PART I – SYNTHESIS OF PHOTOCHROMIC FULGIDES

PART II – SYNTHETIC STUDIES TOWARDS ANTI-SARS AGENT AG7088

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NATIONAL UNIVERSITY OF SINGAPORE

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SUMMARY

Photochromism is defined as a light-induced reversible change of colour. It is a process whereby, a reversible transformation of a single chemical species is being induced in one or both directions, by the absorption of electromagnetic radiation between two forms. Herein we report the design and synthesis of several photochromic fulgides, including a new class of fulgides – the Cycloalkylidene fulgides. The photochromic properties of the new fulgides were also investigated. Furthermore, the development of a new methodology towards the synthesis of the imide derivatives of the fulgides have been developed and optimized. Accomplishments include the reduction in the use of organic solvents as well as shorter reaction times used for the reactions.

Our synthetic studies towards the synthesis of anti-SARS agent AG7088 led us to the discovery of a novel methodology involving the application of indium-mediated allylation as a key step towards a key intermediate. Our study included the synthesis of 2 key fragments, towards the synthesis of AG7088. Further extension of the project involved olefin metathesis, towards other compounds, analogous to AG7088.

To further enhance our investigations, we also subjected small molecules in our molecular library to Zebrafish embryo (Danio rerio) testing. This "chemical genetic" approach is rapid, inexpensive, requires no long-term breeding, and can, in theory, target every gene product in the vertebrate genome through a variety of physiological and behavioural screens (see APPENDIX).

List of Abbreviations

anhyd	Anhydrous
Ar	Aryl
atm	Atmospheric pressure
Bp	Boiling point
br	Broad
C	Closed-form / Coloured form
Calcd	Calculated
d	Doublet
dd	Doublet of doublets
ddd	Doublet of doublet of doublets
ddt	Doublet of doublet of triplets
de	Diastereomeric excess
dq	Doublet of quartet
dt	Doublet of triplets
DMF	*N*,*N*-dimethyl formamide
DMSO	Dimethyl sulfoxide
ee	Enantiomeric excess
EI	Electron impact
equiv	Equivalent(s)
ESI	Electro-spray ionization
Expt	Experiment
FAB	Fast-atom bombardment

FGI	Functional group interconversion
FTIR	Fourier transform infrared spectrometry
h / hr	Hour(s)
hept	heptet
Hex	Hexane
HRMS	High resolution mass spectrometry
Hz	Hertz
iPr	Isopropyl
IUPAC	International Union of Pure and Applied Chemistry
M	Molar concentration
m	Multiplet
MALDI-TOF	Matrix assisted laser desorption ionization – Time of flight
Me	Methyl
MHz	Mega hertz
mL	Milliliters
mmol	Millimole
mol%	Mole percent
Mp	Melting point
MS	Mass spectrometry
ms	Molecular sieves
nm	Nanometers
O	Open-form
NMR	Nuclear magnetic resonance
Ph	Phenyl

ppm	Parts per million
Pr	Propyl
q	Quartet
quint	Quintet
rbf	Round bottom flask(s)
rt	Room temperature
s	Singlet
t	Triplet
THF	Tetrahydrofuran
TLC	Thin layer chromatography
UV-Vis	Ultraviolet-Visible

PART I

PART I – SYNTHESIS OF PHOTOCHROMIC FULGIDES

PART I

CHAPTER 1

Introduction to Photochromism

1.1. INTRODUCTION TO PHOTOCHROMISM

Photochromism is defined as a light-induced reversible change of colour. It is a process whereby, a reversible transformation of a single chemical species is being induced in one or both directions, by the absorption of electromagnetic radiation between two forms. The two states will subsequently have different absorption spectra.[1] In addition, Organic Photochromism is straightforwardly defined as a light-induced reversible change of colour of organic molecules.

To elaborate further, two chemical species namely, A and B, having different absorption spectra will be used as a simple model (Figure 1). The thermodynamically stable form A is transformed by irradiation into form B. The back reaction can occur thermally (*Photochromism of **type T***) or photochemically (*Photochromism of **type P***).

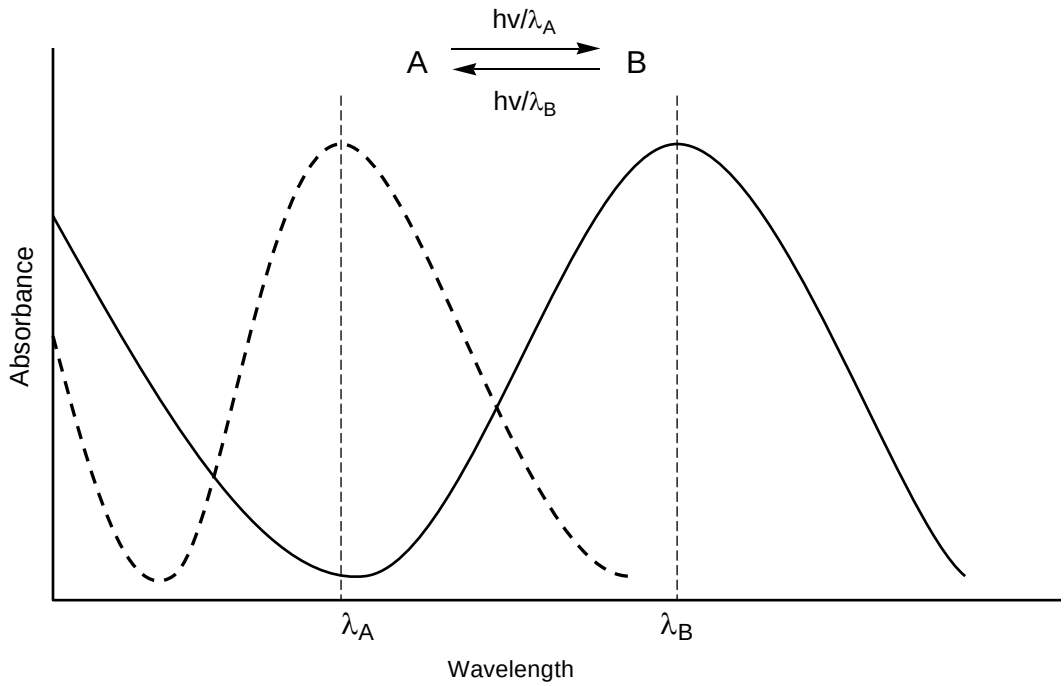


Figure 1. Diagram depicting photochromism of molecule A, converting to molecule B

[1] *Photochromism: Molecules and Systems*; Dürr, H.; Bouas-Laurent, H.; Eds. Elsevier, Amsterdam, **1990**.

The most prevalent organic photochromic systems involve unimolecular reactions. Most common photochromic molecules have a colourless or pale yellow form A and a coloured form B (e.g., red or blue). This phenomenon is referred to as positive photochromism. Other systems are bimolecular, such as those involving photocycloaddition reactions. When λ_{max} (A) > λ_{max} (B), photochromism is negative or inverse.

1.2. INTRODUCTION TO FULGIDES – A *HISTORICAL* REVIEW OF FULGIDE CHEMISTRY

Hans Stobbe[2] first investigated fulgides[3] around the turn of the century. He reported their synthesis by the reaction now known as the Stobbe Condensation, which was extensively investigated by Johnson and his co-workers who reviewed the subject in 1951.[4] Fulgides were first and extensively synthesized by Stobbe *et al.* early in the 20th century.[2, 5] Stobbe, in his article stated that he named the derivatives of 1,3-butadiene-2,3-dicarboxylic acid and its acid anhydride as "fulgenic acid" and "fulgide" respectively (Figure 2). The name fulgide[6] was derived due to the fact that some of the derivatives exhibited a variety of characteristic colours by light and they usually formed shiny crystals.

[2] Stobbe, H. *Die Fulgide, Annalen* **1911**, *380*, 1-129.
[3] Stobbe, H. *Ber.* **1904**, *37*, 2236.
[4] *Org. Reactions. 6*; Johnson, W. S.; Daub, G. H.; **1951**.
[5] Stobbe, H. *Ber. Dtsch. Chem. Ges.* **1905**, *40*, 3372-3382.
[6] *Latin* word "*fulgere*" means to glitter or shine.

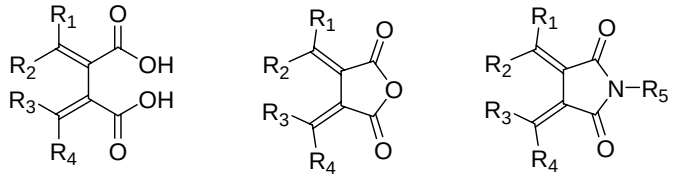
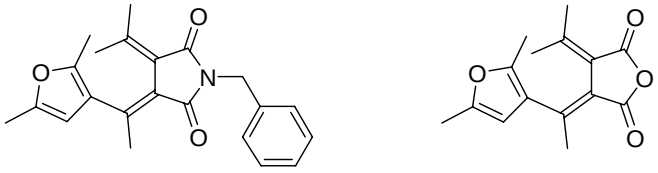


Figure 2. Depicts fulgenic acid, fulgide and fulgimide generic molecular structure with different R_n substituents

The name "fulgimide" was first introduced by Heller *et al.*[7] for the succinimide of the corresponding fulgide (Figure 2), though fulgimides had been synthesized earlier by Goldschmidt and co-workers in 1957.[8] Fulgimides have been widely prepared so far, because it is convenient to attach another substituent onto the fulgide core without a significant change of photochromic properties. Such molecular tailoring of the original fulgide moiety have been carried out by several groups (e.g., Tomoda *et al.* and Matsushima *et al.*)[9a, b] and many articles have also been published in the 1990s.[10a-e] As an illustration, fulgimides were used for the attachment of the fulgide core to side chains of polymers,[10a, b] attachment of a fluorescent group for control of fluorescence[10c] and binding to proteins for regulation of substrate binding.[10d, e]

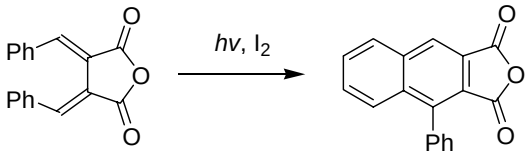
[7] Heller, H. G.; Hart, R. J.; Salisbury, K. *J. Chem. Soc., Chem. Commun.* **1968**, 1627-1628.
[8] Goldschmidt S.; Riedle, R.; Reichardt, A. *Justus Liebigs Ann. Chem.* **1957**, *604*, 121-132.
[9] (a) Tomoda, A.; Tsuboi, H.; Kaneko, A.; Matsushima, R. *Nippon Kagaku Kaishi* **1993**, 209-212. (b) Matsushima, R.; Sakaguchi, H. *J. Photochem. Photobiol., A* **1997**, *108*, 239.
[10] (a) Deblauwe, V.; Smets, G. *Makromol. Chem.* **1988**, *189*, 2503-2512. (b) Cabrera, I.; Dittrich, A.; Ringsdorf, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 76-78. (c) Walz, J.; Ulrich, K.; Port, H.; Wolf, H. C.; Wonner, J.; Effenberger, F. *Chem. Phys. Lett.* **1993**, *213*, 321-324. (d) Willner, I.; Rubin, S.; Wonner, J.; Effenberger, F.; Bäuerle, P. *J. Am. Chem. Soc.* **1992**, *114*, 3150-3151. (e) Willner, I.; Lion-Digan, M.; Rubin, S.; Wonner, J.; Effenberger, F.; Bäuerle, P. *Photochem. Photobiol.* **1994**, *59*, 491-496.



1 **2**

Figure 3. Fulgimide **1** more fatigue resistant as compared to furyl-fulgide **2**

Comparison of various heteroaromatic fulgides and fulgimides was undertaken by Tomoda *et al.* and Matsushima *et al.*, and superior resistance toward hydrolysis of the imide ring in protic solvents was shown.[9a, b] For example, *N*-benzylfulgimide **1** (Figure 3) was shown to be more resistant to fatigue when compared to the corresponding furyl-fulgide **2**.



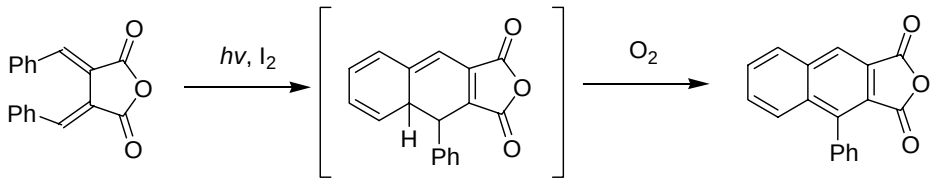
3 **4**

Scheme 1. Photocyclization of bisbenzylidenefulgide **3**

The chemistry of the fulgides was reported in an article by Hans Stobbe in 1907. At that time, the photocolouration mechanism of fulgides was not known. However, Stobbe noticed that 1-phenylnaphthalene-2,3-dicarboxylic anhydride, **4**, was formed from photoirradiation of bisbenzylidenefulgide, **3**, in a benzene or chloroform solution, in the presence of iodine (Scheme 1).[11]

[11] Stobbe, H. *Ber. Dtsch. Chem. Ges.* **1907**, *40*, 3372-3382.

The colouration of the fulgides was believed to occur by *E*-*Z* isomerization of a double bond until the 1960s.[12a, b] Other hypotheses such as formation of coloured radical intermediates during photocyclization[13] and photochemical change between the electronic mesomeric forms[14] were also considered. In 1968, Becker *et al.* confirmed that the coloured form of **3** was oxidized, this time by dioxygen, to yield 1-phenylnaphthalene-2,3-dicarboxylic anhydride **4**. They proposed that photochromism of **3** was due to photocyclization to the 1,8a-dihydro-1-phenylnaphthalene-2,3-dicarboxylic anhydride (1,8a-DHN), **3C,** to account for the formation of 1-phenylnaphthalene anhydride, **4**, from the photooxidation of fulgide **3**.[15]

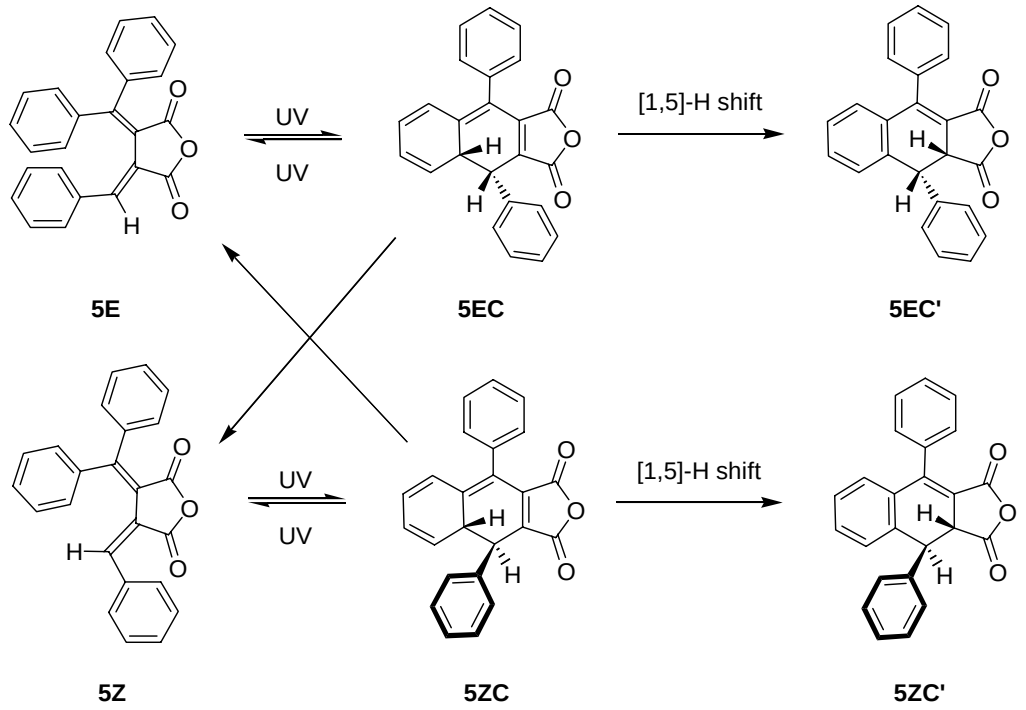


3 **3c** **4**

Scheme 2. Deduction of 1,8a-dihydro-1-phenylnaphthalene-2,3-dicarboxylic anhydride **3c**

The reinvestigation by Heller *et al.* of the reactions of yellow *E*- and *Z*-benzylidene (diphenylmethylene)-succinic anhydrides **5E** and **5Z** showed that they underwent reversible photochemical conrotatory ring closure to form red *cis*- and *trans*-1,8a-DHN intermediates (1,8a-DHNs) **5EC** and **5ZC** respectively. These molecules showed that they also underwent ring opening by a disrotatory mode to yield *Z*- and *E*-fulgides, **5Z** and **5E** respectively.

[12] (a) Chakraborty, D. P.; Sleigh, T.; Stevenson, R.; Swoboda, G. A.; Weinstein, B. *J. Org. Chem.* **1966**, *31*, 3342-3345. (b) Brunow, G.; Tylli, H. *Acta Chem. Scand.* **1968**, *22*, 590-596.
[13] Schonberg, A. *Trans. Faraday Soc.* **1936**, *32*, 514-521.
[14] Gheorghiu, C. V. *Bull. Ec. Polytech. Jassy* **1947**, *2*, 141-155.
[15] Santiago, A.; Becker, R. S. *J. Am. Chem. Soc.* **1968**, *52*, 3654-3658.

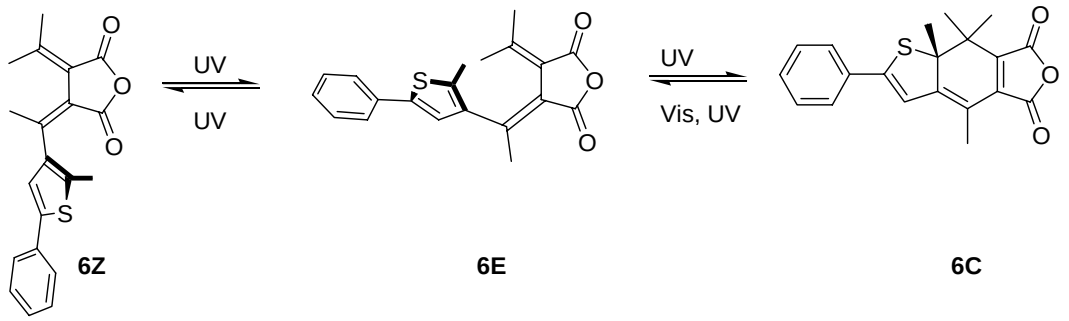


Scheme 3. Heller *et al.* investigated and confirmed the presence of [1,5]-H shifts on prolonged UV-irradiation of fulgides **5E** and **5Z**

Eventually, irreversible rearrangement occurs to lead to the colourless *cis*- and *trans*-1,2-DHNs, **5EC'** and **5ZC'** in two competing thermal processes (Scheme 3).[16] Other related studies have also been reported.[17] On exposure to visible light, 1,8a-DHNs undergo photochemical conrotatory ring opening to the corresponding fulgides.

Since then the colouration mechanism of fulgide has been well understood as the photochemical 6π-electrocyclization of the hexatriene moiety.[18]

[16] Hart, R. J.; Heller, H. G. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1321-1323.
[17] Heller, H. G.; Szewczyk, M. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1487-1492.
[18] Heller, H.G.; Oliver, S. *J. Chem Soc. Perkin Trans. 1.* **1981**, 197. (b) Darcy, P. J.; Heller, H. G.; Strydom, P. J.; Whittall, J. *J. Chem. Soc. Perkin Trans. 1* **1981**, 202. (c) Heller, H. G.; Langan, J. R. *J. Chem Soc., Perkin Trans. 2* **1981**, 341.



Scheme 4. X-ray crystallographic analysis of the coloured form of **6C**

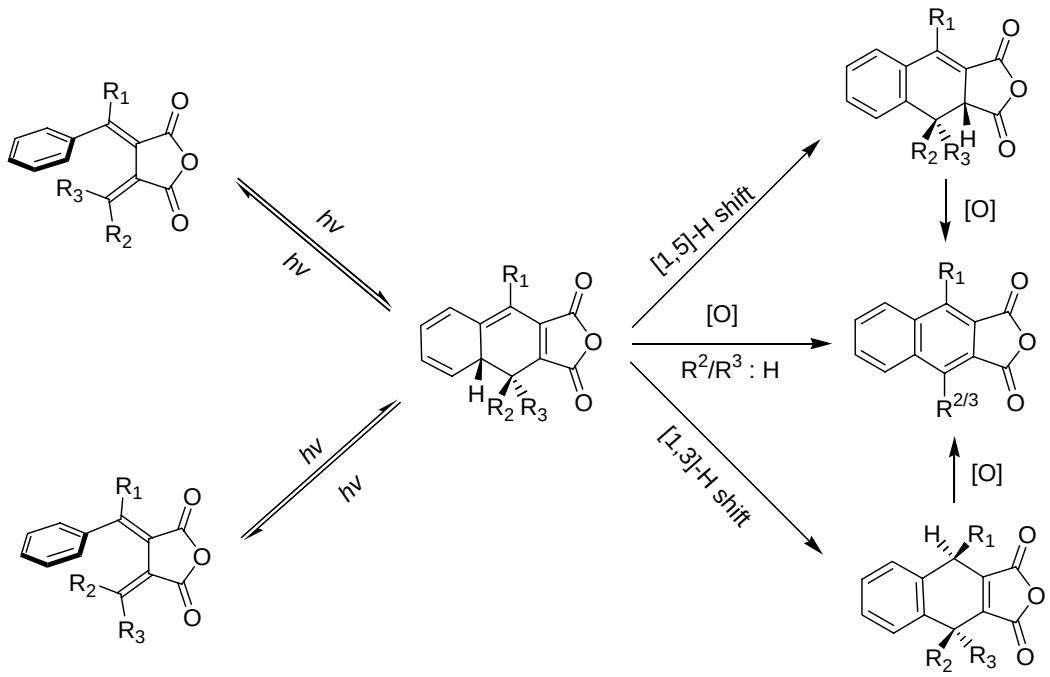
In 1984, Kaftory succeeded in the X-ray crystallographic analysis of the coloured form of a thienylfulgide, **6C** (Scheme 4).[19] This result determined the structure of the coloured form and the photocolouration mechanism unequivocally.

From the late 1960s through the 1970s Heller *et al.* published a series of articles entitled "Overcrowded Molecules",[20a-q] in which the chemistry of fulgides and closely related compounds was dealt with. They clarified the thermal reactions of the coloured form of fulgides as shown (Scheme 5).[20p, q, 21a, b]

[19] Kaftory, M. *Acta Crystallogr.* **1984**, *40*, 1015-1019.

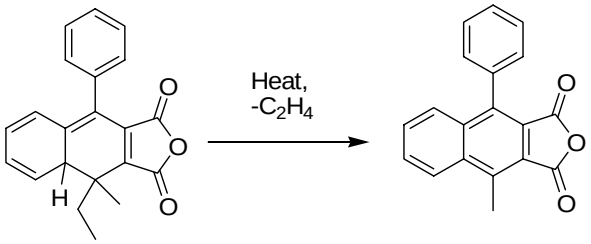
[20] (a) Heller, H. G.; Auld, D.; Salisbury, K. *J. Chem. Soc. C* **1967**, 682-685. (b) Heller, H. G.; Auld, D.; Salisbury, K. *J. Chem. Soc. C* **1967**, 1552-1554. (c) Heller, H. G.; Auld, D.; Salisbury, K. *J. Chem. Soc. C* **1967**, 2457-2459. (d) Heller, H. G.; Salisbury, K. *J. Chem. Soc. C* **1970**, 399-402. (e) Heller, H. G.; Salisbury, K. *J. Chem. Soc. C* **1970**, 873-874. (f) Heller, H. G.; Salisbury, K. *J. Chem. Soc. C* **1970**, 1997-2000. (g) Hart, R. J.; Heller, H. G. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1321-1323. (h) Hastings, J. S.; Heller, H. G. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1839-1842. (i) Heller, H. G.; Megit, R. M. *J. Chem. Soc., Perkin Trans. 1* **1974**, 923-927. (j) Heller, H. G.; Szewczyk, M. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1487-1492. (k) Hastings, J. S.; Heller, H. G.; Tucker, H.; Smith, K. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1545-1548. (l) Hastings, J. S.; Heller, H. G.; Salisbury, K. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1995-1998. (m) Hart, R. J.; Heller, H. G.; Megit, R. M.; Szewczyk, M. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2227-2232. (n) Darcy, P. J.; Hart, R. J.; Heller, H. G. *J. Chem Soc., Perkin Trans. 1* **1978**, 571-576. (o) Heller, H. G.; Piggott, R. D. *J. Chem. Soc., Perkin Trans. 1* **1978**, 989-994. (p) Crescente, O.; Heller, H. G.; Oliver, S. *J. Chem. Soc., Perkin Trans. 1* **1979**, 150-153. (q) Heller, H. G.; Oliver, S.; Shawe, M. *J. Chem. Soc., Perkin Trans. 1* **1979**, 154-157.

[21] (a) *4+2 Systems: Fulgides. Photochromism: Molecules and Systems;* Whittall, J.; Elsevier: Amsterdam, **1990**, 467-492. (b) Heller, H. G.; Oliver, S. *J. Chem. Soc., Perkin Trans. 1* **1981**, 197-201.



Scheme 5. Thermal reactions of fulgides as reported by Heller and co-workers

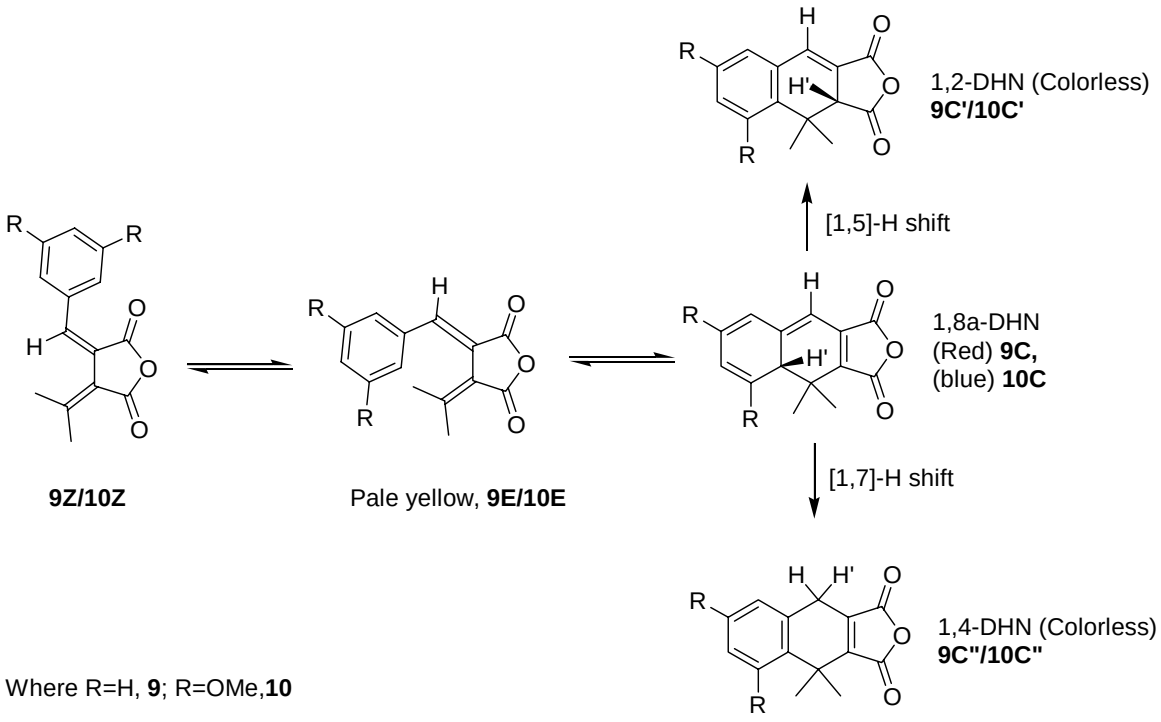
Other than the thermal ring opening, the major thermal reactions are hydrogen rearrangement and (or followed by) dehydrogenative aromatization.



7 **8**

Scheme 6. Ethene liberated to gain aromaticity

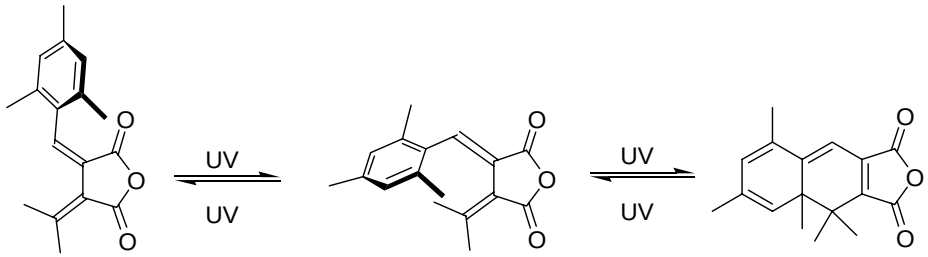
They observed that even ethene was liberated by thermal treatment of cyclized fulgide, **7** to gain aromaticity, to form molecule **8** (Scheme 6).[20n]



Scheme 7. [1,5]- and [1,7]-H shifts that will lead to a loss of colour of the cyclized fulgide

Heller *et al.* also reported that the weakly photochromic pale yellow *E*-fulgide **9E** (R=H) photoisomerizes reversibly to the *Z*-fulgide **9Z** and photocyclizes to the red **9C**. The red **9C** eventually undergoes a 1,5-H shift to form the colourless 1,2-DHN **9C'**. The introduction of methoxy substituents in the 3- and 5- positions of the phenyl moiety results in a more strongly photochromic fulgide, **10E** (R=OMe).

Fulgide **10E** can photocyclize to form the deep blue 1,8a-DHN, **10C**, which can in turn undergo a photochemical 1,7-H shift to the colourless 1,4-DHN **10C"** on prolonged UV irradiation in toluene. The deep blue 1,8a-DHN, **10C** can also undergo the thermal 1,5-H shift to form the 1,2-DHN **10C'** (Scheme 7). These photochromic fulgides have high intrinsic fatigue, namely photodehydrogenation to the naphthalene derivatives, or hydrogen-shift reactions to form the 1,2- or 1,4-dihydronaphthalene derivatives via their intermediates (DHNs).

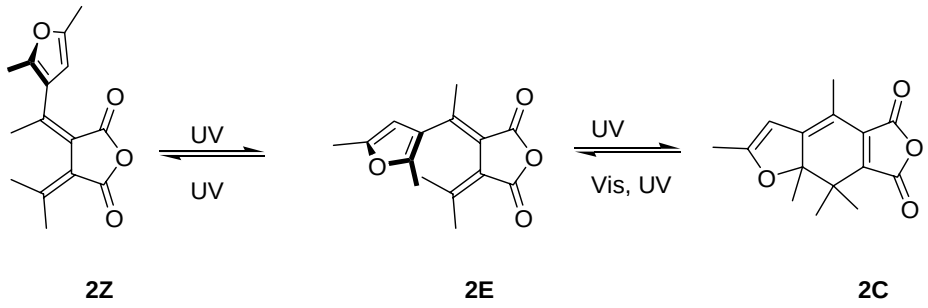


11Z **11E** **11C**

Scheme 8. Side reactions can be prevented by removing reactive hydrogens

Heller *et al.* also further reported that fulgide **11Z/11E**, having a mesitylmethylene group, instead of the benzylidene group and an isopropylidene (IPP) group, prevented the side reactions in which the hydrogen atoms on the ring closing carbon atoms were involved, since there was no hydrogen to rearrange or to be removed (Scheme 8). Furthermore, the vicinal methyl groups on the ring closing aromatic carbon atoms prevented the thermal ring opening of the *C*-form, **11C**, which should occur by way of, different from the photochemical ring opening, the disrotatory pathway; by the steric repulsion between them.

Indeed, they observed that the colour did not fade at 160°C. Unfortunately, the conversion ratio to the coloured form at the photostationary state (pss) was so low that almost no coloured form remained when the solution of the colourless form of **11E** was irradiated with 366 nm light until it reached the photostationary state.[20i]



Scheme 9. Photochromism of 2, 5-dimethyl-3-furyl fulgide **2**

Seven years later, in 1981, Heller reported the photochromism of a 2,5-dimethyl-3-furyl fulgide **2** (Scheme 9).[22a, b] For the same reasons as the mesityl-substituted fulgide **11**, furyl-fulgide **2** showed neither the side reactions nor the detrimental thermal back-reaction. Furthermore, because **2C** had a small molar absorption coefficient at 366 nm where **2E** had a large absorption, the photochemical back-reaction from **2C** to **2E** upon irradiation by 366 nm light was negligible. Therefore, the conversion of **2E** to **2C** was close to 100%. The thermally irreversible photochromic fulgide has been realized for the first time with molecule **2**.

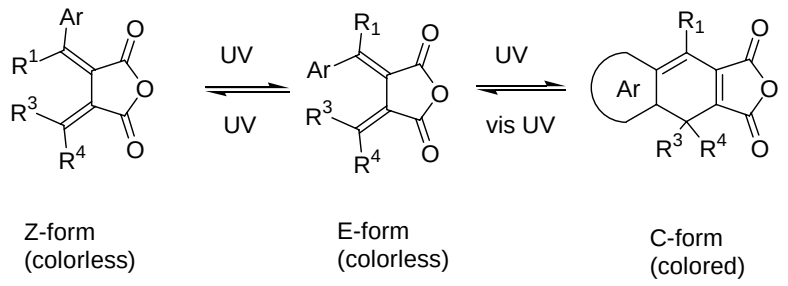
This furyl-fulgide, **2**, is the monument of the long research history of the photochromism of fulgides, as one challenge faced by researchers in this field was to design thermally stable, fatigue-resistant photochromic fulgides that would potentially be suitable for commercial applications. This included optical recording and security printing. The compounds should have high quantum efficiencies for colouring and bleaching and also achieve high conversions into the coloured forms. The valuable information for the molecular design to append thermal irreversibility, i.e., (1)

[22] (a) Heller, H. G.; Oliver, S. *J. Chem. Soc., Perkin Trans. 1* **1981**, 197-201. (b) Darcy, P. J.; Heller, H. G.; Strydom, P. J.; Whittall, J. *J. Chem.Soc., Perkin Trans. 1* **1981**, 202-205.

introduction of substituents other than hydrogen onto the ring-closing carbon atoms and (2) employing a heteroaromatic ring, was thus brought about.

The possible application of thermally irreversible photochromic compounds such as **2** is in rewritable optical recording media.[23a-c] The 1980s and early 1990s were devoted to improve the properties of **2**, while after the early 1990s to date, development of new fulgides rather than improvement has been the main research interest. In this aspect, our efforts have been directed towards the extension of current fulgide chemistry, with the main aim, being the discovery of new photochromic fulgides that might display interesting and possibly useful properties.

1.3. PHOTOCHROMISM OF FULGIDES



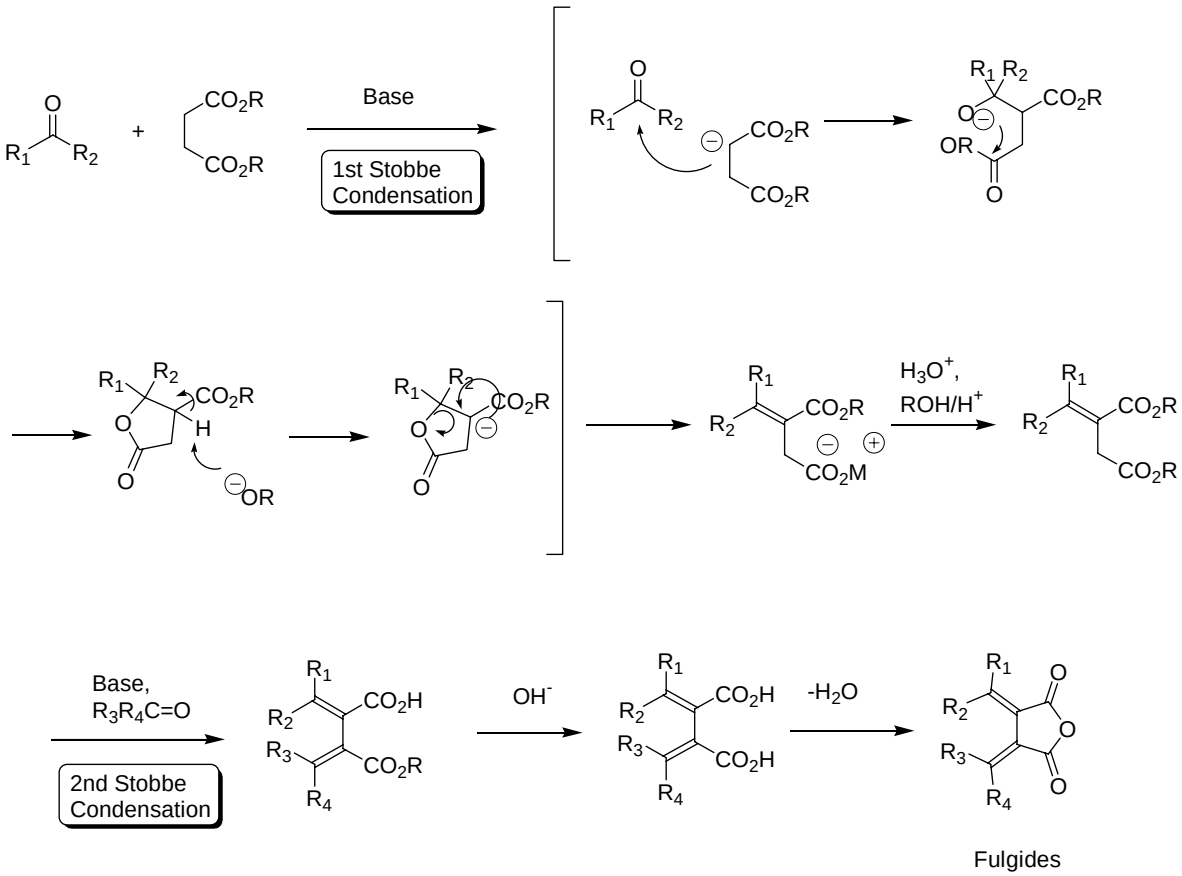
Scheme 10. Photochromism of fulgide under UV irradiation

The photochromism of a fulgide occurs between one of the colourless open forms (hereafter abbreviated as the "*E*-form" (*E*) (Scheme 10) because the geometry of the double bond connecting the aromatic ring and the succinic anhydride is usually *E* and the photocyclized coloured form (abbreviated as the *C*-form (*C*)). However,

[23] (a) Heller, H. G. *Spec. Publ., R. Soc. Chem., Fine Chem. Electron. Ind.* **1986**, *60*, 120-135. (b) *Photochromics for the Future.*; Heller, H. G.; *Electronic Materials, from Silicon to Organics*; Miller, L. S., Mullin, J. B., Eds.; Plenum Publishing, New York, **1991**, 471-483. (c) Feringa, B. L.; Jager, W. F.; de Lange, B. *Tetrahedron* **1993**, *49*, 8267-8310.

there is an additional photochemical *E*-*Z* isomerization pathway. The "*Z*-form" (*Z*), the geometrical isomer of the *E*-form, is not considered as an important member of the photochromic system. To date, there has been no report that the *Z*-form cyclizes directly by absorbing one photon to give the *C*-form. Therefore, *E*-to-*Z* photoisomerization, competing with the photochromic *E*-to-*C* isomerization, is an energy-wasting as well as system-complicating process in terms of "photochromism of fulgides".

1.4. The Stobbe Condensation



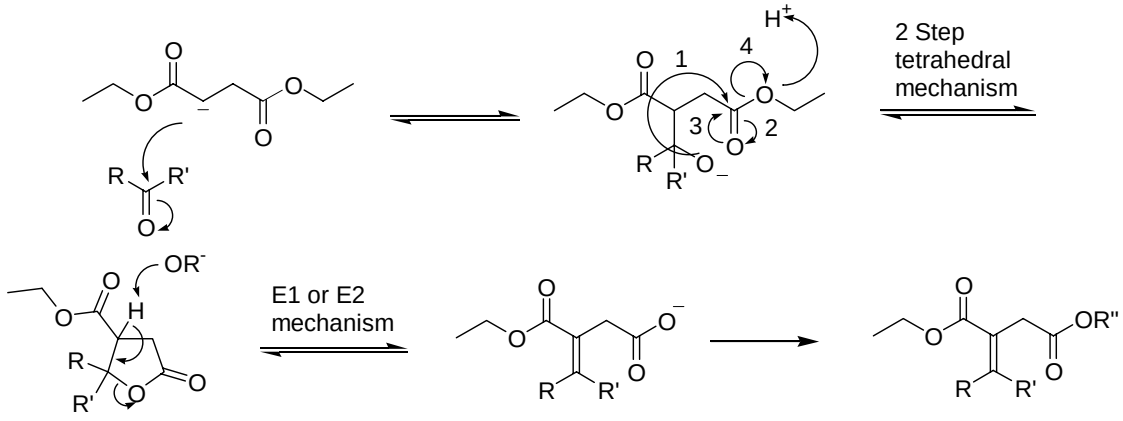
Scheme 11. Synthesis of fulgides via Stobbe condensations

The Stobbe condensation is generally an aldol-type reaction, namely, between carboxylic esters and aldehydes or ketones.[24] This reaction is used widely for the synthesis of target fulgides (Scheme 11). In the presence of a strong base, the α–carbon of a carboxylic ester can condense with the carbonyl carbon of an aldehyde or ketone to give a β-hydroxy ester,[25] which may or may not be dehydrated to the α,β-unsaturated ester. This reaction is sometimes called the Claisen condensation.[26] It is also possible for the α-carbon of an aldehyde or ketone to add to the carbonyl carbon of a carboxylic ester, but this involves nucleophilic substitution and not addition to a C=O bond. It can, however, be a side reaction if the aldehyde or ketone has an α-hydrogen.

Besides ordinary esters (containing an α-hydrogen), the reaction can also be carried out with lactones and with the γ-position of α,β-unsaturated esters. For most esters, a much stronger base is needed, than for aldol reactions ($(^{i}Pr)_2NLi$, Ph_3CNa and $LiNH_2$ are among those employed). However, one type of ester reacts more easily, and such strong bases are not needed: Diethyl succinate and its derivatives condense with aldehydes and ketones in the presence of bases such as NaOEt, NaH, or $KOCMe_3$. One of the ester groups (sometimes both) is hydrolyzed in the course of the reaction.

[24] For a review, see *Org. React*. Johnson, D. **1951**, *6*, 1-73.
[25] If the reagent is optically active because of the presence of a chiral sulfoxide group, the reaction can be enantioselective. For a review of such cases, see *Solladie Chimia*, **1984** *38*, 233-243.
[26] Because Claisen discovered it: *Ber*. **1890,** *23*, 977

1.5. The Stobbe Condensation mechanism



Scheme 12. The Stobbe Condensation mechanism

The mechanism of the Stobbe condensation was elucidated by Johnson *et al.*[27] who demonstrated the formation of an intermediate lactonic ester that subsequently undergoes an irreversible base induced elimination to give the half-ester product (Scheme 12). The anion formed after base addition would attack the electrophilic carbonyl compound. Subsequently, the electron rich oxyanion would then attack the electrophilic ester motif and would undergo a 2-step tetrahedral mechanism which would lead to the lactone transition state. In the presence of a base, the lactone would undergo a E1 or E2 mechanism which would lead to the anionic intermediate, which is hydrolysed to form the half-acid intermediate. Acid-catalysed esterification would afford the subsequent diester. The mechanism accounts for the fact the succinic esters react so much better than others. It also accounts for the mono ester group which is always being cleaved. Furthermore, the alcohol is not the product but the olefin. In addition, intermediate lactones have been isolated from the mixture.[28] The isolation of the lactone intermediates have also been carried out in our lab, as described in the following chapter.

[27] Dunnigan, D. A.; Johnson, W. S.; McClaskey, A. L. *J. Am. Chem. Soc.*, **1950**, *72*, 514.
[28] Robinson, S. *J. Chem. Soc*. **1941**, 582.

1.6. STRATEGY OF MODIFICATION OF FULGIDE CORE STRUCTURE

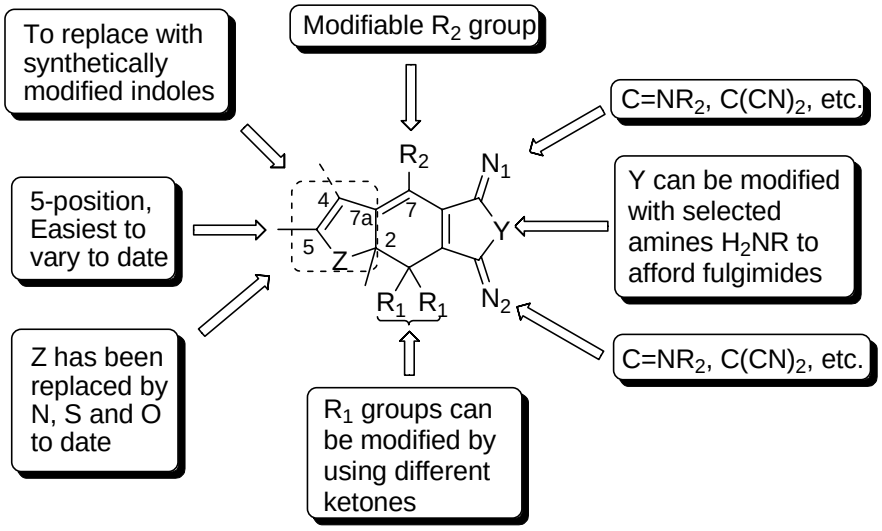


Figure 4. Modification strategy of fulgide structure

As the photochemical 6π-electrocyclization is a known photochromic mechanism, modification of the carbonyl groups, as well as the aromatic rings have been carried out and have been reported extensively by several groups. The process obeys the Woodward-Hoffmann rules (i.e., the photochemical rearrangement occurs in conrotatory fashion).[29] Replacement of the acid anhydride moiety with other functional groups have been carried out.

We seeked to study the modification of this fragment of the molecule by substituting the heteroaromatic fragment with synthetically modified indoles (Figure 4). The replacement of the hydrogen at the fifth position on the heteroaromatic fragment was another avenue we could explore. Our strategy towards the synthetic study of fulgides commenced with the synthesis of reported fulgides. To date, the

[29] Darcy, P. J.; Heller, H. G.; Strydom, P. J.; Whittall, J. *J. Chem. Soc., Perkin Trans. 1.*, **1981**, 202-205.

heteroatom, Z, has been replaced by oxygen, sulphur and nitrogen. Changing the heteroatom from O to S and to N causes the colour of the *C*-form to change from red to purple to blue, respectively.[30a, b] As such, we were also interested in the synthesis of such molecules in order to study their photochromic properties and explore the possibility of further modification.

We also undertook the study of the replacement of the R_1 group with some selected ketones in order to synthesize another class of fulgides that, to our knowledge, have not been reported. The R_2 functionality was another option we had to explore the possibility of fulgide modification. The groups N_1 and N_2 can also be modified at a later stage once the target fulgide has been achieved. Last, but most importantly, we were also interested in the exploration of the synthesis of the imide derivatives of selected fulgides, in order to explore the possibility of discovering more robust photochromic compounds.

[30] Heller, H. G., Harris, S. A., Oliver, S. N. *J. Chem. Soc., Perkin 1*. **1991**, 3259. (b). Heller, H. G., Glaze, A. P., Whittall, J. *J. Chem. Soc., Perkin 2*. **1992**, 591.

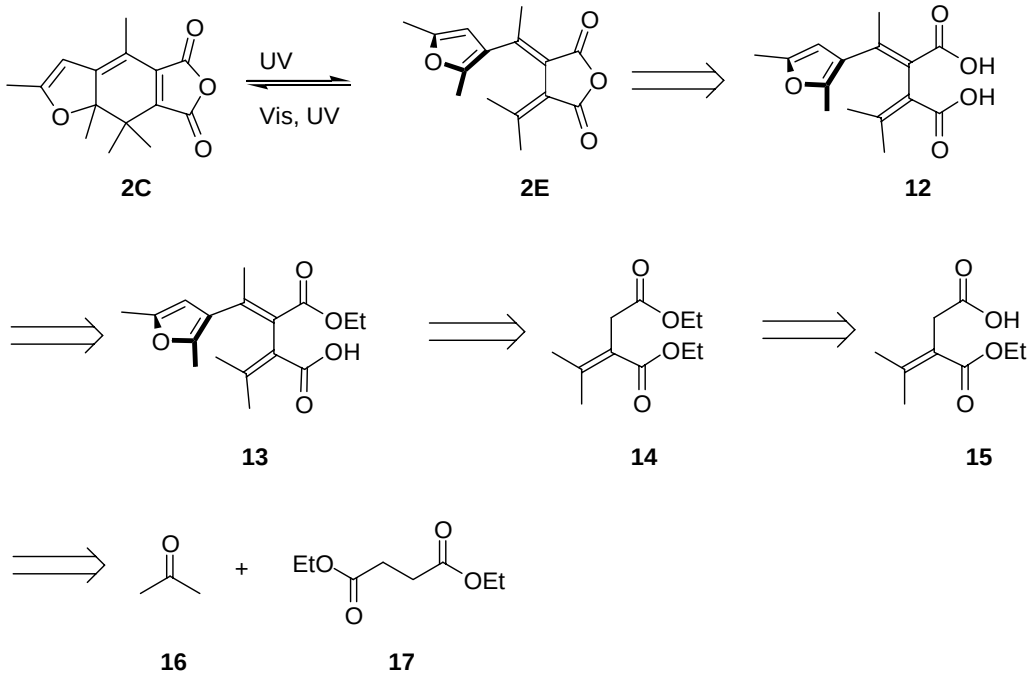
PART I

CHAPTER 2

Synthesis of Model Fulgides

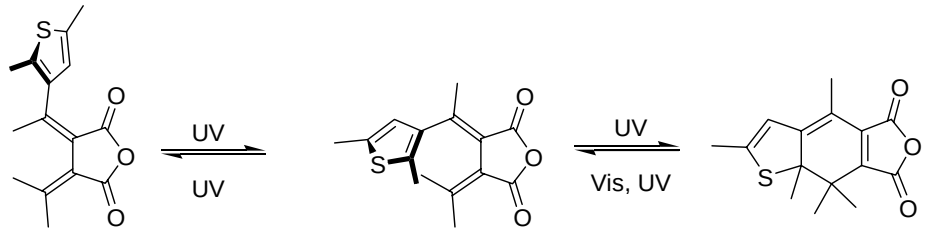
2.1. PRELIMINARY SYNTHESIS OF PHOTOCHROMIC FULGIDES

As a preliminary investigation of the overall synthetic route and reaction dynamics, several fulgides that have been reported previously were chosen. With reference to Scheme 13, the highly photochromic **2E** (*E*)-2-[a-(2,5-dimethyl-3-furyl)ethylidene]-3-isopropylidenesuccinic anhydride, as previously reported by Heller *et al.* was synthesized to explore its photochromic properties.



Scheme 13. Retrosynthetic route of 2,5-dimethyl-3-furyl fulgide, **2**

As we can see from Scheme 13, retrosynthesis of fulgide **2** will lead to diacid **12**, which can be afforded from the mono-acid **13**, synthesized from the second Stobbe condensation with the selected ketone or aldehyde. This mono-acid **13** can be obtained from the isopropylidene (IPP) diester, **14**, synthesized from the first condensation of acetone, **16**, and diethyl succinate, **17**.



18Z **18E** **18C**

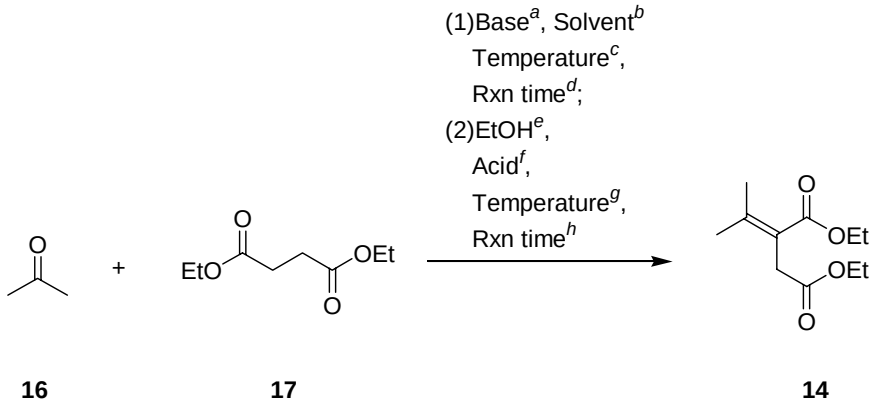
Scheme 14. Photocyclization of **18E** to form **18C**, 7,7a-dihydrobenzothiophene derivative (DHBT)

As a key comparison of intrinsic photochromic properties, **18E** (*E*)-2-[a-(2,5-dimethyl-3-thienyl)ethylidene]-3-isopropylidene-succinic anhydride and **18Z** (*Z*)-2-[-(2,5-dimethyl-3-thienyl)ethylidene]-3-isopropylidene-succinic anhydride (Scheme 14) were also synthesized according to literature with a modification of some reaction conditions and reagents used (Scheme 14).[31] In order to obtain the target fulgides **2** and **18**, the IPP diethyl succinate diester had to be synthesized first as shown in the retro-synthetic pathway (Scheme 13).

The synthesis of the IPP diester **14** was first carried out using potassium tert-butoxide according to the procedure reported by Overberger and Johnson *et al.* (Scheme 15),[32a, b] in 1949 and 1951 respectively. The initial yield (Table 2) of the diester obtained was very low (10 – 27%) and did not warrant a scale up of the reaction (Entries 1 and 2, Table 2). As the reaction did not proceed smoothly, we decided to adopt another more recent procedure as reported by Lees and co-workers[33] in 2001, for the first Stobbe condensation.

[31] Glaze, A. P.; Harris, S. A.; Heller, H. G.; Johncock, W.; Oliver, S. N.; Strydom, P. J.; Whittall, J., *J. Chem. Soc., Perkin Trans. 1* **1985**, *5*, 957-61.
[32] (a) Overberger, R.*; J. Am. Chem. Soc*. **1949**, *71*, 3681 (b) *Org. React.* Johnson, W. S.; Daub, G. H. **1951**, *6*, 1-73.
[33] Thomas, C. J.; Wolak, M. A.; Birge, R. R.; Lees, W. J. *J. Org. Chem.*, **2001**, *66*, 1914-1918.

However, when we followed the procedure as reported, we found that the reaction either afforded low yields or no diester was produced at all. Using an excess of the ^{t}BuOK also did not afford yields that were comparable to the reported literature (up to 75%). In this aspect, we decided to use NaH as the base of choice instead of ^{t}BuOK. Upon increasing reaction times (Tables 1 and 2) of both the base condensation as well as the esterification step (Entries 3 and 4, Table 2), we were able to optimize diester **14**, scale up and obtain yields of up to 68%, after distillation of the crude reaction mixture (Entry 5, Table 2).



Scheme 15. First Stobbe condensation to form IPP diester, **14**

Table 1. First Stobbe condensation (Base condensation) and optimization

Entry	Scale	Base[a]	Solvent[b]	Temp[c](°C)	Rxn time[d](hr)
1	5 mM	^{t}BuOK	THF	0 – reflux	6
2	10 mM	^{t}BuOK	THF	0 – reflux	18
3	10 mM	NaH	THF	0 – r.t.	18
4	20 mM	NaH	THF	0 – r.t.	20
5	0.1 M	NaH	THF	0 – r.t.	18

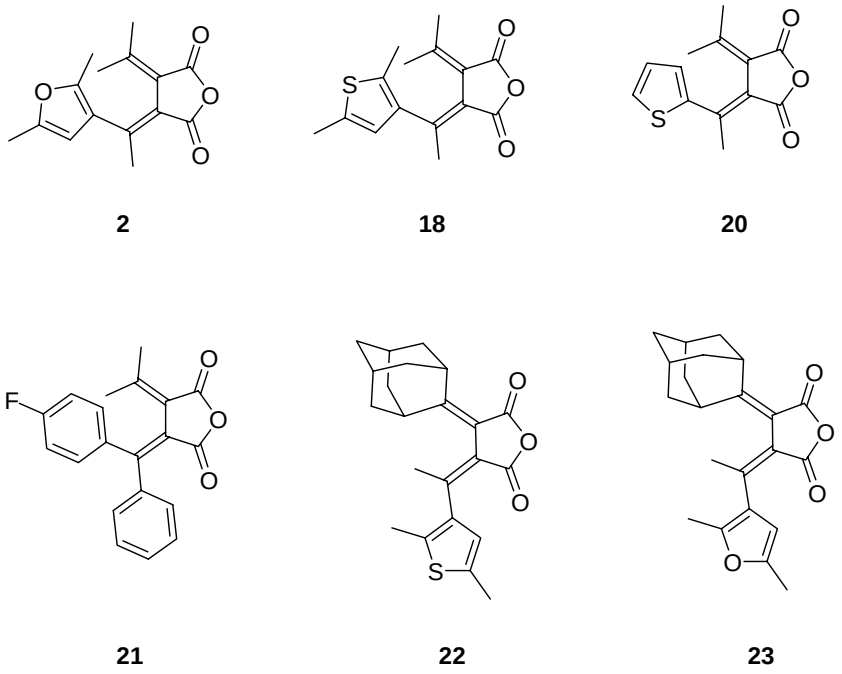
a: Base used for 1st stobbe condensation; *b:* Solvent used for reaction(pre-dried);
c: Temperature of the reaction; *d:* Reaction time.

Table 2. Acid-catalysed esterification and optimization

Entry	Solvent[e]	Acid[f]	Temp[g](°C)	Rxn time[h](hr)	% Yield[i]
1	EtOH	AcCl	r.t.	24	10
2	EtOH	5N H_2SO_4	reflux	24	27
3	EtOH	5N H_2SO_4	reflux	12	36
4	EtOH	5N H_2SO_4	reflux	18	56
5	EtOH	5N H_2SO_4	reflux	20	68

e: Solvent used for reaction; *f:* Acid used; *g:* Temperature of the reaction;
h: Reaction time; *i:* Percentage yield spectroscopically determined.

After the successful synthesis of the target diester, we went on to synthesize several model fulgides as a general study of the dynamics of the reaction route. We decided to further modify the reported procedures in order to achieve optimum yields. We observed that, upon lengthening the reaction times and using an excess of selected reagents, we were able to enable the second key Stobbe condensation of some selected ketones onto the IPP diester to afford the model fulgides that we desired.



2 **18** **20**

21 **22** **23**

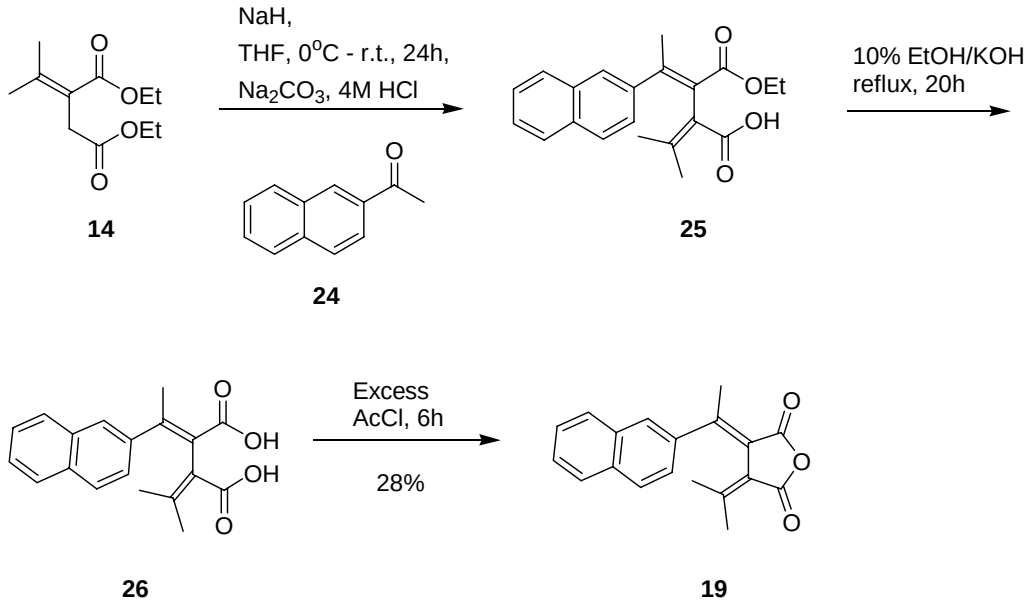
Figure 5. Some model fulgides synthesized

Accordingly, we synthesized the following fulgides (Figure 5) according to reported literature procedures, namely, fulgides **2**, **18**, **19** (Scheme 16),[34] **20**,[31] **21**,[35] **22**[36] and **23.**[37] Fulgides **2** and **18** were chosen as the key model fulgides as they displayed good photochromic properties and have been chosen as the backbone for the modification of the fulgide core.

Generally, the synthetic route follows Scheme 16. The first Stobbe condensation is effected by the use of NaH, in the presence of diester **14** and 2-acetyl naphthalene, **24**. This was followed by the hydrolysis of the ester motif of the crude

[34] Fox, M. A.; Hurst, J. R., *J. Am. Chem. Soc.* **1984**, *106(24)*, 7626-7.
[35] Fulgide **20** was expected to be photochromic, as with previously reported phenyl-substituted fulgides. However, the yellow crystals did not seem to afford any colour change even after 20 minutes of exposure to UV irradiation using a photochemical reactor.
[36] Heller, H. G.; Wenlock, M. C. *Photochromic compounds. PCT Int. Appl.* **1999**, 42. CODEN: PIXXD2 WO 9931107 A1 19990624 CAN 131:52069 AN 1999:404971
[37] Heller, H. G.; Trundle, C. *Photochromic materials. PCT Int. Appl.* **1983**, 19. CODEN: PIXXD2 WO 8300568 A1 19830217 CAN 98:207488 AN 1983:207488

mono-ester, **25** to afford the crude diacid **26** which was purified by acid-base workup and was treated with a slight excess of acetyl chloride for up to 6 hours before subsequent workup and purification. This procedure afforded the synthesized fulgide, **19**, in 28% yield, as yellow crystals.



Scheme 16. Synthesis of fulgide **19**

Fulgide **19** has been reported to fail to cyclize upon excitation, presumably because of the energetic cost for ring disruption of ring aromaticity in the transition state.[34] Fulgide **20** has been reported to be photochromic; however, we were unable to observe preliminary colouration from the TLC of the pure product obtained. We suspect that the fulgide could be undergoing *E-Z* isomerizations only as compared with the furyl fulgide as previously reported.[21b]

As fulgides **20** did not show promising photochromic properties, the fulgide was not investigated further. Fulgide **21** also did not show any photochromic properties that were desirable and its investigation was also abandoned. Fulgides **22**

and **23** showed weak photochromic properties as compared to literature. However, due to their reported high quantum yields and high fatigue resistance, we decided to explore the possibility of improving their photochromic property.

2.2. SYNTHETIC STRATEGY

The ability to successfully select the appropriate ketones to be used for fulgide synthesis and design is of critical importance. As depicted in Figure 6., When R_1 is hydrogen, the photochromic properties are lost or are very poor, and the main photo-reaction is *cis-trans* isomerization. The quantum efficiency for colouring increases with the increasing size of this substituent (e.g., 20% when R_1 is methyl and 62% when R_1 is isopropyl).[38] When R_5 is hydrogen, the photochromic system is more susceptible to photodegradation. A powerful electron-releasing substituent in this position causes a major bathochromic shift in the absorption band of the coloured form and a large hyperchromic effect.[39] If R_1 is an aryl group, the photochromic properties are poor; and if R_1 is hydrogen, then a hydrogen shift occurs in the coloured form and the thermal stability and fatigue resistance are lost.

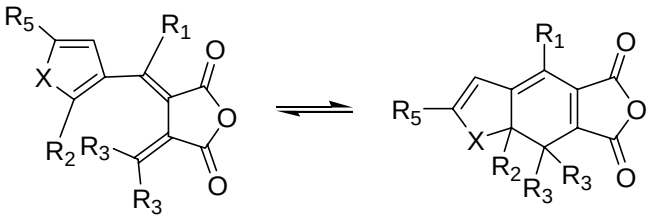
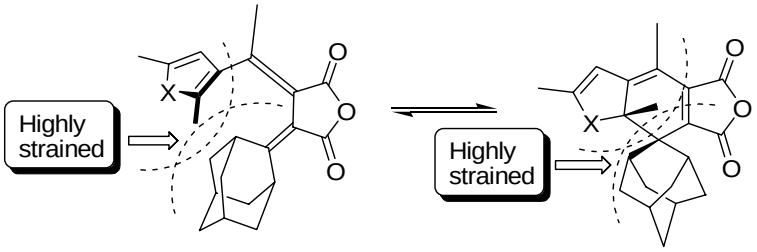


Figure 6. Cyclization of a fulgide to its corresponding tri-cyclic system

[38] Kurita, Y.; Yokoyama, Y.; Goto, T.; Inoue, T.; Yokoyama, M. *Chem. Lett*., **1988,** 1049.
[39] Wood, D. *Studies on Fatigue-Resistant Photochromic Systems. Ph.D. Thesis*, University of Wales, Cardiff, **1991**.



Where X = S, **22**; O, **23**

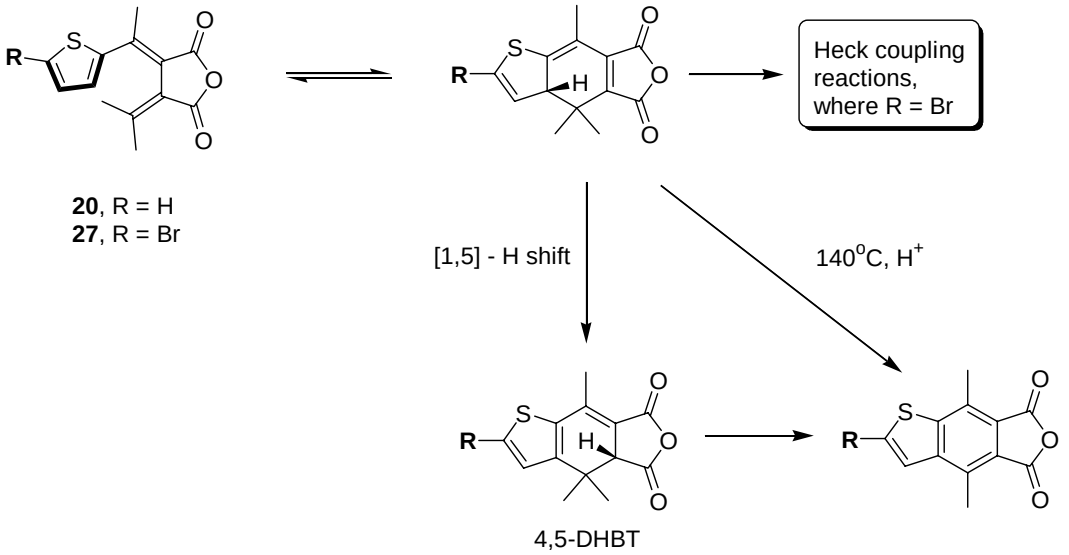
Figure 7. Increase in quantum efficiency for bleaching due to sterically bulky adamantylidene group

Replacement of the methyl groups at R_3 by cyclopropyl groups causes the fulgides to undergo a bathochromic shift of their long-wavelength absorption band.[40] Replacing the isopropylidene group by the bulky inflexible adamantylidene group causes a five- to nine-fold increase in the quantum efficiency for bleaching, presumably due to the weakened 7,7a-sigma bond in the coloured form (Figure 7) by the spiroadamantane moiety.

As can be observed, the selection of the R groups present on a heteroatomic fulgide is the most critical factor that will determine its final photochromic property. Initially, we decided to synthesize fulgide **27** with a bromo-functionality. Several attempts were made but were all unsuccessful. The strategy was to utilize the bromo-functionality and further extend the chemistry of the fulgide by carrying out a Heck coupling with more conjugated systems, in effect, extending the conjugation of the final target molecule. However, with reference to fulgide **20**, the hydrogen at the 3a position can also undergo a [1,5]-H shift to afford the corresponding 4,5-dihydrobenzothiophene (DHBT) derivative, under ambient and higher temperatures.

[40] Heller, H. G.; Oliver, S. N.; Whittall, J.; Johneock, W.; Darcy, P. I.; Trundle, C. *Photochromic Fused-ring Organic Compounds and their Use in Photoreactive Lenses,* G.B. 214327A, **1985**.

In the presence of heat and a catalytic amount of trichloroacetic acid, the 4,5-DHBT can also form the subsequent 4,7-dimethyl[*b*]thiophene-5,6-dicarboxylic anhydride (Scheme 17).



Scheme 17. Unsuccessful attempt to obtain **27** and possible degradation pathways of both **20** and **27**

Our efforts were then directed towards the synthesis of fulgide **2**, **18**, **22** and **23** as they displayed better photochromic properties. Although literature methods were already reported for the synthesis of the fulgides, we had to modify some reaction conditions, in order to obtain the target fulgides with acceptable yields. We managed to obtain fulgide **2** with a yield of 45% and fulgide **18** with a yield of up to 55%, after 3 consecutive steps. Fulgides **22** and **23** were obtained in 54% and 41% respectively. Interestingly, **18Z** was synthesized as reported; and the authors had to obtain **18E** via UV irradiation at 366nm, with a sample placed in toluene, until a nearly quantitative conversion of the **18Z** into the deep-red 7,7a-dihydrobenzothiophene derivative (DHBT) **18C** was obtained.

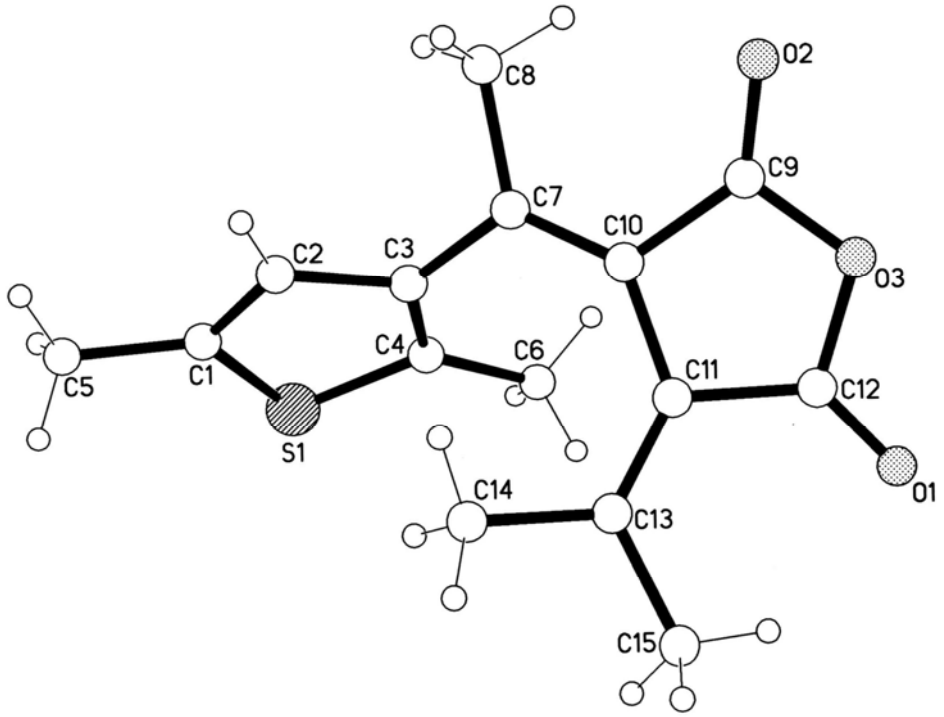


Figure 8. ORTEP plot of **18E** (*E*)-2-[α-(2,5-Dimethyl-3-thienyl)ethylidene]-3-isopropylidenesuccinic Anhydride

This was followed by a subsequent exposure of **18C** to white light until the toluene solution was colourless, indicating that the 7,7a-DHBT has been photoisomerised into the (*E*)-fulgide, **18E** (Figure 8). In our lab, the *E*- and *Z*-fulgides have been successively synthesized in one step via acetyl chloride ring closure followed by flash chromatography of the extracted crude product using a hexane: ethyl acetate (20:1) eluent system. The purified product was subsequently recrystallized in a dichloromethane/ether system to afford two distinct crystals of the *E*- and *Z*-fulgide. As the crystal structure of the fulgide isomers have not been reported before, X-ray analysis was carried out to elucidate the structure of the synthesized fulgides (Figure 8 and 9). The fulgide was fully characterized using ^{1}H NMR, ^{13}C NMR, HiRes-EIMS, melting point determination, X-ray crystallography, IR spectroscopy as well as UV-Vis spectroscopy to study its open and closed forms.

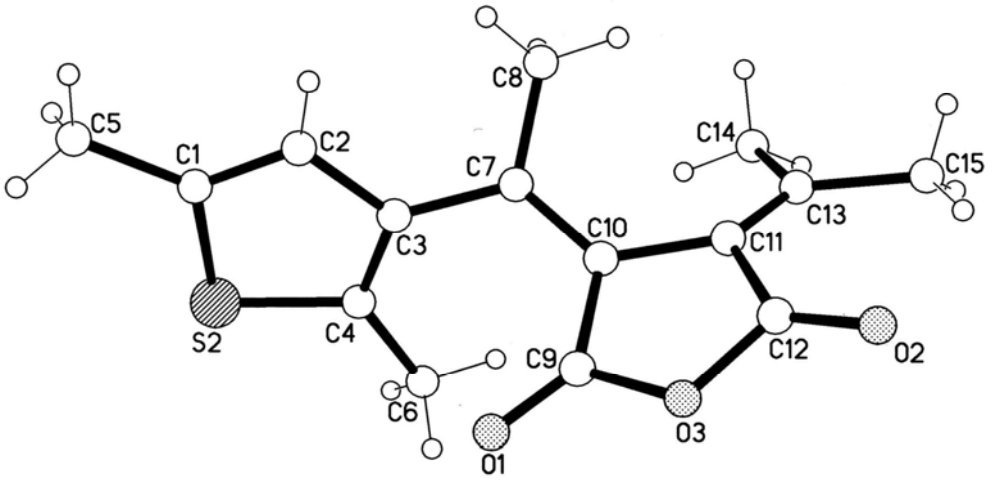
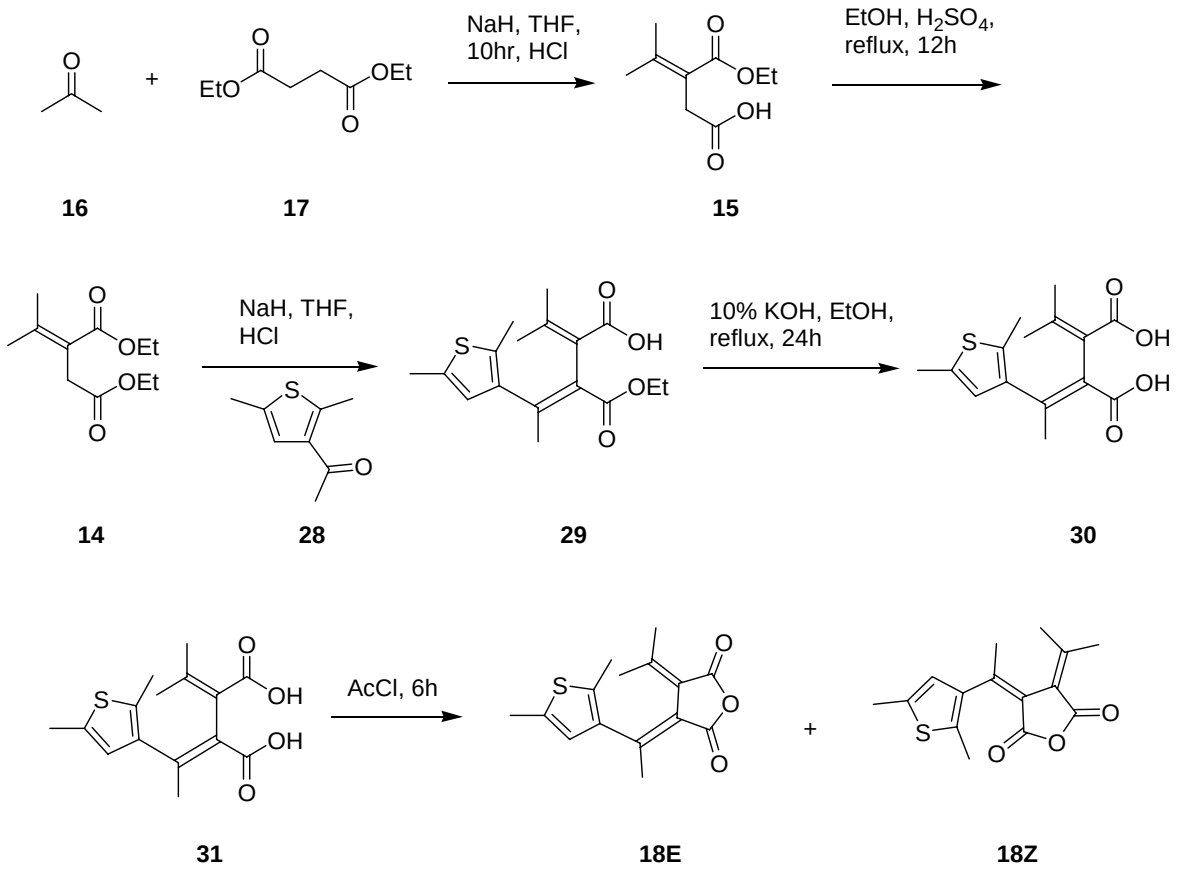


Figure 9. ORTEP plot of **18Z** (*Z*)-2-[α-(2,5-Dimethyl-3-thienyl)ethylidene]-3-isopropylidenesuccinic Anhydride

The (*E*)-fulgide **18E**, displayed good photochromic properties (Scheme 14); and it was converted from an orange crystalline solid to a deep mahogany red 7,7a-DHBT form, under a UV lamp (as a form of preliminary testing of photochromic conversion of states, i.e. from (*E*) to (*C*) form). The (*Z*)-fulgide **18Z** (Figure 9) also displayed photochromic properties, as the yellow needles obtained turned purplish under exposure to a UV lamp albeit taking a longer time. The combined yield of **18E** and **18Z** was about 55%.[41]

[41] The *Z*-form colourizes on exposure to UV irradiation but takes up to 30 seconds longer to obtain comparable colouration of the *E*-form. All data obtained from the characterization were similar to the reported literature values.



Scheme 18. Finalized synthetic route for the synthesis of fulgide **18**

As a further example on the synthetic route to obtain fulgides, we approached the synthesis of **18** as shown in Scheme 18. The synthesis first started with the Stobbe condensation of acetone, **16**, with diethyl succinate, **17**, to afford the mono-acid **15**, which was esterified to form the IPP diester **14**. The diester **14** was treated with NaH and acetyl-thiophene, **28**, to afford the mono-acid **29**, which was purified using acid-base workup. Attempts to purify **29**, via flash chromatography resulted in either no fulgide obtained in the last step or negligible yields. Crude ^{1}H NMR showed the presence of the mono-acid and thus, crude **29** was used directly in the next step to afford crude diacid **30** which was also purified using acid-base workup. Other attempts to purify diacid **30** also resulted in either no fulgide obtained in the last step

or very low yields. This was followed by the treatment of diacid **30** with acetyl chloride to afford the target fulgide **18** with appreciable yields. Having finalized the overall synthetic route for the synthesis of fulgide **18** (Scheme 18), we decided to explore the design and synthesis of new possible fulgides. Apart from applying this synthetic methodology towards the synthesis of fulgides **2**, **22** and **23,** our search for new classes of fulgides led us to the discovery, that to date, more than 1500 fulgides with different heteroatoms and substituents have been reported, under the database of Scifinder Scholar.

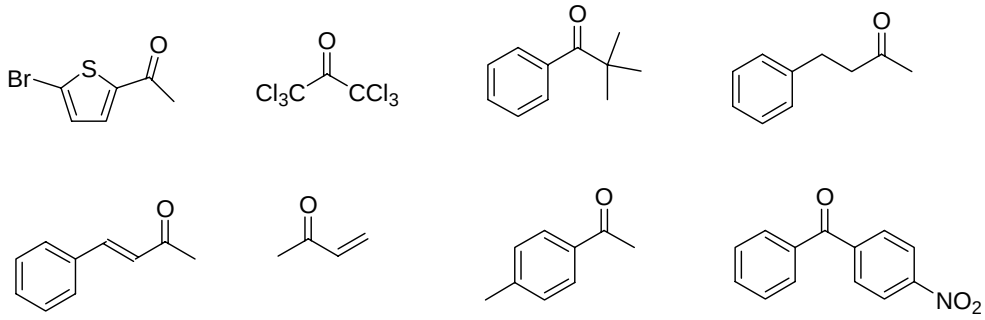


Figure 10. Unsuccessful condensation of some selected ketones

We then decided to synthesize some fulgides with ketones that have not as yet been reported (Figure 10). However, our efforts were futile as the following ketones, did not display any photochromic properties that we would have expected, due to potential [1,5]-H shifts or unsuccessful condensation, probably due to sterically bulky functional groups. With this knowledge, we decided to direct our efforts towards the modification of the R_1 groups (Figure 4), using selected cycloketones, to afford the proposed corresponding cycloalkylidene fulgides. A literature search revealed that the proposed target fulgides have not been reported as yet. As such we decided to use the cycloketones to obtain the target fulgides and to study the effects of increasing ring size on the photochromic properties of the fulgides.

PART I

CHAPTER 3

Synthesis of Cycloalkylidene Fulgides

3.1. INTRODUCTION - SYNTHESIS AND PHOTOCHROMIC PROPERTIES OF A NEW CLASS OF FULGIDES

There have been many comparisons of fulgides and fulgimides with regards to the structural moieties attached to the anhydride core, but studies on cycloalkylidene fulgides such as **32**, **33**, **34**, **35**, **36** and **37** have not been reported (Figure 11).

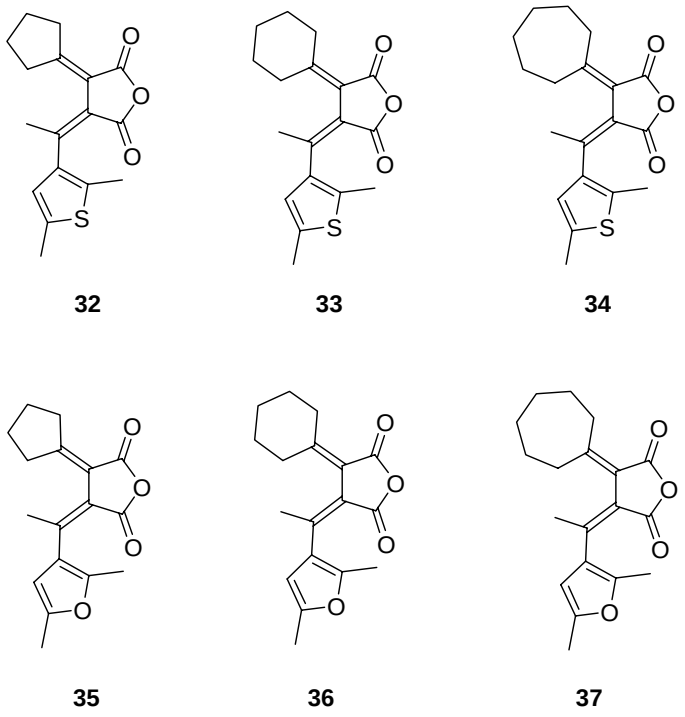


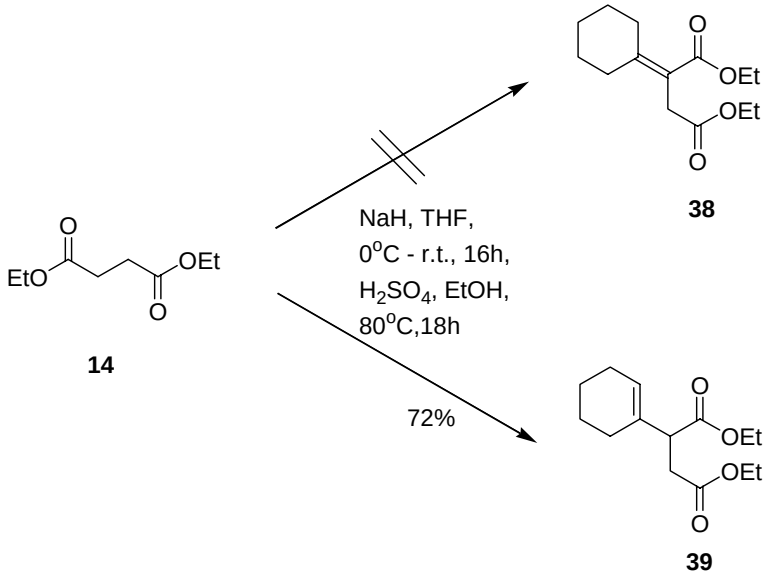
Figure 11. Depicts the cycloalkylidene fulgides synthesized

Herein, we report the synthesis of a series of cycloalkylidene fulgides using either of the diesters obtained from both the use of ^{t}BuOK[42] and NaH.[43] Our efforts have been directed towards the general study and comparison of the structural relationship of the cyclo-alkyl fulgides (Open form – *E*-form or *Z*-form), with

[42] (a) Heller, H.G.; Hughes, D.S.; Hursthouse, M.B.; Rowles, N.G.; *Chem. Commun*. **2000,** 1397. (b) Sun, Z.; Hosmane, R.S. *J. Heterocycl. Chem*. **1995**, *32*, 1819. (c) Yokoyama, Y.; Takahashi, K. *Chem. Lett*. **1996**, 1037. (d) Cabrera, I.; Dittrich, A.; Ringsdorf, H. *Angew. Chem. Int. Engl*. **1991,** *30*, 76.
[43] Liu, J.; Brooks, N. R. *Org. Lett. (Communication)* **2002**, *4(20)*, 3521-3524.

increasing ring sizes, with regards to the extent of effect it had on the absorption maxima of the cyclized form (Coloured form – *C*-form).

3.2. SYNTHESIS OF CYCLO-DIESTERS

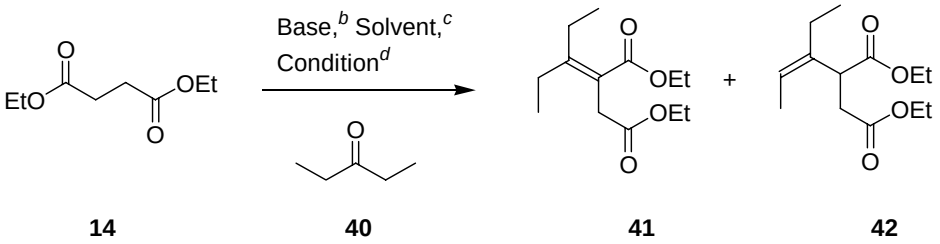


Scheme 19. Synthesis of cyclohexylidene diethyl succinate **39**

Synthesis of fulgides classically involves two successive Stobbe condensations.[44] We expected the Stobbe condensation of diethyl succinate with cyclohexanone to proceed smoothly to furnish the desired α,β–unsaturated cyclohexylidene diethyl succinate, **38** when we used NaH as the base of choice. Unfortunately, we obtained the β,γ–unsaturated cyclohexenyl diethyl succinate, **39** instead (Scheme 19).

[44] For a review, see *Org. React.* Johnson, D. **1951**, *6*, 1-73.

The migration of the double bond to the exocyclic site had been extensively reported by Johnson *et al.* in the 1940s.[45] Rao and Bagavant[46] have also reported the Stobbe condensation of succinic esters with various aldehydes with much success about 20 years later. The observation of the migration of the double bond was also reported then. It would seem that the Stobbe condensation primarily produced *β,γ*–unsaturated diesters. As we required the position of the double bond to be primarily at the *α,β*– position instead of the easily obtained *β,γ*– position, we decided to explore some methods of causing the isomerization of the unusual *β,γ*-unsaturated diester obtained, to form the more conjugated and more stable *α,β*-unsaturated diester instead.



Scheme 20. Synthesis of diisoethylidene diethyl succinate **41**

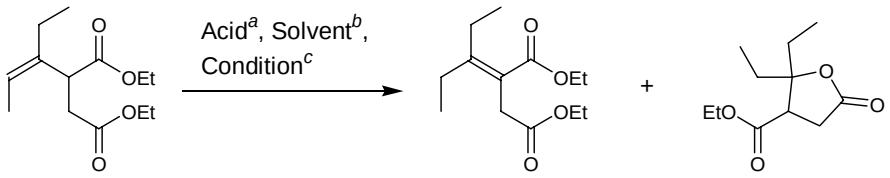
Table 3. Reaction conditions and yields of diester **41** and **42**

Entry	Scale[a]	Base[b]	Solvent[c]	Condition[d]	% Yield
1[46]	5.0	^{t}BuOK	^{t}BuOH	Condensation: 2h, 15 – 20°C Esterification: 18h, reflux	**41** = 0 **42** = 0
2[46]	5.0	^{t}BuOK	^{t}BuOH	Condensation: 1.5h, 15 – 20°C Esterification: 48h, 0°C – r.t.	**41** = 4 **42** = 0
3[47]	60.0	NaH	Hexane	Condensation: 18h, 0°C – r.t. Esterification: 18h, reflux	**41** = 0 **42** = 43
4	60.0	NaH	THF	Condensation: 18h, 0°C – r.t. Esterification: 18h, reflux	**41** = 0 **42** = 32

a: Scale in mmol (mM); *b* : Base used for reaction; *c:* Solvent used for reaction;
d: Reaction conditions.

[45] Johnson, W. S.; Davis, C. E.; Hunt, R. H.; Stork, G.; *J. Am. Chem.. Soc.* **1948**, *70*, 3021.
[46] Rao, R.; K.; Bagavant, G.; *Indian J. Chem.* **1969**, *7*, 859.
[47] Liang, Y.C.; Dvornikov, A. S.; and Rentzepis, P. M.; *Macromolecules* **2002,** *35*, 9377-9382.

We decided to use the synthesis of diisoethylidene diethyl succinate **41** as the model diester for the synthesis of the cyclo-diesters. The starting substrate involved, diethyl ketone **40** (c.f. cyclo-ketones, **40** has two hydrogens in the α-position that might migrate to the α-carbon adjacent to the diester carbonyl functionality (Scheme 20)). We initially tried to obtain the desired α,β-unsaturated diester **41** by following the procedure reported by Rao and Bagavant, but were not successful. We were also not particularly successful when we increased the overall reaction time from 18h to 48h, as only a 4% of **41** yield was obtained, even after prolonged reflux during the esterification step (Entry 2, Table 3). So we next tried using NaH for the condensation and obtained the β,γ-diester **42** instead, with yields of up to 43% (Entry 3, Table 3). A change in solvent for the reaction to THF did not particularly increase the yield of **42** as well (32%, Entry 4, Table 3).



42 **41** **43**

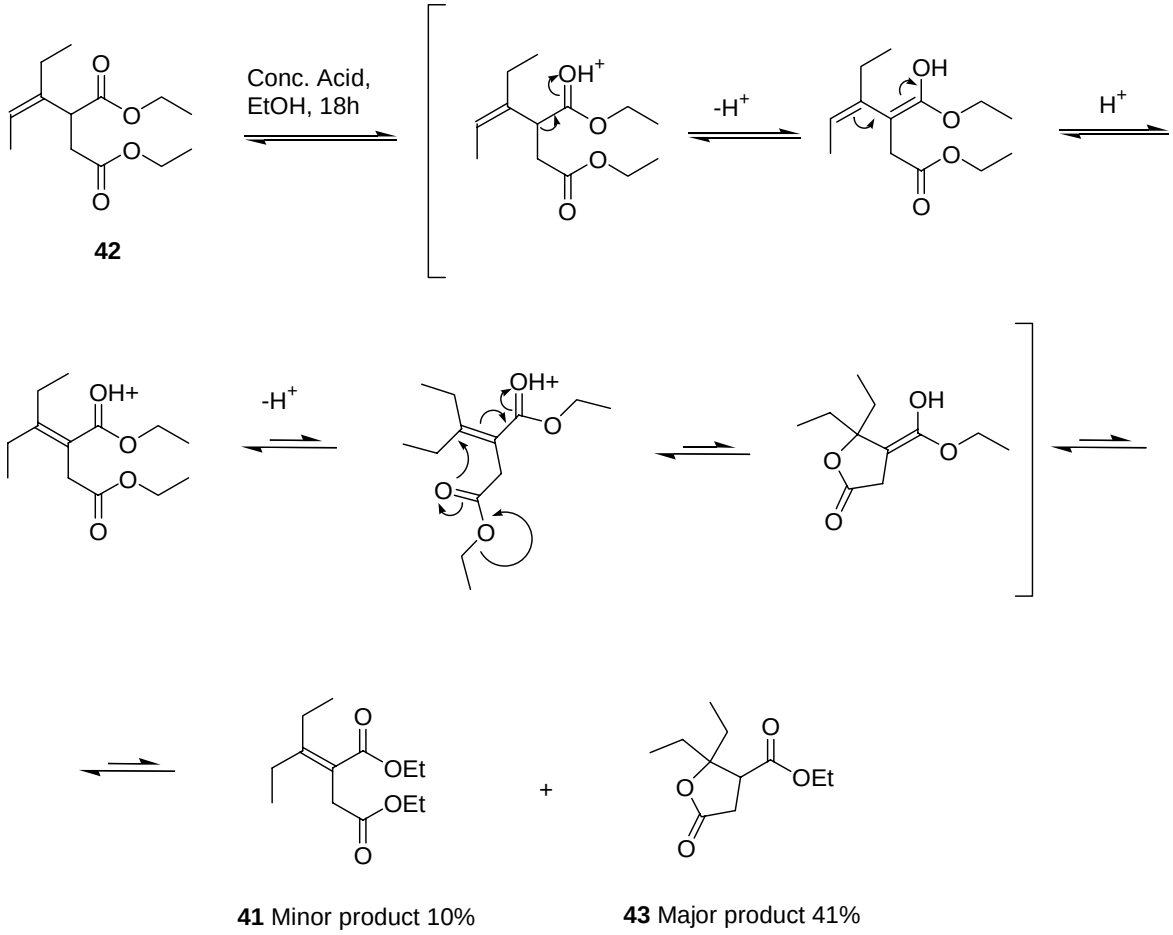
Scheme 21. Acid-catalyzed isomerization

Table 4. Acid-catalyzed formation of α,β-diester

Entry	Scale[a]	Acid[b]	Solvent[c]	Condition[d]	% Yield
1	1.0	H_3PO_4	EtOH	18h, 0°C – r.t.	**41** = 0 **43** = 0
2	1.0	HCl	EtOH	18h, 0°C – r.t.	**41** = 0 **43** = 0
3	1.0	H_2SO_4	EtOH	18h, 0°C – r.t.	**41** = 10 **43** = 41

a: Scale in mmol (mM); *b* : Conc. acid used for reaction (acid used in neat form) ;
c: Solvent used for reaction; *d:* Reaction conditions.

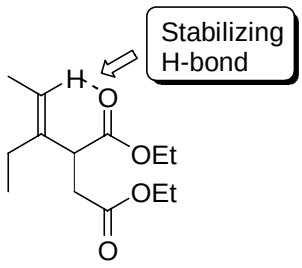
As repeated attempts to obtain the desired α,β-unsaturated diester **41** met with failure, we decided to explore the possibility of causing the migration of the double bond from the β,γ-site (exocyclic) of the major diester, **42**, to the α,β-site (endocyclic) of the minor diester, **41**. With regards to this aspect, we decided to adopt the acid-catalyzed isomerization strategy (Scheme 21).



Scheme 22. Acid-catalysed isomerization mechanism

We envisioned that in the presence of a strong acid, we would be able to effect the subsequent migration of the exocyclic double bond of **42** to afford the more stable, conjugated endocyclic diester **41** (Scheme 22).

We hypothesized that the stabilizing effect of the hydrogen bond between the free-hydrogen of the exocyclic double bond and the oxygen of the ester carbonyl group could cause the β,γ-unsaturated diester to be formed as the major product (Figure 12).



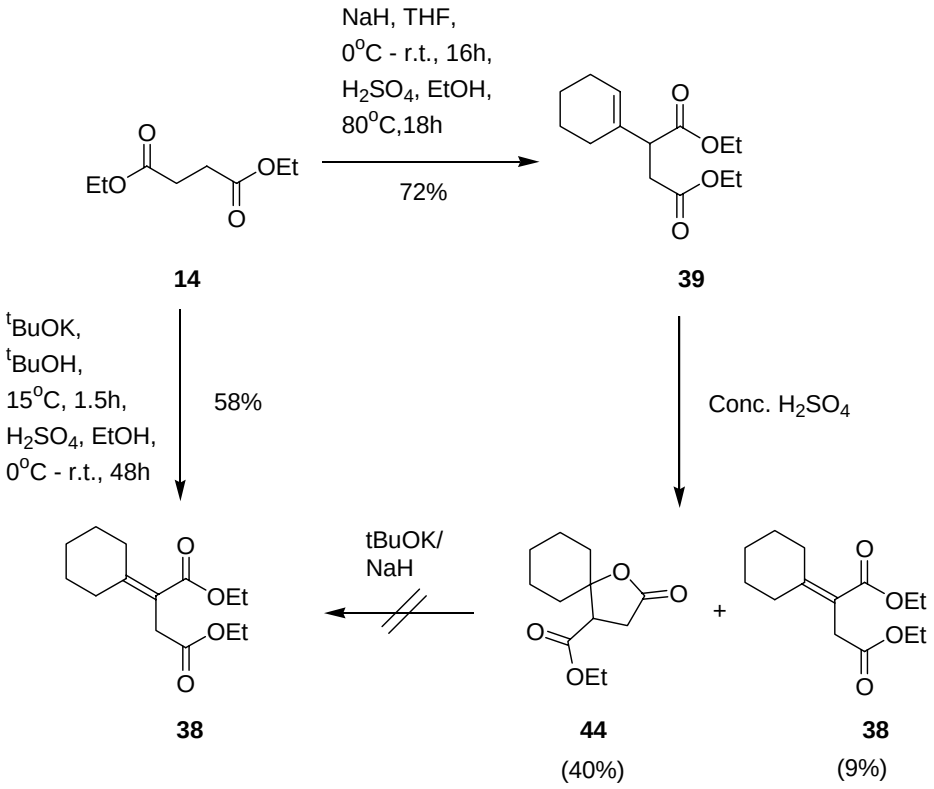
42

Figure 12. Hypothesis of stabilizing effect of H-bond

We chose three concentrated acids (Table 4) as listed and were able to obtain partial conversion of the β,γ-unsaturated diester to afford the desired α,β-unsaturated diester **41**, albeit low yields (Entry 3, Table 4). However, we obtained the cyclized oxo-furan carboxylate side product **43** as the major product with 41% yield.

With the possibility of converting the undesired β,γ-unsaturated diesters to afford the desired α,β-unsaturated diesters, we decided to proceed (and scale-up) with the actual synthesis of the target cyclo-diesters. We decided to use cyclohexanone for the first Stobbe condensation to afford the required α,β–unsaturated cyclohexylidene diethyl succinate, **38**. Referring to Scheme 23, we observed that diester **38** could be obtained in up to 58% yield.[48] As with the synthesis of **42**, we also observed the formation of the β,γ–unsaturated cyclohexenyl diethyl succinate, **39** with yields of up to 72% when NaH was employed instead of ^{t}BuOK (Scheme 23).

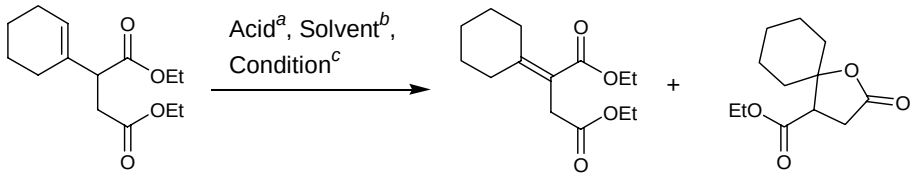
[48] Using the procedure developed by Bagavant *et al.*, reference 46.



Scheme 23. Synthesis of cyclohexylidene diethyl succinate **38**

Attempts to cause the acid catalyzed isomerization (using 2.5M to 10.0M conc. H_2SO_4, Scheme 24), of the double bond from the exocyclic site to the endocyclic site, resulted in the formation of the *γ,γ*-pentamethyleneparaconate **44** as the major product (40%) and cyclohexylidene diethyl succinate **38** as the minor product (9%) (Entry 6, Table 5). In effect, the desired diester was not obtained with satisfactory yields. Further attempts to cause ring opening of **44** to afford **38** also failed (Scheme 23).[49] The *γ,γ*-pentamethyleneparaconate **44** also failed to condense with the selected ketones in both NaH and ^{t}BuOK over 4 days as previously reported by Rao and Bagavant.

[49] As determined from crude ^{1}H NMR of the reaction mixture.



39 **38** **44**

Scheme 24. Acid-catalyzed isomerization

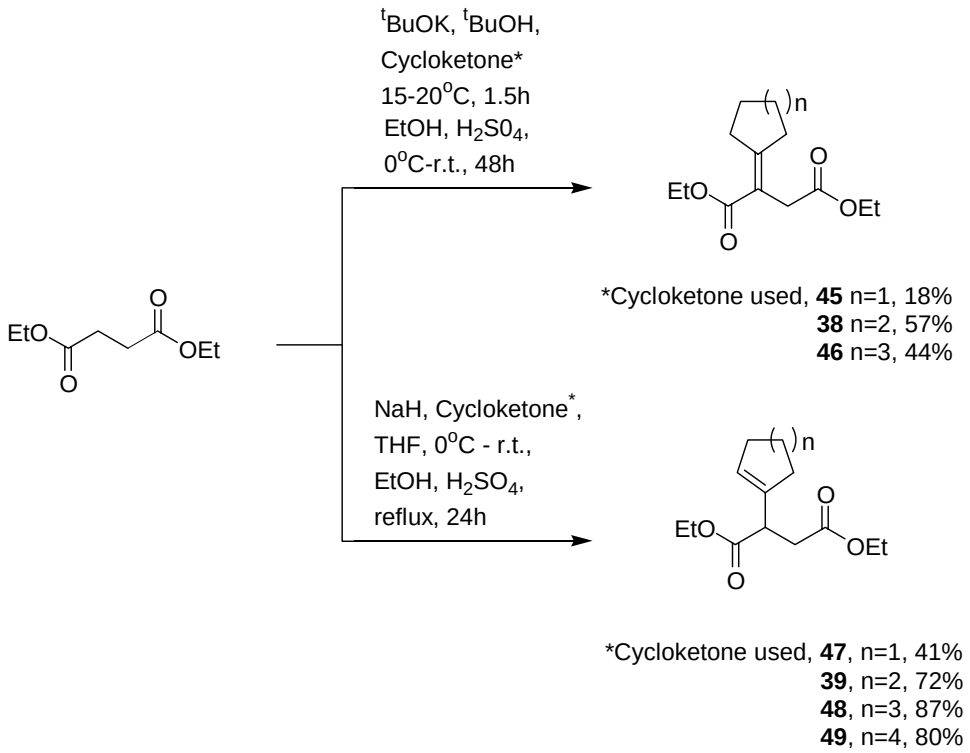
Table 5. Acid-catalysed formation of α,β-diester

Entry	Scale[a]	Acid[b]	Solvent[c]	Condition[d]	% Yield
1	1.0	2.5M H_2SO_4	EtOH	18h, 0°C – r.t.	**39** present
2	1.0	5.0M H_2SO_4	EtOH	18h, 0°C – r.t.	**39** present
3	1.0	6.0M H_2SO_4	EtOH	18h, 0°C – r.t.	**39** present
4	1.0	7.0M H_2SO_4	EtOH	18h, 0°C – r.t.	**38** = 0 **44** = 30
5	1.0	7.5M H_2SO_4	EtOH	18h, 0°C – r.t.	**38** = 0 **44** = 34
6	1.0	10.0M H_2SO_4	EtOH	18h, 0°C – r.t.	**38** = 9 **44** = 40

a: Scale in mmol (mM); *b* : Conc. acid used for reaction (acid used in neat form) ;
c: Solvent used for reaction; *d:* Reaction conditions.

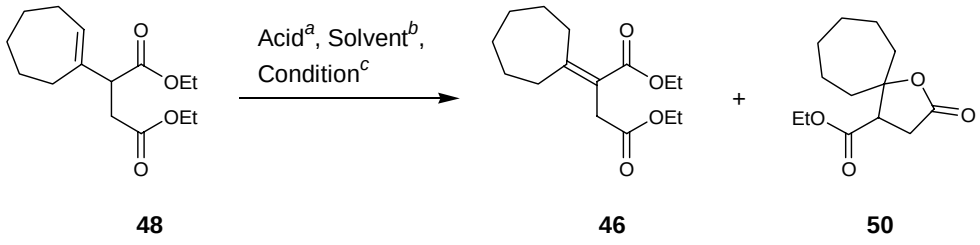
The synthesis of the corresponding cycloalkylidene diethyl succinic diesters **38**, **45** and **46** was carried out using the procedure reported by Rao and Bagavant.[46] Careful control of the reaction temperature afforded diesters with yields ranging 18–57%.[50] The corresponding cycloalkenyl diethyl succinic diesters **39**, **47**, **48** and **49** were obtained using NaH, affording yields ranging 41-87% (Scheme 25). Generally, for the Stobbe condensation using NaH, the reaction conditions were mild and the reactions were easy to setup and products easily purified.

[50] Attempts to obtain the cyclooctylidene succinic diester resulted in the self condensed product from the cyclooctanone; which was only determined from crude NMR and not isolated. The cyclopentanone used to obtain **45** also tend to afford the self condensed product quite readily.



Scheme 25. Synthesis of key cyclodiesters **38**, **39** and **45**-**49**

We encountered problems with the self condensation of the cyclo-ketones, in particular, cyclopentanone, to afford the self-condensed product rather than the desired diesters. Acid-catalyzed isomerization of the cycloheptenyl diester also resulted in formation of the oxo-furan carboxylate product **50** (Scheme 26).[51]

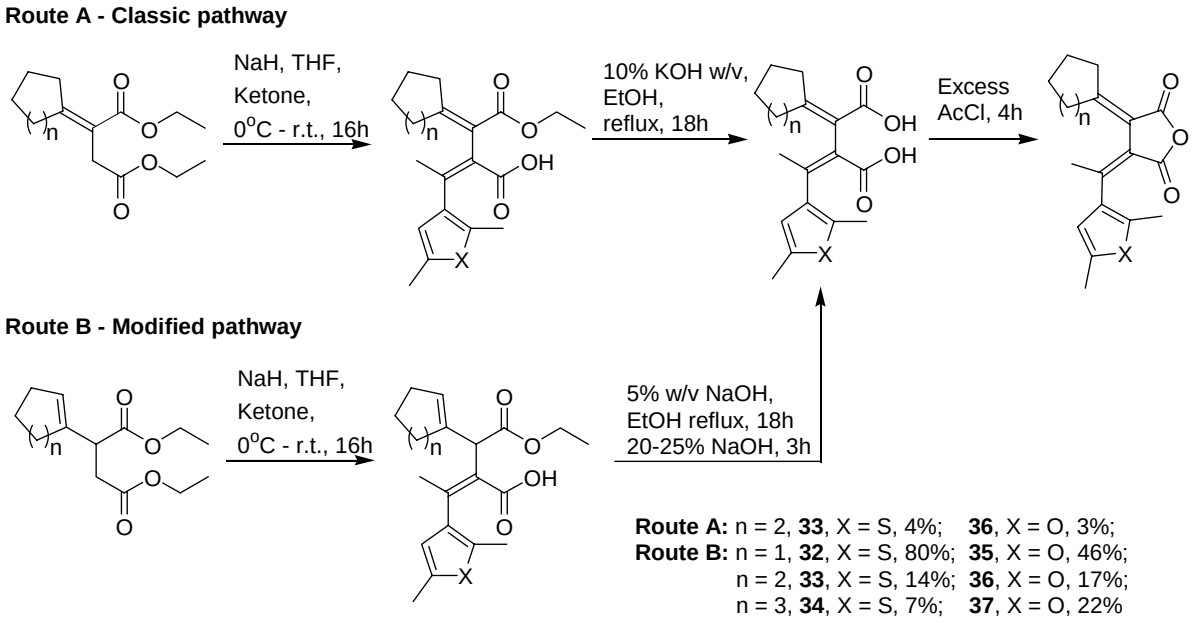


Scheme 26. Acid-catalyzed isomerization of **48**

[51] Solvent used in the reaction was EtOH; as in Table 4 and Table 5. The acid used was 10M H_2SO_4 and the reaction was allowed to stir for 18h.

3.3. SYNTHESIS OF CYCLOALKYLIDENE FULGIDES

After many attempts to cause the isomerization of the β,γ–unsaturated double bond to afford the diester with the desired α,β–double bond, we were not satisfied with the yields obtained as more than 50% of the starting diester to be converted was suspected to have decomposed under such harsh acidic conditions. As such we decided to re-look at the strategy of the isomerization of the double bond and also to explore if we could somehow induce the isomerization during the course of the reaction.

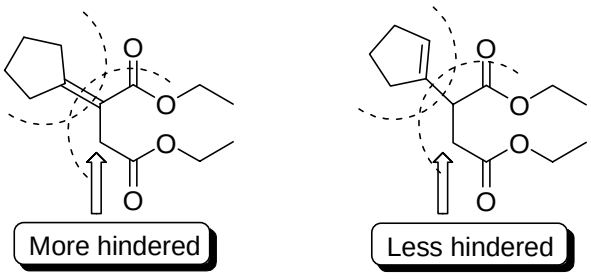


Scheme 27. Synthetic routes A and B towards fulgides **32**-**37**

A detailed examination of the reaction scheme revealed that we could possibly cause a base hydrolysis to obtain the diacid during the second last step, as well as possibly cause a base-induced isomerization of the exocyclic double bond to form the endocyclic double bond. We then decided to initiate the isomerization of the β,γ–

unsaturated double bond to afford the diacid with the desired α,β–double bond, with the usage of 5% w/v ethanolic NaOH, refluxing for approximately 18h. This was followed by stirring in 20%-25% aqueous NaOH for 3h. This was to ensure the complete formation of the diacid and to maximize yield. With this key experimental modification in mind, we initiated the synthesis of the cycloalkylidene fulgides.

With reference to Scheme 27, the diesters were stirred in THF in the presence of NaH with the selected ketones to afford the half-acids. We observed that the well known classic synthetic pathway, involving ethanolic potassium hydroxide and acetyl chloride, towards **33** or **36** resulted in very low yields of the desired molecules (Scheme 27 – Route A), with 4% and 3% respectively. Repeated attempts to optimize the reaction were particularly unsuccessful. We suspected that the main reason behind the low yields could be that the cyclo motifs were actually causing some steric hinderances during the course of the second Stobbe condensation of the more bulky ketones when compared with the less hindered cycloalkenyl diesters (Figure 13).



45 **47**

Figure 13. Cyclo motifs suspected to cause steric hinderances during 2nd Stobbe condenation

Since we were able to obtain acceptable yields for diesters **39**, **47**, **48** and **49**, we decided to proceed with the usage of the cycloalkenyl diesters as they had a more

flexible cyclic moiety which would not pose as much of a steric hindrance as the cycloalkylidene analogs.

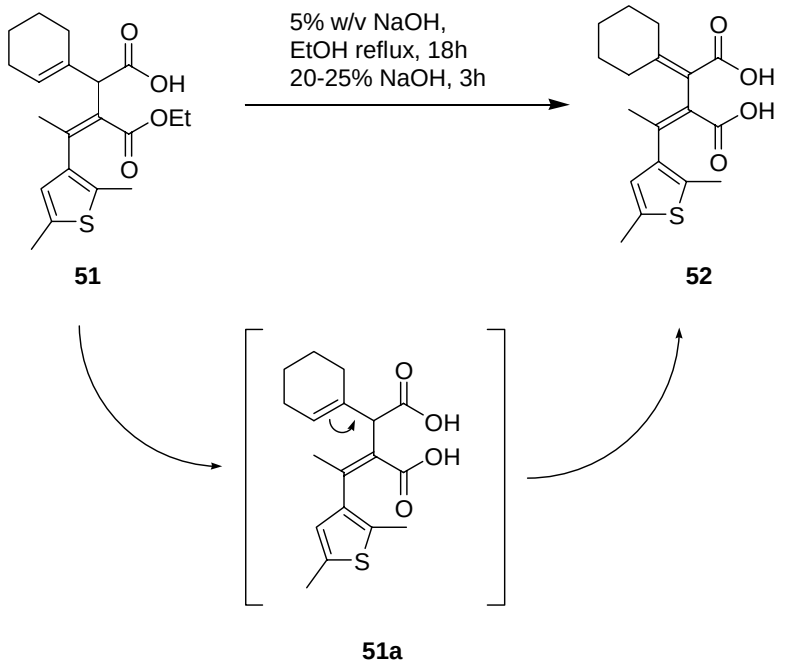


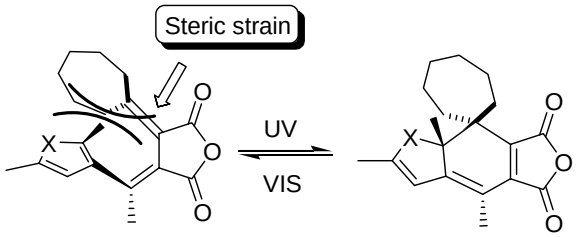
Figure 14. Example of base-catalyzed isomerization of **51**

As an example for the base-catalyzed isomerization as illustrated in Figure 14, the mono-ester **51** can be converted to the desired diacid **52**, via **51a**.[52] When we applied our base-catalyzed isomerization strategy (Figure 14), the reactions proceeded quite smoothly and we were able to obtain the corresponding fulgides. The following ring closure was carried out by treatment of the diacid with excess acetyl chloride, in the dark and stirring the reaction mixture for approximately 4-6 hours. This led to the formation of fulgides **32-37**, with yields ranging 7-80%. An important point to note at this stage was that acid-base workup for each step to purify the mono-ester or diacid was crucial during the preparation for the final ring closure. As reported in the

[52] The disappearance of the crude ^{1}H NMR peak at ~5.55-5.70 ppm would indicate the success of the isomerization.

preceding Chapter, attempts to purify the mono-acid or diacid intermediates resulted in very poor yields of approximately 1-2%.

Good to excellent yields were obtained for **32** and **35**. In an effort to use a milder base for the tandem saponification and isomerization of the double bond, the usage of a 2.5% w/v ethanolic NaOH solution for the formation of the diacid led to relatively lower yields obtained for **33** and **36**, 6% and 8% respectively. However, when we repeated the reactions using the optimized conditions, we could obtain yields of 14 and 17% for fulgides **33** and **36** respectively. The low yield for **34** was exceptional and repeated attempts to improve the yield were not successful. A possible explanation could be attributed to the larger steric hindrance caused by the larger cycloheptyl moiety on the fulgide core (Figure 15). The yields of the fulgides synthesized were observed to decrease with an increase in the cyclo-ring size. Crystals could not be obtained satisfactorily for X-ray crystallographic analysis.



Where X = S, **34**; O, **37**

Figure 15. Photochromism of fulgide **34** and **37**

Repeated attempts to obtain the cyclooctyl fulgide, from the cyclooctenyl diester, were also unsuccessful. The reactions were monitored using TLC/UV light throughout the course of the ring closure step. We suspect that the low yield could be

due to the unfavorable formation of the new C-C bond upon exposure to UV light, as formation of a spot (on TLC) that colourized to purple would indicate the formation of a hexatriene moiety and in turn indicate the presence of the fulgide.[53a, b]

To conclude, we have successfully synthesized and characterized a new series of fulgides – the cycloalkylidene fulgides. The study of the photochromic properties of the synthesized fulgides was carried out next.

[53] Generally, the sigma bond formed after cyclization for thienyl fulgides have been known to be longer compared with furyl fulgides. (Thienyl fulgides = ~3.90Å c.f. Furyl fulgides = ~3.44Å) (a) Yu, L.; Ming, Y.; Zhang, X.; Fan, M.; Lin, N.; Yao, S.; *J. Photochem. Photobiol. A: Chem.* **1993**, *74*, 37-41. (b) Yu, L.; Ming, Y.; Zhao, W.; Fan, M.; *J. Photochem. Photobiol. A: Chem.* **1992,** *68*, 309.

3.4. COMPARISON OF PHOTOCHROMIC PROPERTIES OF CYCLOALKYLIDENE FULGIDES – STRUCTURAL INFLUENCES ON THE UV ABSORBANCES.

After successfully obtaining the above mentioned fulgides **32-37**, we decided to study the implications on the photochromic properties caused by the larger cycloalkyl rings present on the fulgide core. The absorption spectra maxima of the open (*E/Z*) and closed (*C*) forms of the fulgides are listed in Table 6.

Table 6. UV-Vis Absorption Maxima (nm) in CH_2Cl_2, of open and closed form of the fulgides **2**, **18**, **32**–**37**.

Fg*	$\lambda_{max}O^b$ (nm)	A_O	ε_O ($mol^{-1}dm^3cm^{-1}$)	$\lambda_{max}C^c$ (nm)	A_C	ε_C ($mol^{-1}dm^3cm^{-1}$)	$\Delta\lambda_{max}{}^d$ (nm)	% Conversion[e]
18	342	1.48	68465	538	0.69	32063	196	46.8
32[a]	Z: 342 E: 338	Z: 0.81 E: 0.93	Z: 409251 E: 97367	Z: 544 E: 544	Z: 0.27 E: 0.45	Z: 140338 E: 47011	Z: 202 E: 206	Z: 34.3 E: 48.3
33	332	2.00	189749	552	0.48	47015	220	24.8
34	342	1.45	481155	550	0.16	52927	208	11.0
2	346	0.97	52612	510	0.92	50278	164	95.6
35	350	0.74	214335	514	0.49	143152	164	66.8
36	346	0.76	92310	514	0.39	47892	168	51.9
37	350	0.96	304831	526	0.36	115599	176	37.9

Fg*=Fulgide; *a*: **32 was obtained as a mixture of E and Z isomers with 2 distinct spots on TLC. ^{1}H NMR analysis of the spectra did not show distinct chemical shift differences of the 3 CH_3 groups present. E-form of fulgide usually has a larger % conversion; *b*: Absorption maxima of Open-form. (Apart from **32**, all other fulgides obtained in the Z-form due to steric hinderances.); *c*: Absorption maxima of Closed-form (Coloured form); *d*: Difference of Closed-form over Open-form; *e*: Percentage of Open-form converted to Closed-form (ε_c /ε_o x 100). Note: [C] of stock solutions were prepared in 1-8μmol and were repeated in duplicate.

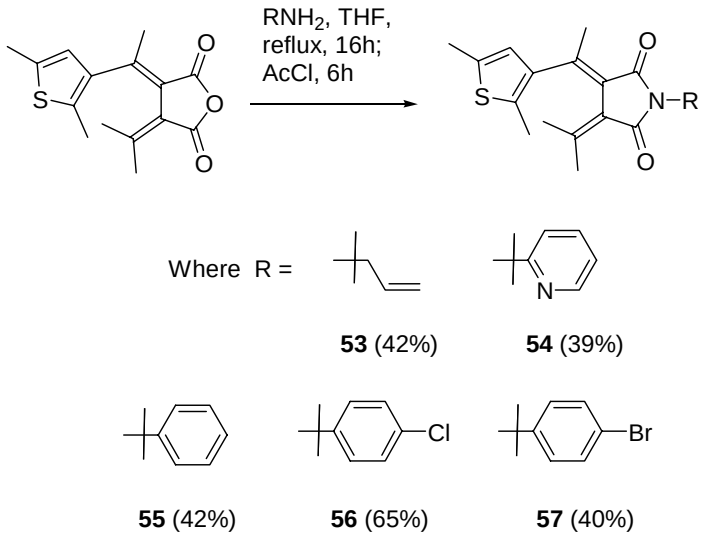
With reference to fulgides **2** and **18** as the key benchmark fulgides, based on their intrinsic photochromic properties, the absorption spectra of the fulgides in their open form have their absorption maxima at approximately 342-346nm. The closed

forms have their maximum absorption at 510-550nm. With regards to the conversion percent of the open (*E/Z*) form to the closed (*C*) form, fulgide **2** displayed a conversion rate of almost 100%, which would make it a potential candidate for use in optical memory media. For fulgide **18**, the conversion rate of close to 50%, displayed a drop of almost 2-fold, when compared with fulgide **2**.

For the thiophene fulgides, the difference of the absorption maxima of the coloured form between the IPP based fulgide **18** and the cycloheptyl analog **35** was a 12nm red shift. Referring to Table 6, it was observed that every additional carbon present in the cyclo-ring, for the thiophene analogs, caused a drop in formation of the coloured form by up to 12%. There was also an increase in the red shift by up to 14nm. As a comparison, for fulgide **18**, the difference of the absorption maxima for the open and closed form is 196nm. For the cyclo-thienyl fulgides, the difference can be up to 220nm, for fulgide **33**. The large red shift of the closed form can be explained by the larger steric strain between the large cycloheptyl ring and the thiophene moiety.

Switching to the furyl fulgides, a similar trend could be seen between the IPP based fulgide **2** and the cycloheptyl analog **37**. A bathochromic shift of up to 16nm was observed on UV-irradiation of the open fulgides. Replacing the furyl moiety of **37** with a thiophene moiety, **34**, caused a red shift of approximately 24nm. It has been observed that every additional carbon present in the cyclo-ring, for the furyl analogs, causes a drop in formation of the coloured form by 14% (Table 6). There was also an increase in the difference of the open and closed form, with a red shift of 12nm.

With an increase in ring size, there was a general increase in the wavenumber. However, the percentage conversion of the opened form to the closed form dropped significantly. This decrease could be attributed to the larger steric hinderance of the cyclo-heptyl groups caused when compared with the much smaller cyclo-pentyl group on the anhydride moiety, which in turns caused an increase in the bleaching effect of the coloured fulgide. The decrease in conversion of the respective fulgides, in descending order, is generally: IPP > cyclo-pentyl> cyclo-hexyl > cyclo-heptyl. Yields of the fulgides with larger cyclo-alkyl groups also generally decreased. The large extinction coefficients observed from the UV studies were obtained using dichloromethane (DCM) as solvent.[54]



Scheme 28. Synthesis of fulgimides **53-57**

[54] For reviews on solvent effects on photochemical reactions, refer to (a) Rappon, M.; Syvitski, R. T. *J. Photochem. Photobiol., A: Chem.* **1996**, *94*, 243-247 (b) Liang, Y.; Dvornikov, A. S.; Rentzepis, P.M. *J. Photochem. Photobiol., A: Chem.* **1999**, *125*, 79-84 (c) Gou, Z.; Tang, Y.; Zhang, F.; Zhao, F.; Song, X. *J. Photochem. Photobiol., A: Chem.* **1997**, *110*, 29-33.

As we observed that the thienyl-fulgides had generally low conversion rates to form the coloured forms, we decided to functionalize the anhydride moiety to form fulgimides (Scheme 28), hoping to obtain better conversion rates and to study other effects. A series of anilines were selected to form the respective fulgimides **53-57**. The IPP-based thienyl fulgide **18** was chosen as the starting material as yield of the fulgide was higher compared to fulgide **2**. The other reason fulgide **2** was chosen was due to its relatively lower rate of conversion to the coloured form. We seeked to explore the possibility of improving the conversion percentage of the open form to the closed form by functionalization of the fulgide core. We also seeked to functionalize the fulgide to enable the possibility of extension of fulgide chemistry by incorporating functional groups that could be further used for other reactions (e.g. Heck coupling, Olefin metathesis, etc.)

The fulgimides were obtained by refluxing the selected amine with the fulgide in THF followed by removal of solvent and treatment of the half-acid with excess acetyl chloride to effect the ring-closure. Yields of the fulgimides ranged 39 – 65%.

Table 7. UV-Vis Absorption Maxima (nm) in CH_2Cl_2, of Open and Closed form of the Fulgides **18**, **53**–**57**.

Fg[a]	$\lambda_{max}O$[b] (nm)	A_O	ε_O ($mol^{-1}dm^3cm^{-1}$)	$\lambda_{max}C$[c] (nm)	A_C	ε_C ($mol^{-1}dm^3cm^{-1}$)	$\Delta\lambda_{max}$[d] (nm)	% Conversion[e]
18	342	1.48	68465	538	0.69	32063	196	46.8
53	330	1.22	50705	526	0.31	12999	196	25.6
54	Z: 330 E: 328	Z: 0.95 E: 0.70	Z: 33718 E: 45171	Z: 532 E: 532	Z: 0.30 E: 0.31	Z: 10709 E: 20044	Z: 202 E: 204	Z: 31.8 E: 44.4
55	Z: 330 E: 328	Z: 0.66 E: 1.28	Z: 18380 E: 39842	Z: 532 E: 534	Z: 0.28 E: 0.52	Z: 7879 E: 16390	Z: 202 E: 206	Z: 42.9 E: 41.1
56	326	1.06	342653	538	0.45	146703	212	42.8
57	334	0.81	175631	538	0.40	86908	204	49.5

a: Fulgide; *b*: Absorption maxima of Open-form. (Apart from **54** and **55**, all other fulgides obtained in the Z-form due to steric hinderances.); *c*: Absorption maxima of Closed-form (Coloured form); *d*: Difference of Closed-form over Open-form; *e*: Percentage of Open-form converted to Closed-form (ε_c /ε_o x 100). Note: [C] of stock solutions were prepared in 1-8μmol and were repeated in duplicate.

As can be observed from Table 7, the absorption maxima for the open forms of the fulgimides are blue-shifted by up to 16nm when the oxygen moiety on the anhydride core is replaced by nitrogen. This blue shift can be caused by the presence of the nitrogen causing the anhydride core to adopt a less planar structure. The absorption maxima for the closed form did not change significantly. The general trend observed for the fulgimides is that the presence of the more conjugated phenyl rings on the fulgide core did not significantly cause an increase in the conversion percentage.

However, with the exception of fulgimide **57**, the conversion percentage is observed to drop. However, with the attachment of the various functional groups like the free-terminal double bond on fulgimide **53** and the bromo functionality on fulgimide **57**, we were given the option to further explore the possibility of enhancing

conjugation or attaching other structural moieties via olefin metathesis or the Heck coupling.

3.5. CONCLUSION

In summary, a series of cycloalkyl-based fulgides have been successfully synthesized and fully characterized, using β,γ-unsaturated diesters and their main photochromic characteristics studied. The presence of a large alkyl group on the fulgide core generally causes a bathochromic shift for the coloured form and a decrease in the conversion rate (i.e. indication of relatively low quantum yields).

The synthesis of five model fulgimides was also successfully completed and fully characterized. Efforts directed towards the improvement of the percentage conversion by functionalizing the fulgide to form the corresponding fulgimides were generally not successful. For our next stage of the synthesis, we were also interested in modifying the fulgide core to explore the further functionalization of such fulgides.

The key modification was to synthesize new fulgimides from the fulgides, using selected amines, with various functional groups in order to allow further extension of the fulgide core.

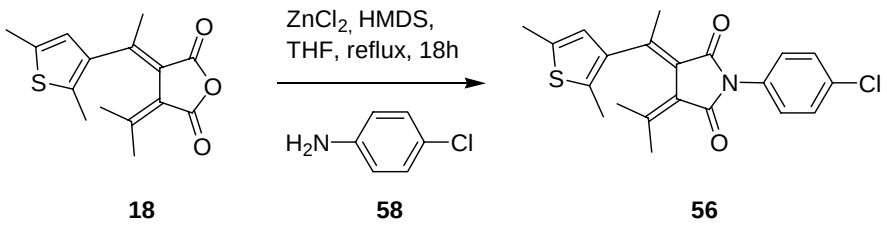
PART I

CHAPTER 4

Molecular Tailoring of Fulgide Core

4.1. INTRODUCTION – MOLECULAR TAILORING OF FULGIDE CORE – MODIFICATION OF 'Y' MOIETY : FULGIMIDE SYNTHESIS

Fulgimides are usually less coloured than their corresponding fulgides, but show similar photochromic properties. Fulgimides have been known to be more resistant to acid- or base-catalyzed hydrolysis than the corresponding fulgides, but their resistance to photodegradation is not markedly improved.[55] The importance of fulgimides is that the N-substituent can be used as a linking group to prepare photochromic Langmuir-Blodgett films,[56] photochromic liquid crystals,[57] photochromic diagnostic devices,[58] and photochromic copolymers.[59]



18 **58** **56**

Scheme 29. Zinc-chloride mediated fulgimide synthesis of **56** - total synthesis time: ~18h

Fulgimides are usually synthesized using the methodology developed by Heller *et al.*[60] He reported the synthesis of fulgimides which required thermal heating of a fulgide and an amine, in an organic solvent (e.g. ethanol, benzene, etc.), to afford the mono-amides, which may take up to 2 hours. This was followed by heating of the

[55] Wolak, M. A.; Thomas, C. J.; Gillespie, N. B.; Birge, R. R.; Lees, W. J. *J. Org. Chem.* **2003,** *68(2),* 319-326.
[56] Cabrera, I.; Achim, D.; Ringsdorf, H.; D.E. 4007636A1.
[57] Cabrera, I.; Achim, D.; Ringsdorf, H. *Angew. Chem. Int. Ed.*, **1991**, *30*, 76.
[58] Willmer, I.; Rubin, S.; Wonner, J.; Effenberger, F.; Bauerle, P. *J. Am. Chem. Soc.*, **1992,** *114*, 3150.
[59] Elliot, C. C. *MSc, Thesis; University of Wales, Cardiff*, **1990**.
[60] Heller, H. G. *Fulgimide derivatives. Brit.* **1972**, 7. CODEN: BRXXAA GB 1271655 19720426 CAN 77:61806 AN 1972:461806

mono-amides in acetyl chloride for up to another 2 hours.[61] Rentzepis and co-workers also developed a novel methodology which usually involved refluxing temperatures of up to 80°C, followed by the addition of hexamethyldisilazane (HMDS) in benzene, through a dropping funnel, over a period of 10 min.[62] The reaction mixture was then refluxed for a further 4-20 h to obtain the fulgimides desired. We synthesized fulgimide **56** accordingly, employing **58** and obtained a yield of only 40% (Scheme 29).[63] Generally, the methods reported required either rather stringent conditions, or the use of rather harsh conditions to obtain the fulgimides in good yield. In our lab, we seeked to explore the possibility of using microwave technology, in order to develop an efficient and fast method of obtaining fulgimides in a mild fashion. Many papers and reviews have been published in recent years concerning microwaves in organic chemistry.[64a-f]

[61] Attempts at refluxing acetyl chloride resulted in many decomposed products and low yields of desired fulgimides. As such, we decided to search for other less harsh methods.
[62] Liang, Y.; Dvornikov, A. S.; Rentzepis, P. M. *Macromolecules*, **2002,** ***35****(25)*, 9377-9382.
[63] Generally, we suspected that the HMDS and the $ZnCl_2$ employed were not dry enough and reaction conditions had to be very stringent in order to obtain high yields as reported by Rentzepis and co-workers.
[64] (a) Abramovitch, R. A.; *Org. Prep. Proced. Int.* **1991**, *23*, 683-711. (b) Whittaker, A. G.; Mingos, D. M. P. *J. Microwave Power Electromangetic Energy* **1994**, *29*, 195-219. (c) Mingos, D. M. P.; *Res. Chem. Intermed*. **1994**, *20*, 85-91. (d) Mingos, D. M. P.; Baghurst, D. R. *Chem. Soc. Rev.* **1991**, *20*, 1-47. (e) Majetich, G.; Hicks, R. *Radiat. Phys. Chem*. **1995**, *45*, 567-579. (f) Caddick, S. *Tetrahedron* **1995**, *51*, 10403-10432.

4.2. ADVANTAGES OF THE MICROWAVE METHODOLOGY

The main advantage microwave heating has over conventional thermal heating methods is the reported rate enhancements of reactions.[65a-f] Other advantages include the rapid but controlled heating of viscous materials or absorbing solids (e.g. absorbing polymers, solvent-free reactions). Microwave is also advantageous for reactions that require fast heating and cooling conditions, resulting in cleaner reactions (e.g. acid-free hydrolysis). Microwave can also be employed for reactions where homogeneous heating is required (e.g. zeolite synthesis) and also for reactions where selective heating is important.[66]

4.3. INTRODUCTION - DEFINITION OF MICROWAVE

Microwaves[67] can be defined as electromagnetic radiation of wavelengths between 1 cm and 1 m. In order not to interfere with radar and telecommunication installations, the magnetrons in domestic and industrial microwave equipment must operate within specified frequency bands. The most common band would be 2.45GHz. Equipment operating within this band is readily available and relatively inexpensive. In addition, at 2.45GHz, polar solvents such as water and DMF readily absorbs microwaves in such a manner that the microwaves are not totally absorbed at the surface but penetrate and consequently heat the interior too.

[65] (a) Kappe C. O., Larhed M. *Angew. Chem. Int. Ed.* **2005**, *44(47)*, 7666-7669. (b) Kappe C. O. *Angew. Chem. Int. Ed.* **2004**, *43(46)*, 6250-6284. (c) Martin, B.; Sekljic, H.; Chassaing, C. *Org. Lett.* **2003**, *5(11)*, 1851-1853. (d) Sun, W. C.; Guy, P. M.; Jahngen, J. H.; Rossomando, E. F.; Jahngen, E. G. E.; *J. Org. Chem.* **1998**, *53*, 4414-4416. (e) Bose, A. K.; Manhas, M. S.; Gosh, M.; Raju, V. S.; Tabei, K.; Urbanczyk-Lipkowska, Z. *Heterocycles*, **1990**, *30*, 741-744. (f) Adamek, F.; Hajek, M. *Tetrahedron Lett.* **1992**, *33*, 2039-2042.

[66] Cablewski, T.; Faux, A., Strauss, C. *J. Org. Chem.* **1994**, *59*, 3408-3412.

[67] Caddick, S. *Tetrahedron* **1995,** *51(38),* 10403 – 10432.

The heating of microwaves arises mainly from the dielectric polarization and conductive losses. Since the frequency of microwaves is in the range of the time associated with the polarization of dipoles, interaction of the dipoles with the oscillating electric field of microwaves is possible and consequently energy is absorbed and dissipated as heat. The factors used to describe the dielectric properties of matter are the well known dielectric constant ε' and the dielectic loss factor ε''. The quotient of ε'' and ε' ($\varepsilon''/\varepsilon'$ = tan δ, where δ is the dissipation factor, and tan δ is the loss tangent) describes how efficiently a material is heated in a microwave field. Generally the larger the dielectric constant, the higher the susceptibility of a material to microwaves. For example water, lower alcohols and DMF have large dielectric constants.[68]

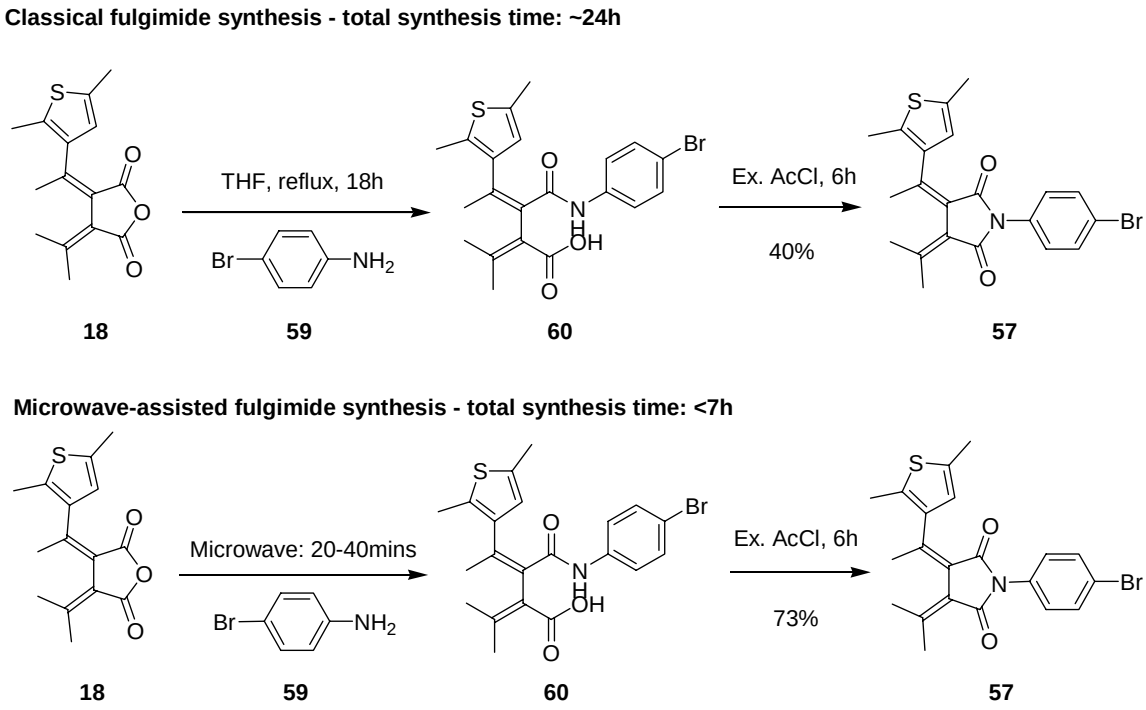
The relatively low cost of modern domestic microwave ovens makes them reasonably readily available to academic and industrial chemists; however somewhat surprisingly only a relatively small number of organic synthesis research groups have reported their use.[69a-c] One disadvantage is that the variable power levels are produced by simply switching the magnetron on and off and this may be problematic if reaction mixtures cool down rapidly. Other potential problems encountered would be the uneven heating and generation of 'hot spots', that might heat the reaction to undesired temperatures.

[68] Properties of: (a) H_2O, b.p.: 100°C, dipole moment: 1.85, dielectric constant: 78.4; (b) MeOH: b.p.: 68°C, dipole moment: 1.70, dielectric constant: 33.0; DMF: b.p.: 153°C, dipole moment: 3.82, dielectric constant: 38.3.

[69] (a) Gedye, R.; Smith, F.; Westaway, K.; *Educ. Chem.* **1988**, 55 (b) Ali, M.; Bond, S. P.; Mbogo, S. A.; McWhinnie, W. R.; Watts, P. M. *J. Organometallic Chemistry*, **1989**, *11*, 371. (c) Bose, A. K.; Manhas, M. S.; Ghosh, M.; Raju, V. S.; Tabei, K.; Urbanezyk-Lipkowska, Z. *Heterocycles*, **1990**, *30*, 741.

4.4. SYNTHESIS OF FULGIMIDES EMPLOYING MICROWAVE

The synthesis of phthalimides using microwave was reported by Bogdal *et al.*,[70a,b] Chandrasekhar *et al.*[71] and Borah *et al.*[72] we decided to investigate if we could also use microwave irradiation for the formation of the mono-amide, as an alternative to the harsher conditions usually employed for the first step towards the synthesis of fulgimides. We also seeked to improve the yields of the fulgimides previously synthesized using thermal methods. We first started an initial synthesis of fulgimide **57** (Scheme 30) in an effort to improve the yield of the molecule using milder conditions.



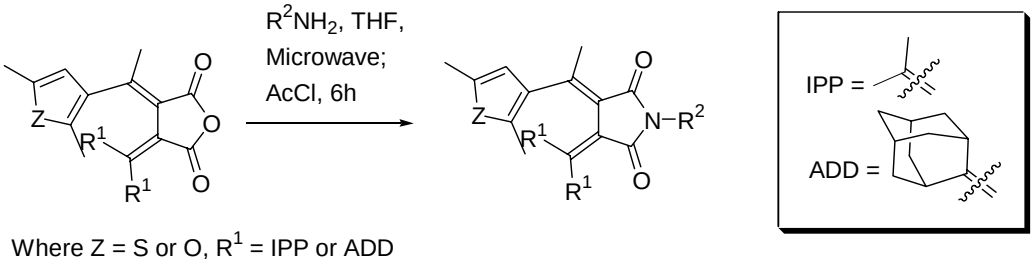
Scheme 30. Microwave assisted fulgimide synthesis vs. classical fulgimide synthesis of **57**

[70] (a) Bogdal, D.; Pielichowski, J.; Boron, A. *Synlett*, **1996,** 873. (b) Bogdal, D.; Pielichowski, J.; Jaskot, K. *Heterocycles*, **1997**, *45*, 715.
[71] Chandrasekhar, S.; Takhi, M.; Uma, G. *Tetrahedron Lett*., **1997**, *38*, 8089,.
[72] Borah, H. N.; Boruah, R. C.; Sandhu, J. S. *J. Chem. Res*. **1998**, *8*, 272.

The reaction to form the half-amide took no longer than 40 minutes, with the subsequent ring closure, employing an excess of acetyl chloride, stirring at room temperature for 4-6 hours afforded fulgimide **57** with yields of up to 73% (Scheme 30). This improvement of yield from the thermal heating route to obtain **57** was almost 2-fold and the reaction time was reduced by almost 3-fold.[73] We also employed the classical fulgimide synthetic route towards fulgimides **53**-**57** as a comparison between the microwave methodology and the thermal heating methodology. Thermal heating was carried out for only the formation of the mono-amide and stirring at room temperature was carried out for the ring-closure step. This was to explore if milder reaction conditions could afford fulgimides with appreciable yields.

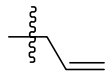
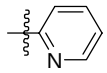
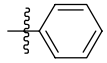
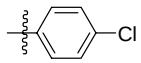
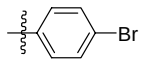
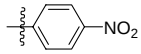
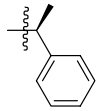
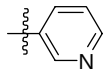
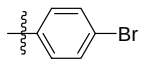
Based on the successful result obtained from the microwave reaction, we decided to screen through a series of amines, to determine if we could also synthesize other less accessible fulgimides, based on our synthetic study. Using the microwave-assisted strategy, we managed to successfully synthesize a series of fulgimides with yields up to 85% (Scheme 31).

[73] We extended the heating time for the synthesis of the half-amide as the reaction was not completed even after 2-4h of heating as reported in literature. It was only after refluxing the mixture overnight or up to 24h were we able to obtain almost complete disappearance of the starting material. Thin layer chromatography (TLC) monitoring was used throughout the reaction.



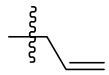
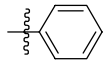
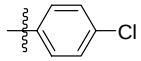
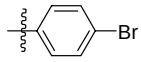
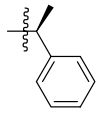
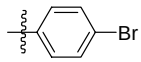
Scheme 31. Synthesis of fulgimides using microwave assistance

Table 8. Improved yields of thienyl-fulgimides obtained through microwave-assisted synthesis

	R^2NH_2	R^1 (IPP/ ADD)	Z (S/O)	Microwave power	Time (min)	$ZnCl_2$ method yield (%)	Thermal heating yield (%)	Microwave yield (%)
53		IPP	S	High	40	-	5-42	47
54		IPP	S	High	40	0-15	20-39	16[a]
55		IPP	S	High	40	-	42	65
56		IPP	S	High	40	40	65	85
57		IPP	S	High	40	-	40	73
61		IPP	S	High	35	-	0	36
62		IPP	S	High	25	-	6-70	74
63		IPP	S	High	40	-	0	2[b]
64		ADD	S	High	40	0	0	60

a: **54** was obtained in low yield and was not pursued further.; *b*: **63** was obtained in very low yield and was used as a comparison to **54**. Product showed photochromic property on TLC but was not promising and synthetically difficult to obtain. *Note: Reactions were carried out in duplicate to ensure reproducibility.*

Table 9. Yields of furyl-fulgimides obtained through microwave-assisted synthesis

	R^2NH_2	R^1 (IPP/ ADD)	Z (S/O)	Microwave power	Time (min)	$ZnCl_2$ method yield (%)	Thermal heating yield (%)	Microwave yield (%)
65		IPP	O	High	40	-	~35	42
66		IPP	O	High	25	-	39	57
67		IPP	O	High	40	-	60	70
68		IPP	O	High	40	-	52	65
69		IPP	O	High	25	-	65	69
70		ADD	O	High	40	-	0	75

With reference to Table 8 and Table 9, we observed that the microwave-assisted synthesis of fulgimides generally led to a yield improvement when compared with the other methods tried. For fulgimide **53**, the yield obtained was almost identical to the traditional method of refluxing the fulgide with the amine. However, the more significant difference with the two reactions would be the faster reaction time and minimal use of organic solvent. We managed to obtain fulgimide **55** with a yield of 65%. This was generally an improvement of 23% over the classical approach. With this in mind, we decided to screen through several aromatic amines to determine if we could obtain better yields. Activated amines generally gave higher yields when we used the microwave approach.[74]

[74] Microwave reactions were carried out in duplicate in order to ascertain the reproducibility of the reaction. Scale up (5mmol) of the reaction towards fulgimide **70** also gave yields up to 70%.

Thienyl-fulgimides **55**, **56** and **57** were obtained with improved yields of up to 85%. Fulgimide **62** was also obtained with a respectable yield of 74%. However fulgimides **54** and **63** were obtained in very low yields for unknown reasons. As an added example to illustrate the synthetic usefulness and extent of this methodology, we tried our hand at using a deactivated amine to determine if we could obtain the fulgimide. After several failed attempts to obtain the 4-nitro-phenyl-thienyl fulgimide **61**, employing high reflux temperatures, we were still left with the starting fulgide, in excess. However, when we employed microwave to effect the condensation to form the half-amide, we were surprised that we were able to cause a high conversion of the starting material and obtain a rather low yield of **61** (36%). The outcome was superior to the thermal procedure.

Prior to the discovery of this microwave methodology, we were also interested in synthesizing the imide derivative of adamantanone(ADD)-thienyl fulgide **22** and ADD-furyl fulgide **23**. The reported literature methods were attempted and we could not obtain any desired product. Riding on the success of the ability to effect functionalization, even for an unactivated amine, we decided to use 4-bromo-aniline, **64**, to synthesize the brominated-adamantanone (ADD) fulgimide derivatives, **64** and **70**. This was to allow us to further extend the chemistry of the fulgimides through a possible Heck reaction with other potential substrates. We were able to obtain satisfactory yields of 60% for fulgimide **64** (Table 8) and 75% for fulgimide **70** (Table 9). Next, we also used furyl-fulgide **2** to synthesize the corresponding fulgimides **65-70**. Yields obtained were not as favorable as the thienyl-fulgimide analogs and were

up to 15% lower overall.[75] Comparatively, the thermal heating route afforded yields lower by up to 18%.

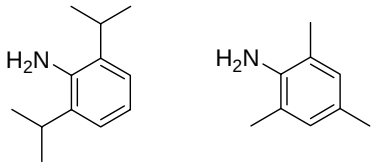


Figure 16. Unsuccessful usage of highly hindered amines to afford fulgimides

Some highly hindered amines were also explored to determine if they could be used to form the desired fulgimides (Figure 16) However, we could not effect the formation of the imide derivatives even after employment of other methods[76] or microwave heating.

[75] Comparison of yields for **56** and **67** which was 85% and 70% respectively

[76] NaH was used in the hope that the presence of a base would deprotonate the amine to facilitate the formation of the half-amide. Wolak, M. A.; Thomas, C. J.;Gillespie, N. B.; Birge, R. R.; Lees, W. J.; *J. Org. Chem.,* **2003**, *68(2),* 319-326.

4.5. COMPARISON OF PHOTOCHROMIC PROPERTIES OF THIENYL- AND FURYL-FULGIMIDES – STRUCTURAL INFLUENCES ON THE UV ABSORBANCES.

With reference to Table 10, using thienyl-fulgides **18** and **22** as references, we can see that the absorption maxima for the open forms of the fulgimides are blue-shifted by up to 16nm when the oxygen moiety on the anhydride core is replaced by nitrogen. This blue shift can be caused by the presence of the nitrogen causing the anhydride core to adopt a less planar structure. However, the absorption maxima for the closed form did decrease by up to 18nm for fulgimide **62**. Fulgimide **64**, with the adamantanone group, was the fulgimide that showed the biggest difference between the absorption maxima of the open form and the closed form. Comparison of the percentage conversion of the open form to the coloured form for fulgide **22** and fulgimide **64** showed a two-fold increase, although they displayed poor conversion percentages.

This result indicates that the presence of an imide functionality can possibly promote conversion rates. The presence of the large adamantylidene (ADD) group on the fulgide/fulgimide core is causing the bleaching of the coloured form. The presence of the large ADD group of **22** and **64** also caused a red shift of up to 36 nm when compared with the isopropylidene (IPP) analog **18**. As a general trend, the corresponding fulgimides displayed conversion rates to their coloured forms with slightly better or similar percentages.

The trend observed for the furyl-fulgimides is that the presence of the imide functionality caused a red shift of the coloured form by up to 20 nm (Table 10, fulgimide **67**). However, the conversion percentage was observed to decrease by up to 69%, for fulgimide **65**. Comparison of ADD-furyl fulgide **23** and ADD-furyl fulgimide **70** displayed that a red shift of up to 14 nm could be obtained by formation of the imide derivative, which is similar to the properties displayed by the IPP-furyl fulgimides.

4.6. CONCLUSION

Conversion rates to the coloured form were almost identical which indicated that the presence of the imide functionality did not affect the planarity of the coloured hexatriene moiety on colouration. As before, the attachment of the various functional groups like the free-terminal double bond on fulgimides **53, 65** and the bromo functionality on fulgimide **57**, **64**, **68**, and **70,** provides us with the option to further explore the possibility of enhancing conjugation, or attaching other structural moieties via olefin metathesis or the Heck coupling.

To conclude, we have successfully demonstrated the synthesis of fulgimides employing the microwave-assisted strategy to obtain satisfactory yields under mild conditions and short reaction times.

Table 10. UV-Vis Absorption Maxima (nm) in CH_2Cl_2, of Open and Closed form of the thienyl-fulgides **18** and **22**, furyl-fulgides **2** and **23** and corresponding fulgimides **53-70**.

Fg[a]	$\lambda_{max}O$[b] (nm)	A_O	ε_O ($mol^{-1}dm^3cm^{-1}$)	$\lambda_{max}C$[c] (nm)	A_C	ε_C ($mol^{-1}dm^3cm^{-1}$)	$\Delta\lambda_{max}$[d] (nm)	% Conversion[e]
18	342	1.48	68465	538	0.69	32063	196	46.8
22	340	2.20	40533	574	0.06	1099	234	2.7
53	330	1.22	50705	526	0.31	12999	196	25.6
54	Z: 330 E: 328	Z: 0.95 E: 0.70	Z: 33718 E: 45171	Z: 532 E: 532	Z: 0.30 E: 0.31	Z: 10709 E: 20044	Z: 202 E: 204	Z: 31.8 E: 44.4
55	Z: 330 E: 328	Z: 0.66 E: 1.28	Z: 18380 E: 39842	Z: 532 E: 534	Z: 0.28 E: 0.52	Z: 7879 E: 16390	Z: 202 E: 206	Z: 42.9 E: 41.1
56	326	1.06	342653	538	0.45	146703	212	42.8
57	334	0.81	175631	538	0.40	86908	204	49.5
61	330	0.65	27192	548	0.31	12951	218	47.6
62	330	1.99	199684	520	0.62	62106	190	31.1
63	330	2.36	298602	524	0.66	83877	194	28.1
64	340	1.09	43570	574	0.06	2297	234	5.3
2	346	0.97	52612	510	0.92	50278	164	95.6
23	348	1.25	51881	538	0.27	11069	190	21.3
65	338	0.85	18178	508	0.23	4911	170	27.0
66	336	1.19	57994	514	0.65	31587	178	54.5
67	334	0.91	88969	518	0.45	40648	184	45.7
68	336	1.31	60274	518	0.59	26988	182	44.8
69	338	0.97	36251	508	0.30	11249	170	31.0
70	340	1.08	322536	544	0.22	67897	204	21.1

a: Fulgide; *b*: Absorption maxima of Open-form.; *c*: Absorption maxima of Closed-form (Coloured form); *d*: Difference of Closed-form over Open-form; *e*: Percentage of Open-form converted to Closed-form (ε_c /ε_o x 100). Note: [C] of stock solutions were prepared in 1-8μmol and were repeated in duplicate.

PART I

CHAPTER 5

Exploration of other Potential Fulgides

5.1. EXPLORATION OF THE SYNTHESIS OF OTHER POTENTIAL FULGIDES

After the successful synthesis of the cycloalkylidene fulgides and the development of the microwave assisted fulgimide synthesis, we decided to explore the possibility of synthesizing more novel fulgides, in an attempt to extend the current chemistry of photochromic fulgides. In this respect, we decided to explore the synthesis of potential indolyl-fulgides,[77a-g] modifying the heteroatomic fragment of the fulgide core (Figure 4). We also seeked to explore the modification of R_2, in an effort to synthesize more possible analogs.

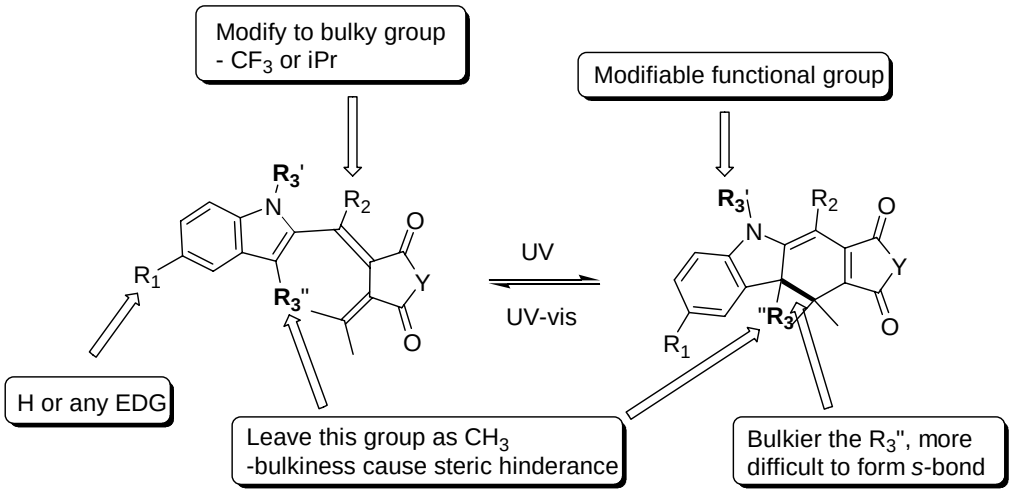
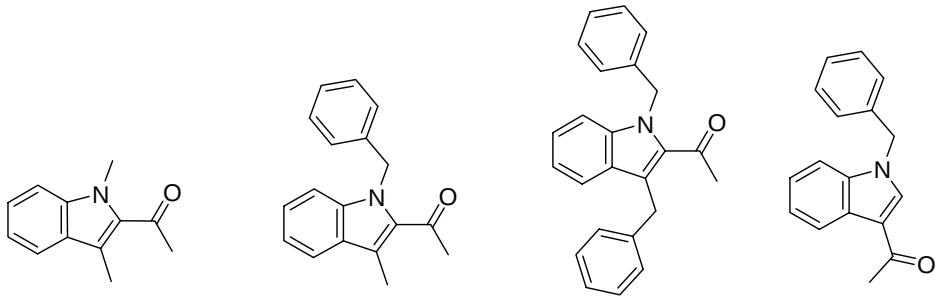


Figure 17. Modification strategy of indolyl fulgides

[77] (a) Minkin, V. I.; Medyantseva, E. A.; Lyashik, T.; Metelitsa, A. V.; Andreeva, I. M.; Knyazhankii, M. I.; Volbushiko, N. V. *Khim. Geterosiki Soedin*, **1986,** *11*, 1569-1570. (Chem. Abstr. 107, 58780, 1987). (b) Wang, H. Z. *Synthesis and photochromic reactions of indolyl fulgides, Doctoral dissertation, Beijing Institute oftechnology, Beijing, China* **1989**. (c) Li, Y. Z. *Synthesis and photochromic properties of heterocyclic fulgides, Doctoral dissertation, Beijing Institute of technology, Beijing, China* **1990**. (d) Matsushima, R.; Kaneko, A.; Tomoda, A.; lshizuka, M.; Suzuki, H. *Bull. Chem. Soc. Jpn.*, **1988,** *61(10),* 3569-3573. (d) Yokoyama, Y.; Kurita, Y. *J. Syn. Org. Chem. Jpn.*, **1991,** *49(5),* 364-372. (d) Wang, F.; Wang, H. Z.; Li, Y. Z.; Fan, G. Y.; Cui, X. S.; Liu, Z. C. *Acta. Chimica. Sinica Engl. Ed.*, **1989,** *4*, 349-355. (e) Fan, G. Y.; Wang, H. Z.; Cui, X. S.; Li, V. Z.; Zhu, H. S. *Acta Physico-Chimica Sinica*, **1992,** *8(4),* 545-549. (f) Y. Yokoyama, Y. Kurita, *Dyestuffs Chemicals*, **1992,** *37(6),* 143-154. (g) Yokoyama, Y.; Kurita, Y. *J. Chem. Soc. Jpn., Chem. Indus. Chem.*, **1992**, 998-1006.

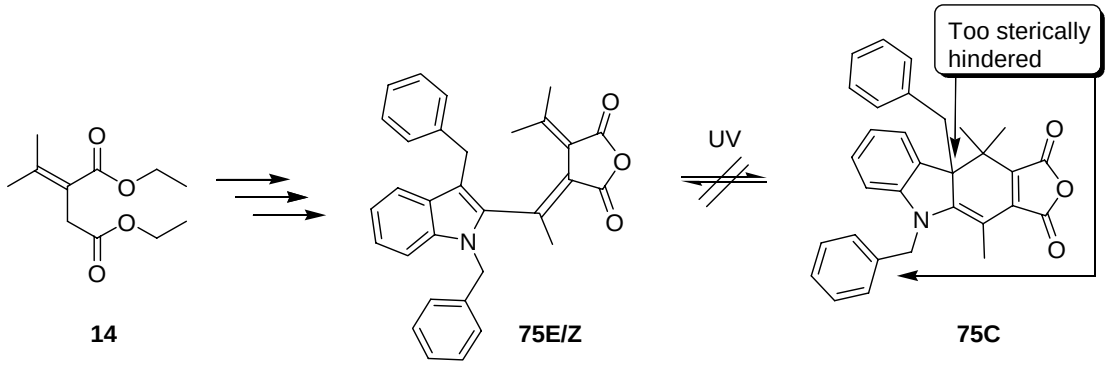
Referring to Figure 17, we noted that we could modify R_1 with electron-donating substituents (EDG), in order to increase bathochromic shifts.[77f, g, 78] R_2 could be modified to include bulkier groups such as CF_3 or ^{i}Pr (c.f. CH_3). R_3' and R_3" could also be modified with other functional groups.



71 (76%) **72** (12%) **73** (35%) **74** (44%)

Figure 18. Some acetylated indoles synthesized

With these several possible avenues of molecular tailoring options open to us, we managed to synthesize several acetylated indoles to be used to synthesize some proposed indolyl-based fulgides. The following acetyl indoles, **71**-**74**, were designed and synthesized according to literature procedures and were afforded with yields ranging 12 – 76% (Figure 18).



14 **75E/Z** **75C**

Scheme 32. Unsuccessful synthesis of fulgide **75**

[78] Yokoyama, Y.; Tanaka, T.; Yamane, T.; Kurita, Y. *Chem. Lett*. **1991**, 1125-1128.

Upon preliminary synthesis of the target indolyl-fulgides, even when we employed LDA instead of NaH as the base of choice for the second Stobbe condensation, we were not able to afford the fulgides that we desired, as even the crude NMR of the mono-acid did not show peaks that would indicate otherwise. To that extent, we suspected that the sterically bulky benzylated indoles were perhaps too bulky to afford even the mono-acids. We encountered this problem even when we tried to synthesize the already reported indolyl-fulgide using indole **71**. Usage of indoles **72** and **73** did not lead to any desired products.

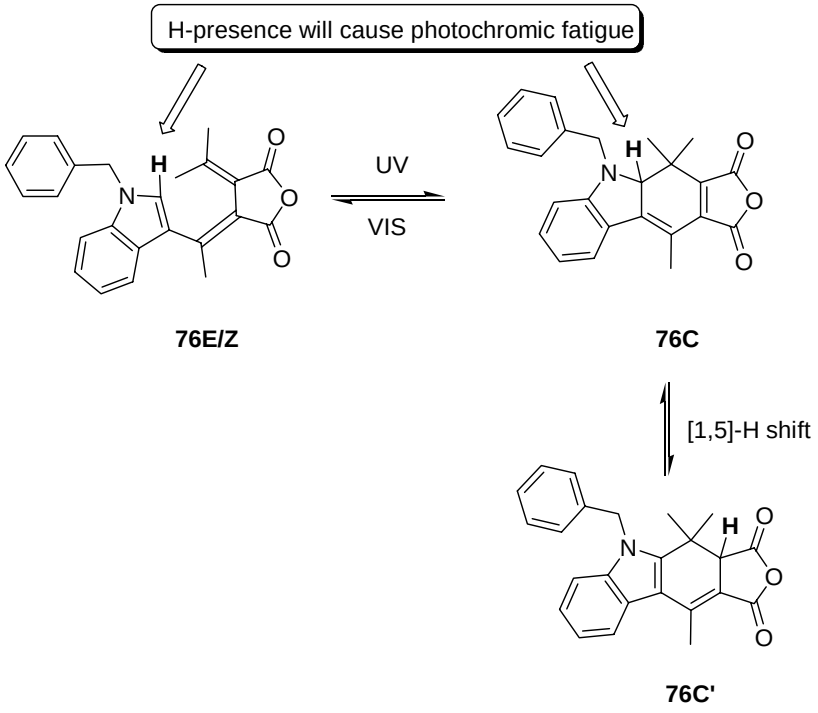


Figure 19. Potential [1,5]-H shifts that would potentially cause photochromic fatigue of fulgide **76**

We decided not to use indole **74**, as from literature reports, we suspected that there would be in fact [1,5]-H shifts that would cause photochromic fatigue of proposed fulgide **76C** and was deemed not a promising indolyl-fulgide to target (Figure 19).

5.2. POSSIBLE EXTENSION OF FULGIDE CHEMISTRY – INCORPORATION OF POLYHEDRAL OLIGOMERIC SILSESQUIOXANES (POSS)

Polyhedral Oligomeric Silsesquioxanes or POSS are a versatile class of hybrid materials. Silsesquioxanes usually have a general formula $(RSiO_{1.5})_n$ where n = 8 – 14 and R can be an organic functionality, hydrogen, $OSiR_3$, etc. These compounds are basically a hybrid between silicones (R_2SiO) and silica (SiO_2). Since the 1930s, silsesquioxanes have been used in silicone technology for coatings in electronics and optical devices and optical fiber coatings.[79a-d]

Some properties of POSS-based system(polymers) include "self-healing" high-temperature nanocomposites and space-survivable coatings,[80a, b] increased thermal stability (extended temperature range), low-k dielectric materials,[81] high glass transition temperature, lowering of overall density, reduced flammability, high chemical resistance, increased oxygen permeability, enhanced blend miscibility, oxidative resistance, altered mechanicals and reduced viscosity.[82] POSS-based systems can also serve as templates for the preparation of nanostructured materials such as liquid crystalline polymers, catalysts, dendrimers, and multiarm star polymers.[83a-e]

[79] (a) Voronkov, M. G.; Lavrent'yev, V. I.; *Top. Curr. Chem*. **1982**, 102, 199. (b) Baney, R. H.; Itoh, M.; Sakakibara, A.; Suzuki, T. *Chem. Rev*. **1995**, *95*, 1409. (c) Agaskar, P. A. *Inorg. Chem.* **1991**, *30*, 2707. (d) Lucke, S.; Stoppek-Langner, K. *Applied Surface Science*. **1999**, 144-145, 713-317.
[80] (a) Gonzalez, R. I.; Phillips, S. H.; Hoflund, G. B. *J. Spacecr. Rockets* **2000**, *37*, 463. (b) Hoflund G. B.; Gonzalez, R. I.; Phillips, S. H. *J. Adhes. Sci. Technol.* **2001**, *15*, 1199.
[81] Hacker, N. P. *MRS Bull.* **1997**, *22*, 33.
[82] Please refer to the website: www.hybridplastics.com for more information.
[83] (a) Laine, R. M.; Zhang, C.; Sellinger, A.; Viculis, L. *Appl. Organomet. Chem.* **1998**, *12*, 715. (b) Feher, F. J.; Newman, D. A.; Walzer, J. F. *J. Am. Chem. Soc.* **1989**, *111*, 1741. (c) Duchateau, R.; Abbenhuis, H. C. L.; van Santen, R. A.; Meetsma, A.; Thiele, S. K.-H.; van Tol, M. F. H. *Organometallics* **1998**, *17*, 5663. (d) Ropartz, L.; Foster, D. F.; Morris, R. E.; Slawin, A. M. Z.; Cole-

In our lab, we were hoping to be able to incorporate the fulgides synthesized earlier into POSS-based systems; in this case, we were targeting the synthesis of photochromic POSS-based siloxy-cubes. We intended to use the bromo- or olefin-functionality to effect the formation of (up to eight) possible photochromic components on the POSS-cube. We decided to use octavinyl-POSS (OVPOSS) for the intended reactions. As can be seen from Figure 20, OVPOSS has a thermally and chemically robust framework to allow further molecular tailoring of its octavinyl-functionality.

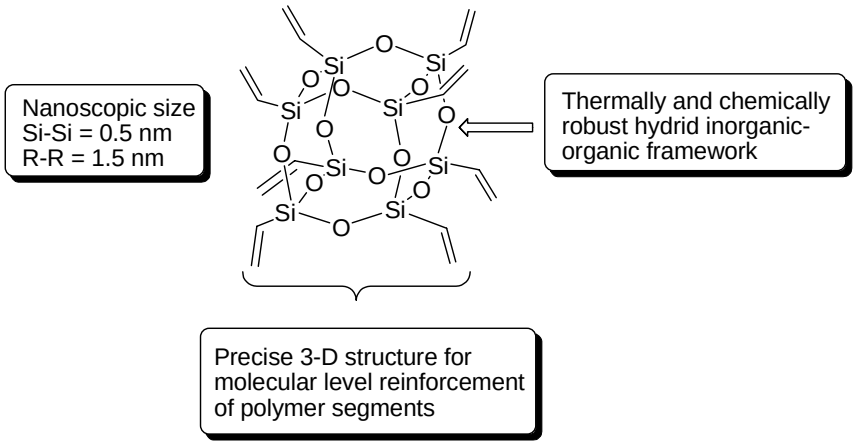
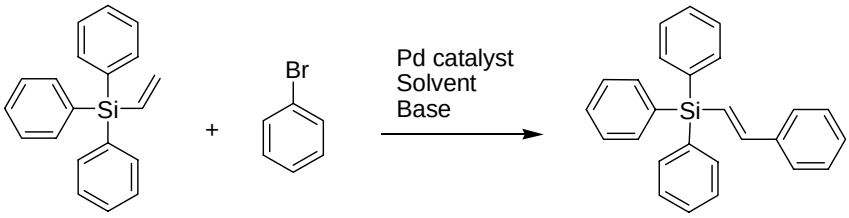


Figure 20. Octavinyl-Polyhedral Oligomeric Silsesquioxanes (OVPOSS) cage structure

As a preliminary study into the possible coupling of substituents on the olefin substituents on OVPOSS, we decided to investigate the viability of the Heck coupling with vinyl substituents on a siloxy-based system. Taking this into consideration, we decided to utilize tri-phenyl vinyl silane, **77**, and bromo-benzene, **78**, for model Heck[84, 85a-i] coupling studies (Scheme 31). Attempts to use styrene or a-methyl styrene in place of the vinyl silane surprisingly resulted in negative results.

Hamilton, D. J. *J. Chem. Soc., Dalton Trans.* **2002**, 1997. (e) Mengel, C.; Meyer, W. H.; Wegner, G. *Macromol. Chem. Phys.* **2001**, *202*, 1138.
[84] Heck, R. F. *Acc. Chem. Res.* **1979,** *12,* 146-152.



77 **78** **79**

Scheme 33. Heck coupling of tripehnyl vinyl silane **77** with bromo-benzene **78**

We were not able to afford the desired target molecule when we used reported literature methods employing classical thermal methods or more recently reported procedures.[86a-d] As such, we decided to explore the possibility of employing other methods to afford the Heck-coupled product **79**.

[85] Selected leading reviews and monographs on the Heck reaction and related reactions promoted by Pd catalysts: (a) *Palladium Reagents in Organic Synthesis*; Heck, R. F.; Academic Press: London, UK, 1985. (b) *Comprehensive Organic Synthesis*; Heck, R. F.; Trost, B. M.; Flemming, I.; Eds.; Pergamon: New York, **1991**; *4(4.3)*. (c) *Palladium Reagents and Catalysts*; Tsuji, J.; John Wiley: Chichester, UK, **1995**. (d) *Metal Catalyzed Cross Coupling Reactions;* Bräse, S.; de Meijere, A.; Diederich, F.; Stang, P. J.; Eds. Wiley: New York, **1998**, *3*. (e) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379-2411. (f) Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427-436. (g) Casey, M.; Lawless, J.; Shirran, C. *Polyhedron* **2000**, *19*, 517-520. (h) Beletskaya, I. P.; Cheprokov, A. *Chem. Rev.* **2000**, *100*, 3009-3066. For a recent discussion on the industrial aspects of the Heck reaction, see: Tucker, C. E.; de Vries, J. G. *Top. Catal.* **2002**, *19*, 111-118.

[86] (a) Heck, R. F.; Nolley, Jr. J. P. *J. Org. Chem*, **1972,** *37(14)*, 2320-2322. (b) Malek, N. J.; Moormann, A. E. *J. Org. Chem*, **1982**, *47*, 5395-5397. (c) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.*, **2001,** *123(29)*, 6989-7000. (d) Yao, Q.; Kinney, E. P.; Yang, Z. *J. Org. Chem*. **2003**, *68*, 7528-7531.

Table 11. Ligandless, ionic-liquid supported, microwave-assisted Heck coupling towards molecule **79**.

Entry	Halide	Catalyst	Base	Solvent	Co-solvent	Reaction condition[g]	% Yield
1[a]	Br-aniline	$Pd[P(^tBu)_3]_2$	NCy_2Me	1,4-dioxane	-	Heat 110°C (18h)	0
2	PhBr	$Pd(OAc)_2$	NaOAc	N,N-DMF	-	Heat 140°C (24h)	<1
3	PhBr	$Pd(OAc)_2$	NaOAc	N,N-DMF	-	MW (10m, M)	41
4[b]	PhBr	$Pd(OAc)_2$	$N(nBu)_3$	-	-	MW (10m, M)	<1
5[c]	PhBr	$Pd(OAc)_2$	$N(nBu)_3$	N,N-DMF	-	MW (10m, M)	5
6	PhBr	$Pd(OAc)_2$	NCy_2Me	N,N-DMF	-	MW (10m, M)	0
7[d]	PhBr	$Pd(OAc)_2$	NCy_2Me	N,N-DMF	$[BMIM][BF_4]$	MW (10m, M)	3
8[e]	PhBr	$Pd(OAc)_2$	NaOAc	N,N-DMF	$[BMIM][BF_4]$	MW (10m, M)	79
9	PhBr	$Pd(OAc)_2$	NCy_2Me	N,N-DMF	$[BMIM][BF_4]$	MW (10m, M)	3
10	PhBr	$Pd(OAc)_2$	NaOAc	N,N-DMF	$[BMIM][BF_4]$	MW (10m, M)	79
11[f]	PhBr	$PdCl_2$	NaOAc	N,N-DMF	$[BMIM][PF_6]$	MW (10m, ML)	3
12	PhBr	$Pd(OAc)_2$	NaOAc	N,N-DMF	$[BMIM][BF_4]$	MW (10m, ML)	86
13	PhBr	$Pd(OAc)_2$	NaOAc	N,N-DMF	$[BMIM][PF_6]$	MW (10m, ML)	82
14[f]	PhBr	$PdCl_2$	NaOAc	N,N-DMF	$[BMIM][BF_4]$	MW (10m, ML)	57

a: Ref: 83c. *b*: Attempted solvent-free conditions. *c*: Use of organic base $N(nBu)_3$. *d*: Employment of organic base with IL. *e*: Employment of inorganic base with IL. *f*: Vallin, K. S. A., Emilsson, P., Larhed , M., Hallberg A., *J. Org. Chem.*, 67 (17), 6243 -6246, 2002. *g*: Microwave power M = Medium, ML = Medium Low

We were unsuccessful trying to afford product **79** via thermal methods using $Pd(OAc)_2$ or $Pd[P(^tBu)_3]_2$ (Table 11, Entry 1 & 2). We then decided to employ

microwave heating[87a-e] as an alternative solution. On employing this milder and faster approach, we were able to successfully obtain **79** with a yield of 41%, after 10mins of microwave heating (Table 11, Entry 3). Solvent free microwave reaction for Entry 4 did not generate even a trace of the product. Even with a change of base from $N(nBu)_3$ to NCy_2Me, we were not able to obtain any product (Table 11, Entry 5, 6).

With reference to some reported literature methods that ionic liquids could be also used in microwave-assisted Heck reactions, we also decided to explore the avenue of using "green-solvents"[88a-h] to carry out the Heck coupling. However, when we tried the Heck reaction using only ionic liquids[89] as the solvent, we were not able to obtain any coupled product. We also tried running the reaction using both organic base and an ionic liquid (IL), but the reaction only afforded about 3% yield of **79** (Table 11, Entry 7). Undeterred, we went on to use a 1:10 ratio of IL:Solvent and were able to obtain a two-fold increase in the yield obtained for **79** (Table 11, Entry 8) when we employed NaOAc. The IL is suspected to act either as a support for the Pd catalyst or as a dispersant. Initially, we observed that the formation of palladium black was almost instantaneous during the microwave heating. However, we also observed the formation of a relatively homogeneous black solution eventually. This could indicate that the fine particles of the Pd could have been able to disperse and spread more evenly on addition of an IL. This could effectively increase the surface area for

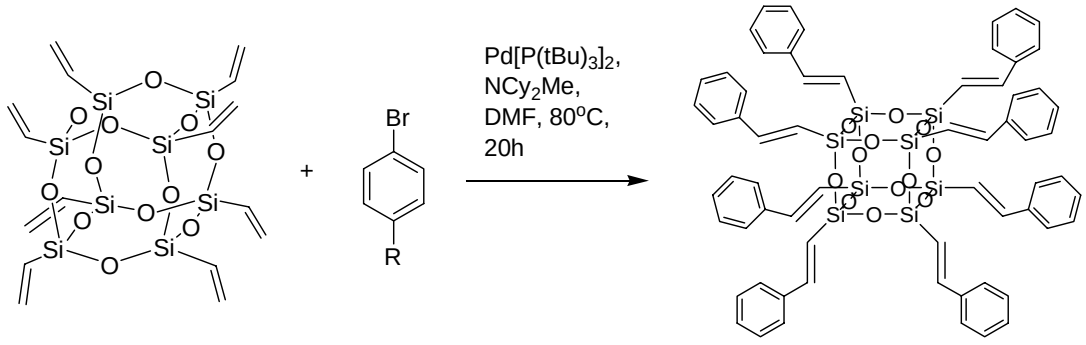
[87] (a) Larhed, M.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 9582-9584. (b) Vallin, K. S. A.; Larhed, M.; Johansson, K.; Hallberg, A. *J. Org. Chem.* **2000**, *65*, 4537-4542. (c) *Drug Discovery Today;* Larhed, M.; Hallberg, A. **2001**, *6*, 406-416. (d) Strauss, C. R.; Trainor, R. W. *Aust. J. Chem.* **1995**, *48*, 1665-1692. (e) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225-9283.

[88] (a) Curran, D. P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1175-1196. (b) *Aqueous Phase Organometallic Catalysis*; Cornils, B., Herrman, W. A., Eds.; Wiley-VCH: Weinheim, Germany, **1998**. (c) Jessop, P. G.; Ikariya, T.; Noyori, R. *Chem. Rev.* **1999**, *99*, 475-493. (d) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009-3066.(e) Welton, T. *Chem. Rev.* **1999**, *99*, 2017-2083. (f) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3772-3789. (g) Sheldon, R. *Chem. Commun.* **2001**, 2399-2407. (h) Leadbeater, N. E.; Torenius, H. M. *J. Org. Chem.* **2002**, *67*, 3145-3148.

[89] Ionic liquids (IL) used: $[BMIM][BF_4]$ and $[BMIM][PF_6]$.

the Pd to catalyze the reaction. We then went back to the usage of an organic base, NCy_2Me, but were again disappointed with the results (Table 11, Entry 9). The usage of $PdCl_2$ instead of $Pd(OAc)_2$ and using IL [BMIM][PF_6] instead of [BMIM][BF_4] did not effectively increase the yield as well (Table 11, Entry 11). We then re-employed $Pd(OAc)_2$, NaOAc and [BMIM][BF_4] and were able to get a better yield of up to 86% (Table 11, Entry 12) with a lower power setting as well. The change of IL used from [BMIM][BF_4] to [BMIM][PF_6] in the presence of $Pd(OAc)_2$ seemed to lower the yield slightly to 82% (Table 11, Entry 13). The usage of $PdCl_2$ and [BMIM][PF_6] also resulted in a lower yield (Table 11, Entry 14).[90]

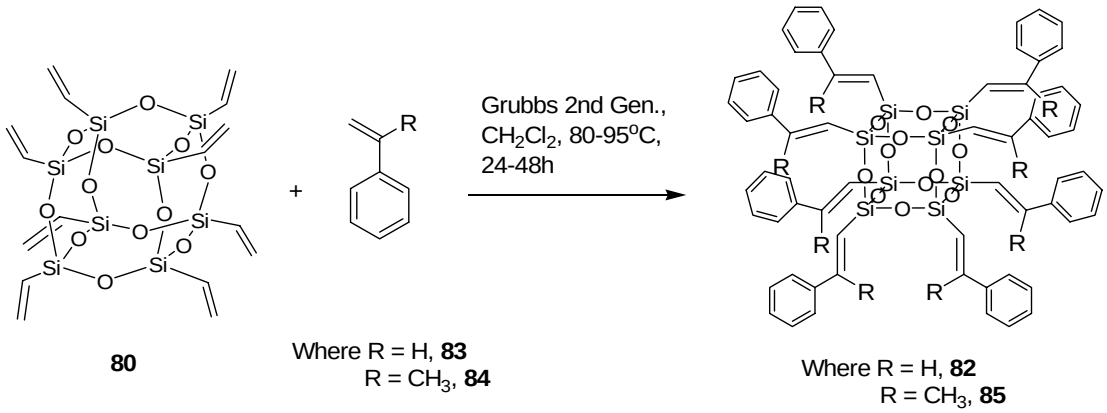
Based on the success of this ligandless, ionic liquid supported and microwave-assisted Heck coupling methodology, we decided to use this method towards the synthesis of the photochromic POSS-based siloxy-cubes.



Scheme 34. Octasubstituted POSS **82**

[90] On prolonged heating on medium power, HF is suspected to evolve from the reaction vessel as white fumes can be observed although not confirmed.

We decided to use OVPOSS, **80**, with bromobenzene, **81** (R=H), as the final model for the Heck coupling first as we wanted to ensure that the microwave-assisted Heck coupling could also be applied for the POSS systems. We were not able to effect the coupling of bromobenzene to the OVPOSS cage and only managed to obtain the coupled product **82** in 17% yield (Scheme 34).[91]



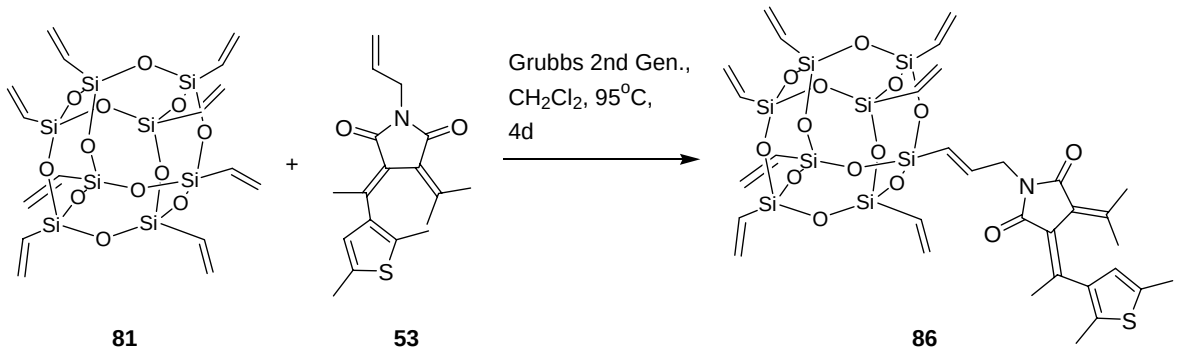
Scheme 35. Octasubstituted **POSS 82** and **85**

Due to the presence of the octa vinyl-functionality on OVPOSS (Figure 20), we decided also to explore the possibility of carrying out olefin metathesis reactions on the siloxy-cage. In fact a few literature reports have already been published with regards to this particular strategy. Kubicki *et al.*[92] has published an article stating this methodology with great success. We also employed Grubbs Second generation catalyst to reproducible success in the cross-metathesis reaction involving OVPOSS and styrene (Scheme 35). We managed to obtain **82** with an almost quantitative yield and **85** with a yield of up to 60%.[93] **82** could be obtained with excellent yield by just refluxing the reaction mixture overnight or up to 24h, using Grubbs second generation

[91] This was after numerous attempts changing base used, Pd catalyst used, catalyst loading, reaction time, reaction temperature, microwave power, solvents used, co-solvents used and usage of phosphine ligands.
[92] Itami, Y.; Marciniec, B.; Kubicki, M. *Chem. Eur. J*. **2004**, *10*, 1239-1248.
[93] MALDI-TOF results indicated the presence of a major peak at 1349.5580 (c.f. 1349.0973).

catalyst. In fact, when we employed Grubbs first generation catalyst, we were also able to obtain **82** with a yield of up to 95%.[94] MALDI-TOF was used to determine the presence of the coupled product and the obtained results matched the expected results very closely.

However, interestingly, we were not able to obtain **85** after 18 – 24h of stirring at 80°C. When we stirred the mixture at 95°C for 48h, we were able to obtain the octa-substituted product as the major product with up to 60% yield. The heptyl-substituted product was also present in a smaller amount. MALDI-TOF analysis indicated the presence of the octa-substituted product at a m/z of 1461.7550 (+ Ag; c.f. Calcd. 1461.2225) and the heptyl-substituted product at a m/z of 1371.6720 (+ Ag; c.f. Calcd. 1371.1756). The presence of a free olefin motif was also confirmed by ^{1}H NMR.[95]



81 **53** **86**

Scheme 36. Mono-substituted POSS **86**

As we were able to obtain respectable yields of the required coupled products, we were spurred on to use fulgimide **53** to investigate if we could potentially obtain

[94] We were able to obtain the octa-substituted product as the major product with traces of heptyl-substituted product.
[95] Please refer to the chapter of supporting information.

the octyl-substituted POSS that we desired. However, from preliminary ^{1}H NMR and MALDI-TOF results, we seemed to have only obtained the mono-substituted product **86**, in low unisolable yield. From TLC, we could still observe the large presence of the starting fulgimide **53** in the presence of streaks, which did indicate the presence of photochromic products as they changed from colourless to slightly purplish upon exposure to UV-irradiation. This result was only obtained after we refluxed the reaction mixture for 4 days in the presence of Grubbs second generation catalyst. When we employed Grubbs first generation catalyst, we did not obtain any product at all and only starting fulgimide **53** was present.

5.3. CONCLUSION AND FUTURE WORK – EXPLORATION OF PHOTOCHROMIC NANOPARTICLES

Our future work would include the further extension of the chemistry of fulgides and the possibility of synthesizing photochromic polymers with the utilization of OVPOSS. We hope to be able to form photochromic nanoparticles that could be, in turn, formed into polymers. We are also targeting the synthesis of photochromic indolyl-based fulgides as these fulgides seem to display good photochromic as well fluorescent properties. The key strategy towards such fulgides would be the modification of substituents on the indole moiety, in order to study other effects that might affect photochromic properties. We have also selected several fulgides to be included in the chemical genetics screening project (Please refer to APPENDIX section).

PART II

PART II – SYNTHETIC STUDIES TOWARDS ANTI-SARS AGENT AG7088

PART II

CHAPTER 1

Introduction to SARS

1.1. INTRODUCTION TO SEVERE ACUTE RESPIRATORY SYNDROME (SARS)

Severe Acute Respiratory Syndrome (SARS) was first reported in Asia in February 2003. Epidemiological evidence suggests that the transmission of this pathogen occurs mainly by face-to-face contact, although other routes of transmission cannot be fully excluded. Over a few months, the disease has spread from its likely origin in Southern China to more than two dozen countries in North America, South America, Europe, and Asia with more than 8000 cases of infection (Table 1).[1]

Table 1. Number of infections and deaths caused by SARS (based on data as of 31st December 2003)

Country	Infections	Deaths
China	5237	349
Hong Kong	1755	299
Taiwan	346	37
Canada	251	43
Singapore	238	33
Viet Nam	63	5
The World	**8096**	**774**

At present, no efficacious therapy is available. However, even though the outbreak has been well-contained, there is the possibility that the disease might re-emerge once again, especially during the colder and more humid winter months.[1b] It is therefore paramount that we still carry on the search for a possible cure. SARS is mainly characterized by high fever, malaise, rigor, headache, and non-productive cough or dyspnoea and may progress to generalized interstitial infiltrates in the lung.

[1] Please refer to: (a) http://www.who.int/csr/sars/country/en/ (b) http://www.cdc.gov/ncidod/sars/ (c) http://sarsdisease.org/who.shtml

This might require intubations and possible mechanical ventilation.[2] The fatality rate among people with the illness is around 15%.[1b]

Human coronaviruses (HCoV) are major causes of upper respiratory tract illness in humans, in particular, the common cold.[3] To date, only the 229E strain of HCoV has been characterized in detail because it used to be the only isolate that grows efficiently in cell culture. A novel coronavirus has been identified as the causative agent of severe acute respiratory syndrome (SARS). The viral main proteinase (M^{pro}, also frequently called $3CL^{pro}$), controlling the activities of the coronavirus replication complex, represents an attractive target for therapy.[4b]

1.2. SARS-CoV 3CL PROTEASE ($3CL^{PRO}$) BACKGROUND

Generally, viruses have proteases to process their proteins into active form. Because of its pivotal role in the viral life cycle, proteases are primary targets for the development of antiviral agents. 3CL protease ($3CL^{pro}$), a viral cysteine proteinase, plays an important role in co-translational proteolytic processing of coronavirus polyproteins. The $3CL^{pro}$ cleaves as much as 11 sites in the replicase polyproteins and also releases the key replicative functions of polymerase and helicase. $3CL^{pro}$ is the only coronavirus protein for which structural information is available and basically comprises three domains. The substrate-binding site is expected to be located between domains I and II, and domain III is a globular cluster comprising five helices.

[2] Lee, N.; Hui, D.; Wu, A.; Chan, P.; Cameron, P.; Joynt, G. M.; Ahuja, A.; Yung, M. Y.; Leung, C. B.; To, K. F.; Lui, S. F.; Szeto, C. C.; Chung, S.; Sung, J. *N. Engl. J. Med.* **2003,** *348*, 1986-1994.
[3] *The Coronavirdae*, Myint, S. H.; S. G. Siddell, Ed. **1995**, 389.

The spike (S) glycoprotein is a good candidate for vaccines because neutralizing antibodies are directed against S. Blockade of the specific virus receptor on the surface of the host cell by monoclonal antibodies or other ligands can prevent virus entry. The polyprotein of the replicase protein is cleaved into functional units by virus-encoded protease. Protease inhibitors may block replication. The membrane (M) protein required for virus budding, the envelope (E) protein plays a role in coronavirus assembly, the nucleocapsid (N) phosphoprotein associated with viral RNA inside the virion. Theoretically, all these steps can be used as targets to screen anti-SARS drugs.[4a-e]

However, the SARSCoV $3CL^{pro}$ is a preferred target for the task of discovering anti-SARS drugs by the following reasons: (1) the SARS-CoV $3CL^{pro}$ possibly plays an important role in the SARS-CoV replication as deduced from the function of the $3CL^{pro}$ of other coronaviruses; (2) numerous inhibitors of other $3CL^{pro}$ are available and several of them are in clinical test, if some of them show anti-SARS activity, they can be developed as anti-SARS drug rapidly; (3) SARS-CoV $3CL^{pro}$ can be expressed in *E. coli* strain, and thus screening model can be establish quickly; (4) homology modeling can be employed to construct the three-dimensional (3D) structure of this protease because highly homologous protein with X-ray crystal structure has been found, thereby structure-based drug design methods, such as virtual

[4] (a) Holmes, K. V. *J. Clin. Invest.* **2003**, *111*, 1605-1609. (b) Anand, K.; Ziebuhr, J.; Wadhwani, P.; Mesters, J. R.; Hilgenfeld, R. *Science* **2003**, *300(16)*, 1763-1773. (c) Li, G.; Chen, X.; Xu, A. *N. Eng. J. Med.* **2003**, *349*, 508-509. (d) Simmons, G.; Reeves, J.D.; Rennekamp, A.J.; Amberg, A.M.; Piefer, A.J.; Bates, P. *Proc. Natl. Acad. Sci.* **2004**, *101(12)*, 4240-4245. (e) Loutfy, M.R.; Blatt, L.M.; Siminovitch, K.A.; Ward, S.; Wolff, B.; Lho, H.; Pham, D.H.; Deif, H.; LaMere, E.A.; Chang, M.; Kain, K.C.; Farcas, G.A.; Ferguson, P.; Latchfold, M.; Levy, G.; Dennis, J.W.; Lai, E.K.; Fish, E.N. *Jama* **2003**, *290*, 3222-3228.

screening, can be applied to search active compounds from the compound databases.[5a-d]

The SARS-CoV proteins required for genome replication and transcription are encoded by the large replicase gene. This gene encodes two very large replicative polyproteins, namely pp1a (~450 kDa) and pp1b (~750 kDa) that are subsequently processed by virus-encoded proteases to release a group of functional subunits of the replication complex. The cleavage of the polyproteins is usually executed by two to three cystein proteases, one with a chymotripsin fole and the other two with a papain-like topology. It is known that the central and C-proximal regions of pp1a and pp1b are cleaved by the 33 kDa viral protease with the chymotripsin fold which was called 'main protease' or alternatively, the '3C-like protease ($3CL^{pro}$)' to indicate the similarity with the picovirus 3C protease in sharing the chymotripsin fold and cleavage specificity.

The SARS-CoV $3CL^{pro}$ is a chymotrypsin-like protease that uses a Cys rather than a Ser residue as the nucleophile in the active site. The SARS-CoV $3CL^{pro}$ employs a catalytic Cys-His dyad and contains 304 amino acids, folded into three domains. Domains I and II (residues 8 to 99 and 100 to 183, respectively) are six-stranded antiparallel β barrels and together resemble the architecture of chymotrypsin and of piconavirus 3C protease. The substrate-binding site is located in a cleft

[5] (a) Chou, K. C.; Wei, D. Q.; Zhong, W. Z. *Biochem. Biophys. Res. Commun.* **2003**, *308*, 148. (b) Yang, H.; Yang, M.; Ding, Y.; Liu, Y.; Lou, Z.; Zhou, Z.; Sun, L.; Mo, L.; Ye, S.; Pang, H.; Gao, G.F.; Anand, K.; Bartlam, M.; Hilgenfeld, R.; Rao, Z.; *Proc. Nat. Acad. Sci*. **2003**, *100(23)*, 13190-13195. (c) Yamamoto, N.; Yang, R.; Yoshinaka, Y.; Amari, S.; Nakano, G.; Cinatl, J.; Rabenau, H.; Doerr, H.W.; Hunsmann, G.; Otaka, A.; Tamamura, H.; Fujii, N.; Yamamoto, N. *Biochem. Biophys. Res. Commun*. **2004**, *318*, 719-725. (d) Xiong, B.; Gui, C.S.; Xu, X.Y.; Luo, C.; Chen, J.; Luo, H.B.; Cheng, L.L.; Li, G.W.; Sun, T.; Yu, C.Y.; Yue, L.D.; Duan, W.H.; Shen, J.K.; Qinm L.; Shi, T.L.; Li, Y.X.; Chen, K.X.; Luo, X.M.; Shen, X.; Shen, J.H.; Jiang, H.L. *Acta. Pharmacol. Sin.* **2003**, *24(6)*, 497-504.

between these two domains. A long loop (residues 184 to 199) connects domain II to the Cterminal domain (domain III, residues 200 to 300). The SARS-CoV $3CL^{pro}$ cleaves the polyprotein at no less than 11 conserved sites involving Leu-Gly ↓ (Ser,Ala,Gly) sequences (the cleavage site is indicated by ↓), a process initiated by the enzyme's own autolytic cleavage from pp1a and pp1ab. This cleavage pattern appears to be conserved in the $3CL_{pro}$ from SARS-CoV.[6a-g]

1.3. ACTIVE SITE AND BINDING POCKET OF SARS-COV $3CL^{PRO}$ FOR INHIBITORS.

In contrast to common serine proteases, which have a Ser-His-Asp catalytic triad, SARS-CoV $3CL^{pro}$ has a Cys-His catalytic dyad (Cys-145 and His-41). This is similar to transmissible gastrointestinal virus main protease (TGEV M^{pro}) and human coronavirus main protease (HcoV M^{pro}) (Cys-144 and His-41). In the substrate catalytic reaction of SARSCoV $3CL^{pro}$, Cys145 acts as the nucleophilic attacking agent and His145 figures as an acid base catalyst. The distance between the S atom of Cys145 and Nε2 atom of His41 is 3.81 Å. The substrate-binding site is located in the deep cleft between domains I and II, lined by hydrophobic residues and oxyanion hole (Figure 1).[5b]

[6] (a) Zieburhr, J.; Heusipp, G.; Siddell, S.G. *J. Virol*. **1997**, *71*, 3992-3007. (b) Fan, K.; Wei, P.; Feng, Q.; Chen, S.; Huang, C.; Ma, L.; Lai, B.; Pei, J.; Lui, Y.; Chen, J.; Lai, L.; *J. Bio. Chem*. **2004**, 1637-1642. (c) Huang, C.; Wei, P.; Fan, K.; Liu, Y.; Lai, L.; *Biochem* **2004**, *43*, 4568-4574. (d) Lin, C.W.; Tsai, C.H.; Tsai, F.J.; Chen, P.J.; Lai, C.C.; Wan, L.; Chiu, H.H.; Lin, K.H. *FEBS Lett* **2004**, *574*, 131-137. (e) Zhang, X.W.; Yap, Y.L. *Bioorg. & Med. Chem.* **2004**, *12*, 2219-2223. (f) Lee, V.S.; Wittayanarakul, K.; Remsungnen, T.; Parasuk, V.; Sompornpisut, P.; Chantratita, W.; Sangma, C.; Vannarat, S.; Srichaikul, P.; Hannongbua, S.; Saparpakorn, P.; Treesuwan, W.; Aruksakulwong, O.; Pasomsub, E.; Promsri, S.; Chuakheaw, Hannongbua, S. *ScienceAsia* **2003**, *29*, 181-188. (g) Zieburhr, J. *Curr. Opin. Microbiol.* **2004**, *7*, 412-419.

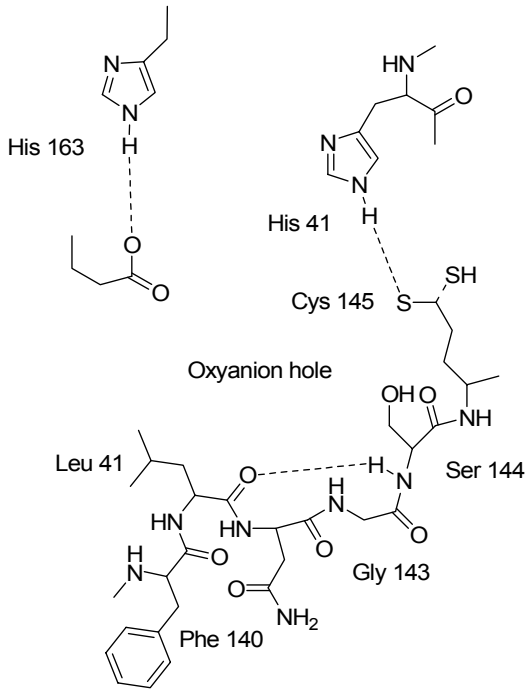


Figure 1. A schematic presentation of the substrate binding pocket of SARS-CoV $3CL^{pro}$

There is a relatively large number of lead compounds from several molecular structure classes that reported thus far for inhibiting SARS-CoV $3CL^{pro}$. The SARS-CoV $3CL^{pro}$ inhibitor AG7088 fall into the general class of peptide based analogues.

1.3.1. PEPTIDE SARS-COV $3CL_{PRO}$ INHIBITORS

The SARS-CoV $3CL^{pro}$/inhibitor complex structures have been determined by X-ray crystallography and have been used to guide the rational design of SARS-CoV $3CL^{pro}$ inhibitors. Structure of the complex formed by SARS-CoV $3CL^{pro}$ with the substrate analogue hexapeptidyl chloromethyl ketone (CMK) inhibitor, Cbz-Val-Asn-Ser-Thr-Leu-Gln-CMK, showed that a covalent bond between the Sγ atom of Cys-145 and the methylene group of the CMK stabilize the conformation of substrate-analogue CMK in the substrate binding site. This crystal structure provides a solid

basis for the design of anti-coronaviral drugs.[5b] Chou *et al.* studied the binding interactions of KZ7088 by molecular docking. KZ7088 is a derivative of AG7088, the latter was developed by *Pfizer* and its currently in clinical trials for the treatment of rhinovirus, a pathogen that can cause the common cold (Figure 2). Although it is a putative candidate for docking studies related to SARS drug finding, AG7088 has a p-fluorophenylalanine side chain (p-fluorobenzyl), with might be too long (or bulky) to fit into the relevant binding pocket. Accordingly, KZ7088 with a modified side chain by removing $–CH_2$ could serve as a starting point for modification that will quickly lead to effective drug candidates for the treatment of SARS. It has been observed that KZ7088 interacts with the active site of SARS-CoV $3CL^{pro}$ through six hydrogen bonds.[5a]

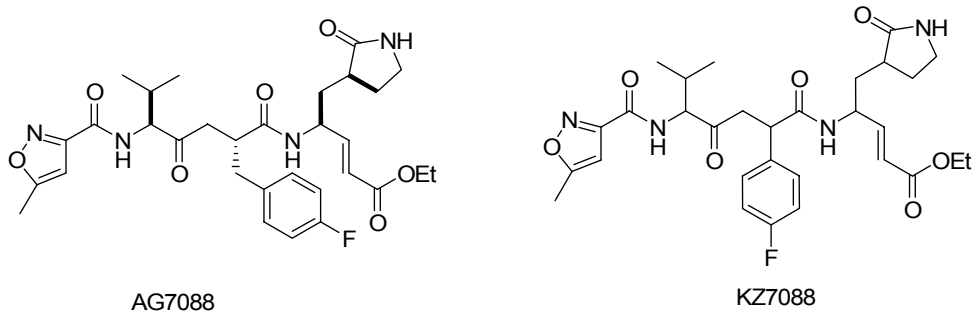


Figure 2. Molecular structure of AG7088 and its analog KZ7088

Amongst the many possible approaches, proteinase inhibitor development is perhaps the most attractive route for synthetic chemists. Proteinases play an important role in the process of virus replication as well as in the pathophysiology of many viral diseases. Many viruses, including the SARS coronavirus, rely on a protein-cleaving enzyme called main proteinase to activate their replication. Such viruses must

replicate themselves in order to cause infection, making this enzyme a primary target for the drug to be developed.

In order to find an efficient therapy for SARS, many scientists are focusing on the development of drugs that inhibit the viral main proteinase (SARS-CoV M^{pro}) and disrupt the replication cycle of the virus. In May 2003, Hilgenfeld and co-workers showed that the substrate-binding site in SARS-CoV M^{pro} is well conserved compared to those in two other coronavirus main proteinases (HCoV 229E and TGEV M^{pro}).[5b] In addition, they reported similarities between substrate/inhibitor-binding modes of SARS-CoV M^{pro} and the distantly related human rhinovirus 3C proteinase (HRV $3C^{pro}$). Molecular modeling also showed that the lactone derivative of glutamine and the 5-methyl-isoxazole-3-carbonyl group on AG7088 can be easily accommodated by the SARS main proteinase. However, the *p*-fluorobenzyl moiety might be too long to fit into the active site of the proteinase.[5a]

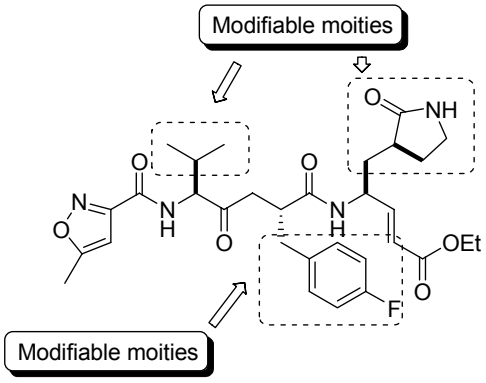
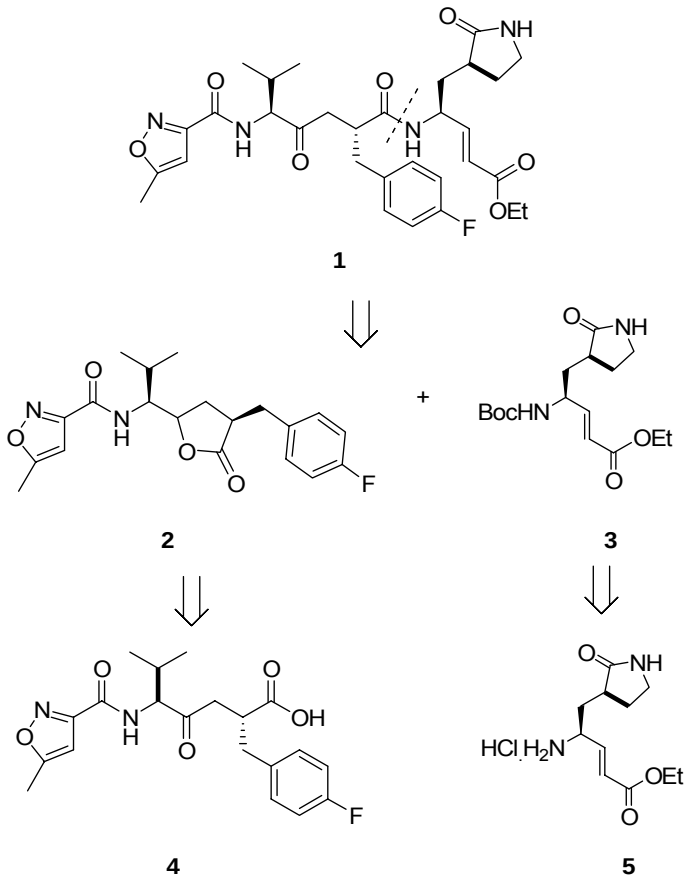


Figure 3. Molecular structure of AG7088, **1**

Based on these findings, it was suggested that the HRV $3C^{pro}$ inhibitor, AG7088, could serve as a good starting point for modifications leading to an efficient inhibitor for the SARS-CoV M^{pro} and possibly other coronavirus main proteinases.

AG7088 is currently under clinical trial for treatment of the "common cold" caused by HRV. As shown in Figure 1, we envisioned the possibility to modify three key components of the structural core of AG7088, **1**, as highlighted in Figure 3.

1.4. FORMAL SYNTHESIS OF AG7088 – RETROSYNTHETIC STRATEGY



Scheme 1. Retrosynthesis of AG7088, **1**

There have been various procedures reported for the total synthesis of AG7088.[7a-d] With reference to Scheme 1, the retrosynthesis of AG7088, **1**, is shown

[7] (a) Tian, Q.; Nayyar, N. K.; Srinivasan, B.; Chen, L.; Tao, J.; Moran, T.; Dagnino, R.; Remarchuk, T.; Melnick, M.; Mitchell, L.; Bender, S. *Canadian patent no CA 02376509* **2001**. (b) Tian, Q.; Nayyar, N. K.; Srinivasan, B.; Dagnino, R.; Remarchuk, T.; Moran, T.; McGee, K. *Canadian patent no CA 02376452* **2001**. (c) Dragovich, P. S.; Prins, T. J.; Zhou, R.; Johnson, T. O.; Brown, E. L.; Maldonado, F. C.; Fuhrman, S. A.; Zalman, L. S.; Patick, A. K.; Matthews, D. A.; Hou, X. J.; Meador, J. W. III.;

with the strategy of disconnecting at the amide bond. This is to make the synthetic route convergent and hence efficient. Our strategy is to couple lactone **2** and lactam **5** towards the synthesis of **1**.

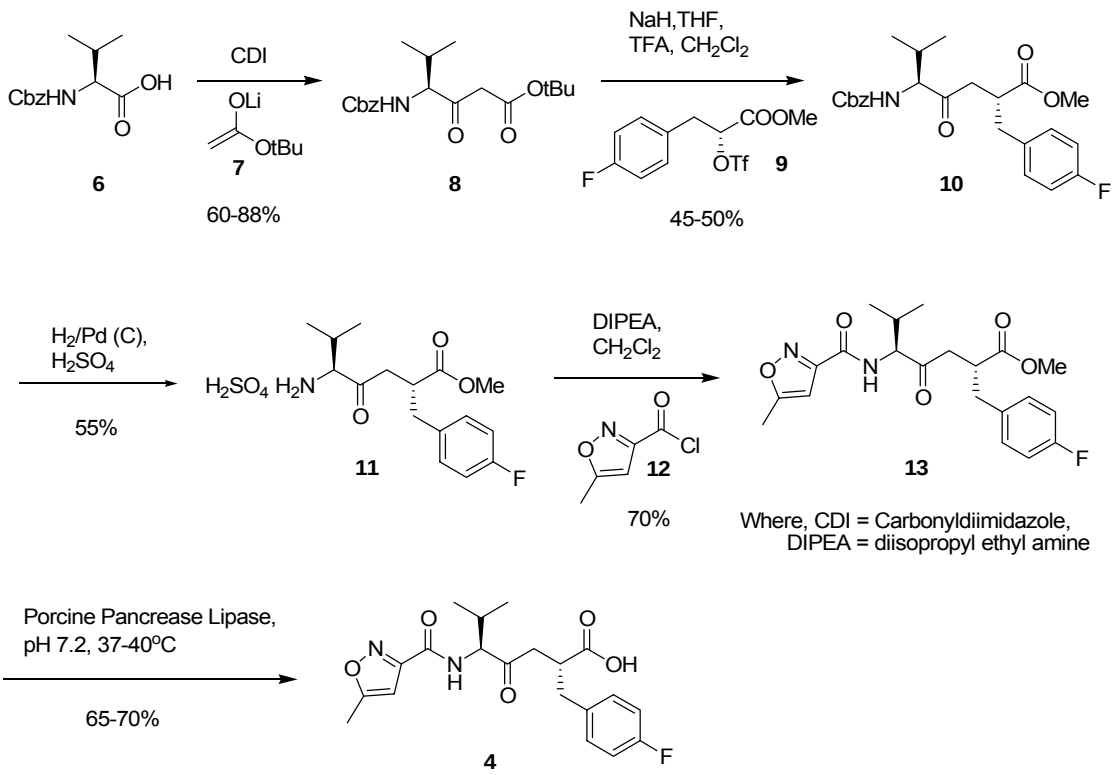
Ferre, R. A.; Worlandy, S. T. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 733. (d) Tian, Q.; Nayyar, N. K.; Srinivasan, B.; Chen, L.; Tao, J.; Lee, S.; Tibbetts, A.; Moran, T.; Liou, J.; Guo, M.; Kennedy, T. P. *Tetrahedron Lett.* **2001**, *42*, 6807-6809.

PART II

CHAPTER 2

Synthesis of Lactone 2

2.1. INTRODUCTION – SYNTHESIS OF LACTONE 2



Scheme 2. Synthesis of analogous molecule **11**

Before we commenced on the synthesis of lactone **2** (Scheme 1), we conducted an in depth literature search on how this fragment had been synthesized in the past. We observed that the synthetic route adopted by Tian and co-workers, towards the synthesis of **4**, was not very efficient.

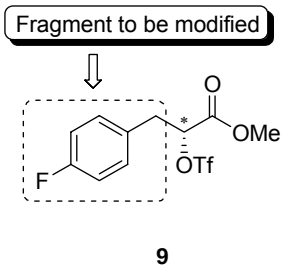


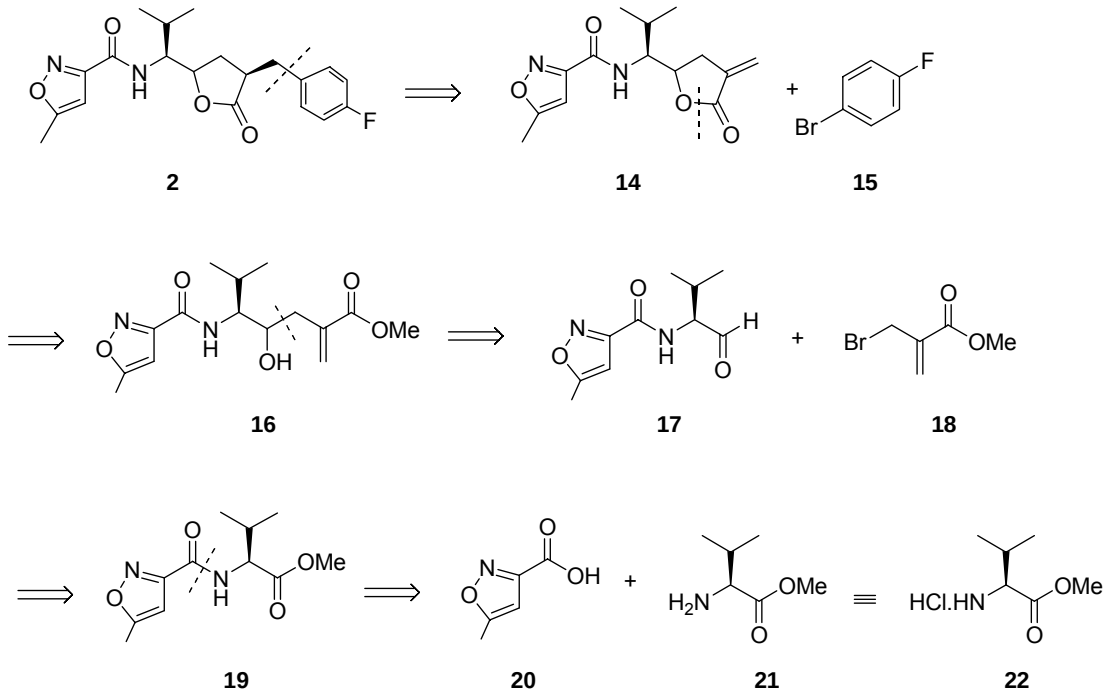
Figure 4. Fragment of **9** to be modified

Scheme 2 illustrates the synthesis of **4,** according to Canadian Patent CA02376509.[7a] Firstly, we envisioned difficulty in synthesizing analogues of AG7088, **1**, from this synthetic route, as molecular tailoring of the *p*-fluorobenzyl group, highlighted in Figure 4, would require the synthesis of other chiral molecules analogous to **9**. This would increase the number of steps required for the synthesis of other analogs of fragment **4**.

Next, from Scheme 2, we observed that the 5-methyl-isoxazole-3-carbonyl group, **12** was being introduced in the second last step of the synthesis, towards **13**. This particular step requires the addition of two steps, namely, protection and deprotection of the amino group (with Cbz, towards **8**). This would lengthen the synthetic route as well as decrease the efficiency. Furthermore, Tian *et al.* reported, that the last step towards **4** was carried out using enzymes. This presented a major limitation in our lab as the success of the last step would greatly depend on the availability and quality of the enzyme used.

Taking these limitations into consideration, more efficient methods towards the synthesis of fragment **4** and its analogs were needed. Hilgenfeld *et al.* suggested that most parts of AG7088, **1**, could be accommodated by the active site of the SARS-CoV M^{pro}. Based on molecular modeling, only the *p*-fluorobenzyl group might be too long to fit into the pocket. In our formal synthesis of **2**, the *p*-fluorobenzyl group is introduced in the final step, allowing us to generate analogues of **1** by simply changing the organocuprate reagent employed.

2.2. RETROSYNTHESIS OF LACTONE 2

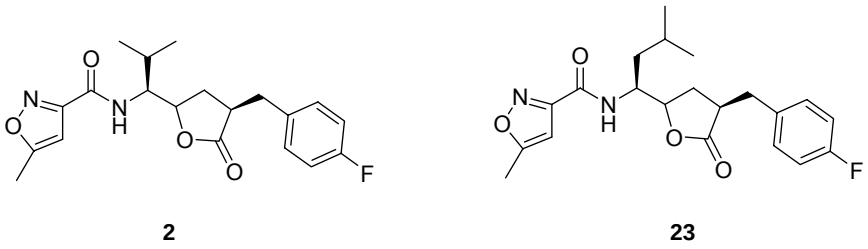


Scheme 3. Retrosynthesis of **2**

Examining the structure of **2**, we can see that the *p*-fluorobenzyl group can be introduced via a Michael addition reaction to α-methylene-γ-butyrolactone **14** (Scheme 3). Lactone **14** can be obtained from the corresponding homoallylic alcohol **16**, which can be disconnected at the C atom bearing the hydroxyl group to result in aldehyde **17** and the allylic bromide **18**. Functional group interconversion provides ester **19**, which can be in turn obtained from the coupling of 5-methyl-isoxazole-3-carboxylic acid **20** and L-valine amino acid **21**. L-valine (as well as L-leucine) are natural occurring amino acids and are commercially available.

The stereochemistry of the *p*-fluorobenzyl group is the most critical criteria in determining the success in the synthesis of fragment **2**. Similar types of Michael

addition reactions have been reported with high selectivity, provided that the stereochemistry of lactone **16** is correct. The stereochemistry of this lactone however is derived from the corresponding alcohol **13**, which is the product of an indium allylation. Therefore, controlling the stereochemistry of the indium allylation reaction is a critical step in this synthetic route.

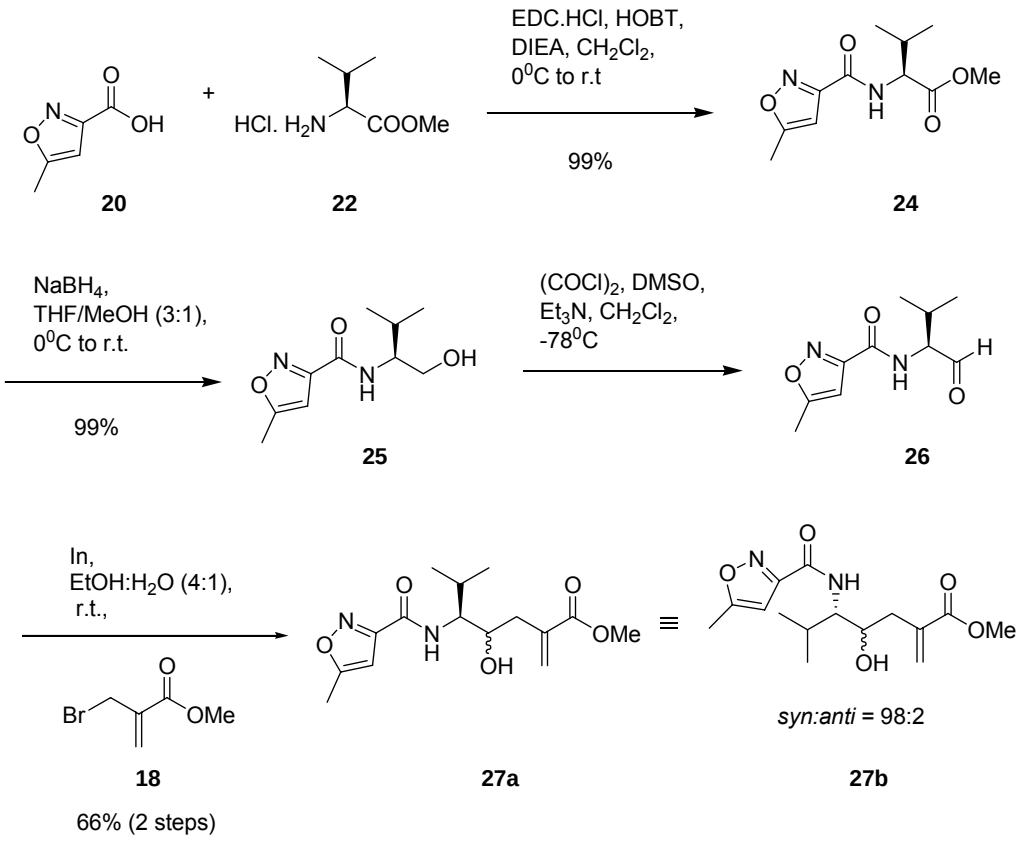


2 **23**

Figure 5. Analogous structures lactone **2** and **23**

By simply replacing L-valine amino acid with L-leucine amino acid (Figure 5), we were able to effect a small modification to the overall structure of lactone **2** to generate lactone **23**. We can easily modify the structure of lactone **2** in order to generate other analogs that might also potentially display anti-SARS properties. This amino acid residue is believed to remain intact during the synthesis of lactone **2**. Accordingly, we also believed that there was not much difference between the L-leucine analog **23** when compared with the L-valine analog **2** in terms of the reactions that lead towards the synthesis of fragment **2**. Finally, in our synthesis of **2**, the *p*-fluorobenzyl group introduced in the final step, providing us with another avenue to generate analogues of AG7088 by simply changing the organocuprate reagent employed.

2.3. SYNTHESIS OF KEY INTERMEDIATE 27

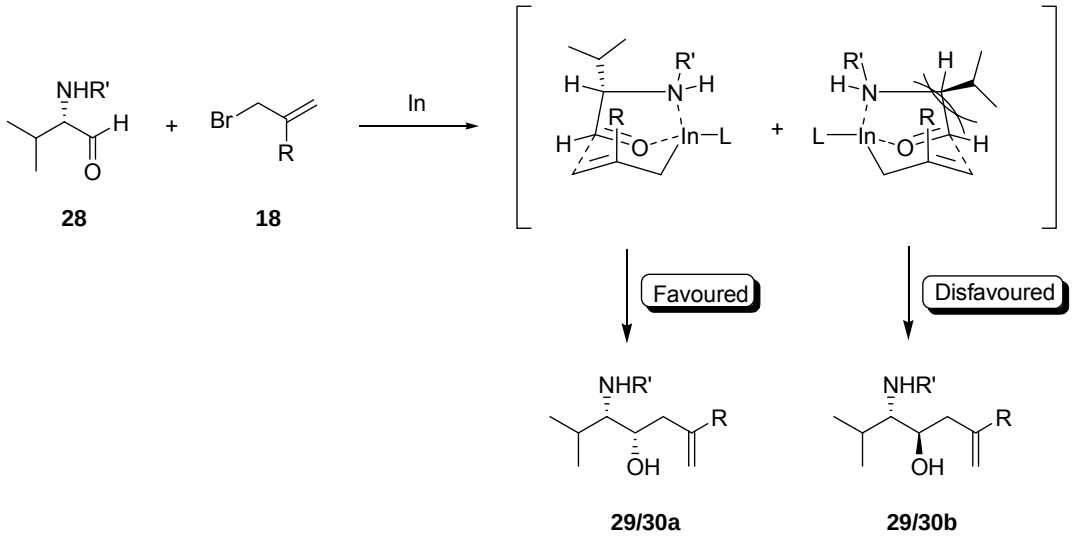


Scheme 4. Synthesis of **2** via key intermediate **27**

With reference to Scheme 4, the L-valine methyl ester hydrochloride salt **22** was first coupled with 5-methylisoxazole-3-carboxylic acid **20**[8] to give methyl ester **24** in almost quantitative yield. Subsequently, $NaBH_4$ reduction of **24** in methanol afforded β-aminoalcohol **25** in 99% yield. Alcohol **25** was then oxidized to α-aminoaldehyde **26** under Swern conditions. As α-aminoaldehydes are particularly prone to epimerization, no purification was performed on **26**.[9] Instead, the crude product from Swern oxidation was used directly in the subsequent indium-mediated allylation reaction. Thus, crude aldehyde **26** was reacted with methyl 2-

[8] **20** was obtained in yields ranging 11-45% by refluxing acetonylacetone for 1h in HNO_3.
[9] Jurczak, J.; Gołębiowski, A. *Chem. Rev.* **1989**, *89*, 149-164.

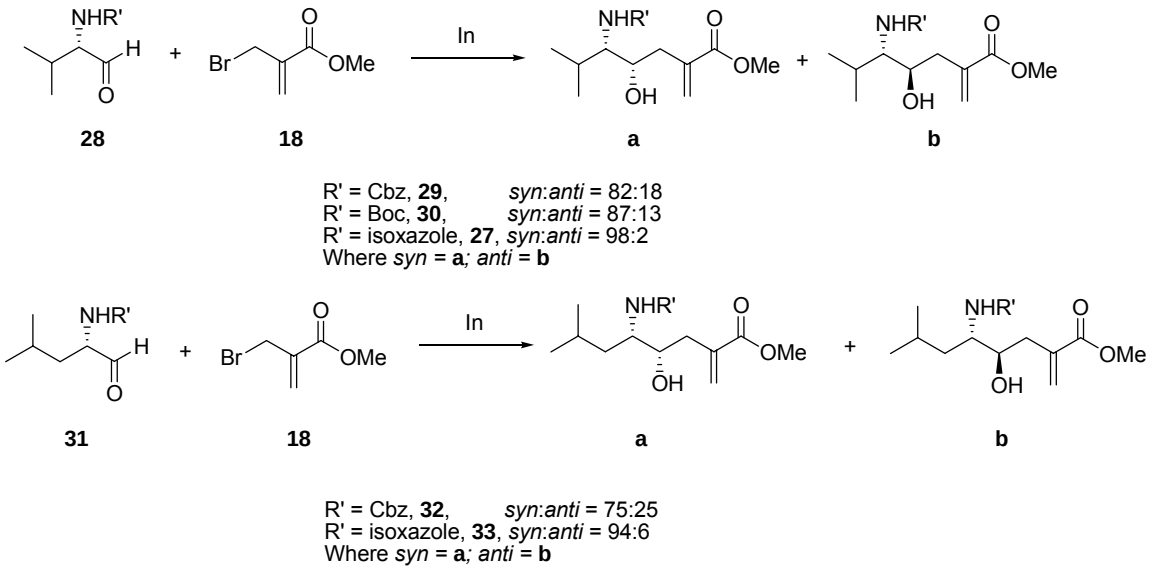
(bromomethyl)acrylate **18** in the presence of indium metal to furnish homoallylic alcohol **27** in overall 66% yield (from **25**) with almost complete *syn* diastereoselectivity (*syn*:*anti* = 98:2).



Scheme 5. Felkin – Anh chelation model

The unusually high diastereoselectivity for the indium-mediated allylation might be explained based on the Felkin – Anh chelation model.[10a, b] As shown in Scheme 5, the α-nitrogen atom can coordinate to the indium metal to form a five-membered chelation ring. We can see in the transition state leading to the *anti* isomer **29b,** that there is more pronounced steric repulsion between the *i*-propyl group and the R group in the axial position (R = COOMe). As a result, the *syn* isomer **29a** is favoured.

[10] (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199-2204. (b) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145-162.



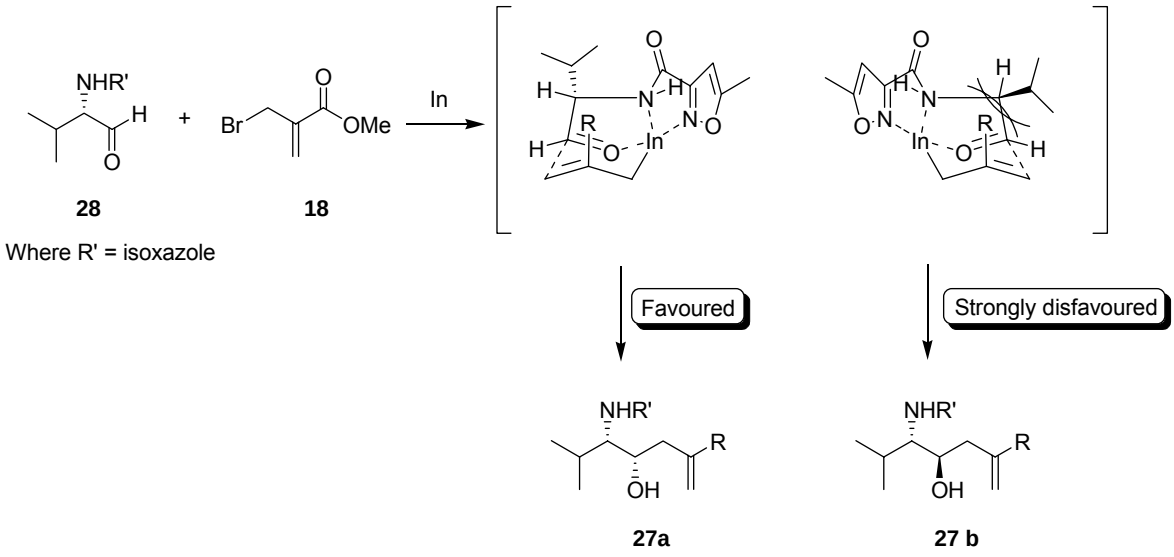
Scheme 6. High *syn: anti* ratio obtained for isoxazole analogs **27a, b** and **33a, b**

However, it has been reported by Podlech et. al. that when the α-amino group was protected using benzyloxycarbonyl (Cbz), the indium-mediated allylation of the corresponding L-valinal gave **29a**:**29b** with a *syn*:*anti* diastereoisomeric ratio of only 82:18.[11a, b] In addition, when we performed the same indium-mediated allylation reaction on N-*t*-butyloxycarbonyl-L-valinal, we obtained the homoallylic alcohol **30a**:**30b** as an 87:13 mixture of *syn*:*anti* isomers (Scheme 6). Clearly, chelation of the α-nitrogen atom and the steric bulkiness of the *i*-propyl group cannot totally account for the observed selectivity in our reaction. This suggests that the isoxazole motif of **27** could have been involved.

Therefore, we propose that the nitrogen atom of the isoxazole ring coordinates to the indium atom, forming a second five-membered chelated ring (Scheme 7). The

[11] (a) Loh, T. P.; Wang, R. B.; Tan, K. L.; Sim, K. Y. *Main Group Metal Chemistry* **1997**, *20*, 237-240. (b) Steurer, S.; Podlech, J. *Eur. J. Org. Chem.* **1999**, 1555-1560.

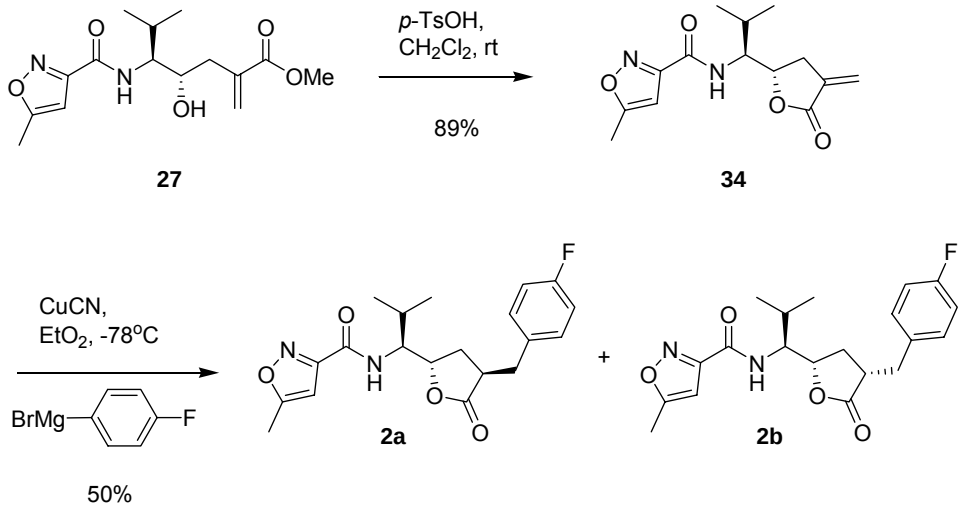
interaction of the isoxazole motif with indium metal causes the transition state to be more rigid (compare Schemes 5 and 7).



Scheme 7. Formation of 5-membered chelation ring with isoxazole motif towards **27a** and **27b**

Less puckering of the transition state (R' = isoxazole, **27**) is now possible (compared to R' = Cbz, **29** or Boc, **30**) to minimize the steric repulsion between the *i*-propyl group and the ester motif. The transition state leading to the *anti* product, **27b**, is therefore further destabilized, resulting in the increase in the *syn*:*anti* (**a**:**b**) selectivity from 82:18 and 87:13 to 98:2, respectively. In our synthesis of the L-leucine analogue of fragment **2**, an improvement in the *syn*:*anti* selectivity of **32** and **33** was also clearly demonstrated (Scheme 6). The excellent diastereoselectivity in the allylation step makes our synthetic strategy of **2** very efficient and paves the way for controlling the second stereogenic centre in the molecule.

2.4. CONJUGATE ADDITION OF 34 TOWARDS LACTONE 2



Scheme 8. Conjugate addition of the organocuprate reagent to **34** to afford **2**

Upon accomplishing this critical step, homoallylic alcohol **27** was cyclized using *p*-toluenesulfonic acid in dichloromethane to afford α,β-unsaturated lactone **34** in high yield (89%), (Scheme 8). Conjugate addition of the organocuprate reagent (formed *in situ* from *p*-fluorobenzylmagnesium bromide and copper(I) cyanide) to **34** finally provided key intermediate lactone **2** in 50% yield as a mixture of isomers (*cis*:*trans* = 39:61). The desired *trans* isomer **2a** was obtained as the major product (confirmed by NOE experiments, experimental section). Overall, fragment **2** was synthesized in six steps from L-valine methyl ester hydrochloride (Scheme 4 and 8).

Herein, we have completed the asymmetric synthesis of a key intermediate, lactone **2** in our synthetic approach towards AG7088 and its analogues. The critical step in the synthesis involved a highly diastereoselective indium-mediated allylation reaction. We next moved on to the synthesis of key fragment, lactam **3**.

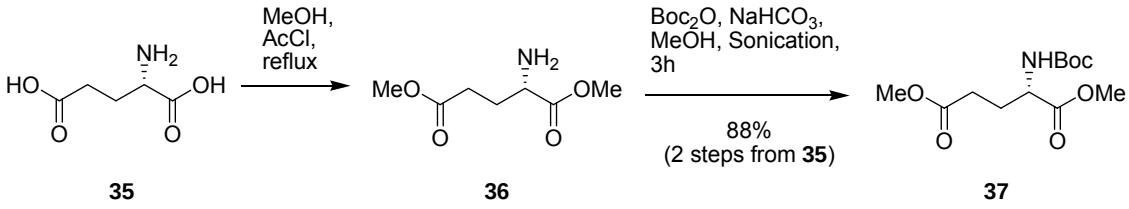
PART II

CHAPTER 3

Synthesis of Lactam 3

3.1. INTRODUCTION – SYNTHESIS OF DIESTER 37 TOWARDS LACTAM 3

Synthesis of lactam **3** was carried out using a combination of reported literature procedures. The key papers were reported by Tian *et al.* in 2001[7d] and in their patent, reported in 2002.[7b] We decided to adopt the scheme reported then with some minor modifications.

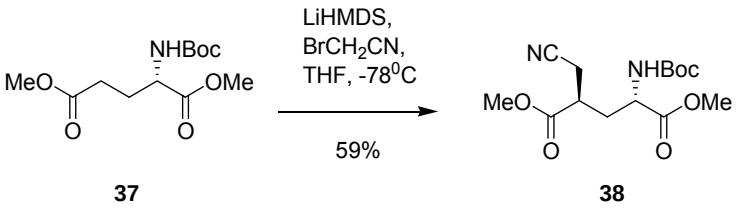


Scheme 9. Synthesis of protected diester **37**

Although the route might look simple, there are several key points and steps to note. The synthesis of **37** started with the esterification of commercially available L-(+)-glutamic acid **35** to afford crude diester **36**. After a standard acid-base workup, the crude diester was used directly of the next step. We decided to modify the protection step by employing sonication which reduced reaction time used and afforded the required protected diester **37** in 88% smoothly.[12]

[12] Einhorn, J.; Einhorn, C.; Luche, J. L. *Synlett*, **1991**, 37. This reduced the reaction time required for the amine protection from 18-20h employing classical conditions to 3-4h, employing sonication.

3.2. CYANOALKYLATION OF DIESTER 37 TOWARDS DIESTER 38



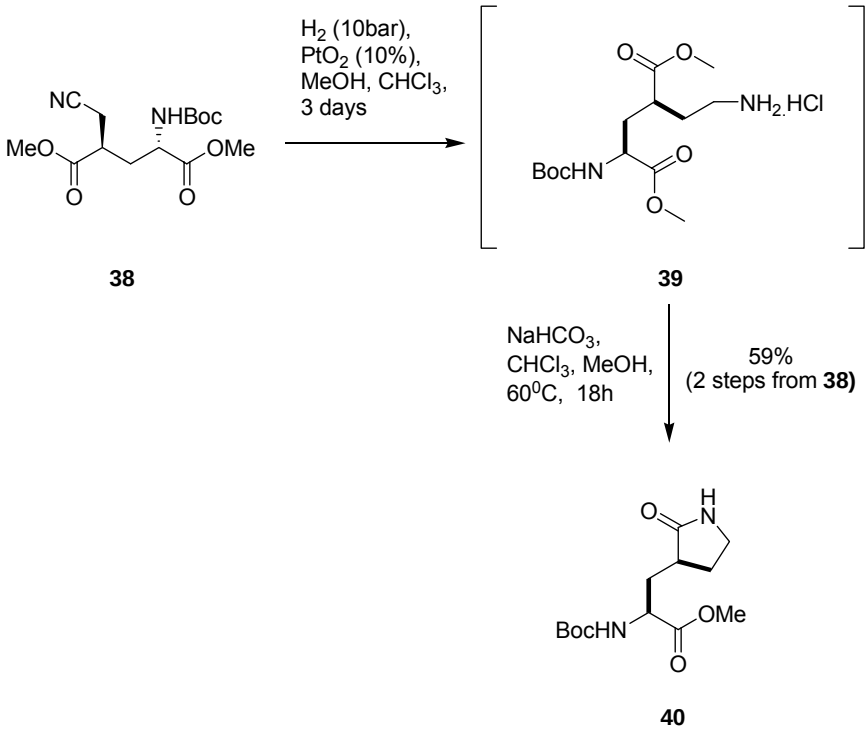
37 **38**

Scheme 10. Cyanoalkylation of diester **37** to afford **38**

Our synthesis continued with the next key step which was the dianionic alkylation of **37** using LiHMDS and bromoacetonitrile. The *γ*-alkylations of glutamate derivatives have been known to be highly dependent on the nature of the N–substituent and the ester group.[13] A method of novel stereochemistry was first developed by Hanessian *et al.* who reported a highly stereoselective 1,3-asymmetric dianionic alkylation of N-Boc-L-(+)-glutamic acid dimethyl ester.[14a, b] Accordingly, Tian *et al.* also adopted this as a key step and reported that the cyanomethylation reaction of the same compound was highly stereoselective (*de*>98%) and applied this as a key step to synthesize lactam **3**.[7d] As expected, we managed to obtain the highly stereo-selective cyano-alkylated diester **39**, in good yield after several attempts, at 59%.[15] However, unlike the reported procedure by Tian *et al.*, we had to purify diester **37** well before commencing the next step. If the crude reaction mixture was used as reported, we could not obtain any product for the next step.

[13] Hanessian, S.; Schaum, R. *Tetrahedron Letters* **1997**, *38*, 163.
[14] (a) Hanessian, S.; Margarita, R. *Tetrahedron Lett*. **1998**, 39, 5877-5890. (b) Hanessian, S.; Margarita, R., Hall, A.; Luo, X. *Tetrahedron Lett*. **1998**, *39*, 5883-5886.
[15] Our obtained cyano-alkylated diester was characterized and the data obtained matched the product from reference 6d exactly. No indication of the syn-iomer was observed in the ^{1}H NMR. Several attempts had to be carried out for this step. An excess of base and bromoacetonitrile had to be used as well. This step in particular had to be carried out under very stringent conditions and was particularly demanding.

3.3. HYDROGENATION OF INTERMEDIATE 39 TOWARDS LACTAM 40



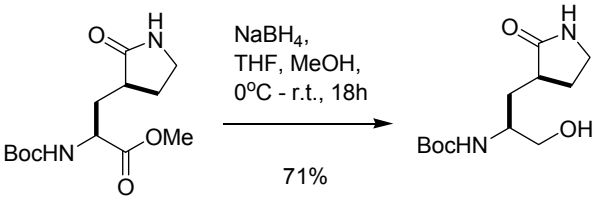
Scheme 11. Ring closure towards the synthesis of **39**

The next task was the selective reduction of the cyano motif in the presence of ester functional groups. For this step, hydrogenation offered the best method as reported by Secrist and Logue.[16] The crude product, which was the hydrochloride salt form of the amine, **39** could not be separated or purified and was used immediately in the next step. Initially we met with some difficulties and had to carry out the hydrogenation under ambient conditions to obtain the amine-HCl salt, **39** (after 7 days).[17] Yields obtained for **40** were in the range of 15 – 30% (2-step yield) at best. When the reaction was carried out employing a hydrogenation Parr bomb, we were able to synthesize **40** (after 3 days) with a yield of 59%, which was comparable to the

[16] Secrist, III, J. A.; Logue, M. W. *J. Org. Chem.* **1972**, *37*, 335-336.
[17] The reaction was carried out bubbling hydrogen from a balloon under ambient conditions with the needle of the balloon place in the solvent so as to allow the gas to bubble through the reaction mixture. This was done as we had no access to any hydrogenation bombs. Bad yields were obtained even after bubbling hydrogen for 10 days.

reported yield in the patent by Tian *et al.*[7b] In order to generate lactam **40**, we also decided to use $NaHCO_3$ as the base of choice over Na_2CO_3 as we were able to obtain better yields **40**.[18] In an alternative procedure, Reddy and co-workers reported lactam **40** could be obtained from **38** with yields of up to 80% by employing $NaBH_4$ and $CoCl_2$.[19] However, after several attempts, we were not able to obtain even a trace of the required lactam **40**. Furthermore, Tian *et al.* reported two different procedures towards synthesizing **40**. One procedure utilizes a catalytic amount of Pd(C) for the hydrogenation, followed by addition of triethylamine for the cyclization. The other procedure utilizes a catalytic amount of PtO_2 and sodium bicarbonate. Both the systems were attempted and the second system (PtO_2/$NaHCO_3$) afforded a much better yield of lactam **40** compared to the first. This was probably due to the better catalytic effect of PtO_2 in hydrogenation.[20]

3.4. REDUCTION OF 40 TOWARDS ALCOHOL 41



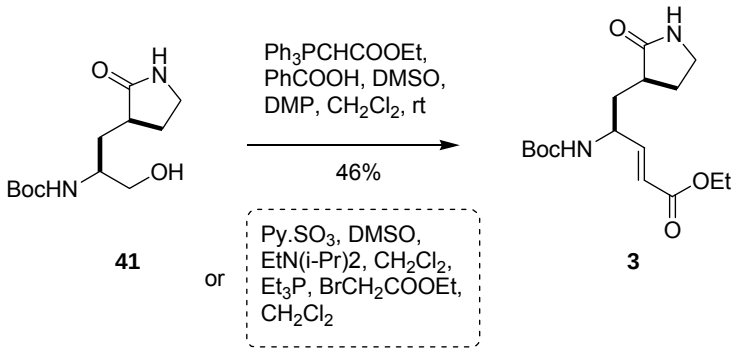
40 **41**

Scheme 12. Reduction of **40** to afford alcohol **41**

[18] Yields obtained for **40** using Na_2CO_3 and Et_3N were in the range of 5-30% and 3-25% respectively. These two bases were used by Tian et. al. in the references 6d and 6b respectively.
[19] Reddy, P. A.; Hsiang, B. C. H.; Latifi, T. N.; Hill, M. W.;Woodward, K. E.; Rothman, S. M.; Ferrendelli, J. A.; Covey, D. F. *J. Med. Chem*. **1996**, *39*, 1898–1906.
[20] The low yields of 20% vs 8% (2 step yield) was due to the reaction being carried out under ambient conditions.

Proceeding on, we managed to reduce lactam **40** using $NaBH_4$ to afford lactam alcohol **41**, a white solid, with a 71% yield (Scheme 12).[21] No side products were observed and the ester group was reduced specifically.

3.5. TANDEM OXIDATION / WITTIG REACTION TOWARDS KEY LACTAM 3



Scheme 13. Oxidation and Wittig reaction towards lactam **3**

With reference to Tian *et al.*'s report that the formation of the α-aminoaldehyde intermediate from the lactam alcohol **41** would result in high water solubility was also prone to epimerization,[22] we anticipated difficulty of isolating the aldehyde and also decided to incorporate the oxidation and following Wittig reaction in one step (Scheme 13).[23] For the initial oxidation, we could either employ Dess-Martin Periodinane (DMP) or pyridine.SO_3 in DMSO as the oxidizing agents. The best yield we could obtain for the final coupled lactam, **3** was 46% using DMP.[24] We managed to obtain a *de* of 94% for lactam **3**. Lactam **3** was exclusively the *E*-isomer as well, as no trace of the *Z*-isomer was observed from NMR analysis.[25]

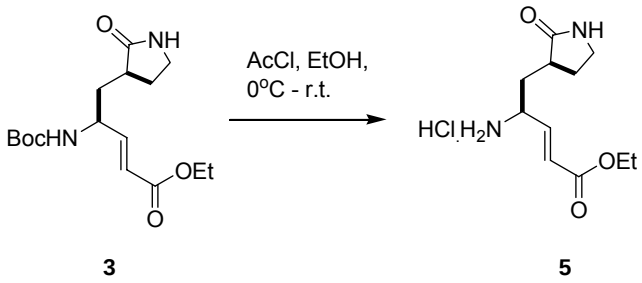
[21] Huang, S.-B.; Nelson, J. S.; Weller, D. D. *Synth*. *Commun*. **1989**, 3485–3496.
[22] Jurczak, J.; Gołębiowski, A. *Chem. Rev.* **1989**, *89*, 149-164.
[23] Hamada, Y.; Shibata, M.; Sugiura, T.; Hato, S.; Shioiri, T. *J. Org*. *Chem*. **1987**, *52(7)*, 1252–1255.
[24] Our yield obtained for **3** was low (c.f. Tian *et al.*'s reported yield of 85%), using pyridine.SO_3, we only obtained up to 36% yield. There was much difficulty in obtaining **3** after many numerous attempts as well. Lactam **3** was confirmed by comparison of ^{1}H NMR, ^{13}CNMR, and Hi-Res MS.
[25] The reported *de* by Tian *et al.* was 98%. *de* was determined using ^{1}H NMR.

PART II

CHAPTER 4

Coupling of Lactone 2 and Lactam 5

4.1. COUPLING OF LACTONE 2 AND LACTAM 5 TOWARDS AG7088, 1



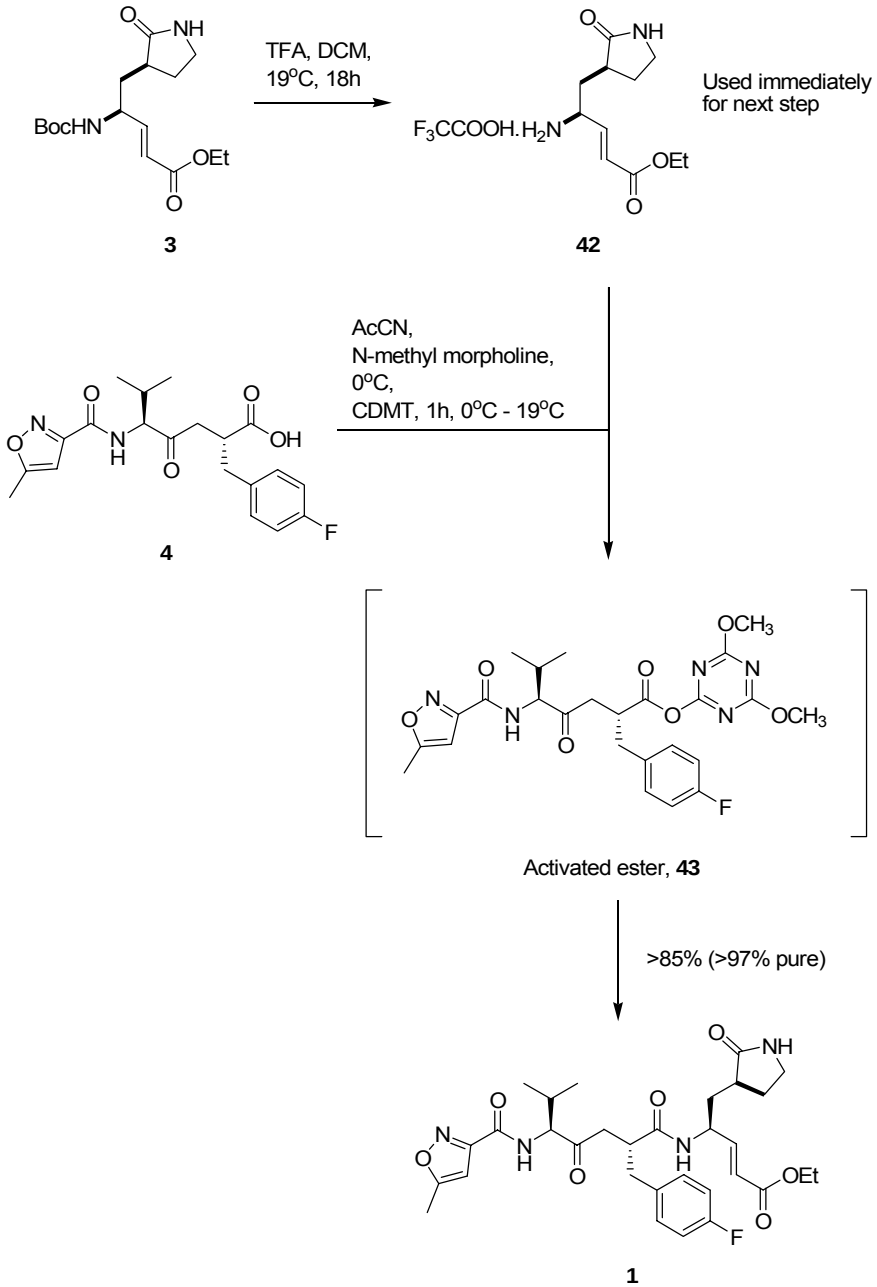
3 **5**

Scheme 14. Deprotection of **3** to afford **5**

The final step towards AG7088, **1** required the deprotection of the acid labile amino-protecting tert-buytyloxycarbonyl (BOC) group. This was effectively obtained by the stirring of **3** in a solution of EtOH with the addition of AcCl dropwise at 0°Cand the reaction was stirred overnight.[26] After completion of the reaction, we decided to use **5** directly for the next step without purification as the hydrochloride salt is very difficult to purify.[7a] Tian *et al.* also reported the deprotection of their compound using trifluoroacetic acid (TFA) in dichloromethane (DCM), stirring overnight and using product **5** immediately for the next step without purification (Scheme 14).

[26] Nudelman, A.; Bechor, Y.; Falb, E.; Fischer, B.; Wexler, B. A.; Nudelman, A. *Synth. Commun*. **1998**, *28*, 471.

According to the procedure reported by Tian and co-workers, after the deprotection of lactam **3**, the carboxylic-acid analog of fragment **2**, **4** was transformed into an activated ester **43** using a coupling reagent, Chloro-dimethoxy-triazine (CDMT). Once the reaction was completed, AG7088, **1**, was precipitated out of solution by the slow addition of water to the reaction mixture.[27]

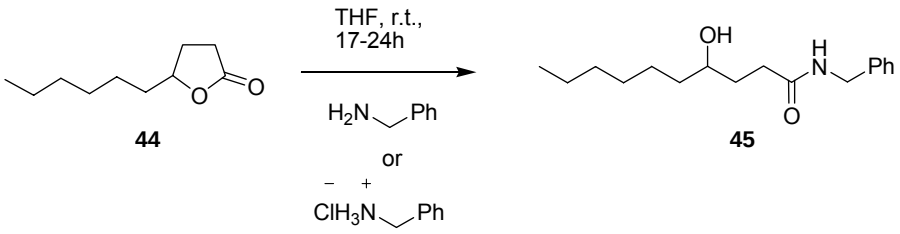


Scheme 15. Synthesis of AG7088, **1** by Tian and co-workers

[27] Water is used to precipitate out AG7088 and is used as an antisolvent.

4.2. SYNTHETIC STRATEGY OF COUPLING LACTONE 2 AND LACTAM 5

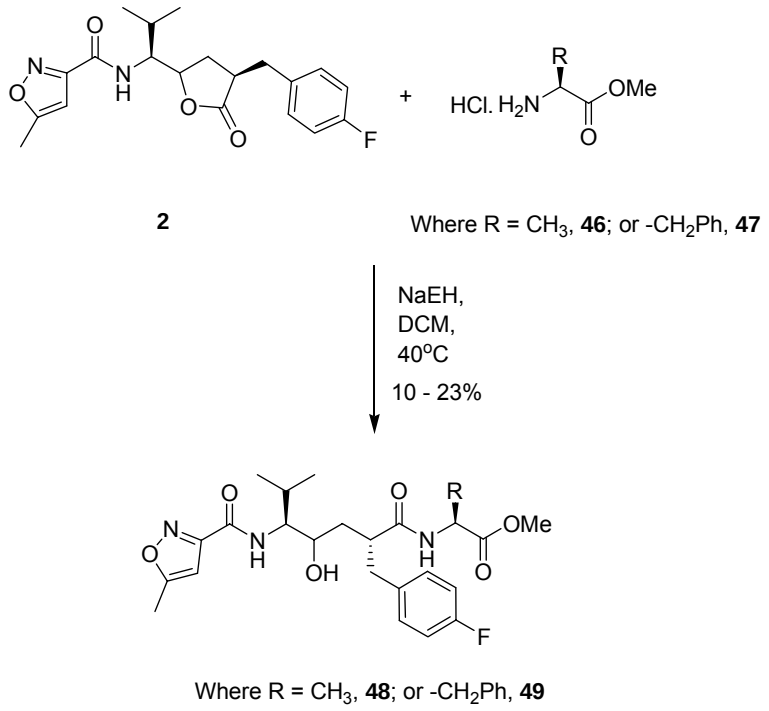
Dragovich and co-workers also reported the synthesis of AG7088, **1** via a different protocol.[28] In our lab, we decided to use sodium 2-ethylhexanoate (NaEH) to open up fragment **2**, in order to allowing the coupling to fragment 3a.[29] This methodology was developed by Liu *et al.* and as illustrated in Scheme 16, they observed the ring opening of lactone **44** as well as the coupling of selected amines to afford **45**. Molecule **44** was analogous to our synthesized lactone **2** and we hypothesized the possible application of this methodology to our synthesis of AG7088, **1**.



Scheme 16. Aminolysis of γ-decanolactone with benzylamine or benzylamine hydrochloride by Liu et. al.

[28] Peter S. Dragovich, Thomas J. Prins, Ru Zhou, Stephen E. Webber, Joseph T. Marakovits, Shella A. Fuhrman, Amy K. Patick, David A. Matthews, Caroline A. Lee, Clifford E. Ford, Benjamin J. Burke, Paul A. Rejto, Thomas F. Hendrickson, Tove Tuntland, Edward L. Brown, James W. Meador III, Rose Ann Ferre, James E. V. Harr, Maha B. Kosa, and Stephen T. Worland; *J. Med. Chem.* **1999,** *42,* 1213-1224

[29] Liu, W.; Xu, D. D.; Repic, O.; Blacklock, T. J. *Tetrahedron Lett.* **2001**, *42*, 2439-2441. NaEH was synthesized in 2 steps and was used directly after filtration.

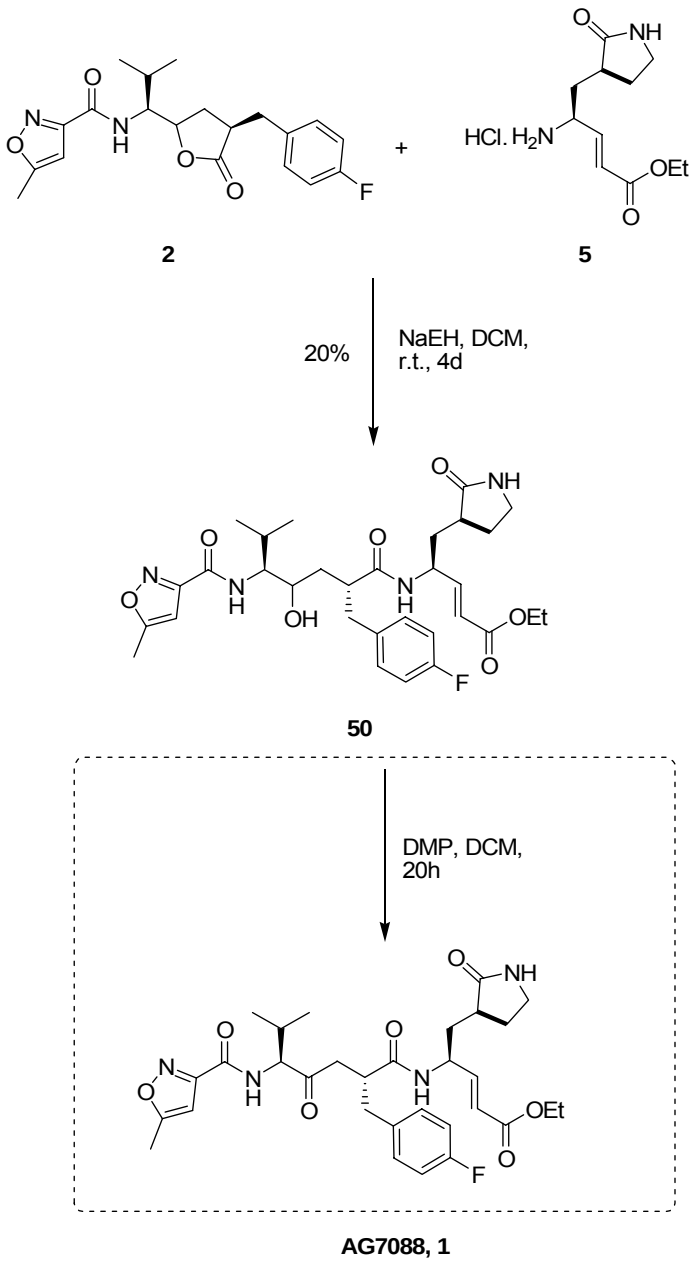


Scheme 17. Coupling studies towards AG7088, **1**

Prior to the actual coupling of **2** and **5**, we did some model studies on the efficiency of the coupling reactions, employing different reagents. L-alanine methyl ester hydrochloride **46** was used in place of **5**, obtaining **48** at 23%. The phenyl alanine methyl ester hydrochloride **47** analog, was obtained with yields of up to 19%. These two model hydrochloride amines were used in place of **5** and we observed that the coupled product was obtained in very small amounts. Synthesis of the coupled products **48** or **49** proved difficult and usually, the starting material, fragment **2** is recovered in up 90%. This was so even when we employed NaEH for the coupling reaction (Scheme 17).[30]

[30] For the L-alanine and phenyl-alanine methyl ester analogs of coupled product **18**, we only partially characterized the products using ^{1}H and ^{19}F NMR. Once we had a positive result, we then went on to attempt the coupling of fragment **2** and **3** successfully. Another analog using benzyl amine was also attempted and a yield of only 2% was obtained (Coupling was also carried out using $AlMe_3$). Products are obtained with a mixture of isomers.

4.3. CONCLUSION



Scheme 18. Coupling of fragment **2** and **5** in the presence of NaEH

We met with some difficulties during the coupling of fragment **2** and **5** but were able to afford **47** with a low yield of 20%, using the above mentioned protocol. Preliminary Hi-Res MS of the sample showed that we had obtained the coupled product, however, we had too little of the sample for further analysis. As such, we are

working towards the scaling up of molecule **47**, and this will be subjected to Dess-Martin oxidation conditions to convert the alcohol into the target carbonyl functionality to afford AG7088, **1** (Scheme 18).

Furthermore, we would need to test the compounds synthesized from this project against 3CL protease in a traditional inhibition assay (HPLC, fluorescence, etc) in order to determine if the fragments of the molecule might be potentially active in inhibiting the protease. To date, a number of potential inhibitors of SARS-CoV $3CL^{pro}$ have been proposed using molecular modeling and virtual screening techniques. However, the inhibitory activities of most of the proposed inhibitors have not yet been examined in *in vitro* assays. The most widely used proteolytic assays for SARS-CoV $3CL^{pro}$ are HPLC-based cleavage assay and fluorescence-based kinetic analysis. Rather than using peptides modified with chromophores or fluorophores, HPLC assay allows the use of natural peptide substrate. But the analysis is relatively time-consuming and difficult for kinetic studies and for a high throughput screen for inhibitors. Clearly, a high-throughput enzyme assay for SARS-CoV $3CL^{pro}$ will speed up discovery of novel inhibitors. Fluorescence assay has been successfully for enzyme kinetics studies and high-throughput screening of inhibitors.[31a-c]

[31] (a) Lin C-W, Tsai C-H, Tsai F-J, Chen P-J, Lai C-C, Wan L, Chiu H-H, and Lin K-H. Characterization of trans- and cis-cleavage activity of the SARS coronavirus 3CLpro protease: basis for the in vitro screening of anti-SARS drugs. FEBS Lett 2004; 574: 131-137. (b) Kuo C-J, Chi Y-H, Hsu J T-A, and Liang P-H. Characterization of SARS main protease and inhibitors assay using a fluorogenic substrate. Biochem Biophys Res Commun 2003; 308: 148-151. (c) Hsu J T-A, Kuo C-J, Hsieh H-P, Wang Y-C, Huang K-K, Lin C P-C, Huang P-F, and Chen X, Liang P-H. FEBS Lett 2004; 574: 116-120.

PART II

CHAPTER 5

Future Work and Extension of Chemistry

5.1. FUTURE WORK – SCALE UP OF AG7088

With some limited success on the synthesis of **50**, we still had to oxidize **50** in order to obtain AG7088, **1**. In order to obtain a manageable amount of AG7088, we would have to synthesize a larger amount of fragments **2** and **3**. We also intend to explore the possibility of synthesizing more analogs of AG7088 if possible.

5.2. EXTENSION OF CHEMISTRY – OLEFIN METATHESIS OF FRAGMENT 2

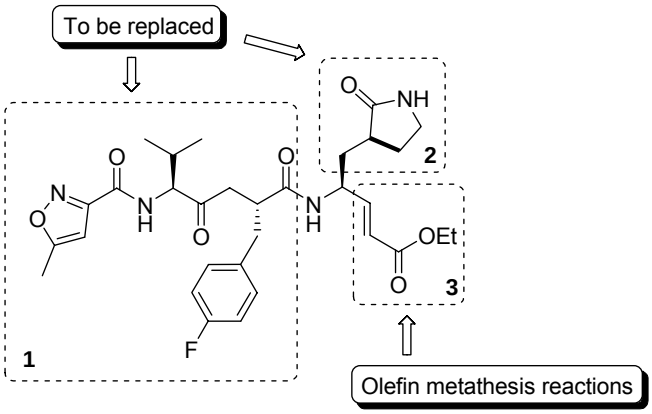
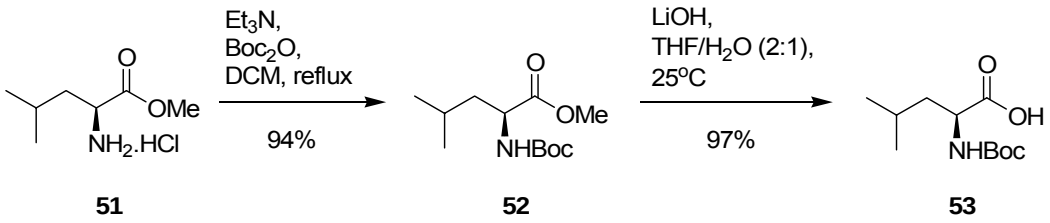


Figure 6. Modification strategy of AG7088

As we edged towards the total synthesis of AG7088, we envisioned the possibility of a further extension of chemistry by using olefin metathesis as a key step towards the generation of analogs. From Figure 6, we can replace sub-fragment 1, 2 and 3 with analogous structures that would simplify the synthetic route. In this aspect, we can replace the isoxazole-*p*-fluoro benzyl motif (sub-fragment 1) with a structurally simpler leucine moiety. Leucine has been known to be able to fit in the sub-site of the SARS-CoV M^{Pro} well. Next, the glutamate derived lactam (sub-fragment 2) can be replaced easily by a serine motif. And lastly, we can employ olefin

metathesis towards sub-fragment 3, thereby generating analogous structures to AG7088.

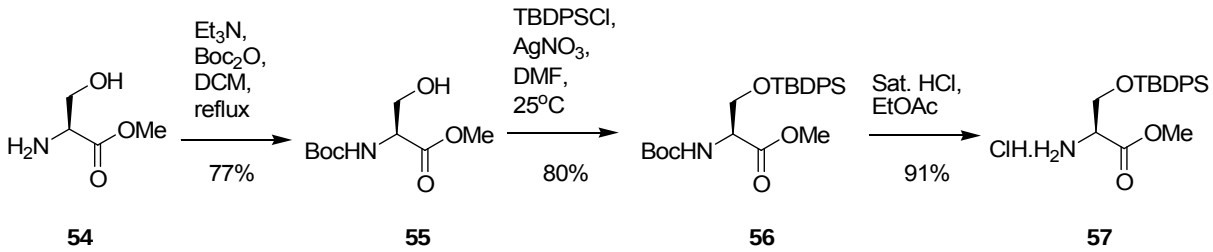
5.3. SYNTHESIS OF CARBOXYLIC ACID 53



Scheme 19. Synthesis of Boc-protected leucine carboxylic acid **53**

The Boc-protected leucine carboxylic acid, **53** was synthesized according to Scheme 19. L-leucine methyl ester hydrochloride **51** was protected using ^{t}Boc to afford the corresponding ester, **52**, with up to 94% yield. Hydrolysis of the ester was effected by usage of LiOH, which afforded the corresponding acid **53,** with a yield of 97%.

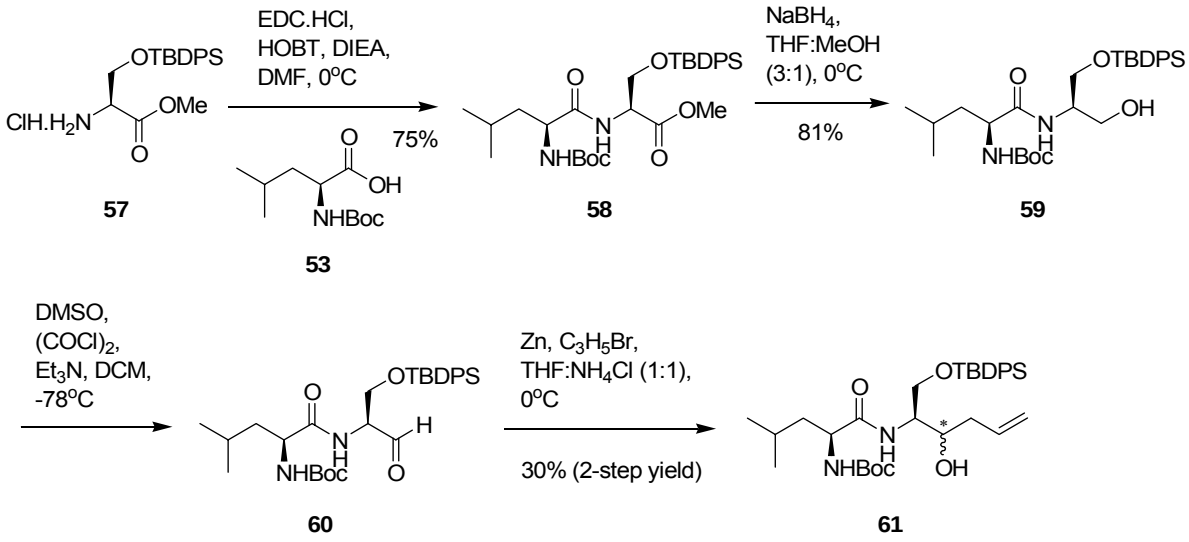
5.4. SYNTHESIS OF METHYL ESTER 57



Scheme 20. Synthesis of TBDPS-protected serine methyl ester **57**

Referring to Scheme 20, L-serine methyl ester **54** was first protected with ^{t}Boc to afford **55** in 77% yield. This was followed by the protection of the alcohol functionality using TBDPSCl, which afforded the di-protected serine methyl ester **56** with a yield of 80%. Subsequent hydrolysis of the ^{t}Boc group afforded the TBDPS-protected amine, **57**, in 91%.

5.5. SYNTHESIS OF ALLYIC PRODUCT 61

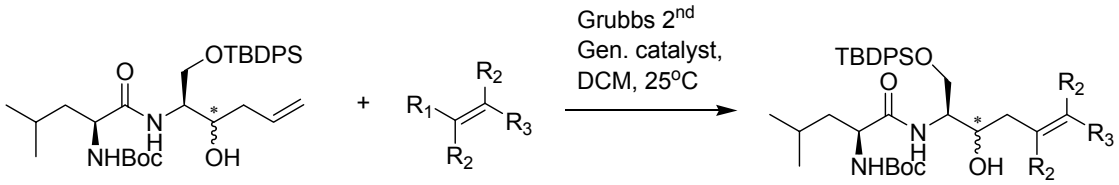


Scheme 21. Synthesis of allylic product **61**

We next coupled **53** and **57** to obtain **58** in 75% yield. $NaBH_4$ reduction of ester **58** provided us with alcohol **59** with a yield of 81%. Alcohol **59** was further functionalized under Swern oxidation conditions to afford the epimerization prone α-aminoaldehyde **60** which was used immediately in the next step. Zinc-mediated allylation of **60** afforded the key allylic product, **61,** with a yield of 30% (2-step yield, Scheme 21).

5.6. SYNTHESIS OF METATHESIS PRODUCTS 68-72

Key allylic product **61** was used as the starting material for the subsequent investigation towards the generation of possible analogs of AG7088. We employed the olefin metathesis strategy with the allylic functionality of **61** with other olefinic substrates according to Table 2.



Where R1 = Me,
R2 = H,
R3 = Carbonyl funtionality

Scheme 22. Synthesis of metathesis products

The synthesis of the possible metathesis is illustrated in Scheme 22. Grubbs 2nd generation catalyst was employed in catalytic amounts, in the presence of DCM under ambient conditions to effect the olefin metathesis. As can be observed from the yields of the obtained olefin metathesis products **68-72** in Table 2, the reaction involving methyl acrylate **62** afforded molecule **68** with the best yield at 92% (Entry 1). However, the presence of a methyl group at the *β*-positon of methyl acrylate **63** caused the yield of **68** to decrease to 63% (Entry 2, Table 2). When we coupled methyl but-3-enoate **64** with **61**, we obtained the metathesis product **69** in 60% yield (Entry 3), which was comparable to Entry 2. As such, the extension of the olefin functionality one extra carbon away from the ester functionality did not affect the yield of the coupled product drastically. Replacing the ester group of **62-64** with a

methyl group of **65** caused a decrease in the overall yield of **70** at 54% (Entry 4). Further replacement of the ketonic fragment of **65** with aldehyde **66** caused a further decrease in the yield of **71** to 51% (Entry 5). Yields of the metathesis product dropped even more drastically when we substituted aldehyde **66** with allylic alcohol **67**, affording a **72** with 35% yield.

5.7. CONCLUSION

The usage of the olefins in Figure 7 did not afford any of the expected products even after several attempts. To conclude, we observed that the olefin metathesis strategy employed to generate more analogous structures to AG7088, **1,** is a fast and efficient method. The astute selection of olefinic substrates is required, preferably substituted esters, in order to obtain appreciably yields of the corresponding metathesis products. It is not surprising that the *trans*-methyl substituted α,β-unsaturated amides were unreactive.

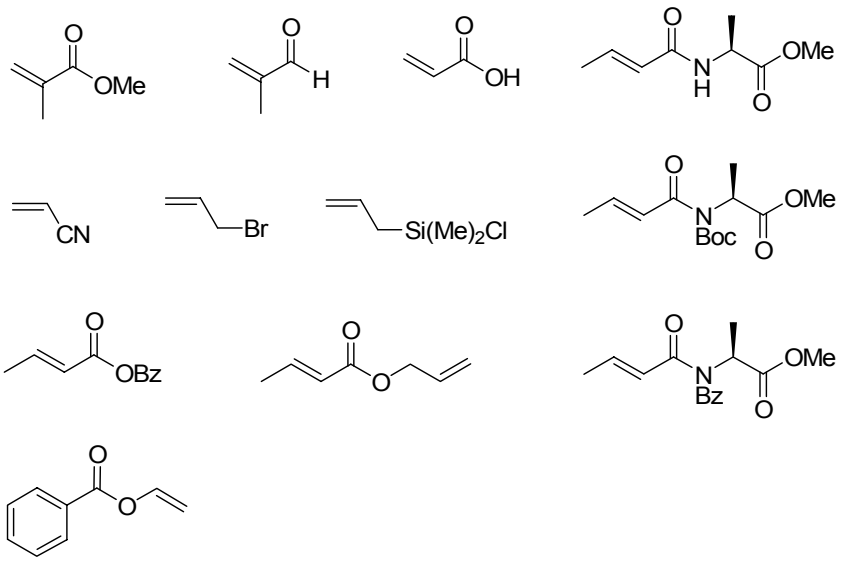
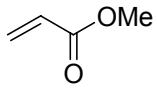
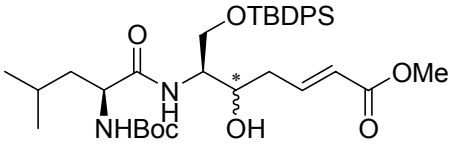
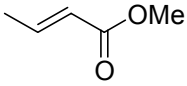
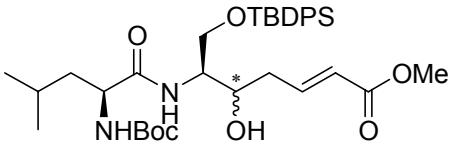
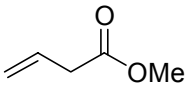
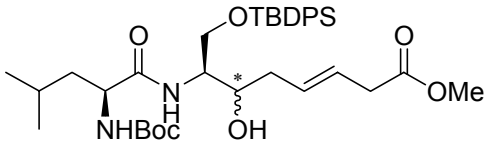
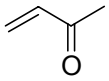
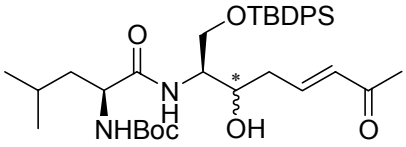
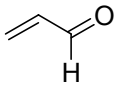
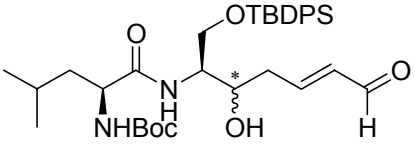
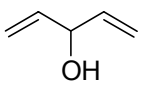
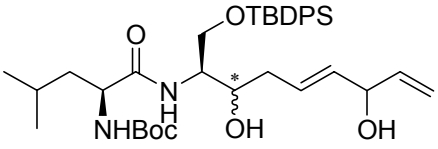


Figure 7. Unsuccessful usage of olefins employing metathesis strategy

The thus synthesized products have been also sent for further biological testing in order to study their effects on morphology and genetics (Please refer to APPENDIX section).

Table 2. Olefin metathesis products obtained through coupling of **61** with selected alkenes

Entry[a]	Olefin	Metathesis product	% Yield[b]
1	 **62**	 **68**	92
2	 **63**	 **68**	63
3	 **64**	 **69**	60
4	 **65**	 **70**	54
5	 **66**	 **71**	51
6	 **67**	 **72**	35

a = Reactions were carried out with 1 eqv. of 25 and 2 eqv. of olefin with 10 mol% of Grubbs 2nd generation catalyst at 25°C for 24h. *b* = Isolated yield

CHAPTER 6

Experimental Section

Part I – Synthesis of Photochromic Fulgides

6.1. GENERAL INFORMATION

Experiments involving moisture and/or air sensitive components were performed under a positive pressure of nitrogen in oven/flame-dried glassware, equipped with a rubber septum. Solvents and liquid reagents were transferred by oven-dried syringes cooled in a dessicator or via double-tipped cannular needles. Reactions were stirred with Teflon-coated magnetic stirring bars unless otherwise stated. Moisture in non-volatile reagents or compounds was removed by the addition anhydrous THF, followed by the removal of the solvent and traces of moisture *in vacuo* by means of a vacuum pump (~20 mmHg, 23-45^{o}C) and subsequent purging with nitrogen. All experiments were monitored by analytical thin layer chromatography (TLC). Solvents were removed *in vacuo* (~30 mmHg, 23-45^{o}C) using a Büchi rotary evaporator with cold (0-5^{o}C) running water.

6.2. MATERIALS

All commercially available materials were used without further purification with the following exceptions: Hexane, dichloromethane, ethyl acetate were fractionally distilled prior to use. Anhydrous THF and diethyl ether were obtained by distillation under a nitrogen atmosphere from a deep purple solution resulting from sodium and benzophenone. Anhydrous dichloromethane (DCM) and hexane were distilled over calcium hydride under a nitrogen atmosphere.

Triethylamine was distilled over calcium hydride under a nitrogen atmosphere and stored over 4Å molecular sieves. Hydrochloric acid was diluted from 12M solution. Sulfuric acid was diluted from 10M solution. Sodium hydroxide solution was prepared from sodium hydroxide pellets. Saturated solutions of sodium chloride,

sodium bicarbonate, sodium carbonate, sodium thiosulphate and ammonium chloride were prepared from their respective solids.

6.3. CHROMATOGRAPHY

Analytical thin layer chromatography (TLC) was performed using Merck 60 F_{254} precoated silica gel plate (0.25 mm thickness). Subsequent to elution, ultraviolet (UV) illumination of the chromatogram at 254 nm allowed the visualization of UV active material. Further visualization was possible by staining with basic solution of potassium permanganate or acidic solution of ceric molybdate, followed by heating on a hot plate.

Preparative thin layer chromatography was performed using Merck 60 F_{254} precoated silica gel plate (0.25 mm thickness, 20 cm x 20 cm). Compounds were diluted with 100-300μL of the appropriate solvent and applied to the plate as a narrow band ~16-18 cm long and 2 cm above the base, using a glass capillary tube. After elution, the chromatogram was visualized under UV light or by staining a thin strip, cut out from the side of the plate. The desired compound was then isolated by manually scraping the appropriate band off the plate using a spatula. The silica was then dissolved using an appropriate solvent followed by standing in anhydrous $MgSO_4$ before filtering through filter paper or celite. This was followed by the removal of solvent *in vacuo*.

Flash chromatography was performed using Merck silica gel 60 with freshly distilled solvents. Columns were typically packed as slurry of silica gel in hexane and equilibrated with the appropriate solvent system prior to use. The analyte was loaded

neat or as a concentrated solution using the appropriate solvent system. The elution was assisted by applying pressure of about 2 atm with an air pump.

6.4. INSTRUMENTS AND EQUIPMENT

INFRARED SPECTROSCOPY

Infrared spectra were recorded in a Bio-RAD FTS 165 FT-IR spectrometer. Solid samples were analysed as a KBr pressed-disk while liquid samples were either examined neat between KBr salt plates or as a solution in dichlormethane using NaCl liquid cells.

MASS SPECTROSCOPY

Mass spectrometry (MS) was performed by the staff from the Chemical and Molecular analysis Centre of the National University of Singapore. MS-electron impact (EI) spectra were recorded on a Hewlett-Packard 5890A gas chromatogram. High-resolution MS (HRMS-EI) spectra were recorded on a V.G. Micromass 7035 micromass mass spectrophotometer at a source temperature of 200 ºC and at an ion current of 70 eV.. MS and HRMS were reported in units of mass to charge ratio (m/z). MALDI-TOF spectra were obtained on an Applied Biosystems Voyger System 4134, with mode of operation either reflector or linear mode. Matrix used is Ag-TFA Ditranol. Mass reported in units of mass to charge ratio (m/z).

NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) were performed on a Bruker Avance DPX 300 (300MHz) and Bruker

AMX 500 (500MHz), NMR spectrometer. Chemical shifts are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.00) and relative to the signal of the residual solvent signal of, deuterio chloroform-*d* (^{1}H NMR, δ 7.2600 ppm, singlet; ^{13}C NMR, δ 77.04 ppm, triplet) and deuterium oxide, D_2O (^{1}H NMR, δ 4.7500 ppm, singlet). Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); dd (doublets of doublet); ddd (doublets of doublets of doublet); dddd (doublets of doublets of doublets of doublet); dt (doublets of triplet); or m (multiplets). The number of protons (n) for a given resonance is indicated by nH. Coupling constants are reported as a *J* value in Hz.

ULTRAVIOLET SPECTROSCOPY

The cyclized forms (*C*-form) of each fulgide were obtained by irradiating the *E*- or *Z*-form fulgide in dichloromethane solution with ~ 330-370 nm light using a Rayonet RPR-100 Photochemical Reactor fitted with 16 Vilber-Lourmat T-8M UV tubes. UV-Vis studies were carried out using a Hp 8452A diode array spectrophotometer (Denoted: UV(VIS) *O: Open* form; *C: Closed* form).

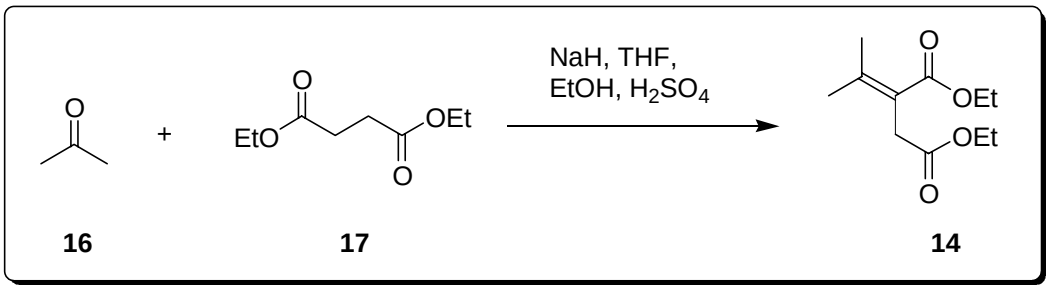
MELTING POINTS

Melting points were determined using a Buchi B-540 melting point apparatus. An observable amount of the solid is placed in the melting point capilaruy and the temperature was raised by 1^{o}C every 2 seconds. The melting point was recorded down at the instant the solid was observed to melt.

NOMENCLATURE

Systematic nomenclature for the compounds would follow the numbering system as defined by the International Union of Pure and Applied Chemistry (IUPAC).[1] Compounds were also named using the ChembridgeSoft ChemOffice 2004, ChemDraw Ultra 8.0 naming feature.

6.5. PROCEDURES AND SUPPORTING INFORMATION FOR PART I



Preparation of Isopropylidene (IPP) Diethyl Succinate (14)

Diethyl succinate **17** (33.5 ml, 0.200 mol, 1.00 eq) was added to a ice-cooled solution of sodium hydride (55-65%, moistened with mineral oil) (7.2 g, 0.300 mol, 1.50 eq) in THF and stirred for 10 mins. 2 drops of EtOH or MeOH was added to initiate the reaction. Acetone **16** (18.4 ml, 0.250 mol, 1.25 eq) was added dropwise over 15 mins and the reaction mixture was allowed to stir for 18 h at room temperature. The reaction was quenched with 4M HCl and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent was removed in vacuo.

[1] http://www.chem.qmul.ac.uk/iupac/

The resulting brown syrup was dissolved in ethanol (200 mL) and acidified with conc H_2SO_4 (~5 – 10 mL) and stirred for 1h at 0°C. The reaction mixture was warmed up to room temperature and refluxed for 16 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent was removed in vacuo. Vacuum distillation afforded isopropylidene diethyl succinate, **14**, as a clear colorless oil (29.8 g, 69% yield).

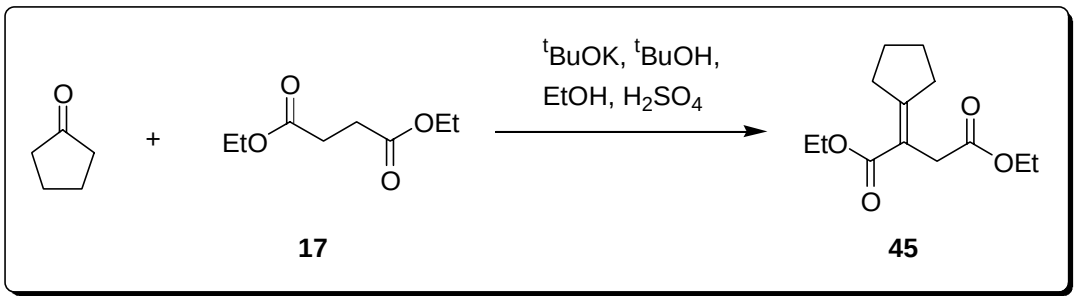
Rf: 0.46 (hexane: ethyl acetate = 4:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.18 (q, J = 7.1 Hz, 2H, $CO_2C\mathbf{H}_2CH_3$), 4.13 (q, J = 7.1 Hz, 2H, $CO_2C\mathbf{H}_2CH_3$), 3.36 (s, 2H, $C\mathbf{H}_2CO_2CH_2CH_3$), 2.14 (s, 3H, $C=C(C\mathbf{H}_3)(CH_3)$), 1.86 (s, 3H, $C=C(CH_3)(C\mathbf{H}_3)$), 1.27 (t, J = 7.1 Hz, 3H, $CO_2CH_2C\mathbf{H}_3$), 1.24 (t, J = 7.1 Hz, 3H, $CO_2CH_2C\mathbf{H}_3$) ppm.

^{13}C NMR (500 MHz, $CDCl_3$) δ 171.5, 167.9, 148.9, 120.7, 60.7, 60.2, 35.5, 23.3, 23.2, 14.2 ppm.

FTIR (Film): 2983, 2938, 2909, 1738, 1719, 1642, 1446, 1369, 1335, 1283, 1223, 1178, 1135, 1079, 1032 cm^{-1}.

HRMS (EI) Calcd for $C_{11}H_{18}O_4$ [M^+]: 214.1205. Found: 214.1207; [M^+-CH_3]: 199.0970, Found: 199.0971.



Preparation of Cyclopentylidene Diethyl Succinate (45)

Tert-butanol (10.0 ml) was stirred and cooled to 15-20^{o}C, followed by the addition of potassium tert-butoxide (0.88 g, 7.84 mmol, 1.3 eq). The mixture was stirred for 10 mins, followed by the addition of a solution of diethyl succinate **17** (1.00 ml, 6.00 mmol, 1.0 eq) and the corresponding cyclopentanone (0.64 ml, 7.2 mmol, 1.2 eq) in 2.0 ml tert-butanol, dropwise. The reaction mixture was allowed to stir for 1.5-2 h at 15-20^{o}C. The reaction was quenched with 4M HCl and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent was removed in vacuo.

The resulting reddish brown syrup was dissolved in ethanol (25 ml) and acidified with conc H_2SO_4 (2-4 ml mL) and stirred for 1h at 0^{o}C. The reaction mixture was warmed up to room temperature and stirred for 48 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent was removed in vacuo.

The resulting reddish oil was purified via flash chromatography (8:1 hexane/ethyl acetate), yielding a colorless oil of **45** with 18% yield.

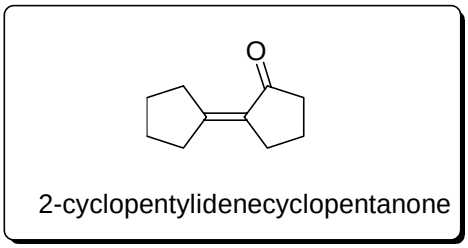
Rf: 0.53 (hexane: ethyl acetate = 4:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.18 (q, J = 7.1 Hz, 2H, $CO_2C\mathbf{H}_2CH_3$), 4.13 (q, J = 7.1 Hz, 2H, $CO_2C\mathbf{H}_2CH_3$), 3.33 (s, 2H, $C\mathbf{H}_2CO_2CH_2CH_3$), 2.82 (t, J = 7.2 Hz, 2H, C=C($C\mathbf{H}_2CH_2CH_2CH_2$), 2.41 (t, J = 7.0 Hz, 2H, C=C($C\mathbf{H}_2CH_2CH_2CH_2$), 1.77 – 1.67 (m, 4H, C=C($CH_2CH_2C\mathbf{H}_2C\mathbf{H}_2$), 1.27 (t, J = 7.2 Hz, 3H, $CO_2CH_2C\mathbf{H}_3$), 1.25 (t, J = 7.2 Hz, 3H, $CO_2CH_2C\mathbf{H}_3$) ppm.

^{13}C NMR (300 MHz, $CDCl_3$) δ 171.6, 167.2, 164.5, 117.1, 60.6, 60.1, 36.2, 34.5, 34.2, 27.0, 25.6, 14.3, 14.2 ppm.

FTIR (Film): 2982, 2941, 2907, 2876, 2338, 1735, 1645, 1372, 1191, 1162, 1098, 1032 cm^{-1}.

HRMS (EI) Calcd for $C_{13}H_{20}O_4$ [M^+]: 240.1362, Found: 240.1364.



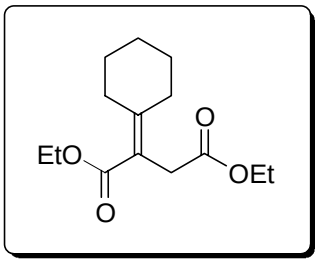
Partial characterization of 2-cyclopentylidenecyclopentanone

Another isolated fraction provided the β,γ–unsaturated Cyclopentenyl Diethyl Succinate **47** in 7% yield and the self-condensed 2-cyclopentylidenecyclopentanone product in more than 30% yield.

Rf: 0.48 (hexane: ethyl acetate = 4:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.80-2.77 (m, 2H, COC**H**$_2$), 2.54-2.52 (m, 2H, C**H**$_2$CCO), 2.31-2.27 (m, 6H, C**H**$_2$, C**H**$_2$C**H**$_2$), 2.01-1.83 (m, 2H, C**H**$_2$C=C), 1.71-1.69 (m, 2H, C=C C**H**$_2$) ppm.

^{13}C NMR (300 MHz, $CDCl_3$) δ 207.4, 158.6, 127.9, 39.8, 34.3, 32.5, 29.5, 26.9, 25.2, 20.1 ppm.



Preparation of Cyclohexylidene Diethyl Succinate (38)

Synthesis was accomplished in a manner similar to that for, **45**.

57% yield, clear yellowish oil.

Rf: 0.48 (hexane: ethyl acetate = 4:1).

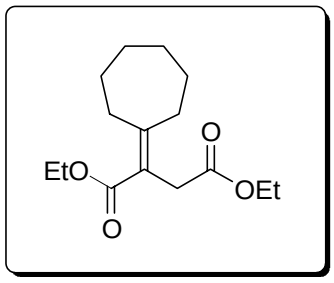
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20 (q, J = 7.1 Hz, 2H, CO_2C**H**$_2CH_3$), 4.12 (q, J = 7.1 Hz, 2H, CO_2C**H**$_2CH_3$), 3.37 (s, 2H, C**H**$_2CO_2CH_2CH_3$), 2.64 (t, J = 5.4 Hz, 2H, C=C(C**H**$_2CH_2CH_2CH_2CH_2$), 2.25 (t, J = 5.6 Hz, 2H, C=C(CH_2C**H**$_2CH_2CH_2CH_2$), 1.70 – 1.61 (m, 6H, C=C(CH_2CH_2C**H**$_2$C**H**$_2$C**H**$_2$), 1.28 (t, J = 7.1 Hz, 3H, CO_2CH_2C**H**$_3$), 1.25 (t, J = 7.1 Hz, 3H, CO_2CH_2C**H**$_3$) ppm.

^{13}C NMR (300 MHz, $CDCl_3$) δ 171.5, 168.6, 154.5, 117.8, 60.7, 60.3, 35.1, 32.5, 32.4, 28.2, 28.0, 26.4, 14.2 ppm.

FTIR (Film): 2983, 2933, 2857, 2337, 1720, 1634, 1446, 1372, 1241, 1178, 1097,

1035 cm^{-1}.

HRMS (EI) Calcd for $C_{14}H_{22}O_4$ [M^+]: 254.1518, Found: 254.1519; [M^+- C_2H_5O]: 209.1178, Found: 209.1174.



Preparation of Cycloheptylidene Diethyl Succinate (46)

Synthesis was accomplished in a manner similar to that for, **45**.

44% yield, clear yellowish oil.

Rf: 0.49 (hexane: ethyl acetate = 4:1).

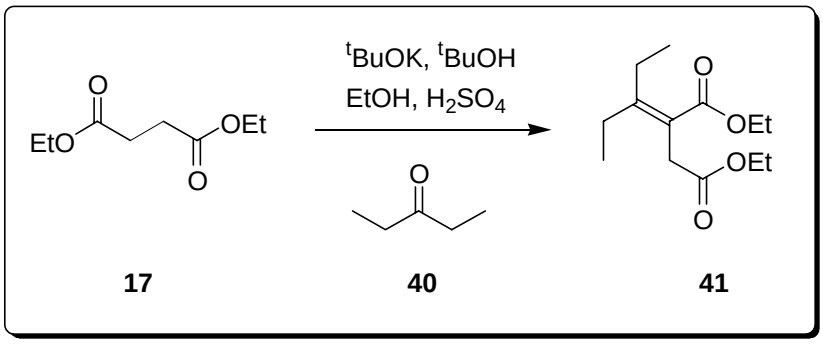
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.21 – 4.10 (m, 4H, $(CO_2C\mathbf{H}_2CH_3)_2$), 3.37 (s, 2H, $C\mathbf{H}_2CO_2CH_2CH_3$), 2.71 (t, J = 6.1, Hz, 2H, C=C($C\mathbf{H}_2CH_2CH_2CH_2$), 2.38 (t, J = 6.2 Hz, 2H, C=C($CH_2C\mathbf{H}_2CH_2CH_2$), 1.70 – 1.51 (m, 8H, C=C($CH_2CH_2(C\mathbf{H}_2)_4$), 1.27 – 1.25 (m, 6H, $(CO_2CH_2C\mathbf{H}_3)_2$), ppm.

^{13}C NMR (300 MHz, $CDCl_3$) δ 171.6, 168.1, 157.2, 120.7, 60.3, 60.2, 35.2, 34.1, 33.7, 28.5, 27.4, 26.3, 14.2 ppm.

FTIR (Film): 2982, 2928, 2856, 2338, 1737, 1625, 1446, 1368, 1242, 1178, 1165, 1096, 1034 cm^{-1}.

HRMS (EI) Calcd for $C_{15}H_{24}O_4$ [M^+]: 268.167, Found: 268.1674; [M^+- C_2H_5O]: 223.1334, Found: 223.1326.

(Note: Another fraction provided the *β,γ*–unsaturated Cycloheptenyl diethyl succinic diester **48** in a trace amount that was not separable.)



Preparation of diethyl 2-(pentan-3-ylidene)succinate (41)

Tert-butanol (10.0 ml) was stirred and cooled to 15-20^{o}C, followed by the addition of potassium tert-butoxide (1.3 eq). The mixture was stirred for 10 mins, followed by the addition of a solution of diethyl succinate **17** (1.0 eq) and the corresponding cyclopentanone (1.2 eq) in 2.0 ml tert-butanol, dropwise. The reaction mixture was allowed to stir for 1.5-2 h at 15-20^{o}C. The reaction was quenched with 4M HCl and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent was removed in vacuo.

The resulting reddish brown syrup was dissolved in ethanol (25 ml) and acidified with conc H_2SO_4 (2-4 ml mL) and stirred for 1h at 0^{o}C. The reaction mixture was warmed up to room temperature and stirred for 48 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent was removed

in vacuo. The resulting reddish oil was purified via flash chromatography (8:1 hexane/ethyl acetate), yielding a colorless oil of **41** with 4% yield.

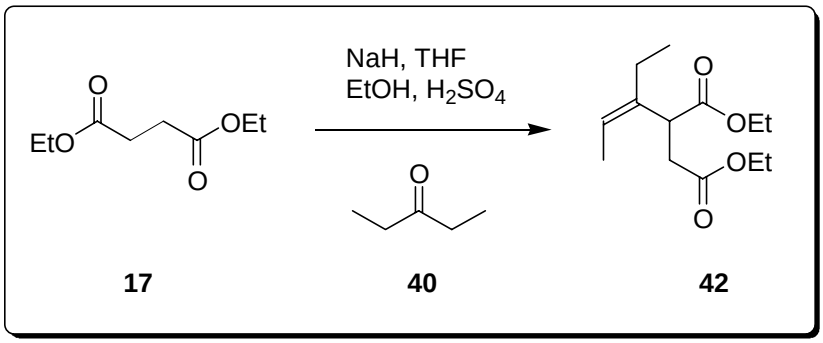
Rf: 0.58 (hexane: ethyl acetate = 4:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.18 (q, J = 7.4 Hz, 2H, $CO_2C\mathbf{H}_2CH_3$), 4.13 (q, J = 7.4 Hz, 2H, $CO_2C\mathbf{H}_2CH_3$), 3.35 (s, 2H, $C\mathbf{H}_2CO_2CH_2CH_3$), 2.48 (q, J = 7.4 Hz, 2H, $C=C(C\mathbf{H}_2CH_3)(CH_2CH_3)$), 2.17 (q, J = 7.4 Hz, 2H, $C=C(CH_2CH_3)(C\mathbf{H}_2CH_3)$), 1.27-1.24 (dt, J = 7.4, 15.3 Hz, 6H, $C=C(CH_2C\mathbf{H}_3)(CH_2C\mathbf{H}_3)$), 1.09 (t, J = 7.4 Hz, 3H, $CO_2CH_2C\mathbf{H}_3$), 1.04 (t, J = 7.4 Hz, 3H, $CO_2CH_2C\mathbf{H}_3$) ppm.

^{13}C NMR (300 MHz, $CDCl_3$) δ 171.6, 167.9, 158.9, 120.2, 60.6, 60.2, 35.2, 27.1, 27.0, 14.2, 13.3, 12.5 ppm.

FTIR (Film): 2922, 2852, 1734, 1463, 1377, 1179, 1058 cm^{-1}.

HRMS (EI) Calcd for $C_{13}H_{22}O_4$ [M^+]: 242.1518. Found: 242.1518; [M^+- C_2H_5O]: 196.1099, Found: 196.1103.



Preparation of diethyl 2-(pent-2-en-3-yl)succinate (42)

Diethyl succinate **17** (1.00 eq) was added to a ice-cooled solution of sodium hydride (55-65%, moistened with mineral oil) (1.50 eq) in THF and stirred for 10 mins. 2 drops of EtOH or MeOH was added to initiate the reaction. Diethyl ketone **40** (1.25

eq) was added dropwise over 15 mins and the reaction mixture was allowed to stir for 18 h at room temperature. The reaction was quenched with 4M HCl and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent was removed in vacuo.

The resulting brown syrup was dissolved in ethanol (200 mL) and acidified with conc H_2SO_4 (~5 – 10 mL) and stirred for 1h at 0^oC. The reaction mixture was warmed up to room temperature and refluxed for 16 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent was removed in vacuo. Flash chromatography afforded, **42**, as a clear colorless oil (43% yield).

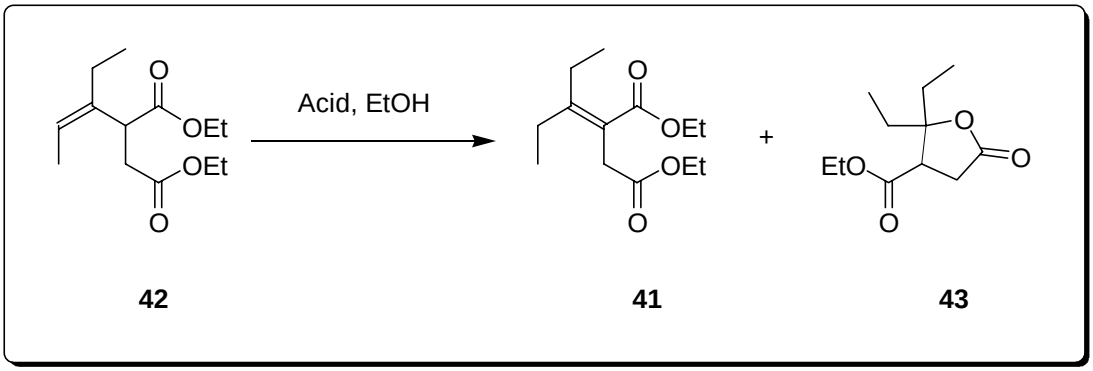
Rf: 0.49 (hexane: ethyl acetate = 4:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.39 (q, J = 6.9 Hz, 1H, **H**$(CH_3)C=C(CH_2CH_3)$), 4.16-4.09 (m, 4H, $(CO_2C\mathbf{H}_2CH_3)_2$), 3.44 (dd, J = 5.6, 10.2 Hz, 1H, C=CC**H**(CO_2Et)), 2.90 (dd, J =10.2, 16.7 Hz, 1H, C**H**$HCO_2CH_2CH_3$), 2.45 (dd, J = 5.09, 16.6 Hz, 1H, CH**H**$CO_2CH_2CH_3$), 2.15-2.04 (m, 2H, $H(CH_3)C=C(C\mathbf{H}_2CH_3)$), 1.61 (d, J = 6.9 Hz, 3H, $H(C\mathbf{H}_3)C=C(CH_2CH_3)$), 1.23 (dt, J = 6.9 Hz, J = 1.4 Hz, 6H, $(CO_2CH_2C\mathbf{H}_3)_2$), 0.97 (t, J = 7.6 Hz, 3H, $H(CH_3)C=C(CH_2C\mathbf{H}_3)$) ppm.

^{13}C NMR (500 MHz, $CDCl_3$) δ 173.5, 172.0, 138.4, 122.5, 60.7, 60.5, 47.9, 36.4, 22.6, 14.2, 14.1, 13.3, 12.9 ppm.

FTIR (Film): 2980, 2937, 2909, 2877, 1737, 1466, 1372, 1244, 1160 1032 cm^{-1}.

HRMS (EI) Calcd for $C_{13}H_{22}O_4$ [M^+]: 242.1518. Found: 242.1519.



Preparation of ethyl 2,2-diethyl-tetrahydro-5-oxofuran-3-carboxylate 43

Diester **42** (1.00 eq.) was added into 3 round bottomed flasks with 2 mls of cooled EtOH (0^oC) each. Acids, H_3PO_4, HCl and H_2SO_4 were added neat (1ml into each flask) and the flasks were allowed to warm up to room temperature. Reactions were allowed to stir for 18h and were monitored by TLC until the disappearance of the spot indicative of starting material **42**. After the reaction was completed, TLC indicated the presence of **41** and **43** as 2 distinct spots visible under UV light or $KMnO_4$ staining. **41** was obtained as a clear colorless oil with a yield of 10%. **43** was obtained as a colorless oil with a yield of 41%. Supporting information for **41** has been reported previously.

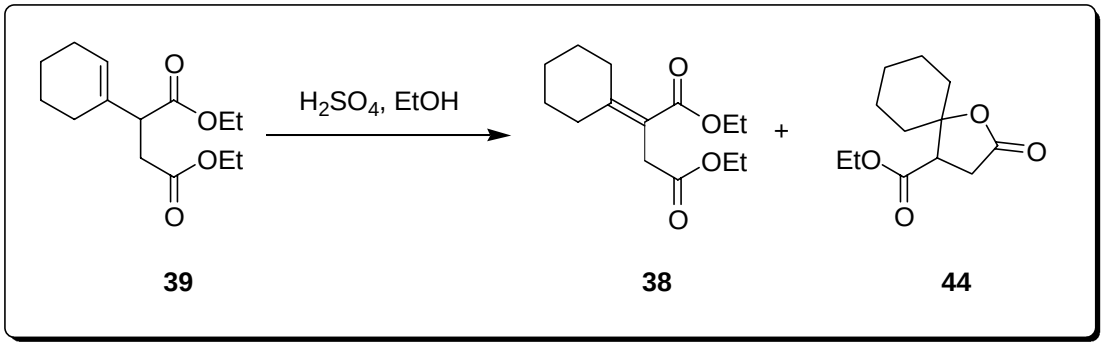
Rf: 0.35 (hexane: ethyl acetate = 4:1).

^{1}H NMR ($CDCl_3$) δ 4.20 (q, J = 2.0 Hz, 2H, $CO_2C\mathbf{H}_2CH_3$), 3.30 (t, *J* = 5.6 Hz, 1H, $COC\mathbf{H}CH_2$), 3.08 (dd, *J* = 5.6, 10.8 Hz, 1H, $COCHC\mathbf{H}H$), 2.69 (dd, *J* = 5.6, 10.8 Hz, 1H, $COCHCH\mathbf{H}$), 1.89 (dd, *J* = 4.4, 8.6 Hz, 1H, $CCH\mathbf{H}CH_3$), 1.81 (dd, *J* = 4.4, 8.6 Hz, 1H $CC\mathbf{H}HCH_3$), 1.73 (dd, *J* = 4.4, 8.9 Hz, 1H, $CCH\mathbf{H}CH_3$), 1.60 (dd, *J* = 4.4, 8.9 Hz, 1H, $CC\mathbf{H}HCH_3$), 1.29 (t, *J* = 4.5 Hz, 3H, $CO_2CH_2C\mathbf{H}_3$), 0.99 (t, *J* = 4.5 Hz, 3H, $CCH_2C\mathbf{H}_3$), 0.99 (t, *J* = 4.5 Hz, 3H, $CCH_2C\mathbf{H}_3$) ppm.

^{13}C NMR ($CDCl_3$) δ 174.5, 170.3, 89.2, 61.5, 46.8, 32.2, 29.8, 27.7, 14.1, 7.63, 7.57 ppm. DEPT-90 (CH) δ 46.8 ppm. DEPT-135 (CH) δ 46.8 ppm. (CH_3) δ 14.1, 7.66, 7.60 ppm. (CH_2) δ 61.5, 32.2, 29.8, 27.7 ppm.

FTIR (Film): 3530, 3449, 2979, 2944, 2887, 1779, 1723, 1460, 1374, 1222, 1180, 1033, 962 cm^{-1}.

HRMS Calcd for $C_{11}H_{18}O_4$ – C_2H_5: [M^+ - C2H5]: 185.0814. Found: 185.0813. Norminal EIMS shows presence of fragmentation of 2 moieties of -C_2H_5 at 157.1. (Molecular ion peak was still not observed after repeated attempts at EIMS).



39 **38** **44**

Preparation of lactone 44

Diester **39** (1.00 eq.) was added into several round bottomed flasks with 2 mls of cooled EtOH (0°C). H_2SO_4 was prepared accordingly to 2.5M, 5.0M, 6.0M, 7.0M, 7.5M and 10M in H_2O and 1 ml of the acid was added to each flask. The flasks were allowed to warm up to room temperature. Reactions were allowed to stir for 18h and were monitored by TLC until the disappearance of the spot indicative of starting material **39**. After the reaction was completed, TLC indicated the presence of **44** and **38** as 2 distinct spots visible under UV light or $KMnO_4$ staining. **38** was obtained as a

clear colorless oil with a yield of 9%. **44** was obtained as a colorless oil with a yield of 40%. Supporting information for **38** has been reported previously.

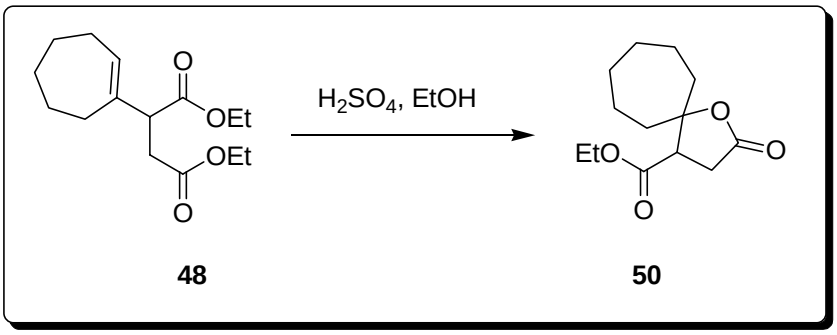
Rf: 0.30 (hexane: ethyl acetate = 4:1).

^{1}H NMR ($CDCl_3$) δ 4.30 (q, J = 7.3 Hz, 2H, $CO_2C\mathbf{H}_2CH_3$), 3.06 (t, *J* = 5.2 Hz, 1H, $COC\mathbf{H}CH_2$), 3.00 (dd, *J* = 5.2, 13.2 Hz, 1H, $COCHC\mathbf{H}H$), 2.67 (dd, *J* = 5.2, 14.3 Hz, 1H, $COCHCH\mathbf{H}$), 1.78-1.59 (m, 10H, $(C\mathbf{H}_2)_5$), 1.27 (t, J= 7.3 Hz, 3H, $CO_2CH_2C\mathbf{H}_3$) ppm.

^{13}C NMR ($CDCl_3$) δ 174.4, 169.9, 85.9, 61.4, 50.4, 37.3, 32.3, 31.5, 24.8, 22.4, 21.6, 14.1 ppm. DEPT-90 (CH) δ 50.4 ppm. DEPT-135 (CH) δ 50.4 ppm. (CH_3) δ 14.1 ppm. (CH_2) δ 61.4, 37.3, 32.3, 31.5, 24.8, 22.4, 21.6 ppm.

FTIR (Film): 2939, 2864, 1779, 1733, 1448, 1375, 1271, 1222, 963 cm^{-1}.

HRMS Calcd for $C_{12}H_{18}O_4$ [M^+]: 226.1205. Found: 226.1202.



48 **50**

Preparation of lactone 50

Synthesis was accomplished with a similar procedure for lactone **44**. **50** was obtained exclusively as a clear yellowish oil with a yield of 38%.

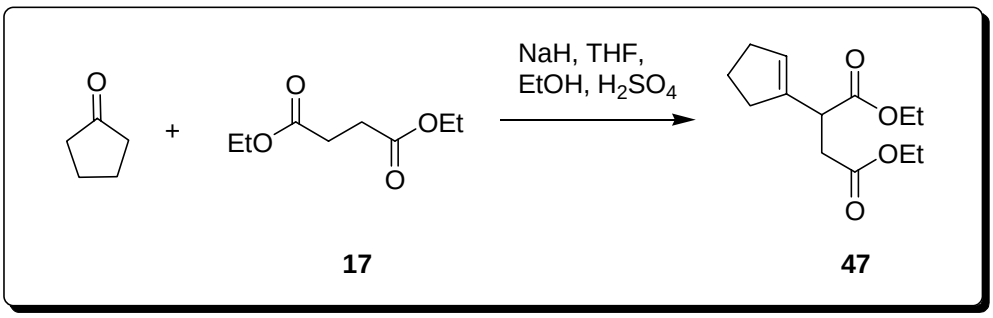
Rf: 0.26 (hexane: ethyl acetate = 4:1).

^{1}H NMR ($CDCl_3$) δ 4.21 (q, J = 7.3 Hz, 2H, $CO_2C\mathbf{H}_2CH_3$), 3.08 (t, *J* = 7.7 Hz, 1H, $COC\mathbf{H}CH_2$), 3.03 (dd, J = 7.7, unresolved Hz, 1H, $COCHC\mathbf{H}H$), 2.70-2.62 (dd, J = 7.7, 17.0 Hz, 1H, $COCHCH\mathbf{H}$), 2.12-2.01 (m, 2H, $C\mathbf{H}_2(CH_2)_4CH_2$), 1.81-1.52 (m, 8H, $(C\mathbf{H}_2)_4$), 1.43-1.12 (m, 2H, $CH_2(CH_2)_4C\mathbf{H}_2$), 1.31 (t, *J* = 7.3 Hz, 3H, $CO_2CH_2C\mathbf{H}_3$) ppm.

^{13}C NMR ($CDCl_3$) δ 174.4, 169.9, 89.9, 61.5, 51.2, 41.5, 34.5, 31.7, 29.5, 28.9, 22.7, 21.8, 14.2 ppm.

FTIR (Film): 3630, 3535, 2981, 2930, 2860, 1780, 1733, 1462, 1376, 1247, 1197, 1174, 1015, 941 cm^{-1}.

HRMS Calcd for $C_{13}H_{20}O_4$ [M^+]: 240.1362. Found: 240.1357.



Preparation of Cyclopentenyl Diethyl Succinate (47)

Synthesis was accomplished in a manner similar to that for the preparation of Isopropylidene (IPP) Diethyl Succinate **14**. The cyclopentanone was added into the stirring mixture of diethyl succinate **17** and NaH dropwise over 1h. Usual esterification, workup and purification of the crude reaction mixture using flash chromatography (8:1 hexane/ethyl acetate) afforded a clear colorless oil, **47** in 41% yield.

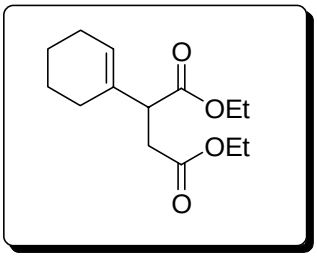
Rf: 0.49 (hexane: ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.55 (s, 1H, **H**C=CCH), 4.18 (q, *J* = 7.2 Hz, 2H, $CO_2C\mathbf{H}_2CH_3$), 4.12 (q, *J* = 7.2 Hz, 2H, $CO_2C\mathbf{H}_2CH_3$), 3.64 (dd, *J* = 5.2, 9.4 Hz, 1H, C=CC**H**CO_2Et), 2.93 (dd, *J* = 9.9, 16.5 Hz, 1H, C**H**H$CO_2CH_2CH_3$), 2.54 (dd, *J* = 5.4, 16.6 Hz, 1H, CH**H**$CO_2CH_2CH_3$), 2.35-2.30 (m, 4H, $C\mathbf{H}_2C\mathbf{H}_2CH_2$) 1.89-1.84 (m, 2H, $CH_2CH_2C\mathbf{H}_2$), 1.28-1.22 (dt, *J* = 4.7, 6.9 Hz, 6H, $(CO_2CH_2C\mathbf{H}_3)_2$) ppm.

^{13}C NMR (500 MHz, $CDCl_3$) δ 172.6, 171.7, 139.9, 127.5, 60.8, 60.5, 43.5, 35.4, 33.4, 32.3, 23.1, 14.1 ppm.

FTIR (Film): 2981, 2935, 2907, 2850, 1738, 1647, 1446, 1371, 1275, 1161, 1096, 1031, 858 cm^{-1}.

HRMS (EI) Calcd for $C_{13}H_{20}O_4$ [M^+]: 240.1362, Found: 240.1358; [M^+- C_2H_6O]: 194.0943, Found: 194.0944.



Preparation of Cyclohexenyl diethyl succinic diester (39)

Synthesis was accomplished in a manner similar to that for **47**.

A clear colorless oil of **39** was obtained in 72% yield.

Rf: 0.53 (hexane: ethyl acetate = 4:1).

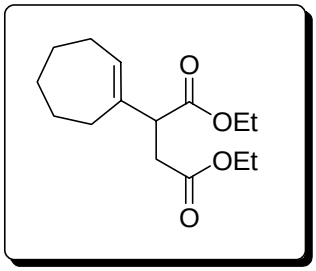
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.61 (s, 1H, **H**C=CCH), 4.19-4.09 (dq, *J* = 2.0, 6.9 Hz, 4H, $(CO_2C\mathbf{H}_2CH_3)_2$), 3.40 (dd, *J* = 5.6, 9.8 Hz, 1H, C=CC**H**CO_2Et), 2.89 (dd, *J* = 9.8,

16.4 Hz, 1H, C**H**HCO$_2$CH$_2$CH$_3$), 2.46 (dd, *J* = 5.9, 16.4 Hz, 1H, CH**H**CO$_2$CH$_2$CH$_3$), 2.05-1.70 (m, 4H, C**H**$_2$CH$_2$CH$_2$C**H**$_2$), 1.63-1.54 (m, 4H, CH$_2$C**H**$_2$C**H**$_2$CH$_2$), 1.25 (dt, *J* = 2.4, 6.9 Hz, 6H, (CO$_2$CH$_2$C**H**$_3$)$_2$) ppm.

^{13}C NMR (500 MHz, CDCl$_3$) δ 173.1, 172.0, 134.1, 125.4, 60.7, 60.5, 49.0, 35.4, 26.4, 25.3, 22.8, 22.1, 14.2 ppm. DEPT-90 (CH) δ 125.4, 49.0 ppm. DEPT-135 (CH) δ 125.4, 49.0 ppm. (CH$_3$) δ 14.2 ppm. (CH$_2$) δ 60.7, 60.5, 35.4, 26.4, 25.3, 22.8, 22.1 ppm.

FTIR (Film): 2981, 2933, 2859, 2839, 1777, 1737, 1665, 1448, 1370, 1250, 1220, 1173, 1097, 1032 cm^{-1}.

HRMS (EI) Calcd for C$_{14}$H$_{22}$O$_4$ [M$^+$]: 254.1518, Found: 254.1517.



Preparation of Cycloheptenyl diethyl succinic diester (48)

Synthesis was accomplished in a manner similar to that for **47**.

A clear colorless oil of **48** was obtained in 87% yield.

Rf: 0.60 (hexane: ethyl acetate = 4:1).

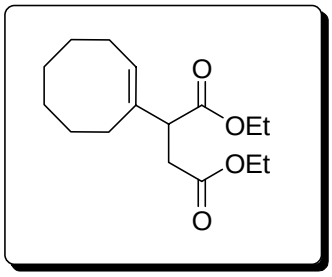
^{1}H NMR (500 MHz, CDCl$_3$) δ 5.77 (t, *J* = 6.5 Hz, 1H, **H**C=CCH), 4.14 (dq, *J* = 3.6, 6.6 Hz, 4H, (CO$_2$C**H**$_2$CH$_3$)$_2$), 3.47 (dd, *J* = 3.6, 5.3 Hz, 1H, C=CC**H**CO$_2$Et), 2.92 (dd, *J* = 5.6, 10.0 Hz, 1H, C**H**HCO$_2$CH$_2$CH$_3$), 2.48 (dd, *J* = 3.9, 9.7 Hz, 1H, CH**H**CO$_2$CH$_2$CH$_3$), 2.39-2.02 (m, 4H, C**H**$_2$(CH$_2$)$_3$C**H**$_2$), 1.55-1.46 (m, 6H,

$CH_2(C\mathbf{H}_2)_3CH_2$), 1.26 (t, *J* = 6.9 Hz, 3H, $CO_2CH_2C\mathbf{H}_3$) 1.25 (dt, *J* = 3.1, 7.0 Hz, 3H, $CO_2CH_2C\mathbf{H}_3$) ppm.

^{13}C NMR (500 MHz, $CDCl_3$) δ 173.1, 171.9, 140.5, 130.9, 60.8, 60.5, 50.9, 35.6, 32.5, 30.4, 28.4, 26.8, 26.7, 14.2 ppm.

FTIR (Film): 2981, 2924, 2851, 1734, 1662, 1447, 1369, 1250, 1174, 1158, 1097, 1032 cm^{-1}.

HRMS (EI) Calcd for $C_{15}H_{24}O_4$ [M^+]: 268.1675, Found: 268.1672.



Preparation of Cyclooctyneyl diethyl succinic diester (49)

Synthesis was accomplished in a manner similar to that for **47**.

A clear colorless oil of **49** was obtained in 80% yield.

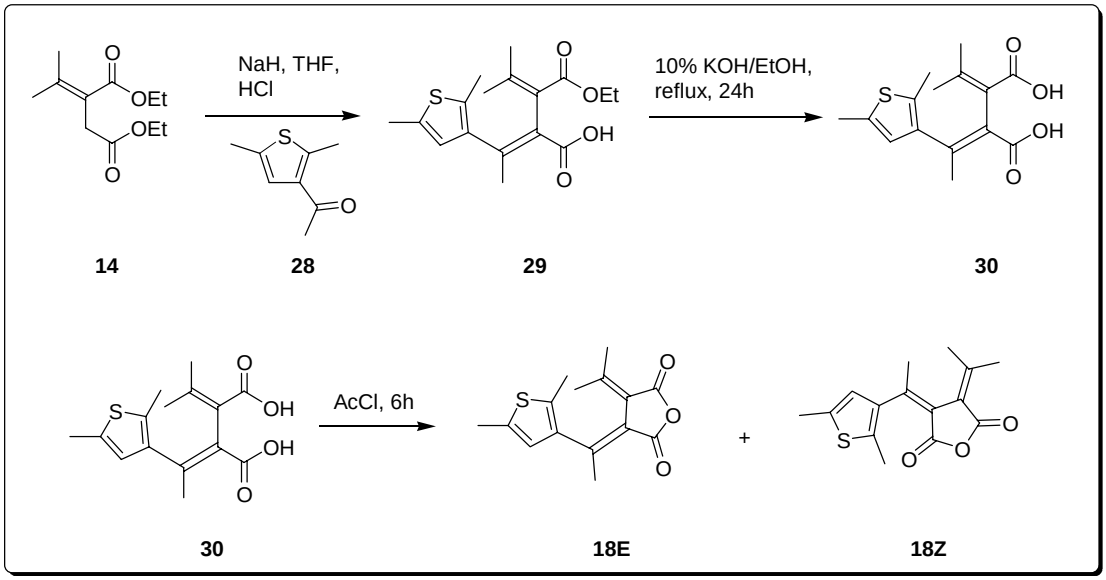
Rf: 0.63 (hexane: ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.56 (t, *J* = 8.3 Hz, 1H, 1H, **H**C=CCH), 4.13 (dq, *J* = 3.6, 7.4 Hz, 4H, $(CO_2C\mathbf{H}_2CH_3)_2$), 3.46 (dd, *J* = 5.3, 9.9 Hz, 1H, C=CC**H**CO_2Et), 2.91 (dd, *J* = 10.2, 16.6 Hz, 1H, C**H**H$CO_2CH_2CH_3$), 2.42 (dd, *J* = 5.6, 16.6 Hz, 1H, CH**H**$CO_2CH_2CH_3$), 2.35-2.03 (m, 4H, $C\mathbf{H}_2(CH_2)_4C\mathbf{H}_2$), 1.60-1.45 (m, 8H, $CH_2(C\mathbf{H}_2)_4CH_2$), 1.26-1.22 (dt, *J* = 3.2, 7.1 Hz, 6H, $(CO_2CH_2C\mathbf{H}_3)_2$) ppm.

^{13}C NMR (500 MHz, $CDCl_3$) δ 173.3, 172.0, 136.8, 128.5, 60.7, 60.6, 48.9, 35.9, 29.5, 28.9, 27.9, 26.4, 26.3, 26.2, 14.2, 14.1 ppm.

FTIR (Film): 2981, 2928, 2856, 1735, 1701, 1468, 1447, 1371, 1329, 1298, 1245, 1212, 1162, 1096, 1032 cm^{-1}.

HRMS (EI) Calcd for $C_{16}H_{26}O_4$ [M^+]: 282.1831, Found: 282.1836; [M^+- C_2H_6O]: 236.1412, Found: 236.1414.



Preparation of 2,5-dimethylthiophene isopropylidene fulgide (18)

A mixture of isopropylidene (IPP) diethyl succinate **14** (1eq) and 3-acetyl-2,5-dimethyl thiophene **28** (1.1 eq) in a solution of THF (5ml) was added dropwise into an ice-cooled suspension of NaH (55-65%, moistened with mineral oil) (1.5-1.8 eq) pre-washed with hexane and resolvated in THF. The reaction was also initiated with 2-3 drops of EtOH before immediate addition of the reagents into the stirred NaH suspension. The mixture was then allowed to stir overnight followed by pouring of the reaction mixture onto crushed ice. 10% Na_2CO_3 was used to extract the half-ester followed by the acidification of the basic solution with 4M HCl to liberate the acid-

ester. 4 x 25 ml of ethyl acetate was used to extract the liberated acid-ester and the solvent was removed in vacuo to afford a dark brown gum.

Saponification of the half-ester, **29**, was initiated by adding 10% w/v KOH to a solution of EtOH and the brown suspension stirred for 15 mins before refluxing overnight to afford the diacid, **30**. A second acid base workup as before afforded the diacid as a brown solid.

The crude reaction mixture was washed with brine and dried by standing in anhydrous $MgSO_4$. Solvents were removed in vacuo before the addition of excess acetyl chloride to the diacid in the dark to initiate the ring closure to afford the desired fulgide. The mixture was allowed to stir for approximately 4-6 h before removing the acetyl chloride in vacuo.

Purification of the crude reaction mixture using flash chromatography (7:1 hexane/ethyl acetate) afforded **18** in 55% yield (E/Z combined yield); *E*-form: orange cubes, mp 112-114 ^{o}C, (39% of 55% combined yield).

Rf: 0.54 (hexane: ethyl acetate = 4:1).

^{1}H NMR (300MHz, $CDCl_3$) δ 6.52 (s, 1H, C=C**H**), 2.60 (s, 3H, C=CC**H**$_3$), 2.40 (s, 3H, C**H**$_3$CSCCH$_3$), 2.30 (s, 3H, CH$_3$CSCC**H**$_3$), 2.13 (s, 3H, (CH$_3$)(C**H**$_3$)C=CCO), 1.28 (s, 3H, (C**H**$_3$)(CH$_3$)C=CCO) ppm.

^{13}C NMR (500 MHz, $CDCl_3$) δ 163.8, 163.2, 155.4, 149.2, 139.5, 137.8, 134.7, 125.3, 120.9, 120.6, 25.6, 22.9, 22.8, 15.1, 14.8 ppm.

UV(VIS)O: 342 nm, C: 538 nm.

FTIR (KBr): 3448, 2917, 2360, 1809, 1767, 1627, 1585, 1423, 1265, 1213, 1118, 1016, 924, 840, 760 cm^{-1}.

HRMS (EI) Calcd for $C_{15}H_{16}O_3S$, $[M^+]$: 276.0820, Found: 276.0821.

(61% of 55% combined yield) *Z*-form: yellow needles, mp 135-137 ^oC.

Rf: 0.45 (hexane: ethyl acetate = 4:1).

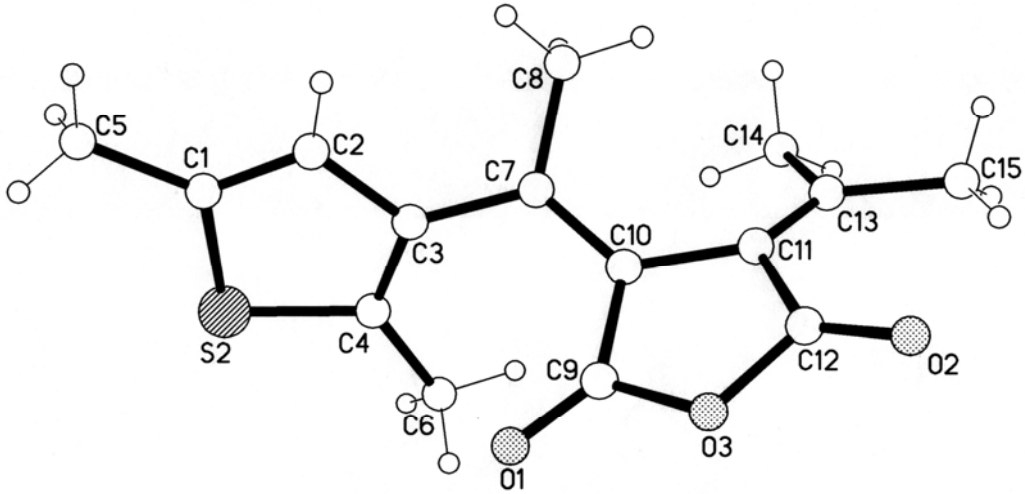
^1H NMR (300MHz, $CDCl_3$) δ 6.55 (s, 1H, C=C**H**), 2.44 (s, 3H, $CH_3CSCC\mathbf{H}_3$), 2.41 (s, 3H, $C\mathbf{H}_3CSCCH_3$), 2.31 (s, 3H, $(CH_3)(C\mathbf{H}_3)C=CCO$), 2.11 (s, 3H, $C=CC\mathbf{H}_3$), 2.01 (s, 3H, $(C\mathbf{H}_3)(CH_3)C=CCO$) ppm.

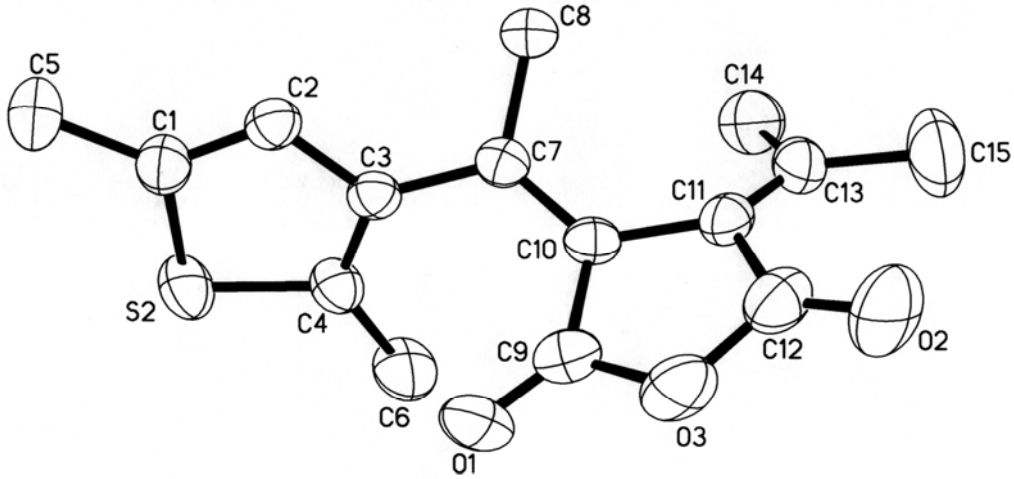
^{13}C NMR (500 MHz, $CDCl_3$) δ 163.4, 160.8, 153.9, 147.1, 139.3, 136.1, 135.4, 124.5, 121.8, 121.5, 27.0, 26.3, 22.4, 15.1, 14.3 ppm.

UV(VIS)O: 345 nm, C: 540 nm.

HRMS (EI) Calcd for $C_{15}H_{16}O_3S$, $[M^+]$: 276.0820, Found: 276.0822.

CRYSTAL STRUCTURE OF Z-THIENYL FULGIDE (18Z)

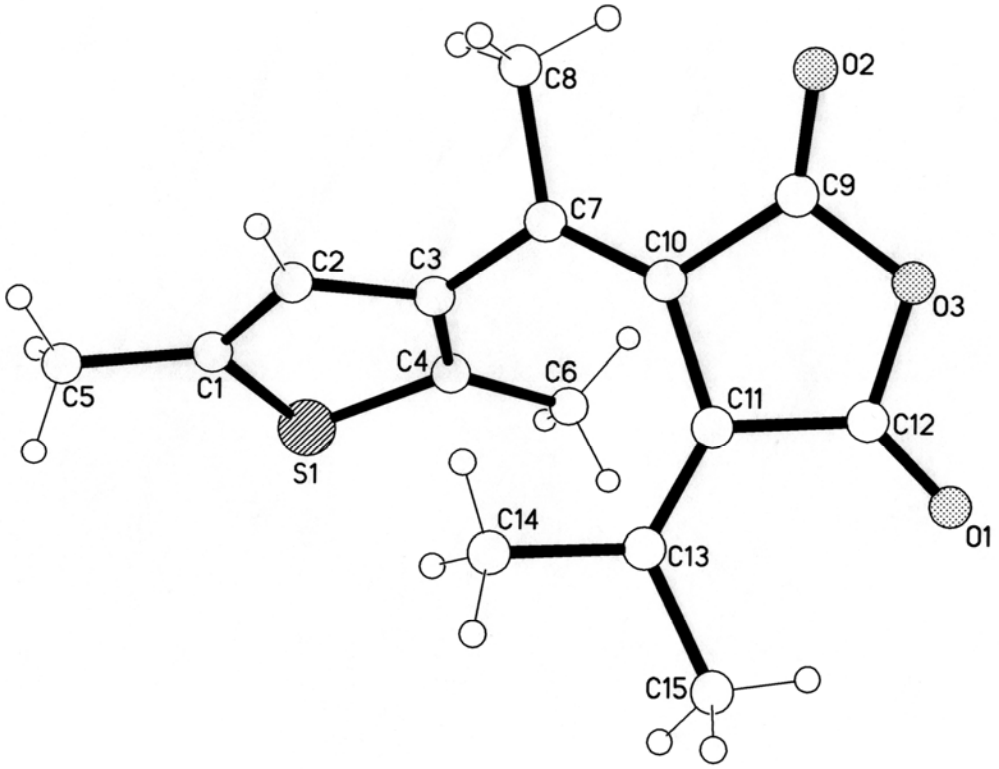


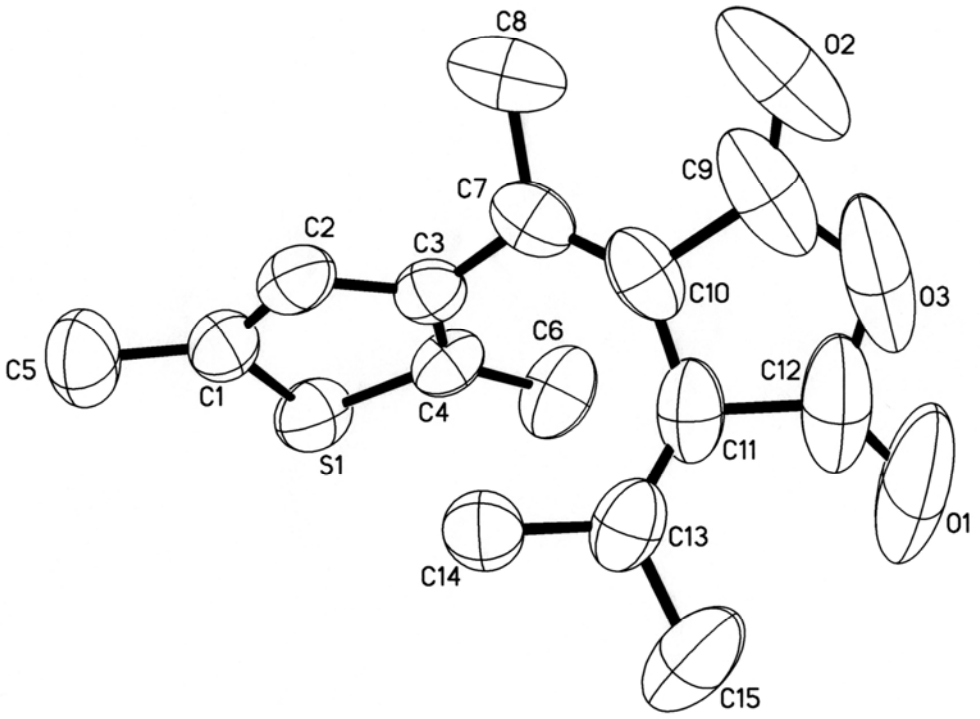


CRYSTAL DATA AND STRUCTURE REFINEMENT FOR (18Z):

Crystal growing solvent	Dichloromethane and Ether
Empirical formula	C15 H16 O3 S
Formula weight	276.34
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space groups	Pbca
Unit cell dimensions	a = 15.4088(8) Å α = 90°. b = 7.5348(4) Å β = 90°. c = 24.0381(13) Å γ = 90°.
Volume	2790.9(3) $Å^3$
Z	8
Density (calculated)	1.315 Mg/m^3
Absorption coefficient	0.233 mm^{-1}
F(000)	1168
Crystal size	0.50 x 0.20 x 0.08 mm^3
Theta range for data collection	1.69 to 25.00°.
Index ranges	-18<=h<=17, -8<=k<=8, -28<=l<=18
Reflections collected	14954
Independent reflections	2455 [R(int) = 0.0353]
Completeness to theta = 25.00°	99.8%
Absorption correction	Sadabs, (Sheldrick 2001)
Max. and min. transmission	0.9816 and 0.8925
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2455 / 0 / 236
Goodness of fit on F^2	1.226
Final R indices [I>2sigma(I)]	R1 = 0.0635, wR2 = 0.1430
R indices (all data)	R1 = 0.0728, wR2 = 0.1486
Largest diff. peak and hole	0.339 and -0.150 e. $Å^3$

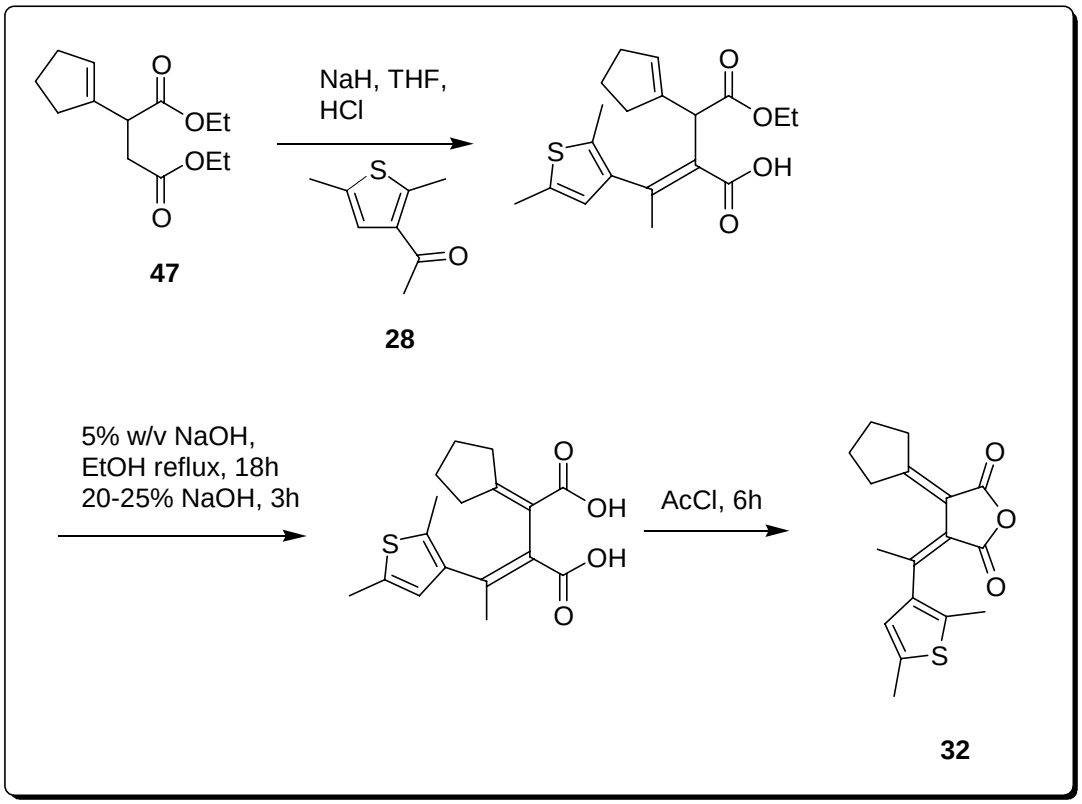
Crystal structure of Z-thienyl fulgide (18E)





CRYSTAL DATA AND STRUCTURE REFINEMENT FOR (18E):

Crystal growing solvent	Dichloromethane and Ether
Empirical formula	C15 H16 O3 S
Formula weight	276.34
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space groups	P2(1)/c
Unit cell dimensions	a = 11.5984(10) Å α = 90°. b = 7.9080(7) Å β = 90°. c = 15.9745(15) Å γ = 90°.
Volume	1447.4(2) $Å^3$
Z	4
Density (calculated)	1.268 Mg/m^3
Absorption coefficient	0.224 mm^{-1}
F(000)	584
Crystal size	0.26 x 0.30 x 0.50 mm^3
Theta range for data collection	1.78 to 25.00°.
Index ranges	-13<=h<=13, -9<=k<=9, -14<=l<=18
Reflections collected	8100
Independent reflections	2554 [R(int) = 0.0294]
Completeness to theta = 25.00°	99.8%
Absorption correction	Sadabs, (Sheldrick 2001)
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2554 / 0 / 177
Goodness of fit on F^2	1.063
Final R indices [I>2sigma(I)]	R1 = 0.0661, wR2 = 0.1692
R indices (all data)	R1 = 0.0818, wR2 = 0.1806
Largest diff. peak and hole	0.324 and -0.162 e. $Å^3$



Preparation of 2,5-dimethylthiophene cyclopentylidene fulgide (32)

Cyclopentenyl diethyl succinate **47** (1eq.) was added into in a solution of ice-cooled THF containing NaH (55-65%, moistened with mineral oil) (1.5-1.8 eq.) prewashed with hexane and stirred for 15 mins. 2-3 drops of EtOH was added into the reaction mixture before dropwise addition of 3-acetyl-2,5-dimethyl thiophene, **28** (1.1 eq.) over 30 mins. The mixture was then allowed to stir overnight followed by quenching of the reaction using ice-cold water. 10% Na_2CO_3 was used to extract the half-ester followed by the acidification of the basic solution with 4M HCl to liberate the acid-ester. 4 x 25 ml of ethyl acetate was used to extract the liberated acid-ester and the solvent was removed in vacuo to afford a dark brown oil (Crude nmr indicated the presence of the half-ester).

Saponification of the half-ester and double-bond isomerization of the β,γ-unsaturation to the α,β site was initiated with 5% w/v NaOH in EtOH. The mixture was allowed to stir for 1h before refluxing for approximately 16h. After which, an aqueous solution (20-50 mls) of 25% NaOH was added and the reaction mixture allowed to stir for an additional 3h. A second acid base workup as before afforded the diacid as a brownish solid. The crude reaction mixture was washed with brine and dried by standing in anhydrous $MgSO_4$. Solvents were removed in vacuo before the addition of excess acetyl chloride to the diacid in the dark to initiate the ring closure to afford the desired fulgide. The mixture was allowed to stir for approximately 5 h before removing the acetyl chloride in vacuo. Purification of the crude reaction mixture using flash chromatography (8:1 hexane/ethyl acetate) afforded **32** in 80% yield (*Z*-isomer); yellow plates, mp 125-127 ^{o}C. The *E*-isomer was observed to be present on TLC, but was not isolable.

Rf: 0.61 (*E*-siomer), 0.53 (*Z*-isomer) (hexane: ethyl acetate = 4:1).

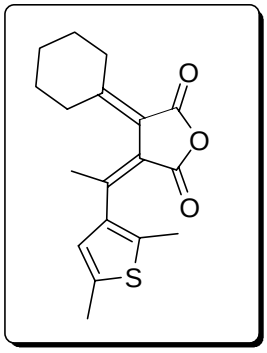
^{1}H NMR (500MHz, $CDCl_3$) δ 6.56 (s, 1H, C=C**H**), 3.00 (t, J = 4.4 Hz, 2H, $CH_2(CH_2)_2C\mathbf{H}_2C$=CCO), 2.42 (s, 3H, $CH_3CSCC\mathbf{H}_3$), 2.36 (t, J = 4.2 Hz, 2H, $C\mathbf{H}_2(CH_2)_2CH_2C$=CCO), 2.30 (s, 3H, $C\mathbf{H}_3CSCCH_3$), 2.13 (s, 3H, C=CC**H**$_3$), 1.90 (t, J = 4.4 Hz, 2H, $CH_2(CH_2C\mathbf{H}_2)CH_2C$=CCO), 1.82 (t, J = 4.2 Hz, 2H, $CH_2(C\mathbf{H}_2CH_2)CH_2C$=CCO) ppm.

^{13}C NMR (500 MHz, $CDCl_3$) δ 167.7, 164.3, 163.4, 148.8, 139.6, 137.7, 135.2, 125.8, 121.1, 117.5, 36.3, 35.2, 26.2, 25.6, 23.2, 15.1, 14.9 ppm.

FTIR (KBr): 3449, 2917, 2870, 1806, 1763, 1617, 1438, 1262, 1230, 1100, 927, 760 cm^{-1}.

UV(VIS)O: 342 nm, C: 544 nm.

HRMS (EI) Calcd for $C_{17}H_{18}O_3S$, [M^+]: 302.0977, Found: 302.0973; [M^+-CH_3]: 287.0742, Found: 287.0747.



Preparation of 2,5-dimethylthiophene cyclohexylidene fulgide (33)

Synthesis was accomplished in a manner similar to that for the cyclopentylidene fulgide **32,** using the corresponding diester.

32 was obtained as orange plates with a yield of 14% (*Z*-isomer), mp 128-130 ^oC.

E-isomer observed to be present as a faint spot on TLC, and was not isolable.

Rf: 0.59 (hexane: ethyl acetate = 4:1).

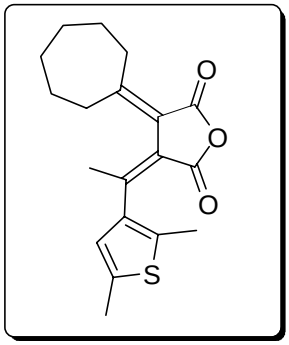
^1H NMR (300MHz, $CDCl_3$) δ 6.51 (s, 1H, C=C**H**), 2.95-2.86 (m, 2H, $CH_2(CH_2)_3CH_2C$=CCO), 2.55 (s, 3H, CH_3CSCCH_3), 2.40 (s, 3H, CH_3CSCCH_3), 2.14 (s, 3H, C=CCH_3), 1.65-1.57 (m, 4H, $CH_2(CH_2CH_2CH_2)CH_2C$=CCO), 1.49-1.44 (m, 2H, $CH_2(CH_2)_3CH_2C$=CCO), 1.27-1.19 (m, 2H, $CH_2(CH_2CH_2CH_2)CH_2C$=CCO) ppm.

^{13}C NMR (500 MHz, $CDCl_3$) δ 163.7, 163.2, 162.4, 148.7, 139.3, 137.8, 134.1, 125.2, 120.9, 118.0, 33.9, 30.6, 27.6, 27.0, 25.3, 22.8, 15.1, 14.8.

FTIR (KBr): 2954, 2923, 2851, 1736, 1716, 1458, 1364, 1218 cm^{-1}

UV(VIS)O: 345 nm, C: 552 nm.

HRMS (EI) Calcd for $C_{18}H_{20}O_3S$, [M^+]: 316.1133, Found: 316.1134; [M^+-CH_3]: 301.0898, Found: 301.0902.



Preparation of 2,5-dimethylthiophene cycloheptylidene fulgide (34)

Synthesis was accomplished in a manner similar to that for the cyclopentylidene fulgide **32,** using the corresponding diester.

34 was obtained with a 7% yield. The *E*-isomer was observed to be absent on TLC.

Rf: 0.54 (hexane: ethyl acetate = 4:1).

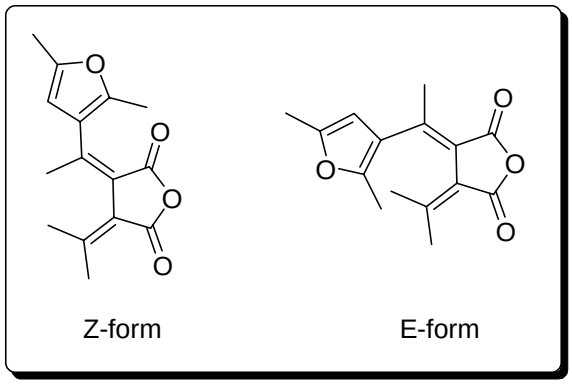
^{1}H NMR δ 6.51 (s, 1H, C=C**H**), 2.90-3.10 (m, 2H, $CH_2(CH_2)_4C\mathbf{H}_2C$=CCO), 2.59 (s, 3H, $CH_3CSCC\mathbf{H}_3$), 2.40 (s, 3H, $C\mathbf{H}_3CSCCH_3$), 2.13 (s, 3H, C=$CC\mathbf{H}_3$), 1.65-1.33 (m, 4H, $C\mathbf{H}_2(CH_2$ $CH_2CH_2C\mathbf{H}_2)CH_2C$=CCO), 1.35-1.26 (m, 4H, $CH_2(C\mathbf{H}_2CH_2C\mathbf{H}_2CH_2)CH_2C$=CCO), 0.90-0.85 (m, 2H, $CH_2(CH_2C\mathbf{H}_2CH_2CH_2)CH_2C$=CCO).

^{13}C NMR (300 MHz, $CDCl_3$) δ 165.7, 163.9, 163.1, 148.9, 139.8, 137.8, 134.7, 125.2, 121.3, 119.9, 36.7, 31.6, 29.7, 28.7, 27.4, 25.5, 23.0, 15.1, 14.8.

FTIR (KBr): 3476, 2920, 2854, 1809, 1763, 1685, 1445, 1263, 1229, 924, 716, 497 cm^{-1}.

UV(VIS)O: 342 nm, C: 550 nm.

HRMS (EI) Calcd for $C_{18}H_{20}O_3S$, [M^+]: 330.1290, Found: 330.1289; [M^+-CH_3]: 315.1055, Found: 315.1054.



Preparation of 2,5-dimethylfuran isopropylidene fulgide (2)

Synthesis was accomplished in a manner similar to that for the isopropylidene thienyl fulgide **18** analog.

18 was obtained with a yield of 45% (*E*-isomer) as orange plates, mp 110-112 ^oC.

Rf: 0.44 (hexane: ethyl acetate = 4:1).

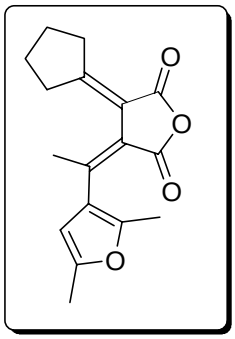
^1H NMR (500MHz, $CDCl_3$) δ 5.92 (s, 1H, C=C**H**), 2.58 (s, 3H, C=CC**H**$_3$), 2.34 (s, 3H, C**H**$_3$COCCH$_3$), 2.25 (s, 3H, CH$_3$CSCC**H**$_3$), 2.00 (s, 3H, (CH$_3$)(C**H**$_3$)C=CCO), 1.36 (s, 3H, (C**H**$_3$)(CH$_3$)C=CCO) ppm.

^{13}C NMR (500 MHz, $CDCl_3$) δ 163.9, 163.3, 153.7, 151.3, 148.4, 146.8, 124.3, 121.0, 114.2, 105.9, 26.8, 22.6, 22.2, 13.9, 13.3 ppm.

FTIR (KBr): 3425, 2956, 2855, 1810, 1761, 1653, 1226, 928 cm^{-1}.

UV(VIS)O: 346 nm, C: 510 nm.

HRMS (EI) Calcd for $C_{15}H_{16}O_4$, [M^+]: 260.1049, Found: 260.1052; [M^+-CH_3]: 245.0814, Found: 245.0812.



Preparation of 2,5-dimethylfuran cyclopentylidene fulgide (35)

Synthesis was accomplished in a manner similar to that for the cyclopentylidene fulgide **32,** using the appropriate diester.

32 was obtained with a 46% yield as orange plates, mp 102-105 ^{o}C. The *E*-isomer was observed to be present on TLC, but was not isolable.

Rf: 0.60 (*E*-siomer), 0.53 (*Z*-isomer) (hexane: ethyl acetate = 4:1).

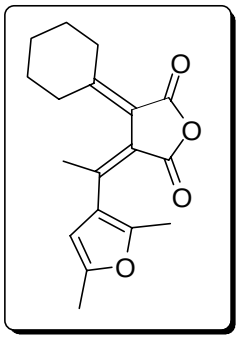
^{1}H NMR (300MHz, $CDCl_3$) δ 5.98 (s, 1H, C=C**H**), 2.98-2.93 (m, br, 2H, $CH_2(CH_2)_2C\mathbf{H}_2C$=CCO), 2.60 (s, 3H, $CH_3COCC\mathbf{H}_3$), 2.27 (s, 3H, $C\mathbf{H}_3COCCH_3$), 1.90 (s, 3H, C=CC$\mathbf{H}_3$), 1.72-1.69 (m, br, 2H, $C\mathbf{H}_2(CH_2)_2CH_2C$=CCO), 1.57-1.54 (m, br, 2H, $CH_2(CH_2C\mathbf{H}_2)CH_2C$=CCO), 1.28-1.24 (m, br, 2H, $CH_2(C\mathbf{H}_2CH_2)CH_2C$=CCO) ppm.

^{13}C NMR (500 MHz, $CDCl_3$) δ165.7, 164.4, 163.5, 151.3, 148.8, 146.3, 124.5, 119.2, 117.9, 106.3, 37.8, 35.0, 26.1, 25.7, 22.5, 14.0, 13.3 ppm.

FTIR (KBr): 3005, 2970, 2926, 1739, 1716, 1431, 1420, 1363, 1222, 1092, 928, 529 cm^{-1}.

UV(VIS)O: 350 nm, C: 514 nm.

HRMS (EI) Calcd for $C_{17}H_{18}O_4$, [M^+]: 286.1205, Found: 286.1206; [M^+-CH_3]: 271.0970, Found: 271.0970.



Preparation of 2,5-dimethylfuran cyclohexylidene fulgide (36)

Synthesis was accomplished in a manner similar to that for the cyclopentylidene fulgide **32,** using the appropriate diester.

36 was obtained with a yield of 17% (*Z*-isomer) as pale yellowish needles, mp 115-117 ^{o}C.

Rf: 0.55 (hexane: ethyl acetate = 4:1).

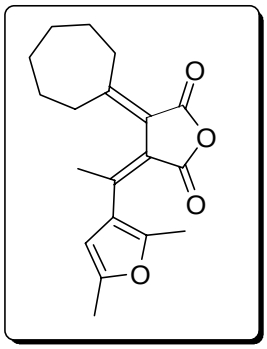
^{1}H NMR (300MHz, $CDCl_3$) δ 5.92 (s, 1H, C=C**H**), 2.95 (t, J = 3.7 Hz, 2H, $CH_2(CH_2)_3C\mathbf{H}_2C{=}CCO$), 2.54 (s, 3H, $CH_3COCC\mathbf{H}_3$), 2.25 (s, 3H, $C\mathbf{H}_3CSCCH_3$), 2.03 (s, 3H, $C{=}CC\mathbf{H}_3$), 1.71-1.61 (m, 4H, $CH_2(C\mathbf{H}_2CH_2C\mathbf{H}_2)CH_2C{=}CCO$), 1.53-1.49 (m, 2H, $C\mathbf{H}_2(CH_2)_3CH_2C{=}CCO$), 1.26 (t, J = 3.7 Hz, 2H, $CH_2(CH_2C\mathbf{H}_2CH_2)CH_2C{=}CCO$) ppm.

^{13}C NMR (500 MHz, $CDCl_3$) δ 163.7, 163.2, 161.1, 151.3, 147.4, 146.5, 128.9, 123.9, 105.9, 34.5, 30.6, 27.8, 26.6, 25.4, 22.1, 14.0, 13.3 ppm.

FTIR (KBr): 3411, 2956, 2918, 2850, 1735, 1719, 1486, 1376, 1217 cm^{-1}.

UV(VIS)O: 346 nm, C: 514 nm.

HRMS (EI) Calcd for $C_{18}H_{20}O_4$, [M^+]: 300.1362, Found: 300.1366; [M^+-CH_3]: 285.1127, Found: 285.1130.



Preparation of 2,5-dimethylfuran cycloheptylidene fulgide (37)

Synthesis was accomplished in a manner similar to that for the cyclopentylidene fulgide **32** using the appropriate diester.

37 was obtained with a yield of 22% (*Z*-isomer). The *E*-isomer was observed to be absent on TLC.

Rf: 0.53 (hexane: ethyl acetate = 4:1).

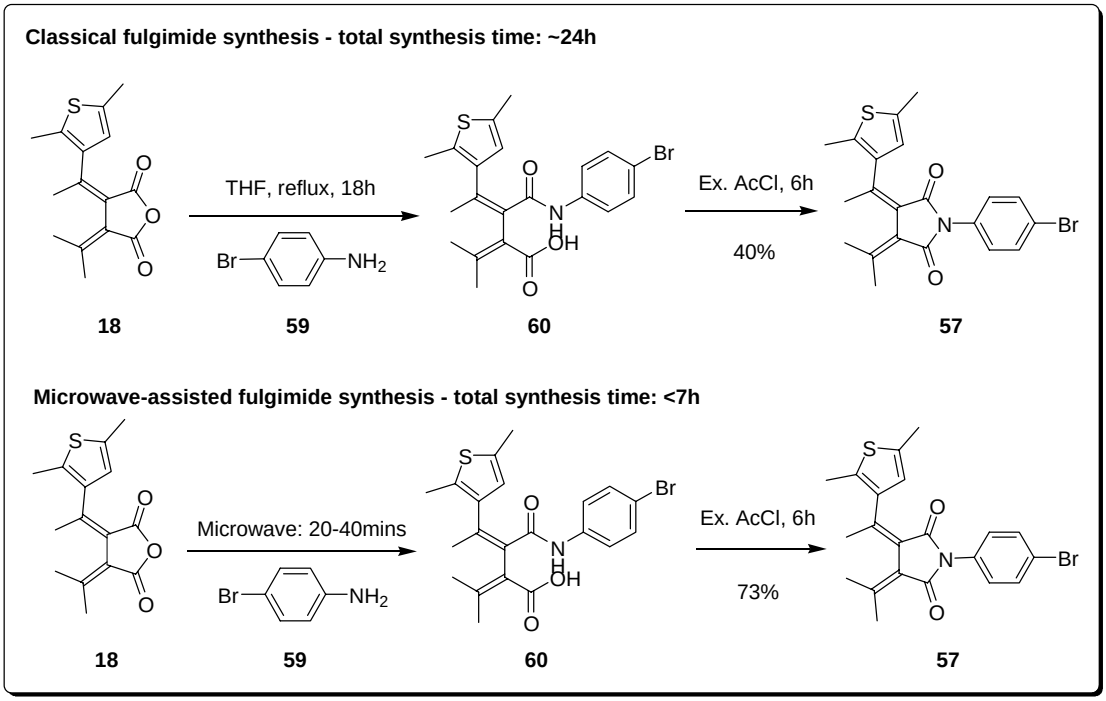
^{1}H NMR (300MHz, $CDCl_3$) δ 5.92 (s, 1H, C=C**H**), 3.01-2.99 (m, 2H, $CH_2(CH_2)_4C\mathbf{H}_2C$=CCO), 2.57 (s, 3H, $CH_3COCC\mathbf{H}_3$), 2.31 (t, J = 3.6 Hz, 2H, $C\mathbf{H}_2(CH_2)_4CH_2C$=CCO), 2.25 (s, 3H, $C\mathbf{H}_3CSCCH_3$), 1.98 (s, 3H, C=CC**H**$_3$), 1.75-1.35 (m, 8H, $CH_2(C\mathbf{H}_2)_4CH_2C$=CCO), 2ppm.

^{13}C NMR (500 MHz, $CDCl_3$) δ 164.2, 163.9, 163.1, 151.3, 148.1, 146.6, 124.4, 120.3, 119.5, 105.9, 37.6, 31.9, 30.6, 28.7, 27.4, 25.3, 22.3, 14.0, 13.3 ppm.

FTIR (KBr): 3452, 2956, 2918, 2850, 1734, 1716, 1458, 1219, 929 cm^{-1}.

UV(VIS)O: 350 nm, C: 526 nm.

HRMS (EI) Calcd for $C_{19}H_{22}O_4$, [M^+]: 314.1518, Found: 314.1525; [M^+-CH_3]: 299.1283, Found: 299.1283.



Preparation of 2,5-dimethylthiophene isopropylidene *p*-bromo-phenyl-fulgimide (57)

METHOD A – THERMAL HEATING METHOD

2,5-dimethylthiophene cyclopentylidene fulgide **18** (1 eq.) was added into a round bottom flask and stirred in THF. *p*-bromo aniline **59**, (1.1 eq.) was added in 1 lot and the reaction mixture stirred overnight (18h). Reaction was monitored using TLC. If large presence of fulgide was observed to be still present, it was possible to reflux the mixture for about 6h. The excess solvent was removed in vacuo and excess acetyl chloride was added in the dark and stirred for approximately 6h. THF was added into the reaction flask and the liquids were removed in vacuo. Flash chromatography afforded **57** with a yield of 45%.

METHOD B – MICROWAVE HEATING METHOD

To a round bottomed flask (RBF) containing fulgide **18** and amine **59**, was added 2mls of THF. The mixture was allowed to dissolve and was mixed well before being subjected to microwave radiation using a conventional (domestic) microwave oven. The reaction was carried out without a stopper or plug so as to allow the evaporation of solvent and prevent a build-up of pressure in the reaction vessel. After 40 minutes, the RBF was removed and the crude reaction mixture treated with acetyl chloride for up to 6 hours. This was followed by removal of excess acetyl chloride and volatiles via vacuo, before subjecting the crude mixture to flash chromatography which afforded fulgimide **57** with a yield of 73%.

Rf: 0.60 (*E*-isomer), 0.50 (*Z*-isomer) (hexane: ethyl acetate = 4:1).

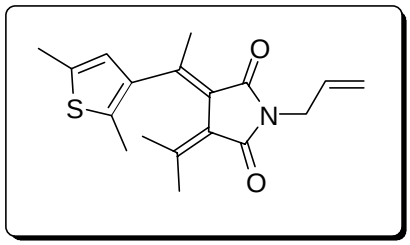
Z-form: ^{1}H NMR (300MHz, $CDCl_3$) δ 7.51 (d, J = 8.7 Hz, 2H, NC(C**H**=CH)$_2$), 7.22 (t, J = 8.7 Hz, 2H, NC(CH=C**H**)$_2$), 6.54 (s, 1H, C=C**H**), 2.46 (s, 3H, C=CC**H**$_3$), 2.40 (s, 3H, C**H**$_3$CSCCH$_3$), 2.33 (s, 3H, CH$_3$CSCC**H**$_3$), 2.11 (s, 3H, (CH$_3$)(C**H**$_3$)C=CCO), 2.02 (s, 3H, (C**H**$_3$)(CH$_3$)C=CCO) ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ 167.1, 164.5, 149.4, 142.9, 137.8, 136.2, 135.6, 131.8, 131.1, 128.5, 124.8, 123.7, 121.5, 27.1, 26.4, 21.9, 15.2, 14.3 ppm.

FTIR (KBr): 3465, 2916, 2851, 1744, 1701, 1626, 1493, 1436, 1368, 1143, 1015, 840, 751 cm^{-1}.

UV(VIS) *Z*-form: O: 334 nm, C: 538 nm.

HRMS (EI) Calcd for $C_{21}H_{20}BrNO_2S$, [M^+]: 429.0398, Found: 429.0390; [M^+-CH_3]: 414.0163, Found: 414.0159.



Preparation of 2,5-dimethylthiophene isopropylidene allyl-fulgimide (53)

Synthesis was accomplished in a manner similar to that for the fulgimide **57**.

Method A: Purification of the crude reaction mixture using flash chromatography (~9-8:1 hexane/ethyl acetate) afforded **53** in 42% yield (*E/Z* combined yield).

Method B: 47% yield.

Rf: 0.62 (*E*-isomer), 0.53 (*Z*-isomer) (hexane: ethyl acetate = 4:1).

E-form: ^{1}H NMR (300MHz, $CDCl_3$) δ 6.51 (s, 1H, C=C**H**), 5.91-5.80 (m, 1H, $CH_2C\mathbf{H}CH_2$), 5.24-5.16 (dd, *J* = 8.0, 13.9 Hz, 2H, $CH_2CHC\mathbf{H}_2$), 4.10 (d, *J* = 3.7 Hz, 2H, $C\mathbf{H}_2CHCH_2$), 2.60 (s, 3H, C=CC$\mathbf{H}_3$), 2.39 (s, 3H, $C\mathbf{H}_3CSCCH_3$), 2.27 (s, 3H, $CH_3CSCC\mathbf{H}_3$), 2.11 (s, 3H, $(CH_3)(C\mathbf{H}_3)C$=CCO), 1.25 (s, 3H, $(C\mathbf{H}_3)(CH_3)C$=CCO) ppm.

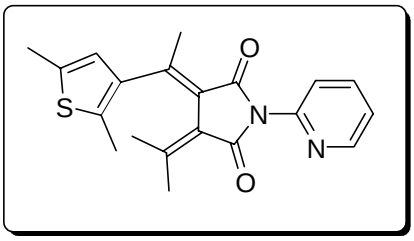
Z-form: ^{1}H NMR (300MHz, $CDCl_3$) δ 6.52 (s, 1H, C=C**H**), 5.83-5.74 (m, 1H, $CH_2C\mathbf{H}CH_2$), 5.20-5.10 (dd, *J* = 10.1, 12.9 Hz, 2H, $CH_2CHC\mathbf{H}_2$), 4.10 (d, *J* = 5.9 Hz, 2H, $C\mathbf{H}_2CHCH_2$), 2.43 (s, 3H, $C\mathbf{H}_3CSCCH_3$), 2.41 (s, 3H, $C\mathbf{H}_3CSCCH_3$), 2.29 (s, 3H, $CH_3CSCC\mathbf{H}_3$), 2.04 (s, 3H, $(CH_3)(C\mathbf{H}_3)C$=CCO), 1.96 (s, 3H, $(C\mathbf{H}_3)(CH_3)C$=CCO) ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ 168.1, 165.4, 147.7, 141.3, 137.1, 136.5, 135.5, 131.9, 125.6, 124.9, 124.1, 117.6, 39.9, 26.9, 26.1, 21.6, 15.2, 14.1 ppm.

FTIR (KBr): 3437, 2920, 2857, 1810, 1762, 1695, 1627, 1438, 1383, 1267, 1226, 1144, 927, 845 cm^{-1}.

UV(VIS)O: 330 nm, C: 526 nm.

HRMS (EI) Calcd for $C_{18}H_{21}NO_2S$, [M^+]: 315.1293, Found: 315.1290; [M^+-CH_3]: 300.1058, Found: 300.1067.



Preparation of 2,5-dimethylthiophene isopropylidene pyridin-2-yl-fulgimide (54)

Synthesis was accomplished in a manner similar to that for the fulgimide **57**.

Method A: Purification of the crude reaction mixture using flash chromatography (~9-8:1 hexane/ethyl acetate) afforded **54** with a 39% yield (*E/Z* combined yield).

Method B: 16% yield.

Rf: 0.48 (*E*-isomer), 0.35 (*Z*-isomer) (hexane: ethyl acetate = 4:1).

E-form: ^{1}H NMR (300MHz, $CDCl_3$) δ 8.70 (t, J = 1.1 Hz, 1H, C=NC**H**), 7.86 (dt, J = 1.1, 4.4 Hz, 1H, C=NCHCHC**H**CH), 7.40-7.34 (m, 2H, C=NCHC**H**CHC**H**), 6.54 (s, 1H, C=C**H**), 2.63 (s, 3H, C=CC**H**$_3$), 2.40 (s, 3H, C**H**$_3$CSCCH$_3$), 2.31 (s, 3H, CH$_3$CSCC**H**$_3$), 2.19 (s, 3H, (CH$_3$)(C**H**$_3$)C=CCO), 1.29 (s, 3H, (C**H**$_3$)(CH$_3$)C=CCO) ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ 167.5, 166.9, 150.9, 149.7, 146.7, 145.3, 140.5, 138.0, 137.1, 134.0, 125.7, 124.0, 123.4, 122.9, 122.8, 29.7, 25.7, 22.3, 15.1, 14.8 ppm.

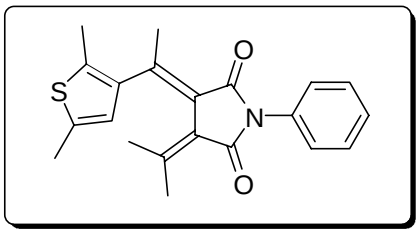
Z-form: ^{1}H NMR (300MHz, $CDCl_3$) δ 8.62 (d, J = 2.5 Hz, 1H, C=NC**H**), 7.77 (t, J = 4.6 Hz, 1H, C=NCHCHC**H**CH), 7.30-7.28 (m, 2H, C=NCHC**H**CHC**H**), 6.54 (s, 1H, C=C**H**), 2.47 (s, 3H, C=CC**H**$_3$), 2.38 (s, 3H, C**H**$_3$CSCCH$_3$), 2.33 (s, 3H, CH$_3$CSCC**H**$_3$), 2.11 (s, 3H, (CH$_3$)(C**H**$_3$)C=CCO), 2.01 (s, 3H, (C**H**$_3$)(CH$_3$)C=CCO) ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ 167.0, 164.4, 149.5, 146.7, 142.9, 138.0, 137.9, 136.2, 135.5, 125.1, 124.9, 123.9, 123.3, 122.9, 27.0, 26.3, 21.9, 15.2, 14.3 ppm.

FTIR (KBr): 3448, 3160, 2919, 2360, 2338, 1750, 1701, 1627, 1465, 1434, 1341, 1263, 1209, 1157, 906, 766 cm^{-1}.

UV(VIS) *E*-form: O: 328 nm, C: 532 nm; *Z*-form: O: 330 nm, C: 532 nm.

HRMS (EI) Calcd for $C_{20}H_{20}N_2O_2S$, [M^+]: 352.1245, Found: 352.1249; [M^+-CH_3]: 337.1011, Found: 337.1011.



Preparation of 2,5-dimethylthiophene isopropylidene phenyl-fulgimide (55)

Synthesis was accomplished in a manner similar to that for the fulgimide **57**.

Method A: Purification of the crude reaction mixture using flash chromatography (~9-8:1 hexane/ethyl acetate) afforded **55** with a 42% yield (*E/Z* combined yield).

Method B: 65% yield.

Rf: 0.0.45 (*E*-isomer), 0.36 (*Z*-isomer) (hexane: ethyl acetate = 4:1).

E-form: ^{1}H NMR (300MHz, $CDCl_3$) δ 7.48-7.38 (m, 5H, C(C**H**)$_5$), 6.55 (s, 1H, C=C**H**), 2.63 (s, 3H, C=CC**H**$_3$), 2.41 (s, 3H, C**H**$_3$CSCCH$_3$), 2.30 (s, 3H, CH$_3$CSCC**H**$_3$), 2.19 (s, 3H, (CH$_3$)(C**H**$_3$)C=CCO), 1.30 (s, 3H, (C**H**$_3$)(CH$_3$)C=CCO) ppm.

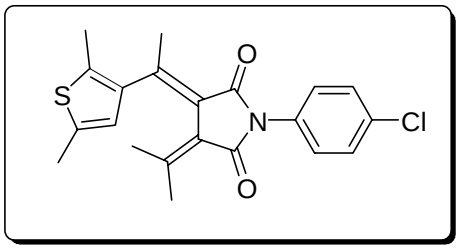
Z-form: ^{1}H NMR (300MHz, $CDCl_3$) δ 7.42-7.28 (m, 5H, C(C**H**)$_5$), 6.54 (s, 1H, C=C**H**), 2.47 (s, 3H, C=CC**H**$_3$), 2.40 (s, 3H, C**H**$_3$CSCCH$_3$), 2.33 (s, 3H, CH$_3$CSCC**H**$_3$), 2.11 (s, 3H, (CH$_3$)(C**H**$_3$)C=CCO), 2.02 (s, 3H, (C**H**$_3$)(CH$_3$)C=CCO) ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ167.5, 164.9, 148.7, 142.3, 137.5, 136.3, 135.5, 132.1, 128.9, 128.7, 128.1, 127.9, 127.0, 125.3,124.9, 124.0, 27.1, 26.3, 21.8, 15.2, 14.2 ppm.

FTIR (KBr): 3469, 2915, 2851, 1743, 1701, 1627, 1497, 1437, 1369, 1141, 903, 841, 749, 692, 621 cm^{-1}.

UV(VIS) *E*-form: O: 328 nm, C: 534 nm; *Z*-form: O: 330 nm, C: 532 nm.

HRMS (EI) Calcd for $C_{21}H_{21}NO_2S$, [M^+]: 351.1293, Found: 351.1294; [M^+-CH_3]: 336.1058, Found: 336.1057.



Preparation of 2,5-dimethylthiophene isopropylidene *p*-chloro-phenyl-fulgimide (56)

Synthesis was accomplished in a manner similar to that for the fulgimide **57**.

Method A: Purification of the crude reaction mixture using flash chromatography (~9-8:1 hexane/ethyl acetate) afforded **56** with a 65% yield (*E/Z* combined yield).

Method B: 85% yield.

Rf: 0.65 (*E*-isomer), 0.56 (*Z*-isomer) (hexane: ethyl acetate = 4:1).

E-form: ^{1}H NMR (300MHz, $CDCl_3$) δ 7.45 (d, J = 8.9 Hz, 2H, NC(C**H**=CH)$_2$), 7.35 (d, J = 8.9 Hz, 2H, NC(CH=C**H**)$_2$), 6.53 (s, 1H, C=C**H**), 2.62 (s, 3H, C=CC**H**$_3$), 2.40 (s, 3H, C**H**$_3$CSCCH$_3$), 2.30 (s, 3H, CH$_3$CSCC**H**$_3$), 2.18 (s, 3H, (CH$_3$)(C**H**$_3$)C=CCO), 1.29 (s, 3H, (C**H**$_3$)(CH$_3$)C=CCO) ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ 167.7, 167.1, 150.6, 145.0, 140.4, 137.2, 133.9, 133.7, 130.6, 129.1, 128.2, 125.7, 25.7, 22.3, 15.1, 14.8 ppm.

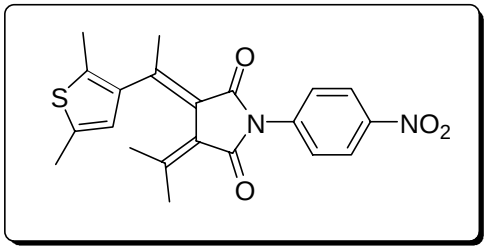
Z-form: ^{1}H NMR (300MHz, $CDCl_3$) δ 7.37 (d, 9.0 Hz, 2H, NC(C**H**=CH)$_2$), 7.32 (d, 9.0 Hz, 2H, NC(CH=C**H**)$_2$), 6.54 (s, 1H, C=C**H**), 2.46 (s, 3H, C=CC**H**$_3$), 2.39 (s, 3H, C**H**$_3$CSCCH$_3$), 2.32 (s, 3H, CH$_3$CSCC**H**$_3$), 2.11 (s, 3H, (CH$_3$)(C**H**$_3$)C=CCO), 2.02 (s, 3H, (C**H**$_3$)(CH$_3$)C=CCO) ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ 167.1, 164.5, 149.2, 142.8, 137.6, 136.2, 135.6, 133.4, 130.6, 128.8, 128.2, 124.9, 124.8, 123.7, 27.1, 26.3, 21.9, 15.2, 14.2 ppm.

FTIR (KBr): 3494, 2978, 2937, 2874, 1675, 1596, 1579, 1448, 1378, 1213, 1165, 1144, 1072, 845, 692, 644 cm^{-1}.

UV(VIS) *Z*-form: O: 326 nm, C: 538 nm.

HRMS (EI) Calcd for $C_{21}H_{20}ClNO_2S$, [M^+]: 385.0903, Found: 385.0901; [M^+-CH_3]: 370.0669, Found: 370.0665.



Preparation of 2,5-dimethylthiophene isopropylidene *p*-nitro-phenyl-fulgimide (61)

Synthesis was accomplished in a manner similar to that for the fulgimide **57**.

Method A: 0% yield.

Method B: Purification of the crude reaction mixture using flash chromatography (~9-8:1 hexane/ethyl acetate) afforded **61** with a 36% yield. **61** was obtained as the *Z*-isomer. The *E*-isomer was present in unisolable amounts, observed to be present on TLC only.

Rf: 0.58 (*E*-isomer), 0.48 (*Z*-isomer) (hexane: ethyl acetate = 4:1).

E-form: ^{1}H NMR (300MHz, $CDCl_3$) δ 8.34 (d, J = 5.6 Hz, 2H, NC(CH=C**H**)$_2NO_2$), 7.70 (d, J = 5.6 Hz, 2H, NC(C**H**=CH)$_2NO_2$), 6.54 (s, 1H, C=C**H**), 2.63 (s, 3H, C=CC**H**$_3$), 2.41 (s, 3H, C**H**$_3$CSCCH$_3$), 2.32 (s, 3H, CH$_3$CSCC**H**$_3$), 2.19 (s, 3H, (CH$_3$)(C**H**$_3$)C=CCO), 1.31 (s, 3H, (C**H**$_3$)(CH$_3$)C=CCO) ppm.

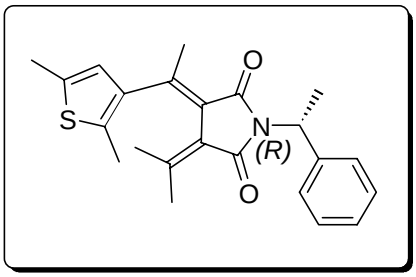
Z-form: ^{1}H NMR (300MHz, $CDCl_3$) δ 8.25 (d, 2H, NC(CH=C**H**)$_2NO_2$), 7.61 (d, 2H, NC(C**H**=CH)$_2NO_2$), 6.54 (s, 1H, C=C**H**), 2.48 (s, 3H, C=CC**H**$_3$), 2.41 (s, 3H, C**H**$_3$CSCCH$_3$), 2.34 (s, 3H, CH$_3$CSCC**H**$_3$), 2.13 (s, 3H, (CH$_3$)(C**H**$_3$)C=CCO), 2.05 (s, 3H, (C**H**$_3$)(CH$_3$)C=CCO) ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ 166.6, 164.0, 150.5, 144.0, 137.9, 135.9, 127.3, 127.2, 125.6, 124.7, 124.1, 123.9, 123.4, 27.2, 26.5, 22.1, 15.2, 14.3 ppm.

FTIR (KBr): 3465, 2932, 2916, 2899, 2850, 1751, 1703, 1626, 1530, 1447, 1371, 1140, 820 cm^{-1}.

UV(VIS) *Z*-form: O: 330 nm, C: 548 nm.

HRMS (EI) Calcd for $C_{21}H_{20}N_2O_4S$ [M^+]: 396.1144, Found: 396.1135; [M^+-CH_3]: 381.0909, Found: 381.0909.



Preparation of 2,5-dimethylthiophene isopropylidene R-(+)-methyl benzyl-fulgimide (62R)

Synthesis was accomplished in a manner similar to that for the fulgimide **57**.

Method A: Purification of the crude reaction mixture using flash chromatography (~9-8:1 hexane/ethyl acetate) afforded **62** with a 70% yield.

Method B: 74% yield.

Rf: 0.63 (*E*-isomer), 0.53 (*Z*-isomer) (hexane: ethyl acetate = 4:1).

E-form: ^{1}H NMR (300MHz, $CDCl_3$) δ 7.45-7.25 (m, 5H, C(C**H**)$_5$), 6.47 (s, 1H, C=C**H**), 5.53 (q, J = 7.3 Hz, 1H, NC**H**(CH_3)Ph), 2.56 (s, 3H, C=CC**H**$_3$), 2.37 (s, 3H, C**H**$_3$CSCCH$_3$), 2.24 (s, 3H, CH$_3$CSCC**H**$_3$), 2.09 (s, 3H, (CH_3)(C**H**$_3$)C=CCO), 1.87 (d, J = 7.3 Hz, 3H, NCH(C**H**$_3$)Ph), 1.19 (s, 3H, (C**H**$_3$)(CH_3)C=CCO) ppm.

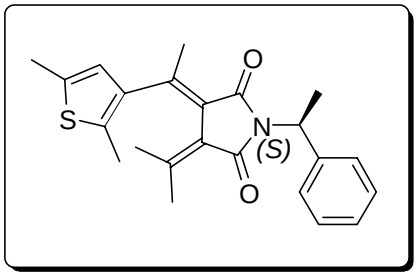
Z-form: ^{1}H NMR (300MHz, $CDCl_3$) δ 7.44-7.22 (m, 5H, C(C**H**)$_5$), 6.50 (s, 1H, C=C**H**), 5.45 (q, J = 7.4 Hz, 1H, NC**H**(CH_3)Ph), 2.41 (s, 3H, C=CC**H**$_3$), 2.37 (s, 3H, C**H**$_3$CSCCH$_3$), 2.23 (s, 3H, CH$_3$CSCC**H**$_3$), 2.00 (s, 3H, (CH_3)(C**H**$_3$)C=CCO), 1.92 (s, 3H, NCH(C**H**$_3$)Ph), 1.79 (d, J = 7.3 Hz, 3H, (C**H**$_3$)(CH_3)C=CCO) ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ 168.7, 168.2, 148.8, 143.2, 140.7, 140.6, 136.9, 133.6, 128.4, 127.4, 127.3, 125.8, 124.4, 123.2, 48.9, 25.6, 22.0, 21.9, 17.2, 15.1, 14.7 ppm.

FTIR (KBr): 3486, 2955, 2951, 1677, 1497, 1455, 1379, 1140, 905, 845, 748, 690 cm^{-1}.

UV(VIS) *Z*-form: O: 330 nm, C: 520 nm.

HRMS (EI) Calcd for $C_{23}H_{25}NO_2S$ [M^+]: 379.1606, Found: 379.1610; [M^+-CH_3]: 376.1371, Found: 376.1373.



Preparation of 2,5-dimethylthiophene isopropylidene S-(-)-methyl benzyl-fulgimide (62S)

Synthesis was accomplished in a manner similar to that for the fulgimide **57**.

Method A: Purification of the crude reaction mixture using flash chromatography (~9-8:1 hexane/ethyl acetate) afforded **63** with a 72% yield.

Method B: 76% yield.

Rf: 0.63 (*E*-isomer), 0.53 (*Z*-isomer) (hexane: ethyl acetate = 4:1).

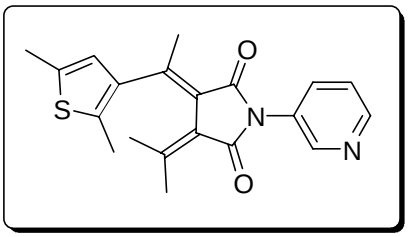
E-form: ^{1}H NMR (300MHz, $CDCl_3$) δ 7.48-7.31 (m, 5H, C(C**H**)$_5$), 6.47 (s, 1H, C=C**H**), 5.57 (q, J = 4.4 Hz, 1H , NC**H**(CH_3)Ph), 2.56 (s, 3H, C=CC**H**$_3$), 2.37 (s, 3H, C**H**$_3$CSCCH_3), 2.23 (s, 3H, CH_3CSCC**H**$_3$), 2.09 (s, 3H, (CH_3)(C**H**$_3$)C=CCO), 1.87 (d, J = 4.4 Hz, 3H, NCH(C**H**$_3$)Ph), 1.19 (s, 3H, (C**H**$_3$)(CH_3)C=CCO) ppm.

^{13}C NMR (300MHz, $CDCl_3$)δ 168.7, 168.2, 148.8, 143.2, 140.7, 140.7, 136.9, 133.6, 128.4, 127.4, 127.3, 125.8, 124.4, 123.2, 48.9, 25.6, 22.0, 21.9, 17.2, 15.1, 14.7 ppm.

FTIR (KBr): 3493, 2951, 2943, 1673, 1499, 1449, 1370, 1141, 908, 748, 697 cm^{-1}.

UV(VIS) *Z*-form: O: 330 nm, C: 520 nm.

HRMS (EI) Calcd for $C_{23}H_{25}NO_2S$ [M^+]: 379.1606, Found: 379.1613; [M^+-CH_3]: 364.1371, Found: 364.1372.

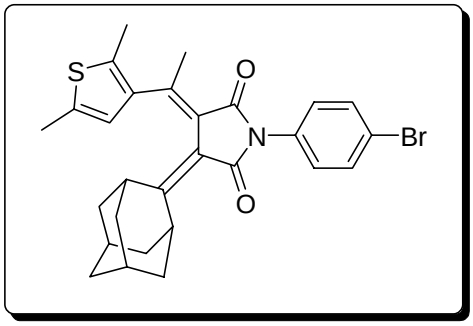


Preparation of 2,5-dimethylthiophene isopropylidene pyridine-3-yl-fulgimide (63)

Synthesis was accomplished in a manner similar to that for the fulgimide **57**.

Method A: Purification of the crude reaction mixture using flash chromatography (~9-8:1 hexane/ethyl acetate) afforded **63** with a ~2% (*E/Z* combined yield). Molecule was not pursued further as low yield was not favorable for synthetic scale up.

Method B: 0% yield.



Preparation of Preparation of 2,5-dimethylthiophene adamantylidene *p*-bromo-phenyl-fulgimide (64)

Synthesis was accomplished in a manner similar to that for the fulgimide **57**.

Method A: 0% yield.

Method B: Purification of the crude reaction mixture using flash chromatography (~9-8:1 hexane/ethyl acetate) afforded **64** with a 60% yield. The Z-isomer was synthesized exclusively. No E-isomer was detected on TLC or NMR.

Rf: 0.80 (hexane: ethyl acetate = 4:1).

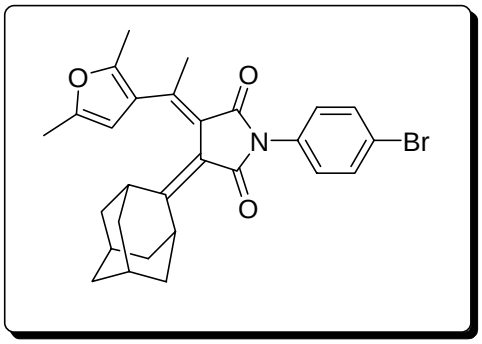
Z-form: ^{1}H NMR (300MHz, $CDCl_3$) δ 7.52 (dd, J = 1.9, 6.9 Hz, 2H, NC(C**H**=CH)$_2$), 7.25 (dd, J = 1.9, 6.9 Hz, 2H, NC(CH=C**H**)$_2$), 6.51 (s, 1H, C=C**H**), 4.54 (s, 1H, C=CC**H**(CH)), 2.73 (s, 1H C=CCH(C**H**)), 2.39 (s, 3H, C**H**$_3$CSCCH$_3$), 2.30 (s, 3H, CH$_3$CSCC**H**$_3$), 2.15 (s, 3H, (CH$_3$)(C**H**$_3$)C=CCO), 2.06-1.93 (m, 12H, ADA) ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ 167.2, 166.8, 164.4, 142.6, 136.3, 135.6, 131.7, 131.2, 128.4, 124.6, 121.4, 117.2, 39.6, 37.7, 36.5, 32.8, 27.4, 26.2, 15.2, 14.2 ppm.

FTIR (KBr): 3441, 2936, 2916, 2899, 2850, 1753, 1710, 1620, 1487, 1361, 1129, 821, 778, 756, 504 cm^{-1}.

UV(VIS) *Z*-form: O: 340 nm, C: 574 nm.

HRMS (EI) Calcd for $C_{28}H_{28}BrNO_2S$, [M^+]: 521.1024, Found: 521.1020; [M^+-CH_3]: 506.0789, Found: 506.0819.



Preparation of 2,5-dimethylfuran adamantylidene *p*-bromo-phenyl-fulgimide (70)

Method A: 0% yield.

Method B: Synthesis was accomplished in a manner similar to that for the 2,5-dimethylthiophene adamantylidene *p*-bromo-phenyl-fulgimide, **64,** affording **70** with a 75%. The *Z*-isomer was obtained exclusively.

Rf: 0.68 (hexane: ethyl acetate = 4:1).

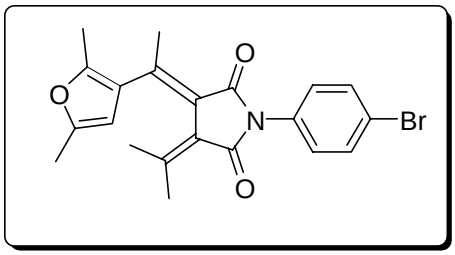
Z-form: ^{1}H NMR (300MHz, $CDCl_3$) δ 7.58 (d, 2H, NC(C**H**=CH)$_2$), 7.32 (d, 2H, NC(CH=C**H**)$_2$), 5.94 (s, 1H, C=C**H**), 4.43 (s, 1H, C=CC**H**(CH)), 2.53 (s, 3H, C**H**$_3$COCCH$_3$), 2.43 (s, 1H, C=CCH(C**H**)), 2.26 (s, 3H, CH$_3$COCC**H**$_3$), 2.09 (s, 3H, (CH$_3$)(C**H**$_3$)C=CCO), 1.96-1.61 (m, 12H, **ADA**) ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ 167.3, 167.0, 166.0, 150.9, 145.7, 141.9, 131.9, 131.3, 128.5, 124.4, 122.0, 121.6, 117.1, 106.5, 39.9, 38.4, 37.2, 36.4, 32.7, 27.3, 21.7, 13.9, 13.4 ppm.

FTIR (KBr): 3429, 2911, 2849, 1746, 1701, 1621, 1489, 1377, 1170, 1136, 1013, 823, 780, 756, 504 cm^{-1}.

UV(VIS) *Z*-form: O: 340 nm, C: 544 nm.

HRMS (EI) Calcd for $C_{28}H_{28}BrNO_3$, $[M^+]$: 505.1253, Found: 505.1248; $[M^+-CH_3]$: 490.1018, Found: 490.1032.



Preparation of 2,5-dimethylfuran isopropylidene *p*-bromo-phenyl-fulgimide (68)

Synthesis was accomplished in a manner similar to that for the fulgimide **57**.

Method A: Purification of the crude reaction mixture using flash chromatography (~9-8:1 hexane/ethyl acetate) afforded **68** with a 52% yield. **68** was obtained with the *E*-isomer as the major isomer with a trace of the *Z*-isomer which was not isolable.

Method B: 65% yield.

Rf: 0.68 (*E*-isomer), 0.60 (*Z*-isomer) (hexane: ethyl acetate = 4:1).

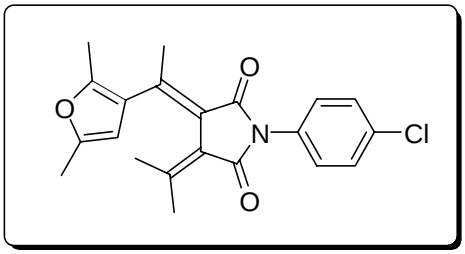
E-form: ^{1}H NMR (300MHz, $CDCl_3$) δ 7.59 (d, J = 8.7 Hz, 2H, NC(C**H**=CH)$_2$), 7.29 (d, J = 8.7 Hz, 2H, NC(CH=C**H**)$_2$), 5.93 (s, 1H, C=C**H**), 2.59 (s, 3H, C**H**$_3$COCCH$_3$), 2.34 (s, 3H, C=CCH(C**H**)), 2.25 (s, 3H, CH$_3$COCC**H**$_3$), 2.05 (s, 3H, (CH$_3$)(C**H**$_3$)C=CCO), 1.38 (s, 3H, (C**H**$_3$)(CH$_3$)C=CCO) ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ 167.6, 167.1, 150.8, 149.3, 147.7, 142.7, 132.0, 131.2, 128.5, 124.7, 123.2, 122.3, 121.7, 106.2, 26.8, 22.2, 21.7, 13.8, 13.3 ppm.

FTIR (KBr): 3440, 2920, 2855, 1752, 1704, 1627, 1490, 1441, 1368, 1224, 1172, 1123, 1071, 1011, 825, 789, 756, 644, 509 cm^{-1}.

UV(VIS) *Z*-form: O: 336 nm, C: 518 nm.

HRMS (EI) Calcd for $C_{21}H_{20}BrNO_3$, [M^+]: 413.0627, Found: 413.0619; [M^+-CH_3]: 398.0392, Found: 398.0385.



Preparation of 2,5-dimethylfuran isopropylidene *p*-chloro-phenyl-fulgimide (67)

Synthesis was accomplished in a manner similar to that for the fulgimide **57**.

Method A: Purification of the crude reaction mixture using flash chromatography (~9-8:1 hexane/ethyl acetate) afforded **67** with a 60% yield. **67** was obtained with the *E*-isomer as the major isomer with a trace of the *Z*-isomer which was not isolable.

Method B: 70% yield.

Rf: 0.65 (*E*-isomer), 0.56 (*Z*-isomer) (hexane: ethyl acetate = 4:1).

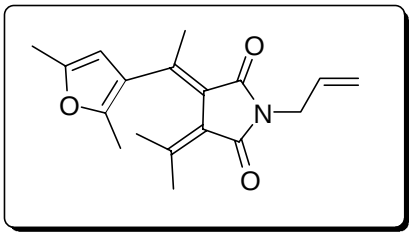
E-form: ^{1}H NMR (300MHz, $CDCl_3$) δ 7.43 (dt, J = 2.3, 8.7 Hz, 2H, NC(C**H**=CH)$_2$), 7.35 (dt, J = 2.4, 8.7 Hz, 2H, NC(CH=C**H**)$_2$), 5.94 (s, 1H, C=C**H**), 2.60 (s, 3H, C**H**$_3$COCCH$_3$), 2.34 (s, 3H, C=CCH(C**H**)), 2.25 (s, 3H, CH$_3$COCC**H**$_3$), 2.05 (s, 3H, (CH$_3$)(C**H**$_3$)C=CCO), 1.38 (s, 3H, (C**H**$_3$)(CH$_3$)C=CCO) ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ 167.7, 167.1, 150.8, 149.3, 147.7, 142.6, 133.7, 130.7, 129.1, 128.2, 124.7, 123.2, 122.3, 106.2, 26.8, 22.2, 21.7, 13.8, 13.3 ppm.

FTIR (KBr): 3447, 2922, 2852, 1705, 1627, 1493, 1369, 1224, 1176, 1122, 1091, 1018, 829, 791, 757, 650, 512 cm^{-1}.

UV(VIS) *Z*-form: O: 334 nm, C: 518 nm.

HRMS (EI) Calcd for $C_{21}H_{20}ClNO_3$, $[M^+]$: 369.1132, Found: 369.1133; $[M^+-CH_3]$: 354.0897, Found: 354.0899.



Preparation of 2,5-dimethylfuran isopropylidene allyl-fulgimide (65)

Synthesis was accomplished in a manner similar to that for the fulgimide **57**.

Method A: Purification of the crude reaction mixture using flash chromatography (~9-8:1 hexane/ethyl acetate) afforded **65** with a 35% yield (*E/Z* combined yield). **65** was obtained with the *E*-isomer as the major isomer with a trace of the *Z*-isomer which was not isolable.

Method B: 42% yield.

Rf: 0.61 (*E*-isomer), 0.55 (*Z*-isomer) (hexane: ethyl acetate = 4:1).

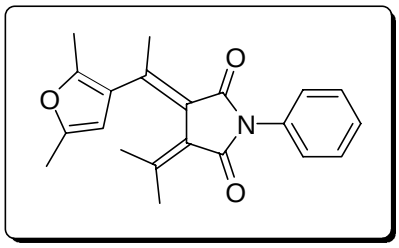
E-form: ^{1}H NMR (500MHz, $CDCl_3$) δ 5.90 (s, 1H, C=C**H**), 5.86 (dd, J = 10.2, 17.1 Hz, 1H, $CH_2C\mathbf{H}CH_2$), 5.23-5.16 (ddd, J = 1.4, 10.2, 17.1 Hz, 2H, $CH_2CHC\mathbf{H}_2$), 4.21-4.19 (dt, J = 3.2, 1.4 Hz, 2H, $C\mathbf{H}_2CHCH_2$), 2.57 (s, 3H, C=CC**H**$_3$), 2.31 (s, 3H, C**H**$_3$CSCCH$_3$), 2.23 (s, 3H, CH$_3$CSCC**H**$_3$), 1.98 (s, 3H, (CH$_3$)(C**H**$_3$)C=CCO), 1.32 (s, 3H, (C**H**$_3$)(CH$_3$)C=CCO) ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ 168.6, 168.1, 150.6, 147.9, 147.4, 141.3, 131.9, 124.7, 123.5, 117.3, 106.2, 39.8, 26.6, 21.9, 21.4, 13.7, 13.3 ppm.

FTIR (KBr): 2921, 2855, 1768, 1670, 1628, 1494, 1363, 1223, 1124, 835 cm^{-1}.

UV(VIS)O: 338 nm, C: 508 nm.

HRMS (EI) Calcd for $C_{18}H_{21}NO_3$, [M^+]: 299.1521, Found: 299.1526; [M^+-CH_3]: 284.1287, Found: 284.1285.



Preparation of 2,5-dimethylfuran isopropylidene phenyl-fulgimide (66)

Synthesis was accomplished in a manner similar to that for the fulgimide **57**.

Method A: Purification of the crude reaction mixture using flash chromatography (~9-8:1 hexane/ethyl acetate) afforded **66** with a 39% yield (*E/Z* combined yield). **66** was obtained with the *E*-isomer as the major isomer with a trace of the *Z*-isomer which was not isolable.

Method B: 57% yield.

Rf: 0.63 (*E*-isomer), 0.55 (*Z*-isomer) (hexane: ethyl acetate = 4:1).

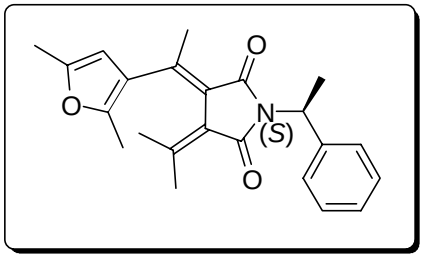
E-form: ^{1}H NMR (300MHz, $CDCl_3$) δ 7.50-7.36 (m, 5H, C(C**H**)$_5$), 5.94 (s, 1H, C=C**H**), 2.61 (s, 3H, C=CC**H**$_3$), 2.34 (s, 3H, C**H**$_3$COCCH$_3$), 2.25 (s, 3H, CH$_3$COCC**H**$_3$), 2.06 (s, 3H, (CH$_3$)(C**H**$_3$)C=CCO), 1.38 (s, 3H, (C**H**$_3$)(CH$_3$)C=CCO) ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ 168.0, 167.5, 150.7, 148.8, 147.6, 142.1, 132.2, 128.9, 128.0, 127.1, 124.8, 123.4, 122.6, 106.3, 26.7, 22.1, 21.6, 13.8, 13.3 ppm.

FTIR (KBr): 2920, 1750, 1708, 1703, 1630, 1591, 1496, 1368, 1172, 1123, 1069, 803 cm^{-1}.

UV(VIS) *E*-form: O: 336 nm, C: 514 nm.

HRMS (EI) Calcd for $C_{21}H_{21}NO_3$, [M^+]: 335.1521, Found: 335.1522; [M^+-CH_3]: 320.1287, Found: 320.1281.



Preparation of 2,5-dimethylthiophene isopropylidene S-(-)-methyl benzyl-fulgimide (69)

Synthesis was accomplished in a manner similar to that for the fulgimide **57**.

Method A: Purification of the crude reaction mixture using flash chromatography (~9-8:1 hexane/ethyl acetate) afforded **69** with a 65% yield. **69** was obtained with the *E*-isomer as the major isomer with a trace of the *Z*-isomer which was not isolable.

Method B: 69% yield.

Rf: 0.60 (hexane: ethyl acetate = 4:1).

E-form: ^{1}H NMR (300MHz, $CDCl_3$) δ 7.48 (d, J = 7.4 Hz, 2H, C(C**H**)$_2$(CH)$_2$CH), 7.34-7.31 (m, 2H, C(CH)$_2$(C**H**)$_2$CH), 7.27 – 7.23 (m, 1H, C(CH)$_2$(CH)$_2$C**H**), 5.88 (s, 1H, C=C**H**), 5.55 (d, J = 4.34 Hz, 1H, NC**H**(CH_3)Ph), 2.54 (s, 3H, C=CC**H**$_3$), 2.28 (s,

3H, C**H**$_3$COCCH$_3$), 2.20 (s, 3H, CH$_3$COCC**H**$_3$), 1.97 (s, 3H, (CH$_3$)(C**H**$_3$)C=CCO), 1.86 (s, 3H, NCH(C**H**$_3$)Ph), 1.28 (s, 3H, (C**H**$_3$)(CH$_3$)C=CCO) ppm.

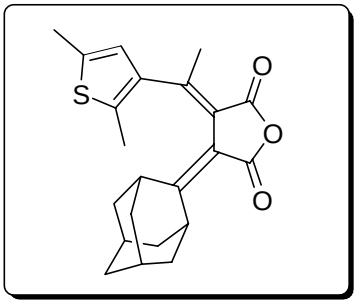
^{13}C NMR (300MHz, CDCl$_3$) δ 168.7, 168.2, 150.5, 147.5, 140.7, 130.9, 128.8, 128.4, 127.4, 127.3, 124.8 123.5, 122.8, 106.3, 48.8, 26.7, 21.9, 21.3, 17.1, 13.7, 13.3 ppm.

Z-form: ^{1}H NMR (CDCl$_3$) δ 7.44-7.22 (m, 5H), 6.50 (s, 1H), 5.45 (q, 1H), 2.41 (s, 3H), 2.37 (s, 3H), 2.23 (s, 3H), 2.00 (s, 3H), 1.92 (s, 3H), 1.79 (d, 3H).

FTIR (KBr): 2925, 2850, 1739, 1712, 1695, 1651, 1495, 1364, 1218, 1031, 928 cm^{-1}.

UV(VIS) *Z*-form: O: 338 nm, C: 508 nm.

HRMS (EI) Calcd for C$_{23}$H$_{25}$NO$_3$ [M$^+$]: 363.1834, Found: 363.1822.



Preparation of 2,5-dimethylthiophene adamantylidene fulgide (22)

Synthesis was accomplished in a manner similar to that for the for the thienyl fulgide **2** analog. Purification of the crude reaction mixture using flash chromatography (~9-8:1 hexane/ethyl acetate) afforded **22** with a 54% yield. **22** was obtained with the *Z*-isomer as the major isomer.

Rf: 0.65 (hexane: ethyl acetate = 4:1).

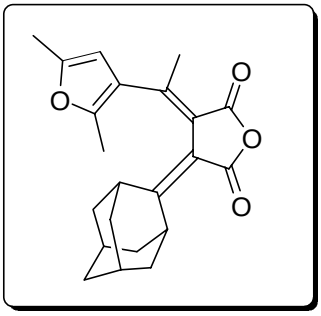
E-form: ^{1}H NMR (300MHz, $CDCl_3$): δ6.50 (s, 1H, C=C**H**), 4.18 (br, s, 1H, C=CC**H**(CH)), 2.51 (s, 1H, C=CCH(C**H**)), 2.40 (s, 3H, C**H**$_3$CSCCH$_3$), 2.22 (s, 3H, CH$_3$CSCC**H**$_3$), 2.16 (s, 3H, (CH$_3$)(C**H**$_3$)C=CCO), 2.07-1.93 (m, 12H, **ADA**) ppm.

^{13}C NMR ($CDCl_3$): δ171.7, 163.8, 163.2, 148.1, 139.2, 133.6, 129.0, 127.5, 126.9, 124.8, 120.6, 114.5, 39.8, 38.1, 36.3, 33.6, 27.2, 27.0, 15.1, 14.6 ppm.

FTIR (KBr): 2959, 2848, 2799, 1809, 1757, 1660, 1469, 1392, 1230, 933 cm^{-1}.

UV(VIS) *Z*-form: O: 340 nm, C: 574 nm.

HRMS (EI) Calcd for $C_{22}H_{24}O_3S$ [M^+]: 368.1446, Found: 368.1449; [M^+-CH_3]: 353.1211, Found: 353.1213.



Preparation of 2,5-dimethylfuran adamantylidene fulgide (23)

Synthesis was accomplished in a manner similar to that for the for the thienyl fulgide **2** analog. Purification of the crude reaction mixture using flash chromatography (~9-8:1 hexane/ethyl acetate) afforded **23** with a 41% yield. **23** was obtained with the *Z*-isomer as the major isomer.

Rf: 0.63 (hexane: ethyl acetate = 4:1).

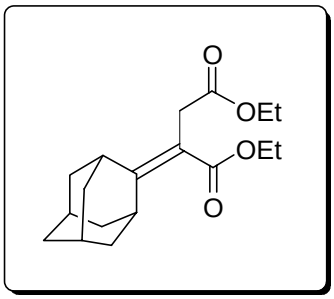
E-form: ^{1}H NMR (300MHz, $CDCl_3$) δ 5.92 (s, 1H, C=C**H**), 4.22 (br, s, 1H, C=CC**H**(CH)), 2.51 (s, 3H, C**H**$_3$COCCH$_3$), 2.34 (s, 1H, C=CCH(C**H**)), 2.25 (s, 3H, CH$_3$COCC**H**$_3$), 2.00 (s, 3H, (CH$_3$)(C**H**$_3$)C=CCO), 1.96-1.61 (m, 12H, **ADA**) ppm.

^{13}C NMR ($CDCl_3$): δ 170.7, 163.7, 163.2, 151.4, 146.1, 145.9, 123.8, 119.0, 114.5, 106.1, 40.0, 38.5, 37.3, 36.2, 33.5, 27.1, 22.2, 13.9, 13.3 ppm.

FTIR (KBr): 3430, 2950, 2921, 2848, 1808, 1757, 1610, 1466, 1362, 1231, 932 cm^{-1}.

UV(VIS) *Z*-form: O: 348 nm, C: 538 nm.

HRMS (EI) Calcd for $C_{22}H_{24}O_4$ [M^+]: 352.1675, Found: 352.1680; [M^+-CH_3]: 337.1440, Found: 337.1446.



Preparation of adamantylidene (ADD) diethyl succinate (31)

Synthesis was accomplished in a manner similar to that for the for the IPP diester **14**. Purification of the crude reaction mixture using flash chromatography afforded the diester **31** with a 57% yield. Clear yellowish oil.

Rf: 0.53 (hexane: ethyl acetate = 4:1).

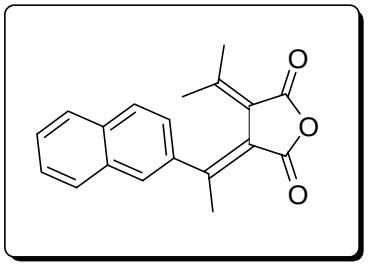
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.22 (q, J = 7.4 Hz, 2H, $CO_2C\mathbf{H}_2CH_3$), 4.12 (q, J = 7.4 Hz, 2H, $CO_2C\mathbf{H}_2CH_3$), 3.66 (s, 1H, C=CC**H**(CH)), 3.35 (s, 2H, C**H**$_2$CO$_2$CH$_2$CH$_3$),

2.81 (s, 1H, C=CCH(C**H**)), 1.94-1.81 (m, 12H, **ADA**), 1.29-1.23 (m, 6H, $(CO_2CH_2C\mathbf{H}_3)_2$) ppm.

^{13}C NMR (500 MHz, $CDCl_3$) δ 171.5, 168.6, 162.4, 114.4, 60.6, 60.2, 39.3, 39.1, 36.7, 35.1, 34.7, 34.6, 27.7, 14.2, 14.1 ppm.

FTIR (Film): 2981, 2912, 2852, 2337, 1739, 1714, 1628, 1450, 1368, 1236, 1176, 1063, 1044 cm^{-1}.

HRMS Calcd for $C_{18}H_{26}O_4$ [M^+]: 306.1831. Found: 306.1828; [M^+-CH_2CH_3]: 277.1440, Found: 277.139.



Preparation of 2-napthyl isopropylidene fulgide (19)

Synthesis was accomplished in a manner similar to that for the thienyl fulgide **18** affording a 28% yield.

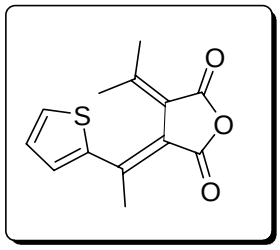
Rf: 0.43 (hexane: ethyl acetate = 4:1).

^{1}H NMR (300MHz, $CDCl_3$) δ 7.85 - 7.79 (m, 3H, **Napth**), 7.56-7.53 (m, 2H, **Napth**), 7.40-7.37 (m, 2H, **Napth**), 2.82 (s, 3H, C=C(C**H**$_3$)(Napth)), 2.19 (s, 3H, C=C(C**H**$_3$)(CH_3)), 1.02 (s, 3H, C=C(CH_3)(C**H**$_3$)) ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ 163.9, 163.2, 128.8, 128.4, 127.8, 127.4, 127.3, 126.9, 124.8, 26.3, 22.7, 22.6 ppm.

FTIR (KBr): 3466, 2922, 1805, 1759, 1624, 1422, 1365, 1257, 1224, 1132, 977, 947, 925, 760, 739, 480 cm^{-1}.

HRMS (EI) Calcd for $C_{19}H_{16}O_3$ [M^+]: 292.1099, Found: 292.1095; [M^+-CH_3]: 277.0865, Found: 277.0866.



Preparation of 2-thienyl isopropylidene fulgide (20)

Synthesis was accomplished in a manner similar to that for the thienyl fulgide **18** affording a 20% yield.

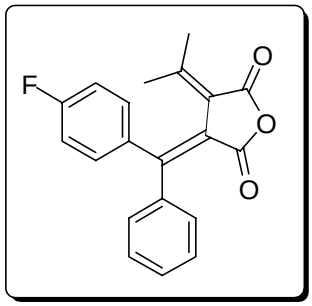
Rf: 0.55 (hexane: ethyl acetate = 4:1).

^{1}H NMR (300MHz, $CDCl_3$) δ 7.46-7.44 (dd, J = 1.0, 5.2 Hz, 1H, CHCHSCC**H**), 7.26-7.24 (m, 1H, CHC**H**SCCH), 7.07-7.05 (dd, J = 3.7, 5.1 Hz, 1H, C**H**CHSCCH), 2.74 (s, 3H, C=CC**H**$_3$), 2.29 (s, 3H, (CH_3)(C**H**$_3$)C=CCO), 1.46 (s, 3H, (C**H**$_3$)(CH_3)C=CCO) ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ 163.8, 163.2, 155.8, 145.3, 144.2, 129.3, 127.8, 121.9, 120.3, 119.6, 26.2, 23.2, 22.6 ppm.

FTIR (KBr): 3460, 2924, 2852, 1808, 1760, 1633, 1516, 1458, 1260, 1224, 927, 702 cm^{-1}.

HRMS (EI) Calcd for $C_{13}H_{12}O_3S$ [M^+]: 248.0507, Found: 248.0502; [M^+-CH_3]: 233.0272, Found: 233.0262.



Preparation of 4-fluoro-diphenyl isopropylidene fulgide (21)

Synthesis was accomplished in a manner similar to that for the thienyl fulgide **18** affording a 37% yield.

Rf: 0.60 (hexane: ethyl acetate = 4:1).

^{1}H NMR (300MHz, $CDCl_3$) δ 7.38 – 7.33 (m, 4H, C(C**H**)$_4$F), 7.22 – 7.06 (m, 5H, C(C**H**)$_5$), 2.29 (s, 3H, (CH_3)(C**H**$_3$)C=CCO), 2.17 (s, 3H, (C**H**$_3$)(CH_3)C=CCO) ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ 163.5, 163.1, 128.8, 128.4, 127.8, 127.4, 127.3, 126.9, 124.8, 26.3, 22.7, 22.6 ppm.

FTIR (Film): 3466, 2955, 2922, 2850, 1806, 1761, 1506, 1223, 944, 752 cm^{-1}.

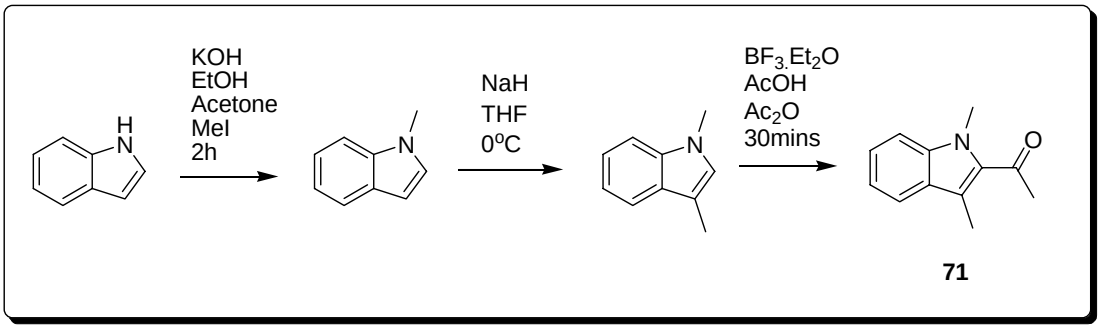
UV-Vis: 350 nm.

HRMS (EI) Calcd for $C_{20}H_{15}FO_3$ [M^+]: 322.1005, Found: 322.1005; [M^+-CH_3]: 307.0770, Found: 307.0768.

Table 1. UV-Vis Absorption Maxima (nm) in CH_2Cl_2, of Open and Closed form of the thienyl-fulgides **18** and **22**, furyl-fulgides **2** and **23** and corresponding fulgimides **53-70**.

Fg[a]	$\lambda_{max}O$[b] (nm)	A_O	ε_O ($mol^{-1}dm^3cm^{-1}$)	$\lambda_{max}C$[c] (nm)	A_C	ε_C ($mol^{-1}dm^3cm^{-1}$)	$\Delta\lambda_{max}$[d] (nm)	% Conversion[e]
18	342	1.48	68465	538	0.69	32063	196	46.8
22	340	2.20	40533	574	0.06	1099	234	2.7
53	330	1.22	50705	526	0.31	12999	196	25.6
54	Z: 330 E: 328	Z: 0.95 E: 0.70	Z: 33718 E: 45171	Z: 532 E: 532	Z: 0.30 E: 0.31	Z: 10709 E: 20044	Z: 202 E: 204	Z: 31.8 E: 44.4
55	Z: 330 E: 328	Z: 0.66 E: 1.28	Z: 18380 E: 39842	Z: 532 E: 534	Z: 0.28 E: 0.52	Z: 7879 E: 16390	Z: 202 E: 206	Z: 42.9 E: 41.1
56	326	1.06	342653	538	0.45	146703	212	42.8
57	334	0.81	175631	538	0.40	86908	204	49.5
61	330	0.65	27192	548	0.31	12951	218	47.6
62	330	1.99	199684	520	0.62	62106	190	31.1
63	330	2.36	298602	524	0.66	83877	194	28.1
64	340	1.09	43570	574	0.06	2297	234	5.3
2	346	0.97	52612	510	0.92	50278	164	95.6
23	348	1.25	51881	538	0.27	11069	190	21.3
65	338	0.85	18178	508	0.23	4911	170	27.0
66	336	1.19	57994	514	0.65	31587	178	54.5
67	334	0.91	88969	518	0.45	40648	184	45.7
68	336	1.31	60274	518	0.59	26988	182	44.8
69	338	0.97	36251	508	0.30	11249	170	31.0
70	340	1.08	322536	544	0.22	67897	204	21.1

a: Fulgide; *b*: Absorption maxima of Open-form.; *c*: Absorption maxima of Closed-form (Colored form); *d*: Difference of Closed-form over Open-form; *e*: Percentage of Open-form converted to Closed-form (ε_c /ε_o x 100). Note: [C] of stock solutions were prepared in 1-8μmol and were repeated in duplicate.

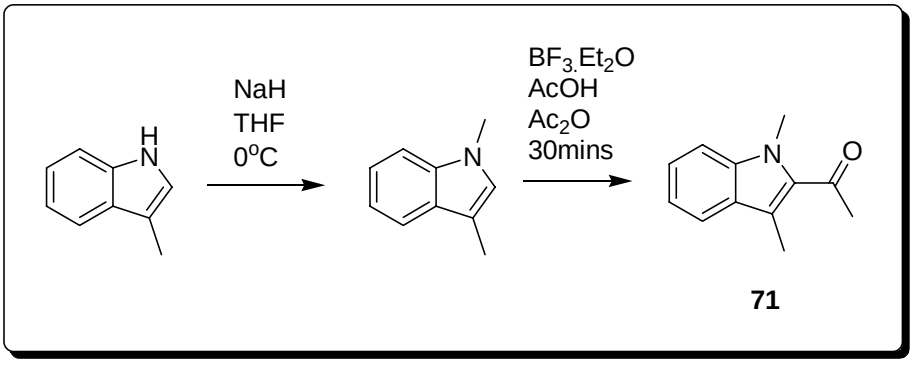


Preparation of 2-Acetyl-1,3-dimethylindole (71)

Method A

A 50 ml rbf was charged with a solution of indole (1 eq.) dissolved in EtOH (25 ml ~ 180 eq.). Solid KOH (1.25 eq.) was added into the rbf and the reaction mixture stirred until all the solid have been observed to be dissolved. The solvent was removed *in vacuo* and resolvated in acetone (25 ml) and stirred. Methyl Iodide (1.2 eq.) was added directly in one lot and the formation of a white precipitate was observed. The exothermic reaction was allowed to stir for 2h before purification via flash chromatography which afforded the 1' methylated indole with up to 65% yield. NaH (up to 10 eq.) was added into an rbf with ice-cooled THF. The purified 1' methyl indole was then redissolved in THF and added dropwise into the NaH/THF mixture. Upon completion of addition, the mixture was allowed to stir for 1h and allowed to warm up to room temperature. Methyl iodide (1.5 eq.) was added dropwise into the rbf and the reaction mixture allowed to stir for 6h resulting in the formation of 1,3-dimethylindole with up to 51% yield. After flash chromatography of the 1,3-dimethylindole, the compound was dissolved in acetic anhydride (15 eq.) and acetic acid (30 eq.). The reaction mixture was allowed to stir for 5-10 mins and was

followed by the dropwise addition of $BF_3.Et_2O$ (0.9 eq.). The reaction was allowed to stir for 15-30 mins and a white precipitate was observed to be formed. After the reaction was deemed to be completed, water was added to the reaction mixture (150 ml). The white precipitate was collected after filtration, washed with water and dried.



71

Method B

NaH (up to 10 eq.) was added into an rbf with ice-cooled THF. Commercially available 3-methylindole was then dissolved in THF and added dropwise into the NaH/THF mixture. Upon completion of addition, the mixture was allowed to stir for 1h and allowed to warm up to room temperature. Methyl iodide (1.5 eq.) was added dropwise into the rbf and the reaction mixture allowed to stir for 6h resulting in the formation of 1,3-dimethylindole with up to 40% yield. After flash chromatography of the 1,3-dimethylindole, the compound was dissolved in acetic anhydride (15 eq.) and acetic acid (30 eq.). The reaction mixture was allowed to stir for 5-10 mins and was followed by the dropwise addition of $BF_3.Et_2O$ (0.9 eq.). The reaction was allowed to stir for 15-30 mins and a white precipitate was observed to be formed. After the reaction was deemed to be completed, water was added to the reaction mixture (150 ml). The white precipitate was collected after filtration, washed with water and dried.

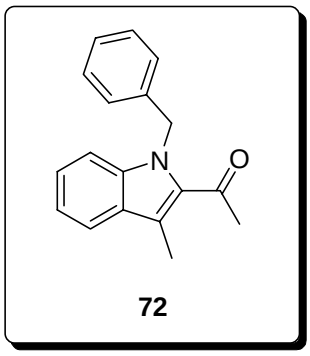
White precipitate, 76% yield.

^{1}H NMR (300MHz, $CDCl_3$) δ 7.70-7.12 (m, 4H, C(C**H**$_4$)C), 3.98 (s, 3H, NC**H**$_3$), 2.65 (s, 3H, COC**H**$_3$), 2.64 (s, 3H, C=CC**H**$_3$) ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ 192.5, 139.1, 135.9, 127.3, 126.0, 120.9, 119.9, 119.5, 110.2, 32.6, 31.6, 11.9 ppm.

FTIR (Film): 2956, 2929, 1730, 1646, 1400, 1330, 1236, 958, 739 cm^{-1}.

HRMS (EI) Calcd for $C_{12}H_{13}NO$ [M^+]: 187.0997, Found: 187.0995.



72

Preparation of 2-acetyl-1-benzyl-3-methylindole (72)

The synthesis of **72** was accomplished accordingly to **71** using method B, employing benzyl bromide instead of methyl iodide.

12% yield.

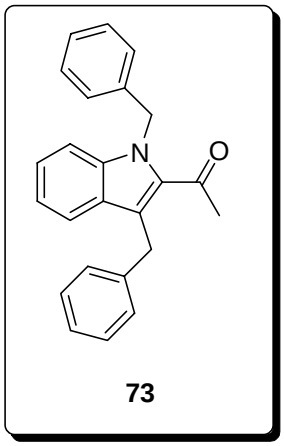
Rf: 0.46 (hexane: ethyl acetate = 4:1).

^{1}H NMR (300MHz, $CDCl_3$) δ 7.77-7.03 (m, 9H, C(C**H**)$_5$, C(C**H**)$_4$), 5.78 (s, 2H, NC**H**$_2$C(CH)$_5$), 2.69 (s, 3H, COC**H**$_3$), 2.61 (s, 3H, C=CC**H**$_3$) ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ 192.2, 139.0, 138.8, 133.1, 128.4, 127.5, 126.9, 126.3, 120.9, 120.2, 110.7, 48.3, 31.5, 11.9 ppm.

FTIR (Film): 3460, 2911, 2855, 1685, 1647, 1559, 1408, 1263, 948, 746, 729 cm^{-1}.

HRMS (EI) Calcd for $C_{18}H_{17}NO$ [M^+]: 263.1310, Found: 263.1310; [M^+-CH_3]: 248.1075, Found: 248.1081.



73

Preparation of 2-acetyl-1-benzyl-3-methylindole (73)

The synthesis of **73** was accomplished accordingly to **71** using method A, employing benzyl bromide instead of methyl iodide.

35% yield.

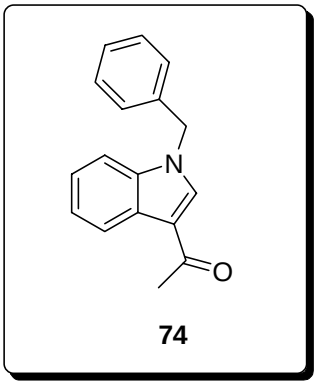
Rf: 0.60 (hexane: ethyl acetate = 4:1).

^{1}H NMR (300MHz, $CDCl_3$) δ 7.66–7.04 (m, 14H, $(C(C\mathbf{H})_5)_2$, $C(C\mathbf{H})_4$), 5.79 (s, 2H, $NC\mathbf{H}_2C(CH)_5$), 4.55 (s, 2H, $CC\mathbf{H}_2C(CH)_5$), 2.48 (s, 3H, $COC\mathbf{H}_3$) ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ 192.6, 139.9, 139.1, 138.7, 128.6, 128.5, 127.9, 127.7, 127.0, 126.32, 126.28, 126.25, 121.9, 121.3, 120.7, 110.8, 48.5, 31.4, 30.9 ppm.

FTIR (Film): 2960, 2915, 2849, 1735, 1718, 1654, 1261, 1097, 1023, 801, 740 cm^{-1}.

HRMS (EI) Calcd for $C_{24}H_{21}NO$ [M^+]: 339.1623, Found: 339.1625.



74

Preparation of 2-acetyl-1-benzyl-3-methylindole (74)

The synthesis of **74** was accomplished accordingly to **71** using method A, employing benzyl bromide instead of methyl iodide. **74** was obtained as a side product leading to indole **73**.

44% yield.

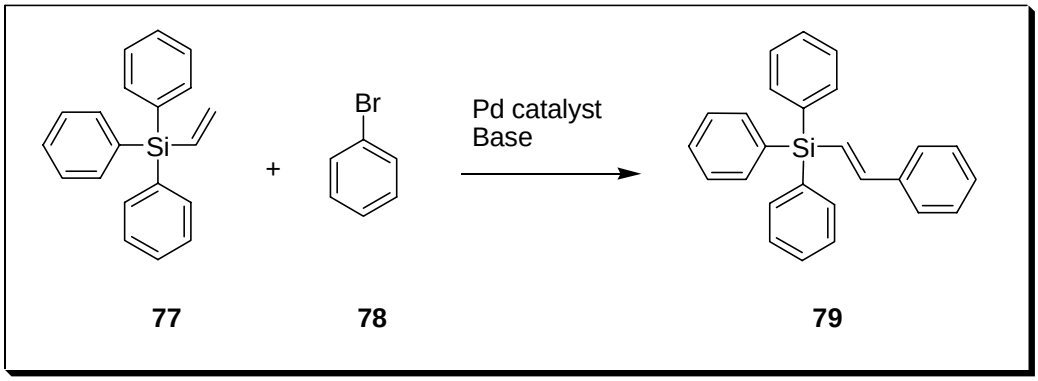
Rf: 0.25 (hexane: ethyl acetate = 4:1).

^{1}H NMR (300MHz, $CDCl_3$) δ 8.40-8.38 (m, 1H, NC**H**=CCOCH$_3$) 7.75-7.15 (m, 9H, C(C**H**)$_5$, C(C**H**)$_4$), 5.35 (s, 2H, NC**H**$_2$C(CH)$_5$), 2.52 (s, 3H, COC**H**$_3$) ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ 193.1, 137.2, 135.8, 134.9, 129.1, 128.3, 127.0, 126.5, 123.5, 122.7, 117.6, 110.1, 50.8, 27.7 ppm.

FTIR (Film): 3025, 2968, 2918, 2850, 1736, 1635, 1365, 1229, 1215, 732 cm^{-1}.

HRMS (EI) Calcd for $C_{17}H_{15}NO$ [M^+]: 249.1154, Found: 249.1151; [M^+-CH_3]: 234.0919, Found: 234.0921.



Preparation of triphenyl(styryl)silane (79)

Method A – Thermal heating method

Entry 1, Table 11.

Triphenylvinylsilane **77**, was added into a round bottomed flask, in the presence of *p*-bromoaniline. This was followed by the addition of 1,4-dioxane, NCy_2Me and the addition of a catalytic amount of $Pd[P(^tBu)_3]_2$. A reflux condenser was attached to the rbf and the reaction mixture was heated to 110^{o}C using an oil-bath for 18h. The dark/blackish reaction mixture was allowed to cool down and a TLC was conducted. Presence of the starting material indicated no desired coupling had occurred.

Entry 2, Table 11.

Triphenylvinylsilane **77**, was added into a round bottomed flask, in the presence of bromo-benzene. This was followed by the addition of N,N-DMF, NaOAc and the addition of a catalytic amount of $Pd(OAc)_2$. A reflux condenser was attached to the rbf and the reaction mixture was heated to 110^{o}C using an oil-bath for 18h. The dark/blackish reaction mixture was allowed to cool down and a TLC was conducted. As the TLC did not indicate the presence of the desired product, the temperature was

raised to 140°C and the reaction allowed to stir for another 18h. Presence of the starting material indicated no desired coupling had occurred.

METHOD B – MICROWAVE HEATING METHOD

Entries 3-14, Table 11.

Triphenylvinylsilane **77**, was added into a round bottomed flask, in the presence of bromo-benzene, **78**. This was followed by the addition of N,N-DMF, NaOAc and the addition of a catalytic amount of $Pd(OAc)_2$. A domestic microwave oven was employed for the heating of reaction mixture. The rbf containing the substrates was then heated for 10 mins employing a medium or medium-low power setting. Monitoring of the reaction was carried out using TLC and showed presence of product after 10 mins of microwave heating. Extraction of the crude reaction mixture was carried out using 100 ml of water with 4 x ethyl acetate. The organics were then combined and allowed to stand in $MgSO_4$. After removal of solvent *in vacuo*, the crude mixture was then subjected to flash chromatography which afforded **79** with yield of up to 41%. Addition of a 10% w/v of an ionic liquid [BMIM][BF_4] enhanced the yield with up to 86% of **79** synthesized.

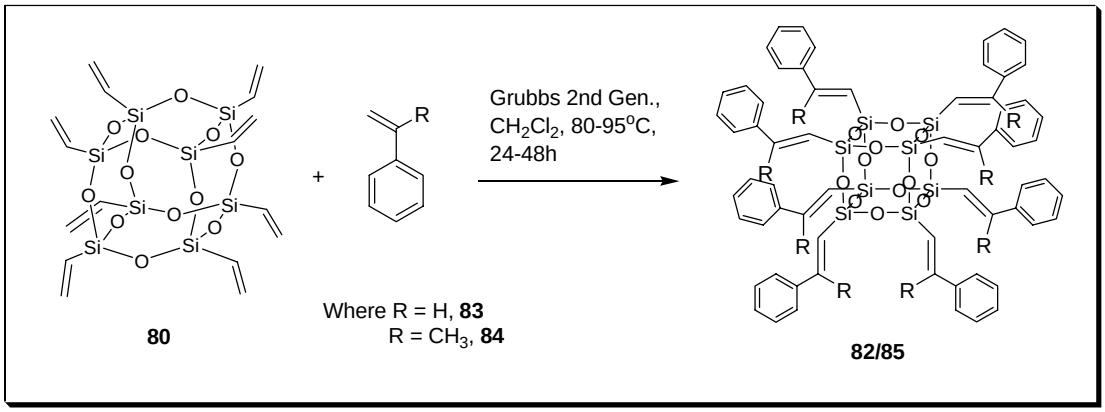
Rf: 0.48 (hexane 100%, 2 runs).

^{1}H NMR (300MHz, $CDCl_3$) δ 7.64-7.52 (m, 6H, **Ph**), 7.49-7.30 (m, 14H, **Ph**), 7.08-6.99 (dd, J = 3.2, 19.2 Hz, 2H, C**H**=C**H**) ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ 148.9, 138.1, 136.4, 136.1, 135.8, 135.2, 134.5, 129.6, 128.6, 128.5, 127.9, 126.8, 122.9 ppm. DEPT-90 (CH) δ 148.9, 136.4, 136.1, 135.8, 135.2, 129.6, 128.6, 127.9, 126.8, 122.9 ppm. DEPT-135 (CH) δ 148.9, 136.4, 136.1, 135.8, 135.2, 129.6, 128.6, 127.9, 126.8, 122.9 ppm.

FTIR (Film): 3061, 2958, 2923, 2851, 1602, 1484, 1425, 1107, 1026, 787, 760, 735, 505 cm^{-1}.

HRMS (EI) Calcd for $C_{26}H_{22}Si$ [M^+]: 362.1491, Found: 362.1492.



Preparation of octa-substituted poly oligomeric silsequioxanes (82) and (85)

To a round bottomed flask was charged –equivalent of **80** in the presence of anhydrous CH_2Cl_2. Styrene **83**, or a-methyl styrene, **84**, was then added in one lot and the reaction mixture allowed to stir until the solution was clear. Grubbs 2nd generation catalyst was then added in one lot and the reaction mixture heated for 24h at 85°C to afford the styrene analog, **82** with yield of up to 95%. The reaction mixture with **84** was heated for up to 48h at 95°C to afford **85** with 60% yield.

82 was obtained as a white, slightly green solid, 95% yield.

Rf: 0.58 (hexane: ethyl acetate = 4:1).

^{1}H NMR (300MHz, $CDCl_3$) δ 7.52-7.28 (m, 40H, **Ph**$_8$), 6.33 (d, J = 19.2Hz, 8H, (C**H**=C**H**)$_4$) ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ 149.3, 137.4, 128.9, 128.6, 126.9, 117.5 ppm.

FTIR (Film): 3059, 2924, 1606, 1573, 1492, 1448, 1199, 989, 851, 817, 733, 688, 555 cm^{-1}.

MALDI-TOF MS (Applied Biosystems Voyager System 4134) Calcd for $C_{64}H_{56}AgO_{12}Si_8$ [M^++Ag]: 1347.0977, Found: 1347.2558, 1348.2582, 1349.2575, 1350.2608, 1351.2569.

MALDI-TOF MS (Bruker Daltonics FlexAnalysis) Calcd for $C_{64}H_{56}AgO_{12}Si_8$ [M^++Ag]: 1347.0977, Found: 1349.5580.

85 was obtained as a white, slightly green solid, 60% yield.

Rf: 0.63 (hexane: ethyl acetate = 4:1).

^{1}H NMR (300MHz, $CDCl_3$) δ 7.55-7.51 (m, 17H, **Ph**$_3$), 7.38-7.20 (m, 24H, **Ph**$_5$), 6.15-6.12 (m, ~1H, CH=C**H**), 5.89-5.61 (m, ~7H, (C**H**=C)$_{7-8}$), 5.63-5.60 (m, 2H), 2.45-2.31 (m, 24H, (C**H**$_3$)$_8$) ppm.

Note: Even after repeated attempts to repurify the product, the desired octa-substituted product was not isolated cleanly. ^{1}H NMR indicates the slight presence of the heptyl-substituted product as well. This is observed in the MALDI-TOF MS results as well.

^{13}C NMR (300MHz, $CDCl_3$) δ 156.8, 156.6, 156.2, 143.6, 128.6, 128.2, 128.1, 128.0, 127.8, 127.1, 125.7, 117.2, 117.0, 28.7, 21.3 ppm. DEPT-90 (CH) δ 128.2, 128.0, 127.1, 125.7, 117.2, 117.0 ppm. DEPT-135 (CH) δ 128.2, 128.0, 127.1, 125.7, 117.2, 117.0 ppm. (CH_3) δ 28.7, 21.3.

Note: The CH_2 indicative of the presence of the heptyl-substituted product was not observed from the DEPT-135 spectra. A small additional peak indicative of CH_3 was present at 28.7ppm and its presence is unknown and is suspected to be due to impurities.

FTIR (Film): 2919, 1603, 1492, 1442, 1100, 814, 748, 692 cm^{-1}.

MALDI-TOF MS (Applied Biosystems Voyager System 4134)

Calcd for $C_{72}H_{72}AgO_{12}Si_8$ [M^++Ag]: 1459.2229, Found: 1459.3014, 1461.3028, 1463.3006, 1464.2996.

Calcd for $C_{65}H_{66}AgO_{12}Si_8$ [M^++Ag]: 1369.1759, Found: 1371.2873, 1372.3065, 1373.2874.

MALDI-TOF MS (Bruker Daltonics FlexAnalysis)

Calcd for $C_{72}H_{72}AgO_{12}Si_8$ [M^++Ag]: 1459.2229, Found: 1461.7550.

Calcd for $C_{65}H_{66}AgO_{12}Si_8$ [M^++Ag]: 1369.1759, Found: 1371.6520.

CHAPTER 6

Experimental Section

Part II – Synthetic studies towards anti-SARS agent AG7088

6.6. GENERAL INFORMATION

Experiments involving moisture and/or air sensitive components were performed under a positive pressure of nitrogen in oven/flame-dried glassware, equipped with a rubber septum. Solvents and liquid reagents were transferred by oven-dried syringes cooled in a dessicator or via double-tipped cannular needles. Reactions were stirred with Teflon-coated magnetic stirring bars unless otherwise stated. Moisture in non-volatile reagents or compounds was removed by the addition anhydrous THF, followed by the removal of the solvent and traces of moisture *in vacuo* by means of a vacuum pump (~20 mmHg, 23-45^{o}C) and subsequent purging with nitrogen. All experiments were monitored by analytical thin layer chromatography (TLC). Solvents were removed *in vacuo* (~30 mmHg, 23-45^{o}C) using a Büchi rotary evaporator with cold (0-5^{o}C) running water.

6.7. MATERIALS

All commercially available materials were used without further purification with the following exceptions: Hexane, dichloromethane, ethyl acetate were fractionally distilled prior to use. Anhydrous THF and diethyl ether were obtained by distillation under a nitrogen atmosphere from a deep purple solution resulting from sodium and benzophenone. Anhydrous dichloromethane (DCM) and hexane were distilled over calcium hydride under a nitrogen atmosphere.

Triethylamine was distilled over calcium hydride under a nitrogen atmosphere and stored over 4Å molecular sieves. Hydrochloric acid was diluted from 12M solution.

Sulfuric acid was diluted from 10M solution. Sodium hydroxide solution was prepared rom sodium hydroxide pellets. Saturated solutions of sodium chloride, sodium bicarbonate, sodium carbonate, sodium thiosulphate and ammonium chloride were prepared from their respective solids.

6.8. CHROMATOGRAPHY

Analytical thin layer chromatography (TLC) was performed using Merck 60 F_{254} precoated silica gel plate (0.25 mm thickness). Subsequent to elution, ultraviolet (UV) illumination of the chromatogram at 254 nm allowed the visualization of UV active material. Further visualization was possible by staining with basic solution of potassium permanganate or acidic solution of ceric molybdate, followed by heating on a hot plate.

Preparative thin layer chromatography was performed using Merck 60 F_{254} precoated silica gel plate (0.25 mm thickness, 20 cm x 20 cm). Compounds were diluted with 100-300μL of the appropriate solvent and applied to the plate as a narrow band ~16-18 cm long and 2 cm above the base, using a glass capillary tube. After elution, the chromatogram was visualized under UV light or by staining a thin strip, cut out from the side of the plate. The desired compound was then isolated by manually scraping the appropriate band off the plate using a spatula. The silica was then dissolved using an appropriate solvent followed by standing in anhydrous $MgSO_4$ before filtering through filter paper or celite. This was followed by the removal of solvent *in vacuo*.

Flash chromatography was performed using Merck silica gel 60 with freshly distilled solvents. Columns were typically packed as slurry of silica gel in hexane and equilibrated with the appropriate solvent system prior to use. The analyte was loaded neat or as a concentrated solution using the appropriate solvent system. The elution was assisted by applying pressure of about 2 atm with an air pump.

6.9. INSTRUMENTS AND EQUIPMENT

INFRARED SPECTROSCOPY

Infrared spectra were recorded in a Bio-RAD FTS 165 FT-IR spectrometer. Solid samples were analysed as a KBr pressed-disk while liquid samples were either examined neat between KBr salt plates or as a solution in dichlormethane using NaCl liquid cells.

MASS SPECTROSCOPY

Mass spectrometry (MS) was performed by the staff from the Chemical and Molecular analysis Centre of the National University of Singapore. MS-electron impact (EI) spectra were recorded on a Hewlett-Packard 5890A gas chromatogram. High-resolution MS (HRMS-EI) spectra were recorded on a V.G. Micromass 7035 micromass mass spectrophotometer at a source temperature of 200 ºC and at an ion current of 70 eV.. MS and HRMS were reported in units of mass to charge ratio (m/z).

NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

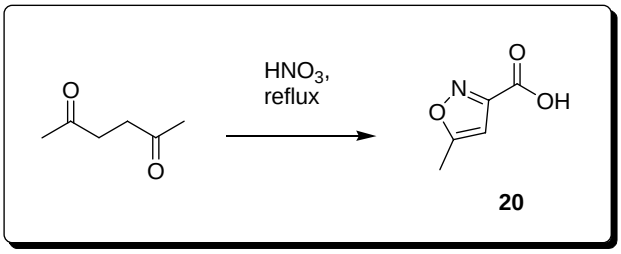
Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) were performed on a Bruker Avance DPX 300 (300MHz) and Bruker AMX 500 (500MHz), NMR spectrometer. Chemical shifts are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.00) and relative to the signal of the residual solvent signal of, deuterio chloroform-*d* (^{1}H NMR, δ 7.2600 ppm, singlet; ^{13}C NMR, δ 77.04 ppm, triplet) and deuterium oxide, D_2O (^{1}H NMR, δ 4.7500 ppm, singlet). Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); dd (doublets of doublet); ddd (doublets of doublets of doublet); dddd (doublets of doublets of doublets of doublet); dt (doublets of triplet); or m (multiplets). The number of protons (n) for a given resonance is indicated by nH. Coupling constants are reported as a *J* value in Hz.

NOMENCLATURE

Systematic nomenclature for the compounds would follow the numbering system as defined by the International Union of Pure and Applied Chemistry (IUPAC).[1] Compounds were also named using the ChembridgeSoft ChemOffice 2004, ChemDraw Ultra 8.0 naming feature.

[1] http://www.chem.qmul.ac.uk/iupac/

6.10. PROCEDURES AND SUPPORTING INFORMATION FOR PART II



Preparation of 5-methyl-3-isoxazole carboxylic acid (20)

To a 2-necked 100 ml round bottomed flask (rbf) was fitted a condenser and 5.88 ml of acetonylacetone and 40 ml dilute HNO_3 (diluted from 20 ml HNO_3 and 43 ml H_2O) was added via a dropping funnel. The oxidation was initiated by refluxing the reaction mixture in an oil-bath set at 120^{o}C. The reaction mixture was allowed to reflux for 1 hr before allowing to cool -15^{o}C (using ethylene glycol/dry ice bath) before the appearance of yellow crystals was observed. The reaction mixture was filtered using a Buchner funnel and the filtrate washed twice with ice-cold H_2O. The yellow crystals, **20**, were then pressed dried using filter paper, with a yield of 42%.

Rf: 0.15(hexane: ethyl acetate = 4:1).

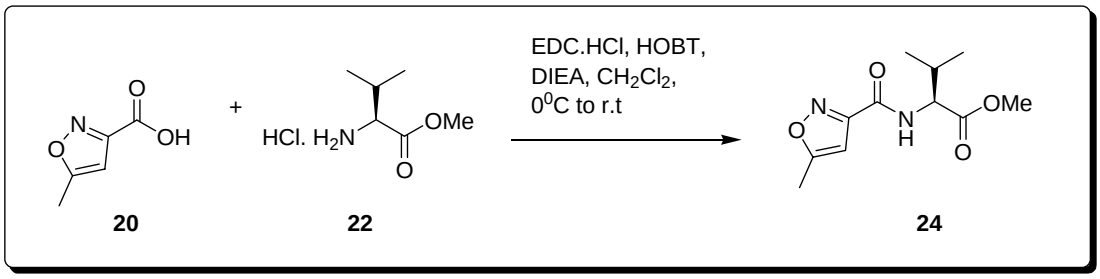
^{1}H NMR (300 MHz, D_2O) δ 6.47 (s, 1H, NOC=C**H**), 2.45 (s, 3H, NOCC**H**$_3$) ppm.

Note: Peak indicating acidic proton was not resolved.

^{13}C NMR (500 MHz, D_2O) δ 175.6, 165.5, 159.5, 104.6, 13.9 ppm.

FTIR (Film): 3474, 3139, 2744, 1707, 1595, 1488, 1466, 1369, 1269, 1225, 1002, 925, 858, 766, 545 cm^{-1}.

HRMS Calcd for $C_5H_5NO_3$ [M^+]: 127.0269. Found: 127.0269.



Preparation of methyl 2-(5-methylisoxazole-3-carboxamido)-3-methylbutanoate (24)

To a 25 ml round bottomed flask (rbf) containing 5-methyl-isoxazole-3-carboxylic acid, **20** (0.1271g, 1.00 mmol, 1eq), L-valine methyl ester hydrochloride, **22** (0.1844g, 1.10 mmol, 1.1 eq), 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDC.HCl) (0.2100g, 1.10 mmol, 1.1 eq) and 1-hydroxy benzotriazole hydrate (HOBT) (0.1486g, 1.10 mmol, 1.1 eq) in dichloromethane (5 ml) was added N-ethyl diisopropyl amine (DIEA) (0.6 ml, 3.50 mmol, 3.5 eq) dropwise, while maintaining the reaction temperature at 0^oC. The reaction was allowed to warm to room temperature and was stirred overnight or for up to 20h. The reaction mixture was then diluted with 10 ml of ether and washed with 20 ml of saturated $NaHCO_3$ solution followed by 10 ml of brine. The organic layer was dried over anhydrous $MgSO_4$. Solvents were removed *in vacuo*. Purification through flash column chromatography afforded **24** as a white solid (0.2350g , 99% yield).

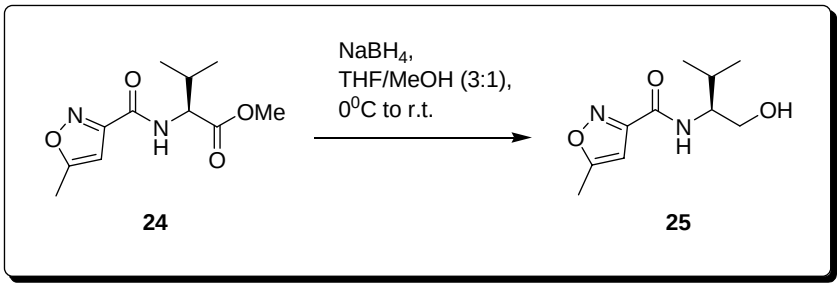
Rf: 0.30 (hexane: ethyl acetate = 4:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, J = 8.03 Hz, 1H, CON**H**), 6.43 (d, J = 0.81 Hz, 1H, C=C**H**), 4.70 (dd, J = 5.02, 9.03 Hz, 1H, CONHC**H**), 3.76 (s, 3H, OC$\mathbf{H}_3$), 2.48 (d(hept), J = 5.22, 6.82 Hz, 1H, C**H**$(CH_3)_2$), 1.00 (d, J = 7.63 Hz, 3H, $CHCH_3(C\mathbf{H}_3)$), 0.98 (d, J = 7.23 Hz, 3H, $CH(C\mathbf{H}_3)CH_3$) ppm.

^{13}C NMR (500 MHz, $CDCl_3$) δ 171.6, 171.2, 158.9, 158.3, 101.3, 57.1, 52.2, 31.3, 18.9, 17.7, 12.2 ppm.

FTIR (Film): 3583, 3407, 3343, 3140, 2966, 1715, 1681, 1597, 1539, 1458, 1208, 1003, 921, 813, 775 cm^{-1}.

HRMS Calcd for $C_{11}H_{16}N_2O_4$ [M^+]: 240.1110. Found: 240.1112.



Preparation of 1-hydroxy-3-methylbutan-2-yl)-5-methylisoxazole-3-carboxamide (25)

To a solution of **24** (0.7625g, 3.00 mmol, 1 eq) in 9 ml of THF, pro-cooled at 0^{o}C, was added 0.9705 g $NaBH_4$ (24.00 mmol, 8 eq) slowly in several portions. The solution was allowed to stir for 15 minutes before 3 ml of methanol was added dropwise to initiate the reaction. The reaction was allowed to warm to room temperature before allowing to stir overnight. Upon completion of the reaction, the reaction mixture was cooled using an ice bath. 1M HCl was added slowly until all the solids dissolved. The reaction mixture was then extracted with ethyl acetate (3 x 15 ml) and the combined extracts were washed with saturated sodium bicarbonate and dried over anhydrous $MgSO_4$. Solvent was removed *in vacuo*. Purification through flash column chromatography afforded 0.6245g of the desired product **25** as a white solid with 99 % yield.

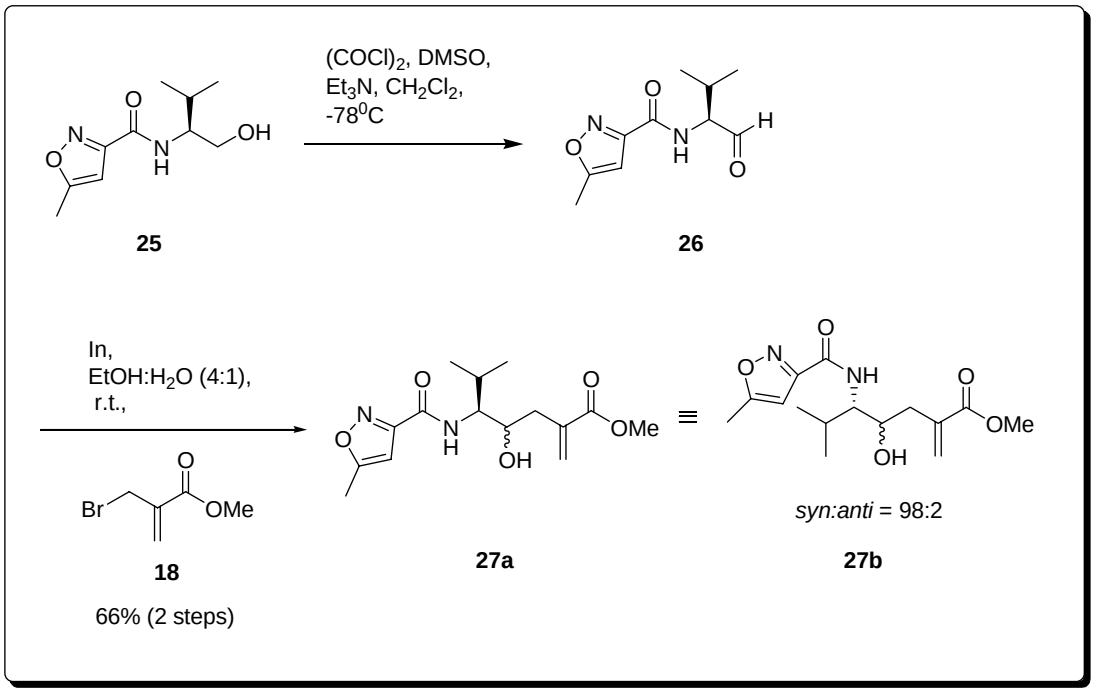
Rf: 0.22 (hexane: ethyl acetate = 4:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (d, J = 6.42 Hz, 1H, CON**H**), 6.43 (d, J = 0.80 Hz, 1H, C=C**H**), 3.95-3.86 (m, 1H, CONHC**H**), 3.80 (dd, J = 3.82, 11.45 Hz, 1H, C**H**HOH), 3.74 (dd, J = 6.02, 11.64 Hz, 1H, CH**H**OH), 2.47 (s, 3H, C**H**$_3$C=C), 2.04-1.93 (m, 1H, C**H**$(CH_3)_2$), 1.01 (d, J = 7.23, 3H, $CHCH_3$(C**H**$_3$)), 0.99 (d, J = 6.83 Hz, 3H, CH(C**H**$_3$)CH_3) ppm.

^{13}C NMR (500 MHz, $CDCl_3$) δ 170.9, 159.5, 158.6, 101.3, 62.6, 56.9, 28.7, 19.3, 18.6, 12.0 ppm.

FTIR (Film): 3441, 3314, 3155, 2967, 2939, 1655, 1602, 1548, 1456, 1289, 1219, 1145, 1068, 1006, 908, 819, 696, 622, 548 cm^{-1}.

HRMS Calcd for $C_{10}H_{16}N_2O_3$ [M^+-H]: 211.1083. Found: 211.2421.



Preparation of homoallylic alcohol (27)

A flame-dried rbf was purged, with nitrogen and charged with CH_2Cl_2 (6 ml) and oxalyl chloride (0.78 ml, 9.00 mmol, 3 eq). The solution was cooled to -78°C and 1.28 ml of DMSO (18.00 mmol, 6 eq) was added dropwise. The solution was allowed to stir for a few minutes before a solution of **25** (0.6784g, 3.00 mmol, 1 eq) in 6 ml of CH_2Cl_2 was added dropwise. This was followed by the addition of Et_3N (3.76 ml, 27.00 mmol, 9 eq) and the solution stirred for 5 mins at -78°C before being allowed to warm up to room temperature. After reaction completion, water was added to dissolve the solids (25 ml). The aqueous layer was then separated and extracted with CH_2Cl_2 (2 x 30 ml). The combined organic extracts were washed with water (2 x 30 ml), saturated sodium bicarbonate (20 ml), brine (20 ml) and dried over anhydrous $MgSO_4$. Solvent was removed *in vacuo*. The crude α-aminoaldehyde **26** (viscous

yellow liquid) was used immediately in the allylation step without any further purification.

26, *Rf*: 0.53 (hexane: ethyl acetate = 1:1). The TLC for the oxidation indicated the presence of the desired aldehyde as one spot with the disappearance of the spot at *Rf*: 0.22 from alcohol **25**.

Rf: 0.24 (ether: hexane = 2:1).

^{1}H NMR (*syn*) (300 MHz, $CDCl_3$) δ 9.65 (s, 1H, C**H**O), 7.29 (d, J = 6.83 Hz, 1H, CON**H**), 6.37 (d, J = 1.20 Hz, 1H, C=C**H**), 4.63 (dd, J = 4.62, 8.23 Hz, 1H, CONHC**H**), 2.42 (d, J = 0.81 Hz, 3H, C=C**H**$_3$), 2.42-2.31 (m, 1H, C**H**$(CH_3)_2$), 1.02 (d, J = 6.82 Hz, 3H, $CHCH_3$(C**H**$_3$)), 0.97 (d, J = 6.83 Hz, 3H, CH(C**H**$_3$)CH_3) ppm.

^{13}C NMR (300 MHz, $CDCl_3$) δ 198.8, 171.3, 159.4, 158.1, 101.2, 63.1, 28.9, 18.9, 17.6, 12.1 ppm.

HRMS Calcd for $C_{10}H_{14}N_2O_3$ [M^+]: 210.1004. Found: 210.0996.

The crude α-aminoaldehyde **26** was dissolved in 24 ml of ethanol followed by the addition of 6 ml of water. The solution was then charged with 0.6880g of Indium powder (6.00 mmol, 2 eq) followed by 1.074g of **18** (7.50 mmol, 2.5 eq) at room temperature. The reaction was monitored by TLC and was completed after 5 hours. 1M HCl (10 ml) was then added to dissolve the metal. The solution was then extracted with ethyl acetate (3 x 30ml). The combined organic layer was washed with a saturated solution of sodium bicarbonate, brine and was dried over anhydrous $MgSO_4$. Solvents were removed *in vacuo*. Purification through flash column chromatography afforded 0.6140g of product **27** (*syn:anti = 94:6*) as a white solid, with a yield of 66% 2 step yield (total yield of 2 products)).

Rf: 0.30 (*syn*) (ether: hexane = 2:1).

Rf: 0.24 (*anti*) (ether: hexane = 2:1).

^{1}H NMR (*syn*) (300 MHz, $CDCl_3$) δ 7.14 (d, J = 10.03 Hz, 1H, CON**H**), 6.39 (s, 1H, C=C**H**), 6.18 (s, 1H, C=C**H**H), 5.66 (s, 1H, C=CH**H**), 4.01 (ddd, J = 1.60, 4.32, 8.13 Hz, 1H, CONHC**H**), 3.73 - 3.67 (m, 1H, C**H**OH), 3.69 (s, 3H, OC**H**$_3$); 2.48 (dd, J = 4.22, 13.85 Hz, 1H, C**H**H(=CH_2)), 2.42 (s, 3H, =CC**H**$_3$), 2.39 (dd, J = 8.03, 14.05 Hz, 1H, CH**H**(=CH_2)), 2.00 – 1.88 (m, 1H, C**H**(CH_3)$_2$), 0.96 (d, J = 6.83 Hz, 3H, $CHCH_3$(C**H**$_3$)), 0.92 (d, J = 6.82 Hz, 3H, CH(C**H**$_3$)CH_3) ppm.

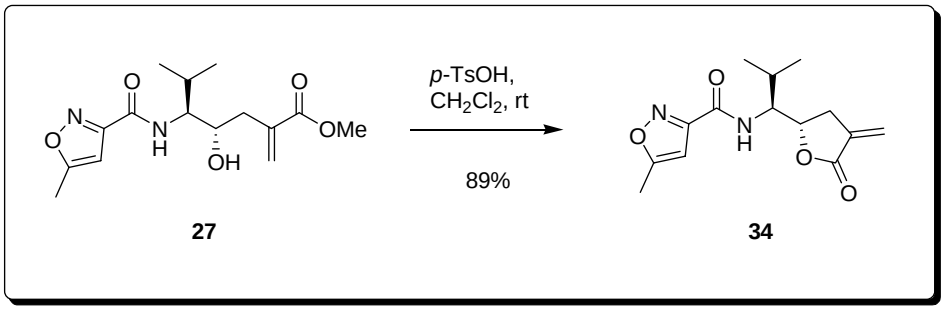
^{13}C NMR (300 MHz, $CDCl_3$) δ 171.0, 168.2, 159.4, 158.6, 136.8, 128.6, 101.4, 69.5, 58.5, 52.0, 38.6, 30.2, 19.6, 19.3, 12.1 ppm.

FTIR (neat) (*syn*): 3404, 2959, 1720, 1666, 1543, 1440, 1209, 1155, 1059, 950, 818 cm^{-1}.

HRMS Calcd for $C_{15}H_{22}N_2O_5$ [M^+]: 310.1529. Found: 310.1516.

^{1}H NMR (*anti*) (300 MHz, $CDCl_3$) δ 6.75 (d, J = 10.02 Hz, 1H, CON**H**)

FTIR (neat) (*anti*): 3402, 2960, 1717, 1667, 1541, 1450, 1210, 1155, 1059, 1035, 1003, 818 cm^{-1}.



Preparation of lactone (34)

To a solution of **27** (0.3240g, 1.00 mmol, 1.0 eq) in CH_2Cl_2 (10 ml) was added *p*-TsOH (0.095g, 0.50 mmol, 0.5 eq) and the reaction mixutre was stirred overnight. After reaction completion, 10 ml of saturated sodium bicarbonate solution was added. The 2 layers were separated and the aqueous layer was further extracted with CH_2Cl_2 (2 x 10 ml). The combined organic layer was then extracted with brine and dried over anhydrous $MgSO_4$. Solvents were removed *in vacuo*. Purification through flash column chromatography afforded 0.2471 g of product **34** with 89% yield.

Rf: 0.28 (ether: hexane = 2:1) (*syn*)

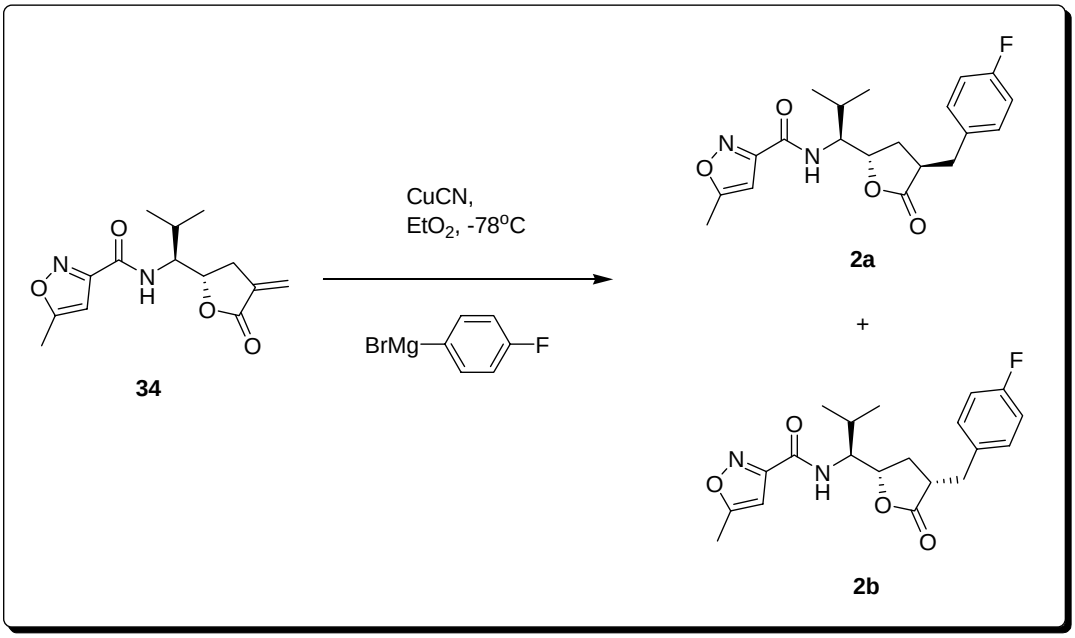
Rf: 0.15 (ether: hexane = 2:1) (*anti*)

^{1}H NMR (*syn*) (300 MHz, $CDCl_3$) δ 6.75 (d, *J* = 10.03, 1H, CON**H**), 6.39 (d, *J* = 0.80, 1H, C=C**H**), 6.14 (dd, *J* = 2.81, 3.22, 1H, C=C**H**H), 5.55 (dd, *J* = 2.41, 2.41, 1H, C=CH**H**), 4.85 (ddd, *J* = 1.61, 6.32, 7.93 Hz, 1H, C**H**OCO), 4.00 (ddd, *J* = 1.61, 8.73, 10.14 Hz, 1H, CONHC**H**), 2.99 (ddt, *J* = 2.56, 7.83, 17.47 Hz, 1H, C**H**HC(=CH_2)), 2.79 (ddt, *J* = 3.01, 6.43, 17.27 Hz, 1H, CH**H**C(=CH_2)), 2.45 (d, *J* = 0.8 Hz, 3H, C=CC**H**$_3$), 2.03 (d(hept), *J* = 6.82, 8.83 Hz, 1H, C**H**(CH_3)$_2$), 1.08 (d, *J* = 6.83 Hz, 3H, CHC**H**$_3$), 1.00 (d, *J* = 6.83 Hz, 3H, CH(C**H**$_3$)CH_3) ppm.

^{13}C NMR (300 MHz, $CDCl_3$) δ 171.4, 169.9, 160.1, 157.9, 133.7, 122.2, 101.3, 76.0, 57.4, 30.7, 30.5, 19.7, 19.4, 12.3 ppm.

FTIR (neat): 3406, 2967, 1770, 1683, 1600, 1508, 1456, 1216, 1188, 1159, 1001, 822 cm^{-1}.

HRMS Calcd for $C_{14}H_{18}N_2O_4$ [M^+]: 278.1267. Found: 278.1260.



Preparation of lactone (2)

To a 150 ml flame-dried rbf was added CuCN (2.82g, 31.50 mmol) and ether. (20 ml). *p*-fluorobenzylmagnesium bromide (Prepared from 60.00 mmol C_6H_4BrF, 6.60g; 75 mmol Mg, 1.80g and 60 ml ether), was prepared and added dropwise, via a dropping funnel at -78°C. The reaction mixture was then stirred at 0°C until a homogeneous mixture was observed. **34** was then dissolved in 100 ml of ether and added via dropping funnel at 0°C. Upon completion of addition, the reaction mixture was allowed to stir for an additional 3 hr at 0°C. Workup of the reaction was initiated by

the addition of saturated NH_4Cl (60 ml) followed by the extraction of the organic extract using ether (3 x 30 ml). The combined organic layer was then extracted with brine and dried over anhydrous $MgSO_4$, filtered and concentrated. Flash chromatography afforded 1.4609g of lactone **2** with a yield of 50% [2 was obtained as a mixture of isomers (*cis*:*trans* = 39:61). The desired *trans* isomer **2a** was obtained as the major product (confirmed by NOE experiments)].

Rf: 0.60 (100% ether) (*trans*, **2a**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14-6.94 (m, 4H, C(C_4**H**$_4$)F),), 6.74 (d, *J* = 10.04 Hz, 1H, CON**H**), 6.40 (d, *J* = 0.80 Hz, 1H, C=C**H**), 4.47 (ddd, *J* = 2.01, 6.32, 8.13 Hz, 1H, C**H**OCO), 3.91 (ddd, *J* = 2.01, 8.33, 10.14 Hz, 1H, CONHC**H**), 3.04-2.80 (m, 3H, C**H**$_2$PhF), 2.47 (s, 3H, C=CC**H**$_3$), 2.19 – 2.01 (m, 2H, CHC**H**$_2$CH), 1.93 (d (hept), *J* = 6.83, 8.03 Hz, 1H, C**H**(CH_3)$_2$), 0.98 (d, *J* = 6.83 Hz, 3H, $CHCH_3$(C**H**$_3$)), 0.95 (d, *J* = 6.82 Hz, 3H, CH(C**H**$_3$)CH_3) ppm.

^{13}C NMR (300 MHz, $CDCl_3$) δ 178.4, 171.6, 161.9, 160.0, 158.1, 133.3, 130.5, 115.6, 101.4, 77.6, 57.3, 41.0, 35.8, 30.6, 29.4, 19.7, 19.2, 12.3 ppm.

^{19}F NMR (300 MHz, $CDCl_3$) δ -40.36 (s, 1F) ppm.

FTIR (KBr): 3391, 3328, 2928, 2851, 2360, 1771, 1682, 1627, 1536, 1509, 1219, 1154, 1020, 805 cm^{-1}.

HRMS Calcd for $C_{20}H_{23}FN_2O_4$ [M^+]: 374.1642. Found: 374.1631.

Rf: 0.54 (100% ether) (*cis*, **2b**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05-6.75 (m, 4H, C(C_4**H**$_4$)F),), 6.60 (d, *J* = 10.04 Hz, 1H, CON**H**), 6.34 (d, *J* = 0.80 Hz, 1H, C=C**H**), 4.65 (ddd, *J* = 1.61, 5.82, 10.44 Hz, 1H, C**H**OCO), 3.91 (ddd, *J* = 1.61, 8.43, 10.24 Hz, 1H, CONHC**H**), 2.95-2.87 (m, 3H, C**H**$_2$PhF), 2.50 (s, 3H, C=CC**H**$_3$), 2.28-2.14 (m, 2H, CHC**H**$_2$CH), 1.96 (d (hept), *J* =

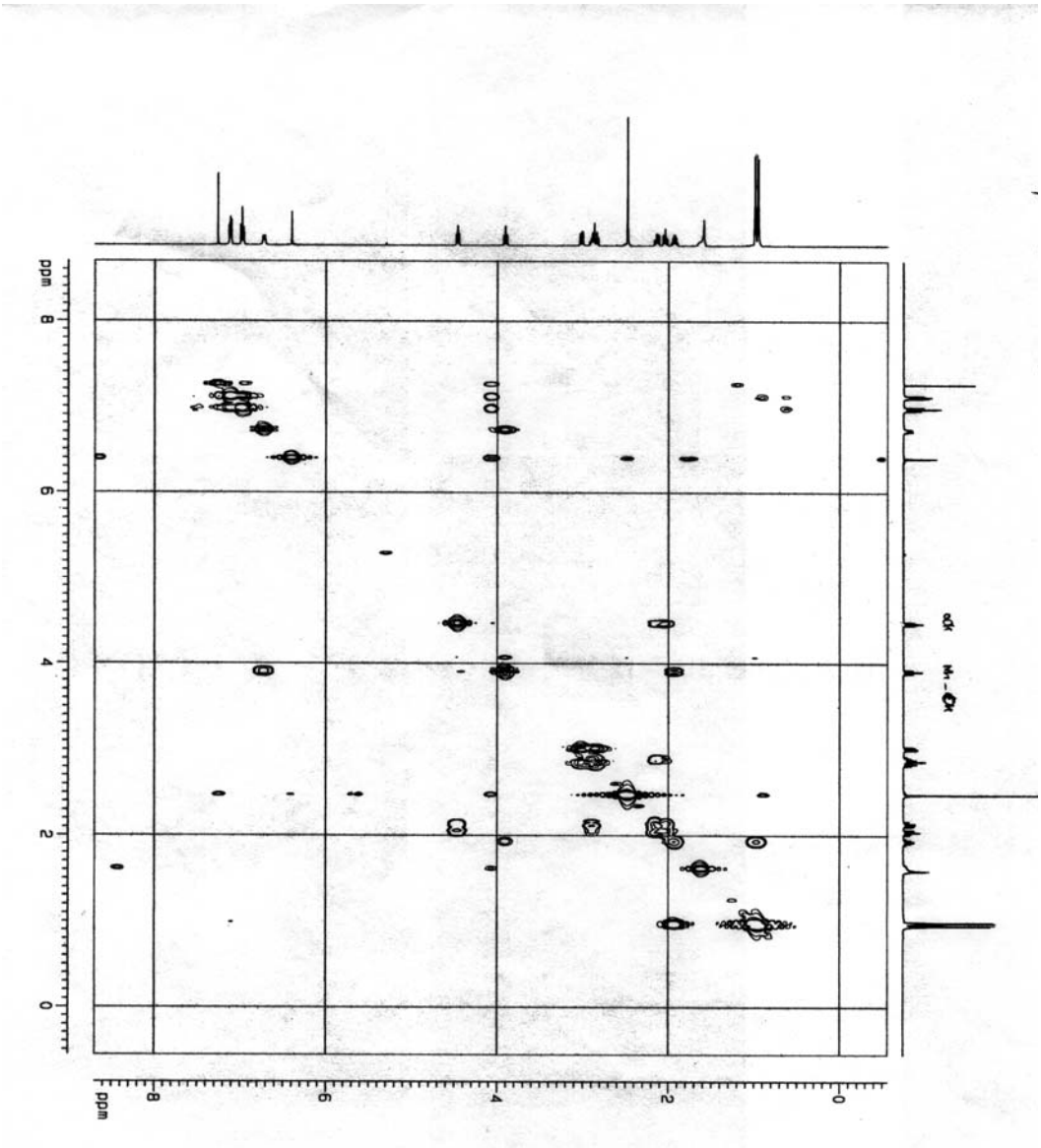
6.83, 8.03 Hz, 1H, C**H**$(CH_3)_2$), 1.03 (d, *J* = 6.83 Hz, 3H, $CHCH_3(C\mathbf{H}_3)$), 0.96 (d, *J* = 6.83 Hz, 3H, $CH(C\mathbf{H}_3)CH_3$) ppm.

^{13}C NMR (300 MHz, $CDCl_3$) δ 177.3, 171.5, 161.5, 159.6, 157.6, 133.1, 130.7, 115.1, 101.2, 77.1, 55.8, 41.7, 33.9, 30.9, 29.5, 19.6, 19.3, 12.2 ppm.

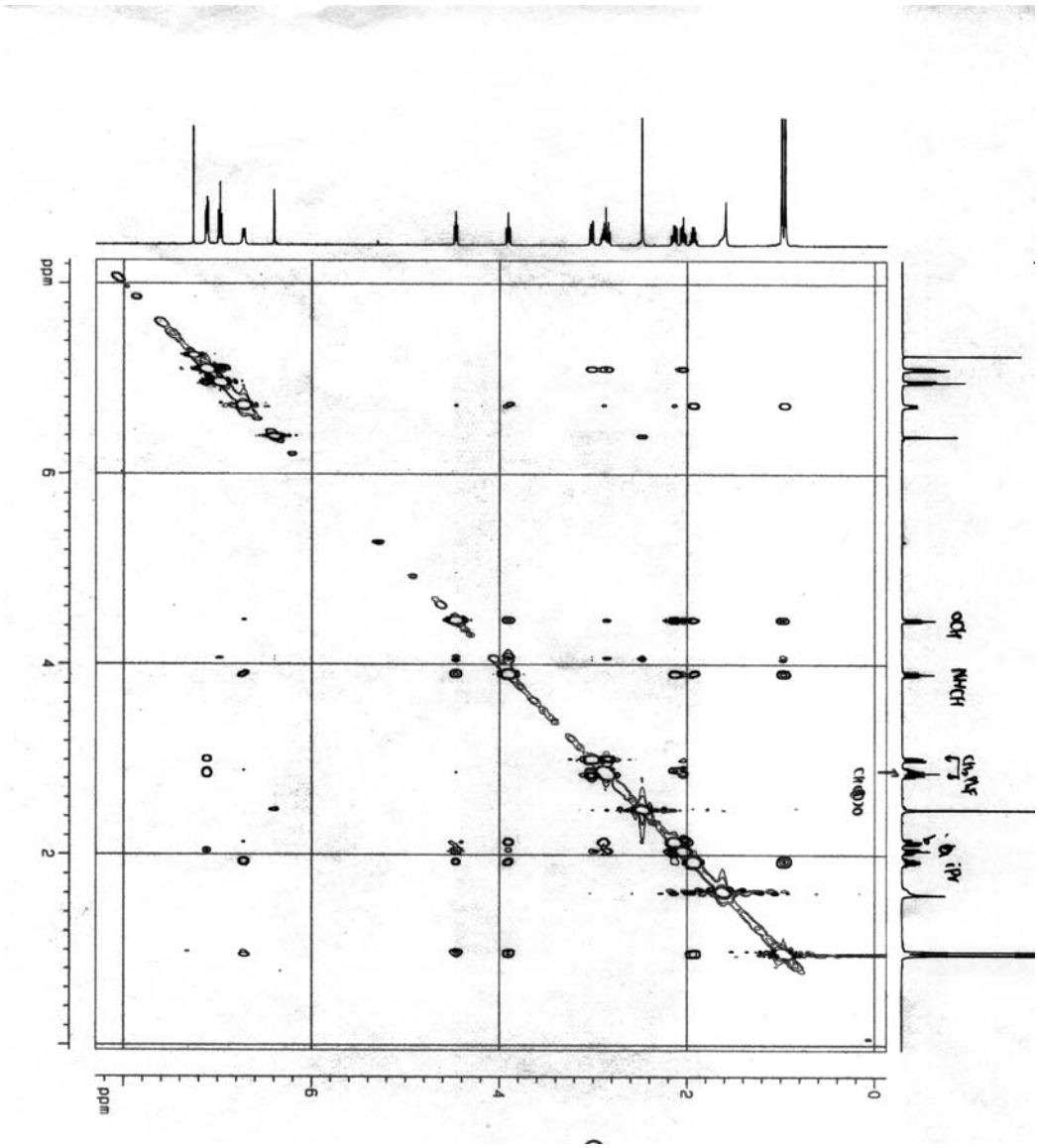
^{19}F NMR (300 MHz, $CDCl_3$) δ -40.36 (s, 1F) ppm.

FTIR (KBr): 3406, 3145, 2967, 2926, 1770, 1683, 1600, 1530, 1508, 1456, 1216, 1186, 1159, 1026, 1001, 822, 561 cm^{-1}.

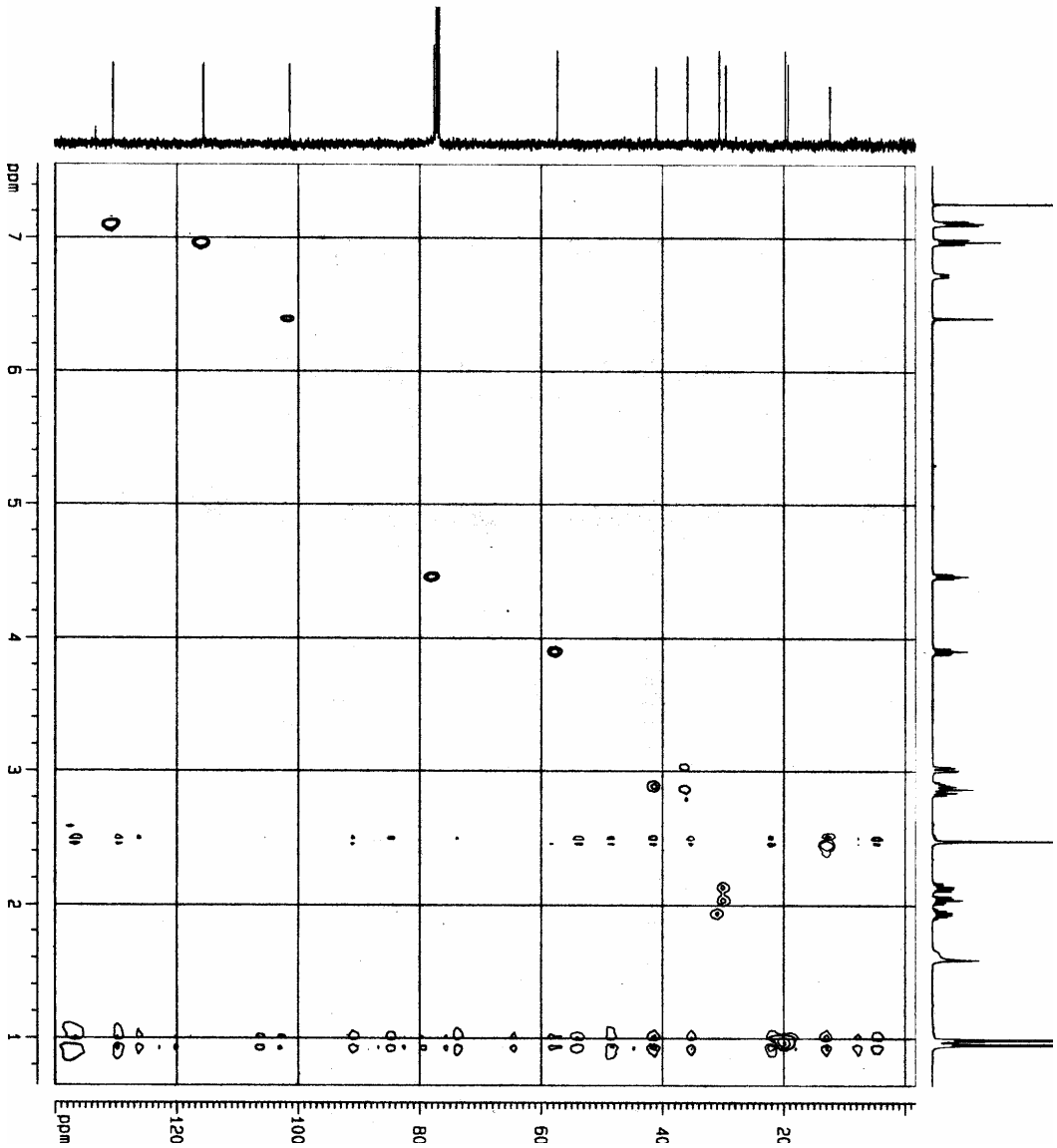
COSY spectrum of 2a

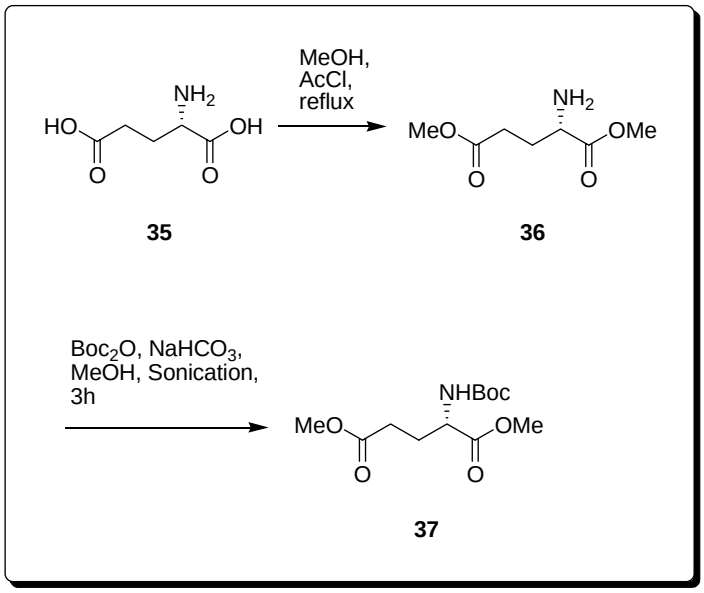


NOESY spectrum of 2a



HMQC spectrum of 2a





Preparation of N-Boc-L-(+)-glutamic dimethyl ester (37)

An oven dried 100 ml rbf was charged with 1.4713g of L-(+)-glutamic acid, **35** (10.00 mmol, 1 eq) and 25ml of methanol (excess). The mixture was cooled to 0^{o}C before acetyl chloride (0.15 ml, 2.00 mmol, 0.2 eq) was added dropwise until all the solid had dissolved. After which, the mixture was stirred in the presence of an ice bath for 30 mins. A 100 ml dropping funnel containing activated molecular sieves (4Å) was attached to the top of the rbf which was further attached to an ice-cooled reflux condenser above it. The mixture was then allowed to reflux overnight. Molecular sieves were used to remove water (generated during the reaction) from the reaction mixture. The excess solvents were removed *in vacuo*. The crude diester, **36**, was used immediately in the next step without any further purification. To a 150 ml rbf, was added 2.5g $NaHCO_3$ and 30 ml of MeOH. **36** was transferred in together with 20 ml MeOH (Magnetic stirring bar must be removed and not placed in rbf as vibrations might cause the rbf to crack). Di-tert-butyldicarbonate (2.4ml, 12 mmol, 1.2 eq) was added next. The rbf was then placed in the ultrasonic bath and was sonicated for up to

4 hrs. The reaction was monitored by TLC until reaction completion after 3 hrs. The solid was filtered and the reaction mixture was diluted with ether and was further washed with brine and then concentrated *via vacuo*. Purification through flash column chromatography afforded 1.9835g of diester **37** as a colorless, viscous liquid, 7.21 mmol, with up to 72% yield from **35**.

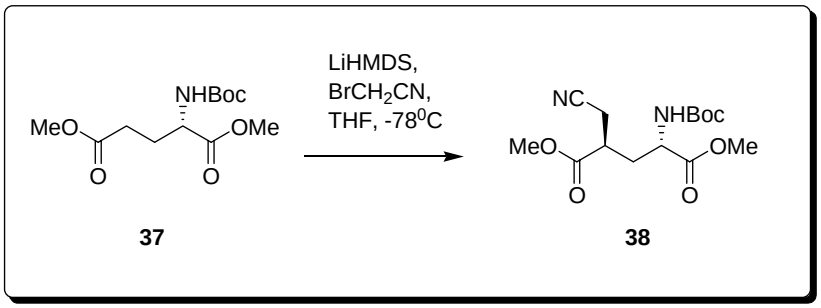
Rf: 0.55 (solvent Hex: EA = 1:1)

^{1}H NMR (300MHz, $CDCl_3$ solvent): δ 5.09 (b, 1H, N**H**) 4.32 (b, 1H, NHC**H**), 3.74 (s, 3H, OC**H**$_3$), 3.61 (s, 3H, OC**H**$_3$), 2.44-2.37 (m, 2H, C**H**$_2$COOMe), 2.02-1.88 (m, 1H, C**H**CHCH$_2$COOMe), 2.25-2.11 (m, 1H, CHC**H**CH$_2$COOMe), 1.44 (s, 9H, -C(C**H**$_3$)$_3$) ppm.

^{13}C NMR (300MHz, $CDCl_3$ solvent): δ 173.1, 172.6, 55.0, 60.3, 52.8, 52.3, 51.7, 30.0, 28.2, 27.8 ppm.

FTIR (Film): 3420, 3363, 2980, 2927, 1716, 1510, 1438, 1368, 1263, 1166, 1055, 738 cm^{-1}.

HRMS (ESI): Calcd for $C_{12}H_{21}NO_6$ [M^++Na^+]: 298.1267. Found: 298.1260.



37 38

Preparation of alkylated diester (38)

A solution of N-Boc L-(+)-glutamic acid dimethyl ester (0.7984, 2.90 mmol, 1 equiv.) in THF (10 mL) was added dropwise to a stirring solution of LiHMDS (8.7 mL, 1M in THF, 8.70 mmol, 3 equiv.) at -78°C under a N_2 atmosphere. The resulting dark mixture was stirred at -78°C for 2 hrs. Freshly distilled bromoacetonitrile (0.4mL, 5.90 mmol, 2.0 equiv.) was added dropwise over a period of 1 hour. The reaction mixture was stirred at -78°C for an additional 2 hrs. The reaction was quenched by addition of pre-cooled 1M HCl (20 mL) and cold H_2O (10 mL). The layers were separated, and the aqueous layer was further extracted with ether (3 x 30 ml). The combined organic extract was washed with saturated $NaHCO_3$ brine and dried over anhydrous $MgSO_4$. Solvent was removed *in vacuo* to afford a brown oil (15.2 g). Purification through flash column chromatography afforded 0.2808g of product **38** as a brown liquid, with a 59% yield.

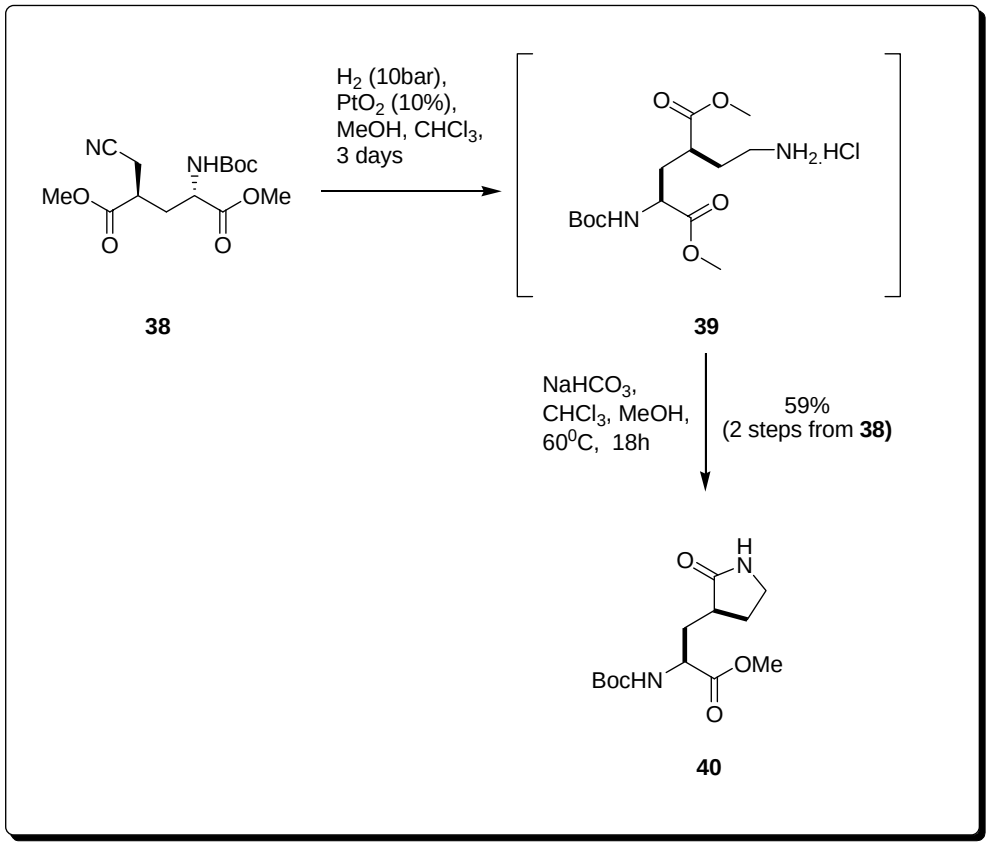
Rf: 0.46 (solvent Hex: EA = 1:1)

^{1}H NMR (300MHz, $CDCl_3$ solvent) δ 5.09 (d, J = 6.0 Hz, 1H, N**H**), 4.39 (b, 1H, NHC**H**), 3.76 (s, 3 H, OC**H**$_3$), 3.75 (s, 3 H, OC**H**$_3$), 2.89-2.80 (m, 1 H, C**H**CH_2CN), 2.77-2.73 (m, 2 H, C**H**$_2$CN), 2.24-2.12 (m, 2 H, C**H**$_2$CHNHBoc), 1.44 (s, 9 H, C(C**H**$_3$)$_3$) ppm.

^{13}C NMR (300 MHz, $CDCl_3$ solvent): δ 172.4, 171.9, 155.9, 117.1, 80.4, 52.6, 50.9, 38.1, 33.7, 28.1, 19.6 ppm.

FTIR (Film): 3370, 2980, 2957, 1734, 1713, 1514, 1442, 1368, 1250, 1164, 1051, 1027, 736 cm^{-1}.

HRMS (ESI): Calcd for $C_{14}H_{22}N_2O_6$, $[M^+ + Na^+]$: 337.1376. Found 337.1379.



Preparation of N-Boc-lactone (40)

To a glass-sleeved, Parr high-pressure bomb, equipped with a stirring bar was added 0.515g of **38** (1.64 mmol, 1 eq) in a mixture of 6 ml MeOH and 0.6 ml $CHCl_3$. 0.0397g PtO_2 (0.17 mmol, 0.11 eq) was added in one lot and the Parr bomb charged with H_2 with a pressure of 10bar. The reaction was then allowed to stir for 3 days and

the pressure maintained. After 3 days, the pressure was released and the crude reaction mixture transferred to a 50 ml rbf via a glass pipette. $NaHCO_3$ (0.212g, 2 mmol) was added to the reaction mixture and the reaction mixture was heated to 60^oC (oil bath ~ 85^0C) for 18 hr. The reaction mixture was then filtered through celite and washed with ethyl acetate. The filtrate was then washed with brine (30 ml) and dried over anhydrous $MgSO_4$. Solvents were removed *in vacuo* and purification via flash column chromatography afforded lactone **40** as a white solid with 59% yield.

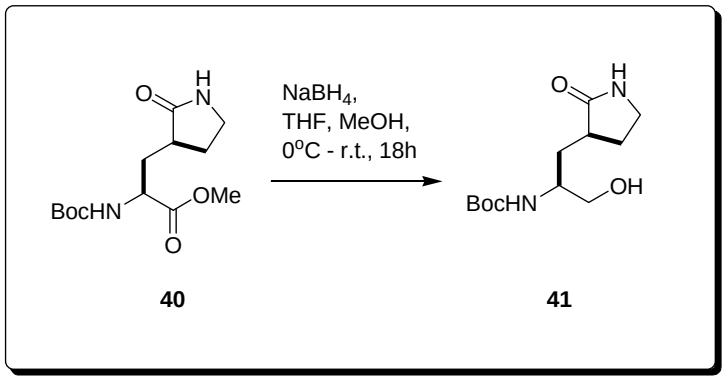
Rf: 0.30 (100% ethyl acetate)

^1H NMR (300MHz, $CDCl_3$ solvent) δ 6.40 (s, br, 1 H, $CH_2N\mathbf{H}$), 5.56 (d, J = 8.4 Hz, 1 H, CHN**H**), 4.36-4.21 (m, 1 H C**H**NH), 3.72 (s, 3H, COOC$\mathbf{H}_3$), 3.34 (d, J = 8.7 Hz, 2H, CONHC$\mathbf{H}_2$), 2.51-2.39 (m, 1 H, C**H**CONH), 2.09-2.07 (m, 2 H, $CONHCH_2C\mathbf{H}_2$,) 1.84-1.72 (m, 2H C$\mathbf{H}_2$CHNHBoc) 1.37 (s, 9 H, C(C$\mathbf{H}_3)_3$) ppm.

^{13}C NMR (300MHz, $CDCl_3$ solvent): δ 179.7, 172.9, 155.8, 79.9, 52.4, 52.3, 40.4, 38.1, 34.1, 28.3, 28.1 ppm.

FTIR (Film): 3367, 2978, 1736, 1678, 1522, 1439, 1390, 1361, 1215, 1167, 1051, 735 cm^{-1}.

HRMS (ESI): Calcd for $C_{13}H_{22}N_2O_5$, $[M^+ + Na^+]$: 309.1426. Found 309.1450.



Preparation of lactone alcohol (41)

To a solution of **40** (0.0858g, 0.30 mmol, 1 eq) in 0.9 ml of THF, pre-cooled to 0°C, was added 0.068 g $NaBH_4$ (1.80 mmol, 6 eq) slowly in several portions. The solution was allowed to stir for 15 minutes before 0.3 ml of methanol was added dropwise. The ice bath was then removed and the reaction mixture was allowed to stir overnight. Upon reaction completion, the reaction mixture was cooled in an ice bath and 1M HCl was added slowly until all the solids dissolved. The reaction mixture was then extracted with ethyl acetate (3 x 15 ml) and the combined organic extract was washed with saturated sodium bicarbonate and dried over anhydrous $MgSO_4$. Solvent was removed *in vacuo*. Purification through flash column chromatography afforded 43.37mg of the desired alcohol **41** as a white solid, 0.168 mmol with 71 % yield.

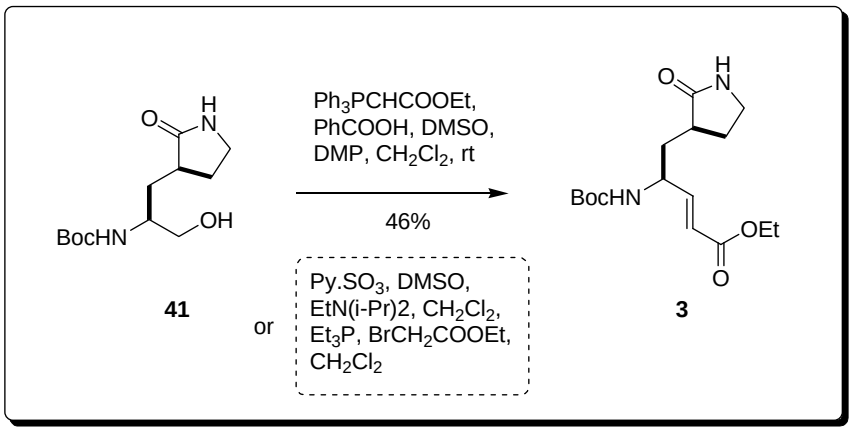
Rf: 0.15 (solvent EA)

^{1}H NMR (300MHz, $CDCl_3$ solvent): δ 6.24 (s, br, 1H, N**H**Boc), 5.47 (s, br, 1H, NHCOC**H**), 3.79-3.65 (m, 1H, C**H**NH), 3.61 (dd, J = 2.4, 4.0 Hz, 2H, C$\mathbf{H}_2$OH), 3.37-3.33 (dd, J = 4.0, 9.2 Hz, 2H, NHCH_2C$\mathbf{H}_2$), 2.51-2.40 (m, 3H, C$\mathbf{H}_2$C**H**CH_2NH) 2.04-1.91 (m, 2 H, C$\mathbf{H}_2$CHNHBoc), 1.89-1.58 (m, 1H, CHC$\mathbf{H}_2$CH), 1.44 (s, 9H, C(C$\mathbf{H}_3$)$_3$) ppm.

^{13}C NMR (300MHz, $CDCl_3$ solvent): δ 181.0, 156.6, 79.5, 65.9, 51.0, 40.5, 38.1, 32.6, 28.3, 28.1 ppm.

FTIR (Film): 3447, 3267, 2984, 2663, 1691, 1555, 1470, 1280, 1047, 729 cm^{-1}.

HRMS (ESI): Calcd for $C_{12}H_{22}N_2O_4$, $[M^+ + Na^+]$: 281.1488. Found 281.1478.



Preparation of lactone (3)

METHOD A

To a solution of **41** (0.0903g, 0.35 mmol, 1 eq.), in CH_2Cl_2 (7.5 ml) was added benzoic acid (0.1710g, 1.40 mmol, 4 eq.), (Carboethoxymethylenetriphenyl)-phosphorane (0.7316g, 2.10 mmol, 6 eq.) and DMSO (0.45 ml). Dess-Martin periodinane (0.6000g, 1.40 mmol, 4 eq.) was prepared and added in several portions to the solution. The reaction mixture was then stirred for 5-6 hrs at ambient temperature until the disappearance of the starting material **41**. Saturated $NaHCO_3$ solution was added and the mixture allowed to stir for 30 mins. A white soild was observed to precipitate out. Workup of the reaction included washing with saturated brine and using CH_2Cl_2 (3 x 30 ml) to extract the organic component. The organic

layer was combined, allowed to stand in anhydrous $MgSO_4$ and concentrated *via vacuo*. Flash chromatography afforded **3** with 46% (0.0521g) yield as a white solid.

METHOD B

To a solution of **41** (0.0700g, 0.17 mmol, 1 eq.), DMSO (1.00 ml) was added Et_3N (0.0180 ml, 0.14 mmol, 0.5 eq.). The resulting solution was cooled to 0-5^oC using an ice-bath. This was followed by the addition of sulfur trioxide-pyridine complex (0.2588g, 1.62 mmol, 6.0 eq.). The reaction was stirred for 20 mins and the ice-bath removed. The reaction was then allowed to stir for an additional 1 hr. (Carboethoxymethylenetriphenyl)-phosphorane (0.1696g, 0.49 mmol, 1.8 eq.) was added in one lot and the reaction stirred at ambient temperature for 3 hrs. The reaction was quenched by the addition of saturated brine, and extracted with ethyl acetate (3 x 30 ml). The combined organic phases were washed with saturated brine and allowed to dry over anhydrous $MgSO_4$. The crude reaction mixture was filtered, concentrated and purified via flash chromatography. **3** was obtained as a white solid (0.0200g, 35%).

COMPARISON OF DATA FROM PATENT[2] AND SYNTHESIZED LACTONE **3**.

REPORTED DATA FROM PATENT.

^1H NMR ($CDCl_3$ solvent): δ 6.80 (dd, J = 5.1, 15.6 Hz, 1H), 5.90 (dd, J = 1.8, 15.6 Hz, 1H), 5.68 (s, 1H), 5.13 (d, J = 7.5 Hz, 1H), 4.35-4.20 (m, 1H), 4.13 (q, J = 7.2 Hz,

[2] Tian, Q.; Nayyar, N. K.; Srinivasan, B.; Dagnino, R.; Remarchuk, T.; Moran, T.; McGee, K. *Canadian patent no CA 02376452* **2001**.

2H), 3.37-3.20 (m, 2H), 2.50-2.30 (m, 2H), 2.00-1.85 (m, 1H), 1.84-1.66 (m, 1H), 1.58-1.53 (m, 1H), 1.38 (s, 9H), 1.22 (t, *J* = 7.2 Hz, 3H) ppm.

HRMS (EI) Calcd for $C_{16}H_{26}N_2O_5$, [M^+]: 326.1842. Found: 326.1846.

98% *de*, 100% *E*-isomer

DATA FROM SYNTHESIZED LACTONE **3**.

Rf: 0.15 (solvent 100% EA)

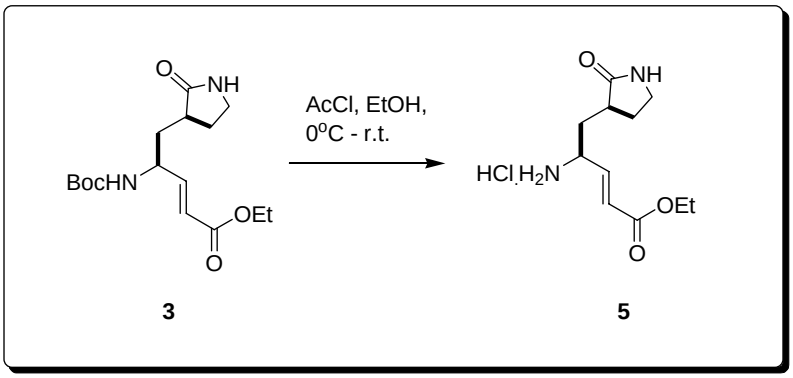
^{1}H NMR (300MHz, $CDCl_3$ solvent): δ 6.85 (dd, *J* = 5.22, 15.67 Hz, 1H, HC**H**C=CHCOOEt), 5.95 (dd, *J* = 1.62, 15.63 Hz, 1H, HCHC=C**H**COOEt), 5.70 (s, 1H, NHCOC**H**), 5.19 (d, *J* = 7.17 Hz, 1H, N**H**COCH), 4.35-4.25 (m, 1H, **H**CHC=CHCOOEt), 4.18 (q, *J* = 7.20 Hz, 2H, COOC**H**$_2$CH$_3$), 3.38-3.33 (m, 2H, NHC**H**$_2$CH$_2$), 2.49-2.38 (m, 2H, NHCH$_2$C**H**$_2$), 2.06-1.89 (m, 1H, NHCH$_2$CH$_2$C**H**), 1.86-1.67 (m, 1H, C**H**HCHNH), 1.58-1.55 (m, 1H, CH**H**CHNH), 1.44 (s, 9H, C(C**H**$_3$)$_3$), 1.28 (t, *J* = 7.14 Hz, 3H, COOCH$_2$C**H**$_3$) ppm.

^{13}C NMR (300MHz, $CDCl_3$ solvent): δ 179.8, 166.3, 155.6, 148.1, 120.9, 79.8, 60.5, 50.2, 40.3, 38.1, 35.9, 28.5, 28.4, 14.2 ppm.

FTIR (Film): 3467, 3139, 2855, 2745, 1707, 1595, 1487, 1447, 1369, 1269, 1220, 1001, 925, 856, 766, 545 cm^{-1}.

HRMS (ESI) Calcd for $C_{16}H_{26}N_2O_5$, [M^++Na^+]: 349.1739 (100%), 350.1773 (17.3%). Found: 349.1751 (100%), 350.1773 (17.8%).

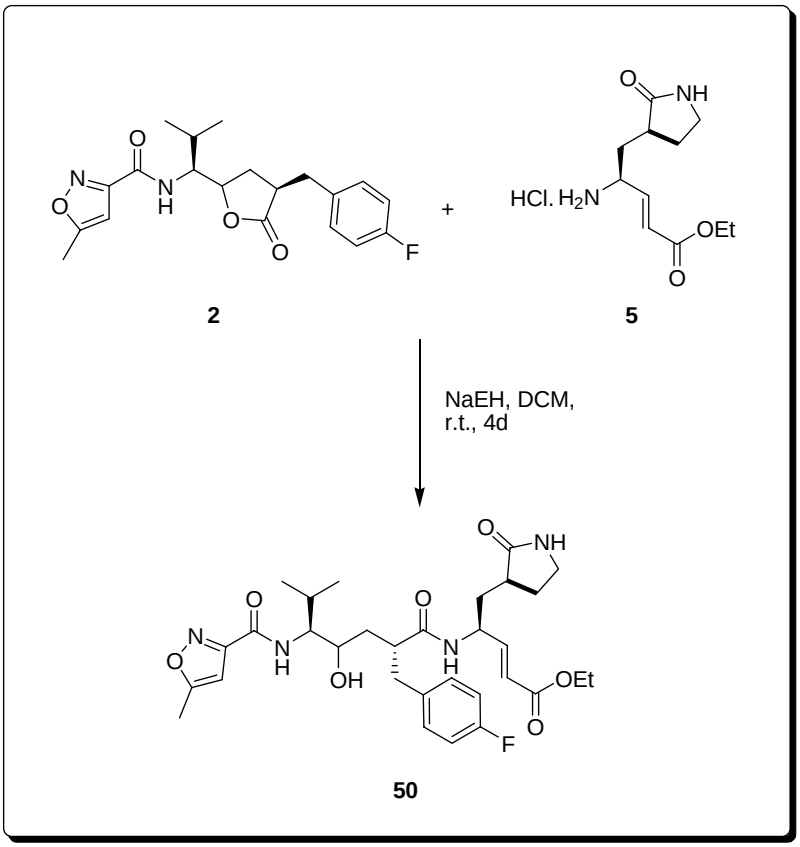
94% *de*, 100% *E*-isomer



3 **5**

Preparation of product (50)

To a 5 ml rbf containing lactone **3** (0.0056g, 0.017 mmol, 1 eq.) was added 0.30 ml of EtOH. The contents were allowed to stir with an ice-bath at 0°C for 30 mins before the dropwise addition of AcCl (~0.03 ml, 0.043 mmol, 2.5 eq.). The reaction mixture was then allowed to stir for 5 hrs at 0°C. As TLC did not show any presence of the product, another 5 eq. of AcCl (~0.06 ml, 0.085 mmol, 5 eq.) was added and 0.20 ml of EtOH was again added. The reaction mixture was then allowed to stir overnight. TLC (R_f (**5**) = 0.05, 100% ether; R_f (**3**) = 0.20, 100% ether) revealed the presence of the product with no starting material present. The solvents were then removed *in vacuo* and the crude product used directly in the next step.



2 **5**

50

Compound **2** (0.0320g, 0.018 mmol, 1 eq.) was dissolved in 0.20 ml of CH_2Cl_2 and was added via syringe to the rbf containing the crude product **5** (0.017 mmol, 1 eq.). After which, the solvents were removed and THF (2 x 1.0 ml) was used to removed water azotropically. After purging with nitrogen, 0.20 ml of CH_2Cl_2 was added into the rbf and Sodium 2-ethylhexanoate (NaEH) (0.1495g, 0.90 mmol, 5 eq.). Another 0.20 ml of CH_2Cl_2 was added to allow better stirring efficiency, and the reaction mixture was allowed to stir for 4 days. Flash chromatography afforded compound **50** in low yield at 20% (0.0014g) as a pale gel. (Crude NMR of the reaction mixture shows a large amount of the starting material **2**)

Rf: 0.38 (solvent 100% EA, 2 runs)

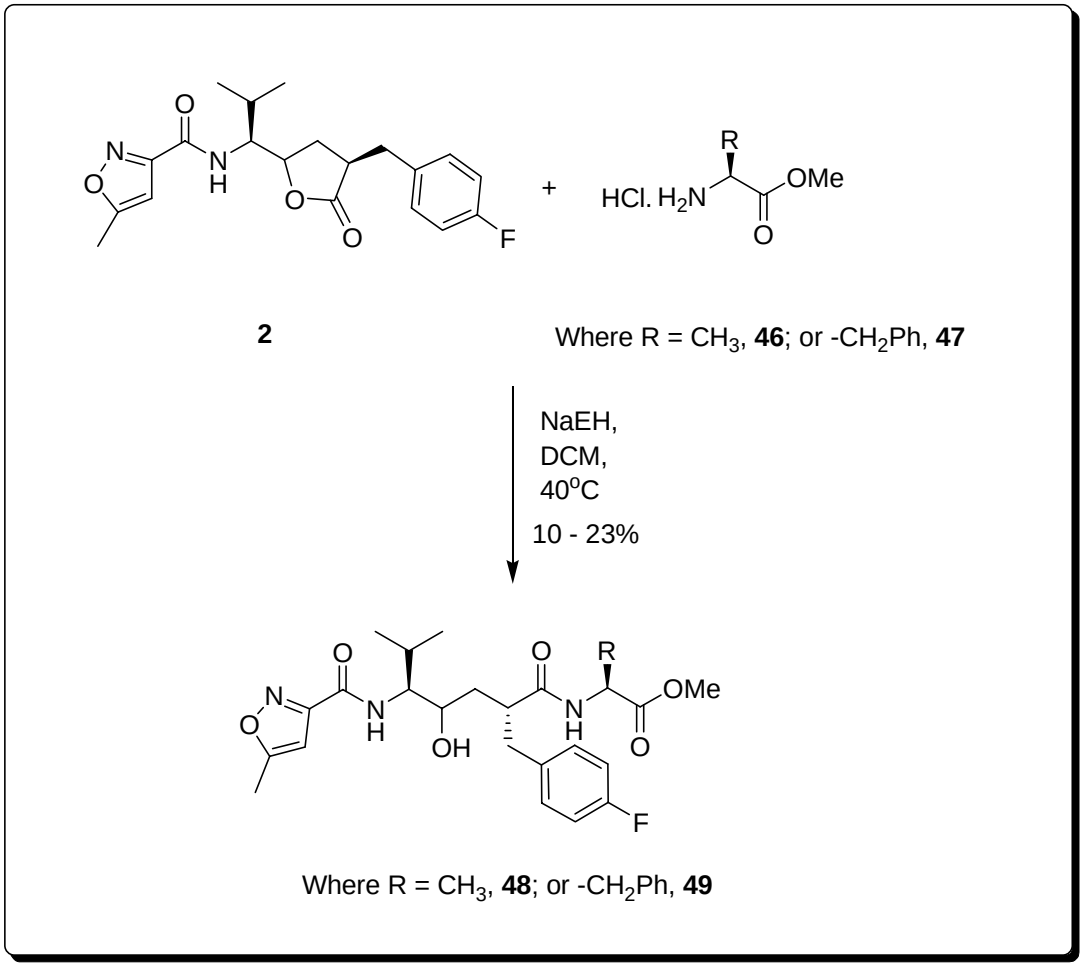
^{1}H NMR (300MHz, $CDCl_3$ solvent): δ 7.20-6.72 (m, 5H, C(C_5**H**$_4$)F, HC**H**C=CHCOOEt), 6.41 (s, br, 1H, CON**H**), 5.95 (dd, seen as a doublet; *J* = unresolved, 1H, HCHC=C**H**COOEt), 5.80 (s, br, 1H, NHCOC**H**), 5.30-5.28 (m, 1H), 4.28-4.11 (m, 3H, **H**CHC=CHCOOEt, COOC**H**$_2$$CH_3$), 4.05-3.91 (m, 1H, C**H**OH), 3.72-3.49 (m, 1H, C**H**iPr), 3.46-2.81 (m, 2H, NHC**H**$_2$$CH_2$), 2.76-2.59 (m, 2H, C**H**$_2$PhF), 2.52-2.32 (s, br, 4H, NOCHC**H**$_3$, C**H**(CH_3)$_2$), 2.35-1.90 (m, br, 1H, CHO**H**), 1.90-1.63 (m, br, 1H, NHCH$_2$CH$_2$C**H**), 1.56-1.12 (m, br, 7H, C**H**$_2$CHNH, COOCH$_2$C**H**$_3$), 1.05-0.81 (m, br, 6H, CH(C**H**$_3$)$_2$) ppm.[3]

^{19}F NMR (300 MHz, $CDCl_3$) δ -41.55 (s, 1F) ppm.

FTIR (Film): 3391, 2982, 2939, 2897, 1708, 1650, 1446, 1379, 1323, 1124, 1091, 1046, 948, 842, 800 cm^{-1}.

HRMS (ESI) Calcd for $C_{31}H_{41}FN_4O_7$, [M^++Na^+]: 623.2857 (100%), 624.2891 (33.5%). Found: 623.2858 (100%), 624.2896 (36.18%).

[3] Due to time constraints and the small amount of compound **50** synthesized, we were unable to obtain the ^{13}C NMR spectrum.



Preparation of (48) or (49)

48 and **49** were prepared before the actual coupling of fragment **2** and **5**, employing NaEH in CH_2Cl_2 stirred at 40°C. Synthesis of **48** and **49** was analagous to the method employed towards the synthesis of **50**. Partial characterization was carried out for 48. On observation of a successful coupling to afford **48**, we proceeded with the coupling of the bulkier benzyl analog to afford **49**.

48 was obtained as a mixture of 2 isomers with a 23% yield (0.0272g).

Rf: 0.48 (solvent 100% ether) (1st isomer)

Rf: 0.33 (solvent 100% ether) (2nd isomer)

^{1}H NMR (300MHz, $CDCl_3$ solvent): δ 7.19-6.72 (m, 4H, C(C_4**H**$_4$)F), 6.62 (d, J = 8.43 Hz, 1H, CON**H**CH), 6.36 (s, 1H, CON**H**), 4.67 (dd, J = 6.01, 10.50 Hz, 1H, CONHC**H**CH_3COOCH_3), 3.94 (t, br, J = 9.55 Hz, 1H, C**H**OH), 3.12-2.90 (s, br, 3H, COOC**H**$_3$), 2.55 (s, 1H, C**H**^{i}Pr), 2.15-2.28 (m, 3H, NOCC**H**$_3$), 1.78-1.49 (m, br, 6H, C**H**C**H**$_2$CH, C**H**$_3$), 0.93 (dd, J = 4.50, 6.60 Hz, 6H, CH(C**H**$_3$)$_2$) ppm.[4]

FTIR (KBr) (**48**): 3456, 2964, 1751, 1651, 1548, 1603, 1450, 1385, 1220, 1152, 1035 828, 777, 654 cm^{-1}.

49 was obtained as a mixture of 2 isomers with a 10% yield (0.0090g).

Rf: 0.30 (solvent 100% ether) (1st isomer)

Rf: 0.28 (solvent 100% ether) (2nd isomer, very low yield ~35% of 0.0090g)

^{1}H NMR (300MHz, $CDCl_3$ solvent): δ 7.20-6.72 (m, 9H, C(C_4**H**$_4$)F, C(C_5**H**$_5$)), 6.41 (s, 1H, CON**H**), 5.95 (d, J = 8.43 Hz, 1H, CON**H**CH), 4.89-4.83 (m, 1H, C**H**CH_2Ph), 3.92-3.88 (m, 1H, C**H**OH), 3.66 (s, 3H, COC**H**$_3$), 3.65-3.63 (m, 1H, C**H**^{i}Pr), 3.59-3.56 (m, 1H, CHC**H**$_2$Ph), 3.00-2.77 (m, 2H, C**H**C**H**$_2$Ph), 2.60-2.55 (m, C**H**^{i}Pr), 2.48 (s, 3H, C**H**$_3$CON), 1.98-1.86 (m, 1H, O**H**), 1.72-1.62 (m, 2H, OHCHC**H**$_2$CH), 0.95 (dd, J = 5.22, 6.42 Hz, 6H, CH(C**H**$_3$)$_2$) ppm.

^{13}C NMR (300MHz, $CDCl_3$ solvent): δ 174.6 (**C**ONH), 171.5 (**C**OOCH_3), 171.3 (CNO**C**=C), 160.6 (ON=C**C**ONH), 158.6 (ON**C**CONH), 136.2 (**C**(C_5H_5)), 134.8 (C(C_5H_4)F), 130.3, 130.2 (C(**C**$_5H_4$)F), 128.6, 127.1 (C(**C**$_5H_5$), 115.2, 115.0 (C(**C**$_5H_4$)F), 101.5 (NOC=**C**), 67.7 (**C**HOH), 59.7 (**C**HiPr), 53.1 (CONH**C**HCOOCH_3), 52.3 (CONHCHCOO**C**H_3), 37.9 (**C**H_2PhF), 37.2 (**C**H_2Ph),

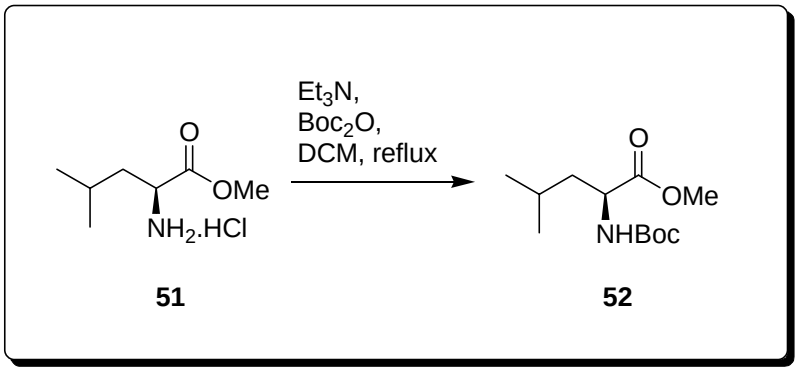
[4] We were only interested in obtaining a positive result for the coupling reaction. As such, we decided to carry out another reaction to synthesize compound **49**.

36.9 (**C**HOHCH$_2$), 29.6 (CH**C**H(CH$_3$)$_2$), 20.0, 18.8 (CHCH(**C**H$_3$)$_2$), 12.3 (NOC**C**H$_3$) ppm.

^{19}F NMR (300 MHz, CDCl$_3$) δ -41.36 (s, 1F) ppm.

FTIR (KBr) (**49**): 3412, 2954, 1741, 1650, 1541, 1508, 1456, 1219, 1156, 1031, 920, 745, 699 cm^{-1}.

HRMS (ESI) Calcd for $C_{30}H_{36}FN_3O_6$, [M^++Na^+]: 576.2486 (100.0%), 577.2519 (32.4%). Found: 576.2479 (100.0%), 577.2518 (34.40%).



51 **52**

Preparation of Boc-protected L-leucine methyl ester (52)[5]

To a 150 ml rbf was charged L-leucine methyl ester hydrochloride **51** (1.8166g, 10.00 mmol, 1 eq.), CH_2Cl_2 (30 ml) and Et_3N (1.82 ml, 13.00 mmol, 1.3 eq). Di-tert-butyldicarbonate (3.45 ml, 15.00 mmol, 1.5 eq) was added in one lot and the reaction mixture allowed to reflux overnight, up to 20 hr. The reaction was allowed to cool and 1M HCl was added to quench the mixture. The organic layer was washed with NaHCO3, H2O and brine solution and extracted with CH_2Cl_2 (2 x 40 ml). The organic

[5] Partial characterization was carried out for compounds **52-71**, as further characterization is for future work. The compounds synthesized here is to display the possibility of the extension of the study towards other possible analogs of AG-7088.

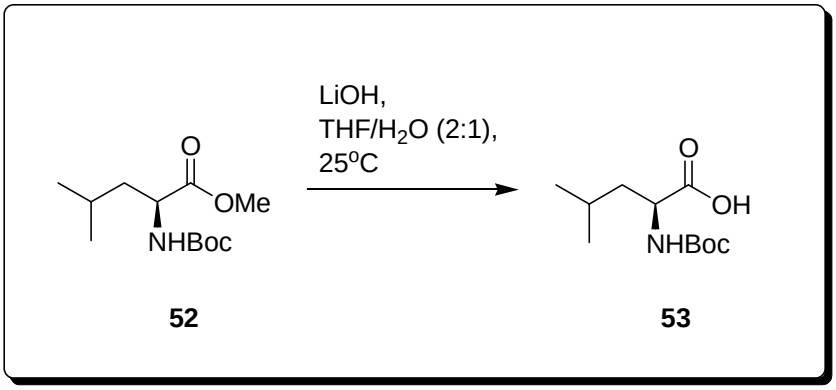
layer was allowed to stand in anhydrous $MgSO_4$ and concentrated *via vacuo*. Flash chromatography afforded 2.2940g of **52** with a yield of 94%.

Rf: 0.38 (hexane: ethyl acetate = 8:1).

^{1}H NMR (300MHz, $CDCl_3$) δ 4.87 (m, br, 1H, N**H**Boc), 4.31 (d, br, J = 5.22 Hz, 1H, C**H**NH), 3.73 (s, 3H, COOC**H**$_3$), 1.78-1.41 (m, 3H, C**H**C**H**$_2$CH), 1.44 (s, 9H, OC(C**H**$_3$)$_3$, 0.94 (dd, J = 2.60, 6.62 Hz, 6H, (C**H**$_3$)$_2$CH) ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ 173.9 (**C**OOCH$_3$), 155.3 (**C**OOC(CH$_3$)$_3$), 79.6 (COO**C**(CH$_3$)$_3$), 60.2 (COO**C**H$_3$), 51.9 (NH**C**H), 41.6 (**C**H$_2$NHCH), 28.2 (COOC(**C**H$_3$)$_3$), 24.6 (**C**H(CH$_3$)$_3$), 22.7 and 21.7 (CH(**C**H$_3$)$_3$) ppm.

HRMS (ESI) Calcd for $C_{12}H_{23}NO_4$, [M^++Na^+]: 268.1525 (100.0%), 269.1558 (13.0%). Found: 268.1526 (100.0%), 269.1557 (15.25%).



Preparation of Boc-protected L-leucine carboxylic acid (53)

To a 100 ml rbf charged with **52** (2.2766g, 9.30 mmol, 1 eq.), was added THF (20 ml) and H_2O (10 ml). This was added followed by the addition of LiOH.H_2O (0.6714g, 16.00 mmol, 1.72 eq.). The reaction was allowed to stir for 1.5 hr and was monitored via TLC. On the disappearance of the starting material **52**, the reaction mixture was

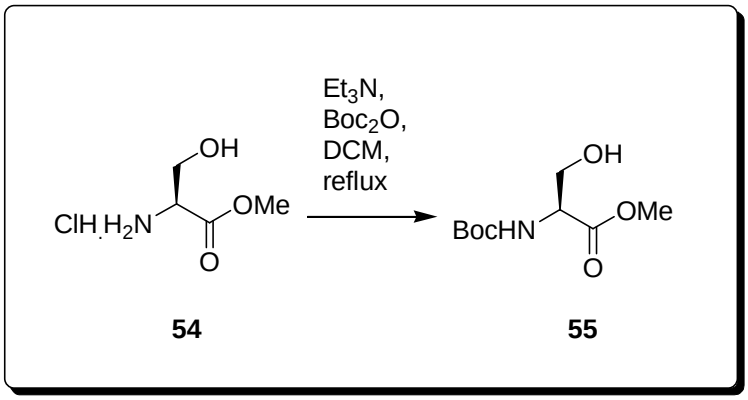
acidified to pH=2 using 1M HCl. The reaction mixture was extracted using ethyl acetate (4 x 30 ml), allowed to stand in anhydrous $MgSO_4$ and concentrated *via vucuo*, affording 2.0860g of **53** with a yield of 97%.

Rf: 0.20 (hexane: ethyl acetate = 2:1).

^{1}H NMR (300MHz, $CDCl_3$) δ 10.10 (s, br, 1H, COO**H**), 6.24 (s, br, N**H**Boc, due to intermediate H exhange), 4.98 (d, br, J = 7.62 Hz, 1H, C**H**NH), 4.30 (d, br, unresolved, 1H, C**H**NH), 1.78-1.49 (m, 3H, C**H**C**H**$_2$CH), 1.43 (s, 9H, OC(C**H**$_3$)$_3$, 0.94 (d, br, J = 6.03 Hz, 6H, (C**H**$_3$)$_2$CH) ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ 178.2 (**C**OOH), 155.7 (**C**OOC(CH$_3$)$_3$), 80.1 (COO**C**(CH$_3$)$_3$), 52.0 (NH**C**H), 41.5 (**C**H$_2$NHCH), 28.3 (COOC(**C**H$_3$)$_3$), 24.8 (**C**H(CH$_3$)$_3$), 22.8 and 21.8 (CH(**C**H$_3$)$_3$) ppm.

HRMS (ESI) Calcd for $C_{11}H_{21}NO_4$, [M^++Na^+]: 254.1368. Found: 254.1369.



Preparation of Boc-protected L-serine methyl ester (55)

To a 50 ml rbf was charged L-serine methyl ester hydrochloride **54** (0.7779g, 5.00 mmol, 1 eq.), CH_2Cl_2 (20 ml) and Et_3N (0.9060 ml, 6.50 mmol, 1.3 eq). Di-tert-butyldicarbonate (1.72 ml, 7.50 mmol, 1.5 eq) was added in one lot and the reaction

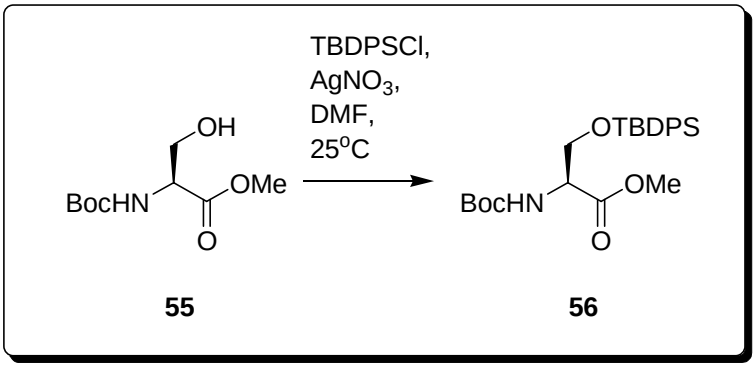
mixture allowed to reflux overnight, up to 20 hr. The reaction was allowed to cool and 1M HCl was added to quench the mixture. The organic layer was washed with NaHCO3, H2O and brine solution and extracted with CH_2Cl_2 (2 x 30 ml). The organic layer was allowed to stand in anhydrous $MgSO_4$ and concentrated *via vacuo*. Flash chromatography afforded 0.8440g of **55** with a yield of 77%.

Rf: 0.35 (hexane: ethyl acetate = 1:1).

^{1}H NMR (300MHz, $CDCl_3$) δ 5.42 (s, br, 1H, N**H**), 4.39 (s, br, 1H, NHC**H**), 3.96-3.91 (m, 2H, C**H**$_2$OH), 3.79 (s, 3H, COOC**H**$_3$), 1.46 (s, 9H, OC(C**H**$_3$)$_3$ ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ 171.4 (**C**OOCH$_3$), 155.8 (**C**OOC(CH$_3$)$_3$), 80.3 (COO**C**(CH$_3$)$_3$), 63.2 (**C**H$_2$OH), 55.7 (NH**C**H), 52.5 (COO**C**H$_3$), 28.2 (COOC(**C**H$_3$)$_3$) ppm.

HRMS (ESI) Calcd for $C_9H_{17}NO_5$, [M^++Na^+]: 242.1004 (100.0%), 243.1038 (9.7%). Found: 242.1002 (100%), 243.1037 (29.18%)



Preparation of TBDPS/Boc-protected L-serine methyl ester (56)

To a 150 ml rbf was charged ester **55** (0.6554g, 3.00 mmol, 1 eq.), N,N-DMF (15 ml) and $AgNO_3$ (1.0193g, 6.00 mmol, 2.0 eq). Tert-butylchlorodiphenylsilane (1.17 ml, 4.50 mmol, 1.5 eq) was added in one lot and the reaction mixture allowed to stir at

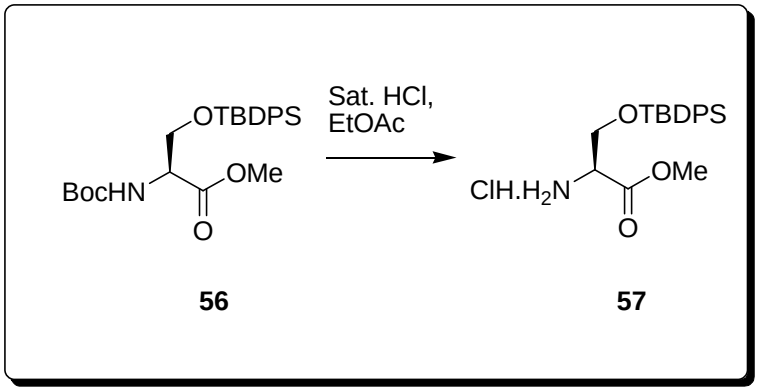
ambient temperature. After the disappearance of the starting material, the organic layer was washed with H_2O (50 ml) and extracted with ethyl acetate (3 x 40 ml). The organic layer was allowed to stand in anhydrous $MgSO_4$ and concentrated *via vacuo*. Flash chromatography afforded 0.8990g of **56** with a yield of 80%.

Rf: 0.80 (hexane: ethyl acetate = 1:1).

^{1}H NMR (300MHz, $CDCl_3$) δ 7.73-7.35 (m, 10H, $(C_6\mathbf{H}_5)_2$), 5.40 (d, J = 8.04 Hz, 1H, N**H**), 4.40 (d, J = 8.82 Hz, 1H, NHC**H**), 4.09-3.87 (m, 2H, C$\mathbf{H}_2$OH), 3.74 (s, 3H, COOC$\mathbf{H}_3$), 1.46 (s, 9H, OC(C$\mathbf{H}_3)_3$, 1.03 (s, 9H, SiC(C$\mathbf{H}_3)_3$ ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ 171.2 (**C**$OOCH_3$), 155.3 (**C**$OOC(CH_3)_3$), 135.5 (OSi**C**(C_5H_5)), 134.8 (OSiC(**C**$_5H_5$)), 129.8 (OSiC(**C**$_5H_5$)), 127.7 (OSiC(**C**$_5H_5$)), 79.9 (COO**C**$(CH_3)_3$), 64.6 (**C**H_2OSi), 55.5 (NH**C**H), 52.2 (COO**C**H_3), 28.3 (COOC(**C**$H_3)_3$), 26.7 (OSiC(**C**$H_3)_3$), 19.2 (OSi**C**$(CH_3)_3$) ppm.

HRMS (ESI) Calcd for $C_{25}H_{35}NO_5Si$, $[M^+ + Na^+]$: 480.2182 (100.0%), 481.2216 (27.0%). Found: 480.2187 (100.0%), 481.2212 (34.48%).



56 **57**

Preparation of TBDPS-protected L-serine methyl ester hydrochloride (57)

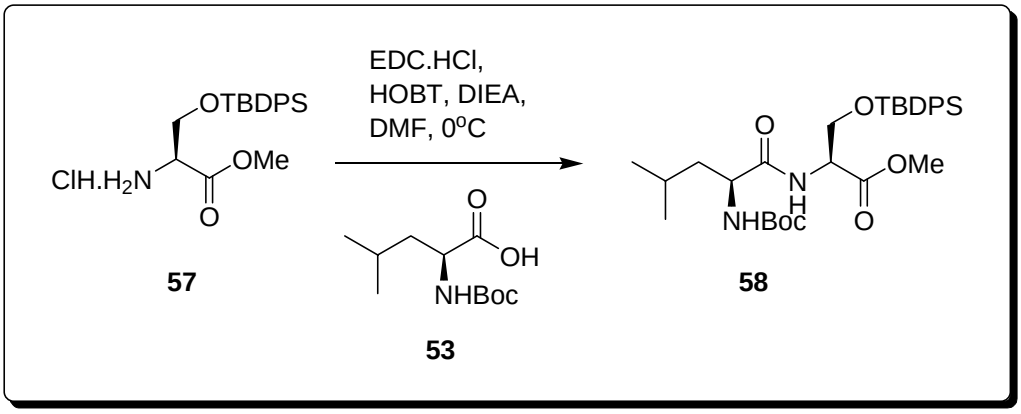
To a 50 ml rbf was charged ester **56** (3.2113g, 7.00 mmol, 1 eq.) and 20 ml ethyl acetate, pre-saturated with HCl (HCl (g) was generated from a saturated stirring solution of NaCl in H_2O, with the slow addition of H_2SO_4. Upon formation of fumes, a tubing was connected to the rbf containing 50 ml of ethyl acetate to allow the fumes to mix with the ethyl acetate. An exhaust was fitted to allow the escape of excess HCl fumes. The ethyl acetate was stirred with the HCl fumes for up top 6 hr.). The reaction mixture allowed to stir at ambient temperature overnight. Saturated Na_2CO_3 was added to the reaction mixture followed by extraction with ethyl acetate (3 x 30 ml). The combined extracts was washed with brine and allowed to stand in anhydrous $MgSO_4$. After concentration *via vacuo*, **57** was afforded a yield of 91% (2.3800g).

Rf: 0.35 (hexane: ethyl acetate = 2:1).

^{1}H NMR (300MHz, $CDCl_3$) δ 7.73-7.34 (m, 10H, $(C_6\mathbf{H}_5)_2$), 4.02-3.90 (m, 2H, $C\mathbf{H}_2OH$), 3.71 (s, 3H, $COOC\mathbf{H}_3$), 3.64 (s, br, 1H, NHC**H**), 1.04 (s, 9H, $SiC(C\mathbf{H}_3)_3$ ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ 173.5 (**C**$OOCH_3$), 135.5 (OSi**C**(C_5H_5)), 134.8 (OSiC(**C**$_5H_5$)), 129.9 (OSiC(**C**$_5H_5$)), 127.7 (OSiC(**C**$_5H_5$)), 65.4 (**C**H_2OSi), 56.0 (NH**C**H), 52.2 (COO**C**H_3), 26.7 (OSiC(**C**$H_3)_3$), 19.3 (OSi**C**$(CH_3)_3$) ppm.

Nominal MS (FAB) Calcd for $C_{20}H_{27}NO_3Si$, [M^+]: 357.18. Found: 358.20.



Preparation of peptide (58)

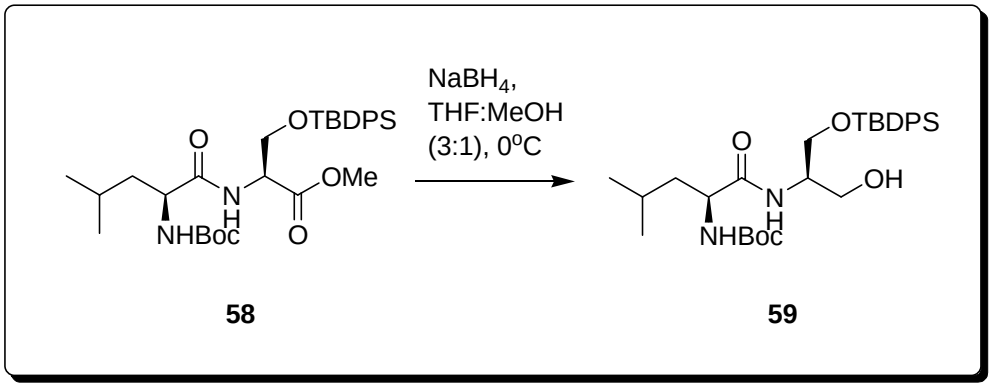
To a 25 ml round bottomed flask (rbf) containing **57** (0.3939g, 1.00 mmol, 1eq), **53** (0.2544g, 1.10 mmol, 1.1 eq), 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDC.HCl) (0.2863g, 1.50 mmol, 1.5 eq) and 1-hydroxy benzotriazole hydrate (HOBT) (0.1486g, 1.10 mmol, 1.1 eq) in N,N-DMF (5 ml) was added N-ethyl diisopropyl amine (DIEA) (0.6 ml, 3.50 mmol, 3.5 eq) dropwise, while maintaining the reaction temperature at 0°C. The reaction was allowed to warm to room temperature and was stirred overnight or for up to 20h. The reaction mixture was then diluted with 10 ml of ethyl acetate and washed with saturated $NaHCO_3$ (20 ml) solution followed by H2O (2 x 10 ml) and brine (30 ml). The organic layer was dried over anhydrous $MgSO_4$. Solvents were removed *in vacuo*. Purification through flash column chromatography afforded **58** (0.5701g , 75% yield).

Rf: 0.43 (hexane: ethyl acetate = 4:1).

^{1}H NMR (300MHz, $CDCl_3$) δ 7.62-7.32 (m, 10H, $(C_6\mathbf{H}_5)_2$), 6.79 (d, J = 7.62 Hz, 1H, N**H**Boc), 4.81 (br, 1H, CON**H**), 4.63 (dt, br, J = 3.00, 8.04 Hz, 1H, NHC**H**), 4.16-4.09 (dt, br, J = 3.51, 12.84, 2H, NHC$\mathbf{H}_2$OSi), 3.89 (dd, J = 3.02, 10.25 Hz, 1H, C**H**NHBoc), 3.73 (s, 3H, COOC$\mathbf{H}_3$), 1.70-1.66 (m, br, 1H, $(CH_3)_2$C**H**), 1.53-1.50 (m, br, 2H, $(CH_3)_2$CHC$\mathbf{H}_2$), 1.45 (s, 9H, OC(C$\mathbf{H}_3)_3$, 1.04 (s, 9H, SiC(C$\mathbf{H}_3)_3$), 0.94 (dd, J = 2.61, 6.21 Hz, 6H, (C$\mathbf{H}_3)_2$CH) ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ 172.3 (**C**OOCH_3), 170.4 (**C**ONH), 155.3 (**C**OOC$(CH_3)_3$), 135.4 (OSi**C**(C_5H_5)), 132.6 (OSiC(**C**$_5H_5$)), 129.8 (OSiC(**C**$_5H_5$)), 127.7 (OSiC(**C**$_5H_5$)), 79.7 (COO**C**$(CH_3)_3$), 64.1 (**C**H_2OSi), 60.2 (NH**C**H), 54.0 (**C**HNHBoc), 52.2 (COO**C**H_3), 41.7 (**C**H_2C$(CH_3)_3$), 28.4 (COOC(**C**$H_3)_3$), 26.6 (OSiC(**C**$H_3)_3$), 24.6 (**C**H$(CH_3)_3$), 19.1 (OSi**C**$(CH_3)_3$) ppm.

HRMS (ESI) Calcd for $C_{31}H_{46}N_2O_6Si$, [M^++Na^+]: 593.3023 (100.0%), 594.3056 (33.5%). Found: 593.3017 (100.0%), 594.3047 (40.52%).



58 **59**

Preparation of (59)

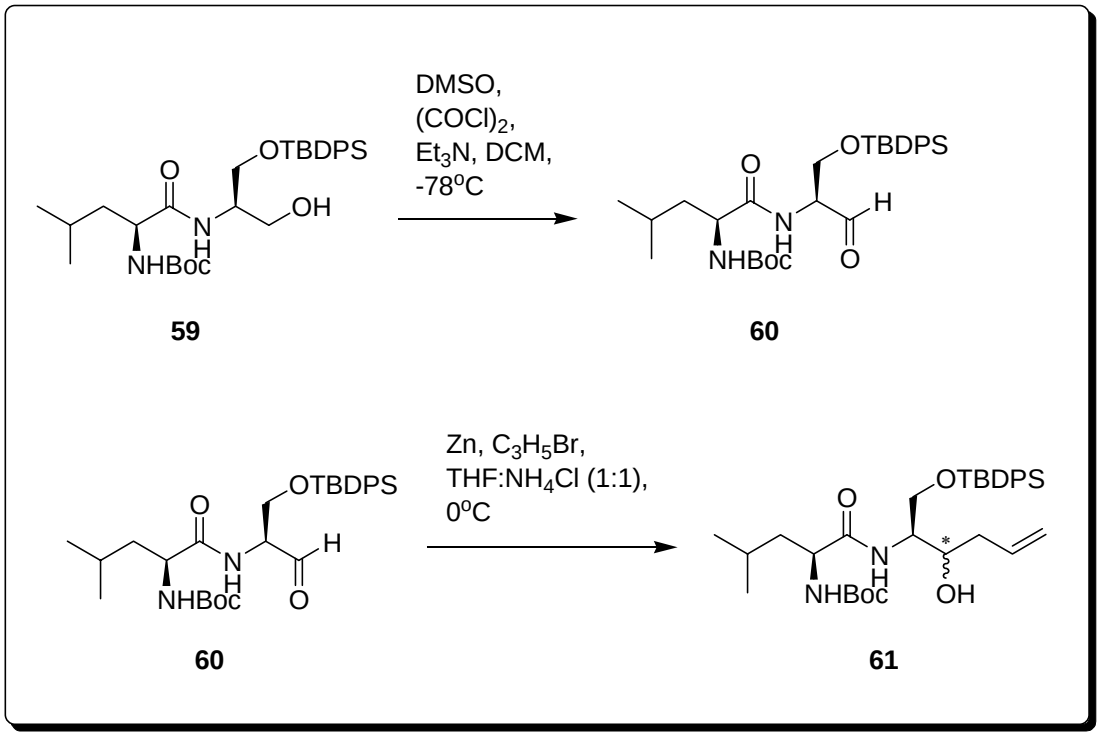
To a solution of **58** (0.5707g, 1.00 mmol, 1 eq) in 9 ml of THF, pro-cooled at 0°C, was added $NaBH_4$ (0.1617g, 4.00 mmol, 4 eq) slowly in several portions. The solution was allowed to stir for 30 minutes before 3 ml of methanol was added dropwise to initiate the reaction. The reaction was allowed to warm to room temperature before allowing to stir overnight. Upon completion of the reaction, the reaction mixture was cooled using an ice bath. 1M HCl was added slowly until all the solids dissolved. The reaction mixture was then extracted with ethyl acetate (3 x 15 ml) and the combined extracts were washed with saturated sodium bicarbonate and dried over anhydrous $MgSO_4$. Solvent was removed *in vacuo*. Purification through flash column chromatography afforded 0.4390g of the desired product **59** with 81 % yield.

Rf: 0.38 (hexane: ethyl acetate = 2:1).

^{1}H NMR (300MHz, $CDCl_3$) δ 7.65-7.36 (m, 10H, $(C_6\mathbf{H}_5)_2$), 6.80 (d, J = 7.62 Hz, 1H, N**H**Boc), 5.15 (br, 1H, CON**H**), 4.00 (br, 1H, NHC**H**), 3.84 (dd, J = 4.21, 10.25 Hz, 2H, NHC$\mathbf{H}_2$OSi), 3.78-3.64 (m, 3H, C**H**C$\mathbf{H}_2$OH), 1.62-1.58 (m, br, 1H, $(CH_3)_2$C**H**), 1.57-1.40 (m, 2H, $(CH_3)_2$CHC$\mathbf{H}_2$), 1.39 (s, 9H, OC(C$\mathbf{H}_3)_3$), 1.06 (s, 9H, SiC(C$\mathbf{H}_3)_3$), 0.89 (dd, J = 2.79, 6.42 Hz, 6H, (C$\mathbf{H}_3)_2$CH) ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ 172.9 (**C**$OOCH_3$), 171.0 (**C**ONH), 155.5 (**C**$OOC(CH_3)_3$), 135.4 (OSi**C**(C_5H_5)), 132.8 ($OSiC($**C**$_5H_5)$), 129.7 ($OSiC($**C**$_5H_5)$), 127.7 ($OSiC($**C**$_5H_5)$), 79.9 (COO**C**$(CH_3)_3$), 62.6 (**C**H_2OSi), 61.8 (NH**C**H), 52.3 (**C**HNHBoc), 41.4 (**C**$H_2C(CH_3)_3$), 28.1 ($COOC($**C**$H_3)_3$), 26.7 ($OSiC($**C**$H_3)_3$), 24.6 (**C**$H(CH_3)_3$), 19.0 (OSi**C**$(CH_3)_3$) ppm.

HRMS (ESI) Calcd for $C_{30}H_{46}N_2O_5Si$, $[M^+ + Na^+]$: 565.3074 (100.0%), 566.3107 (32.4%). Found: 565.3079 (100.0%), 566.3101 (40.80%).



Preparation of homoallylic alcohol (61)

A flame-dried rbf was purged, with nitrogen and charged with CH_2Cl_2 (6 ml) and oxalyl chloride (0.78 ml, 9.00 mmol, 3 eq). The solution was cooled to -78°C and 1.28 ml of DMSO (18.00 mmol, 6 eq) was added dropwise. The solution was allowed to stir for a few minutes before a solution of **59** (0.5420g, 1.00 mmol, 1 eq) in 6 ml of

CH_2Cl_2 was added dropwise. This was followed by the addition of Et_3N (1.25 ml, 9.00 mmol, 9 eq) and the solution stirred for 5 mins at -78°C before being allowed to warm up to room temperature. After reaction completion, water was added to dissolve the solids (25 ml). The aqueous layer was then separated and extracted with CH_2Cl_2 (2 x 30 ml). The combined organic extracts were washed with water (2 x 30 ml), saturated sodium bicarbonate (20 ml), brine (20 ml) and dried over anhydrous $MgSO_4$. Solvent was removed *in vacuo*. The crude α-aminoaldehyde **60** was used immediately in the allylation step without any further purification. (*Note: ^1H and ^{13}C NMR indicates the possible presence of the epimer of the aldehyde.*)

60, *Rf*: 0.83 (hexane: ethyl acetate = 2:1).

^{1}H NMR (300MHz, $CDCl_3$) δ 9.60 (d, J = 6.00 Hz, 1H, C**H**O), 7.75-7.34 (m, 10H, $(C_6\mathbf{H}_5)_2$), 7.08 (d, J = 6.84 Hz, 1H, N**H**Boc), 5.12 (d, br, J = 8.82 Hz, 1H, CON**H**), 4.53 (br, 1H, NHC**H**), 4.22 (dt, J = 2.01, 12.45 Hz, 2H, NHC$\mathbf{H}_2$OSi), 4.18-4.10 (m, 1H, C**H**NHBoc), 1.72-1.61 (m, br, 1H, $(CH_3)_2$C**H**), 1.50-1.41 (m, 2H, $(CH_3)_2$CHC$\mathbf{H}_2$), 1.39 (s, 9H, OC(C$\mathbf{H}_3)_3$), 1.05 (s, 9H, SiC(C$\mathbf{H}_3)_3$), 0.89 (dd, J = 2.42, 3.62 Hz, 6H, (C$\mathbf{H}_3)_2$CH) ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ 198.14 (**C**HO, *198.10, possible epimer*), 173.03 (**C**ONH, *172.99, possible epimer*), 155.4 (**C**OOC$(CH_3)_3$), 135.41 (OSi**C**(C_5H_5), *135.38, possible epimer*), 132.47 (OSiC($\mathbf{C}_5H_5$), *132.29, possible epimer*), 129.98 (OSiC($\mathbf{C}_5H_5$), *129.92, possible epimer*), 127.81 (OSiC($\mathbf{C}_5H_5$), *127.64, 127.45, possible epimer*), 80.0 (COO**C**$(CH_3)_3$), 61.65 (**C**H_2OSi, *62.52, possible epimer*), 60.3 (NH**C**H), 41.5 (**C**H_2C$(CH_3)_3$), 28.25 (COOC(**C**$H_3)_3$, *28.17, possible epimer*), 26.70 (OSiC(**C**$H_3)_3$), *26.66, possible epimer*), 24.7 (**C**H$(CH_3)_3$), 19.1 (OSi**C**$(CH_3)_3$) ppm.

The crude α-aminoaldehyde **60** was dissolved in 10 ml of THF followed by the addition of Zinc powder (0.1308g, 2.00 mmol, 2 eq). The reaction mixture was cooled to 0oC using and ice-bath followed by the addition of 10 ml of 0.3M solution of NH_4Cl followed by the addition of allyl bromide (0.2419g, 2.00 mmol, 2 eq). Upon completion of reaction, 5 ml ethyl acetate was added followed by the dropwise addition of 1N NaOH until the disappearance of the white precipitate. The solution was then extracted with ethyl acetate (3 x 30ml). The combined organic layer was washed with a saturated solution of brine and was dried over anhydrous $MgSO_4$. Solvents were removed *in vacuo*. Purification through flash column chromatography afforded 0.1750g of product **61** as a mixture of isomers which could not be separated, with a yield of 30%.

Rf: 0.63, 0.55 (hexane: ethyl acetate = 2:1).

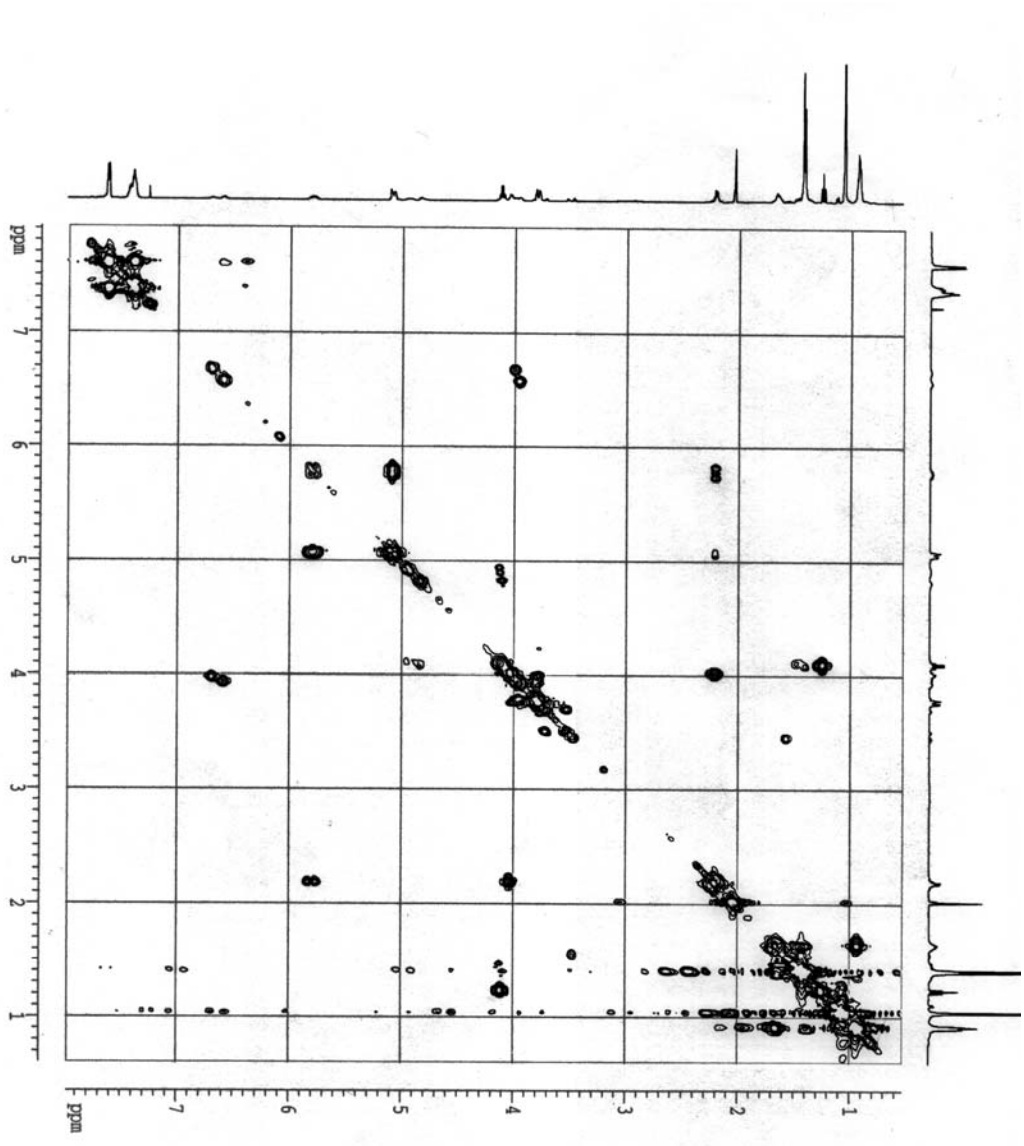
^{1}H NMR (300MHz, $CDCl_3$) δ 7.64-7.36 (m, 10H, $(C_6\mathbf{H}_5)_2$), 6.57 (d, J = 8.82 Hz, 1H, N**H**Boc), 5.80 (m, 1H, **H**C=CH_2), 5.11-5.06 (m, 2H, HC=C**H**$_2$), 4.92-4.79 (m, 1H, NHC**H**), 4.13-3.78 (m, br, 4H, NHC**H**$_2$OSi, CHC**H**OH, NHC**H**CHOH), 2.24-2.19 (m, 2H, C**H**$_2$CH=CH_2), 1.67-1.64 (m, 3H, $(CH_3)_2$C**H**, $(CH_3)_2$CHC**H**$_2$), 1.43 (s, 9H, OC(C**H**$_3)_3$), 1.06 (s, 9H, SiC(C**H**$_3)_3$), 0.94 (dd, J = 2.79, 8.11 Hz, 6H, (C**H**$_3)_2$CH) ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ 172.67 (**C**ONH, *172.60, possible epimer*), 155.4 (**C**OOC$(CH_3)_3$), 135.57 (OSi**C**(C_5H_5), *135.53, possible epimer*), 134.22 (**C**H=CH_2, *134.17, possible epimer*), 132.63 (OSiC(**C**$_5H_5$), *132.60, possible epimer*), 130.1 (OSiC(**C**$_5H_5$)), 127.9 (OSiC(**C**$_5H_5$), 118.08 (**C**H=CH_2, *117.98, possible epimer*), 80.1 (COO**C**$(CH_3)_3$), 71.48 (**C**HOH, *71.16, possible epimer*), 65.67 (**C**H_2OSi, *65.47, possible epimer*), 52.49 (NH**C**H, *52.45, possible epimer*), 41.7 (**C**$H_2C(CH_3)_3$), 38.5 (**C**H_2CH=CH_2), 28.3 (COOC(**C**$H_3)_3$), 26.90 (OSiC(**C**$H_3)_3$, *26.87, possible epimer*),

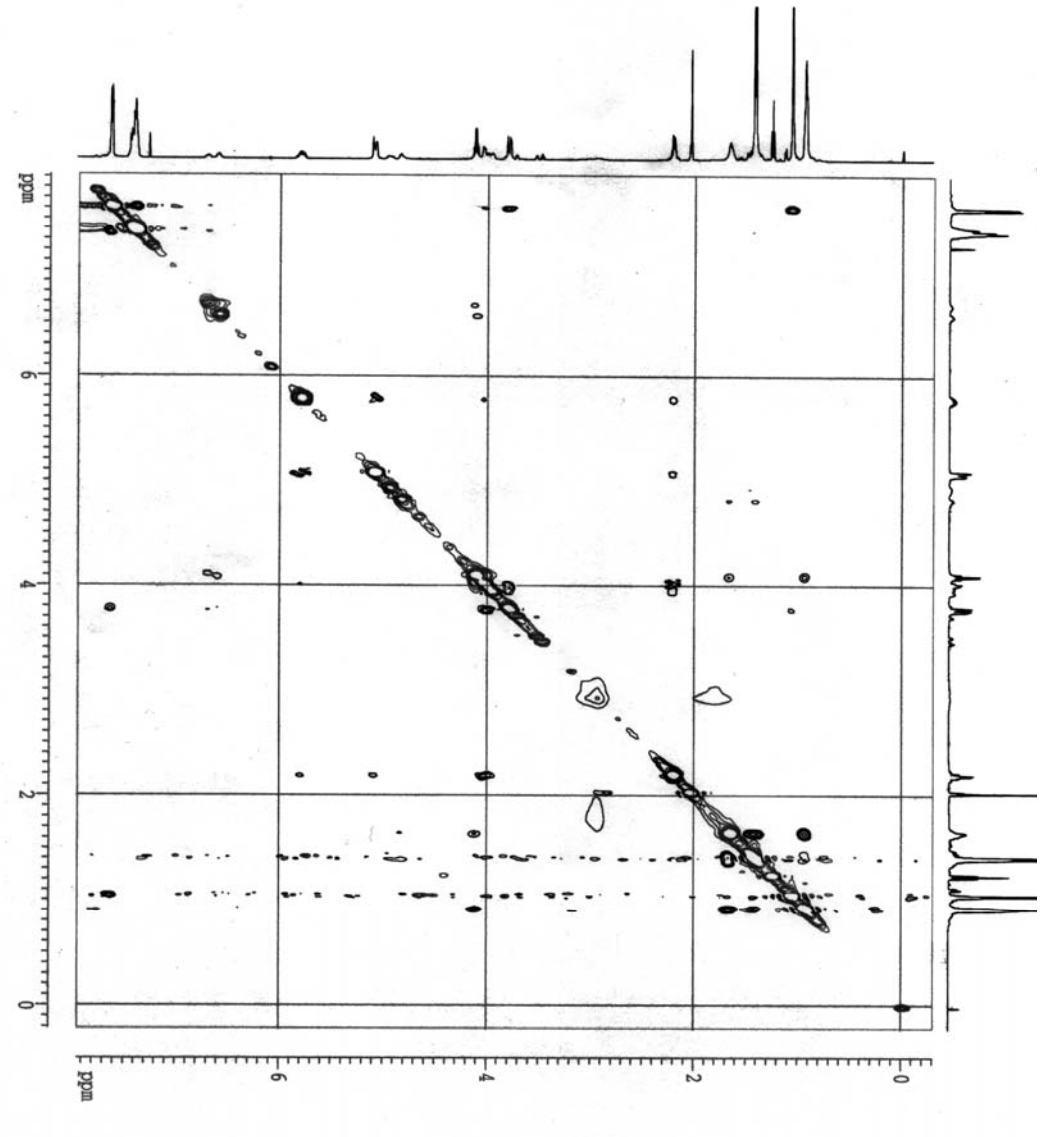
24.85 (**C**H$(CH_3)_3$, *24.75, possible epimer*), 19.17 (OSi**C**$(CH_3)_3$, *19.14, possible epimer*) ppm.

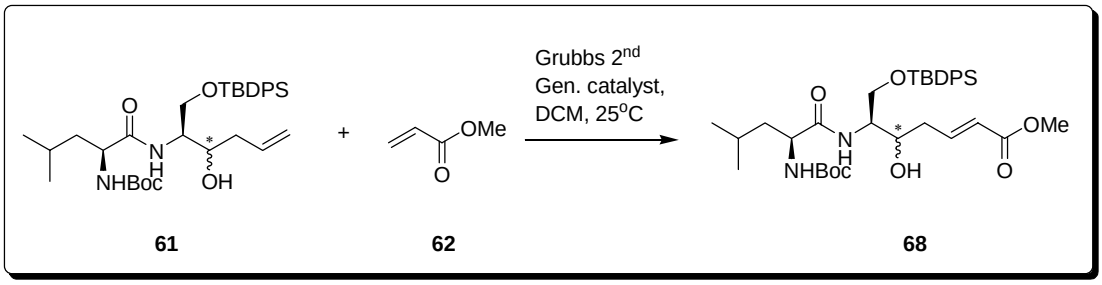
HRMS (ESI) Calcd for $C_{33}H_{50}N_2O_5Si$, $[M^+ + Na^+]$: 605.3387 (100.0%), 606.3420 (35.7%). Found: 605.3391 (100.0%), 606.3425 (42.82%).

COSY spectrum for 61



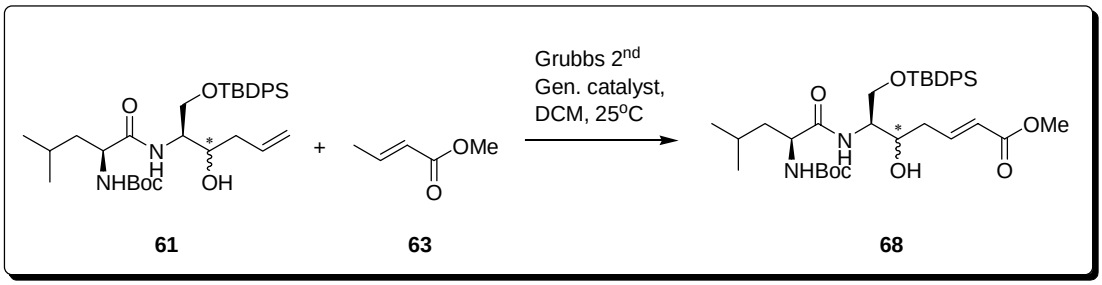
NOESY spectrum for 61





Preparation of olefin metathesis product (68)

To a 25 ml rbf charged with **61** (g, 0.05 mmol, 1 eq) and **62** (g, 0.05 mmol, 1 eq), was added Grubbs 2nd Generation catalyst (g, 5 mol %, 0.05 eq) and CH_2Cl_2 (5 ml). After stirring for 30 mins, another equivalent of Grubbs 2nd Generation catalyst (g, 5 mol %, 0.05 eq) was added and the reaction allowed to stir for 6 hr. Workup of the reaction involved the filtering of the reaction mixture through celite followed by concentration of the reaction mixture via vacuo. Flash chromatography afforded 0.0290g of **68** with a 92% yield as a mixture of unisolable isomers.



Employment of **63** afforded 0.0200g of **68** with a yield of 63%.

Rf: 0.53 (hexane: ethyl acetate = 2:1).

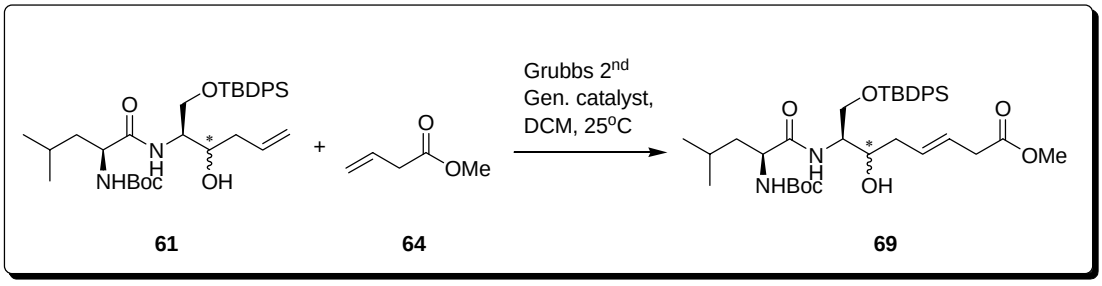
^{1}H NMR (300MHz, $CDCl_3$) δ 7.63-7.38 (m, 10H, $(C_6\mathbf{H}_5)_2$), 7.01-6.90 (m, 1H, $\mathbf{H}C{=}CH_2$), 6.64 (d, J = 8.82 Hz, 1H, N**H**Boc), 5.89 (dd, J = 5.21, 15.65 Hz, 1H,

HC=C**H**COOCH$_3$), 4.81 (d, *J* = 6.03 Hz, 1H, NHC**H**), 3.95-3.74 (m, br, 4H, NHC**H**$_2$OSi, CHC**H**OH, NHC**H**CHOH), 3.68 (s, 3H, COOC**H**$_3$), 2.39-2.28 (m, br, 3H, C**H**C**H**$_2$CH=CH), 1.72-1.58 (m, 3H, (CH$_3$)$_2$C**H**, (CH$_3$)$_2$CHC**H**$_2$), 1.42 (s, 9H, OC(C**H**$_3$)$_3$), 1.06 (s, 9H, SiC(C**H**$_3$)$_3$), 0.93 (dd, *J* = 3.81, 5.82 Hz, 6H, (C**H**$_3$)$_2$CH) ppm.

^{13}C NMR (300MHz, CDCl$_3$) δ 172.8 (**C**ONH), 166.8 (**C**OOCH$_3$), 155.4 (**C**OOC(CH$_3$)$_3$), 144.9 (**C**H=CHCOOCH$_3$), 135.5 (OSi**C**(C$_5$H$_5$)), 132.5 (OSiC(**C**$_5$H$_5$)), 130.0 (OSiC(**C**$_5$H$_5$)), 127.9 (OSiC(**C**$_5$H$_5$), 123.5 (CH=**C**HCOOCH$_3$), 80.2 (COO**C**(CH$_3$)$_3$), 70.8 (**C**HOH), 65.3 (**C**H$_2$OSi), 53.6 (NH**C**H), 52.9 (COO**C**H$_3$), 41.5 (**C**H$_2$C(CH$_3$)$_3$), 36.9 (**C**H$_2$CH=CH$_2$), 28.3 (COOC(**C**H$_3$)$_3$), 26.9 (OSiC(**C**H$_3$)$_3$), 24.8 (CH(**C**H$_3$)$_3$), 22.9 (CH(**C**H$_3$)$_2$), 21.9 (**C**H(CH$_3$)$_2$), 19.1 (OSi**C**(CH$_3$)$_3$) ppm.

FTIR (KBr): 3421, 2959, 2934, 2858, 1711, 1661, 1518, 1428, 1166, 1111, 738, 703 cm^{-1}.

HRMS (ESI) Calcd for C$_{35}$H$_{52}$N$_2$O$_7$Si, [M$^+$+Na$^+$]: 663.3441 (100.0%), 664.3475 (37.9%). Found: 663.3453 (88.58%), 664.3485 (38.95%).



61 **64** **69**

Preparation of olefin metathesis product (69)

To a 25 ml rbf charged with **61** (g, 0.05 mmol, 1 eq) and **64** (g, 0.05 mmol, 1 eq), was added Grubbs 2nd Generation catalyst (g, 5 mol %, 0.05 eq) and CH$_2$Cl$_2$ (5 ml). After

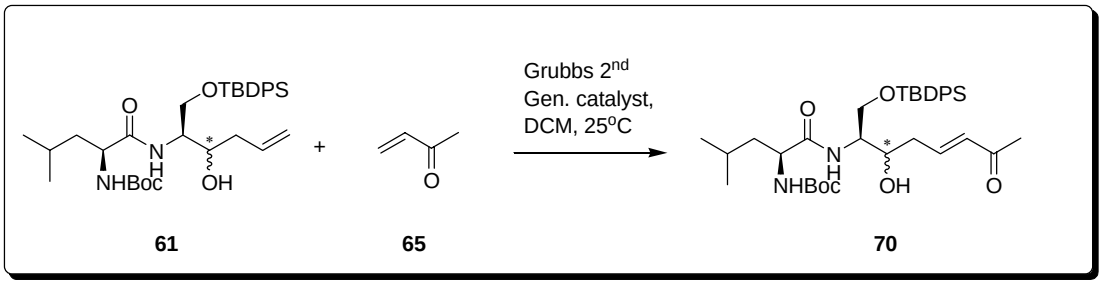
stirring for 30 mins, another equivalent of Grubbs 2nd Generation catalyst (g, 5 mol %, 0.05 eq) was added and the reaction allowed to stir for 6 hr. Workup of the reaction involved the filtering of the reaction mixture through celite followed by concentration of the reaction mixture via vacuo. Flash chromatography afforded 0.0194g of **69** with a 60% yield as a mixture of unisolable isomers.

Rf: 0.45 (hexane: ethyl acetate = 2:1).

^{1}H NMR (300MHz, $CDCl_3$) δ 7.64-7.40 (m, 10H, $(C_6\mathbf{H}_5)_2$), 6.56 (d, br, J = 9.24 Hz, 1H, N**H**Boc), 5.59 (m, 2H, **H**C=C**H**CH_2COOCH_3), 4.89 (br, 1H, NHC**H**), 4.03-3.78 (m, br, 4H, NHC$\mathbf{H}_2$OSi, CHC**H**OH, NHC**H**CHOH), 3.68 (s, 3H, COOC$\mathbf{H}_3$), 3.06 (d, J = 5.22 Hz, 2H, HC=CHC$\mathbf{H}_2$COOCH_3), 2.23-2.17 (m, 2H, C$\mathbf{H}_2$HC=CHCH_2), 1.81-1.55 (m, 3H, $(CH_3)_2$C**H**, $(CH_3)_2$CHC$\mathbf{H}_2$), 1.43 (s, 9H, OC(C$\mathbf{H}_3)_3$), 1.07 (s, 9H, SiC(C$\mathbf{H}_3)_3$), 0.93 (dd, J = unresolved, 6.03 Hz, 6H, (C$\mathbf{H}_3)_2$CH) ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ 172.7 (**C**ONH), 172.3 (**C**OOCH_3), 155.0 (**C**OOC$(CH_3)_3$), 135.6 (OSi**C**(C_5H_5)), 132.6 (OSiC(**C**$_5H_5$)), 130.0 (OSiC(**C**$_5H_5$)), 127.9 (OSiC(**C**$_5H_5$), 125.4 (HC=**C**HCH_2COOCH_3), 80.1 (COO**C**$(CH_3)_3$), 71.84 (**C**HOH), 65.5 (**C**H_2OSi), 52.6 (NH**C**H), 51.8 (COO**C**H_3), 41.8 (**C**H_2C$(CH_3)_3$), 37.9 (HC=CH**C**H_2COOCH_3), 37.2 (**C**H_2HC=CHCH_2), 28.3 (COOC(**C**$H_3)_3$), 26.9 (OSiC(**C**$H_3)_3$), 24.9 (CH(**C**$H_3)_3$), 23.0 (CH(**C**$H_3)_2$), 22.0 (**C**H$(CH_3)_2$), 19.2 (OSi**C**$(CH_3)_3$) ppm.

FTIR (KBr): 3412, 3342, 2956, 2933, 2858, 1736, 1716, 1670, 1513, 1428, 1365, 1166, 1111, 739, 703 cm^{-1}.



61 **65** **70**

Preparation of olefin metathesis product (70)

To a 25 ml rbf charged with **61** (g, 0.05 mmol, 1 eq) and **65** (g, 0.05 mmol, 1 eq), was added Grubbs 2nd Generation catalyst (g, 5 mol %, 0.05 eq) and CH_2Cl_2 (5 ml). After stirring for 30 mins, another equivalent of Grubbs 2nd Generation catalyst (g, 5 mol %, 0.05 eq) was added and the reaction allowed to stir for 6 hr. Workup of the reaction involved the filtering of the reaction mixture through celite followed by concentration of the reaction mixture via vacuo. Flash chromatography afforded 0.0168g of **70** with a 54% yield as a mixture of unisolable isomers.

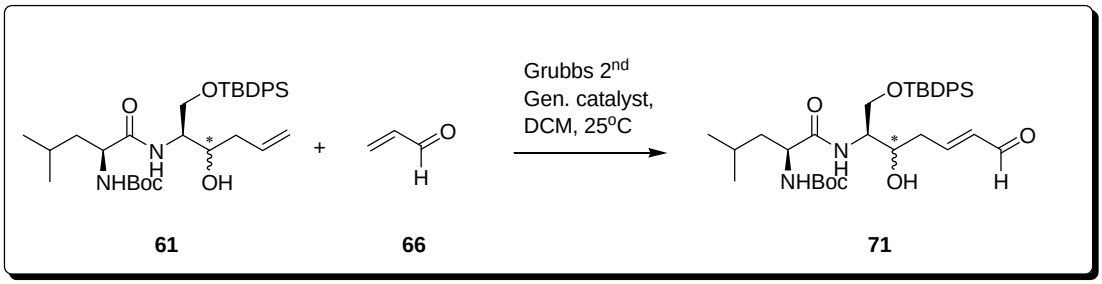
Rf: 0.48 (hexane: ethyl acetate = 2:1).

^{1}H NMR (300MHz, $CDCl_3$) δ 7.63-7.37 (m, 10H, $(C_6\mathbf{H}_5)_2$), 6.80 (dt, J = 7.58, 16.02, 1H, $\mathbf{H}C{=}CHCOCH_3$), 6.68 (d, J = 9.06 Hz, 1H, N**H**Boc), 6.10 (dd, br, J = 4.17, 16.02 Hz, 1H, $HC{=}C\mathbf{H}COCH_3$), 4.78 (br, 1H, NHC**H**), 3.88-3.75 (m, br, 4H, $NHC\mathbf{H}_2OSi$, $CHC\mathbf{H}OH$, $NHC\mathbf{H}CHOH$), 2.38-2.30 (m, br, 2H, $CHC\mathbf{H}_2CH{=}CH$), 2.23 (s, 3H, $COC\mathbf{H}_3$), 1.58-1.73 (m, 3H, $(CH_3)_2C\mathbf{H}$, $(CH_3)_2CHC\mathbf{H}_2$), 1.42 (s, 9H, $OC(C\mathbf{H}_3)_3$), 1.07 (s, 9H, $SiC(C\mathbf{H}_3)_3$), 0.93 (dd, J = 4.19, 5.93 Hz, 6H, $(C\mathbf{H}_3)_2CH$) ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ 198.4 ($\mathbf{C}OCH_3$), 172.9, ($\mathbf{C}ONH$,), 155.5 ($\mathbf{C}OOC(CH_3)_3$), 143.6 ($\mathbf{C}H{=}CHCOCH_3$), 135.6 ($OSi\mathbf{C}(C_5H_5)$), 133.5 ($CH{=}\mathbf{C}HCOCH_3$), 132.5 ($OSiC(\mathbf{C}_5H_5)$), 130.0 ($OSiC(\mathbf{C}_5H_5)$), 127.9 ($OSiC(\mathbf{C}_5H_5)$, 80.4 ($COO\mathbf{C}(CH_3)_3$), 71.3 ($\mathbf{C}HOH$), 65.6 ($\mathbf{C}H_2OSi$), 52.9 ($NH\mathbf{C}H$), 41.5

(**C**H_2C(CH_3)$_3$), 37.1 (**C**H_2CH=CH_2), 28.3 (COOC(**C**H_3)$_3$), 26.9 (OSiC(**C**H_3)$_3$), 24.8 (CH(**C**H_3)$_3$), 22.9 (CH(**C**H_3)$_2$), 21.9 (**C**H(CH_3)$_2$), 19.1 (OSi**C**(CH_3)$_3$) ppm.

FTIR (KBr): 3412, 3353, 2957, 2936, 2859, 1710, 1660, 1518, 1428, 1367, 1167, 1111, 703 cm^{-1}.



61 **66** **71**

Preparation of olefin metathesis product (71)

To a 25 ml rbf charged with **61** (g, 0.05 mmol, 1 eq) and **66** (g, 0.05 mmol, 1 eq), was added Grubbs 2nd Generation catalyst (g, 5 mol %, 0.05 eq) and CH_2Cl_2 (5 ml). After stirring for 30 mins, another equivalent of Grubbs 2nd Generation catalyst (g, 5 mol %, 0.05 eq) was added and the reaction allowed to stir for 6 hr. Workup of the reaction involved the filtering of the reaction mixture through celite followed by concentration of the reaction mixture via vacuo. Flash chromatography afforded 0.0155g of **71** with a 51% yield as a mixture of unisolable isomers.

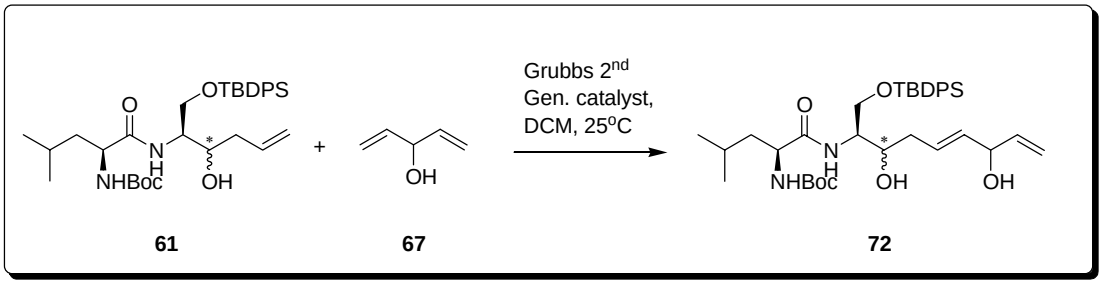
Rf: 0.45 (hexane: ethyl acetate = 2:1).

^{1}H NMR (300MHz, $CDCl_3$) δ 9.53-9.50 (m, 1H, C**H**O), 7.63-7.38 (m, 10H, (C_6**H**$_5$)$_2$), 6.88 (dt, br, *J* = 7.43, 16.05, 1H, **H**C=CHCHO), 6.69 (d, *J* = 8.43 Hz, 1H, N**H**Boc), 6.15 (dd, br, *J* = 8.01, 15.66 Hz, 1H, HC=C**H**CHO), 4.71 (br, 1H, NHC**H**), 4.23-3.71 (m, br, 4H, NHC**H**$_2$OSi, CHC**H**OH, NHC**H**CHOH), 2.54-2.36 (m, br, 2H,

CHC**H**$_2$CH=CHCHO), 1.60-1.73 (m, 3H, $(CH_3)_2$C**H**, $(CH_3)_2$CHC**H**$_2$), 1.44 (s, 9H, OC(C**H**$_3)_3$), 1.08 (s, 9H, SiC(C**H**$_3)_3$), 0.97-0.91 (m, 6H, (C**H**$_3)_2$CH) ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ 193.8 (**C**HO), 172.8, (**C**ONH,), 154.0 (**C**OOC$(CH_3)_3$), 135.6 (OSi**C**(C_5H_5)), 134.9 (CH=**C**HCOCH$_3$), 132.3 (OSiC(**C**$_5H_5$)), 130.2 (OSiC(**C**$_5H_5$)), 128.0 (OSiC(**C**$_5H_5$), 81.0 (COO**C**$(CH_3)_3$), 71.3 (**C**HOH), 65.7 (**C**H$_2$OSi), 52.9 (NH**C**H), 41.3 (**C**H$_2$C$(CH_3)_3$), 37.2 (**C**H$_2$CH=CH$_2$), 28.3 (COOC(**C**H$_3)_3$), 26.9 (OSiC(**C**H$_3)_3$), 24.8 (CH(**C**H$_3)_3$), 21.9 (CH(**C**H$_3)_2$), 21.7 (**C**H$(CH_3)_2$), 19.2 (OSi**C**$(CH_3)_3$) ppm.

FTIR (KBr): 3421, 3357, 2957, 2936, 2858, 1715, 1664, 1511, 1424, 1365, 1166, 1111, 702 cm^{-1}.



61 **67** **72**

Preparation of olefin metathesis product (71)

To a 25 ml rbf charged with **61** (g, 0.05 mmol, 1 eq) and **67** (g, 0.05 mmol, 1 eq), was added Grubbs 2nd Generation catalyst (g, 5 mol %, 0.05 eq) and CH_2Cl_2 (5 ml). After stirring for 30 mins, another equivalent of Grubbs 2nd Generation catalyst (g, 5 mol %, 0.05 eq) was added and the reaction allowed to stir for 6 hr. Workup of the reaction involved the filtering of the reaction mixture through celite followed by concentration of the reaction mixture via vacuo. Flash chromatography afforded 0.0095g of **72** with a 30% yield as a mixture of unisolable isomers.

Rf: 0.30 (hexane: ethyl acetate = 2:1).

^{1}H NMR (300MHz, $CDCl_3$) δ 7.63-7.40 (m, 10H, $(C_6\mathbf{H}_5)_2$), 6.61 (d, J = 8.43 Hz, N**H**Boc), 5.94-5.52 (m, 1H, OHCH**H**C=CH_2), 5.68-5.57 (ddd, br, J = 1.59, 3.62, 17.27, 1H, C**H**=CHCHOHCHHC=CH_2), 5.14-5.09 (dq, J = 1.40, 10.44 Hz, 1H, CH=C**H**CHOHCHHC=CH_2), 4.74 (br, 1H, NHC**H**), 4.57 (br, 1H, CH=CHC**H**OHCHHC=CH_2), 4.13-3.95 m, br, 4H, NHC$\mathbf{H}_2$OSi, CHC**H**OH, NHC**H**CHOH), 3.85-3.71 (m, br, 3H, C**H**C$\mathbf{H}_2$OSi), 3.68-3.60 (m, br, 1H, C**H**OH), 1.72-1.58 (m, 5H, CHC$\mathbf{H}_2$CH=CH, $(CH_3)_2$C**H**, $(CH_3)_2$CHC$\mathbf{H}_2$), 1.43 (s, 9H, OC(C$\mathbf{H}_3)_3$), 1.07 (s, 9H, SiC(C$\mathbf{H}_3)_3$), 0.94-0.92 (m, 6H, (C$\mathbf{H}_3)_2$CH) ppm.

^{13}C NMR (300MHz, $CDCl_3$) δ 172.6, (**C**ONH,), 155.4 (**C**OOC$(CH_3)_3$), 139.5 (CH_2CH=CHCHOH**C**H=CH_2), 135.6 (OSi**C**(C_5H_5)), 134.9 (CH_2**C**H=CHCHOH), 135.1 (CH_2CH=**C**HCHOH), 132.5 (OSiC(**C**$_5H_5$)), 130.0 (OSiC(**C**$_5H_5$)), 127.9 (OSiC(**C**$_5H_5$), 127.0 (CH=**C**HCOOCH_3), 114.9 (CH_2CH=CHCHOHCH=**C**H_2), 80.2 (COO**C**$(CH_3)_3$), 73.5 (CH_2CH=CH**C**HOHCH=CH_2), 71.4 (NHCH**C**HOH), 65.7 (**C**H_2OSi), 52.3 (NH**C**H), 41.6 (**C**H_2C$(CH_3)_3$), 36.9 (**C**H_2CH=CH_2), 28.3 (COOC(**C**$H_3)_3$), 26.9 (OSiC(**C**$H_3)_3$), 24.8 (CH(**C**$H_3)_3$), 23.0 (CH(**C**$H_3)_2$), 21.8 (**C**H$(CH_3)_2$), 19.2 (OSi**C**$(CH_3)_3$) ppm.

FTIR (Neat): 3424, 2956, 2927, 1655, 1517, 1463, 1367, 1296, 1165, 1111, 989, 703 cm^{-1}.

APPENDIX

FORWARD CHEMICAL GENETICS UTILIZING ZEBRAFISH EMBRYO

PHENOTYPE SCREENING OF ZEBRAFISH EMBRYOS

TRANSGENIC ZEBRAFISH SCREENING

A.1. PHENOTYPE AND TRANSGENIC SCREENING OF ZEBRAFISH EMBRYOS. - FORWARD CHEMICAL GENETICS USING ZEBRAFISH EMBRYO (*DANIO RERIO*)[1]

Chemical genetics, in its simplest form, is the systematic use of small molecules as tools for studying complex biological systems.[2] This approach serves as an important complement to bio-chemical and genetic analyses. Small molecules allow rapid, conditional, reversible, selective, and dose-dependent control of biological functions. The zebrafish embryos were generated by natural pairwise matings of wild-type Singapore zebrafish as described by Westerfield.[3, 4]Embryos were screened for developmental defects in structures such as brain, heart, somites, notochord, otoliths etc.[5]

A.2. INFERENCE FROM PHENOTYPE SCREENING OF ANTI-SARS AGENT AG7088 AND ITS FRAGMENTS USING THE ZEBRAFISH EMBRYO

As can be observed from Table 1, we did not observe any phenotypic effects on the zebrafish embryo. This result is expected and not surprising as we suspected that the anti-SARS fragments would most likely have an effect on a similar coronavirus.

[1] Biological testing was conducted by **Ms. Wu Yilain** (Phenotype screening), **Dr. K. N. Sulochana** (Transgenic screening - GFP) and **Dr. Farooq** (Transgenic screening – GFP/RFP) in the Department of Biological Sciences, National University of Singapore.

[2] Mitchison, T. J. *Chem. Biol.* **1994**, *1*, 3-6.

[3] Westerfield, M., *The Zebrafish book: a guide for the laboratory use of the zebrafish (Danio rerio).* Eugene, OR: University of Oregon, Institute of Neuroscience, **1995**.

[4] For the preliminary screening, synchronized developing embryos were collected and aliquoted, three per well, in 96-well plates containing 200 μl of E3 medium[4] supplemented with 40 units of penicillin G and 40 μg of streptomycin (Sigma, USA). Compounds were prepared and diluted to a stock concentration of 3 μM in dimethylsulfoxide (DMSO). 1 μl of the stock solution was added to the embryos at the 16-32 cell stage. Molecules to be tested were prepared with a concentration of ~ 3.000 x 10^{-6} M in DMSO. Control embryos were treated with equivalent amount of DMSO solution. Embryos were incubated at 28.5^{o}C and phenotypic changes were observed using a Zeiss inverted microscope over 1, 2 and 3 days.

[5] Sprague, J.; Doerry, E.; Douglas, S.; Westerfield, M.; *The Zebrafish Information Network (ZFIN): a resource for genetic, genomic and developmental research. Nucleic Acids Res.* **2001,** *29*, 87-90.

A.3. INFERENCE FROM PHENOTYPE AND TRANSGENIC[6, 7] SCREENING OF PHOTOCHROMIC FULGIDES

As can be observed from Table 2 and 3, the fulgides are essentially a class of photochromic molecules that could be potentially used as non-toxic optical media memory as they do not seem to cause any observable phenotypical developmental malformations or defects.

The effects observed from the transgenic screen could indicate the possibility of using fulgides as potential anti-angiogenic molecules that could again be potentially turned 'on' or 'off' according to their open or closed conformations. This would be an avenue for future work in our lab.

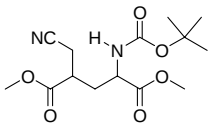
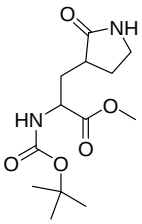
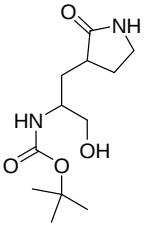
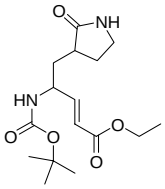
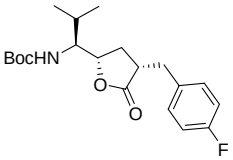
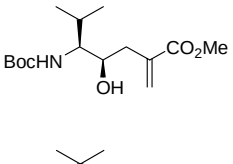
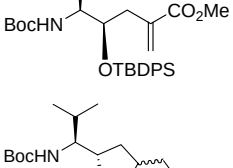
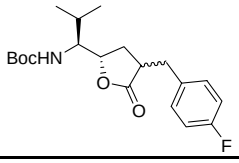
However, we must be aware that small molecules can also cause intrinsic effects like the retardation of blood vessel formation and other effects not observed as yet. This line is currently unpublished, and as such, is the focus of future work from our group.[8]

[6] The samples of the molecules were diluted by 100x, 1000x and 10,000 times in milli Q water. The 96-well plate format was used for this screen. 5-10 embryos were added into each well plate followed by 200 μl of the diluted solution containing the test chemicals. The chemicals were added at the 16 somite stage, as after this stage, the blood vessel system in the zebrafish embryo will be formed. The main aim of addition of the chemicals at this stage is to study the effect the selected chemicals would have on the formation of the blood vessels in the zebrafish embryo. After which, on complete formation of the blood vessels, addition of the chemicals would have no effect on the formation; as the blood vessels would then have already been formed. Embryos were incubated at 28.5^{o}C and at 24 hpf, the formation of intrasomitic vessels were being compared to the control. After every 24 hours the intrasomitic vessels were compared to the control before pictures were taken. Cardiac development related phenotype like cardiac size, blood circulation, cardiac beating, any other abnormalities like cardia edema, etc. were checked in each treated chemical well and were compared to the non-treated control. Similarly, the toxicity of the chemical was judged by the mortality rate compared to the untreated control. For liver formation, a transgenic line was constructed in our lab, which was a triple transgenic line. The blood vessels are under fli-1 promoter expressing the GFP, and GFP was fused to elastase A promoter, so that the pancreas will also express GFP. RFP was fused to LFABP promoter so the liver would also express red fluorescence. The size, presence or absence of liver function can be checked by observing the RFP.

[7] All GFP pictures are taken at approximately 3 dpf unless otherwise stated.

[8] **Dr. K. N. Sulochana** (Transgenic screening - GFP) and **Dr. Farooq** (Transgenic screening – GFP/RFP) in the Department of Biological Sciences, National University of Singapore.

Table 1. Phenotype effects caused by anti-SARS fragments

Structure	Primary effect	Mark day	Lethal day	All general effects	Suspected gene affected	Picture
	-	-	-	No effect	N/A	-
	-	-	-	No effect	N/A	-
	-	-	-	No effect	N/A	-
	-	-	-	No effect	N/A	-
	-	-	-	No effect	N/A	-
	-	-	-	No effect	N/A	-
	-	-	-	No effect	N/A	-
	-	-	-	No effect	N/A	-

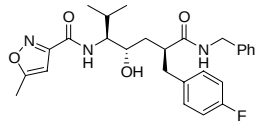
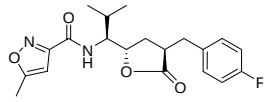
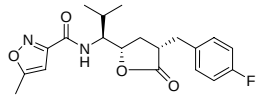
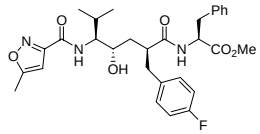
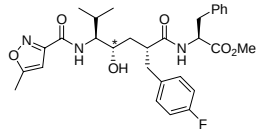
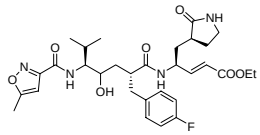
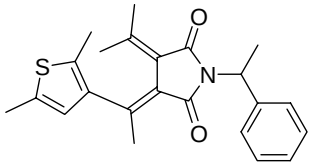
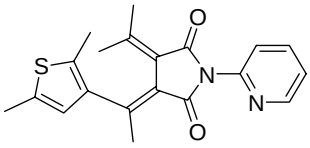
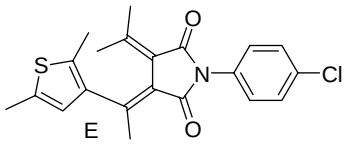
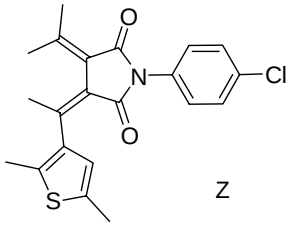
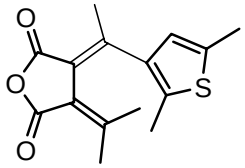
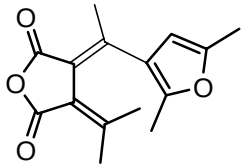
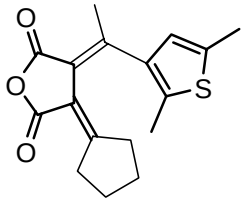
Structure	Primary effect	Mark day	Lethal day	All general effects	Suspected gene affected	Picture
	-	-	-	No effect	N/A	-
	-	-	-	No effect	N/A	-
	-	-	-	No effect	N/A	-
	-	-	-	No effect	N/A	-
	-	-	-	No effect	N/A	-
	-	-	-	No effect	N/A	-

Table 2. Phenotype Screening – Photochromic fulgides

Molecular Structure	Primary effect	Mark day	Lethal day	All general effect	Suspected gene affected	Pictures
	Lethal	1	1	-	*Unknown*	-
	Lethal	1	1	-	*Unknown*	-
	-	-	-	No effect	N/A	-
	-	-	-	No effect	N/A	-
	-	-	-	No effect	N/A	-
	-	-	-	No effect	N/A	-
	-	-	-	No effect	N/A	-

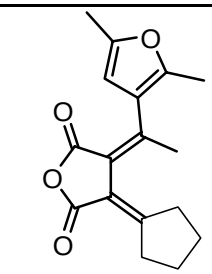
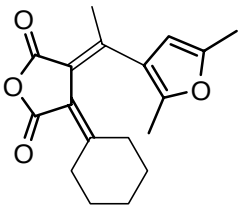
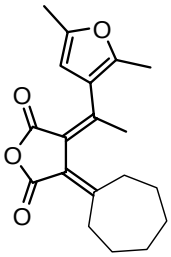
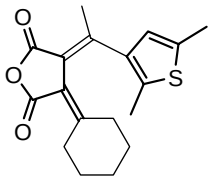
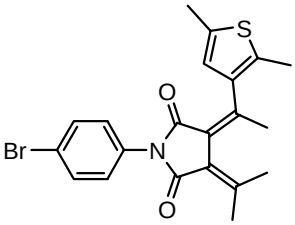
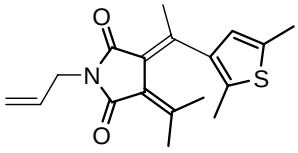
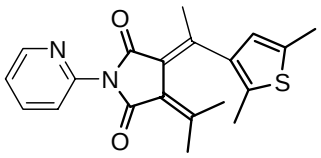
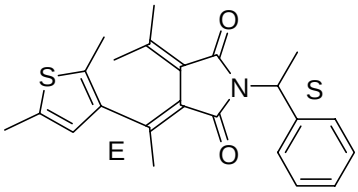
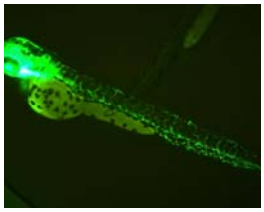
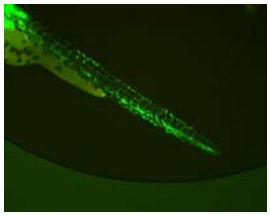
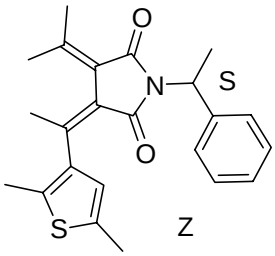
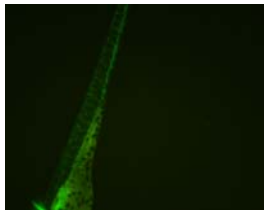
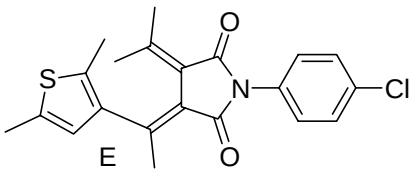
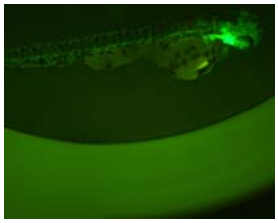
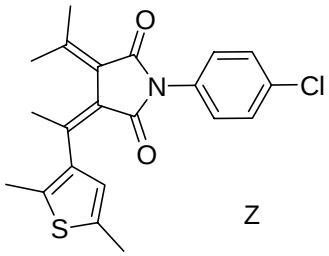
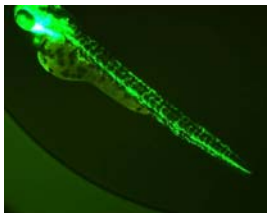
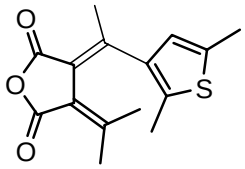
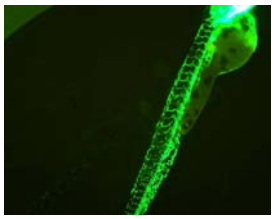
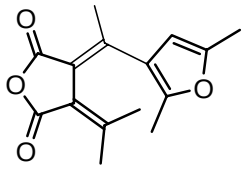
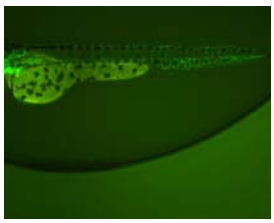
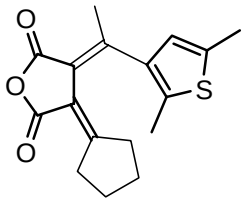
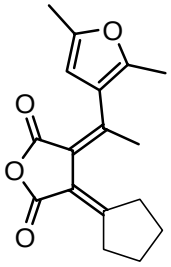
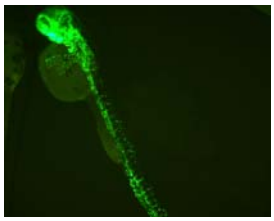
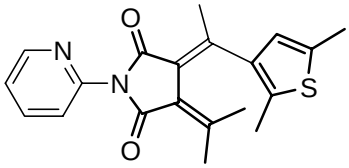
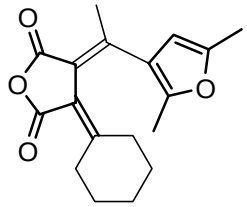
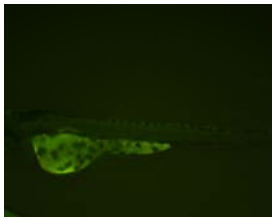
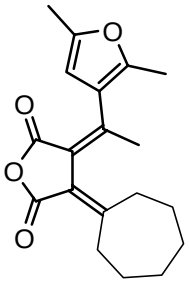
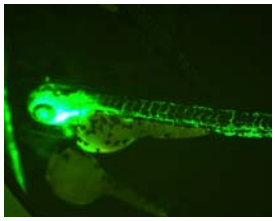
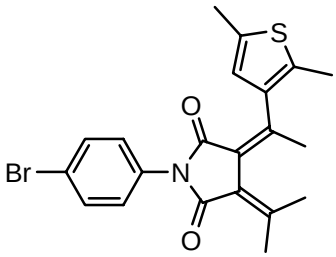
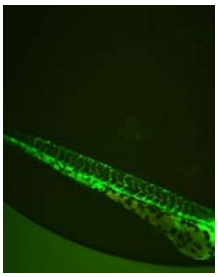
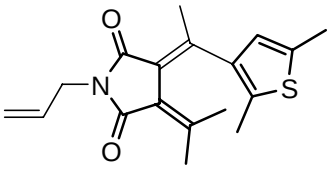
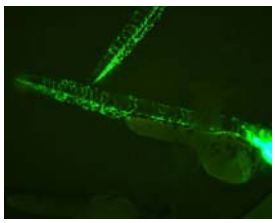
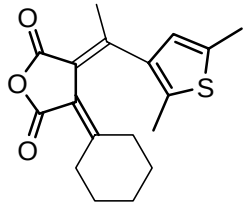
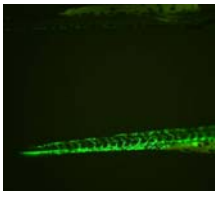
Molecular Structure	Primary effect	Mark day	Lethal day	All general effect	Suspected gene affected	Pictures
	-	-	-	No effect	N/A	-
	-	-	-	No effect	N/A	-
	-	-	-	No effect	N/A	-
	-	-	-	No effect	N/A	-
	-	-	-	No effect	N/A	-
	-	-	-	No effect	N/A	-
	-	-	-	No effect	N/A	-

Table 3. Transgenic Screening – Photochromic fulgides

Molecular Structure	Primary effect	All general effect	Pictures
	ISV change	Slow blood vessel development	 
	ISV change	Sparse blood vessel development	
	Normal development	N/A	
	ISV Over-expression	Abnormal blood vessel development	

Molecular Structure	Primary effect	All general effect	Pictures
	ISV Over-expression	Slow blood vessel development	
	ISV change	N/A	
	ISV change	Anti-angiogenic effect	
	ISV change	Abnormal blood vessel development	
	ISV change	Abnormal development	

Molecular Structure	Primary effect	All general effect	Pictures
	ISV change	Anti-angiogenic effect	
	ISV change	Abnormal development	
	ISV Over-expression	Abnormal development	
	ISV change	Abnormal development	
	ISV change	Abnormal development	

A.4. INFERENCES AND FUTURE WORKS

We have tested a series of molecular fragments from anti-SARS agent AG7088. The screening of a series of photochromic fulgides was also carried out and further tests are required to determine other possible morphological or phenotypical effects these molecules might cause (use of transgenic GFP zebrafish embryos).

Until the target of a given small molecule is identified, it would be difficult to demonstrate conclusively its specificity for that target. However, phenotypic specificity and reproducibility over a broad concentration range are suggestive of high molecular specificity for a given gene product.

Small molecules with poor specificity would be expected to cause a broad range of developmental defects, especially at high concentrations. The results of this study indicate that large-scale developmental screens can identify small molecules that disrupt developmental events with specificity approaching that of genetic mutation. Through careful and creative design of screens, any developmental or clinically relevant process can be studied.

The zebrafish can thus provide a forward genetic approach for assigning function to genes, and positioning them in developmental and/or disease-related pathways.

Publications

1. *Microwave-assisted fulgimide synthesis*; Wei-Woon, Wayne Lee, Leong-Ming Gan, Teck-Peng Loh, The manuscript has been submitted, **2006**.

2. *Total Synthesis and Biological Evaluation of Antillatoxin and Fragments Using Zebrafish Embryo;* Kiew-Ching Lee, Wei-Woon, Wayne Lee, Yi-Lian Wu, Teck-Peng Loh – *Poster Presentation* – Singapore International Chemical Conference-4, Singapore (8 – 10 December, **2005**), The manuscript has been submitted, **2006**.

3. *Cycloalkylidene Fulgides: Synthesis and Comparison of Photochromic Properties*; Wei-Woon, Wayne Lee, Leong-Ming Gan and Teck-Peng Loh – *Oral Presentation* – 3rd International Conference on Materials for Advanced Technologies (ICMAT 2005) and 9th International Conference on Advanced Materials (ICAM 2005); Symposium M: Photonic Materials and Devices, **2005**.

4. *Cycloalkylidene Fulgides: Synthesis and Comparison of Photochromic Properties with selected Fulgimides*; Wei-Woon, Wayne Lee, Leong-Ming Gan, Teck-Peng Loh, *SynLett*; 16, 2473-2477, **2005**.

5. *Synthetic Studies towards anti-SARS Agents: Application of an Indium-mediated Allylation of α-Aminoaldehydes as the Key Step towards an Intermediate*; Shu-Sin Chng, Truong-Giang Hoang, Wei-Woon Wayne Lee, Mun-Pun Tham, Hui-Yvonne Ling and Teck-Peng Loh, *Tetrahedron Letters*, 45, 9501-9504, **2004**.

6. *Cycloalkylidene Fulgides: Synthesis and Comparison of Photochromic Properties*, Wei-Woon, Wayne Lee, Leong-Ming Gan, Teck-Peng Loh, Poster Presentation – IMRE-NUS Chemistry Department Joint Symposium 2004, Singapore (25 November, **2004**)

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