The Development of New Methodologies for the Synthesis of Biologically Active Compounds

A thesis submitted for the degree of

Doctor of Philosophy

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Declaration

I declare that, to the best of my knowledge, the material presented in this thesis represents the result of original work carried out by the author during the period 2017-2021 and has not been presented for examination for any other degree. This thesis is less than 100,000 words in length. Established methodologies have been acknowledged, wherever possible, by citation of the original publications from which they derive.

Madushani Chathurika Kumari Amarasiri

November, 2021

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Finally, I would like to thank my husband, parents, and family for all their help, support, and patience. Specially for comforting me and motivating me to move forward when things were not going well.

Publications

The following publications emerged from the research work undertaken during the course of the author's PhD studies.

1. Khan, F.; Fatima, M.; Shirzaei, M.; Vo, Y.; Amarasiri, M.; Banwell, M. G.; Ma, C.; Ward, J. S.; Gardiner, M. G., Tandem Ullmann–Goldberg Cross-Coupling/Cyclopalladation-Reductive Elimination Reactions and Related Sequences Leading to Polyfunctionalized Benzofurans, Indoles, and Phthalanes. *Organic Letters* **2019,** *21* (16), 6342-6346.

2. Amarasiri, M.; Vo, Y.; Gardiner, M. G.; Poh, P.; Soo, P.; Pavy, M.; Hein, N.; Ferreira, R.; Hannan, K. M.; Hannan, R. D.; Banwell, M. G., The Synthesis and Biological Evaluation of Some C-9 and C-10 Substituted Derivatives of the RNA Polymerase I Transcription Inhibitor CX-5461. *Australian Journal of Chemistry* **2021**, *74* (7), 540-556.

Table of Contents

Abstract

This thesis details the author's research on four research projects, each of which is concerned with the chemical synthesis (CS) of either natural or designed targets that embody carbo- or hetero-cyclic frameworks of relevance in medicinal chemistry.

Chapter One provides an introduction as to how CS is used as a tool for aiding biological and medical (pharmaceutical) research. A summary of the four research projects follows and each of these is then detailed in the subsequent chapters.

Chapter Two is concerned with the synthesis of certain ring-fused *gem*-dihalocyclopropane and their electrocyclic ring-opening for the purposes of constructing new heterocyclic frameworks.

Chapter Three describes the establishment of new methodologies allowing for the synthesis of functionalized benzofurans, indoles and phthalanes. In particular, it describes tandem Ullmann−Goldberg cross-coupling/cyclopalladation-reductive elimination reactions that have been deployed for this purpose.

Chapter Four details the author's efforts to establish a total synthesis of the structurally novel diaryl cycloheptanoid giffonin U, a macrocyclic and biologically active compound recently obtained from the leafy covers of hazelnuts.

The work described in ***Chapter Five*** concerns efforts to establish the cellular targets of the cancer therapeutic agents CX-5461 and PMR-116 by adorning them with suitably located alkynyl residues that could be engaged in click reaction with azides bearing biologically relevant tags.

Chapter Six details all of the experimental protocols and spectral data that underpin the research work described in Chapters Two to Five.

Glossary

AIBN	azobisisobutyronitrile
°C	degrees Celsius
CS	chemical synthesis
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublet of doublets
DIAD	di-*iso*-propyl azodicarboxylate
DIBAl-H	di-*iso*-butylaluminium hydride
DIPEA	di-*iso*-propylethylamine (Hünig's base)
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dt	doublet of triplets
et al.	*et alia* (and others)
g	gram
gem	geminal
h	hour (s)
hept	heptet
HWE	Horner-Wadsworth-Emmons
Hz	Hertz

IR	infrared spectroscopy
J	coupling constant (Hz)
LiHMDS	lithium bis(trimethylsilyl)amide
m	multiplet
M	molarity
m.p.	melting point
m/z	ratio of mass-to-charge
MeOH	methanol
MeCN	acetonitrile
mg	milligram
min	minute(s)
mL	millilitre
mmol	millimole
mol	mole
MS	mass spectrometry
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
NSP	nucleolar surveillance pathway
NSR	nucleolar stress response
ORTEP	oak ridge thermal ellipsoid plot
pH	logarithm of the reciprocal of the hydrogen ion concentration
p-TsOH	*para*-toluensulfonic acid
q	quartet

RiBi	ribosome biogenesis
RPs	ribosomal proteins
rRNA	ribosomal RNA
Pol I	RNA polymerase I
TBAB	tetra-*n*-butylammonium bromide
TEA	triethylamine
TEBAC	benzyltriethylammonium chloride
TfO	trifluoromethanesulfonyl
THF	tetrahydrofuran
TIPS	tri-*iso*-propylsilyl
TLC	thin layer chromatography
v/v	unit volume per unit volume (ratio)
viz.	*videlicit* (that is, namely)
w/v	unit weight per unit volume (%)
δ	chemical shift (parts per million, ppm)
λ_{max}	wavelength (cm^{-1})
µL	microlitre
π	pi (denotes double bond)

Chapter One

1.01 Chemical Synthesis as a Tool for Aiding Biological and Pharmaceutical Research

Chemical synthesis (CS) represents an extraordinarily powerful means for preparing substances of either natural or designed (non-natural) form. As a result, CS, an ever-evolving discipline, has provided a raft of benefits to society including by generating compounds (normally carbon-based) ranging from pharmaceuticals, dyes and cosmetics to agrochemicals. Over the last two centuries, but particularly in recent times, the practitioners of CS have been able, for example, to assemble, *de novo,* some of nature's most intriguing molecular structures for deployment in biology and medicine.[1] This is because the discovery of manifold and sophisticated catalytic reactions together with other synthetic processes has dramatically enhanced the power of CS and such that entirely new forms of organic matter are constructed on a daily basis. The result has been a dramatic enhancement of humankind's capacity to explore chemical space[2] and this has had profound impacts not just in chemistry but also in biology and medicine (**Figure 1.01**).[1]

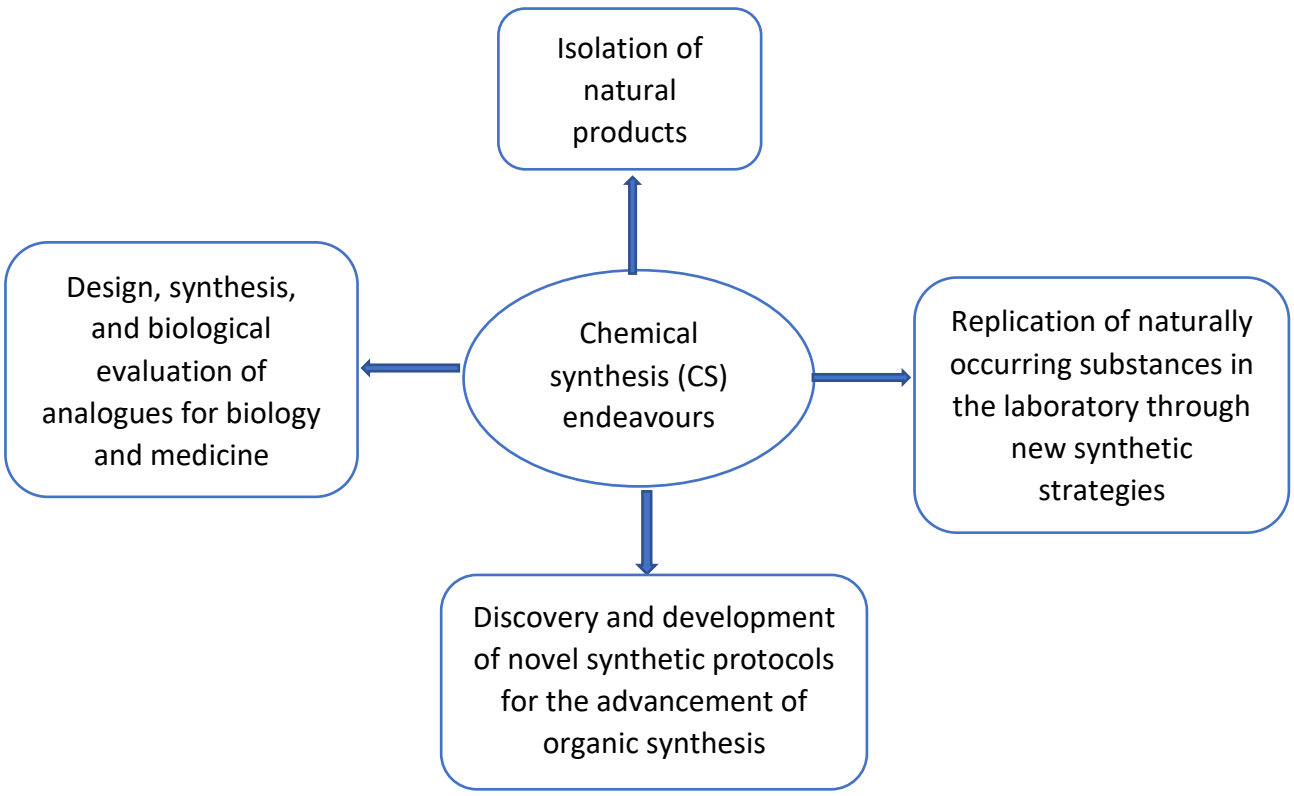


Figure 1.01: *The relationship between chemical synthesis (CS) endeavours and various aspects of chemistry, biology and/or medicine*

1.02 The Chemical Synthesis of Natural Products and Their Analogues

As a follow on from what is now called ethnopharmacology (essentially the study of traditional medicines), the screening of natural product extracts for biological activity and, where appropriate, the isolation of the active compounds is a major activity. It underpins the development of many new drugs and is such a successful endeavour because of, at least in part, the structural and stereochemical diversity encountered amongst natural products, most particularly secondary metabolites.[3] These have often proven to be exceptionally useful in the fragrance, crop science, pharmaceutical and other industries. In many instances, however, the quantities of the compounds of interest available from the natural source(s) are not adequate to allow for their full evaluation and/or their deployment in commercial settings. This is described as the "supply problem" and often can only be addressed by using the techniques of CS. Such is the utility of these techniques that not only can the natural product be prepared at useful scale in the laboratory (or even the manufacturing plant), but otherwise inaccessible analogues and derivatives can also be obtained for the purposes of identifying compounds with superior properties. Of course, there is a synergistic aspect to such activities because as structurally novel natural products are identified, the current techniques of CS are challenged, and new chemical reactions and processes must be (and are) invented.[1,4]

1.03 Chemical Synthesis in the Development of Drug Candidates

CS has been and remains a major driver in the opening stages of the drug discovery process. Indeed, it is indispensable in this setting and has, arguably, underpinned the dramatic improvements in human health over (at least) the past century. New technologies associated with CS continue to emerge as the demand for ever more efficient and sustainable chemical transformations becomes an imperative. In other areas of endeavour, accelerating drug discovery through, for example, the development of combinatorial chemistry has provided new means for more rapidly exploring chemical space. High-throughput, robot-managed synthesis and screening techniques represent other aspects of CS that are being developed as part of such endeavours.[4,5] As always, the development of new chemical transformations is an integral part of such activities and the author's efforts in this area of CS are summarised below.

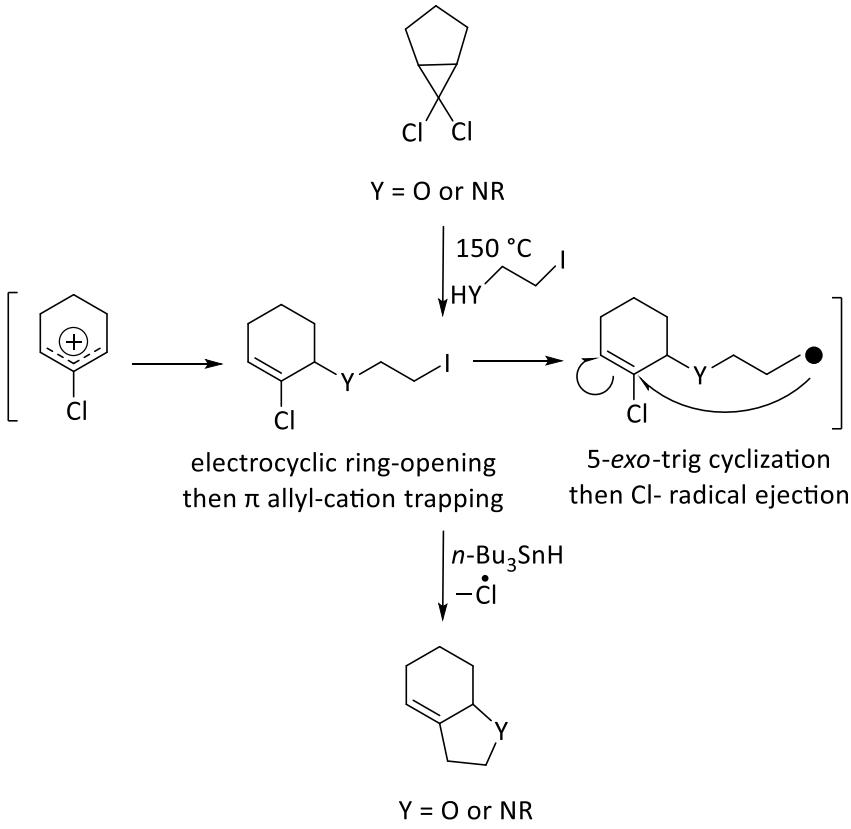
1.04 Overview of the Contents of the Remaining Parts of This Thesis

The author's work described in this thesis has been directed towards the CS of either natural or designed targets that embody privileged carbo- or hetero-cyclic frameworks of relevance in medicinal chemistry.

Chapter Two details work concerned with the CS of heterocycles by exploiting readily available and highly strained *gem*-dichlorocyclopropanes as starting materials. The reaction sequence used involves the following steps (**Scheme 1.01**):

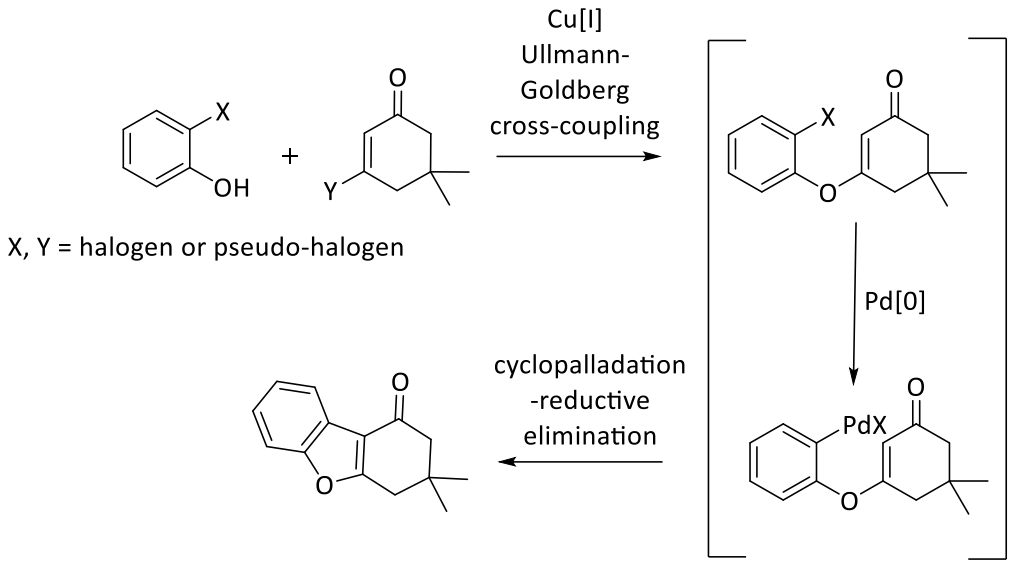
1. A thermally-induced electrocyclic ring-opening of certain ring-fused *gem*-dichlorocyclopropanes;
2. nucleophilic trapping of the π-allyl cation resulting from the electrocyclic ring-opening reaction;
3. engagement of the allylically substituted 1-halocyclohexene formed *via* steps 1 and 2 in a 5-*exo*-trig radical cyclization reaction that establishes the target heterocyclic framework.

The third step allows for the maintenance of the position of the cyclohexenyl double bond in the new ring system. In addition, new and versatile homochiral building blocks can be generated *via* desymmetrising electrocyclic ring-opening reactions using a chiral amine as the trapping nucleophile. The product frameworks are prevalent in bioactive compounds and can thus be considered as important (privileged) structural motifs encountered in various natural products and pharmaceuticals.



Scheme 1.01: *Reaction sequence used for the construction of certain ring systems from* ***gem-dichlorocyclopropane***

The research described in Chapter Three focuses on using a tandem palladium-catalyzed Ullmann–Goldberg coupling/cyclopalladation/reductive elimination sequence (**Scheme 1.02**) to form privileged heterocyclic frameworks bearing some similarities to those shown in **Scheme 1.01**.



Scheme 1.02: *One-pot synthesis of benzofuran via a tandem Ullmann–Goldberg cross-coupling/cyclopalladation–reductive elimination reaction*

This tandem reaction sequence has been applied, as revealed in Chapter Three, to various combinations of either phenols or anilines (as the nucleophilic coupling partners) and β-halogenated-α,β-unsaturated ketones and so affording, in a one-pot process, a range of benzofurans, indoles or phthalanes.

The work described in Chapter Four was directed towards establishing a total synthesis of giffonin U (**Figure 1.02**), a natural product that has been isolated from the leafy covers of hazelnuts. This compound, which embodies unusual stereochemical elements, has not been the subject of any successful total synthesis so far. Three distinct strategies were pursued in efforts to prepare this compound, one being potentially biomimetic in nature.

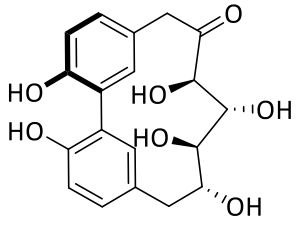
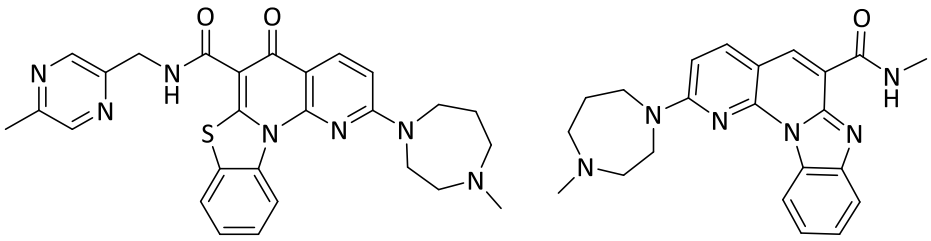


Figure 1.02: *The structure assigned to the diarylheptanoid giffonin U and the target of the work described in Chapter Four*

Chapter Five is concerned with efforts to probe/establish the biological targets of the entirely synthetic compounds CX-5461 and PMR-116 (**Figure 1.03**), these being selective Inhibitors of Polymerase I transcription.



CX-5461 PMR-116

Figure 1.03: *The structures of CX-5461 and PMR-116*

Specifically, it was anticipated that by attaching alkyne residues to these compounds at sites that do not adversely impact activity then these (alkyne units) could be used as the locus for click reactions with azides incorporating biotin or fluorescent tags. The resulting [3+2]-cycloadducts would then be tested against a relevant cell line. If retaining at least some of the activity of the parent compounds, nuclear extracts from cells treated with the biotinylated compounds would be generated and the protein complexes affinity-purified on streptavidin coated beads prior to analysis by standard shotgun proteomics/LC-MS/MS techniques (compared to unlabeled CX-5461 and PMR-116). On the other hand, active adducts incorporating fluorescent groups could be used for imaging purposes and so assist in identifying the subcellular organelles interacting with the CX-5461 and PMR-116 pharmacophores.

Chapter Six, the final one, contains all the experimental procedures related to work described in Chapters Two, Three, Four and Five together with the characterization data for all the new compounds prepared by CS.

1.05 References

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3. (a) Newman, D. J.; Cragg, G. M., *J. Nat. Prod.* **2020**, *83*, 770–803*;* (b) Cragg, G. M.; Newman, D. J., *Biochem. Biophys. Acta, Gen. Subj*. **2013**, 1830*,* 3670-3695; (c) Mishra, B. B.; Tiwari, V. K., *Eur. J. Med. Chem.* **2011**, 46*,* 4769-4807.

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5. (a) Cordier, C.; Morton, D.; Murrison, S.; Nelson, A.; O'Leary-Steele, C., *Nat. Prod. Rep*., **2008**, 25, 719-737; (b) Grabowski, K.; Baringhaus, K. H.; Schneider, G., *Nat. Prod. Rep*. **2008**, 25, 892-904; (c) Vasilevich, N. I.; Kombarov, R. V.; Genis, D. V.; Kirpichenok, M., *A. J. Med. Chem*., **2012**, 55, 7003-7009.

Chapter Two

2.01 An Introduction to Cyclopropanes

Cyclopropane (molecular formula C_3H_6) is the smallest member of the cycloalkane class of hydrocarbon. Its derivatives are encountered in a large number of natural products as well as in pharmaceutical agents.[1] The first synthesis of the parent compound was achieved by August Freund in 1882[2] and in more recent times certain substituted forms have proven to be particularly versatile building blocks in organic synthesis. Cyclopropanes incorporate relatively short C–C bonds (1.51 Å) as well as shorter and stronger C–H bonds relative to those encountered in alkanes. The cyclopropane ring more closely resembles the C-C double bond than the cyclobutane ring: which is a small ring with "double bond character". Furthermore, despite the significant ring strain (27.5 kcal mol^{-1}) incorporated within the three-membered ring, cyclopropanes possess significant kinetic stability and so making them unique amongst carbocyclic compounds.[3] Despite such stability, the notable angular and torsional strain associated these compounds can often be released under controlled conditions in a range of synthetically valuable ring-opening, ring-expansion and/or isomerisation reactions and so leading to new molecular assemblies.[4] Accordingly, the reactions of variously substituted cyclopropanes have provided elegant routes to a diverse range of compounds including antiviral, antibacterial, antifungal and anticancer agents.[5] It is, therefore, fair to say that the study of the chemistry of cyclopropanes is a continuously developing area in chemical synthesis (CS), in medicinal chemistry, in pharmacology and even in materials science.

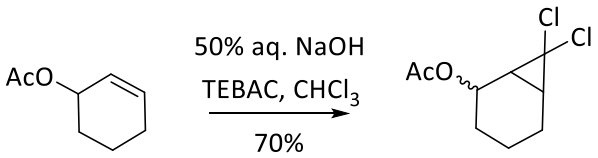
2.02 Synthesis of Dihalocyclopropanes

Dihalocyclopropanes are a particularly important subset of the vast family of cyclopropanes and were first described by Doering and Hoffman in 1954.[6] These researchers showed that dihalocarbene, which can be generated by reacting a haloform and the *tert*-butoxide anion in a non-polar solvent, reacts with an added alkene to afford the title compounds. After 1954, different methods for generating dihalocarbenes were developed. A much more utilitarian means for generating dihalocarbenes was reported by Makosza and Brinker[7, 8] in 1969 that involves the vigorous stirring of the appropriate haloform (normally chloroform or bromoform) containing an alkene with concentrated aqueous sodium hydroxide in the

presence of a phase-transfer catalyst (normally a quaternary ammonium salt). By such means *gem*-dichloro- and *gem*-dibromo-cyclopropanes became readily accessible compounds and, therefore, the subjects of extensive study. As a consequence, and as detailed in the following section, the synthetic utility of such compounds has become increasingly evident. So, for example, they have proven to be valuable precursors to monohalocyclopropanes, poly-substituted cyclopropanes, cyclopropenes, allenes and various heterocyclic ring systems.[9]

2.03 Phase-Transfer Catalysis in the Synthesis of *gem*-Dihalocyclopropanes

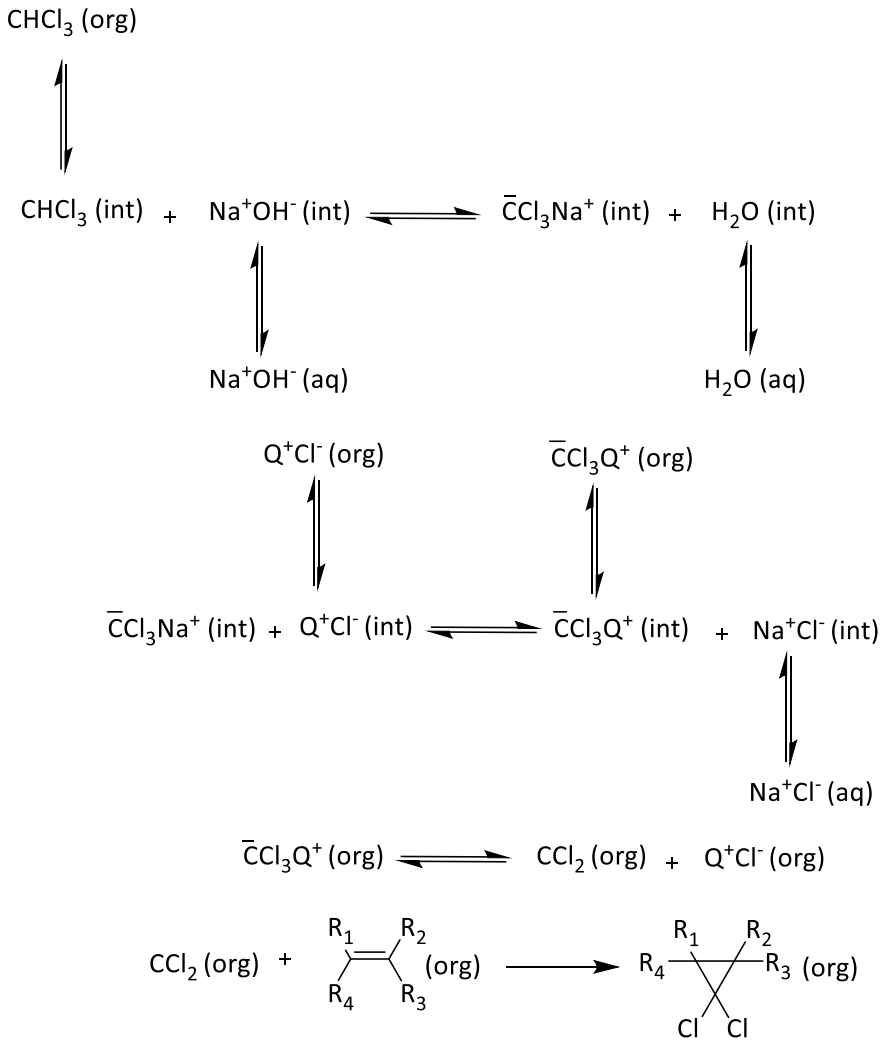
Although several methods are available for the dihalocyclopropanation of alkenes, the most commonly employed method is the one involving phase-transfer catalysis. For example, Banwell[10] has shown (**Scheme 2.01**) that reaction of allylic acetate **2.01** with a combination of chloroform and 50% (w/w) aqueous sodium hydroxide in the presence of a quaternary ammonium salt such as triethylbenzylammonium chloride (TEBAC) affords the *geminally*-dichlorinated cyclopropane **2.02** in 70% yield and as a *ca* 3:2 mixture of diastereoisomers.



2.01 **2.02**

Scheme 2.01: *Phase-transfer-catalyzed synthesis of cyclopropane **2.02** from alkene **2.01** and chloroform*

In the two-phase reaction mixture involved, TEBAC is acting as a phase-transfer catalyst (PTC) and one of the important consequences of this "set-up" is that despite a very high concentration of hydroxide ion being used, no acetate group cleavage is observed. Indeed, the pH of the organic phase is close to neutral. The interfacial reaction mechanism formulated by Makosza in 1974[11] (**Scheme 2.02**) accounts for this very useful result. He suggested that deprotonation of the chloroform occurs in the interfacial region between the chloroform (in which the alkene is dissolved) and the immiscible aqueous NaOH solution. The resulting trichloromethyl anion then associates with the added tetraalkylammonium cation to form a lipophilic ion pair that is transferred into the bulk organic phase. The trichloromethyl anion can then lose a chloride ion to form dichlorocarbene (as well as regenerating the PTC) that adds to the alkene and so forming the *gem*-dichlorocyclopropane.

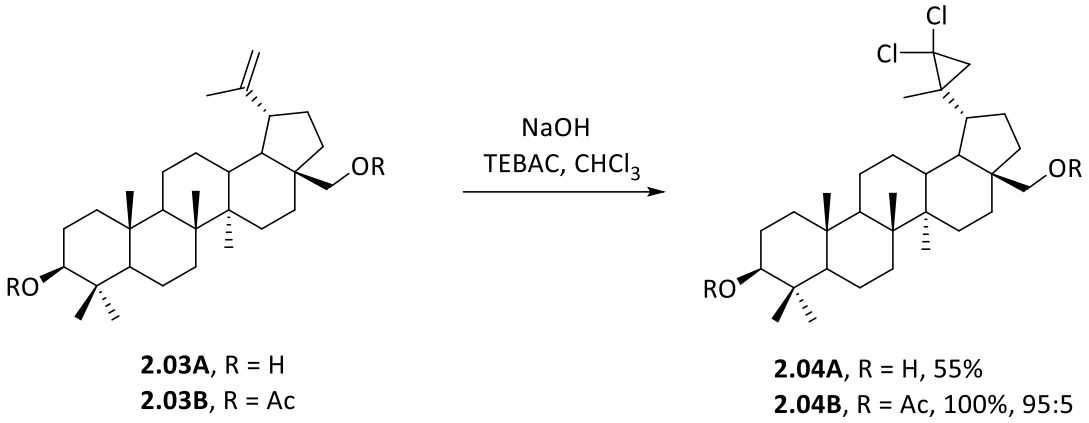


Scheme 2.02: *Makosza's mechanism for the generation of dichlorocarbene under phase transfer conditions from chloroform and its addition to an alkene*

Of course, upon replacing chloroform with bromoform in this type of reaction then the corresponding and sometimes more utilitarian *gem*-dibromocyclopropanes can be obtained. Such reactions can be and often are carried out at relatively large scale.

Given the capacity of halocarbenes to insert into OH bonds, it is often beneficial to protect alcohols as the corresponding esters and thereby increasing the efficiency of the desired cyclopropanation reaction. So, for example, in 2004, Yunusov and co-workers[12] reported that reaction of the triterpene and unsaturated diol betulin (**2.03A**) (**Scheme 2.03**) with dichlorocarbene generated under phase-transfer conditions affords the cyclopropane **2.04A**

in modest yield. In contrast, when diacetate **2.03B** was reacted under analogous conditions then compound **2.04B** was obtained in quantitative yield.

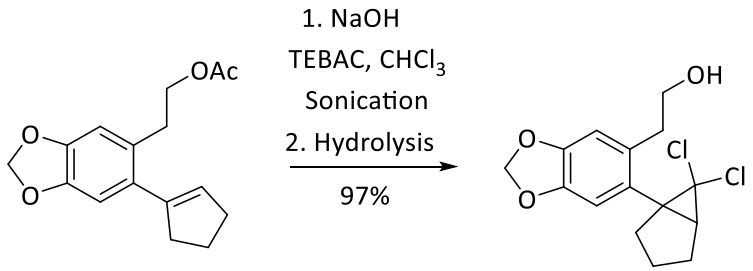


2.03A, R = H
2.03B, R = Ac

2.04A, R = H, 55%
2.04B, R = Ac, 100%, 95:5

Scheme 2.03: *Dichlorocyclopropanation of betulin (**2.03A**) and its diacetate **2.03B** under phase-transfer catalysis conditions*

The utility of the phase-transfer catalysis method for generating dihalocarbenes was further demonstrated by Banwell and co-workers[13] during the course of a synthesis of certain erythrina alkaloids. So, treatment of a chloroform solution of alkene **2.05** (**Scheme 2.04**) with sodium hydroxide under the phase-transfer conditions with accompanying ultra-sonication, as recommended by Xu and Brinker,[8] afforded, after acetate hydrolysis in a subsequent step, the anticipated/required *gem*-dichlorocyclopropane **2.06** in 97% yield.

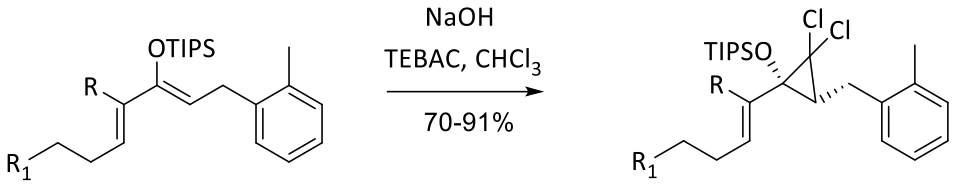


2.05

2.06

Scheme 2.04: *Dichlorocyclopropanation of cyclopentene **2.05** leading to adduct **2.06***

The electrophilic nature of dihalocarbenes sometimes allows for their selective reaction with more electron-rich alkenes in polyunsaturated systems. For example, West and Grant[14] were able to selectively convert, in good yield, the silyoxydienes of the general form **2.07** (**Scheme 2.05**) into the corresponding mono-dichlorocarbene adducts **2.08**.



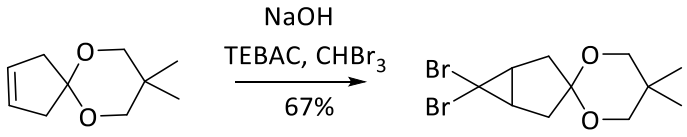
2.07 **2.08**

R = H, Me

R_1 = Ph, 3-MeO-Ph, 4-MeO-Ph, 2-Me-Ph, 2-Br-Ph

Scheme 2.05: *Selective dichlorocyclopropanation of silylenol ethers **2.07** leading to adducts **2.08***

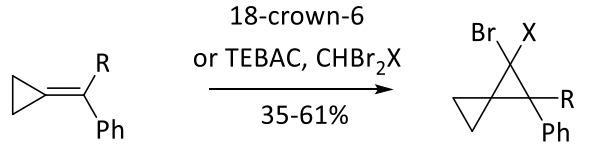
As a general rule, *gem*-dibromocyclopropanes are more reactive, particularly as this applies to ring-opening reactions, than their dichlorinated counterparts and often, therefore, more widely applied in chemical synthesis. Such dibrominated systems are also readily prepared under phase-transfer conditions (but now using bromoform in place of chloroform) as shown, for example, in **Scheme 2.06**.[15] In this instance, cyclopentene **2.09** affords adduct **2.10**, a potential precursor to the alkaloid tazettine.



2.09 **2.10**

Scheme 2.06: *Dibromocyclopropanation of cyclopentene **2.09** leading to adduct **2.10***

The cyclopropanation of alkylidenecyclopropanes **2.11** (**Scheme 2.07**) under phase-transfer conditions has been reported[16] to give dihalospiropentanes of the general form **2.12**. In this instance, 18-crown-6 or TEBAC could be used as the phase-transfer catalyst in conjunction with either bromoform or the "mixed" analogue $CHBr_2X$ where X = F or Cl.



R = Ph, Me, H X = F, Cl, Br

2.11 **2.12**

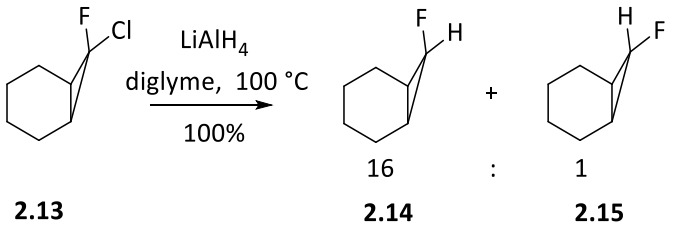
Scheme 2.07: *Synthesis of gem-dihalospiropentanes **2.12***

2.04 The Applications of *gem*-Dihalocyclopropanes in Organic Synthesis

gem-Dihalocyclopropanes can undergo a range of transformations involving either preservation of the three-membered ring or cleavage of it. Notable examples of each of these diverse processes are presented below.

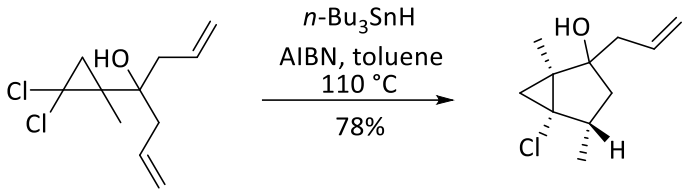
A variety of reagents is capable of removing one or both halogens in *gem*-dihalocyclopropanes. The *cis*/*trans* or *exo*/*endo* ratio of monoreduction products depends on many, usually complex, factors. For example, as shown in **Scheme 2.08**, lithium aluminum hydride[17] can reductively dechlorinate cyclopropane **2.13** and so affording, in quantitative yield, a 16:1 mixture of the monofluoro-cyclopropanes **2.14** and **2.15** in which the former, *endo*- isomer predominates.

Analogous reductions are achieved using alkali metals in protic solvents[18] or tri-*n*-butyltin hydride (in the presence of an initiator such as AIBN).[19] Such protocols are often simpler and more efficient than the direct routes involving addition of a monohalocarbene or the parent carbene to the relevant alkene.



Scheme 2.08: *Reductive dehalogenation of the ring-fused gem-dihalocyclopropane* ***2.13***[20]

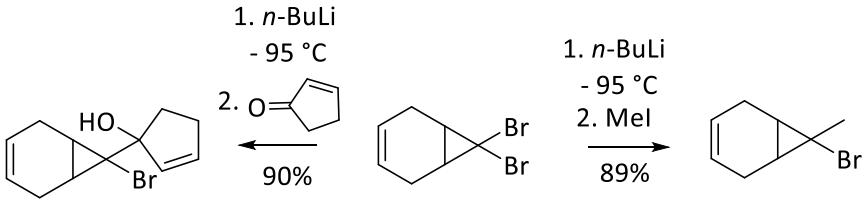
Halocyclopropyl radicals generated by reacting *gem*-dihalocyclopropanes such as **2.16** with tri-*n*-butyltin hydride and AIBN as an initiator, can engage in intermolecular or intramolecular additions[21] to alkenes (**Scheme 2.09**) and so delivering, in the latter case, the corresponding cyclization products (**2.17**).



2.16 **2.17**

Scheme 2.09: *The conversion, via reductive radical cyclization, of cyclopropane **2.16** into the bicyclo[3.1.0]hexane **2.17** [22]*

Metal-for-halogen exchange can occur when *gem*-dihalocyclopropanes are treated with an alkyllithium and thus producing cyclopropylidene lithium halocarbenoids that remain intact at low temperatures and can be intercepted by added electrophiles[23] such as aldehydes, acid chlorides, alkyl halides, trimethylsilyl or stannyl chlorides, carbon dioxide, ketones and iminium salts to form adducts wherein the cyclopropane ring is retained. So, for example, when compound **2.18** (**Scheme 2.10**) is treated with *n*-BuLi at –95 °C and thereafter with either cyclopent-2-en-1-one or methyl iodide then the initially generated lithium bromocarbenoid is trapped to afford, with high diastereoselectivity, the mono-substituted cyclcopropanes **2.19** and **2.20**, respectively.

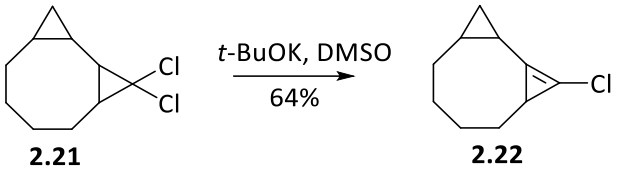


2.19 **2.18** **2.20**

Scheme 2.10: *Conversion of the ring-fused gem-dibromocyclopropane **2.18** into derivatives **2.19** and **2.20** via sequential reaction with n-BuLi then either cyclopent-2-en-1-one or methyl iodide [24]*

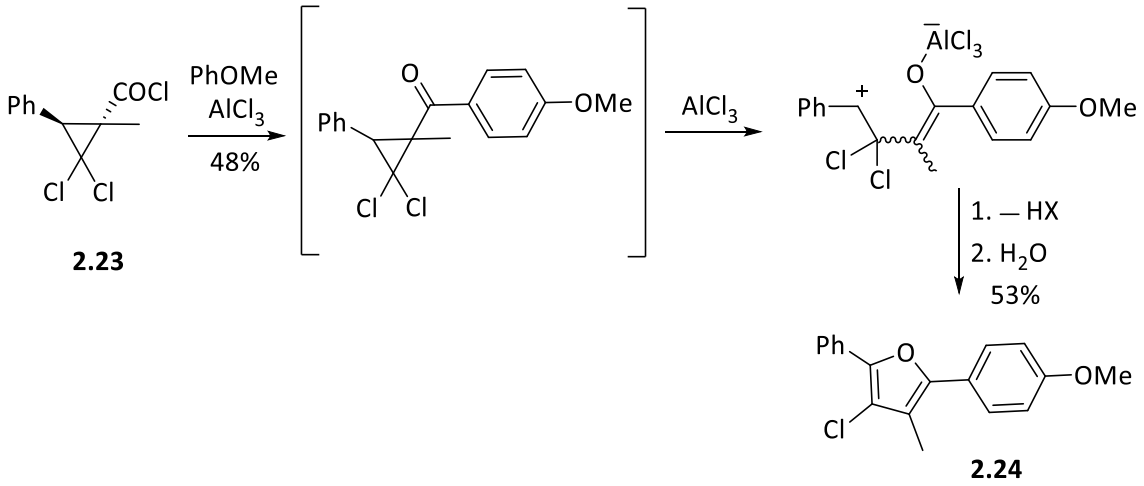
gem-Dihalocyclopropanes can also be transformed, *via* dehydrohalogenation, into the corresponding halocyclopropenes.[25] Depending the method used and the precise structure of these (often) highly strained products, they can be isolated or, more frequently, trapped by an appropriate reagent, often an added diene that results in the formation of a Diels-Alder adduct. In other circumstances they can react further to give a range of distinctive products.[26] The regioselective reaction of *gem*-chlorocyclopropane **2.21** with potassium *tert*-butoxide to

give, in surprisingly good yield, the ring-fused and isolable cyclopropane **2.22** is shown in **Scheme 2.11**.



Scheme 2.11: *The base-induced dehydrochlorination of compound **2.21** leading to cyclopropane **2.22**[27]*

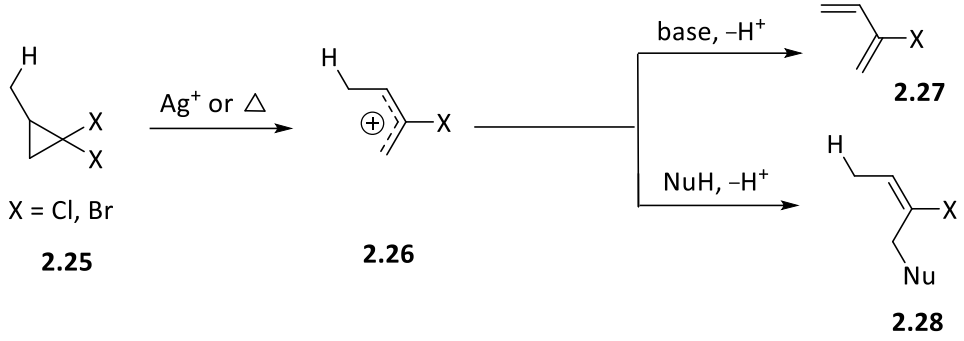
gem-Dichlorocyclopropanes often undergo ring-opening reactions in the presence of Lewis acids such as $AlCl_3$ or $FeCl_3$ to produce the corresponding chloroallyl cation. Those product cations incorporating a pendant nucleophile can then cyclize to give a range of useful products. For example, as shown in **Scheme 2.12**, the acid chloride residue within compound **2.23** can be engaged, in the presence of $AlCl_3$, in a Friedel-Crafts acylation reaction with anisole and with the product so-formed participating in a Lewis acid-promoted ring-opening reaction to afford an allylic cation that itself undergoes a cyclization reaction that ultimately provides the tetra-substituted furan **2.24** in serviceable yield.[28]



Scheme 2.12: *The conversion of the gem-dichlorocyclopropane **2.23** into furan **2.24***

While *gem*-dihalocyclopropanes are strained organic molecules, they also often possess a remarkable kinetic stability. Wang and co-workers found that the formation of a film in a liquid-liquid systems and formation of a crust of a product on the surface of the solid reactant in solid-liquid systems make significant contributions to the observed kinetics.[29] Indeed, the reactivity of *gem*-dihalocyclopropanes can often be considered "orthogonal" to those of most

other functionalities encountered in organic compounds. This derives, in part, from the capacity to engage *gem*-dihalocyclopropanes in thermally-induced electrocyclic ring-opening reactions at an appropriate point in the reaction sequence. Such processes take place in a concerted, disrotatory fashion with concomitant ionization of one of the carbon-halogen bonds to afford an allylic cation as typified by the conversion **2.25** → **2.26** shown in **Scheme 2.13**. The latter species can then be deprotonated by added base to give diene **2.27** or captured by the ejected halide ion (or an added nucleophile), often in a stereo-controlled manner, to give the allylically substituted product **2.28**.[30]

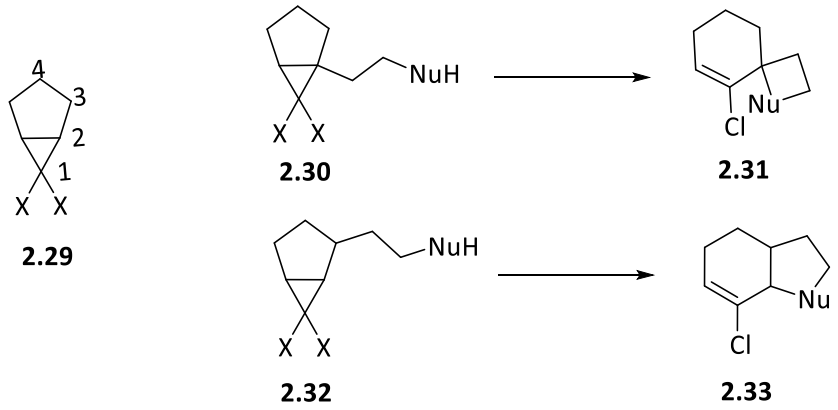


Scheme 2.13: *The electrocyclic ring-opening of the gem-dihalocyclopropane **2.25** leading to the generation of a π-allyl cation **2.26** that can itself form diene **2.27** or the nucleophilic trapping adduct **2.28***

The facility of such conversions is dictated by a range of factors, most notably the nature of the non-halogen substituents attached to the participating cyclopropane. In those instances where the thermal process has too high activation barrier then silver salts such as $AgNO_3$ or $AgBF_4$ can be used to facilitate the necessary abstraction of the halide ion. If the resulting π-allyl cation is unsymmetrical and external nucleophiles are used to trap such species, then mixtures of regioisomeric products are often formed. In contrast, intramolecular nucleophilic trapping is normally a completely regioselective process.

From a synthetic point-of-view, the conversion **2.25** → **2.26** → **2.28** (**Scheme 2.13**) is noteworthy because a mono-functional starting material is converted, in a single chemical operation, into a tri-functional product. Another "value-adding" aspect of this sequence is that product **2.28** can participate in palladium-catalyzed cross-coupling reactions and thereby replacing the halogen with carbon-based groups. The same reaction sequence can also provide a stereo-controlled pathway to tri- or tetra-substituted olefins, compounds that are often difficult to obtain by more conventional methods.[30]

Those *gem*-dihalocyclopropanes, *viz*. 6,6-dihalobicyclo[3.1.0]hexanes, arising from dihalocarbene addition to cyclopentenes are particularly interesting. This is because such adducts readily engage, as a result of their inherent strain, in ring-opening reactions to deliver functionalized and synthetically valuable cyclohexenes. The electrocyclic ring-opening reaction necessarily involves departure of the *endo*-disposed halogen in concert with cleavage of the cyclopropane sigma bond common to the two rings and such that a ring-expanded and *cis*-configured π-allyl cation is formed. There are, within the bicyclo[3.1.0]hexane framework, four distinct positions, as shown in structure **2.29** (**Scheme 2.14**), to which tethered nucleophiles can be attached when intramolecular trapping of the derived π-allyl cation is a process of interest. So, for example, reaction of derivative **2.30** should deliver, through loss of HX, a spirocyclic product (**2.31**) while analogous reaction of isomer **2.32** would generate the more conventionally annulated compound **2.33**. In each instance, the tethered nucleophile would be expected to attack the proximate rather than the remote terminus of the intermediate π-allyl cation because the latter pathway would generate anti-Bredt products.[30]

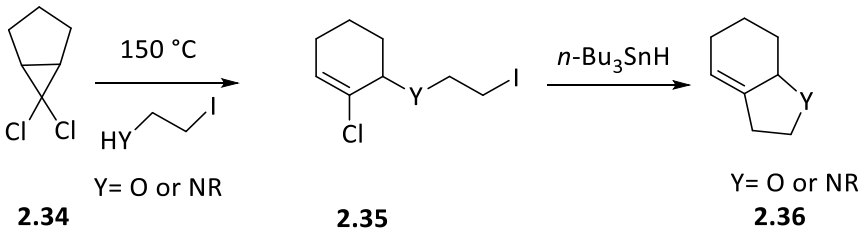


Scheme 2.14: *The products of tandem electrocyclic ring-opening/intramolecular trapping of gem-dihalocyclopropanes bearing differentially positioned, tethered nucleophiles*

2.05 Proposed Reaction Scheme for the Construction of Certain New Mono- and Poly-Cyclic Ring Systems

The major thrust of the author's research on the chemistry of *gem*-dihalocyclopropanes was concerned with exploring the utility (or otherwise) of the two-step reaction sequence shown, in general terms, in **Scheme 2.15**. Specifically, it was anticipated that thermolysis of compounds such **2.34** in the presence of 2-iodoethanol or an amino equivalent should deliver

the ring-expanded/nucleophilic capture product **2.35**. Furthermore, and based on the precedent detailed below, treatment of the latter compound with tri-*n*-butyltin hydride (*n*-Bu_3SnH) should generate the corresponding hexahydrobenzofuran **2.36**. This second step was expected to start with homolysis of the C-I bond in substrate **2.35** and the resulting primary radical then adding in a 5-*exo*-trig fashion to the attached chloroalkene. The secondary radical so-formed would collapse, through ejection of a chlorine radical, to form product **2.36** in which the double-bond is located at the ring-junction. Depending on the nature of *gem*-dichlorocyclopropane involved, the nature of the nucleophile used, and length of the tether between the nucleophile-bearing and iodinated centres various carbo- and/or hetero-cyclic systems would be obtained.



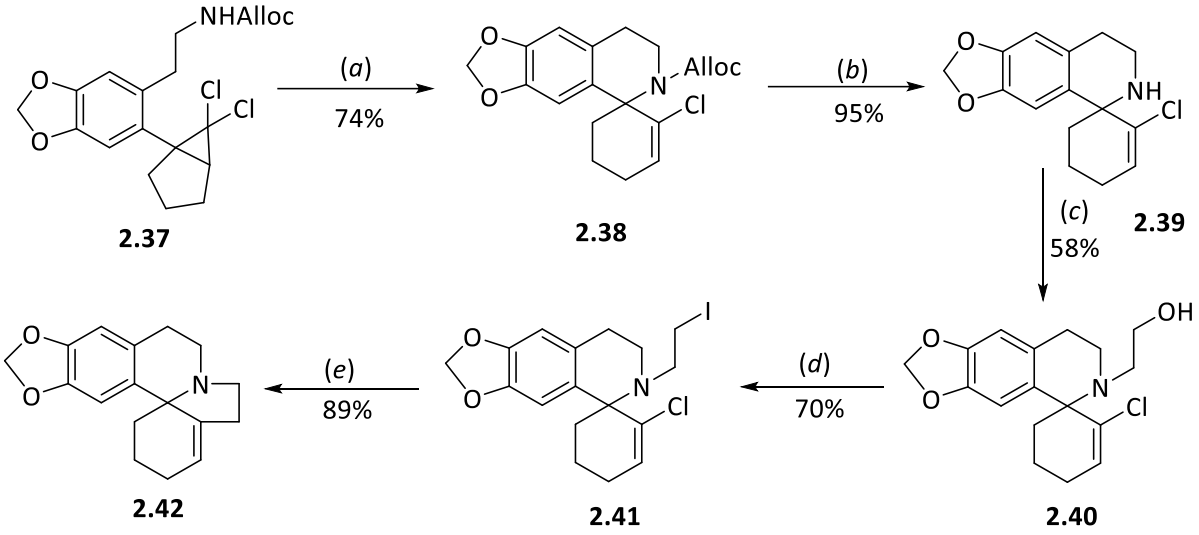
Scheme 2.15: *Example of* a *synthetic strategy for preparing various carbo- and hetero-cyclic frameworks from ring-fused gem-halocyclopropanes such as* ***2.34***

2.06 Precedent for the Proposed Synthetic Plan

In 2006, and in a precedent for the synthetic plan detailed above, Banwell and co-workers reported[31] the concise preparation of the framework of the erythrina alkaloids using a spirocyclization process initiated by the Ag(I)-promoted electrocyclic ring-opening of a ring-fused *gem*-dichlorocyclopropane, trapping of the resulting π-allyl cation by a tethered nitrogen nucleophile followed by a C-radical addition/halide radical elimination process. Specifically, and as shown in **Scheme 2.16**, treatment of the conjugate base of compound **2.37** with silver tetrafluoroborate resulted an electrocyclic ring-opening, intramolecular nucleophilic trapping sequence to afford the spirocyclic compound **2.38**.

Removal of the Alloc group within this product under standard conditions and reaction of the product piperidine **2.39** with an excess of ethylene oxide then gave the amino alcohol **2.40** that was converted, under standard conditions, into the corresponding iodide **2.41**. In the second pivotal and final step of the synthesis, a toluene solution of iodide **2.41** was reacted with *n*-Bu_3SnH in the presence of a trace of AIBN (a free radical initiator) and so effecting the

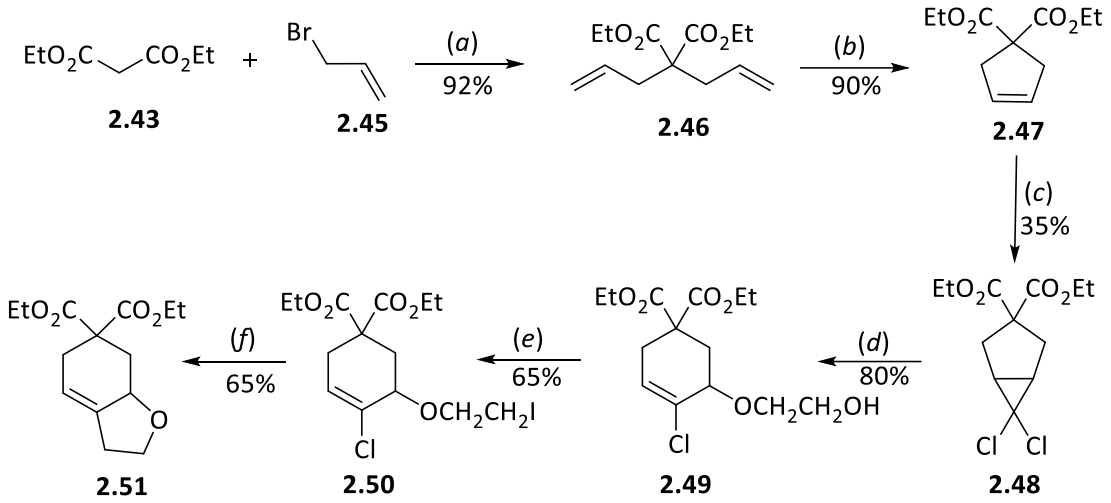
type of radical cascade described above and thereby generating the target compound **2.42** in 89% yield.



Scheme 2.16: *Reagents and Conditions* (*a*) LiHMDS, THF, –40 to 0 °C, 0.66 h, $AgBF_4$, 0 to 18 °C then 45 °C, 3 h; (*b*) Pd[0], dimedone, THF, 18 °C, 16 h; (*c*) ethylene oxide, MeOH, 45 °C, 24 h; (*d*) PPh_3, I_2, imidazole, toluene, 18 °C, 16 h; (*e*) *n*-Bu_3SnH, AIBN, toluene, 80 °C, 3.5 h

2.07 Proof of Concept: Facile Preparation of a Hexahydrobenzofuran

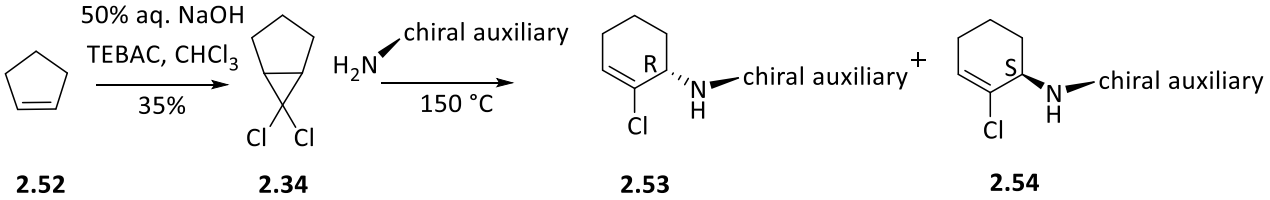
The author's efforts to implement the synthetic strategy outlined above towards benzofurans (**Scheme 2.15**) is shown in **Scheme 2.17**. To begin, diethyl malonate (**2.43**) was subjected to a base-promoted diallylation reaction using allyl bromide (**2.45**) and the product diene **2.46** subjected to ring-closing metathesis and so producing the cyclopentene **2.47**. Dichlorocarbene generated under phase transfer condition then added to this olefin and so producing the targeted ring-fused cyclopropane **2.48** albeit in just 35% yield. All the spectral data acquired on this compound were in complete accord with the assigned structure. Thermolysis of a solution of compound **2.48** in ethylene glycol at elevated temperatures then gave the anticipated ring-expanded/nucleophilic capture product **2.49** that was converted into the corresponding iodide **2.50** by subjecting the readily derived mesylate to a Finkelstein reaction. Treatment of the product iodide **2.51** with *n*-Bu_3SnH resulted, *via* the radical pathway described above, in the formation of the hexahydrobenzofuran **2.51** in 65% yield. Once again, all the spectral data recorded on this compound were entirely consistent with the illustrated structure.



Scheme 2.17: *Reagents and Conditions* (*a*) NaH, THF, reflux, 1 h; (*b*) Grubbs' (II) cat., DCM, reflux, 2 h; (*c*) 50% (w/w) aq. NaOH, TEBAC, $CHCl_3$, 16 h; (*d*) ethylene glycol, 150 °C, 16 h; (*e*) methanesulfonyl chloride, TEA, DCM, 30 min then NaI, acetone, reflux, 16 h; (*f*) *n*-Bu_3SnH, AIBN, toluene, 80 °C, 3.5 h

2.08 Ring-Opening of C_2-Symmetric *gem*-Dihalocyclopropanes and Trapping the Product π-Allyl Cations with Homochiral Amines

The ring-opening/nucleophilic trapping step **2.48** → **2.49** shown in **Scheme 2.17** affords a racemic product (**2.49**) and so the final compound (**2.51**) associated with this sequence is also racemic. In an effort to establish a means of adapting such chemistry to the preparation of homochiral products the implementation of the reaction sequence outlined in general terms in **Scheme 2.18** was contemplated.

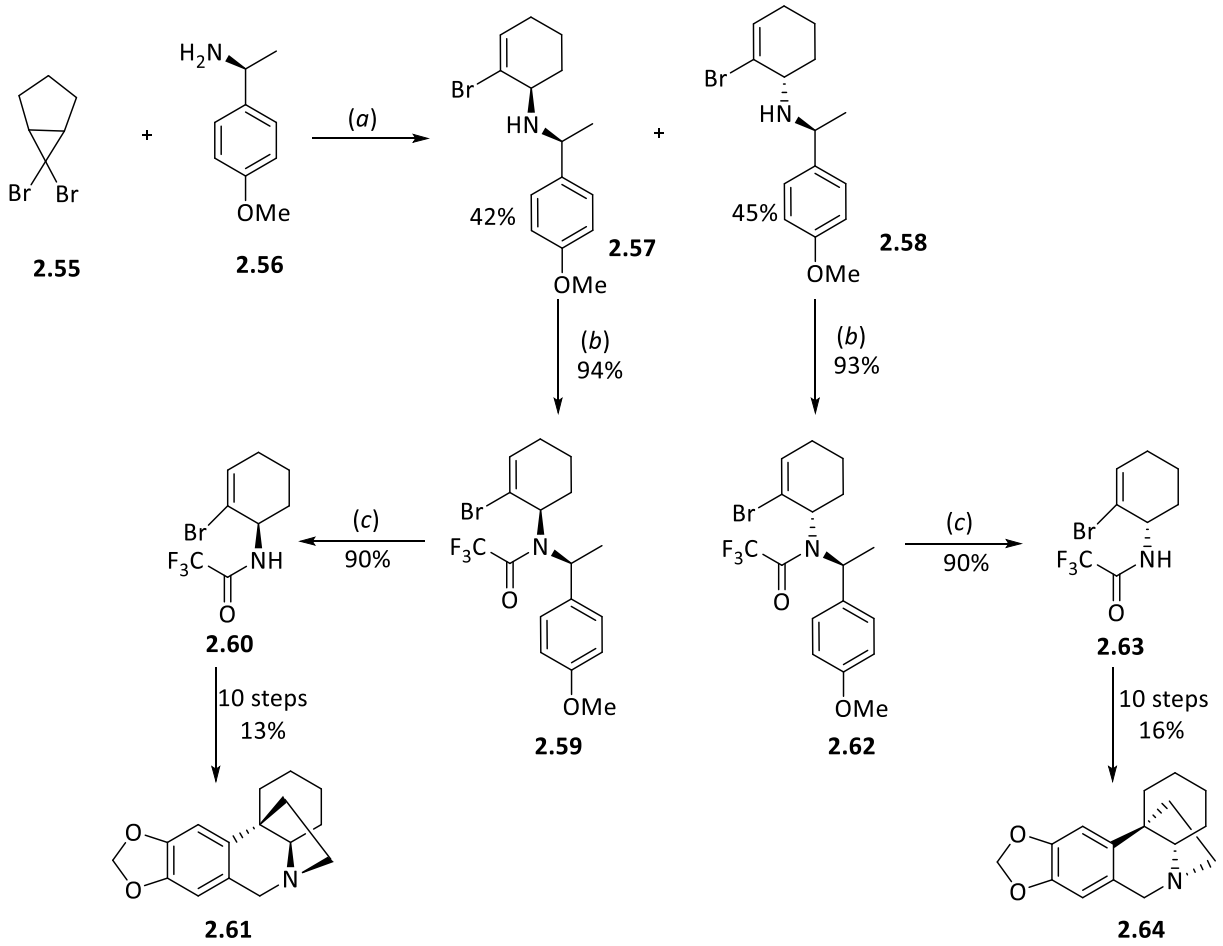


Scheme 2.18: *Electrocyclic ring-opening of ring fused gem-dichlorocyclopropane on capture with chiral nucleophiles*

In particular, the cyclopropane **2.34** derived from a C_2-symmetric olefin such as **2.52** would afford, on thermolysis,[32] a similarly symmetric π-allyl cation that could be intercepted by, for example, homochiral amines and so generating mixtures of the diastereoisomeric trapping products **2.53** and **2.54**. It was expected that these products, which should be capable of

separation by conventional chromatographic methods,[31a] could then be carried forward independently to generate homochiral forms of compounds **2.36** (Y=NR) (**Scheme 2.15**).

2.09 A Route to Homochiral, Bromocyclohexenes from C_2-Symmetric 6,6-Dibromobicyclo[3.1.0]hexane



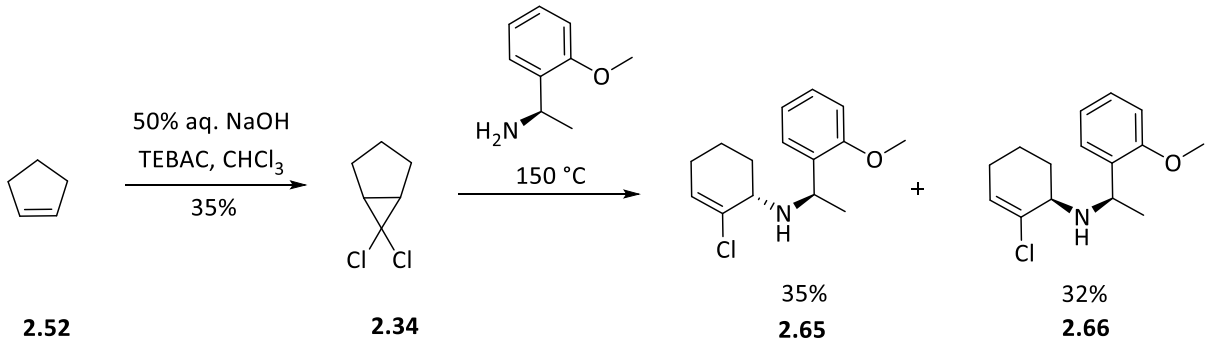
Scheme 2.19: *Reagents and Conditions* (*a*) 55 °C, 8 h; (*b*) TFAA, pyridine, 22 °C, 2 h; (*c*) TfOH, anisole, DCM, 22 °C, 3 h

The concept presented in **Scheme 2.18** has some precedent. Thus, in the opening stages of total syntheses of the (+)- and (–)-forms of the alkaloidal derivative crinine (**Scheme 2.19**), Banwell and co-workers[32a] reacted, under thermolytic conditions, the C_2-symmetric cyclopropane **2.55** with the commercially available and homochiral amine **2.56** and so affording the chromatographically separable 1-amino-2-bromo-2-cyclohexenes **2.57** and **2.58**. The chiral auxiliary in each of these was then removed over two steps, the first involving their conversion into the corresponding trifluoroacetamides **2.59** and **2.62**. Independent treatment of the latter compounds with triflic acid in the presence of the anisole then gave

the enantiomerically pure trifluoroacetamides **2.60** (90%) and **2.63** (90%), respectively. After a further ten steps, the target natural product frameworks **2.61** and **2.64** were obtained from these trifluoroacetamides.

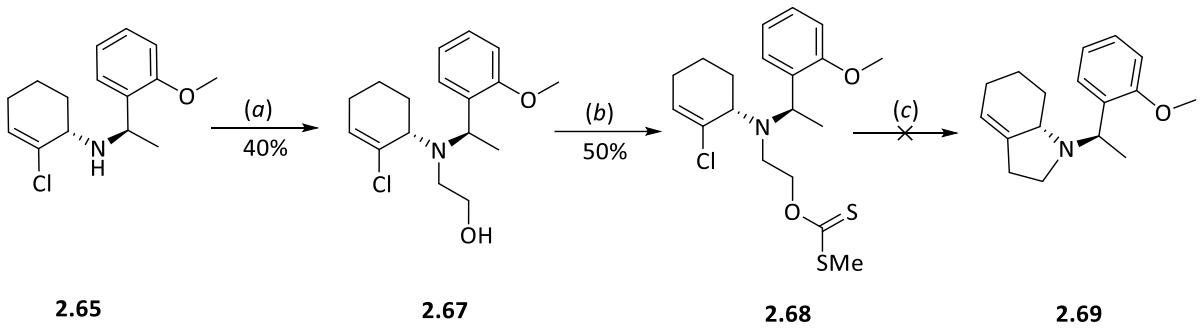
2.10 Developing Protocols for the Formation of Enantiomerically Pure Hexahydroindoles Starting from 6,6-Dichlorobicyclo[3.1.0]hexanes

Attempts to adapt the chemistry shown immediately above to the synthesis of homochiral forms of compounds such as **2.36** (**Scheme 2.15**) were pursued by the pathway shown in **Scheme 2.20**. Specifically, 6,6-dichlorobicyclo[3.1.0]hexane (**2.34**) was heated with a four-fold excess of the illustrated and commercially available chiral amine (no added solvent) at 150 °C for 3 h. This produced the chromatographically separable diastereoisomers **2.65** and **2.66**, the structures of which were assigned based on their chromatographic mobilities and optical rotations in the same way that Banwell and Lan established the configurations of a related series of bromocyclohexenes.[32a]



Scheme 2.20: *Synthesis of the diastereoisomeric allylic amines **2.65** and **2.66** by thermally-induced reaction of gem-dichlorocyclopropane **2.34** with a homochiral amine*

In an effort to carry forward the slightly more abundant diastereoisomer **2.65** in the proposed reaction sequence, this was reacted (**Scheme 2.21**) with 2-bromoethanol in the presence of potassium carbonate and so affording the anticipated product **2.67**, albeit in just 40% yield.



2.65 **2.67** **2.68** **2.69**

Scheme 2.21: *Reagents and Conditions* (*a*) 2-bromoethanol, K_2CO_3, MeCN, reflux, 8 h; (*b*) NaH, CS_2, MeI, THF, 1 h; (*c*) *n*-Bu_3SnH, AIBN, toluene, 80 °C, 3.5 h

The alcohol residue associated with the last compound could be transformed into the corresponding xanthate **2.68** (50%) under relatively standard conditions but every effort to convert this new functional group into the corresponding primary carbon-centred radical using, for example, the Barton-McCombie protocol[33] failed. Invariably, complex product mixtures were obtained. As such, and because of the emergence of a new research project presented to the author, no further efforts were made to develop this area of cyclopropane chemistry.

2.11 References

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Chapter Three

3.01 New Routes to Benzofurans, Indoles and Related, Privileged Heterocycles†

Heterocycles incorporating either the indole or benzofuran ring system are important classes of compound and such that they are often described as privileged frameworks. This is in part because compounds embodying these motifs display notable physiological and/or pharmacological properties and are, therefore, constituents of many biologically important molecules.[1] So, for example, indole-containing compounds have been deployed as anticancer, antimalarial, antitubercular and anti-HIV agents while, as shown in **Figure 3.01**, many clinically important alkaloids embody this same motif with maridianin A (**3.01**) possessing antibacterial activity while both brasilidine A (**3.02**) and eudistomin K (**3.03**) have proven activity against certain bacteria and HIV.[2] On the other hand, bromocriptine (**3.04**) promotes uterine muscle contraction, provides migraine relief and has served as a treatment for mammary carcinomas.

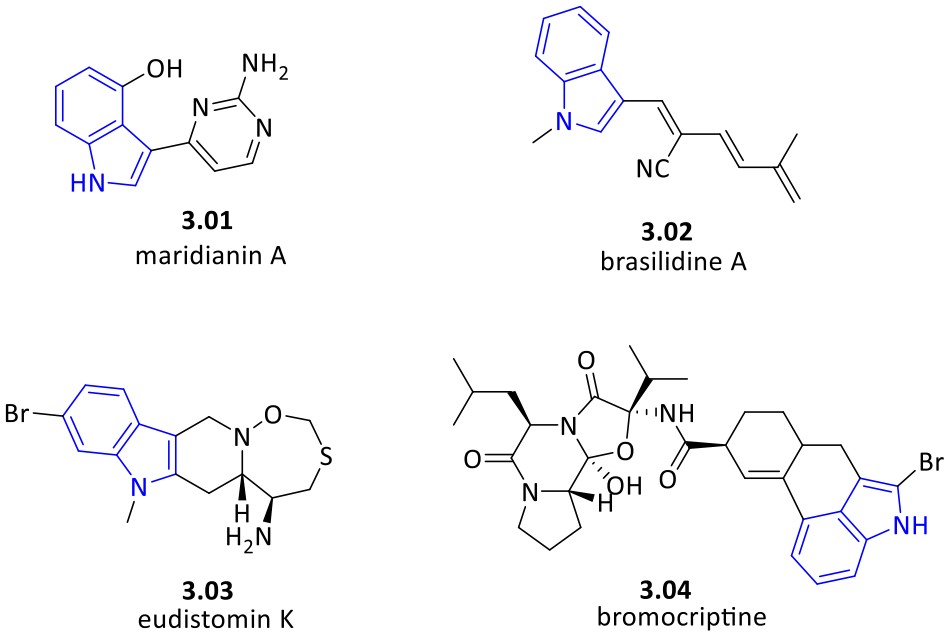


Figure 3.01: *Clinically important indole alkaloids*

† (Key aspects of the work described in this chapter have been published - Khan, F.; Fatima, M.; Shirzaei, M.; Vo, Y.; Amarasiri, M.; Banwell, M. G.; Ma, C.; Ward, J. S.; Gardiner, M. G., *Org. Lett.* **2019,** *21 (16),* 6342-6346.

Compounds embodying the benzofuran ring system display similarly diverse biological profiles with various clinically-approved drugs incorporating this motif. Thus, as shown in **Figure 3.02**, trioxsalen (**3.05**) serves as a photosensitizer used to increase skin tolerance to sunlight and enhance pigmentation while dronedarone (**3.06**) and amiodarone (**3.07**) act as antiarrhythmic agents. Methoxsalen (**3.08**), on the other hand, is used to treat psoriasis, eczema, vitiligo and cutaneous lymphomas.[3]

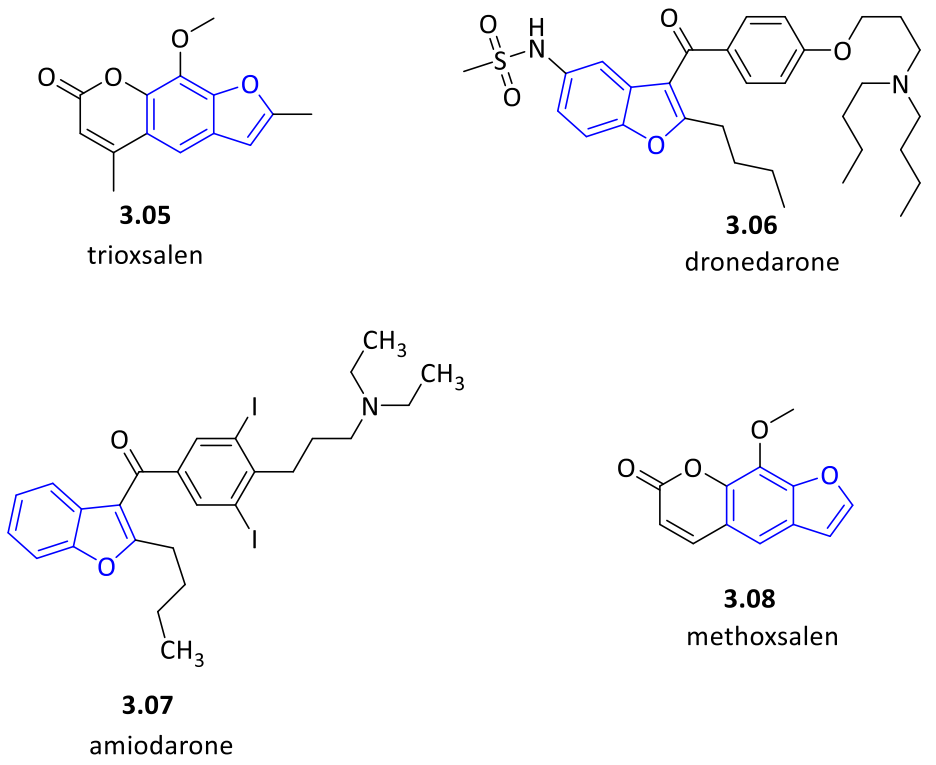
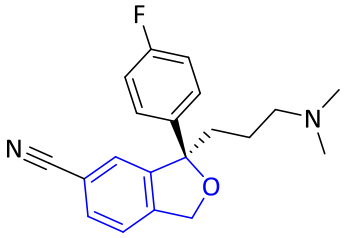


Figure 3.02: *Clinically important benzofuran ring-containing compounds*

The phthalane or 1,3-dihydro-2-benzofuran framework, which is sometimes referred to as isocoumaran, is also of related significance with one of its derivatives, the drug Citalopram (**3.09**, **Figure 3.03**), being a widely prescribed antidepressant use to treat major depressive disorders, obsessive compulsive disorder, panic disorder as well as certain social phobias.[4]



3.09

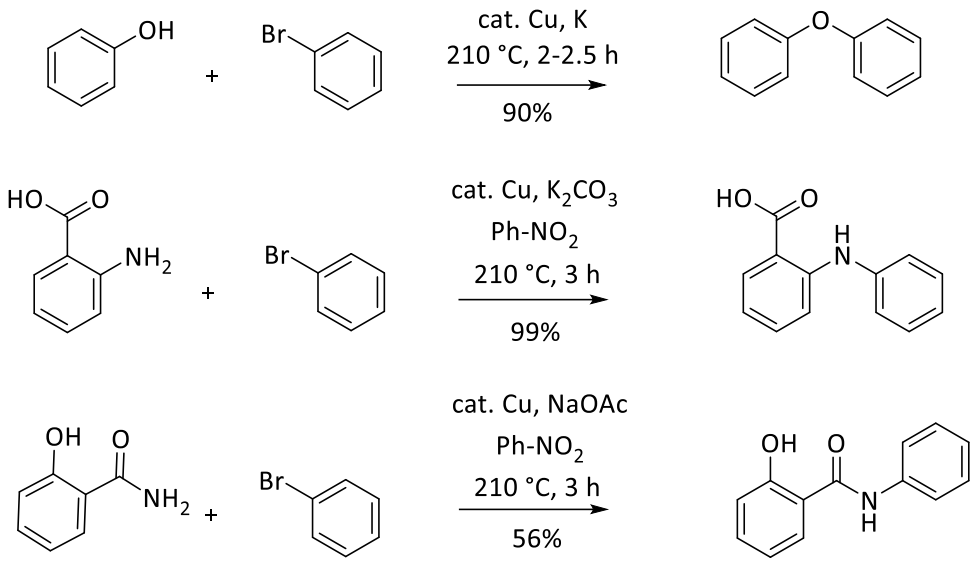
Figure 3.03: *The structure of Citalopram*

Given the foregoing, there is an ongoing need for the development of mild and selective methods for the construction of the title heterocyclic ring systems. Such a need is especially acute when the target compounds are structurally complex ones as encountered in various indole- and benzofuran-containing natural products.[5] Since these frameworks incorporate C-N or C-O bonds and certain reactions allow these to be formed under (potentially) mild conditions, a brief discussion of some such transformations is now provided.

3.02 The Ullmann Cross-Coupling Reactions

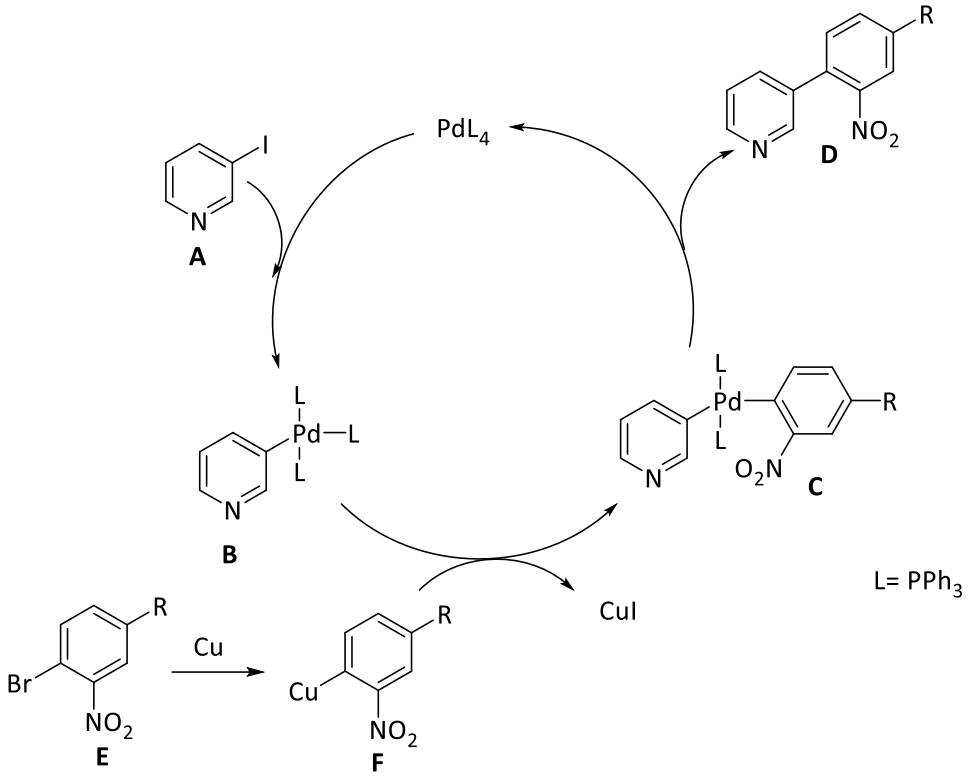
Fritz Ullmann and Irma Goldberg reported the first copper-mediated C-N, C-O and C-C bond forming reactions over one hundred years ago and with a particular focus (by Goldberg) being on the formation of aryl ethers and amines, some examples of which are shown in **Scheme 3.01**. Certain catalytic variants followed thereafter and soon such processes were being deployed in accessing intermediates of interest in pharmaceutical, agrochemical, fine chemical and/or polymer chemistry settings.[6]

Despite the obvious value of such conversions, the harsh reaction conditions required, and the limited substrate scope hindered their broader application, particularly within the arena of natural product synthesis.



Scheme 3.01: *Examples of the Ullmann ether synthesis, the Ullmann–Goldberg amination reaction and the Goldberg amidation reaction*

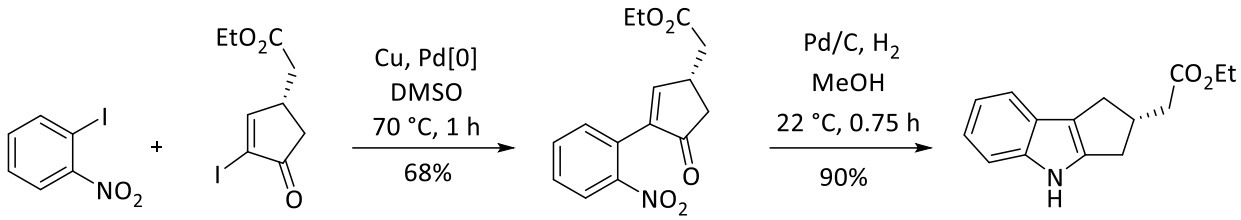
In 1993, Shimizu and collaborators reported that the (copper-mediated) Ullmann cross-coupling reaction between halopyridines and 2-bromonitrobenzenes could be catalyzed by low-valent palladium species such as $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$ or $PdCl_2$ and so affording (2-nitrophenyl)pyridine derivatives under distinctly mild conditions and in good yield.[7] The mechanism proposed for this process is shown in **Scheme 3.02** and the first step is the generation of the active Pd[0] species that itself undergoes oxidative addition to the halopyridine **A** to form complex **B**. In a parallel step, Cu[0] reacts with the nitroarene in the illustrated manner to afford organocuprate **F**. Transmetalation and reductive elimination steps then follow and so delivering the observed, cross-coupled product **D** as well as regenerating the Pd[0] catalyst that can re-enter the reaction cycle.



Scheme 3.02: *Proposed mechanism for the palladium-catalyzed Ullmann cross-coupling reaction*

3.03 Applications of Pd[0]-Catalyzed Ullmann Cross-Coupling/Reductive Cyclization Sequences in Organic Synthesis

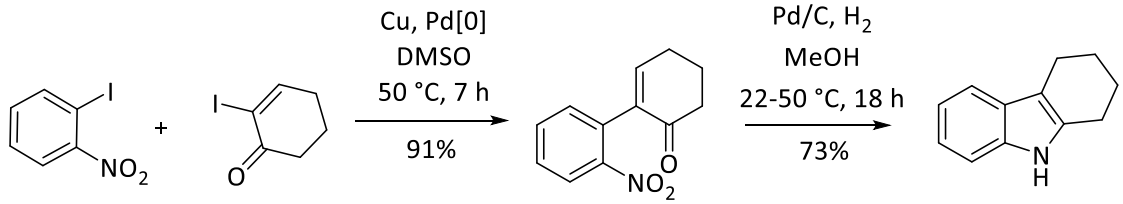
In 2003, Banwell and co-workers developed a reaction sequence involving the palladium-catalyzed Ullmann cross-coupling of α-halo-enones or α-halo-enals with *o*-halonitroarenes and reductive cyclization of the resulting α-arylated-enones or α-arylated-enals to deliver indoles or annulated variants there-of.[8] Thus, as shown in **Scheme 3.03**, *o*-iodonitrobenzene (**3.10**) could be cross-coupled with the 2-iodocyclopent-2-en-1-one (**3.11**) to afford compound **3.12** and that upon exposure of this to molecular hydrogen in the presence of 10% Pd on C this delivered, *via* reductive cyclization, the indole **3.13**.



3.10 **3.11** **3.12** **3.13**

Scheme 3.03: *A palladium-catalyzed Ullmann cross-coupling/reductive cyclization sequence involving an o-halonitroarene (**3.10**) and α-halo-enone (**3.11**) leading, via an intermediate (**3.12**) to an indole (**3.13**)*

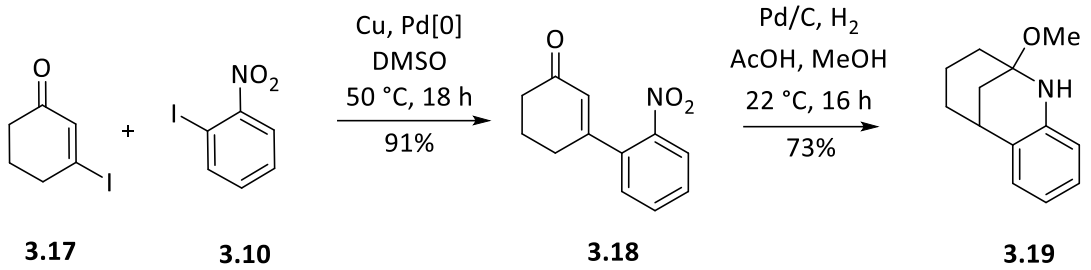
In a related sequence (**Scheme 3.04**)[9] compound **3.10** could be cross-coupled, in a very high yielding reaction taking place at 50 °C, with the readily prepared α-iodoenone **3.14**. Product **3.15**, which was obtained free of contamination by its homo-coupled congeners arising the two starting iodides, could itself be engaged in a facile and operationally simple reductive cyclization reaction and so delivering the tetrahydrocarbazole **3.16**.



3.10 **3.14** **3.15** **3.16**

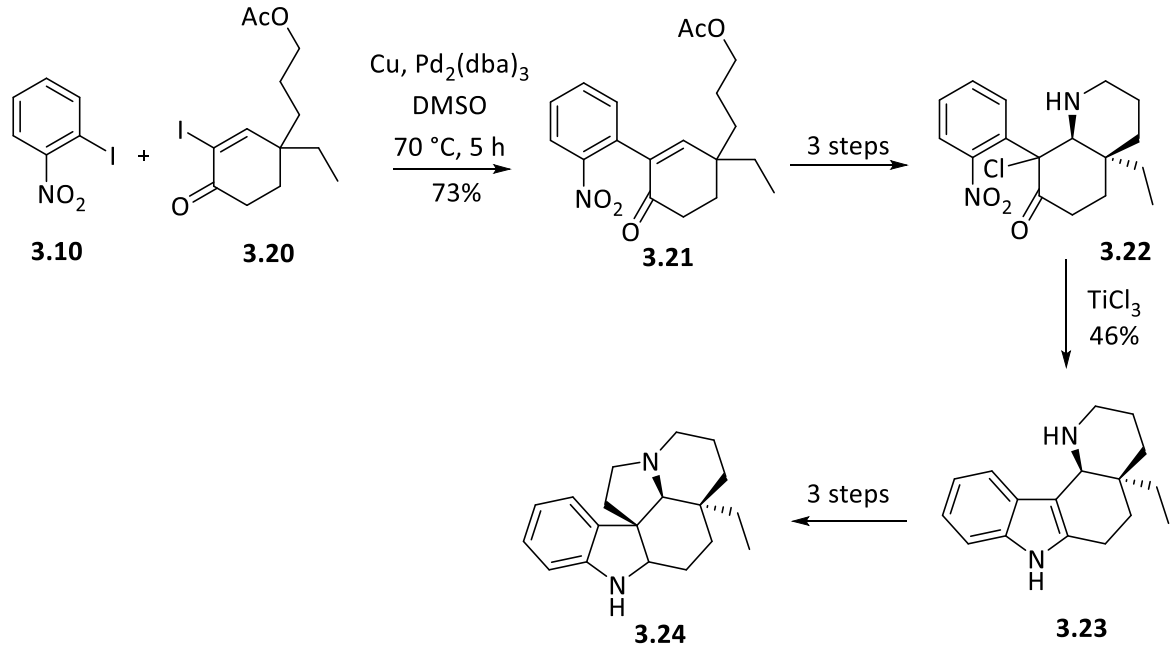
Scheme 3.04: *A palladium-catalyzed Ullmann cross-coupling/reductive cyclization sequence involving an o-halonitroarene (**3.10**) and α-iodoenone (**3.14**) leading, via an intermediate (**3.15**) to an indole (**3.16**)*

In a rather interesting variant on such processes, it was shown[10] (**Scheme 3.05**) that the palladium-catalyzed Ullmann cross-coupling of compound **3.17** (a regioisomer of **3.14**) with *o*-iodonitrobenzene (**3.10**) afforded, in high yield, the expected product **3.18** and that reductive cyclization of this produced the novel tricyclic product **3.19**. *o*-Halobenzonitriles could be similarly engaged to deliver related end-products considered to be of pharmacological utility.



Scheme 3.05: *A palladium-catalyzed Ullmann cross-coupling/reductive cyclization sequence involving β-halogenated α,β-unsaturated carbonyl compound (**3.17**) and o-halonitroarene (**3.10**) leading, via an intermediate (**3.18**) to tricyclic product (**3.19**)*

3.04 Applications of Ullmann Cross-Coupling/Reductive Cyclization Sequences in the Synthesis of Natural Products



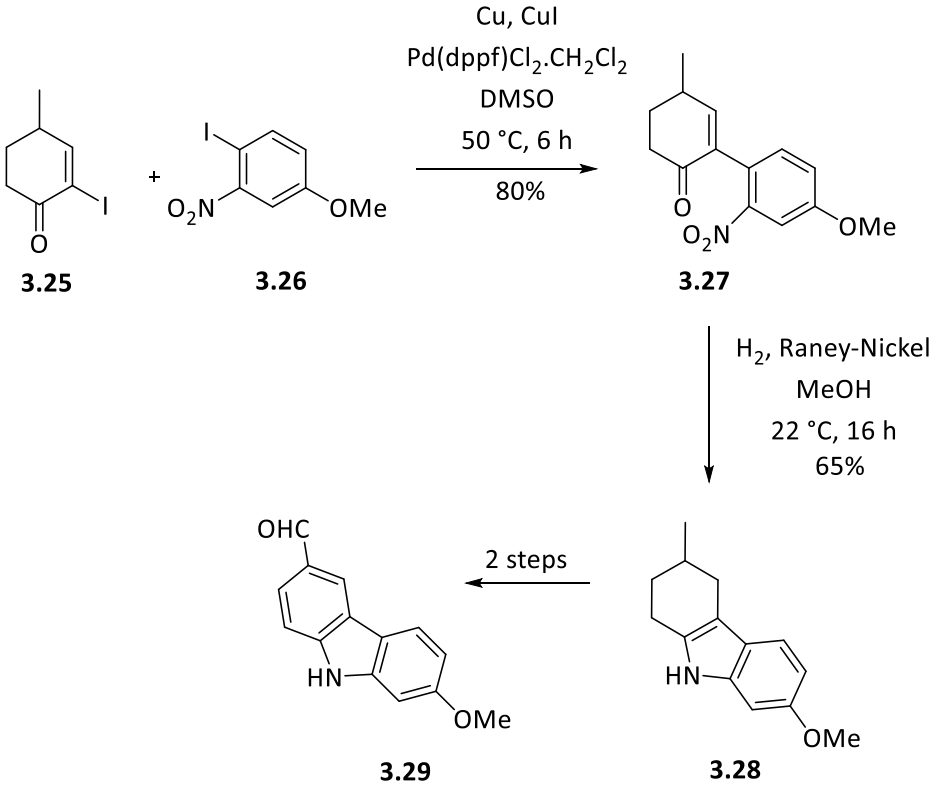
Scheme 3.06: *A total synthesis of aspidospermidine (**3.24**)*

In 2005, Banwell and co-workers reported[12] exploiting the types of protocols described in the preceding section in a total synthesis of alkaloid aspidospermidine. Thus, as shown in **Scheme 3.06**, the α-iodinated cyclohexanone **3.20** was cross-coupled, under by now standard conditions, with arene **3.10** and so affording the pivotal arylated enone **3.21**.

This last compound was then converted, over 3 steps, into an α-chloroketone **3.22** that was itself treated with titanium trichloride in the presence of ammonium acetate to afford the

reduction product **3.23**. A further three steps then delivered, in good overall yield, the targeted indole alkaloid aspidospermidine (**3.24**).[12]

The utility of the title protocols was further reinforced through its deployment in a synthesis of clauszoline K[13] as shown in **Scheme 3.07**. So, the iodinated cyclohexenone **3.25** was cross-coupled with the 2-iodonitroarene **3.26** and the anticipated arylated cyclohexanone **3.27** engaged in a by now standard reductive cyclization reaction to give tetrahydrocarbazole **3.28**. A further two steps, including a benzylic oxidation reaction, then afforded the naturally-occurring aldehyde **3.29** (clauszoline K) in 66% yield.

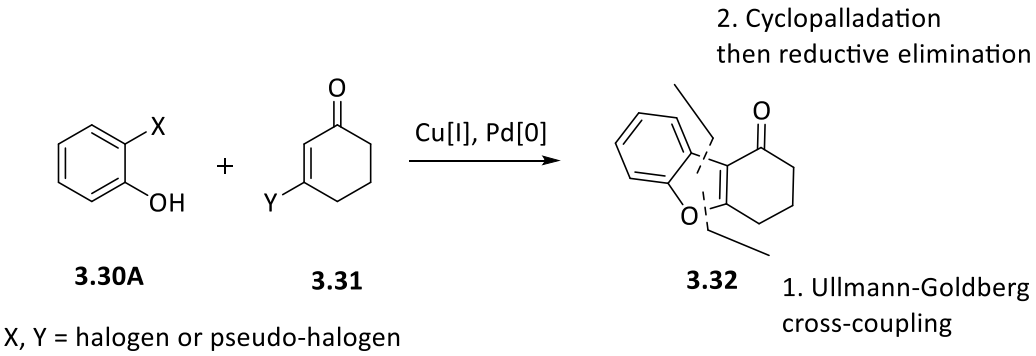


Scheme 3.07: *A total synthesis of clauszoline K (**3.29**)*

3.04 Tandem Ullmann–Goldberg Cross-Coupling/Cyclopalladation/Reductive Elimination Reactions Leading to Polyfunctionalized Heterocyclic Frameworks

The development of multi-catalyst systems that promote two or more chemical transformations in a single operational event is a matter of ongoing interest because of the attendant efficiencies that can be realized.[14] One such possibility that builds upon the chemistries described in the preceding sections is outlined in **Scheme 3.08** and in which it was

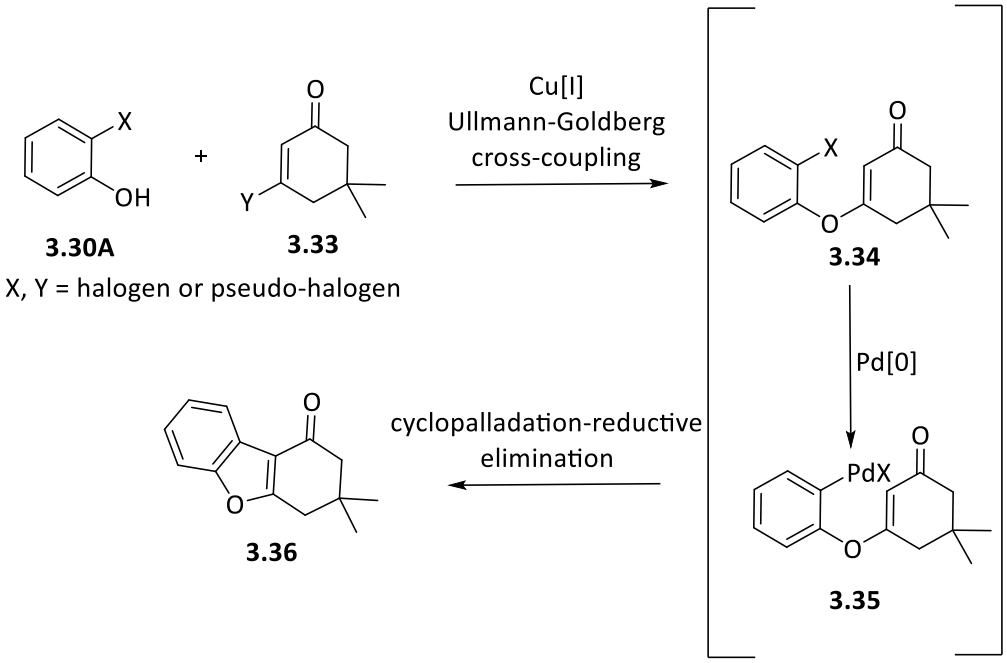
anticipated, based on some initial observations, that an *o*-halo- or pseudohalo-phenol (**3.30A**, X = I, Br or OTf) would react with a 3-halocyclohexenone (**3.31**, Y = I or Br) in an initial Cu[I]-catalyzed Ullmann−Goldberg cross-coupling reaction and this would be followed by a cyclopalladation-reductive elimination process to afford, in a one-pot process, the annulated benzofuran (**3.32**). Such a process, if successful, would represent the reverse of the bond-forming steps used in Larock's approach to benzofurans.[14,15] Replacing the *o*-halophenol in such a sequence with the corresponding aniline should deliver indoles. The exploration of such a potentially useful new approach to these heterocyclic systems was the objective of the work undertaken by the author and the results of these endeavours are now described.



Scheme 3.08*: Proposed reaction sequence for the formation of annulated benzofurans*

3.05 A Tandem Ullmann-Goldberg Cross-Coupling/Cyclopalladation/ Reductive Elimination Reaction Sequence Leading to Benzofurans

As the starting point for the exploration of the proposed new approach to benzofurans (**Scheme 3.08**), the reaction of substrates of the general form **3.30A** and **3.33** (**Scheme 3.09**) was pursued. The expectation was that these would be coupled in an Ullmann-Goldberg type reaction to generate the ether **3.34** that would, in turn, undergo an oxidative addition with a Pd[0]-species to afford adduct **3.35**. A cyclopalladation-reductive elimination reaction process would then follow to complete the reaction sequence and thus deliver the annulated benzofuran **3.36**.



Scheme 3.09: *Possible mechanism for a palladium-catalyzed Ullmann-Goldberg cross-coupling/reductive cyclization sequence leading to benzofurans such as **3.36***

3.06 Optimization Studies

The outcomes of the author's initial studies undertaken in an effort to find the optimal conditions for effecting the desired conversion (**Scheme 3.09**) are presented in **Table 3.01**. Initially, it was established that when a mixture of 1 equivalent of the *o*-halophenol **3.30A** (X = I) and 1.5 equivalents of 3-halocyclohexenone **3.33** (Y = I) was treated with cuprous iodide (0.5 mol equivalents), $Pd_2(dba)_3$ (5 mol %) and triethylamine (TEA) (2 mol equivalents) in DMSO at 120 °C for 20 h (Entry 1) then the benzofuran **3.36** was obtained in 43% yield.

The stepwise addition of the cuprous iodide then $Pd_2(dba)_3$ (Entry 2) raised the product yield to 61%. As revealed in Entry 3, when the 3-bromoenone (Y = Br) was reacted with *o*-iodophenol (X = I) under the same condition then benzofuran **3.36** was obtained in 47% yield. In contrast, when the equivalent process involved *o*-bromophenol **3.30A** (X = Br) and iodoenone **3.33** (Y = I) (Entry 4) the Ullmann−Goldberg product **3.34** (X = Br) was obtained in 32% yield. Similarly, when both coupling partners incorporated bromine (Entry 5), the same product (**3.34**) was now obtained in only 19% yield. The enol triflate **3.33** (Y = OTf) reacted in a similar fashion but in this case 5 mol % of tetra-*n*-butylammonium bromide (TBAB) was added to the reaction mixture (Entry 6) for the purposes of effecting the *in situ* formation of

3.33 (X = Br) (through a halogen-for-pseudohalogen exchange). On adding just CuI (alone) to the reaction mixture (Entry 7) and heating this to 80 °C for 2 h then substrates **3.30A** (X = I) and **3.33** (Y = I) only engaged in the Ullmann-Goldberg reaction and forming the enol ether **3.34** (X = I) which was obtained in 63% yield. On resubjecting compound **3.34** (X = I) to the same reaction conditions but now with just Pd[0] present (Entry 8), benzofuran **3.36** was obtained in 91% yield.

Table 3.01*: Optimization of the reaction conditions for producing benzofuran **3.36***

Entry	Substrate	Additives[a]	Time/ Temperature	Product (%)
1	**3.30A** (X = I) **3.33** (Y = I)	CuI, Pd[0]	20 h/ 120 °C	**3.36** (43%)
2	**3.30A** (X = I) **3.33** (Y = I)	CuI, Pd[0]	2 h then 20 h/ 60 then 120 °C[c]	**3.36** (61%)
3	**3.30A** (X = I) **3.33** (Y = Br)	CuI, Pd[0]	2 h then 20 h/ 60 then 120 °C[c]	**3.36** (47%)
4	**3.30A** (X = Br) **3.33** (Y = I)	CuI, Pd[0]	2 h then 20 h/ 60 then 120 °C[c]	**3.34** (X = Br) (32%)
5	**3.30A** (X = Br) **3.33** (Y = Br)	CuI, Pd[0]	2 h then 20 h/ 60 then 120 °C[c]	**3.34** (X = Br) (19%)
6	**3.30A** (X = Br) **3.33** (Y =OTf)	CuI, Pd[0] TBAB[b]	2 h then 20 h/ 60 then 120 °C[c]	**3.36** (15%)
7	**3.30A** (X = I) **3.33** (Y = I)	CuI	2 h/ 80 °C	**3.34** (X = I) (63%)
8	**3.34** (X = I)	Pd[0]	20 h/ 120 °C	**3.36** (91%)
9	**3.30A** (X = I) **3.33** (Y = I)	Pd[0]	20 h/ 120 °C	NR[d]

[a]0.5 mol equivalents of CuI and 5 mol % of Pd[0] used together with 2 mol equivalents of Et_3N. [b]5 mol % used except for entries 4 and 5 where 10 mol % used. [c]Initial reaction mixture containing just the copper salt was stirred for 2 h at 60 °C, then a source of Pd[0] was added and the reaction mixture was heated to 120 °C for 20 h. [d]NR = no reaction

Notably, when a DMSO solution of substrates **3.30A** (X = I) and **3.33** (Y = I) was treated with just $Pd_2(dba)_3$ (0.05 mol equivalents) and TEA (no cuprous iodide present) at 120 °C then no reaction was observed. This outcome suggests that the first step of the successful reaction sequence (leading to **3.36**) is indeed an Ullmann−Goldberg reaction and not, for example, a conjugate addition/elimination reaction. Such outcomes accord with the notion that an Ullmann-Goldberg coupling of iodophenol **3.30A** and β-iodoenone **3.33** takes place in the first instance to afford the (isolable) aryl ether **3.34** that engages in a cyclopalladation/reductive elimination sequence to give the observed benzofuran **3.36**, the structure of which was confirmed by single-crystal X-ray analysis (**Figure 3.03**).

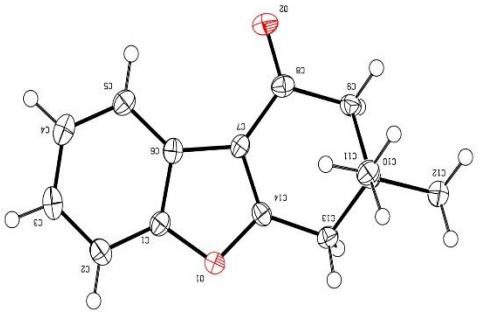
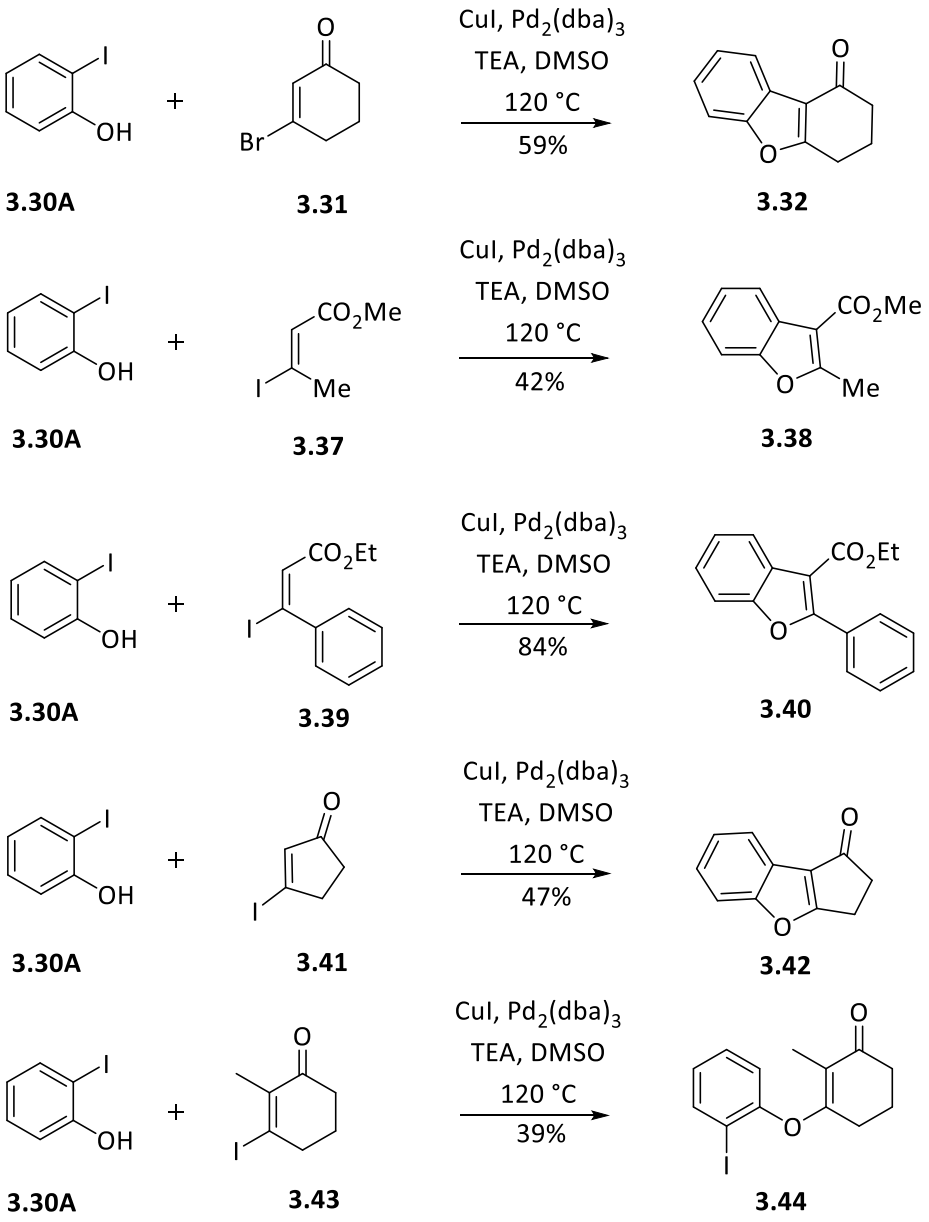


Figure 3.03: *ORTEP derived from the single-crystal X-ray analysis of benzofuran* ***3.36***

The optimized protocol defined in Entry 2 of **Table 3.01** could be extended to the synthesis of several other benzofurans. For example, as shown in **Scheme 3.10**, coupling of *o*-iodophenol (**3.30A**) with the cyclohexenones **3.33** (Y = I, Br or OTf) delivered the expected benzofuran product **3.32** in 10, 59 and 30% yields, respectively. Acyclic iodides such as the crotonate **3.37** and cinnamate **3.39** reacted in the same manner to afford the 2,3-disubstituted benzofurans **3.38** (42%) and **3.40** (84%), respectively. The iodinated cyclopentenone **3.41** also participated in an analogous reaction sequence to give compound **3.42** (47%). However, 2-methyl-3-iodoenone (**3.43**) only coupled to *o*-iodophenol **3.30A** to deliver, presumably as a result of steric effects preventing further reaction, the Ullmann−Goldberg product **3.44**. This was obtained in 39% yield.

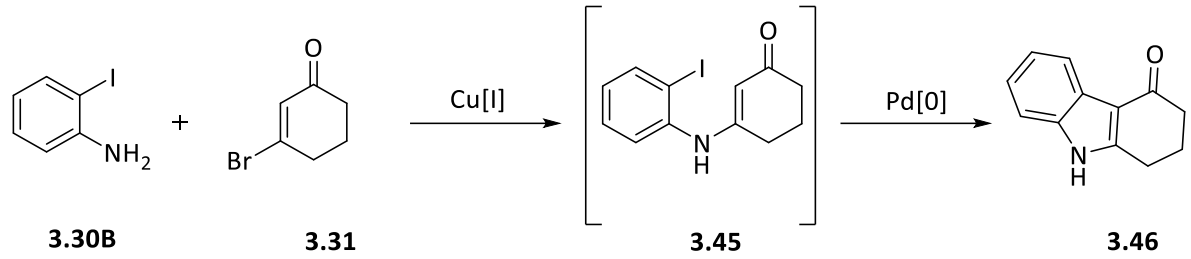


Scheme 3.10: *Further examples of palladium-catalyzed Ullmann-Goldberg cross-coupling/reductive cyclization reactions leading to benzofurans*

3.07 Tandem Ullmann-Goldberg Cross-Coupling/Cyclopalladation/Reductive Elimination Reactions Sequence Leading to Indoles

Indoles are also can be synthesized using the protocols just described by simply replacing the *o*-halogenated phenol with, for example, *o*-iodoaniline since this also cross-couples with enone **3.31** (Y = Br) to deliver, presumably *via* the intermediacy of enamine **3.45**, the cyclohexannulated indole **3.46** (60%), the structure of which was also confirmed by single-

crystal X-ray analysis (**Figure 3.04**). In this case, various attempts to prepare and isolate the enamine **3.45** proved fruitless.



3.30B **3.31** **3.45** **3.46**

Scheme 3.11: *Possible mechanism for palladium-catalyzed Ullmann-Goldberg cross-coupling/reductive cyclization reaction of **3.30B** and **3.31** leading to indole **3.46***

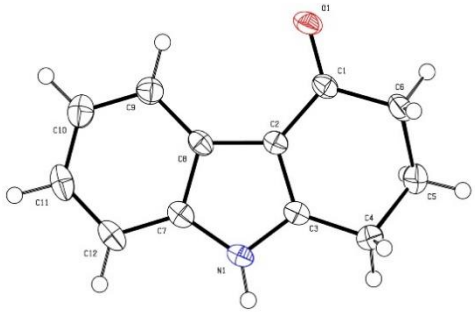
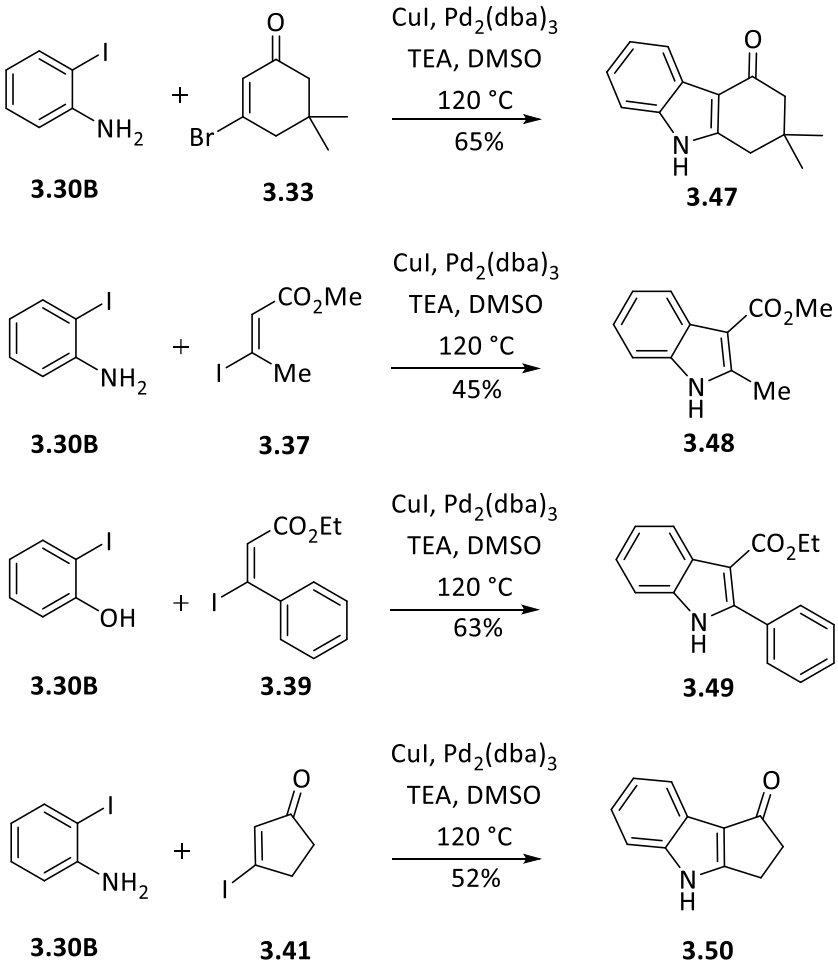


Figure 3.04: *ORTEP derived from single-crystal X-ray analysis of indole **3.46***

As revealed in **Scheme 3.12**, *o*-iodoaniline (**3.30B**) could be coupled in an analogous way with a range of other reaction partners to afford other indoles. So, by using cyclohexenone **3.33** (Y = Br) as the coupling partner then the expected indole **3.47** (65%) was obtained while by using acyclic iodides such as the crotonate **3.37** and cinnamate **3.39** the anticipated 2,3-disubstituted indoles **3.48** (45%) and **3.49** (63%), respectively, were produced. The iodinated cyclopentenone **3.41** could be used to form the 2,3-annulated indole **3.50** in 52% yield.

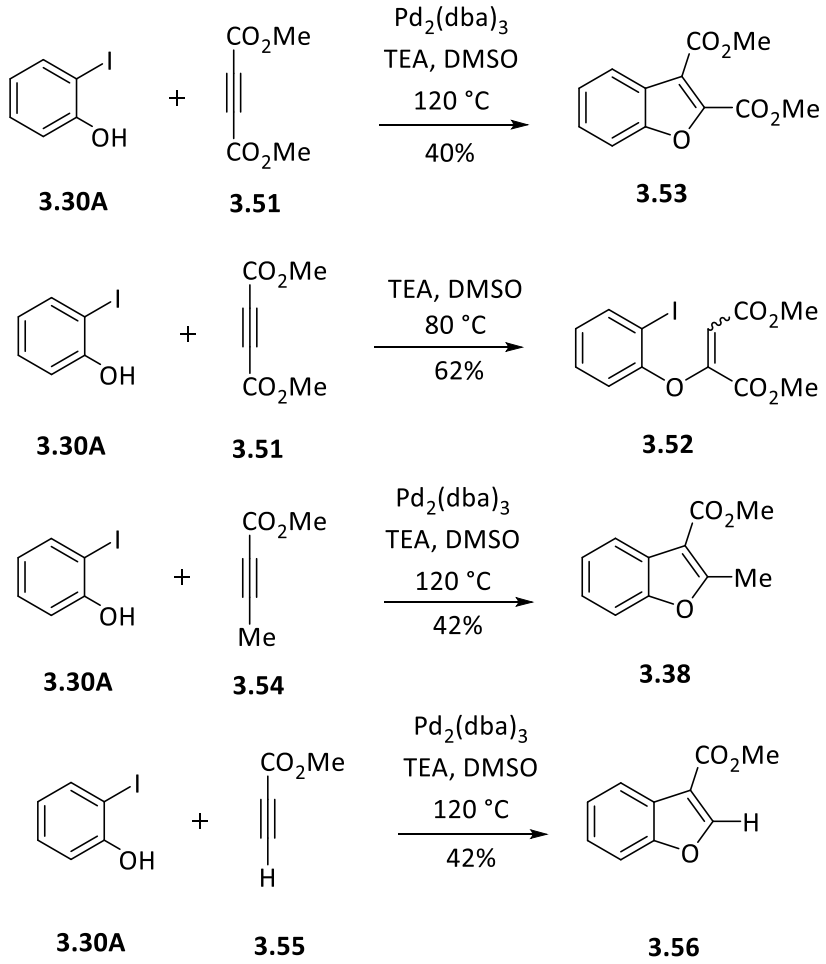


Scheme 3.12: *Further examples of palladium-catalyzed Ullmann-Goldberg cross-coupling/reductive cyclization reactions leading to indoles*

3.08 Hetero-Michael Addition/Cyclopalladation/Reductive Elimination Reactions Sequence Leading to Benzofurans and Indoles

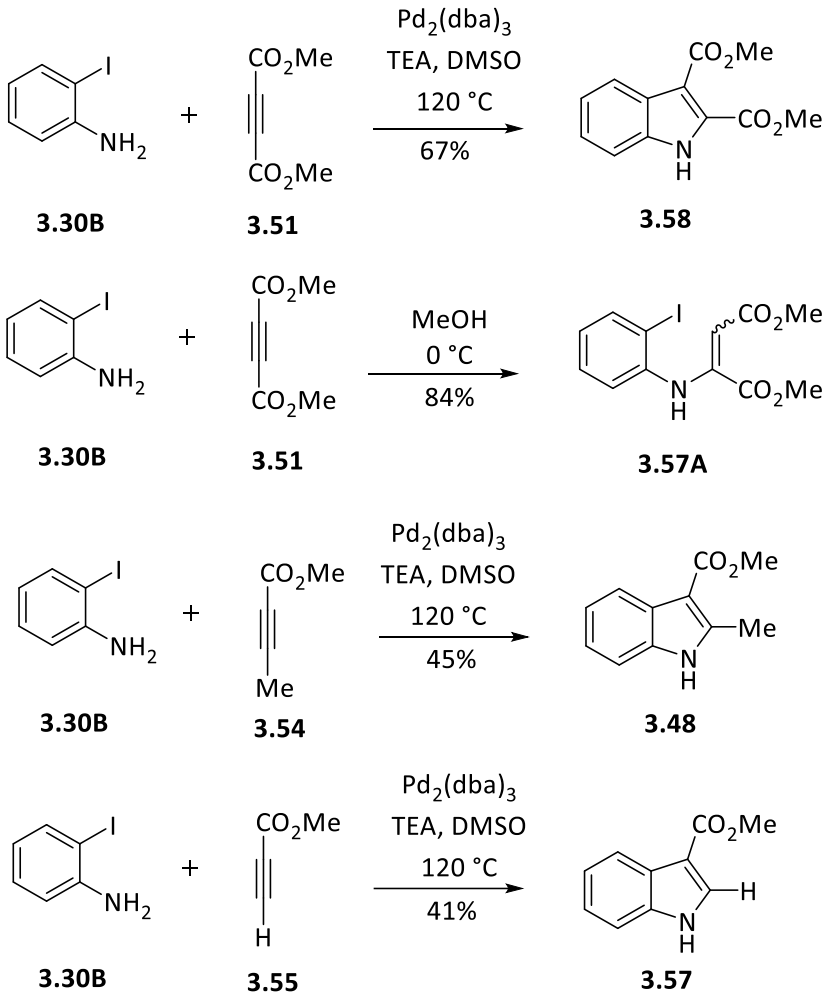
As described above, the likely intermediacy of the enol ethers such **3.34** and enamines such **3.45** in the benzofuran- and indole-forming reactions, respectively, prompted consideration of other means for preparing these, particularly by conjugate addition of *o*-halogenated phenols or anilines to propiolates and related alkynes bearing electron withdrawing-groups. Consistent with such expectations, when *o*-iodophenol (**3.30A**) and dimethyl acetylenedicarboxylate (DMAD, **3.51**) (**Scheme 3.13**) were reacted in the presence of Pd[0] and TEA, then benzofuran **3.53** was obtained in 40% yield. In contrast, when the same coupling partners were treated with TEA (alone) at 80 °C then the hetero-Michael addition product **3.52** (62%) was formed and as a single geometric isomer. Further, on exposure of this adduct to Pd[0] (alone) then the cyclization product, *viz.* benzofuran **3.53**, was obtained in

37% yield. In other tandem reactions, propiolates **3.54** and **3.55** reacted regioselectively with *o*-iodophenol (X = I) to give benzofurans **3.38** (42%) and **3.56** (42%), respectively.



Scheme 3.13: *Hetero-Michael addition/cyclopalladation/reductive elimination reaction sequences leading to benzofurans*

Similarly, and as shown in **Scheme 3.14**, DMAD (**3.51**) reacted with *o*-iodoaniline (**3.30B**) in the presence of Pd[0] and TEA to give the indole **3.58** in 67% yield. When a methanolic solution of the same coupling partners was simply maintained at 0 °C (no additives) then the hetero-Michael addition product **3.57A** was obtained in 84% yield and as a single geometric isomer. Exposure of this adduct to Pd[0] resulted in formation of the anticipated cyclization product, *viz.* indole **3.58**, which was obtained in 66% yield. Propiolates **3.54** and **3.55** reacted analogously and in a regioselective manner with *o*-iodoaniline to give indoles **3.48** (45%) and **3.57** (41%), respectively. The structures of both indoles **3.58** and **3.48** were confirmed by single-crystal X-ray analyses (see **Figures 3.06** and **3.05**).



Scheme 3.14: *Hetero-Michael addition/cyclopalladation/reductive elimination reactions sequence leading to indoles*

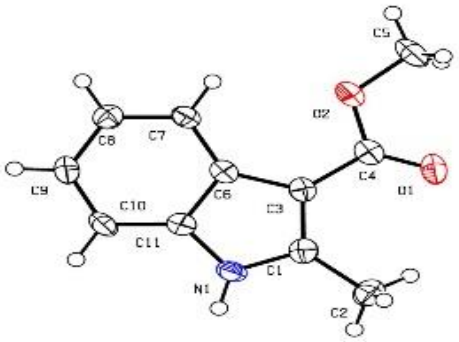


Figure 3.05: *ORTEP derived from single-crystal X-ray analysis of indole **3.48***

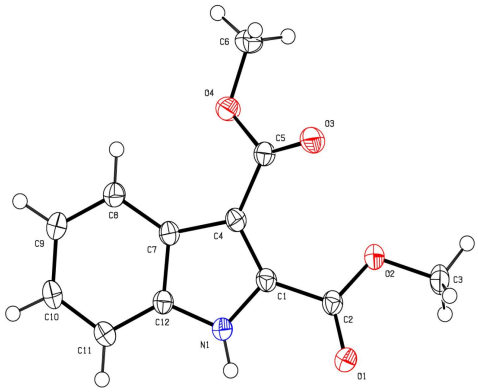
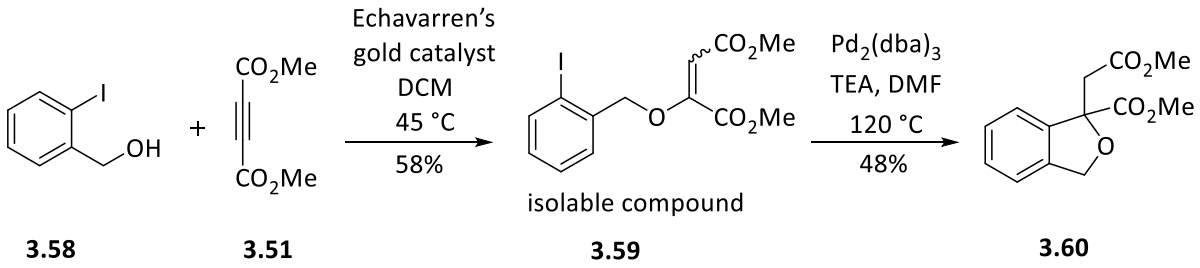


Figure 3.06: *ORTEP derived from single-crystal X-ray analysis of indole **3.58***

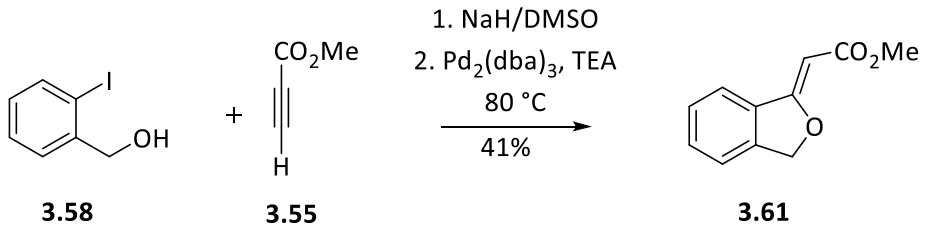
3.09 Hetero-Michael Addition/Heck Cyclization Reactions Sequence Leading to Phthalanes

Phthalanes also can be obtained by means (**Scheme 3.15**) similar to those described immediately above for generating benzofurans. So, for example, when a DCM solution of *o*-iodobenzyl alcohol (**3.58**) and DMAD (**3.51**) was exposed to Au[I] (in the form of Echavarren's catalyst), the isolable hetero-Michael addition product **3.59** was obtained in 58% yield and as a single geometric isomer, albeit of undefined configuration. In the absence of the Au[I] catalyst compound **3.59** was not obtained. On treating product **3.59** with a palladium catalyst in the presence of TEA, a Heck-type cyclization reaction took place to give phthalane **3.60** in 48% yield. This reaction is presumed to generate, in its initial phases, a palladated cyclization product that cannot undergo β-hydride elimination. In such circumstances, TEA is presumed to serve as the source of second hydrogen incorporated into the exocyclic methylene unit of the observed product **3.60**.



Scheme 3.15: *Hetero-Michael addition/Heck cyclization reactions sequence leading to phthalane (**3.60**)*

In a variation on the above theme, the terminal alkyne **3.55** (**Scheme 3.16**) could be reacted with *o*-iodobenzyl alcohol (**3.58**) in the presence of sodium hydride to deliver an adduct that engaged in a slightly more conventional Heck-type cyclization to afford, after β-hydride elimination, phthalane **3.61** in 41% yield.



Scheme 3.16: *Hetero-Michael addition/Heck cyclization reactions sequence involving an* o*-iodobenzyl alcohol (**3.58**) and alkyne (**3.55**) leading to phthalane (**3.61**)*

3.10 Conclusion

The results disclosed above clearly establish that Ullman-Goldberg cross-coupling reactions can be linked with reductive cyclization (and related) processes, including those preceded by an initial hetero-Michael addition reaction, so as to provide operationally simple, and exceptionally concise, means of constructing a useful range of heterocyclic compounds. These compounds may possess substitution patterns and/or modes of annulation that can be readily applied in the construction of, for example, certain biologically active natural products or their associated pharmacophores.

3.11 References

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Chapter Four

4.01 The Diarylheptanoids

Many phenolic compounds are renowned for their disease-prevention and/or health-promoting effects. They are frequently encountered as the active principals in traditional medicines and/or in pharmaceutical preparations while epidemiological as well as follow-up *in vitro* and *in vivo* studies have unequivocally proven their numerous health benefits.[1] Diarylheptanoids are a group of complex phenolic compounds characterised by the presence of a seven-carbon chain bearing an oxygenated phenyl ring at each end. From a structural perspective, these compounds can be subdivided into linear and cyclic forms with structure **A** in **Figure 4.01** being a representative form of the first type. Cyclic diarylheptanoids can be further divided into *meta*, *meta*-bridged biphenyls **B** and *meta*, *meta*-bridged diphenyl ether heptanoids **C** according to the nature of the connection between the constituent phenyl rings.[1 a, b]

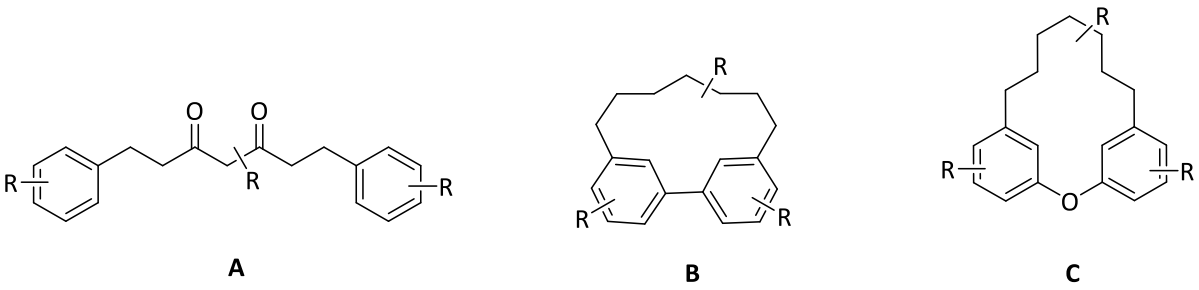


Figure 4.01: *Types of diarylheptanoids*

These compounds are structurally diverse secondary metabolites that have been isolated from the leaves, fruits, seeds, roots, barks and/or rhizomes of different pant families including the *Myricaceae*, *Betulaceae*, *Zingiberaceae*, *Aceraceae*, *Leguminosae* and *Burseraceae*.

4.02 Biological Activities of the Diarylheptanoids

Naturally-derived diarylheptanoids have attracted considerable attention because of their notable and diverse biological activities including anti-inflammatory, anti-microbial, anti-carcinogenic and antioxidant ones. Representative examples of natural products displaying such properties are discussed in the following sections.

Anti-Inflammatory Activity

Certain diarylheptanoids exhibit significant anti-inflammatory properties with hirsutenone (**Figure 4.02**), a compound isolated from the bark of *A. japonica*, being able to suppress early T-cell activation and thereby inhibiting the degranulation of mast cells and so making it a potential candidate for treating atopic dermatitis.[2]

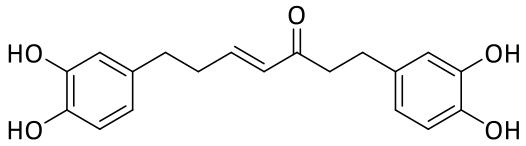


Figure 4.02: *The structure of hirsutenone*

The stem bark of the Japanese plant *Aceraceae* or *Acer nikoense* has been used as a folk medicine for the treatment of hepatic disorders and eye diseases. Recent studies have revealed that acerogenin M (**Figure 4.03**), a new cyclic diarylheptanoid that has been isolated from *Acer nikoense*, displays strong anti-inflammatory activity.[3]

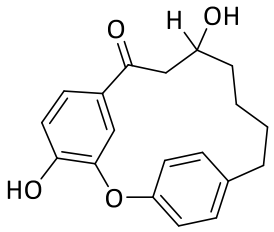


Figure 4.03: *The structure of acerogenin M*

Anti-Microbial and Anti-Viral Activity

Diarylheptanoids are said to possess anti-bacterial, anti-fungal and anti-viral activities. Curcumin (**Figure 4.04**), the first diarylheptanoid to be identified (by Vogel and Pelletier in 1815),[4] is encountered as the yellow pigment of turmeric[4] and has been shown to inhibit the growth of bacterial species like *Streptococcus*, *Staphylococcus* and *Lactobacillus* while turmeric oil is known to be active against several fungi including *Aspergillus flavus*, *Aspergillus parasiticus*, *Fusarium moniliforme* and *Penicillium digitatum*.

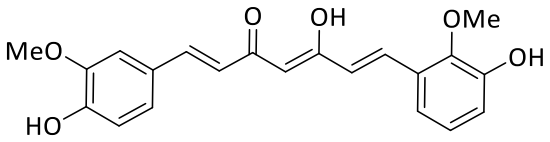


Figure 4.04: *The structure of curcumin*

Hirsutenone (**Figure 4.02**), on the other hand, exhibits strong papain-like protease inhibitory activity and so suppressing the replication of the severe acute respiratory syndrome coronavirus (SARS-CoV). As such, it is considered to be a potential drug candidate for the treatment of SARS.[5]

Anti-Carcinogenic Activity

Diarylheptanoids are also known for their anti-cancer effects. Cymodienol (**Figure 4.05**), one of the two diaryl cycloheptanoids recently isolated from specimens of the sea grass *Cymodocea nodosa*, was found to exhibit significant cytotoxic activity against two lung cancer cell lines.[6]

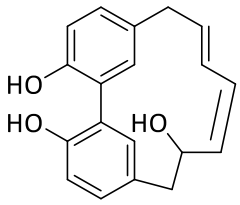


Figure 4.05: *The structure of cymodienol*

Myricanone (**Figure 4.06**), extracted from the bark of Myrica cerifera, has been reported to possess apoptosis-promoting abilities and, therefore, potential for development as an anti-cancer agent. It appears to have been effectively deployed as a hepato-protective and anti-cancer drug in various complementary and alternative systems of medicine.[7]

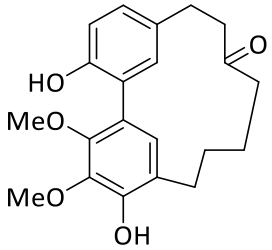


Figure 4.06: *The structure of myricanone*

Antioxidant Activity

Phenolic compounds often display direct as well as indirect antioxidant properties and frequently as a result of their free-radical scavenging or neutralizing capacities. Mistletonone (**Figure 4.07**), a structurally novel acyclic diarylheptanoid, has been isolated from the branches and leaves of *Viscum coloratum* and shown to act a scavenger of both hydroxyl radicals and superoxide anion radicals at levels comparable to those of the gold standard (−)-epigallocatechin gallate.[8]

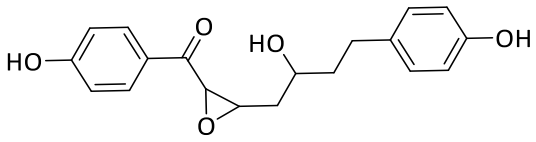


Figure 4.07: *The structure of mistletonone*

Similarly, the diarylheptanoid 7-(3,4-dihydroxyphenyl)-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)heptan-3-one (**Figure 4.08**), which has been isolated from the rhizomes of *Zinigiber officinale*, effectively scavenges superoxide anion radicals and so inhibiting the formation of lipid peroxides in liver microsomes.[9]

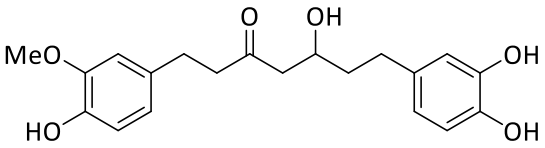
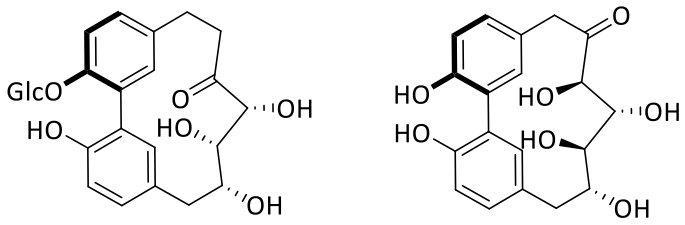


Figure 4.08: *The structure of 7-(3,4-dihydroxyphenyl)-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)heptan-3-one*

4.03 The Isolation, Structural Features, and Biological Properties of Cyclic Diarylheptanoids Derived from Hazelnut (*Corylus avellana L.*)

After almond, Hazelnut or *Corylus avellana* (*L.*) is the second most significant nut in commercial terms. Hazelnuts are a major source of fats, proteins and vitamins as well as being utilized extensively as an ingredient in dairy, bakery, confectionery, candy and chocolate products. On the other hand, the leaves of the Hazelnut tree are used in folk medicine for the treatment of haemorrhoids, varicose veins, phlebitis and as employed enemas.[10] While the kernel, the skin, hard shell, and green leafy cover as well as the leaves of the Hazel nut tree are considered, within the food industry, to be waste products,[11] extracts of certain of these

of these plant parts are reported to display antioxidant activity and so prompting efforts to identify the active principals responsible for such desirable effects. As a result, the diarylheptanoids known as giffonins A−P have been isolated from the leaves of the *C. avellana* while giffonins Q− S have been identified in the flowers of the *C. avellana cultivar*. Certain of these have been shown to prevent oxidative damage of human plasma lipids.[12] More recently, Piacente and co-workers reported on the chemical composition of the green leafy covers of *C. avellana* and in so doing they have reported obtaining and structurally characterizing giffonin T (**4.01**) and giffonin U (**4.02**) (**Figure 4.09**).[13] The second of these natural products was shown to possess antioxidant activity (IC_{50} = 18.2 μg/mL in a DPPH assay) while in a traditional antimicrobial assay it produced, at 40 μg of compound/disk, notable zones of inhibition on plates growing either Gram-positive or Gram-negative bacteria.



4.01 **4.02**

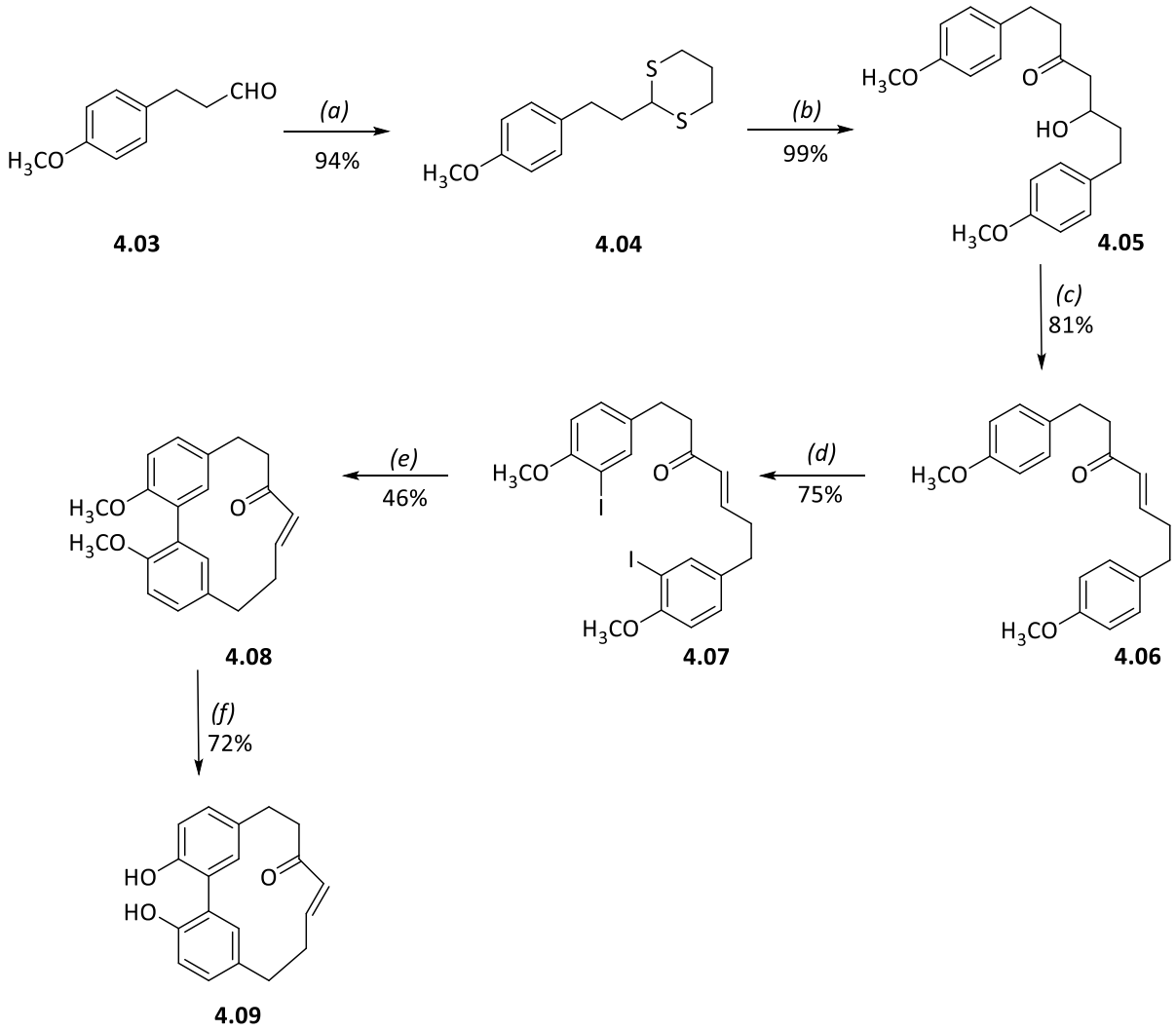
Figure 4.09: *The structures of giffonin T (**4.01**) and giffonin U (**4.02**)*

4.04 The Total Synthesis of Diaryl Cyclohepatanoids

As a result of their intriguing range of biological activities as well as their distinctive structural features, considerable effort has been devoted to establishing synthetic routes to the diaryl cyclohepatanoids, especially the cyclic variants. In this connection, the formation of the necessary aryl–aryl bond has been a particular focal point and with the Suzuki-Miyaura cross-coupling reaction, the Ullmann reaction and various photochemical process having been exploited to good effect and often at a late-stage in the synthesis.[14]

In 1981, Semmelhack and co-workers[15] reported a total synthesis for alnusone (**Scheme 4.01**) that started with the conversion of 3-(4-methoxyphenyl)propanal (**4.03**) into the corresponding thioacetal **4.04** that was subjected to lithiation with the derived anion adding to 2-(4-methoxyphenethyl)oxirane and so delivering the diarylated heptane **4.05**. Dehydration of the last compound gave enone **4.06** that upon two-fold iodination afforded

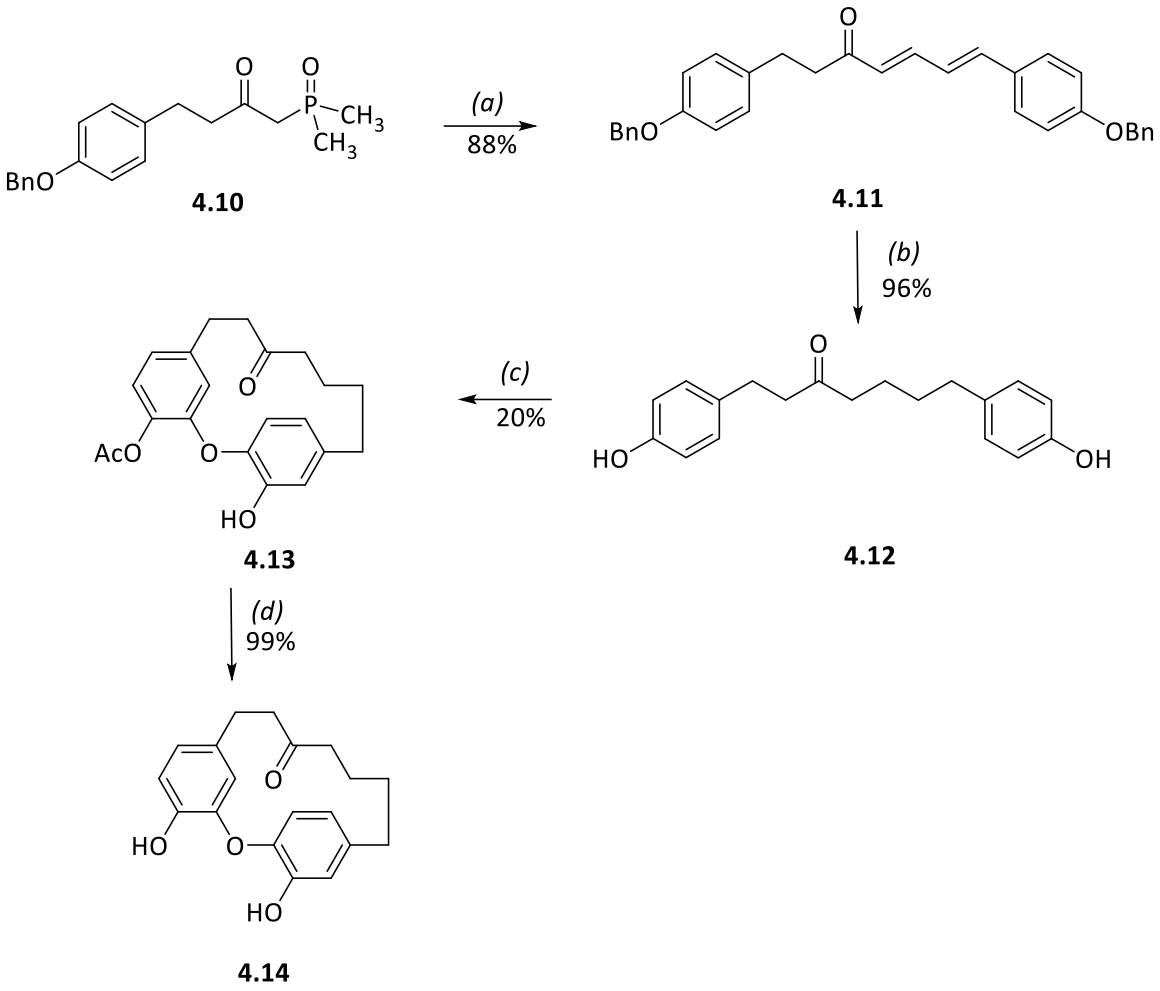
the diaryl di-iodide **4.07** which served as the substrate in a nickel-catalyzed intramolecular diaryl coupling to afford the bis-methyl ether **4.08** of alnusone. The acid-catalyzed deprotection of this last compound then produced alnusone (**4.09**) itself in 72% yield.



Scheme 4.01:*Total synthesis of alnusone (**4.09**)* (*a*) propane-1,3-dithiol, $BF_3.OEt_2$, CH_2Cl_2, 0 °C, 2 h; (*b*) *n*-BuLi, THF, –30 to 0 °C, 16 h then 2-(4-methoxyphenethyl)oxirane, H_2O, HgO, $HgCl_2$, reflux, 18 h; (*c*) Ac_2O, RT, 16 h then DBU, RT, 0.5 h; (*d*) CF_3CO_2Ag, I_2, RT, 1 h; (*e*) $Ni(PPh_3)_4$, DMF, 25 °C, 20 min then 50 °C, 40 h; (*f*) H_2SO_4, HOAc, reflux, 12 min

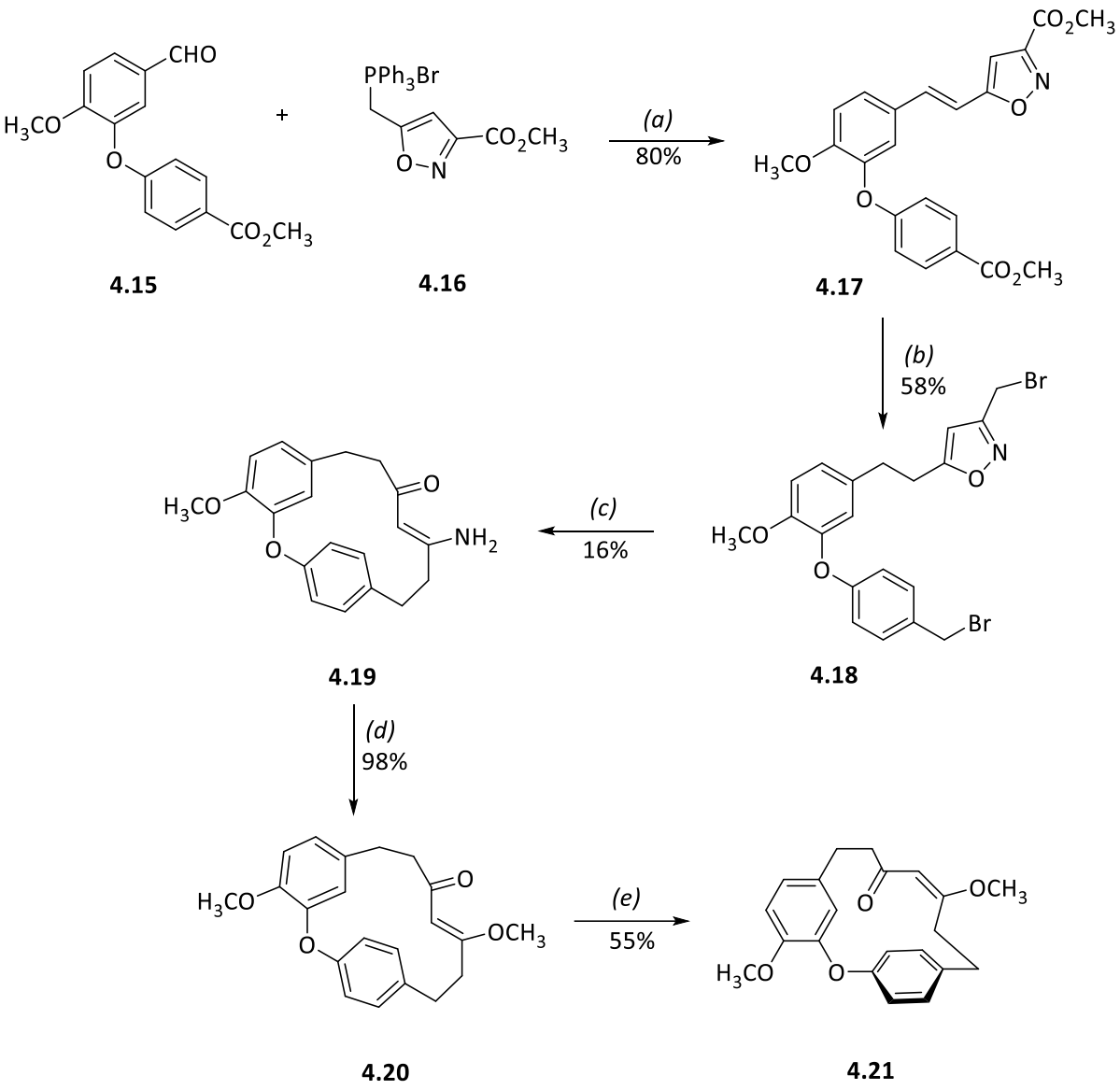
More recently (2017), Salih and Beaudry[16] reported a synthetic route to pterocarine that commenced (**Scheme 4.02**) with a Horner–Wadsworth–Emmons (HWE) reaction between phosphonate **4.10** and (*E*)-3-(4-(benzyloxy)phenyl)acrylaldehyde and so affording diene **4.11**. Exposure of this last compound to hydrogen in the presence of palladium on carbon effected two-fold hydrogenation and hydrogenolysis reactions to give acerogenin G (**4.12**) (96%) that upon reaction with PbO_2 in acetic acid engaged in an intramolecular oxidative coupling and,

thereby, the formation of acetyl pterocarine (**4.13**), conventional hydrolysis of which gave pterocarine (**4.14**).



Scheme 4.02: *Total synthesis of pterocarine* (*a*) (*E*)-3-(4-(benzyloxy)phenyl)acrylaldehyde, DBU, THF, 60 °C, 18 h; (*b*) H_2, Pd/C, EtOAc, RT, 24 h; (*c*) PbO_2, HOAc, RT, 60 h; (*d*) NaOH, CH_3OH, RT, 2 h

A distinctive macrocyclization protocol was employed by Vermes and co-workers[17] in their notable synthesis of garugamblin I (**Scheme 4.03**). So, a Wittig reaction between the aldehyde **4.15** and the ylide derived from phosphonium salt **4.16** was the opening step and gave the anticipated alkene **4.17**. The last compound was then converted, over three conventional steps, into the dibromide **4.18** that was engaged in an intramolecular Wurtz-type coupling using sodium and tetraphenylethene to deliver, after accompanying fragmentation of the isoxazole ring, enamine **4.19**, albeit in just 16% yield. A two-step methanolysis of compound **4.19** led to enol ether **4.20** and on prolonged standing in chloroform at room temperature this isomerized to give garugamblin I (**4.21**).



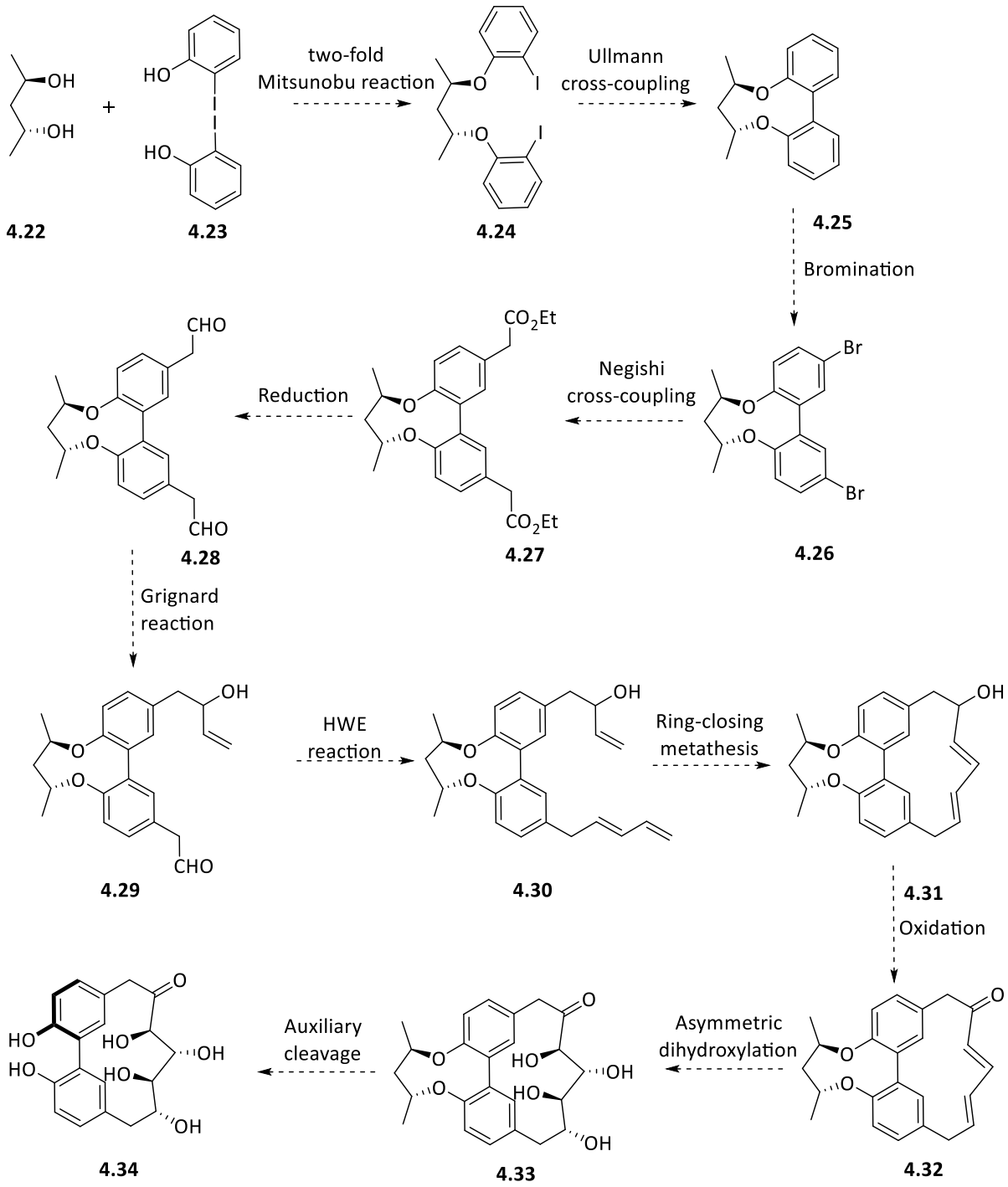
Scheme 4.03: *Total synthesis of garugamblin I* (*a*) KOt-Bu, DMSO, RT, 24 h; (*b*) H_2, Pd/C, RT, 16 h, $LiAlH_4$, -5 °C, 1 h then PBr_3, RT, 16 h; (*c*) Na, tetraphenylethene, RT, 1 h; (*d*) aq. HOAc then CH_2N_2, RT, 24 h; (*e*) $CHCl_3$, RT, 2 weeks

4.05 The Author's Efforts Directed Towards the Total Synthesis of Certain Structurally Novel Diaryl Cycloheptanoids

It is against the background of synthetic endeavors outlined above that the author embarked on a campaign to establish a route to the recently isolated and highly oxygenated diaryl cyclohepatanoid giffonin U (**4.02**), the structure of which was determined by 1D and 2D NMR spectroscopic studies. The relative (but not absolute) configurations shown were proposed on the basis of a combined quantum mechanical and NMR approach.[18] Since hindered rotation about the *o*-disubstituted biaryl axis within compound **4.02** might be expected to

give rise to atropisomerism, an additional stereochemical feature is introduced into the system that significantly increases the synthetic challenges presented by such a natural product target.[18]

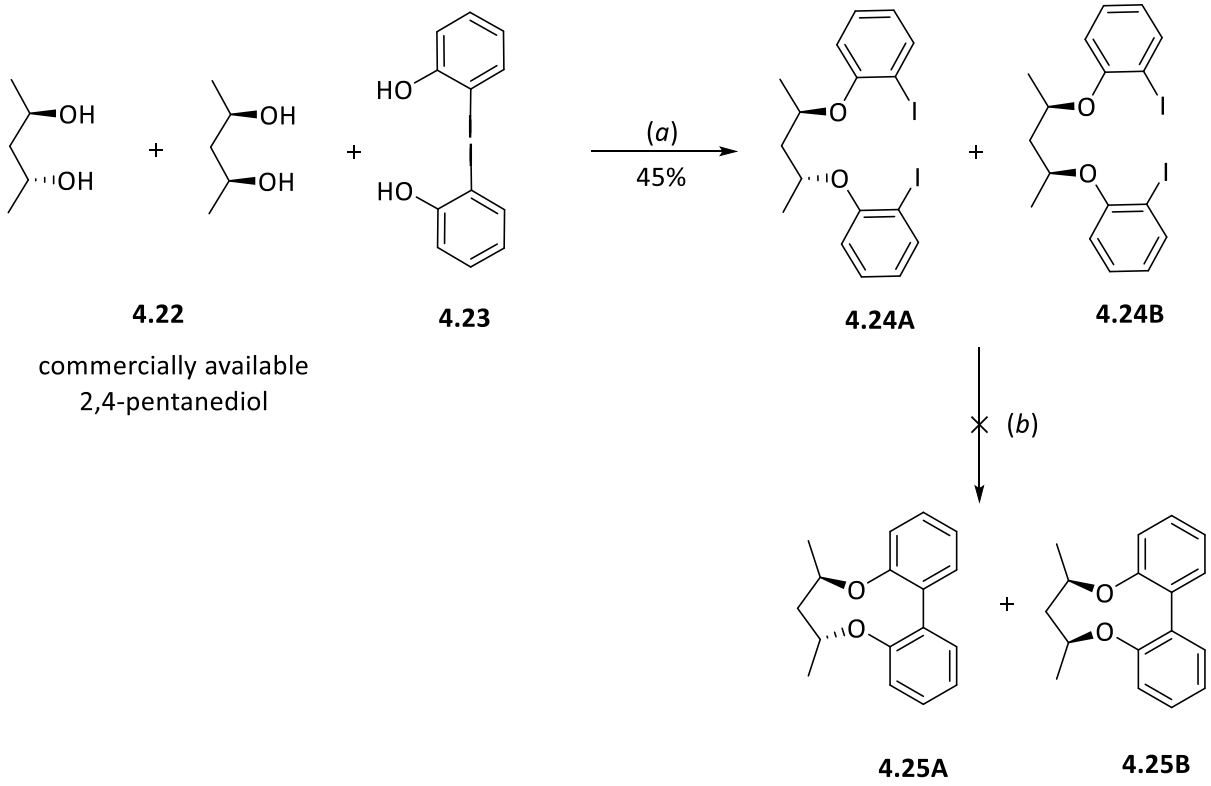
The synthetic plan that was pursued in the opening stages of the author's work in the area is shown in **Scheme 4.04**. In this approach the necessary biaryl unit was to be established early on and with the intention of using a chiral auxiliary to control the axis of chirality present in the final target. So, the proposed synthesis was to begin with a two-fold Mitsunobu reaction between one equivalent of chiral 2,4-pentanediol and 2 equivalents of *o*-iodophenol. The resulting adduct was expected to undergo an intra-molecular Ullmann cross-coupling reaction to afford the compound **4.25**, two-fold bromination of would lead to dibromide **4.26** that was to serve as a substrate for a Negishi cross-coupling with the Reformatsky reagent to give the diester **4.27**. The associated phenylacetic acid ester residues were to serve as the "jumping off points" for the creation of the cycloheptanoid residue of the target natural product. Specifically, then, partial reduction of the diester was expected to give dialdehyde **4.28** that upon reaction with one equivalent of vinyl magnesium bromide would deliver the alcohol **4.29**. A HWE reaction using diethyl allyl phosphonate would then be carried out on the remaining aldehyde residue to generate compound **4.30** and so providing a substrate that could be engaged, using one of the Grubbs' catalysts, in a ring-closing metathesis (RCM) reaction and thus forming the required macrocyclic framework, as embodied in alcohol **4.31**, of the target natural product. A simple oxidation to give ketone **4.32** followed by an asymmetric dihydroxylation reaction was expected to deliver compound **4.33** and cleavage of the auxiliary, as the final step, would produce compound **4.34** that embodies all the relevant functional features of the target but may or may not deliver the required stereochemical ones. That said, a comparison of the NMR and other spectra derived from a compound such as **4.34** with those reported for giffonin U (**4.02**) should allow for some "calibration" of stereochemical detail and, eventually, a means for establishing its absolute configuration. Of course, the successful implementation of such a reaction sequence would provide compounds of defined stereochemistry that could be subject to biological evaluation.



Scheme 4.04: *Synthetic strategy leading to diaryl cyclohepatanoid **4.34***

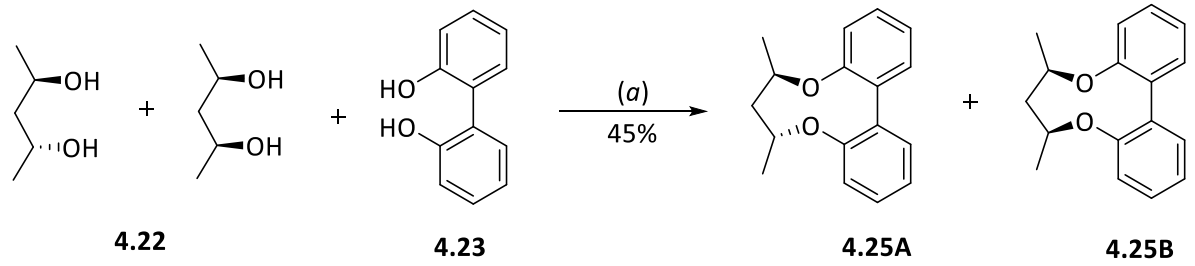
The implementation of the first steps of the proposed reaction pathway is shown in **Scheme 4.05**. At this juncture, and because stereochemical issues were less of a concern, the commercially available pentane-2,4-diol (**4.22**), consisting of a mixture of the *meso*- and D/L-forms, was used as a partner in the foreshadowed two-fold Mitsunobu reaction with *o*-iodophenol (**4.23**). The reaction proceeded under conventional conditions to deliver, as

judged by NMR spectroscopic analysis, the anticipated mixture of stereoisomeric biaryl ethers **4.24A** and **4.24B**. This mixture was submitted to a variety of Ullmann cross-coupling conditions, but all failed to deliver the required biaryl **4.25A** or even the corresponding (achiral) *meso*-product (**4.25B**).



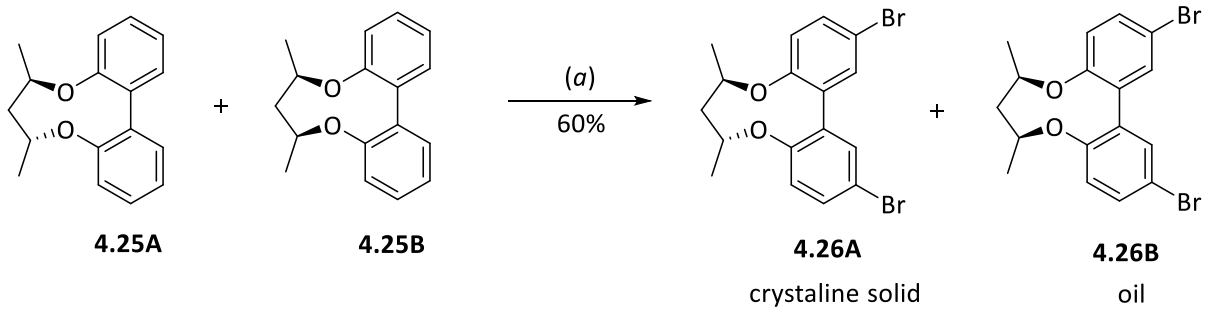
Scheme 4.05: *Reagents and Conditions* (*a*) PPh_3, DIAD, THF, 0 °C, 2 h; (*b*) CuI, $Pd_2(dba)_3$, TEA, DMSO, 120 °C, 2 h

In order to circumvent the "dead end" described above, *o*-iodophenol was replaced with 2,2'-biphenol (**4.23**) (**Scheme 4.06**) and now the illustrated two-fold Mitsunobu reaction led to the anticipated product **4.25** as a mixture of diastereoisomers in a 45% combined yield.



Scheme 4.06: *Reagents and Conditions (a)* PPh_3, DIAD, THF, 0 °C, 2 h

Having solved the teething problems associated with the originally proposed synthetic plan, compound **4.25A/B** was brominated (**Scheme 4.07**) using molecular bromine generated in situ from sodium bromide and oxone with a 1:1 v/v mixture of acetone and water serving as the reaction medium. The corresponding mixture of dibromides **4.26A** and **4.26B** was thus obtained and using fractional crystallisation techniques the former diastereoisomer could be isolated as a crystalline solid and in a form suitable for single-crystal X-ray analysis. The derived ORTEP is shown in **Figure 4.10** and clearly reveals that the compound is D/L-diastereoisomeric form and so it follows that the other (oily) isomer, which was also fully characterised, is the *meso* compound **4.26B**.



4.25A **4.25B** **4.26A** crystaline solid **4.26B** oil

Scheme 4.07: *Reagents and Conditions* (*a*) NaBr, oxone, acetone/water (1:1 v/v), RT, 16 h

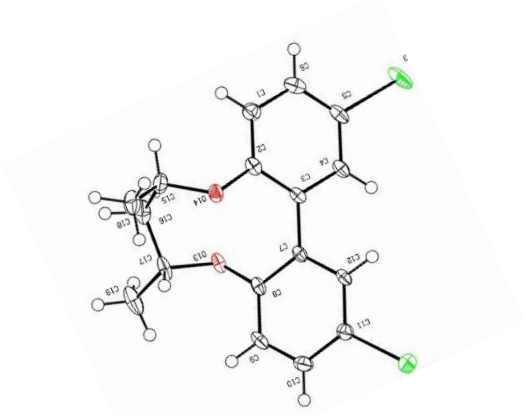
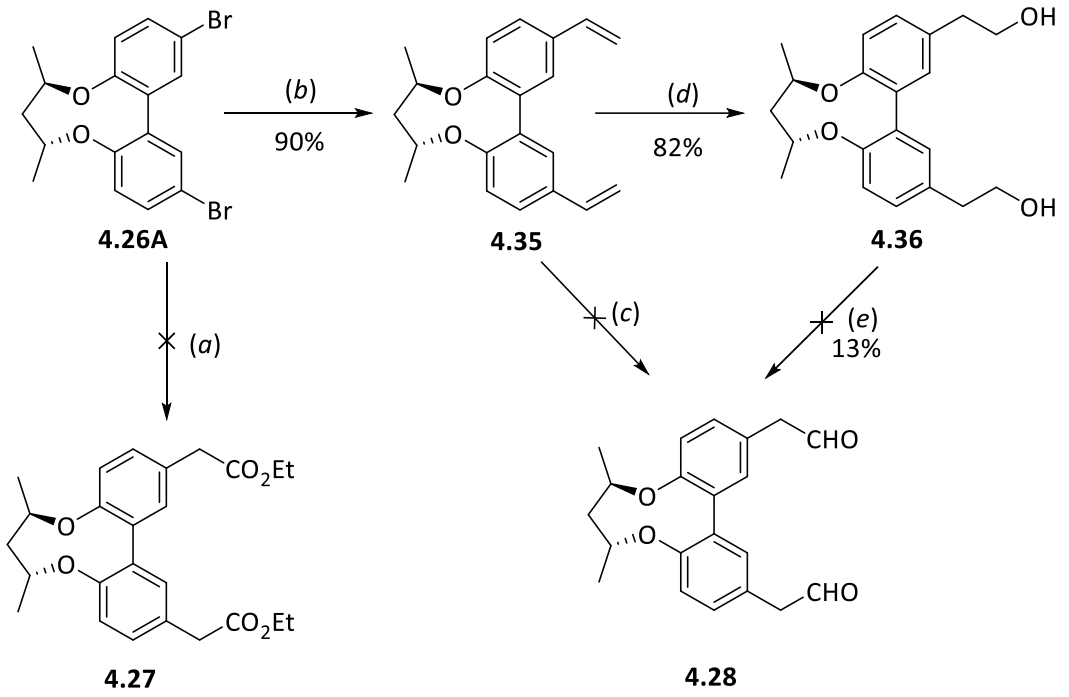


Figure 4.10: *ORTEP derived from single-crystal X-ray analysis of racemic dibromide **4.26A***

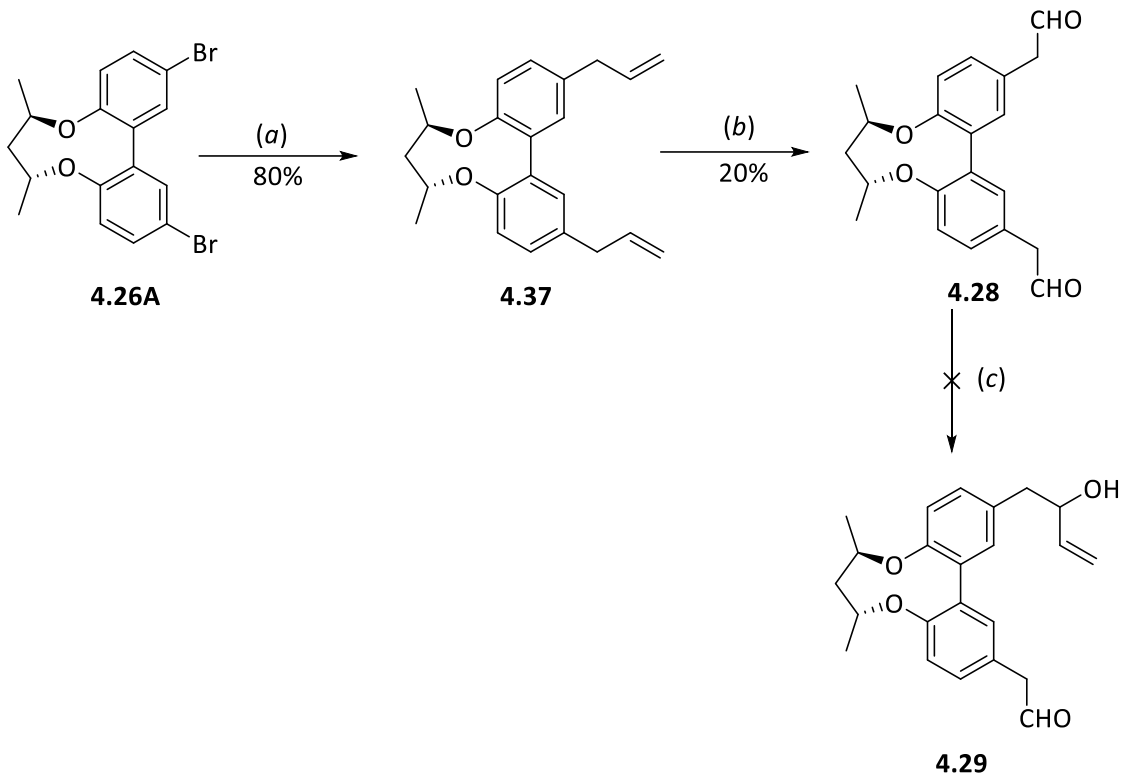
With the racemic dibromide **4.26A** in hand, attention turned to the preparation of the diester **4.27** shown in **Scheme 4.08**. However, attempts to affect a Negishi cross-coupling of the former compound with the Reformatsky enolate derived from ethyl α-bromoacetate failed. In contrast, the dibromide participated in a Stille cross-coupling with vinyl tributyltin in the presence of $Pd(PPh_3)_4$ and so affording the bis-styrene **4.35** in 90% yield. Attempts to engage compound **4.35** in an anti-Markovnikov-Wacker oxidation under the conditions described by Grubbs[19] failed to generate dialdehyde **4.28**. In contrast, on treating diene **4.35** with the

borane-tetrahydrofuran complex and then treating the (presumed) resulting bis-borane with alkaline hydrogen peroxide gave the diol **4.36** in good yield. Disappointingly, however, all effects to convert this, by two-fold oxidation, into the corresponding di-aldehyde failed.



Scheme 4.08: *Reagents and Conditions* (*a*) $BrCH_2CO_2C_2H_5$, activated zinc, $Pd(PPh_3)_4$, THF , 60 °C, 16 h; (*b*) vinyl tributyltin, $Pd(PPh_3)_4$, toluene, 80 °C, 16 h; (*c*) $PdCl_2(MeCN)_2$, H_2O, *p*-benzoquinone, *t*-BuOH, 85 °C, 15 min; (*d*) BH_3.THF, THF, RT, 16 h then H_2O, NaOH, H_2O_2, 40 °C, 1 h; (*e*) DMP, pyridine, DCM, RT, 3 h

The difficulties detailed immediately above (*viz*. in accessing di-aldehyde **4.28**) could be circumvented by employing the protocols shown in **Scheme 4.09**. The three-step synthetic sequence used to produce this sub-target started with the conversion of racemic bromide into the diallylated compound **4.37** (80%) under Stille cross-coupling conditions and using two equivalents of allyl tributyltin in the presence of $Pd(PPh_3)_4$. Diene **4.37** was then subjected to oxidative cleavage using ozone and the resulting bis-ozonide reduced with triphenylphosphine. As a result, di-aldehyde **4.28** was obtained albeit in 20% yield, an outcome attributed to the likely ready air oxidation of this product. Accordingly, the unpurified di-aldehyde was immediately treated with varying equivalents of vinyl magnesium bromide but the desired alcohol **4.29** was not observed under the reaction conditions explored.

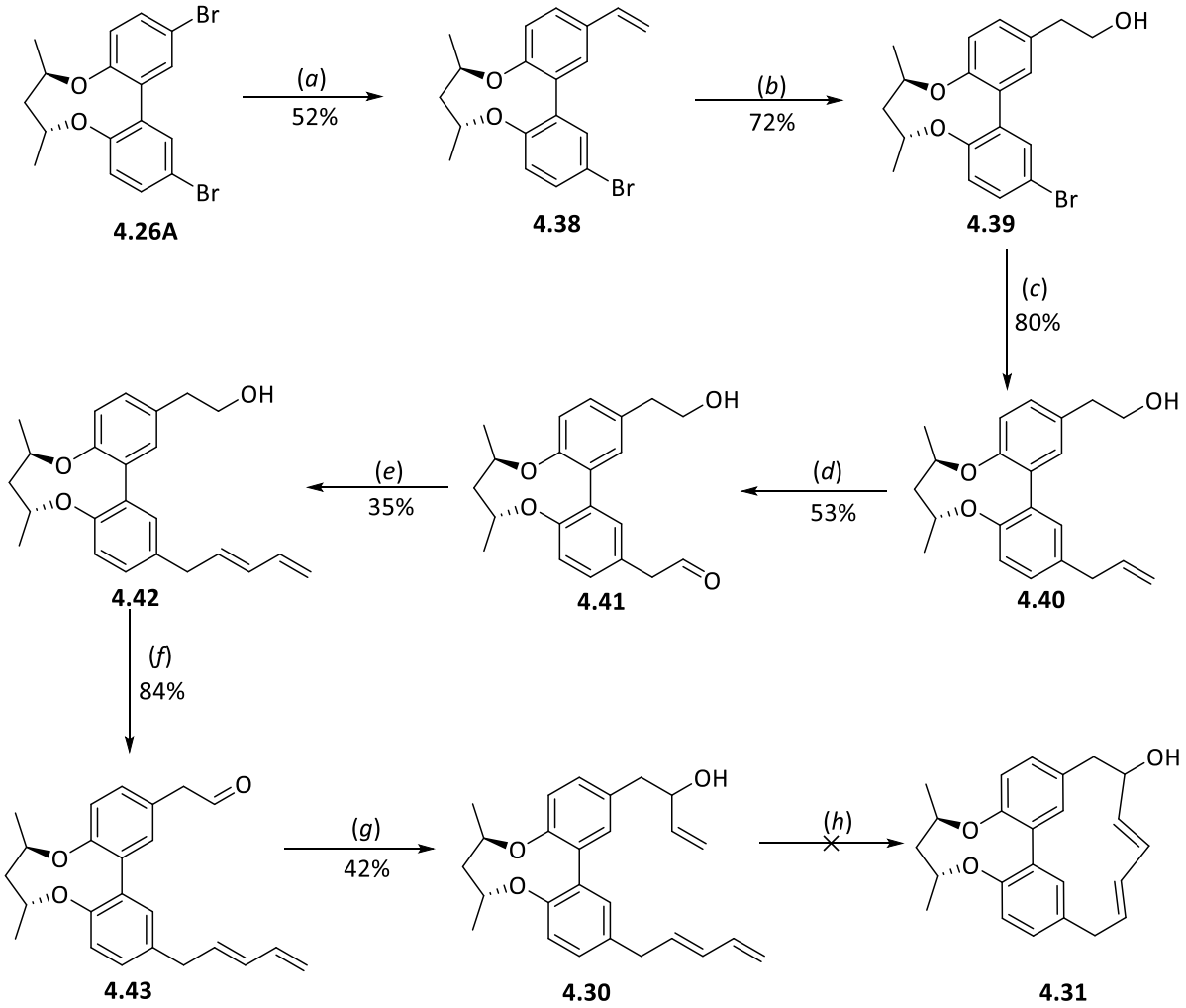


4.26A **4.37** **4.28** **4.29**

Scheme 4.09: *Reagents and Conditions* (*a*) Allyl tributyltin, $Pd(PPh_3)_4$, toluene, 80 °C, 16 h; (*b*) ozone, DCM, −78 °C, then PPh_3, 18 °C, 1 h; (*c*) vinyl magnesium bromide, THF, −78 °C, 1 h

It was thought the "issue" encountered during the course of the studies described immediately above could be circumvented by preparing a less refractory mono-rather than di-aldehyde. Such an approach would result in the necessary desymmetrizing of the biaryl core although an attendant increase in the complexity of the derived NMR spectra would result. Based on the preceding results, and as shown in **Scheme 4.10**, a Suzuki–Miyaura cross-coupling of dibromide **4.26A** with just one equivalent of vinylboronic acid pinacol ester [and $Pd(PPh_3)_2Cl_2$ as catalyst] resulted in the formation of compound **4.38**. This olefin was itself subjected to a hydroboration-oxidation reaction and thereby affording alcohol **4.39**. A Stille cross-coupling, now using an allylstannane, provided compound **4.40**, the double bond of which was oxidatively cleaved using ozone and after a reductive work-up the aldehyde **4.41** obtained. Compound **4.41** could be engaged in a HWE reaction with the anion derived from diethyl allyl phosphonate and so affording the diene **4.42** albeit in just 35% yield. Oxidation of the primary alcohol residue within this last compound was effected using the Dess-Martin periodinane (DMP) and the aldehyde **4.43** (84%) so-formed then reacted with vinyl

magnesium bromide at −15 °C to give compound **4.30** in 42% yield and as an inseparable mixture of diastereoisomers.



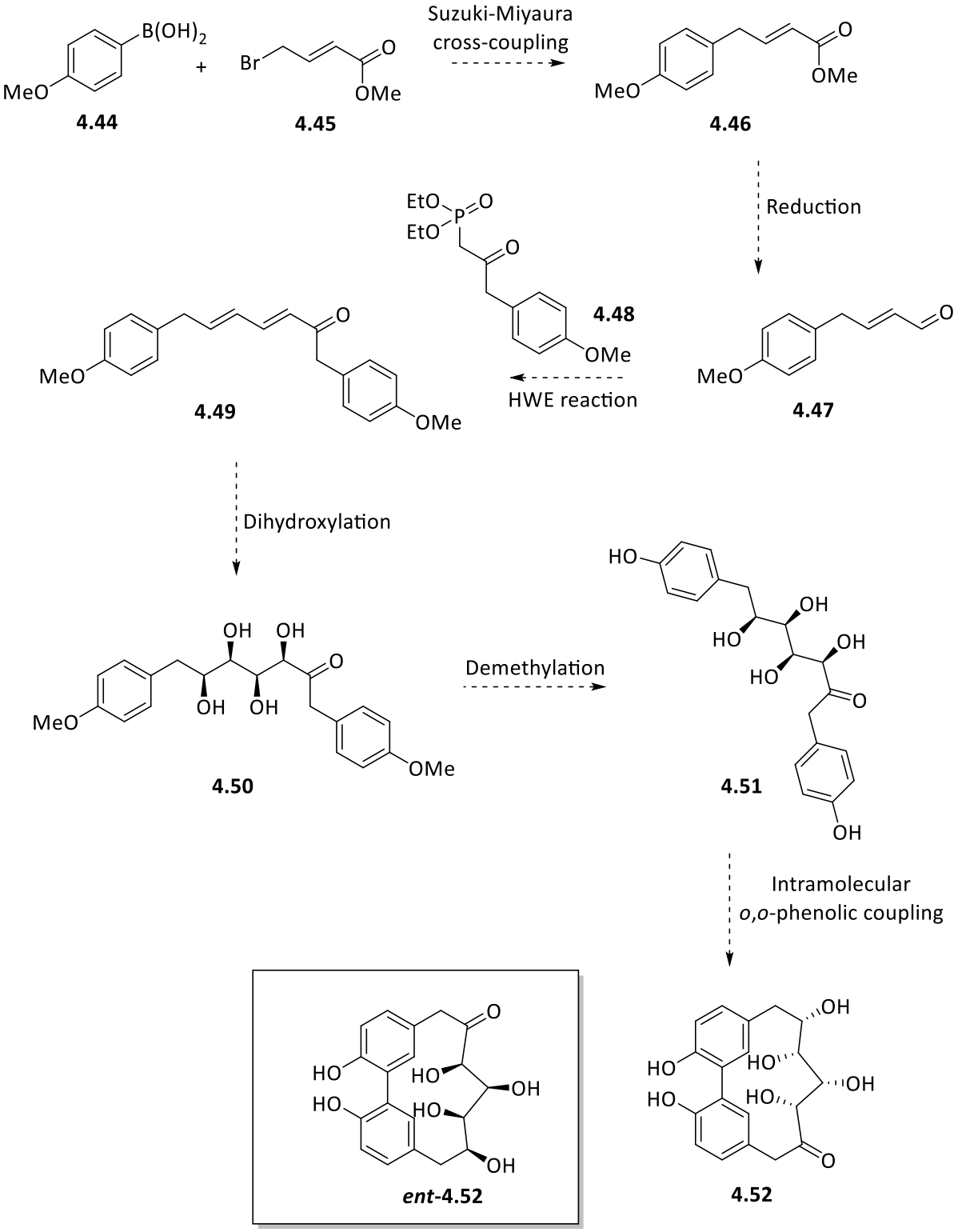
Scheme 4.10: *Reagents and Conditions (a)* vinylboronic acid pinacol ester, $Pd(PPh_3)_2Cl_2$, Cs_2CO_3, dioxane, 75 °C, 16 h; (*b*) BH_3.THF, THF, RT, 16 h then H_2O, NaOH, H_2O_2, 40 °C, 1 h; (*c*) allyl tributyltin, $Pd(PPh_3)_4$, toluene, 80 °C, 16 h; (*d*) ozone, DCM, −78 °C, then PPh_3, RT, 1 h; (*e*) *n*-BuLi, diethyl allyl phosphonate, THF, −78 °C, 2 h then RT, 16 h; (*f*) DMP, DCM, RT, 16 h; (*g*) $CeCl_3$, vinyl magnesium bromide, THF, −78 °C, 1 h; (*h*) Grubbs' (II) cat., DCM, reflux, 2 h

In an effort to generate macrocycle **4.31**, triene **4.30** was exposed to the second-generation Grubbs' catalyst. Sadly, however, the hoped-for product (*viz*. **4.31**) was not observed. Indeed, only complex mixtures of products were observed during the course of the many attempts (by varying the concentration of the catalyst or temperature) made by the author to effect the desired RCM reaction.

The problems encountered during the course of the work described above prompted a major re-evaluation of the approach to be taken in attempting to prepare macrocyclic diaryl cycloheptanoids. The new approach focussed on efforts to prepare a 1,7-diarylated heptanone in the hope that this could then be engaged in an intramolecular phenolic coupling and so establishing, at a late-stage, the crucial biaryl bond of giffonin U (**4.02**). Such an approach, which may be considered biomimetic in nature, is described in Section **4.05**.

4.06 New Approach to the Total Synthesis of 1,7-Diarylated Heptanones

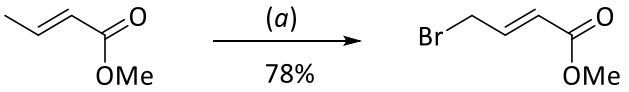
The new approach is outlined in **Scheme 4.11** and was to start with the Suzuki-Miyaura cross-coupling of (4-methoxyphenyl)boronic acid (**4.44**) and methyl (*E*)-4-bromobut-2-enoate (**4.45**) under conditions reported by Tramutola.[20] Reduction of the resulting arylcrotonate **4.46** to give aldehyde **4.47** and the engagement of this in a HWE reaction with phosphonate **4.48** should afford the conjugated product **4.49**. Dihydroxylation of both double bonds of the diene residue associated with compound **4.49** followed by cleavage of the aryl ether units was expected to give, *via* intermediate **4.50**, a substrate, **4.51**, suitable for participation in an intermolecular phenolic coupling reaction[21] leading to the diaryl cycloheptanoid **4.52**. Of course, the illustrated sequence would afford a racemic mixture of compound **4.52** and *ent*-**4.52** but by using asymmetric dihydroxylation techniques[22] it should be possible to make one or other of these enantioselectively.



Scheme 4.11: *A new synthetic strategy leading to the 1,7-diaryl cycloheptanoid **4.52***

The implementation of opening steps of this proposed synthesis proved straightforward. Thus, as shown in **Scheme 4.13**, the required halide **4.45** was obtained by radical-based

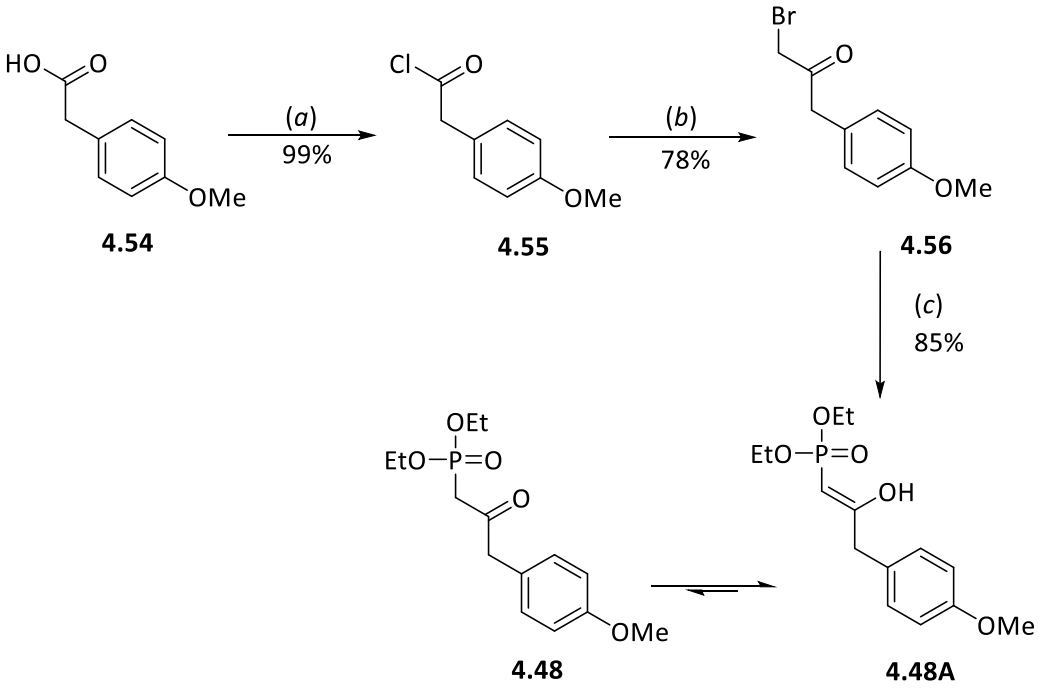
bromination of methyl crotonate (**4.53**) at the γ–position using *N*-bromosuccinimide (NBS) in the presence of AIBN.



4.53 **4.45**

Scheme 4.12: *Reagents and Conditions* (*a*) NBS, AIBN, MeCN, reflux, 3.5 h

Phosphonate **4.48**, another crucial coupling partner in the proposed synthetic plan, was obtained by the pathway shown in **Scheme 4.13**. So, *p*-methoxyphenylacetic acid (**4.54**) was converted into the corresponding acid chloride under standard conditions and then reacted with trimethylsilyldiazomethane and HBr to deliver the bromide **4.56**. Heating this bromide in neat triethyl phosphite, so as to affect a Michaelis-Arbuzov reaction, then gave the phosphonate **4.48A** in 85% yield and which appeared, as judged by spectroscopic analysis, to reside largely in its enolic form.[23]



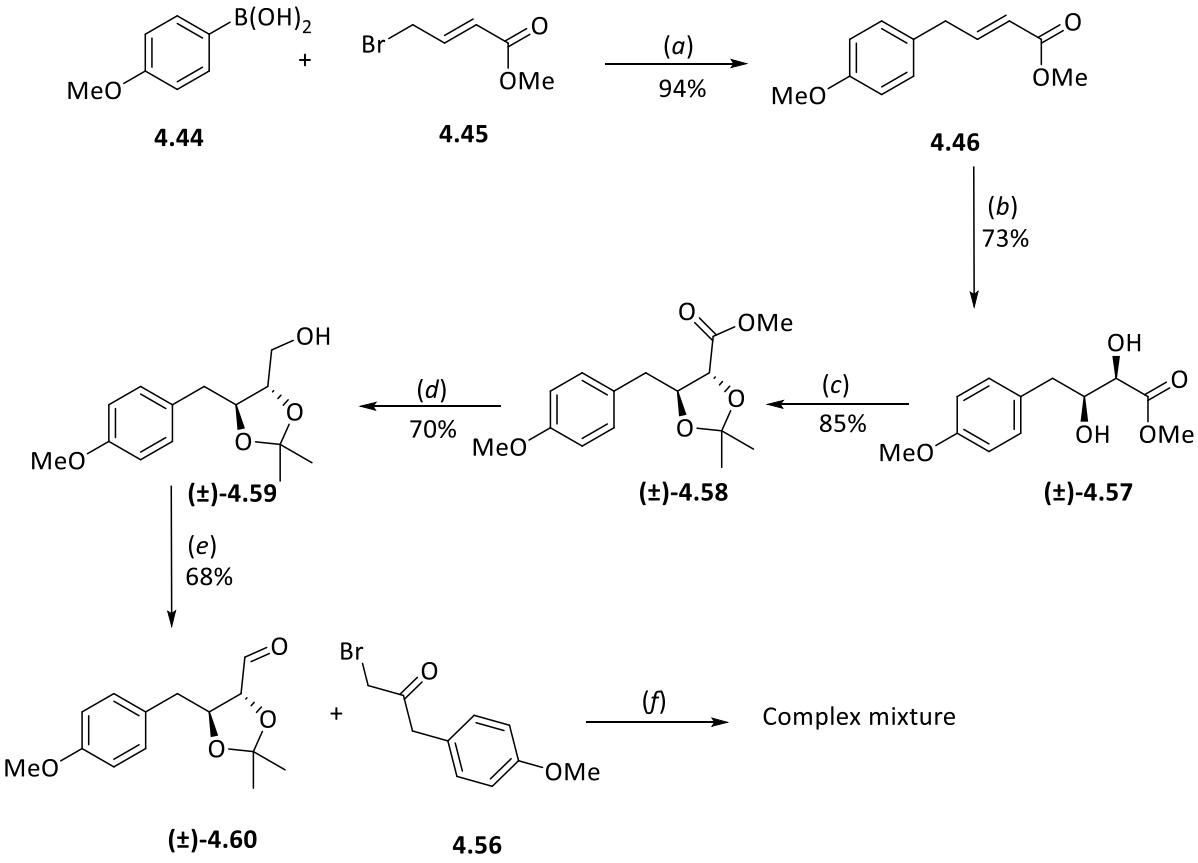
4.54 **4.55** **4.56**

4.48 **4.48A**

Scheme 4.13: *Reagents and Conditions* (*a*) $(COCl)_2$, DMF, DCM, RT, 2 h; (*b*) $TMSCHN_2$, HBr, MeCN, RT, 4 h; (*c*) triethyl phosphite, 110°C, 3 h

In furthering the synthetic plan shown in **Scheme 4.11**, cross-coupling of the arylboronic acid **4.44** with the halide **4.45** (**Scheme 4.14**) was pursued and this proceeded smoothly. Upjohn dihydroxylation[24] of the product alkene **4.46** using osmium tetroxide as a catalyst and a

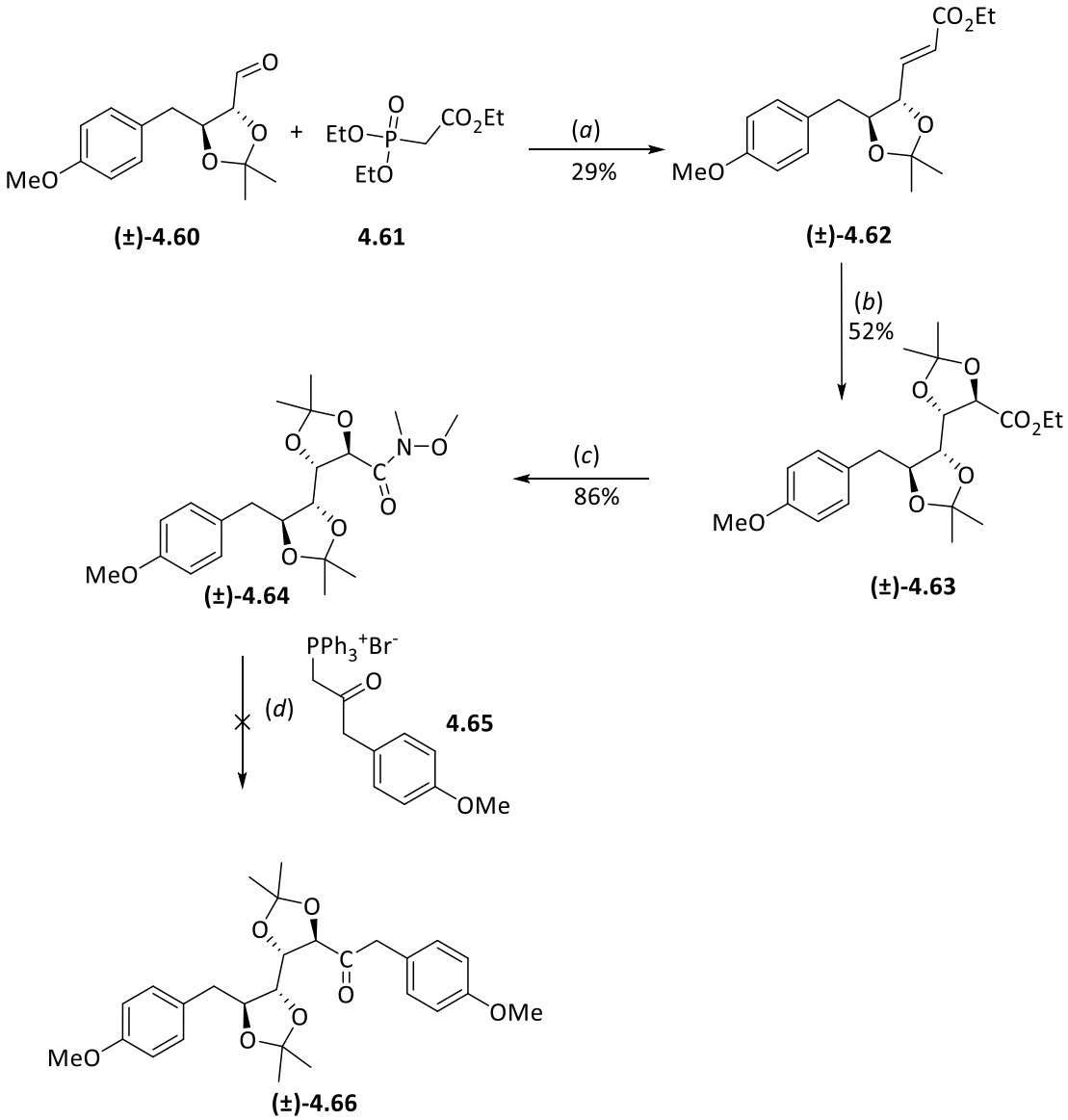
stoichiometric amount of NMO as the oxidant gave, in racemic form, the anticipated diol **(±)-4.57**. This last compound was converted into the corresponding acetonide **(±)-4.58** under standard conditions and reduction of the ester motif associated with this product using DIBAl-H gave the primary alcohol **(±)-4.59**. This last compound was oxidized to the corresponding aldehyde **(±)-4.60** but all efforts to engage this in a HWE reaction with phosphonate ester **4.48** failed. In an effort to side-step this problem, aldehyde **(±)-4.60** was reacted with the bromoketone **4.56** in the presence of base and in the hope that a Darzens reaction would take place to give an epoxide that could be elaborated further in pursuit of target **4.52**. However, all efforts directed toward such an outcome were in vain – once again, only complex mixtures of products were obtained.



Scheme 4.14: *Reagents and Conditions* (*a*) KF, $Pd(OAc)_2$, dioxane, RT, 2 h; (*b*) NMO, $K_2OsO_2(OH)_4$, citric acid, *t*-BuOH/H_2O (1:1 v/v), RT, 16 h; (*c*) 2,2 DMP, *p*-TsOH, DCM, RT, 2 h; (*d*) DIBAl-H, Et_2O, −40 to 0 °C, 3 h; (*e*) DMP, pyridine, DCM, RT, 3 h; (*f*) KHMDS, THF, −55 °C, 2 h

In an effort to establish a more facile synthetic route to target **4.52** (**Scheme 4.15**), a HWE reaction involving ethyl 2-(diethoxyphosphoryl)acetate (**4.61**) and aldehyde **(±)-4.60** was carried out in the presence of *n*-butyl lithium to furnish α,β-unsaturated ester **4.62**. Without

further purification, this alkene was dihydroxylated under standard conditions and the resulting diol immediately converted into the corresponding acetonide **(±)-4.63**, this being obtained, after chromatographic purification, in 52% yield.

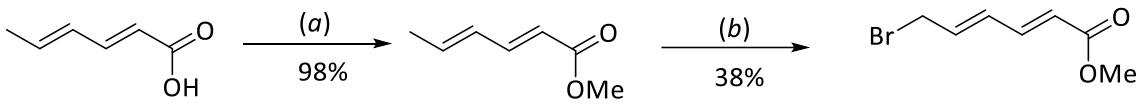


Scheme 4.15: *Reagents and Conditions* (*a*) *n*-BuLi, THF, -78 °C to RT, 6 h; (*b*) $K_2OsO_2(OH)_4$, NMO, citric acid, *t*-BuOH/H_2O (1:1 v/v), RT, 16 h then 2,2 DMP, *p*-TsOH, DCM, RT, 2 h; (*c*) HCl.HN(OMe)Me, *i*-PrMgCl, THF, −15 to 0 °C, 1 h; (*d*) *n*- BuLi, THF, −78 to 0 °C, 3 h

In 2005, Murphy and co-workers[25] reported a direct and efficient method for converting Weinreb amides into ketones through their reaction with alkylidene triphenylphosphoranes followed by *in situ* hydrolysis of the initially formed adduct. In an effort to implement such a process (**Scheme 4.15**) and thus form the 1,7-diarylated and highly oxygenated heptanoid (±)-**4.66**, ethyl ester **(±)-4.63** was treated, at –15 °C, with the hydrochloride salt of *N*,*O*-dimethylhydroxylamine in the presence of *iso*-propylmagnesium chloride and so generating

the Weinreb amide **(±)-4.64** (86%). However, upon submitting this to reaction with the ylide derived from triphenylphosphonium bromide **4.65** only complex product mixtures were obtained. The reaction of amide **(±)-4.64** with (4-methoxybenzyl)magnesium bromide was also explored but this too was unproductive since, once again, complex product mixtures were obtained on each occasion.

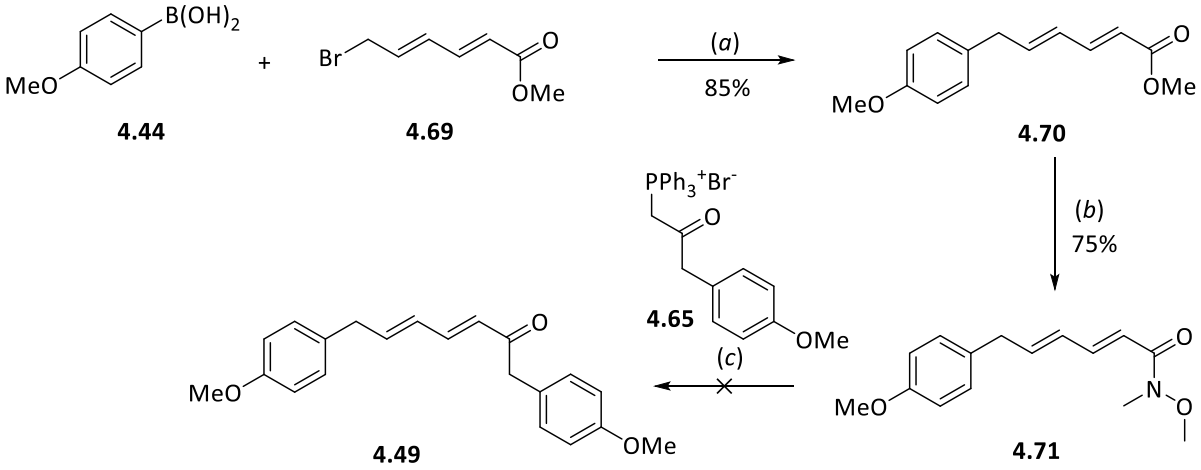
The failure to implement the Weinreb ketone synthesis described immediately above prompted consideration of a variation on this approach wherein the substrate for such a process contained alkene rather than acetonide residues. To that end, the simple, two-step reaction sequence shown in **Scheme 4.16** was implemented and wherein the commercially available sorbic acid [(2*E*,4*E*)-hexa-2,4-dienoic acid, **4.67**] was first converted into the corresponding methyl ester under standard conditions. A regioselective, radical-based bromination of ester **4.68** at the γ–position using *N*-bromosuccinimide (NBS) in the presence of AIBN then afforded the anticipated bromo-diene **4.69** albeit in just 38% yield.



4.67 **4.68** **4.69**

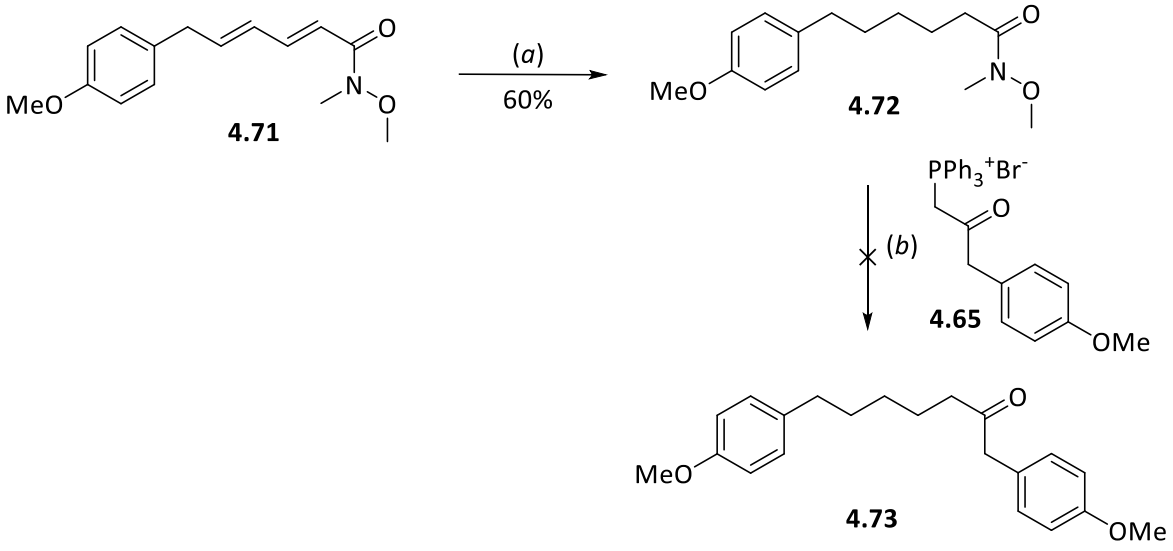
Scheme 4.16: *Reagents and Conditions* (*a*) $SOCl_2$, MeOH, reflux, 2 h; (*b*) NBS, AIBN, MeCN, 110°C, 3.5 h

As shown in Scheme **4.17**, Suzuki-Miyaura coupling of (4-methoxyphenyl)boronic acid (**4.44**) with the bromide **4.69** afforded the desired coupling product **4.70** and this was converted into the corresponding Weinreb amide **4.71** under standard conditions. Disappointingly, however, on reacting this last compound with either the ylide derived from triphenylphosphonium bromide (**4.65**) or with (4-methoxybenzyl)magnesium bromide only complex product mixtures were observed.



Scheme 4.17: *Reagents and Conditions* (*a*) KF, $Pd(OAc)_2$, dioxane, RT, 2 h; (*b*) HCl.HN(OMe)Me, *i*-PrMgCl, THF, −15 to 0 °C, 1 h; (*c*) *n*-BuLi, THF, −78 to 0 °C, 3 h

On the basis that the conversion **4.71** → **4.49** might have failed because of the presence of the potentially sensitive conjugated diene reside within the substrate, this Weinreb amide was subjected to exhaustive hydrogenation and so affording the fully saturated derivative **4.72** in 60% yield. Once again, however, on reacting the latter compound with the ylide derived from salt **4.65** only complex product mixtures were obtained.



Scheme 4.18: *Reagents and Conditions* (*a*) H_2, Pd/C, DCM, RT, 16 h; (*b*) *n*-BuLi, THF, −78 to 0 °C, 3 h

The reasons for the author's inability to exploit any of the Weinreb amides reported above in the synthesis of 1,7-diarylated heptanoids remains unclear at the present time. Efforts to exploit various aspects of reaction sequences described above continue and the outcomes of such efforts will be reported in due course.

4.07 References

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Chapter Five

5.01 Targeting RNA Polymerase I Transcription for Cancer Therapeutics

Cancer is among the leading causes of death worldwide. In biological terms, cancer is defined as uncontrolled cell growth, a condition that often metastasizes to other cells and organs.[1] The highest percentages of cancers occur in the breast, prostate, lung, bronchus, colon rectum, thyroid and urinary bladder.[2] More particularly, prostate and breast cancers are among the major ones afflicting men and women, respectively. At the cellular level, cancer is a result of a series of successive gene mutations that activate oncogenes and/or deactivate the tumour suppressor genes and so leading to uncontrolled cell cycles. Chemical carcinogens, viruses, bacteria, and/or radiation are often the underpinning causes of cancer.[3,4] Over the last five decades, great effort has been expended world-wide to understand these malignant diseases and so devise effective therapies. Since cancer is, in fact, a heterogeneous collection of diseases this presents major challenges both in terms of diagnosis and treatment.[5]

Many of the most effective current cancer treatments involve small molecules, antibodies, and/or immunotherapies. Gratifyingly, the modern variants of such therapies are capable, in favourable cases, of selectively targeting the aberrant cells and so reducing side effects. An underpinning feature of such approaches has been the identification of previously unexplored but essential biological processes that can then be disrupted in some effective (and selective) way. Ribosome biogenesis (RiBi) is one such process that has been drawing increasing attention in recent times.

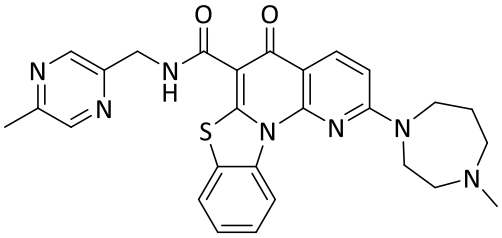
RiBi[6] (*viz*. the production of ribosomes) is the most versatile and energy-demanding of biological processes. Ribosomes are responsible for the translation of information contained in mRNAs into functional proteins. The human 80S ribosome is composed of two subunits namely 40S [containing 18S ribosomal RNA (rRNA) and 33 ribosomal proteins (RPs)] and 60S (containing 5S, 5.8S and 28S rRNAs and 47 RPs).[7] Processing of the 47S pre-rRNA through transcription of RNA polymerase I (Pol I) generates 18S, 5.8S and 28S rRNAs while the 5S rRNA and the multiple RPs are transcribed by RNA Polymerase III (Pol III) and RNA polymerase II (Pol II), respectively.[8] Aberrant elevation of nucleolar size and number is a reflective

measurement of high rates of RiBi, and these have been recognized as hallmarks of many cancers.

As a result of sensing perturbations to RiBi, the nucleolus can initiate the nucleolar stress response (NSR), also termed the "nucleolar surveillance pathway" (NSP).[9] This can occur when rRNA synthesis is acutely disrupted through blocking of the binding of the Pol I re-initiation complex (PIC) and thereby stalling elongation or altering the processing of the 47S rRNA. As a result, there is an excess of "free" ribosomal proteins, namely those that are not incorporated into the ribosomal subunits. Consequently, free ribosomal proteins can bind MDM2-releasing p53,[10] a tumour suppressor gene, so that p53 basal level of expression is no longer regulated by degradation. The resulting rapid accumulation of p53 triggers a variety of downstream effects including cell cycle arrest, DNA repair and apoptosis. Not surprisingly, then, mutations in p53 mediating a loss of function results in uncontrolled growth and tumour development. Activation of the NSR could cause cell death and thus supporting the concept that RiBi is a pre-eminent candidate for targeted cancer therapeutics. Pursuing such possibilities through inhibition of Pol I transcription has added advantages since this enzyme only transcribes a single pre-RNA transcript, an indication of a highly selective and regulated process, extensive application for various cancer types and less sensitivity of healthy somatic cells towards the Pol I inhibition, which indirectly increase the selectivity towards malignant cells.[11]

5.02 Selective Inhibitors of Polymerase I Transcription

Even though many currently approved cancer therapeutics act by inhibiting rRNA synthesis, none is known to do so by directly interacting with the Pol I multiprotein enzyme complex. As such, targeting Pol I for the purposes of developing new anti-cancer agents is considered to be a fertile area of research. In an effort to explore such possibilities, in 2012, Haddach and co-workers[12] identified the polycyclic quinolone CX-5461 (**5.01**) as the first direct and selective inhibitor of Pol I and so representing a new anti-cancer agent possessing a novel mode of action.



5.01

Figure 5.01: *The structure of CX-5461 (**5.01**)*

Indeed, CX-5461 was identified as a suitable clinical development candidate that selectively inhibits Pol I at low concentrations in a range of cancer cell lines with a selectivity some 200-fold higher than its inhibition of Pol II. Furthermore, the compound is orally bioavailable as well as displaying high potency in both mechanistic and antiproliferative cellular assays. At the time of writing, CX-5461 has successfully passed through phase I clinical trials [conducted in Australia (ACTRN12613001061729)] in patients with advanced haematological cancers.[13] It is also in phase I clinical trials, in Canada (NCT02719977), for the treatment of solid tumours.[14] The compound is also well-tolerated and efficacious in treating haematological cancers (acute myeloid leukemia and multiple myeloma) and solid cancers (prostate and ovarian cancers) as well as in treating non-cancerous diseases such as multiple sclerosis, infections of African trypanasomiasis, the human cytomegalovirus and type-1 herpes simplex.[8, 15, 16]

5.03 Current Challenges with CX-5461

Notwithstanding its utility as a therapeutic agent for treating cancer, the direct cellular target(s) or interactor(s) and underlying molecular mechanism(s) of action of CX-5461 remain unclear. This is in part because of its seemingly broad mechanisms of action. So, for example, in p53 wild-type cancers CX-5461 induces apoptosis by activating the NSP through nucleolar disruption. More specifically, when CX-5461 inhibits Pol I transcription this, in turn, results in the rapid accumulation of the p53 protein that itself transcriptionally regulates those genes involved in cell cycle arrest, apoptosis and genome stability. In contrast, in p53-null cancers, a DNA-damage-like response is activated that induces a G2/M cell-cycle arrest.[10] Furthermore, CX-5461 may exert off-target effects such as topoisomerase II poisoning and chromosomal DNA G-quadruplex stabilisation which may have an impact on both its efficacy and toxicity profiles (as well as any acquired resistance mechanisms).[18]

5.04 Exploiting Click Chemistry Techniques for Identifying the Cellular Targets of CX-5461†

Click Chemistry, wherein an organic azide adds to an alkyne, provides a useful means of attaching small organic molecules (drugs) to, for example, fluorophores and other systems (e.g. biotin) that allow for probing of the potential cellular targets of the drug.[17] Accordingly, the thrust of the author's work in this area was to attach alkyne residues at sites on the framework of CX-5461 (**5.01**) that would not adversely impact the activity of the compound but to which suitable tags could be added *via* click chemistry. Specifically, these alkyne units could be utilized to conduct click reactions with azides bearing biotin or fluorescent tags. The resulting [3+2]-cycloadducts would then be submitted to biological assays using appropriate cancer cell lines. To such ends the two regio-isomeric alkynyl-substituted CX-5461 compounds **5.02** and **5.03** (**Figure 5.02**) were targeted for synthesis.

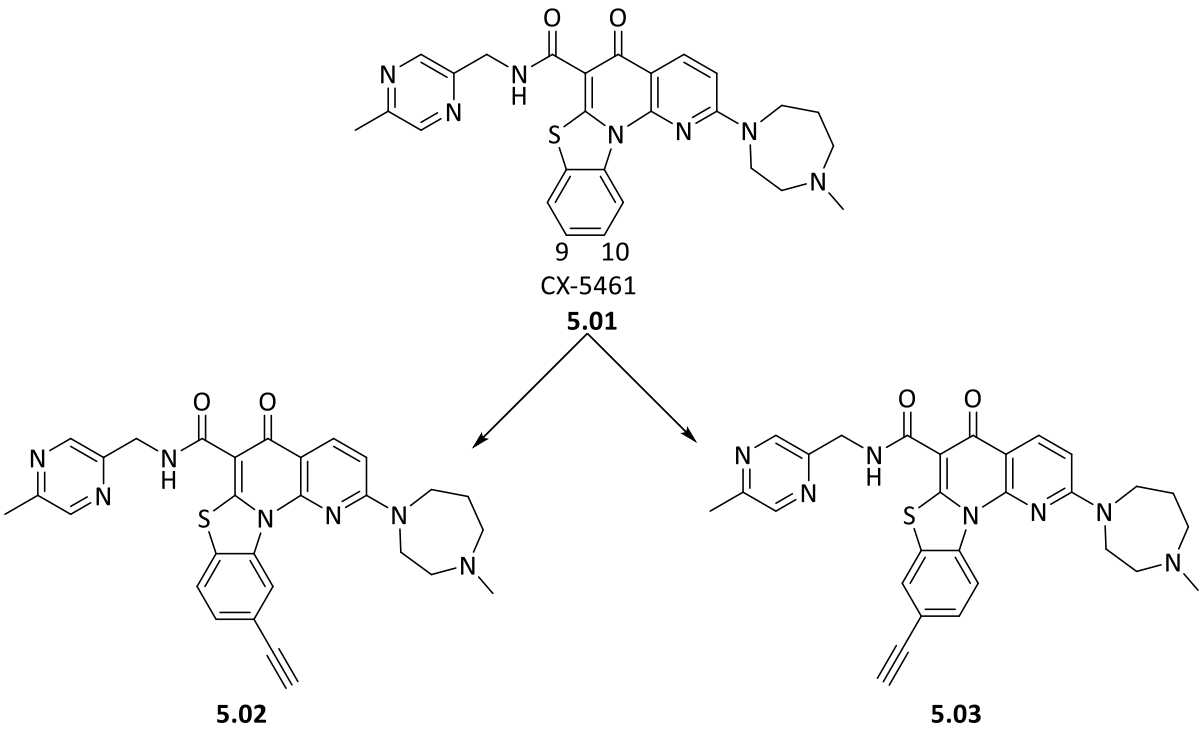


Figure 5.02: *The structures, **5.02** and **5.03**, of two regio-isomeric alkynyl-substituted CX-5461 (**5.01**) analogues targeted for synthesis in the present study*

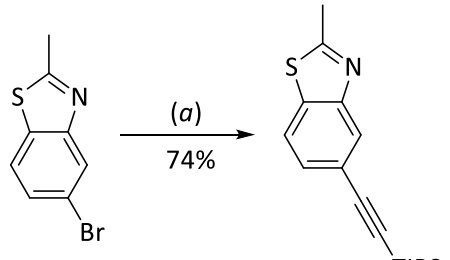
† (Key aspects of the work described in this area have been published - Amarasiri, M.; Vo, Y.; Gardiner, M. G.; Poh, P.; Soo, P.; Pavy, M.; Hein, N.; Ferreira, R.; Hannan, K. M.; Hannan, R. D.; Banwell, M. G., *Aust. J. Chem.* **2021**, *74* (7), 540-556.

This was because it was not only thought that functionalization of the C9 and C10 positions of the parent framework would be straightforward but also that they were remote from the heteroatoms within in CX-5461 and that, therefore, the introduction of groups at these sites would not interfere with the necessary docking of the compound (drug) at its receptor or receptors.

Details of the preparation of the first of these target compounds (*viz*. **5.02** and **5.03**) are provided in the following section.

5.05 Preparation of the Alkynyl-Substituted CX-5461 Analogue 5.02

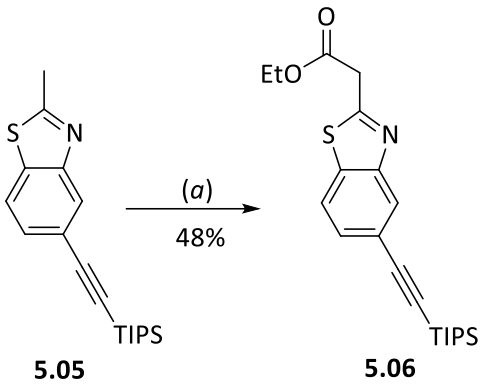
The route used to produce the required analogues of CX-5461 proved quite straightforward and exploited some preliminary "trail-blazing efforts" undertaken by the author's colleague Dr. Yen Vo. So, the protocol employed in preparing CX-5461 itself[12] was followed but now using the commercially available 5-bromo-substituted 2-methylbenzo[*d*]thiazole (**5.04**) (**Scheme 5.01**) as the starting material. In the pivotal and opening step of the reaction sequence, the starting halide was engaged in a Sonogashira cross-coupling reaction with ethynyltriisopropylsilane and so producing, in a very clean reaction, the TIPS-capped alkyne **5.05**.



5.04 **5.05**

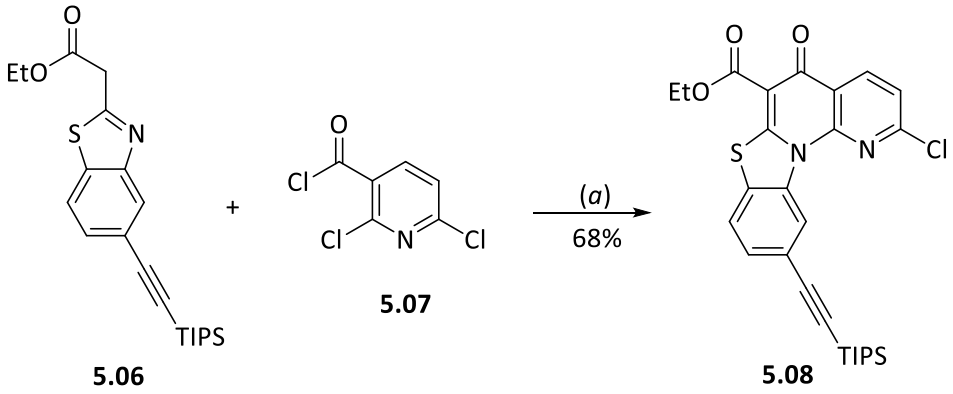
Scheme 5.01: *Reagents and Conditions (a)* ethynyltriisopropylsilane, $Pd(PPh_3)_4$, CuI, TEA/MeCN (1:1 v/v), 80 °C, 30 h

When the coupling product **5.05** was treated with *n*-butyl lithium (*n*-BuLi) then the corresponding 2-methylbenzo[*d*]thiazole anion was formed (**Scheme 5.02**) and this then trapped with ethyl chloroformate to generate ester **5.06** albeit in modest yield.



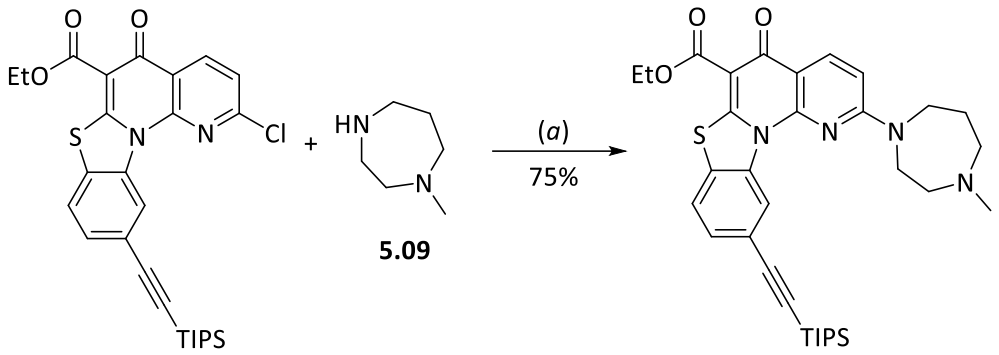
Scheme 5.02: *Reagents and Conditions* (*a*) *n*-BuLi, THF, -78 °C, 4 h then ethyl chloroformate, -78 °C to RT, 2 h

Reaction of this last compound (**5.06**) with commercially available 2,6-dichloronicotinoyl chloride (**5.07**) (**Scheme 5.03**) in the presence of magnesium chloride and triethylamine (TEA) resulted in *C*-acylation and *N*-arylation reactions (no order implied) to afford, after accompanying double-bond migration, the azaquinolone **5.08**. This was obtained in 68% yield.



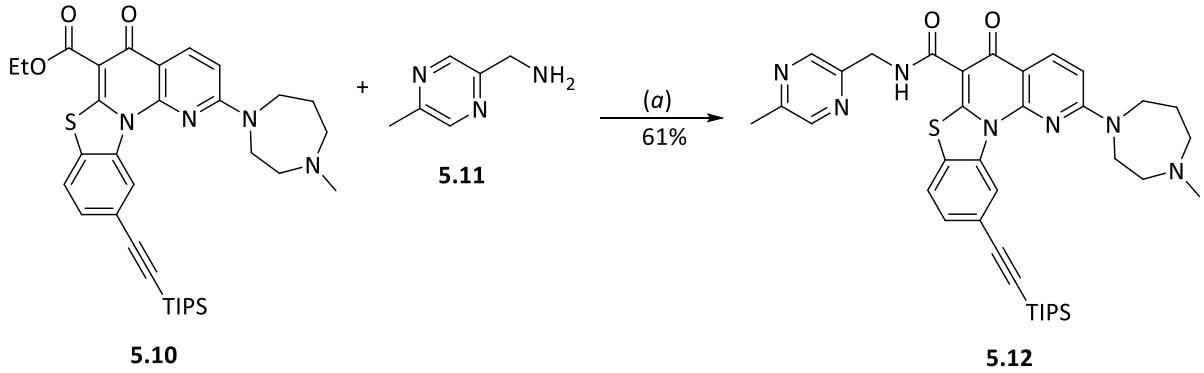
Scheme 5.03: *Reagents and Conditions* (*a*) TEA, $MgCl_2$, MeCN, -10 °C to 0 °C, 1 h

With compound **5.08** in hand the introduction of the 1,4-diazepane ring could be carried out using the nucleophilic addition/elimination reaction shown in **Scheme 5.04**. This was performed by refluxing 2-chloropyridine **5.08** with commercially available *N*-methyl-1,4-diazepane (**5.09**) in acetonitrile (**Scheme 5.04**) and so cleanly affording compound **5.10** incorporating the now nearly complete polyheterocyclic framework of CX-5461.



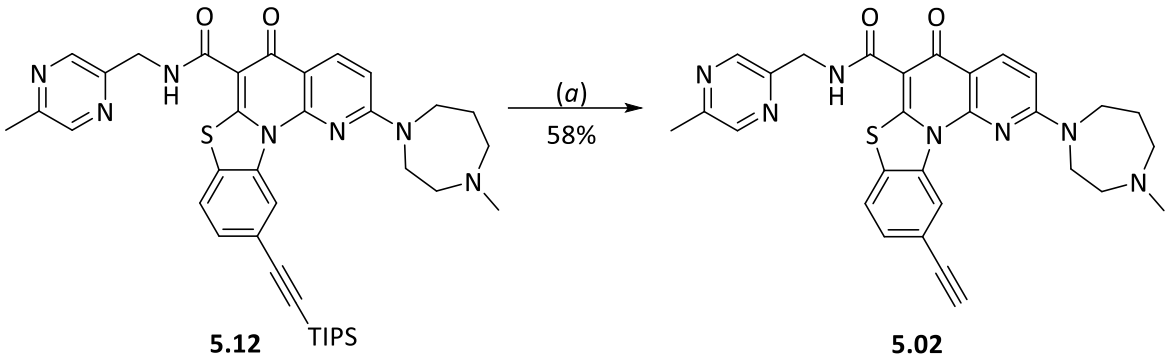
Scheme 5.04: *Reagents and Conditions* (*a*) MeCN, reflux, 4 h

Product **5.10** from the reaction shown above was subjected to a Lewis-acid catalyzed amidation reaction using commercially available (5-methylpyrazin-2-yl)methanamine (**5.11**) in the presence of the non-nucleophilic base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). This afforded amide **5.12** in 61% yield.



Scheme 5.05: *Reagents and Conditions* (*a*) $AlCl_3$, DBU, DCM, -5 °C, 1 h

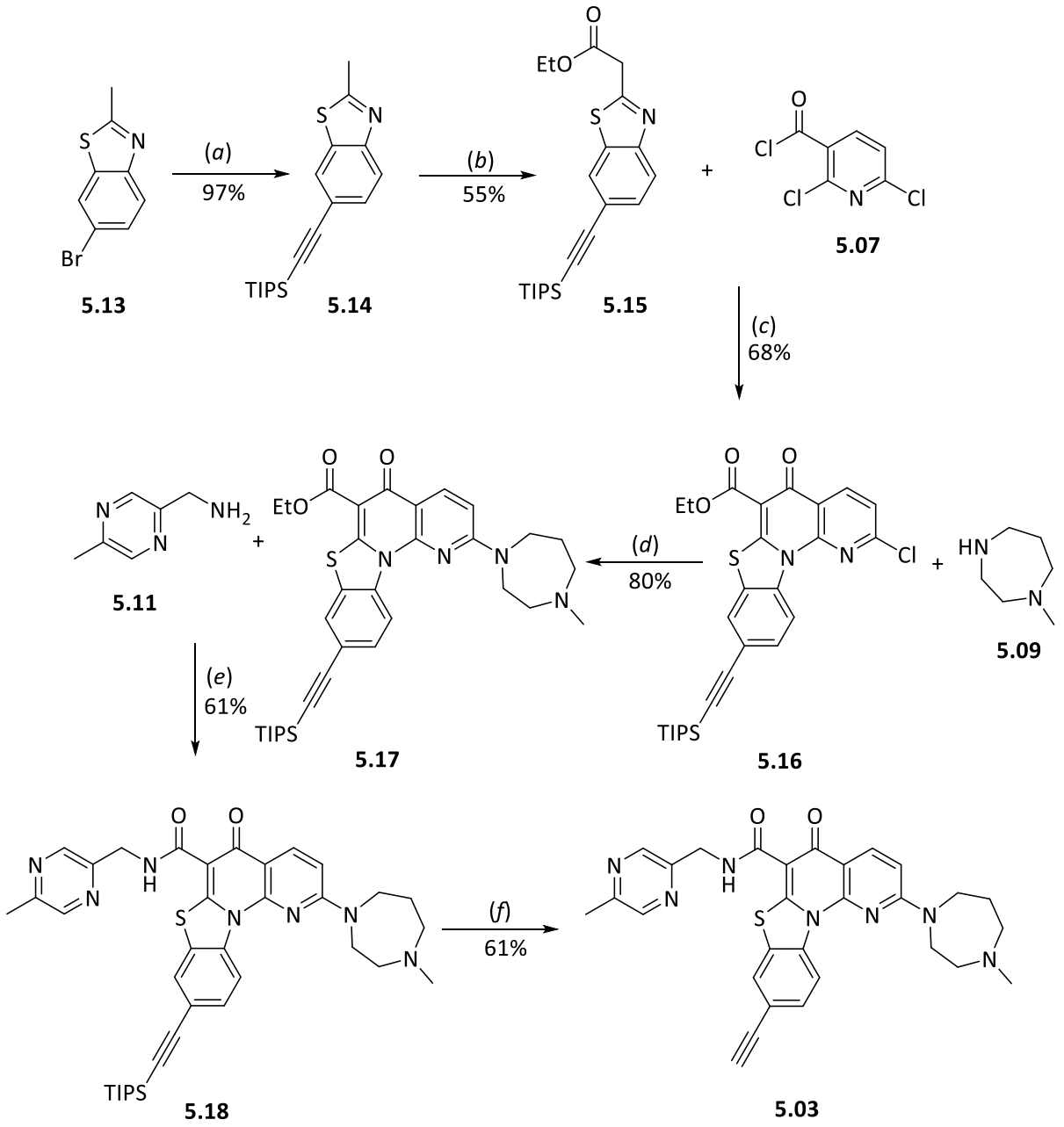
The final step of the reaction sequence is shown in **Scheme 5.06** and was carried out using the reaction conditions described by Hernandez and coworkers[20] for removing triisopropylsilyl groups from so capped terminal alkynes. Thus, treatment of compound **5.12** with silver fluoride in methanol afforded the targeted terminal alkyne **5.02** in 58% yield.



Scheme 5.06: *Reagents and Conditions* (*a*) AgF, MeOH, RT, 3 h

5.06 Preparation of the Alkynyl-Substituted CX-5461 Analogue 5.03

Having obtained the C10 alkynyl substituted derivative **5.02** of CX-5461 by the pathway detailed above, the synthesis of the corresponding C9 isomer **5.03** was pursued using the route shown in **Scheme 5.07**. In this case synthesis started with commercially available 6-bromo-2-methylbenzo[*d*]thiazole (**5.13**) and all six steps of the reaction sequence proceeded uneventfully to give compound **5.03** in workable overall yield.



Scheme 5.07: *Reagents and Conditions (a)* ethynyltriisopropylsilane, $Pd(PPh_3)_4$, CuI, TEA/MeCN (1:1 v/v), 80 °C, 30 h; (*b*) *n*-BuLi, THF, -78 °C, 4 h then ethyl chloroformate, -78 °C to RT, 2 h; (*c*) TEA, $MgCl_2$, MeCN, -10 °C to 0 °C, 1 h; (*d*) MeCN, reflux, 4 h; (*e*) $AlCl_3$, DBU, DCM, -5 °C, 1 h; (*f*) AgF, MeOH, RT, 3 h

With the targeted C9 and C10 substituted CX-5461 derivatives in hand, both of them and all of their precursors were screened for their suitability for unequivocal characterization by single-crystal X-ray analysis. As it transpired only the starting materials **5.04** and **5.13** proved useful in this regard and the resulting plots are shown in **Figure 5.03**.

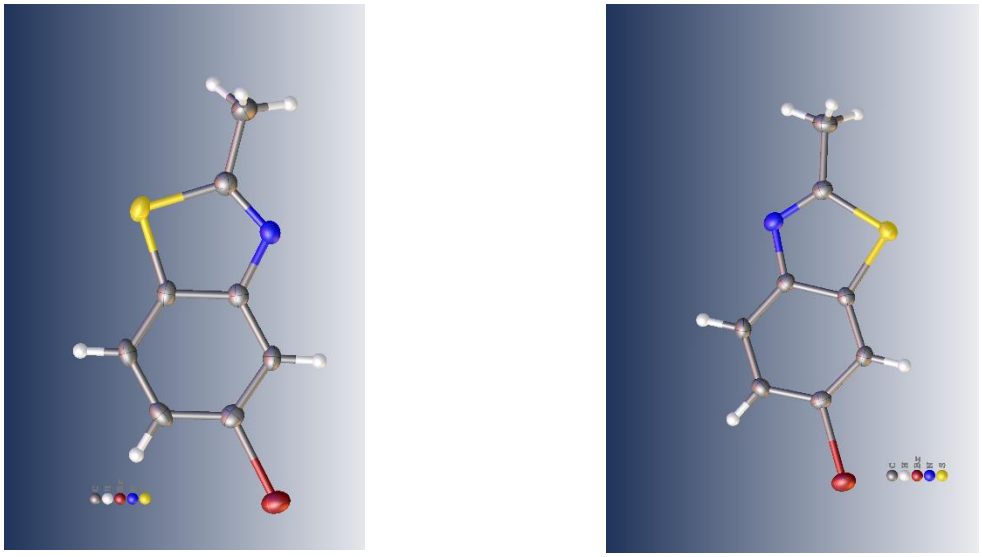


Figure 5.03: *Plots derived from single-crystal X-ray analyses of starting materials* ***5.04*** *and* ***5.13***

Table 5.01 provides a comparison of the ^{1}H NMR spectral data reported for CX-5461 (**5.01**)[12] with those of derivatives **5.02** and **5.03**. As can be discerned, these compounds share notable similarities as well as the anticipated differences due to the inclusion of an alkynyl residue in each of the latter pair. In the spectra of compounds **5.02** and **5.03**, one-proton singlets are observed (Entry 12, **Table 5.01**) at δ_H 3.05 and 3.17, respectively, and these are assigned to the hydrogens of the associated terminal acetylenes.

In the ^{1}H NMR spectrum of compound **5.02**, the resonances due to H8 and H9 (**Figure 5.04**) appeared as mutually coupled one-proton doublets (J = 8.1 Hz) at δ_H 7.61 and 7.45, respectively (see Entries 6 and 7, **Table 5.01** and **Figure 5.04**) while that due to the isolated proton H11 appeared at δ_H 8.43 [as part of a multiplet due to overlap with the resonance arising from another aromatic proton (see Entries 4 and 5, **Table 5.01**)].

Table 5.01: *A comparison of the ^{1}H NMR spectroscopic data reported for CX-5461 (**5.01**) with those obtained for derivatives **5.02** and **5.03***

Entry[A]	**δ_H**[B]		
	Compound 5.01 ($C_{27}H_{27}N_7O_2S$)	**Compound 5.02** ($C_{29}H_{27}N_7O_2S$)	**Compound 5.03** ($C_{29}H_{27}N_7O_2S$)
1	11.26 (t, *J* = 5.2 Hz, 1H)	11.18 (m, 1H)	11.19 (t, *J* = 5.6 Hz, 1H)
2	9.37 (d, *J* = 8.4 Hz, 1H)	9.57 (br. s, 1H)	9.40 (d, *J* = 9.1 Hz, 1H)
3	8.59 (d, *J* = 1.6 Hz, 1H)	8.57 (s, 1H)	8.57 (s, 1H)
4	8.45 (d, *J* = 4.4 Hz, 1H)	8.43 (m, 2H)	8.50 (d, *J* = 8.9 Hz, 1H)
5	8.42 (s, 1H)		8.45 (br. s, 1H)
6	7.67 (dd, *J* = 7.2 and 1.6 Hz, 1H)	7.61 (d, *J* = 8.1 Hz, 1H)	7.81 (d, *J* = 1.6 Hz, 1H)
7	7.37 (m, 2H)	7.45 (d, *J* = 8.1 Hz, 1H)	7.54 (dd, *J* = 8.9 and 1.6 Hz, 1H)
8	6.67 (d, *J* = 9.2 Hz, 1H)	6.68 (d, *J* = 9.1 Hz, 1H)	6.75 (d, *J* = 9.1 Hz, 1H)
9	4.85 (d, *J* = 6.0 Hz, 2H)	4.83 (d, *J* = 5.6 Hz, 2H)	4.85 (d, *J* = 5.6 Hz, 2H)
10	3.87 (br.[C] s, 2H)	4.00–3.40 (comp. m, 4H)	4.05–3.65 (comp. m, 4H)
11	3.78 (br. s, 2H)		
13	-	3.05 (s, 1H)	3.17 (s, 1H)
13	2.80 (br. t, *J* = 4.0 Hz, 2H)	2.87 (br. s, 2H)	2.83 (br. s, 2H)
14	2.60 (br. t, *J* = 4.8 Hz, 2H)	2.60 (m, 2H)	2.61 (br. s, 2H)
15	2.55 (s, 3H)	2.54 (s, 3H)	2.55 (s, 3H)
16	2.40 (s, 3H)	2.39 (s, 3H)	2.41 (s, 3H)
17	2.09[D] (m, 2H)	2.11 (br. s, 2H)	2.11 (br. s, 2H)

[A]All spectra recorded in $CDCl_3$ at 400 MHz.
*[B]Data for compound **5.01** taken from ref. [12]*
[C]br. = broad or broadened.
*[D]In ref. [12] three protons are assigned to this resonance, but this is inconsistent with the total proton count for compound **5.01***

The first two of these three resonances compare favourably with those due to their counterparts in the starting benzo[*d*]thiazole **5.04**, these appearing as mutually coupled one-proton doublets (*J* = 8.4 Hz) at δ_H 7.65 and 7.44, respectively (**Figure 5.04**). In contrast, the signal due to the counterpart to H11 in compound **5.04** appeared as a doublet (*J* = 1.8 Hz) at δ_H 8.08. The greater deshielding of the resonance due to H11 itself in compound **5.02** (appearing at δ_H 8.43) is attributed to the impacts of the proximate pyridine nitrogen.

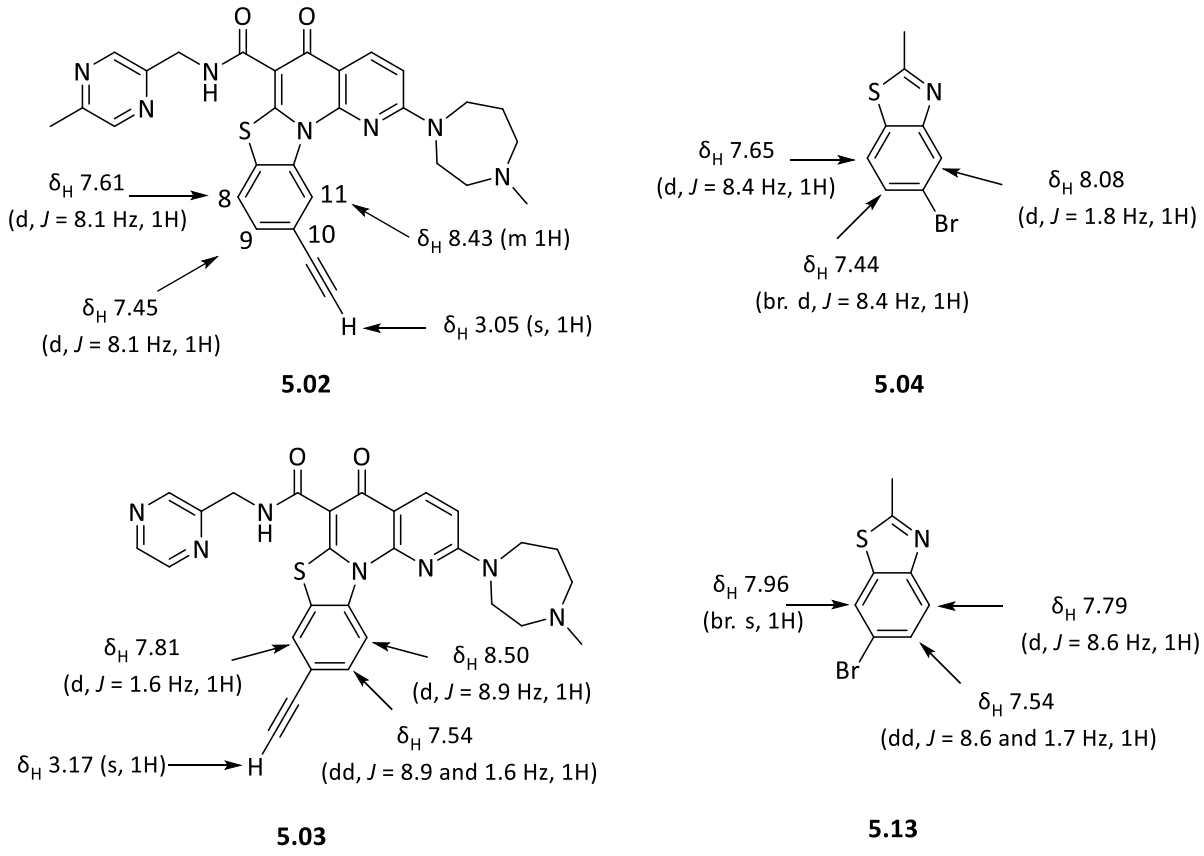


Figure 5.04: *Resonances (δ_H) observed for protons associated with the benzo[d]thiazole substructures within compounds **5.02** and **5.03** as well as their respective precursors **5.04** and **5.13***

In the ^{1}H NMR spectrum of compound **5.03**, the signals due to H10 and H11 appear as mutually coupled resonances (J = 8.9 Hz) at δ_H 7.54 and 8.50, respectively (see Entries 7 and 4, **Table 5.01** and **Figure 5.04**), with the former also showing *meta*-coupling to H8 (J = 1.6 Hz) that appears at δ_H 7.81. The protons equivalent to H10 and H11 in the starting benzo[*d*]thiazole **5.13** appear (**Figure 5.04**) as vicinally coupled one-proton doublets (J = 8.6 Hz) at δ_H 7.54 and 7.79, respectively. The former resonance also reveals *meta*-coupling (J = 1.7 Hz) to the H8 equivalent that resonates as a broad, one-proton singlet at δ_H 7.96.

The ^{13}C{^{1}H} NMR spectral data obtained on derivatives **5.02** and **5.03** (**Figure 5.06**) were consistent with the assigned structures with each spectrum displaying twenty-eight resonances (one obscured or overlapping in each case). The only significant chemical shift difference observed was for the resonances due to the terminal acetylene carbons – in derivative **5.02** this appeared at δ_C 77.7 and in derivative **5.03** at δ_C 78.7.

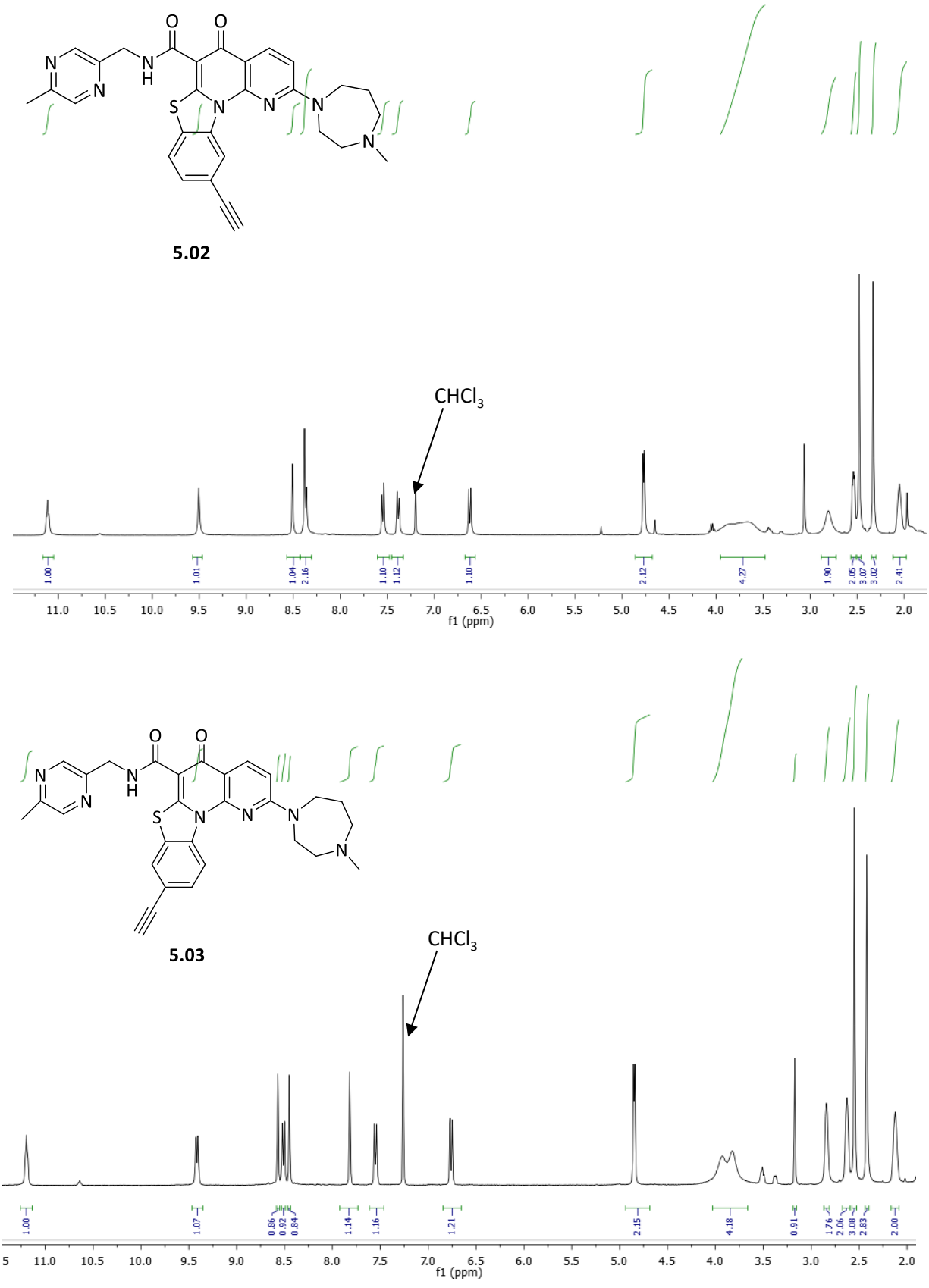
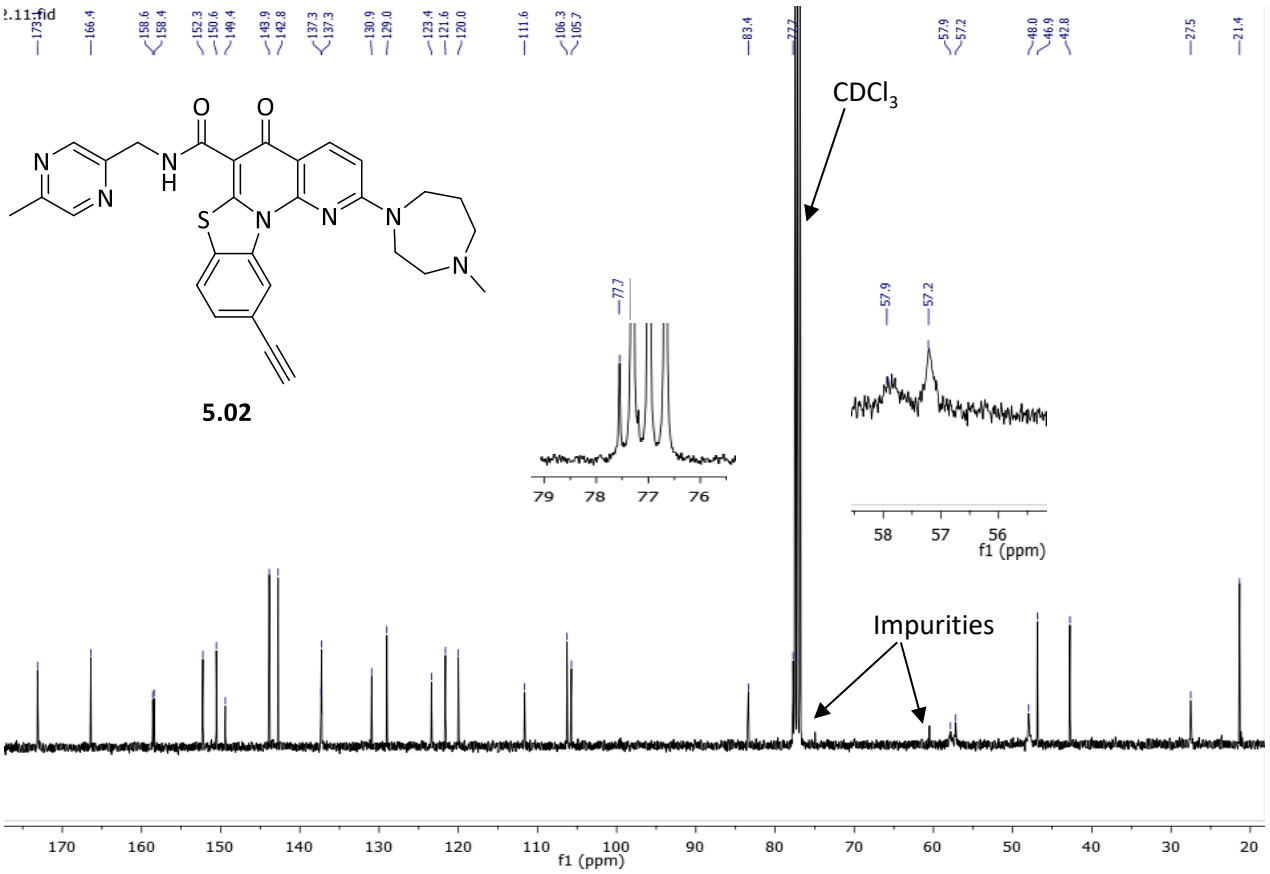
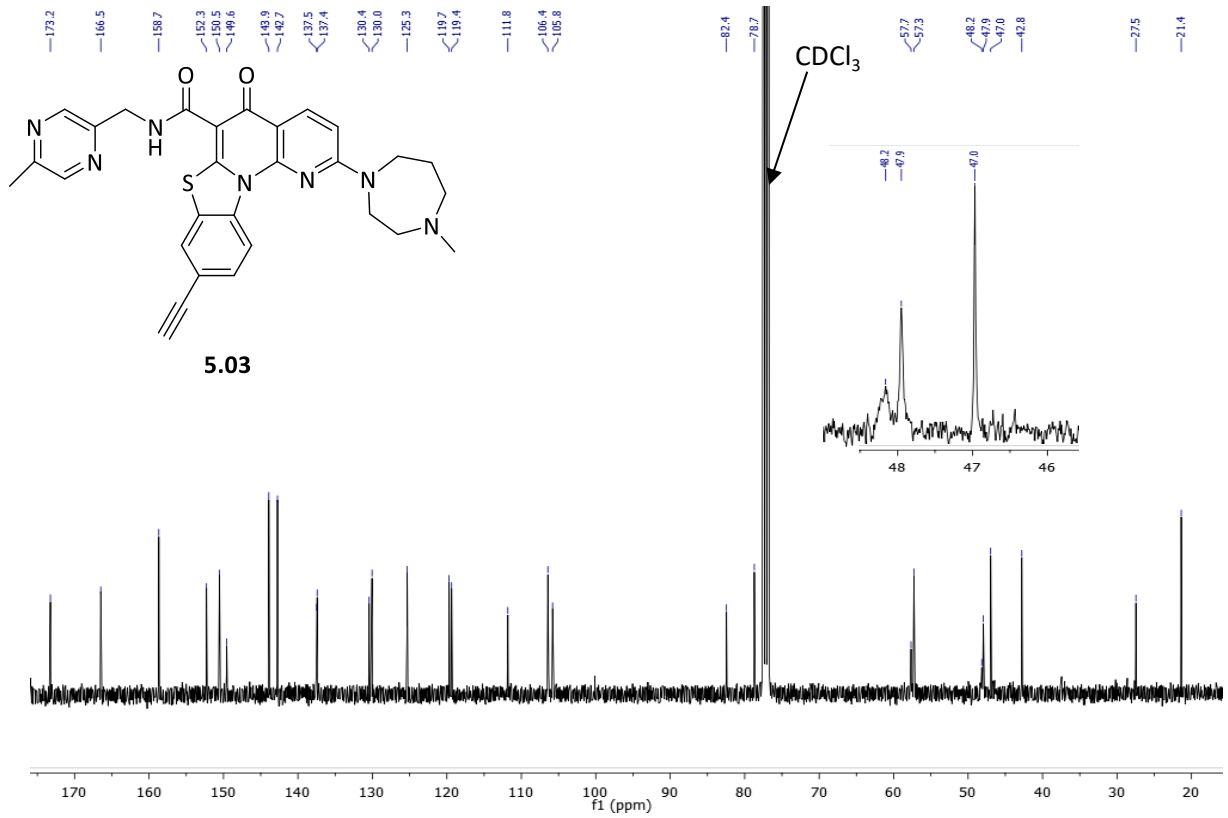


Figure 5.05: *400 MHz ^{1}H NMR spectra of compounds **5.02** and **5.03** (each recorded in $CDCl_3$)*



5.02



5.03

Figure 5.06: *101 MHz $^{13}C\{^{1}H\}$ NMR spectra of compounds **5.02** and **5.03** (each recorded in $CDCl_3$)*

5.07 Preparation of Tagged Azides for Use in Click Reactions with Alkynes 5.02 and 5.03

In order to perform the [3+2]-cycloaddition (click) reactions with alkynes **5.02** and **5.03**, azides incorporating biotin or fluorescent tags were required. The four azides considered most suited for this purpose are shown in **Figure 5.07** with the first three being known and readily prepared compounds. The only difference between the members of this trio of compounds is the length of the associated PEG-type linker. These were chosen to allow for, in a reasonably meaningful manner, various possible receptor/interactor architectures.[21]

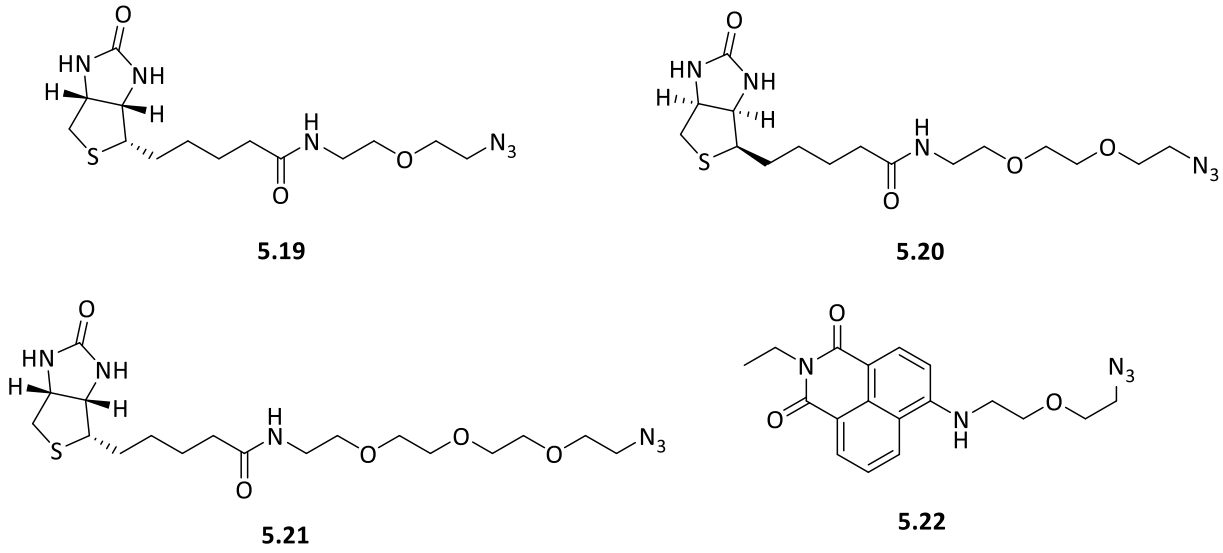
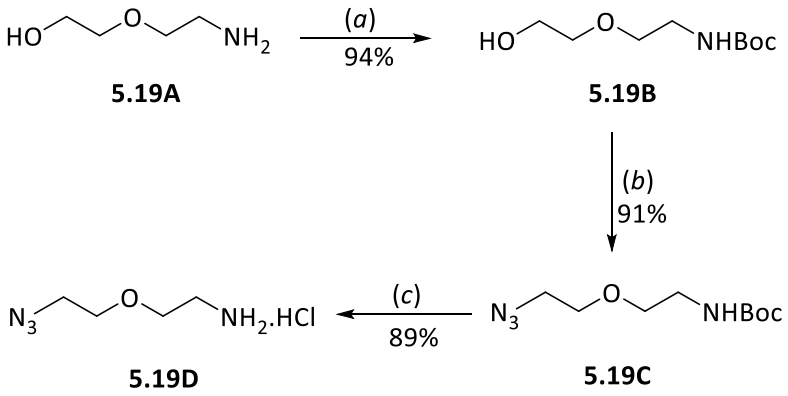


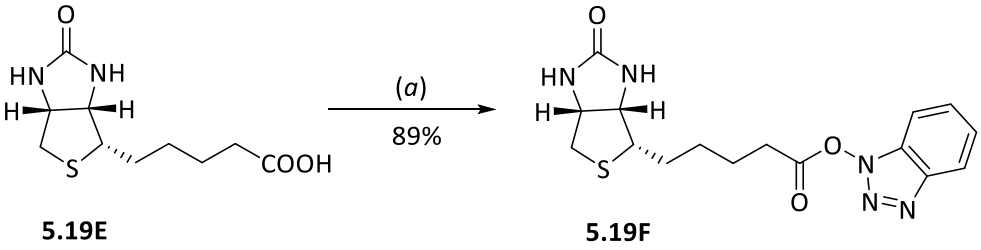
Figure 5.07: *The azides **5.19**–**5.22** sought for forming [3+2]-cycloadducts with alkynes **5.02** and **5.03***

The preliminary step associated with the synthesis of the target azides was to prepare a key part of the linker unit, details of which are shown in **Scheme 5.08**. Thus, amino-alcohol **5.19A** was first Boc-protected to deliver carbamate **5.19B** that was mesylated and the resulting sulfonate ester displaced with azide to give compound **5.19C**. Finally, the Boc group in this last compound was cleaved using HCl in dioxane and so forming the HCl salt, **5.19D**, of the liberated amine.



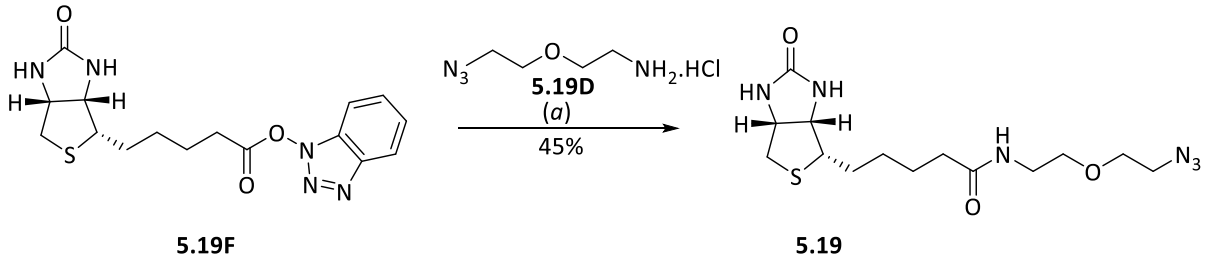
Scheme 5.08: *Reagents and Conditions* (*a*) di-*tert*-butyl dicarbonate, DCM, 0 °C to RT, 16 h; (*b*) 1. methanesulfonyl chloride, TEA, DCM, 0 °C to RT, 16 h; 2. NaN_3, acetone, water, 70 °C, 16 h; (*c*) 4 M aq. HCl, dioxane, RT, 2 h

With compound **5.19D** in hand, attention turned (**Scheme 5.09**) to the preparation of the biotin-containing building block and this simply involved activating, by conventional means, the associated carboxylic residue using 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetra-methylaminium tetrafluoroborate (TBTU) and so affording compound **5.19F** in 89% yield.



Scheme 5.09: *Reagents and Conditions* (*a*) DIPEA, TBTU, DMF, RT, 4 h

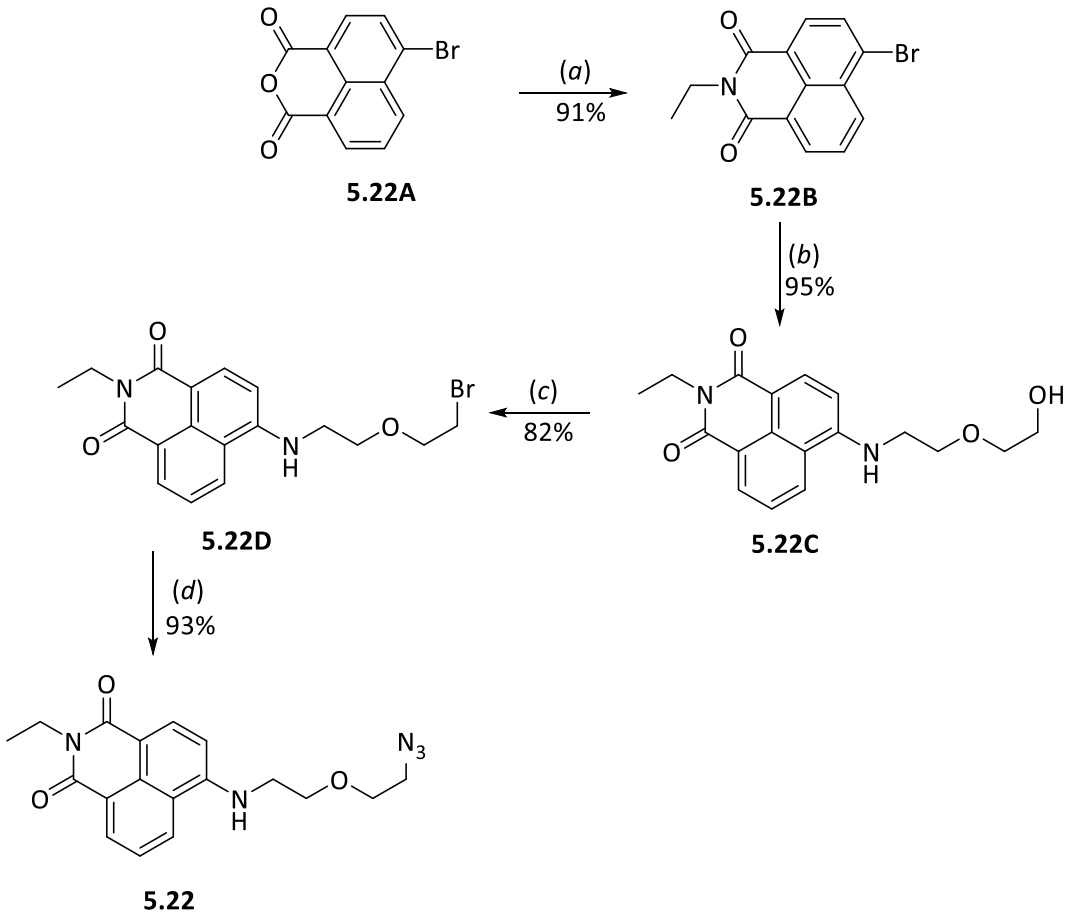
The coupling of the activated biotin **5.19F** with amine **5.19D** was readily achieved (**Scheme 5.10**) in the presence of di-*iso*-propylethylamine (DIPEA) and so yielding the biotin-tagged azide **5.19** in 45% yield.



Scheme 5.10: *Reagents and Conditions* (*a*) DIPEA, DCM, RT, 16 h

The same synthetic steps were employed when preparing azides **5.20** and **5.21** using the appropriate PEG type linkers. Full details are provided in the experimental section. In contrast, azide **5.22** (**Figure 5.07**) which incorporates, *via* a short linker, the potent 4-amino-1,8-naphthalimide fluorophore, has not been prepared previously even though it could be a valuable tool for the dynamic monitoring of changes in biological micro-environments.[22] As such, and when linked, through click chemistry, to either alkynes **5.02** or **5.03**, it offers the possibility of visualising the distribution of either one of these putative Pol I transcription inhibitors within the target cells.

The synthesis of compound **5.22** was accomplished over the four discrete steps shown in **Scheme 5.11**, the first of which involved reaction of naphthalic anhydride **5.22A** and ethylamine to afford the corresponding isoquinoline-1,3-dione **5.22B**. Treatment of later compound with an excess of 2-(2-aminoethoxy)ethanol then delivered the *N*-alkylated product **5.22C**. The primary alcohol moiety associated with the last compound was converted into the corresponding bromide **5.22D** (82%) using a mixture of tetra-*n*-butylammonium bromide, triphenylphosphine and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in CH_2Cl_2 at room temperature. Finally, reaction of bromide **5.22D** with sodium azide afforded, as a result of a nucleophilic substitution reaction, the target compound **5.22** in 93% yield.



Scheme 5.11: *Reagents and Conditions* (*a*) $EtNH_2$, dioxane, reflux, 8 h; (*b*) 2-(2-aminoethoxy) ethanol, DIPEA, *n*-butanol, 120 °C, 4 h; (*c*) DDQ, tetra-*n*-butylammonium bromide, triphenylphosphine, DCM, RT, 16 h; (*d*) NaN_3, DMF, 60 °C, 4 h

5.08 Biological Evaluations of the CX-5461 Analogues 5.02 and 5.03

In the dose-response studies used to test compounds **5.02** and **5.03** as potential Pol I transcription inhibitors, CX-5461 was employed as the positive control. The control study, the results of which are shown in **Figure 5.08**, used MV4-11 cells, a human acute myeloid leukemia (AML) cell line (and derived from the blast cells of a 10-year-old male suffering from biphenotypic B-myelomonocytic leukemia). Specifically, the MV4-11 cells were treated for 3 h with CX-5461 at concentrations ranging from 3 to 10,000 nM and the expression of the pre-rRNA transcript (pre-rRNA) and cFOS were analysed by qRT–PCR and compared with the vehicle, namely 0.1% DMSO (**Figure 5.08**). A concentration-dependent inhibition of pre-rRNA expression was observed and thus indicating an on-target inhibition of Pol I transcription. To confirm that the observed effects are specifically due to Pol I inhibition, the expression levels of cFOS, an early response gene transcribed by RNA Pol II with a similar half-life to the pre-

rRNA, was also analysed. Indeed, cFOS expression levels did not change across all concentrations (of CX-5461) tested and so confirming the pre-established Pol I specificity of CX-5461. The data shown in **Figure 5.08** were also used to establish that the on-target half maximal inhibitory concentration (TIC_{50}) value for CX-5461 was 295 nM.

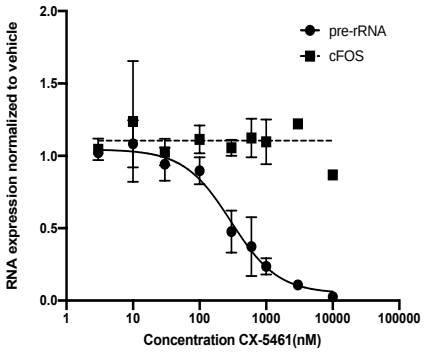


Figure 5.08: *A dose–response curve showing pre-rRNA and cFOS RNA expression in MV4-11 cells treated with increasing concentrations of CX-5461 (**5.01**). Graph shows mean and standard deviation of three biological replicates. All these biological assays were conducted in the JCSMR by K. M. Hannan and associates*

The outcomes of subjecting analogues **5.02** and **5.03** to the same *in vitro* testing regime as employed for CX-5461 are shown in **Figure 5.09**. These revealed that only the C9 alkyne **5.03** was active and clearly indicating the placing the same substituent at C10 (as manifest in compound **5.02**) caused a loss activity.

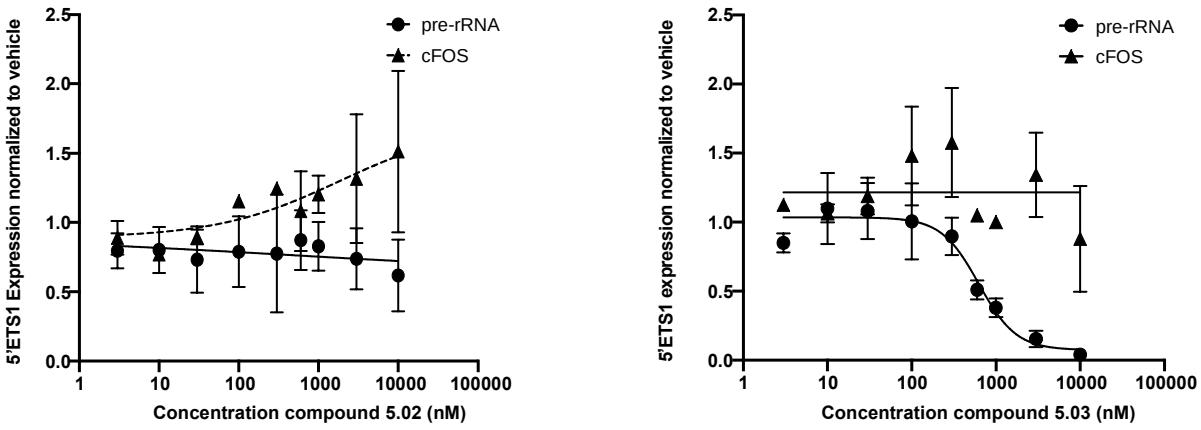


Figure 5.09: *Dose–response curves showing 5'ETS and cFOS RNA expression in MV4-11 cells treated with increasing concentrations of compounds **5.02** (left) and **5.03** (right). Graphs show mean and standard deviation of three biological replicates. All these biological assays were conducted in the JCSMR by K. M. Hannan and associates*

A comparison of activities of the parent compound CX-5461 (**5.01**) with the alkyne substituted derivative **5.03** is provided in **Figure 5.10** and so revealing that the latter is less active by a factor of the two (TIC_{50} of 633 versus 295 nM).

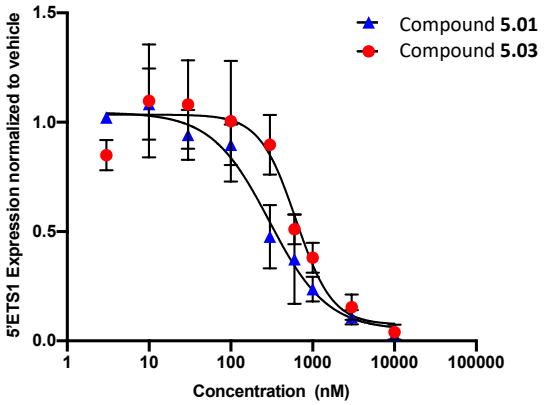


Figure 5.10: *Dose–response curves showing pre-rRNA expression in MV4-11 cells treated with increasing concentrations of active compounds **5.01** (blue) and **5.03** (red). Graph shows mean and standard deviation of three biological replicates. All these biological assays were conducted in the JCSMR by K. M. Hannan and associates*

5.09 Deploying [3+2]-Cycloadducts in Searching for the Cellular Targets of CX-5461

Preliminary biological evaluations of compounds **5.02** and **5.03** revealed (as outlined above) that only the latter retained the inhibitory activity of the parent CX-5461. Accordingly, the foreshadowed click addition studies were confined to the reactions of alkyne **5.03** with azides **5.19**–**5.22**. The four targeted adducts, namely compounds **5.23**–**5.26** (**Figure 5.11**), were each obtained through coupling of the relevant pairs of reactants in the presence of sodium ascorbate and copper(II) sulfate.[23] THF/water/DMSO mixtures were used as solvent and when the reactions were run at ambient temperatures overnight the anticipated adducts were obtained in yields ranging from 55 to 82% after purification by conventional flash chromatography.

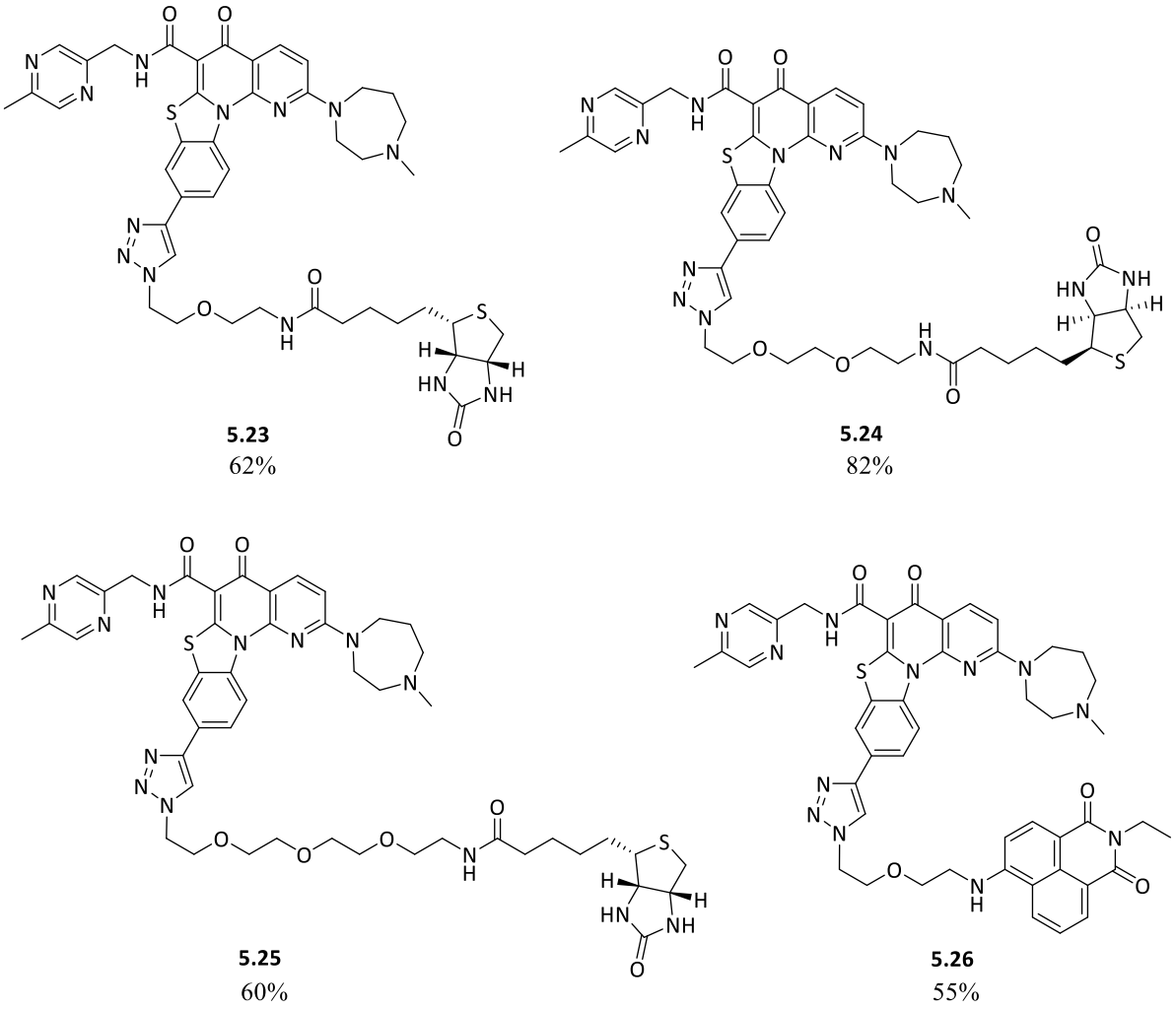


Figure 5.11: *The [3+2]-cycloadducts **5.23**–**5.26** obtained by click reaction of azides **5.19**–**5.22** with alkyne **5.03***

The [3+2]-cycloadducts ***5.23***–***5.26*** were tested for biological activity in relevant cancer cell lines, the intention being that if any of these retained similar activity to the parent CX-5461 then nuclear extracts from cells treated with them would be generated and the protein complexes affinity-purified on streptavidin-coated beads before analysis by standard shotgun proteomics/LC-MS/MS techniques (and compared with unlabelled CX-5461). On the other hand, if the [3+2]-cycloadduct **5.26** incorporating the fluorescent group was active then this could be used for imaging purposes and so assisting in the identification of subcellular organelles interacting with the CX-5461 pharmacophore. The same protocol described above for testing the activities of compound **5.02** and **5.03** was applied to adducts **5.23** to **5.26** (**Figure 5.12**). Disappointingly, however, the results revealed that all the four adducts were devoid of activity.

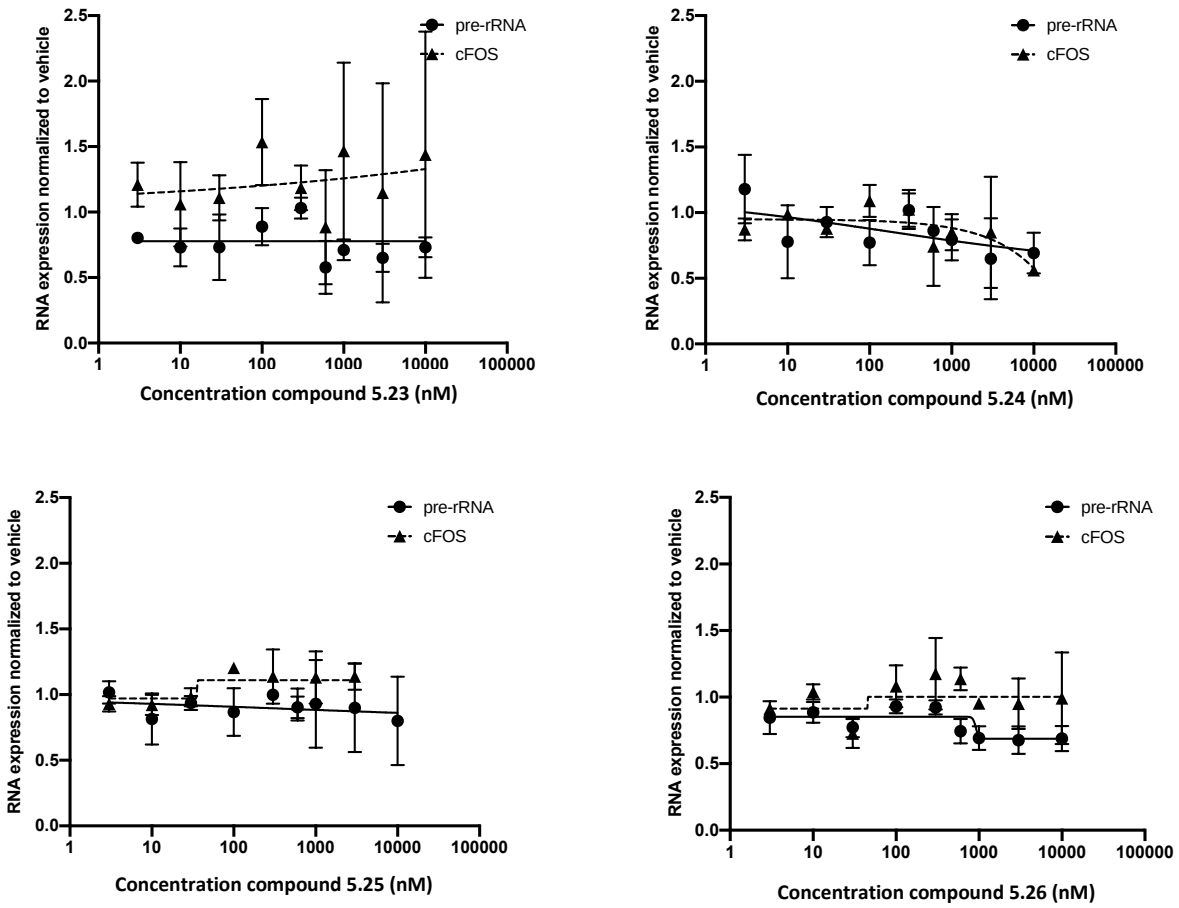


Figure 5.12: *Dose–response curves showing 5'ETS and cFOS RNA expression in MV4-11 cells treated with increasing concentrations of compounds **5.23** (top left) and **5.24**–**5.26** (bottom right). Graphs show mean and standard deviation of three biological replicates. All these biological assays were conducted in the JCSMR by K. M. Hannan and associates*

In MV4-11 cells Pol I inhibition by CX-5461 activates the NSR and promotes the stabilisation of p53. To establish whether the tagged compounds could be interacting, albeit at modest levels perhaps, with the same pathway, MV4-11 cells were treated for 3 h with 1 μM solutions of compounds **5.01**, **5.03**, and **5.24**. In the first case, and as expected, Pol I transcription was inhibited by 90% and and a consequent activation of the nucleolar stress response was observed. The resulting abundance of the p53 protein was detected by Western blotting (**Figure 5.13**). As expected, cells treated with the vehicle show undetectable levels of p53 while compounds **5.01** and **5.03** both elevated p53 although notably less so in the latter case. On the other hand, the biotinylated click product **5.24** completely failed to induce p53.

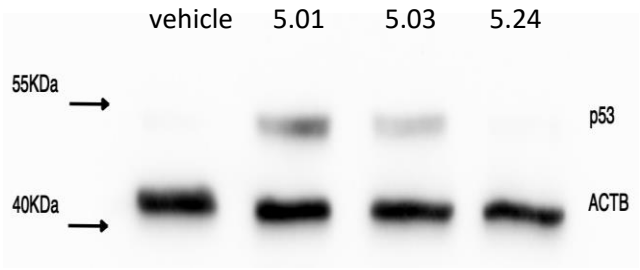


Figure 5.13: *A representative Western blot revealing the capacities of compounds CX-5461 (**5.01**), **5.03** and **5.24** to stabilise p53 in MV4–11 cells 3 h after treatment with 1 μM solutions of each in DMSO (ACTB=loading control). All these biological assays were conducted in the JCSMR by K. M. Hannan and associates*

At a more holistic level, the same compounds (namely **5.01**, **5.03**, and **5.24**) were evaluated for their capacities to inhibit MV4-11 cell proliferation as 1 μM solutions in 0.1 % DMSO. As shown in **Figure 5.14**, the expected trends were observed with compound **5.01** inhibiting proliferation as did analogue **5.03** while the [3+2]-cycloadduct **5.24** was as ineffective as the negative control (0.1 % DMSO) in inhibiting proliferation.

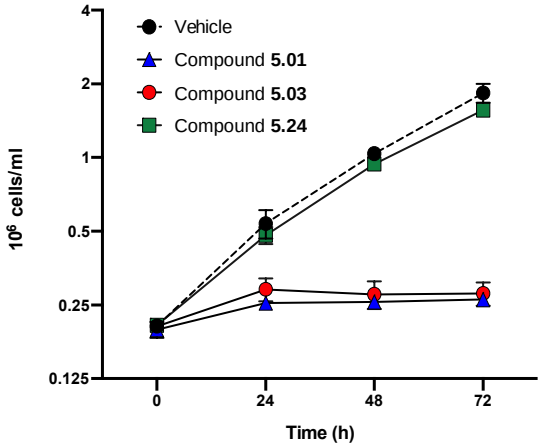
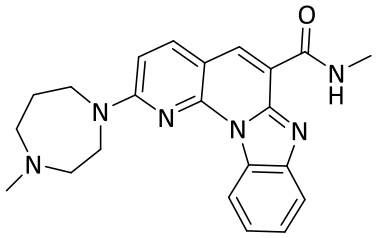


Figure 5.14: *Proliferation profiles of MV4-11 cells treated with 1 μM solutions of compounds CX-5461 (**5.01**), **5.03** and **5.24** in DMSO. All these biological assays were conducted in the JCSMR by K. M. Hannan and associates*

5.10 Second Generation Pol I Inhibitors

Following the development of the first-generation Pol I inhibitor CX-5461, a series of orally available and more selective analogues has emerged in recent times. PMR-116 (**5.27**) (**Figure 5.14**) is notable among these and seen as a potentially powerful anti-cancer drug. This is because it, *inter alia*, has improved survival rates in murine models of acute myeloid leukemia and B-cell lymphoma when administrated at maximal tolerated dosages. Further, when compared to CX-5461, PMR-116 shows improved toxicology, tissue distribution (penetration of the blood brain barrier) and lower plasma protein binding. However, and as

is the case with CX-5461, the underlying molecular mechanisms of action and the cellular targets of this new drug candidate remain unknown[8].



5.27

Figure 5.14: *Structure of PMR-116 (**5.27**)*

Figure 5.15 shows the outcomes of a dose-response study carried out using PMR-116 and reveals that when MV4-11 cells are treated with this compound, the on-target half-maximal inhibitory concentration (TIC_{50}) is 399 nM.

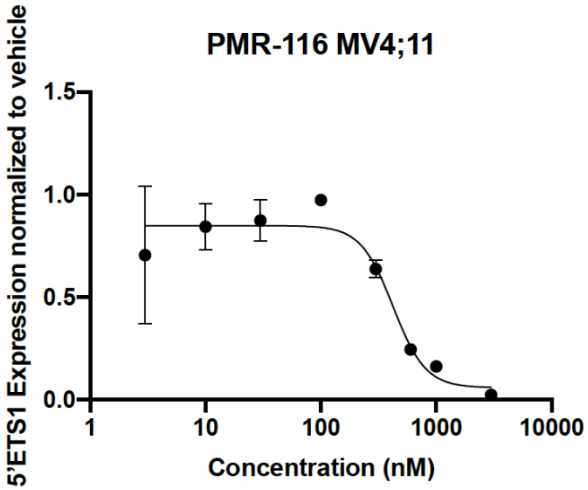


Figure 5.15: *Dose–response curve showing 5'ETS RNA expression in MV4-11 cells treated with increasing concentrations of compound PMR-116 (**5.27**). All these biological assays were conducted in the JCSMR by K. M. Hannan and associates*

In the same way in which the tagging of CX-5461, through the applications of click chemistry, was pursued as a means of establishing it cellular target, analogous studies were used to study PMR-116. To that end, the four regio-isomeric alkynyl-substituted analogues of PMR-116, namely compounds **5.28**-**5.31** (**Figure 5.16**) were sought. Efforts to prepare these are described in the following sections.

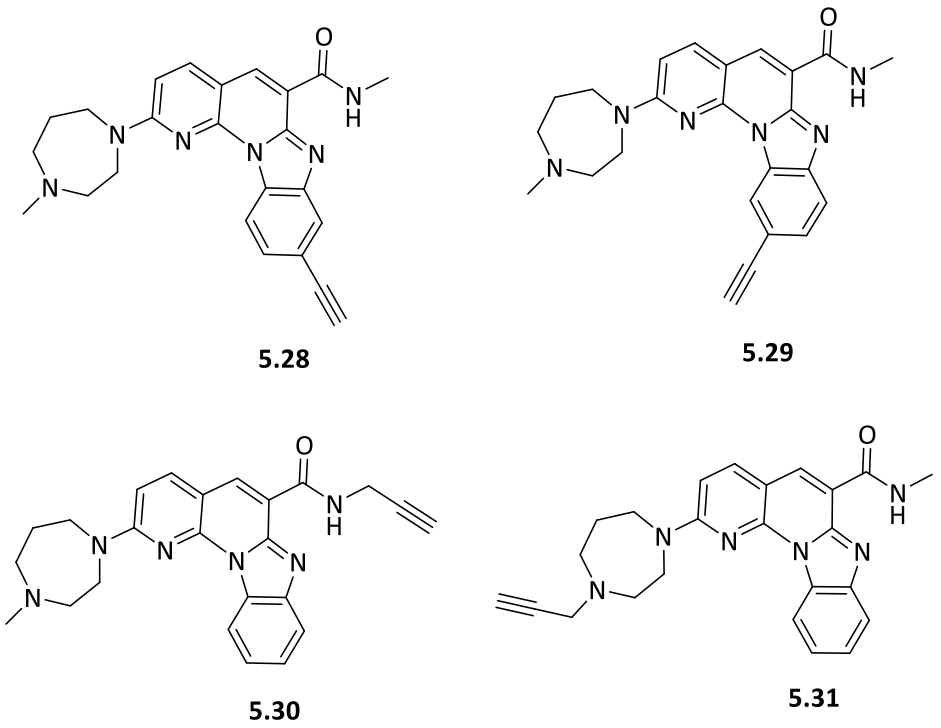


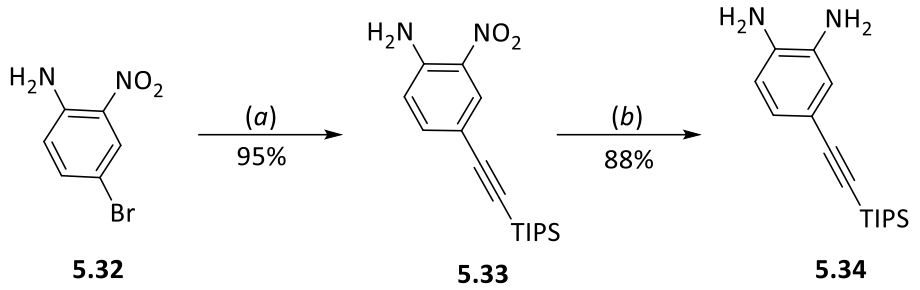
Figure 5.16: *The structures, **5.28, 5.29, 5.30** and **5.31**, of the four regio-isomeric alkynyl-substituted PMR-116 analogues targeted for synthesis in the present study*

Of course, once to hand, these analogues would be engaged in click reactions with azides **5.19** to **5.21**, so as to attach biotinylated tags and the adducts so-formed then subjected to biological assays. All these biological assays were conducted in JCSMR by Dr. K. M. Hannan and associates. Nuclear extracts from cells treated with these adducts would then be generated and the relevant protein complexes (if any) affinity purified on streptavidin coated beads. The resultant mix of post-digestion peptides would then be analysed by standard shotgun LC-MS/MS techniques. To identify the sites of drug occupancy on chromatin, Chem-seq techniques would be applied using Bio-PMR-116 to map genome-wide drug-chromatin target interactions.[24]

5.11 Preparation of Alkynyl-Substituted PMR-116 Analogues

Based on the reaction series which is used to synthesize PMR-116, the opening stages used in preparing the target alkynes **5.28** and **5.29** involved subjecting 4-bromo-2-nitroaniline (**5.32**) to a Sonogashira cross-coupling reaction with ethynyltriisopropylsilane and thereby producing the TIPS-capped compound **5.33** in 95% yield. The nitro group within this product

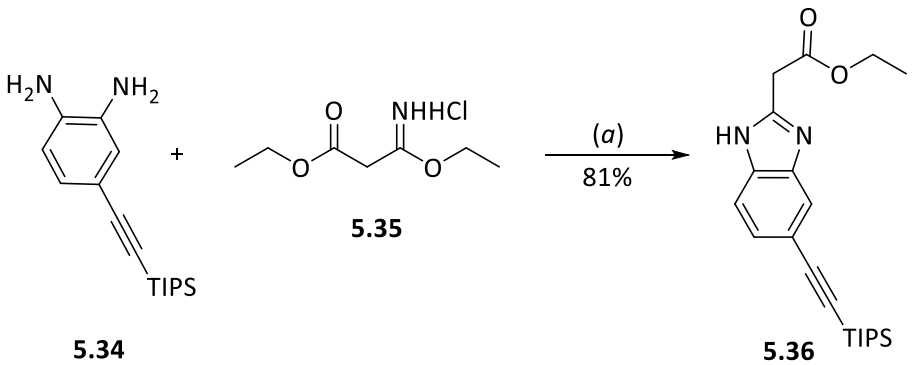
was reduced to the corresponding amino group using zinc in acetic acid and so affording the 1,2-phenylenediamine **5.34** in 88% yield.



5.32 **5.33** **5.34**

Scheme 5.12: *Reagents and Conditions* (*a*) ethynyltriisopropylsilane, $Pd(PPh_3)_4$, CuI, DIPEA, DMF, 100°C, 16 h; (*b*) Zn dust, EtOH, AcOH, RT, 3 h

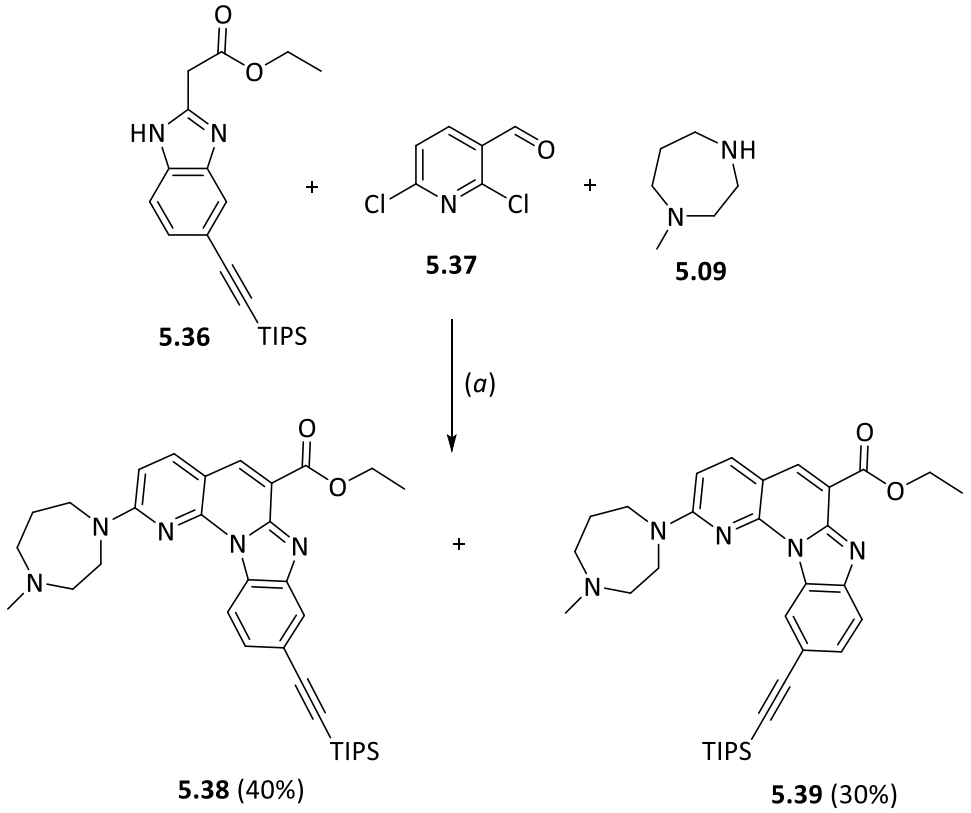
As shown in **Scheme 5.13**, diamine **5.34** was then reacted with ethyl 3-ethoxy-3-iminopropanoate hydrochloride (**5.35**) in the presence of ethanol to deliver the benzoimidazole **5.36** (**Scheme 5.13**).[25]



5.34 **5.35** **5.36**

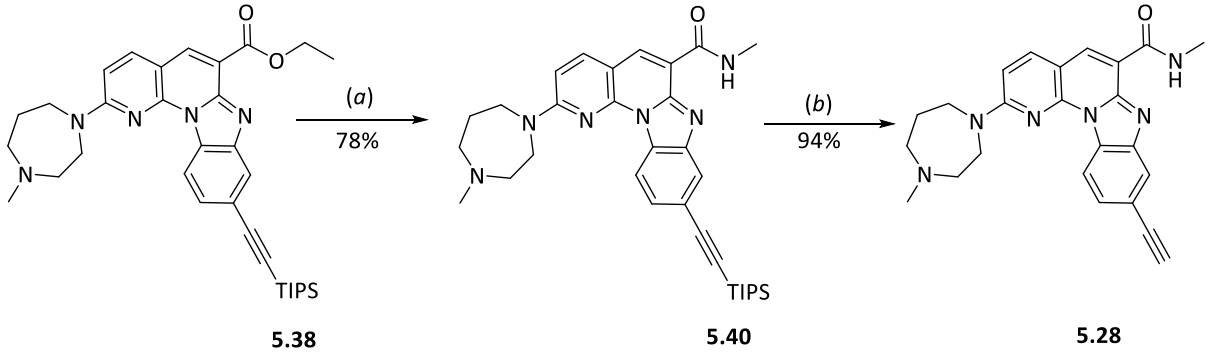
Scheme 5.13: *Reagents and Conditions* (*a*) EtOH, 80°C, 16 h

As shown in **Scheme 5.14**, when compound **5.36** was treated, sequentially and in the presence of DIPEA, with the dichlorinated pyridine **5.37** and then the commercially available *N*-methyl-1,4-diazepane (**5.09**) the anticipated sequence of substitution and condensation reactions took place to give a mixture of compounds **5.38** and **5.39**. These could be separated from one another by conventional chromatographic means and as well by applying the usual array of spectroscopic techniques. As detailed below, each of the regio-isomeric products was then carried forward independently in the closing stages of the synthesis of the targets.



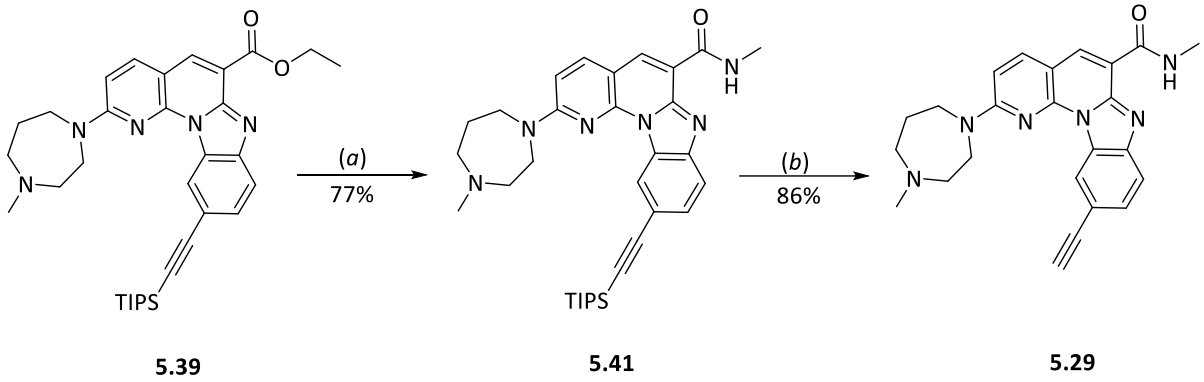
Scheme 5.14: *Reagents and Conditions* (*a*) DIPEA, EtOH, 65°C, 18 h

The ester **5.38** was smoothly converted, as shown in **Scheme 5.15**, into amide **5.40** (78%) on reacting the former compound with methylamine in the presence of lanthanum(III) triflate and under microwave irradiation. The TIPS group associated with the latter compound was then cleaved with silver fluoride in methanol and thus affording target **5.28** in 94% yield and the structure was further confirmed by single-crystal X-ray analysis (details provided in Chapter 6).



Scheme 5.15: *Reagents and Conditions* (*a*) lanthanum(III) triflate, $MeNH_2$, microwave irradiation, 70 °C, 4 h; (*b*) AgF, MeOH, RT, 4 h

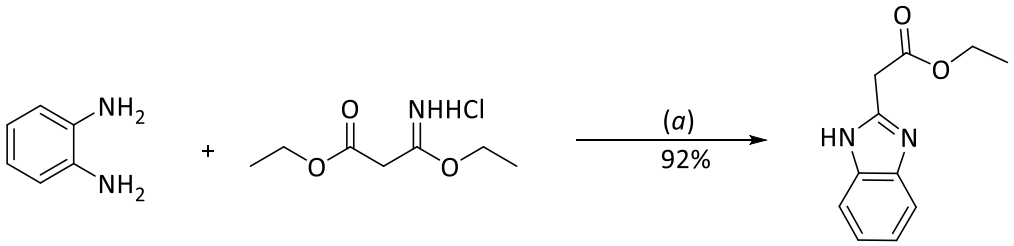
By applying an analogous reaction sequence, as shown in **Scheme 5.16**, then the other alkyne **5.29** could be obtained. Each of compounds **5.28** and **5.29** was subjected to the usual suite of spectroscopic characterization techniques and so serving to support their illustrated structures.



5.39 **5.41** **5.29**

Scheme 5.16: *Reagents and Conditions* (*a*) lanthanum(III) triflate, $MeNH_2$, microwave irradiation, 70 °C, 4 h; (*b*) AgF, MeOH, RT, 4 h

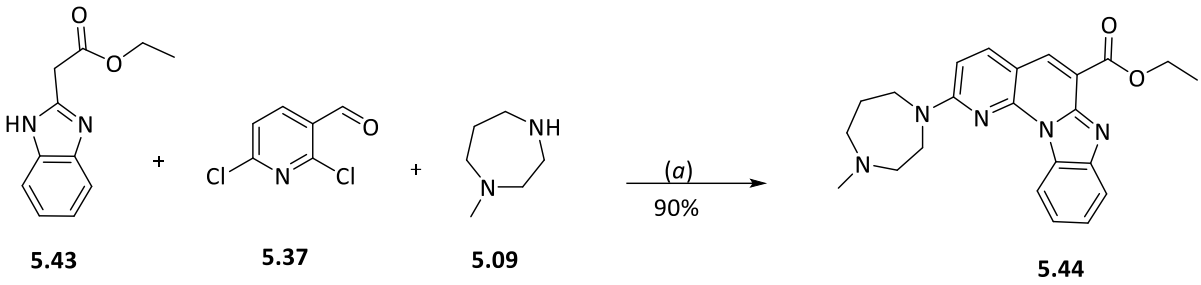
The synthesis of the PMR-116 analogue **5.30** started, as shown in **Scheme 5.17**, with a thermally-promoted reaction between 1,2-phenylenediamine (**5.42**) and ethyl 3-ethoxy-3-iminopropanoate hydrochloride (**5.35**). This afforded the C2-substituted benzimidazole **5.43** in 92% yield.



5.42 **5.35** **5.43**

Scheme 5.17: *Reagents and Conditions* (*a*) EtOH, 80 °C, 16 h

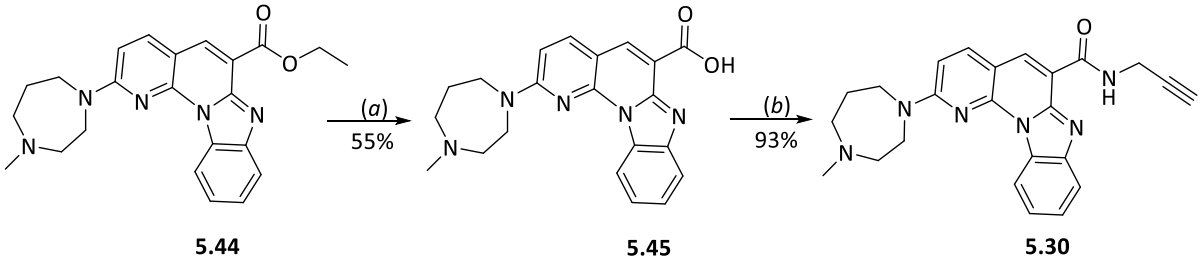
On subjecting ester **5.43** to sequential reaction with 2,6-dichloronicotinaldehyde (**5.37**) then *N*-methyl-1,4-diazepane (**5.09**) (**Scheme 5.18**) in the presence of DIPEA then the anticipated product **5.44** was obtained in 90% yield.



5.43 5.37 5.09 5.44

Scheme 5.18: *Reagents and Conditions* (*a*) DIPEA, EtOH, 65°C, 18 h

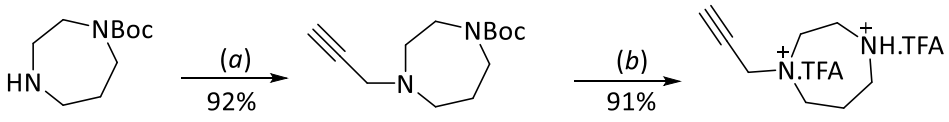
Hydrolysis of the ester residue within compound **5.44** was readily achieved using sodium hydroxide in aqueous methanol (**Scheme 5.19**) and after acidic work-up the free acid **5.45** was obtained in 55% yield. Finally, this last compound was coupled with propargyl amine in the presence of TBTU and DIPEA and so producing the target amide **5.30** in 93% yield. Once again, all the spectral data acquired on compound **5.30** were in full accord with the assigned structure.



5.44 5.45 5.30

Scheme 5.19: *Reagents and Conditions* (*a*) aq. NaOH, MeOH, 60 °C, 2 h; (*b*) propargyl amine, TBTU, DIPEA, DMF, RT, 16 h

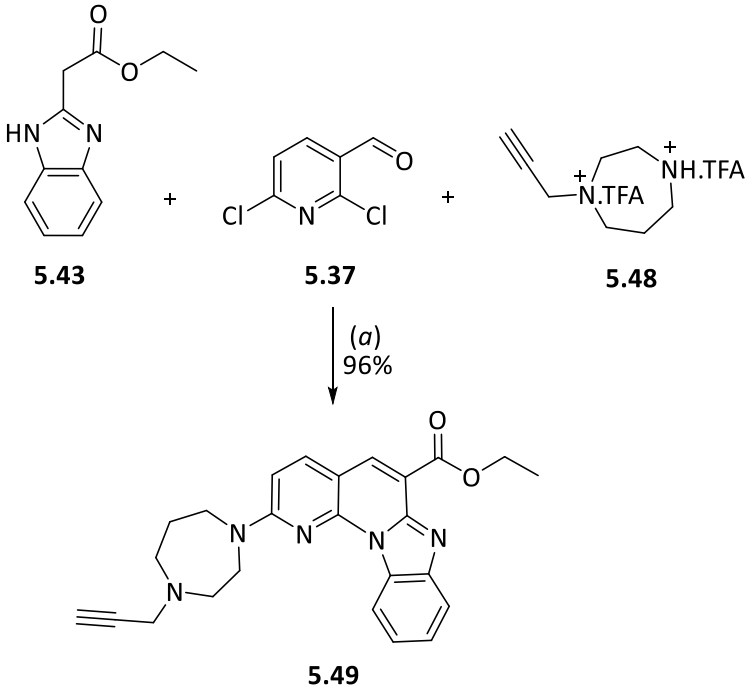
The synthesis of the final alkynylated PMR-116 derivative, **5.31**, began (**Scheme 5.20**) with the coupling of propargyl bromide and commercially available amine **5.46**. The presumed product of this reaction, namely compound **5.47**, was treated dropwise with trifluoroacetic acid to effect cleavage of the associated Boc group and thereby affording compound **5.48** which was obtained in 91% yield.



5.46 5.47 5.48

Scheme 5.20: *Reagents and Conditions* (*a*) propargyl bromide, DIPEA, DCM, RT, 24 h; (*b*) TFA, DCM, RT, 0 °C to RT, 2 h

As shown in **Scheme 5.21**, when compound **5.43** was engaged as a coupling partner in a reaction sequence also involving compounds **5.37** and **5.48** then the expected product **5.49** was obtained in 96% yield.

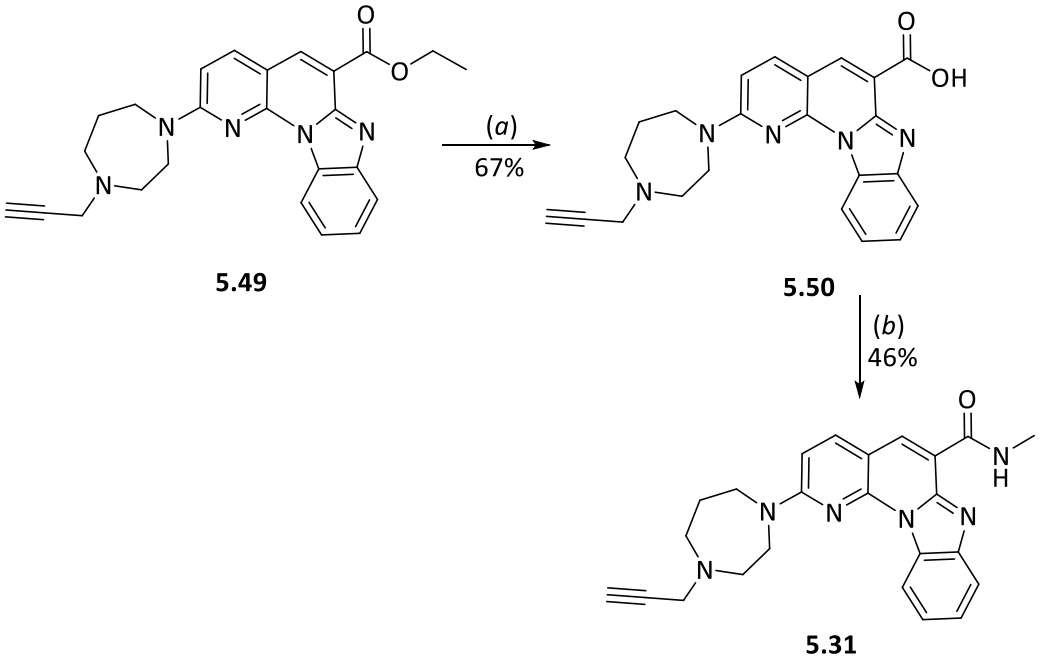


5.43 **5.37** **5.48**

5.49

Scheme 5.21: *Reagents and Conditions* (*a*) DIPEA, EtOH, 65 °C, 16 h

The synthesis of the required PMR-116 analogue (**5.31**) was completed by the pathway shown in **Scheme 5.22** and wherein compound **5.49** was converted into the corresponding carboxylic acid **5.50** that was itself coupled with methyl amine to give amide **5.31** albeit in just 46% yield. Once again, all the spectral data acquired on this last compound were in full accord with the assigned (illustrated) structure.



5.49 **5.50** **5.31**

Scheme 5.22: *Reagents and Conditions* (*a*) aq. NaOH, MeOH, 60 °C, 2 h; (*b*) $MeNH_2$, DIPEA, HATU, DMF, RT, 16 h

5.12 Biological Evaluation of the PMR-116 Analogues 5.28-5.31

Subjection of the PMR-116 analogues **5.28**, **5.29**, **5.30** and **5.31** to the same *in vitro* testing regime as employed for PMR-116 itself revealed that out of the four analogues, three (**5.28**, **5.29** and **5.30**) were active (see Figures **5.16**-**5.19** for the derived dose-response curves). Compound **5.31**, on the other hand, failed to retain the activity of the parent system.

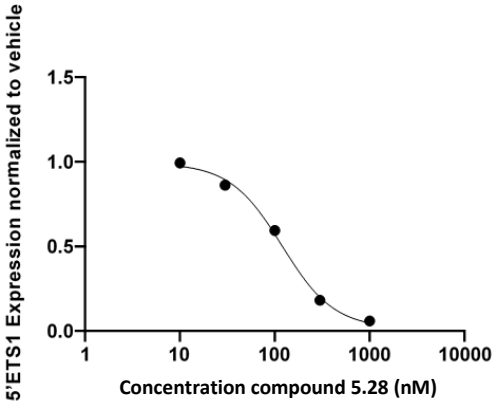


Figure 5.16: *Dose–response curve showing 5'ETS RNA expression in MV4-11 cells treated with increasing concentrations of compound **5.28** (TIC_{50}=119.6 nM, n=3). All these biological assays were conducted in the JCSMR by K. M. Hannan and associates*

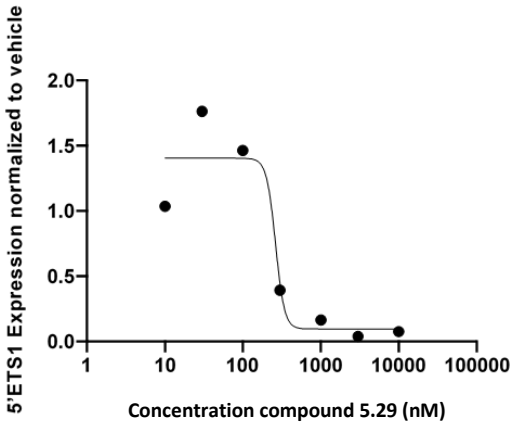


Figure 5.17: *Dose–response curve showing 5'ETS RNA expression in MV4-11 cells treated with increasing concentrations of compound **5.29** (TIC_{50}=261.8 nM, n=2). All these biological assays were conducted in the JCSMR by K. M. Hannan and associates*

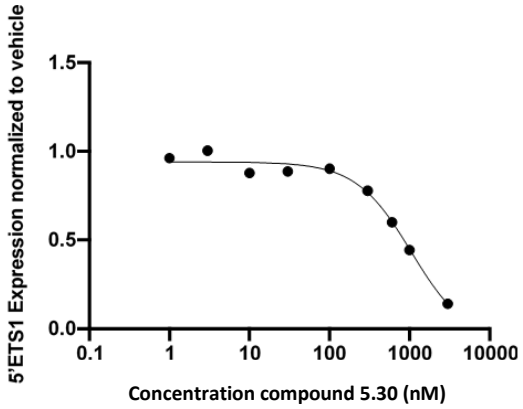


Figure 5.18: *Dose–response curve showing 5'ETS RNA expression in MV4-11 cells treated with increasing concentrations of compound **5.30** (TIC_{50} =1.05 uM, n=3). All these biological assays were conducted in the JCSMR by K. M. Hannan and associates*

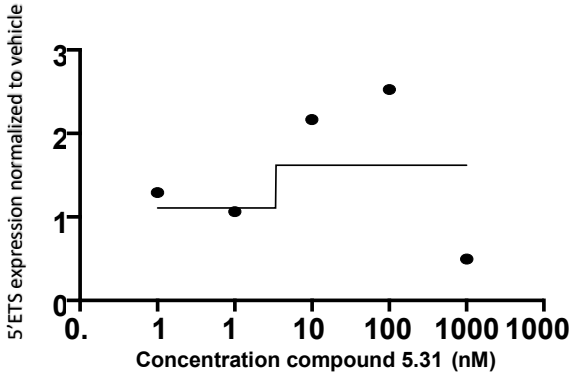


Figure 5.19: *Dose–response curve showing 5'ETS RNA expression in MV4-11 cells treated with increasing concentrations of compound **5.31** (not active, n=1). All these biological assays were conducted in the JCSMR by K. M. Hannan and associates*

Having obtained the targeted and active derivatives of PMR-116, the next step was to perform the click addition reactions on them using the azides **5.19**-**5.22** incorporating biotin and fluorescent tags. All of these [3+2]-cycloaddition reactions proceeded in the expected manner and the structure of the resulting adducts are shown in Chapter Six (the Experimental Section of this thesis). All of the spectral data obtained on these adducts were in accord with the assigned structures and the biological evaluation of these compounds is now underway (albeit taking place more slowly than hoped for because of the limited laboratory access available under the lockdowns imposed at the ANU as part of the ACT Government's response to the COVID-19 pandemic).

5.13 Conclusion

The studies detailed above have revealed the high sensitivity of the molecular architecture of CX-5461 to structural modifications that retain activity since only the C9 regio-isomeric alkynyl-substituted derivative **5.03** (and not C10 regio-isomer **5.02**) retains (albeit reduced) transcriptional activity *in vitro*. Furthermore, this was lost following [3+2]-cycloadduct formation. The most reasonable explanation for the varying activities of the derivatives is that the receptor/interactor binding pocket in MV4-11 cells accommodating the benzo[*d*]thiazole residue of CX-5461 is a 'tight' one that does not readily tolerate substituents, particularly at the C10 position. That said, the lack of any observed *in vitro* biological effects exerted by the [3+2]-adducts **5.23**, **5.24**, and **5.25** may reflect the inability of these biotinylated systems to cross the outer membrane of MV4-11 cells (rather than an inability to bind to the receptor/interactor within such cells). On this basis it is conceivable that after such cells are treated with the active CX-5461 derivative **5.03** and this has bound to its receptor/interactor then lysing of the cells followed by *ex vitro* 'clicking' of the drug conjugate with any of the biotinylated azides **5.19**–**5.21** could deliver [3+2]-adducts capable of isolation (and subsequent characterisation) using affinity chromatography, a protocol that has been applied in other cases.[26]

PMR-116 is a 2nd generation RNA Pol I inhibitor possessing has improved toxicology, tissue distribution, lower plasma protein binding and higher efficacy compared to CX-5461. More importantly, it does not cause DNA damage. Furthermore, in contrast to the alkynylated CX-

5461 analogues described above, certain of their PMR-116 counterparts are far more active and so suggesting that through the application of the click chemistry protocols espoused above the identification of the drug's cellular receptor(s) could be identified in the near future. Work directed towards such ends is ongoing and will be reported in due course.

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Chapter Six

General Experimental Procedures

Unless otherwise specified, proton (^{1}H) and proton-decoupled carbon [^{13}C{^{1}H}] NMR spectra were recorded at room temperature in base-filtered $CDCl_3$, CD_3OD or $(CD_3)_2SO$ on a Bruker spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. For ^{1}H NMR spectra, signals arising from the residual protio-forms of the solvent were used as the internal standards. ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) *J* (Hz), relative integral] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. The signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ "triplet" appearing at δ_C 77.16 were used to reference ^{1}H and ^{13}C{^{1}H} NMR spectra, respectively.

Infrared spectra (ν_{max}) were recorded on a Perkin–Elmer 1800 Series FTIR Spectrometer and samples were analysed as thin films.

All microwave irradiation experiments were carried out in a CEM Explorer microwave apparatus operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300 W using the standard absorbance level of 300 W to represent maximum power. The reactions were carried out in 10 mL sealed Pyrex vessels (working volume of 3 mL) equipped with a magnetic stirrer. The temperature was measured with a fibre optic temperature sensor immersed in the reaction vessel. After the specified irradiation period, the reaction vessel was cooled rapidly (1–2 min) to ambient temperatures using a nitrogen jet.

Low-resolution ESI mass spectra were recorded using a single-quadrupole mass spectrometer interfaced with a liquid chromatograph, while high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on a magnetic-sector machine.

Melting points were measured on a Reichert melting point microscope and are uncorrected.

Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates as supplied by Merck. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included anisaldehyde : sulfuric acid (conc.) : ethanol (3 mL : 4.5 mL : 200 mL) or potassium

permanganate : potassium carbonate : 5% sodium hydroxide aqueous solution : water (3 g : 20 g: 5 mL : 300 mL). Flash chromatographic separations were carried out following protocols defined by Still *et al*.[1] with silica gel 60 (40–63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated.

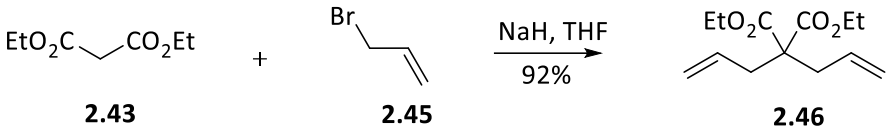
Starting materials and reagents were generally available from the Sigma–Aldrich, Merck, TCI, Strem or Lancaster Chemical Companies and were used as supplied. Drying agents and other inorganic salts were purchased from the AJAX, BDH or Unilab Chemical Companies. Tetrahydrofuran (THF), methanol and dichloromethane were dried using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs *et al*.[2] Petroleum ether refers to the fraction boiling between 40 and 60 °C.

Where necessary, reactions were performed under a nitrogen atmosphere using standard Schlenk techniques and, unless otherwise specified, stirred magnetically. Deoxygenated solutions were obtained by bubbling nitrogen through the relevant solution for at least 15 min. Ambient temperature was assumed to be *ca*. 18 °C. Temperatures higher than ambient were attained using thermostated oil baths. To attain temperatures lower than ambient, a cooled, water-circulating bath (0 to 10 °C) or relevant cryostats [ice/water, 0 °C; ice/saturated aqueous ammonium chloride, −15 °C; dry-ice/acetone, −78 °C] were used.

Ozonolysis reactions were performed using a Model 500 Fischer portable ozonegenerator with the luteinizing power and flow rate adjusted to 80 V and 50 L/h, respectively.

Experimental Procedures Related to Work Described in Chapter Two

Diethyl 2,2-Diallylmalonate (2.46)



2.43 **2.45** **2.46**

A magnetically stirred solution of diethyl malonate (**2.43**) (2.0 mL, 13.1 mmol) in THF (30 mL) maintained at 0 °C was treated, in portions, with sodium hydride (1.3 g of 60% w/w dispersion in mineral oil, 32.82 mmol) and stirring continued for 0.15 h thereafter. The resulting mixture was treated with allyl bromide (**2.45**) (3.5 mL, 39.34 mmol) then heated under reflux for 1 h. The cooled reaction mixture was quenched with NH_4Cl (50 mL of a saturated aqueous solution) then extracted with ethyl acetate (3 × 20 mL) and the combined organic phases were washed with brine (1 × 10 mL) before being dried (Na_2SO_4), filtered then concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) and concentration of the appropriate fractions (R_f = 0.7) gave compound **2.46**[3] (2.89 g, 92%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65 (ddt, *J* = 16.5, 10.4, 7.4 Hz, 2H), 5.11 (dt, *J* = 6.5, 1.4 Hz, 2H), 5.08 (t, *J* = 1.2 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 4H), 2.63 (dt, *J* = 7.5, 1.2 Hz, 4H), 1.24 (t, *J* = 7.1 Hz, 6H);

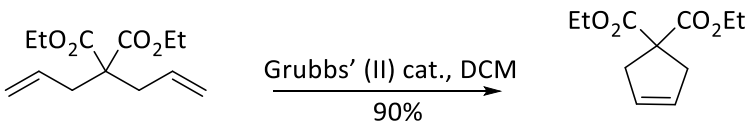
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.9, 132.4, 119.3, 61.4, 57.4, 36.9, 14.3;

IR ν_{max} 2955, 1732, 1644, 1435 cm^{-1};

MS (ESI, +ve) *m/z* 263 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) *m/z* 263.1422$(M+Na)^+$, calcd for $C_{13}H_{20}O_4Na$ 263.1411.

Diethyl Cyclopent-3-ene-1,1-dicarboxylate (2.47)



2.46 **2.47**

A magnetically stirred solution of compound **2.46** (500 mg, 2.08 mmol) in dry dichloromethane (50 mL) maintained at 20 °C was treated, via cannula, with a solution of

Grubbs' second-generation catalyst (130 mg, 0.16 mmol) in dichloromethane (20 mL). The ensuing mixture was heated under reflux for 2 h then cooled and concentrated under reduced pressure. Subjection of the residue thus obtained to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) and concentration of the appropriate fractions (R_f = 0.7) gave cyclopentene **2.47**[4] (397 mg, 90%) as a clear, brown oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60 (s, 2H), 4.19 (q, *J* = 7.1 Hz, 4H), 3.01 (s, 4H), 1.24 (t, *J* = 7.1 Hz, 6H);

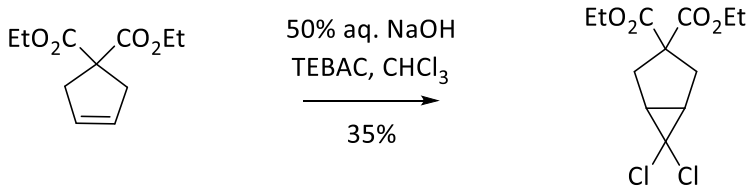
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.4, 127.9, 61.7, 51.8, 41.0, 14.2;

IR ν_{max} 3082, 2959, 1728, 1438, 1273, 1249, 1156, 1073, 969 cm^{-1};

MS (ESI, +ve) *m/z* 235 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) *m/z* 235.1022 $(M+Na)^+$, calcd for $C_{11}H_{16}O_4Na$ 235.1021.

Diethyl 6,6-Dichlorobicyclo[3.1.0]hexane-3,3-dicarboxylate (**2.48**)



2.47 **2.48**

A mixture of NaOH (14 mL of a 50 % w/v aqueous solution), benzyl triethylammonium chloride (10 mg, 3 mol %) and chloroform (6.5 mL) was stirred at 500 rpm with a magnetic stirring bar while being maintained at 0 °C. After 10 min, the reaction mixture was treated, in one portion, with cyclopentene **2.47** (500 mg, 2.35 mmol) and stirring continued for 16 h. Thereafter, the reaction mixture was extracted with diethyl ether (3 × 30 mL) and the combined organic phases then washed with water (1 × 50 mL) before being dried (Na_2SO_4), filtered then concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 19:1 v/v hexane/ethyl acetate elution) and concentration of the appropriate fractions (R_f = 0.8) afforded cyclopropane **2.48** (243 mg, 35%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (m, 4H), 2.82-2.68 (complex m, 2H), 2.41 (m, 2H), 2.30-2.20 (complex m, 2H), 1.25 (m, 6H);

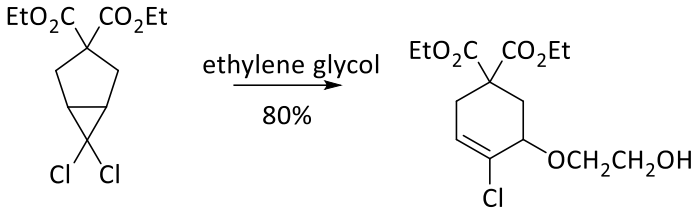
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 172.2, 169.8, 67.8, 62.1, 61.8, 37.8, 35.9, 14.2;

IR ν_{max} 3085, 2965, 1613, 1750, 1621, 1445, 1213, 1056, 980 cm^{-1};

MS (ESI, +ve) *m/z* 321, 319 and 317 [$(M+Na)^+$, 10, 60 and 100%];

HRMS (ESI, +ve) *m/z* 317.0711$(M+Na)^+$, calcd for $C_{12}H_{16}{}^{35}Cl_2O_4Na$ 317.0713.

Diethyl 4-Chloro-5-(2-hydroxyethoxy)cyclohex-3-ene-1,1-dicarboxylate (**2.49**)



2.48 **2.49**

A magnetically stirred solution of *gem*-dichlorocyclopropane **2.48** (200 mg, 0.68 mmol) in ethylene glycol (5 mL, 89 mmol) was heated at 150 °C (oil bath temperature) for 16 h and while being maintained under a nitrogen atmosphere. After this time, the reaction mixture was cooled then diluted with water (15 mL). The separated aqueous phase was extracted with ethyl acetate (3 × 5 mL) and the combined organic phases then dried (Na_2SO_4), filtered then concentrated under reduced pressure. The light-yellow oil thus obtained was subjected to flash chromatography (silica, 7:3 v/v hexane/ethyl acetate elution) and concentration of the appropriate fractions (R_f = 0.3) afforded compound **2.49** (173 mg, 80%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.99 – 5.91 (m, 1H), 4.25 – 4.07 (m, 4H), 3.95 (dt, *J* = 4.8, 2.4 Hz, 1H), 3.74 – 3.59 (m, 4H), 2.90 (dt, *J* = 18.0, 2.3 Hz, 1H), 2.59 – 2.51 (m, 1H), 2.44 – 2.25 (m, 3H), 1.23 (dddt, *J* = 8.7, 7.2, 3.9, 1.8 Hz, 6H);

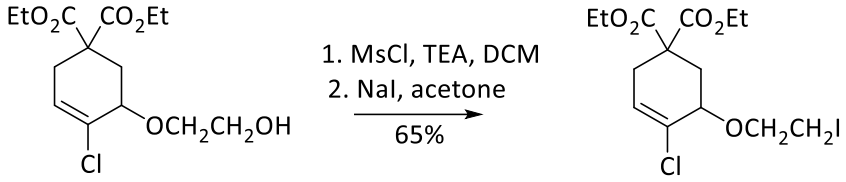
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 170.8, 170.5, 131.1, 125.6, 75.3, 71.7, 61.9, 50.9, 33.7, 31.5, 14.1;

IR ν_{max} 3561, 2934, 2864,1728, 1578, 1443, 1296, 814 cm^{-1};

MS (ESI, +ve) *m/z* 345 and 343 [$(M+Na)^+$, 30 and 100%];

HRMS (ESI, +ve) *m/z* 343.1020 $(M+Na)^+$, calcd for $C_{14}H_{21}{}^{35}ClO_6Na$ 343.1022.

Diethyl 4-Chloro-5-(2-iodoethoxy)cyclohex-3-ene-1,1-dicarboxylate (**2.50**)



2.49 **2.50**

A magnetically stirred solution of alcohol **2.49** (60 mg, 0.19 mmol) in dichloromethane (5 mL) maintained under a nitrogen atmosphere at ambient temperatures was treated with triethylamine (TEA) (78 µL, 0.57 mmol) then MsCl (22 µL, 0.29 mmol). The ensuing mixture was stirred for a further 1 h then treated with $NaHCO_3$ (10 mL of a saturated aqueous solution) before being extracted with dichloromethane (3 × 5 mL). The combined organic phases were then dried (Na_2SO_4), filtered and concentrated under reduced pressure to give an orange oil. This oil, which is presumed to contain the anticipated mesylate, was immediately submitted to the next step of the reaction sequence. Specifically, a magnetically stirred solution of the mesylate in acetone (15 mL) was treated with sodium iodide (100 mg, 0.70 mmol) and the resulting solution heated under reflux for 16 h before being cooled, diluted with diethyl ether (50 mL) and filtered. The filtrate was washed with water (3 × 15 mL) before being dried (Na_2SO_4), filtered then concentrated under reduced pressure. The light-sensitive oil thus obtained was subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) and concentration of the appropriate fractions (R_f = 0.8) afforded iodide **2.50** (35 mg, 65%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (t, *J* = 4.1 Hz, 1H), 4.28 – 4.07 (m, 4H), 4.01 (dd, *J* = 5.8, 4.2 Hz, 1H), 3.87 – 3.79 (m, 2H), 3.29 – 3.15 (m, 2H), 2.87 (ddd, *J* = 17.9, 4.2, 1.6 Hz, 1H), 2.46 (t, *J* = 5.1 Hz, 3H), 1.25 (td, *J* = 7.1, 4.4 Hz, 6H);

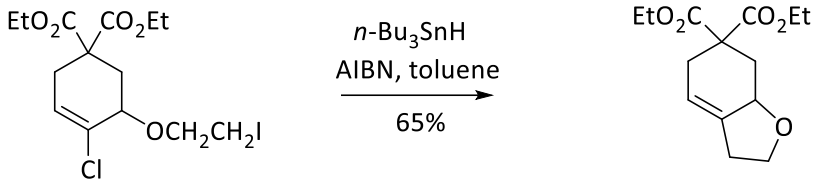
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.8, 170.2, 131.2, 125.9, 75.3, 71.3, 62.0, 61.9, 51.4, 34.2, 31.5, 14.1, 14.1, 2.4;

IR ν_{max} 3122, 2934, 2864,1728, 1578, 1443, 1296, 814 cm^{-1};

MS (ESI, +ve) *m/z* 455 and 453 [$(M+Na)^+$, 30 and 100%];

HRMS (ESI, +ve) *m/z* 453.0096 $(M+Na)^+$, calcd for $C_{14}H_{20}{}^{35}ClIO_5Na$ 453.0095.

Diethyl 3,5,7,7*a*-Tetrahydrobenzofuran-6,6(2*H*)-dicarboxylate (**2.51**)



2.50 **2.51**

Bu_3SnH (99 µL, 367 µmol) was added, via syringe pump, over a period of 3 h to a magnetically stirred solution of AIBN (5 mg, 33 µmol added in two equal aliquots at the 0 and 2 h time points) and iodide **2.50** (100 mg, 232 µmol) in anhydrous toluene (15 mL) maintained at 80 °C under a nitrogen atmosphere. The ensuing mixture was kept at 80 °C for a further 1.5 h then cooled to ambient temperatures before being concentrated under reduced pressure. The oily residue thus obtained was subjected to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate elution) and concentration of the appropriate fractions (R_f = 0.6) afforded compound **2.51** (40 mg, 65%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.52 – 5.46 (m, 1H), 4.19 (dddd, *J* = 14.2, 8.5, 6.8, 4.4 Hz, 4H), 3.92 (dd, *J* = 8.2, 5.9 Hz, 2H), 3.88 – 3.79 (m, 1H), 2.92 (dtd, *J* = 18.0, 2.3, 1.1 Hz, 1H), 2.78 (ddd, *J* = 12.2, 5.4, 1.1 Hz, 1H), 2.60 – 2.45 (m, 2H), 2.30 (ddd, *J* = 18.1, 3.3, 2.0 Hz, 1H), 1.80 – 1.69 (m, 1H), 1.24 (td, *J* = 7.1, 5.1 Hz, 6H);

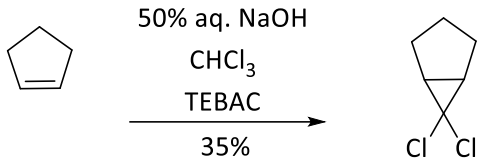
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.6, 170.9, 139.0, 116.0, 73.6, 66.7, 61.8, 61.8, 53.0, 33.4, 31.3, 30.5, 14.2, 14.1;

IR ν_{max}3344, 2941, 2863, 2148, 1621, 1578, 1510, 1296, 881 cm^{-1};

MS (ESI, +ve) *m/z* 391 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) *m/z* 391.1361 $(M+Na)^+$, calcd for $C_{14}H_{20}O_5Na$ 391.1362.

6,6-Dichlorobicyclo[3.1.0]hexane (**2.34**)



2.52 **2.34**

A mixture of NaOH (20 mL of a 50 % w/v aqueous solution), benzyl triethylammonium chloride (130 mg, 5 mol %) and chloroform (20 mL) was stirred at 500 rpm with a magnetic stirring bar while being maintained at 0 °C. After 10 min, the reaction mixture was treated, in one portion, with cyclopentene **2.52** (1.0 mL, 11.31 mmol) and stirring continued for 16 h. Thereafter, the reaction mixture was extracted with diethyl ether (3 × 30 mL) and the combined organic phases then washed with water (1 × 50 mL) before being dried (Na_2SO_4), filtered then concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 19:1 v/v hexane/ethyl acetate elution) and concentration of the appropriate fractions (R_f = 0.8) afforded cyclopropane **2.34**[5] (598 mg, 35%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.14-1.91 (complex m, 6H), 1.82-1.57 (complex m, 2H);

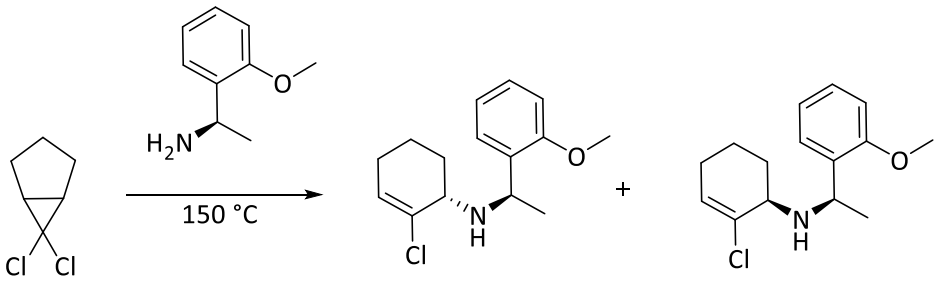
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 68.4, 38.3, 27.9, 25.3;

IR ν_{max} 3520, 2980, 1488, 1438, 1375, 1319, 1200, 1075, 1013, 881, 819 cm^{-1};

MS (ESI, +ve) *m/z* 155, 153 and 151 [$(M+H)^+$, 30, 60 and 100%];

HRMS (ESI, +ve) *m/z* 151.0011 $(M+H)^+$, calcd for $C_6H_9{}^{35}Cl_2$ 151.0018.

(*R*)-2-Chloro-*N*-((*R*)-1-(2-methoxyphenyl)ethyl)cyclohex-2-en-1-amine (**2.65**) **and (*S*)-2-Chloro-*N*-((*R*)-1-(2-methoxyphenyl)ethyl)cyclohex-2-en-1-amine** (**2.66**)



2.34 35% **2.65** 32% **2.66**

A magnetically stirred solution of *gem*-dichlorocyclopropane **2.34** (5.0 g, 33.11 mmol) in (*R*)-1-(2-methoxyphenyl)ethan-1-amine (5.0 mL, 330.12 mmol) was heated at 150 °C (oil bath temperature) and under a nitrogen atmosphere for 16 h before being cooled then diluted with water (15 mL). The separated aqueous phase was extracted with ethyl acetate (3 × 5 mL) and the combined organic phases then dried (Na_2SO_4), filtered then concentrated under reduced pressure. The yellow oil thus obtained was subjected to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate elution) and a series of fractions (R_f ca. 0.6) thereby obtained. While most of these contained mixtures of the title compounds, certain of the earlier or later eluting ones contained pure samples of compounds **2.65** (3.1 g, 35%) and **2.66** (2.8 g, 32%) each of which was obtained as a clear, colourless oil. The spectral data derived from each of these pure samples are provided immediately below.

Compound **2.65**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.20 (td, *J* = 7.8, 1.8 Hz, 1H), 6.94 (td, *J* = 7.5, 1.1 Hz, 1H), 6.85 (dd, *J* = 8.2, 1.1 Hz, 1H), 5.86 (t, *J* = 4.1 Hz, 1H), 4.34 (q, *J* = 6.6 Hz, 1H), 3.84 (s, 3H), 3.20 (t, *J* = 3.3 Hz, 1H), 2.14 – 1.92 (m, 2H), 1.63 (qd, *J* = 10.8, 6.8 Hz, 3H), 1.52 – 1.39 (m, 1H), 1.37 (d, *J* = 6.6 Hz, 3H);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.4, 135.5, 131.3, 129.5, 128.4, 127.8, 120.1, 110.6, 59.4, 56.7, 55.2, 51.6, 47.7, 29.2, 26.2, 21.4, 15.3;

IR ν_{max} 2974, 2928, 1629, 1493, 1377, 1267, 1121, 821 cm^{-1};

MS (ESI, +ve) *m/z* 290 and 288 [$(M+Na)^+$, 30 and 100%];

HRMS (ESI, +ve) *m/z* 266.7821 $(M+H)^+$, calcd for $C_{15}H_{21}{}^{35}ClNO$ 266.7831.

Compound **2.66**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.22 (td, *J* = 7.8, 1.8 Hz, 1H), 6.95 (td, *J* = 7.4, 1.1 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 5.89 (t, *J* = 4.1 Hz, 1H), 4.17 (q, *J* = 6.7 Hz, 1H), 3.84 (s, 3H), 2.96 (dt, *J* = 5.1, 2.8 Hz, 1H), 2.18 – 1.94 (m, 2H), 1.84 – 1.68 (m, 1H), 1.72 – 1.59 (m, 1H), 1.48 (s, 1H), 1.49 – 1.33 (m, 3H);

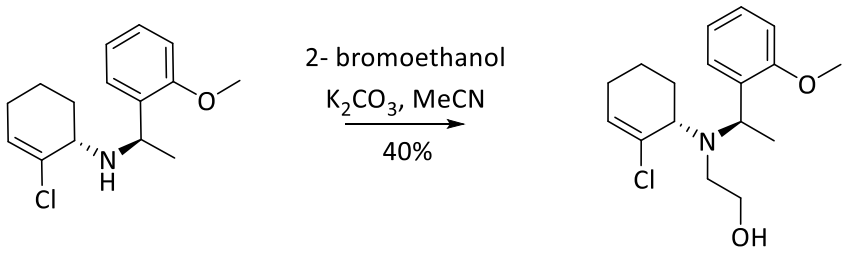
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.4, 135.5, 131.5, 129.9, 128.7, 127.9, 120.1, 111.6, 59.5, 56.8, 55.3, 52.6, 48.8, 29.2, 26.4, 21.4, 15.3;

IR ν_{max} 2980, 2930, 1639, 1490, 1378, 1266, 1021, 811 cm^{-1};

MS (ESI, +ve) *m/z* 290 and 288 [$(M+Na)^+$, 30 and 100%];

HRMS (ESI, +ve) *m/z* 288.7811 $(M+Na)^+$, calcd for $C_{15}H_{20}{}^{35}ClNONa$ 288.7821.

2-(((*S*)-2-Chlorocyclohex-2-en-1-yl)((*R*)-1-(2-methoxyphenyl)ethyl)amino)ethan-1-ol (**2.67**)



2.65 **2.67**

A magnetically stirred solution of compound **2.65** (100 mg, 0.37 mmol) in acetonitrile (5 mL) and maintained under nitrogen was treated with K_2CO_3 (155 mg, 1.12 mmol) and 2-bromoethanol (80 µmol, 0.52 mmol). The resulting mixture was heated under reflux for 16 h then cooled before being treated with dichloromethane (10 mL) and water (10 mL). The separated aqueous phase was extracted with dichloromethane (2 × 5 mL) and the combined organic layers were then dried (Na_2SO_4), filtered then concentrated under vacuum. The residue thus obtained was subjected to flash chromatography (silica, 7:3 v/v hexane/ethyl acetate elution) and concentration of the appropriate fractions (R_f = 0.3) afforded compound **2.67** (46 mg, 40%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.22 (m, 3H), 6.95 (t, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 5.94 (p, *J* = 2.3 Hz, 1H), 4.64 (q, *J* = 7.0 Hz, 1H), 3.85 (s, 3H), 3.76 (dt, *J* = 9.6, 4.8 Hz, 1H), 3.55

(d, *J* = 5.7 Hz, 1H), 3.38 (ddt, *J* = 7.4, 5.0, 2.3 Hz, 1H), 2.97 – 2.80 (m, 2H), 2.11 – 1.81 (m, 4H), 1.68 (dp, *J* = 15.2, 5.0 Hz, 1H), 1.54 – 1.44 (m, 1H), 1.38 (d, *J* = 7.0 Hz, 3H);

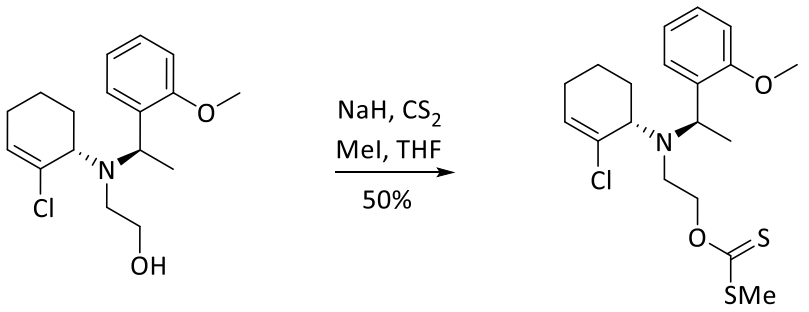
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 157.4, 135.5, 131.3, 129.5, 128.4, 127.8, 120.1, 110.6, 59.4, 56.7, 55.2, 51.6, 47.8, 29.2, 26.2, 21.4, 15.3;

IR ν_{max} 3454, 2936, 1628, 1585, 1491, 1336, 1264, 731 cm^{-1};

MS (ESI, +ve) *m/z* 334 and 332 [$(M+Na)^+$, 30 and 100%];

HRMS (ESI, +ve) *m/z* 332.1533 $(M+Na)^+$, calcd for $C_{17}H_{25}{}^{35}ClNO_2Na$ 332.1521.

***O*-(2-(((*S*)-2-Chlorocyclohex-2-en-1-yl)((*R*)-1-(2-methoxyphenyl)ethyl)amino)ethyl) *S*-methyl carbonodithioate (2.68)**



2.67 **2.68**

A magnetically stirred solution of compound **2.67** (50 mg, 160 µmol) in anhydrous THF (3 mL) was treated with sodium hydride (10 mg of 60% w/w dispersion in mineral oil, 242 µmol). The ensuing mixture was stirred for 0.25 h before being treated, sequentially, with carbon disulfide (15 µL, 242 µmol) and methyl iodide (15 µL, 242 µmol). Stirring was continued for 0.33 h then the reaction mixture was diluted with ethyl acetate (5 mL) and quenched with water (10 mL). The separated aqueous layer was extracted with ethyl acetate (1 × 10 mL) and the combined organic phases were washed with brine (1 × 20 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate elution) and concentration of the appropriate fractions (R_f = 0.7) afforded xanthate **2.68** (32 mg, 50%) as a light-yellow coloured oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.44 (m, 1H), 7.19 (ddd, *J* = 8.2, 7.3, 1.8 Hz, 1H), 6.93 (td, *J* = 7.5, 1.1 Hz, 1H), 6.84 (dd, *J* = 8.2, 1.1 Hz, 1H), 5.95 (dt, *J* = 5.0, 2.6 Hz, 1H), 4.77 (q, *J* = 6.8 Hz, 1H), 4.04 (t, *J* = 7.3 Hz, 2H), 3.82 (s, 3H), 3.41 (ddt, *J* = 8.8, 6.3, 3.0 Hz, 1H), 3.06 (dt, *J* = 14.4,

7.1 Hz, 1H), 2.81 (dt, *J* = 14.8, 7.5 Hz, 1H), 2.02 (s, 5H), 1.89 – 1.78 (m, 1H), 1.76 – 1.62 (m, 3H), 1.49 – 1.40 (m, 1H), 1.34 (d, *J* = 6.9 Hz, 3H);

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 171.1, 157.0, 135.9, 134.3, 129.5, 127.8, 127.6, 120.5, 110.6, 65.6, 60.0, 55.4, 54.2, 44.8, 30.7, 26.5, 21.4, 21.1, 20.2;

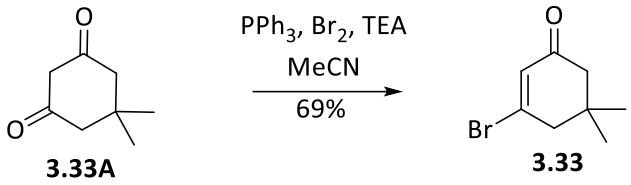
IR ν_{max} 3100, 2568, 2950, 1600, 1500, 1345, 1200, 1060, 881 cm^{-1};

MS (ESI, +ve) *m/z* 424 and 422 [$(M+Na)^+$, 30 and 100%];

HRMS (ESI, +ve) *m/z* 422.1110 $(M+Na)^+$, calcd for $C_{19}H_{26}{}^{35}ClNO_2S_2Na$ 422.1111.

Experimental Procedures Related to Work Described in Chapter Three

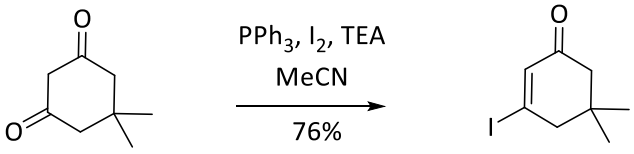
3-Bromo-5,5-dimethylcyclohex-2-en-1-one (**3.33**) (Y = Br)



3.33A **3.33**

A magnetically stirred solution of PPh_3 (1.40 g, 5.50 mmol) in dry acetonitrile (25 mL) maintained at 0 °C was treated, dropwise, with a solution of molecular bromine (0.3 mL, 5.50 mmol) in dry acetonitrile (2.3 mL). The resulting mixture was warmed to 22 °C and after 0.5 h it was treated with TEA (800 mL, 6.00 mmol) then dimedone (**3.33A**) (700 mg, 5.00 mmol) before being stirred under reflux for 16 h. The cooled reaction mixture was concentrated under reduced pressure and the residue thus obtained stirred vigorously with diethyl ether (20 mL) and the supernatant liquid then decanted. This process was repeated twice and the combined organic phases then diluted with 40-60 petroleum ether (30 mL) to precipitate residual any triphenylphosphine oxide. The ensuing mixture was filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the filtrate concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:9 v/v diethyl ether/pentane elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.2), compound **3.33** (Y = Br) (700 mg, 69%) as a clear, pale-yellow oil. The spectral data obtained on this material matched those reported in the literature.[6]

3-Iodo-5,5-dimethylcyclohex-2-en-1-one (**3.33**) (Y = I)

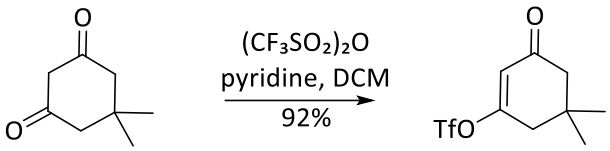


3.33A **3.33**

A magnetically stirred solution of PPh_3 (2.96 g, 11.31 mmol) in dry acetonitrile (50 mL) maintained at 22 °C was treated, in portions, with powdered molecular iodine (3.00 g, 11.81 mmol). After 0.5 h the reaction mixture was treated with TEA (1.72 mL, 12.3 mmol) then 5,5-dimethyl-1,3-cyclohexanedione (**3.33A**) (1.44 g, 10.31 mmol) and the resulting mixture heated under reflux for 16 h. The cooled reaction mixture was concentrated under reduced

pressure and the residue thus obtained stirred vigorously with diethyl ether (30 mL) before the supernatant liquid was decanted. This process was repeated twice and the combined organic phases then diluted with 40-60 petroleum ether (50 mL) to precipitate any residual triphenylphosphine oxide. The ensuing mixture was filtered through a plug of TLC grade silica gel topped with diatomaceous earth and the filtrate concentrated under reduced pressure to afford compound **3.33** (Y = I) (1.95 g, 76%) as a clear, colourless oil. The spectral data obtained on this material matched those reported in the literature.[6]

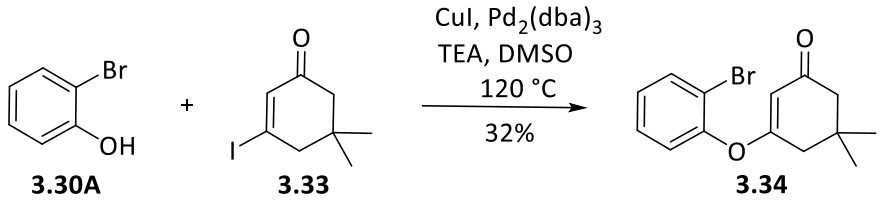
5,5-Dimethyl-3-oxocyclohex-1-en-1-yl trifluoromethanesulfonate (**3.33**) (Y = OTf)



3.33A **3.33**

A magnetically stirred solution of 5,5-dimethyl-1,3-cyclohexanedione (**3.33A**) (421 mg, 3.00 mmol) in dry dichloromethane (15 mL) maintained at −78 °C was treated with pyridine (483 µL, 6.00 mmol). After 10 min the reaction mixture was treated, dropwise over 5 minutes at −78 °C, with trifluoromethanesulfonic anhydride (605 µL, 3.60 mmol). After 0.33 h the reaction mixture was allowed to warm to 22 °C over 1 h then quenched with hydrochloric acid (10 mL of a 1 M aqueous solution). The separated aqueous phase was extracted with dichloromethane (2 × 10 mL) and the combined organic phases were washed with sodium bicarbonate (1 × 20 mL of a saturated aqueous solution), water (1 × 20 mL) and brine (1 × 20 mL) before being dried (Na_2SO_4), filtered then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:19 v/v diethyl ether/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.1), compound **3.33** (Y = OTf) (751 mg, 92%) as a clear, pale-yellow oil**.** The spectral data obtained on this material matched those reported in the literature.[7]

3-(2-Bromophenoxy)-5,5-dimethylcyclohex-2-en-1-one (**3.34**) (X = Br)



A magnetically stirred solution of compound **3.33** (Y = I) (125 mg, 0.50 mmol), *o*-bromophenol [**3.30A** (X = Br)] (130 mg, 0.75 mmol) and copper(I) iodide (48 mg, 0.25 mmol) in dry DMSO (5 mL) maintained at 60 °C was treated with TEA (139 µL, 1.00 mmol). After 2 h the reaction mixture was treated with $Pd_2(dba)_3$ (46 mg, 0.05 mmol) then heated to 120 °C. After 20 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL) and the ensuing mixture filtered through a plug of TLC-grade silica topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (2 × 25 mL of a 5% v/v aqueous solution), water (1 × 25 mL) and brine (1 × 25 mL) before being dried (Na_2SO_4), filtered, then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:3 v/v diethyl ether/40-60 petroleum ether gradient elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.2), compound **3.34** (X = Br) (47 mg, 32%) as a clear, yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.0 Hz, 1H), 7.34 (t, *J* = 7.7 Hz, 1H), 7.20-7.06 (complex m, 2H), 4.96 (s, 1H), 2.56 (s, 2H), 2.25 (s, 2H), 1.16 (s, 6H);

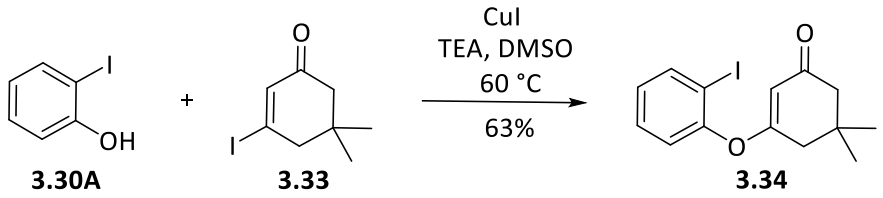
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 199.2, 175.3, 149.9, 134.0, 128.9, 127.6, 123.4, 116.0, 104.9, 50.7, 41.9, 32.8, 28.3.;

IR ν_{max} 2960, 1658, 1617, 1469, 1366, 1213, 1134, 1046, 762, 659 cm^{-1};

MS (ESI, +ve) *m/z* 615, 613 and 611 [$(2M+Na)^+$, 50, 100, 50%], 319 and 317 [$(M+Na)^+$, 65 and 66], 297 and 295 [$(M+H)^+$, 19 and 19];

HRMS (ESI, +ve) *m/z* 295.0330 $[M+H]^+$, calcd for $C_{14}H_{15}{}^{79}BrO_2$, 295.0328.

3-(2-Iodophenoxy)-5,5-dimethylcyclohex-2-en-1-one (**3.34**) (X = I)



3.30A **3.33** **3.34**

A magnetically stirred solution of compound **3.33** (Y = I) (104 mg, 0.42 mmol), *o*-iodophenol [**3.30A** (X = I)] (137 mg, 0.62 mmol) and copper(I) iodide (40 mg, 0.21 mmol) in dry DMSO (5 mL) maintained at 60 °C was treated with TEA (116 µL, 0.83 mmol). After 2 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL) and the ensuing mixture filtered through a plug of TLC-grade silica topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (2 × 25 mL of a 5% v/v aqueous solution), water (1 × 25 mL) and brine (1 × 25 mL) before being dried (Na_2SO_4), filtered, then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:3 v/v the diethyl ether/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.2), compound **3.34** (X = I) (90 mg, 63%) as a clear, yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.8 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.06 (d, *J* = 7.8 Hz, 1H), 6.99 (t, *J* = 7.8 Hz, 1H), 4.95 (s, 1H), 2.57 (s, 2H), 2.25 (s, 2H), 1.17 (s, 6H);

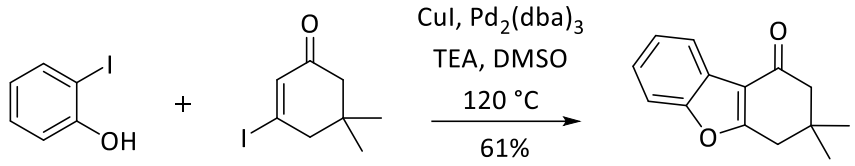
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 199.2, 175.3, 152.8, 140.0, 129.9, 127.8, 122.6, 105.1, 90.0, 50.7, 42.1, 32.9, 28.4;

IR ν_{max} 2958, 1657, 1617, 1575, 1464, 1368, 1208, 1135, 1021, 764 cm^{-1};

MS (ESI, +ve) *m/z* 707 [$(2M+Na)^+$, 100%], 365 [$(M+Na)^+$, 46], 343 [$(M+H)^+$, 70];

HRMS (ESI, +ve) *m/z* 365.0009 [$M+Na]^+$, calcd for $C_{14}H_{15}IO_2Na$, 365.0009.

3,3-Dimethyl-3,4-dihydrodibenzo[*b*,*d*]furan-1(2*H*)-one (**3.36**)



3.30A **3.33** **3.36**

A magnetically stirred solution of compound **3.33** (Y = I) (58 mg, 0.23 mmol), *o*-iodophenol [**3.30A** (X = I)] (76 mg, 0.35 mmol) and copper(I) iodide (22 mg, 0.12 mmol) in dry DMSO (2.3 mL) maintained at 60 °C was treated with TEA (64 µL, 0.46 mmol). After a further 2 h the reaction mixture was treated with $Pd_2(dba)_3$ (11 mg, 0.01 mmol) then heated to 120 °C. After 20 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (3 mL) and the ensuing mixture filtered through a plug of TLC-grade silica topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (12 mL). The combined filtrates were washed with ammonia (2 × 15 mL of a 5% v/v aqueous solution), water (1 × 15 mL) and brine (1 × 15 mL) before being dried (Na_2SO_4), filtered, then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:4 v/v diethyl ether/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.3), compound **3.36** (30 mg, 61%) as a yellow, crystalline solid, m.p. = 119-120 °C (lit.[8] m.p. = 121-122 °C).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (m, 1H), 7.48 (m, 1H), 7.33 (m, 2H), 2.91 (s, 2H), 2.49 (s, 2H), 1.21 (s, 6H);

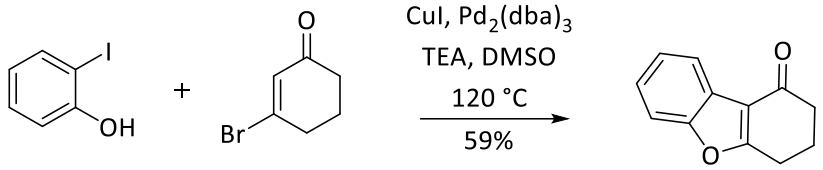
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 194.1, 169.9, 154.9, 124.8, 124.4, 123.6, 121.7, 115.3, 111.1, 52.2, 37.7, 35.2, 28.7;

IR ν_{max} 2960, 1665, 1588, 1479. 1444, 1406, 1173, 1040, 840, 748, 672 cm^{-1};

MS (ESI, +ve) *m/z* 215 [$(M+H)^+$, 100%];

HRMS (ESI, +ve) *m/z* 215.1071 $[M+H]^+$, calcd for $C_{14}H_{14}O_2$, 215.1071.

3,4-Dihydrodibenzo[*b*,*d*]furan-1(2*H*)-one (**3.32**)



3.30A **3.31** **3.32**

A magnetically stirred solution of compound **3.31** (X = Br) (100 mg, 0.57 mmol), *o*-iodophenol [**3.30A** (X = I)] (189 mg, 0.86 mmol) and copper(I) iodide (54 mg, 0.29 mmol) in dry DMSO (5 mL) maintained at 60 °C was treated with TEA (159 µL, 1.14 mmol). After 2 h the reaction mixture was treated with $Pd_2(dba)_3$ (26 mg, 0.03 mmol) then heated to 120 °C. After a further 20 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL) and the ensuing mixture filtered through a plug of TLC-grade silica topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (2 × 25 mL of a 5% v/v aqueous solution), water (1 × 25 mL) and brine (1 × 25 mL) before being dried (Na_2SO_4), filtered, then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:9 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.3), compound **3.32**[8] (63 mg, 59%) as a clear, brown oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (m, 1H), 7.47 (m, 1H), 7.32 (m, 2H), 3.04 (t, *J* = 6.3 Hz, 3H), 2.61 (t, *J* = 6.5 Hz, 2H), 2.28 (m, 2H);

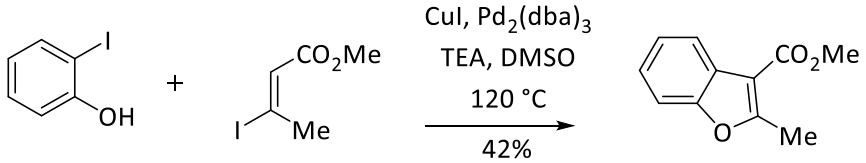
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 194.7, 170.8, 154.5, 124.9, 124.4, 123.7, 121.8, 116.5, 111.0, 37.9, 23.8, 22.5;

IR ν_{max} 2959, 1676, 1482, 1451, 1169, 1012, 751 cm^{-1};

MS (ESI, +ve) *m/z* 209 [$(M+Na)^+$, 100%], 187 [$(M+H)^+$, 25];

HRMS (ESI, +ve) *m/z* 187.0749 $[M+H]^+$, calcd for $C_{12}H_{10}O_2$, 187.0754.

Methyl 2-Methylbenzofuran-3-carboxylate (**3.38**)



3.30A **3.37** **3.38**

A magnetically stirred solution of compound **3.37** (100 mg, 0.44 mmol), *o*-iodophenol [**3.30A** (X = I)] (146 mg, 0.66 mmol) and copper(I) iodide (42 mg, 0.22 mmol) in dry DMSO (5 mL) maintained at 60 °C was treated with TEA (123 µL, 0.88 mmol). After 2 h the reaction mixture was treated with $Pd_2(dba)_3$ (20 mg, 0.02 mmol) then heated to 120 °C. After a further 20 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL) and the ensuing mixture filtered through a plug of TLC-grade silica topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (2 × 25 mL of a 5% v/v aqueous solution), water (1 × 25 mL) and brine (1 × 25 mL) before being dried (Na_2SO_4), filtered and then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:5 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.6), compound **3.38**[9] (35 mg, 42%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (m, 1H), 7.42 (m, 1H), 7.30 (m, 2H), 3.95 (s, 3H), 2.77 (s, 3H);

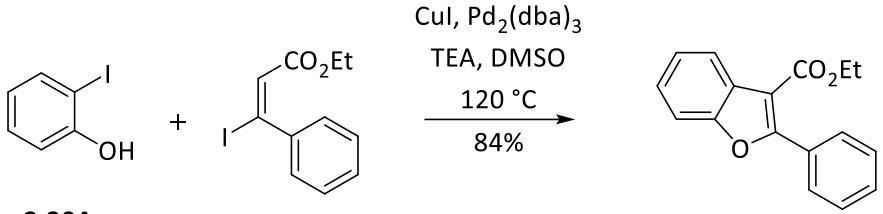
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.9, 163.7, 153.6, 126.1, 124.3, 123.7, 121.7, 110.7, 108.9, 51.4, 14.4;

IR ν_{max} 2952, 1712, 1454, 1237, 1106, 1085, 785, 750 cm^{-1};

MS (ESI, +ve) *m/z* 245 [(M+Na+MeOH)$^+$, 100%], 191 [(M+H)$^+$, 40];

HRMS (ESI, +ve) *m/z* 191.0706 [M+H]$^+$, calcd for $C_{11}H_{10}O_3$ 191.0708.

Ethyl 2-Phenylbenzofuran-3-carboxylate (**3.40**)



3.30A **3.39** **3.40**

A magnetically stirred solution of compound **3.39** (74 mg, 0.25 mmol), *o*-iodophenol [**3.30A** (X = I)] (81 mg, 0.37 mmol) and copper(I) iodide (23 mg, 0.12 mmol) in dry DMSO (2.5 mL) maintained at 60 °C was treated with TEA (68 µL, 0.49 mmol). After 3 h the reaction mixture was treated with $Pd_2(dba)_3$ (11 mg, 0.01 mmol) then heated to 120 °C. After a further 18 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (2.5 mL) and the ensuing mixture filtered through a plug of TLC-grade silica topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (10 mL). The combined filtrates were washed with ammonia (2 × 20 mL of a 5% v/v aqueous solution), water (1 × 20 mL) and brine (1 × 20 mL) before being dried (Na_2SO_4), filtered and then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:3 v/v dichloromethane/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.2), compound **3.40**[9] (55 mg, 84%) as a clear, yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12-7.97 (complex m, 3H), 7.60-7.44 (complex m, 4H), 7.37 (m, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H);

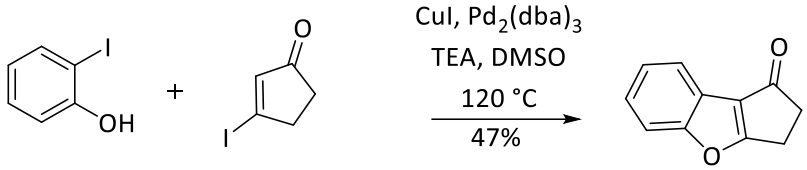
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.0, 160.7, 153.8, 130.2, 129.6, 129.5, 128.0, 127.1, 125.2, 124.0, 122.7, 111.1, 109.0, 60.6, 14.3;

IR ν_{max} 2984, 1712, 1454, 1443, 1224, 1195, 1090, 1049, 748, 691 cm^{-1};

MS (ESI, +ve) *m/z* 289 [$(M+Na)^+$, 100%], 267 [$(M+H)^+$, 10];

HRMS (ESI, +ve) *m/z* 289.0841 $[M+Na]^+$, calcd for $C_{17}H_{14}O_3Na$, 289.0841.

2,3-Dihydro-1*H*-cyclopenta[*b*]benzofuran-1-one (3.42)



3.30A **3.41** **3.42**

A magnetically stirred solution of compound **3.41** (100 mg, 0.48 mmol), *o*-iodophenol [**3.30A** (X = I)] (158 mg, 0.72 mmol) and copper(I) iodide (46 mg, 0.24 mmol) in dry DMSO (5 mL) maintained at 60 °C was treated with TEA (130 µL, 0.96 mmol). After 2 h the reaction mixture was treated with $Pd_2(dba)_3$ (22 mg, 0.02 mmol) then heated to 120 °C. After a further 24 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL) and then the ensuing mixture was filtered through a plug of TLC-grade silica topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (25 mL). The combined filtrates were washed with ammonia (2 × 25 mL of a 5% v/v aqueous solution), water (1 × 25 mL) and brine (1 × 25 mL) before being dried (Na_2SO_4), filtered then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:9 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.2), compound **3.42**[10] (39 mg, 47%) as a light-brown, crystalline solid, m.p. = 141-142 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (m, 1H), 7.53 (m, 1H), 7.38-7.31 (complex m, 2H), 3.16 (m, 2H), 3.08 (m, 2H);

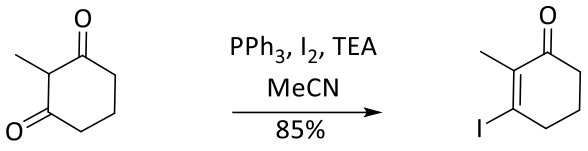
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 194.9, 186.7, 161.3, 125.4, 124.6, 124.4, 121.5, 121.4, 112.2, 41.3, 22.7;

IR ν_{max} 2917, 2851, 1689, 1591, 1481, 1436, 1038, 818, 755 cm^{-1};

MS (ESI, +ve) *m/z* 173 [$(M+H)^+$, 100%];

HRMS (ESI, +ve) *m/z* 173.0604 $[M+H]^+$, calcd for $C_{11}H_8O_2$, 173.0603.

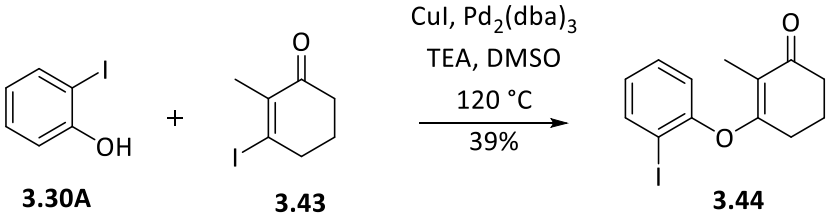
3-Iodo-2-methylcyclohex-2-en-1-one (**3.43**)



3.43A **3.43**

A magnetically stirred solution of PPh_3 (2.89 g, 11.0 mmol) in dry acetonitrile (50 mL) maintained at 22 °C was treated, in portions, with powdered molecular iodine (2.92 g, 11.5 mmol). After 0.5 h the reaction mixture was treated with TEA (1.67 mL, 12.0 mmol) then 2-methyl-1,3-cyclohexanedione **3.43A** (1.26 g, 10.0 mmol) and the resulting mixture heated under reflux for 20 h. The cooled reaction mixture was then concentrated under reduced pressure and the residue thus obtained was stirred vigorously with diethyl ether (40 mL) and the supernatant liquid decanted. This process was repeated twice and the combined organic phases then diluted with 40-60 petroleum ether (90 mL) to precipitate any residual triphenylphosphine oxide before being filtered and then concentrated under reduced pressure. The resulting oily solid was filtered through a plug of TLC-silica gel topped with diatomaceous earth and the solids thus retained washed with dichloromethane/40-60 petroleum ether (300 mL of a 1:1 v/v mixture) and the filtrate concentrated under reduced pressure to afford compound **3.43** (2.01 g, 85%) as a white, crystalline solid m.p. = 63.5 °C. The spectral data obtained on this material matched those reported in the literature.[6]

3-(2-Iodophenoxy)-2-methylcyclohex-2-en-1-one (**3.44**)



3.30A **3.43** **3.44**

A magnetically stirred solution of compound **3.43** (118 mg, 0.50 mmol), *o*-iodophenol [**3.30A** (X = I)] (220 mg, 1.00 mmol) and copper(I) iodide (24 mg, 0.13 mmol) in dry DMSO (5 mL) maintained at 60 °C was treated with TEA (349 µL, 2.50 mmol). After 2 h the reaction mixture was treated with $Pd_2(dba)_3$ (23 mg, 0.03 mmol) then heated to 120 °C. After a further 20 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL) and the ensuing mixture filtered through a plug of TLC-grade silica topped with diatomaceous earth and the

solids so retained were washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (2 × 25 mL of a 5% v/v aqueous solution), water (1 × 25 mL) and brine (1 × 25 mL) before being dried (Na_2SO_4), filtered then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:9 v/v ethyl acetate/40-60 petroleum spirit elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.1), compound **3.44** (63 mg, 39%) as a clear, yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 7.9 and 1.5 Hz, 1H), 7.32 (m, 1H), 6.98-6.87 (complex m, 2H), 2.40 (t, *J* = 6.6 Hz, 2H), 2.24 (m, 2H), 1.94 (m, 2H), 1.83 (s, 3H);

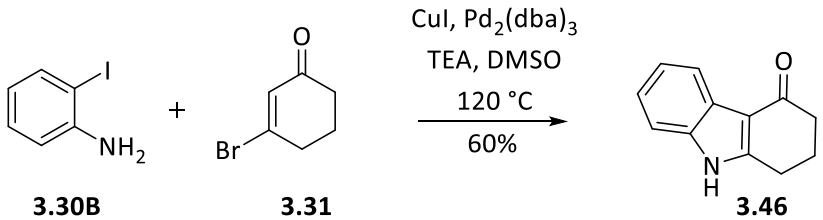
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 199.2, 168.3, 153.9, 139.7, 129.6, 126.5, 120.5, 119.6, 89.7, 36.6, 27.0, 20.9, 8.0;

IR ν_{max} 2954, 2857, 1633, 1575, 1463, 1375, 1347, 1258, 1219, 1195, 1115, 1083, 1019, 762 cm^{-1};

MS (ESI, +ve) *m/z* 351 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) *m/z* 350.9857 $[M+Na]^+$, calcd for $C_{13}H_{13}IO_2Na$, 350.9858.

1,2,3,9-Tetrahydro-4*H*-carbazol-4-one (**3.46**)



3.30B **3.31** **3.46**

A magnetically stirred solution of compound [**3.31** (X = Br)] (100 mg, 0.57 mmol), *o*-iodoaniline (**3.30B**) (188 mg, 0.86 mmol) and copper(I) iodide (54 mg, 0.29 mmol) in dry DMSO (5 mL) maintained at 60 °C was treated with TEA (159 µL, 1.14 mmol). After 2 h the reaction mixture was treated with $Pd_2(dba)_3$ (26 mg, 0.03 mmol) then heated to 120 °C. After 24 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL) and the ensuing mixture filtered through a plug of TLC-grade silica topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (2 × 25 mL of a 5% v/v aqueous solution), water (1 × 25 mL) and brine (1 × 25 mL) before being dried (Na_2SO_4), filtered and then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 3:7

v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.1), compound **3.46**[11] (64 mg, 60%) as a white, crystalline solid, m.p. = 220-221 °C.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.84 (broad s, 1H), 7.89 (m, 1H), 7.39 (d, J = 7.9 Hz, 1H), 7.21-7.07 (complex m, 2H), 2.96 (t, J = 6.2 Hz, 2H), 2.42 (t, J = 6.5 Hz, 2H), 2.11 (m, 2H);

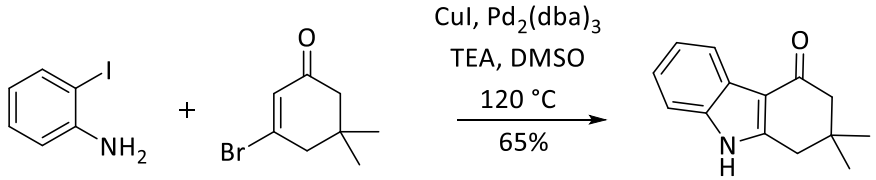
^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 192.9, 152.3, 135.8, 124.5, 122.4, 121.5, 120.2, 111.7, 111.5, 37.8, 23.4, 22.7;

IR (ATR) ν_{max} 3061, 2917, 2854, 1603, 1575, 1456, 1177, 1015, 752 cm^{-1};

MS (ESI, +ve) *m/z* 208 [(M+Na)$^+$, 100%], 186 [(M+H)$^+$, 16];

HRMS (ESI, +ve) *m/z* 208.0740 [M+Na]$^+$, calcd for $C_{12}H_{11}NONa$, 208.0738.

2,2-Dimethyl-1,2,3,9-tetrahydro-4*H*-carbazol-4-one (**3.47**)



3.30B **3.33** **3.47**

A magnetically stirred solution of compound **3.33** (Y = Br) (100 mg, 0.40 mmol), *o*-iodoaniline (**3.30B**) (132 mg, 0.60 mmol) and copper(I) iodide (38 mg, 0.20 mmol) in dry DMSO (4 mL) maintained at 60 °C was treated with TEA (120 µL, 0.80 mmol). After 2 h the reaction mixture was treated with $Pd_2(dba)_3$ (18 mg, 0.02 mmol) then heated to 120 °C. After a further 20 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (4 mL) and the ensuing mixture filtered through a plug of TLC-grade silica topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (15 mL). The combined filtrates were washed with ammonia (2 x 20 mL of a 5% v/v aqueous solution), water (1 × 20 mL) and brine (1 × 20 mL) before being dried (Na_2SO_4), filtered then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 3:7 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.4), compound **3.47** (55 mg, 65%) as a brown powder, m.p. = 96-97 °C (lit.[12] m.p. = 94-96 °C).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (broad s, 1H), 8.21 (d, *J* = 7.2 Hz, 1H), 7.35 (d, *J* = 7.4 Hz, 1H), 7.27 – 7.18 (complex m, 2H), 2.84 (s, 2H), 2.47 (s, 2H), 1.17 (s, 6H);

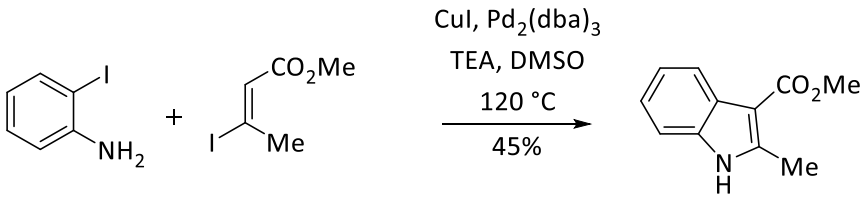
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 193.6, 149.8, 135.8, 124.7, 123.2, 122.5, 121.5, 112.3, 110.8, 52.3, 37.4, 35.7, 29.7, 28.7;

IR ν_{max} 3186, 2962, 2918, 2852, 1608, 1456, 1142, 1061, 733, 614 cm^{-1};

MS (ESI, +ve) *m/z* 236 [$(M+Na)^+$, 100%], 214 [$(M+H)^+$, 15];

HRMS (ESI, +ve) *m/z* 236.1050 $[M+Na]^+$, calcd for $C_{14}H_{15}NONa$, 236.1051.

Methyl 2-Methyl-1*H*-indole-3-carboxylate (**3.48**)



3.30B **3.37** **3.48**

A magnetically stirred solution of compound **3.37** (100 mg, 0.44 mmol), *o*-iodoaniline (**3.30B**) (146 mg, 0.66 mmol) and copper(I) iodide (42 mg, 0.22 mmol) in dry DMSO (5 mL) maintained at 60 °C was treated with TEA (123 µL, 0.88 mmol). After 2 h the reaction mixture was treated with $Pd_2(dba)_3$ (20 mg, 0.02 mmol) then heated to 120 °C. After a further 20 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL) and the ensuing mixture filtered through a plug of TLC-grade silica topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (2 × 25 mL of a 5% v/v aqueous solution), water (1 × 25 mL) and brine (1 × 25 mL) before being dried (Na_2SO_4), filtered then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:4 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.5), compound **3.48**[13] (38 mg, 45%) light-brown, crystalline solid m.p. = 164 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (broad s, 1H), 8.02 (d, *J* = 7.5 Hz, 1H), 7.23 (d, *J* = 7.2 Hz, 1H), 7.18-7.09 (complex m, 2H), 3.86 (s, 3H), 2.67 (s, 3H);

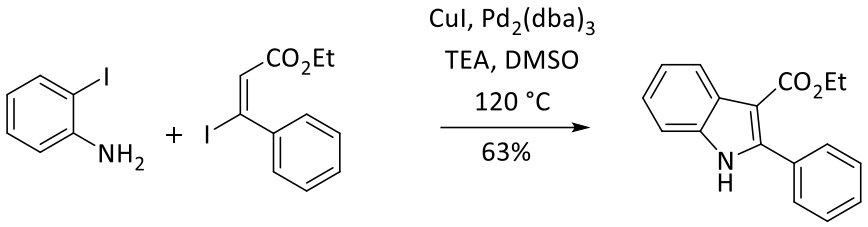
$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.5, 143.9, 134.4, 127.1, 122.4, 121.7, 121.3, 110.4, 104.5, 50.8, 14.2;

IR ν_{max} 3271, 1669, 1460, 1264, 1204, 733, 704 cm^{-1};

MS (ESI, +ve) *m/z* 212 [$(M+Na)^+$, 100%], 190 [$(M+H)^+$, 22];

HRMS (ESI, +ve) *m/z* 190.0863 $[M+H]^+$, calcd for $C_{11}H_{11}NO_2$, 190.0868.

Ethyl 2-Phenyl-1*H*-indole-3-carboxylate (3.49)



3.30B **3.39** **3.49**

A magnetically stirred solution of compound **3.39** (100 mg, 0.33 mmol), *o*-iodoaniline (**3.30B**) (109 mg, 0.50 mmol) and copper(I) iodide (32 mg, 0.17 mmol) in dry DMSO (3 mL) maintained at 60 °C was treated with TEA (92 µL, 0.66 mmol). After 2 h the reaction mixture was treated with $Pd_2(dba)_3$ (15 mg, 0.02 mmol) then heated to 120 °C. After a further 20 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (3 mL) and the ensuing mixture filtered through a plug of TLC-grade silica topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (12 mL). The combined filtrates were washed with ammonia (2 × 15 mL of a 5% v/v aqueous solution), water (1 × 15 mL) and brine (1 × 15 mL) before being dried (Na_2SO_4), filtered then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:19 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.4), compound **3.49**[14] (55 mg, 63%) as a yellow powder, m.p. = 145-146 °C.

^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (broad s, 1H), 8.23 (m, 1H), 7.67 (m, 2H), 7.51-7.44 (complex m, 3H), 7.41 (m, 1H), 7.33-7.26 (complex m, 2H), 4.32 (q, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H);

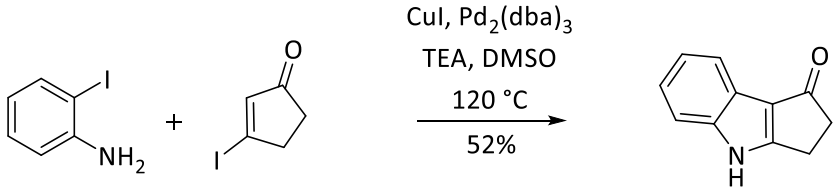
$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.3, 144.4, 135.1, 132.0, 129.6, 129.2, 128.1, 127.6, 123.2, 122.2, 122.1, 110.9, 104.8, 59.7, 14.3;

IR ν_{max} 3291, 2922, 1668, 1446, 1426, 1277, 1211, 1127, 1048, 742, 696 cm^{-1};

MS (ESI, +ve) *m/z* 288 [(M+Na)$^+$, 100%], 266 [(M+H)$^+$, 31];

HRMS (ESI, +ve) *m/z* 266.1183 [M+H]$^+$, calcd for $C_{17}H_{15}NO_2$, 266.1181.

3,4-Dihydrocyclopenta[*b*]indol-1(2*H*)-one (**3.50**)



3.30B **3.41** **3.50**

A magnetically stirred solution of compound **3.41** (100 mg, 0.48 mmol), *o*-iodoaniline (**3.30B**) (157 mg, 0.72 mmol) and copper(I) iodide (46 mg, 0.24 mmol) in dry DMSO (5 mL) maintained at 60 °C was treated with TEA (134 µL, 0.96 mmol). After 2 h the reaction mixture was treated with $Pd_2(dba)_3$ (22 mg, 0.02 mmol) then heated to 120 °C. After a further 20 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL) and the ensuing mixture filtered through a plug of TLC-grade silica topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (2 × 25 mL of a 5% v/v aqueous solution), water (1 × 25 mL) and brine (1 × 25 mL) before being dried (Na_2SO_4), filtered then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:19 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.4), compound **3.50**[15] (43 mg, 52%) as a brown powder, m.p. = 253-255 °C.

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.66 (d, *J* = 7.7 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.327.05 (complex m, 2H), 3.36 (broad s, 1H), 3.07 (t, *J* = 4.8 Hz, 2H), 2.81 (t, *J* = 4.8 Hz, 2H);

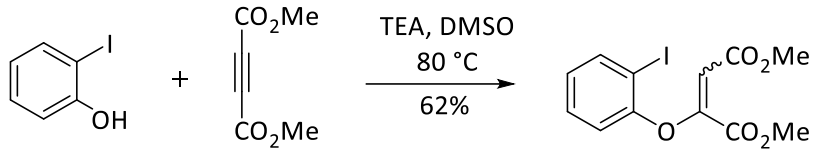
^{13}C{^{1}H} NMR (100 MHz, $(CD_3)_2SO$) δ 195.2, 168.3, 142.7, 123.4, 122.0, 121.4, 119.9, 119.6, 113.1, 41.1, 21.5;

IR ν_{max} 3199, 2928, 1652, 1470, 1429, 1050, 739, 639 cm^{-1};

MS (ESI, +ve) *m/z* 194 [(M+Na)$^+$, 100%], 172 [(M+H)$^+$, 8];

HRMS (ESI, +ve) *m/z* 172.0761 [M+H]$^+$, calcd for $C_{11}H_9NO$, 172.0762.

Dimethyl 2-(2-Iodophenoxy)but-2-enedioate (**3.52**)



3.30A **3.51** **3.52**

A magnetically stirred solution of dimethyl acetylenedicarboxylate (**3.51**) (50 mg, 0.35 mmol) and *o*-iodophenol (**3.30A**) (116 mg, 0.53 mmol) in dry DMSO (4 mL) maintained at 80 °C was treated with TEA (98 µL, 0.70 mmol). After 8 h the reaction mixture was cooled to 22 °C, diluted with water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic phases were dried (Na_2SO_4), filtered and then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:9 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.2), compound **3.52** (60 mg, 62%) as a clear, colourless oil and as a single geometric isomer.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.8 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.15 (d, *J* = 7.8 Hz, 1H), 7.01 (t, *J* = 7.8 Hz, 1H), 5.01 (s, 1H), 3.94 (s, 3H), 3.68 (s, 3H);

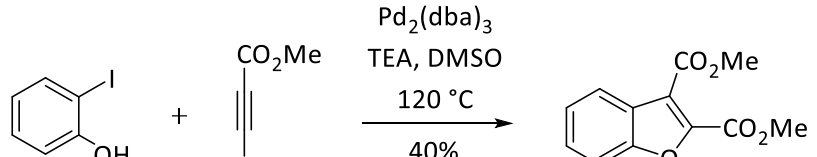
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.5, 162.8, 159.2, 152.7, 140.4, 130.1, 128.1, 121.9, 99.3, 89.1, 53.1, 51.8;

IR ν_{max} 2952, 1750, 1719, 1636, 1464, 1437, 1364, 1210, 1129, 780 cm^{-1};

MS (ESI, +ve) *m/z* 385 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) *m/z* 384.9550 $[M+Na]^+$, calcd for $C_{12}H_{11}IO_5Na$, 384.9549.

Dimethyl Benzofuran-2,3-dicarboxylate (**3.53**)



3.30A **3.51** **3.53**

A magnetically stirred solution of dimethyl acetylenedicarboxylate (**3.51**) (50 mg, 0.35 mmol), *o*-iodophenol [**3.30A** (X = I)] (116 mg, 0.53 mmol) and TEA (98 µL, 0.70 mmol) in dry DMSO (4

mL) maintained at 120 °C was treated with $Pd_2(dba)_3$ (16 mg, 0.02 mmol). After 8 h the reaction mixture was cooled to 22 °C, diluted with water (50 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic phases were dried (Na_2SO_4), filtered and then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:3 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.6), compound **3.53**[16] (32 mg, 40%) as a yellow powder, m.p. = 65 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.9 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.50 (m, 1H), 7.39 (m, 1H), 4.02 (s, 6H);

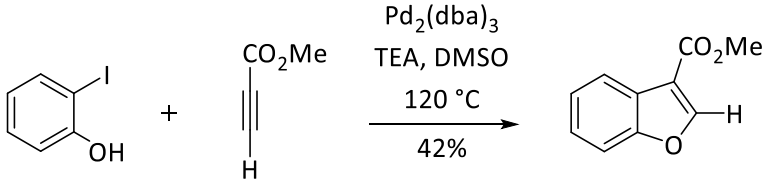
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.8, 159.1, 154.1, 145.5, 128.1, 125.4, 124.8, 122.9, 118.2, 112.2, 52.9, 52.5;

IR ν_{max} 2953, 1733, 1582, 1438, 1367, 1305, 1294, 1243, 1212, 1159, 1147, 1066, 749 cm^{-1};

MS (ESI, +ve) *m/z* 257 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) *m/z* 257.0426 $[M+Na]^+$, calcd for $C_{12}H_{10}O_5Na$, 257.0426.

Methyl Benzofuran-3-carboxylate (**3.56**)



3.30A **3.55** **3.56**

A magnetically stirred solution of compound **3.55** (120 µL, 1.35 mmol), *o*-iodophenol [**3.30A** (X = I)] (200 mg, 0.90 mmol) and TEA (251 µL, 1.80 mmol) in dry DMSO (3 mL) maintained at 120 °C in a sealed tube was treated with $Pd_2(dba)_3$ (42 mg, 0.05 mmol). After 24 h the reaction mixture was cooled to 22 °C, diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried (Na_2SO_4), filtered then concentrated under reduced pressure and the residue so obtained was subjected to flash column chromatography (silica, 1:2:3 v/v/v ethyl acetate/dichloromethane/40-60 petroleum ether elution). Concentration of the appropriate fractions (R_f = 0.7) then afforded compound **3.56**[17] (67 mg, 42%) as a clear, yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 8.05 (m, 1H), 7.54 (m, 1H), 7.37 (m, 2H), 3.94 (s, 3H);

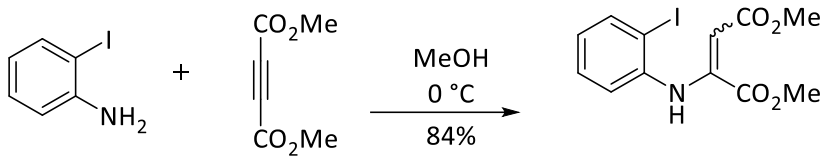
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.8, 155.5, 150.9, 125.3, 124.5, 124.1, 122.0, 114.4, 111.6, 51.6;

IR ν_{max} 3148, 2953, 1721, 1566, 1451, 1287, 1234, 1123, 1050, 149 cm^{-1};

MS (EI, +ve) *m/z* 176 ($M^{+\bullet}$, 50%), 145 (100);

HRMS *m/z* 176.0474 $[M+H]^+$, calcd for $C_{10}H_8O_3$, 176.0473.

Dimethyl 2-((2-Iodophenyl)amino)but-2-enedioate (**3.57A**)



3.30B **3.51** **3.57A**

A magnetically stirred solution of *o*-iodoaniline (**3.30B**) (1.10 g, 5.00 mmol) in dry methanol (10 mL) maintained at 0 °C was treated, dropwise, with dimethyl acetylenedicarboxylate (**3.51**) (782 mg, 5.50 mmol) before being warmed to 22 °C After 2 h the reaction mixture was concentrated under reduced pressure, diluted with diethyl ether (20 mL), washed with water (2 × 10 mL) and brine (1 × 20 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:19 v/v diethyl ether/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.1), compound **3.57A** (1.52 g, 84%) as a yellow, crystalline solid, m.p. = 75 °C, and as a single geometric isomer.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (s, 1H), 7.82 (d, *J* = 7.9 Hz, 1H), 7.24 (m, 1H), 6.86-6.69 (complex m, 2H), 5.55 (s, 1H), 3.77 (s, 3H), 3.68 (s, 3H);

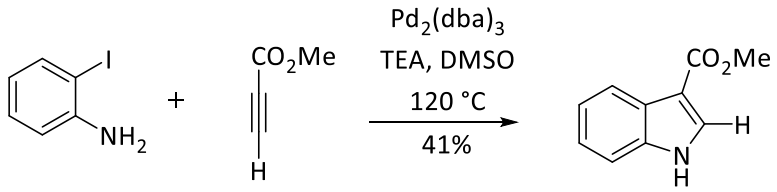
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.5, 164.4, 146.8, 141.8, 139.4, 128.7, 125.6, 120.7, 95.8, 91.9, 52.8, 51.5;

IR ν_{max} 2591, 1735, 1668, 1607, 1581, 1435, 1215, 1145, 1011, 821, 751, 642 cm^{-1};

MS (ESI, +ve) *m/z* 416 $[(M+Na+MeOH)^+$, 34%], 384 $[(M+Na)^+$, 100], 362 $[(M+H)^+$, 5];

HRMS (ESI, +ve) *m/z* 361.9888 $[M+H]^+$, calcd for $C_{12}H_{12}INO_4$, 361.9889.

Methyl 1*H*-Indole-3-carboxylate (3.57)



3.30B **3.55** **3.57**

A magnetically stirred solution of compound **3.55** (120 µL, 1.35 mmol), *o*-iodoaniline (**3.30B**) (200 mg, 0.91 mmol) and TEA (251 µL, 1.80 mmol) in dry DMSO (3 mL) maintained at 120 °C in a sealed tube was treated with $Pd_2(dba)_3$ (42 mg, 0.05 mmol). After 24 h the reaction mixture was cooled to 22 °C, diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried (Na_2SO_4), filtered then concentrated under reduced pressure. The ensuing residue was subjected to flash column chromatography (silica, 1:2:3 v/v/v ethyl acetate/dichloromethane/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.6), compound **3.57**[18] (65 mg, 41%) as a white, crystalline solid, m.p. = 123 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (broad s, 1H), 8.20 (m, 1H), 7.93 (s, 1H), 7.43 (m, 1H), 7.32-7.25 (complex m, 2H), 3.93 (s, 3H);

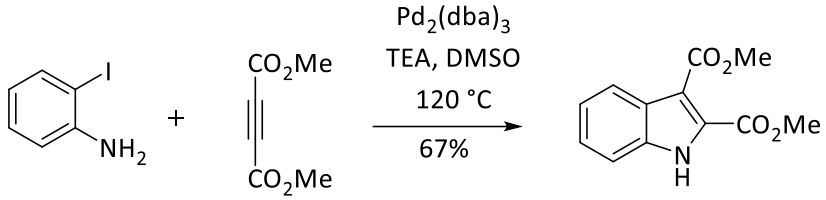
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.6, 136.0, 130.9, 125.8, 123.2, 122.1, 121.5, 111.4, 108.9, 51.1;

IR ν_{max} 3325, 1695, 1533, 1442, 1193, 1169, 1125, 1050, 780, 754 cm^{-1};

MS (ESI, +ve) *m/z* 198 [$(M+Na)^+$, 100%], 176 [$(M+H)^+$, 38];

HRMS *m/z* 198.0533 $[M+Na]^+$, calcd for $C_{10}H_9NO_2Na$, 198.0531.

Dimethyl 1*H*-Indole-2,3-dicarboxylate (**3.58**)



3.30B **3.51** **3.58**

A magnetically stirred solution of dimethyl acetylenedicarboxylate (**3.51**) (50 mg, 0.35 mmol), *o*-iodoaniline (**3.30B**) (116 mg, 0.53 mmol) and triethylamine (98 µL, 0.70 mmol) in dry DMSO (4 mL) maintained at 120 °C was treated with $Pd_2(dba)_3$ (16 mg, 0.02 mmol). After 8 h the reaction mixture was cooled to 22 °C, diluted with water (50 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic phases were dried (Na_2SO_4), filtered then concentrated under reduced pressure. The ensuing residue was subjected to flash column chromatography (silica, 1:3 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.3), compound **3.58**[19] (53 mg, 67%) as a yellow, crystalline solid, m.p. = 106 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (broad s, 1H), 8.06 (d, *J* = 8.2 Hz, 1H), 7.44 (dd, *J* = 8.2 and 1.1 Hz, 1H), 7.38 (ddd, *J* = 8.2, 7.0 and 1.2 Hz, 1H), 7.29 (d, *J* = 7.0 Hz, 1H), 3.99 (s, 6H);

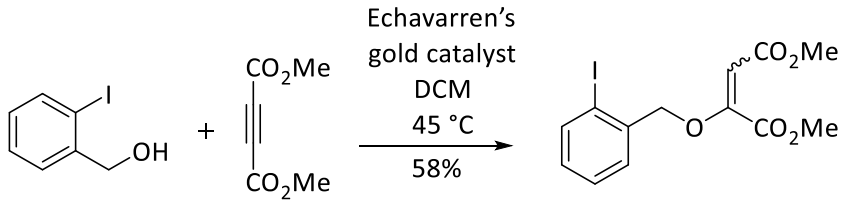
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.5, 161.3, 134.7, 128.0, 126.8, 126.0, 122.8, 122.6, 112.0, 111.8, 52.7, 51.9;

IR ν_{max} 3308, 2951, 1695, 1537, 1443, 1249, 1219, 1070, 749 cm^{-1};

MS (ESI, +ve) *m/z* 256 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) *m/z* 256.0584 $[M+Na]^+$, calcd for $C_{12}H_{11}NO_4Na$, 256.0586.

Dimethyl 2-((2-Iodobenzyl)oxy)but-2-enedioate (**3.59**)



3.58 **3.51** **3.59**

A magnetically stirred solution of 2-iodobenzyl alcohol (**3.58**) (300 mg, 1.28 mmol) in dry dichloromethane (10 mL) was treated, dropwise, with dimethyl acetylenedicarboxylate (**3.51**) (157 µL, 1.28 mmol) and then Echavarren's gold catalyst (CAS No. 866641-66-9, 50 mg, 0.06 mmol). The resulting mixture was heated at 45 °C for 16 h then cooled and concentrated under reduced pressure. The ensuing residue was subjected to flash column chromatography (silica, 1:2:17 v/v/v ethyl acetate/dichloromethane/40-60 petroleum ether elution) to afford, after concentration of the appropriate fractions (R_f = 0.2), compound **3.59** (280 mg, 58%) as a white, crystalline solid, m.p. = 49 °C, and as a single geometric isomer.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.02 (t, *J* = 7.8 Hz, 1H), 6.31 (s, 1H), 5.17 (s, 2H), 3.85 (s, 3H), 3.75 (s, 3H);

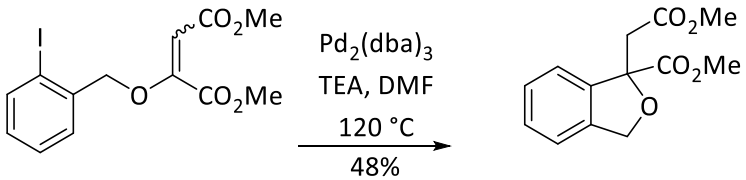
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.6, 163.2, 153.5, 139.1, 138.7, 129.6, 129.1, 128.4, 109.9, 97.1, 78.9, 53.0, 51.8;

IR ν_{max} 2946, 1727, 1699, 1623, 1434, 1363, 1226, 1122, 1007, 886, 743, 657 cm^{-1};

MS (ESI, +ve) *m/z* 399 [(M+Na)$^+$, 100%];

HRMS (ESI, +ve) *m/z* 398.9703 [M+Na]$^+$, calcd for $C_{13}H_{13}IO_5Na$, 398.9705.

Methyl 1-(2-Methoxy-2-oxoethyl)-1,3-dihydroisobenzofuran-1-carboxylate (**3.60**)



3.59 **3.60**

A round-bottom flask was charged with compound **3.59** (100 mg, 0.26 mmol) and $Pd_2(dba)_3$ (12 mg, 0.01 mmol) then evacuated before being refilled with nitrogen and treated with TEA

(74 µL, 0.53 mmol) and degassed DMF (2 mL). The resulting mixture was heated at 120 °C for 6 h then cooled to 22 °C before being diluted with ethyl acetate (10 mL). The solution thus obtained was washed with water (2 × 5 mL) then dried (Na_2SO_4), filtered then concentrated under reduced pressure. The ensuing residue was subjected to flash column chromatography (silica, 1:4 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.2), compound **3.60** (32 mg, 48%) as a clear, colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.21 (complex m, 4H), 5.35 (d, *J* = 12.2 Hz, 1H), 5.22 (d, *J* = 12.2 Hz, 1H), 3.75 (s, 3H), 3.70 (s, 3H), 3.51 (d, *J* = 16.3 Hz, 1H), 2.86 (d, *J* = 16.3 Hz, 1H);

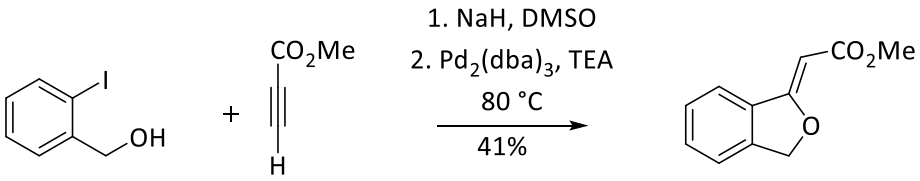
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.6, 169.9, 139.0, 138.8, 129.1, 127.9, 122.0, 121.2, 88.0, 73.8, 52.8, 52.0, 43.4;

IR ν_{max} 2954, 1732, 1436, 1255, 1199, 1167, 1052, 1014, 780, 739, 698 cm^{-1};

MS (ESI, +ve) *m/z* 273 [(M+Na)$^+$, 100%];

HRMS (ESI, +ve) *m/z* 273.0734 [M+Na]$^+$, calcd for $C_{13}H_{14}O_5Na$, 273.0739.

Methyl (*Z*)-2-(Isobenzofuran-1(3*H*)-ylidene) acetate (**3.61**)



3.58 **3.55** **3.61**

A magnetically stirred solution of compound **3.58** (100 mg, 1.35 mmol) in dry DMSO (3 mL) maintained at 22 °C in a sealed tube was treated with sodium hydride (15 mg, 0.65 mmol). After 0.25 h the reaction mixture was treated with $Pd_2(dba)_3$ (42 mg, 0.05 mmol), TEA (110 µL, 0.86 mmol) and compound **3.55** (58 µL, 0.65 mmol) before being heated to 80 °C. After 24 h the reaction mixture was cooled to 22 °C then diluted with water (10 mL) and extracted with ethyl acetate (3 ×10 mL). The combined organic phases were dried (Na_2SO_4), filtered then concentrated under reduced pressure and the residue so obtained subjected to flash column chromatography (silica, 1:2:3 v/v/v ethyl acetate/dichloromethane/40-60 petroleum ether elution). Concentration of the appropriate fractions (R_f = 0.6) then afforded compound **3.61**[20] (33 mg, 41%) as a yellow, crystalline solid, m.p. = 99 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (m, 1H), 7.51 (m, 1H), 7.43 (m, 2H), 5.58 (s, 2H), 5.53 (s, 1H), 3.77 (s, 3H);

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.0, 166.8, 141.4, 132.9, 131.4, 128.5, 121.5, 121.3, 85.7, 51.0 (one signal obscured or overlapping);

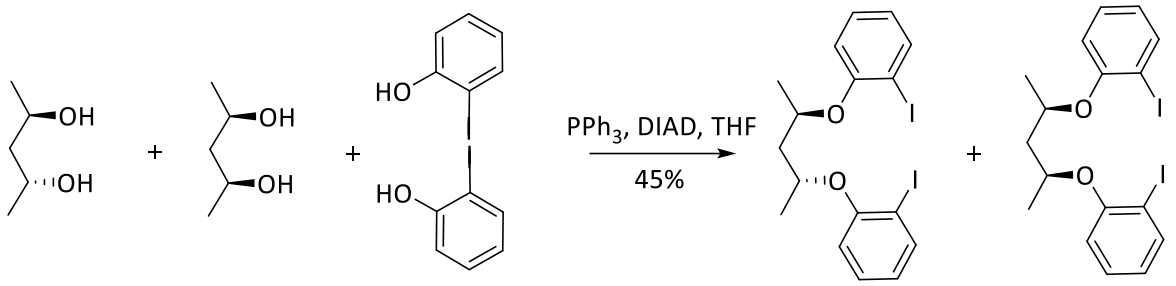
IR ν_{max} 2948, 1699, 1644, 1295, 1152, 1067, 1003, 769 cm^{-1};

MS (ESI, +ve) *m/z* 213 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) *m/z* 213.0529 $[M+Na]^+$, calcd for $C_{11}H_{10}O_3Na$, 213.0528.

Experimental Procedures Related to Work Described in Chapter Four

2,2'-(((2*R*,4*R*)-Pentane-2,4-diyl)bis(oxy))bis(iodobenzene) (**4.24A**) **and 2,2'-(((2*R*,4*S*)-Pentane-2,4-diyl)bis(oxy))bis(iodobenzene)** (**4.24B**)



4.22 **4.23** **4.24A** **4.24B**

A magnetically stirred solution of *o*-iodophenol (**4.23**) (100 mg, 0.45 mmol) in anhydrous THF (20 mL) maintained at 0 °C under nitrogen was treated with 2,4-pentanediol (**4.22**) (1:1 mixture of diastereoisomers) (24 mg, 0.23 mmol) then PPh_3 (540 mg, 2.05 mmol). The ensuing mixture was stirred at 0 °C for 0.25 h then DIAD (407 mg, 2.05 mmol) was added to the reaction mixture. The resulting solution was ultrasonicated in an ice-bath for 1 h. After this time, diethyl ether (20 mL) was added to the reaction mixture and the insoluble material filtered off. The filtrate was dried (Na_2SO_4), filtered then concentrated under reduced pressure and the residue thus obtained subjected to flash column chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.7), compound **4.24** (53 mg, 45%) as a colourless oil and 2:1 mixture of diastereoisomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.74 (m, 1H), 7.68 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.30 (ddd, *J* = 8.3, 7.3, 1.7 Hz, 1H), 7.10 (ddd, *J* = 8.2, 7.3, 1.6 Hz, 1H), 6.99 (dd, *J* = 8.5, 1.3 Hz, 1H), 6.75 – 6.65 (m, 2H), 6.59 (td, *J* = 7.6, 1.4 Hz, 1H), 4.76 (ddt, *J* = 14.4, 12.5, 6.0 Hz, 2H), 2.40 – 1.80 (m, 2H), 1.39 (dd, *J* = 6.1, 1.5 Hz, 6H);

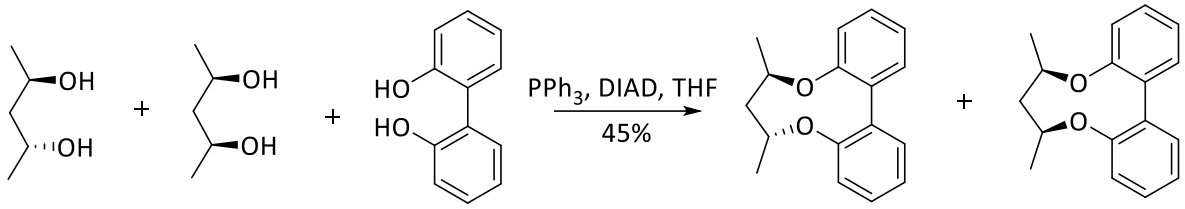
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.8, 139.8, 139.4, 129.6, 129.5, 122.6, 122.5, 114.3, 113.8, 88.2, 87.9, 72.8, 72.3, 45.2, 42.8, 20.5, 20.0;

IR ν_{max} 2980, 1600, 1487, 1340 1250, 1207, 1116, 900, 881 cm^{-1};

MS (ESI, +ve) *m/z* 530[$(M+Na)^+$, 100%].

HRMS (ESI, +ve) *m/z* 508.9455 $[M+H]^+$, calcd. for $C_{17}H_{19}I_2O_2$ 508.9451.

(6*R*,8*R*)-6,8-Dimethyl-7,8-dihydro-6*H*-dibenzo[*f*,*h*][1,5]dioxonine (**4.25A**) **and (6*R*,8*S*)-6,8-Dimethyl-7,8-dihydro-6*H*-dibenzo[*f*,*h*][1,5]dioxonine** (**4.25B**)



4.22 **4.23** **4.25A** **4.25B**

A magnetically stirred solution of 2,2-biphenol (**4.23**) (1.05 g, 5.37 mmol) in anhydrous THF (30 mL) maintained at 0 °C under nitrogen, was treated with 2,4-pentanediol (**4.22**) (1:1 mixture of diastereoisomers) (560 mg, 5.37 mmol) then PPh_3 (2.81 g, 10.74 mmol). The ensuing mixture was stirred at 0 °C for 0.25 h then DIAD (2.17 g, 10.74 mmol) was added, dropwise, to the reaction mixture. The resulting solution was ultrasonicated in an ice-bath for 1 h then diethyl ether (50 mL) was added to the reaction mixture and the insoluble material removed by filtration. The filtrate was dried (Na_2SO_4), filtered then concentrated under reduced pressure and the residue thus obtained subjected to flash column chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.7), compound **4.25** (610 mg, 45%) as clear, colourless oil and 2:1 mixture of diastereoisomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.11 (m, 8H), 7.01 (d, *J* = 7.6 Hz, 7H), 4.54 (d, *J* = 5.7 Hz, 2H), 1.81 (t, *J* = 4.2 Hz, 2H), 1.30 (d, *J* = 6.5 Hz, 6H);

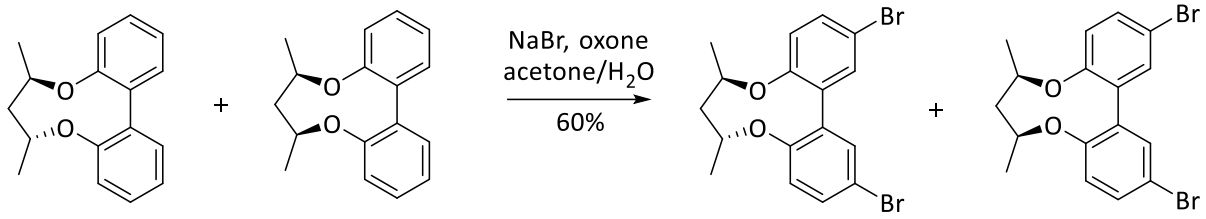
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.1, 131.5, 129.7, 128.3, 122.7, 122.5, 117.2, 74.5, 42.6, 41.4, 24.0, 22.3;

IR ν_{max} 2973, 1592, 1477, 1440, 1257, 1217, 1086, 932, 749 cm^{-1};

MS (ESI, +ve) *m/z* 277[$(M+Na)^+$, 100%];

HRMS (ESI, +ve) *m/z* 255.1374 $[M+H]^+$, calcd. for $C_{17}H_{19}O_2$ 255.1379.

(6*R*,8*R*)-2,12-Dibromo-6,8-dimethyl-7,8-dihydro-6*H*-dibenzo[*f*,*h*][1,5]dioxonine (**4.26A**) **and (6*R*,8*S*)-2,12-Dibromo-6,8-dimethyl-7,8-dihydro-6*H*-dibenzo[*f*,*h*][1,5]dioxonine]** (**4.26B**)



4.25A **4.25B** **4.26A** crystaline solid **4.26B** oil

Sodium bromide (610 mg, 5.88 mmol) was added to a magnetically stirred solution of compound **4.25** (510 mg, 1.96 mmol of a 2:1 mixture of diastereoisomers) in acetone/water (30 mL of a 1:1 v/v mixture) and this was followed by the dropwise addition of a solution of Oxone® (1.81 g, 5.88 mmol) in water (10 mL). The resulting solution was stirred at room temperature for 16 h then quenched with sodium thiosulfate (20 mL of saturated aqueous solution) and extracted with diethyl ether (3 × 30 mL). The combined organic phases were washed with water (1 × 30 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 7:3 v/v hexane/dichloromethane elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.6), compound **4.26A** (480 mg, 60%) as a white, crystalline solid, m.p. = 152- 154°C. While most of later eluting fractions contained mixtures of the title compounds, certain of them provided pure samples of compound **4.26B** (110 mg, 15%) which was obtained as a clear, colourless oil. The spectral data derived from each of these pure samples are provided immediately below.

Compound **4.26A**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 2.5 Hz, 1H), 7.40 (d, *J* = 2.5 Hz, 1H), 7.36 (d, *J* = 2.5 Hz, 2H), 6.97 (d, *J* = 8.6 Hz, 2H), 4.58 (dt, *J* = 6.5, 4.1 Hz, 2H), 1.90 (t, *J* = 4.2 Hz, 2H), 1.39 (d, *J* = 6.5 Hz, 6H);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.5, 132.7, 132.5, 131.9, 119.4, 115.3, 75.5, 41.7, 22.6;

IR ν_{max} 2973, 2977, 1477, 1378, 1264, 1209, 1120, 1085, 818, 735 cm^{-1};

HRMS (ESI, +ve) *m/z* 413.9477 $[M+H]^+$, calcd. for $C_{17}H_{17}{}^{81}Br_2O_2$ 413.9476.

Compound **4.26B**

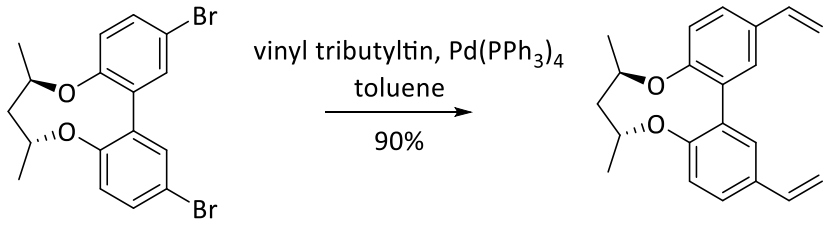
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dt, *J* = 8.6, 2.1 Hz, 2H), 7.36 (d, *J* = 2.0 Hz, 2H), 6.97 (dd, *J* = 8.6, 1.7 Hz, 2H), 4.62 – 4.53 (m, 2H), 1.94 – 1.85 (m, 2H), 1.39 (dd, *J* = 6.5, 1.6 Hz, 6H);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.4, 132.6, 132.5, 131.9, 119.1, 115.5, 75.8, 41.9, 22.6;

IR ν_{max} 2970, 2978, 1480, 1379, 1254, 1201, 1130, 1085, 818, 735 cm^{-1};

HRMS (ESI, +ve) *m/z* 413.9473 $[M+H]^+$, calcd. for $C_{17}H_{17}O_2{}^{81}Br_2$ 413.9476.

(6*R*,8*R*)-6,8-Dimethyl-2,12-divinyl-7,8-dihydro-6*H*-dibenzo[*f*,*h*][1,5]dioxonine (**4.35**)



4.26A **4.35**

A two-neck, round-bottom flask fitted with a Liebig condenser and a rubber septum was charged with dibromide **4.26A** (100 mg, 0.24 mmol) and $Pd(PPh_3)_4$ (14 mg, 0.05 mmol). The flask was evacuated at low pressure then refilled with nitrogen and the contents of the flask were dissolved in anhydrous toluene (5 mL). The resulting solution was treated, dropwise, with vinyl tributyltin (2.00 mL, 0.61 mmol) then heated at 80 °C for 16 h. After cooling, the reaction mixture was concentrated under reduced pressure and the residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution). Concentration of the appropriate fractions (R_f = 0.8) afforded compound **4.35** (67 mg, 90%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dq, *J* = 5.1, 2.3 Hz, 4H), 7.06 (d, *J* = 8.9 Hz, 2H), 6.70 (dd, *J* = 17.6, 10.9 Hz, 2H), 5.66 (dd, *J* = 17.6, 1.0 Hz, 2H), 5.21 – 5.13 (m, 2H), 4.62 (dtd, *J* = 10.8, 6.5, 4.2 Hz, 2H), 1.91 (t, *J* = 4.2 Hz, 2H), 1.40 (d, *J* = 6.5 Hz, 6H);

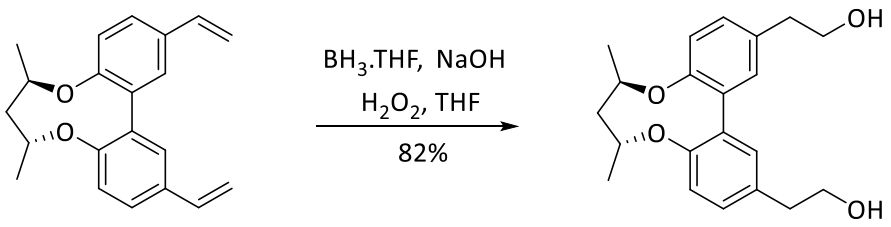
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.2, 136.5, 132.6, 131.7, 127.9, 126.9, 117.7, 112.5, 75.1, 41.9, 22.7;

IR ν_{max} 2974, 1479, 1398, 1227, 1120, 1088, 831,719 cm^{-1};

MS (ESI, +ve) *m/z* 307 $[(M+H)^+$, 100%];

HRMS (ESI, +ve) *m/z* 307.1635 $[M+H]^+$, calcd. for $C_{21}H_{23}O_2$ 307.1633.

2,2'-((6*R*,8*R*)-6,8-Dimethyl-7,8-dihydro-6*H*-dibenzo[*f*,*h*][1,5]dioxonine-2,12-diyl)bis(ethan-1-ol) (**4.36**)



4.35 **4.36**

A magnetically stirred solution of compound **4.35** (100 mg, 0.33 mmol) in dry THF (10 mL) maintained under nitrogen at ambient temperatures was treated, dropwise, with borane-THF complex (1.0 mL of 1.0 M solution in tetrahydrofuran, 1.0 mmol). The ensuing mixture was stirred for 16 h then treated, sequentially, with water (1 mL), sodium hydroxide (1 mL of a 3 M aqueous solution) and hydrogen peroxide (1 mL of a 30% w/w solution in water). The resulting mixture was slowly warmed to 40 °C and stirred at this temperature for 1 h before being cooled then diluted with diethyl ether (50 mL) and washed with brine (1 × 20 mL). The separated aqueous layer was washed with diethyl ether (2 × 20 mL) and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:9 v/v hexane/ethyl acetate elution) and concentration of the appropriate fractions (R_f = 0.2) afforded alcohol **4.36** (91 mg, 82%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 – 6.96 (m, 6H), 4.59 (q, *J* = 4.6 Hz, 2H), 3.81 (t, *J* = 6.6 Hz, 4H), 2.81 (t, *J* = 6.6 Hz, 4H), 1.88 (t, *J* = 4.3 Hz, 2H), 1.37 (d, *J* = 6.5 Hz, 6H);

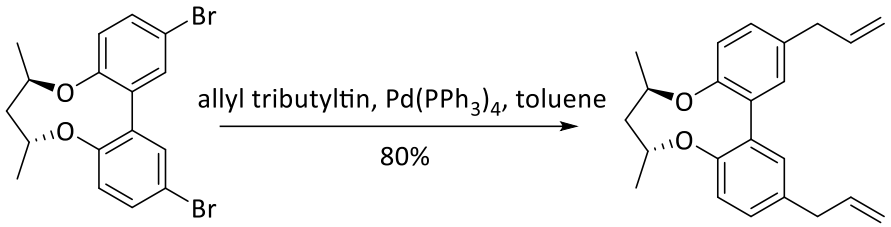
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 155.8, 133.0, 131.5, 130.7, 129.2, 117.7, 75.1, 63.7, 41.8, 38.7, 22.7;

IR ν_{max} 3654, 2987, 2665, 2547, 1654, 1540, 1434, 1190, 885 cm^{-1};

MS (ESI, +ve) *m/z* 365 [(M+Na)$^+$, 100%];

HRMS (ESI, +ve) *m/z* 365.1835 [M+Na]$^+$, calcd. for $C_{21}H_{26}O_4Na$ 365.1833.

(6*R*,8*R*)-2,12-Diallyl-6,8-dimethyl-7,8-dihydro-6*H*-dibenzo[*f*,*h*][1,5]dioxonine (**4.37**)



4.26A **4.37**

A two-neck, round-bottom flask fitted with a Liebeig condenser and a rubber septum was charged with dibromide **4.26A** (100 mg, 0.24 mmol) and $Pd(PPh_3)_4$ (14 mg, 0.05 mmol). The flask was evacuated at low pressure then refilled with nitrogen and then the contents thereof were dissolved in anhydrous toluene (5 mL). The resulting and magnetically stirred solution was treated, dropwise, with allyl tributyltin (3.0 mL, 0.61 mmol) and the ensuing reaction mixture heated at 80 °C for 16 h. After cooling, the reaction mixture was concentrated under reduced pressure and the residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution). Concentration of the appropriate fractions (R_f = 0.8) then afforded compound **4.37** (64 mg, 80%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 – 7.07 (m, 4H), 7.04 (d, *J* = 8.2 Hz, 2H), 6.10 – 5.95 (m, 2H), 5.17 – 5.05 (m, 4H), 4.60 (m, 2H), 3.40 (d, *J* = 6.8 Hz, 4H), 1.91 (t, *J* = 4.3 Hz, 2H), 1.39 (d, *J* = 1.6 Hz, 6H);

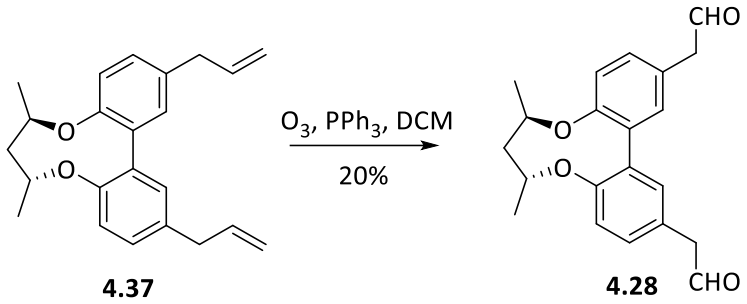
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 155.7, 137.7, 134.3, 131.6, 130.2, 128.5, 117.5, 115.7, 75.0, 41.9, 39.8, 22.8;

IR ν_{max} 2978, 1489, 1365, 1267, 1129, 1098, 838, 709 cm^{-1};

MS (ESI, +ve) *m/z* 335 [$(M+H)^+$, 100%];

HRMS (ESI, +ve) *m/z* 357.1965 $[M+Na]^+$, calcd. for $C_{23}H_{26}O_2Na$ 357.1963.

2,2'-((6*R*,8*R*)-6,8-Dimethyl-7,8-dihydro-6*H*-dibenzo[*f*,*h*][1,5]dioxonine-2,12-diyl)diacetaldehyde (**4.28**)



4.37 **4.28**

A magnetically stirred solution of alkene **4.37** (500 mg, 1.49 mmol) in dichloromethane (25 mL) was cooled to −78 °C and ozone bubbled through it until a dark-blue colour persisted (*ca.* 10 min). At this point PPh_3 (3.92 g, 14.97 mmol) was added to the reaction mixture which was then warmed to 18 °C and kept at this temperature for 1 h before being concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 4:1 v/v hexane/ ethyl acetate elution) and concentration of the appropriate fractions (R_f = 0.7) afforded dialdehyde **4.28** (100 mg, 20%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (t, *J* = 2.5 Hz, 2H), 7.19 – 7.14 (m, 3H), 7.12 – 7.07 (m, 3H), 4.63 (dtd, *J* = 10.8, 6.8, 4.7 Hz, 2H), 3.66 (d, *J* = 2.4 Hz, 4H), 1.92 (t, *J* = 4.2 Hz, 2H), 1.40 (d, *J* = 6.5 Hz, 6H);

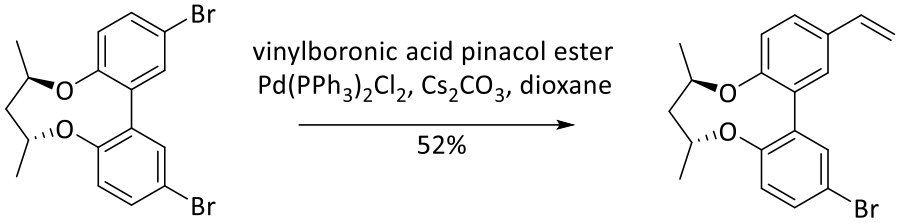
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 199.8, 156.8, 131.9, 131.3, 130.1, 126.2, 118.3, 75.3, 50.1, 41.9, 22.7;

IR ν_{max} 2974, 1658, 1479, 1398, 1227, 1120, 1088, 831, 719 cm^{-1};

MS (ESI, +ve) *m/z* 339 [$(M+H)^+$, 100%];

HRMS (ESI, +ve) *m/z* 339.1599 $[M+H]^+$, calcd. for $C_{21}H_{23}O_4$ 339.1597.

(6*R*,8*R*)-2-Bromo-6,8-dimethyl-12-vinyl-7,8-dihydro-6*H*-dibenzo[*f*,*h*][1,5]dioxonine (**4.38**)



4.26A **4.38**

A magnetically stirred solution of dibromide **4.26A** (100 mg, 0.24 mmol) and vinylboronic acid pinacol ester (40 mg, 0.24 mmol) in 1,4-dioxane (1.6 mL) was treated with a solution of caesium carbonate (190 mg, 0.61 mmol) in water (400 mL). The flask was evacuated at low pressure then refilled with nitrogen and after which $Pd(PPh_3)_2Cl_2$ (20 mg, 8 mol%) was added and the resulting mixture was flushed with additional nitrogen before being heated at 75 °C for 16 h. The cooled reaction mixture was then concentrated under reduced pressure and the resulting light-yellow oil subjected to flash chromatography (silica, 9:1 v/v hexane/ ethyl acetate elution). Concentration of the appropriate fractions (R_f = 0.7) afforded compound **4.38** (45 mg, 52%) as a clear, light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.15 (m, 4H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.91 – 6.85 (m, 1H), 6.61 (td, *J* = 10.9, 5.4 Hz, 1H), 5.58 (d, *J* = 17.6 Hz, 1H), 5.10 (dd, *J* = 10.9, 3.2 Hz, 1H), 4.59 – 4.45 (m, 2H), 1.83 (q, *J* = 3.7 Hz, 2H), 1.31 (dd, *J* = 6.5, 3.4 Hz, 6H);

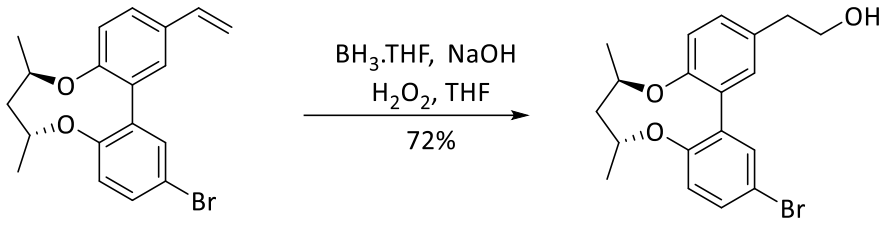
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.9, 156.6, 136.3, 133.7, 132.8, 132.7, 131.3, 131.4, 130.4, 127.7, 127.2, 119.4, 117.6, 115.2, 112.7, 75.5, 75.1, 41.7, 22.7, 22.6;

IR ν_{max} 2974, 2927, 1479,1398, 1370, 1284, 1227, 1120, 1088, 908, 819 cm^{-1};

MS (ESI, +ve) *m/z* 381 and 379 [$(M+Na)^+$, both 100%];

HRMS (ESI, +ve) *m/z* 359.0689 $[M+H]^+$, calcd. for $C_{19}H_{19}{}^{81}BrO_2$ 359.0688.

2-((6*R*,8*R*)-12-Bromo-6,8-dimethyl-7,8-dihydro-6*H*-dibenzo[*f*,*h*][1,5]dioxonin-2-yl)ethan-1-ol (**4.39**)



4.38 **4.39**

A magnetically stirred solution of compound **4.38** (100 mg, 0.27 mmol) in dry THF (10 mL) maintained at ambient temperatures under nitrogen was treated, dropwise, with borane-THF complex (1.0 mL of 1.0 M solution in THF, 1.0 mmol). The ensuing mixture was stirred for 16 h then treated, sequentially, with water (1 mL), sodium hydroxide (1 mL of a 3 M aqueous solution) and hydrogen peroxide (1 mL of a 30% w/w solution in water). The resulting mixture was slowly warmed to 40 °C and stirred at this temperature for 1 h before being cooled then diluted with diethyl ether (50 mL) and washed with brine (1 × 20 mL). The separated aqueous layer was extracted with diethyl ether (2 × 20 mL) and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:1 v/v hexane/ethyl acetate elution) and concentration of the appropriate fractions (R_f = 0.3) afforded alcohol **4.39** (75 mg, 72%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.32 (m, 2H), 7.13 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.06 – 6.99 (m, 2H), 6.99 – 6.94 (m, 1H), 4.61 – 4.49 (m, 2H), 3.77 (t, *J* = 6.6 Hz, 2H), 2.79 (t, *J* = 6.7 Hz, 2H), 1.88 (q, *J* = 4.7 Hz, 2H), 1.37 (d, *J* = 6.6 Hz, 6H);

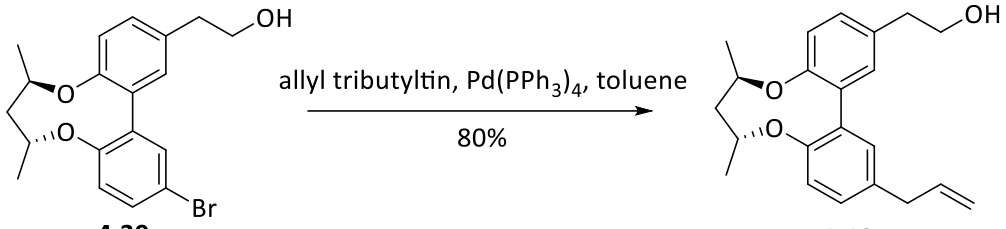
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.3, 155.5, 133.7, 133.0, 132.6, 131.2, 130.3, 130.0, 129.6, 119.3, 117.5, 115.0, 75.5, 74.8, 63.4, 41.6, 38.4, 22.5, 22.5;

IR ν_{max} 3399, 2991, 2973, 1494, 1482, 1264, 907, 729 cm^{-1};

MS (ESI, +ve) *m/z* 399 and 397 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) *m/z* 377.0450 $[M+H]^+$, calcd. for $C_{19}H_{22}O_3{}^{81}Br$ 377.0747.

2-((6*R*,8*R*)-12-Allyl-6,8-dimethyl-7,8-dihydro-6*H*-dibenzo[*f*,*h*][1,5]dioxonin-2-yl)ethan-1-ol (**4.40**)



4.39 **4.40**

A two-neck, round-bottom flask fitted with a Liebig condenser and a rubber septum was charged with bromide **4.39** (100 mg, 0.26 mmol) and $Pd(PPh_3)_4$ (50 mg, 0.05 mmol). The flask was evacuated at low pressure then refilled with nitrogen. The resulting mixture was dissolved in anhydrous toluene (5 mL) and the ensuing, magnetically stirred solution treated, dropwise, with allyl tributyltin (2.0 mL, 0.53 mmol). The solution so-formed was heated at 80 °C for 16 h before being cooled then concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:1 v/v hexane/ethyl acetate elution) and concentration of the appropriate fractions (R_f = 0.4) afforded compound **4.40** (53 mg, 80%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 – 6.97 (m, 4H), 6.94 (dd, *J* = 8.2, 2.3 Hz, 2H), 5.92 (ddt, *J* = 16.8, 10.0, 6.8 Hz, 1H), 5.11 – 4.85 (m, 2H), 4.52 (tq, *J* = 6.5, 3.3, 2.5 Hz, 2H), 3.75 (q, *J* = 6.5 Hz, 2H), 3.30 (d, *J* = 6.8 Hz, 2H), 2.75 (t, *J* = 6.6 Hz, 2H), 1.81 (t, *J* = 4.2 Hz, 3H), 1.30 (d, *J* = 6.6 Hz, 6H);

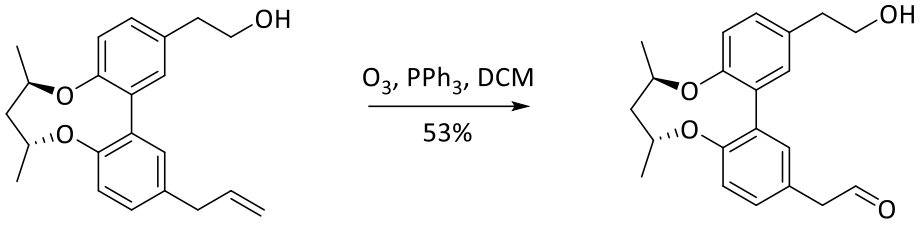
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 155.9, 155.6, 137.7, 134.4, 132.8, 130.7, 130.2, 129.1, 128.6, 117.7, 117.6, 115.8, 75.1, 75.0, 63.7, 41.9, 39.7, 38.7, 22.8, 22.8;

IR ν_{max} 3391, 2972, 2925, 2870, 1493, 1377, 1262, 1255, 1122, 1088, 1045, 823, 732 cm^{-1};

MS (ESI, +ve) *m/z* 361 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) *m/z* 339.1954 $[M+H]^+$, calcd. for $C_{22}H_{27}O_3$ 339.1955.

2-((6*R*,8*R*)-12-(2-Hydroxyethyl)-6,8-dimethyl-7,8-dihydro-6*H*-dibenzo[*f*,*h*][1,5]dioxonin-2-yl)acetaldehyde (**4.41**)



4.40 **4.41**

A magnetically stirred solution of alkene **4.40** (100 mg, 0.31 mmol) in dichloromethane (20 mL) was cooled to −78 °C and ozone bubbled through it until a dark-blue colour persisted (*ca.* 10 min). At this point PPh_3 (770 mg, 2.95 mmol) was added to the reaction mixture that was then warmed to 18 °C and kept at this temperature for 1 h before being concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 1:1 v/v hexane/ ethyl acetate elution) and concentration of the appropriate fractions (R_f = 0.3) afforded compound **4.41** (53 mg, 53%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (t, *J* = 2.4 Hz, 1H), 7.21 – 6.99 (m, 6H), 4.72 – 4.60 (m, 2H), 3.88 (t, *J* = 6.5 Hz, 2H), 3.68 (s, 2H), 2.87 (t, *J* = 6.6 Hz, 2H), 1.93 (d, *J* = 4.4 Hz, 2H), 1.42 (d, *J* = 6.4 Hz, 6H);

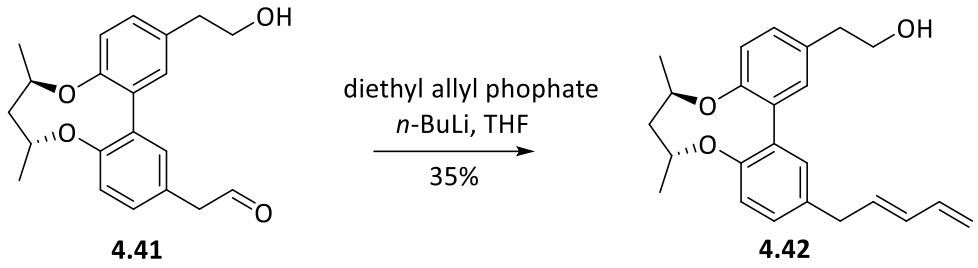
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 199.9, 156.8, 156.0, 132.9, 132.3, 131.4, 131.2, 130.6, 129.8, 129.4, 126.1, 118.2, 117.8, 75.3, 75.1, 63.8, 50.1, 41.9, 38.7, 22.8, 22.7;

IR ν_{max} 3391, 2960, 2900, 2865, 1628, 1400, 1265, 1022, 1045, 813 cm^{-1};

MS (ESI, +ve) *m/z* 341 [$(M+H)^+$, 100%];

HRMS (ESI, +ve) *m/z* 341.1735 $[M+H]^+$, calcd. for $C_{21}H_{25}O_4$ 341.1733.

2-((6*R*,8*R*)-6,8-Dimethyl-12-((*E*)-penta-2,4-dien-1-yl)-7,8-dihydro-6*H*-dibenzo[*f*,*h*][1,5]-dioxonin-2-yl)ethan-1-ol (**4.42**)



4.41 **4.42**

A magnetically stirred solution of diethyl allyl phosphate (35 mg, 0.18 mmol) in THF (2 mL) maintained under nitrogen at −78 °C was treated, dropwise, with *n*-butyllithium (300 mL of a 1.5 M solution in hexane, 0.35 mmol). The ensuing mixture was stirred for another 15 min. then a solution of aldehyde **4.41** (30 mg, 0.09 mmol) in THF (1 mL) was added. The resulting suspension was stirred to −78 °C for another 2 h before being warmed to 18 °C and stirred for a further 16 h then quenched with ammonium chloride (10 mL of a saturated aqueous solution). The separated aqueous layer was extracted with diethyl ether (3 × 2 mL) and the combined organic phases were washed with brine (1 × 5 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 3:2 v/v hexane/ ethyl acetate elution) and concentration of the appropriate fractions (R_f = 0.5) afforded compound **4.42** (11 mg, 35%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.3 Hz, 1H), 7.11 – 7.07 (m, 1H), 7.06 – 7.00 (m, 2H), 6.34 (dd, *J* = 17.7, 9.4 Hz, 1H), 6.19 – 6.02 (m, 1H), 5.87 (dt, *J* = 14.5, 7.0 Hz, 1H), 5.14 (d, *J* = 17.0 Hz, 1H), 5.01 (d, *J* = 10.1 Hz, 1H), 4.59 (d, *J* = 6.4 Hz, 2H), 3.89 (t, *J* = 6.1 Hz, 2H), 3.41 (d, *J* = 7.1 Hz, 2H), 2.86 (t, *J* = 6.4 Hz, 2H), 1.90 (t, *J* = 4.2 Hz, 2H), 1.39 (d, *J* = 6.5 Hz, 6H);

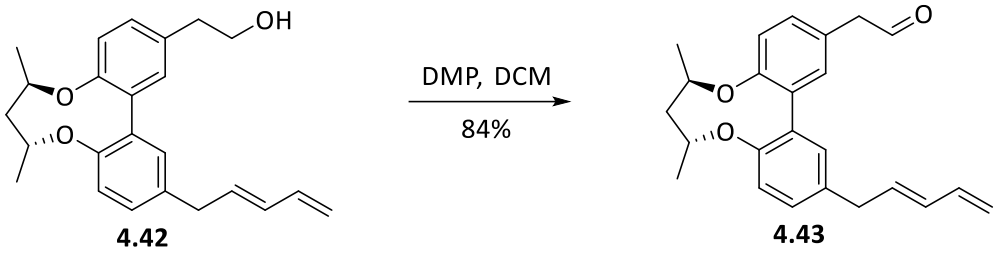
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.1, 155.7, 137.2, 134.5, 133.9, 132.7, 132.1, 131.9, 131.5, 130.7, 130.2, 129.2, 128.7, 117.8, 117.6, 115.7, 75.1, 63.9, 42.0, 38.8, 38.5, 22.8;

IR ν_{max} 3546, 2974, 1479, 1398, 1227, 1120, 1088, 831, 719 cm^{-1};

MS (ESI, +ve) *m/z* 387 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) *m/z* 387.2015 $[M+Na]^+$, calcd. for $C_{24}H_{28}O_3Na$ 387.2013.

2-((6*R*,8*R*)-6,8-Dimethyl-12-((*E*)-penta-2,4-dien-1-yl)-7,8-dihydro-6*H*-dibenzo[*f*,*h*][1,5]dioxonin-2-yl)acetaldehyde (**4.43**)



4.42 **4.43**

A magnetically stirred solution of alcohol **4.42** (10 mg, 27 µmol) in dichloromethane (5 mL) maintained at 0 °C was treated with the Dess-Martin periodinane (DMP) (34 mg, 82 µmol). The ensuing mixture was warmed to 18 °C and stirred for 16 h at this temperature then treated with sodium thiosulfate (15 mL of a saturated aqueous solution) and NaOH (15 mL of 1 M aqueous solution). The separated aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic phases were washed with brine (1 × 10 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 3:2 v/v hexane/ ethyl acetate elution) and concentration of the appropriate fractions (R_f = 0.7) afforded compound **4.43** (83 mg, 84%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (t, *J* = 2.4 Hz, 1H), 7.17 – 6.97 (m, 6H), 6.40 – 6.26 (m, 1H), 6.13 (dd, *J* = 15.0, 10.5 Hz, 1H), 5.87 (dt, *J* = 14.6, 7.1 Hz, 1H), 5.14 (d, *J* = 16.9 Hz, 1H), 5.01 (d, *J* = 10.1 Hz, 1H), 4.60 (q, *J* = 6.4, 6.0 Hz, 2H), 3.65 (d, *J* = 2.5 Hz, 2H), 3.41 (d, *J* = 7.1 Hz, 2H), 1.90 (d, *J* = 4.7 Hz, 2H), 1.39 (dd, *J* = 6.2, 3.0 Hz, 6H);

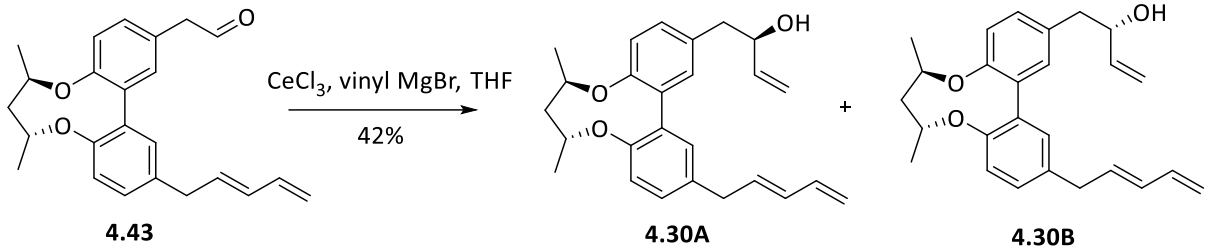
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 200.0, 156.8, 155.7, 137.1, 134.6, 133.8, 132.4, 132.1, 131.4, 131.1, 130.1, 129.8, 128.9, 126.1, 118.2, 117.7, 115.8, 75.2, 75.1, 50.1, 41.9, 38.5, 22.8, 22.8;

IR ν_{max} 2654, 1628, 1500, 1400, 1267, 1150, 1090, 850 cm^{-1};

MS (ESI, +ve) *m/z* 363 [$(M+H)^+$, 100%];

HRMS (ESI, +ve) *m/z* 363.1978 $[M+H]^+$, calcd. for $C_{24}H_{27}O_3$ 363.1979.

(*R*)-1-((6*R*,8*R*)-6,8-Dimethyl-12-((*E*)-penta-2,4-dien-1-yl)-7,8-dihydro-6*H*-dibenzo[*f*,*h*][1,5]dioxonin-2-yl)but-3-en-2-ol (**4.30A**) **and (*S*)-1-((6*R*,8*R*)-6,8-Dimethyl-12-((*E*)-penta-2,4-dien-1-yl)-7,8-dihydro-6*H*-dibenzo[*f*,*h*][1,5]dioxonin-2-yl)but-3-en-2-ol** (**4.30B**)



4.43 **4.30A** **4.30B**

A two-neck, round-bottom flask was charged with finely powdered cerium chloride heptahydrate (90 mg, 0.24 mmol) and a stirring bar then heated (under nitrogen) to 140 °C for 1 h. The flask and its contents were then cooled to room temperature and thereafter in an ice-bath. Anhydrous THF (3 mL) was then added to the reaction mixture and the resulting suspension stirred for 16 h at room temperature. The flask was then re-immersed in an ice-bath and vinyl magnesium bromide (1 mL of 1.53 M solution in THF, 1.53 mmol) added. The ensuing mixture was stirred for at 0 °C for 1.5 h then aldehyde **4.43** (10 mg, 0.02 mmol) was added. After a further 1 h the reaction mixture was poured into ammonium chloride (10 mL of a saturated aqueous solution) and the separated aqueous layer extracted with ethyl acetate (1 × 10 mL). The combined organic phases were then washed with brine (1 × 10 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing light-yellow residue was subjected to flash chromatography (silica, 3:2 v/v hexane/ethyl acetate elution) and concentration of the appropriate fractions (R_f = 0.4) afforded compound **4.30** (3.0 mg, 42%) as a clear, colourless oil and as an inseparable mixture of diastereoisomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (dt, *J* = 8.2, 2.1 Hz, 1H), 7.13 – 6.98 (m, 5H), 6.35 (ddd, *J* = 17.5, 11.4, 9.5 Hz, 1H), 6.13 (dd, *J* = 15.0, 10.3 Hz, 1H), 6.03 – 5.81 (m, 2H), 5.28 (dq, *J* = 17.3, 1.8 Hz, 1H), 5.18 – 5.09 (m, 2H), 5.01 (dd, *J* = 10.1, 2.0 Hz, 1H), 4.64 – 4.55 (m, 2H), 4.36 (s, 1H), 3.41 (d, *J* = 7.0 Hz, 2H), 2.93 – 2.81 (m, 1H), 2.75 (dtd, *J* = 13.7, 8.0, 1.9 Hz, 1H), 1.90 (t, *J* = 4.2 Hz, 2H), 1.39 (dd, *J* = 6.5, 1.7 Hz, 6H);

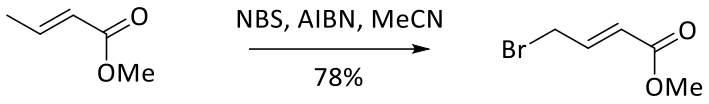
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 156.2, 155.7, 140.4, 137.2, 134.5, 133.9, 132.1, 132.0, 131.5, 131.3, 131.2, 130.3, 129.7, 128.7, 117.7, 117.7, 117.6, 115.6, 115.0, 114.9, 75.1, 73.8, 73.6, 43.5, 43.4, 41.9, 38.5, 22.8;

IR ν_{max} 3453, 2988, 2974, 1565, 1479, 1365, 1299, 1227, 1190, 1108, 811 cm^{-1};

MS (ESI, +ve) *m/z* 413 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) *m/z* 413.2205 $[M+Na]^+$, calcd. for $C_{26}H_{30}O_3Na$ 413.2209.

Methyl (*E*)-4-Bromobut-2-enoate (**4.45**)



4.53 **4.45**

A two-neck, round-bottom flask fitted with a Liebig condenser and rubber septum was charged with methyl crotonate (**4.53**) (7.44 g, 7.43 mmol) and a solution of NBS (7.94 g, 4.46 mmol) in acetonitrile (100 mL). The resulting mixture was heated under reflux and AIBN (2.0 mg, 1.39 µmol) then added to the reaction mixture. After 3.5 h the reaction mixture was cooled to room temperature and the resulting white precipitate was removed by filtration. The filtrate thus obtained was washed with water (2 × 50 mL) then dried (Na_2SO_4) and filtered. The filtrate was then fractionally distilled under reduced pressure and the fraction boiling between 55-60 °C at 2 mmHg collected to afford *E*-methyl 4-bromocrotonate **4.45**[19] (6.11 g, 78%) as a clear, colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (dt, *J* = 15.4, 7.4 Hz, 1H), 6.02 – 5.89 (m, 1H), 3.98 – 3.89 (m, 2H), 3.70 – 3.62 (m, 3H);

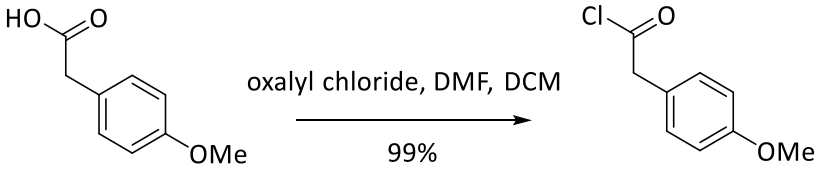
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 165.8, 142.0, 124.1, 51.8, 29.6;

IR ν_{max} 2999, 2953, 2845, 1725, 1659, 1436, 1324, 1285, 1200, 1136 cm^{-1};

MS (ESI, +ve) *m/z* 178 and 176 [$(M+H)^+$, both 100%];

HRMS (ESI, +ve) *m/z* 177.9930 $[M+H]^+$, calcd. for $C_5H_7{}^{81}BrO_2$ 177.9924.

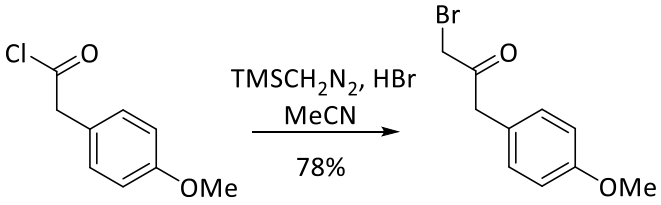
2-(4-Methoxyphenyl)acetyl chloride (**4.55**)



4.54 **4.55**

A magnetically stirred solution of 2-(4-methoxyphenyl)acetic acid (**4.54**) (1.60 g, 9.98 mmol acid in dichloromethane (25 mL) was treated with oxalyl chloride (1.80 mL, 19.96 mmol) and DMF (two drops). The ensuing mixture was stirred for 2 h at room temperature then concentrated under reduced pressure to give the title acid chloride **4.55**[22] (1.90 g, 99%) as a clear, colourless oil that was used, without purification, in the next step (see immediately below).

1-Bromo-3-(4-methoxyphenyl)propan-2-one (**4.56**)



4.55 **4.56**

A magnetically stirred solution of 2-(4-methoxyphenyl)acetyl chloride **4.55** (1.00 g, 5.43 mmol) in acetonitrile (30 mL) maintained under nitrogen at ambient temperatures was treated, dropwise, with trimethylsilyldiazomethane (14.1 mL of a 2 M solution in hexane, 28.26 mmol). The resulting mixture was stirred for 3 h and then concentrated under reduced pressure to give an orange oil. This oil was dissolved in THF (5 mL) and the resulting solution cooled to 0 °C before being treated, in one portion, with HBr (1.50 mL, 48% w/v solution in water) 28.3 mmol). After 1 h the reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (1 × 20 mL). The separated organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing light-yellow residue was subjected to flash chromatography (silica, 9:1 v/v hexane/ ethyl acetate elution) and concentration of the appropriate fractions (R_f = 0.5) afforded compound **4.56**[23] (1.00 g, 78%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 – 6.99 (m, 2H), 6.82 – 6.72 (m, 3H), 3.80 (s, 2H), 3.75 (s, 2H), 3.68 (d, *J* = 5.2 Hz, 3H);

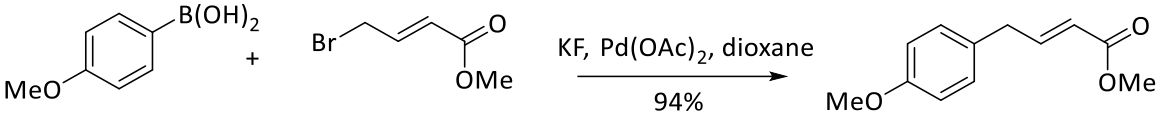
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 199.8, 159.0, 130.5, 125.1, 114.5, 55.3, 45.9, 33.7;

IR ν_{max} 2754, 1654, 1489, 1298, 1230, 1100, 1080, 831 cm^{-1};

MS (ESI, +ve) *m/z* 243 and 241 [$(M+H)^+$, both 100%];

HRMS (ESI, +ve) *m/z* 243.9985 $[M+H]^+$, calcd. for $C_{10}H_{12}{}^{81}BrO_2$ 243.9986.

Methyl (*E*)-4-(4-Methoxyphenyl)but-2-enoate (**4.46**)



4.44 **4.45** **4.46**

A magnetically stirred solution of (4-methoxyphenyl)boronic acid (**4.44**) (114 mg, 0.75 mmol) and KF (130 mg, 2.25 mmol) in 1,4-dioxane (2 mL) was stirred for 10 min. Then, a solution of $Pd(OAc)_2$ (3.0 mg, 0.01 mmol) and methyl 4-bromocrotonate (**4.45**) (90 mg, 0.49 mmol) in 1,4-dioxane (3 mL) was added. The ensuing mixture was stirred at ambient temperatures for 2 h then filtered through a pad of TLC-grade silica gel that was washed with diethyl ether (15 mL). The combined filtrates were dried (Na_2SO_4), filtered then concentrated under reduced pressure. The ensuing light-yellow residue was subjected to flash chromatography (silica, 9:1 v/v hexane/ ethyl acetate elution) and concentration of the appropriate fractions (R_f = 0.8) afforded compound **4.46**[24] (97 mg, 94%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 – 7.02 (m, 3H), 6.89 – 6.81 (m, 2H), 5.81 (dt, *J* = 15.5, 1.7 Hz, 1H), 3.77 (s, 3H), 3.71 (s, 3H), 3.45 (dd, *J* = 6.9, 1.7 Hz, 2H);

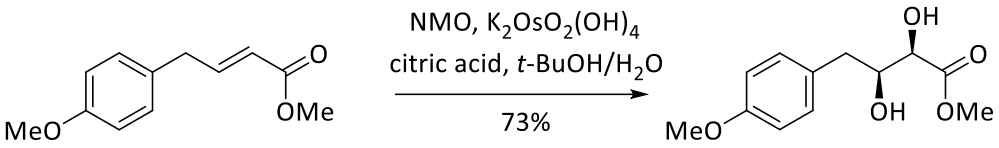
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.8, 158.3, 148.0, 129.5, 121.5, 114.0, 55.1, 51.3, 37.5;

IR ν_{max} 2981, 1717, 1655, 1511, 1436, 1271, 1245,1180, 1034, 825 cm^{-1};

MS (ESI, +ve) *m/z* 229 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) *m/z* 229.1132 $[M+Na]^+$, calcd. for $C_{12}H_{14}O_3Na$ 229.11135.

Methyl (±)-(2*R*,3*S*)-2,3-Dihydroxy-4-(4-methoxyphenyl)butanoate ((±)-4.57)



4.46 **(±)-4.57**

A magnetically stirred solution of olefin **4.46** (1.00 g, 4.85 mmol) and citric acid (690 mg, 3.64 mmol) in *tert*-butyl alcohol/water (16 mL of a 1:1 v/v mixture) was treated with potassium osmate (0.02 g, 0.01 mol) then 4-methylmorpholine *N*-oxide (NMO) (5 mL of a 50% w/v solution in water, 5.33 mmol). The ensuing mixture was stirred at ambient temperatures for 3 h then acidified with HCl (20 mL of a 1.0 M aqueous solution) and extracted with ethyl acetate (2 × 10 mL). The combined organic phases were dried (Na_2SO_4), filtered then concentrated under reduced pressure. The ensuing green residue was subjected to flash chromatography (silica, 2:3 v/v hexane/ethyl acetate elution) and concentration of the appropriate fractions (R_f = 0.5) afforded compound **(±)-4.57** (850 mg, 73%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 – 7.11 (m, 2H), 6.89 – 6.79 (m, 2H), 4.15 – 4.02 (m, 2H), 3.75 (d, *J* = 6.6 Hz, 6H), 2.87 (d, *J* = 7.3 Hz, 2H);

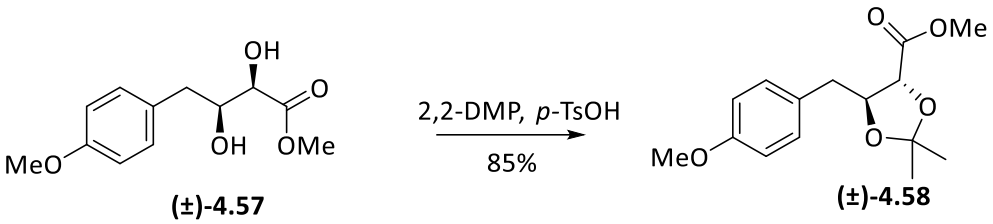
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 174.2, 158.3, 130.4, 129.6, 114.0, 73.8, 72.0, 55.2, 52.6, 39.0;

IR ν_{max} 3453, 2954, 1736, 1611, 1512, 1264, 1033, 731 cm^{-1};

MS (ESI, +ve) *m/z* 263 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) *m/z* 263.0899 $[M+Na]^+$, calcd. for $C_{12}H_{16}O_5Na$ 263.0895.

Methyl (±)-(4*R*,5*S*)-5-(4-Methoxybenzyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (±)-4.58)



(±)-4.57 **(±)-4.58**

A magnetically stirred solution of diol **(±)-4.57** (0.15 g, 0.62 mmol) and 2,2-dimethoxypropane (2,2-DMP) (210 mL, 1.24 mmol) in dichloromethane (5 mL) was treated with *p*-toluenesulfonic acid (*p*-TsOH) (90 mg, 0.49 mmol). The mixture so-formed was stirred at ambient temperatures for 2 h then quenched with sodium hydrogen carbonate (50 mL of a saturated aqueous solution) and extracted with ethyl acetate (3 × 100 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The light-yellow oil so-formed was subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) and concentration of the appropriate fractions (R_f = 0.8) afforded compound **(±)-4.58** (150 mg, 85%) as a clear, colourless foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 – 7.12 (m, 2H), 6.86 – 6.78 (m, 2H), 4.34 (td, *J* = 7.1, 4.2 Hz, 1H), 4.15 (d, *J* = 7.7 Hz, 1H), 3.75 (s, 3H), 3.70 (s, 3H), 3.04 (dd, *J* = 14.4, 4.3 Hz, 1H), 2.92 (dd, *J* = 14.4, 6.7 Hz, 1H), 1.40 (d, *J* = 6.5 Hz, 6H);

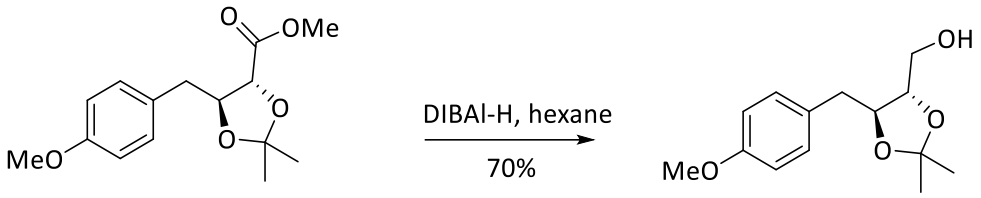
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.1, 158.4, 130.7, 128.7, 113.7, 110.9, 79.5, 77.9, 55.1, 52.2, 34.0, 27.1, 25.8;

IR ν_{max} 2996, 1760, 1513, 1247, 1098, 818 cm^{-1};

MS (ESI, +ve) *m/z* 303 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) *m/z* 303.1208 $[M+Na]^+$, calcd. for $C_{15}H_{20}O_5Na$ 303.1208.

((±)-(4*S*,5*S*)-5-(4-Methoxybenzyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (**(±)-4.59**)



(±)-4.58 **(±)-4.59**

A magnetically stirred solution of ester **(±)-4.58** (1.0 g, 3.56 mmol) in dry hexane (30 mL) maintained under a nitrogen atmosphere at −78 °C was treated with di-*iso*-butylaluminium hydride (DIBAl-H) (7.13 mL of 1.0 M solution in hexane, 7.13 mmol). The ensuing mixture was stirred at −78 °C for 2 h then quenched with tartaric acid (40 mL of a 1.0 M aqueous solution). The resulting mixture was stirred at room temperature for 1 h and the separated aqueous layer extracted with diethyl ether (2 × 20 mL). The combined organic phases were then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 7:3 v/v hexane/ethyl acetate elution) and concentration of the appropriate fractions (R_f = 0.3) afforded compound **(±)-4.59** (600 mg, 70%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 – 7.09 (m, 2H), 6.87 – 6.79 (m, 2H), 4.16 – 4.03 (m, 1H), 3.88 – 3.74 (m, 4H), 3.51 (ddd, *J* = 12.1, 4.8, 2.9 Hz, 1H), 3.30 (ddd, *J* = 11.6, 6.5, 4.7 Hz, 1H), 2.98 (dd, *J* = 14.0, 6.4 Hz, 1H), 2.77 (dd, *J* = 14.0, 6.3 Hz, 1H), 1.39 (s, 6H);

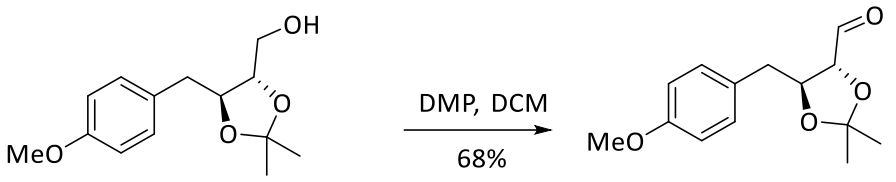
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.5, 130.3, 129.0, 114.0, 108.8, 81.3, 77.4, 62.2, 55.3, 38.6, 27.4, 27.2, 14.3;

IR ν_{max} 3467, 2836, 1611, 1440, 1299, 1116, 1033, 894 cm^{-1};

MS (ESI, +ve) *m/z* 275 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) *m/z* 275.1435 $[M+Na]^+$, calcd. for $C_{14}H_{20}O_4Na$ 275.1433.

(±)-(4*R*,5*S*)-5-(4-Methoxybenzyl)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (**(±)-4.60**)



(±)-4.59 **(±)-4.60**

A magnetically stirred solution of alcohol **(±)-4.59** (500 mg, 1.98 mmol) in dichloromethane (10 mL) maintained at 0 °C was treated with the DMP (1.68 g, 3.96 mmol). The ensuing mixture was allowed to warm to ambient temperatures, stirred for 16 h then quenched with sodium thiosulfate (15 mL of a saturated aqueous solution) and NaOH (15 mL of a 1 M aqueous solution). The separated aqueous layer was extracted with diethyl ether (3 × 5 mL) and the combined organic phases were washed with brine (1 × 10 mL) before being dried (Na_2SO_4), filtered then concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 7:3 v/v hexane/ethyl acetate elution) and concentration of the appropriate fractions (R_f = 0.5) afforded compound **(±)-4.60** (330 mg, 68%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.55 (d, *J* = 2.0 Hz, 1H), 7.25 – 7.02 (m, 2H), 6.94 – 6.70 (m, 2H), 4.24 (ddd, *J* = 7.7, 6.3, 5.3 Hz, 1H), 4.02 (dd, *J* = 7.7, 2.0 Hz, 1H), 3.77 (s, 3H), 3.04 – 2.86 (m, 2H), 1.52 – 1.27 (m, 6H);

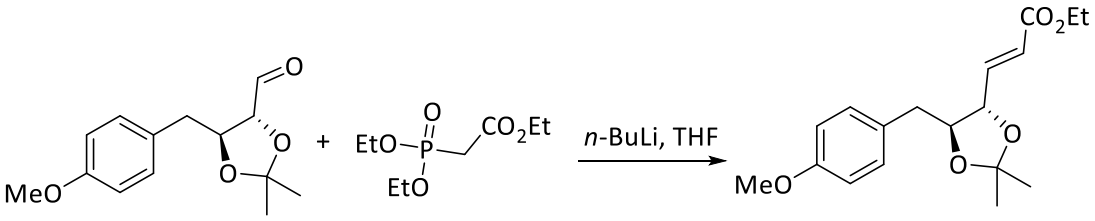
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 200.7, 158.6, 130.7, 118.4, 114.0, 84.0, 77.7, 55.3, 38.2, 27.1, 26.3;

IR ν_{max} 2974, 1538, 1499, 1368, 1220, 1120, 1098, 831 cm^{-1};

MS (ESI, +ve) *m/z* 251 [$(M+H)^+$, 100%];

HRMS (ESI, +ve) *m/z* 251.1205 $[M+H]^+$, calcd. for $C_{14}H_{18}O_4$ 251.1203.

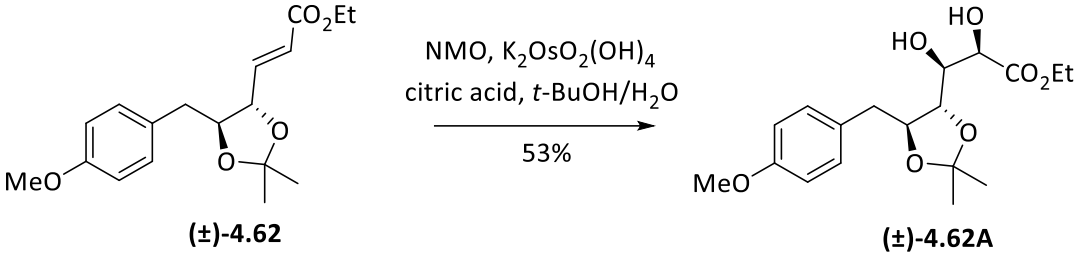
Ethyl (*E*)-3-((±)-(4*S*,5*S*)-5-(4-Methoxybenzyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (±)-4.62)



(±)-4.60 **4.61** **(±)-4.62**

A magnetically stirred solution of ethyl bromoacetate (1.00 g, 5.98 mmol) and triethylphosphite (1.10 mL, 6.58 mmol) was heated at 110 °C for 2 h. The cooled reaction mixture was concentrated under reduced pressure and the compound **4.61** thus obtained was used, without purification. Thus, a magnetically stirred solution of phosphonate **4.61** (100 mL, 0.75 mmol) in dry THF (10 mL) maintained at 0 °C under a nitrogen atmosphere was treated with *n*-butyllithium (500 mL of 1.5 M solution in THF, 0.75 mmol). The ensuing mixture was stirred at 0 °C for 10 min then cooled to –78 °C and treated with a solution of aldehyde **(±)-4.60** (100 mg, 0.40 mmol) in THF (5 mL). The resulting mixture was stirred at −78 °C for 0.5 h then warmed to ambient temperatures and stirring continued for a further 3 h. The reaction was then quenched with ammonium chloride (20 mL of a saturated aqueous solution) and the separated aqueous layer extracted with diethyl ether (3 × 5 mL). The combined organic phases were dried (Na_2SO_4) then filtered and concentrated under reduced pressure. The material thus obtained as a yellow oil and presumed to contain compound **(±)-4.62**, was subjected to the next reaction as detailed immediately below.

Ethyl (±)-(2*R*,3*R*)-2,3-Dihydroxy-3-((±)-(4*S*,5*S*)-5-(4-methoxybenzyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propanoate (±)-4.62A

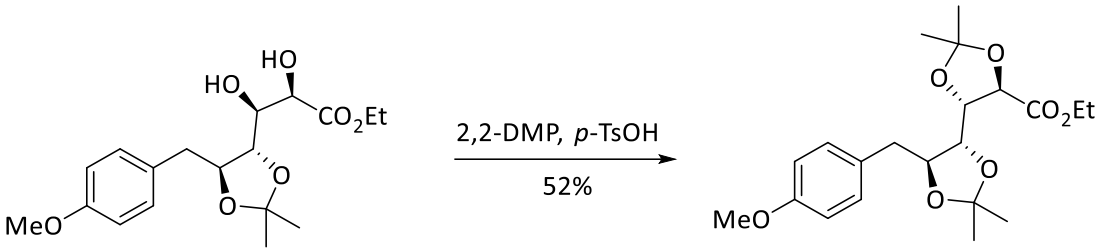


(±)-4.62 **(±)-4.62A**

A magnetically stirred solution of the crude olefin **(±)-4.62** (500 mg, 1.56 mmol) and citric acid (225 mg, 1.12 mmol) in *tert*-butyl alcohol/water (10 mL of a 1:1 v/v mixture) was treated with potassium osmate (7 mg, 1 mol%) then NMO (3 mL of a 50% w/v solution in water, 1.71 mmol). The ensuing mixture was stirred at ambient temperatures for 3 h then acidified with HCl (10 mL of a 1.0 M aqueous solution) and extracted with ethyl acetate (2 × 15 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure and the ensuing green residue was subjected to flash chromatography (silica, 2:3 v/v hexane/ ethyl acetate elution). Concentration of the appropriate fractions (R_f = 0.6) afforded diol **(±)-4.62A** (293 mg, 53%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 – 7.06 (m, 2H), 6.80 – 6.72 (m, 2H), 4.36 (d, *J* = 1.5 Hz, 1H), 4.28 – 4.14 (m, 3H), 3.83 (ddd, *J* = 8.2, 4.9, 1.9 Hz, 1H), 3.71 (s, 3H), 2.94 (dd, *J* = 14.2, 4.3 Hz, 1H), 2.84 – 2.72 (m, 1H), 1.34 – 1.28 (m, 6H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H);
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.5, 158.4, 130.7, 130.1, 113.9, 109.5, 81.2, 79.1, 74.0, 70.8, 62.5, 55.4, 39.7, 27.7, 27.4, 14.4;
IR ν_{max} 3460, 2850, 1588, 1513, 1300, 1153, 908 cm^{-1};
MS (ESI, +ve) *m/z* 377 [$(M+Na)^+$, 100%];
HRMS (ESI, +ve) *m/z* 377.1576 $[M+Na]^+$, calcd. for $C_{18}H_{26}O_7Na$ 377.1576.

Ethyl (±)-(4*S*,4'*R*,5*R*,5'*S*)-5'-(4-Methoxybenzyl)-2,2,2',2'-tetramethyl-[4,4'-bi(1,3-dioxolane)]-5-carboxylate (**(±)-4.63**)



(±)-4.62A **(±)-4.63**

A magnetically stirred solution of diol **(±)-4.62A** (200 mg, 0.56 mmol) and 2,2-DMP (1.00 mL, 1.12 mmol) in dichloromethane (5 mL) was treated with *p*-TsOH (77 mg, 0.44 mmol). The mixture so-formed was stirred at ambient temperatures for 2 h then quenched with sodium hydrogen carbonate (25 mL of a saturated aqueous solution) before being extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The light-yellow oil so-formed was subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) and concentration of the appropriate fractions (R_f = 0.8) afforded compound **(±)-4.63** (115 mg, 52%) as a clear, colourless foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 – 7.12 (m, 2H), 6.87 – 6.78 (m, 2H), 4.45 (d, *J* = 5.8 Hz, 1H), 4.21 (ddp, *J* = 10.2, 7.6, 3.4 Hz, 4H), 3.84 – 3.79 (m, 1H), 3.77 (d, *J* = 4.7 Hz, 3H), 3.04 – 2.92 (m, 1H), 2.91 – 2.81 (m, 1H), 1.46 – 1.34 (m, 12H), 1.28 (td, *J* = 7.2, 2.5 Hz, 3H);

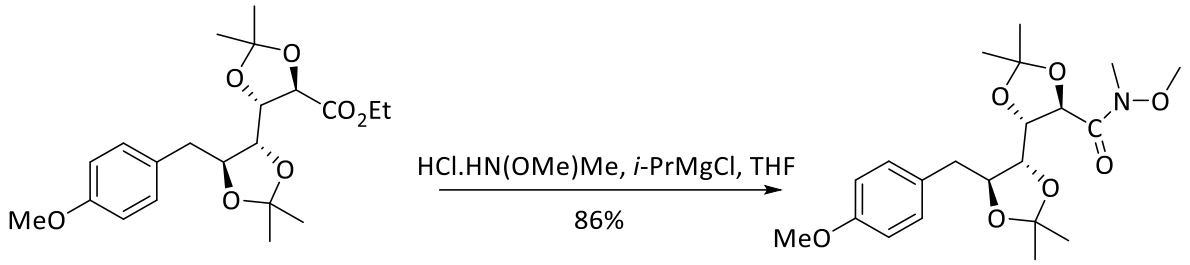
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.6, 158.5, 130.6, 129.6, 113.9, 112.0, 109.7, 80.1, 79.9, 77.0, 61.6, 55.3, 38.7, 27.6, 27.2, 27.1, 26.0, 14.3;

IR ν_{max} 2839, 1760, 1513, 1381, 1216, 1088, 819 cm^{-1};

MS (ESI, +ve) *m/z* 417 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) *m/z* 417.2018 $[M+Na]^+$, calcd. for $C_{21}H_{30}O_7Na$ 417.2015.

(±)-(4*S*,4'*R*,5*R*,5'*S*)-*N*-Methoxy-5'-(4-methoxybenzyl)-*N*,2,2,2',2'-pentamethyl-[4,4'-bi(1,3-dioxolane)]-5-carboxamide (**(±)-4.64**)



(±)-4.63 **(±)-4.64**

A magnetically stirred solution of ethyl ester **(±)-4.63** (500 mg, 1.27 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (310 mg, 5.08 mmol) in dry THF (10 mL) maintained under nitrogen was cooled to −15 °C then treated, dropwise over 20 min via syringe pump, with *iso*-propylmagnesium chloride (3.81 mL of a 2.0 M solution in THF, 7.62 mmol). The ensuing mixture was stirred at −15 °C for 1 h then quenched with ammonium chloride (5 mL of a saturated aqueous solution) and the separated aqueous phase extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried (Na_2SO_4), filtered then concentrated under reduced pressure and the resulting yellow oil subjected to flash chromatography (silica, 7:3 v/v hexane/ethyl acetate elution). Concentration of the relevant fractions (R_f = 0.4) afforded compound **(±)-4.64** (440 mg, 86%) as a clear, colourless, oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 – 7.17 (m, 2H), 6.85 – 6.81 (m, 2H), 4.85 (s, 1H), 4.57 (t, *J* = 6.6 Hz, 1H), 4.23 – 4.01 (m, 2H), 3.78 (s, 3H), 3.75 (s, 3H), 3.23 (s, 3H), 3.03 (dd, *J* = 14.4, 3.6 Hz, 1H), 2.86 – 2.79 (m, 1H), 1.45 (d, *J* = 5.7 Hz, 6H), 1.32 (d, *J* = 5.0 Hz, 6H);

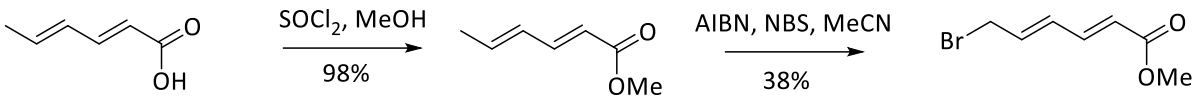
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.3, 130.8, 130.0, 113.8, 111.7, 109.5, 80.6, 80.0, 78.9, 55.4, 38.3, 27.5, 27.5, 27.1, 26.43;

IR ν_{max} 2986, 2936, 1668, 1513, 1380, 1245, 1066, 838 cm^{-1};

MS (ESI, +ve) *m/z* 432 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) *m/z* 432.1996 [$M+Na]^+$, (calcd. for $C_{21}H_{31}NO_7Na$ 432.1998.

Methyl (2*E*,4*E*)-6-Bromohexa-2,4-dienoate (**4.69**)



4.67 **4.68** **4.69**

A magnetically stirred solution of sorbic acid (**4.67**) (2.00 g, 17.8 mmol) in MeOH (100 mL) maintained at 0 °C was treated, dropwise with $SOCl_2$ (1.30 mL, 17.8 mmol). The ensuing mixture was heated under reflux for 3 h then cooled to ambient temperatures before being diluted with dichloromethane (100 mL). The resulting solution was washed with $NaHCO_3$ (1 × 50 mL of a saturated aqueous solution) and the organic phase then dried (Na_2SO_4) then filtered and concentrated under reduced pressure. The crude methyl ester **4.68** thus obtained was subjected to the next reaction without purification. Thus, a magnetically stirred solution of methyl sorbate (**4.68**)[23] (1.00 g, 7.91 mmol) and NBS (1.70 g, 9.83 mmol) in acetonitrile (100 mL) was heated under reflux then treated, in one portion, with benzoyl peroxide (500 mg, 2.13 mmol). After a further 4 h, the reaction mixture was cooled then concentrated under reduced pressure and the residue thus formed dissolved in diethyl ether (100 mL). The resulting solution was washed with NaOH (10% w/v aqueous solution) until the washings were clear (50 mL) and then with water (1 × 20 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 9:1 v/v hexane/ ethyl acetate elution) and concentration of the relevant fractions (R_f = 0.6) afforded compound **4.69**[25] (600 mg, 38%) as a clear, colourless, oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (dd, *J* = 15.4, 10.9 Hz, 1H), 6.22 (ddq, *J* = 15.1, 10.8, 0.9 Hz, 1H), 6.12 – 6.03 (m, 1H), 5.77 (d, *J* = 15.4 Hz, 1H), 3.87 (dd, *J* = 7.6, 0.9 Hz, 2H), 3.60 (d, *J* = 8.1 Hz, 3H);

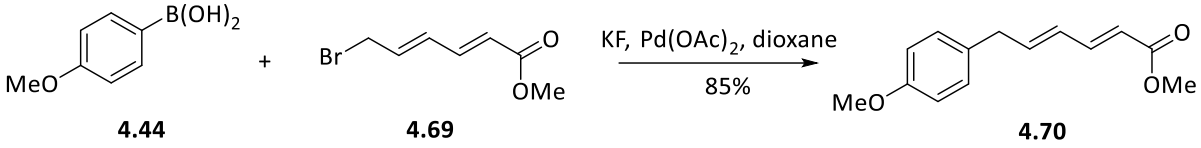
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.0, 142.9, 136.8, 132.0, 122.9, 51.9, 31.3;

IR ν_{max} 2750, 1664, 1454, 1299, 1240, 1100, 1080, 811 cm^{-1};

MS (ESI, +ve) *m/z* 205 and 203 [$(M+H)^+$, both 100%];

HRMS (ESI, +ve) *m/z* 204.9911 $[M+H]^+$, calcd. for $C_7H_{10}{}^{81}BrO_2$ 204.9913.

Methyl (2*E*,4*E*)-6-(4-Methoxyphenyl)hexa-2,4-dienoate (**4.70**)



4.44 **4.69** **4.70**

A magnetically stirred solution of (4-methoxyphenyl)boronic acid (**4.44**) (114 mg, 0.75 mmol) and KF (130 mg, 2.25 mmol) in 1,4-dioxane (2 mL) was stirred for 10 min then a solution of $Pd(OAc)_2$ (3.0 mg, 0.01 mmol) and methyl (2*E*,4*E*)-6-bromohexa-2,4-dienoate **4.69** (100 mg, 0.49 mmol) in 1,4-dioxane (3 mL) was added. The ensuing mixture was stirred at ambient temperatures for 2 h before being filtered through a pad of TLC-grade silica gel that was washed with diethyl ether (15 mL). The combined filtrates were then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 9:1 v/v hexane/ ethyl acetate elution) and concentration of the appropriate fractions (R_f = 0.8) afforded compound **4.70** (96 mg, 85%) as a clear, colourless oil.

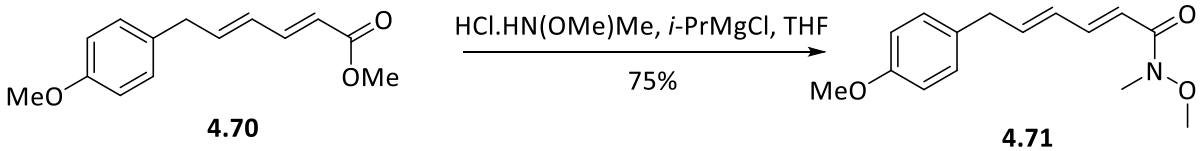
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (dd, J = 15.2, 10.1 Hz, 1H), 7.08 (d, J = 8.5 Hz, 2H), 8.85 (d, J = 8.5 Hz, 2H), 6.32-6.12 (m, 2H), 5.82 (d, J = 15.4 Hz, 1H), 3.78 (s, 3H), 3.73 (s, 3H), 3.43 (d, J = 6.3 Hz, 2H);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.6, 158.3, 144.9, 143.0, 130.8, 129.7, 129.0, 119.7, 114.1, 55.3, 51.5, 38.4;

IR ν_{max} 2990, 1810, 1658, 1530, 1438, 1265, 1250, 1190, 1014, 815 cm^{-1};

MS (ESI, +ve) *m/z* 233 [$(M+H)^+$, 100%];
HRMS (ESI, +ve) *m/z* 233.2810 $[M+H]^+$, calcd. for $C_{14}H_{16}O_3$ 233.2815.

(2*E*,4*E*)-*N*-Methoxy-6-(4-methoxyphenyl)-*N*-methylhexa-2,4-dienamide (**4.71**)



4.70 **4.71**

A magnetically stirred solution of methyl ester **4.70** (295 mg, 1.27 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (310 mg, 5.08 mmol) in dry THF (10 mL) maintained under nitrogen was cooled to −15 °C then treated, dropwise over 20 min via syringe pump,

with *iso*-propylmagnesium chloride (3.81 mL of a 2.0 M solution in THF, 7.62 mmol). The ensuing mixture was stirred at −15 °C for 1 h then quenched with ammonium chloride (5 mL of a saturated aqueous solution) and the separated aqueous phase extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried (Na_2SO_4) then filtered and concentrated under reduced pressure and the resulting yellow oil subjected to flash chromatography (silica, 7:3 v/v hexane/ethyl acetate elution). Concentration of the relevant fractions (R_f = 0.4) afforded compound **4.71** (248 mg, 75%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 1H), 7.16 – 7.05 (m, 2H), 6.92 – 6.79 (m, 2H), 6.40 (d, *J* = 15.2 Hz, 1H), 6.32 – 6.15 (m, 2H), 3.79 (s, 3H), 3.69 (s, 3H), 3.44 (d, *J* = 5.4 Hz, 2H), 3.25 (s, 3H);

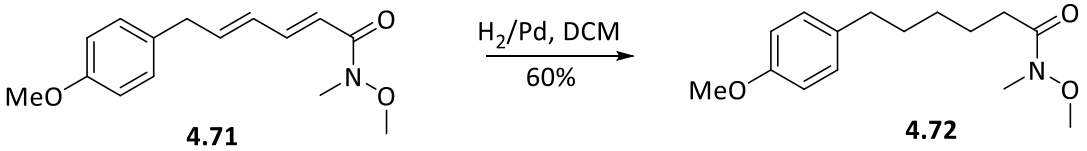
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.4, 144.0, 142.2, 131.2, 129.6, 117.9, 114.2, 61.9, 55.4, 38.5, 32.6;

IR ν_{max} 2936, 1656, 1627, 1511,1380, 1245, 1002, 904 cm^{-1};

MS (ESI, +ve) *m/z* 262 [$(M+H)^+$, 100%];

HRMS (ESI, +ve) *m/z* 262.1455 $[M+H]^+$ (calcd. for $C_{15}H_{20}NO_3$ 262.1458).

***N*-Methoxy-6-(4-methoxyphenyl)-*N*-methylhexanamide** (**4.72**)



4.71 **4.72**

A two-neck round-bottom flask fitted with a rubber septum was charged with amide **4.71** (50 mg, 0.19 mmol) and Pd/C (15 mg of 10 mol% material). The flask was evacuated under low pressure and backfilled with nitrogen twice. Dichloromethane (1 mL) was added, and the resulting suspension was stirred for 0.25 h. A balloon containing hydrogen was then attached and the whole set up was evacuated under reduced pressure and backfilled with hydrogen twice. The ensuing mixture was stirred at ambient temperatures for 16 h before being concentrated under reduced pressure. The resulting suspension subjected to flash chromatography (silica, 7:3 v/v hexane/ethyl acetate elution) and concentration of the relevant fractions (R_f = 0.4) afforded compound **4.72** (30 mg, 60%) as a clear, colourless, oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 – 7.01 (m, 2H), 6.82 – 6.74 (m, 2H), 3.73 (s, 3H), 3.62 (s, 3H), 3.13 (s, 3H), 2.53 (t, *J* = 7.7 Hz, 2H), 2.38 (t, *J* = 7.6 Hz, 2H), 1.61 (dq, *J* = 19.4, 7.6 Hz, 4H), 1.41 – 1.27 (m, 2H);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.5, 134.6, 129.1, 113.5, 61.0, 55.0, 34.7, 32.0, 31.7, 31.4, 28.9, 24.4;

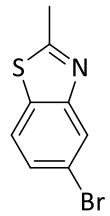
IR ν_{max} 2933, 1661, 1585, 1511,1453, 1299, 1243, 1175, 1034, 830 cm^{-1};

MS (ESI, +ve) *m/z* 288 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) *m/z* 288.1712 [$M+Na]^+$, calcd. for $C_{15}H_{23}NO_3Na$ 288.1715.

Experimental Procedures Related to Work Described in Chapter Five

5-Bromo-2-methylbenzo[*d*]thiazole (**5.04**)



5.04

This compound was obtained from commercial sources as a white, crystalline solid, m.p. = 78-80 °C (lit.[26] m.p. = 77.8-78.4 °C).

^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 8.06 (d, *J* = 2.0 Hz, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.49 (dd, *J* = 8.5 and 2.0 Hz, 1H), 2.77 (s, 3H);

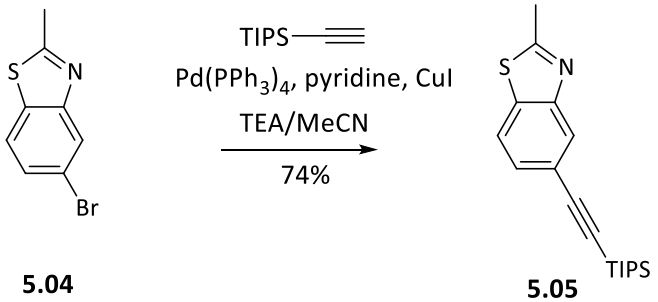
^{13}C{^{1}H} NMR [101 MHz, $(CD_3)_2SO$] δ 169.3, 154.2, 134.4, 127.4, 124.4, 123.6, 118.8, 19.8;

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 1.8 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.44 (br. d, *J* = 8.4 Hz, 1H), 2.82 (s, 3H);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.9, 154.7, 134.6, 127.9, 125.4, 122.5, 119.6, 20.3;

MS (ESI, +ve) *m/z* 228 and 230 [$(M+H)^+$, both 100%].

2-Methyl-5-((triisopropylsilyl)ethynyl)benzo[*d*]thiazole (**5.05**)



5.04 **5.05**

A degassed and magnetically stirred mixture of 5-bromo-2-methylbenzo[*d*]thiazole (**5.04**) (50 mg, 0.21 mmol), $Pd(PPh_3)_4$ (20 mg, 0.01 mmol) and CuI (10 mg, 0.02 mmol) in TEA/acetonitrile (5 mL of a 1:1 v/v mixture) was treated with ethynyltriisopropylsilane (150 mg, 0.66 mmol)

and pyridine (1 mL). The resulting mixture was degassed again for 2 min then heated at 80 °C for 30 h. The cooled reaction mixture was concentrated under reduced pressure and the residue thus obtained subjected to flash column chromatography (silica gel, 95:5 v/v hexane/ethyl acetate elution) to give, after concentration of the appropriate fractions (R_f = 0.6), compound **5.05** (50 mg, 74%) as a pale-yellow solid. m.p. = 73-75 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (br. s, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.44 (dd, *J* = 8.2 and 1.2 Hz, 1H), 2.82 (s, 3H), 1.15 (s, 21H);

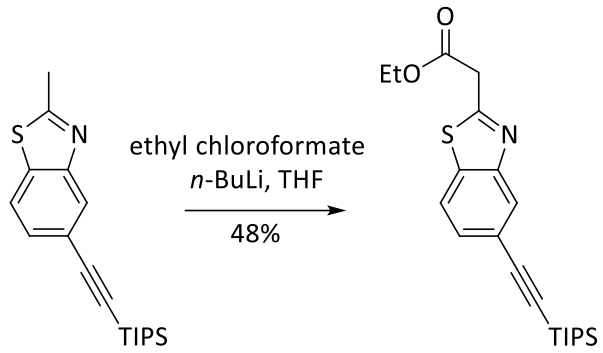
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.0, 153.4, 136.0, 128.4, 126.1, 121.4, 121.3, 106.9, 91.0, 20.3, 18.8, 11.5;

IR ν_{max} 2941, 2854, 2150, 1449, 1265, 1216, 1159, 995, 827 cm^{-1};

MS (ESI, +ve) *m/z* 330 [$(M+H)^+$, 100%];

HRMS (ESI, +ve) *m/z* 330.1721 $(M+H)^+$, calcd for $C_{19}H_{28}NSSi$, 330.1712.

Ethyl 2-(5-((Triisopropylsilyl)ethynyl)benzo[*d*]thiazol-2-yl)acetate (**5.06**)



5.05 **5.06**

A magnetically stirred solution of compound **5.05** (180 mg, 0.54 mmol) in anhydrous THF (3 mL) was cooled to –78 °C then treated with *n*-BuLi (330 mL of a 2 M solution in hexane, 0.66 mmol). The temperature was maintained at –78 °C for 4 h and after this time ethyl chloroformate (710 mg, 0.65 mmol) was added to the reaction mixture which was then warmed to –60 °C. After 2 h the reaction mixture was quenched by pouring it into ice/water. The separated aqueous layer was extracted with ethyl acetate (2 × 10 mL) and the combined organic phases were then dried (Na_2SO_4), filtered then concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl

acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.3), compound **5.06** (100 mg, 48%) as a clear, pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 1.4 Hz, 1H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.48 (dd, *J* = 8.3 and 1.4 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 4.16 (s, 2H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.15 (s, 21H);

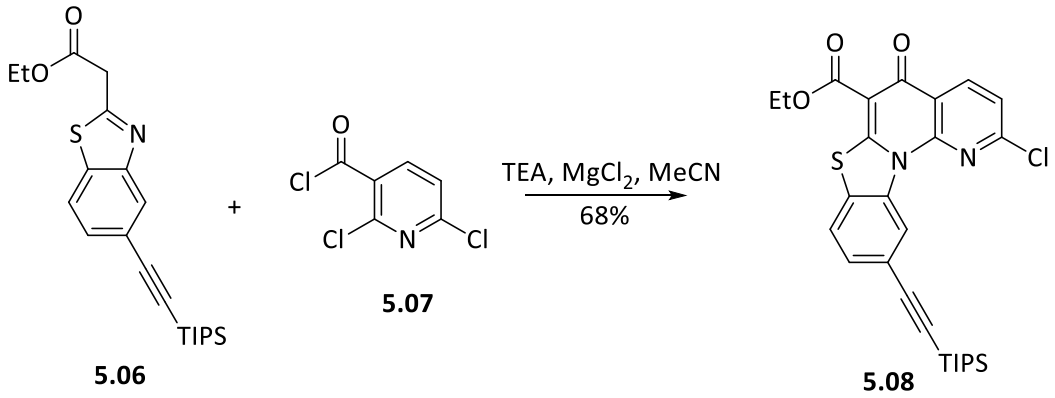
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.5, 163.8, 152.7, 136.1, 128.9, 126.8, 121.4, 106.7, 91.3, 62.0, 40.0, 18.8, 14.3, 11.5;

IR ν_{max} 2942, 2854, 2156, 1746, 1698, 1476, 1185, 1013, 882 cm^{-1};

MS (ESI, +ve) *m/z* 424 [(M+Na)$^+$, 100%];

HRMS (ESI, +ve) *m/z* 424.1605 (M+Na)$^+$, calcd for $C_{22}H_{31}NNaO_2SSi$ 424.1603.

Ethyl 2-Chloro-5-oxo-10-((triisopropylsilyl)ethynyl)-5*H*-benzo[4,5]thiazolo[3,2-*a*][1,8]-naphthyridine-6-carboxylate (**5.08**)



A magnetically stirred solution of compound **5.06** (320 mg, 0.40 mmol) in acetonitrile (3 mL) maintained at 0 °C was treated, in portions, with $MgCl_2$ (70 mg, 0.74 mmol). The resulting suspension was cooled below 5 °C then a solution of dichloronicotinyl chloride (**5.07**) (100 mg, 0.48 mmol) in acetonitrile (1 mL) was added to the reaction mixture over a period of 5 min. The mixture thus obtained was cooled to between –10 to 0 °C before being treated with TEA (100 µL, 0.72 mmol). After stirring for 1 h the cooling bath was removed, and water added (2 × 1 mL aliquots at 0 and 10 min) to the reaction mixture that was then concentrated under a stream of nitrogen and the residue extracted with dichloromethane (20 mL). The combined organic phases were concentrated under reduced pressure and the residue was dissolved in acetonitrile (3 mL) and the resulting solution treated with TEA (130 µL, 0.93 mmol). The

suspension so formed was heated under reflux for 2 h then the cooled reaction mixture concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 7:3 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.3), compound **5.08** (140 mg, 68%) as an off-white solid, m.p. = 218–220 °C.

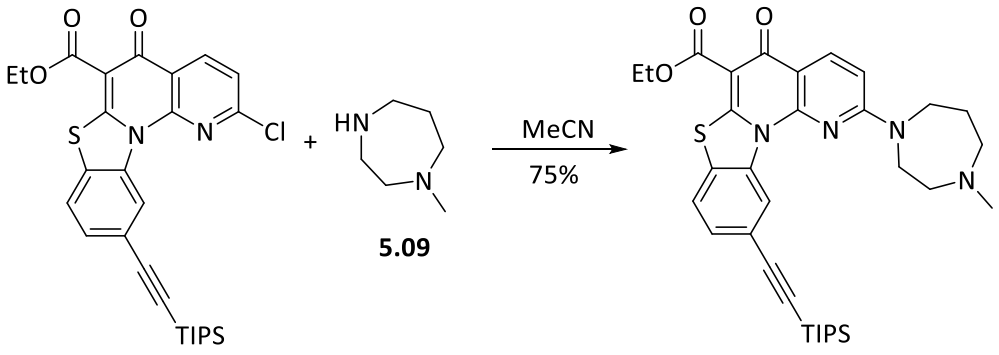
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (d, *J* = 1.3 Hz, 1H), 8.83 (d, *J* = 8.2 Hz, 1H), 7.68 (d, *J* = 8.2 Hz, 1H), 7.56 (m, 2H), 4.52 (q, *J* = 7.1 Hz, 2H), 1.49 (t, *J* = 7.1 Hz, 3H), 1.18 (br. s, 21H);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 163.0, 153.0, 140.3, 137.5, 129.6, 128.5, 124.2, 123.2, 123.1, 121.7, 106.4, 92.9, 62.0, 18.8, 14.6, 11.5 (five signals obscured or overlapping);

IR ν_{max} 2942, 2854, 2156, 1663, 1635, 1568, 1490, 1473, 1414, 1291, 1254, 1127, 1069, 955, 881, 824, 795 cm^{-1};

MS (ESI, +ve) *m/z* 563 and 561 [$(M+Na)^+$, 30 and 100%]; 541 and 539 [$(M+H)^+$, 40 and 85]; **HRMS** (ESI, +ve) *m/z* 539.1389 $(M+H)^+$, calcd for $C_{28}H_{32}{}^{35}ClN_2O_3SSi$ 539.1387.

Ethyl 2-(4-Methyl-1,4-diazepan-1-yl)-5-oxo-10-((triisopropylsilyl)ethynyl)-5*H*-benzo-[4,5]thiazolo[3,2-*a*][1,8]naphthyridine-6-carboxylate (**5.10**)



5.08 **5.09** **5.10**

A magnetically stirred suspension of compound **5.08** (200 mg, 0.50 mmol) in acetonitrile (5 mL) was treated with *N*-methyl-1,4-diazepane (**5.09**) (120 mg, 1.01 mmol) and the ensuing mixture heated under reflux for 4 h. The cooled reaction mixture was concentrated under reduced pressure and the residue thus obtained subjected to flash column chromatography (silica, 9:1 v/v dichloromethane/ammonia-saturated methanol) and thus affording, after concentration of the appropriate fractions (R_f = 0.4), compound **5.10** (170 mg, 75%) as a white solid, m.p. = 158-160 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (br. s, 1H), 8.56 (d, *J* = 9.0 Hz, 1H), 7.63 (d, *J* = 8.1 Hz, 1H), 7.52 (d, *J* = 8.1 Hz, 1H), 6.76 (d, *J* = 9.0 Hz, 1H), 4.48 (m, 2H), 3.91 (br. s, 4H), 2.88 (br. s, 2H), 2.60 (br. s, 2H), 2.40 (s, 3H), 2.16 (br. s, 2H), 1.48 (m, 3H), 1.16 (br. s, 21H);

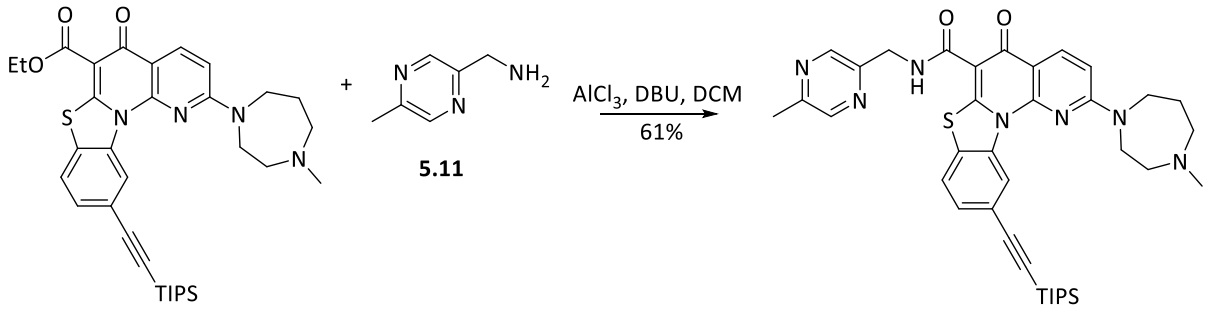
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.8, 167.9, 161.3, 158.6, 149.6, 138.3, 137.7, 130.3, 129.0, 125.0, 121.0, 119.3, 113.1, 106.2, 105.6, 105.5, 92.6, 61.6, 57.8, 57.3, 47.9, 47.0, 27.5, 18.9, 14.7, 11.5 (one signal obscured or overlapping);

IR ν_{max} 2942, 2855, 2156, 1662, 1611, 1482, 1423, 1394, 1294, 1261, 1179, 1153, 1071, 882, 794 cm^{-1};

MS (ESI, +ve) *m/z* 617 [$(M+H)^+$, 100%];

HRMS (ESI, +ve) *m/z* 617.2994 $(M+H)^+$, calcd for $C_{34}H_{45}N_4O_3SSi$ 617.2982.

2-(4-Methyl-1,4-diazepan-1-yl)-*N*-((5-methylpyrazin-2-yl)methyl)-5-oxo-10-((triisopropylsilyl)ethynyl)-5*H*-benzo[4,5]thiazolo[3,2-*a*][1,8]naphthyridine-6-carboxamide (**5.12**)



A magnetically stirred solution of compound **5.10** (100 mg, 0.16 mmol) in dichloromethane (5 mL) was treated with (5-methylpyrazin-2-yl)methanamine (**5.11**) (40 mg g, 0.32 mmol) and DBU (670 mg, 0.49 mmol). The ensuing mixture was cooled to –5 °C then treated with aluminium trichloride granules (40 mg, 0.27 mmol) and stirring continued for 50 min. after which time the reaction mixture was treated with sodium hydroxide (15 mL of a 1:1 w/v aqueous solution) and the resulting suspension stirred for another 1 h before being filtered and the solids thus retained washed with dichloromethane. The combined filtrates were dried (Na_2SO_4), filtered then concentrated under reduced pressure and the residue so obtained subjected to flash chromatography (silica, 9:1 v/v dichloromethane/ammonia-saturated methanol) and thus affording, after concentration of the appropriate fractions (R_f = 0.5), compound **5.12** (70 mg, 61%) as a white solid, m.p. = 258-260 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.19 (t, *J* = 5.7 Hz, 1H), 9.56 (s, 1H), 8.56 (br. s, 1H), 8.50-8.40 (complex m, 2H), 7.62 (d, *J* = 8.1 Hz, 1H), 7.48 (dd, *J* = 8.1 and 1.4 Hz, 1H), 6.73 (d, *J* = 9.1 Hz, 1H), 4.83 (d, *J* = 5.6 Hz, 2H), 4.03-3.65 (complex m, 4H), 2.84 (br. s, 2H), 2.54 (m, 5H), 2.37 (s, 3H), 2.10 (s, 2H), 1.16 (s, 21H);

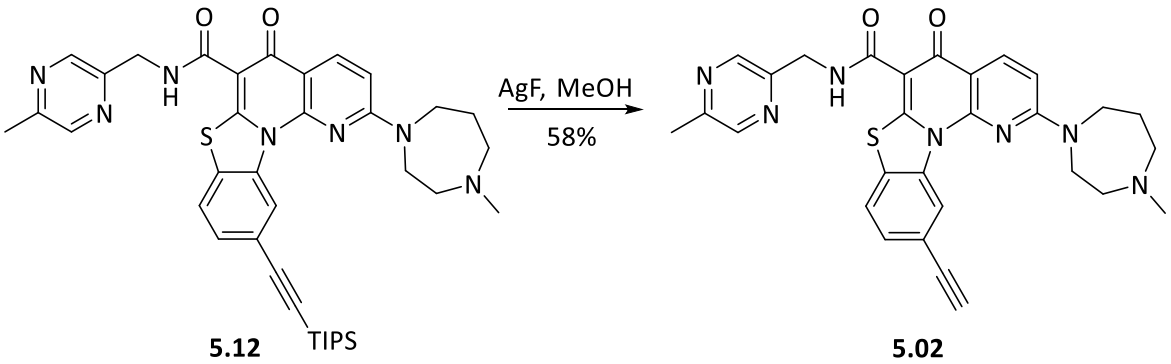
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.2, 166.5, 158.8, 158.7, 152.3, 150.5, 149.6, 143.9, 142.7, 130.3, 130.2, 129.2, 128.4, 125.4, 125.1, 121.2, 119.3, 111.9, 106.4, 105.8, 105.6, 92.6, 57.6, 57.2, 47.9, 46.9, 42.8, 27.3, 21.4, 18.9, 11.5;

IR ν_{max} 3148, 2941, 2863, 2158, 1641, 1613, 1524, 1484, 1460, 1426, 1360, 1266, 883 cm^{-1};

MS (ESI, +ve) *m/z* 857 (100%), 694 [$(M+H)^+$, 20], 579 (67);

HRMS (ESI, +ve) *m/z* 694.3350 $(M+H)^+$ 694.3359, calcd for $C_{38}H_{48}N_7O_2SSi$ 694.3359.

10-Ethynyl-2-(4-methyl-1,4-diazepan-1-yl)-*N*-((5-methylpyrazin-2-yl)methyl)-5-oxo-5*H*-benzo[4,5]thiazolo[3,2-*a*][1,8]naphthyridine-6-carboxamide (**5.02**)



5.12 **5.02**

A degassed, magnetically stirred solution of compound **5.12** (100 mg, 0.15 mmol) in methanol (3 mL), and protected from light, was treated with silver fluoride (40 mg, 0.23 mmol). The resulting mixture was stirred for 3 h at ambient temperatures then concentrated under reduced pressure and the residue so obtained subjected to flash column chromatography (silica, 4:1 v/v dichloromethane/ammonia-saturated methanol). Concentration of the appropriate fractions (R_f = 0.5) then gave compound **5.02** (40 mg, 58%) as a white, crystalline solid. m.p. = 238-240 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.19 (t, *J* = 5.6 Hz, 1H), 9.40 (d, *J* = 8.9 Hz, 1H), 8.57 (s, 1H), 8.50 (d, *J* = 9.1 Hz, 1H), 8.45 (s, 1H), 7.81 (d, *J* = 1.6 Hz, 1H), 7.54 (dd, *J* = 8.9, 1.6 Hz, 1H), 6.75 (d, *J*

= 9.1 Hz, 1H), 4.85 (d, *J* = 5.5 Hz, 2H), 3.86 (d, *J* = 41.9 Hz, 4H), 3.17 (s, 1H), 2.83 (t, *J* = 4.8 Hz, 2H), 2.63-2.59 (complex m, 2H), 2.55 (s, 3H), 2.41 (s, 3H), 2.11 (p, *J* = 6.0 Hz, 2H);

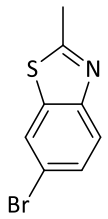
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 173.1, 166.4, 158.6, 158.4, 152.3, 150.6, 149.4, 143.9, 142.8, 137.3(4), 137.3(1), 130.9, 129.0, 123.4, 121.6, 120.0, 111.6, 106.3, 105.7, 83.4, 77.7, 57.9, 57.2, 48.0, 46.9, 42.8, 27.5, 21.4 (one signal obscured or overlapping);

IR ν_{max} 3222, 3053, 2937, 2794, 1638, 1612, 1571, 1524, 1485, 1427, 1359, 732 cm^{-1};

MS (ESI, +ve) *m/z* 538 [$(M+H)^+$, 100%], 560 [$(M+Na)^+$, 25];

HRMS *m/z* 560.1844 $(M+Na)^+$, calcd for $C_{29}H_{27}N_7NaO_2S$ 560.1845.

6-Bromo-2-methylbenzo[*d*]thiazole (**5.13**)



5.13

This compound was obtained from commercial sources as a white, crystalline solid, m.p. = 84-86 °C (lit.[25] m.p. = 87-88 °C).

^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 8.31 (br. s, 1H), 7.84 (d, *J* = 8.6 Hz, 1H), 7.61 (dd, *J* = 8.6 and 2.1 Hz, 1H), 2.79 (s, 3H);

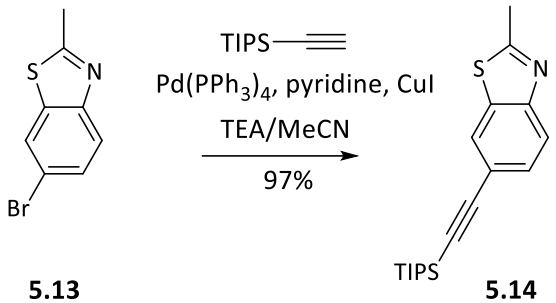
$^{13}C\{^{1}H\}$ NMR [101 MHz, $(CD_3)_2SO$] δ 168.3, 152.0, 137.3, 129.1, 124.5, 123.5, 117.3, 19.7;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (br. s, 1H), 7.79 (d, *J* = 8.6 Hz, 1H), 7.54 (dd, *J* = 8.6 and 1.7 Hz, 1H), 2.82 (s, 3H);

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 167.7, 152.4, 137.5, 129.5, 124.1, 123.7, 118.4, 20.3;

MS (ESI, +ve) *m/z* 228 and 230 [$(M+H)^+$, both 100%].

2-Methyl-6-((Triisopropylsilyl)ethynyl)benzo[*d*]thiazole (**5.14**).



5.13 **5.14**

A degassed and magnetically stirred mixture of 6-bromo-2-methylbenzo[*d*]thiazole (**5.13**) (500 mg, 2.19 mmol), $Pd(PPh_3)_4$ (130 mg, 0.11 mmol) and CuI (60 mg, 0.32 mmol) in TEA/acetonitrile (10 mL of a 1:1 v/v mixture) was treated with ethynyltriisopropylsilane (1.47 g, 6.57 mmol) and pyridine (1 mL). The resulting mixture was degassed again for 2 min then heated at 80 °C for 30 h. The cooled reaction mixture was concentrated under reduced pressure and the residue thus obtained subjected to flash column chromatography (silica gel, 95:5 v/v hexane/ethyl acetate elution) to give, after concentration of the appropriate fractions (R_f = 0.3), compound **5.14** (700 mg, 97%) as a pale-yellow, crystalline solid, m.p. = 76-78 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (br. s, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.54 (dd, *J* = 8.4 and 1.4 Hz, 1H), 2.82 (s, 3H), 1.14 (s, 21H);

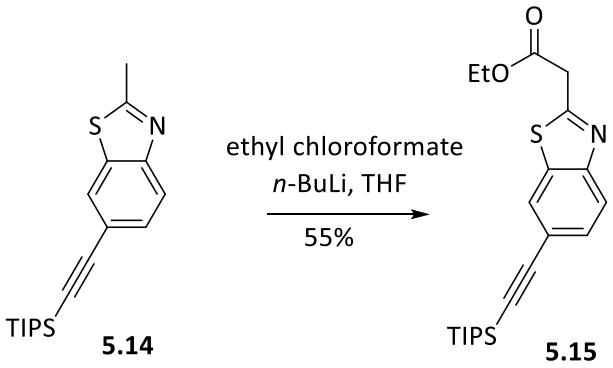
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.4, 153.1, 135.7, 130.1, 125.2, 122.2, 120.2, 106.8, 91.3, 20.3, 18.9, 11.5;

IR ν_{max} 2941, 2854, 2149, 1449, 1169, 1071, 995, 907, 882 cm^{-1};

MS (ESI, +ve) *m/z* 330 [$(M+H)^+$, 100%];

HRMS (ESI, +ve) *m/z* 330.1703 $(M+H)^+$, calcd for $C_{19}H_{28}NSSi$, 330.1706.

Ethyl 2-(6-((triisopropylsilyl)ethynyl)benzo[*d*]thiazol-2-yl)acetate (**5.15**)



A magnetically stirred solution of compound **5.14** (200 mg, 0.61 mmol) in anhydrous THF (3 mL) was cooled to –78 °C then treated with *n*-BuLi (300 mL of a 2 M solution in hexane, 0.66 mmol). The temperature was maintained at –78 °C for 4 h then ethyl chloroformate (790 mg, 0.73 mmol) was added to the reaction mixture that was then warmed to –60 °C. After 2 h, the reaction mixture was quenched by pouring it into ice/water. The separated aqueous layer was extracted with ethyl acetate (2 × 10 mL) and the combined organic phases were then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.3), compound **5.15** (130 mg, 55%) as a clear, pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 1.5 Hz, 1H), 7.91 (d, *J* = 8.5 Hz, 1H), 7.56 (dd, *J* = 8.5 and 1.5 Hz, 1H), 4.25 (d, *J* = 7.2 Hz, 2H), 4.16 (s, 2H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.14 (s, 21H);

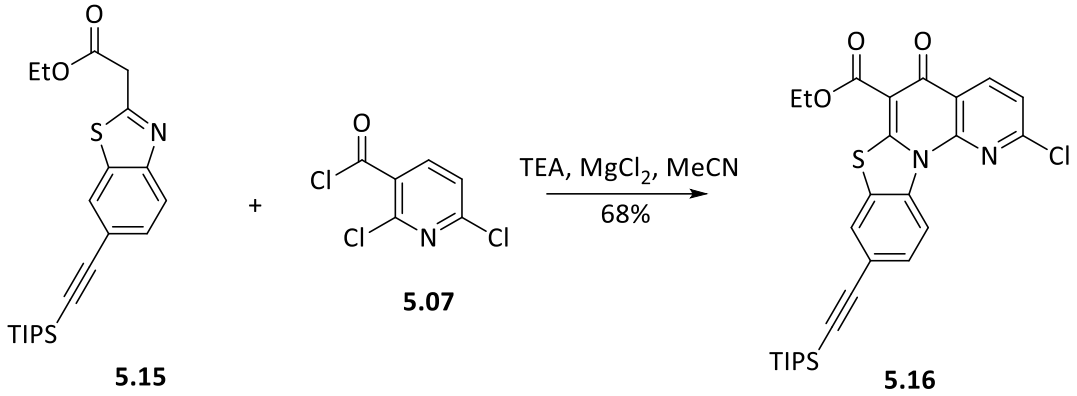
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.4, 164.1, 152.4, 135.9, 130.3, 125.3, 122.8, 120.8, 106.6, 91.8, 62.0, 40.0, 18.8, 14.3, 11.5;

IR ν_{max} 2941, 2854, 2156,1742, 1449, 1169, 1071, 995, 907, 882 cm^{-1};

MS (ESI, +ve) *m/z* 465 (100%), 424 [$(M+Na)^+$, 50];

HRMS (ESI, +ve) *m/z* 424.1601 $(M+Na)^+$, calcd for $C_{22}H_{31}NNaO_2SSi$ 424.1603.

Ethyl 2-Chloro-5-oxo-9-((triisopropylsilyl)ethynyl)-5*H*-benzo[4,5]thiazolo[3,2-*a*][1,8]naphthyridine-6-carboxylate (**5.16**)



A magnetically stirred solution of compound **5.15** (320 mg, 0.79 mmol) in acetonitrile (3 mL) maintained at 0 °C was treated, in portions, with $MgCl_2$ (110 mg, 1.18 mmol). The resulting suspension was cooled below 5 °C then a solution of dichloronicotinyl chloride (**5.07**) (170 mg, 0.83 mmol) in acetonitrile (1 mL) was added to the reaction mixture over a period of 5 min. The mixture thus obtained was cooled to between –10 to 0 °C before being treated with TEA (120 µL, 0.87 mmol). After stirring for 1 h the cooling bath was removed, and water added (2 × 1 mL aliquots at 0 and 10 min) to the reaction mixture that was then concentrated under a stream of nitrogen and the residue extracted with dichloromethane (2 × 10 mL). The combined organic phases were concentrated under reduced pressure and the residue was dissolved in acetonitrile (3 mL). The resulting solution treated with triethylamine (230 µL, 1.66 mmol) and the suspension so formed was heated under reflux for 2 h then cooled and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 7:3 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.2), compound **5.16** (270 mg, 64%) as an off-white, crystalline solid, m.p. = 223-225 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (d, *J* = 9.0 Hz, 1H), 8.79 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 1.5 Hz, 1H), 7.65 (dd, *J* = 9.0 and 1.5 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 4.49 (q, *J* = 7.1 Hz, 2H), 1.48 (t, *J* = 7.1 Hz, 3H), 1.16 (br. s, 21H);

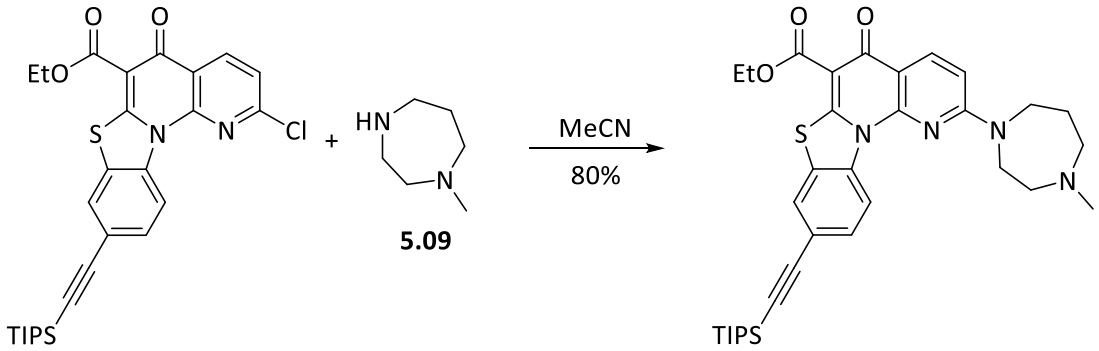
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.8, 167.1, 163.0, 152.8, 148.0, 140.3, 136.8, 131.6, 128.6, 124.9, 123.1, 122.0, 121.5, 119.9, 106.4, 105.3, 93.4, 62.0, 18.8, 14.6, 11.4;

IR ν_{max} 2941, 2854, 2157, 1662, 1640, 1588 1492, 1413, 1414, 1127, 881 cm^{-1};

MS (ESI, +ve) *m/z* 563 and 561 [$(M+Na)^+$, 30 and 100%];

HRMS (ESI, +ve) *m/z* 561.1404 $(M+Na)^+$, calcd for $C_{28}H_{31}{}^{35}ClN_2O_3SSiNa$ 561.1405.

Ethyl 2-(4-Methyl-1,4-diazepan-1-yl)-5-oxo-9-((triisopropylsilyl)ethynyl)-5*H*-benzo-[4,5]thiazolo[3,2-*a*][1,8]naphthyridine-6-carboxylate (**5.17**)



5.16 **5.09** **5.17**

A magnetically stirred suspension of compound **5.16** (270 mg, 0.51 mmol) in acetonitrile (5 mL) was treated with *N*-methyl-1,4-diazepane (**5.09**) (120 mg, 1.01 mmol) and the ensuing mixture was heated under reflux for 4 h. The cooled reaction mixture was concentrated under reduced pressure and the residue thus obtained subjected to flash column chromatography (silica, 9:1 v/v dichloromethane/ammonia-saturated methanol) and thus affording, after concentration of the appropriate fractions (R_f = 0.4), compound **5.17** (250 mg, 80%) as a white, crystalline solid, m.p. = 213-215 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (d, *J* = 8.9 Hz, 1H), 8.49 (d, *J* = 8.9 Hz, 1H), 7.75 (d, *J* = 1.8 Hz, 1H), 7.53 (dd, *J* = 8.9 and 1.8 Hz, 1H), 6.67 (d, *J* = 8.9 Hz, 1H), 4.48 (q, *J* = 7.1 Hz, 2H), 3.95-3.66 (complex m, 4H), 2.81 (br. s, 2H), 2.59 (m, 2H), 2.40 (s, 3H), 2.10 (m, 2H), 1.48 (t, *J* = 7.1 Hz, 3H), 1.15 (s, 21H);

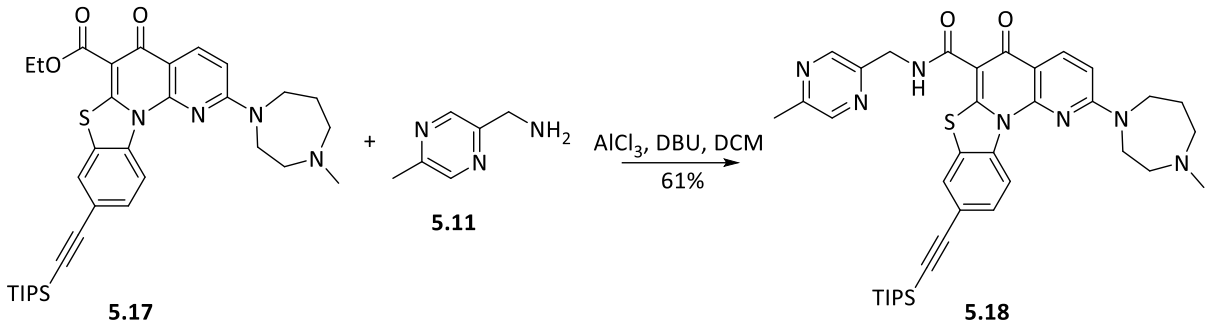
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.6, 167.8, 161.1, 158.5, 149.5, 138.1, 137.6, 130.3, 128.9, 124.9, 120.9, 119.3, 113.0, 106.1, 105.6, 105.4, 92.5, 61.5, 57.7, 57.3, 48.1, 47.8, 47.0, 27.5, 18.8, 14.6, 11.4;

IR ν_{max} 3482, 2941, 2854, 2157, 1662, 1609, 1483, 1422, 1394 cm^{-1};

MS (ESI, +ve) *m/z* 617 [$(M+H)^+$, 100%];

HRMS (ESI, +ve) *m/z* 617.2982 $(M+H)^+$, calcd for $C_{34}H_{45}N_4O_3SSi$ 617.2988.

2-(4-Methyl-1,4-diazepan-1-yl)-*N*-((5-methylpyrazin-2-yl)methyl)-5-oxo-9-((triisopropylsilyl)ethynyl)-5*H*-benzo[4,5]thiazolo[3,2-*a*][1,8]naphthyridine-6-carboxamide (**5.18**)



A magnetically stirred solution of compound **5.17** (100 mg, 0.16 mmol) in dichloromethane (5 mL) was treated with (5-methylpyrazin-2-yl)methanamine (**5.11**) (40 mg, 0.32 mmol) and DBU (670 mg, 0.49 mmol). The ensuing mixture was cooled to –5 °C, treated with aluminium trichloride granules (40 mg, 0.27 mmol) and stirring then continued for 50 min. after which time the reaction mixture was treated with sodium hydroxide (15 mL of a 1:1 w/v aqueous solution). The resulting suspension stirred for another 1 h then filtered and the solids thus retained washed with dichloromethane. The combined filtrates were dried (Na_2SO_4), filtered then concentrated under reduced pressure and the residue so obtained subjected to flash chromatography (silica, 9:1 v/v dichloromethane/ammonia-saturated methanol) and thus affording, after concentration of the appropriate fractions (R_f = 0.5), compound **5.18** (70 mg, 61%) as a white, crystalline solid, m.p. = 251-253 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.18 (t, *J* = 5.7 Hz, 1H), 9.33 (d, *J* = 8.9 Hz, 1H), 8.56 (s, 1H), 8.46-8.34 (complex m, 2H), 7.76 (d, *J* = 1.4 Hz, 1H), 7.52 (dd, *J* = 8.9 and 1.4 Hz, 1H), 6.66 (d, *J* = 9.1 Hz, 1H), 4.83 (d, *J* = 5.7 Hz, 2H), 3.87 (br. s, 2H), 3.76 (br. s, 2H), 2.80 (m, 2H), 2.60-2.55 (complex m, 2H), 2.53 (s, 3H), 2.39 (s, 3H), 2.07 (m, 2H), 1.15 (br. s, 21H);

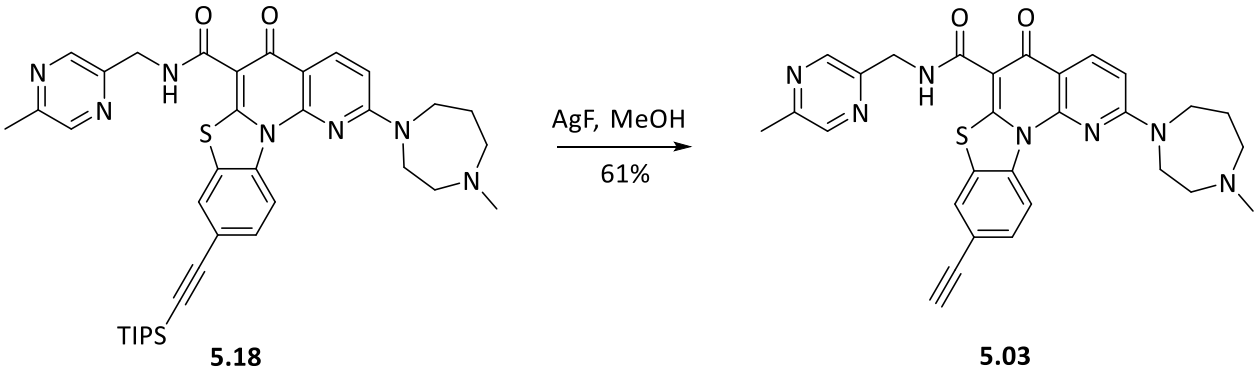
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.2, 166.5, 158.7, 158.6, 152.2, 150.6, 149.5, 143.9, 142.7, 137.5, 137.0, 130.3, 130.1, 125.1, 121.1, 119.3, 111.8, 106.3, 105.8, 105.7, 92.6, 57.7, 57.3, 48.2, 47.9, 46.9, 42.8, 27.4, 21.4, 18.9, 11.5;

IR ν_{max} 3157, 2941, 2853, 2157, 1643, 1613, 1526, 1485, 1427, 1351 cm^{-1};

MS (ESI, +ve) *m/z* 694 [$(M+H)^+$, 100%], 716 [$(M+Na)^+$, 75];

HRMS (ESI, +ve) *m/z* 694.3351 $(M+H)^+$ 694.3351, calcd for $C_{38}H_{48}N_7O_2SSi$ 694.3354.

9-Ethynyl-2-(4-methyl-1,4-diazepan-1-yl)-*N*-((5-methylpyrazin-2-yl)methyl)-5-oxo-5*H*-benzo[4,5]thiazolo[3,2-*a*][1,8]naphthyridine-6-carboxamide (**5.03**)



5.18 **5.03**

A degassed, magnetically stirred solution of compound **5.18** (100 mg, 0.15 mmol) in methanol (3 mL), and protected from light, was treated with silver fluoride (40 mg, 0.23 mmol). The resulting mixture was stirred for 3 h at ambient temperatures then concentrated under reduced pressure and the residue so obtained subjected to flash column chromatography (silica, 4:1 v/v dichloromethane/ammonia-saturated methanol). Concentration of the appropriate fractions (R_f = 0.4) then gave compound **5.03** (50 mg, 61%) as a white, crystalline solid, m.p. 240-242 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.18 (t, *J* = 5.7 Hz, 1H), 9.57 (s, 1H), 8.57 (s, 1H), 8.43 (d, *J* = 8.3 Hz, 2H), 7.61 (d, *J* = 8.1 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 6.68 (d, *J* = 9.1 Hz, 1H), 4.83 (d, *J* = 5.6 Hz, 2H), 3.81 (d, *J* = 69.3 Hz, 4H), 2.87 (s, 2H), 2.57 (d, *J* = 24.8 Hz, 5H), 2.39 (s, 3H), 2.11 (p, *J* = 5.9 Hz, 2H);

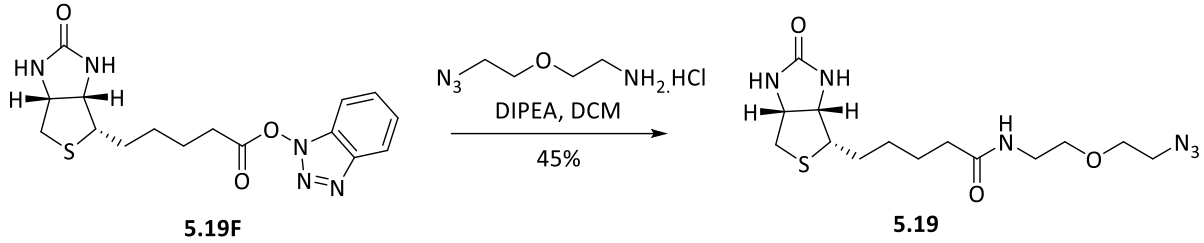
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.2, 166.5, 158.7, 152.3, 150.5, 149.6, 143.9, 142.7, 137.5, 137.4, 130.4, 130.0, 125.3, 119.7, 119.4, 111.8, 106.4, 105.8, 82.4, 78.7, 57.7, 57.3, 48.2, 47.9, 47.0, 42.8, 27.5, 21.4 (one signal obscured or overelapping);

IR ν_{max} 3218, 2938, 2850, 2788, 2241, 1638, 1526, 1485, 1427, 1360 cm^{-1};

MS (ESI, +ve) *m/z* 538 [$(M+H)^+$, 100%];

HRMS *m/z* 538.2025 $(M+H)^+$, calcd for $C_{29}H_{28}N_7O_2S$ 538.2025.

***N*-(2-(2-Azidoethoxy)ethyl)-5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)pentanamide** (**5.19**)



5.19F **5.19**

Step i: A magnetically stirred solution of commercially-derived *tert*-butyl (2-(2-azidoethoxy)ethyl)carbamate (3.40 g, 14.76 mmol) in 1,4-dioxane (20 mL) maintained at ambient temperatures was treated with hydrochloric acid (22 mL of a 4 M solution in 1,4-dioxane). After 2 h the solvent was removed under reduced pressure and the solid residue washed with diethyl ether and then dried under reduced pressure to afford the HCl salt of 2-(2-azidoethoxy)ethan-1-amine (2.18 g, 89%) as an off-white solid. This material was used, without further purification, in step ii of the reaction sequence as detailed below.

Step ii: A magnetically stirred suspension of biotin (3.00 g, 12.28 mmol) in DMF (15 mL) was treated with di-*iso*-propylethylamine (DIPEA) (4.30 mL, 24.6 mmol) and 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate (TBTU) (4.73 g, 14.7 mmol). The initially formed suspension dissolved then a white precipitate slowly formed. After 4 h, the reaction mixture was filtered and the white solid so obtained washed with dichloromethane then dried to give an activated biotin derivative **5.19F** (3.95 g, 89%). A magnetically stirred suspension of this material (2.71 g, 7.50 mmol) and the HCl salt of 2-(2-azidoethoxy)ethan-1-amine (2.00 g, 13.08 mmol) (obtained from step i) in dichloromethane (50 mL) was treated with DIPEA (5.2 mL, 30.0 mmol) and the ensuing mixture stirred at ambient temperatures for 16 h then washed with $NaHCO_3$ (1 × 50 mL of a saturated aqueous) and brine (1 × 50 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:4 v/v methanol/ethyl acetate elution) and concentration of the appropriate fractions (R_f = 0.3) gave azide **5.19**[26] (1.20 g, 45%) as a white, crystalline solid, m.p. = 109-111 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (s, 1H), 6.56 (t, *J* = 5.7 Hz, 1H), 5.77 (s, 1H), 4.49 (m, 1H), 4.30 (m, 1H), 3.65 (m, 2H), 3.57 (m, 2H), 3.43 (m, 2H), 3.36 (m, 2H), 3.13 (m, 1H), 2.89 (dd, *J* = 12.8

and 4.8 Hz, 1H), 2.72 (d, *J* = 12.8 Hz, 1H), 2.21 (t, *J* = 7.5 Hz, 2H), 1.65-1.76 (complex m, 4H), 1.42 (m, 2H);

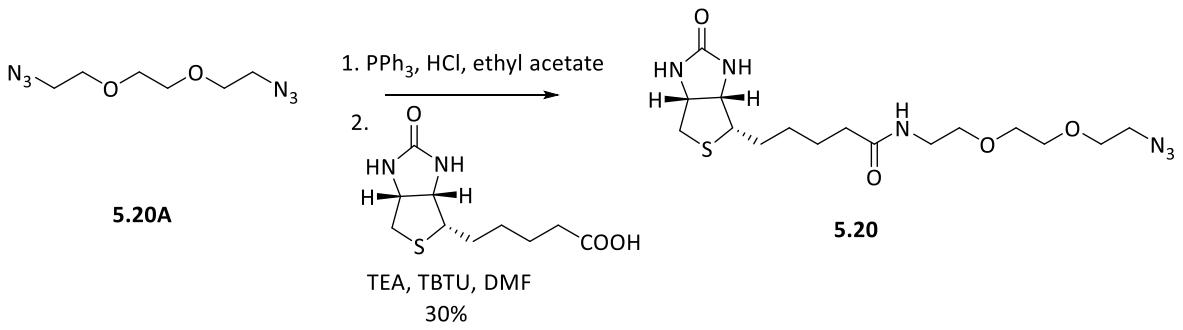
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 173.5, 164.3, 70.0(1), 69.9(7), 61.9, 60.3, 55.8, 50.7, 40.7, 39.1, 36.1, 28.4, 28.2, 25.7;

IR ν_{max} 2982, 2746, 2099, 1733, 1623, 1541, 1439, 1368, 1330, 1308, 1271, 1191, 1159, 1029, 741 cm^{-1};

MS (ESI, +ve) *m/z* 379 [$(M+Na)^+$, 100%], 357 [$(M+H)^+$, 70%];

HRMS (ESI, +ve) *m/z* 357.1702 $(M+H)^+$, calcd for $C_{14}H_{25}N_6O_3S$ 357.1703.

***N*-(2-(2-(2-Azidoethoxy)ethoxy)ethyl)-5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)pentanamide** (**5.20**)



Step i: A magnetically stirred mixture of commercially-derived 1,2-bis(2-azidoethoxy)ethane (**5.20A**) (2.60 g, 12.99 mmol) and hydrochloric acid (14 mL of a 1M aqueous solution) in ethyl acetate (60 mL) was treated with triphenylphosphine (3.68 g, 14.02 mmol). The ensuing mixture was stirred under nitrogen for 16 h then treated with water (10 mL) and the separated aqueous phase was washed with ethyl acetate (5 × 20 mL). The aqueous phase was basified (to pH 13) using NaOH (45 mL of a 6 M aqueous solution) before being extracted with dichloromethane (5 × 20 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford 2-(2-(2-azidoethoxy)ethoxy)ethan-1-amine) (670 mg, 60%) as a clear, colourless oil. This material was used, without purification, in the next (step ii) of the reaction sequence as detailed immediately below.

Step ii: A suspension of biotin (670 mg, 2.74 mmol) in DMF (10 mL) was treated with TEA (1.5 mL, 11.0 mmol) and TBTU (1.32 g, 4.11 mmol). The resulting suspension dissolved and then a

white precipitate began to form. After 2 h, the reaction mixture was treated with 2-(2-(2-azidoethoxy)ethoxy)ethan-1-amine) (570 mg, 3.29 mmol) in DMF (5 mL) and the ensuing mixture was stirred at ambient temperatures overnight before being concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 4:1 v/v methanol/ethyl acetate) and concentration of the appropriate fractions (R_f = 0.2) gave compound **5.20**[29] (330 mg, 30%) as a white, crystalline solid, m.p. = 118-120 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (s, 1H), 6.70 (t, *J* = 5.6 Hz, 1H), 5.96 (s, 1H), 4.47 (m, 1H), 4.27 (m, 1H), 3.68-3.57 (complex m, 6H), 3.54 (t, *J* = 5.1 Hz, 2H), 3.42-3.35 (complex m, 4H), 3.11 (m, 1H), 2.87 (dd, *J* = 12.8 and 4.8 Hz, 1H), 2.71 (d, *J* = 12.8 Hz, 1H), 2.19 (t, *J* = 7.5 Hz, 2H), 1.74-1.59 (complex m, 4H), 1.40 (m, 2H);

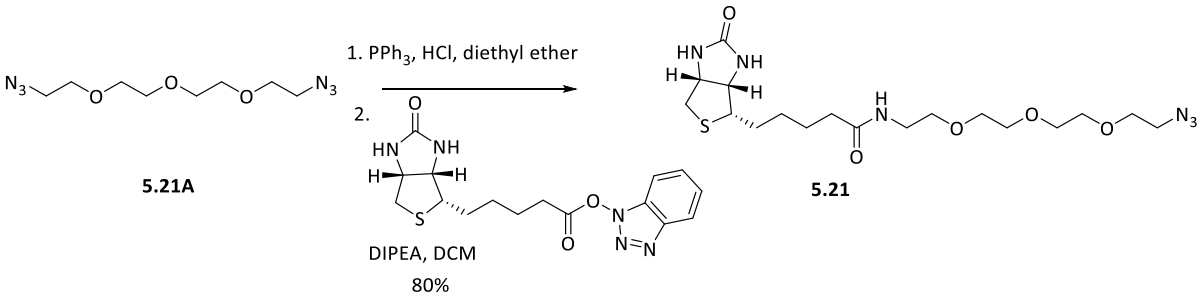
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.4, 164.4, 70.4, 70.1(4), 70.1(1), 70.0, 61.9, 60.3, 55.8, 50.7, 40.5, 39.1, 36.1, 28.4, 28.2, 25.7;

IR ν_{max} 3274, 2928, 2860, 2102, 1705, 1643, 1553, 1460, 1281, 1119 cm^{-1};

MS (ESI, +ve) *m/z* 423 [(M+Na), 100%], 401 [(M+H), 50];

HRMS (ESI, +ve) *m/z* 401.1962 $(M+H)^+$, calcd for $C_{16}H_{29}N_6O_4S$ 401.1966.

***N*-(2-(2-(2-(2-Azidoethoxy)ethoxy)ethoxy)ethyl)-5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)pentanamide** (**5.21**)



Step i: A magnetically stirred solution of tetraethylene glycol (10.0 g, 51.5 mmol) in dichloromethane (100 mL) maintained at 0 °C was treated with TEA (21.6 mL, 154.46 mmol) then, dropwise, with methanesulfonyl chloride (11.9 mL, 154.5 mmol). After 0.5 h, the reaction mixture was allowed to warm to ambient temperatures then stirred for a further 16 h before being quenched with hydrochloric acid (50 mL of a 1M saturated aqueous solution), washed with $NaHCO_3$ (1 × 50 mL of a saturated aqueous solution) and brine (1 × 50 mL) then

dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue thus obtained was dissolved in acetone/water (175 mL of a 5:2 v/v mixture) and the resulting solution treated with sodium azide (10.0 g, 154.5 mmol) then heated at 70 °C for 16 h. The cooled reaction mixture was concentrated under a stream of nitrogen and the residue so formed diluted with water (50 mL) and the resulting mixture extracted with ethyl acetate (3 × 100 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure and the residue thus obtained subjected to flash chromatography (silica, 50:50 v/v diethyl ether/hexane elution). Concentration of the appropriate fractions (R_f = 0.2) afforded **5.21A**[32] (11.5 g, 91%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72-3.61 (complex m, 12H), 3.38 (t, *J* = 5.0 Hz, 4H);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 70.8, 70.2, 50.8 (one signal obscured or overlapping);

IR ν_{max} 2870, 2100, 1443, 1345, 1290, 1120, 936, 852 cm^{-1}.

Step ii: A magnetically stirred mixture of **5.21A** (5.20 g, 21.3 mmol) and hydrochloric acid (60 mL of a 1 M aqueous solution) in diethyl ether (100 mL) was treated with triphenylphosphine (5.58 g, 21.3 mmol). The ensuing mixture was stirred under nitrogen for 16 h then water (40 mL) was added, and the separated aqueous layer washed with ethyl acetate (5 × 50 mL). The aqueous phase was basified (to pH 13) using NaOH (6 M aqueous solution) before being extracted with dichloromethane (5 × 20 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure to provide 2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethan-1-amine[28] (27.5 g, 59%) as a clear, colourless oil. This was used without further purification in step iii as detailed immediately below.

Step iii: A suspension of 2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethan-1-amine (500 mg, 2.29 mmol) and TBTU-activated biotin (1.00 g, 2.77 mmol) (activation achieved in the same way as detailed in procedure for the preparation of compound **5.20**) in dichloromethane (20 mL) was treated with DIPEA (1.6 mL, 9.2 mmol). The reaction mixture thus obtained was stirred at ambient temperatures for 16 h then washed with $NaHCO_3$ (1 × 20 mL of a saturated aqueous solution) and brine (1 × 20 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue so produced was subjected to flash chromatography (silica, 1:9 v/v methanol/dichloromethane elution) and concentration of the appropriate fractions (R_f = 0.2) gave compound **5.21**[31](820 mg, 80%) as a white, crystalline solid, m.p. = 121-123 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (s, 1H), 6.81 (t, *J* = 5.6 Hz, 1H), 6.00 (s, 1H), 4.46 (m, 1H), 4.26 (m, 1H), 3.64-3.59 (complex m, 10H), 3.53 (t, *J* = 5.0 Hz, 2H), 3.40-3.34 (complex m, 4H), 3.09 (m, 1H), 2.85 (dd, *J* = 12.8 and 4.8 Hz, 1H), 2.70 (d, *J* = 12.8 Hz, 1H), 2.18 (t, *J* = 7.5 Hz, 2H), 1.75-1.60 (complex m, 4H), 1.39 (m, 2H);

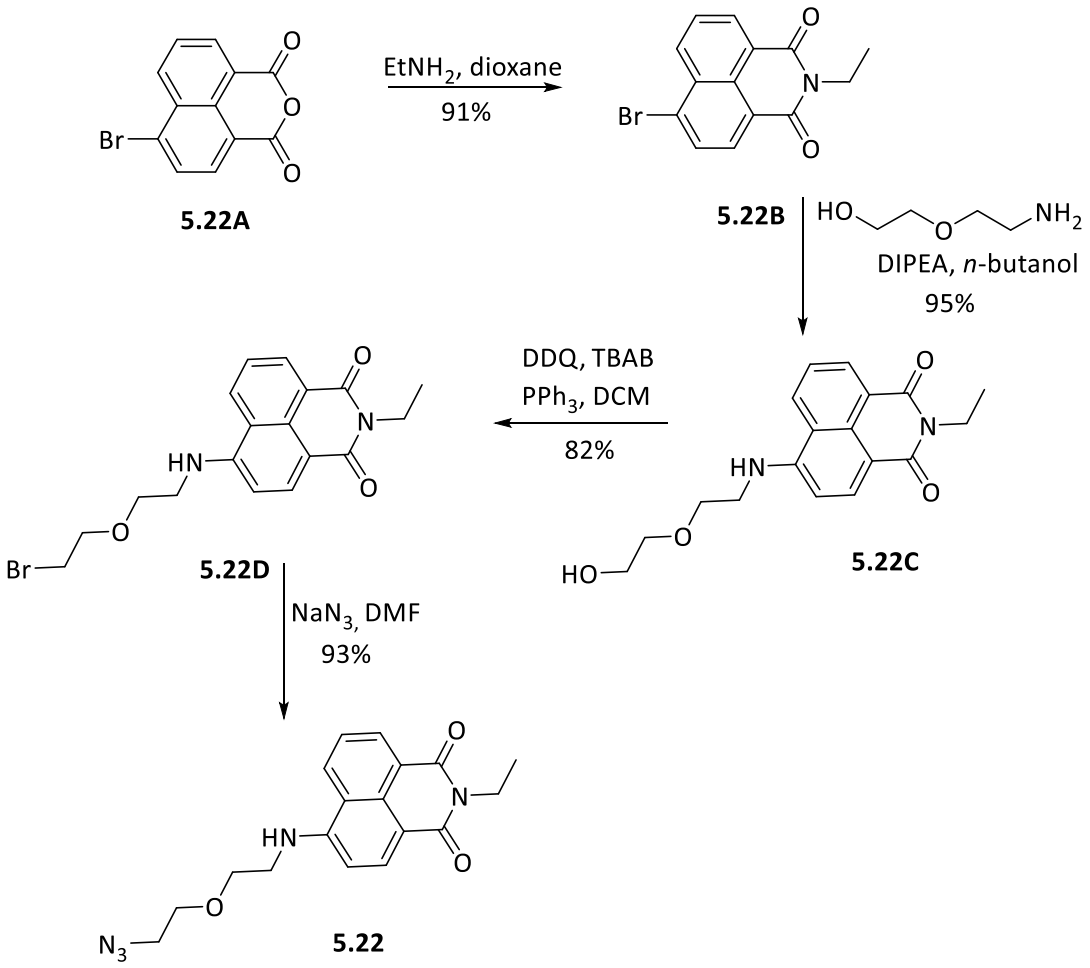
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.4, 164.4, 70.7, 70.5, 70.1(0), 70.0(6), 70.0, 61.8, 60.3, 55.8, 50.7, 40.6, 39.2, 36.1, 28.4, 28.2, 25.7 (one signal obscured or overlapping);

IR ν_{max} 3256, 2928, 2851, 2101, 1702, 1642, 1552, 1450, 1424, 1303, 1280, 1243, 1111, 857 cm^{-1};

MS (ESI, +ve) *m/z* 467 [$(M+Na)^+$, 100%], 445 [$(M+H)^+$, 5];

HRMS (ESI, +ve) *m/z* 445.2223 $(M+H)^+$, calcd for $C_{18}H_{33}N_6O_5S$ 445.2228.

6-((2-(2-Azidoethoxy)ethyl)amino)-2-ethyl-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**5.22**)



Step i: A magnetically stirred solution of 4-bromo-1,8-napthalic anhydride (**5.22A**) (2.00 g, 7.22 mmol) in 1,4-dioxane (100 mL) was treated with ethylamine (1.2 mL of a 70% aqueous solution, 14.44 mmol). The ensuing mixture was heated under reflux for 8 h then the cooled reaction mixture was concentrated under reduced pressure and the residue thus obtained subjected to flash chromatography (silica, 1:1 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions (R_f = 0.5) gave 6-bromo-2-ethyl-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**5.22B**) (2.00 g, 91%) as a lime-coloured, crystalline solid, m.p. = 162-164 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, *J* = 7.3 Hz, 1H), 8.57 (d, *J* = 8.5 Hz, 1H), 8.42 (d, *J* = 7.9 Hz, 1H), 8.04 (d, *J* = 7.9 Hz, 1H), 7.85 (m, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 163.6(4), 163.6(1), 133.4, 132.1, 131.3, 131.2, 130.8, 130.3, 129.2, 128.2, 123.4, 122.5, 35.8, 13.5;

IR ν_{max} 2979, 1693, 1652, 1660, 1587, 1567, 1456, 1434, 1371, 1339, 1242, 1201, 1060, 961, 775 cm^{-1};

MS (ESI, +ve) *m/z* 328 and 326 [$(M+Na)^+$, both 95%], 306 and 304 [$(M+H)^+$, both 100];

HRMS (ESI, +ve) *m/z* 303.9975 $(M+H)^+$, calcd for $C_{14}H_{11}{}^{79}BrNO_2$ 303.9973.

Step ii: Four separate microwave vessels were each charged with a stirrer bar, compound **5.22B** (100 mg, 0.33 mmol), 2-(2-aminoethoxy)ethanol (330 mL, 3.28 mmol), DIPEA (290 mL, 1.64 mmol) and *n*-butanol (1.5 mL). The resulting mixture was subjected to microwave irradiation at 120 °C for 4 h. The four cooled reaction mixtures were combined then concentrated under reduced pressure the residue thus obtained subjected to flash chromatography (silica, 1:9 v/v methanol/ethyl acetate elution). Concentration of the appropriate fractions (R_f = 0.4) afforded 2-ethyl-6-((2-(2-hydroxyethoxy)ethyl)amino)-1*H*-benzo[*de*]isoquinoline-1,3-(2*H*)-dione (**5.22B**) (410 mg, 95%) as a yellow, crystalline solid, m.p. = 187-189 °C.

^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 8.67 (d, *J* = 8.4 Hz, 1H), 8.42 (d, *J* = 7.3 Hz, 1H), 8.25 (d, *J* = 8.5 Hz, 1H), 7.72 (t, *J* = 5.6 Hz, 1H), 7.67 (m, 1H), 6.82 (d, *J* = 8.5 Hz, 1H), 4.64 (t, *J* = 5.0 Hz, 1H), 4.04 (q, *J* = 7.0 Hz, 2H), 3.73 (t, *J* = 5.8 Hz, 2H), 3.56 (m, 2H), 3.51 (m, 4H), 1.17 (t, *J* = 7.0 Hz, 3H);

^{13}C{^{1}H} NMR [101 MHz, $(CD_3)_2SO$] δ 163.5, 162.7, 150.6, 134.1, 130.6, 129.3, 128.5, 124.3, 121.9, 120.1, 107.9, 103.9, 72.3, 68.1, 60.2, 42.8, 34.3, 13.3;

IR ν_{max} 3413, 3375, 1984, 2908, 1678, 1628, 1611, 1586, 1471, 1428, 1371, 1344, 1249, 1236, 1124, 1065, 898, 774 cm^{-1};

MS (ESI, +ve) *m/z* 679 [$(2M+Na)^+$, 50%], 351 [$(M+Na)^+$, 100], 329 [$(M+H)^+$, 40];

HRMS (ESI, +ve) *m/z* 351.1306 $(M+H)^+$, calcd for $C_{18}H_{21}N_2O_4$ 351.1315.

Step iii: Following the procedure developed by Firouzabadi,[32] a magnetically stirred solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (300 mg, 1.34 mmol) and triphenylphosphine (350 mg, 1.34 mmol) in dichloromethane (20 mL) maintained at ambient temperatures was treated with tetra-*n*-butylammonium bromide (TBAB) (430 mg, 1.34 mmol). After 5 min, compound **5.22C** (400 mg, 1.22 mmol) was added to the reaction mixture. After 16 h, the reaction mixture was concentrated under reduced pressure and residue thus obtained subjected to flash chromatography (silica, 1:9 v/v ethyl acetate/dichloromethane elution). Concentration of the appropriate fractions (R_f = 0.3) afforded 6-((2-(2-bromoethoxy)ethyl)amino)-2-ethyl-1*H*-benzo[*de*]isoquinoline-1,3(2*H*) -dione (**5.22D**) (390 mg, 82%) as a yellow, crystalline solid, m.p. = 160-162 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 7.3 Hz, 1H), 8.43 (d, *J* = 8.3 Hz, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 7.59 (m, 1H), 6.65 (d, *J* = 8.4 Hz, 1H), 5.75 (br. s, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 3.90 (m, 4H), 3.57 (m, 4H), 1.31 (t, *J* = 7.0 Hz, 3H);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 164.6, 164.0, 149.4, 134.3, 131.2, 129.8, 126.3, 124.9, 123.2, 120.6, 111.0, 104.5, 70.8, 68.6, 43.0, 35.3, 31.3, 13.6;

IR ν_{max} 3385, 2980, 2933, 2861, 1671, 1631, 1572, 1544, 1445, 1428, 1385, 1364, 1344, 1285, 1237, 1121, 1106, 1054, 769 cm^{-1};

MS (ESI, +ve) *m/z* 415 and 413 [$(M+Na)^+$, both 25%], 393 and 391 [(M+H)+, both 100];

HRMS (ESI, +ve) *m/z* 393.0640 $(M+H)^+$, calcd for $C_{18}H_{20}{}^{81}BrN_2O_3$ 393.0631.

Step iv: A magnetically stirred solution of compound **5.22D** (390 mg, 1.00 mmol) in DMF (10 mL) was treated with sodium azide (130 mg, 2.00 mmol). The resulting mixture was heated at 60 °C for 4 h before being cooled and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:2 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) gave compound **5.22** (330 mg, 93%) as a yellow, crystalline solid, m.p. = 144-146 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 7.3 Hz, 1H), 8.44 (d, *J* = 8.3 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.59 (m, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 5.72 (br. s, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.88 (m, 2H), 3.77 (m, 2H), 3.59 (m, 2H), 3.45 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H);

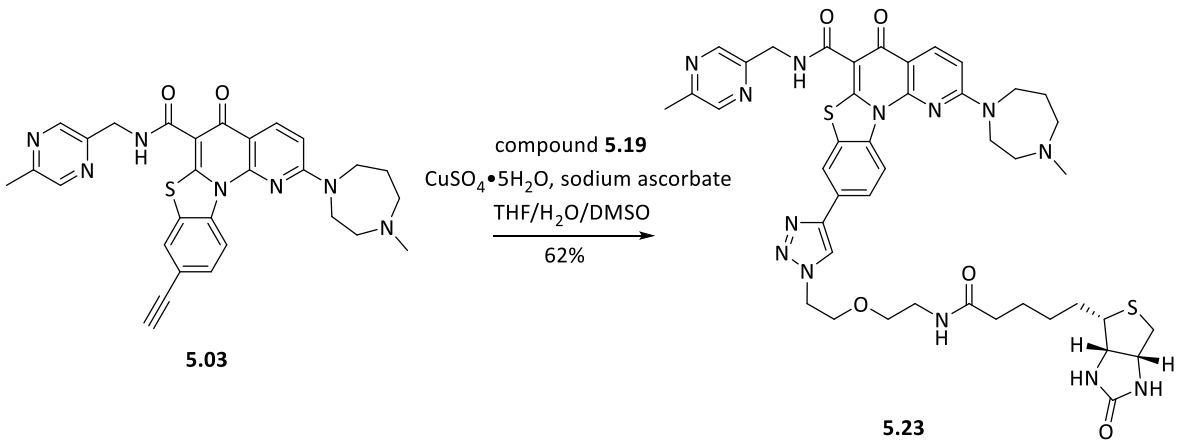
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 164.6, 164.1, 149.4, 134.3, 131.2, 129.8, 126.3, 124.9, 123.2, 120.6, 111.0, 104.5, 70.4, 68.9, 50.8, 43.2, 35.3, 13.6;

IR ν_{max} 3379, 2975, 2931, 2869, 2114, 1677, 1637, 1573, 1544, 1432, 1390, 1363, 1346, 1299, 1248, 1126, 1097, 1064, 915, 878, 769, 758 cm^{-1};

MS (ESI, +ve) *m/z* 729 [$(2M+Na)^+$, 100%], 376 [$(M+Na)^+$, 90], 354 [$(M+H)^+$, 35];

HRMS (ESI, +ve) *m/z* 376.1369 $(M+Na)^+$, calcd for $C_{18}H_{19}N_5NaO_3$ 376.1380.

2-(4-Methyl-1,4-diazepan-1-yl)-*N*-((5-methylpyrazin-2-yl)methyl)-5-oxo-9-(1-(2-(2-(5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)pentanamido)ethoxy)eth-yl)-1*H*-1,2,3-triazol-4-yl)-5*H*-benzo[4,5]thiazolo[3,2-*a*][1,8]naphthyridine-6-carboxamide (**5.23**)



5.03 **5.23**

A magnetically stirred solution of alkyne **5.03** (30 mg, 0.06 mmol) and azide **5.19** (20 mg, 0.06 mmol) in THF/H_2O/DMSO (2 mL of a 10:5:1 v/v/v mixture) maintained at ambient temperatures was treated with sodium ascorbate (10 mg, 0.01 mmol) and $CuSO_4$•$5H_2O$ (10 mg, 0.02 mmol). After 16 h the reaction mixture was concentrated under a stream of nitrogen and the residue thus obtained subjected to flash column chromatography (silica, 9:1 v/v dichloromethane/ammonia-saturated methanol elution). Concentration of the appropriate fractions (R_f = 0.3) gave compound **5.23** (30 mg, 62%) as a light-yellow, crystalline solid, m.p. = 254-256 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.23 (t, *J* = 5.6 Hz, 1H), 9.20 (d, *J* = 9.0 Hz, 1H), 8.58 (br. s, 1H), 8.45 (br. s, 1H), 8.35 (d, *J* = 9.0 Hz, 1H), 8.09 (br. s, 1H), 8.02 (br. s, 1H), 7.74 (d, *J* = 9.0 Hz, 1H), 6.78 (m 1H), 6.64 (d, *J* = 9.0 Hz, 1H), 6.27 (br. s, 1H), 5.49 (br. s, 1H), 4.80 (br. s, 2H), 4.62 (m, 2H), 4.44 (m, 1H), 4.24 (m, 1H), 3.94 (m, 2H), 3.89-3.64 (complex m, 3H), 3.60 (m, 2H), 3.44 (m, 2H), 3.04 (m, 1H), 2.82 (m, 2H), 2.68 (m, 1H), 2.56 (s, 3H), 2.40 (s, 3H), 2.25-1.75 (complex m, 9H), 1.65-1.54 (complex m, 3H), 1.29 (m, 2H);

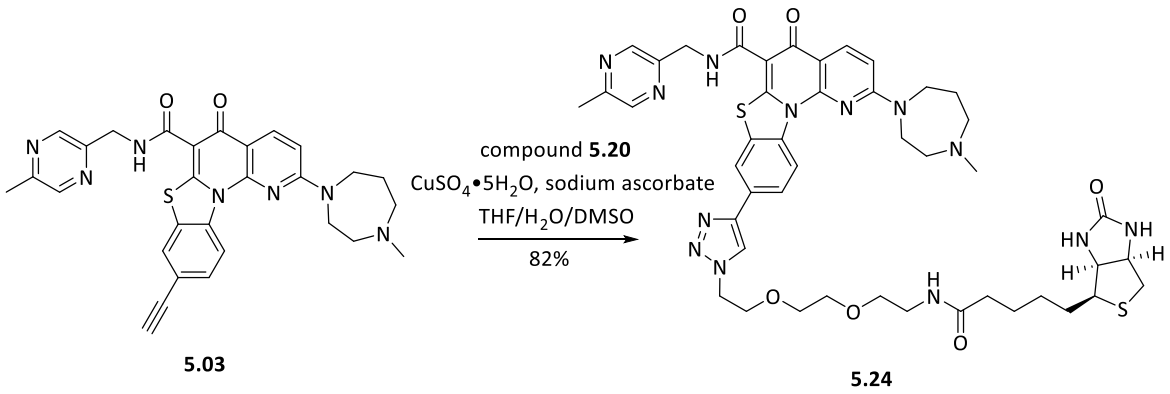
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.6, 173.0, 166.5, 163.9, 158.5, 158.3, 152.4, 150.6, 149.3, 146.3, 143.9, 142.8, 136.8, 130.5, 128.2, 123.6, 121.7, 119.8, 119.3, 111.6, 106.3, 105.4, 70.1, 68.9, 61.9, 60.2, 57.6, 57.2, 55.8, 50.5, 47.9, 46.9, 42.8, 41.1, 40.7, 39.1, 35.9, 28.2, 28.1, 27.3, 25.7, 21.4 (one signal obscured or overlapping);

IR ν_{max} 3267, 2927, 1696, 1638, 1554, 1523, 1485, 1429, 1351, 1254, 905 cm^{-1};

MS (ESI, +ve) *m/z* 894 [$(M+H)^+$, 100%];

HRMS (ESI, +ve) *m/z* 894.3635 $[M+H]^+$, calcd. for $C_{43}H_{52}N_{13}O_5S_2$ 894.3656.

2-(4-Methyl-1,4-diazepan-1-yl)-*N*-((5-methylpyrazin-2-yl)methyl)-5-oxo-9-(1-(2-(2-(2-(5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)pentanamido)ethoxy)-ethoxy)ethyl)-1*H*-1,2,3-triazol-4-yl)-5*H*-benzo[4,5]thiazolo[3,2-*a*][1,8]naphthyridine-6-carboxamide (**5.24**)



5.03 **5.24**

A magnetically stirred solution of alkyne **5.03** (30 mg, 0.06 mmol) and azide **5.20** (20 mg, 0.06 mmol) in THF/H_2O/DMSO (2 mL of a 10:5:1 v/v/v mixture) maintained at ambient temperatures was treated with sodium ascorbate (10 mg, 0.01 mmol) and $CuSO_4$•$5H_2O$ (10 mg, 0.02 mmol). After 16 h the reaction mixture was concentrated under a stream of nitrogen the residue thus obtained subjected to flash column chromatography (silica, 9:1 v/v

dichloromethane/ammonia-saturated methanol elution). Concentration of the relevant fractions (R_f = 0.3) then gave compound **5.24** (40 mg, 82%) as a light-yellow, crystalline solid, m.p. = 261-263 °C.

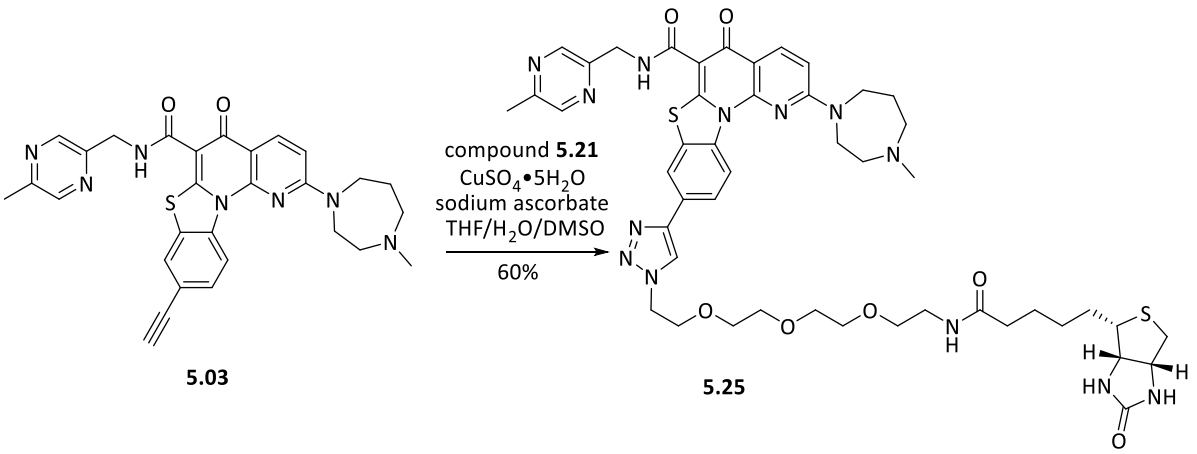
^{1}H NMR (400 MHz, $CDCl_3$) δ 11.17 (t, *J* = 5.7 Hz, 1H), 9.10 (d, *J* = 8.9 Hz, 1H), 8.55 (s, 1H), 8.44 (s, 1H), 8.28 (d, *J* = 9.0 Hz, 1H), 8.08 (s, 1H), 7.94 (s, 1H), 7.69 (d, *J* = 9.0 Hz, 1H), 6.89 (s, 1H), 6.59 (m, 2H), 5.84 (s, 1H), 4.76 (m, 2H), 4.59 (m, 2H), 4.44 (m, 1H), 4.26 (m, 1H), 3.95 (m, 3H), 3.80-3.25 (complex m, 14H), 3.06 (m, 1H), 2.90-2-25 (complex m, 6H), 2.10 (m, 4H), 1.75-1.50 (complex m, 6H), 1.36 (br. s, 3H);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.6, 172.8, 166.4, 164.2, 158.4, 158.1, 152.3, 150.5, 149.1, 146.1, 143.9, 142.7, 137.0, 136.6, 130.3, 128.2, 123.5, 121.6, 119.5, 118.1, 111.4, 106.2, 105.3, 70.5, 70.1, 70.0, 69.4, 61.9, 60.3, 57.4, 57.0, 55.9, 50.4, 47.7, 46.6, 42.7, 40.7, 39.2, 36.0, 28.3, 28.2, 27.0, 25.7, 21.3 (one signal obscured or overlapping);

IR ν_{max} 3279, 2925, 1698, 1637, 1612, 1552, 1485, 1454, 1426, 1411, 1361, 1264, 1053 cm^{-1}; **MS** (ESI, +ve) *m/z* 938 [$(M+H)^+$,100%];

HRMS (ESI, +ve) *m/z* 938.3952 $[M+H]^+$, calcd. for $C_{45}H_{56}N_{13}O_6S_2$ 938.3918.

2-(4-Methyl-1,4-diazepan-1-yl)-*N*-((5-methylpyrazin-2-yl)methyl)-5-oxo-9-(1-(13-oxo-17-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)-3,6,9-trioxa-12-aza-heptadecyl)-1*H*-1,2,3-triazol-4-yl)-5*H*-benzo[4,5]thiazolo[3,2-*a*][1,8]naphthyridine-6-carboxamide (**5.25**)



5.03 **5.25**

A magnetically stirred solution of alkyne **5.03** (30 mg, 0.06 mmol) and azide **5.21** (30 mg, 0.07 mmol) in THF/H_2O/DMSO (2 mL of a 10:5:1 v/v/v mixture) maintained at ambient

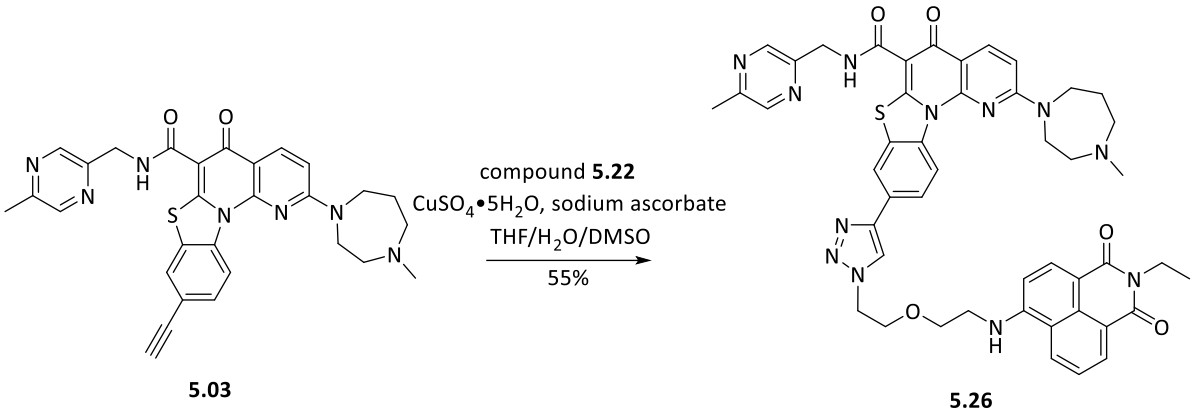
temperatures was treated with sodium ascorbate (10 mg, 0.01 mmol) and $CuSO_4 \bullet 5H_2O$ (10 mg, 0.02 mmol). After 16 h the reaction mixture was concentrated under a stream of nitrogen and the residue thus obtained subjected to flash column chromatography (silica, 9:1 v/v dichloromethane/ammonia-saturated methanol elution). Concentration of the appropriate fractions (R_f = 0.3) then gave compound **5.25** (30 mg, 60%) as a light-yellow, crystalline solid, m.p. = 263-265 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.21 (t, *J* = 5.6 Hz, 1H), 9.27 (br. s, 1H), 8.56 (s, 1H), 8.45 (s, 1H), 8.39 (d, *J* = 9.0 Hz, 1H), 8.16 (s, 1H), 8.01 (s, 1H), 7.87 (d, *J* = 9.0 Hz, 1H), 6.83 (m, 1H), 6.67 (d, *J* = 9.0 Hz, 1H), 6.41 (s, 1H), 5.50 (br. s, 1H), 4.80 (d, *J* = 5.5 Hz, 2H), 4.62 (t, *J* = 5.0 Hz, 2H), 4.47 (m, 1H), 4.27 (m, 1H), 4.00-3.25 (complex m, 12H) 3.10-2.60 (complex m, 10H), 2.55 (s, 3H), 2.46 (s, 3H), 2.40-1.90 (complex m, 4H), 1.60-1.00 (complex m, 8H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 173.5, 173.0, 166.5, 164.0, 158.5, 158.3, 152.4, 150.5, 146.2, 143.9, 142.7, 137.3, 136.7, 130.4, 128.5, 123.7, 121.8, 119.7, 118.3, 111.7, 106.3, 105.5, 70.6, 70.5, 70.1, 70.0, 69.5, 61.9, 60.3, 57.5, 57.1, 55.8, 50.5, 47.8, 46.6, 42.7, 41.1, 40.7, 39.2, 35.9, 28.3, 28.2, 27.0, 25.7, 21.4 (two signals obscured or overlapping);

IR ν_{max} 3279, 2924, 2859, 1701, 1639, 1612, 1523, 1454, 1427, 1261, 1234, 1120, 910 cm^{-1}; **MS** (ESI, +ve) *m/z* 1004 [$(M+Na)^+$, 100%], 982 [$(M+H)^+$, 99];

HRMS (ESI, +ve) *m/z* 982.3173 $[M+H]^+$, calcd. for $C_{47}H_{60}N_{13}O_7S_2$ 982.3175.

9-(1-(2-(2-((2-Ethyl-1,3-dioxo-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-6-yl)amino)etho-xy)-ethyl)-1*H*-1,2,3-triazol-4-yl)-2-(4-methyl-1,4-diazepan-1-yl)-*N*-((5-methylpyrazin-2-yl)-methyl)-5-oxo-5*H*-benzo[4,5]thiazolo[3,2-*a*][1,8]naphthyridine-6-carboxamide (**5.26**)



5.03 **5.26**

A magnetically stirred solution of alkyne **5.03** (30 mg, 0.06 mmol) and azide **5.22** (20 mg, 0.07 mmol) in THF/H_2O/DMSO (2 mL of a 10:5:1 v/v/v mixture) maintained at ambient temperatures was treated with sodium ascorbate (10 mg, 0.01 mmol) and $CuSO_4$•$5H_2O$ (10 m g, 0.02 mmol). After 16 h the reaction mixture was concentrated under a stream of nitrogen and the residue thus obtained subjected to flash column chromatography (silica, 9:1 v/v dichloromethane/ammonia-saturated methanol elution). Concentration of the relevant fractions (R_f = 0.4) then gave compound **5.26** (30 mg, 55%) as a yellow, crystalline solid, m.p. = 285-287 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.12 (t, *J* = 5.6 Hz, 1H), 8.87 (m, 1H), 8.58 (s, 1H), 8.45 (m, 2H), 8.26 (m, 2H), 7.98 (m, 2H), 7.85 (s, 1H), 7.43 (d, *J* = 8.9 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 6.67 (d, *J* = 9.0 Hz, 1H), 6.56 (d, *J* = 8.4 Hz, 1H), 5.72 (s, 1H), 5.50 (br. m, 1H), 4.79 (d, *J* = 5.5 Hz, 2H), 4.64 (m, 2H), 4.05 (m, 3H), 3.86 (m, 3H), 3.70 (br. s, 2H), 3.50 (m, 2H), 3.29 (s, 2H), 3.15 (s, 2H), 2.78 (s, 3H), 2.55 (s, 3H), 2.38 (s, 3H), 1.10 (t, *J* = 8.0 Hz, 3H);

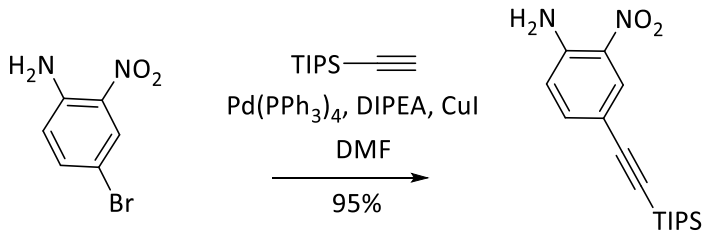
^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 173.1, 166.4, 164.1, 163.8, 158.6, 158.5, 152.2, 150.4, 149.1, 146.4, 143.8, 142.6, 137.6, 136.8, 134.0, 130.9, 130.7, 129.5, 127.9, 126.1, 124.8, 123.4, 122.8, 121.0, 120.3, 119.4, 118.2, 111.9, 106.2, 105.7, 104.2, 69.0, 68.8, 57.5, 56.9, 50.4, 47.6, 46.3, 43.0, 42.7, 34.9, 27.0, 22.7, 22.6, 21.2, 14.1, 13.4;

IR ν_{max} 3260, 2932, 1698, 1645, 1576, 1552, 1485, 1454, 1426, 1411, 1347 cm^{-1};

MS (ESI, +ve) *m/z* 891 [$(M+H)^+$, 100%];

HRMS (ESI, +ve) *m/z* 891.3517 $[M+H]^+$, calcd. for $C_{47}H_{47}N_{12}O_5S$ 891.3513.

2-Nitro-4-((Tri-*iso*propylsilyl)ethynyl)aniline (**5.33**)



5.32 **5.33**

A degassed and magnetically stirred mixture of 4-bromo-2-nitroaniline (**5.32**) (1.00 g, 4.60 mmol), $Pd(PPh_3)_4$ (80.9 mg, 0.12 mmol) and CuI (43.9 mg, 0.23 mmol) in DMF (10 mL) was treated with DIPEA (2.40 mL, 13.8 mmol). The resulting mixture was degassed again for 5 min and then treated with ethynyltriisopropylsilane (1.2 mL, 5.53 mmol) before being heated at 100 °C for 16 h. The cooled reaction mixture was quenched with water (30 mL) and the separated aqueous phase was extracted with ethyl acetate (2 × 10 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 3:17 v/v ethyl acetate/hexane) and concentration of the appropriate fractions (R_f = 0.3) afforded compound **5.33** (900 mg, 62%) as an orange-coloured, crystalline solid, m.p. = 126 - 128 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 1.8 Hz, 1H), 7.43 (dd, *J* = 8.6, 1.8 Hz, 1H), 6.74 (d, *J* = 8.6 Hz, 1H), 6.18 (s, 2H), 1.12 (appeared s, 21H);

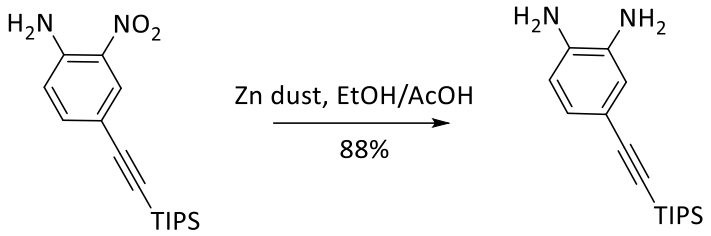
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 144.4, 138.9, 131.7, 130.0, 118.8, 112.6, 105.1, 90.1, 18.8 (6×CH_3), 11.5 (3×CH);

IR ν_{max} 3470, 3349, 2955, 240, 2852, 2161, 2145, 1631, 1552, 1513, 1460, 1412, 1364, 1345, 1283, 1247, 1209, 1170, 1075, 997, 938, 883, 834, 805 cm^{-1};

MS (ESI, +ve) *m/z* 341 [$(M+Na)^+$, 100%];

HRMS *m/z* 319.1844 $(M+H)^+$, calcd for $C_{17}H_{27}N_2O_2Si$ 319.1836.

4-((Triisopropylsilyl)ethynyl)benzene-1,2-diamine (**5.34**)



5.33 **5.34**

A magnetically stirred solution of compound **5.33** (750 mg, 2.35 mmol) in ethanol/acetic acid (15 mL of a 2:1 v/v mixture) was treated, in three portions, with zinc dust (1.54 g, 23.55 mmol). After 3h, the solid was filtered off and washed with dichloromethane (20 mL). The combined filtrates were concentrated under reduced pressure and the residue thus obtained was subjected to flash chromatography (silica, 1:1 v/v ethyl acetate/hexane). Concentration of the appropriate fractions (R_f = 0.3) afforded compound **5.34** (610 mg, 88%) as a clear, light-purple coloured oil that, being unstable, was immediately subjected to the next step of the reaction sequence.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (dd, *J* = 7.9, 1.7 Hz, 1H), 6.85 (d, *J* = 1.7 Hz, 1H), 6.59 (d, *J* = 7.9 Hz, 1H), 3.43 (s, 4NH), 1.12 (appeared s, 21H);

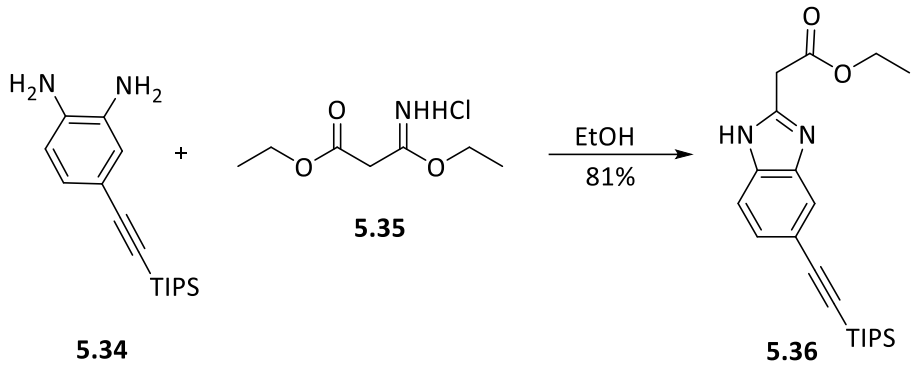
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 135.9, 134.0, 125.1, 120.4, 116.0, 114.7, 108.1, 87.5, 18.8 (6×CH_3), 11.5 (3×CH);

IR ν_{max} 3344, 2941, 2863, 2148, 1621, 1578, 1510, 1296, 881 cm^{-1};

MS (ESI, +ve) *m/z* 311 [$(M+Na)^+$, 100%];

HRMS *m/z* 289.2121$(M+H)^+$, calcd for $C_{17}H_{28}N_2SiNa$ 289.2131.

Ethyl 2-(5-((Triisopropylsilyl)ethynyl)-1*H*-benzo[*d*]imidazol-2-yl)acetate (**5.36**)



5.34 **5.35** **5.36**

A magnetically stirred solution of compound **5.34** (600 g, 2.08 mmol) and ethyl 3-ethoxy-3-iminopropanoate hydrochloride (**5.35**) (0.4 g, 2.08 mmol) in ethanol (20 mL) was heated at 80 °C for 16 h. The cooled reaction mixture was partitioned between ethyl acetate (20 mL) and $NaHCO_3$ (20 mL of a saturated aqueous solution). The separated organic phase was washed with brine (2 × 10 mL) then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:1 v/v ethyl acetate/hexane) and concentration of the appropriate fractions (R_f = 0.2) afforded compound **5.36** (700 mg, 81%) as a clear, yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.49 (d, *J* = 8.3 Hz, 1H), 7.37 (dd, *J* = 8.3, 1.4 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.05 (s, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.13 (s, 21H);

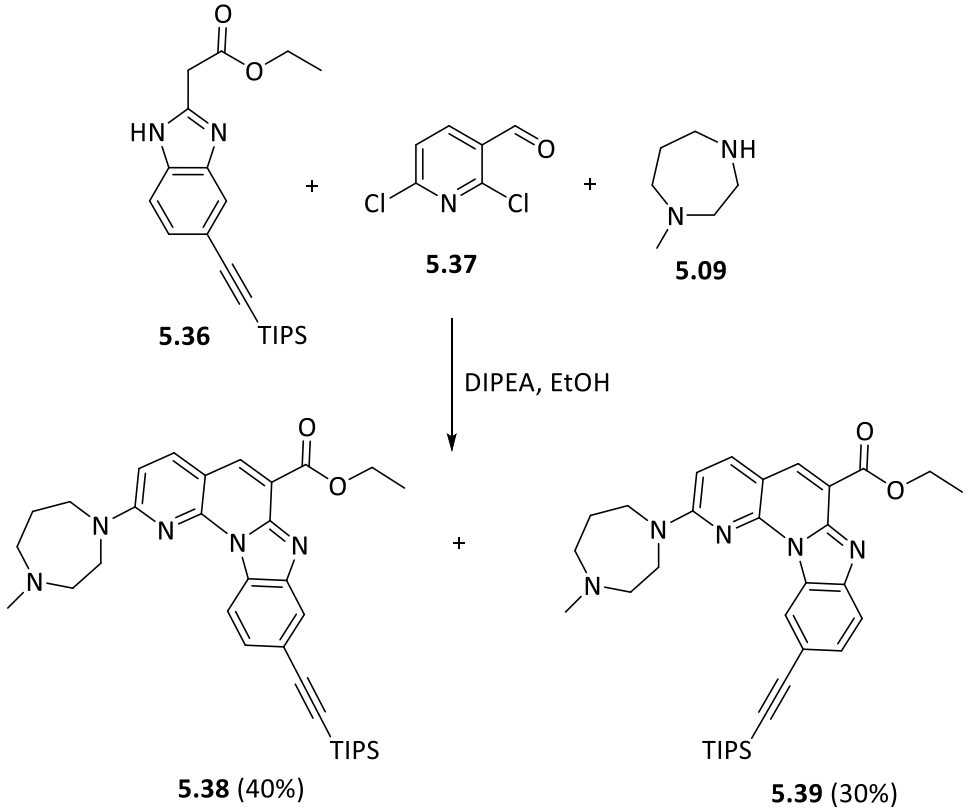
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.7, 148.6, 138.6, 127.1, 117.9, 108.0, 89.1, 62.0, 34.7, 18.8, 14.2 (6×CH_3), 11.5 (3×CH);

IR ν_{max} 2942, 2891, 2864, 2151, 1738, 1453, 1421, 1369, 1298, 1263, 1195, 1151, 1029, 1018, 995, 881, 812, 738, 664 cm^{-1};

MS (ESI, +ve) *m/z* 385 [$(M+H)^+$, 100%], 407 [$(M+Na)^+$, 70%];

HRMS *m/z* 385.2305 $(M+H)^+$, calcd for $C_{22}H_{33}N_2O_2Si$ 385.2306.

Ethyl 2-(4-Methyl-1,4-diazepan-1-yl)-10-((triisopropylsilyl)ethynyl)benzo[4,5]imidazo[1,2-*a*][1,8]naphthyridine-6-carboxylate (**5.38**) **and Ethyl 2-(4-Methyl-1,4-diazepan-1-yl)-9-((triisopropylsilyl)ethynyl)benzo[4,5]imidazo[1,2-*a*][1,8]naphthyridine-6-carboxylate** (**5.39**)



5.38 (40%) **5.39** (30%)

A magnetically stirred solution of 2,6-dichloropyridine-3-carboxaldehyde (**5.37**) (448 mg, 2.55 mmol) and ((triisopropylsilyl)ethynyl)-1*H*-benzo[d]imidazol-2-yl)acetate (**5.36**) (980 mg, 2.55 mmol) in ethanol (10 mL) maintained at ambient temperatures was treated with *N*-methyl-1,4-diazepane (**5.09**) (320 mL, 2.55 mmol) and DIPEA (680 mL, 5.09 mmol). The resulting mixture was heated at 65 °C for 16 h then cooled and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, from 1:9 to 1:4 v/v *iso*-propanol/dichloromethane) and thereby affording two fractions, A and B.

Concentration of fraction A (R_f = 0.3) afforded compound **5.38** (600 mg, 40%) as a yellow, crystalline solid, m.p. = 177-179 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 8.26 (s, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 8.9 Hz, 1H), 7.64 (dd, *J* = 8.4, 1.5 Hz, 1H), 6.43 (d, *J* = 8.9 Hz, 1H), 4.53 (q, *J* = 7.1 Hz, 2H), 4.13 (brs, 2H), 3.54 (brs, 2H), 2.86 (brs, 2H), 2.57 (m, 2H), 2.37 (s, 3H), 2.09 (appeared s, 2H), 1.48 (t, *J* = 7.1 Hz , 3H), 1.17 (s, 21H);

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ δ 164.2, 158.6, 147.9, 145.1, 139.1, 135.6, 129.5, 129.1, 120.5, 119.9, 116.7, 113.1, 108.7, 106.4, 104.8, 88.9, 61.5, 57.5, 57.2, 48.2, 47.8, 46.9, 27.3, 25.5, 18.9 (6×CH_3), 14.6, 11.6 (3×CH);

IR ν_{max} 2940, 2863, 2145, 1724, 1699, 1626, 1602, 1588, 1514, 1452, 1406, 1364, 1345, 1207, 1182, 1128, 1094, 880, 815 cm^{-1};

MS (ESI, +ve) *m/z* 606 [$(M+Na)^+$, 30%], 584 [$(M+H)^+$, 100%];

HRMS *m/z* 584.3417 $(M+H)^+$, calcd for $C_{34}H_{46}N_5O_2Si$ 584.3415.

Concentration of fraction B (R_f = 0.1) afforded compound **5.39** (450 mg, 30%) as a yellow, crystalline solid, m.p. = 188-200 °C.

^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 8.5 Hz, 1H), 8.11 (s, 1H), 7.99 (s, 1H), 7.43 (obscured d, *J* = 8.2 Hz, 2H), 6.21 (d, *J* = 8.9 Hz, 1H), 4.48 (q, *J* = 7.1 Hz, 2H), 3.78 (brs, 2H), 3.43 (brs, 2H), 2.71 (appeared s, 2H), 2.50 (m, 2H), 2.33 (s, 3H), 1.97 (m, 2H), 1.46 (t, *J* = 7.1 Hz, 3H), 1.16 (s, 21H);

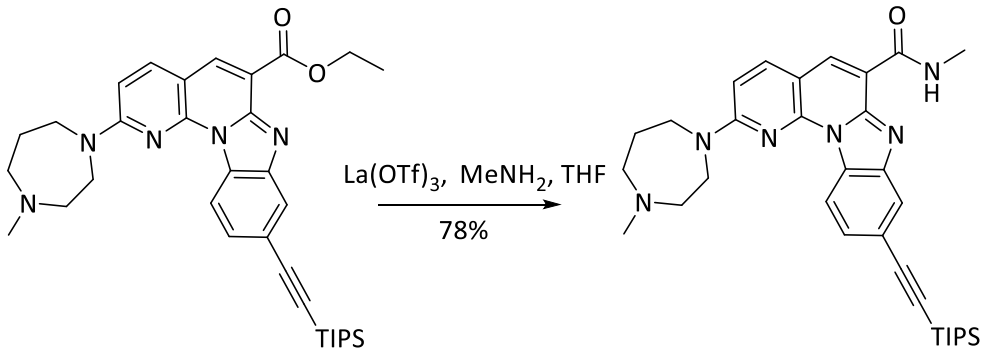
$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 163.9, 158.1, 147.4, 144.5, 138.6, 135.2, 129.5, 125.9, 123.6, 119.7, 116.0, 112.6, 108.1, 105.9, 104.6, 89.8, 61.3, 57.4, 57.1, 47.4 (2×CH_2), 46.8, 27.2, 18.8 (6×CH_3), 14.6, 11.5 (3×CH);

IR ν_{max} 2941, 2864, 2151, 1724, 1627, 1603, 1591, 1542, 1518, 1466, 1410, 1355, 1210, 1185, 1146, 1100, 908, 730 cm^{-1};

MS (ESI, +ve) *m/z* 584 [$(M+H)^+$, 100%];

HRMS *m/z* 584.3416 $(M+H)^+$, calcd for $C_{34}H_{46}N_5O_2Si$ 584.3415

***N*-Methyl-2-(4-methyl-1,4-diazepan-1-yl)-9-((triisopropylsilyl)ethynyl)benzo[4,5] imidazo[1,2-*a*][1,8]naphthyridine-6-carboxamide** (**5.40**)



5.38 **5.40**

A microwave vessel charged with a stir bar, compound **5.38** (100 mg, 0.17 mmol) and lanthanum (III) triflate (10 mg, 0.02 mmol) was evacuated under reduced pressure then refilled with nitrogen before being treated with methylamine (6 mL of a 2 M solution in THF). The resulting mixture was subjected to microwave irradiation at 70 °C for 4 h then cooled and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:9 v/v methanol/dichloromethane) and concentration of the appropriate fractions (R_f = 0.4) afforded compound **5.40** (77 mg, 78%) as a yellow, crystalline solid, m.p. = 180 - 182 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.23 (q, *J* = 4.7 Hz, 1H), 8.91 (s, 1H), 8.46 (s, 1H), 7.82 (d, *J* = 8.9 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.62 (dd, *J* = 8.4, 1.5 Hz, 1H), 6.61 (d, *J* = 8.9 Hz, 1H), 4.00 (brs, 2H), 3.75 (brs, 2H), 3.15 (d, *J* = 4.7 Hz, 3H), 2.84 (appeared s, 2H), 2.57 (m, 2H), 2.38 (s, 3H), 2.11 (m, 2H), 1.19 (s, 21H);

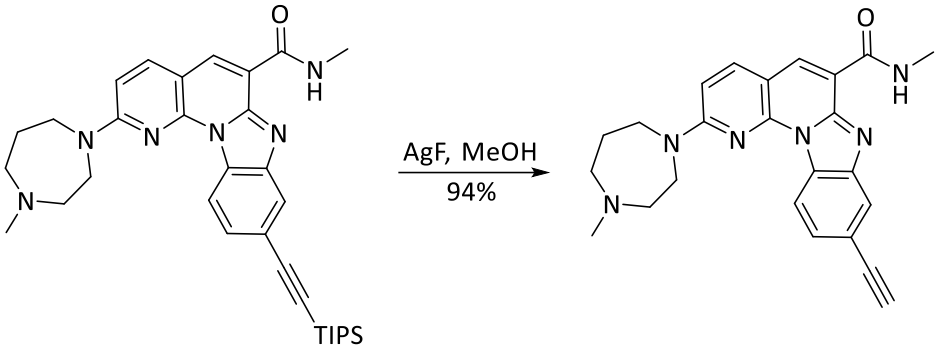
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 164.1, 158.3, 148.4, 147.0, 143.4, 139.4, 134.0, 129.4, 129.3, 120.6, 118.5, 116.8, 114.5, 108.5, 107.2, 105.0, 89.0, 57.6, 57.2, 47.8 (2×CH_2), 46.9, 27.3, 26.6, 18.9 (6×CH_3), 11.6 (3×CH);

IR ν_{max} 3257, 2940, 2863, 2228, 2147, 1657, 1565, 1516, 1461, 1216, 815 cm^{-1};

MS (ESI, +ve) *m/z* 569 [$(M+H)^+$, 100%];

HRMS *m/z* 569.3403 $(M+H)^+$, calcd for $C_{33}H_{45}N_6OSi$ 569.3419.

10-Ethynyl-*N*-methyl-2-(4-methyl-1,4-diazepan-1-yl)benzo[4,5]imidazo[1,2-a][1,8]naphthyridine-6-carboxamide (**5.28**)



5.40 **5.28**

A degassed, magnetically stirred solution of compound **5.40** (50 mg, 0.09 mmol) in methanol (3 mL), and protected from light, was treated with silver fluoride (21 mg, 0.13 mmol). The resulting mixture was stirred at ambient temperatures for 3 h then concentrated under reduced pressure. The ensuing residue was subjected to flash column chromatography (silica, 1:9 v/v ammonia-saturated methanol/dichloromethane) and concentration of the appropriate fractions (R_f = 0.4) afforded compound **5.28** (34 mg, 94%) as a yellow, crystalline solid, m.p. = 150-152 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.15 (d, *J* = 4.5 Hz, 1H), 8.81 (s, 1H), 8.42 (s, 1H), 7.74 (d, *J* = 8.9 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 6.50 (d, *J* = 8.9 Hz, 1H), 3.93 – 3.71 (m, 4H), 3.14 (d, *J* = 4.5 Hz, 3H), 3.10 (s, 1H), 2.84 (appeared s, 2H), 2.60 (m, 2H), 2.39 (s, 3H), 2.11 (m, 2H);

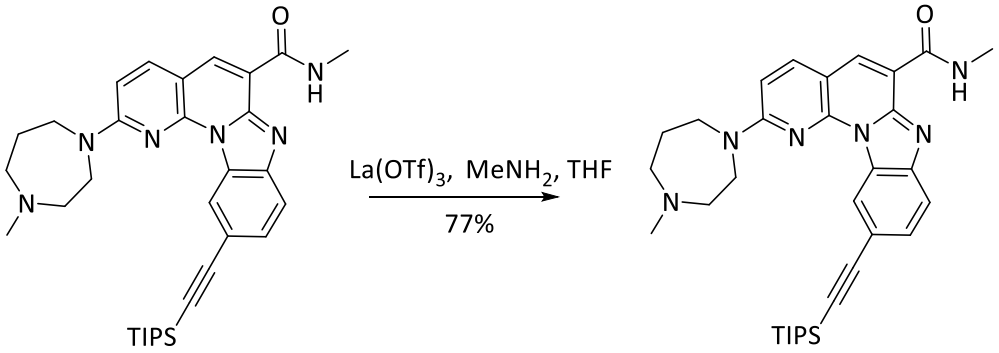
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 164.1, 158.2, 148.3, 146.8, 143.5, 139.2, 134.1, 129.2, 128.9, 120.9, 118.5, 115.2, 114.4, 107.1, 105.0, 84.9, 76.1, 57.6, 57.2, 47.6 (2×CH_2), 46.8, 27.2, 26.6;

IR ν_{max} 3192, 2939, 2800, 1658, 1569, 1515, 1459, 1405, 1384, 1349, 1214, 1153, 1107, 1016, 880, 794 cm^{-1};

MS (ESI, +ve) *m/z* 413 [$(M+H)^+$, 100%];

HRMS *m/z* 413.2072 $(M+H)^+$, calcd for $C_{24}H_{25}N_6O$ 413.2084.

***N*-Methyl-2-(4-methyl-1,4-diazepan-1-yl)-9-((triisopropylsilyl)ethynyl)benzo[4,5] imidazo[1,2-*a*][1,8]naphthyridine-6-carboxamide** (**5.41**)



5.39 **5.41**

A microwave vessel charged with a stir bar, compound **5.39** (120 mg, 0.20 mmol) and lanthanum (III) triflate (10 mg, 0.02 mmol) was evacuated under reduced pressure then refilled with nitrogen before being treated with methylamine (600 mL of a 2 M solution in THF). The resulting mixture was subjected to microwave irradiation at 70 °C for 4 h then cooled and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:9 v/v methanol/dichloromethane) and concentration of the appropriate fractions (R_f = 0.4) afforded compound **5.41** (90 mg, 77%) as a yellow, crystalline solid, m.p. = 258-260 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.28 (d, *J* = 4.6 Hz, 1H), 8.71 (d, *J* = 8.4 Hz, 1H), 8.49 (s, 1H), 8.00 (s, 1H), 7.78 (d, *J* = 8.9 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 6.55 (d, *J* = 8.9 Hz, 1H), 3.93 (brs, 2H), 3.78 (brs, 2H), 3.15 (d, *J* = 4.6 Hz, 3H), 2.84 (brs, 2H), 2.61 (m, 2H), 2.41 (s, 3H), 2.12 (m, 2H), 1.18 (s, 21H);

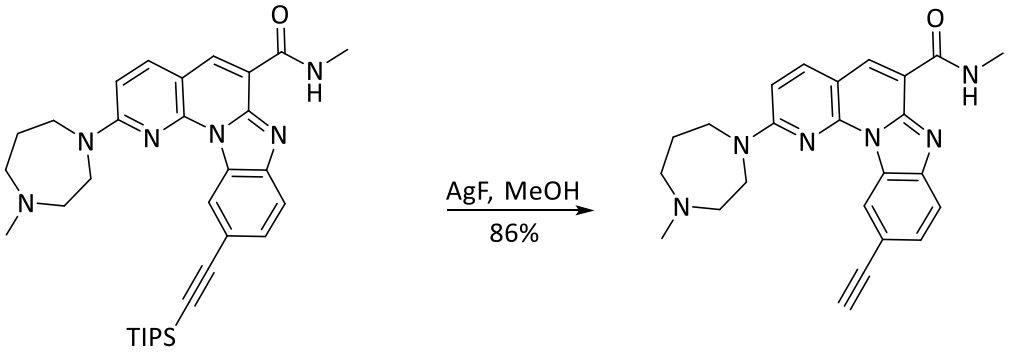
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 164.2, 157.9, 148.2, 146.7, 142.9, 139.1, 133.9, 129.5, 126.0, 122.4, 120.0, 116.2, 114.3, 107.9, 106.9, 104.7, 89.9, 57.5, 57.1, 47.5 (2xCH_2), 46.8, 27.2, 26.5, 18.9 (6×CH_3), 11.5 (3×CH);

IR ν_{max} 3478, 2941, 2864, 2151, 1655, 1589, 1519, 1454, 1408, 1252, 1148, 1028, 883, 806 cm^{-1};

MS (ESI, +ve) *m/z* 569 [$(M+H)^+$, 100%];

HRMS *m/z* 569.3406 $(M+H)^+$, calcd for $C_{33}H_{45}N_6OSi$ 569.3419.

9-Ethynyl-*N*-methyl-2-(4-methyl-1,4-diazepan-1-yl)benzo[4,5]imidazo[1,2-*a*][1,8]naphthyridine-6-carboxamide (**5.29**)



5.41 **5.29**

A degassed, magnetically stirred solution of compound **5.41** (64 mg, 0.11 mmol) in methanol (3 mL), and protected from light, was treated with silver fluoride (27 mg, 0.17 mmol). The resulting mixture was stirred at ambient temperatures for 3 h then concentrated under reduced pressure. The ensuing residue was subjected to flash column chromatography (silica, 1:9 v/v ammonia-saturated methanol/dichloromethane) and concentration of the appropriate fractions (R_f = 0.4) afforded compound **5.29** (40 mg, 86%) as a yellow, crystalline solid, m.p. = 162-164 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.21 (d, *J* = 4.6 Hz, 1H), 8.61 (d, *J* = 8.4 Hz, 1H), 8.46 (s, 1H), 7.95 (s, 1H), 7.73 (d, *J* = 8.9 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 6.51 (d, *J* = 8.9 Hz, 1H), 3.87 (brs, 2H), 3.74 (brs, 2H), 3.16 (d, *J* = 4.6 Hz, 3H), 3.14 (s, 1H), 2.79 (appeared s, 2H), 2.57 (m, 2H), 2.39 (s, 3H), 2.09 (m, 2H);

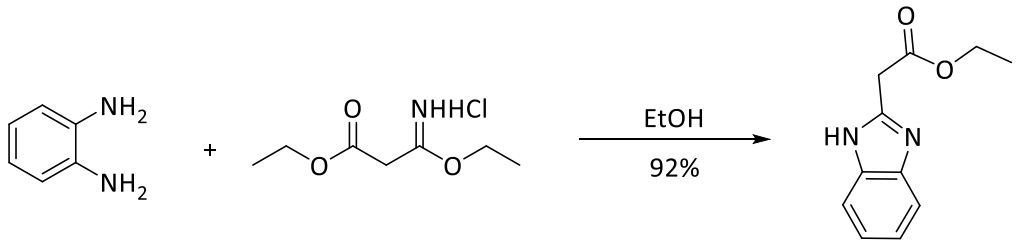
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 164.2, 158.1, 148.3, 146.9, 143.0, 139.3, 134.2, 129.9, 126.0, 122.6, 118.6, 116.4, 114.5, 107.1, 105.0, 84.4, 76.8, 57.6, 57.2, 47.8, 47.7, 46.9, 27.3, 26.6;

IR ν_{max} 3512, 2945, 1653, 1582, 1540, 1520, 1408, 1256, 1169, 1036, 641 cm^{-1};

MS (ESI, +ve) *m/z* 435 [$(M+Na)^+$, 90%], 413 [$(M+H)^+$, 100];

HRMS *m/z* 435.1902 $(M+Na)^+$, calcd for $C_{24}H_{24}N_6NaO$ 435.1909.

Ethyl 2-(1*H*-benzo[*d*]imidazol-2-yl) acetate (**5.43**)



5.42 **5.35** **5.43**

A magnetically stirred solution of benzene-1,2-diamine (**5.42**) (3.00 g, 27.74 mmol) and ethyl 3-ethoxy-3-iminopropanoate hydrochloride (**5.35**) (5.43 g, 27.74 mmol) in ethanol (80 mL) was heated at 80 °C for 16 h. The cooled mixture was partitioned between ethyl acetate (200 mL) and $NaHCO_3$ (200 mL of a saturated aqueous solution). The separated organic phase was washed with brine (1 x 10 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:19 v/v methanol/dichloromethane) and concentration of the appropriate fractions (R_f = 0.3) afforded compound **5.43** (5.20 g, 92%) as a tan-coloured, crystalline solid, m.p. =130-132 °C.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.36 (brs, 1H), 7.51 (brs, 2H), 7.16 – 7.14 (m, 2H), 4.14 (q, *J* = 7.09 Hz, 2H), 3.96 (s, 2H), 1.20 (t, *J* = 7.09 Hz, 3H);

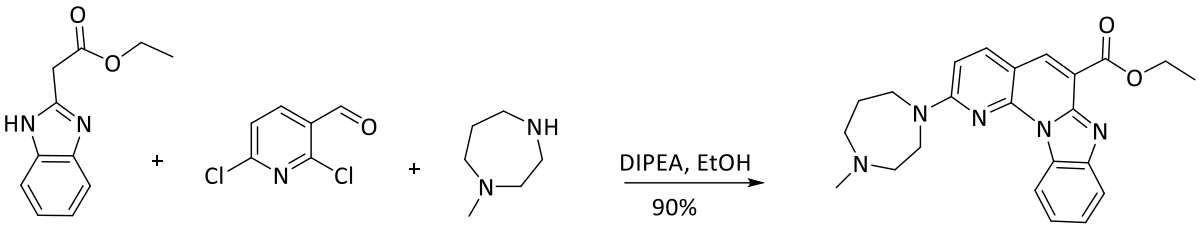
^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 168.7, 147.8, 143.1, 134.4, 121.9, 121.1, 118.4, 111.1, 60.8, 35.1, 14.0;

IR ν_{max} 2982, 2746, 1733, 1623, 1541, 1439, 1368, 1330, 1308, 1271, 1191, 1159, 1029, 741 cm^{-1};

MS (ESI, +ve) *m/z* 227 [$(M+Na)^+$, 45%], 205 [$(M+H)^+$, 100];

HRMS *m/z* 205.0971 $(M+H)^+$ calcd for $C_{11}H_{13}N_2O_2$ 205.0972.

Ethyl 2-(4-Methyl-1,4-diazepan-1-yl)benzo[4,5]imidazo[1,2-*a*][1,8]naphthyridine-6-carboxylate (**5.44**)



5.43 **5.37** **5.09** **5.44**

A magnetically stirred solution of 2,6-dichloropyridine-3-carboxaldehyde (**5.37**) (1.48 g, 8.42 mmol) and ethyl 2-(1*H*-benzo[d]imidazol-2-yl)acetate (**5.43**) (1.72 g, 8.42 mmol) in ethanol (50 mL) maintained at ambient temperatures was treated with *N*-methyl-1,4-diazepane (**5.09**) (1.05 mL, 8.42 mmol) and DIPEA (2.90 mL, 16.84 mmol). The resulting mixture was heated at 65 °C for 16 h then cooled and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 25:75 v/v methanol (10% NH_3)/ethyl acetate) and concentration of the appropriate fractions (R_f = 0.3) afforded compound **5.44** (3.07 g, 90%) as a yellow-orange coloured, crystalline solid, m.p. = 235-237 °C.

^{1}H NMR (400 MHz, CD_3OD) δ 8.12 (d, *J* = 8.1 Hz, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.57 (brs, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.12 (brs, 1H), 7.00 (brs, 1H), 5.87 (m, *J* = 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.44 – 3.02 (m, 4H), 2.56 (m, 2H), 2.44 (m, 2H), 2.28 (s, 3H), 1.82 (m, 2H), 1.44 (t, *J* = 7.1 Hz, 3H);

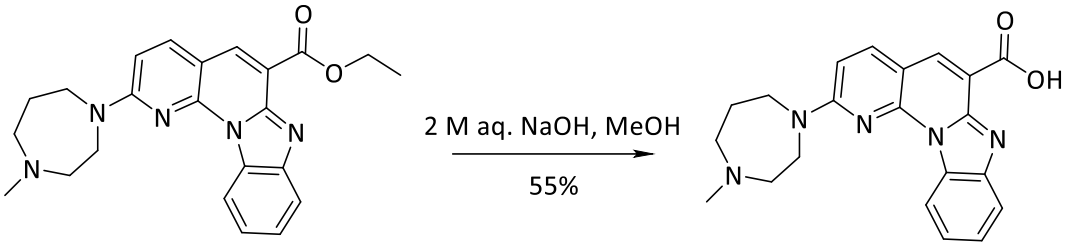
^{13}C{^{1}H} NMR (101 MHz, CD_3OD) δ 163.5, 157.6, 146.3, 145.6, 143.4, 138.0, 135.2, 128.7, 124.6, 121.7, 118.0, 116.1, 110.6, 105.2, 104.3, 60.7, 57.0, 56.7, 46.8, 46.5, 45.2, 26.0, 13.5;

IR ν_{max} 2938, 2784, 1720, 1625, 1589, 1515, 1447, 1364, , 1205, 1032, 727 cm^{-1};

MS (ESI, +ve) *m/z* 404 [$(M+H)^+$, 100%];

HRMS *m/z* 404.2083 $(M+H)^+$ calcd for $C_{23}H_{26}N_5O_2$ 404.2081.

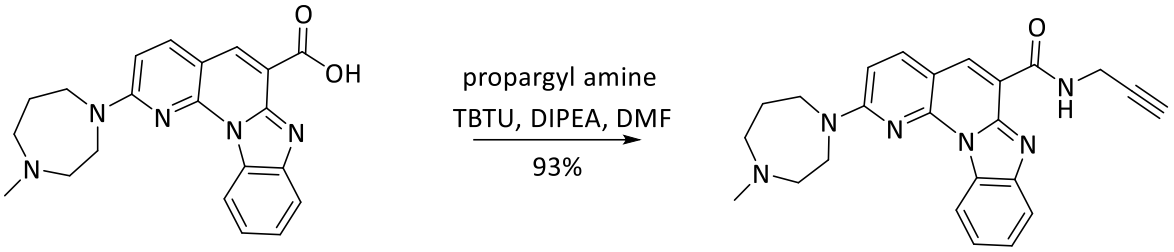
2-(4-Methyl-1,4-diazepan-1-yl)benzo[4,5]imidazo[1,2-*a*][1,8]naphthyridine-6-carboxylic acid (**5.45**)



5.44 **5.45**

A magnetically stirred solution of compound **5.44** (0.5 g, 1.24 mmol) in methanol was treated with NaOH (1.2 mL of a 2 M aqueous solution, 2.48 mmol). The resulting mixture was heated at 60 °C for 2 h then cooled and neutralised using Dowex resin (H^+ form). The solid was removed by filtration and the filtrate concentrated under reduced pressure to give carboxylic acid **5.45** (300 mg, 55%) as a yellow solid. This material was used directly in the next step of the reaction sequence.

2-(4-Methyl-1,4-diazepan-1-yl)-*N*-(prop-2-yn-1-yl)benzo[4,5]imidazo[1,2-*a*][1,8]naphthyri - dine-6-carboxamide (**5.30**)



5.45 **5.30**

A magnetically stirred solution of compound **5.45** (270 mg, 0.72 mmol) in DMF (10 mL) maintained at ambient temperatures was treated with DIPEA (250 mL, 1.44 mmol) and TBTU (280 mg, 0.86 mmol). After 1 h additional DIPEA (250 mL, 1.44 mmol) was added followed by propargyl amine (65 µL, 1.01 mmol). The resulting mixture was stirred for 16 h before being concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:2:2 v/v/v ammonia-saturated methanol/ethyl acetate/dichloromethane) and concentration of the appropriate fractions (R_f = 0.3) afforded compound **5.30** (0.28 g, 93%) as a yellow, crystalline solid, m.p. = 220-222 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.82 (t, *J* = 5.4 Hz, 1H), 8.71 (d, *J* = 7.7 Hz, 1H), 8.44 (s, 1H), 7.89 (d, *J* = 7.7 Hz, 1H), 7.70 (d, *J* = 8.9 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 1H), 7.37 (t, *J* = 7.7 Hz, 1H), 6.46 (d, *J* = 8.9 Hz, 1H), 4.42 (dd, *J* = 5.4, 2.5 Hz, 2H), 3.90 – 3.72 (brm, 4H), 2.83 (appeared s, 2H), 2.61 (m, 2H), 2.41 (s, 3H), 2.33 (t, *J* = 2.5 Hz, 1H), 2.11 (m, 2H);

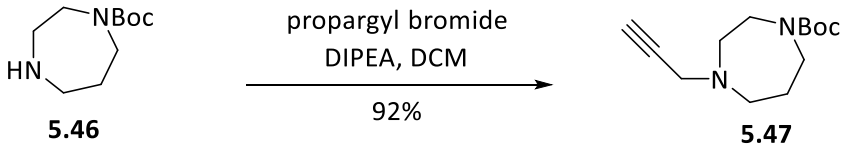
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 163.7, 158.1, 147.3, 147.3, 143.3, 139.3, 134.1, 129.8, 125.2, 122.3, 118.9, 116.5, 113.8, 106.9, 104.6, 80.5, 71.1, 57.6, 57.1, 47.6, 47.5, 46.8, 29.4, 27.1;

IR ν_{max} 3224, 2939, 2797, 1655, 1626, 1588, 1538, 1516, 1448, 1406, 1382, 1347, 1211, 1152, 1138 cm^{-1};

MS (ESI, +ve) *m/z* 413 [$(M+H)^+$, 100%];

HRMS *m/z* 413.2084 $(M+H)^+$ calcd for $C_{24}H_{25}N_6O$ 404.2084

***tert*-Butyl 4-(prop-2-yn-1-yl)-1,4-diazepane-1-carboxylate** (**5.47**)



5.46 **5.47**

A magnetically stirred solution of *tert*-butyl 1,4-diazepane-1-carboxylate (**5.46**) (2.00 g, 9.98 mmol) in chloroform (40 mL), maintained at ambient temperatures, was treated with DIPEA (1.90 mL, 10.98 mmol) and then, dropwise, with propargyl bromide (1.20 mL of an 80% solution in toluene, 10.98 mmol). The resulting mixture was stirred for 24 h before being washed with $NaHCO_3$ (40 mL of a saturated aqueous solution) and brine (1 x40 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:1 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) afforded compound **5.47** (2.20 g, 92%) as a clear, colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.49 – 3.32 (complex m, 4H), 3.32 (s, 2H), 2.66 – 2.59 (m, 4H), 2.18 (s, 1H), 1.80 (dp, *J* = 12.1, 6.2 Hz, 2H), 1.40 (s, 9H);

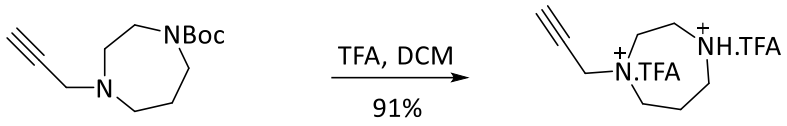
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 155.6 and 155.5 (rotamers), 79.3(5) and 79.31 (rotamers), 72.7(8) and 72.7(6) (rotamers), 55.9 and 55.5 (rotamers), 54.5 and 54.2 (rotamers), 47.9, 46.6, 46.0, 45.0, 28.5, 27.9;

IR ν_{max} 3242, 2974, 2933, 2821, 1686, 1461, 1410, 1365, 1324, 1242, 1172, 1149, 1124 cm^{-1};

MS (ESI, +ve) *m/z* 261 [$(M+Na)^+$, 38], 239 [$(M+H)^+$, 35];

HRMS *m/z* 239.1755 $(M+H)^+$ calcd for $C_{13}H_{23}N_2O_2$ 239.1751.

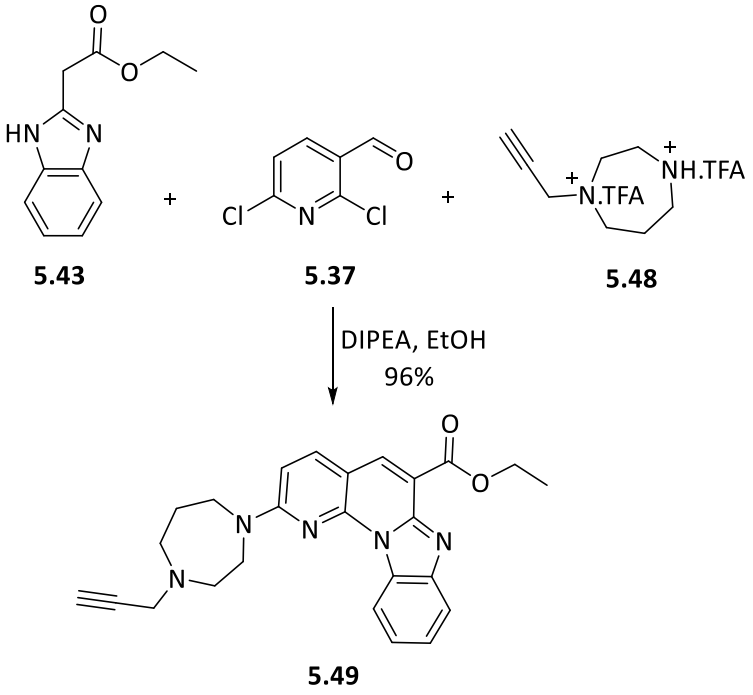
1-(Prop-2-yn-1-yl)-1,4-bis(2,2,2-trifluoroacetyl)-1,4-diazepane-1,4-diium (**5.48**)



5.47 **5.48**

A magnetically stirred solution of compound **5.47** (2.21 g, 9.23 mmol) in dichloromethane (20 mL) and maintained at 0 °C (ice-bath) was treated, dropwise, with trifluoroacetic acid (10 mL). The resulting mixture was then allowed to warm to ambient temperatures over 2 h after which the volatiles were removed under a gentle stream of nitrogen and so affording compound **5.48** (2.78 g, 91%) as an off-white solid. This material was used directly in the next step of the reaction sequence.

Ethyl 2-(4-(Prop-2-yn-1-yl)-1,4-diazepan-1-yl)benzo[4,5]imidazo[1,2-*a*][1,8]naphthyridine-6-carboxylate (**5.49**)



5.43 **5.37** **5.48**

5.49

A magnetically stirred solution of the compound **5.48** (2.26 g, 6.82 mmol), 2,6-dichloropyridine-3-carboxaldehyde (**5.37**) (1.20 g, 6.82 mmol), and ethyl 2-(1*H*-benzo[*d*]imidazol-2-yl)acetate (**5.43**) (1.40 g, 6.82 mmol) in ethanol (40 mL) maintained at ambient temperatures was treated with DIPEA (4.7 mL, 27.3 mmol). The ensuing mixture was heated at 65 °C for 16 h then cooled and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 2:9:9 v/v methanol/ethyl acetate/dichloromethane) and concentration of the appropriate fractions (R_f = 0.3) afforded compound **5.49** (2.81 g, 96%) as a yellow, crystalline solid, m.p. = 142-144 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, *J* = 8.2 Hz, 1H), 8.05 (overlapped s, 1H), 8.04 (overlapped d, *J* = 7.2 Hz, 1H), 7.53 – 7.41 (m, 2H), 7.34 (t, *J* = 7.6 Hz, 1H), 6.20 (d, *J* = 8.9 Hz, 1H), 4.50 (q, *J* = 7.1 Hz, 2H), 3.85 (brs, 2H), 3.35 (d, *J* = 2.2 Hz, 2H), 3.35 (overlapped brs, 2H), 2.82 (appeared s, 2H), 2.62 (m, 2H), 2.17 (t, *J* = 2.2 Hz, 1H), 1.96 (appeared s, 2H), 1.47 (t, *J* = 7.1 Hz, 3H);

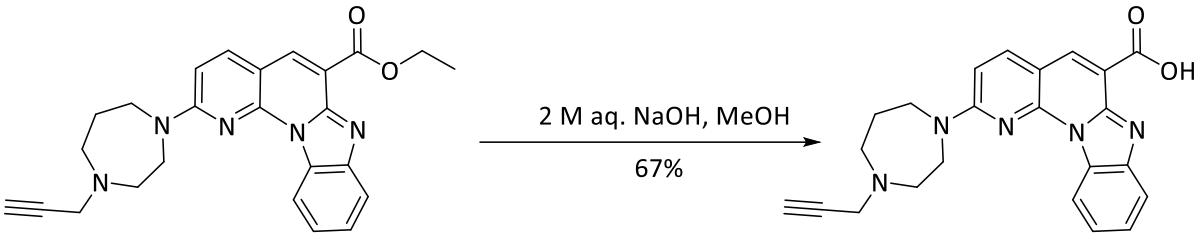
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 164.1, 158.1, 147.6, 146.6, 144.8, 138.7, 135.0, 129.7, 124.7, 121.9, 120.0, 116.2, 112.8, 106.0, 104.2, 79.0, 73.1, 61.2, 54.5, 54.4, 54.2, 47.9, 47.3, 27.2, 14.6;

IR ν_{max} 3200, 2937, 2824, 2095, 1721, 1698, 1626, 1600, 1591, 1541, 1518, 1448, 1410, 1220, 1207, 1177, 1137, 1093 cm^{-1};

MS (ESI, +ve) *m/z* 428 [$(M+H)^+$, 100%];

HRMS *m/z* 428.2078 $(M+H)^+$ calcd for $C_{25}H_{26}N_5O_2$ 428.2081.

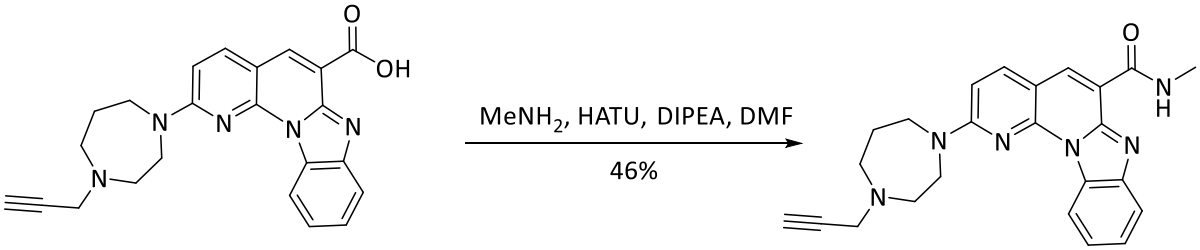
2-(4-(Prop-2-yn-1-yl)-1,4-diazepan-1-yl)benzo[4,5]imidazo[1,2-*a*][1,8]naphthyridine-6-carboxylic acid (**5.50**)



5.49 **5.50**

A magnetically stirred solution of ester **5.49** (500 mg, 1.17 mmol) in methanol (15 mL) was treated with NaOH (2.34 mL of a 2 M aqueous solution, 4.68 mmol). The resulting mixture was heated at 60 °C for 2 h before cooled to ambient temperatures then neutralised with Dowex resin (H^+ form). The solid was filtered off and the filtrate concentrated under reduced pressure to afford acid **5.50** (310 mg, 67%) as a yellow solid. This material was used directly in the next step of the reaction sequence.

***N*-Methyl-2-(4-(prop-2-yn-1-yl)-1,4-diazepan-1-yl)benzo[4,5]imidazo[1,2-*a*][1,8]naphthyridine-6-carboxamide** (**5.31**)



5.50 **5.31**

A magnetically stirred solution of compound **5.50** (310 mg, 0.77 mmol) in DMF (5 mL) maintained at ambient temperatures was treated with DIPEA (410 mL, 2.35 mmol), HATU (450 mg, 1.18 mmol) then methylamine (790 µL of a 2 M solution in THF, 1.57 mmol). The resulting mixture was stirred for 16 h before being concentrated under reduced pressure and

the residue thus obtained subjected to flash chromatography (silica, 2:9:9 v/v/v methanol/ethyl acetate/dichloromethane elution). Concentration of the appropriate fractions (R_f = 0.3) then afforded compound **5.31** (150 mg, 46%) as a yellow, crystalline solid, m.p. = 185-187°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.36 (d, *J* = 4.9 Hz, 1H), 8.62 (d, *J* = 8.2 Hz, 1H), 8.39 (s, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.9 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 6.31 (d, *J* = 8.9 Hz, 1H), 3.67 (br m, 4H), 3.37 (d, *J* = 2.5 Hz, 2H), 3.16 (d, *J* = 4.8 Hz, 3H), 2.86 (m, 2H), 2.64 (m, 2H), 2.18 (s, 1H), 2.02 (m, 2H);

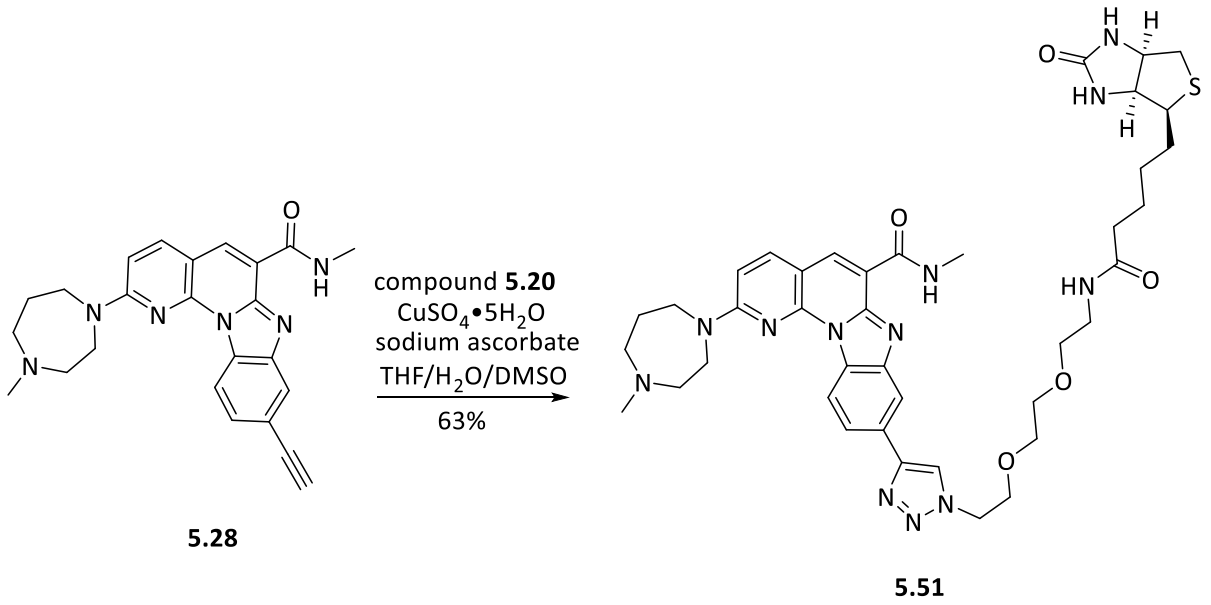
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 164.4, 157.7, 147.4, 147.0, 143.2, 139.0, 133.6, 129.7, 125.0, 122.1, 118.6, 116.5, 114.4, 106.9, 104.3, 79.0, 73.1, 54.5, 54.2, 48.0, 47.4 (2×CH_2), 27.2, 26.6;

IR ν_{max} 3254, 2938, 2234, 1721, 1652, 1625, 1588, 1568, 1538, 1519, 1448, 1405, 1346, 1237, 1209, 1150, 1177, 1136, 907 cm^{-1};

MS (ESI, +ve) *m/z* 413 [$(M+H)^+$, 100%];

HRMS *m/z* 413.2079 $(M+H)^+$ calcd for $C_{24}H_{25}N_6O$ 413.2084.

10-(1-(2-(2-((2-Ethyl-1,3-dioxo-2,3-dihydro-1*H*-benzo[de]isoquinolin-6-yl)amino)ethoxy)ethyl)-1*H*-1,2,3-triazol-4-yl)-*N*-methyl-2-(4-methyl-1,4-diazepan-1-yl)benzo[4,5]imidazo[1,2-*a*][1,8]naphthyridine-6-carboxamide (**5.51**)



5.28 **5.51**

A magnetically stirred solution of compounds **5.28** (30 mg, 0.07 mmol) and **5.20** (31 mg, 0.09 mmol) in THF/H_2O/DMSO (2 mL of a 2:2:1 v/v/v mixture) maintained at ambient temperatures was treated with sodium ascorbate (3.0 mg, 0.01 mmol) and $CuSO_4$•$5H_2O$ (5.0 mg, 0.02 mmol). After 16 h the reaction mixture was concentrated under reduced pressure and the residue dissolved in a minimum volume with methanol. The resulting solution was subjected to flash chromatography (silica, 1:9 v/v ammonia-saturated methanol/dichloromethane elution) and concentration of the appropriate fractions (R_f = 0.4) afforded compound **5.51** (35 mg, 63%) as a yellow, crystalline solid, m.p.= 200-202 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.29 (q, *J* = 4.6 Hz, 1H), 8.67 (d, *J* = 8.4 Hz, 1H), 8.47 (s, 1H), 8.17 (s, 1H), 8.08 (s, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.9 Hz, 1H), 6.59 (t, *J* = 5.4 Hz, 1H), 6.56 (d, *J* = 8.9 Hz, 1H), 6.33 (s, 1H), 5.46 (s, 1H), 4.64 (t, *J* = 5.0 Hz, 2H), 4.40 (m, 1H), 4.20 (m, 1H), 3.98 (t, *J* = 5.1 Hz, 2H), 3.98 – 3.67 (overlapped brs, 4H), 3.66 (m, 2H), 3.62 (m, 2H), 3.54 (m, 2H), 3.40 (m, 2H), 3.15 (d, *J* = 4.6 Hz, 3H), 3.01 (q, *J* = 7.1 Hz, 1H), 2.86 (brs, 2H), 2.81 (dd, *J* = 12.8, 4.9 Hz, 1H), 2.67 (d, *J* = 12.8 Hz, 1H), 2.63 (m, 2H), 2.42 (s, 3H), 2.11 (m, 4H), 1.57 (m, 4H), 1.30 (m, 2H);

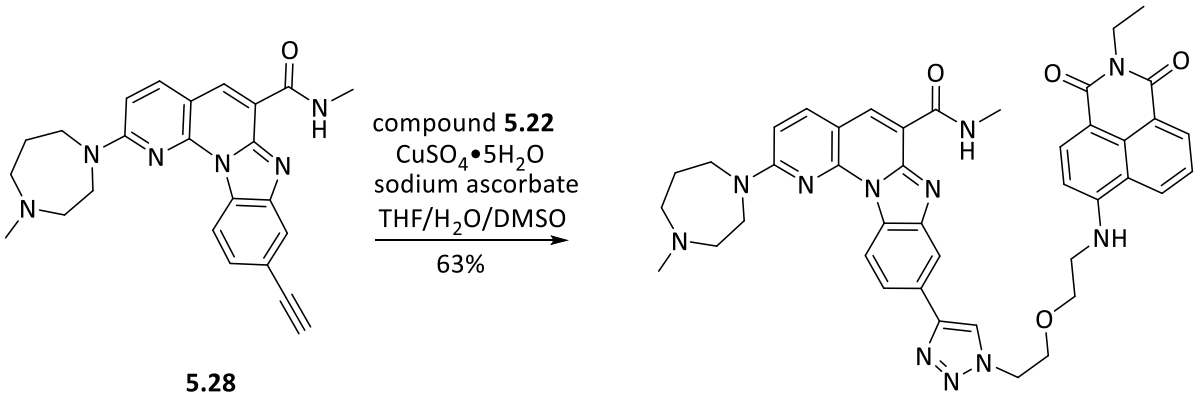
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 173.5, 164.4, 163.9, 158.2, 148.2, 148.1, 147.0, 143.7, 139.4, 133.9, 129.6, 127.7, 121.2, 120.2, 116.8, 115.3, 114.4, 107.2, 104.9, 70.6, 70.3, 70.1, 69.6, 61.9, 60.2, 57.6, 57.2, 55.6, 50.5, 47.6 (2×CH_2), 46.8, 40.7, 39.3, 35.9, 28.2, 28.2, 27.2, 26.6, 25.7.

IR ν_{max} 3263, 2926, 2864, 1699, 1652, 1587, 1538, 1519, 1450, 1408, 1246, 1147, 1120, 732 cm^{-1};

MS (ESI, +ve) *m/z* 813 [$(M+H)^+$, 100%];

HRMS *m/z* 813.3964 $(M+H)^+$ calcd for $C_{40}H_{53}N_{12}O_5S$ 813.3977.

10-(1-(2-(2-((2-Ethyl-1,3-dioxo-2,3-dihydro-1*H*-benzo[de]isoquinolin-6-yl)amino)ethoxy)ethyl)-1*H*-1,2,3-triazol-4-yl)-*N*-methyl-2-(4-methyl-1,4-diazepan-1-yl)benzo[4,5]imidazo[1,2-*a*][1,8]naphthyridine-6-carboxamide (**5.52**)



5.28 **5.52**

A magnetically stirred solution of compounds **5.28** (30 mg, 0.07 mmol) and **5.22** (31 mg, 0.09 mmol) in THF/H_2O/DMSO (2 mL of a 2:2:1 v/v/v mixture) maintained at ambient temperatures was treated with sodium ascorbate (3.0 mg, 0.01 mmol) and $CuSO_4$•$5H_2O$ (5.0 mg, 0.02 mmol). After 16 h the reaction mixture was concentrated under reduced pressure and the residue dissolved in a minimum volume with methanol. The resulting solution was subjected to flash chromatography (silica, 1:9 v/v ammonia-saturated methanol/dichloromethane elution) and concentration of the appropriate fractions (R_f = 0.4) afforded compound **5.52** (35 mg, 63%) as a yellow, crystalline solid, m.p. = 245-247°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.28 (q, *J* = 4.4 Hz, 1H), 8.68 (d, *J* = 8.5 Hz, 1H), 8.51 (s, 1H), 8.38 (d, *J* = 8.0 Hz, 1H), 8.29 (d, *J* = 7.4 Hz, 1H), 8.09 (m, 2H), 7.96 (s, 1H), 7.81 (m, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 6.61 (t, *J* = 8.0 Hz, 2H), 5.78 (m, 1H), 4.68 (m, 2H), 4.09 (m, 4H), 3.89 (m, 2H), 3.80 (overlapped brs, 4H), 3.56 (m, 2H), 3.15 (d, *J* = 4.4 Hz, 3H), 2.82 (m, 2H), 2.60 (m, 2H), 2.39 (s, 3H), 2.10 (m, 2H), 1.24 (t, *J* = 6.9 Hz, 3H);

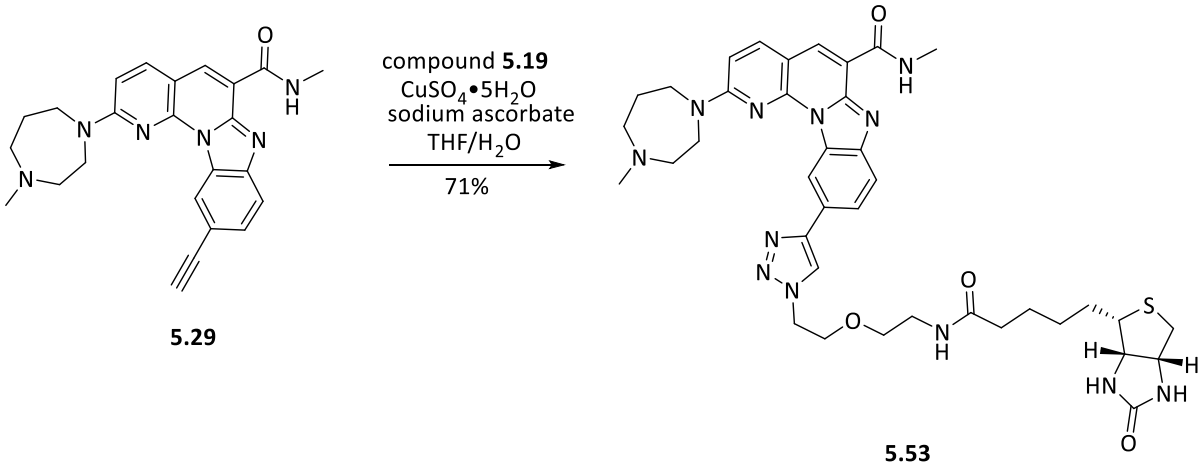
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 164.4, 164.3, 163.9, 158.3, 149.4, 148.4, 148.2, 147.1, 143.6, 139.4, 134.1, 134.0, 130.9, 129.7, 129.6, 127.4, 126.5, 124.9, 122.9, 120.8, 120.5, 120.0, 116.7, 115.3, 114.5, 110.9, 107.2, 105.0, 104.2, 69.3, 68.9, 57.7, 57.2, 50.4, 47.7 (2×CH_2), 46.9, 43.2, 35.1, 27.4, 26.6, 13.5;

IR ν_{max} 3364, 2932, 1682, 1645, 1576, 1538, 1519, 1450, 1408, 1391, 1367, 1347, 1247, 1121, 732 cm^{-1};

MS (ESI, +ve) *m/z* 766 [$(M+H)^+$, 100%];

HRMS *m/z* 766.3557 $(M+H)^+$ calcd for $C_{42}H_{44}N_{11}O_4$ 766.3557.

***N*-Methyl-2-(4-methyl-1,4-diazepan-1-yl)-9-(1-(2-(2-(5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)pentanamido)ethoxy)ethyl)-1*H*-1,2,3-triazol-4-yl)benzo[4,5]imidazo[1,2-*a*][1,8]naphthyridine-6-carboxamide** (**5.53**)



5.29 **5.53**

A magnetically stirred solution of compounds **5.29** (30 mg, 0.07 mmol) and **5.19** (31 mg, 0.09 mmol) in THF/H_2O (2 mL of a 4:1 v/v mixture) maintained at ambient temperatures was treated with sodium ascorbate (3.0 mg, 0.01 mmol) and $CuSO_4$•$5H_2O$ (5.0 mg, 0.02 mmol). After 16 h the reaction mixture was concentrated under reduced pressure and the residue dissolved in a minimum volume with methanol. The resulting solution was subjected to flash

chromatography (silica, 1:4 v/v ammonia-saturated methanol/dichloromethane elution) and concentration of the appropriate fractions (R_f = 0.6) afforded compound **5.53** (40 mg, 71%) as a yellow, crystalline solid, m.p. = 248-250 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.24 (q, *J* = 4.6 Hz, 1H), 9.13 (s, 1H), 8.34 (s, 1H), 7.85 (s, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 8.9 Hz, 1H), 6.95 (brs, 1H), 6.44 (d, *J* = 8.9 Hz, 1H), 6.30 (s, 1H), 5.58 (s, 1H), 4.63 (t, *J* = 4.6 Hz, 2H), 4.38 (m, 1H), 4.08 (m, 1H), 3.95 (t, *J* = 4.6 Hz, 2H), 3.77 (brs, 4H), 3.61 (t, *J* = 4.7 Hz, 2H), 3.43 (t, *J* = 4.7 Hz, 2H), 3.14 (d, *J* = 4.6 Hz, 3H), 2.89 (m, 3H), 2.76 (dd, *J* = 12.8, 4.6 Hz, 1H), 2.63 (d, *J* = 12.8 Hz, 1H), 2.58 (m, 2H), 2.37 (s, 3H), 2.08 (m, 4H), 1.62 – 1.37 (m, 4H), 1.21 (m, 2H);

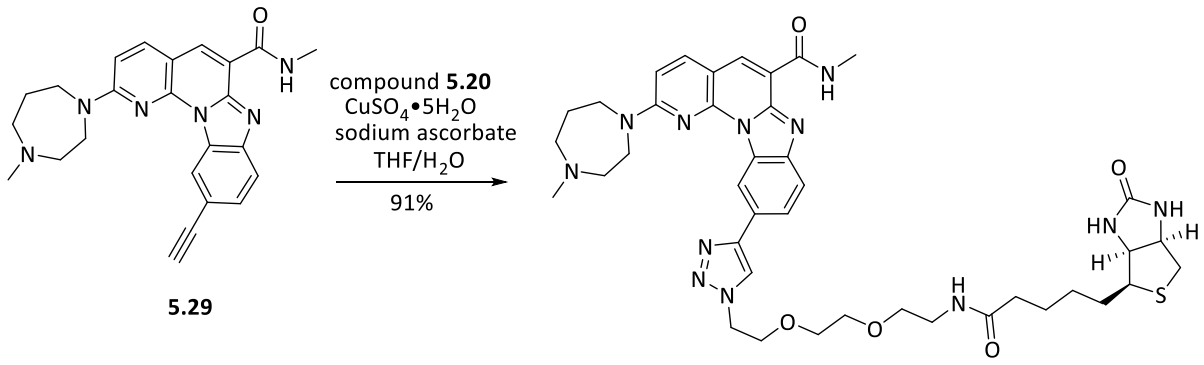
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.6, 164.4, 163.9, 158.0, 148.4, 147.9, 146.9, 143.1, 139.2, 133.8, 130.0, 124.7, 123.0, 120.5, 118.6, 114.2, 113.7, 107.0, 104.8, 70.2, 69.2, 61.8, 60.2, 57.8, 57.2, 55.7, 50.4, 47.6 (2×CH_2), 46.7, 40.7, 39.1, 35.8, 28.2, 28.1, 27.1, 26.6, 25.6;

IR ν_{max} 3268, 2933, 1694, 1650, 1571, 1537, 1518, 1450, 1405, 1250, 1213, 1130, 1057, 777 cm^{-1};

MS (ESI, +ve) *m/z* 769 [$(M+H)^+$, 100%];

HRMS *m/z* 769.3700 $(M+H)^+$ calcd for $C_{38}H_{49}N_{12}O_4S$ 769.3715.

***N*-Methyl-2-(4-methyl-1,4-diazepan-1-yl)-10-(1-(2-(2-(2-(5-((3a*R*,4*R*,6a*S*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)pentanamido)ethoxy)ethoxy)ethyl)-1*H*-1,2,3-triazol-4-yl)benzo[4,5]imidazo[1,2-*a*][1,8]naphthyridine-6-carboxamide** (**5.54**)



5.29 **5.54**

A magnetically stirred solution of compounds **5.29** (50 mg, 0.12 mmol) and **5.20** (58 mg, 0.14 mmol) in THF/H_2O (2 mL of a 4:1 v/v mixture) maintained at ambient temperatures was

treated with sodium ascorbate (5.0 mg, 0.02 mmol) and $CuSO_4 \bullet 5H_2O$ (9.0 mg, 0.04 mmol). After 16 h the reaction mixture was concentrated under reduced pressure and the residue dissolved in a minimum volume with methanol. The resulting solution was subjected to flash chromatography (silica, 1:4 v/v ammonia-saturated methanol/dichloromethane elution) and concentration of the appropriate fractions (R_f = 0.4) afforded compound **5.54** (90 mg, 91%) as a yellow, crystalline solid, m.p. = 140-142°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.21 (q, *J* = 4.8 Hz, 1H), 9.15 (s, 1H), 8.31 (s, 1H), 7.89 (s, 1H), 7.71 (s, 2H), 7.64 (d, *J* = 8.9 Hz, 1H), 6.80 (brs, 1H), 6.52 (s, 1H), 6.42 (d, *J* = 8.9 Hz, 1H), 5.81 (s, 1H), 4.62 (t, *J* = 4.8 Hz, 2H), 4.36 (m, 1H), 4.15 (m, 1H), 3.97 (t, *J* = 4.8 Hz, 2H) 3.90 – 3.50 (overlapped brs, 4H), 3.65 (m, 2H), 3.59 (m, 2H), 3.50 (m, 2H), 3.36 (m, 2H), 3.11 (d, *J* = 4.8 Hz, 3H), 2.96 (m, 1H), 2.90 (brs, 2H), 2.77 (dd, *J* = 12.8, 4.8 Hz, 1H), 2.64 (d, *J* = 12.8 Hz, 1H), 2.59 (brs, 2H), 2.37 (s, 3H), 2.19 – 1.99 (m, 4H), 1.64 – 1.46 (m, 4H), 1.27 (m, 2H);

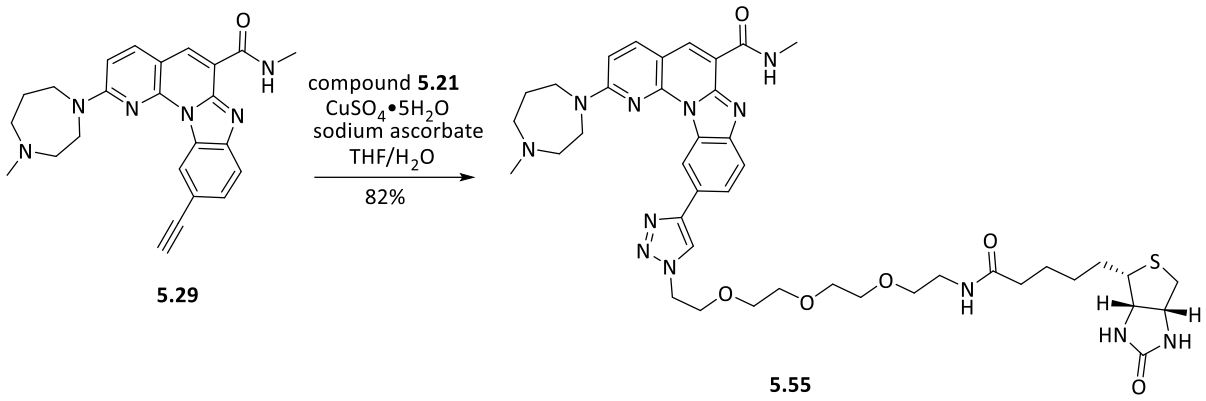
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.6, 164.3, 164.1, 157.9, 148.3, 147.8, 146.9, 143.0, 139.1, 133.7, 129.9, 124.7, 122.9, 120.5, 118.6, 114.2, 113.6, 106.9, 104.8, 70.5, 70.1, 70.0, 69.6, 61.8, 60.2, 57.6, 57.1, 55.7, 50.4, 47.6 ($2\times CH_2$), 46.6, 40.6, 39.2, 35.9, 28.3, 28.1, 26.9, 26.6, 25.7;

IR ν_{max} 3263, 2930, 1698, 1651, 1566, 1537, 1518, 1450, 1405, 1349, 1255, 1212, 1126, 908, 727 cm^{-1};

MS (ESI, +ve) *m/z* 835 [$(M+Na)^+$, 50%], 813 [$(M+H)^+$, 100];

HRMS *m/z* 813.3995 $(M+H)^+$ calcd for $C_{40}H_{53}N_{12}O_5S$ 813.3983.

***N*-Methyl-2-(4-methyl-1,4-diazepan-1-yl)-10-(1-(13-oxo-17-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-d]imidazol-4-yl)-3,6,9-trioxa-12-azaheptadecyl)-1*H*-1,2,3-triazol-4-yl)benzo[4,5]imidazo[1,2-*a*][1,8]naphthyridine-6-carboxamide** (**5.55**)



5.29 **5.55**

A magnetically stirred solution of compounds **5.29** (30 mg, 0.07 mmol) and **5.21** (39 mg, 0.09 mmol) in THF/H_2O (2 mL of a 4:1 v/v mixture) maintained at ambient temperatures was treated with sodium ascorbate (3.0 mg, 0.01 mmol) and $CuSO_4$•$5H_2O$ (5.0 mg, 0.02 mmol). After 16 h the reaction mixture was concentrated under reduced pressure and the residue dissolved in a minimum volume with methanol. The resulting solution was subjected to flash chromatography (silica, 3:8 v/v ammonia-saturated methanol/dichloromethane elution) and concentration of the appropriate fractions (R_f = 0.5) afforded compound **5.55** (51 mg, 82%) as a yellow, crystalline solid, m.p. = 170-172°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.18 (q, *J* = 4.7 Hz, 1H), 9.28 (s, 1H), 8.35 (s, 1H), 7.92 (s, 1H), 7.70 (m, 3H), 6.72 (t, *J* = 5.5 Hz, 1H), 6.46 (d, *J* = 8.9 Hz, 1H), 6.40 (s, 1H), 5.57 (s, 1H), 4.58 (t, *J* = 5.1 Hz, 2H), 4.35 (m, 1H), 4.14 (m, 1H), 3.92 (t, *J* = 5.1 Hz, 2H), 3.92 – 3.57 (overlapped brs, 4H), 3.62 (m, 2H), 3.57 (m, 2H), 3.52 (m, 2H), 3.49 (m, 2H), 3.41 (m, 2H), 3.29 (q, *J* = 5.5 Hz, 2H), 3.08 (d, *J* = 4.7 Hz, 3H), 2.96 (m, 1H), 2.90 (overlapped brs, 2H), 2.75 (dd, *J* = 12.8, 4.9 Hz, 1H), 2.62 (overlapped d, *J* = 12.8 Hz, 1H), 2.62 (overlapped brs, 2H), 2.38 (s, 3H), 2.13 (m, 2H), 2.06 (t, *J* = 7.5 Hz, 2H), 1.54 (m, 4H), 1.26 (m, 2H);

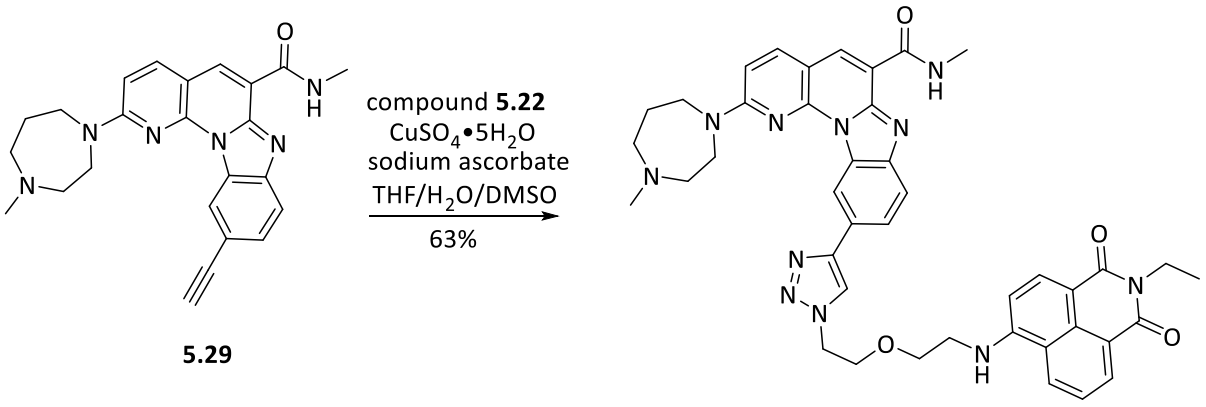
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.5, 171.3, 164.4, 164.1, 158.2, 148.3, 148.0, 147.1, 143.1, 139.4, 133.9, 130.2, 124.9, 123.0, 120.7, 118.7, 114.4, 113.8, 107.2, 104.9, 70.6, 70.5, 70.5, 70.1, 70.0, 69.7, 61.8, 60.5, 60.2, 55.7, 50.4, 47.6 (2×CH_2), 46.5, 40.6, 39.2, 35.9, 28.3, 28.2, 26.6, 25.7, 21.2, 14.3;

IR ν_{max} 3343, 2934, 1653, 1630, 1571, 1518, 1461, 1406, 1253, 1133, 777 cm^{-1};

MS (ESI, +ve) *m/z* 857 [$(M+H)^+$, 100%];

HRMS *m/z* 857.4227 $(M+H)^+$ calcd for $C_{42}H_{57}N_{12}O_6S$ 857.4239.

10-(1-(2-(2-((2-Ethyl-1,3-dioxo-2,3-dihydro-1*H*-benzo[de]isoquinolin-6-yl)amino)ethoxy)ethyl)-1*H*-1,2,3-triazol-4-yl)-*N*-methyl-2-(4-methyl-1,4-diazepan-1-yl)benzo[4,5]imidazo[1,2-*a*][1,8]naphthyridine-6-carboxamide (**5.56**)



5.29 **5.56**

A magnetically stirred solution of compounds **5.29** (30 mg, 0.07 mmol) and **5.22** (31 mg, 0.09 mmol) in THF/H_2O/DMSO (2 mL of a 2:2:1 v/v/v mixture) maintained at ambient temperature was treated with sodium ascorbate (3.0 mg, 0.01 mmol) and $CuSO_4$•$5H_2O$ (5.0 mg, 0.02 mmol). After 16 h the reaction mixture was concentrated under reduced pressure and the residue dissolved in a minimum volume with methanol. The resulting solution was subjected to flash chromatography (silica, 1:9 v/v ammonia-saturated methanol/dichloromethane elution) and concentration of the appropriate fractions (R_f = 0.4) afforded compound **5.56** (35 mg, 63%) as a yellow, crystalline solid, m.p. = 205-207 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.23 (q, *J* = 4.8 Hz, 1H), 8.84 (s, 1H), 8.34 (s, 1H), 8.22 (d, *J* = 8.4 Hz, 1H), 7.95 (m, 1H), 7.87 (d, *J* = 7.6 Hz, 1H), 7.79 (s, 1H), 7.71 (m, 1H), 7.66 (d, *J* = 8.3 Hz, 1H), 7.62 (d, *J* = 8.9 Hz, 1H), 6.93 (brs, 1H), 6.53 (d, *J* = 8.4 Hz, 1H), 6.37 (d, *J* = 8.9 Hz, 1H), 5.77 (brs, 1H), 4.66 (t, *J* = 4.4 Hz, 2H), 4.12 – 3.94 (m, 4H), 3.87 (m, 2H), 3.73 (brs, 2H), 3.52 (m, 4H), 3.15 (d, *J* = 4.8 Hz, 3H), 2.85 (brs, 2H), 2.58 (brs, 2H), 2.37 (s, 3H), 2.08 (brs, 2H), 1.20 (t, *J* = 6.9 Hz, 3H);

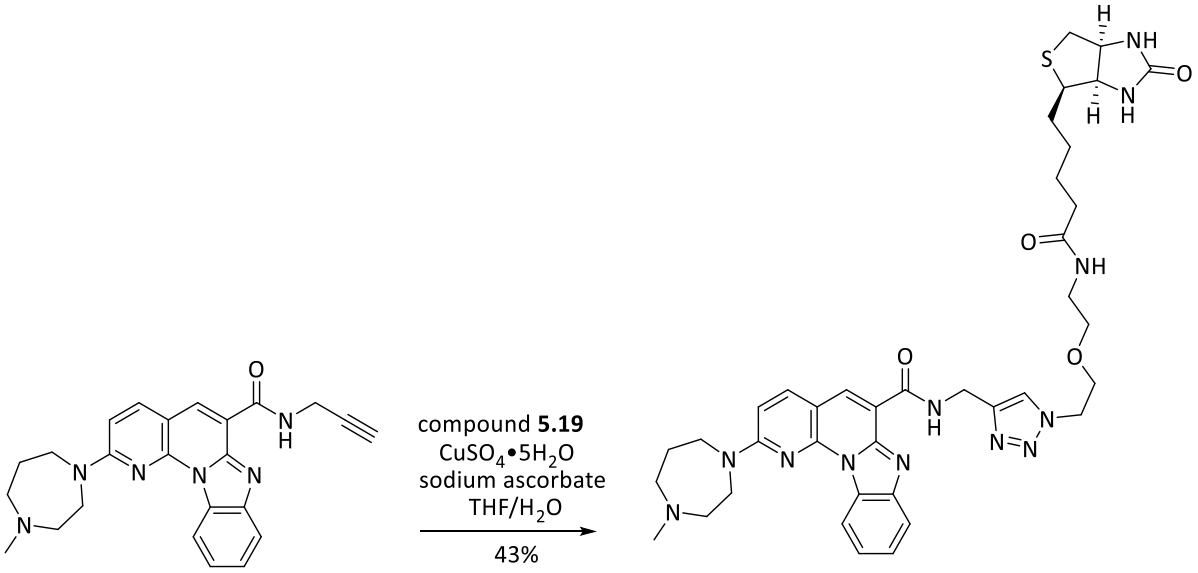
$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 164.3, 163.9, 163.7, 157.7, 149.3, 148.5, 147.8, 146.6, 143.1, 139.1, 133.8, 133.7, 130.5, 129.8, 129.4, 126.2, 124.6, 124.3, 122.7, 122.4, 120.2, 120.1(8), 118.6, 114.5, 113.7, 110.5, 107.0, 104.6, 104.0, 69.2, 68.9, 57.8, 57.0, 50.4, 47.4 (2×CH_2), 46.6, 43.2, 35.1, 26.9, 26.6, 13.5;

IR ν_{max} 3374, 2938, 1678, 1641, 1612, 1576, 1518, 1450, 1392, 1367, 1347, 1296, 1249, 1126, 1065, 775 cm^{-1};

MS (ESI, +ve) *m/z* 766 [$(M+H)^+$, 100%], 788 [$(M+Na)^+$, 40%];

HRMS *m/z* 766.3549 $(M+H)^+$ calcd for $C_{42}H_{44}N_{11}O_4$ 766.3572.

2-(4-Methyl-1,4-diazepan-1-yl)-*N*-((1-(2-(2-(5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-d]imidazol-4-yl)pentanamido)ethoxy)ethyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzo[4,5]imidazo[1,2-*a*][1,8]naphthyridine-6-carboxamide (**5.57**)



5.30 **5.57**

A magnetically stirred solution of compounds **5.30** (50 mg, 0.12 mmol) and **5.19** (47 mg, 0.13 mmol) in THF/H_2O (2 mL of a 4:1 v/v mixture) maintained at ambient temperatures was treated with sodium ascorbate (5.0 mg, 0.02 mmol) and $CuSO_4$•$5H_2O$ (9.0 mg, 0.04 mmol). After 16 h the reaction mixture was concentrated under reduced pressure and the residue dissolved in a minimum volume with methanol. The resulting solution was subjected to flash chromatography (silica, 1:9 v/v ammonia-saturated methanol/dichloromethane elution) and

concentration of the appropriate fractions (R_f = 0.3) afforded compound **5.57** (40 mg, 43%) as a yellow, crystalline solid, m.p. = 178-180 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.03 (t, *J* = 6.0 Hz, 1H), 8.68 (d, *J* = 8.3 Hz, 1H), 8.32 (s, 1H), 7.92 (s, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.64 (d, *J* = 8.9 Hz, 1H), 7.47 (appeared t, *J* = 7.6 Hz, 1H), 7.33 (appeared t, *J* = 7.6 Hz, 1H), 6.89 (t, *J* = 5.7 Hz, 1H), 6.60 (s, 1H), 6.42 (d, *J* = 8.9 Hz, 1H), 5.82 (s, 1H), 4.86 (d, *J* = 6.0 Hz, 2H), 4.52 (t, *J* = 5.0 Hz, 2H), 4.42 (dd, *J* = 7.9, 4.9 Hz, 1H), 4.23 (dd, *J* = 7.9, 4.5 Hz, 1H), 3.81 (m, 4H), 3.65 (brs, 2H), 3.49 (t, *J* = 4.9 Hz, 2H), 3.32 (m, 2H), 3.01 (q, *J* = 7.1 Hz, 1H), 2.83 – 2.78 (m, 3H), 2.66 (d, *J* = 12.7 Hz, 1H), 2.57 (m, 2H), 2.38 (s, 3H), 2.16 – 2.00 (m, 4H), 1.65 (m, 1H), 1.60 – 1.47 (m, 3H), 1.38 – 1.24 (m, 2H);

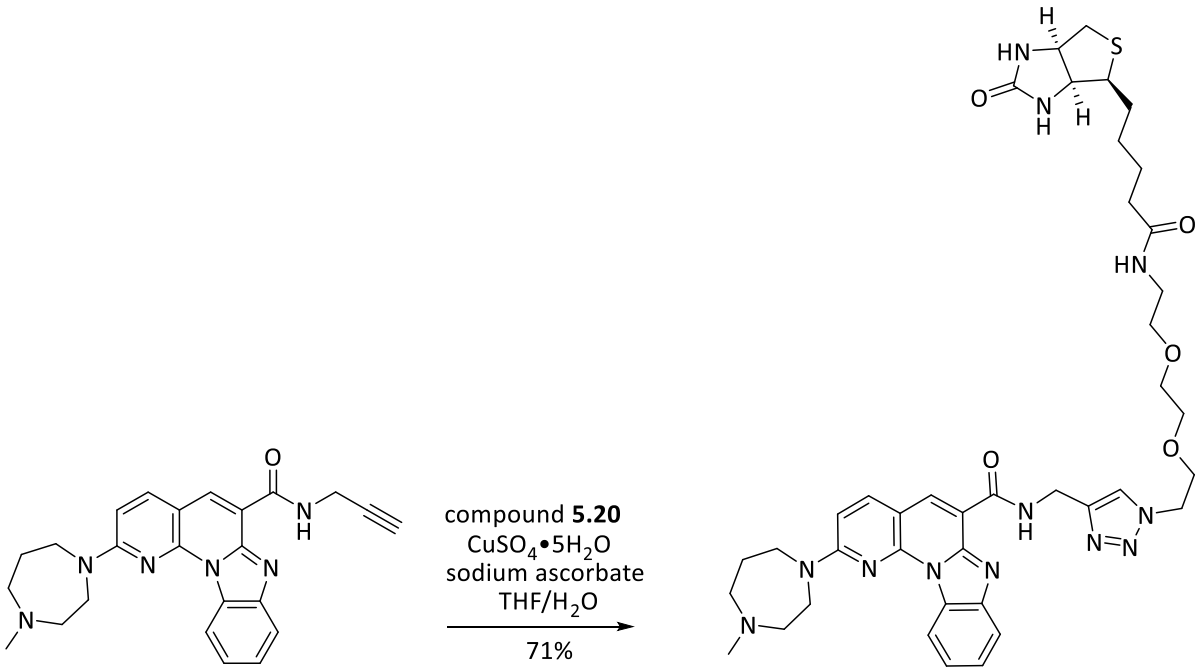
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.7, 164.2, 164.1, 158.1, 147.2, 147.1, 145.7, 143.2, 139.3, 133.9, 129.7, 125.2, 124.0, 122.2, 118.8, 116.5, 113.7, 106.8, 104.8, 69.9, 69.1, 61.8, 60.2, 57.6, 57.1, 55.8, 50.2, 47.5 (2 × CH_2), 46.8, 40.7, 39.2, 35.8, 35.6, 28.2, 28.1, 27.1, 25.7;

IR ν_{max} 3257, 3053, 2932, 2864, 1698, 1651, 1588, 1538, 1519, 1448, 1408, 1348, 1264, 1211, 1151, 1137, 730, 699 cm^{-1};

MS (ESI, +ve) *m/z* 791 [$(M+Na)^+$, 100], 769 [$(M+H)^+$, 40%];

HRMS *m/z* 769.3715 $(M+H)^+$ calcd for $C_{38}H_{49}N_{12}O_4S$ 769.3715.

2-(4-Methyl-1,4-diazepan-1-yl)-*N*-((1-(2-(2-(2-(5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-d]imidazol-4-yl)pentanamido)ethoxy)ethoxy)ethyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzo[4,5]imidazo[1,2-*a*][1,8]naphthyridine-6-carboxamide (**5.58**)



5.30 **5.58**

A magnetically stirred solution of compounds **5.30** (50 mg, 0.12 mmol) and **5.20** (47 mg, 0.14 mmol) in THF/H_2O (2 mL of a 4:1 v/v mixture) maintained at ambient temperatures was treated with sodium ascorbate (5.0 mg, 0.02 mmol) and $CuSO_4$•$5H_2O$ (9.0 mg, 0.04 mmol). After 16 h the reaction mixture was concentrated under reduced pressure and the residue dissolved in a minimum volume with methanol. The resulting solution was subjected to flash chromatography (silica, 1:4 v/v ammonia-saturated methanol/dichloromethane elution) and concentration of the appropriate fractions (R_f = 0.3) afforded compound **5.58** (70 mg, 71%) as a yellow, crystalline solid, m.p. = 193-195°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.04 (t, *J* = 5.9 Hz, 1H), 8.70 (d, *J* = 8.2 Hz, 1H), 8.37 (s, 1H), 7.93 (s, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.69 (d, *J* = 8.9 Hz, 1H), 7.47 (appeared t, *J* = 7.7 Hz, 1H), 7.34 (appeared t, *J* = 7.7 Hz, 1H), 7.00 (t, *J* = 5.6 Hz, 1H), 6.57 (s, 1H), 6.43 (d, *J* = 8.9 Hz, 1H), 5.82 (s, 1H), 4.87 (d, *J* = 5.9 Hz, 2H), 4.52 (t, *J* = 5.1 Hz, 2H), 4.40 (dd, *J* = 7.9, 4.9 Hz, 1H), 4.21 (dd, *J* = 7.9, 4.6 Hz, 1H), 3.85 (m, 4H), 3.67 (brs, 2H), 3.57 – 3.43 (m, 6H), 3.37 (t, *J* = 5.4 Hz, 2H), 3.01

(m, 1H), 2.77 (m, 3H), 2.65 (d, *J* = 12.7 Hz, 1H), 2.56 (m, 2H), 2.37 (s, 3H), 2.16 (t, *J* = 7.4 Hz, 2H), 2.11 – 2.02 (m, 2H), 1.70 – 1.51 (m, 4H), 1.34 (m, 2H);

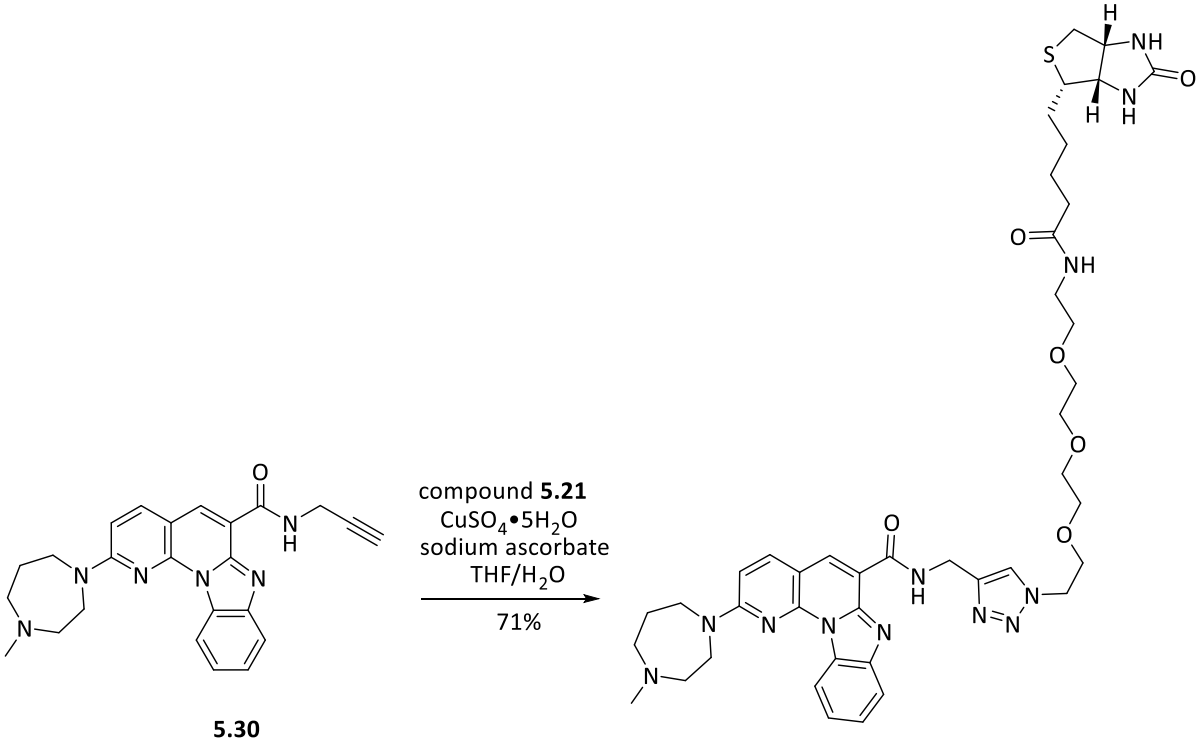
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 173.6, 164.1, 164.2, 158.1, 147.2, 147.2, 145.7, 143.2, 139.3, 133.9, 129.7, 125.1, 123.9, 122.2, 118.8, 116.5, 113.8, 106.8, 104.8, 70.4, 70.0(5), 70.0(1), 69.4, 61.8, 60.2, 57.5, 57.1, 55.7, 50.2, 47.5 (2×CH_2), 46.8, 40.6, 39.3, 36.0, 35.5, 28.3, 28.1, 27.1, 25.7;

IR ν_{max} 3244, 3073, 2928, 2852, 1702, 1647, 1587, 1538, 1519, 1448, 1408, 1348, 1235, 1210, 1136, 1114, 776 cm^{-1};

MS (ESI, +ve) *m/z* 835 [$(M+Na)^+$, 100%], 813 [$(M+H)^+$, 50];

HRMS *m/z* 813.3983 $(M+H)^+$ calcd for $C_{40}H_{53}N_{12}O_5S$ 813.3977.

2-(4-Methyl-1,4-diazepan-1-yl)-*N*-((1-(13-oxo-17-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)-3,6,9-trioxa-12-azaheptadecyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzo[4,5]imidazo[1,2-*a*][1,8]naphthyridine-6-carboxamide (**5.59**)



5.30 **5.59**

A magnetically stirred solution of compounds **5.30** (50 mg, 0.12 mmol) and **5.21** (81 mg, 0.18 mmol) in THF/H_2O (2 mL of a 4:1 v/v mixture) maintained at ambient temperatures was

treated with sodium ascorbate (5.0 mg, 0.01 mmol) and $CuSO_4 \bullet 5H_2O$ (9.0 mg, 0.04 mmol). After 16 h the reaction mixture was concentrated under reduced pressure and the residue dissolved in a minimum volume with methanol. The resulting solution was subjected to flash chromatography (silica, 1:9 v/v ammonia-saturated methanol/dichloromethane elution) and concentration of the appropriate fractions (R_f = 0.3) afforded compound **5.59** (40 mg, 71%) as a yellow, crystalline solid, m.p. = 186-188 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.06 (t, *J* = 5.8 Hz, 1H), 8.82 (d, *J* = 8.1 Hz, 1H), 8.49 (s, 1H), 7.88 (overlapped s, 1H), 7.87 (overlapped d, *J* = 7.5 Hz, 1H), 7.82 (d, *J* = 8.9 Hz, 1H), 7.51 (appeared t, *J* = 7.6 Hz, 1H), 7.39 (appeared t, *J* = 7.6 Hz, 1H), 6.87 (t, *J* = 5.4 Hz, 1H), 6.57 (d, *J* = 8.9 Hz, 1H), 6.45 (s, 1H), 5.58 (s, 1H), 4.91 (d, *J* = 5.8 Hz, 2H), 4.53 (t, *J* = 5.1 Hz, 2H), 4.43 (dd, *J* = 7.9, 4.9 Hz, 1H), 4.24 (dd, *J* = 7.9, 4.7 Hz, 1H), 4.02 – 3.64 (m, 5H), 3.55 (m, 4H), 3.49 (m, 6H), 3.41 – 3.29 (m, 2H), 3.05 (m, 1H), 2.82 (m, 3H), 2.68 (d, *J* = 12.7 Hz, 1H), 2.60 (m, 2H), 2.40 (s, 3H), 2.18 (t, *J* = 7.4 Hz, 2H), 2.11 (m, 2H), 1.71 – 1.58 (m, 4H), 1.37 (m, 2H);

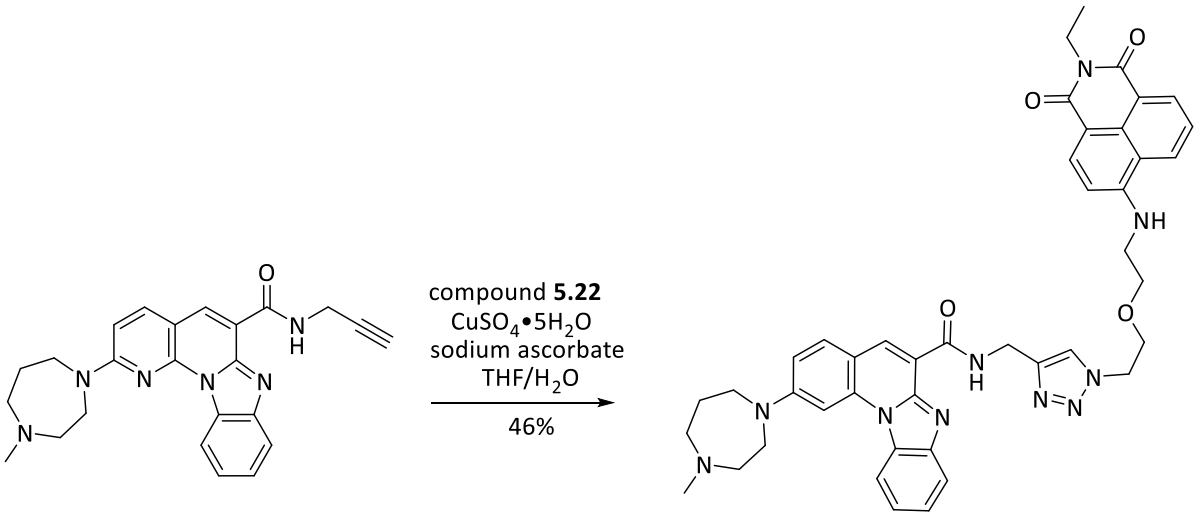
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.4, 164.1, 164.0, 158.4, 147.4, 145.7, 143.3, 139.5, 134.0, 129.8, 125.2, 123.8, 122.3, 119.0, 116.6, 114.1, 107.0, 104.9, 70.7, 70.5 (2×CH_2), 70.2, 70.0, 69.6, 61.8, 60.3, 57.7, 57.2, 55.6, 50.3, 47.7 (2×CH_2), 46.9, 40.6 (2×CH_2), 39.2, 36.0, 35.6, 28.3, 28.2, 27.3, 25.7;

IR ν_{max} 3236, 3069, 2923, 2864, 1703, 1649, 1588, 1537, 1521, 1448, 1407, 1347, 1210, 1139, 1114, 776, 735 cm^{-1};

MS (ESI, +ve) *m/z* 879 [$(M+Na)^+$, 70%], 857 [$(M+H)^+$, 100];

HRMS *m/z* 857.4242 $(M+H)^+$ calcd for $C_{42}H_{57}N_{12}O_6S$ 857.4239.

***N*-((1-(2-(2-((2-Ethyl-1,3-dioxo-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-6-yl)amino)ethoxy)ethyl)-1*H*-1,2,3-triazol-4-yl)methyl)-2-(4-methyl-1,4-diazepan-1-yl)benzo[4,5]imidazo[1,2-*a*][1,8]naphthyridine-6-carboxamide** (**5.60**)



5.30 **5.60**

A magnetically stirred solution of compounds **5.30** (35 mg, 0.09 mmol) and **5.22** (45 mg, 0.13 mmol) in THF/H_2O (2 mL of a 4:1 v/v mixture) maintained at ambient temperatures was treated with sodium ascorbate (3.0 mg, 0.01 mmol) and $CuSO_4$•$5H_2O$ (6.4 mg, 0.03 mmol). After 16 h the reaction mixture was concentrated under reduced pressure and the residue dissolved in a minimum volume with methanol. The resulting solution was subjected to flash chromatography (silica, 3:17 v/v ammonia-saturated methanol/dichloromethane elution) and concentration of the appropriate fractions (R_f = 0.3) afforded compound **5.60** (30 mg, 46%) as a yellow, crystalline solid, m.p. = 210-212 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.95 (t, *J* = 5.6 Hz, 1H), 8.60 (d, *J* = 8.2 Hz, 1H), 8.22 (d, *J* = 7.2 Hz, 1H), 8.18 (s, 1H), 8.05 (s, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.56 (d, *J* = 8.9 Hz, 1H), 7.44 (appeared t, *J* = 7.6 Hz, 1H), 7.39 (appeared t, *J* = 7.8 Hz, 1H), 7.32 (appeared t, *J* = 7.7 Hz, 1H), 6.44 (d, *J* = 8.9 Hz, 1H), 6.12 (d, *J* = 8.4 Hz, 1H), 5.48 (t, *J* = 5.0 Hz, 1H), 4.89 (d, *J* = 5.6 Hz, 2H), 4.63 (t, *J* = 4.9 Hz, 2H), 4.07 (q, *J* = 7.0 Hz, 2H), 3.97 – 3.69 (overlapped brs, 4H), 3.96 (t, *J* = 4.9 Hz, 2H), 3.70 (t, *J* = 5.0 Hz, 2H), 3.26 (q, *J* = 5.0 Hz, 2H), 2.82 (brs, 2H), 2.61 (m, 2H), 2.41 (s, 3H), 2.10 (m, 2H), 1.23 (t, *J* = 7.0 Hz, 3H);

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 164.2, 164.0, 163.6, 158.1, 148.9, 146.9(7), 146.9(2), 146.2, 143.0, 139.2, 133.6 (2 × CH), 130.8, 129.5, 129.0, 126.2, 125.0, 124.6, 124.0, 122.4, 122.2,

120.0, 118.6, 116.5, 113.6, 110.2, 106.6, 104.6, 103.7, 69.5, 68.9, 57.6, 57.2, 50.3, 47.7 ($2\times CH_2$), 46.9, 43.2, 35.9, 35.1, 27.3, 13.5;

IR ν_{max} 3333, 2937, 1686, 1651, 1587, 1538, 1524, 1392, 1383, 1366, 1348, 1294, 1248, 1131, 1053, 773cm^{-1};

MS (ESI, +ve) *m/z* 766 [$(M+H)^+$, 100%];

HRMS *m/z* 766.3557 $(M+H)^+$ calcd for $C_{42}H_{44}N_{11}O_4$ 766.3572.

6.05 References

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Appendices

Appendix One: *Plot Derived from Single-Crystal X-ray Analysis of Compound 3.36*

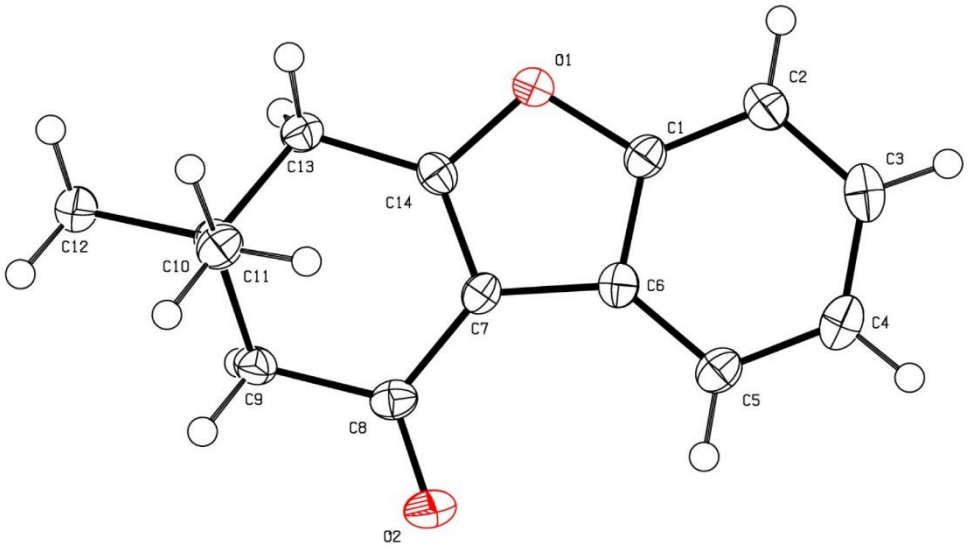

Figure A1: *Structure of compound **3.36** (CCDC 1935464). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii*

Appendix Two: *Plot Derived from Single-Crystal X-ray Analysis of Compound 3.42*

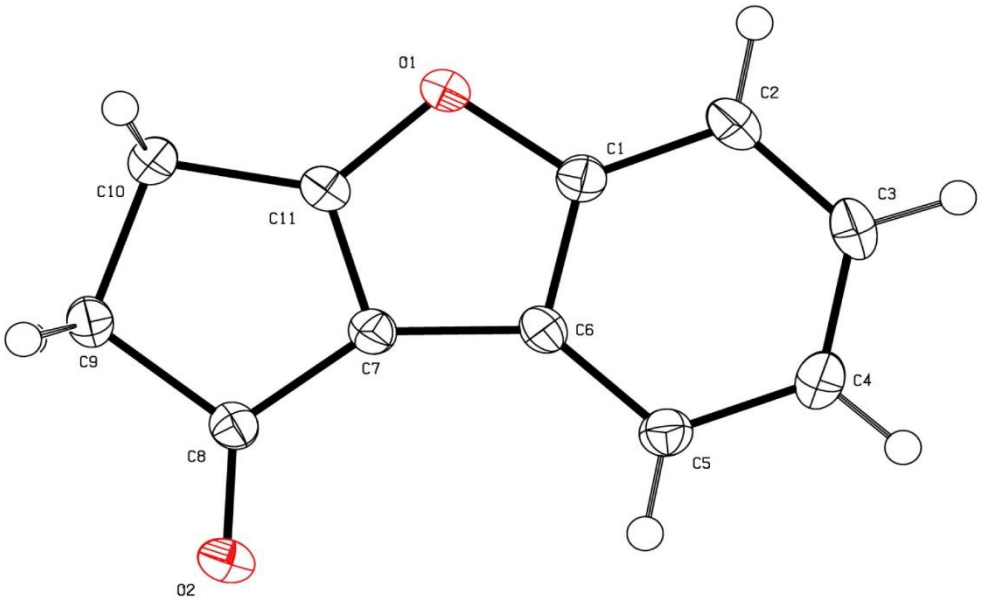

Figure A2: *Structure of compound **3.42** (CCDC 1935465). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii*

Appendix Three: *Plot Derived from Single-Crystal X-ray Analysis of Compound 3.46*

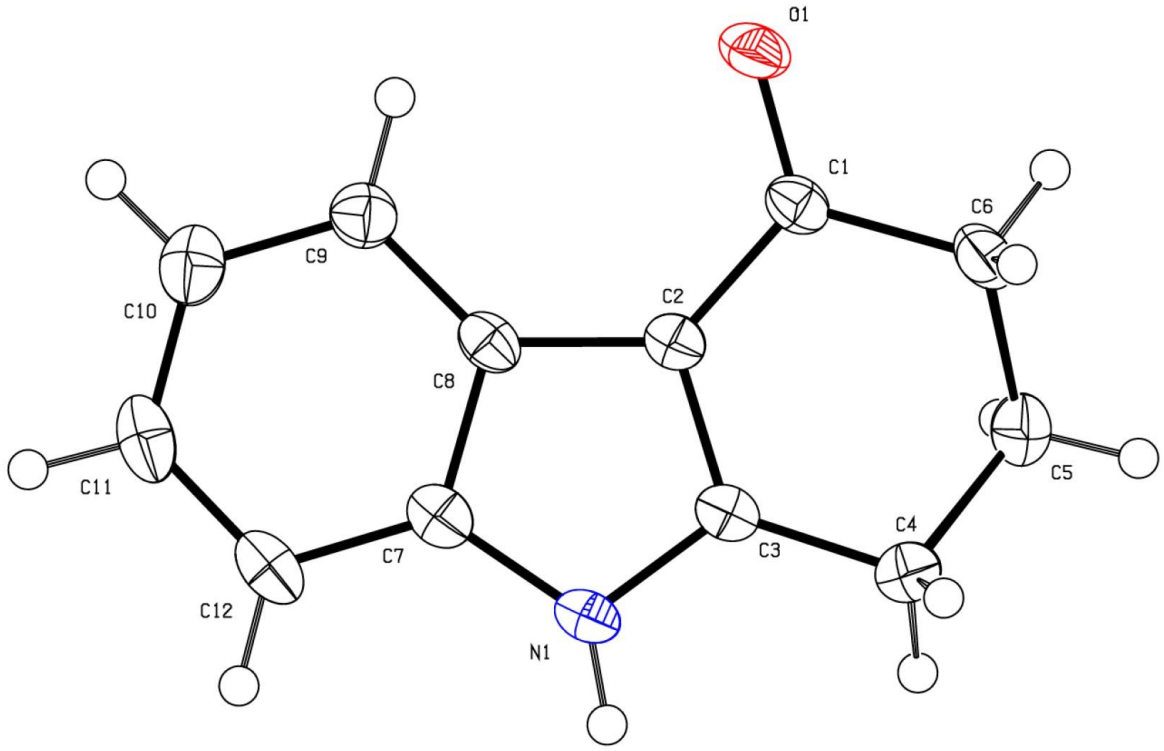

Figure A3: *Structure of compound **3.46** (CCDC 1935466). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii*

Appendix Four: *Plot Derived from Single-Crystal X-ray Analysis of Compound 3.48*

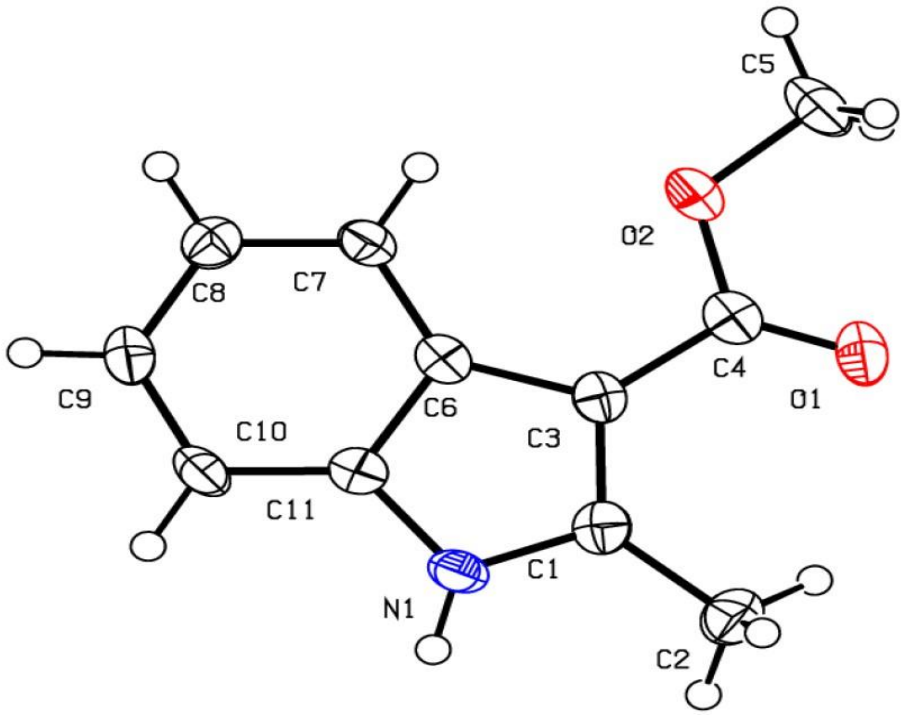

Figure A4: *Structure of compound **3.48** (CCDC 1935467). Anisotropic displacement ellipsoids show 30% probability levels. For clarity, only one of two crystallographically independent molecules in the asymmetric unit is shown (both have similar geometries). Hydrogen atoms are drawn as circles with small radii*

Appendix Five: ***Plot Derived from Single-Crystal X-ray Analysis of Compound 3.49***

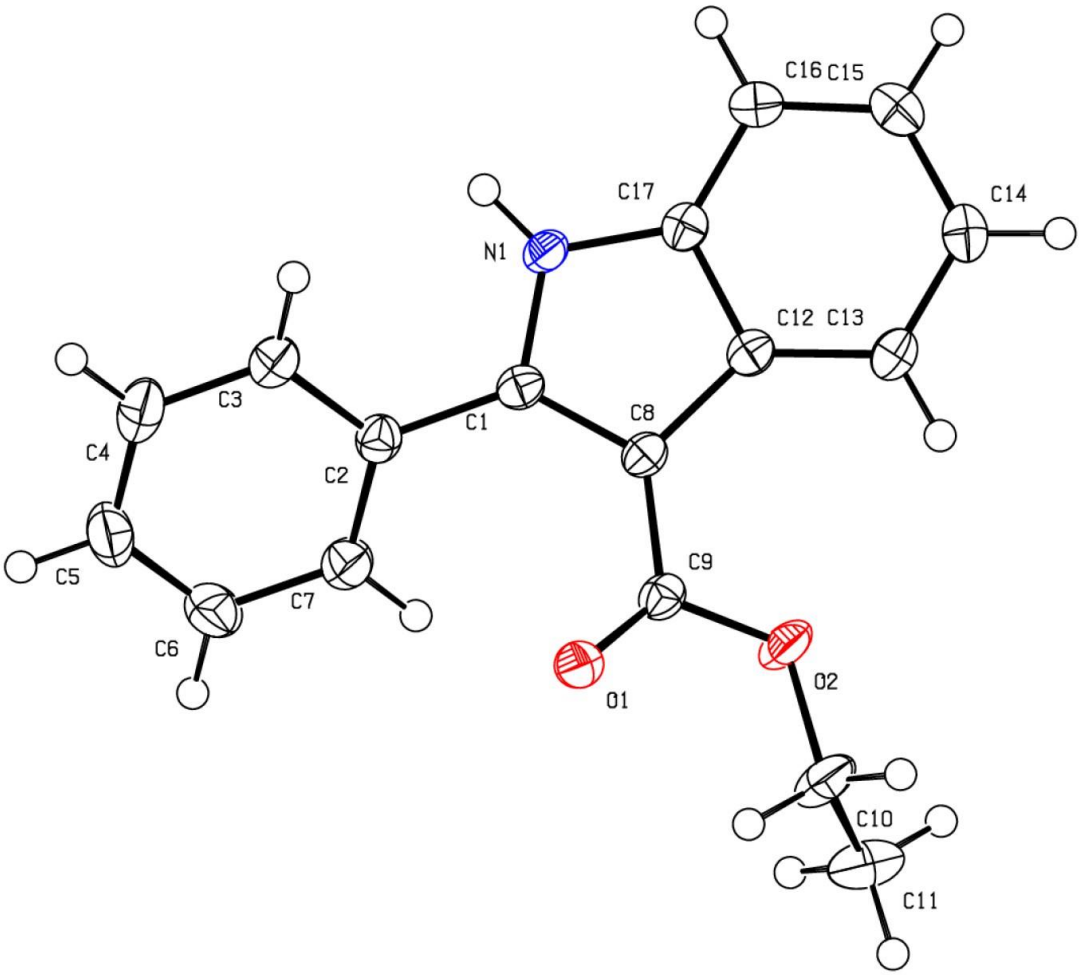

Figure A5: *Structure of compound **3.49** (CCDC 1935468). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.*

Appendix Six: *Plot Derived from Single-Crystal X-ray Analysis of Compound 3.58*

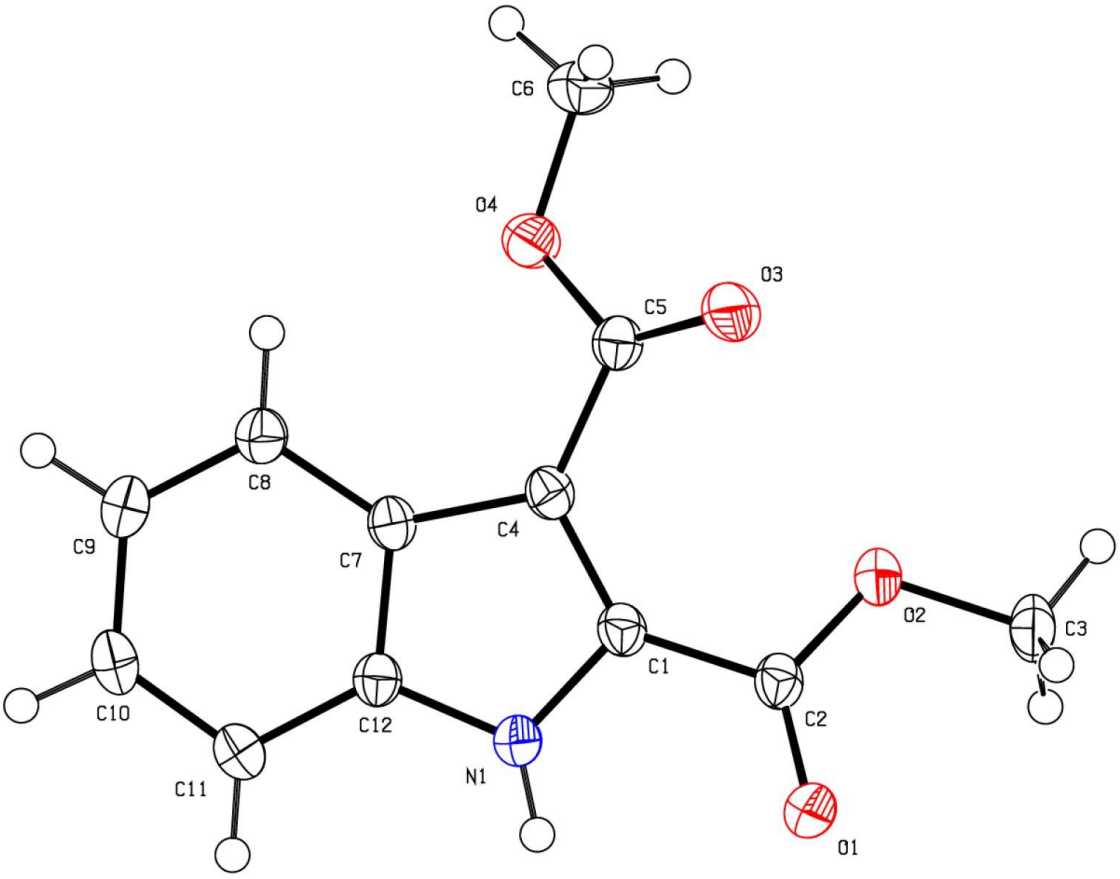

Figure A6: *Structure of compound **3.58** (CCDC 1935469). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii*

Appendix Seven: ***Plot Derived from Single-Crystal X-ray Analysis of Compound 4.26A***

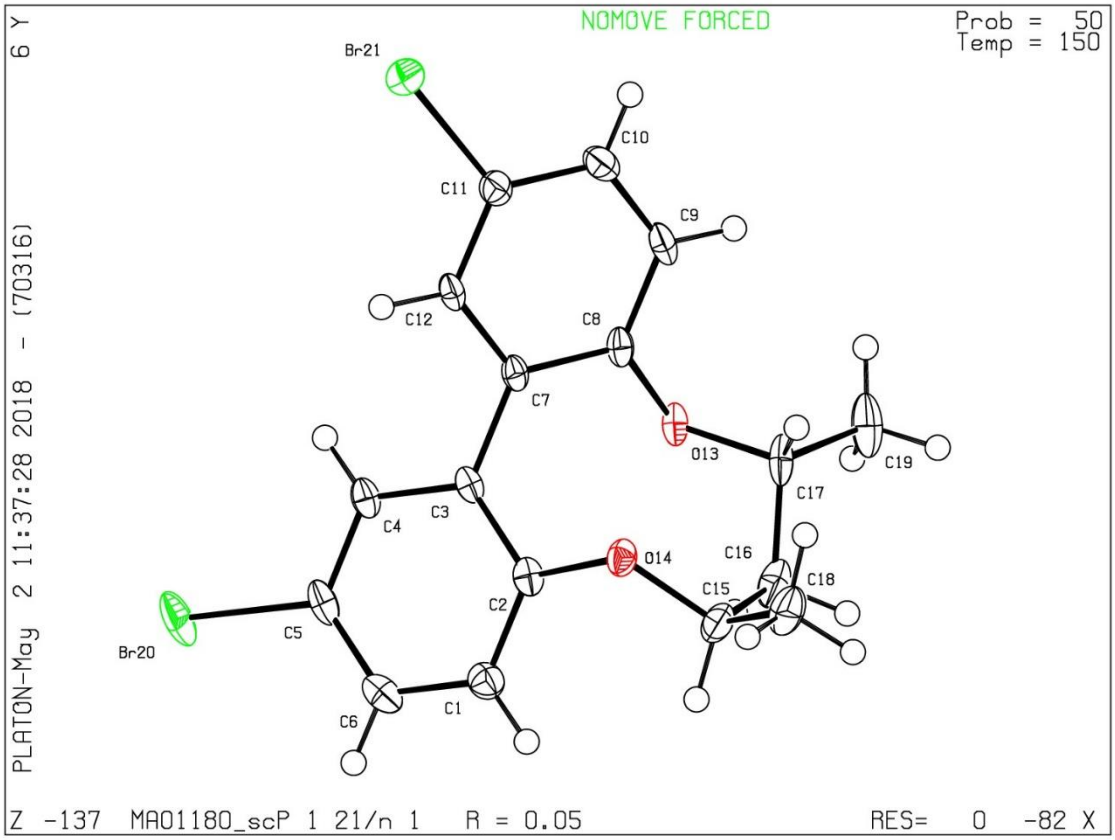

Figure A7: *Structure of compound **4.26A** with labelling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii*

Appendix Eight: *Plot Derived from Single-Crystal X-ray Analysis of Compound 5.04*

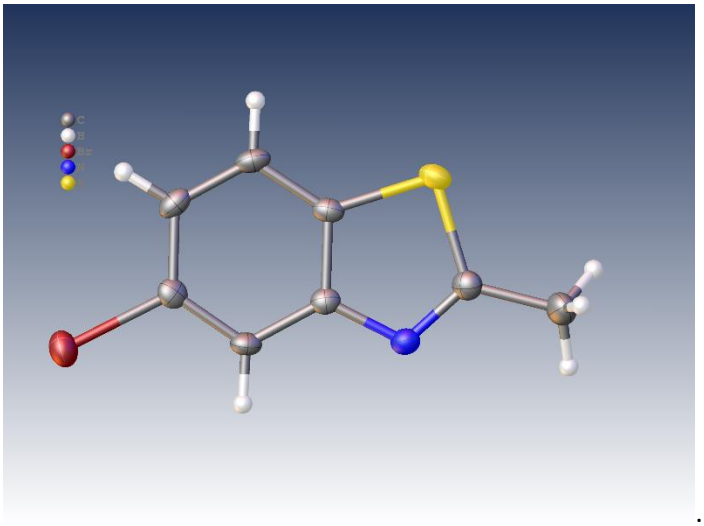

Figure A8: *Structure of compound **5.04** (CCDC 2058495) with labelling of selected atoms. Anisotropic displacement ellipsoids show 50% probability levels. Hydrogen atoms are drawn as circles with small radii. Disorder has been omitted for clarity*

Appendix Nine: *Plot Derived from Single-Crystal X-ray Analysis of Compound 5.13*

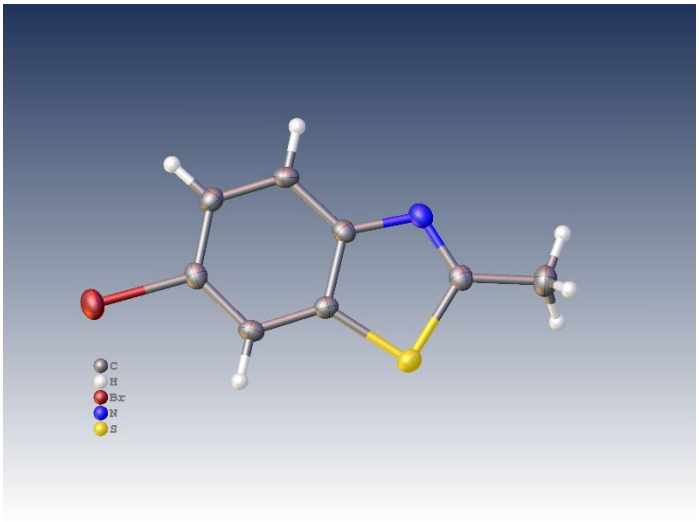

Figure A9: *Structure of compound **5.13** (CCDC 2058496) with labelling of selected atoms. Anisotropic displacement ellipsoids show 50% probability levels. Hydrogen atoms are drawn as circles with small radii. Disorder has been omitted for clarity*

Appendix Ten: *Plot Derived from Single-Crystal X-ray Analysis of Compound 5.28*

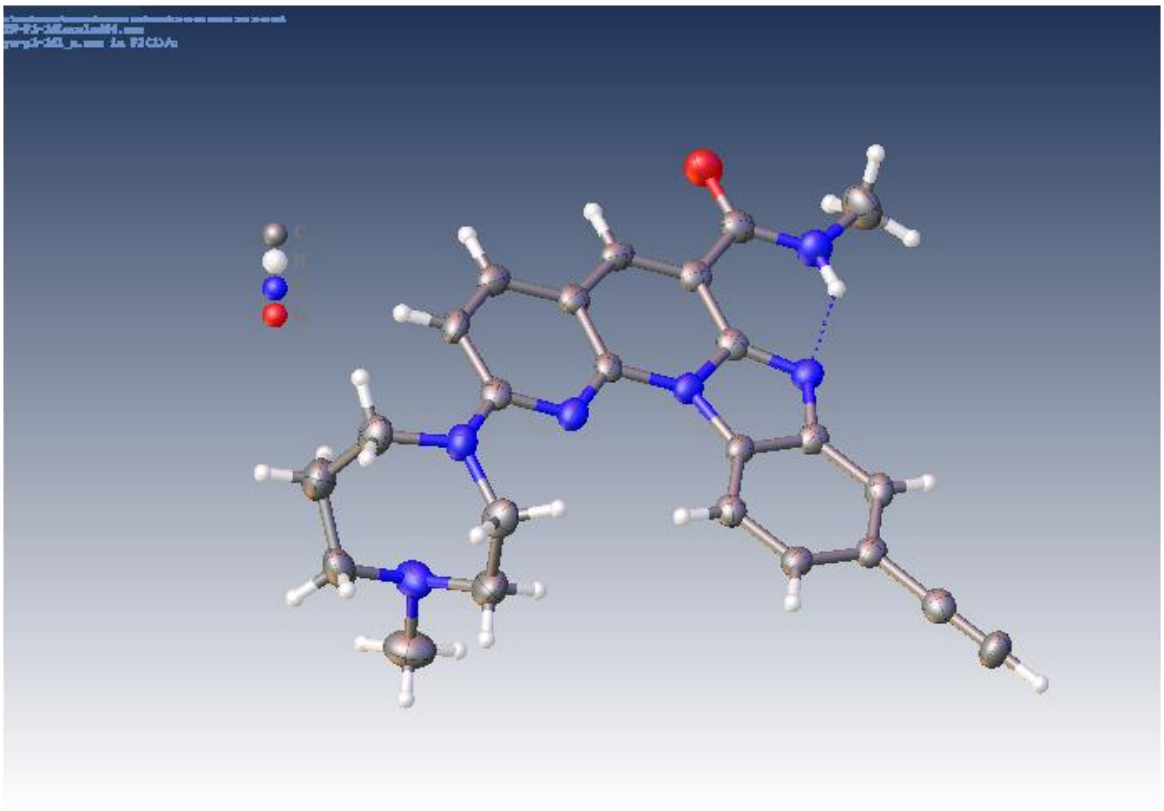

Figure A10: *Structure of compound **5.28** (atomic displacement parameters shown at 50% probability level). Disorder in the saturated heterocyclic substituent and a disordered chloroform molecule (H-bonded to the amide O-atom) have been removed for clarity. Intramolecular H-bonding is shown*