University of St. Andrews
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Chemical Library Designs based on Indazolinones

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Thesis submitted to the University of St Andrews in application for the degree of
Doctor of Philosophy

October 2005

Declaration

I, Nicolas Stanislas Jean Isambert, hereby certify that this thesis, which is approximately 53,000 words in length, has been written by me, that it is the record of work carried out by me and that it has not been submitted in any previous application for a higher degree.

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Abstract

Chemical genetics is an approach to studying biological function through the use of small molecules. An efficient way of accessing these small molecules is high throughput synthesis on solid phase resins. The advantages of this technique include the use of excess reagents to push reactions to completion and washing reagents and by-products before cleaving the specie of interest at the final step. The purity of the compounds is good enough to perform biological screening without need of purification provided the chemistry is well established.

The indazolinone core-structure has been selected for its small core and number of functional groups available for diversity incorporation. However, selective functionalisation of each position in the bicyclic system has not been reported yet. Small molecules based on indazolinones have also been shown to exhibit biological activity.

A reaction sequence allowing diversity incorporation on the indazolinone system in a selective manner has been developed. This includes the use of an allyl group that can be rearranged from the O position to the N2 position by an aza-Claisen rearrangement. This sigmatropic rearrangement has been studied on the indazolinone system with a range of allyl containing groups under different reaction conditions including thermal (microwave based) and catalytic methods (Palladium (0) and (II)).

An indazolinone derivative that can be loaded onto a silicon-based resin has been successfully synthesised. Two key steps in this synthesis involve a Suzuki coupling and a copper-mediated cyclisation in the presence of hydrazine on an iodobenzoic acid derivative. Initial studies using this derivative allowed us to design a route for diversity incorporation in the solution phase by modelling the solid support by a TIPS group. This strategy was then transferred onto a solid support. Comparison of authentic compounds synthesised in solution with compounds made on the resin, by the use of LC/MS technology, enabled us to confirm that the developed chemistry is of relevance to library generation.

N2, *O*-substituted indazolinones contain two diene functional groups. Studies to determine if these dienes are susceptible to the Diels-Alder reaction with reactive electron deficient dienophile were carried out. A novel compound has been identified as the product of a possible Diels-Alder reaction.

Acknowledgments

I would like to thank Dr Nicholas J. Westwood for his support and his guidance on this project and his encouragement for the last four years.

I would also like to thank Dr Westwood's lab group, Cristina, Richard, Szilvia, Federica, Enamul, Neil, Dr Stephen Paterson, Dr Till Blum for their help and the good atmosphere in the lab. A special thank you goes to Dr John Hollick, Dr Russell Pearson and Dr David Taddei for helping me in correcting this thesis, thank you guys!

I would like to thank Dr Nawaf Almaharik for his great advices.

I would also like to thank Cédric Khan and Dr. Julien Sançon for supporting me and encouraging me; they have been part of this trip so far and I thank them for the good time spent at Montpellier when we were studying at the University. Hope to see you soon!

I would like to thank Melanja Smith for her help for the use of the manual NMR, Alex Slawin for the crystal structure studies, and Caroline Horsburgh for the mass spectrometry services.

Je voudrai aussi remercier ma famille, mes parents, mes frères Sébas et Benja, et ma soeur Marie-Julie pour m'avoir encouragé durant toutes ces années. Merci à mes parents pour m'avoir donné la possibilité de choisir, d'étudier, de me réaliser, et de n'avoir jamais douté de moi. Merci à mes frangin(e)s pour la motivation et les conseils. Merci pour tout.

Al final, me gustaría agradecer la persona que ha sufrido lo mas durante esos tres ultimos años, Rakel. Ha sido siempre a mi lado, en los momentos, a veces los peores, a veces los mejores, pero nunca ha dudado. Gracias por tu paciencia, darme animos para esta tesis; sin ti, no hubiera sido acabada. Gracias también por abrirme los ojos y llevarme a tu lado en diferentes sitios del mundo que no hubiera visto sin ti. Muchas Gracias para todo, "Petit Bout". Animo para tu tesis y suerte para el futuro.

Contents

Abbreviations and Symbols

The following abbreviations and symbols are used throughout this thesis.

9-BBN	9-borabicyclo[3,3,1]nonane
Å	angstrom, length unit (10^{-10}m)
AcOH	acetic acid
ADDP	1,1 -(Azodicarbonyl)dipiperidine
Bn	benzyl radical, $C_6H_5CH_2$-
BnCl	benzyl chloride
Boc	tert-butyloxycarbonyl radical, $(CH_3)_3COCO$-
b.p.	boiling point
Buli	butyl lithium, strong base
ca.	approximately
calcd	calculated
CAN	ceric ammonium nitrate
cGMP	cyclic guanosine monophosphate, nucleotide metabolism
CI	chemical ionisation
COSY	correlation spectroscopy, 2D NMR technique
DCM	dichloromethane
DEAD	diethylazodicarboxylate, used in Mitsunobu reaction
DIBAL-H	diisobutylaluminium hydride
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DOS	diversity-oriented synthesis
e.g.	exempli gratia, latin, for instance
equiv.	equivalents
ES	electron impact, ionisation technique
ESI	electrospray ionisation
Et	ethyl radical, CH_3CH_2-
et al.	"et alii", latin, for "and other"
Et_3N	triethylamine
EtOH	ethanol

FT	Fourier Transform, mathematical process
h	hours, time unit
Hal	halogen atom, either F, CL, Br, I usually
HMBC	heteronuclear multiple bond connectivity, 2D NMR technique
HOMO	highest occupied molecular orbital
HR	high resolution, mass spectrometry
HSAB	hard soft acid base concept
HSQC	heteronuclear single quantum correlation, 2D NMR technique
Hünig's base	*N,N*-diisopropylethylamine
Hz	Hertz, frequency unit
i.e.	*id est*, latin, that is
IR	infrared
J	coupling constant, Hz
LC/MS	liquid chromatography coupled to mass spectrometry
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
LR	low resolution, mass spectrometry
M	concentration, mol.L^{-1}
Mol.	molar
m.p.	melting point
m/z	mass over charge ratio
Me	methyl radical, CH_3-
MeOH	methanol
Min	minutes, time unit
m.p.	melting point
MRSA	methicillin resistant *Staphylococcus Aureus*
MS	mass spectrometry
N/A	non applicable
NaOMe	sodium methoxide, CH_3ONa
NMR	nuclear magnetic resonance
Nu	nucleophile
°	degrees, angle unit
°C	degrees centigrade, temperature unit
OMe	methoxy radical, CH_3O-
o/n	overnight

PBu_3	tributylphosphine
PE	petroleum ether 40-60°C
Ph	phenyl radical, C_6H_5-
PIFA	phenyliodine(III) bis(trifluoroacetate)
PPh_3	triphenylphosphine
ppm	part per million
PTAD	4-phenyl-1,2,4-triazoline-3,5-one, really reactive dienophile
Quant.	quantitative
R_f	retention factor, chromatography
RNA	ribonucleic acid
rt	room temperature
SAR	structure-activity relationship
sRNAi	small RNA interference, technique used in biology
TBAF	tetrabutylammonium fluoride
^{t}BuOK	potassium *t*-butoxide
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPA	*N*,*N*,*N'*,*N'*-tetraisopropylazodicarboxamide
TIPS	triisopropylsilyl radical, $[(CH_3)_2CH]_3Si$-
TIPSOTf	triisopropylsilyl trifluoromethanesulfonate
TLC	thin layer chromatography
TMAD	*N*,*N*,*N'*,*N'*-tetramethylazodicarboxamide
TOS	targeted-oriented synthesis
UV	ultraviolet
Z	benzyloxycarbonyl radical, $C_6H_5CH_2OCO$-
δ	chemical shift, ppm
χ	electronegativity symbol

1. Introduction

1.1. Discovery of Bioactive Compounds

1.1.1. Natural Product Extracts

1.1.1.1. Opportunities

Before the first cars were built, before written language was invented and even before culturing of plants was developed for food purposes, our requirement to relieve pain and prolong life drove us to search for medicines. It is not really clear what the earliest humans did to treat their "aches" (e.g. headache, stomach ache) but they must have used the natural resources around them (plants, animals and minerals).

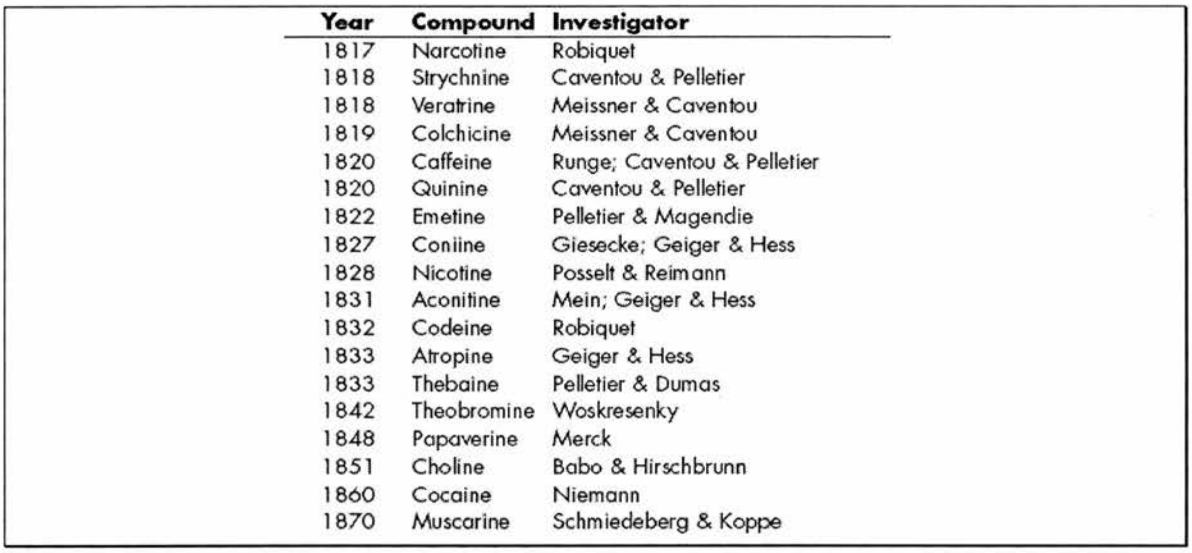
Extracts of natural substances have been used for centuries to kill parasites, neutralize venom and cure diseases, but no purification, analysis or separation techniques were available at that time to determine specifically the compound(s) responsible for the biological effect. It was believed that these extracts contained mixtures that could act against the "infection".

During the 19th century, the concept of "pure" substances emerged from progress in analytical chemistry and the development of isolation and separation techniques. Indeed, in 1815, F. W. Sertürner, a German chemist/pharmacist,[1] isolated for the first time in a pure form "*morphium*", known as morphine **(1)**, as the principal alkaloid in opium (derived from *Papaver somniferum L. or P. Album Mill, Papaveraceae*).[2] Morphine **(1)** and other alkaloids found in opium are used clinically as analgesics to reduce pain without loss of consciousness.

(1)

Figure 1: Structure of Morphine **(1)** and the opium poppy, *Papaver somniferum*.

Natural products were therefore the first source of biologically active molecules, being present as mixtures in plant extracts, or as pure products when identification/isolation was possible. Table 1 summarizes the timeline for isolation of the first alkaloids and the investigators associated with their discovery.



Year	Compound	Investigator
1817	Narcotine	Robiquet
1818	Strychnine	Caventou & Pelletier
1818	Veratrine	Meissner & Caventou
1819	Colchicine	Meissner & Caventou
1820	Caffeine	Runge; Caventou & Pelletier
1820	Quinine	Caventou & Pelletier
1822	Emetine	Pelletier & Magendie
1827	Coniine	Giesecke; Geiger & Hess
1828	Nicotine	Posselt & Reimann
1831	Aconitine	Mein; Geiger & Hess
1832	Codeine	Robiquet
1833	Atropine	Geiger & Hess
1833	Thebaine	Pelletier & Dumas
1842	Theobromine	Woskresenky
1848	Papaverine	Merck
1851	Choline	Babo & Hirschbrunn
1860	Cocaine	Niemann
1870	Muscarine	Schmiedeberg & Koppe

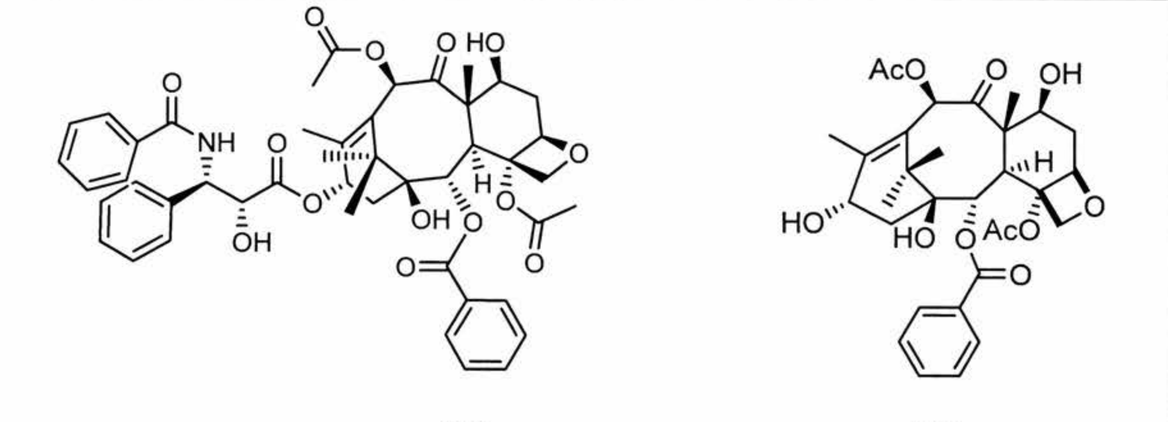
Table 1: Isolation of alkaloids following the discovery of morphine **(1)**.[1]

There is no doubt that our natural resources are extensive and can provide a multitude of bioactive compounds, which are extremely diverse and structurally innovative.

1.1.1.2. Limitations

Extraction from plants or microbes or insects allows the isolation of mixtures of compounds but raises difficulties such as identifying the active substance and subsequently separating and isolating it. Isolation of the compound of interest is sluggish, time-consuming, expensive and requires extensive resources. To follow the example of morphine **(1)** cited previously, the production of 1.3 kg of this alkaloid requires 13 kg of opium, which can be extracted from a one hectare field of opium poppies.[2]

There are also other hurdles to be overcome in natural products extraction. Environmental issues can increase the difficulties of isolating natural products. Taxol® **(2)** (Scheme 1) is extracted from the bark of the Pacific yew tree (*Taxus brevifolia*) but the plant is protected and is one of the slowest growing trees in the world. Six one hundred-year old trees are needed to provide enough active material to treat just one patient (300 mg).[3-5]



(2) (3)

Scheme 1: Structure of Taxol® **(2)** [4] and Baccatin III **(3)**.[3]

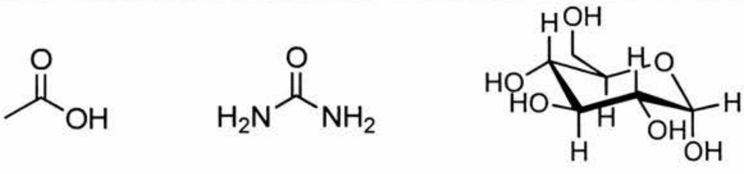
Extracting natural products from nature remains a difficult and low yielding procedure. Isolating and identifying bioactive molecules from natural sources is time consuming, limited technically and fraught from certain legal and ethical points of view depending on the origin of the plant/microbe (e.g. the extraction of Taxol® **(2)** is not only technically challenging but almost legally impossible).

Chemist can play an important role in overcoming the problems discussed above. Semi synthetic routes can be developed. For example, Taxol® **(2)** is now synthesised from Baccatin III **(3)** extracted from the renewable needles of the European Yew, *Taxus baccata L.* (Taxaceae).[3] A second option is the total synthesis of the natural product, which overcomes any problems relating to extraction.[6, 7]

1.1.2. The Total Synthesis of Natural Products and Medicinal Chemistry

1.1.2.1. Total Synthesis

The 19th century was the era of analytical science but also included a scientific revolution. The power of chemistry was about to be discovered: the birth of total synthesis. Indeed, in 1845, Kolbe synthesised acetic acid **(4)** from elemental carbon. The word "synthesis" was used for the first time by this German chemist to describe the process of assembling a chemical compound from other substances. Seventeen years before, Wöhler transformed an inorganic material (ammonium cyanate) into an organic substance, urea **(5)**. Fischer obtained in 1902 the Nobel Prize for chemistry [8] for his work including the total synthesis of glucose **(6)**. Dealing with the complexity of the target, including the stereochemistry (five stereogenic centres, four controllable and the anomeric position), was a real challenge at the beginning of the 20th century.

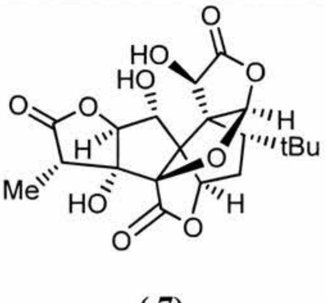


(4) **(5)** **(6)**

Scheme 2: Structures of acetic acid **(4)**, urea **(5)** and glucose **(6)**.

In the 20th century, scientists built on the success of the previous century. The complexity of the synthesised molecules increased dramatically, due to the "genius" of Fischer, Robinson [9], Woodward [10] and others.

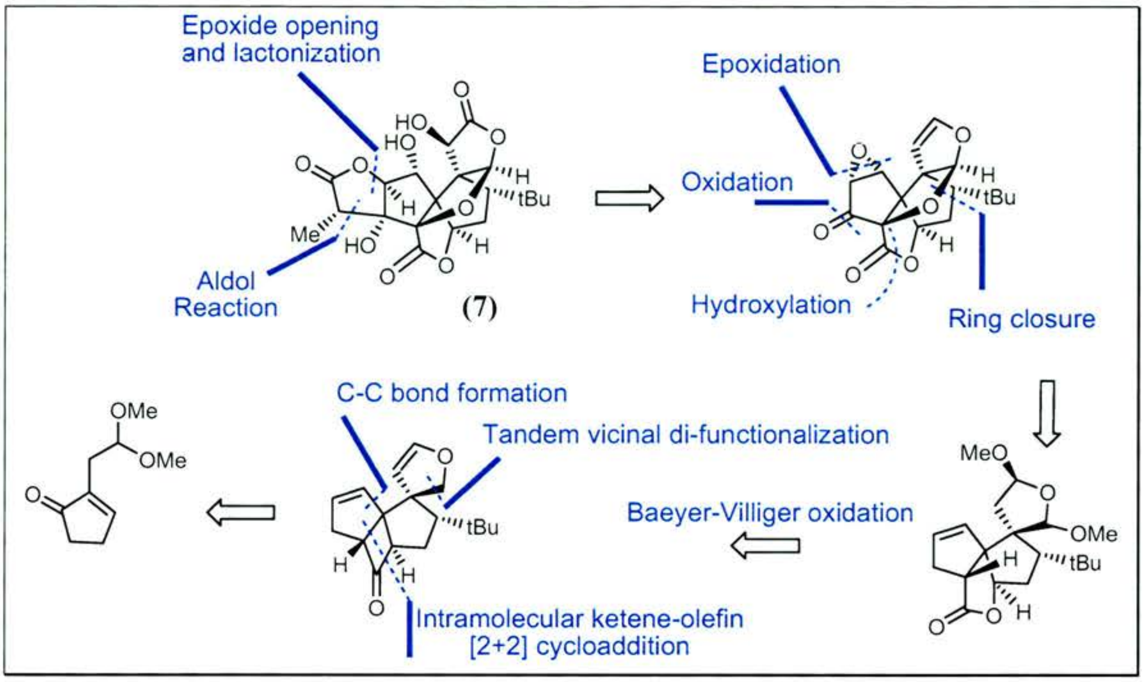
This arguably culminated in 1959 when E.J. Corey (Nobel price in 1990 [11, 12]) introduced and developed two distinctive elements: retrosynthetic analysis and new synthetic methods. The concept of retrosynthesis was a new way of viewing and analysing complex structures.[13] Breaking down the complexity of target structures such as natural products by understanding the chemical functionality and planning their synthesis from less complex molecules was the new way of synthesising natural products. This revolutionary idea is now a standard approach to solve problems in organic chemistry.



(7)

Scheme 3: Structure of Ginkgolide B **(7)**.

For example, to synthesise a complex structure such as Ginkgolide B **(7)**,[14] Corey started by looking at the final structure and broke it down into simpler starting materials as described in Scheme 4.



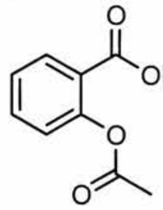
Scheme 4: Strategic bond disconnections and retrosynthetic analysis of Ginkgolide B **(7)**.[14]

The total synthesis of natural products is a great challenge and has proved to be a difficult and interesting science but also an art as K. C. Nicolaou described.[15] His review highlights the astonishing achievements of organic chemists over the past century in responding to nature's complexity by developing new methodologies and creating new reactions. Nowadays, methodologies have been established, mechanisms understood and when combined with retrosynthetic analysis, it is difficult to imagine a problem that could not eventually be resolved in a natural product total synthesis.

However, copying nature to access complex natural products is long and generally low yielding. For example, the synthesis of the alkaloid morphine **(1)** has recently been achieved in 23 steps with an overall yield of 0.77%.[16]

1.1.2.2. Medicinal Chemistry [17-19]

Importantly, less complex small molecules can also exhibit biological activity. Indeed, acetyl salicylic acid (Scheme 5) better known as aspirin **(8)** proved to be of interest. The realisation that rather simple chemical structures can also be of medical importance calls into question the necessity of putting effort into the synthesis of complex structures such as Taxol® **(2)** or morphine **(1)**.



(8)

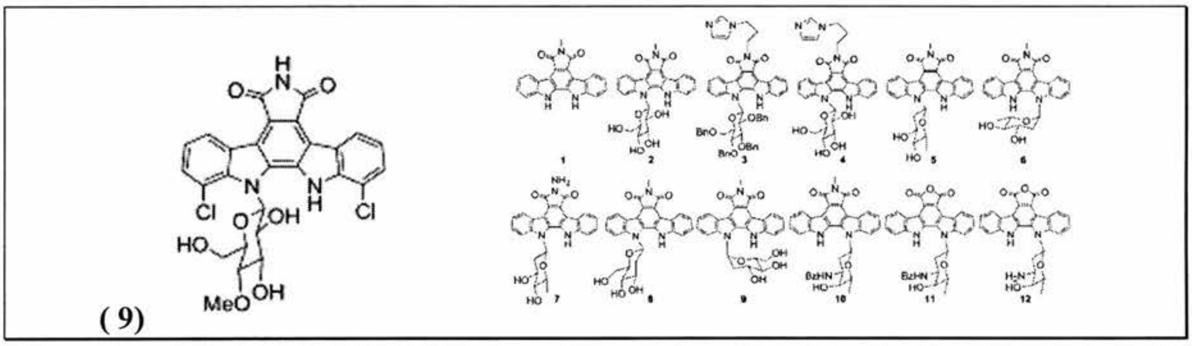
Scheme 5: Structure of Aspirin **(8)**.

Chemists can (and do) focus on developing compounds with relatively less complex structures (compared to natural products) and work on them in order to find and improve biological properties. Such an approach for generating small molecule lies at the heart of medicinal chemistry. In this strategy, the first step is to identify a protein target that is directly involved in the disease state. The second step and by no means the simplest is to identify a bioactive compound. This is usually done by developing a screen to select a chemical that will interact with this target. The third step is to optimise the preliminary hit by making a large range of analogues. Compounds are made individually, one by one, and optimised based on the results obtained in biological testing. This process follows the concept described by Ehrlich, i.e., the core of the active compound remains essentially unchanged and the chemist prepares analogues by changing the groups attached to the core.

> "The germicidal capability of a molecule depended on its structure, particularly its side-chains, which could bind to the disease-causing organism."
>
> P. Ehrlich [20]

It is of interest to consider the efficiency of this approach. A medicinal chemist using traditional synthesis methods can synthesise, on average, between one and five compounds for biological testing per week. If a hit has been discovered, many months/many years follow in which large numbers of analogues are prepared. This step-by-step approach leads to important bioactive products but is arguably not the most efficient method.

A recent example on a polycyclic structure supports this view. Rebeccamycin **(9)**, a potential anticancer compound, is a natural product extracted from fermentation. Since 1985, when the structure was elucidated, the indolocarbazole core has been extensively studied as a pharmacophore. To date, 300 analogues have been made and some of these have been studied in clinical trials. Thus, analogues of this polycyclic structure are still generated using medicinal chemistry to find more potent molecules.[21] The carbohydrate moiety of Rebeccamycin **(9)** seems to have an important role in its activity. Indeed, common sugars have been added to the core and biological results showed a variation in potency across the series. This observation led medicinal chemists to synthesise new analogues by inserting less common sugars on the pharmacophore.


(9)

Scheme 6: Structure of Rebeccamycin **(9)** and analogues synthesised with uncommon sugars.[21]

This example shows the strategy of medicinal chemistry. The first step of the approach was the identification of the hit. Chemists then prepared analogues of the primary hit, moving towards a potential anticancer agent. Further biological studies led chemists to design and make new analogues, which gave further information about the interactions of the small molecule and its target. Key positions on the aglycone moiety were identified leading to additional sets of analogues for further studies. Therefore, medicinal chemistry focuses on a rational stepwise approach. This strategy leads to successful results, but can be slow depending on the available resources.

1.1.3. High Throughput Synthesis

Another, potentially more efficient, way of approaching the discovery of bioactive compounds is to prepare a large collection (>200) of compounds up front and then to screen them all using high throughput screening technology. By creating large number of analogues, it is possible to perform rapidly structure-activity relationship studies in order to optimise efficiently the side chains. There are two main approaches to high throughput synthesis.

1.1.3.1. Parallel Synthesis

1.1.3.1.1. Solution Phase High Throughput Synthesis

By definition, parallel synthesis is a strategy whereby sets of discrete compounds are prepared simultaneously in arrays of physically separate reaction vessels or micro compartments without interchange of intermediates during the assembly process. This strategy allows the chemist to create a large range of individual compounds usually with the aid of automation. This technique can also be used to optimise reactions, because of the ease of changing several reaction parameters in parallel (concentration, temperature, solvent etc.). The inconvenience of this approach is that a purification step is needed, because the reactions are performed in solution and the products have to be separated from the reagents, starting material and/or catalyst etc.

The quantities created are in general 50-100 mg of compound and the number of compounds is typically less than 1000.

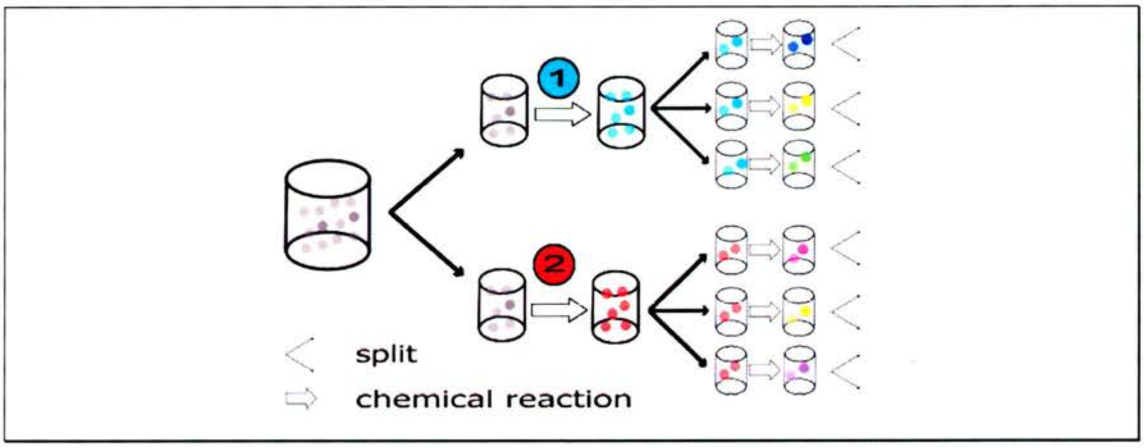
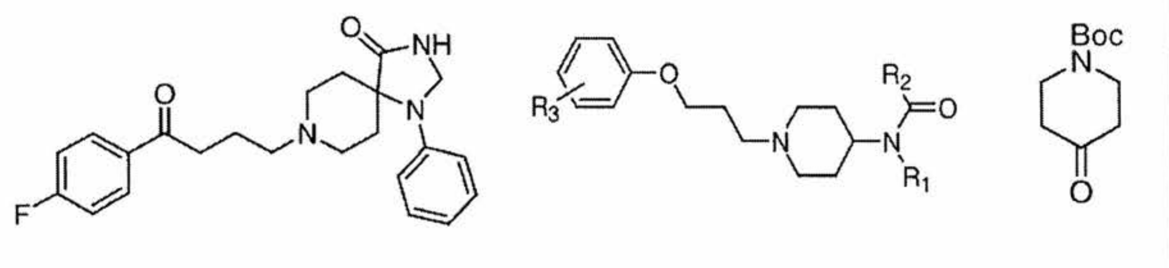


Figure 2: Principle of solution phase high throughput synthesis, each reaction is performed in a separate vessel; the last step of the procedure consists of a purification step to isolate the product of interest from the reagents and by-products.

Scheme 7 summarises an example of this approach. A library of 240 members was made in order to synthesise non-spiro analogues of spiperone **(10)**, known to be an antipsychotic agent.[22] Reductive amination of the aminoketone allowed the authors to insert 5 different substituents at the R1 position. At this stage, reactions were pushed to completion by the use of excess piperidone. A liquid/liquid extraction was then performed to give the desired products in high purity and good yields (over 85% except for one case). The acylation of the newly introduced nitrogen brought in 8 other groups at the R2 position. The last step was alkylation of the secondary nitrogen which had been released previously by deprotection of the Boc group under acidic conditions.



(10) **(11)** **(12)**

Scheme 7: Structure of spiperone **(10)**, general structure of libraries members **(11)** and starting material for the library **(12)**.[22]

The library generation of spiperone **(10)** analogues of type **11** in solution phase proved to be successful since two compounds with improved selectivity for the receptor under study (5-HT_{2A}) were identified. A clever combination of purification through extractions and polymer-supported reagents allowed the isolation of products in adequate purity.

Purification procedures have to be well planned in order to generate compounds that are sufficiently pure for biological testing. This minimises the number of false positives resulting from remaining reagents and by-products. Purification remains a problem for parallel synthesis when a large number of analogues are prepared [23] and generally involves preparative HPLC for final purification.[24-27]

Another example of biological importance is the targeted library based on vancomycin. This glycopeptide is used often as the last resort for treatment of infections by methicillin resistant *Staphylococcus aureus* (MRSA), a resistant strain of *Staphylococus aureus*. However, vancomycin resistant strains of bacteria are emerging.[28-30] The need to overcome this problem led Nicolaou *et al.* to develop a library based on the glycopeptide vancomycin by inserting diversity at the C terminal, N terminal and carbohydrate positions. Several active compounds against vancomycin-resistant bacteria were identified from the vancomycin-based library,[31] proving that this approach can lead to new hits.

Using a known bioactive molecule and inserting diversity onto it is the aim of targeted libraries and new active structures with improved properties can be accessed by this approach.

1.1.3.2. Combinatorial Synthesis

1.1.3.2.1. Solid Phase Chemistry

R.B. Merrifield[32] (Nobel Price in 1984) introduced the idea of solid phase chemistry for the first time in 1963. The principle was to attach an amino acid by the C terminal to a resin and to grow the peptidic chain using the N terminal. A suitable protection and deprotection strategy was also required. Different protecting groups are used on the side chain of the amino acids to avoid their deprotection during the amide bond forming steps. These side chain protecting groups are removed at the end of the synthesis to give, after cleavage from the resin, the peptide in solution (Figure 3). The aim of this concept was to drive the amide bond forming reaction to completion by addition of excess reagents and to avoid any purification step (by washing away the excess reagents and cleaving the products in the final stage). Another advantage of this technique was the potential for automation.

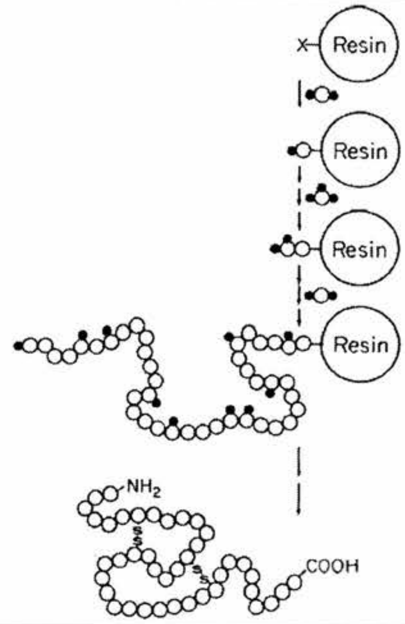
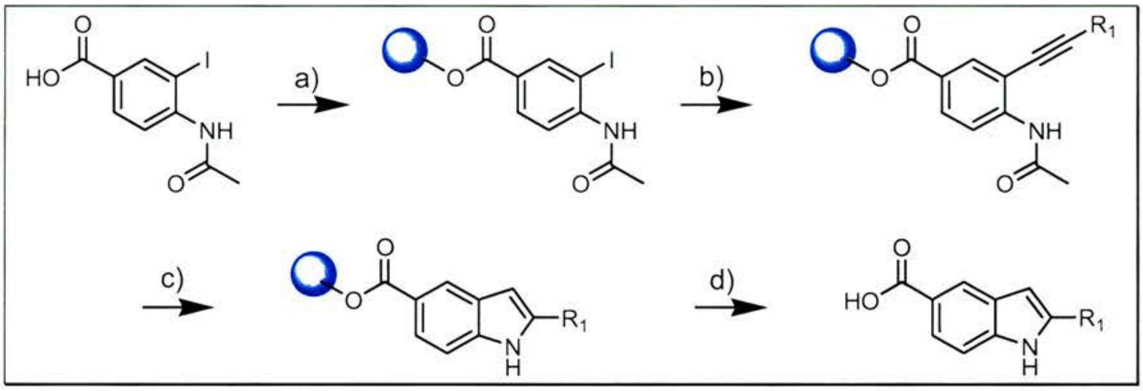


Figure 3: Principle of solid phase chemistry introduced for peptides by R.B. Merrifield.[32] The peptidic chain is elongated by use of excess reagents (removed by washing) and the peptide was cleaved off the resin at the final stage of the synthesis.

This technique has also become important in organic synthesis in general. In particular, solid phase synthesis has increased dramatically in academia and to some extent in industry due to the multiple advantages of the technique. The technique has even improved over the years and new ideas have emerged from this concept: substrate are immobilised on solid support (peptide chemistry),[33] but also reagents are immobilised onto solid support to avoid bad odours,[34] to facilitate purification or reduce risk [35] or to allow the regeneration/recycling of reagents.[36, 37] These issues have been described by Steven V. Ley in 2000 in a review entitled "Multi-step organic synthesis using solid-supported reagents and scavengers: a new paradigm in chemical library generation".[38] Scheme 8 exemplifies the use of solid supported synthesis in general organic chemistry for the synthesis of indoles on a Tenta-Gel S resin.[33]



Scheme 8: Example of organic chemistry developed on solid phase;[33] a) Mitsunobu reaction, PPh_3, DEAD, Tenta-Gel S resin, b-c) $Pd(PPh_3)_2Cl_2$, CuI, TMG, alkyne, d) NaOH.

1.1.3.2.2. Split and Pool Synthesis [39]

The main concept in combinatorial synthesis is the generation of large collections or "libraries" of compounds by synthesising **all possible combinations** of a small set of chemical structures or "building blocks" on an insoluble polymer (resin). The key technology for achieving this is split and pool synthesis.

Practically, the solid support is **split** into portions, each of which is subjected to reaction with a single building block. **Pooling** these portions results in a single batch of solid support in which each bead bears multiple copies of a single chemical entity (Figure 4). Repetition of the split and pool processes results in a library where each discrete bead of solid support carries a single library member. Split-pool synthesis is often referred to as a "one bead-one compound" approach.

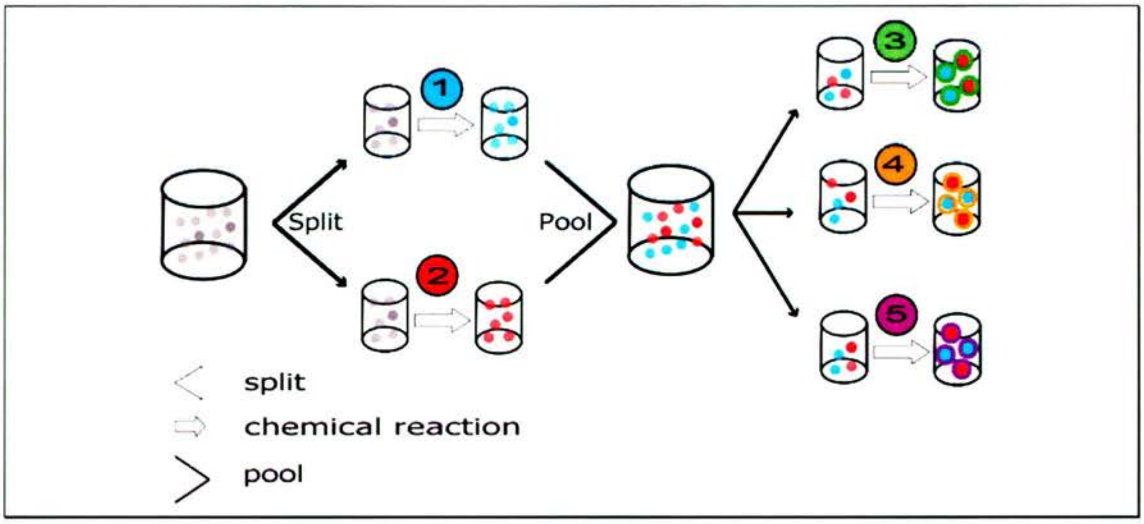


Figure 4: Principle of split and pool synthesis.

The advantages of this technique are multiple:

1. The use of an excess of reagent is possible to push the reaction to completion.

2. No purification steps are needed (excess of reagent eliminated by washes). Compounds are ready to be screened after cleavage from the resin or on bead.

3. Microgram quantities of compound produced hence reduction in reagent costs.

4. Rapid synthesis (many fewer reaction steps than required to create an analogous library using parallel synthesis).

5. Access to a very large number of compounds (more than 1000 structures): 29,400 discrete compounds were synthesised in 2002 using one solid phase library synthesis in the ICCB at Boston .[40]

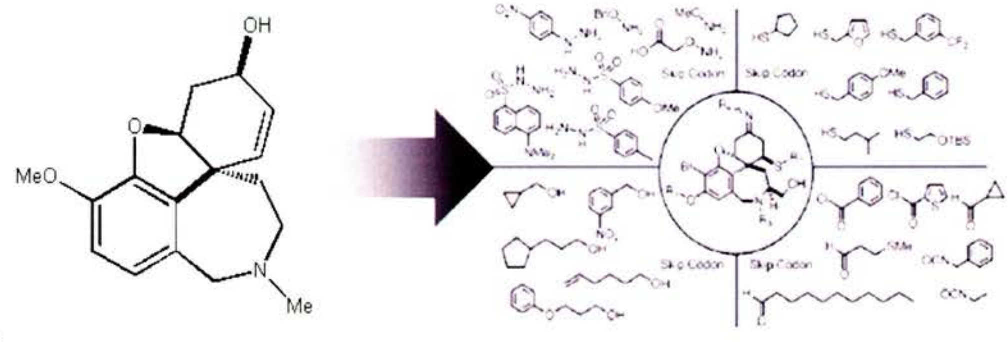
6. Large data sets can be generated by screening leading to improved interpretation of structure-activity relationships and therefore better guidelines for hit and lead optimisation.

7. Possibility of automation for synthesis and analysis.

1.1.3.2.3. Unbiased libraries, DOS [41-43]

In academia, split and pool synthesis has been used predominantly in the context of diversity-oriented synthesis. When linked together, these two techniques provide chemists with a very powerful method of preparing large unbiased compound libraries. This means that the compounds that are selected for synthesis have no preexisting link to a biological system or target. The chemist prepares the collection with two main criteria in mind. First, the chemistry is compatible with the synthetic technology. Second, as much structural diversity as possible is generated. The unbiased library is then screened in as many assays as possible in an attempt to identify a novel biological activity.

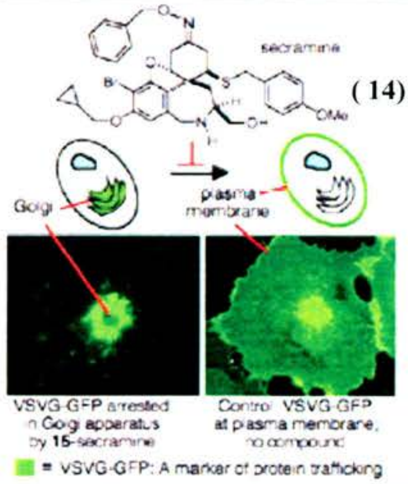
The example given below is a library based on the core structure of a natural product galanthamine **(13)**.[44] The core structure was not chosen because of the known bioactivity of galanthamine **(13)** as an acetylcholine esterase inhibitor but because of its interesting polycyclic structure, and the range of diversity-generating reactions that could be applied. Indeed, different reactions have been performed on the oxygen carried by C-7 (Mitsunobu reaction), then at C-1 (conjugate addition), at the N-10 position (acylation or alkylation) and finally at C-3 (formation of oxime and hydrzones).



(13)

Scheme 9: Structure of galanthamine **(13)** and the building blocks used for library generation.[44]

As discussed above, galanthamine **(13)** itself is a potent acetylcholinesterase inhibitor,[45] but screening of this unbiased library using an assay to detect compound that perturb secretory pathways led to the identification of a potent inhibitor called secramine **(14)** from this galanthamine-based library.



(14)

Figure 5: Structure of secramine **(14)** and protein traffic perturbed by secramine **(14)**.[44]

The previous sections have highlighted how important small molecules are to the study of biology processes and as drugs. They have also provided an overview of the synthetic techniques that are applied in efforts to identify novel small molecule modifiers of protein function. This research area is currently undergoing a resurgence in interest and the systematic discovery of novel small molecule tools has recently been referred to as "chemical genetics". The next section briefly outlines the key components of this approach.

1.2. Chemical Genetics [46-49]

1.2.1. The Origin of Chemical Genetics [50]

At the end of the 19th century, Paul Emil Fischer used the metaphor of a "lock and key" to describe the interaction between a small molecule and an enzyme at the molecular level. The "lock and key" concept was valid but Ehrlich updated the idea by introducing the concept of a "RECEPTOR" as follows:

> "... Designed for the purpose of serving as *toxic receptors* for substances....
>
> As these receptors, ..., become occupied by the toxin, the relevant normal function of this group is eliminated."
>
> P. Ehrlich [20]

Therefore, as stated more than 100 years ago, small molecules were known to have a powerful effect on biological systems by acting as the key. The key (or the toxin according to Ehrlich's definition) was usually well characterised but the lock was not as well identified. Ehrlich observed carefully that the small molecule could have an important effect on biological system by eliminating the normal function associated with the receptor. We know nowadays that these receptors are proteins, DNA or RNA. Therefore, we can consider that chemical genetics was born from Fischer and Ehrlich's ideas.

1.2.2. Definition of Chemical Genetics

The term "chemical genetics" symbolizes the idea of systematically using small molecules to perturb, and thus determine, the function of proteins in the same way that mutations are used in conventional genetics. As described in Figure 6, the genetic approach consists of modifying the genetic information, which will ultimately be processed to give a modified protein. Wild-type protein and modified protein may not have the same function in a cellular context, in which case phenotypic differences are likely to be observed. In the case of chemical genetics, a small molecule is used in order to "modify the protein" and therefore cause an alteration in the intracellular function of the protein.

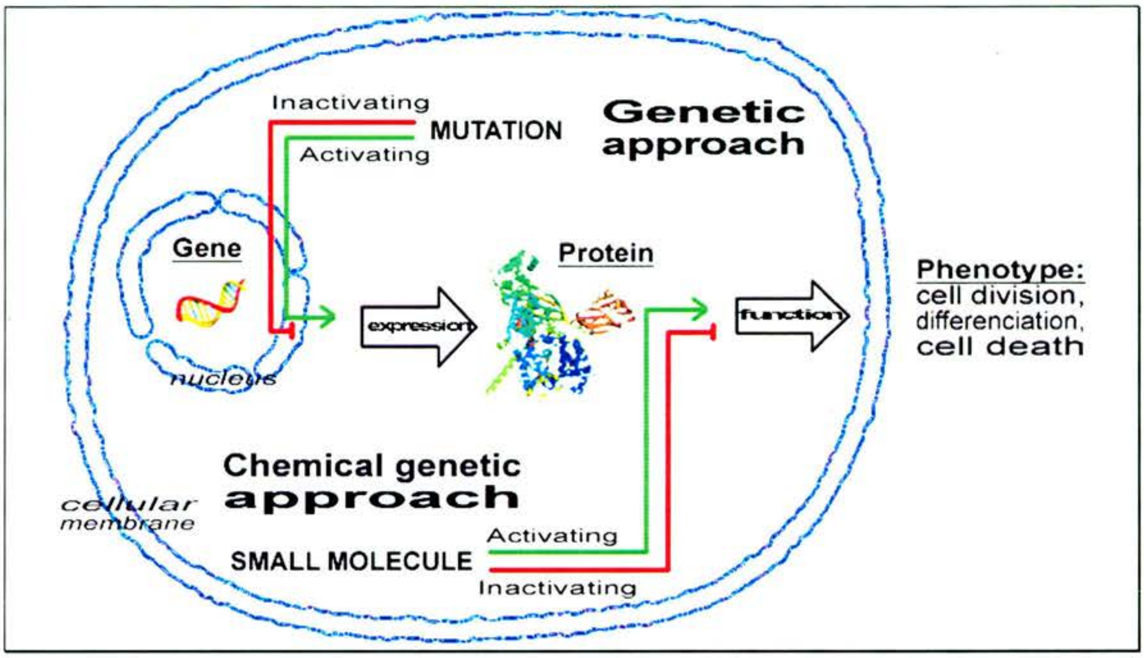
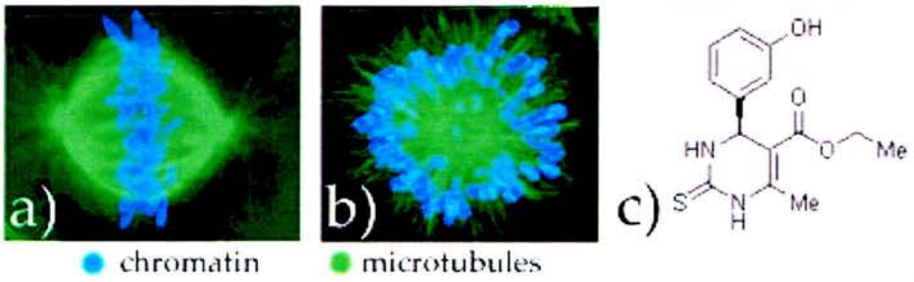


Figure 6: A comparison of chemical genetics and classical genetic approaches. In chemical genetics, a small molecule is used at the protein level to induce (or not) changes in the phenotype. In pure genetics, a mutation at the DNA level leads to the translation of a modified protein which will induce (or not) a different phenotype.

1.2.3. Advantages of Chemical Genetics

The use of small molecules in chemical genetics differs from their traditional use in the industrial area, for example as therapeutics. Chemical genetics involves identification and use of research tools for enhancing our understanding of the detailed mechanisms by which a biological system works. A recent example[51] is the small molecule monastrol **(15)** which binds the protein Eg5, a motor protein involved in mitosis (a brief but essential event in the cell cycle during which the previously replicated chromosomes are segregated into newly-forming daughter cells; this process ensures that each daughter cell inherits a genome identical to the one of the parental cell). The result of the action of monastrol **(15)** on a cell during mitosis and the structure of this molecule are shown in Figure 7.[52-57] Monastrol **(15)** was initially identified in a whole-cell immunoassay designed to identify compounds that arrest cells in mitosis.[54]



(15)

Figure 7: a) Immunofluorescence staining of a mitotic spindle in BSC-1 (green monkey) cells, b) Monastrol treatment of mitotic cells replaces the normal bipolar spindle with a monastrol microtubule array (green) surrounded by a ring of chromosomes (blue), c) Structure of monastrol **(15)**.[54, 58]

Small molecule tools also provide the first step towards a therapeutic drug, in two ways. First, they provide a means of testing whether the function of a given protein is involved in a disease, and second, their chemical structure provides a starting point for drug development.

Small molecules have several advantages over genetic technologies. They can induce their biological effect rapidly and often reversibly. They can also be applied to study a process of interest in a wide range of organisms, whereas the genetic approach, demands that the desired genetic modification has to be regenerated every time the experimental system is switched.[59] They also offer the capacity to study essential genes at any stage in development.[60] They are versatile research tools that can be rapidly adopted by many labs and used for the precise control of protein function in cells where genetic manipulation is difficult.

In addition, washing out a small molecule from a biological system does not present any difficulties, whereas removing a mutation in the genetic information is impossible. Changing the genetic information by mutating the DNA induces the expression of a unique alteration which cannot be turned on or off at will.[61]

Even advanced techniques such as sRNAi which reduces the expression of a protein from a gene by using a 21 bases sequence complementary to a portion of the gene of interest are not widely applicable, as it is difficult to apply these approaches to a broad range of cells or in whole animals.[62]

1.2.4. Reverse and Forward Chemical Genetics

1.2.4.1. Forward Chemical Genetics[54]

Forward chemical genetics involves the screening of a library of small molecules using a cell-based assay. The observation of an abnormal phenomenon, at the phenotype level, is investigated further in order to identify the protein(s) targeted by the small molecule. In order to identify the possible effect of the small molecules at the phenotypic level, several options are available. If a cell-based assay is performed, automated microscopy will enable morphological observations (e.g. the discovery of monastrol **(15)**, Figure 7), whereas the use of reporter-gene assay will provide information on the activity of the target protein (e.g. transcriptional regulation) through an easily detectable enzymatic activity (e.g. the use of luciferase to process luciferin with the linked production of light). Alternatively, cytotoxicity assays or "whole-cell immunoassays" are described as broader methods but offer the potential to find compounds which disrupt the activity of poorly characterized or even unknown targets.[59]

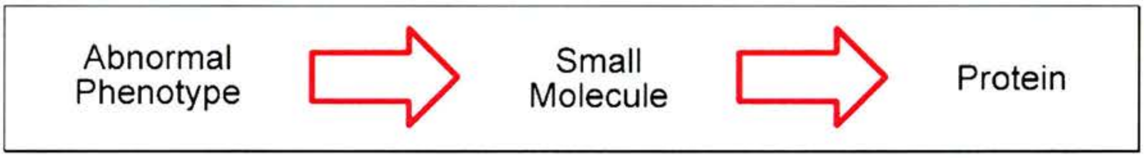


Figure 8: Concept of forward chemical genetics.

This concept is schematised in Figure 8. As illustrated in Figure 7, abnormal mitosis observed by microscopy during the screening was caused by the presence of monastrol **(15)**. Further studies revealed that monastrol **(15)** binds to a motor protein Eg5, which is responsible for the abnormal phenotype. Such studies allow researchers to discover and understand a protein's function by using small molecules.

1.2.4.1.1. Target Identification [63]

1.2.4.1.1.1. By isolation of the target

When the biological assay has been performed with a purified protein, the protein target of the small molecule is obvious. When a forward chemical genetic approach has been followed, using a cell-based assay, identifying the target protein of the "hit" remains a difficult challenge.[64] However, it is not impossible and biochemical techniques allow the identification of the target proteins when a screen is performed. Several approaches to target identification are reviewed here.

(a) Tracing the labelled compound bound to the target

Biochemical purification including the use of traceable derivatives (e.g. radiolabelling of the bioactive compound and following it during fractionation of cell extracts) is a proven method of identifying protein targets.[65]

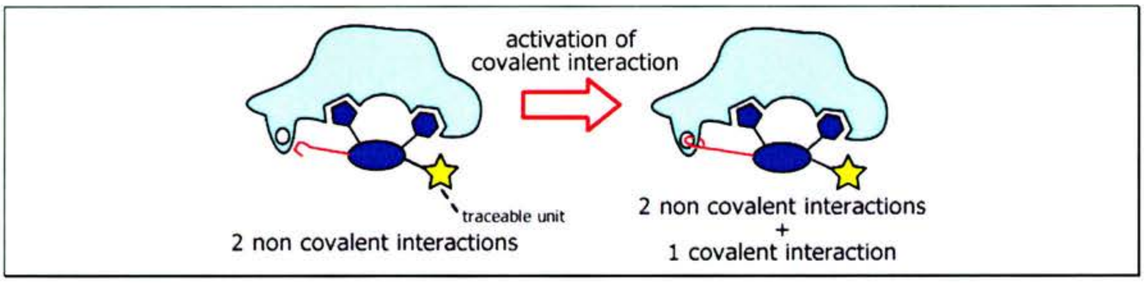


Figure 9: Principle of tracing a protein by binding covalently a small molecule (scheme adapted from [65]).

(b) Affinity chromatography

Affinity chromatography is also a technique used for this purpose. It involves the immobilisation of the small molecule of interest on a solid phase support (Figure 10). Cell extracts are then passed over the solid support enabling the binding of the target protein to its substrate. Washing away the excess of non-binding protein followed by disrupting the specifically bound protein with a solution of the original small molecule allows the isolation of the target protein(s).[66]

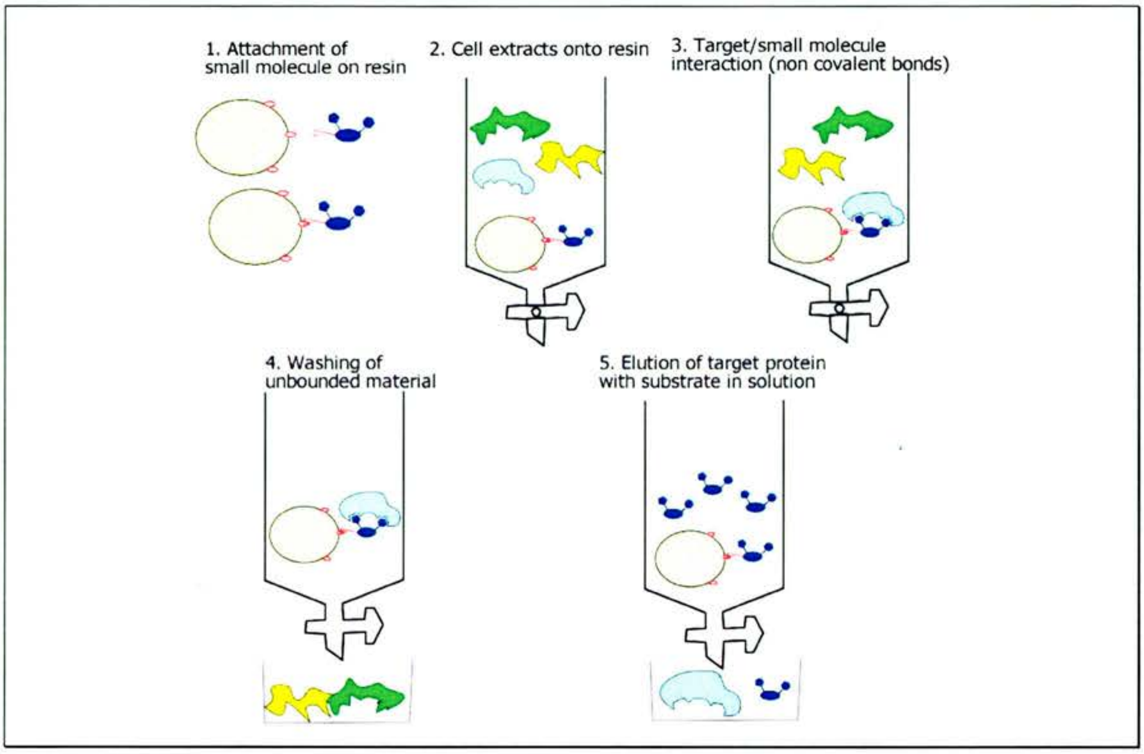


Figure 10: Principle of affinity chromatography (Scheme adapted from [65]).

1.2.4.1.1.2. By identifying an interaction (or non-interaction) [67]

(a) Yeast two-hybrid system, [68] disrupting a known interaction

The yeast two-hybrid system is a technique allowing the study of protein-protein interactions by the means of a reporter gene. One protein is built with two sub-structures: a DNA binding domain (DBD, in red) which will bind to the promoter of the gene of interest and the protein of interest Y (green). The second protein is also comprised of two sub-units: a protein of interest, X (blue) bound to a reporter gene activation domain (AD, red).

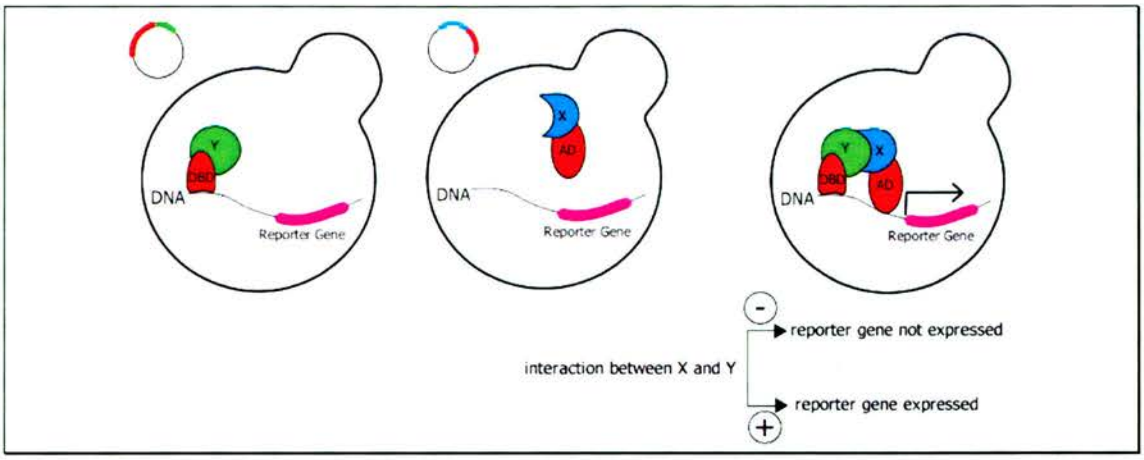


Figure 11: Principle of yeast two-hybrid system (Scheme adapted from [68]), DBD for DNA Binding Domain, AD for Activation Domain.

The DBD domain and AD domain are known to be essential for the expression of the reporter gene. However, the transcription of the reporter gene will be activated only if the two proteins of interest Y (green) and X (blue) interact with each other. The role of the small molecule in this system is to disrupt the protein-protein interaction. If a small molecule binds Y as its target, the interaction X-Y will not take place, then, the reporter gene will not be expressed.

A variant of this system called the reverse two hybrid system has been developed. The same principle is used in a different manner: the reporter gene involves a trigger for cell death. Uninterrupted interaction of X with Y will therefore induce the death of the cell. However, if a small molecule disrupts the interaction, the cell does not die.

The two-hybrid system is simple and inexpensive but has a tendency to produce false positives.

(b) Yeast three-hybrid system, [68] by reading out an interaction

It is a further extension of this technology to the yeast three hybrid system that is of particular relevance to target identification studies. This system involves the construction of two sets of fusion proteins which are different to those described in the previous system in the sense that Y and X do not interact directly but through a third element, a small molecule, often referred to as chemical inducer of dimerization (CID).

CIDs [69] are composed of two units: one (A, green circle) which is known to interact with Y, the other one (B) which is derived from the hit compound. Y and A will interact, bringing B close to the reporter gene. If B and X interact (i.e. if protein X can bind to small molecule B), case 1, the activation domain will activate the reporter gene. If B and X do not interact, case 2, the hybrid X-AD will not activate the reporter gene. A library of X-AD protein fusions are prepared and used to identify proteins that bind to B.

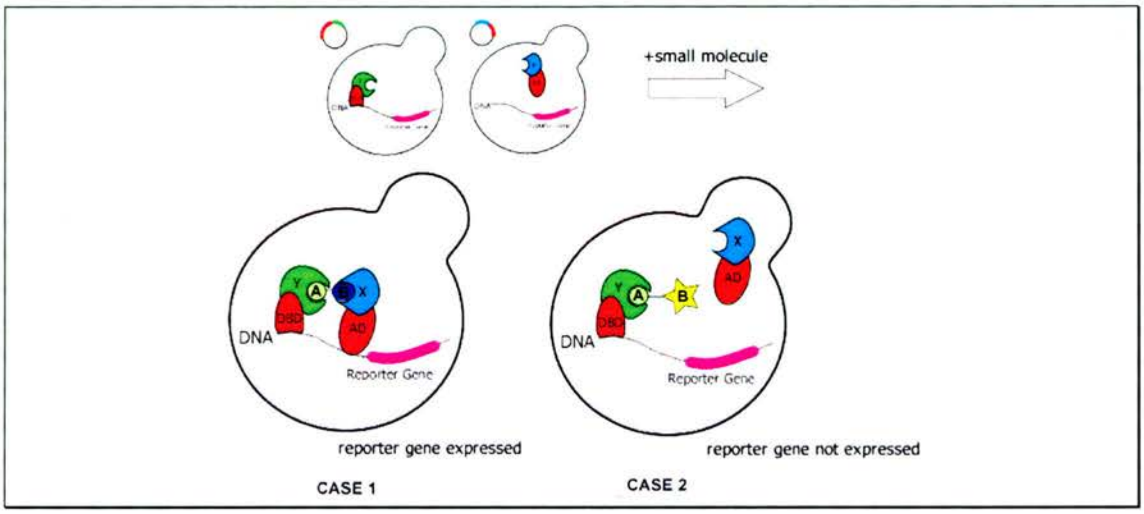


Figure 12: Principle of yeast three-hybrid system, DBD for DNA Binding Domain, AD for Activation Domain.[68]

Reviews on the yeast forward and reverse "n"-hybrid systems have recently been published [70] and highlight the details of the systems described here in outline.

1.2.4.2. Reverse chemical genetics

Reverse chemical genetics involves screening a small molecules library against a purified protein of interest. This allows the identification of hits that bind to and/or modify the activity of the protein of interest. Once a hit has been identified, it is possible by looking at the phenotype to probe the role of the protein in cells. As illustrated in Figure 13, the protein is the first element of the sequence. A small molecule inducing changes at the phenotype level would be selected for further studies.

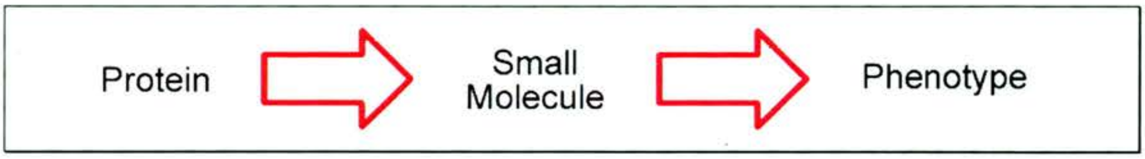
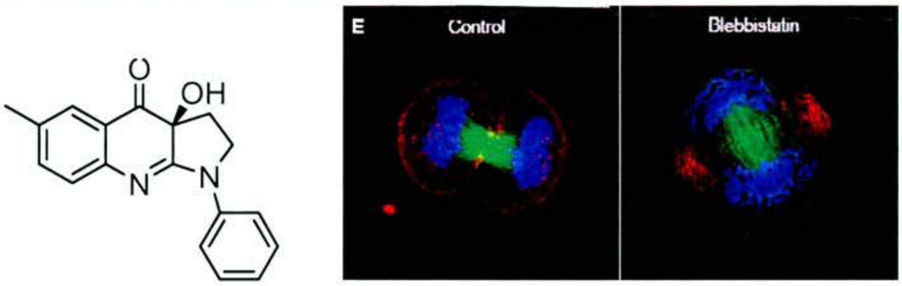


Figure 13: Concept of reverse chemical genetics.

The small molecule (S)-(-)-blebbistatin **(16)** was discovered using the reverse chemical genetics approach in a high throughput screening targeting non-muscle myosin II.[71] The small molecule disrupts directed cell migration and cytokinesis in vertebrate cells.



(16)

Scheme 10: Structure of blebbistatin **(16)** and effect of blebbistatin **(16)**, HeLa cells untreated (control) or treated (blebbistatin) with 100 μM (±)-blebbistatin and stained for DNA (blue), α-tubulin (green), and non-muscle myosin II (red).[71]

1.3. The Project

1.3.1. Background

As mentioned previously, the starting point for chemical genetics is the compound libraries. Libraries can be obtained commercially, by collecting together individual compounds or by generating efficiently large numbers of compounds using the techniques described in section 1.1.3. Commercial libraries provide few attractive synthetic challenges from a chemist's point of view. Collecting compounds and synthesising large numbers of compounds by using classical methods in organic synthesis is time consuming. Therefore, designing strategies to create "**efficiently**" libraries of large numbers of compounds are the main goals for a chemist involved in chemical genetics. "Efficiently" is the term used by S. L. Schreiber to describe the manner in which **generating diversity** must be achieved.[42]

However, this requires a significant change in the way chemists currently think. Planning the synthesis of a defined target is well precedented and clear guidelines exist. Driving chemical synthesis from the stand point of incorporating diversity is less well precedented and the rules are only just emerging. Several of the factors that are currently viewed as important in diversity oriented synthesis are discussed below.

1.3.1.1. Core Decoration

The way of accessing diversity described so far was to select a small molecule, with or without biological precedents, and to decorate this core by incorporation of building blocks (Figure 14). The galanthamine-inspired library described in section

1.1.3.2.3 (page 21) illustrates the strategy of core decoration.[44] Indeed, the four reactive sites on the core-structure are reacted orthogonally without a requirement for the use of protecting groups. A library of 2527 members was synthesised and successfully analysed by LC/MS after cleavage from the resin.[44]

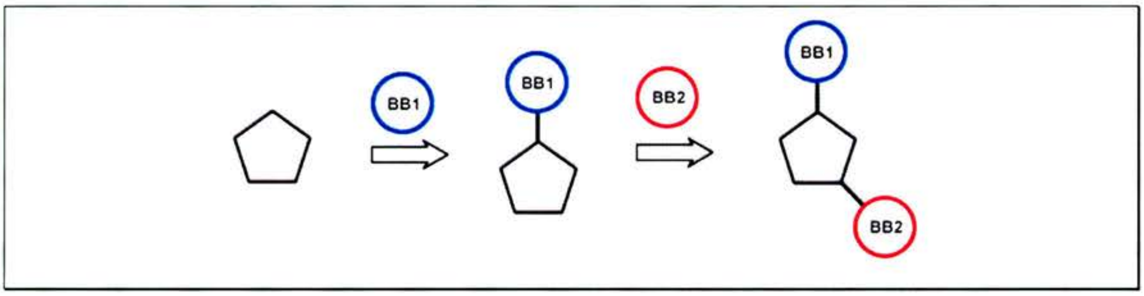


Figure 14: Core decoration principle; diversity incorporation by use of building blocks.[72] The core structure, unchanged along the synthesis, carries the functional groups which are reacted orthogonally to insert the different building blocks.

By decorating the core, the central structure remains unchanged, i.e., the 3-dimensional structure of the scaffold holding the building blocks is identical in all the library members. In the library based on the galanthamine core, the 2527 members of the library have the same inner skeleton.

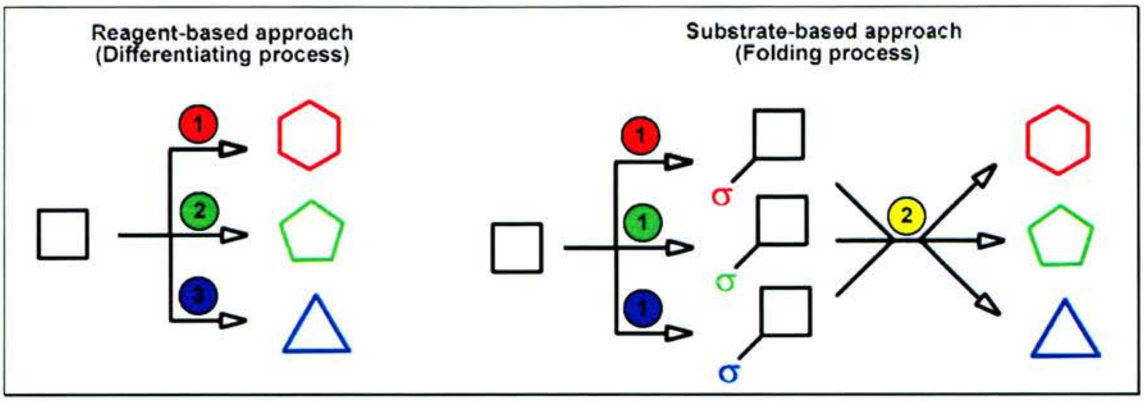
1.3.1.2. Skeletal diversity

Diversity can also be generated by altering other factors in addition to building block incorporation. Reactions involving the core structure would allow the introduction of another degree of diversity in which the 3-dimensional structure is transformed and starting from one core, another core can be generated by means of a single reaction carried out on all members of a library. Creating one library of n members and transforming it by a single reaction to another one would give a 2n member library. In the past few years, the concept of generating diversity at the level of the core structure rather than only through the use of building blocks has been described by S. L. Schreiber as "skeletal diversity".[41, 72]

Skeletal diversity generation can be achieved using two strategies (Scheme 11):

- by using different reagents on a common substrate to give different core structures. This has also been termed **reagent-based approach**.

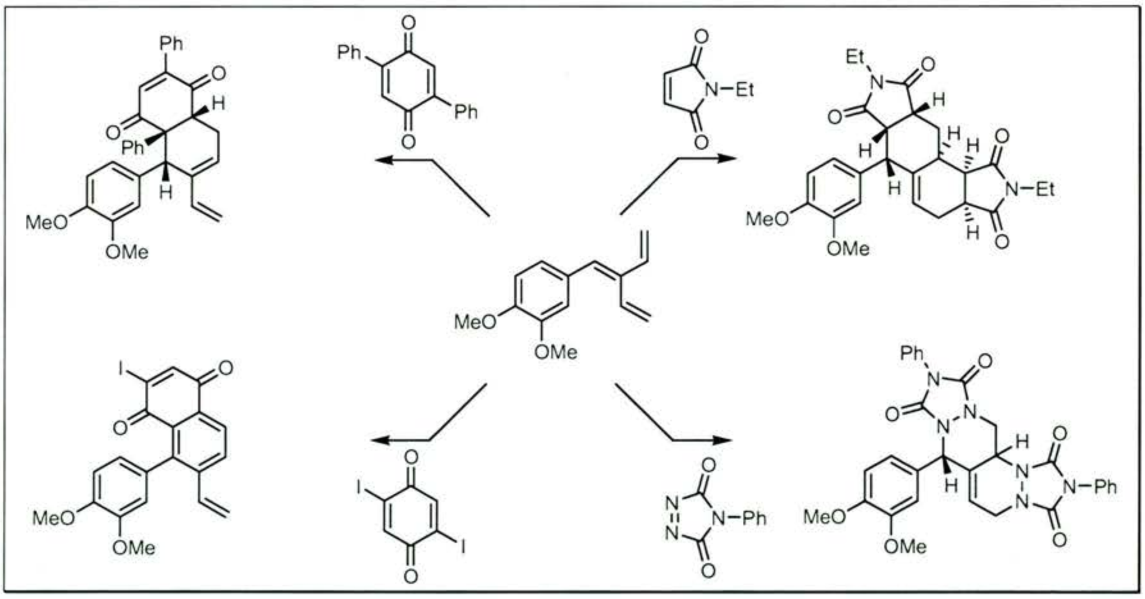
- by using a common reagent on different substrates (synthesised from a common starting material in a previous step) called **substrate-based approach**.



Scheme 11: Two general approaches for planning synthesis pathways to generate skeletal diversity.

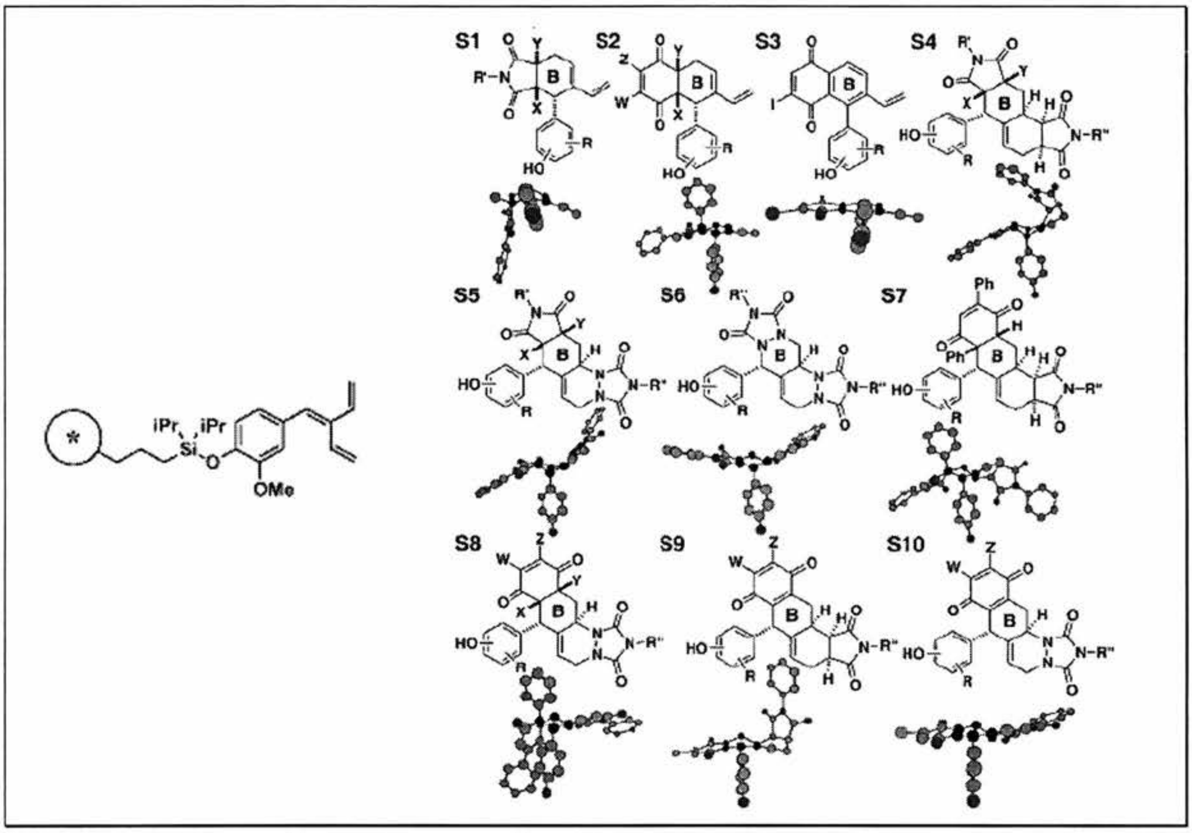
1.3.1.2.1. Reagent-based approach

In the reagent-based approach, the diversity is driven by the nature of the common substrate which is reacted with a range of reagents. The nature of the reagents induces diversity in the sense that the products are structurally different.



Scheme 12: Example of generation of skeleton diversity through a Diels-Alder reaction.[40]

In the example shown in Scheme 12 and Scheme 13, ten distinct polycyclic skeletons have been prepared from the same starting material (Scheme 13). The authors define compounds with different: (1) numbers or sizes of rings, (2) ring fusion stereochemistry, and (3) degree of ring fusion saturation as having "different skeletons" [40]. The structure of the reagents and their ability to induce stereoselective reactions on the same substrate allow the creation of diversity/complexity.[73]

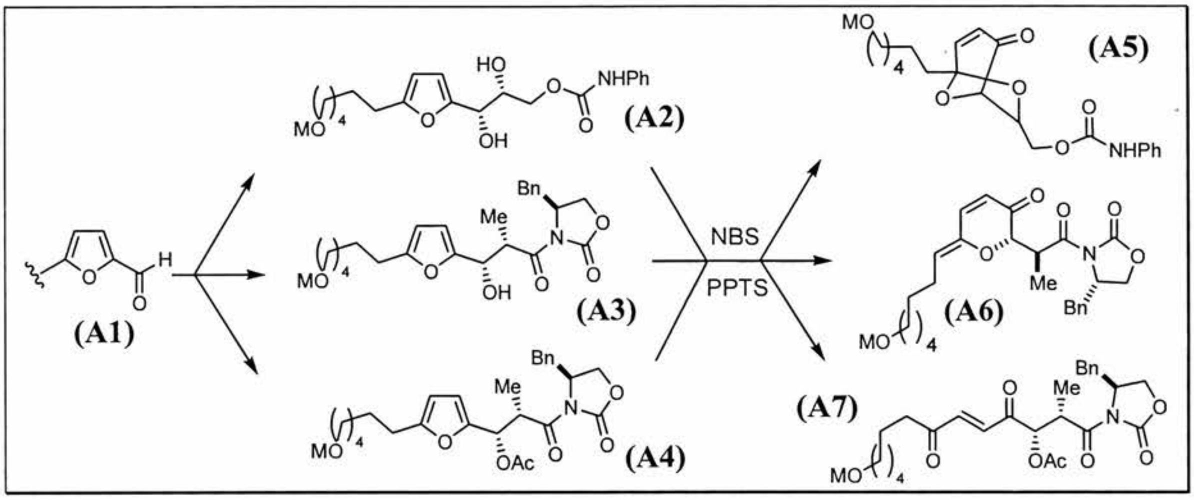


Scheme 13: Skeletons obtained through the Diels-Alder reaction.[40]

1.3.1.2.2. Substrate-based approach

In the substrate-based approach, the starting point of the library involves a unique starting material **A1**. The building blocks reacted at the desired site are chosen for their ability to bring new functional groups to give **A2**, **A3** and **A4**, for example.

Under the same reaction conditions, the new functional groups behave differently in each case to give a particular skeleton.[72] In this example, the Achmatowicz reaction, radical cyclisation, transformed **A2**, **A3** and **A4** to a bridged product of type **A5**, **A6** containing a six-membered ring and **A7** a linear product, respectively.



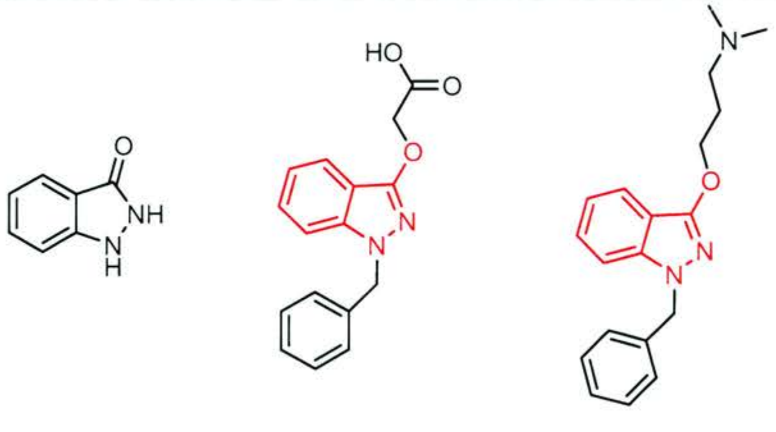
Scheme 14: Example of substrate-based approach for skeleton diversity.[74]

1.3.2. Project goals

The main aim of this project was to establish a library design for an unbiased collection of potentially bioactive small molecules. To achieve this it was necessary to draw on many of the research areas discussed previously. In particular, we wanted to incorporate skeletal diversity into our library design. The system we selected for study was the indazolinone core structure **(17)** for two key reasons. First, indazolinone derivatives have been previously reported to exhibit biological activity. Second, we felt that there were some significant chemical challenges associated with diversity incorporation using this system. As drug-like molecules are often expected to possess a molecular weight of <500 Da (Lipinski´s rules [75]), most library designs must start with a small core structure (MW= 150-200 Da). In order to enable sufficient diversity incorporation several functional groups are required in the core and the challenge therefore becomes how to react each functional group in turn without the excessive use of protecting groups. These challenges are particularly extreme with the indazolinone core structure and the strategies we have developed to deal with this form the major part of this thesis (for an overview, see section 1.3.2.2)

1.3.2.1. Biological activity of indazolinone derivatives

Few substituted indazolinones are reported to have biological effect (Scheme 15). As far as the medical use is concerned, derivatives of 1-benzyl-3-hydroxy-indazole (bendazac **(18)** and benzydamine **(19)**) have a different pharmacological profile: bendazac **(18)** showed a selective inhibition of protein denaturation,[76] while benzydamine **(19)** is a strong anti-inflammatory agent, without any anti-spermatogenic activity.[77]



(17) **(18)** **(19)**

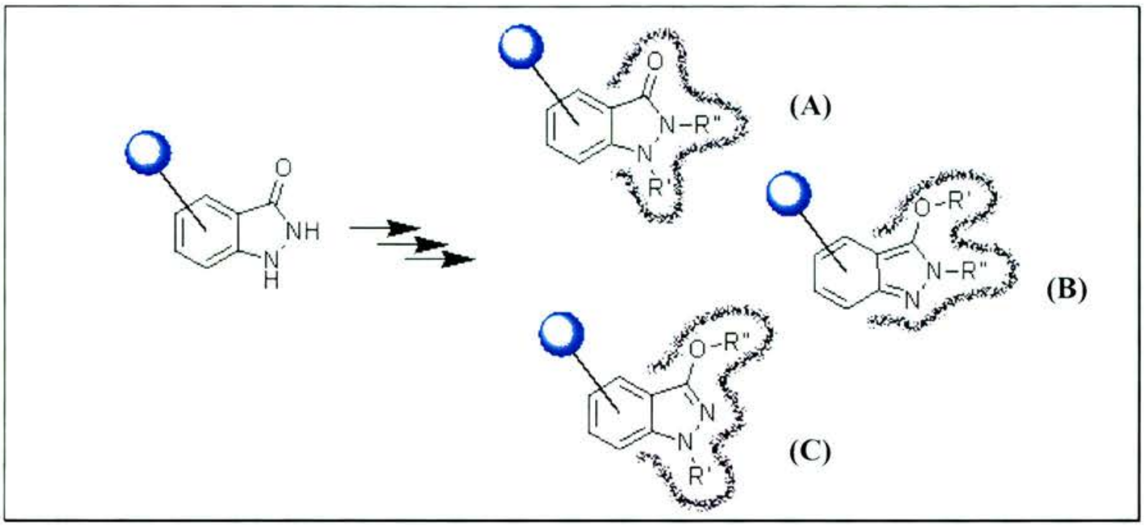
Scheme 15: Structures of indazolinone **(17)**, Bendazac **(18)** and Benzydamine **(19)**.

Bruneau *et al.* [78] have reported that substituted indazolinones were potent inhibitors of the 5-Lipoxygenase enzyme (5-LPO), involved in the arachidonic acid cascade for the synthesis of leukotrienes. This target represents a potential treatment for disease in which elevated levels of leukotrienes are believed to play a role (rheumatoid arthritis, asthma, inflammatory bowel disease).[79-81]

The reported bioactivity of indazolinone and its criterias that are in accordance with Lipinski rules [75] make this molecule a relevant core structure for developing an unbiased library in a chemical genetics project.

1.3.2.2. Diversity incorporation

The indazolinone core structure is compact with various reactive sites. The first goal of our project was to design a robust route to insert diversity in an efficient and specific manner around the indazolinone core. Ideally, we would like to generate three different skeletons from the indazolinone core. As illustrated in Scheme 16, for each of the three isomers, the substituents are in significantly different spatial arrangements.

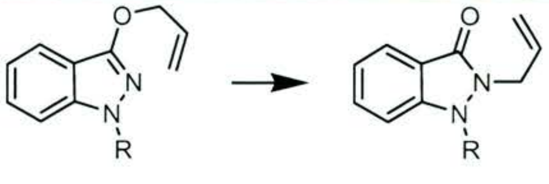


Scheme 16: Project of generating diversity from indazolinone core.

Maximising diversity incorporation around the indazolinone core involved the optimisation of synthetic routes in solution phase. It was then necessary to transfer the chemistry onto the solid phase in order to allow the synthesis of a library using the split and pool technique. The scale used for the solution phase was sufficient to allow full characterization of the products. The transfer from solution to solid phase involved the use of LC/MS techniques to compare the authentic materials synthesised in solution against the material made on and cleaved from the resin.

1.3.2.3. Claisen-type rearrangement as a method for core-switching

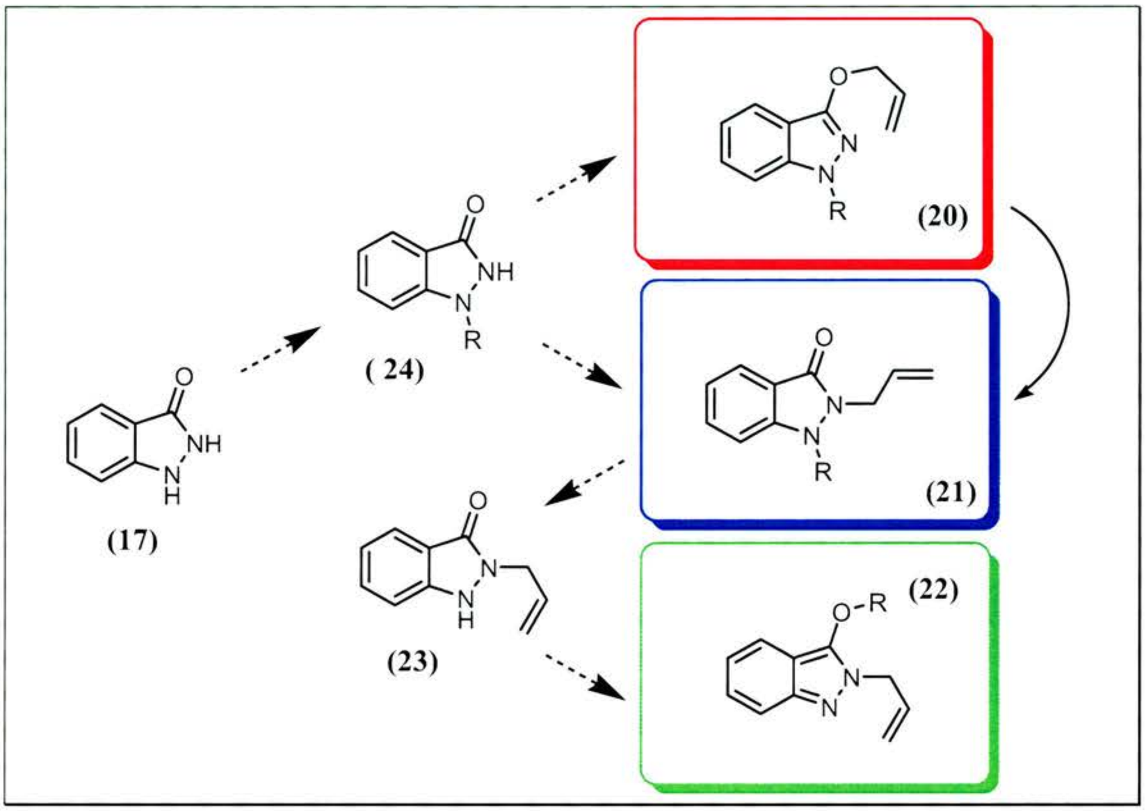
The Claisen rearrangement, one of the sigmatropic rearrangements, has been extensively described in the literature.[82] However, it has not been reported in the context of indazolinones. In our library design, we planned to use a Claisen-type rearrangement on the indazolinone core to convert, for example, **20** to **21** (or structures of type **C** to type **A**, Scheme 16). A key aspect of the project was therefore to study the possibility of rearranging an allyl group on the O position of the indazolinone to the N2 position of the indazolinone.



(20) **(21)**

Scheme 17: Core switching reaction in the indazolinone series using the Claisen rearrangement.

The aza-Claisen rearrangement presented in Scheme 17 would allow the conversion of **20** to **21**. If selected correctly, the group R could then be removed and our strategy would be to identify a second reaction to functionalise **23** on the oxygen position to generate structure of type **22** (Scheme 18, structure C in Scheme 16).

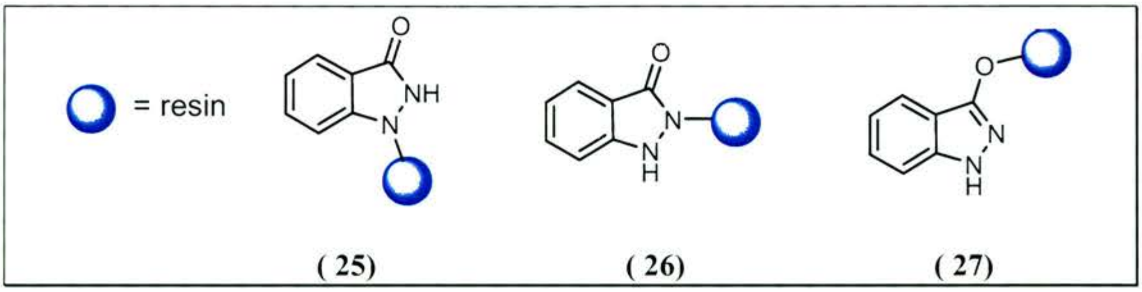


Scheme 18: Skeleton diversity, three skeletons from the indazolinone core using the aza-Claisen rearrangement.

Scheme 18 summarises the initial design for our library, starting from one core **17** and by a carefully controlled and well-designed reaction sequence three different cores **20**, **21**, **22** would be synthesised.

1.3.2.4. Plans for solid phase synthesis

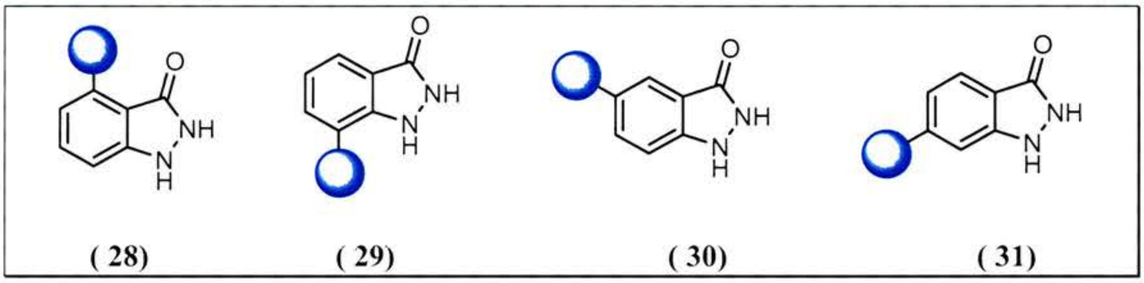
Provided no purification is needed after the final step (the cleavage) and as the compounds are ready for analysis and biological screening, solid phase synthesis remains the technique of choice for combinatorial synthesis. Designing an indazolinone derivative to load onto a solid support was another component of the project.



(25) **(26)** **(27)**

Scheme 19: Loading points on the 5-membered ring.

Several choices were available for loading the indazolinone core onto the resin. However, the use of the 5-membered ring system (**25**, **26** and **27**, Scheme 19) was excluded because it was incompatible with the planned sequence (Scheme 17).



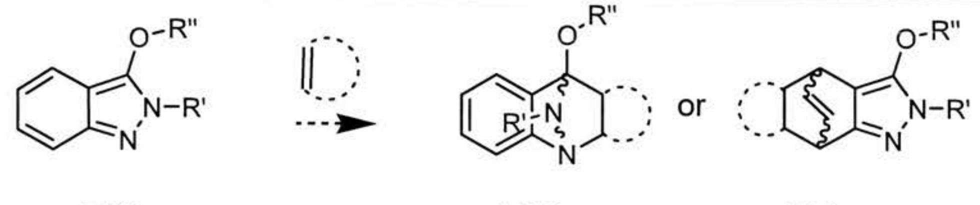
(28) **(29)** **(30)** **(31)**

Scheme 20: Loading points on the 6-membered ring.

Four possibilities involving the 6-membered ring were considered. Factors such as the availability of starting material and the ease of the synthesis were considered. **28** and **29** are acceptable but the position of attachment to the solid support is in close proximity with the reactive sites N1 and O. It was therefore decided to focus initially on structures **30** and **31** where the attachment to the solid support was such that it does not interfere with the reactive sites. Successful synthesis of a compound corresponding to an analogue of **30** was achieved and this core structure proved useful for library synthesis on the solid support.

1.3.3. Potential Diels-Alder approaches

Structures of type **32** (Scheme 21) are one of the three skeletons aimed at in the library generation. The di-diene feature of the molecule attracted our attention in reacting it in the Diels-Alder reaction. Therefore, from a chemical point of view and in the perspective of generating a new core for diversity purposes, we decided to investigate the chemical behaviour of **32** in solution in the aza-Diels-Alder reaction.



(32) (33) (34)

Scheme 21: Idea of Diels-Alder reaction with **32** as a diene.

1.4. Literature review

1.4.1. Introduction to indazolinones

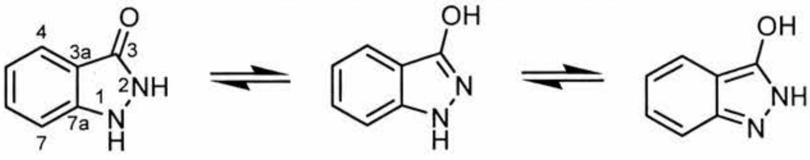
1.4.1.1. Nomenclature and structure [83]

Indazolinones are fused bicyclic structures (Scheme 22). This structure is reported in the literature by several different names including:

1*H*-Indazolo-3-ol
3-hydroxy-1*H*-indazole
3-oxo-1,2-dihydro-3*H*-indazole
1,2-dihydro-3*H*-indazol-3-one
indazolone
indazolinone
indazolol

For the purposes of this review, *O*-substituted indazolinones will be referred to as substituted indazoles rather than substituted indazolinones.

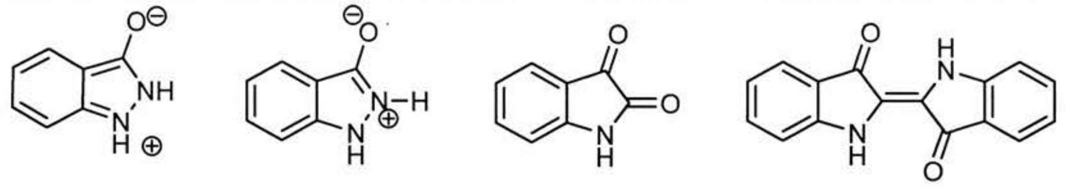
Several analytical studies have been carried out on indazolinones and are described here in order to understand the key problem associated with the indazolinone structure: the issue of tautomerism. The presence of three possible structures has been determined by X-ray, NMR and UV analysis. The indazolinone may exist in the imidate **35** or the lactam tautomer form **17**.



(17) (35) (36)

Scheme 22: Tautomeric structures of indazolinone.

The existence of structure **36** is unlikely given the present knowledge of indazolone tautomerism. Nevertheless, O′Sullivan used infrared techniques to study a range of compounds consisting of a benzene ring fused to a five-membered ring, as in indazolinone **17**. According to his results,[84] the signals observed for indazolinone are analogous to those obtained for isatin **39** and indigo **40**; a strong band from 3100 to 2700 cm^{-1} and a very intense broad band at 1626 cm^{-1}. He described the latter band as too intense to be a C=C stretching frequency, and is probably due to a conjugated carbonyl group involved in hydrogen bonding. This is evidence for the existence of indazolinone in the tautomeric form **17**.



(37) **(38)** **(39)** **(40)**

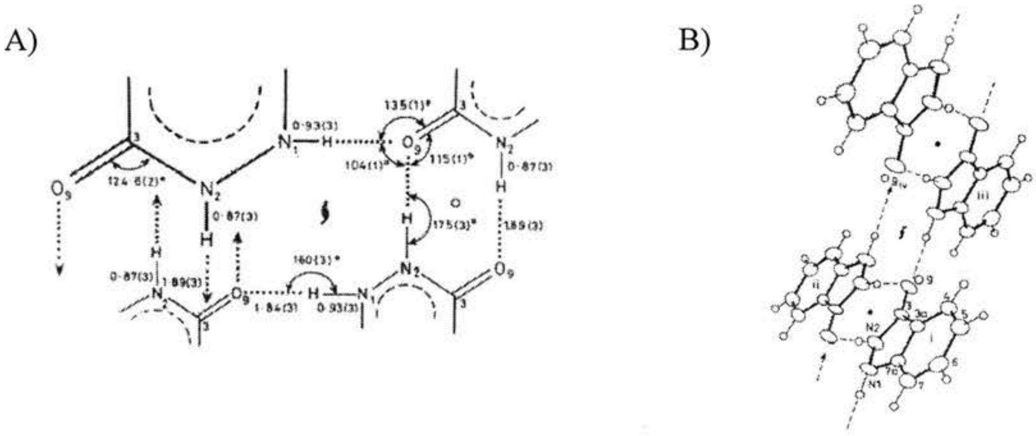
Scheme 23: Structures of indazolinone **37** and **38**, isatin **39** and indigo **40**.

In 1986, Ballesteros *et al.* used X-ray crystallography and NMR (^{15}N, ^{13}C) to determine the structure of indazolinone in the solid state and in solution. They concluded that indazolinone existed as 85% of the enol form **35** and 15% for the lactam form **17** in the solid state structure.[85]

The indazolinone structures will be drawn throughout the document as they appeared in the original papers.

1.4.1.2. Physical properties

The unsubstituted indazolinones are crystalline solids with melting points of ca. 200°C (with some decomposition).They dissolve readily in water and alcohols, but have very poor solubility in apolar organic solvents. The UV spectrum of indazolinone in ethanol shows absorption maxima at 220 nm (ε=2200) and 310 nm (ε=3700). The IR spectrum (KBr disc) presents a very broad maximum between 3000 and 2700 cm^{-1} from the N-H stretching and another broad maximum at 1630 cm^{-1}, corresponding to the C=O vibration, leading to assignment of the indazolinone in the tautomeric form **17** the solid state (Scheme 22). X-ray analysis in 1986 by Ballesteros *et al.* concluded that in the solid state indazolinone exists as such tautomeric form **17** (Scheme 24). ^{1}H NMR spectroscopy (d$_6$-DMSO) shows that all the protons of indazolinone are in the aromatic region between δ 6.8-8.0 ppm. In solution (DMSO), tautomer **17** represents only 15%, with the enol form **35** predominating (85%).

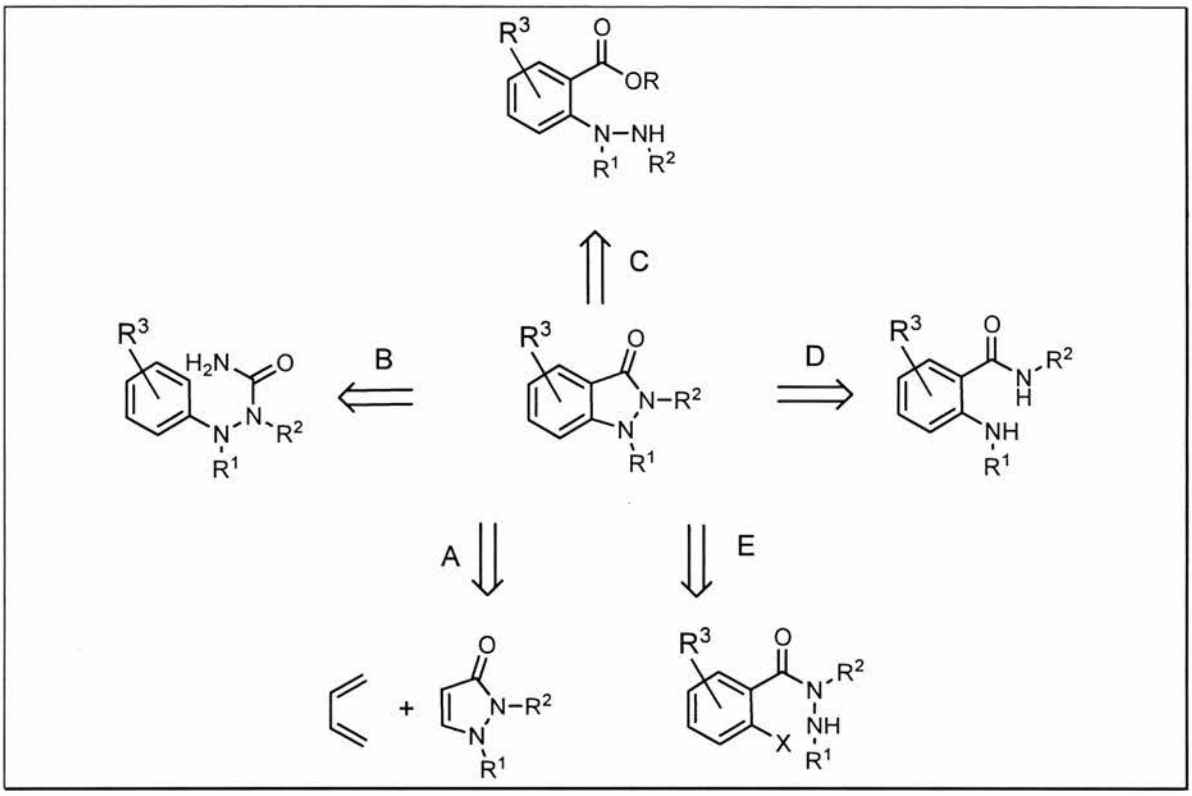


Scheme 24: (A) H-bonding pattern and (B) X-ray structure of indazolinone showing intermolecular H-bonds.[85]

1.4.2. Reported routes to prepare indazolinones

Indazolinones can be synthesised via two distinct strategies. The first one involves assembling either the 6-membered or the 5-membered ring using different coupling methods. The different possibilities for disconnecting the indazolinone system are presented in Scheme 25. The second involves the conversion of existing fused bicyclic systems to the indazolinone structure either by ring expansion or by ring contraction.

1.4.2.1. Building the core



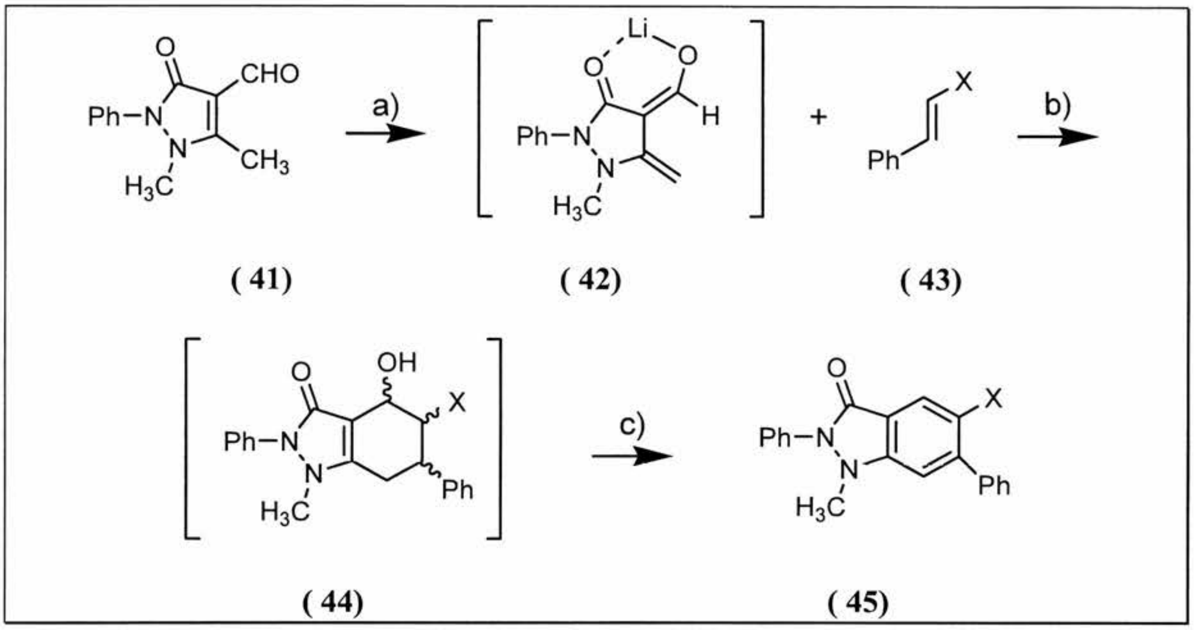
Scheme 25: The different ways to access the heterocycle.

As shown in Scheme 25, five disconnections to generate the indazolinone core have been assessed to date. One route (A) involves the construction of the benzene ring, whereas four routes (B, C, D and E) involve the construction of the 5-membered ring. Routes B, C, D and E lead to the 5-membered ring by 4 different coupling reactions involving C-C, C-N, N-N and N-C bond forming reactions respectively.

A literature survey of the main synthetic routes was carried out at the start of this project to identify the best way to make the core-structure. A point of attachment to the resin (for example an alcohol functionality if a silyl linker strategy was to be employed), the possibility of inserting diversity at the O, N1 and/or N2 positions (the three positions of the indazolinone need to be unsubstituted or protected in such a way that they can be easily deprotected) and a short synthetic sequence are key requirements for the core structure.

1.4.2.2. Method A

The Diels-Alder reaction is one of the methods of choice for building 6-membered ring systems. This synthesis was a relatively new approach to indazolinone discovered in 1999 by Roy *et al.* (Scheme 26).[86] It constructs the 6-membered ring system of the indazolinone using **41** as a precursor of the diene **42**. **42** was generated from **41** in presence of a strong base at low temperature. Coordination of the lithium atom from LDA is proposed to stabilise the diene **42**. Reaction with dienophiles of type **43** induces the Diels-Alder cycloaddition to give **44** which was not isolated but reacted in benzene in the presence of pyridinium tosylate resulting in formation of the aromatic derivative **45**.



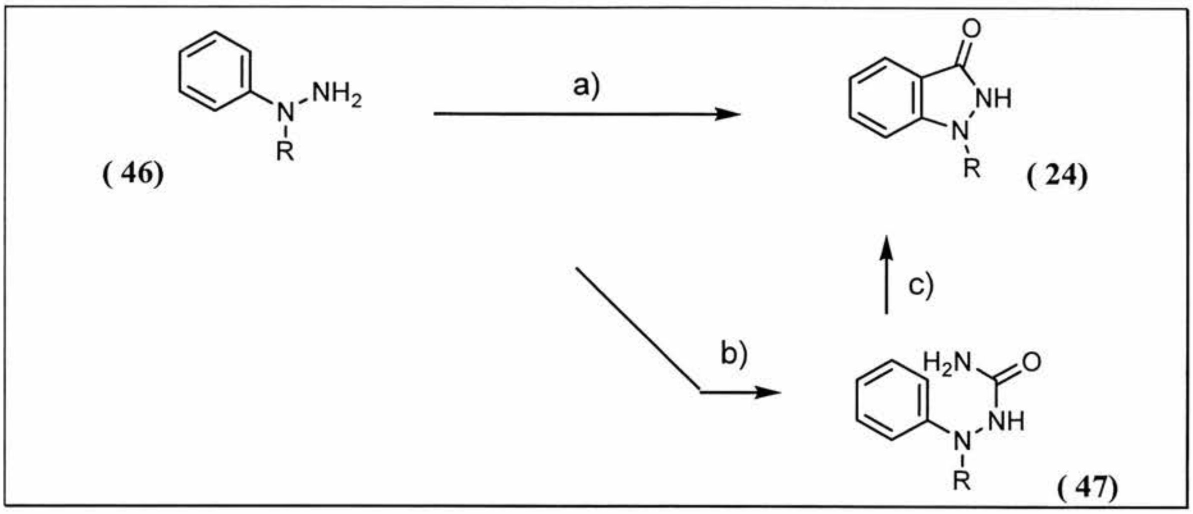
Scheme 26: Aromatisation of the 6-membered ring to give indazolinone **45**; [86] a) LDA/THF, -78°C, b) THF, -78°C, c) pyridinium tosylate, PhH, reflux, high yield, X=NO_2 or COPh.[86]

From the perspective of a library design, *N1*-methyl and *N2*-phenyl in **45** represent a hurdle for diversity incorporation. This sequence was considered as a possible route to the library core-structure but was abandoned due to the difficulties associated with the substituents at the N1 and N2 positions and the long sequence required to generate structures of type **41**.

1.4.2.3. Method B, Disconnection C3-C3a

1.4.2.3.1. From hydrazine derivatives and carbonic acid derivatives

This approach [87, 88] is the oldest method reported for the synthesis of indazolinones, especially those having a substituent (alkyl or aryl) at the N1 position. It involves a C-C bond forming reaction (C3-C3a) by direct synthesis (**46** to **24**) or by synthesis of the intermediate **47** which is cyclised to give **24** on heating (Scheme 27).



(46) (24) (47)

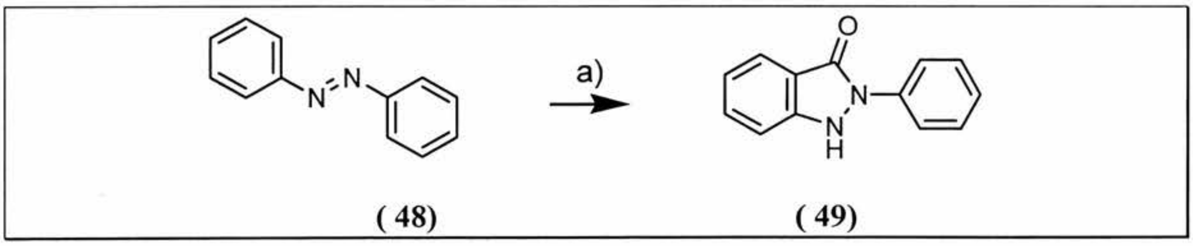
Scheme 27: Indazolinone synthesised by making the C3-C3a bond; a) i) NH_2CONH_2, 180°C, 3 h, ii) 280°C, 3 min, b) KOCN, H^+, heat, c) Heat .[87, 88]

The carbonyl system is incorporated either from urea or from potassium cyanate, the intermediate semicarbazide **47** is not usually isolated. The cyclisation step is a thermal process, occurring at ca. 200°C. Both approaches are generally low-yielding.[87, 88] Moreover, the first route (a) gives a mixture of several compounds because of the high temperatures. This disconnection has been useful for obtaining label indazolinone using ^{14}C urea only (radio labelling) but does not seem appropriate for our library design.

1.4.2.3.2. Carbonylation with CO and metal complexes [89, 90]

1.4.2.3.2.1. Using cobalt salts

This synthesis was reported by Murahashi and Horie in 1956. It converts azobenzene of type **48** to 2-arylindazolones of type **49** in the presence of carbon monoxide with octacarbonyldicobalt (Scheme 28).[91]



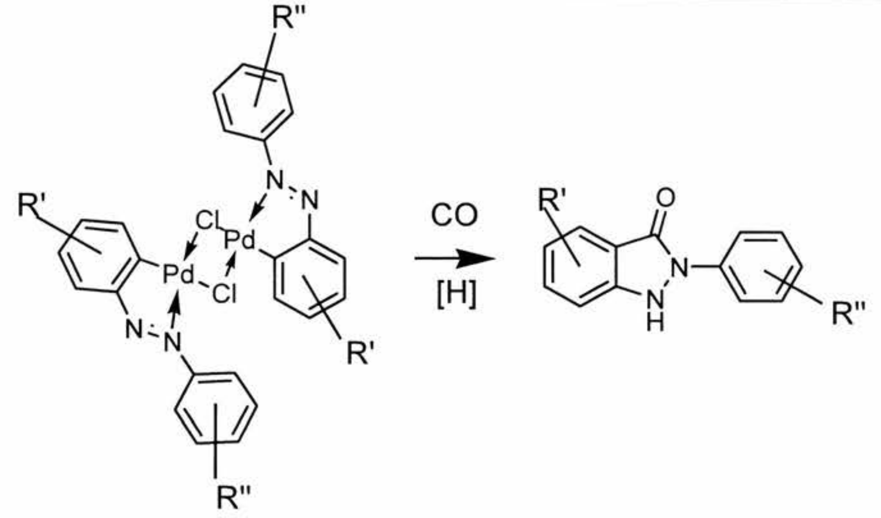
(48) (49)

Scheme 28: Synthesis of indazolinone **49** from azobenzene **48** using cobalt complexes; a) $Co_2(CO)_8$, CO, 190°C, 150 atm, 80%.[91]

Introducing a group containing an alcohol functionality for attachment onto the resin could be possible as the azobenzene does not need to be symmetrical. However, as discussed previously for method A (page 44), the substituent at the N2 position is not compatible with the planned diversity incorporation and increases the difficulty in generating an indazolinone ready for diversity incorporation if the aryl group has to be removed.

1.4.2.3.2.2. Using palladium complexes

Organometallic compounds containing palladium [91] can also be useful for the synthesis of indazolinone. Indeed, azobenzene derivatives in the presence of palladium dichloride induce the formation of intermediates of type **50**. Under carbon monoxide pressure in a protic solvent, this complex is transformed to structures of type **51**.



(50) **(51)**

Scheme 29: Carbonylation of azobenzene-palladium chloride complexes **50**; EtOH or H_2O, CO, 150 atm, 100°C, 5h.[91]

The cyclisation of azobenzenes in the presence of palladium dichloride has been carried out with different substituents and leads to **51** in very good yields (Table 2).

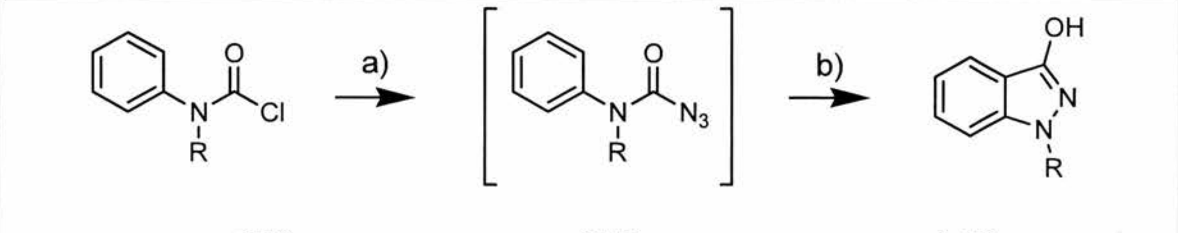
R'	R"	Yield
4-Me	4-Me	97%
4-Cl	4-Cl	96%
4-OMe	H	98%
4-Me	H	84%
4-Cl	H	97%

Table 2: Summary of yields of carbonylation of azobenzene-palladium complexes.[91]

This strategy, despite the high yielding reactions, again involves the synthesis of *N2*-substituted indazolinones, which is not ideal for our route, as diversity incorporation would be limited for structures of type **51**.

1.4.2.3.3. N-arylcarbamoyl azides and Curtius rearrangement [88, 92-94]

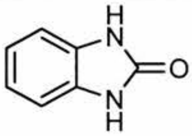
The elegant Curtius rearrangement from the carbamoyl structure **52** produces the *N1*-substituted indazolol **54**. Over a range of substituents, the yields vary from 15% to 70%.



(52) **(53)** **(54)**

Scheme 30: Synthesis of **54** from arylcarbamoyl azide **53** under thermal conditions; a) NaN_3, MeOH, 75°C, b) tetralin, 160-190°C, 1-2h, 15-70% (R=Bn).

Unfortunately, in the majority of the studies, by-products of type **55** are usually isolated with the desired product.



(55)

Scheme 31: By-product **55** obtained from the synthesis of **54**.

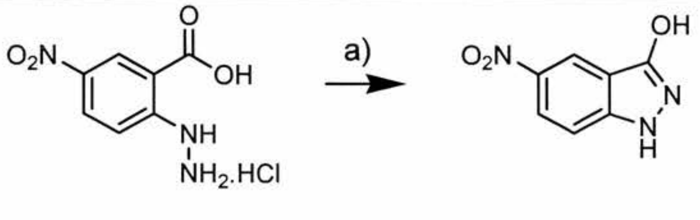
The fact that a by-product is formed, the variable yields obtained in this approach and the stable nature of R at the N1 position make this sequence inappropriate for our planned synthetic strategy.

1.4.2.4. Method C, Disconnection N2-C3

1.4.2.4.1. From hydrazine derivatives

The N2-C3 disconnection has been widely explored for the synthesis of indazolinones. Unsubstituted, *N1*- and *N2*-substituted indazolinones can be made using this strategy.

For example, unsubstituted indazolinones of type **57** can be synthesised when the benzene ring contains an electron withdrawing group such as nitro group in **56**.

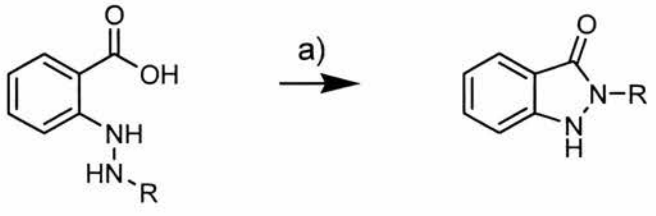


(56) (57)

Scheme 32: Synthesis of **57** by cyclisation of **56**; a) H_2O, 100°C, 30 min, $-H_2O$, -HCl, 89%.[95]

This approach is useful because it results in an unsubstituted indazolinone. Diversity incorporation would therefore be possible without any deprotection steps. The nitro group present on the benzene ring is not required for the cyclisation and could be a positive element for the introduction of the attachment to the resin.

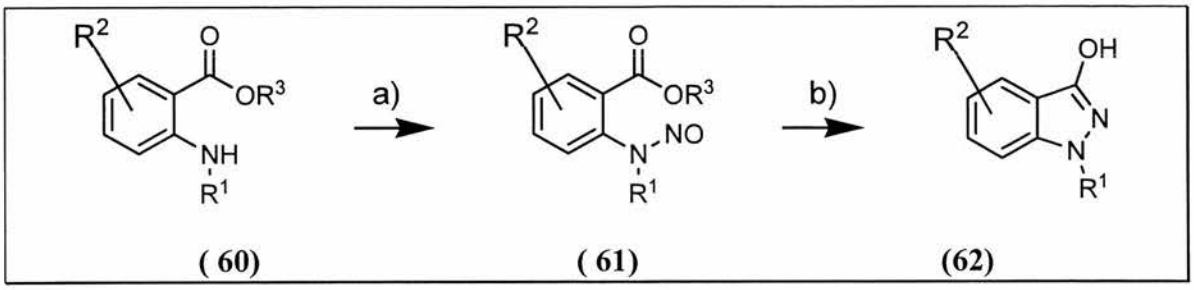
N2-substituted indazolinones of type **59** can be synthesised from hydrazine derivatives of type **58** in acetic acid under reflux but the yield of the reaction is poor (Scheme 33). The benzyl group at the N2 position is also incompatible with the diversity incorporation sequence and would have to be removed.



(58) (59)

Scheme 33: Synthesis of indazolinone **59** from hydrazinobenzoic acid **58**; a) AcOH, reflux, 30 min, 25% (R=Bn).[83, 96]

The N2-C3 disconnection can also lead to anthranilic acids as starting materials. *N*-substituted anthranilic acids or esters of type **60** can be converted with nitrous acid to the corresponding nitroso derivatives **61**.[83] The reduction of the nitroso derivatives **61** gives the hydrazine which cyclises onto the carboxylate functionality to give **62**.



(60) **(61)** **(62)**

Scheme 34: Synthesis of indazolone **62** from anthranilic acid derivative **60**; a) HNO_2, H_3O^+, b) Raney-Nickel, Pd/C.[83]

The formation of the nitroso derivatives is generally easy, but their reduction is only possible with specific agents such as sodium hydrosulfide in an alkaline medium when R^1=H, Hal, Me, Bn, or by catalytic hydrogenation. The reduction of the nitroso group could be a problem if the substituents R^2 or R^1 are sensitive to the reaction conditions being used. The yields of this procedure vary from 45% to 85%.

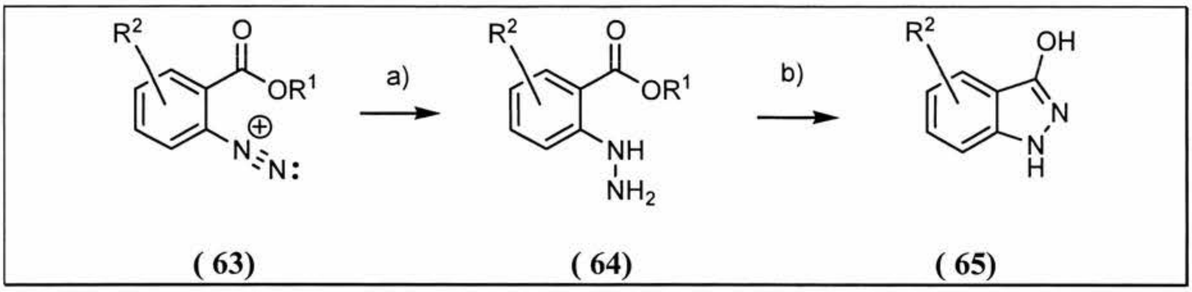
R^2	R^1	Reducing agent	Yield
6-Cl	$C_6H_5CH_2$	Sodium hydrosulfite	86%
H	2,6-xylyl	Zinc	56%
5-Cl	4-Cl-C_6H_4	Lithium Aluminium Hydride	46%

Table 3: Comparison of different reducing agents for the *N*-nitroso functionality.

As mentioned previously, synthetic routes resulting in *N*-substituted indazolinones do not present any advantages for the development of our library design.

1.4.2.4.1.1. Reduction of diazonium salt [83, 95]

Anthranilic acids and derivatives can be reacted in another way to give indazolinones. Indeed, unsubstituted indazolinones (Scheme 35) can be prepared by diazotation of anthranilic acid derivatives to give the corresponding diazonium salt of type **63**. This salt is then reduced to the corresponding o-hydrazinobenzoic acid **64** by sulfite or sulphur dioxide. **64** is then cyclised by action of phosphoryl chloride or in boiling nitrobenzene, or aqueous solutions (acidic) to give indazolinone derivatives of type **65**.



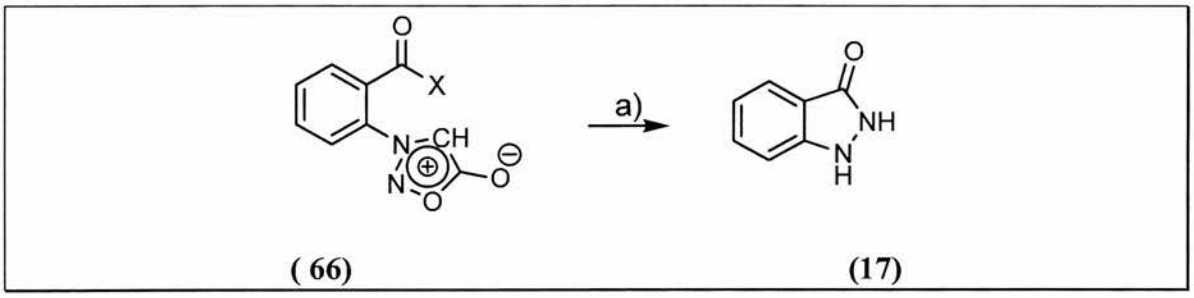
(63) **(64)** **(65)**

Scheme 35: Reduction of diazonium salt **63** to generate phenyl hydrazine derivatives **64** and cyclisation to give **65**; a) $Na_2S_2O_3$, b) HCl, 80°C, 20 h, 86%.[83]

This approach is a straight forward synthesis leading to unsubstituted indazolinones and presents potential advantages for the incorporation of the linker that will be used to load the core-structure onto the solid phase. Indeed, indazolinones presenting methyl groups (5 and 7 positions) or chloro (5 or 6 position) have been reported in the literature.[83] This sequence has been explored for the synthesis of our core-structure (see section 2.3.1.3.1).

1.4.2.4.1.2. From sydnone

Unsubstituted indazolinones can also be synthesised by the N2-C3 bond formation by using the cyclisation of sydnones (Scheme 36). Sydnones are masked hydrazines.[97, 98]



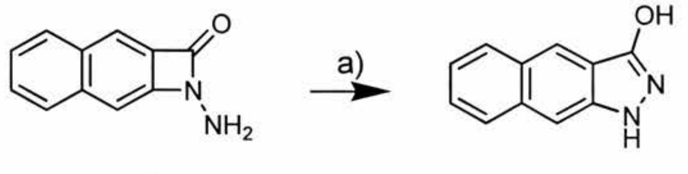
(66) **(17)**

Scheme 36: Synthesis of **17** from sydnone **66**; a) HCl, 50 to 96% (X= NH_2, NHMe, $NHNH_2$, N_3, OMe).[97, 98]

The synthesis of unsubstituted indazolinones from sydnone is an attractive point for the synthesis of the library core-structure. Moreover, the yields of the transformation are good to excellent. This approach is a potential sequence that can be used in the synthesis of the core-structure we are interested in.

1.4.2.4.2. Approaches involving ring enlargement

The ring enlargement of four-membered heterocycles to the corresponding five-membered pyrazole nucleus is interesting mechanistically, but has no practical importance. Indazolinone derivatives of type **68** have been synthesised in reasonable yield from **67**.


(67) **(68)**

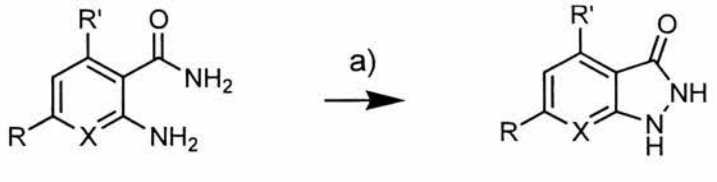
Scheme 37: Ring enlargement of **67** to give indazolinone derivative of type **68**; a) AcOH, rt, 62%.[99]

This synthesis has only been reported on substrate **67**, but is interesting since an unsubstituted indazolinone is generated. Even if it is reported that this synthesis has no practical importance, this route is potentially of relevance for our library core structure.

1.4.2.5. Method D, Disconnection N1-N2 [100]

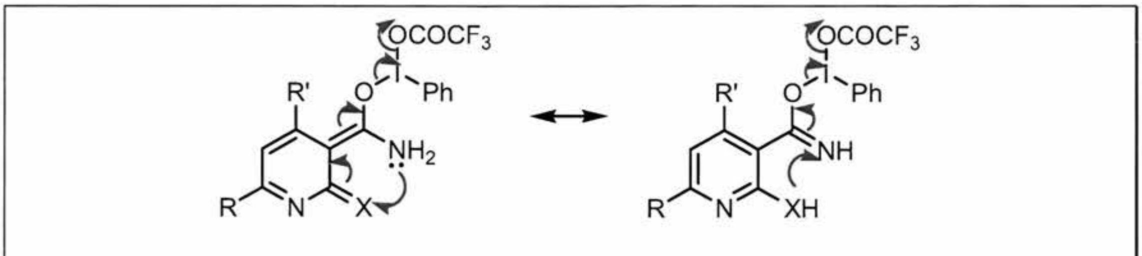
To our knowledge, only two methods report N-N bond forming reactions as an approach to indazolinones and their derivatives.[78, 100]

The first one is a method that has been applied for the synthesis of isoxazolo and pyrazolo-pyridines and is interesting because the 5-membered ring system is not substituted.


(69) **(70)**

Scheme 38: Creation of Nitrogen-Nitrogen bond; a) Phenyliodine(III) bis(trifluoroacetate) (PIFA), DMF/H_2O (1:1), pyridine, rt, R=alkyl, aryl and R'=CF_3. [100]

However, the substituents R and R' in **69** are crucially important and must be electron-withdrawing groups [100] (yield ca. 70%). Indeed, in the intermediates **71-72** (Scheme 39) proposed to be formed en route to **70**, the substituents on the aromatic system are thought to stabilise the delocalisation as the X-N bond is formed. The reaction does not occur when this additional electronic delocalisation is absent.

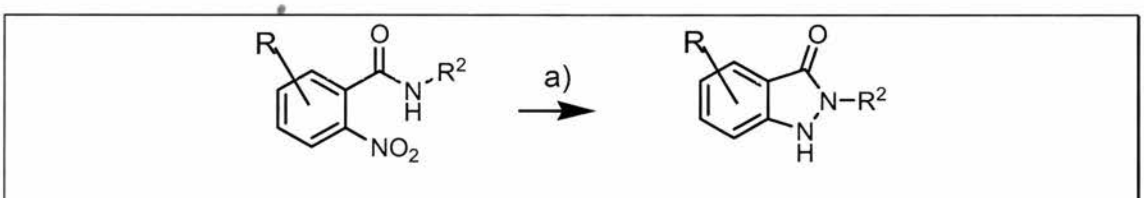


(71) **(72)**

Scheme 39: Intermediates during the formation of N1-N2 bond with PIFA.[100]

The synthesis has not been reported for the generation of indazolinones, raising the question of whether the nitrogen is essential for the cyclisation or not.

The second method involves the formation of N-N bond by the use of metallic zinc. The 2-nitrobenzamide derivative **73** is reduced and cyclised to give **74** in alkaline medium in modest yields.[78]



(73) **(74)**

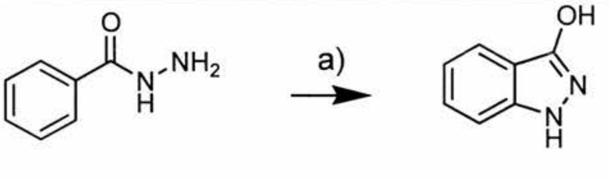
Scheme 40: Creation of Nitrogen-Nitrogen bond; a) Zn, NaOH, MeOH, reflux, 10-40%.[78]

N2-substituted indazolinones of type **74** presents problems for the synthesis of the library core structure that have already been discussed. This synthesis was therefore not part of the different strategies attempted for core structure generation.

1.4.2.6. Method E, Disconnection N1-C7a

1.4.2.6.1. Barton's route

The synthesis of unsubstituted indazolinone **35** from benzhydrazides of type **75** has been reported by Sir D. Barton. The presence of a strong base, such as *n*-butyl lithium used by Barton,[101] is claimed to lead to the formation of a polyanionic species (see page 143, Scheme 151) which, when the temperature rises to room temperature, reacts to give indazolone **35** in 80% yield.



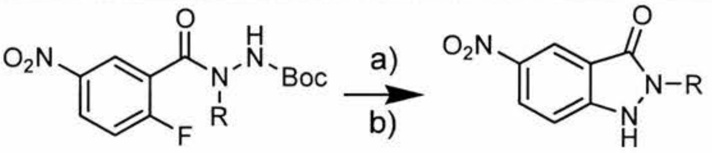
(75) **(35)**

Scheme 41: Synthesis of **35** by cyclisation of **75**; a) n-BuLi, THF, -78°C to rt, 80%.[101]

Barton's route in the context of library generation appears to be an easy and flexible synthesis because of the availability of benzoic acid derivatives as starting materials. This approach was therefore the focus of our early efforts for the synthesis of the library core structure. The results of these studies are shown in section 2.3.1.4.

1.4.2.6.2. From 2-halogenobenzoic acid derivative

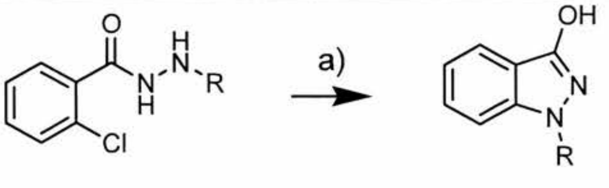
The cyclisation of the N1 onto the C7a in the indazolinone system can be achieved by the displacement of a leaving group.[102] This leaving group is typically a halogen atom. For example, the fluorine atom can be displaced by the terminal nitrogen of the hydrazide functionality in **76** to give **77** (Scheme 42).



(76) **(77)**

Scheme 42: Synthesis of *N2*-substituted indazolinone **77** from 2-fluoro-5-nitrobenzhydrazide derivative **76**; a) 20% TFA/CH_2Cl_2, 4 h, b) PS-morpholine, DMF, 36 h, 50%.[102]

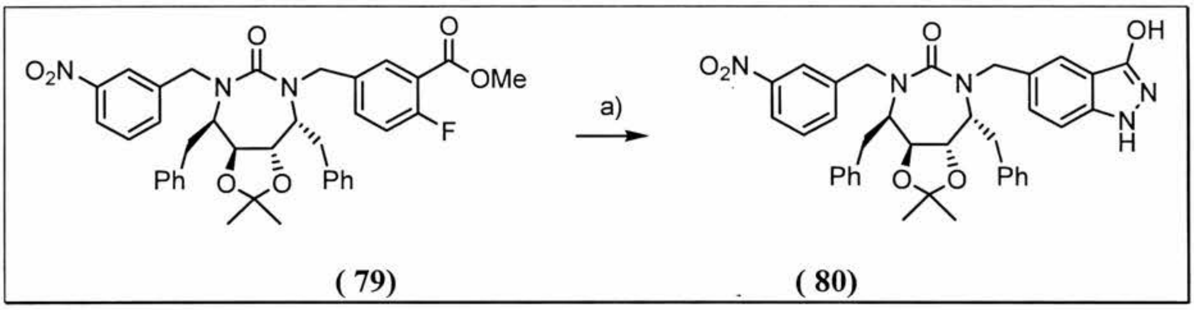
The halogen atom can also be chlorine. In this synthesis, the cyclisation conditions involve the use of copper metal for the formation of indazolol of type **54** (Scheme 43). The metal helps in the displacement of the chlorine atom α of the carbonyl group.



(78) **(54)**

Scheme 43: Synthesis of indazolinone **54** from 2-chlorobenzhydrazide **78**; a) K_2CO_3, Cu, pentanol, reflux, 17 h, 44% (R=Ph).[83]

As stated previously, synthesis of *N*-substituted indazolinones are not useful in the context of library generation. However, *N*-substitution can be avoided in this procedure. For example, when the 2-fluorobenzoic acid derivative **79** was subjected to the copper mediated reaction in the presence of hydrazine, the unsubstituted indazolinone contained in **80** was formed in 42%.



(79) **(80)**

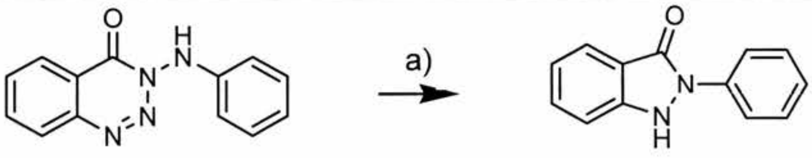
Scheme 44: Formation of unsubstitued indazolinone from 2-fluorobenzoic acid derivative **79** used in the synthesis of SE063.[103]

The cyclisation to the unsubstituted indazolinone is straight forward and is compatible with the possibility of diversity incorporation. This reaction has been the main reaction used by us to make the library core-structure in this project. The reaction has also been optimised in our system (section 2.3.1.3.3).

1.4.2.7. Approaches involving Ring Contraction

1.4.2.7.1. From two fused six-membered rings

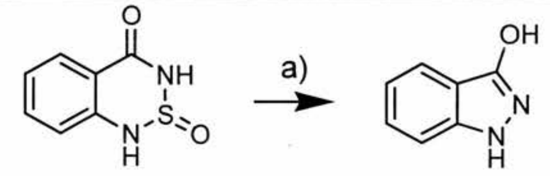
Indazolinones can be synthesised easily and in good yield by thermolysis of benzotriazin-4(3*H*)-one **81** (Scheme 45). The problem with this approach is the substituent at the N2 position that can reduce the diversity incorporation.



(81) **(49)**

Scheme 45: *N2*-phenyl indazolinone **49** synthesis by ring contraction of 3-amino-1,2,3-benzotriazin-4(3*H*)-one **81**; a) 1-methylnaphthalene, reflux, 88%.[104, 105]

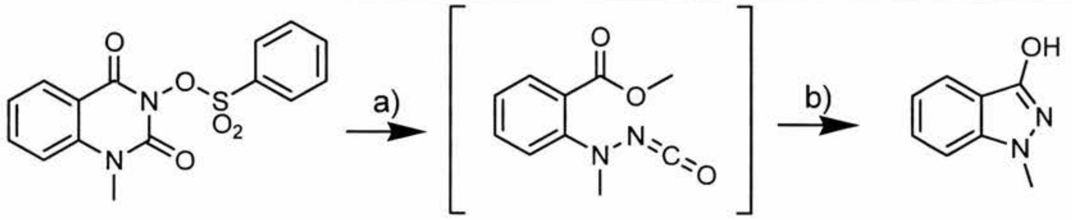
Indazolinones can also be made by oxidative treatment of 1*H*-2,1,3-benzothiadiazin-4(3*H*)-one 2-oxide **82** in acidic conditions in a reasonable yield (Scheme 46).



(82) **(35)**

Scheme 46: Synthesis of indazolinone from 1*H*-2,1,3-benzothiadiazin-4(3*H*)-one 2-oxide **82**; a) H_2O_2, AcOH, 100°C, 2h, 52%.[106]

The final example of the use of a ring contraction reaction to access indazolinones involves an alkali-induced Lossen rearrangement of 1-methyl-3-[(phenylsulfonyl)oxy]-2,4(1*H*, 3*H*)-quinazolinedione **83**. The intermediate **84** generated by action of the base undergoes a ring closure to give 1-methyl-1*H*-indazol-3-ol **85** in a good yield of 78%. Only the synthesis of unsubstituted indazolinones is useful for our project, this approach will therefore not be considered further.

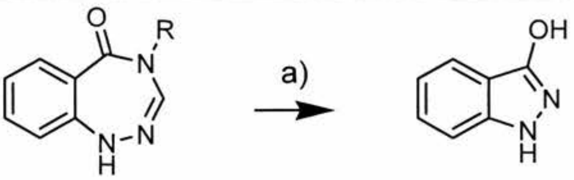


(83) **(84)** **(85)**

Scheme 47: Synthesis of 1-methyl-1*H*-indazol-3-ol **85** from 1-methyl-3-[(phenylsulfonyl)oxy]-2,4(1*H*, 3*H*)-quinazolinedione **83**; a) NaOMe, DMF, reflux, b) H_2O, 78%.[107]

1.4.2.7.2. From benzotriazepinones [108]

The indazolinone structure can be accessed via a ring contraction reaction starting from benzotriazepinone of type **86**. The acidic conditions give indazolinones in a rather low yield.



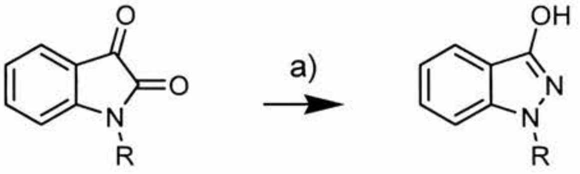
(86) **(35)**

Scheme 48: Synthesis of indazolol **35** from benzotriazepinone **86**; a) HCl, EtOH, H_2O, reflux, 2h, 20%.[108]

The sequence of ring contraction from benzotriazepinone is interesting as it leads to unsubstituted indazolinone. Due to the low yielding reaction, this approach would be considered as potentially valuable if the previous prioritised routes failed.

1.4.2.8. By ring modification

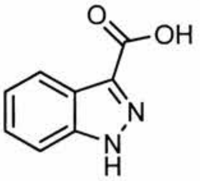
1*H*-indole-2,3-diones (isatins) **87** react in alkaline media undergoing a ring opening reaction to give (2-aminophenyl)(oxo)acetic acids, which cyclise on diazotation, followed by reduction with sodium hydrogen sulfite, to give indazolinones of type **54**. The yield of 26% shows that this route is inefficient (R=Ph). The other disadvantage of this approach is the substitution that is required on the nitrogen of the isatin.



(87) **(54)**

Scheme 49: Conversion of isatin **87** to indazolinone **54**; a) i) NaOH, ii) $NaNO_2$, H_2SO_4, iii) $NaHSO_3$ or $SnCl_2/HCl$ (R= Ph).[83]

Interestingly, when R in **87** is a hydrogen, the product of the reaction sequence is **88** (1*H*-indazole-3-carboxylic acid).



(88)

Scheme 50: By-product isolated during the synthesis of **88**.

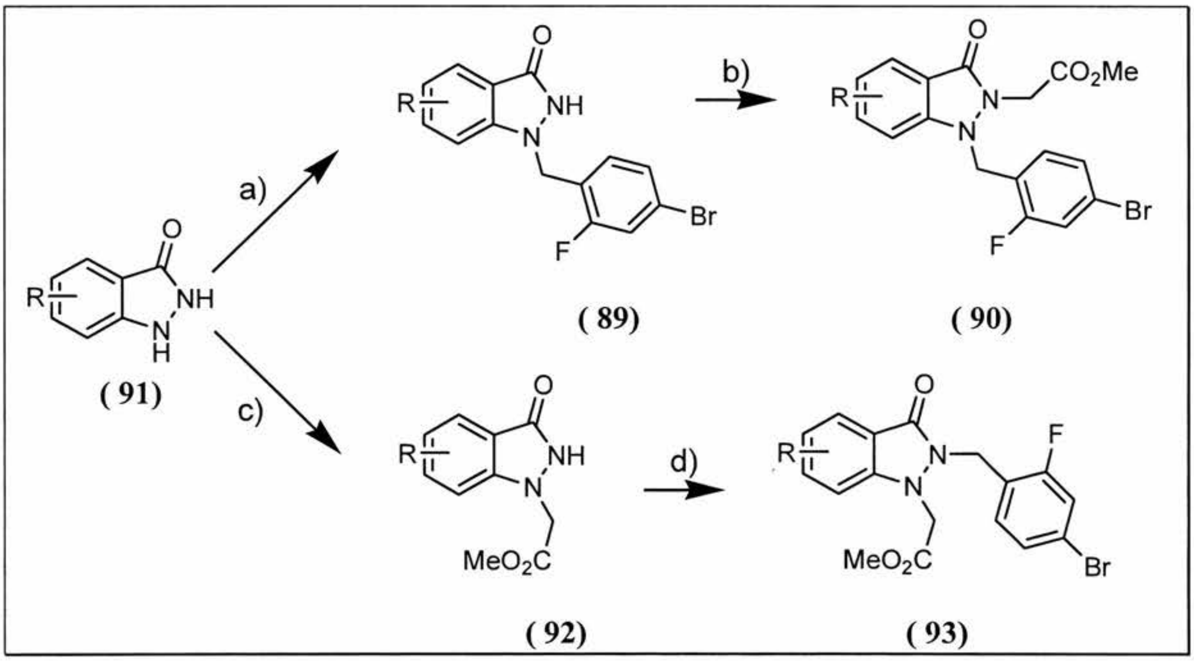
1.4.3. Reported routes to functionalise indazolinones

As the central goal of this project is to create a library design for use on solid phase based on the indazolinone core structure, it is also necessary to develop a synthetic sequence that involves selective and very high yielding reactions using the indazolinone heteroatoms. This section will focus on the reported routes to insert substituents at the different positions of the indazolinone core. Reactions leading to mixtures of compounds are not considered useful in the context of solid supported synthesis.

1.4.3.1. Selective functionalisation at the N1 position

1.4.3.1.1. From unsubstituted indazolinone

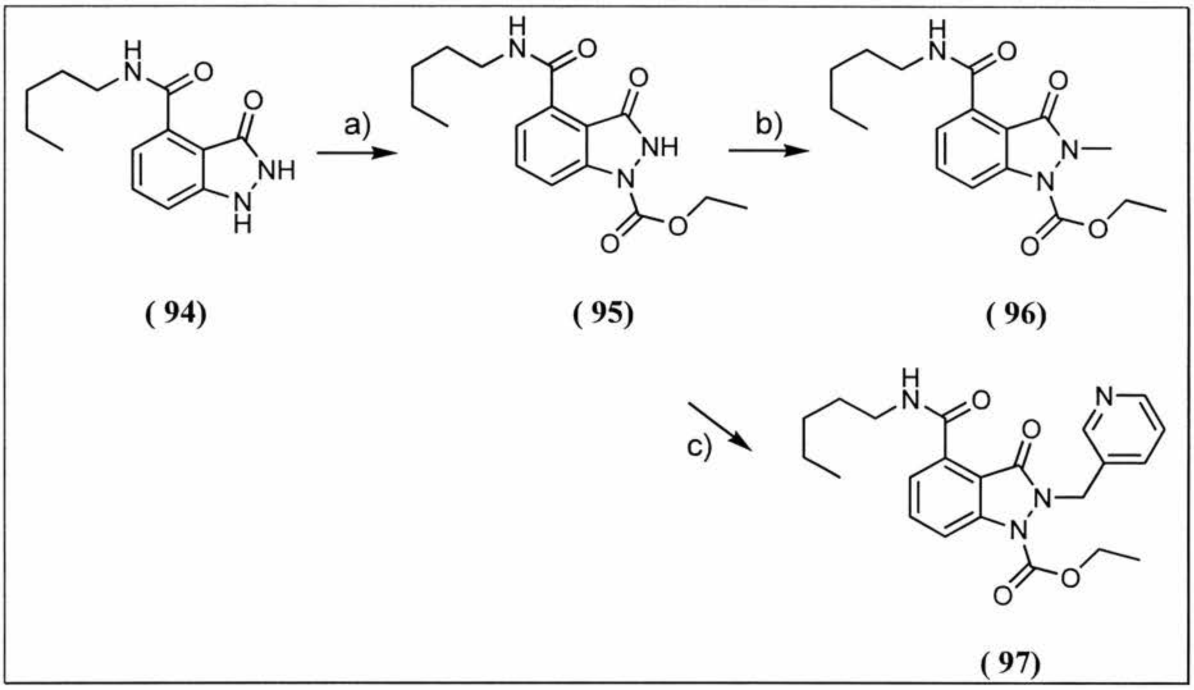
Malamas *et al.* [109] reported two sequences for the synthesis of *N1*, *N2*-substituted indazolinones (Scheme 51). The authors proposed that using different electrophones they could influence the selectivity for the N1 over the N2 position and vice-versa. However, the selectivity was poor in both cases and *N1*-functionalised products **89** and **92** were isolated in only ca. 30% from **91**. Such low yields can be explained by two factors: incomplete reaction or the formation of undesired product (positional isomers). The authors do not comment in sufficient detail however, the second case seems very feasible in the case of indazolinones as the N2 and O positions can also react with the electrophile.



Scheme 51: Reaction on the nitrogens using two kinds of base; a) K_2CO_3, DMF, 4-bromo-2-fluorobenzylbromide, 31% b) NaH, DMF, methylbromoacetate, 90% c) K_2CO_3, DMF, methylbromoacetate, 31% d) NaH, DMF, 4-bromo-2-fluorobenzylbromide, 89%.[110]

Incomplete reaction is a problem that can be solved by the use of large excesses of reagents to push the reaction to completion in solid supported synthesis. However, the problem of generating isomers is more complex.

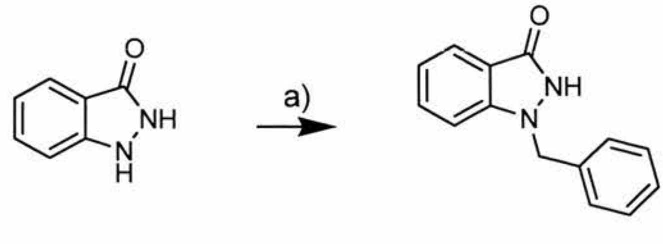
One approach to solving the isomer issue is to protect the indazolinone using carbamate groups. Bruneau *et al.* [78] described the synthesis of **95** in 78% yield by reacting unsubstitued indazolinone **94** with ethyl chloroformate in the presence of pyridine at reflux (Scheme 52). **95** was subsequently converted to **96** and **97**. The selectivity of these reactions is discussed in section 1.4.3.1.2.



Scheme 52: Substitution on nitrogen with other reagents; a) EtOCOCl, pyridine, reflux, 78%, b) NaH, DMF, MeI, 70%, c) 3-pyridylcarbinol, PPh_3, DEAD, 20%. [78]

An analogous approach was used by Patel *et al.* in their synthesis of the indazolinone core of the unsymmetrical cyclic urea SE063.[103] They selectively protected the N1 position in 79% yield using a Boc group. This was achieved in a two step protocol involving an excess of Boc anhydride to over-protect the indazolinone giving a mixture of the N1,N2 and N1,O di-protected isomers. The mixture of isomers was then reacted in presence of methanol and ammonia to deprotect the O and N2 positions giving the N1-Boc protected indazolinone. This selective protection can be incorporated in our sequence as it leaves the N2 and O position available for further substitution.

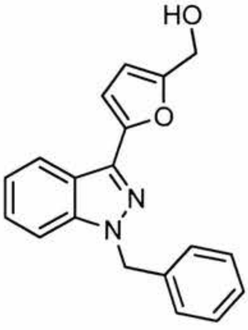
Gordon *et al.* reported that unsubstituted indazolinone **(17)** was selectively functionalised at the N1 position in 99% yield (Scheme 53) using sodium hydroxide, benzyl chloride and ethanol.[111]



(17) **(98)**

Scheme 53: Quantitative alkylation at the *N1* position of **17**; a) BnCl, EtOH, NaOH, 99%.[111]

This synthesis has been carried out with furopyrazole derivatives in Pfizer Central Research in Kent, UK, for the synthesis of YC-1 **(99)** (Scheme 54).[111]



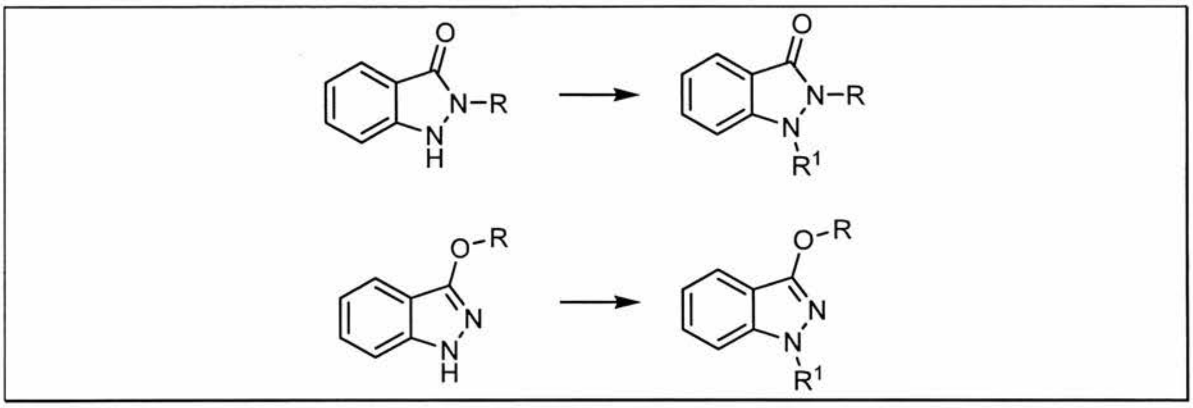
(99)

Scheme 54: Structure of YC-1 **(99)**.

This route is also of interest for our planned strategy. However, whilst it is clearly useful in solution, it is less useful for solid phase chemistry as the resin needs to swell properly to allow the reagent to go in the deepest cavities. From a practical point of view, polystyrene beads do not swell in ethanol. Moreover, from a chemistry perspective, the selective reaction might be possible with benzyl chloride derivatives only, reducing the possibility of diversity incorporation.

1.4.3.1.2. From substituted indazolinone

To our knowledge, *O*- and *N2*-substituted indazolinones react selectively at the N1 position as described in Scheme 55.



Scheme 55: N1-substitution of *O*- and *N2*-substituted indazolinones.[83]

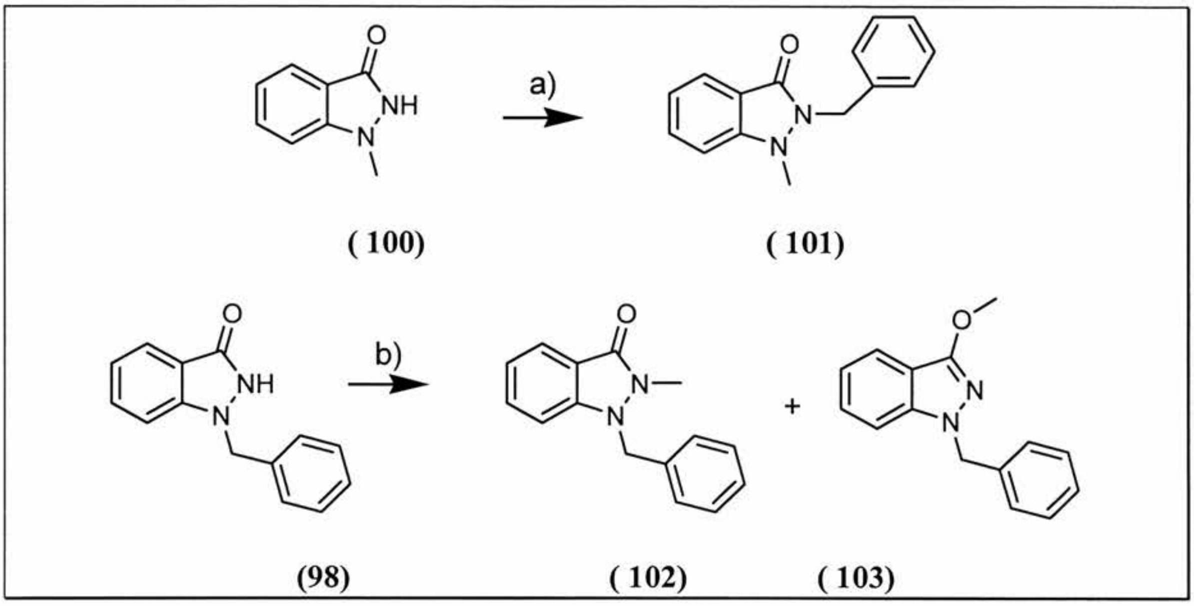
Accessing selectively *O*-substituted indazolinone (when the substituent R is allyl) therefore enables us to direct diversity incorporation at the N1 position. Subsequently, rearrangement of the allyl moiety from the O to the N position would then be possible. Inserting an allyl substituent at the O position is therefore a crucial detail in the plan.

1.4.3.2. Selective functionalisation at the N2 or O position

Inserting substituents at the O or N2 position of *N1*-substituted indazolinones has been reported. Selective reactions at the N2 position can be achieved (ca. 90%) [109] but this is not our main interest. We need to selectively functionalise the O position with an allyl group.

In Scheme 52, however, the 20% reaction yield at the N2 position suggests that the reaction is incomplete or the rest of the material is the O-alkylated isomer. In this case, the Mitsunobu reaction seems to be a method to insert substituents at the O position.

Steric effects could also direct the selectivity O/N2 substitution. The difference between a bulky group and a small group has been studied with the *N1*-methylindazolinone and the *N1*-benzylindazolinone under alkylation (Scheme 56).



(100) (101) (98) (102) (103)

Scheme 56: Difference between the bulkiness of groups in the *N*-alkylation step; a) BnCl, Et_3N, 67% N-isomer **101**, b) CH_2N_2, 21% *N*-methyl **102**, 64% *O*-methyl isomer **103**.[78]

Bruneau *et al.* report obtaining only **101** in the reaction between **100** and benzyl chloride in presence of triethylamine.[78] However, the yield is only 67%, 33% of the material based on the starting material is missing. It is possible that a mixture of O and N2 benzylated products was obtained or the reaction did not go to completion.

By reacting **98** with diazomethane, a mixture of **102** and **103** was obtained; the majority of the product was the O-methylated product **103**.

1.4.4. Summary

Reviewing the different possibities to synthesise the indazolinone core structure was the first essential step in this project. It allowed us to choose a synthetic way that leads to an unsubstituted indazolinone which was subjected to diversity incorporation. This route must allow us to insert a linker unit that was used for the loading of the small molecule onto the resin.

Different possibilities for inserting the linker on the indazolinone core structure were presented; only two of them were selected. One has been optimised in our studies and led us to an indazolinone that we loaded successfully onto the resin.

From the perspective of diversity incorporation, the literature provided some interesting guidelines but in general indicated that selective reactions on the indazolinone system are not yet available.

2. Results and Discussion

2.1. Project Overview

The central goal of this thesis was to develop an efficient library design that had as its key step a rearrangement reaction that allows additional diversity incorporation. Subsequently, the chemical route needed to be validated on a solid support, enabling the potential synthesis of hundreds of analogues.

In order to address the goals of the project, three main issues had to be dealt with separately. Investigating the rearrangement of an allyl moiety from the oxygen to the nitrogen atom of the indazolinone core was the first priority (Scheme 78, page 82). This was an unprecedented rearrangement for indazolinones prior to our work. Additional questions included whether this sigmatropic rearrangement could be used on solid support and whether the chemical method used for the rearrangement allowed for the use of a suitably large diversity of building blocks.

The second objective of the project was to access a molecule containing the indazolinone core that was both compatible with incorporation of building blocks and contained a linker for attachment to a solid support. This linker must not interfere with the key functionality in the indazolinone core. Section 1.4 reviews the literature surrounding the synthesis of indazolinones. It was clear from this review that structures of this type are not easy to manipulate due to the comparable nucleophilicity of the 3 heteroatoms.

The final goal was to prove that the chemistry carried out in solution phase could be transferred to the solid phase. This involved the comparison of authentic compounds prepared in solution with material cleaved from the solid support. This is best achieved by using the technique of liquid chromatography coupled with mass spectrometry (LC/MS). Arguably, this is the only method of analysis as the fact that tens of milligrams of resin carrying only nanomolar quantities of compound makes it difficult to use other spectroscopic methods. Importantly, this technique can be easily automated for the analysis of large compound libraries.

2.2. The Aza-Claisen Rearrangement

2.2.1. Introduction

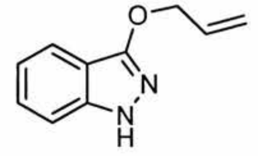
The following section is organised into **four main sections**. In the first, the **synthesis** of the required compounds containing an allyl functionality is described using procedures from the literature and exploring new methods of accessing the required compounds in improved yields. The second section explores **different methods of rearranging** the allyl group from the *O* position to the *N2* position in the indazolinone system. Palladium-catalysed mechanisms and microwave-assisted approaches were studied for this rearrangement reaction. In the third section, the chemical technology was transferred to the **solid phase** to prove that the rearrangement reaction was applicable to library generation. Finally, **mechanistic questions** associated with the aza-Claisen rearrangement were addressed.

It is important to note that a significant effort was required to assign the structures of many of the indazolinones prepared during this project. This is not a new problem. Indeed, in 1960, O'Sullivan reported a detailed study using infrared methods to assign indazolinone structure.[84] In 1982, Professor Sir Derek Barton characterised indazolinones by both ^{1}H NMR analysis and by chemical methods. He reduced the indazolinones in the presence of zinc and hydrochloric acid to the corresponding ortho-amino carboxylic acid and compared the melting points of these compound with literature values.[101] This technique was also used by Ruiz *et al.* .[112] X-ray and NMR (including ^{15}N NMR) studies were performed by Ballesteros *et al.* on indazolinone derivatives.[85] In 1993, Arán *et al.* introduced ^{13}C NMR to characterise the resulting products.[113] In 1995, Arán *et al.* used ^{13}C NMR and conformational analysis (AM1 semi-empirical method) to probe the structure of indazolinones in more detail.[114] Bruneau *et al.* subsequently published a paper entitled "The tautomerism of indazolinones in aqueous solution. A note on the principle of vinylogy" in which they report a study of unsubstituted, monosubstituted and disubstituted indazolinones and their preferred tautomeric forms.[115]

In this programme, we will use extensively 2D NMR techniques including COSY (^{1}H-^{1}H correlation experiments), HSQC and HMBC (^{1}H-^{13}C correlation experiments) to confirm the proposed structures. X-ray crystallographic analysis also proved a useful tool to compare related structures (e.g. compounds **104** and **23**, Scheme 66).

2.2.2. Synthesis of 3-allyloxyindazole **104**

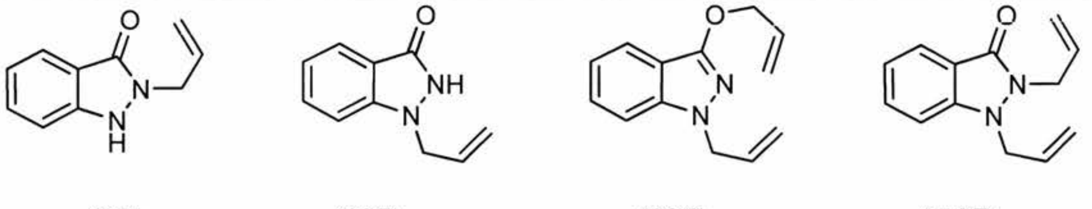
2.2.2.1. Synthesis of **104** from indazolinone **17**



(104)

Scheme 57: Structure of 3-allyloxyindazole **104**.

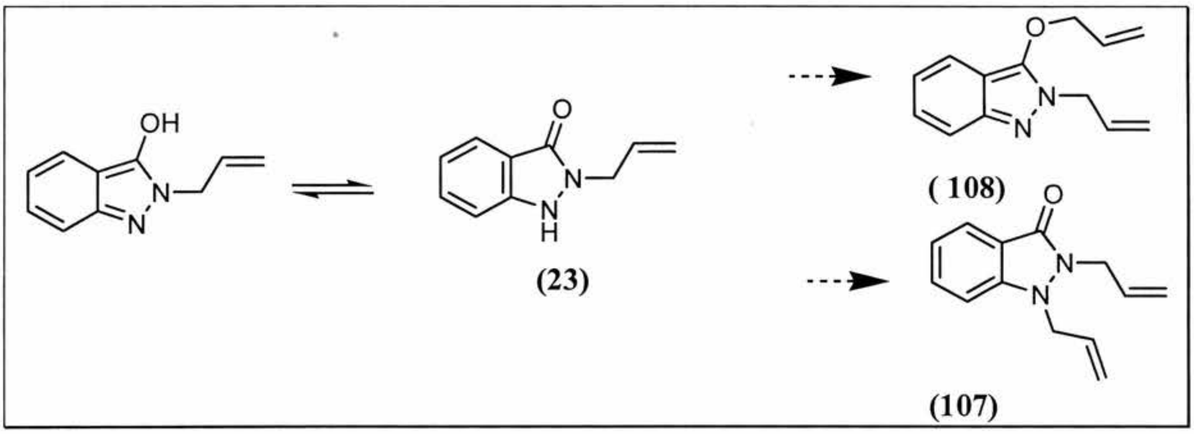
In order to prepare **104,** the use of a Mitsunobu reaction described in the literature[116] appeared to be an appropriate route as it was reported to give the *O*-alkylated species in 30% yield. Different alcohols were used in the literature. Our target required the use of allyl alcohol as the Mitsunobu partner combined with commercially available indazolinone **(17)** in the presence of diethylazodicarboxylate (DEAD) and triphenylphosphine in toluene. The ^1H NMR analysis of the crude Mitsunobu reaction revealed a complex mixture, with at least three different compounds containing allyl groups. These corresponded to the three mono-substituted indazolinones, **104** isolated in 38% and **23** and **105**, which were difficult to isolate in pure form from the reaction mixture (Scheme 58). Two other di-substituted products were also present in the crude reaction mixture, **106** and **107**, but were not isolated. Evidence to support the presence of **106** and **107** came from comparison of the ^1H NMR spectra of authentic materials prepared in solution (Section 2.2.7.2.4) and the crude reaction mixture.



(23) **(105)** **(106)** **(107)**

Scheme 58: Products of allylation obtained by Mitsunobu reaction of **17** with allyl alcohol in the presence of DEAD and triphenylphosphine in toluene.

A third possibility for a di-substituted product is **108** (Scheme 59). Indeed, structures of type **23** are known to exist in two tautomeric forms.[85] Because of these two tautomeric forms, reagents can be inserted on either position, depending on the nature of the electrophile (see section 1.4.3). However, the formation of **108** in this reaction did not occur. This became evident when the ^{1}H NMR spectrum of the crude reaction mixture was compared with an authentic sample of **107** prepared whilst studying the alkylation of the *N2*-substituted indazolinone **23** (Section 2.2.7).

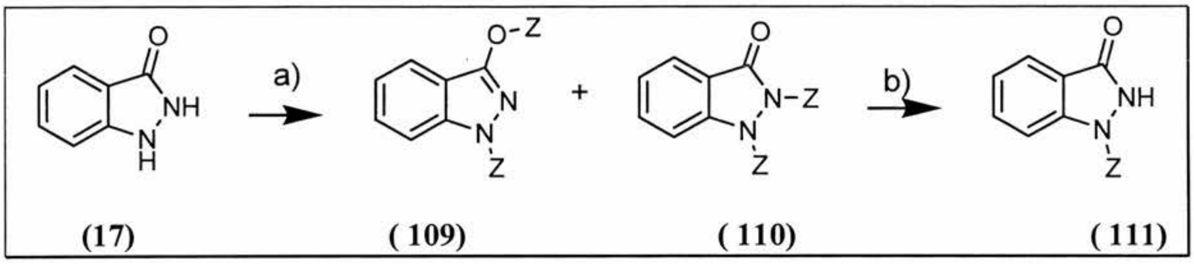


Scheme 59: Tautomeric forms of *N2*-allyl indazolinones and possible products from allylation of **23**.

2.2.2.2. An improved synthesis of **104**:

Due to isolation problems associated with this approach, it was decided to identify an improved method of preparing **104**. Ballesteros *et al.* showed that *N1*-methyl indazolinone exists in 2 tautomeric forms.[85] Whilst it is less applicable when a methyl group is present at the N1 position, the idea of protecting one position to reduce the possibilities of tautomerism is of importance. Indeed, thirty years after Ballesteros, Patel *et al.* [103] described the synthesis of an *N1*-Boc protected indazolinone derivative by treating the indazolinone with an excess of Boc anhydride and using ammonia and methanol to selectively deprotect one of the two Boc groups. The reported overall yield for this transformation was 61%.

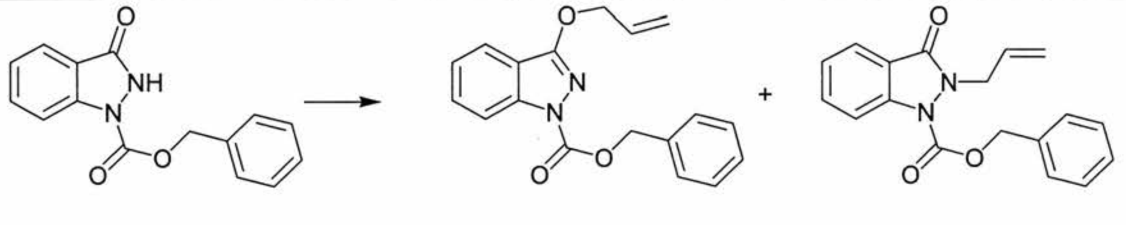
Based on these two literature precedents, it was decided to react an excess of benzyl chloroformate with indazolinone **(17)** to protect fully the heterocyclic core, yielding **109** and **110** (Scheme 60). These two compounds were not isolated but treated with one equivalent of a nucleophilic amine, for example morpholine. This resulted in the selective deprotection of the Z group present in the O and N2 positions, leaving **111** in which the N1 position is protected. The overall yield of the reaction was similar to the one obtained by Patel *et al.* in 1999 (61%).[103]



(17) **(109)** **(110)** **(111)**

Scheme 60: Selective protection via selective deprotection for the synthesis of *N1*-protected indazolinone **111**; a) Et_3N, BnOCOCl, THF, rt, o/n, b) morpholine, THF, rt, 2 h, 70%.

N1-protected indazolinone **111** was then submitted to the Mitsunobu-mediated allylation step. Literature precedent in an analogous system indicated that it would be necessary to warm the solution overnight at 80°C.[116] When this was attempted using **111**, it resulted in a complicated TLC containing multiple spots. However, the reaction improved when it was run at room temperature. After optimisation, the Mitsunobu reaction to couple the indazolinone **111** with allyl alcohol proved to be an efficient process with the yield of the reaction being essentially quantitative. ^1H NMR studies of the crude reaction showed the presence of the two isomers **112** and **113** (Scheme 61) in a ratio O/N isomer of 0.74:1 (**112:113**). Isolation followed by characterisation of both compounds revealed a ratio O/N isomer of 0.62:1 (**112:113**).



(111) **(112)** **(113)**

Scheme 61: Allylation of **111** by Mitsunobu reaction.

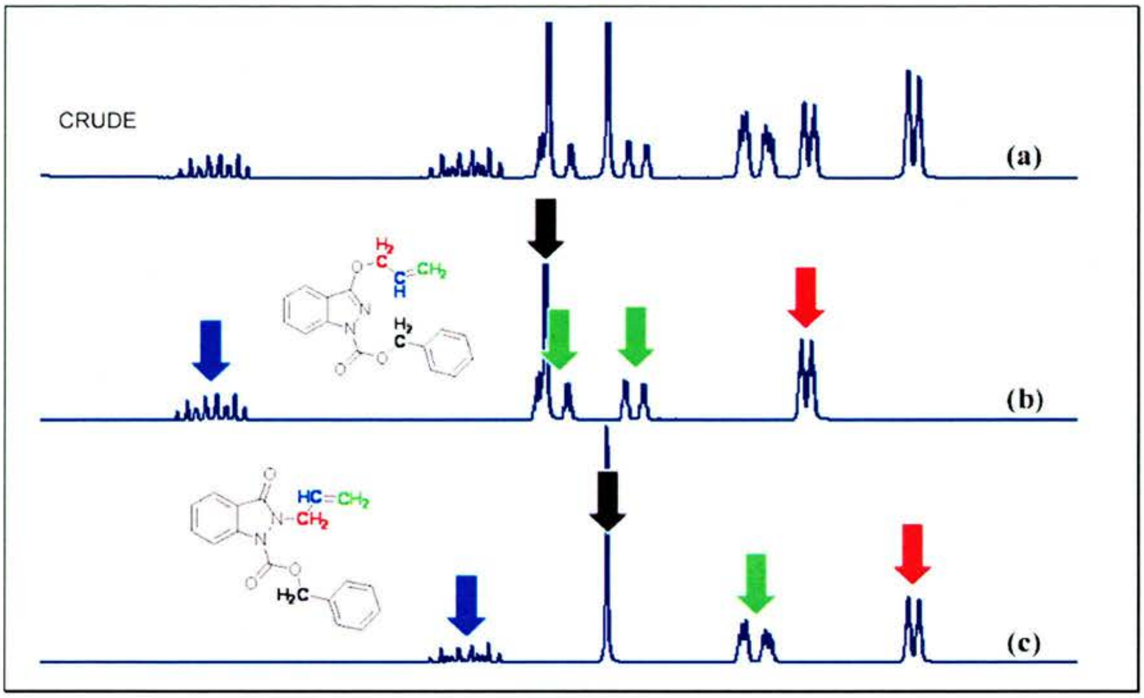


Figure 15: A section (6.5 to 4.5 ppm) of the ^{1}H NMR spectra obtained on the Mitsunobu reaction of **111** to give **112** and **113**, 1H NMR spectrum of a) crude reaction, b) **112**, and c) **113**.

Figure 15 represents an expansion between 6.5 and 4.5 ppm of the ^{1}H NMR spectra associated with this Mitsunobu reaction. Spectrum (a) is of the crude reaction mixture, spectra (b) and (c) correspond to purified **112** and **113** respectively. Full spectroscopic analysis using isolated material (**112** and **113**) allowed the assignment of all the signals. Special focus on the allyl moiety showed the difference between the signals for each isomer. As a general comment, the ^{1}H NMR signals for the allyl moiety are shifted to higher field when the allyl group is on the N2 nitrogen ($\chi_O > \chi_N$) as expected. The terminal alkene protons in **112** appear at two different p.p.m positions as a doublet of doublets whereas in the N2 isomer **113** both protons come on top of each other as an apparent multiplet.

The two isomers were easily separated using flash chromatography.

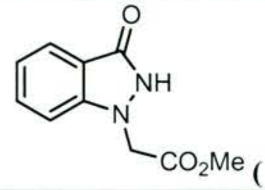
R_{f112} 0.37 in 10% ethyl acetate/hexane

R_{f113} 0.1 in 10% ethyl acetate/hexane

2.2.2.3. Unsuccessful approaches to **112** and **113**

During the course of this study, other procedures to prepare **112** were attempted. Indeed, deprotonation of **111** with sodium hydride and allylation with allyl bromide was attempted, but the carbamate protecting group did not survive the reaction conditions. This procedure was used by another group to benzylate the N2 position of **114** (88%

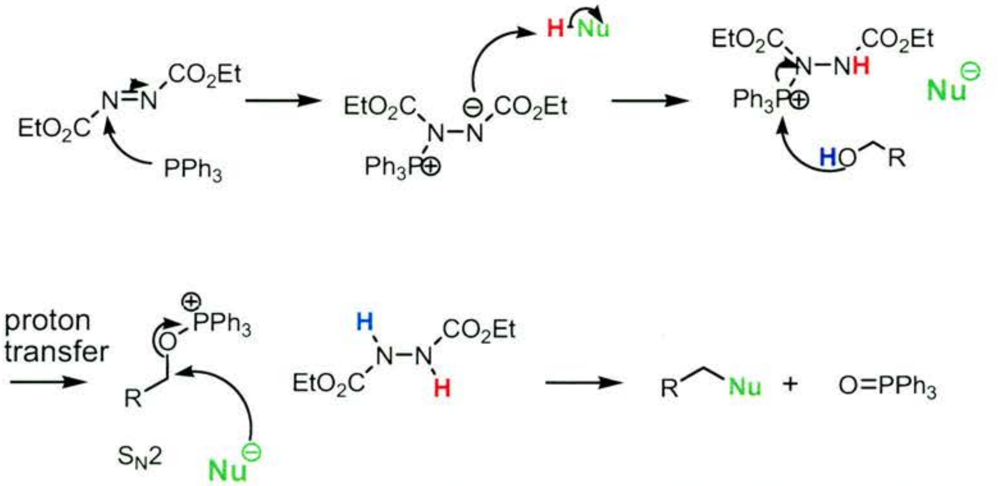
yield reported).[109] The N1 substituent in **114** was stable to the reaction conditions used (Scheme 62). The reaction involving the treatment of **111** with sodium hydride as base and allyl bromide as the electrophile yielded a diallylated compound, which has been characterised as **107** (Scheme 58).


(114)

Scheme 62: Substrate used in the sodium hydride/benzyl bromide reaction.[109]

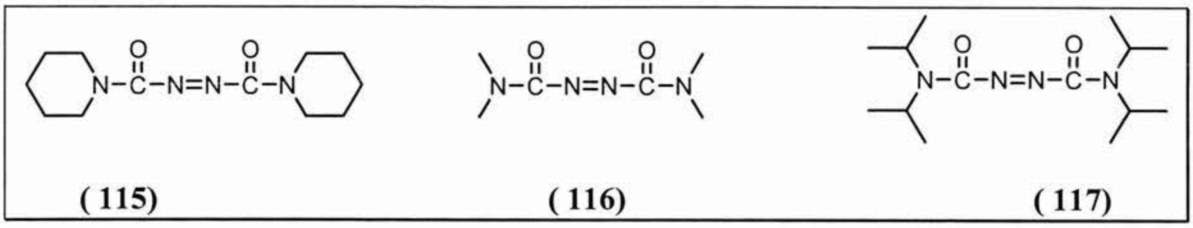
A procedure involving allyl bromide in refluxing chloroform was also ruled out because the transformation did not go to completion. In addition, the ratio between *O*/*N2*-allylated compounds **112** and **113** was comparable to that observed under the Mitsunobu conditions.

2.2.2.4. Mitsunobu reaction mechanism [117-120]



Scheme 63: Mechanism of Mitsunobu reaction using triphenyl phosphine and DEAD with a primary alcohol and a NuH as the nucleophile.

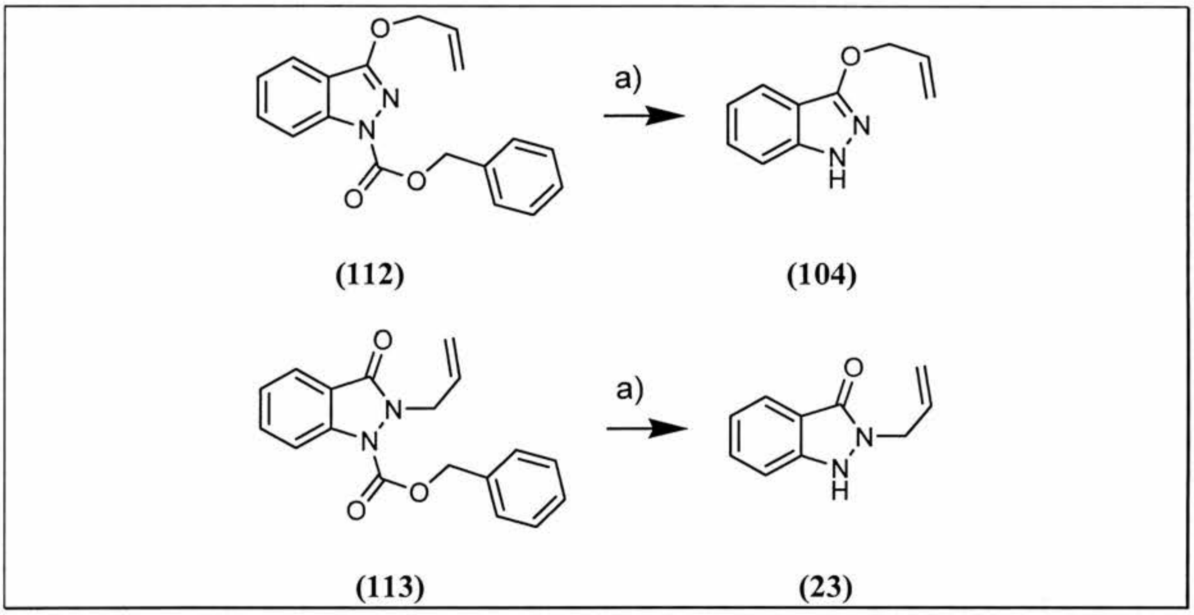
New reagents used in the Mitsunobu reagent are available including the use of ADDP (**115**), TMAD (**116**) or TIPA (**117**) coupled with PBu_3. [119, 120] An attempt was made to use ADDP (**116**) with PBu_3 in an attempt to improve the observed ratio of **112**:**113**. The yield of the compound of interest **112** was not increased using this system.



Scheme 64: Structure of ADDP **115**, TMAD **116** and TIPA **117**.[120]

As the pK_a of indazolinones such as **111** is in the appropriate range for the use of DEAD, it was decided that there was no reason to use these new reagents. We therefore carried out the synthesis with the conventional reagents, i.e. diethylazodicarboxylate (DEAD) and triphenylphosphine.

2.2.2.5. Deprotection of **112** and **113**



Scheme 65: Synthesis of **104** and **23** by lithium hydroxide; a) LiOH aq. in THF, rt, 2 days, quant.

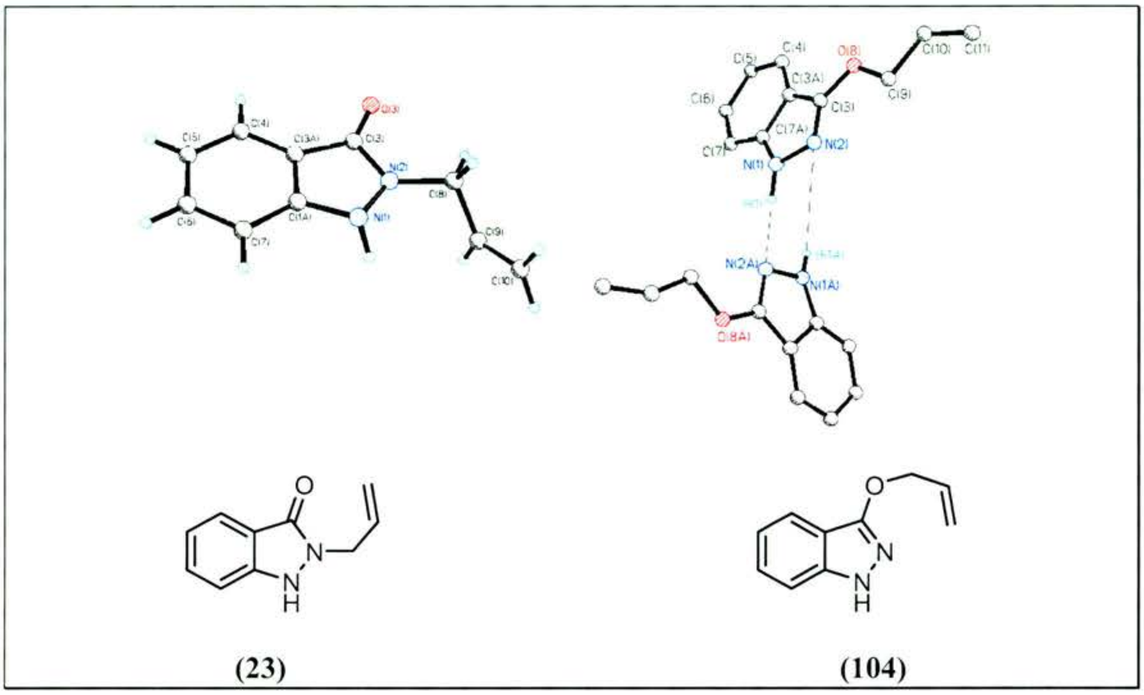
Both isomers **112** and **113** were deprotected using aqueous lithium hydroxide solution in THF.[14] The solvent used for this reaction was a mixture of THF/water, 10/1 with vigorous stirring as the reaction was biphasic. The reaction went to completion in 48 hours although the time was found to be dependent on the substrate:

112 to **104**: 72 hours

113 to **23**: 48 hours

2.2.2.6. Structural assignments using X-ray crystallography

The assignment of the structures **104** and **23** was facilitated by X-ray techniques. The products **104** and **23** obtained after chromatography were both recrystallised from dichloromethane (m.p. 81-82°C for **104,** m.p. 113-114°C for **23**). The crystal structures are presented below and crystallographic data is shown in appendices A and B.



(23) **(104)**

Scheme 66: Crystal structures of *N2*-allyl indazolinone **23** and 3-allyloxyindazole **104**.

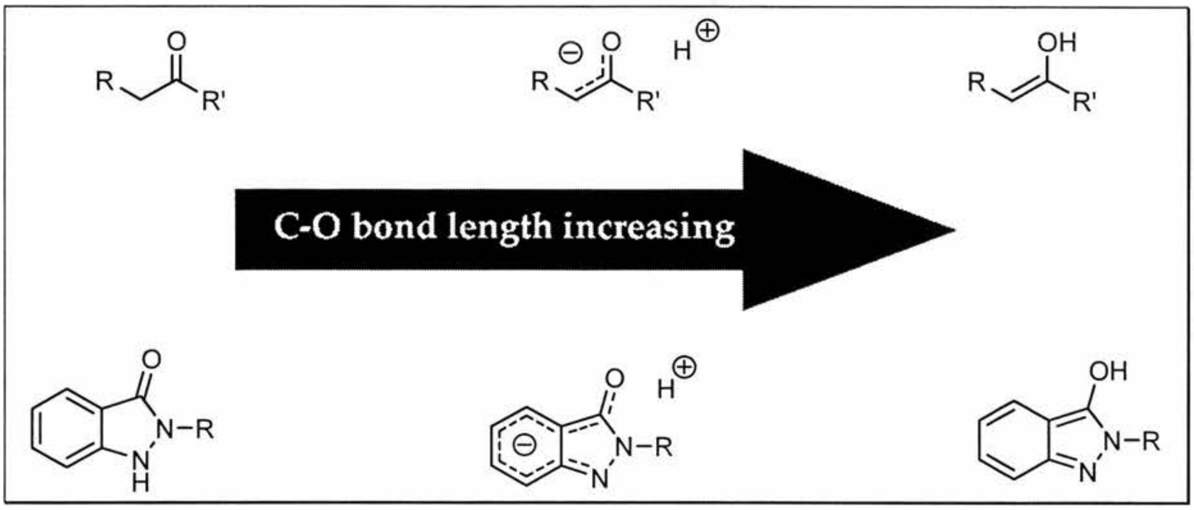
A detailed study of the bond lengths in the crystals shown above allows the comparison of the C-O bond in the two different isomers:

C-O bond length in *N2*-allyl indazolinone **23**: 1.2514 (19)Å

C-O bond length in 3-allyloxyindazole **104**: 1.355 (5)Å

C-O bond length in indazolinone **17** [85]: 1.264 (2)Å

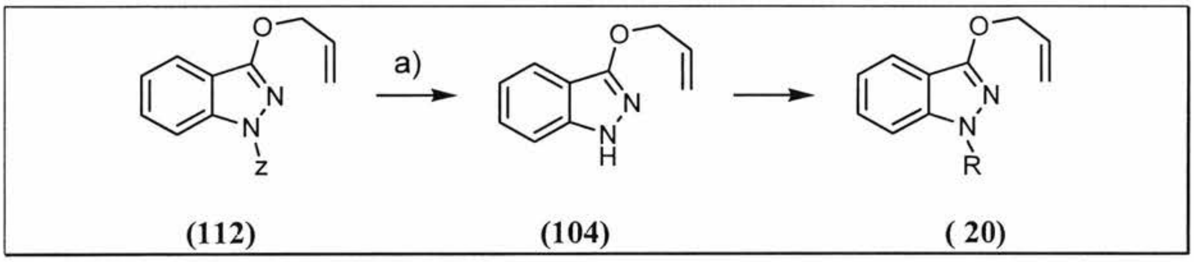
The value of the C-O bond in the *N2*-allyl indazolinone **23** shows that, in the solid state, the preferred tautomeric form is the keto form rather than the enol form (Scheme 67).



Scheme 67: Extreme tautomeric forms based on the C-O bond length.

2.2.3. *N1*-substitution of **104**

As presented previously (section 2.2.2.2), an alternative method to access 3-allyloxyindazole **104** in reasonable overall yield from indazolinone **17** has been developed. Relatively few examples of *N1,O*-protected indazolinones have been reported in the literature but examples exist where the R group in **20** is acyl, alkyl, benzyl, phenyl or a sulfonyl group.[109, 111, 121-123] Only one example of a urea moiety on the N1 position has been reported.[116] Diversity incorporation at the N1 position of the indazolinone core was a factor we wanted to investigate. A general route from **112**, through **104**, leading to new indazolinones of general type **20** is presented below (Scheme 68).



(112) **(104)** **(20)**

Scheme 68: Sequence of deprotection and substitution at the N1 position; a) LiOH, H_2O/THF.

These reactions include epoxide opening as a method of bringing new diversity at the N1 position.

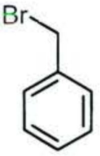
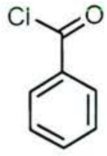
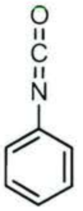
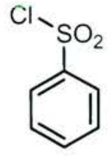
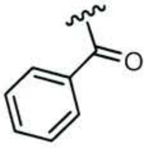
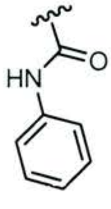
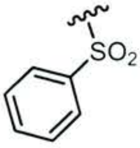
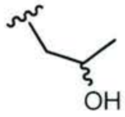
Reagents						 **(±)**
Substituent						 **(±)**
	(118)	**(119)**	**(120)**	**(121)**	**(106)**	**(122)**
Yield	**99%**	**40%**	**89%**	**99%**	**89%**	**65%**

Table 4: R groups introduced on the *N1* position in the 3-allyloxyindazole system.

As presented in Table 4, the yields of the reaction designed to insert diversity at the N1 position are good (**122**) to excellent (**106**, **118**, **120**, **121**). The range of commercially available reagents that can be introduced at the N1 position is very broad.

2.2.4. Rearrangement in solution phase

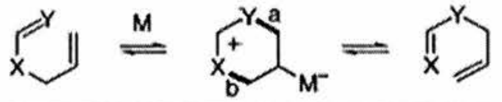
Whilst the terminal alkene of the allyl moiety in **20** could be useful as a means of incorporating diversity, the diversity within this library design would then come exclusively from the use of different building blocks, as in section 2.2.3. The presence of an allyl group in **20** allows for a second type of diversity to be incorporated using a core switching reaction (section 1.3.1). The potential of the allyl moiety in the designed system can be seen by comparison with the related imidate structure (Scheme 69) in which the aza-Claisen rearrangement reaction can be used to convert the *O*-allyl system **123** to the *N*-allyl system **124**.

(20) **(21)** **(123)** **(124)**

Scheme 69: Similarity between the aza-Claisen rearrangement of imidate **123** to amide **124** and 3-allyloxyindazole **20** to indazolinone **21**.

2.2.4.1. Applications of Aza-Claisen rearrangement in organic synthesis

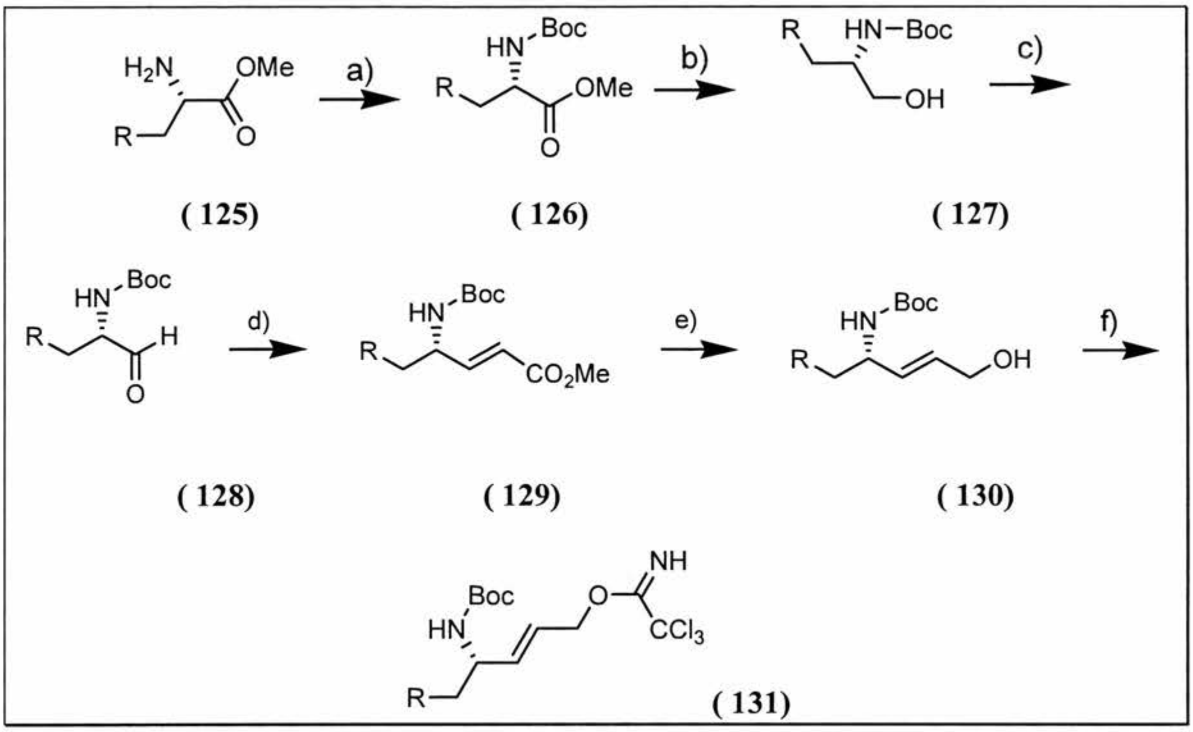
The Claisen rearrangement was discovered almost 100 years ago and has been studied and used extensively in organic chemistry. In a comprehensive review of the Claisen rearrangement, A.M.M. Castro summarised the Claisen type rearrangement over the past nine decades [82]. In this brief review, the focus will be on selected applications of the aza-Claisen rearrangement. The aza-Claisen rearrangement is described as a sigmatropic rearrangement when X=O and Y=N (Scheme 70). The aza-Claisen rearrangement, in contrast to the other sigmatropic rearrangement, is characterized by non-reversibility due to the exothermic transformation from the imidate to the amide, measured at ca. 14 kcal mol^{-1}.[124] This unique transformation is involved in many different strategies in organic synthesis. Some examples are presented below.



Scheme 70: General Claisen rearrangement by metal catalysis.[125]

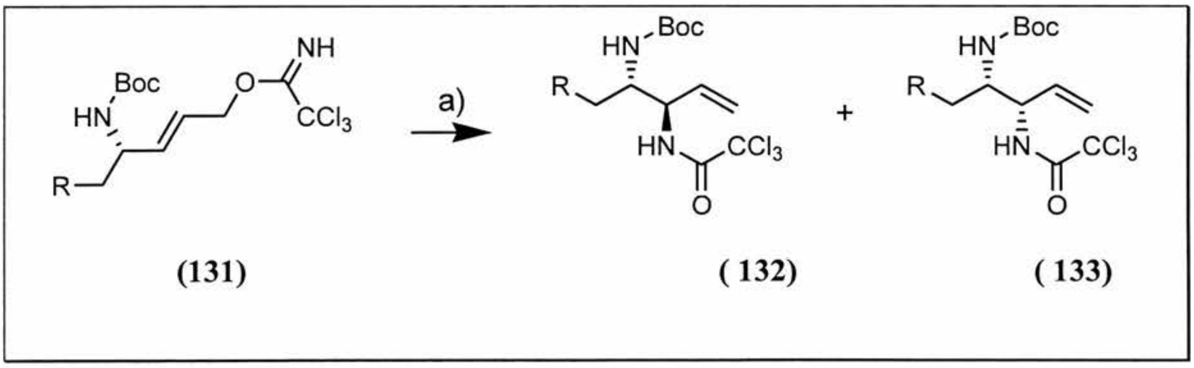
2.2.4.1.1. Making 1,2-diamines by diastereoselective synthesis [126]

In 1993, Bellus *et al.* published an article proving that the aza-Claisen rearrangement was a useful way of making 1,2-diamines (Scheme 71 and Scheme 72).



Scheme 71: Preparation of **131** from a chiral source **125** to prepare 1,2-diamines; a) $(Boc)_2O$, DCM, Et_3N, b) DIBAL-H, THF, c) $(COCl)_2$, DMSO, DCM, Et_3N, d) $Ph_3P{=}CHCO_2Me$, DCM, e) DIBAL-H, DCM, $BF_3.OEt_2$, f) CCl_3CN, NaH, Et_2O.

Starting from α-amino acids of general structure **125** as a chiral source, it is possible to access 1,2-diamine **134** in a high stereoselective way. According to Scheme 71, the amino acid **125** is transformed to the corresponding allylic alcohol **130** by chain elongation developed by T. Moriwake *et al.*.[127] The terminal alcohol was transformed to the corresponding trichloroacetimidate **131**. The trichloroacetamide **131** was then rearranged immediately due to its relative instability (Scheme 72).



Scheme 72: Rearrangement of **131** for synthesis of diamines **132** and **133**.[126]

Thermal conditions for the rearrangement using xylene (140°C) gave good yields but low diastereoselectivity and the deprotection of the protecting group (Boc) was also observed. However, metal-catalysed rearrangement using $PdCl_2(MeCN)_2$, a source of Pd(II), induced the formation of **132** in a high diastereomeric excess (de ≥ 99:1).

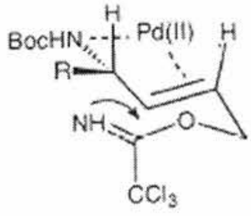
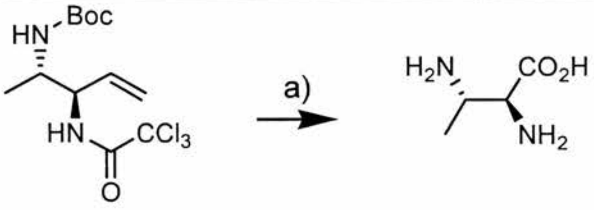


Figure 16: Proposed transition state for the sigmatropic rearrangement of **131**.[126]

This high diastereoselectivity is explained by the fact that the two faces of the chiral olefin are diastereotopic. The coordination of the palladium is guided in by the nitrogen atom selectively from the α-face due to the presence of the Boc group (Figure 16).



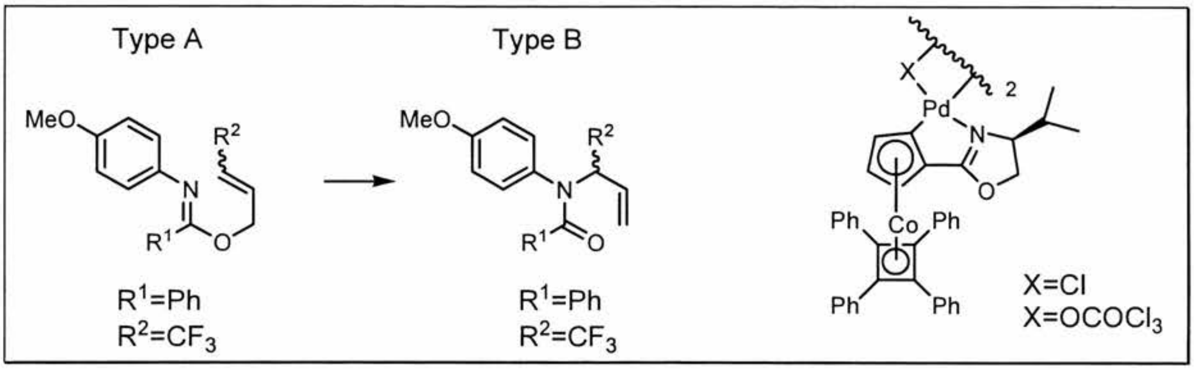
(132) **(134)**

Scheme 73: Deprotection and oxidation of **132** (when R=H) to give **134**; a) i) Cat. $RuCl_9.H_2O$, $NaIO_4$, $CCl_4/CH_3CN/H_2O$, rt, 2h, 81%, ii) $NaBH_4$, MeOH, rt, 1h, 3 M aq. HCl, 100°C, 15 min, iii) propene oxide, EtOH, 62%.

Oxidation of the terminal alkene followed by deprotection of the Boc group and the trichloroacetamide yielded **134**, (2S,3S)-diaminobutanoic acid (Scheme 73), which occurs in amphomycin antibiotics.[128-131]

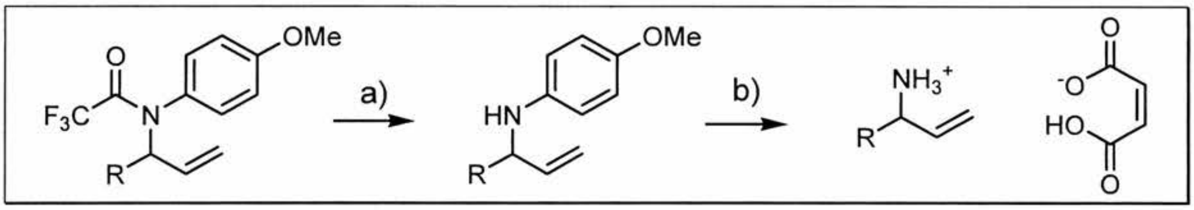
2.2.4.1.2. Making chiral amines from imidates [125, 132]

The aza-Claisen rearrangement is also used in the stereoselective synthesis of chiral amines from prochiral allylic alcohols. As described by L.E. Overman, the transformation of structures of type A to type B was achieved in good yields (58-99%) with an excellent enantioselectivity (73-97%) depending on the catalyst.



Scheme 74: Rearrangement of prochiral allylic imidates.[132]

This rearrangement was then followed by two deprotection steps: treatment with sodium ethoxide to hydrolyse the amide moiety and the use of ceric ammonium nitrate (CAN) to deprotect the 4-methoxyphenyl protecting group.



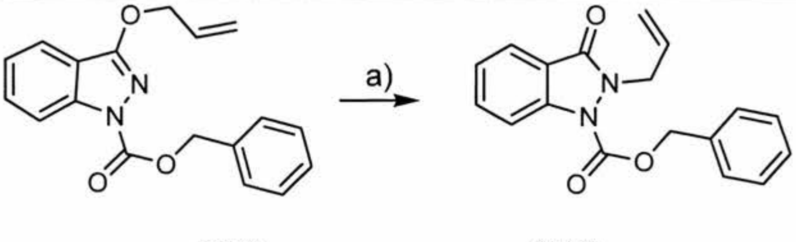
Scheme 75: Deprotection of allylic amides; a) NaOEt, EtOH, 54°C, 12 h, b) i) CAN, 0°C, 3 h, ii) maleic acid.[132]

The combination of catalyst, suitable protecting groups and well designed substrates allowed the synthesis of enantiomerically pure allyl amines.

2.2.4.2. Thermal rearrangement of 3-allyloxyindazoles

2.2.4.2.1. The use of standard thermal methods:

The rearrangement of **112** was attempted under thermal conditions under atmospheric pressure. Different solvents were used including *n*-hexane, toluene and THF. No rearrangement was observed due to the limited temperature that is accessible using these solvents.



(112) **(113)**

Scheme 76: Attempt of rearrangement of **112** to **113** under thermal conditions.

High boiling-point solvents including decaline (b.p. = 189-191°C) were also used. A small amount of the rearranged product **113** could be detected by ^{1}H NMR analysis of the crude reaction mixture. However, the difficulty in removing the solvent was a further barrier to the use of this approach. In summary, the use of thermal conditions was not applicable to the conversion of the 3-allyloxyindazoles **112** to the *N*-substituted indazolinones **113**.

2.2.4.2.2. The use of microwave techniques [133]

Microwaves have wavelengths of between 1mm and 1m, corresponding to frequencies between 0.3 and 300 GHz. Heating foods with microwaves was introduced over 50 years ago. In the late 1970s, the use of microwaves in inorganic chemistry was reported and about 10 years later, this technique became standard in organic chemistry. The difference between normal heating and microwave heating is that, in the first technique (oil bath, sand baths, heating jackets), the heating is slow and temperature gradients can develop within the sample. Local overheating can also lead to product, solvent, substrate, and/or catalyst decomposition. In the microwave approach, the energy is directly transferred to the reaction component without heating the reaction vessel.

(i) The theory:

All magnetic irradiations can be divided into two components:

- an electric field and
- a magnetic field.

When microwaves are applied to a system, both fields (electric and magnetic) interact with the solvent. The magnetic field does not have any effect on the solvent. However, the electric field produces two kinds of interaction:

-the dipolar polarization mechanism
-the conduction mechanism

The **dipolar polarization mechanism** is described as the sensitivity of a dipole to external electric fields. This dipole will attempt to align itself with the field by rotation, as shown in Figure 17. The energy contained in the applied field is transformed into rotational energy. For low frequency irradiation, the molecules of a liquid will rotate in phase generating only a small heating effect. However, when high frequencies are applied, the dipole is unable to respond and rotate in phase, consequently, heat is not produced. This is why microwave frequencies are useful, because the effect is in between these two extremes. Indeed, the frequency is low enough to allow the dipole to rotate and not high enough for the rotation to be out of phase. This is the origin of constant rotation of the dipole, inducing molecular collisions that give rise to dielectric heating.

Figure 17: Dipolar molecules which try to align with an oscillating electric field.

The **conduction mechanism** is due to the interaction of the electric field and another factor: charged particles. Indeed, charged particles are sensitive to electric field. In solution, a charged particle will move through the solution under the influence of the electric field. Because of the viscosity of the liquid, the kinetic energy of the particles will be lost by heat generation due to the collision effect as shown in Figure 18.

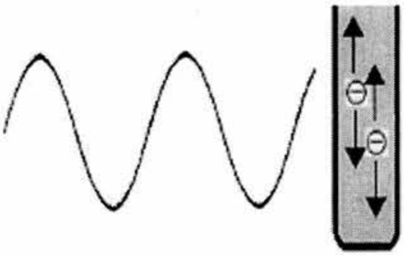


Figure 18: Charged particles in a solution will follow the applied electric field.

(ii) The equipment:

The machine used in our laboratory was the CEM Discover. The system was equipped with a temperature detector and a pressure device to report on certain parameters from the reaction. The circular cavity directs the microwave energy into a defined area, resulting in a homogenous field pattern surrounding the sample.

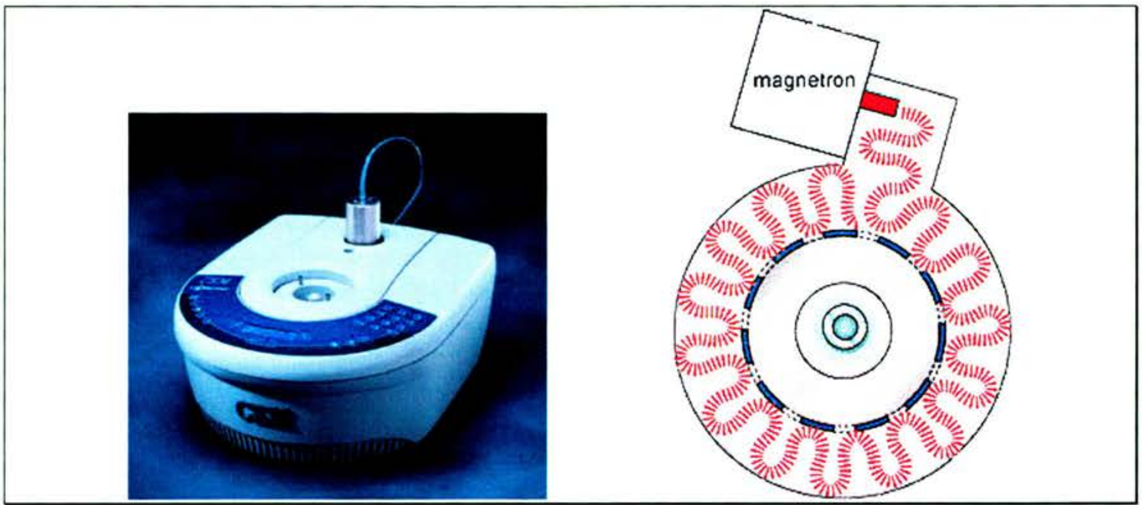
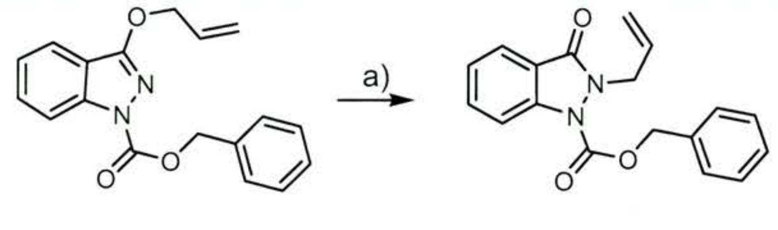


Figure 19: CEM Discover microwave and homogenous irradiation around the sample.[134]

(iii) Results

Due to the unsatisfactory results obtained using standard thermal heating techniques, microwave-based approaches were used to attempt the rearrangement of the 3-allyloxyindazole **112** to the corresponding *N*-allyl indazolinone **113**.



(112) **(113)**

Scheme 77: Attempt to rearrange *N1*-Z 3-allyloxyindazole **113** using microwave techniques.

112 was irradiated under microwave conditions in dry DMF. The reaction was successful, however, the yield of the isolated product **113** was very low (10%). Moreover, the TLC of the crude reaction revealed the presence of multiple other products. Careful study of the ^{1}H NMR spectrum of the crude reaction mixture revealed the presence of the deprotected compounds **104** and **23**.

This experiment suggests that the Z group is not stable under the reaction conditions used in the microwave.

The experiment described above was run under microwave conditions at **200°C**, for **5 min** in DMF as **solvent**. Several parameters of this initial experiment were changed in an attempt to optimise this reaction (Table 5).

A standard run time of 5 minutes was used and the substrate **112** was irradiated in different solvents at different temperatures. As Table 5 indicates, the only experiment where **112** was transformed was using DMF at 200°C (pressure of 60 psi).

	50°C	100°C	150°C	200°C
DCM	×	×	× (120 psi)	N/A
THF	×	×	×	× (110 psi)
Decalin	×	×	×	× (30 psi)
Toluene	×	×	×	× (45 psi)
DMF	×	×	×	✓ (60 psi)

Table 5: Attempts to rearrange **112** in different solvents at different temperatures. (✓:change, ×: no change by TLC)

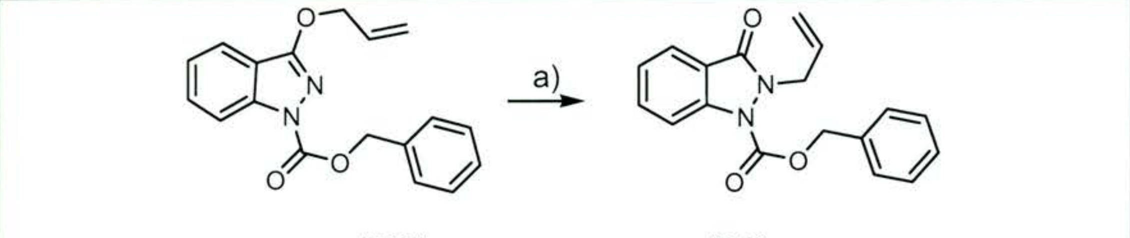
Unfortunately, the results were not satisfactory. None of the conditions attempted gave the desired rearrangement product **113** in good yield.

The rearrangement can occur under microwave conditions but the *N1*-substituent needs to be less labile (see section 2.2.6.2). Meanwhile, catalysts were applied in an attempt to carry out the rearrangement of the allyl moiety under milder conditions.

2.2.4.3. Rearrangement of **112** using Palladium catalysts:

Canadian researchers reported studies on transition metal-catalysed aza-Claisen rearrangements of allyl imidate substrates.[135] Rhodium(I), iridium(I) and palladium were the different transition metals used. Palladium at either the (0) or (II) oxidation level was the transition metal studied most extensively in order to understand mechanistic and stereoselectivity issues (for a further discussion of mechanistic issues, see Section 2.2.6). We therefore decided to investigate if the desired rearrangement would occur under palladium catalysis.

2.2.4.3.1. The rearrangement on N1-Z protected indazolinone:



(112) **(113)**

Scheme 78: Rearrangement of **112** using tetrakis(triphenylphosphine)palladium(0); $Pd(PPh_3)_4$ (10% mol.), rt, 16 h, quant.

112 was therefore reacted in the presence of a palladium (0) catalyst in THF at room temperature under an inert atmosphere. After 16 hours, the reaction was stopped purified and the products of the reaction analysed. ^1H NMR analysis of the crude reaction mixture showed that traces of the starting material **112** were present but the major product was **113**. A sample of **113** prepared as described in section 2.2.2.2 aided product assignment. To visualise in detail the differences and similarities of **112** and **113**, the region of the ^1H NMR spectra containing the alkene protons (6.50-4.50 ppm) has been expanded (Figure 20).

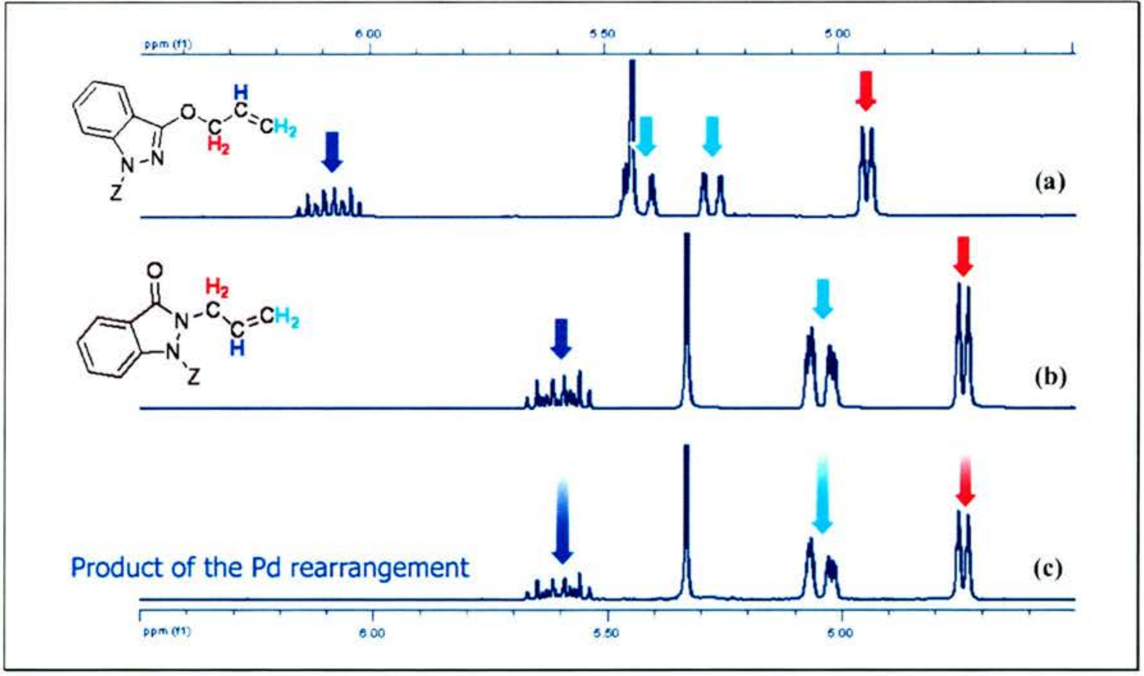
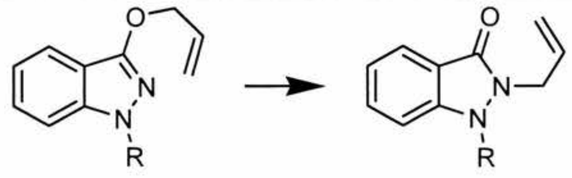


Figure 20: Comparison by ^1H NMR (6.50 to 4.50 ppm) of the a) *N1*-Z 3-allyloxyindazole **112**, b) *N1*-Z *N2*-allyl indazolinone **113** and c) product of the reaction of **112** under palladium (0) catalysis.

The first two spectra are from analysis of **112** and **113** prepared via the Mitsunobu reaction. It is clear from the signals that each set of protons from the allyl moiety appears in a specific window. The bottom spectrum in Figure 20 represents the purified product of the reaction of **112** under Pd(0) catalysis. The fact that the signals corresponding to **113** and this product overlap provides good evidence that **113** and the rearranged product are the same. The Pd (0) rearrangement is therefore an efficient way of converting *N1*-Z 3-allyloxyindazole **112** to **113**.

2.2.4.3.2. The rearrangement on *N1*-substituted indazolinone

Applying the aza-Claisen rearrangement on structure of type **20** would allow us to generate structures of type **21** in a single step. In terms of library generation, skeletal diversity would therefore be generated.



(20) **(21)**

Scheme 79: Rearrangement of *N1*-substituted 3-allyloxyindazoles of type **20** to *N1*-substituted *N2*-allyl indazolinones of type **21**.

The results from the rearrangement carried out with the *N1*-substituted 3-allyloxyindazoles **118, 119, 120, 121** previously prepared (page 73) are summarised in Table 6.

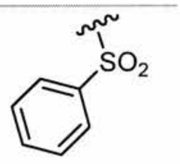
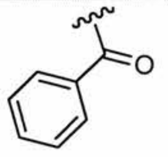
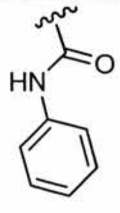
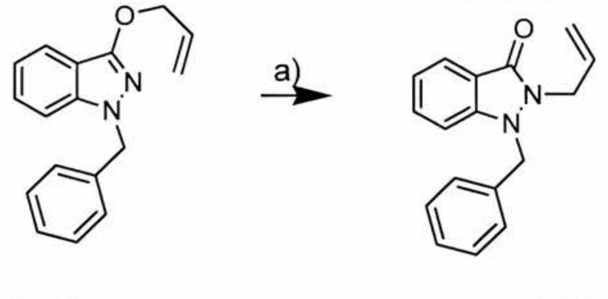
R groups	 **(118)**	 **(121)**	 **(119)**	 **(120)**
Yield of the transformation	**90%**	**91%**	**5%**	**0%**
	(135)	**(136)**	**(137)** **40% of 107**	**(138)** **45% of 107**

Table 6: Rearrangement of **118, 119, 120, 121** under palladium (0) catalysis.

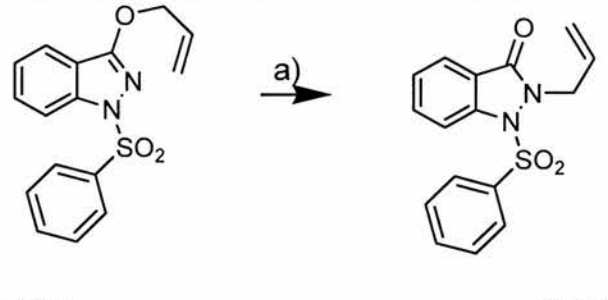
The rearrangement of **118** and **121** yielded the corresponding *N2*-allyl indazolinone of type **21** in excellent yields. Tetrakis(triphenylphosphine)palladium(0) induced the rearrangement of the allyl group of **118** to give **135** in 90% yield and **121** to **136** in 91%.



(118) **(135)**

Scheme 80: Synthesis of **135** by rearrangement of **118** under palladium (0) catalysis; a) $Pd(PPh_3)_4$, THF, 90%.

In the infrared spectrum, the band characteristic of the C=N bond at 1527 cm^{-1} in **118** disappeared after the reaction to give a new product with an IR band at 1661 cm^{-1} characteristic of a C=O bond (expected in **135**). In the ^1H NMR spectrum, the doublet of triplets corresponding to the allylic CH_2 shifted from 4.83 ppm in **118** to 4.52 ppm in **135** as expected due to the difference in electronegativity between the oxygen and the nitrogen atoms.

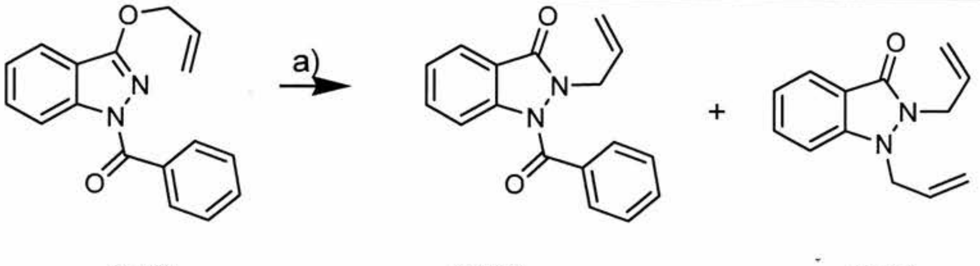


(121) **(136)**

Scheme 81: Synthesis of **136** by rearrangement of **121** under palladium (0) catalysis; a) $Pd(PPh_3)_4$, THF, 91%.

The positive outcome of the rearrangement of **121** by tetrakis(triphenylphosphine)palladium(0) was confirmed by infrared as the band at 1543 cm^{-1} in **121** characteristic of the imidate functionality disappeared and a new band at 1704 cm^{-1} characteristic of an amide functionality appeared in the product **136**. In the ^{13}C NMR spectrum, the signal of the carbon of the allylic CH_2 shifted from 70.2 ppm in **121** to 49.9 ppm in **136**, a chemical shift which is consistent with the structural assignment of **136** due to the greater electronegativity of the oxygen compared to nitrogen.

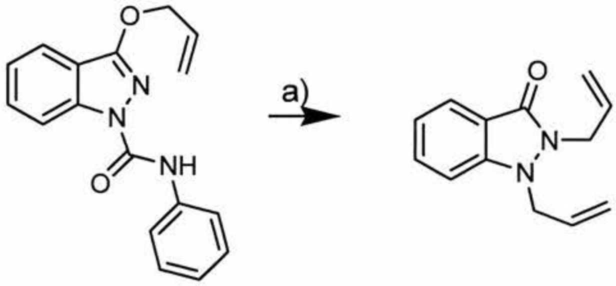
However, the rearrangement of **119** and **120** gave mainly an undesired product and the desired product only in low yield or not at all. The main product from both of these reactions was identical as judged by TLC. Further investigation and comparison with material already characterised proved that the main product isolated from the rearrangement of **119** and **120** was **107**.



(119) **(137)** **(107)**

Scheme 82: Rearrangement of **119** by tetrakis(triphenylphosphine)palladium(0); a) $Pd(PPh_3)_4$.

The rearrangement of **119** under tetrakis(triphenylphosphine)palladium(0) catalysis also yielded **137** as a minor product of the reaction. The ^{13}C NMR spectrum confirmed the rearrangement to **137** due to the chemical shift change in the allylic CH_2 carbon from 70.2 ppm in **119** to 47.8 ppm in **137**, ($\chi_O > \chi_N$).



(120) **(107)**

Scheme 83: Rearrangement of **120** by tetrakis(triphenylphosphine)palladium(0); a) $Pd(PPh_3)_4$.

The rearrangement of **120** did not yield the desired product (**138**) but only gave **107** as judged by ^1H NMR of the crude reaction mixture.

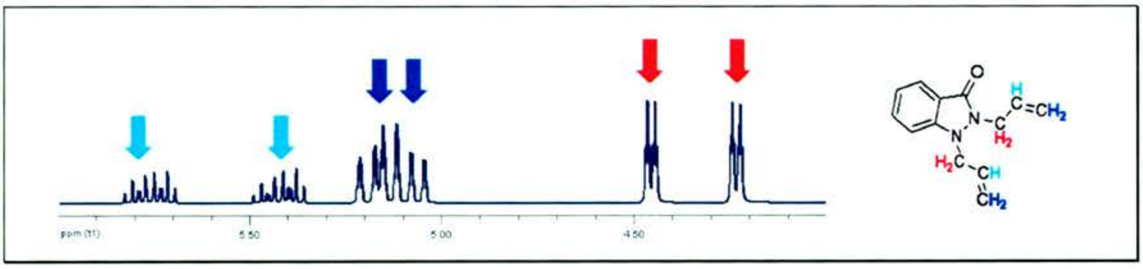


Figure 21: Expansion of ^{1}H NMR spectrum (6.00 to 4.00 ppm) of *N1,N2*-diallyl indazolinone **107**.

The ^{1}H NMR spectrum of **107** showed that signals corresponding to the presence of 6 proton environments in the 4.00-6.00 ppm range.

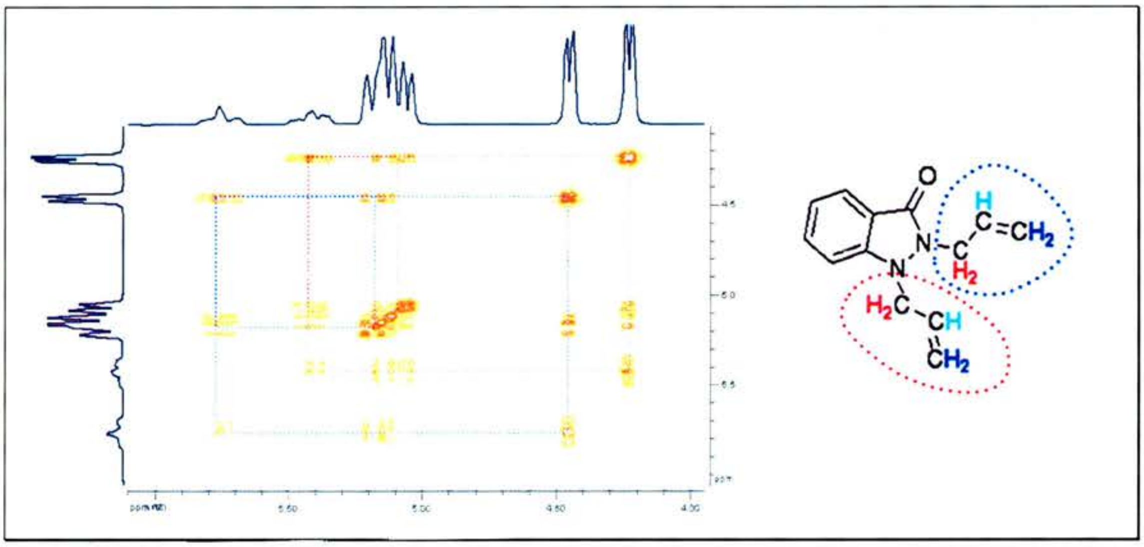


Figure 22: Expansion of COSY spectrum (6.00 to 4.00 ppm) of *N1,N2*-diallyl indazolinone **107**, and identification of two allyl groups.

The COSY spectrum for **107** allows us to determine which protons couple with each other. Analysis of this spectrum leads to the conclusion that two allyl groups are present in **107**.

A structural element that has not been elucidated at this point is the position of the two allyl groups. It was assumed that both the allyl groups were on the nitrogens (position of the two X-C$\underline{H}_2$ signals between 4.00 and 4.50 ppm). However further evidence in support of this was required. The chosen method for doing this was another 2D NMR experiment which measures the connectivity between the carbon skeleton and the protons. Two types of measurement are possible: a short distance coupling, where a proton couples to the carbon that it is directly bonded to (HSQC); a long distance coupling where a proton couples to carbons in the β, γ or δ position (HMBC).

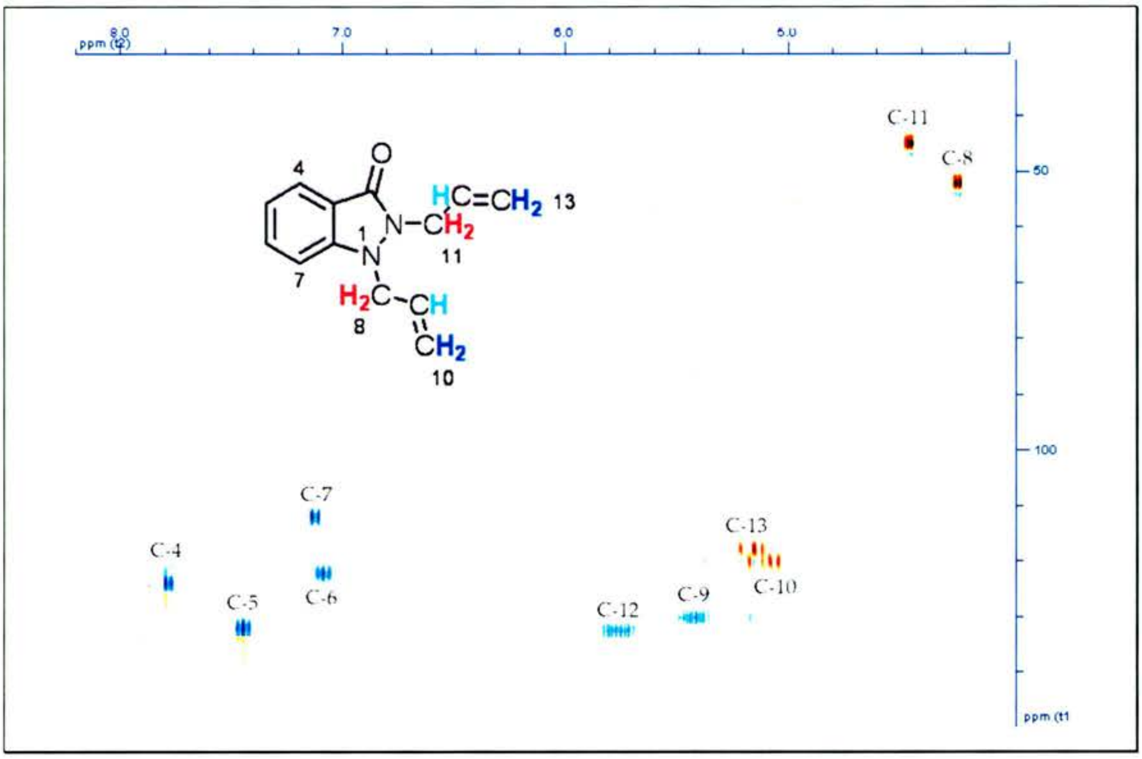


Figure 23: HSQC spectrum (x scale: 8-4.2 ppm, y scale: 150-30 ppm) of **107**.

From the HSQC spectrum (Figure 23), 10 carbons could be assigned as expected.

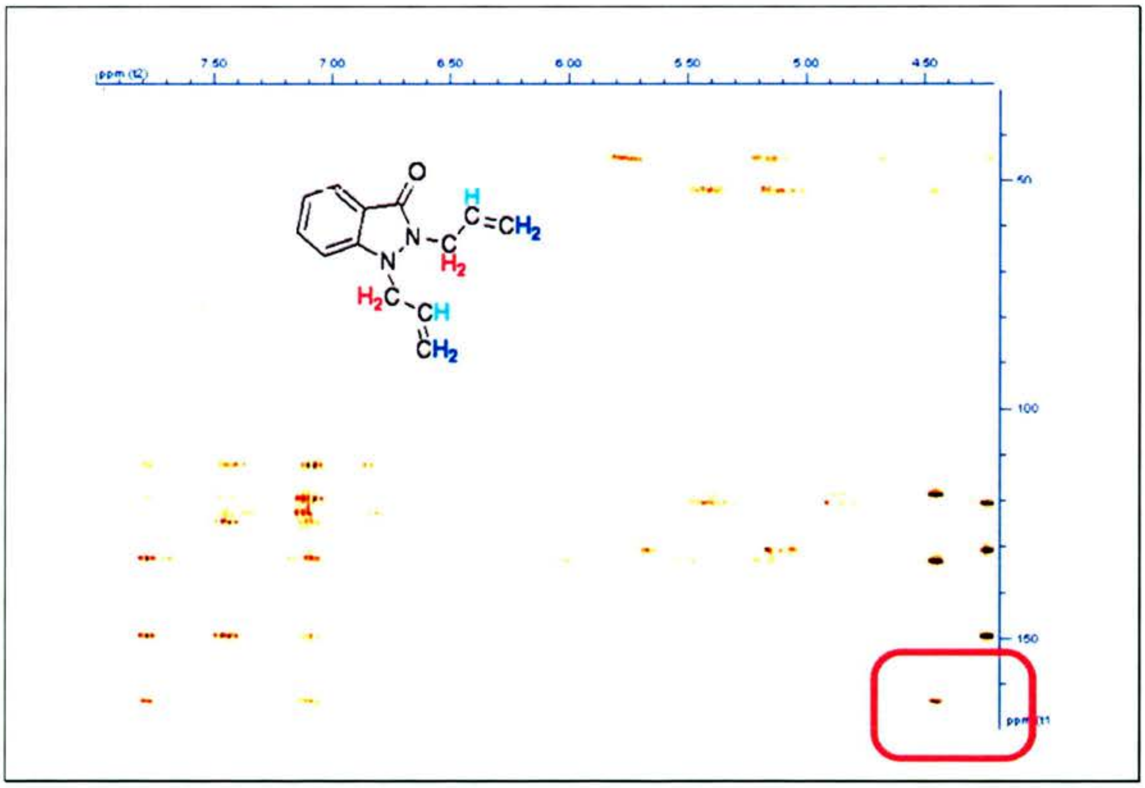


Figure 24: HMBC spectrum (x scale: 8-4.2 ppm, y scale: 170-30 ppm) of **107**.

Analysing the HMBC spectrum led to the conclusion that the compound was the *N1,N2*-diallyl substituted indazolinone **107**. The red rectangle would have been expected to contain two cross-peaks in the case of an alternative isomer *N2*-allyl 3-allyloxyindazole **108** (two C**H**$_2$ coupling with the **C** from C=O, two signals). Figure 25 provides a more detailed view of this argument. In the case of **106** and **107**, only one set of X-C**H**$_2$ protons is coupled to the carbon atom of the carbonyl group. This interaction will be visible in the HSQC spectrum as a single cross peak (case 1, Figure 25). However, *N2*-allyl 3-allyloxyindazole of type **108** would show two sets of protons X-C**H**$_2$ that couple to the carbon of the carbonyl. These couplings will be seen as two cross peaks in the HSQC spectrum (this remark is valid only if the chemical shifts of the two sets of protons X-C**H**$_2$ are different, case 2, Figure 25).

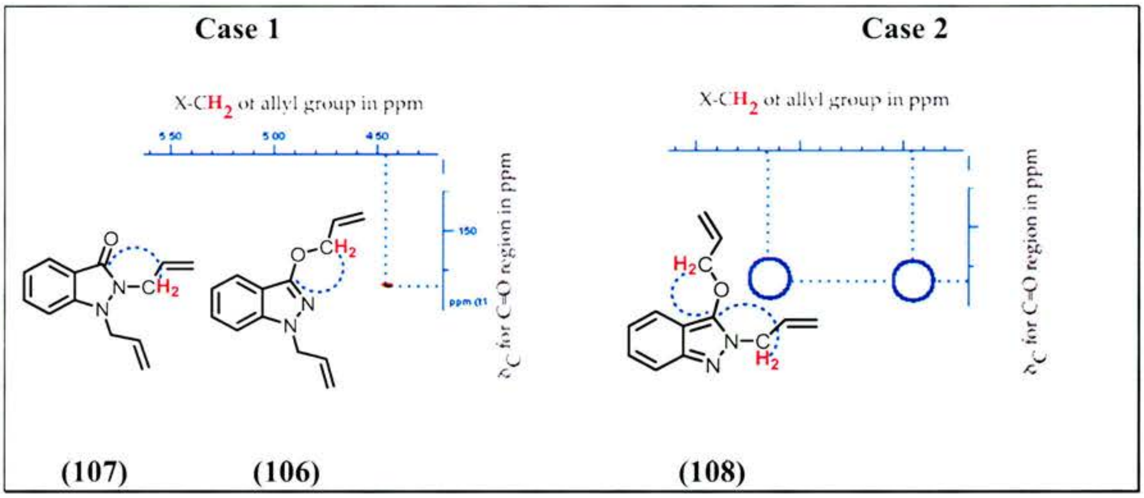
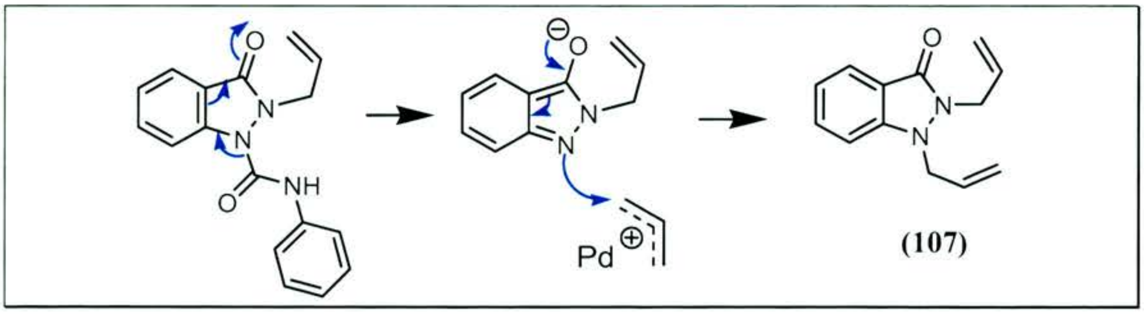


Figure 25: Prediction of HMBC spectra for diallylated indazolinones.

A possible explanation for the formation of **107** comes from the labile C-N bond at the N1 position in the product of the rearrangement as the electrons of this bond can be delocalised and stabilised by the oxygen atom. This stabilisation of the negative charge helps the C-N bond to break and enables allylation at the N1 position (Scheme 84).



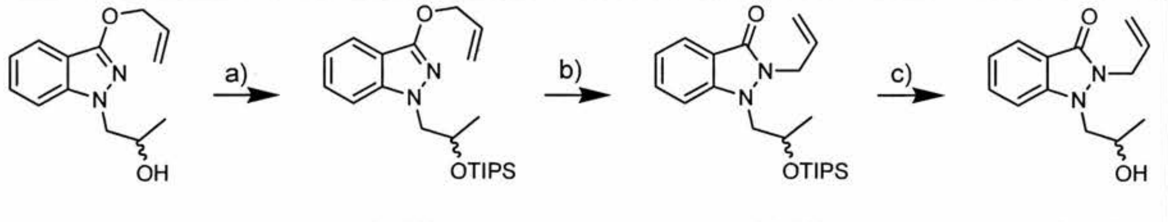
Scheme 84: Possible mechanism explaining the formation of **107**.

This study on *N1*-substituted indazolinone defines the scope of substituents that are compatible with the palladium rearrangement (benzyl and sulfonyl groups). Importantly, this chemistry is also compatible with an N1-carbamate group (see section 2.2.4.3.1). Acylating agents or isocyanate building blocks do not survive under palladium catalysis both yielding the same by-product **107**.

2.2.5. Rearrangement on solid phase

Using the methodology described in section 2.2.4.3, it was decided to synthesise a substrate which could be loaded onto a resin in order to attempt the rearrangement reaction in the solid phase. **122** contains a secondary alcohol functional group that could be used to load **122** onto a silicon based resin.[136, 137]

Model studies were initially carried out using a TIPS protecting group (solution phase) to mimic the solid phase. The reaction sequence involved the use of the palladium (0) catalysed rearrangement reaction. Removing the TIPS protecting group in solution phase is equivalent to cleaving the material from the resin (solid phase).



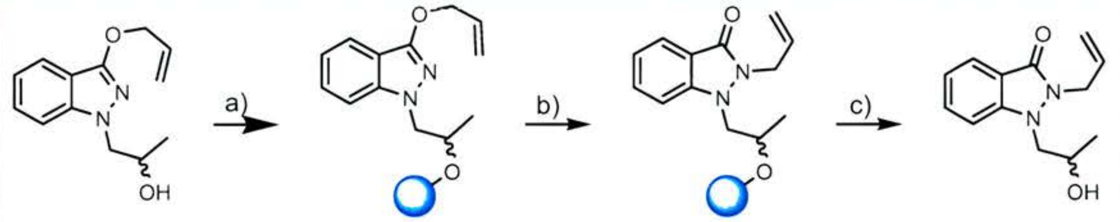
(122) **(139)** **(140)** **(141)**

Scheme 85: Synthesis of **141** from **122**; a) TIPSOTf, NEt_3, THF, rt, 85%, b) $Pd(PPh_3)_4$, 60%, c) TBAF, THF; 60%.

The protection of the secondary alcohol in **122** was achieved in 85% yield using triisopropylsilyl trifluoromethanesulfonate in the presence of triethylamine in THF at room temperature. Evidence in support of the formation of **139** came from mass spectroscopy in CI^+ mode (*m/z* increased from 233 for **122** to *m/z*: 389, mass increase of 156, characteristic of the insertion of the triisopropylsilyl (TIPS) group $[(CH_3)_2CH]_3Si$ (157) and the abstraction of the proton of the secondary alcohol).

The rearrangement of **139** to **140** was confirmed by the change in the chemical shift of the allylic CH_2 carbon from 69.6 ppm in **139** to 45.0 ppm in **140**, indicating the rearrangement of the allyl group from the oxygen to the nitrogen position and no change in the molecular mass (*m/z*: 389 in CI^+) was observed as expected.

The cleavage of the TIPS group from **140** to **141** was achieved by using a source of fluoride, tetrabutylammonium fluoride, in THF. The loss of 156 in mass between **141** and **140** supported the fact that the TIPS group had been removed. Furthermore, the infrared spectrum indicates a band at 3332 cm^{-1} characteristic of a free alcohol (OH stretch). This reaction sequence enabled the synthesis and full characterisation of an authentic sample of **141**. Comparison of **141** prepared in this way with material cleaved from the resin would allow validation of the solid phase chemistry. Scheme 86 shows the reaction sequence that was carried out on the solid phase.



(122) **(142)** **(143)** **(141)**

Scheme 86: Example of the aza-Claisen rearrangement on the solid phase, synthesis of **141** in the solid phase; a) loading, b) $Pd(PPh_3)_4$, c) HF/pyridine then methoxytrimethylsilane (○ silicon-based resin).

2.2.5.1. Using catalyst

After **122** was loaded onto the alkylsilyl tethered resin following the literature procedure,[136] the rearrangement was induced using tetrakis(triphenylphosphine)palladium(0) in THF at room temperature. After 2 days under a nitrogen atmosphere, the insoluble polymer was washed as described in the literature [136]. The reaction time was extended to 2 days from 16 hours in solution phase due to expected differences in reaction kinetics for solid phase versions of solution phase reactions. Despite the black appearance of the beads (presumably residues of palladium black), the beads were exposed to HF/pyridine in order to cleave the product(s) from the resin. The solvent was evaporated and the non-volatile compounds were analysed by ^{1}H NMR.

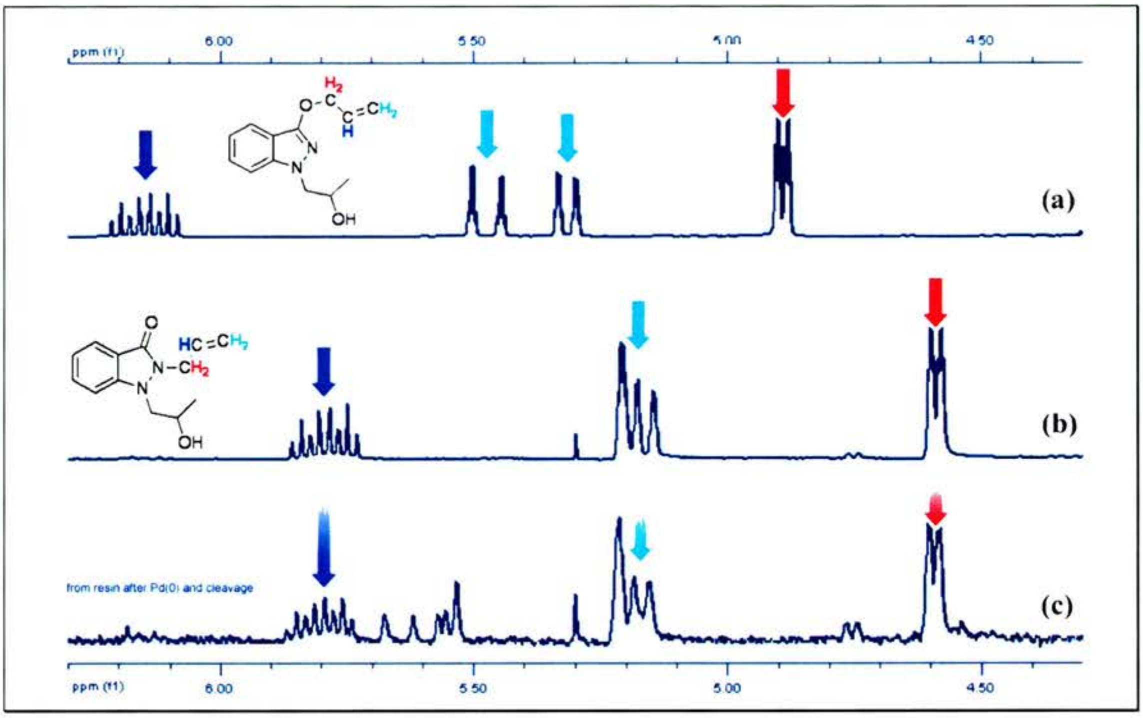


Figure 26: Comparison of solution and solid phase rearrangement induced by transition metal catalyst (Pd(PPh_3)$_4$) by ^1H NMR (6.3 to 4.3 ppm).

The three spectra shown in Figure 26 are the ^1H NMR traces of authentic **122** and **141** prepared as described in Scheme 85 and the crude product obtained from the solid phase sequence. The similarities in the ^1H NMR spectra obtained from **141** and the crude product from the resin allowed us to conclude that both products were the same. However, the expected product is also contaminated by the presence of an unidentified by-product as seen in the ^1H NMR spectrum of the crude reaction mixture. Attempts to isolate by-products from this reaction were unsuccessful. The rearrangement on the solid phase was therefore viewed as successful as the crude reaction mixture contains predominantly **141** after cleavage from the resin.

2.2.5.2. Using thermal approaches

2.2.5.2.1. Microwave conditions

The rearrangement on the solid phase with **142** was not carried out under microwave conditions due to time constraints. Because the system using the alcohol connected onto the N1 position does not allow diversity incorporation at the N1 nitrogen, microwave rearrangement was further optimised using a different substrate (section 2.3.4.4.2).

2.2.5.2.2. Thermal conditions

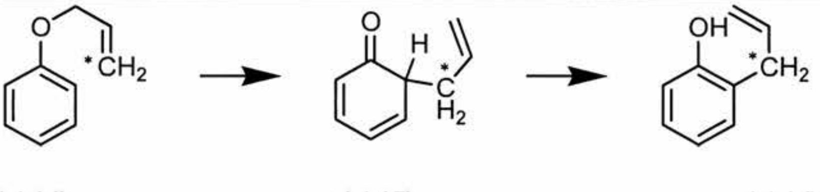
As a result of the poor results obtained in solution (section 2.2.5.2.2), attempts to carry out this transformation under standard thermal conditions were not pursued.

2.2.6. Mechanistic issues relating to the aza-Claisen rearrangement

2.2.6.1. Introduction

The Claisen rearrangement is an important and useful process in organic synthesis (see section 2.2.4). This chemical transformation leads to the creation of a C-C bond. This sigmatropic rearrangement is also interesting mechanistically.

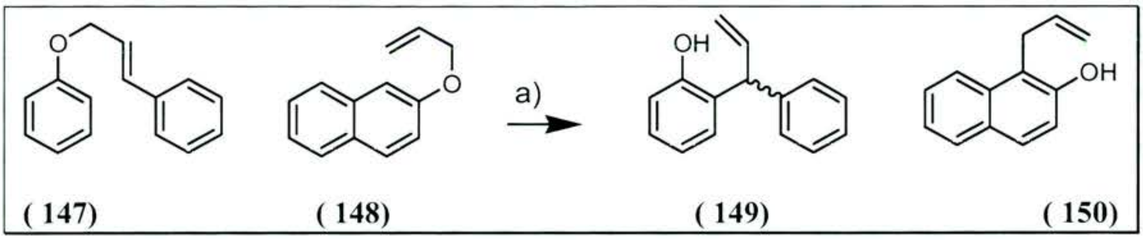
Detailed studies reported in the literature [138] on **144** lead to the conclusion that the thermal rearrangement is concerted. This experiment relied on the use of a ^{14}C label at the terminal alkene carbon to prove the reaction mechanism [138].



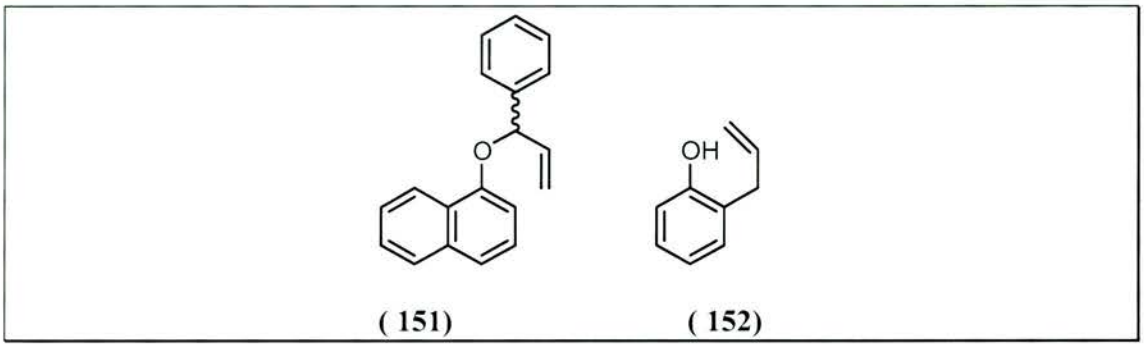
(144) **(145)** **(146)**

Scheme 87: Claisen rearrangement under thermal conditions of ^{14}C labelled allyl phenyl ether **144**.

A second experiment was used to provide further evidence that the allyl moiety was transferred in an intramolecular manner rather than intermolecularly. This experiment (Scheme 88) was designed by Hurd in 1937 and proved that the allyl moiety rearranged intramolecularly.[139] Indeed, when **147** and **148** were heated simultaneously, the products that are formed are the same (**149** and **150**) as when **147** and **148** are heated separately. No evidence for the formation of the cross-over products (**151** and **152**) was obtained.

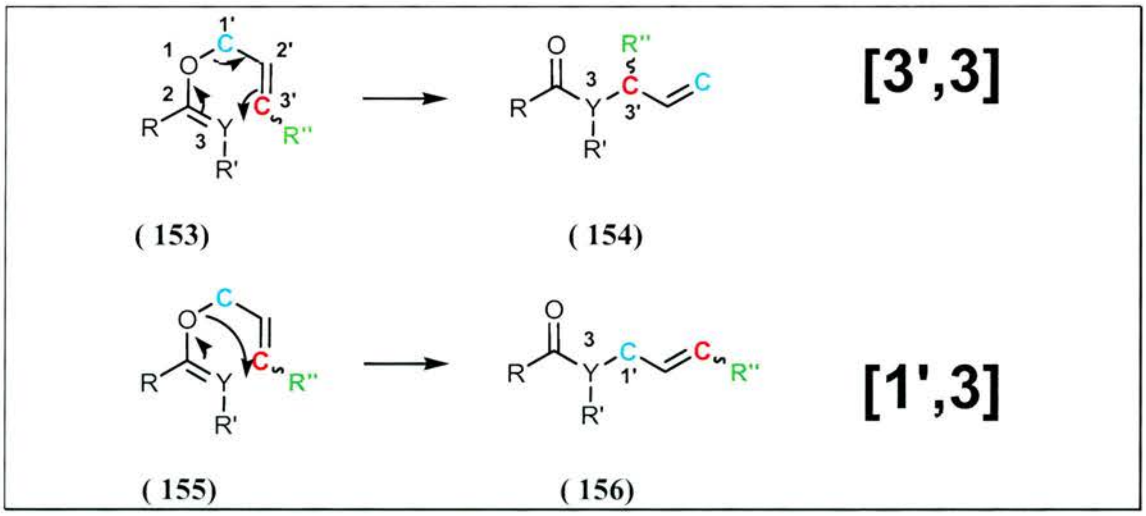


Scheme 88: Evidence in support of a concerted and intramolecular mechanism under thermal activation.



Scheme 89: Additional products expected if an intermolecular process was taking place (Scheme 88).

The rest of this section focuses on our studies on the mechanism of the aza-Claisen rearrangement in the indazolinone system. As discussed previously (section 2.2.4), this system is very similar to the rearrangement of allyl imidates.

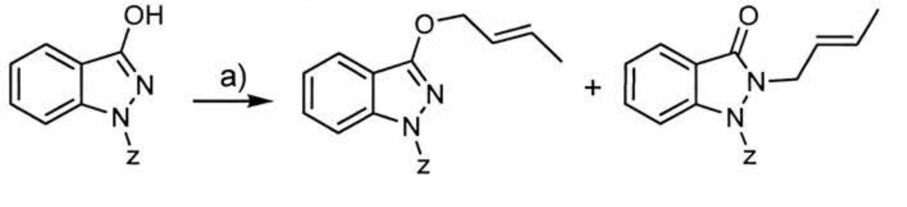


Scheme 90: [3',3] and [1',3] sigmatropic rearrangements terminology and general understanding.

The mechanism of the rearrangement has been studied for allyl groups carrying substituents on the terminal alkene carbon to determine which of the two different reaction pathways shown in Scheme 90 and known as [3',3] and [1',3] rearrangement occurs. Obviously, an allyl imidate carrying R''=H cannot provide any useful information regarding the mechanism as the product of the rearrangement will be the same whatever the mechanism.

2.2.6.2. Synthesis of precursors for aza-Claisen rearrangement:

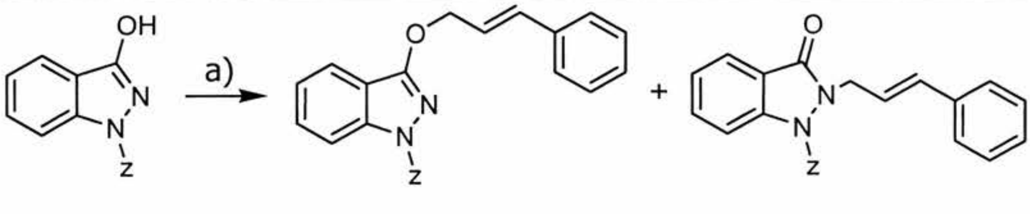
The precursors for the aza-Claisen rearrangement **158** (Scheme 91) and **160** (Scheme 92) were synthesised from **112** using the Mitsunobu procedure described in Section 2.2.2.2. As expected from the result obtained in the Mitsunobu reaction between **112** and allyl alcohol (Scheme 61), the N2 isomers **159** and **161** were also obtained from the Mitsunobu reaction between **112** and crotyl alcohol (Scheme 91) and cinnamyl alcohol (Scheme 92) respectively.



(111) **(157)** **(158)**

Scheme 91: Synthesis of **157** and **158** by Mitsunobu reaction with crotyl alcohol; a) DEAD, crotyl alcohol, triphenylphosphine, toluene, 44% of **157** and 54% of **158**.

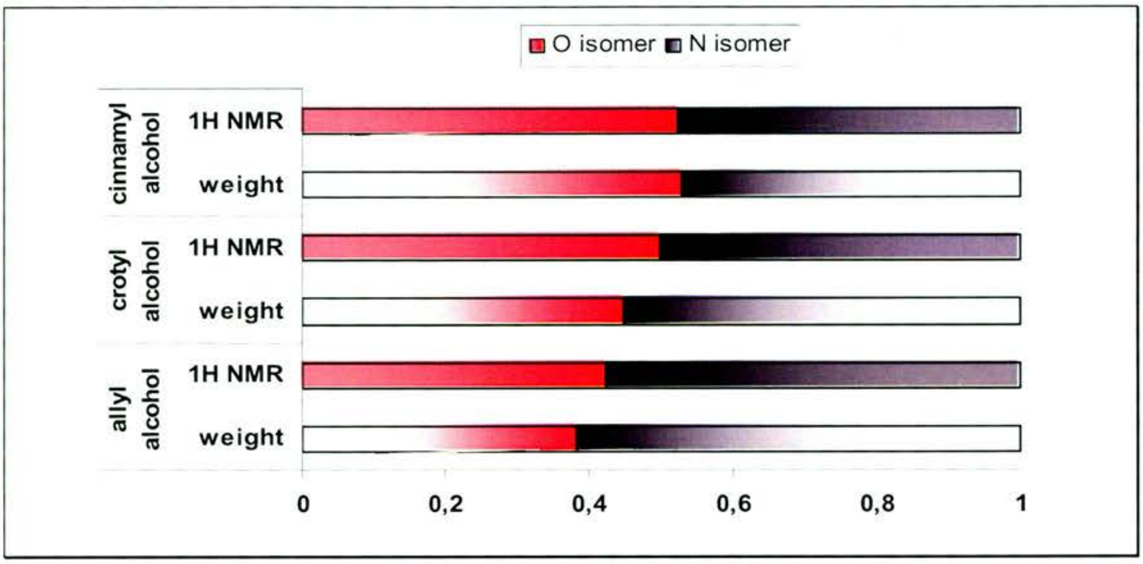
157 was obtained in an isolated yield of 44% and **158** in 54% yield (a ratio of 0.81:1). Analysis of the ^{1}H NMR spectrum of the crude reaction reveals a ratio of **157**:**158** of 1:1.



(111) **(159)** **(160)**

Scheme 92: Synthesis of **159** and **160** by Mitsunobu reaction with cinnamyl alcohol; a) DEAD, cinnamyl alcohol, PPh_3, $PhCH_3$, 45% of **159** and 40% of **160**.

159 and **160** were isolated in pure form in 45% and 40% yields respectively, corresponding to a ratio of **159**:**160** of 1.1:1. The ratio calculated from the ^{1}H NMR spectrum of the crude reaction mixture indicates a ratio of **159**:**160** 1.10:1. Scheme 93 summarises the results of this study.



Scheme 93: Comparison of O/N2 isomers ratios obtained in the Mitsunobu reaction with **111** and allyl, crotyl and cinnamyl alcohols measured by ^{1}H NMR of the crude reation and isolated yield of the products.

In summary, we observed a slight variation in the ratio of O and N2 alkylation as a function of the electrophile. One possible explanation for these subtle differences may be steric. At first glance, this appears counter-intuitive as the bulky Z group would be expected to reduce the amount of reaction at the N2 position. However, the peri-H may also introduce significant steric interactions disfavouring O-alkylation hence explaining the trend that as the alcohol increases in steric bulk the reaction is more N2 selective.

2.2.6.3. Aza-Claisen rearrangement studies

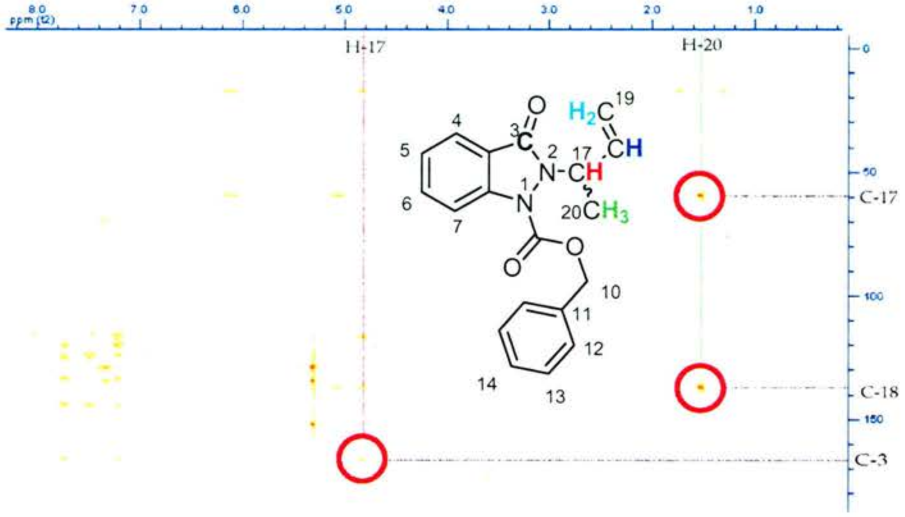
2.2.6.3.1. Transition metal catalysed aza-Claisen rearrangement

2.2.6.3.1.1. With tetrakis(triphenylphosphine)palladium(0) as Pd (0) source

2.2.6.3.1.1.1. Effect of tetrakis(triphenylphosphine)palladium(0) on 157

In initial studies, we attempted to rearrange **157** using palladium (0) catalysis. The ^{1}H NMR spectrum of the crude reaction mixture showed several signals corresponding to three different crotyl groups. Unreacted starting material **157** was present, but two other sets of signals corresponding to a crotyl group could also be identified. After purification, ^{1}H NMR analysis of the two new products led to their assignment as **158** (37%) resulting from a [1',3] rearrangement and **161** (63%) resulting from a [3',3] rearrangement.

The structure of **161** was elucidated using 1D ^{1}H NMR and 2D experiments (HSQC and HMBC). Evidence in support of the structure assignment of **161** is presented in Figure 27.



(161)

Figure 27: Structure of **161** and 2D spectrum (HMBC), C-3 and H-17 are coupling to each other, so are H-20 and C-17/C-18, which are the characteristic coupling expected in **161**.

2.2.6.3.1.1.2. Effect of tetrakis(triphenylphosphine)palladium(0) on 159

The tetrakis(triphenylphosphine)palladium(0) catalysed reaction of **159** yielded a single product **160**. This product was compared by ^{1}H NMR with authentic **160** obtained from the Mitsunobu reaction of **111** with cinnamyl alcohol. This comparison concluded that **159** had been cleanly converted to **160**. This result proved that, for this substrate, Pd(0) induced a [1',3] rearrangement of the cinnamyl moiety.

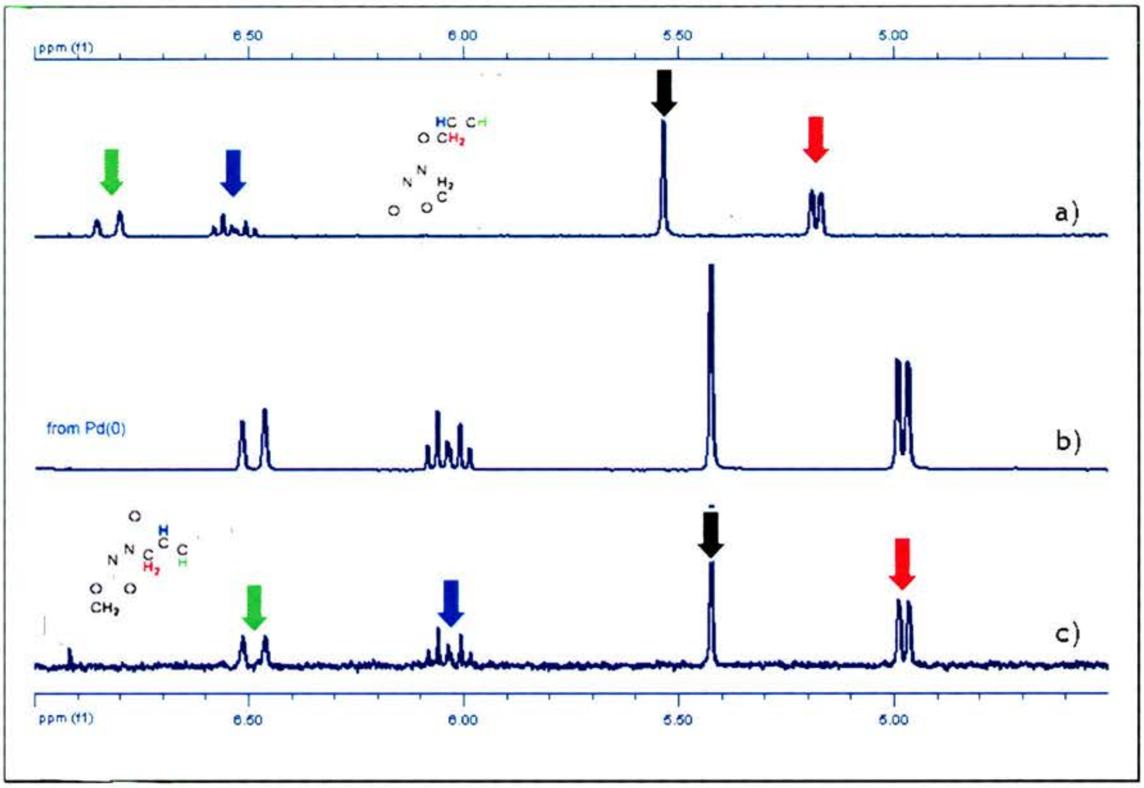


Figure 28: Comparison of a) ^{1}H NMR spectra from **159**, b) the product obtained on the rearrangment of **159** with Pd(PPh$_3$)$_4$ and c) authentic **160** (7.00-4.50 ppm).

2.2.6.3.1.2. With dichlorobis(acetonitrile) palladium (II) as Pd (II) source

2.2.6.3.1.2.1. Effect of dichlorobis(acetonitrile) palladium (II) on 157:

To a solution of **157** in THF was added dichlorobis(acetonitrile) palladium (II) (mol. 10%). The reaction was stirred under an inert atmosphere at room temperature for 16 hours. The ^{1}H NMR spectrum of the crude reaction showed that the starting material **157** disappeared completely, and a new product was formed. The product was compared with **158**, to see if a [1',3] rearrangement occurred, but the ^{1}H NMR spectra were different (Figure 29). It was then compared with **161** by ^{1}H NMR (data not shown). Both spectra matched perfectly and we therefore concluded that the rearrangement of **157** using dichlorobis(acetonitrile) palladium (II) gave a [3',3] rearrangement product as the unique product of the reaction as judged by the ^{1}H NMR of the crude reaction mixture (Figure 29, spectrum b).

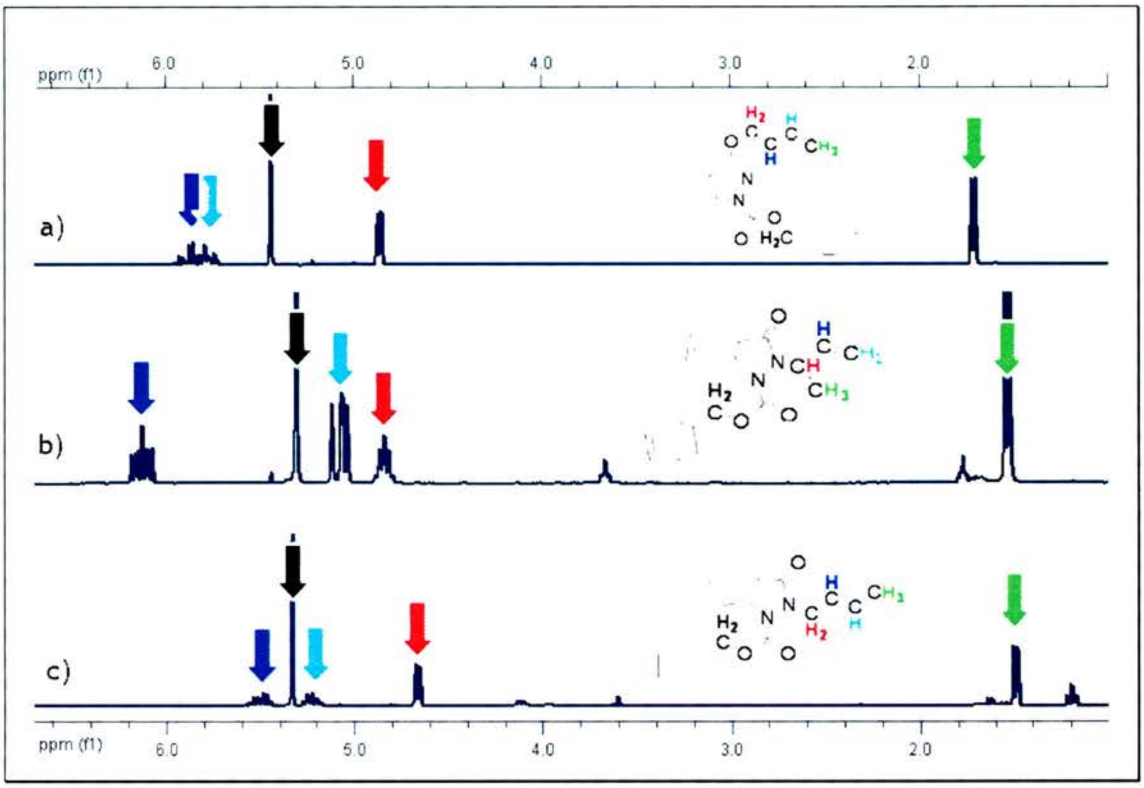


Figure 29: Comparison of ^{1}H NMR spectra from a) **157**, b) the product obtained on rearrangement of **157** with $Pd(PPh_3)_4$ and c) authentic **158** (6.7 to 1 ppm).

2.2.6.3.1.2.2. *Effect of dichlorobis(acetonitrile) palladium (II) on 159:*

When a solution of **159** in THF was treated with dichlorobis(acetonitrile) palladium (II) no reaction was observed even when the reaction time was extended to 48 hours. In order to rearrange the allyl moiety, the palladium catalyst needs to undergo an oxidative addition onto the alkene of the allyl moiety. This step is necessary to initiate the rearrangement. A possible reason not to observe the rearrangement in the case of **159** could be that the addition of Pd(II) on the cinnamyl moiety does not occur as required (Scheme 94, page 100) due to steric hindrance.

2.2.6.3.2. Summary of Transition metal catalysed aza-Claisen rearrangement

The results from the catalysed Claisen rearrangement studies on **159** and **157** are shown below in Table 7. These results are in accordance with the literature for aza-Claisen rearrangements in other systems.[135]

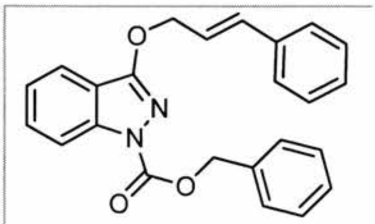
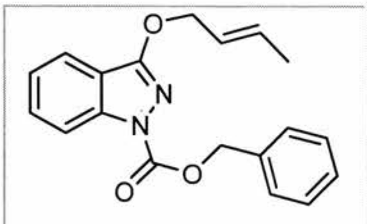
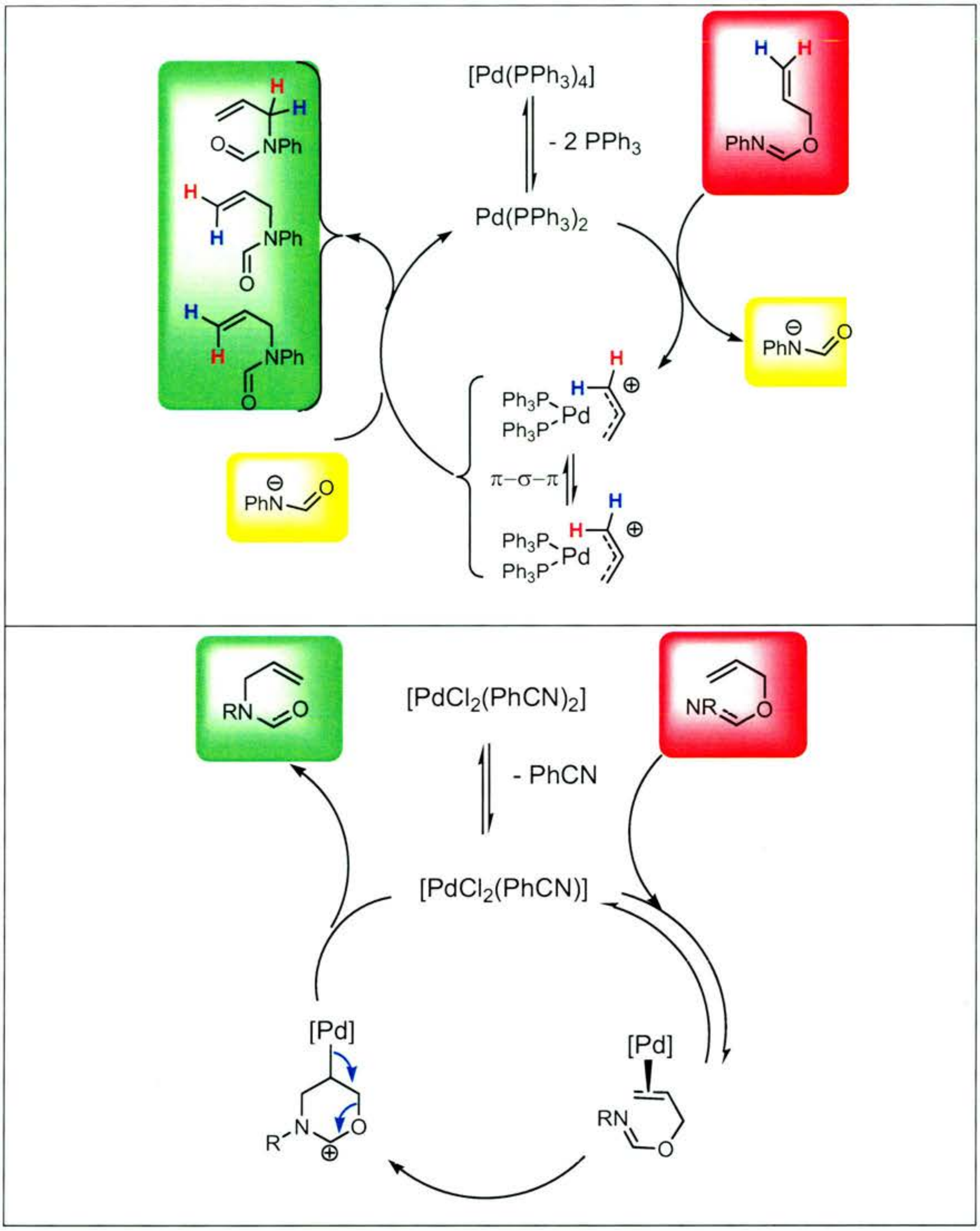
Substrates		 **(159)**	 **(157)**
Pd (0)	**yield**	**92%**	**93%**
	[1',3]	100%	37%
	[3',3]	0%	63%
Pd (II)	**yield**	No reaction after 48 hours	**97%**
	[1',3]		0%
	[3 ,3]		100%

Table 7: Percentage of [1',3] and [3',3] sigmatropic rearrangement with different N1-Z 3-allyloxyindazoles using different catalysts, Pd(0) and Pd(II) (Percentage determined by ^{1}H NMR analysis of the crude reaction mixture).

The Pd(0) catalysis induced the expected rearrangement of the allyl moiety from the O position to the N position in both cases (crotyl and cinnamyl). When **159** was rearranged with Pd(0), only one product assigned as **160** was obtained from a non-concerted mechanism of type [1 ,3]. When **157** was rearranged under the same reaction conditions previously used for **159**, **158** and **161** were isolated in 37% and 63% respectively. These observations are in accordance with the literature [135] since the same results have been reported from rearrangement studies on various allyl imidates. Indeed, the cinnamyl derivative was rearranged to give only the product of the [3 ,3] rearrangement whilst the crotyl derivative gave a 50:50 mixture of products resulting from [1 ,3] and [3′,3] mechanism.

Our results reinforced the mechanism due to the fact that the Pd(0) mechanism occurs via the π-allyl intermediate (Scheme 94) and the nucleophilic attack on the alkene depends on the substituents; a small substituent such as methyl allows the attack at C1 and C3 on the p-allyl cation, whereas the phenyl group blocks the attack at the C3 to induce the attack only at the C1 position.



Scheme 94: Pd(II) and Pd(0) mechanisms.[135]

These studies have proved that the Pd(II) can insert into the crotyl moiety and induce rearrangement via a concerted [3',3] mechanism creating a new stereogenic centre C17 in **161** which is racemic. These observations are in accordance with the literature [135] since the same results have been reported from rearrangement studies on various allyl imidates. However, the Pd(II) catalyst was inactive on the cinnamyl containing compound **159**. The lack of reactivity of **159** is presumably connected with the difficulty of forming the complex or the sterically hindered six-membered ring system with the phenyl group α to the C-Pd bond.

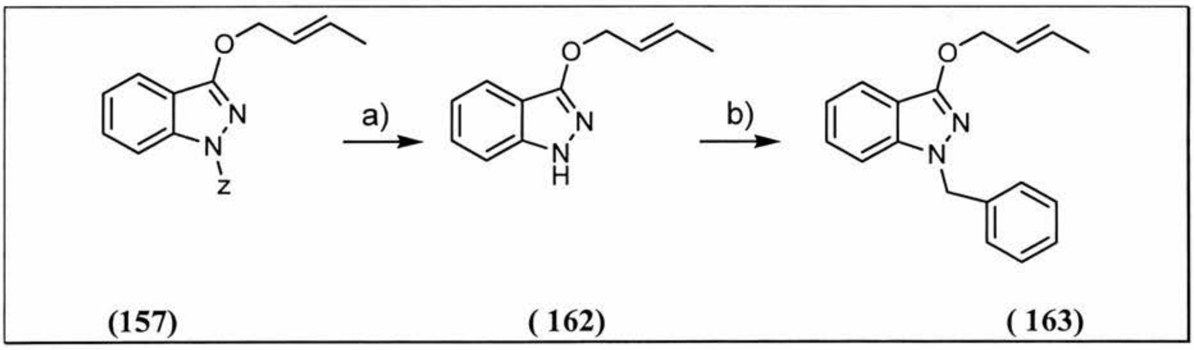
The concerted mechanism induced by Pd(II) is explained by the fact the transition metal coordinates to the alkene. This intermediate undergoes a six-membered ring formation and by loss of palladium, the ketone is formed whereas the allyl group ends up on the nitrogen atom (Scheme 94).

2.2.6.4. Thermal aza-Claisen rearrangement

As described previously in section 2.2.4.2.2 (page 78), the rearrangement can also be carried out under microwave irradiation. The main problem faced in our initial studies was that the Z group did not survive under the reaction conditions. We therefore decided to incorporate a less labile group on N1 to enable us to study the mechanism and the products obtained. A benzyl group was selected.

2.2.6.4.1. The synthesis of the starting materials:

The reaction sequence described previously (section 2.2.3, page 72) was applied to compounds **157** and **159**. The carbamate group was removed and a benzyl group inserted at the N1 position (Scheme 95 and Scheme 96). The deprotection step was carried out in the presence of lithium hydroxide and gave **162** and **164** respectively, which were subsequently benzylated in presence of potassium *t*-butoxide and benzyl bromide in THF at room temperature to yield to **163** and **165** respectively in good yields for the 2 step procedure.



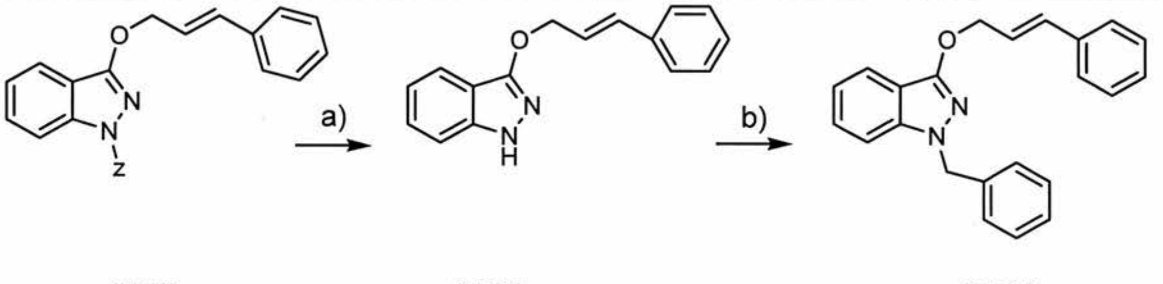
Scheme 95: Synthesis of **163** from **157**; a) LiOH aq., THF, rt, 99%, b) BnBr, ^{t}BuOK, THF, rt, 66%.

The deprotection of **157** was judged to have been successful by infrared spectroscopic analysis of **162** as the new band at 3154 cm^{-1}, characteristic of the NH bond, was observed, while the band of the carbonyl of the carbamate (at 1727 cm^{-1} in

157) disappeared. The loss of 134 Da observed by mass spectroscopy also supported the formation of **162**.

The benzylation of **162** appeared to occur specifically at the N1 position as in the ^{1}H NMR spectrum of the crude reaction a unique singlet appeared in the 5-5.5 ppm region of the spectrum. By infrared, the characteristic band for the NH also disappeared. The high resolution mass spectroscopy indicated a *m/z* of 301.1316 characteristic of the formula $C_{18}H_{18}N_2ONa$ (calcd *m/z*: 301.1317), which corresponds to the sodium adduct of our target compound **163**.

The same sequence was reproduced starting with **159** (Scheme 96). The deprotection of **159** was achieved using an aqueous solution of lithium hydroxide in THF and afforded **164** as the only product. Indeed, the TLC of the crude reaction mixture showed a single spot (Rf_{164} = 0.45 in 20% ethyl acetate/petroleum ether 40-60°C).



(159) **(164)** **(165)**

Scheme 96: Synthesis of **165** from **159**; a) LiOH aq., THF, rt, 96%, b) BnBr, ^{t}BuOK, THF, rt, 91%.

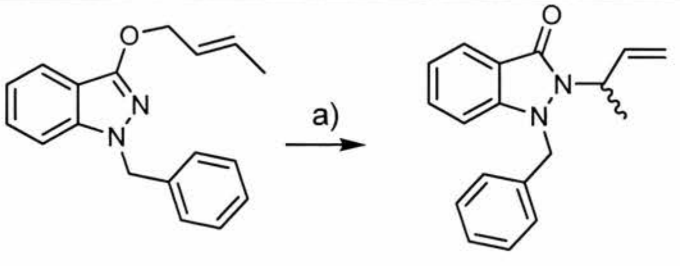
High resolution mass spectroscopic analysis gave *m/z*: 273.1003 corresponding to a formula of $C_{16}H_{14}N_2ONa$ which was in accordance with the formula of the sodium adduct of our target **164** (calcd *m/z*: 273.1004). X-ray crystallographic data were consistent with the proposed structure **164** (Appendix D).

164 was then submitted to the benzylation reaction. The ^{1}H NMR spectrum and the TLC of the crude reaction mixture revealed the presence of one new product as a single spot different from the starting materials and a unique singlet in the benzylic region was observed. The mass spectroscopic analysis gave a *m/z* of 363 (low resolution), corresponding to the sodium adduct and in high resolution in a *m/z* of 363.1479, in accordance with the molecular formula of $C_{23}H_{20}N_2ONa$ (calcd 363.1473) which fits with the sodium adduct of **165**.

2.2.6.4.2. Rearrangement of 163 and 165:

The rearrangement conditions were selected based on our previously described optimisation studies (Table 5, page 81), i.e., dimethylformamide as solvent (1 mL), 200°C, for 10 minutes (time was extended to push the reaction to completion). The pressure in the sealed tube increased to 100 psi. The work up with DMF is standard and consists of adding water which is miscible with DMF, extracting with diethyl ether (twice) and washing the organic extracts with water to remove the traces of DMF extracted into the diethyl ether. We believe that this work up procedure does result in the loss of some of the product into the aqueous phase explaining the moderate yields obtained (66% and 50% for **166** and **167** respectively). We have not been able to obtain any evidence in support of the formation of additional products as the TLC of the crude reaction showed only one product.

163 was irradiated under microwave conditions in DMF for 10 minutes at 200°C. The reaction was cooled down to room temperature and the reaction worked up as previously mentioned. The organic extracts were concentrated *in vacuo* and purified by flash column chromatography. A single product was isolated.



(163) **(166)**

Scheme 97: Synthesis of **166** by rearrangement of **163** by microwave irradiations; a) DMF, 200°C, 10 minutes, 66%.

This product was compared with the starting material **163** using ^{1}H NMR analysis but was different (Figure 30). The mass spectroscopic analysis is in accordance with the proposed formula of **166** as *m/z*: 301 was obtained (sodium adduct of **166**). The structure was also assigned using NMR techniques.

It is clear from the ^{1}H NMR spectra of **163** and **166** that there has been a significant rearrangement of the crotyl moiety, as previously observed in **161** (Figure 29, page 98).

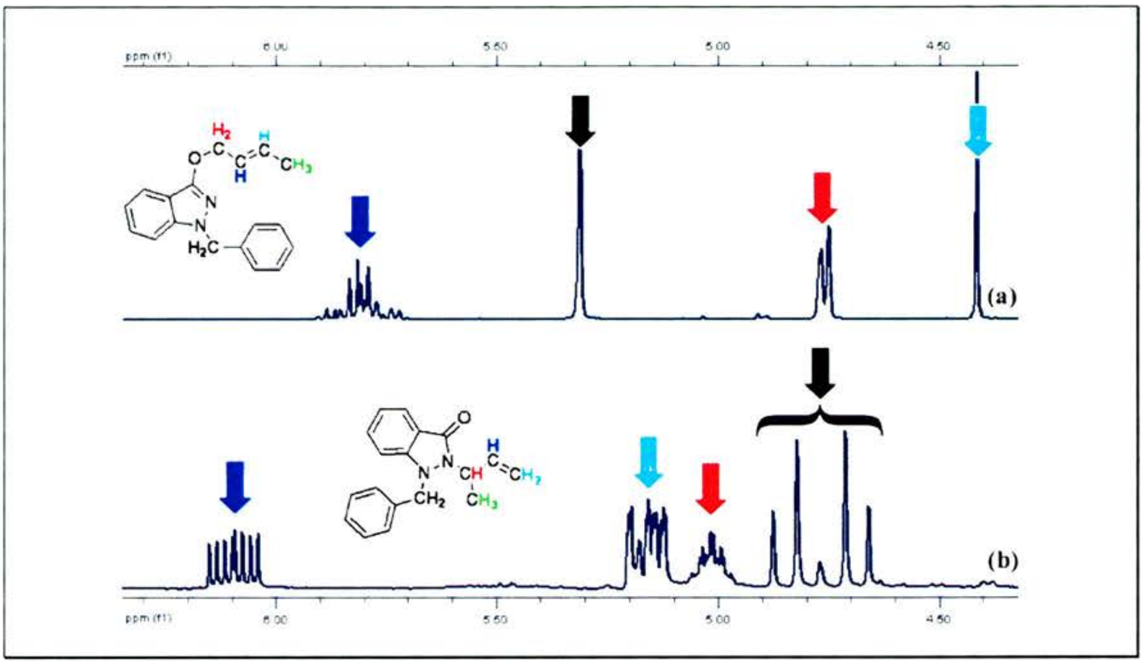
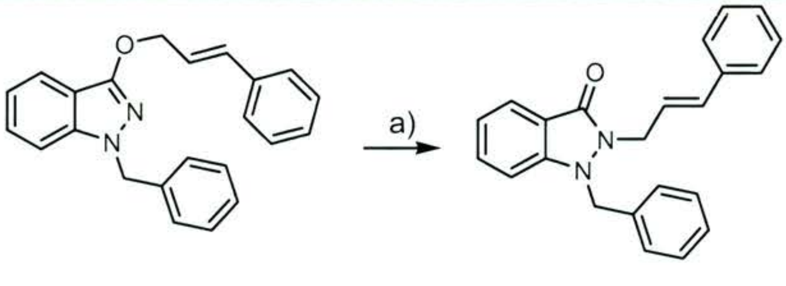


Figure 30: ^{1}H NMR (6.35-4.30 ppm) comparison of a) **163** and b) **166**, product of microwave rearrangement.

Moreover, the benzylic protons that appeared as a singlet in **163** are completely different in **166**. They appear as an ABX system consistent with the CH_2 hydrogens being diastereotopic. This indicates that a stereogenic centre is present in the product. The formation of a stereogenic centre can be explained by a concerted mechanism to give the product of a [3',3] mechanism. The 2D NMR experiments allowed us to confirm the proposed structure of **166** as the CH proton couples to the carbon α to the N2 in the HSQC and couples with the carbon of the CH and CH_3 in the HMBC.

165 was also irradiated using microwave conditions in DMF as described for the rearrangement of **163**. After work up and purification, a single product was isolated in 50% yield.



(165) **(167)**

Scheme 98: Synthesis of **167** by rearrangement of **165** under microwave conditions; a) DMF, 200ºC, 10 minutes, 50%.

The ^{1}H NMR of the product **167** was compared to that of **165** as shown in Figure 31. Despite the fact that the chemical shifts of the different signals between 6.90 and 4.50 ppm have moved to higher field, the pattern of each signal remained the same.

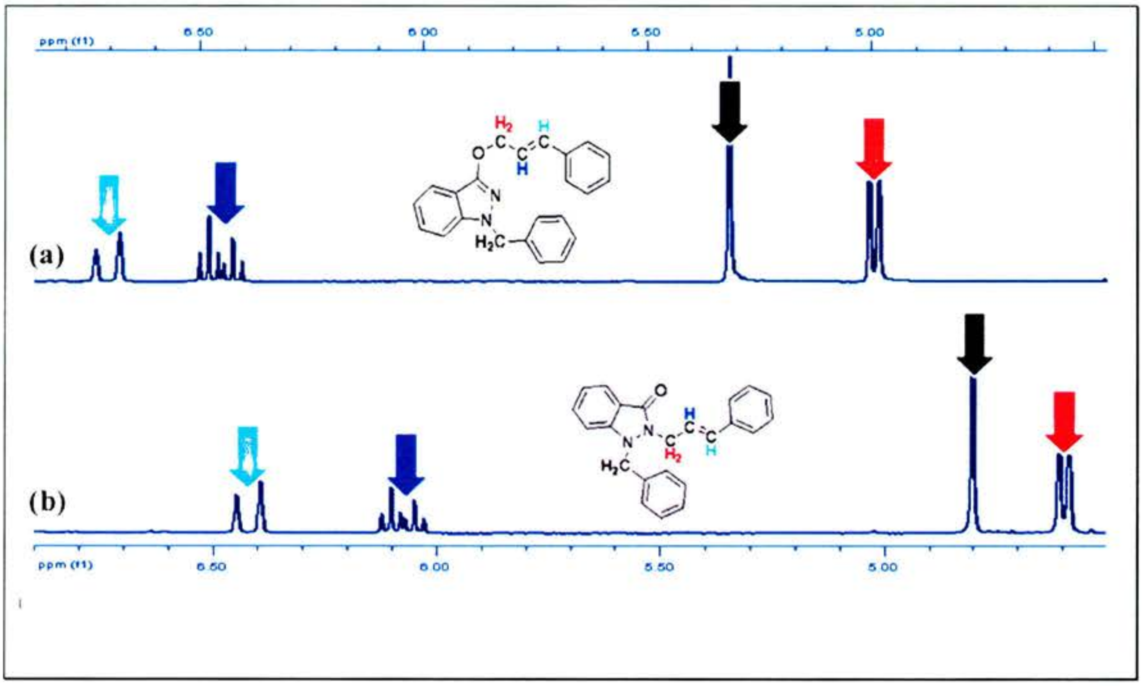


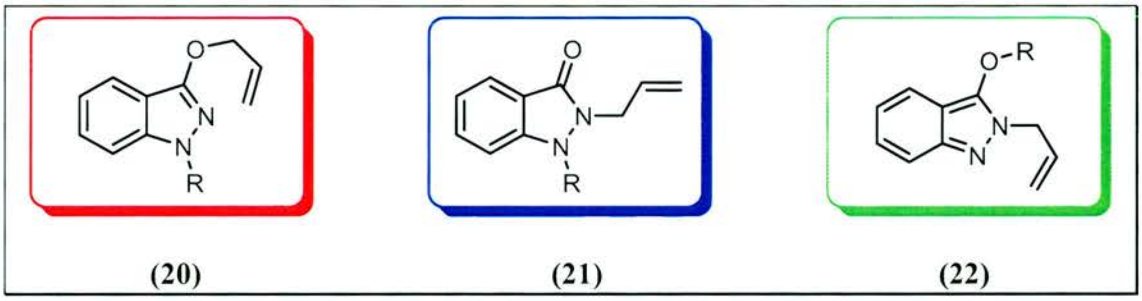
Figure 31: ^{1}H NMR (6.90-4.50 ppm) comparison of a) **165** and b) **167**, product from microwave rearrangement.

This difference indicates that the cinnamyl moiety of **165** has moved from the O-position to the N2-position via a [1',3] mechanism, yielding **167** as the only product of the reaction. TLC of the crude reaction mixture showed a single spot.

2.2.7. Reactivity of *N2*-allyl indazolinones

2.2.7.1. Overview

As described in Section 1.3.2, the main goal of this project was to develop a library blueprint based on the indazolinone core. Section 2.2.3 focused on methods of incorporating diversity at the N1 position to access structures of type **20** (page 72). The aza-Claisen rearrangement applied on **20** allowed us to generate structures of general type **21** (page 83). The ability to generate a third structural class of type **22** from **21** was the final step in our library design (Scheme 99).



Scheme 99: Generating structural diversity from indazolinone.

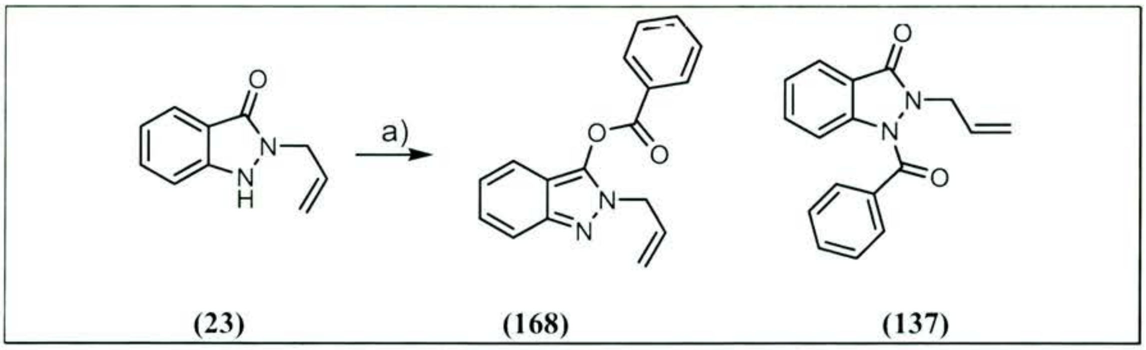
The aza-Claisen rearrangement transforms structures of type **20** into type **21**. Simple deprotection of **21**, when R group is a carbamate yields compound **23** (Scheme 100). To our knowledge, little has been reported about the reactivity of **23** or analogous structures. Indazolinone **23** can exist in two tautomeric forms (Scheme 59), however, all our experimental evidence suggests that **23** exists in the keto form as the major tautomer in both solution and in the solid state. X-ray crystallographic data indicates a C-O bond length of 1.2514(19) Å. This bond length is characteristic of a C=O bond corresponding to a carbonyl group (see Appendix). In solution, the ^{13}C NMR contains a signal assigned as C-3 at 162.0 ppm corresponding to a carbonyl carbon as expected for tautomer **23**.

2.2.7.2. Is diversity incorporation possible?

Due to the fact that little is known about the reactivity of compounds of type **23** with electrophiles [140], we decided to investigate this issue by reacting **23** with a series of electrophiles previously used in Section 2.2.3 (Table 4).

2.2.7.2.1. Reaction with benzoyl chloride

Benzoyl chloride was reacted with **23** (Scheme 100). The crude reaction mixture was analysed by TLC and showed two new spots that were really close to each other.

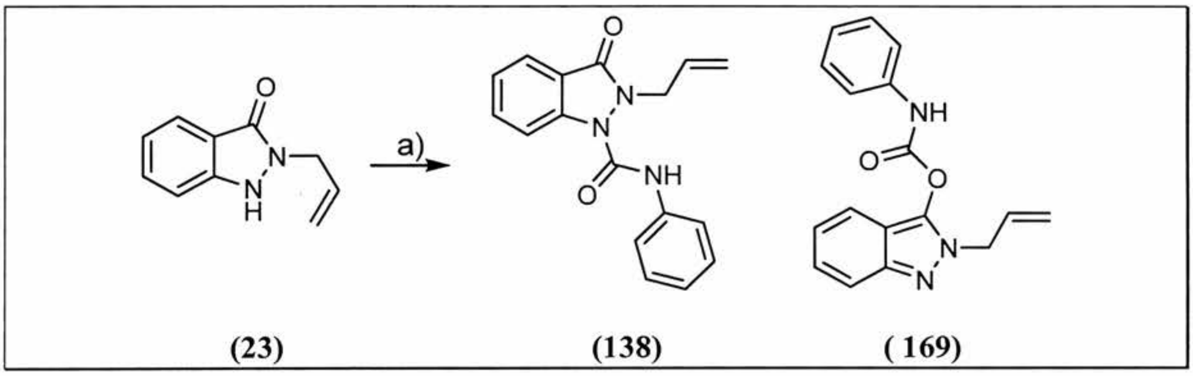


Scheme 100: Reaction of **23** with benzoyl chloride; a) PhCOCl, Et_3N, THF, rt.

^1H NMR analysis of the crude reaction mixture was studied in detail and compared with that for the previously prepared **137** (page 83). Integration of the allyl signals revealed the presence of a mixture of two products **168**:**137** in a ratio 1:1.5, indicating a non-selective functionalisation of the indazolinone core. The two isomers could not be separated by flash chromatography. This initial result persuaded us not to investigate further the use of acid chlorides because library generation on solid phase requires the development of efficient selective methods of generating pure compounds.

2.2.7.2.2. Reaction with phenyl isocyanate

Phenyl isocyanate was reacted with **23** in the presence of potassium *t*-butoxide in THF at room temperature.



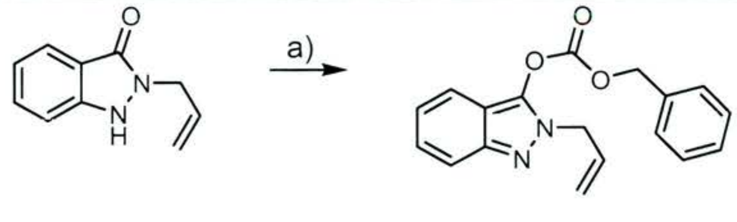
(23) **(138)** **(169)**

Scheme 101: Reaction of **23** with phenyl isocyanate; a) PhNCO, ^tBuOK, THF, rt, 0% i.e. no reaction.

No reaction was observed under these conditions, as judged by ^1H NMR and TLC of the crude reaction mixture. Only unreacted starting material was present.We believe the deprotonation of **23** occurred as the colour changed from colourless to yellow, however, after work up the ^1H NMR spectrum of the crude reaction mixture showed only signals corresponding to the unreacted starting material.

2.2.7.2.3. Reaction with benzyl chloroformate

23 was reacted with benzyl chloroformate in the presence of triethylamine in THF. Analysis of the crude reaction by TLC indicated the apparent formation of a single new compound. Analysis of the ^1H NMR spectrum of the crude reaction mixture showed a set of signals corresponding to a single allyl group.



(23) **(170)**

Scheme 102: Synthesis of **170** from **23**; a) Et_3N, PhOCOCl, THF, 97%.

Further analysis of the ^1H NMR spectrum confirmed that the product also contained the indazolinone core and a benzyloxycarbonyl group. Comparison with **113** (prepared as described in Scheme 61, page 67) showed that the two compounds were different as judged by ^1H NMR spectroscopy. The product was therefore assigned structure **170**. HSQC and HMBC data are consistent with this assignment.

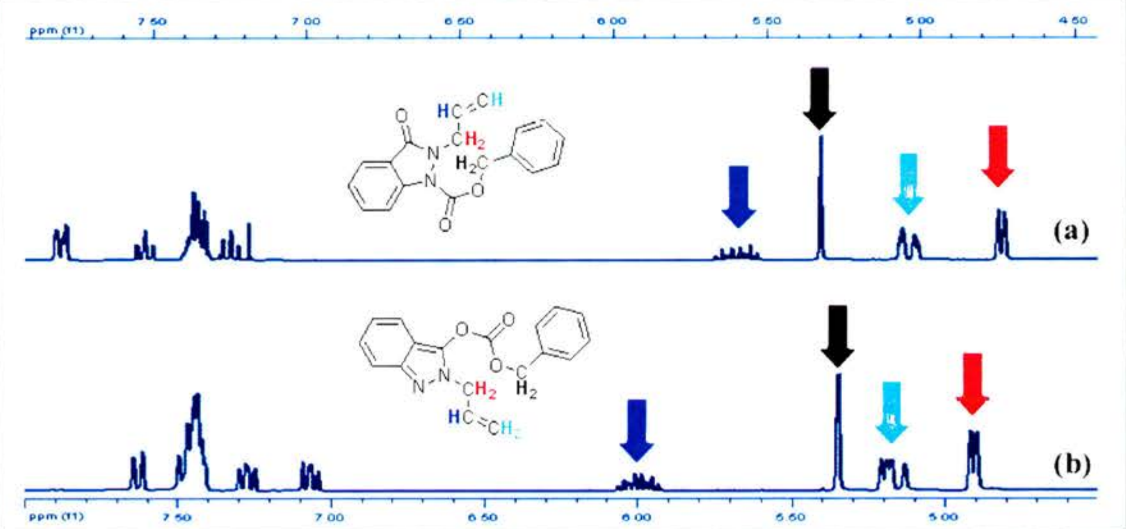
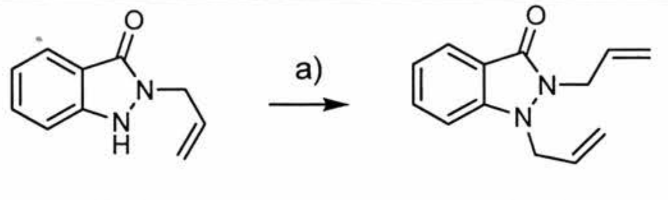


Figure 32: ^1H NMR (8.00-4.50 ppm) comparison of a) **113** and b) **170**.

Moreover, the ^{13}C NMR spectra led to the same conclusion, as the chemical shift of C-3 in the indazolinone ring in **113** is 164.7 ppm, corresponding to the carbon of the carbonyl (C=O) group whereas the C-3 of the indazole **170** appeared at 136.8 ppm.

2.2.7.2.4. Reaction with allyl and benzyl bromide

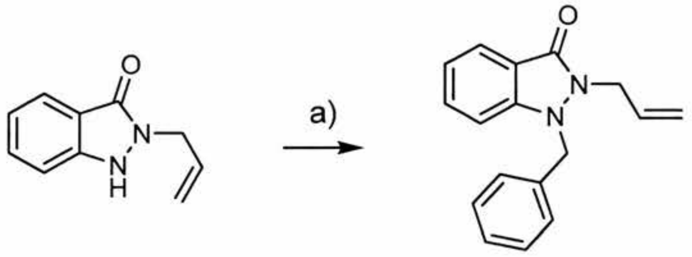
23 was reacted with allyl bromide in the presence of potassium *t*-butoxide and benzyl bromide in the presence of the same base (^tBuOK) with THF as the solvent in both cases. The analysis of the crude reactions by TLC revealed a single spot in both reactions.



(23) **(107)**

Scheme 103: Synthesis of **107** by allylation of **23**; a) allyl bromide, ^{t}BuOK, THF, 96%.

The ^{1}H NMR spectrum of the crude reaction mixture showed the presence of only two different allyl moieties, indicating that a single product was produced when **23** was reacting with allyl bromide. We had previously prepared diallyl substituted indazolinones **106** and **107** (section 2.2.2.1, page 65) and comparison with the analytical data for these compounds led to the conclusion that the *N1*, *N2*-diallyl substituted indazolinone **107** was formed in this reaction. The allylation therefore occurred exclusively on the N1 position (Scheme 103).



(23) **(135)**

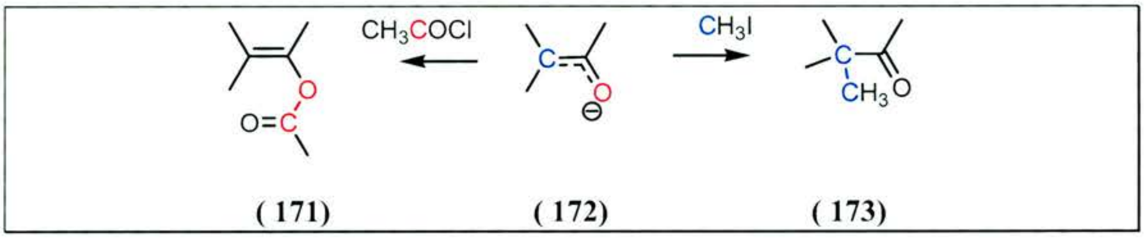
Scheme 104: Synthesis of **135** by benzylation of **23**; a) BnBr, ^{t}BuOK, THF, 99%.

The reaction involving benzyl bromide showed by ^{1}H NMR analysis the presence of a single allyl moiety and a unique singlet corresponding to the benzylic CH_2 protons. This result proved the presence of one isomer. The ^{1}H NMR spectrum of the newly formed product was then compared with that of a sample of **135** (^{1}H, HSQC, HMBC) that had previously been prepared as described in section 2.2.4.3.2 (page 83). The identical spectra led us to the conclusion that benzylation of **23** gives **135** in excellent yield through functionalisation of the N1 position (Scheme 104).

2.2.7.3. Conclusion

Different parameters, described below, govern nucleophilic attack of an electrophile by an ambident nucleophile. The concept of hard soft acid base (HSAB) allows chemists to rationalise the observed product ratio.[141-144]

Previous examples of the use of the concept of HSAB include the reported reaction of enolate **172** with two separate electrophiles to give two different products. As the oxygen atom is the more electronegative atom in the enolate, it bears the majority of the negative charge. It would therefore be easy to think that the oxygen atom would act as the nucleophile.



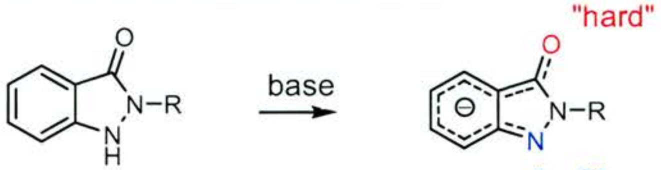
Scheme 105: Difference between hard and soft electrophile on an enolate.[142]

However, as illustrated in Scheme 105, the outcome of the reaction depends also on the electrophile. As methyl iodide is a "softer" reagent than acetyl chloride, the iodine atom will be displaced by the "softer" nucleophilic centre of the enolate, which is in this case the C-3 carbon atom. The product of this attack is **173**. The acetyl chloride is a "harder" electrophile and will therefore be attacked by the "harder" nucleophile of the enolate, the oxygen atom, to give **171**.

As the chemical reactivity results from the interplay of "charge control" and "orbital control", external parameters can influence this concept. Indeed, the leaving group of the electrophile, the use of a solvent which is capable of stabilising any developing charges and the base all have an important practical role in the HSAB concept.[141-144]

This general concept can be applied to the anion of indazolinone **23**. When structures of type **23** are deprotonated, the resulting anion is stabilised by the two heteroatoms, nitrogen at the N1 position and oxygen. The nucleophilic substitution can occur either by attack of the nitrogen or the oxygen on the electrophilic centre.

The oxygen atom can be considered as the "hard" center because of its greater electronegativity and the nitrogen atom as the "soft center" (Scheme 106). This is of importance as the results obtained previously can be explained by the HSAB concept.



(23)

Scheme 106: "Hard" and "soft" nucleophile centres in indazolinone after deprotonation.

Benzyl chloride and allyl bromide are classified as "soft" electrophiles because the carbon bearing the halogen atom is not highly polarised. The isolation of N1 functionalised products (Scheme 103 and Scheme 104) is in accordance with the attack of the "soft" donor, the N1 atom, onto the "soft" acceptor.

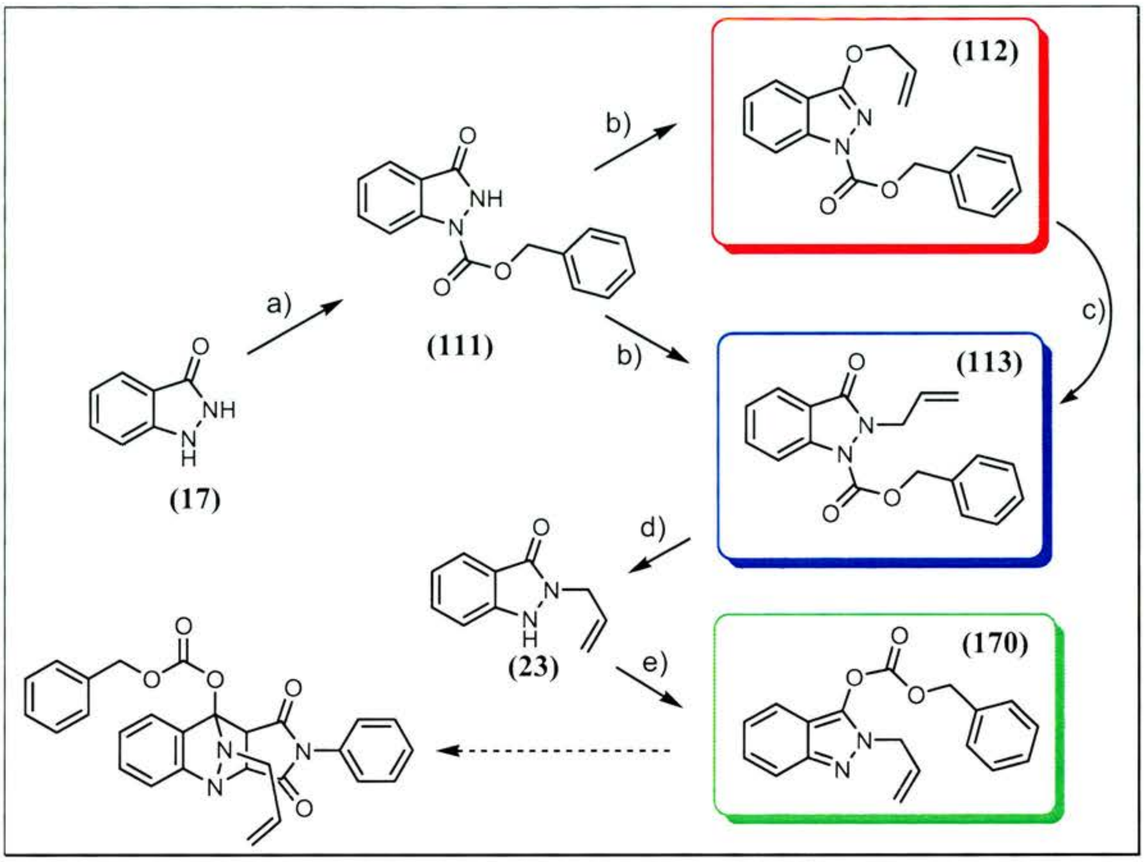
The isolation of **170** (page 108) when **23** was reacted with benzyl chloroformate is also in accordance with the HSAB concept. The carbonyl of the chloroformate is highly polarised because of the other groups attached to it (the two electron-withdrawing oxygen atoms make the carbon atom electron deficient). This carbon is therefore considered as a "hard" centre which reacts with "hard" nucleophiles. The indazolinone therefore reacts through the "hard" centre, the oxygen atom.

The hardness (softness) of the carbon in the case of benzoyl chloride is in between the two extremes discussed above and therefore leads to a mixture of products.

Investigating the reactivity of structures of type **23** led us to the conclusion that it is possible to access selectively compounds of general type **22** (Scheme 99, page 106) as described in the goals of the project. Indeed, benzyl chloroformate reacted specifically on the O position of **23** to give a unique product.

However, specific O-functionalisation only occurred with benzyl chloroformate. The isocyanate, acid chloride and alkyl halides tried did not react in the same manner. The carbonate moiety in **170** is unfortunately relatively labile and therefore functionalisation through the oxygen atom with chloroformates is not a useful route to incorporate into a library design.

Using methyl triflate in the presence of potassium hexamethyl disilylazide could have been a possibility to alkylate on the oxygen but this was not investigated due to time constraints.



Scheme 107: Overview of the synthesis of the three cores from the indazolinone.

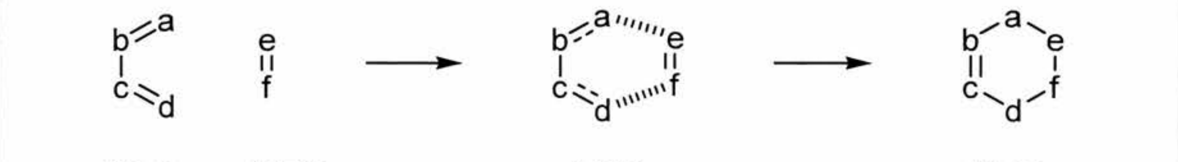
From a chemical perspective, however, we remained interested in structures of type **22**, as exemplified by **170**. One interesting feature of **170** (Scheme 102) was the presence of two dienes in the same molecule.

We proposed that this chemical feature could be relevant to our library design as shown in Scheme 107. We therefore decided to investigate the reactivity of **170** in the Diels-Alder reaction in solution. The reactivity of this diene was expected to occur through the azo-diene moiety considering that the product of the reaction would keep the aromaticity in the benzene ring to give **191** (Scheme 113) after reaction of one equivalent of diene with one equivalent of dienophile.

2.2.7.4. Attempted aza-Diels-Alder reactions of **170**

2.2.7.4.1. Overview

The Diels-Alder reaction is a pericyclic $[\pi_{4s}+\pi_{2s}]$ cycloaddition reaction involving a diene **174** (in the *s-cis* conformation) and a dienophile **175** (Scheme 108). The formation of two σ bonds and the disappearance of 2 π bonds in the **transition state (176)** results in a six-membered ring system **177** containing one unsaturated C=C bond, if the dienophile **175** is alkene-based, or two unsaturated C=C bonds when the dienophile **175** contains an alkyne moiety.



(174) **(175)** **(176)** **(177)**

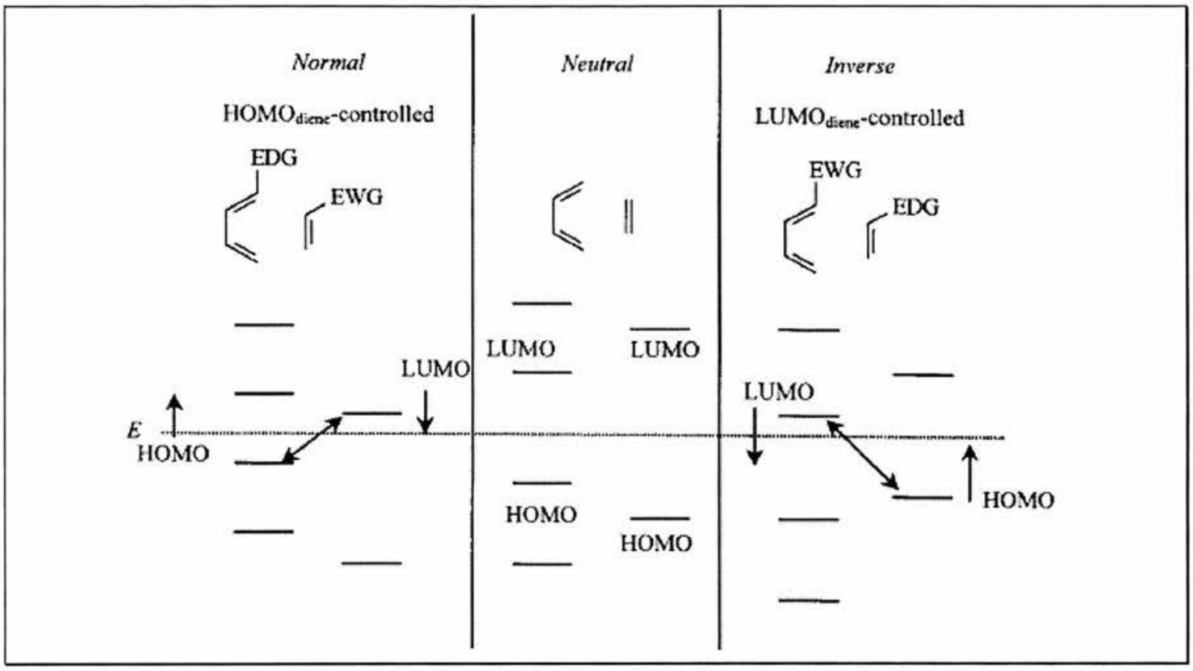
Scheme 108: Principle of Diels-Alder reaction.

In a real situation, substituents are present on the reaction partners and depending on the electronic properties of these substituents, Diels-Alder reactions can be classified into three main types: (I) Normal ($\text{HOMO}_{\text{diene}}$-controlled) and (III) inverse electron demand ($\text{LUMO}_{\text{diene}}$-controlled) compared to (II) neutral Diels-Alder reactions (Scheme 109).[145]

As shown in Scheme 109, a neutral Diels-Alder reaction occurs when the partners are not perturbed by electronic factors (very rare). The efficiency of the interaction of the two relevant molecular orbitals is increased if their energy separation is decreased.[146, 147]

The reaction can be activated by controlling the energy level of the HOMO of the diene. In the *normal* electron demand Diels-Alder reaction, activation of this HOMO by electron-donating substituents will tend to increase its energy and consequently, decrease the energy separation between the $\text{HOMO}_{\text{diene}}$ and $\text{LUMO}_{\text{dienophile}}$ molecular orbitals, while electron-withdrawing substituents on the dienophile will decrease the energy level of the $\text{LUMO}_{\text{dienophile}}$.

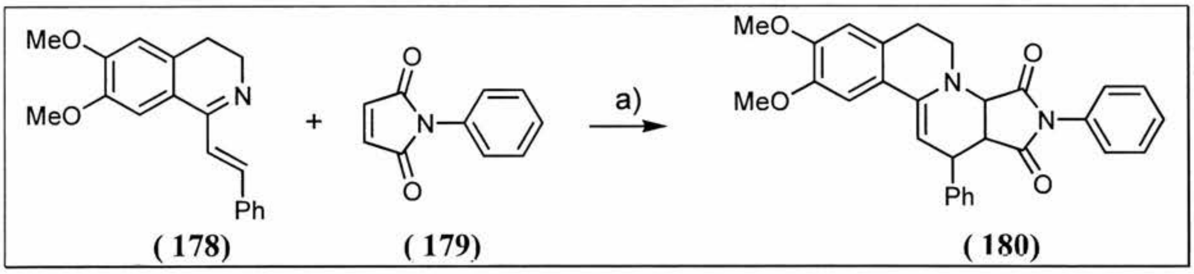
In the *inverse* electron demand Diels-Alder reaction, decreasing the energy separation between the molecular orbitals is helped by a decrease in energy of the $\text{LUMO}_{\text{diene}}$ and an increase in energy of the $\text{HOMO}_{\text{dienophile}}$ orbital. This is achieved by inserting electron-withdrawing substituents on the diene and electron-donating substituents on the dienophile.



Scheme 109: Diagram showing the three different types of Diels-Alder reactions.[146]

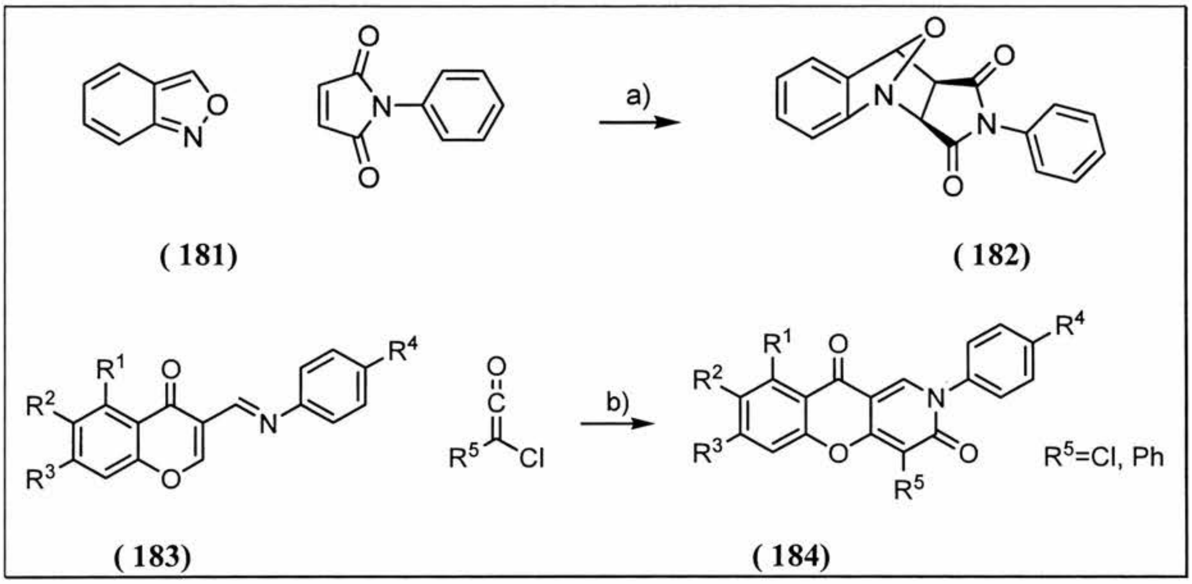
Indazolinone **170** contains an aza-diene system (Scheme 107). This section therefore focuses on a brief review of the aza-Diels-Alder reaction.[148]

Simple aza-dienes, due to their intrinsically **electron-deficient nature** favor participation in "inverse electron demand" LUMO$_{diene}$-controlled Diels-Alder reactions but by modifying the substituents on the diene and the dienophile, "normal" aza-Diels-Alder reactions can also be observed.[149] For example, the 1-azabutadiene system **178** was shown to react with an electron-deficient dienophile such as maleic anhydride **179** to give the corresponding six-membered ring product **180** (Scheme 110).



Scheme 110: Early reports of successful Diels-Alder reaction with 1-azadienes derivatives; a) neat, 125-130°C, 1 h.[148]

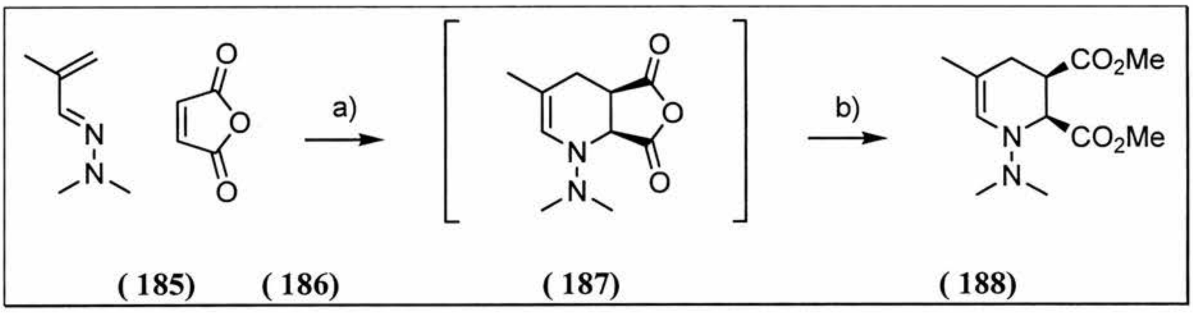
When the nitrogen atom is substituted with an electron-donating group, the diene behaves in the *normal* pattern and reacts as an electron rich diene (Scheme 109). Indeed, electron-rich dienes substituted with an oxygen at the C-4 position of the diene, similar to **170**, have been reported to react with *N*-phenylmaleimide (synthesis of **182**, Scheme 111) or dichloro/chlorophenyl ketene to give structures of type **184** (Scheme 111).



(181) **(182)** **(183)** **(184)**

Scheme 111: Diels-Alder reactions of aza-dienes; a) 125°C, neat , 17%, b) Et_3N, PhH, reflux, 21-85%.[150, 151]

170 can also be seen as containing an "internal" hydrazone as the N1 nitrogen is bonded to another nitrogen. This type of substrate, α,β-unsaturated hydrazones, has also been reported by L. Ghosez to undergo cycloaddition reactions with electron-deficient dienophiles such as maleic anhydride (Scheme 112).[152]



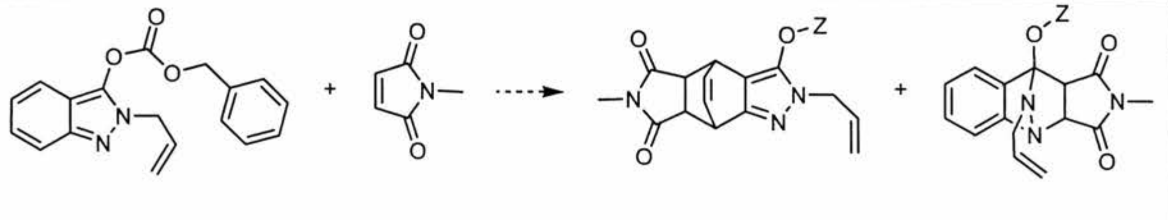
(185) **(186)** **(187)** **(188)**

Scheme 112: α,β-unsaturated hydrazones in aza-Diels-Alder reactions with electron deficient dienophiles ; a) DCM, 30 minutes, 20°C, b) MeOH, CH_2N_2, 56%.[152]

To our knowledge, Diels-Alder reactions on systems like **170** have not been reported. We therefore decided to attempt aza-Diels-Alder reactions using **170**.

2.2.7.4.2. Initial studies

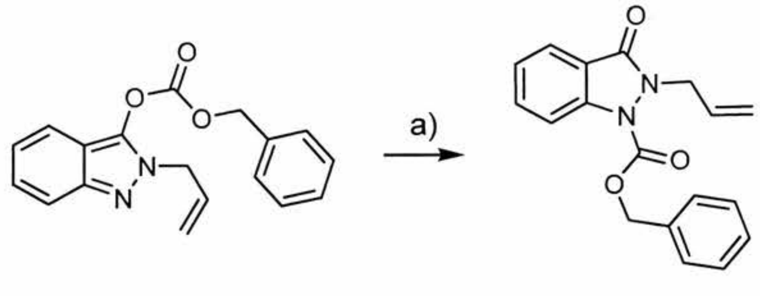
170 could react along two different pathways in the Diels-Alder reaction (Scheme 113) to give either **191** through the reaction with the aza-diene or **190** via the cyclohexadiene. The formation of **190** was considered unlikely as the formation of the fully aromatic benzene ring was considered a strong thermodynamic driving force for formation of **191**.



(170) **(189)** **(190)** **(191)**

Scheme 113: Possible Diels-Alder adducts by reacting **170** with N-methyl maleimide **189**.

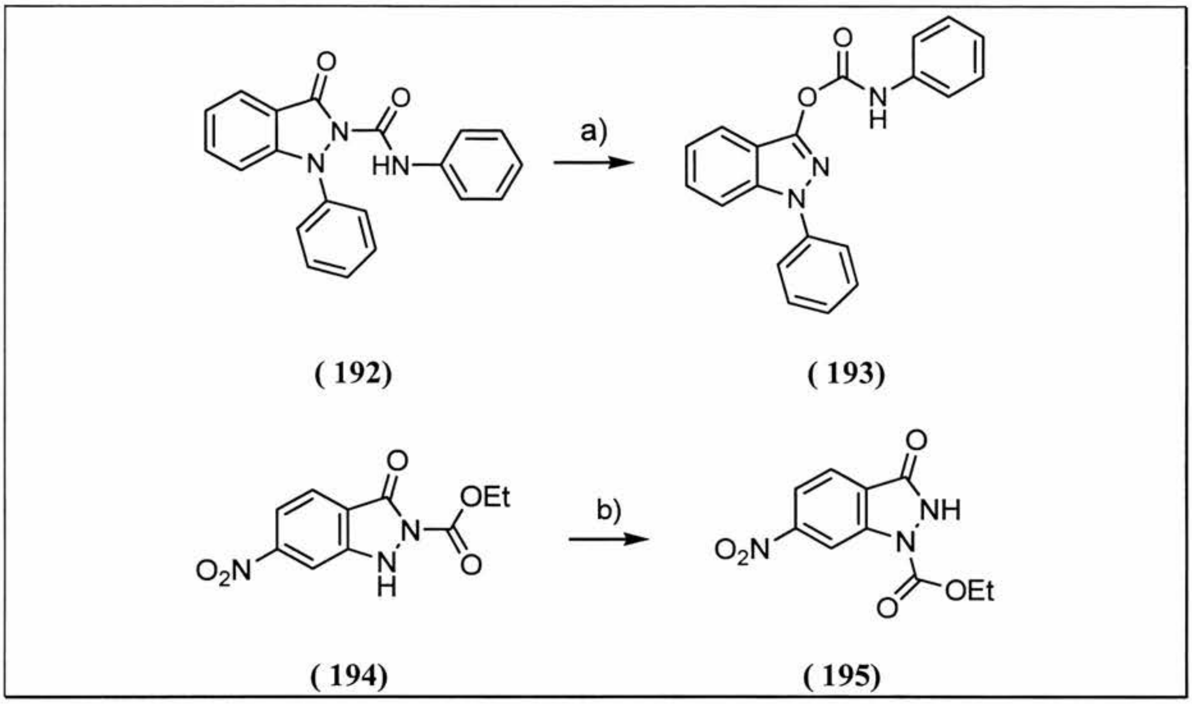
The reaction shown in Scheme 113 was tried under microwave irradiation (100°C, neat, 10 minutes). The reaction was stopped when TLC analysis indicated that there was no starting material present. None of the desired product was detected by ^{1}H NMR.



(170) **(113)**

Scheme 114: Rearrangement of **170** to **113**; a) *N*-methyl maleimide **189**, microwave, 10 minutes, 100°C, solvent free.

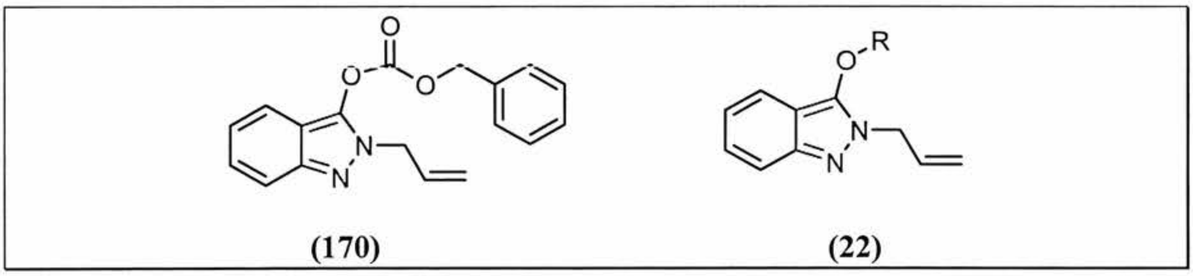
The isolated product was analysed and the structure assigned as **113** by comparison with authentic material prepared as described in Scheme 58. Under these conditions, the Z group rearranges from the oxygen to the N1 position presumably in an intermolecular process. Similar examples have also been described for rearrangement of a substituent from the N2 to the O-position (Scheme 115) [153] and from N2 to N1 position. In both cases the kinetic product was transformed to the thermodynamic product on heating.[83]



Scheme 115: Rearrangement of **192** to **193** and **194** to **195**; a) $CHCl_3$, 70°C, reflux, [153] b) 50-100°C.[83]

This result reinforces the fact that the original synthesis of **170** is under kinetic control and **113** is the thermodynamic product as described in the literature [83]. This hypothesis was validated by taking **170** and heating in the microwave at 100°C for 10 minutes in solvent free conditions. The purified product was found to be identical to **113** formed in the Diels-Alder reaction attempt. As the carbonate group in **170** is labile under thermal reaction conditions, carrying out the Diels-Alder reaction with **170** is not a viable strategy.

In order to study further the behaviour of indazolinone derivatives in the Diels-Alder reaction, a substrate of type **22** containing a non labile R group (alkyl) on the oxygen needed to be synthesised.



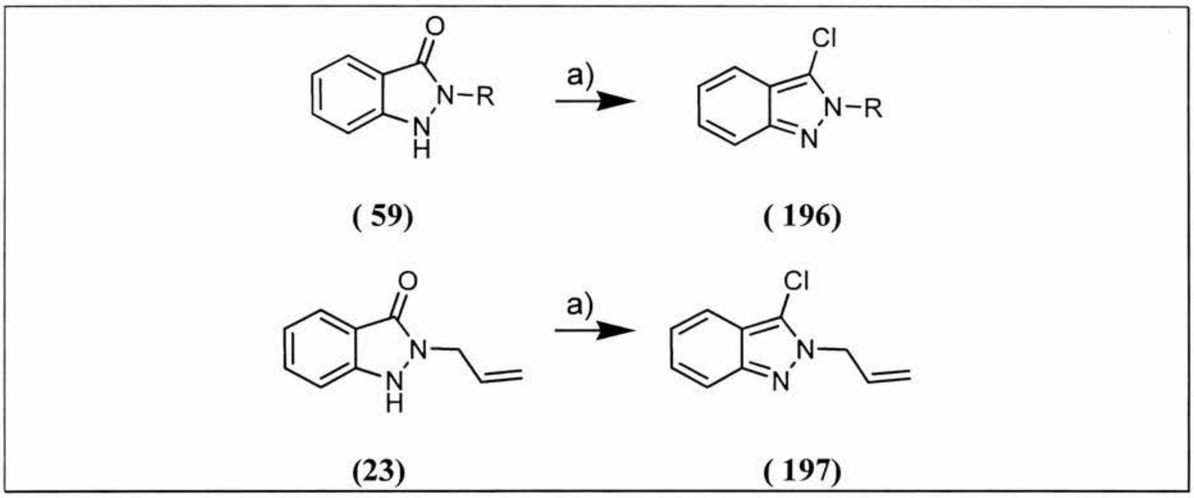
Scheme 116: Target compound for the Diels-Alder reaction.

As described in section 2.2.7.2 (page 106), functionalising the oxygen of **23** in a specific manner to obtain a stable compound proved to be difficult by direct alkylation.

We therefore decided to adopt an alternative approach to synthesise structures of type **22**.

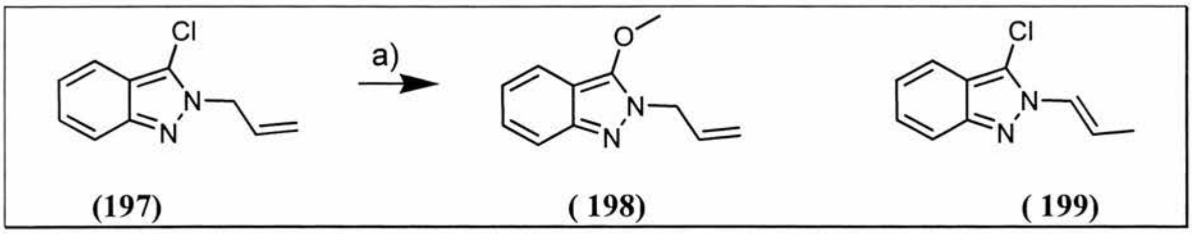
2.2.7.4.3. An alternative synthesis of substrates for Diels-Alder reaction

A previous literature report describes a procedure to transform *N2*-substituted indazolinones of type **59** to **196** in refluxing phosphorus oxychloride (Scheme 117).[154] The reaction was therefore performed on **23** and the desired product **197** was isolated by flash column chromatography (Scheme 117). **197** was isolated in 54% and assigned using mass spectroscopy (molecular weight increased by 18 (from 175 to 193), corresponding to the lost of OH (*m/z*: 17) and the gain of chlorine). A characteristic band at 1504 cm^{-1} in the infrared spectrum of **197** appeared corresponding to the C-Cl stretching frequency. The bands at 1628 cm^{-1} (C=O) and 3069 cm^{-1} (NH) in **23** were not present in **197**.



Scheme 117: Synthesis of **197** from **23**; a) $POCl_3$, reflux, o/n, 54%.[154]

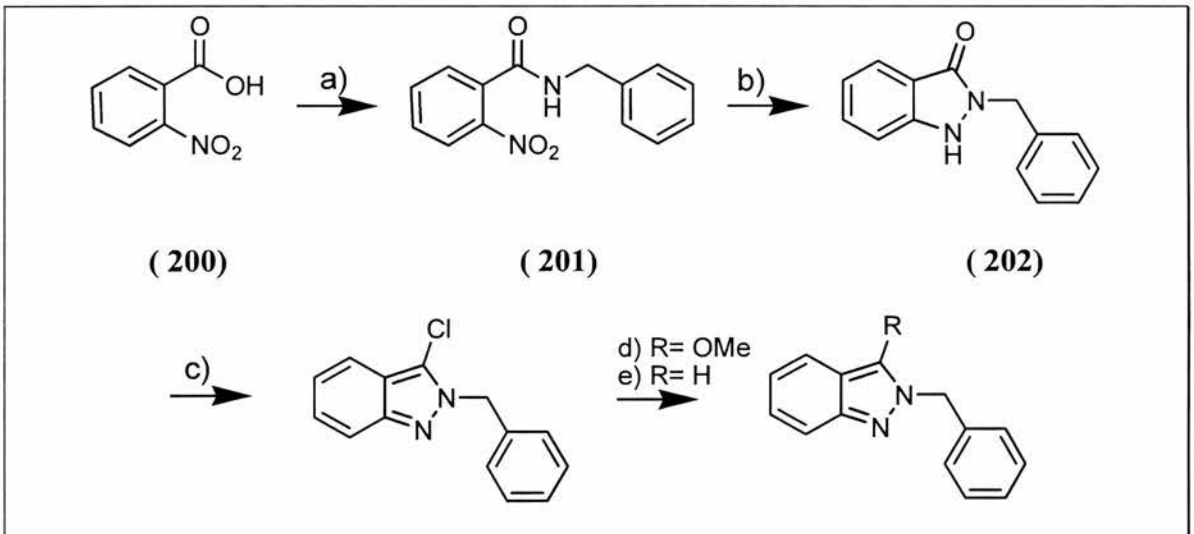
In the second step, **197** was treated with sodium methoxide. The displacement of the chlorine by a nucleophile is reported on systems of type **196** when R substituents are aromatic rings such as phenyl groups. **197** was treated with sodium methoxide in methanol under microwave heating for 10 minutes at 100°C. The ^{1}H NMR spectrum of the crude reaction mixture showed no starting material, but also no signals corresponding to the methoxy group in the expected material. We therefore concluded that the nucleophilic displacement of the chlorine atom by the methoxy group did not occur. Evidence to support isomerisation of the double bond in **197** to give **199** instead of **198** was found in the ^{1}H NMR spectrum of the crude reaction. This unexpected result has not been the subject of further investigation due to time constraints.



(197) **(198)** **(199)**

Scheme 118: Synthesis of **199** during attempts to prepare **198** from **197**; a) NaOMe, MeOH, microwaves, 100°C, 10 minutes, 100 psi, 95%.

Our interest in reacting an analogue of **170** containing a non-labile group on the oxygen in the Diels-Alder reaction next led us to a reaction sequence that had already been reported in the literature. The route involved conversion of nitrobenzoic acid **200** to the corresponding amide **201**, which was subsequently cyclised by the action of zinc under basic conditions in methanol to afford **202** (Scheme 119).[78] Aromatic (and aliphatic) nitro compounds can be reduced to amines in acidic conditions. However, aromatic nitro compounds are reduced with zinc in water under neutral conditions to give the corresponding hydroxylamine derivative [155]. This reaction therefore involves initial hydroxylamine formation followed by conversion to **202** by attack of the nitrogen of the amide (presumably aided by deprotonation of the amide by sodium hydroxide).



(200) **(201)** **(202)**

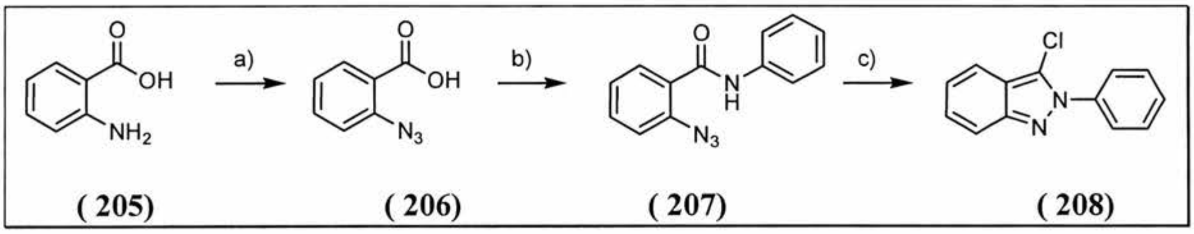
(203) **(204) R= H**

Scheme 119: Synthesis of **203** and **204**; a) $(COCl)_2$, DMF (cat.), DCM, 3 h, rt, then Et_3N and $PhCH_2NH_2$, o/n, rt, 99%, b) Zn, NaOH, MeOH, 71%,[78] c) $POCl_3$, reflux, o/n, 33%,[156, 157] d) MeONa, THF, 0%, e) Zn, AcOH, 78%.[157, 158]

202 was transformed to **203** using phosphorus oxychloride, according to the procedure described by Ardakani *et al.*. [156, 157] The transformation was successful as judged by the fact that the signals corresponding to the benzylic protons appeared as a singlet that was shifted from 5.06 ppm in **202** to 5.55 ppm in **203**.

Previous reports in the literature suggested that alkoxides cannot displace the chlorine in **203**.[157] However, we attempted the displacement with sodium methoxide anyway but replaced the conventional heating with microwave irradiation. Unfortunately, this did not give any of the desired compound **204**. Reduction of **203** using zinc metal in acetic acid under reflux yielded **204** in good yield [157, 158]. Comparing spectroscopic data for **204** with that reported in the literature confirmed that the product of this reaction was **204**, as expected. These two new compounds **203** and **204** were selected for further study.

In a second route, the starting anthranilic acid **205** was transformed to the corresponding azide compound **206**.[157] Spectroscopic evidence in support of **206** included the observation of a characteristic band for the azide functional group at 2101 cm^{-1} in the infrared spectrum [156]. Activation of the carboxylic acid **206** through formation of the acid chloride (not isolated) enabled the synthesis of **207** on reaction with aniline in dichloromethane. **207** was then cyclised in boiling thionyl chloride to give **208** in 91% yield (m.p. = 36-37°C; literature m.p. = 34°C).[156] The infrared spectrum of **208** also showed the disappearance of the band at 2127 cm^{-1}, characteristic of the azide functional group in **207**.

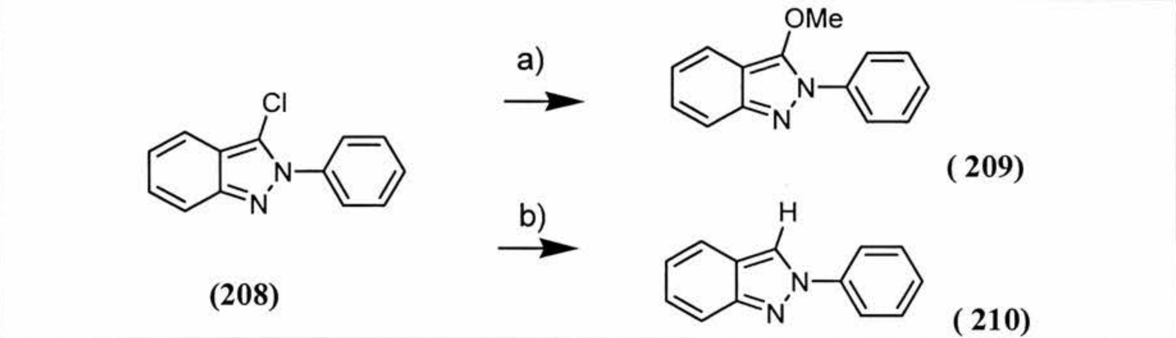


(205) **(206)** **(207)** **(208)**

Scheme 120: Synthesis of **208**; a) i) HCl, $NaNO_2$, ii) NaN_3, AcONa, 54%, b) i) $(COCl)_2$, DMF (cat.), DCM, 3 h, rt, ii) Et_3N, $PhNH_2$, 2 h, rt, 84%, c) $SOCl_2$, reflux, 2 h, 84% (lit. 91% [156]).

208 was then submitted to reaction with sodium methoxide (Scheme 121) to give **209** in 11% yield along with 81% of the starting material **208**. A singlet at 4.17 ppm in the ^1H NMR spectrum of **209** integrated for 3 protons and therefore provided evidence in support of the fact that a methoxy group had displaced the chlorine atom.

The reduction of **208** using zinc metal in acetic acid under reflux occurred according to literature procedures [78, 157] to give the desired product **210** in 76% [158] (Scheme 121). The mass spectral data showed a difference of 34 (35-1) between **210** and **208**, corresponding to the loss of chlorine (35) and the gain of a proton (1).



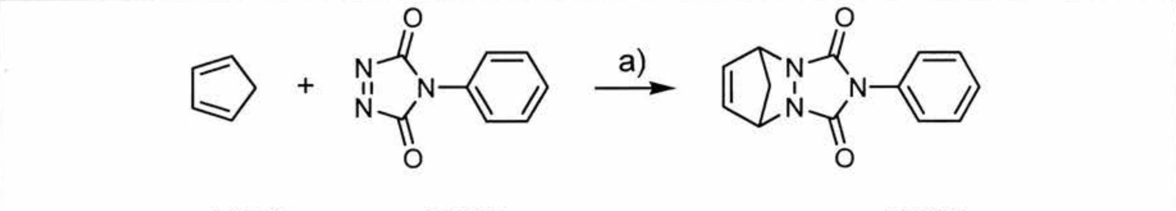
(208) **(209)** **(210)**

Scheme 121: Synthesis of **209** and **210**; a) NaOMe, MeOH, 11%,[157] b) Zn, AcOH, reflux, 76% [157, 158].

Substrates **203**, **204**, **208**, **209** and **210** were selected for studies on the reactivity of the indazole/indazolinone core in the presence of a dienophile (the Diels-Alder reaction).

2.2.7.4.4. Attempt to carry out a Diels-Alder reaction:

To increase the chances of performing the Diels-Alder reaction successfully, we decided to use 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) **212**. PTAD **212** is known to be a highly reactive dienophile.[159] This class of reagent is more reactive than common dienophiles such as maleic anhydride, *N*-phenylmaleimide, diethylazodicarboxylate and dimethyl acetylenedicarboxylate. For example, **212** reacts rapidly with cyclopentadiene **211** without a catalyst at -78°C (Scheme 122).[160] Other examples have been reported in the literature.[161]



(211) **(212)** **(213)**

Scheme 122: Reaction of cyclopentadiene **211** with PTAD **212**; a) acetone, -78°C.[160]

In initial studies, the different substrates **203**, **204**, **208**, **209** and **210** were submitted to the Diels-Alder reaction in the presence of **212**. The results of the reactions are presented in Table 8.

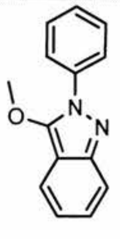
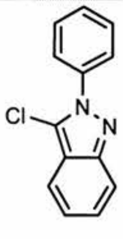
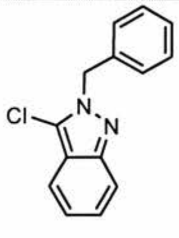
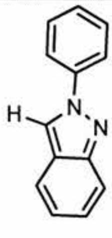
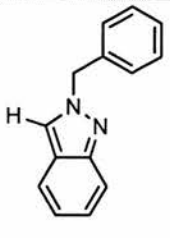
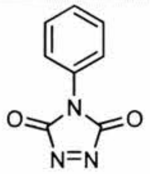
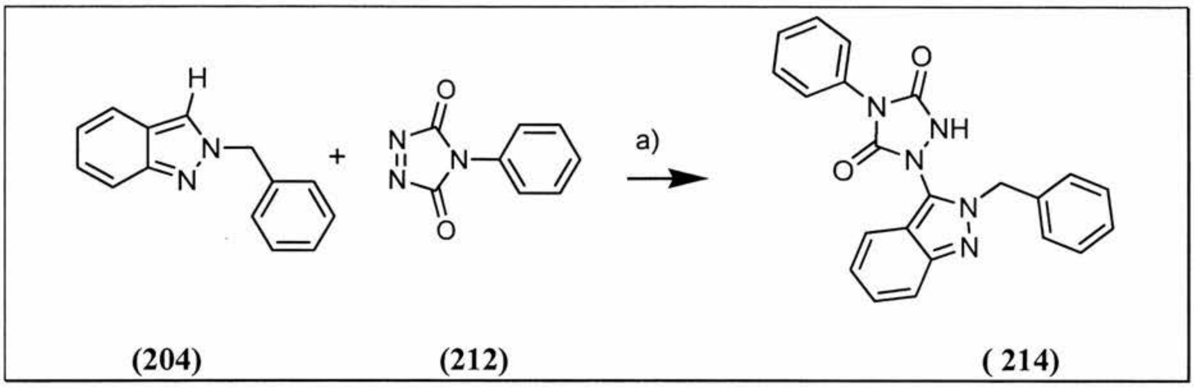
	 **(209)**	 **(208)**	 **(203)**	 **(210)**	 **(204)**
 **(212)**	No reaction	No reaction	No reaction	No starting material present	No starting material present

Table 8: Summary of the outcome of the Diels-Alder reaction with **212**.

As presented in Table 8, at room temperature, the indazolinone **209** did not react with dienophile **212**. This reaction was refluxed in chloroform for four hours under an inert atmosphere but the bright red colour of the dienophile did not fade. TLC and ^{1}H NMR analysis of the crude reaction showed only the presence of unreacted starting materials. The same observations were made with the 2-phenyl-3-chloro-2*H*-indazole **208** and 2-benzyl-3-chloro-2*H*-indazole **203** under analogous reaction conditions.

However, **204** and **210** did react with **212** in refluxing chloroform. In both cases, the bright red colour of the dienophile faded to give a colourless solution, indicating the consumption of **212**.

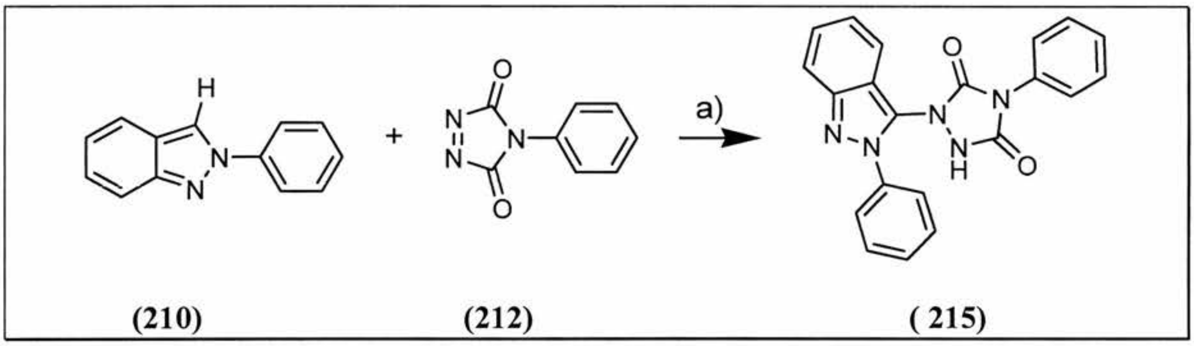
The crude mixture obtained on reaction of **204** with **212** was purified by flash column chromatography and a single product was isolated. Mass spectroscopic analysis of the product in chemical ionisation mode showed a *m/z* ratio of 384 in positive mode, corresponding to an adduct of **204**:**212** in the ratio 1:1. In the infrared spectrum of the product, a broad signal at 3494 cm^{-1} characteristic of an NH group and a strong signal at 1726 cm^{-1} characteristic of a carbonyl group were observed. Moreover, in the ^{1}H NMR spectrum, signals corresponding to a benzylic CH_2 were shifted from 5.52 ppm in the starting material **204** to 5.49 ppm in the product suggesting relatively little change in the core structure. Based on these and other pieces of spectroscopic evidence, the product of this reaction was assigned as **214** (Scheme 123).



(204) **(212)** **(214)**

Scheme 123: Synthesis of **214** by reaction of **204** with **212**; a) 70°C, $CHCl_3$, 6 h, 82%.

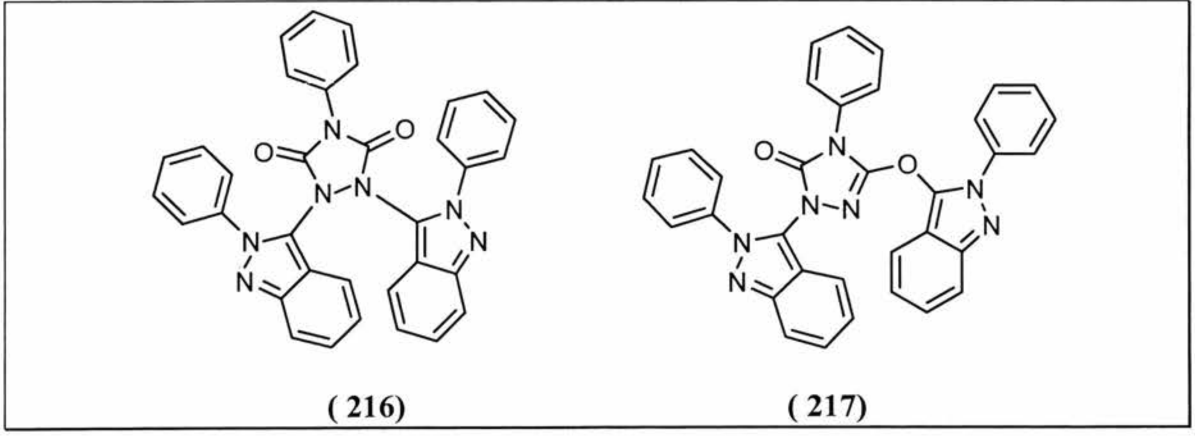
As described in Table 8, the reaction between **210** and **212** also showed the consumption of the starting material (TLC indicated that the starting materials were both absent from the reaction mixture).



(210) **(212)** **(215)**

Scheme 124: Synthesis of **215** by reaction of **210** on **212**; a) 70°C, $CHCl_3$, 6 h, 75%.

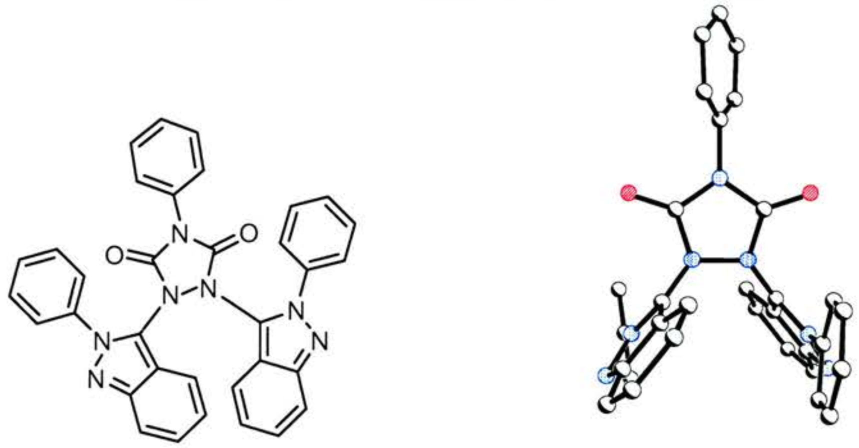
The product **215** of the reaction between **210** and **212** was isolated in 75% yield (Scheme 124). Mass spectroscopic analysis of **215** was consistent with a 1:1 ratio of **210** and **212** (*m/z*: 368 in negative electrospray mode). A broad band in the infrared spectrum at 3468 cm^{-1} characteristic of the presence of the NH bond and a strong signal at 1725 cm^{-1} characteristic of a carbonyl group were both observed for **215**.



(216) **(217)**

Scheme 125: Possible side-products from the reaction between **212** and **210**.

However, a side product was also obtained and isolated in 5% yield. The ^{1}H NMR spectrum shows only aromatic protons and the infrared spectrum is similar to the main product **215**, except for the absence of a signal corresponding to NH. According to the mass spectroscopic analysis (*m/z*: 584 in positive mode), this side product could correspond to the sodium adduct of a molecule containing a ratio 1:2 of **212**: **210**. Two possible structures **216** and **217** could be assigned to the isolated product (Scheme 125). X-ray crystallographic analysis solved the assignment problem showing that the structure was in fact **216** (Scheme 126).

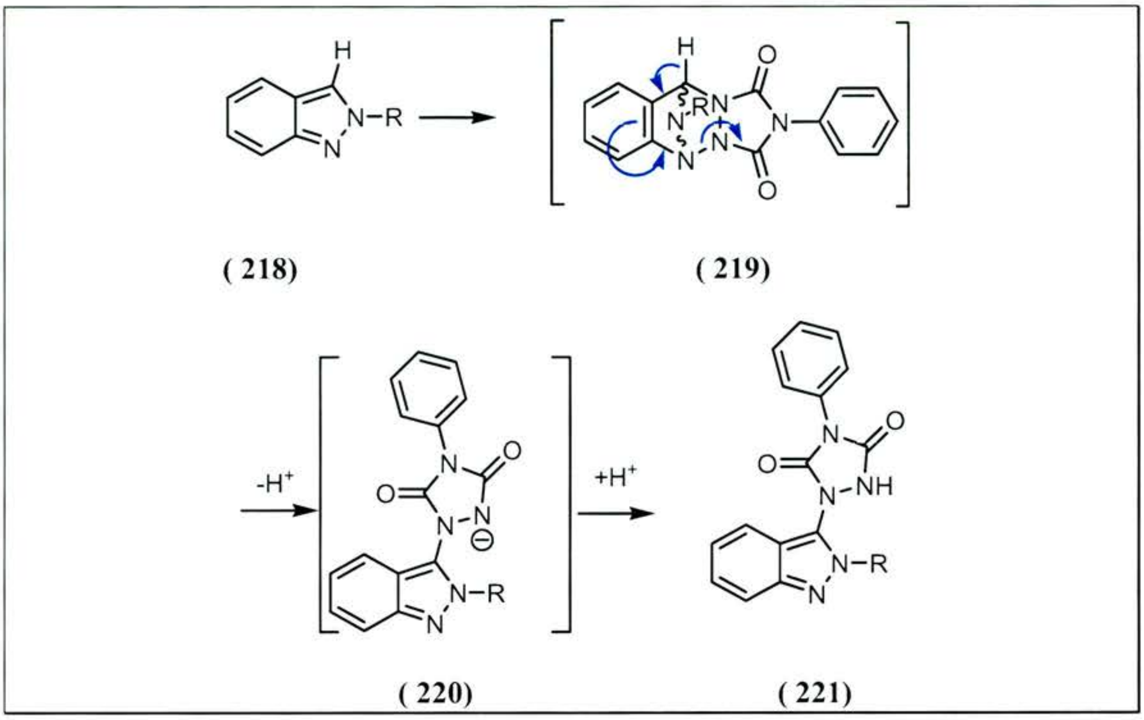


(216)

Scheme 126: Structure of **216** confirmed by X-ray analysis.

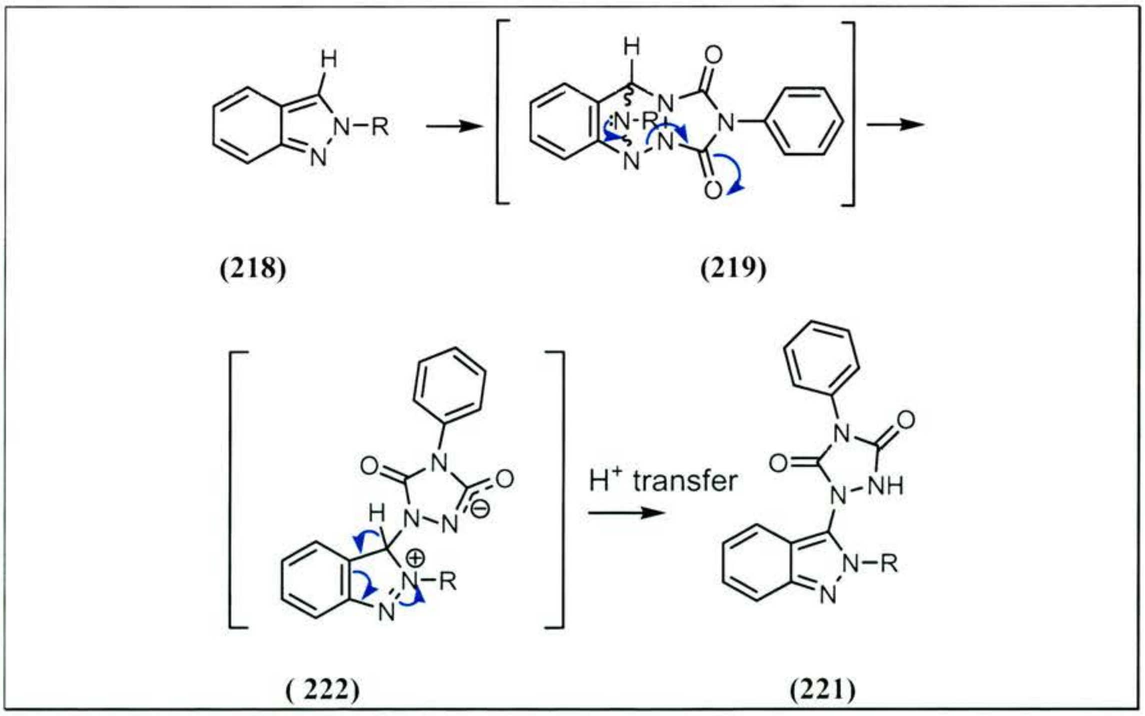
2.2.7.4.5. Mechanistic considerations:

The formation of products **214** and **215** could have occurred via a Diels-Alder mechanism. If the first step of the reaction is a Diels-Alder reaction, the general intermediate **219** can be drawn as the result of the [4+2] cycloaddition. Subsequent cleavage of one of the N-N bonds in **219** would lead to **221** by either of the two mechanisms shown in Scheme 127 and Scheme 128.



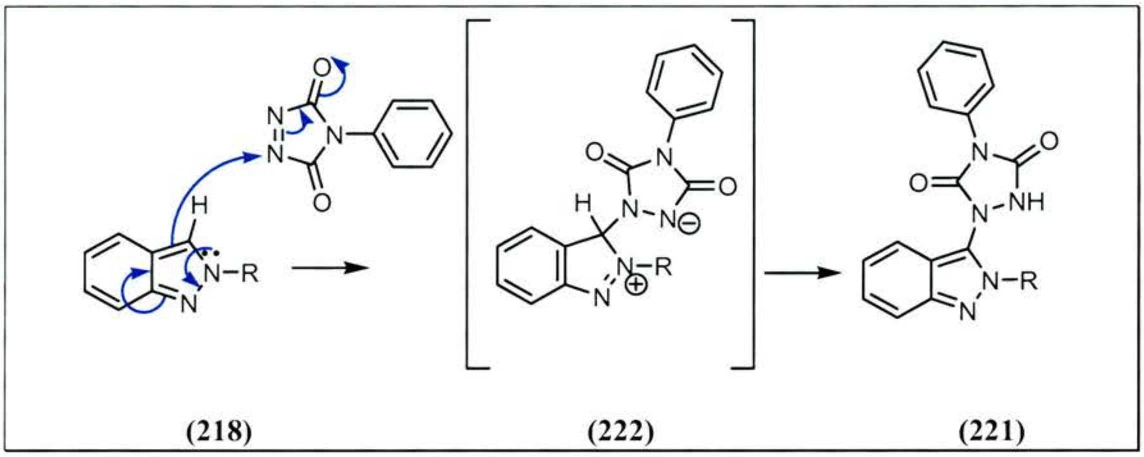
Scheme 127: Possible mechanism explaining the formation of structure of type **221** by proton transfer.

Our current view is that the mechanism shown in Scheme 127 is more likely based on stereoelectronic arguments.



Scheme 128: Possible mechanism for the formation of **221** with participation of the lone pair of the bridged nitrogen inducing ring fragmentation (R= Ph or Bn).

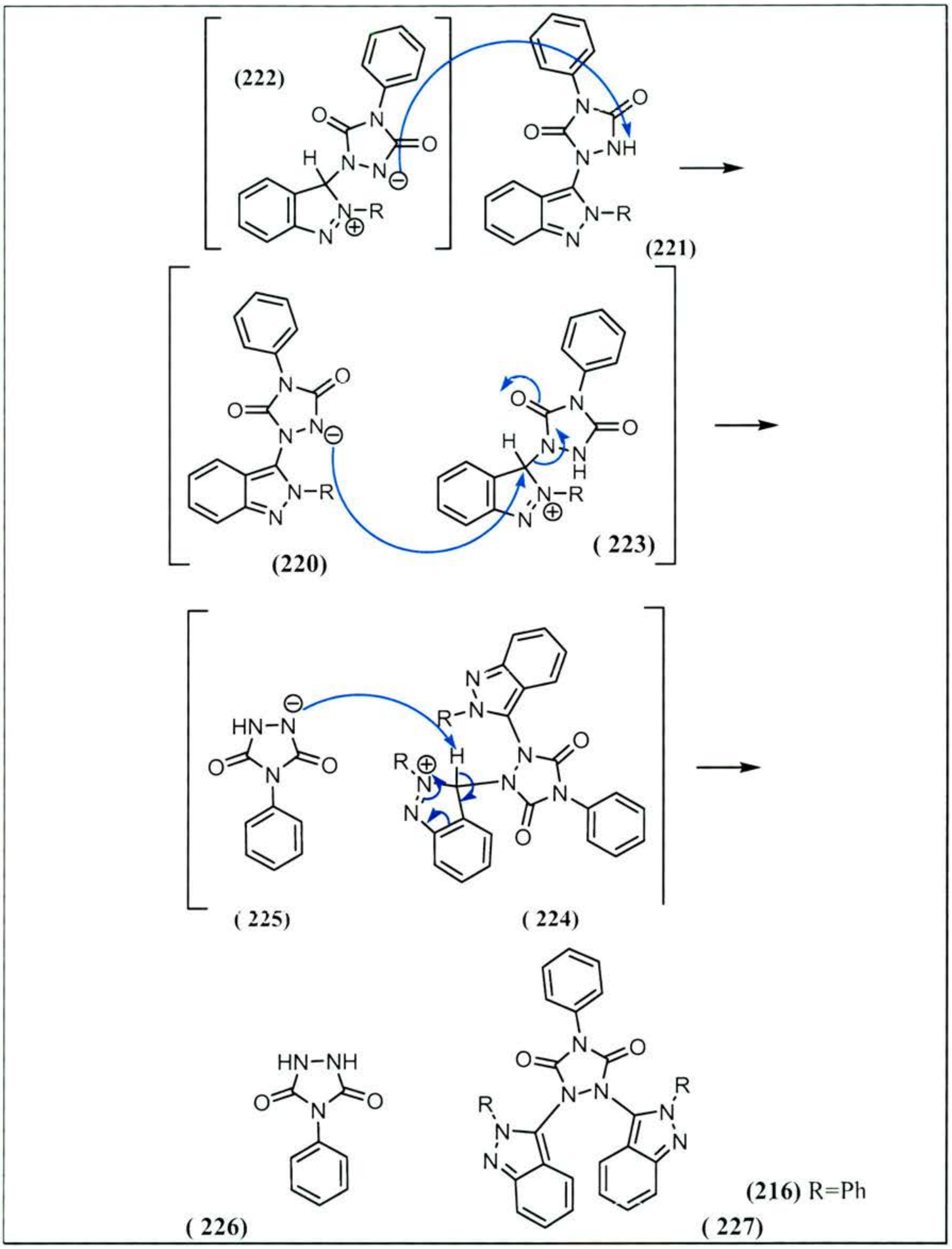
However, another (perhaps more likely) option for explaining the formation of the two new compounds **214** and **215** (Scheme 123 and Scheme 124) is nucleophilic attack involving the lone pair on the N2 nitrogen of the indazole core **218** (Scheme 128). The initially formed adduct of type **222** could then undergo a proton transfer to give the structure **222** (Scheme 129).



(218) **(222)** **(221)**

Scheme 129: Alternative mechanism for the formation of **214** and **215** (R=Ph or Bn respectively).

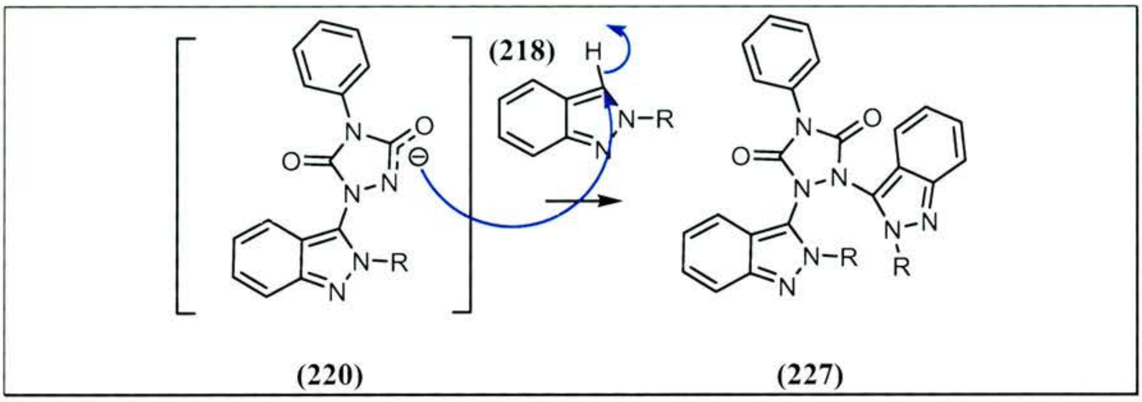
This mechanism is quite appealing because it involves the formation of an intermediate of type **222**. The intermediate **222** can also be invoked as an intermediate en route to the side product **216** of type **227** as shown in Scheme 130.



Scheme 130: Possible mechanism for the formation of **227**.

One possible explanation as to why the product **216** is observed but an analogous product from the reaction of **210** is not is that the intermediate **222** is sufficiently long lived due to the increased stability arising from extended conjugation in **222** (R=Ph) to enable a competing reaction (Scheme 130).

An alternative mechanism for formation of **227** is shown in Scheme 131. This mechanism seems unlikely due to the requirement for hydride (H^-) to act as a leaving group (Scheme 131).



Scheme 131: A possible mechanism for formation of **227** involving hydride as a leaving group.

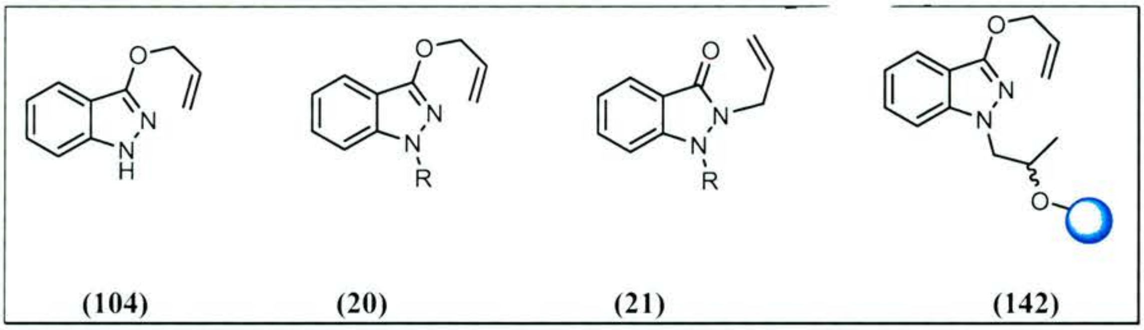
2.2.8. Conclusions

From the studies presented in this section, we are able to draw the following conclusions.

1) A synthetic route to 3-allyloxyindazole **104** in a good yield was established (Scheme 60).

2) **104** was shown to react exclusively at the N1 position, whatever the electrophilic character of the reagent (soft or hard).

3) In the analogous system of type **20**, conditions to carry out a aza-Claisen rearrangement were investigated (Scheme 69, page 73). This was attempted under conventional thermal and microwave approaches and in the presence of a catalyst in solution phase. In addition, the Claisen rearrangement of **142** was achieved on solid phase under palladium catalysis.



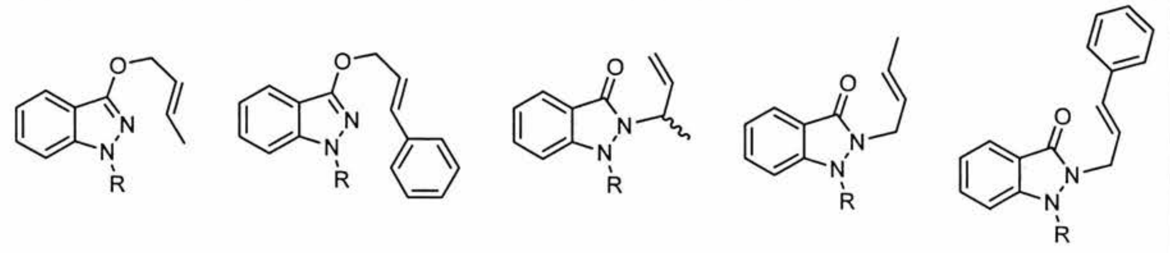
Scheme 132: Summary structures.

The rearrangement did not work under standard thermal conditions. The required energy delivered through this technique was presumably not sufficient to induce rearrangement prior to degradation. However, the microwave irradiation proved to be an excellent alternative. 10 minutes at 200°C in DMF resulted in complete conversion of compounds of type **20** to the corresponding N-isomer **21**, provided that the *N1* position was substituted by a non labile group, i.e. benzyl group. Transition metal catalysed rearrangement was also very efficient and supported results in the literature for aza-Claisen rearrangements in unrelated core structures [135]. In addition, when applied on the solid phase, the palladium (0)-catalysed rearrangement was successful in inducing the desired sigmatropic rearrangement (page 81).

4) The results described in 3) are also very interesting from a mechanistic prespective. Depending on the method and the terminal substituent of the allyl group, different mechanisms are observed. Indeed, as the literature described from an unrelated core [162], microwave irradiation induces a [3 ;3] mechanism. This is confirmed in our experiment by the use of a crotyl moiety, where we obtained a racemic product which is readily assigned using ^{1}H NMR (ABX system). However, a [1 ;3] mechanism is observed with the cinnamyl moiety (**159**, **165**, Scheme 133). A possible explanation for this result presumably involves a steric interaction that does not allow the phenyl ring α to the N2 position but also electronic factors might be involved in the stabilisation of the π-allyl cation.

Under palladium catalysis, the use of palladium (0) is required for bulky groups such as the cinnamyl group and induces a [1 ;3] mechanism. The palladium (0) method is less useful for less bulky substituents such as crotyl moiety where a mixture of compounds resulting from [1 ;3] and [3 ;3] rearrangement were formed.

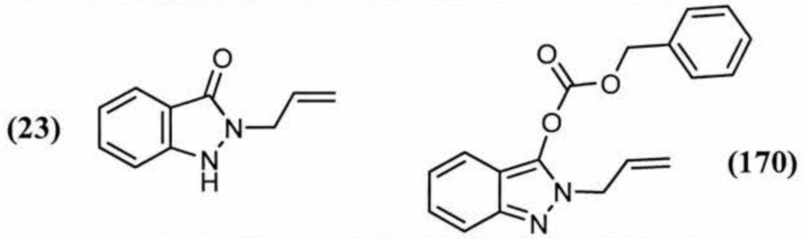
In contrast, the use of a palladium (II) catalyst led to highly selective reaction when the crotyl group was present (**157**), inducing a [3 ;3] rearrangement. However, no rearrangement of the cinnamyl group (**159**) was observed. This can be rationalised by the fact that addition of the metal to a sterically hindered alkene is difficult, stopping the reaction before it has begun.



Scheme 133: Summary structures.

5) The reactivity of *N2*-allyl indazolinones of type **23** (**21** when R=H) was also studied with different electrophiles and the results were rationalised based on the HSAB (hard soft acid base) concept. "Soft" electrophiles reacted at the soft centre of the indazolinone, the nitrogen position; hard electrophones at the hard centre, the oxygen.

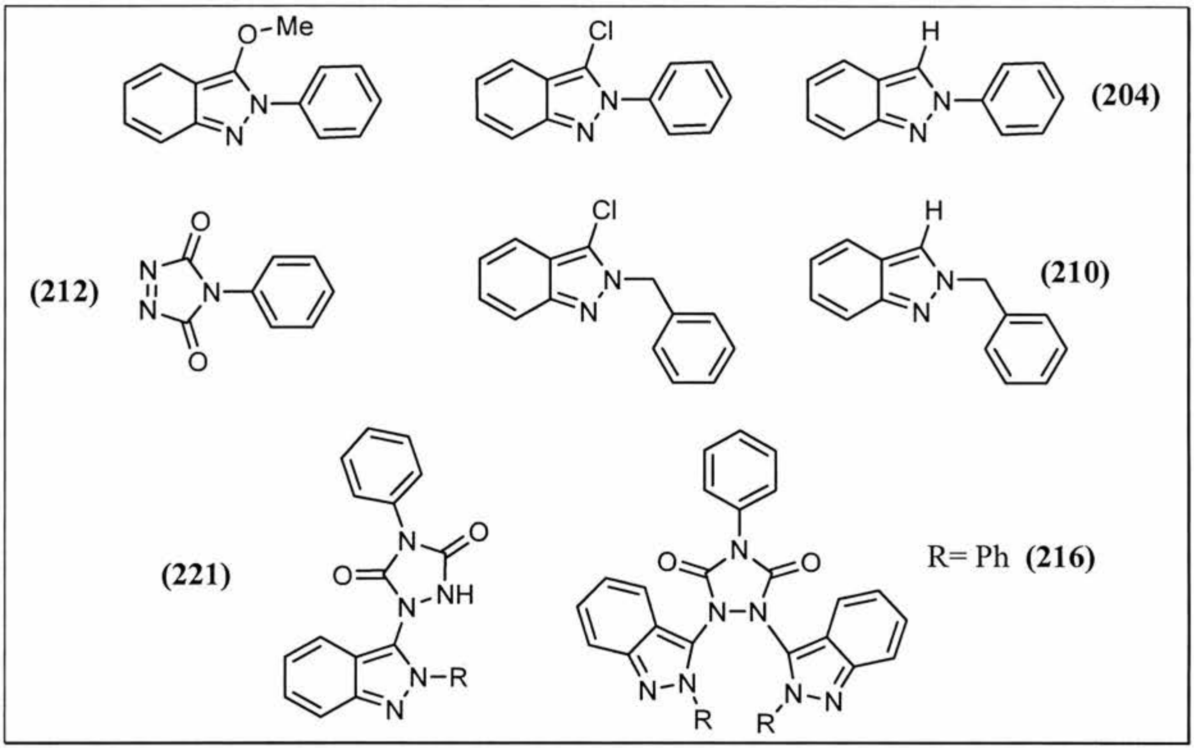
We proved by reacting benzyl chloroformate with **23** that a single product **170** was obtained. This product was shown to be the kinetic product of this reaction since rearrangement of the Z group from the O position to the N1 position was induced thermally. Identifying a method of preparing exclusively O, N2-substituted indazolinone was one of the key goals of the project as it would enable us to access all the three isomers in the library. However, due to the instability of carbonates of this type under assay conditions, the use of chloroformate reagents does not represent an attractive building block for the creation of the library.[163, 164]



Scheme 134: Summary structures.

6) Analogues were synthesised in which the O to N1 shift was not possible. Structures of type **22** (Scheme 116) were prepared and when R=methyl proved not to react under standard Diels-Alder reaction. When the C-3 of the indazole was substituted with a chlorine, no reaction was observed under standard Diels-Alder conditions. However, when the chlorine was reduced to give **204** and **210**, reaction with **212** gave the adduct of type **221** as the main product. The formation of this product can be explained by a possible Diels-Alder mechanism (Scheme 128) although an alternative

mechanism seems more likely. The formation of **216** supports this alternative mechanism (Scheme 130).



Scheme 135: Summary structures.

2.3. The Library Design

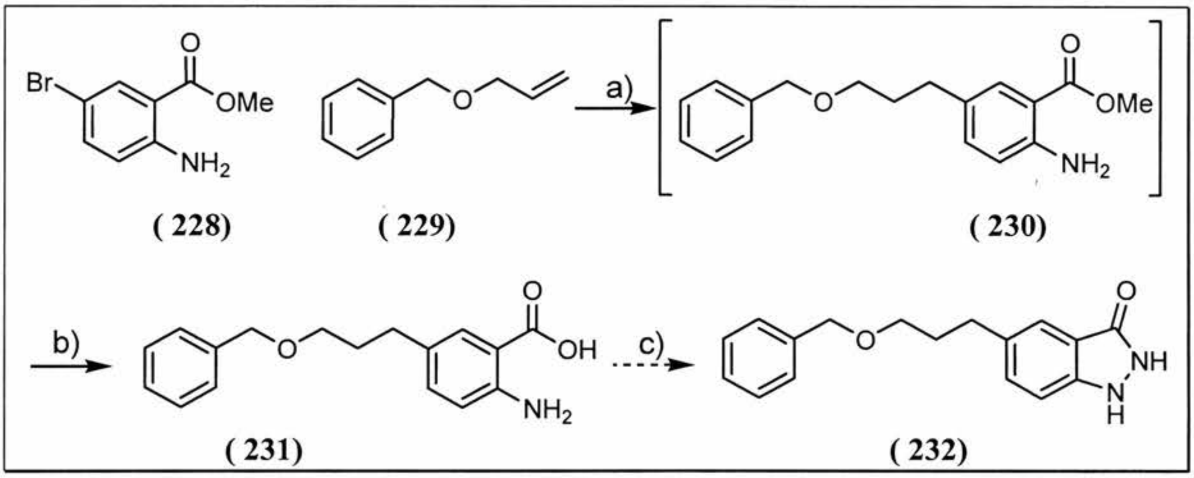
2.3.1. Synthesis of the Library Core Structure

2.3.1.1. Overview

In order to develop the solid phase route, a target molecule that could be loaded onto a resin needed to be synthesised. This molecule must contain, as previously described, the indazolinone core and a functional group that is compatible with the selected linker methodology. The mode of attachment to the resin must be orthogonal to the heteroatoms already present in the indazolinone core and must contain an alcohol functionality to load the oxygen on to the resin through formation of a Si-O linkage. The following section will focus on the synthetic path we developed to access a compound of this type. Alternative and less successful approaches for reaching the same type of target are also briefly described later in this section.

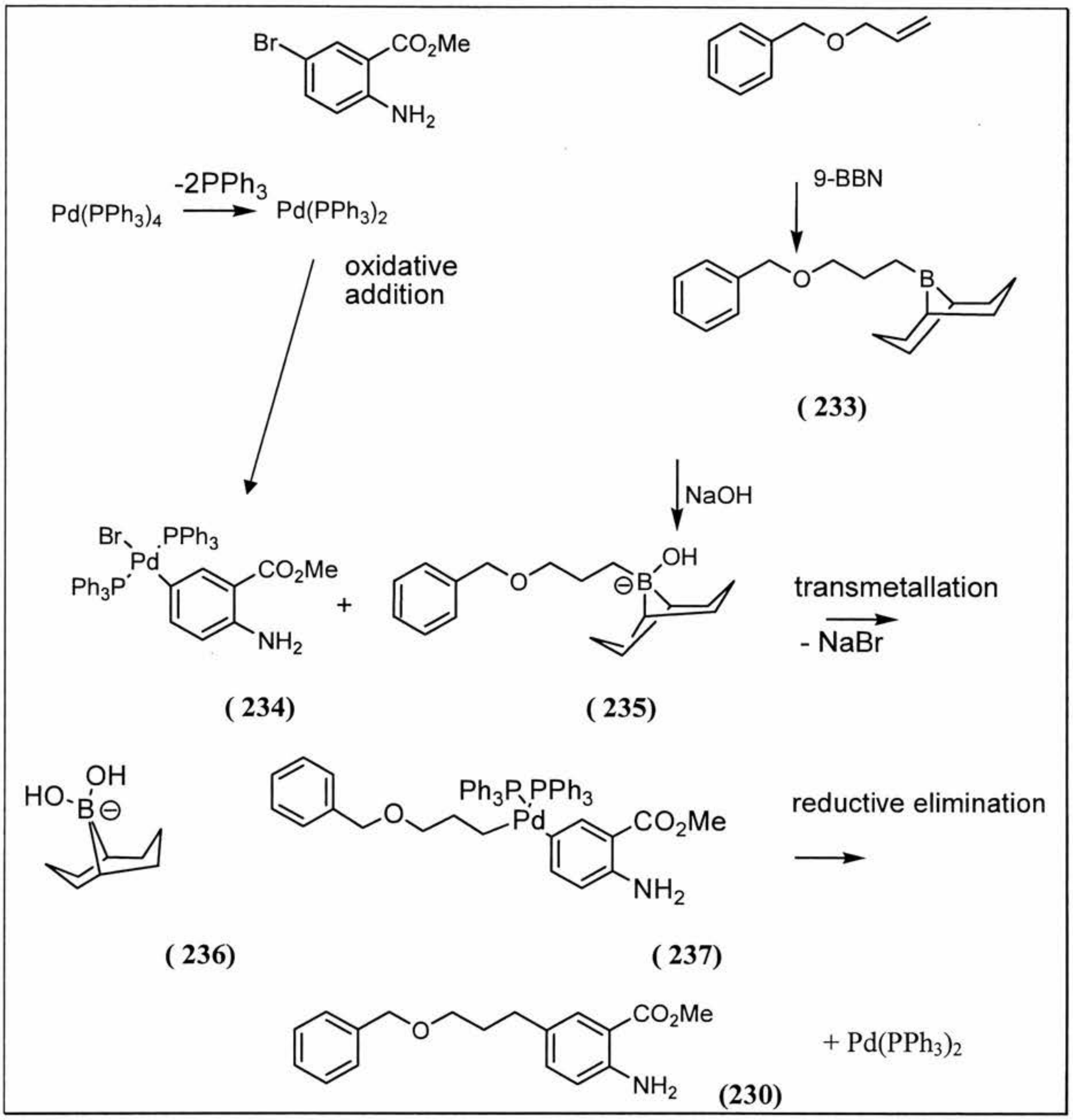
2.3.1.2. Suzuki coupling

Allylbenzyl ether **229** was reacted with 9-borabicyclo[3.3.1]nonane (9-BBN) to give the corresponding boron derivative **233** (Scheme 137) which was coupled via Suzuki methodology to the anthranilate **228**. The reduction of the alkene with 9-BBN occurs via anti-Markovnikov addition, giving **233** (Scheme 137) with the boron atom attached to the terminal carbon atom. An important step that must occur before the transmetallation takes place is the formation of the boronate **235** (Scheme 137). Sodium hydroxide is used in order to form **235**.



Scheme 136: Synthesis of **231**; a) i) allylbenzyl ether **229** and 9-BBN, THF, 3h, rt, ii) **228**, $Pd(PPh_3)_4$, NaOH aq., reflux, THF, 24h, quantitative; b) NaOH, MeOH, reflux, 1h, quantitative.

The coupling reaction was successful as analysis of the oil that was isolated after purification showed a singlet at 3.75 ppm in the ^1H NMR spectrum, corresponding to the methyl ester, but also three signals at 3.37, 2.51 and 1.79 ppm each integrating for two protons. We assigned these signals as the three methylenes present in the aliphatic chain formed in the coupling reaction. The two bands in the infrared spectrum at 3481 and 3374 cm^{-1} provided evidence in support of the presence of the NH_2 moiety in **230**.



Scheme 137: Mechanism of Suzuki coupling [165-167].

The presence of sodium hydroxide in the reaction mixture also leads to a side reaction which is an advantage in our synthesis. It converts the methyl ester **230** to the corresponding carboxylic acid **231** (Scheme 136). In practice, the hydrolysis of the ester **230** was driven to completion by addition of a further aliquot of sodium hydroxide after the coupling reaction was complete and the reaction was refluxed for a further 24 hours. The one-pot reaction (coupling-hydrolysis) yielded the acid **231**. The new signal at 1670 cm^{-1} present in the infrared spectrum of **231** supported the fact that the ester, appearing at 1691 cm^{-1} in **230**, had been transformed to the acid **231**. High resolution mass spectroscopic data also supported the assignment (*m/z*: 284.1279, negative electrospray mode corresponding to the formula $C_{17}H_{18}NO_3$ (calculated *m/z*: 284.1287) of **231** [*M*-H]$^-$).

The purification step of **231**, however, provided major difficulties. Indeed, by-products believed to result from the 9-BBN were not separable by flash chromatography and contaminated the desired product **231**. An attempt to destroy these by-products using sodium hydroxide followed by hydrogen peroxide [168] was made, but unfortunately **231** degraded under these reaction conditions yielding unindentified products and considerably decreasing the yield.

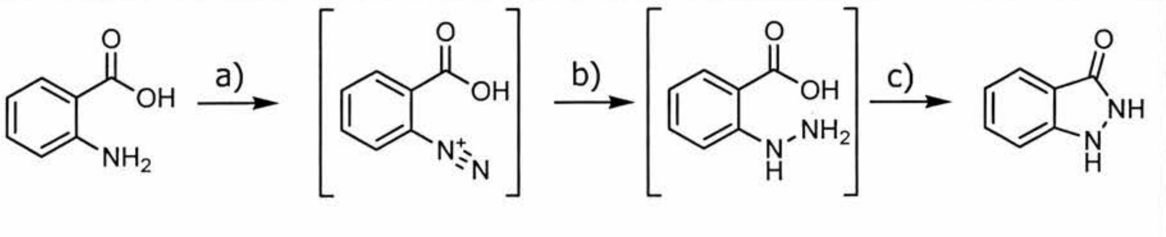
An alternative approach involving the extraction of acid **231** into a solution of sodium hydroxide, followed by washing with DCM, neutralisation and re-extraction with an organic solvent was attempted but the by-products were also carried through this procedure.

A solution was found when the oily crude reaction mixture was triturated with hot petroleum ether 40-60°. This enabled the separation of the oily 9-BBN by-products and the 5-[3(benzyloxy)propyl] anthranilic acid **231**. The oily residues were not soluble in hot petroleum ether and were separated from the product **231** which was partially soluble in hot petroleum ether. Further time consuming trituration eventually yielded **231** as a white solid after evaporation of the solvent.

2.3.1.3. Cyclisation of **231**

2.3.1.3.1. A complicated procedure

Due to the difficulties in purification, **231** (page 132) was a relatively precious material, so initial cyclisation studies to form the indazolinone were carried out on the commercially available anthranilic acid **205** according to a procedure reported by Baiocchi [83]. The sequence consisted of diazotisation followed by reduction with sodium thiosulfate and finally acid-catalysed cyclisation of the corresponding hydrazine derivative **238** to afford indazolinone **17** (Scheme 138). This procedure was successful in our hands yielding **17** in 82% compared with the published yield of 86% [83].



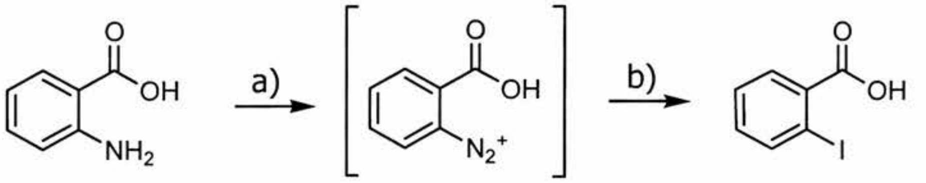
(205) **(206)** **(238)** **(17)**

Scheme 138: Synthesis of indazolinone **17** via diazotation, reduction of the diazonium salt, and cyclisation; a) $NaNO_2$, HCl, b) $Na_2S_2O_3$, c) HCl, 80°C, 20 h, 82% [83].

Having shown that this one-pot reaction worked in our hands, the next step was to attempt the reaction with anthranilic acid derivative **231**. Unfortunately, none of the desired indazolinone **232** was produced. In the synthesis of **17**, the product precipitates when the pH of the solution was adjusted to pH=5. No precipitate was observed when the pH was adjusted to pH=5 in the reaction using **231**. Extraction of the aqueous media with organic solvent and subsequent analysis of the organic extracts by ^{1}H NMR did not show the presence of the expected product **232**. This three step-one pot reaction was acceptable for the synthesis of **17**, but the problem with a one pot-multistep reaction of this kind is that when it does not work, it is often difficult to determine the weak step. We therefore studied this reaction in more detail.

2.3.1.3.2. Is the first step failing?

The diazotation step in this method of making the desired indazolinone **232** is the first crucial step that had to be checked. Diazotisation of anthranilic acid **205** was performed according to a procedure published by Vogel [169] and was followed by conversion of the diazonium salt **206** to the aryl iodide **239**. The success of the diazotisation was measured by monitoring the amount of iodobenzoic acid **239** that precipitated out of the reaction mixture and was isolated by filtration.



(205) **(206)** **(239)**

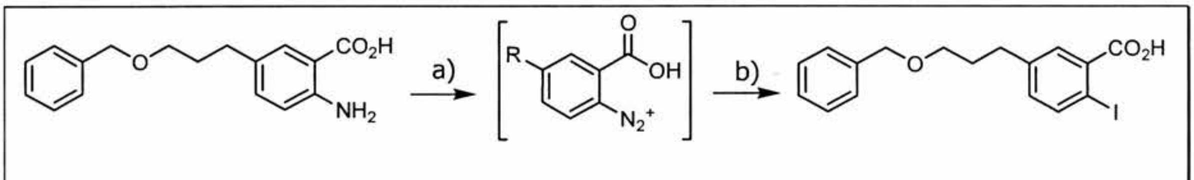
Scheme 139: Synthesis of **239** by diazotisation of anthranilic acid **205**; a) HCl, $NaNO_2$, b) KI, heating. [169]

To optimise the reaction different conditions were used, especially changing the solvent. The standard conditions were diazotisation/iodination of benzoic acid **205** (200 mg) in 2 mL of solvent (variable), 300 μL of hydrochloric acid and 100 mg of sodium nitrite. The sodium nitrite was added as an aqueous solution dropwise at 0°C and the solution was stirred for 30 minutes.[169] The displacement of the diazonium salt **206** by iodide was carried out by adding solid potassium iodide and refluxing the dark solution for 10 minutes. The iodobenzoic acid **239** was expected to precipitate out of the solution.

Solvent	H_2O	10% MeCN	25% MeCN	50% MeCN	75% MeCN	10% THF	25% THF	50% THF	75% THF
Precipitate	✓	✓	✓	✓	✓	✓	✗ 2 phases	✗ 2 phases	✗ 2 phases
Yield	15%	70%	75%	45%	40%	66%	✗	✗	✗

Table 9: Optimisation of diazotisation of anthranilic acid **205** by variation of solvent.

Table 9 details the results of this study. In summary, the use of 100% water and the use of a solvent mixture that resulted in a biphasic system led to poor yields of **239**. Helping the reagents and substrate to be in a homogeneous media was the key in this reaction and seemed to improve the yield dramatically. Over a defined range (10-75% CH_3CN/H_2O) acetonitrile and water are miscible. The best ratio of acetonitrile/water to run the diazotisation reaction in was found to be 25% acetonitrile/water. These conditions were selected as the standard conditions for any further diazotisation reactions. These conditions were then applied to the desired substrate anthranilic acid **231** in order to convert it into the corresponding iodobenzoic acid **241**.



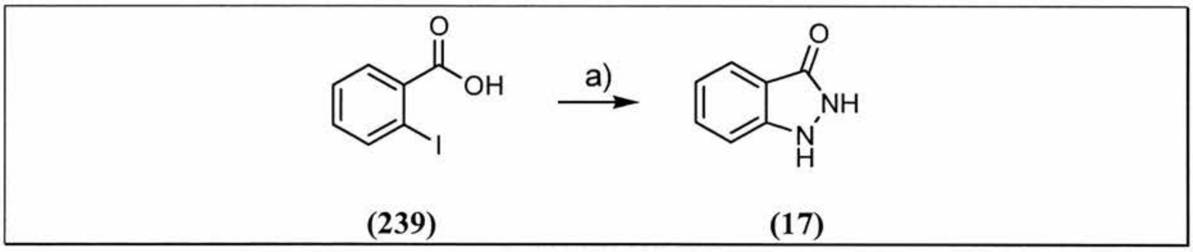
(231) **(240)** **(241)**

Scheme 140: Synthesis of **241** from **231**; a) $NaNO_2$, HCl, b) KI, heating, 86%.

The conditions developed using anthranilic acid **205** proved to be reliable with substrate **231**. Indeed, the yield of the reaction reached 86% conversion. Knowing that the diazotisation was working in 25% acetonitrile/water, we next attempted to repeat the multistep procedure to synthesise **17** with this solvent combination. From analysis of the ^{1}H NMR of the crude reaction, we observed that the signals of the indazolinone **17** were not present, whereas the reaction carried out in water alone was successful. We therefore decided to abandon this multistep procedure as a route to **232** due to the limited amount of **231** that was available.

2.3.1.3.3. An improved protocol for the cyclisation

There are several literature reports on the preparation of indazolinones starting from 2-halogen substituted benzoic acids.[83, 103] This approach consists of reacting hydrazine and the 2-halogen substituted benzoic acid in isopropanol in the presence of copper metal. This cyclization reaction has been described with 2-chloro and 2-fluoro benzoic acid but not with 2-iodobenzoic acid **239**. We therefore investigated and subsequently optimised the cyclisation of **239** to form **17**.



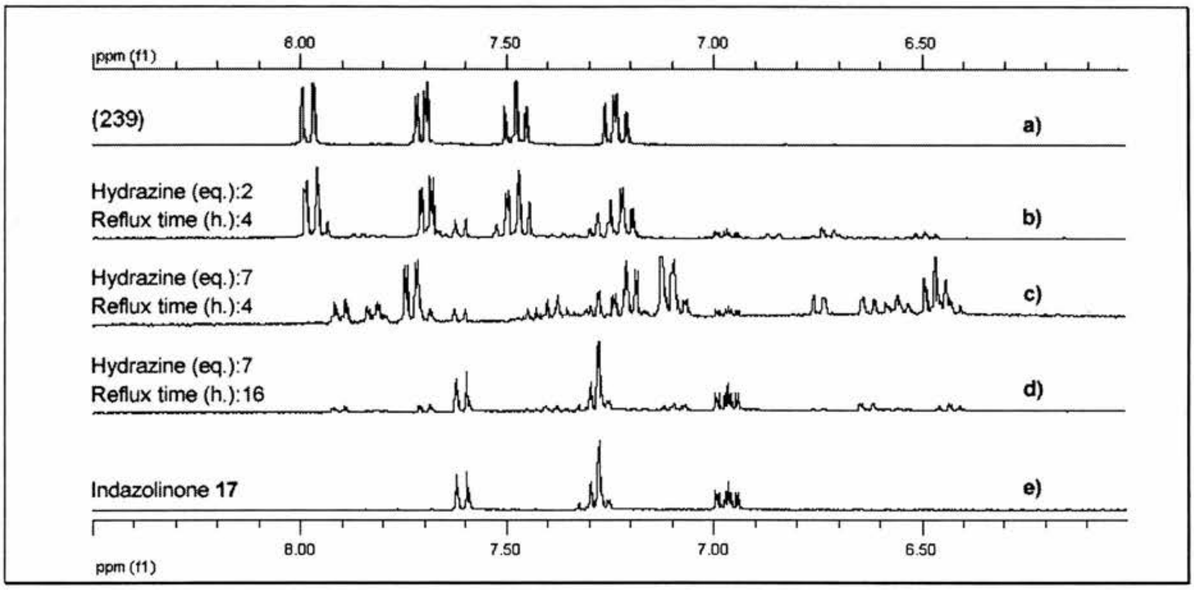
(239) **(17)**

Scheme 141: Cyclisation of iodobenzoic acid **239** to indazolinone **17**; a) CuI, $NH_2NH_2.H_2O$, IPA, reflux, o/n, >90% (judged by ^{1}H NMR, as purification was difficult).

For cyclisation of 2-fluoro benzoic acid, [83] the literature procedure involves the use of metallic copper (0.9 equiv.) and 2 equivalents of hydrazine hydrate. The reaction is then refluxed for 4 hours in isopropanol. When we repeated this procedure with **239**, throughout the reaction what was assumed to be a copper residue was present as a suspension. The copper was activated by removing any copper oxide coating with dilute sulfuric acid as described in the literature. [169] The copper was then washed with water and acetone and dried *in vacuo*.

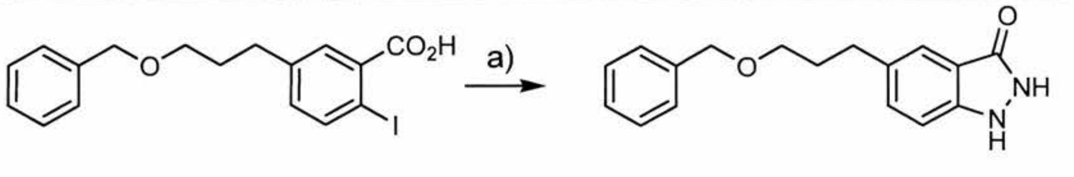
The reaction of **239** under these conditions was monitored by analysis of the crude reaction mixture by ^{1}H NMR. This avoided the need for work up and hence eliminated any error resulting from the fact that indazolinone **17** may dissolve in aqueous solution.

Following the literature conditions, the ^{1}H NMR of the crude reaction mixture after 4 hours showed the presence of predominantly starting material **239** (Scheme 142b). When the reaction was repeated using 7 equiv. of hydrazine, the major product is not the starting material **239** or the desired product **17** (Scheme 142c). Traces of **17** were observed, however, and the reaction was further improved by extending the time of reflux to 16 hours (rather than 4 hours, Scheme 142d).



Scheme 142: ^{1}H NMR comparison of cyclisation optimisation; a) ^{1}H NMR of 2-iodobenzoic acid **239**, b) ^{1}H NMR of cyclisation of **239** with 2 equiv. of hydrazine, reflux 4 h, c) cyclisation of **239** with 7 equiv. of hydrazine, reflux 4 h, d) cyclisation of **239** with 7 equiv. of hydrazine, reflux 16 h, e) ^{1}H NMR of indazolinone **17**.

From these model studies, we had identified optimised conditions for the formation of **17** from **239**. We therefore applied these optimised conditions to **241** in order to prepare indazolinone **232** (Scheme 143).



(241) **(232)**

Scheme 143: Synthesis of **232** by cyclisation of **241**; a) $NH_2NH_2.H_2O$, Cu metal, IPA, reflux, 16 h, 51%.

Diazotisation of **231** followed by treatment with iodine using the conditions described previously afforded **241** as an oil in 85% yield. The presence of the aliphatic chain helped to solubilise the product in organic solvents by decreasing the polarity so that flash column chromatography was used to purify **241**. The cyclisation of **241** in isopropanol in the presence of hydrazine hydrate (7 equiv.) and copper metal allowed the isolation of **232** in 51% after 16 hours under reflux. Figure 34 shows the ^{1}H NMR spectrum of **232** along with the corresponding assignments.

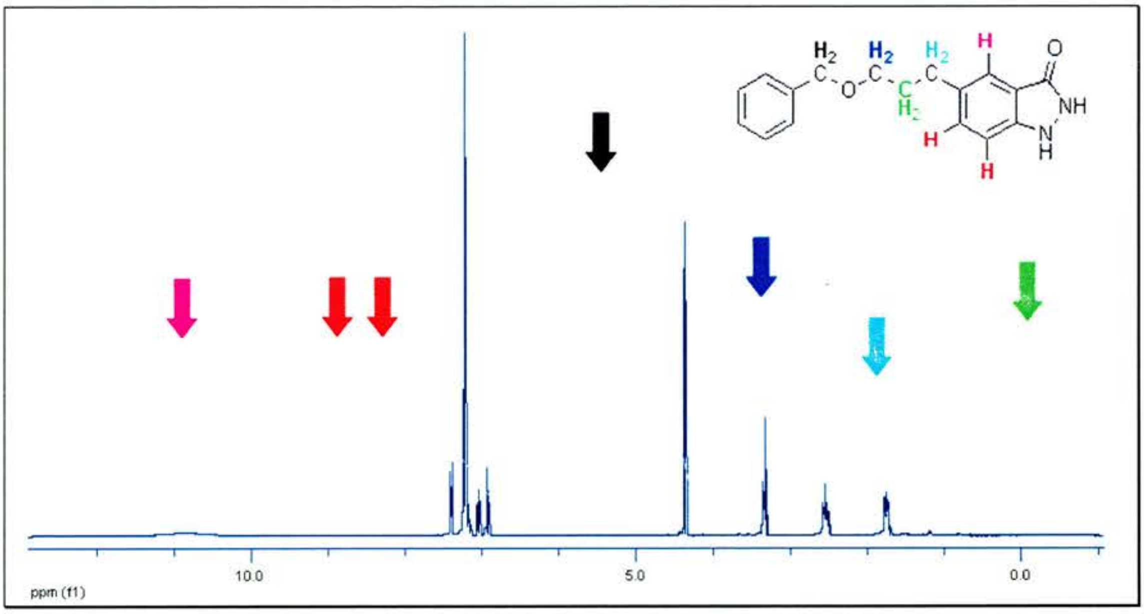


Figure 33: ^{1}H NMR spectrum of **232** (CDCl$_3$, 300 MHz).

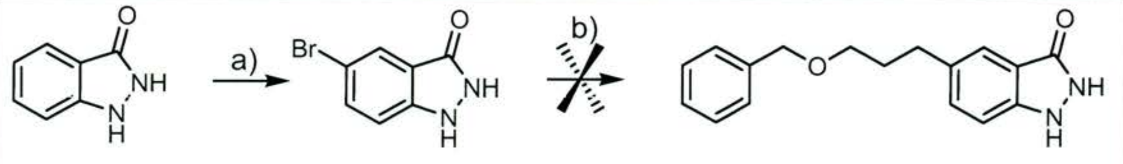
2.3.1.4. Unsuccessful approaches to a library core structure

2.3.1.4.1. Methods involving attachment of the linker to the indazolinone core structure

2.3.1.4.1.1. Derivatising the indazolinone

2.3.1.4.1.1.1. Starting from indazolinone

Indazolinone **17** is known to react with bromine leading to incorporation of bromine at position 5. Using this bromo derivative in a Suzuki coupling reaction with the boronate derived from allyl benzyl ether **229** by reaction with 9-BBN was proposed as an alternative route to **232**.



(17) **(242)** **(232)**

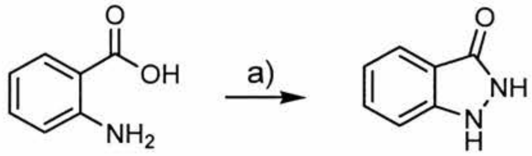
Scheme 144: Synthesis of **232**, attempt to react under Suzuki reaction conditions; a) Br$_2$, AcOH, rt, 2h, 30%, [85] b) attempt of Suzuki coupling, allylbenzyl ether reacted with 9-BBN, THF, 3h, rt, assumed to be quantitative, then bromoindazolinone, Pd(PPh$_3$)$_4$, NaOH, reflux, 24h, 0%.

No problems in repeating the synthesis of **242** were encountered. Unfortunately, we were unable to improve the previously reported difficult separation of mono- and dibrominated products in chloroform as stated in the publication. Attempts to carry out a Suzuki coupling using 5-bromoindazolinone **242** failed due to the fact that **242** was not soluble in THF. This approach could have been significantly shorter than our successful approach to **232** but due to time restriction and because of the low yielding reaction to prepare **242** (30%), no further optimisation studies were attempted.

2.3.1.4.1.1.2. Starting from anthranilic acid derivatives

a) The model

As discussed previously, indazolinone **17** can be synthesised from anthranilic acid **205** through diazotation, reduction of the formed diazonium salt to the hydrazine containing derivative and cyclisation.



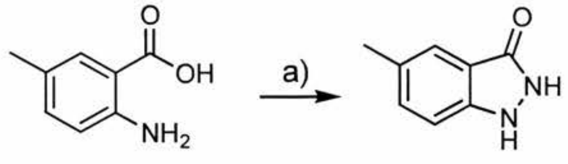
(205) **(17)**

Scheme 145: Synthesis of **17** from **205**; a) i) $NaNO_2$, H_2O, HCl, under 5°C, 4h, ii) $Na_2S_2O_3$, o/n, rt, iii) reflux, o/n, 85% [83].

This route is also applicable to starting materials containing a side chain that could be used to insert a point of attachment for loading onto a resin.

b) Substrates containing a methyl group

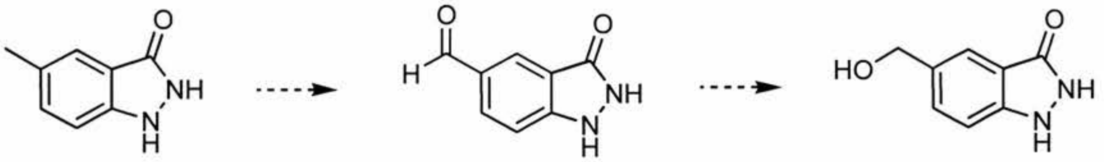
It was proposed that having a methyl group on the aromatic ring may prove useful due to the possibility of subsequently oxidising the methyl group and ultimately accessing a benzylic alcohol functionality. Following the same procedure, 5-methyl anthranilic acid **243** was converted to the corresponding indazolinone **244**.



(243) **(244)**

Scheme 146: Synthesis of 5-methyl indazolinone **244** from **243**; a) i) $NaNO_2$, H_2O, HCl, under 5°C, 4h, ii) $Na_2S_2O_3$, o/n, rt, iii) reflux, o/n, 86%.

Using oxidising agents to transform the methyl to the carboxylic acid functionality would have provided an alternative strategy of linking the indazolinone derivative onto the solid support.



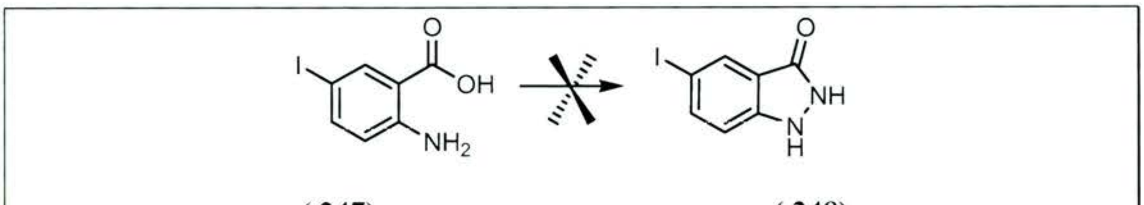
(244) **(245)** **(246)**

Scheme 147: Strategy for derivatising **244** to load through an alcohol moiety to the silicon-based resin.

Attempts to react **244** with IBX according to the procedure of Nicolaou [170] did not give any of the desired product and was therefore abandoned. However, the strategy of cyclising a suitably substituted anthranilic acid was still valid and it was proposed that other substituents on the aromatic ring such as a halogen atom could be incorporated to carry out a palladium coupling reaction.

c) Substrate containing an iodine group

An attempt was made to convert the commercially available 5-iodo-anthranilic acid **247** (Scheme 148) to **248** under the previously described diazotisation/reduction-cyclisation conditions. Unfortunately, the expected final product **248** did not precipitate from the reaction mixture after adjusting the pH to 5-5.5. Different pHs were tried but no precipitation was observed. This approach was therefore abandoned.



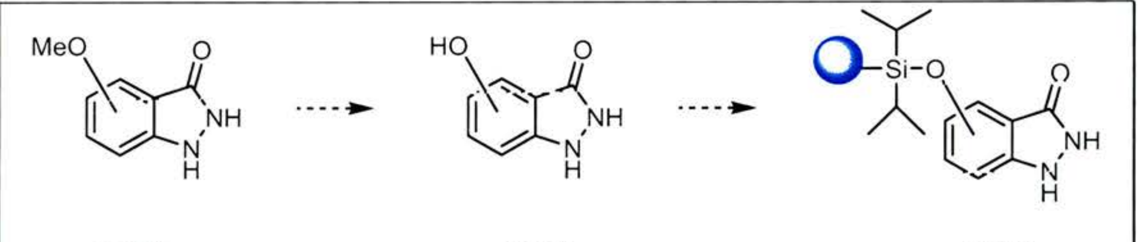
(247) **(248)**

Scheme 148: Attempt of cyclising **247** to give **248**; a) i) $NaNO_2$, H_2O, HCl, under 5°C, 4h, ii) $Na_2S_2O_3$, o/n, rt, iii) reflux, o/n, 0%.

2.3.1.4.1.2. Making the indazolinone with the chain already in place

2.3.1.4.1.2.1. Barton's route

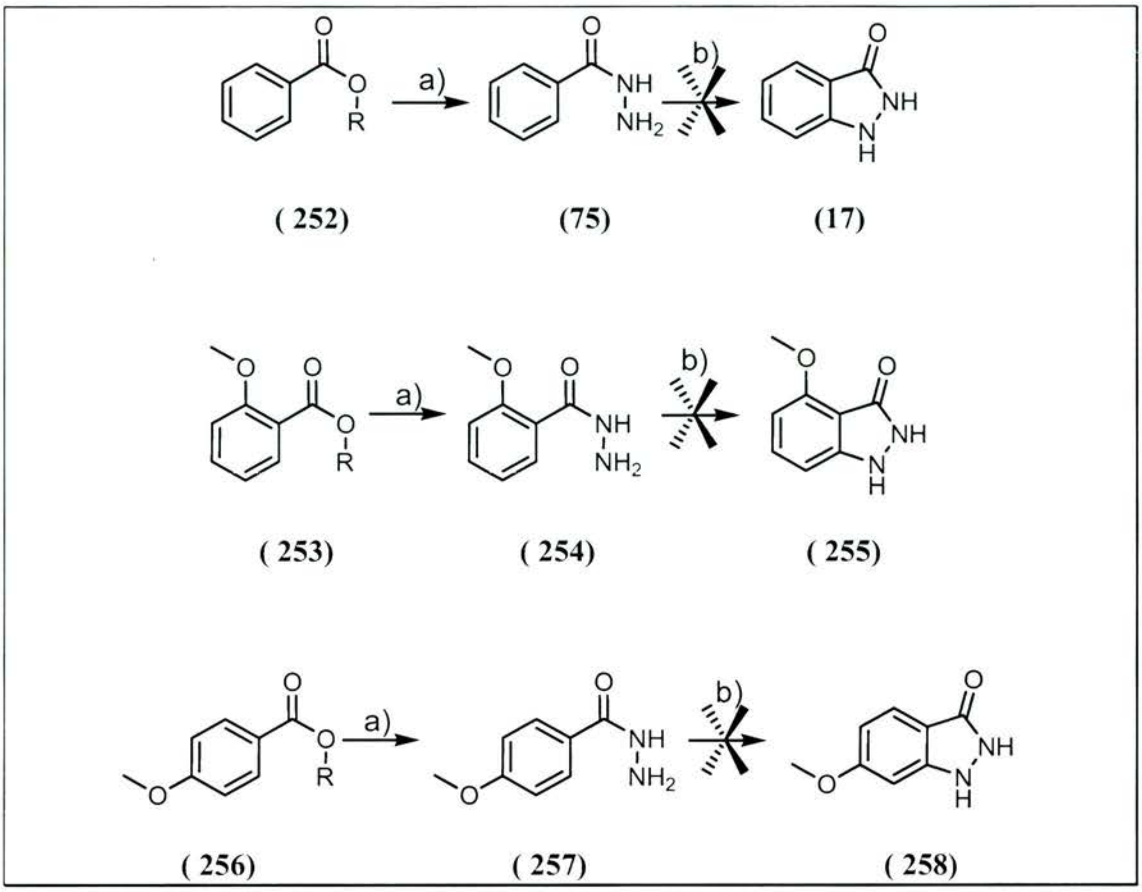
Our first route to generate indazolinones for this project was inspired by the work of Sir Derek Barton. In a paper published in 1982, he reported a versatile method to access indazolinones containing electron-donating substituents in the aromatic ring.[101] This strategy was first attempted due to the availability of starting materials **253** and **256**. The key feature in **253** and **256** was the presence of the methoxy functionality **(249)**, which could potentially be transformed later on to a phenol moiety **(250)**. This phenol could then be used to link the indazolinone core onto an insoluble polymer through the formation of a Si-O linkage **(251)**(Scheme 149).



(249) **(250)** **(251)**

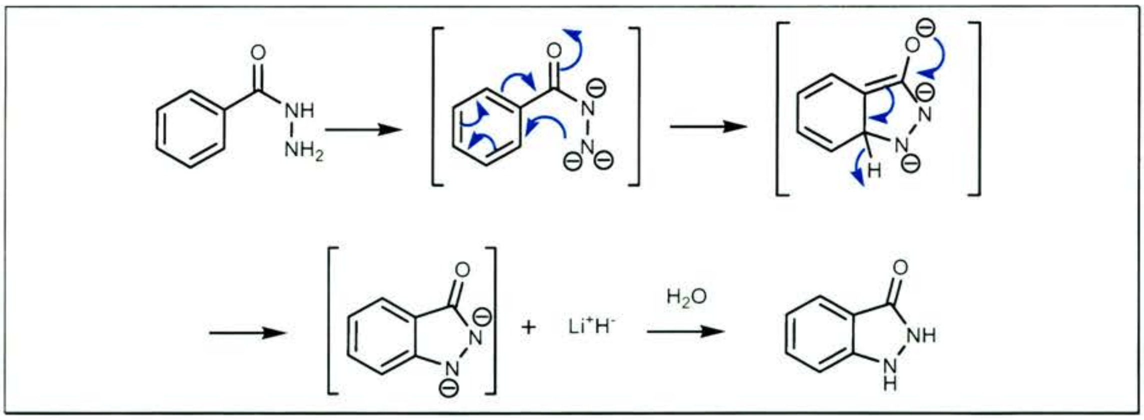
Scheme 149: Strategy of linkage through a phenol moiety.

The commercially available esters **252**, **253** and **256** were converted to the corresponding hydrazides **75**, **254** and **257** respectively. These hydrazides were subsequently treated with three equivalents of a strong base, *n*-butyl lithium at –78°C according to Barton´s protocol.



Scheme 150: Attempted formation of indazolinones from **252, 253** and **256** following Barton´s method; a) $NH_2NH_2.H_2O$, THF, 99%, b) *n*-BuLi, THF, -78°C.

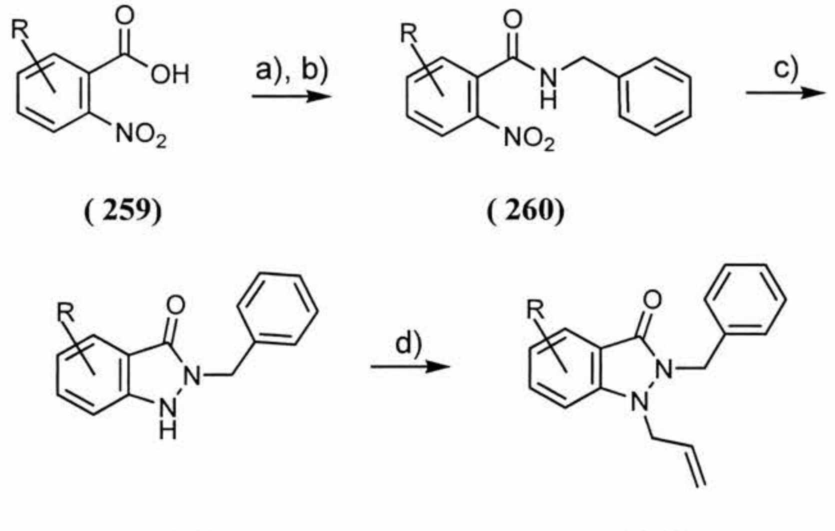
Scheme 151 shows the mechanism for the formation of the indazolinones as published by Barton in 1982.[101] This involved the generation of a polyanionic species, which was then described to cyclise as shown. In our hands, none of these reactions were successful despite us taking great care to exclude water and air from the reaction.



Scheme 151: Barton's proposed mechanism for indazolinone synthesis published in 1982.[101]

2.3.1.4.1.2.2. *With nitro benzoic acid derivatives*

In another approach, we decided to explore the possibility that a derivative of type **259** containing a linker unit (R) could be transformed to the corresponding amide **260** and then cyclised to *N2*-substituted indazolinone **261** (Scheme 152). Different derivatives of 2-nitro benzoic acid are commercially available and could have been of interest to cyclise to a suitable indazolinone system. This strategy relied on our ability to remove the group present at the N2 position (e.g. use of p-methoxybenzyl followed by CAN deprotection).



(259)

(260)

(261)

(262)

Scheme 152: Synthesis of *N1*-allyl *N2*-benzyl indazolinone **262** from nitrobenzoic acid **259**; a) $(COCl)_2$, DMF cat., THF, rt, 5 hours, b) $BnNH_2$, THF, o/n, rt, 99%, c) Zn, NaOH, EtOH, 80°C, o/n, 71%, d) i) Hünig's base, THF, 2h, rt, ii) allyl bromide, o/n, rt, 99%.

As stated in section 2.2.7.1, the alkylation (allylation) of **262** (R=H) occurs specifically at the N1 position. Whilst it proved possible to prepare **269** (R=H) by this route, it was reasoned that even if the required deprotection of the N2 substituent occurred, the product would still be a *N1*-substituted indazolinone. Analogues of **261** would have been functionalised at the N1 position. Structures of type **262** could not be subjected to the Claisen rearrangement, a crucial step of our library design. Consequently, this strategy was rapidly abandoned.

2.3.2. Substrate(s) for loading onto the resin

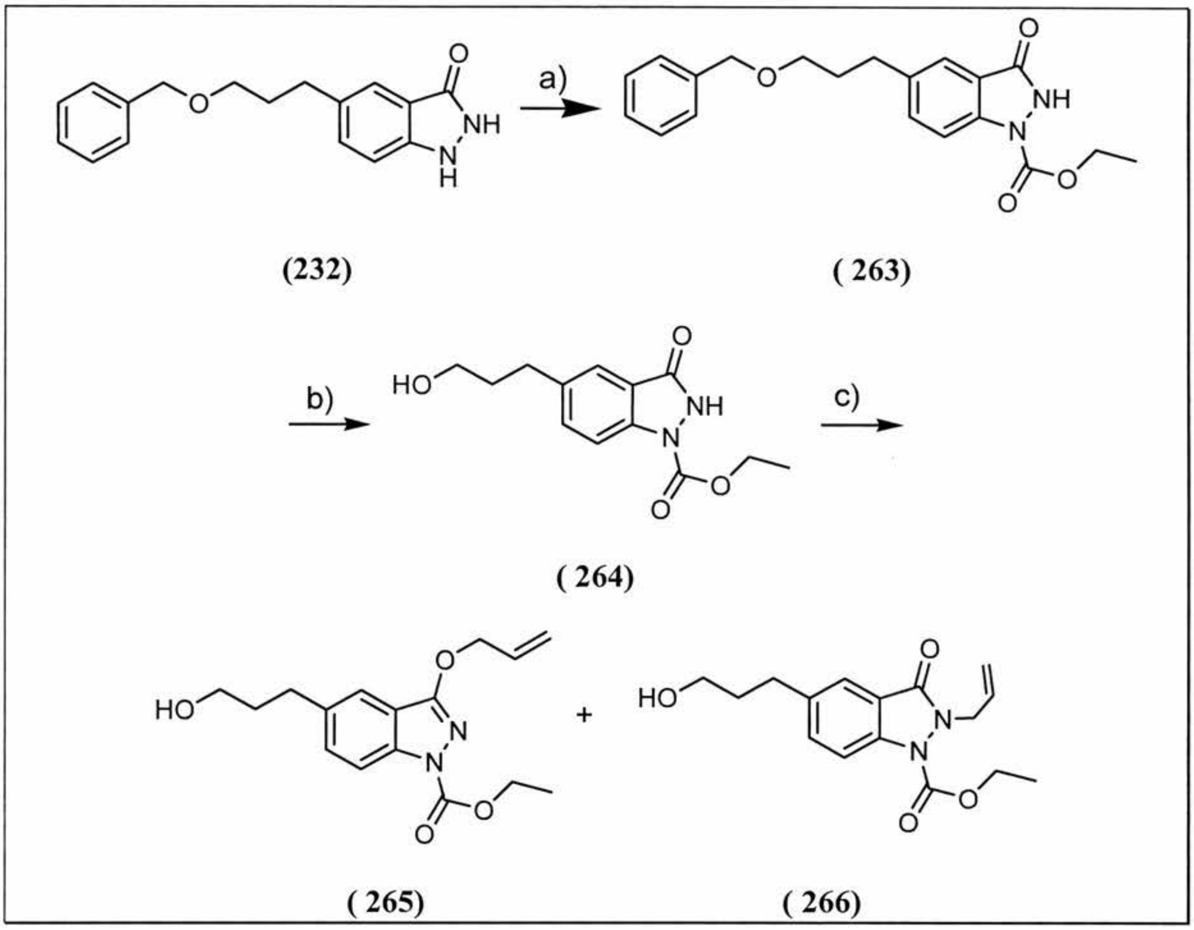
As presented in section 2.3.1.3.3 (page 136), an indazolinone core containing a handle for linking to a resin was synthesised, but there was still a benzyl group present that protects the oxygen on the chain. This benzyl group must be removed to enable loading onto the resin. Moreover, because of the isomer issues known to be associated with the indazolinone core structure, care had to be taken in order to avoid low yielding reactions.

We decided that only one strategy could meet all of our requirements based on the following criteria:

1. If benzyl deprotection was the first step of the sequence, a primary alcohol would be generated, making the task of selectively protecting the indazolinone core more difficult.

2. Selective debenzylation during the last step of the route is not possible due to the possible reduction of the allyl alkene functionality under the hydrogen, Pd/C conditions used to remove the benzyl group.

3. Treatment with excess ethyl chloroformate (not benzyl chloroformate, because it would be deprotected under hydrogenolysis conditions) and partial deprotection would give the *N1*-protected indazolinone **263**. **263** could then be debenzylated to afford **264** and a Mitsunobu reaction using an excess of allyl alcohol could be used to enable reaction of the amide of **264** to give **265** and **266** without homodimerisation or potential polymerisation of **264**. We therefore decided to pursue the strategy shown in Scheme 153.



Scheme 153: Synthesis of **265** and **266** from **232**; a) i) EtOCOCl, Et_3N, THF, ii) morpholine, 89%, b) Pd/C 10%, H_2 (20 bars), 86%, c) allyl alcohol, PPh_3, DEAD, toluene, 30% of **265** and 60% of **266**.

N1-protection on **232** did not present any problems. This strategy had previously been used with benzyl chloroformate (section 2.2.2.2) and was as effective when ethyl chloroformate was used. The two-step procedure including reaction with excess ethyl chloroformate and partial deprotection using morpholine gave **263** in 89% overall yield.

Removal of the benzyl protecting group in **263** was attempted at room temperature. Using hydrogen in a balloon at atmospheric pressure, the reaction went to completion after 4 days (on 100 mg scale); whereas, when the pressure was increased to 20 bars the reaction rate increased and the reaction was complete in 2 days. Depending on the scale of the reaction, the autoclave was kept between 2 and 7 days under 20 bars of pressure of hydrogen at room temperature. The work up of the reaction was straight forward. Filtration through celite was necessary to remove the palladium on charcoal. The solid residue was then washed with methanol and the solvent removed *in vacuo* to give a white solid which was identified as **264**. No further purification step was necessary because of the excellent purity as judged by ^{1}H NMR analysis.

At this stage, **264** is a base and acid sensitive molecule that contains two functional groups which could react depending on the reaction conditions. Nevertheless, one of the future steps in the sequence is the formation of a Si-O bond. The amide moiety could compete with the primary alcohol for reaction with a silylating reagent. Alkylating the amide using the Mitsunobu reaction was therefore a priority to avoid obtaining mixtures of isomers during loading onto the resin. However, by adopting this strategy it was possible that both of the two alcohols present could participate in the Mitsunobu [117] reaction (i.e. the allyl alcohol to make the 3-allyloxyindazole derivative and the alcohol present in the terminal position of the alkyl chain in **264**). It was proposed that the use of excess allyl alcohol would favour the coupling with allyl alcohol and so avoid an intermolecular coupling between two molecules of **264**. The first attempt at this reaction showed complete coupling between allyl alcohol and indazolinone **264** and the intermolecular reaction was not observed.

The ^{1}H NMR spectrum of the crude reaction mixture shows the presence of both the *O*-allyl **265** and *N*-allyl **266** derivatives.

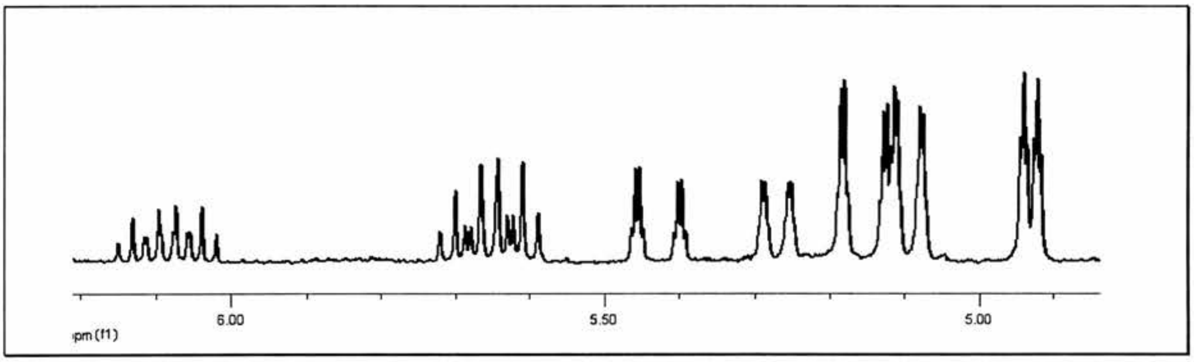


Figure 34: ^{1}H NMR spectrum (6.2-4.8 ppm) of the crude Mitsunobu reaction on **264** to obtain **265** and **266**.

265 and **266** were therefore synthesised from commercially available methyl 5-bromoanthranilate **228** and correspond to the starting point for our library blueprint.

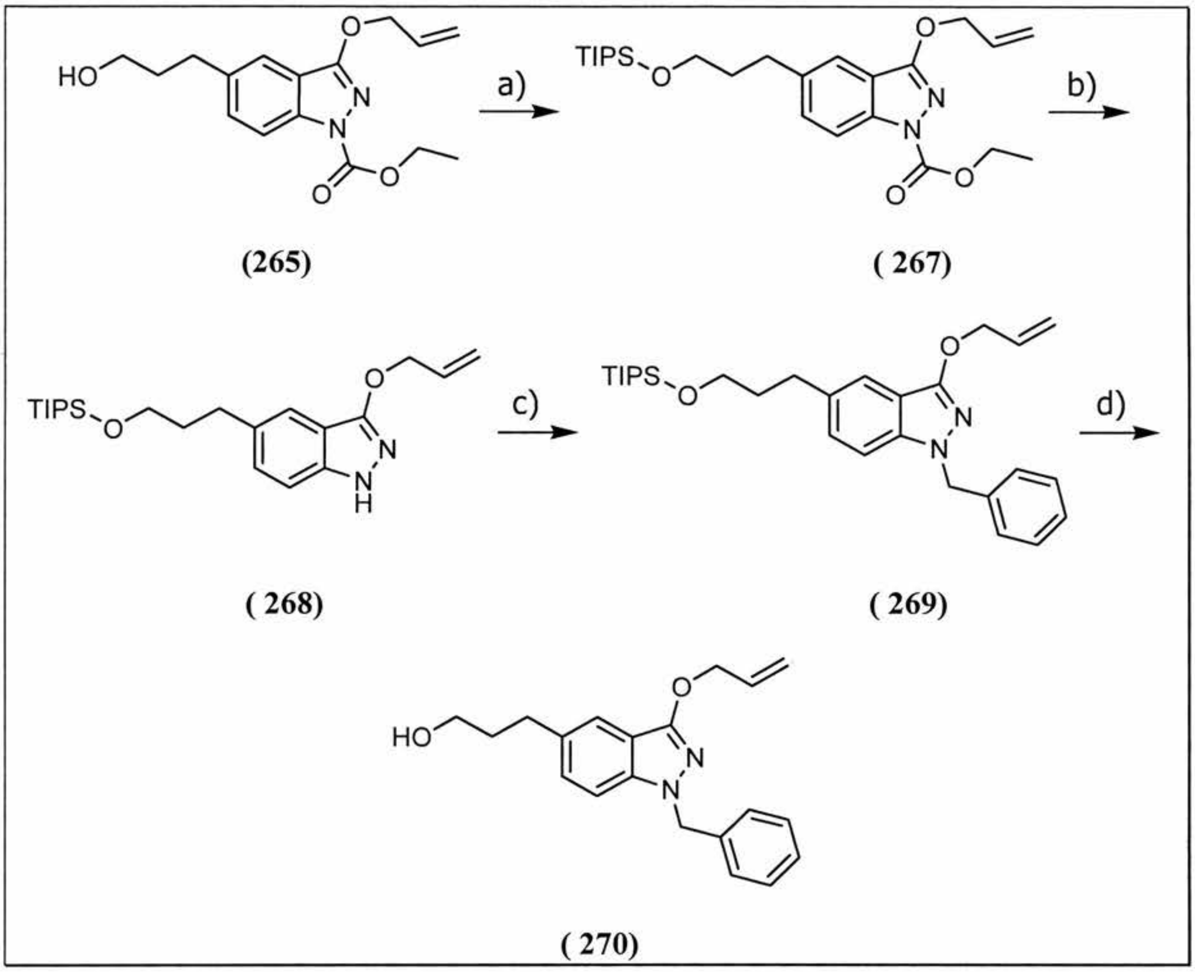
2.3.3. Solution phase studies

The previous section described the preparation of **265**, a substrate that can be loaded onto the solid support. The general sequence developed for the library synthesis has previously been described in section 2.2. The combination of these two studies is described in the following section which culminates in the transfer of all the described chemistry from the solution to the solid phase. The different targets and intermediates were all prepared in solution to allow full analytical characterisation of the products.

Because solid phase synthesis does not easily allow the synthesis of large quantities of product, it was decided to synthesise the targets and intermediates on the solid support and then compare them with the authentic materials synthesised in solution phase using LC/MS techniques.

2.3.3.1. Synthesis of **270**

As mentioned previously in the goals of the project, a silicon-based resin was chosen to carry out the solid phase synthesis. The solution-phase analogue of the silicon-based resin was the triisopropylsilyl (TIPS) moiety. The reagent used in order to protect the primary alcohol in **265** was triisopropylsilyl trifluoromethane sulfonate (TIPSOTf), which allowed, in the presence of triethylamine, the synthesis of **267** in quantitative yield. Evidence to support the successful displacement of the triflate by the primary alcohol in **265** came from the fact that the polarity of **267** decreased dramatically compared with **265**. Flash column chromatography of **267** was run in neat hexane whereas **265** was purified using 20% ethyl acetate/hexane. In addition, the multiplet at 0.99 ppm in the ^1H NMR spectrum of **267** integrated for 21 protons corresponded to the two types of protons (CH_3 and CH) present in the TIPS group.



Scheme 154: Synthesis of **270** in solution; a) TIPSOTf, Et_3N, THF, 1 h, rt, quantitative, b) aq. LiOH, THF, o/n, rt, 75%, c) BnBr, ^tBuOK, THF, o/n, rt, 67%, d) TBAF, THF, 16 h, rt, 89%.

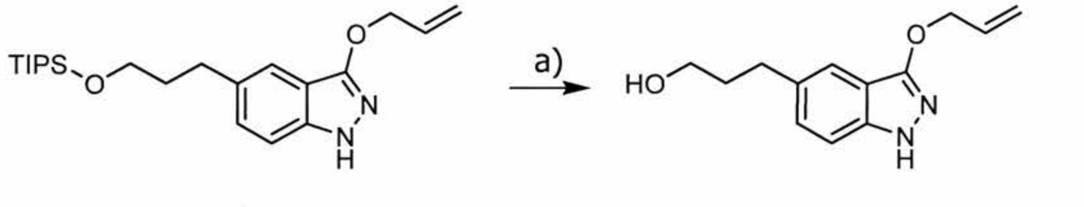
In order to insert diversity at the N1 position, the carbamate functionality in **267** must be removed. This was achieved in a vigorously stirred biphasic system of aqueous lithium hydroxide and THF. **268** was the expected product of the deprotection. The presence of a new band at 3205 cm^{-1} in the infrared spectrum of **268** was consistent with the deprotection of the carbamate group as this band was assigned to the NH in **268**. The absence of the bands at 1755 and 1725 cm^{-1} reinforced our view that N1 deprotection has occured, as these two bands were assigned to the carbonyl group of the carbamate protecting the N1 position in **267**. The deprotection of **267** to **268** was achieved in 75 % yield after purification of **268** by flash column chromatography.

In the next step, we decided to use an alkylating agent as an example of diversity incorporation at the N1 position. **268** was therefore reacted with potassium *t*-butoxide and benzyl bromide in THF. The reaction was quenched after 30 minutes as TLC analysis showed that all the starting material **268** had reacted. High resolution mass spectroscopic analysis of **269** is consistent with the assigned structure (chemical ionisation mode *m/z*: 479.3094, corresponding to the molecular formula $C_{29}H_{43}N_2O_2Si$

$[M+H]^+$ (calculated for **269** 479.3092)). Absence of the signal at 3205 cm^{-1} in the infrared spectrum (corresponding to the NH functionality) and the presence of a singlet at 5.23 ppm in the ^{1}H NMR spectrum (integrating to 2 protons, benzylic CH_2), that coupled with C-8 (52,3 ppm) in the HSQC spectrum provided evidence that the benzyl group was in the N1 position. **269** was isolated in 67% yield.

The final step en route to **270** in solution was the deprotection of the TIPS group [171]. Generally, Si-O bonds are cleaved with a source of fluoride [172, 173] due to the fact that the Si-F bond strength is 3 kcal/mol greater than the Si-O bond strength [173]. As purification is possible in solution phase to remove the by-products, the silicon-oxygen bond was cleaved with an inorganic source of fluoride, tetrabutylammonium fluoride (TBAF) in THF to yield **270** in 89%. The presence of the primary alcohol in **270** was confirmed by the presence of a broad signal at 7.41 ppm in the ^{1}H NMR spectrum. The presence of the allyl group on the oxygen was confirmed by HSQC and HMBC experiments. Indeed, the allylic CH_2 (4.83 ppm) was coupled with C-3 (155.4 ppm) in the HMBC spectrum. This indicates that the allyl moiety is on the oxygen of the indazolinone core. Finally, high resolution mass spectroscopic analysis of **270** was consistent with the assigned structure (*m/z:* 323.1752 indicates a general formula of $C_{20}H_{22}N_2O_2$, (calculated for **270** 323.1760)).

To enable facile characterisation of products cleaved from the solid phase resin, it is necessary to compare them with authentic samples prepared in solution. For this purpose, all TIPS-containing intermediates (e.g. **268**) were deprotected to give the corresponding alcohols (e.g. **271**).



(268) **(271)**

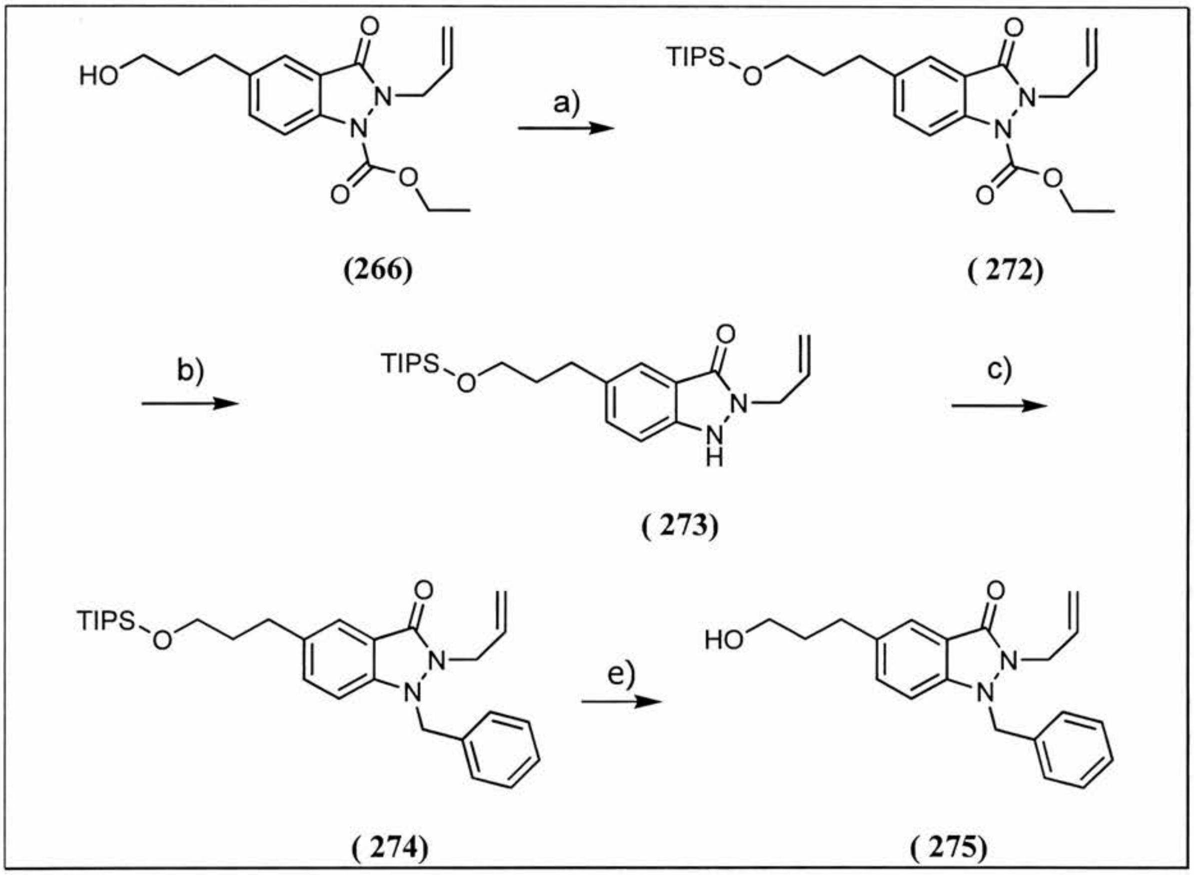
Scheme 155: Synthesis of **271** in solution; a) TBAF, THF, 16 hours, rt, 66%.

The conditions used in the deprotection of the TIPS group in **269** were also applied to the substrate **268** (Scheme 155) to yield **271** in 66%. No signals corresponding to a TIPS group were present in the ^{1}H NMR spectrum of **271**. The broad singlet at 8.90 ppm in the ^{1}H NMR spectrum, also present at 8.74 ppm in the starting material **268**, was assigned as the NH in **271**.

2.3.3.2. Synthesis of **275**

2.3.3.2.1. Synthesis of **275** from **266** (Route 1)

As described in section 2.2.7 (page 105), alkylation of *N2*-substituted indazolinones of type **23** occurs at the N1 position. A route to **275** that takes advantage of this observation was therefore pursued starting from **266** (page 146). The reaction sequence involves protection of the primary alcohol using triisopropyl trifluoromethane sulfonate (TIPSOTf), deprotection of the carbamate group at the N1 position and benzylation of the N1 nitrogen to give **274**. Finally, removal of the silyl protecting group would give **275**. This strategy is described in Scheme 156.



Scheme 156: Synthesis of **275** from **266** in solution; a) TIPSOTf, Et_3N, THF, 2 h, rt, 99%, b) aq. LiOH, THF, o/n, rt, 60%, c) BnBr, Et_3N, THF, o/n, rt, 99%, e) TBAF, THF, o/n, rt, 74%.

The first step of the sequence involved the protection of the primary alcohol present in **266** by a silicon-based reagent. Triisopropylsilyl trifluoromethane sulfonate was used in THF in the presence of triethylamine to prepare **272**, which was isolated in 99% yield. Transforming the alcohol in **266** to the silyl ether **272** decreased the polarity considerably;

$Rf_{\mathbf{266}}$: 0.07 (50% EtOAc/PE) and $Rf_{\mathbf{272}}$: 0.43 (20% EtOAc/PE).

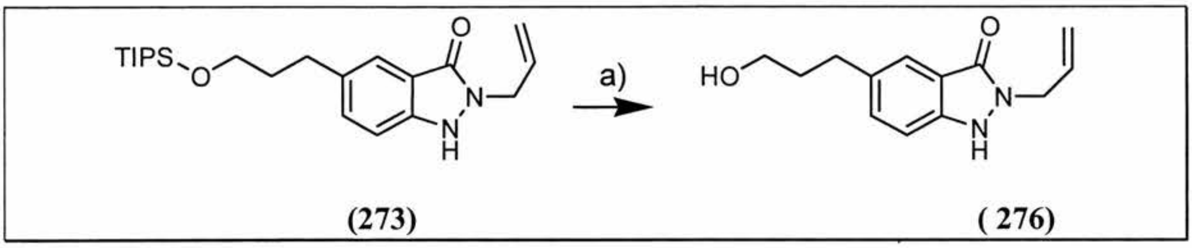
The insertion of the TIPS group was also confirmed by the disappearance of the band at 3426 cm^{-1} in the infrared spectrum, corresponding to the alcohol functionality in **266**, and the coupling observed in the HSQC spectrum between the protons observed at 0.99 ppm (^{1}H NMR), corresponding to the CH and CH_3 of TIPS group, and the two signals at 12.0 ppm and 18.0 ppm (^{13}C NMR) corresponding to the two different carbon environments in the isopropyl moiety.

272 was then reacted with a biphasic system of aqueous lithium hydroxide and THF. The biphasic system was stirred vigorously for 16 hours. The crude reaction mixture was purified using flash column chromatography to give **273** in 75% yield. The preparation of **273** was confirmed by ^{1}H NMR spectroscopy with the presence of a new signal at 7.39 ppm corresponding to the NH group and the disappearance of the quadruplet at 4.36 ppm (CH_2 of the ethyl carbamate) and the triplet at 1.38 ppm (CH_3 of the ethyl carbamate) being consistent with the assigned structure of **273**. **273** is a low melting solid (m.p. = 63-65°C), suggesting that hydrogen-bond interactions between the carbonyl and the NH are presumably present.

273 was then reacted with benzyl bromide in the presence of potassium *t*-butoxide in THF at room temperature for 16 hours to give **274** in 99% yield. A band at 1674 cm^{-1} in the infrared spectrum supported the presence of the carbonyl of the indazolinone in **274**. Moreover, a signal at 53.7 ppm in the ^{13}C NMR spectrum was assigned as the benzylic carbon. The chemical shift indicates that the benzyl group is bonded to the N1 position, as the equivalent carbon in **269** appears in the same region (δ: 52.3 ppm). The interpretation of the HMBC spectrum for **274** also confirmed that benzylation of the N1 position had occurred as no coupling between the benzylic protons and the C-3 of the indazolinone was observed. This coupling would have been observed if O-benzylation had occurred.

274 was then deprotected to the corresponding alcohol using tetrabutylammonium fluoride to give **275** in 74% yield after flash column chromatography. The successful deprotection of the alcohol was confirmed by the presence of a band at 3362 cm^{-1} in the infrared spectrum, characteristic of an OH functional group, and the absence of two signals at 12.0 and 18.3 ppm in the ^{13}C NMR spectrum of **275** (these two types of carbon environment were present in **275** and have been assigned to the carbons in the isopropyl group).

Deprotection of **273** was also carried out under standard conditions to give an authentic sample of **276** in a modest 60% yield.



(273) **(276)**

Scheme 157: Synthesis of **276** in solution; a) TBAF, THF, o/n, rt, 60%.

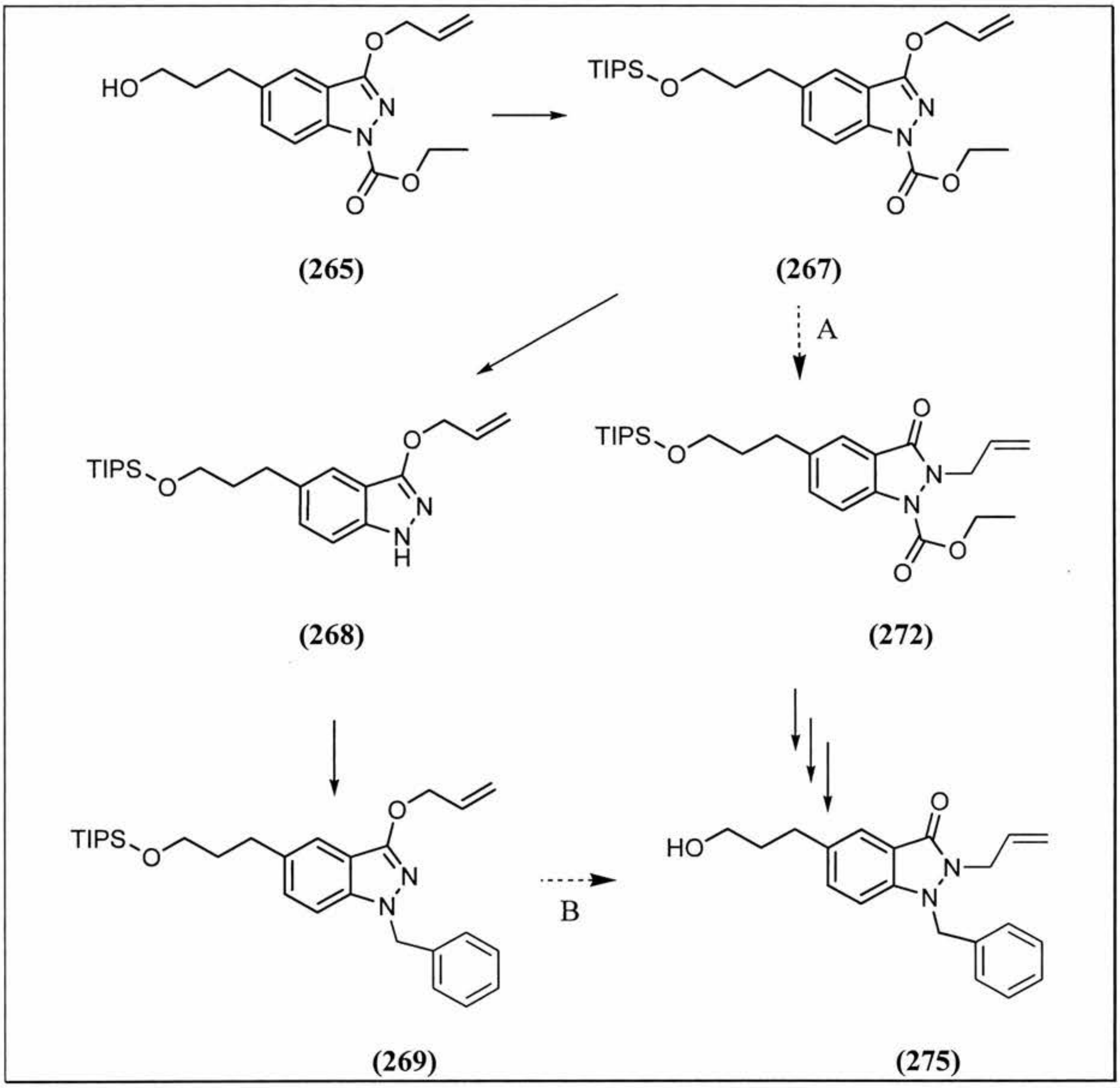
The preparation of **276** was considered successful as the signals characteristic of the TIPS group at 11.9 and 18.0 ppm in the ^{13}C NMR spectrum of **273** were not present in the spectrum of **276**. High resolution mass spectroscopic analysis of **276** confirmed that the molecular formula of **276** was as expected (*m/z:* 233.1288 corresponded to $[M+H]^+$, $C_{13}H_{17}N_2O_2$ (calculated *m/z:* 233.1290)).

2.3.3.2.2. Synthesis of 275 by Claisen rearrangement (Route 2)

The strategy described in section 2.3.3.2.1 relies on the fact that benzylation (alkylation) occurs specifically at the N1 position of *N2*-substituted indazolinones. Two strategies leading to **275** are possible starting from **265**, one of which also relies on this information. Starting from the 3-allyloxyindazole derivative **265**, the rearrangement of the allyl moiety from the O position to the N2 position can be induced at two different stages (dotted arrows in Scheme 158):

A) when the N1 position is protected by the carbamate group, from **267** to **272**.

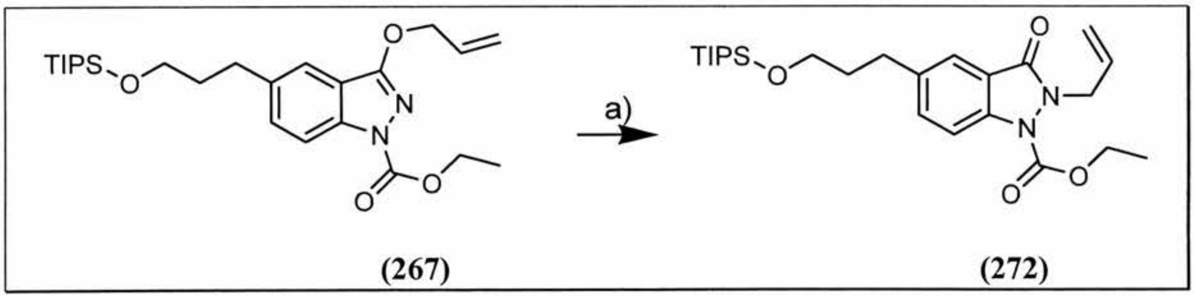
B) when the N1 position is substituted by the benzyl group, from **269** to **274**.



Scheme 158: Two paths to **275** from **265**.

2.3.3.2.2.1. Synthesis of 272 from 265 via 272

The preparation of **275** from **272** was successful (Scheme 156, page 151). Therefore, in order to show that **275** can be prepared from **265** via route A, it was necessary to show that the rearrangement of **267** to **272** (Scheme 159) was possible.



Scheme 159: Synthesis of **267** from **272**; a) $Pd(PPh_3)_4$, THF, 90%.

267 was dissolved in dry THF and a catalytic amount of tetrakis(triphenylphosphine)palladium(0) was added. The reaction was protected from the light by foil and stirred at room temperature under an inert atmosphere for 16 hours. The product isolated from the reaction was compared to the starting material **267** and to the expected product **272**. The ^{1}H NMR spectra comparison shows clearly that the starting material (Figure 35a) was converted to the desired product of the rearrangement reaction (Figure 35b). The material obtained after the rearrangement reaction was then compared to the expected product (Figure 35c). The similarity of the signals in the allyl region (6.3-4.5 ppm) indicates that the material obtained after rearrangement of **267** is the same as the product made in solution by direct synthesis (**272**) (Section 2.3.3.2.1).

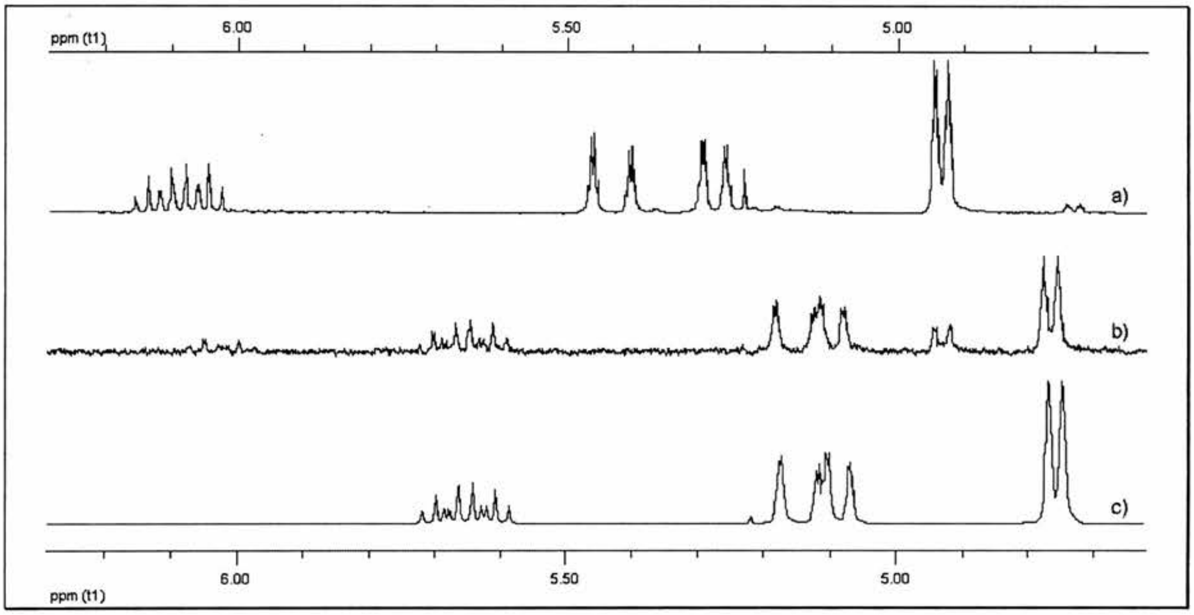
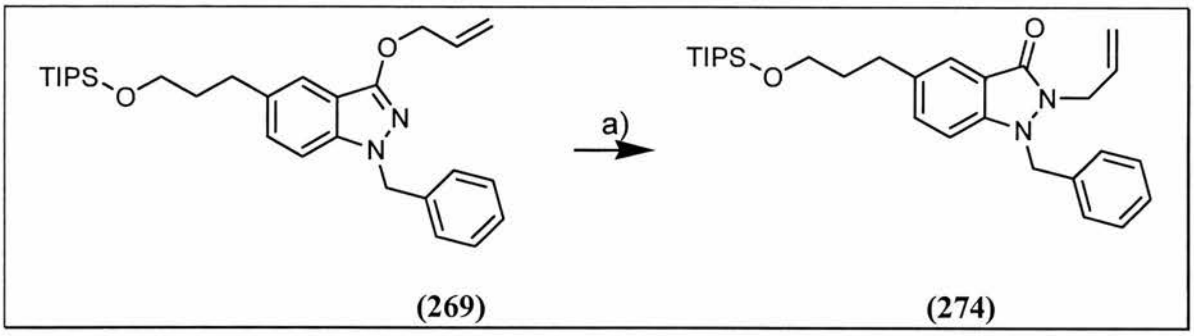


Figure 35: ^{1}H NMR spectra comparison of a) starting material **267**, b) **267** after reaction with tetrakis(triphenylphosphine)palladium(0), and c) expected product **272**.

2.3.3.2.2.2. Synthesis of 275 from 265 via 269

We have previously described the successful preparation of **269** from **265** (Scheme 154, page 149). Subsequent rearrangement of **269** to give **274** was therefore attempted.



Scheme 160: Synthesis of **274** from **269**; a) Pd(PPh_3)$_4$, THF, 90%.

269 was treated with tetrakis(triphenylphosphine)palladium(0) in THF at room temperature under an inert atmosphere. The reaction was stirred for 16 hours and the crude reaction mixture was purified by flash column chromatography to give **274** in 90% yield. The ^{1}H and ^{13}C NMR spectra of **274** prepared by this route were compared with the material prepared by route 1 (section 2.3.3.2.2.1) and were found to be identical.

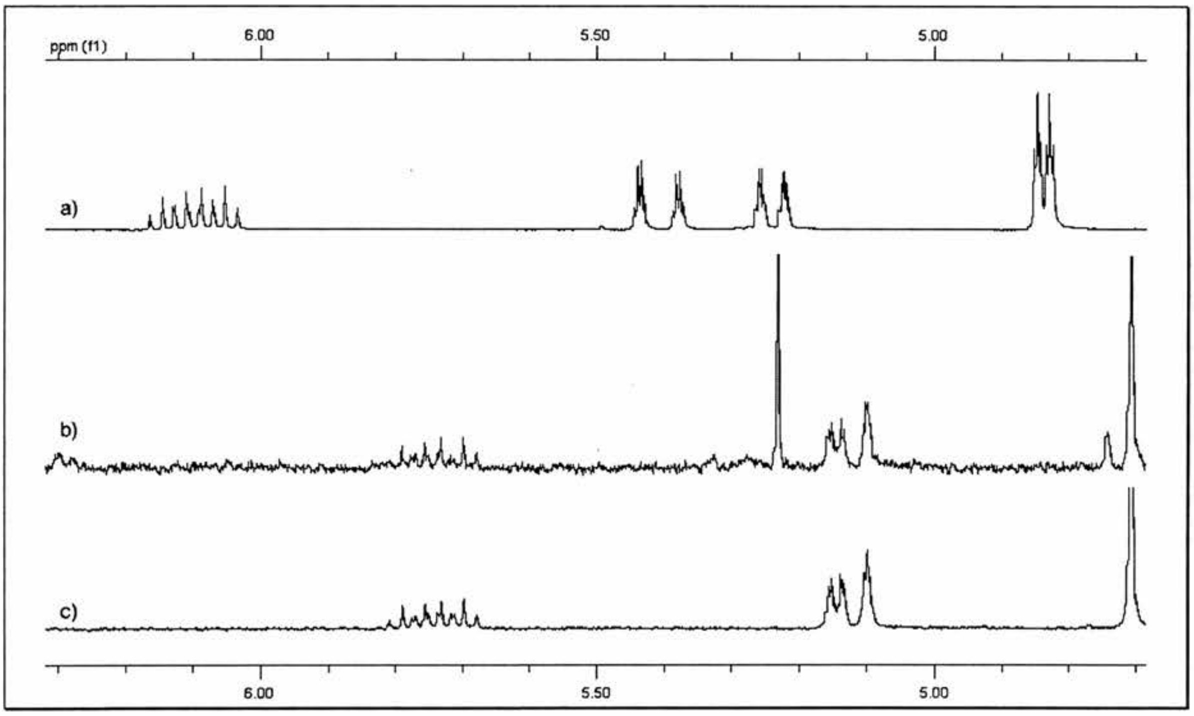


Figure 36: ^{1}H NMR spectra comparison of a) starting material **269**, b) **269** after reaction with Pd(PPh_3)$_4$ and c) authentic **274**.

2.3.4. Solid phase studies

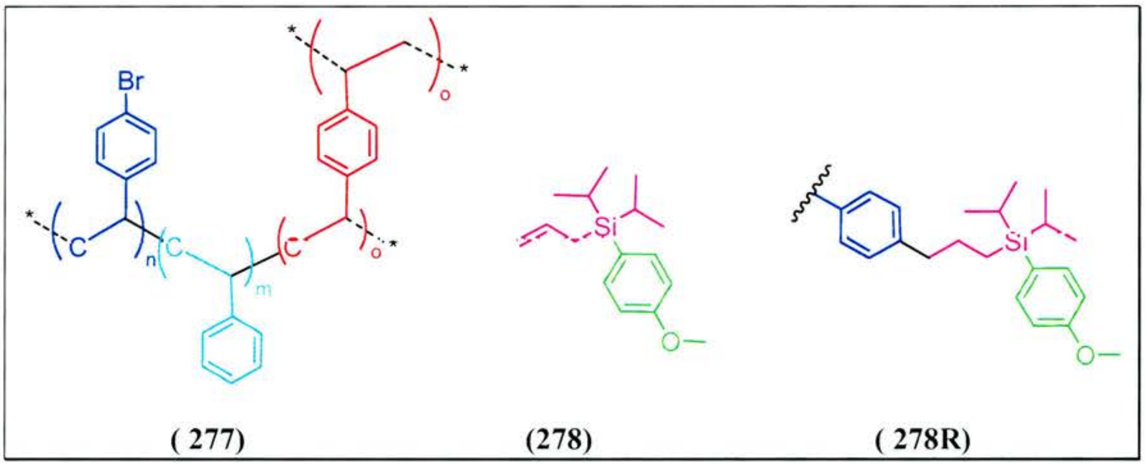
In order to evaluate the synthesis developed on insoluble polymer, every step was analysed by LC/MS to compare the product synthesised on the resin and cleaved from the solid support with the fully characterised authentic material made in solution.

The LC/MS conditions were set up and optimised using the authentic materials using a C18 reverse phase column.

2.3.4.1. The loading

2.3.4.1.1. The solid support and the loading reaction

The TIPS group previously used in the solution phase was viewed as a model of the silicon-tethered resin planned for the solid phase synthesis. The details of this commercially available resin (Novabiochem, 50-100 µm, 1.50 mmol per gram of resin) appear in Scheme 161. This resin is a copolymer based on polystyrene, made from 4-bromostyrene (in blue), styrene (in clear blue) and a cross linker unit, divinylbenzene (in red) (**277**). The bromine was then replaced using a Suzuki coupling reaction with the boronate derived from the allyl moiety in **278** to insert the three carbon chain (purple). The methoxy phenyl moiety (in green) is the group that allows the activation of the resin **278R** and the loading of the small molecule of interest through an alcohol functional group.



(277) **(278)** **(278R)**

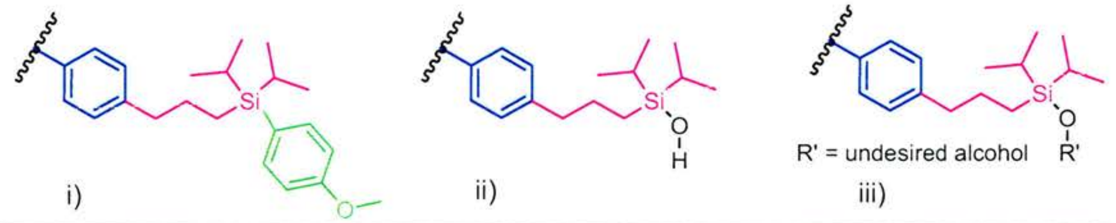
Scheme 161: Structure of the bromopolystyrene resin **277**, **278** and **278R**, silicon-based resin before activation.

The activation of the resin **278R** is generally carried out in the presence of triflic acid (trifluoromethanesulfonic acid), one of the strongest organic acids [159]. It is employed as a protonating reagent. The protonation of the paramethoxyphenyl group allows its removal, giving a very electrophilic silicon atom which is then attacked by the alcohol of interest in the presence of a non-nucleophile base (e.g. 2,6-lutidine) (Scheme 162).

(278R) **(279)** **(280)**

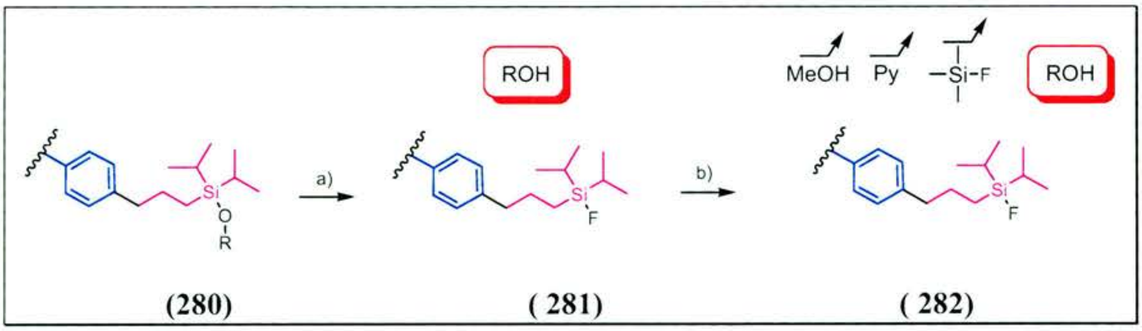
Scheme 162: Loading of alcohol on the silicon-based resin, a) TFA, DCM, rt, 30 min. b) i) 2,6-lutidine, DCM, rt, 15 min. ii) ROH, DCM, rt, 10 h.

Any trace of water or competing nucleophiles must be avoided as they could interfere during the loading procedure. This would result in residual reactive sites on the resin (Scheme 163) and would contaminate the compound of interest after final cleavage.



Scheme 163: Possible residual site on the resin due to i) incomplete activation, unreacted resin **278R**, ii) presence of water, iii) presence of undesired alcohol during activation/loading step.

The advantages of this resin are that the reaction conditions for the cleavage are specific as the Si-O bond is cleaved by fluoride anion. HF/pyridine is typically used for cleavage when this resin is used.[159] The reaction is quantitative and occurs at room temperature under mild conditions.[136] The main advantage of this strategy is the fact when the cleavage reaction is quenched with methoxy trimethylsilane, all the by-products are volatile. Thus, there is no contamination of the desired product of the reaction (Scheme 164).



Scheme 164: Cleavage of resin **280** by HF/pyridine and quenching with methoxy trimethylsilane; a) HF/pyridine, THF, 3h, rt, b) Me_3SiOMe, 30 min, rt.

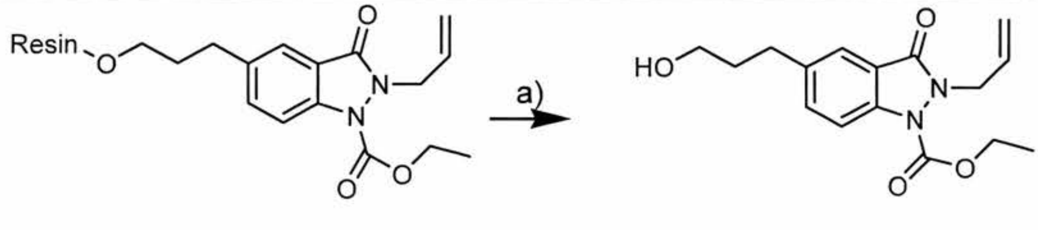
The loading level was determined by mass differences. Two equivalents of alcohol were used for the loading step. Any unloaded alcohol was recovered by filtration and carefully purified. The difference between the initial mass of alcohol and the mass obtained after loading/purification gave the mass of alcohol loaded onto the resin.

After loading, a small amount of the resulting resin was cleaved and the product analysed by LC/MS. The nanomolar quantities of product cleaved from the resin were collected and injected on a C18 reverse column and compared with the corresponding authentic material.

2.3.4.1.2. Loading and proof of loading of the N-allyl isomer **266**

266 was prepared and dried initially by azeotropic distillation with toluene and then under high vacuum [136] in order to remove any traces of moisture. **266** was then loaded onto the solid support according to the standard procedure.[136] The quantity of material recovered from the loading after careful purification led to a calculated loading level of 33%. Whilst disappointingly low it was still possible to carry out the desired reactions using this material.

In order to prove the loading reaction was successful, **266R** (Scheme 165) was cleaved using HF/pyridine according to the standard procedure.[136] The solution was then separated from the insoluble polymer by filtration and solvent and by-products were evaporated *in vacuo*. The residue was dissolved in a mixture of water/methanol 1:1 and injected onto the C18 reverse phase column.



(266R) **(266)**

Scheme 165: Cleavage of **266R**; a) i) HF-Pyridine, THF, 3 h, rt, ii) Me_3SiOMe, 30 min, rt.

LC/MS traces of the authentic material **266** made in solution phase (page 146) and the material cleaved from the solid support **266R** are shown in Figure 37.

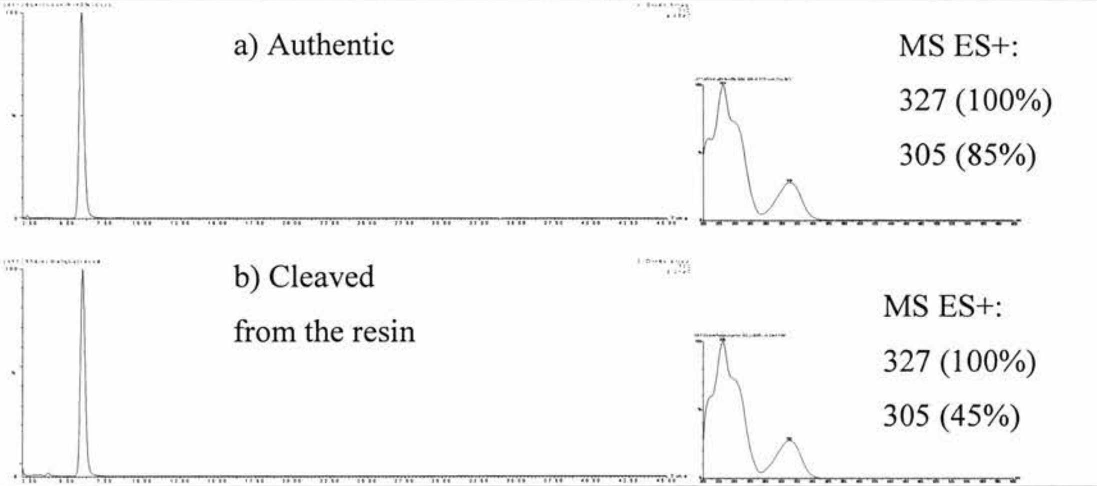


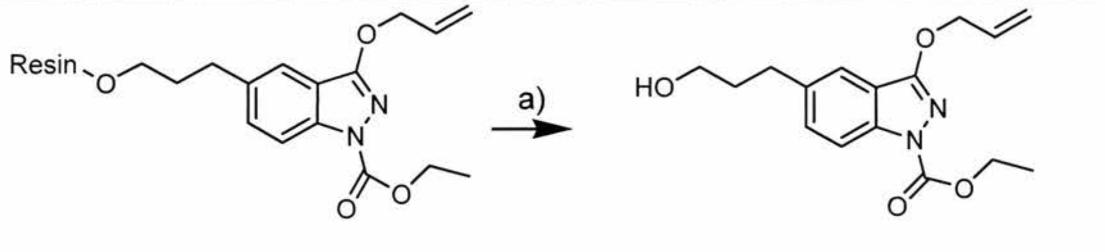
Figure 37: Comparison by LC/MS of a) **266** authentic material obtained by direct synthesis and b) material cleaved off the resin **266R**.

The retention times of **266** and material cleaved of **266R** are near identical (Figure 37). Moreover, additional data confirmed that the products are the same (*m/z*: 327 corresponding to $[M\text{+H}]^+$ in both products). Finally, UV traces recorded on the diode array concluded that the product **266** loaded onto the resin to make **266R**, and cleaved off the resin afforded **266** as the only product loaded onto the resin.

2.3.4.1.3. Loading and proof of loading of the O-allyl isomer 265

265 was prepared and dried in order to remove any trace of moisture. **265** was then loaded onto the solid support.[136] The quantity of material recovered from the loading after careful purification led us to a loading level of 33%.

265R (Scheme 166) was then cleaved using HF/pyridine according to the standard procedure[136] to judge the success of the loading reaction. The solution was then separated from the insoluble polymer by filtration and solvent and by-products were evaporated *in vacuo*. The residue was dissolved in a mixture of water/methanol 1:1 and injected onto the C18 reverse phase column.



(265R) **(265)**

Scheme 166: Cleavage of **265R**; a) i) HF-Pyridine, THF, 3 h, rt, ii) Me_3SiOMe, 30 min, rt.

LC/MS traces of the authentic material **265** made in solution phase and the material cleaved from the solid support **265R** are shown in Figure 38.

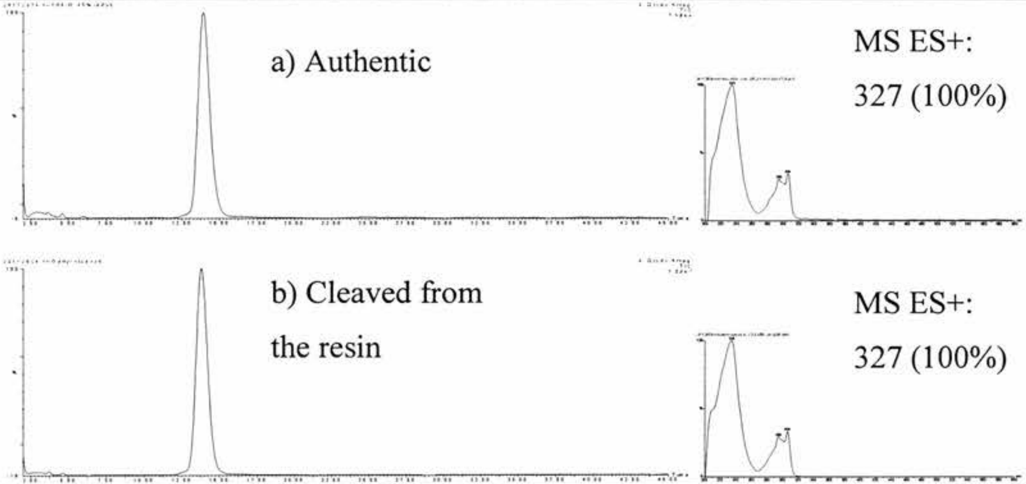


Figure 38: Comparison by LC/MS of a) **265** authentic material obtained by direct synthesis and b) the material cleaved off the resin **265R**.

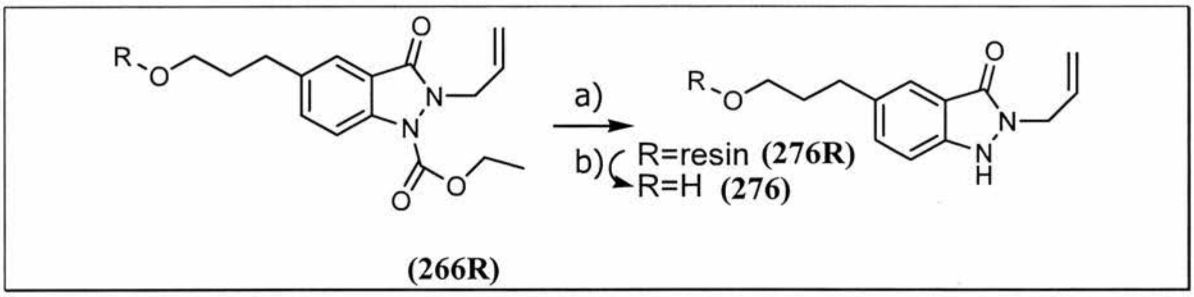
The retention times of **265** and material cleaved of **265R** are very similar (Figure 38). Moreover, data collected confirmed that the products are the same, with *m/z*: 327 corresponding to $[M+H]^+$ in both products. Finally, UV traces recorded on the diode array concluded that the product **265** loaded onto the resin to make **265R**, and cleaved off the resin afforded **265** as the only product loaded onto the resin.

2.3.4.2. Deprotection of the carbamate using LiOH

The loadings of **265** and **266** were both successful. The next step in order to transfer the solution phase reaction sequence to the solid support was to remove N1-ethyl carbamate protecting groups on resin **265R** and **266R** to allow for subsequent functionalisation.

2.3.4.2.1. N1 deprotection of **266R**

The resin **266R** was treated with a suspension of LiOH in THF/H_2O. Multiple conditions were tried, but 300 µL of 2M LiOH in 3 mL of THF, despite the fact that it resulted in a biphasic mixture, was shaken vigorously and allowed the complete deprotection over 2 days, at room temperature. The product resulting from the lithium hydroxide treatment was subsequently cleaved off the resin by a solution of hydrogen fluoride/pyridine in THF (Scheme 167). The solvent was removed *in vacuo* and the product was injected onto the C18 reverse phase column.



(266R)

Scheme 167: Synthesis of **276** on solid phase; a) LiOH, THF, 48 h, rt, b) i) HF-Pyridine, THF, 3 h, rt, ii) Me_3SiOMe, 30 min, rt.

LC/MS traces of the authentic material **276** (page 153) made in solution phase and the material made on the solid support from **266R** are shown in Figure 39 .

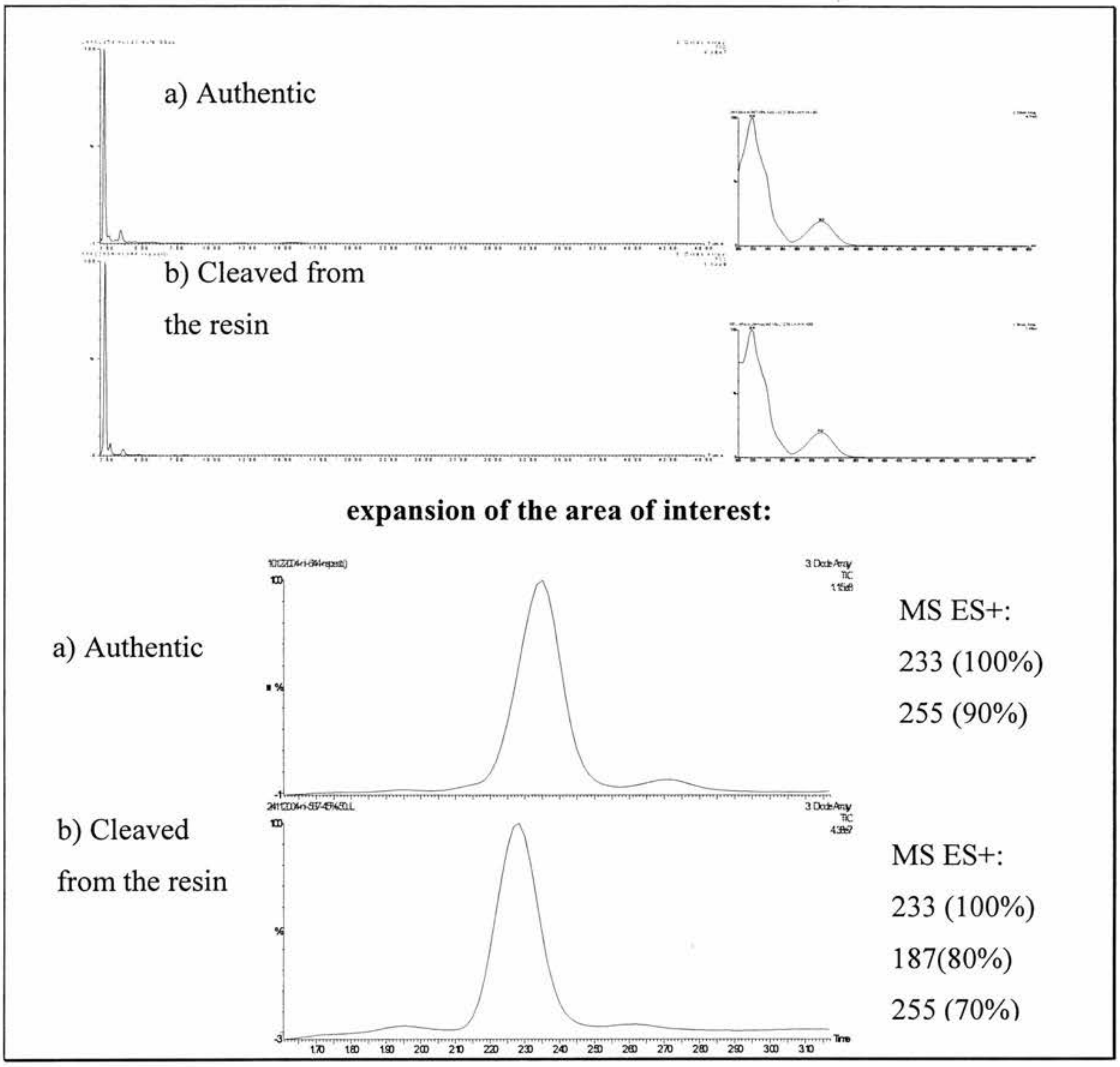


Figure 39: Comparison by LC/MS of a) **276** authentic material obtained by direct synthesis and b) the material cleaved off the resin after treatment with lithium hydroxide, and expansion of the area of interest.

Figure 39 shows that **276** obtained by direct synthesis and **276** made from **266R** via **276R** and cleaved by HF/pyridine are identical confirming that the deprotection step on the solid phase had worked. The retention times are slightly different (10 seconds) due to a different internal pressure in the system. However, the UV traces show two maxima at 219 and 313 nm for both the authentic material **276** and for the material cleaved from resin **276R.** Moreover, identical masses (*m/z*: 233 $[M\text{+H}]^+$) allowed us to conclude that the deprotection of the N1 carbamate of **266R** on solid phase was successful.

The idea of a biphasic system (THF/LiOH) was initially viewed as a possible disadvantage but the experiment proved that this concern was unjustified.

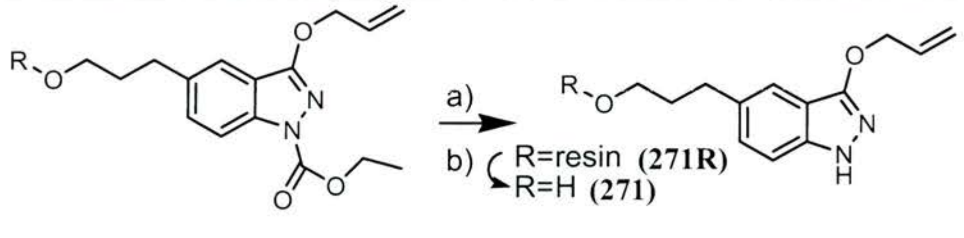
2.3.4.2.2. N1 deprotection of **265R**

The conditions previously used for the deprotection of **266R** on solid support were used for the deprotection of **265R**. However, after two days, no deprotection of the carbamate on **265R** was observed. The carbonyl carbon in the carbamate of **265R** is less electrophile than in **266R** as the resulting N2 substituted indazolinone **283** is a better leaving group that the O isomer **284**, due to the increased stabilisation of the negative charge by the oxygen atom (O atom more electronegative than N atom) (Scheme 168).

(283) **(284)**

Scheme 168: **283** as a better leaving group by stabilisation of the negative charge by the carbonyl.

Therefore, the deprotection conditions had to be changed to remove the carbamate group on **265R**. From 2 days at room temperature (to deprotect *N2*-allyl indazolinone **266R**), the conditions needed were set up at 2 days at 50°C to allow complete deprotection in the N1 position.



(265R)

Scheme 169: Synthesis of **271** on solid support; a) LiOH in THF, 50°C for 2 days, b) i) HF-Pyridine, THF, 3 h, rt, ii) Me_3SiOMe, 30 min, rt.

LC/MS traces of the authentic material **271** (page 150) made in solution phase and the material cleaved of the solid support **271R** are shown in Figure 40.

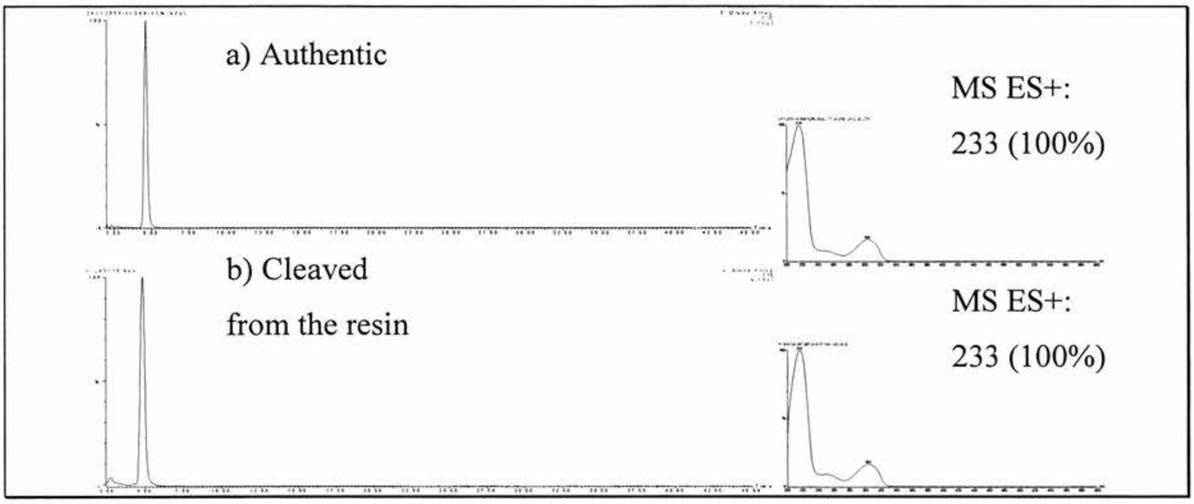


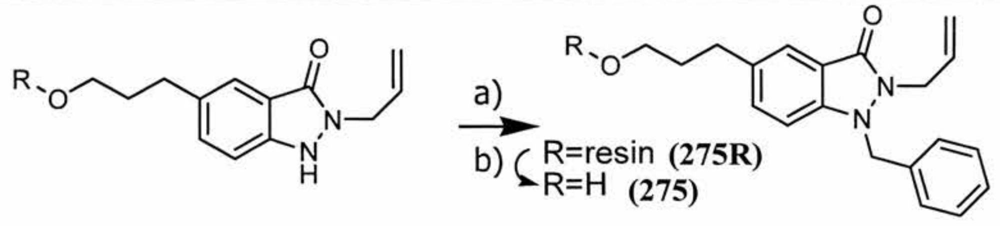
Figure 40: Comparison by LC/MS of a) **271** authentic material obtained by direct synthesis and b) the material cleaved off the resin **271R**.

The similar retention times, 4.70 min for the authentic material **271** and 4.50 min for the material cleaved of the resin **271R** provides some support for the fact that the deprotection of **265R** on the solid phase gave the product of interest. Mass spectroscopic analysis gave the same major peak (*m/z*: 233 $[M\text{+H}]^+$) and UV data showed the maxima at 216 and 303/304 nm in both products. Despite the slightly different retention times due to the fact that the two samples were run at different days, the deprotection of **265R** by lithium hydroxide treatment at 50°C for 2 days was successful and gave **271** as the unique product of the reaction.

2.3.4.3. N1-functionalisation

2.3.4.3.1. Functionalisation of 276R

The benzylation of **276R** (page 162) was achieved by vigorously shaking the resin in the presence of potassium *t*-butoxide and benzyl bromide in THF for 2 days at room temperature. The resulting product was cleaved off the resin according to the procedure reported in the literature [136] (Scheme 170).



(276R)

Scheme 170: Synthesis of **275** on solid phase; a) BnBr, ^{t}BuOK, THF, 48 h, rt, b) i) HF-Pyridine, THF, 3 h, rt, ii) Me_3SiOMe, 30 min, rt

LC/MS traces of the authentic material **275** (page 151) made in solution phase and the material cleaved from the solid support **275R** are shown in Figure 41.

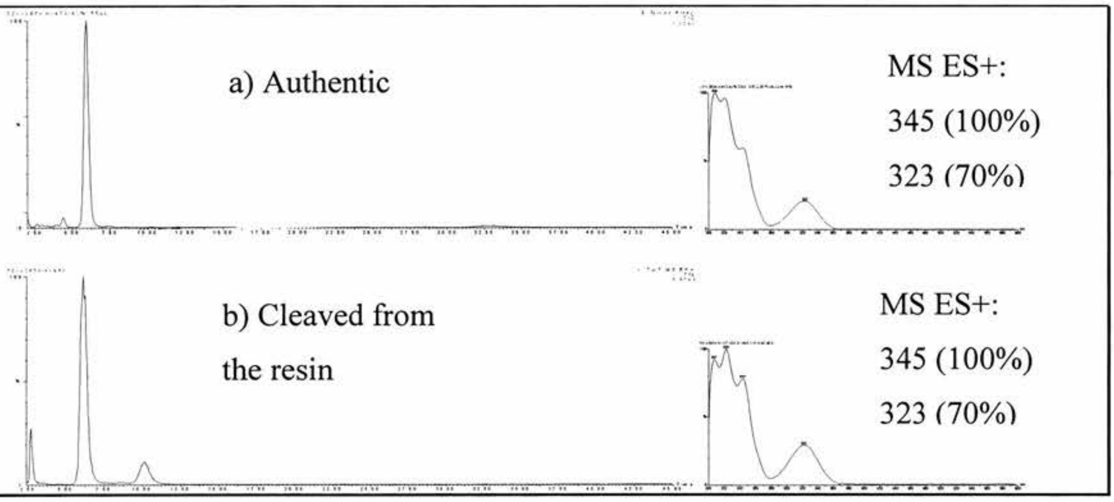
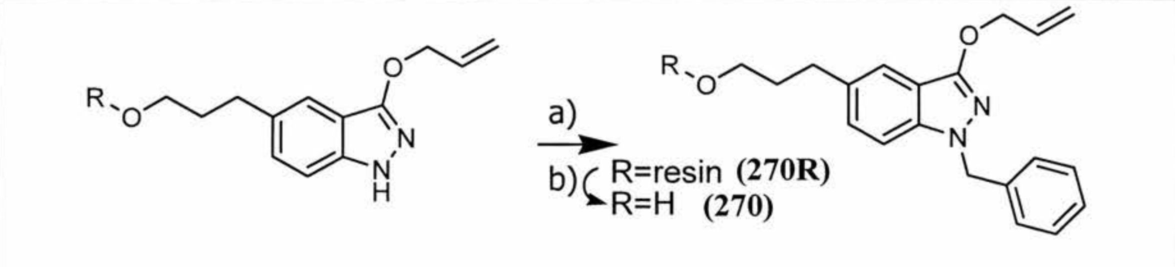


Figure 41: Comparison by LC/MS of a) **275** authentic material obtained by direct synthesis and b) the material cleaved of the resin **275R**.

The chromatograms of the authentic material **275** and the material cleaved off the resin **275R** show similar retention time at 6.00 minutes. The UV spectra show also the same maxima at 207, 223, 244 and 322(±1) nm for both products. The mass spectroscopic analysis showed the same major peaks at *m/z*: 345 (100%) corresponding to the sodium adduct $[M\text{+Na}]^+$ and at *m/z*: 323 (70%) corresponding to $[M\text{+H}]^+$ of $C_{20}H_{22}N_2O_2$. The synthesis of **275** on the solid support was therefore successful after 2 days of reaction. Another minor product that appeared in the chromatogram at a retention time of 10.25 minutes has not been identified. However, it has been compared with the materials previously obtained and does not correspond to the unreacted starting material **276**.

2.3.4.3.2. Functionalisation of **271R**

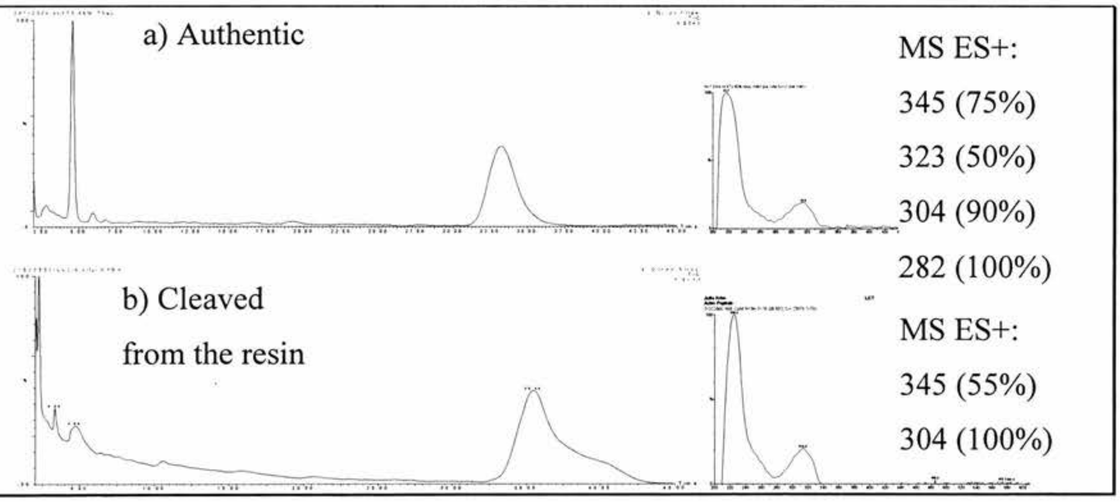
The benzylation of **271R** was attempted using the same conditions previously described for the benzylation of the *N2*-allyl isomer **276R**. However, a reaction time of two days was not enough to push the reaction to completion as unreacted starting material was detected by LC/MS. The reaction was pushed to completion by leaving the beads in contact with benzyl bromide and the base (^{t}BuOK) for 5 days at room temperature (Scheme 171). The resin **270R** was then submitted to the cleavage conditions (HF/pyridine then MeOSi(Me)$_3$).[136]



(271R)

Scheme 171: Synthesis of **270** on solid phase; a) BnBr, ^{t}BuOK, THF, 5 days, rt, b) i) HF-Pyridine, THF, 3 h, rt, ii) Me$_3$SiOMe, 30 min, rt

LC/MS traces of the authentic material **270** made in solution phase and the material made on the solid support **270R** are shown in Figure 42.



MS ES+:
345 (75%)
323 (50%)
304 (90%)
282 (100%)

MS ES+:
345 (55%)
304 (100%)

Figure 42: Comparison by LC/MS of a) **270** authentic material obtained by direct synthesis and b) the material cleaved off the resin **270R**.

The material cleaved off the resin **270R** has a retention time different by 2 minutes compared to authentic **270**. This difference is explained by the differences in back pressure in the HPLC system at the moment of the analysis (the two spectra were recorded on different days). However, the UV properties of the two materials appeared to be almost identical as **270** shows two maxima at 217 and 315 nm and the product cleaved from **270R** gave two maxima in the same regions, 225 and 313 nm. Moreover, the authentic material of formula $C_{20}H_{22}N_2O_2$ shows on the chromatogram a peak at *m/z*: 345, corresponding to the sodium adduct $[M\text{+Na}]^+$ and a peak at *m/z*: 323, corresponding to the protonated species $[M\text{+H}]^+$ and two fragments at *m/z*: 304 and 282. The material cleaved off the resin contains peaks at *m/z*: 345 and 304, corresponding to the sodium adduct of the material of interest and the common fragment $[M\text{-19}]^+$ respectively.

This data has been interpreted as supporting the successful synthesis of **270** on the solid support.

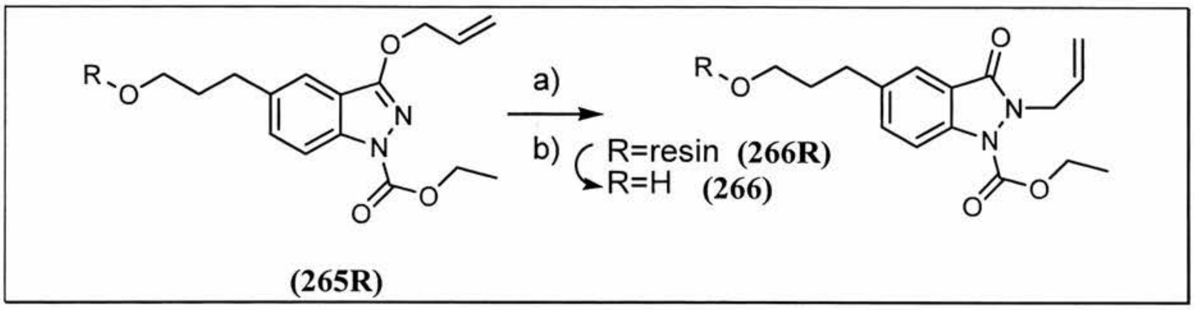
2.3.4.4. The rearrangement

One of the main driving forces of the project is the aza-Claisen rearrangement of the allyl moiety from the oxygen to the nitrogen position. Described in Scheme 18 (page 39), our aim was to access different cores from a single starting material. We have shown so far that we could make the two targets on solid support. However, the synthesis of these targets does not involve the aza-Claisen rearrangement. In this section, the rearrangement of the allyl moiety was studied to prove that the aza-Claisen rearrangement can be used as a skeleton diversity reaction in the case of indazolinones on the solid phase resin. The rearrangement of the two species **265R** and **270R** by the use of the two methods described previously in solution (section 2.2.4, page 73) (palladium-catalysis and microwave-induced) was the ultimate goal of our project.

2.3.4.4.1. Pd(PPh_3)$_4$ Rearrangement

2.3.4.4.1.1. Rearrangement of **265R** using palladium (0) catalysis

The resin **265R** was treated with tetrakis(triphenylphosphine)palladium(0) in solution in THF. The reaction was left for 24 hours at room temperature under an inert atmosphere. Then, the insoluble polymer was washed and submitted to the cleavage conditions[136] (Scheme 172).



Scheme 172: Synthesis of **266** on solid phase; a) $Pd(PPh_3)_4$, THF, 24 h, rt b) i) HF-Pyridine, THF, 3 h, rt, ii) Me_3SiOMe, 30 min, rt.

LC/MS traces of the authentic material **266** (page 146) made in solution phase and the material made on the solid support from **265R** via **266R** are shown in Figure 43.

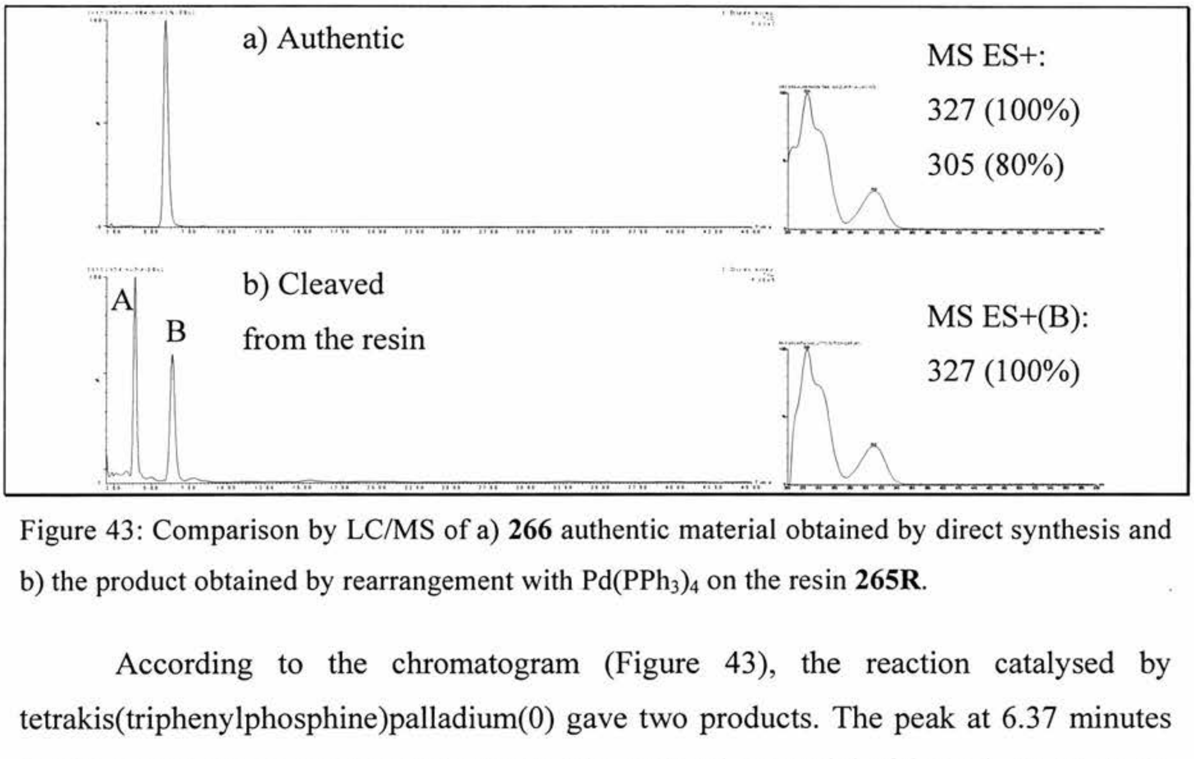
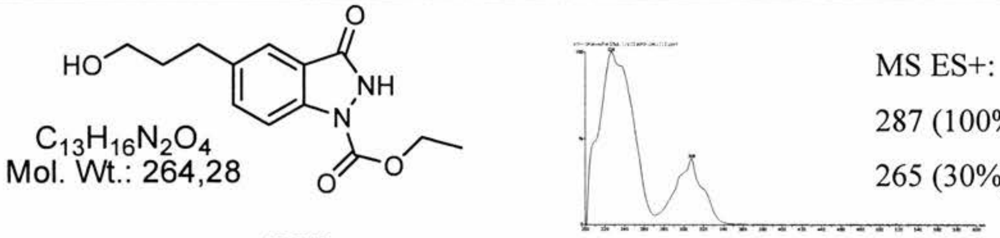


Figure 43: Comparison by LC/MS of a) **266** authentic material obtained by direct synthesis and b) the product obtained by rearrangement with $Pd(PPh_3)_4$ on the resin **265R**.

According to the chromatogram (Figure 43), the reaction catalysed by tetrakis(triphenylphosphine)palladium(0) gave two products. The peak at 6.37 minutes corresponds to the expected product **266**. The authentic material of formula $C_{16}H_{20}N_2O_4$ shows on the chromatogram a peak at *m/z*: 327, corresponding to the sodium adduct $[M\text{+Na}]^+$ and a peak at *m/z*: 305, corresponding to the protonated species $[M\text{+H}]^+$. The material cleaved off the resin contains peaks at *m/z*: 327 corresponding to the sodium adduct of the material of interest. The UV spectra show the same maxima at 310 and 225 nm.

The signal appearing at 3.90 minutes shows a UV spectrum characteristic of indazolinones (data not shown). According to the molecular mass (*m/z*: 287), the product was assigned as the de-allylated compound **264**. The peak at *m/z*: 287 could correspond to the sodium adduct of **264** (264+23(Na)=287 $[M\text{+Na}]^+$) and the peak at *m/z*: 265 to the $[M\text{+H}]^+$ adduct of **264** (Scheme 173).



MS ES+:
287 (100%)
265 (30%)

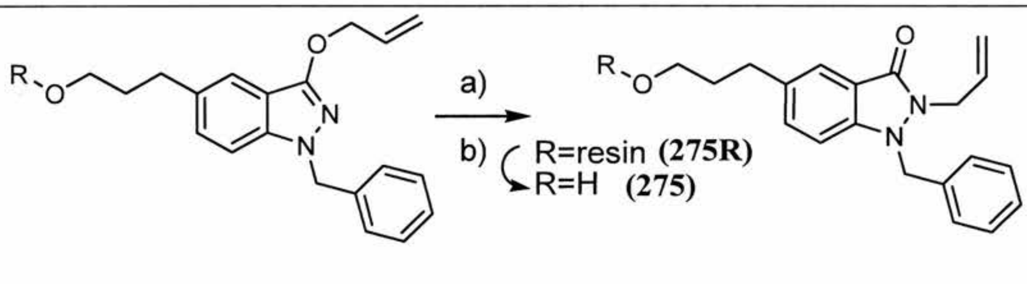
(264)

Scheme 173: Structure and UV spectrum of **264**.

The use of excess tetrakis(triphenylphosphine)palladium(0) in this reaction is a possible reason of obtaining **264**. It is known that palladium (0) can be used to deprotect *N*-allyl[174] and *O*-allyl[175] compounds in the presence of a nucleophile. The presence of adventitious water acting as nucleophile might have aided the removal of the allyl group, either in the starting material or in the expected product, giving **264** in both cases.

It has been shown that the rearrangement of the allyl moiety from the O to the N2 position on the solid phase is possible. It is believed that the amount of the observed the side reaction could be decreased by reducing the amount of catalyst. This transformation has not been optimised further due to time constraints.

2.3.4.4.1.2. Rearrangement of **270R** by palladium catalysis



(270R)

Scheme 174: Synthesis of **275** on solid phase; a) $Pd(PPh_3)_4$, THF, 24 h, rt, b) i) HF-Pyridine, THF, 3 h, rt, ii) Me_3SiOMe, 30 min, rt.

LC/MS traces of the authentic material **275** made in solution phase and the material obtained after reaction of **270R** with tetrakis(triphenylphosphine)palladium(0) are shown in Figure 44.

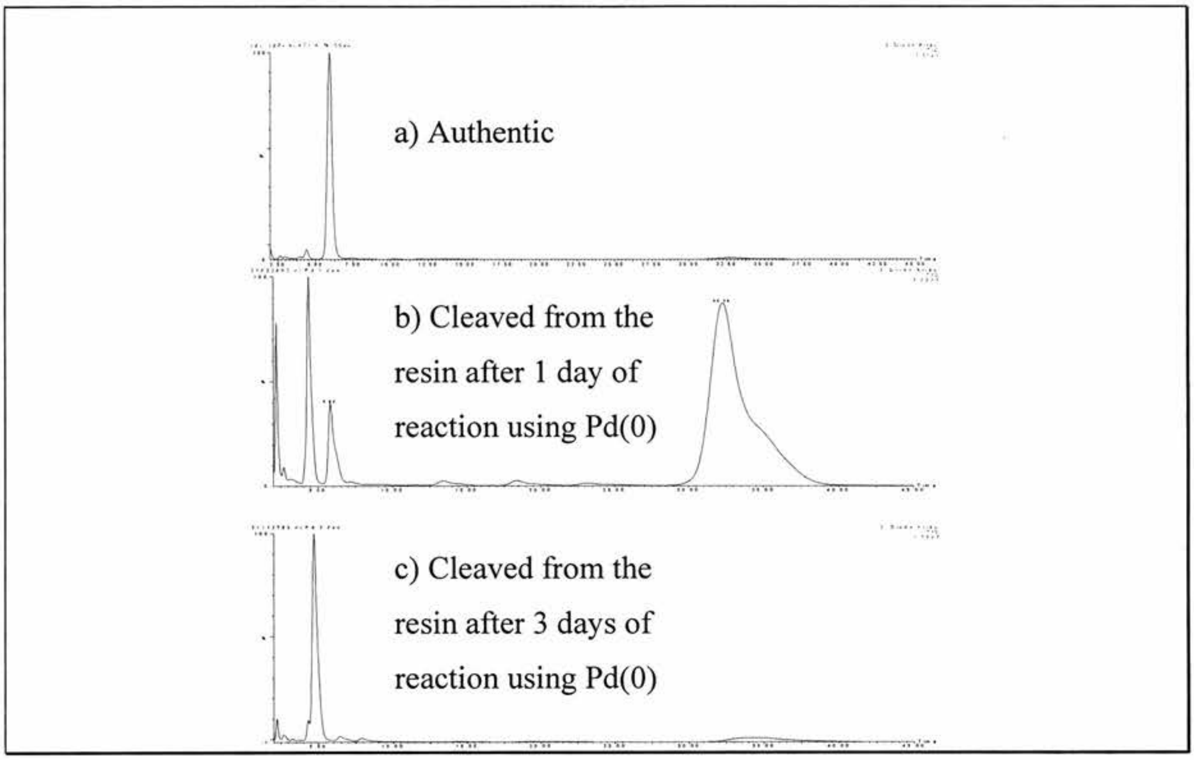
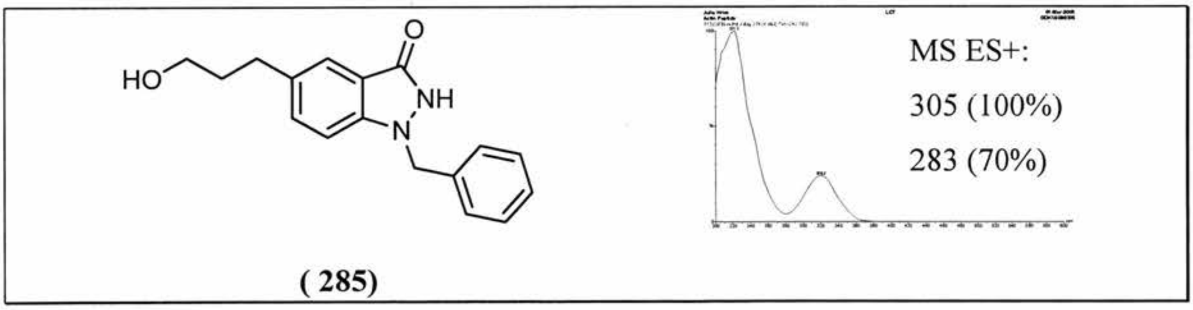


Figure 44: Comparison by LC/MS of a) **275** authentic material made by direct synthesis in solution, b) the products obtained by rearrangement with Palladium on the resin after 24 hours, c) the product obtained by rearrangement with Palladium on the resin after 72 hours.

The rearrangement of **270R** under these conditions shows that there is unreacted starting material present after 24 hours (peak at r.t= 32.3 min). However, the peak with a retention time of 7 minutes corresponds to the desired product **275** as seen by the comparison with authentic material. Unfortunately, an analogous problem to that observed for **265R** was also seen. The peak at 4.5 minutes corresponds to **285** resulting from deprotection of the allyl group (Scheme 175). The mass corresponding to this peak is *m/z*: 283 (70%), $[M\text{+H}]^+$ of **285** and *m/z*: 305 (100%), $[M\text{+Na}]^+$ of **285**.



(285)

Scheme 175: Structure, UV spectrum and main ion currents observed by mass spectroscopy of **285**.

When the reaction was repeated with an extended reaction time (72 hours), the material cleaved off the resin corresponded predominantly to **285**. However, even after

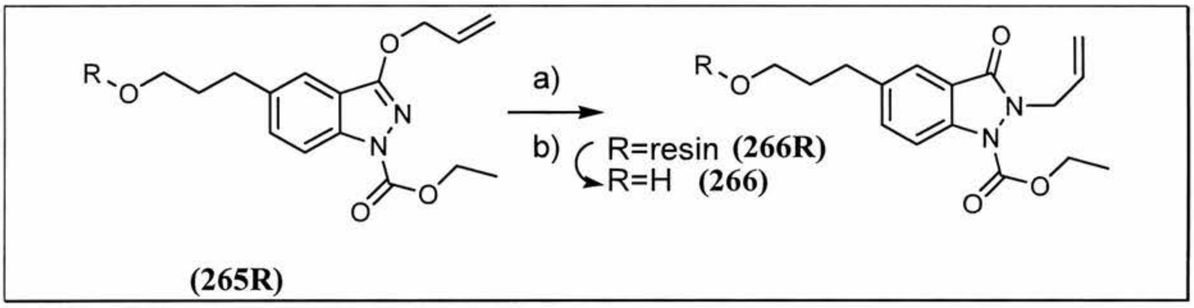
72 hours, a broad flat peak appearing at 33 minutes reveals the presence of unreacted starting material **270** (Figure 44).

As discussed above, the formation of 285 probably occurs via Pd(0) catalysed deallylation in the presence of adventitious water (nucleophile).

2.3.4.4.2. Rearrangement using Microwave

2.3.4.4.2.1. Rearrangement of **265R**

Our solution phase studies (Section 2.2.4) suggested that the use of microwave irradiation to induce rearrangement of the N1-protected indazolinone **265R** were unlikely to be successful as the required reaction conditions cleaved the N-C bond in the carbamate protecting group, resulting in N1 deprotection. However, we decided to try this reaction.



Scheme 176: Synthesis of **266** on solid phase; a) Microwave irradiation in DMF, b) i) HF-Pyridine, THF, 3 h, rt, ii) Me_3SiOMe, 30 min, rt.

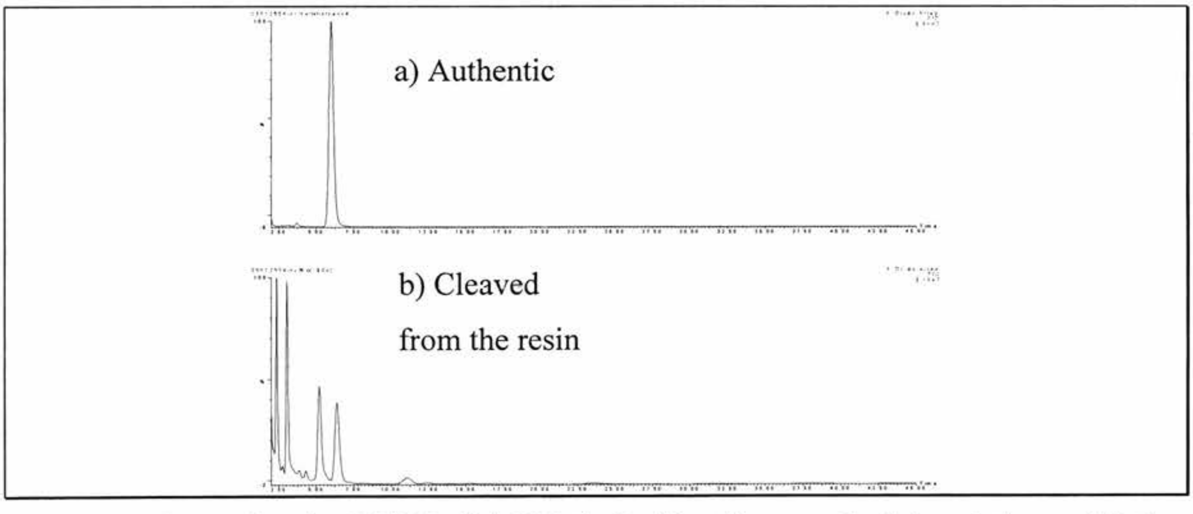


Figure 45: Comparison by LC/MS of a) **266** obtained by direct synthesis in solution and b) the products obtained by rearrangement with microwave on the resin **265R**.

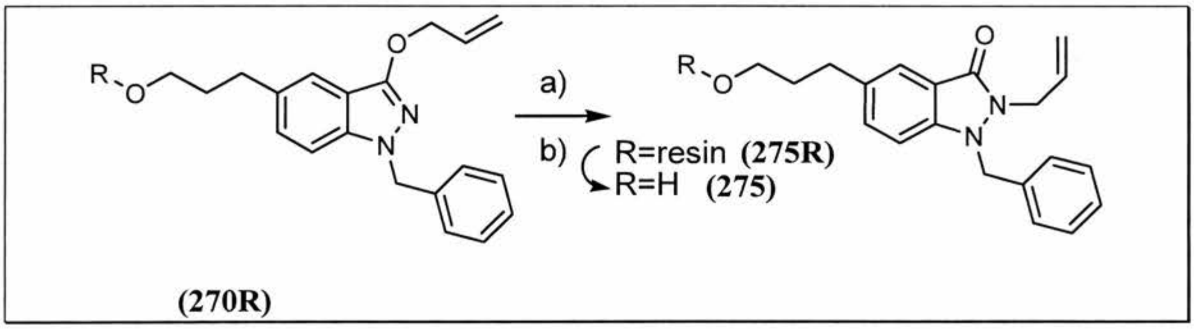
Studying the LC/MS traces obtained for the rearrangement reaction of **265R** induced by microwave irradiation revealed that all the starting material has reacted.

However, the reaction did not produce a single product. Four peaks corresponding to four products were detected. Each product was compared with the intermediates already characterised and assigned as follows:

- R_t= 2.5 minutes: **276** (page 162), product of the rearrangement that has been subsequently deprotected
- R_t= 3.0 minutes: unidentified product
- R_t= 5.0 minutes: **271** (page 150), deprotected starting material
- R_t= 6.2 minutes: **266** (37%) (page 146) desired product from the rearrangement.

According to the result of this experiment, it has been shown that the allyl group can be rearranged from the O to the N2 position under microwave conditions. However, when the N1 position is substituted by a carbamate group this group does not survive the reaction.

2.3.4.4.2.2. Rearrangement of **270R**



Scheme 177: Synthesis of **275** on solid phase; a) microwave irradiation in DMF, b) i) HF-Pyridine, THF, 3 h, rt, ii) Me_3SiOMe, 30 min, rt.

The comparison of the authentic material **275** made in solution and the material made on the solid support by LC/MS leads to the conclusion that a successful rearrangement under microwave irradiation has occurred. As shown in Figure 46, the retention times are very similar. Moreover, the UV properties are similar and maxima are observed at 323 and 225 nm. The masses recorded for the two samples are identical, i.e. *m/z*: 345 corresponding to the sodium adduct of the desired product **275** and *m/z*: 323 ($[M+H]^+$). This result proves that microwave induced rearrangement of **270** on solid phase gives **275** as the major product of the transformation.

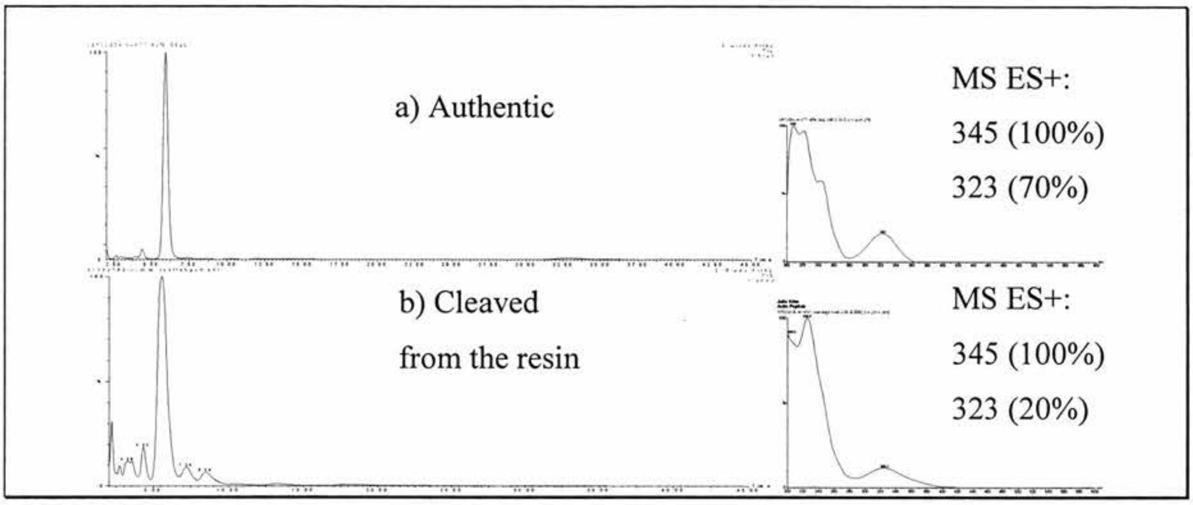
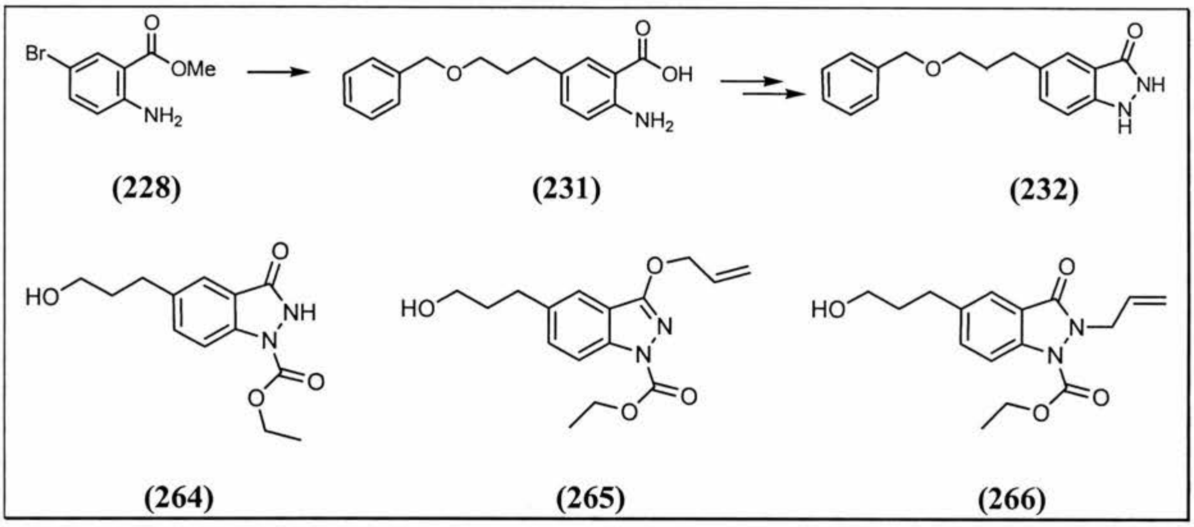


Figure 46: Comparison by LC/MS of a) **275** authentic product made in solution and b) the product obtained by rearrangement with microwave on the resin.

2.3.5. Conclusions

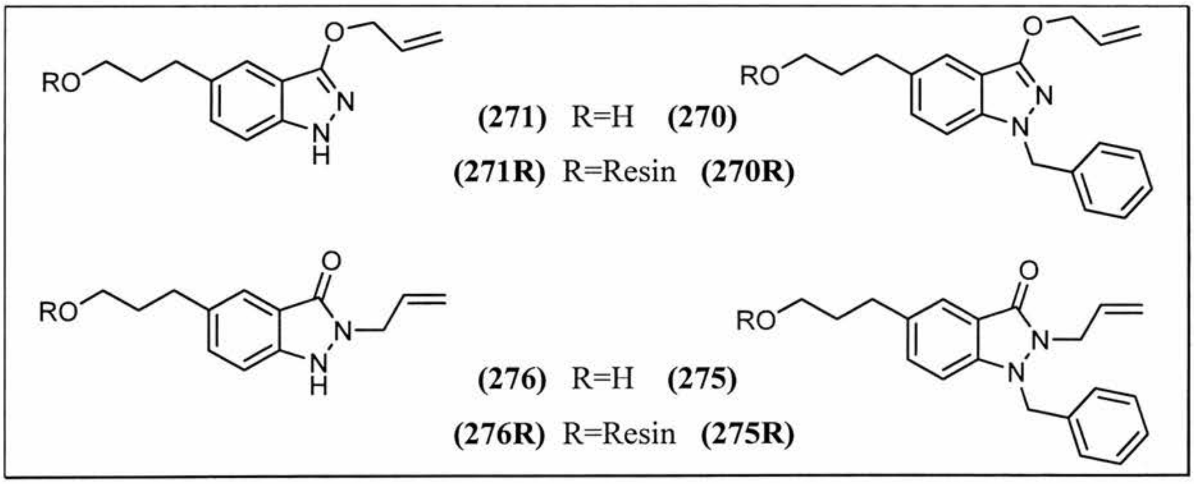
The final part of the project was to develop the methodology reported in section 2.2 so that it was applicable to the synthesis of a library based on indazolinones as the central core.

The objectives were to create and synthesise an indazolinone derivative containing a linker that enabled it to be loaded onto a solid phase resin. The covalent bond formed between the solid support and the small molecule was chosen to be a silicon-oxygen bond. Therefore, the indazolinone derivative had to contain an alcohol functionality. The synthesis of **231** by Suzuki coupling of commercially available anthranilic derivative **228** followed by iodination and cyclisation proved a successful route to reach the targeted indazolinone derivative **232**. Orthogonal protecting groups were chosen to synthesise **264**, which was submitted to Mitsunobu conditions with allyl alcohol to access **265** and **266** as the two key structures designed for solid phase studies.



Scheme 178: Summary structures.

Indeed, **265** and **266** were protected first by a TIPS group to simulate attachment to a solid support. A series of reactions were then carried out to provide authentic material. The same sequence was repeated with solid supported material after loading **265** and **266** onto the silicon-based resin. Cleavage of the small molecules from the solid support by HF-pyridine treatment and analysis by LC/MS on a reverse phase column were used to analyse reaction success. Both **265** and **266** were successfully loaded onto the polystyrene-based resin. Deprotection of the carbamate on the N1 position with lithium hydroxide allowed the synthesis of **271** and **276** respectively. Finally, alkylation of **271** and **276** on the solid support was successful in the presence of potassium *t*-butoxide and benzyl bromide to give **270** and **275** respectively.



Scheme 179: Summary structures.

The aza-Claisen rearrangement studied in section 2.2.4 involving palladium catalysts and thermal methods (microwave) was applied to **265R** and **270R** in an attempt to transform them into **266** and **275** respectively after Si-O cleavage.

Tetrakis(triphenylphosphine)palladium(0) catalysed sigmatropic rearrangement led to the formation of the desired products when the N1 position was protected by a carbamate group **265** or functionalised by a benzyl group **270.** Unfortunately, additional deallylated products were also present. This result could be explained either by the use of excess Pd(0) or by the presence of an adventitious nucleophile trapping the π–allyl palladium reactive species.

The microwave-induced rearrangement showed analogous results when the N1 position was protected by the ethyl carbamate group. The high temperatures do not allow the C-N bond of the carbamate to survive causing its cleavage presumably by adventitious water. However, the allyl group was rearranged successfully from the O position to the N position in **270R**, giving the desired product **275** as the unique product of the reaction after cleavage from the insoluble polymer.

3. Conclusion

3.1. General conclusions

This project is based on indazolinone core and involves three mains sections:

- The use of an aza-Claisen rearrangement of 3-allyloxyindazoles to the corresponding N isomers. This sigmatropic rearrangement was induced by thermal and catalytic methods. The classical thermal method using an oil bath and high boiling point solvent did not show any interesting results. However, an alternative method using microwave heating did show interesting results when the group at the N1 position of the indazolinone was sufficiently stable. Mechanistic studies using substituted allyl groups proved that the mechanism of the rearrangement is dependent of the substrate. Under microwave conditions, the crotyl group was rearranged via a [1 ;3] mechanism exclusively, whereas the cinnamyl group followed a [3 ;3] mechanism exclusively. This is rationalised on steric grounds with a bulky group such a phenyl not allowing the [1 ;3] rearrangement. The mechanism of the transition metal catalysed aza-Claisen rearrangements with other tetrakis(triphenylphosphine)palladium(0) or dichlorobis(acetonitrile) palladium (II) were consistent with literature results on unrelated structures. The palladium (0) induces a unselective rearrangement of the crotyl group to give a mixture of products corresponding to [1 ;3] and [3 ;3] mechanisms but induces exclusive [1 ;3] rearrangement of the cinnamyl group. Palladium (II) based catalyst rearranged the crotyl group via a [3 ;3] rearrangement exclusively but did not have any influence of the cinnamyl group.

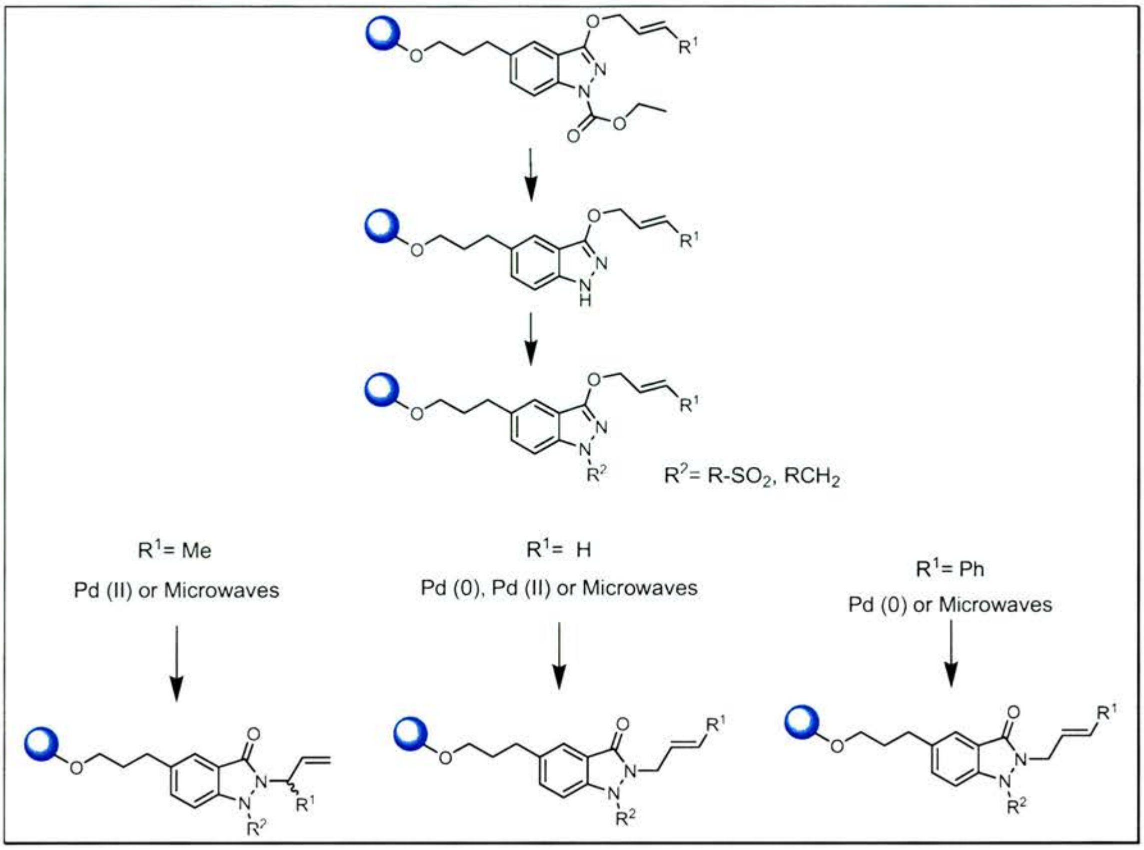
- Inspired by Schreiber's core-switching concept (section 1.3.1), the rearrangement was the main driving force of the project. Example of potential library building block were added onto the indazolinone structure and then submitted to the rearrangement reaction. It has been noticed that building blocks such as isocyanate and acid chloride could not be included in this library strategy. These substrates, under the palladium (0) conditions resulted in formation of a single product which was unfortunately not the desired product. However, electrophiles such as alkyl bromides, sulfonyl chlorides, epoxides could be involved in building block selection because the rearrangement was successful on these examples.

The successful synthesis of an indazolinone derivative capable of being loaded onto a resin was the starting point of the solid supported synthesis. The next step in this approach was to simulate the solid support by use of a TIPS group and to develop the synthesis in solution to create authentic compounds. These were fully characterised by standard analytical method. The transfer of the reaction sequence to the solid support involved the development of suitable analysis system, LC/MS system using a reverse phase column. Comparison of the authentic compounds made in solution and the products from the solid phase synthesis was the method of choice to validate the solid phase strategy.

Deprotection of the carbamate and functionalisation on the N1 position were optimised on the solid phase successfully. Aza-Claisen rearrangement at different points of the route (*N1*-protected and *N1*-benzylated) using different methods (catalysts and microwave) concluded that the microwave irradiation on indazolinones with a non-labile group attached on the N1 position (e.g. benzyl group) was the best method to arrive at the desired products.

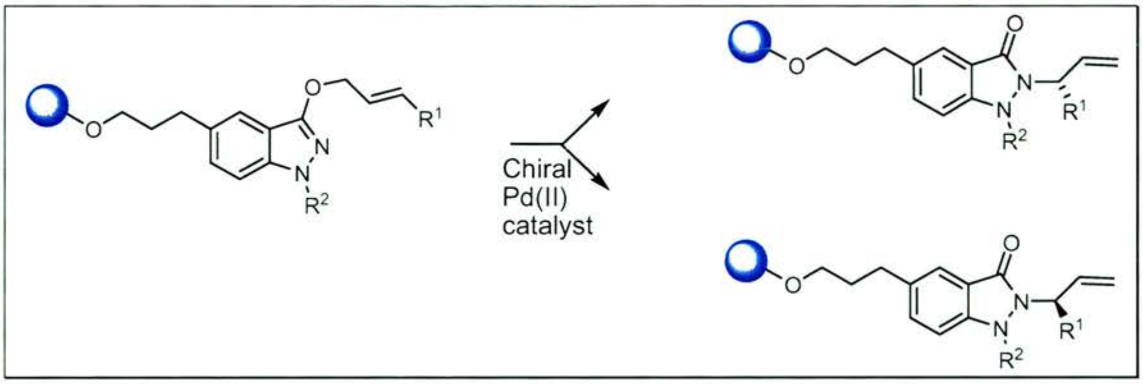
3.2. Possible future directions

Through the combination of the solid phase synthesis studies, the diversity incorporation in the N1 position tolerated by the aza-Claisen rearrangement conditions and the mechanistic studies on substituted allyl moieties, a compound library could be generated.



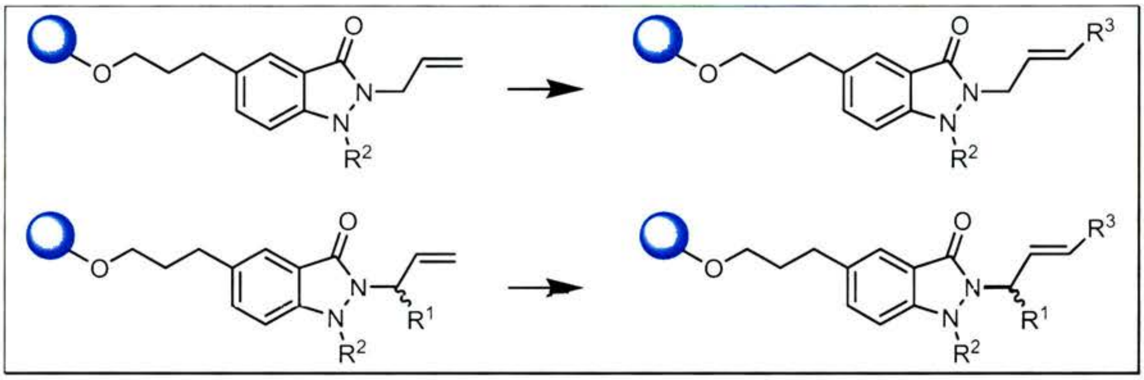
Scheme 180: Possible diversity generation by core-switching reaction using aza-Claisen rearrangement methodology (catalysis or microwave irradiation).

The dichlorobis(acetonitrile) palladium (II) converts the crotyl group by inducing a [3';3] mechanism and creates a new stereogenic center. At present, because a an achiral catalyst has been used in the rearrangement reaction, the product is racemic. However, a possible future direction for this project, after preliminary biological assays, would be to investigate the importance of the absolute stereochemistry of the new stereogenic centre using different chiral ligands on the transition metal to aid synthesis of the enantiomerically enriched compounds. An analogous approach has been described by Overman and it is the method of choice for synthesising chiral amines from imidates (see section 2.2.4.1).



Scheme 181: Possible diversity generation involving aza-Claisen rearrangement using optically pure ligands on the transition metal to induce enantiomerically enriched compounds.

When the terminal alkene is not substituted (R^1=H or R^1 = Me after Pd(II) or microwave rearrangement), another level of diversity could be incorporated by using an olefin metathesis reaction to couple the double bond of the allyl group, classified as type 1, to another double bond of for example type 3 according to Grubbs' classification [176, 177].



Scheme 182: Possible diversity incorporation on terminal alkene by metathesis reaction.

4. Experimental

Unless otherwise stated, all reactions were performed under an atmosphere of argon/oxygen free nitrogen. All glassware was dried at 140°C prior to use. Chemicals and solvents were purchased from Acros, Aldrich, Avocado or Fluka and were used as received unless otherwise stated. Tetrahydrofuran (THF) was dried by refluxing with sodium-benzophenone under an N_2 atmosphere and collected by distillation. Dichloromethane (DCM) was dried by heating under reflux over calcium hydride and distilled under N_2 atmosphere. Toluene was dried by refluxing with sodium under an N_2 atmosphere and collected by distillation. "Petrol" (petroleum ether) refers to that fraction in the boiling range 40-60°C. Thin-layer chromatography (TLC) was performed on glass plates coated with Merck Kieselgel 60 F_{254}. Developed plates were air-dried and scrutinised under a UV lamp (254&366 nm), and where necessary, stained with iodine, ninhydrin or potassium permanganate to aid identification. Melting points were determined using an Electrothermal 9100 melting point apparatus and are uncorrected. Flash column chromatography was performed using Kieselgel 60 (0.040-0.063 mm mesh, Merck 9385).

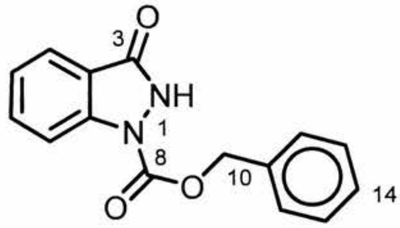
^{1}H nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker Avance 300 (300.1 MHz) or a Varian Gemini 2000 (300.0 MHz) spectrometer using the deuterated solvent as the lock and the residual solvent as the internal reference in all cases. ^{13}C NMR spectra using the PENDANT sequence were recorded in a Bruker Avance 300 (75.5 MHz) spectrometer. All other ^{13}C spectra were recorded on a Varian Gemini 2000 (75.5 MHz) spectrometer using composite pulse ^{1}H decoupling. Unless otherwise stated, NMR spectra were run in $CDCl_3$. Assigned carbon resonances have been assigned using HSQC and HMBC. All coupling constants are quoted to the nearest 0.1 Hz. In NMR, s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, br = broad.

Low resolution (LRMS) and high-resolution (HRMS) spectra recorded using electron impact (EI) or chemical ionisation (CI) were acquired using the VG Autospec instrument and low resolution spectra recorded using Electrospray Ionisation (ESI) were acquired using the VG Platform I instrument at the MS service as the University of St Andrews.

I.R. spectra were recorded using Perkin-Elmer Paragon series 1000 Fourier Transform spectrometer. Absorption maxima are reported in wavenumbers (cm^{-1}). Intensities of the maxima are quoted as strong (stg), medium (m), weak (w), broad (br).

Microanalyses were carried out in the Centre for Solid characterisation at the University of St Andrews.

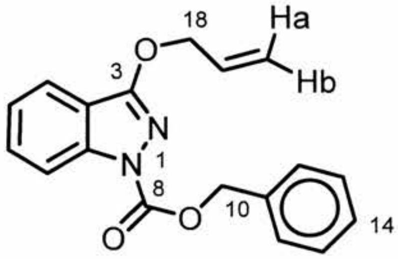
Synthesis of *N1*-benzyloxycarboxy-2*H*-indazolinone **17**



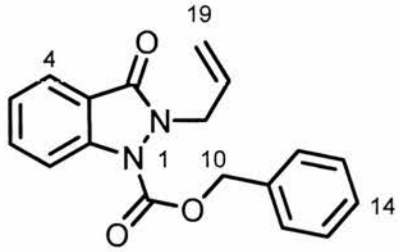
To a solution of **17** (3.00 g, 22.4 mmol) in dry THF (250 mL) was added triethylamine (9.36 mL, 67.2 mmol, 3.00 equiv.); the mixture was stirred for two hours at room temperature under an inert atmosphere. To this solution was added benzyl chloroformate (9.55 mL, 67.2 mmol, 3.00 eq.) and stirring was maintained for 16 hours. The reaction was quenched by addition of a saturated solution of ammonium chloride (10 mL) and extracted with ethyl acetate (5×50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was redissolved in dry THF (100 mL). To this solution was added morpholine (1.96 mL, 22.4 mmol, 1.00 equiv.). After stirring overnight at room temperature under an inert atmosphere, the reaction was quenched by addition of a saturated solution of ammonium chloride (10 mL) and extracted with ethyl acetate (5×50 mL). The combine organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was recrystallised from ethyl acetate to give **111** as a white solid (3.05 g, 11.8 mmol, 53%); mp 191-192°C; ^{1}H NMR δ 8.02 (br s, 1H; **NH**), 7.72 (d, J = 7.9 Hz, 1H; **H-4**), 7.54-7.23 (m, 8H; **H-aromatic**), 5.45 (s, 2H; **H-10**); ^{13}C NMR δ 160.4 (**C-3**), 149.9 (**C-8**), 140.3 (**C-7a**), 134.8 (**C-12**), 131.2 (**C-aromatic**), 128.9 (**C-aromatic**), 128.8 (**C-aromatic**), 128.7 (**C-aromatic**), 124.5 (**C-quat.**), 123.8 (**C-aromatic**), 121.5 (**C-4**), 69.2 (**C-10**), one **C-quat.** too weak to observe; LR MS (ES$^-$) *m/z*: 267 $[M\text{-H}]^-$, HR MS (ES$^-$) calcd for $C_{15}H_{11}N_2O_3$ $[M\text{-H}]^-$ 267.0770, found 267.0775; IR (thin film, cm^{-1}) 3426 m (br) (N-H), 3054 m, 2999 m, 2362 m, 1721 stg (C=O), 1603 stg (C=O), 749 stg;

Synthesis of *N1*-benzyloxycarboxy 3-allyloxyindazole **112** and *N1*-benzyloxycarboxy *N2*-allyl indazolinone **113**

To a solution of **111** (6.00 g, 22.4 mmol, 1.0 equiv.), triphenylphosphine (6.46 g, 24.6 mmol, 1.1 equiv.) and allyl alcohol (1.67 mL, 24.6 mmol, 1.1 equiv.) in dry toluene (400 mL) was slowly added diethylazodicarboxylate (3.87 mL, 24.6 mmol, 1.1 equiv.). The reaction mixture was stirred at room temperature overnight under an inert atmosphere. The solvent was removed under reduced pressure and a saturated solution of ammonium chloride was added. The aqueous layer was extracted with ethyl acetate (3×50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography eluting with 5% to 20% ethyl acetate/petrol to give **112** (2.65 g, 38%) as a white solid and **113** (4.23 g, 61%) as a colourless oil;

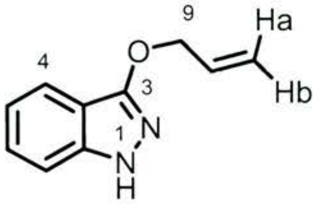


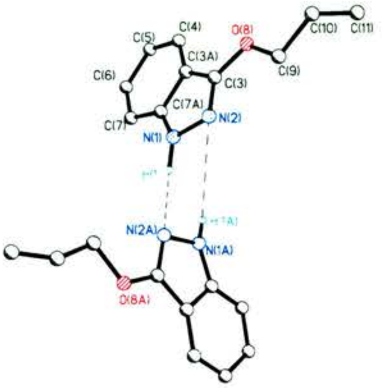
(112): R_f (10% ethyl acetate/hexane) 0.37; mp 68-69°C; ^{1}H NMR δ 8.07 (br d, 1H; **H-7**), 7.70 (dt, J = 7.9, 1.0 Hz, 1H; **H-4**), 7.45-7.18 (m, 7H; **H-aromatic**), 6.07 (ddt, J =17.2, 10.5, 5.7 Hz, 1H; **H-19**), 5.42 (s, 2H, **H-10**), 5.41 (dq, J = 17.2, 1.5 Hz, 1H; **H-20a**), 5.25 (ddt, J =10.5, 2.6, 1.2 Hz, 1H; **H-20b**), 4.92 (dt, J = 5.7, 1.3 Hz, 2H; **H-18**); ^{13}C NMR δ 159.6 (**C-3**), 150.8 (**C-8**), 140.3 (**C-7a**), 135.3 (**C-11**), 132.3 (**C-19**), 130.0 (**C-aromatic**), 128.7 (**C-aromatic**), 128.6 (**C-aromatic**), 128.5 (**C-aromatic**), 123.5 (**C-aromatic**), 120.0 (**C-4**), 118.7 (**C-20**), 117.3 (**C-3a**), 114.8 (**C-7**), 70.0 (**C-18**), 68.8 (**C-10**); LR MS (CI$^+$) *m/z*: 309 [M+H]$^+$; HR MS (CI$^+$) calcd for $C_{18}H_{17}N_2O_3$ [M+H]$^+$ 309.1239, found 309.1236; IR (thin film, cm^{-1}) 3060 m, 3035 m, 2970 m, 2360 m, 1723 stg (C=O);



(113): R_f (10% ethyl acetate/hexane) 0.1; ^{1}H NMR δ 7.87 (m, 2H; **H-4 and H-aromatic**), 7.59 (ddd, J = 8.6, 7.3, 1.3 Hz, 1H; **H-aromatic**); 7.43 (m, 5H; **H-aromatic**), 7.31 (m, 1H; **H-aromatic**), 5.67 (ddt, J = 17.2, 9.9, 6.3 Hz, 1H; **H-18**), 5.40 (s, 2H; **H-10**), 5.11 (m, 2H; **H-19**), 4.81 (dt, J = 6.3, 1.2 Hz, 2H; **H-17**); ^{13}C NMR δ 164.7 (**C-3**), 150.7 (**C-8**), 143.0 (**C-aromatic**), 134.3 (**C-aromatic**), 133.5 (**C-18**), 131.4 (**C-aromatic**), 129.0 (**C-aromatic**), 128.8 (**C-aromatic**), 128.6 (**C-aromatic**), 124.6 (**C-aromatic**), 123.8 (**C-aromatic**), 119.2 (**C-19**), 118.6 (**C-3a**), 115.3 (**C-aromatic**), 69.4 (**C-10**), 49.1 (**C-17**); LR (CI$^+$) *m/z*: 309 [M+H]$^+$; HR (CI$^+$) calcd for $C_{18}H_{17}N_2O_3$ [M+H]$^+$ 309.1239, found 309.1246; IR (thin film, cm^{-1}) 1738 stg (C=O), 1700 stg (C=O), 1462 m, 1279 m, 751 m;

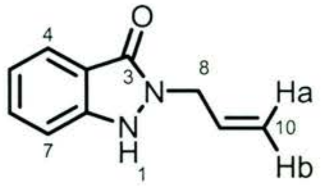
Synthesis of 3-allyloxyindazole **104**

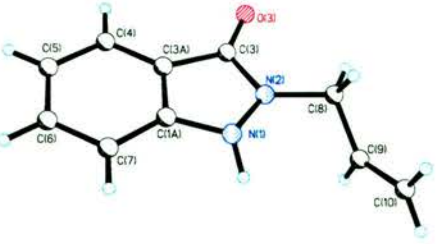




To a solution of **112** (2.50 g, 8.1 mmol, 1.0 equiv.) in THF (50 mL) was added a solution of sodium hydroxyde 2 M (50 mL). The solution was stirred overnight at room temperature. The organic solvent was removed *in vacuo* and the basic solution was neutralised with diluted hydrochloric acid (10%) before extracting with ethyl acetate (3×50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude orange oil was purified by flash chromatography eluting with 20% ethyl acetate/petrol to give **104** as a white solid (1.43 g, 99%); R_f (20% ethyl acetate/petrol) 0.14; mp 81-82°C; ^{1}H NMR δ 9.12 (br s, 1H; **H-1**), 7.71 (dt, J = 8.1, 1.0 Hz, 1H; **H-aromatic**), 7.39-7.25 (m, 2H; **H-aromatic**), 7.10 (ddd, J = 7.9, 6.7, 1.0 Hz, 1H; **H-aromatic**), 6.17 (ddt, J = 17.2, 10.6, 5.5 Hz, 1H; **H-10**), 5.48 (dq, J = 17.2, 1.6 Hz, 1H; **H-11a**), 5.32 (dq, J = 10.5, 1.4 Hz, 1H; **H-11b**), 4.93 (dt, J = 5.5, 1.5 Hz, 2H; **H-9**); ^{13}C NMR δ 157.1 (**C-3**), 142.5 (**C-7a**), 133.1 (**C-10**), 127.8 (**C-6**), 119.9 (**C-4**), 119.8 (**C-5**), 117.8 (**C-11**), 112.6 (**C-3a**), 109.6 (**C-7**), 69.5 (**C-9**); LR MS (ES$^+$) *m/z*: 175 [*M*+H]$^+$; HR MS (ES$^+$) calcd $C_{10}H_{11}N_2O$ [*M*+H]$^+$ 175.0871, found 175.0871; IR (thin film, cm^{-1}) 3175 m (br) (N-H), 2925 m, 2858 w, 1625 m, 1525 stg (C=O), 1503 m, 1436 m, 1420 m, 1336 stg, 1250 m, 1154 m, 989 m, 932 m, 766 stg, 746 m;

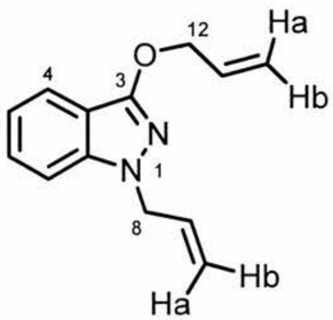
Synthesis of *N2*-allyl indazolinone **23**





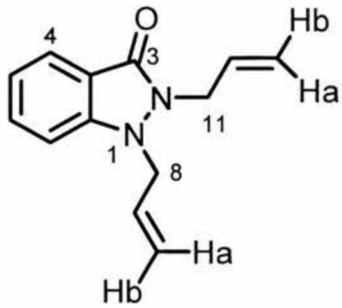
To a solution of **113** (64.0 mg, 0.021 mmol) in THF (10 mL) was added a solution of sodium hydroxide 2 M (2 mL). The solution was stirred at room temperature overnight. The solution was neutralised with a solution of hydrochloric acid (5%) and extracted with dichloromethane (3×50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (50% and 100% ethyl acetate/hexane) to give **23** (35.0 mg, 97%) as a white solid; R_f (50% ethyl acetate/petrol) 0.04; mp 113-114ºC; ^{1}H NMR δ 8.58 (br s, 1H; **H-1**), 7.69 (dt, J = 7.9, 0.9 Hz, 1H; **H-4**), 7.40 (ddd, J = 8.3, 7.2, 1.2 Hz, 1H; **H-6**), 7.14 (dt, J = 8.3, 0.8 Hz, 1H; **H-7**), 7.07 (ddd, J = 7.9, 7.2, 0.8 Hz, 1H; **H-5**), 5.80 (ddt, J = 17.1, 10.1, 5.9 Hz, 1H; **H-9**), 5.34 (dq, J = 13.8, 1.4 Hz, 1H; **H-10a**), 5.14 (dq, J = 6.8, 1.2 Hz, 1H; **H-10b**), 4.43 (dt, J = 5.9, 1.4 Hz, 2H; **H-8**); ^{13}C NMR δ 162.0 (**C-3**), 146.5 (**C-7a**), 131.8 (**C-6**), 131.6 (**C-9**), 123.5 (**C-5**), 122.1 (**C-4**), 119.1 (**C-10**), 118.4 (**C-3a**), 112.3 (**C-7**), 46.6 (**C-8**); LR MS (ES$^+$) *m/z*: 175 [*M*+H]$^+$; HR MS (ES$^+$) calcd for $C_{10}H_{11}N_2O$ [*M*+H]$^+$ 175.0871, found 175.0867; IR (thin film, cm^{-1}) 3069 m (N-H), 2924 m, 2848 m, 2737 stg, 1628 stg (C=O), 1326 m, 926 stg, 747 m; Calculated for $C_{10}H_{10}N_2O$: C 68.95, H 5.79, N 16.08; found C 68.54, H 5.88, N 16.37%.

Synthesis of *N1*-allyl 3-allyloxyindazole **106**



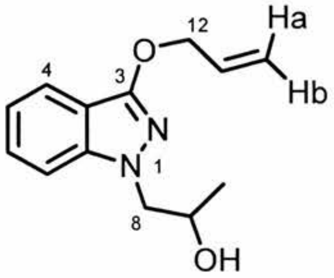
To a solution of **104** (79.0 mg, 0.45 mmol) in dry THF (3.00 mL) was added potassium *t*-butoxide (61.0 mg, 0.54 mmol, 1.2 equiv.) and allyl bromide (45.0 µL, 0.50 mmol, 1.1 equiv.). The solution was stirred for 16 hours at room temperature. The reaction was quenched by addition of saturated ammonium chloride solution (20 mL) and extracted with ethyl acetate (3×10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by flash chromatography eluting with 10% ethyl acetate/hexane to give the desired product **106** as a bright yellow oil (87.0 mg, 89%); R_f (40% ethyl acetate/petrol) 0.79; ^{1}H NMR δ 7.60 (dt, J = 8.1, 0.9 Hz, 1H; **H-4**), 7.24 (ddd, J = 8.5, 6.8, 1.1 Hz, 1H; **H-6**), 7.12 (dt, J = 8.6, 0.9 Hz, 1H; **H-7**), 6.95 (ddd, J = 7.8, 6.9, 0.8 Hz, 1H; **H-5**), 6.08 (ddt, J = 17.1, 10.4, 5.5 Hz, 1H; **H-13**), 5.88 (ddt, J = 17.1, 10.4, 5.4 Hz, 1H; **H-9**), 5.38 (dq, J = 17.2, 1.6 Hz, 1H; **H-14a**), 5.21 (ddd, J = 10.5, 2.8, 1.3 Hz, 1H; **H-14b**), 5.08 (ddd, J = 10.3, 2.8, 1.4 Hz, 1H; **H-10b**), 5.00 (ddd, J = 17.1, 3.0, 1.6 Hz, 1H; **H-10a**), 4.82 (dt, J = 5.6, 1.4 Hz, 2H; **H-12**), 4.71 (dt, J = 5.4, 1.6 Hz, 2H; **H-8**) ; ^{13}C NMR δ 155.5 (**C-3**), 141.5 (**C-7a**), 133.23 and 133.18 (**C-9** and **C-13**), 127.2 (**C-6**), 120.0 (**C-4**), 119.0 (**C-5**), 117.7 and 117.0 (**C-14** and **C-10**), 112.9 (**C-3a**), 108.8 (**C-7**), 69.6 (**C-12**), 51.1 (**C-8**); LR MS (CI$^+$) *m/z*: 215 [*M*+H]$^+$; HR MS (CI$^+$) calcd for $C_{13}H_{15}N_2O$ [*M*+H]$^+$: 215.1184; found: 215.1193; IR (thin film, cm^{-1}) 3081 w, 2924 w, 2363 w, 1619 m, 1527 stg (C=N), 1494 m (C=N), 1442 m, 1417 m, 1342 m, 1259 w, 1195 m, 1144 w, 1035 w, 985 m, 923 w, 740 stg (C=C).

Synthesis of *N1*,*N2*-diallylindazolinone **107**



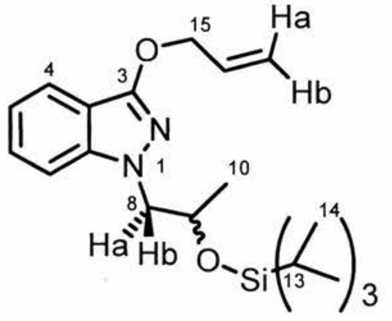
To a solution of **23** (100 mg, 0.57 mmol) in dry THF (10.0 mL) was added potassium carbonate (87 mg, 0.63 mmol, 1.1 equiv.). After 30 minutes, allyl bromide (55.0 μL, 0.63 mmol, 1.1 equiv.) was added and the reaction was stirred at room temperature under an inert atmosphere for 16 hours. The reaction was quenched by addition of saturated ammonium chloride solution (20 mL) and extracted with ethyl acetate (3×30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by flash chromatography eluting with 50% ethyl acetate/hexane to give the desired product **107** as a yellow oil (114 mg, 96%); R_f (50% ethyl acetate/petrol) 0.28; ^{1}H NMR δ 7.78 (m, 1H; **H-4**) , 7.45 (ddd, J = 8.4, 7.2, 1.3 Hz, 1H; **H-5**), 7.10 (m, 2H; **H-6** and **H-7**), 5.76 (ddt, J = 17.1, 10.2, 5.9 Hz, 1H; **H-12**), 5.42 (ddt, J = 17.0, 10.2, 6.1 Hz, 1H; **H-9**), 5.19 (ddd, J = 11.6, 2.7, 1.4 Hz, 1H; **H-13**), 5.14 (m, 2H; **H-10** and **H-13**), 5.06 (dq, J = 10.2, 1.2 Hz, 1H; **H-10**), 4.46 (dt, J = 5.9, 1.5 Hz, 2H; **H-11**), 4.23 (dt, J = 6.2, 1.2 Hz, 2H; **H-8**); ^{13}C NMR δ 163.2 (**C-3**), 148.9 (**C-7a**), 132.6 (**C-12**), 132.0 (**C-6**), 130.2 (**C-9**), 124.0 (**C-4**), 122.1 (**C-5**), 120.0 (**C-10**), 118.8 (**C-3a**), 117.9 (**C-13**), 111.7 (**C-7**), 51.8 (**C-8**), 44.7 (**C-11**); LR MS (CI^+) *m/z*: 215 $[M+H]^+$; HR MS (CI^+) calcd for $C_{13}H_{15}N_2O$ $[M+H]^+$: 215.1184, found: 215.1185; IR (thin film, cm^{-1}) 3086 w, 2979 w, 2928 w, 1666 stg (C=O), 1615 m, 1479 m, 1461 m, 1258 m, 926 m, 756 stg (C=C);

Synthesis of *N1*-(2-hydroxypropyl) 3-allyloxyindazole **122**



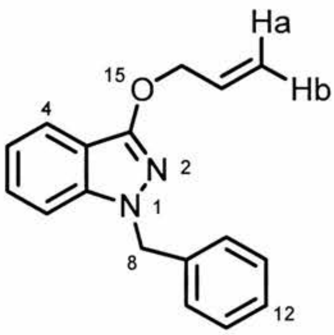
To a solution of **104** (200 mg, 1.15 mmol, 1.0 equiv.) in dry THF (10.0 mL) was added potassium *t*-butoxide (257 mg, 2.30 mmol, 2.0 equiv.). The solution was stirred 1 hour at room temperature. To the resulting solution was added propylene oxide (400 μL, 5.70 mmol, 5.0 equiv.) and the reaction was stirred at room temperature for 16 hours. The reaction was quenched by addition of saturated ammonium chloride solution (15 mL) and extracted with ethyl acetate (3×10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by flash chromatography eluting with 20% ethyl acetate/hexane to give the desired product **122** as an orange oil (174 mg, 65%); R_f (10% ethyl acetate/hexane) 0.08; ^{1}H NMR δ 7.60 (dt, *J* = 8.1, 1.0 Hz, 1H; **H-4**), 7.28 (ddd, *J* = 8.4, 6.8, 1.0 Hz, 1H; **H-6**), 7.14 (dt, *J* = 8.7, 1.0 Hz, 1H; **H-7**), 7.96 (ddd, *J* = 7.9, 6.8, 0.8 Hz, 1H; **H-5**), 6.06 (ddt, *J* = 17.2, 10.5, 5.6 Hz, 1H; **H-13**), 5.38 (dq, *J* = 17.2, 1.6 Hz, 1H; **H-14a**), 5.22 (dq, *J* = 10.5, 2.7 Hz, 1H; **H-14b**), 4.80 (dt, *J* = 5.6, 1.4 Hz, 2H; **H-12**), 4.05 (m, 3H; **H-8** and **H-9**), 3.24 (br s, 1H; **OH**), 1.15 (d, *J* = 6.3 Hz, 3H; **H-10**); ^{13}C NMR δ 155.7 (**C-3**), 142.0 (**C-7a**), 133.0 (**C-13**), 127.7 (**C-6**), 120.1 (**C-4**), 119.3 (**C-5**), 118.0 (**C-14**), 112.1 (**C-3a**), 108.5 (**C-7**), 69.7 (**C-12**), 67.5 (**C-9**), 54.4 (**C-8**), 20.1 (**C-10**); LR MS (CI$^+$) *m/z*: 233 $[M+H]^+$; HR MS (CI$^+$) calcd for $C_{13}H_{17}N_2O_2$ $[M+H]^+$: 233.1290; found 233.1282; IR (thin film, cm^{-1}) 3379 m (br)(O-H), 2971 stg, 2928 stg, 1617 stg, 1529 m (C=N), 1494 m (C=N), 1444 m, 1417 m;

Synthesis of *N1*-(2-triisopropylsilyloxy)propyl 3-allyloxyindazole **139**



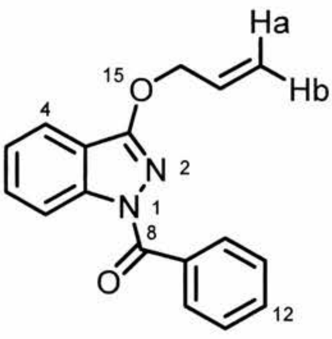
To a solution of **122** (80.0 mg, 0.34 mmol, 1.0 equiv.) in dry THF (5 mL) was added triethylamine (150 µL, 1.0 mmol, 3.0 equiv.). The solution was stirred 10 minutes at room temperature. To the resulting solution was added triisopropylsilyl trifluoromethanesulfonate (180 µL, 0.52 mmol, 1.5 equiv.) and the reaction was stirred at room temperature for 1 hour. The reaction was then quenched by addition of saturated ammonium chloride solution (10 mL) and extracted with ethyl acetate (3×10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by flash chromatography eluting with 5% ethyl acetate/hexane to give the desired product **139** as a colourless oil (114 mg, 85%); R_f (10% ethyl acetate/hexane) 0.56; ^{1}H NMR δ 7.56 (dt, J = 8.1, 0.9 Hz, 1H; **H-4**), 7.22 (m, 2H; **H-6 and H-7**), 6.93 (ddd, J = 7.84, 6.52, 1.15 Hz, 1H; **H-5**), 6.09 (ddt, J = 17.2, 10.5, 5.6 Hz, 1H; **H-16**), 5.39 (dq, J = 17.2, 1.59 Hz, 1H; **H-17a**), 5.22 (ddt, J = 10.4, 2.80, 1.29 Hz, 1H; **H-17b**), 4.81 (dt, J = 5.6, 1.39 Hz, 2H; **H-15**), 4.36 (sext., J = 6.1 Hz, 1H; **H-9**), 4.04 (ABX , J = 14.1, 6.2 Hz, 2H; **H-8a** and **H-8b**), 1.09 (d, J = 6.09 Hz, 3H; **H-10**), 0.89 (s, 21H; **H-13** and **H-14**); ^{13}C NMR δ 155.3 (**C-3**), 142.0 (**C-7a**), 133.4 (**C-16**), 127.0 (**C-6**), 119.8 (**C-4**), 118.8 (**C-5**), 117.8 (**C-17**), 112.2 (**C-3a**), 109.0 (**C-7**), 69.6 (**C-15**), 68.0 (**C-9**), 56.0 (**C-8**), 22.0 (**C-10**), 17.9 (**C-14**), 12.4 (**C-13**); LR MS (CI$^+$) *m/z*: 389 [*M*+H]$^+$; HR MS (CI$^+$) calcd for $C_{22}H_{37}N_2O_2Si$ [*M*+H]$^+$: 389.2624, found: 389.2627; IR (thin film, cm^{-1}) 2943 m, 2870 m, 2348 m, 1526 m (C=N), 988 m.

Synthesis of *N1*-benzyl-3-allyloxyindazole **118**



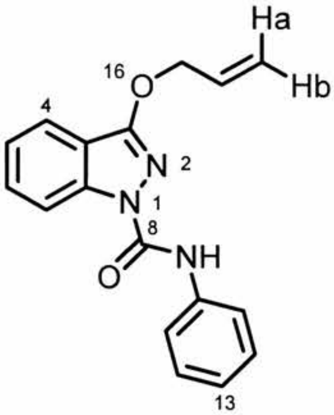
To a solution of **104** (100 mg, 0.58 mmol, 1.0 equiv.) in dry THF (10 mL) was added potassium carbonate (87.0 mg, 0.63 mmol, 1.1 equiv.), the solution was stirred at room temperature under an inert atmosphere for 30 minutes. Benzyl bromide (75 μL, 0.63 mmol, 1.1 equiv.) was added to the solution and the reaction was stirred overnight at room temperature under an inert atmosphere. The reaction was quenched by addition of ammonium chloride (12 mL) and extracted with ethyl acetate (3×10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by flash chromatography eluting with 5% ethyl acetate/petrol to afford **118** (90.0 mg) as a yellow oil in 99% yield based on recovered starting material (41.0 mg) (60% conversion, 40% of starting material recovered); R_f (20% ethyl acetate/petrol) 0.47; ^{1}H NMR δ 7.60 (dd, J = 8.1, 0.6 Hz, 1H; **H-4**), 7.15 (m, 8H; **H-aromatic**), 6.94 (m, 1H; **H-5**), 6.08 (m, 1H; **H-17**), 5.38 (dt, J = 17.2, 1.3 Hz, 1H; **H-18a**), 5.30 (s, 1H; **H-8**), 5.21 (d, J = 10.4 Hz, 1H; **H-18b**), 4.83 (dd, J = 5.6, 1.2 Hz, 2H; **H-16**); ^{13}C NMR δ 155.6 (**C-3**), 141.6 (**C-7a**), 137.4 (**C-9**), 133.2 (**C-17**), 128.5 (**C-aromatic**), 127.4 (**C-aromatic**), 127.3 (**C-aromatic**), 126.9 (**C-aromatic**), 120.1 (**C-4**), 119.1 (**C-5**), 117.8 (**C-18**), 113.0 (**C-3a**), 108.8 (**C-7**), 69.6 (**C-16**), 52.3 (**C-8**); LR MS (CI$^+$) *m/z*: 265 [*M*+H]$^+$; HR MS (CI$^+$) calcd for $C_{17}H_{17}N_2O$ [*M*+H]$^+$: 265.1341; found 265.1340; IR (thin film, cm^{-1}) 3060 m (C-H), 3030 m, 2924 m, 2852 m, 1615 m, 1527 stg (C=N), 1494 m (C=N), 1444 m, 1342 m, 1187 m, 1144 m;

Synthesis of *N1*-benzoyl-3-allyloxyindazole **119**



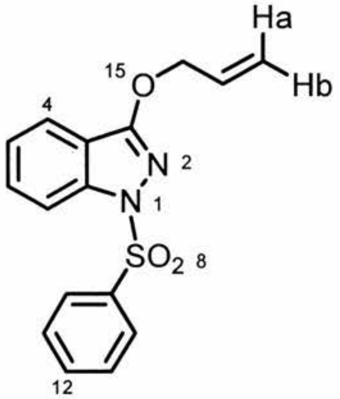
To a solution of **104** (100 mg, 0.57 mmol) in dry THF (5 mL) was added triethylamine (88.0 μL, 0.63 mmol, 1.1 equiv.), the solution was stirred at room temperature under an inert atmosphere for 30 minutes. Benzoyl chloride (73.0 μL, 0.63 mmol, 1.1 equiv.) was added to the solution and the reaction was stirred 16 hours at room temperature under an inert atmosphere. The reaction was quenched by addition of ammonium chloride and extracted with ethyl acetate (3×30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by flash chromatography eluting with 10% ethyl acetate/hexane to afford **119** (71.0 mg) as a white solid (99% based on starting material recovery, 45% conversion); R_f (20% ethyl acetate/petrol) 0.48; mp 66-68°C; ^{1}H NMR δ 8.46 (dt, J = 8.4, 0.8 Hz, 1H; **H-4**), 8.04 (m, 2H; **H-aromatic**), 7.67 (app. dt, J = 7.9, 1.0 Hz, 1H; **H-aromatic**), 7.57-7.39 (m, 4H; **H-aromatic**), 7.31 (ddd, J = 8.0, 7.2, 0.9 Hz, 1H; **H-5**), 6.06 (ddt, J = 17.2, 10.4, 5.8 Hz, 1H; **H-17**), 5.40 (dq, J = 17.2, 1.5 Hz, 1H; **H-18a**), 5.28 (ddd, J = 10.4, 2.6, 1.2 Hz, 1H; **H-18b**), 4.83 (dt, J = 5.8, 1.3 Hz, 2H; **H-16**); ^{13}C NMR δ 168.4 (**C-8**), 160.0 (**C-3**), 142.4 (**C-aromatic**), 134.7 (**C-aromatic**), 133.0 (**C-aromatic**), 132.5 (**C-17**), 131.9 (**C-aromatic**), 131.1 (**C-aromatic**), 130.5 (**C-aromatic**), 127.9 (**C-aromatic**), 124.6 (**C-aromatic**), 119.9 (**C-aromatic**), 119.1 (**C-18**), 116.5 (**C-aromatic**), 70.2 (**C-16**); LR MS (CI$^+$) *m/z*: 279 [M+*H*]$^+$; HR MS (CI$^+$) calcd for $C_{17}H_{15}N_2O_2$ [M+*H*]$^+$: 279.1134, found: 279.1131; IR (thin film, cm^{-1}) 3060 w, 2933 m, 2856 w, 1876 stg (C=O), 1548 stg (C=N), 1445 stg (C=N), 1406 stg, 1375 stg, 1336 stg (C=C), 1236 w, 1186 m, 878 stg, 750 stg (C=C), 694 m;

Synthesis of *N1*-(*N*-phenylcarboxamide)-3-allyloxyindazole **120**



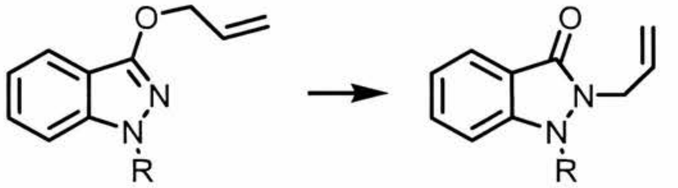
To a solution of **104** (100 mg, 0.58 mmol, 1.0 equiv.) in dry THF (10 mL) was added potassium *t*-butoxide (71 mg, 0.63 mmol, 1.1 equiv.), the solution was stirred at room temperature under an inert atmosphere for 30 minutes. Phenyl isocyanate (70 μL, 0.63 mmol, 1.1 equiv.) was added to the solution and the reaction was stirred 16 hours at room temperature under an inert atmosphere. The reaction was quenched by addition of ammonium chloride and extracted with ethyl acetate (3×10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by flash chromatography eluting with 20% ethyl acetate/hexane to afford **120** as a white solid (150 mg, 89%); R_f (20% ethyl acetate/petrol) 0.44; mp 89-91°C; ^{1}H NMR *δ* 8.58 (br s, 1H; **NH**), 8.26 (d, *J* = 8.5 Hz, 1H; **H-7**), 7.62-7.17 (m, 7H; **H-aromatic**), 7.04 (t, *J* = 7.4 Hz, 1H; **H-13**), 6.09 (m, 1H; **H-18**), 5.44 (dq, *J* = 17.2, 1.4 Hz, 1H; **H-19a**), 5.29 (dq, *J* = 10.5, 1.4 Hz, 1H; **H-19b**), 4.89 (dt, *J* = 5.7, 1.4 Hz, 2H; **H-17**); ^{13}C NMR *δ* 157.8 (**C-3**), 149.0 (**C-8**), 140.6 (**C-7a**), 137.3 (**C-10**), 132.2 (**C-18**), 130.2 (**C-6**), 129.1 (**C-12**), 124.0 (**C-13**), 122.9 (**C-5**), 119.9 (**C-4**), 119.6 (**C-11**), 118.8 (**C-19**), 116.6 (**C-3a**), 114.8 (**C-7**), 70.0 (**C-17**); LR MS (CI$^+$) *m/z*: 294 [*M*+H]$^+$; HR MS (CI$^+$) calcd for $C_{17}H_{16}N_3O_2$ [*M*+H]$^+$: 294.1243, found 294.1236; IR (thin film, cm^{-1}) 3375 m (N-H), 2928 w (C-H), 2852 w (C-H), 1716 stg (C=O), 1596 m (C=O), 1524 stg (C=N), 1446 m, 1406 m, 1361 m, 1344 m, 1219 m, 1097 m, 973 m, 928 m, 748 m;

Synthesis of 3-allyloxy-*N1*-benzylsulfonylindazole **121**



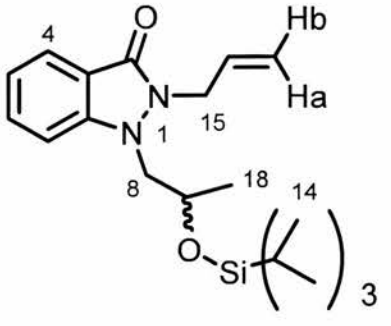
To a solution of **104** (100 mg, 0.58 mmol, 1.0 equiv.) in dry THF (10 mL) was added triethylamine (90 μL, 0.64 mmol, 1.1 equiv.), the solution was stirred at room temperature under an inert atmosphere for 30 minutes. Benzyl sulfonyl chloride (121 mg, 0.64 mmol, 1.1 equiv.) was added to the solution and the reaction was stirred 16 hours at room temperature under an inert atmosphere. The reaction was quenched by addition of ammonium chloride and extracted with ethyl acetate (3×30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by flash chromatography eluting with 20% ethyl acetate/hexane to afford **121** as a white solid (68.0 mg, 37% conversion, 100% yield based on the recovered starting material); R_f (20% ethyl acetate/petrol) 0.28; mp 100-101°C; ^{1}H NMR δ 8.06 (dt, J = 8.4, 0.8Hz, 1H; **H-4**), 7.78 (m, 2H; **H-aromatic**) 7.36 (m, 6H; **H-aromatic**), 5.99 (tdd, J = 17.1, 10.5, 5.7 Hz, 1H; **H-17**), 5.35 (dq, J = 17.2, 1.5 Hz, 1H; **H-18a**), 5.22 (dq, J = 10.4, 1.2 Hz, 1H; **H-18b**), 4.85 (dt, J = 5.7, 1.4 Hz, 2H; **H-16**); ^{13}C NMR δ 161.7 (**C-3**), 143.5 (**C-7a**), 137.1 (**C-9**), 134.2 (**C-12**), 132.4 (**C-17**), 130.6 (**C-6**), 129.3 (**C-11**), 128.0 (**C-10**), 124.7 (**C-5**), 120.7 (**C-4**), 119.2 (**C-18**), 118.5 (**C-3a**), 114.7 (**C-7**), 70.6 (**C-16**); LR MS (CI$^+$) *m/z*: 315 $[M+H]^+$; HR MS (CI$^+$) calcd for $C_{16}H_{15}N_2O_3S$ $[M+H]^+$: 315.0803, found: 315.0806; IR (thin film, cm^{-1}) 2920 m, 2847 m, 1543 m (C=N), 1372 stg (SO_2-N), 1342 m, 1181 stg (SO_2-N), 569 m.

General procedure for the rearrangement with tetrakis(triphenylphosphine)palladium(0)



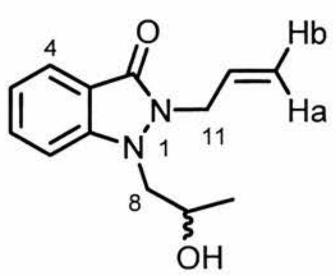
To a solution of the substrate (allyloxyindazole specie of type **20**) in dry THF was added tetrakis(triphenylphosphine)palladium(0) 5 mol. %. The reaction was stirred at room temperature under an inert atmosphere for 16 hours and protected from the light with aluminium foil. The reaction was quenched by addition of ammonium chloride (10 mL) and extracted with ethyl acetate (3×30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by flash chromatography.

Synthesis of *N1*-[2-(triisopropylsilyloxy)propyl]-*N2*-allyl indazolinone **140**



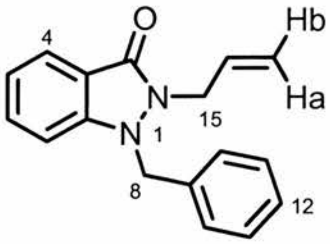
139 (56.0 mg, 0.14 mmol) was submitted to the general conditions of the rearrangement. After work up, the crude material was purified by flash chromatography eluting with 30% ethyl acetate/hexane to afford **140** as a colourless oil (34.0 mg, 60%); R_f (20% ethyl acetate/hexane) 0.08, ^{1}H NMR δ 7.77 (m, 1H; **H-4**), 7.42 (ddd, J = 8.4, 7.1, 1.2 Hz, 1H; **H-6**), 7.11 (dt, J = 8.4, 0.7 Hz, 1H; **H-7**), 7.03 (ddd, J = 8.0, 7.1, 0.7 Hz, 1H; **H-5**), 5.72 (ddt, J = 16.3, 10.6, 5.7 Hz, 1H; **H-16**), 5.10 (m, 2H; **H-17**), 4.53 (tt, J = 5.6, 1.5 Hz, 2H; **H-15**), 4.08 (dd, J = 12.4, 6.2 Hz, 1H; **H-9**), 3.68 (ABX system, J = 53.2, 15.4, 6.3 Hz, 2H; **H-8**), 0.97 (d, J = 6.1 Hz, 3H; **H-18**), 0.92 (m, 21H; **H-12, H-13** and **H-14**); ^{13}C NMR δ 162.9 (**C-3**), 148.3 (**C-7a**), 132.5 (**C-16**), 132.0 (**C-6**), 124.1 (**C-4**), 121.0 (**C-5**), 117.8 (**C-17**), 116.8 (**C-3a**), 110.9 (**C-7**), 66.6 (**C-9**), 55.8 (**C-8**), 45.0 (**C-15**), 22.4 (**C-18**), 18.0, 17.9, 12.5 (**C-12, C-13, C-14,**); LR MS (CI$^+$) *m/z*: 389 [M+*H*]$^+$; HR MS (CI$^+$) calcd for $C_{22}H_{37}N_2O_3Si$ [M+*H*]$^+$: 389.2624, found: 389.2629; IR (thin film, cm^{-1}) 2945 stg, 2866 stg, 1681 stg (C=O), 1621 m, 1484 m, 1464 m, 1263 w, 1144 m, 1112 w, 999 m, 920 w, 883 m, 750 m, 681 m.

Synthesis of *N1*-(2-hydroxypropyl)-*N2*-allyl indazolinone **141**



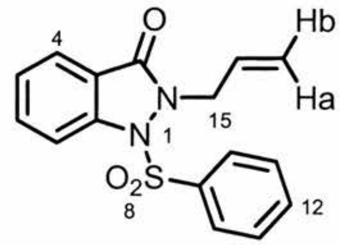
To a solution of **140** (30.0 mg, 0.077 mmol) in dry THF (2 mL) was added tetrabutyl ammonium fluoride (20 mg, 0.077 mmol, 1.0 equiv.) and the reaction was stirred at room temperature for 16 hours. The reaction was quenched by addition of ammonium chloride (10 mL) and extracted with ethyl acetate (3×15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by flash chromatography eluting with 50% ethyl acetate/hexane to afford **141** as a brown oil (11.0 mg, 60%); R_f (100% ethyl acetate) 0.19; ^{1}H NMR δ 7.77 (dt, J = 0.9, 7.7 Hz, 1H; **H-4**), 7.46 (ddd, J = 8.4, 7.1, 1.2 Hz, 1H; **H-6**), 7.14 (d, J = 8.4 Hz, 1H; **H-7**), 7.07 (ddd, J = 7.9, 7.2, 0.7 Hz, 1H; **H-5**), 5.73 (ddt, J = 16.1, 10.6, 5.6 Hz, 1H; **H-12**), 5.11(m, 2H; **H-13**), 4.52 (dt, J = 5.6, 1.5 Hz, 2H; **H-11**), 3.98 (m, 1H; **H-9**), 3.66 (d, J = 3.7Hz, 1H; **H-8**), 3.6 (d, J = 1.1 Hz, 1H; **H-8**), 1.9 (br s, 1H; **O-H**), 1.12 (d, J = 6.3 Hz, 3H; **H-10**); ^{13}C NMR δ 163.0 (**C-3**), 148.9 (**C-7a**), 132.5 (**C-12**), 132.3 (**C-6**), 124.2 (**C-4**), 121.7 (**C-5**), 117.9 (**C-13**), 111.3 (**C-7**), 65.7 (**C-9**), 56.7 (**C-8**), 45.2 (**C-11**), 20.9 (**C-10**), **C-3a** not visible even by 2D experiment; LR MS (CI$^+$) *m/z*: 233 [M+*H*]$^+$; HR MS (CI$^+$) calcd for $C_{13}H_{17}N_2O_2$ [M+*H*]$^+$: 233.1290, found: 233.1299; IR (thin film, cm^{-1}) 3332 m (br) (O-H), 2971 w, 2924 w, 2860 stg, 1640 s (C=O), 1487 m, 1461 m, 1329 m, 1272 m, 1132 m, 940 m, 751 stg (C=C), 681 m, 543 m.

Synthesis of *N1*-benzyl-*N2*-allyl indazolinone **135**



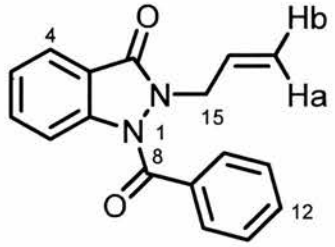
118 (30.0 mg, 0.11 mmol) was submitted to the general conditions of the rearrangement. After completion of the reaction, the reaction was quenched by addition of ammonium chloride (10 mL) and extracted with ethyl acetate (3×10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by flash chromatography eluting with 50% ethyl acetate/hexane to afford **135** as an orange oil (27.0 mg, 90%); R_f (50% ethyl acetate/petrol) 0.24; ^{1}H NMR δ 7.86 (dd, J = 7.8, 1.1 Hz, 1H; **H-aromatic**), 7.50 (m, 1H; **H-aromatic**), 7.18 (m, 7H; **H-aromatic**), 5.82 (ddt, J =17.1, 10.1, 5.8 Hz, 1H; **H-16**), 5.21 (m, 2H, **H-18**), 4.84 (s, 2H; **H-8**), 4.52 (dt, J = 5.7, 1.3 Hz, 2H; **H-15**); ^{13}C NMR δ 163.2 (**C-3**), 149.2 (**C-7a**), 134.6 (**C-9**), 132.4 (**C-16**), 132.1 (**C-aromatic**), 128.6 (**C-aromatic**), 128.1 (**C-aromatic**), 127.6 (**C-aromatic**), 124.1 (**C-4**), 121.9 (**C-aromatic**), 118.3 (**C-3a**), 117.9 (**C-17**), 111.6 (**C-aromatic**), 53.2 (**C-8**), 45.0 (**C-15**); LR MS (ES$^+$) *m/z*: 287 [*M*+Na]$^+$, HR MS (ES$^+$) calcd for $C_{17}H_{16}N_2ONa$ [*M*+Na]$^+$: 287.1160, found: 287.1171; IR (thin film, cm^{-1}) 3060 m (C-H), 3026 m (C-H), 2924 m (C-H), 2856 w (C-H), 1661 stg (C=O), 1615 m (C=C), 1496 m, 1482 m, 1464 m, 1454 m, 1324 m, 1261 m, 1152 m, 990 m, 928 m, 753 m, 700 m.

Synthesis of *N1*-benzyl sulfonyl *N2*-allyl indazolinone **136**



121 (35.0 mg, 0.12 mmol) was submitted to the general conditions of the rearrangement. After completion of the reaction, the reaction was quenched by addition of ammonium chloride and extracted with ethyl acetate (3×10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by flash chromatography eluting with 20% ethyl acetate/hexane to afford **136** as an orange oil (32.0 mg, 91%); R_f (50% ethyl acetate/petrol) 0.44; ^{1}H NMR δ 7.96 (dt, *J* = 8.3, 0.8 Hz, 1H; **H-aromatic**), 7.60 (ddd, *J* = 8.4, 7.3, 1.3 Hz, 1H; **H-aromatic**), 7.54 (ddd, *J* = 7.8, 1.3, 0.8 Hz, 1H; **H-aromatic**), 7.41 (m, 3H; **H-aromatic**), 7.24 (m, 3H; **H-aromatic**), 5.77 (ddt, *J* = 16.5, 10.1, 6.3 Hz, 1H; **H-16**), 5.26 (dq, *J* = 17.1, 1.3 Hz, 1H; **H-17a**), 5.17 (ddd, *J* = 10.1, 2.2, 1.0 Hz, 1H; **H-17b**), 4.75 (dt, *J* = 6.3, 1.2 Hz, 2H; **H-15**); ^{13}C NMR δ 166.5 (**C-3**), 145.6 (**C-7a**), 134.5 (**C-aromatic**), 133.5 (**C-aromatic**), 130.9 (**C-16**), 130.6 (**C-aromatic**), 128.8 (**C-aromatic**), 128.6 (**C-aromatic**), 126.8 (**C-aromatic**), 124.1 (**C-aromatic**), 121.8 (**C-aromatic**), 120.0 (**C-17**), 118.1 (**C-aromatic**), 49.9 (**C-15**); LR MS (EI^+) *m/z*: 314 $[M]^+$; HR MS (EI^+) calcd for $C_{16}H_{14}N_2O_3S$ $[M]^+$: 314.0725, found: 314.0725; IR (thin film, cm^{-1}) 2928 m, 2853 m, 1704 stg (C=O), 1609 m, 1478 w, 1460 w, 1446 w, 1375 stg (SO_2N), 1182 stg (SO_2N), 1147 w, 1086 w, 761 stg (C=C), 729 m, 683 stg, 571 stg;

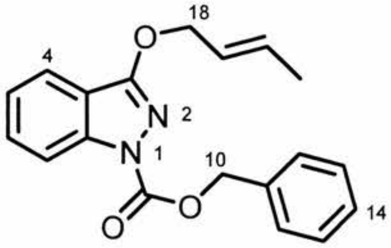
Synthesis of *N1*-benzoyl *N2*-allyl indazolinone **137**



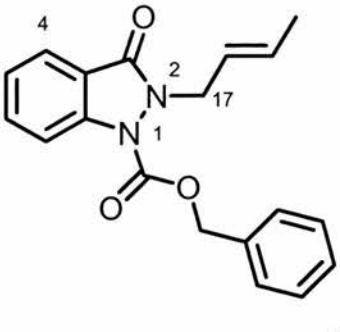
119 (100 mg, 0.36 mmol) was submitted to the general conditions of the rearrangement. After completion of the reaction, the reaction was quenched by addition of ammonium chloride and extracted with ethyl acetate (3×15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by flash chromatography eluting with 10% ethyl acetate/ hexane to afford **137** as an orange oil (5 mg, 5%); R_f (100% ethyl acetate) 0.70; ^{1}H NMR δ 7.86 (m, 1H; **H-aromatic**), 7.75 (m, 2H; **H-aromatic**), 7.64 (m, 1H; **H-aromatic**), 7.50 (m, 3H; **H-aromatic**), 7.40 (ddd, J = 8.1, 6.7, 1.1 Hz, 1H; **H-aromatic**), 7.24 (m, 1H; **H-aromatic**), 5.73 (ddt, J = 16.6, 10.1, 6.5 Hz, 1H; **H-16**), 5.16 (dq, J = 8.8, 1.2 Hz, 1H; **H-17a**), 5.11 (m, 1H; **H-17b**), 4.76 (dt, J = 6.5, 1.2 Hz, 2H; **H-15**); ^{13}C NMR δ 166.3 (**C-8**), 133.5 (**C-aromatic**), 133.0 (**C-aromatic**), 131.6 (**C-aromatic**), 130.2 (**C-aromatic**), 129.6 (**C-aromatic**), 129.3 (**C-aromatic**), 128.5 (**C-aromatic**), 124.6 (**C-aromatic**), 124.4 (**C-aromatic**), 119.8 (**C-17**), 113.1 (**C-aromatic**), 47.8 (**C-15**); LR MS (CI$^+$) *m/z*: 279 $[M+H]^+$, HR MS (CI$^+$) calcd for $C_{17}H_{15}N_2O_2$ $[M+H]^+$: 279.1134, found: 279.1136; IR (thin film, cm^{-1}) 2924 stg, 2852 stg, 1703 stg, 1461 m, 1280 m, 1264 m, 910 m, 735 stg.

Synthesis of *N1*-benzyloxycarbonyl 3-crotyloxyindazole **157** and *N1*-benzyloxycarbonyl *N2*-allylindazolinone **158**

To a solution of **111** (1.03 g, 3.94 mmol, 1.0 equiv.), triphenylphosphine (1.04 g, 3.96 mmol, 1.01 equiv.) and crotyl alcohol (0.34 mL, 4.02 mmol, 1.02 equiv.) in dry toluene (30 mL) was slowly added diethylazodicarboxylate (0.63 mL, 3.96 mmol, 1.01 equiv.). The reaction mixture was stirred at room temperature for 16 hours under an inert atmosphere. The solvent was then removed under reduced pressure and a saturated solution of ammonium chloride was added. The aqueous layer was extracted with ethyl acetate (3×50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography eluting with 5% to 20% ethyl acetate/petrol to give **157** (0.53 g, 44%) as a white solid and **158** (0.65 g, 54%) as a off-white solid;



(157): R_f (20% ethyl acetate/petrol) 0.70; mp 60-61°C; ^{1}H NMR δ 8.06 (br s, 1H; **H-7**), 7.68 (dt, J = 7.9, 1.0 Hz, 1H; **H-4**), 7.54-7.36 (m, 6H; **H-aromatic**), 7.27 (ddd, J = 7.9, 7.2, 0.8 Hz, 1H; **H-6**), 5.88 (m, 2H; **H-19 and H-20**), 5.52 (s, 2H; **H-10**), 4.94 (app d, J = 6.3 Hz, 2H; **H-18**), 1.79 (ddd, J = 6.3, 2.3, 1.1 Hz, 3H; **H-21**); ^{13}C NMR δ 159.7 (**C-3**), 150.8 (**C-8**), 141.5 (**C-7a**), 135.3 (**C-11**), 132.0 (**C-19**), 129.9 (**C-6**), 128.6 (**C-aromatic**), 128.5 (**C-aromatic**), 128.4 (**C-aromatic**), 125.2 (**C-20**), 123.4 (**C-5**), 120.0 (**C-4**), 117.4 (**C-3a**), 114.7 (**C-7**), 70.1 (**C-18**), 68.7 (**C-10**), 17.9 (**C-21**); LR MS (CI$^+$) *m/z*: 323.14 [M+H]$^+$; HR MS (CI$^+$) calcd for $C_{19}H_{19}N_2O_3$ [M+H]$^+$: 323.1396, found: 323.1399; IR (thin film, cm^{-1}) 3030 w, 2948 w, 1727 stg (C=O), 1543 stg (C=O), 1444 stg, 1419 stg, 1403 stg, 1356 stg, 1236 stg, 1173 stg, 1028 stg, 749 stg (C=C).

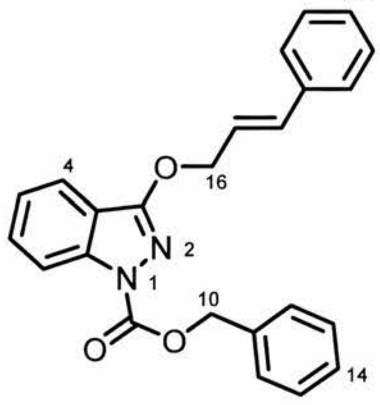


(158): R_f (20% ethyl acetate/petrol) 0.42 ; mp 68-69°C; ^{1}H NMR δ 7.87 (m, 2H; **H-4** and **H-7**), 7.60 (ddd, J = 8.4, 7.3, 1.3 Hz, 1H; **H-5**), 7.48-7.39 (m, 5H; **H-aromatic**), 7.31 (ddd, J = 8.0, 7.4, 0.8 Hz, 1H; **H-6**), 5.58 (m, 1H, **H-18**), 5.40 (s, 2H; **H-10**), 5.30 (dtq, J = 15.0, 6.6, 1.5 Hz, 1H; **H-19**), 4.73 (dt, J = 6.7, 1.0 Hz, 2H; **H-17**), 1.56 (ddd, J = 6.6, 2.6, 1.1 Hz, 3H; **H-20**); ^{13}C NMR δ 164.8 (**C-3**), 150.8 (**C-8**), 143.1 (**C-7a**), 134.5 (**C-**

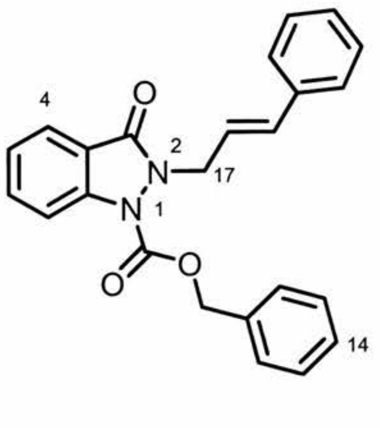
11), 133.4 (**C-6**), 131.1 (**C-18**), 129.0 (**C-aromatic**), 128.8 (**C-aromatic**), 128.7 (**C-aromatic**), 124.6 (**C-5**), 124.2 (**C-19**), 123.9 (**C-4**), 118.8 (**C-3a**), 115.4 (**C-7**), 69.4 (**C-10**), 48.7 (**C-17**), 17.7 (**C-20**); LR MS (CI^+) *m/z*: 323.14 $[M+H]^+$; HR MS (CI^+) calcd for $C_{19}H_{19}N_2O_3$ $[M+H]^+$: 323.1396, found: 323.1398; IR (thin film, cm^{-1}) 2933 m, 2852 m, 1742 stg (C=O), 1704 stg (C=O), 1457 m, 1279 stg, 1150 w, 1032 w, 964 w, 751 m;

Synthesis of *N1*-benzyloxycarbonyl 3-cinnamyloxyindazole **159** and *N1*-benzyloxycarbonyl *N2*-cinnamyl indazolinone **160**

To a solution of **111** (1.0 g, 3.5 mmol, 1.0 equiv.), triphenylphosphine (1.04 g, 3.97 mmol, 1.10 equiv.) and cinnamyl alcohol (0.52 mL, 3.85 mmol, 1.10 equiv.) in dry toluene (30 mL) was slowly added diethylazodicarboxylate (0.63 mL, 3.85 mmol, 1.1 equiv.). The reaction mixture was stirred at room temperature overnight under an inert atmosphere. The solvent was then removed under reduced pressure and a saturated solution of ammonium chloride was added. The aqueous layer was extracted with ethyl acetate (3×50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography eluting with 5% to 20% ethyl acetate/petrol to give **159** (0.61 g, 45%) as a white solid and **160** (0.54 g, 40%) as an off-white solid;

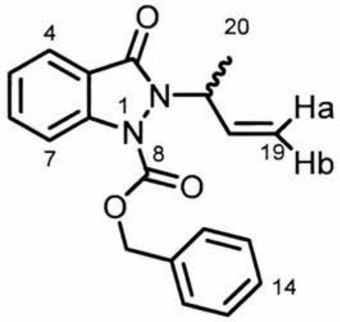


(159): R_f (20% ethyl acetate/petrol) 0.39; mp 86-87°C; ^{1}H NMR δ 7.98 (s, 1H; **H-7**), 7.60 (d, J = 7.9 Hz, 1H; **H-4**), 7.45-7.14 (m, 12H; **H-aromatic**), 6.71 (d, J = 15.9 Hz, 1H; **H-18**), 6.42 (dt, J = 15.9, 6.3 Hz, 1H; **H-17**), 5.42 (s, 2H; **H-10**), 5.07 (dd, J = 6.3, 1.0 Hz, 2H; **H-16**) ; ^{13}C NMR δ 159.7 (**C-3**), 150.9 (**C-8**), 141.3 (**C-quat.**), 136.3 (**C-quat.**), 135.4 (**C-quat.**), 134.6 (**C-18**), 130.1 (**C-aromatic**), 128.8 (**C-aromatic**), 128.7 (**C-aromatic**), 128.6 (**C-aromatic**), 128.2 (**C-aromatic**), 126.8 (**C-aromatic**), 123.6 (**C-aromatic**), 123.3 (**C-17**), 120.1 (**C-4**), 117.4 (**C-quat.**), 114.9 (**C-7**), 70.1 (**C-16**), 68.9 (**C-10**); LR MS (CI$^+$) *m/z*: 385.16 [*M*+H]$^+$; HR MS (CI$^+$) calcd for $C_{24}H_{21}N_2O_3$ [*M*+H]$^+$: 385.1552, found: 385.1546; IR (thin film, cm^{-1}) 3026 m, 2941 m, 1729 stg (C=O), 1547 stg (C=N), 1357 m, 1239 m, 1029 m, 750 stg (C=C);



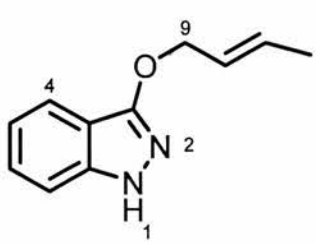
(160): R_f (20% ethyl acetate/petrol) 0.12; mp 66-67°C; ^{1}H NMR δ 7.74 (m, 2H; **H-4** and **H-7**), 7.43 (ddd, J = 8.5, 7.3, 1.3 Hz, 1H; **H-6**), 7.33-7.05 (m, 11H; **H-aromatic**), 6.35 (d, J = 15.8 Hz, 1H; **H-19**), 5.91 (dt, J = 15.8, 6.8 Hz, 1H; **H-18**), 5.27 (s, 2H; **H-10**), 4.85 (dd, J = 6.9, 0.9 Hz, 2H; **H-17**); ^{13}C NMR δ 164.7 (**C-3**), 150.8 (**C-8**), 143.1 (**C-quat.**), 136.0 (**C-quat.**), 134.6 (**C-19**), 134.2 (**C-quat.**), 133.6 (**C-aromatic**), 129.0 (**C-aromatic**), 128.8 (**C-aromatic**), 128.7 (**C-aromatic**), 128.4 (**C-aromatic**), 127.9 (**C-aromatic**), 126.5 (**C-aromatic**), 124.7 (**C-aromatic**), 123.8 (**C-aromatic**), 122.6 (**C-18**), 118.7 (**C-quat.**), 115.5 (**C-aromatic**), 69.4 (**C-10**), 48.9 (**C-17**); LR MS (CI^+) *m/z*: 385.16 $[M+H]^+$; HR MS (CI^+) calcd for $C_{24}H_{21}N_2O_3$ $[M+H]^+$: 385.1552, found: 385.1556; IR (thin film, cm^{-1}) 3026 m, 1738 stg (C=O), 1700 stg (C=O), 1466 m, 1287 m, 1147 m, 752 stg (C=C),

Synthesis of *N1*-benzyloxycarbonyl-*N2*-(but-3-en-2-yl)indazolinone **161**



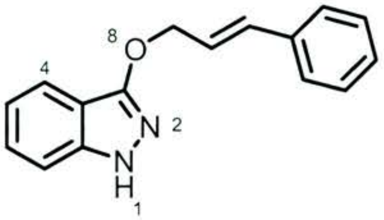
To a solution of **157** (150 mg, 0.47 mmol) in dry THF (5 mL) was added 5 mol % of dichlorobis(acetonitrile) palladium (II) (6.00 mg, 0.023 mmol) under an inert atmosphere. The solution was stirred at room temperature for 16 hours under an inert atmosphere. The solvent was concentrated *in vacuo* and the reaction mixture was purified by flash chromatography eluting with 5% ethyl acetate/hexane to give **161** as an orange oil (146 mg, 97%); R_f (20% ethyl acetate/petrol) 0.22; ^{1}H NMR δ 7.73 (ddd, J = 7.7, 1.7, 1.0 Hz, 2H; **H-aromatic**), 7.49 (ddd, J = 8.6, 7.3, 1.3 Hz, 1H; **H-aromatic**), 7.34 (m, 5H; **H-aromatic**), 7.21 (m, 1H; **H-aromatic**), 6.12 (ddd, J = 17.0, 10.3, 6.5 Hz, 1H; **H-18**), 5.30 (s, 2H; **H-10**), 5.09 (dq, J = 15.0, 1.3 Hz, 1H; **H-19a**), 5.04 (dq, J = 8.0, 1.3 Hz, 1H; **H-19b**), 4.83 (m, 1H; **H-17**), 1.53 (d, J = 7.0 Hz, 3H; **H-20**); ^{13}C NMR δ 166.3 (**C-3**), 151.9 (**C-7a**), 144.1 (**C-11**), 136.8 (**C-18**), 134.2 (**C-aromatic**), 133.4 (**C-aromatic**), 129.0 (**C-aromatic**), 128.78 (**C-aromatic**), 128.76 (**C-aromatic**), 124.8 (**C-aromatic**), 123.6 (**C-aromatic**), 119.8 (**C-3a**), 116.5 (**C-19**), 115.6 (**C-aromatic**), 69.6 (**C-10**), 59.3 (**C-17**), 17.5 (**C-20**); LR MS (CI^+) *m/z*: 323.14 $[M+H]^+$; HR MS (CI^+) calcd for $C_{19}H_{19}N_2O_3$ $[M+H]^+$: 323.1396, found: 323.1398; IR (thin film, cm^{-1}) 3069 m, 3030 m, 2979 m, 2937 m, 1742 stg (C=O), 1700 stg (C=O), 1614 stg (C=C), 1462 m.

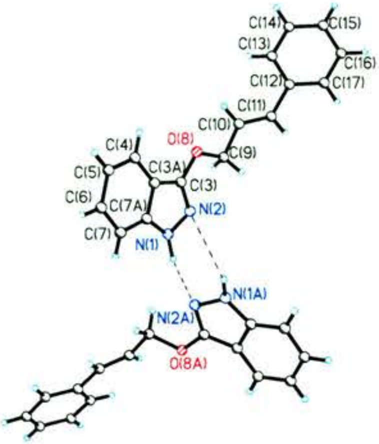
Synthesis of 3-crotyloxyindazole **162**



To a solution of **157** (100 mg, 0.31 mmol) in THF (10 mL) was added a solution of lithium hydroxide (3 mL, 2 M) and the solution was stirred at room temperature for 16 hours. The reaction was neutralised by addition of dilute hydrochloric acid (10%) to pH 7 and extracted with ethyl acetate (3×10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by flash chromatography eluting with 15% ethyl acetate/hexane to afford **162** (59.0 mg, 100%) as a white solid; R_f (20% ethyl acetate/petrol) 0.40; mp 81°C, ^{1}H NMR δ 9.07 (br s, 1H; **NH**), 7.63 (dd, J = 8.1, 0.9 Hz, 1H; **H-4**), 7.24 (m, 2H; **H-6 and H-7**), 7.00 (dd, J = 6.7, 1.0 Hz, 1H; **H-5**), 5.81 (m, 2H; **H-10 and 11**), , 4.78 (m, 2H; **H-9**), 1.70 (dd, J = 5.8, 0.9, 3H; **H-12**), ^{13}C NMR δ 157.3 (**C-3**), 142.5 (**C-7a**), 131.1 (**C-10 or C-11**), 127.8 (**C-6**), 125.9 (**C-11 or C-10**), 119.9 (**C-4**), 119.8 (**C-5**), 112.7 (**C-3a**), 109.6 (**C-7**), 69.6 (**C-9**), 17.9 (**C-12**); LR MS (ES$^+$) *m/z*: 211 [*M*+Na]$^+$; HR MS (ES$^+$) calcd for $C_{11}H_{12}N_2ONa$ [*M*+Na]$^+$: 211.0847, found: 211.0841; IR (thin film, cm^{-1}) 3154 m (br) (NH), 3040 m, 2922 m, 1623 stg, 1522 stg (C=N), 1507 stg, 1438 stg, 1360 stg, 1339 stg, 1250 stg, 1160 stg, 972 stg, 739 m.

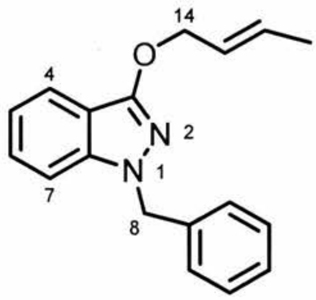
Synthesis of 3-cinnamyloxyindazole **164**





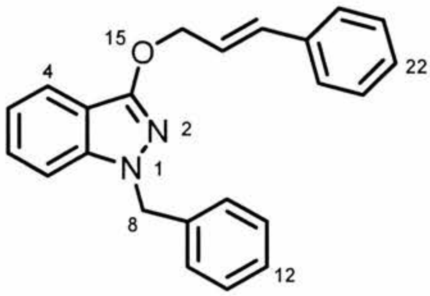
To a solution of **159** (108 mg, 0.28 mmol) in THF (10 mL) was added a solution of lithium hydroxide (2 M, 3 mL) and the solution was stirred at room temperature for 16 hours. The reaction was neutralized to pH 7 by addition of dilute hydrochloric acid (10%) and extracted with ethyl acetate (3×15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography eluting with 15% ethyl acetate/hexane to afford **164** as a white solid (69.0 mg, 96%); R_f (20% ethyl acetate/petrol) 0.32; mp 109°C; ^{1}H NMR δ 9.22 (br s, 1H; **NH**), 7.64 (dt, J = 8.1, 1.0 Hz, 1H; **H-aromatic**), 7.26 (m, 7H; **H-aromatic**), 7.00 (ddd, J = 7.9, 6.8, 1.0 Hz, 1H; **H-aromatic**), 6.70 (d, J = 16.0 Hz, 1H; **H-11**), 6.45 (dt, J = 15.9, 6.1 Hz, 1H; **H-10**), 5.00 (dd, J = 6.1, 1.3 Hz, 2H; **H-9**); ^{13}C NMR δ 157.1 (**C-3**), 142.5 (**C-7a**), 136.4 (**C-12**), 133.6 (**C-11**), 128.5 (**C-aromatic**), 127.9 (**C-aromatic**), 127.8 (**C-aromatic**), 126.6 (**C-aromatic**), 124.2 (**C-10**), 119.9 (**C-aromatic**), 119.8 (**C-aromatic**), 112.6 (**C-3a**), 109.7 (**C-aromatic**), 69.4 (**C-9**); LR MS (ES$^+$) *m/z*: 273 [*M*+Na]$^+$; HR MS (ES$^+$) calcd for $C_{16}H_{14}N_2ONa$ [*M*+Na]$^+$: 273.1004, found 273.1003; IR (thin film, cm^{-1}) 2873 m, 1523 stg (C=N), 1438 m, 1343 m, 1149 m, 1106 m, 958 m, 738 stg (C=C).

Synthesis of *N1*-benzyl 3-crotyloxyindazole **163**



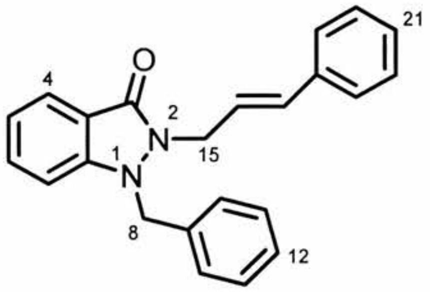
To a solution of **162** (48.0 mg, 0.25 mmol, 1.0 equiv.) was added solid potassium *t*-butoxide (34.0 mg, 0.31 mmol, 1.2 equiv.). The solution was stirred 30 minutes under an inert atmosphere at room temperature. To that solution was added benzyl bromide (30 μL, 0.31 mmol, 1.2 equiv.) and the solution was stirred at room temperature under argon for 16 hours. The reaction was quenched by addition of ammonium chloride (10 mL) and extracted with ethyl acetate (3×15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by flash chromatography eluting with hexane to afford **163** as a colourless oil (47.0 mg, 66%); R_f(20% ethyl acetate/petrol) 0.51; ^{1}H NMR δ 7.60 (dt, J = 8.1, 1.0 Hz, 1H; **H-7**), 7.20 (m, 7H; **H-aromatic**), 6.94 (ddd, J = 6.8, 0.8 Hz, 1H; **H-aromatic**), 5.81 (m, 2H; **H-15** and **H-16**), 5.31 (s, 2H; **H-8**), 4.76 (dd, J = 5.2, 1.0 Hz, 2H; **H-14**), 1.69 (ddt, J = 5.9, 1.1, 0.9 Hz, 3H; **H-17**); ^{13}C NMR δ 155.7 (**C-3**), 141.6 (**C-7a**), 137.5 (**C-9**), 131.1 (**C-aromatic**), 128.5 (**C-aromatic**), 127.4 (**C-aromatic**), 127.0 (**C-aromatic**), 126.9 (**C-aromatic**), 126.1 (**C-aromatic**), 120.1 (**C-aromatic**), 119.1 (**C-aromatic**), 113.1 (**C-3a**), 108.8 (**C-15**), 69.6 (**C-16**), 52.3 (**C-14**), 17.9 (**C-17**) ; LR MS (ES$^+$) *m/z*: 301; HR MS (ES$^+$) calcd for $C_{18}H_{18}N_2ONa$ $[M+Na]^+$: 301.1317, found: 301.1316; IR (thin film, cm^{-1}) 3060 m, 3030 m, 2937 m, 1615 stg (C=C), 1530 stg (C=N), 1496 m (C=N), 1436 m, 1351 m, 1185 m, 968 m, 739 stg (C=C), 696 m.

Synthesis of *N1*-benzyl 3-cinnamyloxyindazole **165**



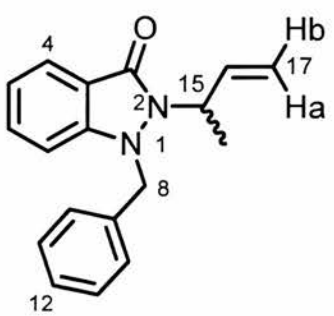
To a solution of **164** (53.0 mg, 0.21 mmol, 1.0 equiv.) in dry THF (10 mL) was added potassium *t*-butoxide (32.0 mg, 0.25 mmol, 1.2 equiv.) and the solution was stirred 30 minutes. To that solution was added benzyl bromide (30 μL, 0.25 mmol, 1.2 equiv.) and the reaction was stirred at room temperature under an inert atmosphere for 16 hours. The reaction was quenched by addition of ammonium chloride (10 mL) and extracted with ethyl acetate (3×15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by flash chromatography eluting with 5% ethyl acetate/hexane to afford **165** as a colourless oil (66.0 mg, 91%); R_f (20% ethyl acetate/petrol) 0.45; ^{1}H NMR δ 7.62 (dt, *J* = 8.1, 1.0 Hz, 1H; **H-aromatic**), 7.21 (m, 12H; **H-aromatic**), 6.95 (ddd, *J* = 7.9, 6.8, 0.8 Hz, 1H; **H-aromatic**), 6.71 (d, *J* = 16.0 Hz, 1H; **H-18**), 6.45 (dt, *J* = 15.9, 6.1 Hz, 1H; **H-17**), 5.32 (s, 2H; **H-8**), 4.99 (dd, *J* = 6.1, 1.3 Hz, 2H; **H-16**); ^{13}C NMR δ 155.6 (**C-3**), 141.6 (**C-aromatic**), 137.4 (**C-aromatic**), 136.5 (**C-aromatic**), 133.6 (**C-18**), 128.5 (**C-aromatic**), 127.8 (**C-aromatic**), 127.42 (**C-aromatic)**, 127.37 (**C-aromatic**), 127.0 (**C-aromatic**), 126.6 (**C-aromatic**), 124.4 (**C-17**), 120.1 (**C-aromatic**), 119.2 (**C-aromatic**), 113.1 (**C-3a**), 108.8 (**C-aromatic**), 69.4 (**C-16**), 52.3 (**C-8**); LR MS (ES$^+$) *m/z*: 363 [*M*+Na]$^+$; HR MS (ES$^+$) calcd for $C_{23}H_{20}N_2ONa$ [*M*+Na]$^+$: 363.1473, found: 363.1479; IR (thin film, cm^{-1}) 3060 w, 3026 w, 2933 w, 1617 m (C=C), 1527 stg (C=N), 1496 m (C=N), 1447 m, 1434 m, 1354 stg, 1254 w, 1185 m, 1142 w, 963 m, 741 stg, 691 m.

Synthesis of *N1*-benzyl-*N2*-cinnamylindazolinone **167**



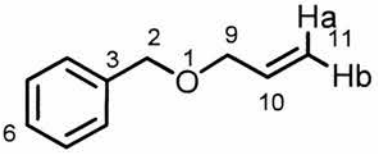
A solution of **165** (33.0 mg, 0.097 mmol) in dry DMF (2 mL) was submitted to microwave irradiations (200°C, 300W) for 10 min under a maximum pressure of 105 psi. The crude reaction was cooled down at room temperature. Water (10 mL) was added to the mixture and the aqueous solution was extracted with ether (2×5 mL). The combined organic extracts were washed with water (5 mL) and dried ($MgSO_4$). The crude material was purified by flash chromatography eluting with 30% ethyl acetate/hexane to afford **167** as a orange oil (14.0 mg, 42%) as the only product of the reaction. R_f (20% ethyl acetate/petrol) 0.04; ^{1}H NMR δ 7.80 (d, J = 7.8 Hz, 1H; **H-aromatic**), 7.43 (ddd, J = 8.3, 7.3, 1.2 Hz, 1H; **H-aromatic**), 7.13 (m, 12H; **H-aromatic**), 6.42 (dt, J = 15.9, 1.3 Hz, 1H; **H-17**), 6.07 (dt, J = 15.9, 6.3 Hz, 1H; **H-16**), 4.80 (s, 2H; **H-8**), 4.60 (dd, J = 6.3, 1.3 Hz, 2H; **H-15**); ^{13}C NMR δ 163.2 (**C-3**), 149.2 (**C-aromatic**), 136.1 (**C-aromatic**), 134.8 (**C-aromatic**), 133.1 (**C-17**), 132.2 (**C-aromatic**), 128.7 (**C-aromatic**), 128.5 (**C-aromatic**), 128.2 (**C-aromatic**), 127.9 (**C-aromatic**), 127.7 (**C-aromatic**), 126.5 (**C-aromatic**), 124.3 (**C-aromatic**), 123.9 (**C-16**), 122.0 (**C-aromatic**), 111.6 (**C-aromatic**), 53.6 (**C-8**), 44.9 (**C-15**); LR MS (ES$^+$) *m/z*: 363 [M+Na]$^+$; HR MS (ES$^+$) calcd for $C_{23}H_{20}N_2ONa$ [M+Na]$^+$: 363.1473, found: 363.1465; IR (thin film, cm^{-1}) 2925 stg, 2853 stg, 1671 stg (C=O), 1618 w (C=C), 1484 w, 1451 m, 1254 w, 1152 w, 965 w, 752 stg (C=C), 696 stg.

Synthesis of *N1*-benzyl-*N2*-(but-3-en-2-yl) indazolinone **166**



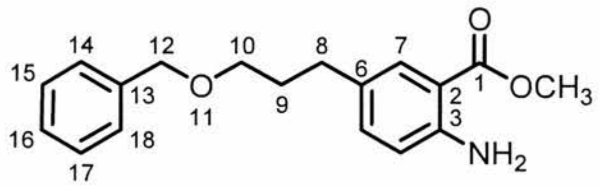
A solution of **163** (15.0 mg, 0.054 mmol) in dry DMF (1 mL) was submitted to microwave irradiations (200ºC, 300W) for 10 min under a maximum pressure of 96 psi. The crude reaction was cooled down at room temperature. Water (10 mL) was added to the mixture and the aqueous solution was extracted with ether (2×5 mL). The combined organic extracts were washed with water (5 mL) and dried ($MgSO_4$). The crude material was purified by flash chromatography eluting with 30% ethyl acetate/hexane to afford **166** as a orange oil (10.0 mg, 67%). R_f (20% ethyl acetate/petrol) 0.07 ; ^{1}H NMR δ 7.76 (d, J = 7.8 Hz, 1H; **H-aromatic**), 7.36 (ddd, J = 8.4, 7.2, 1.2 Hz, 1H; **H-aromatic**), 7.12 (m, 3H; **H-aromatic**), 7.05 (m, 2H; **H-aromatic**), 6.89 (d, J = 8.3 Hz, 1H; **H-aromatic**), 6.10 (ddd, J = 17.5, 10.6, 5.0 Hz, 1H; **H-16**), 5.18 (ddd, J = 12.6, 1.9, 0.9 Hz, 1H; **H-17a**), 5.13 (ddd, J = 5.7, 1.9, 0.9 Hz, 1H; **H-17b**), 5.00 (m, 1H; **H-15**), 4.77 (ABX system, J = 48.7, 15.9 Hz, 2H; **H-8**), 1.46 (d, J = 7.0 Hz, 3H; **H-18**); ^{13}C NMR δ 160.4 (**C-3**), 150.7 (**C-7a**), 138.0 (**C-16**), 132.3 (**C-aromatic**), 130.9 (**C-aromatic**), 128.7 (**C-aromatic**), 128.0 (**C-aromatic**), 127.6 (**C-aromatic**), 124.2 (**C-aromatic**), 122.1 (**C-aromatic**), 116.1 (**C-17**), 112.0 (**C-aromatic**), 55.0 (**C-8**), 53.5 (**C-15**), 17.3 (**C-18**), **C-3a** not observed; LR MS (ES$^+$) *m/z*: 301 [*M*+Na]$^+$; HR MS (ES$^+$) calcd for $C_{18}H_{18}N_2ONa$ [*M*+Na]$^+$: 301.1317, found: 301.1319 ; IR (thin film, cm^{-1}) 2920 stg, 2852 stg, 1725 w, 1674 stg (C=O), 1615 m, 1483 w, 1457 m, 1262 m, 1075 w, 1019 w, 798 m, 751 m (C=C), 700 m.

Synthesis of allylbenzyl ether **229** [178]



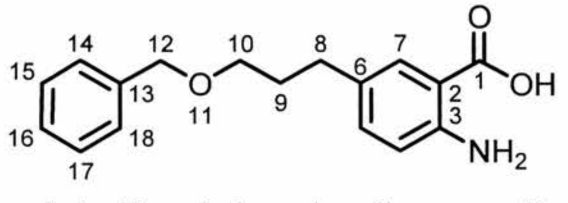
To a suspension of sodium hydride (10.2 g, 254 mmol, 1.1 eq.) in dry THF (250 mL) was added via cannula a solution of benzyl alcohol (25.0 g, 231 mmol, 1.0 eq.) in dry THF (50 mL). The reaction was stirred at room temperature for two hours under an inert atmosphere. Allyl bromide (23.0 mL, 254 mmol, 1.1 eq.) was then added dropwise. The resulting suspension was stirred overnight at room temperature. The solvent was partially removed *in vacuo* and saturated ammonium chloride solution (100 mL) was added. The aqueous phase was extracted with ethyl acetate (3×150 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude oil was purified by flash chromatography eluting with 5% ethyl acetate/hexane to give the desired product **229** as a colourless oil (34.0 g, 229 mmol, 99%); ^{1}H NMR δ 7.39-7.27 (m, 5H; **H-aromatic**), 5.98 (ddt, J = 17.3, 10.4, 5.6 Hz, 1H; **H-10**), 5.33 (ddt, J = 17.3, 1.6, 1.6 Hz, 1H; **H-11a**), 5.22 (ddt, J = 10.4, 1.4, 1.4 Hz, 1H; **H-11b**), 4.54 (s, 2H; **H-2**), 4.05 (ddd, J = 5.6, 1.4, 1.4 Hz, 2H; **H-9**); IR (thin film, cm^{-1}) 2924 m, 2852 m, 1717 m, 1449 m, 1270 w, 743 stg, 709 stg (C=C), 692 m;

Synthesis of methyl 2-amino-5-[3-(benzyloxy)propyl]benzoate **230** and 2-amino-5-[3-(benzyloxy)propyl]benzoic acid **231**



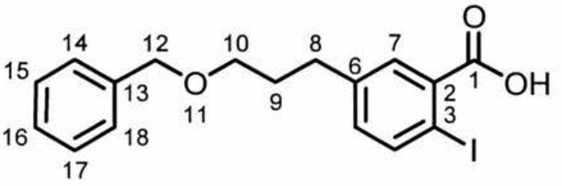
Solid 9-BBN (4.38 g, 35.9 mmol, 1.65 eq.) was transferred to a 500 mL 3-neck flask fitted with a condenser under an inert atmosphere. Freshly distilled dry THF (220 mL) and allylbenzyl ether **229** (5.60 g, 37.8 mmol, 1.74 eq.) were added. The reaction mixture was then stirred for 3 hours at room temperature. The final concentration of the allyl benzyl ether in THF is 0.16M, [136] which is the appropriate concentration for the subsequent Suzuki coupling. To the resulting alkylborane-containing THF solution was added methyl 5-iodoanthranilate (5.00 g, 21.7 mmol, 1.0 eq.), tetrakis(triphenylphosphine)palladium(0) (627 mg, 2.50 mol %) and NaOH solution (2.0 M, 21.7 mL, 2.0 eq.). The reaction was then heated to reflux for 24 hours. The presence of 9-BBN by-products made the purification of **230** difficult; for purpose of characterisation, **230** was purified from an aliquot of the reaction by flash chromatography eluting with 20% ethyl acetate/hexane giving an orange oil; R_f (20% ethyl acetate/petrol) 0.23; ^{1}H NMR δ 7.59 (d, J = 2.2 Hz, 1H; **H-aromatic**), 7.26-7.14 (m, 5H; **H-aromatic**), 6.99 (dd, J = 8.4, 2.1 Hz, 1H; **H-aromatic**), 6.48 (d, J = 8.4 Hz, 1H; **H-aromatic**), 4.40 (s, 2 H; **H-12**), 3.75 (s, 3H; **H-20**), 3.37 (t, J = 6.3 Hz, 2H; **H-10**), 2.51 (m, 2H; **H-8**), 1.79 (m, 2H; **H-9**); ^{13}C NMR δ 168.5 (**C-1**), 148.5 (**C-aromatic**), 138.5 (**C-aromatic**), 134.5 (**C- aromatic**), 130.3 (**C-aromatic**), 129.5 (**C-aromatic**), 128.2 (**C-aromatic**), 127.5 (**C-aromatic**), 127.4 (**C-aromatic**), 116.8 (**C-aromatic**), 110.5 (**C-aromatic**), 72.8 (**C-12**), 69.3 (**C-10**), 51.3 (**C-20**), 31.3 (**C-9**), 31.1 (**C-8**); LRMS (CI$^+$) *m/z*: 300 [*M*+H]$^+$, HRMS (CI$^+$) calcd for $C_{18}H_{22}NO_3$ [*M*+H]$^+$: 300.1600, found: 300.1595; IR (thin film, cm^{-1}) 3481(N-H), 3374 br (N-H), 2950 m, 2856 m, 1691 stg (C=O), 1632 stg (C=C), 1585 m (C=C), 1496 m, 1436 w, 1291 m, 1096 m, 828 m.

2-amino-5-[3-(benzyloxy)propyl]benzoic acid **231**



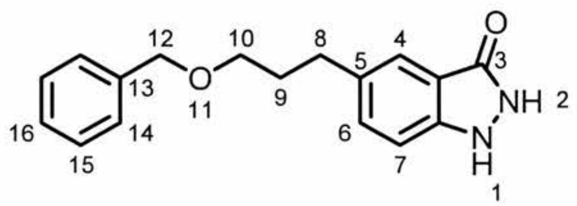
A solution of aqueous sodium hydroxide (2.0 M, 20 mL) was added to the crude reaction mixture and the biphasic solution refluxed for 5 days. The mixture was then cooled, filtered through celite, neutralised with diluted aqueous hydrochloric acid solution to pH 7, and extracted with ethyl acetate (3×100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The resulting oil was extracted with hot petrol (5×200 mL) and on cooling the desired product **231** was obtained as an off white solid (3.50 g, 60%); mp 90-91°C; ^{1}H NMR δ 7.74 (d, J = 2.3 Hz, 1H, **H-aromatic**), 7.36-7.25 (m, 5 H; **H-aromatic**), 7.16 (dd, J = 8.5, 2.3 Hz, 1H; **H-aromatic**), 6.64 (d, J = 8.5 Hz, 1H; **H-aromatic**), 4.51 (s, 2H; **H-12**), 3.48 (t, J = 6.4 Hz, 2H; **H-10**) 2.62 (m, 2H; **H-8**), 1.89 (m, 2H, **H-9**); ^{13}C NMR δ 173.5 (**C-1**), 148.3 (**C-quat.**), 138.6 (**C-quat.**), 135.9 (**C-aromatic**), 131.4 (**C-aromatic**), 130.1 (**C-quat.**), 128.5 (**C-aromatic**), 127.8 (**C-aromatic**), 127.7 (**C-aromatic**), 117.2 (**C-aromatic**), 109.7 (**C-quat.**), 73.1 (**C-12**), 69.5 (**C-10**), 31.5 (**C-8**), 31.3 (**C-9**); LRMS (ES$^-$) *m/z*: 284 [*M*-H]$^-$; HRMS (ES$^-$) calcd for $C_{17}H_{18}NO_3$ [*M*-H]$^-$: 284.1287, found 284.1279, IR (thin film, cm^{-1}) 3460 br (N-H), 3358 br (N-H), 2971 stg, 2869 stg, 1670 stg (C=O), 1457 m, 1249 m, 1126 m, 734 m.

Synthesis of 2-iodo-5-[3-(benzyloxy)propyl]benzoic acid **241**



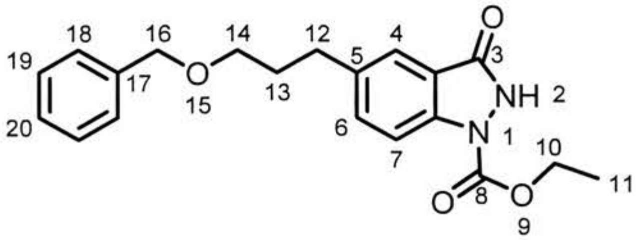
A solution of sodium nitrite (125 mg, 1.77 mmol, 1.03 eq.) in water/acetonitrile (1:1, 5.0 mL) was added with continuous stirring to a solution of **231** in aqueous hydrochloric acid solution (13%, v/v) at such a rate that the reaction temperature remained below 5°C. After addition was complete, the solution was stirred for 15 minutes and potassium iodide (454 mg, 2.74 mmol, 1.56 eq.) in aqueous sulphuric acid solution (10%, v/v, 5 mL) was added. The reaction was then heated for 10 minutes at reflux and cooled to room temperature. Saturated sodium thiosulphate solution (5 mL) was added and the reaction was extracted with ethyl acetate (3×30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude oil was purified by flash chromatography eluting with 20 to 100% ethyl acetate/hexane to give the desired compound **241** as a viscous oil (593 mg, 85%); R_f (100% ethyl acetate) 0.54; ^{1}H NMR δ 11.3 (br s, 1H; **O-H**), 7.83 (d, J = 7.9 Hz, 1H; **H-aromatic**), 7.6 (d , J = 1.8 Hz, 1H; **H-aromatic**), 7.28-7.17 (m, 5H; **H-aromatic**), 6.93 (dd, J = 7.9, 1.8 Hz, 1H; **H-aromatic**), 4.44 (s, 2H; **H-12**), 3.41 (t, J = 6.1 Hz, 2H; **H-10**), 2.65 (t, J = 7.4 Hz, 2H; **H-8**), 1.81 (m, 2H; **H-9**); ^{13}C NMR δ 170.9 (**C-1**), 142.1 (**C-quat.**), 141.6 (**C-aromatic**), 138.0 (**C-quat.**), 133.8 (**C-aromatic**), 133.2 (**C-quat.**), 132.1 (**C-aromatic**), 128.3 (**C-aromatic**), 127.7 (**C-aromatic**), 127.6 (**C-aromatic**), 91.1 (**C-3**), 72.8 (**C-12**), 68.8 (**C-10**), 31.5 (**C-8**), 30.7 (**C-9**); LRMS (ES$^+$) *m/z*: 418.96 $[M+\text{Na}]^+$; HRMS (ES$^+$) calcd for $C_{17}H_{17}IO_3Na$ $[M+\text{Na}]^+$: 419.0120, found 419.0124; IR (thin film, cm^{-1}) 3031 m, 2933 m, 2862 m (O-H), 1699 stg (C=O), 1462 m, 1449 m, 1262 m, 1101 m, 735 m, 700 m.

Synthesis of 5-[3-(benzyloxy)propyl]indazolinone **232**



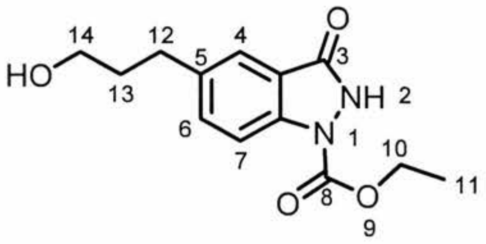
A suspension of **241** (800 mg, 2.02 mmol, 1.0 eq.), freshly prepared copper powder [169](115 mg, 1.82 mmol, 0.90 eq.) and 99% hydrazine hydrate solution (440 μL, 14.0 mmol, 7.0 eq.) in isopropanol (12 mL) was refluxed overnight. After cooling, the solution was filtered and solid residues washed with methanol (3×20 mL). The combined organic extracts were then concentrated *in vacuo*. The crude product was purified by flash chromatography eluting with 50-100% ethyl acetate/hexane to give the desired product **232** (270 mg, 52%) as a white solid; R_f (100% ethyl acetate) 0.23; mp 120-122°C; ^{1}H NMR δ 9.64 (br s, 1H; **N-H**), 7.45 (s, 1H; **H-4**), 7.28-7.16 (m, 5H; **H-aromatic**), 7.12 (dd, J = 8.6, 1.5 Hz, 1H; **H-aromatic**), 6.99 (d, J = 8.6 Hz, 1H; **H-aromatic**), 4.39 (s, 2H; **H-12**), 3.37 (t, J = 6.3 Hz, 2H; **H-10**), 2.61 (m, 2H; **H-8**), 1.85-1.76 (m, 2H; **H-9**); ^{13}C NMR δ 162.6 (**C-3**), 144.5 (**C-7a**), 138.4 (**C-aromatic**), 134.5 (**C-aromatic**), 132.3 (**C-aromatic**), 128.3 (**C-aromatic**), 127.6 (**C-aromatic**), 127.5 (**C-aromatic**), 121.2 (**C-aromatic**), 115.8 (**C-aromatic**), 111.6 (**C-3a**), 72.8 (**C-12**), 69.3 (**C-10**), 31.9 (**C-8**), 31.4 (**C-9**); LRMS (ES$^-$) *m/z*: 281.1590 [*M*-H]$^-$; HRMS (ES$^-$) calcd for $C_{17}H_{17}N_2O_2$ [*M*-H]$^-$: 281.1290, found 281.1290; IR (thin film, cm^{-1}) 3062 m, 2926 m, 2864 m, 1623 stg (C=O), 1589 stg, 1492 m, 1107 m, 699 m.

Synthesis of N1-ethyloxycarbonyl-5-[3-(benzyloxy)propyl]indazolinone **263**



To a solution of **232** (120 mg, 0.42 mmol, 1.0 eq.) in THF (5 mL) was added triethylamine (0.20 mL, 1.26 mmol, 3.0 eq.). The solution was stirred at room temperature under an inert atmosphere for 30 minutes. To the resulting solution was added ethyl chloroformate (0.13 mL, 1.26 mmol, 3.0 eq.) and the reaction stirred at room temperature for 16 hours. The reaction was then quenched by addition of saturated ammonium chloride solution (20 mL) and extracted with ethyl acetate (3×50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by flash chromatography eluting with 30% ethyl acetate/hexane to give N1, N2 and N1,O acylated isomers as an off white solid (150 mg) (The two isomers were not isolated). Morpholine (45 µL , 0.42 mmol, 1.2 eq.) was added to a solution of the white solid (150 mg, 1.0 eq.) in dry THF (15 mL) and the mixture was stirred 30 minutes at room temperature. The reaction was then quenched by addition of saturated ammonium chloride solution (10 mL) and extracted with ethyl acetate (3×30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by recrystallisation in hot ethyl acetate to give **263** as white minute needles (135 mg, 89%); mp 139-140°C, ^{1}H NMR δ 7.95 (br s, 1H; **NH**), 7.64 (s, 1H; **H-aromatic**), 7.44 (dd, J = 8.6, 1.6 Hz, 1H; **H-aromatic**), 7.37-7.27 (m, 6H; **H-aromatic**), 4.55 (q, J = 7.2 Hz, 2H; **H-10**), 4.51 (s, 2H; **H-16**), 3.5 (t, J = 6.2 Hz, 2H; **H-14**), 2.85 (m, 2H; **H-12**), 2.05-1.94 (m, 2H; **H-13**), 1.53 (t, J = 7.2 Hz, 3H; **H-11**); ^{13}C NMR δ 160.1 (**C-3**), 150.1 (**C-8**), 138.4 (**C-quat.**), 137.7 (**C-quat.**), 132.2 (**C-aromatic**), 128.3 (**C-aromatic**), 127.6 (**C-aromatic**), 127.5 (**C-aromatic**), 120.2 (**C-aromatic**), 117.6 (**C-quat.**), 114.2 (**C-aromatic**), 72.1 (**C-16**), 69.1 (**C-14**), 63.6 (**C-10**), 32.0 (**C-12**), 31.5 (**C-13**), 14.3 (**C-11**); LRMS (ES$^-$) *m/z*: 353 [*M*-H]$^-$; HRMS (ES$^-$) calcd for $C_{20}H_{21}N_2O_4$ [*M*-H]$^-$: 353.1501, found: 353.1489; IR (thin film, cm^{-1}) 2966 m, 2864 m, 1736 stg (C=O), 1458 m, 1373 m, 1271 m, 744 m; calculated for $C_{20}H_{22}N_2O_4$: C 67.78, H 6.26, N 7.90. Found: C 67.72, H 6.36, N 8.00%.

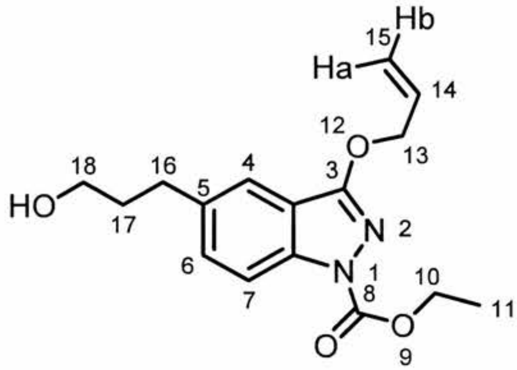
Synthesis of *N1*-ethyloxycarbonyl-5-(3-hydroxypropyl)indazolinone **264**



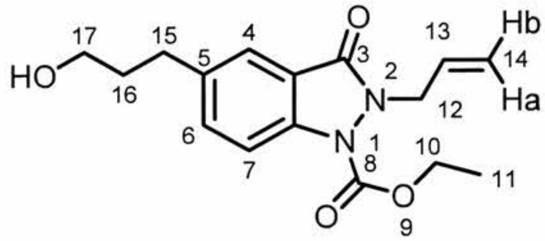
To a solution of **263** (400 mg, 1.13 mmol, 1.0 eq.) in dry THF (15 mL) in an autoclave was added a catalytic amount of palladium on carbon (10%). The reaction mixture was degassed under vacuum and charged with hydrogen (20 bars). The reaction was stirred at room temperature for five days, filtered through celite and concentrated *in vacuo*. The solid residues were washed with methanol (3×20 mL), the combined organic extracts were concentrated *in vacuo* to give the desired product **264** as a white solid (260 mg, 86%); mp 168-170°C, ^{1}H NMR δ 7.81 (d, J = 8.4 Hz, 1H; **H-7**), 7.48 (s, 1H; **H-4**), 7.37 (d, J = 8.4 Hz, 1H; **H-6**), 4.38 (q, J = 7.1 Hz, 2H; **H-10**), 3.50 (t, J = 6.3 Hz, 2H; **H-14**), 2.71 (t, J = 7.7 Hz, 2H; **H-12**), 1.83-1.74 (m, 2H; **H-13**), 1.36 (t, J = 7.1 Hz, 3H; **H-11**); ^{13}C NMR ([d6] DMSO) δ 152.2, 151.7, 141.6 , 129.7, 123.7, 111.7, 109.6, 105.8, 55.0, 52.3, 25.8, 23.0, 5.2; LRMS (ES^{+}) *m/z*: 287 [*M*+Na]$^{+}$; HRMS (ES^{+}) calcd for $C_{13}H_{16}N_2O_4Na$ [*M*+Na]$^{+}$: 287.1008, found: 287.1011; IR (thin film, cm^{-1}) 3430 br (O-H), 2977 stg, 2892 stg, 2835 m, 1725 stg (C=O), 1640 stg (C=O), 1453 m, 1379 m, 727 m.

Synthesis of *N1*-ethyloxycarbonyl-*N2*-allyl-5-(3-hydroxypropyl) indazolinone **265** and *N1*-ethyloxycarbonyl-3-allyloxy-5-(3-hydroxypropyl) indazole **266**

To a solution of **264** (310 mg, 1.17 mmol, 1.0 eq.), allyl alcohol (1.2 mL, 17.6 mmol, 15 eq.), and triphenylphosphine (338 mg, 1.29 mmol, 1.05 eq.) in toluene (50 mL) was added slowly diethylazodicarboxylate (0.20 mL, 1.29 mmol, 1.05 eq.) under an inert atmosphere. The reaction was stirred at room temperature for 16 hours. The solvent was partially removed by evaporation, the reaction quenched by addition of saturated ammonium chloride solution (20 mL) and extracted with ethyl acetate (3×25 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by flash chromatography eluting with 10-20% ethyl acetate/hexane to give **265** (103 mg, 0.35 mmol, 30%) as an off white solid and **266** (208 mg, 0.70 mmol, 60%) as an off white solid.



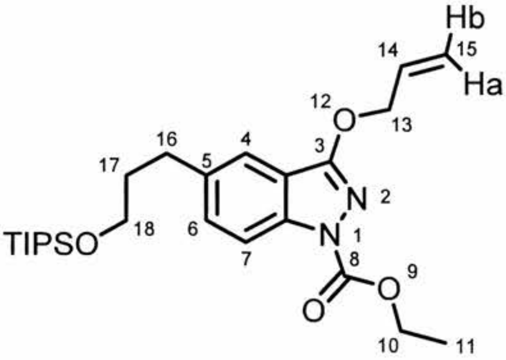
(265): R_f (50% ethyl acetate/petrol) 0.25; mp 58-59°C , ^{1}H NMR δ 7.92 (br s, 1H; **H-7**), 7.43 (m, 1H; **H-4**), 7.32 (dd, *J* = 8.7, 1.6 Hz, 1H; **H-6**), 6.09 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H; **H-14**), 5.43 (ddt, *J* = 17.2, 1.5, 1.5 Hz, 1H; **H-15a**), 5.27 (ddt, *J* = 10.4, 1.4, 1.4 Hz, 1H; **H-15b**), 4.94 (ddd, *J* = 5.7, 1.4, 1.4 Hz, 2H; **H-13**), 4.47 (q, *J* = 7.1 Hz, 2H; **H-10**), 3.31 (t, *J* = 6.3 Hz, 2H; **H-18**), 2.74 (m, 2H; **H-16**), 1.86 (m, 2H; **H-17**); 1.42 (t, *J* = 7.1 Hz, 3H; **H-11**); ^{13}C NMR δ 159 **(C-3)**, 150.9 **(C-8)**, 139.7 **(C-7a)**, 137.3 **(C-5)**, 132.3 **(C-14)**, 131.0 **(C-6)**, 118.9 **(C-4)**, 118.7 **(C-15)**, 117.4 **(C-3a)**, 114.6 **(C-7)**, 70.0 **(C-13)**, 63.5 **(C-10)**, 62.0 **(C-18)**, 34.3 **(C-17)**, 31.6 **(C-16)**, 14.5 **(C-11)**; LR MS (ES$^+$) *m/z*: 327.12 [*M*+Na]$^+$; HR MS (ES$^+$) calcd for $C_{16}H_{20}N_2O_2Na$ [*M*+Na]$^+$: 327.1321, found: 327.1319 ; IR (thin film, cm^{-1}) 2971 m, 2882 m, 2843 w, 1457 stg (C=N), 1372 m, 717 m.



(266): R_f (50% ethyl acetate/petrol) 0.07; mp = 139-140°C , ^{1}H NMR δ 7.79 (dd, *J* = 8.5, 0.7 Hz, 1H; **H-7**), 7.71 (dd, *J* = 1.9, 0.7 Hz, 1H; **H-4**), 7.48 (dd, *J* = 8.5, 1.9 Hz, 1H; **H-6**), 5.72 (ddt, *J* = 17.1, 10.1, 6.3 Hz, 1H;

H-13), 5.23 (ddt, J = 17.1, 1.4, 1.4 Hz, 1H; **H-14a**), 5.17 (ddt, J = 10.1, 1.3, 1.3 Hz, 1H; **H-14b**), 4.83 (dt, J = 6.3, 1.3 Hz, 2H; **H-12**), 4.44 (q, J = 7.1 Hz, 2H; **H-10**), 3.68 (t, J = 6.3 Hz, 2H; **H-17**), 2.81 (m, 2H; **H-15**), 1.92 (m, 2H; **H-16**), 1.45 (t, J = 7.1 Hz, 3H; **H-11**); ^{13}C NMR δ 164.8 (**C-3**), 151.0 (**C-8**), 141.6 (**C-7a**), 138.7 (**C-5**), 134.3 (**C-6**), 131.6 (**C-4**), 122.9 (**C-13**), 119.1 (**C-14**), 118.8 (**C-3a**), 115.3 (**C-7**), 63.9 (**C-10**), 61.7 (**C-17**), 49.2 (**C-12**), 34.0 (**C-16**), 31.4 (**C-15**), 14.4 (**C-11**); LRMS (ES$^+$) *m/z*: 327.12 $[M\text{+Na}]^+$; HRMS (ES$^+$) Calcd for $C_{16}H_{20}N_2O_2$ $[M\text{+Na}]^+$: 327.1321, found: 327.1321; IR (thin film, cm^{-1}) 3426 br (O-H), 2984 m, 2837 m, 1661 stg (C=O), 1491 m, 1283 m, 1045 m.

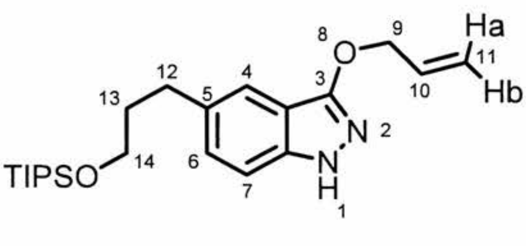
Synthesis of *N1*-ethyloxycarbonyl-3-allyloxy-5-(3-triisopropylsilyloxy)propyl) indazole **267**



To a solution of **265** (40.0 mg, 0.13 mmol, 1.0 eq.) in dry THF (5 mL) was added triethylamine (1.01 mL, 2.60 mmol, 20.0 eq.). Triisopropylsilyl trifluoromethanesulfonate (0.52 mL, 1.95 mmol, 15.0 eq.) was added and the reaction mixture stirred for 30 minutes at room temperature. The reaction was quenched by addition of saturated ammonium chloride solution (10 mL) and extracted with ethyl acetate (3×15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude oil was purified by flash chromatography eluting with hexane to give the desired product **267** as a colourless oil (57 mg, 95%): R$_f$ (20% ethyl acetate/petrol) 0.43; ^{1}H NMR δ 7.91 (br d, 1H; **H-7**), 7.44 (dd, J = 1.6, 0.8 Hz, 1H; **H-4**), 7.32 (dd, J = 8.7, 1.6 Hz, 1H; **H-6**), 6.08 (ddt, J = 17.2, 10.5, 5.8 Hz, 1H; **H-14**), 5.42 (ddt, J = 17.2, 1.5, 1.5 Hz, 1H; **H-15a**), 5.26 (ddt, J = 10.5, 1.5, 1.5 Hz, 1H; **H-15b**), 4.93 (ddt, J = 5.8, 1.5, 1.5 Hz, 2H, **H-13**), 4.46 (q, J = 7.1 Hz, 2H; **H-10**), 3.63 (t, J = 6.1 Hz, 2H; **H-18**), 2.76 (m, 2H; **H-16**), 1.85-1.76 (m, 2H, **H-17**), 1.42 (t, J = 7.1 Hz, 3H; **H-11**), 0.99 (m, 21H; **H-20**, **H-21**, **H-22**); ^{13}C NMR δ 159.3 (**C-3**), 150.9 (**C-8**), 139.8 (**C-7a**), 137.8 (**C-5**), 132.3 (**C-14**), 131.2 (**C-6**), 118.9 (**C-4**), 118.5 (**C-15**), 117.3 (**C-3a**), 114.5 (**C-7**), 69.9 (**C-13**), 63.4 (**C-10**), 62.2 (**C-18**), 34.8 (**C-17**), 31.7 (**C-16**), 18.0 (**C-21** and **C-22**), 14.5 (**C-11**), 12.0 (**C-20**); LRMS (ES$^+$) *m/z*: 461 $[M\text{+H}]^+$, 483 $[M\text{+Na}]^+$; HRMS (ES$^+$) calcd for $C_{25}H_{41}N_2O_4Si$ $[M\text{+H}]^+$: 461.2836, found: 461.2856;

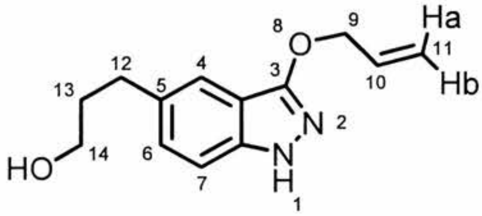
Calcd for $C_{25}H_{41}N_2O_4Si$ $[M+Na]^+$: 483.2648, found: 483.2655; IR (thin film, cm^{-1}) 2937 m, 2860 m, 1755 stg (C=O), 1725 stg (C=O), 1547 stg (C=N), 1487 stg, 1444 m, 1406 w, 1377 m, 1342 w, 1240 m, 1206 m, 1096 m, 1041 m, 973 m, 879 w, 751 m, 675 stg;

Synthesis of 3-allyloxy-5-[3-(triisopropylsilyloxy)propyl] indazole **268**



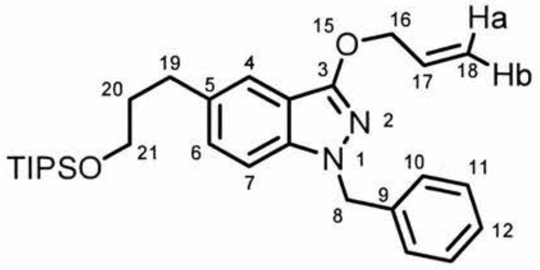
Aqueous lithium hydroxide (2 M, 2.0 mL) was added to a solution of **267** (57.0 mg, 0.12 mmol, 1.0 eq.) in THF (5 mL) and the reaction stirred vigorously for 16 hours at room temperature. The solvent was partially removed *in vacuo*. The reaction was then neutralised with diluted hydrochloric acid solution (10%) to pH 7 and extracted with ethyl acetate (3×25 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo.* The crude material was purified by flash chromatography eluting with 10% ethyl acetate/hexane to give the desired product **268** as a colourless oil (36 mg, 75%): R_f (20% ethyl acetate/hexane) 0.19 ; ^{1}H NMR δ 8.74 (br s, 1 H; **NH**), 7.34 (s, 1H; **H-aromatic**), 7.07 (d, J = 1.5 Hz, 1H; **H-aromatic**), 7.06 (d, J = 0.9 Hz, 1H; **H-aromatic**), 6.00 (ddt, J = 17.2, 10.5, 5.4 Hz, 1H; **H-10**), 5.31 (ddt, J = 17.2, 1.5, 1.5 Hz, 1H; **H-15a**), 5.14 (ddt, J = 10.5, 1.5, 1.5 Hz, 1H; **H-15b**), 4.75 (dt, J = 5.4, 1.5 Hz, 2H; **H-9**), 3.55 (t, J = 6.2 Hz, 2H; **H-14**), 2.63 (m, 2H; **H-12**), 1.72 (m, 2H; **H-13**), 0.92-0.88 (m, 21H; **H-16** and **H-17**); ^{13}C NMR δ 157.3 (**C-3**), 141.9 (**C-quat.**), 134.5 (**C-quat.**), 133.6 (**C-10**), 129.9 (**C-aromatic**), 118.9 (**C-aromatic**), 118.2 (**C-11**), 109.9 (**C-aromatic**), 69.9 (**C-9**), 62.9 (**C-14**), 32.3 (**C-13**), 35.5 (**C-12**), 18.5 and 12.4 (**C-16** and **C-17**); LR MS (CI^+) *m/z*: 389.26 $[M+H]^+$; HR MS (CI^+) calcd for $C_{22}H_{37}N_2O_2Si$ $[M+H]^+$: 389.2624, found: 389.2615; IR (thin film, cm^{-1}) 3205 br (N-H), 2941 m, 2860 m, 1525 stg (C=N), 1496 m (C=N), 1461 stg, 1321 m, 1249 m, 1202 m, 1100 m, 981 w, 883 w;

Synthesis of 3-allyloxy-5-[3-hydroxypropyl] indazole **271**



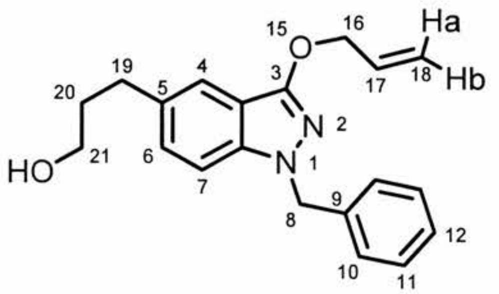
To a solution of **268** (23.0 mg, 0.059 mmol, 1.0 equiv.) in THF (5 mL) was added tetrabutyl ammonium fluoride (TBAF) (30 mg, 0.12 mmol, 2.00 equiv.) and the mixture was stirred at room temperature for 16 hours. The reaction mixture was then quenched by addition of ammonium chloride (5 mL) and extracted with ethyl acetate (3×5 mL). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo*. The crude material was purified by flash chromatography eluting with 40% ethyl acetate/hexane to give the desired product **271** as a yellow oil (9.00 mg, 66%); R_f (50% ethyl acetate/petrol) 0.16; ^{1}H NMR δ 8.90 (br s, 1H; N**H**), 7.44 (s, 1H; **H-4**), 7.16 (d, J = 1.6 Hz, 2H; **H-6**, **H-7**), 6.11 (ddt, J = 17.2, 16.0, 5.5 Hz, 1H; **H-10**), 5.41 (dq, J = 17.2, 1.6 Hz, 1H; **H-11a**), 5.25 (dq, J = 10.5, 1.3 Hz, 1H; **H-11b**), 4.84 (dt, J = 5.5, 1.4 Hz, 2H; **H-9**), 3.62 (t, J = 6.4 Hz, 2H; **H-14**), 2.73 (m, 2H; **H-12**), 1.86 (m, 2H; **H-13**), 1.63 (br s, 1H; **OH**); ^{13}C NMR δ 157.0 (**C-3**), 141.5 (**C-7a**), 133.4 (**C-10**), 133.1 (**C-5**), 128.2 (**C-6**), 118.5 (**C-4**), 117.9 (**C-11**), 112.9 (**C-3a**), 109.6 (**C-7**), 69.5 (**C-9**), 62.1 (**C-14**), 34.5 (**C-12**), 31.8 (**C-13**); LR MS (ES$^+$) *m/z*: 255 [*M*+Na]$^+$, HR MS (ES$^+$) calcd for $C_{13}H_{16}N_2O_2Na$ [*M*+Na]$^+$: 255.1109, found 255.1105; IR (thin film, cm^{-1}) 3256 br, 2928 stg, 2852 m, 1529 stg, 1499 stg, 1458 m, 1324 stg, 1253 m, 1207 m, 983 stg, 929 m, 766 m.

Synthesis of *N1*-benzyl-*3*-allyloxy-5-[3-(triisopropylsilyloxy)propyl] indazole **269**



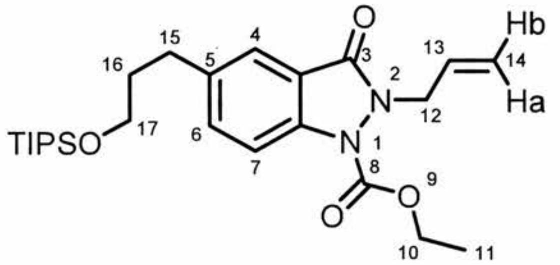
To a solution of **268** (36.0 mg, 0.09 mmol, 1.0 eq.) in dry THF (5 mL) was added potassium *t*-butoxide (20.0 mg, 0.18 mmol, 2.0 eq.) and benzyl bromide (0.02 mL, 0.14 mmol, 1.50 eq.) under an inert atmosphere. The solution was stirred at room temperature for 30 minutes. The reaction was quenched by addition of saturated ammonium chloride solution (10 mL) and extracted with ethyl acetate (3×15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by flash chromatography eluting with 0-10% ethyl acetate/hexane to give the desired product **269** as a colourless oil (28.0 mg, 67%); R_f (20% ethyl acetate/petrol) 0.57; ^{1}H NMR δ 7.42-7.41 (m, 1H; **H-aromatic**), 7.23-7.07 (m, 6 H; **H-aromatic**), 7.00 (dd, J = 8.7, 0.8 Hz, 1H; **H-aromatic**), 6.09 (ddt, J = 17.2, 10.5, 5.6 Hz, 1H; **H-17**), 5.40 (ddt, J = 17.2, 1.6, 1.6 Hz, 1H; **H-18a**), 5.23 (s, 2H; **H-8**), 5.22 (ddt, J = 10.5, 1.6, 1.3 Hz, 1H, **H-18b**), 4.83 (m, 2H; **H-16**), 3.64 (t, J = 6.3 Hz, 2H; **H-21**), 2.69 (m, 2H; **H-19**), 1.79 (m, 2H; **H-20**), 0.99 (m, 21H; **H-23**, **H-24**); ^{13}C NMR δ 155.3 (**C-3**), 140.6 (**C-quat.**), 137.5 (**C-quat.**), 133.3 (**C-17**), 129.0 (**C-aromatic**), 128.5 (**C-aromatic**), 127.4 (**C-aromatic**), 127.0 (**C-aromatic**), 118.6 (**C-aromatic**), 117.8 (**C-18**), 113.2 (**C-3a**), 108.7 (**C-aromatic**), 69.6 (**C-16**), 62.5 (**C-21**), 52.3 (**C-8**), 35.0 (**C-20**), 31.8 (**C-19**), 18.0 and 12.0 (**C-23** and **C-24**); LR MS (CI$^+$) *m/z*: 479 [M+H]$^+$, HR MS (CI$^+$) calcd for $C_{29}H_{43}N_2O_2Si$ [M+H]$^+$: 479.3092, found: 479.3094; IR (thin film, cm^{-1}) 2945 m, 2865 m, 1534 stg (C=N), 1491 m (C=N), 1453 m, 1338, 1211, 1100 m, 981 w, 883 m, 798 stg (Si-C), 683 w;

Synthesis of *N1*-benzyl-*3*-allyloxy-5-[3-(hydroxy)propyl] indazole **270**



To a solution of **269** (47.0 mg, 0.10 mmol, 1.0 eq.) in dry THF (5 mL) was added tetrabutylammonium fluoride (55 mg, 0.20 mmol, 2.0 eq.) and the reaction mixture was stirred at room temperature for 16 hours. The reaction was quenched by addition of saturated ammonium chloride solution (10 mL) and extracted with ethyl acetate (3×15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by flash chromatography eluting with 20-100% ethyl acetate/hexane to give the desired product **270** as a colourless oil (30 mg, 89%); R_f (50% ethyl acetate/petrol) 0.3 ; ^{1}H NMR δ 7.41 (br s, 1H; **OH**), 7.23-7.07 (m, 7H; **H-aromatic**), 7.00 (br d, 1H; **H-aromatic**), 6.09 (ddt, J = 17.2, 10.4, 5.6 Hz, 1H; **H-17**), 5.40 (ddt, J = 17.2, 1.6, 1.6 Hz, 1H; **H-18a**), 5.29 (s, 2H, **H-8**), 5.22 (ddt, J = 10.4, 1.4, 1.4 Hz, 1H; **H-18b**), 4.83 (ddd, J = 5.6, 1.4, 1.4 Hz, 2H; **H-16**), 3.60 (t, J = 6.4 Hz, 2H; **H-21**), 2.73-2.68 (m, 2H; **H-19**), 1.88-1.79 (m, 2H; **H-20**); ^{13}C NMR δ 155.4 (**C-3**), 140.8 (**C-7a**), 137.7 (**C-quat.**), 133.4 (**C-aromatic**), 132.8 (**C-quat.**), 128.9 (**C-aromatic**), 128.7 (**C-aromatic**), 127.6 (**C-aromatic**), 127.2 (**C-aromatic**), 118.8 (**C-aromatic**), 118.0 (**C-17**), 113.4 (**C-18**), 109.0 (**C-aromatic**), 69.8 (**C-16**), 62.4 (**C-21**), 52.6 (**C-8**), 34.7 (**C-20**), 61.9 (**C-19**); LR MS (CI^+) *m/z*: 232.18 $[M+H]^+$; HR MS (CI^+) Calcd for $C_{20}H_{22}N_2O_2$ $[M+H]^+$: 323.1760, found: 323.1752; IR (thin film, cm^{-1}) 2920 m, 2853 m, 1526 stg (C=N), 1492 m (C=N), 1334 m, 1209 m, 1039 stg , 977 m;

Synthesis of *N1*-ethyloxycarbonyl-*N2*-allyl-5-[3-(triisopropylsilyloxy) propyl] indazolinone **272**

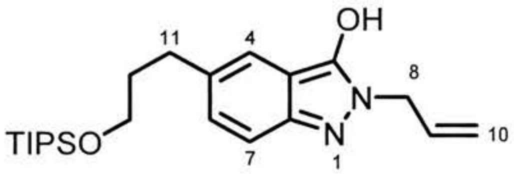


To a solution of **266** (52.0 mg, 0.17 mmol, 1.0 eq.) in dry THF (5 ml) was added triethylamine (0.12 mL, 0.85 mmol, 5.0 eq.) and triisopropylsilyl trifluoromethanesulfonate (0.09 mL, 0.34 mmol, 2.0 eq.) under an inert atmosphere. The solution was stirred at room temperature for 30 minutes. The reaction mixture was quenched by addition of saturated ammonium chloride solution (15 mL) and extracted with ethyl acetate (3×15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by flash chromatography eluting with 10% ethyl acetate/hexane to give the desired product **272** as a colourless oil (80 mg, 99%): R_f (20% ethyl acetate/ petrol) 0.34; ^{1}H NMR *δ* 7.71 (d, *J* = 8.5 Hz, 1H; **H-aromatic**), 7.63 (d, *J* = 1.7 Hz, 1H; **H-aromatic**), 7.40 (dd, *J* = 8.5, 1.7 Hz, 1H; **H-aromatic**), 5.65 (ddt, *J* = 16.5, 10.1, 6.2 Hz, 1H; **H-13**), 5.12 (m, 2H; **H-14**), 4.76 (m, 2H; **H-12**), 4.36 (q, *J* = 7.1 Hz, 2H; **H-10**), 3.64 (t, *J* = 6.1 Hz, 2H; **H-17**), 2.73 (m, 2H; **H-15**), 1.80 (m, 2H; **H-16**), 1.38 (t, *J* = 7.1 Hz, 3H; **H-11**), 0.99 (m, 21H; **H-19** and **H-20**); ^{13}C NMR *δ* 164.8 (**C-3**), 151 (**C-8**), 141.5 (**C-7a**), 139.2 (**C-5**), 134.3 (**C-6**), 131.6 (**C-13**), 122.9 (**C-4**), 118.9 (**C-14**), 118.7 (**C-3a**), 115.1 (**C-7**), 63.7 (**C-10**), 62.1 (**C-17**), 49.1 (**C-12**), 34.6 (**C-16**), 31.5 (**C-15**), 18.0 (**C-20**), 14.3 (**C-11**), 11.9 (**C-19**); LR MS (ES$^+$) *m/z*: 461.27 [*M*+H]$^+$; 483.25 [*M*+Na]$^+$; HR MS (ES$^+$) Calcd for $C_{25}H_{40}N_2O_4$ [*M*+Na]$^+$: 483.2655, found: 483.2651 ; IR (thin film, cm^{-1}) 2937 m, 2860 m, 1742 stg (C=O), 1700 stg (C=O), 1487 m, 1283 m, 1211 m, 1104 m, 879 w, 679 w;

Synthesis of **272** using the Claisen rearrangement

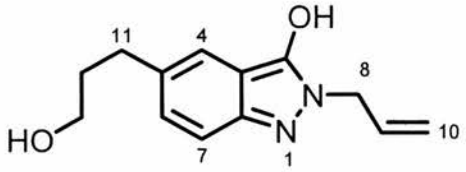
To a solution of **267** (5 mg, 0.0106 mmol, 1.0 eq.) in dry THF (5 mL) was added a catalytic amount of tetrakis(triphenylphosphine)palladium(0) (5% mol.). The reaction was stirred at room temperature for 16 hours under nitrogen. The solvent was removed *in vacuo* and the crude solid was purified by flash chromatography eluting with 0-10% ethyl acetate/petrol to give the desired product **272** as a colourless oil; ^{1}H NMR identical to the product obtained by reaction of **266** with tri(isopropyl)silyl trifluromethanesulfonate.

Synthesis of *N2*-allyl-5-[3-(triisopropylsilyloxy)propyl]indazolinol **273**



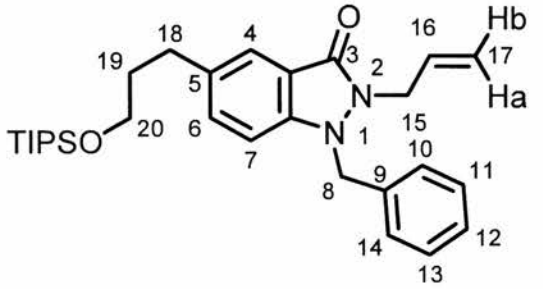
To a solution of **272** (80.0 mg, 0.17 mmol, 1.0 eq.) in THF (10 mL) was added an aqueous lithium hydroxide solution (2 M, 2.0 mL, 4.0 mmol, 4.0 eq.). The reaction mixture was stirred vigorously at room temperature for 16 hours. The reaction was then neutralised with diluted hydrochloric acid solution (10%) to pH 7 and extracted with ethyl acetate (3×15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by flash chromatography eluting with 30% ethyl acetate/hexane to give the desired product **273** as a white solid (44 mg, 65%); R_f (20% ethyl acetate/hexane) 0.13; mp 63-65°C; ^{1}H NMR δ 7.56 (br s, 1H; **H-aromatic**), 7.39 (s, 1H; **H-OH**), 7.29 (dd, J = 8.4, 1.7 Hz, 1H; **H-aromatic**), 7.06 (d, J = 8.4 Hz, 1H; **H-aromatic**), 5.82 (m, 1H; **H-9**), 5.27-5.18 (m, 2H, **H-10**), 4.40 (m, 2H; **H-8**), 3.63 (t, J = 6.2 Hz, 2H; **H-13**), 2.69 (m, 2H; **H-11**), 1.78 (m, 2H, **H-12**), 0.98 (m, 21H; **H-15** and **H-16**); ^{13}C NMR δ 162.5 (**C-3**), 145.4 (**C-7a**), 137.1 (**C-5**), 133.0 (**C-6**), 131.9 (**C-9**), 122.8 (**C-4**), 119.5 (**C-3a**), 119.3 (**C-10**), 112.3 (**C-7**), 62.3 (**C-13**), 46.7 (**C-8**), 34.8 (**C-11**), 31.7 (**C-12**), 18.0 and 11.9 (**C-15** and **C-16**); LR MS (ES$^-$) *m/z*: 387 [*M*-H]$^-$, HR MS (ES$^-$) Calcd for $C_{22}H_{35}N_2O_2Si$ [*M*-H]$^-$: 387.2468, found: 387.2460; IR (thin film, cm^{-1}) 2945 m, 2865 m, 1632 m, 1500 stg (C=N), 1461 m (C=N), 1104 m, 883 m, 679 m.

Synthesis of *N2*-allyl-5-[3-hydroxy propyl]indazolinone **276**



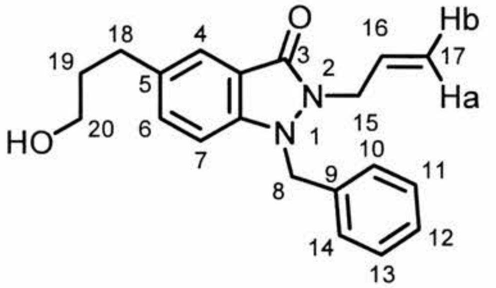
To a solution of **273** (20.0 mg, 0.052 mmol) in THF (5 mL) was added tetrabutylammonium fluoride (27.0 mg, 0.10 mmol, 2.0 equiv.). The reaction mixture was stirred for 16 hours at room temperature. The reaction was quenched by addition of saturated solution of ammonium chloride and extracted with ethyl acetate (3×10 mL). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo*. The crude product was purified by flash chromatography eluting with ethyl acetate to afford the desired compound **276** as a yellow oil (7 mg, 60%); R_f (100% ethyl acetate) 0.06; ^{1}H NMR δ 7.57 (s, 1H; **H-4**), 7.30 (dd, J = 8.5, 1.3 Hz, 1H; **H-6**), 7.08 (d, J = 8.3 Hz, 1H; **H-7**), 5.86 (ddt, J = 16.3, 10.1, 6.2 Hz, 1H; **H-9**), 5.29 (br d, J = 11.8 Hz, 1H; **H-10**), 5.25 (br d, J = 5.4 Hz, 1H; **H-10**), 4.44 (d, J = 6.0 Hz, 2H; **H-8**), 3.59 (t, J = 6.3 Hz, 2H; **H-13**), 2.71 (t, J = 7.6 Hz, 2H; **H-11**), 1.82 (m, 2H; **H-12**), 1.72 (br s, 2H; **NH** and **OH**); ^{13}C NMR δ 145.5 (**C-3**), 136.8 (**C-5**), 132.9 (**C-6**), 131.8 (**C-9**), 122.9 (**C-4**), 119.6 (**C-10**), 112.5 (**C-7**), 100.2 (**C-quat.**), 61.8 (**C-13**), 46.8 (**C-8**), 34.2 (**C-12**), 31.5 (**C-11**), one **C-quat.** too weak to observe; LR MS (CI$^+$) *m/z*: 233 [*M*+H]$^+$, HR MS (CI$^+$) calcd for $C_{13}H_{17}N_2O_2$ [*M*+H]$^+$: 233.1290, found 233.1288; IR (thin film, cm^{-1}) 2928 stg, 2856 stg, 1627 stg (C=N), 1496 m (C=N), 1457 m, 1058 w;

Synthesis of *N1*-benzyl-*N2*-allyl-5-[3-(triisopropylsilyloxy)propyl] indazolinone **274**



To a solution of **269** (20.0 mg, 0.04 mmol, 1.0 eq.) in dry THF (5 mL) was added tetrakis(triphenylphosphine)palladium (0) (10.0 mg , 8.66 μmol, 20% mol.). The solution was stirred in the dark at room temperature under an inert atmosphere for 16 hours. The reaction was quenched with addition of ammonium chloride (5 mL) and extracted with ethyl acetate (3×15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The product was purified by flash chromatography eluting with hexane to afford **274** as a colourless oil (18.0 mg, 90%); R_f (20% ethyl acetate/petrol) 0.1 ; ^{1}H NMR δ 7.58 (s, 1H; **H-aromatic**), 7.29-6.94 (m, 7H; **H-aromatic**), 5.73 (m, 1H; **H-16**); 5.14 (m, 1H; **H-17a**); 5.10 (m, 1H; **H-17b**); 4.71 (s, 2H; **H-8**); 4.43 (dt, J = 5.7, 1.4 Hz, 2H; **H-15**); 3.63 (t, J = 6.2 Hz, 2H; **H-20**); 2.69 (m, 2H; **H-18**); 1.79 (m, 2H; **H-19**); 0.99 (m, 21H; **H-22** and **H-23**); ^{13}C NMR δ 163.5 (**C-3**), 148.1 (**C-quat.**), 136.4 (**C-quat.**), 134.8 (**C-quat.**), 133.2 (**C-aromatic**), 132.6 (**C-16**), 128.6 (**C-aromatic**), 128.1 (**C-aromatic**), 127.8 (**C-aromatic**), 123.0 (**C-4**), 118.7 (**C-3a**), 117.9 (**C-17**), 111.7 (**C-aromatic**), 62.4 (**C-20**), 53.7 (**C-8**), 45.1 (**C-15**), 34.7 (**C-19**), 31.6 (**C-18**), 18.03 and 12.0 (**C-22** and **C-23**); LR MS (ES$^+$) *m/z*: 501 [M+Na]$^+$; HRMS (CI$^+$) Calcd for $C_{29}H_{43}N_2O_2Si$ [M+H]$^+$: 479.3094, found: 479.3092; IR (thin film, cm^{-1}) 2941 m, 2869 m, 1674 stg (C=O), 1496 m, 1453 m, 1257 m, 1100 m, 879 stg, 679 stg.

Synthesis of *N1*-benzyl-*N2*-allyl-5-(3-hydroxypropyl)indazolinone **275**



To a solution of **274** (2.00 mg, 0.0042 mmol, 1.0 eq.) in dry THF (10 mL) was added tetrabutylammonium fluoride solid (5 mg, 0.023 mmol, 5.0 eq.). The reaction mixture was stirred at room temperature under an inert atmosphere for 16 hours. The reaction was quenched by addition of ammonium chloride (3 mL) and extracted with ethyl acetate (3×2 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The product was purified by flash chromatography eluting with ethyl acetate to give **275** as a colourless oil (1.00 mg, 74%); R_f (ethyl acetate) 0.19; ^{1}H NMR δ 7.59 (s, 1H; **H-4**), 7.27 (dd, J = 8.5, 1.7 Hz, 1H; **H-6**), 7.21-7.16 (m, 3H; **H-aromatic**), 7.03 (m, 2H; **H-aromatic**), 6.96 (d, J = 8.4 Hz, 1H; **H-7**), 5.75 (m, 1H; **H-16**), 5.12 (m, 2H; **H-17**), 4.71 (s, 2H; **H-8**), 4.44 (d, J = 5.6 Hz, 2H; **H-15**), 3.60 (t, J = 6.3 Hz, 2H; **H-20**), 2.70 (t, J = 7.6 Hz, 2H; **H-18**), 1.91 (br s, 1H; **OH**), 1.83 (m, 2H; **H-19**); ^{13}C NMR δ 163.5 (**C-3**), 148.2 (**C-quat.**), 136.1 (**C-quat.**), 134.9 (**C-quat.**), 133.3 (**C-6**), 132.7 (**C-16**), 128.8 (**C-aromatic**), 128.4 (**C-aromatic**), 127.9 (**C-aromatic**), 123.2 (**C-4**), 118.7 (**C-quat.**), 118.1 (**C-17**), 111.7 (**C-7**), 62.0 (**C-20**), 53.7 (**C-8**), 45.3 (**C-15**), 34.3 (**C-19**), 31.6 (**C-18**); LR MS (ES$^+$) *m/z*: 345 [*M*+Na]$^+$; HR MS (ES$^+$) Calcd for $C_{20}H_{22}N_2O_2Na$ [*M*+Na]$^+$: 345.1579, found: 345.1580; IR (thin film, cm^{-1}) 3362 br (O-H), 2941 m, 2852 m, 1661 stg (C=O), 1491 m, 700 m.

The loading procedure for solid-supported synthesis

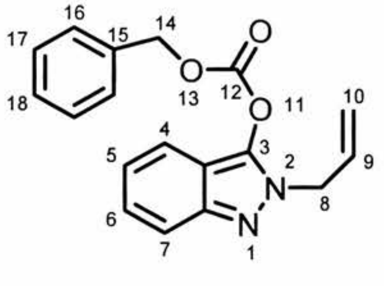
Activation: Silicon functionalised resin (1.43 mequiv. Si/g) that had been dried under high vacuum for 12 hours was weighed (260 for O-allylated isomer and 226 mg for N-allylated isomer, 1 equiv.) into a 10 mL polypropylene PD-10 column fitted with a Teflon stopcock and swollen in DCM (2.0 mL, 10 mL of solvent/g of resin) under N_2 atmosphere for 30 min. The solvent was then drained under positive N_2 pressure and 5,2 and 4.5 mL of a 4% trifluoromethanesulfonic acid/DCM solution (6 equiv. of TfOH relative to Si) respectively was added by syringe. The resin turned bright red/orange upon acid treatment and was then gently agitated for 30 min. while still under N_2 atmosphere. Once activation was completed, two DCM washes remoed excess acid.

Loading: Treatment of the silicon-based resin with 2,6-lutidine (450 and 420 μL respectively, 8.0 equiv. relative to Si) for 15 minutes followed by addition of 0.5 mL of an azeotropically dried 1.0 M solution of **265** (147 mg)/ **266** (137 mg) (2.0 equiv.) resulted in a colorless resin. The beads are then gently agitated for an additional 10 hour under N_2 atmosphere. The beads were drained, exposed to atmosphere, and subjected to the following wash protocol : CH_2Cl_2 (2×3 mL for 45 minutes), THF (2×3 mL for 30 minutes), THF/IPA (3:1, 2×3 mL for 30 minutes), THF/H_2O (3:1, 2×3 mL for 30 minutes), THF/IPA (3:1, 2×3 mL for 30 minutes), THF/IPA (3:1, 2×3 mL for 30 minutes), DMF (2×3 mL for 30 minutes), THF (2×3 mL for 30 minutes). The resin was air-dried for 3 h and then placed under high vacuum for 24 h to remove trace of solvent and H_2O. The mass of the loaded and dried resin indicated an apparent loading efficiency of 35% and 28% respectively based on weight gain and recovered starting material.

The cleavage procedure from the solid support

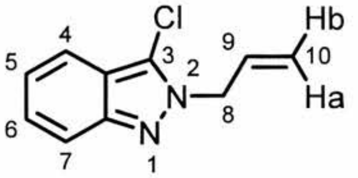
Vacuum-dried resin was weighed (>5 mg) out into a solvent resistant scintillation vial and allowed to swell in 1.0 mL of THF for 30 min. The THF solution was removed and replaced with a fresh 0.95 mL of THF and 0.05 mL of HF/pyridine solution (7:3 ratio HF/pyridine, available from Aldrich Co.) The vial was sealed and agitated for 3 h at which time 0.1 mL of methoxytrimethylsilane was added to quench unreacted HF. (Note : quench is mildly exothermic therefore use caution). The beads are further agitated for 30 minutes to ensure complete quenching. The solution was removed and the beads washed twice with additional 1.0 mL portions of fresh THF. All solvents were combined and concentrated *in vacuo*. The material recovered from the cleavage was then analysed by LC/MS and compared with the traces of authentic materials.

Synthesis of *N2*-allyl 3-benzyloxycarbonyloxyindazole **170**



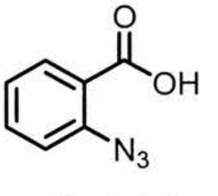
To a solution of **23** (250 mg, 1.44 mmol, 1.0 equiv.) in dry THF (15 mL) was added triethylamine (241 μL, 1.73 mmol, 1.20 equiv.) and the solution was stirred at room temperature under an inert atmosphere for 30 minutes. Benzyl chloroformate (225 μL, 1.58 mmol, 1.10 equiv.) was added and the solution was stirred under the same conditions for 1 hour. The reaction was quenched by addition of saturated ammonium chloride solution (20 mL) and extracted with ethyl acetate (3×30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by flash chromatography eluting with 20% ethyl acetate/hexane to afford **170** as an orange oil (431 mg, 97%); R_f (20% ethyl acetate/petrol) 0.15 ; ^{1}H NMR δ 7.61 (d, J = 8.8 Hz, 1H; **H-7**), 7.44 (m, 6H; **H-aromatic**), 7.25 (m, 1H; **H-6**), 7.05 (m, 1H; **H-5**), 5.98 (m, 1H; **H-**), 5.33 (s, 2H; **H-14**), 5.18 (d, J = 5.9 Hz, 1H; **H-10**), 5.13 (d, J = 12.7 Hz, 1H; **H-10**), 4.89 (d, J = 5.9 Hz, 2H; **H-8**) ; ^{13}C NMR δ 151.2 (**C-12**), 147.1 (**C-7a**), 136.8 (**C-3**), 133.9 (**C-15**), 131.3 (**C-9**), 129.3 (**C-aromatic**), 128.8 (**C-aromatic**), 126.6 (**C-6**), 121.9 (**C-5**), 118.9 (**C-10**), 118.6 (**C-4**), 117.8 (**C-7**), 110.4 (**C-3a**), 71.8 (**C-14**), 52.0 (**C-8**); LR MS (EI$^+$) *m/z*: 308 $[M]^+$; HR MS (EI$^+$) calcd for $C_{18}H_{16}N_2O_3$ $[M]^+$: 308.1161, found: 308.1157; IR (thin film, cm^{-1}) 3037 w, 2925 w, 1750 stg (C=O), 1700 stg, 1615 w, 1457 stg, 1389 m, 1280 stg, 752 stg;

Synthesis of *N2*-allyl 3-chloroindazole **197** [154]



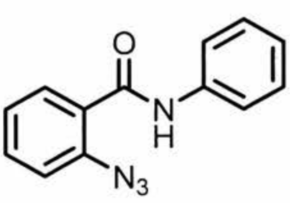
23 (100 mg, 0.57 mmol) were introduced in a flask containing phosphorus oxychloride (3.00 mL). The solution was refluxed for 16 hours under an inert atmosphere. The excess of phosphorus oxychloride was removed by co-distillation using toluene (4×6 mL). The crude oil was purified by flash chromatography eluting with 20% ethyl acetate/petrol to afford **197** as a brown oil (60.0 mg , 54%); R_f (20% ethyl acetate/petrol) 0.33; ^{1}H NMR δ 7.58 (dt, J = 8.8, 0.9 Hz, 1H; **H-7**), 7.49 (dt, J = 8.5, 1.0 Hz, 1H; **H-4**), 7.23 (ddd, J = 8.8, 6.6, 1.1 Hz, 1H; **H-6**), 7.04 (ddd, J = 8.4, 6.6, 0.8 Hz, 1H; **H-5**), 5.98 (ddt, J = 17.0, 10.3, 5.7 Hz, 1H; **H-9**), 5.23 (ddd, J = 10.2, 2.3, 1.3 Hz, 1H; **H-10b**), 5.12 (ddd, J = 17.0, 2.5, 1.5 Hz, 1H; **H-10a**), 4.99 (dt, J = 5.8, 1.5 Hz, 2H; **H-8**); ^{13}C NMR δ 148.0 (**C-7a**), 131.2 (**C-9**), 126.9 (**C-6**), 122.2 (**C-5**), 118.9 (**C-10**, **C-3** overlapping), 118.6 (**C-4, C-3a** overlapping), 117.9 (**C-7**), 52.9 (**C-8**); LR MS (CI$^+$) *m/z*: 193 [M+H]$^+$, HR MS (CI$^+$) calcd for $C_{10}H_{10}N_2Cl$ [M+H]$^+$: 193.0533, found: 193.0534; IR (thin film, cm^{-1}) 3056 w, 2937 w, 1627 m (C=C), 1504 m (C=N), 1461 m, 1364 stg, 1287 m, 1245 m, 1053 stg, 985 m, 921 m, 862 w, 739 stg;

Synthesis of 2-azido benzoic acid **206** [157]



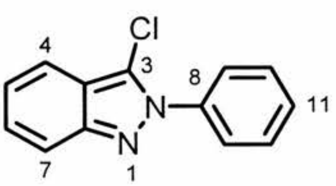
To a solution of 2-amino benzoic acid (4.11 g, 30.0 mmol) in concentrated hydrochloric acid (60 mL) and water (60 mL) was added dropwise a solution of sodium nitrite (2.32 g, 33.6 mmol) in water (30 mL) at a rate such that the temperature of the reaction mixture remained below 5°C. After completion of sodium nitrite addition, the diazonium solution was filtered and added dropwise to a stirred solution of sodium azide (2.05 g, 30.0 mmol, 1.00 equiv.) and sodium acetate (30.10 g, 0.36 mol, 12 equiv.) in water (60 mL). The yellow solution was stirred for 15 minutes. The white precipitate was filtered and recrystallised from toluene as white needles, **206** (1.90 g, 43%), mp 145-146°C (lit. 155°C), IR (nujol, cm^{-1}) 2946 stg, 2926 stg, 2893 stg, 2101 m (N≡N), 1694 m, 1595 w, 1578 w, 1459 m (nujol), 1377 m (nujol), 1270 m.

Synthesis of 2-azido *N*-phenyl benzamide **207** [156, 157]



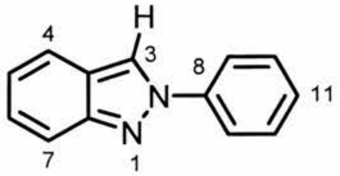
To a solution of **206** (1.80 g, 11.0 mmol) in dichloromethane (50 mL) was added oxalyl chloride (1.07 mL, 12.0 mmol, 1.10 equiv.) and a catalytic amount of DMF. The reaction was stirred for 2 hours at room temperature under an inert atmosphere. The resulting solution was added via cannula to a solution of aniline (1.20 mL, 13.2 mmol, 1.20 equiv.) and Hunig's base (2.30 mL, 13.0 mmol, 1.20 equiv.) in DCM (50 mL). The reaction mixture was stirred for 30 min at room temperature, quenched by addition of saturated ammonium chloride (50 mL) then extracted with ethyl acetate (3×30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography eluting with 10% ethyl acetate/hexane to afford **207** as a brown solid (2.20 g, 84%); mp 128°C (lit. [156]136°C), ^{1}H NMR 9.24 (s, 1H; **NH**), 8.19 (dd, *J* = 7.9, 1.6 Hz, 1H; **H-aromatic**), 7.62 (app. dd, *J* = 8.5, 0.9 Hz, 2H; **H-aromatic**), 7.49 (ddd, *J* = 8.0, 7.4, 1.7 Hz, 1H; **H-aromatic**), 7.31 (m, 2H, **H-aromatic**), 7.22 (m, 2H; **H-aromatic**), 7.09 (app. tt, *J* = 7.4, 1.3 Hz, 1H; **H-aromatic**) ; IR (thin film, cm^{-1}) 3293 w, 3060 w, 3030 w, 2925 w, 2127 stg, 1656 stg, 1597 stg, 1542 stg, 1497 stg, 1441 stg, 1322 stg, 1277 m, 751 stg, 690 m;

Synthesis of 3-chloro-2-phenyl-2*H*-indazole **208** [156]



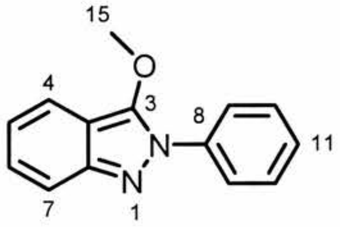
2-azido *N*-phenyl benzamide **207** (2.00 g, 8.40 mmol) was refluxed in thionyl chloride (10 mL) for 16 hours under an inert atmosphere. The excess of thionyl chloride was removed by co-distillation with toluene (3×30 mL). The crude oil was purified by flash chromatography eluting with 10% ethyl acetate/hexane to afford the desired compound **208** (1.53 g, 80%) as a white solid; mp 36-37°C (lit. [156] 34°C); ^{1}H NMR δ 7.65-7.59 (m, 3H; **H-aromatic**), 7.54 (dt, *J* = 8.5, 1.0 Hz, 1H; **H-aromatic**), 7.49-7.40 (m, 3H; **H-aromatic**), 7.27 (ddd, *J* = 8.8, 6.6, 1.1 Hz, 1H; **H-6**), 7.07 (ddd, *J* = 8.5, 6.6, 0.8 Hz, 1H; **H-5**) ;^{13}C NMR δ 148.5, 138.4, 129.1, 127.5, 125.7, 122.7, 119.8, 119.4, 118.9, 118.2 (one carbon missing due to overlapping); LR MS (CI^{+}) *m/z*: 229 [*M*+H]$^{+}$; HR MS (CI^{+}) calcd for $C_{13}H_{10}N_2{}^{35}Cl$ [*M*+H]$^{+}$: 229.0533, found: 229.0538 ; IR (thin film, cm^{-1}) 3063 w, 3040 w, 1627 m, 1596 m, 1516 stg, 1497 stg, 1454 m, 1369 stg, 1263 w, 1108 w, 1016 m, 824 w, 760 stg, 742 stg, 692 stg;

Synthesis of 2-phenyl-2*H*-indazole **210** [157]



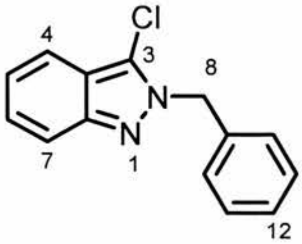
To a solution of **208** (200 mg, 0.88 mmol) in glacial acetic acid (5 mL) was added zinc dust (340 mg, 5.28 mmol, 6.00 equiv.). The stirred reaction was heated under reflux for 2 hours. The reaction was cooled down to room temperature, the solvent was removed *in vacuo*. The oily residue was solubilised in dichloromethane (20 mL) and the excess of acetic acid was removed by washing the organic phase with water (2×10 mL) and saturated sodium bicarbonate solution (1×10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography eluting with 10% ethyl acetate/hexane to afford **210** (130 mg, 76%) as an off white solid; R_f (20% ethyl acetate/petrol) 0.36; ^{1}H NMR δ 8.31 (s, 1H, **H-3**), 7.81 (m, 2H; **H-aromatic**), 7.72 (dd, J = 8.8, 0.8 Hz, 1H; **H-aromatic**), 7.62 (d, J = 8.5 Hz, 1H; **H-aromatic**), 7.43 (t, J = 7.8 Hz, 2H; **H-aromatic**), 7.31 (t, J = 7.4 Hz, 1H; **H-11**), 7.24 (ddd, J = 8.7, 6.6, 1.0 Hz, 1H; **H-aromatic**), 7.03 (dd, J = 8.2, 6.8 Hz, 1H; **H-aromatic**); LR (ES$^+$) *m/z*: 195 $[M+H]^+$; HR (ES$^+$) calcd for $C_{13}H_{11}N_2$ $[M+H]^+$: 195.0922, found: 195.0918;

Synthesis of 3-methoxy-2-phenyl-2*H*-indazole **209** [157]



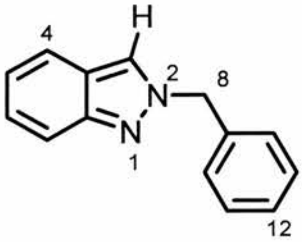
208 (200 g, 0.88 mmol) was heated under reflux for 24 h with a solution of sodium methoxide [sodium (200 mg) in methanol (10 mL)]. The reaction mixture was cooled and the solvent was removed *in vacuo*. The residue was adsorbed onto silica and purified by flash chromatography eluting with 10% ethyl acetate/hexane to afford **209** as an brown oil (22.0 mg, 11%); R_f (20% ethyl acetate/petrol) 0.29; ^{1}H NMR δ 7.72 (m, 2H; **H-aromatic**), 7.62 (dt, J = 8.6, 1.0 Hz, 1H; **H-6**), 7.49 (dt, J = 8.9, 0.9 Hz, 1H; **H-5**), 7.39 (m, 2H; **H-aromatic**), 7.28 (m, 1H; **H-11**), 7.14 (ddd, J = 8.9, 6.6, 1.0 Hz, 1H; **H-4**), 6.84 (ddd, J = 8.6, 6.6, 0.8 Hz, 1H; **H-7**), 4.17 (s, 3H; **H-15**); ^{13}C NMR δ 147.9 (**C-7a**), 146.7 (**C-3**), 138.5 (**C-aromatic**), 128.9 (**C-aromatic**), 127.7 (**C-11**), 126.9 (**C-4**), 123.9 (**C-aromatic**), 120.1 (**C-7**), 119.7 (**C-6**), 117.9 (**C-5**), 107.7 (**C-3a**), 60.6 (**C-15**); LR (ES$^+$) *m/z*: 225 $[M+H]^+$; HR (ES$^+$) calcd for $C_{14}H_{13}N_2O$ $[M+H]^+$: 225.1028, found: 225.1032; IR (thin film, cm^{-1}) 3063 w, 2925 m, 2853 w, 1625 stg, 1596 stg, 1551 stg, 1523 stg, 1513 stg, 1490 m, 1460 m, 1414 stg, 1382 stg, 1285 m, 1159 m, 1143 m, 1127 stg, 1076 stg, 762 stg, 740 stg, 692 stg;

Synthesis of 2-benzyl-3-chloro-2*H*-indazole **203** [154]



202 (2.00 g, 8.93 mmol) was refluxed in phosphorus oxychloride (3 mL, 3.60 equiv.) for 16 hours under an inert atmosphere. The excess of phosphorus oxychloride was removed by co-distillation with toluene (4×10 mL). The crude product was then transferred onto silica and purified by flash chormatography eluting with 20% ethyl acetate/petrol to afford **203** as an off-white solid (700 mg, 33%); R_f (20% ethyl acetate/petrol) 0.51, ^{1}H NMR δ 7.59 (dt, J = 8.8, 0.9 Hz, 1H; **H-4**), 7.47 (dt, J = 8.5, 1.0 Hz, 1H; **H-7**), 7.26-7.16 (m, 6H; **H-aromatic**), 7.03 (ddd, J = 8.4, 6.6, 0.8 Hz, 1H; **H-6**), 5.55 (s, 2H; **H-8**); ^{13}C NMR δ 148.0, 135.2, 128.8, 128.2, 127.6, 126.9, 122.3, 119.3, 119.1, 118.7, 118.0, 54.2 ; LR (ES$^+$) *m/z*: 265 $[M\text{+Na}]^+$; IR (thin film, cm^{-1}) 3063 w, 3037 w, 2945 w, 1628 m, 1507 m, 1496 m, 1468 m, 1455 m, 1368 s, 1291 m, 1246 m, 1175 w, 1147 w, 1058 m, 880 w, 758 m, 742 stg, 705 stg;

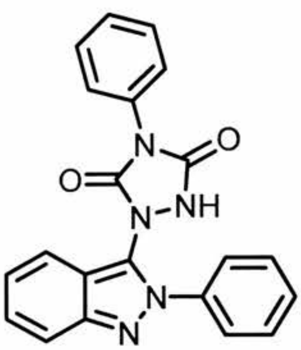
Synthesis of 2-benzyl-2*H*-indazole **204** [157]



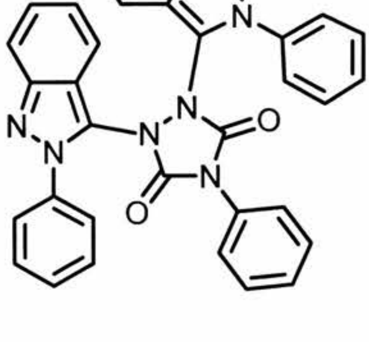
To a solution of **203** (297 mg, 1.23 mmol) in glacial acetic acid (5 mL) was added zinc dust (160 mg, 2 equiv.). The reaction was stirred under reflux for 16 hours, filtered whilst hot, and the residue washed with methanol (2×10 mL). The solvent was removed *in vacuo*. The product was solubilised in dichloromethane (20 mL) and the excess of acetic acid was removed by washing the organic phase with water (2×10 mL) and saturated sodium bicarbonate solution (1×10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography eluting with 10% ethyl acetate/hexane to afford **204** as a yellow oil (199 mg, 78%); R_f (20% ethyl acetate/petrol) 0.19; ^{1}H NMR δ 7.80 (d, J = 0.8 Hz, 1H; **H-3**), 7.66 (ddd, J = 8.7, 1.8, 0.9 Hz, 1H; **H-4**), 7.54 (dt, J = 8.4, 1.0 Hz, 1H; **H-7**), 7.32-7.17 (m, 6H; **H-aromatic**), 7.00 (ddd, J = 8.4, 6.6, 0.9 Hz, 1H; **H-aromatic**), 5.52 (s, 2H; **H-8**); LR (CI$^+$) *m/z*: 209 $[M\text{+H}]^+$; HR (CI$^+$) calcd for $C_{14}H_{13}N_2$ $[M\text{+H}]^+$: 209.1079, found: 209.1081; IR (thin film, cm^{-1}) 3063 m, 3033 m, 2932 m, 1628 m, 1515 m, 1496 m, 1470 m, 1455 m, 1390 m, 1310 m, 1156 m, 1135 m, 1029 w, 1009 w, 981 w, 906 w, 839 w, 784 m, 758 stg, 705 w, 644 w;

Synthesis of 4-phenyl-1-(2-phenyl-2*H*-indazol-3-yl)-1,2,4-triazolidine-3,5-dione **215** and 4-phenyl-1,2-bis(2-phenyl-2H-indazol-3-yl)-1,2,4-triazolidine-3,5-dione **216**

To a solution of **210** (83.0 mg, 0.43 mmol) in chloroform (8 mL) was added 4-phenyl-3H-1,2,4-triazoline-3,5-dione (75.0 mg, 0.43 mmol, 1.00 equiv.). The reaction was refluxed until the bright red colour faded to a colourless solution (16 hours). The crude reaction mixture was evaporated *in vacuo* and purified by flash chromatography eluting with 20-50% ethyl acetate petrol to afford **215** as a white solid (118 mg, 75%) and **216** as a white crystalline solid (15 mg, 6%);



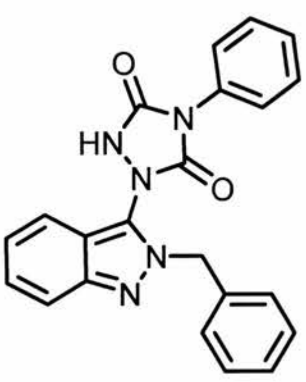
(215) : R_f (50% ethyl acetate/petrol) 0.29; mp 184-185°C; ^{1}H NMR [Methanol-d$_4$] δ 7.36-7.32 (m, 13H; **H-aromatic**), 7.23 (m, 1H; **H-aromatic**); ^{13}C NMR [Methanol-d$_4$] δ 154.4, 153.5, 149.5, 139.7, 132.5, 131.0, 130.6, 130.3, 129.8, 127.4, 126.6, 126.4, 125.5, 120.2, 119.7, 119.1, one C missing due to overlapping; LR (ES$^-$) *m/z*: 368 [*M*-H]$^-$; HR (ES$^-$) calcd for $C_{21}H_{14}N_5O_2$ [*M*-H]$^-$: 368.1147, found: 368.1148; IR (thin film, cm^{-1}) 3468 br (N-H), 3060 w, 2954 m, 2924 m, 2852 w, 1785 w, 1725 stg (C=O), 1634 w, 1597 w, 1526 w, 1501 m, 1411 m, 1376 w, 1240 w, 1139 w, 833 w, 762 m, 691 m, 633 w, 615 w.



(216) : R_f (50% ethyl acetate/petrol) 0.45; mp 220°C; ^{1}H NMR δ 7.69 (m, 2H; **H-aromatic**), 7.55 (m, 2H; **H-aromatic**), 7.47-7.24 (m, 7H; **H-aromatic**), 7.19-7.04 (m, 9H; **H-aromatic**), 6.93 (d, *J* = 8.5 Hz, 1H; **H-aromatic**), 6.87 (dd, *J* = 8.2, 1.3 Hz, 1H; **H-aromatic**), 6.80 (m, 1H; **H-aromatic**); ^{13}C NMR δ 151.6 (**C=O.**), 148.2 (**C=O**), 147.9 (**C-quat.**), 138.0 (**C-quat.**), 137.2 (**C-quat.**), 130.0 (**C-aromatic**), 129.7 (**C-aromatic**), 129.6 (**C-aromatic**), 129.4 (**C-aromatic**), 129.0 (**C-aromatic**), 127.5 (**C-aromatic**), 127.0 (**C-aromatic**), 126.1 (**C-aromatic**), 125.9 (**C-aromatic**), 125.4 (**C-aromatic**), 125.2 (**C-aromatic**), 124.7 (**C-aromatic**), 124.5 (**C-aromatic**), 119.8 (**C-quat.**), 119.2 (**C-aromatic**), 118.8 (**C-aromatic**), 118.4 (**C-quat.**), 117.2 (**C-aromatic**), 116.9 (**C-**

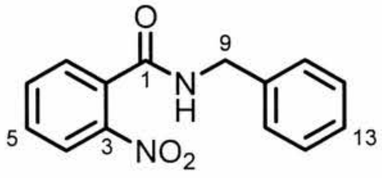
aromatic), 114.6 (**C-quat.**); LR (ES^+) *m/z*: 584 $[M+Na]^+$; HR (ES^+) calcd for $C_{34}H_{24}N_7O_2$ $[M+H]^+$: 562.1991, found: 562.1989; IR (thin film, cm^{-1}) 2924 stg, 2852 m, 1788 w, 1734 stg (C=O), 1596 w, 1524 w, 1499 m, 1454 w, 1404 m, 1377 w, 760 m, 735 m, 690 m.

Synthesis of 1-(2-benzyl-2H-indazol-3-yl)-4-phenyl-1,2,4-triazolidine-3,5-dione **214**



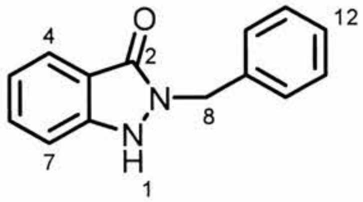
To a solution of **204** (20.0 mg, 0.096 mmol) in chloroform (3 mL) was added 4-phenyl-3*H*-1,2,4-triazoline-3,5-dione (16.8 mg, 0.096 mmol, 1.0 equiv.). The solution was refluxed for 16 hours until the bright red colour disapeared. The crude mixture was concentrated *in vacuo* and purified by flash chromatography eluting with 20-50% ethyl acetate/petrol to afford **214** as an pale orange oil (30 mg, 82%); R_f (100% ethyl acetate) 0.52; ^{1}H NMR δ 7.56 (d, J = 8.8 Hz, 1H; **H-aromatic**), 7.47-7.05 (m, 13H; **H-aromatic**), 5.49 (s, 2H; **H-8**) ; ^{13}C NMR δ 154.6 (**C=O**), 153.1 (**C=O**), 151.0 (**C-quat.**), 147.4 (**C-quat.**), 135.0 (**C-quat.**), 130.5 (**C-quat.**), 129.3 (**C-aromatic**), 129.0 (**C-aromatic**), 128.8 (**C-aromatic**), 128.5 (**C-aromatic**), 127.4 (**C-aromatic**), 126.9 (**C-aromatic**), 125.5 (**C-aromatic**), 124.6 (**C-quat.**), 123.8 (**C-aromatic**), 118.3 (**C-aromatic**), 118.0 (**C-aromatic**), 117.2 (**C-quat.**), 54.8 (**C-8**); LR (CI^+) *m/z*: 384 $[M+H]^+$; HR (CI^+) calcd for $C_{22}H_{18}N_5O_2$ $[M+H]^+$: 384.1461, found: 384.1457; IR (thin film, cm^{-1}) 3494 br (NH), 3069 m, 2958 m, 2928 m, 2856 w, 1788 m, 1726 stg (C=O), 1634 w, 1601 w, 1501 m, 1419 stg, 1277 m, 1142 w, 762 m, 733 m, 710 m, 690 m, 631 w.

Synthesis of 2-nitro-*N*-benzylbenzamide **201** [179]



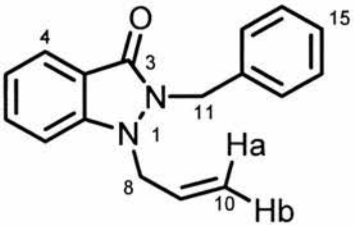
A solution of 2-nitrobenzoic acid (5 g, 19.5 mmol) in thionyl chloride (10 mL) was refluxed for 2 h under an inert atmosphere. The excess of thionyl chloride was distilled off and the traces of $SOCl_2$ were removed by azeotropic distillations with toluene (2×20 mL). The acid chloride was redissolved in DCM (20 mL) and cannulated onto a solution of benzylamine (3.27 mL, 31.1 mmol, 1.60 equiv.) and Hunigs base (5.2 mL, 54.2 mmol, 2.78 equiv.) in DCM (50 mL). The solution was stirred at room temperature under an inert atmosphere for 16 hours. The reaction was quenched by addition of saturated ammonium chloride (30 mL) and extracted with ethyl acetate (3×30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo.* The crude material was recrystallised from hot ethyl acetate to afford **201** as an orange solid (7.65 g, 99%); mp 125°C (lit. 126-127°C[179]); ^{1}H NMR δ 7.97 (dd, J = 8.1, 1.1 Hz, 1H; **H-aromatic**), 7.58 (dt, J = 7.5, 1.3 Hz, 1H; **H-aromatic**), 7.48 (ddd, J = 8.1, 7.6, 1.6 Hz, 1H; **H-aromatic**), 7.43 (dd, J = 7.4, 1.4 Hz, 1H; **H-aromatic**), 7.32-7.20 (m, 5H; **H-aromatic**), 6.14 (br s, 1H; **NH**), 4.55 (d, J = 5.7 Hz, 2H; **H-9**); LR (ES$^-$) *m/z*: 255 [*M*-H]$^-$; HR (ES$^-$) calcd for $C_{14}H_{11}N_2O_3$ [*M*-H]$^-$: 255.0770, found: 255.0772.

Synthesis of *N2*-benzyl indazolinone **202** [78, 140]



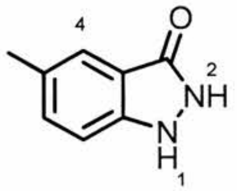
To a solution of **201** (7.67 g, 29.9 mmol, 1.0 equiv.) in methanol (72 mL) and sodium hydroxide (4.93 g in 96 mL of water, 4.10 equiv.) was added solid zinc (5.92 g, 91 mmol, 3.0 equiv) and the solution was refluxed for 24 h. The reaction was then cooled down at room temperature; the zinc solid was removed by filtration. The product was precipitated out of the solution by neutralisation with dilute hydrochloric acid. The collected precipitate was further purified by flash chromatography eluting with ethyl acetate to afford the desired product **202** as an off-white solid (4.73 g, 72%); mp 169°C (lit. 168°C [140]); R_f (50% ethyl acetate/petrol) 0.08; ^{1}H NMR δ 7.90 (app. dt, *J* = 7.9, 0.9 Hz, 1H; **H-4**), 7.50 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H; **H-6**), 7.38-7.31 (m, 5H; **H-aromatic**), 7.20 (m, 2H; **H-aromatic**), 5.06 (s, 2H; **H-8**); LR (ES$^-$) *m/z*: 223 [*M*-H]; HR (ES$^-$) calcd for $C_{14}H_{11}N_2O$ [*M*-H]$^+$: 223.0871, found: 223.0869; IR (thin film, cm^{-1}) 3063 w, 3033 w, 2935 w, 1624 s, 1456 m, 1422 m, 1325 m, 1274 w, 1252 w, 746 m, 700 stg, 678 m;

Synthesis of *N1*-allyl *N2*-benzyl indazolinone **262**



To a solution of **202** (100 mg, 0.46 mmol, 1.0 equiv.) in dry THF (10 mL) was added potassium *t*-butoxide (60 mg, 0.54 mmol, 1.20 equiv.) and the solution was stirred at room temperature under an inert atmosphere for 30 minutes. Allyl bromide (50 μL, 0.54 mmol, 1.20 equiv.) was added and the solution was stirred under the same conditions for 2 hours before the solvent was removed *in vacuo*. The reaction was quenched by addition of saturated ammonium chloride solution (20 mL) and extracted with ethyl acetate (3×30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by flash chromatography eluting with 30% ethyl acetate/hexane to afford the desired compound **262** as an orange oil (117 mg, 99%); R_f (20% ethyl acetate/petrol) 0.06; ^{1}H NMR δ 7.83 (dt, *J* = 7.8, 0.9 Hz, 1H; **H-4**), 7.43 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H; **H-6**), 7.19 (m, 5H; **H-aromatic**), 7.08 (m, 2H; **H-aromatic**), 5.35 (ddt, *J* = 16.3, 10.1, 6.2 Hz, 1H; **H-9**), 5.05 (dq, *J* = 12.8, 1.3 Hz, 1H; **H-10a**), 5.02 (s, 2H; **H-11**), 5.00 (ddd, *J* = 5.7, 2.3, 1.1 Hz, 1H; **H-10b**), 4.17 (dt, *J* = 6.2, 1.1 Hz, 2H; **H-8**); ^{13}C NMR δ 163.7 (**C-3**), 149.0 (**C-7a**), 136.3 (**C-12**), 132.1 (**C-aromatic**), 130.2 (**C-9**), 128.7 (**C-aromatic**), 127.9 (**C-aromatic**), 127.7 (**C-aromatic**), 124.3 (**C-aromatic**), 122.2 (**C-aromatic**), 120.1 (**C-10**), 118.9 (**C-3a**), 111.9 (**C-aromatic**), 52.0 (**C-8**), 46.0 (**C-11**); LR MS (CI$^+$) *m/z*: 265 [*M*+H]$^+$; HR MS (CI$^+$) calcd for $C_{17}H_{17}N_2O$ [*M*+H]$^+$: 265.1341, found: 265.1342; IR (thin film, cm^{-1}) 3064 w, 3030 w, 2933 w, 1670 stg (C=O), 1619 m, 1482 m, 1464 m, 1352 w, 1327 w, 1259 m, 1152 w, 1134 w, 992 m, 928 m, 755 m, 698 m, 683 m;

Synthesis of 5-methyl indazolinone **244** [180]



A solution of sodium nitrite (2.55 g, 37.0 mmol) in water (5.5 mL) was added dropwise with continuous stirring to a mixture of 5-methylanthranilic acid (5.00 g, 33.1 mmol), water (33.5 mL) and concentrated hydrochloric acid (7.5 mL) at 0-5°C over 15 minutes. After stirring for 30 minutes, a solution of sodium sulfite (12.8 g, 102 mmol) in water (33.5 mL) was added. After 2 hours, concentrated hydrochloric acid (11 mL) was added and the mixture was stirred for 12 hours. The mixture was then heated to 70°C for 16 hours. After cooling to room temperature, the pH was adjusted to 5-5.5 with dilute sodium hydroxide (2 M). The resulting yellow/brown precipitate was filtered under vacuum, washed with water (3×50 mL) and dried under vacuum to give **244** (4.23 g, 86%); mp 235-237°C (lit. 240-242°C [180]); ^{1}H NMR (DMSO-d_6) δ 11.28 (br s, 1H; **NH**), 10.60 (br s, 1H; **NH**), 7.55 (s, 1H; **H-4**), 7.32 (m, 2H; **H-6** and **H-7**), 2.50 (s, 3H; **H-8**); ^{13}C NMR δ 156.3 (**C-3**), 141.7 (**C-7a**), 129.6 (**C-4**), 127.8 (**C-5**), 119.5 (**C-6**), 113.3 (**C-3a**), 110.5 (**C-7**), 21.2 (**C-8**); LR MS (ES^{-}) *m/z*: 147 [*M*-H]$^{-}$.

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6. Appendices

Appendix A

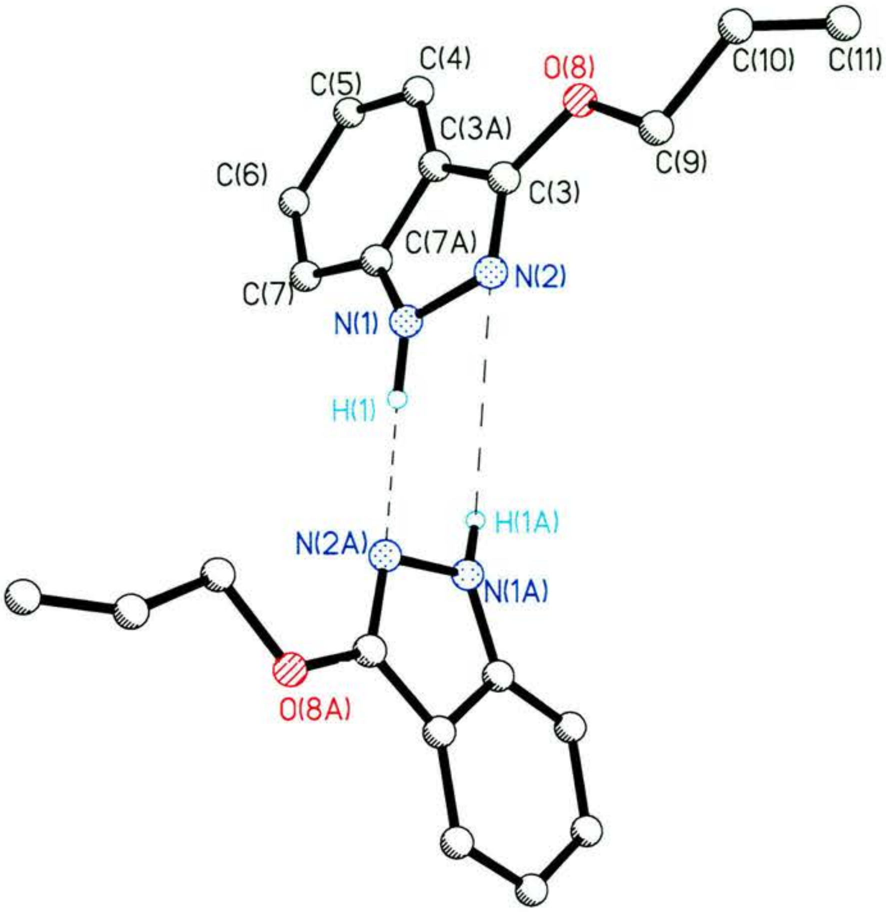


Table 1. Crystal data and structure refinement for ninw4.

Identification code	ninw4	
Empirical formula	C10 H10 N2 O	
Formula weight	174.20	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 11.652(8) Å	α= 90°.
	b = 4.850(3) Å	β= 105.10(2)°.
	c = 17.171(10) Å	γ = 90°.
Volume	937.0(10) $Å^3$	
Z	4	
Density (calculated)	1.235 Mg/m^3	
Absorption coefficient	0.082 mm^{-1}	
F(000)	368	
Crystal size	.1 x .1 x .05 mm^3	
Theta range for data collection	2.44 to 24.71°.	
Index ranges	-13<=h<=13, -5<=k<=4, -20<=l<=13	
Reflections collected	3371	
Independent reflections	1463 [R(int) = 0.0699]	
Completeness to theta = 24.71°	91.4 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.00000 and 0.5445	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1463 / 1 / 123	
Goodness-of-fit on F^2	0.903	
Final R indices [I>2sigma(I)]	R1 = 0.0637, wR2 = 0.1194	
R indices (all data)	R1 = 0.2000, wR2 = 0.1591	
Extinction coefficient	0.009(3)	
Largest diff. peak and hole	0.131 and -0.143 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for ninw4. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	3314(3)	2536(8)	7159(3)	70(1)
N(2)	3818(3)	4459(7)	7754(2)	65(1)
C(3A)	5226(4)	2828(8)	7156(3)	53(1)
C(3)	4938(4)	4601(9)	7728(3)	58(1)
C(4)	6225(4)	2218(9)	6898(3)	66(1)
C(5)	6138(4)	272(10)	6317(3)	78(2)
C(6)	5062(6)	-1095(9)	5974(3)	80(2)
C(7A)	4137(4)	1483(8)	6812(3)	59(1)
C(7)	4064(5)	-498(10)	6219(3)	75(1)
O(8)	5740(2)	6305(6)	8208(2)	68(1)
C(9)	5309(4)	7865(9)	8786(3)	68(1)
C(10)	6307(5)	9600(12)	9226(4)	106(2)
C(11)	6664(6)	10000(13)	9946(4)	133(2)

Table 3. Bond lengths [Å] and angles [°] for ninw4.

N(1)-C(7A)	1.354(5)
N(1)-N(2)	1.395(5)
N(2)-C(3)	1.319(5)
C(3A)-C(4)	1.381(5)
C(3A)-C(3)	1.411(5)
C(3A)-C(7A)	1.412(5)
C(3)-O(8)	1.355(5)
C(4)-C(5)	1.358(6)
C(5)-C(6)	1.405(6)
C(6)-C(7)	1.366(6)
C(7A)-C(7)	1.387(6)
O(8)-C(9)	1.438(4)
C(9)-C(10)	1.474(7)
C(10)-C(11)	1.213(6)

C(7A)-N(1)-N(2)	111.3(4)
C(3)-N(2)-N(1)	104.0(4)
C(4)-C(3A)-C(3)	136.7(4)
C(4)-C(3A)-C(7A)	120.6(5)
C(3)-C(3A)-C(7A)	102.8(4)
N(2)-C(3)-O(8)	122.9(5)
N(2)-C(3)-C(3A)	114.1(4)
O(8)-C(3)-C(3A)	123.0(4)
C(5)-C(4)-C(3A)	118.5(4)
C(4)-C(5)-C(6)	121.5(5)
C(7)-C(6)-C(5)	120.6(5)
N(1)-C(7A)-C(7)	132.1(5)
N(1)-C(7A)-C(3A)	107.7(4)
C(7)-C(7A)-C(3A)	120.2(5)
C(6)-C(7)-C(7A)	118.6(5)
C(3)-O(8)-C(9)	115.5(3)
O(8)-C(9)-C(10)	106.5(4)
C(11)-C(10)-C(9)	129.0(7)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x 10^3$) for ninw4. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	37(3)	76(3)	96(3)	-1(2)	16(2)	-5(2)
N(2)	39(2)	72(2)	84(3)	1(2)	16(2)	2(2)
C(3A)	36(3)	56(2)	64(3)	7(2)	8(3)	1(2)
C(3)	34(3)	62(3)	74(3)	11(3)	6(3)	0(2)
C(4)	54(3)	74(3)	69(3)	-3(3)	16(3)	-3(3)
C(5)	55(3)	95(4)	86(4)	2(3)	22(3)	7(3)
C(6)	97(5)	79(3)	60(4)	-5(2)	15(4)	16(3)
C(7A)	54(3)	54(3)	63(3)	8(2)	7(3)	7(2)
C(7)	68(4)	76(3)	73(4)	14(3)	6(3)	-7(3)
O(8)	41(2)	75(2)	85(2)	-5(2)	14(2)	-3(2)
C(9)	46(3)	84(3)	70(3)	-4(3)	10(3)	2(3)
C(10)	82(5)	133(4)	95(5)	-35(4)	10(4)	12(4)
C(11)	93(5)	165(5)	127(6)	-44(5)	2(5)	29(4)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for ninw4.

	x	y	z	U(eq)
H(1)	2534(16)	1850(70)	7190(30)	100(16)
H(4A)	6941	3120	7117	79
H(5A)	6807	-167	6141	93
H(6A)	5028	-2419	5577	96
H(7A)	3351	-1400	5992	90
H(9A)	5055	6640	9155	81
H(9B)	4641	9005	8514	81
H(10A)	6721	10515	8908	127
H(11A)	6291	9149	10300	160
H(11B)	7310	11158	10145	160

Table 6. Torsion angles [°] for ninw4.

C(7A)-N(1)-N(2)-C(3)	2.5(5)
N(1)-N(2)-C(3)-O(8)	178.7(3)
N(1)-N(2)-C(3)-C(3A)	-1.2(4)
C(4)-C(3A)-C(3)-N(2)	179.7(5)
C(7A)-C(3A)-C(3)-N(2)	-0.4(4)
C(4)-C(3A)-C(3)-O(8)	-0.2(7)
C(7A)-C(3A)-C(3)-O(8)	179.7(4)
C(3)-C(3A)-C(4)-C(5)	178.9(4)
C(7A)-C(3A)-C(4)-C(5)	-1.0(6)
C(3A)-C(4)-C(5)-C(6)	0.5(7)
C(4)-C(5)-C(6)-C(7)	0.0(7)
N(2)-N(1)-C(7A)-C(7)	178.2(4)
N(2)-N(1)-C(7A)-C(3A)	-2.8(5)
C(4)-C(3A)-C(7A)-N(1)	-178.2(4)
C(3)-C(3A)-C(7A)-N(1)	1.9(4)
C(4)-C(3A)-C(7A)-C(7)	0.9(6)
C(3)-C(3A)-C(7A)-C(7)	-179.0(4)
C(5)-C(6)-C(7)-C(7A)	0.0(7)
N(1)-C(7A)-C(7)-C(6)	178.4(4)
C(3A)-C(7A)-C(7)-C(6)	-0.4(6)
N(2)-C(3)-O(8)-C(9)	3.2(5)
C(3A)-C(3)-O(8)-C(9)	-176.9(3)
C(3)-O(8)-C(9)-C(10)	-178.8(4)
O(8)-C(9)-C(10)-C(11)	-134.2(7)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for ninw4 [Å and °].

D-H...A	d(D-H)d(H...A)	d(D...A)	<(DHA)	
N(1)-H(1)...N(2)#1	0.9800(13)	1.981(11)	2.935(5)	164(3)

Symmetry transformations used to generate equivalent atoms:

#1 -x+1/2,y-1/2,-z+3/2

Appendix B

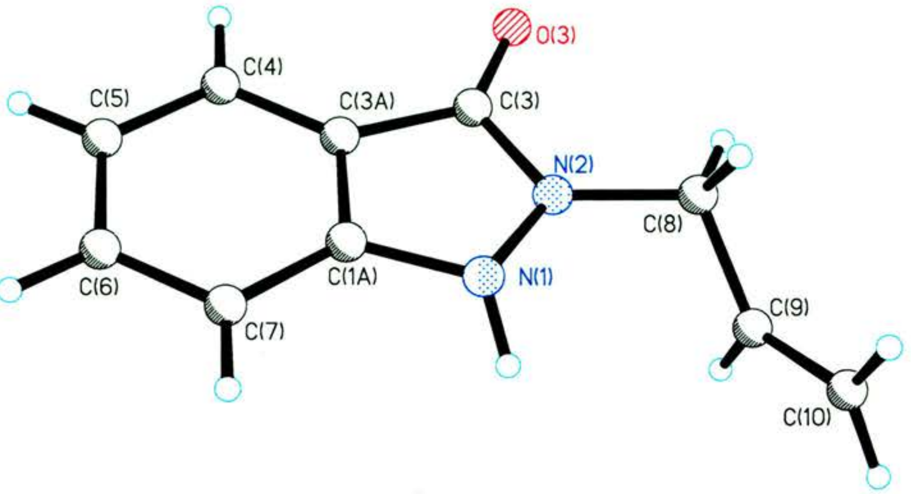


Table 1. Crystal data and structure refinement for ninw2.

Identification code ninw2

Empirical formula C10 H10 N2 O

Formula weight 174.20

Temperature 125(2) K

Wavelength 0.71073 Å

Crystal system Monoclinic

Space group P2(1)/c

Unit cell dimensions a = 12.691(4) Å α= 90°.

b = 6.1123(17) Å β= 102.673(5)°.

c = 11.694(3) Å γ = 90°.

Volume 885.1(4) Å^3

Z 4

Density (calculated) 1.307 Mg/m^3

Absorption coefficient 0.087 mm^{-1}

F(000) 368

Crystal size .12 x .03 x .03 mm^3

Theta range for data collection 1.64 to 23.25°.

Index ranges -14<=h<=14, -4<=k<=6, -13<=l<=12

Reflections collected 3466

Independent reflections 1216 [R(int) = 0.0392]

Completeness to theta = 23.25° 95.8 %

Absorption correctionSADABS

Max. and min. transmission 1.00000 and 0.434168

Refinement method Full-matrix least-squares on F^2

Data / restraints / parameters 1216 / 1 / 123

Goodness-of-fit on F^2 1.003

Final R indices [I>2sigma(I)]R1 = 0.0362, wR2 = 0.0888

R indices (all data) R1 = 0.0446, wR2 = 0.0921

Extinction coefficient 0.020(4)

Largest diff. peak and hole 0.184 and -0.137 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for ninw2. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	7392(1)	2102(2)	1394(1)	22(1)
N(2)	8002(1)	1285(2)	2458(1)	22(1)
C(3)	7756(1)	2302(3)	3402(1)	21(1)
O(3)	8111(1)	1710(2)	4440(1)	27(1)
C(3A)	7032(1)	4071(2)	2916(1)	21(1)
C(4)	6545(1)	5747(3)	3435(1)	25(1)
C(5)	5915(1)	7251(3)	2707(2)	27(1)
C(6)	5781(1)	7099(3)	1487(2)	28(1)
C(7)	6250(1)	5454(3)	962(1)	25(1)
C(1A)	6868(1)	3918(3)	1701(1)	21(1)
C(8)	8577(1)	-775(3)	2467(1)	25(1)
C(9)	9344(1)	-762(3)	1661(1)	25(1)
C(10)	9297(1)	-2142(3)	798(2)	31(1)

Table 3. Bond lengths [Å] and angles [°] for ninw2.

N(1)-C(1A)	1.381(2)
N(1)-N(2)	1.4046(18)
N(2)-C(3)	1.362(2)
N(2)-C(8)	1.454(2)
C(3)-O(3)	1.2514(19)
C(3)-C(3A)	1.452(2)
C(3A)-C(1A)	1.393(2)
C(3A)-C(4)	1.402(2)
C(4)-C(5)	1.383(2)
C(5)-C(6)	1.403(2)
C(6)-C(7)	1.379(2)
C(7)-C(1A)	1.395(2)
C(8)-C(9)	1.496(2)
C(9)-C(10)	1.307(2)

C(1A)-N(1)-N(2)	105.02(12)
C(3)-N(2)-N(1)	112.06(13)
C(3)-N(2)-C(8)	126.36(13)
N(1)-N(2)-C(8)	119.53(12)
O(3)-C(3)-N(2)	123.82(14)
O(3)-C(3)-C(3A)	131.08(14)
N(2)-C(3)-C(3A)	105.10(13)
C(1A)-C(3A)-C(4)	120.64(14)
C(1A)-C(3A)-C(3)	106.82(13)
C(4)-C(3A)-C(3)	132.53(14)
C(5)-C(4)-C(3A)	118.01(15)
C(4)-C(5)-C(6)	120.48(15)
C(7)-C(6)-C(5)	122.20(15)
C(6)-C(7)-C(1A)	117.02(15)
N(1)-C(1A)-C(3A)	110.25(13)
N(1)-C(1A)-C(7)	128.13(14)
C(3A)-C(1A)-C(7)	121.62(15)
N(2)-C(8)-C(9)	112.64(13)

C(10)-C(9)-C(8)	123.92(15)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($\AA^2 x 10^3$) for ninw2. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	29(1)	24(1)	16(1)	0(1)	10(1)	2(1)
N(2)	29(1)	23(1)	17(1)	2(1)	10(1)	2(1)
C(3)	24(1)	25(1)	17(1)	1(1)	11(1)	-4(1)
O(3)	35(1)	32(1)	18(1)	2(1)	12(1)	5(1)
C(3A)	22(1)	22(1)	23(1)	0(1)	12(1)	-5(1)
C(4)	27(1)	28(1)	23(1)	-4(1)	13(1)	-3(1)
C(5)	26(1)	27(1)	32(1)	-1(1)	13(1)	4(1)
C(6)	25(1)	29(1)	31(1)	5(1)	7(1)	2(1)
C(7)	25(1)	30(1)	21(1)	3(1)	7(1)	-4(1)
C(1A)	22(1)	21(1)	22(1)	1(1)	10(1)	-5(1)
C(8)	31(1)	21(1)	24(1)	2(1)	10(1)	3(1)
C(9)	26(1)	24(1)	27(1)	-2(1)	10(1)	-1(1)
C(10)	31(1)	32(1)	32(1)	-3(1)	12(1)	1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10 ^{3}) for ninw2.

	x	y	z	U(eq)
H(1N)	7746(13)	2240(30)	733(11)	51(6)
H(4A)	6646	5846	4263	30
H(5A)	5570	8396	3036	32
H(6A)	5352	8165	1005	34
H(7A)	6157	5371	135	30
H(8A)	8046	-1969	2233	30
H(8B)	8984	-1080	3275	30
H(9A)	9897	314	1783	30
H(10A)	8753	-3237	653	37
H(10B)	9808	-2051	315	37

Table 6. Torsion angles [°] for ninw2.

C(1A)-N(1)-N(2)-C(3)	9.10(16)
C(1A)-N(1)-N(2)-C(8)	173.86(12)
N(1)-N(2)-C(3)-O(3)	172.46(13)
C(8)-N(2)-C(3)-O(3)	9.0(2)
N(1)-N(2)-C(3)-C(3A)	-7.08(16)
C(8)-N(2)-C(3)-C(3A)	-170.57(13)
O(3)-C(3)-C(3A)-C(1A)	-177.23(15)
N(2)-C(3)-C(3A)-C(1A)	2.27(16)
O(3)-C(3)-C(3A)-C(4)	4.0(3)
N(2)-C(3)-C(3A)-C(4)	-176.52(15)
C(1A)-C(3A)-C(4)-C(5)	-1.0(2)
C(3)-C(3A)-C(4)-C(5)	177.67(15)
C(3A)-C(4)-C(5)-C(6)	-0.6(2)
C(4)-C(5)-C(6)-C(7)	0.9(2)
C(5)-C(6)-C(7)-C(1A)	0.3(2)
N(2)-N(1)-C(1A)-C(3A)	-7.35(16)
N(2)-N(1)-C(1A)-C(7)	172.65(14)
C(4)-C(3A)-C(1A)-N(1)	-177.73(13)
C(3)-C(3A)-C(1A)-N(1)	3.31(17)
C(4)-C(3A)-C(1A)-C(7)	2.3(2)
C(3)-C(3A)-C(1A)-C(7)	-176.70(13)
C(6)-C(7)-C(1A)-N(1)	178.12(14)
C(6)-C(7)-C(1A)-C(3A)	-1.9(2)
C(3)-N(2)-C(8)-C(9)	-140.94(15)
N(1)-N(2)-C(8)-C(9)	56.67(17)
N(2)-C(8)-C(9)-C(10)	-121.56(18)

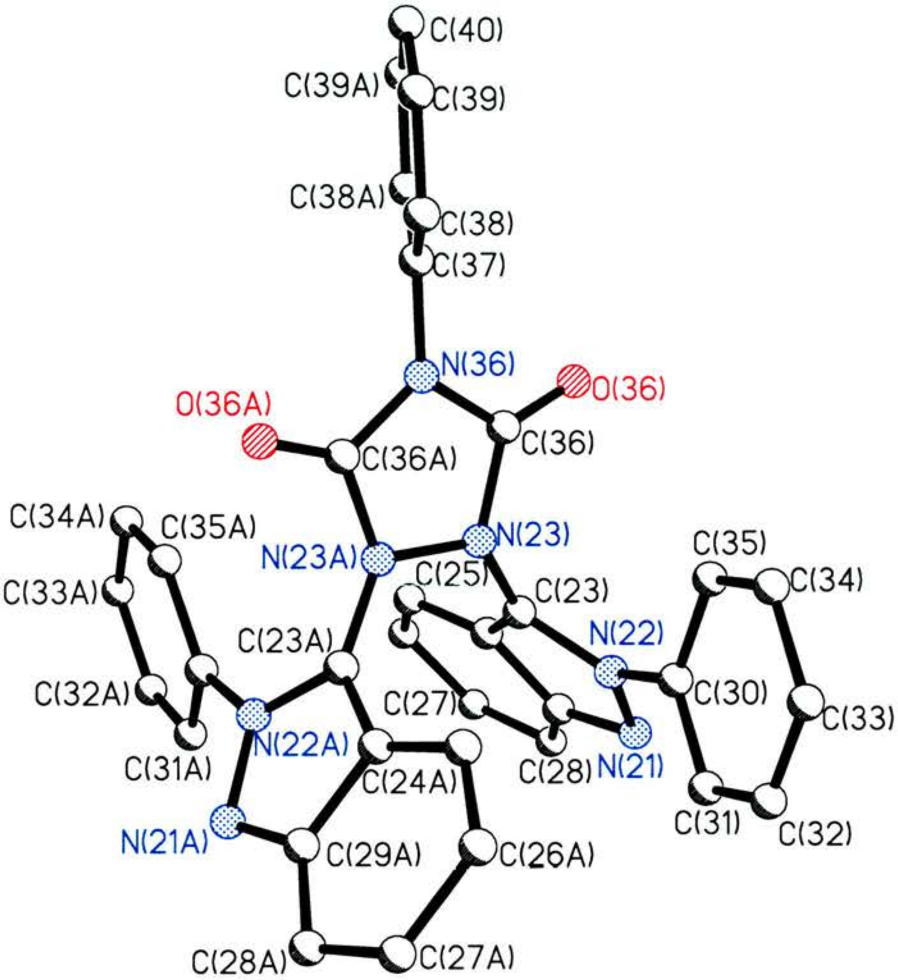
Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for ninw2 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1N)...O(3)#1	0.979(5)	1.796(8)	2.7386(17)	160.6(17)

Symmetry transformations used to generate equivalent atoms:

#1 x,-y+1/2,z-1/2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C(39)
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C(38)
C(37)
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O(36A)
O(36)
C(36A)
C(36)
C(34A)
C(35A)
N(23A)
N(23)
C(25)
C(35)
C(34)
C(33A)
C(23)
N(22)
C(23A)
C(32A)
C(27)
C(30)
C(33)
N(22A)
C(31A)
C(24A)
C(28)
N(21)
C(31)
C(32)
N(21A)
C(29A)
C(26A)
C(28A)
C(27A)

Table 1. Crystal data and structure refinement for ninw6.

Identification code	ninw6	
Empirical formula	C34 H23 N7 O2	
Formula weight	561.59	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2/n	
Unit cell dimensions	a = 16.062(4) Å	α= 90°.
	b = 11.3230(18) Å	β= 114.113(8)°.
	c = 16.052(4) Å	γ = 90°.
Volume	2664.6(10) Å^3	
Z	4	
Density (calculated)	1.400 Mg/m^3	
Absorption coefficient	0.091 mm^{-1}	
F(000)	1168	
Crystal size	0.1000 x 0.0300 x 0.0300 mm^3	
Theta range for data collection	1.80 to 25.35°.	
Index ranges	-14<=h<=19, -13<=k<=13, -19<=l<=17	
Reflections collected	14698	
Independent reflections	4791 [R(int) = 0.0612]	
Completeness to theta = 25.35°	97.8 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.0000 and 0.5693	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4791 / 0 / 175	
Goodness-of-fit on F^2	1.101	
Final R indices [I>2sigma(I)]	R1 = 0.2586, wR2 = 0.5255	
R indices (all data)	R1 = 0.2797, wR2 = 0.5347	
Extinction coefficient	0.0001(8)	
Largest diff. peak and hole	1.037 and -0.881 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3)

for ninw6. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	6363(8)	-1213(10)	587(8)	18(2)
N(2)	7001(7)	-381(10)	994(7)	13(2)
C(3)	6768(10)	382(13)	1512(10)	23(3)
N(3)	7358(8)	1307(11)	2018(8)	23(3)
C(4)	5938(8)	30(12)	1472(8)	13(3)
C(5)	5344(9)	471(13)	1884(9)	19(3)
C(6)	4552(9)	-96(13)	1653(9)	20(3)
C(7)	4315(11)	-1086(14)	1029(11)	29(3)
C(8)	4872(10)	-1521(14)	642(10)	23(3)
C(9)	5704(9)	-928(12)	880(9)	18(3)
C(10)	7851(9)	-455(12)	878(9)	18(3)
C(11)	8232(10)	-1545(15)	965(10)	28(3)
C(12)	9082(12)	-1705(17)	937(12)	36(4)
C(13)	9537(10)	-709(14)	834(10)	26(3)
C(14)	9144(10)	414(13)	738(10)	23(3)
C(15)	8282(9)	522(13)	768(9)	21(3)
C(16)	7192(10)	2452(13)	1750(10)	21(3)
O(16)	6888(7)	2794(10)	939(7)	30(3)
N(16)	7500	3121(14)	2500	15(3)
C(17)	7500	4463(16)	2500	11(4)
C(18)	8332(9)	5006(12)	2796(9)	17(3)
C(19)	8332(10)	6212(14)	2818(10)	25(3)
C(20)	7500	6826(18)	2500	19(4)
N(21)	10598(8)	5778(11)	1489(8)	21(3)
N(22)	10995(7)	4850(10)	2032(7)	15(2)
C(23)	11555(9)	4242(12)	1748(9)	17(3)
N(23)	12033(8)	3268(11)	2249(8)	23(3)
C(24)	11496(9)	4766(12)	935(9)	18(3)
C(25)	11877(10)	4551(14)	330(10)	27(3)
C(26)	11666(9)	5230(13)	-424(10)	21(3)
C(27)	11045(10)	6208(14)	-591(10)	25(3)
C(28)	10658(10)	6443(13)	40(10)	22(3)
C(29)	10901(9)	5739(12)	808(9)	18(3)
C(30)	10876(9)	4640(13)	2850(9)	19(3)

C(31)	10927(10)	5592(14)	3417(10)	26(3)
C(32)	10872(10)	5382(14)	4248(11)	28(3)
C(33)	10721(11)	4272(15)	4482(12)	33(4)
C(34)	10676(12)	3288(16)	3923(12)	36(4)
C(35)	10714(10)	3480(14)	3079(10)	27(3)
C(36)	11736(10)	2087(14)	2035(10)	24(3)
O(36)	10981(8)	1752(10)	1494(8)	34(3)
N(36)	12500	1392(14)	2500	14(3)
C(37)	12500	155(17)	2500	14(4)
C(38)	12747(9)	-458(13)	3314(9)	19(3)
C(39)	12747(10)	-1672(14)	3305(11)	26(3)
C(40)	12500	-2270(20)	2500	24(5)

Table 3. Bond lengths [Å] and angles [°] for ninw6.

N(1)-N(2)	1.347(15)
N(1)-C(9)	1.362(17)
N(2)-C(3)	1.354(18)
N(2)-C(10)	1.454(16)
C(3)-C(4)	1.366(19)
C(3)-N(3)	1.423(19)
N(3)-C(16)	1.358(19)
N(3)-N(3)#1	1.42(2)
C(4)-C(9)	1.389(19)
C(4)-C(5)	1.454(18)
C(5)-C(6)	1.336(19)
C(5)-H(5A)	0.9500
C(6)-C(7)	1.45(2)
C(6)-H(6A)	0.9500
C(7)-C(8)	1.37(2)
C(7)-H(7A)	0.9500
C(8)-C(9)	1.40(2)
C(8)-H(8A)	0.9500
C(10)-C(15)	1.35(2)
C(10)-C(11)	1.36(2)
C(11)-C(12)	1.39(2)
C(11)-H(11A)	0.9500
C(12)-C(13)	1.39(2)
C(12)-H(12A)	0.9500
C(13)-C(14)	1.40(2)
C(13)-H(13A)	0.9500
C(14)-C(15)	1.41(2)
C(14)-H(14A)	0.9500
C(15)-H(15A)	0.9500
C(16)-O(16)	1.251(18)
C(16)-N(16)	1.335(17)
N(16)-C(16)#1	1.335(17)
N(16)-C(17)	1.52(2)
C(17)-C(18)	1.367(15)
C(17)-C(18)#1	1.367(15)
C(18)-C(19)	1.37(2)
C(18)-H(18A)	0.9500
C(19)-C(20)	1.405(18)

C(19)-H(19A)	0.9500
C(20)-C(19)#1	1.405(18)
C(20)-H(20A)	0.9500
N(21)-N(22)	1.347(16)
N(21)-C(29)	1.367(17)
N(22)-C(23)	1.352(17)
N(22)-C(30)	1.422(17)
C(23)-N(23)	1.395(18)
C(23)-C(24)	1.402(19)
N(23)-N(23)#2	1.38(2)
N(23)-C(36)	1.415(19)
C(24)-C(25)	1.36(2)
C(24)-C(29)	1.418(19)
C(25)-C(26)	1.35(2)
C(25)-H(25A)	0.9500
C(26)-C(27)	1.44(2)
C(26)-H(26A)	0.9500
C(27)-C(28)	1.41(2)
C(27)-H(27A)	0.9500
C(28)-C(29)	1.38(2)
C(28)-H(28A)	0.9500
C(30)-C(31)	1.39(2)
C(30)-C(35)	1.42(2)
C(31)-C(32)	1.39(2)
C(31)-H(31A)	0.9500
C(32)-C(33)	1.36(2)
C(32)-H(32A)	0.9500
C(33)-C(34)	1.41(2)
C(33)-H(33A)	0.9500
C(34)-C(35)	1.40(2)
C(34)-H(34A)	0.9500
C(35)-H(35A)	0.9500
C(36)-O(36)	1.228(18)
C(36)-N(36)	1.390(17)
N(36)-C(36)#2	1.390(17)
N(36)-C(37)	1.40(2)
C(37)-C(38)	1.386(17)
C(37)-C(38)#2	1.386(17)
C(38)-C(39)	1.37(2)
C(38)-H(38A)	0.9500

C(39)-C(40)	1.365(19)
C(39)-H(39A)	0.9500
C(40)-C(39)#2	1.365(19)
C(40)-H(40A)	0.9500

N(2)-N(1)-C(9)	102.3(11)
N(1)-N(2)-C(3)	113.4(11)
N(1)-N(2)-C(10)	117.8(10)
C(3)-N(2)-C(10)	128.7(11)
N(2)-C(3)-C(4)	107.1(12)
N(2)-C(3)-N(3)	122.2(12)
C(4)-C(3)-N(3)	130.6(13)
C(16)-N(3)-N(3)#1	106.2(8)
C(16)-N(3)-C(3)	121.5(12)
N(3)#1-N(3)-C(3)	117.7(10)
C(3)-C(4)-C(9)	104.3(12)
C(3)-C(4)-C(5)	133.4(13)
C(9)-C(4)-C(5)	122.3(12)
C(6)-C(5)-C(4)	115.9(13)
C(6)-C(5)-H(5A)	122.1
C(4)-C(5)-H(5A)	122.1
C(5)-C(6)-C(7)	121.1(14)
C(5)-C(6)-H(6A)	119.5
C(7)-C(6)-H(6A)	119.5
C(8)-C(7)-C(6)	123.8(15)
C(8)-C(7)-H(7A)	118.1
C(6)-C(7)-H(7A)	118.1
C(7)-C(8)-C(9)	115.4(14)
C(7)-C(8)-H(8A)	122.3
C(9)-C(8)-H(8A)	122.3
N(1)-C(9)-C(4)	112.9(12)
N(1)-C(9)-C(8)	125.5(13)
C(4)-C(9)-C(8)	121.6(13)
C(15)-C(10)-C(11)	121.5(13)
C(15)-C(10)-N(2)	121.7(12)
C(11)-C(10)-N(2)	116.5(12)
C(10)-C(11)-C(12)	121.3(16)
C(10)-C(11)-H(11A)	119.3
C(12)-C(11)-H(11A)	119.3
C(13)-C(12)-C(11)	117.9(16)

C(13)-C(12)-H(12A)	121.1
C(11)-C(12)-H(12A)	121.1
C(12)-C(13)-C(14)	121.0(15)
C(12)-C(13)-H(13A)	119.5
C(14)-C(13)-H(13A)	119.5
C(13)-C(14)-C(15)	118.7(14)
C(13)-C(14)-H(14A)	120.7
C(15)-C(14)-H(14A)	120.7
C(10)-C(15)-C(14)	119.6(14)
C(10)-C(15)-H(15A)	120.2
C(14)-C(15)-H(15A)	120.2
O(16)-C(16)-N(16)	127.3(14)
O(16)-C(16)-N(3)	124.6(13)
N(16)-C(16)-N(3)	107.7(12)
C(16)#1-N(16)-C(16)	110.8(17)
C(16)#1-N(16)-C(17)	124.6(8)
C(16)-N(16)-C(17)	124.6(8)
C(18)-C(17)-C(18)#1	126.6(18)
C(18)-C(17)-N(16)	116.7(9)
C(18)#1-C(17)-N(16)	116.7(9)
C(17)-C(18)-C(19)	116.7(14)
C(17)-C(18)-H(18A)	121.7
C(19)-C(18)-H(18A)	121.7
C(18)-C(19)-C(20)	119.6(15)
C(18)-C(19)-H(19A)	120.2
C(20)-C(19)-H(19A)	120.2
C(19)#1-C(20)-C(19)	120.7(19)
C(19)#1-C(20)-H(20A)	119.6
C(19)-C(20)-H(20A)	119.6
N(22)-N(21)-C(29)	105.3(11)
N(21)-N(22)-C(23)	112.5(11)
N(21)-N(22)-C(30)	121.4(11)
C(23)-N(22)-C(30)	125.8(11)
N(22)-C(23)-N(23)	119.6(12)
N(22)-C(23)-C(24)	107.3(12)
N(23)-C(23)-C(24)	133.1(13)
N(23)#2-N(23)-C(23)	123.1(9)
N(23)#2-N(23)-C(36)	108.6(8)
C(23)-N(23)-C(36)	123.7(12)
C(25)-C(24)-C(23)	135.1(14)

C(25)-C(24)-C(29)	120.6(13)
C(23)-C(24)-C(29)	104.3(12)
C(26)-C(25)-C(24)	120.9(15)
C(26)-C(25)-H(25A)	119.6
C(24)-C(25)-H(25A)	119.6
C(25)-C(26)-C(27)	120.3(14)
C(25)-C(26)-H(26A)	119.9
C(27)-C(26)-H(26A)	119.9
C(28)-C(27)-C(26)	119.1(14)
C(28)-C(27)-H(27A)	120.5
C(26)-C(27)-H(27A)	120.5
C(29)-C(28)-C(27)	118.9(14)
C(29)-C(28)-H(28A)	120.5
C(27)-C(28)-H(28A)	120.5
N(21)-C(29)-C(28)	129.1(13)
N(21)-C(29)-C(24)	110.5(12)
C(28)-C(29)-C(24)	120.2(13)
C(31)-C(30)-C(35)	121.2(13)
C(31)-C(30)-N(22)	118.6(13)
C(35)-C(30)-N(22)	120.2(13)
C(30)-C(31)-C(32)	118.9(15)
C(30)-C(31)-H(31A)	120.5
C(32)-C(31)-H(31A)	120.5
C(33)-C(32)-C(31)	120.7(16)
C(33)-C(32)-H(32A)	119.7
C(31)-C(32)-H(32A)	119.7
C(32)-C(33)-C(34)	121.5(16)
C(32)-C(33)-H(33A)	119.3
C(34)-C(33)-H(33A)	119.3
C(35)-C(34)-C(33)	118.8(16)
C(35)-C(34)-H(34A)	120.6
C(33)-C(34)-H(34A)	120.6
C(34)-C(35)-C(30)	118.7(15)
C(34)-C(35)-H(35A)	120.6
C(30)-C(35)-H(35A)	120.6
O(36)-C(36)-N(36)	127.2(14)
O(36)-C(36)-N(23)	127.0(14)
N(36)-C(36)-N(23)	105.6(12)
C(36)#2-N(36)-C(36)	111.1(17)
C(36)#2-N(36)-C(37)	124.5(8)

C(36)-N(36)-C(37)	124.5(8)
C(38)-C(37)-C(38)#2	119.9(18)
C(38)-C(37)-N(36)	120.1(9)
C(38)#2-C(37)-N(36)	120.1(9)
C(39)-C(38)-C(37)	119.5(14)
C(39)-C(38)-H(38A)	120.3
C(37)-C(38)-H(38A)	120.2
C(40)-C(39)-C(38)	120.1(16)
C(40)-C(39)-H(39A)	119.9
C(38)-C(39)-H(39A)	119.9
C(39)-C(40)-C(39)#2	121(2)
C(39)-C(40)-H(40A)	119.6
C(39)#2-C(40)-H(40A)	119.6

Symmetry transformations used to generate equivalent atoms:

#1 -x+3/2,y,-z+1/2 #2 -x+5/2,y,-z+1/2

Table 4. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for ninw6.

	x	y	z	U(eq)
H(5A)	5510	1122	2294	23
H(6A)	4137	155	1902	24
H(7A)	3741	-1456	879	34
H(8A)	4705	-2179	239	27
H(11A)	7914	-2211	1047	33
H(12A)	9341	-2470	987	44
H(13A)	10124	-791	829	31
H(14A)	9452	1090	654	27
H(15A)	8005	1276	711	25
H(18A)	8882	4566	2977	20
H(19A)	8893	6634	3047	30
H(20A)	7500	7665	2500	23
H(25A)	12296	3917	439	32
H(26A)	11929	5060	-844	25
H(27A)	10897	6688	-1117	30
H(28A)	10237	7073	-62	26
H(31A)	10999	6373	3240	31
H(32A)	10941	6019	4656	34
H(33A)	10645	4157	5032	39
H(34A)	10621	2511	4118	43
H(35A)	10632	2844	2667	32
H(38A)	12915	-42	3873	23
H(39A)	12920	-2097	3861	31
H(40A)	12500	-3106	2500	29

Table 5. Torsion angles [°] for ninw6.

C(9)-N(1)-N(2)-C(3)	0.1(14)
C(9)-N(1)-N(2)-C(10)	176.2(11)
N(1)-N(2)-C(3)-C(4)	1.5(16)
C(10)-N(2)-C(3)-C(4)	-174.0(12)
N(1)-N(2)-C(3)-N(3)	178.3(12)
C(10)-N(2)-C(3)-N(3)	3(2)
N(2)-C(3)-N(3)-C(16)	106.4(16)
C(4)-C(3)-N(3)-C(16)	-78(2)
N(2)-C(3)-N(3)-N(3)#1	-119.9(16)
C(4)-C(3)-N(3)-N(3)#1	56(2)
N(2)-C(3)-C(4)-C(9)	-2.4(15)
N(3)-C(3)-C(4)-C(9)	-178.8(15)
N(2)-C(3)-C(4)-C(5)	179.0(14)
N(3)-C(3)-C(4)-C(5)	3(3)
C(3)-C(4)-C(5)-C(6)	177.7(15)
C(9)-C(4)-C(5)-C(6)	-1(2)
C(4)-C(5)-C(6)-C(7)	0(2)
C(5)-C(6)-C(7)-C(8)	1(2)
C(6)-C(7)-C(8)-C(9)	-1(2)
N(2)-N(1)-C(9)-C(4)	-1.7(15)
N(2)-N(1)-C(9)-C(8)	179.2(13)
C(3)-C(4)-C(9)-N(1)	2.6(16)
C(5)-C(4)-C(9)-N(1)	-178.6(12)
C(3)-C(4)-C(9)-C(8)	-178.2(13)
C(5)-C(4)-C(9)-C(8)	1(2)
C(7)-C(8)-C(9)-N(1)	179.2(14)
C(7)-C(8)-C(9)-C(4)	0(2)
N(1)-N(2)-C(10)-C(15)	141.7(13)
C(3)-N(2)-C(10)-C(15)	-43(2)
N(1)-N(2)-C(10)-C(11)	-43.8(17)
C(3)-N(2)-C(10)-C(11)	131.5(15)
C(15)-C(10)-C(11)-C(12)	-1(2)
N(2)-C(10)-C(11)-C(12)	-175.0(14)
C(10)-C(11)-C(12)-C(13)	1(2)
C(11)-C(12)-C(13)-C(14)	-2(2)
C(12)-C(13)-C(14)-C(15)	1(2)
C(11)-C(10)-C(15)-C(14)	0(2)
N(2)-C(10)-C(15)-C(14)	174.5(12)

C(13)-C(14)-C(15)-C(10)	-1(2)
N(3)#1-N(3)-C(16)-O(16)	-176.6(14)
C(3)-N(3)-C(16)-O(16)	-38(2)
N(3)#1-N(3)-C(16)-N(16)	9.8(17)
C(3)-N(3)-C(16)-N(16)	148.0(11)
O(16)-C(16)-N(16)-C(16)#1	-177.3(18)
N(3)-C(16)-N(16)-C(16)#1	-4.0(7)
O(16)-C(16)-N(16)-C(17)	2.7(18)
N(3)-C(16)-N(16)-C(17)	176.0(7)
C(16)#1-N(16)-C(17)-C(18)	69.1(10)
C(16)-N(16)-C(17)-C(18)	-110.9(10)
C(16)#1-N(16)-C(17)-C(18)#1	-110.9(10)
C(16)-N(16)-C(17)-C(18)#1	69.1(10)
C(18)#1-C(17)-C(18)-C(19)	1.6(10)
N(16)-C(17)-C(18)-C(19)	-178.4(10)
C(17)-C(18)-C(19)-C(20)	-3.2(19)
C(18)-C(19)-C(20)-C(19)#1	1.7(10)
C(29)-N(21)-N(22)-C(23)	1.8(15)
C(29)-N(21)-N(22)-C(30)	176.6(12)
N(21)-N(22)-C(23)-N(23)	178.7(12)
C(30)-N(22)-C(23)-N(23)	4(2)
N(21)-N(22)-C(23)-C(24)	-2.9(15)
C(30)-N(22)-C(23)-C(24)	-177.5(12)
N(22)-C(23)-N(23)-N(23)#2	-109.9(18)
C(24)-C(23)-N(23)-N(23)#2	72(2)
N(22)-C(23)-N(23)-C(36)	96.8(16)
C(24)-C(23)-N(23)-C(36)	-81(2)
N(22)-C(23)-C(24)-C(25)	-179.0(16)
N(23)-C(23)-C(24)-C(25)	-1(3)
N(22)-C(23)-C(24)-C(29)	2.7(15)
N(23)-C(23)-C(24)-C(29)	-179.2(14)
C(23)-C(24)-C(25)-C(26)	179.0(15)
C(29)-C(24)-C(25)-C(26)	-3(2)
C(24)-C(25)-C(26)-C(27)	1(2)
C(25)-C(26)-C(27)-C(28)	0(2)
C(26)-C(27)-C(28)-C(29)	1(2)
N(22)-N(21)-C(29)-C(28)	175.4(14)
N(22)-N(21)-C(29)-C(24)	0.1(15)
C(27)-C(28)-C(29)-N(21)	-177.9(14)
C(27)-C(28)-C(29)-C(24)	-3(2)

C(25)-C(24)-C(29)-N(21)	179.6(13)
C(23)-C(24)-C(29)-N(21)	-1.7(15)
C(25)-C(24)-C(29)-C(28)	4(2)
C(23)-C(24)-C(29)-C(28)	-177.6(13)
N(21)-N(22)-C(30)-C(31)	-43.3(18)
C(23)-N(22)-C(30)-C(31)	130.8(15)
N(21)-N(22)-C(30)-C(35)	137.1(14)
C(23)-N(22)-C(30)-C(35)	-49(2)
C(35)-C(30)-C(31)-C(32)	4(2)
N(22)-C(30)-C(31)-C(32)	-175.7(13)
C(30)-C(31)-C(32)-C(33)	-4(2)
C(31)-C(32)-C(33)-C(34)	4(3)
C(32)-C(33)-C(34)-C(35)	-5(3)
C(33)-C(34)-C(35)-C(30)	5(2)
C(31)-C(30)-C(35)-C(34)	-5(2)
N(22)-C(30)-C(35)-C(34)	174.7(13)
N(23)#2-N(23)-C(36)-O(36)	-168.8(16)
C(23)-N(23)-C(36)-O(36)	-12(2)
N(23)#2-N(23)-C(36)-N(36)	5.9(17)
C(23)-N(23)-C(36)-N(36)	162.6(11)
O(36)-C(36)-N(36)-C(36)#2	172.5(19)
N(23)-C(36)-N(36)-C(36)#2	-2.2(6)
O(36)-C(36)-N(36)-C(37)	-7.5(19)
N(23)-C(36)-N(36)-C(37)	177.8(6)
C(36)#2-N(36)-C(37)-C(38)	60.1(10)
C(36)-N(36)-C(37)-C(38)	-119.9(10)
C(36)#2-N(36)-C(37)-C(38)#2	-119.9(10)
C(36)-N(36)-C(37)-C(38)#2	60.1(10)
C(38)#2-C(37)-C(38)-C(39)	0.2(10)
N(36)-C(37)-C(38)-C(39)	-179.8(10)
C(37)-C(38)-C(39)-C(40)	0(2)
C(38)-C(39)-C(40)-C(39)#2	0.2(10)

Symmetry transformations used to generate equivalent atoms:

#1 -x+3/2,y,-z+1/2   #2 -x+5/2,y,-z+1/2

Appendix D

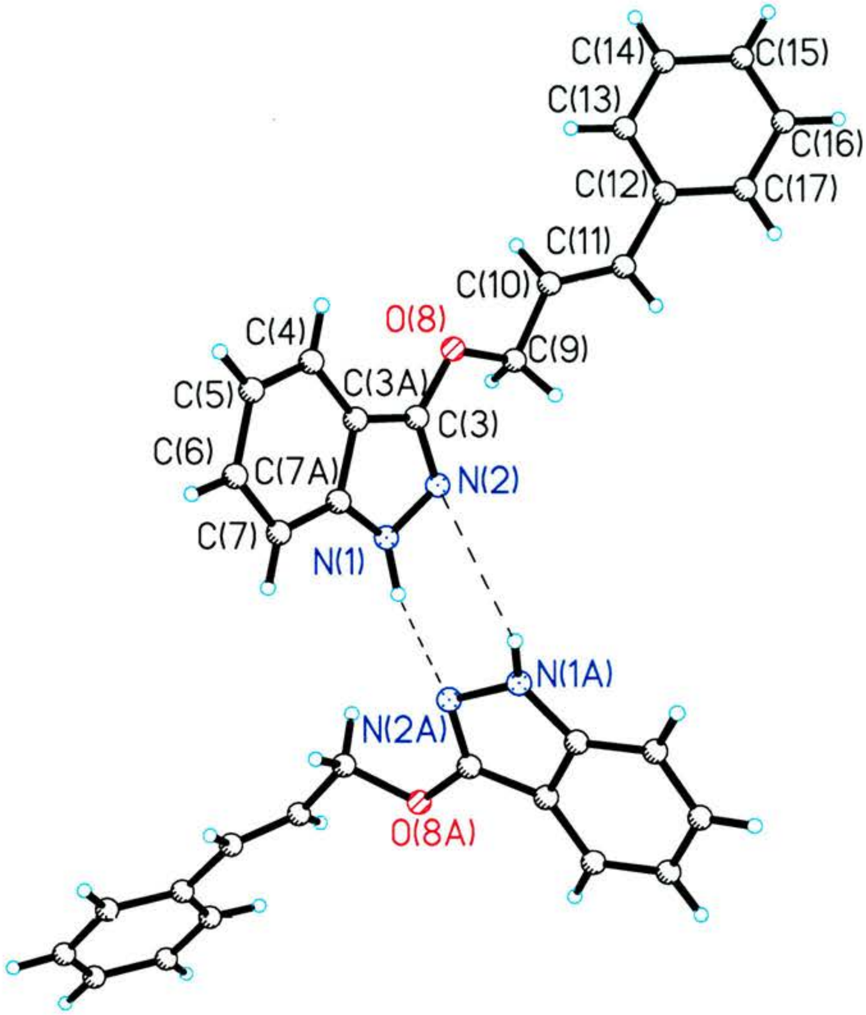
C(14)
C(15)
C(13)
C(16)
C(12)
C(17)
C(11)
C(10)
O(8)
C(4)
C(9)
C(3A)
C(5)
C(3)
C(6)
C(7A)
N(2)
C(7)
N(1)
N(1A)
N(2A)
O(8A)

Table 1. Crystal data and structure refinement for ninw3.

Identification code	ninw3	
Empirical formula	C16 H14 N2 O	
Formula weight	250.29	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pna2(1)	
Unit cell dimensions	a = 11.736(6) Å	α= 90°.
	b = 25.753(13) Å	β= 90°.
	c = 4.414(2) Å	γ = 90°.
Volume	1334.0(12) Å^3	
Z	4	
Density (calculated)	1.246 Mg/m^3	
Absorption coefficient	0.079 mm^{-1}	
F(000)	528	
Crystal size	.2 x .06 x .06 mm^3	
Theta range for data collection	2.35 to 24.70°.	
Index ranges	-13<=h<=9, -30<=k<=27, -5<=l<=4	
Reflections collected	4929	
Independent reflections	1991 [R(int) = 0.0891]	
Completeness to theta = 24.70°	96.3 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.00000 and 0.5321	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1991 / 2 / 177	
Goodness-of-fit on F^2	0.893	
Final R indices [I>2sigma(I)]	R1 = 0.0619, wR2 = 0.0819	
R indices (all data)	R1 = 0.1901, wR2 = 0.1089	
Absolute structure parameter	1(3)	
Extinction coefficient	0.0040(11)	
Largest diff. peak and hole	0.138 and -0.126 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)

for ninw3. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	9051(4)	4749(2)	6464(10)	61(1)
N(2)	8782(4)	5182(2)	4695(11)	60(1)
C(3)	7662(5)	5171(2)	4680(14)	50(1)
C(3A)	7169(4)	4769(2)	6383(13)	47(2)
C(4)	6059(5)	4594(2)	7036(14)	68(2)
C(5)	5952(5)	4176(3)	8875(14)	75(2)
C(6)	6912(5)	3924(2)	10054(13)	69(2)
C(7)	8001(5)	4082(2)	9452(12)	62(2)
C(7A)	8110(5)	4510(2)	7547(12)	52(2)
O(8)	7036(3)	5536(2)	3195(8)	61(1)
C(9)	7687(4)	5935(2)	1677(14)	60(2)
C(10)	6869(4)	6315(2)	383(12)	63(2)
C(11)	6850(5)	6809(3)	1065(12)	68(2)
C(12)	6096(5)	7223(2)	-116(14)	57(2)
C(13)	5163(5)	7113(2)	-1821(15)	82(2)
C(14)	4460(6)	7502(3)	-2871(16)	101(3)
C(15)	4673(6)	8007(3)	-2209(18)	88(2)
C(16)	5593(7)	8120(2)	-437(16)	86(2)
C(17)	6307(5)	7734(3)	525(17)	86(2)

Table 3. Bond lengths [Å] and angles [°] for ninw3.

N(1)-C(7A)	1.351(6)
N(1)-N(2)	1.396(5)
N(2)-C(3)	1.314(5)
C(3)-O(8)	1.361(6)
C(3)-C(3A)	1.403(6)
C(3A)-C(7A)	1.389(6)
C(3A)-C(4)	1.408(6)
C(4)-C(5)	1.354(6)
C(5)-C(6)	1.401(7)
C(6)-C(7)	1.367(6)
C(7)-C(7A)	1.392(6)
O(8)-C(9)	1.446(5)
C(9)-C(10)	1.484(6)
C(10)-C(11)	1.307(6)
C(11)-C(12)	1.482(7)
C(12)-C(13)	1.358(6)
C(12)-C(17)	1.368(6)
C(13)-C(14)	1.378(7)
C(14)-C(15)	1.355(8)
C(15)-C(16)	1.364(7)
C(16)-C(17)	1.367(7)
C(7A)-N(1)-N(2)	112.1(4)
C(3)-N(2)-N(1)	102.2(5)
N(2)-C(3)-O(8)	121.8(6)
N(2)-C(3)-C(3A)	115.2(5)
O(8)-C(3)-C(3A)	122.9(5)
C(7A)-C(3A)-C(3)	102.9(5)
C(7A)-C(3A)-C(4)	120.4(6)
C(3)-C(3A)-C(4)	136.7(6)
C(5)-C(4)-C(3A)	117.6(6)
C(4)-C(5)-C(6)	121.2(6)
C(7)-C(6)-C(5)	122.7(6)
C(6)-C(7)-C(7A)	116.1(5)
N(1)-C(7A)-C(3A)	107.5(5)
N(1)-C(7A)-C(7)	130.5(6)
C(3A)-C(7A)-C(7)	122.0(6)
C(3)-O(8)-C(9)	115.4(4)

O(8)-C(9)-C(10)	107.8(4)
C(11)-C(10)-C(9)	124.3(5)
C(10)-C(11)-C(12)	129.1(6)
C(13)-C(12)-C(17)	117.5(6)
C(13)-C(12)-C(11)	121.7(6)
C(17)-C(12)-C(11)	120.8(6)
C(12)-C(13)-C(14)	121.2(6)
C(15)-C(14)-C(13)	120.9(7)
C(14)-C(15)-C(16)	118.3(7)
C(15)-C(16)-C(17)	120.6(7)
C(16)-C(17)-C(12)	121.5(6)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2$x 10^3) for ninw3. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}	
N(1)27(3)	76(4)	80(4)	1(3)	-6(3)	2(3)	
N(2)34(3)	61(4)	85(3)	4(3)	4(3)	-5(3)	
C(3)46(4)	42(4)	61(4)	-10(3)	0(4)	11(3)	
C(3A)	46(4)	45(4)	51(4)	-6(3)	-7(3)	- 9(3)
C(4)54(4)	66(5)	84(5)	2(4)	4(3)	-7(4)	
C(5)44(4)	89(5)	90(6)	-9(5)	-5(4)	-4(4)	
C(6)72(4)	55(4)	81(5)	12(4)	-2(4)	-12(4)	
C(7)53(4)	65(4)	68(4)	8(4)	-15(4)	12(3)	
C(7A) 3(4)	40(4)	52(4)	62(4)	-5(4)	-8(4)	
O(8)40(2)	55(3)	89(3)	7(2)	13(2)	-11(2)	
C(9)41(4)	58(4)	83(4)	-5(4)	-5(3)	2(3)	
C(10)66(4)	63(4)	59(4)	-1(4)	-5(4)	-12(4)	
C(11)58(4)	64(4)	82(5)	-1(4)	-6(3)	-9(4)	
C(12)48(4)	55(5)	68(4)	3(4)	-2(3)	-11(4)	
C(13)61(5)	50(5)	134(5)	-7(5)	-12(5)	-7(4)	
C(14)78(5)	86(5)	139(7)	-2(7)	-30(5)	9(5)	
C(15)80(6)	87(7)	97(6)	15(5)	1(5)	16(5)	
C(16)131(7)	52(5)	75(5)	12(5)	10(5)	21(5)	
C(17)85(5)	57(5)	117(6)	4(4)	-26(4)	-8(4)	

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for ninw3.

	x	y	z	U(eq)
H(1N)	9835(13)	4716(14)	7200(90)	52(15)
H(4A)	5422	4759	6233	81
H(5A)	5229	4055	9365	89
H(6A)	6805	3636	11298	83
H(7A)	8631	3914	10268	74
H(9A)	8146	5784	79	73
H(9B)	8190	6106	3105	73
H(10A)	6336	6193	-1004	75
H(11A)	7385	6914	2492	82
H(13A)	4997	6769	-2288	98
H(14A)	3830	7417	-4050	122
H(15A)	4205	8269	-2944	106
H(16A)	5734	8462	121	103
H(17A)	6952	7821	1641	103

Table 6. Torsion angles [°] for ninw3.

C(7A)-N(1)-N(2)-C(3)	-2.7(6)
N(1)-N(2)-C(3)-O(8)	179.5(5)
N(1)-N(2)-C(3)-C(3A)	1.7(6)
N(2)-C(3)-C(3A)-C(7A)	-0.1(6)
O(8)-C(3)-C(3A)-C(7A)	-177.9(5)
N(2)-C(3)-C(3A)-C(4)	-179.2(6)
O(8)-C(3)-C(3A)-C(4)	3.0(9)
C(7A)-C(3A)-C(4)-C(5)	1.5(8)
C(3)-C(3A)-C(4)-C(5)	-179.6(6)
C(3A)-C(4)-C(5)-C(6)	-0.8(8)
C(4)-C(5)-C(6)-C(7)	0.5(9)
C(5)-C(6)-C(7)-C(7A)	-0.8(8)
N(2)-N(1)-C(7A)-C(3A)	2.8(6)
N(2)-N(1)-C(7A)-C(7)	-177.7(5)
C(3)-C(3A)-C(7A)-N(1)	-1.6(5)
C(4)-C(3A)-C(7A)-N(1)	177.6(5)
C(3)-C(3A)-C(7A)-C(7)	178.8(5)
C(4)-C(3A)-C(7A)-C(7)	-1.9(8)
C(6)-C(7)-C(7A)-N(1)	-177.9(6)
C(6)-C(7)-C(7A)-C(3A)	1.5(7)
N(2)-C(3)-O(8)-C(9)	-0.6(8)
C(3A)-C(3)-O(8)-C(9)	177.1(4)
C(3)-O(8)-C(9)-C(10)	-176.1(4)
O(8)-C(9)-C(10)-C(11)	120.9(6)
C(9)-C(10)-C(11)-C(12)	178.7(5)
C(10)-C(11)-C(12)-C(13)	10.9(10)
C(10)-C(11)-C(12)-C(17)	-170.3(6)
C(17)-C(12)-C(13)-C(14)	0.2(10)
C(11)-C(12)-C(13)-C(14)	179.1(6)
C(12)-C(13)-C(14)-C(15)	-0.6(12)
C(13)-C(14)-C(15)-C(16)	-1.0(12)
C(14)-C(15)-C(16)-C(17)	2.9(11)
C(15)-C(16)-C(17)-C(12)	-3.4(10)
C(13)-C(12)-C(17)-C(16)	1.8(9)
C(11)-C(12)-C(17)-C(16)	-177.1(6)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for ninw3 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1N)...N(2)#1	0.9799(12)	1.979(13)	2.922(6)	161(3)

Symmetry transformations used to generate equivalent atoms:

#1 -x+2,-y+1,z+1/2