 1.1 as conversion of $\mathbf{Int_{cat}}$ to **P**). Alternatively, if different starting material(s) $\mathbf{SM_2}$, with a higher associated chemical potential, which are converted to high-energy intermediate(s) $\mathbf{Int_{rct}}$, is/are employed, then a pathway to **P** exists which is significantly more favourable than the direct conversion of $\mathbf{SM_1}$ (*i.e.* the associated activation energy $\Delta^{\ddagger}G_{\text{rct}}^{\ominus}$ is much less than $\Delta^{\ddagger}G_{\text{direct,1}}^{\ominus}$). This is the case despite the greater overall disruption – indicated by a greater displacement along the reaction coordinate axis – associated with direct conversion of $\mathbf{SM_2}$ to **P** with respect to $\mathbf{SM_1}$.

The simplicity of the multiple minor rearrangements that make up a "reactive pathway" with respect to rearrangement of a SM to product in a single step – and the

lower associated enthalpic and entropic costs of forming the corresponding transition states – leads to lower $\Delta^{\ddagger}G^{\ominus}$-values for the individual elementary reaction steps, including, crucially, the one which limits the overall rate of conversion of SM to product. The overall transformation can therefore proceed at an exponentially higher rate.

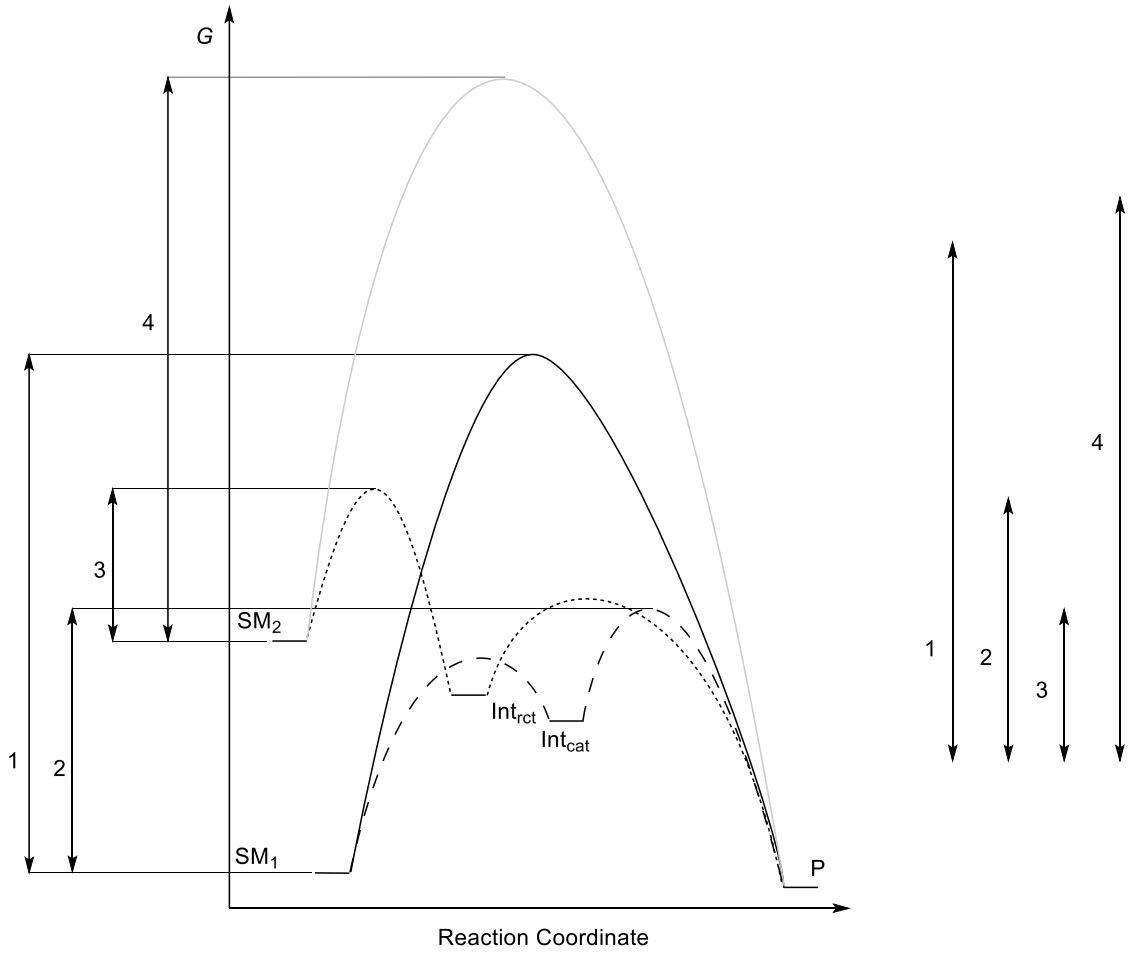



**Figure 1.1.** Reaction energy profile of four reactions. Direct conversion of starting material(s) **SM1** to **P** (solid) with associated activation energy $\Delta^{\ddagger}G_{\text{direct},1}^{\ominus}$ (1), conversion of **SM1** to **P** aided by a catalyst or other promoter (coarse dashed) with associated activation energy of rate-determining step $\Delta^{\ddagger}G_{\text{cat}}^{\ominus}$ (2), and conversion of different starting material(s) **SM2** to **P** *via* a reactive intermediate **Int**$_{\text{rct}}$ (fine dashed), with associated activation energy of rate-determining step $\Delta^{\ddagger}G_{\text{rct}}^{\ominus}$ (3). If conversion of **SM2** to **P** were to proceed directly (grey), associated activation energy $\Delta^{\ddagger}G_{\text{direct},2}^{\ominus}$ (4) would be even higher than $\Delta^{\ddagger}G_{\text{direct},1}^{\ominus}$. For ease of comparison, the energy barriers are also shown relative to a common ground state (right).

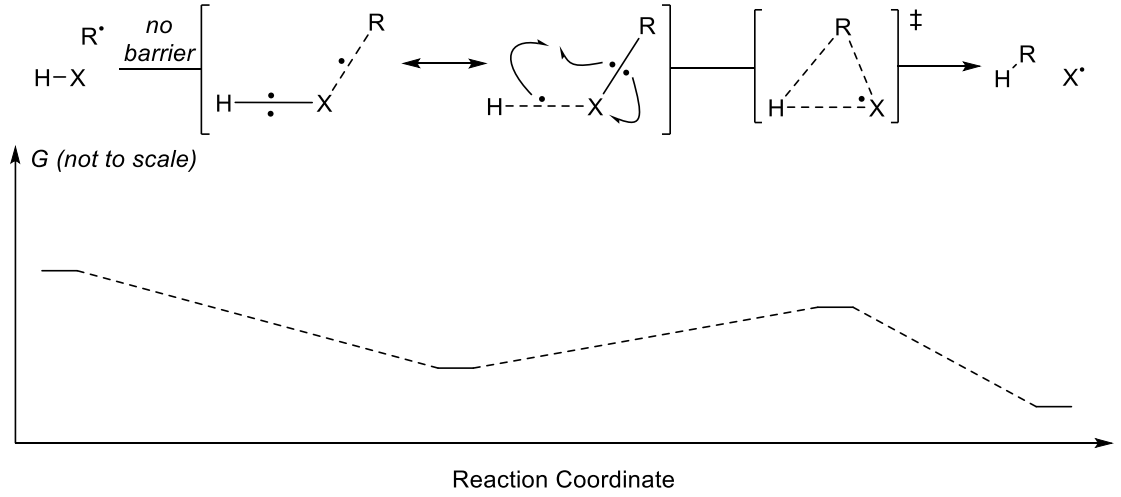
Knowledge of organic chemical reactivity can be defined as an understanding of the existence (or otherwise) of reactive pathways, and the sense in which they connect possible SMs to products. Synthetic method development is the discovery of reactive pathways which become accessible under invented conditions. A selective synthetic method consists of a choice of SM, reagents, and conditions which give rise to one reactive pathway that is significantly lower in energy than any others, so that one product forms in much greater quantity than any others (which themselves must proceed *via* pathways with higher associated $\Delta^{\ddagger}G^{\ominus}$-values).

**The Kinetic Case for Free Radical Chemistry in Synthesis**

Free radicals are chemical species containing at least one unpaired electron and as reactive intermediates go, they offer many benefits. The high chemical potential of species with SOMOs enables formation of energetic or strained systems which cannot always be obtained from reactions that proceed *via* heterolytic mechanisms, and transformations of free radicals typically have high *k*-values[iii] as a result of small associated $\Delta^{\ddagger}G^{\ominus}$-values. Indeed, H-abstraction processes from hydrogen halides by carbon-centred radicals in the gas phase have negative $\Delta^{\ddagger}G^{\ominus}$-values. This was first reported for the *tert*-butyl radical and HBr in 1988 (*1*) with additional studies on the same process in the case of methyl, ethyl, and isopropyl radicals, (*2*) and is rationalised by

[iii] A review of radical rearrangements whose (unimolecular) rate constants are characterised, and which are used as "radical clocks" to evaluate the rate of another radical process (*72*) indicates a range between 660 $s^{-1}$ and $1.3 \times 10^{8}$ $s^{-1}$ at 25 °C, although processes involving radical addition into an alkyne or benzene ring are slower. For comparison, the rate constant for the reaction of *n*-propyl bromide with KI in acetone at 25 °C is $1.4 \times 10^{-3}$ $s^{-1} \cdot M^{-1}$ (*429*) and the rate constant for hydrolysis of *tert*-butyl chloride in water at 25 °C is $2.9 \times 10^{-2}$ $s^{-1}$. (*430*)

barrierless exergonic formation of a bound complex, followed by extrusion of the halogen radical, with an associated barrier lower than the energy of the SMs (Scheme 1.1).




**Scheme 1.1.** Reaction and energy profile diagram for H-abstraction from hydrogen halides in the gas phase.

The main determinants of the relative stability of radical species are electronic effects and BDEs. Where the singly-occupied orbital can overlap with both filled **and** vacant orbitals of similar energy, the stabilisation is synergistic; this phenomenon is known as the captodative effect. (*3*) In addition to orbital energy considerations, radical rearrangements are enthalpically driven in the direction whereby strong bonds are formed at the expense of weaker ones. In contrast to Brønsted–Lowry acid/base reactions, where an electron pair in a high-energy orbital will abstract a proton to afford a conjugate base with an electron pair in a lower-energy orbital, reaction in the opposite sense is typical of radicals; a radical with a low-energy SOMO will abstract an H atom with a high-energy associated bonding orbital (Scheme 1.2). The bonds between H and electronegative atoms, broken during acid-base reactions, are among the strongest present in organic compounds (Table 1.1). Consequently, functional groups such as alcohols, carboxylic acids and protonated amines/amides – that are ubiquitous in many synthetic targets of biological

interest and susceptible to (de)protonation – often to the detriment of desired reactivity – are left untouched by the conditions imposed during free radical reactions. In contrast to heterolytic reactions dependent on strongly nucleophilic or electrophilic intermediates (which are easily quenched by, *e.g.*, adventitious water, with terminal consequences for an associated synthetic reaction), radical reactions are generally not affected by Lewis acidic/Lewis basic impurities.[iv]



**Scheme 1.2.** H-abstraction from electronegative atoms by radicals centred on less electronegative atoms is disfavoured, whereas proton abstraction from electronegative atoms by anions centred on less electronegative atoms is favoured.

| **Bonds to H** | | **Bonds to C** | | **Bonds to Sn** | |
|---|---|---|---|---|---|
| $H_3C$–H | 439.3 ± 0.4 | $H_3C$–F | 460.2 ± 8.4 | $Me_3Sn$–H | 326.4 |
| $H_3CCH_2C$–H | 420.5 ± 1.3 | $H_3C$–Cl | 350.2 ± 1.7 | $Ph_3Sn$–H | 294.6 |
| $(H_3C)_2HC$–H | 410.5 ± 2.9 | $H_3C$–Br | 294.1 ± 2.1 | Sn–F | 476 ± 8 |
| $(H_3C)_3C$–H | 400.4 ± 2.9 | $H_3C$–I | 238.9 ± 2.1 | $Me_3Sn$–Cl | 425 ± 17 |
| HO–H | 497.10 ± 0.29 | $H_5C_2$–$OCH_3$ | 355.2 ± 5.4 | Sn–Br | 337 ± 13 |
| $H_3CO$–H | 440.2 ± 3 | $H_3C$–$CH_3$ | 377.4 ± 0.8 | Sn–I | 235 ± 3 |
| $H_3CHN$–H | 425.1 ± 8.4 | $H_3C$–SH | 312.5 ± 4.2 | Sn–O | 528 |
| $(H_3C)_2N$–H | 395.8 ± 8.4 | $H_3CS$–$CH_3$ | 307.9 ± 3.3 | Sn–S | 467 |
| $Me_2NC(O)PhN$–H | 387.9 | C–Se | 590.4 ± 5.9 | Sn–Se | 401.2 ± 5.9 |
| $H_3CS$–H | 365.7 ± 2.1 | - | - | - | - |

**Table 1.1.** Selected BDEs; the bond concerned is specified by a dash, and all values are measured at 298 K in kJ·mol$^{-1}$. (*4*)

The formation of reactive chemical intermediates (*i.e.* those of high chemical potential), including free radicals, at reasonable temperatures requires either:

1. The formation of a by-product in a strongly exergonic process to counteract the increase in chemical potential upon formation of a reactive

[iv] It would be disingenuous not to point out that synthetic radical reactions have *bêtes noires* of their own; see page 9.

intermediate from a more stable SM (*e.g.* the release of $N_2$ upon formation of carbenes from diazo compounds, or cations from diazonium salts, both of which entail an increase in entropy),

2. The use of SMs which themselves have high chemical potential (*e.g.* fragmentation of organic peroxides to form alkoxy radicals *via* homolysis of a weak O–O bond),

3. Increasing the energy of the SM by doing work on the system (*e.g.* photochemical reactions),

or some combination of these. A notable method for forming radical species is by SET with a redox-active species, *e.g.* transition metal (*5*,*6*,*7*) or lanthanide (*8*,*9*,*10*,*11*) compounds. The combination of this methodology with excitation by visible light is discussed in greater depth later in this thesis (see page 43). The mechanisms of synthetic radical reactions often involve no overall consumption of radical species; such reactions are known as chain reactions,[v] and allow for many equivalents of substrate to be converted to product for each radical species initially generated as described above. Chain reactions were first proposed in order to rationalise the observation of quantum yields several orders of magnitude higher than unity for the photochemical reaction of $H_2$ and

[v] The term "chain reaction" has acquired an unfortunate connotation of a lack or loss of control not applicable to many processes that proceed *via* a chain mechanism. This is perhaps because of its evolution from a term of art to a phrase used more widely to describe runaway processes (including chain processes incorporating chain *branching* steps, in which propagation steps generate more chain carriers than are consumed, with a resulting exponential increase of reaction rate over time) such as chemical explosions, supercritical nuclear fission processes, and other situations whereby a minor event triggers a cascade of increasingly serious consequences, each precipitated by the last. In part because of the benefits of maintaining a low concentration of radicals in synthetic reactions (see page 8), but also on safety grounds, synthetic radical reactions typically do not proceed *via* mechanisms with possible chain branching steps. The risk of such reactions accelerating out of control as a result of thermal runaway remains, but is also present in the case of reactions that do not proceed *via* a chain mechanism.

$Cl_2$; (*12*) Photochemical dissociation of a single molecule of $Cl_2$ by a single photon affords two eq. of Cl• (Equation 1.2).[vi] Cl• reacts with $H_2$ to give product and another radical species H• (Equation 1.3), which in turn reacts with $Cl_2$, giving a second equivalent of HCl and regenerating Cl• (Equation 1.4). (*13*) The radical species required for, and generated by, propagation reactions are referred to as chain carriers.

| | | |
|---|---|---|
| Initiation: | $Cl_2 \xrightarrow{h\nu} 2\ Cl\bullet$ | 1.2 |
| First Propagation Step: | $Cl\bullet + H_2 \rightarrow HCl + H\bullet$ | 1.3 |
| Second Propagation Step: | $H\bullet + Cl_2 \rightarrow HCl + Cl\bullet$ | 1.4 |

In contrast to reactions that proceed *via* heterolytic mechanisms, where progress is limited by the rate-determining step, generation of products *via* chain processes proceeds at a rate controlled by the population of radical intermediates present, which is a function of both the rate of initiation (usually the rate determining step)[vii] and that of chain termination/inhibition processes. Efficient chain processes, therefore, call for the latter to be limited by:

1. Maintaining, as far as possible, a low concentration of radical species, both by dilution and by choosing an initiation method which is sufficiently slow under the conditions imposed; this often requires reagents to be added portionwise over several minutes or hours, or the use of a syringe pump.

[vi] Bodenstein's hypothesis was that upon irradiation, the $Cl_2$ molecule entered an excited state, facilitating reaction. (*12*) Nernst later proposed that dissociation occurred, (*13*) in what has become the accepted mechanism.

[vii] Chain-growth polymerisation reactions are a notable exception to this. In order to avoid the high polydispersity associated with rapid growth of polymer chains, each initated by radicals formed at different times by, *e.g.* the slow decomposition of a chemical initiator, growth of the polymer is deliberately made slow compared to the rate of initiation.

2. Avoiding the use of solvents – and other species – containing weak bonds that are prone to cleavage as a result of attack by radical species, *e.g.* toluene (weak benzylic C–H bonds due to stability of resulting benzyl radical), THF (weak C–H bonds α to O), ethyl acetate (weak C–H bonds α to O and α to carbonyl), or halogenated solvents (weak C–X bonds)

3. Exclusion of radical species that will sequester synthetically useful radicals *via* dimerisation, *e.g.* peroxides, $O_2$, and other oxidising or reducing agents. (*14*,*15*)

**Evolution of Synthetic Radical Chemistry and the Utility of Stannanes**

It is beyond the scope of this thesis to discuss comprehensively the application of radical transformations to synthetic chemistry; the topic has been reviewed extensively, (*14*,*15*,*16*,*17*,*18*,*19*,*20*,*21*) and is also the subject of several books. (*22*,*23*,*24*,*25*,*26*,*27*) Major developments in the field will, however, be summarised.

The trityl radical was the first free radical to be identified; (*28*) in 1900, Gomberg reported his failure to synthesise hexaphenylethane *via* the reductive homocoupling of bromo- and chlorotriphenylmethane, instead isolating several grams of trityl peroxide *via* recrystallisation as a result of trapping the trityl free radical with atmospheric $O_2$.[viii,ix] The regiochemistry of addition of HBr to allyl bromide was found by Kharasch and coworkers to be determined by the exposure, or otherwise, of the reaction mixture to $O_2$. (*29*) This

[viii] Indeed, this was the first appearance in the literature of the term "free radical", highlighting the existence of trityl as a distinct – if transient – chemical species, rather than merely a conceptual "part" of a molecule; previously, the term "radical" was routinely used where "functional group" or "moiety" would be today. (*431*)

[ix] As if the prospect of recrystallising an organic peroxide in such quantities were not sufficiently terrifying, Gomberg also recorded a melting point for this material (185 – 186 °C).

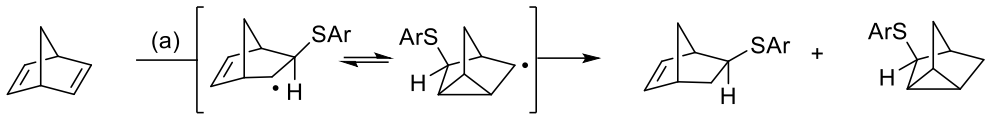
phenomenon, observed in other substrates in the meantime, was later rationalised by a radical mechanism when $O_2$ or peroxides were present:

> "…in the addition of hydrogen bromide to vinyl bromide [in the presence of a radical scavenger], the bromide ion is directed toward the carbon atoms with the lowest electron density to yield 1,1-dibromoethane, and [in the presence of $O_2$ or peroxides] the bromine atom is directed toward the carbon atom with the greater electron density to yield a 1,2-dibromoethyl free radical. This free radical then reacts with hydrogen bromide to yield 1,2-dibromoethane and another bromine atom, which is responsible for the propagation of the chain reaction. According to this mechanism, the function of peroxides or oxygen is to initiate a chain reaction which supplies bromine atoms." (*30*)

This reactivity was subsequently applied to formation of C–C bonds. (*31*,*32*,*33*,*34*,*35*,*36*) The halogenation of olefins in allylic positions was discovered by Wohl in 1919, (*37*) but was not applied to synthesis until 1942, when Ziegler and coworkers published their development of various allylic brominating agents, (*38*) and employed NBS in the synthesis of cantharidine; (*39*) the reaction proceeds *via* a chain mechanism, with a halogen atom acting as chain carrier. (*40*) The first metal-assisted radical reaction was the peroxide-initiated coupling of carbon tetrahalides to symmetrical organomercury species in 1951; (*41*) this work was later extended to asymmetric organomercuries. (*42*)

Radical intermediates undergo rearrangement reactions similar to those observed with the analogous carbocations; the first reported example of this behaviour was the isolation of sulfides **1.4** and **1.5** upon reaction of norbornadiene **1.1** with *para*-thiocresol, owing to reversible rearrangement of the radical intermediate between isomers **1.2** and **1.3** (Scheme 1.3). (*43*) Subsequently, the 5-hexenyl radical – produced first *via* photolysis of cyclohexane (*44*,*45*) and subsequently *via* decomposition of 6-heptenoyl peroxide (*46*)

and Kolbe reaction of 6-heptenoic acid (*47*) – was found to undergo *5-exo-trig* cyclisation, forming a cyclopentylmethyl radical.




**1.1** **1.2** **1.3** **1.4** **1.5**

Ar = *p*-tolyl

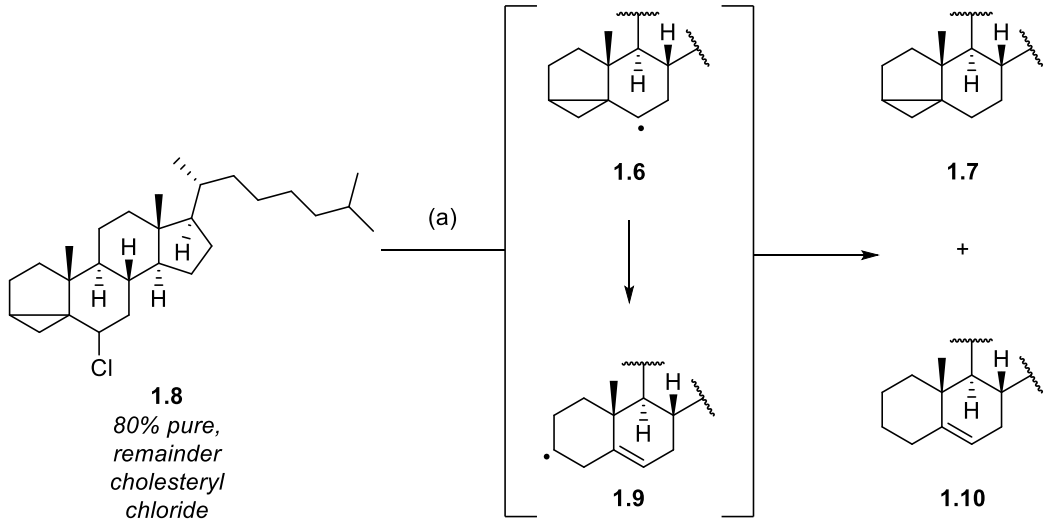
**Scheme 1.3.** Addition of a thiol to **1.1** gave two products owing to rearrangement of the homoallylic radical intermediate. (*43*) Reagents and conditions: (a) 0.97 eq. *para*-thiocresol, –20 °C, 20 min, 91% (combined, based on thiocresol).

It is common for none of the methods of forming radicals from closed-shell species (see page 6) to be viable for a substrate of synthetic interest; in any case, it is beneficial for reasons of atom economy, product selectivity, and control of reaction rate for synthetic radical reactions to be chain processes effected by a small total population of radical species. A method for atom transfer between radical species – formed from a separate radical initiator, chosen specifically for its tendency to form radicals under mild conditions – and closed-shell substrates to afford a chain carrier is therefore essential for the broad application of free radical chemistry to organic synthesis. The weakness of Sn–H bonds and strength of Sn–X bonds (X = Group 16 and Group 17 elements except F, on the grounds of Sn–F bond strength, (*48*) Table 1.1) indicates hydrodehalogenation or hydrodechalcogenation by stannanes as a thermodynamically favoured and broadly applicable means of converting a substrate to a radical intermediate; additionally, the ease of preparation of organohalides and the ability to convert alcohols to derivatives that react under stannane reduction conditions (*49*) lends versatility to the method. The stannyl radical $R_3Sn\bullet$ acts as a chain carrier in reduction processes mediated by Sn hydrides. This fact theoretically allows merely a trace of a radical initiator to be used in maintaining a

low concentration of stannyl radicals. In practice, some protocols, typically involving homolysis of C–Br or C–I bonds, (*16*) do not include a radical initiator[x] and others include radical initiator systems generating *ca.* 0.1 – 0.2 eq. of $R_3Sn\bullet$ slowly over the course of substrate conversion; this replenishment of radicals is necessary because radical chains can be terminated after a few cycles of substrate conversion by, *e.g.*, radical recombination or quenching with dissolved $O_2$ or other radical scavengers (often added to reagents and solvents as stabilisers to sequester the intermediates *via* which decomposition proceeds).

The reduction of halogenated species to the corresponding protonated derivatives by organostannanes was pioneered by van der Kerk and coworkers in 1957, (*50*) although it was not established for another 5 years that the reaction proceeded *via* a radical chain mechanism. (*51*) It did not take long for stannane chemistry to be employed in obtaining a free radical intermediate of interest, rather than simply dehalogenating a compound. Reduction of 5-hexenyl bromide and related compounds was effected with TBTH. (*52*) That cyclisation upon reduction with TBTH occurs "only with radicals possessing unsaturation in the 5,6 position" is noted, as is the recovery of allyl acetate instead of the expected γ-valerolactone upon reduction of allyl chloroacetate, "presumably because of stabili[s]ation of the uncycli[s]ed radical". Similar work with cyclisation of radicals into alkyne traps (*53*) followed, as did that on the rearrangement of radical **1.6** to homoallylic isomer **1.9** during the reduction of cyclocholestanyl chloride **1.8** with triphenylstannane (Scheme 1.4). (*54*)

[x] Although homolysis of distannane impurities in the hydride, traces of $O_2$ or peroxides, (*161*) or photochemical processes may serve to initiate the reaction.




**Scheme 1.4**. Reduction of **1.8** with triphenylstannane afforded isomeric products **1.7** and **1.10** owing to partial rearrangement of the radical intermediate. (*54*) Reagents and conditions: (a) excess triphenylstannane, pentane, *hν*, max. 30 °C, 24 h.

Beckwith and coworkers supplemented Baldwin's Rules (*55*) with *Some Guidelines for Radical Reactions*, (*56*) describing and explaining the tendency for:

1. Radical cyclisations into unsaturated traps under kinetic control to occur in the *exo* sense in the case of resulting formation of normal or small rings,

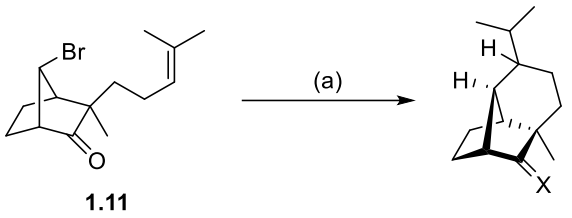
2. Homolytic addition at fully substituted $sp^2$ centres to be restricted,

3. Bonds aligned with a SOMO to undergo homolytic fission more easily than others, and

4. "1,5-Ring closures of substituted hex-5-enyl and related radicals" to afford *cis*-stereochemistry in the case of 1- or 3-substituted starting radicals, and *trans*-stereochemistry in the case of 2- or 4-substitution.

The first total synthesis involving reaction of a stannane-derived radical intermediate was reported in 1976: (*57*) Sativene **1.14** and its epimer copacamphene, **1.15**,

were synthesised *via* reaction of precursor **1.11** with TBTH in the presence of *tert*-butyl perbenzoate, followed by olefination of the resulting ketones **1.12** and **1.13** (Scheme 1.5). Cross-coupling of olefins and free radicals obtained *via* reduction of an organomercury species generated *in situ* was first reported in 1977. (*58*) Various synthetic procedures effecting similar reactivity, but generating the intermediate radical *via* stannane reduction, were subsequently reported by multiple groups, (*59*,*60*,*61*) but the method has come to be known as the Giese reaction, after one of the initial discoverers.



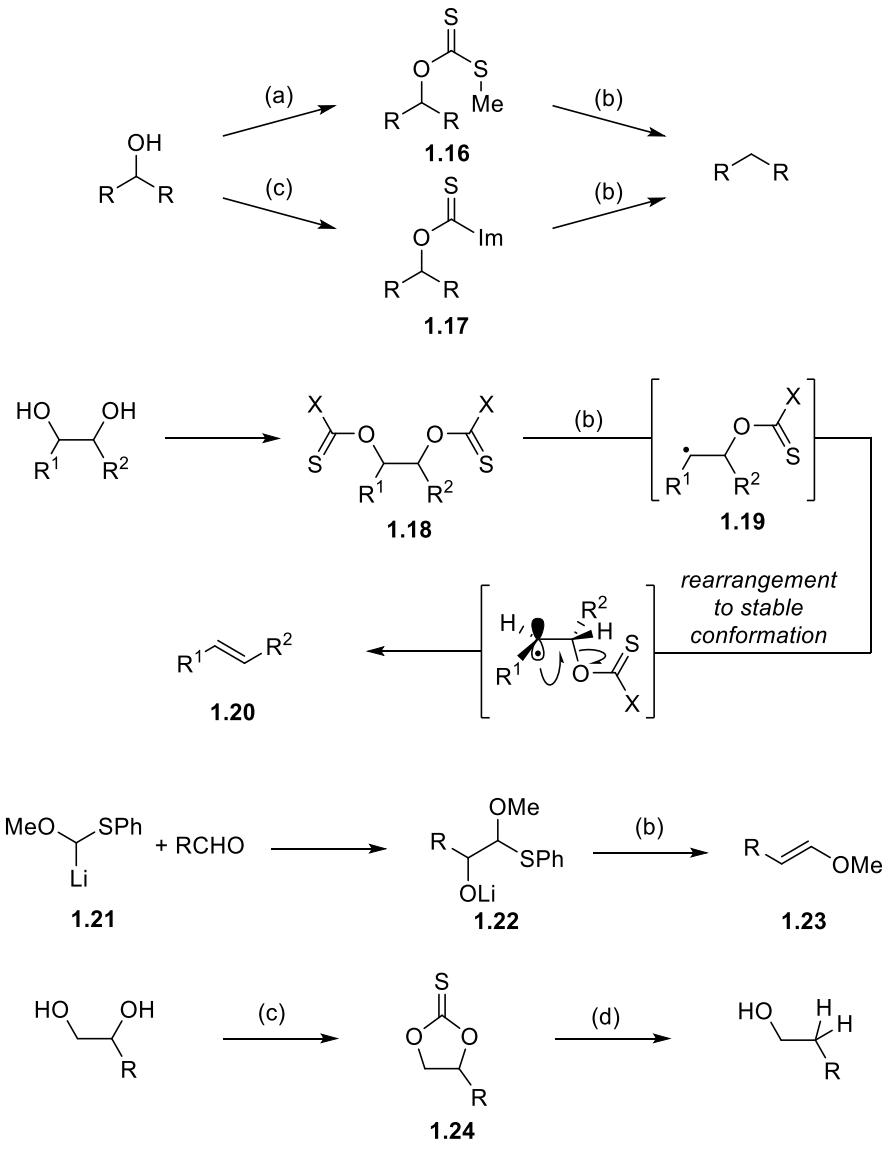

**1.11**

X = O, *cis* isomer: **1.12** (norsativone) 3%
X = O, *trans* isomer: **1.13** (copacamphenilone) 34%
X = $CH_2$, *cis* isomer: **1.14** (sativene)
X = $CH_2$, *trans* isomer: **1.15** (cocamphene)

**Scheme 1.5.** The first stannane-mediated total synthesis. (*57*) Reagents and conditions: 0.06 eq. *tert*-butyl perbenzoate, 0.91 eq. TBTH, *h ν*, 36 °C, 1.5 h. Initial chromatography afforded mixed fractions of **1.12** and **1.13** in 59% combined yield.

The development of a method for the deoxygenation of alcohols was significant; Barton and McCombie noted in their report (*49*) of the reaction that now bears their name that while primary alcohols could be converted to halides, sulfonates, or sulfides and reduced in an $S_N2$ process and tertiary alcohols could be dehydrated and the resulting olefin hydrogenated, there were no satisfactory analogous processes for secondary alcohols. The value of such a method to natural product chemistry was also highlighted; (*49*) aminoglycoside antibiotics, for example, depend on deoxygenation to prevent loss of action to metabolism, and deoxysugars are employed as cancer chemotherapeutics for similar reasons. (*62*) Cleavage of the relevant bonds requires derivatisation; the parent

compounds cannot themselves undergo homolysis owing to the strength of C–O bonds. Synthesis and reduction of several derivatives of alcohols was originally described, (*49*) but subsequent application of the reaction is dominated by use of xanthates **1.16** – typically obtained by deprotonation of the alcohol, followed by reaction sequentially with $CS_2$ and an alkylating agent, usually MeI – and thiocarbonylimidazole compounds **1.17**, obtained by direct reaction of the alcohol with TCDI (Scheme 1.6). (*62*) The formation of α-furfuryl radicals, which is relevant to the work described in Chapter 3, is heavily reliant on this methodology, given the instability of α-halofurans towards elimination, and the ease of preparation of furfuryl alcohols. (*63*) There are also reports of TBTH-mediated desulfurisation, (*64*) deselenation, (*65*) and denitration (*66*) of furan derivatives, which presumably proceed *via* free radical intermediates. Reduction of diols to olefins (*62*) is possible *via* the dixanthates **1.18**, as is monoreduction *via* cyclic thiocarbonate **1.24**. Vinyl ethers **1.23** are accessible *via* reaction of aldehydes with lithiated thioacetal **1.21**, conversion of the resulting alkoxide **1.22** to – for example – a xanthate (not shown), and reduction under radical conditions. (*67*) The Barton decarboxylation represents an efficient one-pot conversion of carboxylic acids to the corresponding nor-alkanes, (*68*) which was previously usually carried out by thermolysis of a peroxyester derivative with poor associated yield. (*19*,*69*)




**Scheme 1.6.** Applications of the Barton–McCombie deoxygenation. Representative reagents and conditions: (a) *i*: butyllithium, THF, –78 °C, 15 min, then $CS_2$, 30 min, reflux, then MeI, 30 min, reflux. (b) 1.1 eq. TBTH, 0.1 eq. AIBN, benzene, reflux. (c) 1.0 eq. TCDI, 0.1 eq. DMAP, DCM, 0 °C. (d) As (b), but excess TBTH.

Given that radical reactions are kinetically controlled, a good understanding of the rates of various radical processes is useful to rationalise the formation of side products, and to identify conditions under which side reactions, such as direct reduction of a substrate instead of a desired rearrangement, for instance, might be suppressed. Photochemically-initiated reactions can be studied *via*, *e.g.*, flash photolysis experiments,

the rotating sector method, (*70*) or EPR analysis, (*71*) but other radical reactions cannot. Carrying out a radical reaction of interest, *e.g.* H-abstraction from a species H–R, using a radical which undergoes a different reaction at a known rate, however, allows the rate of the first reaction to be elucidated merely by the distribution of reaction products; (*72*) this method also has the advantage that specialised (*i.e.* expensive!) spectroscopic equipment – not commonly available to synthetic chemists – is not required. (*72*)

While organotin compounds are valuable reagents for reductively driving free radical transformations, their toxicity represents a major disadvantage. (*73*) Mitigation techniques similar to those described below have been reported in the literature for processes using stannanes, but which do not proceed *via* chain mechanisms – *e.g.* the Stille reaction (*74*) – or ones which involve radical intermediates, but can be achieved *via* an alternative process – *e.g.* reduction of ketones to alcohols. (*75*) This work is included in reviews of techniques for avoiding the use of organotin compounds (*76*,*77*,*78*) and limiting the extent of contamination of products where Sn compounds are used, (*78*) but will not be discussed in this thesis.

## Mitigating Stannane Toxicity: Alternative Reductants

Where processes employ hazardous compounds, elimination of the latter or replacement with innocuous alternatives is considered preferable to controlling the extent to which workers are exposed to risk. (*79*,*80*) Organotin compounds are no exception to this, and their utility has caused great effort to be directed towards the development of H-donors less toxic than stannanes. (*76*,*77*)

**Transition Metal and Group 13 Hydrides**

In addition to their role as SET-based radical initiators (see page 7), zirconocenes (*81*,*82*,*83*) and $CpCr(CO)_3H$ (*84*) have been employed as H-donors in place of stannanes, although the cost of the (stoichiometric) reagents prevented widespread adoption. More recently, however, readily available zinc sulfinates have been employed as sources of C-centred radicals, which can undergo synthetically useful reactions. (*85*)

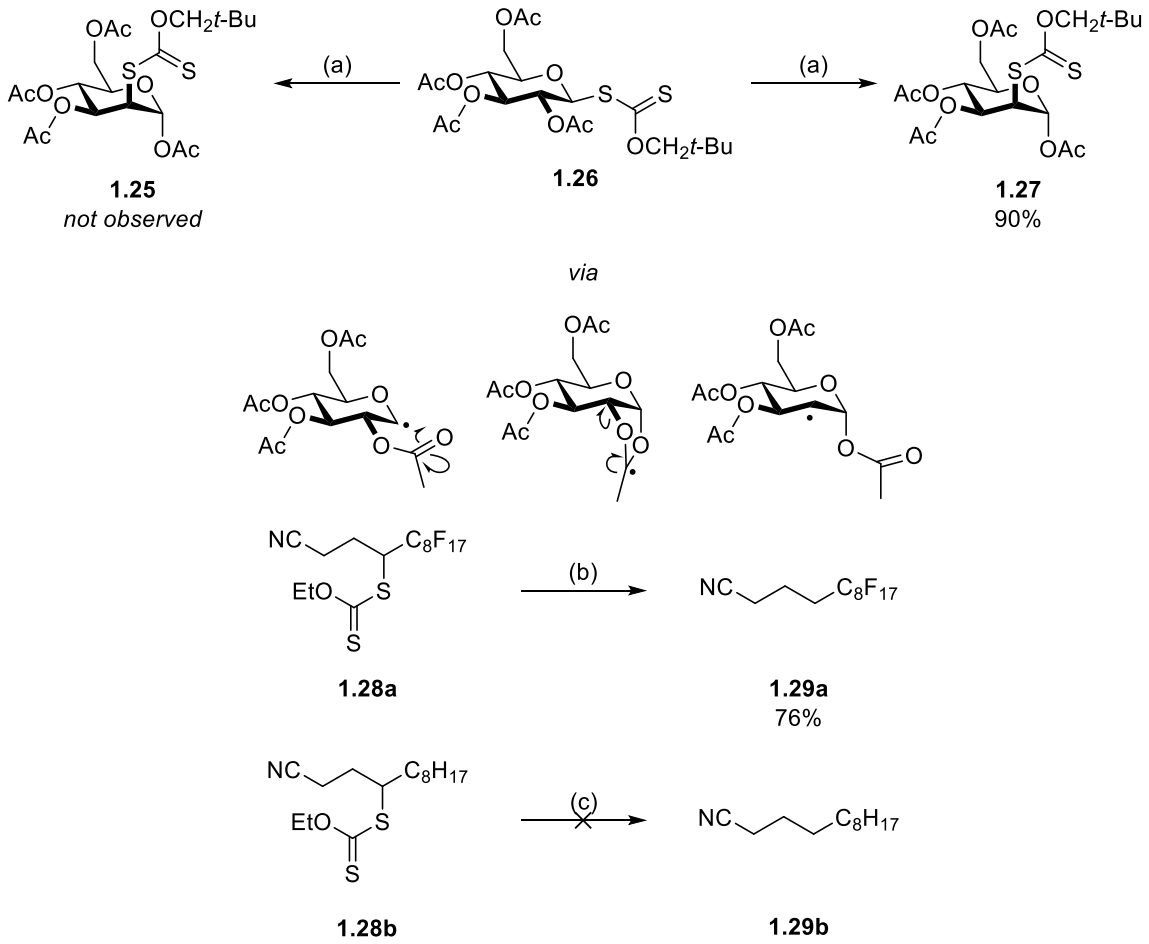
Borohydrides and aluminohydrides have been used to regenerate Sn hydrides, (see Mitigating Stannane Toxicity: Reducing Sn Contamination, page 31) both *in situ*, rendering radical reductions catalytic in stannane, and as a separate step. Borohydrides (*86*) and aluminohydrides, (*87*) however, also exhibit radical reactivity in their own right *via* H-donation. While boranes have strong B–H bonds, and are therefore poor H-donors, complexation with a Lewis base can decrease this bond strength to the extent that radical chains become operative. (*88*,*89*,*90*) The application of phosphine-ligated boranes as H-donors was also studied, (*91*) and N-heterocyclic carbenes have been employed in modulating the reactivity of boranes towards H-donation. (*88*,*89*,*92*)

Alkyl bromides, iodides, and a methyl dithiocarbonate were reduced to the corresponding alkanes in good to excellent yield by addition to $HGaCl_2$, freshly prepared by treatment of $GaCl_3$ with 0.5 eq. of Red-Al, with triethylborane initation. (*93*,*94*) A competition experiment between 1-bromodecane and decanal yielded 1-decanol and unreacted bromide; (*94*) such reductions are known (*95*) to proceed *via* a polar mechanism, in competition with radical reactions. In view of the expense of $GaCl_3$, a catalytic protocol was developed whereby 1.5 eq. of Red-Al was slowly added to a THF solution of the substrate and 0.2 eq. each of $GaCl_3$ and triethylborane. The ability of

$HInCl_2$ (prepared by reaction of $InCl_3$ with TBTH in THF at –78 °C) to reduce alkyl bromides (*95*) indicated the possibility that this reactivity might also be applied to Sn-free radical reductions; direct reductions, cyclisations, and Giese reactions, all catalytic in $InCl_3$ with $NaBH_4$ as a coreductant, were effected in acetonitrile, (*96*) and $HInCl_2$ was prepared by reduction of $InCl_3$ with DIBAL at 0 °C, and used in the reductive cyclisation of allyl 2-iodophenyl ether to a 3-methyl benzo-2,3-dihydrofuran in very good to excellent yield (NMR). (*94*) The expense of In and Ga compounds, and competing polar reducing reactivity has restricted their widespread adoption.

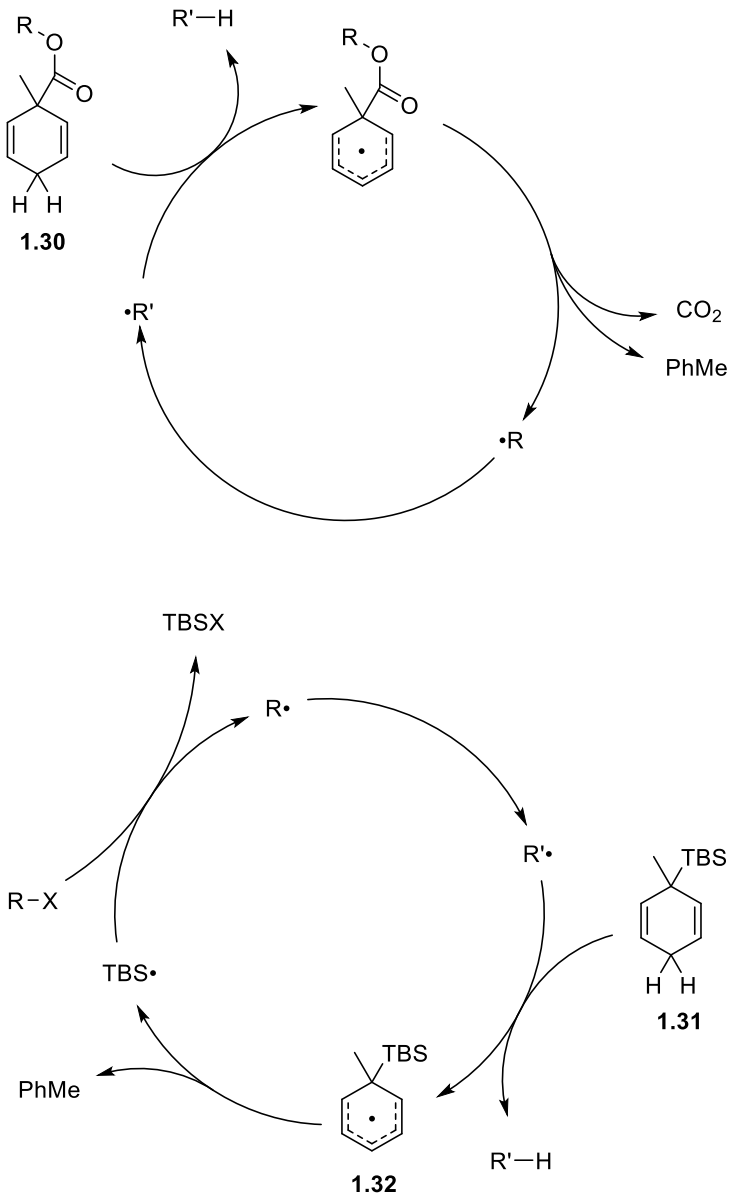
**Group 14 Hydrides**

Organic species containing sufficiently weak C–H bonds can also be employed as H-donors; the attempted rearrangement of anomeric xanthate **1.26** to **1.25** by heating with cyclohexane with lauroyl peroxide did not occur, instead affording deoxysugar derivative **1.27** owing to reduction by the solvent (Scheme 1.7). (*97*) "Secondary iodides flanked by one or more inductive electron-withdrawing groups" exhibit similar behaviour. (*98*) Cyclohexane also exhibited this behaviour in the lauroyl peroxide-initiated reaction of xanthate **1.28a** to nitrile **1.29a**, *via* a strongly electrophilic radical; this reaction does not occur when not polarity-biased in this way; non-fluorous analogue **1.28b** did not react under similar conditions. (*97*) Substituted 1,4-cyclohexadienes, tethered to a substrate, have also seen use as reductants; 1,4-cyclohexadiene itself cannot be used in chain processes as a separate reductant, because the cyclohexadienyl radical arising from H-transfer is too stable to abstract (pseudo)halide from the substrate. (*77*)




**Scheme 1.7.** Serendipitous radical reduction of xanthates and iodides by cyclohexane. (*97*) Reagents and conditions: (a) 0.06 eq. lauroyl peroxide, cyclohexane, reflux. (b) 0.04 eq. lauroyl peroxide, cyclohexane, reflux. (c) As (b).

1-Methylcyclohexa-2,5-diene-1-carboxylate esters **1.30** underwent decomposition to toluene, $CO_2$, and a radical, which could undergo further reaction (Scheme 1.8). (*99*) A silylated derivative **1.31** was also developed, (*100*) which can be used as an external reductant in the same manner as, *e.g.*, TBTH; aromatisation of the radical **1.32**, arising from H-abstraction, liberates the *tert*-butyldimethylsilyl radical, which acts as a chain carrier.




**Scheme 1.8.** Cyclohexadiene-based radical reductions.

The use of silanes as H-donors is too widespread to be discussed comprehensively here, but the subject has been reviewed previously. (*76*,*77*) Commonly available silanes such as triethylsilane and triphenylsilane are unsuitable owing to limited substrate scope and the need for elevated reaction temperatures, (*76*,*77*) although the use of thiol catalysts can ameliorate this issue (see page 30). Tris(trimethylsilyl)silane[xi] and (alkylthio)silanes

[xi] A recent review (*454*) describes the extensive use of this reagent over the last two decades.

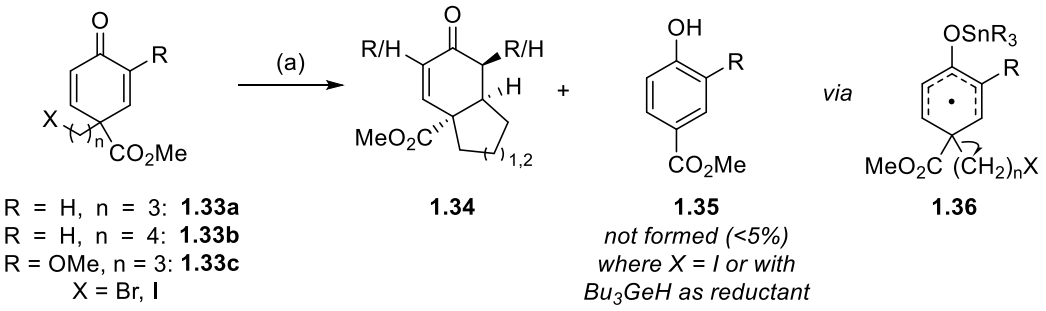
have been developed; (*101*) these species have weaker Si–H bonds than more conventional silanes, and can be employed as direct replacements for stannanes in many cases, (*77*) the rate constants for Si–H abstraction being of the order of that of TBTH. (*102*) Their cost, however, has precluded their broad application.

Ge hydrides, while less reactive than their Sn homologues, (*103*)[xii] are not known to be significantly toxic, although the need for further toxicity studies has been noted. (*104*) To our knowledge, their advantage in this regard was not discussed in peer-reviewed literature (*105*) until 1997, 26 years after the first report of the free radical reaction of a Ge hydride. (*106*).[xiii] Tributylgermane was found to be more effective than TBTH in furnishing lactones by radical cyclisation of (phenylselanyl)methyl and iodomethyl esters, in favour of direct reduction. (*107*) Reduction of brominated substrates **1.33a-c** with TBTH to cyclised species described by structure **1.34** also entailed significant formation of aromatic esters described by structure **1.35** (Scheme 1.9). (*108*) This arose from attack of the carbonyl group by the TBT radical to afford intermediate species **1.36**, and was suppressed in favour of the desired cyclisation when tributylgermane was used instead, or when TBTH was used with iodinated substrates. The decreased reactivity of tributylgermane was harnessed in order to address the problem of direct reduction of the starting halide by TBTH in the Giese reaction of alkyl iodides with acrylonitrile. (*109*) This work was later expanded upon, (*110*) revealing a

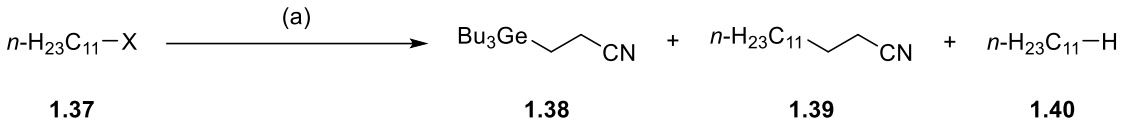
[xii] This is, in some ways, an advantage; while tributylgermane can be synthesised in one step, "for *ca*. 5 – 7 times the price of the purchase of [TBTH,] part of this excess cost is offset by the superior stability and lack of wastage, whereas poor stability, considerable wastage and general frustration are common with the use of [TBTH]." (*104*)

[xiii] There are earlier reports of reduction of organohalogen compounds with Ge hydrides, (*432*) but the operation of a radical mechanism was speculative at the time.

tendency for hydrogermylation of acrylonitrile to occur in attempted Giese reactions with 1-undecyl (pseudo)halides **1.37** (Scheme 1.10 and Table 1.2). Tributylgermane (*104*) and tri(2-furyl)germane (*111*,*112*) can both be prepared in a single step and employed in a variety of transformations conventionally carried out with TBTH; poor chain propagation as a result of slow H-abstraction from tributylgermane was commented upon, and resolved by polarity reversal catalysis (see page 30) with thiophenol. (*104*)




**Scheme 1.9.** Use of tributylgermane, in place of TBTH, for the reductive cyclisation of tethered bromides into cyclohexadienones suppressed competing aromatisation and fragmentation. (*108*) Reagents and conditions: 0.05 eq. AIBN, 1.2 eq. TBTH or tributylgermane, benzene, reflux, 2 – 8 h, then excess 60% aq. KF, 3 h, rt.

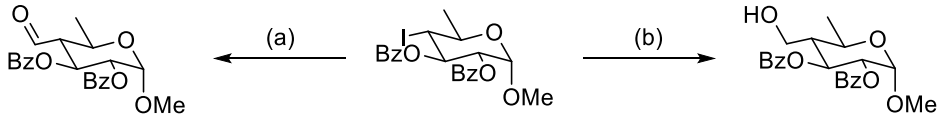



**Scheme 1.10.** Giese reaction of undecyl (pseudo)halides with acrylonitrile and tributylgermane as reductant. (*110*) Reagents and conditions: (a) 1.5 eq. acrylonitrile, 1.0 eq. tributylgermane, 0.1 eq. AIBN, acetonitrile, 80°C, 8 h.

| Entry | X | Product ratio 1.38 : 1.39 : 1.40 (GC) |
|---|---|---|
| 1 | I | <5 : 71 : 11 |
| 2 | Br | 51 : 11 : 11 |
| 3 | Cl | -[a] |
| 4 | SPh | -[a] |
| 5 | SePh | -[a] |

**Table 1.2.** Product distribution for Giese reaction indicated in Scheme 1.10. [a] Only **1.38** observed.

Germanes also exhibit some radical chemistry not possible when using stannanes. Iodinated sugar derivative **1.42** was hydroxymethylated *via* radical carbonylation to afford intermediate **1.41** by reaction with 0.1 eq. each of triphenylgermane and AIBN under CO. 2.9 eq. $NaBH_3CN$ served as a reductant which converts the intermediate aldehyde to isolated product **1.43**, as well as regenerating tributylgermane from the tributylgermyl iodide formed as a by-product of the radical reaction (Scheme 1.11). (*113*) The direct reduction product dominated when TBTH was used, with only a trace of the intended product **1.41** formed.




**1.41**
5%

**1.42**

**1.43**
37%, *via* **1.41**

**Scheme 1.11.** Radical carbonylation to afford **1.41** was inefficient when reduction was carried out with TBTH, and more successful when catalytic triphenylgermane and $NaBH_3CN$ was employed instead to afford alcohol **1.43**. (*113*) Reagents and conditions: (a) 2 eq. TBTH, 0.1 eq. AIBN, 1200 psi CO, benzene, 105 °C, 8 h. (b) 2.9 eq. $NaBH_3CN$, 0.1 eq. triphenylgermane, 0.1 eq. AIBN, 1400 psi CO, 50 : 1 benzene : THF, 105 °C, 12 h.

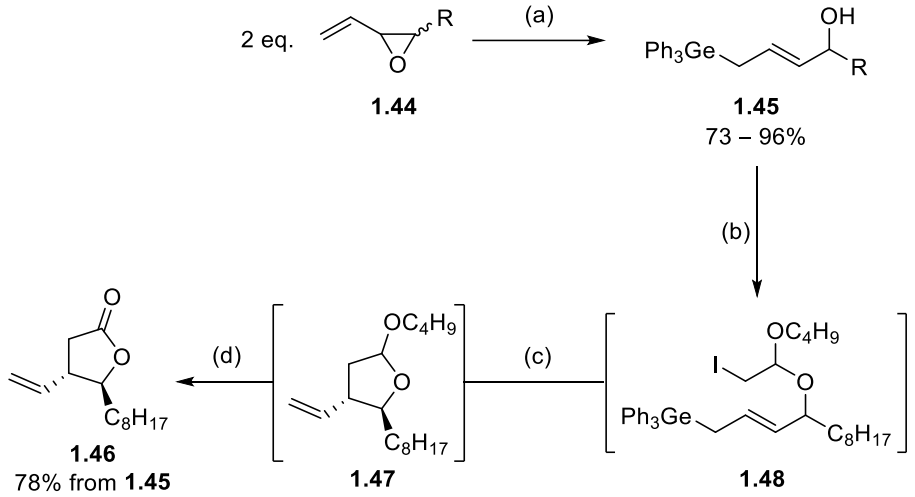
In addition to their work with tris(trimethylsilyl)silane (see page 21), Chatgilialoglu and coworkers have reported tris(trimethylsilyl)germane as a radical reductant; a wide variety of precursors were reduced efficiently by 2 eq. of the germane with initiation by 0.1 eq. AIBN in excellent yield (min. 96%, GC). (*114*) Analysis by the

radical clock method (*72*) indicated a *k*-value for H-abstraction from tris(trimethylsilyl)germane to be $3.1 \times 10^6$ $M^{-1}$ $s^{-1}$ – slightly higher than the associated value for TBTH. (*114*)

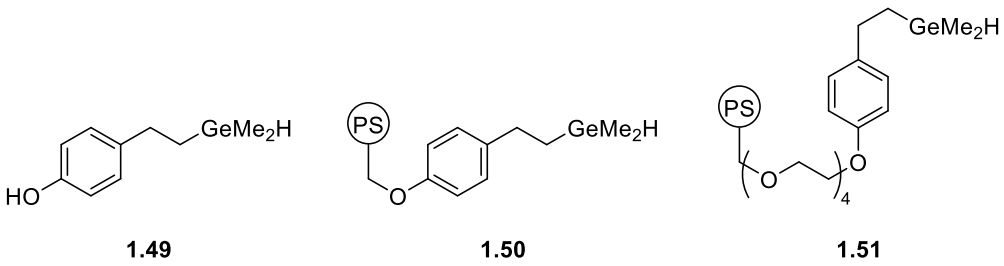
(ω-Haloacyl)germanes were cyclised in the presence of traces of the triphenylgermyl radical, (*115*,*116*) following observation of similar behaviour in (ω-alkenylacyl)germanes. (*117*,*118*) Abstraction – or, in the case of alkene-substitution, addition – processes generate a radical tethered to the acylgermane moiety, which adds to the carbonyl to afford an oxy radical; collapse of this species affords a cyclic ketone, and ejects the germyl chain carrier. (*118*) The analogous acylsilanes do not exhibit the same reactivity, the oxy radical instead undergoing a radical 1,2-Brook rearrangement. (*115*,*119*) In contrast to cyclisations by addition of a germyl radical to an olefin, opening of vinyl-substituted strained rings can occur; the triethylborane-initiated conversion of vinylepoxides of form **1.44** to germanes **1.45** is reported, as is the triphenylgermane-mediated reductive cyclisation of intermediate compound **1.48** to **1.46** (Scheme 1.12). (*120*)

Polystyrene-supported diethylgermanium hydrides have been prepared using similar methods to those employed to prepare analogous stannanes (see page 36). A trend of increasing efficiency of reduction with increasing length of the $(CH_2)_n$ chain (n = 0, 1, 2) linking the germane moiety and the polystyrene backbone (also seen with the analogous stannanes) was observed, and attributed to decreased steric hindrance. (*121*) Dihalobenzenes could be reduced selectively to monohalogenated derivatives in poor yield. Regeneration of the used polymers was effected by "washing twice with ether and [reduction] with [$LiAlH_4$] in refluxing THF for 1 h" (*121*) and the polymers retained 90%

of their activity over several use/regeneration cycles. Polymers **1.50** and **1.51** were prepared by reaction of precursor **1.49** with Merrifield and Quadragel™ resins, respectively (Scheme 1.13), and a variety of radical reactions were carried out with these reductants in variable yield. (*122*)




**Scheme 1.12.** Synthesis of lactones from vinylepoxides using triphenylgermane. (*120*) Reagents and conditions: (a) R = *n*-octyl, H, 2-phenylethyl, 7-methoxyheptyl; 1.0 eq. triphenylgermane, 2.0 eq. triethylborane, hexane, rt, 4 h. (b) R = *n*-octyl only; 1.2 eq. *n*-butyl vinyl ether, 1.2 eq. NIS, DCM, –78 °C – rt. (c) 9.4 eq. triethylborane, 0.094 eq. triphenylgermane, hexane, 12 h. (d) Jones reagent, acetone.




**Scheme 1.13.** Polymer-supported Ge hydrides.

Germanes are not commonly available and the precursor compounds are expensive, and reduced reactivity of many germanes with respect to stannanes makes heavy loadings of initiator necessary. (*110*) Additionally, while their reduced reactivity can be valuable in promoting selectivity and reactivity not exhibited by stannanes, it

detracts from the broad applicability under simple conditions enjoyed by stannanes. Given the possibility of recycling reagents and the effort that has been expended towards Sn-free radical chemistry, these latter concerns are probably why Ge hydride reductions have not been widely adopted despite their greatly reduced toxicity with respect to stannanes.

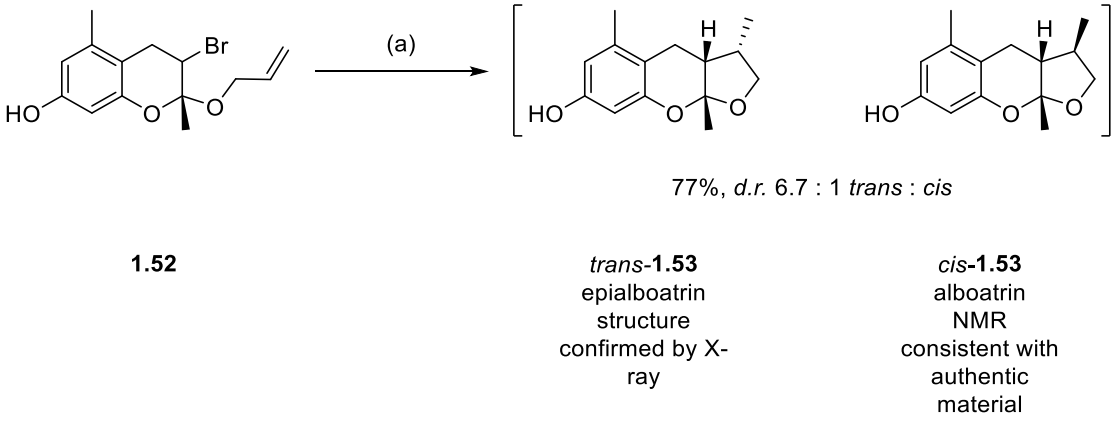
**Phosphorus-based H-donors**

The role of P-centred radicals specifically within the field of organic chemistry has been reviewed previously. (*123*,*124*) A dimethyl- or diethylphosphite-mediated Barton–McCombie deoxygenation, with benzoyl peroxide acting as an initiator, (*125*) was the first P hydride-mediated radical reaction to be reported. It was possible to employ diethyl phosphite as the solvent as well as the reductant, but attempts to employ AIBN as an initiator were not successful, and the proclivity of $(MeO)_2PH$ to add across double bonds is noted. (*126*) Use of $(HO)_2PH$, and amine salts thereof,[xiv] is also described; (*127*) AIBN initiation is possible in such cases. Dehalogenation in aqueous solution was achieved by treatment with $H_3PO_2$, with $NaHCO_3$ acting as a *pH* buffer and AIBN as initiator; (*128*) this methodology was extended to Giese reactions and *5-exo-trig* cyclisations by other workers. (*129*,*130*) Dibutylphosphine oxide is vaunted as a reductant that can be employed in only modest excess with a variety of radical initiators to reduce moisture-sensitive substrates (*131*) – $(HO)_2PH$ is hygroscopic and complete removal of $H_2O$ is difficult – and diphenylphosphine oxide can also be used. (*132*) This deoxygenation protocol has been applied to erythromycins using the monosodium salt of

[xiv] Use of the amine salts prevents the rearrangement of protected sugar derivatives, which was observed when the acid was used *per se*. (*126*)

hypophosphorus acid, (*133*,*134*) and the preparation of enantiopure (*R*)-malates of (*R*,*R*)-tartrates, *via* conversion to the corresponding cyclic thionocarbonates and monodeoxygenation with hypophosphorous acid. (*135*)

The 5-*exo*-*trig* cyclisations of aryl iodides (*136*) and 3-bromotetrahydropyrans (*136*,*137*) have similarly been achieved – the first examples of radical C–C bond-forming reactions using a P hydride reductant. EPHP was used with AIBN to effect the reductive cyclisation of **1.52** to alboatrin and its epimer. (*138*) The major epimer *trans*-**1.53** was confirmed to correspond to the originally proposed (*139*) structure (XRD), but NMR spectra of authentic material corresponded to the minor epimer. These findings informed reassignment of the structure of alboatrin to *cis*-**1.53**.

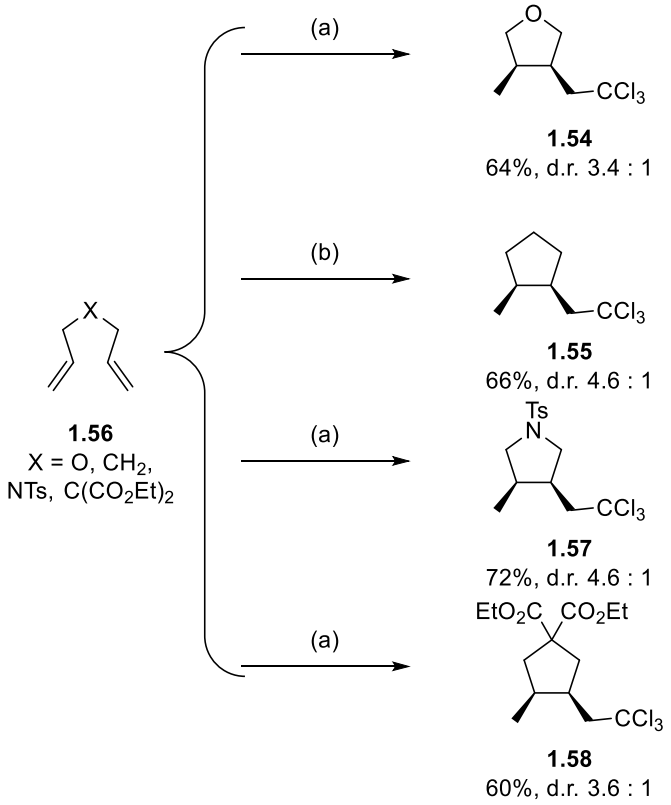



**Scheme 1.14.** Phosphite-mediated radical cyclisation, the final step of the total synthesis of alboatrin and its epimer. (*138*) Reagents and conditions: (a) 10 eq. EPHP, 0.11 eq. AIBN, benzene, reflux, 3 h.

The Kharasch addition of $BrCCl_3$ to olefins has been reported. (*140*,*141*) In addition to attempts to trap the intermediate radical with organic H-donors,[xv] reduction with 10 eq. of various phosphite esters and 4 eq. $CCl_4$ was attempted. (*141*) A more

[xv] In a screen of such donors, conditions affording the highest yield of hydrodehalogenated products consisted of 2 eq. of bromochloroform with respect to the olefin, in THF at rt and with *no* H-donor present. It was noted that the trichloromethyl radical may have abstracted H from added organic H-donors in preference to adding to the olefin.

complex atom-transfer radical addition incorporating a cyclisation of diallyl compounds described by structure **1.56** had previously been performed (Scheme 1.15): (*142*) *cis*-cyclopentanes **1.55** and **1.57**, and heterocycles **1.54** and **1.56** were obtained in moderate to good yield.



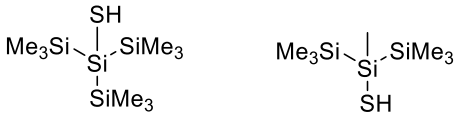

**Scheme 1.15.** Giese addition of $CCl_4$ to olefins in tandem with cyclisation processes. (*142*) Reagents and conditions: (a) 5 eq. diethyl phosphite, 4 eq. $CCl_4$, 0.4 eq. benzoyl peroxide, 1,4-dioxane, Δ. (b) As (a), but with lauryl peroxide and cyclohexane in place of benzoyl peroxide and 1,4-dioxane, respectively.

EPHP was used in the Giese coupling of alkyl iodides with electron-deficient vinyl compounds; (*143*) initation was effected with triethylborane/$O_2$, and yields were excellent. Cyclisation of allylic 2-iodoanilines and allylic 2-iodophenyl ethers was also effected with 10 eq. of EPHP and AIBN initiation, to afford hexahydrocarbazoles in moderate to good yields, and hexahydrodibenzofurans in poor yield, respectively. (*144*)

Radical reactions employing P-based reductants benefit from the aqueous solubility and relative non-toxicity of phosphites and their by-products, but suffer from a need for high loadings of reductant and initiator, and undesired side reactions of olefins.

**Thiols**

Thiyl radicals are unable to act reliably as chain carriers in reductive chain reactions, (*77*) but *tert*-butylthiol has been employed in place of stannanes in the Barton decarboxylation. (*68*,*145*) Silylsilylated thiols **1.59** (*146*) and **1.60** (*147*) (Chart 1.1) can also generally be employed; the thiol moiety can donate H to radical species effectively, and the resulting thiyl radical undergoes 1,2-silyl transfer to afford a silyl radical, which is competent at abstracting (pseudo)halides.




**1.59** **1.60**

**Chart 1.1.** (Trimethylsilyl)silylated thiols are competent H-transfer agents, in contrast to most thiols.

Thiols have also been employed as polarity reversal catalysts, (*148*) most importantly in facilitating the reduction of substrates with alkylsilanes. (*149*,*150*,*151*,*152*,*153*,*154*) The latter are not effective reductants as H-transfer between most C-centred radicals and alkylsilanes is disfavoured on polarity and bond strength grounds.

The overarching problem with alternatives to stannanes is that any one reagent cannot be applied to any given reaction with the same degree of confidence possible with stannanes – to quote a previous reviewer of the topic, “Currently, we have a tin hydride

substitute for every transformation, however, no reagent is as broadly applicable as the parent tin hydrides." (*77*)

## Mitigating Stannane Toxicity: Reducing Sn Contamination

The removal of toxic organotin residues is not trivial. Conventional purification techniques are generally inadequate for removal of organotin species from reaction mixtures. Their high molecular weight and extreme lipophilicity/miscibility preclude removal by distillation and extractive techniques, respectively. Chromatographic purification of non-polar compounds is frustrated by poor separation as a result of the lipophilicity of organotin residues, and – in the case of tributyltin halides excluding fluoride – streaking owing to slow hydrolysis on the stationary phase. (*155*) Work in this area has been reviewed previously, (*76*,*77*,*78*) but will nevertheless be summarised here, categorised by approach.

### Catalytic Use of Tin

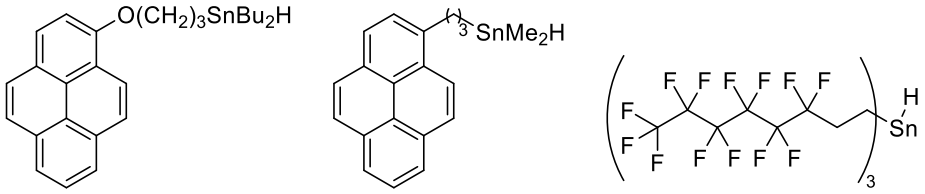
The pioneers of organotin chemistry found that trialkyltin halides can be reduced to the corresponding hydrides, (*50*,*156*,*157*,*158*,*159*,*160*) and on the strength of this, free radical reductions using catalytic amounts of an organotin species have been developed; a variety of p-block hydrides has been employed as terminal reductants: *e.g.* $LiAlH_4$, (*161*,*162*) $NaBH_4$ (*163*,*164*,*165*,*166*,*167*,*168*) or $NaBH_3CN$, (*169*,*170*) and silanes (*171*,*172*,*173*,*174*,*175*,*176*) or PMHS. (*174*,*177*,*178*,*179*,*180*,*181*)

Si-based reductants do not regenerate Sn hydrides from the corresponding chlorides, bromides, or iodides generated during reactions – the aforementioned methods regenerate hydride from Sn (alk)oxide or amide species instead – but PHMS reduced

TBTCl to TBTH when 2 eq. of aqueous KF[xvi] was present. (*182*) These methods have the obvious disadvantage that a reduction in Sn loading (typically *ca.* 10-fold) alone will not reduce Sn contamination in products arising from ineffective separation techniques to the levels acceptable for industrial use.

**Modified Tin Hydrides**

Stannanes incorporating functionality to facilitate easy separation from products have been synthesised; ease of separation, however, only limits contamination of products. Modified stannanes are not postulated to be any less toxic than, *e.g.* TBTH and its associated residues, and their associated waste products must still be disposed of. Pyrene-functionalised stannanes **1.61** and **1.62** have been prepared (Chart 1.2); (*183*,*184*) while the former has insufficient affinity to be easily removed from reaction mixtures, **1.62** and its associated by-products can be sequestered from reaction mixtures by treatment with activated C, although remaining Sn levels are rather high (3100 ppm Sn, ICP-MS).




**1.61** **1.62** **1.63**

**Chart 1.2.** Non-polar functionalised stannanes intended to be removed from reaction mixtures owing to their affinity for polyaromatic or fluorous phases.

The development of fluorous stannane **1.63**, of a protocol for its use in reductions *via* a radical chain mechanism, and of an effective fluorous/hydrocarbon partition method

[xvi] With respect to the hydromethylsiloxane repeat unit; 2.2 eq. with respect to the substrate. 0.06 – 0.25 Eq. of TBTCl with respect to the substrate was also present.

for separation of Sn residues from the product, is also reported; (*170*) a procedure for reductions catalytic in **1.63**, based on work by Stork, (*169*) was also developed. Fluorous solvents themselves are expensive and represent an environmental liability, owing to their extreme persistence and scope for bioaccumulation, (*185*) and high global warming potential. (*186*) Additionally, disposal by incineration liberates extremely noxious products. (*187*)

With the above exceptions, other functionalised stannanes rely on polarity or water-solubility to facilitate removal of Sn residues from non-polar products. Tris[3-(2-methoxyethoxy)propyl]stannane **1.64** (*188*) enables radical reactions to be carried out in $H_2O$ with ACVA as an initiator (Chart 1.3). (*189*) Water-soluble substrates were reduced in good yield, and the reduction in benzene of 1-bromooctane with **1.64** and AIBN as reductant and initiator, respectively, occurred in quantitative yield. The selectivity with which products can be separated from Sn residues by extraction from water is not discussed, but **1.65** is obtained by treatment of the reaction mixture with aqueous HCl; recovery is possible *via* extraction, and **1.64** can be regenerated by reaction with $BH_3$ in THF. (*189*)

The synthesis of stannane **1.66** and its use in the reduction of hexadecyl halides is reported. (*190*) Reactivity of **1.66** was comparable to that of TBTH, and its polarity allowed the organotin halide byproduct to be separated from the product and recovered *via* chromatography in excellent yield.[xvii] Stannane **1.68** was developed as a reducing agent whose reactivity is improved by anchimeric assistance and was employed in radical dehalogenations. (*171*) The resulting Sn residues were polar and crystalline. The authors

[xvii] Regeneration of the hydride with $LiAlH_4$ proceeded in 50 – 60% yield.

do not describe the selectivity of this partition process, but the polarity of **1.68** and its associated by-products presumably aided chromatographic purification if they were present as contaminants of the products. Similarly, stannanes **1.69** and **1.70** were used in the reduction of *n*-decyl, 3-phenylprop-1-yl, and naphthyl halides. (*191*) The "easy separation and recovery of the tin halide after the reaction" (implied to be the case only for **1.70**) is commented upon. 4-[2-(Diphenylstannyl)ethyl]pyridine **1.67** is reported to undergo the same reactivity as TBTH and triphenylstannane *viz.* reduction and hydrostannation in comparable yields, and to afford sufficiently polar degradation products as to render chromatography easy, but extraction from ether with 6 M HCl was incomplete. (*192*)

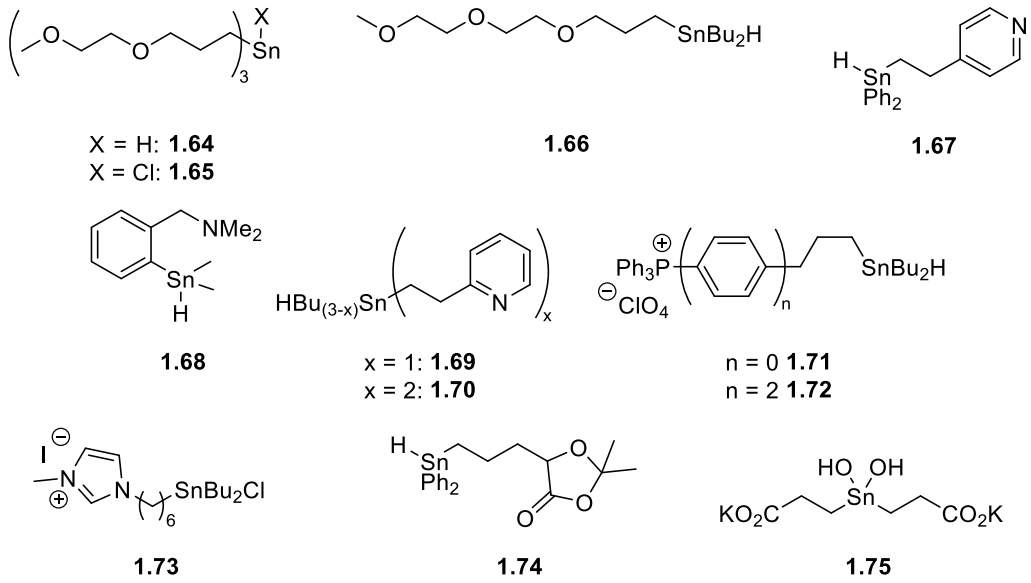



**Chart 1.3.** Water-soluble or polar stannanes, or those furnished with non-polar side chains susceptible to hydrolysis, allow retention in the aqueous phase upon extractive workup or, failing that, easy chromatographic separation.

Tetraarylphosphonium-functionalised stannane **1.72** was employed as a catalytic reductant to dehalogenate a variety of organobromine compounds and an aryl iodide in good to quantitative yield; (*193*) the analogous stannyl chloride was added to the reaction

and reduced *in situ* with $NaBH_3CN$. A simpler compound **1.71** was found to decompose partially *via* C–P bond cleavage upon attempted regeneration. Precipitation from DCM with hexane removed all but 5 ppm (ICP-AES) of Sn contamination from the product. 3-Methylimidazolium-based stannane **1.73** was prepared and substrates reduced with 1.5 eq. $NaBH_4$ and 0.01 eq. of **1.73** – and, in some cases, 0.01 eq. of AIBN – in 99 : 1 acetonitrile : methanol at reflux. (*194*) Halogenated substrates including 1-chlorohexadecane[xviii] were reduced to the corresponding hydrocarbons in moderate to excellent yield, although partial reductive homocoupling of 9-bromoanthracene was observed. Purification was effected by filtering the crude reaction mixture in ethereal solution through a short pad of silica, and afforded products containing <5 ppm (ICP-AES). Use of stoichiometric **1.73** was also possible, leading to <8 ppm Sn contamination in the products (ICP-AES).

The development, and use in test reactions, of **1.74** is also reported. (*195*) In contrast to other stannanes intended to be removed by aqueous workup, **1.74** is non-polar; concentration of the crude reaction mixture and stirring the residue in aq. THF for 1.5 – 3 h effects hydrolysis of the dioxolanone moiety, rendering the various Sn species soluble in $H_2O$. The effectiveness of this treatment was assessed by $^1H$ NMR analysis. Other workers report the preparation of dialkyltin hydroxide **1.75** and reduction to the dihydride *in situ* with $NaBH_4$; attempts to isolate the hydride "met with little success." (*167*)

Generally, modified tin hydrides have not been adopted industrially because while separation is easier than conventional tin hydrides, their removal from products to <10

[xviii] The iodide counterion of **1.73** may have facilitated this transformation; hexadecane was obtained in 81% isolated yield, but this decreased to 55% where the counterion was $BF_4^-$.

ppm (a commonly accepted limit for metal contamination in pharmaceuticals) is not achieved; indeed, few of the reports detailed above quantify the Sn residues present after treatment, instead considering the non-detection of Sn residues by NMR analysis to be indication enough that the methodology removes organotin impurities.

**Stannanes on Polymeric or Insoluble Supports**

Immobilisation of the substrate of an organotin-mediated radical reaction on a polymer support allows products uncontaminated with Sn to be obtained, in addition to the other benefits of this methodology. This is done by extensive washing of the polymer support before further reaction and/or cleavage of the substrate from the support. (*196*,*197*,*198*,*199*) Synthesis of polymer-supported tin hydrides for conversion of free substrates is also described. Both methods render removal of gross Sn contamination trivial, and recycling of the reagent is often possible in a separate step, circumventing the possibility of the substrate undergoing side reactions with the terminal reductant, as is a risk with catalytic protocols.

The first polymer-supported stannane was prepared in 1975. (*200*) The vast majority of polymer supports used in this area are polystyrene-based, but $Al_2O_3$ and $SiO_2$ have also been employed, (*201*,*202*) and the copolymerisation of styrene, *para*-divinylbenzene, and 3-(dibutylstannyl)propyl methacrylate afforded a stannane **1.78** supported on a copolymer backbone (Chart 1.4). (*164*) Additionally, copolymer **1.79** has been prepared from **1.76**, **1.77**, and crosslinking agent **1.80**. (*203*) Stannanes supported on polystyrene itself have been synthesised, both *via* grafting of stannanes to pre-formed polystyrene or derivative beads (*200*,*204*,*205*,*206*,*207*,*208*) and by copolymerisation of stannane monomers with styrene and crosslinking agents. (*166*,*209*,*210*,*211*,*212*,*213*,*214*)

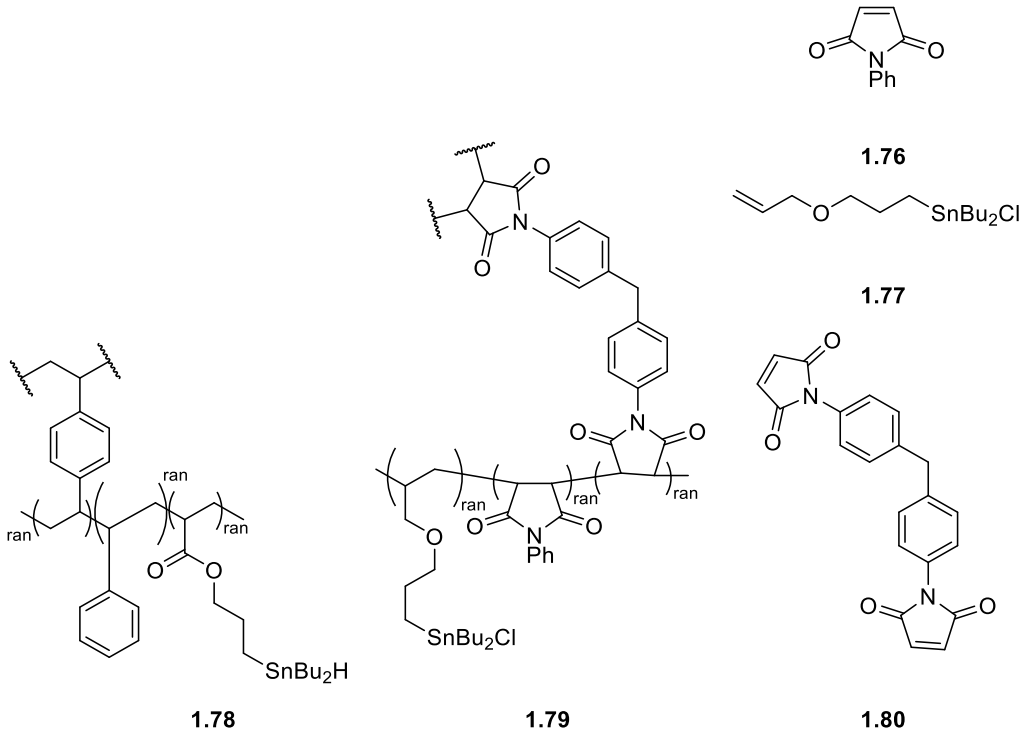



**Chart 1.4.** Stannanes supported on polymers other than polystyrene.

The phase-transfer/stannyl chloride cocatalyst system for $NaBH_4$-mediated radical reduction (*165*,*166*,*200*,*209*) inspired the preparation of a random copolymer based on partially phenylmethylated polystyrene, incorporating both phenyltin dihydride [xix] and benzo-15-crown-5 functionality (*210*) which displayed a marked advantage in rate of reduction of octyl bromide and dodecyl bromide with respect to cases where one or both of these functionalities was supported on a polymer separately from the other; use of free TBTCl and benzo-15-crown-5 entailed an increase of reaction rate by *ca.* 50% with respect to the copolymer.

The degree to which Sn contamination of products is avoided with use of polymer-supported stannanes was not consistently investigated. After an initial loss of *ca.*

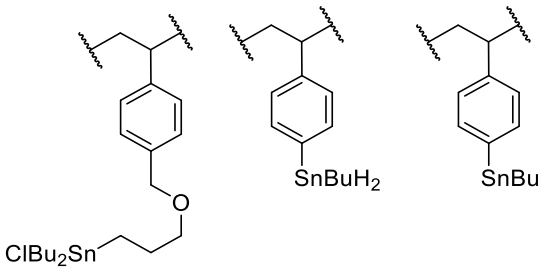
[xix] The authors report a discrepancy between the amount of active tin present on the polymer and the amount of tin indicated by elemental analysis, which is attributed to crosslinking during introduction of Sn to the polymer by deprotonation of phenylmethylated polystyrene and reaction with phenyltin trichloride.

15%, attributed to "loosely bound Sn–H [being] initially present," the degree of functionalisation on $SiO_2$ remained constant (XPS). (*202*) Leaching of Sn from reductions using polymer **1.79** was investigated by suspending a sample (0.1 eq. Sn) in a DME solution of adamantane for 6 h under varying conditions; the polymer was then removed by filtration and the filtrate concentrated. Sn levels were between 220 and 800 ppm (atomic absorption spectroscopy), depending on stirring and temperature. Other workers carried out the cyclisation of 2-bromophenyl allyl ether to 2,3-dihydro-3-methylbenzofuran using **1.79**, (*215*) finding 120 ppm Sn in the product (ICP-AES). Stannanes bound to polystyrene with 3- and 4-carbon alkyl linkers, as opposed to the more common 2-carbon linker,[xx] were prepared. (*206*,*207*) Reduction of 3-iodo-5-cholestene was carried out with both TBTH and these polymers, with similar yields in each case; residual Sn, however, was present at 45 ppm in the crude product obtained from reduction by polymer and at 7000 ppm after crystallisation of the product obtained from TBTH reduction (ICP-MS). (*206*) Later work (*216*) describes the need for four product crystallisations to reduce Sn contamination in the TBTH case to similar levels. Non-crosslinked polymer **1.81** (Chart 1.5) was employed as a catalyst with $NaBH_4$ as a terminal reductant in the reduction of a variety of substrates. (*208*) Samples of dodecane and biphenyl thus obtained were found to contain 5.4 ± 0.1 ppm and 11.1 ± 0.1 ppm Sn, respectively.

The pioneers in the field of polymer-supported stannanes found that regeneration of polymer **1.82** by reaction of the corresponding stannyl halide by-products with $LiAlH_4$ was inefficient; Sn–H functionality was found to be present only in minimal quantity (IR),

[xx] The monomer required for preparation of such compounds is obtained easily by radical hydrostannylation of *para*-divinylbenzene.

with no reduction in Sn content (elemental analysis). (*200*) These observations were attributed to the formation of divalent Sn species **1.83**; other workers using di- and trisubstituted polymer-supported stannanes also reported a 30 – 50% loss of activity upon recycling their polymers. (*209*)




**1.81** **1.82** **1.83**

**Chart 1.5.** Polymer **1.81** was used as a catalyst with $NaBH_4$ as a terminal reductant. Pioneering polymer-supported stannane **1.82** was not regenerated efficiently after use, due to reduction to Sn(II) species **1.83**.

A non-crosslinked derivative of **1.78** could not be recycled effectively, which was attributed to radical coupling of the tethered tin moieties giving the distannane, and it was suggested that crosslinking of the copolymer isolated the Sn-centred radicals from one another, preventing coupling. (*164*) Recycling of **1.79** by treatment with $NaBH_4$ was not successful; this was attributed to pore-blocking by $NaBH_4$ residues. (*215*) Benzylic H-abstraction on the ethylene tethers joining Sn to the polystyrene backbone, followed by β-scission of the stannane moiety, was postulated as as mechanism for leaching of Sn from polymers consisting of stannanes attached to the backbone *via* an ethylene linker, (*212*) although other workers propose β-H elimination by the active stannyl radical. (*206*) Use of longer linkers did not compromise reaction yields, but leaching of Sn, while reduced, was still evident (ICP-AES). (*212*) Leaching was found to occur to a lesser extent when reactions were carried out at lower temperatures, and the diphenylstannyl moiety was associated with poor recyclability of the polymer. (*214*)

Polymer-supported reagents showed promise as a means of preventing Sn contamination of the products of radical reductions, but the partial leaching of Sn, the additional complexities of carrying out reactions with polymer-supported reagents, and the prohibitive cost of the reagent if not reused prevented widespread application of this technology.

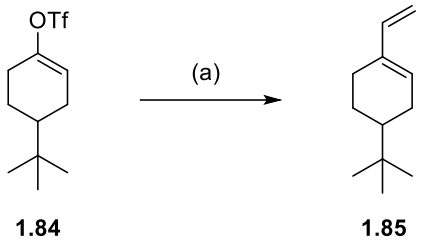
**Reaction Additives and Modified Workup Techniques**

Where stannanes are not functionalised or immobilised on a support for easy separation, additional steps in the workup procedure of a reaction can aid separation of Sn residues from products. The adulteration, however, of reaction mixtures with reagents to sequester Sn residues can induce vulnerable functionality to undergo side reactions.[xxi] (*217*) Where the desired product is sufficiently polar, extraction of the crude product from petrol with acetonitrile is possible, leaving organotin residues in the petroleum phase. (*218*) TBT chloride/bromide/iodide, which are unstable to hydrolysis during aqueous workup and chromatography, can be removed from mixtures by conversion to the fluoride, which is polymeric and poorly soluble in organic solvents and in water. (*219*) Conversion can be effected by washing the crude reaction mixture with a solution of KF in $H_2O$ (*68*,*219*) or an alcohol; (*220*) the resulting precipitate can be removed *via* filtration. A 2 : 1 mixture of CsF : CsOH, prepared by melting the separate salts in a Ni crucible, was also used to convert TBT iodide[xxii] to the corresponding fluoride. (*221*) Attempts to convert TBTCl to TBT fluoride *in situ* during the Stille coupling of triflate **1.84** with

[xxi] If the adulterant is also a radical scavenger, its addition can obviously have a serious effect on the progress of the desired radical reaction.

[xxii] An alkyl mesylate was converted to the corresponding alkane with 1.7 eq. TBTH in THF, in the presence of LiI, HMPA, and $SmI_2$; the crude product was treated with a solution of $I_2$ in ether and the resulting mixture concentrated, redissolved in 5 : 1 pentane : ether and treated with 5.0 eq. fluoride (as in the mixture described) and silica, before elution of the product through more silica.

vinyltributylstannane, to afford diene **1.85**, were complicated by the role of LiCl/LiBr in promoting the synthetic reaction (Scheme 1.16). (*222*) More recently, the use of KF supported on $CaF_2$ (prepared *via* "evaporation of a $CaF_2$ suspension in aqueous KF solution") (*223*) has been proposed as a solid reagent for conversion of organotin residues to polymeric fluorides.




**Scheme 1.16.** Stille coupling of compound **1.84** with vinyltributylstannane. (*222*) Reagents and conditions: (a) 0.02 eq. tetrakis(triphenylphosphine)palladium(0), 3.0 eq. LiCl, THF, reflux.

Organotin compounds can be degraded by stirring with a mixture of concentrated aq. HCl and $HNO_3$. (*224*) This converts the contaminants to inorganic Sn(IV), which can be converted to sparingly soluble (2 ppm in $H_2O$ at 18 °C) $SnS_2$ by thioacetamide. The disadvantages of such harsh conditions are obvious, and borne out by the need to separate the product from the Sn residues by alternative means before applying this treatment. (*221*) The hydrolysis of trialkyltin halides was reportedly promoted by DBU in undried ether; (*225*) any distannanes or unreacted hydride were converted to stannyl iodides *via* addition of $I_2$. The resulting tin hydroxide, which exists "in rapid equilibrium at room temperature with the [distannoxane]," (*225*) was retained by the stationary phase during chromatographic purification. Stirring reaction mixtures with 1 M aq. NaOH was reported as an alternative means of hydrolysis for use with base-sensitive compounds; (*217*) the arising biphasic mixture limits exposure of the latter to strongly basic conditions.

In contrast to conversion of unstable Sn residues to polar or insoluble material to aid removal, reduction to the starting hydride renders these residues non-polar which, in the case of polar products, aids separation either chromatographically or *via* acetonitrile/petrol extraction (see page 40). (*155*) Regeneration in this manner also has the advantage that the stannane can be reused where the expense of the hydride or the scale of the reaction warrants doing so. $Me_3Al$ can also be used to convert trisubstituted stannyl halides to stable lipohilic tetrasubstituted stannanes, (*217*) which are similarly lipophilic and stable on silica.

Modification of the stationary phase employed for chromatography is an alternative to adding reagents to the reaction or workup mixture. The same physico-chemical properties exhibited by organotin residues and harnessed towards their removal can be applied towards enhancing chromatographic separation. In the case of polar compounds, reverse-phase chromatography, (*226*) or elution of the crude mixture through a short plug of reverse-phase silica, (*227*) are reported to be effective in retaining organotin residues. Chromatography using silica loaded with KF is also reported, and is significantly more effective than sequential acetonitrile/hexane extraction and chromatography on conventional silica (Table 1.3); (*228*) The stationary phase is hygroscopic, and "On prolonged standing, this leads to a loss of fluidity in the stationary phase which in turn reduces its efficacy for… the removal of reactive organotin species." (*229*) Subsequently, it was found that the basicity of KF, and not its propensity to convert organotin residues to polymeric material, was responsible for the ability of KF-silica to remove organotin impurities. (*229*) An alternative stationary phase, consisting of 9 : 1 silica : powdered anhydrous $K_2CO_3$, was found to reduce Sn contamination in the same

test protocol[xxiii] employed in previous work, (*228*) and could be stored "for many months without significant loss in fluidity or activity." (*229*) Use of 9 : 1 silica : $H_2O$ in chromatographic removal of 1,3-dichloro-1,1,3,3-tetrabutyldistannoxane and dibutyltin oxides from reaction mixtures is reported. (*230*) The moisture on the silica did not compromise separability.

| Entry | Method | Reference | Sn remaining/ppm | Basis for Sn measurement |
|---|---|---|---|---|
| 1 | Crude reaction mixture | (*228*) | 2000000 | Initial loading |
| 2 | Chromatography (silica) | | 500000 | $^1$H NMR |
| 3 | Acetonitrile//hexane partition, then chromatography (silica) | | ~250000 | $^1$H NMR |
| 4 | Stirring with aq. KF, then chromatography ($SiO_2$) | | ~50000 | $^1$H NMR |
| 5 | Second chromatographic purification of above mixture | | -[a] | Elemental analysis, $^1$H NMR |
| 6 | Chromatography (9 : 1 $SiO_2$ : KF) | | <30 | Elemental analysis |
| 7 | 9 : 1 $SiO_2$ : $K_2CO_3$ | (*229*) | 13[b] | Elemental analysis |
| 8 | Crude reaction mixture | (*230*) | 20000 – 40000 | Initial loading |
| 9 | 9 : 1 $SiO_2$ : $H_2O$ | | <7 | ICP-MS |

**Table 1.3.** Efficacy of chromatographic techniques for removal of organotin residues. [a] Product pure by elemental analysis, but traces of organotin visible by $^1$H NMR. [b] See entry 1 for initial Sn contamination present.

## Open-Shell Species From Excited Electronic States

Despite the efforts described above, no satisfactory alternative to stannane-based means of generating free radicals for synthesis became established, and free radical

[xxiii] *Viz*. reduction of 5-bromo-6-(1,3-dithian-2-yl)benzo[*d*][1,3]dioxole with 2 eq. of TBTH and 4 eq. of TBAF in toluene.

chemistry saw little use in the manufacture of pharmaceuticals (*168*) and agrochemicals until the development of synthetic photoredox catalysis.[xxiv] When chemical species absorb light, they enter excited electronic states, and can undergo reactivity which is not feasible in their ground states. The first photochemical reaction[xxv] was reported in 1614, when Angelo Sala described the blackening of powdered silver nitrate on exposure to sunlight, (*231*) and humanity has since applied this phenomenon to various useful processes, from photography (*232*) to rapid document replication. (*233*) The first report of a photo**catalytic** process – whereby a compound absorbs light and enters an excited state, facilitating reaction of another species without overall consumption of the light-absorbing species – was in 1911, concerning the bleaching of Prussian Blue by illumination in the presence of ZnO. (*234*) Some photocatalytic processes proceed solely *via* the transfer of energy between catalytic species and substrate, and this process is often referred to as photosensitisation; (*235*) photoredox catalysis, however, refers to processes whereby an excited chromophore **PC***, functioning as the photoredox catalyst and obtained *via* irradiation of precatalyst **PC**, is quenched *via* redox reaction with another species (usually, but not always, *via* SET).

Such a process must generate radical species and represents, therefore, a means of generating free radicals with all the benefits and associated reactivity (see page 4), without the toxicity and separation issues associated with reductive generation of free

[xxiv] Some reviewers of alternative reductants in radical chemistry clearly consider the hegemony of stannanes to be an emotive topic: *cf.* "Most importantly, however, tin-based methods exercise an autocratic influence in the domain of radical ring closures. A plethora of such annulations pervades the recent literature. Unsaturated alkyl, aryl, vinyl, acyl, aminyl, alkoxyl, and other heteroradicals propagate their cycles on chain gangs ceaselessly disciplined by the vigilant agents of tin." (*76*)

[xxv] It has been suggested (*433*) that the image on the Shroud of Turin is the product of an unidentified photographic process. $^{14}C$ analysis indicates that the plant matter from which the Shroud is made was alive between 1260 and 1357. (*434*)

radicals using tin hydride species. While limited use of photoredox catalysis in promoting organic redox processes occurred from 1978, (*236*,*237*,*238*,*239*) their application to the generation of radical intermediates in major bond-forming reactions is a much more recent phenomenon; the first reaction employing a photoredox-derived radical was reported in 2008. (*240*)

The photoexcited catalyst species **PC*** can be quenched *via* donation of an electron to another species (oxidative quenching), forming ground state oxidised species $\mathbf{PC}^{+}$, or *via* acceptance of an electron from another species (reductive quenching), generating $\mathbf{PC}^{-\bullet}$.[xxvi] These species also exhibit redox activity, tending to regenerate **PC**. Only one mode of quenching is operative in any one photoredox transformation; the feasibility of a quenching mode depends on the redox behaviour of both the quencher and the photocatalyst, and can be evaluated using Equations 1.5 and 1.6,[xxvii] in which $\Delta G$ denotes the change in Gibbs free energy on quenching, $F$ the Faraday constant, and $E$ the electrode potential associated with the indicated reduction process. (*241*) Quenching of **PC*** affords oxidised ($\mathbf{PC}^{+}$) or reduced ($\mathbf{PC}^{-}$) species, which themselves exhibit redox activity; oxidation of $\mathbf{PC}^{-}$ or reduction of $\mathbf{PC}^{+}$ *via* SET processes regenerates **PC**.

$$\Delta G_{\text{oxidative quench}} \approx -F[\,E(\text{quencher}/\text{quencher}^{-\bullet}) - E(\mathbf{PC}^{+}/\mathbf{PC}^{*})] \qquad 1.5$$

$$\Delta G_{\text{reductive quench}} \approx -F[E(\mathbf{PC}^{*}/\mathbf{PC}^{-}) - E(\text{quencher}^{+\bullet}/\text{quencher})] \qquad 1.6$$

[xxvi] This terminology makes sense when considering what is done **to** the excited catalyst, not what is done **by** the excited catalyst. The resulting species are redox agents in the same sense as the quenching mechanism by which they arose; $\mathbf{PC}^{+}$ is obtained by oxidative quenching and is an oxidising agent, $\mathbf{PC}^{-}$ is obtained by reductive quenching and is a reducing agent.

[xxvii] These expressions are derived from the equation for the Gibbs energy of photoinduced electron transfer (often incorrectly named the Rehm–Weller equation), and are technically approximations, but are nevertheless informative in terms of evaluating the feasibility of quenching processes. A review on organic photoredox organocatalysis (*241*) describes in detail the derivation and approximations involved therein.

The substrate can undergo SET during quenching of **PC*** or during the regeneration of **PC** in the ground state. Where the substrate and derivative intermediates only undergo one SET process with a catalytic species, an additive is necessary to facilitate the other and close the catalytic cycle. This can be a sacrificial reagent, ultimately serving as the terminal oxidant or reductant, or can engage in further reaction with the substrate-derived intermediate; this is the basis of photoredox-mediated coupling reactions.[xxviii] In other cases, the substrate can undergo SET with a photocatalytic species, engage in reactivity as a radical ion, and then close the catalytic cycle by reverting to a neutral species *via* SET in the opposite sense. (*240*,*242*,*243*,*244*)

With some exceptions, *e.g.* organic compounds, (*241*) cerium complexes, (*245*) and uranyl complexes, (*246*) photoredox transformations generally employ polypyridyl complexes of Ru(II) and Ir(III) as catalysts. These can be biased towards reductive or oxidative quenching behaviour *via* choice of ligand; (*247*) electron-donating ligands, for example, raise the energy of all catalyst FMOs, encouraging (oxidative) quenching of the excited state *via* donation of an electron from the $e_g$* LUMO, in addition to discouraging acceptance of an electron into the $t_{2g}$ HOMO, *i.e.* reductive quenching. The electrochemical behaviours of several different photoredox catalysts have been compiled, (*241*,*247*) allowing comparison and selection of suitable catalysts for a particular transformation.

The first example of a photoredox-mediated bonod-forming reaction to be reported was the formal [2+2] cycloaddition of bis-unsaturated dicarbonyl compounds of

[xxviii] In many cases, "engagement in further reaction" of a sacrificial redox agent consists of a second SET with substrate-derived intermediate in an uncatalysed reaction, making the reaction an overall two-electron process.

form **1.86**, in 2008 (Scheme 1.17); (*240*) the substrates cyclise in the presence of $LiBF_4$ and Hünig's base; reduction of the electrophilic lithium adduct of the SM **1.88** by the electron-rich reduced photocatalytic species affords radical **1.89**. Cycloaddition *via* sequential *5-exo* and *4-exo* cyclisations affords species **1.90**. Reductive quenching of the excited photocatalyst by Hünig's base is invoked in favour of oxidative quenching by the substrate, based on observation of no reaction with 0.2 eq. of catalyst and no Hünig's base. The fate of **1.90** is not explained, but radical coupling and collapse of the resulting quarternary hemiaminal zwitterion **1.92** to afford the product is plausible; in this case, Hünig's base would be acting as a cocatalyst to facilitate closing of the photoredox cycle.

Concurrently with the work described above,[xxix] Nicewicz and MacMillan reported the photoredox-catalysed stereoselective coupling of aldehydes to α-halocarbonyl compounds (Scheme 1.18). (*248*) Reductive cleavage of the C–Br bond in the latter by the reduced form of the photocatalyst affords tris(bpy)ruthenium(II) dichloride and an electrophilic radical **1.98**, which adds to an enamine **1.95** – derived from the starting aldehyde and chiral imidazolinone **1.94** – to afford aminyl radical **1.96**, formed diastereoselectively. Reductive quenching of the excited photocatalyst affords iminium species **1.97**, which decomposes to liberate the enantioenriched product **1.93** and **1.94**. A reductive quench by the enamine is invoked, based on Stern–Volmer

[xxix] Nicewicz and MacMillan published their work a month afterwards, but Ischay and coworkers note their awareness of it *via* personal correspondence in a footnote.

experiments with **1.95** as the quencher and the non-observation of quenching by the brominated substrates used.

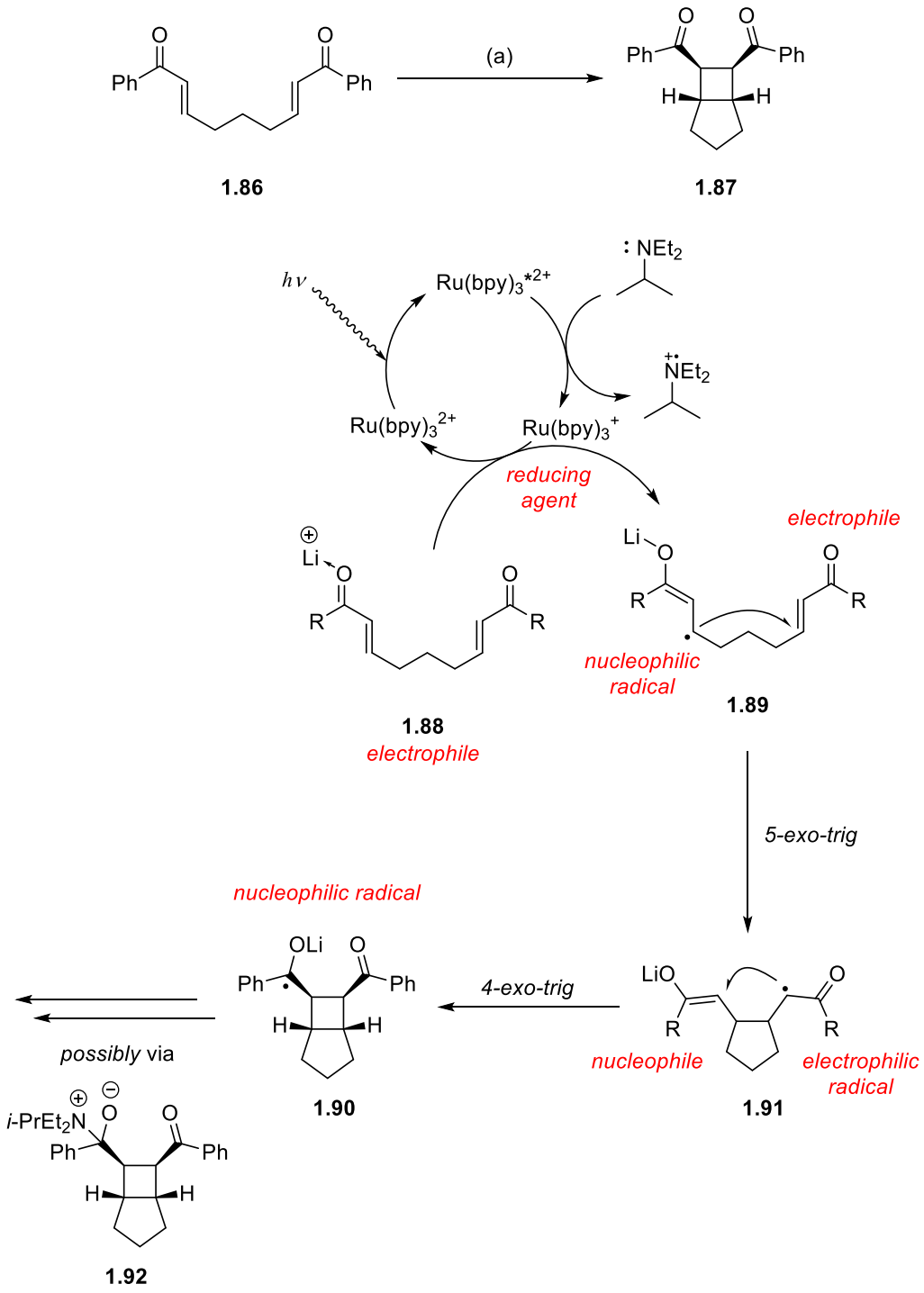
In the same vein as Nicewicz and MacMillan's use of α-halocarbonyl species to generate neutral radicals *via* photocatalytic reduction, the radical dehalogenation of benzylic bromides and α-halocarbonyl species **1.99 – 1.108** was effected (Scheme 1.19). (*249*) This work is directly analogous to the common free radical reduction of organohalides by TBTH, although the photocatalytic protocol is more discerning as to which halides are abstracted. Bromide is abstracted from the benzylic position of pyrroloindolines **1.100** and **1.101** in favour of the aryl bromide, and bromide and chloride are both removed from the 2-position of the phenylacetyl moieties in substrates **1.102** – **1.107**, in favour of aryl or vinylic halides.

Reduction of aryl and alkyl halides has been effected by tributylamine and formic acid in the presence of 10-phenylphenothiazine **1.109** (Scheme 1.20). (*250*) The reaction could be conducted in the presence of air, and the feasibility of employing the resulting radicals as intermediates for subsequent reaction was demonstrated by reduction of allyl (2-bromophenyl) ether to 3-methyl benzotetrahydrofuran.

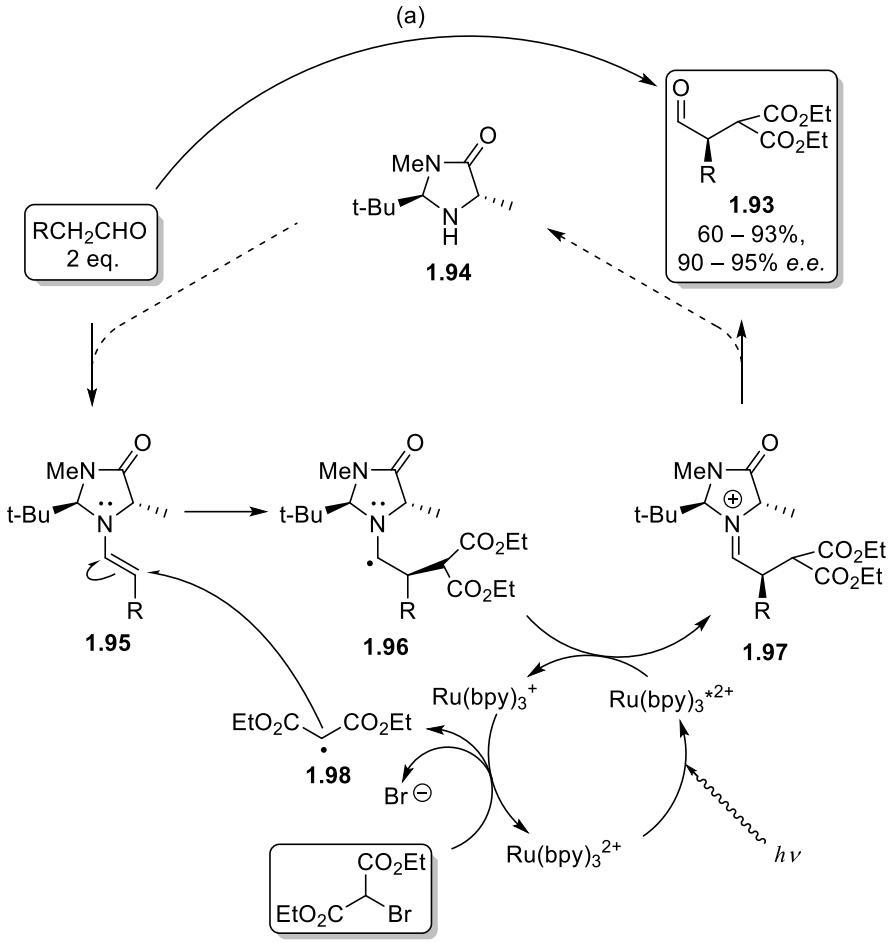
Photoredox catalyst/visible light irradiation systems have been used as initiators for chain processes; indeed, chain processes have been proposed as alternative mechanisms to other photoredox trasformations. (*251*) Photoredox-mediated chain initiation has also been applied to radical polymerisation; this methodology was pioneered in 2011, (*252*) and has been reviewed since. (*253*,*254*,*255*,*256*) The atom-transfer radical addition of thiols to olefins was achieved *via* irradiation with a photoredox catalyst (Scheme 1.21). (*257*) The proposed photoredox cycle comprises reductive

quenching of the catalyst by the thiol **1.110**, affording thiol radical cation **1.114**, and loss of a proton to afford the thiyl radical chain carrier **1.115**; regeneration of the catalyst occurs *via* reoxidation with atmospheric $O_2$. Product sulfides described by structure **1.112** were obtained *via* sequential addition of the thiyl radical to unsaturated substrate **1.111**, and H-abstraction of another thiol molecule by intermediate **1.116**. While addition occurred in poor yield when tris(bpy)ruthenium(II) dichloride was used as the photocatalyst, using a more strongly oxidising derivative, tris(bpz)ruthenium(II) hexafluorophosphate **1.113** (referred to in subsequent chapters of this thesis as **2.8**) allowed excellent conversion.

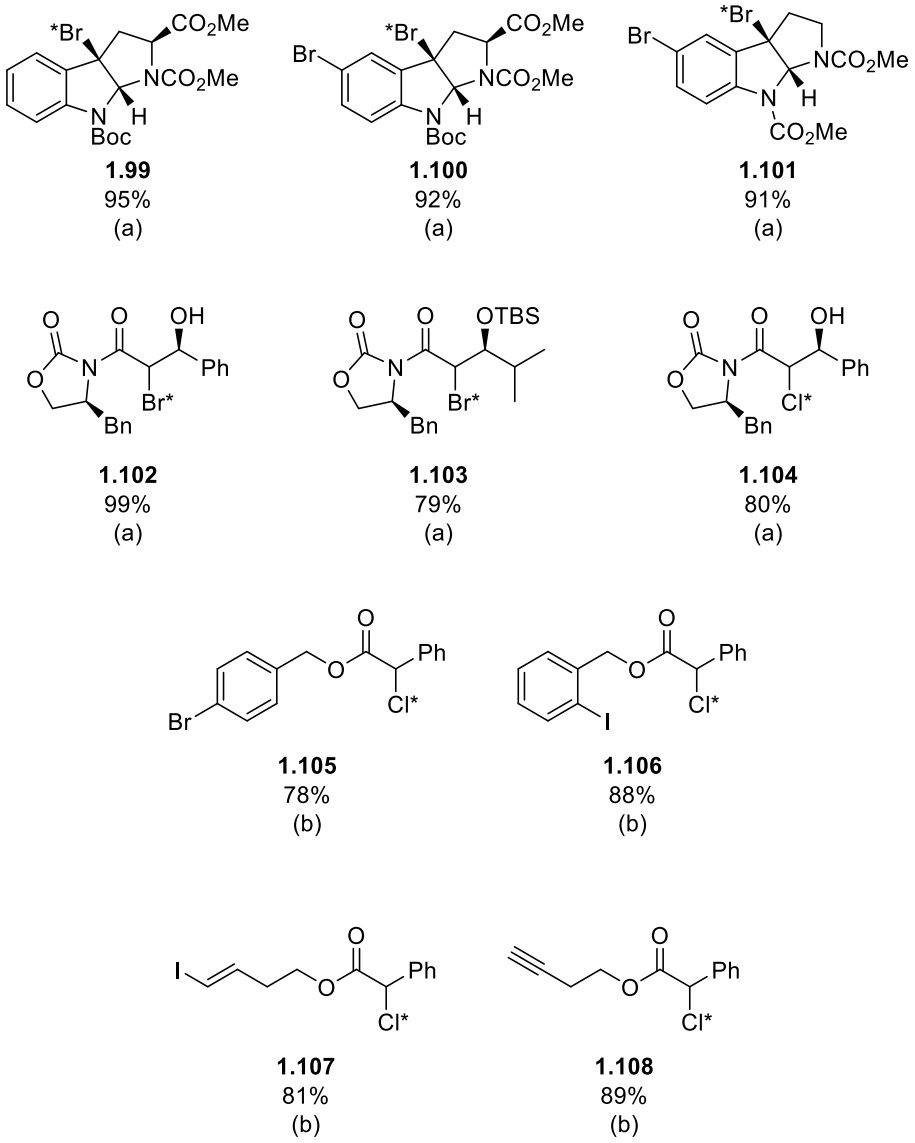
In addition to the use of photoredox catalysts to effect photochemical reactions via irradiation at more convenient wavelengths than are possible by direct excitation of the substrate, and reduction of activated halides, direct C–H functionalisation of substrates *via* H-abstraction has also been achieved. For example, the coupling of electron-deficient cyanoarenes to the allylic position of various unactivated olefins in the presence of $Ir(ppy)_3$ and triisopropylsilanethiol is reported (Scheme 1.22), (*258*) as are benzylic aminations in the presence of 9,10-dicyanoanthracene, (*259*) and aminations/oxidations in the presence of Ir complex **1.117**. (*260*)



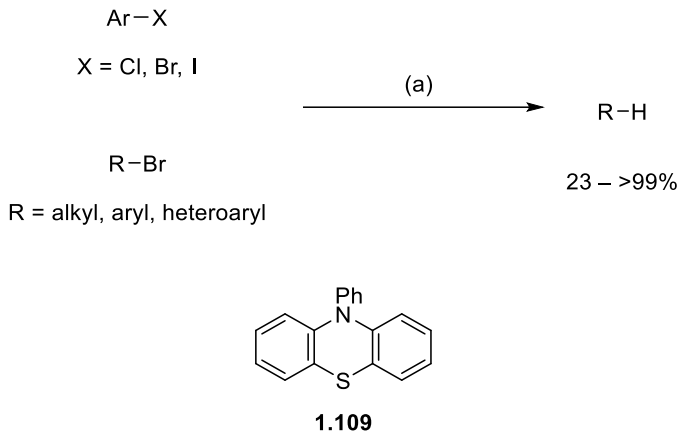

**Scheme 1.17.** Photoredox-mediated formal [2+2] cycloaddition of an enone with other unsaturated carbonyl functionality. (*240*) Reagents and conditions: (a) 0.05 eq. $Ru(bpy)_3Cl_2$, 2.0 eq. Hünig's base, 0.2 eq. $LiBF_4$, *hv* (275 W incandescent lamp), 10 min – 22 h.



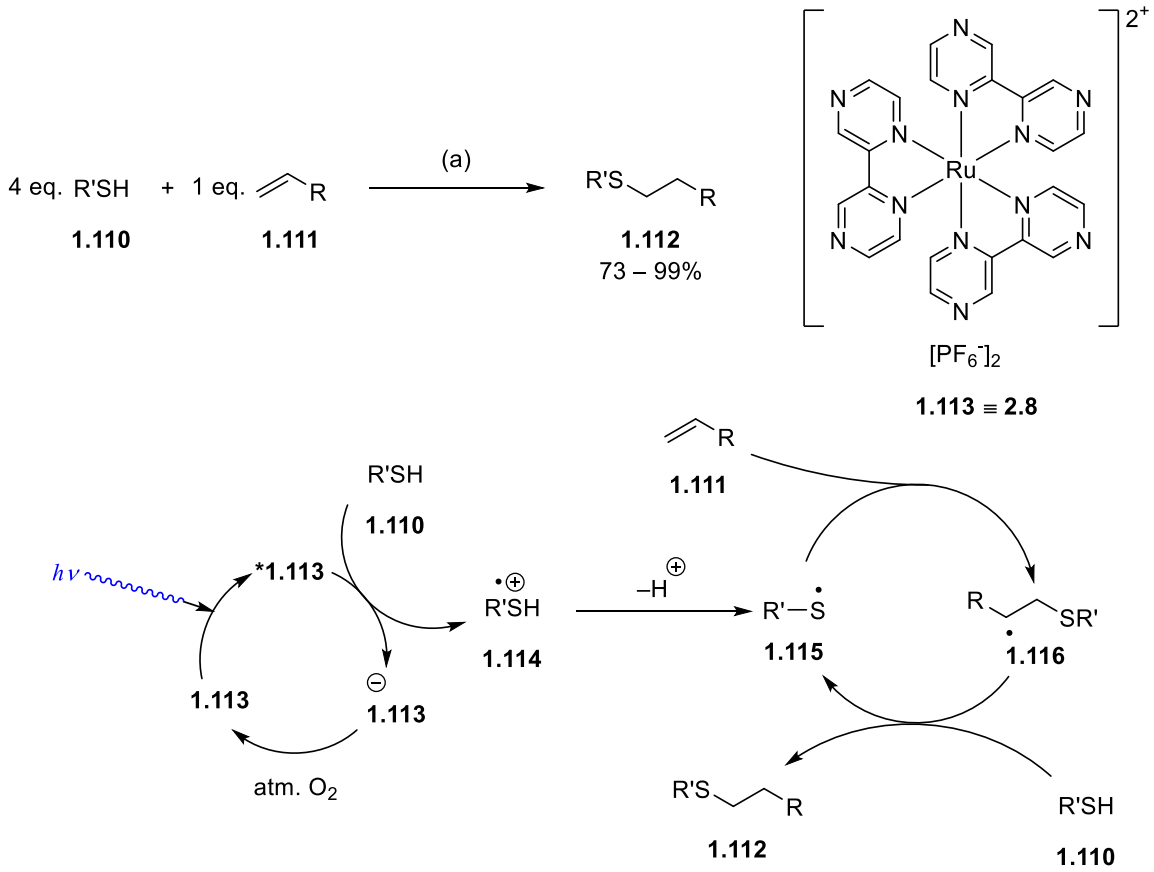

**Scheme 1.18.** Enantioselective radical coupling of halocarbonyl species with aldehydes. (*248*) Reagents and conditions: (a) 0.005 eq. $Ru(bpy)_3Cl_2$, 0.2 eq. **1.94**, 2.0 eq. 2,6-lutidine, $h\nu$ (15 W CFL or 0.5 W LED $\lambda_{max,irr}$ 465 nm), DMF, rt, 6 h with CFL or 90 min with LED.



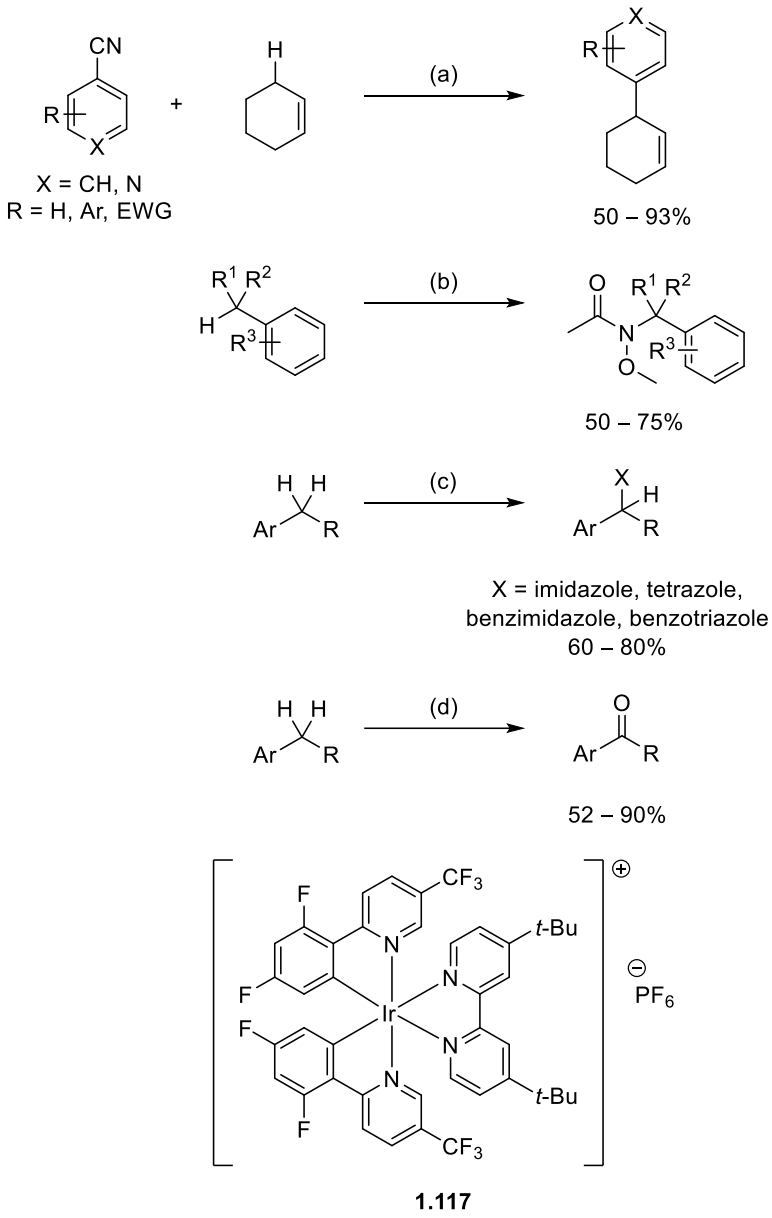

**Scheme 1.19.** Photoredox mediated radical dehalogenation using $HCO_2H$ as a terminal reductant. (*249*) Yields are for products obtained by replacement with H of halides indicated by an asterisk. Reagents and conditions: (a) 0.025 eq. $Ru(bpy)_3Cl_2$, 10 eq. Hünig's base, 10 eq. $HCO_2H$, $h\nu$ (15 W CFL), DMF, rt, 4 h. (b) 0.025 eq. $Ru(bpy)_3Cl_2$, 2 eq. Hünig's base, 1.1 eq. Hantzsch ester, $h\nu$ (15 W CFL), DMF, rt, 4 – 24 h.




**Scheme 1.20.** 10-Phenylphenothiazine-catalysed photoredox reductiohn of halides. (*250*) Reagents and conditions: (a) 0.05 eq. **1.109**, 5.0 eq. tributylamine, 5.0 eq. $HCO_2H$, $h\nu$ (1.8 μW·cm$^{-2}$ LED, $\lambda_{max,irr}$ 380 nm), acetonitrile, rt, 1 – 72 h.




**Scheme 1.21.** Photoredox-initiated atom-transfer radical addition of thiols to unsaturated compounds. Reagents and conditions: (a) 0.025 eq. **1.113**, $h\nu$ (2.25 W blue LED strip), acetonitrile, rt, 1 – 26 h.



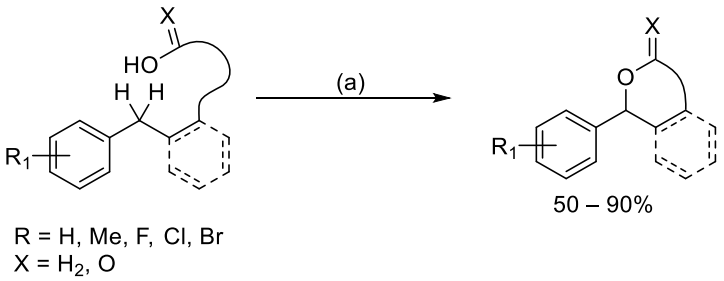

**1.117**

**Scheme 1.22.** Photoredox-mediated intermolecular coupling reactions. Reagents and conditions: (a) 1.0 – 5.0 eq. alkene, 0.01 eq. $Ir(ppy)_3$, 0.05 eq. triisopropylsilanethiol, 0.05 – 0.5 eq. $K_2CO_3$, $h\nu$ (52 W CFL), acetone, rt. (b) 0.0075 eq. 9,10-dicyanoanthracene, 1.5 eq. *N*-methoxyacetamide, h$\nu$ (450 W medium-pressure Hg discharge, 410 nm filter), acetonitrile, 12 – 15 h. (c) 0.01 eq. **1.117**, 1.5 eq. amine, 1.5 eq. $BrCCl_3$, 1.5 eq. $K_2CO_3$, $h\nu$ (3 W LED, $\lambda_{max,irr}$ 445 nm), acetonitrile, rt, 16 h. (d) 0.01 eq. **1.117**, 2.2 eq. $BrCCl_3$, 2.2 eq. $K_2CO_3$, $h\nu$ (3 W LED, $\lambda_{max,irr}$ 445 nm), 20 : 1 acetonitrile : $H_2O$, rt, 16 h.

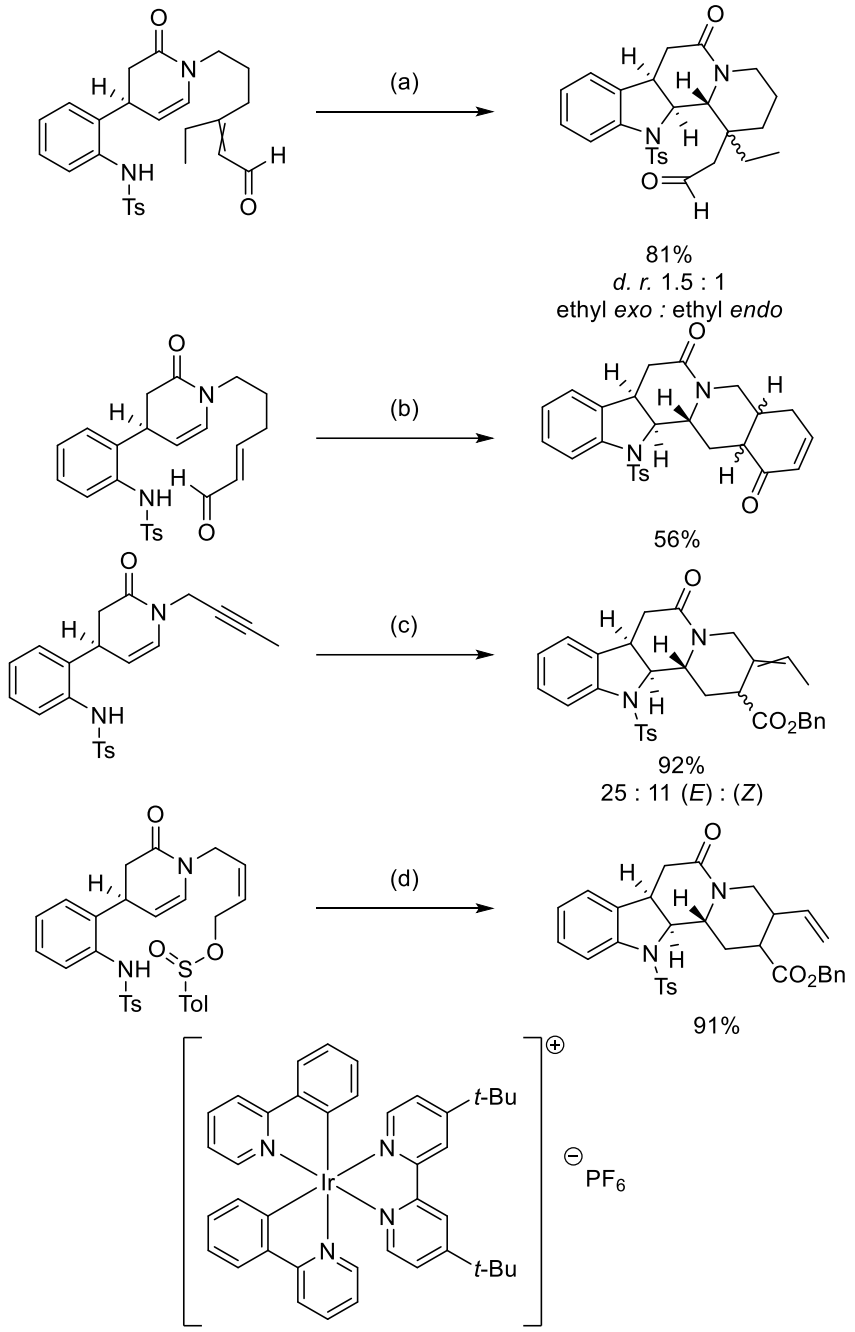
Intramolecular reactions are also reported: oxidative cyclisations of alcohols or carboxylic acids to afford tetrahydrofurans and lactones, respectively, has been achieved in the presence of triphenylpyrylium tetrafluoroborate (Scheme 1.23). (*261*) Multiple

polycyclic indolines, including 33 indole alkaloid natural products, have also been synthesised *via* sequential deprotonation and **1.118**-mediated single-electron oxidation of tosylamides to afford an aminyl radical intermediate disposed to cyclise and couple with an electron-deficient olefin (Scheme 1.24). (*262*)

This precedent work made a good case for the reactivity proposed in Chapter 2, and the work published after we began our experimental work lends further, retrospective, support.




**Scheme 1.23.** Triphenylpyrylium-catalysed oxidative synthesis of cyclic ethers and lactones. (*261*) Reagents and conditions: (a) 0.05 eq. triphenylpyrylium tetrafluoroborate, 0.3 eq. $ZnI_2$, 1.0 eq. acetic acid, $h\nu$ (15 W blue LEDs), 6 : 1 DCM : 1,1,1,3,3,3-hexafluoropropan-2-ol, $O_2$ atmosphere, rt, 72 h.




**1.118**

**Scheme 1.24.** Synthesis of alkaloid precursors *via* photoredox-mediated formation of an aryltosylamidyl radical, and subsequent cyclisation/coupling cascade. (*262*) Reagents and conditions: (a) 0.01 eq. **1.118**, 5.0 eq. $KHCO_3$, $h\nu$ (30 W blue LEDs), acetonitrile, 35 °C, 10 h. (b) *i*: 0.005 eq. **1.118**, 10.0 eq. $KHCO_3$, rt, 15 min, then 1.2 eq. MVK, $h\nu$ (30 W blue LEDs), THF, 25 °C, 10 h. *ii*: 1.0 eq. *para*-toluenesulfonic acid, toluene, 60 °C, 3 h. (c) 0.01 eq. **1.118**, 5.0 eq. $KHCO_3$, 5.0 eq. benzyl acrylate, $h\nu$ (30 W blue LEDs), THF, 35 °C, 32 h. (d) 0.005 eq. **1.118**, 5.0 eq. $KHCO_3$, 5.0 eq. benzyl acrylate, $h\nu$ (15 W blue LEDs), acetonitrile, 35 °C, 36 h.

# 2 Photocatalytic Generation of α-Furfuryl Radicals

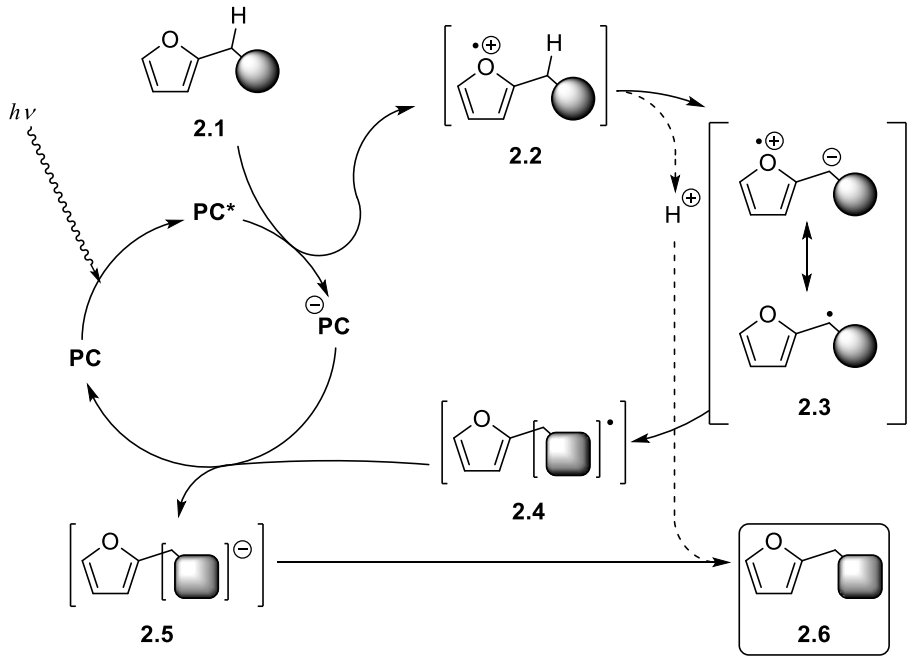
*"Kein Operationsplan reicht mit einiger Sicherheit über das erste Zusammentreffen mit der feindlichen Hauptmacht hinaus."*
(No plan of operations extends with any certainty beyond first contact with the main enemy force.)
Helmuth von Moltke the Elder (1800 – 1891), Chief of Prussian General Staff 1857 – 1887

## Initial Proposal

Furans undergo oxidation readily, (*263*) and it was expected that furan functionality as represented in cartoon **2.1** (Scheme 2.1) might act to direct formation of a free radical; single-electron oxidation of a furan moiety by a suitable photocatalytic species **PC*** – formed by irradiation of the corresponding ground state species **PC** – would generate a radical cation **2.2**, formed *via* reductive quenching of **PC*** to **PC**$^{-}$. Loss of a proton would afford neutral α-furfuryl radical **2.3**, which could then engage in a variety of radical transformations. We envisaged that products of such radical reactions **2.4** might receive an electron *via* back-SET, regenerating ground-state photocatalyst **PC** and affording anion **2.5** which, upon protonation, would afford product **2.6**, completing an overall isomerisation process. The proclivity of furan towards oxidation means that in addition to directing free radical formation, furan functionality could serve as a viable precursor to other desirable functionality.

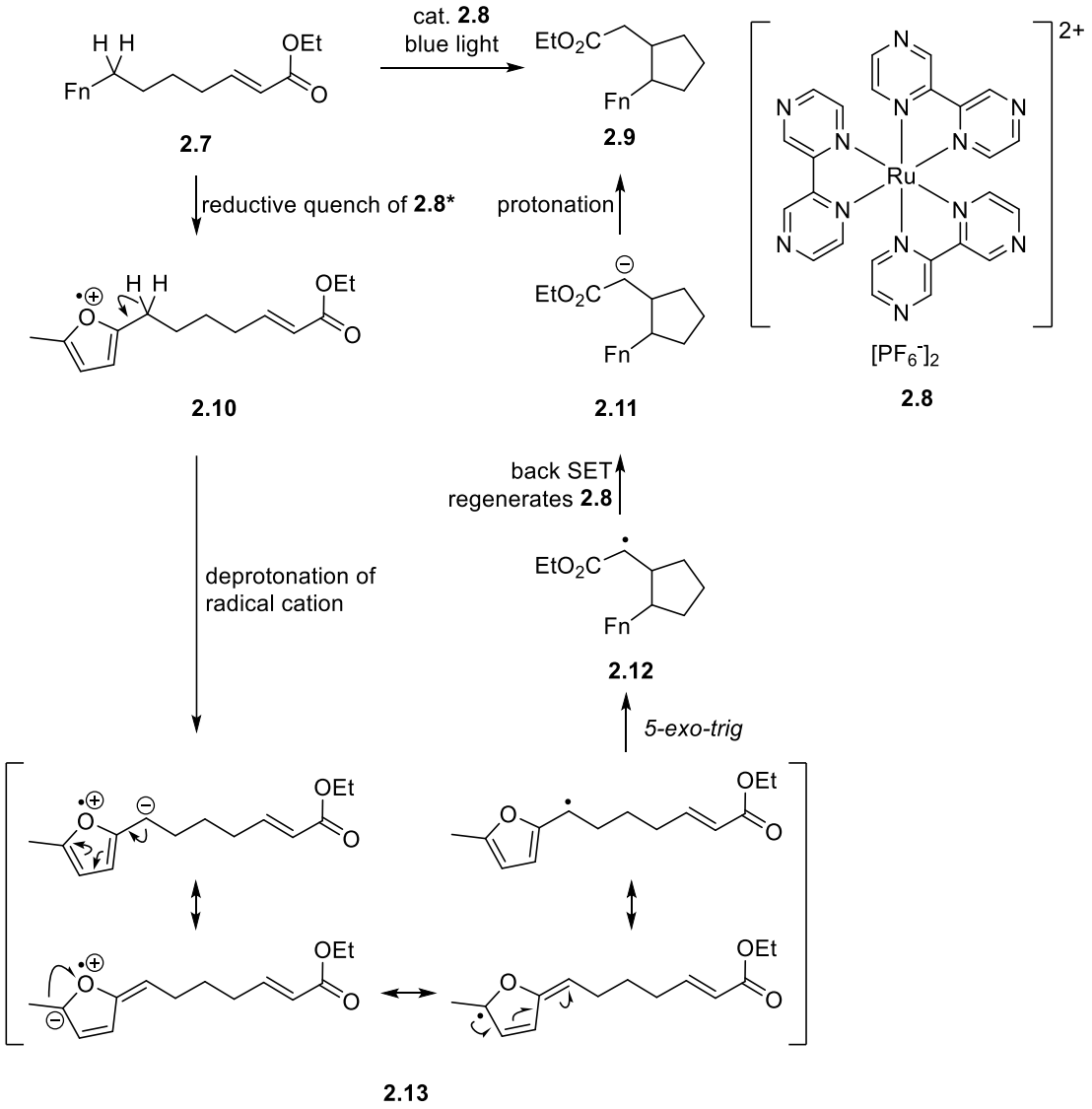
*5-Exo-trig* cyclisations are favourable on kinetic grounds; (*55*) the rate constant of cyclisation of the 5-hexenyl radical has been found to be *ca.* $10^5$ $s^{-1}$ under a variety of conditions, (*72*,*264*) and analogous values for derivative radicals are also known. (*265*,*266*) A *5-exo-trig* cyclisation was therefore chosen as a model radical reaction: an unsaturated ester was expected to act as an electron-poor trap to encourage attack by

nucleophilic radical species that might be formed under the conditions imposed. Monosubstituted furans were expected to be prone to side reactions, and of limited use as a group to direct formation of a radical; disubstitution of the furan would facilitate formation of radical cation **2.10** and render the SET between the substrate and photocatalyst tris(2,2'-bipyrazyl)ruthenium(II) hexafluorophosphate **2.8** (Scheme 2.2) more plausible.[xxx] In consideration of the above, compound **2.7** was used as an initial test substrate, cyclised product **2.9** being expected to form *via* radical intermediates**2.12** and **2.13** and anion **2.11**.




**Scheme 2.1.** A generalised proposal for the use of furan to direct photocatalytic formation of a radical localised α to furan in **2.3** *via* sequential oxidation by excited photocatalyst PC* and loss of a proton.

[xxx] The half-wave oxidation potentials for furan and 2,5-dimethylfuran are 1.70 V and 1.20 V respectively; (*435*) the reduction potential for couple **2.8***/**2.8**$^{-}$ is +1.45 V. (*436*)

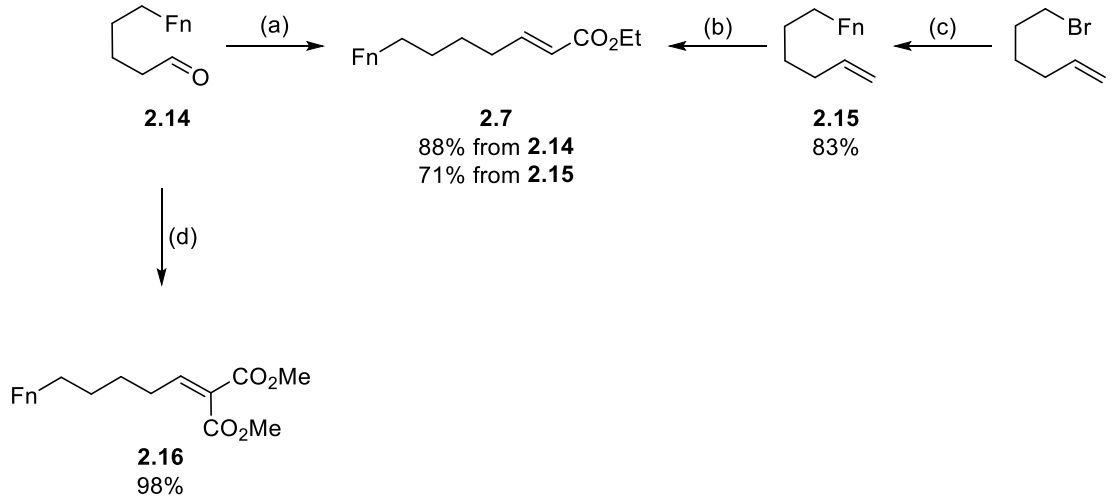



**Scheme 2.2.** A test reaction to validate the concept of using a 5-methylfuran-2-yl moiety as a directing group for photocatalytic formation of a free radical.

## Substrate and Catalyst Syntheses

Substrate **2.7** was obtained as the (*E*)-isomer *via* Masamune–Roush olefination (*267*) of aldehyde **2.14** (Scheme 2.3); (*E*)**-2.7** was also accessed *via* olefin metathesis of alkene **2.15** with ethyl acrylate, representing a two-step route from commercially available material, although the cost of both 5-bromo-1-pentene and olefin metathesis catalysts deterred use of this route on large scale. Synthesis from the aldehyde was also

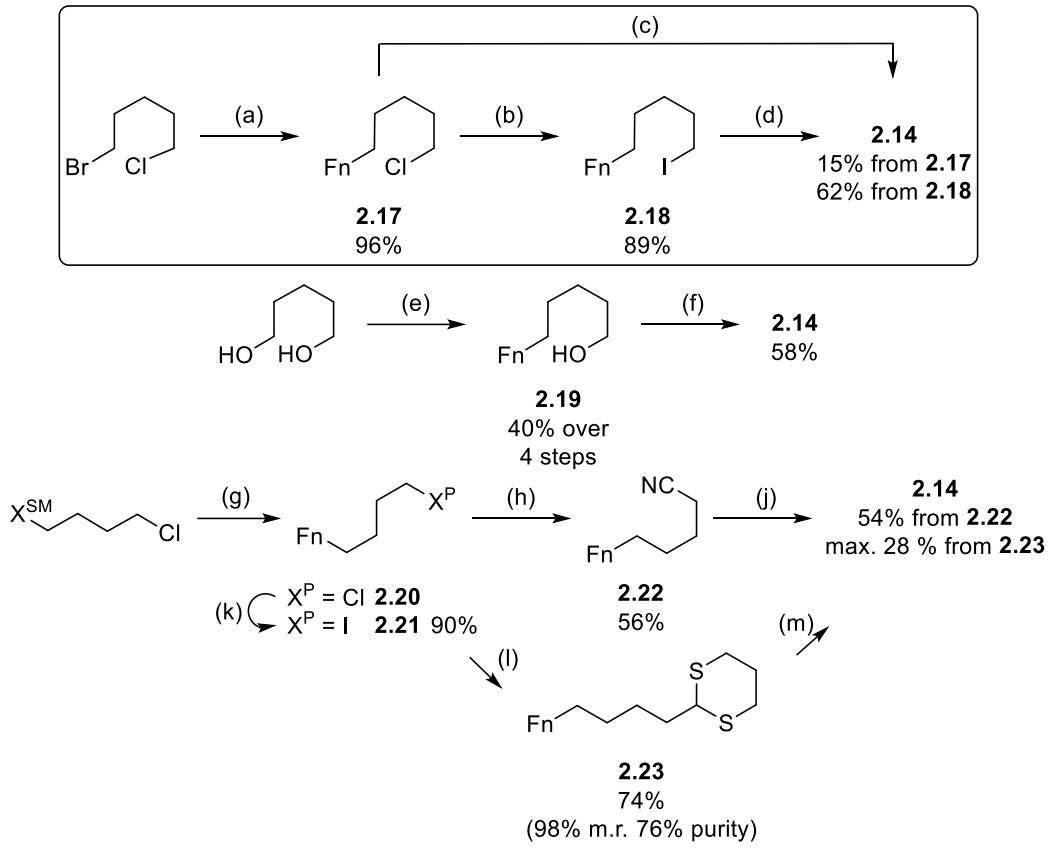
chosen because we anticipated the need for preparation of a diversity of substrates with other electron-poor functionality, *e.g.* malonate derivative **2.16**, not all of which would be readily available *via* metathesis from a common intermediate. Compound **2.14** was accessed *via* multiple routes (Scheme 2.4), including monoprotection of 1,5-pentanediol with TBS chloride, Appel reaction to afford the corresponding iodide, displacement with 2-lithio-5-methylfuran and deprotection to afford alcohol **2.19**, and *via* reduction of nitrile **2.22** which was in turn obtained by $S_N2$ displacement of chloride from compound **2.20** with NaCN. Eventually, Kornblum oxidation of iodide **2.18** was decided upon for large-scale preparation of **2.14**. Displacement of bromide from 1-bromo-5-chloropentane with 2-lithio-5-methylfuran afforded chloride **2.17**, and a Finkelstein reaction afforded **2.18**. Attempts to obtain the aldehyde from **2.17** in one step by carrying out the Kornblum oxidation in the presence of NaI led to partial conversion, and chromatographic isolation of the product in poor yield.




**Scheme 2.3.** Synthesis of test substrates. Reagents and conditions: (a) 1.2 eq. LiCl, 1.2 eq. DBU, 1.2 eq. triethyl phosphonoacetate, acetonitrile, rt, 16.8 h. (b) 3.0 eq. ethyl acrylate, 0.01 eq. H-G II, toluene, reflux,

48 min. (c) 1.33 eq. Fn-Li, THF, 0 °C – rt, 12.6 h. (d) 0.1 eq. proline, DMSO, rt, 5 min then 2 eq. dimethyl malonate, rt, 21.5 h.

The main disadvantage of this route lies in the moderate yield of the Kornblum oxidation (due to loss of material to aqueous workup, thermal decomposition, and chromatographic purification) in comparison to the very good/quantitative yields and purity of intermediates associated with other steps. In attempting to elucidate a route to **2.7** free of chromatographic purification, the possibility of introducing the aldehyde functionality *via* $S_N2$ reaction of ω-iodofuran **2.21** with 2-lithio-1,3-dithiane was investigated. Conversion of the resulting dithiane **2.23** to aldehyde **2.14**, however, was problematic. While Hg-mediated methods for unmasking **2.14** in large quantities were dismissed in view of the toxicity of the associated waste products, oxidative methods were unsuccessful due to competing reactivity of the furan. The best conditions were found to consist of stirring the dithiane with excess methyl iodide and $NaHCO_3$ at rt in aqueous acetonitrile. (*268*) When samples of **2.14** prepared in this manner were used to afford substrate **2.7**, however, the yield was considerably lower for samples of aldehyde **2.14** prepared by alternative routes. An impurity present in dithiane-derived samples of aldehyde **2.14** was likely responsible for the failure of the usually robust olefination.

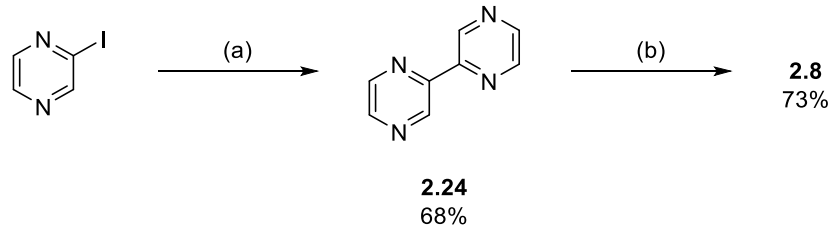



**Scheme 2.4.** Synthesis of aldehyde **2.14** was carried out by various means in search of a cheap, scalable route free of chromatography; the last of these attributes was not attained. Reagents and conditions: (a) 1.2 eq. Fn-Li, THF, 0 °C – rt, 3.7 h. (b) 2.0 eq. NaI, acetone, reflux, 18 h. (c) 1.0 eq. NaI, 2 eq. $NaHCO_3$, DMSO, 120 °C, 3.7 h. (d) 4 eq. $NaHCO_3$, DMSO, 110 °C, 1.0 h. (e) *i*: 1.3 eq. NaH, THF, 0 °C – rt, 45 min then 1.0 eq. TBSCl, 0 °C – rt, 45 min, 90 %. *ii*: 1.2 eq. $PPh_3$, 1.5 eq. imidazole then 1.2 eq. $I_2$, 4 : 1 ether : acetonitrile, 0 °C, 45 min, 76%. *iii*: 1.2 eq. Fn-Li, THF, –78 °C – rt, 2.8 h, 89%. *iv*: 1.1 eq. TBAF, THF, rt, 65 h, 66%. (f) 1.2 eq. BAIB, 2.0 eq. $NaHCO_3$, 0.04 eq. TEMPO, DCM, 0 °C – rt, 8.0 h. (g) $X^{SM}$ = Br, $X^P$ = Cl, 1.05 eq. Fn-Li, 0 °C, 2.5 h, 95%; $X^{SM}$ = I, $X^P$ = Cl, 1.2 eq. Fn-Li, THF, 0 °C, 2.5 h, 93%. (h) SM **2.20**; 1.1 eq. NaCN, DMSO, 80 °C, 5 h. (j) 1.2 eq. DIBAL, 47 : 3 DCM : hexanes. –78 °C, 5 min. (k) As (b), but reaction time 16 h. (l) SM **2.21** 1.1 eq. 2-lithio-1,3-dithiane, THF, –50 °C – rt, 3.3 h. (m) 10 eq. MeI, 11 eq. $NaHCO_3$, 9 : 1 acetonitrile : $H_2O$, rt, 20 h.

We elected to synthesise both complex **2.8** and its constituent ligand **2.24**; Of the various reported methods for obtaining the latter, the Pd-catalysed reductive homocoupling of 2-iodopyrazine was employed (Scheme 2.5),[xxxi] (*269*,*270*) as others

[xxxi] The oxidative coupling of pyrazine (which is much cheaper than 2-iodopyrazine) *via* the cuprate (*404*) was also carried out, using DDQ in place of duroquinone, affording **2.24** in poor yield (22%, 40 mmol scale; lit. 76%, 2 mmol scale and 65%, 40 mmol scale), rendering this route a false economy. On large

suffer from poor yield (*271*,*272*,*273*,*274*,*275*) or involve working with undesirable reagents. (*276*,*277*) Synthesis of **2.24** from 2-iodopyrazine using the conditions described by Schultz and coworkers (*269*) afforded the ligand in good yield, and catalyst **2.8** was then prepared by heating $RuCl_3 \cdot xH_2O$ in ethylene glycol with a slight excess of the ligand to reflux, followed by precipitation with $KPF_6$.



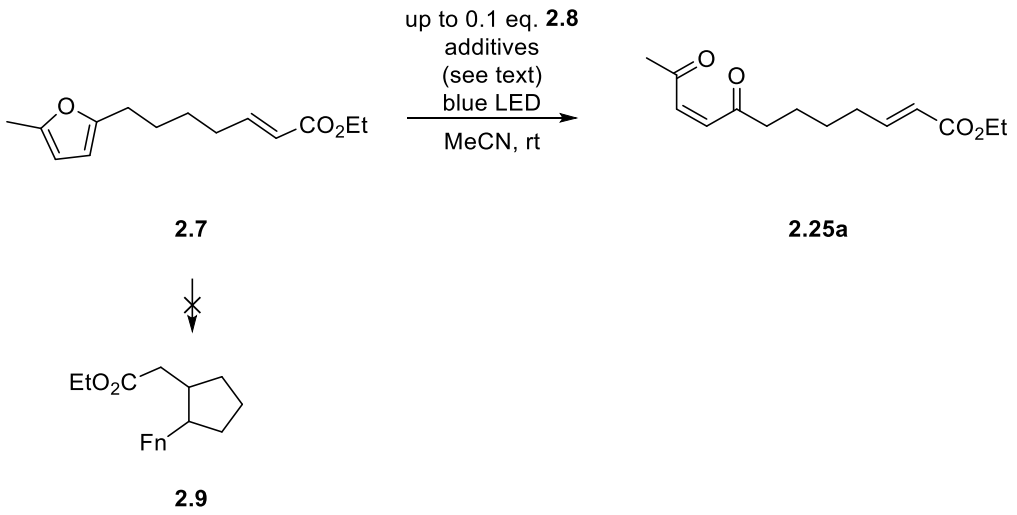

**Scheme 2.5.** Catalyst synthesis. Reagents and conditions: (a) 2.0 eq. *i*-PrOH, 1.5 eq. $K_2CO_3$, DMF, 100 °C, 2 h. (*269*) (b) 0.22 eq. $RuCl_3 \cdot xH_2O$ (Ru analysis performed by supplier indicates $x = 5.5$), ethylene glycol, 170 °C, 20 h; Yield based on Ru.

## Attempted Photoredox Cyclisation

Upon exposure of substrate (*E*)-**2.7** to blue light in the presence of compound **2.8**, cyclisation was not observed (Scheme 2.6); the starting material was recovered unchanged, save for traces of a compound determined to be (*Z*)-**2.25a** by MS and $^{13}C$ NMR analysis, and by comparison with material oxidised with *m*CPBA (Scheme 2.7 and Table 8.1, see Appendix 1: Details of Visible Light- and UV-mediated Photocatalytic Runs), which is known to oxidise furans to afford enedicarbonyls. (*278*) When the reaction mixture of a repeat run was continuously sparged with $N_2$, formation of (*Z*)-**2.25a** was not detected (NMR). Carrying out the reaction in the presence of $K_2CO_3$, TEA, sodium ethoxide, or excess 2-methylfuran also returned SM with traces of enedione (*Z*)-**2.25a** (not shown). Thiols undergo PCET with excited photoredox catalysts (see page 48),

scale, preparation of 2-iodopyrazine from the much cheaper 2-chloropyrazine (*437*,*438*) would be beneficial.

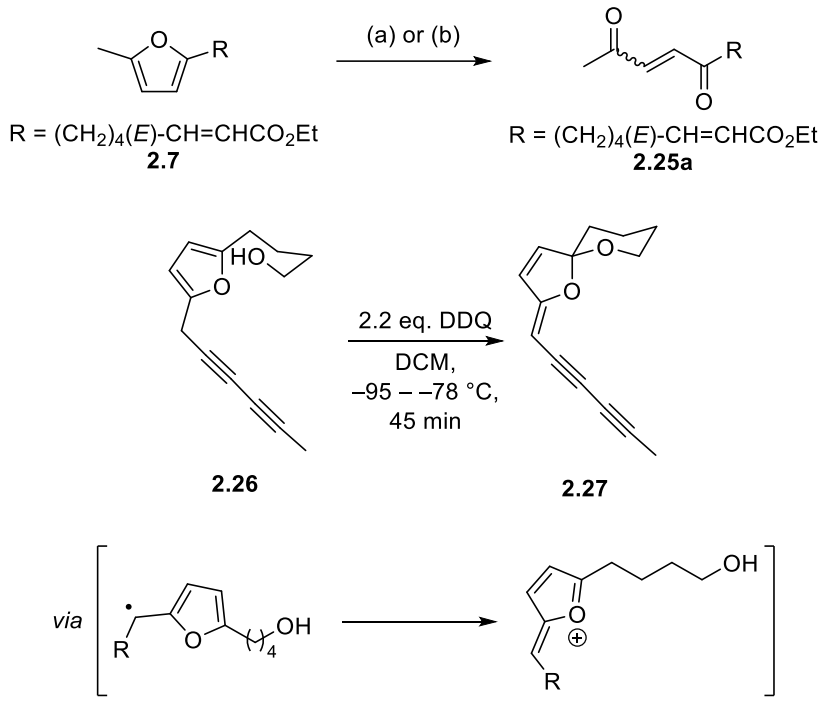
and the resulting thiyl radical can abstract hydrogen atoms from electron-rich positions; for this reason, thiols have been used as HAT catalysts. (*279*,*280*) Addition of thiols to the **2.7**/**2.8** mixture did not promote cyclisation, nor was the electrophilic unsaturated ester moiety affected under these conditions. Addition of $LiBF_4$ or molecular sieves also had no effect, and independent of additives, extended reaction times effected decomposition, with traces of **2.25a** occasionally surviving.




**Scheme 2.6.** Result of irradiating substrate **2.7** with blue light in the presence of catalyst **2.8**.

The possibility of the loss of two electrons from 2,5-disubstituted furans *via* successive SETs is supported by work previously carried out by the Robertson group on the oxidation of alkynylmethylfurans with DDQ to afford spiroacetal enol ethers, including homo-tonghaosu **2.27**, obtained from substrate **2.26** (Scheme 2.7). (*281*) It is also possible, however, that generation of **2.25a** under photoredox conditions occurs *via* a Diels–Alder reaction of the furan moiety with $O_2$, the excited photocatalyst acting as a

triplet sensitiser.[xxxii] Reaction of **2.7** with DDQ afforded **2.25a** as a mixture of (*E*)/(*Z*) isomers.




**Scheme 2.7.** Validation of **2.25a** as an oxidation product of attempted photoredox cyclisation by stoichiometric oxidation of the SM by *m*CPBA and DDQ; the latter oxidises furan *via* successive SETs. This oxidation was also carried out *via* SET-oxidation with DDQ, as previously carried out by the group in the synthesis of homotonghaosu **2.27**. (*281*) Reagents and conditions: (a) 1.5 eq. *m*CPBA, $CHCl_3$, rt, 20 min, then excess $H_2O$; 17%, d.r. 1 : 9 (*E*):(*Z*). (b) 1 eq. DDQ, DCM, –78 – 0 °C, 45 min, then excess $H_2O$; 23%, d.r. 19 : 1 (*E*):(*Z*).

## An Alternative Photocatalyst

The description of the stereoselective addition of benzodioxolanes to α,β-unsaturated ketones, *via* H-abstraction at C-2 of the dioxolane by the photocatalyst TBADT **2.28** (Chart 2.1) (*282*) encouraged us to attempt the cyclisation of **2.7** to **2.9** under similar conditions. It was expected that direct H-abstraction from the substrate and subsequent cyclisation might compete favourably with similar oxidation processes to

[xxxii] The mechanism by which this transformation proceeds is discussed further on page 110.

those which occurred under photoredox conditions (see page 63). TBADT is reported to abstract H primarily *via* a HAT mechanism, SET competing in the presence of easily oxidised functionality. (*283*,*284*,*285*,*286*)

While the structure of the decatungstate ion has been known for almost 50 years, (*287*) and its photocatalytic activity was first described in 1984, (*288*) the identity of the active species **2.28*** in TBADT-promoted reactions proved elusive until recently, as a result of the difficulty of running DFT calculations on such a complex and heavy-atom-rich system. The consensus in the literature is that **2.28*** is a triplet state biradical. (*289*,*290*) The most recent study proposes that the $A_{2g}$-symmetric LSOMO (represented by the blue coarse-dashed ellipses), which accepts electron density from the substrate during H-abstraction, is chiefly composed of *p*-type atomic orbitals localised around the outer O atoms bridging apical and non-apical W atoms (labelled $O^2$ in Chart 2.1), with minor contributions from the other bridging oxygens, $O^4$ and $O^6$. (*289*) The $A_{1u}$-symmetric HSOMO (represented by the red fine-dashed ellipses) is delocalised mainly onto the eight non-apical W atoms (labelled $W^2$), with a minor $O^2$ p-orbital contribution.

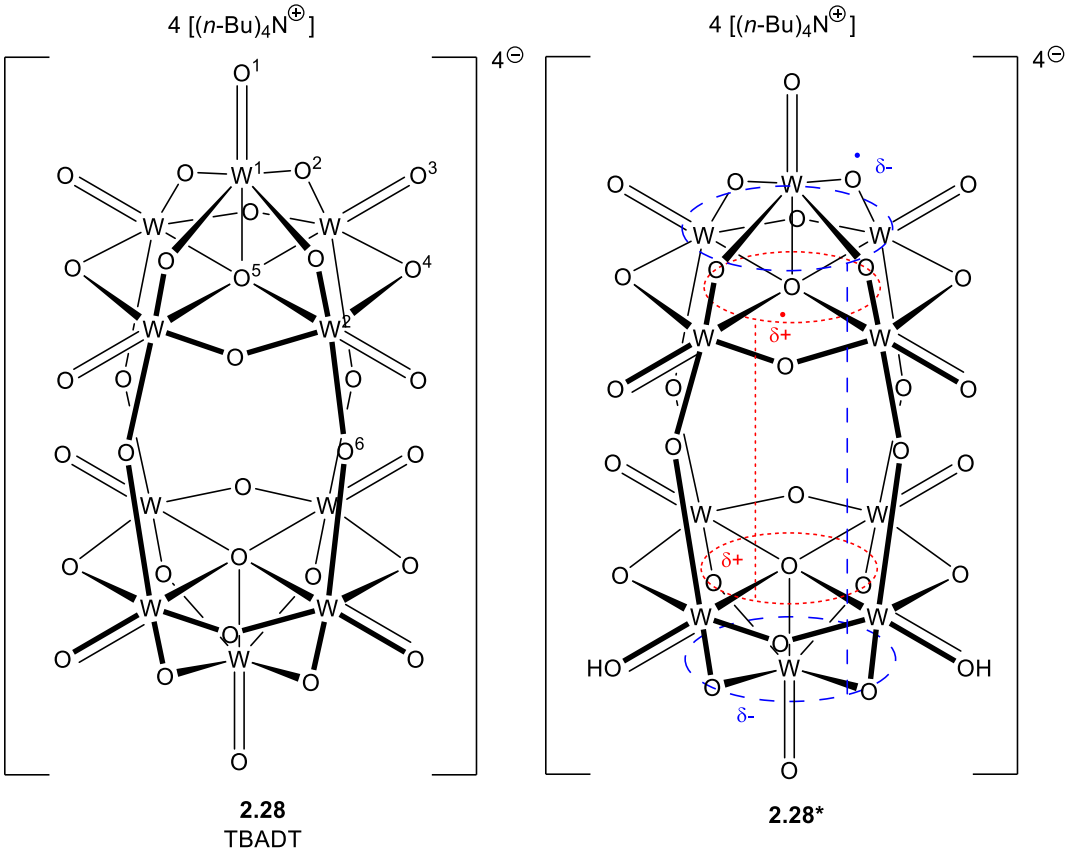
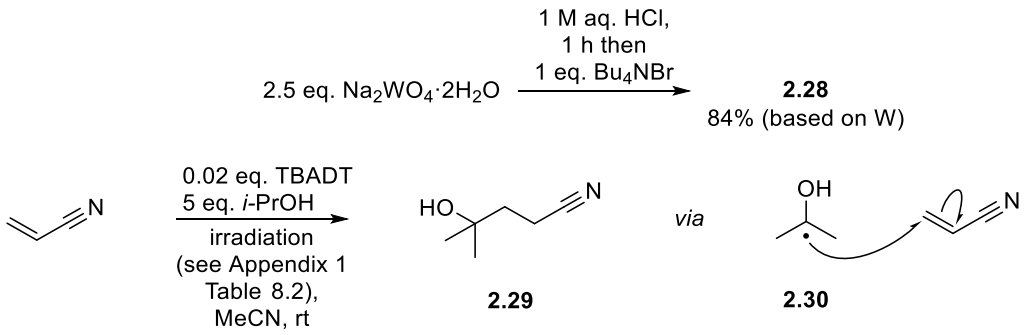



**Chart 2.1.** The structures of the ground state and catalytically active states of TBADT **2.28**. (*289*)

## Synthesis of TBADT

Catalyst **2.28** was synthesised by boiling $Na_2WO_4$ in hydrochloric acid, then precipitating the product with tetrabutylammonium bromide (Scheme 2.8). Samples of **2.28** thus prepared were characterised by IR, UV, and thermogravimetric analysis.[xxxiii] Test reactions were also carried out to confirm the purity of this material, and to establish the viability of experimental setups to initiate photocatalytic generation of radicals.

[xxxiii] We are indebted to Drs. Robert Jacobs and Ashley Shepherd for running the TGA for us.




**Scheme 2.8.** Synthesis of TBADT **2.28**, and test reaction performed to confirm viability of catalyst and experimental setup.

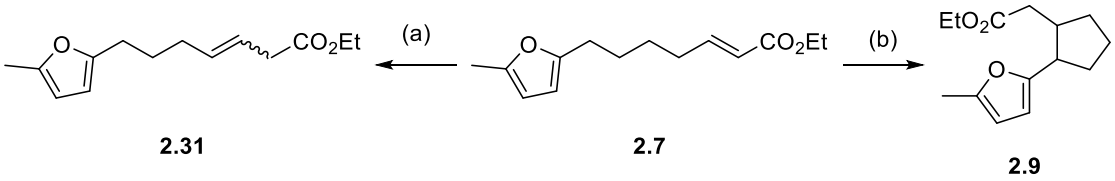
## Confirming the Viability of TBADT and Reaction Setup

The synthesis of compound **2.29** by UV irradiation of acrylonitrile and excess isopropanol in the presence of TBADT is reported. (*291*) The reaction proceeds *via* polarity-matched H-abstraction at C-2 of isopropanol to afford radical **2.30**, which adds in a conjugate sense to acrylonitrile; non-polarity-matched H-abstraction from H–TBADT by the radical thus formed affords product **2.29**. Conversion occurred upon irradiation at 254 or 365 nm, which did not occur in the absence of TBADT (Table 8.2, see Appendix 1: Details of Visible Light- and UV-mediated Photocatalytic Runs), although the product was not isolated in the high yield described in the literature; (*291*) $^{1}$H NMR analysis of the crude reaction mixture suggested that this result is not intrinsic to our reaction setup or reagents, and it seems likely that the product decomposed *via* intramolecular Pinner reaction during chromatographic purification.[xxxiv]

[xxxiv] Purification was carried out by distillation in the original preparation; we carried out test reactions on insufficient scale to to make this practicable. It is presumed that a polar imidate was formed *via* a Pinner reaction, mediated by silica, and this material, or a degradation product thereof, was retained on the stationary phase during chromatography. Had subsequent hydrolysis and elution of the resulting 4,4-dimethylbutyrolactone occurred, the boiling point of this material is sufficiently high (205 – 210 °C) (*439*) that it would not have been lost upon concentration of the eluate.

**Cycloisomerisation with TBADT**

Having determined the prepared samples of **2.28** to be catalytically viable, cyclisation of **2.7** was attempted (Scheme 2.9 and Table 2.1). Irradiation with UV light at 254 nm effected (*E*/*Z*)-isomerisation, and partial conversion to regioisomer **2.31** (entry 1). (*292*) When a control reaction was carried out, consisting of irradiation in the absence of **2.28**, complete conversion to **2.31** occurred, and the product was obtained as a 2 : 1 mixture of isomers in 26% combined yield (entry 2). Use of a 365 nm LED, more powerful than the 254 nm cold cathode Hg lamp previously employed, effected partial conversion to **2.9** (entry 3). Addition of $H_2O$ and/or $LiClO_4$ (reported to promote the coupling of toluenes with electron-deficient olefins) (*293*) revealed that imposition of these conditions did not aid cyclisation (entries 4 – 6); the presence of water merely facilitated partial oxidation to **2.25a** and a decreased conversion to product. Further studies revealed that increased conversion occurred in runs with a high substrate concentration or catalyst loading, at the cost of loss of material to decomposition (Table 8.3, see Appendix 1: Details of Visible Light- and UV-mediated Photocatalytic Runs). The best compromise was found to be 0.02 eq. of catalyst at a concentration in SM of 200 mM; 44% conversion was achieved within 48 h with no discernable decomposition (assessed by comparison of the $^1$H NMR peak intensities of SM and product with those of an internal standard). Higher catalyst loadings accelerated decomposition, even in more dilute solution, and addition of the catalyst gradually, *vs.* in one portion, did not have a beneficial effect. Attempts to drive the reaction to completion *via* irradiation for extended periods caused decomposition of the substrate.




**2.31** **2.7** **2.9**

**Scheme 2.9.** Irradiation at 365 nm in the presence of TBADT effected the partial cycloisomerisation of **2.7**. Reagents and conditions: (a) irradiation, $\lambda_{max,irr}$ 254 nm, $P_{irr}$ 175 mW, acetonitrile, rt. See Table 2.1 for details and results. (b) TBADT, $\lambda_{max,irr}$ 365 nm, $P_{irr}$ 1 W, acetonitrile, rt. See Table 2.1 and Table 8.3 (see Appendix 1: Details of Visible Light- and UV-mediated Photocatalytic Runs) for details of additives, reaction times, and results.

| Entry | Conditions[a] | [SM]/ mM | Rxn time/ h | Conv. (NMR, %) | $\lambda_{max,irr}$/nm, $P_{irr}$/*mW* | Product(s), yield (chromatographic, %) |
|---|---|---|---|---|---|---|
| 1 | A | 60.5 | 7.6 | 70 | 254, 175 | - |
| | | | 27.0 | 100 | 254, 175 | (*Z*)-**2.7** (7), 2 : 1 **2.31** : (*E*)-**2.7** (31)[b] |
| 2 | B | 60.5 | 14.9 | 100 | 254, 175 | **2.31** (26), *d.r.* 65 : 35 |
| 3 | A | 100 | 21.0 | 33 | 365, 1000 | 2 : 1 (*E*)-**2.7** : **2.9** (11)[c] |
| 4 | C | 100 | 18.5 | 16 | 365, 1000 | - |
| 5 | D | 100 | 18.5 | 15 | 365, 1000 | - |
| 6 | E | 100 | 18.5 | 12 | 365, 1000 | - |

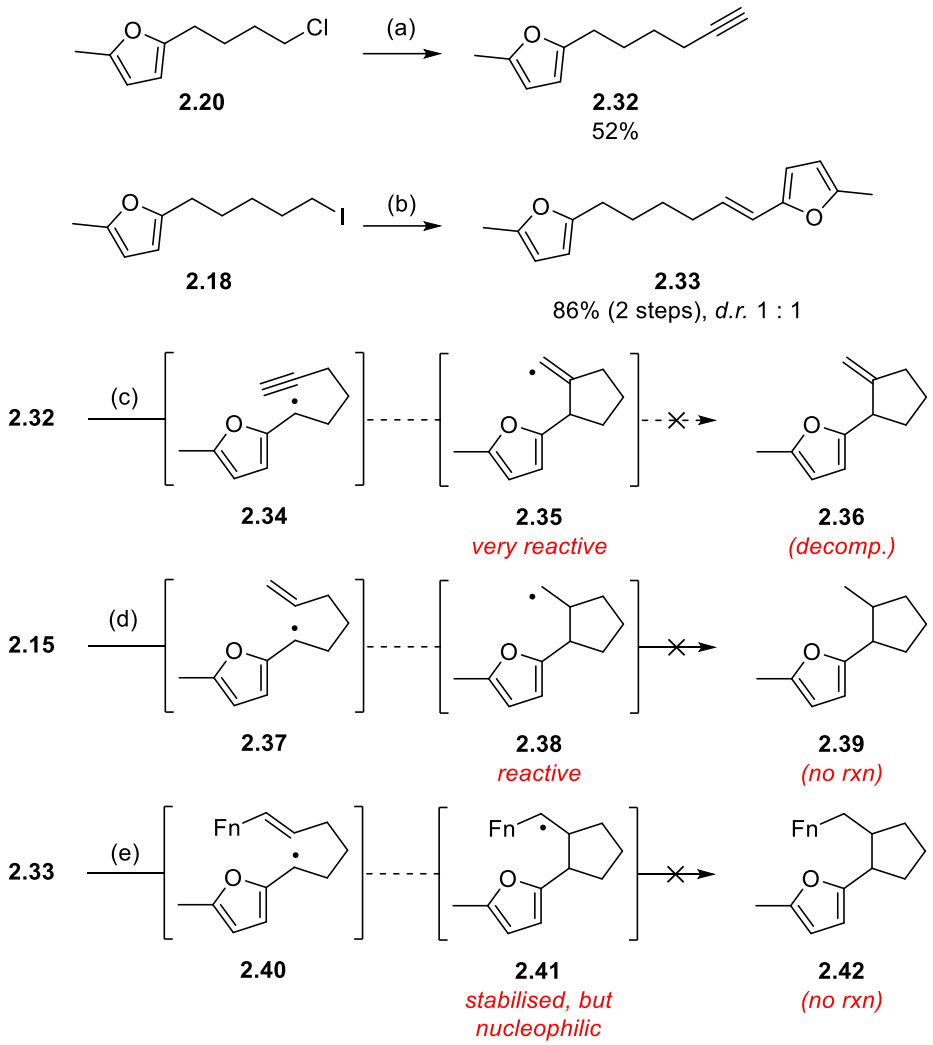
**Table 2.1.** Details of conditions for attempted cyclisation of compound **2.7** *via* UV irradiation in the presence of TBADT. [a] A: 0.02 eq. TBADT, acetonitrile; B: As A, but TBADT omitted; C: 0.02 eq. TBADT, 5 : 1 acetonitrile : $H_2O$; D: 5.0 eq. $LiClO_4$, 0.02 eq. TBADT, 5 : 1 acetonitrile : $H_2O$; E: As D, but solution oxygenated before reaction. [b] Yield includes SM. [c] Mixture not separated, but yield refers to cyclised component only.

## Studies of Polarity Effects

Although successful photocatalysed coupling of substrates to electron-poor olefins proceed *via* an analogous process, (*291*,*293*) we considered that the observed poor conversion of material to **2.9** could be ascribed to inefficient H-abstraction by **2.12**. Exposure of substrates with unactivated alkene (**2.15**) or alkyne (**2.32**) functionality to UV light in the presence of TBADT was expected to lead to furfuryl radicals **2.37** and **2.34**, respectively, *via* H-abstraction; cyclisation would then afford reactive intermediate radicals **2.38** and **2.35**, respectively (Scheme 2.10). Compound **2.32** was synthesised by

reaction of **2.20** with lithium acetylide ethylenediamine complex in the presence of NaI. Substrate **2.33**, incorporating a vinylenefuran moiety, was also prepared in the expectation that irradiation of **2.33** in the presence of TBADT would afford intermediate **2.40**, and that **2.40** would undergo cyclisation [xxxv] to give (nucleophilic) radical intermediate **2.41**. Reaction of iodide **2.18** with triphenylphosphine afforded a phosphonium salt (not shown), which was coupled to 5-methylfurfural in a Wittig reaction under previously reported conditions, (*294*) affording substrate **2.33** as a 1 : 1 mixture of (*E*)/(*Z*) isomers in excellent yield. Inexplicably, the expected cyclised products **2.36**, **2.39**, and **2.42** were not formed under these conditions; substrates **2.15** and **2.33** were recovered largely unchanged, while alkyne **2.32** decomposed in the first run, a result that could not be replicated.

[xxxv] At this time, radical **2.40** had been generated already *via* stannane chemistry (see page 89); this radical was prone to cyclisation in spite of poor polarity matching.



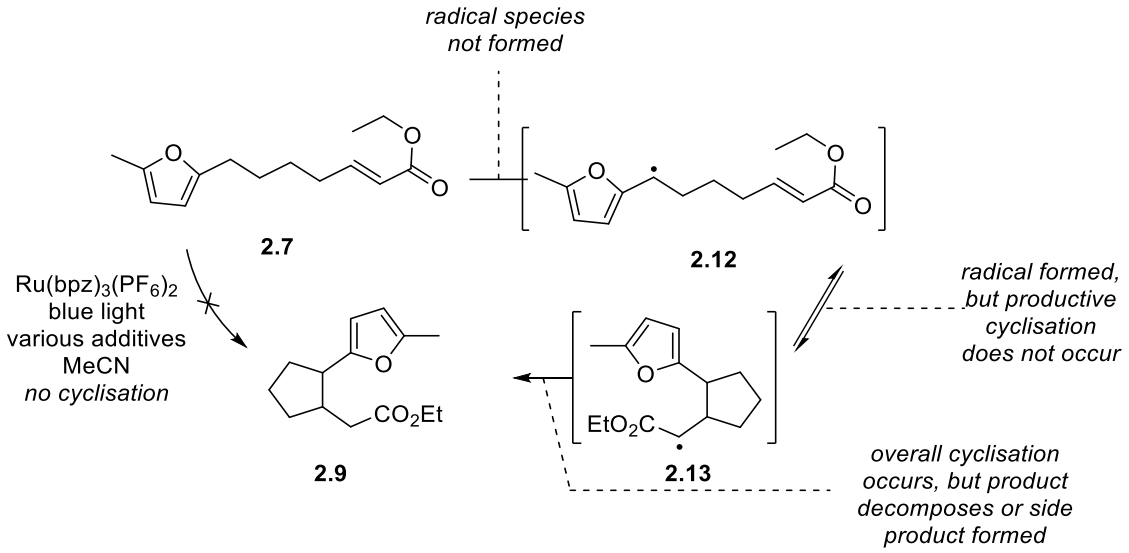

**Scheme 2.10.** Preparation and attempted cyclisation of compounds **2.15**, **2.32**, and **2.33**. Reagents and conditions: (a) 0.16 eq. NaI, 1.6 eq. lithium acetylide ethylenediamine complex, DMSO, rt, 5 h. (b) *i*: 2.0 eq. triphenylphosphine, toluene, reflux, 94%; *ii*: 1.2 eq. $K_2CO_3$, 1,4-dioxane then 1.0 eq. 5-methylfurfural, reflux, 20 h, 91%. (c) 0.02 eq. TBADT, 0.25 eq. dtbbp, acetonitrile-$d_3$, 365 nm irradiation (1 W), 24 h.

## Conclusions

There is no indication that radical **2.13** was formed upon irradiation with blue light in the presence of Ru complex **2.8**. In conjunction with other results (see Chapters 3 and 4), it seems that irreversible oxidation of furan to an enedione occurs in favour of formation of an α-furfuryl radical under these conditions; cyclisation of radical **2.13** occurs upon formation either under classical TBTH-mediated reductive conditions, or

upon exposure of the substrate to 365 nm light in the presence of TBADT. The directed photocatalytic formation of an α-furfuryl radical (which is, to our knowledge, without literature precedent) has been achieved. This reaction could not be driven to completion without decomposing the substrate, nor could the cyclised product (which forms non-selectively as a mixture of diastereomers) be separated from the uncyclised SM.

The failure of test substrate **2.7** to cycloisomerise upon irradiation with blue light in the presence of **2.8** suggested either that no such radical was formed under the reaction conditions, or that radical species **2.13** did not react as predicted (Scheme 2.11). Considering that SM **2.7** could be recovered largely unchanged from attempted visible light-mediated cyclisations, it is unlikely that successful cyclisation to radical **2.12** was followed by a side reaction, preventing the formation of product **2.9**.




**Scheme 2.11.** Possible explanations for failure of **2.7** to cyclise to **2.9**; decomposition following successful formation of **2.12** is not consistent with recovery of SM **2.7**.

## Further Work

It was necessary to confirm the behaviour of α-furfuryl radicals, in order to address the question of whether cyclisation was prevented by some unforeseen obstacle: *e.g.* kinetic barriers to cyclisation, or thermodynamic considerations leading to a negligible population of cyclised **2.12** in the cyclised/uncyclised equilibrium mixture of radicals; efforts to do so are the subject of Chapter 3. UV-mediated cyclisation in the presence of TBADT had not yet been achieved at the time that this work began, and the limited propensity of **2.7** to cyclise under TBADT/UV conditions might be attributed to the unusual (and heretofore uncharacterised) behaviour of furfuryl radicals.

Long-term UV-irradiation of substrate in the presence of TBADT causes decomposition of the substrate, and highly concentrated reaction mixtures are, in general, associated with good conversion, although the solubility of the catalyst limits the extent to which this can be carried out at ambient temperature. Warming the reaction mixtures may allow larger quantities of the catalyst to be dissolved, as well as introducing the potential for removal of the catalyst by crystallisation, making purification easier. Both the visible light-mediated and UV-mediated photocatalytic reactions were carried out in acetonitrile, a solvent from which nucleophilic radicals such as **2.13** could readily abstract H atoms on polarity matching grounds. It is possible that the limited reactivity of compound **2.7** towards cyclisation arose from rapid termination of any furfuryl radicals formed prior to productive reaction. A change of solvent might, therefore, be advantageous, although solvents sufficiently polar to dissolve even **2.8** or **2.28** either suffer the same disadvantage as acetonitrile or would themselves be prone to H-

abstraction/oxidation *via* SET by an excited photocatalytic species.[xxxvi] The replacement of $PF_6^-$ in **2.8** with, for example, tetra-(4-fluorophenyl)borate, and use of more lipophilic ligands, may aid dissolution in less polar solvents.

The formal two-electron oxidation of furan (which may proceed *via* a Diels–Alder reaction with singlet $O_2$, with **2.8** acting as a sensitiser, and not *via* a photoredox pathway, see page 110 for discussion of the likely mechanism) that appears to occur in preference to single-electron oxidation prevented the formation and reaction of an α-furfuryl radical under all attempted photoredox conditions. Relying on SET from cyclised species **2.12** to close the photocatalytic cycle may have been too ambitious. Cyclisation was more successful with HAT catalyst **2.28**, but UV irradiation has associated disadvantages; the light used is damaging to vulnerable chemical functionality – which can be found both in substrates and in the chemist performing the work – and sources are inefficient (with associated heat dissipation problems) and/or expensive. It would be beneficial to attempt the transformation of **2.7** to **2.9** *via* visible-light HAT catalysis using *e.g.* fluorenone, xanthone or DCA. On the other hand, while two-electron oxidation of furan substrates may be difficult to avoid, reliance solely on the RSI cycle may have led us to overlook viable SET-based conditions. It may be possible to employ an oxidatively-quenched photoredox catalyst, such as $Ir(ppy)_3$, and an oxidising additive to effect an OSP cycle, in which the furan substrate **2.7** is oxidised by $\mathbf{PC}^+$, and the resulting cyclised radical species **2.12** undergoes a radical coupling with a radical anion generated by quenching **PC***.

[xxxvi] The catalyst need not necessarily be dissolved; heterogeneous photoredox catalysis has been reviewed. (*440*,*441*,*442*,*443*)

# 3 Behaviour of α-Furfuryl and Related Radicals

*"Доверяй, но проверяй."*
(Trust, but verify.)
Russian proverb

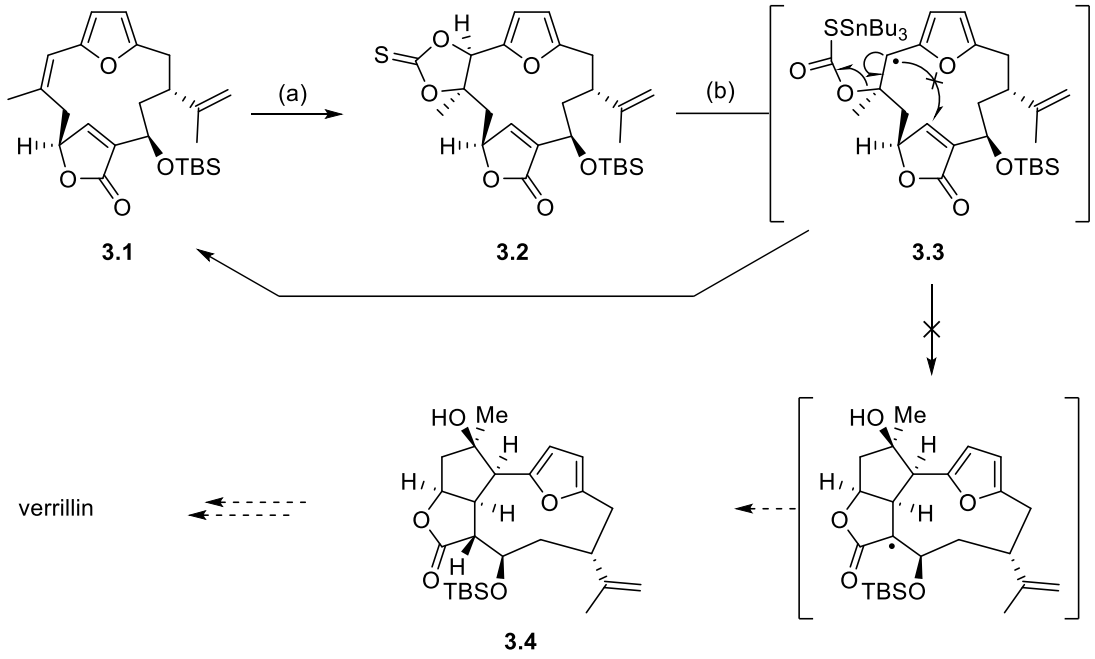
## Rationale for Stannane-mediated Formation of α-Furfuryl Radicals

While substrate **2.7** was designed specifically for the purpose of cyclising as a certain indicator of the formation of radical **2.13**, we wished to satisfy ourselves of this beyond any doubt. The use of tin hydrides to generate free radical intermediates, including those adjacent to furan, is described extensively in the literature (see Chapter 1, page 11 onwards). However, to our knowledge, only direct reduction of the resulting furfuryl radical is described (*i.e.* the Barton–McCombie deoxygenation, see page 15); there are no reports of any rearrangements or elaboration of structure, such as our proposed cyclisation of compound **2.7**, with one exception; unpublished work towards verrillin (*295*) includes an attempted *5-exo-trig* cyclisation of radical **3.3** to afford **3.4**, but submission of precursor **3.2** to TBTH and AIBN afforded starting olefin **3.1** instead of the desired rearrangement product (Scheme 3.1). We set about establishing a synthetic route to radicals relevant to our proposed catalytic cycle *via* classical, tin-mediated, conditions, with a view to establishing:

1. Whether the cyclisation of **2.13** is feasible,

2. The reversibility of the cyclisation of **2.13**, and

3. The extent to which polarity effects affect (1) and (2).

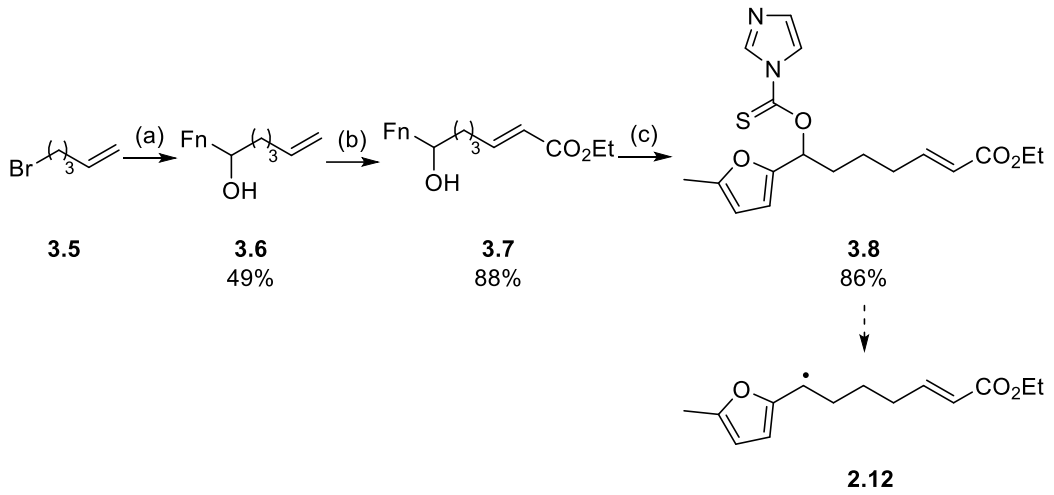



**Scheme 3.1.** An abortive *5-exo-trig* cyclisation (*295*) is, to our knowledge, the only reaction described, apart from direct reduction, involving an α-furfuryl radical prior to the work described in this thesis. Reagents and conditions: (a) *i*: $OsO_4$, NMO; *ii*: TCDI. (b) AIBN, $Bu_3SnH$.

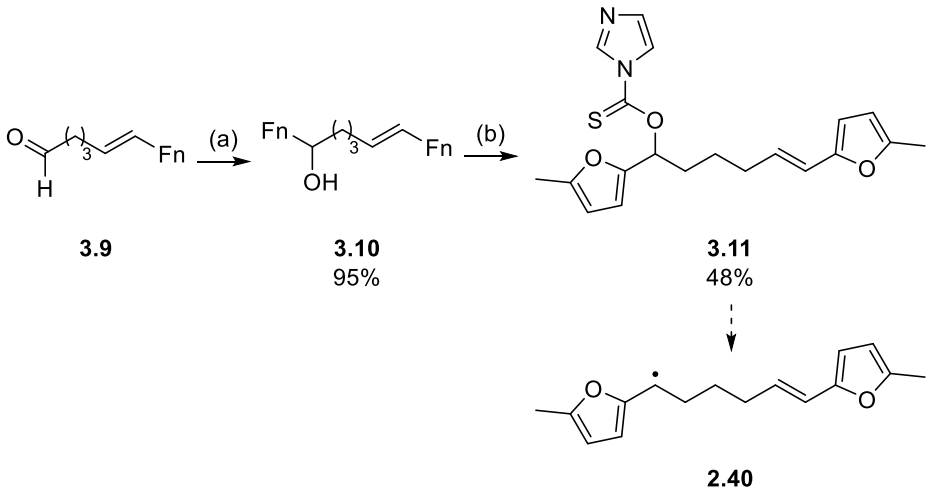
## Synthesis of Precursors to Radicals of Interest

Radical progenitor **3.8** was synthesised in three steps (Scheme 3.2); addition of a Grignard reagent, formed *in situ* from commercial bromide **3.5**, to 5-methylfurfural afforded alcohol **3.6**, which was elaborated to compound **3.7** *via* olefin metathesis with ethyl acrylate. Alcohol **3.7** was converted to the thiocarbonyl derivative **3.8** by treatment with TCDI and DMAP.

Compound **3.11** was selected to serve as the precursor to radical **2.40**, which is of interest as an analogue of radical **2.13** in which polarity effects are absent and therefore of no significance with respect to cyclisation behaviour. Compound **3.11** was obtained from the (*E*)-isomer of aldehyde **3.9** *via* intermediate alcohol **3.10** (Scheme 3.3); attempts to achieve olefin metathesis between **3.6** and 2-methyl-5-vinylfuran were not successful.




**Scheme 3.2.** Synthesis of compound **3.8**, progenitor of radical **2.13**. Reagents and conditions: (a) 1.6 eq. Mg, 0.1 eq. DBE, THF, reflux, 30 min; then 5-methylfurfural, 0 °C, 1 h. (b) 3 eq. ethyl acrylate, 0.1 eq. H-G II, chloroform, reflux, 40 min. (c) 1 eq. DMAP, 3 eq. TCDI, DCM, 0 °C, 2.7 h.

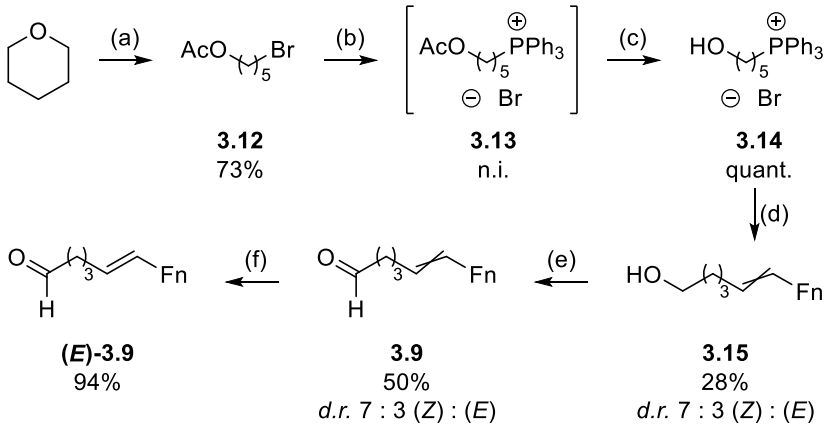



**Scheme 3.3.** Synthesis of radical progenitor **3.11**. Reagents and conditions: (a) 1.5 eq. Fn-Li, THF, –78 °C – rt 16.6 h. (b) 1 eq. DMAP, 3 eq. TCDI, DCM, 0 °C, 2.3 h.

Aldehyde **3.9** was obtained from tetrahydropyran (Scheme 3.4). Triphenylphosphonium salt **3.14** was obtained following a known procedure; (*296*) fragmentation of tetrahydropyran to 5-bromopentyl acetate **3.12** was achieved by heating to reflux with zinc dust and acetyl bromide,[xxxvii] then heating with triphenylphosphine

[xxxvii] The analogous transformation was attempted with iodotriethylsilane formed *in situ*, (*444*) but was abandoned due to issues with undesired deprotection during chromatographic purification.

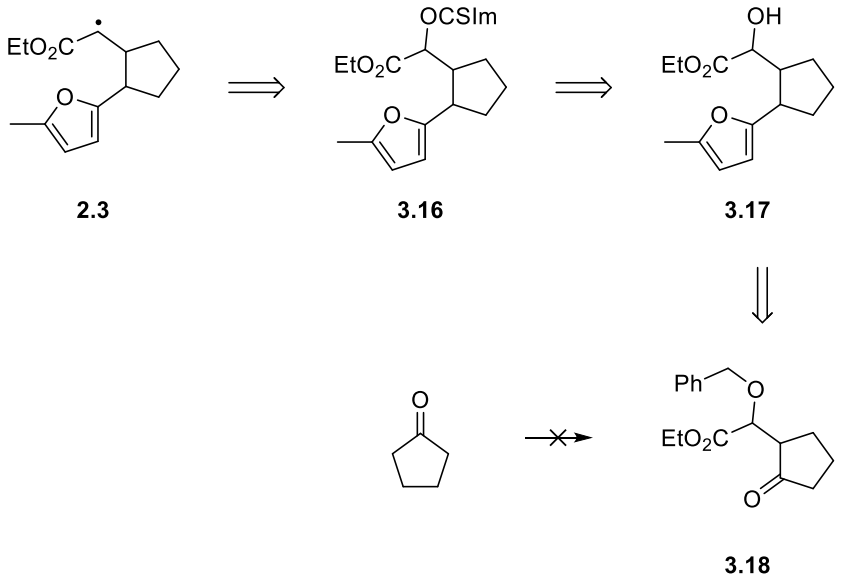
afforded intermediate **3.13**. Hydrolysis was performed *in situ* to give **3.14** in 80% overall yield. A Wittig reaction with butyllithium as base and 5-methylfurfural as a coupling partner afforded alkene **3.15** as a mixture of (*E*)/(*Z*) isomers in poor yield; isolation of significant amounts of the starting aldehyde and 5-methylfurfuryl alcohol indicates that this may have been due to incomplete deprotonation of the Wittig salt and competing reduction of the aldehyde by the Wittig reagent. A similar reaction using $K_2CO_3$ was much more successful (see page 71). Compound **3.15** was then oxidised with BAIB in the presence of TEMPO to afford **3.9**; the *d.r.* seen in the SM was conserved, and this material was converted completely to the (*E*)-isomer by stirring with $I_2$ in benzene in the presence of $K_2CO_3$ to inhibit decomposition.




**Scheme 3.4.** Synthesis of aldehyde **3.9** as the (*E*)-isomer from tetrahydropyran. Reagents and conditions: (a) 0.01 eq. Zn, 1.06 eq. acetyl bromide, 10 min, then reflux, 40 min. (b) 1 eq. triphenylphosphine, 120 °C, 12 h. (c) 0.07 eq. $K_2CO_3$, 10 : 1 methanol : $H_2O$, rt, 23 h. (d) 2 eq. butyllithium, THF, 0 °C, 3.3 h, then 1.1 eq. 5-methylfurfural, 1 h. (e) 5 eq. $NaHCO_3$, 0.05 eq. TEMPO, 1.2 eq. BAIB, 0 °C 1 h then rt, 24 h. (f) 0.1 eq. $K_2CO_3$, 0.1 eq. $I_2$, benzene, rt.

We expected cyclised radical **2.12** to be generated from compound **3.16** (Scheme 3.5) in direct analogy to radicals **2.13** and **2.40**, but an attempted aldol condensation of cyclopentanone and ethyl glyoxylate to afford the precursor (not shown) of intermediates **3.17** and **3.18** was not successful; this route was therefore abandoned in favour of

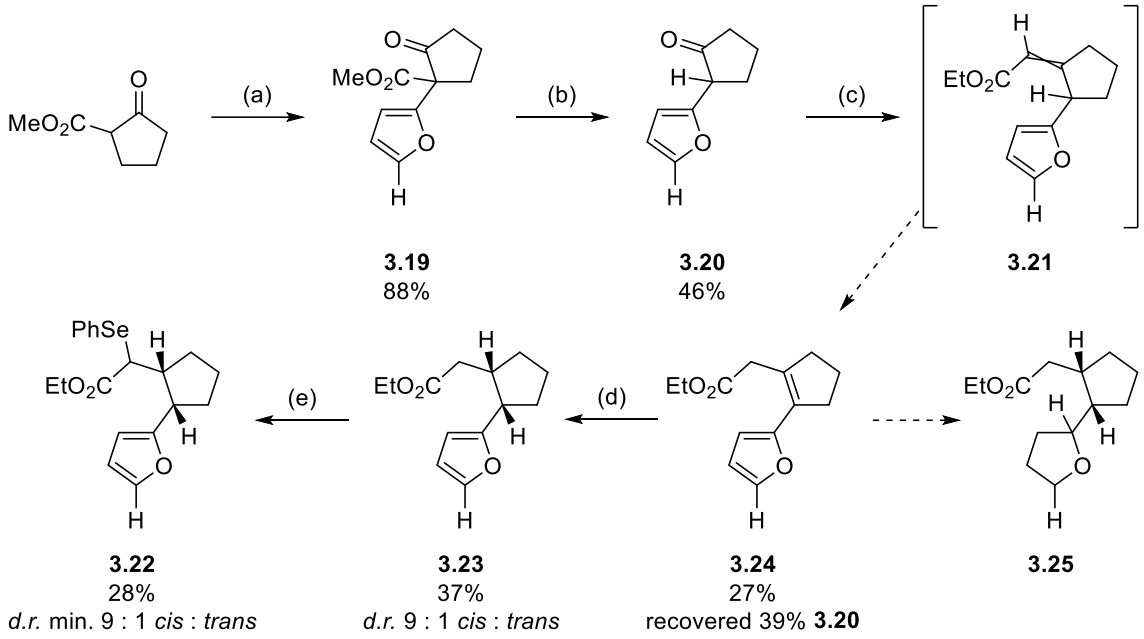
synthesis of **3.22**, the progenitor of the *nor*-methyl derivative of radical **2.12** (Scheme 3.6).




**Scheme 3.5.** Extension of the methodology established for synthesis of compounds **3.8** and **3.11** met with failure at the first step.

Methyl 2-oxocyclopentanecarboxylate was elaborated to structure **3.19** by separate and simultaneous addition of 2,5-dimethoxy-2,5-dihydrofuran and $ZnCl_2$ in the presence of water and acetic acid, and decarboxylated under modified Krapcho conditions in a known overall procedure. (*297*) The unstable 2-furylketone **3.20** thus obtained was subjected to a Wittig reaction, affording compound **3.21**, which converted slowly upon standing to more stable isomer **3.24**. Hydrogenation of **3.24** to afford *cis*-**3.23** was problematic; the fine balance between failing to convert the substrate and over-reduction to a complex mixture of tetrahydrofurans described by structure **3.25**[xxxviii] was never achieved to our satisfaction (Table 3.1).

[xxxviii] Our proposal of reduction of the furan moiety is substantiated by the lack of $sp^2$-H resonances in NMR spectra of over-reduced material.




**Scheme 3.6.** Synthesis of alternative radical progenitor **3.22**. Reagents and conditions: (a) 1 eq. DMDHF, 1.5 eq. $ZnCl_2$, acetic acid, $H_2O$, THF, reflux, 75 min. (b) 2 eq. LiCl, 6 : 15 : 250 $H_2O$ : acetic acid : NMP, 171 °C – reflux, 105 min. (c) 1.2 eq. (carbethoxymethylene)triphenylphosphorane, toluene, reflux, 22 h; recovered 38% SM. (d) $H_2$, Pd/C; see Table 3.1 for details. (e) 1.1 eq. LDA, THF, –78 °C, 30 min, then 1.1 eq. phenylselenyl bromide, 2 h.

The presence of an alcohol in the solvent mixture was necessary for any conversion of SM **3.24** (entries 1 – 4). A change of solvent to ethanol allowed reaction, but overreduction occurred (entry 5). A shorter reaction time allowed a mixture of **3.23** and **3.25** to be obtained (entry 6), and slight selectivity for the desired product **3.23** was possible with a small Pd loading (entry 7). Reaction for an extended period of time was associated with only a poorer selectivity for product over undesired THF **3.25** when the reaction was performed on large scale, even with a comparatively high Pd loading (entry 8). Attempts to entrain a large quantity of $H_2$ into the mixture before addition of the substrate entailed poorer selectivity, despite dilution of the solvent mixture with (aprotic) ethyl acetate to lower the rate of hydrogenation (*298*) and shorter reaction times (entries 9 and 10).

| Entry | Scale/ µmol | Concent-ration/ mM[a] | Cat. loading on support (% w/w) | Active cat. in mixture, eq.[a] | Solvent[b] | Rxn time | M.R.[c] (%) | Material isolated[d] | Notes |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 91 | 91 | 5 | 0.0036 | Ethyl acetate | 6 h | - | SM | SM as mixture of isomers |
| 2 | 91 | 91 | 10 | 0.046 | Ethyl acetate | 45 min | 75 | " | " |
| 3 | 91 | 91 | 20 | 0.08 | Ethyl acetate | 6 h | - | " | $Pd(OH)_2/C$ used as catalyst |
| 4 | 182 | 91 | 100 | 0.36 | Ethyl acetate | 6 h | 90 | " | " |
| 5 | 717 | 72 | 10 | 0.092 | Ethanol | 18.5 h | 85 | **3.25** | |
| 6 | 110 | 110 | 10 | 0.22 | Ethanol | 3.5 h | 92 | 29 : 21 **3.23** : **3.25** | Traces of pure **3.23** isolated chromatographically. |
| 7 | 681 | 91 | 10 | 0.0086 | Ethanol | 3.3 h | Quant. | 71 : 29 **3.23** : **3.21** | Best conditions. |
| 8 | 937 | 94 | 10 | 0.022 | Ethanol | 16 h | 96 | 41 : 59 **3.23** : **3.25** | **3.23** obtained chromatographically, 37% yield |
| 9 | 499 | 50 | 10 | 0.0056 | 1 : 1 Ethanol : ethyl acetate | 1.9 h[e] | 85 | 56 : 44 **3.23** : **3.25** | $H_2$ bubbled through solution for 15 min before stirring under $H_2$ atm. **3.23** obtained chromatographically, 28% yield |
| 10 | | 113 | 5 | 0.0083 | Ethanol | 45 min[e] | 62 | 4 : 6 **3.23** : **3.25** | $H_2$ bubbled through solution for 10 min before stirring under $H_2$ atm. |

**Table 3.1.** Conditions for hydrogenation of olefin **3.24**. (a) Specified with respect to SM. (b) Mixtures are expressed as (v/v) ratios. (c) Mass recovery. (d) Ratios describe (w/w) composition of product mixtures. (e) This value includes time to entrain $H_2$ (see note in rightmost column).

The configuration of compound **3.23**, while expected, was verified as *cis* by nOe analysis (see Appendix 4: Nuclear Overhauser Effect Analysis of Compound **3.23**).[xxxix] Deprotonation of *cis*-**3.23** with LDA, and reaction with phenylselenyl bromide prepared *in situ*, afforded radical progenitor **3.22** as a separable mixture of diastereomers in poor yield. Analysis of nOes assured that both diastereomers had the substituents on the central ring disposed *cis* to one another (see Appendix 3: Nuclear Overhauser Effect Analysis of Compound **3.22**).[xxxix]

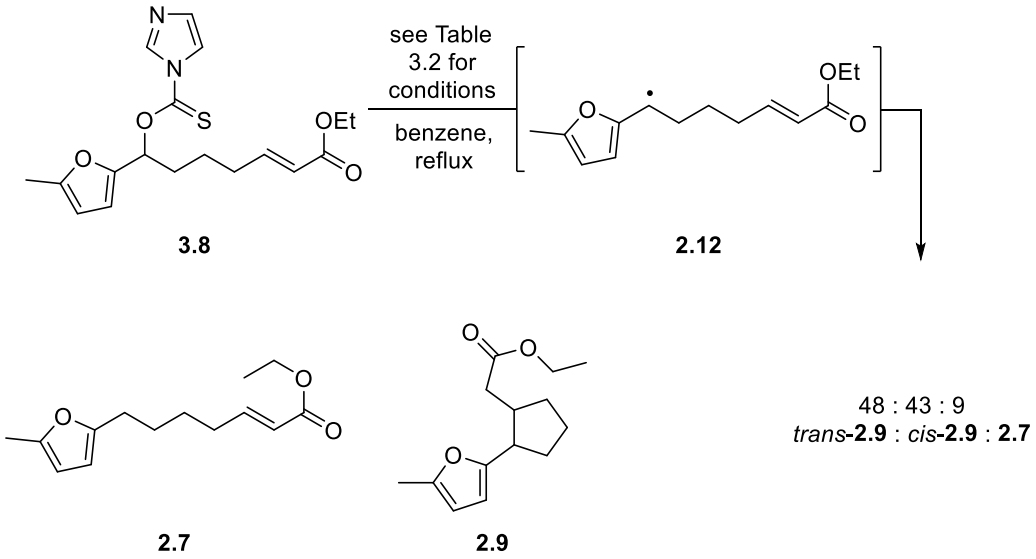
## Radical Cyclisations

With precursors **3.8**, **3.11**, and **3.22** in hand, all three substrates were subjected to reduction conditions (Table 3.2). NMR analysis of the crude reaction mixture with **3.8** as the substrate indicated partial conversion into two diastereomers, neither of which contained olefin protons (entry 1); purification of a second run afforded a mixture of compounds comprising 48% *trans*-**2.9**, 43% *cis*-**2.9**[xl] and only 9% direct reduction product **2.7** (Scheme 3.7), despite the presence of the full charge of stannane from the beginning of the reaction (Table 3.2 entry 2).

Compound **3.22** (9 : 1 *cis* : *trans*) was submitted to similar conditions (Scheme 3.8), and an erosion of stereochemistry resulted (entry 4); expected product **3.23** was obtained as a mixture of diastereomers, with no uncyclised product isolated. Together with the information gleaned from the behaviour of radical **2.13**, this is consistent with opening of the radical *cis*-**3.26** converting to radical **3.27** (with unspecified

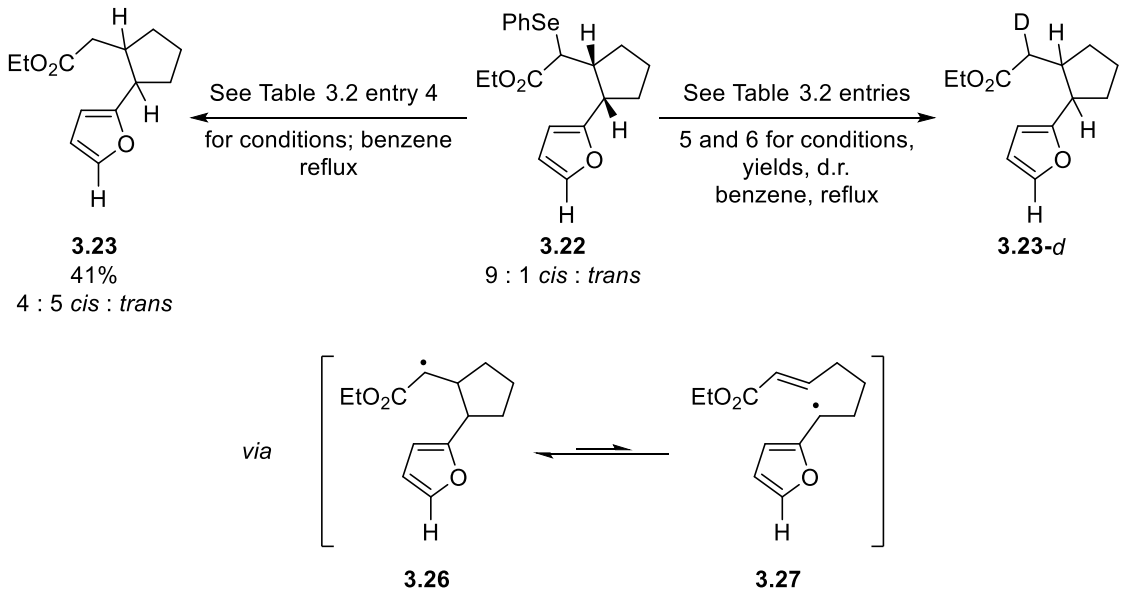
[xxxix] We thank Dr. Barbara Odell for running the necessary experiments, and for confirming the validity of our interpretation of the data.
[xl] The identities of the major and minor cyclised products as the trans- and cis-diastereomers respectively were established by nOe analysis,[xxxix] see Appendix 2: Nuclear Overhauser Effect Analysis of Compound **2.9**

stereochemistry) *via* β-scission of the indicated bond, then reverting to **3.26** as a mixture of diastereomers, before H-abstraction from TBTH. We could not rule out, however, the possibility that other processes, *e.g.* intermolecular or intramolecular H-abstraction, might have brought about the same result. When *cis*-**3.23** was submitted to similar conditions (entry 7), no scrambling of stereochemistry was observed; the initiation of radical chains was confirmed by consumption of 0.2 eq. of added (2-bromoethyl)benzene.[xli] An isotopic labelling study was also undertaken to establish as clearly as possible that the observed stereochemical scrambling was indeed arising from a reversible cyclisation with the equilibrium favouring the closed form. TBTH-*d*, prepared by reduction of TBTCl with $NaBD_4$, (*299*) was used to reduce compound **3.22** under the usual conditions. Deuteration was only observed to have occurred α to the ester, affording **3.23**-*d* (entries 5 and 6).




**Scheme 3.7.** Reduction of radical progenitor **3.8** formed radical **2.13**, which cyclised efficiently.

[xli] Monitored by GC.



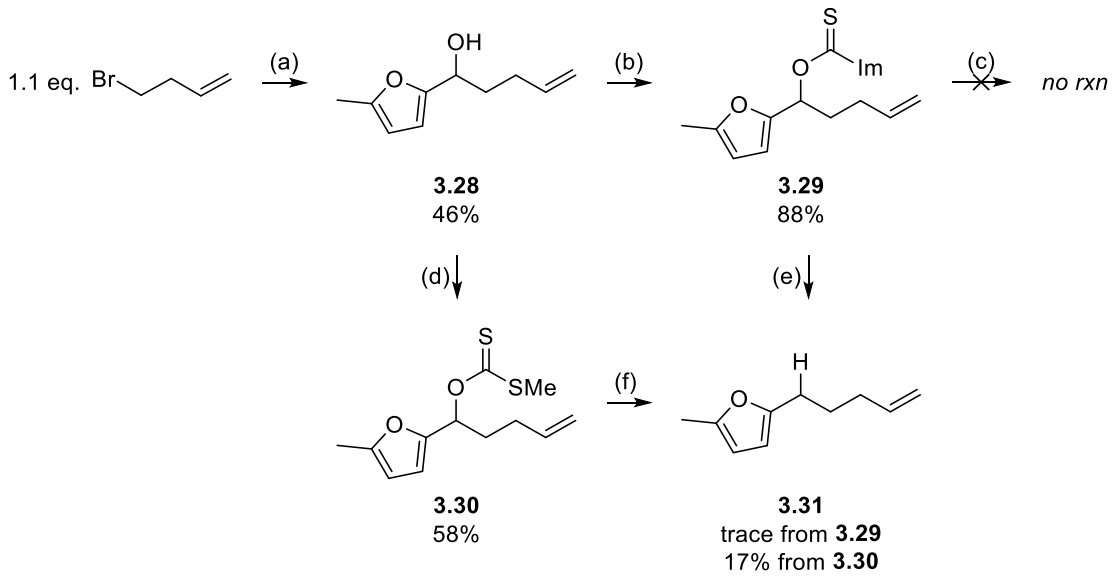

**Scheme 3.8.** Reduction of compound **3.22** highly enriched in one diastereomer afforded expected product **3.23** as a mixture of diastereomers. Stereochemistry was retained when *cis*-**3.23** was exposed to identical conditions, and isotopic labelling indicates the origin of the loss of stereochemical information.

Chromatographic separation of organotin residues from products arising from reduction of **3.11** was expected to be especially difficult owing to the extreme lipophilicity of the species concerned; significant loss of material was experienced during purification of the reduction products of **3.8** and **3.22**.[xlii] The reduction of compound **3.29** under standard conditions was expected to afford ω-furylpentene **3.31**; the intention was then to perform a screen for suitable purification protocols. Compound **3.28** was therefore prepared and converted to thiocarbonyl derivative **3.29** (Scheme 3.9).

[xlii] Recovery of both products was around 40%, but NMR analysis of both crude reaction mixtures indicated that conversion was clean; we therefore attribute the loss of material to adsorption on silica.

| Entry, Substrate | Conc.[a]/ mM | AIBN loading, eq.[a] | Reductant identity, loading[a] | Rxn time/ h | Product(s), *d.r.* of **3.23**[b] | Yield of cyclised products (%)[c] | Notes |
|---|---|---|---|---|---|---|---|
| 1, **3.8** | 4.2 | 0.1 | TBTH, 1.1 | 2.0 | No rxn | - | TBTH added *via* syringe pump over 2 h; reaction failed to initiate. |
| | 4.0 | 0.1[d] | - | 15.3 | 61 : 39 SM : **3.23**, 1 : 1 | - | Partial reduction observed; olefin-containing product also obtained; not **2.7** or (*Z*)-isomer thereof |
| 2, **3.8** | 5.1 | 0.1 | TBTH, 1.1 | 1.5 | No rxn | - | TBTH added *via* syringe pump over 1.5 h; not under Ar atm. Stannane consumed, AIBN and SM still present (NMR). |
| | | - | TBTH, 1.1[e] | 5.5 | 1 : 9 **2.7** : **3.23**, 5 : 4 | 37 | Mixture purged with Ar before reheating; reaction half-complete after 2.8 h (NMR). |
| 3, **3.8** | 5.0 | 0.05 | TBTH, 1.05 | 2.1 | No rxn | - | Experiment performed to confirm viability of reagents/solvent (see page 88); 1.05 eq. TBTH and AIBN added *via* syringe pump over 1.3 h. |
| | | 0.05[e] | - | 2.5 | 2 : 1 SM : **3.23**, 5 : 4 | trace | Indicated product distribution/*d.r.* as at 1.3 h. Diastereomers separated during chromatography in negligible yield. |
| 4, **3.22** | 6.2 | 0.1 | TBTH, 1.1 | 1.8 | Inconclusive | - | TLC monitoring ambiguous; additional AIBN added as a precaution against possible failure to initiate (see below). |
| | | 0.1[e] | - | 0.5 | **3.23**, 5 : 4 | 41 | - |
| 5, **3.22** | 5.0 | 0.1 | TBTH-*d*, 1.0 | 0.5 | No rxn | - | TBTH-*d* 67% pure ($^{13}$C NMR); rxn carried out at 75 °C. |
| | 4.7 | 0.1[f] | - | 16.0 | 4 : 5 SM : **3.23-d** 2 : 3 | 74[g] | Oil bath warmed to 85 °C; reaction half-complete after 1.8 h. |
| 6, **3.22** | 50 | 0.1 | TBTH-*d,* 0.8 | 1.0 | - | - | TBTH-*d* 67% pure ($^{13}$C NMR). |
| | 44 | - | TBTH-*d*, 0.4 | 0.9 | **3.23-d**, 15 : 85 | 56 | - |
| 7, *cis*-**3.23** | 4.2 | 0.1 | TBTH, 1.3 | 2.5 | No rxn | 68 | 0.2 Eq. phenethyl bromide added; consumption verified initiation. |
| 8, **3.11** | 5.0 | 0.2 | $Ph_3SnH$, 1.5 | 1.1 | 64 : 35 :1 **2.42** : **3.11** : **2.33** | 38 | - |

**Table 3.2.** Results of radical reduction of substrates **3.8**, **3.11**, and **3.22**. (a) Specified wrt substrate. (b) Determined by NMR analysis of crude reaction mixture; product distributions are mol : mol, *d.r.* values are *trans* : *cis.* (c) All yields are chromatographic and for both diastereomers. (d) Added to mixture as solution in benzene. (e) Added to mixture neat. (f) Added to mixture as solution in benzene in four equal portions at 24 min, 32 min, 46 min, 96 min. (g) Mass recovery 99%, contaminated with 24% w/w ether.




**Scheme 3.9.** Reduction of compound **3.29** was not successful under conditions previously employed; a different reductant and less mild conditions facilitated reduction. Reagents and conditions: (a) 0.9 eq. Mg, cat. $I_2$, THF, rt, 1.5 h, then 0.9 eq. 5-methylfurfural, rt, 40 min. (b) 2.9 eq. TCDI, 1 eq. DMAP, DCM, 0 °C, 90 min. (c) various conditions; max. 0.2 eq. AIBN, max. 2.2 eq. TBTH, benzene, reflux, max. 17 h. (d) 1.2 eq. NaH, 0 °C, THF, 40 min then 2.4 eq. $CS_2$, 67 min, then methyl iodide, 30 min. (e) 0.2 eq. AIBN, 1.5 eq. triphenylstannane, benzene-$d_6$, 75 °C, 22 h. (f) 0.08 eq. AIBN, 1.5 eq. triphenylstannane, toluene-$d_8$, reflux, 45 min.

A self-sustaining chain reaction did not occur under conditions which had afforded the same with substrates **3.8** and **3.22**. Use of higher loadings of initiator were not successful, and the possibility that a trace impurity at undetectable levels had been introduced to the solvent or reagents was investigated by repeating the reduction of **3.8** (Table 3.2 entry 3), deliberately employing a low loading of initiator to avoid forcing to completion a reaction potentially rendered capricious by introduction of impurities to the reagents employed. While reduction did not proceed to completion and initiation was, indeed, not successful, some conversion was observed. A very slight change in the $^1$H NMR spectrum of **3.29** upon attempted reduction[xliii] engendered suspicion that the

[xliii] The resonances associated with the Im group and with the proton at C-1 of the side chain shifted upfield 0.01 ppm, in contrast to all other resonances, which were not shifted. Signals were stable after the initial change; all spectra were of the reaction mixture and recorded in benzene-$d_6$.

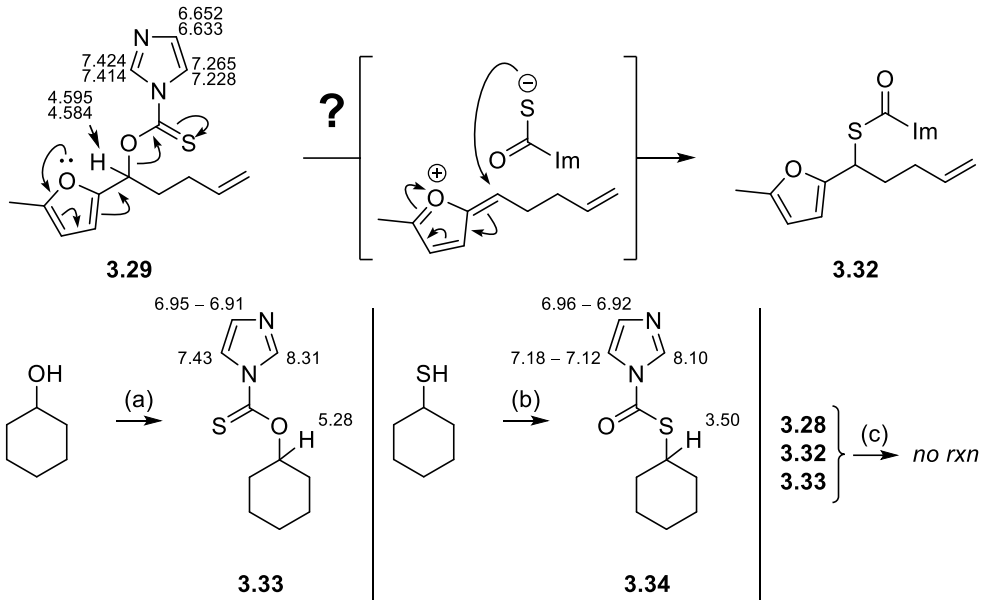
substrate was rearranging to similar compound **3.32**,[xliv] *via* fragmentation and reassembly (Scheme 3.10), and that this was unreactive towards reduction by TBTH. This possibility was investigated and discounted by synthesis of isomeric models **3.33** and **3.34**; $^{1}$H NMR analysis indicated that rearrangement would entail changes of chemical shift far in excess of those observed. Additionally, both test substrate **3.29** and models **3.33** and **3.34** were heated without AIBN/TBTH and no rearrangement occurred. We conclude that the source of the change in chemical shift is not associated with conversion of substrate **3.29** to an unreactive form, although the true cause has not been identified conclusively. The change may be attributable to an alteration of the solvent environment in the NMR sample owing to the presence of components of the crude reaction mixture; use of a more electrophilic reducing agent bore fruit; compound **3.29** was successfully reduced with triphenylstannane, affording an impure sample of **3.31** in low yield,[xlv] but reaction progress was sluggish compared to that with substrates **3.8** and **3.22**, even under comparatively harsh conditions; conversion was complete after 22 h in refluxing benzene with 0.2 eq. of initiator and 1.5 eq. of stannane. (*63*) Compound **3.30** was also prepared, and reduction under similar conditions, but with toluene-$d_8$ as solvent, enabled complete conversion in less than 1 h owing to the higher reflux temperature.

These conditions were applied successfully to the reduction of compound **3.11**, generating radical **2.40** (Scheme 3.11 and Table 3.2 entry 8); cyclised compound **2.42** was obtained as a mixture of diastereomers. The presence of merely a trace of directly reduced product **2.33** was inferred from an NMR spectrum of the crude reaction mixture.

---

[xliv] *Cf.* the Newman–Kwart rearrangement of aryl thiocarbamates; (*445*,*446*) a different mechanism is obviously operative in our case, but the driving force at work (formation of $\pi_{C-O}$ at the expense of $\pi_{C-S}$) is common to both types of subtrate.

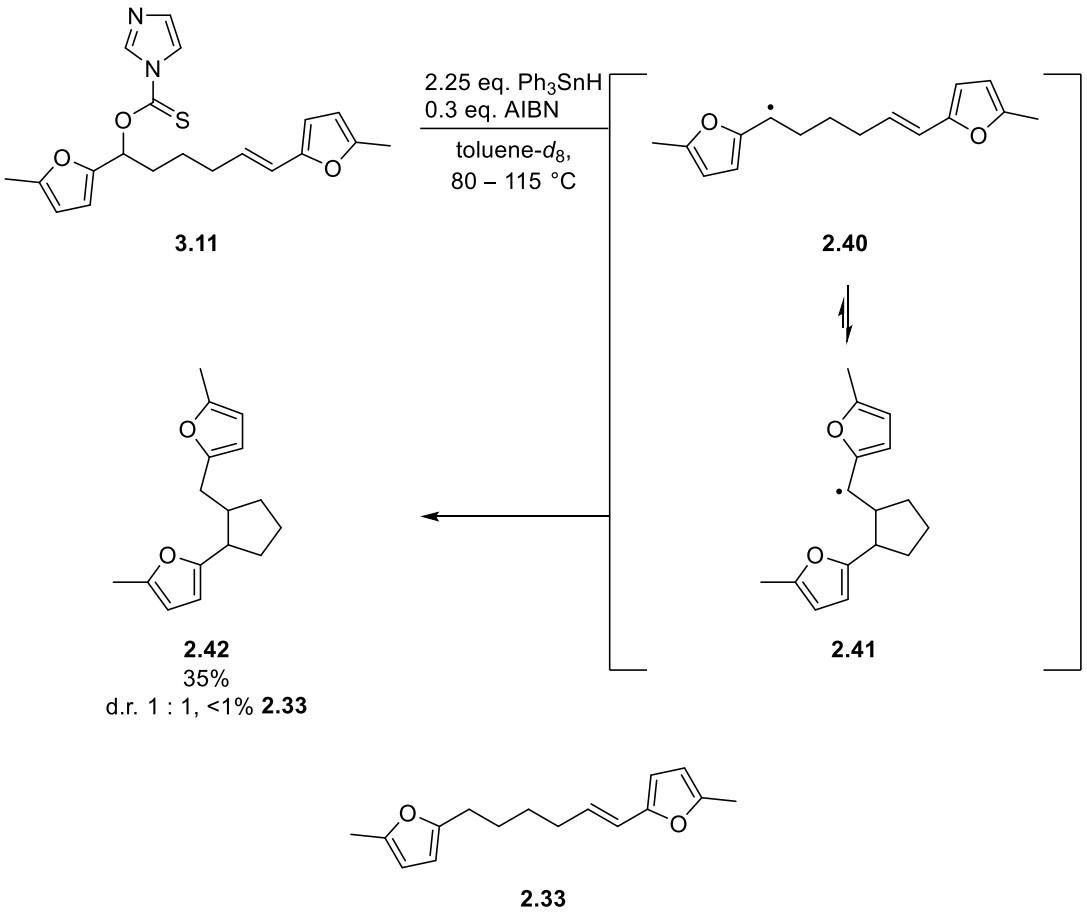
[xlv] We attribute the poor yield of this reaction to the volatility of the product.




**Scheme 3.10.** A possible rearrangement of **3.29** to **3.32** was ruled out by synthesis of compounds **3.33** and **3.34**, and comparison of their $^{1}$H NMR spectra. For $^{1}$H NMR chemical shift data, top values were measured before heating, bottom values afterwards. Reagents and conditions: (a) 3.0 eq. TCDI, 1.0 eq. DMAP, DCM, 0 °C, 22 h. (b) 2.2 eq. CDI, DCM, reflux, 22 h. (c) benzene-$d_6$, reflux.

## Conclusions

Results gleaned from the reduction of **3.8** and **3.22** indicate that α-furfuryl radicals cyclise rapidly and reversibly into traps consisting of electron-poor olefins. While it is conceivable that a disparity in the relative rates of hydrogen abstraction by **2.13** and other, less nucleophilic, radicals (including **2.12**) plays a part in the product distributions observed upon reduction of compounds **3.8** and **3.22**, the complete cyclisation of radical **2.40** upon formation suggests that *5-exo-trig* cyclisation of α-furfuryl radicals into both electron-poor **and** electron rich radical traps is favoured on both kinetic and thermodynamic grounds. To our knowledge, such cyclisations of furfuryl radicals are not reported, and reassurance as to the likely behaviour of such species when generated photocatalytically was important in encouraging our perseverence with alternative photocatalytic methods (see page 69).

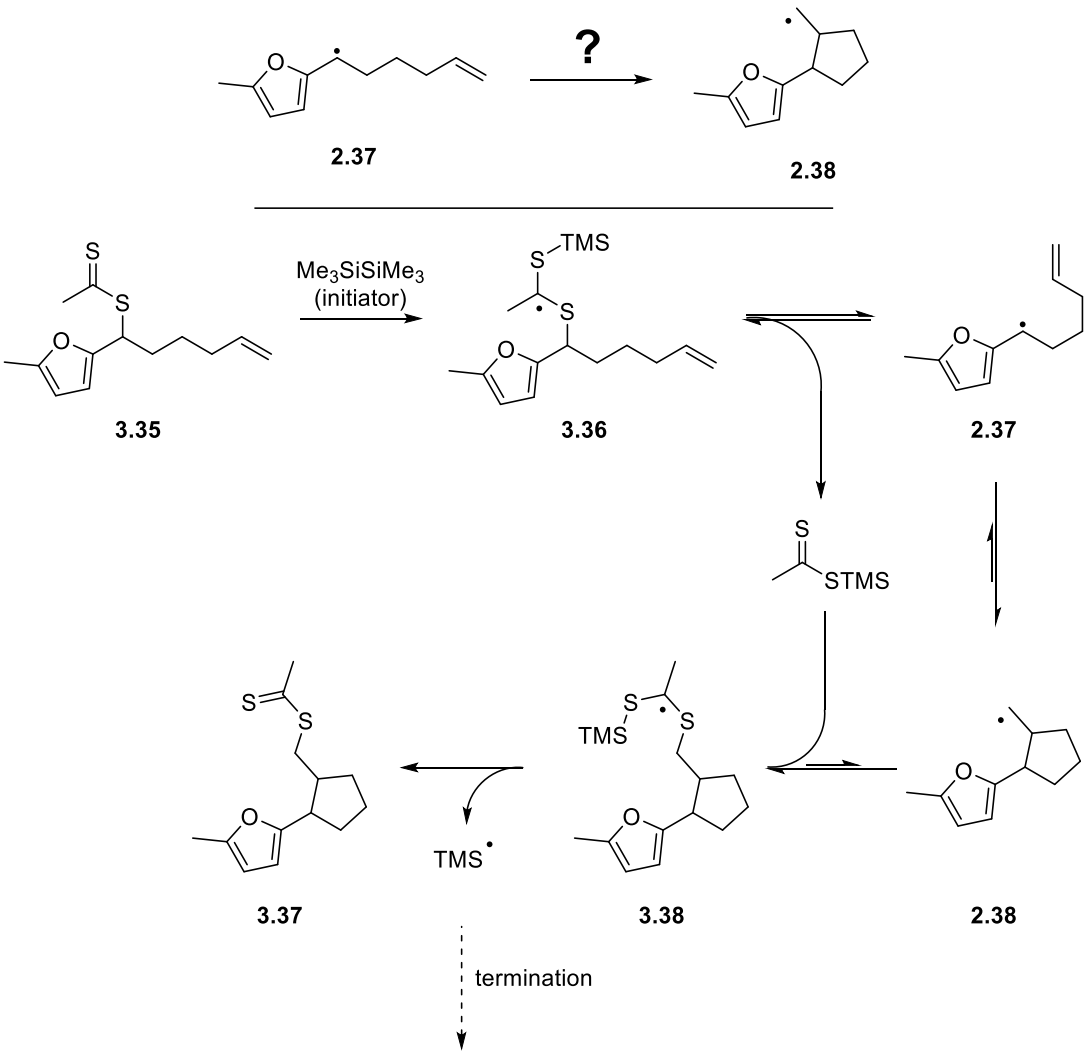



**Scheme 3.11.** Compound **3.11** was reduced to cyclised product **2.42**; sluggish chain propagation necessitated harsh conditions.

## Further Work

The remarkable stability of α-furfuryl radicals may allow reversible deactivation techniques (normally applied to chain growth polymerisation) to be applied to the radical-mediated transformation of small molecules. The cyclisation behaviour of radical **2.37** (Scheme 3.12) was not evaluated by unambiguous generation from a progenitor *via* stannane reduction, but if it were found to cyclise efficiently, then reaction of dithioester **3.35** in the presence of an initiator such as hexamethyldisilane could lead to cycloisomerisation to **3.37** *via* reversible addition-fragmentation in the same vein as previous work on atom-transfer radical addition; (*97*) the reduced stability of cyclised

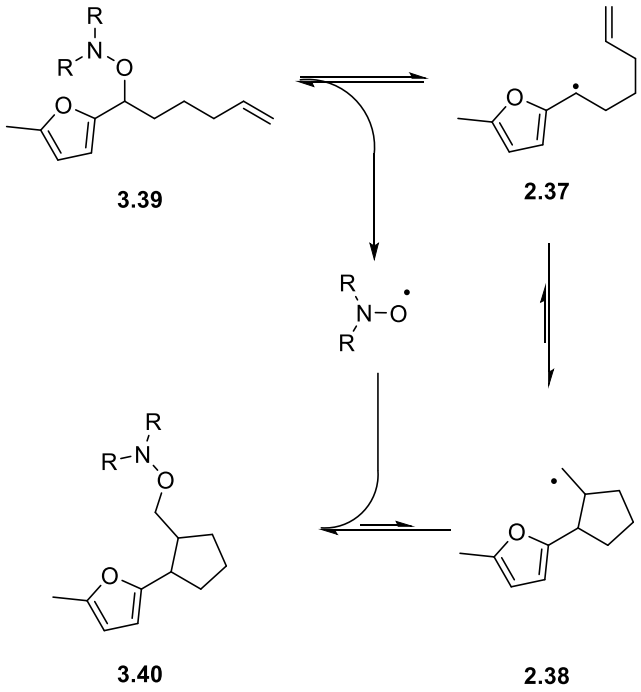
radical **2.38** with respect to **2.37** would prevent reversion. Alternatively, nitroxide-mediated polymerisation techniques, and cyclisations *via* a similar mechanism, (*300*,*301*) lend themselves to application to a furan-containing system; heating of alkoxyamino species **3.39** could effect cyclisation to **3.40 (**Scheme 3.13**)**.




**Scheme 3.12.** RAFT-inspired cycloisomerisation may be possible if cyclisation of radical **2.37** to **2.38** is viable.

Upon reaction of triethylborane with $O_2$, the ethyl radical is released. If site-selective abstraction of a furylic hydrogen atom from a substrate can be effected under

these conditions (possibly at low temperature) based on BDE, then cyclisation may then result.




**Scheme 3.13.** Potential nitroxide-mediated cyclisation of an α-(aminooxy)furan.

# 4 Development of Conditions for Oxidation of Furans to Enediones

*"It's not a bug, it's a feature!"*
Anonymous

## Existing Methods for Furan Oxidation

The unexpected partial oxidation of compound **2.7** to enedione **2.25a**, instead of SET and proton loss to afford a free radical intermediate (see page 63), prompted the investigation of these conditions as a general preparation of 2-ene-1,4-dicarbonyls. Electron-rich furan species are easily oxidised, and this chemistry has been long exploited, (*263*) including photooxygenations, (*302*) and including the conversion of furans to enediones.[xlvi] (*303*)

## Optimisation Studies

The oxidation of compound **2.7** to enedione **2.25a** upon irradiation with blue light in the presence of Ru complex **2.8** was suspected to be due to the presence of adventitious water and oxygen (see page 63); therefore, conditions for complete and deliberate oxidation were based upon irradiation of substrates with **2.8** in aqueous acetonitrile under an $O_2$ atmosphere. Conversion (estimated by $^1$H NMR analysis of the reaction mixture according to Equation 4.1; see Appendix 5: Explanation of Formulae for Conversion and Polymerisation of Furan in Oxidation Reactions for a derivation) of substrate **2.23** to the expected enedione (*Z*)-**4.1a**[xlvii] (Scheme 4.1) was apparent with as little as 0.1 mol.% of **2.8**. Consumption of the SM was complete in aqueous acetonitrile (Table 4.1, entry 1),

[xlvi] The Achmatowicz reaction converts furfuryl alcohols to 6-hydroxypyran-3-ones, which can be considered an intramolecular hemiacetal of an enedione.
[xlvii] The furan oxidation products are assigned as enediones, 2,5-dioxy-2,5-dihydrofurans, and products of 5-*exo*-*trig* cyclisation by the suffixes **a**,**b**, and **c** respectively.

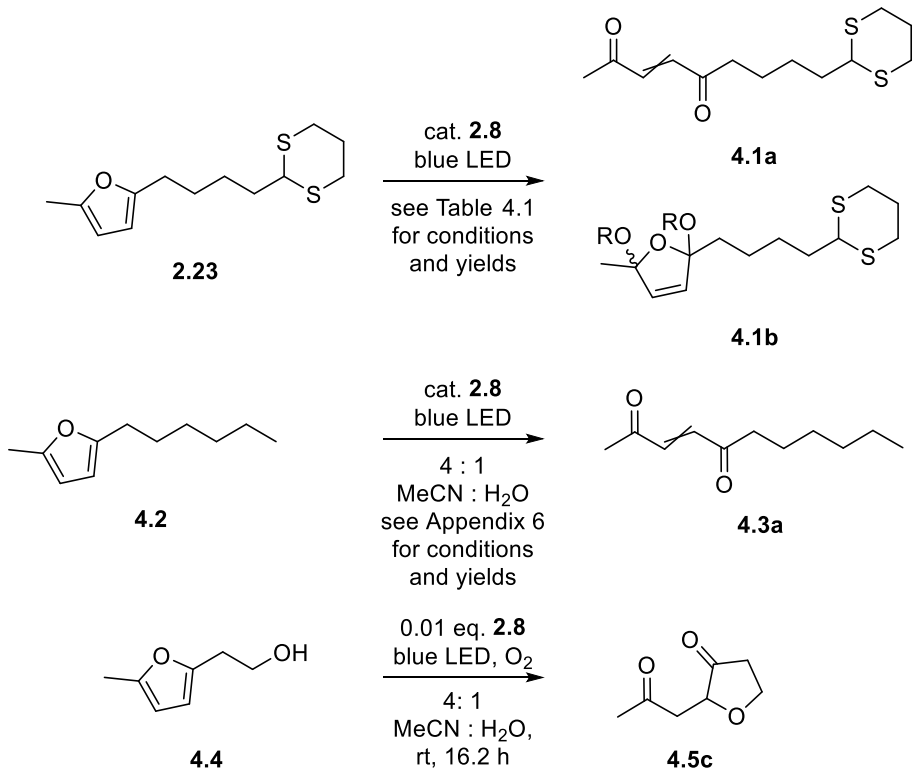
but only partial in dry acetonitrile (entry 2);[xlviii] slow isomerisation to the (*E*)-form was also observed. Irradiation with blue light was confirmed to be necessary for conversion in a control experiment (entry 3). Despite complete conversion of substrate with (*Z*)-**4.1a** as the major product, chromatographic isolation was not achieved except in one case (entry 4). A complex mixture of products – including (*E*)-**4.1a** and material to which we later tentatively assigned as structure **4.1b** – was apparent in the reaction mixture by NMR analysis. In order to confirm that (*Z*)-**4.1a** was indeed the major product of oxidation, the reaction was repeated in the presence of an internal NMR standard (entry 5); while (*Z*)-**4.1a** was not the only oxidation product formed, failure to isolate any of these products suggested that the purification protocol employed was at fault.

$$\text{Extent of conversion} \approx \frac{\sum \int_{products} y_t(\delta)\, \mathrm{d}\delta}{\sum \int_{\text{products}} y_t(\delta)\, \mathrm{d}\delta + 1.06 \int_{\text{SM}} y_t(\delta)\, \mathrm{d}\delta} \times 100\% \qquad 4.1$$

| Entry | Cat. Loading/eq.[a] | Solvent[b] | Rxn. time/h | Conversion (NMR, %)[c] | Product distribution (NMR)[d] | Yield (chromato-graphic, %) |
|---|---|---|---|---|---|---|
| 1 | 0.001 | A | 22.0 | 100 | (*Z*)- **4.1a** only | 0 (dec.) |
| 2 | 0.005 | B | 5.0 | 15 | (*Z*)- **4.1a** only | - |
| | | | 22.0 | 50 | 85 : 15 : 0 : 0 | - |
| 3 | 0.005 | A | 16.0 | 0[e] | - | - |
| 4 | 0.005 | C | 14.5 | 55 | 65 : 10 : 25 : 0 | - |
| | | | 33.3 | 80 | 20 : 55 : 25 : 0 | 5 [(*E*)-isomer] |
| 5 | 0.01 | D | 3.4 | 25[f] | 70 : 30 : 0 : 0 | - |
| | | | 5.7 | 70[f] | (*Z*)-**4.1a** only | - |
| | | | 20.0 | 75[f] | 40 : 20 : 20 : 20 | 0 (dec.) |

**Table 4.1.** Details of screening for oxidation conditions with dithiane **2.23** as substrate. [a] Specified with respect to SM. [b] A = 9 : 1 acetonitrile-$d_3$ : $D_2O$; B = acetonitrile-$d_3$ only; C = 9: 1 acetonitrile-$d_3$ : $H_2O$; D = 9 : 1 acetonitrile : $H_2O$; E = 4 : 1 acetonitrile : $H_2O$. [c] Calculated according to Equation 4.1 and rounded to nearest 5% (except entry 5, see note f). [d] Ratios are (*Z*)-**4.1a** : (*E*)-**4.1a** : **4.1b**: unknown. [e] Run in darkness. [f] NMR analysis based on 0.11 eq. dtbbp added as internal standard.

[xlviii] That conversion occurred at all under these conditions was unexpected; it could be explained by the inadvertent introduction of water to the reaction mixture, or by the generation of water from $O_2$ during a redox process.



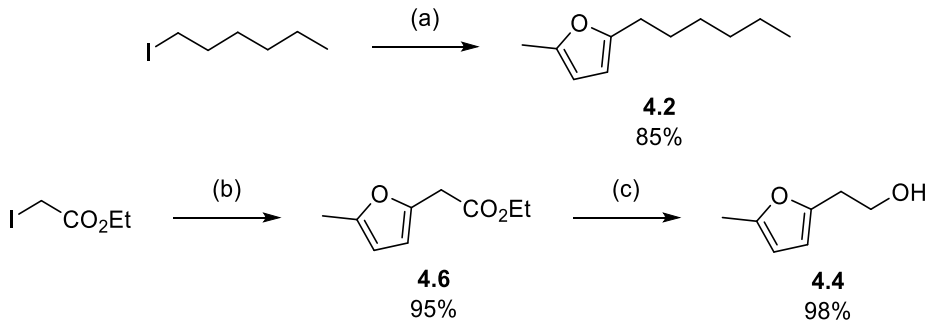

**Scheme 4.1.** Oxidation of furans in aqueous acetonitrile afforded impure products with poor mass recovery.

Traces of aldehyde products were observed in the reaction mixtures described above, which were presumed to have arisen from oxidative deprotection of the dithiane functionality. Use of a substrate with a side chain less prone to oxidation simplified matters; alkyl-functionalised furan **4.2** was synthesised by reaction of 2-lithio-5-methylfuran with *n*-hexyl iodide (Scheme 4.2). Oxidation to enedione (*Z*)-**4.3a** occurred as expected (Scheme 4.1), but the intensity of the signal corresponding to the olefinic protons[xlix] in NMR spectra of the material isolated was low in comparison to those of the other signals, which were broadened. $^{13}$C NMR analysis confirmed that this observation arose from decomposition of the product; $^{13}$C resonances were not broadened, but very

[xlix] While chemically inequivalent, the olefinic proton resonances appear as one singlet in $^{1}$H NMR spectra when the furan substituents are similar and the sample is dissolved in $CDCl_3$.

numerous. Varying the water content of the reaction solvent, the catalyst loading, and the concentration did not prevent this decomposition.

Substrate **4.4**, prepared by reduction of ester **4.6** [in turn prepared *via* Baciocchi reaction (*304*,*305*) (Scheme 4.2)], did not decompose in this manner upon similar treatment, but was converted into material to which the structure **4.5c** is assigned; this cyclisation, which has been reported previously with other substrates under acid catalysis, (*306*,*307*,*308*,*309*) indicated that conjugate addition of the hydroxyl group to the enedione inhibited the decomposition described above (with which the disappearance of olefinic NMR signals is associated).




**Scheme 4.2.** Syntheses of those substrates employed in optimising reaction conditions which are not described elsewhere. Reagents and conditions: (a) 1.2 eq. 2-lithio-5-methylfuran, THF, 0 °C – rt, 16 h. (b) 0.5 eq. $FeSO_4 \cdot 7H_2O$, 2.5 eq. $H_2O_2$, 14.8 eq. 2-methylfuran, DMSO, 0 °C – rt. (c) 1.09 eq. $LiAlH_4$, THF, 0 °C – rt, 90 min.

A screen of nucleophilic additives was carried out to investigate whether they might inhibit decomposition of other substrates, as the tethered nucleophile in substrate **4.4** did (Table 8.6, see Appendix 6: Details of Optimisation of Conditions for Furan Oxidation). Pyridine, in addition to suppressing decomposition, accelerated conversion to **4.3a** and afforded predominantly the (*E*)-enedione instead of the (*Z*)-isomer previously observed as the major product. Ammonium acetate and *t*-butanol engendered

decomposition, 2,2,2-trifluoroethanol had no apparent effect, and thiophenol inhibited the reaction, presumably by acting as a sacrificial oxygen scavenger until it was fully consumed, at which stage the substrate decomposed. Replacement of pyridine with $CaCO_3$ was detrimental to the reaction rate[1] and appeared to be less effective than pyridine at inhibiting decomposition; furthermore, its removal during workup caused more pronounced decomposition to occur during purification. Further experiments (Table 8.7, see Appendix 6: Details of Optimisation of Conditions for Furan Oxidation) showed that at least 2 equivalents of pyridine were needed, and that 2,6-di-*tert*-butylpyridine was less effective and did not effect isomerisation of the product from the (*Z*)-configuration.

A control experiment, in which substrate **4.2** was recovered intact after stirring with pyridine *N*-oxide, suggests that pyridine does not act as a co-oxidant in these reactions. Furthermore, the *pH* of the reaction mixture was monitored during the oxidation of **4.4** and found to decrease to *ca.* 3 with no pyridine, and to be buffered at *ca.* 6 with 1.2 eq. of pyridine. Finally, the failure of *t*-butanol and 2,2,2-trifluoroethanol to inhibit decomposition, where $CaCO_3$ did so to a limited extent, suggested that pyridine simply acts as a base in this reaction (see page 112, however, for discussion of other possibilities).

Despite the effects of including pyridine in the reaction mixture, the recovery of impure oxidation products **4.1a** and **4.3a** in poor yield upon extraction of these reaction mixtures from water, combined with apparently clean conversion as judged by NMR analysis, led to the suspicion that NMR analysis was not indicating accurately the product

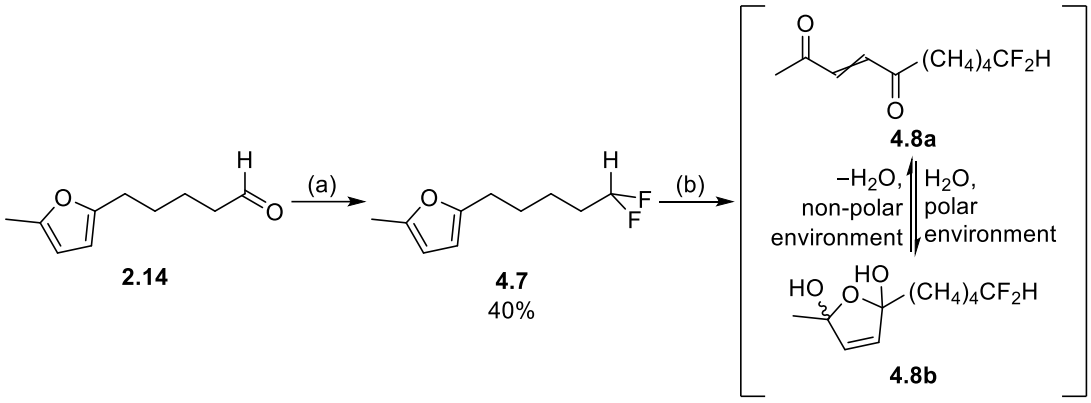
[1] This effect may have been due to the scattering of the incident light by the suspended $CaCO_3$ (present as a powder).

distribution in the reaction mixture. The very dilute and relatively anhydrous environment experienced by the oxidised product mixture *via* addition of a small portion of the reaction mixture to $CDCl_3$ was very different to that of the comparatively concentrated solutions, containing significant quantities of $H_2O$, present during extraction. F-labelled substrate **4.7** was synthesised by reaction of aldehyde **2.14** with DAST (Scheme 4.3), and on submission to established conditions, $^{19}F\{^1H\}$ NMR analysis of a concentrated sample of the reaction mixture in acetonitrile-$d_3$ betrayed the complexity of the product distribution; five distinct species could be observed in the partially converted reaction mixture [not inconsistent with the presence of SM, (*Z*)-isomer, (*E*)-isomer, *cis*-dioxydihydrofuran and *trans*-dioxydihydrofuran]. This prompted deeper thought on the trace impurities that appeared in NMR spectra of the crude reaction mixture, but that were not apparent in spectra of worked up material. While **a**, the major components of the product mixture in dilute NMR samples, were relatively non-polar, aqueous extraction would dramatically shift the position of equilibrium to favour formation of the water-soluble dioxydihydrofuran form **b**, which would then remain in the aqueous phase (Scheme 4.3). Increasing the ionic strength of the aqueous phases used during workup did not resolve this issue with other substrates. Extraction was therefore avoided altogether; the reaction mixture was adsorbed on to a silica plug, and the product eluted with a non-polar mixture of solvents. Concentration of the eluate afforded the product, predominantly in the **a** form. This workup protocol afforded fluorinated enedione **4.8a**[li] in modest yield (Table 4.2 entry 3, see page 105).[lii] Consequently, the following standard conditions were adopted:

[li] $^1H$ and $^{19}F$ (but not $^{13}C$) NMR spectra of this material indicate a 6 : 1 mixture of **4.8a** and another compound containing a $CH_2CF_2H$ moiety. A $^1H$ NMR triplet at $\delta = 3.65$ ppm leads us to tentatively assign this other compound as **4.8b**.

[lii] The substrate **4.7** was poorly soluble in the solvent mixture; if this property is also exhibited by the product **4.8**, then purification losses as a result of bonding to silica could reasonably be expected to be more severe than was the case for other substrates.

reaction by the bubbling of $O_2$ through a 4 : 1 acetonitrile : $H_2O$ solution of the substrate with 0.01 eq. of **2.8** and 2.2 eq. of pyridine, the mixture being irradiated with blue light during this time, followed by direct elution through a plug of silica. Treatment of substrates **2.23** and **4.2** in this manner afforded (*E*)-**4.1a** (entry 1) and **4.3a** (entry 2), respectively, in good yield.



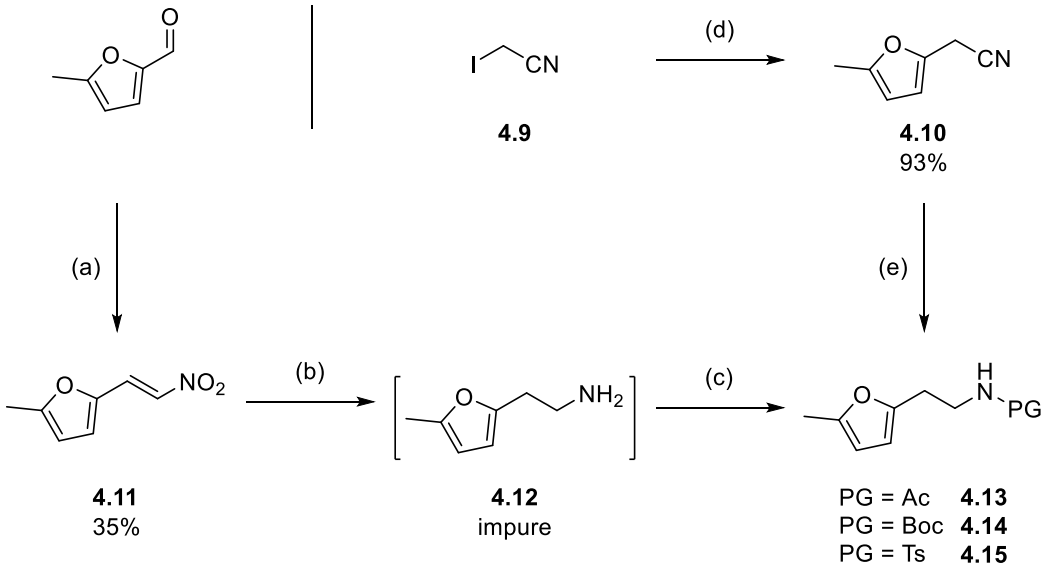

**Scheme 4.3.** Synthesis and oxidation of *gem*-difluoride **4.7**. Reagents and conditions: (a) 1.2 eq. DAST, DCM, –78 °C – rt, 1.8 h. (b) For reagents and conditions, see Scheme 4.6; for result, see Table 4.2 entry 3.

## Synthesis of Substrates

Protected aminoethyl furans **4.13** and **4.14** were obtained by Baciocchi (*304*) reaction of commercially obtained iodoacetonitrile **4.9** with 2-methylfuran to afford intermediate compound **4.10**, followed by reduction with $NaBH_4$ in the presence of $NiCl_2$, and acetic anhydride and di-*tert*-butyldicarbonate, respectively (Scheme 4.4). Tosylamide **4.15** was not obtained upon similar reduction in the presence of *p*-toluenesulfonyl chloride; it was necessary to prepare unprotected furfurylethylamine **4.12**, which was not isolated, by reduction with $LiAlH_4$ of Henry adduct **4.11**.

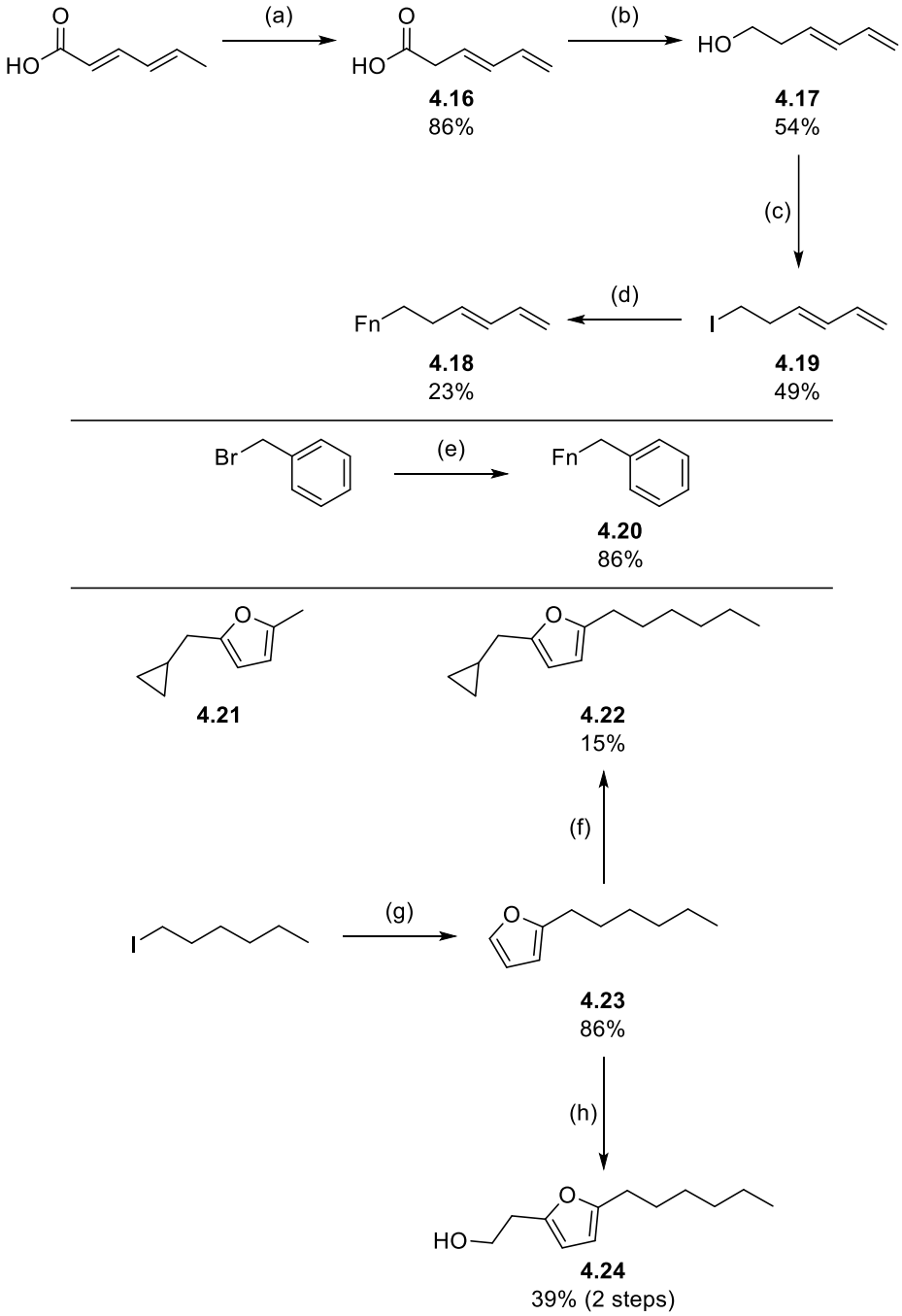
Additional substrates were synthesised (Scheme 4.5): diene **4.18** was prepared in order to determine the extent to which Diels–Alder reaction of the diene and singlet

oxygen[liii] competed with furan oxidation (which might itself proceed *via* a similar Diels–Alder mechanism, see page 110). Sorbic acid was deconjugated to isomer **4.16** by treatment with LDA, and reduction with $LiAlH_4$ afforded hexa-3,5-dien-1-ol, **4.17**. An Appel reaction then afforded iodoalkene **4.19**, which was reacted with 2-lithio-5-methylfuran to afford test substrate **4.18**. Benzyl-substituted substrate **4.20** was prepared by reaction of benzyl bromide with 2-lithio-5-methylfuran.




**Scheme 4.4.** Preparation of *N*-protected furfurylethylamines. Reagents and conditions: (a) 0.85 eq. $NH_4OAc$, nitromethane, reflux, 52 min. (b) 1.5 eq. $LiAlH_4$, ether, 0 °C – rt, 65 min. (c) PG = Ac, 1.7 eq. acetic anhydride, 2.0 eq. TEA, DCM, rt, 15.0 h, 65%; PG = Boc, 1.1 eq. di-*tert*-butyldicarbonate, 2.0 eq. NaOH, DCM, 0 °C – rt, 15.2 h 60%; PG = Ts, 3.0 eq. TEA, 1.1 eq. para-toluenesulfonyl chloride, 0.05 eq. DMAP, DCM, 0 °C – rt , 14.9 h, 62%. (d) 0.4 eq. $FeSO_4 \cdot 7H_2O$, 4 eq. aq. $H_2O_2$, 15.0 eq. 2-methylfuran, DMSO, rt, 17.8 h. (e) PG = Ac, 2.0 eq. acetic anhydride, 1.0 eq. $NiCl_2 \cdot 6H_2O$, 7.0 eq. $NaBH_4$, methanol, 0 ° – rt, 1.3 h, 37%; PG = Boc, 2.0 eq. di-*tert*-butyldicarbonate, 1.0 eq. $NiCl_2 \cdot 6H_2O$, 7.0 eq. $NaBH_4$, methanol, 0 ° – rt, 53%.

[liii] The latter could potentially arise *via* triplet annihilation of **2.8*** and dissolved $O_2$ in the ground state.




**Scheme 4.5.** Synthesis of miscellaneous oxidation substrates not previously described. Reagents and conditions: (a) 2.2 eq. LDA, THF, –10 °C, 54 min, then aq. HCl. (b) 0.8 eq. $LiAlH_4$, THF, reflux, 3 h, then aq. NaOH. (c) 1.2 eq. triphenylphosphine, 1.2 eq. $I_2$, 1.3 eq. imidazole, 3 : 2 DCM : ether, 0 °C, 35 min. (d) 2.0 eq. 2-lithio-5-methylfuran, –10 °C – rt, 15.5 h. (e) 1.2 eq. 2-lithio-5-methylfuran, THF. –10 °C – rt, 15.3 h. (f) 1.4 eq. butyllithium, THF, –78 – 0 °C, 3 h, then cyclopropylmethyl bromide, THF, 0 °C – rt, 17.0 h. (g) 1.2 eq. 2-lithiofuran, THF, 0 °C – rt, 19.0 h. (h) *i*: 3.0 eq. $FeSO_4 \cdot 7H_2O$, 2 eq. ethyl iodoacetate, 10 eq. aq. $H_2O_2$, DMSO, 0 °C, 2.5 h, 42%. *ii*: 0.75 eq. $LiAlH_4$, THF, reflux, 3.5 h, then aq. NaOH, 92%.

Isolation of 3-oxo-THF **4.5** (Scheme 4.1, see page 97) in significant yield was frustrated by its volatility and similar problems were encountered with cyclopropylmethyl furan **4.21**, originally intended as an alternative probe to formation of a furfuryl radical during the work discussed in Chapter 2; we therefore synthesised high-boiling derivatives **4.22** and **4.24** from 2-hexylfuran **4.23**, itself prepared by reaction of 1-iodohexane with 2-lithiofuran. Preparation of 2-hexyl-5-lithiofuran by reaction of **4.23** with butyllithium, and reaction with cyclopropylmethyl bromide furnished **4.22** in poor yield; the reaction was much more sluggish than other reactions of alkyl bromides with furyllithium species owing to steric hindrance, and only partial conversion was achieved before quenching. While cyclopropylmethyl bromide could be removed by evaporation, chromatographic separation of **4.22** and **4.23** was necessary and inefficient. Alcohol **4.24** was prepared *via* Baciocchi reaction of ethyl iodoacetate with 2-hexylfuran **4.23**, followed by reaction of the resulting ester (not shown) with $LiAlH_4$. While the reduction proceeded in excellent yield, recovery of the ester was more modest owing to incomplete conversion of **4.23**, and minor chromatographic losses.[liv]

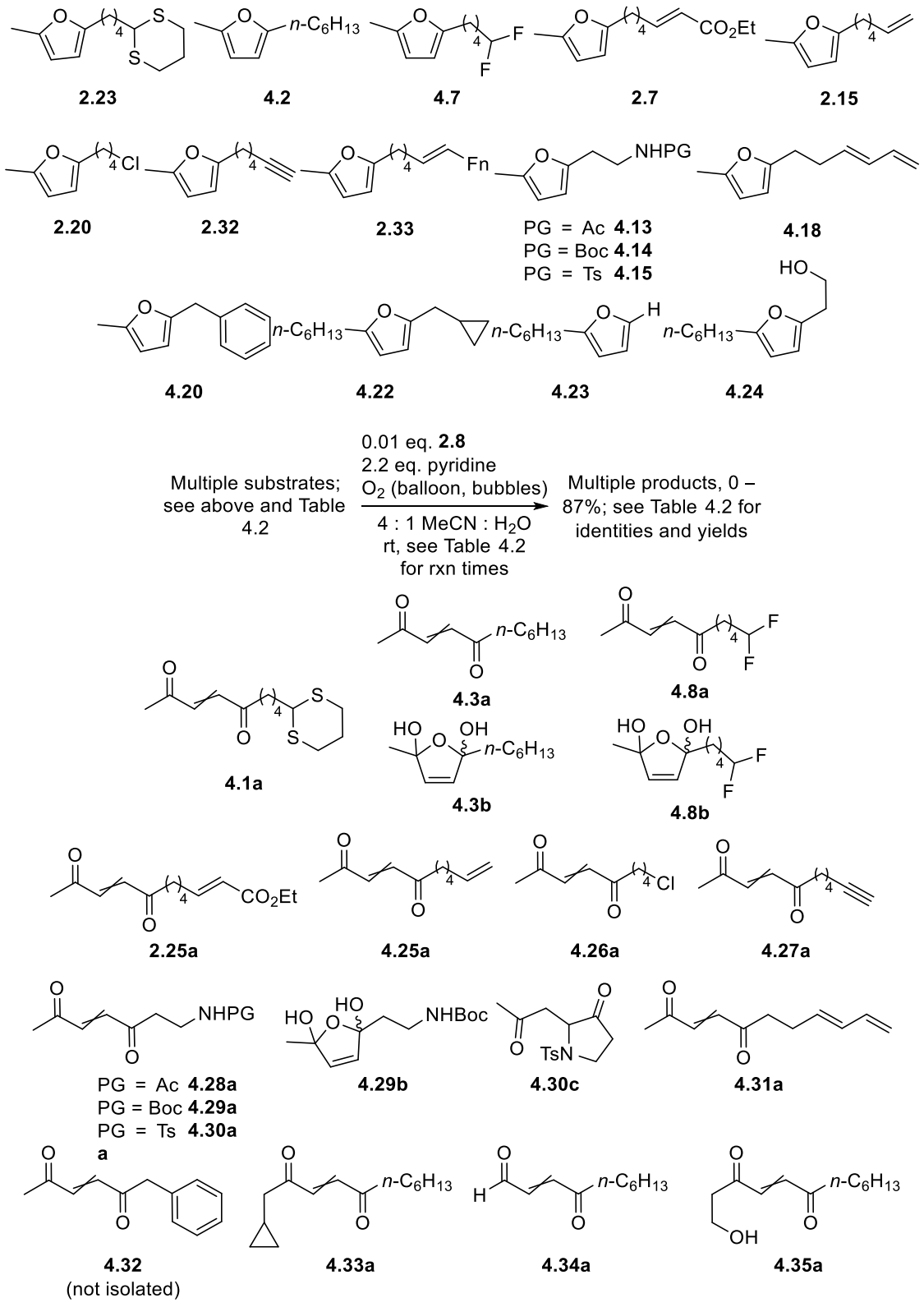
## Evaluation of Reaction Scope

These compounds, and others described elsewhere in this thesis, were also subjected to oxidation under standard conditions (Scheme 4.6 and Table 4.2). Isolated yields were between 50% and 60%, with some exceptions. Ester (*E*)-**2.25a** was isolated

[liv] This reaction proceeds much more efficiently with a large excess of the heterocycle, as demonstrated by the syntheses of compounds **4.6** (see page 98) and **4.10** (see page 101). Under identical conditions to those indicated in Scheme 4.5, a worker in the Robertson group obtained ethyl 2-[5-(4-hydroxybutyl)furan-2-yl] acetate in 70% yield. (*447*) Other workers describe similar yields to that obtained by us with a 2-fold excess of furan, and also describe removal of unreacted iodoacetate by reaction with zinc and acid hydrolysis of the resulting Reformatsky reagent. (*305*)

| Entry | SM | $R^1$ | $R^2$ | Time /h | Product(s) | Yield[a] | Identified Impurities[b] |
|---|---|---|---|---|---|---|---|
| 1 | **2.23** | Me | $(CH_2)_4$Dth | 1.9 | (*E*)-**4.1a** | 68 | Pyridine (9) |
| 2 | **4.2** | | *n*-$C_6H_{13}$ | 3.3 | 9 : 1 (*E*)-**4.3a** : **4.3b** | >99[c] | - |
| 3 | **4.7**[d] | | $(CH_2)_4CF_2H$ | 2.7 | 7 : 1 (*E*)-**4.8a** : **4.8b**[e] | 38 | Toluene (3) |
| 4 | **2.7** | | $(CH_2)_4$(*E*)-CH=CHCO$_2$Et | 3.0 | (*E*)-**2.25a** | 75 | Pyridine (8) |
| 5 | **2.15** | | $(CH_2)_4CH=CH_2$ | 3.0 | (*E*)-**4.25a** | 50[f] | (*Z*)-**4.25a** (2)[f] |
| 6 | **2.20** | | $(CH_2)_4Cl$ | 4.1 | (*E*)-**4.26a** | 41[g] | - |
| 7 | **2.32** | | $(CH_2)_4C\equiv CH$ | 1.5 | (*E*)-**4.27a** | 71[h] | Polymer (15) |
| 8 | **2.33** | | $(CH_2)_4CH=CHFn$ | 2.1 | - | 0[i] | - |
| 9 | **4.13** | | $(CH_2)_2NHAc$ | 7.0[i] | (*E*)-**4.28a** | 56[j] | - |
| | | | | | (*Z*)-**4.28a** | 72[j] | **4.13** (68) |
| 10 | **4.14** | | $(CH_2)_2NHBoc$ | 2.0 | 9 : 1 (*E*)-**4.29a** : **4.29b** | 88 | Pyridine (5), DCM (1), ethyl acetate (6) |
| 11 | **4.15** | | $(CH_2)_2NHTs$ | 2.2 | (*E*)-**4.30a**[k] | 42 | - |
| 12 | **4.15** | | $(CH_2)_2NHTs$ | 2.2 | **4.30c**[l] | 14 | - |
| 13 | **4.18**[m] | | $(CH_2)_2$(*E*)-CH=CH-CH=$CH_2$ | 2.2 | (*E*)-**4.31a** | 55 | DCM (52) |
| | | | | | **4.18** | 49[n] | |
| 14 | **4.20** | | Bn | 2.2 | **4.32** | 0[o] | - |
| 15 | **4.22** | *n*-$C_6H_{13}$ | $CH_2$*c*-Pr | 1.5 | (*E*)-**4.33a** | 12 | - |
| | | | | | (*Z*)-**4.33a** | 39 | |
| | | | | | **4.40** | 4 | |
| 16 | **4.23** | | H | 4.1 | (*E*)-**4.34a** | 29 | - |
| | | | | | **4.23** | 7 | - |
| 17 | **4.24** | | $(CH_2)_2OH$ | 3.7 | (*E*)-**4.35a** | 84 | Pyridine (13), DCM (6) |
| 18 | | | | 22.0 | | 43[p] | - |

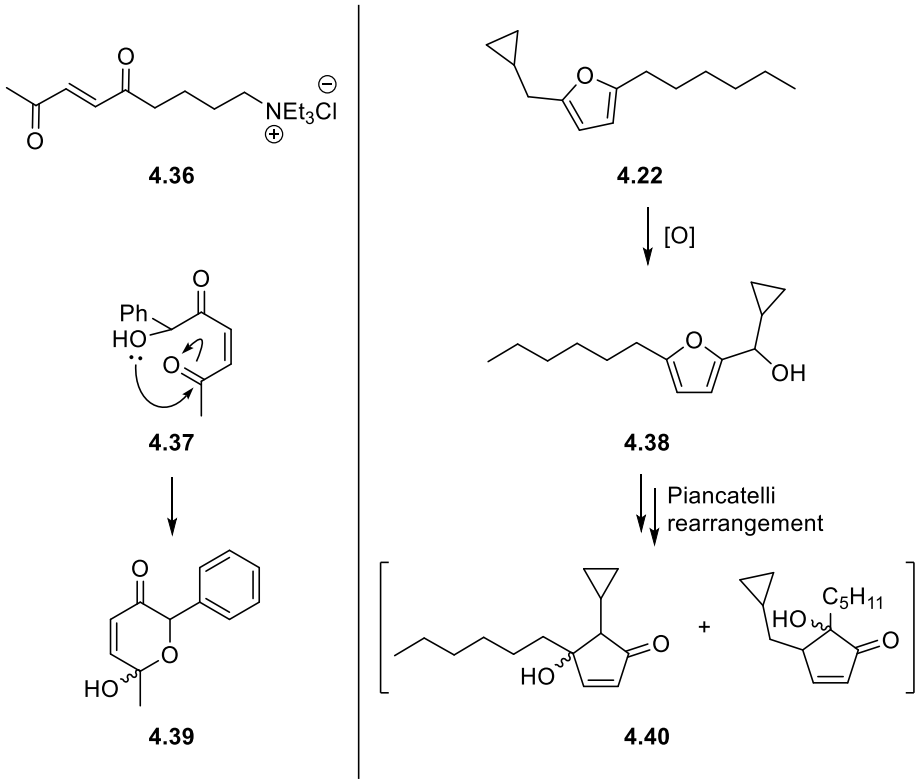
**Table 4.2.** Demonstration of substrate scope for oxidation reaction under standard conditions, see Scheme 4.6. [a] Percent, calculated from isolated mass; identified impurities are included in these values. [b] Numbers in parentheses are % (w/w) of isolated material. [c] Partially polymerised; isolated 37% (*E*)-**4.3** after further chromatography. [d] 0.2 eq. fluorobenzene added as internal standard. [e] See footnote li, page 100. [f] Isolated 42% (*E*)-isomer and 9% of a mixture with *d.r.* 3 : 1 (*E*) : (*Z*). [g] Isolated (*E*)-**4.26** (60%, containing 20% w/w pyridine and 9% w/w **4.36**; these were removed by further chromatography). [h] Obtained as pure material (41%) and an additional partially polymerised fraction (15%, containing *ca.* 15% polymerised material). [i] Decomposed to complex mixture. [j] Average of 2 runs, one with pyridine omitted. [k] W/u consisted of dilution with 10 volumes of acetonitrile, drying over $Na_2SO_4$ and activated carbon, then filtration and concentration. [l] Estimated product distribution in reaction mixture after 1.8 h was 2 : 1 : 1 (*E*)- **4.30a** : (*Z*)-**4.30a** : **4.30c**. [m] Reaction carried out in 11 : 5 : 4 acetonitrile : benzene-$d_6$ : $H_2O$. [n] Preparative TLC was necessary to achieve separation from product. [o] Product observed in reaction mixture (NMR), but not isolated. [p] Pyridine omitted, product not pure.




**Scheme 4.6.** Standard conditions developed for the oxidation of **4.2** to **4.3** were applied to other substrates (see also Table 4.2); expected products are also shown (for side products, see **Scheme 4.7**).

in 67% yield; the relatively high levels of pyridine contamination present in the product may have prevented more effectively the decomposition and resulting loss of material on silica that was experienced by other substrates. While oxidation of chloride **2.20** proceeded with moderate associated mass recovery, the product was contaminated with pyridine to a significant level, and signals suggestive of by-product **4.36** (Scheme 4.7), visible in the $^{1}$H NMR spectrum of the isolated material, indicate reaction with TEA, present in the eluant during purification; repurification, with associated losses, afforded product (*E*)-**4.26a** in 42% yield. Difuryl substrate **2.33** was submitted to the oxidation conditions to investigate whether the vinylenefuran moiety was oxidised in preference to its non-vinylene-substituted counterpart, and, if so, the manner in which oxidation occurred. A complex mixture of products was obtained, and chromatographic repurification did not clarify the mixture. Oxidation of Boc-protected furfurylethylamine **4.14** furnished (*E*)-**4.29a** in unexpectedly high yield; this was also the case for the reaction of hydroxyethyl substrate **4.24** to (*E*)-**4.35a**, but not that of amides **4.13** and **4.15**. It is possible that reversible conjugate addition of the heteroatom into the enedione moiety inhibited decomposition by polymerisation, or permanent adsorption to silica during purification in the case of products **4.29a** and (*E*)-**4.35a**, whereas the nitrogen lone pairs of **4.13** and **4.15** were insufficiently available to do so. Tosyl-protected analogue **4.15** appeared by NMR analysis of the crude reaction mixture (chloroform-*d* solvent) primarily to oxidise to (*E*)-**4.30a**, with traces of both the (*Z*)-isomer and cyclised form **4.30c**, but chromatography afforded only **4.30c** in 14% yield. When the reaction was repeated, NMR analysis (acetonitrile-$d_3$ solvent) of the reaction mixture indicated conversion only to (*E*)-**4.30a**, and when the product was isolated without recourse to chromatography, (*E*)-**4.30a** was isolated in 42% yield. This material was subsequently

purified by column chromatography without incident. The reaction mixture in which partial cyclisation was observed may have been contaminated with acid, leading to cyclisation and decomposition during purification. Diene **4.18** was partially oxidised under standard conditions, in order to determine the selectivity of the conditions for oxidation of furan. Selective oxidation of the furan moiety, producing (*E*)-**4.31a**, was apparent by NMR analysis of a worked up aliquot of the reaction mixture, and competing oxidation of the diene functionality was not detected. Partial separation of product from starting material was achieved by column chromatography, but broadened product signals and the indication of heavy triethylammonium contamination in the $^{1}$H NMR spectrum of the product-containing fractions necessitated further purification *via* preparative TLC, which furnished a trace of product (*E*)-**4.31a** (3%) and 49% SM. It is possible that the minimal yield of this reaction was due to competing oxidation of the diene moiety, the products of which were not detected; the endoperoxide obtained by submission of cyclohexa-1,3-diene to the reaction conditions decomposed upon exposure to silica, and the purified product was not obtained (see page 111).




**Scheme 4.7.** Side products formed during oxidation reactions.

Oxidation of benzylfuran **4.20** appeared, by NMR analysis of the reaction mixture, to proceed cleanly (NMR), but the expected product **4.32** was not recovered. The 5-*enol* tautomer of **4.32**, stabilised by the phenyl group, may have acted as a nucleophilic initiator of polymerisation; in one run, traces of impure material tentatively assigned structure **4.39** (the double bond of which is not susceptible to polymerisation *via* a polar mechanism) were obtained after chromatography. We suspect that benzylic hydroxylation (either before or after oxidation of the furan to an enedione) afforded intermediate compound **4.37**, which cyclised to afford the hydroxypyrone product. Oxidation of cyclopropylmethylfuran **4.22** afforded **4.33a** as a separable mixture of isomers in 51% overall yield, and traces of material believed to be an inseparable diastereomeric and regioisomeric mixture of cyclopentenones **4.40** (4%) were also obtained, which could be explained by hydroxylation α to the cyclopropyl group, followed by Piancatelli

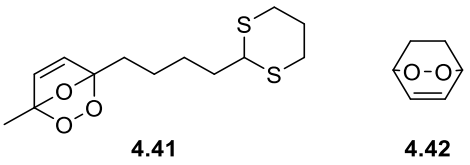
rearrangement. Monosubstituted furan **4.23** was subjected to oxidation conditions to determine the feasibility of obtaining 4-oxo-2-enals under these conditions. The reaction appeared to be more sluggish than that of 2,5-disubstituted furans, as might be expected on FMO grounds; reaction was incomplete after 4 hours. This – combined with the increased reactivity of the product with respect to the analogous diketones – accounts for the decreased yield. When alcohol **4.24** was oxidised under air, instead of pure $O_2$, the yield of (*E*)-**4.35a** was decreased, which is attributed to the extended reaction time necessary for complete conversion, allowing polymerisation to compete. In contrast to homologue **4.4**, the cyclised form was not obtained, even when pyridine was omitted from the reaction.

## Mechanism of Oxidation and the Role of Pyridine

Reactions of furans with $O_2$ are generally accepted to proceed *via* Diels–Alder reaction, the $O_2$ being converted to the singlet state *via* irradiation in the presence of a dye acting as a triplet sensitiser; (*310*) Such a reaction is denoted hereafter by SODA (**s**inglet **o**xygen **D**iels–**A**lder) within this thesis. The ability of transition metal complexes to act as triplet sensitisers (in addition to, or instead of, promoting photoinduced electron transfer) is well established, (*311*,*312*,*313*,*314*) and **2.8** specifically has been found to exhibit such behaviour. (*315*) On the other hand, the sequential two-electron oxidation of furans *via* sequential SET processes has also been reported both photocatalytically with $Na_2S_2O_8$ acting as a terminal oxidant (*316*) and with DDQ. (*281*,*317*)

Some experiments useful to the investigation of the mechanism operative under our conditions have already been described. A SODA mechanism is inconsistent with our observation that oxidation of **2.23** was suppressed in dry acetonitrile; the endoperoxide

**4.41** (Chart 4.1), that would have built up in the case of an operative SODA reaction was not detected.[lv] Oxidation of the diene moiety present in **4.18** was also not observed upon submission to the reaction conditions. Experiments to rule out a SODA mechanism conclusively, however, introduced ambiguity. Irradiation of compound **2.23** at 560 nm instead of 480 nm, and with 0.0083 eq. Rose Bengal in place of compound **2.8**, but under otherwise standard conditions, led to oxidation to **4.1** and partial decomposition of the dithiane moiety. This result demonstrates that the reaction conditions in terms of solvent, concentration, temperature, etc do not preclude a SODA mechanism. 1,3-Cyclohexadiene was found to be converted to 2,3-dioxabicyclo[2.2.2]octane **4.42** under the standard conditions by comparison of $^1$H NMR signals, although isolation was prevented by decomposition during purification. This result was taken as evidence that the SODA mechanism is operative, at least with 1,3-cyclohexadiene as a substrate.




**4.41** **4.42**

**Chart 4.1.** The endoperoxide that would have formed in the case of a Diels–Alder reaction with singlet $O_2$, which was not observed upon reaction in dry acetonitrile. Reaction of 1,3-cyclohexadiene afforded endoperoxide **4.42** (not isolated).

Attempts to show at least the possibility of an electron-transfer mechanism, by replacing $O_2$ with alternative terminal oxidants, required a reagent which would not

[lv] Concern that the material assigned here as the **b**-forms might actually be endoperoxides was assuaged by comparison of $^1$H chemical shifts; olefinic dioxydihydrofuran protons resonate at 5.9 – 6.0 ppm, whereas the corresponding protons in the endoperoxides obtained by photooxygenation of 2,5-dimethylfuran and 2,5-diphenylfuran resonate at 6.20 and 6.81 ppm, respectively. (*448*)

oxidise furans in the absence of a photocatalyst; ammonium persulfate was chosen for the oxidation of **4.2**, and only limited conversion to (*E*)-**4.3a** was observed (Table 4.3).

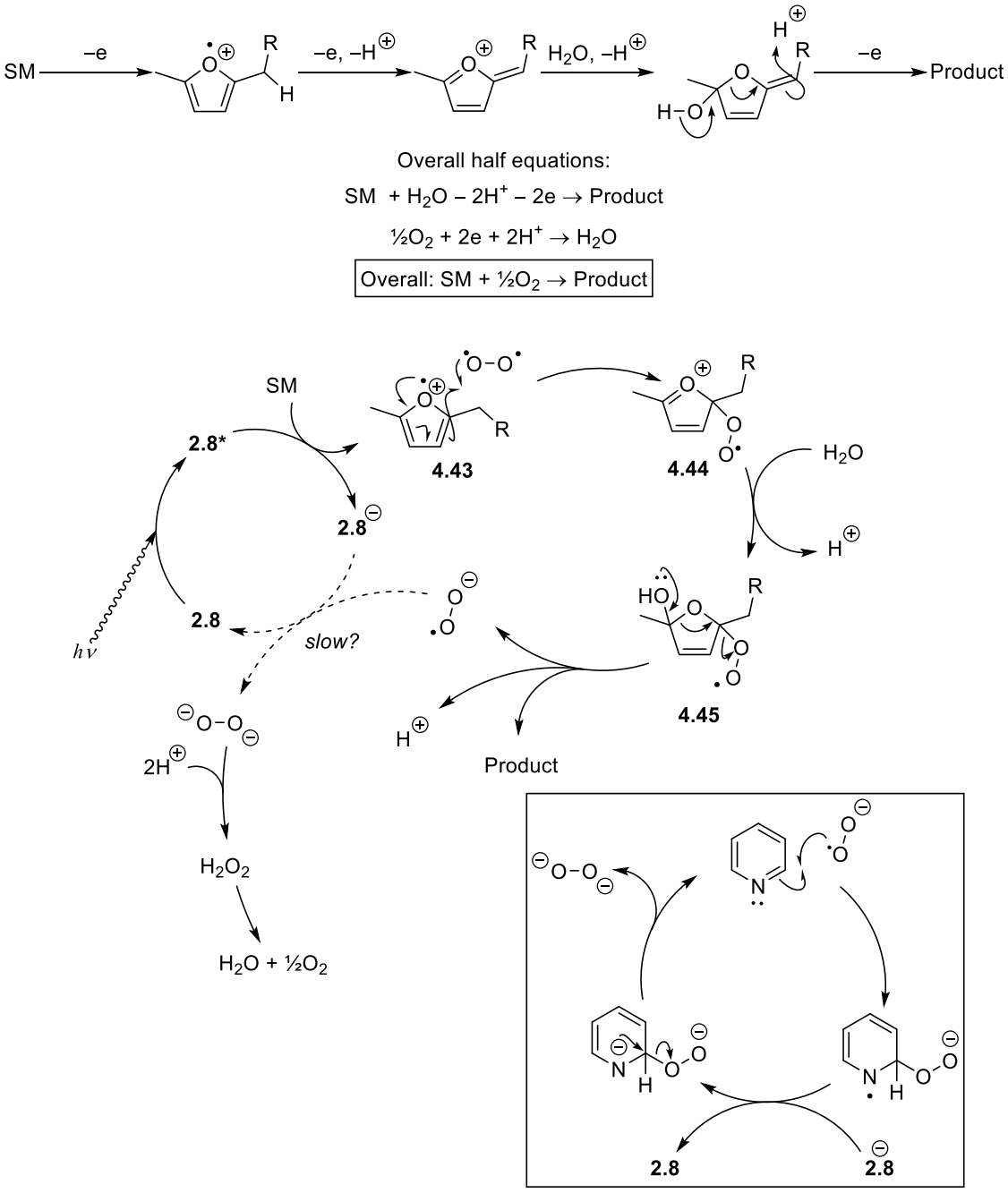
| Entry | Pyridine loading/eq.[a] | $(NH_4)_2S_2O_8$ loading/eq.[a] | Rxn time/h | Yield of **4.3** (%)[b] |
|---|---|---|---|---|
| 1 | 2 | 1 | 2.3 | 20[c] |
| 2 | 5 | 1 | 5.3 | 10 |
| | | | 7.9 | 40[d] |
| 3 | 10 | 4 | 2.1[e] | 10 |

**Table 4.3.** Conditions and results for the oxidation of **4.2** with $(NH_4)_2S_2O_8$, and under $N_2$, but otherwise under standard conditions. [a] Specified with respect to SM. [b] Rounded to nearest 10%. [c] Based on ratio of SM : product isolated. [d] Based on material present at w/u, according to Equation 4.1. [e] Reaction mixture was purged with $N_2$ throughout.

Slow partial oxidation was evident in all cases (supporting a photoredox mechanism), with not insignificant conversion in one case (entry 2), but hydrolysis of the terminal oxidant to $H_2O_2$, conversion in turn to $O_2$, and oxidation *via* the SODA mechanism is possible. The reaction was repeated, therefore, with a continual purge of the reaction mixture with $N_2$ to remove $O_2$ as and when it was formed (entry 3), and partial conversion was still observed. These results are inconsistent with the hypothesis of a SODA-mediated oxidation, although the drastically reduced rate of this reaction with respect to those employing $O_2$ as a terminal oxidant suggests that the latter may, indeed, proceed *via* a SODA mechanism. Other work (*316*) suggests that addition of DMSO to the solvent mixture and replacement of the $(NH_4)_2S_2O_8$ with a different persulfate may have led to better conversion and, in turn, a more conclusive indication that the oxidation can proceed with terminal oxidants other than $O_2$.

The finding that reaction mixtures became acidic with progression of the oxidation is inconsistent with the SODA pathway. Photoredox mechanisms also appear to be *pH*-neutral (Scheme 4.8) but if one is operative, then it would seem likely that the

radical cation **4.43** couples with triplet $O_2$ to afford **4.44**, in preference to other reactivity based on the persistent radical effect. Addition of water and fragmentation affords the product, *via* intermediate **4.45**, with concomitant release of two protons. If the reoxidation of the catalyst by the superoxide ion, released during fragmentation of **4.45**, is disfavoured on kinetic grounds, then further reaction will be inhibited, and only one of the protons released during formation of the product will be neutralised, causing decomposition of the substrate as it forms. Pyridine may accelerate this step and thereby prevent decomposition of the product, either by facilitating proton transfer to convert superoxide into the hydroperoxide radical which is then able to regenerate the catalyst, by acting as a coreductant (as shown, perhaps, in Scheme 4.8, for example), or simply acting as a cosolvent to render the reoxidation of the catalyst by superoxide possible.The need for at least 2 eq. of pyridine lends support to the last of these possible explanations; it may be that a minimum proportion of the solvent mixture must be pyridine to facilitate clean reaction, rather than it being necessary to have a given molar excess of pyridine present with respect to the substrate.




**Scheme 4.8.** Demonstration of the overall *pH*-neutrality of the furan oxidation reaction. A possible RSI-type mechanism for the reaction is shown, in addition to a proposal for the mechanism by which pyridine aids regeneration of **2.8** and prevents buildup of protons.

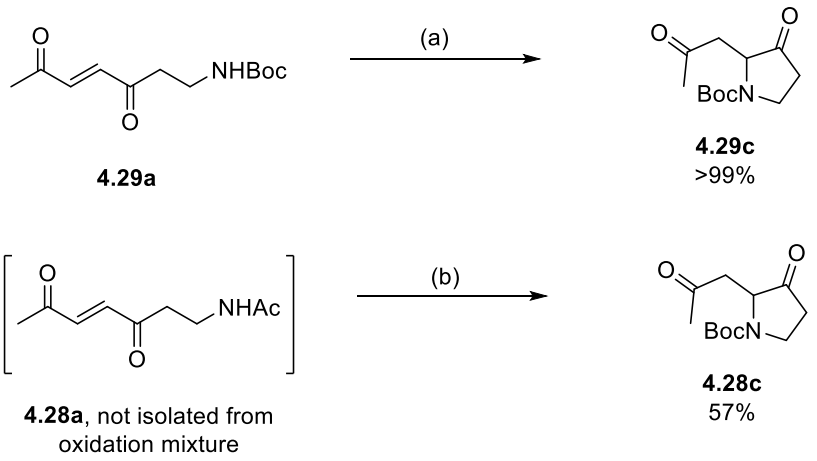
## Cyclisation *in situ* via Conjugate Addition of Tethered Nucleophiles

The conversion of **4.4** to **4.5c**, and the partial cyclisation of **4.30a** to **4.30c** in the reaction mixture, prompted further investigation. In contrast to ubiquitous γ-lactones and 2-pyrrolidones, the 3-oxo regioisomers are less available, and routes that do not comprise a furan oxidation are usually expensive or lengthy. (*318*,*319*,*320*,*321*,*322*,*323*,*324*,*325*,*326*,*327*) Conjugate addition of a tethered nucleophile to an enedione upon activation by acid, however, has been reported (*306*,*307*,*309*,*328*,*329*,*330*) and applied to the total synthesis of multiple natural products: plakoridines A and B, (*331*) longianone, (*332*) norcembrenolides B and C, (*333*) merrekentrone C, (*334*) the ABC-fragment of the pectenotoxins, (*308*,*335*) pandamarine, (*336*) alkaloids 167B and 209D, (*337*) pandalizines A and B, (*337*) and heliotridane. (*337*)

Attempts to promote cyclisation *via* conjugate addition by means other than treatment with acid were not successful. The possibility that cyclisation of **4.30a** to **4.30c** occurred by the action of base, silica, or both was investigated and discounted by treatment of analogous Boc-protected enedione **4.29a** with NaHMDS and KOH, and stirring with 1.2 wt. eq. of silica in 99 : 1 chloroform-*d* : TEA. Cyclisation was not observed in either case. Addition of 2.2 eq. of acetic acid (forming 2.2 eq. of pyridinium acetate from the pyridine added before starting the oxidation) to the reaction mixture after formation of **4.29a** similarly did not engender cyclisation, nor did addition of a further 2.5 eq. of acetic acid. Stirring **4.29a** with 0.25 eq. of *para*-toluenesulfonic acid in DCM-$d_2$, for 5.2 h, however, afforded material tentatively assigned structure **4.29c**[lvi] in

[lvi] The $^{13}$C NMR spectrum of this material was complex and appeared to contain traces of the open form (reflected in the $^{1}$H NMR spectrum of the same sample, but not those of more dilute samples); characterisation is otherwise complete (see page 228).

quantitative yield (Scheme)[lvii]. Oxidation of furan **4.14** under air and in the absence of pyridine, but otherwise under standard conditions, did not give rise to any conversion of the SM.




**Scheme 4.9.** Treatment of N-bearing enediones with *para*-toluenesulfonic acid afforded 3-pyrrolinones. Reagents and conditions: (a) 0.25 eq. *para*-toluenesulfonic acid, DCM-$d_2$, 5.2 h, rt. (b) 0.05 eq. *para*-toluenesulfonic acid

When the oxidation of **4.15** was repeated with no pyridine in the reaction mixture, the open form of the product **4.30a** was obtained. Addition of 0.4 eq. of *para*-toluenesulfonic acid to the mixture without intermediate isolation and stirring for 7.6 h caused cyclisation, affording impure **4.30c** with 77% mass recovery (not shown, see Scheme 4.6, page 106 for structures of **4.15**, **4.30a**, and **4.30c**). Addition of 0.1 eq. of *para*-toluenesulfonic acid to the reaction mixture after oxidation of **4.13** to open form **4.28a**, and stirring for an additional 90 h, afforded **4.28c** in 22% yield. After oxidation of the substrate in the absence of pyridine, but otherwise under standard conditions, addition of 0.05 eq. of acid and stirring for 3.5 h afforded **4.28c** in 57% yield.

[lvii] Stirring with 0.4 eq. of acid for 3 days effected decomposition, although traces of product **4.29c** were isolated from the mixture.

## Conclusions

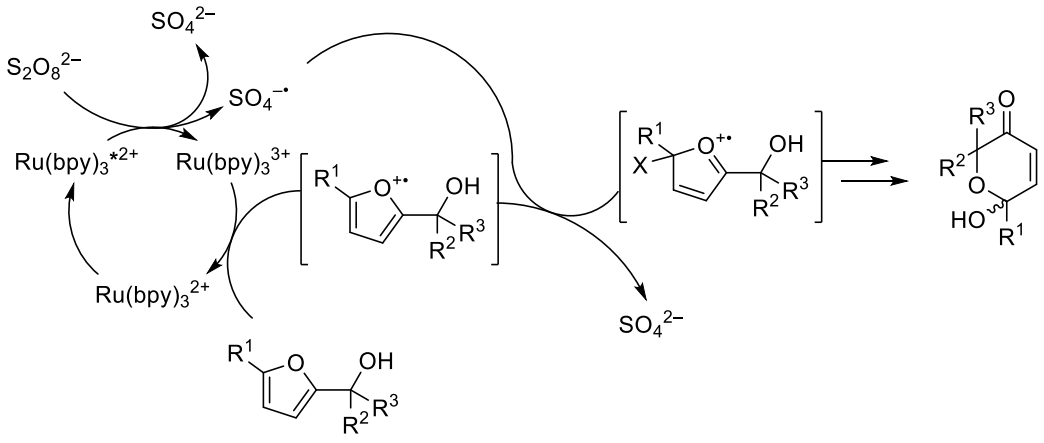
A method for the oxidation of furans to 2-ene-1,4-dicarbonyls has been developed, consisting of stirring a solution of the SM with 0.01 eq. of **2.8** and 2.2 eq. of pyridine in aqueous acetonitrile, under $O_2$ and with blue light illumination. This method complements existing methods for the oxidation of furans to these products and avoids the need for use of chemical oxidants not present in the Earth's atmosphere, or lengthy purification steps to remove the associated by-products. Existing singlet-$O_2$-based protocols typically rely on organic sensitisers that require lengthy chromatographic processes to remove, (*338*,*339*,*340*) whereas elution of the reaction mixture through a short silica plug is completely effective in removing compound **2.8** from the reaction mixture. Furthermore, photosensitised oxygenations often employ the use of a stoichiometric reductant such as triphenylphosphine (*341*,*342*) or dimethyl sulfide (*338*,*337*) to destroy peroxo species prior to concentration. This appears to be unnecessary with the protocol described here; organic peroxo species were not observed in the reaction mixture or the worked up products. We are not the first to develop a furan oxidation process where this is the case. Endoperoxide species obtained by the Rose Bengal-mediated photooxygenation of furans in $H_2O$ (*309*) decomposed *via* solvolysis, and a protocol for a photoredox-mediated Achmatowicz reaction (*316*) employed $Na_2S_2O_8$ as a terminal oxidant and a 2 : 1 : 1 $H_2O$ : acetonitrile : DMSO mixture as a solvent. The mechanism invoked by the authors (Scheme 4.10) to explain enedione formation does not involve production of peroxides;[lviii] in any case, if any had formed, they would have decomposed under the reaction conditions, and the resulting $H_2O_2$ would

[lviii] Upon carrying out the reaction without degassing the solvent, a hydroxybutenolide was obtained as a minor side product, which the authors attribute to formation of the endoperoxide *via* Diels–Alder reaction with $O_2$, sensitised by the photocatalyst.

have been removed during aqueous workup. The conditions developed here, however, enable more lipophilic furans [lix] to be oxidised, without the need to destroy hydroperoxides.

## Further Work

The cyclisation of tethered nucleophiles into the enedione functionality in acidic solution was not reliable; yields were lower than those associated with previously reported procedures, and some substrates that were expected to cyclise did not. The aqueous solvent mixture used for oxidation may be incompatible with efficient cyclisation [after oxidation in $H_2O$, cyclisation of substrates by the action of *para*-toluenesulfonic acid or acetic anhydride and pyridine, or on silica, **after** extraction into ethyl acetate is described in the literature (*309*)]; further investigation (not limited to acidification of the oxidation reaction mixture) of the circumstances under which cyclisation of enediones occurs would be beneficial.



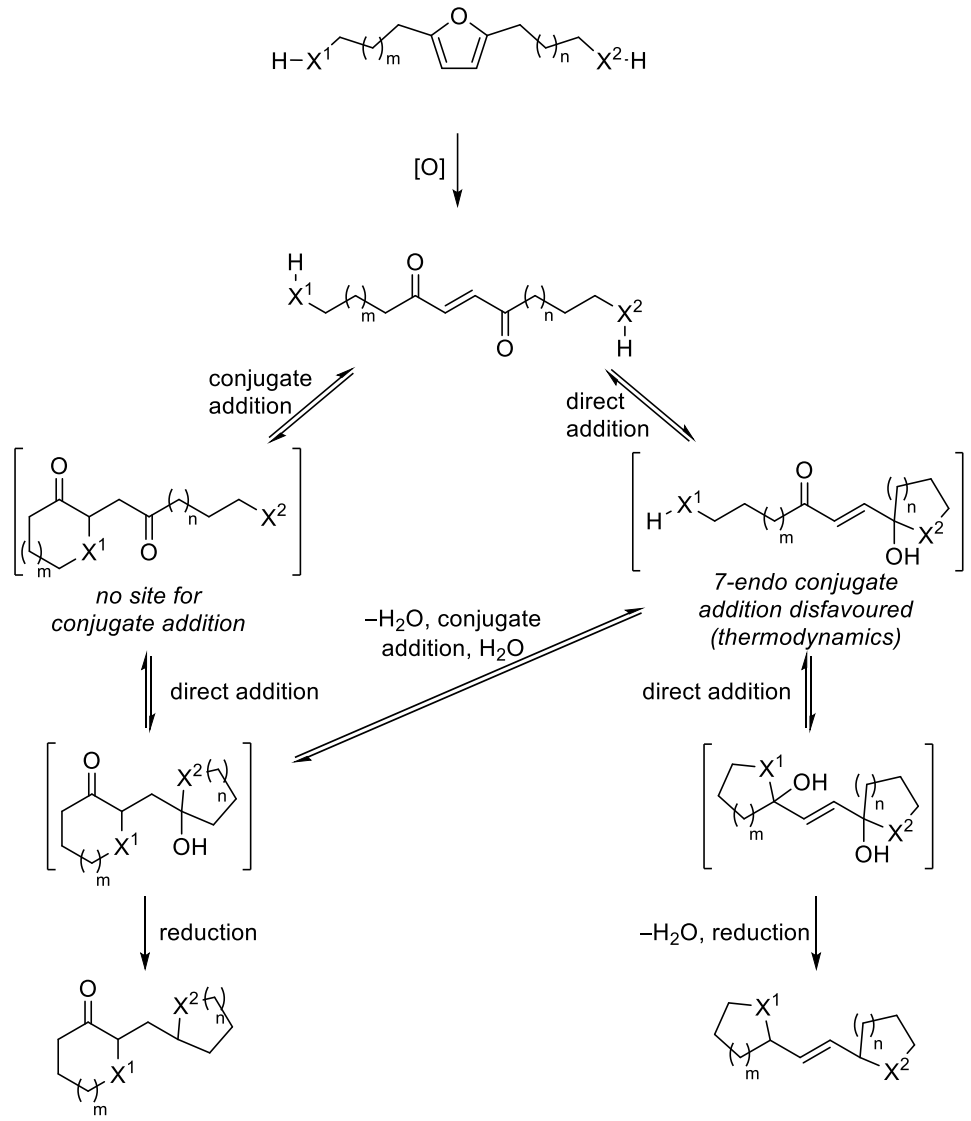

**Scheme 4.10.** Proposed catalytic cycle for photoredox-mediated Achmatowicz reaction. (*316*)

[lix] The substrate scope of the photoredox catalysed Achmatowicz reactions was obviously restricted to furfuryl alcohols; it would be instructive to screen simpler furans under the same conditions.

If a furan with multiple tethered nucleophiles were to be oxidised, competition as to which nucleophile adds to the available electrophilic sites could arise (Scheme 4.11). Assuming equilibration during the cyclisations to a thermodynamic mixture can be averted (perhaps by reducing hemiacetal species as they are formed with, *e.g.* $NaBH_3CN$ and a Lewis acid catalyst), subjecting several enediones with two tethered nucleophiles would allow the establishment of a reactivity series describing the relative propensity of tethers to add in a conjugate manner. The lengths of the tethers may also determine whether direct addition of one chain into a carbonyl group inhibits conjugate addition of the other. This would allow for selective formation of saturated heterocycles linked *via* a carbon chain. Only 2,5-disubstituted SMs are shown, but 3- and 4-substitution would allow for more possibilities.

While pyridine suppressed decomposition of the product by polymerisation, typical yields under the standard conditions were still only moderate. Use of $H_2O_2$ as the oxidant, (*343*) instead of relying on $O_2$ bubbled through the mixture, may speed up the oxidation reaction, further limiting the opportunity for the product to decompose (long reaction times appear to be associated with polymerisation). If the base to suppress polymerisation, and the catalyst decomposing $H_2O_2$, were to be immobilised on a support, purification would be simpler and less prone to eroding the yield of product; *e.g.* the supported catalyst and base might be removed by filtration, the residual oxygen by sparging with nitrogen, and water by azeotropic drying. The mechanism by which pyridine inhibits decomposition has not been conclusively established, however, and immobilisation may not be an option. Concentration of further work on elucidating the mode by which pyridine acts, perhaps by use of analogous bases, electron shuttles, and

polar cosolvents, would be beneficial, and may shed light on the mechanism *via* which the entire transformation proceeds.




**Scheme 4.11.** Competitive conjugate addition of tethered nucleophiles to a furan-derived enedione may allow for selective formation of heterocycles linked by a carbon chain. $X^1$ refers to the group more prone to conjugate addition, and $X^2$ to the group less prone.

The maximum scale on which these conditions oxidise furans effectively was not investigated; polymerisation is likely to become more of a problem on large scale if the reaction is undertaken at a higher concentration, and unless $O_2$ is introduced to the reaction mixture at a proportionally higher rate, full conversion will require longer

reaction times, at the risk of loss of product to polymerisation. Furthermore, oxidations using $O_2$ are notorious for their safety issues during scaleup owing to the flammability of substrates and solvent. (*344*) For all of these reasons, development of a flow technique for rapid oxidation, again possibly immobilising upon a support a catalyst generating singlet oxygen from $H_2O_2$, would be beneficial. Suppression of polymerisation would necessitate continuous purification, or "protection" of the vulnerable functionality, as is the case in the **b** form of the product. The circumstances under which the **b** form dominates, would also benefit, therefore, from further investigation.

# 5 A Short Total Synthesis

*"If it ain't broke, don't fix it."*
Thomas Bertram Lance, Director of the U.S. Office of Management and Budget 1977

## Bacterial Pyrrolizidine Alkaloids

Pyrrolizidine alkaloids are a large class of over 600 natural products, consisting broadly of plant-based compounds arising from secondary metabolism of putrescine; (*345*) however, a subset is biosynthesised by bacteria belonging to the genus *Streptomyces*. Beginning with clazamycin **5.1** (Chart 5.1), the isolation of which was reported in 1979,[lx] (*346*) as of the end of October 2018 there are 41 known pyrrolizidine alkaloids where pyrrolizidine biosynthesis is believed to occur within a bacterium; all but nine of these originate from members of the genus *Streptomyces* (Table 5.1). 21 of the bacterial pyrrolizidine alkaloids contain a common 5,7a-dimethyl-5,6,7,7a-tetrahydropyrrolizin-1-one core first observed in bohemamine A (**5.21**) (Chart 5.2), isolated from *Actinosporangium*[lxi] sp.[lxii] C36,145. (*347*) We have elected to describe natural products containing this core, but not named as bohemamines, as bohemamoids within this thesis.

[lx] Earlier isolation was reported in conference proceedings (*449*) and a patent. (*450*)
[lxi] This genus was later reclassified as a subset of *Streptomyces*.
[lxii] Owing to the asexual nature of bacterial reproduction, the possibility of horizontal (interspecies) gene transfer, and difficulty of obtaining and characterising cultures of a single type of organism – a prerequisite for naming a new species – designation of organisms by genus only is a common practice in the literature.

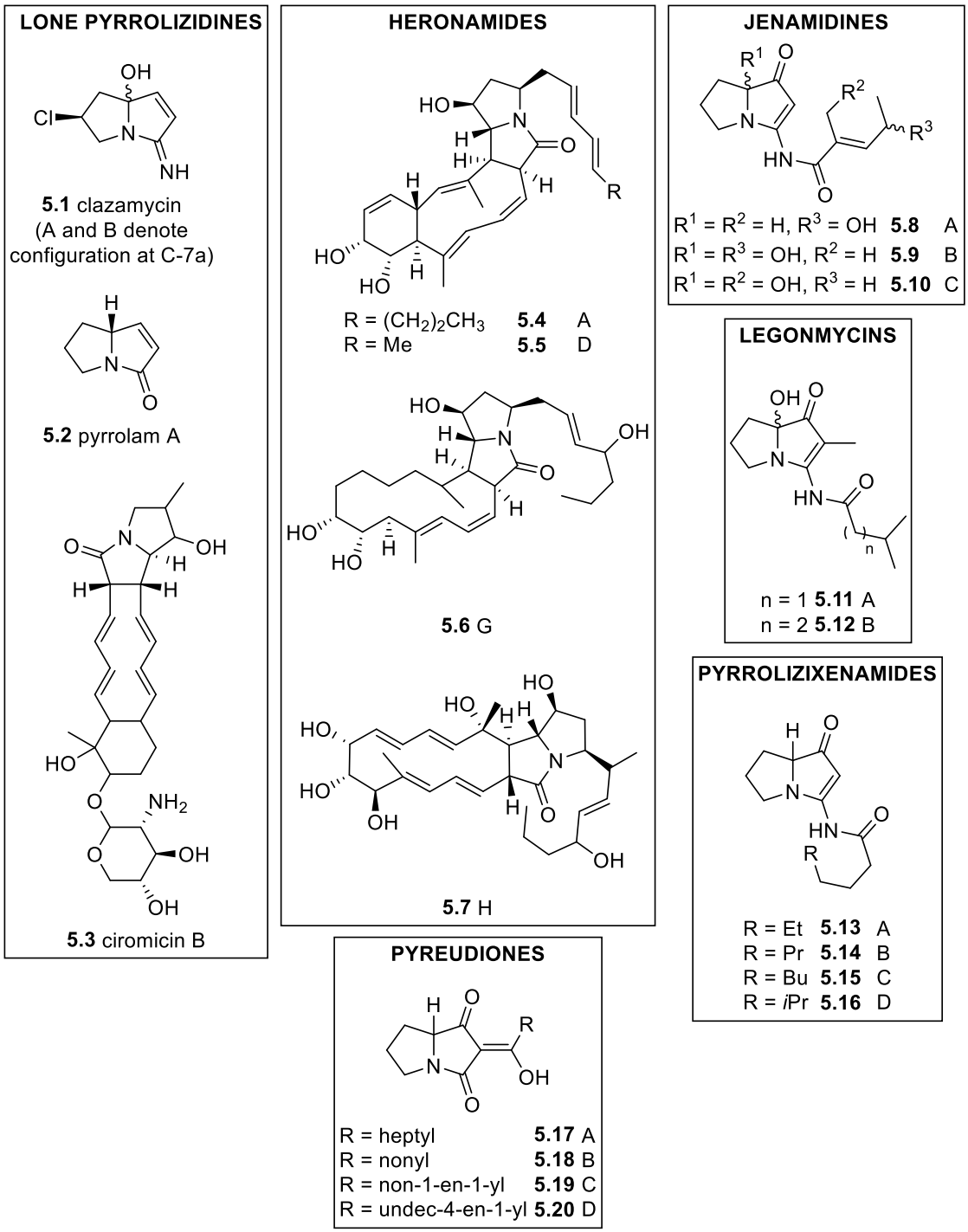



**Chart 5.1.** The known bacterial pyrrolizidine alkaloids, excluding the bohemamines and other related structures (see Chart 5.2).

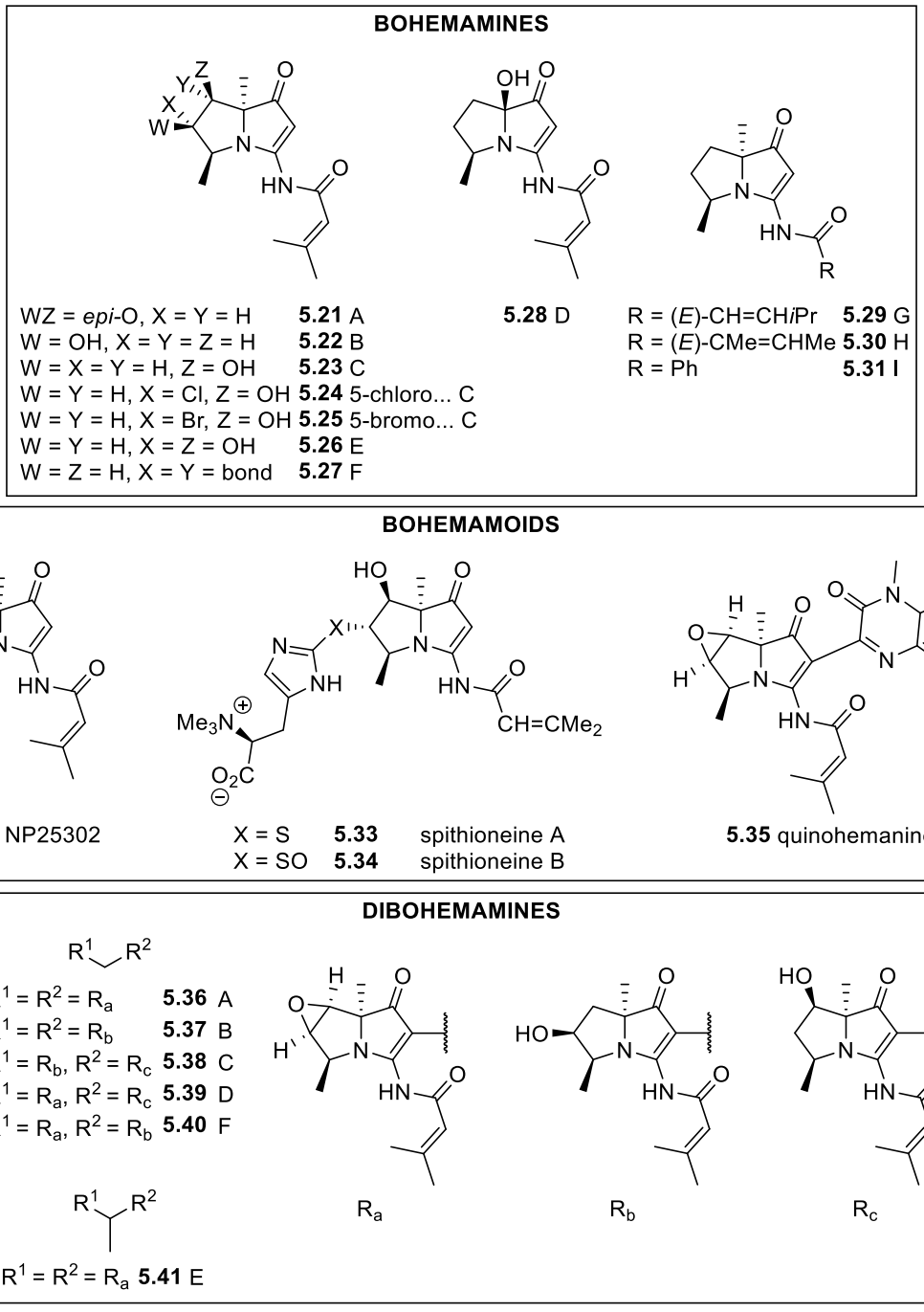


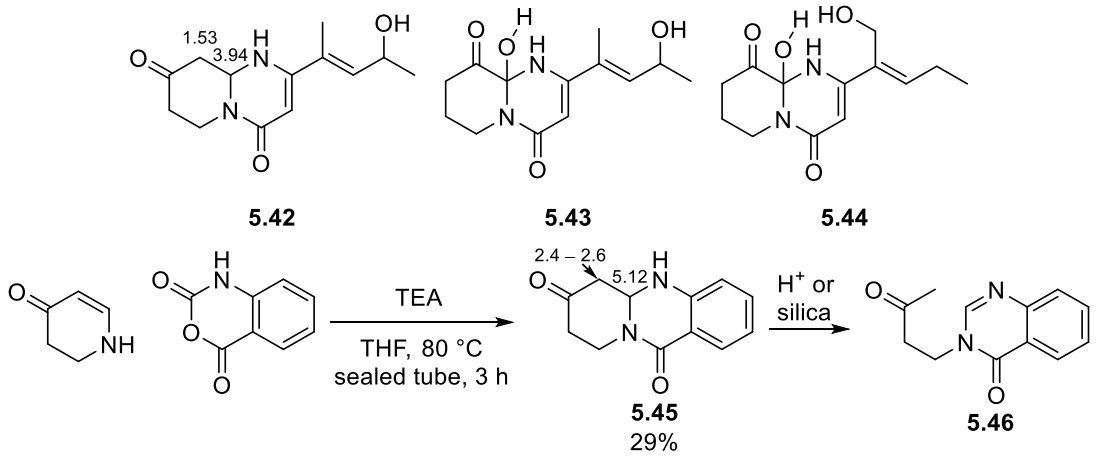

**Chart 5.2.** Known bohemamines, dibohemamines and bohemamoids.

| Class | Members, Structure | First isolation | Isolated from strain[a] | Bohemamine core present? | Total Syntheses |
|---|---|---|---|---|---|
| clazamycin | **5.1** | 1979 (*346*) | *S. puniceus doliceus* NRRL11160, MF990-BF4 | N | - |
| bohemamines | A, **5.21** | 1980 (*347*) | C36,145 | Y | - |
| | B, **5.22;** C, **5.23;** 5-chloro-C, **5.24** | 2006 (*348*) | CNQ-583 | Y | - |
| | D, **5.28**; E, **5.26**; F, **5.27**; G, **5.29**; H, **5.30**; I, **5.31** | 2016 (*349*) | *S. spinoverrucosus* SNB-048 | Y | - |
| | 5-bromo-C, **5.25** | 2016 (*350*) | *S. spinoverrucosus* SNB-032 | Y | - |
| dibohemamines | A, **5.36;**B, **5.37;** C, **5.38** | | | Y | - |
| | D, **5.39;** E, **5.41;** F, **5.40** | 2017 (*351*) | CPCC 200497 | Y | - |
| pyrrolam A | **5.2** | 1990 (*352*) | *S. olivaceus omniyanesis* | N | See Note[a] |
| jenamidines | A, **5.8** | 2003 (*353*) | HKI0297 | N | 2005 (*354*) |
| | B, **5.9**; C, **5.10** | | | N | - |
| NP25302 | **5.32** | 2003 (*355*) | UMA-044 | Y | 2006, (*356*) 2011 (*357*) |
| heronamides | A, **5.4** | 2010 (*358*) | CMB-M0406 | N | 2016 (*359*) |
| | D, **5.5** | 2014 (*360*) | SCSIO 03032 | N | - |
| | G, **5.6**; H, **5.7** | 2018 (*361*) | *S. niveus* | N | - |
| | | | | N | - |
| spithioneines | A, **5.33**; B, **5.34** | 2015 (*362*) | *S. spinoverrucosus* SNB-048[b] | Y | - |
| legonmycins | A, **5.11** | 2015 (*363*) | MA37 | N | This thesis |
| | B, **5.12** | | | N | This thesis |
| pyrrolizix-enamides | A, **5.13**; B, **5.14**; C, **5.15**; D, **5.16** | 2015 (*364*) | *Xenorhabdus stockiae* DSM17904[c] | N | - |
| ciromicins | B, **5.3** | 2015 (*365*) | Coculture of *Nocardiopsis* ΔApoS and *Rhodococcus wratislaviensis* | N | - |
| pyreudiones | A, **5.17;** B, **5.18** | 2016 (*366*) | *Pseudomonas fluorescens* HKI0770 | N | 2016 (*366*) |
| | C, **5.19;** D, **5.20** | | | | - |
| quinohemanine | **5.35** | 2018 (*367*) | CPCC 200497 | Y | - |

**Table 5.1.** Details of the known bacterial pyrrolizidine alkaloids. [a] *Streptomyces* sp. unless otherwise specified. [b] *cf.* bohemamines D-I. [c] The pyrrolizixenamides were obtained by heterologous expression in *E. coli* of a gene cluster found in *X. stockiae* and multiple other bacteria, including *Streptomyces cattleya*. [a] 1996, (*368*) 1997, (*369*) 1997, (*370*) 2000, (*371*) 2004, (*372*) 2007, (*373*) 2007, (*374*) 2014 (*375*)

Pyrrolam A **5.2** was isolated with three other products, (*352*) although it was later suggested (*372*) that pyrrolams B (methoxy group at C-7a in place of a proton), C (hydroxyl group at C-7a) and D (mixed ethyl/pyrrolam C acetal of acetaldehyde) were isolation artefacts.

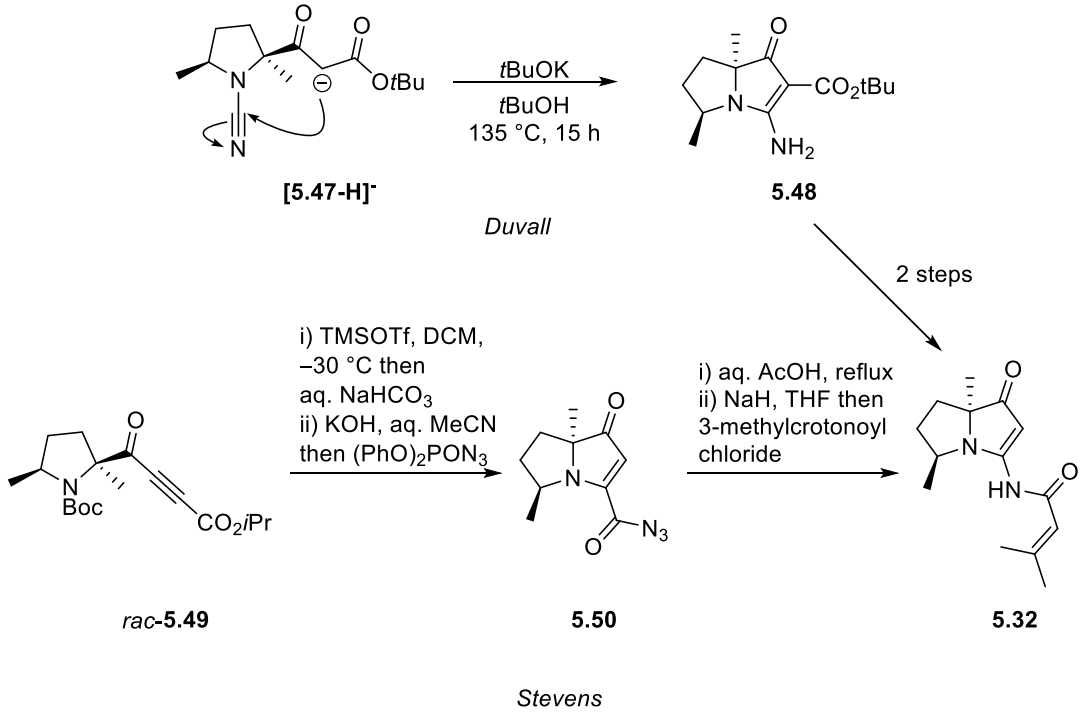
The isolation of the jenamidines was described in 2003; (*353*) the structures **5.42**, **5.43** and **5.44** were assigned to jenamidines A, B and C respectively (Scheme 5.1). Model **5.45** for these compounds was synthesised prior to an attempted total synthesis. (*376*) The differing position of the ketone in **5.42** with respect to **5.43** and **5.44**, and decomposition of model compound **5.45** to **5.46** under the conditions reported for isolation of the jenamidines, in addition to significant disparity between NMR chemical shifts of **5.45** and **5.42**, led the authors to assign new structures **5.8**, **5.9** and **5.10** to jenamidines A, B and C respectively.




**Scheme 5.1.** Structures of the jenamidines proposed upon isolation (top). Synthesis of a model compound **5.45** cast doubt upon the validity of structure **5.42**, prompting reassignment of the jenamidines to currently accepted structures **5.8**, **5.9**, and **5.10**.

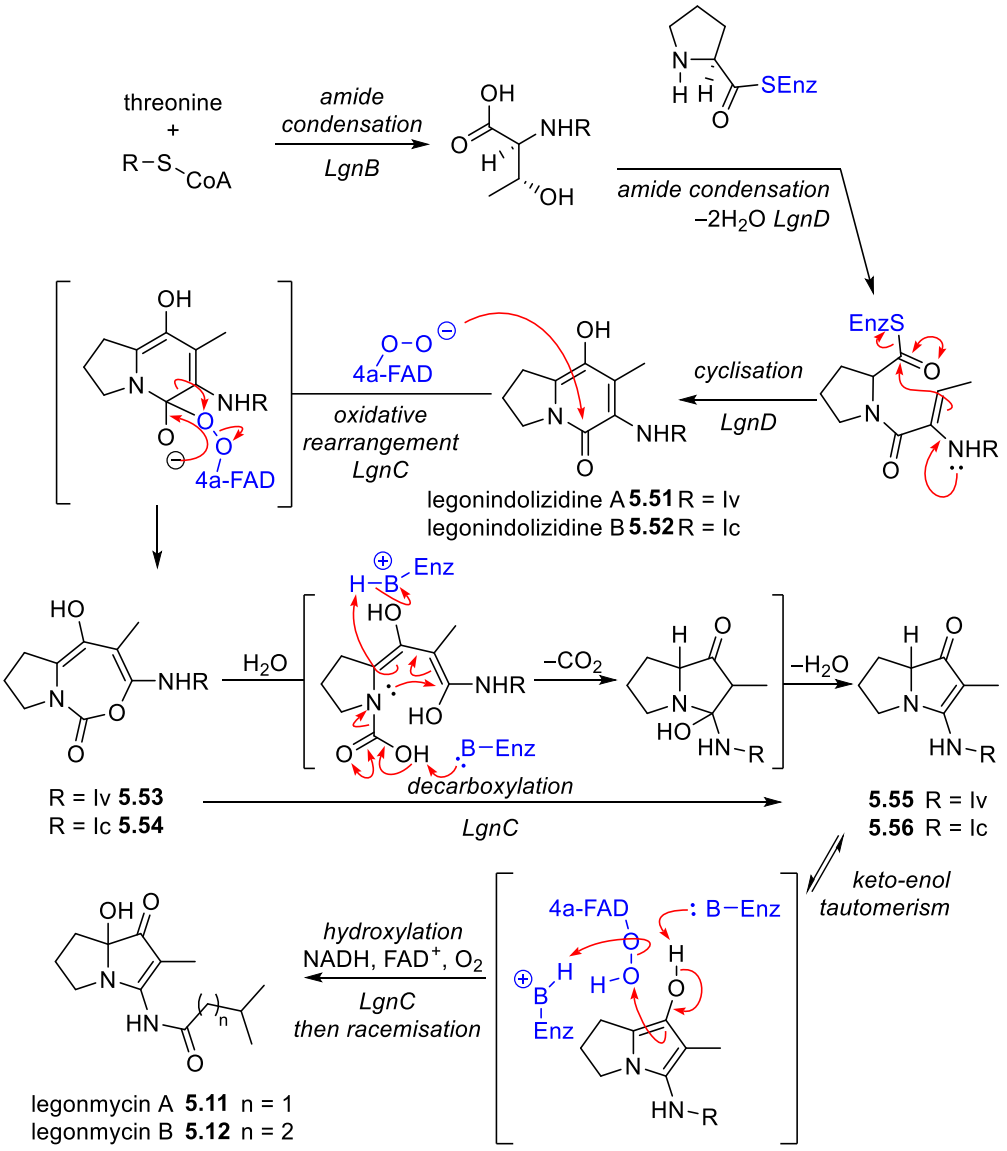
Both jenamidine A and the related compound NP25302, **5.32**, isolated separately from the jenamidines, (*355*) succumbed to synthesis (Scheme 5.2). (*356*) The key step of

the route is cyclisation of β-ketoester **5.47** into the cyanamide functionality present in the same molecule to afford bohemamine core **5.48**; this was in turn acylated and treated with TFA/DCM to afford the natural product. An alternative route to compound **5.32** as the racemate is also reported. (*357*) A Curtius rearrangement is employed to form the vinylogous urea moiety spanning C-1/C-2/C-3; the substrate for this transformation, **5.50**, is in turn produced *via 5-endo-dig* cyclisation of nitrogen into the 2-yne-1,4-dicarbonyl system of intermediate **5.49**.




**Scheme 5.2.** Key steps in the syntheses of NP25302 **5.32**.

The metabolic pathway to bacterial pyrrolizidines was unknown until the legonmycins **5.11** (A) and **5.12** (B) were isolated from a culture of *Streptomyces* sp. MA37; (*363*) the four proteins and associated genes, *lgnA–lgnD*, required for biosynthesis of these compounds were identified as part of this work (Scheme 5.3).




**Scheme 5.3.** The biosynthesis of the legonmycins is aided by four proteins, and proceeds from proline, threonine and isovaleric/isocaproic acid, *via* legonindolizidines **5.51**/**5.52** and prelegonmycins **5.55**/**5.56** (4a-FAD = 4a-flavin adenine dinucleotide radical).

The authors propose that *N*-acylation of threonine with the appropriate coenzyme A derivative is mediated by a non-ribosomal peptide synthetase (NRPS) for which a gene named *lgnB* codes. A gene named *lgnD* codes for a second NRPS which facilitates the coupling of proline to this fragment, and cyclisation releases the substrate from the enzyme, affording legonindolizidines **5.51** and **5.52**. A third gene, *lgnC*, codes for a flavin-dependent monooxygenase (FDMO), which promotes conversion of **5.51** and **5.52**

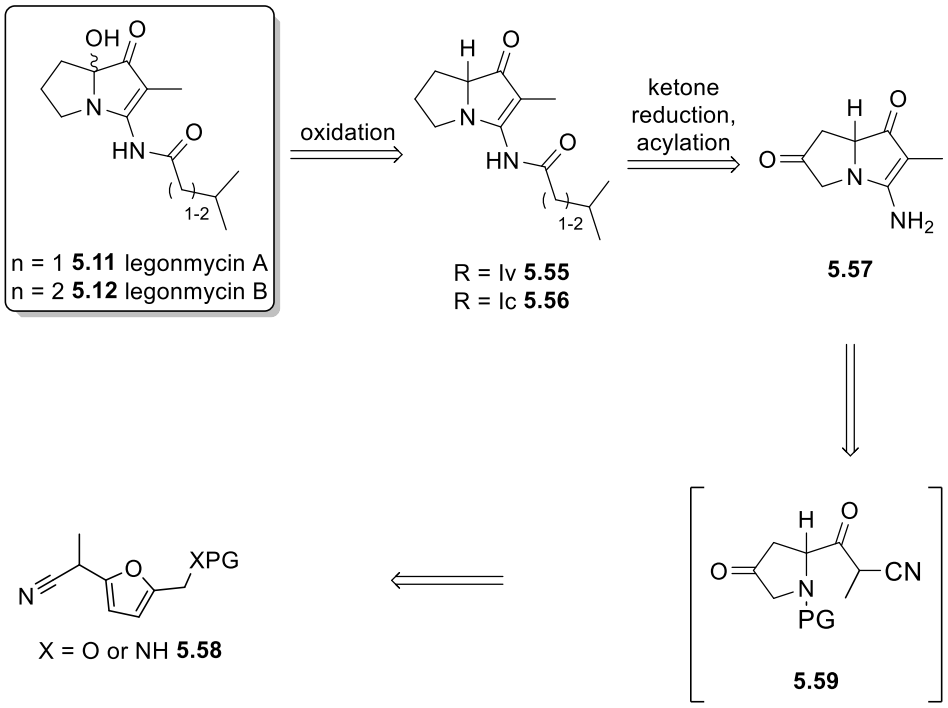
to carbamates **5.53** and **5.54** respectively, in a transformation similar in mechanism to the Baeyer–Villiger oxidation. The same FDMO is also invoked to explain hydrolysis of **5.53** and **5.54**, and decarboxylation/elimination of water to afford deoxylegonmycins **5.55** and **5.56**, referred to as "prelegonmycins" by the authors. Hydroxylation affords **5.11** and **5.12**; **5.11** was confirmed to be racemic by CD and chiral HPLC, and the authors claim that "LgnC may mediate a stereospecific hydroxylation at the C7 *(sic)* position of [**5.55** and **5.56**], but the corresponding products could readily undergo racemization at neutral pH." The specific role of the thioesterase for which the gene *lgnA* codes has not been established.

## Legonmycins from a Furan-derived Enedione

The presence of the 3-oxopyrrolidine substructure within many bacterial pyrrolizidine alkaloids, the Robertson group's previous experience in the synthesis of NP25302, **5.32**, (*357*) and the desire for an escape from what had become monotonous and unrewarding work in method development prompted us to consider the synthesis of another pyrrolizidine alkaloid *via* the furan oxidation conditions previously developed (see Chapter 4). We envisaged that **5.11** and **5.12** would both be accessible from a simple furan precursor; while these compounds are not particularly suitable substrates to be accessed *via* cyclisation of an aminoethylfuran oxidation product, the simple stereochemistry of these products, combined with the fact that they had not previously been synthesised, encouraged us to evaluate a possible synthetic approach.

It was expected that the legonmycins could be accessible from bicyclic precursor **5.57** *via* sequential reduction of the ketone at C-6, *N*-acylation, and hydroxylation at C-7a (Scheme 5.4). We considered possible routes to **5.57** from a furan precursor such as

**5.58**, but it was apparent that this strategy would involve subjecting sensitive functionality to harsh and incompatible conditions or attempting an anti-Baldwin cyclisation, to say nothing of the multiple changes in oxidation state, often in opposing directions; the potential for the ketone at C-6 to be employed in the synthesis of legonmycin derivatives[lxiii] encouraged us to proceed regardless.



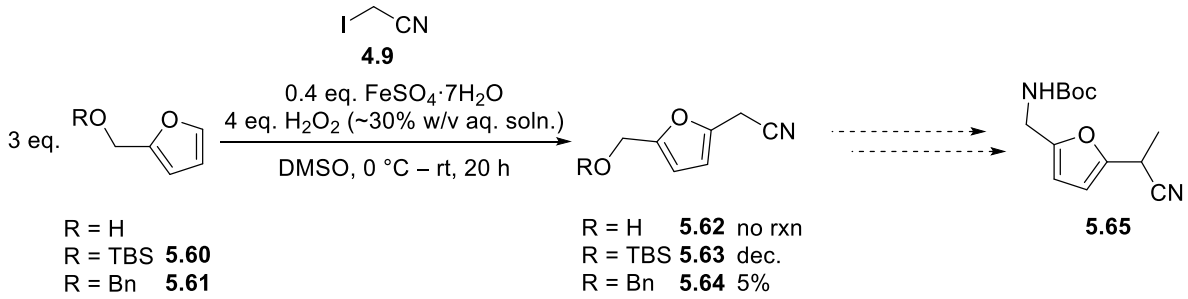

**Scheme 5.4.** Retrosynthetic analysis of the legonmycins via common pyrrolizidine **5.57** was not promising.

We began synthetic work towards **5.65** (Scheme 5.5), but were quickly discouraged; attempted Baciocchi (*304*) coupling of iodoacetonitrile **4.9**[lxiv] and furfuryl alcohol, and derivatives **5.60** and **5.61** returned significant quantities of SM and little or

[lxiii] Chemists, both human and bacterial, producing the legonmycins and similar natural products employ proline or substituted derivatives thereof in their synthesis of the C-(5,6,7) ring. The latter are limited in availability; a means of late-stage functionalisation at these positions would therefore be beneficial to synthesis of analogues of the legonmycins.

[lxiv] Commercial iodoacetonitrile was used for work described in previous chapters, but it is expensive. In view of the quantities that we anticipated might be used in the work described in this chapter, it was prepared by Finkelstein reaction of chloroacetonitrile. (*411*)

no product, in contrast to the analogous reaction with **4.9** and 2-methylfuran to afford **4.10** (see page 101). Compound **5.64** was obtained in only 5% yield and TBS-protected analogue **5.63** decomposed prior to purification.




**Scheme 5.5.** Baciocchi coupling to afford protected 5-cyanomethyl-substituted furfuryl alcohol derivatives was unsuccessful.

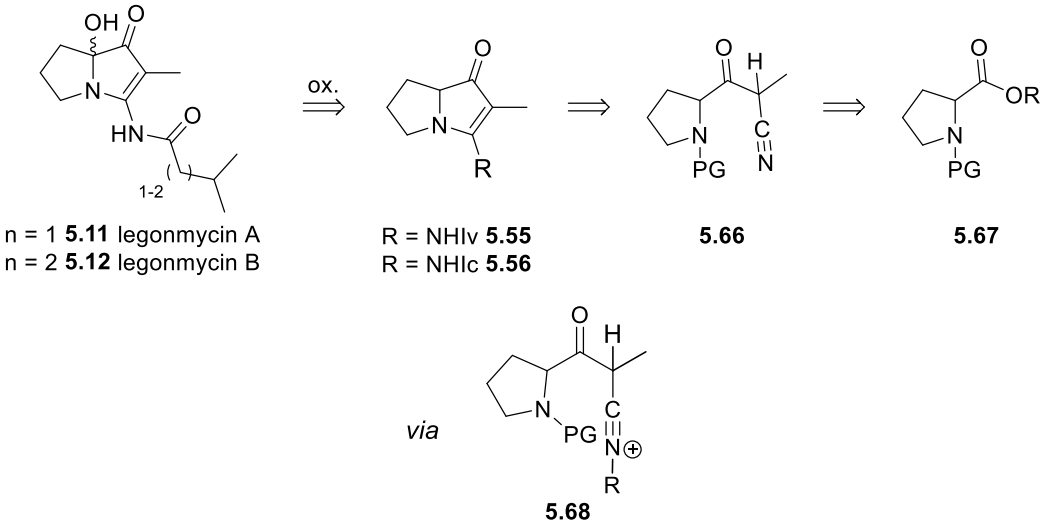
## Attempted Synthesis *via* Cyclisation of *N*-Acylnitrilium Ion

At this stage, it was decided to investigate alternative routes to the legonmycins. As a naturally occurring amino acid, proline is readily available and has a pyrrolidine ring already present, making it a much better choice to begin a synthesis of pyrrolizidines with a bare C-(5,6,7) skeleton; indeed, syntheses of the jenamidines and many other natural products containing a pyrrolidine substructure proceed from proline. (*377*,*378*) Precursors **5.55** and **5.56** were considered to be accessible from cyanoketones of general structure **5.66** upon activation of the nitrile by a reactive acylating agent, affording an acylnitrilium species **5.68** (Scheme 5.6) and reaction *in situ*; **5.66** in turn could be accessed *via* Claisen condensation of propionitrile with *N*-protected proline-derived esters described by general structure **5.67**.

*N*-Alkyl and *N*-aryl nitrilium species have been comprehensively reviewed. (*379*) To our knowledge, the only description of *N*-**acylation** of nitriles is:

> "Addition of benzoyl triflate (from benzoyl chloride and silver triflate) to a solution of benzonitrile in benzene and warming at 80–90 °C for 5 min gave a deep red solution from which yellow crystals of $[PhCNCOPh]^+ {}^-OTf$ (Tf = $O_2SCF_3$) (31% yield, m.p. 114 – 118 °C) precipitated. The i.r. spectrum of this compound had no band in the region 2350 – 2400 $cm^{-1}$, but instead had a strong band in the $\nu_{C=N}$ region at 1590 $cm^{-1}$, in addition to a strong carbonyl absorption at 1620 $cm^{-1}$." (*380*)

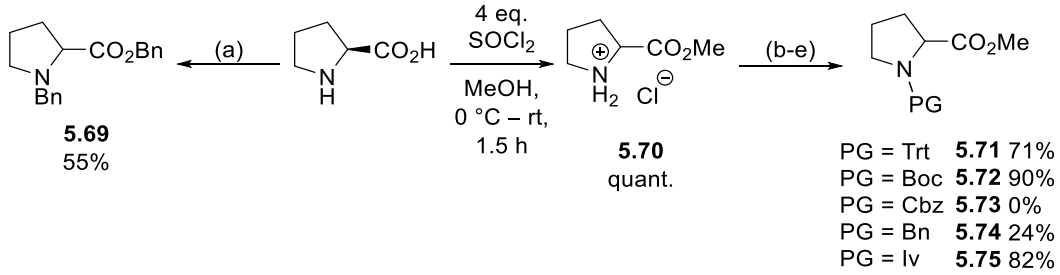
The *N*-acylation of potassium cyanotriethylborate (*381*) and *N*-acylation of AgCN to afford an *N*-acyl isocyanide ion are known. (*382*) Additionally, the acylation of the nitrile moiety of dialkylcyanamides has been described, with the resultant *N*-acylnitrilium species being trapped by nitrogen-containing functionality. (*383*)




**Scheme 5.6.** Retrosynthetic analysis of the legonmycins to an *N*-protected prolinate ester **5.67**, *via N*-acylnitrilium intermediate **5.68**.

The identity of the group protecting the proline nitrogen was expected to be critical in the cyclisation depicted in Scheme 5.6; variably protected proline-derived cyanoketones were therefore targeted. Methyl prolinate hydrochloride **5.70** was obtained by reaction of proline with $SOCl_2$ in methanol (Scheme 5.7). (*384*) Although the natural legonmycins were isolated as racemates, on grounds of cost, L-proline was employed as SM instead of the racemate; the retention or otherwise of stereochemistry in subsequent

steps was not investigated. Trityl- and Boc-protected esters **5.71** (*385*) and **5.72**, (*386*) respectively, were prepared in good yield, but the expected Cbz-protected analogue **5.73** was not obtained upon reaction of **5.70** with benzyl chloroformate in spite of precedent; (*387*) benzyl amine **5.74** was isolated instead (Scheme 5.7). [lxv] Methyl *N*-isovalerylprolinate **5.75** was also prepared as a precursor to cyanoketone **5.78**, to rule out formation of the latter as a side product in the attempted nitrile acylation (see page 132). Benzyl-protected benzyl ester **5.69** was also prepared as part of an abortive attempt to develop a one-pot protocol to afford the pyrrolizidine core of the legonmycins in a single reaction vessel.

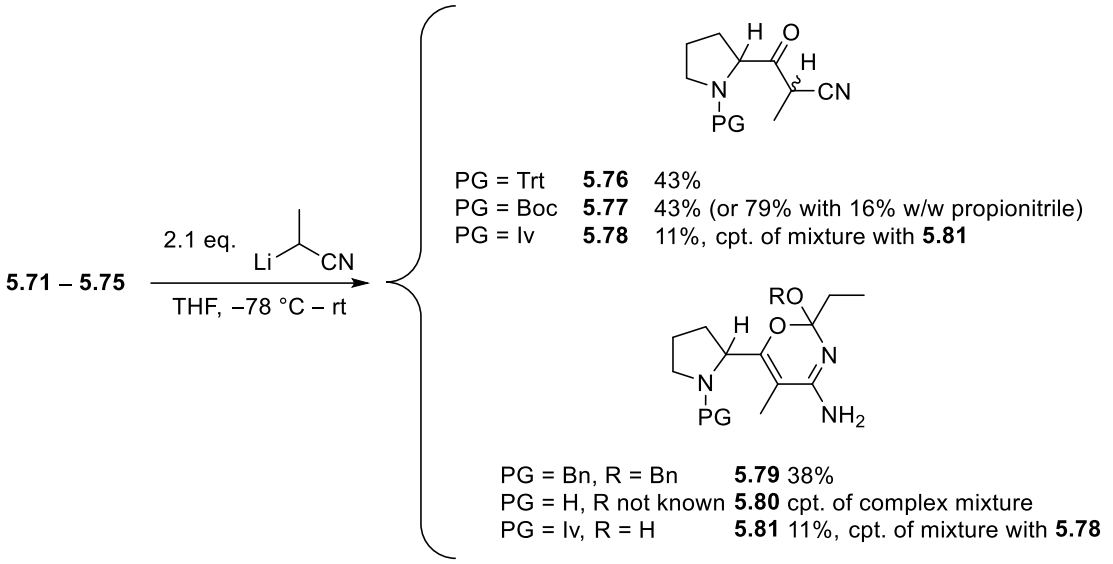



**Scheme 5.7.** Syntheses of protected prolinate esters. (a) 0.02 eq. DMF, 2.05 eq. BnBr, 2.07 eq. DIPEA. THF, reflux, 25 h. (b) 1.05 eq. TrtCl, 3 eq. TEA, DCM, rt, 20 h, product **5.71**. (c) 1 eq. $Boc_2O$, 3 eq. TEA, DCM, rt, 42 h, product **5.72**. (d) 1 eq. CbzCl, 3 eq. TEA, DCM, rt, 19 h, product **5.74**. (e) 3 eq. IvCl, 3 eq. TEA, 0.1 eq. DMAP, DCM, rt, 18 h, product **5.75**.

Cyanoketones **5.76** and **5.77** were then obtained by condensation of the lithiated anion of propionitrile with the appropriately protected prolinate esters (Scheme 5.8). Two eq. of the anion were necessary to drive the reaction to completion (owing to the greater acidity of the product with respect to propionitrile), and while forming the nitrile anion, adequate control of the temperature was essential; failure to do so entailed return of the starting esters and consumption of propionitrile; we propose that the anion of

[lxv] Our suspicions that the CbzCl had decomposed to BnCl prior to use in this reaction were assuaged by $^1$H NMR analysis.

propionitrile underwent self-condensation at elevated temperature. Both of these cyanoketones were obtained as mixtures of diastereomers; a trace of the enol form of **5.76** was also apparent, and NMR spectra of **5.77** were further complicated by the existence of each diastereomer as rotamers at rt. Spectra recorded in DMSO-$d_6$ at 90 °C gave rise to broad, but non-rotameric, signals.

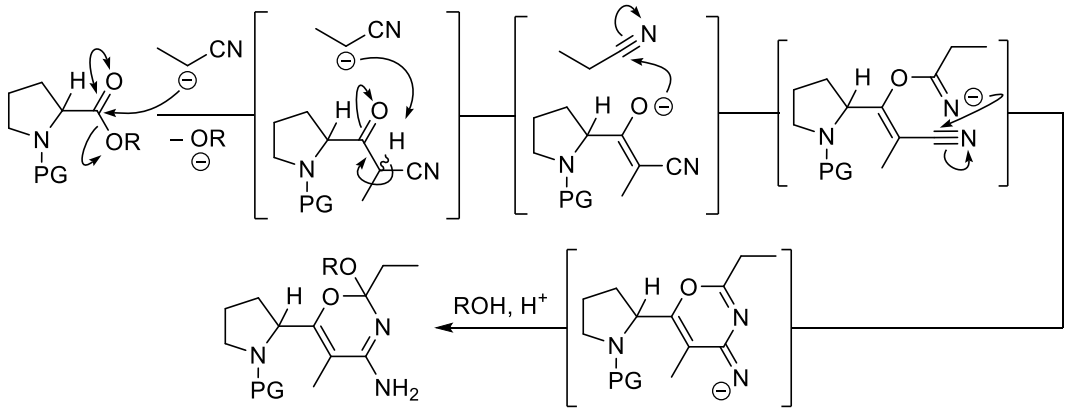



**Scheme 5.8.** Claisen condensation of the anion of propionitrile and various N-protected prolinate esters afforded cyanoketones and, in some cases, an oxazine side product.

Attempts to carry out the same transformation on substrate **5.69** afforded a side product to which structure **5.79** is tentatively assigned based upon MS/NMR analysis.[lxvi] We believe this side product arises from condensation of the anion of the intended products, through O, into the second eq. of propionitrile, after an initial proton exchange (Scheme 5.9). Attempts to perform this transformation without a protecting group entailed decomposition to a complex mixture, apparently including analogous oxazine

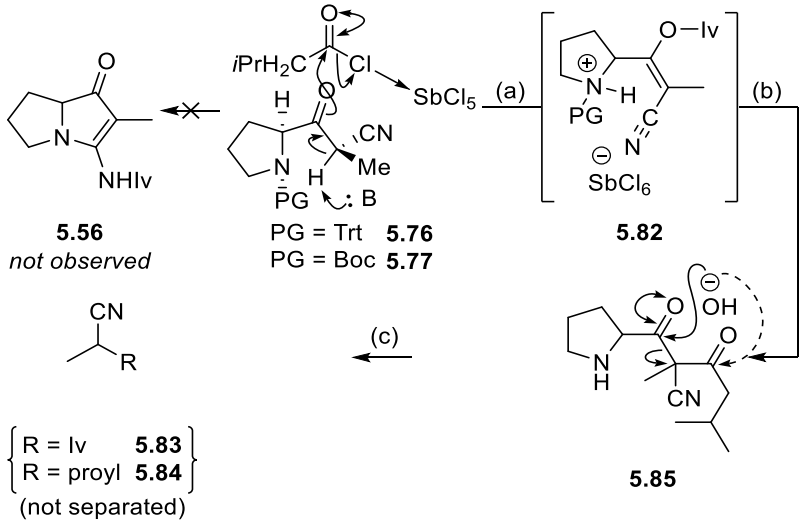
[lxvi] Mass spectra showed strong peaks corresponding to the oxazinium ions obtained by loss of $BnO^-$ from compound **5.79**. $^{13}C$ NMR spectra lacked ketone signals, but suggested olefinic quaternary carbons, and in $^1H$ NMR spectra, chemical shift and lack of coupling suggests that the methyl protons in **5.79** are allylic; 2 superimposed quartets and a triplet, characteristic of an ethyl group adjacent to a stereocentre, are also apparent.

**5.80**. Iv-protected cyanoketone **5.78** was co-eluted with side product **5.81** upon chromatographic purification.



**Scheme 5.9.** Proposed mechanism of formation of **5.79** – **5.81**.

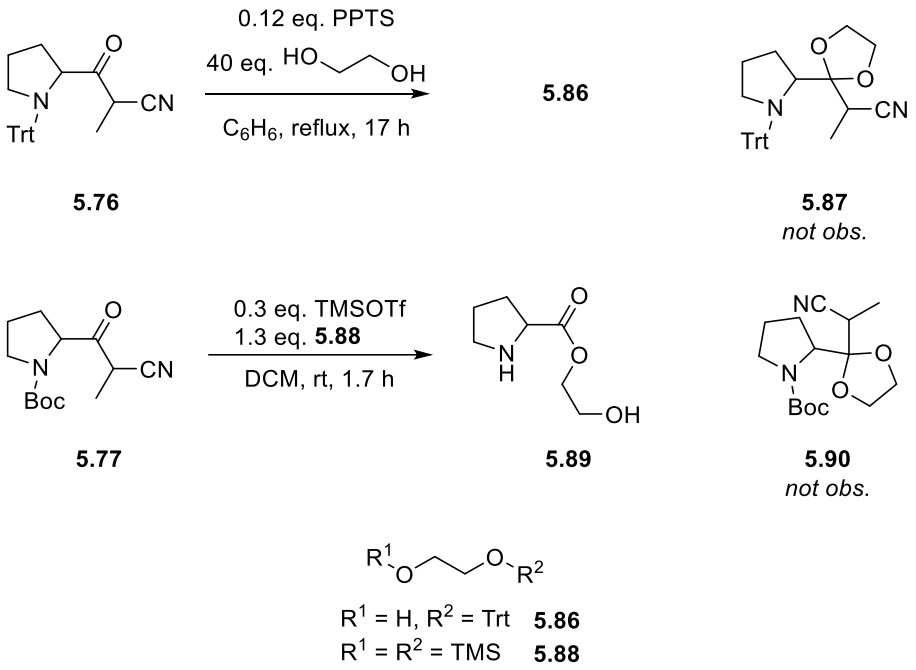
Attention was turned next to the nitrile *N*-acylation of **5.76** and **5.77** following the procedure described for the acylation of cyanamides. (*383*) Upon addition of **5.76** to a mixture of 2 eq. each of IvCl and $SbCl_5$, an immediate colour change to bright yellow occurred, and traces of converted material were obtained (Scheme 5.10).



**Scheme 5.10.** Attempted *N*-acylation of cyanoketones **5.76** and **5.77** did not afford prelegonmycin A **5.55**; traces of 2-cyano-1,3-dicarbonyl compound **5.85** were instead isolated. Reagents and conditions: (a) 1.0 – 3.5 eq. IvCl·$SbCl_5$, DCM, –78 °C – rt, 2 h. (b) [1,3]-acyl transfer, loss of PG. (c) 1 M aq. NaOH during w/u.

Direct NMR comparison with **5.78** ruled out proline *N*-acylation and deprotection, and the $^{13}C$ NMR spectrum of this material included signals at 197.0 and 171.5 ppm, suggesting preservation of ketone functionality and successful acylation. The $^{15}N$-HMBC spectrum was inconsistent with target compound **5.55**, however; instead, we assign the structure **5.85** to the product, which we believe is obtained *via C*-acylation of the enol ester initially formed, **5.82**, followed by loss of the *O*-acyl group. Deprotection of proline-N is mediated by the protons released upon initial acylation. Repeating this reaction with substrate **5.77**, followed by basic workup (1 M aq. NaOH) effected decomposition of the product; chromatography afforded impure material which appeared to contain cyanoketones **5.83** and **5.84**.

In order to avoid *O*-acylation and the resulting undesired reactivity exhibited by cyanoketones **5.76** and **5.77**, the protection of ketone functionality as a 1,3-dioxolane, to afford targets **5.87** and **5.90**, respectively, was attempted (Scheme 5.11). Heating compound **5.76** to reflux with 5 eq. ethylene glycol and 0.05 eq. pyridinium *para*-toluenesulfonate in benzene engendered decomposition of the SM; only **5.86**, arising from transfer of the *N*-trityl group to ethylene glycol, was isolated. Exposure of compounds **5.76** and **5.77** to bis-silyl ether **5.88** and catalytic TMSOTf (*388*) did not engender conversion; further addition of trimethylsilyl trifluoromethanesulfonate caused decomposition of **5.76**. to material tentatively assigned the structure **5.89**.

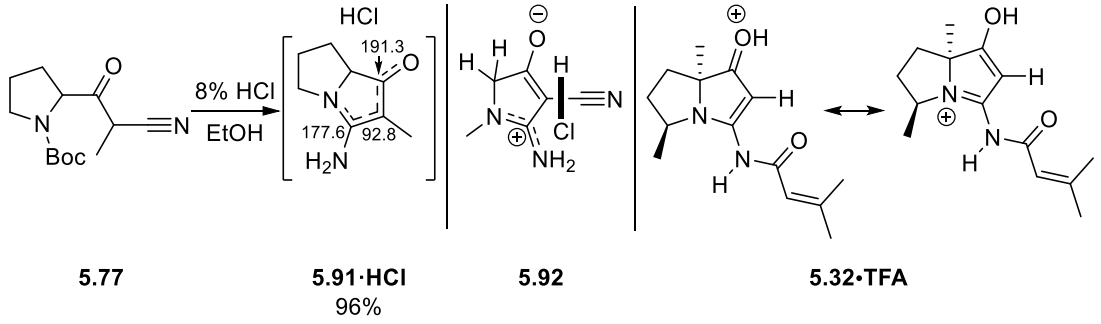



**Scheme 5.11.** Attempted acetalisation of **5.76** and **5.77** afforded neither of the desired compounds **5.87** and **5.90**.

## A Less Ambitious Route

Direct acylation of cyanoketones **5.66** and protection of the ketone therein both proving fruitless, it was decided to abandon our attempts to promote formation of the C-(1,2,3) ring *via* acylation with the desired side chain. Activation of nitriles towards nucleophilic attack has been known since 1877, (*389*) although the only reports of this transformation occurring on a β-ketonitrile are as part of a 2-cyano-1,3-dicarbonyl system. (*356*,*390*,*391*) We were glad to observe that this behaviour extends to compound **5.77**; stirring in ethanolic HCl (*390*) afforded tetrahydropyrrolizine **5.91** as the hydrochloride salt in excellent yield (Scheme 5.12). Although crystals of this material suitable for X-ray analysis were not obtained, crystal structures of similar compound **5.92** (*390*) and the

TFA salt of NP25302 **5.32** (*357*) both suggest *O*-protonation; we propose analogous behaviour in compound **5.91·HCl**.[lxvii]



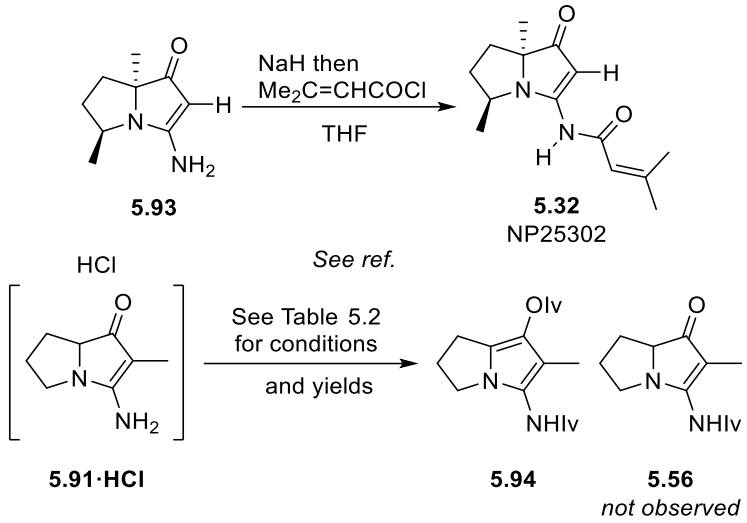

**Scheme 5.12.** Stirring in ethanolic HCl led to efficient conversion of **5.77** to **5.91** as the hydrochloride salt. Molecular structures of **5.92** and **5.32** (determined by single-crystal XRD) are shown for comparison.

Attempts to isolate compound **5.91** as the free base by washing with aqueous base led to decomposition, and purification by chromatography led to significant loss of material. The decomposition of the Boc group to solely gaseous by-products proved, therefore, to be of significant benefit. The presence of propionitrile (an impurity carried through from synthesis of SM **5.77**) was associated with contamination of the product by unidentified organic impurities.

With a short route to the pyrrolizidine core established, attention was turned to acylation to afford the 7a-deoxy precursor to the natural products, **5.55** and **5.56** (Scheme 5.13 and Table 5.2). In the Robertson group's total synthesis of (±)–NP25302, product **5.32** was afforded in 76% yield by treatment of precursor **5.93** with 1.25 eq. NaH and the appropriate acid chloride. (*357*) Deprotonation of **5.91·HCl** with 2 eq. NaH, followed by treatment with a slight excess of isovaleryl chloride afforded traces of *N,*O-bis-acylated by-product **5.94** (entry 1); considering the decreased *pKa* of the proton at C-7a, and that

[lxvii] This hypothesis is also supported by the single-bond character of the C–O bond in **5.91·HCl** implied by $^{13}C$ chemical shift and IR data.

biosynthesis of the legonmycins proceeds *via* hydroxylation of a similar enol, this reactivity is not a surprise. Unexpectedly, treatment of **5.91·HCl** with an excess both of NaH and of isovaleryl chloride afforded **5.94** in only 15% yield (entry 2), owing to decomposition on silica during purification; a protocol that did not necessitate chromatography was therefore required. Acylation of both uncharged ureas (*392*) and their vinylogues (*393*) with TEA as a proton scavenger is also reported. Continuing to employ an excess of acylating agent, various THF/toluene/TEA solvent mixtures were trialled with moderate success (entries 3–5), but pure material could not be obtained without resorting to chromatography, entailing serious loss of material. Use of benzene as a solvent allowed reaction by-products to be removed *via* filtration but use of only 1.15 eq. of acylating agent produced a mixture of SM and product, and chromatography led to complete loss of material (entry 6). The reaction was found to proceed well in acetonitrile at room temperature with pyridine as a proton scavenger, and as this solvent was compatible with most of the oxidation conditions trialled (see below), these conditions were employed for preparation of compound **5.94**.

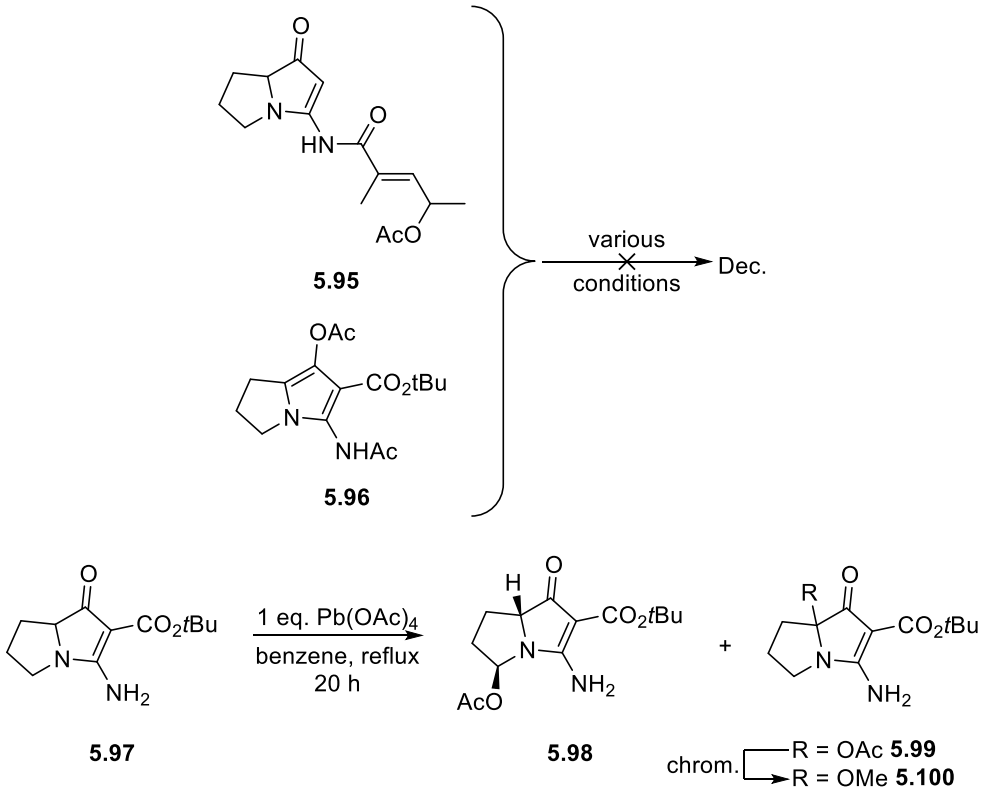



**Scheme 5.13.** Acylation of **5.91** under reported conditions (*357*) did not afford **5.55**, instead giving 2,3-dihydro-[*1H*]-pyrrolizine **5.94**.

| Entry | Isovaleryl chloride loading[a] | Base Identity, loading[a] | Temp-erature /° C | Solvent (concentration in SM/mM) | Product(s) | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | 1.25 | NaH, 1.95 | rt | THF (38.3) | **5.94** | 8 |
| 2 | 12.40 | NaH, 12.40 | rt | THF (81.8) | **5.94** | -[b] |
| 3 | 5.20 | Solvent, 2.90 | 80 | 30 : 20 : 1 THF : toluene : TEA (38.2) | **5.94** | 66[c] |
| 4 | 4.95 | Solvent, 9.90 | 80 | 6 : 4 : 1 THF : toluene : TEA (81.9) | **5.94** | 62[d] |
| 5 | 2.50 | Solvent, 3.60 | 80 | 15 : 10 : 1 THF : toluene : TEA (77.5) | **5.94** | 82[e] |
| 6 | 1.15 | TEA, 4.00 | reflux | Benzene (166) | 1 : 1 **5.91** : **5.94** | 52[f] |
| 7 | 1.00 | Pyridine, 4.00 | rt | Acetonitrile (530) | 1 : 1 **5.91** : **5.94** | n.i. |
| 8 | 1.00 | - | rt | Added to mixture above | **5.94** | 102[g] |

**Table 5.2.** Conditions for acylation of **5.91.HCl**. [a] eq. wrt SM; rounded to nearest 0.05. [b] Crude yield not recorded; combined with entry 4, average chromatographic yield 15%. [c] 136% mass recovery, contaminated with 31% w/w IvOH, 21% w/w IvCl; decomposed upon attempted hydrolysis. [d] 129% mass recovery, contaminated with 33% w/w IvCl, 19% w/w diisopropyldiketene. This material was later purified with the crude product from entry 2. [e] 101% mass recovery, contaminated with 18% w/w IvCl. [f] Crude yield, decomposed during purification. [g] Crude yield, could be used in next step without purification; chromatographic yield 42%.

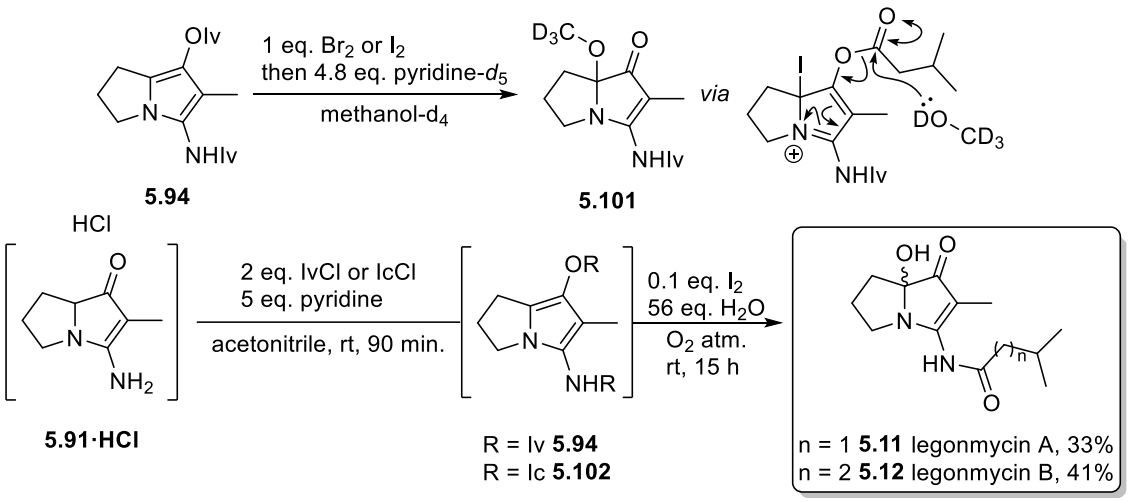
With a route to the synthesis, if not the purification, of dihydropyrrolizine **5.94** available, it occurred to us that these compounds might be more prone to oxidation at C-7a than our intended product **5.55**; indeed, the corresponding oxidation step in the biosynthesis of legonmycin proceeds on the enol form of compounds **5.55** and **5.56**. Previous synthetic effort towards jenamidine B consisted of attempted oxidation of jenamidine A acetate **5.95**, and of compound **5.96**; both substrates decomposed under all conditions imposed. (*356*) Oxidation of precursor **5.97** with 1 eq. of $Pb(OAc)_4$ afforded separable acetoxylated regioisomers **5.98** and **5.99** as a 3 : 2 ratio in favour of the desired product. (Scheme 5.14).




**Scheme 5.14.** Literature precedent for attempted hydroxylation of pyrrolizidines similar to the legonmycins was not encouraging. (*356*)

Compound **5.94** was nevertheless submitted to a screen of oxidative conditions, and we were happy to observe that 1 eq. of either $Br_2$ or $I_2$ in methanol-$d_4$ effected clean

conversion (Scheme 5.15). Upon addition of pyridine-$d_5$ to the mixture, the $^{1}H$ and $^{13}C$ NMR spectra matched exactly those reported for legonmycin A, (*363*) but MS indicated a species with molecular formula $C_{14}H_{19}D_3N_2O_3$. We attribute this observation to electrophilic iodination of **5.94** at C-7a, and exchange of iodine with solvent to afford product **5.101**. On the basis of the identical NMR spectra, we postulate that when Huang and coworkers recorded NMR spectra of **5.11** in methanol-$d_4$, a similar exchange process eliminated water, giving the same species **5.101**.




**Scheme 5.15.** Oxidation of compound **5.94** with 1 eq. of halogen effected clean oxidation; in light of difficulties in obtaining clean samples of **5.94**, this step was successfully combined with acylation of **5.91** to afford both legonmycins **5.11** and **5.12** in separate one-pot protocols.

Successful oxidation of compound **5.94** also occurred in acetonitrile, and it proved possible to carry out the oxidation immediately after formation of the substrate by acylation of **5.91**. Additional base is necessary to sequester HI, released by the displacement of iodide with water at C-7a, and upon hydrolysis of the ester functionality present in **5.94**.[lxviii] The mixture was diluted to 4 : 1 acetonitrile : water, and addition of

[lxviii] Insufficient base was added to deprotonate the carboxylic acid thus formed; doing so may have aided purification.

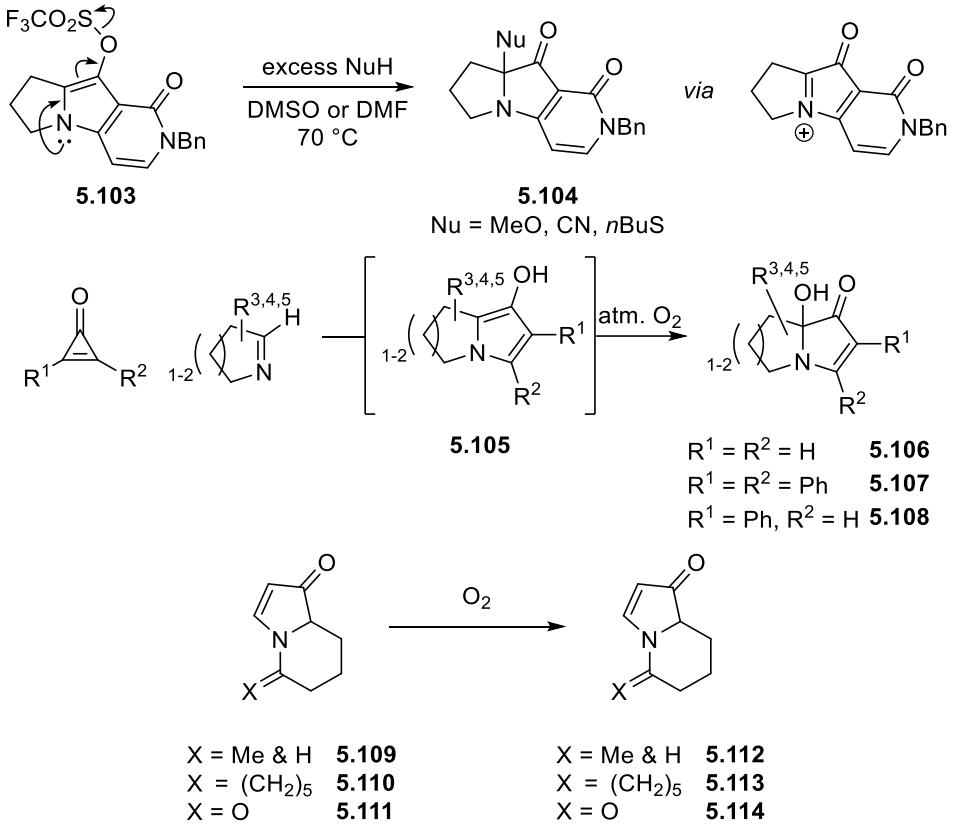
$I_2$,[lxix] followed by chromatography with an acetone/ethyl acetate/toluene eluant system, afforded legonmycin A in 63% yield from **5.91·HCl**. NMR spectra were identical to those reported for legonmycin **5.11** in both methanol-$d_4$ and DMSO-$d_6$. MS and IR data were also concordant with those reported for material isolated from *Streptomyces*. (*363*) This methodology was extended to the synthesis of legonmycin B, and the natural product was obtained in 41% yield;[lxx] attempts to isolate intermediate dihydropyrrolizine **5.102** were not successful.

## Conclusions

The first chemical synthesis of the legonmycins **5.11** and **5.12** has been devised. Both natural products are available in four steps, the final two of which can be carried out in the same reaction vessel, from commercially available 1-*tert*-butyl-2-methylpyrrolidine-1,2-dicarboxylate **5.72**. Divergence of the syntheses from a common synthetic intermediate **5.91** occurs at the last pair of telescoped transformations. While the synthesis draws heavily on previous work in the field, the use of $I_2$ to introduce hydroxyl functionality selectively at the C-7a position of pyrrolizidine alkaloids is, to our knowledge, without precedent, although a remarkably similar transformation of trifluoromethanesulfonate ester **5.103** to compounds of the form **5.104**, *via* internal redox and elimination of the trifluoromethanesulfinate anion, is reported (Scheme 5.16). (*394*) The spontaneous aerobic oxidation of dihydropyrrolizinones **5.105** to hydroxylated derivatives described by structures **5.106**, **5.107**, and **5.108**, is also described, (*395*) and

[lxix] This could be substoichiometric, with an $O_2$ atmosphere serving as the terminal oxidant, but full conversion was not reliable under these conditions.
[lxx] In a separate run, **5.12** was obtained in 117% mass recovery and 74% purity (NMR) using stoichiometric $I_2$ under $N_2$; corresponding to an 87% yield.

similar compounds **5.109 – 5.111** were found to be oxidised aerobically to hemiaminals **5.112 – 5.114**. (*396*,*397*,*398*)




**Scheme 5.16.** Reported oxidations similar to that described in this work.

## Further Work

The relative ease and selectivity with which both these compounds and **5.94** were hydroxylated with respect to compounds **5.95**, **5.96**, and **5.97** (see page 142) merits further investigation of the functional group tolerance of oxidation with $I_2$, concentrating especially on the possibility that the $I_2$ methodology may be applicable to the preparation of jenamidines $B_1$, $B_2$ and C.

The only biological testing described for the legonmycins is an antibacterial assay performed on legonmycin A, (*363*) with neither activity against *E. coli* ATCC 25922 nor

against *Staphylococcus aureus* ATCC 25923 discovered. With a chemical synthesis of both legonmycins now available, more extensive testing of biological activity could be undertaken, especially if the last step of the synthesis could be scaled up. Preparation of analogues of the legonmycins is also now an option, which may bear fruit *viz.* the discovery of more active derivatives. NMR analysis of the crude hydroxylation reaction mixture that affords the legonmycins suggests that it is a selective process; no side products were observed. This begs investigation of the possibility that purification following the final step might be achieved non-chromatographically, which would render the entire synthesis free of chromatography. If the final oxidation can be carried out in benzene, and the product is soluble in that solvent, all by-products should be removable *via* filtration only. Other possibilities include preparation of a crystalline derivative of the legonmycins, perhaps a hemiaminal ether in place of the hemiaminal moiety of the legonmycins themselves, or a hydriodide salt.

It has been established that cyanoketones derived from *N*-protected prolinate esters can be prepared, although in some cases a side product formed by incorporation of an additional eq. of nitrile to form a putative 2-oxyoxazin-4-amine arises. Confirming the identity of these side products, the circumstances leading to their formation, and the viability of their conversion to dihydropyrrolizines **5.94** and **5.102** would be beneficial. Were **5.94** and **5.102** to be available by, *e.g.* hydrogenolysis of compound **5.79** *in situ*,[lxxi] the synthesis of the legonmycins might be carried out in a two-pot synthesis.

[lxxi] Duvall and coworkers obtained compound **5.97** by hydrogenolysis of Cbz on the proline nitrogen and allowing the isolated material to stand for a day. (*356*)

# 6 Experimental Section

*"Sometimes science is more art than science, Morty."*
Rick Sanchez, *Rick and Morty*, Warner Bros. Television Distribution

## General Remarks

Synthetic procedures for compounds can be found under the heading corresponding to the section of this thesis in which they are first mentioned. THF was distilled over Na/benzophenone prior to use unless indicated otherwise. All other reagents or solvents were used as received from commercial suppliers, unless indicated otherwise. Dry solvent was obtained from an MBraun SPS-800 solvent purification system. Column chromatography was performed using Merck Geduran Si 60 silica gel as the stationary phase unless otherwise specified. "Brine" refers to sat. aq. NaCl. Where yields are reported with an associated purity, the yield refers to the implicit quantity of pure material present, as a proportion of the theoretical maximum. TLC was performed with Merck TLC 60 Silica gel $F_{254}$ plates as stationary phase, and spots were visualised with $KMnO_4$, vanillin, anisaldehyde or ultraviolet light (254 nm); $R_f$-values are quoted to the nearest 0.05. NMR spectra were recorded on Bruker AVIII HD 500, AVII 500, AVIII HD 400 or DPX200 spectrometers. 500/125 MHz NMR spectra were recorded by the NMR Service at the Chemistry Research Laboratory, University of Oxford. Chemical shifts are reported in ppm relative to tetramethysilane for $^{1}H$ and $^{13}C$ spectra (with residual protiated solvent used as a reference), relative to tetramethylsilane-$d_{12}$ for $^{2}H$ spectra (with *ca.* 0.01% v/v deuterated solvent used as a reference), and relative to tetramethylstannane for $^{119}Sn$ spectra. Coupling constants $J$ are quoted as observed and rounded to the nearest 0.5 Hz, except in cases of heteronuclear coupling, where they are rounded to the nearest 1 Hz. Resonances arising from multiple chemically equivalent nuclei with different atom

numbers under the IUPAC rules are assigned with comma separators between atom numbers, *e.g.* (m, 2H, Ph-2,6); Resonances arising from chemically inequivalent nuclides which overlap are assigned with the separator "and," *e.g.* (m, 2H, Fn-3 and Fn-4). However, overlapping resonances arising from diastereotopic nuclides are not assigned separately, *e.g.* (m, 2H, H-3) or (m, 2H, $CH_2$) and not (m, 2H, H-3 and H-3'). Resonances of ambiguous origin are assigned with "or," *e.g.* 205.0 (C-2 or C-5), 201.5 (C-2 or C-5). IR absorption spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer on a diamond ATR module, and $\lambda_{max,abs}$-values are expressed in wavenumbers·$cm^{-1}$. UV spectra were recorded on a PerkinElmer Lambda20 UV/Vis spectrometer. HRMS was performed by the Mass Spectrometry Service at the Chemistry Research Laboratory, University of Oxford, using a Bruker microTOF spectrometer. Values of *m*/*z* are calculated to 0.0001 Da from the chemical formula, and all reported values are within 5 ppm of the calculated theoretical values. Melting points were recorded on a Griffin mp apparatus and are uncorrected.

# Index of Compounds by Systematic Name

(*E*)-10,10-Difluorodec-3-ene-2,5-dione....209
(*E*)-1-Hydroxydodec-4-ene-3,6-dione....232
(*E*)-2-(Hexa-3,5-dien-1-yl)-5-methylfuran....217
(*E*)-2,5-Dioxoundec-3-ene....206
(*E*)-4-Oxodec-2-enal....231
(*E*)-6-Iodohexa-1,3-diene....218
(*E*)-9-(1,3-Dithian-2-yl)-non-3-ene-2,5-dione....204
(*E*)-9-Chloronon-3-ene-2,5-dione....225
(*E*)-Hexa-3,5-dien-1-ol....217
(*E*)-*N*-(3,6-Dioxohept-4-en-1-yl)-4-methylbenzenesulfonamide....228
(*E*)-*N*-(3,6-Dioxohept-4-en-1-yl)acetamide....226
(*E*)-Undec-3-en-10-yne-2,5-dione....225
(*E*)-Undeca-3,10-diene-2,5-dione....224
(*S*)-1-Benzylproline benzyl ester....238
(*S*)-1-*tert*-Butyloxycarbonyl-2-methoxycarbonyl pyrrolidine....239
(*S*)-2-(Methoxycarbonyl)-pyrrolidin-1-ium chloride....238
(*S*)-2-methyl-3-[1-(3-methylbutanoyl)pyrrolidin-2-yl]-3-oxopropanenitrile....244
(*S*)-2-Methyl-3-oxo-3-(1-tritylpyrrolidin-2-yl)propanenitrile....242
(*S*)-3-Amino-2-methyl-5,6,7,7a-tetrahydro-1*H*-pyrrolizin-1-one hydrochloride....249
(*S*)-Methyl 1-(3-methylbutanoyl)pyrrolidine-2-carboxylate....241
(*S*)-Methyl 1-benzylpyrrolidine-2-carboxylate....240
(*S*)-Methyl 1-triphenylmethylpyrrolidin-2-carboxylate....239
(*S*)-*tert*-Butyl 2-(2-cyanopropanoyl)pyrrolidine-1-carboxylate....243
1-(5-Methylfuran-2-yl)hex-5-en-1-ol....181
1-(5-Methylfuran-2-yl)pent-4-en-1-ol....199
1,6-Bis-(5-methylfuran-2-yl)hex-1-ene....178
1,6-Bis(5-methylfuran-2-yl)hex-5-en-1-ol....185
1-[2-(4-Amino-2-ethyl-2-hydroxy-5-methyl-2H-1,3-oxazin-6-yl)-(*S*)-pyrrolidin-1-yl]-3-methylbutan-1-one....246
1-Acetyl-2-(2-oxopropyl)pyrrolidin-3-one....226

1-Cyclopropylundec-3-ene-2,5-dione ..... 230
2-(2-Oxopropyl)-1-tosylpyrrolidin-3-one ..... 229
2-(2-Oxopropyl)-dihydrofuran-3(2*H*)-one ..... 207
2-(4-Chlorobutyl)-5-methylfuran ..... 168
2-(4-Iodobutyl)-5-methylfuran ..... 169
2-(5,5-Difluoropentyl)-5-methylfuran ..... 208
2-(5-Chloropentyl)-5-methylfuran ..... 164
2-(5-Hexylfuran-2-yl)ethan-1-ol ..... 222
2-(5-Iodopentyl)-5-methylfuran ..... 165
2-(5-Methylfuran-2-yl)acetonitrile ..... 210
2-(5-Methylfuran-2-yl)ethan-1-amine ..... 212
2-(5-Methylfuran-2-yl)ethan-1-ol ..... 206
2-(Benzyloxy)-6-[1-benzyl-(*S*)-pyrrolidin-2-yl]-2-ethyl-5-methyl-2H-1,3-oxazin-4-amine ..... 245
2-(Cyclopropylmethyl)-5-hexylfuran ..... 221
2-(Cyclopropylmethyl)-5-methylfuran ..... 220
2-(Furan-2-yl)cyclopentan-1-one ..... 190
2-(Hex-5-en-1-yl)-5-methylfuran ..... 162
2-(Hex-5-yn-1-yl)-5-methylfuran ..... 177
2-(Triphenylmethoxy)ethanol ..... 248
2,2,7,7-Tetramethyl-3,6-dioxa-2,7-disilaoctane ..... 249
2,2'-Bipyrazine ..... 172
2-[(Benzyloxy)methyl]furan ..... 236
2-[(*S*)-Pyrrolidine-2-carbonyl]-5-methyl-3-oxohexanenitrile ..... 247
2-[4-(1,3-Dithian-2-yl)butyl]-5-methylfuran ..... 170
2-{5-[(Benzyloxy)methyl]furan-2-yl}acetonitrile ..... 237
2-Benzyl-5-methylfuran ..... 219
2-Hexyl-5-methylfuran ..... 205
2-Hexylfuran ..... 222
2-Methyl-5-(2-nitrovinyl)furan ..... 211
2-Methyl-5-(pent-4-en-1-yl)furan ..... 201
2-Methyl-5-[(5-thiomethyl)pentyl]furan ..... 252

2-Methyl-5-{[2-(5-methylfuran-2-yl)cyclopentyl]methyl}furan....179
3,5-Hexadienoic acid....216
4-Hydroxy-4-methylpentanenitrile....175
4-Methyl-*N*-[2-(5-methylfuran-2-yl)ethyl]benzenesulfonamide....215
5-(5-Methylfuran-2-yl)pentan-1-ol....166
5-(5-Methylfuran-2-yl)pentanal....160
5-(5-Methylfuran-2-yl)pentanenitrile....170
5-Bromopentyl acetate....187
5-Hydroxypentyltriphenylphosphonium bromide....188
6-(5-Methylfuran-2-yl)hex-5-en-1-ol....188
6-(5-Methylfuran-2-yl)hex-5-enal....184
6-Hydroxy-6-methyl-2-phenyl-2*H*-pyran-3(6*H*)-one....232
6-Methyl-5-(3-methylbutanamido)-2,3-dihydro-1*H*-pyrrolizin-7-yl 3-methylbutanoate....250
Di[(1*H*)-imidazol-1-yl]methanethione, TCDI....253
Dimethyl 2-[5-(5-methylfuran-2-yl)pentylidene]malonate....163
Ethyl (2*E*)-8,11-dioxododeca-2,9-dienoate....173
Ethyl (*E*)-7-(5-methylfuran-2-yl)hept-2-enoate....158
Ethyl (*E*)-7-[(1*H*-imidazole-1-carbonothioyl)oxy]-7-(5-methylfuran-2-yl)hept-2-enoate....183
Ethyl (*E*)-7-hydroxy-7-(5-methylfuran-2-yl)hept-2-enoate....182
Ethyl 2-(5-methylfuran-2-yl)acetate....208
Ethyl 2-[(5-methylfuran-2-yl)cyclopentyl]acetate....159
Ethyl 2-[2-(furan-2-yl)cyclopent-1-en-1-yl]acetate....198
Ethyl 2-[2-(furan-2-yl)cyclopentyl]-2-(phenylselanyl)acetate....192
Ethyl 2-[2-(furan-2-yl)cyclopentyl]acetate....194
Ethyl 2-[2-(furan-2-yl)cyclopentyl]acetate-*d*....196
Ethyl 2-[2-(furan-2-yl)cyclopentylidene]acetate....191
Ethyl 7-(5-methylfuran-2-yl)hept-3-enoate....176
Iodoacetonitrile....210
Methyl 1-(furan-2-yl)-2-oxocyclopentane-1-carboxylate....189
*N*-(7a-Hydroxy-2-methyl-1-oxo-5,6,7,7a-tetrahydro-1*H*-pyrrolizin-3-yl)-3-

methylbutanamide ..... 234
*N*-(7a-Hydroxy-2-methyl-1-oxo-5,6,7,7a-tetrahydro-1*H*-pyrrolizin-3-yl)-3-methylpentanamide ..... 235
*N*-[2-(5-Methylfuran-2-yl)ethyl]acetamide ..... 213
*O*-[1-(5-Methylfuran-2-yl)pent-4-en-1-yl] 1*H*-imidazole-1-carbothioate ..... 199
*O*-[1,6-Bis(5-methylfuran-2-yl)hex-5-en-1-yl] 1H-imidazole-1-carbothioate ..... 186
*O*-Cyclohexyl 1*H*-imidazole-1-carbothioate ..... 201
*S*-Cyclohexyl 1*H*-imidazole-1-carbothioate ..... 202
*S*-Methyl *O*-[1-(5-methylfuran-2-yl)pent-4-en-1-yl] carbonodithioate ..... 200
TBTH-*d* ..... 252
*tert*-Butyl (*E*)-(3,6-dioxohept-4-en-1-yl)carbamate ..... 227
*tert*-Butyl [2-(5-methylfuran-2-yl)ethyl]carbamate ..... 213
*tert*-Butyl 3-oxo-2-(2-oxopropyl)pyrrolidine-1-carboxylate ..... 228
*tert*-Butyl(furan-2-ylmethoxy)dimethylsilane ..... 236
Tetrabutylammonium decatungstate (TBADT) ..... 175
Tris(2,2'-bipyrazyl)ruthenium(II) hexafluorophosphate ..... 157

# Index of Compounds by Number


Tris(2,2'-bipyrazyl)ruthenium(II) hexafluorophosphate (1.113) ..... 157
Ethyl (*E*)-7-(5-methylfuran-2-yl)hept-2-enoate (2.7) ..... 158
Tris(2,2'-bipyrazyl)ruthenium(II) hexafluorophosphate (2.8) ..... 159
Ethyl 2-[(5-methylfuran-2-yl)cyclopentyl]acetate (2.9) ..... 159
5-(5-Methylfuran-2-yl)pentanal (2.14) ..... 160
2-(Hex-5-en-1-yl)-5-methylfuran (2.15) ..... 162
Dimethyl 2-[5-(5-methylfuran-2-yl)pentylidene]malonate (2.16) ..... 163
2-(5-Chloropentyl)-5-methylfuran (2.17) ..... 164
2-(5-Iodopentyl)-5-methylfuran (2.18) ..... 165
5-(5-Methylfuran-2-yl)pentan-1-ol (2.19) ..... 166
2-(4-Chlorobutyl)-5-methylfuran (2.20) ..... 168
2-(4-Iodobutyl)-5-methylfuran (2.21) ..... 169
5-(5-Methylfuran-2-yl)pentanenitrile (2.22) ..... 170
2-[4-(1,3-Dithian-2-yl)butyl]-5-methylfuran (2.23) ..... 170
2,2'-Bipyrazine (2.24) ..... 172
Ethyl (2*E*)-8,11-dioxododeca-2,9-dienoate (2.25a) ..... 173
Tetrabutylammonium decatungstate (TBADT, 2.28) ..... 175
4-Hydroxy-4-methylpentanenitrile (2.29) ..... 175
Ethyl 7-(5-methylfuran-2-yl)hept-3-enoate (2.31) ..... 176
2-(Hex-5-yn-1-yl)-5-methylfuran (2.32) ..... 177
1,6-Bis-(5-methylfuran-2-yl)hex-1-ene (2.33) ..... 178
2-Methyl-5-{[2-(5-methylfuran-2-yl)cyclopentyl]methyl}furan (2.42) ..... 179
1-(5-Methylfuran-2-yl)hex-5-en-1-ol (3.6) ..... 181
Ethyl (*E*)-7-hydroxy-7-(5-methylfuran-2-yl)hept-2-enoate (3.7) ..... 182
Ethyl (*E*)-7-[(1*H*-imidazole-1-carbonothioyl)oxy]-7-(5-methylfuran-2-yl)hept-2-enoate (3.8) ..... 183
6-(5-Methylfuran-2-yl)hex-5-enal (3.9) ..... 184
1,6-Bis(5-methylfuran-2-yl)hex-5-en-1-ol (3.10) ..... 185
*O*-[1,6-Bis(5-methylfuran-2-yl)hex-5-en-1-yl]-[1*H*]-imidazole-1-carbothioate (3.11) 186
5-Bromopentyl acetate (3.12) ..... 187
5-Hydroxypentyltriphenylphosphonium bromide (3.14) ..... 188
6-(5-Methylfuran-2-yl)hex-5-en-1-ol (3.15) ..... 188
Methyl 1-(furan-2-yl)-2-oxocyclopentane-1-carboxylate (3.19) ..... 189
2-(Furan-2-yl)cyclopentan-1-one (3.20) ..... 190

Ethyl 2-[2-(furan-2-yl)cyclopentylidene]acetate (3.21).....191
Ethyl 2-[2-(furan-2-yl)cyclopentyl]-2-(phenylselanyl)acetate (3.22).....192
Ethyl 2-[2-(furan-2-yl)cyclopentyl]acetate (3.23).....194
Ethyl 2-[2-(furan-2-yl)cyclopentyl]acetate-*d* (3.23-d).....196
Ethyl 2-[2-(furan-2-yl)cyclopent-1-en-1-yl]acetate (3.24).....198
1-(5-Methylfuran-2-yl)pent-4-en-1-ol (3.28).....199
*O*-[1-(5-Methylfuran-2-yl)pent-4-en-1-yl] 1*H*-imidazole-1-carbothioate (3.29).....199
*S*-Methyl *O*-[1-(5-methylfuran-2-yl)pent-4-en-1-yl] carbonodithioate (3.30).....200
2-Methyl-5-(pent-4-en-1-yl)furan (3.31).....201
*O*-Cyclohexyl 1*H*-imidazole-1-carbothioate (3.33).....201
*S*-Cyclohexyl 1*H*-imidazole-1-carbothioate (3.34).....202
(*E*)-9-(1,3-Dithian-2-yl)-non-3-ene-2,5-dione [(*E*)-4.1a].....204
2-Hexyl-5-methylfuran (4.2).....205
(*E*)-2,5-Dioxoundec-3-ene [(*E*)-4.3a].....206
2-(5-Methylfuran-2-yl)ethan-1-ol (4.4).....206
2-(2-Oxopropyl)-dihydrofuran-3(2*H*)-one (4.5c).....207
Ethyl 2-(5-methylfuran-2-yl)acetate (4.6).....208
2-(5,5-Difluoropentyl)-5-methylfuran (4.7).....208
(*E*)-10,10-Difluorodec-3-ene-2,5-dione [(*E*)-4.8a].....209
Iodoacetonitrile (4.9).....210
2-(5-Methylfuran-2-yl)acetonitrile (4.10).....210
2-Methyl-5-(2-nitrovinyl)furan (4.11).....211
2-(5-Methylfuran-2-yl)ethan-1-amine (4.12).....212
*N*-[2-(5-Methylfuran-2-yl)ethyl]acetamide (4.13).....213
*tert*-Butyl [2-(5-methylfuran-2-yl)ethyl]carbamate (4.14).....213
4-Methyl-*N*-[2-(5-methylfuran-2-yl)ethyl]benzenesulfonamide (4.15).....215
3,5-Hexadienoic acid (4.16).....216
(*E*)-Hexa-3,5-dien-1-ol (4.17).....217
(*E*)-2-(Hexa-3,5-dien-1-yl)-5-methylfuran (4.18).....217
(*E*)-6-Iodohexa-1,3-diene (4.19).....218
2-Benzyl-5-methylfuran (4.20).....219
2-(Cyclopropylmethyl)-5-methylfuran (4.21).....220
2-(Cyclopropylmethyl)-5-hexylfuran (4.22).....221
2-Hexylfuran (4.23).....222
2-(5-Hexylfuran-2-yl)ethan-1-ol (4.24).....222

(*E*)-Undeca-3,10-diene-2,5-dione [(*E*)-4.25a] ..... 224
(*E*)-9-Chloronon-3-ene-2,5-dione [(*E*)-4.26a] ..... 225
(*E*)-Undec-3-en-10-yne-2,5-dione [(*E*)-4.27a] ..... 225
(*E*)-*N*-(3,6-Dioxohept-4-en-1-yl)acetamide [(*E*)-4.28a] ..... 226
1-Acetyl-2-(2-oxopropyl)pyrrolidin-3-one (4.28c) ..... 226
*tert*-Butyl (*E*)-(3,6-dioxohept-4-en-1-yl)carbamate [(*E*)-4.29a] ..... 227
*tert*-Butyl 3-oxo-2-(2-oxopropyl)pyrrolidine-1-carboxylate (4.29c) ..... 228
(*E*)-*N*-(3,6-Dioxohept-4-en-1-yl)-4-methylbenzenesulfonamide [(*E*)-4.30a] ..... 228
2-(2-Oxopropyl)-1-tosylpyrrolidin-3-one (4.30c) ..... 229
1-Cyclopropylundec-3-ene-2,5-dione (4.33a) ..... 230
(*E*)-4-Oxodec-2-enal [(*E*)-4.34a] ..... 231
(*E*)-1-Hydroxydodec-4-ene-3,6-dione [(*E*)-4.35a] ..... 232
6-Hydroxy-6-methyl-2-phenyl-2*H*-pyran-3(6*H*)-one (4.39) ..... 232
*N*-(7a-Hydroxy-2-methyl-1-oxo-5,6,7,7a-tetrahydro-1*H*-pyrrolizin-3-yl)-3-methylbutanamide (Legonmycin A, 5.11) ..... 234
*N*-(7a-Hydroxy-2-methyl-1-oxo-5,6,7,7a-tetrahydro-1*H*-pyrrolizin-3-yl)-3-methylpentanamide (Legonmycin B, 5.12) ..... 235
*tert*-Butyl(furan-2-ylmethoxy)dimethylsilane (5.60) ..... 236
2-[(Benzyloxy)methyl]furan (5.61) ..... 236
2-{5-[(Benzyloxy)methyl]furan-2-yl}acetonitrile (5.64) ..... 237
(*S*)-1-Benzylproline benzyl ester (5.69) ..... 238
(*S*)-2-(Methoxycarbonyl)-pyrrolidin-1-ium chloride (5.70) ..... 238
(*S*)-Methyl 1-triphenylmethylpyrrolidine-2-carboxylate (5.71) ..... 239
(*S*)-1-*tert*-Butyloxycarbonyl-2-methoxycarbonylpyrrolidine (5.72) ..... 239
(*S*)-Methyl 1-benzylpyrrolidine-2-carboxylate (5.74) ..... 240
(*S*)-Methyl 1-(3-methylbutanoyl)pyrrolidine-2-carboxylate (5.75) ..... 241
(*S*)-2-Methyl-3-oxo-3-(1-tritylpyrrolidin-2-yl)propanenitrile (5.76) ..... 242
(*S*)-*tert*-Butyl 2-(2-cyanopropanoyl)pyrrolidine-1-carboxylate (5.77) ..... 243
(*S*)-2-Methyl-3-[1-(3-methylbutanoyl)pyrrolidin-2-yl]-3-oxopropanenitrile (5.78) ..... 244
2-(Benzyloxy)-6-[1-benzyl-(*S*)-pyrrolidin-2-yl]-2-ethyl-5-methyl-[2*H*]-1,3-oxazin-4-amine (5.79) ..... 245
1-[2-(4-Amino-2-ethyl-2-hydroxy-5-methyl-[2*H*]-1,3-oxazin-6-yl)-(*S*)-pyrrolidin-1-yl]-3-methylbutan-1-one (5.81) ..... 246
2-[(*S*)-Pyrrolidine-2-carbonyl]-5-methyl-3-oxohexanenitrile (5.85) ..... 247
2-(Triphenylmethoxy)ethanol (5.86) ..... 248
2,2,7,7-Tetramethyl-3,6-dioxa-2,7-disilaoctane (5.88) ..... 249

(*S*)-3-Amino-2-methyl-5,6,7,7a-tetrahydro-1*H*-pyrrolizin-1-one hydrochloride (5.91) .....249
6-Methyl-5-(3-methylbutanamido)-2,3-dihydro-1*H*-pyrrolizin-7-yl 3-methyl-butanoate (5.94).....250
TBTH-*d*.....252
2-Methyl-5-[(5-thiomethyl)pentyl]furan.....252
Di[(1*H*)-imidazol-1-yl]methanethione, TCDI .....253

# Chapter 1

**Tris(2,2'-bipyrazyl)ruthenium(II) hexafluorophosphate (1.113)**

To a solution of 2,2'-bipyrazine **2.24** (400 mg, 2.53 mmol) in ethylene glycol (15 mL) was added $RuCl_3 \cdot xH_2O$ (165 mg, 0.625 mmol, *x* assumed to be 3). The reaction mixture was heated to 170 °C under $N_2$ for 28 h. The mixture was then cooled to rt and diluted with sat. aq. $KPF_6$ (9 mL) and stirred for 1 h 30 min. The mixture was filtered, and the resulting brown solid was washed with water, then purified by column chromatography (alumina, acetonitrile) to afford the title compound as a scarlet powder (269 mg, 50%).

Data are consistent with literature values: (*269*) $R_f$ 0.30 (1 : 1 methanol : acetonitrile); $^1$H NMR (400 MHz, $CD_3CN$) δ 9.78 (d, *J* = 1.0 Hz, 6H, H-3), 8.64 (d, *J* = 3.0 Hz, 6H, H-5), 7.83 (dd, *J* = 3.0, 1.0 Hz, 6H, H-6);$^{13}$C NMR (101 MHz, $CD_3CN$) δ 151.2 (C-2), 149.7 (C-5), 148.0 (C-3), 146.4 (C-6); mp >300 °C; UV (acetonitrile) $\lambda_{max,abs}$ 237 (log $\varepsilon$ 4.34), 292 (log $\varepsilon$ 4.73), 341sh, 413sh, 440 nm (log $\varepsilon$ 4.16) [lit. (*399*) 240 (log $\varepsilon$ 4.30), 291 (log $\varepsilon$ 4.71), 440 nm (log $\varepsilon$ 4.11)].

# Chapter 2

**Ethyl (*E*)-7-(5-methylfuran-2-yl)hept-2-enoate (2.7)**

Masamune–Roush olefination: To a suspension of LiCl (64.0 mg, 1.51 mmol) in dry acetonitrile (6 mL) at rt and under Ar was added sequentially triethyl phosphonoacetate (145 µL, 722 µmol) and DBU (110 µL, 722 µmol). The mixture was stirred for 10 min, after which time a solution of aldehyde **2.14** (100 mg, 602 µmol) in dry acetonitrile (300 µL) was added. The mixture was stirred at rt for 16 h, then diluted with $H_2O$ (60 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried over $Na_2SO_4$ and concentrated to afford the *title compound* as a geranium-scented colourless oil (125 mg, 88%).

Olefin metathesis with ethyl acrylate: To a solution of 2-(hex-5-en-1-yl)-5-methylfuran **2.15** (200 mg, 846 µmol) in toluene (7 mL) was added ethyl acrylate (260 µL, 2.57 mmol). The mixture was deoxygenated by bubbling Ar through for 10 min. H-G Ⅱ (33 mg, 52.3 µmol) was added and the mixture heated to reflux on a preheated oil bath for 45 min, after which time the mixture was purified directly by column chromatography (1 : 0 – 9 : 1 PE : ether) to afford the *title compound* as a colourless oil (143 mg, 71%).

$R_f$ 0.65 (4 : 1 PE : ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.95 (dt, $J$ = 15.5, 7.0 Hz, 1H, H-3), 5.85 – 5.78 (m, 2H, Fn-3 and Fn-4), 5.81 (dt, J = 15.5, 1.5 Hz, 1H, H-2), 4.18 (q, $J$ = 7.0 Hz, 2H, O$CH_2$CH$_3$), 2.57 (t, $J$ = 7.5 Hz, 2H, H-7), 2.28 – 2.17 (m, 2H, H-4), 2.25 (s, 3H, Fn-Me), 1.71 – 1.58 (m, 2H, H-6), 1.51 (dqd, $J$ = 8.5, 7.0, 1.0 Hz, 2H, H-5), 1.28 (t, $J$ = 7.0 Hz, 3H, OCH$_2$C$H_3$); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 166.8 (C-1), 154.1

(Fn-2 or Fn-5), 150.4 (Fn-2 or Fn-5), 149.1 (C-3), 121.6 (C-2), 105.9 (Fn-3 or Fn-4), 105.6 (Fn-3 or Fn-4), 60.3 (O*C*$H_2CH_3$), 32.0 (C-4), 27.9 (C-7), 27.8 (C-6), 27.6 (C-5), 14.4 (OCH$_2$*C*H$_3$), 13.6 (Fn-Me); IR (ATR) ν 2934w (C–H), 1718s (C=O), 1654w (C=C), 1178s, 779s; HRMS (APCI, $NH_3$) found 237.1484, calc. for $C_{14}H_{20}O_3$ $[M+H]^+$ 237.1485.

**Tris(2,2'-bipyrazyl)ruthenium(II) hexafluorophosphate (2.8)**

See page 157.

**Ethyl 2-[(5-methylfuran-2-yl)cyclopentyl]acetate (2.9)**

To a solution of compound **3.8** (18.0 mg, 50.5 μmol) in benzene (7 mL) was added a solution of AIBN (0.83 mg, 5.05 μmol) in benzene (9 mL). The mixture was deoxygenated by bubbling Ar through for 10 min and TBTH (16.2 mg, 55.6 μmol) added. The mixture was heated to reflux under Ar for 5 h 30 min, and the mixture was then concentrated and purified by column chromatography [9 : 1 (w/w) $SiO_2$/KF, 1 : 0 – 47 : 3 PE : ether] to afford a mixture of **2.7** (<10%) and the diastereomers (11 : 10 *trans* : *cis* by NMR) of the *title compound* as a colourless oil (4.1 mg, 37%).

$R_f$ 0.30 (9 : 1 PE : ether); $^1$H NMR (500 MHz, $C_6D_6$, diastereomers assigned by nOe analysis, see Appendix 2: Nuclear Overhauser Effect Analysis of Compound **2.9**) δ 5.88 (d, *J* = 3.0 Hz, 0.5H, *trans*-Fn-3), 5.80 (d, *J* = 3.0 Hz, 0.5H, *cis*-Fn-3), 5.78 – 5.76 (m, 0.5H, *trans*-Fn-4), 5.76 – 5.73 (m, 0.5H, *cis*-Fn-4), 3.95 (q, *J* = 7.0 Hz, 1H, *cis*-OC$H_2$CH$_3$), 3.91 (q, *J* = 7.0 Hz, 1H, *trans*-OC$H_2$CH$_3$), 3.22 (q, *J* = 7.5 Hz, 0.5H, *cis*-cyclopentyl-2), 2.68 – 2.61 (m, 0.5H, *cis*-cyclopentyl-1), 2.60 (d, *J* = 4.0 Hz, 0.5H, *trans*-H-2), 2.58 – 2.47 (m, 1H, *trans*-cyclopentyl-1 and *trans*-cyclopentyl-2), 2.23 (dd, *J* = 16.0, 6.5 Hz, 0.5H, *cis*-H-2), 2.15 – 2.11 (m, 0.5H, *trans*-H-2), 2.09 (d, *J* = 4.0 Hz, 0.5H,

*cis*-H-2), 2.08 – 2.04 (m, 0.5H, *trans*-cyclopentyl-4), 2.02 (d, $J$ = 1.0 Hz, 1.5H, *trans*-Fn-Me), 2.01 (d, $J$ = 1.0 Hz, 1.5H, *cis*-Fn-Me), 1.86 (m, 0.5H, *trans*-cyclopentyl-5), 1.82 – 1.75 (m, 2H, *cis*-cyclopentyl-3 and *trans*-cyclopentyl-4 and *cis*-cyclopentyl-5), 1.75 – 1.66 (m, 0.5H, *cis*-cyclopentyl-4), 1.61 – 1.52 (m, 0.5H, *trans*-cyclopentyl-3), 1.52 – 1.42 (m, 1H, *trans*-cyclopentyl-3 and *cis*-cyclopentyl-4), 1.42 – 1.31 (m, 0.5H, cis-cyclopentyl-3), 1.28 – 1.16 (m, 0.5H, *trans*-cyclopentyl-5), 0.95 (t, $J$ = 7.0 Hz, 1.5H, *cis*-$OCH_2CH_3$), 0.93 (t, $J$ = 7.0 Hz, 1.5H, *trans*-$OCH_2CH_3$); $^{13}$C NMR (126 MHz, $C_6D_6$) δ 172.7 (*cis* C-1), 172.3 (*trans* C-1), 156.3 (*trans*-Fn-2), 155.9 (*trans*-Fn-2), 150.7 (Fn-5), 150.6 (Fn-5), 107.0 (*cis*-Fn-3), 106.3 (Fn-4), 106.2 (Fn-4), 105.7 (*trans*-Fn-3), 60.0 ($OCH_2CH_3$), 59.9 ($OCH_2CH_3$), 45.3 (*trans*-cyclopentyl-2), 42.4 (*trans*-cyclopentyl-1), 41.8 (*cis*-cyclopentyl-2), 40.6 (*cis*-cyclopentyl-1), 39.3 (*trans* C-2), 36.5 (*cis* C-2), 32.3 (*trans*-cyclopentyl-4), 32.1 (*trans*-cyclopentyl-5), 31.5 (*cis*-cyclopentyl-5), 29.9 (*cis*-cyclopentyl-3), 23.9 (*trans*-cyclopentyl-3), 23.8 (*cis*-cyclopentyl-4), 14.3 (*cis*-$OCH_2CH_3$), 14.3 (*trans*-$OCH_2CH_3$), 13.5 (Fn-Me); IR (ATR) ν 2956m (C–H), 1735s (C=O), 1178m, 1023m, 781m; HRMS (APCI, $NH_3$) found 237.1492, calc. for $C_{14}H_{20}O_3$ $[M+H]^+$ 237.1496.

**5-(5-Methylfuran-2-yl)pentanal (2.14)**

Reduction of nitrile: To a solution of nitrile **2.22** (2.20 g, 13.5 mmol) in dry DCM (270 mL) at −78 °C and under $N_2$ was added dropwise DIBAL (16.2 mL, 1.0 M in hexanes, 16.2 mmol). When addition was complete, sat. aq. sodium potassium tartrate (50 mL) was added and the mixture stirred for 1 h at rt, after which time the aqueous phase was washed with DCM (200 mL). The organic phases were combined, dried over

$MgSO_4$ and concentrated. The residue was then purified by column chromatography (1 :0 – 0 : 1 PE : ether) to give the title compound as a pale yellow oil (0.96 g, 43%).

Kornblum oxidation of iodide: A suspension of $NaHCO_3$ (10.1 g, 120 mmol) in DMSO (60 mL)[lxxii] was heated to 110 °C under $N_2$, and a solution of iodide **2.18** (8.34 g, 30.0 mmol) in DMSO (7 mL) was added. The mixture was stirred for 49 min and filtered. The residue was washed with ether (50 mL) and DCM (30 mL), and the combined phases washed with $H_2O$ (3 ×50 mL). The combined aqueous phases were back-extracted with DCM (3 ×50 mL) The combined organic phases were washed with water (2 × 20 mL) and brine (20 mL), dried over $Na_2SO_4$, and concentrated. The residue was purified by column chromatography (99 : 1 : 0 – 74 : 1 : 25 cyclohexane : TEA : ether) to give the title compound as a pale yellow oil (3.11 g, 62%).

TEMPO/BAIB oxidation of alcohol: To a solution of BAIB (1.15 g, 3.57 mmol) in DCM (20 mL) was added $NaHCO_3$ (500 mg, 5.95 mmol). The mixture was cooled to 0 °C and stirred in darkness. A solution of alcohol **2.19** (501.4 mg, 2.98 mmol) in DCM (5 mL) was added, followed by a solution of TEMPO (4.7 mg, 30 μmol) in DCM (5 mL). The mixture was stirred at 0 °C in darkness for 1 h. An additional portion of TEMPO (12.1 mg, 0.07 mmol) was added and the mixture warmed to rt. The mixture was stirred for an additional 5 h, and the reaction was then quenched by the addition of sat. aq. $Na_2S_2O_3$ (5 mL). The aqueous phase was extracted with DCM (10 mL) and ethyl acetate (5 mL). The combined organic phases were washed with brine (10 mL) and the aqueous phase washed with ethyl acetate (5 mL). The combined organic phases were dried over $Na_2SO_4$, filtered and concentrated. The residue was then purified by column

[lxxii] All DMSO used in this experiment was dried by distillation and by subsequent storage over $CaH_2$.

chromatography (1 : 0 – 4 : 1 PE : ether) to afford the title compound as a slightly pink oil (286 mg, 58%).

Cleavage of dithiane: To dithiane **2.23** (1.02 g, 0.396 mmol) was added sequentially acetonitrile (9 mL), $H_2O$ (1 mL), $NaHCO_3$ (3.61 g, 42.9 mmol), and $CH_3I$ (2.45 mL, 39.3 mmol). The mixture was stirred under $N_2$ at rt for 20 h and concentrated. The residue was partitioned between $CHCl_3$ (10 mL) and brine (3 mL). The brine was then extracted with $CHCl_3$ (3 × 10 mL) and the combined organic phases dried over $Na_2SO_4$, filtered, and concentrated to afford the title compound as a yellow oil (185 mg, 28%).

Data are consistent with literature values: (*400*) $R_f$ 0.40 (4 : 1 PE : ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 9.76 (t, *J* = 2.0 Hz, 1H, H-1), 5.85 – 5.80 (m, 2H, Fn-3 and Fn-4), 2.59 (t, *J* = 7.0 Hz, 2H, H-5), 2.45 (td, *J* = 7.0, 2.0 Hz, 2H, H-2), 2.24 (d, *J* = 1.0 Hz, 3H, Me), 1.72 – 1.63 (m, 4H, H-3 and H-4); $^1$H NMR (400 MHz, Acetone-$d_6$) δ 9.73 (t, *J* = 1.5 Hz, 1H, H-1), 5.89 (d, *J* = 3.0 Hz, 1H, Fn-3), 5.86 (dq, *J* = 3.0, 1.0 Hz, 1H, Fn-4), 2.57 (t, *J* = 7.0 Hz, 2H, H-5), 2.53 – 2.42 (m, 2H, H-2), 2.20 (d, *J* = 1.0 Hz, 3H, Me), 1.70 – 1.57 (m, 4H, H-3 and H-4); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 202.7, (C-1), 153.9 (Fn-5), 150.5 (Fn-2), 105.9 and 105.7 (Fn-3 and Fn-4), 43.8 (C-2), 27.9 (C-5), 27.8 (C-4), 21.7 (C-3), 13.7 (Me).

**2-(Hex-5-en-1-yl)-5-methylfuran (2.15)**

To a solution of 2-methylfuran (610 µL, 6.76 mmol) in THF (6.10 mL) at −78 °C and under Ar was added dropwise butyllithium (2.54 mL, 1.6 M in hexanes, 3.66 mmol). The mixture was warmed to 0 °C and stirred for 3 h. A 600 µL aliquot of the mixture was

removed,[lxxiii] and 6-bromo-1-hexene (497 mg, 3.05 mmol) was added *via* syringe. The mixture warmed to rt and stirred for 15 h, then quenched by addition of sat. aq. $NH_4Cl$ (6 mL) The mixture was diluted with $H_2O$ (50 mL) and extracted with DCM (3 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated to afford the title compound as a yellow oil (414 mg, 83%).

$R_f$ 0.15 (4 : 1 PE : toluene); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.88 – 5.73 (m, 3H, Fn-3, Fn-4, and H-5), 5.01 (dq, *J* = 17.0, 1.5 Hz, 1H, H-6 *trans* to H-5), 4.94 (ddt, *J* = 10.0, 2.5, 1.5 Hz, 1H, H-6 *cis* to H-5), 2.57 (t, *J* = 7.5 Hz, 2H, H-2), 2.25 (s, 3H, Fn-Me), 2.11 – 2.04 (m, 2H, H-4), 1.68 – 1.59 (m, 2H, H-2), 1.49 – 1.40 (m, 2H, H-3); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 154.7 (Fn-2), 150.2 (Fn-5), 139.0 (C-5), 114.6 (C-6), 105.9 (Fn-3), 105.3 (Fn-4), 33.7 (C-4), 28.6 (C-1), 28.1 (C-3), 27.8 (C-2), 13.7 (Fn-Me); IR (ATR) ν 2928s, 2859m, 1570m, 1220s, 1020m, 911m, 779s; HRMS not observed.

**Dimethyl 2-[5-(5-methylfuran-2-yl)pentylidene]malonate (2.16)**

To a solution of piperidine (6.0 µL, 0.06 mmol) in dry DCM (0.25 mL) at rt and under Ar was added a solution of AcOH (3.0 µL, 0.06 mmol) in dry DCM (0.25 mL). Dimethyl malonate (70 µL, 0.66 mmol) was added to the mixture, followed dropwise by a solution of aldehyde **2.14** (100 mg, 0.602 mmol) in dry DCM (0.50 mL). The mixture was stirred for 30 min at rt. A portion of 4 Å molecular sieves (87.5 mg) was added and the mixture stirred at rt for 17 h. The mixture was partitioned between DCM (5 mL) and $H_2O$ (5 mL) and the aqueous phase extracted with ethyl acetate (2 × 5 mL). The combined organic phases were dried over $Na_2SO_4$, filtered and concentrated and the residue purified

[lxxiii] For use in another reaction.

by column chromatography (1 : 0 – 4 : 1 PE : ether) to afford the *title compound* contaminated with dimethyl malonate. The latter was removed under high vacuum to afford the *title compound* as a colourless oil (17.8 mg, 11%).

$R_f$ 0.20 (9 : 1 PE : ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.96 (t, *J* = 7.5 Hz, 1H, H-1′), 5.76 (app s, 2H, Fn-3 and Fn-4), 3.76 (s, 3H, $CO_2$*Me*), 3.71 (s, 3H, $CO_2$*Me*), 2.50 (t, *J* = 7.5 Hz, 2H, H-5′), 2.26 (q, *J* = 7.5 Hz, 2H, H-2′), 2.18 (s, 3H, Fn-Me), 1.62 – 1.53 (m, 2H, H-4′), 1.51 – 1.42 (m, 2H, H-3′); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 166.0 (*C*$O_2$Me), 164.5 (*C*$O_2$Me), 154.0 (Fn-2), 150.4 (Fn-5), 150.3 (C-1′), 128.2 (C-2), 105.9 (Fn-3), 105.6 (Fn-4), 52.5 ($CO_2$*Me*), 52.4 ($CO_2$*Me*), 29.7 (C-5′), 27.8 (C-4′ and C-3′), 27.8 (C-2′), 13.6 (Fn-Me); IR (ATR) ν 2951w (C–H), 1729s (C=O), 1436m, 1256m, 1222s, 1062w, 1020w, 738w; HRMS (ESI$^+$) found 303.1205, calc. for $C_{15}H_{20}O_5$ $[M+Na]^+$ 303.1203.

**2-(5-Chloropentyl)-5-methylfuran (2.17)**

To a solution of 2-methylfuran (7.60 mL, 84.2 mmol) in THF (60 mL) at −78 °C and under $N_2$ was added butyllithium (32.0 mL, 1.6 M in hexanes, 56.0 mmol) dropwise. The reaction mixture was warmed to 0 °C and stirred for 2 h, after which time 1-chloro-5-iodopentane (10.0 g, 43.0 mmol) was added as a solution in THF (60 mL). The mixture was stirred for a further 3 h 40 min at 0 °C and then quenched by addition of sat. aq. $NH_4Cl$ (50 mL). The mixture was extracted with ethyl acetate (3 × 50 mL) and the combined organic phases dried over $MgSO_4$, filtered and concentrated to give the title compound as a brown oil (8.8 g, 96%).

Data are consistent with literature values: (*401*) $R_f$ 0.40 (PE); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.84 (s, 2H, Fn), 3.54 (t, *J* = 6.5 Hz, 2H, H-5), 2.58 (t, *J* = 7.5 Hz, 2H, H-1), 2.25 (s, 3H, Me), 1.80 (m, 2H, H-4), 1.71 – 1.58 (m, 2H, H-2), 1.55 – 1.42 (m, 2H, H-3); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 154.3 (Fn-2), 150.4 (Fn-5), 105.9, 105.5 (Fn-3 and Fn-4), 45.1 (C-5), 32.5 (C-4), 28.0 (C-3), 27.6 (C-2), 26.6 (C-1), 13.7 (Me).

**2-(5-Iodopentyl)-5-methylfuran (2.18)**

To a solution of furan **2.17** (8.73 g, 46.8 mmol) in acetone (47 mL) was added NaI (14.0 g, 93.5 mmol). The mixture was stirred at reflux under $N_2$ for 15 h, then concentrated and the residue taken up in $H_2O$ (50 mL). The mixture was extracted with ether (2 × 50 mL) and the combined organic phases washed with sat. aq. $Na_2S_2O_3$ (10 mL) and brine (10 mL), then dried over $MgSO_4$ and concentrated to give the *title compound* as a pale brown oil. (11.5 g, 89%).

$R_f$ 0.40 (PE); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.88 – 5.81 (m, 2H, Fn-3 and Fn-4), 3.19 (t, *J* = 7.0 Hz, 2H, H-5), 2.58 (t, *J* = 7.5 Hz, 2H, H-1), 2.26 (s, 3H, Me), 1.86 (p, *J* = 7.0 Hz, 2H, H-4), 1.65 (p, *J* = 7.5 Hz, 2H, H-2), 1.51 – 1.40 (m, 2H, C-3); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 154.1 (Fn-2 or Fn-5), 150.3 (Fn-2 or Fn-5), 105.9 (Fn-3 or Fn-4), 105.5 (Fn-3 or Fn-4), 33.4 (C-4), 30.1 (C-3), 27.9 (C-1), 27.2 (C-2), 13.6 (Me), 7.0 (C-5); IR (ATR) ν 2932s, 2859m, 1570m, 1218s, 1020s, 781s; HRMS (APCI, $NH_3$) found 279.0241, calc. for $C_{10}H_{15}IO$ $[M+H]^+$ 279.0240.

**5-(5-Methylfuran-2-yl)pentan-1-ol (2.19)**

To a suspension of NaH (60% dispersion in mineral oil, 5.00 g, 125 mmol) in PE (20 mL) and dry THF (150 mL)[lxxiv] under Ar at 0 °C was added a solution of 1,5-pentanediol (10.0 g, 96 mmol) in dry THF (150 mL) *via* cannula over *ca.* 2 min. The mixture was warmed to rt and stirred for 45 min. The mixture was cooled to 0 °C and a solution of *tert*-butylchlorodimethylsilane (14.5 g, 96 mmol) in dry THF (60 mL) was added and the mixture stirred for 45 min. The reaction was then quenched by addition of sat. aq. $Na_2CO_3$ (50 mL) and $H_2O$ (150 mL). The mixture was extracted with ether (4 × 100 mL) and the combined organic phases washed with brine (60 mL), dried over $Na_2SO_4$, filtered, and concentrated to afford 5-[(*tert*-butyldimethylsilyl)oxy]pentan-1-ol as a pale orange oil (18.9 g, 90%).

Data are consistent with literature values: (*402*) $R_f$ 0.15 (10% ether/PE); $^1$H NMR (400 MHz, $CDCl_3$) δ 3.68 – 3.64 (m, 2H, H-1), 3.62 (t, $J$ = 6.5 Hz, 2H, H-5), 1.64 – 1.49 (m, 4H, H-2, H-4), 1.45 – 1.35 (m, 2H, H-3), 0.89 (s, 9H, $CMe_3$), 0.05 (s, 6H, $SiMe_2$).

To triphenylphosphine (13.0 g, 49.4 mmol) and imidazole (4.21 mg, 61.8 mmol) was added a solution of 5-[(*tert*-butyldimethylsilyl)oxy]pentan-1-ol (9.00 g, 41.2 mmol) in dry ether (330 mL) and dry acetonitrile (83 mL). The mixture was cooled to 0 °C and $I_2$ (12.9 g, 50.8 mmol) was added in portions of *ca.* 500 mg over 50 min; the mixture stirred for a further 30 min after addition was complete. The mixture was quenched by adding sat. aq. $Na_2S_2O_3$ until the mixture decolourised. The organic phase was then washed with $H_2O$ (100 mL). This portion of water was extracted with PE (3 × 20 mL)

[lxxiv] THF used in the preparation of 5-[(*tert*-butyldimethylsilyl)oxy]pentan-1-ol was used as received from the SPS-800 system.

and all organic phases were then combined, washed with brine (50 mL) and concentrated. The residue was purified by redissolving in 9 : 1 PE : DCM and passing through a short silica plug, affording *tert*-butyl[(5-iodopentyl)oxy]dimethylsilane as a colourless oil (10.3 g, 76%).

Data are consistent with literature values: (*402*) $R_f$ 0.75 (9 : 1 PE : ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 3.61 (t, *J* = 6.0 Hz, 2H, H-1), 3.19 (t, *J* = 7.0 Hz, 2H, H-5), 1.84 (p, *J* = 7.0 Hz, 2H, H-4), 1.57 – 1.48 (m, 2H, H-2), 1.48 – 1.39 (m, 2H, H-3), 0.89 (s, 9H, $CMe_3$), 0.04 (s, 6H, $SiMe_2$); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 63.0 (C-1), 33.5 (C-4), 31.8 (C-2), 27.1 (C-3), 25.8 (C*Me*$_3$), 18.5 (*C*$Me_3$), 4.6 (C-5), -5.1 ($SiMe_2$).

To a solution of 2-methylfuran (3.30 mL, 36.6 mmol) in THF (35 mL) at −78 °C and under Ar was added dropwise butyllithium (18.3 mL, 1.6 M in hexanes, 29.2 mmol) dropwise. The mixture was warmed to 0 °C and stirred for 3 h. The mixture was then cooled to −78 °C and a solution of *tert*-butyl[(5-iodopentyl)oxy]dimethylsilane (8.00 g, 24.4 mmol) in THF (14 mL) added dropwise. The mixture was allowed to warm to rt and stirred for 15 h, then quenched with sat. aq. $NH_4Cl$ (10 mL). The aqueous phase was extracted with ether (3 × 10 mL). The combined organic phases were washed with brine (5 mL), decolourised with activated charcoal, dried over $Na_2SO_4$ and concentrated to afford the *novel compound tert*-butyldimethyl{[5-(5-methylfuran-2-yl)pentyl]oxy}silane as a pale brown oil (6.14 g, 89%).

$R_f$ 0.80 (9 :1 PE : ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.83 (s, 2H, Fn-3 and Fn-4), 3.61 (t, *J* = 6.5 Hz, 2H, H-1), 2.61 – 2.50 (m, 2H, H-5), 2.25 (s, 3H, Fn-Me), 1.68 – 1.59 (m, 2H), 1.59 – 1.50 (m, 2H), 1.43 – 1.34 (m, 2H), 0.89 (s, 9H, $CMe_3$), 0.05 (s, 6H, $SiMe_2$); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 154.7 (Fn-2), 150.2 (Fn-5), 105.9 (Fn-3), 105.3

(Fn-4), 63.3 (C-1), 32.7(C-5), 28.2 (C-2), 28.2 (C-3), 26.1 (C*Me*$_3$), 25.6 (C-4), 18.5 (*C*Me$_3$), 13.7 (Fn-Me), -5.1 (SiMe$_2$); IR (ATR) ν 2928m, 2857s, 1254w, 1101m, 834s, 774s; HRMS (APCI, $NH_3$) found 283.2094, calc. for $C_{16}H_{28}O_2Si$ $[M+H]^+$ 283.2088.

To a solution of *tert*-butyldimethyl([5-(5-methylfuran-2-yl)pentyl]oxy)silane (6.00 g, 21.2 mmol) in THF (1 mL) was added TBAF (24.0 mL, 1.0 M in THF, 24.0 mmol). The mixture was stirred at rt for 19 h, then concentrated and the residue purified by column chromatography (1 : 0 – 7 : 3 PE : ether) to afford the title compound as a pale yellow oil (2.34 g, 66%).

Data are consistent with literature values: (*403*) $R_f$ 0.45 (PE); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.84 (s, 2H, Fn-3 and Fn-4), 3.65 (t, *J* = 6.5 Hz, 2H, H-1), 2.58 (t, *J* = 7.5 Hz, 2H, H-5), 2.25 (s, 3H, Fn-Me), 1.70 – 1.54 (m, 4H, H-2 and H-4), 1.49 – 1.34 (m, 2H, H-3), 1.26 (s, 1H, O*H*); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 154.5 (Fn-2), 150.3 (Fn-5), 105.9 (Fn-3), 105.4 (Fn-4), 63.1 (C-1), 32.6 (C-2), 28.1 (C-5), 28.1 (C-3), 25.5 (C-4), 13.7 (Fn-Me).

**2-(4-Chlorobutyl)-5-methylfuran (2.20)**

To a solution of 2-methylfuran (23.0 mL, 255 mmol) in THF (156 mL) at –78 °C and under Ar was added dropwise butyllithium (19.1 mL, 11.0 M in hexanes, 210 mmol). When addition was complete, the reaction mixture was warmed to 0 °C and stirred for 3 h, after which time 1-bromo-4-chlorobutane (23.1 mL, 200 mmol) was added. The mixture was warmed to rt and stirred overnight. The reaction was then quenched with $H_2O$ (5 mL) and sat. aq. $NH_4Cl$ (5 mL). Solid $NH_4Cl$ (6 g) was added slowly and washed in with $H_2O$ (20 mL) to afford a biphasic mixture. The organic phase was then

concentrated and partitioned between PE (200 mL) and $H_2O$ (100 mL). The aqueous phase from the quenched reaction was extracted with PE (2 × 50 mL) and ethyl acetate (50 mL). All organic phases were combined, washed with $H_2O$ (200 mL) and brine (30 mL), then dried over $MgSO_4$ and concentrated to give the title compound as an orange oil (32.8 g, 95%).

Data are consistent with literature values: (*401*) $R_f$ 0.80 (1 : 1 ethyl acetate : PE); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.94 – 5.77 (m, 2H, Fn-3 and Fn-4), 3.55 (t, $J$ = 6.5 Hz, 2H, H-4), 2.61 (t, $J$ = 7.0 Hz, 2H, H-1), 2.25 (s, 3H, Me), 1.91 – 1.68 (m, 4H, H-2 and H-3); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 153.7 (Fn-2), 150.5 (Fn-5), 105.9 (Fn-3 or Fn-4), 105.8 (Fn-3 or Fn-4), 44.9 (C-4), 32.1 (C-3), 27.4(C-2), 25.6 (C-1), 13.6 (Me).

**2-(4-Iodobutyl)-5-methylfuran (2.21)**

To a solution of chloride **2.20** (32.8 g, 190 mmol) in acetone (190 mL) was added NaI (57.0 g, 380 mmol). The mixture was placed under $N_2$ and heated to 80 °C for 18 h. The mixture was concentrated and the residue partitioned between $H_2O$ (200 mL) and PE (150 mL). The aqueous phase was extracted with PE (50 mL) and ether (50 mL). The combined organic phases were washed sequentially with $Na_2S_2O_3$, $H_2O$, and brine (20 mL each), then dried over $MgSO_4$, decolourised with activated charcoal, filtered, and concentrated to afford the *title compound* as an orange to brown soap-scented oil (45.1 g, 90%).

$R_f$ 0.45 (PE); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.90 – 5.79 (m, 2H, Fn), 3.20 (t, $J$ = 7.0 Hz, 2H, H-4), 2.60 (t, $J$ = 7.5 Hz, 2H, H-1), 2.25 (d, $J$ = 1.0 Hz, 3H, Me), 1.94 – 1.81 (m, 2H, $CH_2$), 1.79 – 1.65 (m, 2H, $CH_2$); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 153.7 (Fn-2 or

Fn-5), 150.5 (Fn-2 or Fn-5), 106.0 (Fn-3 or Fn-4), 105.8 (Fn-3 or Fn-4), 33.1 (C-2 or C-3), 29.2 (C-2 or C-3), 27.1 (C-1), 13.7 (*C*$H_3$), 6.6 (C-4); IR (ATR) ν 1569w, 1218m, 1020m, 778s; HRMS (APCI, $CH_4$) found 265.0072, calc. for $C_9H_{13}IO$ $[M+H]^+$ 265.0084.

**5-(5-Methylfuran-2-yl)pentanenitrile (2.22)**

To a solution of NaCN (1.33 g, 27.1 mmol) in DMSO (17 mL) at 80 °C and under $N_2$ was added a solution of furan **2.20** (4.25 g, 24.6 mmol) in DMSO (3.4 mL) dropwise and under vigorous stirring. The mixture was stirred at 80 °C for 5 h, after which time the reaction mixture was cooled, then diluted with $H_2O$ (150 mL) and extracted with ether (3 × 100 mL). The organic phases were combined and dried over $MgSO_4$, then filtered and concentrated under reduced pressure to give the title compound as a brown oil (2.21 g, 56%).

Data are consistent with literature values: (*400*) $R_f$ 0.60 (1: 1 ether : PE); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.86 (d, *J* = 3.0 Hz, 1H, Fn-3), 5.83 (dd, *J* = 3.0, 1.0 Hz, 1H, Fn-4), 2.61 (t, *J* = 7.0 Hz, 2H, H-5), 2.34 (t, *J* = 7.0 Hz, 2H, H-2), 2.24 (d, *J* = 1.0 Hz, 3H, Me), 1.83 – 1.62 (m, 4H, H-3, H-4); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 153.0 (Fn-2), 150.5 (Fn-5), 119.7 (C-1), 106.0 (Fn-3 or Fn-4), 105.9 (Fn-3 or Fn-4), 27.2 (C-5), 27.1 (C-4), 24.8 (C-3), 16.9 (C-2), 13.5 (Me).

**2-[4-(1,3-Dithian-2-yl)butyl]-5-methylfuran (2.23)**

To 1,3-dithiane (26.6 g, 221 mmol) was added THF (190 mL). The mixture was cooled to –40 °C and butyllithium (19 mL, 11.0 M in hexanes, 209 mmol) added dropwise. The temperature was controlled between –35 °C and –45 °C, and when addition was

complete, the pale yellow mixture was stirred for a further 3 h between –30 °C and –40 °C, after which time a solution of iodide **2.21** (50.0g, 189 mmol) in PE (15 mL) was added, keeping the temperature at or below –15 °C. The mixture was allowed to warm to rt and stirred for 20 h.[lxxv] The reaction was quenched by addition of water (5 mL) followed by a solution of $NH_4Cl$ (7.46 g, 140 mmol) in $H_2O$ (20 mL). The aqueous phase was extracted with ether (50 mL), while the organic phase of the reaction mixture was concentrated, combined with the organic extract of the aqueous phase, and partitioned between PE (150 mL) and $H_2O$ (100 mL). This aqueous phase was extracted with ether (50 mL) and the combined organic phases were dried over $MgSO_4$, decolourised with activated charcoal, filtered and concentrated to afford the *title compound* as a strongly garlic-scented pale yellow oil (47.4 g, containing *ca.* 8% w/w 1,3-dithiane, 90%). This material was used without further purification.

$R_f$ 0.25 (49 : 1 PE : ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.91 – 5.78 (m, 2H, Fn-3 and Fn-4), 4.04 (t, $J$ = 7.0 Hz, 1H, Dth-2), 2.94 – 2.76 (m, 4H, Dth-4,6), 2.57 (t, $J$ = 7.5 Hz, 2H, H-1), 2.25 (s, 3H, Me), 2.18 – 2.06 (m, 1H, Dth-5), 1.94 – 1.83 (m, 1H, Dth-5), 1.78 (q, $J$ = 7.0 Hz, 2H, H-4), 1.70 – 1.50 (m, 4H, H-2 and H-3); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 154.3 (Fn-2 or Fn-5), 150.3 (Fn-2 or Fn-5), 105.9 (Fn-3 or Fn-4), 105.5 (Fn-3 or Fn-4), 47.7 (Dth-1), 35.3 (C-4), 30.6 (Dth-4,6), 28.0 (C-1 or C-2 or C-3), 27.9 (C-1 or C-2 or C-3), 26.3 (C-1 or C-2 or C-3), 26.2 (Dth-5), 13.7 (Me); IR (ATR) 2934m (C–H), 2901m (C–H), 2858w (C–H), 1569m, 1453m, 1431m, 1422m, 1218m, 1019s, 778s; HRMS (CI, $CH_4$) found 257.1025, calc. for $C_{13}H_{20}OS_2$ $[M+H]^+$ 257.1028.

[lxxv] NMR analysis of the crude reaction mixture indicated full conversion after 3 h.

**2,2'-Bipyrazine (2.24)**

Pd-catalysed homocoupling of 2-iodopyrazine: (*269*) To a solution of iodopyrazine (4.30 g, 20.9 mmol), $Pd(OAc)_2$ (227 mg, 1.01 mmol), 2-propanol (3.20 mL, 41.8 mmol) and DMF (60 mL) under $N_2$ was added $K_2CO_3$ (4.32 g, 31.3 mmol). The reaction mixture was then stirred at 100 °C for 2 h. The mixture was diluted with brine (300 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The residue was then dried under high vacuum and purified by trituration with PE to give the title compound as maroon crystals (1.12 g, 68%).

Oxidative coupling of organocuprate: (*404*) To a suspension of $CuCl_2$ (anhydrous, 9.86 g, 73.3 mmol) in *n*-butanol (250 mL), at reflux and under $N_2$, was added a solution of TMEDA (8.50 g, 73.1 mmol) in *n*-butanol (25 mL). Reflux was continued for a further 12 min; the solution was then cooled to rt and a solid precipitated by the addition of hexane. The precipitates obtained from from addition of successive portions of hexane were recovered by filtration and dried under high vacuum to afford the TMEDA complex of $CuCl_2$ (15.0 g, 85 %) as a turquoise solid.

To a vigorously stirred solution of $CuCl_2$·TMEDA (10.0 g, 39.9 mmol) in THF (100 mL) at 0 °C and under Ar, was added butyllithium (16.0 mL, 2.5 M in hexanes, 40.0 mmol). A solution of H-TMP (13.6 mL, 80.6 mmol) in THF (40 mL) was prepared separately and cooled to 0 °C. Butyllithium (32.0 mL, 2.5 M in hexanes, 80.0 mmol) was added dropwise to the H-TMP solution, and when addition was complete, the resulting mixture was added dropwise to the Cu-containing mixture at 0 °C. A solution of pyrazine (3.20 g, 40.0 mmol) in THF (20 mL) was added dropwise, and the reaction mixture stirred

at rt for 2 h. DDQ (10.9 g, 48.0 mmol) was added and the mixture sonicated for 90 min. The reaction was quenched by the addition of $H_2O$ (2000 mL) and extracted with DCM (500 mL). The organic phase was dried over $MgSO_4$ and evaporated to dryness. The residue was purified by column chromatography (1 : 1 ethyl acetate : PE) to give the title compound as beige crystals (607 mg, 19%).

Data are consistent with literature values: $R_f$ 0.40 (1 : 1 PE : ethyl acetate); $^1$H NMR (400 MHz, $CDCl_3$) δ 9.61 (s, 2H, H-3), 8.67 (s, 4H, H-5 and H-6);$^{13}$C NMR (101 MHz, $CDCl_3$) δ 145.4 (C-6), 144.0 (C-5), 143.7 (C-3), 100.1 (C-2); mp 170 °C (lit. (*405*) 164 °C).

**Ethyl (2*E*)-8,11-dioxododeca-2,9-dienoate (2.25a)**

Oxidation with *m*CPBA: To a solution of furan **2.7** (30.0 mg, 127 μmol) in $CHCl_3$ (650 μL) was added a solution of *m*CPBA (<77% purity, 43.0 mg, 190 μmol) in $CHCl_3$. The mixture was stirred at rt for 20 min and then diluted with $CHCl_3$ (5 mL), washed with sat aq. $Na_2S_2O_3$ (2 mL), sat. aq. $NaHCO_3$, (2 mL), $H_2O$ (2 mL) and brine (2 mL). The organic phase was dried by passing through a short plug of $Na_2SO_4$, then purified by column chromatography (1 : 0 – 1 : 1 PE : ether) to afford a mixture of diastereomers (7 : 1 2*E*,9*Z* : 2*E*,9*E*, NMR) of the *title compound* as a colourless oil (6.0 mg, 18%).

Oxidation with DDQ: To a solution of DDQ (7.9 mg, 34.8 μmol) in dry DCM (5 mL), which had been deoxygenated *via* 3 FPTCs, cooled to –78 °C and placed under Ar was added a similarly deoxygenated solution of furan **2.7** (10.0 mg, 34.8 μmol) in DCM (5 mL).The mixture was allowed to warm to 0 °C and stirred for 45 min. The mixture was then quenched by addition to sat. aq. $Na_2S_2O_3$ (50 mL), and ether (15 mL) was added.

The aqueous phase was extracted a further two times with ether (2 × 15 mL) and the combined organic phases washed with $H_2O$, dried over $Na_2SO_4$, filtered, and concentrated. The residue was purified by chromatography (1 : 0 – 1 : 1 PE : ether) to afford a mixture of diastereomers (19 : 1 2*E*,9*E* : 2*E*,9*Z*, NMR) of the *title compound* as a colourless oil (2.5 mg, 23%).

Oxidation with $O_2$/**2.8**: Prepared according to General Procedure for Oxidation of Furan Mediated by **2.8** (see page 204) from ethyl 7-(5-methylfuran-2-yl)hept-2-enoate **2.33** (100 mg, 423 μmol). Reaction time 2h 55 min, chromatography performed with 1 : 1 PE : ether as eluant, to afford the *title compound* (>19 : 1 2*E*,9*E* : 2*E*,9*Z*, NMR) as a colourless oil (71.5 mg, 67%).

**(*Z*)-isomer:** $R_f$ 0.30 (1 : 1 PE : ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.94 (dt, *J* = 15.5, 7.0 Hz, 1H, H-3), 6.30 (s, 2H, H-9 and H-10), 5.81 (dt, *J* = 15.5, 1.5 Hz, 1H, H-2), 4.18 (q, *J* = 7.0 Hz, 2H, OC*H*$_2$CH$_3$), 2.55 (t, *J* = 7.0 Hz, 2H, H-7), 2.29 (s, 3H, H-12), 2.22 (qd, *J* = 7.0, 1.5 Hz, 2H, H-4), 1.72 – 1.62 (m, 2H, H-6), 1.55 – 1.45 (m, 2H, H-7), 1.28 (t, *J* = 7.0 Hz, 3H, OCH$_2$C*H*$_3$); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 200.5 (C-8 or C-11), 197.1 (C-8 or C-11), 166.8 (C-1), 148.7 (C-3), 135.9 (C-9 or C-10), 135.8 (C-9 or C-10), 121.8 (C-2), 60.3 (O*C*H$_2$CH$_3$), 42.2 (C-7), 32.1 (C-4), 30.0 (C-5), 27.5 (C-12), 23.0 (C-8), 14.4 (OCH$_2$*C*H$_3$); IR (ATR) ν 2982w (C–H), 2937w (C–H), 2867w, (C–H) 1715s (ketone), 1698s (ester), 1653w (C=C), 1268m, 1183m, 1042m; HRMS (ESI$^+$) found 253.1436, calc. for $C_{14}H_{20}O_4$ $[M+H]^+$ 253.1434.

**(*E*)-isomer:** $R_f$ 0.10 (1 : 1 PE : ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.92 (dt, *J* = 15.5, 7.0 Hz, 1H, H-3), 6.81 (s, 2H, H-9 and H-10), 5.80 (dtd, *J* = 15.5, 1.5, 1.0 Hz, 1H, H-2), 4.16 (qd, *J* = 7.0, 1.0 Hz, 2H, OC*H*$_2$CH$_3$), 2.66 (t, *J* = 7.0 Hz, 2H, H-7), 2.36 (q, *J*

= 1.0 Hz, 3H, H-12), 2.22 (qd, *J* = 7.0, 4.0 Hz, 2H, H-4), 1.76 – 1.57 (m, 2H, H-6), 1.57 – 1.39 (m, 2H, H-5), 1.27 (td, *J* = 7.0, 1.0 Hz, 3H, $OCH_2CH_3$); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 200.3 (C-8 or C-11), 198.5 (C-8 or C-11), 166.7 (C-1), 148.4 (C-3), 137.1 (C-9 or C-10), 137.1 (C-9 or C-10), 121.9 (C-2), 60.3 ($OCH_2CH_3$), 41.1 (C-7), 32.0 (C-4), 28.3 (C-12), 27.5 (C-5), 23.2 (C-6), 14.4 ($OCH_2CH_3$).

**Tetrabutylammonium decatungstate (TBADT, 2.28)**

To a suspension of $Na_2WO_4.2H_2O$ (6.40 g, 19.4 mmol) in boiling $H_2O$ (40 mL) was added aqueous hydrochloric acid (12.0 M, 3.4 mL). The resulting yellow mixture was stirred for 5 min, after which time a solution of tetrabutylammonium bromide (2.50 g, 7.75 mmol) in $H_2O$ (4 mL) was added. The resulting white suspension was stirred at 100 °C for 30 min, then filtered overnight and the residue washed with $H_2O$ (2 × 50 mL), then dried at 50 °C under high vacuum to afford the title compound as an off-white powder (5.41 g, 84%), which could be used without further purification.

Data are consistent with literature values: (*406*) $T_{max}$ 414 °C (lit. 407 °C); IR (ATR) ν 2970w (C–H), 2943w (C–H), 2881w (C–H) 1481m, 980s, 904m, 805br s, 603s; UV $\lambda_{max,abs}$ 278 nm, $\varepsilon_{278}$ 18060 $m.cm^{-1}$ (lit. 267 nm).

**4-Hydroxy-4-methylpentanenitrile (2.29)**

To a flask was added TBADT **2.28** (147 mg, 44.2 μmol), acetonitrile (22 mL), 2-propanol (837 μL, 11.0 mmol) and dtbbp as an internal standard (30.8 mg, 116 μmol). The mixture was deoxygenated by bubbling through Ar for 5 min, and acrylonitrile (52 μL, 800 μmol) was added. The mixture was transferred to vials (1 mL in a septum-capped MS vial, 5 mL in a Suba-Seal®-capped 21 mL vial, and the remaining 17 mL in a second

Suba-Seal®-capped 21 mL vial). The vials were each irradiated with an LED ($\lambda_{max,irr}$ 365 nm, $P_{irr}$ 1000 mW) for 3 h 15 min. The mixtures were combined, oxygenated by bubbling through $O_2$, filtered through a short Celite plug and concentrated. The residue was purified by column chromatography (99 : 1 : 0 – 99 : 2 : 99 PE : TEA : ethyl acetate) to afford the title compound as a straw-coloured soy sauce-scented oil (81.6 mg, 33%).

Data are consistent with literature values: (*291*) $R_f$ 0.35 (1 : 1 PE : ethyl acetate); $^1$H NMR (400 MHz, $CDCl_3$) δ 2.50 – 2.40 (m, 2H, H-2), 1.85 (dd, $J$ = 8.5, 7.0 Hz, 2H, H-3), 1.42 (br s, 1H, OH), 1.26 (s, 6H, H-5 and Me); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 120.6 (C-1), 69.8 (C-4), 38.7 (C-2), 29.3 (C-3), 12.2 (C-5 and Me).

**Ethyl 7-(5-methylfuran-2-yl)hept-3-enoate (2.31)**

A solution of ethyl (*E*)-7-(5-methylfuran-2-yl)hept-2-enoate **2.7** (33.0 mg, 139 μmol) in acetonitrile (10 mL) was deoxygenated by bubbling Ar through for 10 min. The mixture was then transferred to a quartz-lined 2-necked vessel and irradiated through the quartz liner with a cold-cathode mercury discharge lamp ($\lambda_{max,irr}$ 254 nm, $P_{irr}$ 175 mW) at 0 °C for 20 h. The mixture was then concentrated to afford a brown oil, which was purified by column chromatography (19 : 1 PE : ether) to afford a mixture of diastereomers [3 : 7 (*E*) : (*Z*) by NMR] of the *title compound* as a colourless oil (11.3 mg, 34%).

$R_f$ 0.50 (9 : 1 PE : ether); $^1$H NMR (500 MHz, $CDCl_3$) δ 5.85 – 5.81 (m, 2H, Fn-3 and Fn-4), 5.62 – 5.52 (m, 2H, H-3 and H-4), 4.18 – 4.09 (m, 2H, OC$H_2$CH$_3$), 3.07 – 3.06 [m, 0.6H, (*E*)-H-2], 3.03 – 3.01 [m, 1.4H, (*Z*)-H-2], 2.56 (td, $J$ = 7.5, 4.0 Hz, 2H, H-7), 2.25 (d, $J$ = 1.5 Hz, 3H, Fn-Me), 2.13 – 2.05 (m, 2H, H-5), 1.75 – 1.65 (m, 2H, H-

6), 1.26 (t, $J$ = 7.0 Hz, 3H, $OCH_2CH_3$); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 172.3 [(*Z*)-$CO_2Et$], 172.1 [(*E*)-$CO_2Et$], 154.3 [(*Z*)-Fn-2], 154.2 [(*E*)-Fn-2], 150.3 [(*E*)-Fn-5], 150.3 [(*Z*)-Fn-5], 134.1 [(*Z*)-C-4], 132.8 [(*E*)-C-4], 122.5 [(*Z*)-C-3], 121.7 [(*E*)-C-3], 105.9 [(*E*)-Fn-3], 105.9 [(*Z*)-Fn-3], 105.6 [(*E*)-Fn-4], 105.5 [(*Z*)-Fn-4], 60.8 [(*E*)-$OCH_2CH_3$], 60.7 [(*Z*)-$OCH_2CH_3$], 38.3 [(*Z*)-C-2], 33.2 [(*E*)-C-2], 32.0 [(*Z*)-C-7], 27.9 [(*E*)-C-7], 27.7 [(*Z*)-C-5], 27.6 [(*E*)-C-5], 27.5 [(*Z*)-C-6], 26.9 [(*E*)-C-6], 14.4 ($OCH_2CH_3$), 13.6 (Fn-Me); IR (ATR) ν 2982w (C–H), 2936w (C–H), 2862w (C–H) 1736s (C=O) 1175m, 1020m, 781m; HRMS (CI, $NH_3$) found 237.1486, calc. for $C_{14}H_{20}O_3$ $[M+H]^+$ 237.1485.

**2-(Hex-5-yn-1-yl)-5-methylfuran (2.32)**

To NaI (146 mg, 0.971 mmol) and lithium acetylide ethylenediamine complex (695 mg, 7.55 mmol) was added DMSO (distilled over $CaH_2$, 6.0 mL). The reaction vessel was immersed in a rt water bath, and chloride **2.20** (901 mg, 5.28 mmol) was added dropwise over 5 min. The mixture was then stirred in the water bath for 5 h, after which time the reaction mixture was quenched by dropwise addition over 7 min to ice-cold water (60 mL).[lxxvi] The mixture was extracted with PE (3 × 20 mL) and the combined organic phases washed with $H_2O$ (20 mL) and brine (20 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated to afford the title compound as a yellow pineapple-scented oil (439 mg, 52%).

$R_f$ 0.70 (pentane); $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.85 (d, $J$ = 3.0 Hz, 1H, Fn-3), 5.84 (dq, $J$ = 3.0, 1.0 Hz, 1H, Fn-4), 2.59 (t, $J$ = 7.5 Hz, 2H, H-1), 2.25 (d, $J$ = 1.0 Hz,

[lxxvi] A worker in the Robertson group reports isolating the undesired regioisomer of an analogous compound upon workup at rt. (*451*)

3H, Fn-Me), 2.22 (td, *J* = 7.0, 2.5 Hz, 2H, H-4), 1.95 (t, *J* = 2.5 Hz, 1H, H-6), 1.80 – 1.69 (m, 2H, H-2), 1.63 – 1.54 (m, 2H, H-3); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 154.2 (Fn-2 or Fn-5), 150.4 (Fn-2 or Fn-5), 105.9 (Fn-3 or Fn-4), 105.5 (Fn-3 or Fn-4), 84.5 (C-5), 68.5 (C-6), 28.1 (C-3), 27.7 (C-1), 27.4 (C-2), 18.3 (C-4), 13.7 (Fn-Me); IR (ATR) ν 3300m (acetylene C–H), 2943s, 2925m, 2864m, 2118w (acetylene C≡C stretch), 1570m, 1219m, 1020s, 781s, 635s; HRMS (APCI, $CH_4$) found 163.1117, calc. for $C_{11}H_{14}O$ $[M+H]^+$ 163.1117.

**1,6-Bis-(5-methylfuran-2-yl)hex-1-ene (2.33)**

To triphenylphosphine (1.20 g, 4.57 mmol) was added a solution of iodide **2.18** (631 mg, 2.27 mmol) in toluene (2.3 mL). The mixture was placed under Ar and heated to reflux overnight. The mixture was then directly purified by column chromatography (3 : 1 DCM : methanol) and the fractions concentrated carefully to avoid the formation of a foam, then dried under a stream of $N_2$ to afford the novel compound 5-(5-methylfuran-2-yl)-pentyltriphenylphosphonium iodide as a pale brown glass (1.15 g, containing 5% DCM, 89%), which was used without further purification.

*R*$_f$ 0.65 (9 : 1 DCM : methanol); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.75 (m, 9H, *meta*- and *para*-Ph), 7.70 (td, *J* = 7.5, 3.5 Hz, 6H, *ortho*-Ph), 5.78 (d, *J* = 1.5 Hz, 2H, Fn-3 and Fn-4), 3.83 – 3.69 (m, 2H, H-1), 2.51 (t, *J* = 7.5 Hz, 2H, H-5), 2.20 (s, 3H, Me), 1.73 (q, *J* = 8.0, 7.5 Hz, 2H), 1.69 – 1.53 (m, 4H).

To 5-(5-methylfuran-2-yl)-pentyltriphenylphosphonium iodide (1.14 g, 2.11 mmol) was added sequentially $K_2CO_3$[lxxvii] (350 mg, 2.53 mmol), dry 1,4-dioxane (2 mL)

[lxxvii] Dried in an oven at *ca.* 80 °C, at atm. pressure

and 5-methylfurfural (210 μL, 2.11 mmol). The mixture was placed under Ar and heated to 95 °C for 21 h. The mixture was filtered, and the residue washed with ether. The filtrate and washings were combined and concentrated, and the residue purified by column chromatography (1 : 0 – 4 : 1 PE : ether) to afford a mixture of diastereomers [3 : 1 (*Z*) : (*E*)] of the *title compound* as a yellow oil (468 mg, 91%).

$R_f$ 0.70 (9 : 1 PE : ether); $^1$H NMR (400 MHz, $CDCl_3$)[lxxviii,lxxix] δ 6.20 – 6.04 (m, 2H, H-1 and vn-Fn-3), 5.98 – 5.94 (m, 1H, vn-Fn-4), 5.84 (s, 2H, nvn-Fn-3 and nvn-Fn-4), 5.45 (dt, *J* = 12.0, 7.5 Hz, 1H, H-2), 2.60 (t, *J* = 7.5 Hz, 2H, H-6), 2.45 (qd, *J* = 7.5, 2.0 Hz, 2H, H-3), 2.30 (s, 3H, vn-Fn-Me), 2.25 (s, 3H, nvn-Fn-Me), 1.75 – 1.62 (m, 2H, H-5), 1.58 – 1.44 (m, 2H, H-4); $^{13}$C NMR[lxxviii] (101 MHz, $CDCl_3$) δ 154.7 (Fn-2 or Fn-5), 151.9 (Fn-2 or Fn-5), 151.2 (Fn-2 or Fn-5), 150.2 (Fn-2 or Fn-5), 129.6 (C-2), 117.6 (C-1), 110.0 (Fn-3 or Fn-4), 107.2 (Fn-3 or Fn-4), 105.9 (Fn-3 or Fn-4), 105.3 (Fn-3 or Fn-4), 29.2 (C-4), 29.1 (C-3), 28.1 (C-6), 28.0 (C-5), 13.9 (Me), 13.7 (Me); IR (ATR) ν 2924s (alkene C–H), 2859w, 1570m, 1220m, 1020s, 780s; HRMS (EI) found 244.1460, calc. for $C_{16}H_{20}O_2$ $[M]^+$ 244.1463.

**2-Methyl-5-{[2-(5-methylfuran-2-yl)cyclopentyl]methyl}furan (2.42)**

To *O*-[1,6-bis(5-methylfuran-2-yl)hex-5-en-1-yl] 1*H*-imidazole-1-carbothioate **3.11** (34.1 mg, 92.0 μmol) was added a solution of triphenylstannane (48.5 mg, 60% pure by NMR, 138 μmol) in toluene-$d_8$ (500 μL) and a solution of AIBN (3.02 mg, 18.4 μmol)

[lxxviii] Only signals for the (*Z*)-isomer are reported; "vn-" and "nvn-" assign furan resonances as vinylene-substituted and non-vinylene-substituted, respectively.
[lxxix] The following distinct signals attributable to the (*E*)-isomer were visible in the $^1$H NMR spectrum of the product as isolated: $^1$H NMR (400 MHz, $CDCl_3$) δ 6.13 – 6.03 (m, 1H, H-2), 5.99 (d, *J* = 3.0 Hz, 1H, vn-Fn-3), 5.93 – 5.90 (m, 1H, vn-Fn-4), 5.85 – 5.82 (m, 1H, H-1), 2.62 – 2.55 (m, 2H, H-6), 2.29 – 2.27 (m, 3H, vn-Fn-Me), 2.19 (q, *J* = 7.0 Hz, 2H, H-3); all other resonances are presumed to be obscured by the (*Z*)-isomer signals.

in toluene-$d_8$ (420 μL). The mixture was degassed *via* 3 FPTCs, placed under Ar and heated to reflux for 30 min, after which time an additional charge of triphenylstannane (22.3 mg, 63.6 μmol) in toluene-$d_8$ (230 μL), and of AIBN (1.51 mg, 9.2 μmol) in toluene-$d_8$ (210 μL) were added. Reflux was resumed for a further 35 min, and the residue was purified directly by column chromatography (pentane) to afford the *title compound* (*d.r.* 1 : 1 by NMR) as a colourless oil (7.9 mg, 35%).

$R_f$ 0.80 (pentane); $^1$H NMR (400 MHz, $C_6D_6$) δ 5.93 – 5.72 (m, 4H, Fn), 3.15 (q, $J$ = 7.5 Hz, 0.5H, cyclopentyl-2), 2.96 – 2.87 (m, 0.5H, cyclopentyl-2), 2.71 – 2.61 (m, 1H, C$H_2$Fn), 2.57 – 2.49 (m, 0.5H, cyclopentyl-1), 2.49 – 2.38 (m, 1H, C$H_2$Fn), 2.32 (dd, $J$ = 15.0, 10.0 Hz, 0.5H, cyclopentyl-1), 2.07 – 2.03 (m, 6H, Me), 1.97 – 1.27 (m, 6H, cyclopentyl-3,4,5); $^{13}$C NMR (126 MHz, $C_6D_6$) δ 157.0 (Fn-2 or Fn-5), 156.0 (Fn-2 or Fn-5), 154.4 (Fn-2 or Fn-5), 153.9 (Fn-2 or Fn-5), 150.5 (Fn-2 or Fn-5), 150.5 (Fn-2 or Fn-5), 150.3 (Fn-2 or Fn-5), 150.2 (Fn-2 or Fn-5), 107.0 (Fn-3 or Fn-4), 106.8 (Fn-3 or Fn-4), 106.4 (Fn-3 or Fn-4), 106.3 (Fn-3 or Fn-4), 106.3 (Fn-3 or Fn-4), 106.2 (Fn-3 or Fn-4), 105.4 (Fn-3 or Fn-4), 45.2 (*C*H$_2$Fn), 44.9 (*C*H$_2$Fn), 43.3 (C-1), 42.4 (C-2), 33.2 (C-2), 32.3 (cyclopentyl-3 or cyclopentyl-4 or cyclopentyl-5), 32.2 (cyclopentyl-3 or cyclopentyl-4 or cyclopentyl-5), 31.2 (cyclopentyl-3 or cyclopentyl-4 or cyclopentyl-5), 30.2 (C-1), 29.8 (cyclopentyl-3 or cyclopentyl-4 or cyclopentyl-5), 24.1 (cyclopentyl-3 or cyclopentyl-4 or cyclopentyl-5), 23.5 (cyclopentyl-3 or cyclopentyl-4 or cyclopentyl-5), 13.6 (Me), 13.5 (Me); IR (ATR) ν 2951s, 2922s, 2873m, 1568s, 1219s, 1021s, 778s; HRMS (ESI$^+$) found 245.1537, calc. for $C_{16}H_{20}O_2$ [M+H]$^+$ 245.1536.

# Chapter 3

**1-(5-Methylfuran-2-yl)hex-5-en-1-ol (3.6)**

To a suspension of Mg (228 mg, 9.38 mmol) in THF (500 µL) under Ar was added DBE (50.0 µL, 0.580 mmol). The mixture was heated to reflux and a solution of 5-bromopent-1-ene (710 µL, 6.00 mmol) in THF (9.5 mL) added as slowly as possible until the mixture was seen briefly to go cloudly, at which point addition was stopped and the heat source immediately removed. Slow addition of the remaining bromide solution took place over 1 h, and when this was complete, the mixture was heated to reflux for 30 min, then cooled by immersion in ice. A solution of 5-methylfurfural (780 µL, 7.80 mmol) in THF (40 mL) was added slowly and the mixture stirred at 0 °C for 1 h. The mixture was then quenched with sat. aq. $NH_4Cl$ (15 mL) and diluted with $H_2O$ (50 mL). The aqueous phase was extracted with ether (3 × 10 mL), and the combined organic phases were washed with $H_2O$, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (1 : 0 – 7 : 3 PE : ether) to afford the title compound as a pale brown oil (928 mg, 86%).

Data are consistent with literature values: (*407*) $R_f$ 0.70 (9 : 1 DCM : ethyl acetate); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.09 (d, *J* = 3.0 Hz, 1H, Fn-3), 5.89 (dq, *J* = 3.0, 1.0 Hz, 1H, Fn-4), 5.80 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, H-5), 5.01 (app dq, *J* = 17.0, 1.5 Hz, 1H, H-6 *trans* to H-5), 4.95 (ddt, *J* = 10.0, 2.5, 1.0 Hz, 1H, H-6 *cis* to H-5), 4.60 (td, *J* = 7.0, 4.0 Hz, 1H, H-1), 2.28 (d, *J* = 1.0 Hz, 3H, Fn-Me), 2.15 – 2.02 (m, 2H, H-4), 1.84 (tdd, *J* = 8.5, 7.0, 1.0 Hz, 2H, H-3), 1.61 – 1.49 (m, 1H, H-2), 1.48 – 1.35 (m, 1H, H-2); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 155.0 (Fn-2), 151.8 (Fn-5), 138.7 (C-6), 114.9 (C-5), 106.8 (Fn-3), 106.1 (Fn-4), 67.8 (C-1), 35.0 (C-3), 33.6 (C-4), 25.1 (C-2), 13.7 (Fn-

Me); IR (ATR) ν 3354br (O–H), 1020m, 996m (alkene C-H bend), 910m (alkene C-H bend), 783m; HRMS ($ESI^+$) calc. for $C_{11}H_{16}O_2$ $[M+H]^+$ 181.1226, found 181.1223.

**Ethyl (*E*)-7-hydroxy-7-(5-methylfuran-2-yl)hept-2-enoate (3.7)**

A solution of olefin **3.6** (60% pure, contaminated with 5-methylfurfural, 195 mg, 649 μmol) in toluene (7 mL) was deoxygenated by bubbling Ar through for 5 min and ethyl acrylate (360 μL, 3.30 mmol) and H-G Ⅱ (71.0 mg, 114 μmol) was added. The resulting mixture was heated to reflux, under Ar, in a preheated oil bath for 40 min, after which time the mixture was concentrated to 1 mL and diluted to 4 mL with PE, then directly purified by column chromatography, (1 : 0 – 3 : 2 PE : ether) affording the *title compound* as a pink oil (144 mg, 88%).

$R_f$ 0.15 (7 : 3 PE : ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.94 (dt, *J* = 15.5, 7.0 Hz, 1H, H-3), 6.09 (d, *J* = 3.0 Hz, 1H, Fn-3), 5.89 (dq, *J* = 3.0, 1.0 Hz, 1H, Fn-4), 5.81 (dt, *J* = 15.5, 1.5 Hz, 1H, H-2), 4.60 (td, *J* = 7.0, 5.0 Hz, 1H, H-7), 4.17 (q, *J* = 7.0 Hz, 2H, $OCH_2CH_3$), 2.28 (d, *J* = 1.0 Hz, 3H, Fn-Me), 2.26 – 2.20 (m, 2H, H-5), 1.85 (dt, *J* = 8.0, 7.0 Hz, 2H, H-4), 1.70 – 1.56 (m, 1H, H-6), 1.56 – 1.40 (m, 2H, H-6), 1.28 (t, *J* = 7.0 Hz, 3H, $OCH_2CH_3$); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 166.8 (C-1), 154.7 (Fn-2), 151.9 (Fn-5), 148.8 (C-3), 121.8 (C-2), 107.0 (Fn-3 or Fn-4), 106.1 (Fn-3 or Fn-4), 67.7 (C-7), 60.3 ($OCH_2CH_3$), 34.9 (C-6), 32.0 (C-4), 24.2 (C-5), 14.4 ($OCH_2CH_3$), 13.7 (Fn-Me); IR (ATR) ν 3428br (O–H stretch), 1716s (C=O stretch), 1652m (C=C stretch), 1185s, 1040s, 1020s, 784s; HRMS ($ESI^+$) found 270.1695, calc. for $C_{14}H_{20}O_4$ $[M+H]^+$ 270.1700.

**Ethyl (*E*)-7-[(1*H*-imidazole-1-carbonothioyl)oxy]-7-(5-methylfuran-2-yl)hept-2-enoate (3.8)**

To a solution of TCDI (85.0 mg, 477 μmol) in DCM (800 μL) at 0 °C and under $N_2$ was added DMAP (22.0 mg, 180 μmol) and a solution of alcohol **3.7** (40.0 mg, 159 μmol) in DCM (800 μmol). The mixture was stirred at 0 °C for 35 min and directly purified by column chromatography (1 : 0 – 19 : 1 DCM : methanol) to afford the *title compound* as a bright yellow oil. (49.4 mg, 86%).

$R_f$ 0.35 (19 : 1 DCM : methanol); $^1$H NMR (500 MHz, $C_6D_6$) δ 7.99 (d, *J* = 1.5 Hz, 1H, Im-2), 7.03 (t, *J* = 1.5 Hz, 1H, Im-5), 6.96 – 6.88 (m, 1H, H-3), 6.87 (d, *J* = 1.5 Hz, 1H, Im-4), 6.00 (d, *J* = 3.0 Hz, 1H, Fn-3), 5.82 (dt, *J* = 15.5, 1.5 Hz, 1H, H-2), 5.66 (dq, *J* = 3.0, 1.0 Hz, 1H, Fn-4), 4.77 (dd, *J* = 9.0, 6.5 Hz, 1H, H-7), 4.04 (q, *J* = 7.0 Hz, 2H, OC*H*$_2$CH$_3$), 1.95 (d, *J* = 1.0 Hz, 3H, Fn-Me), 1.90 – 1.80 (m, 1H, H-6), 1.75 – 1.68 (m, 3H, H-6 and H-4), 1.37 – 1.20 (m, 2H, H-5), 0.99 (t, *J* = 7.0 Hz, 3H, OCH$_2$C*H*$_3$); $^{13}$C NMR (126 MHz, $C_6D_6$) δ 166.0 (C-1), 165.2 (C=S), 152.6 (Fn-2), 150.5 (Fn-5), 147.8 (C-3), 135.5 (Im-2), 131.5 (Im-4), 122.4 (C-2), 115.8 (Im-5), 109.4 (Fn-3), 106.9 (Fn-4), 60.1 (O*C*H$_2$CH$_3$), 43.7 (C-7), 33.5 (C-6), 31.4 (C-4), 25.9 (C-5), 14.4 (OCH$_2$*C*H$_3$), 13.4 (Fn-Me); IR (ATR) ν 1715s (C=O stretch), 1692s, 1654w (C=C stretch), 1287m, 1270m, 1214s (C=S stretch), 884s; HRMS (APCI, $NH_3$) found 235.1320, calc. for $C_{18}H_{22}N_2O_4S$ $[M–C_4H_3N_2OS]^+$ 235.1329.

**6-(5-Methylfuran-2-yl)hex-5-enal (3.9)**

To a solution of alcohol **3.15** (700 mg, 3.89 mmol) in DCM (53 mL) was added $NaHCO_3$ (1.63 g, 19.5 mmol). The mixture was cooled to 0 °C, placed under $N_2$, and light was excluded from the reaction vessel with aluminium foil. TEMPO (31.0 mg, 195 μmol) was added dropwise as a solution in DCM (5 mL). A solution of BAIB (175 mg, 0.546 mmol) in DCM (20 mL) was added over 1 h *via* syringe pump. The foil was removed from the outside of the reaction vessel, and the mixture warmed to rt and stirred for 24 h. The reaction mixture was washed with sat. aq. $Na_2S_2O_3$ (2 × 30 mL), water (20 mL) and brine (20 mL), and the organic phase was separated and dried over $MgSO_4$, then concentrated and the residue purified by column chromatography (1 : 0 – 4 : 1 PE : ether) to afford a mixture of diastereomers [7 : 3 (*Z*) *:* (*E*) by NMR] of the *title compound* as a yellow oil (350 mg, 50%).

$R_f$ 0.60 (DCM); $^1$H NMR[lxxx] (400 MHz, $C_6D_6$) δ 9.30 (t, *J* = 1.5 Hz, 1H, H-1), 6.16 (dt, *J* = 11.5, 1.5 Hz, 1H, H-6), 6.06 (d, *J* = 3.0 Hz, 1H, Fn-3), 5.82 – 5.78 (m, 1H, Fn-4), 5.18 (dt, *J* = 11.5, 7.5 Hz, 1H, H-5), 2.33 (qd, *J* = 7.5, 1.5 Hz, 2H, H-4), 2.01 (d, *J* = 1.0 Hz, 3H, Me), 1.87 (td, *J* = 7.5, 1.5 Hz, 2H, H-2), 1.48 (p, *J* = 7.5 Hz, 2H, H-3); $^{13}$C NMR[lxxx] (101 MHz, $C_6D_6$) δ 200.6 (C-1), 152.1 (Fn-2 or Fn-5), 151.5 (Fn-2 or Fn-5), 128.2 (C-6), 118.7 (C-5), 110.8 (Fn-3), 107.7 (Fn-4), 43.2 (C-2), 28.8 (C-4), 22.1 (C-3), 13.5 (Me); IR (ATR) ν 2926w (alkene C–H), 1724s (C=O stretch), 1020m, 996w [(*E*)-alkene C-H bend], 785s [(*Z*)-alkene C-H bend]; HRMS (ESI$^+$) found 179.1070, calc. for $C_{11}H_{14}O_2$ $[M+H]^+$ 179.1067.

[lxxx] Signals reported for (*Z*)-isomer only: for (*E*)-isomer signals, see below.

A portion of this material (100 mg) was converted to the (*E*)-isomer (*d.r.* 19 : 1) *via* dissolution in benzene (4.3 mL) and the sequential addition of $K_2CO_3$ (13.3 mg, 17.2 μmol) and a solution of $I_2$ (13.2 mg, 56.1 μmol) in benzene (1.32 mL) to this mixture. The mixture thus obtained was stirred in darkness for 1 h at rt, after which time the mixture was shaken vigorously with sat. aq. $Na_2S_2O_3$ (2 ×1 mL), and the organic phase passed through a plug of $Na_2SO_4$, then concentrated to afford the *title compound* as a yellow oil (93.8 mg, 94%).

$^1$H NMR (400 MHz, $CDCl_3$) δ 9.79 (t, *J* = 1.5 Hz, 1H, H-1), 6.19 – 6.11 (br dt, *J* = 16.0, 1.0 Hz, 1H, H-5), 6.07 – 5.97 (m, 2H, Fn-3 and H-6), 5.93 (dq, *J* = 3.0, 1.0 Hz, 1H, Fn-4), 2.49 (td, *J* = 7.5, 1.5 Hz, 2H, H-2), 2.29 (br d, *J* = 1.0 Hz, 3H, Fn-Me), 2.21 (br qd, *J* = 7.5, 1.0 Hz, 2H, H-4), 1.80 (p, *J* = 7.5 Hz, 2H, H-3); $^1$H NMR (500 MHz, $C_6D_6$) δ 9.25 (t, *J* = 1.5 Hz, 1H, H-1), 6.06 – 6.02 (m, 2H, H-5 and H-6), 5.96 (d, *J* = 3.0 Hz, 1H, Fn-3), 5.80 (br dq, *J* = 3.0, 1.0 Hz, 1H, Fn-4), 2.02 (d, *J* = 1.0 Hz, 3H, Me), 1.87 – 1.81 (m, 2H, H-4), 1.75 (td, *J* = 7.5, 1.5 Hz, 2H, H-2), 1.38 (p, *J* = 7.5 Hz, 2H, H-3); $^{13}$C NMR (126 MHz, $C_6D_6$) δ 200.4 (C-1), 152.1 (Fn-2 or Fn-5), 151.5 (Fn-2 or Fn-5), 127.1 (C-5), 120.1 (C-6), 108.0 (Fn-3), 107.6 (Fn-4), 43.0 (C-2), 32.2 (C-4), 21.8 (C-3), 13.5 (Fn-Me).

**1,6-Bis(5-methylfuran-2-yl)hex-5-en-1-ol (3.10)**

To 2-methylfuran (95.0 μL, 1.05 mmol) in THF (2 mL) at 0 °C and under Ar was added butyllithium (316 μL, 2.5 M in hexanes, 790 μmol) dropwise. The mixture was stirred for 2 h 30 min, then cooled to −78 °C. A solution of *(E)*-**3.9** (93.8 mg, 526 μmol) in THF (630 μL) was added, and the resulting mixture was warmed to rt and stirred over 16 h, then quenched with sat. aq. $NH_4Cl$ (1 mL) and extracted with ethyl acetate (3 × 2

mL). The combined organic phases were washed with brine (3 mL), dried over $Na_2SO_4$, filtered and concentrated to afford the *title compound* as a pale yellow oil (130 mg, 95%).

$R_f$ 0.10 (4 : 1 PE : ether); $^1$H NMR (400 MHz, $C_6D_6$) δ 6.21 (dt, $J$ = 16.0, 7.0 Hz, 1H, H-5), 6.09 (dt, $J$ = 16.0, 1.5 Hz, 1H, H-6), 5.96 (d, $J$ = 3.0 Hz, 1H, Fn-3), 5.94 (d, $J$ = 3.0 Hz, 1H, Fn-3), 5.79 (dq, $J$ = 3.0, 1.0 Hz, 1H, Fn-4), 5.75 (dq, $J$ = 3.0, 1.0 Hz, 1H, Fn-4), 4.42 (t, $J$ = 7.0 Hz, 1H, H-1), 2.07 – 1.96 (m, 8H, Fn-Me and H-4), 1.81 – 1.72 (m, 2H, H-3), 1.61 – 1.48 (m, 1H, H-2), 1.48 – 1.33 (m, 1H, H-2), 1.23 (br s, 1H, OH); $^{13}$C NMR (101 MHz, $C_6D_6$) δ 153.7 (Fn-2 or Fn-5), 151.3 (Fn-2 or Fn-5), 128.1 (C-5 obscured by solvent signal, but HSQC indicates presence), 119.6 (C-6), 107.7 (Fn-3 or Fn-4), 107.5 (Fn-3 or Fn-4), 106.6 (Fn-3 or Fn-4), 106.4 (Fn-3 or Fn-4), 67.9 (C-1), 35.6 (C-3), 32.9 (C-4), 25.8 (C-2), 13.6 (Me), 13.4 (Me); IR (ATR) ν 3389br, 2944w (alkene C–H), 1020s, 962m, 782s; HRMS (APCI, $NH_3$) found 261.1487, calc. for $C_{16}H_{20}O_3$ $[M+H]^+$ 261.1485.

**_O_-[1,6-Bis(5-methylfuran-2-yl)hex-5-en-1-yl]-[1*H*]-imidazole-1-carbothioate (3.11)**

To a solution of alcohol **3.10** (50.0 mg, 192 μmol) in DCM (1 mL) under $N_2$ was added DMAP (28.2 mg, 231 μmol). This mixture was transferred to a solution of TCDI (103 mg, 576 μmol) in DCM (1 mL) at 0 °C and the resulting mixture was stirred in darkness at 0 °C for 2 h 20 min and then purified directly by column chromatography (1 : 0 – 3 : 2 PE : ether) to afford the *title compound* as a yellow oil (34.1 mg, 48%).

$R_f$ 0.10 (DCM); $^1$H NMR (400 MHz, $C_6D_6$) δ 8.00 (t, $J$ = 1.0 Hz, 1H, Im-2), 7.04 (t, $J$ = 1.5 Hz, 1H, Im-5), 6.87 (dd, $J$ = 1.5, 1.0 Hz, 1H, Im-4), 6.18 – 6.09 (m, 2H, H-5 and H-6), 6.04 (d, $J$ = 3.0 Hz, 1H, Fn-3), 5.96 (d, $J$ = 3.0 Hz, 1H, Fn-3), 5.80 – 5.77 (m, 1H, Fn-4), 5.69 – 5.66 (m, 1H, Fn-4), 4.87 (dd, $J$ = 8.5, 7.0 Hz, 1H, H-1), 2.07 – 1.92 (m,

9H, Me and H-2 and H-4), 1.92 – 1.81 (m, 1H, H-2), 1.42 – 1.31 (m, 2H, H-3); $^{13}$C NMR (101 MHz, $C_6D_6$) δ 164.9 (C=S), 152.1 (Fn-2 or Fn-5), 151.7 (Fn-2 or Fn-5), 151.1 (Fn-2 or Fn-5), 150.4 (Fn-2 or Fn-5), 135.1 (Im-2), 131.1 (Im-4), 126.8 (C-5), 119.6 (C-6), 115.4 (Im-5), 108.9 (Fn-3 or Fn-4), 107.6 (Fn-3 or Fn-4), 107.2 (Fn-3 or Fn-4), 106.5 (Fn-3 or Fn-4), 43.5 (C-1), 33.2 (C-2), 32.0 (C-4), 27.0 (C-3), 13.2 (Me), 13.0 (Me); IR (ATR) ν 1692s, 1216s (C=S), 885s; HRMS (ESI$^+$) found 243.1381, calc. for $C_{20}H_{22}N_2O_3S$ $[M–C_4H_3N_2OS]^+$ 243.1380.

**5-Bromopentyl acetate (3.12)**

To zinc (32.2 mg, 492 μmol) under $N_2$ was added acetyl bromide (4.55 mL, 61.6 mmol). The mixture was warmed to 60 °C and stirred for 10 min. The reaction vessel was then immersed in a rt cooling bath and tetrahydropyran (5.68 mL, 58.1 mmol) was added dropwise. When addition was complete, the mixture was warmed to 90 °C and stirred at reflux for 40 min, then cooled and poured on to ice (20 mL). The mixture was extracted with ether (20 mL) and the organic phase washed with sat. aq. $NaHCO_3$ (20 mL) and brine (10 mL), then dried over $Na_2SO_4$, filtered, and concentrated to afford the title compound as an orange oil (9.23 g, 73% from tetrahydropyran).

Data are consistent with literature values: (*296*) $R_f$ 0.30 (pentane); $^1$H NMR (400 MHz, $CDCl_3$) δ 4.07 (t, $J$ = 6.5 Hz, 2H, H-1'), 3.41 (t, $J$ = 6.5 Hz, 2H, H-5'), 2.05 (s, 3H, H-2), 1.95 – 1.83 (m, 2H, H-4'), 1.72 – 1.60 (m, 2H, H-2'), 1.57 – 1.46 (m, 2H, H-3'); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 171.3 (C-1), 64.3 (C-1'), 33.6 (C-5'), 32.4 (C-4'), 27.9 (C-2'), 24.8 (C-3'), 21.1 (C-2).

**5-Hydroxypentyltriphenylphosphonium bromide (3.14)**

Prepared according to a literature procedure: (*296*) To 5-bromopentyl acetate **3.12** (9.23 g, 44.2 mmol) was added triphenylphosphine (11.6 g, 44.2 mmol). The mixture was placed under $N_2$, heated to reflux and stirred for 18 h, then cooled to afford a brown glass, which was dissolved in MeOH (90 mL) and $H_2O$ (9 mL). $K_2CO_3$ (400 mg, 2.89 mmol) was added and the mixture stirred at rt for 24 h. The mixture was concentrated, and the residue partitioned between acetonitrile (30 mL) and PE (30 mL). The (bottom) acetonitrile phase was dried over $MgSO_4$, filtered, concentrated, and reconcentrated from toluene to afford the title compound as a brown foam, which was used without further purification (20.5 g, >99%).

**6-(5-Methylfuran-2-yl)hex-5-en-1-ol (3.15)**

To phosphonium salt **3.14** (19.9 g, 46.6 mmol) under $N_2$ was added toluene (10 mL) and THF (35 mL). The mixture was cooled to 0 °C and butyllithium (37.3 mL, 2.5 M in hexanes, 93.2 mmol) added over 2 h while the mixture was shaken vigorously. DIPA (13.5 mL, 95.7 mmol) was added, followed by 5-methylfurfural (5.1 mL, 51.3 mmol) over 5 min. The mixture was stirred for 1 h and the reaction mixture acidified to *pH* 5 by addition of sat. aq. $NH_4Cl$. The organic phase was concentrated, and the residue purified by column chromatography (1 : 0 – 1 : 1 PE : ether) to afford the a mixture of diastereomers [7 : 3 (*Z*) : (*E*) by NMR] of the *title compound* as a golden oil (2.32 g, 28%).

$R_f$ 0.20 (49 : 1 DCM : methanol); $^1$H NMR[lxxxi] (400 MHz, $CDCl_3$) δ 6.17 – 6.02 (m, 2H, Fn-3 and H-6), 5.96 (dt, *J* = 2.0, 1.0 Hz, 1H, Fn-4), 5.45 (dt, *J* = 11.5, 7.5 Hz, 1H, H-5), 3.65 (t, *J* = 6.5 Hz, 2H, H-1), 2.46 (qd, *J* = 7.5, 2.0 Hz, 2H, H-4), 2.30 (d, *J* = 1.0 Hz, 3H, Me), 1.83 (br s, 1H, OH), 1.68 – 1.58 (m, 2H, H-2), 1.58 – 1.47 (m, 2H, H-3); $^{13}$C NMR [(*Z*)-isomer] (101 MHz, $CDCl_3$) δ 151.8 (Fn-2 or Fn-5), 151.2 (Fn-2 or Fn-5), 129.3 (C-5), 117.7 (C-6), 110.0 (Fn-3), 107.2 (Fn-4), 62.8 (C-1), 32.5 (C-2), 28.9 (C-4), 25.7 (C-3), 13.8 (Me); $^{13}$C NMR [(*E*)-isomer] (101 MHz, $CDCl_3$) δ 151.7 (Fn-2 or Fn-5), 151.2 (Fn-2 or Fn-5), 127.9 (C-6), 119.1 (C-5), 107.3 (Fn-3 or Fn-4), 107.1 (Fn-3 or Fn-4), 62.8 [C-1, obscured by (*Z*)-signal], 32.5 (C-4), 32.3 (C-2), 25.5 (C-3), 13.7 (Me); IR (ATR) ν 3343 br (O–H), 2928s, 2860m, 1020s [(*E*)-C-H bend], 781s [(*Z*)-C-H bend]; HRMS (APCI, $NH_3$) found 181.1226, calc. for $C_{11}H_{16}O_2$ $[M+H]^+$ 181.1223.

**Methyl 1-(furan-2-yl)-2-oxocyclopentane-1-carboxylate (3.19)**

A solution of methyl 2-oxocyclopentanecarboxylate (6.20 mL, 50.0 mmol) in THF (40 mL) was prepared in a 3-neck round-bottomed flask, fitted with two addition funnels and a reflux condenser. A solution of $ZnCl_2$ (10.2 g, 75.0 mmol) in 5 : 1 $H_2O$ : acetic acid (12.0 mL) was diluted to 20 mL with THF and transferred to one of the addition funnels. DMDHF (6.10 mL, 50.0 mmol) was dissolved in THF to a total volume of 20 mL and the solution transferred to the second addition funnel. With vigorous stirring, both solutions were added dropwise and simultaneously to the methyl 2-oxocyclopentanecarboxylate solution. When addition was complete, the mixture was

[lxxxi] Signals reported for (*Z*)-isomer only; the following distinct signals attributable to the (*E*)-isomer were visible in the $^1$H NMR spectrum of the product as isolated: $^1$H NMR (400 MHz, $CDCl_3$) δ 6.17 – 6.02 (m, 1H, H-6), 5.99 (d, *J* = 3.0 Hz, 1H, Fn-3), 5.91 (dq, *J* = 3.0, 1.0 Hz, 1H, Fn-4), 3.63 [t, *J* = 6.5 Hz, 2H, H-1, partially obscured by (*Z*)-isomer signal], 2.28 (d, *J* = 1.0 Hz, 3H, Fn-Me), 2.19 (q, *J* = 7.0 Hz, 2H, H-4); all other resonances are presumed to be obscured by the (*Z*)-isomer signals.

heated to reflux for 1 h and then poured on to ice (500 mL). When the ice had melted, the mixture was extracted with ether (3 × 50 mL), and the combined organic phases were washed with sat. aq. $NaHCO_3$ (30 mL) and $H_2O$ (30 mL). The organic phase was dried over $Na_2SO_4$ and concentrated to afford the title compound as a pale orange oil (9.20 g, 88%).

Data are consistent with literature values: (*297*) $R_f$ 0.40 (4 : 1 PE : ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 2.0, 1.0 Hz, 1H, Fn-5), 6.36 (dd, *J* = 3.5, 2.0 Hz, 1H, Fn-4), 6.32 (dd, *J* = 3.5, 1.0 Hz, 1H, Fn-3), 3.75 (s, 3H, Me), 2.79 – 2.61 (m, 2H, cyclopentyl-4), 2.53 – 2.38 (m, 2H, cyclopentyl-3), 2.14 – 1.83 (m, 2H, cyclopentyl-5); $^1$H NMR (400 MHz, DMSO) δ 7.66 (dd, *J* = 2.0, 1.0 Hz, 1H, Fn-5), 6.44 (dd, *J* = 3.5, 2.0 Hz, 1H, Fn-4), 6.36 (dd, *J* = 3.5, 1.0 Hz, 1H, Fn-3), 3.66 (s, 3H, Me), 2.57 (dd, *J* = 7.5, 6.5 Hz, 2H, cyclopentyl-4), 2.48 – 2.38 (m, 2H, cyclopentyl-3), 2.03 – 1.91 (m, 1H, cyclopentyl-5), 1.87 – 1.74 (m, 1H, cyclopentyl-5); $^{13}$C NMR (101 MHz, DMSO) δ 209.5 (cyclopentyl-1), 169.7 (*C*$O_2$Me), 148.6 (Fn-2), 143.5 (Fn-5), 110.6 (Fn-4), 108.5 (Fn-3), 52.9 (Me), 36.9 (cyclopentyl-3), 33.5 (cyclopentyl-4), 19.4 (cyclopentyl-5).

**2-(Furan-2-yl)cyclopentan-1-one (3.20)**

A solution of methyl ester **3.19** (9.20 g, 44.2 mmol) and LiCl (3.75 g, 88.4 mmol), 50 : 3 : 1 NMP : acetic acid : $H_2O$ (48.6 mL) was prepared, and added *via* syringe to an Ar-filled round bottomed flask fitted with a reflux condenser which had been preheated to 130 °C in a sand bath. The mixture was heated to 185 °C and stirred at reflux for 2 h. As soon as the starting material was consumed (NMR), the mixture was poured on to ice (200 mL) and diluted to 500 mL with $H_2O$. The mixture was extracted with ethyl acetate (3 × 50 mL), the aqueous phase discarded and the combined organic layers washed with

$H_2O$ (3 × 10 mL) and 1 M aq. NaOH (30 mL). The organic phase was then dried over $Na_2SO_4$, filtered and concentrated to afford the title compound as an orange oil (2.46 g, 37%), which could be used without further purification. Chromatography (1 : 0 – 9 : 1 PE : ether) could be employed to give analytically pure material in poor yield.

Data are consistent with literature values: (*297*) $R_f$ 0.30 (4 : 1 PE : ether); bp (corrected) 246 °C (lit. 116 °C, 15 Torr, corrected 241 °C); $^1$H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.30 (m, 1H, Fn-5), 6.39 – 6.24 (m, 1H, Fn-4), 6.18 (d, *J* = 3.0 Hz, 1H, Fn-3), 3.43 (t, *J* = 9.5 Hz, 1H, H-2), 2.52 – 2.28 (m, 3H), 2.26 – 2.07 (m, 2H), 2.02 – 1.80 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 215.5 (C-1), 151.6 (Fn-2), 142.1 (Fn-5), 110.4 (Fn-4), 106.8 (Fn-3), 48.7 (C-2), 38.0 (C-5), 29.5 (C-3), 21.1 (C-4); HRMS (ESI$^+$) found 151.0754, calc. for $C_9H_{10}O_2$ $[M+H]^+$ 151.0754.

**Ethyl 2-[2-(furan-2-yl)cyclopentylidene]acetate (3.21)**

Isomers occasionally coisolated with compound **3.24**.

Major diastereomer: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.27 (dd, *J* = 2.0, 1.0 Hz, 1H, Fn-5), 6.23 (dd, *J* = 3.0, 2.0 Hz, 1H, Fn-4), 5.92 – 5.89 (m, 2H, Fn-3 and H-2), 4.73 – 4.63 (m, 1H, cyclopentylidene-2), 4.06 (qd, *J* = 7.0, 1.0 Hz, 2H, $OCH_2CH_3$), 2.76 – 2.61 (m, 1H, cyclopentylidene-5), 2.50 (td, *J* = 8.0, 2.0 Hz, 1H, cyclopentylidene-5), 2.14 – 1.86 (m, 2H, cyclopentylidene-3), 1.86 – 1.64 (m, 2H, cyclopentylidene-4), 1.17 (t, *J* = 7.0 Hz, 3H, $OCH_2CH_3$); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 166.0 (C-1 or cyclopentylidene-1), 165.8 (C-1 or cyclopentylidene-1), 156.8 (Fn-2), 140.9 (Fn-5), 114.7 (C-2), 110.1 (Fn-4), 104.7 (Fn-3), 59.8 ($OCH_2CH_3$), 42.0 (cyclopentylidene-2), 35.0 (cyclopentylidene-5), 33.1 (cyclopentylidene-3), 23.2 (cyclopentylidene-4), 14.3 ($OCH_2CH_3$).

Minor diastereomer: $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 2.0, 1.0 Hz, 1H, Fn-5), 6.31 (dd, *J* = 3.0, 2.0 Hz, 1H, Fn-4), 6.09 (dt, *J* = 3.0, 1.0 Hz, 1H, Fn-3), 5.66 (q, *J* = 2.5 Hz, 1H, H-2), 4.13 (qd, *J* = 7.0, 1.0 Hz, 2H, $OCH_2CH_3$), 3.77 (ddt, *J* = 10.0, 7.5, 2.5 Hz, 1H, cyclopentylidene-2), 3.09 – 2.98 (m, 1H, cyclopentylidene-5), 2.90 – 2.78 (m, 1H, cyclopentylidene-5), 2.16 – 1.87 (m, 2H, cyclopentylidene-3), 1.87 – 1.62 (m, 2H, cyclopentylidene-4), 1.25 (t, *J* = 7.0 Hz, 3H, $OCH_2CH_3$); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 167.8 (C-1 or cyclopentylidene-1), 167.0 (C-1 or cyclopentylidene-1), 155.3 (Fn-2), 141.9 (Fn-5), 113.9 (C-2), 110.3 (Fn-4), 106.2 (Fn-3), 59.8 ($OCH_2CH_3$), 46.4 (cyclopentylidene-2), 32.7 (cyclopentylidene-5), 31.9 (cyclopentylidene-3), 24.8 (cyclopentylidene-4), 14.5 ($OCH_2CH_3$).

**Ethyl 2-[2-(furan-2-yl)cyclopentyl]-2-(phenylselanyl)acetate (3.22)**

To a solution of DIPA (48 μL, 0.274 mmol) in THF (500 μL), cooled to 0 °C under Ar, was added butyllithium (175 μL, 1.6 M in hexanes, 0.280 mmol) dropwise. The reaction mixture was stirred for 17 min, then cooled to –78 °C and a solution of *cis*-**3.23** (57.0 mg, 0.26 mmol) in THF (200 μL) added slowly. The mixture was stirred for 30 min at −78 °C, during which time separate solutions were prepared of diphenyldiselenide (45.0 mg, 0.14 mmol) in THF (500 μL) and $Br_2$ (100 μL, 1.95 mmol) in THF (7.0 mL), both under Ar. A portion of the bromine solution (500 μL) was added to the vigorously stirred diphenyldiselenide solution at rt. A rapid colour change of the diphenyldiselenide solution from yellow to dark brown was observed; stirring was continued for 5 min, after which time the resulting mixture was transferred to the enolate solution dropwise *via* syringe. The mixture was stirred for 2 h, and the reaction was then quenched by the addition of sat. aq. $Na_2S_2O_3$ solution (2 mL) and sat. aq. $NH_4Cl$ solution (3 mL). The

mixture was then allowed to warm to rt and was extracted with ether (3 × 5 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (4 : 1 PE : toluene – 39 : 10 : 1 PE : toluene : ether) to give 2 separated diastereomers (both *cis*-cyclopentanes; configuration differs α to ester) of the *title compound* as a yellow oil (16 + 12 mg, 28%).

Major diastereomer (assigned *cis* by nOe analysis, see Appendix 3: Nuclear Overhauser Effect Analysis of Compound 3.22): $R_f$ 0.10 (49 : 1 PE : ether); $^1$H NMR (400 MHz, $C_6D_6$) δ 7.63 – 7.56 (m, 2H, *ortho*-Ph), 7.02 – 6.91 (m, 4H, *meta*-Ph and *para*-Ph and Fn-5), 6.03 (dd, $J$ = 3.0, 2.0 Hz, 1H, Fn-4), 6.00 (dd, $J$ = 3.0, 1.0 Hz, 1H, Fn-3), 3.97 – 3.75 (m, 2H, OC$H_2$CH$_3$), 3.56 (ddd, $J$ = 8.5, 7.0, 2.0 Hz, 1H, cyclopentyl-2), 3.43 (d, $J$ = 11.5 Hz, 1H, H-2), 2.65 – 2.49 (m, 1H, cyclopentyl-1), 2.06 – 1.95 (m, 1H, cyclopentyl-5), 1.95 – 1.82 (m, 1H, cyclopentyl-5), 1.83 – 1.60 (m, 4H, cyclopentyl-3 and cyclopentyl-4 and cyclopentyl-5), 1.59 – 1.38 (m, 1H, cyclopentyl-4), 0.82 (t, $J$ = 7.0 Hz, 3H, OCH$_2$C$H_3$); $^{13}$C NMR (101 MHz, $C_6D_6$) δ 172.3 (C-1), 157.3 (Fn-2), 141.3 (Fn-5), 135.8 (*ortho*-Ph), 129.0 (*meta*-Ph), 110.2 (Fn-4), 107.4 (Fn-3), 60.5 (O$C$H$_2$CH$_3$), 46.4 (C-2), 46.2 (cyclopentyl-1), 41.2 (cyclopentyl-2), 31.2 (cyclopentyl-5), 29.7 (cyclopentyl-3), 23.9 (cyclopentyl-4), 14.0 (OCH$_2$$C$H$_3$). Resonances corresponding to *ipso*- and *para*-Ph were not observed and are likely to have been obscured by the solvent signal.

Minor diastereomer (assigned *cis* by nOe analysis, see Appendix 3: Nuclear Overhauser Effect Analysis of Compound 3.22): $R_f$ 0.10 (49 : 1 PE : ether); $^1$H NMR (400 MHz, $C_6D_6$) δ 7.69 – 7.58 (m, 2H, *ortho*-Ph), 7.01 (dd, $J$ = 2.0, 1.0 Hz, 1H, Fn-5), 6.98–6.92 (m, 3H, *meta*- and *para*-Ph), 6.00 (dd, $J$ = 3.0, 2.0 Hz, 1H, Fn-4), 5.79 (dd, $J$ = 3.0,

1.0 Hz, 1H, Fn-3), 3.97 – 3.84 (m, 2H, OC*H*$_2$CH$_3$), 3.55 – 3.45 (m, 1H, cyclopentyl-2), 3.35 (d, *J* = 11.5 Hz, 1H, H-2), 2.69 (tt, *J* = 11.5, 7.5 Hz, 1H, cyclopentyl-1), 2.24 – 2.14 (m, 1H, cyclopentyl-5), 1.86–1.64 (m, 4H, cyclopentyl-3 and cyclopentyl-4 and cyclopentyl-5), 1.42–1.28 (m, 1H, cyclopentyl-4), 0.90 (t, *J* = 7.0 Hz, 3H, OCH$_2$C*H*$_3$); $^{13}$C NMR (101 MHz, $C_6D_6$) δ 172.4 (C-1), 157.4 (Fn-2), 141.5 (Fn-5), 136.2 (*ortho*-Ph), 129.1 (*ipso*-Ph), 128.5 (*meta*-Ph), 110.2 (Fn-4), 107.0 (Fn-3), 60.3 (O*C*H$_2$CH$_3$), 46.7 (cyclopentyl-2), 45.9 (cyclopentyl-1), 40.8 (C-2), 31.9 (cyclopentyl-5), 31.2 (cyclopentyl-3), 23.8 (cyclopentyl-4), 14.1 (OCH$_2$*C*H$_3$) Resonance corresponding to and *para*-Ph was not observed and is likely to have been obscured by the solvent signal.; IR (ATR) ν 2960w, 1725s, 1147m, 737s, 692m; HRMS (EI) calc. for $C_{19}H_{22}O_3Se$ [$M^+$] 378.0729, found 378.0727.

**Ethyl 2-[2-(furan-2-yl)cyclopentyl]acetate (3.23)**

Hydrogenation of cyclopentene **3.24**: To palladium (22 mg, 10 wt.% on carbon, 20 μmol Pd) was added a solution of ethyl 2-[2-(furan-2-yl)cyclopent-1-en-1-yl]acetate **3.24** (206 mg, 0.937 mmol) in ethanol (10 mL). A three-way valve was attached, and the mixture was frozen by immersing the reaction vessel in liquid $N_2$. The flask was filled with $N_2$ *via* three pump-fill cycles. A balloon of hydrogen was attached to the three-way valve and the flask refilled with hydrogen *via* three pump-fill cycles. The mixture was allowed to thaw, then stirred for 16 h. The mixture was then refrozen, and the flask refilled with $N_2$ *via* five pump-fill cycles. After thawing, the mixture was passed through a short plug of Celite, which was then rinsed with ethanol (20 mL). The combined liquid was concentrated, and the residue was purified by column chromatography (1 : 0 – 19 : 1 PE :

ether) to afford a mixture of diastereomers (22 : 3 *cis* : *trans* by NMR) of the *title compound* as a floral-smelling colourless oil (76.0 mg, 37%).

Radical reduction of selenide **3.22**: A solution of selenide **3.22** (24.0 mg, 62.3 μmol) in benzene (5 mL) was deoxygenated by bubbling Ar through for 5 min. A solution of AIBN (1 mg, 6.70 μmol) in benzene (1 mL) was similarly deoxygenated and added to the selenide solution. The resulting mixture was heated to reflux with a preheated oil bath and a solution of TBTH (20 mg, 68.5 μmol) in deoxygenated benzene (4 mL) was added over 1 h. An additional portion of AIBN (1 mg, 6.70 μmol) in benzene (1 mL) was added and reflux was maintained for a further 1 h. The mixture was then concentrated and purified directly by column chromatography (benzene) to afford a mixture of diastereomers (5 : 4 *trans* : *cis* by NMR) of the *title compound* as a colourless oil (6 mg, 41%).

*Cis* isomer (assigned by nOe analysis, see Appendix 4: Nuclear Overhauser Effect Analysis of Compound **3.23**): $R_f$ 0.30 (9 : 1 PE : ether); $^1$H NMR (500 MHz, $C_6D_6$) δ 7.06 (dd, *J* = 2.0, 1.0 Hz, 1H, Fn-5), 6.06 (dd, *J* = 3.0, 2.0 Hz, 1H, Fn-4), 5.82 (dt, *J* = 3.0, 1.0 Hz, 1H, Fn-3), 4.00 – 3.86 (m, 2H, $OCH_2CH_3$), 3.20 (q, *J* = 7.5 Hz, 1H, cyclopentyl-2), 2.67 – 2.55 (m, 1H, cyclopentyl-1), 2.14 (dd, *J* = 16.0, 6.5 Hz, 1H, H-2), 2.00 (dd, *J* = 16.0, 9.0 Hz, 1H, H-2), 1.83 – 1.64 (m, 4H, cyclopentyl-3, cyclopentyl-4, and cyclopentyl-5), 1.52 – 1.33 (m, 2H, cyclopentyl-3 and cyclopentyl-5), 0.94 (t, *J* = 7.0 Hz, 3H, $OCH_2CH_3$); $^{13}$C NMR (126 MHz, $C_6D_6$) δ 172.6 (C-1), 157.7 (Fn-2), 141.3 (Fn-5), 110.2 (Fn-4), 106.3 (Fn-3), 59.9 ($OCH_2CH_3$), 41.7 (cyclopentyl-2), 40.8 (cyclopentyl-1), 36.3 (C-2), 31.4 (cyclopentyl-3 or cyclopentyl-5), 29.9 (cyclopentyl-4), 23.7

(cyclopentyl-3 or cyclopentyl-5), 14.3 ($OCH_2CH_3$); IR (ATR) ν 2961w, 1734s, 1164m, 731w; HRMS (APCI, $NH_3$) found 223.1328, calc. for $C_{13}H_{18}O_3$ $[M+H]^+$ 223.1329.

*Trans* isomer (assigned by process of elimination): $R_f$ 0.25 (19 : 1 PE : ether); $^1$H NMR (500 MHz, $C_6D_6$) δ 7.09 (dd, $J$ = 2.0, 1.0 Hz, 1H, Fn-5), 6.09 (dd, $J$ = 3.0, 2.0 Hz, 1H, Fn-4), 5.90 (d, $J$ = 3.0 Hz, 1H, Fn-3), 3.97 – 3.88 (m, 2H, $OCH_2CH_3$), 2.55 – 2.42 (m, 3H, H-2 and cyclopentyl-1 and cyclopentyl-2), 2.13 – 2.06 (m, 1H, H-2), 1.90 – 1.35 (m, 6H, cyclopentyl-3 and cyclopentyl-4 and cyclopentyl-5), 0.93 (q, $J$ = 7.0 Hz, 3H, $OCH_2CH_3$); $^{13}$C NMR (126 MHz, $C_6D_6$) δ 172.2 (C-1), 158.2 (Fn-2), 141.3 (Fn-5), 110.3 (Fn-4), 104.8 (Fn-3), 60.0 ($OCH_2CH_3$), 45.0 (cyclopentyl-1 or cyclopentyl-2), 42.4 (cyclopentyl-1 or cyclopentyl-2), 39.3 (C-2), 32.3 (cyclopentyl-3 or cyclopentyl-5), 32.0 (cyclopentyl-3 or cyclopentyl-5), 23.9 (cyclopentyl-4), 14.3 ($OCH_2CH_3$).

**Ethyl 2-[2-(furan-2-yl)cyclopentyl]acetate-*d* (3.23-d)**

To a solution of selenide **3.22** (13.7 mg, 36.3 μmol) in benzene[lxxxii] (300 μL) was added a solution of TBTH-*d* (12.7 mg, *ca.* 60% pure, *ca.* 26.2 μmol) in benzene (200 μL) and a solution of AIBN (600 μg, 3.60 μmol) in benzene (230 μL). The mixture was degassed *via* 3 FPTCs and heated to reflux for 1 h. An additional portion of TBTH-*d* (6.4 mg, *ca.* 60% pure, *ca.* 13.1 μmol) in benzene (100 μL) was added and the mixture returned to reflux for a further 45 min. The mixture was then concentrated and purified by column chromatography (1 : 0 – 19 : 1 pentane : ether) to afford a mixture of diastereomers (5 : 1 *cis* : *trans* by NMR) of the *title compound* (4.5 mg, 56%).

[lxxxii] All benzene used in this experiment had natural isotopic abundance, except for that used for NMR analysis; see page 147.

$^{2}$H NMR (92 MHz, benzene) δ 2.53 – 2.41 (m, 0.04D), 2.15 – 2.00 (m, 0.34D), 2.01 – 1.87 (m, 0.62D); HMRS (APCI, $NH_3$) found 224.1391, calc. for $C_{13}H_{17}DO_3$ $[M+H]^+$ 224.1391.

*Cis* isomer (assigned by comparison with *cis*-**3.23**): $^{1}$H NMR (500 MHz, $C_6D_6$) δ 7.05 (dd, *J* = 2.0, 1.0 Hz, 1H, Fn-5), 6.06 (dd, *J* = 3.0, 2.0 Hz, 1H, Fn-4), 5.81 (d, *J* = 3.0 Hz, 1H, Fn-3), 3.93 (qd, *J* = 7.0, 3.0 Hz, 2H, OC*H*$_2$CH$_3$), 3.19 (qd, *J* = 7.5, 3.0 Hz, 1H, cyclopentyl-2), 2.64 – 2.58 (m, 1H, cyclopentyl-1), 2.13 (dd, *J* = 16.0, 6.5 Hz, 0.5H, H-2), 2.03 – 1.96 (m, 0.5H, H-2), 1.80 – 1.66 (m, 4H, cyclopentyl-3 and cyclopentyl-4 and cyclopentyl-5), 1.49 – 1.34 (m, 2H, cyclopentyl-3 and cyclopentyl-5), 0.93 (t, *J* = 7.0 Hz, 3H, OCH$_2$C*H*$_3$); $^{13}$C NMR (126 MHz, $C_6D_6$) δ 172.6 (C-1), 157.7 (Fn-2), 141.3 (Fn-5), 110.2 (Fn-4), 106.3 (Fn-3), 59.9 (O*C*H$_2$CH$_3$), 41.7 (cyclopentyl-2), 40.7 (cyclopentyl-1), 36.3 (residual *bis*-protiated C-2), 36.0 (1 : 1 : 1 t, *J* = 20 Hz, C-2), 31.4 (cyclopentyl-3 or cyclopentyl-5), 29.9 (cyclopentyl-4), 23.7 (cyclopentyl-3 or cyclopentyl-5), 14.3 (OCH$_2$*C*H$_3$).

*Trans* isomer (assigned by comparison with *trans*-**3.23**): $^{1}$H NMR (500 MHz, $C_6D_6$) δ 7.08 (dd, *J* = 2.0, 1.0 Hz, 1H, Fn-5), 6.08 (dd, *J* = 3.0, 2.0 Hz, 1H, Fn-4), 5.89 (dd, *J* = 3.0, 1.0 Hz, 1H, Fn-3), 3.93 (qd, *J* = 7.0, 3.0 Hz, 2H, OC*H*$_2$CH$_3$), 2.56 – 2.43 (m, 2.5H, H-2 and cyclopentyl-1 and cyclopentyl-2), 2.14 – 2.05 (m, 0.5H, H-2), 1.86 – 1.33 (m, 6H, cyclopentyl-3 and cyclopentyl-4 and cyclopentyl-5), 0.93 (t, *J* = 7.0 Hz, 3H, OCH$_2$C*H*$_3$). $^{13}$C NMR (126 MHz, $C_6D_6$) δ 172.2 (C-1), 158.2 (Fn-2), 141.3 (Fn-5), 110.3 (Fn-4), 104.8 (Fn-3), 60.0 (O*C*H$_2$CH$_3$), 45.0 (cyclopentyl-1 or cyclopentyl-2), 42.4 (cyclopentyl-1 or cyclopentyl-2), 39.3 (residual *bis*-protiated C-2), 39.0 (1 : 1 : 1 t, *J* = 20 Hz), 38.9 (1 : 1 : 1 t, *J* = 20 Hz), 32.3 (cyclopentyl-3 or cyclopentyl-4 or cyclopentyl-

5), 32.0 (cyclopentyl-3 or cyclopentyl-4 or cyclopentyl-5), 23.9 (cyclopentyl-3 or cyclopentyl-4 or cyclopentyl-5), 14.3 ($OCH_2\mathit{C}H_3$).

**Ethyl 2-[2-(furan-2-yl)cyclopent-1-en-1-yl]acetate (3.24)**

To a solution of carbethoxymethylenetriphenylphosphorane (232 mg, 0.666 mmol) in benzene (750 μL) under Ar was added *via* syringe 2-(furan-2-yl)cyclopentanone **3.20** (100 mg, 0.666 mmol). The mixture was heated to reflux for 20 h, then cooled and purified directly by column chromatography (1 : 0 – 19 : 1 PE : ether) to afford the *title compound*, in some cases with isomers **3.21**, as a colourless to orange oil (41 mg, 28%, recovered 39% SM).

$R_f$ 0.30 (23 : 2 PE : ether); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, $J$ = 2.0 Hz, 1H, Fn-5), 6.37 (dd, $J$ = 3.5, 2.0 Hz, 1H, Fn-4), 6.24 (d, $J$ = 3.5 Hz, 1H, Fn-3), 4.15 (q, $J$ = 7.0 Hz, 2H, $OC\mathit{H}_2CH_3$), 3.58 (t, $J$ = 1.5 Hz, 2H, H-2), 2.76 – 2.65 (m, 2H, cyclopentene-3), 2.63 –2.53 (m, 2H, cyclopentene-5), 1.94 (p, $J$ = 7.5 Hz, 2H, cyclopentene-4), 1.26 (t, $J$ = 7.0 Hz, 3H, $OCH_2C\mathit{H}_3$); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 171.6 (C-1), 152.6 (Fn-2), 141.6 (Fn-5), 131.0 (cyclopentene-1 or cyclopentene-2), 128.1 (cyclopentene-1 or cyclopentene-2), 110.9 (Fn-4), 107.7 (Fn-3), 60.7 ($O\mathit{C}H_2CH_3$), 38.1 (cyclopentene-5), 35.8 (C-2), 34.7 (cyclopentene-3), 22.2 (cyclopentene-4), 14.4 ($OCH_2\mathit{C}H_3$); IR (ATR) ν 1732s (C=O stretch), 1655w (C=C stretch), 1177s, 1155s, 1035m, 1009m, 732s; HRMS (APCI, $NH_3$) found 221.1174, calc. for $C_{13}H_{16}O_3$ $[M+H]^+$ 221.1172.

**1-(5-Methylfuran-2-yl)pent-4-en-1-ol (3.28)**

To a suspension of Mg powder (657 mg, 27.0 mmol) in THF (2 mL) under Ar was added a dilute solution of $I_2$ in THF (0.5 mL). The mixture was heated to reflux, and a solution of 4-bromobut-1-ene (3.00 mL, 29.6 mol) in THF (3 mL) was added dropwise over 90 min. 5-Methylfurfural (2.70 mL, 27.0 mmol) was added dropwise over 10 min, and the mixture was stirred for a further 40 min. The mixture was diluted with sat. aq. $NH_4Cl$ (10 mL) and extracted with ether (2 × 10 mL). The combined organic phases were washed with $H_2O$ (20 mL) and brine (10 mL), then dried over $MgSO_4$, filtered, and concentrated to afford the title compound as a brown oil (3.78 g, 46%) which could be used without further purification. Column chromatography (1 : 0 – 4 : 1 PE : ether) afforded an analytically pure pale yellow oil.

Data are consistent with literature values: (*408*) $R_f$ 0.55 (49 : 1 DCM : methanol); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.10 (d, *J* = 3.0 Hz, 1H, Fn-3), 5.89 (dq, *J* = 3.0, 1.0 Hz, 1H, Fn-4), 5.83 (ddt, *J* = 17.0, 10.5, 7.0 Hz, 1H, H-4), 5.05 (dq, *J* = 17.0, 1.5 Hz, 1H, H-5 *trans* to H-4), 4.99 (ddt, *J* = 10.5, 2.5, 1.5 Hz, 1H, H-5 *cis* to H-4), 4.62 (td, *J* = 7.0, 5.0 Hz, 1H, H-1), 2.28 (d, *J* = 1.0 Hz, 3H, Me), 2.24 – 2.07 (m, 2H, H-2), 1.92 (q, *J* = 7.0 Hz, 2H, H-3); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 154.8 (Fn-3), 151.8 (Fn-4), 138.1 (C-4), 115.2 (C-5), 106.9 (Fn-2 or Fn-5), 106.1 (Fn-2 or Fn-5), 67.3 (C-1), 34.6 (C-2), 30.0 (C-3), 13.7 (Me).

***O*-[1-(5-Methylfuran-2-yl)pent-4-en-1-yl] 1*H*-imidazole-1-carbothioate (3.29)**

A solution of TCDI (167 mg, 937 μmol) in DCM (2 mL) under $N_2$ was added to DMAP (37.3 mg, 305 μmol). A solution of 1-(5-methylfuran-2-yl)pent-4-en-1-ol **3.28**

(53.0 mg, 321 μmol) in DCM (1 mL) was added and the mixture stirred at rt for 1 h, then diluted with PE (10 mL) and purified directly by column chromatography (1: 0 – 7 : 3 PE : ether) to afford the *title compound* as a viscous yellow oil. (73.1 mg, 82%).

$R_f$ 0.40 (49 : 1 DCM : methanol); $^1$H NMR (500 MHz, $C_6D_6$) δ 8.01 (br t, $J$ = 1.0 Hz, 1H, Im-2), 7.05 (br t, J = 1.5 Hz, 1H, Im-5), 6.87 (dd, $J$ = 1.5, 1.0 Hz, 1H, Im-4), 6.04 (d, $J$ = 3.0 Hz, 1H, Fn-4), 5.68 (dq, $J$ = 3.0, 1.0 Hz, 1H, Fn-3), 5.67 – 5.59 (m, 1H, H-5), 4.97 – 4.92 (m, 2H, H-5), 4.88 (dd, $J$ = 8.5, 6.0 Hz, 1H, H-1), 2.13 – 2.02 (m, 1H, H-2), 2.02 – 1.88 (m, 6H, H-2 and H-3 and Me); $^{13}$C NMR (126 MHz, $C_6D_6$) δ 165.1 (C=S), 152.6 (Fn-2), 150.5 (Fn-5), 136.9 (C-4), 135.5 (Im-2), 131.4 (Im-4), 116.0 (C-5), 115.8 (Im-5), 109.4 (Fn-3), 106.8 (Fn-4), 43.4 (C-1), 33.2 (C-2), 31.6 (C-3), 13.4 (Me); IR (ATR) ν 3061w (C–H), 2943w (C–H), 2882w (C–H), 2830w (C–H), 1636m, 1528s, 1483m, 1348s, 802s, 781s, 731s; HRMS (APCI, $NH_3$) found 149.0960, calc. for $C_{14}H_{16}N_2O_2S$ $[M–C_4H_3N_2OS]^+$ 149.0961.

**_S_-Methyl _O_-[1-(5-methylfuran-2-yl)pent-4-en-1-yl] carbonodithioate (3.30)**

To NaH (33.5 mg, 60% w/w dispersion in mineral oil, 838 μmol) under Ar was added THF (0.6 mL). The resulting suspension was cooled to 0 °C and a solution of alcohol **3.28** (100 mg, 600 μmol) in THF (0.6 mL) was added cautiously. The resulting mixture was warmed to rt and stirred for 40 min then cooled to 0 °C. $CS_2$ (100 μL, 1.67 mmol) was added and the mixture stirred for 45 min at 0 °C. $CH_3I$ (70.0 μL, 1.12 mmol) was added and the mixture stirred for 30 min. The reaction was quenched by addition of $H_2O$ (10 mL) and the resulting mixture was extracted with toluene (3 × 3 mL). The organic phase was concentrated and the residue purified by column chromatography (1 : 0 – 9 : 1 PE : ether) to afford the *title compound* as an orange oil (90 mg, 58%).

$R_f$ 0.45 (49 : 1 PE : ether); $^1$H NMR (500 MHz, $C_6D_6$) δ 6.02 (d, $J$ = 3.0 Hz, 1H, Fn-3), 5.68 – 5.58 (m, 2H, H-4 and Fn-4), 5.08 (t, $J$ = 7.5 Hz, 1H, H-1), 4.99 – 4.89 (m, 2H, H-5), 2.20 – 1.94 (m, 4H, H-2 and H-3), 1.90 (d, $J$ = 1.0 Hz, 3H, Fn-Me), 1.88 (s, 3H, SMe); $^{13}$C NMR (126 MHz, $C_6D_6$) δ 188.6 (C=S), 152.1 (Fn-5), 151.7 (Fn-2), 137.2 (C-4), 115.7 (C-5), 108.7 (Fn-3), 106.7 (Fn-4), 42.9 (C-1), 33.6 (C-3), 31.7 (C-2), 13.4 (SMe), 12.6 (Fn-Me); IR (ATR) ν 2928w, 1644m, 867s, 785w; HRMS (APCI, $NH_3$) found 257.0669, calc. for $C_{12}H_{16}O_2S_2$ $[M+H]^+$ 257.0664.

**2-Methyl-5-(pent-4-en-1-yl)furan (3.31)**

A solution of dithiocarbonate **3.30** (38.0 mg, 150 μmol), triphenylstannane (79.0 mg, 225 μmol) and AIBN (2 mg, 12 μmol) in $C_6D_6$ (1.00 mL) was degassed *via* 3 FPTCs and heated to reflux for 48 min. The mixture was then concentrated and purified by column chromatography (pentane) to afford the title compound as a colourless oil (3.9 mg, 17%).

Data are consistent with literature values: (*403*) $R_f$ 0.50 (pentane); $^1$H NMR (400 MHz, $C_6D_6$) δ 5.83 (d, $J$ = 3.0 Hz, 1H, Fn-3 or Fn-4), 5.80 (d, $J$ = 3.0 Hz, 1H, Fn-3 or Fn-4), 5.68 (ddt, $J$ = 17.0, 10.0, 6.5 Hz, 1H, H-4), 5.01 – 4.92 (m, 2H, H-5), 2.49 (t, $J$ = 7.5 Hz, 2H, H-1), 2.06 (s, 3H, Me), 1.99 – 1.89 (m, 2H, H-3), 1.64 (p, $J$ = 7.5 Hz, 2H, H-2).

***O*-Cyclohexyl 1*H*-imidazole-1-carbothioate (3.33)**

To TCDI (535 mg, 3.00 mmol) under Ar was added a solution of DMAP (122 mg, 1.00 mmol) in dry DCM (10 mL). The mixture was cooled to 0 °C and cyclohexanol (100 mg, 1.00 mmol) was added in one portion. The mixture was stirred at 0 °C for 4 h, then warmed to rt and stirred for a further 17 h, at which point the cyclohexanol had been fully converted (NMR). The mixture was then diluted with PE (20 mL) and purified by column

chromatography (1 : 0 – 1 : 1 PE : ether) to afford the title compound as a colourless oil. (160 mg, 76%).

Data are consistent with literature values: (*409*) $R_f$ 0.25 (4 : 1 PE : ether); $^1$H NMR (500 MHz, $C_6D_6$) δ 8.31 (s, 1H, Im-2), 7.43 (t, $J$ = 1.5 Hz, 1H, Im-5), 6.95 – 6.91 (m, 1H, Im-4), 5.28 (tt, $J$ = 8.0, 4.0 Hz, 1H, H-1), 1.61 (ddd, $J$ = 12.0, 8.0, 4.0 Hz, 2H, H-2 and H-6), 1.40 – 1.32 (ddq, $J$ = 14.0, 3.5, 3.5 Hz, 2H, H-3 and H-5), 1.31 – 1.25 (ddd, $J$ = 12.5, 8.5, 4.0 Hz, 2H, H-2 and H-6), 1.21 – 1.14 (m, 1H, H-4), 1.06 (m, 3H, H-3 and H-5 and H-4); $^{13}$C NMR (126 MHz, $C_6D_6$) δ 183.7 (C=S), 136.8 (Im-2), 131.3 (Im-4), 118.2 (Im-5), 82.2 (C-1), 30.5 (C-2 and C-6), 25.3 (C-4), 23.5 (C-3 and C-5); IR (ATR) ν 1379s, 1279s, 1127s, 1092m, 1001m, 964s; HRMS (APCI, $NH_3$) found 211.0904, calc. for $C_{10}H_{14}N_2OS$ $[M+H]^+$ 211.0900.

**_S_-Cyclohexyl 1_H_-imidazole-1-carbothioate (3.34)**

To a solution of 1,1'-carbonyldiimidazole (60 mol% pure by NMR – remainder imidazole, 300 mg, 1.11 mmol) in dry DCM (4.3 mL) was added cyclohexanethiol (105 µL, 0.861 mmol). The mixture was heated to reflux for 21 h, then concentrated and purified by column chromatography (1: 0 – 7 : 3 PE : ether) to afford the *title compound* as a waxy white solid (222 mg, quant.)

$R_f$ 0.30 (59 : 25 :16 PE : ether : DCM); mp 32 °C; $^1$H NMR (500 MHz, $C_6D_6$) δ 8.10 (s, 1H, Im-2), 7.18 – 7.12 (m, 1H, Im-5), 6.96 – 6.92 (m, 1H, Im-4), 3.50 (tt, $J$ = 10.0, 4.0 Hz, 1H, H-1), 1.78 – 1.70 (m, 2H, H-2 and H-6), 1.45 – 1.34 (m, 2H, H-3 and H-5), 1.21 (dtd, $J$ = 13.5, 10.5, 3.5 Hz, 3H, H-2, H-6 and H-4), 1.08 (dtt, $J$ = 13.5, 10.5, 3.5 Hz, 2H, H-3 and H-5), 1.03 – 0.91 (m, 1H, H-4); $^{13}$C NMR (126 MHz, $C_6D_6$) δ 165.6

(C=O), 135.6 (Im-2), 131.4 (Im-5), 115.9 (Im-4), 44.8 (C-1), 32.9 (C-2 and C-6), 25.8 (C-3 and C-5), 25.5 (C-4); IR (ATR) ν 2932m, 1684s (C=O), 1271s, 1219s, 1209s, 1098s, 1061s, 887s, 816s, 760s, 667s; HRMS (APCI, $NH_3$) found 211.0904, calc. for $C_{10}H_{14}N_2OS$ $[M+H]^+$ 211.0900.

# Chapter 4

**General Procedure for Oxidation of Furan Mediated by 2.8**

To a 0.125 M solution of the starting material in acetonitrile in a sample vial was added sequentially pyridine (2.2 eq.), a solution of **2.8** (0.01 eq.) in acetonitrile, and water [0.25 volumes relative to acetonitrile (including that added with the catalyst)]. The vial was sealed with a septum and $O_2$ was bubbled from a balloon through the resulting mixture, which was stirred, and irradiated by a blue LED lamp (12 V DC, 0.06 A, $P_{irr}$ 720 mW, $\lambda_{max,irr}$ 480 nm). When the reaction was deemed complete, the mixture was purified directly by column chromatography and the eluate concentrated to afford the title compound.

**(*E*)-9-(1,3-Dithian-2-yl)-non-3-ene-2,5-dione [(*E*)-4.1a]**

Brown oil produced from 2-[4-(1,3-Dithian-2-yl)butyl]-5-methylfuran **2.23** (422 mg, 70 % pure, 1.00 mmol) according to General Procedure for Oxidation of Furan Mediated by **2.8**. Reaction time 1 h 55 min, chromatography performed with 1 : 1 ether : PE as eluant. Yield 185 mg (59 %).

$R_f$ 0.30 (1 : 1 ether : PE); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.81 (s, 1H, H-3 and H-4), 4.03 (t, $J$ = 7.0 Hz, 1H, Dth-2), 2.96 – 2.75 (m, 4H, Dth-4,6), 2.68 (t, $J$ = 7.5 Hz, 2H, H-6), 2.35 (s, 3H, H-1), 2.21 – 2.00 (m, 1H, Dth-5), 1.95 – 1.80 (m, 1H, Dth-5), 1.80 – 1.69 (m, 2H, H-9), 1.70 – 1.60 (m, 2H, H-7), 1.58 – 1.47 (m, 2H, H-8); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 200.3 (C-5), 198.6 (C-2), 137.2 (C-3 or C-4), 137.1 (C-3 or C-4), 47.4 (Dth-2), 41.2 (C-6), 35.2 (C-9), 30.6 (Dth-4,6), 28.4 (C-1), 26.2 (C-8), 26.1 (Dth-5), 23.3 (C-7); IR (ATR) ν 2980w (C–H), 2934w (C–H), 2903w (C–H), 1702m, 1681s (C=O),

1620w (C=C), 1360m, 1249s, 980m, 908m, 730s; HRMS (EI) found 272.0908, calc. for $C_{13}H_{20}O_2S_2$ $[M]^+$ 272.0899.

**2-Hexyl-5-methylfuran (4.2)**

To a solution of 2-methylfuran (1.80 mL, 20.0 mmol) in THF (20 mL), under $N_2$ and at –78 °C was added dropwise over 7 min butyllithium (6.00 mL, 2.5 M in hexanes, 15.0 mmol). When addition was complete, the mixture was warmed to 0 °C and stirred for 3 h. 1-Iodohexane (1.50 mL, 10.2 mmol) was added and the mixture allowed to warm to rt over 20 h.[lxxxiii] To the reaction mixture was added sat. aq. $NH_4Cl$ (2 mL). The mixture was then concentrated and diluted with $H_2O$ (100 mL) and extracted with PE (5 × 10 mL). The combined organic phases were then washed with water (50 mL) and brine (10 mL), dried over $Na_2SO_4$ and activated charcoal, then filtered and concentrated to afford the title compound as a yellow oil (1.41 g, 85%).

Data are consistent with literature values: (*410*) $R_f$ 0.65 (PE); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.83 (s, 2H, Fn-3 and Fn-4), 2.56 (t, $J$ = 7.5 Hz, 2H, H-1), 2.25 (s, 3H, Fn-Me), 1.61 (p, $J$ = 7.5 Hz, 2H, H-2), 1.46 – 1.24 (m, 6H, H-3,4,5), 0.97 – 0.81 (m, 3H, H-6); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 155.0 (Fn-2 or Fn-5), 150.1 (Fn-2 or Fn-5), 105.8 (Fn-3 or Fn-4), 105.2 (Fn-3 or Fn-4), 31.8, 29.1, 28.3 (C-2), 28.2 (C-1), 22.7, 14.2 (C-6), 13.7 (Fn-Me).

[lxxxiii] $^1$H NMR analysis indicated that the reaction had proceeded to completion within 4 h.

**(*E*)-2,5-Dioxoundec-3-ene [(*E*)-4.3a]**

Cream powder produced from 2-hexyl-5-methylfuran **4.2** (101 mg, 602 μmol) according to General Procedure for Oxidation of Furan Mediated by **2.8**. Reaction time 2 h 30 min, chromatography performed with 84 : 15 : 1 PE : ether : TEA as eluant. Yield 83.4 mg (76 %).

$R_f$ 0.50 (79 : 20 : 1 PE : ether : TEA); mp 35 °C, $^1$H NMR (400 MHz, $CDCl_3$) δ 6.80 (s, 2H, H-3 and H-4), 2.63 (t, $J$ = 7.5 Hz, 2H, H-6), 2.35 (s, 3H, H-1), 1.68 – 1.54 (m, 2H H-7), 1.36 – 1.21 (m, 6H, H-8, H-9, H-10), 0.92 – 0.80 (m, 3H, H-11); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 200.9 (C-5), 198.6 (C-2), 137.3 (C-4), 137.0 (C-3), 41.5 (C-6), 31.6 (C-9), 28.9 (C-8), 28.3 (C-1), 23.8 (C-7), 22.6 (C-10), 14.1 (C-11); IR (ATR) ν 2956m (C–H), 2931m (C–H), 2916m (C–H), 2871w (C–H), 2853w (C–H), 1672s (C=O), 1653s (C=O), 1270m, 1231m, 1173s, 1000s; HRMS (APCI, $CH_4$) found 183.1373, calc. for $C_{11}H_{18}O_2$ $[M+H]^+$ 183.1380.

**2-(5-Methylfuran-2-yl)ethan-1-ol (4.4)**

To a suspension of $LiAlH_4$ (621 mg, 16.3 mmol) in THF (30 mL) maintained at rt *via* a water bath was added a solution of ester **4.6** (5.00 g, 29.7 mmol) in THF (30 mL) dropwise with vigorous stirring. When addition was complete, the mixture was stirred at rt for 1 h 15 min, after which time the mixture was quenched with ethyl acetate (30 mL) and filtered. The filtrate was diluted with sat. aq. sodium potassium tartrate (30 mL) and $H_2O$ (30 mL) and the mixture stirred until no longer an emulsion. The aqueous phase was extracted with ethyl acetate (3 × 50 mL) and organic phases combined, washed with $H_2O$,

dried over $MgSO_4$, filtered and concentrated to give the title compound as a malodourous pale yellow oil (3.68 g, 98%).

Data are consistent with literature values: (*305*) $R_f$ 0.20 (4 : 1 PE : ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.97 (d, *J* = 2.0 Hz, 1H, Fn-3), 5.87 (dq, *J* = 2.0, 1.0 Hz, 1H, Fn-4), 3.84 (q, *J* = 6.0 Hz, 2H, H-1), 2.84 (t, *J* = 6.0 Hz, 2H, H-2), 2.30 – 2.21 (m, 3H, Me), 1.76 – 1.62 (m, 1H, OH); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 151.1 (Fn-5), 150.8 (Fn-2), 107.3 (Fn-4), 106.1 (Fn-3), 61.2 (C-1), 31.7 (C-2), 13.6 (Me).

**2-(2-Oxopropyl)-dihydrofuran-3(2*H*)-one (4.5c)**

To a solution of Ru complex **2.8** in acetonitrile (1.26 mL) and $H_2O$ (320 μL) was added 2-(5-methylfuran-2-yl)ethan-1-ol **4.4**. The mixture was irradiated with a blue LED lamp, (12 V DC, 0.06 A, $\lambda_{max,irr}$ 480 nm) and vigorously stirred under $O_2$ for 16.2 h. The reaction mixture was diluted with $H_2O$ (12 mL) and extracted with DCM (3 × 3 mL), and the organic phases were concentrated (150 mbar, 40 °C), and the residue purified by column chromatography (1 : 0 – 9 : 1 DCM : methanol) to afford the title compound as a hazelnut-scented brown oil (5.7 mg, containing 16% w/w DCM, 22%).

Data are consistent with literature values: (*309*) $R_f$ 0.40 (49 : 1 DCM : methanol); $^1$H NMR (400 MHz, $CDCl_3$) δ 4.34 (tdd, *J* = 9.5, 4.0, 0.5 Hz, 1H, H-5), 4.10 (td, *J* = 9.0, 7.5 Hz, 1H, H-5), 3.96 (dt, *J* = 5.5, 3.5 Hz, 1H, H-2), 3.00 (dd, *J* = 18.0, 3.5 Hz, 1H, Oxp-1), 2.85 (dd, *J* = 18.0, 5.5 Hz, 1H, Oxp-1), 2.75 (dd, *J* = 9.5, 9.0 Hz, 1H, H-4), 2.51 (dddd, *J* = 18.0, 7.5, 4.0, 0.5 Hz, 1H, H-4), 2.17 (s, 3H, Oxp-3); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 215.6 (C-3), 202.7 (Oxp-2), 75.5 (C-2), 65.2 (C-5), 45.1 (Oxp-1), 36.6 (C-4), 30.2 (Oxp-3).

**Ethyl 2-(5-methylfuran-2-yl)acetate (4.6)**

**Ensure that the reaction has gone to completion (with respect to consumption of ethyl iodoacetate) before workup. Failure to do so will render both product and glassware potent lachrymators. Use aq. NaOH to render spills safe.** To a mixture of 2-methylfuran (80 mL) and DMSO (80 mL) was added $FeSO_4 \cdot 7H_2O$ (8.20 g, 29.8 mmol). Ethyl iodoacetate (12.7 g, 59.5 mmol) was added and the reaction vessel immersed in ice water. $H_2O_2$ (35% v/v in $H_2O$, 14.6 mL, 150 mmol) was added over 1 h *via* syringe pump. The mixture was warmed to rt and stirred for 18 h, after which time stirring was stopped. The less dense phase was retained and the denser phase diluted with $H_2O$ (400 mL) and extracted with PE (3 × 50 mL). The combined organic phases were then washed with $H_2O$ (100 mL), dried over $MgSO_4$, filtered, and concentrated to give the title compound as an apple-scented orange oil (9.5 g, 95%).

Data are consistent with literature values: (*305*) $R_f$ 0.60 (4 : 1 PE : ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.07 (d, $J$ = 3.0 Hz, 1H, Fn-3), 5.88 (d, $J$ = 3.0 Hz, 1H, Fn-4), 4.16 (d, $J$ = 7.0 Hz, 2H, C$H_2$CH$_3$), 3.60 (s, 2H, C$H_2$CO$_2$Et), 2.25 (s, 3H, Fn-Me), 1.25 (t, $J$ = 7.0 Hz, 3H, CH$_2$C$H_3$); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 169.9 (C-1), 151.8 (Fn-5), 146.0 (Fn-2), 108.8 (Fn-4), 106.5 (Fn-3), 61.2 (CO$_2$*C*H$_2$), 14.3 (Fn-Me), 13.7 (CH$_2$*C*H$_3$).

**2-(5,5-Difluoropentyl)-5-methylfuran (4.7)**

To a solution of aldehyde **2.14** (158 mg, 952 μmol) in DCM (10 mL), cooled to −78 °C, was added diethylaminosulfur trifluoride (184 mg, 1.14 mmol). The mixture was allowed to warm to rt and stirred for 1 h 45 min, after which time the mixture was cooled to −10 °C and water (5 mL) added. The aqueous phase was extracted with DCM (2 × 5

mL). The combined organic phases were washed with brine (5 mL), dried over $MgSO_4$ and concentrated, and the residue purified by column chromatography (1 : 0 – 47 : 3 PE : ether) to afford the *title compound* as a white semisolid (72.3 mg, 40%).

$R_f$ 0.75 (9 : 1 PE : ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.87 – 5.82 (m, 2H, Fn-3 and Fn-4), 5.80 (tt, $^3J_{HF}$ = 57 Hz, $^3J_{HH}$ = 4.5 Hz, 1H, H-5), 2.59 (t, $J$ = 7.5 Hz, 2H, H-1), 2.25 (d, $J$ = 1.0 Hz, 3H, Me), 1.84 (m, 2H, H-4), 1.68 (p, $J$ = 7.5 Hz, 2H, H-2), 1.56 – 1.46 (m, 2H, H-3); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 153.9 (Fn-2 or Fn-5), 150.5 (Fn-2 or Fn-5), 117.5 (t, $^1J_{CF}$ = 239 Hz, C-5), 105.9 (Fn-3 or Fn-4), 105.7 (Fn-3 or Fn-4), 34.0 (t, $^2J_{CF}$ = 21 Hz, C-4), 27.9 (C-1), 27.80 (C-2), 21.8 (t, $^3J_{CF}$ = 6 Hz, C-3), 13.7 (Me); $^{19}$F NMR (377 MHz, $CDCl_3$) δ –115.8 (dt, $^2J_{FH}$ = 57 Hz, $^3J_{FH}$ = 18 Hz); IR (ATR) ν 2928w (C–H), 2867w (C–H), 1121s, 1020s, 780s; HRMS (APCI) found 189.1085, calc. for $C_{10}H_{14}OF_2$ $[M+H]^+$ 189.1086.

**(*E*)-10,10-Difluorodec-3-ene-2,5-dione [(*E*)-4.8a]**

White semisolid produced from 2-(5,5-difluoropentyl)-5-methylfuran **4.7** (50.0 mg, 266 μmol) according to General Procedure for Oxidation of Furan Mediated by **2.8**. Reaction time 2 h 45 min, chromatography performed with 89 : 10 : 1 – 79 : 20 : 1 pentane : ether : TEA as eluant. Yield 19.0 mg, (35 %).

$R_f$ 0.05 (10% ether/pentane, 1% TEA); $^1$H NMR (400 MHz, $C_6D_6$) δ 6.50 (d, $J$ = 16.5 Hz, 1H, H-3 or H-4), 6.41 (d, $J$ = 16.5 Hz, 1H, H-3 or H-4), 5.31 (tt, $^3J_{HF}$ = 57 Hz, $^3J_{HH}$ = 4.5 Hz, 1H, H-10), 1.86 (t, $J$ = 7.0 Hz, 2H, H-6), 1.71 (s, 3H, H-1), 1.44 – 1.30 (m, 2H, H-9), 1.30 – 1.21 (m, 2H, H-7), 1.08 – 0.97 (m, 2H, H-8); $^{13}$C NMR (101 MHz, $C_6D_6$) δ 198.9 (C-5), 197.2 (C-2), 136.6 (C-3 and C-4), 117.4 (t, $^1J_{CF}$ = 239 Hz, C-10), 40.5 (C-

6), 34.0 (t, $^{2}J_{CF}$ = 21 Hz, C-9), 27.7 (C-1), 22.92 (C-7), 21.64 (t, $^{3}J_{CF}$ = 6 Hz, C-8); $^{19}$F NMR (377 MHz, $C_6D_6$) δ –115.7 (dt, $^{2}J_{FH}$ = 57 Hz, $^{3}J_{FH}$ = 18 Hz);[lxxxiv] IR (ATR) ν 2959w (C–H), 2919w (C–H), 2580w (C–H), 1682s (C=O stretch), 1621w (C=C stretch), 1363m, 1252s, 1120s, 1061s, 1023s, 981s; HRMS ($ESI^+$) found 205.1036, calc. for $C_{10}H_{15}O_2F_2$ $[M+H]^+$ 205.1035.

**Iodoacetonitrile (4.9)**

Prepared according to a reported procedure. (*411*) To a suspension of NaI (6.75 g, 45.0 mmol) in acetone (22 mL), cooled in a water bath, was added dropwise chloroacetonitrile (1.90 mL, 30 mmol). The mixture was stirred at rt for 45 min and diluted with pentane (10 mL). The mixture was filtered and the filtrate concentrated, then redissolved in DCM (50 mL) and again filtered and concentrated to afford the title compound as a yellow oil (3.72 g, contaminated with 4% w/w toluene and 0.6% w/w acetone, 74%).

Data are consistent with literature values: (*412*,*413*) $R_f$ 0.15 (9 : 1 pentane : ether); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 3.50 (s, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 116.1 (C-1), –32.3 (C-2).

**2-(5-Methylfuran-2-yl)acetonitrile (4.10)**

To a solution of iodoacetonitrile **4.9** (501 mg, 3.00 mmol) and 2-methylfuran (4.1 mL, 45.4 mmol) in DMSO (60 mL), cooled with a water bath at rt, was added $FeSO_4 \cdot 7H_2O$ (335 mg, 1.2 mmol). $H_2O_2$ (1.40 mL, 30% w/v in $H_2O$, 4.67 mmol) was

[lxxxiv] The resonance corresponding to a trace (<10%) of the (*Z*)-isomer (–115.6 ppm; dt, $^{2}J_{FH}$ = 57 Hz, $^{3}J_{FH}$ = 18 Hz) was also visible.

added dropwise. The mixture was stirred at rt for 18 h and diluted with water (60 mL). The mixture was extracted with ether (3 × 50 mL) and the aqueous phase diluted with brine (30 mL). The aqueous phase was then extracted a further two times with ether (2 × 50 mL). All organic phases were combined and washed with sat. aq. $Na_2S_2O_3$ (25 mL), $H_2O$ (3 × 30 mL) and brine (10 mL). The organic phase was then dried over $Na_2SO_4$, filtered, and concentrated to afford the title compound as an orange oil (338 mg, 93%).

Data are consistent with literature values: (*414*) $R_f$ 0.40 (4 : 1 pentane : ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.23 – 6.14 (m, 1H, Fn-3), 5.92 (dq, *J* = 3.0, 1.0 Hz, 1H, Fn-4), 3.71 (d, *J* = 1.0 Hz, 2H, H-2), 2.29 – 2.26 (m, 3H, Me); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 153.0 (Fn-5), 140.8 (Fn-2), 115.8 (C-1), 109.2 (Fn-3), 106.7 (Fn-4), 17.5 (C-2), 13.5 (Me).

**2-Methyl-5-(2-nitrovinyl)furan (4.11)**

To ammonium acetate (2.96 g, 38.4 mmol) was added a solution of 5-methylfurfural (4.50 mL, 45.4 mmol) in nitromethane (40 mL). The mixture was heated to reflux for 50 minutes, then cooled to rt, concentrated and reconcentrated twice from DCM. The residue was taken up in a minimum of DCM and the addition of a layer of pentane on top of the DCM solution caused crystals to form. The liquid was discarded and the crystals recovered, affording the title compound as orange needles (2.45 g, 35%).

Data are consistent with literature values: (*415*) $R_f$ 0.35 (4 : 1 ether : PE); mp 77 °C (lit. 71 – 74 °C); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 13.0 Hz, 1H, H-1), 7.46 (d, *J* = 13.0 Hz, 1H, H-2), 6.80 (d, *J* = 3.5 Hz, 1H, Fn-4), 6.20 (dd, *J* = 3.5, 1.0 Hz, 1H, Fn-

3), 2.38 (br s,[lxxxv] 3H, Me); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 158.5 (Fn-2), 145.4 (Fn-5), 133.5 (C-2), 125.6 (C-1), 122.3 (Fn-4), 110.4 (Fn-3), 14.2 (Me).

**2-(5-Methylfuran-2-yl)ethan-1-amine (4.12)**

To a suspension of $LiAlH_4$ (620 mg, 16.3 mmol) in THF (20 mL) in a 2-neck round bottomed flask fitted with a septum and reflux condenser, under $N_2$ and cooled to 0 °C was added dropwise a solution of 2-methyl-5-(2-nitrovinyl)furan **4.11** as a solution in THF (6 mL). The mixture was brought to reflux and stirred for 2 h 30 min.[lxxxvi] The mixture was cooled to 0 °C and quenched by sequential and dropwise addition of water (600 μL), 4 M aq. NaOH (600 μL) and water (1.80 mL). The mixture was stirred vigorously for 18 min, $MgSO_4$ added and the mixture stirred for a further 15 min, after which time the mixture was filtered and the residue washed with ether (50 mL). The filtrate was concentrated to afford the title compound as a brown oil (877 mg, containing *ca.* 20% w/w $H_2O$, 10% w/w THF, *ca.* 76%) which was used immediately, without further purification.

Data are consistent with literature values: (*415*) $R_f$ not obtained (decomposes); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.92 (d, $J$ = 3.0 Hz, 1H, Fn-3), 5.85 (dd, $J$ = 3.0, 1.0 Hz, 1H, Fn-4), 2.95 (t, $J$ = 6.5 Hz, 2H, H-1), 2.71 (t, $J$ = 6.5 Hz, 2H, H-2), 2.32 – 2.19 (m, 3H, Me).

[lxxxv] Coupling with Fn-4 may be occurring, but the signal is sufficiently broadened that the resulting splitting of the signal cannot be observed.
[lxxxvi] Completion of the reaction was verified by $^1$H NMR analysis.

***N*-[2-(5-Methylfuran-2-yl)ethyl]acetamide (4.13)**

To a solution of 2-(5-methylfuran-2-yl)acetonitrile **4.10** (368 mg, 3.04 mmol) in methanol (24.5 mL) was added $NiCl_2 \cdot 6H_2O$ (727 mg, 3.06 mmol) and acetic anhydride (575 µL, 6.08 mmol). The mixture was cooled to 0 °C and $NaBH_4$ (810 mg, 21.4 mmol) added cautiously portionwise. The mixture was stirred and the reaction quenched after 75 min by addition of $H_2O$ (5 mL) and sat. aq. $NH_4Cl$ (1 mL). The mixture was then extracted with ethyl acetate (3 × 5 mL). The combined organic phases were washed with $H_2O$ (2 mL), dried over $Na_2SO_4$, filtered, and concentrated to afford the title compound as a raisin-scented brown oil (189 mg, 37%).

Data are consistent with literature values: (*416*) $R_f$ 0.50 (9 : 1 DCM : methanol); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.92 (d, *J* = 3.0 Hz, 1H, Fn-3), 5.85 (dq, *J* = 3.0, 1.0 Hz, 1H, Fn-4), 5.72 (s, 1H, NH), 3.49 (td, *J* = 6.5 Hz, 2H, H-1'), 2.76 (t, *J* = 6.5 Hz, 2H, H-2'), 2.24 (d, *J* = 1.0 Hz, 3H, Fn-Me), 1.95 (s, 3H, H-2); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 170.2 (C-1), 151.2 (Fn-2 or Fn-5; resonance for other nuclide not observed), 107.1 (Fn-3), 106.1 (Fn-4), 38.3 (C-1'), 28.3 (C-2'), 23.4 (C-2), 13.6 (Fn-Me); IR (ATR) ν 3293br (N–H stretch), 2974w (C–H), 2924w (C–H), 2885w (C–H), 1651s (C=O stretch), 1556s, 1435m, 1369m, 1296m, 1238m, 1219m, 1021s, 782s; HRMS (APCI, $NH_3$) found 168.1020, calc. for $C_9H_{13}O_2N$ $[M+H]^+$ 168.1019.

***tert*-Butyl [2-(5-methylfuran-2-yl)ethyl]carbamate (4.14)**

Direct protection of amine: To a solution of impure amine **4.12** (250 mg, 1.32 mmol) in DCM (2 mL) was added NaOH (4 mL, 1.0 M in water, 4.0 mmol). The mixture was cooled to 0 °C and a solution of di-*tert*-butyl dicarbonate (480 mg, 2.20 mmol) in

DCM (1.10 mL) added. The mixture was stirred for 63 h while being allowed to warm to rt. The aqueous phase was extracted with DCM (2 × 5 mL) and the combined organic phases washed with sat. aq. $NH_4Cl$ (5 mL). The $NH_4Cl$-containing phase was extracted with DCM (2 × 5 mL) and all organic phases combined, washed with brine (5 mL), dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by column chromatography (4 : 1 : 0 – 24 : 25 : 1 PE : ether : ethanol) to afford the *title compound* as an orange oil (271 mg, 91%).

Nickel boride reduction: To a solution of 2-(5-methylfuran-2-yl)acetonitrile **4.10** (121 mg, 1 mmol) in dry MeOH (2 mL), under $N_2$ and cooled to 0 °C, was added sequentially anhydrous $NiCl_2$ (65.2 mg, 0.503 mmol) and di-*tert*-butyl dicarbonate (437 mg, 2.00 mmol). $NaBH_4$ (84.0 mg, 2.22 mmol) was added cautiously against a counterflow of $N_2$ and a black precipitate formed immediately. The mixture was allowed to warm to rt and stirred for 16 h, after which time $H_2O$ (2 mL) was added carefully. The mixture was concentrated, diluted with $H_2O$ (2 mL) and extracted with ethyl acetate (3 × 2 mL). The combined organic phases were dried over $Na_2SO_4$ and concentrated, and the residue purified by column chromatography (1 : 0 – 1 : 1 PE : ether) to afford the *title compound* as a yellow oil (79.1 mg, 35%).

$R_f$ 0.70 (1 : 1 PE : ether); $^1$H NMR (500 MHz, DMSO) δ 6.89 (t, $J$ = 6.0 Hz, 1H, NH), 5.97 (d, $J$ = 3.0 Hz, 1H, Fn-3), 5.92 (dd, $J$ = 3.0, 1.0 Hz, 1H, Fn-4), 3.13 (td, $J$ = 7.5, 6.0 Hz, 2H, H-1), 2.64 (t, $J$ = 7.5 Hz, 2H, H-2), 2.20 (s, 3H, Fn-Me), 1.37 (s, 9H, $CMe_3$); $^{13}$C NMR (126 MHz, DMSO) δ 155.5 (C=O), 151.28 (Fn-2), 149.8 (Fn-5), 106.4 (Fn-3), 106.2 (Fn-4), 77.6 (O*C*Me$_3$), 38.7 (C-1), 31.3 (C-2), 28.2 (C*Me*$_3$), 13.3 (Fn-Me); IR (ATR) ν 2979w (C–H), 2926w (C–H), 1693 (carbamate C=O), 1511br m, 1366m,

1250s, 1168s, 780s; HRMS ($ESI^+$) calc. for $C_{12}H_{19}O_3N$ $[M+Na]^+$ 248.1257, found 248.1258.

**4-Methyl-*N*-[2-(5-methylfuran-2-yl)ethyl]benzenesulfonamide (4.15)**

To a solution of impure amine **4.12** (250 mg, 1.32 mmol) in DCM (6 mL) was added TEA (840 μL, 6.00 mmol) and DMAP (15.3 mg, 123 μmol). The mixture was cooled to 0 °C and a solution of 4-methylbenzenesulfonyl chloride (210 mg, 1.10 mmol) in DCM (4 mL) added. The mixture was stirred for 63 h while being allowed to warm to rt. Sat. aq. $NaHCO_3$ (7 mL) was added, and the aqueous phase extracted with DCM (5 mL). The organic phases were combined and washed with sat. aq. $NH_4Cl$ (7 mL) The $NH_4Cl$-containing phase was extracted with DCM (2 × 5 mL) and all organic phases combined, washed with brine (5 mL), dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by column chromatography (4 : 1 : 0 – 24 : 25 : 1 PE : ether : ethanol) to afford the title compound as a maroon oil (227 mg, 62%).

Data are consistent with literature values: (*417*) $R_f$ 0.30 (1 : 1 PE : ether); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.67 (m, 2H, Ts-2,6), 7.32 – 7.28 (m, 2H, Ts-3,5), 5.87 (d, *J* = 3.0 Hz, 1H, Fn-3), 5.83 (dq, *J* = 3.0, 1.0 Hz, 1H, Fn-4), 4.49 (t, *J* = 6.5 Hz, 1H, NH), 3.21 (q, *J* = 6.5 Hz, 2H, H-1), 2.71 (t, *J* = 6.5 Hz, 2H, H-2), 2.43 (s, 3H, Ts-Me), 2.21 (d, *J* = 1.0 Hz, 3H, Fn-Me); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 151.6 (Fn-5), 150.0 (Fn-2), 143.6 (Ts-4), 137.1 (Ts-1), 129.8 (Ts-3,5), 127.2 (Ts-2,6), 107.9 (Fn-4), 106.2 (Fn-3), 41.9 (C-1), 28.4 (C-2), 21.7 (Ts-Me), 13.6 (Fn-Me).

**3,5-Hexadienoic acid (4.16)**

To a solution of DIPA (1.95 mL, 13.8 mmol) in THF (10 mL), in a round-bottomed flask equipped with a reflux condenser, cooled to –78 °C and under $N_2$, was added butyllithium (5.3 mL, 2.3 M in hexanes, 12.1 mmol). The mixture was warmed to –10 °C and stirred for 54 min, after which time a solution of sorbic acid (618.2 mg, 5.51 mmol) in THF (5 mL) was added. The flask in which the sorbic acid solution was prepared was rinsed with THF (2 mL) and the resulting liquid was transferred to the reaction mixture. The colour of the mixture changed from colourless to orange and solidified, then melted on warming to rt. The mixture was stirred at rt for 50 min, after which time the mixture was cooled to 0 °C and aq. HCl (10 mL, 2 M, 20 mmol) added slowly, a significant exotherm being observed. The aqueous phase of the mixture was extracted with ether (3 × 5 mL). The remaining aqueous phase was then re-acidified to below *pH* 2 and extracted with ether (2 × 5 mL). The organic phases from the second extraction were combined and dried over $Na_2SO_4$, then concentrated to afford the title compound as a yellow oil (523 mg, 85%).

Data are consistent with literature values: (*418*) $R_f$ 0.60 (1 : 1 PE : ethyl acetate); $^1$H NMR (400 MHz, $CDCl_3$) δ 10.37 (br s, 1H, $CO_2H$), 6.34 (dt, *J* = 17.0, 10.0 Hz, 1H, H-4), 6.26 – 6.11 (m, 1H, H-5), 5.77 (dt, *J* = 15.0, 7.0 Hz, 1H, H-3), 5.19 (dd, *J* = 17.0, 1.5 Hz, 1H, H-6 *trans* to H-5), 5.14 – 5.03 (m, 1H, H-6 *cis* to H-5), 3.17 (dd, *J* = 7.0, 1.5 Hz, 2H, H-2); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 177.9 (C-1), 136.3 (C-4), 135.1 (C-5), 124.7 (C-3), 117.5 (C-6), 37.7 (C-2).

**(*E*)-Hexa-3,5-dien-1-ol (4.17)**

To $LiAlH_4$ (143 mg, 3.78 mmol) in a flask fitted with a reflux condenser was added THF (4 mL). A solution of 3,5-hexadienoic acid **4.16** (523 mg, 4.72 mmol) in THF (3 mL) was added dropwise. The flask in which the hexadienoic acid solution was prepared was rinsed with THF (3 mL) and the resulting solution also added dropwise. The mixture was warmed to reflux for 3 h, then cooled to 0 °C and quenched after a further 40 min by the sequential addition of $H_2O$ (150 µL), NaOH (150 µL, 4.0 M in $H_2O$, 600 µmol) and $H_2O$ (450 µL). The mixture was stirred for 15 min and $MgSO_4$ added. The resulting suspension was filtered through Celite under reduced pressure and the residue washed extensively with ether. To the combined filtrates was added toluene (5 mL) and the resulting mixture was concentrated to afford the title compound as a pale yellow oil, which was used without further purification (332 mg, contaminated with 30% w/w toluene, 54%).

Data are consistent with literature values: (*418*) $R_f$ 0.15 (4 : 1 PE : ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.41 – 6.26 (m, 1H, H-3), 6.17 (m, 1H, H-5), 5.69 (dtd, *J* = 15.0, 7.0, 0.5 Hz, 1H, H-4), 5.15 (ddt, *J* = 17.0, 1.5, 0.5 Hz, 1H, H-6 *trans* to H-5), 5.02 (ddd, *J* = 10.0, 1.5, 1.0 Hz, 1H, H-6 *cis* to H-5), 3.69 (t, *J* = 6.5 Hz, 2H, H-1), 2.43 – 2.30 (m, 2H, H-2), 1.54 – 1.36 (br s, 1H, OH); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 136.9 (C-3), 134.0 (C-5), 130.7 (C-4), 116.2 (C-6), 62.1 (C-1), 36.1 (C-2).

**(*E*)-2-(Hexa-3,5-dien-1-yl)-5-methylfuran (4.18)**

To 2-methylfuran (280 µL, 3.10 mmol) was added THF (5 mL). The resulting solution was cooled to –78 °C and butyllithium (1.00 mL, 2.5 M in hexanes, 2.50 mmol)

added dropwise. The mixture was warmed to –10 °C and stirred for 2 h 50 min. 6-iodohexa-1,3-diene **4.19** (259 mg, 1.24 mmol) was added as a solution in benzene (2 mL) and the resulting mixture was allowed to warm to rt and stirred for 14 h, after which time the mixture was diluted with sat. aq. $NH_4Cl$ (2 mL). The aqueous phase was extracted with ether (3 × 5 mL) and the combined organic phases dried over $MgSO_4$. The residue was purified by chromatography (1 : 0 – 19 : 1 pentane : DCM) to afford the *title compound* as a colourless oil (46.7 mg, 23%).

$R_f$ 0.25 (96 : 3 : 1 pentane : ethanol : TEA); $^1$H NMR (400 MHz, $C_6D_6$) δ 6.24 (dt, *J* = 17.0, 10.5 Hz, 1H, H-3), 5.98 (dd, *J* = 15.0, 10.5 Hz, 1H, H-4), 5.88 – 5.74 (m, 2H, Fn-3 and Fn-4), 5.53 (dt, *J* = 15.0, 7.0 Hz, 1H, H-5), 5.03 (d, *J* = 17.0 Hz, 1H, H-6 *trans* to H-5), 4.91 (d, *J* = 10.0 Hz, 1H, H-6 *cis* to H-5), 2.54 (t, *J* = 7.5 Hz, 2H, H-1), 2.28 (app q, *J* = 7.5 Hz, 2H, H-2), 2.05 (s, 3H, Me); $^{13}$C NMR (101 MHz, $C_6D_6$) δ 153.8 (Fn-2), 150.4 (Fn-5), 137.6 (C-3), 133.9 (C-5), 132.1 (C-4), 115.3 (C-6), 106.4 (Fn-3), 106.2 (Fn-4), 31.5 (C-1), 28.2 (C-2), 13.5 (Me); IR (ATR) ν 2922w (furan C–H), 1021m, 1003s, 899m, 779s; HRMS (APCI, $CH_4$) found 163.1117, calc. for $C_{11}H_{14}O$ $[M+H]^+$ 163.1117.

**(*E*)-6-Iodohexa-1,3-diene (4.19)**

To a solution of imidazole (227 mg, 3.33 mmol) and triphenylphosphine (797 mg, 3.04 mmol) in dry DCM (10 mL), cooled to 0 °C, was added dropwise a solution of $I_2$ (770 mg, 3.03 mmol) in ether (99.5% over molecular sieves, as received from Acros Organics, 10 mL). The mixture was stirred for 20 min, after which time a solution of **4.17** (232 mg, 2.53 mmol) in DCM (5 mL) was added dropwise to the iodophosphonium iodide solution and the resulting mixture stirred for 50 min. Sat. aq. $Na_2S_2O_3$ (5 mL) was added, and the organic phase was washed with brine (5 mL) and concentrated, then

redissolved in a minimum of DCM. A layer of pentane was placed above the solution and the biphasic mixture left in the freezer overnight. The supernatant was concentrated and a second set of crystals obtained by a second precipitation by dissolution in a minimum of DCM and layer addition of pentane. The supernatant was then concentrated and purified by chromatography (0 : 1 – 19 : 1 pentane : DCM) to afford the title compound as a colourless oil (259 mg, 49%).

Data are consistent with literature values: (*418*) $R_f$ 0.55 (9 : 1 PE : DCM); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.32 (dt, *J* = 17.0, 10.0 Hz, 1H, H-4), 6.13 (dd, *J* = 15.0, 10.0 Hz, 1H, H-2), 5.63 (dt, *J* = 15.0, 7.0 Hz, 1H, H-3), 5.18 (d, *J* = 17.0 Hz, 1H, H-1 *trans* to H-2), 5.07 (d, *J* = 10.0 Hz, 1H, H-1 *cis* to H-2), 3.17 (t, *J* = 7.5 Hz, 2H, H-6), 2.66 (q, *J* = 7.0 Hz, 2H, H-5); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 136.7 (C-4), 133.3 (C-2), 132.7 (C-3), 116.8 (C-1), 36.7 (C-5), 4.9 (C-6).

**2-Benzyl-5-methylfuran (4.20)**

To a solution of 2-methylfuran (3.60 mL, 40.0 mmol) in THF (60 mL), cooled to –78 °C and under Ar was added dropwise butyllithium (14.4 mL, 2.5 M in hexanes, 36.0 mmol). The reaction mixture was then warmed to –10 °C and stirred for 3 h, after which time benzyl bromide (3.57 mL, 20.9 mmol) was added. The mixture was warmed to rt and stirred for 15 h 20 min, and the reaction was then quenched by the addition of sat. aq. $NH_4Cl$ (2 mL) and $NH_4Cl$ (535 mg, 10.0 mmol), and the mixture concentrated. The residue was diluted with pentane (10 mL) and $H_2O$ (30 mL), and the aqueous phase of the resulting mixture extracted with pentane (3 ×10 mL). The combined organic phases were washed with water (10 mL) and brine (5 mL), then dried over $MgSO_4$ and concentrated to afford the title compound as an orange oil (4.46 g, 86%).

Data are consistent with literature values: (*403*) $R_f$ 0.45 (PE); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.17 (m, 5H, Ph), 5.84 (s, 2H, Fn-3 and Fn-4), 3.90 (s, 2H, C*H*$_2$Ph), 2.23 (s, 3H, Me); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 152.8 (Fn-2 or Fn-5), 151.1 (Fn-2 or Fn-5), 138.6 (Ph-1), 128.8 (Ph-2,6 or Ph-3,5), 128.6 (Ph-2,6 or Ph-3,5), 126.5 (Ph-4), 107.0 (Fn-3 or Fn-4), 106.1 (Fn-3 or Fn-4), 34.7 ($CH_2$), 13.7 (Me).

**2-(Cyclopropylmethyl)-5-methylfuran (4.21)**

To NaI (163 mg, 1.09 mmol) under $N_2$ was added THF (20 mL) and 2-methylfuran (1.80 mL, 20.0 mmol). The mixture was cooled to −78 °C and butyllithium (6.0 mL, 2.5 M in hexanes, 15.0 mmol) added dropwise, over 7 min. When addition was complete, the mixture was warmed to 0 °C and stirred for 3 h. Cyclopropylmethyl bromide (970 μL, 10.0 mmol) was added and the mixture warmed to rt, then stirred for 46 h. Sat. aq. $NH_4Cl$ (2 mL) was added, and the resulting mixture was added to $H_2O$ (100 mL). This mixture was extracted with PE (5 × 10 mL). The combined organic phases were then washed with $H_2O$ (50 mL) and brine (10 mL), dried over $MgSO_4$ and activated charcoal and concentrated with care to afford the *title compound* as a pale orange oil (1.25 g, 92%; containing 11% w/w THF).[lxxxvii]

$R_f$ 0.55 (PE); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.95 (d, *J* = 3.0 Hz, 1H, Fn-3), 5.87 (dd, *J* = 3.0, 1.0 Hz, 1H, Fn-4), 2.50 (d, *J* = 7.0 Hz, 2H, Fn-C*H*$_2$-*c*-Pr), 2.27 (s, 3H, Me), 1.08 – 0.96 (m, 1H, *c*-Pr-1), 0.57 – 0.47 (m, 2H, *c*-Pr-2,3), 0.19 (dt, *J* = 6.0, 4.5 Hz, 2H, *c*-Pr-2,3); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 154.3 (Fn-2 or Fn-5), 150.4 (Fn-2 or Fn-5), 105.9 (Fn-3 or Fn-4), 105.5 (Fn-3 or Fn-4), 32.9 (Fn-*C*H$_2$), 13.7 (Me), 9.6 (*c*-Pr-1), 4.5

[lxxxvii] The THF contamination can be removed by evaporation, leading to significant loss of the volatile product.

(*c*-Pr-2,3); IR (ATR) ν 3079w (C–H), 3005w(C–H), 2923w (C–H), 1569m, 1219m, 1019s, 778s; HRMS (EI) found 136.0882, calc. for $C_9H_{12}O$ $[M]^+$ 136.0883.

**2-(Cyclopropylmethyl)-5-hexylfuran (4.22)**

To a solution of 2-hexylfuran **4.23** (200 mg, 1.33 mmol) in THF (5 mL), cooled to −78 °C was added dropwise butyllithium (1.2 mL, 1.23 M in hexanes, 1.48 mmol). The mixture was warmed to 0 °C and stirred for 2 h 30 min, after which time a solution of cyclopropylmethyl bromide (180 mg, 1.33 mmol) in THF (2 mL) was added. The mixture was stirred and allowed to warm to rt over 17 h, after which time the mixture was diluted with sat. aq. $NH_4Cl$ (10 mL) and $H_2O$ (10 mL), and extracted with ether (3 × 10 mL). The combined organic phases were washed with brine (5 mL), dried over $MgSO_4$ and concentrated to afford an orange oil, which was purified by chromatography (1 : 0 – 19 : 1 pentane : ether) to afford the *title compound* as a pale yellow oil (39.8 mg, 15%).

$R_f$ 0.40 (pentane); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.96 (d, $J$ = 3.0 Hz, 1H, Fn-3), 5.87 (d, $J$ = 3.0 Hz, 1H, Fn-4), 2.57 (t, $J$ = 7.5 Hz, 2H, Hx-1), 2.51 (d, $J$ = 7.0 Hz, 2H, *c*-PrC*H*$_2$Fn), 1.67 – 1.56 (m, 2H, Hx-2), 1.42 – 1.24 (m, 6H, Hx-3 and Hx-4 and Hx-5), 1.00 (dddd, $J$ = 13.0, 7.0, 5.0, 2.5 Hz, 1H, *c*-Pr-1), 0.95 – 0.82 (m, 3H, Hx-6), 0.54 – 0.48 (m, 2H, *c*-Pr-2,3), 0.18 (m, 2H, *c*-Pr-2,3); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 155.0 (Fn-2 or Fn-5), 154.1 (Fn-2 or Fn-5), 105.3 (Fn-2), 105.0 (Fn-5), 32.9 (Fn-*C*H$_2$-*c*-*Pr*), 31.8 (Hx-4 or Hx-5), 29.1 (Hx-3), 28.2 (Hx-1 and Hx-2), 22.7 (Hx-4 or Hx-5), 14.2 (Hx-6), 9.6 (*c*-Pr-1), 4.5 (*c*-Pr-2 and *c*-Pr-3); IR (ATR) ν 2927s (C–H), 2858m (C–H), 1460m, 1014m, 779s, 725s; HRMS (APCI, $CH_4$) found 207.1742, calc. for $C_{14}H_{22}O$ $[M+H]^+$ 207.1743.

**2-Hexylfuran (4.23)**

To a solution of furan (670 µL, 9.21 mmol) in THF (12 mL), cooled to −78 °C, was added butyllithium (3.0 mL, 2.5 M in hexanes, 7.50 mmol) dropwise. The resulting mixture was warmed to 0 °C and stirred for 1 h. 1-Iodohexane (1.30 g, 6.13 mmol) was added, then the mixture was warmed to rt and stirred for 18 h. The mixture was quenched by addition of sat. aq. $NH_4Cl$ (2 mL) and concentrated. The resulting mixture was diluted with $H_2O$ (10 mL) and extracted with ether (3 × 5 mL) The combined organic phases were washed with brine (5 mL), dried over $MgSO_4$ and concentrated to afford the title compound as an orange oil (799 mg, containing 5% w/w DCM, 86%).

Data are consistent with literature values: (*342*) $R_f$ 0.70 (24 : 1 pentane : ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 2.0, 1.0 Hz, 1H, Fn-5), 6.27 (dd, *J* = 3.0, 2.0 Hz, 1H, Fn-4), 5.97 (dq, *J* = 3.0, 1.0 Hz, 1H, Fn-3), 2.66 – 2.58 (m, 2H, H-1), 1.69 – 1.57 (m, 2H, H-2), 1.40 – 1.24 (m, 6H, H-3 and H-4 and H-5), 0.94 – 0.84 (m, 3H, H-6); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 156.8 (Fn-2), 140.8 (Fn-5), 110.2 (Fn-4), 104.6 (Fn-3), 31.7 (C-4), 29.0 (C-1), 28.2 (C-3), 28.1 (C-2), 22.7 (C-5), 14.2 (C-6).

**2-(5-Hexylfuran-2-yl)ethan-1-ol (4.24)**

To a solution of 2-hexylfuran **4.23** (400 mg, 2.66 mmol) in DMSO (45 mL) was added $FeSO_4 \cdot 7H_2O$ (2.22g, 7.98 mmol) and ethyl iodoacetate (630 µL, 5.32 mmol). The mixture was cooled to 0 °C and stirred for 5 min, after which time $H_2O_2$ (30% w/v, 3 mL, 26.6 mmol) was added over 2 min with vigorous stirring. The mixture was stirred for 2.5 h[lxxxviii] and partitioned between ether (30 mL) and brine (30 mL). The aqueous phase was

[lxxxviii] NMR analysis indicated the reaction was complete within 1 h 40 min.

then extracted with ether (2 × 30 mL) and the combined organic phases washed with sat. aq. $Na_2S_2O_3$ (2 × 5 mL), $H_2O$ (3 × 20 mL), and brine (10 mL). The organic phases were then dried over $Na_2SO_4$, concentrated, and purified by column chromatography (1 : 0 – 1 : 1 PE : ether) to afford ethyl (5-hexylfuran-2-yl)acetate as a colourless oil (265 mg, 42%).

Data are consistent with literature values: (*410*) $R_f$ 0.65 (9 : 1 PE : ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.12 – 6.06 (m, 1H, Fn-3), 5.90 (dt, *J* = 3.0, 1.0 Hz, 1H, Fn-4), 4.18 (q, *J* = 7.0 Hz, 2H, OC*H*$_2$CH$_3$), 3.62 (d, *J* = 1.0 Hz, 2H, H-2), 2.62 – 2.53 (m, 2H, H-1'), 1.66 – 1.57 (m, 2H, H-2'), 1.27 (m, 9H, OCH$_2$C*H*$_3$ and H-3' and H-4' and H-5'), 0.92 – 0.85 (m, 3H, H-6'); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 169.8 (C-1), 156.3 (Fn-2 or Fn-5), 145.8 (Fn-2 or Fn-5), 108.5 (Fn-3), 105.6 (Fn-4), 61.2 (O*C*H$_2$CH$_3$), 34.4 (C-2), 31.7 (C-4' or C-5'), 29.0 (C-3'), 28.2 (C-1'), 28.1 (C-2'), 22.7 (C-4' or C-5'), 14.3 (OCH$_2$*C*H$_3$), 14.2 (C-6'); IR (ATR) ν 2956w (C–H), 2929m (C–H), 2858w (C–H), 1740s (C=O), 1261m, 1222m, 1176m, 1140s, 1032s, 1016m, 782s; HRMS (APCI, $NH_3$) found 239.1641, calc. for $C_{14}H_{22}O_3$ $[M+H]^+$ 239.1642.

To a suspension of $LiAlH_4$ (46.0 mg, 788 μmol) in THF (1 mL) was added dropwise a solution of ethyl-2-(5-hexylfuran-2-yl)acetate (258 mg, 1.05 mmol) in THF (2 mL). The mixture was brought to reflux and stirred for 3 h 30 min, after which time the mixture was quenched by the sequential and dropwise addition of water (300 μL) NaOH (300 μL, 4.0 M in $H_2O$, 1.2 mmol) and $H_2O$ (1 mL). The resulting mixture was stirred for 1 h 15 min, and $MgSO_4$ added. The mixture was then filterered through Celite, washed with ether (2 × 5 mL), and the combined filtrates concentrated to afford the *title compound* as a colourless oil (189.5 mg, 92%).

$R_f$ 0.10 (4 : 1 PE : ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.03 – 5.94 (m, 1H, Fn-3), 5.93 – 5.84 (m, 1H, Fn-4), 3.85 (app q, $J$ = 6.0 Hz, 2H, H-1), 2.85 (td, $J$ = 6.0, 1.0 Hz, 2H, H-2), 2.61 – 2.52 (m, 2H, H-1'), 1.74 – 1.53 (m, 3H, OH and H-2'), 1.42 – 1.23 (m, 6H, H-3' and H-4' and H-5'), 0.97 – 0.79 (m, 3H, H-6'); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 155.8 (Fn-2), 150.6 (Fn-5), 107.0 (Fn-3), 105.1 (Fn-4), 61.2 (C-1), 31.7 (C-2), 31.6 (C-4'), 28.9 (C-3'), 28.1 (C-1'), 28.0 (C-2'), 22.6 (C-5'), 14.1 (C-6'); IR (ATR) ν 3347br,w (O–H), 2955 (C–H), 2928s (C–H), 2858 (C–H), 1567w, 1047s, 780s; HRMS (ESI$^+$) found 197.1538, calc. for $C_{12}H_{20}O_2$ $[M+H]^+$ 197.1536.

**(*E*)-Undeca-3,10-diene-2,5-dione [(*E*)-4.25a]**

Pale yellow oil produced from 2-(hex-5-en-1-yl)-5-methylfuran **2.15** (65.6 mg, 400 μmol) according to General Procedure for Oxidation of Furan Mediated by **2.8**. Reaction time 2 h 55 min, chromatography performed with 99 : 1 : 0 – 98 : 1 : 1 PE : TEA : ethanol as eluant. Yield 36.1 mg (50%).

$R_f$ 0.20 (4: 1 PE : ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.82 (s, 2H, H-3 and H-4), 5.78 (ddt, $J$ = 17.0, 10.0, 6.5 Hz, 1H, H-10), 5.00 (dq, $J$ = 17.0, 1.5 Hz, 1H, H-11 *trans* to H-10), 4.95 (ddt, $J$ = 10.0, 2.0, 1.0 Hz, 1H, H-11 *cis* to H-10), 2.65 (t, $J$ = 7.5 Hz, 2H, H-6), 2.36 (s, 3H, H-1), 2.12 – 2.01 (m, 2H, H-9), 1.72 – 1.59 (m, 2H, H-7), 1.48 – 1.37 (m, 2H, H-8); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 200.7 (C-5), 198.6 (C-2), 138.4 (C-10), 137.3 (C-4), 137.0 (C-3), 115.0 (C-11), 41.3 (C-6), 33.6 (C-9), 28.4 (C-8), 28.3 (C-1), 23.3 (C-7); IR (ATR) ν 2933w (C–H), 1684s (C=O), 1640w (C=C), 1631m, 1251m, 1171m, 982m, 922m; HRMS (APCI) 181.1223, calc for $C_{11}H_{17}O_2$ $[M+H]^+$ 181.1223.

**(*E*)-9-Chloronon-3-ene-2,5-dione [(*E*)-4.26a]**

Pale yellow oil produced from 2-(4-chlorobutyl)-5-methylfuran **2.20** (250 mg, 1.45 mmol) according to General Procedure for Oxidation of Furan Mediated by **2.8**. Reaction time 4 h 5 min, chromatography performed with 50 : 49 : 1 : 0 – 0 : 0 : 0 : 1 ether : PE : TEA : DCM as eluant. Yield 237 mg (87%).

$R_f$ 0.10 (4: 1 PE : ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.83 (s, 2H, H-3 and H-4), 3.58 – 3.51 (m, 2H, H-9), 2.74 – 2.66 (m, 2H, H-6), 2.37 (s, 3H, H-1), 1.84 – 1.77 (m, 4H, H-7 and H-8); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 200.0 (C-5), 198.5 (C-2), 137.2 (C-4), 137.0 (C-3), 44.6 (C-9), 40.5 (C-6), 31.9 (or C-8), 28.4 (C-1), 21.0 (C-7); IR (ATR) ν 2957w (C–H), 1681s (C=O), 1361m, 1250m, 980m, 647w (C-Cl); HRMS (APCI, $CH_4$) found 189.0679, calc. for $C_9H_{13}O_2{}^{35}Cl$ $[M+H]^+$ 189.0677.

**(*E*)-Undec-3-en-10-yne-2,5-dione [(*E*)-4.27a]**

Tan solid produced from 2-(hex-5-yn-1-yl)-5-methylfuran **2.32** (114 mg, 705 μmol) according to General Procedure for Oxidation of Furan Mediated by **2.8**. Reaction time 1 h 30 min, chromatography performed with 1 : 1 PE : ethyl acetate as eluant. Yield 52.0 mg (41%).

$R_f$ 0.60 (1 : 1 PE : ethyl acetate); mp, 38-41 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 6.80 (s, 2H, H-3 and H-4), 2.66 (t, $J$ = 7.5 Hz, 2H, H-6), 2.34 (s, 3H, H-1), 2.19 (td, $J$ = 7.0, 2.5 Hz, 2H, H-9), 1.93 (t, $J$ = 2.5 Hz, 1H, H-11), 1.80 – 1.68 (m, 2H, H-7), 1.59 – 1.47 (m, 2H, H-8); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 200.2 (C-5), 198.5 (C-2), 137.1 (C-3 or C-4), 137.1 (C-3 or C-4), 83.9 (C-10), 68.9 (C-11), 40.8 (C-6), 28.3 (C-1), 27.8 (C-9), 22.8 (C-8), 18.3 (C-7); IR (ATR) ν 3284br (alkyne C–H), 2934br, 2166w (C≡C), 1681

(C=O), 1361m, 1251s, 1167m, 1101m, 980sm, 637br,s; HRMS (APCI) 179.1070, calc for $C_{11}H_{15}O_2$ $[M+H]^+$ 179.1067.

**(*E*)-*N*-(3,6-Dioxohept-4-en-1-yl)acetamide [(*E*)-4.28a]**

To a solution of *N*-([5-methylfuran-2-yl]ethyl)acetamide **4.13** (30.0 mg, 159 µmol) in acetonitrile (1.00 mL) was added sequentially $H_2O$ (320 µL), a solution of $Ru(bpz)_3(PF_6)_2$ (1.38 mg) in acetonitrile (277 µL), and pyridine (28 µL, 350 µmol). The reaction vessel was capped with a septum, which was pierced with a needle. The mixture was stirred for 22 h and irradiated by a blue LED lamp (12 V DC, 0.06 A, $P_{irr}$ 720 mW, $\lambda_{max,irr}$ 480 nm). The mixture was then purified directly by column chromatography (1 : 0 – 9 : 1 DCM : methanol), together with an identical run in which the pyridine had been omitted, to afford the *title compound* as a yellow solid (36.3 mg, 56%).

$R_f$ 0.25 (1 : 1 pentane : ethyl acetate); mp 46 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 6.85 (d, *J* = 17.0 Hz, 1H, H-4' or H-5'), 6.79 (d, *J* = 17.0 Hz, 1H, H-4' or H-5'), 6.03 (br s, 1H, NH) 3.55 (q, *J* = 6.0 Hz, 2H, H-1'), 2.95 – 2.89 (m, 2H, H-2'), 2.38 (s, 3H, H-7'), 1.94 (s, 3H, H-2); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 200.1 (C-3'), 198.2 (C-6'), 155.8 (C-1), 137.7 C-4' or C-5'), 136.8 (C-4' or C-5'), 40.9 (C-2'), 34.1 (C-1'), 28.4 (C-7'), 23.4 (C-2); IR (ATR) ν 3660w (N–H), 2981s, 2972s, 1680m (ketone), 1656m (amide), 1381s, 1253m, 1153m, 1081m, 1022m, 955m; HRMS (APCI, $NH_3$) found 184.0969, calc. for $C_9H_{13}NO_3$ 184.0968.

**1-Acetyl-2-(2-oxopropyl)pyrrolidin-3-one (4.28c)**

To a solution of *N*-([5-methylfuran-2-yl]ethyl)acetamide **4.13** (75.0 mg, 396 µmol) in acetonitrile (2.6 mL) was added $H_2O$ (800 µL) and a solution of $Ru(bpz)_3(PF_6)_2$ (3.43

mg, 3.96 μL) in acetonitrile (688 μL). The reaction vessel was capped with a septum, and $O_2$ bubbled through, with irradiation by a blue LED lamp (12 V DC, 0.06 A, $P_{irr}$ 720 mW, $\lambda_{max,irr}$ 480 nm) for 7 h. The mixture was then purified directly *via* column chromatography (99 : 0 : 1 – 89 : 10 : 1 DCM : methanol : acetic acid) to afford the *title compound* as a pale brown oil (41.1 mg, 57%).

$R_f$ 0.30 (19 : 1 DCM : methanol); $^1$H NMR (400 MHz, $CDCl_3$) δ 4.04 (br t, $J$ = 4.0 Hz, 1H, H-2), 4.00 – 3.83 (m, 2H, H-5), 3.76 (dd, $J$ = 19.0, 4.0 Hz, 1H, Oxp-1), 3.16 (dd, $J$ = 19.0, 3.5 Hz, 1H, Oxp-1), 2.91 (dddd, $J$ = 18.5, 8.0, 3.5, 1.0 Hz, 1H, H-4), 2.80 – 2.63 (m, 1H, H-4), 2.09 (s, 3H, Oxp-3), 2.08 (s, 3H, Ac-Me); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 211.9 (C-3), 206.8 (Oxp-2), 170.6 (Ac-1), 57.9 (C-2), 45.6 (C-5), 44.6 (Oxp-1), 36.9 (C-4), 29.3 (Oxp-3), 21.7 (Ac-Me); IR (ATR) ν 2979w (C–H), 2933w (C–H), 1757s (ring ketone C=O), 1713s (ketone C=O), 1623s (amide C=O), 1424m, 1370m, 1267m, 1218m, 1165m; HRMS (ESI$^+$) found 184.0971, calc. for $C_9H_{13}NO_2$ $[M+H]^+$ 184.0968.

***tert*-Butyl (*E*)-(3,6-dioxohept-4-en-1-yl)carbamate [(*E*)-4.29a]**

Orange oil produced from *tert*-butyl [2-(5-methylfuran-2-yl)ethyl]carbamate **4.14** (79.2 mg, 351 μmol) according to General Procedure for Oxidation of Furan Mediated by **2.8**. Reaction time 2 h, chromatography performed with 1: 1 : 0 – 0 : 0 : 1 pentane : ether : ethyl acetate as eluant. Yield 72.7 mg, (86%).

$R_f$ 0.15 (1 : 1 pentane : ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.81 (d, $J$ = 16.5 Hz, 1H, H-4 or H-5), 6.79 (d, $J$ = 16.5 Hz, 1H, H-4 or H-5), 4.99 (br s, 1H, NH), 3.43 (q, $J$ = 6.0 Hz, 2H, H-1), 2.89 (t, $J$ = 6.0 Hz, 2H, H-2), 2.37 (s, 3H, H-7), 1.49 – 1.35 (s, 9H,

C[C$H_3$]$_3$); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 199.8 (C-3), 198.4 (C-6), 156.0 (Boc-C=O), 137.5 (C-4), 137.0 (C-3), 79.5 (*C*Me$_3$), 41.3 (C-2), 35.2 (C-1), 28.4 (C*Me*$_3$), 28.3 (C-7); IR (ATR) ν 3369br (NH), 2978w, 1683s (C=O stretch), 1517m, 1456w, 1393w, 1366m, 1251s, 1168s; HRMS (ESI$^+$) found 264.1207 calc. for $C_{12}H_{19}O_4NNa$ $[M+Na]^+$ 264.1206.

***tert*-Butyl 3-oxo-2-(2-oxopropyl)pyrrolidine-1-carboxylate (4.29c)**

To a suspension of *para*-toluenesulfonic acid monohydrate (0.4 mg, 2.1 μmol) in DCM-$d_2$ was added a solution of *tert*-butyl (*E*)-(3,6-dioxohept-4-en-1-yl)carbamate **4.29a** (1.9 mg, 7.9 μmol) in DCM-$d_2$ (500 μL). The mixture was stirred under $N_2$ for 5 h 10 min, then concentrated and purified by column chromatography to afford the *title compound* as a pale yellow oil (2.4 mg, >99 %).

$R_f$ 0.15 (59 : 40 : 1 pentane : ethyl acetate : TEA); $^1$H NMR (500 MHz, $CDCl_3$) δ 3.86 (br m, 1H), 3.63 (br m, 2H), 3.44 (dt, $J$ = 6.8, 4.8 Hz, 1H), 3.40 – 3.29 (m, 1H), 3.10 (dd, $J$ = 18.5, 3.0 Hz, 1H), 2.81 (ddd, $J$ = 18.5, 8.5, 3.0 Hz, 1H), 2.68 – 2.52 (m, 1H), 2.11 (s, 3H, H-3'), 1.47 (s, 9H, C*Me*$_3$); IR (ATR) ν 2980m, 1759m, 1714s, 1694s, 1517m, 1394s, 1367s, 1251m, 1164s, 1119m; HRMS (ESI$^+$) found 264.1207, calc. for $C_{12}H_{19}O_4N$ $[M+Na]^+$ 264.1206. A clean $^{13}$C NMR spectrum of this material was not obtained owing to decomposition of material. Two dimensional proton experiments suggest resonances at 212.8 (Oxp-2), 206.3 (C-3), 158.5 (Boc-C=O), 80.2 (*C*Me$_3$), 57.9, 45.5, 42.8, 36.5, 29.6 (Oxp-3), 28.5 (C*Me*$_3$) ppm.

**(*E*)-*N*-(3,6-Dioxohept-4-en-1-yl)-4-methylbenzenesulfonamide [(*E*)-4.30a]**

Brown oil produced from 4-methyl-*N*-(2-(5-methylfuran-2-yl)ethyl)benzenesulfonamide **4.15** (92.7 mg, 332 μmol) according to General Procedure

for Oxidation of Furan Mediated by **2.8**. Reaction time 2 h 55 min, chromatography **not** performed, mixture instead diluted with acetonitrile (20 mL), dried over $Na_2SO_4$ and activated charcoal, then concentrated. Yield 40.9 mg (42%).

$^1$H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.70 (m, 2H, H-2,6), 7.30 (d, *J* = 8.0 Hz, 2H, H-3,5), 6.79 (d, *J* = 16.5 Hz, 2H, H-4' or H-5'), 6.74 (d, *J* = 16.5 Hz, 2H, H-4' or H-5'), 5.28 (br s, 1H, NH), 3.22 (m, 2H, H-1'), 2.90 (t, *J* = 6.0 Hz, 2H, H-2'), 2.41 (s, 3H, Ts-Me), 2.35 (s, 3H, H-7'); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 199.4 (C-3' or C-6'), 198.3 (C-3' or C-6'), 143.7 (Ts-4), 137.8 (C-5'), 137.0 (Ts-1), 136.5 (C-4'), 129.9 (Ts-3,5), 127.1 (Ts-2,6), 41.0 (C-1'), 37.9 (C-2'), 28.4 (C-7'), 21.6 (Ts-Me); IR (ATR) ν 3270br (N–H), 2980w, (C–H), 2925w (C–H), 2885w (C–H), 1709m (C=O), 1681m (C=O), 1598w (C=C), 1362m (S=O), 1156s (S=O), 1093m, 816s, 683m, 662s; HRMS (ESI$^-$) found 296.0953, calc. for $C_{14}H_{17}NO_4S$ $[M–H]^-$ 296.0951.

**2-(2-Oxopropyl)-1-tosylpyrrolidin-3-one (4.30c)**

Brown oil produced from 4-methyl-*N*-(2-(5-methylfuran-2-yl)ethyl)benzenesulfonamide **4.15** (24.3 mg, 94.5 μmol) according to General Procedure for Oxidation of Furan Mediated by **2.8**. After reaction for 2 h, *para*-toluenesulfonic acid monohydrate (7.2 mg, 9.5 μmol) was added, and stirring was resumed without irradiation for an additional 7.5 h 30 min. Chromatography performed with acetonitrile as eluant. Yield 20.2 mg, (77 %).

$R_f$ 0.10 (50 : 49 : 1 ether : pentane : TEA); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.65 (m, 2H, Ts-2,6), 7.37 – 7.30 (m, 2H, Ts-3,5), 3.86 (ddd, *J* = 11.0, 9.0, 7.0 Hz, 1H, H-5), 3.55 – 3.46 (m, 2H, H-2 and H-5), 3.42 (dd, *J* = 18.5, 4.0 Hz, 1H, Oxp-1), 3.15 (dd,

*J* = 18.5, 3.0 Hz, 1H, Oxp-1), 2.75 (dddd, *J* = 18.0, 8.5, 6.0, 0.5 Hz, 1H, H-4), 2.43 (s, 3H, Ts-Me), 2.35 – 2.20 (m, 1H, H-4), 2.12 (s, 3H, Oxp-3); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 210.9 (C-3), 205.3 (Oxp-2), 144.5 (Ts-4), 133.4 (Ts-1), 130.2 (Ts-3,5), 127.7 (Ts-2,6), 59.3 (C-2), 47.1 (Oxp-1), 44.9 (C-5), 36.0 (C-4), 29.8 (Oxp-3), 21.7 (Ts-Me); IR (ATR) ν 2961 (C–H), 2921 (C–H), 1758s (C=O stretch), 1715 (C=O stretch), 1597m, 1400m, 1339s (S=O stretch), 1156s (S=O stretch), 1092s, 1066m, 1038m, 817m, 709m, 660s; HRMS (APCI, $NH_3$) found 296.0950, calc. for $C_{14}H_{17}NO_4S$ $[M+H]^+$ 296.0951.

**1-Cyclopropylundec-3-ene-2,5-dione (4.33a)**

Pale brown oil produced from 2-(cyclopropylmethyl)-5-hexylfuran **4.22** (31.2 mg, 151 μmol) according to General Procedure for Oxidation of Furan Mediated by **2.8**. Chromatography performed with 1: 0 – 4 : 1 pentane : ether as eluant.Yield of (*E*)-isomer 4.2 mg (12%); yield of (*Z*)-isomer 13.7 mg (39%).

**(*E*)-isomer:** $R_f$ 0.40 (4 : 1 PE : ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.94 (d, *J* = 16.0 Hz, 1H, H-3 or H-4), 6.87 (d, *J* = 16.0 Hz, 1H, H-3 or H-4), 2.65 (app t, *J* = 8.0, 7.5 Hz, 2H, H-6), 2.54 (d, *J* = 7.0 Hz, 2H, H-1), 1.68 – 1.60 (m, 2H, H-7), 1.38 – 1.24 (m, 6H, H-8 and H-9 and H-10), 1.08 – 0.98 (m, 1H, *c*-Pr-1), 0.93 – 0.84 (m, 3H, H-11), 0.64 – 0.56 (m, 2H, *c*-Pr-2 and *c*-Pr-3), 0.16 (dt, *J* = 6.0, 4.5 Hz, 2H, *c*-Pr-2 and *c*-Pr-3); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 200.9 (C-5), 200.4 (C-2), 136.5 (C-4), 136.0 (C-3), 47.0 (C-1), 41.9 (C-6), 31.7 (C-9), 29.0 (C-8), 23.9 (C-7), 22.6 (C-10), 14.2 (C-11), 6.2 (*c*-Pr-1), 4.7 (*c*-Pr-2 and *c*-Pr-3); IR (ATR) ν 2956m, 2929m, 2858m, 1697s (C=O stretch), 1609w (C=C stretch), 1392m, 1073w; HRMS (APCI, $CH_4$) found 222.1622, calc. for $C_{14}H_{22}O_2$ $[M]^+$ 222.1625.

**(*Z*)-isomer:** $R_f$ 0.15 (4 : 1 PE : ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.38 (d, *J* = 12.0 Hz, 1H, H-3 or H-4), 6.31 (d, *J* = 12.0 Hz, 1H, H-3 or H-4), 2.52 (t, *J* = 7.5 Hz, 2H, H-6), 2.44 (d, *J* = 7.0 Hz, 2H, H-1), 1.68 – 1.54 (m, 2H, H-7), 1.37 – 1.19 (m, 6H, H-8 and H-9 and H-10), 1.06 – 0.93 (m, 1H, *c*-Pr-1), 0.93 – 0.80 (m, 3H, H-11), 0.62 – 0.52 (m, 2H, *c*-Pr-2 and *c*-Pr-3), 0.15 (dt, *J* = 6.0, 4.5 Hz, 2H, *c*-Pr-2 and *c*-Pr-3); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 203.1 (C-5), 203.0 (C-2), 136.1 (C-4), 135.5 (C-3), 47.8 (C-1), 42.8 (C-6), 31.7 (C-9), 28.9 (C-8), 23.6 (C-7), 22.6 (C-10), 14.2 (C-11), 6.0 (*c*-Pr-1), 4.7 (*c*-Pr-2).

**(*E*)-4-Oxodec-2-enal [(*E*)-4.34a]**

Brown oil produced from 2-hexylfuran **4.23** (92.1 g, 605 μmol) according to General Procedure for Oxidation of Furan Mediated by **2.8**. Reaction time 4 h 5 min, chromatography performed with 1 : 0 – 1 : 1 as eluant. Yield 32.1 mg (29%).

Data are consistent with literature values: (*419*) $R_f$ 0.20 (4 : 1 PE : ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 9.76 (d, *J* = 7.0 Hz, 1H, H-1), 6.86 (d, *J* = 16.0 Hz, 1H, H-3), 6.75 (dd, *J* = 16.0, 7.0 Hz, 1H, H-2), 2.71 – 2.61 (m, 2H, H-5), 1.71 – 1.56 (m, 2H, H-6), 1.38 – 1.16 (m, 6H, H-7 and H-8 and H-9), 0.86 (m, 3H, H-10); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 200.3 (C-4), 193.5 (C-1), 145.1 (C-3), 137.4 (C-2), 41.4 (C-5), 31.7 (C-9), 28.9 (C-8), 23.8 (C-6), 22.6 (C-7), 14.1 (C-10); IR (ATR) ν 2956w (C–H), 2929m (C–H), 2858m (C–H), 1692s (C=O), 1116m, 1078m, 981m; HRMS (APCI, $NH_3$) found 169.1216, calc. for $C_{10}H_{16}O_2$ $[M+H]^+$ 169.1223.

**(*E*)-1-Hydroxydodec-4-ene-3,6-dione [(*E*)-4.35a]**

Brown oil produced from 2-(5-hexylfuran-2-yl)ethan-1-ol **4.24** (100 mg, 509 μmol) according to General Procedure for Oxidation of Furan Mediated by **2.8**. Reaction time 3.7 h, chromatography performed with 1 : 0 – 0 : 1 PE : ether as eluant. Yield 79.5 mg, (74 %).

$R_f$ 0.05 (9 : 1 PE : ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.91 (d, $J$ = 16.0 Hz, 1H, H-4 or H-5), 6.85 (d, $J$ = 16.0 Hz, 1H, H-4 or H-5), 4.97 (br s, 1H, OH), 3.94 (t, $J$ = 5.5 Hz, 2H, H-1), 2.91 (t, $J$ = 5.5 Hz, 2H, H-2), 2.64 (t, $J$ = 7.5 Hz, 2H, H-7), 1.69 – 1.54 (m, 2H, H-8), 1.38 – 1.21 (m, 6H, H-9 and H-10 and H-11), 0.95 – 0.81 (m, 3H, H-12); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 200.8 (C-3 or C-6), 200.7 (C-3 or C-6), 137.2 (C-5), 136.1 (C-4), 57.7 (C-1), 43.4 (C-2), 41.9 (C-7), 31.7 (C-11), 28.9 (C-10), 23.8 (C-8), 22.6 (C-9), 14.1 (C-12); IR (ATR) ν 3330br (O–H stretch), 2656w (C–H), 2927m (C–H), 2859w (C–H), 1715s (C=O stretch), 1391m, 1384m, 1298m, 1093m, 1053m, 1015m, 997m; HRMS ($ESI^-$) 211.1337, calc. for $C_{12}H_{19}O_3$ $[M–H]^-$ 211.1340.

**6-Hydroxy-6-methyl-2-phenyl-2*H*-pyran-3(6*H*)-one (4.39)**

Colourless oil formed by oxidation of 2-benzyl-5-methylfuran (2 ×100 mg, 1.16 mol) according to General Procedure for Oxidation of Furan Mediated by **2.8**. Isolated by column chromatography (99 : 0 : 1 – 89 : 10 : 1 cyclohexane : ether : TEA) from 2 combined runs, reaction times 1 h 25 min and 3 h 50 min. Yield 1.8 mg (0.8%, 2 : 1 mixture of diastereomers).

$R_f$ 0.25 (89 : 10 : 1 cyclohexane : ether : TEA); $^1$H NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 1H, OH), 7.98 – 7.84 (m, 2H, *ortho*-Ph), 7.63 – 7.53 (m, 1H, *para*-Ph), 7.54 –

7.42 (m, 2H, *meta*-Ph), 7.16 [d, $J$ = 3.5 Hz, 0.3H, H-5 (minor)], 7.11 [dd, $J$ = 3.5, 0.5 Hz, 0.7H, H-5 (major)], 6.22 [dq, $J$ = 3.5, 0.5 Hz, 1H, H-4 (major)], 6.18 [dt, $J$ = 3.5 Hz, 1H, H-4 (minor)], 4.06 (s, 1H, H-2), 2.53 – 2.37 (s, 3H, Me).

# Chapter 5

**_N_-(7a-Hydroxy-2-methyl-1-oxo-5,6,7,7a-tetrahydro-1_H_-pyrrolizin-3-yl)-3-methylbutanamide (Legonmycin A, 5.11)**

To 3-aminopyrrolizine hydrochloride **5.91·HCl** (37.2 mg, 0.197 mmol) was added sequentially a solution of pyridine (890 μL, 0.985 mmol) in acetonitrile (2.0 mL) and isovaleryl chloride (70 μL, 0.294 mmol). The mixture was stirred for 17 h 35 min, and $H_2O$ (200 μL) and $I_2$ (6.6 mg, 0.026 mmol) were added sequentially. $O_2$ was bubbled gently through the solution for 21 h, and the mixture concentrated. The residue was purified by column chromatography (3 : 2 : 0 – 1 : 4 : 5 toluene : ethyl acetate : acetone) to afford the title compound as a yellow amorphous solid (16.3 mg, 33%).

*Data are consistent with literature values:* (*363*) $R_f$ 0.10 (2 : 2 : 1 toluene : ethyl acetate : acetone); mp 128 °C; $^1$H NMR (400 MHz, DMSO) δ 10.16 (s, 1H, NH), 6.06 (s, 1H, OH), 3.20 (ddd, *J* = 11.0, 7.5, 4.5 Hz, 1H, Pz-5), 2.91 (dt, *J* = 11.0, 7.5 Hz, 1H, Pz-5), 2.34 – 2.20 (m, 2H, Iv-2), 2.18 – 1.98 (m, 2H, Iv-3 and Pz-6), 1.89 – 1.79 (m, 1H, Pz-6), 1.78 – 1.67 (m, 1H, Pz-7), 1.55 – 1.46 (m, 1H, Pz-7), 1.44 (s, 3H, Pz-Me), 0.92 (d, *J* = 6.5 Hz, 3H, Iv-Me), 0.92 (d, *J* = 6.5, 3H, Iv-Me); $^1$H NMR (400 MHz, $CD_3OD$) δ 3.43 (ddd, *J* = 11.0, 8.0, 4.0 Hz, 1H, Pz-5), 3.04 (ddd, *J* = 11.0, 8.5, 7.0 Hz, 1H, Pz-5), 2.44 – 2.27 (m, 3H, Iv-2 and Pz-6), 2.16 (dq, *J* = 13.5, 7.0 Hz, 1H, Iv-3), 2.11 – 1.99 (m, 1H, Pz-6), 1.93 (ddd, *J* = 13.0, 6.5, 3.5 Hz, 1H, Pz-7), 1.65 (ddd, *J* = 13.0, 10.5, 7.5 Hz, 1H, Pz-7), 1.01 (d, *J* = 6.5 Hz, 3H, Iv-Me), 1.01 (d, *J* = 6.5 Hz, 3H, Iv-Me); $^{13}$C NMR (101 MHz, $CD_3OD$) δ 201.2 (Pz-1)[lxxxix], 172.9 (Iv-1), 169.4 (Pz-3), 99.3 (Pz-2)[lxxxix], 97.7 (Pz-7a), 49.3 (Pz-5), 46.6 (Iv-2), 33.8 (Pz-7), 27.8 (Pz-6), 27.2 (Iv-3), 22.7 (Iv-Me), 22.6 (Iv-

[lxxxix] These signals were extremely low in intensity, even in comparison to other quaternary signals.

Me), 7.0 (Pz-Me); IR (ATR) 3234br (O–H), 2958m (N–H), 2931w (C–H), 2872w (C–H), 1667m (amide C=O), 1571s (vinylogous urea C=O), 1517s, 1437s, 1197m, 730m; HRMS ($ESI^+$) found 235.1439, calc. for $C_{13}H_{20}N_2O_3$ $[M–OH]^+$ 235.1441.

**_N_-(7a-Hydroxy-2-methyl-1-oxo-5,6,7,7a-tetrahydro-1_H_-pyrrolizin-3-yl)-3-methylpentanamide (Legonmycin B, 5.12)**

To 3-aminopyrrolizine hydrochloride **5.91·HCl** (65.7 mg, 0.348 mmol) was added a solution of pyridine (138 μL, 1.74 mmol) in acetonitrile (3.5 mL). Isocaproyl chloride (32 μL, 235 μmol) was added, and the mixture was stirred for 17 h 40 min and $H_2O$ (350 μL) and $I_2$ (8.4 mg, 33.1 μmol) were added sequentially. $O_2$ was bubbled gently through the solution for 21 h, and the mixture concentrated. The residue was purified by column chromatography (3 : 2 : 0 – 0 : 0 : 1 toluene : ethyl acetate : acetone) to afford the title compound as a yellow glass (34.7 mg, 41%).

Data are consistent with literature values: (*363*) $R_f$ 0.40 (2 : 1 : 1 acetone : ethyl acetate : toluene); mp 49 °C; $^1$H NMR (400 MHz, DMSO) δ 10.16 (s, 1H, NH), 6.04 (s, 1H, OH), 3.20 (ddd, *J* = 11.0, 7.5, 4.5 Hz, 1H, Pz-5), 2.91 (dt, *J* = 11.0, 7.5 Hz, 1H, Pz-5), 2.40 (m, 2H, Ic-2), 2.19 – 2.04 (m, 1H, Pz-6), 1.88 – 1.76 (m, 1H, Pz-6), 1.71 (ddd, *J* = 13.0, 6.5, 4.0 Hz, 1H, Pz-7), 1.60 – 1.37 (m, 7H, Pz-7 and Me and Ic-3 and Ic-4), 0.89 (d, *J* = 6.5 Hz, 3H, Ic-Me), 0.88 (d, *J* = 6.5 Hz, 3H, Ic-Me); $^{13}$C NMR (101 MHz, DMSO) δ 198.8 (Pz-1), 170.9 (Ic-1), 166.1 (Pz-3), 97.3 (Pz-2), 95.6 (Pz-7a), 47.6 (Pz-5), 34.0 (Ic-2), 33.7 (Ic-3), 33.0 (Pz-7), 27.2 (Ic-4), 26.1 (Pz-6), 22.2 (Ic-Me), 22.2 (Ic-Me), 7.3 (Pz-Me); IR (ATR) ν 3234br (OH) 2957m (N–H) 2928m (C–H), 2871w (C–H), 1698m (amide C=O), 1668m (urea C=O), 1571s, 1518m, 1454m, 1195m; HRMS ($ESI^+$) found 267.1703, calc. for $C_{14}H_{22}O_3N_2$ $[M+H]^+$ 267.1703.

**_tert_-Butyl(furan-2-ylmethoxy)dimethylsilane (5.60)**

To a solution of imidazole (4.15 g, 60.9 mmol) and furfuryl alcohol (5.00 g, 51.0 mmol) in DMF (12 mL) in a water bath at rt was added slowly a solution of *tert*-butylchlorodimethylsilane (8.44 g, 56.0 mmol) in DMF (24 mL) and DCM (6 mL). The mixture was stirred at rt for 2 h and diluted with water (500 mL). The resulting mixture was extracted with pentane (3 × 50 mL) and the combined organic phases dried over $Na_2SO_4$, decolourised with activated charcoal, filtered and concentrated (150 mbar, 40 °C) to afford the title compound as a pale brown oil found by NMR to be (10.8 g, containing 11% w/w *tert*-butyldimethylsilanol and 1.5% w/w DMF, 88%).

Data are consistent with literature values: (*420*) $R_f$ 0.75 (9 : 1 pentane : ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 2.0, 1.0 Hz, 1H, Fn-5), 6.32 (dd, *J* = 3.0, 2.0 Hz, 1H, Fn-4), 6.22 (dq, *J* = 3.0, 1.0 Hz, 1H, Fn-3), 4.66 – 4.61 (m, 2H, $OCH_2$), 0.91 (s, 9H, *t*-Bu), 0.08 (s, 6H, Me); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 154.5 (Fn-2), 142.2 (Fn-5), 110.3 (Fn-4), 107.3 (Fn-3), 58.3 ($CH_2$), 26.0 (C*Me*$_3$), 18.6 (*C*$Me_3$), –5.1 ($SiMe_2$).

**2-[(Benzyloxy)methyl]furan (5.61)**

To a solution of NaOH (3.08 g, 77.0 mmol) in DMSO (15 mL) was added furfuryl alcohol (5.00 g, 51.0 mmol). The mixture was stirred for 40 min and benzyl chloride (6.45 mL, 56.0 mmol) was added. The mixture was stirred for 40 h, then diluted with $H_2O$ (150 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic phases were then washed with $H_2O$ (10 mL) and brine (5 mL), dried over $Na_2SO_4$ and concentrated to afford the title compound as a pale yellow oil (9.56 g, >99%).

Data are consistent with literature values: (*421*) $R_f$ 0.45 (9 : 1 pentane : ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 2.0, 1.0 Hz, 1H, Fn-5), 7.41 – 7.27 (m, 5H, Ph), 6.36 (dd, *J* = 3.0, 2.0 Hz, 1H, Fn-4), 6.34 (dd, *J* = 3.0, 1.0 Hz, 1H, Fn-3), 4.56 (s, 2H, PhC*H*$_2$O), 4.50 (s, 2H, FnC*H*$_2$O); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 151.9 (Fn-2), 142.9 (Fn-5), 138.1 (*ipso*-Ph), 128.5 (*ortho*- or *meta*-Ph), 128.0 (*ortho*- or *meta*-Ph), 127.8 (*para*-Ph), 110.4 (Fn-4), 109.5 (Fn-3), 72.0 (Ph*C*H$_2$O), 64.0 (Fn*C*H$_2$O).

**2-{5-[(Benzyloxy)methyl]furan-2-yl}acetonitrile (5.64)**

To a solution of $FeSO_4 \cdot 7H_2O$ (1.11 g, 4.00 mmol) in DMSO (100 mL), in a 500 mL round-bottomed flask, was added sequentially 2-(benzyloxy)methylfuran **5.61** (5.65 g, 30.0 mmol) and iodoacetonitrile **4.9 (**1.67 g, 10.0 mmol). The reaction vessel was immersed in water and $H_2O_2$ (30 % w/v in $H_2O$, 3.4 mL, 30.0 mmol) was added dropwise. The mixture was stirred for 23 h and diluted with water (1000 mL), and the resulting mixture was extracted with ethyl acetate (5 × 100 mL). The combined organic phases were washed with water (2 × 100 mL) and a 1 : 1 v/v mixture of sat. aq. $Na_2S_2O_3$ : brine (40 mL), dried over $Na_2SO_4$, filtered and concentrated to afford a brown oil (5.26 g), which was purified by column chromatography to afford iodoacetonitrile **4.9** (445 mg, 27% recovery), starting material **5.61** (3.86 g, 68% recovery) and the *title compound* as an amber oil (104 mg, 5%).

$R_f$ 0.30 (20% ether/pentane); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.27 (m, 5H, Ph), 6.30 (s, 2H, Fn-3 and Fn-4), 4.56 (s, 2H, PhC*H*$_2$O), 4.45 (s, 2H, FnC*H*$_2$O), 3.75 (s, 2H, C*H*$_2$CN); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 152.6 (Fn-5), 143.3 (Fn-2), 137.7 (*ipso*-Ph), 128.5 (*meta*-Ph), 127.9 (*ortho*-Ph), 127.8 (*para*-Ph), 115.4 (CN), 110.6 (Fn-4), 109.2 (Fn-3), 72.2 (*C*H$_2$Ph), 63.7 (Fn*C*H$_2$OBn), 17.6 (*C*H$_2$CN); IR (ATR) ν 2918w (C–H),

2859w (C–H), 2257w (C≡N), 1454m, 1356m, 1207m (C-O), 1177m, 1068s (C-O), 1023s, 798s, 738s, 698s; HRMS (APCI, $NH_3$) not observed.

**(*S*)-1-Benzylproline benzyl ester (5.69)**

To L-proline (925 mg, 8.00 mmol) was added THF (10 mL), DIPEA (2.90 mL, 16.6 mmol), DMF (10.0 µL, 12.9 µmol) and benzyl bromide (1.95 mL, 16.4 mmol). The mixture was stirred at rt for 12 d.[xc] The mixture was heated to 80 °C overnight and concentrated, and the residue purified by column chromatography to afford the title compound as a colourless oil (1.30 g, 55%).

Data are consistent with literature values: (*422*) $R_f$ 0.75 (1 : 1 pentane : ethyl acetate); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.16 (m, 10H, Ph), 5.23 (d, *J* = 12.5 Hz, 1H, OC*H*$_2$Ph), 5.18 (d, *J* = 12.5 Hz, 1H, OC*H*$_2$Ph), 4.19 (d, *J* = 13.5 Hz, 1H, NC*H*$_2$Ph), 3.42 (d, *J* = 13.5 Hz, 1H, Pld-5), 3.36 (d, *J* = 13.5 Hz, 1H, NC*H*$_2$Ph), 2.90 (m, 2H, Pld-5 and Pld-2), 2.45 (q, *J* = 8.5 Hz, 1H, Pld-3), 2.12 (ddd, *J* = 13.5, 8.5, 4.5 Hz, 1H, Pld-3), 1.93 – 1.82 (m, 1H, Pld-4), 1.82 – 1.68 (m, 1H, Pld-4).

**(*S*)-2-(Methoxycarbonyl)-pyrrolidin-1-ium chloride (5.70)**

To a suspension of L-proline (1.20 g, 10.4 mmol) in methanol (11 mL), cooled to 0 °C and under $N_2$, was added dropwise $SOCl_2$ (3.05 mL, 41.7 mmol). The mixture was then heated to reflux for 1 h 55 min and concentrated to afford the title compound as a beige glass (1.76 g, >99%).

[xc] NMR indicated no conversion of material had occurred; Reaction progress was not monitored more frequently as this procedure coincided with a period of holiday leave.

Data are consistent with literature values: (*384*) $R_f$ 0.20 (94 : 5 : 1 DCM : methanol : TEA); $^1$H NMR (400 MHz, $CD_3OD$) δ 4.44 (t, *J* = 8.0 Hz, 1H, Pld-2), 3.86 (s, 3H, Me), 3.46 – 3.33 (m, 2H, Pld-5), 2.49 – 2.35 (m, 1H. Pld-3), 2.20 – 2.11 (m, 1H, Pld-3), 2.11 – 2.01 (m, 2H, Pld-4); $^{13}$C NMR (101 MHz, $CD_3OD$) δ 170.5, (C=O), 60.7 (Pld-2), 53.9 (Me), 47.2 (Pld-5), 29.3 (Pld-3), 24.5 (Pld-4).

**(*S*)-Methyl 1-triphenylmethylpyrrolidine-2-carboxylate (5.71)**

To a 1.0 M solution of methyl prolinate hydrochloride **5.70** (497 mg, 3.00 mmol) in DCM was added TEA (1.3 mL, 9.0 mmol) and a solution of triphenylmethyl chloride (836 mg, 3.00 mmol) in DCM (1 mL). The mixture was stirred for 20 h and diluted with 2 : 1 sat. aq. $NH_4Cl$ : aq. $NH_4OH$ (28% w/w) (4 mL total). The organic phase was dried over $Na_2SO_4$ and concentrated, then dried under vacuum to afford the title compound as a beige semi-solid (841 mg, 75%).

Data are consistent with literature values: (*385*) $R_f$ 0.25 (4 : 1 pentane : ether); mp 82 °C [lit. for (*S*)-enantiomer 116-118 °C]; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.57 (ddd, *J* = 8.5, 2.0, 1.0 Hz, 6H, *ortho*-Ph), 7.35 – 7.20 (m, 6H, *meta*-Ph), 7.21 – 7.11 (m, 3H, *para*-3H), 3.90 (dt, *J* = 9.0, 2.5 Hz, 1H, Pld-2), 3.69 (s, 3H, Me), 3.42 (m, 1H, Pld-5), 2.90 – 2.78 (m, 1H, Pld-5), 1.67 – 1.52 (m, 1H, Pld-4), 1.55 – 1.44 (m, 1H, Pld-3), 1.02 (m, 1H, Pld-3), 0.93 (m, 1H, Pld-4); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 177.3 (C=O), 144.9 (*ipso*-Ph), 129.4 (*ortho*-Ph), 127.8 (*meta*-Ph), 126.3 (*para*-Ph), 77.4 (*C*$Ph_3$), 62.9 (C-2), 51.7 (OMe), 50.1 (C-5), 31.4 (C-3), 24.4 (C-4).

**(*S*)-1-*tert*-Butyloxycarbonyl-2-methoxycarbonylpyrrolidine (5.72)**

A solution of di-*tert*-butyl dicarbonate (1.66 g, 7.59 mmol), TEA (3.2 mL, 22.8

mmol), and methyl prolinate hydrochloride **5.70** (1.27 g, 7.59 mmol) in DCM (76 mL) was stirred at rt for 42 h and concentrated. The residue was redissolved in a minimum of DCM and the resulting solution diluted with ether. The resulting suspension was filtered and the filtrate concentrated to afford the title compound as a colourless oil, comprising a 3 : 2 mixture of rotamers (1.57 g, 90%).

Data are consistent with literature values: (*386*) $R_f$ 0.35 (20% ether/pentane); $^1$H NMR (400 MHz, $CDCl_3$) δ 4.31 (dd, $J$ = 8.5, 3.5 Hz, 0.4H, Pld-2; minor), 4.21 (dd, $J$ = 8.5, 4.0 Hz, 0.6H, Pld-2; major), 3.71 (s, 3H, OMe; both rotamers), 3.59 – 3.30 (m, 2H, Pld-5; both rotamers), 2.33 – 2.10 (m, 1H, Pld-3; both rotamers), 2.09 – 1.77 (m, 3H, Pld-3 and Pld-4; both rotamers), 1.46 (s, 3.8H, $C(CH_3)_3$; minor), 1.40 (s, 5.2H, $C(CH_3)_3$; major); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 173.9 ($CO_2$Me; major), 173.6 ($CO_2$Me; minor), 153.9 [O(*C*O)N; both rotamers], 80.0 [$C(CH_3)_3$; both rotamers], 59.3 (Pld-2; major), 58.9 (Pld-2; minor), 52.2 (OMe; minor), 52.1 (OMe; major), 46.7 (Pld-5; minor), 46.4 (Pld-5; major), 31.0 (Pld-3; major), 30.1 (Pld-3; minor), 28.6 [C$Me_3$; minor], 28.4 [C$Me_3$; major], 24.5 (Pld-4; minor), 23.8 (Pld-4; major).

**(*S*)-Methyl 1-benzylpyrrolidine-2-carboxylate (5.74)**

To a solution of TEA (400 μL, 3.00 mmol) in DCM (9 mL) was added benzyl chloroformate (143 μL, 1.01 mmol). The mixture was cooled to 0 °C and a solution of methyl prolinate hydrochloride **5.70** (166 mg, 1.00 mmol) in DCM (1 mL) added dropwise. The resulting mixture was stirred and allowed to warm to rt for 19 h, and purified directly by column chromatography (1 : 0 – 9 : 1 DCM : methanol) to afford the title compound as a colourless oil (53.5 mg, containing 23% w/w proline, 19%).

Data are consistent with literature values: (*423*) $R_f$ 0.60 (1 : 1 pentane : ethyl acetate); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.20 (m, 5H, Ph), 3.89 (d, *J* = 13.0 Hz, 1H, PhC*H*$_2$), 3.65 (s, 3H, Me), 3.58 (d, *J* = 13.0 Hz, 1H, PhC*H*$_2$), 3.25 (dd, *J* = 9.0, 6.5 Hz, 1H, Pld-2), 3.13 – 3.01 (m, 1H, Pld-5), 2.44 – 2.34 (m, 1H, Pld-5), 2.21 – 1.72 (m, 4H, Pld-3 and Pld-4); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 174.7 (C=O), 138.4 (*ipso*-Ph), 129.4 (*ortho*-Ph or *meta*-Ph), 128.3 (*ortho*-Ph or *meta*-Ph), 127.2 (*para*-Ph), 65.5 (Pld-2), 58.9 ($PhCH_2$), 53.4 (Pld-5), 51.9 (Me), 29.5 (Pld-3), 23.1 (Pld-4).

**(*S*)-Methyl 1-(3-methylbutanoyl)pyrrolidine-2-carboxylate (5.75)**

To a solution of TEA (400 µL, 3.00 mmol) in DCM (9 mL) was added isovaleryl chloride (365 µL, 3.00 mmol) and 4-(dimethylamino)pyridine (20.5 mg, 168 µmol). The mixture was cooled to 0 °C and a solution of methyl prolinate hydrochloride **5.70** (166 mg, 1.00 mmol) in DCM (1 mL) added dropwise. The resulting mixture was stirred for 18 h and purified directly by column chromatography (1 : 0 – 97 : 3 DCM : methanol) to afford the title compound as a colourless oil (174 mg, 82%).

Data are consistent with literature values: (*424*) $R_f$ 0.25 (1 : 1 pentane : ethyl acetate); $^1$H NMR (400 MHz, $CDCl_3$) δ 4.52 – 4.47 (m, 1H, Pld-2), 3.72 (s, 3H, OMe), 3.68 – 3.60 (m, 1H, Pld-5), 3.56 – 3.46 (m, 1H, Pld-5), 2.30 – 1.86 (m, 7H, Iv-2 and Iv-3 and Pld-3 and Pld-4), 0.98 – 0.96 (m, 6H, Iv-Me); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 173.1 (Iv-1), 171.8 (*C*$O_2$Me), 58.7 (Pld-2), 52.3 (OMe), 47.3 (Pld-5), 43.5 (Iv-2), 29.4 (Pld-3), 25.7 (Iv-3), 25.0 (Pld-4), 22.8 (Iv-Me), 22.7 (Iv-Me); IR (ATR) ν 2956 (C–H), 2872 (C–H), 1744s (ester C=O), 1644s (amide C=O), 1420s, 1196s, 1172s; HRMS (ESI$^+$) found 214.1435, calc. for $C_{11}H_{19}O_3N$ $[M+H]^+$ 214.1438.

**(*S*)-2-Methyl-3-oxo-3-(1-tritylpyrrolidin-2-yl)propanenitrile (5.76)**

To LHMDS (6.8 mL, 1.0 M in THF, 6.8 mmol) cooled to −78 °C and under $N_2$, was added dropwise propionitrile (500 μL, 6.98 mmol). The resulting mixture was stirred at −78 °C for 1 h 50 min and a solution of methyl tritylprolinate **5.71** (1.23 g, 3.31 mmol) in THF (4.2 mL) added dropwise. The mixture was stirred at −78 °C for 1 h and was then allowed to warm to rt. The mixture was diluted with $H_2O$ (10 mL) and extracted with ether (10 mL). The aqueous phase was then acidified to *pH* 4 with glacial acetic acid (1 mL) and sat. aq. $NH_4Cl$. The resulting mixture was extracted with ether (2 × 10 mL) and ethyl acetate (10 mL). All organic phases were combined, washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (1 : 0 – 1 : 1 pentane : ethyl acetate) to afford the *title compound* (as a 46 : 35 : 19 mixture of major *keto* diastereomer : minor *keto* diastereomer : enol) as a yellow crystalline solid (1.11 g, 84%).

$R_f$ 0.65 (1 : 1 pentane : ethyl acetate); mp 72 – 77 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.54 [m, 4.86H, *ortho*-Ph (both keto)], 7.49 – 7.42 [m, 1.14H, *ortho*-Ph (enol)], 7.39 – 7.28 [m, 6H, *meta*-Ph (all isomers)], 7.28 – 7.19 [m, 3H, *para*-Ph (all isomers)], 4.53 [d, $J$ = 4.5 Hz, 0.19H, Pld-2 (enol)], 4.50 [dd, $J$ = 9.5, 3.0 Hz, 0.35H, Pld-2 (minor)], 4.33 [dd, $J$ = 9.5, 3.0 Hz, 0.46H, Pld-2 (major)], 3.52 – 3.43 [m, 1.27H, Pld-5 (both keto) and Cnp-2 (minor)], 3.30 [ddd, $J$ = 11.5, 7.5, 6.0 Hz, 0.19H, Pld-5 (enol)], 3.21 [q, $J$ = 7.0 Hz, 0.46H, Cnp-2 (major)], 3.04 – 2.87 [m, 1H, Pld-5 (all isomers)], 1.83 [app d, $J$ = 1.0 Hz, 0.57H, Cnp-3 (enol)], 1.65 – 1.49 [m, 1.81H, Pld-3 (both keto) and Pld-4 (all isomers)], 1.46 [d, $J$ = 7.5 Hz, 1.05H, Cnp-3 (minor)], 1.42 [d, $J$ = 7.0 Hz, 1.38H, Cnp-3 (major)], 1.39 – 1.28 [m, 0.81H, Pld-3 (both keto)], 1.05 – 0.89 [m, 1H, Pld-4 (all

isomers)]; $^{13}$C NMR (101 MHz, $CDCl_3$) δ 204.7 [Cnp-1 (minor)], 204.4 [Cnp-1 (major)], 169.9 [Cnp-1 (enol), 147.0 [Cnp-2 (enol)], 144.5 [*ipso*-Ph (all isomers), 129.4 [*ortho*-Ph (enol)], 129.3[*ortho*-Ph (minor)], 129.3[*ortho*-Ph (major)], 128.0 [*meta*-Ph (enol)], 128.0 [*meta*-Ph (minor)], 127.9 [*meta*-Ph (major)], 127.1 [*para*-Ph (enol)], 126.5 [*para*-Ph (minor)], 126.5 [*para*-Ph (major)], 121.0 [CN (enol)], 118.3 [CN (minor)], 118.2 [CN (major)], 78.2 [*C*$Ph_3$ (enol)],[xci] 77.5 [*C*$Ph_3$ (minor)], 77.3 [*C*$Ph_3$ (major)], 76.0[*C*$Ph_3$ (enol)],[xci] 67.8 [Pld-2 (major)], 67.7 [Pld-2 (minor)], 62.7 [Pld-2 (enol)], 51.6 [Pld-5 (enol)], 50.8 [Pld-5 (minor)], 50.5 [Pld-5 (major)], 35.6 [Cnp-2 (major)], 34.4 [Cnp-2 (minor)], 30.7 [Pld-3 (major)], 30.6 [Pld-3 (minor)], 24.7 [Pld-4 (enol)], 24.4 [Pld-4 (major)], 24.3 [Pld-4 (minor)], 14.8 [Cnp-3 (minor)], 14.5 [Cnp-3 (major)], 12.1 [Cnp-3 (enol)]; IR (ATR) ν 3060m (C–H), 2960m (C–H), 2202w (C≡N), 2189w (C≡N), 1736 (C=O), 1620m, 1510s, 1491s, 1447s, 702s; HRMS ($ESI^+$) found 395.2119, calc. for $C_{27}H_{26}ON_2$ $[M+H]^+$ 395.2118.

**(*S*)-*tert*-Butyl 2-(2-cyanopropanoyl)pyrrolidine-1-carboxylate (5.77)**

To LHMDS (100 mL, 1.0 M in THF, 100 mmol), cooled to −78 °C and under $N_2$, was added dropwise propionitrile (7.33 mL, 102. 5 mmol). The mixture was stirred vigorously at −78 °C for 40 min, after which time a solution of proline derivative **5.72** (11.2 g, 48.8 mmol) in THF (60 mL) was added dropwise *via* syringe. The mixture was warmed to rt and stirred for 42 h. The mixture was then diluted with 3 : 1 (v/v) $H_2O$ : acetic acid (20 mL), concentrated, and extracted with ethyl acetate (3 × 100 mL). The combined organic phases were washed with $H_2O$ (40 mL) and brine (10 mL), then dried over $Na_2SO_4$ and concentrated to afford a pale yellow to tan solid which was used without

[xci] Only one of these signals arises from the trityl moiety in the enol; the other is due to a minor impurity.

further purification (14.1 g, containing 5% w/w propionitrile and 10% w/w trimethylsilyl acetate, 99%); Chromatography (1 : 0 – 4 : 1 pentane : ethyl acetate) afforded analytically pure *title compound* as a white solid (43%, mixture of diastereomers and rotamers).

$R_f$ 0.50 (1 : 1 pentane : ethyl acetate); mp 92-102 °C, $^1$H NMR (500 MHz, DMSO, 90 °C) δ 4.64 – 4.50 (br m, 1H, Pld-2), 4.21 – 4.11 (br m, 2H, Pld-5), 3.44 – 3.34 (m, 1H, Cnp-2), 2.32 – 2.11 (br m, 1H, Pld-3), 1.95 – 1.70 (br m, 3H, Pld-3 and Pld-4) 1.49 – 1.32 (m, 12H, Cnp-3 and $CMe_3$); $^{13}$C NMR (126 MHz, DMSO, 90 °C) δ 201.1 and 200.9 (Cnp-1), 168.7 and 152.8 (Boc-C=O), 120.1 and 117.9 (CN), 79.0, 78.9, 78.2 and 78.0 ($CMe_3$), 62.9, 62.6 and 58.4 (Pld-2), 46.4, 46.2 and 46.1 (Pld-5), 39.5, 33.8 (Cnp-2), 30.9 and 27.7 (Pld-3) and 27.6 ($CMe_3$), 23.0 (Pld-4), 14.3, 13.5 and 12.1 (Cnp-3); IR (ATR) ν 3009w (C–H), 2935w, (C–H), 2879 (C–H), 2244, 2185, 1738m (ketone), 1688 (carbamate), 1454m, 1394s, 1367s, 1256m, 1163s, 1119m, 773m; HRMS (ESI$^+$) found 275.1366, calc. for $C_{13}H_{20}O_3N_2$ $[M+Na]^+$ 275.1366.

**(*S*)-2-Methyl-3-[1-(3-methylbutanoyl)pyrrolidin-2-yl]-3-oxopropanenitrile (5.78)**

Impurity co-isolated with **5.81**. $^1$H NMR (400 MHz, $CDCl_3$) δ 4.71 – 4.64 [m, 1H, Pld-5 (both diastereomers)], 3.95 [q, $J$ = 7.2 Hz, 0.6H, Cnp-2 (major)], 3.71 [q, $J$ = 7.5 Hz, 0.4H, Cnp-2 (minor)], 3.66 – 3.50 [m, 3H, Pld-5 (both diastereomers)], 2.39 – 1.65 [m, 7H, Pld-3, Pld-4, Iv-2 and Iv-3 (both diastereomers)], 1.52 [d, $J$ = 7.5 Hz, 1.2H, Cnp-3 (minor)], 1.46 [d, $J$ = 7.0 Hz, 1.8H, Cnp-3 (major)], 1.00 – 0.87 [m, 6H, Iv-Me (both diastereomers)]; $^{13}$C NMR ($CDCl_3$) 200.5 (Cnp-1, major), 200.2 (Cnp-1, minor), 172.4 (Iv-1, minor), 171.6 (Iv-1, major), 118.1 (CN, both diastereomers), 63.7 (Pld-2, minor), 63.2 (Pld-2, major), 47.6 (Pld-5, major), 47.5 (Pld-5, minor), 43.3 (Iv-2, minor), 43.1 (Iv-2, major), 36.4 (Cnp-2, major), 35.1 (Cnp-2, minor), 29.5 (Pld-3, major), 29.0 (Pld-3,

minor), 25.7 (Iv-3 or Pld-4, major), 25.6 (Iv-3 or Pld-4, major), 25.4 (Iv-3 or Pld-4, minor), 25.3 (Iv-3 or Pld-4, minor), 22.7 (Iv-Me, minor), 22.6 (Iv-Me, minor), 22.6 (Iv-Me, major), 22.6 (Iv-Me, major), 14.5 (Cnp-3, minor), 13.0 (Cnp-3, major); HRMS ($ESI^+$) found 259.1418, calc. for $C_{13}H_{20}O_2N_2$ $[M+Na]^+$ 259.1417.

**2-(Benzyloxy)-6-[1-benzyl-(*S*)-pyrrolidin-2-yl]-2-ethyl-5-methyl-[2*H*]-1,3-oxazin-4-amine (5.79)**

To LHMDS (16.0 mL, 1.0 M in THF, 16.0 mmol), cooled to −84 °C and under $N_2$, was added propionitrile (1.16 mL, 16.0 mmol). The mixture was stirred at −84 °C for 3 h 40 min and a 1.1 M solution of benzyl benzylprolinate **5.69** (1.30 g, 4.4 mmol) added. The mixture was warmed to rt and stirred for 22 h 30 min. The mixture was quenched by addition of acetic acid (1.0 M aq. solution) and concentrated at 150 mbar. The mixture was then extracted with ethyl acetate (30 mL) and the *pH* adjusted below 5 with acetic acid (1 M aq. solution). The aqueous phase was re-extracted with ethyl acetate (2 × 30 mL) and the combined organic phases washed with brine (10 mL), dried over $Na_2SO_4$ and concentrated. The residue was purified by column chromatography (pentane – ethyl acetate) to afford the a mixture of diastereomers (1 : 1 by NMR) of the *title compound* as a colourless oil (677 mg, 38%).

$R_f$ 0.50 (1 : 1 pentane : ethyl acetate); $^1H$ NMR (500 MHz, $CDCl_3$) δ 9.21 (br s, 2H, $NH_2$), 7.25 – 7.11 (m, 10H, Ph), 4.58 (s, 2H, OC$H_2$Ph), 3.71 (d, $J$ = 13.0 Hz, 1H, NC$H_2$Ph), 3.58 (d, $J$ = 13.0 Hz, 1H, NC$H_2$Ph), 3.20 (dd, $J$ = 10.5, 4.5 Hz, 1H, Pld-2), 3.07 (ddd, $J$ = 9.5, 6.5, 2.0 Hz, 1H, Pld-5), 2.82 – 2.63 (m, 2H, oxazine-C$H_2$$CH_3$), 2.41 (ddd, $J$ = 10.5, 9.5, 6.5 Hz, 1H, Pld-5), 2.17 (dtd, $J$ = 13.0, 10.5, 8.0 Hz, 1H, Pld-3), 1.83 (m, 1H, Pld-3), 1.79 – 1.69 (m, 1H, Pld-4), 1.69 – 1.59 (m, 4H, oxazine-$CH_3$ and Pld-4),

0.92 (t, $J$ = 7.5 Hz, 3H, oxazine-$CH_2CH_3$); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 172.1 (oxazine-6), 153.9 (oxazine-4), 141.1 (*ipso*-$OCH_2Ph$), 137.8 (*ipso*-$NCH_2Ph$), 128.8 (*ortho*-Ph), 128.6 (Ph), 127.9 (Ph), 127.7 (Ph), 127.1 (*ortho*-Ph), 120.2 (oxazine-5), 90.8 (oxazine-2), 68.2 (Pld-2), 65.4 ($OCH_2Ph$), 60.4 ($NCH_2Ph$), 54.7 (Pld-5), 31.1 (Pld-3), 25.8 (oxazine-$CH_2CH_3$), 24.6 (Pld-4), 14.6 (oxazine-Me), 12.9 (oxazine-$CH_2CH_3$); IR (ATR) ν 3458br, 3262br, 2974w, 2956w, 2874w, 2205m, 1706s, 1621s, 1493s, 1454s, 701s; HRMS (ESI$^+$) found 298.1912, calc. for $C_{25}H_{31}N_3O_2$ $[M–BnO]^+$ 298.1914.

**1-[2-(4-Amino-2-ethyl-2-hydroxy-5-methyl-[2*H*]-1,3-oxazin-6-yl)-(*S*)-pyrrolidin-1-yl]-3-methylbutan-1-one (5.81)**

To LHMDS (1.63 mL, 1.0 M in THF, 1.63 mmol), cooled to −78 °C and under $N_2$, was added dropwise propionitrile (120 µL, 1.64 mmol). The mixture was stirred for 80 min and a solution of methyl (isovaleryl)prolinate **5.75** (170 mg, 797 µmol) in THF (800 µL) added dropwise. The mixture was allowed to warm to rt and stirred for 21 h. The mixture was quenched by addition to acetic acid (2 mL, 1.0 M in $H_2O$). $H_2O$ (5 mL) was added and the mixture extracted with ethyl acetate (3 × 5 mL). The combined organic phases were washed with brine (5 mL), dried over $Na_2SO_4$ and concentrated. The residue was purified by column chromatography (1 : 0 – 1 : 1 pentane : ethyl acetate) to afford a mixture of the *title compound* and 2 diastereomers of **5.78** (56 : 25 :19 **5.81** : **5.78** : **5.78**) as a pale yellow oil (49.4 mg, 56% pure, 11%).

$R_f$ 0.20 (1 : 1 pentane : ethyl acetate); $^1$H NMR (400 MHz, $CDCl_3$) δ 9.53 (br s, 3H, OH and $NH_2$), 4.75 – 4.61 (m, 1H, Pld-2), 3.57 – 3.50 (m, 1H, Pld-5), 3.43 (td, $J$ = 10.0, 7.5 Hz, 1H, Pld-5), 2.86 (app qdd, $J$ = 7.5, 1.5, 1.0 Hz, 2H, Oxazine-$CH_2CH_3$), 2.62 – 2.48 (m, 1H, Pld-3), 2.25 – 1.88 (m, 5H, Pld-4, Iv-2 and Iv-3), 1.82 (s, 3H, Oxazine-

Me), 1.80 – 1.70 (m, 1H, Pld-3) 1.07 (t, $J$ = 7.5 Hz, 3H, Oxazine-$CH_2CH_3$), 1.00 – 0.87 (m, 6H, Iv-Me); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 174.4 (Iv-1), 168.5 (Oxazine-6), 154.5 (Oxazine-2), 120.5 (Oxazine-4), 91.5 (Oxazine-5), 60.4 (Pld-2), 48.0 (Pld-5), 43.4 (Iv-2), 26.2 (Oxazine-$CH_2CH_3$), 26.1 (Pld-3), 25.7 (Iv-3), 25.2 (Pld-4), 22.8 (Iv-Me), 14.8 (Oxazine-Me), 12.9 (Oxazine-$CH_2CH_3$); IR (ATR) ν 3257br (N–H), 3214br (amine), 3140br (O–H), 2958m (C–H), 2873w (C–H), 2206w (C≡N), 1712m (ketone C=O), 1619 (amide C=O), 1421s; HRMS (ESI$^+$) found 314.1839, calc for [M–$H_2O$, +Na]$^+$ 314.1839.

**2-[(*S*)-Pyrrolidine-2-carbonyl]-5-methyl-3-oxohexanenitrile (5.85)**

Side product from abortive nitrile acylation with isovaleryl chloride and $SbCl_5$. To a solution of isovaleryl chloride (13.3 mg, 110 μmol) in dry DCM (440 μL, cooled to –78 °C and under $N_2$, was added sequentially $SbCl_5$ (110 μL, 1.0 M in DCM, 110 μmol) and a solution of cyanoketone **5.76** (39.5 mg, 100 μmol) in dry DCM (500 μL). The mixture was warmed to rt and stirred for 5 min. Half of the mixture was passed through a plug of activated charcoal and concentrated, the remainder was added slowly to sat. aq. $NaHCO_3$ (5 mL) and the aqueous phase extracted with DCM 3 × 5 mL). Both organic phases were concentrated and the residue purified, together with that from another attempted preparation[xcii] by column chromatography (1 : 0 – 49 : 1 DCM : methanol) to afford the *title compound* as a colourless oil (combined yield 3.0 mg, 8%).

$R_f$ 0.50 (49 : 1 DCM : methanol); $^1$H NMR (700 MHz, $CDCl_3$) δ 4.97 (dd, $J$ = 8.5, 5.2 Hz, 1H, Pld-2), 3.73 – 3.68 (m, 1H, Pld-5), 3.61 – 3.56 (m, 1H, Pld-5), 2.41 – 2.33

[xcii] Procedure for second reaction was as described above, but carried out on 51 μmol of **5.76**, added as a 2.0 M solution in dry DCM to acylation mixture (prepared by addition of 110 μmol of isovaleryl chloride (0.5 M in dry DCM) to μmol of $SbCl_5$ (1.0 M in DCM). Temperature –20 °C, reaction time 2.0 h. The entire reaction mixture was quenched by addition of 1 mL sat. aq. $NaHCO_3$, and the resulting mixture extracted with DCM. The organic phase was concentrated and the residue purified by column chromatography.

(m, 1H, Pld-3), 2.23 (s, 3H, 2-Me), 2.22 – 2.09 (m, 4H, H-4 and H-5 and Pld-4), 2.08 – 1.99 (m, 2H, Pld-3 and Pld-4), 1.00 – 0.94 (m, 6H, H-6 and 5-Me); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 197.0 (C-3), 171.5 (proline-*C*O), 116.6 (CN), 59.9 (Pld-2), 58.4 (C-2), 47.6 (Pld-5), 43.3 (C-4), 30.9 (Pld-3), 28.6 (2-Me), 25.7 (Pld-4), 25.5 (C-5), 22.8 (5-Me or C-6), 22.7 (5-Me or C-6); IR (ATR) ν 2959s (N–H), 2929m, 2872m, 2171w (C≡N), 1728s, 1635s, 1447s, 1262m, 1168m, 1034m; HRMS (APCI, $NH_3$) found 237.1600, calc. for $C_{13}H_{20}O_2N_2$ $[M+H]^+$ 237.1598.

**2-(Triphenylmethoxy)ethanol (5.86)**

Isolated as by-product from abortive acetalisation of **5.76**. To a solution of trityl-protected cyanoketone **5.76** (100 mg, 253 μmol) in dry DCM (750 μL) was added a solution of bis-silyl ether **5.88** (67.9 mg, 529 μmol) in dry DCM (750 μL). The resulting mixture was cooled to −78 °C and a solution of distilled trimethylsilyl trifluoromethanesulfonate (500 nL, 2.53 μmol) in dry DCM (1 mL) was added. The mixture was allowed to warm to rt and stirred for 17h 30 min, after which time additional trimethylsilyl trifluoromethanesulfonate (20 μL) was added neat. The mixture was stirred for 1 h 40 min and quenched by addition of pyridine (400 μL) and pouring of the resulting mixture into sat. aq. $NaHCO_3$ (5 mL). The mixture was extracted with DCM (3 × 2 mL), dried over 1 : 1 (v/v) $Na_2CO_3$ : $Na_2SO_4$ and concentrated. The residue was purified by column chromatography (12 : 12 : 1 – 0 : 0 : 1 pentane : ether : ethanol) to afford the title compound as a colourless oil (8.6 mg, 11%).

Data are consistent with literature values: (*425*) $R_f$ 0.25 (12 : 12 : 1 pentane : ether : ethanol); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.41 (m, 6H, *ortho*-Ph), 7.34 – 7.28 (m, 6H, *meta*-Ph), 7.27 – 7.22 (m, 3H, *para*-Ph), 3.75 (br t, $J$ = 4.5 Hz, 2H, H-1), 3.36 – 3.21

(m, 2H, H-2), 1.97 (s, 1H, OH); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 143.9 (*ipso*-Ph), 128.7 (*meta*-Ph), 127.9 (*ortho*-Ph), 127.1 (*para*-Ph), 86.7 (*C*$Ph_3$), 64.8 (C-2), 62.4 (C-1).

**2,2,7,7-Tetramethyl-3,6-dioxa-2,7-disilaoctane (5.88)**

To a solution of ethan-1,2-diol (450 μL, 8.00 mmol) in dry DCM (33 mL) was added TEA (3.30 mL, 23.8 mmol). The mixture was cooled to 0 °C and trimethylsilyl chloride (2.50 mL, 19.8 mmol) added dropwise. The mixture was stirred for 65 min and allowed to warm to rt, after which time the mixture was recooled to 0 °C. Sat. aq. $NH_4Cl$ (2 mL) was added and the mixture filtered *via* suction through Celite, and the residue washed with DCM. The organic phases were combined and washed with an equal volume of brine and concentrated. The residue was then taken up in ether, filtered through Celite and concentrated to afford the title compound as a colourless oil (1.56 g, 94% pure (w/w), 88%).

Data are consistent with literature values: (*426*) $R_f$ not recorded, decomposes; $^1$H NMR (400 MHz, $CDCl_3$) δ 3.64 (s, 4H, $OCH_2$), 0.12 [s, 18H, $Si(CH_3)_3$]; $^{13}$C NMR (101 MHz, $CDCl_3$) δ 64.0 ($OCH_2$), -0.3 ($SiMe_3$).

**(*S*)-3-Amino-2-methyl-5,6,7,7a-tetrahydro-1*H*-pyrrolizin-1-one hydrochloride (5.91)**

**Caution: 2 eq. of gas is liberated in the course of this reaction; an exit needle was inadequate to prevent a small but noticeable buildup of pressure in the reaction vessel, and containment of the reaction mixture in the (half-full) flask used occurred more by good fortune than by design. We recommend that the reaction be carried out in a vessel no more than 25% full and vented to the atmosphere *via* at least one unobstructed neck.** To ethanol (40 mL) at −10 °C and under $N_2$ was added slowly and

cautiously acetyl chloride (6 mL, 84.1 mmol). Ethanol (6 mL) and cyanoketone **5.77** (13.1 g, 51.9 mmol) were added,[xciii] after which time the mixture was warmed to rt and stirred for 5 h 20 min. The mixture was concentrated. The solid residue was then suspended in toluene, (50 mL) heated at 150 °C for 1 h, then concentrated to afford the *title compound* as a solid with the appearance and scent of brown sugar (9.45 g, 96%).

$R_f$ 0.10 (9 : 1 ethyl acetate : methanol); mp 47 °C; $^1$H NMR (400 MHz, $CD_3OD$) δ 3.83 (dd, $J$ = 9.0, 7.0 Hz, 1H, H-7a), 3.30 (ddt, $J$ = 8.5, 7.5, 3.5 Hz, 1H, H-5), 3.12 (ddd, $J$ = 10.5, 8.5, 7.0 Hz, 1H, H-5), 2.18 – 2.02 (m, 3H, H-6 and H-7), 1.58 (s, 3H, Me), 1.41 – 1.26 (m, 1H, H-7); $^{13}$C NMR (101 MHz, $CD_3OD$) δ 194.3 (C-1), 177.6 (C-3), 93.0 (C-2), 71.1 (C-7a), 47.9 (C-5), 29.0 (C-6), 28.1 (C-7), 5.6 (Me); IR (ATR) ν 3283br, 3140br, 2975m, 1661m, 1607m, 1522s, 1483s, 1446s, 1382s, 1334m, 1306m, 1276m, 1168m, 1110m, 1007m, 971m, 697s, 642br; HRMS (ESI$^+$) found 153.1022, calc. for $C_8H_{13}N_2O$ $[M]^+$ 153.1022.

**6-Methyl-5-(3-methylbutanamido)-2,3-dihydro-1*H*-pyrrolizin-7-yl 3-methyl-butanoate (5.94)**

To 3-aminopyrrolizine hydrochloride **5.91·HCl** (1.00 g, 5.30 mmol) was added sequentially acetonitrile (10 mL), distilled pyridine (1.70 mL, 21.1 mmol) and isovaleryl chloride (0.65 mL, 5.35 mmol). The mixture was stirred for 1 h 35 min, after which time an additional portion of isovaleryl chloride (0.65 mL, 5.35 mmol) was added. The resulting mixture was stirred for 20 h and filtered. The residue was washed with toluene and the combined filtrates concentrated to afford a magenta[xciv] oil (1.74 g, >99%) which

[xciii] Cyanoketone **5.77** should be added portionwise; the ethanol was used to rinse the container.
[xciv] We believe that this observation may be due to the reaction of traces of $CDCl_3$ with pyridine, $H_2O$, and an unidentified base, possibly trace $CaH_2$ (over which the pyridine was stored after distillation), to afford

was used without further purification. This material could be purified by column chromatography (1 : 0 – 0 : 1 pentane : ethyl acetate) to afford the *title compound* as an unstable pale yellow wax (41%, 13 : 7 mixture of rotamers).

$R_f$ 0.50 (1 : 1 pentane : ethyl acetate); mp 57 °C; $^1$H NMR (500 MHz, $CDCl_3$) δ 6.98 [s, 0.35H, NH (minor)], 6.95 [s, 0.65H, NH (major)], 3.75 (2 superimposed t's, $J$ = 7.0 Hz, 2H, Pz-3), 2.79 [t, $J$ = 7.5 Hz, 0.7H, Pz-1 (minor)], 2.73 [t, $J$ = 7.5 Hz, 1.3H, Pz-1 (major)], 2.45 – 2.32 [m, 4H], 2.27 – 2.00 (m, 6H), 1.80 [s, 1.05H, Me (minor)], 1.78 [s, 1.95H, Me (major)], 1.06 – 0.91 [m, 12H, Iv-Me]; $^{13}$C NMR (101 MHz, $CDCl_3$) δ 172.8, 171.6, 126.7, 123.0, 122.3, 114.6, 108.7, 45.8, 45.7, 45.0, 43.3, 43.3, 27.1, 26.5, 26.1, 25.2, 24.7, 24.5, 22.6, 22.5, 8.1; IR (ATR) 3242br (N–H), 1192s, 1166s, 735m; HRMS (ESI$^+$) found 321.2174, calc. for $C_{18}H_{28}O_3N_2$ $[M+H]^+$ 321.2173.

this colour; decomposition of pyridine in presence of various organic halides with concomitant intense coloration of the mixture is known. (*452*) This was the only run in which this colour was observed, although it was also seen in our preparation of compound **4.15** (see page 215).

## Other Compounds

**TBTH-*d***

To sodium borodeuteride (342 mg, 8.16 mmol) under Ar at −10 °C was added dry DME (11.7 mL). A solution of TBTCl (1.00 g, 3.07 mmol) in dry DME (7.3 mL) was added over 10 min. The mixture was stirred for 5 further min and then flash-evaporated. The residue was resuspended in dry ether (10 mL) and filtered under Ar, then left under high vacuum at −10 °C to afford the title compound as a malodourous, colourless oil. (589 mg, contaminated with 12% w/w $[Bu_3Sn_2]O$, 58%).

Data are consistent with literature values: (*427*) $^1$H NMR (500 MHz, $C_6D_6$) δ 1.56 (m, 6H), 1.35 (m, 6H), 0.91 (m, 15H); $^2$H NMR (76.8 MHz, $C_6H_6$) δ 5.11 (s, 1H, Sn-D), 4.82 (s, 0.07H, $D_2$); $^{13}$C NMR (126 MHz, $C_6D_6$) δ 30.3, 27.1, 16.9, 13.5; $^{119}$Sn NMR (187 MHz, $C_6D_6$) δ 90.37 (t, $J$ = 246 Hz).

**2-Methyl-5-[(5-thiomethyl)pentyl]furan**

Side product formed during Kornblum oxidation of compound **2.18**. Yield 988 mg (17%).

$R_f$ 0.75 (89 : 10 : 1 cyclohexane : ether : TEA); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.83 (m, 2H, H-3 and H-4), 2.57 (m, 2H, H-1'), 2.54 – 2.44 (m, 2H, H-5'), 2.27 – 2.22 (s, 3H, Fn-Me), 2.09 (s, 3H, SMe), 1.70 – 1.57 (m, 4H, H-2' and H-4'), 1.50 – 1.38 (m, 2H, H-3'); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 154.5 (C-2 or C-5), 150.3 (C-2 or C-5), 105.9 (C-3 or C-4), 105.4 (C-3 or C-4), 34.3 (C-5'), 29.1 (C-4'), 28.5 (C-3'), 28.1 (C-2'), 28.0 (C-

1'), 15.7 (SMe), 13.6 (Fn-Me); IR (ATR) ν 2922m (C–H), 2858w (C–H), 1617m, 1218m, 1019s, 777s; HRMS (APCI, $CH_4$) found 199.1151, calc for $C_{11}H_{18}O^{32}S$ $[M+H]^+$ 199.1151.

**Di[(1*H*)-imidazol-1-yl]methanethione, TCDI**

To a solution of imidazole (11.8 g, 174 mmol) in chloroform (95 mL) under Ar was added a solution of thiophosgene (5.00 g, 43.5 mmol) in benzene (35 mL) dropwise. The mixture was then stirred for 1 h and the mixture filtered under $N_2$. The residue was washed with benzene (20 mL) and the combined filtrates concentrated. The viscous brown residue was dried under vacuum to afford the title compound as a yellow solid (7.39 g, 95%) which was used without further purification.

Data are consistent with literature values: (*428*) $^1$H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 1.0 Hz, 2H, H-2'), 7.50 (d, *J* = 1.5 Hz, 2H, H-5'), 7.14 (d, *J* = 1.5 Hz, 2H, H-4'); $^{13}$C NMR ($CDCl_3$) δ 172.7 (C-1), 138.3 (C-2'), 132.0 (C-5'), 120.7 (C-4').

# 7 References

*"Imitation is the sincerest form of flattery that mediocrity can pay to greatness."*
Oscar Wilde (1854 – 1900), poet and playwright


1. Russell, J.; Seetula, J.; Timonen, R.; Gutman, D.; Nava, D. *J. Am. Chem. Soc.* **1988,** *110* (10), 3084 – 3091.
2. Russell, J.; Seetula, J.; Gutman, D. *J. Am. Chem. Soc.* **1988,** *110* (10), 3092 – 3099.
3. Viehe, H.; Janousek, Z.; Merényi, R. *Acc. Chem. Res.* **1985,** *18* (5), 148 – 154.
4. Luo, Y. R. *Comprehensive Handbook of Chemical Bond Energies;* CRC Press: Boca Raton, Florida, 2007.
5. Bhandal, H.; Pattenden, G.; Russell, J. *Tetrahedron Lett.* **1986,** *27* (20), 2299 – 2302.
6. Hackmann, C.; Schäfer, H. *Tetrahedron* **1993,** *49* (21), 4559 – 4574.
7. Snider, B. *Chem. Rev.* **1996,** 339.
8. Saldick, J. *J. Polym. Sci.* **1956,** *19,* 73 – 75.
9. Girard, P.; Namy, J.; Kagan, H. *J. Am. Chem. Soc.* **1980,** *102* (8), 2693 – 2698.
10. Kagan, H.; Namy, J.; Girard, P. *Tetrahedron* **1981,** *37* (Supplement 1), 175 – 180.
11. Ananthanarayan, T.; Gallagher, T.; Magnus, P. *J. Chem. Soc. Chem. Commun.* **1982,** No. 12, 709 – 710.
12. Bodenstein, M. *Z. Physik. Chem.* **1913,** *85U* (1), 329 – 397.
13. Nernst, W. *Z. Electrochem.* **1918,** *24* (21 – 22), 335 – 336.
14. Curran, D. *Synthesis* **1988,** No. 6, 417 – 439.
15. Curran, D. *Synthesis* **1988,** No. 7, 489 – 513.
16. Kuivila, H. *Synthesis* **1970,** No. 10, 499 – 509.
17. Hart, D. *Science* **1984,** *223* (4639), 883 – 887.
18. Neumann, W. *Synthesis* **1987,** No. 8, 665 – 683.
19. Ramaiah, M. *Tetrahedron* **1987,** *43* (16), 3541 – 3676.
20. Jasperse, C.; Curran, D.; Fevig, T. *Chem. Rev.* **1991,** *91* (6), 1237 – 1286.
21. McCarroll, A.; Walton, J. *J. Chem. Soc. Perkin Trans 1* **2001,** No. 24, 3215 – 3229.
22. Davies, D.; Parrott, M. *Reactivity and Structure: Concepts in Organic Chemistry;* Springer: New York, 1978; Vol. 7.
23. Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds;* Pergamon Press: Oxford, 1986.
24. Pereyre, M.; Quintard, J.; Rahm, A. *Tin in Organic Synthesis,* 1st ed.; Butterworth–Heinemann: Oxford, 1987.
25. Motherwell, W.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis,* 1st ed.; Elsevier: Amsterdam, 1992.
26. Zard, S. *Radical Reactions in Organic Synthesis;* Oxford University Press: New

York, 2003.
27. Togo, H. *Advanced Free Radical Reactions for Organic Synthesis,* 1st ed.; Elsevier: Oxford, 2004.
28. Gomberg, M. *J. Am. Chem. Soc.* **1900,** *22* (11), 757 – 771.
29. Kharasch, M.; Mayo, F. *J. Am. Chem. Soc.* **1933,** *55* (6), 2468 – 2496.
30. Kharasch, M.; Engelmann, H.; Mayo, F. *J. Org. Chem.* **1937,** *2* (3), 288 – 302.
31. Kharasch, M.; Jensen, E.; Urry, W. *Science* **1945,** *102* (2640), 128.
32. Kharasch, M.; Urry, W.; Jensen, E. *J. Am. Chem. Soc.* **1945,** *67* (9), 1626.
33. Marvel, C.; Dec, J.; Corner, J. *J. Am. Chem. Soc.* **1945,** *67* (10), 1855.
34. Kharasch, M.; Jensen, E.; Urry, W. *J. Am. Chem. Soc.* **1946,** *68* (1), 154 – 155.
35. Kharasch, M.; Jensen, E.; Urry, W. *J. Am. Chem. Soc.* **1947,** *69* (5), 1100 – 1105.
36. M., K.; Skell, P.; Fisher, P. *J. Am. Chem. Soc.* **1948,** *70* (3), 1055 – 1059.
37. Wohl, A. *Ber. Dtsch. Chem. Ges.* **1919,** *52* (1), 51 – 63.
38. Ziegler, K.; Speath, A.; Schaaf, E.; Schamann, W.; Winkelmann, E. *Liebigs Ann.* **1942,** *551* (1), 80 – 119.
39. Ziegler, K.; Schenck, G.; Krockow, E.; Siebert, A.; Wenz, A.; Weber, H. *Liebigs Ann.* **1942,** *551* (1), 1 – 79.
40. Adam, J.; Gosselain, P.; Goldfinger, P. *Nature* **1953,** *171* (4355), 704 – 705.
41. Borisov, A. *Izv. Akad. Kauk SSSR, Ser. Khim.* **1951,** 524 – 529.
42. Nesmeyanov, A.; Borisov, A.; Kovredov, A.; Golubeva, E. *Tetrahedron Lett.* **1960,** *1* (24), 25 – 26.
43. Cristol, S.; Brindell, G.; Reeder, J. *J. Am. Chem. Soc.* **1958,** *80* (3), 635 – 640.
44. Arai, S.; Sato, S.; Shida, S. *J. Chem. Phys.* **1960,** *33* (4), 1277 – 1278.
45. Gordon, A.; Smith, S. *J. Phys. Chem.* **1962,** *66* (3), 521 – 524.
46. Lamb, R.; Ayers, P.; Toney, M. *J. Am. Chem. Soc.* **1963,** *85* (21), 3483 – 3486.
47. Garwood, R.; Scott, C.; Weedon, B. *Chem. Commun. (London)* **1965,** No. 1, 14 – 15.
48. Menapace, L.; Kuivila, H. *J. Am. Chem. Soc.* **1964,** *86* (15), 3047 – 3051.
49. Barton, D.; McCombie, S. *J. Chem Soc., Perkin Trans. 1* **1975,** No. 16, 1574 – 1585.
50. van der Kerk, G.; Noltes, J.; Luijten, J. *J. Appl. Chem.* **1957,** *7* (7), 366 – 369.
51. Kuivila, H.; Menapace, L.; Warner, C. *J. Am. Chem. Soc.* **1962,** *84* (18), 3584 – 3586.
52. Walling, C.; Cooley, J.; Ponaras, A.; Racah, E. *J. Am. Chem. Soc.* **1966,** *88* (22), 5361 – 5363.
53. Crandall, J.; Keyton, D. *Tetrahedron Lett.* **1969,** *10* (21), 1653 – 1656.
54. Cristol, S.; Barbour, R. *J. Am. Chem. Soc.* **1968,** *90* (11), 2832 – 2838.
55. Baldwin, J. *J. Chem. Soc. Chem. Commun.* **1976,** No. 18, 734 – 736.
56. Beckwith, A.; Easton, C.; Serelis, A. *J. Chem. Soc. Chem. Commun.* **1980,** No. 11, 482 – 483.
57. Bakuzis, P.; Campos, O.; Bakuzis, M. *J. Org. Chem.* **1976,** *41* (20), 3261 – 3264.

58. Giese, B.; Meister, J. *Angew. Chem. Int. Ed. Engl.* **1977,** *16* (3), 178 – 179.
59. Burke, S.; Fobare, W.; Armistead, D. *J. Org. Chem.* **1982,** *47* (17), 3348 – 3350.
60. Adlington, R.; Baldwin, J.; Basak, A.; Kozyrod, R. *J. Chem. Soc. Chem. Commun.* **1983,** No. 17, 944 – 945.
61. Giese, B.; González-Gomez, J.; Witzel, T. *Angew. Chem. Int. Ed. Engl.* **1984,** *23* (1), 69 – 70.
62. Hartwig, W. *Tetrahedron* **1983,** *39* (16), 2609 – 2645.
63. Ogilvie, W.; Yoakim, C.; Dô, F.; Haché, B.; Lagacé, L. N. J.; O'Meara, J.; Déziel, R. *Bioorg. Med. Chem.* **1999,** *7* (8), 1521 – 1531.
64. Krafft, G.; Meinke, P. *Tetrahedron Lett.* **1985,** *26* (2), 135 – 138.
65. Yoshimatsu, M.; Watanabe, H.; Koketsu, E. *Org. Lett.* **2010,** *12* (18), 4192 – 4194.
66. Ono, N.; Jun, T.; Kaji, A. *Synthesis* **1987,** No. 9, 821 – 823.
67. Vatele, J. *Tetrahedron Lett.* **1984,** *25* (52), 5997 – 6000.
68. Barton, D.; Crich, D.; Motherwell, W. *Tetrahedron* **1985,** *41* (19), 3901 – 3924.
69. Barton, D.; Dowlatshahi, H.; Motherwell, W.; Villemin, D. *J. Chem. Soc. Chem. commun.* **1980,** No. 15, 732 – 733.
70. Burnett, G.; Melville, H. *Proc. Roy. Soc. A* **1947,** *189* (1019), 456 – 480.
71. Griller, D.; Ingold, K. *Acc. Chem. Res.* **1980,** *13* (7), 193 – 200.
72. Griller, D.; Ingold, K. *Acc. Chem. Res.* **1980,** *13* (9), 317 – 323.
73. Boyer, I. *Toxicology* **1989,** *55* (3), 253 – 298.
74. Milstein, D.; Stille, J. *J. Am. Chem. Soc.* **1979,** *101* (17), 4992 – 4998.
75. Kuivila, H.; Beumel, O. *J. Am. Chem. Soc.* **1958,** *80* (14), 3798.
76. Baguley, P.; Walton, J. *Angew. Chem. Int. Ed.* **1998,** *37* (22), 3072 – 3082.
77. Studer, A.; Amrein, S. *Synthesis* **2002,** No. 7, 835 – 849.
78. le Grognec, E.; Chrétien, J.; Zammattio, F.; Quintard, J. *Chem. Rev.* **2015,** *115* (18), 10207 – 10260.
79. Anastas, P.; Warner, J. *Green Chemistry: Theory and Practice;* Oxford University Press: New York, 1998; p 30.
80. Health and Safety Executive. *Working With Substances Hazardous to Health: A Brief Guide to COSHH,* 5th ed.; HSE Books, 2012.
81. Fujita, K.; Nakamura, T.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2001,** *123* (13), 3137 – 3138.
82. Fujita, K.; Yorimitsu, H.; Oshima, K. *Synlett* **2002,** No. 2, 337 – 339.
83. Hirano, K.; Fujita, K.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2004,** *6* (4), 595 – 595.
84. Smith, D.; Pulling, M.; Norton, J. *J. Am. Chem. Soc.* **2007,** *129* (4), 770 – 771.
85. Fujiwara, Y.; Dixon, J.; O'Hara, F.; Funder, E.; Dixon, D.; Rodriguez, R.; BAxter, R.; Herlé, B.; Sach, N.; Collins, M.; Ishihara, Y.; Baran, P. *Nature* **2012,** *492* (7427), 95 – 99.
86. Kawamoto, T.; Ryu, I. *Org. Biomol. Chem.* **2014,** *12* (48), 9733 – 9742.

87. Chung, S.; Chung, F. *Tetrahedron Lett.* **1979,** *20* (27), 2473 – 2476.
88. Ueng, S.; Makhlouf Brahmi, M.; Derat, É.; Fensterbank, L.; Lacôte, E.; Malacria, M.; Curran, D. *J. Am. Chem. Soc.* **2008,** *130* (31), 10082 – 10083.
89. Ueng, S.; Solovyev, A.; Yuan, X.; Geib, S.; Fensterbank, L.; Lacôte, E.; Malacria, M.; Newcomb, M.; Walton, J.; Curran, D. *J. Am. Chem. Soc.* **2009,** *131* (31), 11256 – 11262 and references therein.
90. Walton, J. *Angew. Chem. Int. Ed.* **2009,** *48* (10), 1726 – 1728.
91. Barton, D.; Jacob, M. *Tetrahedron Lett.* **1998,** *39* (11), 1331 – 1334.
92. Curran, D.; Solovyev, A.; Makhlouf Brahmi, M.; Fensterbank, L.; Malacria, M.; Lacôte, E. *Angew. Chem. Int. Ed.* **2011,** *50* (44), 10294 – 10317.
93. Mikami, S.; Fujita, K.; Nakamura, T.; Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. *Org. Lett.* **2001,** *3* (12), 1853 – 1855.
94. Takami, K.; Mikami, S.; Yorimiotsu, H.; Shinokubo, H.; Oshima, K. *Tetrahedron* **2003,** *59* (34), 6627 – 6635.
95. Miyai, T.; Inoue, K.; Yasuda, M.; Shibata, I.; Baba, A. *Tetrahedron Lett.* **1998,** *39* (14), 1929 – 1932.
96. Inoue, K.; Sawada, A.; Shibata, I.; Baba, A. *J. Am. Chem. Soc.* **2002,** *124* (6), 906 – 907.
97. Quiclet-Sire, B.; Zard, S. *J. Am. Chem. Soc.* **1996,** *118* (38), 9190 – 9191.
98. Boivin, J.; Quiclet-Sire, R. L.; Zard, S. *Chem. Commun.* **1997,** No. 4, 353 – 354.
99. Binmore, G.; Walton, J.; Cardellini, L. *J. Chem. Soc., Chem. Commun.* **1995,** No. 1, 27 – 28.
100. Studer, A.; Amrein, S. *Angew. Chem. Int. Ed.* **2000,** *39* (17), 3080 – 3082.
101. Chatgilialoglu, C. *Acc. Chem. Res.* **1992,** *25* (4), 188 – 194.
102. Chatgilialoglu, C.; Dickhaut, J.; Giese, B. *J. Org. Chem.* **1991,** *56* (22), 6399 – 6403.
103. Lusztyk, J.; Maillard, B.; Lindsay, D.; Ingold, K. *J. Am. Chem. Soc.* **1983,** *105* (11), 3578 – 3580.
104. Bowman, R.; Krintel, S.; Schilling, M. *Org. Biomol. Chem.* **2004,** *2* (4), 585 – 592.
105. Mochida, K.; Sugimoto, H.; Yokoyama, Y. *Polyhedron* **1997,** *16* (10), 1767 – 1770.
106. Sakurai, H.; Mochida, K. *J. Chem. Soc., Chem. Commun.* **1971,** No. 24, 1581.
107. Beckwith, A.; Pigou, P. *J. Chem. Soc., Chem. Commun.* **1986,** No. 1, 85 – 86.
108. Beckwith, A.; Roberts, D. *J. Am. Chem. Soc.* **1986,** *108* (19), 5893 – 5901.
109. Pike, P.; Hershberger, S.; Hershberger, J. *Tetrahedron Lett.* **1985,** *26* (51), 6289 – 6290.
110. Pike, P.; Hershberger, S.; Hershberger, J. *Tetrahedron* **1988,** *44* (20), 6295 – 6304.
111. Nakamura, T.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Synlett* **1999,** No. 9, 1415 – 1416.
112. Nakamura, T.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2001,** *74* (4), 747 – 752.

113. Gupta, V.; Kahne, D. *Tetrahedron Lett.* **1993,** *34* (4), 591 – 594.
114. Chatgilialoglu, C.; Ballestri, M. *Organometallics* **1995,** *14* (11), 5017 – 5018.
115. Curran, D.; Palovich, M. *Synlett* **1992,** 631 – 632.
116. Curran, D.; Diederichsen, U.; Palovich, M. *J. Am. Chem. Soc.* **1997,** *119* (21), 4797 – 4804.
117. Kiyooka, S.; Kaneko, Y.; Matsue, H.; Hamada, M.; Fujiyama, R. *J. Org. Chem.* **1990,** *55* (21), 5562 – 5564.
118. Curran, D.; Liu, H. *J. Org. Chem.* **1991,** *56* (11), 3463 – 3465.
119. Tsai, Y.; Cherng, C. *Tetrahedron Lett.* **1991,** *32* (29), 3515 – 3518.
120. Tanaka, S.; Nakamura, T.; Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. *Synlett* **2001,** No. 8, 1278 – 1280.
121. Mochida, K.; Sugimoto, H.; Yokoyama. *Polyhedron* **1997,** *16* (10), 1767 – 1770.
122. Bowman, W.; Krintel, S.; Schilling, M. *Synlett* **2004,** No. 7, 1215 – 1218.
123. Bentrude, W. *Acc. Chem. Res.* **1982,** *15* (4), 117 – 125.
124. Leca, D.; Fensterbank, L.; Lacôte, E.; Malacria, M. *Chem. Soc. Rev.* **2005,** *34* (10), 858 – 865.
125. Barton, D.; Jang, D.; Jaszberenyi, J. *Tetrahedron Lett.* **1992,** *33* (17), 2311 – 2314.
126. Barton, D.; Jang, J.; Jaszberenyi, J. *J. Org. Chem.* **1993,** *58* (24), 6838 – 6842.
127. Barton, D.; Jang, D.; Jaszberenyi, J. *Tetrahedron Lett.* **1992,** *33* (39), 5709 – 5712.
128. Jang, D. *Tetrahedron Lett.* **1996,** *37* (30), 5367 – 5368.
129. Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Chem. Lett.* **2000,** *29* (2), 104 – 105.
130. Yorimitsu, H.; Shinokubo, H.; Oxhima, K. *Bull. Chem. Soc. Jpn.* **2001,** *74* (2), 225 – 235.
131. Jang, D.; Cho, D.; Barton, D. *Synlett* **1998,** No. 1, 39 – 40.
132. Jang, D.; Cho, D.; Kim, J. *Synth. Commun.* **1998,** *28* (19), 3559 – 3565.
133. Sato, T.; Koga, H.; Tsuzuki, K. *Heterocycles* **1996,** *42* (2), 499 – 502.
134. Graham, A.; Thomas, A.; Yang, R. *J. Org. Chem.* **2000,** *65* (8), 2583 – 2585.
135. Jang, D.; Song, S. *Tetrahedron Lett.* **2000,** *41* (2), 247 – 249.
136. Graham, S.; Murphy, J.; Coates, D. *Tetrahedron Lett.* **1999,** *40* (12), 2415 – 2416.
137. McCague, R.; Pritchard, R.; Stoodley, R.; Williamson, D. *Chem. Commun.* **1998,** *34* (24), 2691 – 2692.
138. Graham, S.; Murphy, J.; Kennedy, A. *J. Chem., Soc. Perkin Trans. 1* **1999,** 3071 – 3073.
139. Ichihara, A.; Nonaka, M.; Sakamura, S.; Sato, R.; Tajimi, A. *Chem. Lett.* **1988,** *17* (1), 27 – 30.
140. Heintz, M.; Leny, G.; Nedelec, J. *Tetrahedron Lett.* **1984,** *25* (50), 5767 – 5768.
141. Barks, J.; Gilbert, B.; Parsons, A.; Upeanadran, B. *Synlett* **2001,** No. 11, 1719 – 1722.
142. Barks, J.; Gilbert, B.; Parsons, A.; Upeandran, B. *Tetrahedron Lett.* **2001,** *42* (17), 3137 – 3140.
143. Jang, D.; Cho, D.; Chung, C. *Synlett* **2001,** No. 12, 1923 – 1924.

144. Gonzalez Martin, C.; Murphy, J.; Smith, C. *Tetrahedron Lett.* **2000,** *41* (11), 1833 – 1836.
145. Crich, D.; Ritchie, T. *J. Chem. Soc., Chem. Commun.* **1988,** No. 22, 1461 – 1463.
146. Ballestri, M.; Chatgilialoglu, C.; Seconi, G. *J. Organomet. Chem.* **1991,** *408* (1), C1 – C4.
147. Daroszewski, J.; Lusztyk, J.; Degueil, M.; Navarro, C.; Maillard, B. *J. Chem. Soc., Chem. Commun.* **1991,** No. 8, 586 – 587.
148. Roberts, B. *Chem. Soc. Rev.* **1999,** *28* (1), 25 – 35.
149. Cole, S.; Kirwan, J.; Roberts, B.; Willis, C. *J. Chem. Soc., Perkin Trans. 1* **1991,** No. 1, 103 – 112.
150. Dang, H.; Roberts, B. *Tetrahedron Lett.* **1995,** *36* (16), 2875 – 2878.
151. Haque, M.; Roberts, B. *Tetrahedron Lett.* **1996,** *37* (50), 9123 – 9126.
152. Dang, H.; Roberts, B. *J. Chem. Soc., Perkin Trans. 1* **1998,** No. 1, 67 – 76.
153. Dang, H.; Elsegood, M.; Kim, K.; Roberts, B. *J. Chem. Soc., Perkin Trans. 1* **1999,** No. 15, 2061 – 2068.
154. Dang, H.; Roberts, B. *Tetrahedron Lett.* **1999,** *40* (50), 8929 – 8933.
155. Crich, D.; Sun, S. *J. Org. Chem.* **1996,** *61* (20), 7200 – 7201.
156. Nitsche, S.; Wick, M. *Angew. Chem.* **1957,** *69* (3), 96.
157. Kuivila, H.; Sawyer, A.; Armour, A. *J. Org. Chem.* **1960,** *26* (5), 1426 – 1429.
158. Hayashi, K.; Iyoda, J.; Shiihara, I. *J. Organometal. Chem.* **1967,** *10* (1), 81 – 94.
159. Itoi, K.; Kumano, S. *Kogyo Kagaku Zasshi* **1967,** *70* (1), 82 – 86.
160. Grady, G.; Kuivila, H. *J. Org. Chem.* **1967,** *34* (6), 2014 – 2016.
161. Kuivila, H.; Menapace, L. *J. Org. Chem.* **1963,** *28* (9), 2165 – 2167.
162. Sanders, A.; Giering, W. *J. Org. Chem.* **1973,** *38* (17), 3055.
163. Corey, E.; Suggs, J. *J. Org. Chem.* **1975,** *40* (17), 2554 – 2555.
164. Ueno, Y.; Chino, K.; Watanabe, M.; Moriya, O.; Okawara, M. *J. Am. Chem. Soc.* **1982,** *104* (20), 5564 – 5566.
165. Bergbeiter, D.; Blanton, J. *J. Org. Chem.* **1987,** *52* (3), 472 – 473.
166. Gerigk, U.; Gerlach, M.; Neumann, W.; Vieler, R.; Weintritt, V. *Synthesis* **1990,** No. 6, 448 – 452.
167. Rai, R.; Collum, D. *Tetrahedron Lett.* **1994,** *35* (34), 6221 – 6224.
168. Attrill, R.; Blower, M.; Mulholland, K.; Roberts, J.; Richardson, J.; Teasdale, M.; Wanders, A. *Org. Process Res. Dev.* **2000,** *4* (2), 98 – 101.
169. Stork, G.; Sher, P. *J. Am. Chem. Soc.* **1986,** *108* (2), 303 – 304.
170. Curran, D.; Hadida, S. *J. Am. Chem. Soc.* **1996,** *118* (10), 2531 – 2532.
171. Vedejs, E.; Duncan, S.; Haight, A. *J. Org. Chem.* **1993,** *58* (11), 3046 – 3050.
172. Hays, D.; Fu, G. *J. Org. Chem.* **1996,** *61* (1), 4 – 5.
173. Hays, D.; Scholl, M.; Fu, G. *J. Org. Chem.* **1996,** *61* (19), 6751 – 6752.
174. Hays, D.; Fu, G. *J. Org. Chem.* **1998,** *63* (9), 2796 – 2797.
175. Tormo, J.; Hays, D.; Fu, G. *J. Org. Chem.* **1998,** *63* (16), 5296 – 5297.
176. Hays, D.; Fu, G. *Tetrahedron* **1999,** *55* (29), 8815 – 8832.

177. Lipowitz, J.; Bowman, S. *J. Org. Chem.* **1973,** *38* (1), 161 – 165.
178. Lopez, R.; Hays, D.; Fu, G. *J. Am. Chem. Soc.* **1997,** *119* (29), 6949 – 6950.
179. Lopez, R.; Fu, G. *Tetrahedron* **1997,** *53* (48), 16349 – 16354.
180. Maleczka, R.; Terstiege, I. *J. Org. Chem.* **1998,** *63* (26), 9622 – 9623.
181. Maleczka, R.; Gallagher, W.; Terstiege, I. *J. Am. Chem. Soc.* **2000,** *122* (2), 384 – 385.
182. Terstiege, I.; Maleczka, R. *J. Org. Chem.* **1999,** *64* (2), 342 – 343.
183. Gastaldi, S.; Stein, D. *Tetrahedron Lett.* **2002,** *43* (24), 4309 – 4311.
184. Stein, D.; Gastaldi, S. *J. Org. Chem.* **2004,** *69* (13), 4464 – 4470.
185. Mariussen, E. *Arch. Toxicol.* **2012,** *86* (9), 1349 – 1367.
186. Bravo, I.; Aranda, A.; Hurley, M.; Marston, G.; D., N.; Shine, K.; Smith, K.; Wallington, T. *J. Geophys. Res.* **2010,** *115* (D24), D24317.
187. Trowbridge, L. *Potential Hazards Relating to Pyrolysis of c-C4F8O, n-C4F10 and c-C4F8 in Selected Gaseous Diffusion Plant Operations;* Oak Ridge National Laboratory: Oak Ridge, 2000.
188. Light, J.; Breslow, R. *Org. Synth.* **1995,** *72,* 199 – 208.
189. Light, J.; Breslow, R. *Tetrahedron Lett.* **1990,** *31* (21), 2957 – 2958.
190. Ferkous, F.; Messadi, D.; De Jeso, B.; Degueil-Castaing, M.; Maillard, B. *J. Organomet. Chem.* **1991,** *420* (3), 315 – 320.
191. Suga, S.; Manabe, T.; Yoshida, J. *Chem. Commun.* **1999,** No. 13, 1237 – 1238.
192. Clive, D.; Yang, W. *J. Org. Chem.* **1995,** *60* (8), 2607 – 2609.
193. Poupon, J.; Marcoux, D.; Cloarec, J.; Charette, A. *Org. Lett.* **2007,** *9* (18), 3591 – 3594.
194. Pham, P.; Legoupy, S. *Tetrahedron Lett.* **2009,** *50* (27), 3780 – 3782.
195. Clive, D.; Wang, J. *J. Org. Chem.* **2002,** *67* (4), 1192 – 1198.
196. Routledge, A.; Abell, C.; Balasubramanian, S. *Synlett* **1997,** No. 1, 61 – 62.
197. Berteina, S.; De Mesmaeker, A. *Synlett* **1998,** No. 11, 1227 – 1230.
198. Sibi, M.; Chandramouli, S. *Tetrahedron Lett.* **1997,** *38* (52), 8929 – 8932.
199. Mirizzi, D.; Pulici, M. *Molecules* **2011,** *16* (4), 3252 – 3314.
200. Weinshenker, N.; Crosby, G.; Wong, J. *J. Org. Chem.* **1975,** *40* (13), 1966 – 1971.
201. Schumann, H.; Pachaly, B. *Angew. Chem. Int. Ed.* **1981,** *20* (12), 1043 – 1044.
202. Fu, Q.; Steele, A.; Tsang, S. *Green Chem.* **2001,** *3,* 71 – 73.
203. Chemin, A.; Deleuze, H.; Maillard, B. *J. Chem. Soc. Perkin Trans. 1* **1999,** No. 2, 137 – 142.
204. Miller, B.; Hershberger, J. *J. Polym. Sci. Pol. Let.* **1987,** *25* (5), 219 – 221.
205. Harendza, M.; Leßmann, K.; Neumann, W. *Synlett* **1993,** No. 4, 283 – 285.
206. Ruel, G.; Ngo, K.; Dumartin, G.; Delmond, B.; Pereyre, M. *J. Organometal. Chem.* **1993,** *444* (1 – 2), C18 – C20.
207. Dumartin, G.; Ruel, G.; Kharboutli, J.; Delmond, B.; Connil, M.; Jousseaume, B.; Pereyre, M. *Synlett* **1994,** No. 11, 952 – 954.
208. Enholm, E.; Schulte, J. *Org. Lett.* **1999,** *1* (8), 1275 – 1277.

209. Bergbreiter, D.; Walker, S. *J. Org. Chem.* **1989,** *54* (21), 5138 – 5141.
210. Blanton, J.; Salley, J. *J. Org. Chem.* **1991,** *56* (2), 490 – 491.
211. Chemin, A.; Deleuze, H.; Maillard, B. *Eur. Polym. J.* **1998,** *34* (10), 1395 – 1404.
212. Chemin, A.; Deleuze, H.; Maillard, B. *J. Appl. Polym. Sci.* **2001,** *79* (7), 1297 – 1308.
213. Chemin, A.; Mercier, A.; Deleuze, H.; Maillard, B.; Mondain-Monval, O. *J. Chem. Soc. Perkin Trans. 1* **2001,** No. 4, 366 – 370.
214. Mercier, A.; Deleuze, H.; Maillard, B.; Mondain-Monval, O. *Adv. Synth. Catal.* **2002,** *344* (1), 33 – 36.
215. Lapôtre, D.; Deleuze, H.; Maillard, B.; Mulholland, K. *Synth. Commun.* **2001,** *31* (21), 3207 – 3218.
216. Ruel, G.; Dumartin, G.; Delmond, B.; Lalère, B.; Donard, O.; Pereyre, M. *Appl. Organomet. Chem.* **1995,** *9* (7), 591 – 595.
217. Renaud, P.; Lacôte, E.; Quaranta, L. *Tetrahedron Lett.* **1998,** *39* (15), 2123 – 2126.
218. Berge, J.; Roberts, S. *Synthesis* **1979,** No. 6, 471 – 472.
219. Leibner, J.; Jacobus, J. *J. Org. Chem.* **1979,** *44* (3), 449 – 450.
220. Milstein, D.; Stille, J. *J. Am. Chem. Soc.* **1978,** *100* (11), 3636 – 3638.
221. Edelson, B.; Stoltz, B.; Corey, E. *Tetrahedron Lett.* **1999,** *40* (37), 6729 – 6730.
222. Scott, W.; Stille, J. *J. Am. Chem. Soc.* **1986,** *108* (11), 3033 – 3040.
223. Lapitskaya, M.; Vasiljeva, L.; Pivnitsky, K. *Mendeleev Commun.* **2013,** *23* (5), 257 – 259.
224. Salomon, C.; Danelon, G.; Mascaretti, O. *J. Org. Chem.* **2000,** 9220.
225. Curran, D.; Chang, C. *J. Org. Chem.* **1989,** *54* (13), 3140 – 3157.
226. Farina, V. *J. Org. Chem.* **1991,** *56* (16), 4985 – 4987.
227. Salomon, C.; Mata, E.; Mascaretti, O. *J. Org. Chem.* **1994,** *59* (24), 7259 – 7266.
228. Harrowven, D.; Guy, I. *Chem. Commun.* **2004,** No. 17, 1968 – 1969.
229. Harrowven, D.; Curran, D.; Kostiuk, S. . W.-G. I.; Whiting, S.; Stenning, K.; Tang, B.; Packard, E.; Nanson, L. *Chem. Commun.* **2010,** No. 46, 6335 – 6337.
230. Nishida, T.; Matsuda, D.; Kasuga, I.; Orita, A.; Otera, J. *Chem. Lett.* **2016,** *45* (11), 1280 – 1282.
231. Sala, A. *Septem Planetarum terrestrium Spagirica recencio;* Wilhelm Jansson: Amsterdam, 1614.
232. Wedgewood, T.; Davy, H. *Journal of the Royal Intitution of Great Britain* **1802,** *1* (2), 170 –1 174.
233. Herschel, J. *Philos. Trans. Royal Soc.* **1842,** *132,* 181 – 214.
234. Eibner, A. *Chem-Ztg.* **1911,** *35,* 753 – 755.
235. Michelin, C.; Hoffmann, N. *ACS Catal.* **2018,** *8* (12), 12046 – 12055.
236. Hedstrand, D.; Kruizinga, W.; Kellogg, R. *Tetrahedron Lett.* **1978,** *19* (14), 1255 – 1258.
237. Cano-Yelo, H.; Deronzier, A. *J. Chem. Soc. Perkin Trans. 2* **1984,** No. 6, 1093 –

1098.
238. Cano-Yelo, H.; Deronzier, A. *Tetrahedron Lett.* **1984,** *25* (48), 5517 – 5520.
239. Zen, J.; Liou, S.; Kumar, A.; Hsia, M. *Angew. Chem. Int. Ed.* **2003,** *42* (5), 577 – 579.
240. Ischay, M.; Anzovino, M.; Du, J.; Yoon, T. *J. Am. Chem. Soc.* **2008,** *130* (39), 12886 – 12887.
241. Romero, N.; Nicewicz, D. *Chem. Rev.* **2016,** *116* (17), 10075 – 10166.
242. Johnston, C.; Smith, R.; Allmendinger, S.; MacMillan, D. *Nature* **2016,** *536* (7616), 322 – 325.
243. Ramirez, N.; Gonzalez-Gomez, J. *Eur. J. Org. Chem.* **2017,** No. 15, 2154 – 2163.
244. Roslin, S.; Odell, L. *Eur. J. Org. Chem.* **2017,** No. 15, 1993 – 2007.
245. Qiao, Y.; Schelter, E. *Acc. Chem. Res.* **2018,** *51* (11), 2926 – 2936.
246. Capaldo, L.; Merli, D.; Fagnoni, M.; Ravelli, D. *ACS Catal.* **2019,** *9* (4), 3054 – 3058.
247. Arias-Rotondo, D.; McCusker, J. *Chem. Soc. Rev.* **2016,** *45* (21), 5803 – 5820.
248. Nicewicz, D.; MacMillan, D. *Science* **2008,** *322* (5898), 77 – 80.
249. Narayanam, J.; Tucker, J.; Stephenson, C. *J. Am. Chem. Soc.* **2009,** *131* (25), 8756 – 8757.
250. Discekici, E.; Treat, N.; Poelma, S.; Mattson, K.; Hudson, Z.; Luo, Y.; Hawker, C.; Read de Alaniz, J. *Chem. Commun.* **2015,** *51* (58), 11705 – 11708.
251. Cismesia, M.; Yoon, T. *Chem. Sci.* **2015,** *6* (10), 5426 – 5434.
252. Zhang, G.; Song, I.; Ahn, K.; Park, T.; Choi, W. *Macromolecules* **2011,** *44* (19), 7594 – 7599.
253. Dietlin, C.; Schweizer, S.; Xiao, P.; Zhang, J.; Morlet-Savary, F.; Graff, B.; Fouassier, J.; Lalevée, J. *Polym. Chem.* **2015,** *6* (21), 3895 – 3912.
254. Corrigan, N.; Shanmugam, S.; Xu, J.; Boyer, C. *Chem. Soc. Rev.* **2016,** *45* (22), 6165 – 6212.
255. Chen, M.; Zhong, M.; Johnson, J. *Chem. Rev.* **2016,** *116* (17), 10167 – 10211.
256. Bonardi, A.; Dumur, F.; Noirbent, G.; Lalevée, J.; Gigmes, D. *Beilstein J. Org. Chem.* **2018,** No. 14, 3025 – 3046.
257. Tyson, E.; Ament, M.; Yoon, T. *J. Org. Chem.* **2013,** *78* (5), 2046 – 2050.
258. Cutherbertson, J.; MacMillan, D. *Nature* **2015,** *519* (7541), 74 – 77.
259. Pandey, G.; Laha, R. *Angew. Chem. Int. Ed.* **2015,** *54* (49), 14875 – 14879.
260. Pandey, G.; Laha, R.; Singh, D. *J. Org. Chem.* **2016,** *81* (16), 7161 – 7171.
261. Im, H.; Kang, D.; Choi, S.; Shin, S.; Hong, S. *Org. Lett.* **2018,** *20* (23), 7437 – 7441.
262. Wang, X.; Xia, D.; Qin, W.; Zhou, R.; Zhou, X.; Zhou, Q.; Liu, W.; Dai, X.; Wang, H.; Wang, S.; Tan, L.; Zhang, D.; Song, H.; Liu, X.; Qin, Y. *Chem* **2017,** *2* (6), 803 – 816.
263. Badovskaya, L.; Povarova, L. *Chemistry of Heterocyclic Compounds* **2009,** *45* (9), 1023 – 1034.
264. Newcomb, M.; Glenn, A.; Manek, M. *J. Org. Chem.* **1989,** *54* (19), 4603 – 4606.

265. Ha, C.; Horner, J.; Newcomb, M.; Varick, T. *J. Org. Chem.* **1993,** *58* (5), 1194 – 1198.
266. Musa, O.; Horner, J.; Shahin, H.; Newcomb, M. *J. Am. Chem. Soc.* **1996,** *118* (16), 3862 – 3868.
267. Blanchette, M.; Choy, W.; Davis, J.; Essenfeld, A.; Masamune, S.; Roush, W.; Sakai, T. *Tetrahedron Lett.* **1984,** *25* (21), 2183 – 2186.
268. Tone, H.; Nishi, T.; Oikawa, Y.; Hikota, M.; Yonemitsu, O. *Tetrahedron Lett.* **1987,** *28* (39), 4569 – 4572.
269. Schultz, D.; Sawicki, J.; Yoon, T. *Beilstein J. Org. Chem* **2015,** *11,* 61 – 65.
270. Coe, B.; Peers, M.; Scrutton, N. *Polyhedron* **2015,** *96,* 57 – 65.
271. Lever, A.; Lewis, J.; Nyholm, R. *J. Chem. Soc.* **1964,** No. 0, 1187 – 1189.
272. Haginiwa, J.; Higuchi, Y.; Hirawata, Y.; Hoshino, N.; Sakakura, H. *Yakugaku Zasshi* **1979,** *99* (12), 1176 – 1180.
273. Fort, Y.; Becker, S.; Caubere, P. *Tetrahedron* **1994,** *50* (41), 11893 – 11902.
274. Boully, L.; Darabantu, M.; Turck, A.; Plé, N. *J. Heterocycl. Chem.* **2005,** *42* (7), 1423 – 1428.
275. Lin, S.; Ischay, M.; Fry, C.; Yoon, T. *J. Am. Chem. Soc.* **2011,** *133* (48), 19350 – 19353.
276. Dhital, R.; Kamonsatikul, C.; Somsook, E.; Sakurai, H. *Catal. Sci. Technol.* **2013,** *3* (11), 3030 – 3035.
277. Bronner, C.; Wenger, O. *Phys. Chem. Chem. Phys.* **2014,** *16* (8), 3617 – 3622.
278. Williams, P.; LeGoff, E. *Tetrahedron Lett.* **1985,** *26* (11), 1367 – 1370.
279. Qvortrup, K.; Rankic, D.; MacMillan, D. *J. Am. Chem. Soc.* **2014,** *136* (2), 626 – 629.
280. Hager, D.; MacMillan, D. *J. Am. Chem. Soc.* **2014,** *136* (49), 16896 – 16989.
281. Robertson, J.; Naud, S. *Org. Lett.* **2008,** *10* (23), 5445 – 5448.
282. Murphy, J.; Bastida, D.; Paria, S.; Fagnoni, M.; Melchiorre, P. *Nature* **2016,** *532,* 218 – 222.
283. Tanielian, C.; Duffy, K.; Jones, A. *J. Phys. Chem. B* **1997,** *101* (21), 4276 – 4282.
284. Tanielian, C. *Coord. Chem. Rev.* **1998,** *178 – 180,* 1165 – 1181.
285. Texier, I.; Delaire, J.; Giannotti, C. *Phys. Chem. Chem. Phys.* **2000,** *2* (6), 1205 – 1212.
286. Tanielian, C.; Seghrouchni, R.; Schweitzer, C. *J. Phys. Chem. A* **2003,** *107* (8), 1102 – 1111.
287. Fuchs, J.; Hartl, H.; Schiller, W. *Angew. Chem.* **1973,** *85* (9), 417.
288. Yamase, T.; Takabayashi, N.; Kaji, M. *J. Chem. Soc. Dalton Trans.* **1984,** No. 5, 793 – 799.
289. Martínez, J.; Rivera-Avalos, E.; Vega-Rodríguez, S.; de Loera, D. *Res. Chem. Intermed.* **2018,** *44* (3), 2061 – 2073.
290. Ravelli, D.; Dondi, D.; Fagnoni, M.; Albini, A.; Bagno, A. *Phys. Chem. Chem. Phys.* **2013,** *15* (8), 2890 – 2896.
291. Dondi, D.; Fagnoni, M.; Albini, A. *Chem. Eur. J.* **2006,** *12* (15), 4153 – 4163.

292. Jorgenson, M. *Chem. Commun. (London)* **1965,** *1* (7), 137 – 138.
293. Qrareya, H.; Ravelli, D.; Fagnoni, M.; Albini, A. *Adv. Synth. Catal.* **2013,** *355* (14 – 15), 2891 – 2899.
294. le Bigot, Y.; Delmas, M.; Gaset, A. *Tetrahedron* **1986,** *42* (1), 339 – 350.
295. Saitman, A. Ph. D. Dissertation. University of California: San Diego, 2013; pp 171 – 172.
296. Mikhaylov, A.; Dilman, A.; Novikov, R.; Koroshutina, Y.; Struchkova, M.; Arkhipov, D.; Nelyubina, Y.; Tabolin, A.; Ioffe, S. *Tetrahedron Lett.* **2016,** *57* (1), 11 – 14.
297. Duval, O.; Gomes, L. *Tetrahedron* **1989,** *45* (14), 4471 – 4476.
298. Dyson, P.; Jessop, P. *Catal. Sci. Technol.* **2016,** *6* (10), 3302 – 3316.
299. Birnbaum, E.; Javora, P. *J. Organometal. Chem.* **1967,** *9* (2), 379 – 382.
300. Studer, A. *Angew. Chem. Int. Ed.* **2000,** *39* (6), 1108 – 1111.
301. Henry-Riyad, H.; Tidwell, T. *Can. J. Chem.* **2003,** *81* (6), 697 – 704.
302. Iesce, R.; Cermola, F.; Temussi, F. *Curr. Org. Chem.* **2005,** *9* (2), 109 – 139.
303. Adams, R.; Gold, M. *J. Am. Chem. Soc.* **1940,** *62,* 56 – 61.
304. Baciocchi, E.; Muraglia, E.; Cleiter, G. *J. Org. Chem.* **1992,** *57* (25), 6817 – 6820.
305. Loiseau, F.; Simone, J.; Carcache, D.; Bobal, P.; Neier, R. *Monats. Chem.* **2007,** *138* (2), 121 – 129.
306. Tofi, M.; Koltsida, K.; Vassilikogiannakis, G. *Org. Lett.* **2009,** *11* (2), 313 – 316.
307. Hayes, S.; Knight, D.; Smith, A.; O'Halloran, M. *Tetrahedron Lett.* **2010,** *51* (4), 720– 723.
308. Vassilikogiannakis, G.; Alexopoulou, I.; Tofi, M.; Montagnon, T. *Chem. Commun.* **2011,** *47* (1), 259 – 261.
309. Noutsias, D.; Alexopoulou, I.; Montagnon, T.; Vassilikogiannakis, G. *Green Chem.* **2012,** *14* (3), 601 – 604.
310. Montagnon, T.; Noutsias, D.; Alexopoulou, I.; Tofi, M.; Vassilikogiannakis, G. *Org. Biomol. Chem.* **2011,** *9* (7), 2031 – 2039.
311. Bourdelande, J.; Font, J.; Marques, G.; Abdel-Shafi, A.; Wilkinson, F.; Worrall, D. *J. Photochem. Photobiol. A* **2001,** *138* (1), 65 – 68.
312. Hurtley, A.; Lu, Z.; Yoon, T. *Angew. Chem. Int. Ed.* **2014,** *53* (34), 8991 – 8994.
313. Brachet, E.; Ghosh, T.; Ghosh, I.; König, B. *Chem. Sci.* **2015,** *6* (2), 987 – 992.
314. Scholz, S.; Farney, E.; Kim, S.; Bates, D.; Yoon, T. *Angew. Chem. Int. Ed.* **2016,** *55* (6), 2239 – 2242.
315. Lu, Z.; Yoon, T. *Angew. Chem. Int. Ed.* **2012,** *51* (41), 10329 – 10332.
316. Plutschack, M.; Seeberger, P.; Gilmore, K. *Org. Lett.* **2017,** *19* (1), 30 – 33.
317. Sayama, S.; Inamura, Y. *Heterocycles* **1996,** *43* (7), 1371 – 1374.
318. Amer, F.; Hammounda, M.; El-Ahl, A.; Abdel-Wahab, B. *J. Heterocycl. Chem.* **2008,** *45* (6), 1549 – 1569.
319. Xing, L.; Dong, W.; Lu, J.; Scoltz, U.; Yan, J.; Yang, J. Novel Process for the Manufacture of 3-Oxo-tetrahydrofuran. US9399629, March 12, 2013.

320. Bruson, H.; Grant, F.; Bobko, E. *J. Am. Chem Soc.* **1958,** *80,* 3633 – 3636.
321. Marshall, E.; Kuck, J.; Elderfield, R. *J. Org. Chem.* **1942,** *7* (5), 444 – 456.
322. Wang, J.; Hou, Y.; Wu, P. *J. Chem. Soc. Perkin Trans. 1* **1999,** No. 16, 2277 – 2280.
323. Chen, Q.; Yuang, C. *Synthesis* **2008,** No. 7, 1085 – 1093.
324. Mo, F.; Li, F.; Wang, J. *Sci. Bull.* **2010,** *55* (25), 2847 – 2854.
325. Ye, L.; Cui, L.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2010,** *132* (10), 3258 – 3259.
326. Fu, J.; Shang, H.; Wang, Z.; Chang, L.; Shao, W.; Yang, Z.; Tang, Y. *Angew. Chem. Int. Ed.* **2013,** *52* (15), 4198 – 4202.
327. Cai, J.; Wang, X.; Qian, Y.; Qiu, L.; Hu, W.; Xu, X. *Org. Lett.* **2019,** *21* (2), 369 – 372.
328. Montagnon, T.; Tofi, M.; Vassilikogiannakis, G. *Acc. Chem. Res.* **2008,** *41* (8), 1001 – 1011.
329. Caplin, G.; Ollis, W.; Sutherland, I. *J. Chem. Soc. C* **1968,** No. 0, 2302 – 2310.
330. Kazancioglu, M.; Kazancioglu, E.; Secen, H.; Altundas, R. *Tetrahedron Lett.* **2015,** *56* (50), 6994 – 6997.
331. Etchells, L.; Helliwell, M.; Kershaw, N.; Sardarian, A.; Whitehead, R. *Tetrahedron* **2006,** *62* (47), 10914 – 10927.
332. Lykakis, I.; Zaravinos, I.; Raptis, C.; Stratakis, M. *J. Org. Chem.* **2009,** *74* (16), 6339 – 6342.
333. Saitman, A.; Rulliere, P.; Sullivan, S.; Theodorakis, E. *Org. Lett.* **2011,** *13* (21), 5854 – 5857.
334. Gryparis, C.; Lykakis, I.; Efe, C.; Zaravinos, I.; Vidali, T.; Kladou, E.; Stratakis, M. *Org. Biomol. Chem.* **2011,** *9* (16), 5655 – 5658.
335. Kouridaki, A.; Montagnon, T.; Kalaitzakis, D.; Vassilikogiannakis, G. *Org. Biomol. Chem.* **2013,** *11* (4), 537 – 541.
336. Kalaitzakis, D.; Noutsias, D.; Vassilikogiannakis, G. *Org. Lett.* **2015,** *17* (14), 3596 – 3599.
337. Kalaitzakis, D.; Triantafyllakis, M.; Sofiadis, M.; Noutsias, D.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed.* **2016,** *55* (14), 4605 – 4609.
338. Mihara, S.; Tateba, H. *J. Org. Chem.* **1986,** *51* (7), 1142 – 1144.
339. Gültekin, M.; Göksu, H. *Org. Cummun.* **2016,** *9* (4), 102 – 107.
340. Kouridaki, A.; Huvaere, K. *React. Chem. Eng.* **2017,** *2* (4), 590 – 597.
341. Kyriakopoulos, J.; Papastavrou, A.; Panagiotou, G.; Tzirakis, M.; Triantafyllidis, K.; Alberti, M.; Bourikas, K.; Kordulis, C.; Orfanopoulos, M.; Lycourghiotis, A. *J. Mol. Catal. Chem.* **2014,** *381* (1), 9 – 15.
342. Ioannou, G.; Kalaitzakis, D.; Vassilikogiannakis, G. *Eur. J. Org. Chem.* **2016,** No. 20, 3304 – 3306.
343. Aubry, J. *J. Am. Chem. Soc.* **1985,** *107* (21), 5844 – 5849.
344. Parker, R. *The Flixborough Diasaster: Report of the Court of Inquiry;* H. M. S. O.: London, 1975.

345. Ober, D.; Kaltenegger, E. *Phytochemistry* **2009,** *70* (15 – 16), 1687 – 1695.
346. Horiuchi, Y.; Kondo, S.; Ikeda, T.; Ikeda, D.; Miura, K.; Hamada, M.; Takeuchi, T.; Umazawa, H. *J. Antibiot.* **1979,** *32* (7), 762 – 764.
347. Nettleton, D.; Balitz, D.; Doyle, T.; Bradner, W.; Johnson, D.; O'Herron, F.; Schreiber, R.; Coon, A.; Moseley, J.; Myllymaki, R. *J. Nat. Prod.* **1980,** *43* (3), 242 – 258.
348. Bugni, T.; Woolery, M.; Kauffman, C.; Jensen, P.; Fenical, W. *J. Nat. Prod.* **2006,** *69* (11), 1626 – 1628.
349. Fu, P.; La, S.; MacMillan, J. *J. Nat. Prod.* **2016,** *79* (3), 455 – 462.
350. Fu, P.; Legako, A.; La, S.; MacMillan, J. *Chem. Eur. J.* **2016,** *79* (3), 3491 – 3495.
351. Jiang, B.; Zhao, W.; Li, S.; Liu, H.; Yu, L.; Zhang, Y.; He, H.; Wu, L. *J. Nat. Prod.* **2017,** *80* (10), 2825 – 2829.
352. Grote, R.; Zeeck, A.; Stümpfel, J.; Zähner, H. *Liebigs Ann. Chem.* **1990,** 525 – 530.
353. Hu, J.; Wunderlich, D.; Thiericke, R.; Dahse, H.; Grabley, S.; Feng, X.; Sattler, I. *J. Antibiot.* **2003,** *56* (9), 747 – 754.
354. Snider, B.; Duvall, J. *Org. Lett.* **2005,** *7* (20), 4519 – 4522.
355. Zhang, Q.; Schrader, K.; ElSohly, H.; Takamatsu, S. *J. Antibiot.* **2003,** *56* (8), 672 – 681.
356. Duvall, J.; Wu, F.; Snider, B. *J. Org. Chem.* **2006,** *71* (22), 8579 – 8590.
357. Stevens, K.; Tyrrell, A.; Skerratt, S.; Robertson, J. *Org. Lett.* **2011,** *22* (13), 5964 – 5967.
358. Raju, R.; Piggott, A.; Conte, M.; Capon, R. *Org. Biomol. Chem.* **2010,** *8* (20), 4682 – 4689.
359. Kanoh, N.; Itoh, S.; Fujita, K.; Sakanishi, K.; Sugiyama, R.; Terajima, Y.; Iwabuchi, Y.; Nishimura, S.; Kakeya, H. *Chem. Eur. J.* **2016,** *22* (25), 8586 – 8595.
360. Zhang, W.; Li, S.; Zhu, Y.; Chen, Y.; Chen, Y.; Zhang, H.; Zhang, G.; Tian, X.; Pan, Y.; Zhang, S.; Zhang, W.; Zhang, C. *J. Nat. Prod.* **2014,** *77* (2), 388 – 391.
361. Ding, N.; Han, L.; Jiang, Y.; Li, G.; Zheng, Z.; Cao, B.; Guan, P.; Mu, Y.; Lin, B.; Huang, X. *RSC Adv.* **2018,** *8* (31), 17121 – 17131.
362. Fu, P.; MacMillan, J. *Org. Lett.* **2015,** *17* (12), 3046 – 3049.
363. Huang, S.; Tabudravu, J.; Elsayed, S.; Travert, J.; Peace, D.; Tong, M.; Kyeremeh, K.; Kelly, S.; Trembleau, L.; Ebel, R.; Jaspars, M.; Yu, Y.; Deng, H. *Angew. Chem. Int. Ed.* **2015,** *54* (43), 12697 – 12701.
364. Schimming, O.; Challinor, V.; Tobias, N.; Adihou, H.; Grün, P.; Pöschel, L.; Richter, C.; Schwalbe, H.; Bode, H. *Angew. Chem. Int. Ed.* **2015,** *54* (43), 12702 – 12705.
365. Derewacz, D.; Covington, B.; McLean, J.; Bachmann, B. *ACS Chem. Bio.* **2015,** *10* (9), 1998 – 2006.
366. Klapper, M.; Götze, S.; Barnett, R.; Willing, K.; Stallforth, P. *Angew. Chem. Int. Ed.* **2016,** *55* (31), 8944 – 8947.
367. Jiang, B.; Zhao, W.; Li, S.; Liu, H.; Yu, L.; Niu, W.; He, H.; Wu, L. *J. Antibiot.*

**2018,** *71* (11), 965 – 967.

368. Aoyagi, Y.; Manabe, T.; Ohta, A.; Kurihara, T.; Pang, G.; Yuhara, T. *Tetrahedron* **1996,** *52* (3), 869 – 876.
369. Giovenzana, G.; Sisti, M.; Palmisano, G. *Tetrahedron: Asymmetry* **1997,** *8* (4), 515 – 518.
370. Arisawa, M.; Takezawa, E.; Nishida, A.; Mori, M.; Nakagawa, M. *Synlett* **1997,** No. 10, 1179 – 1180.
371. Huang, P.; Chen, Q.; Chen, C.; Zhang, H. *Tetrahedron: Asymmetry* **2000,** *11* (8), 1843.
372. Watson, R.; Gore, V.; Chandupatla, K.; Dieter, R.; Snyder, J. *J. Org. Chem.* **2004,** *69* (19), 6105 – 6114.
373. Majik, M.; Shet, J.; Tilve, S.; Parameswaran, P. *Synthesis* **2007,** No. 5, 663 – 665.
374. Schobert, R.; Wicklein, A. *Synthesis* **2007,** No. 10, 1499 – 1502.
375. Marsh, B.; Adams, H.; Barker, M.; Kutama, I.; Jones, S. *Org. Lett.* **2014,** *16* (14), 3780 – 3783.
376. Snider, B.; Duvall, J.; Sattler, I.; Huang, X. *Tetrahedron Lett.* **2004,** *45* (36), 6725 – 6727.
377. Robertson, J.; Stevens, K. *Nat. Prod. Rep.* **2014,** *31* (12), 1721 – 1788.
378. Robertson, J.; Stevens, K. *Nat. Prod. Rep.* **2017,** *34* (1), 62 – 89.
379. van Dijk, T.; Slootweg, C.; Lammertsma, K. *Org. Biomol. Chem.* **2017,** *15* (48), 10134 – 10144.
380. Booth, B.; Jibodu, K.; Proença, M. *J. Chem. Soc., Chem. Commun.* **1980,** No. 23, 1151 – 1153.
381. Brehm, E.; Haag, A.; Hesse, G.; Witte, H. *Liebigs Ann. Chem.* **1970,** *737* (1), 70 – 79.
382. Höfle, G.; Lange, B. *Angew. Chem. Int. Ed.* **1977,** *16* (4), 262 – 263.
383. al-Talib, M.; Tashtoush, H. *Tetrahedron, Lett.* **1987,** *28* (3), 353 – 356.
384. Kelleher, F.; Kelly, S. *Tetrahedron Lett.* **2006,** *47* (18), 3005 – 3008.
385. Rioton, S.; Orliac, A.; Antoun, Z.; Bidault, R.; Pardo, D.; Cossy, J. *Org. Lett.* **2015,** *17* (12), 2916 – 2919.
386. Foley, D.; Doveston, R.; Churcher, I.; Nelson, A.; Marsden, S. *Chem. Commun.* **2015,** *51* (56), 11174 – 11177.
387. Pajouhesh, H.; Holland, R.; Zhang, L.; Pajouhesh, H.; Lamontagne, J.; Whelan, B.; Short, G.; Romero, D. Biaryl compounds as inhibitors of the sodium channel and their preparation. WO 2013131018, March 1, 2013.
388. Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981,** *37* (23), 3899 – 3910.
389. Pinner, A.; Klein, F. *Ber. Dtsch. Chem. Ges.* **1877,** *10* (2), 1889 – 1897.
390. Gola, A.; Samartzi, E.; Bardakos, V.; Petroliagi, M.; Igglessi-Markopoulou. *J. Heterocycl. Chem.* **2000,** *37* (4), 681 – 686.
391. Petroliagi, M.; Igglessi-Markopoulou, O. *J. Heterocycl. Chem.* **2001,** *38* (4), 917 – 922.
392. Nate, H.; Sekine, Y.; Oda, K.; Aoe, K.; Nakai, H.; Wada, H.; Takeda, M.; Yabana,

H.; Nagao, T. *Chem. Pharm. Bull.* **1987,** *35* (8), 3253 – 3261.
393. Spitzner, R.; Freitag, S.; Scroth, W. *Monatsh. Chemie* **1987,** *118* (12), 1383 – 1394.
394. Edstrom, E.; Yu, T. *J. Org. Chem.* **1995,** *60* (17), 5382 – 5383.
395. Kondakal, V.; Qamar, M.; Hemming, K. *Tetrahedron Lett.* **2012,** *53* (32), 4100 – 4103.
396. McNab, H.; Monahan, L. *J. Chem. Soc. Perkin Trans. 2* **1988,** No. 5, 759 – 764.
397. Gaber, A.; Hunter, G.; McNab, H. *J. Chem. Soc. Perkin Trans. 1* **2002,** No. 4, 548 – 554.
398. McNab, H.; Morrow, M.; Parsons, S.; Shannon, D.; Withell, K. *Org. Biomol. Chem.* **2009,** *7* (23), 4936 – 4942.
399. Rillema, D.; Allen, G.; Meyer, T.; Conrad, D. *Inorg. Chem.* **1983,** *22* (11), 1617 – 1622.
400. Groen, M. H. B.; Zeelen, F. *Recl. Trav. Chim. Pays-Bas* **1985,** *104* (2), 59 – 62.
401. Kazancioglu, E.; Kazancioglu, M.; Fistikci, M.; Secen, H.; Altundas, R. *Org. Lett.* **2013,** *15* (18), 4790 – 4793.
402. Singh, R.; Ghosh, S. *Tetrahedron* **2010,** *66* (13), 2284 – 2292.
403. Kalaitzakis, D.; Triantafyllakis, M.; Alexopoulou, I.; Sofiadis, M.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed.* **2014,** *53* (48), 13201 – 13205.
404. Graaf, M.; Moeller, K. *J. Org. Chem.* **2015,** *80* (3), 2032 – 2035.
405. Lafferty, J.; Case, F. *J. Org. Chem.* **1967,** *32* (5), 1591 – 1596.
406. Li, H.; Jiang, X.; Zhu, W.; Lu, J.; Shu, H.; Yan, Y. *Ind. Eng. Chem. Res.* **2009,** *48* (19), 9034 – 9039.
407. Co., F. &. New Preparations of cyclopent-2-en-1-one. NL 6502714, September 6, 1965.
408. Dhiman, S.; Ramasastry, S. *Org. Biomol. Chem.* **2013,** *11* (46), 8030 – 8035.
409. Sato, A.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2006,** *128* (13), 4240 – 4241.
410. Ioannou, G.; Mantagnon, T.; Kalaitzakis, D.; Pergantis, S.; Vassilikogiannakis, G. *Org. Biomol. Chem.* **2017,** *15* (48), 10151 – 10155.
411. Denk, G. *Synthesis of Tricyclic Nitrogen Systems;* Dissertation; Institute of Applied Synthetic Chemistry: Vienna, 1995.
412. Friedrich, E.; Abma, C. *J. Am. Chem. Soc.* **1980,** *102* (4), 1367 – 1371.
413. Reis, A.; Rittner, R. *Spectrochim. Acta A* **2007,** *66* (3), 681 – 685.
414. Chang, R.; Kim, K. *Tetrahedron Lett.* **1996,** *37* (43), 7791 – 7794.
415. Oniciu, D.; Dasseux, J.; Barbaras, R.; Kochubey, V.; Kovalsky, D.; Rodin, O.; Geoffroy, O.; Rzepiela, A. Compounds, Compositions and Methods Useful for Cholesterol Mobilisation. WO2012054535, February 18, 2011.
416. Heinrich, M.; Weil, T.; Muller, S.; Kauss, V.; Erdmare, E.; Zemribo, R. 6-Halo-pyrazolo[1,5a]pyridines, A Process for their Preparation and their Use as Metabotrophic Glutamate Receptor (MGluR) Modulators. WO2009095253A1, August 6, 2009.

417. Hashmi, A.; Rudolph, M.; Bats, J.; Frey, W.; Rominger, F.; Oeser, T. *Chem. Eur. J.* **2008,** *14* (22), 6672 – 6678.
418. Brodney, M.; O'Leary, J.; Hansen, J.; Giguere, R. *Synth. Commun.* **1995,** *25* (4), 521 – 531.
419. Moreira, J.; Millar, J. *J. Chem. Ecol.* **2005,** *31* (4), 965 – 968.
420. Rodier, F.; Parrain, J.; Chouraqui, G.; Commeiras, L. *Org. Biomol. Chem.* **2013,** *11* (25), 4178 – 4185.
421. Newton, A.; Deiana, L.; Puleo, D.; Cisneros, J.; Cutrona, K.; Schlessinger, J.; Jorgensen, W. *ACS Med. Chem. Lett.* **2017,** *8* (6), 614 – 617.
422. Goldstein, S.; Overman, L.; Rabinowitz, M. *J. Org. Chem.* **1992,** *57* (4), 1179 – 1190.
423. Poplata, S.; Bach, T. *J. Am. Chem. Soc.* **2018,** 3228 – 3231.
424. Paruszewski, R.; Jaworski, P.; Tautt, J.; Dudkiewicz, J. *Die Pharmazie* **1997,** *52* (3), 206 – 209.
425. Wünsch, M.; Schröder, D.; Fröhr, T.; Teichmann, L.; Hedwig, S.; Janson, N.; Belu, C.; Simon, J.; Heidemeyer, S.; Holtkamp, P.; Rudlof, J.; Klemme, L.; Hinzmann, A.; Neumann, B.; Stammler, H.; Sewald, N. *Beilstein J. Org. Chem.* **2017,** *13,* 2428 – 2441.
426. Cresswell, A.; Davies, S.; Figuccia, A.; Fletcher, A.; Heinen, D.; Lee, J.; Morris, M.; Kennett, A.; Roberts, P.; Thomson, J. *Tetrahedron Lett.* **2015,** *56* (23), 3373 – 3377.
427. Quintard, J.; Degueil-Castaing, M.; Dumartin, G. *J. Organomet. Chem.* **1982,** *234* (1), 27 – 40.
428. Staab, H.; Polenski, B. *Liebigs Ann.* **1962,** *655,* 95 – 102.
429. Fowden, L.; Hughes, E.; Ingold, C. *J. Chem. Soc.* **1955,** No. 0, 3187 – 3192.
430. Fainberg, A.; Winstein, S. *J. Am. Chem. Soc.* **1956,** *78* (12), 2770 – 2777.
431. Watts, H. *A Dictionary of Chemistry and the Allied Branches of Other Sciences;* Longmans, Green & Co.: London, 1868; Vol. V.
432. Kaplan, L. *J. Chem. Soc., Chem. Commun.* **1969,** No. 3, 106 – 107 and references therein.
433. Allen, N. *South African Journal of Art History* **1993,** *11* (1), 23 – 32.
434. Damon, P.; Donahue, D.; Gore, B.; Hatheway, A.; Jull, A.; Linick, T.; Sercal, P.; Toolin, L.; Bronk, C.; Hall, E.; Hedges, R.; Housley, R.; Law, I.; Perry, C.; Bonani, G.; Trumbore, S.; Woelfli, W.; Ambers, J.; Bowman, S.; Leese, M.; Tite, M. *Nature* **1989,** *337* (6208), 611 – 615.
435. Eberson, L.; Nyberg, K. *J. Am. Chem. Soc.* **1966,** *88* (8), 1686 – 1691.
436. Haga, M.; Dodsworth, E.; Eryavec, G.; Seymour, P.; Lever, A. *Inorg. Chem.* **1985,** *24* (12), 1901 – 1906.
437. Plé, N.; Turck, A.; Heynderickx, A.; Quéguiner, G. *Tetrahedron* **1998,** *54* (33), 9701 – 9710.
438. Griffith, D.; Rice, M.; Elliott, R. Pyrazine Derivatives. EP0296722, June 22, 1987.
439. Noyes, W.; Marvel, C. *J. Am. Chem. Soc.* **1917,** *39,* 1267 – 1271.

440. Manley, D.; Walton, J. *Beilstein J. Org. Chem.* **2015,** *11,* 1570 – 1582.
441. Bloh, J.; Marschall, R. *Eur. J. Org. Chem.* **2017,** No. 15, 2085 – 2094.
442. Savateev, A.; Antonietti, M. *ACS Catal.* **2018,** *8* (10), 9790 – 9808.
443. Savateev, A.; Ghosh, I.; König, B.; Antonietti, M. *Angew. Chem. Int. Ed.* **2018,** *57* (49), 15936 – 15947.
444. Ohshita, J. I. A.; Kanetani, F.; Kunai, A. *J. Org. Chem.* **1999,** *64* (21), 8024 – 8026.
445. Kwart, H.; Evans, E. *J. Org. Chem.* **1966,** *31* (2), 410 – 413.
446. Newman, M.; Karnes, H. *J. Org. Chem.* **1966,** *31* (12), 3980 – 3984.
447. Wu, B. *Synthesis of taurospongin A and other biologically active natural products;* D. Phil. Thesis; University of Oxford: Oxford, 2012.
448. Graziano, L.; Lesce, R.; Scarpati, R. *J. Chem. Soc. Perkin Trans. 1* **1982,** 2007 – 2012.
449. Dolak, L.; DeBoer, C. A New Antibiotic from Streptomyces Griseus. *17th Intersci. Conf. on MantiMicr. Agents & Chemoth.*, New York, NY, 1977; p 74.
450. DeBoer, C.; Dolak, L.; Peterson, D. Composition of matter and process. US4113855, September 12, 1978.
451. Barker, J. *Azatrimethylenemethanes (ATMMs): Underused Intermediates for Organic Synthesis;* Part II Thesis; University of Oxford: Oxford, 2016.
452. Fujiwara, K. *Sitzungsberichte und abhandlungen der Naturforschenden Gesellschaft zu Rostock* **1914,** No. 6, 1.
453. Petrakis, L. *J. Chem. Educ.* **1967,** *44* (8), 432 – 436.
454. Chatgilialoglu, C.; Ferreri, C.; Landais, Y.; Timokhin, V. *Chem. Rev.* **2018,** *118* (14), 6516 – 6572.

# 8 Appendices

*"On the one hand, I have wanted to supply documentation on myself by including material relevant to my emotions and ideas in my youth; and, on the other, not to let myself down by publishing inferior material. My poetry comes under the latter head. My only advice to the reader is to skip any verse that he sees coming."*
Edmund Wilson (1895 – 1972), writer and critic

## Appendix 1: Details of Visible Light- and UV-mediated Photocatalytic Runs

| Entry | Substrate | 2.8 loading/eq.[a] | Rxn time/h | Additive, loading/eq.[a] | Result[b] |
|---|---|---|---|---|---|
| 1 | **2.7** | 0.005 | 44.5 | Thiphenol, 0.005 | Dec. |
| 2 | **2.7** | 0.02 | 20.0 | Thiophenol, 0.5 | Dec. |
| 3 | **2.7** | 0.005 | 44.5 | Benzyl thiol, 0.005 | Partial dec., remainder ox. |
| 4 | **2.7** | 0.005 | 44.5 | *tert*-Butyl thiol, 0.005 | 10% Ox. |
| 5 | **2.7** | 0.005 | 44.5 | Cyclohexyl thiol, 0.005 | 5% Ox. |
| 6 | **2.7** | 0.01 | 20.0 | Cyclohexyl thiol,0.01 | No rxn |
| 7 | **2.7** | 0.02 | 15.5 | $LiBF_4$, 5 | No rxn. |
| | | | 51.1 | | 5% Ox. |
| 8 | **2.7** | 0.02 | 15.5 | MS | 5% Ox. |
| | | | 51.1 | | Dec.[c] |
| 9 | **2.16** | 0.02 | 15.5 | - | 10% Ox. |
| | | | 51.1 | | Partial dec., remainder ox. |
| 10 | **2.16** | 0.02 | 15.5 | $LiBF_4$, 5 | No rxn. |
| | | | 51.1 | | 60% Ox. (partial dec.) |
| 11 | **2.16** | 0.02 | 15.5 | MS | 20% Ox. |
| | | | 51.1 | | 40% Ox. |

**Table 8.1.** Details of attempts to cyclise **2.7** by irradiation with blue light in the presence of **2.8**. [a] Specified with respect to SM. [b] "Dec." indicates decomposition, "ox." indicates oxidation to enedione or 2,5-dihydroxy-2,5-dihydrofuran, extent of ox. estimated by $^1$H NMR analysis and rounded to nearest 5%. [c] $^1$H NMR spectrum of this material was broadened, but appeared to show a mixture of SM and (*Z*)-enedione.

| Entry | Scale/mmol[a] | Rxn time/h | Conv.[b] | Yield (NMR) | Yield (chromato-graphic) | Yield (lit., (*291*) isolated) | $\lambda_{max,irr}$/ nm | $P_{irr}$ ($\lambda_{max,irr}$)/ mW |
|---|---|---|---|---|---|---|---|---|
| 1 | 0.8 | 15.9 | - | - | 19 | 72[c] | 254 | 175 |
| 2 | 0.8 | 15.5 | 0 | 0 | - | | 254 | 175 |
| 3 | 1 | 23 | 90[d] | 33 | 2.8 | | 365 | 175 |
| 4 | 2.2 | 3.3 | >95 | 74 | 33 | | 365 | 1000 |

**Table 8.2.** Details of TBADT-mediated coupling of isopropanol and acrylonitrile, see Table 8.2; all conversions and yields are expressed as percentages. [a] Specified with respect to acrylonitrile. [b] Determined by NMR analysis, based on consumption of acrylonitrile; see also note d. [c] Product isolated by distillation. (*291*) [d] Conversion was 66% after 11 h (NMR, based on 0.05 eq. dtbbp added as internal standard).

| Entry | TBADT loading /eq.[a] | [SM]/ mM[a] | Additive[a] | Rxn time/h | Conv. (NMR, %)[b] | Yield (NMR, %)[c] | Product(s), yield (chromato-graphic, %)[d] |
|---|---|---|---|---|---|---|---|
| 1 | 0.005 | 100 | MS | 48 | - | 0* | 1 : 1 (*E*)-2.7 : 2.9 (13)[e] |
| 2 | 0.05 | 100 | | 48 | - | 0* | |
| 3 | 0.01 | 500 | | 48 | 62 | - | |
| 4 | 0.05 | 20 | | 48 | 55 | - | |
| 5 | 0.10 | 100 | | 48 | 52 | - | |
| 6 | 0.02 | 200 | dtbbp | 25.4 | 44 | 44 | 3 : 1 2.9 : 2.7 (4) |
| 7 | 0.02 | 150 | | 25.4 | 62 | 31 | - |
| 8 | 0.02 | 100 | | 25.4 | 52 | 45 | - |
| 9 | 0.02 | 50 | | 25.4 | 15 | 8.5 | - |
| 10 | 0.02 | 25 | | 25.4 | 100 | 0* | - |
| 11 | 0.04 | 100 | | 16.5 | 46 | 36 | - |
| | | | | 39.0 | 100 | 0* | |
| 12 | 0.04[g] | 200 | | 16.5 | 46 | 33 | - |
| | | | | 39.0 | 100 | 0* | |
| 13 | 0.04[h] | 200 | | 16.5 | 46 | 43 | - |
| | | | | 39.0 | 100 | 0* | |
| 14 | 0.10 | 50 | | 16.5 | 51 | 40 | - |
| | | | | 39.0 | 100 | 0* | |
| 15 | 0.10[i] | 50 | | 16.5 | 51 | 37 | - |
| | | | | 39.0 | 100 | 0* | |

**Table 8.3.** Details of experiments to investigate the effects of catalyst loading, reaction concentration, and manner of addition of catalyst to reaction mixture. [a] Specified with respect to SM; "MS" = 4 Å molecular sieves, "dtbbp" = 0.25 eq. dtbpp as internal standard. [b] Evaluated by integration of $OCH_2CH_3$ signals in product and SM, unless spectrum broadened. [c] Evaluated by comparison of $OCH_2CH_3$ signals from product with Ar signals from internal standard. [d] Mixture not separated, but yield refers to cyclised component only. [e] Broadening of 1H NMR spectrum indicated decomposition. [f] Crude product from all runs purified together by chromatography. [g] Half of catalyst added over 6 h. [h] All catalyst added over 18 h. [i] Mixture not deoxygenated before reaction.

# Appendix 2: Nuclear Overhauser Effect Analysis of Compound 2.9

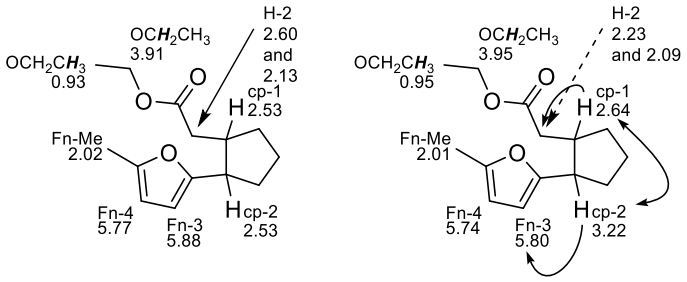



**Chart 8.1.** Discernable $^{1}$H NMR resonances for the major (left) and minor (right) diastereomers of the material obtained by reductive cyclisation of compound **3.8**. nOes (black arrows, see Figure 8.1 for spectra) confirm that the minor isomer has *cis* stereochemistry. "cp" = cyclopentyl.

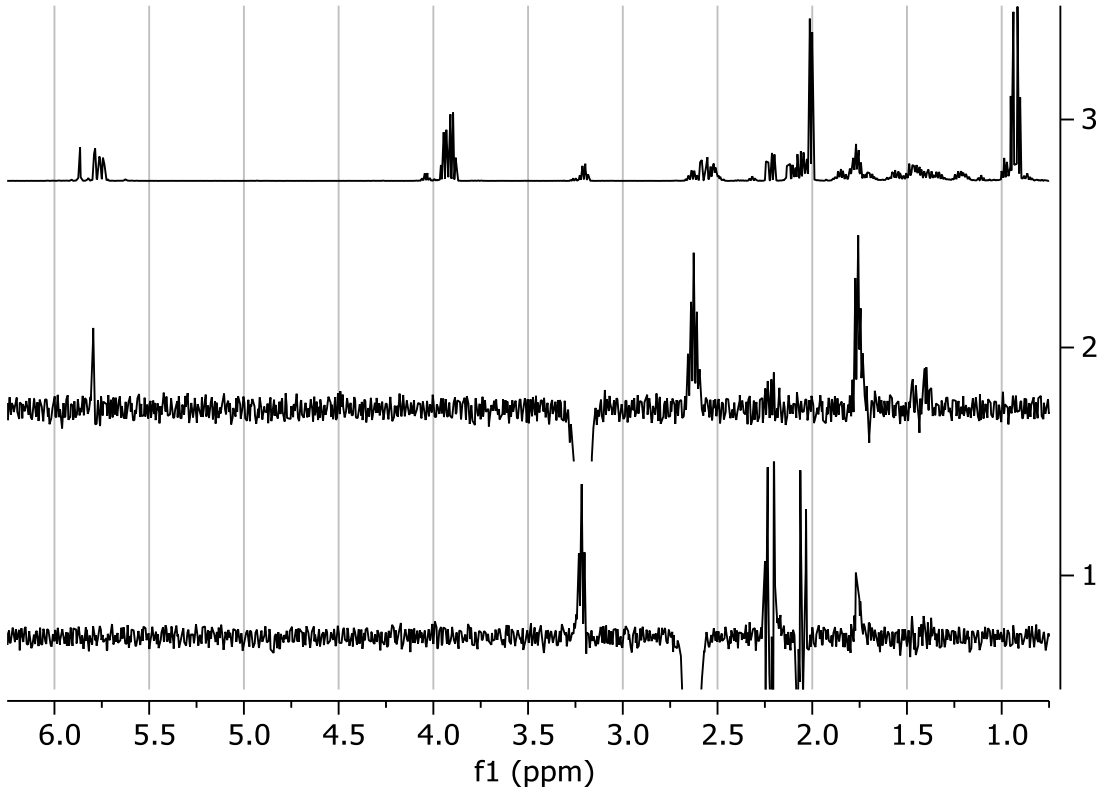



**Figure 8.1.** The $^{1}$H NMR spectrum of material obtained from reductive cyclisation of compound **3.8** (3), and the nOe spectra of the same material arising from irradiation of *cis*-cyclopentyl-2 (2) and *cis*-cyclopentyl-1 (1).

# Appendix 3: Nuclear Overhauser Effect Analysis of Compound 3.22

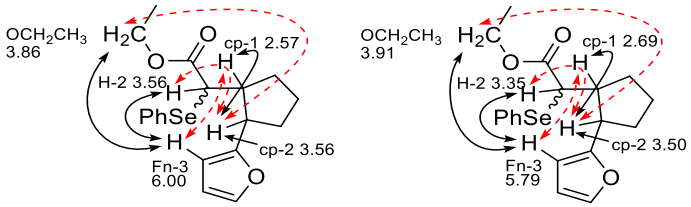



**Chart 8.2.** Indicated nOes (black arrows), and lack thereof (red dashed arrows), support the *cis* configuration of both the major (left) and the minor (right) isolated diastereomers of selenide **3.22**; Coupling between cyclopentyl-1 and cyclopentyl-2, and between Fn-3 and H-2, is apparent, but no discernable coupling between Fn-3 and cyclopentyl-1, or between H-2 and cyclopentyl-2, occurred. Chemical shifts of resonances associated with the relevant protons are shown. "cp" = Cyclopentyl, see Figure 8.2 for nOeSY spectrum.

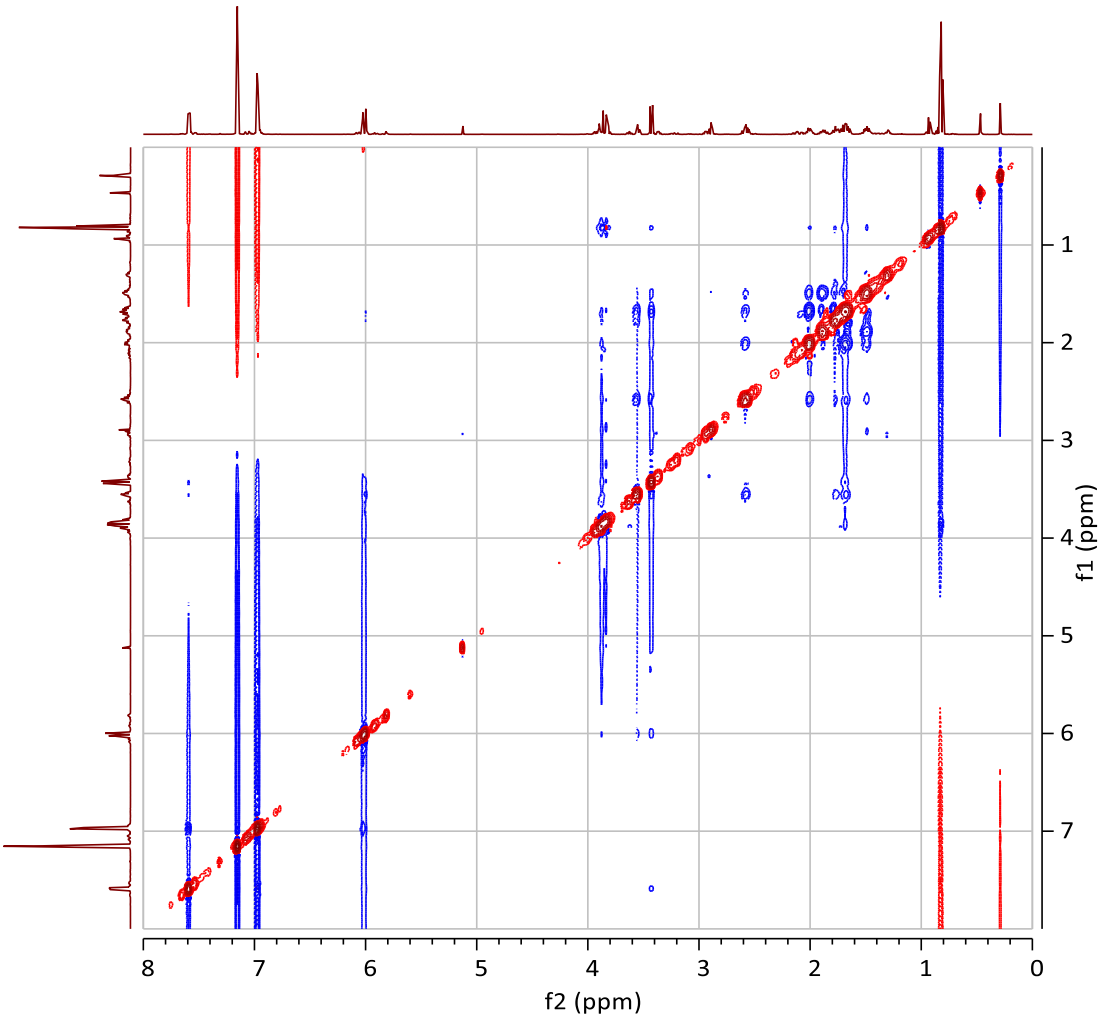



**Figure 8.2.** The 2D nOeSY spectrum of the major isolated diastereomer of compound **3.22**.

# Appendix 4: Nuclear Overhauser Effect Analysis of Compound 3.23

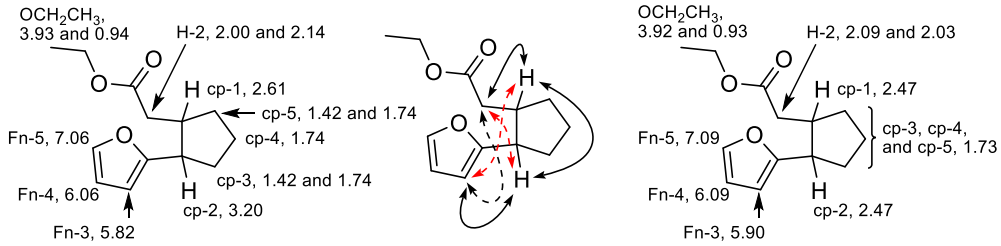



**Chart 8.3.** $^{1}$H NMR assignments for the major diastereomer of material obtained from hydrogenation of olefin **3.24** (left). Selected strong (solid arrows) and weak (dashed arrows) nOes (see Figure 8.3 for spectra) show that this material is the *cis* isomer, and nOes inconsistent with this stereochemical assignment were not detected or very weak (red dashed arrows) (centre). $^{1}$H NMR assignments for the major diastereomer of material obtained from stannane reduction of selenide **3.22** (right). "cp" = cyclopentyl.

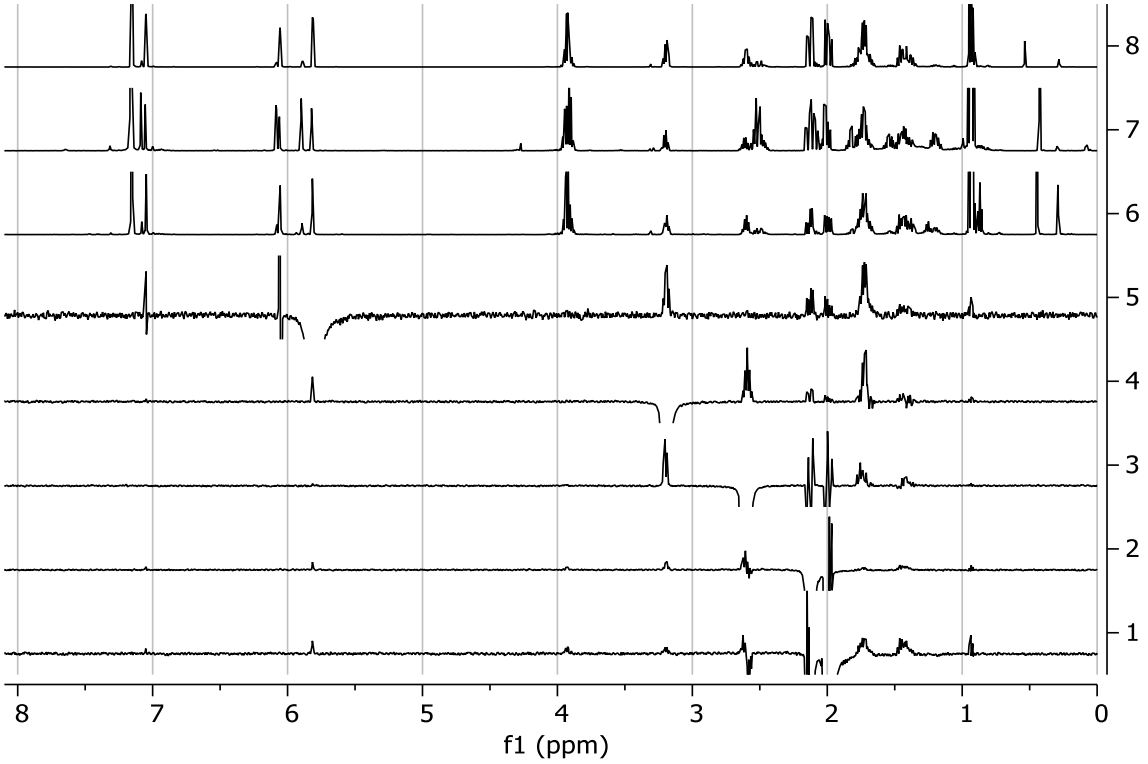



**Figure 8.3.** The $^{1}$H NMR spectrum of material obtained from hydrogenation of olefin **3.24** (8), reduction of selenide **3.22** with TBTH at a concentration of 6.2 mM (7) and reduction of selenide **3.22** with TBTH-*d* at 50 mM (6) and the nOe spectra of material obtained from hydrogenation of olefin **3.24**, arising from irradiation of: Fn-3 (5), cyclopentyl-2 (4), cyclopentyl-1 (3), and both diastereotopes of H-2 (2 and 1). See Chart 8.3 and page 195 for spectroscopic assignments.

# Appendix 5: Explanation of Formulae for Conversion and Polymerisation of Furan in Oxidation Reactions

The extent $\alpha(t)$[xcv] of the reaction of a chemical species after reacting for a time period $t$ can be expressed in terms of the amount remaining of one of the starting materials $n_0(t)$ as a proportion of the amount of that starting material present at the beginning of the reaction $n_0(0)$ by Equation 8.1.

$$\alpha(t) = 1 - \frac{n_0(t)}{n_0(0)} \qquad 8.1$$

Where the total number of species present in a reaction is constant,[xcvi] the total amount of substance, which can be obtained by summation of $n_0(t)$ and the amounts of each product species present, $n_1(t)$,$n_2(t)\ldots n_i(t)$ etc, must be equal to the amount of starting material present at the beginning of the reaction (Equation 8.2). Combining 8.1 and 8.2 furnishes Equation 8.3.

$$n_0(0) = n_0(t) + \sum_1^i n_i(t) \qquad 8.2$$

$$\alpha(t) = 1 - \left(\frac{n_0(t)}{\sum_0^i n_i(t)}\right) \qquad 8.3$$

The integral with respect to δ of a single signal in a $^1$H NMR spectrum $y(\delta)$ between limits $\delta_{max}$ and $\delta_{min}$ is proportional to the number of nuclei resonating $m$ (Relation 8.4);[xcvii] Where there are multiple species present in a spectrum, integration

[xcv] With $\alpha = 0$ corresponding to no conversion and $\alpha = 1$ corresponding to complete conversion.
[xcvi] Except in cases where a reaction involves fragmentation of the starting material or the combination of multiple starting species to form fewer product species.
[xcvii] NMR signals are distributed continuously about a central maximum; the only way to "capture" by integration all resonance arising from a nuclear environment, therefore, is by integrating the entire spectrum, with obvious disadvantages when nuclei in other environments are resonating. One contribution to the *k*-terms in Equation 8.7 will be the proportion of total resonance measured by integration. Ideal NMR signals (requiring a true free induction decay in the time domain, no splitting of peaks, and – most significantly of all – no noise, none of which apply in the NMR spectra on which the analyis described here was applied) have a Lorentzian lineshape. (*453*) For the proportion of total resonance measured by integration of Lorentzian signals to be constant whichever peak is measured, integration within limits separated by a

within limits $\delta_{max,i}$ and $\delta_{min,i}$, chosen to capture only the resonance of nuclei in species $i$ (see footnote xcvii), and introducing a factor $l_i$ to account for the number of nuclei whose resonance is being measured per species gives Relation 8.5.

$$m \propto \int_{\delta_{min}}^{\delta_{max}} y(\delta)\, d\delta \qquad 8.4$$

$$n_i \propto \frac{1}{l_i} \int_{\delta_{min,i}}^{\delta_{max,i}} y(\delta)\, d\delta \qquad 8.5$$

If a sample of the reaction mixture is taken at time $t$, and a $^1$H NMR spectrum $y_t(\delta)$is taken, then application of Relation 8.5 to that spectrum indicates $n_i(t)$ (Relation 8.6). Introducing the constants of proportionality $k_{sample}$, a normalisation term to account for factors that are constant for a given NMR spectrum whichever nuclear resonance is being measured, and $k_{nuc,i}$, denoting a normalisation term for factors that are different from nucleus to nucleus, gives Equation 8.7.

$$n_i(t) \propto \frac{1}{l_i} \int_{\delta_{min,i}}^{\delta_{max,i}} y_t(\delta)\, d\delta \qquad 8.6$$

$$n_i(t) = \frac{k_{nuc,i} k_{sample}}{l_i} \int_{\delta_{min,i}}^{\delta_{max,i}} y_t(\delta)\, d\delta \qquad 8.7$$

$S$ is defined as the sum, over $i$ species, of the products of $k_{nuc,i}$, $l_i$, and the integral of a resonance arising solely from species $i$ (Equation 8.8). substitution into Equation 8.3 of the expression for $n_i(t)$ in Equation 8.7 gives Equation 8.9 after cancellation of $k_{sample}$-terms[xcviii].

given number of peak half-widths at half-maximum either side of the maximum; 1 half-width at half maximum captures 50% of the signal, 3.1 half-widths at half-maximum captures over 90%.

[xcviii] The various $k_{sample}$-terms are not necessarily equal for integrals from different spectra, cancellation is therefore only valid where all integrals are taken from one NMR spectrum.

$$S = \sum_{0}^{i} \frac{k_{nuc,i}}{l_i} \int_{\delta\min,i}^{\delta\max,i} y_t(\delta)\, d\delta \qquad 8.8$$

$$\alpha(t) = 1 - \left( \frac{k_{nuc,0} \int_{\delta_{min,0}}^{\delta_{max,0}} y_t(\delta)\, d\delta}{l_0 S} \right) \qquad 8.9$$

Equation 8.9 can be applied to the oxidation of compound **4.2** to (*E*)-**4.3a**, (*Z*)-**4.3a**, and **4.3b**: Setting δ-values as indicated in Table 8.4 to describe the Fn-3/Fn-4 resonance of compound **4.2**, and the corresponding H-3/H-4 resonances in (*E*)-**4.3a**, (*Z*)-**4.3a**, and **4.3b** gives Equation 8.10. Assuming that $k_{\text{nuc}}$ has the same value for all products and that conversion to products other than (*E*)-**4.3a**, (*Z*)-**4.3a**, and **4.3b** is not significant, and using the notation $\int_{products} y_t(\delta)\, d\delta$ to refer to the sum of the integrals of all product peaks and $\int_{\text{SM}} y_t(\delta)\, \text{d}\delta$ to $\int_{5.81}^{5.86} y_t(\delta)\, d\delta$, simplification to Equation 8.11 is possible.

| **Species** | ***i*** | ***l*$_i$** | **Measured nuclei** | **$\delta_{max,i}$/ppm** | **$\delta_{min,i}$/ppm** |
|---|---|---|---|---|---|
| **4.2** | 0 | 2 | Fn-3 and Fn-4 | 5.86 | 5.81 |
| (*E*)-**4.3a** | 1 | 2 | H-3 and H-4 | 6.84 | 6.81 |
| (*Z*)-**4.3a** | 2 | 2 | H-3 and H-4 | 6.34 | 6.26 |
| **4.3b** | 3 | 2 | Dioxydihydrofuran-3 and -4 | 6.04 | 5.88 |

**Table 8.4.** Details of resonances used for evaluating conversion of **4.2** during oxidation.

Assuming the $k_{\text{nuc}}$-values of the hexyl-$CH_3$ and H-11 protons in compounds **4.2** and (*E*)-**4.3a** are equal, analysis of $^1$H NMR spectra of clean samples of both compounds indicates $\frac{k_{\text{nuc,SM}}}{k_{\text{nuc,(}E\text{)}-\mathbf{4.3a}}} = 1.06$ (Table 8.5); substitution of this value into Equation 8.11 gives Equation 4.1; it is further assumed that the ratio of $k_{\text{nuc,SM}}$ : $k_{\text{nuc,product}}$ is conserved with other substrates.

$$\alpha(t) = \frac{k_{\mathrm{nuc},(E)-\mathbf{4.3a}} \int_{6.81}^{6.84} y_t(\delta)\, d\delta \; + \; k_{\mathrm{nuc},(Z)-\mathbf{4.3a}} \int_{6.26}^{6.34} y_t(\delta)\, d\delta \; + \; k_{\mathrm{nuc},\mathbf{4.3b}} \int_{5.88}^{6.04} y_t(\delta)\, d\delta}{k_{\mathrm{nuc,SM}} \int_{5.81}^{5.86} y_t(\delta)\, d\delta \; + \; k_{\mathrm{nuc},(E)-\mathbf{4.3a}} \int_{6.81}^{6.84} y_t(\delta)\, d\delta \; + \; k_{\mathrm{nuc},(Z)-\mathbf{4.3a}} \int_{6.26}^{6.34} y_t(\delta)\, d\delta \; + \; k_{\mathrm{nuc},\mathbf{4.3b}} \int_{5.88}^{6.04} y_t(\delta)\, d\delta} \tag{8.10}$$

$$\alpha(t) \approx \frac{\int_{\mathrm{products}} y_t(\delta)\, \mathrm{d}\delta}{\int_{\mathrm{products}} y_t(\delta)\, \mathrm{d}\delta + \dfrac{k_{nuc,SM}}{k_{\mathrm{nuc},(E)-\mathbf{4.3a}}} \int_{\mathrm{SM}} y_t(\delta)\, \mathrm{d}\delta} \tag{8.11}$$

$$\text{Extent of conversion} \approx \frac{\sum \int_{products} y_t(\delta)\, \mathrm{d}\delta}{\sum \int_{\mathrm{products}} y_t(\delta)\, \mathrm{d}\delta + \; 1.06 \; \int_{\mathrm{SM}} y_t(\delta)\, \mathrm{d}\delta} \times 100\% \tag{4.1}$$

| Species | $\boldsymbol{\delta_{max}}$**/ppm** | $\boldsymbol{\delta_{min}}$**/ppm** | $\boldsymbol{\int_{\delta_{min}}^{\delta_{max}} y(\delta)\, d\delta}$ | $\boldsymbol{\frac{k_{nuc}}{k_{Me}}}$ |
|---|---|---|---|---|
| **4.2** | 5.86 | 5.81 | 1.71[a] | 0.85 |
| (*E*)-**4.3a** | 6.84 | 6.81 | 1.60[a] | 0.80 |

**Table 8.5.** Integral values from spectra of pure material of resonances used for reaction analysis. [a] Normalised integral values; hexyl-methyl resonance integral set to 3.00.

In the context of oxidation of compound **4.2**, the extent of polymerisation $\alpha_{\text{polym}}(t)$ can be expressed as the amount of starting material that has been incorporated into a polymer $n_{\text{polym}}(t)$, as a proportion of $n_0(0)$, the amount of starting material initially present (Equation 8.12). There is no characteristic resonance associated with polymerised material that is not obscured by resonance of other species, but the signal arising from the hexyl-methyl protons of all species is separate from other resonances. If the amount of non-polymerised material can be evaluated, and the contribution to the hexyl-methyl signal arising from this material can be subtracted from the value obtained by integration, then the value remaining can be used to determine $n_{\text{polym}}(t)$ indirectly.

$$\alpha_{\text{polym}}(t) = \frac{n_{\text{polym}}(t)}{n_0(0)} \qquad 8.12$$

Rearrangement of Equation 8.7 gives Expression 8.13, the formula for the contribution to an NMR signal arising from resonance of a species *i*. Summation of this expression for all species will therefore be equal to the integral of an NMR spectrum of a sample of reaction mixture taken at time *t*, within appropriate limits determined by inspection of spectra to be 0.85 – 0.92 ppm (Equation 8.14).

$$\frac{l_i n_i(t)}{k_{\text{nuc},i} k_{\text{sample}}} \qquad 8.13$$

$$\int_{0.88}^{0.92} y_t(\delta)\, d\delta = \sum_{0}^{i} \frac{l_i n_i(t)}{k_{\text{nuc},i} k_{\text{sample}}} \qquad 8.14$$

The notation $\int_{\text{methyl}} y_t(\delta)\, \mathrm{d}\delta$ is used to represent the integral of the signal arising from resonance of all hexyl-methyl protons in a $^1$H NMR spectrum $y_t(\delta)$. Assuming $k_{\text{nuc},i}$ has a

constant value $k_{\mathrm{Me}}$ for all methyl protons, and taking $l_i$ to be 3 for all $i$,[xcix] the $k$- and $l$-terms can be separated from the summation, giving Equation 8.15.

$$\int_{\text{methyl}} y_t(\delta)\,\mathrm{d}\delta \;\approx\; \frac{3}{k_{Me}k_{sample}} \sum_{0}^{i} n_i(t) \qquad 8.15$$

Rearrangement so as to make $\sum_0^i n_i(t)$ the subject gives an expression for $n_0(0)$ (see Equation 8.2); substitution of this result into 8.12 gives Equation 8.16. An expression for $n_i(t)$ applicable to non-polymerised species is described by Equation 8.7; separation of the summation into its components (again assuming that (*E*)-**4.3a**, (*Z*)-**4.3a**, and **4.3b** and polymer are the only products), and substitution of the expression for $n_i(t)$ into Equation 8.15 gives Equation 8.17. Rearrangement gives an expression for $n_{\mathrm{polym}}(t)$ (Equation 8.18), and substitution into Equation 8.16 gives Equation 8.19; cancellation of terms simplifies 8.19 to Equation 8.20, and substitution of $\frac{k_{\mathrm{nuc}}}{k_{\mathrm{Me}}}$-values obtained by NMR analysis of pure material (Table 8.5) gives Equation 8.21.

$$\alpha_{\mathrm{polym}}(t) \;\approx\; \frac{3}{k_{Me}k_{sample}\int_{\mathrm{methyl}} y_t(\delta)\,\mathrm{d}\delta}\; n_{\mathrm{polym}}(t) \qquad 8.16$$

[xcix] In this case, it should be reiterated that $n_{\mathrm{polym}}(t)$ refers to the molar quantity of monomer that has been polymerised, not the molar quantity of polymer.

$$\int_{\text{methyl}} y_t(\delta)\,\mathrm{d}\delta \;\approx\; \frac{3}{k_{Me}k_{sample}}\left(n_{polym}(t) \;+\frac{k_{\text{nuc,SM}}k_{sample}}{2}\int_{\text{SM}} y_t(\delta)\,\mathrm{d}\delta \;+\frac{k_{\text{nuc,}(E)-\mathbf{4.3a}}k_{sample}}{2}\int_{\text{products}} y_t(\delta)\,d\delta\right) \tag{8.17}$$

$$n_{polym}(t) \;\approx\; \frac{k_{Me}k_{sample}}{3}\int_{\text{methyl}} y_t(\delta)\,\mathrm{d}\delta \;-\frac{k_{\text{nuc,SM}}}{2}\int_{\text{SM}} y_t(\delta)\,\mathrm{d}\delta \;-\frac{k_{\text{nuc,}(E)-\mathbf{4.3a}}}{2}\int_{\text{products}} y_t(\delta)\,d\delta \tag{8.18}$$

$$\alpha_{\text{polym}}(t) \;\approx\; \frac{3}{k_{Me}k_{sample}\int_{\text{methyl}} y_t(\delta)\,\mathrm{d}\delta}\left[\frac{k_{Me}k_{sample}}{3}\int_{\text{methyl}} y_t(\delta)\,\mathrm{d}\delta \;-\frac{k_{\text{nuc,SM}}k_{sample}}{2}\int_{\text{SM}} y_t(\delta)\,\mathrm{d}\delta \;-\frac{k_{\text{nuc,}(E)-\mathbf{4.3a}}k_{sample}}{2}\int_{\text{products}} y_t(\delta)\,d\delta\right] \tag{8.19}$$

$$\alpha_{\text{polym}}(t) \;\approx\; 1 \;-\frac{3k_{\text{nuc,SM}}}{2k_{\text{Me}}\int_{\text{methyl}} y_t(\delta)\,\mathrm{d}\delta}\int_{\text{SM}} y_t(\delta)\,\mathrm{d}\delta \;+\frac{3k_{\text{nuc,}(E)-\mathbf{4.3a}}}{2k_{\text{Me}}\int_{\text{methyl}} y_t(\delta)\,\mathrm{d}\delta}\int_{\text{products}} y_t(\delta)\,d\delta \tag{8.20}$$

$$\alpha_{polym}(t) \;\approx\; \left(1 -\frac{1.28\int_{SM} y\,d\delta \;+\; 1.2\sum\int_{products} y\,\mathrm{d}\delta}{\int_{methyl} y_t(\delta)\,\mathrm{d}\delta}\right) \tag{8.21}$$

# Appendix 6: Details of Optimisation of Conditions for Furan Oxidation

| Entry | Additive, loading/eq. | Rxn time/ h | Conv. (NMR, %)[b] | Polymerisation (NMR, %)[c] | Product distribution (%, NMR)[d] | Yield (isolated, %) |
|---|---|---|---|---|---|---|
| 1 | Pyridine, 5 | 1.2 | 100 | 65 | 10 : 80 : 10 : 0 | - |
| | | 16.0 | 100 | 65 | (*E*)-**4.3a** only | 50[e] |
| 2 | *t*-Butanol, 5 | 1.2 | 65 | 65 | (*Z*)-**4.3a** only | - |
| | | 16.0 | - | >90 | -[f] | - |
| 3 | Ammonium acetate, 5 | 1.2 | Trace[g] | 25 | (*Z*)-**4.3a** only | - |
| | | 16.0 | - | >90 | -[f] | - |
| 4 | 2,2,2-Trifluoro-ethanol, 5 | 1.2 | 80 | 35 | 0 : 30 : 0 : 70[h] | - |
| 5 | Thiophenol, 2 | 1.5 | 0 | 30 | - | - |
| | | 3.5 | 5 | 25 | (*Z*)-**4.3a** only | - |
| | | 20.5 | 100 | - | Dec. | - |
| 6 | $CaCO_3$, 2 | 1.5 | 15 | 25 | (*Z*)-**4.3a** only | - |
| | | 3.5 | 40 | 45 | | - |
| | | 20.5 | 100 | 65 | | 39[i] |

**Table 8.6.** Details of screening for additives to inhibit decomposition; catalyst loading 0.01 eq. with respect to SM throughout. [a] Specified with respect to SM. [b] Calculated according to Equation 4.1 (see page 279) and rounded to nearest 5%. [c] Calculated according to Equation 8.21 (see page 279) and rounded to nearest 5%. [d] Ratios are (*Z*)-**4.3a** : (*E*)-**4.3a** : **4.3b** : unknown. [e] Chromatographic yield. [f] Product and possible SM NMR peaks too small to integrate accurately. [g] <5%. [h] Unknown compound may be 2,5-di(2,2,2-trifluoromethoxy)-2,5-dihydrofuran product. [i] Partial decomposition *via* intramolecular aldol reaction observed.

| Entry | Additive, loading/eq. | Rxn time/ h | Conv. (NMR, %)[b] | Polym. (NMR, %)[c] | Product distribution (%, NMR)[d] | Mass balance (%) |
|---|---|---|---|---|---|---|
| 1 | Pyridine, 10 | 1.3 | 5 | 15 | (*E*)-**4.3** only | 57 |
| 2 | Pyridine, 3 | 1.3 | 30 | 40 | (*E*)-**4.3** only | 74 |
| 3 | Pyridine, 1 | 1.3 | 20 | 30 | (*E*)-**4.3** only | 56 |
| 4 | Pyridine, 0.3 | 1.3 | 100 | 40 | 50 : 40 : 10 : 0 | 72 |
| 5 | Pyridine, 0.1 | 1.3 | 40 | 40 | 90 : 10 : 0 : 0 | 54 |
| 6 | 2,6-Di-*tert*-butylpyridine, 5 | 2.4 | 100 | 65 | 85 : 0 : 15 : 0 | - |
| | | 19.2 | 100 | 45 | 35 : 0 : 35 : 30 | 0[e] |
| 7 | 2,6-Di-*tert*-butylpyridine, 0.3 | 0.5 | Trace[f] | 30 | (*Z*)-**4.3** only | - |
| | | 1.0 | 5 | 40 | | - |
| | | 2.3 | 40 | 70 | | - |
| | | 3.4 | 70 | 80 | | 79 |
| 8 | Pyridine, 5 | 2.5 | 100 | 45 | (*E*)-**4.3** only | 76 |
| 9 | Pyridine, 2.5 | 2.0 | 75 | 55 | (*E*)-**4.3** only | - |
| | | 3.3 | 100 | 0 | 0 : 9 : 1 : 0 | - |
| | | After w/u | 100 | 0 | 0 : 9 : 1 : 0 | >99[g] |

**Table 8.7.** Details of investigations into the effect on pyridine loading, use of a hindered pyridine derivative, and the benefit of avoiding an aqueous workup procedure; Catalyst loading 0.01 eq. with respect to SM throughout. [a] Specified with respect to SM. [b] Calculated according to Equation 4.1 (see page 279) and rounded to nearest 5%. [b] Calculated according to Equation 8.21 (see page 279) and rounded to nearest 5%. [d] Ratios are (*Z*)-**4.3a** : (*E*)-**4.3a** : **4.3b** : unknown. [e] W/u afforded pyridine with (*Z*)-**4.3** and **4.3b** as minor products; no product recovered after chromatography. [f] <1%. [g] No aq. w/u, eluted through silica plug; material almost pure, but repurified by chromatography (37%).