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New processes for the APIs industrial production: the case of silodosin

Ph. D. Thesis of
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Ai miei genitori

Dietro ogni problema c'è un'opportunità

(Behind every problem there is an opportunity)

Galileo Galilei (1564-1642)

ABSTRACT

This thesis is focused on the development of new synthetic processes for the production of already known Active Pharmaceutical Ingredients (APIs). The research work was performed in the laboratories of Dipharma Francis srl, a company which operates in the generic drug market.

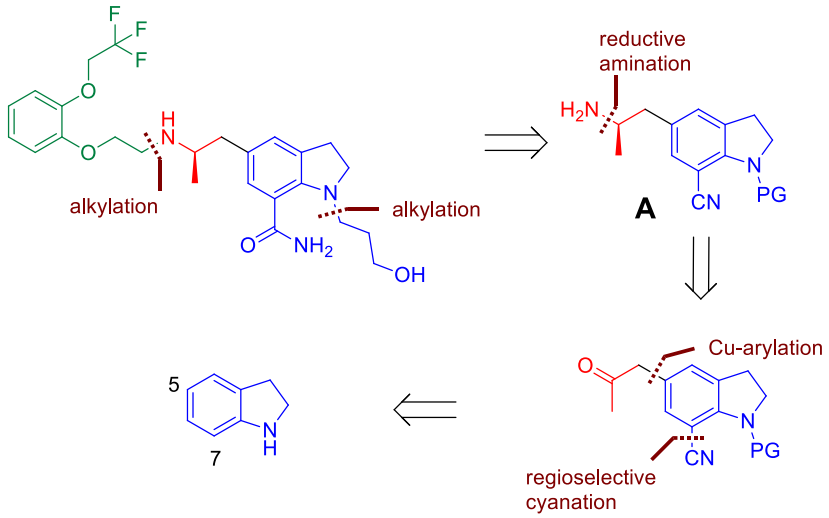
The launch of the generic version of a drug in the market often leads to lowering of product prices for both the branded product and the generic ones. For this reason, the process adopted to produce an API has to be innovative, efficient, safe and, of course, cheaper than the existing ones, in order to be competitive in the market.

During my Ph.D. I worked on the synthesis of some APIs, in particular here I report the feasibility and development studies of an alternative process to produce silodosin. Silodosin is an API used as a treatment for the symptoms of Benign Prostatic Hyperplasia (BPH).

In order to establish the synthetic strategy and to outline our freedom to operate, an accurate survey of the whole patent literature about silodosin has been done.

During the feasibility study several synthetic approaches have been tried in order to functionalise indoline at positions 5 and 7.

A copper(I) catalysed C-arylation reaction and a regioselective electrophilic aromatic substitution revealed to be the best choices to introduce respectively substituents in position 5 and 7 of indoline.



The synthesis continued with a diastereoselective reductive amination which after crystallisation yielded optically pure amine **A** that is the key intermediate for the synthesis of silodosin and ended converting amine **A** into Silodosin using already reported procedures.

Our new process to prepare silodosin starting from commercially available and cheap indoline consists of 11 steps. The whole synthetic route has been performed in gram scale using only 4 purifications of key intermediates. Silodosin has been finally obtained in a 10% overall yield, with a purity greater than 99% measured by HPLC and an optical purity greater than 99% measured by HPLC on chiral stationary phase.

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LIST OF ABBREVIATION

Ac : Acetyl

AE : Atom Economy

ANDA : abbreviated new drug application

API : active pharmaceutical ingredient

AR : adrenoreceptor

ATRC : atom transfer radical cyclisation

AUC : area under the concentration time curve

Bn : benzyl

Boc : tert-butyl carbamate

BPH : benign prostatic hyperplasia

Bz : benzoyl

Cbz : benzyl carbamate

CSA : camphorsulfonic acid

DCM : dichloromethane

DIPEA : di iso-propyl ethyl amine

DMAP : dimethylamino pyridine

DMEDA : N,N'-dimethyl ethylene diamine

DMF : dimethyl formamide

DMSO : dimethyl sulfoxide

DOE : design of experiment

DSC : differenzial scanning calorimetry

EMA : European Medicines agency

EMEA : European agency for the evaluation of medicinal products, now EMA

EXAFS : extended X-ray absorption fine structure

EU : European Union

FC : riedel-Crafts

FDA : Food and Drug Administation

GC-MS : Gas Chromatography and Mass Spectroscopy

HPLC : high performance liquid chromatography

IPA : iso-propyl alcohol

IR : infrared spectroscopy

LTG : lamotrigine

LUTS : lower urinary tract symptoms

MOMCl : chloromethyl methyl ether

Ms : Methanesulfonyl, mesyl

MS : mass spectroscopy

MTBE : methyl tert-butyl ether

MW : molecular weight

NBS : N-bromo succinimide

NCE : new chemical entity

NDA : new drug application

NMR : nuclear magnetic resonance

NTR : narrow therapeutic range

PEI : process excellent index

PhEA : phenyl ethyl amine

PMI : process mass intensity

S-SIPHOX : (S)-2-(2-(diphenylphosphino)phenyl)-4-alkyl-4,5-dihydrooxazole

TCCA : trichloroisocianuric acid

TEA : triethyl amine

TFA : trifluoroacetic acid

TH : hydrogen transfer reduction

THF : tetrahydrofuran

TLC : thin layer chromatography

TOF : turn over frequency

Ts : para-toluensulfonyl, tosyl

UV/Vis : Ultraviolet–visible spectroscopy

US : united states

VH : Vilsmeier-Haack

VTO : volume-time-output

WHO : World Health Organization

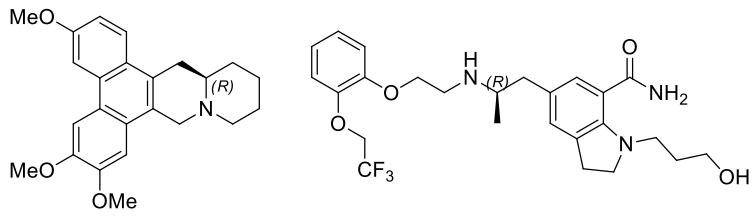
XANES : X-ray absorption near edge structure

PREFACE

During the Ph. D. research work I had been involved in different projects concerning the synthesis of different active pharmaceutical ingredients. The Ph. D. thesis is focused on the synthesis of the API silodosin, this choice was due to the huge amount of data related to silodosin that covers most of the time spent in the Ph. D. research work and to intellectual property reasons related to the other projects.

In addition during the Ph. D. period I have been hosted for 4 months in the laboratory of Professor Ian R. Baxendale at Durham University (U.K.) to know, learn and exploit the flow chemistry technology. Flow chemistry can be a useful tool in R&D research work, but it can be also used for industrial production. Nowadays many industries take advantages of flow chemistry even in fine chemical production.

The experience in Baxendale laboratory led to the ideation of a new synthesis in batch of Boehmeriasin A, a compound with high cytotoxicity. Then, the synthetic route has been converted into a flow chemistry process but the work to complete and optimise the flow chemistry process is still ongoing in the Baxendale group. However the batch synthesis led to the draft of scientific article submitted to the European Journal of Medicinal Chemistry.[1]



(*R*)-boehmeriasin A silodosin

Figure 1: boehmeriasin A and silodosin compounds

[1] Submitted : Christodoulou, M.S.; Calogero, F.; Baumann, M.; García-Argáez, A. N.;c Pieraccini, S.; Sironi, M.; Dapiaggi, F.; Bucci, R.; Broggini, G.; Gazzola, S.; Liekens, S.; Silvani, A.; Lahtela-Kakkonen, M.; Martinet, N.; Nonel-Canals, A.; Santamaría-Navarro, E.; Baxendale, I. R.; Dalla Viac, L.; Passarella, D. "Boehmeriasin A as new lead compound for the inhibition of Topoisomerases and SIRT2", Eur. J. Med. Chem.

DIPHARMA FRANCIS

My Ph.D. thesis has been focused on the development of new processes for the production of already known Active Pharmaceutical Ingredients (APIs).

The research work has been performed in the R&D laboratories of Dipharma Francis Srl, a chemical company which operates in the generic drug market.

With sales of around 100 M€ per year, Dipharma is one of the major European manufacturers of APIs. Dipharma main markets are North America, Europe, and Japan, but in North America (USA, Canada and Mexico) are located the most important customers. (Figure 2)

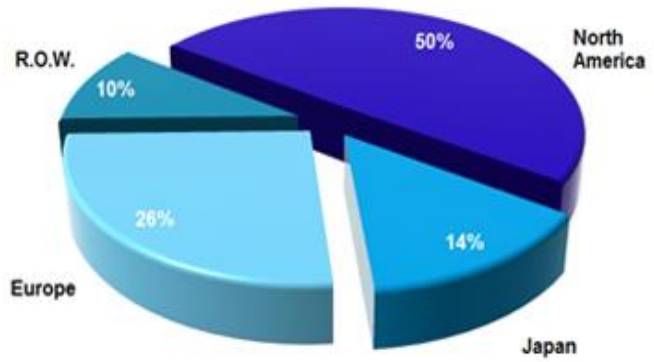


Figure 2: Dipharma market share in the world

Dipharma experience lies in the ability to carry out complex and hazardous operations safely, thanks to the great expertise of Dipharma in civil explosives manufacture matured in the past. In fact Dipharma (former Dinamite S.p.a.) was founded by Mario Biazzi who, in the middle of 1930's invented the continuous

process for the production of nitroglycerine with particular attention to safety of the process.

The core competencies of the company are related to nitration, azidation, nitroesterification and high pressure hydrogenation reactions, but also to the use of enzyme and organometallic chemistry.

This knowledge is applied to the development and the production of APIs in accordance with cGMP, and in accordance with customer quality expectations.

GENERICS

The market of generic drugs is a field of growing interest. An estimated half of all prescriptions in the United States are filled with generic drugs, while in Italy it is not so common yet. These products carry all the medicinal qualities (and side effects) of their brand-name counterparts, but generics tend to have one additional benefit: lower cost.

Generic medicines are those where the original patent has expired and which may be produced by manufacturers other than the original innovator (patent-holding) company. The term "generic drug" or "generic medicine" can have varying definitions in different markets, however the term is commonly understood, as defined by the World Health Organisation (WHO), to mean a pharmaceutical product which:

– is usually intended to be interchangeable with an innovator product,

– is manufactured without a licence from the innovator company, and

– is marketed after the expiry date of the patent or other exclusive rights.

There are differing legal requirements in different jurisdictions that define the specifics of what a generic medicine is. However, one of the main principles underpinning the safe and effective use of generic medicines is the concept of bioequivalence. Bioequivalence has been defined as follows: two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and their bioavailabilities (rate and extent of availability) after administration in the same molar dose are similar to such a degree that their effects, with respect to both efficacy and safety, can be expected to be essentially the same. Pharmaceutical equivalence

implies the same amount of the same active substance(s), in the same dosage form, for the same route of administration and meeting the same or comparable standards[2].

The purpose of establishing bioequivalence is to demonstrate equivalence between the generic medicine and the originator medicine in order to allow bridging of the pre-clinical and clinical testing performed on the originator drug.

Medicines in the United States of America[3]

The US Food and Drug Administration (FDA), which regulates the pharmaceutical market in the United States defines generic medicines as:

> – a drug product that is comparable to brand/reference listed drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use
>
> – copies of brand-name drugs and are the same as those brand name drugs in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use.

The 1984 Drug Price Competition and Patent Term Restoration Act (more commonly known as the Hatch- Waxman Act) in the US allowed for an abbreviated system for approval of generic copies of all drugs approved after 1962, meaning that pre-clinical and clinical testing did not have to be repeated for generics. The intended result of this legislation was to ensure that generic medicines would be less expensive than the equivalent originator medicine because it was not necessary for generic medicine manufacturers to repeat discovery, pre-clinical and clinical studies (Figure 3)

[2] Birkett DJ; *Aust. Prescr.*, **2003**, *26*, 85 – 87.
[3] http://www.fda.gov.

NDA Requirements	ANDA Requirements
1. Labelling	1. Labelling
2. Pharmacology/toxicology	2. Pharmacology/toxicology
3. Chemistry	3. Chemistry
4. Manufacturing	4. Manufacturing
5. Controls	5. Controls
6. Microbiology	6. Microbiology
7. Inspection	7. Inspection
8. Testing	8. Testing
9. Animal study	
10. Clinical study	9. Bioequivalence
11. Bioavailability	

Figure 3: originator (NDA) versus Generic (ANDA) Review Process Requirements

To gain FDA approval, a generic medicine must:

- Contain the same active ingredient as the originator medicine (inactive ingredients may vary)

- be identical in strength, dosage form, and route of administration

- have the same use indications

- be bioequivalent

- meet the same batch requirements for identity, strength, purity, and quality

- be manufactured under the same strict standards of FDA's good manufacturing practice regulations required for originator products[4] .

Bioequivalence is demonstrated when the rate and extent of absorption do not show a significant difference from the originator drug, or where the extent of absorption

[4] Simoens S; *Curr. Med. Res. Opin.*, **2007**, *23*, 2647 – 2654.

does not show a significant difference and any difference in rate is intentional or not medically significant . The FDA's formal definition of bioequivalence is: *the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study*.

Therefore, bioequivalent drugs are pharmaceutical equivalents whose rate and extent of absorption are not statistically different when administrated to patients or subjects at the same molar dose under similar experimental conditions[5].

Currently, bioequivalence limits in use by the FDA when assessing a new generic medicine are that the generic medicine demonstrates 80-125% of the bioavailability of the originator drug. In the US, the limit of 80-125% is unchanged for Narrow Therapeutic Range (NTR) drugs.
However, it should be noted that variations between batches of originator drugs may themselves threaten patient safety. In 2012, Patel et al. reported that (in 2010) patients prescribed Lamotrigine (LTG, an anti-epileptic medication) experienced unexplained toxicity. When investigated, the manufacturer (GlaxoSmithKline) accepted responsibility for an altered formulation due to changes made to the manufacturing process.

Generic Medicines in the European Union

The legal situation regarding authorisation of pharmaceutical products in the EU is more complex than in the US, with each member state having a competent authority in addition to the European Medicines Agency (EMA), which oversees EU-wide authorisation of medicines.The EMA defines a generic medicine as: a medicine that is developed to be the same as a medicine that has already been authorised (the

[5] US-FDA: Guidance for Industry - Bioavailability and Bioequivalence. In FDA Guidances for Industry

'reference medicine'). A generic medicine contains the same active substance(s) as the reference medicine, and it is used at the same dose(s) to treat the same disease(s) as the reference medicine. However, the name of the medicine, its appearance (such as colour or shape) and its packaging can be different from those of the reference medicine[6]. Authorisation of a medicine in the EU can be done via three different routes: the Centralised Procedure, the Decentralised Procedure or the Mutual Recognition Procedure[7]. Additionally, National Procedures are in place in individual member states, which allow a medicine to be authorised by the competent authority in that specific member state.

At the end of the procedure, the product dossier, as proposed by the Reference Member State, is approved. The subsequent steps are identical to the mutual recognition procedure[8]. As in the US, applicants for a marketing authorisation (MA) for a generic medicine in the EU may submit an abbreviated application[9].

Generic medicine applications typically include chemical pharmaceutical data and the results of bioequivalence studies, which demonstrate the similarity of the generic product relative to the reference medicine. As stated previously, the tolerance levels involved have been favourably compared to those acceptable for inter-batch variation during production of the originator medicine. The majority of authorizations for generic medicines are granted through the MRP and the DCP. EU bioequivalence parameters are similar to those mandated in the US, requiring that the test and reference products be contained within an acceptance interval of 80.00 – 125.00% of the AUC (area under the concentration time curve), which reflects the extent of exposure, or C_{max}, at a 90% confidence interval. European guidelines,

[6] Kesselheim, A. S.; Misono, A. S.; Lee, J. L.; Stedman, M. R.; Brookhart, M. A.; Choudhry, N. K.; Shrank, W. H.; *J.A.M.A.*, **2008**, *300*, 2514 – 2526.
[7] Davit, B. M.; Nwakama, P. E.; Buehler, G. J.; Conner, D. P.; Haidar, S. H.; Patel, D. T.; Yang, Y.; Yu, L. X.; Woodcock J.; *Ann. Pharmacother.*, **2009**, *43*, 1583 – 1597.
[8] Patel, V.; Cordato, D. J.; Dias, M.; Beran, R. G.; *Epilepsy Res.*, **2012**, *98,* 269 – 272.
[9] http://www.ema.europa.eu.

however, also provide a tightened acceptance interval of 90.00-111.11% for narrow therapeutic index drugs as well as different assessment requirements for highly variable drug products.

Overall, both EU and US legislation for the authorisation of generic medicines allow for abbreviated applications to be made in the case of generic medicines. In both jurisdictions, pre-clinical and clinical studies do not have to be performed by the generic medicine applicant, but bioequivalence to the originator or "reference" medicine must be demonstrated. This abbreviated application process is often quoted as one of the main reasons for the price difference between generic and originator drugs.

INDUSTRIAL PROPERTY

This research work is closely related to industrial property rights, in particular to the patent issues. Development of non-infringing generics in today's markets is not an easy task, in particular with many hundreds of patents being filed on a particular drug product by the brand company, as well as its potential generic competitors.
The field of industrial property and patent law usually employs patent attorneys who have specialized qualifications. Patent attorneys must have the technical background to understand the inventions they are supporting. Intellectual property function in industry is not necessary regarded to attorneys, and often this job is committed to technical specialists (engineers, chemist, etc.) that cooperate with external attorney agency. These professionals usually conduct background research, monitors the patent literature, investigate new technical areas and draft patents. During the development of a new drug it is important to study patents owned by third parties and advises the client regarding the scope and validity of these patents in order to avoid infringing on valid patents of all other parties.

Industrial property legislation is part of the wider body of law known as intellectual property. The term intellectual property refers broadly to the creations of the human mind. Intellectual property rights protect the interests of creators by giving them property rights over their creations.
Intellectual property relates to items of information or knowledge, which can be incorporated in tangible objects at the same time in an unlimited number of copies at different locations anywhere in the world. Intellectual property rights are also characterized by certain limitations, such as limited duration in the case of copyright and patents.
Intellectual property is usually divided into two branches, namely industrial property (which include patents to protect inventions) and copyright.

Referring to patent field, an invention is not necessarily a complex item. A number of countries, however, define inventions as new solutions to technical problems. The problem may be old or new, but the solution, in order to merit the name of invention, must be a new one. For example, discovering something that already exists in nature, such as a previously unknown plant variety, is not an invention. But the process for extraction of a new substance from a plant may be an invention.
Patents are the most widespread means of protecting the rights of inventors. By granting an exclusive right, patents provide incentives to individuals, offering them recognition for their creativity and material reward for their marketable inventions.

Not all inventions are patentable. Laws generally require that an invention fulfill the following conditions, known as the requirements or conditions of patentability:

Industrial Applicability (utility). The invention must be of practical use, or capable of some kind of industrial application.

Novelty. It must show some new characteristic that is not known in the body of existing knowledge (referred to as prior art) in its technical field.

Inventive step (non-obviousness). It must show an inventive step that could not be deduced by a person with average knowledge of the technical field.

Patentable subject matter. The invention must fall within the scope of patentable subject matter as defined by national law. This varies from one country to another. Many countries exclude from patentability such subject matter as scientific theories, mathematical methods, plant or animal varieties, discoveries of natural substances, methods for medical treatment (as opposed to medical products), and any invention where prevention of its commercial exploitation is necessary to protect public order, good morals or public health.

In chemistry field the patentable subjects are:

- new compound and its application,
- the new use for an already existing compound,
- the process to prepare a chemical entity,
- the use of certain catalyst or reagent,
- the purification process,
- the crystallisation procedure,
- the crystalline form.

A library of new compound differently substituted can be claimed using the Markush formula, disclosing all the possible R claimed in the patent. In describing a chemical, a Markush formula allows the patent-holder to be deliberately vague as to the most active/effective structural formula, concealing that information from competitors.

RESEARCH AND DEVELOPMENT IN INDUSTRY

In a chemical/pharmaceutical industry the Research and development department plays a crucial role, because it should provide new products to be sold, but also the already fixed process could be improved and renewed. R&D differs from the majority of a company's activities which are intended to yield nearly immediate profit or immediate improvements in operations and involve little uncertainty as to the return on investment.

In the pharmaceutical industry a plenty of efforts and money are spent in the drug discovery and drug development; the first is the process by which potential drugs are discovered or designed. In the past most drugs have been discovered either by isolating the active ingredient from traditional remedies or by serendipitous discovery. Modern biotechnology often focuses on understanding the metabolic pathways related to a disease and manipulating these pathways using molecular biology or biochemistry.
In pharmaceutical companies a New Chemical Entity (NCE) is first synthesised by Medicinal Chemists in the Discovery division it does not represent the most efficient route, but the wide substrate range route. Consequently, a Medicinal Chemistry route cannot be scaled up to kilogram quantities without modifications. However, comparing a Medicinal Chemistry route of synthesis with a commercial process is not meaningful because different goals are driving the route selection decisions. After an NCE meets predefined biological and physicochemical criteria, the compound is selected for development, and the project is transferred to Chemical Development where NCE synthesis is scaled up.

While Drug Development refers to activities undertaken after a NCE is identified as a potential drug in order to establish its suitability as a medication. Research in these

areas generally includes a combination of in vitro studies, in vivo studies, and clinical trials. The amount of capital required for late stage development has made it a historical strength of the larger pharmaceutical companies.

In a Generics company this two very expensive research field are absent, and the research is focused essentially on the chemical point of view, this work can be associated to the large field of "Process Chemistry" that is presents in both pharmaceutical and generic companies. In particular, in generic company, the work is focused on the discovery of new chemical processes for the APIs industrial production that should be non-infringing with the already patented ones.
For this reason the R&D must cooperate with other company function, as the marketing and the intellectual property. The marketing function should give the guide lines to the R&D to let them know which product is valued and on demand among the costumers. While the intellectual property function should give the whole patent scenario related to the API under study.
In Dipharma Francis the R&D department itself is divided into four subunits that work together to develop new industrial processes.

- PROCESS RESEARCH

This is the first stage of the API process development, where a cost-effective and non infringing process is the main target of a new project. In this unit researcher works directly in contact with the marketing and IP function to obtain best results. This is the beginning of the research and it is also the most crucial part, because it is subjected to commercial tendency, so a project could be easily deleted even if it could be very interesting. Time is a determining factor to achieve the new API synthesis, and at this stage new synthetic methods and innovative technologies are always considered.

- ANALYTICAL RESEARCH

A full and detailed characterization of products and intermediates is undertaken by a team of skilled technicians, in order to ensure the highest quality requirements for the products under development and the analytical processes that support them.

- PROCESS DEVELOPMENT

Rigorous definition of the process parameters and conditions, together with a complete safety assessment, are the requirements for an easy scale-up, even with so called standard chemistry.

- PROCESS INDUSTRIALIZATION

R&D team supports all the scale-up phases until the process is validated and the first industrial batches are successfully produced, ensuring a complete and smooth know-how transfer from R&D to the production teams.

PROCESS R&D CHEMISTRY

Process chemistry deals with the development and optimization of a synthetic Scheme and pilot plant procedure to manufacture compounds. Process chemistry is different from medicinal chemistry, which is the branch of pharmaceutical chemistry that deals with designing and synthesizing new molecules on small scale in the early drug discovery phase.

Medicinal chemist's goals are synthesising a large number of compounds as quickly as possible from easily tunable chemical building blocks (usually for SAR studies). In contrast, process chemists deals with the identification of new chemical process that at least in theory should finally result safe, cost efficient, "green," and reproducible. Greater flexibility for process design and development typically resides within Process R&D, often chemists must devise creative synthetic solutions that eliminate heavy functional group manipulations and oxidation/reduction steps.
Companies are aiming to accelerate API development by designing more robust, viable, and cost-effective manufacturing processes in early development with the goal of transferring them to manufacturing operations effectively and efficiently with minimal changes. Due to the high project attrition rate in early development, however, these optimization efforts are typically balanced in order to avoid unnecessary 'frontloading'. In order to achieve this goal, it is important that Process R&D chemists have a culture and awareness of the underlying principles of a "Good Chemical Manufacturing Process".
Kilogram-scale synthesis concerns process R&D, where speed, safety, quality control, and economics become important parameters. At this point, several disciplines, including Process Chemistry, Analytical Chemistry, Technical Outsourcing, Process Engineering, and Safety, Regulatory Compliance, and scale-up groups such as Kilolab and Pilot Plant are essential for the design and

development of an economical and scalable route. The API development and supply chain at Dipharma Francis consists of three major chemistry units: Process Research, Process Development, and Process Industrialisation. The aim of Process R&D chemists in Process Research is to secure the first supplies of API for the client's needs, as bioequivalence and quality studies, while defining a route of synthesis that is scalable, safe, robust, and economical and that guarantees the freedom to operate. The project transfers from Process Reseach to Process Development, which evaluates the scalability and further optimizes the transferred process and then validates and transfers the process to Process Industrialisation.

Process Industrialisation supports large-scale manufacturing activities, conducts transfer batches in order to demonstrate the optimized chemical procedure from Process Development, runs primary stability batches for drug substance, performs validation batches, and provides market supplies after product launch. Due to the handovers between the involved chemistry units, a complex picture in terms of route design and selection arises. Comparing different routes of synthesis is challenging due to the diverse viewpoints and different business drivers of the three chemistry units. In addition, elegance and efficiency in terms of molecular design are difficult to reduce to objective and measurable Figures. However, it is understood that the quality of a manufacturing process will ultimately be measured by its financial impact on the business, (i.e. the total production cost of the API). Manufacturing of an API typically involves a multistep chemical synthesis utilising external and internal multipurpose plants. The total API product cost comprises two major areas, namely the material cost and the conversion cost (including waste disposal).

While the material cost constitutes a single category representing the expenses of all chemicals including raw materials and outsourced intermediates, the conversion cost is subcategorized into several readily quantifiable process efficiency and reproducibility criteria. The subsequent section describes the key criteria that have

been presented[10] to evaluate the relative quality of chemical manufacturing processes. The criteria presented herein are a helpful optional tool to assess the process quality or to identify areas for further process improvements.

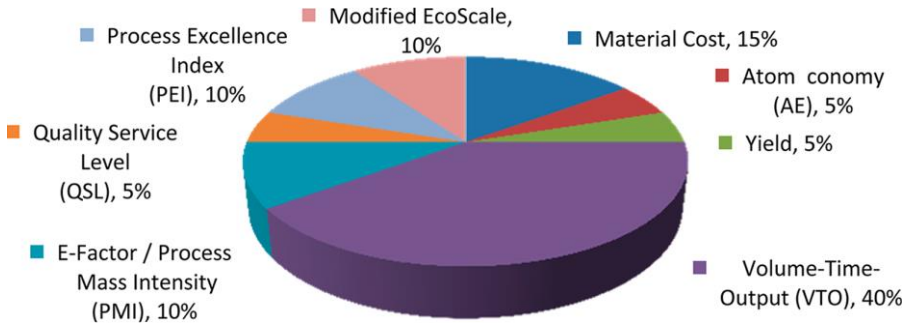


Figure 4: weighting of process assessment criteria

Material Cost.

The material cost is calculated from the cost of all externally procured raw materials, intermediates, reagents, solvents, and catalysts and is highly scale dependent. The selection of an economical raw material strategy is critical for synthetic route design, and Process R&D programs are usually guided by the economical material cost analysis of potential routes.

The material costs depend on the availability of raw materials, the level of outsourcing for intermediates, and the required quantities.

API structure-forming materials can be divided into three categories:

(1) Intermediate: the chemical compound is proprietary to the company and is produced according to an internal technology package consisting of a chemical procedure and analytical specifications by selected custom manufacturing

[10] Dach, R.; Song, J. J.; Roschangar, F.; Samstag, W.; Senanayake C. H.; *Org. Process Res. Dev.*, **2012**, *16*, 1697 – 1706.

companies. In the early development phases the unit cost for such custom-made intermediates is normally high.

(2) Raw material: the chemical is readily available from several commercial suppliers on 10−1000 kg scale and the specifications and method of synthesis may be adapted to those of the suppliers. In general, these raw materials are more economical than the custom-synthesised intermediates.

(3) Commodity chemical: this is the best case in terms of economics.

Conversion cost factor.

The conversion cost in a production facility is derived from time- and equipment-related costs for utilities, depreciation, maintenance, labor, and overhead and waste disposal.11

Atom Economy (AE).

Atom economy12 (AE) is defined as a measure of how many atoms of the starting/raw materials are utilized in the final product, and is calculated as the quotient of the molecular weight (MW) of the product and the sum of the MWs of the raw materials.

Yield.

The yield, also referred to as chemical yield and reaction yield, is the amount of product obtained in a chemical reaction. While AE shows the efficiency of a synthetic strategy, yields represent the actual productivity of the steps measuring the effectiveness of a synthetic step.

When expensive reactants, starting materials, reagents, or solvents are used, the yield has more impact on the overall cost. Consequently, one synthetic design consideration is to use these components as late as possible in the synthesis, in order to minimize their impact on the overall cost. Once the route of synthesis has been selected, all steps will be subjected to systematic and exhaustive optimization with respect to yield by utilizing tools such as design of experiment (DOE).17

Volume−Time−Output (VTO).

VTO is defined as nominal volume of all reactors (m^3) multiplied by the hours per batch, divided by the output per batch in kg (eq 3, determination of VTO). If the resulting number is <1, the process for the chemical step is acceptable; if the number is far above 1, the process needs to be improved.

Environmental Factor (E-Factor)/Process Mass Intensity (PMI).

Procedures for the handling of chemical waste are undergoing significant and continuous changes commensurate with society's heightened awareness and concern for the environmental protection. These changes are resulting in ever-increasing regulations and a corresponding escalation of incurred costs for waste disposal. Consequently, the cost of waste disposal has become a significant part of overall production cost and must be incorporated as an evaluation criterion for any chemical process.

The E-factor calculates the actual amount of generated waste relative to the amount of desired product isolated, and is defined as everything but the desired product. Inherently, the E-factor takes into account the chemical yields.24

While the E-factor calculates the ratio of kg of waste to kg of product, the process mass intensity (PMI) is the ratio of the total kg amount of incoming materials to kg product. When calculating the E-factor or PMI, all materials used in the synthesis are considered, including workup solvents and water.

Process Excellence Index (PEI).

This reproducibility or robustness criterion is a particularly useful tool for Chemical Production processes. The PEI is an indicator for the performance of the process and is utilized to evaluate the performance in terms of yield and cycle time of diverse operations.

AIM OF THE THESIS

The thesis is centred on the ideation and the development of new processes for the industrial production of already existing APIs. Essential requisite of a new process to be successful deals with the legal aspect of the freedom to operate. This means that the new synthetic route must not infringe the rights of third parties namely of third parties patents which are in force both in the country where the API will be produced and in the country where it should be sold. The chemistry involved in the new process should be compatible with Dipharma Francis industrial facilities, and possibly should take advantage of peculiar facilities of the company The process developed during feasibility study should be easily ready to be scaled up, reaction should be performed with industrially appropriate solvents and concentrations. The molar ratio of reagents would be lowered to the minimum amount in order to avoid unwanted waste and cost inefficiency. Products should be isolated and purified only if it is needed and preferably by crystallisation or distillation avoiding any kind of chromatography. The creation of an innovative synthesis that allows to prepare the API in an economical and profitable way to ensure good position in the market is of course essential as well. Of course, if the process will be innovative it could be claimed in a patent application. During my Ph.D. experimental work I have been involved in syntheses of different APIs, anyway most of the time had been spent working on a new process for Silosdosin which will be discussed herein.

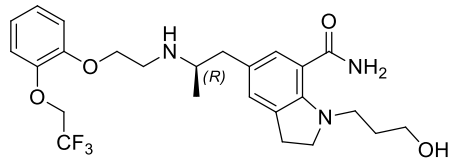


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Figure 5: silodosin structure

SILODOSIN

1 Introduction

The project that was entrusted to me during my PhD thesis in Dipharma dealt with a new synthetic process for the industrial synthesis of Silodosin.
As already said in the preface, the new process must be non-infringing of third parties patents currently in force. The process should be convenient, eligible to industrialisation, cheaper than the existing ones, and if it is possible innovative, to be protected by filing a new patent application.

Silodosin (Figure 1.1) is an Active Pharmaceutical Ingredient claimed in the patent JPH06220015[11] filed by Kissei Pharmaceuticals Co., Ltd in 1992. The API is a medication for the symptomatic treatment of Benign Prostatic Hyperplasia (BPH).

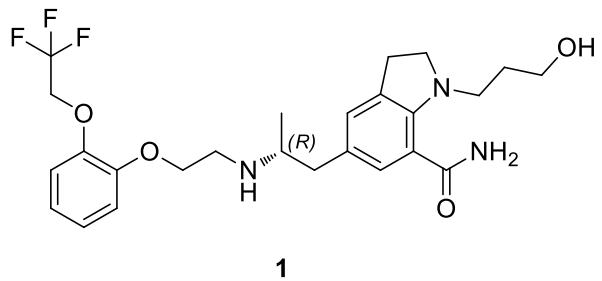

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Figure 1.1: Silodosin structure

Silodosin received the market authorisation in Japan in January 2006 and it has been marketed, with the trade name Urief®, in cooperation with Daiichi Sankyo Pharmaceutical Co., Ltd. since May 2006. The manufacturer markets Silodosin in two different formulation capsules, 4 mg and 8 mg. The 4 mg capsule is principally marketed in USA and Japan while the 8 mg capsule in Europe.
Kissei promoted international development of its original product silodosin through outlicensing.

[11] Kitazawa, M.; Saka, M.; Okazaki, K.; Ozawa, M.; Yazaki, T.; Yamagishi, R.; Kissei Pharmaceutical Ltd, (**1992**), Indoline Derivative, Japan: JPH06220015.

In north America (USA, Canada and Mexico) the production and market share have been licensed to Watson Pharmaceuticals, Inc.. The company submitted the New Drug Application for silodosin to the United States Food and Drug Adminitration on February 2008, which definitively approved it on the October of the same year (commercialised as Rapaflo®).

In Europe silodosin received market authorisation from the European Agency for the Evaluation of Medicinal Products (EMEA, i.e. now European Medicines Agency EMA) in November 2009 and Kissei has licensed Recordati for commercialization of the drug in the whole of Europe (45 countries) and for a further 18 countries in the Middle East and Africa.

Choongwae Pharma Corporation obtained the market authorisation in April 2008 for South Korea commercialisation, while Daiichi Sankyo Pharmaceutical Co., Ltd in China and Synmosa Biopharma Corporation in Taiwan.

1.1 ACTIVITY AND THERAPEUTIC INFORMATION

Silodosin is an α1-adrenoreceptor antagonist used as therapeutic agent for the treatment of symptoms, especially dysuria, of benign prostatic hyperplasia.

Benign prostatic hyperplasia (BPH) is a common problem among men after the age of 40 years. The prevalence of BPH increases from approximately 50% at 60 years to 90% in men older than 85 years.[12] It is a non-malignant enlargement of the prostate due to cellular hyperplasia of both glandular and stromal elements. As the prostate increases in size it may exert pressure on the lumen of the prostatic urethra, resulting in a gradual obstruction to urine flow. Studies have shown that urinary flow rate and prostate size usually do not correlate with the severity and number of symptoms, which vary from subject to subject. BPH is the most important cause of lower urinary tract symptoms (LUTS) in males, and 50% of men with BPH complain of LUTS.[13] Male LUTS can be classified into three categories: voiding or obstructive (hesitancy, slow stream, intermittency, incomplete emptying), storage or irritative (frequency, urgency, nocturia, urge urinary incontinence), and postmicturition (postvoid dribbling). These conditions have a significant impact on overall quality of life. Histologically, BPH develops in the periurethral or transitional zone of the prostate through an increase in the stromal component of the gland, and, to a lesser degree, epithelial cells.[14] This proliferation leads to urethral constriction. The pathogenesis of BPH is still not well understood, but involves several complicated pathways, including inflammation, apoptosis, and cellular proliferation. Treatments for BPH include watchful waiting for mild LUTS, pharmacologic therapies (α1-adrenergic receptor antagonists and/or 5α-reductase inhibitors) for moderate to severe LUTS, and surgery for severe LUTS. Widespread in the lower urinary tract are α_1-adrenergic

[12] Girman, C. J.; Jacobsen, S. J.; Rhodes, T.; Guess, H. A.; Roberts, R. O.; Lieber, M.M.; *Eur. Urol.*, **1999**, *35*, 277 – 284.
[13] Parsons, J. K.; Bergstrom, J.; Silberstein, J.; Barrett-Connor, E.; *Urology*, **2008**, *72*, 318 – 321.
[14] Andersson, K. E.; *Int. J. Clin. Pract. Suppl.*, **2006**, *151*, 8 – 16.

receptors (AR). However, three α_1-AR subtypes (α1A, α1B, and α1D) are described in human tissues, and α_{1A}-AR is the main regulator of smooth muscle tone in the bladder neck, prostate, and prostatic urethra[15]. Approximately 75% of α_1-AR in the prostate belong to the α_{1A} subtype. Therefore, antagonism of this receptor can lead to an improvement in urinary symptoms via relaxation of the lower urinary tract. Moreover, the relief of LUTS mediated by α-blockers is mainly explained by antagonism of the α_{1A} subtype. The α_{1B} subtype is widely found in vascular smooth muscle, thus blocking these proteins and causing orthostatic hypotension. The α_{1D} subtype is predominant and functional in human epicardial coronary arteries, and its inhibition might mediate coronary vasodilatation. To reduce this cardiovascular side effect, α_1-AR inhibitors with higher selectivity for the α_{1A} subtype have been developed.

Prostate contraction is known to be the main contributor to LUTS in BPH, and is predominantly mediated by α_{1A}-AR . In contrast, all α_1-AR (α_{1A}, α_{1B}, α_{1D}) are implicated in blood vessel contraction[16]. Consequently, a highly selective α_{1A}-AR drug can lead to better treatment and fewer cardiovascular side effects than a nonselective drug. The quinazoline α-AR blockers (alfuzosin, doxazosin, and terazosin in Figure 1.2) are nonselective drugs with similar affinity for all α_1-AR, whereas tamsulosin preferentially blocks α_{1A} and α_{1D}-AR, with a 10-fold greater affinity than for α_{1B}-AR

[15] Andersson, K. E.; Lepor, H.; Wyllie, M.G.; *Prostate*, **1997**, *30*, 202 – 215.
[16] Murata, S.; Taniguchi, T.; Muramatsu, I.; *Br. J. Pharmacol.*, **1999**, *127*, 19 – 26.

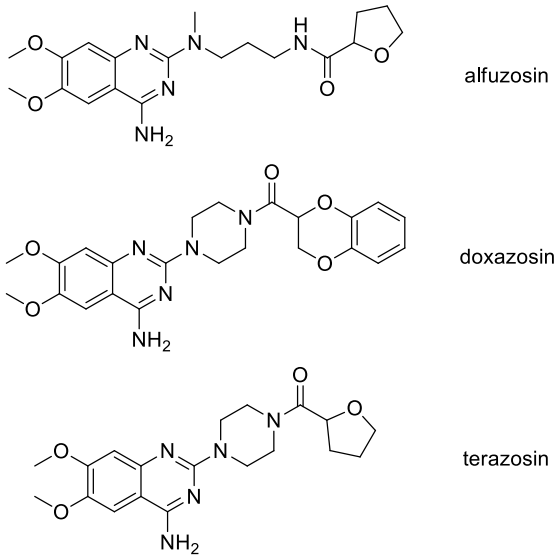


Figure 1.2: Quinazoline drugs

In contrast, silodosin is highly selective for α_{1A}-AR, with a 162-fold greater affinity than α_{1B}-AR and about a 50-fold greater affinity than for α_{1D}-AR. The weak cardiovascular effects of silodosin have been demonstrated in many in vivo models. One showed better uroselectivity with silodosin compared with tamsulosin and prazosin in decerebrate dogs. Moreover, this study also showed that the dose required to reduce blood pressure by 20% was about eight fold greater with silodosin than tamsulosin, and about four fold greater than prazosin after intravenous injection. In another study in dogs, silodosin did not affect blood pressure, heart rate, or electrocardiographic findings at therapeutic doses.

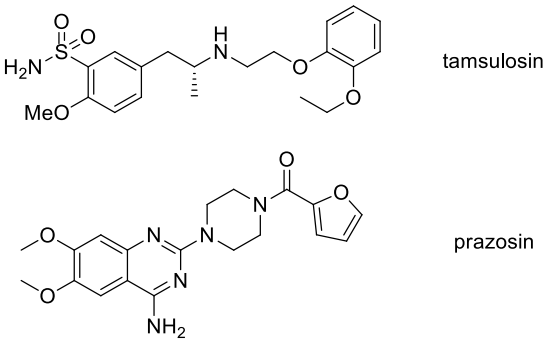


Figure 1.3: BPH family drugs

Silodosin selectively affects the prostate, the urethra, and the trigone of the urinary bladder in the lower urinary tract as a. In particular it reduces urethral resistance by preferentially binding to the alpha (1A) receptors that mainly exist in the prostate, thereby improving dysuria associated with BPH. Compared to previous drugs, Silodosin has features to improve urinary outlet obstruction quickly after dosing and to improve not only symptoms in urinary voiding but also symptoms in urinary retention.

1.2 SILODOSIN STATE OF ART

As said before silodosin will become in the next future a generic product, in order to develop a new synthesis, it is essential to know all the limitations due to third parties patents. For this reason we felt it was important to first prepare a critical overview of the existing syntheses of Silodosin in order to plan how to face the retrosynthetic analysis and conceive a new non-infringing process. Extensive literature research has been done including both patents and scientific papers. We focused our attention to claims, limits and methodologies used in every synthesis. Particular attention has been paid to the patents claims, because some intermediates, processes and even crystalline forms could be protected.

Silodosin was claimed[11] as product in the Japanese patent JPH 06220015. Later the patent was extended in US 5387603 and in EP 600675. A claim in the patent refers to silodosin and to its general Markush formula, but no production process had been claimed in the patent.

The synthesis described in the product patent is a classic medicinal chemistry route, a critical analysis reveals its inapplicability to the industrial production. This is mainly due to the use of expensive, toxic and hazardous reagents and also for the use of unsuitable and complex reactions. An essential point which emerges by a critical analysis not only of the first synthesis described in the Japanese patent but also in all the others approaches that will be discussed later is that all the synthesis are convergent. This is mainly due to the fact that the molecular structure of Silodosin displays two different molecular scaffolds. The first one has an indoline structure (**A**), while the second one has a catechol scaffold (**B**) linked together by a chiral amine functionality (Figure 1.4).

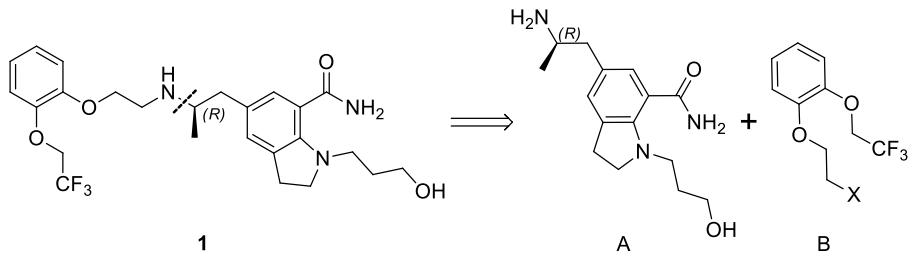


Figure 1.4: Silodosin two main syntons

Catechol scaffold **B** has a more simple structure than trisubstituted indoline **A** and it will be studied from the patent point of view in the next section. Indoline scaffold **A** shows a much more complex structure because of its three different substituents and probably for this reason, most of the literature is focused on the indoline scaffold synthesis.

The disconnections on the indoline structure (Figure 1.5) are situated on position 1, 5 and 7. Position 1 substituent is a C_3 alkyl chain with a terminal hydroxy group, substituent in 5 position is a stereodefined omobenzylic amine (i.e. *R* enantiomer) while in position 7 there is a primary amide group.

Introduction and functionalization of the substituent in position 5 is crucial for the synthesis due to the complexity of the chemical transformations involved to form stereodefined amine in the omobenzylic position. Therefore, it is the main topic of already existing patents.

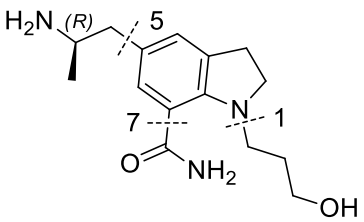


Figure 1.5: Indoline moiety disconnections

From a retrosynthetic point of view, two main approaches have been followed in literature. The first approach makes use of indoline as a nucleophile (synthon C), while the second approach introduces the indoline scaffold using an indoline based reagent employed in the reaction as an elctrophile (synthon D).

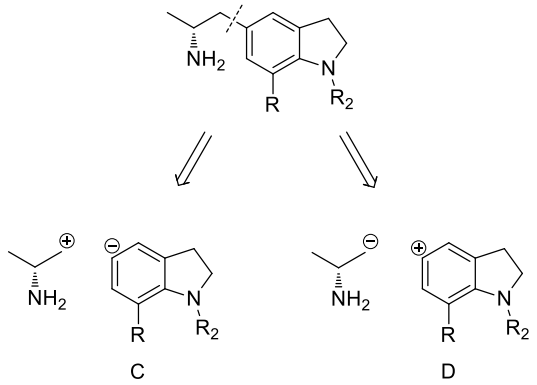


Figure 1.6: Indoline synthons

From a synthetic point of view the nucleophile synthon (C) could be an indoline derivative unsubstituted in position 5, used in an electrophilic aromatic substitution. While the electrophile synthon (D) could be an indoline scaffold substituted in position 5 with a halogen atom or a sulfonate group reacting in a metal catalyzed organometallic reaction. Below a critical review about the main relevant patents will be presented which takes into consideration this two different approaches.

1.2.1 Indoline scaffold (Part A): Nucleophilic indoline reagent

As previously stated, using a theoretical indoline based nucleophilic synthon (C) basically means using an indoline derivative unsubstituted in position 5, in electrophilic aromatic substitution such as acylation, formylation and alkylation reactions or using organometallic nucleophiles as organolithium and Grignard reagents.

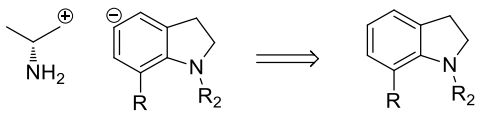


Figure 1.7: The synthetic equivalent of nucleophilic synthon C

In silodosin product patent JPH 06220015 the substituent in position 5 has been introduced *via* Friedel-Crafts[17,18] (FC) acylation (Figure 1.8). Successively some other patents[19,20] and a recent paper[21] have been published which describe a synthetic approach to silodosin using FC reactions as the key reaction for the introduction of a substituent in position 5.

[17] Crafts, J. M.; Ador, E.; *Ber.* **1877**, 10, 2173-2176.
[18] Metivier, P. *Friedel-Crafts acylation* (eds. Sheldon, R. A.,Bekkum, H.) (Weinheim: Wiley-VCH, New York, **2001**)
[19] Pingyue, D.; Fu J.; (**2009**), novel preparation method for silodosin, China: CN101759627.
[20] Joshi, S.; Bhuta, S.; Talukdar, S.; Sawant, S.; Venkataraman, D.; Pise, A.; Metkar, S.; Chavan, D.; Luthra, P. K.; Sandoz AG, (**2009**), Process For The Preparation Of Indoline Derivatives And Their Intermediates Thereof, WO2011030356.
[21] Barve, I. J.; Chen, L. H.; Wei, P. C. P.; Hung, J. T.; Sun, C. M.; *Tetrahedron,* **2013**, *69*, 2834-2843

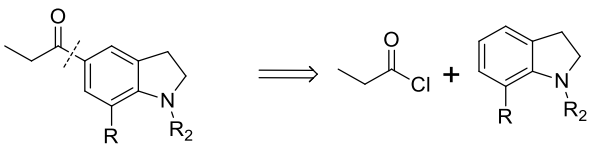
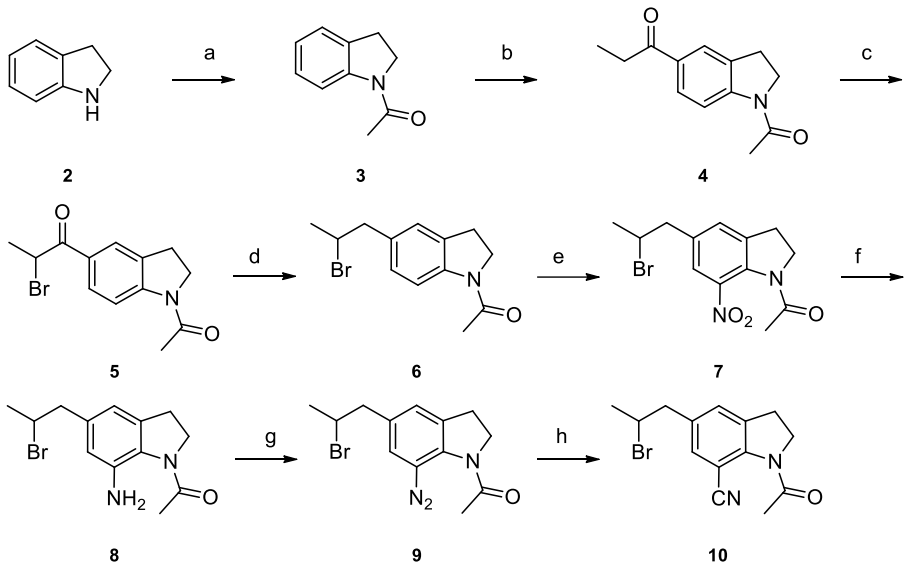


Figure 1.8: FC retrosynthetic disconnection

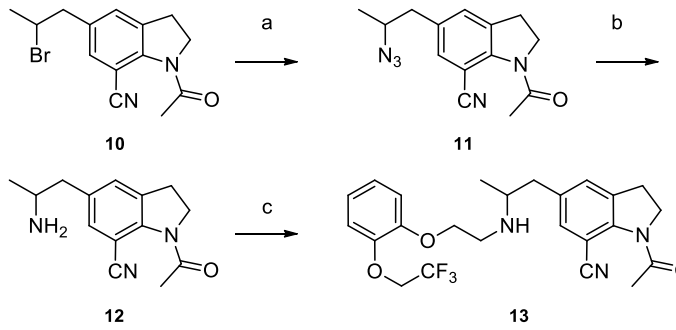
The Friedel Craft reaction described in JPH 06220015 is performed using commercially available indoline **2** and propionyl chloride to give selectively derivative **4**, functionalised in position 5. The ketone **4** is then brominated in α position and reduced to CH_2, using the TFA/triethylsilane reducing system, giving intermediate **6** in 60% yield over two steps. The functionalisation in position 7 is obtained via nitration, reduction of nitro compound **7** to amine **8**, and subsequent convertion into nitrile **10** *via* diazonium salt formation and Sandmeyer reaction using toxic CuCN. Derivative **10** functionalized either in position 5 and 7 is thus obtained in 8 synthetic steps (Scheme 1.1).



Condition: a. AcCl, TEA, Toluene; b. propionyl chloride, $AlCl_3$, CH_2Cl_2; c. PTBr, THF; d. Et_3SH, TFA; e. HNO_3, AcOH; f. PtO_2, H_2, EtOH; g. $NaNO_3$, HCl; h. CuCN, NaCN, H_2O/Toluene.

Scheme 1.1: Intermediate 10 synthesis

Derivative **10** is then treated with sodium azide to yield (Scheme 1.2) the azide **11** which is reduced to racemic primary amine **12** in 44% yield over 4 synthetic steps.



Condition: a. NaN_3, CARBITOL/H_2O; b. H_2, Pd/$BaSO_4$, H_2O; c. **14** or **15**, $NaHCO_3$, EtOH.

Scheme 1.2:Racemate 13 synthesis

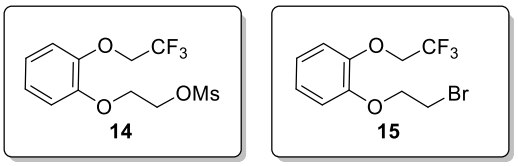
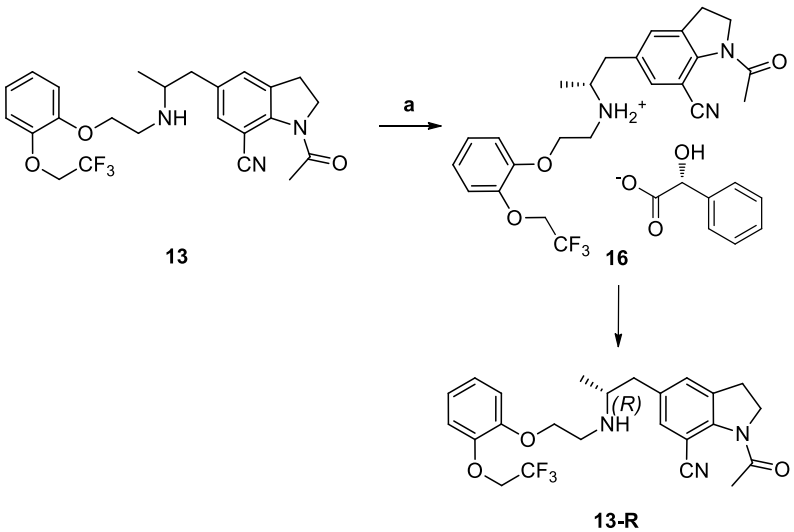


Figure 1.9: Compounds 14 and 15

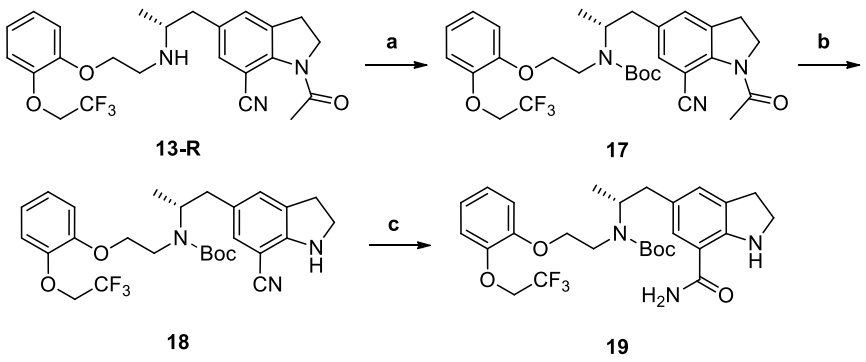
Primary amine **12** is then alkylated using mesylate **14** or bromide **15** (Figure 1.9) bearing part **B** of silodosin giving secondary racemic amine **13** (Scheme 1.2). The optically pure amine **13-R** is obtained via traditional diastereomeric salt resolution using L-mandelic acid as resolving agent (Scheme 1.3). Crystallisation and subsequent cleavage of the diastereomeric salt give the enantiopure amine **13-R** in poor 11% yield. The diastereomeric resolution has been successively optimised by Sun and coworkers[21] who obtained a 34% yield by using ultrasound-assisted diastereomeric crystallisation.



Condition: a. L-mandelic acid, MeOH; b. $NaHCO_3$, EtOAc, H_2O, 11%.

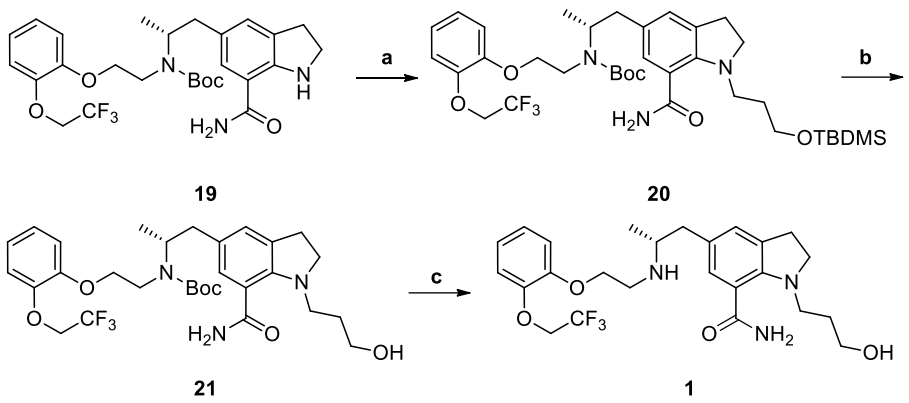
Scheme 1.3: Diastereomeric salt resolution of racemate 13

The optically pure amine **13-R** is then protected as *tert*-butyl carbamate (Boc) and the acetyl group is hydrolysed to obtain the indoline free base **18**. The nitrile function of intermediate **18** is converted into the final carboxyamide using H_2O_2 / NaOH in DMSO giving derivative **19** (Scheme 1.4).



Scheme 1.4: Enantiopure 19 synthesis

Compound **19** is then alkylated using NaH as base and an activated form of propanediol protected on the terminal hydroxyl group as TBDMS (tert-butyldimethylsilyl ether). The final steps deals with the removal of the two protecting groups and give final silodosin after 21 synthetic steps in an overall yield of less than 0.5% (Scheme 1.5).



Condition: a. NaH, TBDMS$(CH_2)_3$Cl, DMF; b. TBAF, H_2O/Toluene; c. HCl, MeOH

Scheme 1.5: Silodosin synthesis

The process presented here yields silodosin in a very low overall yield and shows some problematic chemical steps. The use of toxic cyanide salts is usually restricted and discouraged for pharmaceutical productions. The diastereomeric salt resolution gives a very low yield even with the optimised procedure reported by Sun. It is worth noting that many impurities had been generated in the synthesis, in particular the formation of di-alkylated impurity **I-1** (Figure 1.10) which is the object of many patents dealing with silodosin purification.

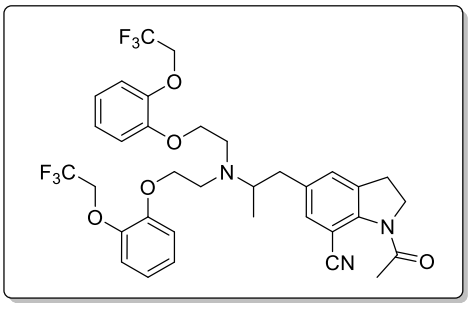
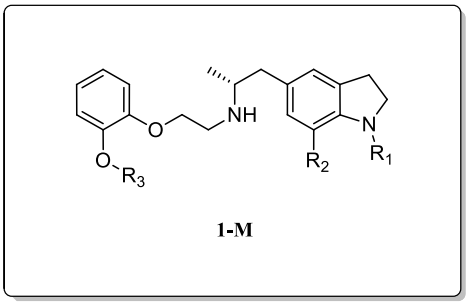


Figure 1.10: Impurity I-1

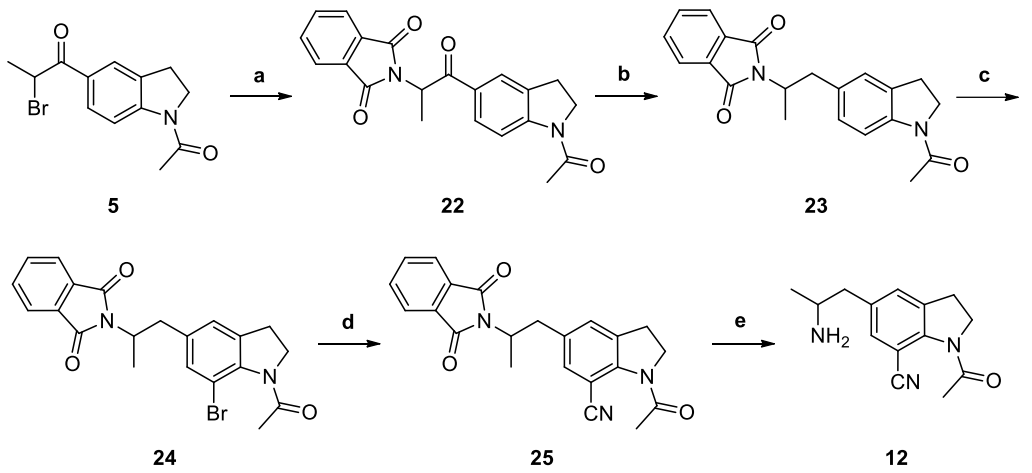
As already stated in this first patent Kissei claimed silodosin itself along with other similar molecules included in the Markush formula **1-M** (Figure 1.11) and their use as treatment for dysuria but the synthetic process was not claimed.



1-M

Figure 1.11: markush formula 1-M claimed in JPH 06220015

In patent literature some other examples using functionalisation in position 5 by Friedel-Crafts acylation can be found. A Chinese patent filed in 2009[19], shows for example a slight modification to Kissei synthetic route focused to reduce the number of synthetic steps and to increase the yields. A modification involves the use of the phthalimide potassium salt instead of sodium azide to install the primary amine of **12** (Scheme 1.6). Thanks to the use of the robust phtalimido group conversion of the ketone functional group to CH_2, bromination of position 7 and subsequent substitution of bromine atom with the nitrile function could be obtained without any problem. After the removal of the phthalimide the key trisubstituted primary amine **12** has been obtained.



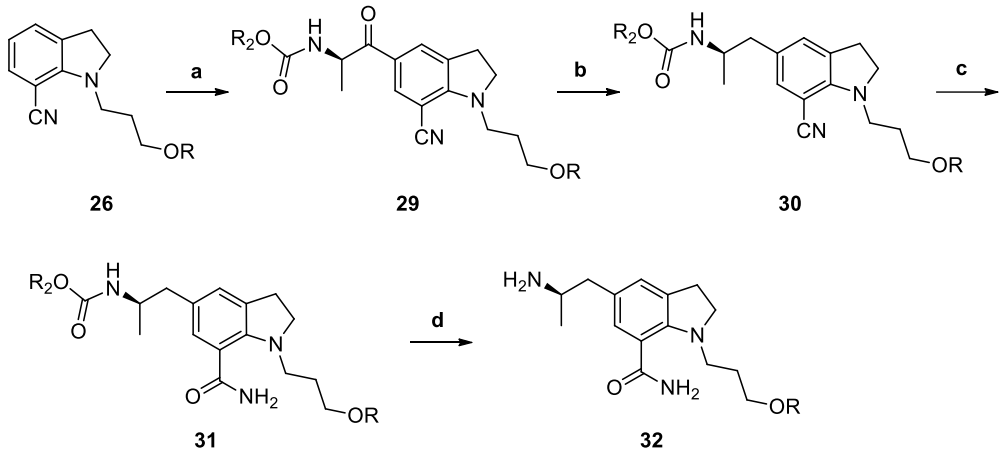
Conditions: a. Potassium phthalimide, THF; b. Et3SH, TFA; c. Br_2, AcOH; d. CuCN, DMF; e. NH_2NH_2, MeOH

Scheme 1.6: Racemate 12 synthesis

These modifications effectively reduce the number of synthetic steps but keep the use of toxic cyanide salt. In addition the use of phthalimide reduces the atom economy of the process.

In this patent the synthetic process has been claimed, but the Chinese application has not been extended in any other country but for China.

Sandoz AG in 2009[20] filed a patent dealing with silodosin synthesis that shows better improvements in the FC reaction and makes use of an enantiopure acyl chloride. Indoline derivative **26** is acylated in position 5 using the acyl chlorides of protected D-alanine aminoacid **27** or **28** (Figure 1.12). The FC reaction gives the enantiopure indoline **29** which is then reduced with TFA/silane reducing system. Conversion of nitrile functional group into carboxyamide, followed by the removal of the carbamate protection gives enantiopure amine **32** (Scheme 1.7).



Conditions: a. **27 or 28,** $AlCl_3/CH_2Cl_2$; b. Silane, TFA, Toluene; c. H_2O_2, NaOH, DMSO; d. KOH, Toluene

Scheme 1.7: Enantiopure intermediate 31 synthesis

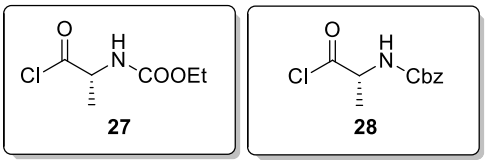
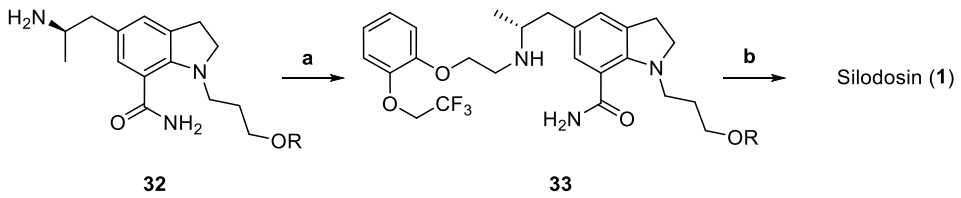


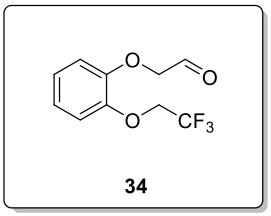
Figure 1.12: Compound 27

Silodosin precursor **33** is finally obtained *via* reductive amination (Scheme 1.8) of aldehyde **34** with amine **32** and removal of the hydroxyl protecting group. (Figure 1.13).



Conditions: a. **34**, Reductive amination; b. Deprotection

Scheme 1.8: Silodosin synthesis



34

Figure 1.13: Compound 34

This process introduces a real innovation in the FC approach to silodosin because the introduction of the stereodefined centre removes the low yielding step of the resolution. Moreover the secondary amine **33** was prepared by a new reductive amination of aldehyde **34** with amine **32**. This reductive amination avoids the formation of impurity **I-1** and aldehyde **34** was a new intermediate when it was disclosed for these reasons Sandoz claimed aldehyde **34**, its preparations and its use for preparing intermediate **33**. Sandoz extended the patent application to all the main countries, Japan, USA and Europe included.

FC acylation revealed an interesting tool to introduce the substituent in position 5 of indoline scaffolds but also the formylation is a well explored reaction to produce intermediates of Silodosin. Vilsmeier-Haack[22],[23] (VH) reaction in particular has been used to introduce substituents both in position 5 and 7 (Figure 1.14). After the introduction of the aldehyde in position 5, the carbonyl group has been used for

[22] Fischer, O.; Muller, A.; Vilsmeier, A.; *J. Prakt. Chem.* **1925**, *109*, 69-87.
[23] Marson, C. M.; *Tetrahedron* **1992**, *48*, 3659 – 3726.

Henry[24,25] or Wittig[26,27] reactions. The scope of subjecting 5-formyl indolines to these reactions was to obtain C_3 alkyl chains already derivatised in the β position.

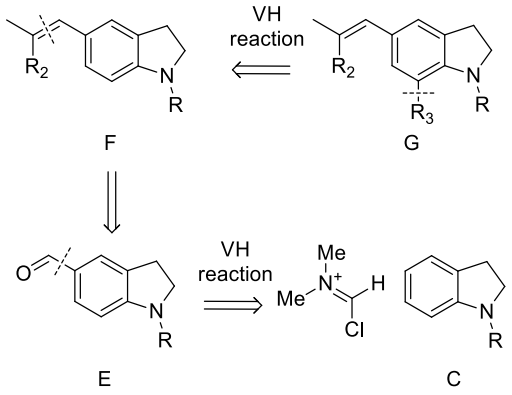


Figure 1.14: Disconnection using Vilsmeier-Haack reaction.

The Henry reaction using nitroethane as nucleophile allows to form intermediate F or G that can be successively converted into several derivatives.[28] In particular compound H has been converted into β-aryl ketone I or β-aryl amine L (Figure 1.15).

[24] Henry, L.; *C.R.Acad.Sci. Ser. C.* **1895**, *120*, 1265.
[25] Luzzio, F. A.; *Tetrahedron* **2001**, *57*, 915-945.
[26] Wittig, G.; Geissler, G.; *Ann.* **1953**, *580*, 44-57.
[27] Murphy, P. J.; Lee, S. E.; *J. Chem. Soc., Perkin Trans. 1* **1999**, 3049 – 3066.
[28] Jacobsen, E.; The nitro-aldol (Henry) reaction. in *The Nitro Group in Organic Synthesis* (ed. Ono, N.), 30-69 (Wiley, New York, **2001**).

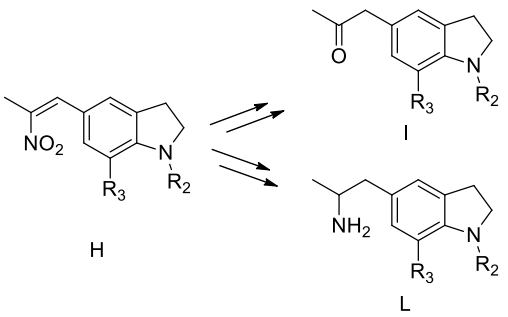


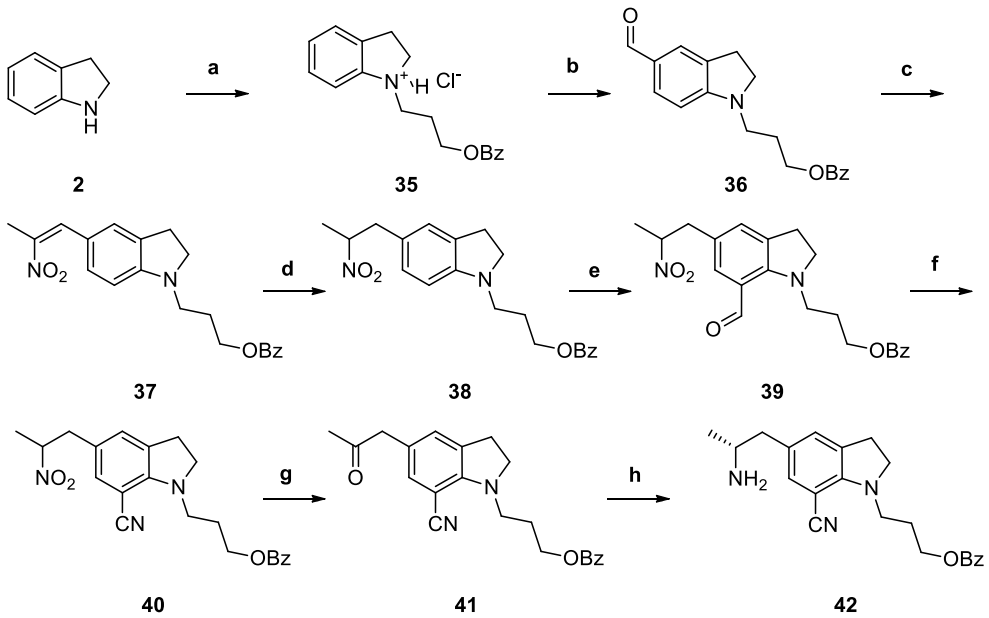
Figure 1.15: Two possible derivatives from Henry reaction

The high versatility of compound G makes this approach the most exploited in the literature. Many patents disclose and claim processes based on VH and Henry reactions. Most of them are light modifications or optimisations of the previous patent. This is due to the ease of the reactions involved if compared with the FC based syntheses.

The first Japanese patent where the VH approach has been reported is JP 2001199956[29][30] from Kissei Pharmaceuticals Ltd. The process starts with the alkylation of indoline **2** using 1-chloropropyl-3-benzoyl ester as alkylating agent, to give N-alkylated indoline **35** which in turn is subjected to the VH reaction to introduce selectively the aldehyde **36** in 5 position in 60% yield over two steps (Scheme 1.9).

[29] Kamijo, T.; Yamaguchi, T.; Teranishi, H.; Tsuchiya, I.; Kissei Pharmaceutical, (**2000**), Method For Producing Optically Active Indoline Derivative And Intermediate For Producing The Derivative, JP 2001199956.

[30] Ranbaxy laboratories Ltd in WO2012014186 presents the same process of JP2001199956 but for the use of methyl propanoate ester as different substituent in the indoline 1 position.



Conditions: a. $Bz(CH_2)_3Cl$, TEA, DMF; b. $POCl_3$, DMF; c. $EtNO_2$, NaOEt, EtOH; d. $NaBH_4$, THF/EtOH; e. $POCl_3$, DMF; f. NH_2OH*HCl, Py, THF, then Ac_2O; g. K_2CO_3, H_2O_2, DMF; h. L-2-phenylglycinol, PtO_2 ,H_2 ,THF.

Scheme 1.9: Derivative 42 synthesis

The carbaldehyde **36** is then reacted with nitroethane in the Henry reaction to form the nitro alkene derivative **37** which in turn is reduced to the saturated derivative **38** At this point using the same VH approach, the aldehyde functionality can be introduced in position 7 giving **39** which is then easily converted into nitrile **40** via formation of the intermediate oxime and dehydration using acetic anhydride.

Derivative **40** is then converted into the β-aryl ketone **41** using the Nef reaction and ketone **41** is reduced into the enantiomerically enriched amine **42** via diastereoselective reductive amination using enantiopure L-phenylglycinol as amine and Adam's catalyst (PtO_2)[31] in H_2 atmosphere as reducing agent. The reaction mixture is then filtered and the catalyst is replaced with Pd/C to perform

[31] Voorhees, V.; Adams, R.; *J. Am. Chem. Soc.*, **1922**, *44*, 1397 – 1405.

hydrogenolysis and obtain primary amine **42**. Resolution of **42** via diastereoisomeric salt formation using tartaric acid as resolving agent yielded enantiopure amine **42** in 45% yield and 97% enantiomeric excess. The patent description ended at this step of the synthesis with an overall yield of 5.5%.

This synthetic route is very smart, easily scalable and yields are reasonable, for these reasons could be the real process employed for the production of silodosin by Kissei Pharmaceutical.

Kissei Pharmaceutical claimed the process to obtain amine **42** using derivative **40** and ketone **41** as intermediate, and the same intermediates **40-M**, **41-M** and **42-M** where R_1 could be a nitrile or an amide and the hydroxyl protecting group R_2 could be aryl, alkyl or ester group.

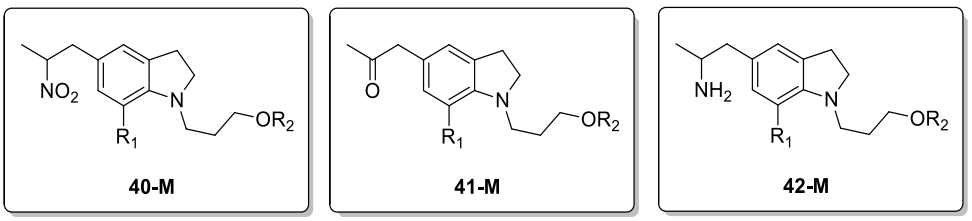
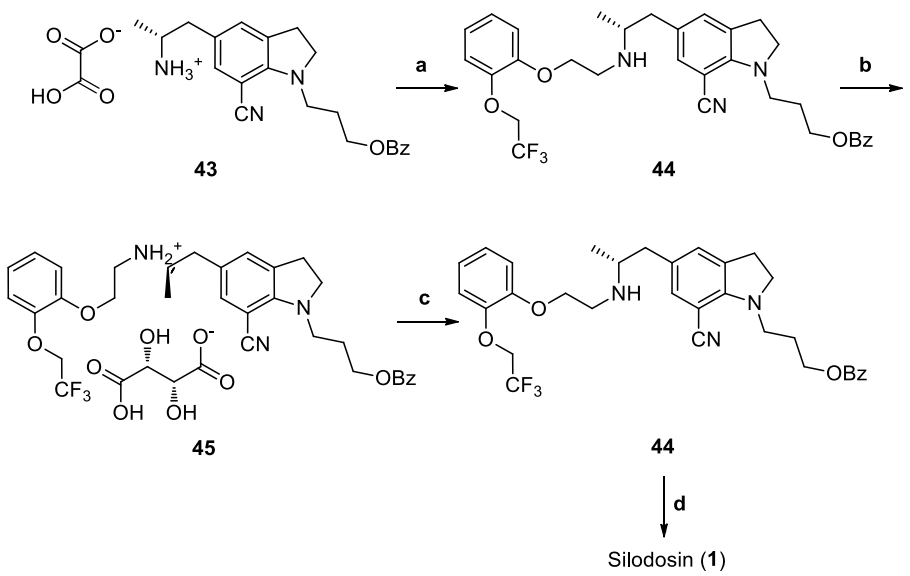


Figure 1.16: Markus structures claimed in patent JP 2001199956

JP 20040313040[32] focuses on the synthesis of silodosin, but starting from the same tartrate salt **43** of amine **42**, previously described. Alkylation of **42** with mesylate **14** gives the secondary amine **44** which is purified by crystallising the tartrate salt **45**.

[32] Kissei Pharmaceutical Ltd, **2004**, Indoline Compound And Process For Producing The Same, Japan: JP20040313040.



Conditions: a. **14**, tBuOH, $NaCO_3$; b. Tartaric acid, IprOH; c. KOH, MeOH/H_2O; d. H_2O_2,NaOH, DMSO

Scheme 1.10: Purification of 44 and Silodosin synthesis

Pure **44** is then converted into silodosin by simultaneous hydration of the nitrile function and hydrolysis of the benzoate ester which yielded, after crystallization, pure Silodosin with an overall yield of 65% over 3 steps. The purification step allows to reduce drastically the amount of **I-1** in the API, from 14% to 0.2%.

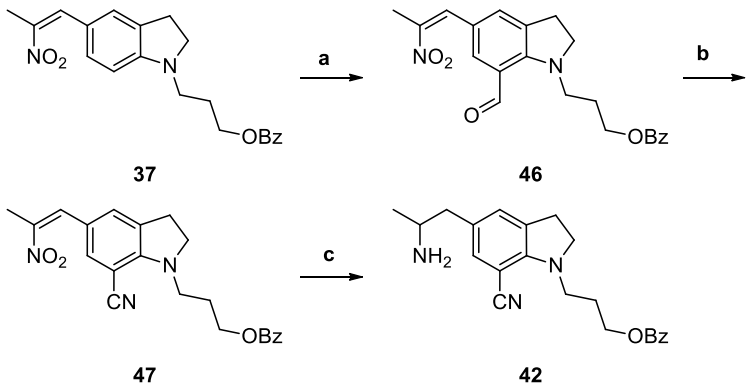
Obviously the main claim of the patent deals with the purification step which gives silodosin with an amount of impurity **I-1** in the range of 0.1-0.3%. This patent has been extended to all the main countries of Europe, America and Asia.[33]

An interesting improvement of the VH approach is disclosed in a Chinese patent[34] filed by Beijing D Venturepharm Laboratories in 2009. The synthesis reported shows

[33] Yamaguchi, T.; Tsuchiya, I.; Kikuchi, K.; Yanagi, T.; Kissei Pharmaceutical, (**2004**), Indoline Compound And Process For Producing The Same, WO2006046499.
[34] Fumin, Z.; Yongjun, C.; Chuanqing, C.; Zhiqiang, Z.; Beijing D Venturepharm Technology Dev Co Ltd, (**2009**), Method for preparing silodosin key intermediate, China: CN102115455,.

the formation of intermediate **47** by performing VH reaction directly on unsaturated nitro alkene **37** to give the aldehyde in position 7 of the indoline scaffold without affecting the double bond. After the conversion of aldehyde **46** into nitrile **47** *via* aldoxime formation and subsequent dehydration, derivative **47** is fully reduced into known primary amine **42** by catalytic hydrogenation.

This patent removes several synthetic steps increasing the overall yield, but at the end racemate amine **42** has been obtained. The patent covers only China and it has not been extended in other countries.



Conditions: a. $POCl_3$, DMF; b. NH_2OH*HCl, Py, THF, then Ac_2O; c. H_2, Pd/C

Scheme 1.11: Racemate 42 synthetic route.

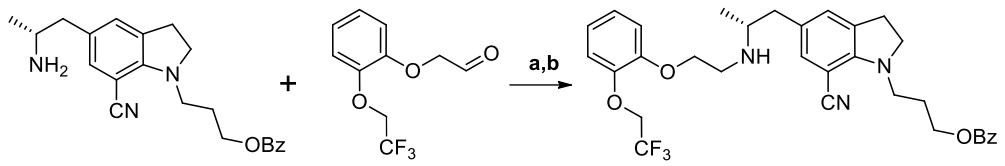
Resolution of racemic amine **42** was plainly reported in WO2011124704[35] filed in 2010 by Ratiopharm. The process starts with the reduction of **37** performed using a hydrogen transfer procedure and the diastereoisomeric salt resolution of **42** is

[35] Gidwani R. M; Kolhatkar M. V.; Ratiopharm GMBH, (**2010**), Process For Preparing An Intermediate For Silodosin, WO2011124704.

performed using L-(+)-tartaric acid, the resolution yields reported in the patent ranges from 17% to a maximum of 23%.

In another process disclosed in WO2012131710[36] by Panacea Biotec Ltd the resolution is performed dissolving the racemate **42** in THF, and an aqueous solution of L-(+)-tartaric acid is added, the process gives diastereomeric salt **40** in a 28% yield with 99% purity and 97% enantiomeric excess.

Sandoz AG in 2011 filed a patent application[37] that is a combination of the process based on VH and Henry reactions with the reductive amination of aldheyde **34** claimed in their previous patent.[20] The process to produce Silodosin performing the reductive amination between the aldehyde **34** and the amine **42** has been clearly claimed. The process gives secondary amine **44** in 18% yield and 85% enantiomeric excess after the resolution with tartaric acid.



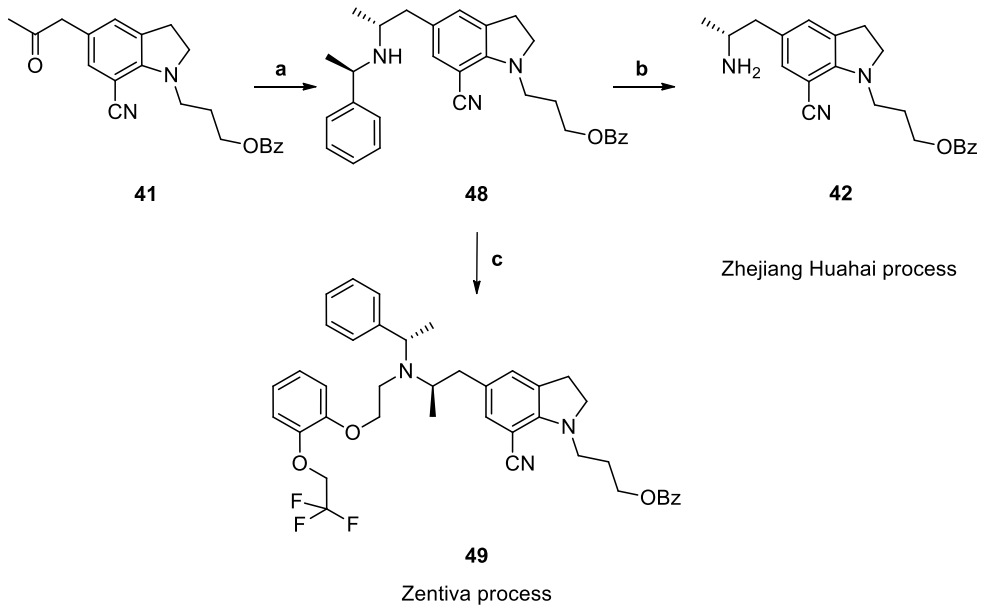
42 **34** **44**

Conditions: a. reducing agents; b. diastereomeric resolution.

Scheme 1.12: reductive amination reported by Sandoz

[36] Jain, R.; Rao, J.; Rao S. M.; Panacea Biotec Ltd, (**2011**), Novel Process For The Synthesis Of Indoline Derivatives, WO2012131710.
[37] Kumar, L. P.; Bhuta, S.; Abhinay, C. P.; Dattatraya, N. C.; Shashikant, D. M.; Sandoz AG, (**2012**), Method For Preparing Silodosin, WO2013056842.

In the process disclosed by Zhejiang Huahai Pharm Co Ltd. [38] in 2008 the reductive amination between ketone **41** and enantiopure (R)-phenyl ethyl amine is described, giving enantioenriched amine **48** which is successively converted into enantiopure amine **42** by catalytic hydrogenation. The whole process has been claimed. (Scheme 1.13). This process does not show any particular improvements being very similar to the one reported by Kissei in JP 2001199956[29] where the diastereoselective reductive amination is performed by using phenylglycinol instead of phenyl ethylamine.



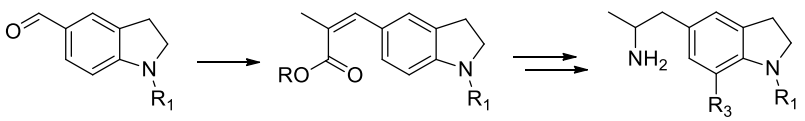
Conditions: a. (*R*)-1-phenylethan-1-amine, BzOH, Adam's catalyst, H_2, THF; b. H_2, Pd/C, HCl, MeOH; c. **14 or 15**, $NaHCO_3$, EtOH.

Scheme 1.13: Zhejiang Huahai and Zentiva processes

[38] Xiaomei, W.; Xiaomei, W.; Zhefeng, W.; Qiang, S.; Huilin, S.; Zhejiang Huahai Pharm Co Ltd, (**2008**), Optical active compound of 1-(3-benzoyloxy-propyl)-5-(2-(1-phenyl ethyl amine) propyl-7-cyano indoline as well as preparation method and application thereof, China: CN101585798.

A slight but smart modification of the reductive amination on substrate **41** is the process reported in CZ 20100836[39] filed by Zentiva in 2010. The process makes use of phenyl ethyl amine in the diastereoselective reductive amination but also as a protecting group in the subsequent alkylation of **48** with mesylate **14**. (Scheme 1.13). Zentiva claimed both compounds **48** and **49** and the process to prepare Silodosin using **48** and **49** as intermediates. The patent has been also extended in WO2012062229.[40]

As already stated, Wittig reaction is the other methodology exploited to functionalise formyl indolines of type E (Scheme 1.14). In fact in this way alkenes M thus obtained can be reduced in enantioselective fashion to give amines L. In literature, two patents have been found, dealing with the use of Wittig type reactions. The first one is JP2002265444 by Kissei Phaemaceuticals Ltd,[41] the second one is WO2013097456 filed by Zhejiang Jiuzhou Pharm Co Ltd in 2011.[42]



E M L

Scheme 1.14: indoline E functionalization using Wittig type reaction

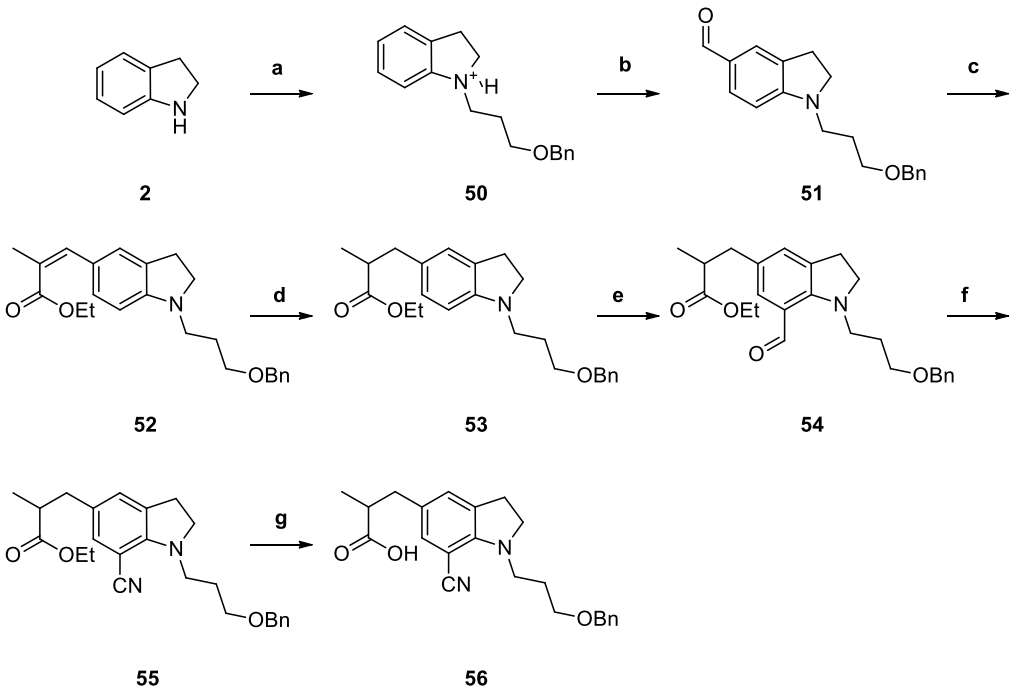
[39] Vlasakova, R.; Hajicek, J.; Slavikova, M.; Zentiva, (**2010**), Process for preparing (-)-1-(3-hydroxypropyl)-5-[(2R)-2-({2,2,2-trifluoroethoxy)phenoxyethyl}amino)propyl]-2,3-dihydro-1H-indole-7-carboxamide, Czech Republic: CZ20100836.

[40] Vlasakova, R.; Hajicek, J.; Slavikova, M.; Zentiva, (**2010**), A Method Of Manufacturing (-)-L-(3-Hydroxypropyl)-5-[(2r)-2-({2,2,2-Trifluoroethoxy)- Phenoxyethyl}Amino)Propyl]-2,3-Dihydro-Lh-Indole-7-Carboxamide, WO2012062229.

[41] Yamaguchi, T.; Takeuchi, H.; Shiobara, H.; Kissei Pharmaceutical, (**2001**),1-(3-Benzyloxypropyl)-5-(2-Substituted Propyl) Indoline Derivative And Method For Using The Same, JP2002265444.

[42] Zhang, B.; Hu, X.; Yan, P.; Zhang, X.; Gao, H.; Li, Y.; Che, D.; Zhejiang Jiuzhou Pharm Co Ltd, (**2011**), Silodosin Intermediate And Preparation Method Therefor, WO2013097456.

In JP2002265444 aldehyde **51** is reacted with triethyl 2-phosphonopropionate in a Horner-Wadsworth-Emmons reaction to give the unsaturated ester **52** in good yield, which successively was converted into ester **53** (Scheme 1.15). The nitrile group in position 7 is introduced *via* the VH reaction to form aldehyde **54** followed by aldoxime formation and dehydration to desired nitrile **55**.

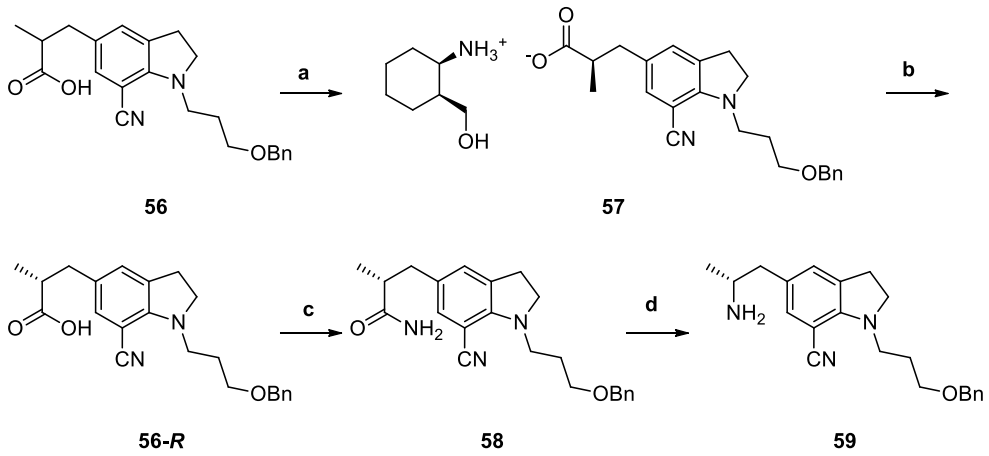


Conditions:a. 3-benzyloxy propylbromide, $NaCO_3$, DMF; b. $POCl_3$, DMF; c. Triethyl 2-phosphonopropionate, n-BuLi, THF/Hex; d. H_2, Pd/C, EtOH; e. $POCl_3$, DMF; f. NH_2OH*HCl, Ac_2O, Toluene/Py; g. NaOH, EtOH/H_2O

Scheme 1.15: synthesis of intermediate 56 disclosed in JP2002265444

The racemic ester **55** is then hydrolysed to **56** that is resolved using (1*S*,2*R*)-2-amino-cyclohexanemethanol obtaining the enantiopure acid **56-R** in 19% yield.

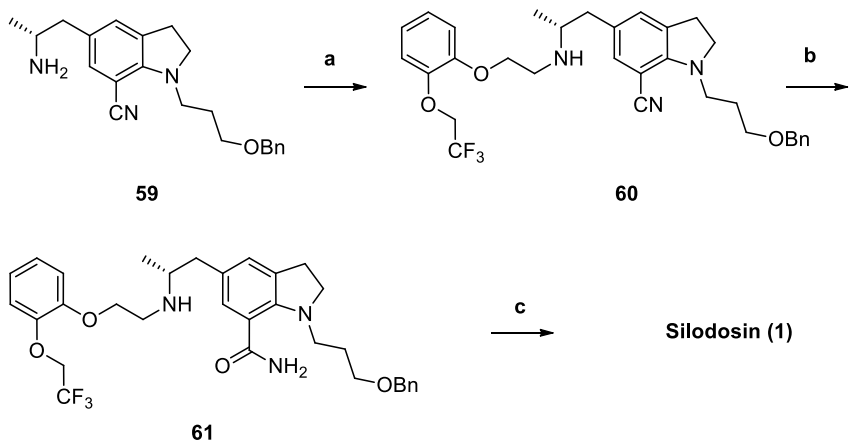
Therefore, the enantiopure acid **56-R** is converted into amide **58** and subjected to Hofmann rearrangement to give amine **59** (Scheme 1.16) with retention of the configuration.



Conditions: a. (1 S,2R)-2-amino-cyclohexanemethanol, active carbon, EtOAc; b. HCl, EtOAc; c. 1,1'-carbonyldiimidazole, NH_3, CH_3CN, d. NaClO, NaOH, H_2O/IprOH

Scheme 1.16: acid 56 resolution and conversion into amine 59

Entiomerically pure **59** is then alkylated with mesylate **14** to form the secondary amine **60** which is subjected to the usual final steps of hydrolysis of the nitrile function to give **61** and deprotection of the benzyl ether to give crude Silodosin which is finally crystallized from ethyl acetate/heptane mixture (Scheme 1.17).



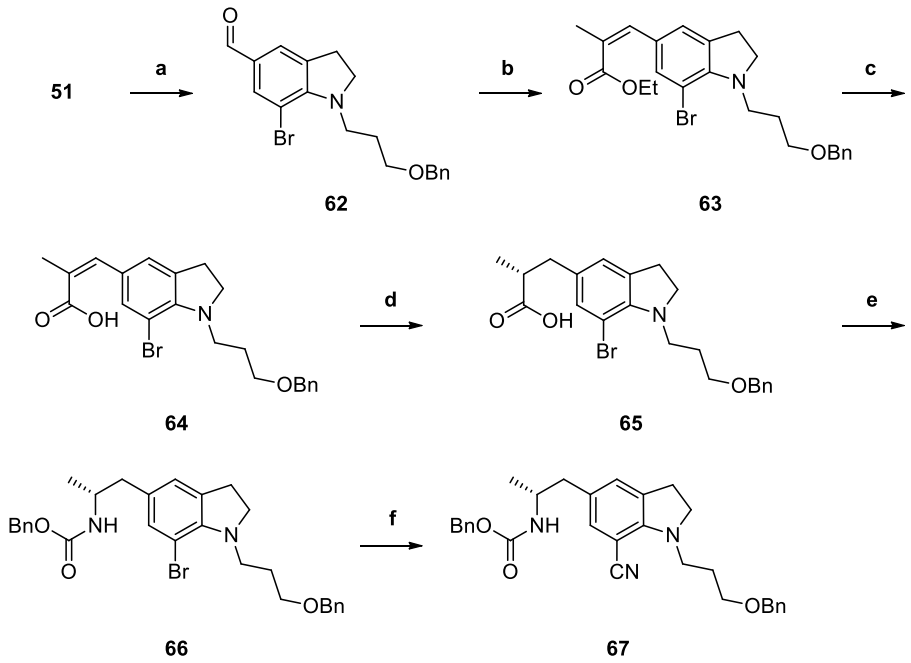
Conditions: a. Na_2CO_3, NaI, **14**, EtOH; b. H_2O_2, NaOH, H_2O; c. H_2, Pd/C

Scheme 1.17: last synthetic steps described in JP2002265444

Kissei claimed the process to obtain silodosin and intermediates **56**, **57**, **56-R**, **58** and **59**. The patent is in force only in Japan and it has not been extended to other countries.

WO2013097456[43] describes only a slight modification of the previous methodology invented by Kissei. The novelty of this process is the achievement of enantiomerically pure **65** obtained by enantioselective catalytic hydrogenation of the unsaturated acid **64** in the presence of *R*-SIPHOX Iridium catalyst. As shown below unsaturated acid **64** is formed from indoline scaffold **52** *via* bromination, Wittig olefination using ethyl 2-(triphenylphosporanylidene)-propionate and hydrolysis to give unsaturated acid **64**. The optimised asymmetric catalytic hydrogenation of **64** gives **65** quantitatively after 50 hours with 97% enantiomeric excess using a substrate/catalyst ratio of 6000 (Scheme 1.18).

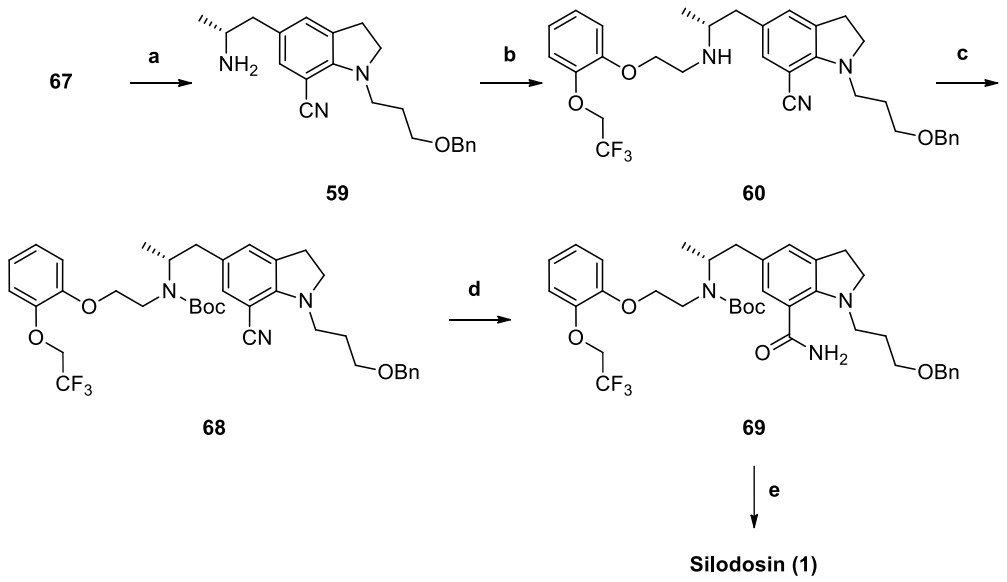
[43] Zhang, B.; Hu, X.; Yan, P.; Zhang, X.; Gao, H.; Li, Y.; Che, D.; Zhejiang Jiuzhou Pharm Co Ltd, (**2011**), Silodosin Intermediate And Preparation Method Therefor, WO2013097456.



Scheme 1.18: Enantioselective synthesis of 68 derivative

The enantioenriched carboxylic acid **65** is then reacted in the Curtius rearrangement conditions to form carbamate **66** which is then subjected to the nitrile introduction in position 7 *via* Rosemund-von Braun reaction to give **67**. Benzyl carbamate protection is removed by catalytic hydrogenation obtaining free amine **59** that is alkylated with mesylate **14** to give the secondary amine **60** which is protected as *tert*-butylcarbamate. Following already described procedures, **69** is first converted into amide **70** which after deprotections gave Silodosin. (Scheme 1.19).

Zhejiang Jiuzhou Pharm Co Ltd claimed the use of Ir-SIPHOX complex in the catalytic enantioselective hydrogenation. The patent was not extended in other countries except China but it has been published in a scientific paper.[44]



Conditions: a. H_2, Pd/C; b. **14**, Na_2CO_3, CH_3SO_3H; c. Boc_2O, CH_2Cl_2; d. H_2O_2, NaOH, H_2O; e. H_2, Pd/C

Scheme 1.19: last steps described in WO2013097456

[44] Yan, P. C.; Zhang, X. Y.; Hu, X. W.; Zhang, B.; Zhang, X. D.; Zhao, M.; Che, D. Q.; Li, Y. Q.; Zhou, Q. L.; Tetrahedron Lett., **2013**, *54*, 1449 – 1451.

The last patent that we are going to describe, making use of the indoline scaffold as a nucleophile is JP2006188470,[45] filed by Kissei Pharmaceutical in 2005. The synthesis disclosed in the patent makes use of a Grignard reagent formed on the position 5 of the indoline scaffold. (Figure 1.17)

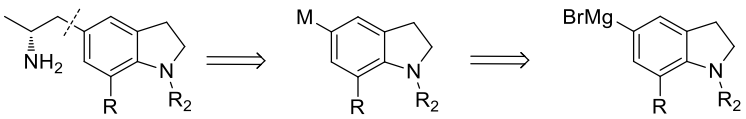


Figure 1.17: Grignard reaction retrosynthetic disconnection

In particular the Grignard reagent prepared from bromide **70**, is reacted with the enantiopure oxazolidinone **71** (Figure 1.18) to form the α-aryl ketone **73** already bearing the desired enantiopure amine protected as Cbz (Scheme 1.20).

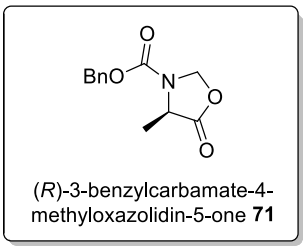
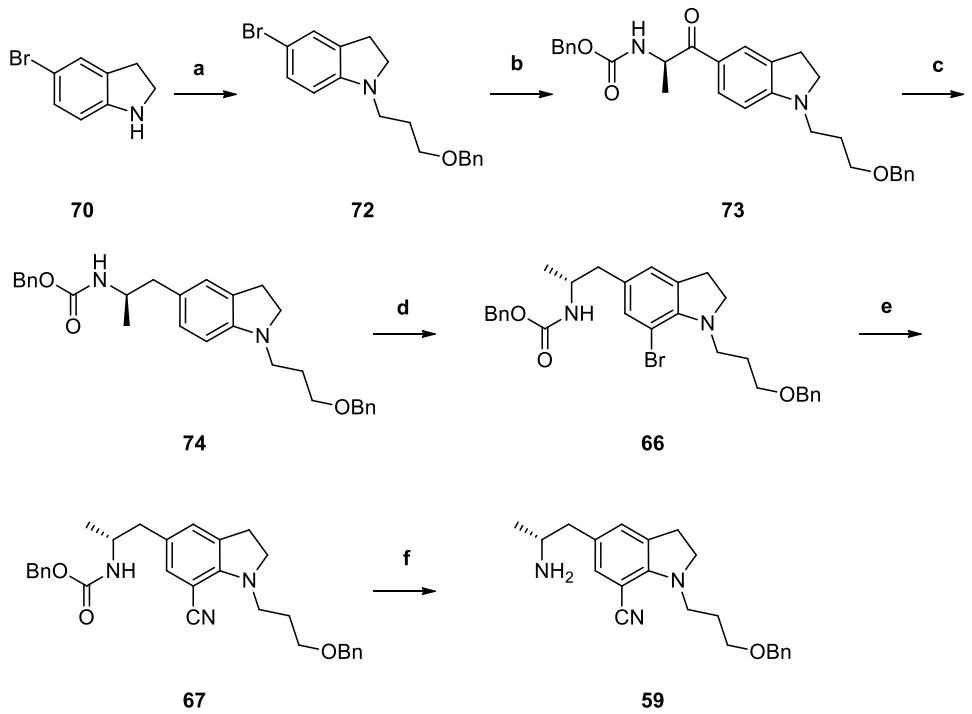


Figure 1.18: enantiopure oxazolidinone reagent 71

[45] Kato, K.; Matsumura, Y.; Kissei Pharmaceutical, (**2005**), Indoline Derivative And Method For Producing The Same, Japan: JP2006188470.

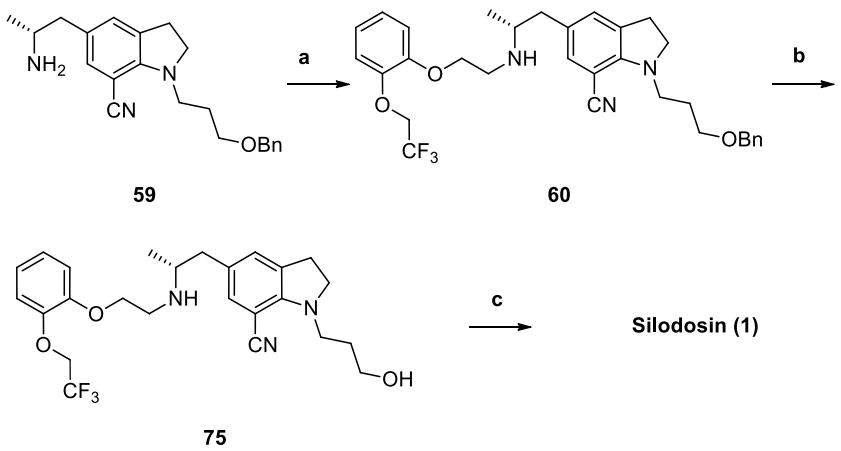
The ketone **73** is then reduced with the TFA/silane reducing system, then brominated to form intermediate **66** which is converted into **67** *via* Rosemund-von Braun reaction (Scheme 1.20).



Conditions:a. $Bn(CH_2)_3Br$, Na_2CO_3, DMF; b. Mg, **71**, THF; c. Et_3SH, TFA; d. Br_2, AcOH; e. CuCN, DMF; f. H_2, Pd/C, EtOH.

Scheme 1.20: Grignard based process to synthesise derivative 59

The benzyl carbamate of **67** is removed *via* catalytic hydrogenation to obtain already known amine **59** that is in turn alkylated to compound **57**. The benzyl ether protecting group is removed and the nitrile is hydrated to the amide obtaining Silodosin (Scheme 1.21).



Conditions: a. **14**, Na_2CO_3; b.H_2, Pd/C; c. H_2O_2, NaOH, H_2O

Scheme 1.21: Last steps of the synthesis described in JP2006188470

Kissei claimed the process to produce silodosin reacting the Grignard reagent of bromide **70** with enantiopure oxazolidinone **71** and the new intermediates disclosed in the patent **73**, **74**, **66** and **67**. The aforementioned process shows an interesting alternative synthesis of silodosin, but unexpectedly the patent deemed to be withdrawn.

1.2.2 Indoline scaffold (part A): Electrophilic indoline reagents

At the beginning of this chapter the syntheses reported in literature have been divided into two main groups according to the retrosynthetic approach used to introduce the substituent in position 5. We have already discussed the approach which makes use of unsubstituted indoline scaffolds as nucleophiles in electrophilic aromatic substitutions. In this paragraph we are going to describe the approach that makes use of indoline scaffolds already substituted in position 5 with a X group which is a halogen or a leaving group to be used as electrophiles (Figure 1.19).

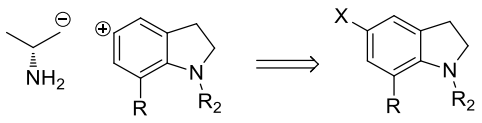
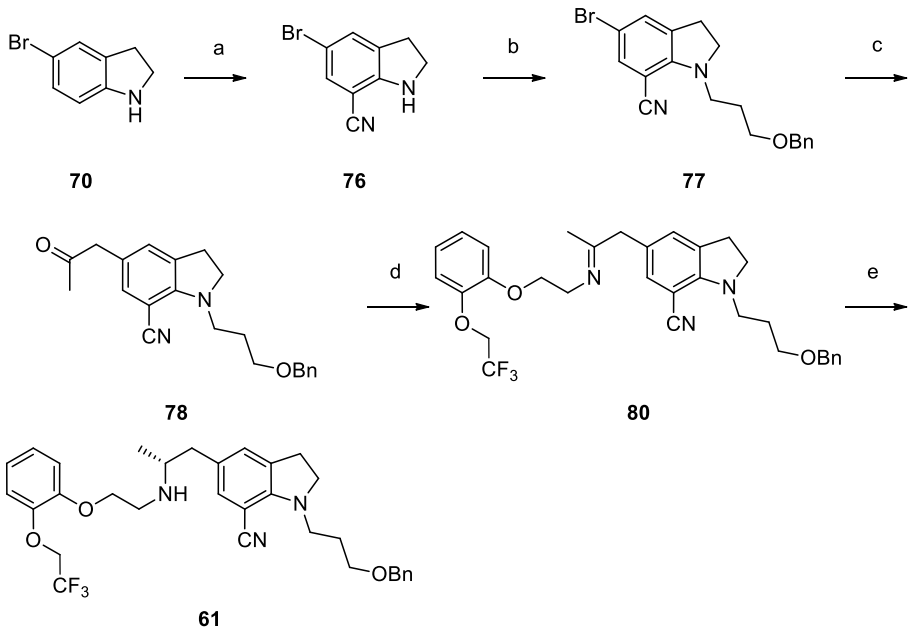


Figure 1.19: The synthetic equivalent of electrophilic synthon D

A relevant synthesis of 5-substituted indolines prepared with this approach is reported in US 8222452.[46] The inventors of the patent claim an enantioselective reductive amination to prepare Tamsulosin, an API used for the treatment of hyperplasia like silodosin, Nevertheless in the patent a possible synthesis of Silodosin is described starting from commercially available 5-bromoindoline **70**. Functionalization in position 7 of intermediate **70** with a nitrile functionality is obtained *via* a modified Houben-Hoesch reaction with methyl thiocyanate.[47] Indoline **76** thus obtained is then alkylated to form the tertiary amine **77** that is the electrophile employed in the following palladium (0) catalysed Stille reaction. The stannane used as nucleophile of this Stille reaction is formed in situ reacting the isopropenyl acetate

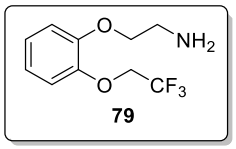
[46] Maeda, S.; Hamari Chemicals Ltd, (**2007**), Method For Producing Optically Active Amines, US8222452.
[47] Adachi, M.; Sugasawa, T.; *Synth. Commun.*, **1990**, *20*, 71 – 84.

with tributyltin methoxide. The cross coupling reaction is performed in presence of tris(dibenzylideneacetone)dipalladium as source of Pd(0) and 2-dicyclohexylphosphino-2'-(dimethylamino)biphenyl as ligand. The resulting ketone **78** is used to verify the industrial applicability of the invention, in fact the reductive amination of **78** in presence of amine **79** using (S)-chloro [(1,2,3,4-η)pentamethyl-2,4-cyclopentadien-1-yl](2-pyrrolidinecarboxamidato-ηN1,κN2) iridium (III) as catalyst at 0°C gave secondary amine **61** with a 80% e.e.



Conditions: a. BCl_3, MeSCN, toluene, 2) NaOMe, MeOH; b. $Br(CH_2)_3OBn$, K_2CO_3, EtOH; c. isoprenylacetate, Sn(t-Bu)OMe, $Pd_2(dba)_3$, DavePhos, toluene; d. **79**, toluene; e. HCOOH, TEA, Ir complex, DCM.

Scheme 1.22: enantioselective synthesis of compound 61



79

Figure 1.20: Compound 79

The enantiomeric purity of **61** was the increased up to 99.6% e.e. by traditional resolution via diastereoisomeric salt formation using D-(-)-tartaric acid as resolving agent.

The poor yield finally obtained and the low enantioselectivity makes the process not properly suitable for the industrial production, in addition the process make use of highly toxic stannane reagent. Probably for these reasons and for the presence in the process of intermediate **78**, already claimed in JP 2001199956[29], the aforementioned process to synthesise silodosin was not claimed.

1.2.3 Catechol scaffold (part B)

The synthesis of the catechol containing scaffolds has not deeply investigated in literature, because preparation of this kind of building blocks is quite linear and the reported approaches are just improvements of the first published synthesis. (Figure 1.21).

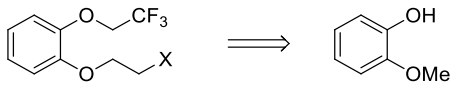
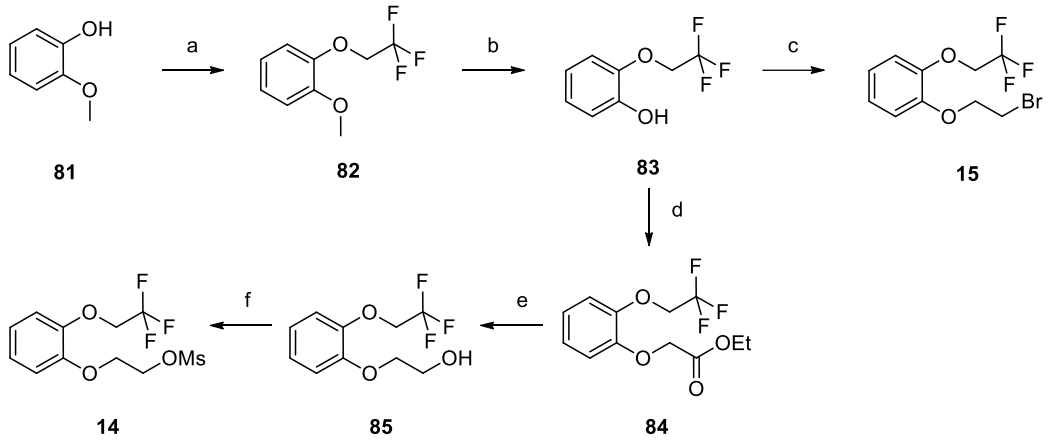


Figure 1.21: guaiacol starting material to form part A reagent

Initially, in fact Kissei disclosed the preparation of mesylate **14** and bromide **15** (Scheme 1.23) in JPH 06220015[11]. Commercially available guaiacole **81** can be easily alkylated with trifluoroiodoethane to form intermediate **82** which after demethylation using borontribromide gives intermediate **83**. Compound **15** is finally formed reacting derivative **83** with 1,2-dibromoethane in aqueous media.



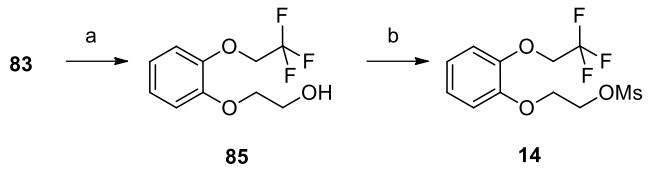
Conditions: a. CF_3CH_2I, K_2CO_3, DMF; b. BBr_3, DCM; c. $BrCH_2CH_2Br$, NaOH, H_2O; d. $ClCH_2COOEt$, K_2CO_3, DMF; e. $LiAlH_4$, THF ; f. MsCl, TEA, DCM.

Scheme 1.23: Derivative 14 and 15 syntheses

Mesylate **14** can be obtained starting from derivative **83** via alkylation with ethyl 2-chloroacetate to form the ester **84** that after reduction to alcohol **85** using $LiAlH_4$ and activation of the hydroxyl group with methanesulfonyl chloride gives mesylate **14**.

Successively Panacea Biotec Ltd proposed and claimed[48] a process where the alkylation of **83** with trifluoroiodoethane is performed with the cheaper trifluoroethyl tosylate. Compound **85** is then synthesised using 2-bromoethanol instead of 1,2-dibromoethane to avoid two synthetic steps.

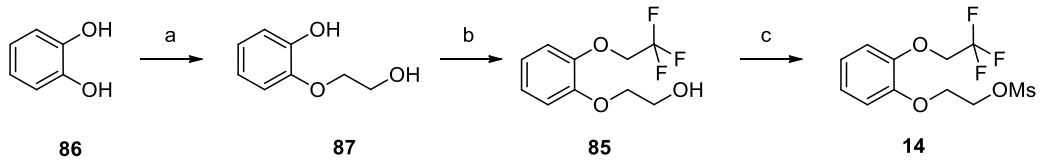
[48] Jain, R.; Jagdeeshwar, R.; Mahender, R. S.; Panacea Biotec Ltd, (**2010**), Novel Process For The Synthesis Of Phenoxyethyl Derivatives, WO2011101864.



condition: a. 2-bromoethanol, K_2CO_3, CH_3CN; b. MsCl, K_2CO_3, CH_3CN

Scheme 1.24: Derivative 14 synthesis

The best improvement in catechol scaffolds synthesis has been probably disclosed by Elworthy et al.[49] According to them mesylate **14** can be prepared in only three synthetic steps starting from catechol **86**. Catechol is reacted in ethylene carbonate in presence of tetrabutylammonium bromide as catalyst at 180°C and the product is triturated in water to obtain compound **87** that after alkylation with trifluoroethyltosylate gives known intermediate **85** easily converted into **14**



Conditions: a. ethylene carbonate; b. CF_3CH_2OTs, K_2CO_3, CH_3CN; c. MsCl, K_2CO_3, CH_3CN.

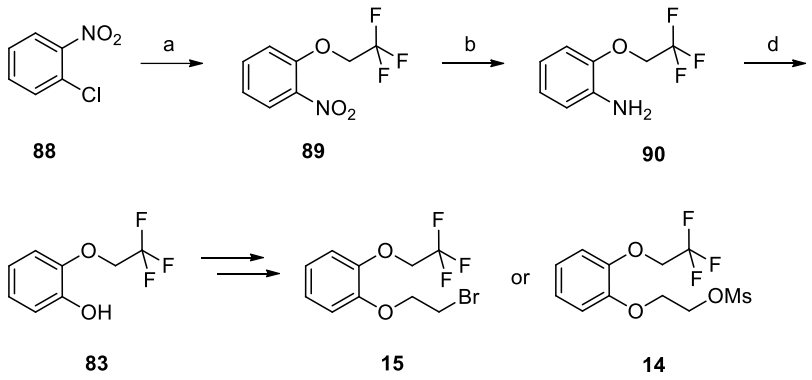
Scheme 1.25: Derivative 14 synthesis

Chinese patent CN102320996[50] reports a different approach described in Scheme 1.26. Starting from 2-chloronitrobenzene via aromatic nucleophilic substitution with

[49] Elworthy, T. R.; Ford, A. P. D. W.; Bantle, G. W.; Morgans, D. J.; Ozer, R. S.; Palmer, W. S.; Repke, D. B.; Romero, M.; Sandoval, L.; Sjogren, E. B.; Talama´s, F. X.; Vazquez, A.; Wu, H.; Arredondo, N. F.; Blue, D. R.; DeSousa, A.; Gross, L. M.; Kava, M. S.; Lesnick, J. D.; Vimont, R. L.; Williams, T. J.; Zhu, Q. M.; Pfister, J. R.; Clarke, D. E.; *J. Med. Chem.*, **1997**, *40*, 2674 – 2687.

[50] Yong, W.; Li, H.; Jie, L.; Xiaocen, L.; Huajie, Y.; Sichuan University, (**2011**), Method for preparing and purifying Silodosin intermediates, China: CN102320996.

trifluoroethanol, intermediate **89** is obtained. The nitro moiety of **89** is then reduced by hydrogenation to amine **90** which is converted into phenol **83** via diazonium salt formation. Phenol **83** can be treated with 1,2-dibromoethane to obtain compound **15** or with 2-bromoethanol to form intermediate **85** that after mesylation gives **14**.



Conditions: a. CF_3CH_2OH; b. H_2, Pd/C; c. 1) $NaNO_2$, H_2SO_4, toluene, 2) H_2SO_4, H_2O.

Scheme 1.26: Derivative 84 synthesis

The main goal of this thesis was to find a new methodology to prepare the indoline moiety of Silodosin, so initially we briefly developed the first synthesis of **14** disclosed by Kissei but successively mesylate **14** has been bought

1.2.4 Polymorphism

As already said in the general introduction about patent, the polymorphism field is a very challenging and treacherous activity in the pharmaceutical research. Different crystal can be patented, and often only one crystalline form could be used in the formulation. In addiction polymorphism patents, if filed after the product patent, could add some years of protection against the generic version of the drug. In this way in fact the generic company can introduce the generic version of the drud only after the expiry date of the polymorphism patent

This is the case of Silodosin, because the product itself was claimed in 1992, but in 2003 Kissei Pharmaceuticals filed JP 4532274,[51] claiming some specific crystalline forms of silodosin and their use in the formulation.

In JP 4532274 three different crystalline forms have been disclosed, namely α, β and γ form and the amorphous, but only form α has been claimed because the other two crystals showed some problems during formulation. The crystal form α can be prepared by dissolving crude Silodosin in several solvents as esters, ketones, ether, nitriles or a mixture of them. Usually it is prepared suspending Silodosin in ethyl acetate, dissolving it under heating and allowing it to cool down to room temperature slowly thus allowing the crystal to grow gradually.

Furthermore, the crystal form β has a manufacturing issue in industrial preparation, since it is prepared by adding a cold, low-boiling solvent (petroleum ether) into a warmed solution of silodosin to make the crystal precipitate suddenly. Another way to form the β crystal is to cool down quickly a solution of Silodosin in ethanol or 1-propanol, but this approach gives no better result because the yield and the purity are

[51] Kissei Pharmaceuticals Ltd, (**2003**), Crystal For Oral Solid Drug And Oral Solid Drug For Dysuria Treatment Containing The Same, Japan: JP4532274.

irregular, in addition different crystal forms are easy to mix therewith depending on the cooling speed, the temperature, the rate and the modality of stirring. Crystal form γ is prepared by cooling the warm solution of Silodosin in toluene, allowing the crystal to precipitate gradually. Apparently there is not any industrial issue to scale up. The problem is in the nature of the solvent used, in fact residual toluene in γ form is really difficult to be removed.

In JP2012131786[52] by Sandoz two new crystalline form are disclosed and claimed (δ and ε). Form δ can be prepared from every known crystal form of Silodosin by dissolving Silodosin in THF and adding an anti-solvent belonging to the alkane group, preferably n-heptane. Under drying condition if the temperature is raised up to 90°C the crystals convert into crystalline form β.

Form ε can be formed only from δ crystal form by slurrying it in 50 % v/v aqueous methanol. Other crystal forms do not convert into ε form treating them in the same conditions. The two new crystal forms are stable at humidity and storage temperature of 40°C.

In the same year Panacea Biotec in WO2012077138 [53]disclosed a new method to obtain crystal form α and β, in particular the method disclosed to prepare form β could be industrialized without any problem. The patent application is deemed to be withdrawn in any country but for India. Beijing Sun Novo Pharm claimed a method to prepare β form in CN102010359,[54] while Qiaogen Zou claimed a new procedure to prepare form δ in CN102229558.[55]

[52] Sandoz AG, (**2010**), Crystalline Form Of Active Pharmaceutical Ingredient, Japan: JP2012131786.
[53] Jain, R.; Siripragada, M. R.; Rao, J. R.; Panacea Biotec , (**2010**), Methods Of Crystallizing (R) -1- (3 - Hydroxypropyl) -5- [2- [2- [2- (2, 2, 2 - Trifluoroethoxy) Phenoxy] Ethylamino] Propyl] Indoline-7 - Carboxamide, WO2012077138.
[54] Qian, L.; Mei, S.; Beijing Sun Novo Pharmaceutical Res Co Ltd, (**2010**), Method For Preparing Silodosin In Beta Crystal Form, China: CN102010359.
[55] Qiaogen Zou, (**2010**), New Silodosin Crystal Form Delta, Preparation Method Thereof And Pharmaceutical Composition Containing The Same, China: CN102229558.

2 Result and Discussion: Feasibility

2.1 FEASIBILITY

2.1.1 INVESTIGATION ON POSITION 5 FUNCTIONALISATION

In the previous chapter, several already published syntheses of Silodosin have been reported. As already discussed, most of them have been accomplished starting from indoline **2** *via* the substituted key intermediate **59**. In any case, the substituent at position 5 of the key intermediate **59** has been introduced reacting a proper 5-unsubstituted indoline scaffold in an electrophilic aromatic substitution reaction.

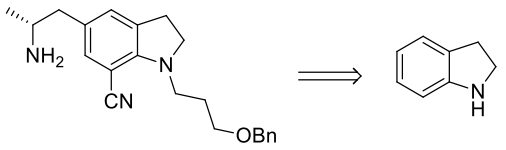
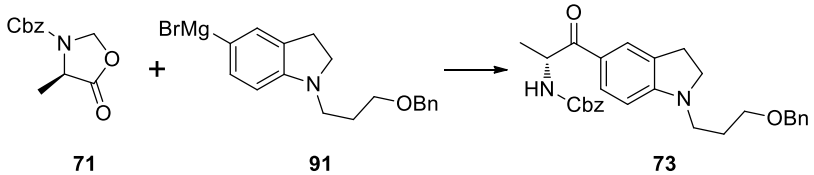


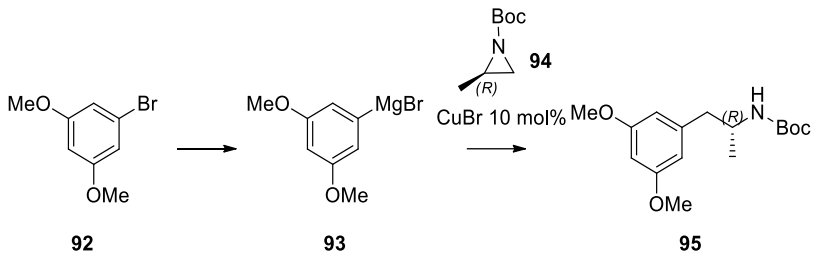
Figure 2.22: Retrosynthesis on compound 56

A nice approach for the introduction of position 5 substitution is described in patent JP 2006188470 where the indoline based Grignard reagent **91** is reacted with oxazolidinone **71** to form ketoamine **73** (Scheme2.1)[45]. Patent JP 2006188470, has been abandoned so we decided to take advantage of this approach.



Scheme 2.27: Gringard reaction disclosed in JP 2006188470

The idea was to perform a reaction by using Grignard reagent **91** with an appropriate electrophile in order to obtain directly the desired amine functional group instead of the ketoamine **73**. We hypothesised that by using a proper chiral protected aziride we could have reached our goal. In fact it is very well known that epoxides and aziridines react with organometallic reagents[56] and in particular aziridines can be opened regioselectively on the unsubstituted carbon by organocuprates.[57] In literature we found that aziridine ring opening had been also accomplished by Bringmann *et al.* by using Grignard reagents and electron-poor aziridines in the presence of only catalytic amount of copper (I) salts (Scheme 2.2)[58]. The reaction is possible because only the in situ generated organocuprate attacks the aziridine while the Grignard reagent is not reactive. At the end of the opening reaction, copper (I) returns in the catalytic cycle thus forming more organocuprate reagent. The nucleophilic attack of the organocuprate on the aziridine is selective on the less substituted carbon and the reactivity can be enhanced by protecting the aziridine nitrogen with electron withdrawing groups, usually carbamates and sulfonates.



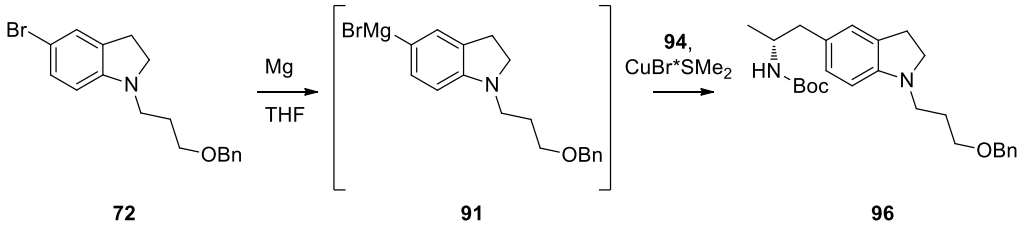
Scheme 2.28: Reported regioselective catalytic cuprate addition

Grignard reagent **93** used in Bringmann's paper, easily prepared from 3,5-dimethoxybromobenzene **92** in THF, treated with catalytic amount of $CuBr*SMe_2$

[56] A. Hassner, A. Kascheres, Tetrahedron Lett., 1970, 4623–4626
[57] M. J. Eis, B. Ganem, Tetrahedron Lett., 1985, 26, 1153–1156
[58] G. Bringmann, T. Gulder, B. Hertlein, Y. Hemberger, F. Meyer, J. Am. Chem. Soc., 2010, 132, 1151–1158

and a solution of aziridine **94** in THF gave desired product **95** in 91% yield as single enantiomer. In the paper, both (R) and (S) conFigured aziridine **94** have been employed, which can be prepared from the corresponding alanine in a three steps.

We planned to form Grignard reagent **91** and to allow it to react it with (R)-**94** in presence of catalytic $CuBr*SMe_2$ (Scheme 2.3).



72 **91** **96**

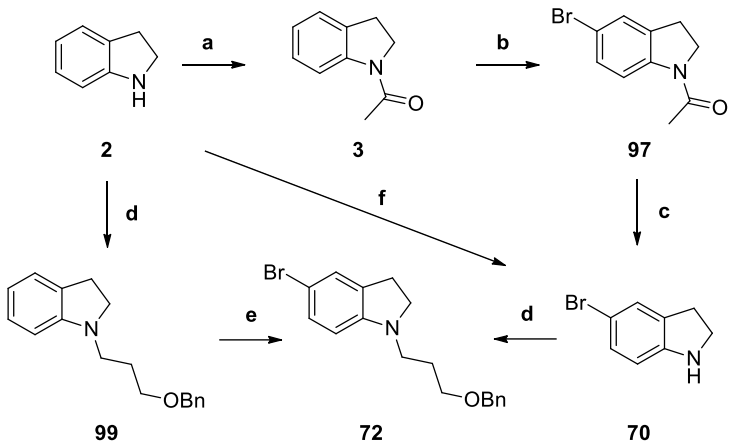
Scheme 2.29: Target Gringnard formation and reaction with aziridine 92

We decided to use compound aryl bromide **72** as starting material because its conversion into Grignard reagent **91** had been already reported[45] and because it already bears the C-3 alkyl chain on the indoline nitrogen. Benzyl protection was chosen due to its stability towards Grignard reagents and its ease removal by hydrogenation. Aryl bromide **72**[59] and aziridine **94**[58] have been then prepared on small scale following the reported procedures. Successively the synthesis of both derivatives has been improved and optimised.

Aryl bromide **72** has been prepared as reported in Scheme 2.4 In order to obtain a selective bromination, indoline **2** was first protected as acetamide and then brominated using a solution of bromine in acetic acid obtaining desired derivative **97**. Acetylation of indoline was optimised increasing the yield from 52% up to 87% adding two more recrystallisation from the mother liquor. Deacetylation of **97** gave oily 5-bromoindoline **70** in 95% yield. In the optimisation phase compound **70** has

[59] Bedford, R.B.; Engelhart, J.U.; Haddow, M.F.; Mitchell, C. J.; Webster, R. L.; *Dalton Trans.*, **2010**, *39*, 10464 – 10472.

been obtained as a white solid directly from the reaction media in quantitative yield (see tables in the experimental part). Compound **70** has been finally alkylated with sulfonate **98** (Figure 2.2), prepared from 1,3-propandiol[60], to give the bromoindoline **72** as an oil (Scheme 2.4). After the optimisation study we performed directly the regioselective bromination on indoline **2** and **99** using NBS in an appropriate solvent avoiding the protection-deprotection step (see table in the experimental part).



Condition: a. AcCl,TEA,DMAP,Toluene, 78%; b. Br_2, AcOH, 98%; c. NaOH 50% in H_2O, MeOH, 95%; d. **98**, K_2CO_3, EtOH, 85%; e. NBS, DMF, 87%; f. NBS, MTBE, 92%.

Scheme 2.30: Synthetic routes to compounds 72

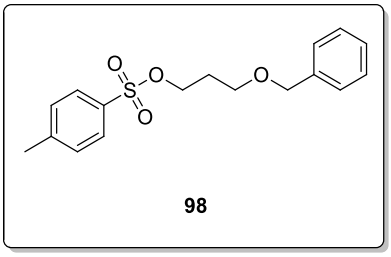
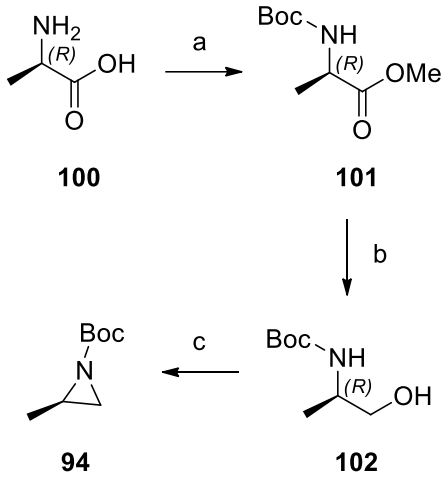


Figure 2.23: Compound 98

[60] Reddy, G. V.; Kumar, R. S. C.; Babu, K. S.; Rao, J. M.; *Tetrahedron Lett.*, **2009**, *50*, 4117 – 4120.

Aziridine **94** has been prepared following Meyer's procedure (Scheme 2.5). Commercially available D-alanine **100** was first converted into its methyl ester derivative using $SOCl_2$ in methanol and then into the Boc protected derivative **101** in a two-steps one-pot procedure. The methyl ester function of **101** was then reduced to alcohol **102** using $NaBH_4$/MeOH procedure[61] instead of using the $LiAlH_4$ procedure used in Meyer's route.[58] Aziridine **94** was finally obtained treating alcohol **102** with p-toluensolfonyl chloride in the presence of potassium hydroxide. (Scheme 2.5).



Condition: a.1) $SOCl_2$, MeOH 2) Boc_2O, $KHCO_3$, MeOH, 98% ; b. $NaBH_4$, MeOH, THF, 90%; c. p-toluensulfonyl chloride, KOH, MTBE, 81%

Scheme 2.31: Enantiopure aziridine synthesis

Once aryl bromide **72** and aziridine **94** had been prepared, we focused on the synthesis of the Grignard reagent **91**. Magnesium turnings were introduced in the minimum amount of THF needed to cover the turnings in the presence of 5% of bromide **72**. Iodine crystals were added to the mixture avoiding any stirring. Iodine

[61] Gonçalvesa, R. S. B.; Pinheiro, A. C.; da Silva, E. T.; da Costa, J. C. S.; Kaiser, C. R.; de Souza, M. V. N.; *Synth. Commun.*, **2011**, *41*, 1276 – 1281.

purple colour disappeared and the temperature of the solvent started to rise revealing the formation of reagent **91**. At this point, the solution of **72** in THF was added dropwise maintained the mixture under stirring. The dropping rate was regulated in order to keep the mixture at the reflux temperature. The mixture was kept at the reflux temperature under stirring until almost complete dissolution of magnesium turnigs was observed. Then the mixture was cooled to room temperature and CuBr*SMe_2 was added, followed by the addition of a solution of aziridine **94** in THF. After 2 hours, TLC analysis showed the disappearance of starting material **72** and formation of a new product. After usual work up, the residue was subjected to flash chromatography purification. The major compound unfortunately revealed to be unsubstituted indoline **99**, probably formed by protonolysis reaction of Grignard reagent **91**.

In order to avoid the formation of the protonolysis product **99**, in a repetition of the reaction, dry THF, already used in the previous experiment, was freshly distilled and stored over molecular sieves. Compounds **72** and **94** were further dehydrated until Karl-Fisher resulted below 0.10%. Once the formation of **91** had started, a sample of the reaction mixture was quenched with deuterium oxide. The sample was then analysed *via* GC-MS, HPLC-MS and ^{1}H-NMR in order to ascertain a quantitative ratio of Grignard reagent **91** versus unreacted **72**. Unfortunately the analyses showed that the mixture was constituted only by starting material **72** and protonolysis product **99**. Some other tests were performed but all of them pointed out the difficulty of converting efficiently aryl bromide **99** into Grignard reagent **91**.

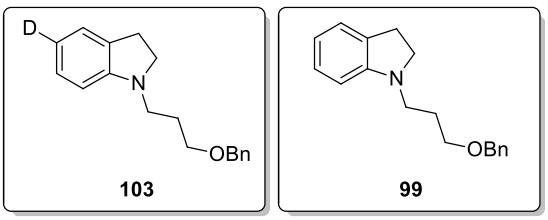


Figure 2.24: Deutereted product 103 and protonolysis product 99

We hypothesised that metal insertion occurred on the aryl bromide as expected but the organometallic specie thus obtained was quenched by a proton source. Nevertheless we tried to generate the Grignard reagent **91** using different methodologies. Rieke metal activation[62] (table 2.1, entry 5), transmetallation with other Grignard reagents[63] (table 2.1, entry 4) and formation of reagent **91** in the presence of LiCl[64] (table 2.1, entry 2) were performed. In any case starting aryl bromide remained unreacted. On the contrary, the activation of magnesium turnings using large amounts of dibromoethane gave complete conversion of starting material but only a small amount of the deutereted product **103** (Figure 2.3) was revealed by the analyses (table 2.1, entry 6,7).

entry	Activation Condition	R	Conversion [a]	99 [a]	103 [a]
1	Mg, I_2, $BrCH_2CH_2Br$	-$(CH_2)_3$OBn (**72**)	NO	-	-
2	Mg, LiCl	-$(CH_2)_3$OBn (**72**)	NO	-	-
3	Mg, I_2, ext. seeding	-$(CH_2)_3$OBn (**72**)	NO	-	-
4	i-$PrMgCl_2Li$	-$(CH_2)_3$OBn (**72**)	NO	-	-
5	$MgCl_2$, Li (Rieke)	-$(CH_2)_3$OBn (**72**)	NO	-	-
6	Mg, $BrCH_2CH_2Br$ (0,25 mol)	-$(CH_2)_3$OBn (**72**)	80%	40%	40%
7	Mg, $BrCH_2CH_2Br$ (0,5 mol)	-$(CH_2)_3$OBn (**72**)	100%	70%	30%
8	Mg, $BrCH_2CH_2Br$ (0,5 mol)	-Boc (**104**)	100%	40%	60%

Condition: reaction mixture sample was quenched with deuterated water. a. ^{1}H-NMR analysis.

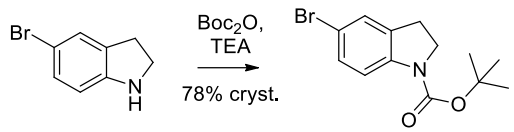
Table 2.1: Grignard formation and deuterated/protonolysis ratio

Moreover subsequent analyses revealed that at high level of conversion of starting material the ratio between the deuterated product **103** and the protonolysis one **99**

[62] Rieke, R. D.; *Science* **246**, 1260 – 1264.
[63] Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.*, **2004**, *43*, 3333.
[64] Knochel, P.; Dohole, W.; Gommermann, N.; Kneisel, F.; Kopp, F.; Korn, T.; Sapountzis, I.; Ahn Vu, V.; *Angew. Chem. Int. Ed.*, **2003**, *42*, 4302.

diminished. For this reason the reaction between the unstable Grignard reagent **91** and aziridine **94** was not repeated anymore.

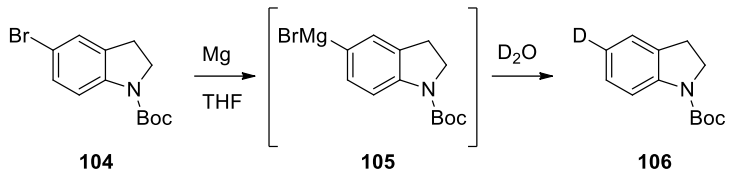
Analysing the problem, we identified a possible drawback in the fact that the aryl ring of substrate **72** is electron-rich, so in order to enhance the metal insertion rate and the stability of the organometallic specie, we decided to try the Grignard reagent formation starting from compound **104** where the indoline nitrogen is protected with the electron withdrawing carbamate Boc. Compound **104** was prepared from derivative **70** in 78% yield after crystallisation (Scheme 2.6).



70 **104**

Scheme 2.32: Synthesis of substrate 104

Aryl bromide **104** was then used in a grignard reagent formation using dibromoethane (0.5 mole ratio, Table 2.1) as activator and analyses, performed as previously described, revealed complete conversion of **104** but also in this case, the amount of deuterated compound **106** (Figure 2.4) did not satisfy our need. The reaction outcome convinced us about the instability of Grignard reagents prepared on the indoline scaffold. The instability is probably due to the acidity of protons present on the non-aromatic indoline portion of the scaffold, in particular of the benzylic protons in position 3.



Scheme 2.33: Grignard formation and quench with D_2O

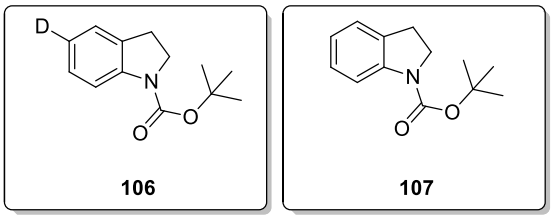
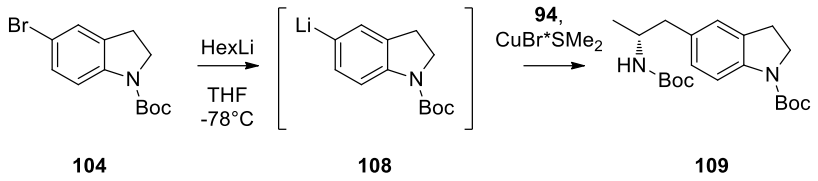


Figure 2.25: Deutered product 106 and protonolysis product 107

In order to demonstrate that the Grignard reagents formation on our indoline scaffolds failed because of the specific nature of the substrate we repeated the reaction reported in literature using 3,5-dimethoxybromobenzene **92** as aryl bromide. Grignard reagent **93** was formed easily (Scheme 2.2) and after treatment with aziridine **94** in presence of $CuBr*SMe_2$, compound **95** has been obtained after chromatographic purification in 70% yield, a value comparable to the reported one.

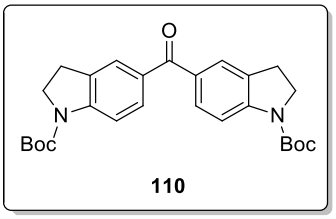
Although results obtained using our indoline based Grignard reagents might not be exiciting we were still confident about the possible usefulness of indoline based organometallic reagents, so we tried to prepare the organolithium derivative **108** in order to perform the reaction with aziridine **94** (Scheme 2.8).



104 108 109

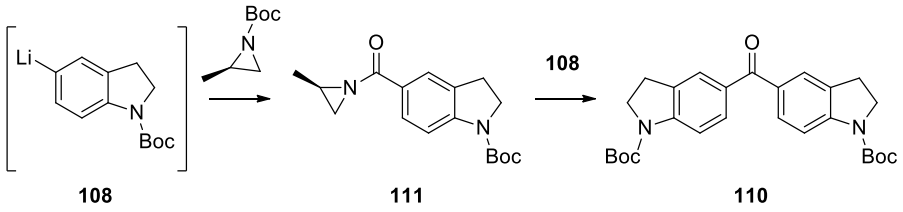
Scheme 2.34: desired Grignard formation on substrate 104

The metal exchange reaction was performed at -78°C adding hexyl lithium to a solution of bromide **104** in THF. The reaction worked perfectly and after 1 hour a quantitative deuteration of the sample was observed by ^{1}H-NMR (see experimental part). The organolithium derivative **108** was then added to aziridine **94** in presence of the usual copper catalyst. TLC analysis revealed after 3 hours the formation of single compound having Rf different from the protonolysis derivative **106** and from starting material **104**. Isolation via flash chromatography and characterisation through ^{1}H-NMR, ^{13}C-NMR and HPLC-MS revealed the newly formed product to be ketone **110** (Figure 2.4). Formation of **110** is probably due to the nucleophilic attack of the organolithium derivative **108** on the carbonyl function of the aziridine protecting Boc group giving intermediate **109** that readily reacts with another equivalent of our organolithium compound **108** to form ketone **110** (Scheme 2.9).



110

Figure 2.26: Side product 110



Scheme 2.35: Compound 110 formation hypothesis.

To take advantage of stability of our organolithium compound **108**, its reaction with the lithium salt of protected D-alanine **112** was performed in order to form the amino ketone **113** (Figure 2.5). Derivative **112** was prepared according to an already reported procedure[65] using an excess of benzyl bromide to yield compound **114** which was then hydrolysed in aqueous alkaline media to give after usual work up, the N-protected aminoacid **115** as white powder without any further purification (Scheme 2.10).

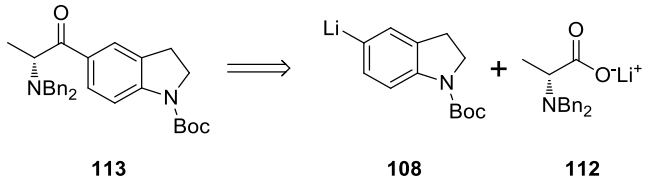
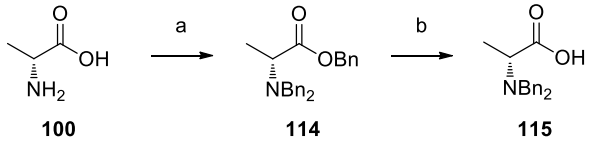


Figure 2.27: Carboxylate idea to exploit lithium derivative reaction



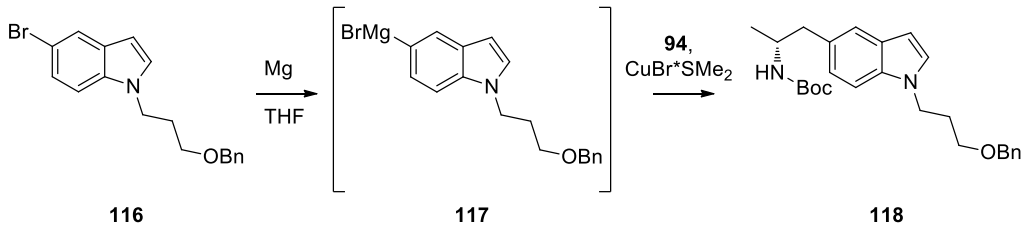
Condition: a. BnBr, EtOH, 80%; KOH, MeOH, dixane, H_2O, 89%

Scheme 2.36: Preparation of derivative 115

[65] Klein, J. J.; Hecht, S; *Org. Lett.*, **2012**, *14*, 330 – 333.

N-protected aminoacid **115** was then converted into the corresponding lithium salt **112** by addition of hexyl lithium to a THF solution, and the solution thus obtained was dropwise added in 1 hour to a solution of organolithium **108**, prepared as previously described, keeping the temperature below -60°C. TLC analysis revealed a plethora of products, nevertheless aqueous work up and crhromatoghaphic purification were performed but unfortunately desired product **113** was not found in any fraction isolated from the chromatographic purification.

Finally we tried to form a Grignard reagent on indole derivative **116** (Scheme 2.11). Indole and indoline in fact have the same heterocyclic structure, and they can be easily interconverted into each other. For example indole **118** can be reduced to indoline **96** via catalytic hydrogenation[66] or using $NaCNBH_3$[67]. In addition in literature there are many examples of indole based Grignard reagents and recently Knochel reported their formation at low temperature using stable iso-propyl magnesium chloride-lithium chloride complexes[68].

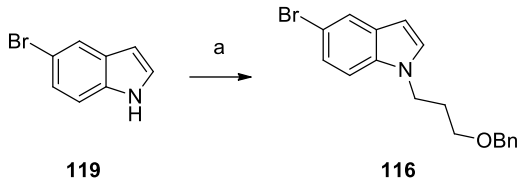


116 117 118

Scheme 2.37: Synthesis of target compound 118

[66] Igarashi, S.; Inami, H.; Hara, H.; Koutoku, H.; Oritami, H; Mase, G.; *Chem. Pharm. Bull.*, **2000**, *48*,1689 – 1697;
[67] Sano, H.; Noguchi, T.; Tanatani, A.; Hashimoto, Y.; Miyachi, H. *Bioorg. Med. Chem.* **2005**, *13*, 3079 – 3091;
[68] Melzig, L.; Dennenwaldt, T.; Gavryushin, A.; Knochel, P.*; J. Org. Chem.*, **2011**, *76*, 8891 - 8906

Indole derivative **116** was prepared starting from commercially available 5-bromoindole **119** by alkylation, using tosylate **98** as electrophile**.** Crude compound **116** was then recrystallised from *iso*-propyl ether obtaining pure **116** as white powder in 75% yield (Scheme 2.12).



119 **116**

Condition: a. NaH, **98**, THF, 75%.

Scheme 2.38: Synthesis of substrate 116

As for compound **72**, bromide **116** was converted into its corresponding Grignard reagent **117.** After 4 hours ^{1}H-NMR analysis of a sample showed a 95% of deuteration (see experimental part) so CuBr*SMe_2 and aziridine **94** were added and after 5 hours, aqueous work up and chromatographic purification, desired compound **118** was finally obtained in 35% yield. The major product of the reaction revealed to be the protonolysis product **120** anyway, so attempts to improve the yield were performed by changing concentration, addition rate, temperature and magnesium activation unfortunately without obtaining any noteworthy result. Also performing the Grignard formation by exchange procedure with *iso*-propylmagnesium chloride lithium chloride complex gave the product in around 35% yield.

Formation of indole **118**, precursor of indoline **96**, was finally accomplished in low 35% yield, for this reason the use of the copper catalysed reaction of organometallic indole/indoline specie with aziridine **94** was abandoned.

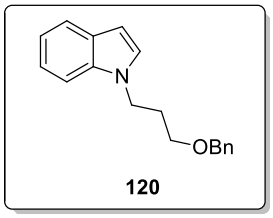
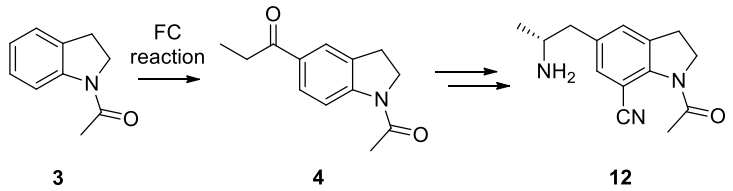


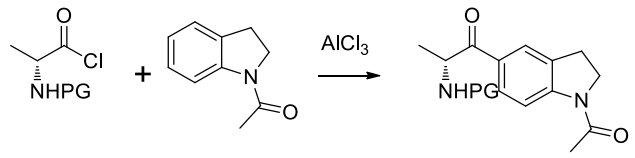
Figure 2.28: Protonolysis product 120

Once the indole/indoline based organometallic strategy had failed, we decided to investigate another interesting approach for the synthesis of amine **12** already disclosed in patent JPH06220015.[11] The key reaction to insert a C_3 chain at the 5 position of an appropriate indoline moiety is performed *via* Friedel-Crafts (FC) reaction. In JPH06220015, the FC alkylation is described using propionyl chloride to obtain the corresponding ketone, and successively the amine functional group was inserted in β-aryl position and resolved to give enantiopure amine **12** (Scheme 2.13).



Scheme 2.39: Position 5 functionalisation *via* FC disclosed in JPH06220015

Our idea was to obtain the enantiopure α-amino ketone moiety **122** performing the FC reaction using N-protected indoline **3** and the D-alanine derivative acyl chloride **121**, easily obtained from commercially available D-alanine **100**.



121 3 122

Scheme 2.40: Synthetic idea based on FC reaction

In literature many articles have been published on enantioselective FC[69,70,71] using protected aminoacid. The main issue of this approach is the choice of the protective group, in fact the strongly acidic conditions of the reaction allow enolisation of carbonyl containing moieties leading to racemisation of alanine. Pines and co-workers in 1964[72] reported FC acylation using N-trifluoroacetyl protected L-alanine with high degree of configurational preservation (Figure 2.8).

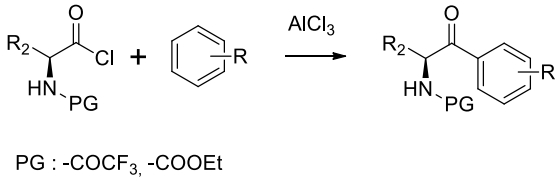
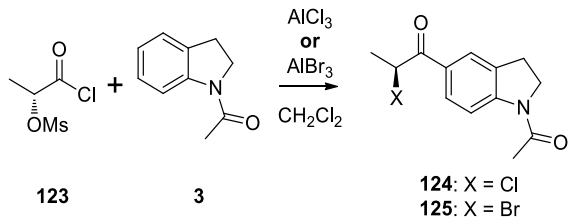


Figure 2.29: Enantioselective FC approach disclosed by Pines

The chance of success of our new approach improved considering that Kissei scientists reported a FC acylation on indoline scaffold **3** using the enantiopure lactic

[69] Nordlander, J. E.; Payne, M. J.; Njoroge, F. J.; Balk, M. A.; Laikos, G. D.;. Vishwanath, V. M.; *J. Org. Chem.*, **1984**, *49*, 4107 – 4111.
[70] Di Gioia, M. L.; Leggio, A.; Liguori, A.; Napoli, A.; Siciliano, C.; Sindona, G.; *J. Org. Chem.*, **2001**, *66*, 7002 – 7007.
[71] Buckley, T. F. III; Rapoport, H.; *J. Am. Chem. Soc.*, **1981**, *103*, 6157 – 6163.
[72] Pines, S. H.; Chemerda, J. M.; Kozlowski, M. A,; Weinstock, L. M.; Davis, P.; Handelsman, B.; Grenda, V. J.; Lindbeg, C. W. *J. Med. Chem.*, **1967**, 10, 725.

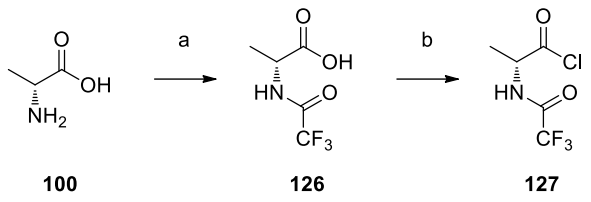
acid derivative **123**. During the acylation reaction also displacement of the mesylate group takes place by chloride or bromide anions (i.e. depending on Al salt used) with inversion of configuration (Scheme 2.9). The authors pointed out also the need of large excess of $AlCl_3$ to perform the reaction and in fact at least 4.5 mole per mole of indoline **3** were recommended.



Scheme 2.41: Enantioselective FC on indoline derivatives

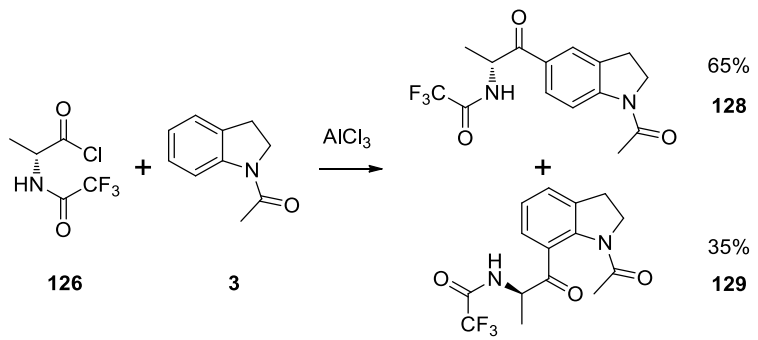
We decided to try the FC strategy employing the operative conditions reported by Kissei using indoline **3** as nucleophile and the trifluoroacetamide protected acyl chloride **127** derived from D-alanine as electrophile. Acid chloride **127** was prepared by reacting D-alanine with ethyl trifluoroacetate to form intermediate **126**[73] which was then converted into desired chloride **127** with $SOCl_2$ in CH_2Cl_2. A solution of acyl chloride **127** was then added to a suspension in CH_2Cl_2 of $AlCl_3$ and compound **3** at room temperature. After 4 hours the reaction was completed as evidenced by TLC analysis, even if two main products had been formed. ^{1}H-NMR analysis of the crude showed two main compound signals in a 65:35 ratio that let us think about the possible formation of the two regioisomers **128** and **129**. Chemical shifts of the signals were very similar and a in fact HPLC-MS analysis revealed the presence of two peaks with the same mass in accordance with our hypothesis.

[73] Curphey, T. J.; *J. Org. Chem.*, **1979**, *44*, 2805 – 2807.



Scheme 2.42: Synthesis of acyl chloride 126

The most abundant regioisomer was isolated *via* flash chromatography and after crystallisation from methanol resulted to be the desired (R)-N-(1-(1-acetylindolin-5-yl)-1-oxopropan-2-yl)-2,2,2-trifluoroacetamide **128** obtained only with an 11% yield. Many efforts were done to minimise the undesired regioisomer formation modifying the concentration and lowering the temperature of the FC reaction. Unfortunately reactions performed at low temperature did not occur (table 2.2, entry 3, 4 and 5), being 20°C the minimum operative temperature, and also at this temperature the ratio between the two regioisomers did not change (Scheme 2.17).



Scheme 2.43: FC reaction using enantiopure 126

entry	Conc. (M)	T (°C)	Conversion (%)	128 [a] (%)	129 [a] (%)
1	0.3	25	100	65	35

2	0.1	25	100	67	33
3[b]	0.3	0	0	-	-
4[b]	0.3	10	0	-	-
5[b]	0.3	15	0	-	-
6	0.3	20	100	68	32

Reaction condition: $AlCl_3$ 4.5 mole ratio, **126** 1 mole ratio, reaction time 4 hours. [a]. ^{1}H-NMR analysis, [b]. reaction time 24 hours.

Table 2.2: Evaluation of regioselectivity in FC reaction

We tried to optimise the FC reaction using activated Hematite (α-Fe_2O_3) as catalyst as reported in 2010[74] This methodology was attractive because of the very low catalyst loading (5-10%) and it seems to work very efficiently in neat condition.

Unfortunately compound **3** is a high melting point solid and we had to use solvent to fluidify the reaction media. Reactions where tried using dichloromethane and 1,2-dichloroethane as solvent, but in any case the reaction did not proceed at all.

[74] Sharghi, H.; Jokar, M.; Doroodmand, M. M.; Khalifeh, R. Adv. Synth. Catal. 2010, 352, 3031 – 3044

After these two unsuccessful approaches we started exploiting simultaneously different methodologies.

1. Propargyl trichloroacetimidates

The first idea was to use an appropriate propargyl trichloroacetimidate[75] which is easily converted into a stabilized carbocations able to alkylate indoline derivative **3** as reported by Reddy and co-workers (Figure 2.9).[76] The propargyl derivative thus obtained could have successively been transformed into the corresponding ketone via hydration of the triple C-C bond (Figure 2.10).

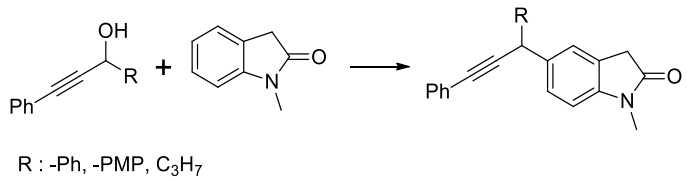


Figure 2.30: Propargylic electrophilic substitution on oxindole derivative

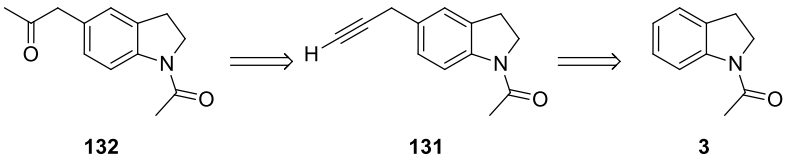
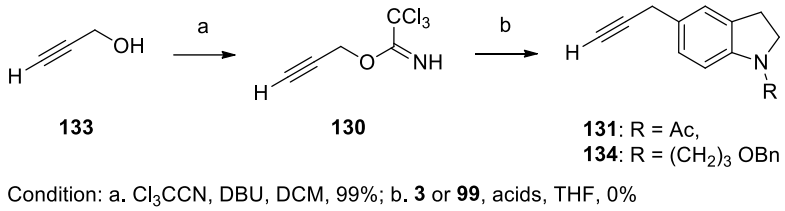


Figure 2.31: Retrosynthetic analysis using trichloroacetimidate approach

We started the new synthetic approach preparing the propargyl trichloroacetimidate **130** following reported procedure.[24] Reactions of trichloroacetimidate **130** with compound **3** and **99** in the presence of different strong Broensted acids (Scheme

[75] a. Guillena, G.; Ramon, D. J.; Yus, M.; *Chem. Rev.*, **2010**, *110*, 1611 – 1641,
b. Guillena, G.; Ramon, D. J.; Yus, M.; *Angew. Chem., Int. Ed.*, **2007**, 46, 2358 – 2364.
[76] Reddy, Ch. R.; Vijaykumar, J.; Gree, R.; *Synthesis*, **2010**, *21*, 3715 – 3723.

2.18) such as methansulfonic acid and p-toluensulfonic acid yielded only trichloroacetamide **135** (Figure 2.11).



Scheme 2.44: Synthesis using tricloroacetoimidate derivative

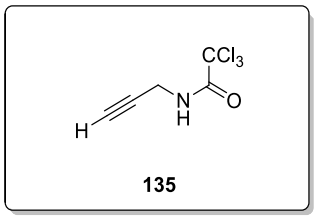


Figure 2.32: Side- product 135

The method was readily abandoned and we did not perform any other experiment using propargyl trichloroacetimidates in order to alkylate the aromatic ring of indulines derivatives.

1. Transition metal catalysed approach

The second idea we tried to realize was to prepare amine derivative **12** using 5-bromoindoline as starting material using a transition metal catalysed reaction to perform the alkylation (Figure 2.12).

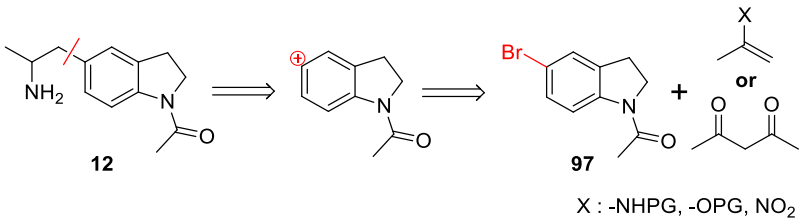


Figure 2.33: Retrosynthetic analysis leading to metal catalysed reaction

To achieve this goal we examined all the different possibilities to introduce on the indoline scaffold an alkyl chain residue which can be easily converted into desired β-aryl amine **12** (Figure 2.13). As we can see in Figure 2.14 most of them make use of Heck[77],[78] or Stille[46] reactions.

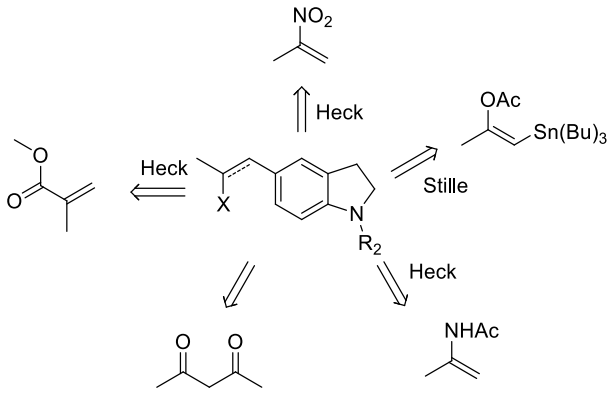
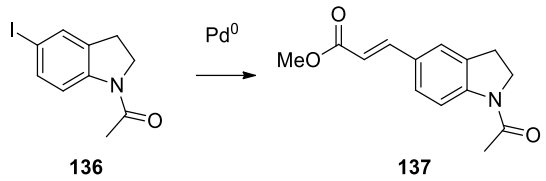


Figure 2.34: various reagents that can be uses in Pd catalytic system

In an example of the use of Heck reaction, 5-iodo-1-acetyl indoline is reacted with methyl acrylate (Scheme 2.19) giving desired product **137** in excellent yield.[77]

[77] Somei, M.; Saida, Y.; Funamoto, T.; Ohta, T.; *Chem. Pharm. Bull.*, **1987**, *35*, 3146 – 3154.
[78] Janssen Pharmaceutica N.V., (**2003**), Quinoline-Derived Amide Modulators Of Vanilloid VR1 Receptor, WO2004069792.

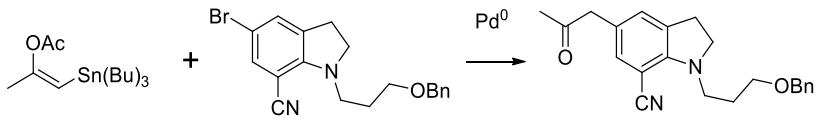


136 137

Condition: Methyl methacrylate, $Pd(OAc)_2$ (mol 10%), TEA, DMF, 96%

Scheme 2.45: Stille reaction disclosed in patent US 8222452

As already discussed during patent analysis, (see Section 1.2.2), also a Stille reaction using organostannane **138** with aryl bromide **77** gave desired ketone **78**[46] (Scheme 2.20).



138 77 78

Scheme 2.46: Stille reaction disclosed in patent US8222452

We would have liked to use 2-nitropropene as Heck acceptor because we considered that a nitroalkene should be a very good acceptor due to the electron-withdrawing effect of the nitro group which makes the double bond particularly electron-poor. The main problem of this synthetic approach was represented by the fact that, starting from an indoline scaffold alkylated with the C_3 substituent on the nitrogen atom, the products of this synthesis would have been be compounds with the Markush

structures depicted in Figure 2.14 where R_1 substituent could be a nitrile or primary carboxyamide and R_2 could be a generic hydroxy protective group.

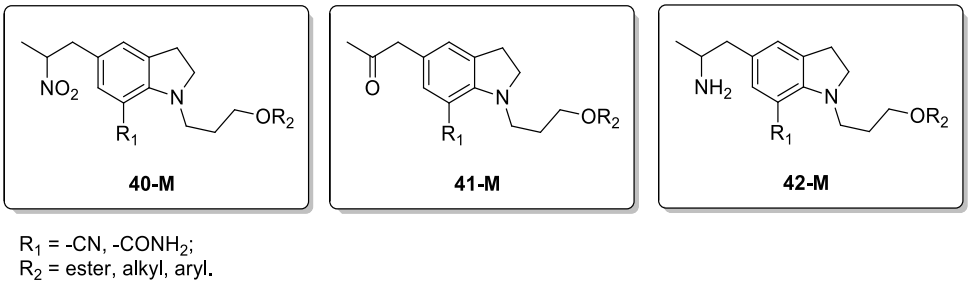


Figure 2.35: Indoline derivatives claimed in JP2001199956

In patent JP2001199956[29] those molecules are specifically claimed so we decided to try both reactions but starting from the acetylated derivative **97** and using 2-nitropropene and methyl methacrylate as Heck acceptors, Figure 2.15. Nitro derivative 117 was synthesised from 2-nitropropanol via activation-elimination of the hydroxyl group[79]. Heck reaction was then tried using 10% of $Pd(OAc)_2$ and 20% of triphenylphosphine as ligand, using triethylamine as base, toluene as solvent and reaction mixture was heated to reflux.

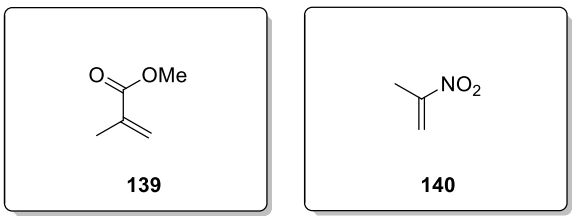
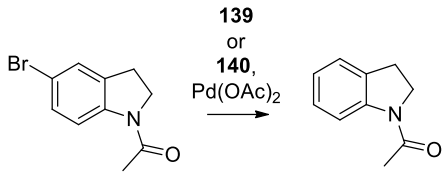


Figure 2.36: Reagents for PD catalysed Heck reaction

[79] Melton, J.; Mc Murry, J. E.; J. Org. Chem., 1975, 40, 2138–2139

After 2 hours TLC analysis showed the disappearance of starting material **97** and formation of a single product. ^{1}H-NMR of the crude revealed that the compound generated in the reaction was 1-acetyl indoline **3** (Scheme 2.21). This result can be explained considering that the formation of the intermediate organopalladium specie had occurred but unfortunately being followed by fast β-hydride elimination. The same result was obtained using the methacrylate acceptor.

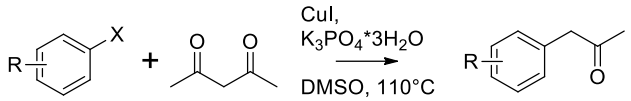


97 **3**

Scheme 2.47: Heck reaction with substrate 97

Some examples of Heck reactions have been reported in literature, making use of methyl methacrylate as acceptor and complex and expensive palladium catalysts so we hoped to let the reaction proceed by using much more easy catalysts but unfortunately this approach did not work and we decided to abandon it.

During the literature-patent critical analysis we noticed an interesting reaction published in 2010 by Lei and co-workers[80]. The reaction formally is a clean acetylacetone C-arylation starting from iodo- or bromoaryls in presence of copper iodide catalyst and acetylacetone (Scheme 2.22) in DMSO.



Scheme 2.48: Copper catalysed reaction with acetylacetone

The work presented in the article was very attractive, because according to the authors the reaction works well with both electron-donating and electron-withdrawing groups on the aromatic ring, and makes use of simple and cheap reagents. The Lei's C-arylation is a cascade reaction where acetylacetone is first arylated to give 2-aryl acetylacetones derivatives **142** which in the same experimental conditions are subjected to a retro-Claisen condensation yielding desired β-aryl ketones **143** (Figure 2.16).

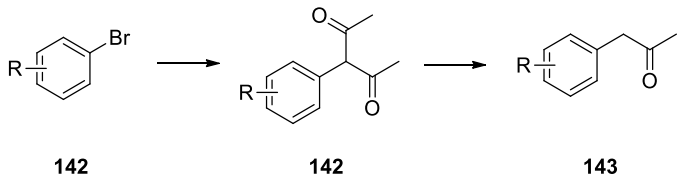
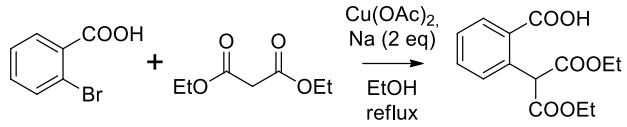


Figure 2.37: Intermediate of cascade reactions involved in Cu arylation

[80] He, C.; Guo, S.; Huang, L.; Lei, A.; *J. Am. Chem. Soc.*, **2010**, *132*, 8273–8275;

The Copper catalysed Lei's arylation of acetylacetone is part of a larger family of reactions involving aryl halides and β-dicarbonyl derivatives called Hurtley reaction[81]. Hurtley in fact discovered that copper bronze or copper acetate can promote the C-arylation of some families of active metylene containing molecules in reaction with *o*-bromobenzoic acid in presence of sodium ethoxide (Scheme 2.23). Copper(I) salts are efficient catalysts for the reaction with β-dicarbonyl derivatives, as shown in this standard organic synthesis procedure by McKillop[82].



Scheme 2.49: Copper-catalysed Hurtley reaction

Ribas and coworkers[83] using a UV/Vis monitoring of the reaction have recently demonstrated that these Cu(I) catalysed arylations proceed via a Cu(I)/Cu(III) cycle. In addition, Lei[84] observed, using a combination of IR, in situ X-ray absorption near-edge structure (XANES) and extended X-ray absorption fine structure (EXAFS), the formation of complex **A** between copper(I) iodide and a β-diketone nucleophile (Figure 2.17).

[81] Hurtley, W. R. H. *J. Chem. Soc.* **1929**, 1870–1873
[82] Bruggink, A.; Ray, S. J.; McKillop, A. *Org. Synth.* **1978**, *58*, 52–54
[83] Casitas, A.; Ribas, X.; *Chem. Sci.*, **2013**, *4*, 2301 – 2318.
[84] He, C.; Zhang, G.; Ke, J.; Zhang, H.; Miller, J. T.; Kropf, A. J.; Lei, A.; *J. Am. Chem. Soc.*, **2013**, *135*, 488 – 493.

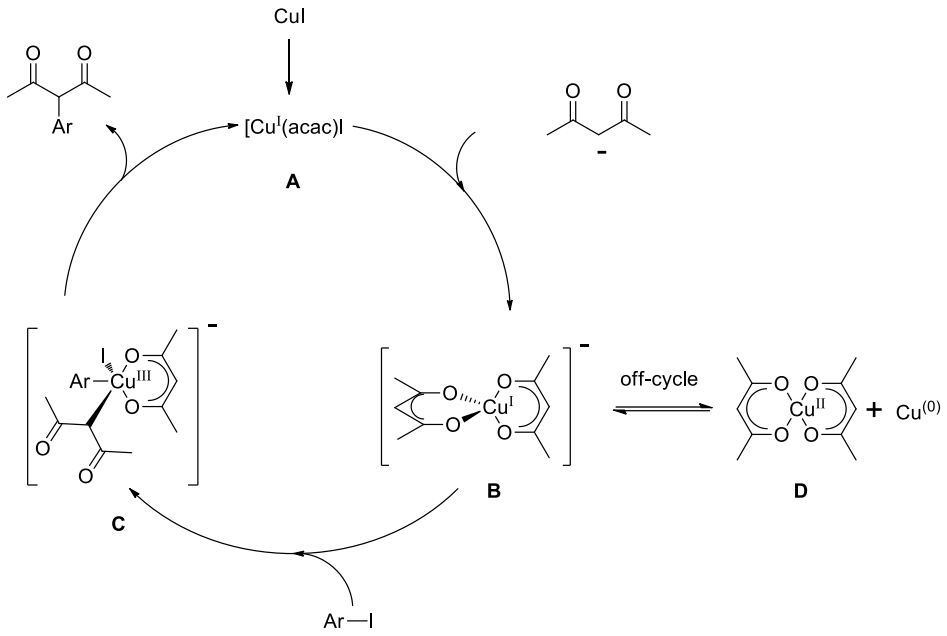


Figure 2.38: Catalytic cycle through labile copper(I) acetylacetonate catalys

Further kinetic studies and computational calculations demonstrated that this labile complex might be the active catalyst of the Hurtley reaction but could also undergo a rapid disproportionation to catalytically inactive copper(0) and copper(II) acetylacetonate (offcycle). The catalytic cycle then involves an oxidative addition of the aryl halide at copper(I) thus leading to the copper(III) complex **C** that deliver the copper(I) catalyst **A** and the arylated product after reductive elimination. The dual role of the β-diketone, as a ligand and as a nucleophile, is worth to note.

The authors also demonstrated that the electronic nature of aryl halides substituents influences seriously the reaction outcome. The introduction of various ligands[8586] largely expanded the scope of substrates even if no particular mechanistical rationale has been understood about the relation between catalytic cycle and transition states.

[85] Huang, Z.; Hartwig, J. F.; *Angew. Chem. Int. Ed.*, **2012**, *51*, 1028 – 1032.
[86] Hennessy, E. J.; Buchwald, S. L.; *Org. Lett.*, **2002**, *4*, 269 – 272.

We really appreciated the Lei's synthetic tool and decided to synthesise the aryl ketone **132** using the copper catalysed C-arylation of acetylacetone of the indoline based aryl bromide **97** and then to convert the thus obtained ketone **132** into the desired amine derivative **144** (Figure 2.18).

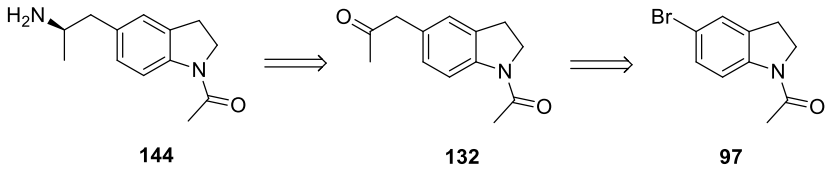
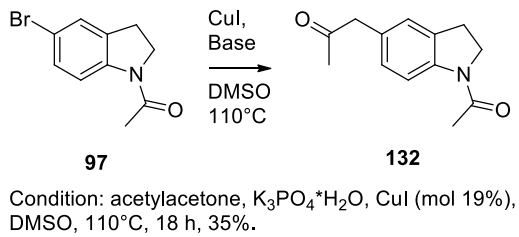


Figure 2.39: Retrosynthesis analysis to take advantage of Cu arylation reaction

Initially we proceeded following the experimental procedures optimized by Lei's group (Scheme 2.24).



Scheme 2.50: Copper mediated arylation on substrate 97 using Lei's optimised procedure

Compound **97** was dissolved in DMSO forming a 0.33 M solution, then acetylacetone, $K_3PO_4*3H_2O$ and CuI were added and stirred at 110°C. The reaction was followed by ^1H NMR analysis and after 4 hours conversion appeared to be around 45%, which resulted unchanged at the following control. We noticed that the inorganic base is insoluble in the reaction media and hampers the stirring of the

reaction mixture. In particular changing the stirring bar with a mechanical stirrer both conversion of starting bromide and yield of isolated ketone, obtained after flash chromatographic purification, increased. (Table 2.2 entry 7). The reaction was also carried out in anhydrous conditions (using anhydrous K_3PO_4) and worked exactly as in the presence of water (Table 2.2, entry 3 and 5)[87] The source of Cu(I) salt did not appear to be relevant in term of reactivity, thus CuI was chosen as catalyst because of its lower cost.

The main impurity in crude mixture revealed to be the de-brominated substrate (1-acetylindoline **3**, Figure 2.19) that has always been isolated between 5 and 10% yield. Another particular impurity that has been found performing the arylation at higher temperature (Table 2.3, entry 3, 4) is sulfone **145** (Figure 2.19).

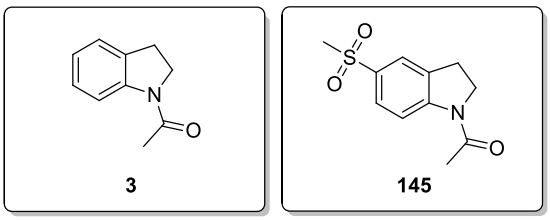


Figure 2 Error! No text of specified style in document..**40: side-products of the copper-catalysed reaction**

[87] After exhaustive studies (Page 142) we found that water is also formed during the reaction due to side condensation reactions of acetylacetone.

Entry	T(°C)	Base	Catalyst	Conc. (M)	t (h)	Conv. [a] (%)	132 [a] (%)
1	110	$K_3PO_4*3H_2O$	CuI	0.27	18	40	35
2	110	$K_3PO_4*3H_2O$	CuI	0.41	30	50	30
3	130	$K_3PO_4*3H_2O$	CuI	0.41	20	60	30
4	130	$K_3PO_4*3H_2O$	$Cu(OAc)_2$	0.41	20	40	32
5	110	K_3PO_4	CuI	0.41	20	50	45
6	110	K_3PO_4	$Cu(OAc)_2$	0.41	20	35	28
7[b]	120	K_3PO_4	CuI	1.38	20	60	55
8	120	$K_3PO_4*3H_2O$	CuI	1.38	20	45	40

Reaction condition: **97** (12.5 mmol), base (3 mole ratio), acetylacetone (3mole ratio), catalyst (10% mol) in DMSO were reacted at settled temperature. [a]. GC-MS analysis, [b]. mechanical stirring

Table 2.3: Brief investigation on copper catalysed reaction parameters

After this first investigation, in order to maximise the yield of our reaction we performed several reactions changing base, solvent and adding ligands for the copper (I) specie. Operative temperature (110°C), concentration (1.38 M), catalyst source and loading (CuI, 10% mol) and reaction time (20 h) were fixed. Diamine ligand N,N'-dimethylethylenediamine[88] (DMEDA, mostly used in copper catalysed Buchwald-Hartwig arylations) inhibited completely the reaction (Table 2.4, entry 2, 3), while carboxylic N,O bidentate ligands (picolinic acid[89] and proline[9091]) expedited the reaction. The nature of the base apparently does not affect so much the reaction yield, but we noticed that cesium carbonate speeds up the reaction kinetic gaining complete conversion in less than 20 hours (Table 2.4, entry 5, 8).

[88] Monguchi, Y.; Maejima, T.; Mori, S.; Maegawa, T.; Sajiki, H.; *Chem. Eur. J.*, **2010**, *16*, 7372–7375.
[89] Yip, S. F.; Cheung, H. Y.; Zou, Z.; Kwong, F. Y.; *Org. Lett.*, **2007**, *9*, 3469 – 3472.
[90] Xie, X.; Cai, G.; Ma, D.; *Org. Lett.*, **2005**, *7*, 4693 – 4695;
[91] Jiang, Y.; Wu, N.; Wu, H.; He, M.; *Synlett*, **2005**, *18*, 2731 – 2734.

Entry	Ligand	Base	Conv. [a] (%)	132 [b] (%)	3 (%)
1	-	$K_3PO_4*3H_2O$	45	40	5
2	DMEDA	$K_3PO_4*3H_2O$	0	-	-
3	DMEDA	K_2CO_3	0	-	-
4	picolinic acid	K_2CO_3	70	60	5
5	picolinic acid	Cs_2CO_3	100	90	5
6	proline	K_2CO_3	75	70	5
7	proline	K_3PO_4	90	82	8
8	proline	Cs_2CO_3	100	93	7

Reaction condition: **97** (12.5 mmol), base (3 mole ratio), acetylacetone (3 mole ratio) CuI(10 mol %), ligand (20 mol%), DMSO (1.38 M), mechanical stirring (550 rpm), temperature (110°C). [a] conversion after 20 hours. [b] chromatography yield.

Table 2.4: Investigation on base and ligand effect

DMSO proved to be the most suitable solvent, in literature other solvents as dioxane[92,89] and DMF[93] seem to work on different substrates but in our case they did not give any good result (Table 2.5, entry 2, 3). The use of alcoholic solvent (Table 2.5, entry 5) leaded to the complete removal of acetamide protection, due to solvolysis reaction.

Proline proved to be the most efficient ligand and finally we could quickly increase the yield of arylation up to 90% after chromatography, the best conditions being CuI (10%), proline (20%), Cs_2CO_3 (3 mole ratio), acetylacetone (3 mol ratio), in DMSO at 110°C.

[92] Deng, W.; Wang, Y. F.; Liu, L.; Guo, Q. X.; *Chin. Chem. Lett.*, **2006**, *17*, 595 – 598.
[93] Xie, X.; Chen, Y.; Ma, D.; *J. Am. Chem. Soc.*, **2006**, *128*, 16050 – 16051.

Entry	solvent	Conc. (M)	t (h)	Conv. [a] (%)	132 [a] (%)
1	DMSO	1.3	20	100	93
2	Dioxane	1.3	20	0	-
3	DMF	1.3	20	30	30
4	Toluene	1.3	20	0	-
5	n-BuOH	1.3	20	100[b]	-

Reaction condition: **97** (12.5 mmol), Cs_2CO_3 (3 mole ratio), acetylacetone (3 mole ratio), CuI (10 mol %), proline (20 mol%), concentration (3 vol, 1.38 M), mechanical stirring (550 rpm), temperature (110°C). a. GC-MS analysis, b. hydrolysis of the starting material.

Table 2.5: Solvents investigation

2.1.2 INTRODUCTION OF 7 POSITION SUBSTITUENT

Once the synthesis of ketone **132** had been accomplished and optimized, a first strategy to fulfil the whole synthesis was to convert ketone **132** into an optical active derivative (e.g. enantiopure alcohol or amine) *via* enantio- or diastereo-selective reaction and then to functionalize the position 7 of the indoline scaffold (Figure 2.20).

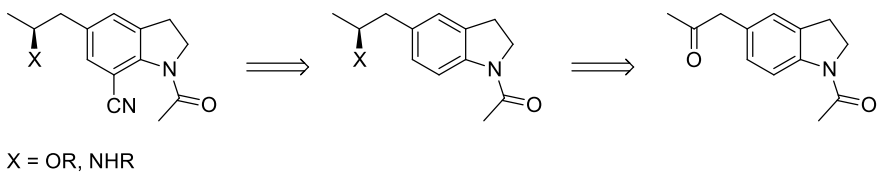


Figure 2.41: First strategy retrosynthetic analysis

A second option was to functionalize position 7 before performing our optimized copper catalysed reaction (Figure 2.21).

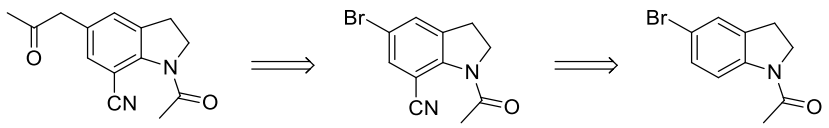


Figure 2.42: Second strategy retrosynthetic analysis

We studied the first strategy to take advantage of our good results and decided to convert **132** into enantiopure alcohol **146** or into amine **144**. (Figure 2.22).

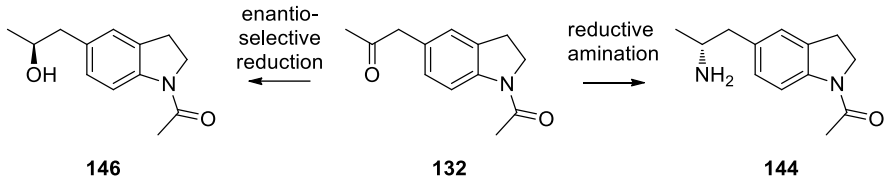


Figure 2.43: Ketone 132 conversion into enantiopure compound

Reducing enantioselectively ketone **132** and then introducing the nitrile group in position 7 and converting the alcohol group into amine via S_N2 displacement would have provided desired amine **59** (Figure 2.24).

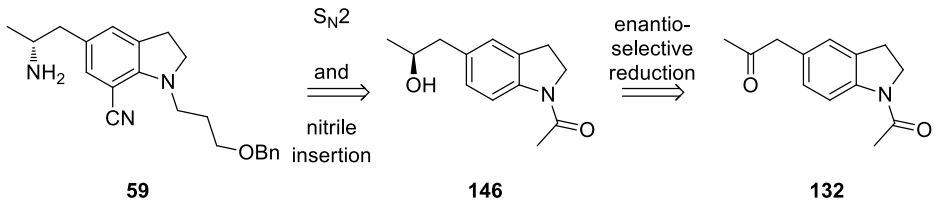


Figure 2.44: retrosynthetic plan exploiting enantioselective reduction

Enantioselective reductions of ketones have been largely studied using enantiopure borane hydride[94] or metal catalysts under hydrogen atmosphere[95]. Lately a lot of works have been published on H-transfer reduction (TH) of ketones to alcohols (Figure 2.24). Taking advantage of a collaboration with Prof. Baratta of Udine University we decided to exploit this recent attractive methodology.

[94] Midland, M. M.; Lee, P.E.; *J. Org. Chem.*, **1985**; *50,* 3239 – 3241.
[95] Ohkuma, T.; Ooka, H.; Yamakawa, M.; Ikariya, T.; Noyori, R.; *J. Org. Chem.*, **1996**, *61*, 4872 - 4873.

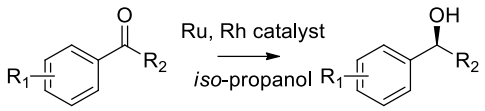
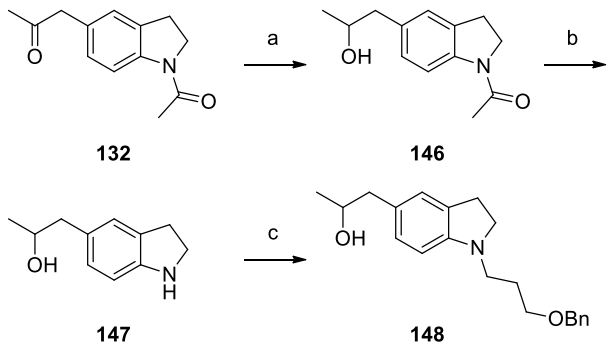


Figure 2.45: General H-transfer reduction of ketones.

Baratta in fact designed and developed a lot of catalysts[96] to be used in H-transfer oxidation and reduction reaction using inexpensive isopropanol as source of H_2. These catalysts are highly efficient in the asymmetric TH of alkyl aryl ketones with TOFs of up to 10^6 h^{-1} at a catalyst loading as low as 0.002 mol%.

The synthetic plan was first demonstrated reducing ketone **132** to obtain racemic alcohol **146** using sodium borohydride in THF, then acetamide protection was hydrolysed in basic aqueous media and indoline **147** was then alkylated in ethanol with compound **98** obtaining compound **148** in 71% yield without traces of O-alkylated product (Scheme 2.25). Compound **148** was recovered from the reaction crude as an oil and did not crystallise under many condition, so it was finally purified by chromatography.



Condition: a. $NaBH_4$, THF; b. NaOH, MeOH, H_2O; c. **98**, K_2CO_3, EtOH, 71% (3 steps).

Scheme 2.51: Synthesis of derivative 148

[96] Baratta, W.; Chelucci, G.; Magnolia, S.; Siega, K.; Rigo, P.; *Chem. Eur. J.*, **2009**, *15*, 726 – 732.

To introduce the nitrile group in position 7 of **148**, we planned to use Vilsmayer-Haack formylation (VH) followed by oxime formation and dehydration to desired nitrile. This reaction could be very useful for us because in VH conditions, alcohols convert into alkyl halide[97] with complete inversion of the configuration (Figure 2.25) and the alkyl halide was a useful functional group to introduce the desired amino group on the side-chain (Scheme 2.26)

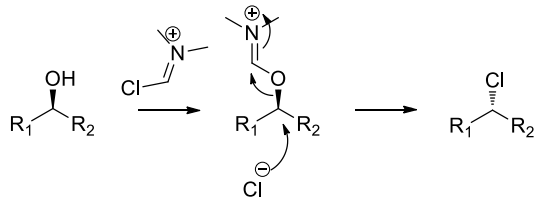


Figure 2.46: mechanism of the inversion using VH reagent

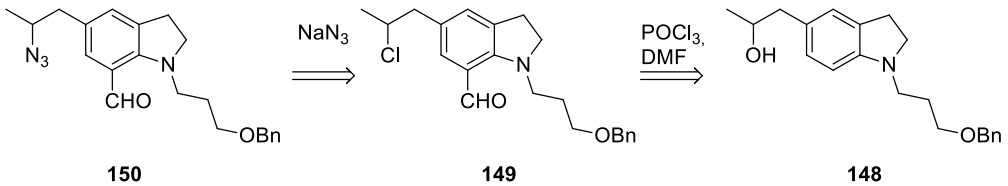


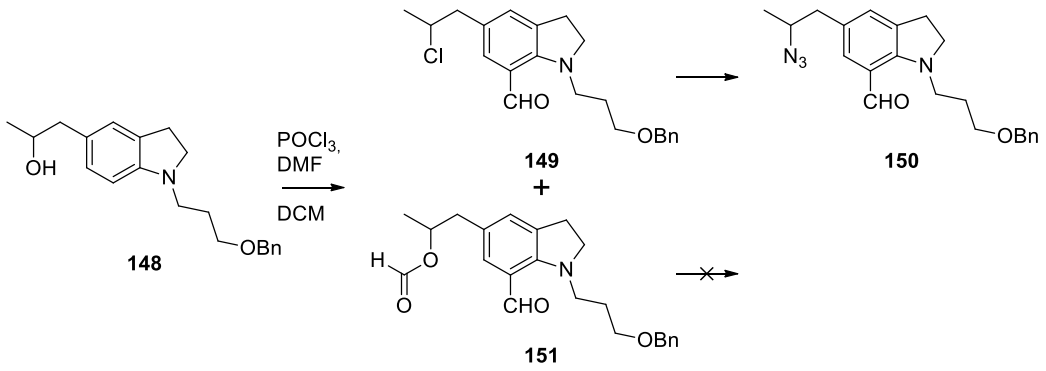
Figure 2.47: Retrosynthetic plan to form azide 151

We tried the VH reaction on compound **148** using two mole of $POCl_3$.

Reaction gave after 3 hours complete conversion of the starting material. TLC analysis showed the formation of a single product, but ^{1}H-NMR of the crude revealed the formation of two compound in a 9:1 ratio. ^{1}H-NMR and mass analysis help us to

[97] M. Yoshihara, T. Eda, K. Sakaki and T. Maeshima, *Synthesis*, **1980**, *9*, 746 – 748.

understand the structures of the two compounds. The major compound resulted to be the chloro derivative **149** (Scheme 2.20) with tipical α-chloro multiplet signal at 4.6 ppm and the aldehyde proton signal at 9.98 ppm, while the minor product was found to be the formate ester **151**, showing the typical formate proton at 8.00 ppm, the aldehydic one at 9.99 ppm and a multiplet at 5.2 ppm. The product could not be purified by crystallisation, even chromatography did not give good results. Therefore, we directly tried a S_N2 reaction on the crude containing both **149** and **151**. In order to avoid elimination reactions and let the substitution reaction occur with chloride we performed the reaction in a very concentrated solution (1.1 M) using DMSO as solvent and sodium azide as nucleophile. After 16 hours at 25°C ^{1}H-NMR revealed that derivative **149** had completely been consumed giving azide **150**, while formate **151** did not react at all.



Scheme 2.52: VH reaction on 142 alcohol derivative

This work demonstrated that having the enatiopure alcohol **148** in hand we could have obtained the desired trisubstitued entiopure amine **59**.

Baratta investigated the enantioselective reduction of ketone **132** to alcohol **146** obtaining good results in terms of chemoselectivity but the enantioselectivity remained very low.

Compound **132** was in fact easily reduced under TH condition using Ru complexes with achiral ligand (**Ru-1** and **Ru-2**, Figure 2.27) obtaining **146** in very good chemoselectivity (95%) and 92% yield. The reaction was carried out in just 1 hour at 70°C using a substrate/catalyst ratio of 2000 performing the reaction in acetonitrile with iso-propanol as source of hydrogen.

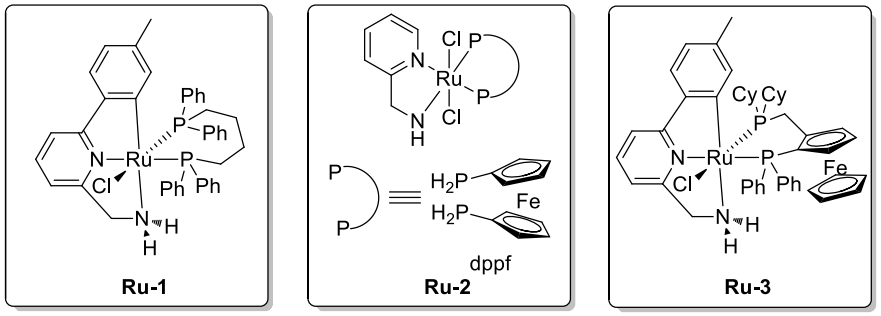


Figure 2.48: Catalysts used in the TH reaction

The use of enantiopure complex Ru(CNN)[S,R-Josiphos(OMe)]Cl (compound **Ru-3**, Figure 2.27) gave product **146** in 88% yield with the same catalyst loading, but in only 30% e.e.. This not very exciting result convinced us to abandon the strategy of converting ketone **132** into enantiopure alcohol **146** so we decided to investigate the second strategy to introduce the nitrile/amide group in position 7 before performing the copper (I) catalysed C-arylation.

In Silodosin the 7 position substituent is a primary amide and in the synthetic strategy the primary amide could be introduced directly[98] or a different functional group that is unreactive towards many reaction conditions can be introduced and then easily converted into desired primary amide (Figure 2.28).

Amide direct insertion was not taken into account because amide is very reactive in several reaction conditions needed to conclude Silodosin preparation and in particular a primary amide could compete in the copper catalysed reaction. For these reasons we decided to use a robust functional group that could be easily converted into primary amide. Basically primary amides can be formed from carboxylic acids[99], esters[100], nitriles[101] and oximes[102] (Figure 2.28), we decided to use the nitrile group because is inert towards many reaction, and it is the most used in Silodosin existing syntheses.

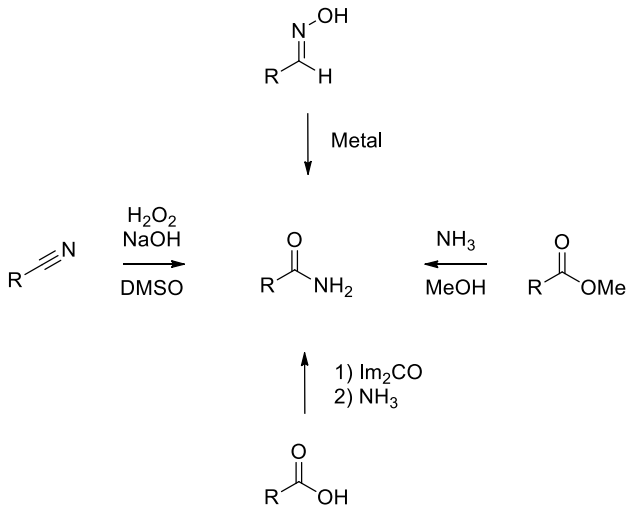


Figure 2.49: Amide formation from different functional group

[98] a. Ren, W.; Yamane, M.; *J. Org. Chem.*, **2010**, *75*, 8410 – 8415.
b. Wan, Y.; Alterman, M.; Larhed, M.; Hallberg, A.; *J. Comb. Chem.*, **2003**, *5*, 82 – 84.
[99] Gernigon, N.; Al-Zoubi, R. M.; Hall, D. G.; *J. Org. Chem.*, **2012**, *77*, 8386-8400
[100] Basha, A.; Lipton, M.; Weinreb, S. M.; *Tetrahedron Lett.*, **1977**, *18*, 4171 - 4172
[101] Kornblum, N.; Singaram, S.; *J. Org. Chem.,* **1979**, *44*, 4727 – 4729.
[102] Allen, C. L.; Ruth Lawrence, R.; Emmett. L.; Williams, J. M. J.; *Adv. Synth. Cat.*, **2011**, *353*, 3262 – 3268.

Nitrile insertion on aromatic ring is mainly performed via formylation (e.g. Vilsmeier-Haack reaction and Duff reaction) followed by oxime formation and dehydration. Traditional methods include also Rosemund von Braun[103] and Sandmeyer[104] reactions that use toxic cyanides. More recently, these methods have been replaced either by transition-metal-catalyzed cyanation of arylhalides with safe metal cyanides as for example $K_4[Fe(CN)_6]$[105]. or by the electrophilic cyanation of aryl nucleophiles (Figure 2.29).

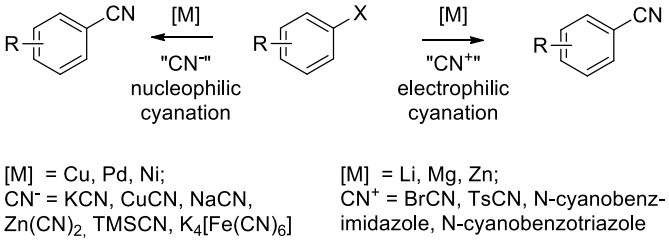


Figure 2.50: Comparison of nucleophilic and electrophilic cyanations ofaryl halides

Nevertheless, one of the general problems in these reactions is the need for a significant amount of catalyst due to the high affinity of the cyanide ion towards Pd, Ni, and Cu, which often results in fast deactivation of the catalytic system[106].

The electrophilic cyanation of aryl halides is a complementary procedure to the transition-metal catalyzed nucleophilic cyanation of aryl halides. Beller[107] procedure should be noticed due to the wide range applicability, it uses Grignard reagent and electrophilic cyanide donor N-cyano-N-phenyl-p-methylbenzenesulfonamide to form in high yields nitrile derivatives.

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[103] Rosenmund, K. W.; Struck, E.; *Chemische Berichte*, **1919**, *52*, 1749.
[104] Sandmeyer, T. *Berichte der deutschen chemischen Gesellschaft*, **1884**, *17*, 1633–1635.
[105] Schareina, T.; Zapf, A.; Beller, M.; *Chem. Commun.*, **2004**, 1388.
[106] M. Sundermeier, A. Zapf, S. Mutyala, W. Baumann, J. Sans, S. Weiss, M. Beller, Chem. Eur. J. 2003, 9, 1828
[107] Anbarasan, P.; Neumann, H.; Beller, M.; *Chem. Eur. J.*, **2011**, *17*, 4217 – 4222

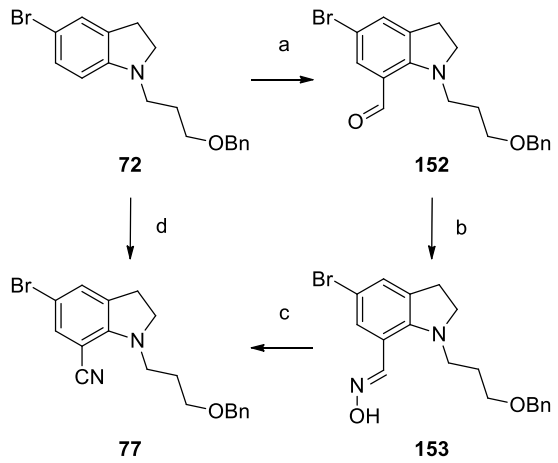
We choose to avoid classical Rosemund von Braun and Sandmeyer reactions due to the use of toxic cyanides and appealing Grignard procedures because of the instability of Grignard reagent (Pages 89-94) generated on the indoline scaffold.

Initially, we would have liked to try a palladium catalysed introduction of nitrile on aromatic ring using nontoxic and stable potassium ferrocyanide $K_4[Fe(CN)_6]$ [108] salt on 1-acetyl-5-bromoindoline **97** but disappointingly we found that patent literature is full of patents claiming this methodology.

To avoid patents issues we tried to improve the VH formylation, convertion into oxime and dehydration process. This procedure can be shortened using hydroxylamine hydrochloride in the reaction media[109]. The procedures were tried on electron-rich indoline **72** to familiarise with the operative experimental conditions and also to look for a new appropriate substrate for our copper catalysed arylation (Scheme 2.27).

[108] $K_4[Fe(CN)_6]$ stability and safety is due to the strong coordination bond formed between cyanide ions and iron that make the complex inert and it could release cyanide gas only when it is treated with strong acids. This property permits potassium ferrocyanide to not decompose in the body, in fact lethal dose (LD_{50}) in rat is only 6400 mg/kg.

[109] Liebscher, J.; Bechstein, U.; *Zeitschrift für Chemie*, **1983**, *23*, 214 – 215.

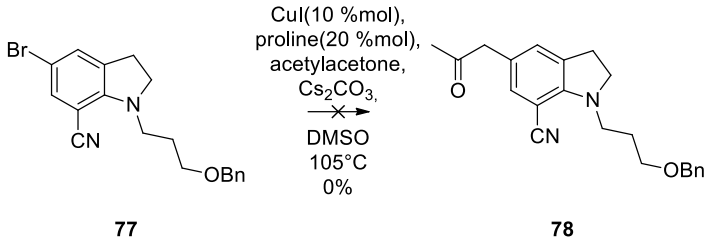


Condition: a. $POCl_3$, DMF, DCM, 70%; b. NH_2OH*HCl, Py,THF,; c. Ac_2O, Py, THF 95% (2 steps); d. $POCl_3$, DMF, NH_2OH*HCl, DCM, 85%.

Scheme 2.53: Classic and one-pot procedures to form nitrile 77

Both procedures worked well furnishing desired product **77** in good yield. The one-pot procedure gave nitrile **77** in 85% yield while the three steps procedure in 66.5%.

Once the indoline scaffold substituted with the nitrile in position 7 was obtained, the copper catalysed reaction was tried on compound **77** using the same conditions developed on substrate **97** (Page 114). We expected the electron-withdrawing nitrile group would have enhanced the reactivity of 5-bromoindoline derivatives and in fact **77** reacted quickly but generating a wide number of degradation by-products. (Scheme 2.28)



77 **78**

Scheme 2.54: Copper catalysed reaction on substrate 77

Unfortunately the N-alkylated derivative **77** proved not to be the substrate of choice for the copper catalysed C-arylation. Moreover alkylated indoline derivatives **72**, **77**, **148** and **149** were prone to oxidation and easily converted at room temperature into the corresponding indole derivatives both in neat and solution conditions (Figure 2.30). Solid derivatives **70** and **147** resulted to be more stable and degraded more slowly.

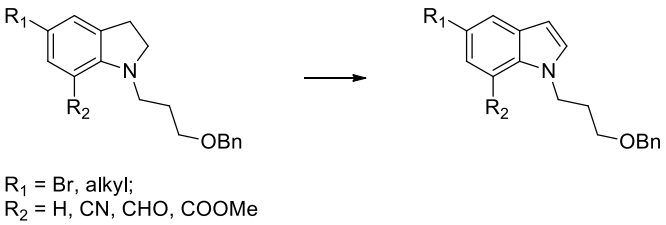
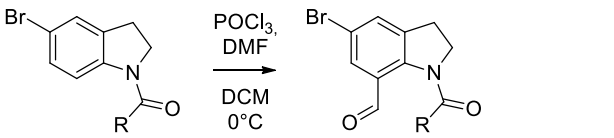


Figure 2.51: Oxidation of indoline derivatives to indole

As most of the intermediates presenting the alkyl C_3 chain on the indoline nitrogen proved to be unstable or not suitable for the C-arylation reaction we decided to keep the indoline intermediates protected as amide as long as possible during the whole synthesis. We tried then to introduce the nitrile in position 7 of 1-acetyl-5-bromoindoline **97** using the VH formylation, convertion into oxime and dehydration process.

First attempt using already tested conditions gave sudden disappearance of the starting material **97**. TLC analysis showed a complete conversion of compound **97** into a single product. Unfortunately ^{1}H-NMR and mass analyses revealed the new compound to be derivative **155** (Figure 2.31) formed by condensation of Vilsmeier reagent with the acetamide residue in the acidic media (Scheme 2.29). Thus, we decided to replace the acetyl protecting group with the benzamide one in order to avoid the condensation reaction. Compound **156** was then subjected to VH reaction in DMF/DCM at room temperature, but the starting material did not react at all. Using DMF as solvent and rising the temperature up to 80°C did not give any conversion as well.



97 : R = CH_3,
156 : R = Ph

154 : R = CH_3, 0% (by-product),
157 : R = Ph, 0% (no reaction)

Scheme 2.55: VH reaction on electron-poor indoline

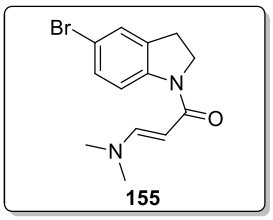
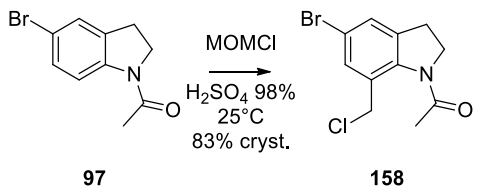


Figure 2.52: Compound 155 derived from VH reagent attacks on acetamide group

We evaluated then different formylation methodologies. We tried the Duff[110] reaction which makes use of hexamethylenetetramine but the reaction did not occur and the Blanc type chloromethylation[111] reaction using methoxymethyl chloride (MOMCl). Chloromethylation reaction works normally in presence of Lewis acids (e.g. $TiCl_4$, $AlCl_3$, $ZnCl_2$, $SnCl_4$) using MOMCl as reactant. MOMCl was synthesised applying a known and safe procedure starting from hexanoyl chloride and dimethoxymethyl ether[112] and avoiding formation of carcinogenic dichlorodimethyl ether by-product.[113]

The lewis acid traditional procedures did not affect the desired functionalization, while we obtained the desired product modifying a reported procedure.[114] Compound **97** was dissolved in concentrated sulphuric acid, then MOMCl was added at room temperature. After 2 hours the starting material was fully converted into desired product **158** as off-white solid after crystallisation in 83% yield. (Scheme 2.30)



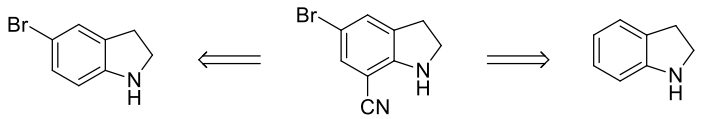
Scheme 2.56: Chloromethylation of 1-acetyl-5-bromoindoline 97

Tentative conversion of methyl chloride group 158 into an aldehyde function via Kornblum oxidation procedure[115] or into desired nitrile using ammonia/iodine

[110] Duff, J. C.; Bills, E. J.; *J. Chem. Soc.*, **1932**, 1987.
[111] Blanc, G. L.; *Bull. Soc. Chim. France*, **1923**, *33*, 313.
[112] Linderman, R. J.; Jaber, M.; Griedel, B. D.; *J.Org. Chem.*, **1994**, *59*, 6499-6500.
[113] Marvel, C. S.; Porter, P. K.; *Organic Syntheses*; Wiley: New York, *1941*; Collect. Vol. I, p. 377 Classic procedure generates dichlorodimethyl ether as by-product
[114] R. Ikan, Y. Fatal, *J. Chem. Eng. Data*, **1971**, *16*, 125 – 126.
[115] Kornblum, N.; Jones, W. J.; Anderson, G. J.*; J. Am. Chem. Soc.*, **1959**, *81*, 4113–4114.

mixtures[116] or trichloroisocianuric acid (TCCA) and ammonia[117] unfortunately did not give the expected results in terms of yields.

Introduction of an electrophile at position 7 of the indoline scaffold bearing a bromine in position 5 and the amide protection on the nitrogen atom revealed to be more challenging than expected so we decided to try the introduction of nitrile directly on N-unprotected indoline **2** and **70** (Figure 2.32).



70 **76** **2**

Figure 2.53: Desired nitrile introduction

We found in literature a singular reaction that allow the introduction of a nitrile regioselectively on *ortho* position of aryl amines.[47,118] This reaction is a modification of the Houben-Hoesch[119] reaction and represents a unique example of regioselective electrophilic aromatic substitution which works without the presence of any ligand or directing group. (Figure 2.33).

[116] Iida, S; Togo, H.; *Synlett*, **2008**, *11*, 1639 – 1642.
[117] Veisi, H.; *Synthesis*, **2010**, *15*, 2631 – 2635.
[118] a. Adachi, M.; Matsumara, H.; Sugasawa, T.; JP19770186, **1986**.
b. Sierre, J-P. R.; Ried-Mörel, A. W.; US5380857, **1995**.
[119] a. Hoesch, K.; *Ber*. **1915**, *48*, 1122 – 1133;
b. Houben, J. *Ber*., **1926**, *59B*, 2878 – 2891;

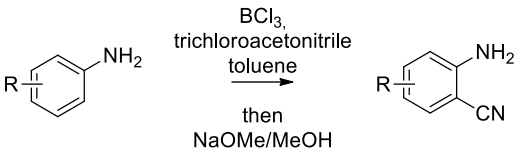


Figure 2.54: Regioselective electrophilic substitution to insert the nitrile

According to the mechanism of the reaction the indoline is reacted with BCl_3 forming a complex which loses HCl upon heating converting into derivative **B** (Figure 2.34). When the electrophile is added (e.i. trichloroacetonitrile or methyl thiocyanate) to the reaction mixture, the lone pair present on the heteroatom of the electrophile generates a complex with the newly formed organoboron compound **B** which is still a lewis acid. This complexation reaction is responsible for the regioselectivity of the final reaction because only an intramolecular electrophilic aromatic substitution occurs, yielding, after addition of methanol, the product of substitution **E** in ortho position to the amine. When the solution containing **E** is treated with a strong base, elimination of chloroform occurs forming desired aryl nitrile **159**.

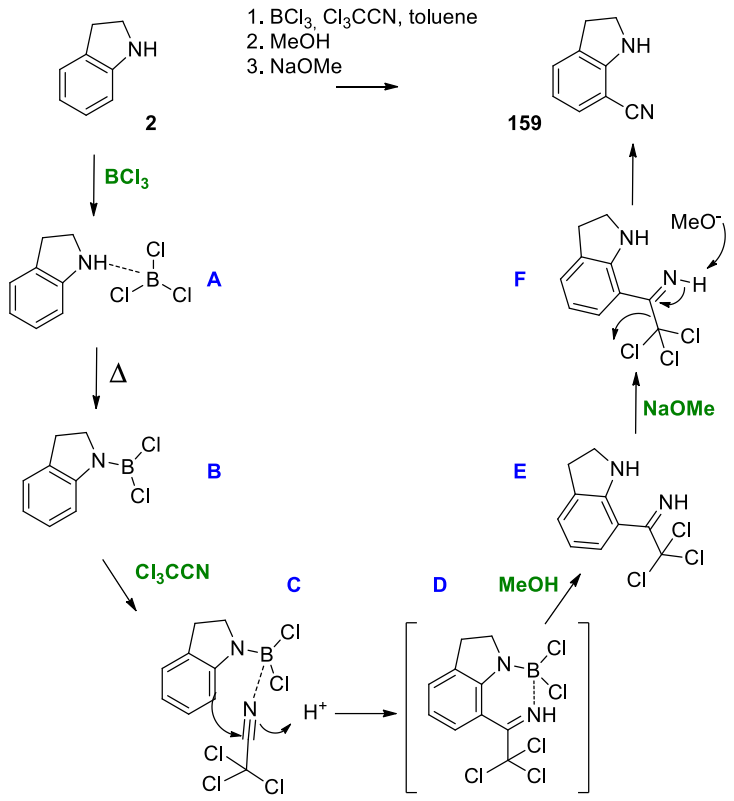
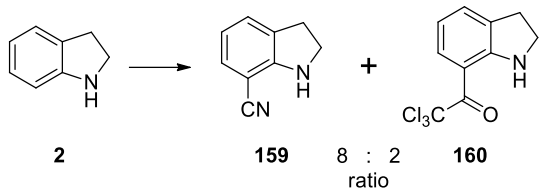


Figure 2.55: Mechanism of BCl_3 regioselective ortho-cyanation

In the first reaction we performed, indoline **2** was dissolved into a 1 M solution of BCl_3 in toluene using 2 mole of lewis acid per mole of indoline. Suddenly a product precipitated and the suspension was heated. At around 60°C the solid dissolved forming a dark red solution which was refluxed for 1 hour. Toluene was distilled off reducing the volume of the solution approximately to 1/3 and then cooled down to 20°C. Trichloroacetonitrile was added to the mixture which was left to react overnight at 50°C. The reaction mixture was cooled to 0°C and treated with a solution of NaOMe in MeOH and the thus obtained mixture was further stirred at room temperature for 2 hours. The crude was obtained after concentration and extraction procedure, TLC revealed the presence of two different compounds. ^{1}H-NMR, ^{13}C-NMR and mass analysis of the crude revealed that nitrile compound **159**

along with trichloroacetophenone derivative **160** (8:2 ratio) were obtained in high yield and high regioselectivity (Scheme 2.31). Trichloroacetophenone derivative **160** might be formed by hydrolysis of intermediate trichloroacetimine **E** because of the presence of moisture in the methoxide solution used in the elimination step. In a second test reaction, the solution containing the imine **E** was poured into a freshly made NaOMe solution, but ketone **160** still formed in the same amount as in previous experiment. Crystallisation of the reaction crude revealed a better solubility of nitrile derivative **159** in most of the solvent used and this allowed us to isolate and characterize pure trichloroacetophenone derivative **160** after 3 consecutive crystallisations.



Scheme 2.57: Formation of nitrile and ketone in BCl_3 reaction

We were trying to obtain the nitrile derivative **159** of course, but unfortunately nitrile was never been obtained selectively and in high yield, on the contrary ketone derivative **160** was easily formed just treating the reaction mixture with water in order to allow the imine intermediate **E** to hydrolyse. In this way ketone **160** could be obtained with complete chemoselectivity and quantitative yield.

Moreover intermediate imine **E** can be converted not only in nitrile **159**, in the ketone **160** but also into the carboxylic acid **161** or its esters (Figure 2.35).

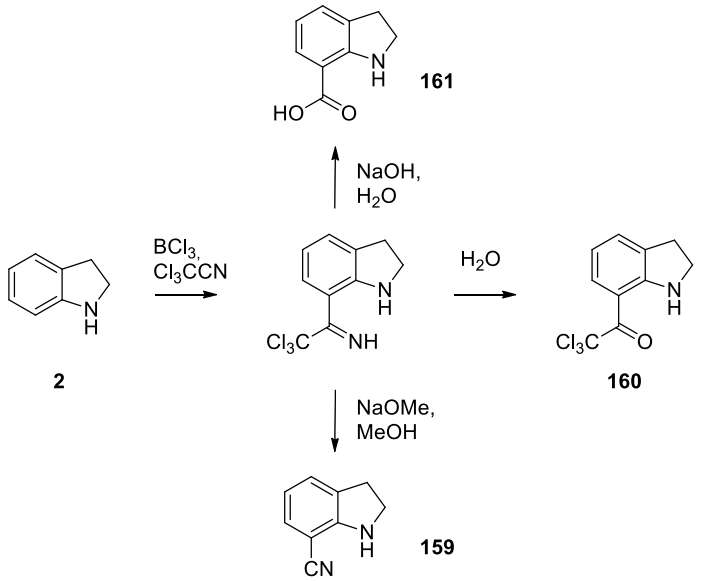


Figure 2.56: Derivatives obtained with different workup procedure

Having optimised the preparation of ketone **160** we decide to try the conversion of **160** into ester **162** and then to convert ester derivative **163** into the amide present in Silodosin (Figure 2.36)

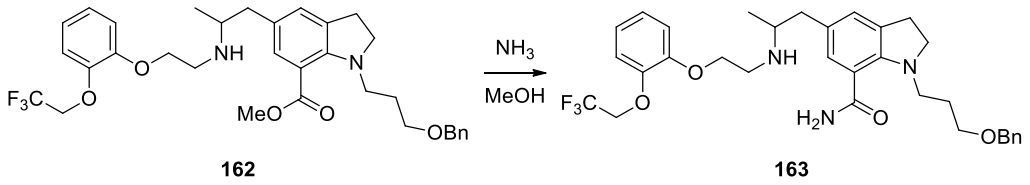
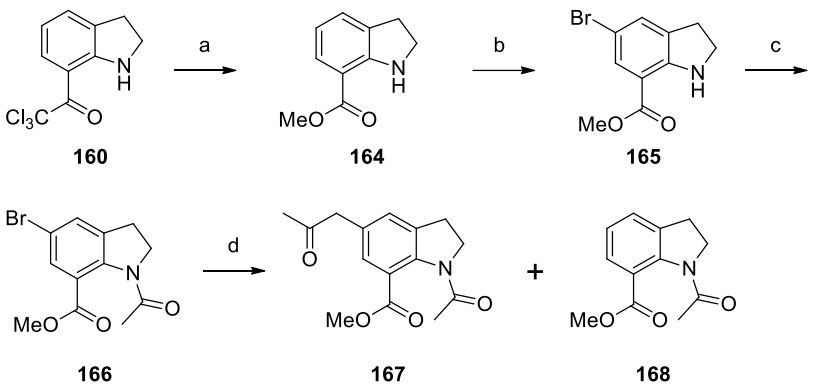


Figure 2.57: Desired conversion of ester into amide.

Methyl ester **164** was obtained by reacting ketone **160** with sodium methoxide in methanol and then it was converted into the brominated derivative **165** using NBS in MTBE isolated as solid crystallising from MTBE/heptane mixture in 66% yield

from compound **160**. The reaction crude was suddenly acetylated using Ac_2O in toluene to obtain compound **166** that crystallised from ethyl acetate in 69% yield. Compound **166** was submitted to the copper catalysed reaction (Scheme 2.32) applying the condition previously optimised for compound **97**. The use of different bases was briefly exploited, obtaining ketone **167** in 65% yield using Cs_2CO_3 as base in DMSO (1.3 M) and proline (mol 20%) as ligand. Chromatography purification was needed also because protonolysis product **161** was formed in 35% yield.



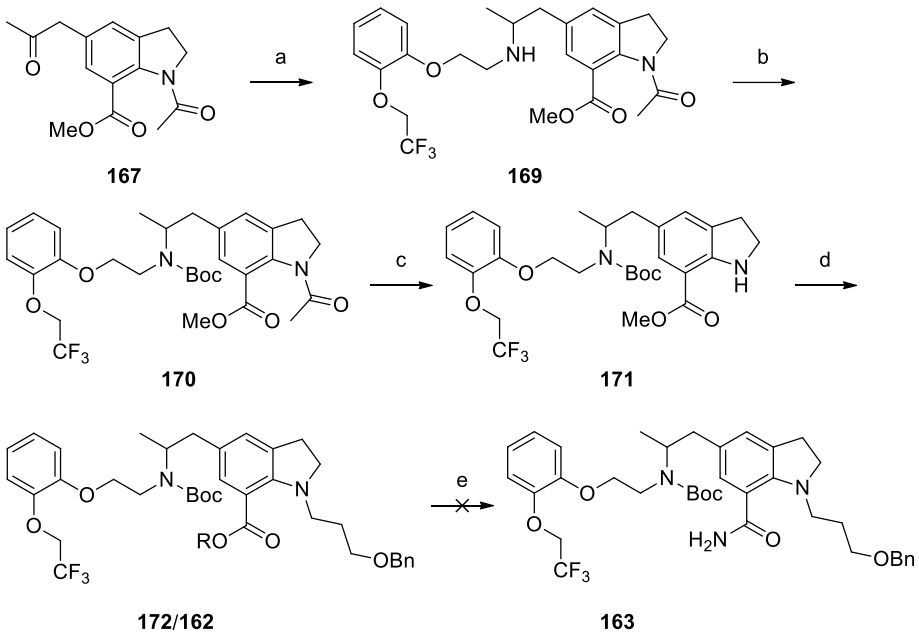
Condition: a. NaOMe, MeOH; b. NBS, MTBE, 66% (2 steps); c. Ac_2O, Toluene, 69%; d. CuI(10 %mol), proline(20 %mol), acetylacetone, Cs_2CO_3, DMSO, 65%.

Scheme 2.58: Synthesis of derivative 160

Once compound **167** had been obtained we decided to use this intermediate to continue our synthesis and to demonstrate that at a proper step of our process the conversion of the ester functional group into the primary amide can be performed. (Figure 2.38)

Ketone **167** was converted into racemic amine **169** in 67% yield by reductive amination with amine **79** in presence of $NaCNBH_3$. Secondary amine **169** was then

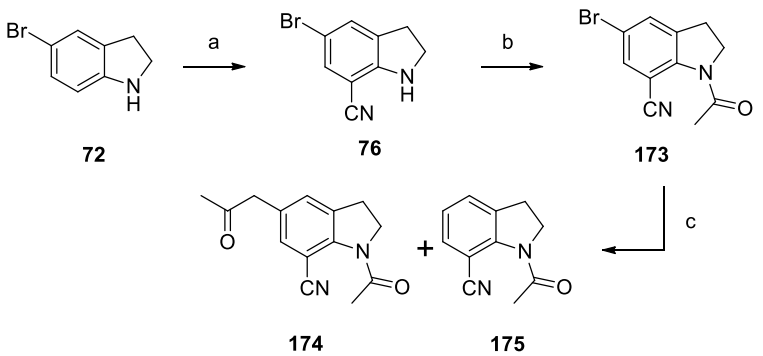
protected as *tert*-butyl carbamate and the acetamide protection was removed in presence of sodium methoxide in anhydrous methanol to let the solvolysis occur without the hydrolysis of the methyl ester. This procedure allowed the removal of acetamide at 25°C giving compound **171** in 94% yield after two steps. Indoline derivative **171** was then alkylated with compound **98** in ethanol as already performed with other substrate (**99**, **72**, **148**). With compound **171** the use of ethanol as solvent gave cuncurrent transesterification reaction obtaining ethyl ester compound **172** along with methyl ester 162 and only 50% conversion. Compound **172** was isolated in very low 30% yield after chromatography. Nevertheless conversion of the ester into the amide was tempted but the reaction with ammonia did not occur at all even performing the reaction in harsh conditions (Scheme 2.33).



Condition: a. **79**, $NaCNBH_3$, THF, 82%; b. Boc_2O, DCM; c. NaOMe, MeOH, 87%; d. **98**, K_2CO_3, EtOH, 30%; e. NH_3, MeOH, 0%. **172** : R = Et; **162** : R = Me

Scheme 2.59: Desired conversion of ester into amide.

This very frustrating result forced us to start again our synthesis. In order to take advantage of our method of introducing susbstituents at position 7 using the BCl_3 mediated procedure, we reconsidered the possibility of introducing the desired nitrile functionality. Instead of using trichloroacetonitrile, the more expensive methyl thiocyanate[47] was used, apparently giving selectively the desired nitrile group. The reaction was performed on substrate **70** as previously described and nitrile **76** was obtained in 73% yield after crystallisation. Acetamide **173** was then formed reacting **76** with acetic anhydride in toluene obtaining **173** in 48% yield after crystallisation from toluene. Bromide **173** was submitted to the copper catalysed C-arylation which gave desired compound **174** in 40% yield after chromatography (Scheme 2.28). Analysing the GC-MS chromatogram of the reaction crude, the starting material was fully converted, and only ketone **174** and protonolysis product **175** were present in a 75% : 25% ratio respectively.



Condition: a. BCl_3, methyl thiocyanate, toluene, then NaOMe, MeOH; b. Ac_2O, Toluene, 48%; d. CuI(10 %mol), proline(20 %mol), acetylacetone, Cs_2CO_3, DMSO, 40%.

Scheme 2.60: Synthesis of compound 168

To clarify why the distribution products ratio of the crude and the yield in **174** were so different, we performed a second reaction checking the reaction mixture without performing any workup procedure on the sample, but only diluting a sample of the

reaction mixture in methanol before injecting it in HPLC and HPLC-MS. The analyses revealed that the sample was constituted by reactant **173**, product **174**, known protonolysis impurity **175** the diketone intermediate **176** (Figure 2.38) but also by some other side products (Figure 2.37). We decided that we had to understand what was really happening in our reaction mixture so we tried to isolate the impurities and characterise them by ^{1}H-NMR, ^{13}C-NMR and mass analysis.

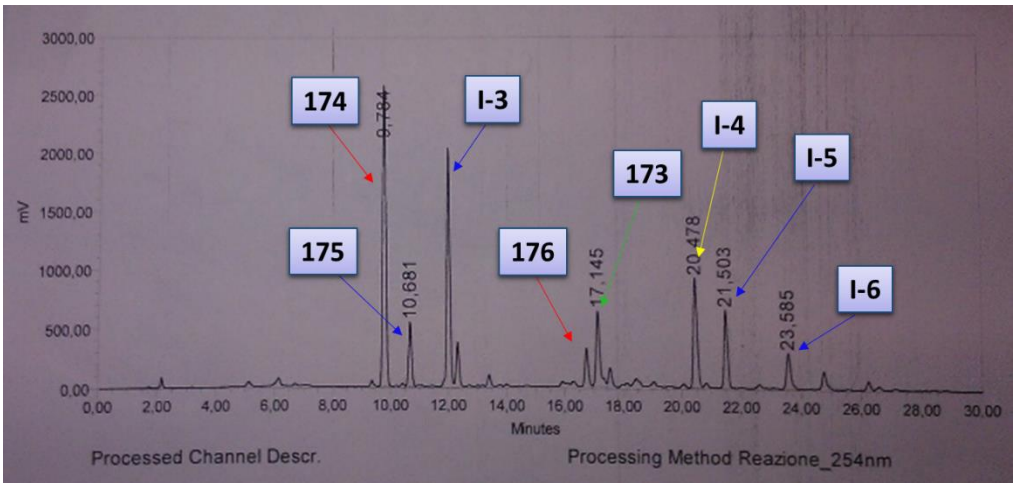


Figure 2.58: HPLC profile of reaction crude

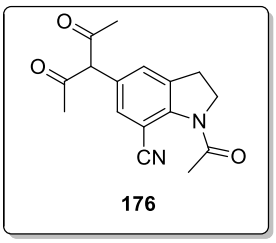


Figure 2.59: intermediate 176

The main side-product **I-3** with retention time of 12.2 minutes resulted to have the same molecular mass of the starting material **173**. While the other three impurities at retention time 20.4 minutes **I-4**, 21.5 min **I-5** and 23.58 min **I-6**, were found to have

phenolic structure. The impurities were isolated after chromatography and characterised by Mass and ^{1}H-NMR analyses. In addition we confirmed the phenolic structure treating them with basic water, in fact the impurities were dissolved in basic aqueous media revealing the acidic phenolic proton. Impurity **I-4** was synthesised performing the reaction using the operative procedure without the starting material, this experiment confirmed the hypothesis about the formation of impurity **I-4**.

Compound **I-3** was found to have tricyclic quinolone structure due to intramolecular condensation of starting material **173**. This hypothesis was confirmed by test reaction carried out without acetylacetone in the reaction media. The reaction gave impurity **I-3** with complete chemoselectivity in just one hour and 87% yield after filtration of the reaction media (Figure 2.39).

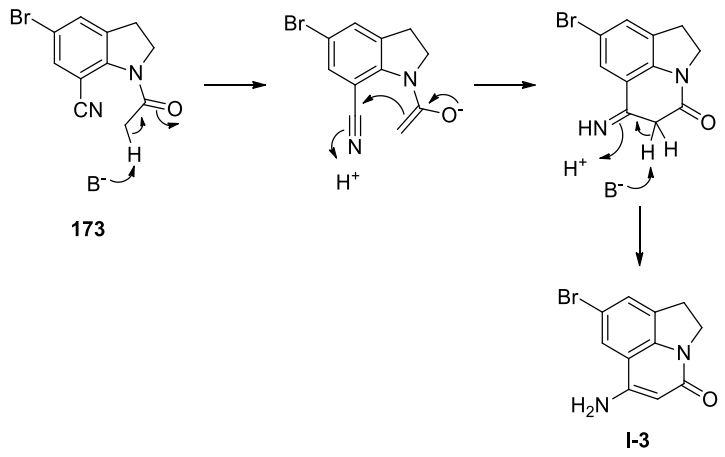


Figure 2.60: 6-enol-endo-dig mechanism of I-3 formation

Impurity **I-3** is due to the attack of the enolic form of acetamide in position 1 to the nitrile function in position 7 according to a favoured 6-exo-dig cyclization to form the 6 membered ring. **I-3** in the first test was not noticed because of the work-up

procedure. In fact treating the reaction mixture with acidic water compound **I-3** dissolved in the water phase and for this reason we were not able to detect it.

We tried to minimise the formation of impurity **I-3** lowering the basicity of the reaction conditions. Organic bases as tributylamine and DIPEA and a weak inorganic base as $NaHCO_3$ did not allow the reaction to work (Table 2.6, entry 4,5 and 6), while the use of potassium hydroxide gave a plethora of side-products along with cyclised impurity **I-3** and hydrolysed indoline **76**.

entry	Base	Conversion [a,b] (%)	174 [a] (%)	I-3 [a] (%)	175[a] (%)	I-5 [a] (%)
1	K_3PO_4	100	40	46	8	4
2	K_2CO_3	70	18	40	17	4
3	Cs_2CO_3	100	42	38	12	6
4	$NaHCO_3$	0	-	-	-	-
5	n-Bu_3N	0	-	-	-	-
6	DIPEA	0	-	-	-	-
7	KOH	100	10	20	4	5
8[c]	K_2CO_3	100	40	33	7	16

Reaction condition: **173** (3.77 mmol), base (3 mole ratio), CuI (10 mol%), proline (20 mol%), DMSO (3 vol, 1.26 M) mechanical stirring (550 rpm), 105°C. a. HPLC average in A%, b. conversion after 20 hours, c. reaction performed with 10% of water complete conversion after 16 hours.

Table 2.6: Investigation of base effect over impurities formation

Phenolic impurities are probably formed because of the aldolic condensation and subsequent aromatisation of acetylacetone with itself (**I-4**), with intermediate **176** (**I-6**) and with ketone **174** (**I-5**) (Figure 2.40). Noteworthy the amount of phenol derivative **I-5** increased a lot by performing the C- arylation in the absence of the proline ligand.

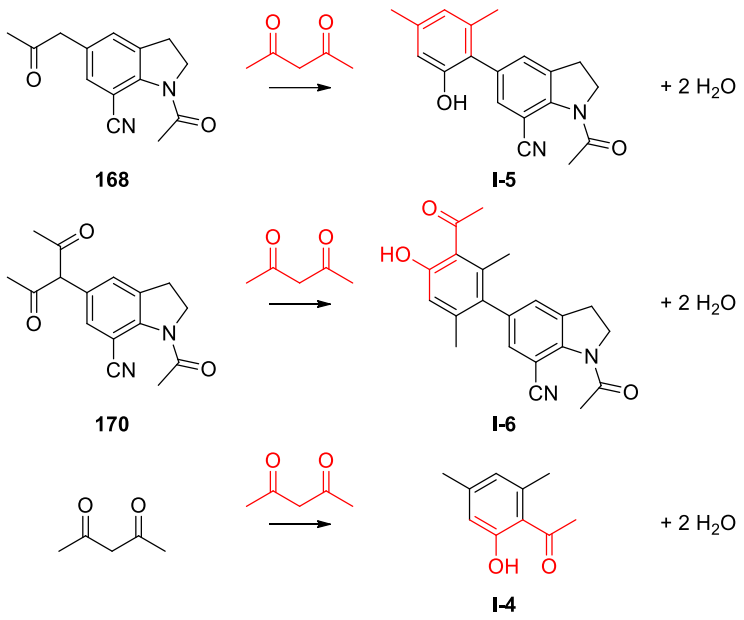


Figure 2.61: Formation of impurities I-4, I-5 and I-6.

Summarising in Figure 2.41 HPLC and structures of any product have been reported.

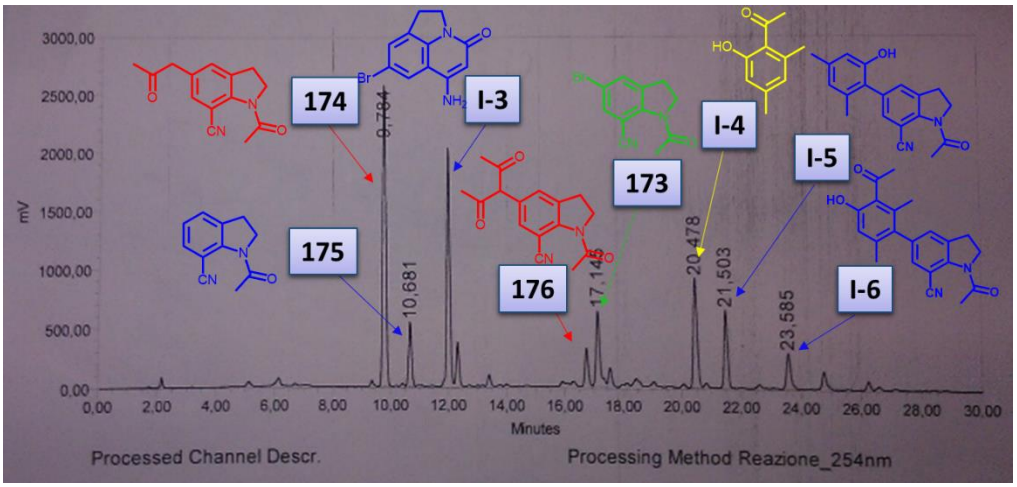


Figure 2.62: 6-enol-endo-dig mechanism of I-3 formation

In order to understand how the kinetic of side condensation reactions affects the formation and the yield of the final product, the C-arylation was repeated in our optimized anhydrous conditions and checked every hour by HPLC analysis(Figure 2.43).

Analyses revealed that after 1 h, impurity **I-3** is already formed (Figure 2.43, T1), the major product is represented by diketone intermediate **176** and only small amount of ketone **174** is formed. Noteworthy phenolic impurity **I-4 I-5** and **I-6** had not been formed in the first 5 hours of reaction. When phenol **I-4** appeared in the HPLC chromatogram (Figure 2.43, T2), the amount of diketone **176** started decreasing and the amount of desired product **174** increased rapidly. This phenomenon can be attributed to the fact that phenolic impurities are formed by aldolic condensation along with 2 moles of water that allowed the retro-Claisen reaction giving ketone **174** (Figure 2.42).

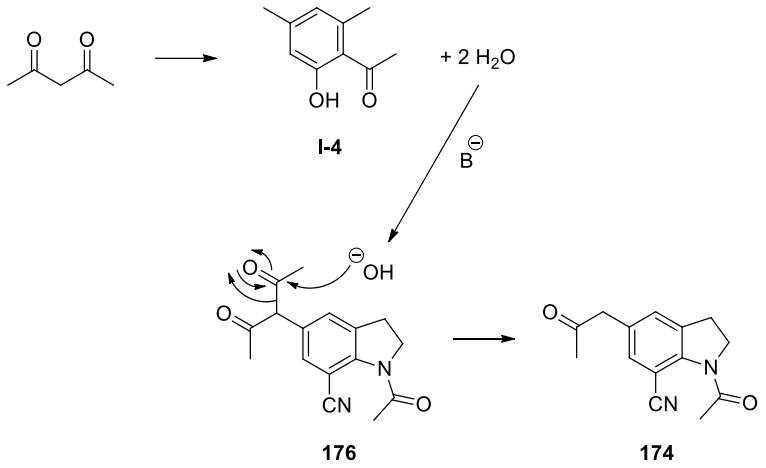


Figure 2.63: Formation of impurities I-4, I-5 and I-6.

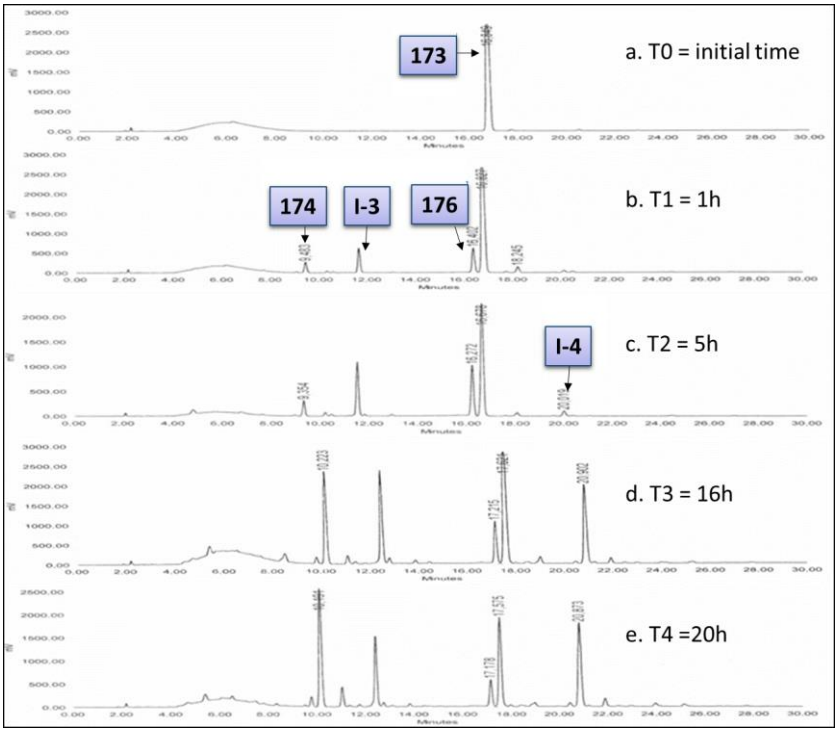


Figure 2.64: Kinetic analysis of copper catalysed reaction

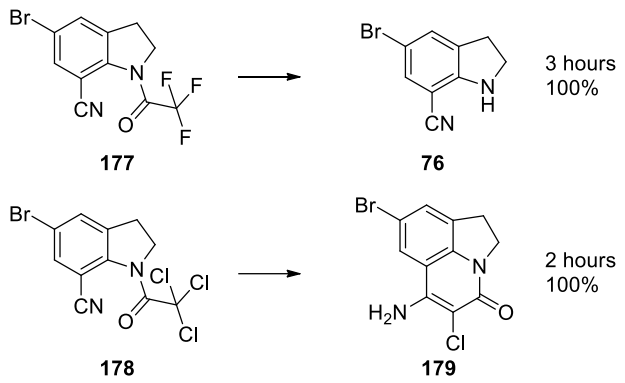
Taking into consideration that water formed in condensation side reactions favours the retro-Claisen mechanism leading desired ketone, we repeated the C-arylation adding 10% of water in the reaction mixture. The reaction in the presence of water gave complete conversion after 16 hours using K_2CO_3 (Table 2.6, entry8), while in anhydrous condition the maximum conversion after 20 hours was 70% (Table 2.6, entry 2), the yield in desired ketone 174 increased and we were able to avoid the formation of impurity **I-6**.

The use of weaker (Table 2.6, entry 4) or organic (Table 2.6, entry 5, 6) bases did not let the C-arylation occur, the addition of water accelerated the formation of ketone **174** but did not decrease the formation of **I-3**. The minimum operative temperature for the reaction was found to be 95°C but **I-3** was found in the same ratio, while at lower temperature (80°C) only **I-3** was formed. This data confirmed

that intramolecular cyclisation is favoured. All the efforts done to avoid the main impurity **I-3** were unsuccessful, so to overcome this issue we decided to change the acetamide protecting groups with a group free of any enolizable proton.

N-Trifluoroacetyl protected indoline derivative **177** prepared from **76** was subjected to C-arylation but easily hydrolysed into compound **76** after 3 hours in quantitative yield (Scheme 2.35). N-Trichloroacetyl protected indoline derivative **178** prepared from **76** in the same conditions gave a product **179** that was isolated after filtration from the reaction media poured in water. The ^{1}H-NMR spectrum of the isolated product did not display neither ketone CH_2 signal at 3.3-3.6 ppm region nor ketone CH_3 signal at 1.9-2.4 ppm region, in addition one of the aromatic proton (presumably the one in the 6 position) moved downfield. The ^{1}H-NMR and the ^{13}C-NMR spectra resulted very similar to the ones of impurity I-3.The mass analysis showed the characteristic Br-Cl isotope pattern distribution and aboundance [(298 (75) - 300 (100) - 302 (25)]. This evidences convinced us to assign quinolone structure to the compound **179** (Scheme 2.35). Formation of **179** has been explained by considering an atomic transfer radical cyclisation (ATRC)[120] between trichloroacetamide and nitrile in position 7 (Scheme 2.35). In fact tricloroacetamides are known to form radicals in the presence of Cu(I) salt[121,122] which easily react with double and triple bond[123], but it should be noted that to the best of our knowledge the ATRAC radical reaction between trichloroacetamides and nitrile has been never reported. This new reaction is now under study to ascertain a future applicability of the reaction.

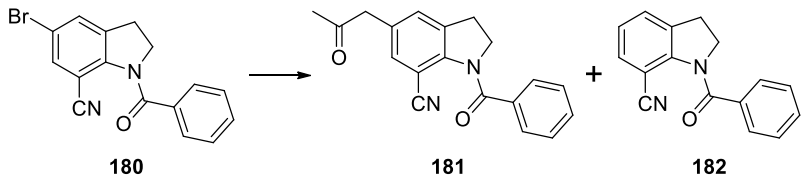
[120] Clark, A. J.; *Chem. Soc. Rev.*, **2002**, *31*, 1 – 11.
[121] Eckenhoff, W. T.; Pintauer, T.; *Catal. Rev. Sci. Eng.*, **2010**, *52*, 1 – 59.
[122] Nagashima, H.; Wakamatsu, H.; Itoh, K.; *J. Chem. Soc., Chem. Commun.*, **1984**, 652 – 653.
[123] Diaba, F.; MartÍnez-Laporta, A.; Bonjoch, J.; Pereira, A.; Muñoz-Molina, J. M.; Pérez, P. J.; Belderrain, T. R.; *Chem. Commun.*, **2012**, *48*, 8799 – 8801.



Condition: CuI(10 %mol), proline(20 %mol), acetylacetone, Cs_2CO_3, DMSO, 105°C.

Scheme 2.61: Products derived from copper catalysed reaction on different indoline substrate

N-Benzoyl protected indoline derivative **180** prepared from **76** converted completely in 20 hours. Flash chromatography of the reaction crude gave desired ketone **181** in 68% yield and the protonolysis product **182** in 18% yield (Scheme 2.36). Only **I-4** and **I-7** by-products (Figure 2.44) were detected in HPLC-MS analysis of the crude as side product. The reaction has been successively fully studied in term of amount of water, nature and amount of ligand and results obtained will be discussed in depth in the next chapter regarding development of the synthetic process.



Condition: CuI (10 %mol), proline (20 %mol), acetylacetone, Cs_2CO_3, DMSO, 105°C, 20 h. **181** = 68%, **182**= 18%

Scheme 2.62: copper arylation on substrate 180

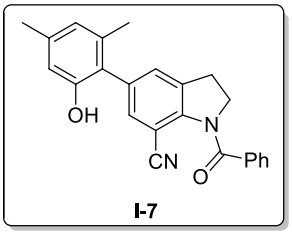
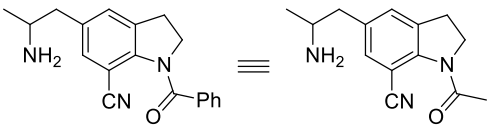


Figure 2.65: Impurity I-7

2.1.3 CONNECTION TO THE FORMAL SYNTHESIS OF SILODOSIN

Once ketone **181** has been obtained we tried to convert it into amine **183** which is a synthetic analogue of amine **12** (Figure 2.45) the most common intermediate of Silodosin.[11]

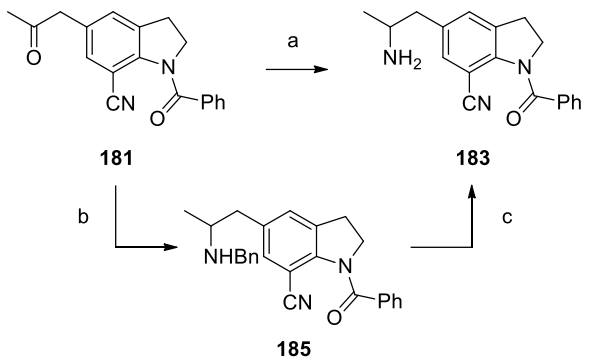


183 **12**

Figure 2.66: Silodosin intermediate synthetic analogues

Initially ketone **181** has been converted into racemic amine **183** by reductive amination in hydrogen transfer conditions using ammonium acetate as ammonia source[124,125]. Primary amine **183** was obtained along with secondary amine **184** (Figure 2.46) as by product which we did not manage to separate. To avoid formation of **184**, ketone **181** was subjected to reductive amination with benzyl amine which after hydrogenolysis gave desired racemic amine **183** in 86% overall yield. (Scheme 2.37).

[124] Gonzalez-Sabin, J.; Gotor, V.; Rebolledo, F.; *Tetrahedron Asymmetry*, **2002**, *13*, 1315 – 1320.
[125] Vahermo, M.; Suominen, T.; Leinonen, A.; Yli-Kauhaluoma, J.; *Archiv der Pharmazie*, **2009**, *342*, 201 – 209.



Condition: a. $NH_4^+HCOO^-$, Pd/C, MeOH, 60%; b. $BnNH_2$, $Na(OAc)_3BH$, THF, 95%; c. H_2, Pd/C, HCl 1M in MeOH, 90%.

Scheme 2.63: : Synthesis of intermediate 177

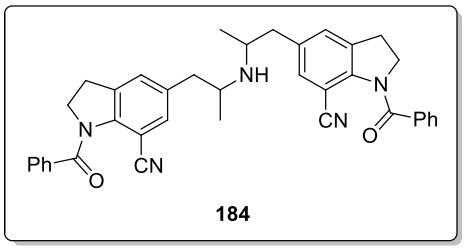


Figure 2.67: Side-product 178

Resolutions of racemic amines **183** (Table 2.7) and **185** (Table 2.8) via diastereoisomeric salt formation have been tempted using several resolving agents, such as L-tartaric acid, L-mandelic acid and (1S)-(+)-10-Camphorsulfonic. In some cases crystalline solids were obtained but unfortunately as racemates or with very low enantiomeric ratio (Table 2.6, entry 4).

entry	resolving agent	Solvent A	Vol.	Yield (%)	e.e. [a] (%)
1	L-mandelic acid	MeOH	4	12	0
2	L-mandelic acid	EtOH	4	46	0
3	L-tartaric acid	EtOH	4	51	0
4[b]	(+)-CSA[c]	MeOH	10	0	10

Reaction condition: starting from **183** (25.8 g, 84.59 mmol) the resolving agent (84.59 mmol) was added in MeOH solution and concentrated in vacuum. The mixture was suspended in solvent and refluxed till dissolution, then cooled to 20°C [a]. chiral HPLC average in A%, [b]. **183** (8.6 g, 28.19 mmol), (+)-CSA (6.5 g, 28.19 mmol) [c]. (+)-camphorsulfonic acid.

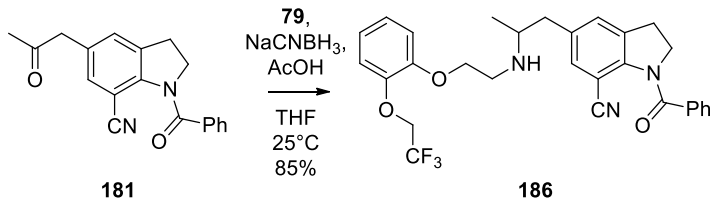
Table 2.7: Substrate 183 diastereomeric salt resolution trials

entry	resolving agent	Solvent A	Solvent B	Vol.	Yield (%)	e.e. [a] (%)
1	L-tartaric acid 0.5 eq	MeOH (9)	H_2O (1)	10	23	0
2	L-tartaric acid 0.5 eq	Acetone (9)	H_2O (1)	10	31	0
3	L-tartaric acid 0.5 eq	EtOH (9)	H_2O (1)	10	27	0
4[b]	L-tartaric acid 0.5 eq	THF (9)	H_2O (1)	10	0	0
5	L-tartaric acid 1.0 eq	MeOH	-	3	74	0
6	L-Mandelic acid 0.5 eq	EtOH	-	4	34	0
7[b]	L-Mandelic acid 1.0 eq	MeOH	-	3	0	-
8	L-Mandelic acid 1.0 eq	acetone	-	4	68	0
9	L-Mandelic acid 1.0 eq	EtOH	-	3	72	0

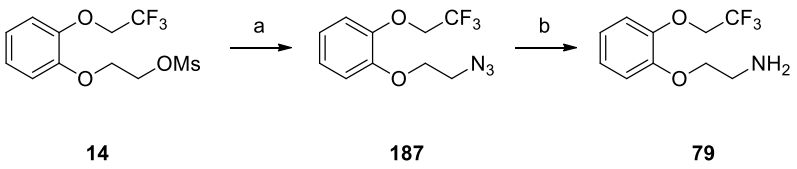
Reaction condition: starting from **185** (3.1 g, 7.08 mmol) the resolving agent was added in MeOH solution and concentrated in vacuum. The mixture was suspended in solvent and refluxed till dissolution, then cooled to 20°C a chiral HPLC average in A%, b no precipitate c.

Table 2.8: Substrate 185 diastereomeric salt resolution trials

In order to try the distereoisomeric salt resolution on a different amine intermediate, a reductive amination of ketone **181** with amine **79** (Scheme 2.38), easily prepared by commercially available mesylate **14** in 89% overall yield (Scheme 2.39), was performed. Racemate **186** thus obtained was reacted with different resolving agents, but also in this case diastereoisomeric resolution did not work.



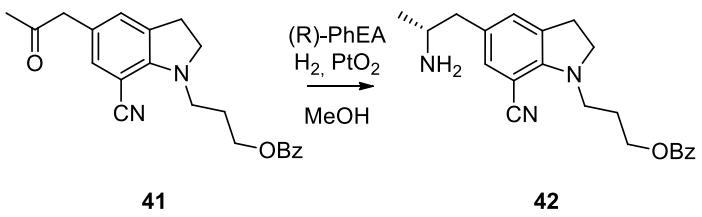
Scheme 2.64: Reductive amination with amine reagent 75



Scheme 2.65: Synthesis of amine 75

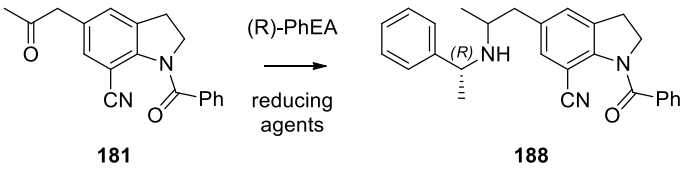
Classical resolution of racemic amines proved not to be the method of choice to obtain the pure enantiomer needed to perform Silodosin synthesis. For this reason we decided to attempt the other classical methodology of the diastereoselctive synthesis to obtain enantioenriched amine **183**. Ketone **182** was in fact subjected to reductive amination with optically pure (R)-phenyl ethylamine ((R)-PhEA) with the hope of obtaining the corresponding secondary amine **188** with a high diastereoisomeric excess and to proceed successively to hydrogenolysis of **188** to obtain **183** with the same value of enantiomeric purity. The choice of (R)-phenyl

ethyl amine was due to the fact that in literature[29] compound **41** is reported to give the correct (R) amine **42** (Scheme 2.40) when subject to diastereoselective reductive amination in presence of (R)-phenyl ethylamine.



Scheme 2.66: Reported diastereomeric reductive amination using (R)-PhEA.

Reductive amination of ketone **181** with (R)-PhEA has been tried using different reducing agents (table 2.8). In any case partial diastereoselectivity was obtained even in case of reductive amination in presence of Adam's catalyst[29] (PtO_2) which gave also a 10% of the already hydrogenolised primary amine **183** as side product.



Scheme 2.67: Conversion of substrate 181

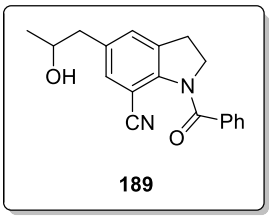
The best reducing agent in term of diastereoselectivity resulted to be sodium triacetoxyborohydride which gave amine **188** in 4:1 diastereoisomeric ratio (Table 2.9, entry 3). In a repetion of the reaction performed by generating *in situ* the reducing agent from sodium borohydride and acetic acid, the reaction worked well

obtaining the same diastereoselectivity and only 3% of alcohol **189** as side-product (Figure 2.47).

entry	reducing agent	solvent	Conversion [a] (%)	Selectivity [a] (%)	d. r. [b] (%)
1	H_2, PtO_2(10mol%)	MeOH	100	89 [c]	3 : 1
2	$NaCNBH_3$	THF	100	100	3 : 2
3	$NaBH(OAc)_3$	THF	100	100	4 : 1
4	$NaBH_4$/AcOH	THF	100	97 [d]	4 : 1

Reaction condition: **181** (1.0 g, 3.26 mmol) solution (0.3 M) reacted at 20°C until disappearance of starting material. a. chiral HPLC average in A%, b. 1H-NMR analysis, c. amine **183** in 10% average, d. alcohol **189** in 3% average.

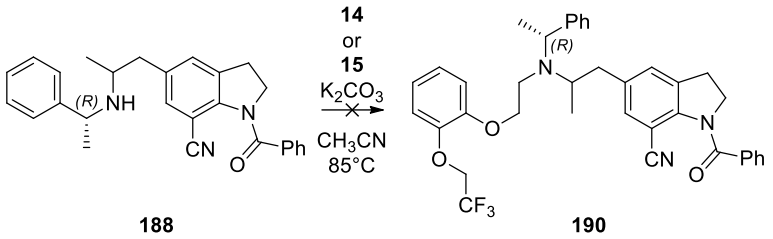
Table 2.9: Diastereomeric ratio related to reducing agents



189

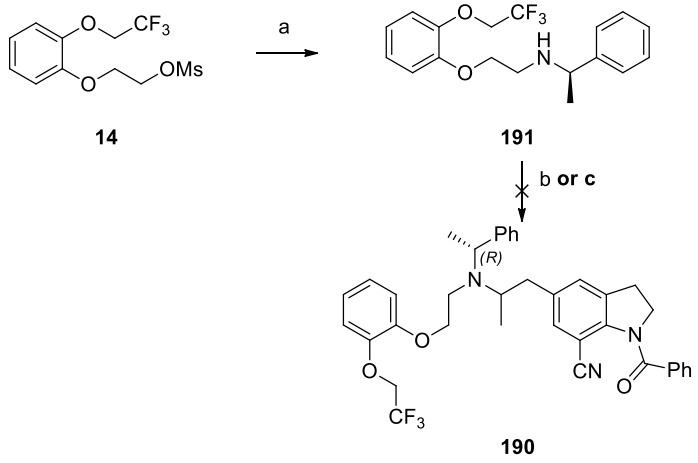
Figure 2.68: Side-product 189

We tried to alkylate amine **188** with our mesylate **14** or bromide **15** (synthesised following reported procedure[11]) in order to form compound **190**. The idea was to keep the phenylethyl group on the amine as protecting group as long as possible during the synthesis and to perform the hydrogenolysis at the end. Unfortunately the alkylations did not occur even when harsh conditions were employed (Scheme 2.42).



Scheme 2.68: Failed synthesis of derivative 190

This result was probably due to the bulkiness of nucleophile **188**. Ketone **181** was also reacted with secondary amine **191**, easily prepared from mesylate **14** (Scheme 2.43)**,** with two different reducing agents (sodium cyanoborohydride and sodium triacetoxyborohydride) in order to get desired amine **190**, but in both cases reaction did not occur at all and starting ketone **181** could be recovered unreacted (Scheme 2.43).

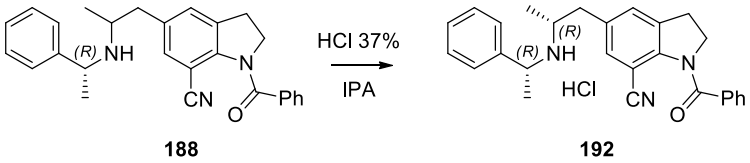


Condition: (R)-PhEA, THF, 89%; b**. 181**, $NaCNBH_3$, AcOH, THF, 0%; c**. 181**, $NaBH(OAc)_3$, AcOH, THF, 0%.

Scheme 2.69: Failed synthesis of derivative 190

As we could not obtain tertiary amine **190**, we decided to use amine **188** to continue our synthesis. The secondary amine **188**, as previously described, could be obtained

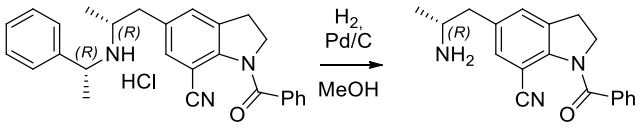
by reductive amination of ketone **181** with (R)-PhEA using $NaBH(OAc)_3$ with a diastereoisomeric ratio of 4:1. We tried to purify it by crystallisation, but we didn't find a suitable solvent. Nevertheless we managed to crystallize the hydrochloride salt of amine **188** from isopropanol (Scheme 2.44).



188 **192**

Scheme 2.70: Non-classic diasteromeric salt resolution of compound 188

Analysing the salt thus obtained by ^{1}H-NMR we noticed pleasantly that the diastereomeric ratio of the product had increased up to 9:1 ratio. Finally hydrogenolysis in methanol (Scheme 2.45) of compound **192** gave desired amine **183**. At this point we could have used **183** to complete the synthesis considering that all the reactions needed to get Silodosin have already been described using its analogue intermediate **12** having the acetamide protection instead of the benzamide one present in **183**.



192 **183**

Scheme 2.71: Removal of phenyl ethyl group via hydrogenolysis

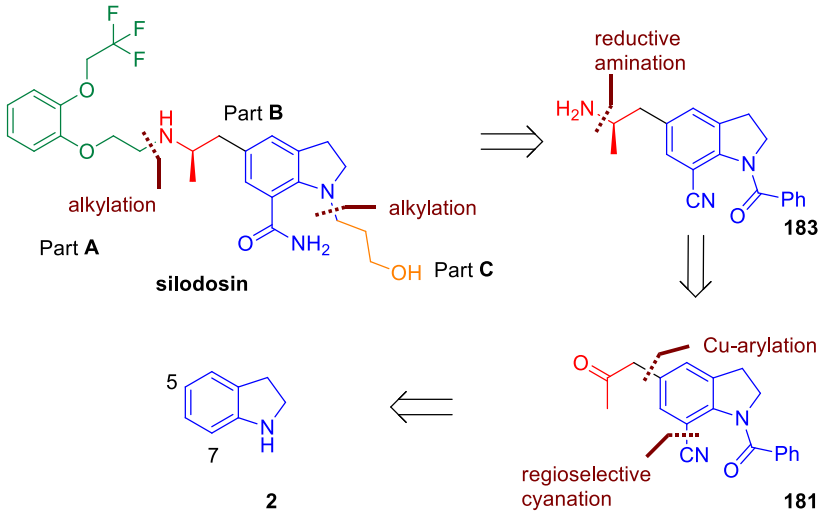
However we decided to develop first the synthetic route to get amine **183** and then with much more material in hand to conclude the synthesis and prepare a sample of Silodosin

2 Result and Discussion: Development

2.2 DEVELOPMENT

In the previous section we stopped the feasibility study of silodosin at level of amine **183** because we decided to develop its synthesis first and then to prepare the sample of the final API.

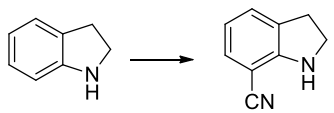
Before describing in details results obtained in the development study it is useful to summarise the synthetic approach which emerged from the previous feasibility study. The key steps of Silodosin synthetic route are highlighted in the retrosynthetic Scheme 2.46. Briefly, starting from indoline **2**, nitrile substituent in position 7 has been introduced by regioselective intramolecular cyanation, the β-ketoalkyl chain in position 5 via a new copper catalyzed C-arylation, the amine group has been introduced with good diastereoselectivity via a diastereoselective reductive amination followed by a selective diastereomeric crystallisation which enabled us to get amine **183** with a 9:1 diastereomeric purity. Alkylation of primary amine and of the indoline nitrogen are the last 2 steps to be studied and developed. These two reactions will be discussed in this section along with results obtained during the scale up study.



Scheme 2.72: Silodosin retrosynthetic disconnection

*2.2.1 COMPOUND **159***

In the feasibility we performed the reaction dissolving indoline **2** onto a 1 M solution of BCl_3 in toluene using 2 mole of lewis acid per mole of indoline. Suddenly a product precipitated and the suspension was heated. At around 60°C the solid dissolved forming a dark red solution which was refluxed for 1 hour. Toluene was distilled off reducing the volume of the solution approximately to 1/3 and then cooled down to 20°C. Methyl thiocyanate was added to the mixture which was left to react overnight at 50°C. The reaction mixture was cooled to 0°C and treated with a solution of NaOMe in MeOH and the thus obtained mixture was further stirred at room temperature for 2 hours. The crude was obtained after concentration and extraction procedure and the crude can be crystallised from n-butanol and hepane in 50% yield. After the first employment of expensive methyl thiocyanate we decided to optimise the reaction using the cheap trichloroacetonitrile and understand the reason of ketone **160** formation in order to modify the procedure and obtain selectively nirile **159**.

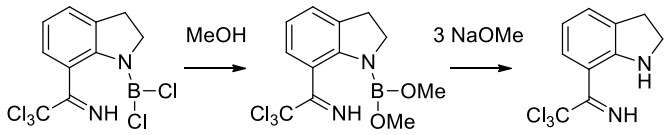


2 **159**

Scheme 2.73: Regioselective nitrile introduction

We studied the elimination of $CHCl_3$ from imine derivative supported by GC-MS analysis. It was noticed that the addition of anhydrous methanol without base did not form ketone **160**, instead the imine derivative resulted stable. Addition of methanol probably forms borane derivative **194** that is converted into **195** in GC-MS analysis

condition. The base was then added gradually in order to understand its effect, addition of 3 mole ratio bring to neutralisation of acidity and allowed the isolation and preliminary characterisation (^{1}H-NMR and GC-MS) of imine derivative **192** (Scheme 2.48). When an additional equivalent is added elimination reaction starts and imine derivative **192** converts into nitrile **159**.



193 **194** **195**

Scheme 2.74: Putative mechanism of intermediate 195 formation

Following the reaction via GC-MS analysis (Figure 2.49) we noticed that stirring the reaction for more than two hours complete conversion into desired nitrile **159** was obtained. Therefore, formation of ketone **160** was due to the uncompleted conversion of imine derivative into nitrile **159**, additional reaction time led to complete conversion. GC-MS analysis help us to understand more deeply the elimination mechanism (Figure 2.48), in fact it can go through elimination of chloroform or it can also go through the formation of methyl imidate intermediate that eliminates forming nitrile. Methyl imidate derivative was noticed to form in 10% average from haloformic reaction between methoxyde and trichloroimine intermediate **196**.

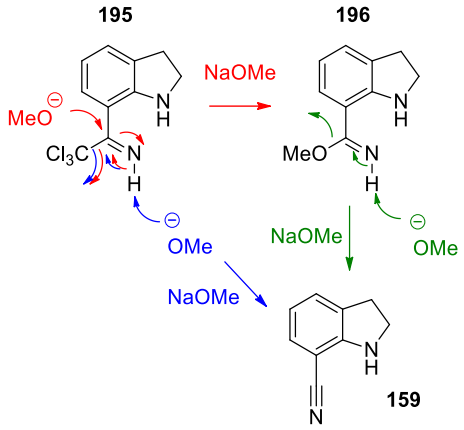


Figure 2.69: Putative formation and conversion of methyl imidate

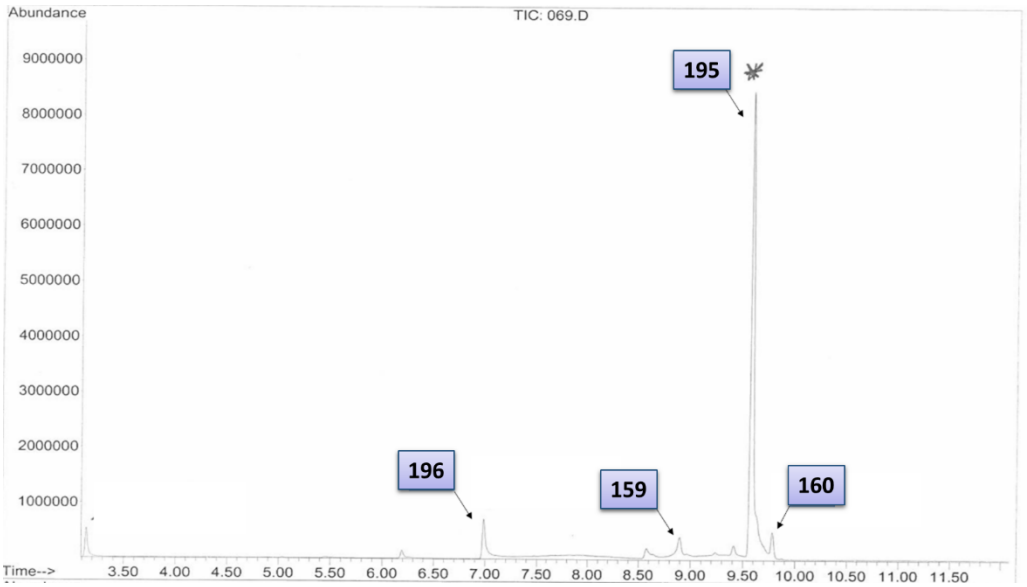


Figure 2.70: GC-MS chromatogram showing intermediates 195 and 196

Nitrile was then isolated crystallising it from n-butanol/heptane mixture (2 volumes[126]) obtaining as off-white solid in 62% yield.

[126] Volume is a conventional term used in industrial chemistry to measure solvents, in particular it relates the solvent to the substrate of the reaction. 1 volume is 1 mL per gram of substrate.

Reaction was then optimised modifying concentration, equivalent of the reagents and operative temperature (table 2.10).

The moles of lewis acid were lowered till 1.0 mole per mole of indoline without noting a decrease of reactivity.

In particular to increase the concentration of the BCl_3 solution we decided to use the cylinder of pure BCl_3 and form the solution at the desired concentration. BCl_3 is not considered a toxic gas, so its use is not restricted. The gas was insufflated in toluene and the quantity of gas dissolved was measured weighting the resulting solution and by titration of the solution with NaOH. The maximum concentration obtained was 2.4 M of BCl_3 in toluene. This operation reduced the cost of the whole reaction because a solution of BCl_3 is more expensive than the in house preparation.

We tried to lower the mole of trichloroacetonitrile employed in the reaction, but we noticed that with less than 2 moles per mole of indoline the reaction slow down reaching the complete conversion after 18 hours. So we decided to use 2 moles per mole of indoline obtaining the complete substitution after 8 hours.

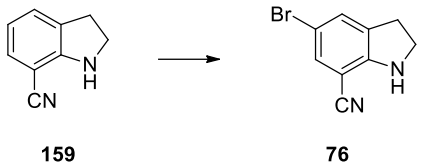
entry	BCl_3 (mole rat.)	Trichloro acetonitrile	Toluene (volume)	NaOMe (mole rat.)	T [b] (h)	Conversion [a] (%)	159 [a] (%)
1	2.0	2.0	10	7	18	100	80
2	1.5	2	6	7	18	100	95
3	1.3	1.5	6	7	18	100	97
4	1.1	1.3	4	5	18	93	90
5	1.0	1.1	4	5	18	90	89
6	1.0	2	4	5	8	96	93
7	1.2	2	4	5	8	100	98

Reaction condition: addition of **2** in BCl_3 solution in Toluene, reflux for 1h, reduction of solvent volume to 1/3, cooling to 20°C. Addition of trichloroacetonitrile and reaction for 4h at 50°C, cooling to 20°C. Addition to methoxide/methanol solution and reaction until completion. [a]. GC-MS analysis; b. time needed for the electrophilic substitution

Table 2.10: Optimisation of regioselective nitrile introduction

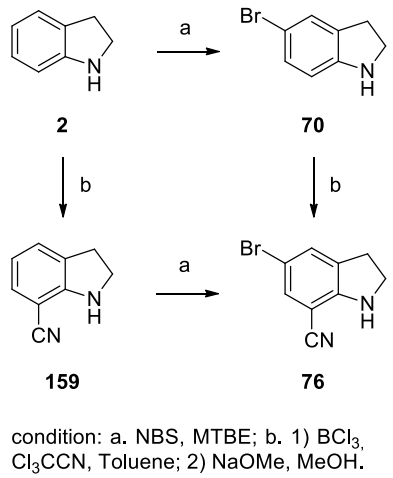
At the end the optimised process was performed dissolving indoline **2** onto a freshly formed 1.5 M solution of BCl_3 in toluene using 1.2 mole of lewis acid per mole of indoline. Suddenly a product precipitated and the suspension was heated. At around 60°C the solid dissolved forming a dark red solution which was refluxed for 1 hour. The solution was cooled down to 20°C and trichloroacetonitrile was added to the mixture which was stirred for 8 hours at 50°C. The reaction mixture was cooled to 0°C and treated with a solution NaOMe in MeOH (5 mole per mole of indoline) and the thus obtained mixture was further stirred at room temperature for 4 hours until the complete conversion into the nitrile monitoring the reaction by GC-MS analysis. The final mixture was treated with NBS in the one pot-two steps process described in the next page.

*2.2.2 COMPOUND **76***



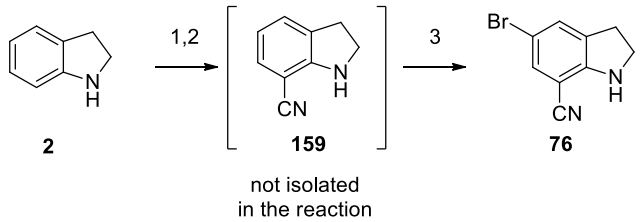
Scheme 2.75: bromination reaction on substrate 159

Planning the synthesis in the development study we can adopt two different route to obtain compound **76**. As already shown in the fesibility section bromination of indoline can be performed regioselectively on indoline **2** with only 7% regioisomer formation, while the introduction of nitrile on indoline **2** is completely regioselective. Therefore we decide to develop the bromination of derivative **159** to obtain compound **76**. (Scheme 2.50).



Scheme 2.76: Two possible synthetic route to derivative 76

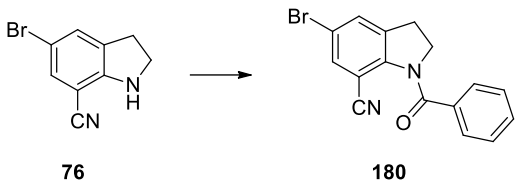
We decided to pursue the second route because nitrile introduction was completely regioselective, while bromination gave 7% of undesired regioisomer. Initially bromination was performed suspending **159** in MTBE and adding 1 equivalent of NBS. After the full conversion the desired product was isolated applying three washing steps with water to remove succinimide waste and the organic layer was concentrated to obtain **76** as oil. Thus, the solvent was changed to methanol letting reaction yield and selectivity unchanged, the next improvement was to perform bromination immediately after the formation of nitrile in the same media before the workup procedure adding NBS to the reaction mixture. The one-pot / two-steps procedure gave intermediate **76** in 51% yield after crystallisation of the benzoylated derivative **180** the yield was comparable to the one obtained from separated two steps procedure (53% after benzoylation). The one-pot procedure avoided the workup procedure after the nitrile introduction step and the use of fresh solvent in the set-up of the bromination step.



one-pot procedure condition: 1) BCl_3, Cl_3CCN, Toluene; 2) NaOMe, MeOH; 3) NBS

Scheme 2.77: Two possible synthetic route to derivative 76

*2.2.3 COMPOUND **180***



76 **180**

Condition: BzCl, TEA, DMAP, Toluene, 51% (from indoline)

Scheme 2.78: Copper catalysed arylation on substrate 180

Benzoylation of amine **76** had been accomplished on crude mixture deriving from cyanation/bromination one pot procedure. The crude was dissolved in toluene with triethylamine, benzoyl chloride was added to the solution. Various parameters had been investigated, in particular the addition of benzoyl chloride to the solution. Usually addition of acyl chlorides increases mixture temperature due to the acid/base reaction, we noticed that the mixture temperature can reach 50°C during the addition without affecting the yield, and no sudden thermal events happens.

Several crystallising solvents had been studied but only toluene and ethyl acetate gave good resuts in term of yield and purity (table 2.11, acetone, methanol and tetrahydrofurane gave only dissolution of the substrate). We obtained the best result in term of yield and impurities precipitating the compound from the reaction mixture adding water.

entry	solvent	volume	yield (%)	purity [a] (%)
1	AcOEt	2	30	98
2	AcOEt	1	41	95
3	toluene	2	43	99
4	toluene	1	50	89
7	MTBE	1	55	75

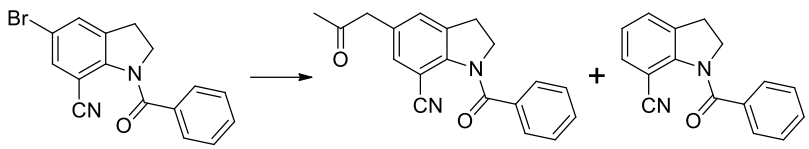
Condition: suspension was heated to reflux for 2 hours then cooled to 20°C and filtrated. a. HPLC analysis

Table 2.11: Study of compound 180 solubility

The procedure optimised after benzoylation of compound **76** led to derivative **180** in 51% yield (calculated on indoline **2** mole). In this way two steps route was optimised performing a one pot-two steps procedure, increasing the yield and avoiding unnecessary workup procedures.

*2.2.4 COMPOUND **181***

As already shown in the previous section (Page 145) the copper reaction on compound **180** led to initial yield of 68% after chromatography purification (Scheme 2.53). Arylation of acetylacetone was investigated in order to make this synthetic step suitable for industrial production and to understand the reaction in depth.



180 **181** **182**

Condition: CuI (10 %mol), proline (20 %mol), acetylacetone, Cs_2CO_3, DMSO, 105°C, **181** = 68%, **182**= 18%

Scheme 2.79: Copper catalysed arylation on substrate 180

An initial work had been performed to understand kinetic and by-products formation (Page 142) allowed us to understand the importance of water. Water could also play an important role in the reaction because Cu(I) disproportionate in Cu(II) and Cu(0) species in the presence of water.

In the presence of water the ligandless reaction (Table 2.12, entry 3) gave better results in term of yield and impurities amount. DMSO containing 5% of water resulted the best amount to allow the retro-Claisen reaction and slower the disproportion of Cu(I). Cesium carbonate and potassium phosphate was replaced by cheap potassium carbonate without affecting the reaction rate, while temperature was lowered to 95°C without affecting the yield but slightly increase the time needed for the complete conversion.

entry	Acac (mol. r.)	K_2CO_3 (mol. r.)	ligand	Time (h)	H_2O	Conc (M)	Conversion [a] (%)	181 (%)	182 (%)
1	3	3	proline	16	10%	1.3	85	50	13
2	3	3	proline	16	10%	1.3	80	51	13
3	3	3	-	16	10%	1.4	95	64 (43)[b]	18
4	3	3	-	15	50%	1.4	0	-	-
5	4	4	-	18	5%	1.4	100	72 (46)[b]	11
6	2	2	-	18	10%	1.4	90	66	25
7	3	3	-	19	5%	1.4	100	68 (43)[b]	15
8	3	3	-	19	10%	1.4	100	65 (41)[b]	18
9	3	3	-	18	5%	1.4	100	62 (45)[b]	28
10	3	3	-	18	10%	1.4	95	60 (45)[b]	22
11	3	3	-	16	10%	1.4	100	68 (46)[b]	17
12	3	3	-	21	10%	1.4	95	65 (45)[b]	15

Reaction condition: **180** (5.0 g, 15.29 mmol), K_2CO_3, CuI (10 mol%), ligand (20 mol%), DMSO/H_2O (3 vol, 1.1 M), 95°C. a. HPLC average in A%, b. crystallisation from acetone 1 volume.

Table 2.12: Optimisation of Cu arylation on substrate 180

Initially the work-up procedure presented the acidification of the reaction mixture, and then the extraction with ethyl acetate. We decided to modify the work-up procedure due to the formation of CO_2 from the neutralisation of K_2CO_3 with HCl. Therefore the reaction mixture was treated with water and extracted with ethyl acetate, then washed with aqueous ammonia solution to remove copper residue. The organic layer was then neutralised with aqueous HCl and washed with brine before concentrating till residue.

Different solubility tests had been done on crystallised Ketone **181** using various solvents (table 2.13), some solvents as methanol, ethyl acetate and acetic acid (table 2.13, entry 1, 2 and 7) gave good result in term of yield but poor purity of the crystallised product. We chose acetone (table 2.13, entry 4) because it gave high HPLC purity in the isolated product even if the crystallisation yield gave only 50%

yield. The reaction mixture had been recrystallised from acetone slurrying the crude at reflux temperature obtaining 45-47% yield of compound **181** with 98% HPLC purity.

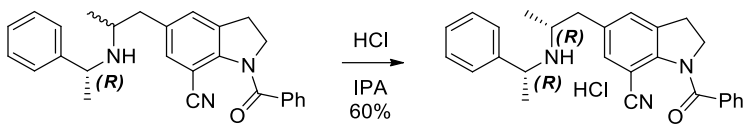
entry	solvent	volume	yield (%)	purity [a] (%)
1	AcOEt	10	80	72
2	MeOH	10	80	66
3	toluene	10	34	58
4	Acetone	10	50	97
5	MEK	10	46	79
6	MEK	5	70	71
7[b]	AcOH	10	90	75

Condition: suspension was heated to reflux for 2 hours then cooled to 20°C and filtrated. a. HPLC analysis, b. complete dissolution of substrate at reflux

Table 2.13: Study of compound 181 solubility

The best condition obtained to perform the reaction (table 2.12, entry 5) and to crystallise the crude (table 2.13, entry 4) had been employed in multi gram scale reaction (250 g) without affecting the yield and obtaining ketone **181** in 47% yield after crystallisation from acetone.

*2.2.5 COMPOUND **192***

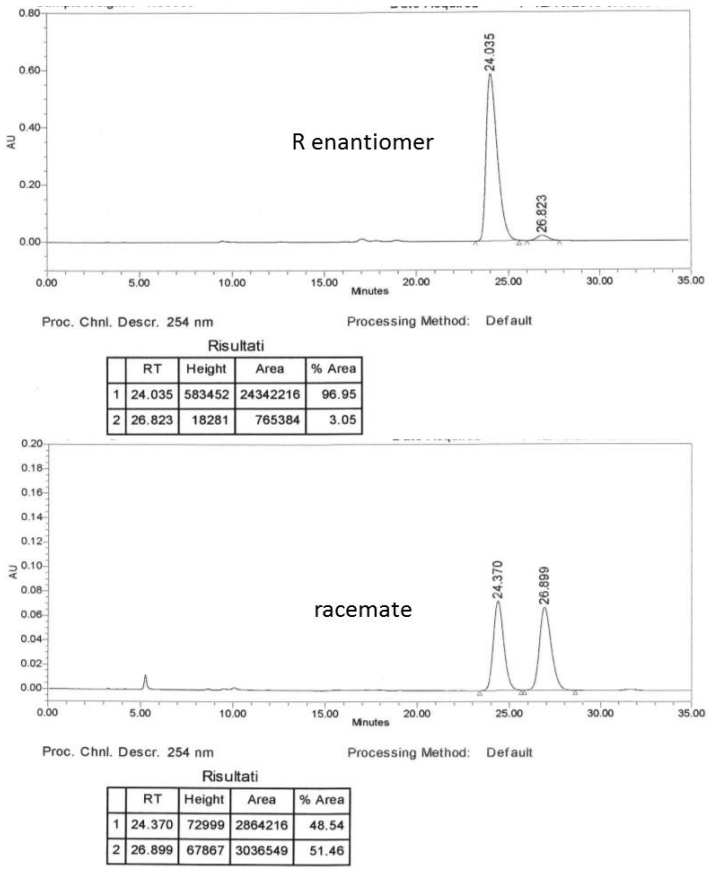


188 **192**

Scheme 2.80: Optimised precipitation of 192

Initial crystallisation of hydrochloride salt **192** (Scheme 2.54) led to a diastereomeric ratio of 9:1, we studied the formation of hydrochloride salt **192** in order to increase the diastereomeric ratio in the solid. During the development of this crystallisation we found the best condition dissolving the compound in iso-propanol and adding aqueous solution of HCl 37% dropwise till the mixture is neutralised, after that the salt starts to precipitate and the suspension was left to stir for 2 hour at 60°C. The filtrate was crystallised two more time to reach the desired diastereomeric excess, the first time from isopropanol and the second one from methanol. Different analytical technique and HPLC condition had been tried, but no one was able to separate the diastereoisomers. Accurate evaluation of the diastereoselection cannot be made using the ^{1}H-NMR, thus removal of ethyl phenyl group was performed prior to evaluate the enantiomeric excess.

The optimised resolution procedures led to amine **183** with an enantiomeric excess of 97% (Figure 2.50).



Risultati

	RT	Height	Area	% Area
1	24.035	583452	24342216	96.95
2	26.823	18281	765384	3.05

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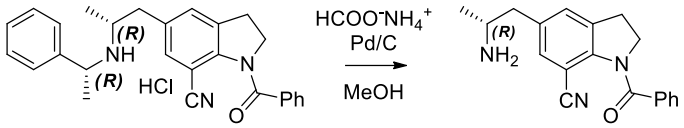
	RT	Height	Area	% Area
1	24.370	72999	2864216	48.54
2	26.899	67867	3036549	51.46

Figure 2.71: Chiral HPLC chromatogram of 183 *R* enantiomer and racemate

*2.2.6 COMPOUND **183***



192 183

Scheme 2.81: Hydrogenolysis of compound 192

Removal of ethyl phenyl group (Scheme 2.55) had been studied performing hydrogenolysis catalysed by Pd with two different reducing agents, H_2 or ammonium formate. We started exploiting hydrogenolysis using different catalyst loading, different solvent and pressure on amine **188** (Table 2.14). In neutral media temperature should be raised up to 60°C to start the reaction, but the reduction of nitrile is favoured and different side-product were formed.

entry	reducent	catalyst	Acid	T (h)	Temperature (°C)	P (atm)	Conversion [a] (%)	Yield [a] (%)
1	H_2	Pd/C 5%	MsOH	24	25	2	0	0
2	H_2	Pd/C 5%	MsOH	5	60	1.5	87	30[b]
3	H_2	Pd/C 20%	-	24	25	2	0	0
4	H_2	Pd/C 20%	-	16	60	1.5	100	85
5	H_2	Pd/C 20%	-	18	60	1.5	100	91
6	NH_4OOCH[c]	Pd/C 5%	AcOH	3	25	1	0	0
7	NH_4OOCH[c]	Pd/C 20%	AcOH	4	55	1	0	0

Legend: a. isolated yield, b. ^{1}H-NMR, c. 5 mole ratio

Table 2.14: Hydrogenolysis study on substrate 188

Hydrogenation reaction on amine **188** needs harsh condition in autoclave (Table 2.14, entry 2, 4 and 5), therefore we decided to exploit removal of benzyl group on hydrochloride salt **192** obtained from diastereomeric resolution. Compound **192** revealed a better substrate for the hydrogenolysis obtaining at room temperature complete conversion into desired amine **183** after 24 hours. Reaction had been tried on 150 gram scale reducing the solvent volume (6 volume instead of 15 volume) but salt **186** was insoluble and the reaction drastically slow down giving only 10% conversion after 10 hours. To avoid the solubility issue we employed H-transfer hydrogenolysis using ammonium formate (5 mole ratio), compound **192** converted into desired **183** in 20 hours at reflux (Table 2.15, entry 4, 5).

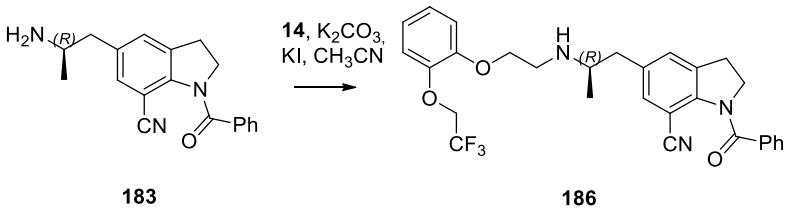
entry	reducent	Pd/C 20%	solvent	T (h)	Temperature (°C)	P (atm)	Conversion [a] (%)	Yield [a] (%)
1	H_2[c]	2%	EtOH	18	25	2	100	90
2	H_2[c]	2%	MeOH	24	25	2	100	91
3	H_2[d]	2%	MeOH	10	25	2	10	10[b]
4	NH_4OOCH[d,e]	2%	EtOH	20	78	1	100	95
5	NH_4OOCH[d,e]	2%	MeOH	25	67	1	95	92

Legend: a. isolated yield, b. ^{1}H-NMR analysis, c. 0.15 M, d. 0.37 M, e. 5 mole ratio.

Table 2.15: Hydrogenolysis on substrate 192

Amine **183** can be used as is in the next reaction or it can also be purified crystallising it with 1 volume of ethyl acetate giving a pink solid with high purity but in 40% yield. Therefore we decided to use it in the next reaction as is without crystallisation procedure.

*2.2.7 COMPOUND **186***



183 **186**

Scheme 2.82: Alkylation of derivative 183

The alkylation of primary amine **183** (analogues of compound **13**) had been already disclosed in different patents, it is a very critical step because it always forms the di-alkylated compound **I-1** (about 17%) that is difficult to eliminate from crystallised product and it is carried over up to final silodosin. Patent JP 20040313040[32] is focused in the removal of impurity **I-1** from compound **13** performing several crystallisation with tartrate salt of it.

In recent publication[21] amine **12** was alkylated using mesylate **14** avoiding the formation of impurity **I-1**. In the article the alkylation had been performed using an excess of amine **12** (1.3 mole ratio) that is recovered at the end of the reaction by chromatography purification. We decided to employ and optimise the procedure disclosed by Sun.

Initially compound **183** was dissolved in acetonitrile (15 volumes, 0.2 M) and reacted at 90°C for 26 hours with mesylate **14** (1.3 mole ratio) and K_2CO_3 as described in the article. The desired product **186** was obtained after chromatography in 95% yield. Our goals were to lower the use of amine **183** avoiding the formation of **I-9** (Figure 2.51) and to purify and separate the two compound without the use of chromatography. Amine loading was lowered till 1.1 mole ratio without affecting the yield, the concentration was increased up to 0.5 M. To enhance the conversion

we decided to add a catalytic amount of KI (0.1 mole ratio). The optimisations applied led to the conversion of the starting material in 14 hours. We studied in depth even the work-up procedure in order to avoid the chromatography. Desired secondary amine **186** had been separated from primary amine **183** performing controlled acidic washing steps using 1 M aqueous HCl. Acidifying water layer to pH 3 revealed to be the best condition to separate compound **193** from unreacted amine **183** with high purity in 90% yield calculated on mesylate **14**. Aqueous phase had been basified and primary amine **183** was recovered and used as starting material in another alkylation reaction.

Surprisingly analysing the different impurities we found di-alkylated compound **I-10** (Figure 2.51) in 1% amount on the crude (HPLC-MS analysis). **I-10** is formed during the reaction due to hydrolysis of benzamide group and subsequent alkylation.

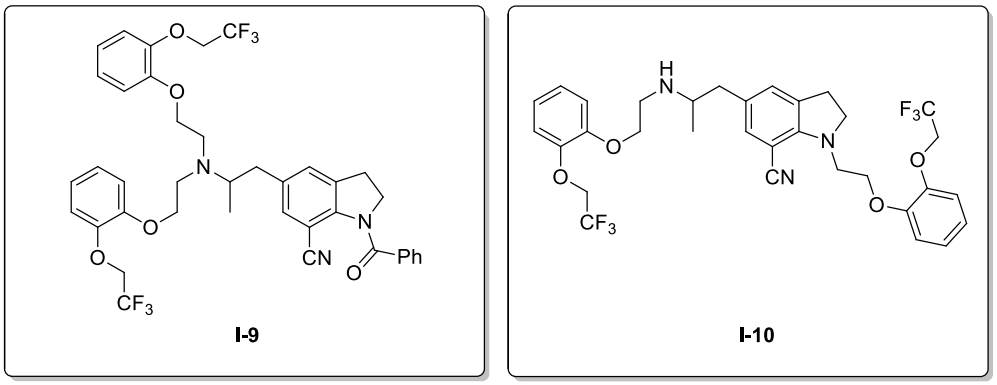
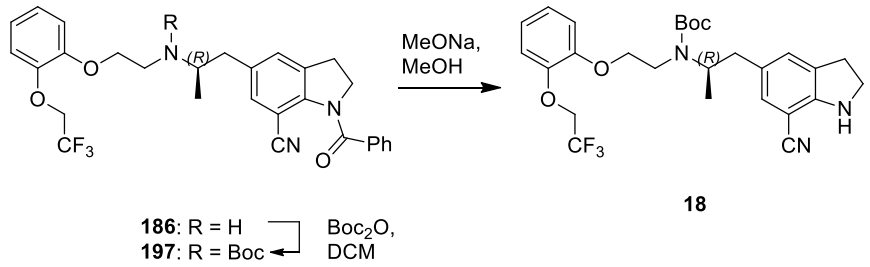


Figure 2.72: Impurities detected in the reaction

*2.2.8 COMPOUND **18***



Scheme 2.83: Preparation of intermediate 18

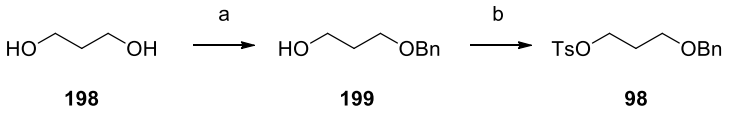
Amine **186** was then protected as tert-butyl carbamate, initially protection was performed using reported procedure[11]: 0.1 M concentration in dichloromethane, 2 mole ratio of triethylamine and 2 mole ratio of Boc_2O. The process was optimised reducing the amount of solvent performing the reaction in 1.5 M concentration avoiding the use of the base and adding just 1.1 molar ratio of Boc_2O. In work-up procedure additional weak acidic washing step using 0.1 M aqueous HCl allowed the use of crude compound **197** in the next synthetic step.

Deprotection of benzamide (Scheme 2.57) was performed with the solvolysis procedure condition already validated and tested on derivative **170**. Solvolysis with NaOMe in MeOH allowed to avoid the hydrolysis of nitrile occurred in 10% under aqueous hydrolysis at 80°C. Noteworthy is the different solubility between racemate and R-enantiomer. Racemate **18** after completion of the solvolysis precipitated from reaction media and it was collected by filtration in 56% yield, on the contrary enantiopure **18** was completely dissolved. Treating the reaction mixture with water (forming a 30% H_2O in MeOH) we were able to isolate **18** as solid. Compound **18** was recovered in 26% yield after filtration, so we decided to add water letting the

hydrolysis of methyl benzoate (i.e. formed in the reaction) happen and after extraction with ethyl acetate compound **18** was used without further purification in the next reaction.

*2.2.9 COMPOUND **98***

In the prior art about silodosin the alkyl chain attached to the 1 position of indoline is usually prepared starting from 1-chloro-3-propanol or 1-bromo-3-propanol, but these compounds are quite dangerous because they are volatile and toxic. In literature has been reported the selective formation of the monobenzyl ether of the 1,3-propanediol[127], so taking advantage of this methodology it was possible to form the corresponding alkylating agent starting from the cheap and non-toxic 1,3-propanediol (Scheme 2.58).



198 **199** **98**

Reaction condition: a. BnBr, NaH, THF, 85%; b. TsCl, TEA, DMAP,Toluene, 58%.

Scheme 2.84: Synthesis of derivative 98

The reported procedure disclose the formation of diol mono alkoxide using a large excess of the starting diol **198**, 10 mole ratio referring to 1 mole of potassium hydride. In this case the selectivity toward the mono benzyloxiether is very high, more than 90%, but the amount of 1,3-propanediol used is excessive. It was found that the best compromise between selectivity and quantity of 1,3-propanediol was a 3:1 mole ratio between the diol and the sodium hydride. The selectivity toward the monobenzyl ether was 85%,

[127] Paterson, I.; Smith, J. D.; Ward, R. A.; *Tetrahedron*, **1995**, 51, 9413-9436

Different purification procedures were tried. Distillation using a simply Claisen apparatus under vacuum (18 mmHg) at 170°C gave in 3 hours alcohol **199** in 84% yield and 93% purity checked by GC-MS analysis. While, fractional distillation using Vigreux apparatus under vacuum (12 mmHg) at 180°C gave after 8 hours alcohol **199** in a 45% yield and a 99% purity checked by GC-MS analysis.

Compound **199** was not found in the tail cut, so DSC analyses were performed to understand the behaviour of the 3-benzyloxi-1-propanol **199**. These analyses shown that the compound has an exothermic phenomenon that increase notably at 260°C and has its peak at 385.68°C with a heat release of 406.27 J/g; when it was scanned a second time the curve showed a different behaviour with the same exothermic phenomenon but with less heat release. This curve can be associated to the degradation of the compound. The second exothermic phenomenon can be associated to the incompleteness of the phenomenon appeared in the first scan (Figure 2.52).

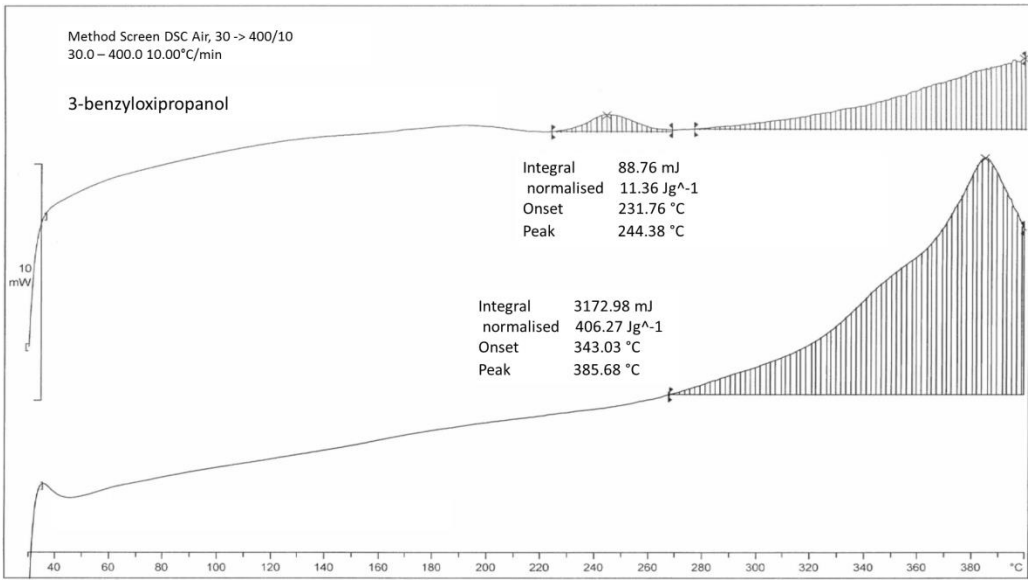


Figure 2.73: Compound 198 DSC analysis

To be sure of the degradation hypothesis a new experiment was settled, a sample was heated up at 180°C for 3 hours and then the DSC analysis was repeated, the exothermic phenomenon showed an heat release of 342.4 J/g, lower if compared to the previous one, that can be explained to the partially degradation of the compound during the 3 hours at 180°C (Figure 2.53).

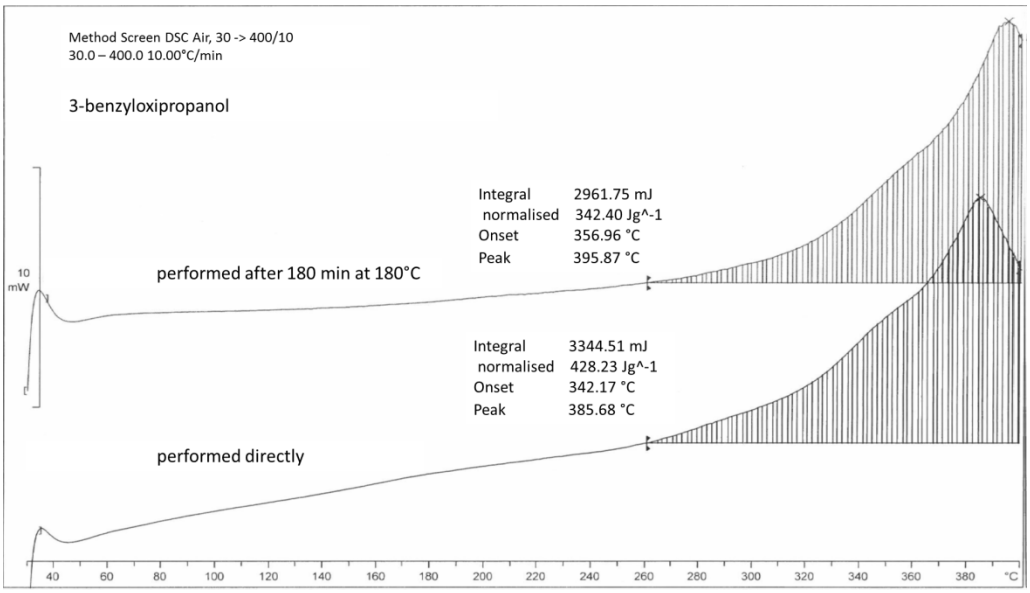


Figure 2.74: Comparison between DSC analysis of compound 198 as is and after 180 min at180°C

A last experiment was settled heating the sample with a 1°C/min instead of 10°C/min; in this case the curve slightly increased during the heating and showed an exothermic phenomenon (Figure 2.54), not comparable with the previous ones though. The heat released was only of 155.83 J/g and it ended before the 300°C, it means that the compound degraded during the slow heating and only little amount alcohol **199** kept stable till the exothermic phenomenon increase rapidly. Analysing closely the previous DSC graph it seems that the curve slightly increase since low

temperature, initially it seemed a baseline deviation but now this could be referred to a slow degradation of the compound.

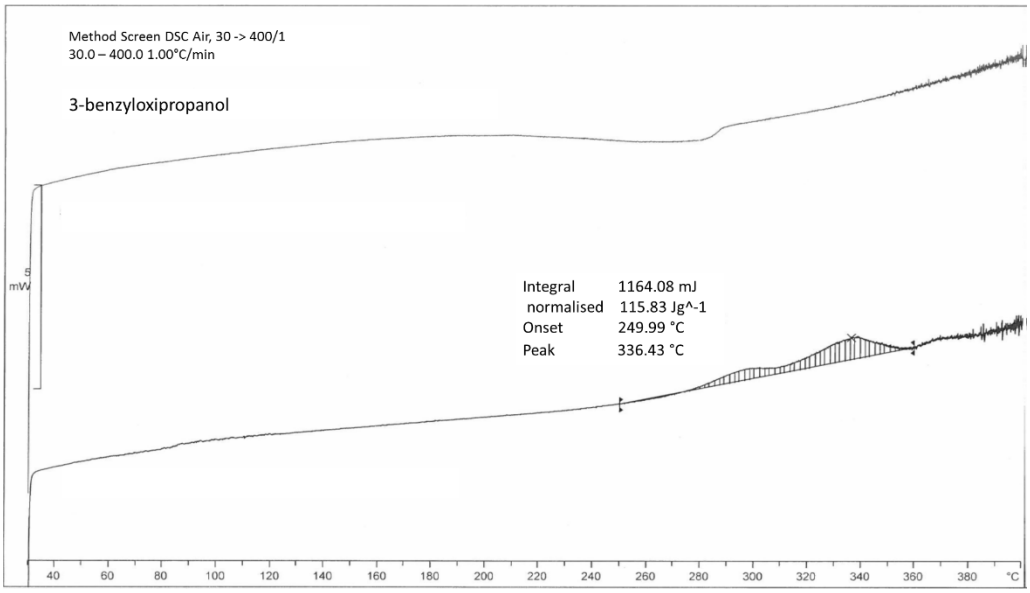


Figure 2.75: DSC experiment performed heating compound 198 at 1°C/min

The 3-benzyloxi-1-propanol **199** was converted into the *para*-toluensulfonate derivative reacting it with the corresponding *para*-toluensulfonyl chloride in the presence of DMAP at 20°C. Crude compound **98** was recovered as oil but when purified by flash chromatography it solidified, the solid has a very low melting point (32-34°C) so it was hardly crystallised.

The pure compound was soluble in almost every solvent but for methyl *tert*-butylether and *iso*-propanol (table 2.16, entry 7, 9). While the crude was not crystallised easily in the same comditions. We finally found a method to crystallise tosylate **98** directly from the reaction crude. The crude was dissolved in 1 volume of *iso*-propanol and cooled down to 0°C. Emulsion readily formed, therefore to avoid the immediate precipitation the mixture was raised to 25°C and seeded with the pure compound, the seeded emulsion was cooled gradually in 30 minutes from 25°C to

0°C. The solid started to precipitate and after 2 hours the suspension was filtered obtaining **98** as white/transparent solid.

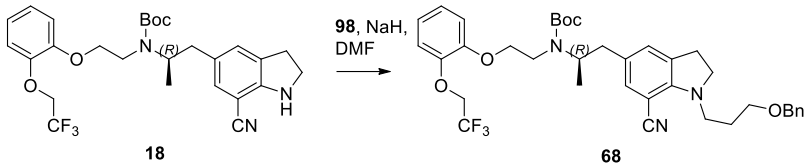
entry	Solvent A	volume	Solvent B	volume	Yield [a] (%)
1	acetone	1	-	-	0
2	Methanol	1	-	-	0
3	Ethyl acetate	1	-	-	0
4	Acetonitrile	1	-	-	0
5	Toluene	1	-	-	0
6	*n*-butanol	1	-	-	0
7	*iso*-propanol	1	-	-	34
8	heptane	1	-	-	0
9	MTBE	1	-	-	28
10	*iso*-propanol	1	H_2O	1	0[b]
11	MTBE	1	H_2O	1	0[b]
12	*Iso*-propanol	1	H_2O	1	58[c]

Legend: a. filtration and washing with 10% solvent volume, b. emulsion, c. seeding at 0°C.

Table 2.16: Study of compound 98 crystallisation condition

The optimised procedure was performed on 150 gram scale. The process consists in the formation of compound **199** using 3 mole ratio of alcohol **198** per mole of NaH, the purification by distillation was performed using Claisen apparatus under vacuum (18 mmHg) at 170°C. Alcohol **198** obtained in 84% yield and 93% purity was then reacted with *para*-toluensulfonyl chloride in the presence of DMAP obtaining after crystallisation from mixture of *iso*-propanol and water compound **98** in 50% overall yield.

*2.2.10 COMPOUND **68***



Scheme 2.85: Alkylation of derivative 18

Initially alkylation of indoline derivative **18** had been performed using the methodology developed on simple indoline derivatives (Page 188). The reaction was performed in acetonitrile and ethanol (6 volumes, 0.3 M) at reflux temperature with sodium carbonate as base and KI as catalyst. In most of the cases the reactions did not occur or gave very low yield (in acetonitrile 15% and in ethanol 23%) after 20 hours. In this condition the formation if indole derivatives **200** and **201** had been noticed in HPLC-MS analysis (Figure 2.59).

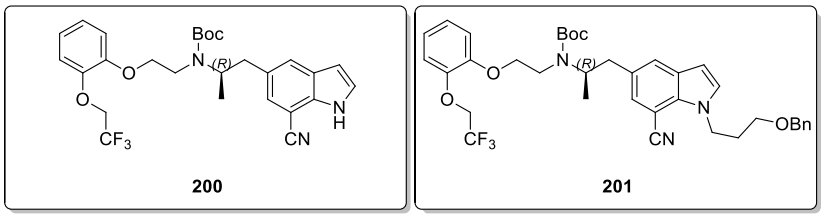
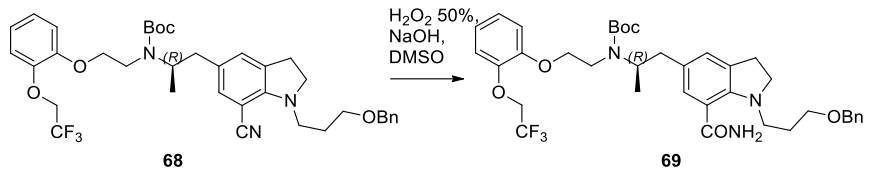


Figure 2.76: Oxidation products 200 and 201 formed in the reaction condition

At this point classic alkylation reaction procedure had been abandoned, while formation of anion on the indoline nitrogen was take into account. The anion formation had been accomplished adding a solution of compound **18** in DMF (6 volumes, 0.3 M) to a suspension of NaH in DMF (1 volume). After anion formation

compound **98** was added portionwise to the suspension and the resulting mixture was stirred at 25°C. With this procedure alkylation of compound **18** was accomplished in only three hours, the starting material was completely converted into compound **68** in 89% yield calculated by HPLC analysis without the formation of oxidated compound **200** or **201**.

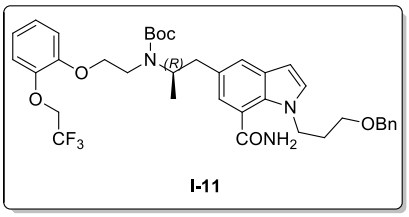
*2.2.11 COMPOUND **69***



Scheme 2.86: partial hydrolysis of nitrile

Hydrolysis of nitrile (Scheme 2.60) to form primary amide revealed trickier than expected, in fact applying reported[11,128] procedure that uses NaOH 5 M aqueous solution and hydrogen peroxide 35% solution the reaction gave only 40 % conversion (table 2.17, entry 1). Noting that compound **68** was not completely soluble in the DMSO/H_2O media we tried to decrease the amount of water in order to solubilise the substrate and let it react in homogenous condition. Strong oxidising media allows the formation of indole compound **I-11** (Figure 2.56) detected at the HPLC-MS analysis. After a brief investigation we found the best condition to perform hydration of nitrile using hydrogen peroxide 50% solution and solid NaOH (table 2.17, entry 7). In this condition nitrile is converted into desired amide **66** in 8 hours, in addition indole **I-11** formation is avoided thanks to short reaction time.

[128] Kornblum, N.; Singaram, S.; *J. Org. Chem.*, **1979**, *44*, 4727 – 4729.



I-11

Figure 2.77: Impurity I-11 formed during the hydratation procedure

entry	base	oxidant	DMSO (vol.)	T (h)	Temperature (°C)	Conversion [a] (%)
1	NaOH 5M	H_2O_2 35%	13	24	25	0
2	NaOH 5M.	H_2O_2 35%	6.6	24	25	40
3[b]	NaOH	H_2O_2 35%	6.6	48	25	92
4	NaOH 5M.	H_2O_2 35%	6	6	80	60
5	TEA	UREA*H_2O_2	6	24	25	0
6	NaOH	UREA*H_2O_2	6	24	25	50
7	NaOH	H_2O_2 50%	6	8	25	100

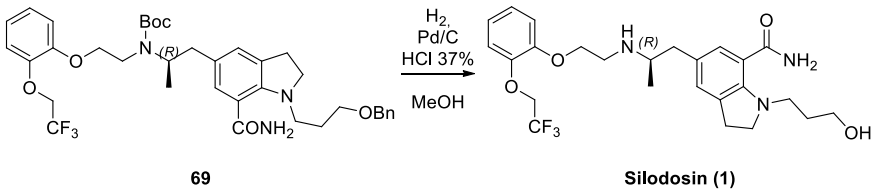
Condition: base (2.5 mole ratio) and oxidant (5 mole ratio) were added to a solution of **68** in DMSO. a. HPLC average in A%, b. addition after 24 hours of NaOH (2.5 mole ratio) and H_2O_2 35% (5 mole ratio).

Table 2.17: Investigation on partial hydrolysis condition

The optimised procedure consisted in dissolving compound **68** in DMSO (6 volumes, 0.25 M), addition of NaOH (2.5 mole ratio) and H_2O_2 50% (5 mole ratio). Thus the reaction was stirred at room temperature for 8 hours until completion, then the work-up consisted in pouring the mixture onto water and extracting with MTBE to avoid DMSO traces into the organic phases. Product **69** was obtained as oil after concentration. As already noted with amine **18** the racemate crystallised while *R*-enantiomer did not. Racemate compound **69** can be crystallised from ethyl acetate (1 volume) giving the pure product as white solid in 43% yield, while *R*-

enantiomer did not crystallise at all in ethyl acetate. Several solvent as acetone, methanol, *iso*-propanol had been tried but no crystals were obtained for the *R*-enantiomer. Compound **69** was used as is in the next reaction to form silodosin.

*2.2.12 COMPOUND **1**: **silodosin***



69 **Silodosin (1)**

Scheme 2.87: Boc and benzyl simultaneous deprotection to form silodosin

Simultaneous deprotection of benzyl ether and tert-butyl carbamate had been easily accomplished performing the reaction in acidic media under hydrogen atmosphere and palladium on carbon catalysis[129] (Scheme 2.61). After the separation of the catalyst from the reaction mixture the solvent was evaporated, the residue was dissolved in water and washed with ethyl acetate to remove organic impurities, then after basification and extraction the crude solidified and it was re-crystallised from ethyl acetate to give white solid powder in 74% yield over 6 synthetic steps (calculated on compound **14**). Only 1% of impurity **I-12** (Figure 2.57) was found in final product coming from hydration using H_2O_2 50% solution, while silodosin **1** obtained from hydration using H_2O_2 35% solution contained **I-12** in 5% amount. **I-12** was hardly removed performing three crystallisation in *iso*-propanol and ethyl acetate reducing drastically the yield (21% instead of 74%).

[129] Yan, P. C.; Zhang, X. Y.; Hu, X. W.; Zhang, B.; Zhang, X. D.; Zhao, M.; Che, D. Q.; Li, Y. Q.; Zhou, Q. L.; *Tetrahedron. Lett.*, **2013**, *54*, 1449 – 1451.

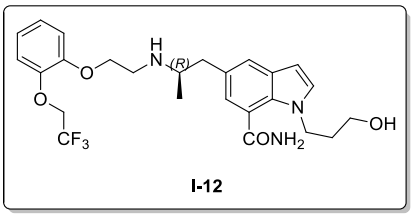


Figure 2.78: Impurity I-12 found in silodosin final product

In the crude of the final product also impurities **I-13** and **I-14** were found, isolated and characterised. **I-13** derived from impurity **I-9** and it was found in 0.2% amount, while **I-14** derived from impurity **I-10** and it was found in 0.8% (Figure 2.58). This two impurities were easily removed during the crystallisation without affecting the yield.

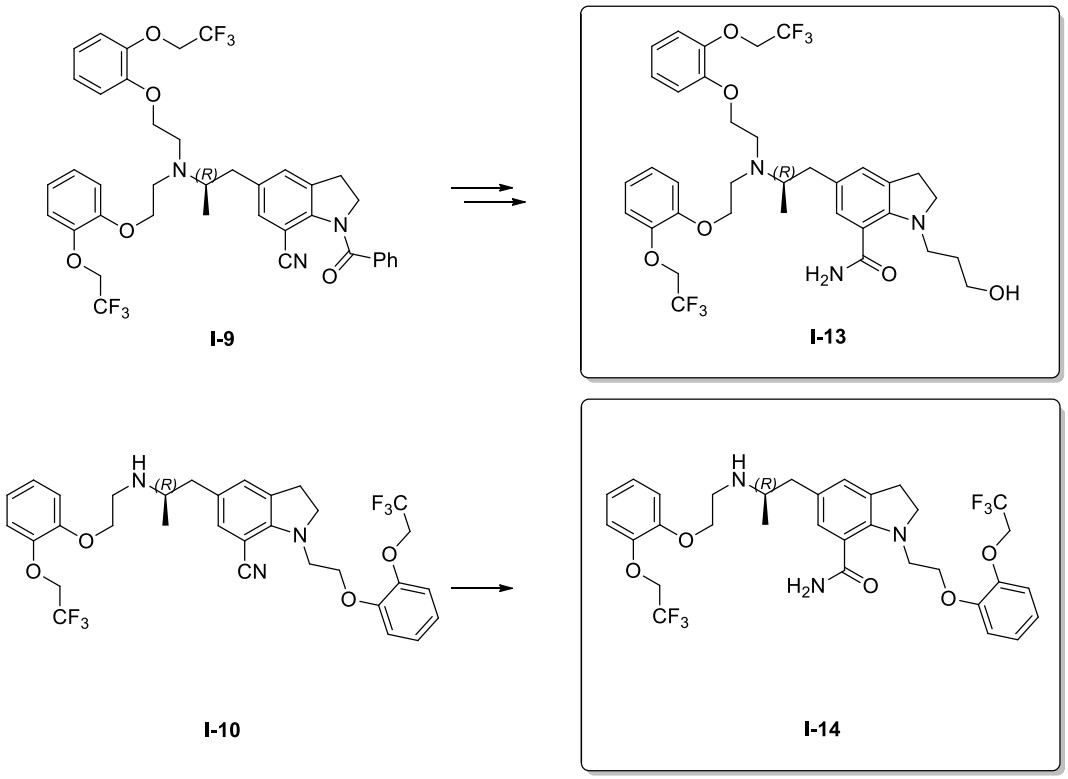


Figure 2.79: Impurities detected in the reaction

With the optimised procedures a sample of silodosin was finally prepared in 50 gram scale obtaining the pure product after crystallisation in 10% overall yield. The enatiomeric excess resulted >99% determined by chiral HPLC (Figure 2.59).

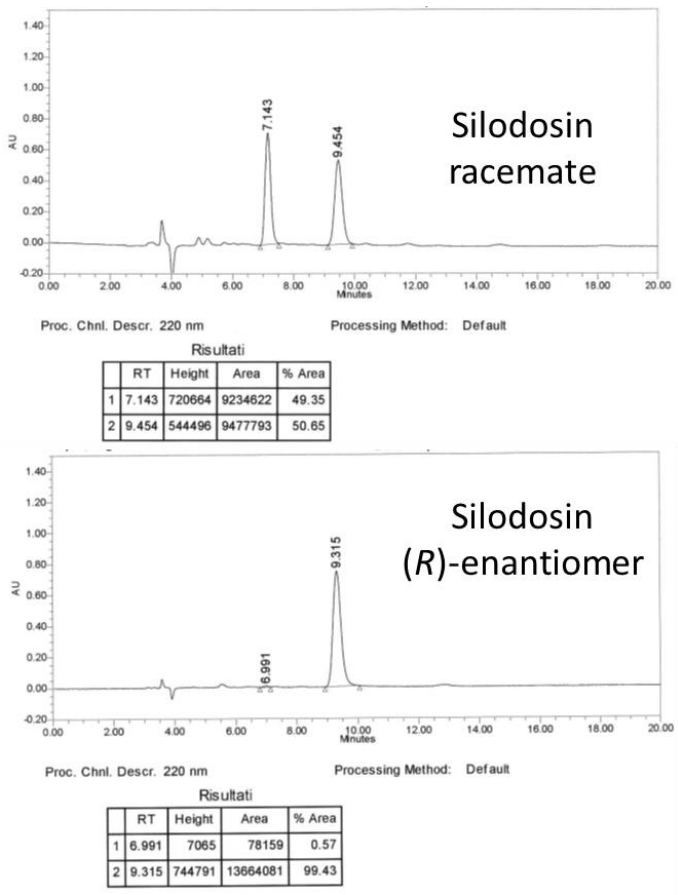
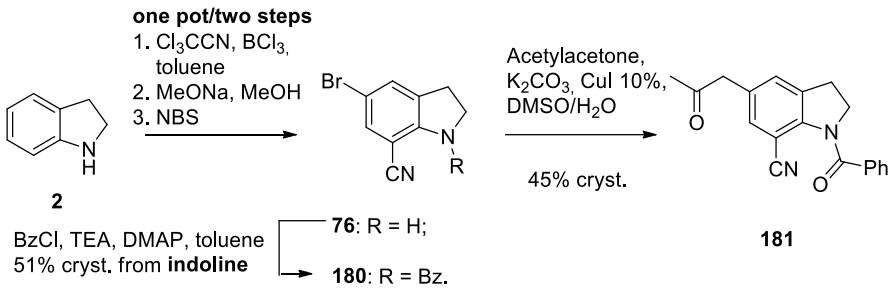


Figure 2.80: chiral HPLC chromatogram for silodosin racemate and *R*-enantiomer

2.2.13 BRIEF SYNTHESIS OF SILODOSIN

With the development of the synthetic steps we were able to synthesise a 50 grams sample of silodosin. Herein I will briefly reported the developed synthesis of silodosin ideated and performed during the research work.

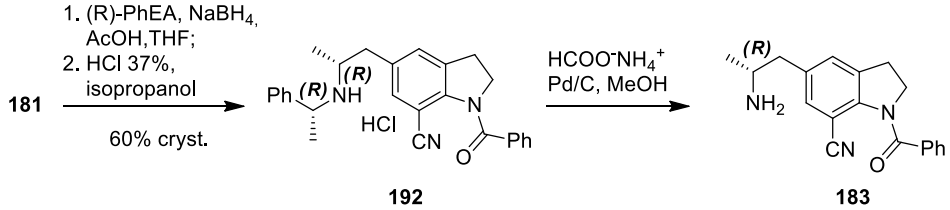
The introduction of the nitrile group on indoline **2** succeeded using the Sugosawa modification[47] of the Houben-Hoesch reaction[119] using Boron trichloride in combination with trichloroacetonitrile. Regioselective cyanation in the 7 position is due to the interaction between nitrogen and boron that directs the electrophilic attack. Bromination of compound **159** was performed directly after the regioselective cyanation adding NBS in the same media obtaining compound **76** in a one-pot two-step procedure (Scheme 2.62). **76** was readily acylated with benzoyl chloride to give compound **180** that was isolated by crystallisation in 51% yield after two steps.



Scheme 2.88: Synthesis of ketone 181

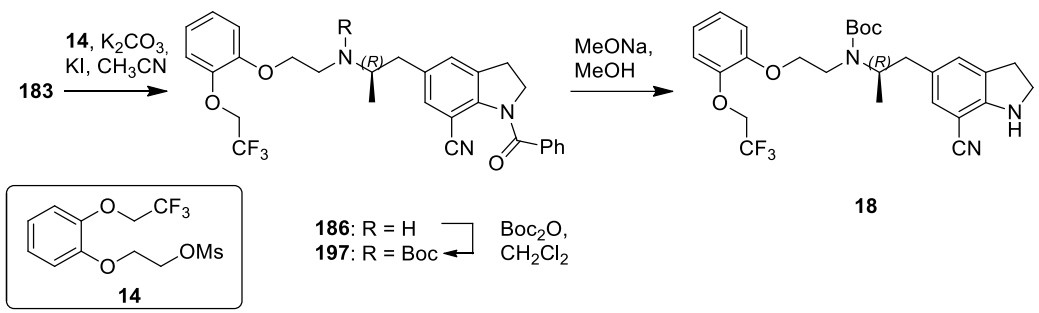
The introduction of the benzylic ketone in position 5 had been accomplished starting from benzoylated aryl bromide **180** by copper catalyzed arylation of acetylacetone. Copper reaction was performed up to 250 g scale reaction obtaining desired benzylic

ketone **181** in a 45% yield after crystallisation (Scheme 2.59). The next synthetic step was the reductive amination, to form the correct amine **192** enantiomer. Benzylic ketone **181** was reacted with (R)-phenylethylamine to give the correct stereochemistry, Sodium triacetoxyborohydride resulted the best choice both in term of selectivity and diastereomeric ratio. In order to avoid the use of expensive $NaBH(OAc)_3$ we formed it in situ reacting $NaBH_4$ and acetic acid. Compound **192** was isolated in high enantiopurity forming the hydrochloride salt and precipitating it from isopropanol (Scheme 2.63). The resulting enantiopure amine was converted into the primary amine **183** via hydrogen transfert debenzylation.



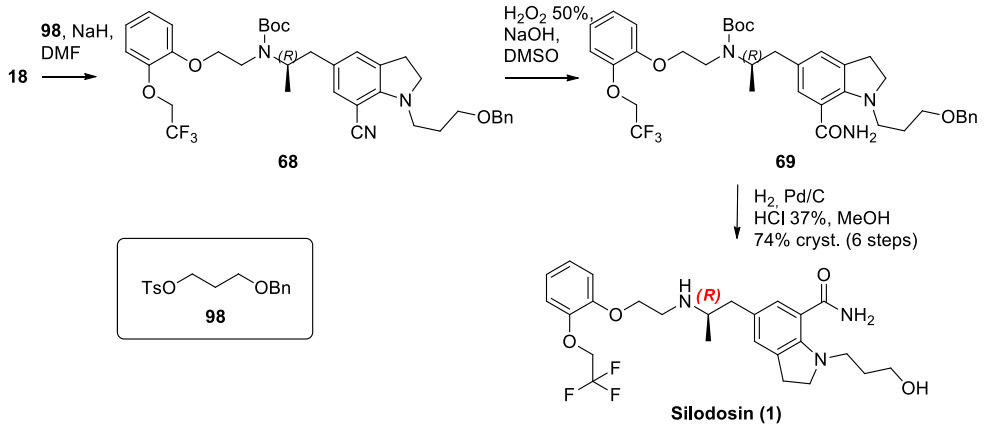
Scheme 2.89: Formation of enantiopure amine 183

Amine **183** was then alkylated with compound **14** obtaining desired secondary amine **186**. At this point, to complete the synthesis of target compound we should perform alkylation of indoline nitrogen and partial hydrolysis of nitrile group. For this reason we first protected the secondary amine with Boc group. Removal of benzoyl group has been accomplished by mild solvolysis reaction using sodium methoxide in methanol at room temperature to avoid nitrile hydrolysis (Scheme 2.64).



Scheme 2.90: Alkylation of amine 183 and protection-deprotection procedure

Compound **18**, thus obtained, had been alkylated with sodium hydride and derivative **98** to form in good yield compound **65**. The selective hydrolysis of the nitrile to form the primary amide **66** is achieved with hydrogen peroxide/NaOH in DMSO[128] (Scheme 2.65).



Scheme 2.91: Silodosin last synthetic steps

Catalytic hydrogenation in the presence of Pd/C and concentrated HCl gives concomitant removal of tert-butyl carbamate and benzyl protecting groups obtaining title compound Silodosin. Purification of the crude product by crystallisation from ethyl acetate gave Silodosin as a white powder in 74% yield from compound **6**.

Silodosin synthesis had been accomplished starting from cheap indoline in 11 steps in 10% overall yield.Silodosin had been synthesised in high purity (> 99%) and enantiomeric excess (> 99%) without the use of chromatography but only 4 crystallisation.

3 Conclusion

The Ph. D. research on silodosin alternative synthesis led to the ideation and development of a new convenient synthesis. The synthesis developed does not infringe the several syntheses already claimed in patents currently in force. Here it was reported an efficient synthesis of Silodosin in 11 steps starting from commercially available and cheap indoline, the route planned had been performed in multigram scale (100-250 grams scale) with only 4 purification steps without involving chromatography. The target product was obtained in a 10 % overall yield, with a > 99 % purity and > 99 % e.e.

All the reaction applied in the synthesis were optimise in order increase the yield, to reduce the waste, all the toxic and expensive reagents were replaced with non-toxic and cheap ones.

The feasibility investigation led us to understand more deeply the issues related to the indoline scaffold reactivity and stability, we were thus able to choose the proper synthesis. The key point of the synthesis are the introduction of substituent in position 5 and 7 because most of the syntheses present in the literature exploit various strategies. It was hard to find different methodologies that employed simple and cheap reagents and at the same time gave good yield. The process thus ideated would be ready to be scaled up with few efforts.

In addition due to the innovative process developed during the investigation the synthesis here disclosed was submitted in patent application[130] the claims regard the process to obtain silodosin, the copper catalysed arylation and the new compounds **175**, **177**, **182**, **186** and **181** (Figure 3.1). In addition the scientific article about the synthesis of silodosin here reported will be submitted to the Journal of Organic Chemistry as soon as the Intellectual Property office of Dipharma Francis will give the approval.

[130] Francesco Calogero, Enrico Brunoldi, Emanuele Attolino, Pietro Allegrini, "Procedimento per la preparazione di un antagonista adrenergico selettivo per gli α1A-adrenorecettori" Italian Patent Application MI2014A000211, Milano, February 14th, 2014.

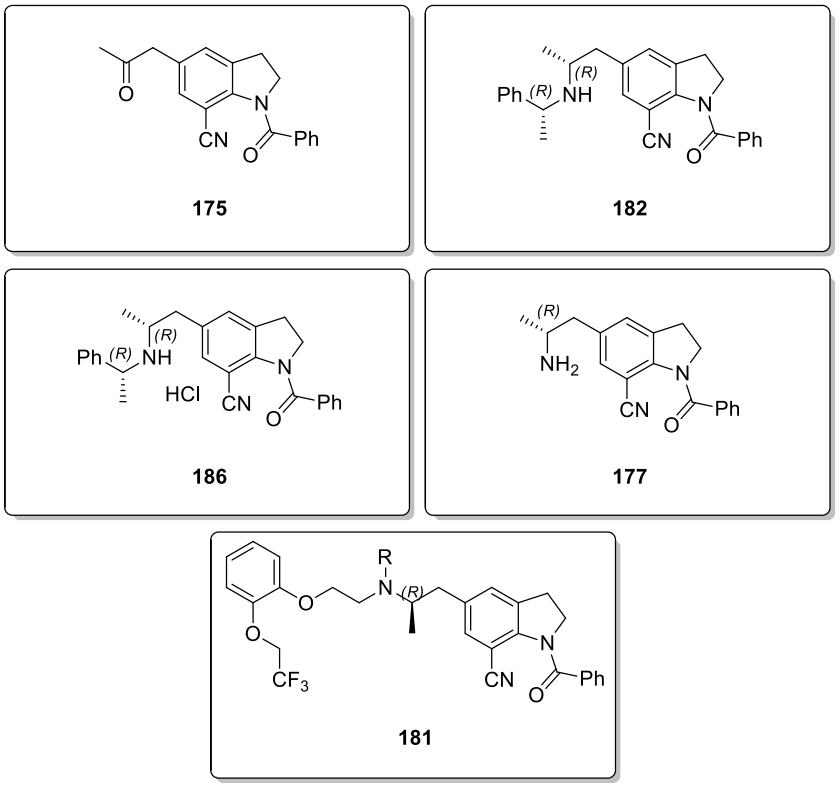
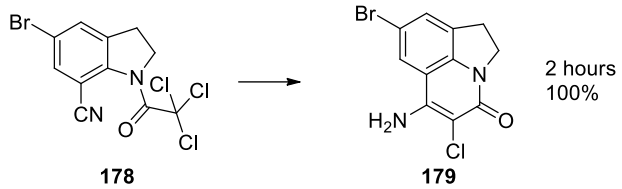


Figure 3.1: Molecules claimed in the patent

The research work allows us to obtain new perspectives about some interesting reactions occurred during the feasibility of the synthetic route. In particular with prof. Passarella we have started the study about the possible application of two interesting reactions discovered during the feasibility study:

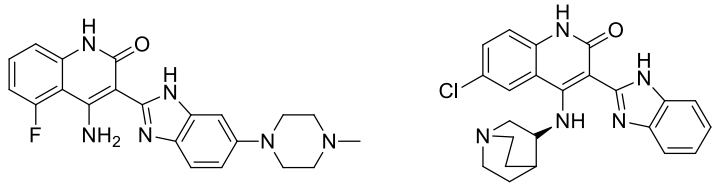
- The atom transfer radical cyclisation (ATRC) reaction to form derivative **179** (section 2.1.2, Page 147) occurred during the study of copper catalysed arylation. Copper (I) is known to form radical on trichloroacetamides and the ATRC reaction has been largely studied with alkene and alkyne forming various cyclic compounds.



Condition: CuI(10 %mol), proline(20 %mol), acetylacetone, Cs_2CO_3, DMSO, 105°C.

Scheme 3.1: formation of by-product 179 from ATRC reaction

Nevertheless ATRC between trichloroderivatives and nitrile group has never been reported. For this reason we planned to study the scope of this reaction and to apply the reaction to the syntheses of already existing quinolone based APIs[131,132] (Scheme 3.2) or to synthesise a library of analogues.



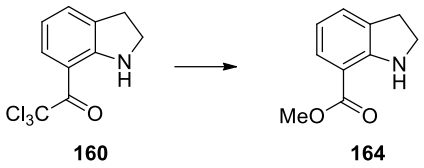
Scheme 3.2: quinolone based existing APIs

- The haloformic type reaction involving α-trichloroketone **160** and sodium methoxide (section 2.1.2, Page 137). α-trichloroketone could be converted into several carbonyl derivatives treating the substrate with the opportune nucleophiles. Some carbonyl derivatives as peroxiacids, hydroxamic acids

[131] Tse, A. N.; Rendahl, K.G.; Sheikh, T.; Cheema, H.; Aardalen, K.; Embry, M.; Ma, S.; Moler, E. J.; Ni, Z. J.; Lopes de Menezes, D. E.; Hibner, B.; Gesner, T.G.; Schwartz, G.K.; *Clin. Cancer. Res.*, **2007**, *13*, 591 – 602.

[132] Renhowe, P. A.; Pecchi, S.; Shafer, C. M.; Machajewski, T. D.; Jazan, E. M.; Taylor, C.; Antonios-McCrea, W.; McBride, C. M.; Frazier, K.; Wiesmann, M.; Lapointe, G. R.; Feucht, P. H.; Warne, R. L.; Heise, C. C.; Menezes, D.; Aardalen, K.; Ye, H.; He, M.; Le, V.; Vora, J.; Jansen, J. M.; Wernette-Hammond, M. E.; Harris, A. L.; *J. Med. Chem.*, **2009**, *52*, 278 – 292.

and hydrazides are hardly synthesised from carboxylic acids and esters. With this procedure, at least in theory, all these carbonyl derivatives could be prepared from α-trichloroketone.



160 **164**

Condition: NaOMe, MeOH, 25°C, 4 hours

Scheme 3.3: haloformic type reaction

4 Experimental Part

Unless otherwise stated, substrates and reagents were purchased from Alfa Aesar, TCI or Sigma Aldrich and used as received. ^{13}C-NMR had been performed only to characterise unknown side-products, impurities and derivatives of the final synthetic route.

^{1}H-NMR spectra were recorded on either Varian Mercury 300 instruments and are reported relative to residual $CHCl_3$ (δ 7.26 ppm) or d_6-DMSO (δ 2.50 ppm). ^{13}C-NMR spectra were recorded on the same instruments (75 MHz) and are reported relative to $CDCl_3$ (δ 77.16 ppm) or d_6- DMSO (δ 39.52 ppm). Data for ^{1}H-NMR are reported as follows: chemical shift (δ/ ppm) (integration, multiplicity, coupling constant (Hz)). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br s = broad singlet, app = apparent. Data for ^{13}C-NMR are reported in terms of chemical shift (δ/ ppm).

HPLC analyses had been performed using an UV detector SPD-20A with lamp D2 polarity + using two different wavelength λ = 220 nm and 254 nm. The column used the HPLC analyses had been SunFire Symmetry C18 250 x 4.6 mm, 5μm. The flow rate 1.0 mL/min.

HPLC method **A**: λ = 220 nm

A% CH_3CN + 0.05% H_3PO_4

B% H_3PO_4 0.07% in H_2O

T (min)	A%	B%
0	30	70
30	90	10
35	90	10

HPLC method **B**: λ = 254 nm.

A% CH_3CN

B% H_3PO_4 0.1% in H_2O

T (min)	A%	B%
0	20	80
30	70	30
45	70	30

HPLC method **C**: λ = 254 nm.

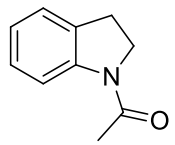
A% CH_3CN

B% H_3PO_4 0.1% in H_2O

T (min)	A%	B%
0	10	90
15	30	70
30	70	30

HPLC analyses had been performed using an UV detector SPD-20A with lamp D2 polarity + using two different wavelength λ = 220 nm and 254 nm. The column used the HPLC analyses had been Chiralpak AD-H 250 x 4.6 mm, 5μm. The flow rate 1.0 mL/min. The eluent used in the analyses had been hexane : ethanol : *tert*-butyl alcohol = 750 : 250 : 1.

*Synthesis of compound **3** :*



1-acetylindoline

Indoline **2** (150 g, 1.26 mol) was dissolved in toluene (900 mL), then TEA (263 mL, 1.89 mol) and DMAP (15 g, 0.13 mol) were added. The mixture was cooled to 5°C, and acetyl chloride (119 g, 1.51 mol) was added dropwise in 30 minutes. The yellow solution was stirred at 20°C monitoring the reaction by TLC (toluene : ethyl acetate = 9 : 1), and after 4 hours the reaction was completed. Then water (1,2 L) and HCl 37% (70 mL) were added to the reaction mixture and it was heated to 50°C and the organic layer was separated at that temperature. The organic layer was washed with water (200 mL) and cooled to 0°C and stirred at this temperature for 24 hours. The suspension was filtered and washed with toluene(100 mL), dried in oven at 40°C under vacuum to give a yellow powder (133 g). The mother liquor was concentrated till 300 mL solution was obtained, then cooled at 0°C under stirring, the precipitate was filtered and washed with toluene (50 mL), dried in oven at 40°C under vacuum to give a yellow powder (27 g). The mother liquor was concentrated till dryness, the crude thus obtained was dissolved in toluene (75 mL) and heptane(75 mL) was added. The suspension was stirred at 20°C overnight, then filtered and dried in oven at 40°C and under vacuum to give a yellow powder (15 g).

The three different solids obtained were combined to obtain compound **3** as yellowish solid (175 g, 1.08 mol, 87% yield).

The ^{1}H-NMR was comparable to the literature one, so no further characterisation had been performed.

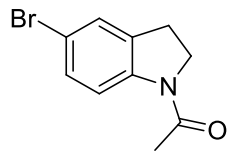
m.p. : 98-99°C (lit. 97-98°C[133]).

GC/MS: *m/z* = 161 (M^+ -0), 119 (M^+ -42).

^{1}H-NMR ($CDCl_3$, 300 MHz), δ (ppm) : 2.19 (3H, s), 3.17 (2H, t, *J* = 8.6 Hz), 4.01 (2H, t, *J* = 8.6 Hz), 6.99 (1H, ddd, *J* = 8.1 Hz, *J* = 7.4 Hz, *J* = 0.7 Hz), 7.15–7.20 (2H, m), 8.20 (1H, d, *J* = 8.0 Hz).

[133] K. P. Landge, K. S. Jang, S. Y. Lee, D. Y. Chi, *J. Org. Chem*. **2012**, *77*, 5705−5713

*Synthesis of compound **97** :*



1-acetyl-5-bromoindoline

Compound **3** (75 g, 0.465 mol) was dissolved in acetic acid (600 mL) and cooled to 14°C, then bromine (36 mL, 0.698 mol) was added dropwise in 90 minutes. After the addition, the mixture was stirred at 20°C overnight. The reaction was monitored by GC-MS analysis, after disappearance of starting material water (1.0 L) was added and a white solid starts to precipitate. Thus NaOH 30% (95 mL) and Na_2SO_3 (75 g) were added. After 30 minutes the suspension was filtered and washed with water (3 x 100 mL), dried in oven at 40°C under vacuum to give compound **97** as white powder (101.5 g, 0.423 mol) 91%.

The ^{1}H-NMR was comparable to the literature one, so no further characterisation had been performed.

m.p. : 118°C (lit. 118-119°C[134]);

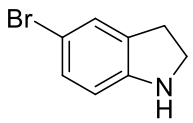
GC/MS: *m/z* = 239 (M^+ -0), 241 (M^+ +2).

[134] Bedford, R.B.; Engelhart, J.U.; Haddow, M.F.; Mitchell, C. J.; Webster, R. L.; *Dalton Trans.*, **2010**, *39*, 10464 – 10472.

^{1}H NMR (300 MHz; $CDCl_3$), δ (ppm) : 8.08 (1H, d, *J* = 8.5 Hz,), 7.30-7.27 (2H, m), 4.04 (2H, t, *J* = 8.3 Hz), 3.16 (2H, t, *J* = 8.3 Hz), 2.21 (3H, s)

^{13}C NMR (75 MHz; $CDCl_3$), δ (ppm) : 168.9, 142.2, 133.6, 130.4, 127.7, 118.3, 116.0, 48.9, 27.8.

*Synthesis of compound **70** :*



5-bromoindoline

Procedure A:

Compound **97** (90 g, 0.333 mol) was suspended in methanol (450 mL) and water (150 mL), NaOH (68 g, 1.66 mol) was added. The reaction mixture was heated till reflux and checked by TLC (ethyl acetate : hexane = 2 : 8, Rf 0.29), after 20h the reaction was completed. The claisen apparatus was assembled, and the methanol (400 mL) was distilled off. Water (150 mL) was added to the mixture and it was cooled to 0°C under stirring for 1 hour. The suspension was filtered, the filtrate washed with water (2 x 100 mL) and heptane (2 x 75 mL) and dried in oven at 30°C and under vacuum to give compound **70** as white powder (62.63 g, 0.316 mol, 95% yield).

The ^{1}H-NMR was comparable to the literature one, so no further characterisation had been performed.

m.p. : 36-38°C;

GC/MS: *m/z* = 197 (M^{+} -0), 199 (M^{+} +2).

^{1}H NMR (300 MHz; d_6-DMSO), δ (ppm) : 7.11 (1H,s), 6.99 (1H, d, *J* = 8.1 Hz), 6.39 (1H, d, *J* = 8.1 Hz), 5.6 (1H, br s), 3.39 (2H, t, *J* = 8.7 Hz), 2.88 (2H, t, *J* = 8.7 Hz).

Procedure B:

Indoline **2** (2.0 g, 0.017 mol) was dissolved in MTBE (20 mL), NBS (3.0 g, 0.017 mol) was added slowly, and the mixture was stirred at room temperature. After completion, the mixture was poured onto water (50 mL) and extracted with MTBE (3 x 20 mL). The combined organic layers were dried with Na_2SO_4, the solid was filtered off and the filtrate was concentrated until dryness obtaining 3.4 g of a crude oil. GC/MS analysis revealed the presence of 7-bromoindoline in 7% amount.

Optimisation of procedure A condition:

entry	Base	eq	T (°C)	Time (h)	MeOH (vol.)	H_2O (vol.)	Conversion (%)	Yield (%)
1	NaOH 30%	2.5	50	48	10	1	92	90 (oil)
2	NaOH 30%	2.0	68 (reflux)	40	10	1	98	88 (oil)
3	NaOH 30%	3.0	68 (reflux)	20	10	1.5	99	98 (oil)
4	NaOH 44%	5.0	75 (reflux)	20	5	1.7	100	84 (solid)
5	NaOH 47%	4.5	73 (reflux)	15	5	1.5	100	92 (solid)
6	NaOH 55%	4.8	73 (reflux)	15	5	1.5	100	99 (solid)
7	KOH 55%	3.4	71 (reflux)	18	5	1.5	100	97 (oil)

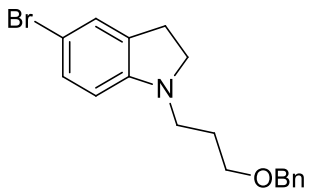
Study of compound **70** crystallisation condition (:

entry	Solvent A	volume	Solvent B	volume	Yield [a] (%)
5	Toluene	1	-	-	33
6	*n*-butanol	1	-	-	51
7	*iso*-propanol	3	-	-	91
8	heptane	3	-	-	87
9	*iso*-propanol	1	-	-	
10	*iso*-propanol	1	water	1	98[b]
11	heptane	3	water	1	0[c]
12	heptane	1	water	2	0[c]
13	*iso*-propanol	1	water	2	98
14	*iso*-propanol	1	water	3	97
15[d]	*Iso*-propanol	1	water	1	0[b]

Legend: [a]. filtration and washing with 10% solvent volume, [b]. no filtration due to inadequate suspension fluidity, [c]. emulsion, [d]. compound obtained from selective bromination with NBS in MTBE

Acetone, methanol, ethyl acetate and acetonitrile dissolved compound **70** with 1 volume.

*Synthesis of compound **72** :*



1-(3-(benzyloxy)propyl)-5-bromoindoline

Procedure A:

Compound **70** (18.0 g, 0.0908 mol) was dissolved in EtOH (120 mL), than K_2CO_3 (18.79 g, 0.1362 mol) and compound **98** (29.11 g, 0.0908 mol) were added to the solution. The mixture was stirred at 75°C monitoring the reaction TLC (ethyl acetate : hexane = 2 : 8), after 4 hours the reaction was completed. The reaction mixture was cooled to 25°C, water (100 mL) was added and the mixture was extracted with AcOEt (3 x 50 mL). The combined organic layers were dried with Na_2SO_4, the solid was filtered off and the filtrate was concentrated until dryness obtaining 30 g of a crude oil. The crude was purified by flash chromatography (toluene Rf 0.32) obtaining compound **72** as a pale yellow oil (26,63 g, 0,077 mol, 85% yield).

GC/MS: *m/z* = 345 (M^+ -0), 347 (M^+ +2).

^{1}H NMR (300 MHz; d_6-DMSO), δ (ppm) : 7.33-7.26 (5H,m), 7.1 (1H, s), 7.06 (1H, d, *J* = 8.1 Hz),, 6.35 (1H, d, *J* = 8.1Hz), 4.44 (2H, s), 3.48 (2H, t, *J* = 6.3Hz), 3.29 (2H, t, *J* = 8.7Hz), 3.08 (2H, t, *J* = 6.9Hz), 2.86 (2H, t, *J* = 8.1Hz), 1.77 (2H, p, *J* = 6.9Hz).

Procedure B:

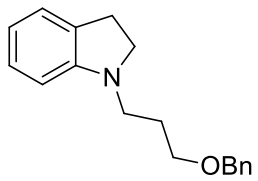
Compound **99** (2.0 g, 7.49 mmol) was dissolved in DMF (20 mL), NBS (1.33 g, 7.49 mmol) was added slowly, and the mixture was stirred at room temperature. After completion, the mixture was poured onto water (100 mL) and extracted with MTBE (3 x 20 mL). The combined organic layers were dried with Na_2SO_4, the solid was filtered off and the filtrate was concentrated until dryness obtaining 3.4 g of crude oil that was purified by flash chromatography (toluene) to obtain compound **72** as yellow pale oil (2.35 g, 6.8 mmol, 91 % yield).

Test reactions with various brominating agent:

entry	Brominating agent	Base	Solvent	Time (h)	Conversion [a] (%)	Yield [b] (%)
1	PTATB	K_2CO_3	CH_2Cl_2/MeOH		69	0[c]
2	TBATB	K_2CO_3	CH_2Cl_2/MeOH		63	0[c]
3	NBS	-	DMF		97	91
4	Br_2	-	AcOH		59	0[c]
5	BTMATB	K_2CO_3	CH_2Cl_2/MeOH		52	0[c]
6	NBS	-	DMF/H_2O 5%		51	45[d]

Reaction condition: brominating agent (1.5 mole ratio), base (2 mole ratio), solvent (10 volumes), temperature 25°C. a.GC/MS analysis, b. isolated yield after chromatography, c. poli-brominated products, d. 1-(3-benzyloxy)propyl-5,7-dibromoindoline compound detected by GC/MS.

*Synthesis of compound **99** :*



1-(3-(benzyloxy)propyl)indoline

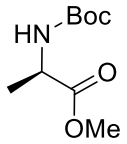
Compound **2** (2.0 g, 0.0167 mol) was dissolved in EtOH (10 mL), than K_2CO_3 (3.46 g, 0.025 mol) and compound 98 (5.35 g, 0.0167 mol) were added to the solution. The reaction mixture was heated till reflux and checked by TLC (ethyl acetate : hexane = 2 : 8), after 3h the reaction was completed. The reaction mixture was cooled down to 25°C, water (100 mL) is added and the mixture is extracted with AcOEt (3 x 50 mL). The combined organic layers are dried with Na_2SO_4, the solid is filtered off and the filtrate is concentrated until dryness obtaining (3.55 g, 0.052 mol) of compound **99** as an oil.

The ^{1}H-NMR was comparable to the literature one, so no further characterisation had been performed.

GC/MS: *m/z* = 267 (M^+ -0).

^{1}H NMR (300 MHz; $CDCl_3$), δ (ppm) : 7.33-7.26 (5H,m), 7.1 (1H, s), 7.06 (1H, d, *J* = 8.1 Hz),, 6.35 (1H, d, *J* = 8.1Hz), 4.44 (2H, s), 3.48 (2H, t, *J* = 6.3Hz), 3.29 (2H, t, *J* = 8.7Hz), 3.08 (2H, t, *J* = 6.9Hz), 2.86 (2H, t, *J* = 8.1Hz), 1.77 (2H, p, *J* = 6.9Hz).

*Synthesis of compound **101** :*



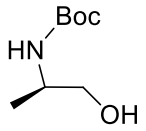
(*R*)-methyl 2-((*tert*-butoxycarbonyl)amino)propanoate

Methanol (50 mL) was cooled down to 0°C and $SOCl_2$ was added dropwise in 40 minutes, after 10 minutes D-alanine **100** (10 g, 0,112 mol) was added portionwise to the stirred solution. The mixture was stirred at 20°C monitoring the reaction by ^{1}H-NMR. After 4 hours the reaction was completed, the mixture was concentrated under vacuum till residue. The residue was dissolved in MeOH (80 mL), $NaHCO_3$ (18,8 g, 0,211 mol) and Boc_2O (24,6 g, 0,112 mol) were added portionwise to the solution. The resulting suspension was stirred at 20°C overnight monitoring the reaction by ^{1}H-NMR. After completion, the mixture was concentrated under vacuum, diluted with ethyl acetate (200 mL) and washed with water (3 x 100 mL). The combined organic layers were dried with Na_2SO_4, the solid was filtered off and the filtrate was concentrated until dryness obtaining compound **101** as transparent oil (22,3 g, 0,109 mol) 98%.

The ^{1}H-NMR was comparable to the literature one, so no further characterisation had been performed.[58]

^{1}H NMR (300 MHz; $CDCl_3$), δ (ppm) : 5.03 (1H,br s), 4.3 (1H, m), 3.73 (3H, s), 1.43 (9H, s), 1.37 (3H, d, J = 6.9 Hz).

*Synthesis of compound **102** :*



(R)-tert-butyl (1-hydroxypropan-2-yl)carbamate

Compound **101** (10 g, 0,049 mol) was dissolved in THF (100 mL) and the solution was cooled down to 0°C, then $NaBH_4$ (4,63 g, 0,123 mol) was added to the solution (the solution warm up to 15 °C). Thus, methanol (11 mL) was added dropwise to the reaction mixture (gas production is noted) and the suspension was stirred at 22°C. The reaction was monitored by TLC (hexane : ethyl acetate = 7 : 3). After 3 hours the reaction was completed, the mixture was diluted with ethyl acetate (100 mL) and acidified with HCl 1 M (100 mL), the aqueous phase was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried with Na_2SO_4, the solid was filtered off and the filtrate was concentrated until dryness obtaining **102** as white solid (7,7 g, 0,044 mol, 90%yield).

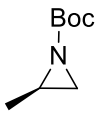
The ^{1}H-NMR was comparable to the literature one, so no further characterisation had been performed.[58]

m.p. : 55°C (lit. m.p. 52-53°C)[135]

^{1}H NMR (300 MHz; $CDCl_3$), δ (ppm) : 3.76 (1H, m), 3.64 (1H, dd, *J* = 3.9Hz, 10.8Hz), 3.50 (1H, dd, *J* = 6.3Hz, 11.1Hz), 1.45 (9H, s), 1.14 (1H, d, *J* = 6.6Hz).

[135] Hamada, Y.; Shibata, M.; Sugiara, T.; Kato, S.; Shioiri, T.; *J. Org. Chem.*, **1987**, *52*, 1252-1255.

*Synthesis of compound **94** :*



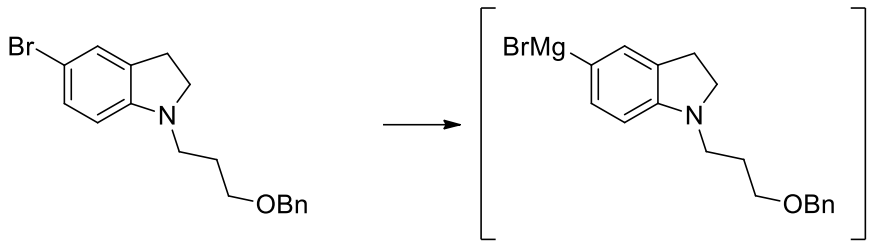
(*R*)-*tert*-butyl 2-methylaziridine-1-carboxylate

Compound **102** (5 g, 0,028 mol) was dissolved in MTBE (100 mL), para-toluensulfonyl chloride (6,4 g, 0,0336 mol) and KOH 6,22 g, 0,112 mol) were added portionwise to the solution. The reaction mixture was stirred at reflux temperature (56°C), the reaction was monitored by ^{1}H-NMR analysis. After 5 hours the reaction was completed, the mixture was poured in iced water (100 mL) and extracted with ethyl acetate (3 x 50 mL), then washed with brine (50 mL). The combined organic layers were dried with Na_2SO_4, the solid was filtered off and the filtrate was concentrated until dryness giving compound **94** as yellow oil (3,55 g, 0,023 mol, 81% yield).

The ^{1}H-NMR was comparable to the literature one, so no further characterisation had been performed.

^{1}H NMR (300 MHz; $CDCl_3$), δ (ppm) : 2.42 (1H, m), 2.23 (1H, d, *J* = 5.7Hz), 1.87 (1H, d, *J* = 3.9Hz), 1.45 (9H, s), 1.27 (1H, d, *J* = 5.4Hz).

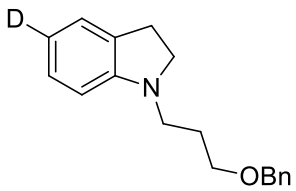
*Formation of Grignard reagent **91** :*



Magnesium turnings (0.75 g, 30.5 mmol) and compound X (0.17 g, 0.5 mmol) were suspended in 1 mL THF and activated with I_2 and dibromoethane (0.54 g, 2.9 mmol). Compound X (1.77 g, 5.8 mmol) in 10 mL abs. THF was added when the suspension temperature stated to raise and the mixture was kept at 67°C during the addition. The reaction was monitored by ^{1}H-NMR quenching the solution with D_2O.

^{1}H-NMR analysis showed with this Magnesium activation methodology only 40 % of Mg insertion and 60% of protonolysis product.

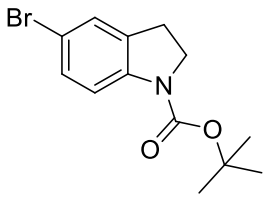
(3-(benzyloxy)propyl)-5-deuteriumindoline **103** :



1-(3-(benzyloxy)propyl)-5-deuteriumindoline

^{1}H NMR (300 MHz; $CDCl_3$), δ (ppm) : 7.33-7.26 (5H,m), 6.708 (1H, d, J = 2.1 Hz), 6.68 (1H, dd, *J* = 8.1, 2.1 Hz), 6.07 (1H, d, *J* = 8.1Hz), 4.44 (2H, s), 3.48 (2H, t, *J* = 6.3Hz), 3.29 (2H, t, *J* = 8.7Hz), 3.08 (2H, t, *J* = 6.9Hz), 2.86 (2H, t, *J* = 8.1Hz), 1.77 (2H, p, *J* = 6.9Hz).

*Synthesis of compound **104** :*

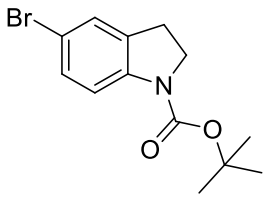


tert-butyl 5-bromoindoline-1-carboxylate

Indoline **70** (20 g, 0.101 mol) was dissolved in DCM (200 mL), then TEA (12.26 g, 0.121 mol) and Boc_2O (2.05 g, 0.016 mol) were added. The mixture was stirred at 25°C monitoring the reaction by TLC (toluene : ethyl acetate 1:1). After 10 hours the reaction was completed, the mixture was poured onto water (200 mL) and extracted with DCM (2 x 50 mL). The combined organic layers were dried with Na_2SO_4, the solid was filtered off and the filtrate was concentrated until dryness giving a crude of 29 g that was crystallised with ethyl acetate (140 mL) obtaining compound **104** as a white solid (12.0 g, 0.040 mol), the mother liquor was concentrated to 1/3 of the volume an stirred at 0°C for 1 hour. The suspension was filtered obtaining compound **104** as white solid (10.0 g, 0.033 mol), the two solide were combined obtaining compound **104** as white solid (22.0 g, 0.074 mol, 73% yield).

^1H NMR (300 MHz; $CDCl_3$), δ (ppm) : 7.56-7.78 (1H, br s), 7.06 (1H, s), 6.99 (1H, d, J = 8.1 Hz), 3.97 (2H, t, J = 8.7 Hz), 3.06 (2H, t, J = 8.7 Hz), 1.55 (9H, s).

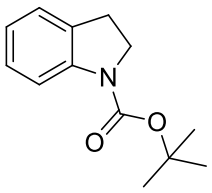
*Organolithium formation on substrate **104** :*



tert-butyl 5-bromoindoline-1-carboxylate

Compound **104** (2.0 g, 6.7 mmol) was dissolved in THF(20 mL) and cooled to -78°C, then Hexyllithium 2.3 M in hexane (3.2 mL) was added dropwise, using a syringe pump, in 60 minutes. monitoring the formation of organolithium quenching a sample in D_2O and performing the ^{1}H-NMR analysis.

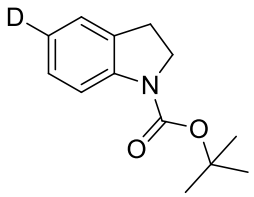
*Compound **107** :*



tert-butyl indoline-1-carboxylate

^{1}H NMR (300 MHz; $CDCl_3$), δ (ppm) : 7.62-7.95 (1H, br s), 7.12-7.19 (2H, m), 6.91 (1H, t, J = 7.5 Hz), 3.97 (2H, t, J = 8.4 Hz), 3.08 (2H, t, J = 8.4 Hz), 1.56 (9H, s).

*Compound **106** :*



tert-butyl 5-deuteriumindoline-1-carboxylate

^{1}H NMR (300 MHz; $CDCl_3$), δ (ppm) : 7.56-7.78 (1H, br s), 6.66 (1H, d, J = 2.1 Hz), 6.62 (1H, dd, J = 8.7, 2.4 Hz), 3.97 (2H, t, J = 8.7 Hz), 3.06 (2H, t, J = 8.7 Hz), 1.55 (9H, s).

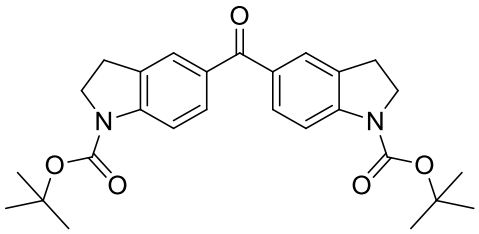
- Reaction with carboxylate salt **112**:

Then a solution of lithium (R)-2-dibenzylamino-propionate **112** (0.0067 mol) in THF (20 mL), formed mixing (R)-2-dibenzylamino-propionic acid **115** (1.80 g, 0.0067 mol) and Hexyllithium 2.3 M in hexane (2.9 mL), was added dropwise in 2 hours (via Syringe pump). After two hours from the addition the TLC shows the protonolysis product along with other spots. The reaction temperature was raised to 25°C and stirred overnight. The reaction was then treated with water (100 mL), and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried with Na_2SO_4, the solid was filtered off and the filtrate was concentrated until dryness obtaining 5 g of a crude oil. The crude was purified by flash chromatography (hexane : ethyl acetate = 7:3) to give compound **107** (300 mg). The other compounds had not been isolated.

- Reaction with aziridine in the presence of $CuBr*SMe_2$:

Then $CuBr*SMe_2$ (0.145 g, 0.7 mmol) was added to the mixture and after 30 minutes a solution of aziridine **94** (1.05 g, 6.7 mmol) in THF (5 mL) was added. The mixture was stirred at -78°C monitoring the reaction by TLC (hexane : ethyl acetate = 7:3). After 6 hours the reaction was completed, the mixture was quenched with water (10 mL) and stirred for 30 minutes. Then the mixture was warmed to 25°C, water (90 mL) was added and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried with Na_2SO_4, the solid was filtered off and the filtrate was concentrated until dryness obtaining 4 g of a crude oil. The crude was purified by flash chromatography (hexane : ethyl acetate = 7:3) to give compound **107** (800 mg) and compound **110** (1.5 g).

*Characterisation of side product **110** :*

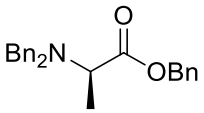


di-*tert*-butyl 5,5'-carbonylbis(indoline-1-carboxylate)

^{1}H NMR (300 MHz; $CDCl_3$), δ (ppm) : 7.65 (2H, br s), 7.48 (2H, m), 7.18 (2H, m)3.99 (4H, t J = 8.7 Hz), 3.15 (4H, t, J = 8.7 Hz), 1.55 (18H, s).

^{13}C NMR (75 MHz; $CDCl_3$), δ (ppm) : 204.1, 152.0 (2C), 141.6 (2C), 137.2 (2C), 127.4 (2C), 126.8 (2C), 114.5 (2C), 113.7 (2C), 81.6 (2C), 47.8 (2C), 28.5 (6C), 27.2 (2C).

*Synthesis of compound **114** :*



(*R*)-benzyl 2-(dibenzylamino)propanoate

A solution of benzyl bromide (54.33 g, 0.317 mol) in ethanol (50 mL) was added dropwise in 15 minutes to a stirred solution of D-alanine **100** (5.66 g, 0.063 mol) and K_2CO_3 (43.83 g, 0.317 mol) in ethanol (200 mL) and water (50 mL). The mixture was stirred at 75°C monitoring the reaction by TLC (Rf 0.5 toluene). After 18 hours the reaction was completed, the reaction mixture was concentrated under vacuum. The suspension was diluted with water (100 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried with Na_2SO_4, the solid was filtered off and the filtrate was concentrated until dryness obtaining compound **114** as colorless oil (18.23 g, 0.051 mol) 80%.

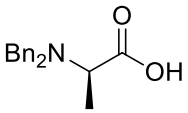
The ^{1}H-NMR was comparable to the literature one, so no further characterisation had been performed.[66]

MS (ESI): *m/z* = 360.12 (M^+ + H),

^{1}H-NMR (300 MHz, CDCl3), δ (ppm) : 7.48 – 7.25 (15H, m), 5.32 – 5.20 (2H, m), 3.92 – 3.68 (4H, m), 3.67 – 3.58 (1H, m), 1.41 (3H, d, J = 7.1 Hz).

^{13}C-NMR (75 MHz, CDCl3), δ (ppm) : 173.63, 139.92, 136.24, 128.74, 128.67, 128.47, 128.41, 128.35, 128.32, 127.02, 66.11, 56.29, 54.50, 15.05 .

*Synthesis of compound **115** :*



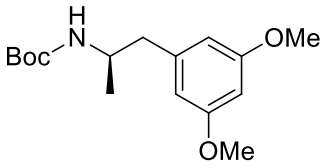
(*R*)-2-(dibenzylamino)propanoic acid

Compound **114** (18.23 g, 0.051 mol) was suspended in a mixture of methanol (20 mL), dioxane (100 mL) and a water solution of KOH (5,6 g, 0.1 mol in 50 mL). The mixture was stirred at 27°C monitoring the reaction by TLC (toluene). After 16 hours the reaction was completed, the mixture was concentrated under vacuum. The suspension was diluted with water (100 mL) and washed with ethyl acetate (50 mL). The aqueous layer was acidified with HCl 3 M (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried with Na_2SO_4, the solid was filtered off and the filtrate was concentrated until dryness obtaining a white solid crude (15.6 g) that was triturated in heptane (110 mL) for 2 hours. The suspension was filtered, washed with heptane (2 x 20 mL) and dried in oven at 30°C under vacuum to give compound **115** as white powder (11.88 g, 0.044 mol) 89%.

The ^{1}H-NMR was comparable to the literature one, so no further characterisation had been performed.[66]

^{1}H-NMR (300 MHz, CDCl3), δ (ppm) : 7.38-7.28 (10H, m), 3.82 (2H, d, J = 13.2Hz), 3.54 (1H, p, J = 7.2Hz), 3.5 (2H, d, J = 13.5Hz), 1.38 (3H, d, J = 7.2Hz).

*Synthesis of compound **95** :*



(*R*)-*tert*-butyl (1-(3,5-dimethoxyphenyl)propan-2-yl)carbamate

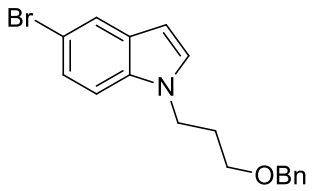
Magnesium turnings (1.00 g, 41.5 mmol) activated with I_2 and dibromoethane were suspended in 5 mL abs. THF under nitrogen. 3,5-dimethoxybromobenzene **92** (2.24 g, 10.3 mmol) in 20 mL abs. THF were added simultaneously at rt. The mixture was refluxed for 2.5 h and then cooled to 0 °C. CuBr*SMe_2 (146 mg, 0.71 mmol) were added and the resulting mixture stirred for 20 min at rt. A solution of aziridine **89** (1.08 g, 6.87 mmol) in 5 mL abs. THF was slowly added and the suspension stirred for 4 h at rt. After cooling to 0 °C the reaction mixture was carefully quenched with saturated $NaHCO_3$ and extracted with MTBE. The combined organic layers were dried with Na_2SO_4, the solid was filtered off and the filtrate was concentrated until dryness. The residue was purified by flash chromatography on deactivated silica gel using heptane/ethyl acetate (5:1, v/v) to yield the N-reference compound **95** as oil (1.42 g, 7.2 mmol, 70%).

The ^{1}H-NMR was comparable to the literature one, so no further characterisation had been performed.[58]

^{1}H-NMR (300 MHz, $CDCl_3$), δ (ppm) : 6.25 (3H, s) 4.32 (1H, br m), 3.88 (1H, br m), 3.72 (6H, s), 2.76 (1H, dd, J = 5.4 Hz, 13.3 Hz), 2.51 (1H, dd, J = 7.5, 13.3 Hz), 1.38 (9 H, s), 1.00 (3 H, d, 3J = 6.3 Hz).

^{13}C-NMR (75 MHz, $CDCl_3$), δ (ppm) : 160.9, 155.4, 140.78, 107.7, 98.67, 85.37, 55.47, 47.46, 43.48, 28.64, 27.63.

*Synthesis of compound **116** :*

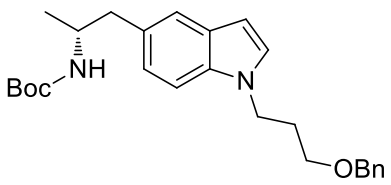


1-(3-(benzyloxy)propyl)-5-bromo-1*H*-indole

5-bromo indole **119** (5.07 g, 0.0255 mol) was dissolved in THF (35 mL), the mixture was cooled down to 0°C. Freshly filtered NaH (0.931 g, 0.0388 mol) was added portionwise to the solution in 15 minutes. After 20 minutes compound **98** (8.57 g, 0.0267 mol) was added to the suspension and the mixture was stirred at 25°C for 18 hours. The mixture was cooled down to 0°C, quenched with water (100 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried with Na_2SO_4, the solid was filtered off and the filtrate was concentrated until dryness obtaining 10.4 g of a crude solid. The solid was recrystallised from *iso*-propyl ether (30 mL) and filtered to obtain compound **116** as white solid (6.61 g, 0.0191 mol) 75%.

^{1}H-NMR (300 MHz, CDCl3), δ (ppm) : 7.73 (1H, dd, J = 2.1, 0.6 Hz), 7.21-7.38 (7H, m), 7.04 (1H, d, J = 3.0 Hz), 6.40 (1H, dd, J = 3.0, 0.6 Hz), 4.46 (2H, s), 4.24 (2H, t, J = 6.9 Hz), 3.36 (2H, t, J = 5.7 Hz), 2.08 (2H, p, J = 6.0 Hz).

*Synthesis of compound **118** :*



(*R*)-*tert*-butyl (1-(1-(3-(benzyloxy)propyl)-1*H*-indol-5-yl)propan-2-yl)carbamate

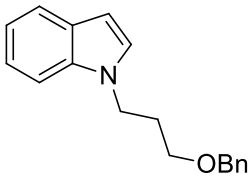
Magnesium turnings (0.50 g, 20.5 mmol) and compound **116** (0.17 g, 0.5 mmol) were suspended in 1 mL THF and activated with I_2 and dibromoethane. Compound **116** (1.77 g, 5.8 mmol) in 10 mL abs. THF was added when the suspension temperature stated to raise and the mixture was kept at 67°C during the addition. The reaction was monitored by 1H-NMR (quench of the solution with D_2O). After 3 hours the formation of Grignard reagent was completed, the mixture was then cooled to 0 °C. CuBr*SMe_2 (0.076 g, 0.35 mmol) was added and the resulting mixture stirred for 20 min at rt. A solution of aziridine **89** (0.56 g, 3.94 mmol) in 2 mL abs. THF was slowly added and the suspension stirred for 4 hours at rt. After cooling to 0 °C the reaction mixture was carefully quenched with saturated $NaHCO_3$ and extracted with MTBE. The combined organic layers were dried with Na_2SO_4, the solid was filtered off and the filtrate was concentrated until dryness obtaining The residue was purified by flash chromatography (toluene : ethyl acetate 3:1) to yield the compound **118** as oil (0.85 g, 2.05 mmol, 35%).

^{1}H-NMR (300 MHz, CDCl3), δ (ppm) : 7.40 (1H, br s), 7.30-7.36 (5H, m), 7.28 (1H, d, J = 8.7 Hz), 7.03 (1H, d, J = 3.0 Hz), 7.02 (1H, dd, J = 8.7, 0.9 Hz), 6.41 (1H, d, J = 3.0 Hz), 4.47 (2H, s), 4.25 (2H, t, J = 6.9 Hz), 3.93 (1H, br m), 3.40 (2H, t, J = 5.7

Hz), 2.94 (1H, dd, J = 5.4, 13.5 Hz), 2.73 (1H, dd, J = 7.5, 13.5 Hz), 2.09 (2H, p, J = 6.0 Hz), 1.43 (9H, s), 1.09 (1H, d, J = 6.6 Hz).

^{13}C-NMR (75 MHz, CDCl3), δ (ppm) : 155.3, 138.2, 134.9, 128.8, 128.7, 128.4 (2C), 128.2, 127.8 (2C), 127.7, 123.3, 121.4, 109.2, 100.7, 78.9, 73.0, 66.7, 42.9, 30.3, 28.4(3C), 27.0, 20.1.

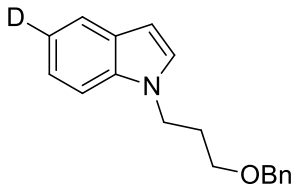
*Compound **120** :*



1-(3-(benzyloxy)propyl)-1*H*-indole

^{1}H NMR (300 MHz; $CDCl_3$), δ (ppm) : 7.63 (1H, d, J = 7.8 Hz), 7.28-7.39 (6H, m), 7.19 (1H, t, J = 8.1 Hz), 7.09 (1H, t, J = 8.1 Hz), 7.05 (1H, d, J = 3.0 Hz), 6.47 (1H, d, J = 3.0 Hz), 4.47 (2H, s), 4.28 (2H, t, J = 6.6 Hz), 3.39 (2H, t, J = 5.7 Hz), 2.10 (2H, p, J = 6.3 Hz).

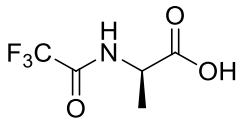
*Compound **120-D** :*



1-(3-(benzyloxy)propyl)-5-deuterium-1*H*-indole

^{1}H NMR (300 MHz; $CDCl_3$), δ (ppm) : 7.62 (1H, s), 7.28-7.39 (6H, m), 7.24 (1H, d, J = 7.2 Hz), 7.04 (1H, d, J = 3.0 Hz), 6.47 (1H, d, J = 3.0 Hz), 4.47 (2H, s), 4.28 (2H, t, J = 6.6 Hz), 3.39 (2H, t, J = 5.7 Hz), 2.10 (2H, p, J = 6.3 Hz).

*Synthesis of compound **126** :*



(*R*)-2-(2,2,2-trifluoroacetamido)propanoic acid

D-alanine **100** (3.2 g, 0.036 mol) and TEA (7.67 g, 0.05 mol) were dissolved in methanol (12 mL), ethyl trifluoro acetate (7.1 g, 0.050 mol) was added and then the mixture was stirred at 25°C monitoring the reaction by TLC (BuOH:AcOH:H2O = 5:3:2). After 16 hours the reaction was completed, the mixture was concentrated under vacuum and the crude was dissolved in MTBE (30 mL) and acidified with HCl 1 M (50 mL). The aqueous layer was extracted with MTBE (2 x 40 mL). The combined organic layers were dried with Na_2SO_4, the solid was filtered off and the filtrate was concentrated until dryness obtaining a white solide that was triturated in heptane (12 mL) obtaining compound **126** as white solid (6,64 g, 0,035 mol, 97% yield).

The ^{1}H-NMR was comparable to the literature one, so no further characterisation had been performed.

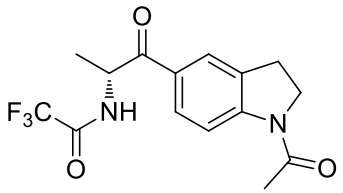
m.p. : 69 °C (lit. m.p. 70-71 °C[136]).

^{1}H-NMR (300 MHz, $CDCl_3$), δ (ppm) : 7.8 (1H, br s), 6.94 (1H, br s), 4.66 (1H, p, J = 7.3 Hz), 1.57 (3H, d, J = 7.3 Hz).

[136] Curphey, T. J.; *J. Org. Chem.*, **1979**, *44*, 2805 – 2807.

^{13}C NMR (75 MHz; $CDCl_3$), δ (ppm) : 176.1, 157.7 (q, J = 41.3 Hz), 157.2, 156.7, 156.2, 121.1 (q, J = J = 279.0 Hz), 117.3, 113.5, 109.7, 48.4 ($\underline{C}HCH_3$), 17.2.

*Synthesis of compound **128** :*



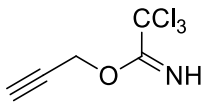
(*R*)-*N*-(1-(1-acetylindolin-5-yl)-1-oxopropan-2-yl)-2,2,2-trifluoroacetamide

N-trifluoroacetylalanine **126** (1.56 g, 0.0084 mol) was dissolved in dichloromethane (30 mL) and cooled to 0°C, then pyridine (0.06 g, 0.0008 mol) and oxalyl chloride (2.67 g, 0.021 mol) were added. The mixture was stirred at 25°C for 4 hours. The mixture was concentrated under vacuum and the crude was dissolved in freshly dichloromethane (5 mL), then 1-acetyl indoline **3** (1.34 g, 0.0084 mol) and AlCl3 (5.15 g, 0.038 mol) were added to the solution. The mixture was stirred at 20°C monitoring the reaction by TLC (toluene : ethyl acetate 1 : 1). After 16 hours the reaction was completed, the mixture was diluted with dichloromethane (40 mL) and acidified with aqueous solution of HCl 1 M (40 mL). The aqueous layer was extracted with dichloromethane (2 x 50 mL) and the combined organic layers were dried with Na_2SO_4, the solid was filtered off and the filtrate was concentrated until dryness obtaining 2.5 g of a crude. The crude was purified by flash chromatography (toluene:ethyl acetate = 1:1) obtaining a mixture of the two regioisomer as solid (1.1 g), the solid was crystallised from methanol (2 mL) obtaining compound **128** (0.327 g, 0.996 mmol, 11%yield)

GC-MS: *m/z* = 328 (M^+ -0).

^{1}H NMR (300 MHz; $CDCl_3$), δ (ppm) : 8.29 (1H, d, J = 8.1 Hz), 7.84 (1H, d, J = 8.1 Hz), 7.82 (1H, s), 7.61 (1H, d, J = 5.7 Hz), 5.46 (1H, p, J = 7.2 Hz), 4.15 (2H, t, J = 8.7 Hz), 3.26 (2H, t, J = 8.4 Hz), 2.27 (3H, s), 1.50 (3H, d, J = 6.9 Hz).

*Synthesis of compound **130** :*



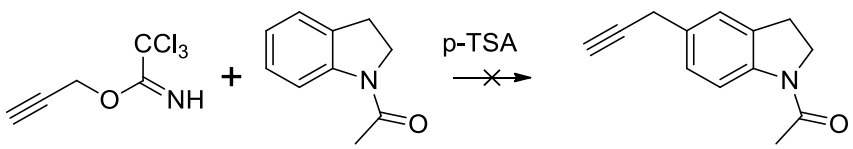
prop-2-yn-1-yl 2,2,2-trichloroacetimidate

Propargylic alcohol **133** (0.78 g, 0.0139 mol) was dissolved in dichloromethane (4 mL) and cooled to 0°C, then DBU (0.21 g, 0.00139 mol) and trichloroacetonitrile (4.0 g, 0.0279 mol) were added. The mixture was stirred at 25°C for 30 minutes, the mixture was concentrated under vacuum and filtered on silica (hexane : AcOEt = 3:1) obtaining O-propargyl trichloroacetoimidate (2.8 g, 0.0139 mol) after concentration until dryness.

^{1}H NMR (300 MHz; $CDCl_3$), δ (ppm) :: 8.52 (1H, br s), 4.92 (2H, d, J = 2.4), 2.54 (1H, t, J = 2.4 Hz).

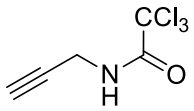
D_2O exchange : 4.92 (2H, d, J = 2.7 Hz), 2.62 (1H, t, J = 2.7 Hz).

*Reaction with compound **130** :*



Compound **130** (2.8 g, 0.0139 mol) and 1-acetyl indoline **3** (2.22 g, 0.0139 mol) were dissolved in DCM (9 mL) and cooled to 0°C. *para*-toluensulfonic acid (0.48 g, 0.0028 mol) was added and the reaction mixture was stirred at 0°C monitoring the reaction by ^{1}H-NMR. After 40 minutes the starting material was unchanged, thus *para*-toluensulfonic acid (0.48 g, 0.0028 mol) was added and temperature raised to 25°C. After 2 hours the ^{1}H-NMR analysis showed only the conversion of O-propargyl trichloroacetoimidate **130** into N-propargyl trichloroacetamide **135** but no conversion into the desired product.

*Characterisation of compound **135** :*



2,2,2-trichloro-*N*-(prop-2-yn-1-yl)acetamide

^{1}H NMR (300 MHz; $CDCl_3$), δ (ppm) : 10.82 (1H, br s), 4.94 (2H, d, J = 2.4), 2.56 (1H, t, J = 2.4 Hz).

D_2O exchange : 4.90 (2H, dd, J = 2.1 Hz, 0.6 Hz), 2.54 (1H, dt, J = 2.1 Hz, 0.6 Hz).

*Synthesis of compound **140** :*

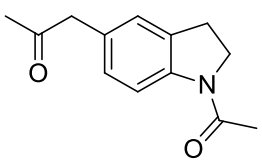
2-nitroprop-1-ene

2-nitropropanol (4.0 g, 0.038 mol) was dissolved in of methylene chloride (40 mL) and cooled to 0°C, and methanesulfonyl chloride (4.6 g, 0.040 mol) was added in one portion. Triethylamine (16.0 g, 0.160 mol) was then added dropwise, and the reaction mixture was stirred at 0°C monitoring the reaction by ^{1}H-NMR. After 15 minutes the reaction was completed and the mixture was poured onto water (50 mL) and the organic layer was washed with water (50 mL), 5% aqueous HCl (50 mL), and brine (50 mL). The organic layer was dried with Na_2SO_4, the solid was filtered off and the filtrate was concentrated until dryness obtaining compound **140** as oil (3.1 g, 0.036 mol, 93% yield).

The ^{1}H-NMR was comparable to the literature one, so no further characterisation had been performed.[79]

^{1}H NMR (300 MHz; $CDCl_3$), δ (ppm) : 6.50 (s), 5.80 (bs, 1, CH), 2.30 (s, 3, CH,).

*Synthesis of compound **132** :*



1-acetyl-5-(2-oxopropyl)indoline

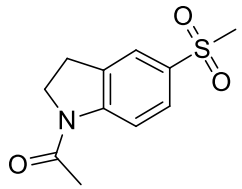
Compound **97** (2.0 g, 8.33 mmol), Cs_2CO_3 (8.1 g, 24.99 mmol), DMSO (8.0 mL), acetylacetone (2.49 g, 24.99 mmol) and proline (0.19 g, 1.66 mmol) were added. The system was degassed and CuI (0.158 g, 0.83 mmol) was added. The mixture was stirred at 110°C with mechanical stirrer, monitoring by GC-MS. After 21 hours the reaction was completed, the mixture was cooled to rt, ethyl acetate (50 mL), H_2O (200 mL). The aqueous layer was extracted with ethyl acetate (3 x 50 mL). Then the organic layer was washed with aqueous NH_3 10 %, aqueous NaOH al 10%, aqueous HCl 1 M and brine. The combined organic layers were dried with Na_2SO_4, the solid was filtered off and the filtrate was concentrated until dryness obtaining a brown oil (2.2 g). The crude thus obtained was purified by flash chromatography (ethyl acetate : toluene = 1:1, Rf: 0.36) obtaining compound **132** as yellow solid (1.7 g, 7.91 mmol, 95% yield).

GC-MS : *m/z* = 217 (M^+ - 0)

^{1}H NMR (300 MHz; $CDCl_3$), δ (ppm) : 8.13 (1H, d, J = 9.0 Hz), 7.0 (1H, s), 6.98 (1H, d, J = 9.0 Hz), 4.03 (2H, t, J = 8.1 Hz), 3.61 (2H, s), 3.15 (2H, t, J = 8.4 Hz), 2.19 (3H, s), 2.12 (3H, s);

^{13}C-NMR (75 MHz, CDCl3), δ (ppm) : 206.7, 168.7, 142.1, 131.9, 129.5, 128.7, 125.5, 117.1, 50.6, 49.0, 29.2, 28.0, 24.1.

*Characterisation of compound **145** :*



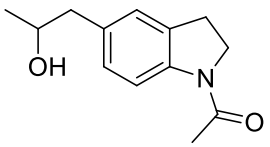
1-acetyl-5-methylsulfonylindoline

GC-MS: *m/z* = 239 (M^+ -0), 197 (M^+ -42).

^{1}H NMR (300 MHz; $CDCl_3$), δ (ppm) : 8.32 (1H, d, J = 8.1 Hz), 7.75 (1H, d, J = 8.1 Hz), 7.69 (1H, s), 4.14 (2H, t, J = 8.4 Hz), 3.24 (2H, d, J = 8.4 Hz), 3.00 (3H, s), 2.24 (3H, s);

^{13}C-NMR (75 MHz, CDCl3), δ (ppm) : 169.6, 147.9, 134.9, 132.6, 128.0, 123.7, 116.8, 49.2, 44.8, 27.5, 24.3.

*Synthesis of compound **146** :*



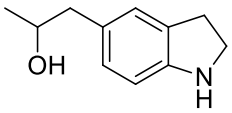
1-acetyl-5-(2-hydroxypropyl)indoline

Compound **132** (3.2 g, 14.7 mmol) was dissolved in a mixture of THF (12 mL) and MeOH (12 mL), the solution was cooled to 0°C. $NaBH_4$ (0.57 g, 15.0 mmol) was added slowly to the solution, the resulting mixture was stirred at 25°C monitoring the reaction by TLC (EtOAc : toluene = 2:1, Rf 0.23). After 2 hours the reaction was completed, the mixture concentrated under vacuum and water (100 mL) and EtOAc (50 mL) were added. The aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were dried with Na_2SO_4, the solid was filtered off and the filtrate was concentrated until dryness obtaining a brown oil (3.2 g) sufficientely pure. Compound **146** was used directly in the next synthetic step to prepare compound **147**.

GC-MS: *m/z* = 219 (M^+ - 0).

^{1}H NMR (300 MHz; $CDCl_3$), δ (ppm) : 8.13 (1H, d, J = 9.0 Hz), 7.04 (1H, s), 7.02 (1H, d, J = 9.0 Hz), 4.05 (2H, t, 8.7 Hz), 3.95 -4.02 (1H, m), 3.18 (2H, t, J = 8.7 Hz), 2.75 (1H, dd, J = 4.5 Hz, 13.5 Hz), 2.63 (1H, dd, J = 7.5 Hz, 13.2 Hz), 2.21 (3H, s), 1.23 (3H, d, J = 6 Hz).

*Synthesis of compound **147** :*



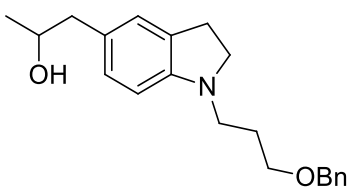
1-(indolin-5-yl)propan-2-ol

Compound **146** (3.2 g, 14.7 mmol) was dissolved in a solution of sodium methoxide 25% in MeOH (12 mL). The resulting mixture was stirred at 25°C monitoring the reaction by TLC (EtOAc : toluene = 3:1, Rf 0.34). After 15 hours the reaction was completed, the mixture poured in water (100 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were dried with Na_2SO_4, the solid was filtered off and the filtrate was concentrated until dryness obtaining a brown oil (2.56 g) sufficientely pure. Compound **147** was used directly in the next synthetic step to prepare compound **148**.

GC-MS: *m/z* = 177 (M^+ - 0).

^{1}H NMR (300 MHz; $CDCl_3$), δ (ppm) : 6.96 (1H, s), 6.84 (1H, d, J = 7.8 Hz), 6.59 (1H, d, J = 7.5 Hz), 3.93 (1H, m), 3.54 (2H, t, 8.4 Hz), 3.00 (2H, t, J = 8.1 Hz), 2.70 (1H, dd, J = 4.8 Hz, 13.8 Hz), 2.54 (1H, dd, J = 8.1 Hz, 13.5 Hz), 1.24 (3H, d, J = 6.3 Hz).

*Synthesis of compound **148** :*



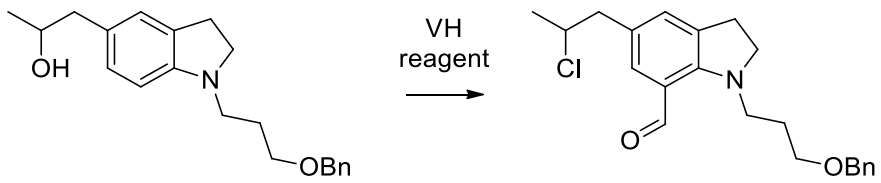
1-(1-(3-(benzyloxy)propyl)indolin-5-yl)propan-2-ol

Compound **147** (2.5 g, 14.2 mmol) was dissolved in EtOH (15 mL), than K_2CO_3 (2.9 g, 21.3 mmol) and compound **98** (5.4 g, 17.0 mmol) were added to the solution. The reaction mixture was heated till reflux and checked by TLC (EtOAc : heptane = 1 : 2, Rf 0.4), after 6 h the reaction was completed. The reaction mixture is cooled down to 25°C, water (100 mL) was added and the mixture was extracted with AcOEt (3 x 50 mL). The combined organic layers were dried with Na_2SO_4, the solid is filtered off and the filtrate is concentrated until dryness obtaining 4.9 g of a crude oil. The crude was purified by flash chromatography (EtOAc : heptane = 1 : 2) to give compound **148** as pale white oil (3.27 g, 10.0 mmol, 71% yield).

GC-MS: m/z = 325 (M^+ - 0).

^{1}H NMR (300 MHz; $CDCl_3$), δ (ppm) : 7.31 – 7.78 (5H, m), 6.92 (1H, s), 6.88 (1H, d, J = 8.1 Hz), 6.46 (1H, d, J = 7.8 Hz), 4.51 (2H, s), 3.87 - 3.98 (1H, m), 3.58 (2H, t, J = 6.3 Hz), 3.33 (2H, t, J = 8.1 Hz), 3.17 (2H, t, J = 6.9 Hz), 2.93 (2H, t, J = 8.1 Hz), 2.79 (1H, dd, J = 4.5 Hz, 13.52 Hz), 2.53 (1H, dd, J = 8.1 Hz, 13.25 Hz), 1.91 (2H, q, J = 6.6 Hz), 1.22 (3H, d, J = 6.0 Hz),

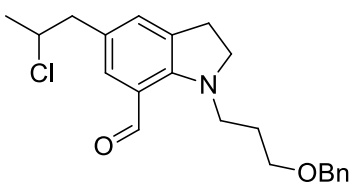
*Vilsmeyer-Haack reaction on derivative **148** :*



$POCl_3$ (1.9 mL, 1.17 g, 7.67 mmol)was added in 20 minutes to DMF (3 mL, 3.14 g, 43.0 mmol) at 0°C and the mixture was stirred for additional 40 minutes at that temperature. A solution of compound **148** (1.0 g, 3.07 mmol) in DMF (3 mL) was added in 30 minutes at 0°C. The reaction was monitored by TLC (EtOAc : heptane = 1 : 3, Rf 0.3). After 5 hours the reaction was completed, the mixture was poured in ice/water mixture (100 g) and stirred for 40 minutes, and the neutralized adding Na_2CO_3 10% aqueous solution. The mixture was extracted with MTBE (3 x 50 mL). The combined organic layers were dried with Na_2SO_4, the solid is filtered off and the filtrate is concentrated until dryness obtaining 1.2 g of a crude oil.

^{1}H-NMR and GC-MS analysis revealed the presence of two compound, found to be compound **149** and **151**.

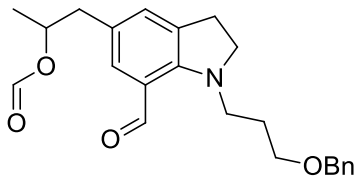
*Characterisation of compound **149** :*



1-(3-(benzyloxy)propyl)-5-(2-chloropropyl)indoline-7-carbaldehyde

^{1}H-NMR (300 MHz; $CDCl_3$), δ (ppm) : 9.96 (1H, s), 7.31 – 7.78 (6H, m), 7.00 (1H, bs), 4.50 (2H, s), 4.08 - 4.21 (1H, m), 3.52 – 3.65 (6H, m), 3.01 (2H, t, J = 8.1 Hz), 2.82 (1H, dd, J = 6.3 Hz, 13.8 Hz), 2.67 (1H, dd, J = 6.3 Hz, 13.8 Hz), 1.93 (2H, q, J = 6.3 Hz), 1.49 (3H, d, J = 6.6 Hz).

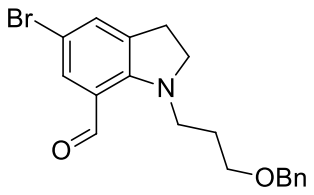
*Characterisation of compound **124** :*



1-(1-(3-(benzyloxy)propyl)-7-formylindolin-5-yl)propan-2-yl formate

^{1}H-NMR (300 MHz; $CDCl_3$), δ (ppm) : 9.98 (1H, s), 8.02 (1H, s), 7.31 – 7.78 (6H, m), 7.00 (1H, bs), 5.11 - 5.20 (1H, m), 4.50 (2H, s), 3.52 – 3.65 (6H, m), 3.01 (2H, t, J = 8.1 Hz), 2.82 (1H, dd, J = 6.3 Hz, 13.8 Hz), 2.67 (1H, dd, J = 6.3 Hz, 13.8 Hz), 1.93 (2H, q, J = 6.3 Hz), 1.25 (3H, d, J = 6.0 Hz).

*Synthesis of compound **152** :*

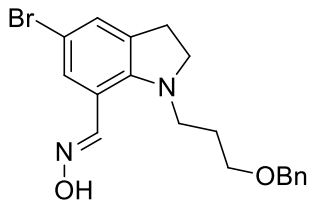


1-(3-(benzyloxy)propyl)-5-bromoindoline-7-carbaldehyde

$POCl_3$ (2.7 mL, 1.66 g, 10.83 mmol) was added in 20 minutes to DMF (6 mL, 6.33 g, 86.7 mmol) at 0°C and the mixture was stirred for additional 40 minutes at that temperature. A solution of compound **72** (3.0 g, 8.67 mmol) in DMF (6 mL) was added in 30 minutes at 0°C. The reaction was monitored by TLC (EtOAc : toluene = 1 : 1, Rf 0.3). After 3 hours the reaction was completed, the mixture was poured in ice/water mixture (100 g) and stirred for 40 minutes, and the neutralized adding Na_2CO_3 10% aqueous solution. The mixture was extracted with MTBE (3 x 50 mL). The combined organic layers were dried with Na_2SO_4, the solid is filtered off and the filtrate is concentrated until dryness obtaining 3.5 g of a crude oil. Purified by flash chromatography (etOAc : toluene = 1 : 1) obtaining compound **152** as a yellow oil (2.26 g, 6.06 mmol, 70% yield).

^{1}H-NMR (300 MHz; $CDCl_3$), δ (ppm) : 9.93 (1H, s), 7.58 (1H, d, J = 1.8 Hz), 7.28 – 7.38 (5H, m), 7.20 (1H, d, J = 1.8 Hz), 4.49 (2H, s), 3.67 (2H, t, J = 8.4 Hz), 3.58 (2H, t, J = 7.2 Hz), 3.54 (2H, t, J = 6.0 Hz), 3.03 (2H, t, J = 8.4 Hz), 1.93 (2H, m).

*Synthesis of compound **153** :*

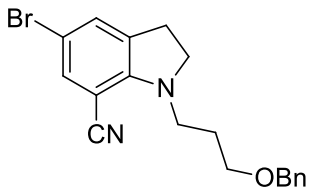


1-(3-(benzyloxy)propyl)-5-bromoindoline-7-carbaldehyde oxime

Compound **152** (2.0 g, 5.34 mmol) was dissolved in THF (3 mL), NH_2OH*HCl (1.11 g, 16.0 mmol) and pyridine (2.0 mL, 2.1 g, 26.7 mmol) were added to the solution. The mixture was stirred at 50°C monitoring the reaction by ^{1}H-NMR. After 90 minutes the reaction was completed. The mixture was concentrated under vacuum, then water (100 mL) and EtOAc (50 mL) were added. The aqueous layer was extracted with EtOAc (2 x 25 mL). The combined organic layers were dried with Na_2SO_4, the solid is filtered off and the filtrate is concentrated until dryness obtaining compound **153** as oil (2.1 g, 5.34 mmol, 100%).

^{1}H-NMR (300 MHz; $CDCl_3$), δ (ppm) : 8.30 (1H, s), 7.42 (1H, d, J = 2.1 Hz), 7.21 – 7.35 (5H, m), 7.13 (1H, d, J = 1.8 Hz), 4.52 (2H, s), 3.56 (2H, t, J = 6.3 Hz), 3.50 (2H, t, J = 8.7 Hz), 3.32 (2H, t, J = 7.1 Hz), 2.98 (2H, t, J = 8.7 Hz), 1.89 (2H, m).

*Synthesis of compound **77** :*



1-(3-(benzyloxy)propyl)-5-bromoindoline-7-carbonitrile

Procedure A:

Compound **153** (2.1 g, 5.34 mmol) and pyridine (0.4 mL, 0.42 g, 5.34 mmol) were dissolved in THF (3 mL), Ac_2O (2.17 g, 21.36 mmol) was added slowly to the solution. The mixture was stirred at 50°C monitoring the reaction by ^{1}H-NMR. After 3 hours the reaction was completed. The mixture was concentrated under vacuum, then water (100 mL) and EtOAc (50 mL) were added. The aqueous layer was extracted with EtOAc (2 x 25 mL). The combined organic layers were dried with Na_2SO_4, the solid is filtered off and the filtrate is concentrated until dryness obtaining compound **77** as brown oil 2.0 g. The crude was purified by flash chromatography (EtOAc : toluene = 1:1) obtaining compound **77** as pale brownish oil(1.58 g, 4.27 mmol, 100%).

Procedure B:

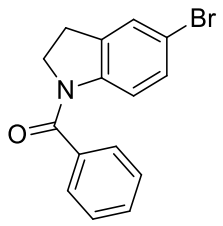
$POCl_3$ (1.76 mL, 2.88 g, 18.78 mmol) was added in 20 minutes to DMF (7.9 mL, 7.38 g, 101.22 mmol) at 0°C and the mixture was stirred for additional 40 minutes at that temperature. A solution of compound **72** (5.0 g, 14.45 mmol) in DMF (10 mL) was added in 30 minutes at 0°C. The reaction was monitored by TLC (EtOAc : toluene = 1 : 1, Rf 0.3). After 3 hours NH_2OH*HCl (4.0 g, 57.81 mmol) was added to the reaction and the mixture was stirred at 25°C overnight. The reaction was completed, the mixture was poured in ice/water mixture (100 g) and stirred for 40 minutes, and the neutralized adding Na_2CO_3 10% aqueous solution. The mixture was extracted with MTBE (3 x 50 mL). The combined organic layers were dried with Na_2SO_4, the solid is filtered off and the filtrate is concentrated until dryness obtaining 3.5 g of a crude oil. Purified by flash chromatography (EtOAc : toluene = 1 : 1) obtaining compound **77** as a brownish oil (4.55 g, 12.28 mmol, 85% yield).

The ^{1}H-NMR was comparable to the literature one, so no further characterisation had been performed.[46]

GC-MS: *m/z* = 370 (M^+ - 0, 100), 372 (M^+ + 2, 90).

^{1}H-NMR (300 MHz; $CDCl_3$), δ (ppm) : 7.27 – 7.34 (5H, m), 7.21 (1H, d, J = 0.9 Hz), 7.12 (1H, d, J = 0.9 Hz), 4.50 (2H, s), 3.61 (2H, t, J = 6.3 Hz), 3.59 (2H, t, J = 8.1 Hz), 3.56 (2H, t, J = 7.5 Hz), 2.985 (2H, t, J = 8.4 Hz), 1.89 (2H, m).

*Synthesis of compound **156** :*



1-benzoyl-5-bromoindoline

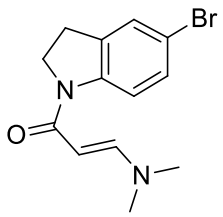
Indoline **70** (20 g, 0.101 mol) was dissolved in toluene (120 mL), then TEA (15.65 g, 0.155 mol) and DMAP (1.28 g, 0.016 mol) were added. The mixture was cooled to 0°C, and benzoyl chloride (17.57 g, 0.125 mol) was added dropwise in 30 minutes. The solution was left to react at room temperature overnight, then HCl 1 M (100 mL) was added and the organic layer was separated. The aqueous layer was extracted with EtOAc (2 x 50 mL). The organic layer was dried with Na_2SO_4, the solid was filtered off and the filtrate was concentrated until dryness obtaining a crude (31 g) that was crystallised with toluene (60 mL) obtaining compound **156** as a white solid (23.2 g, 0.076 mol, 76.7% yield).

GC-MS : m/z = 301 (M^+ -0, 100), 303 (M^+ +2, 90).

^{1}H-NMR (300 MHz; $CDCl_3$), δ (ppm) : 7.42-7.59 (7H, m), 7.33 (1H, d, J = 7.8 Hz), 3.98 (2H, t, J = 8.1 Hz), 3.07 (2H, t, J = 8.1 Hz).

^{13}C-NMR (75 MHz, CDCl3), δ (ppm) : 168.9, 142.7, 137.0, 132.4, 130.3, 128.6 (2C), 127.2, 127.1(2C), 124.9, 123.9, 117.0, 50.6, 28.1.

*Synthesis of compound **155** :*



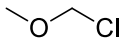
1-(5-bromoindolin-1-yl)-3-(dimethylamino)prop-2-en-1-one

$POCl_3$ (1.1 mL, 1.66 g, 10.83 mmol) was added in 20 minutes to DMF (6.5 mL, 6.08 g, 83.3 mmol) at 0°C and the mixture was stirred for additional 40 minutes at that temperature. A solution of compound **97** (2.0 g, 8.33 mmol) in DMF (6 mL) was added in 30 minutes at 0°C. The reaction was monitored by TLC (EtOAc : toluene = 1 : 1). After 1 hours the reaction was completed, the mixture was poured in ice/water mixture (100 g) and stirred for 40 minutes, the precipitate was filtered obtaining a yellow solid that resulted to be compound **155** (1.1 g, 3.72 mmol).

GC/MS: *m/z* = 294 (M^+ - 0, 100), – 296 (M^+ + 2, 90).

^{1}H-NMR (300 MHz; $CDCl_3$), δ (ppm) : 8.165 (1H, d, J = 10.0 Hz), 7.743 (1H, d, J = 9.0 Hz), 7.456 (1H, s), 7.395 (1H, d, J = 9.0 Hz), 6.678 (1H, d, J = 10.0 Hz), 4.845 (2H, t, J = 7.8 Hz), 3.676 (3H, s), 3.549 (3H, s), 3.314 (2H, t, J = 7.8 Hz).

*Synthesis of **MOMCl** reagent :*



chloromethyl methyl ether

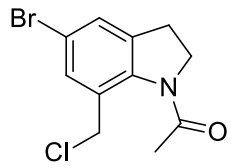
Freshly distilled hexanoyl chloride (14.0 mL, 13.5 g, 0.1 mol) and dimethoxymethane (8.8 mL, 7.6 g, 0.1 mol) were combined neat in a flask. The mixture was stirred at 60°C monitoring the reaction by 1H-NMR. After 16 hours the reaction was completed, the mixture was cooled to 25°C and the Claisen apparatus was connected to the flask. Distillation was carried out at atmospheric pressure. MOMCl was collected at 58-60°C (7.8 g, 0.097 mol, 97%).

The ^{1}H-NMR was comparable to the literature one, so no further characterisation had been performed.[112]

^{1}H-NMR (300 MHz; $CDCl_3$), δ (ppm) : 5.46 (2H, s), 3.51 (3H, s);

^{13}C-NMR (75 MHz, $CDCl_3$), δ (ppm) : 84.8, 57.6.

*Synthesis of compound **158** :*



1-acetyl-5-bromo-7-chloromethylindoline

Compound **97** (5 g, 0.020 mol) was dissolved in H_2SO_4 98% (30 mL), the mixture was cooled to 0°C and MOMCl (6.44 g, 0.080 mol) were added. The mixture was stirred at 25°C, monitoring the reaction by TLC (EtOAc : toluene = 1 : 1). After 2 hours the reaction was completed, the mixture was poured onto ice/water (200 g) and stirred for 40 minutes. The aqueous layer was extracted with EtOAc (3 x 50 mL) and the organic layer was dried with Na_2SO_4, the solid was filtered off and the filtrate was concentrated until dryness obtaining a crude (6 g) that was crystallised with EtOAc (6 mL) obtaining compound **158** as a pale green solid (4.98 g, 0.017 mol, 83.1% yield).

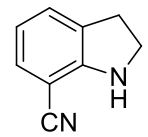
m.p. : 155°C (lit.[114] 169-170°C)

GC-MS: *m/z* = 289 (M^+ + 2, 100), 287 (M^+ - 0, 70), 291 (M^+ +4, 30).

^{1}H-NMR (300 MHz; $CDCl_3$), δ (ppm) : 8.34 (1H, s), 7.37 (1H, s), 4.67 (2H, s), 4.08 (2H, t, J = 8.7 Hz), 3.19 (2H, t, J = 8.4 Hz), 2.22 (3H, s);

^{13}C-NMR (75 MHz, $CDCl_3$), δ (ppm) : 169.0, 142.9, 135.9, 133.8, 129.0, 119.2, 118.0, 49.1, 46.7, 27.6, 24.2.

*Synthesis of compound **159** :*

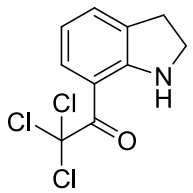


indoline-7-carbonitrile

To a stirred 2.0 M solution of BCl_3 in toluene (5.5 mL, 11.0 mmol) at 0°C, a solution of compound **2** (1.2 g, 10.0 mmol) in toluene (12 mL) was added. The solution was refluxed for 1 hour and 8 mL of toluene were distilled off. The resulting mixture was cooled to 25°C and Cl_3CCN (2.88 g, 20.0 mmol) was added. The mixture was stirred at 60°C overnight monitoring the reaction by TLC (EtOAc : toluene = 1 : 1). After 18 hours the reaction was completed, the mixture was diluted in toluene and poured into a 20% solution of NaOMe in MeOH (20 mL). The resulting mixture was stirred at 25°C for 4 hours. The mixture was concentrated under vacuum water (50 mL) and EtOAc (20 mL) were added and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried with Na_2SO_4, the solid is filtered off and the filtrate is concentrated until dryness obtaining 1.6 g of crude that was crystallysed from n-butanol/heptane mixture (2 mL) obtaining compound **152** (0.9 g, 6.2 mmol, 62% yield).

^{1}H-NMR (300 MHz; $CDCl_3$), δ (ppm) : 7.19 (1H, d, J = 7.5 Hz), 7.14 (1H, d, J = 7.8 Hz), 6.61 (1H, t, J = 7.5 Hz), 4.45 (1H, br s), 3.70 (2H, t, J = 8.4 Hz), 3.09 (2H, t, J = 8.4 Hz).

*Synthesis of compound **160** :*



2,2,2-trichloro-1-(indolin-7-yl)ethanone

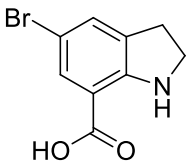
To a stirred 2.0 M solution of BCl_3 in toluene (5.5 mL, 11.0 mmol) at 0°C, a solution of compound **2** (1.2 g, 10.0 mmol) in toluene (12 mL) was added. The solution was refluxed for 1 hour and 8 mL of toluene were distilled off. The resulting mixture was cooled to 25°C and Cl_3CCN (2.88 g, 20.0 mmol) was added. The mixture was stirred at 60°C overnight monitoring the reaction by TLC (EtOAc : toluene = 1 : 1). After 18 hours the reaction was completed, the mixture was poured onto ice/water (50 mL) and stirred at 25°C for 1 hours, then the mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried with Na_2SO_4, the solid is filtered off and the filtrate is concentrated until dryness obtaining 2.7 g of yellow solid that was crystallysed from n-butanol/heptane mixture (3 mL) obtaining compound **160** (2.2 g, 8.3 mmol, 83% yield).

GC-MS: *m/z* = 263 (M^+ - 0, 100), 265 (M^+ + 2, 90), 267 (M^+ +4, 20).

^{1}H-NMR (300 MHz; $CDCl_3$), δ (ppm) : 7.92 (1H, d, J = 8.7), 7.16 (1H, d, J = 6.6 Hz), 6.48 (1H, dd, J = 6.9 Hz, 8.4 Hz), 3.83 (2H, t, J = 9.0 Hz), 3.10 (2H, t, J = 8.7 Hz).

^{13}C-NMR (75 MHz, CDCl3), δ (ppm) : 180.6, 158.0, 132.3, 129.6, 129.1, 114.7, 105.9, 46.5, 27.8.

*Synthesis of compound **161** :*



5-bromoindoline-7-carboxylic acid

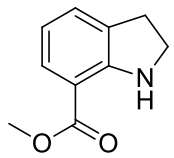
To a stirred 2.0 M solution of BCl_3 in toluene (11 mL, 22.0 mmol) at 0°C, a solution of compound **2** (2.4 g, 20.0 mmol) in toluene (12 mL) was added. The solution was refluxed for 1 hour and 8 mL of toluene were distilled off. The resulting mixture was cooled to 25°C and Cl_3CCN (5.74 g, 40.0 mmol) was added. The mixture was stirred at 60°C overnight monitoring the reaction by TLC (EtOAc : toluene = 1 : 1). After 18 hours the reaction was completed, the mixture was diluted in toluene (5 mL) and poured into cooled solution of NaOH 10% in H_2O (50 mL). The resulting mixture was stirred at 25°C for 2 hours. The suspension was filtered and washed with water obtaining compound **161** light brown solid (1.9 g, 11.6 mmol, 58% yield).

GC-MS: *m/z* = 240 (M^+ - 0, 100), 242 (M^+ +2, 90).

^{1}H-NMR (300 MHz; $CDCl_3$), δ (ppm) : 7.20 (1H, s), 7.19 (1H, s), 5.65 (2H, br s), 3.69 (2H, t, J = 8.7 Hz), 3.02 (2H, t, J = 8.7 Hz).

^{1}H-NMR (300 MHz, CDCl3), δ (ppm) :169.3, 153.2, 134.4, 130.6, 127.2, 111.1, 106.9, 46.9, 28.4.

*Synthesis of compound **164** :*



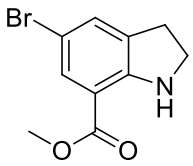
methyl indoline-7-carboxylate

Compound **160** (5 g, 18.9 mmol) was suspended in a 20% solution of NaOMe in MeOH, the mixture was stirred at 25°C monitoring the reaction by TLC (EtOAc : toluene = 1:1). After 4 hours the reaction was completed, the mixture was cooled to 0°C and neutralised adding dropwise HCl 37% in water. The mixture was diluted with water, concentrated under vacuum and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried with Na_2SO_4, the solid is filtered off and the filtrate is concentrated until dryness obtaining 3.4 g of a crude oil sufficiently pure to be used in the next preparation.

GC-MS: *m/z* = 177 (M+ -0).

^{1}H-NMR (300 MHz, CDCl3), δ (ppm) : 7.54 (1H, d, J = 7.5 Hz), 7.10 (1H, d, J = 7.2 Hz), 6.81 (1H, t, J = 7.8 Hz), 3.86 (3H, s), 3.70 (1H, d, J = 8.4 Hz), 3.13 (2H, t, J = 7.8 Hz).

*Synthesis of compound **165** :*



methyl 5-bromoindoline-7-carboxylate

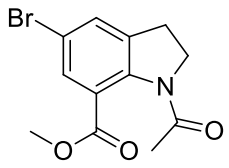
Compound **164** (2.0 g, 11.2 mmol) was dissolved in MTBE (20 mL), NBS (2.0 g, 11.2 mol) was added slowly, and the mixture was stirred at room temperature monitoring the reaction by TLC (EtOAc : toluene = 1:1). After 1 hour the reaction was completed, the mixture was poured onto water (50 mL) and extracted with MTBE (3 x 20 mL). The combined organic layers were dried with Na_2SO_4, the solid was filtered off and the filtrate was concentrated until dryness obtaining 2.9 g of a crude oil. Crystallised from MTBE (1 mL) and heptane (4 mL) obtaining compound **165** as white solid (1.9 g, 7.42 mmol, 66% yield).

GC-MS: *m/z* = 255 (M^+ - 0, 100), 257 (m^+ +2, 90).

^{1}H NMR (300 MHz; $CDCl_3$), δ (ppm) : 7.66 (1H, d, J = 1.2 Hz), 7.22 (1H, d, J = 1.2 Hz), 3.85 (3H, s), 3.72 (2H, t, J = 8.7 Hz), 3.04 (2H, t, J = 8.4 Hz);

^{13}C NMR (75 MHz; $CDCl_3$), δ (ppm) : 167.1, 153.6, 133.5, 131.4, 129.9, 108.7, 107.1, 51.7, 47.0, 28.4.

*Synthesis of compound **166** :*



methyl 1-acetyl-5-bromoindoline-7-carboxylate

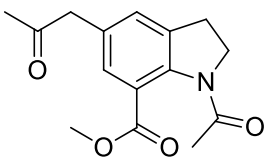
Compound **165** (10.0 g, 39.0 mmol) was dissolved in toluene (40 mL) and Ac_2O (5.9 g, 58.5 mmol) was added. The mixture was stirred at 100°C monitoring the reaction by TLC (EtOAc : toluene = 2 : 1). After 16 hours the reaction was completed, the mixture was cooled to 25°C and poured onto water (100 mL). The aqueous layer was extracted with toluene (3 x 40 mL) and concentrsted under vacuum obtaining a crude solid of 12 g that was crystallised from EtOAc (24 mL) obtaining compound **166** as white solid (8.1 g, 26.9 mmol, 69% yield).

m.p. : 164°C

GC-MS: *m/z* = 255 (M^+ - 43, 100), 257 (M^+ - 41, 90).

^{1}H-NMR (300 MHz; $CDCl_3$), δ (ppm) : 7.58 (1H, d, J = 1.2 Hz), 7.42 (1H, d, J = 1.2 Hz), 4.16 (2H, t, J = 8.1 Hz), 3.86 (3H, s), 3.14 (2H, t, J = 7.8 Hz), 2.21 (3H, s).

*Synthesis of compound **167** :*



methyl 1-acetyl-5-(2-oxopropyl)indoline-7-carboxylate

Compound **166** (5.0 g, 16.77 mmol), Cs_2CO_3 (16.3 g, 50.33 mmol), DMSO (20.0 mL), acetylacetone (5.3 g, 50.33 mmol) and proline (0.38 g, 3.36 mmol) were added. The system was degassed and CuI (0.318 g, 1.67 mmol) was added. The mixture was stirred at 110°C with mechanical stirrer, monitoring by GC-MS. After 21 hours the reaction was completed, the mixture was cooled to rt, ethyl acetate (50 mL), H_2O (200 mL). The aqueous layer was extracted with ethyl acetate (3 x 50 mL). Then the organic layer was washed with aqueous NH_3 10 %, aqueous NaOH al 10%, aqueous HCl 1 M and brine. The combined organic layers were dried with Na_2SO_4, the solid was filtered off and the filtrate was concentrated until dryness obtaining a brown oil (4.9 g). The crude thus obtained was purified by flash chromatography (ethyl acetate : toluene = 3:1, Rf: 0.30) obtaining compound **167** as pale grey solid (2.99 g, 10.9 mmol, 65% yield).

m.p. 220°C

GC-MS: *m/z* = 275 (M+ - 0), 233 (M+ - 42)

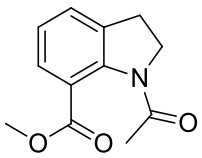
MS (ESI^+) *m/z*: = 234.05 (M+ - 42).

^1H NMR (300 MHz; $CDCl_3$), δ (ppm) : 7.29 (1H, s), 7.16 (1H, s), 4.16 (2H, t, J = 8.4 Hz), 3.85 (3H, s), 3.66 (2H, s), 3.12 (2H, t, J = 8.4 Hz), 2.22 (3H, s), 2.16 (3H, s).

^{13}C-NMR (75 MHz, CDCl3), δ (ppm) : 205.9, 169.5, 167.3, 135.0, 130.4, 128.6, 128.2, 123.8, 119.7, 61.7, 52.2, 50.0, 29.5, 28.8, 23.4.

HPLC method **A**: Retention time: 3.48 min

*Synthesis of compound **168** :*



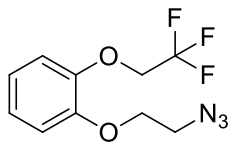
methyl 1-acetylindoline-7-carboxylate

GC-MS: m/z = 219 (M^+ - 0).

^{1}H NMR (300 MHz; $CDCl_3$), δ (ppm) : 7.46 (1H, d, J = 7.5 Hz), 7.30 (1H, d, J = 7.2 Hz), 7.07 (1H, t, J = 7.8 Hz), 4.16 (1H, d, J = 8.4 Hz), 3.86 (3H, s), 3.13 (2H, t, J = 7.8 Hz), 2.22 (3H, s).

HPLC method **A**: Retention time: 4.68 min

*Synthesis of compound **187** :*

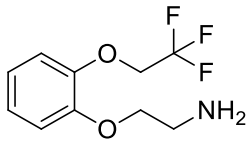


1-(2-azidoethoxy)-2-(2,2,2-trifluoroethoxy)benzene

Compound **14** (5.0 g, 15.9 mmol) was dissolved in DMSO (15 mL) and NaN_3 (2.1 g, 31.8 mmol) was added. The mixture was stirred at 40°C monitoring the reaction by TLC (EtOAc : toluene = 2 : 1). After 6 hours the reaction was completed, the mixture was cooled to 25°C and poured onto water (100 mL). The aqueous layer was extracted with MTBE (3 x 40 mL), the combined organic layers were dried with Na_2SO_4, the solid was filtered off and the filtrate was concentrated until dryness obtaining compound **187** as oil (4.15 g, 15.9 mmol, 100% yield).

^{1}H NMR (300 MHz; $CDCl_3$), δ (ppm) : 6.92-7.09 (4H, m), 4.39 (2H, q, J = 8.1 Hz), 4.18 (2H, t, J = 4.5 Hz), 3.62 (2H, t, J = 4.5 Hz).

*Synthesis of compound **79** :*



2-(2-(2,2,2-trifluoroethoxy)phenoxy)ethanamine

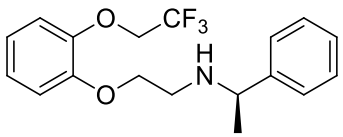
Compound **187** (4.15 g, 15.9 mmol) was dissolved in MeOH (30 mL) and Pd/C 5% (0.4 g, 0.18 mmol) was added. The mixture was evacuated and backfilled with N_2 three times, then the flask was connected to a balloon filled with H_2. The mixture was stirred at 25°C monitoring the reaction by 1H-NMR. After 2 hours the reaction was completed, the mixture filtered on celite and concentrated obtaining compound **79** as colourless oil (3.43 g, 14.7 mmol, 93% yield).

MS (ESI^+) *m/z* = 236.05 (M^+ + H).

^{1}H NMR (300 MHz; $CDCl_3$), δ (ppm) : 6.88-7.07 (4H, m), 4.38 (3H, q, J = 8.1 Hz), 4.05 (2H, t, J = 5.1 Hz), 3.11 (2H, t, J = 5.1 Hz), 1.74 (2H, br s).

HPLC method: Retention time: 4.93 min

*Synthesis of compound **191** :*



(*R*)-1-phenyl-*N*-(2-(2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)ethanamine

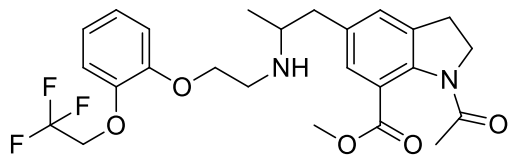
Compound **14** (5.0 g, 15.9 mmol) was dissolved in acetonitrile (15 mL) and (R)-phenylethyl amine (6.73 g, 55.6 mmol) was added. The mixture was stirred at 25°C monitoring the reaction by TLC (EtOAc : toluene = 2 : 1). After 18 hours the reaction was completed, the mixture was c poured onto water (100 mL) and extracted with MTBE (3 x 40 mL) the combined organic layers were dried with Na_2SO_4, the solid was filtered off and the filtrate was concentrated until dryness obtaining compound **191** as oil (5.4 g, 15.9 mmol, 100% yield).

^{1}H NMR (300 MHz; $CDCl_3$), δ (ppm) : 7.27-7.38 (5H, m), 6.86-7.21 (4H, m), 4.36 (2H, q, J = 8.4 Hz), 4.01-4.15 (2H, m), 3.84 (1H, q, J = 6.6 Hz), 2.58-2.84 (2H, m), 1.57 (1H, br s), 1.25 (3H, t, J = 7.5 Hz).

^{13}C-NMR (75 MHz, CDCl3), δ (ppm) : 147.7, 146.7, 137.1, 128.9, 127.9, 124.0 (q, J = 276.6Hz), 123.2, 121.8, 115.9, 114.6, 66.0 (q, 33.9 Hz), 64.7, 57.5, 43.6, 19.4.

HPLC method **A**: Retention time: 6.73 min

*Synthesis of compound **169** :*



methyl 1-acetyl-5-(2-((2-(2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)amino)propyl)indoline-7-carboxylate

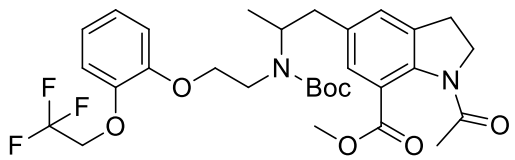
Compound **167** (1.0 g, 3.63 mmol) was dissolved in THF (7 mL), amine **79** (0.85 g, 3.63 mmol) and AcOH (0.5 mL) were added. After 20 minutes NaCNBH4 (0.36 g, 5.44 mmol) was added and the mixture was stirred at 25°C overnight. The mixture was poured onto water (50 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried with Na_2SO_4, the solid was filtered off and the filtrate was concentrated until dryness obtaining a crude oil that was purified by flash chromatography (DCM : MeOH = 9 : 1, Rf 0.29) obtaining compound **169** as oil (1.2 g, 2.43 mmol, 67% yield)

MS (ESI^+) *m/z* = 495.13 (M^+ + H).

^{1}H NMR (300 MHz; $CDCl_3$), δ (ppm) : 7.29 (1H, s), 7.16 (1H, s), 6.85 – 7.08 (4H, m), 4.38 (2H, q, J = 8.7 Hz), 4.15 (2H, t, J = 4.8 Hz), 4.07 (2H, t, 5.4 Hz), 3.85 (3H, s), 3.04 – 3.22 (5H, m), 2.89 (2H, dd, J = 6.0 Hz J = 13.5 Hz), 2.61 (2H, dd, J = 6.8 Hz, 13.5 Hz), 1.12 (3H, d, J = 6.3 Hz).

HPLC method **A**: Retention time: 16.17 min

*Synthesis of compound **170** :*

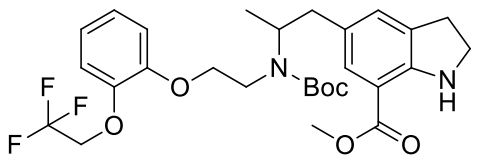


methyl 1-acetyl-5-(2-((*tert*-butoxycarbonyl)(2-(2-(2,2,2-trifluoroethoxy) phenoxy)ethyl)amino)propyl)indoline-7-carboxylate

Compound **169** (1.0 g, 2.02 mmol) was dissolved in DCM (6 mL) and Boc_2O (0.88 g, 4.0 mmol) was added. The mixture was stirred at 25°C monitoring the reaction by TLC (DCM : MeOH = 9 : 1). After 20 hours the reaction was completed, the mixture was diluted with DCM (20 mL) and washed with water (50 mL). The organic layer was dried with Na_2SO_4, the solid was filtered off and the filtrate was concentrated until dryness obtaining compound **170** as oil (1.18 g, 2.0 mmol, 98% yield).

^{1}H NMR (300 MHz; $CDCl_3$), δ (ppm) : 7.27 (1H, s), 7.25 (1H, s), 7.06-6.85 (4H, m), 4.35 (2H, q, J=8.4 Hz), 4.10 (2H, t, J = 9.0 Hz), 4.12-3.96 (2H, m), 3.84 (3H, s), 3.52-3.36 (2H, br m), 3.14 (2H, t, J = 8.4 Hz), 3.03 (2H, t, J = 8.7 Hz), 2.68 (1H, dd, J = 13,2; 6,9 Hz), 2.20 (3H, s), 1.42 (9H, s), 1.24 (3H, d, J = 6.9 Hz).

*Synthesis of compound **171** :*

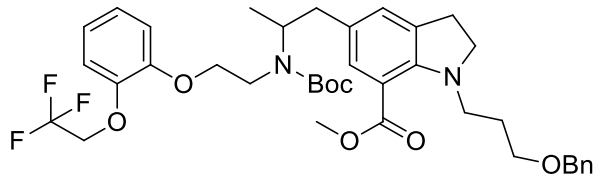


methyl 5-(2-((*tert*-butoxycarbonyl)(2-(2-(2,2,2-trifluoroethoxy)
phenoxy)ethyl)amino)propyl)indoline-7-carboxylate

Compound **170** (1.18 g, 2.0 mmol) was dissolved in a solution of sodium methoxide 25% in MeOH (4 mL). The resulting mixture was stirred at 25°C monitoring the reaction by TLC (EtOAc : toluene = 3:1). After 15 hours the reaction was completed, the mixture neutralised with HCl 1M and extracted with EtOAc (2 x 50 mL). The combined organic layers were dried with Na_2SO_4, the solid was filtered off and the filtrate was concentrated until dryness obtaining a brown oil (1.1 g) sufficientely pure. Compound **171** was used directly in the next synthetic step to prepare compound **162**.

^{1}H NMR (300 MHz; $CDCl_3$), δ (ppm) : 7.35 (1H, s), 7.08-6.83 (5H, m), 4.36 (2H, q, J=8.1 Hz), 4.19-3.85 (3H, br m), 3.83 (3H, s), 3.68 (2H, t, J=8.1 Hz), 3.52-3.36 (2H, br m), 2.98 (2H, t, J=7.8 Hz), 2.81 (1H, m), 2.58 (1H, dd, J=12.9, 6.9 Hz), 1.43 (9H, s), 1.25 (3H, d, J=6.9 Hz).

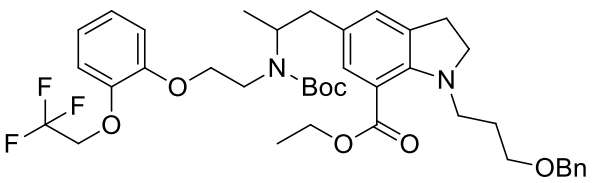
*Synthesis of compound **162** :*



methyl 1-(3-(benzyloxy)propyl)-5-(2-((*tert*-butoxycarbonyl)(2-(2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)amino)propyl)indoline-7-carboxylate

Compound **171** (1.1 g, 2.0 mmol) was dissolved in EtOH (7 mL), than K_2CO_3 (0.42 g, 3.0 mmol) and compound **98** (0.8 g, 2.5 mmol) were added to the solution. The reaction mixture stirred at 70°C monitoring the reaction by TLC (EtOAc : toluene = 1 : 2), after 24 hours the TLC showed 4 different spots. The reaction mixture was cooled down to 25°C, water (100 mL) was added and the mixture was extracted with AcOEt (3 x 50 mL). The combined organic layers were dried with Na_2SO_4, the solid is filtered off and the filtrate is concentrated until dryness obtaining 2.3 g of a crude oil. The crude was purified by flash chromatography (EtOAc : heptane = 1 : 2) to give a pale white oil (0.378 g, 0.5 mmol, 27% yield) that was found to be ethyl ester **172** formed in the reaction resulted to be the ethyl ester derivatives due to transesterification reaction with the solvent.

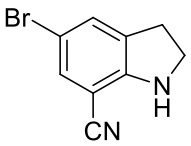
Characterisation of compound **172** :



ethyl 1-(3-(benzyloxy)propyl)-5-(2-((*tert*-butoxycarbonyl)(2-(2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)amino)propyl)indoline-7-carboxylate

^{1}H NMR (300 MHz; $CDCl_3$), δ (ppm) : 7.39-7.25 (5H, m), 7.10-6.87 (6H, m), 4.50 (2H, s), 4.35 (2H, q, J = 8.4 Hz), 4.25-3.84 (5H, m), 3.66 (2H, t, J = 8.7 Hz), 3.50-3.42 (4H, m), 3.45 (2H, t, J = 7.5 Hz), 2.97 (2H, t, J = 8.4 Hz), 2.90-2.75 (1H, m), 2.58 (1H, dd, J = 13.8, 6.3 Hz), 1.86 (2H, p, J = 6.3 Hz), 1.42 (9H, s), 1.25 (3H, d, J = 6.0 Hz), 1.21 (3H, t, J = 7.2 Hz).

*Synthesis of compound **72** :*



5-bromoindoline-7-carbonitrile

Compound **159** (2.0 g, 13.8 mmol) was dissolved in MTBE (20 mL), NBS (2.47 g, 13.8 mol) was added slowly, and the mixture was stirred at room temperature monitoring the reaction by TLC (EtOAc : toluene = 1:1). After 1 hour the reaction was completed, the mixture was poured onto water (50 mL) and extracted with MTBE (3 x 20 mL). The combined organic layers were dried with Na_2SO_4, the solid was filtered off and the filtrate was concentrated until dryness obtaining 2.9 g of a solid directly used in the next preparation.

Optimized two steps-one pot procedure starting from indoline **2** :

In a previously anhydrified flask with mechanical stirring, a solution of BCl_3 in toluene (300 mL, 1.207 mol) was cooled to 0°C. A solution of indoline (120.8 g; 1.015 mol) in toluene (180 mL) was added dropwise, and the resulting suspension was refluxed for 1 hour. The mixture was then cooled to 75°C, trichloroacetonitrile (290.3 g; 2.030 mol) was added dropwise over 20 min, and stirring was continued for 8 hours at 85°C. The reaction mixture was cooled to 5°C, methanol was added (790 mL) dropwise over 1 hour, and then sodium methoxide (274.1 g; 5.075 mol)

was added and stirring was continued for 48 hours at 20°C. The mixture was cooled to 10°C, NBS (173 g; 0.971 mol) was added portionwise and stirred for 90 min, the mixture is then treated with a s.s. $NaHSO_3$ (120 mL) and stirred for 1 hour. The mixture was concentrated under reduced pressure, toluene (300 mL) and aqueous NaOH 10% (1000 mL) were added, the phases were separated and the aqueous phase extracted with toluene (2 x 250 mL). The combined organic layers are dried with Na_2SO_4, the solid is filtered off and the filtrate is concentrated until dryness obtaining a brown oil (184 g). It could be isolated as a brown powder crystallising it with heptane/butanol mixture.

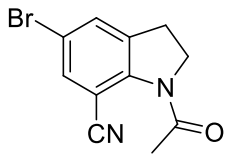
mp: 102-103 °C.

GC-MS : *m/z* = 222 (M+ -0), 224 (M+ +2).

^{1}H NMR (300 MHz; $CDCl_3$), δ (ppm) : 7.26 (2H, s), 7.22 (2H, s), 4.51 (1H, bs), 3.73 (2H, t, J = 8.4 Hz), 3.09 (2H, t, J = 8.4 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz), δ (ppm) : 154.2; 132.7; 131.8; 131.1; 116.6; 108.3; 91.2; 47.2; 29.1.

*Synthesis of compound **173** :*



1-acetyl-5-bromoindoline-7-carbonitrile

Compound **76** (10.0 g, 45.0 mmol) was dissolved in toluene (40 mL) and Ac_2O (6.9 g, 67.2 mmol) was added. The mixture was stirred at 100°C monitoring the reaction by TLC (EtOAc : toluene = 2 : 1). After 16 hours the reaction was completed, the mixture was cooled to 25°C and poured onto water (100 mL). The aqueous layer was extracted with toluene (3 x 40 mL) and concentrsted under vacuum obtaining a crude solid of 12 g that was crystallised from toluene (24 mL) obtaining compound **173** as white solid (5.7 g, 21.6 mmol, 48% yield).

m.p. : 177°C.

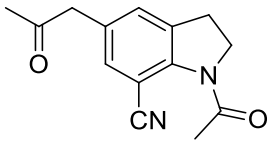
GC-MS : *m/z* = 264 (M+ -0), 266 (M+ +2).

^{1}H NMR (300 MHz; $CDCl_3$), δ (ppm) :7.54 (1H, d, J = 2.1 Hz), 7.48 (1H, d, J = 2.1 Hz), 4.15 (2H, t, J = 8.4 Hz), 3.15 (2H, t, J = 8.4 Hz), 2.29 (3H, s).

^{13}C NMR (75 MHz; $CDCl_3$), δ (ppm) : 168.4, 142.6, 137.3, 134.4, 132.2, 116.3, 115.5, 104.0, 50.1, 28.6, 23.7.

HPLC method **B**: Retention time: 17.14 min

*Synthesis of compound **174** :*



1-acetyl-5-(2-oxopropyl)indoline-7-carbonitrile

In a flask equipped with a mechanical stirrer, 1-acetyl-5-bromoindoline-7-carbonitrile **173** (5 g, 18.86 mmol), K_2CO_3 (7.81 g, 56.60 mmol), acetylacetone (5.66 g, 56.60 mmol), proline (0.43 g; 3.77 mmol) and DMSO (20 mL) were loaded. The system was degassed and CuI (0.36 g, 1.8 mmol) was added, and stirring was continued for 18 hours at 100°C. The mixture was cooled to rt, acidified with HCl 1 M and extracted with AcOEt (3 x 50 mL). The combined organic layers are dried with Na_2SO_4, the solid is filtered off and the filtrate is concentrated until dryness obtaining a crude oil that can be purified through flash chromatography (AcOEt) obtaining 1-acetyl-5-(2-oxopropyl)-indoline-7-carbonitrile as a white solid (2.22 g, 9.16 mmol, 48% yield), while crystallising from AcOEt compound **174** is obtained as off-white solid (0.83 g, 3.42 mmol, 18% yield).

m.p. : 141 °C.

GC-MS : *m/z* = 242 (M+ - 0).

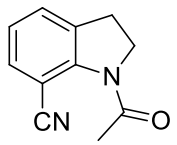
^{1}H NMR (300 MHz; $CDCl_3$), δ (ppm) :7.27 (s, 1H), 7.24 (s, 1H), 4.14 (t, J = 8.4 Hz, 2H), 3.68 (s, 2H), 3.13 (t, J = 8.4 Hz, 2H), 2.31 (s, 3H), 2.20 (s, 3H);

^{13}C-NMR ($CDCl_3$, 75 MHz), δ (ppm) : 205.0, 168.4, 142.3, 135.7, 133.0, 130.7, 130.3, 117.3, 102.4, 50.1, 49.2, 29.7, 28.6, 23.7.

HPLC method **B**: Retention time: 9.78 min

Elemental analysis: Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56; found: C, 68.78; H, 5.69; N, 11.05.

*Synthesis of compound **175** :*



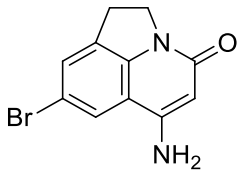
1-acetylindoline-7-carbonitrile

m.p. : 136°C

^{1}H NMR (300 MHz; $CDCl_3$), δ (ppm) : 7.48 (1H, d, J = 7.2 Hz), 7.49 (1H, d, J = 7.2 Hz), 7.08 (1H, t, J = 7.2 Hz), 4.18 (t, J = 8.4 Hz, 2H), , 3.10 (t, J = 8.4 Hz, 2H), 2.16 (s, 3H).

HPLC method **B**: Retention time: 10.68 min

*Synthesis and characterisation of impurity **I-3***



6-amino-8-bromo-1*H*-pyrrolo[3,2,1-*ij*]quinolin-4(2*H*)-one

1-acetyl-5-bromoindoline-7-carbonitrile **173** (5 g, 18.86 mmol), K_2CO_3 (7.81 g, 56.60 mmol), DMSO (20 mL) were charged in a flask and stirred at 100°C for 1 hour. The mixture was cooled to 25°C, water (50 mL) was added, the suspension thus obtained was filtered, the solid was washed with water obtaining compound **I-3** as a white solid (4.79 g, 18.11 mmol) yield 96%.

m.p. : 117-118°C.

MS (ESI^+) *m/z* = 265.04 (M^+ + H, 100), 267.12 (M^+ +3, 90).

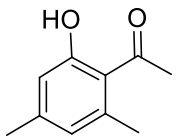
^{1}H-NMR (300 MHz, DMSO-d_6), δ (ppm) : 7.92 (s, 1H), 7.45 (s, 1H), 6.57 (s, 2H), 5.43 (s, 1H), 4.09 (t, J = 7.4 Hz, 2H), 3.27 (t, J = 7.2 Hz, 2H).

^{13}C-NMR (75 MHz, DMSO-d_6), δ (ppm) :161.1, 151.6, 141.8, 133.8, 127.8, 122.0, 113.1, 112.8, 94.6, 45.9, 26.7.

HPLC method **B**: Retention time: 12.20 min

Elemental analysis: Anal. Calcd for $C_{11}H_9N_2O$: C, 49.84; H, 3.42; N, 10.57; found: C, 49.37; H, 3.34; N, 10.13.

*Synthesis and characterisation of impurity **I-4***



1-(2-hydroxy-4,6-dimethylphenyl)ethanone

Acetylacetone (5.0 g, 50.0 mmol), K_2CO_3 (6.9 g, 50.00 mmol), DMSO (20 mL) and CuI (0.9 g, 5.0 mmol) were charged in a flask and stirred at 100°C for 24 hour. The mixture was cooled to 25°C, NaOH 20% in water (50 mL) was added, The aqueous layer was washed with EtOAc (2 x 20 mL) then acidified with HCl 3 M (100 mL). The aqueous layer was then extracted with EtOAc (3 x 40 mL). The combined organic layers were dried with Na_2SO_4, the solid was filtered off and the filtrate was concentrated until dryness obtaining impurity as pale yellow oil (0.8 g, 4.87 mmol, 9.7% yield).

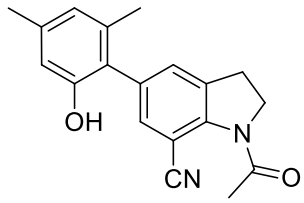
MS (ESI^+) *m/z* = 165.11 (M^+ + H).

GC-MS: m/z = 164 (M^+ - 0).

^1H NMR (300 MHz; $CDCl_3$), δ (ppm) :6.64 (1H, s), 6.53 (1H, s), 6.48 (1H, s), 2.62 (3H, s), 2.54 (3H, s), 2.25 (3H, s).

HPLC method **B**: Retention time: 20.47 min

*Characterisation of impurity **I-5** :*



1-acetyl-5-(2-hydroxy-4,6-dimethylphenyl)indoline-7-carbonitrile

Isolatated by flash chromatography from 5.0 g crude of compound **174** (EtOAc : toluene = 3 : 1) in mixture with compound **174** (1.1 g), **I-5** was crystallised from DCM (2 mL) as white powder (0.329 g, 1.0 mmol, 5.3% yield).

m.p. : 225°C

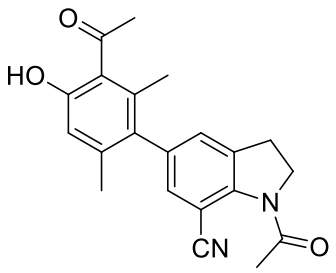
MS (ESI^+) *m/z* = 307.09 (M^+ + H), 265.08 (M^+ - 41).

^{1}H NMR (300 MHz; $CDCl_3$), δ (ppm) :7.39 (1H, d, J = 0.9 Hz), 7.31 (1H, d, J = 0.9 Hz), 6.68 (1H, s), 6.63 (1H, s), 4.20 (2H, t, J = 8.1 Hz), 3.20 (2H, t, J = 8.1 Hz), 2.35 (3H, s), 2.30 (3H, s), 2.02 (3H, s)

^{13}C-NMR (75 MHz, $CDCl_3$), δ (ppm) : 168.75, 152.95, 142.8, 139.3, 137.2, 136.1, 134.2, 133.1, 131.4, 130.3, 123.3, 117.2, 113.8, 103.1, 50.2, 28.8, 23.8, 21.2, 20.4.

HPLC method **B**: Retention time: 21.50 min

*Characterisation of impurity **I-6** :*



1-acetyl-5-(3-acetyl-4-hydroxy-2,6-dimethylphenyl)indoline-7-carbonitrile

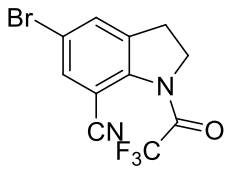
Isolatated by flash chromatography from 5.0 g crude of compound **174** (EtOAc : toluene = 3 : 1) in mixture with compound **I-5** (0.2 g).

MS (ESI^+) *m/z* = 349.05 (M^+ + H).

^{1}H NMR (300 MHz; $CDCl_3$), δ (ppm) :7.28 (1H, s), 7.25 (1H, s), 6.59 (1H, s), 4.14 (2H, t, J = 8.1 Hz), 3.07 (2H, t, J = 8.1 Hz), 2.32 (3H, s), 2.30 (3H, s), 2.20 (3H, s), 1.97 (3H, s).

HPLC method **B**: Retention time: 23.58 min

*Synthesis of compound **177** :*



5-bromo-1-(2,2,2-trifluoroacetyl)indoline-7-carbonitrile

Compound **76** (10.0 g, 45.0 mmol) was dissolved in toluene (40 mL) TEA (6.8 g, 67.5 mmol) and DMAP (0.5 g, 4.5 mmol) were added. The mixture was cooled to 0°C and trifluoroacetyl chloride (7.7 g, 58.5 mmol) was added dropwise in 20 minutes. The mixture was stirred at 25°C monitoring the reaction by TLC (EtOAc : toluene = 2 : 1). After 16 hours the reaction was completed, the mixture was cooled to 25°C and poured onto water (100 mL). The aqueous layer was extracted with toluene (3 x 40 mL) and concentrsted under vacuum obtaining a crude solid of 12 g that was crystallised from toluene (24 mL) obtaining compound **177** as white solid (8.4 g, 26.4 mmol, 55% yield).

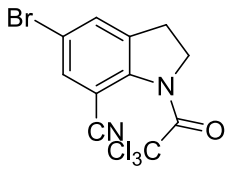
m.p. : 157.6°C.

GC-MS : *m/z* = 318 (M+ -0), 320 (M+ +2).

^{1}H NMR (300 MHz; $CDCl_3$), δ (ppm) :7.66 (1H, s), 7.63 (1H, s), 4.31 (2H, t, J = 7.5 Hz), 3.24 (2H, t, J = 7.8 Hz).

^{13}C-NMR (75 MHz, $CDCl_3$), δ (ppm) : 154.7 (q, J = 38.4 Hz), 141.0, 137.8, 134.7, 132.7, 119.0, 115.9 (q, J = 285.9 Hz), 114.8, 105.0, 49.8, 29.1.

*Synthesis of compound **178** :*



5-bromo-1-(2,2,2-trichloroacetyl)indoline-7-carbonitrile

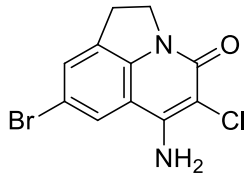
Compound **76** (10.0 g, 45.0 mmol) was dissolved in toluene (40 mL) TEA (6.8 g, 67.5 mmol) and DMAP (0.5 g, 4.5 mmol) were added. The mixture was cooled to 0°C and trifluoroacetyl chloride (10.6 g, 58.5 mmol) was added dropwise in 20 minutes. The mixture was stirred at 25°C monitoring the reaction by TLC (EtOAc : toluene = 2 : 1). After 16 hours the reaction was completed, the mixture was cooled to 25°C and poured onto water (100 mL). The aqueous layer was extracted with toluene (3 x 40 mL) and concentrsted under vacuum obtaining a crude solid of 12 g that was crystallised from toluene (24 mL) obtaining compound **178** as white solid (11.9 g, 32.4 mmol, 72% yield).

m.p. : 198°C.

^{1}H-NMR (300 MHz, $CDCl_3$), δ (ppm) : 7.66 (1H, d, J = 1.8 Hz), 7.62 (1H, d, J = 2.1 Hz), 4.57 (2H, t, J = 7.5 Hz), 3.20 (2H, t, J = 7.5 Hz).

^{13}C-NMR (75 MHz, $CDCl_3$), δ (ppm) :159.2, 143.1, 137.7, 134.5, 132.4, 118.7, 114.8, 105.8, 92.4, 53.3, 29.8.

*Copper catalysed reaction on substrate **178** and characterisation of compound **179** :*



6-amino-8-bromo-5-chloro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-4(2*H*)-one

1-trichloroacetylacetyl-5-bromoindoline-7-carbonitrile **178** (5 g, 18.86 mmol), K_2CO_3 (7.81 g, 56.60 mmol), DMSO (20 mL) were charged in a flask and stirred at 100°C for 1 hour. The mixture was cooled to 25°C, water (50 mL) was added, the suspension thus obtained was filtered, the solid was washed with water obtaining compound **179** as a white solid (4.79 g, 18.11 mmol) yield 96%.

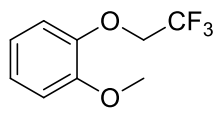
MS (ESI^+) *m/z*: 298 (M^+ + H, 100), 300 (M^+ +3, 75), 302 (M^+ +5, 25).

^{1}H-NMR (300 MHz, d_6-DMSO), δ (ppm) : 8.08 (1H, s), 7.48 (1H, s), 6.84 (2H, s), 4.18 (2H, t, J = 8.4 Hz), 3.30 (2H, t, J = 8.1 Hz).

^{1}H-NMR (300 MHz, d_6-DMSO), δ (ppm) : 156.2, 146.5, 139.3, 133.9, 128.0, 122.0, 113.7, 111.3, 100.2, 46.9, 26.7.

HPLC method **B**: Retention time: 14.3 min

*Synthesis of compound **82** :*



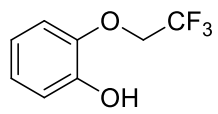
1-methoxy-2-(2,2,2-trifluoroethoxy)benzene

Compound **81** (1.5 g, 12.1 mmol) was dissolved in DMF (15 mL), then K_2CO_3 (5.00 g, 36.6 mmol) and compound 2-trifluoroiodoethane (5.37 g, 24.2 mmol) were added to the solution. The reaction mixture was stirred at 120°C monitoring the reaction by TLC (EtOAc : toluene = 1 : 8), after 19 hours the reaction was completed. The reaction mixture was cooled down to 25°C, water (100 mL) was added and the mixture was extracted with MTBE (3 x 50 mL). The combined organic layers were dried with Na_2SO_4, the solid is filtered off and the filtrate is concentrated until dryness obtaining 2.5 g of a crude oil. Directly used in the preparation of compound **83**.

The ^{1}H-NMR was comparable to the literature one, so no further characterisation had been performed.[11]

^{1}H-NMR (300 MHz, $CDCl_3$), δ (ppm) : 6.85-7.10 (4H, m), 4.39 (2H,q,J=8.4Hz), 3.87 (3H, s).

*Synthesis of compound **83** :*



2-(2,2,2-trifluoroethoxy)phenol

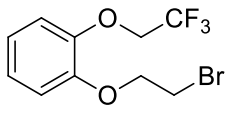
Compound **82** (3.83 g, 18.6 mmol) was dissolved in DCM (50 mL) and the mixture was cooled to 0°C. BBr_3 (2.6 mL, 6.7 g, 27.6 mmol) was added dropwise in 45 minutes. The reaction mixture was stirred at 0°C monitoring the reaction by TLC (EtOAc : toluene = 1 : 8), after 30 minnutes the reaction was completed. The reaction mixture was poured into ice/water (200 g) and stirred for 1 hour. The layers were separated and the aqueous layer was extracted with DCM (3 x 50 mL). The combined organic layers were dried with Na_2SO_4, the solid is filtered off and the filtrate is concentrated until dryness obtaining 3.6 g of a crude oil.

Directly used in the preparation of compound **15**.

The ^{1}H-NMR was comparable to the literature one, so no further characterisation had been performed.[11]

^{1}H-NMR (300 MHz, $CDCl_3$), δ (ppm) : 6.80-7.10 (4H, m), 5.53 (1H, s), 4.42 (2H,q,J=7.9Hz).

*Synthesis of compound **15** :*



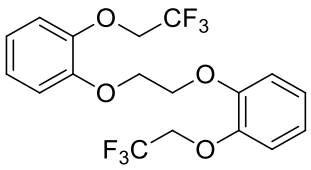
1-(2-bromoethoxy)-2-(2,2,2-trifluoroethoxy)benzene

Compound **83** (3.6 g, 18.6 mmol) was dissolved in a NaOH (0.8 g, 20.0 mmol) in H_2O (18 mL), then 1,2-dibromoethane (1.7 mL, 3.75 g, 20.0 mmol) was added and the mixture was stirred at 100°C monitoring the reaction by 1H-NMR. After 8 hours the reaction was completed, the mixture was cooled to 25°C diluted with water (50 mL) and extracted with DCM (3 x 20 mL). The combined organic layers were dried with Na_2SO_4, the solid is filtered off and the filtrate is concentrated until dryness obtaining 5.6 g of a crude oil. The crude was purified by flash chromatography (toluene : EtOAc = 1 : 1) obtaining compound **15** as oil (4.1 g, 13.7 mmol, 74% yield).

The ^{1}H-NMR was comparable to the literature one, so no further characterisation had been performed.[11]

^{1}H-NMR (300 MHz, $CDCl_3$), δ (ppm) : 6.90-7.20 (4H, m), 4.43 (2H, q, J = 8.2 Hz), 4.34 (2H, t, J = 6.0 Hz), 3.67 (2H, t, J = 6.0 Hz).

*Characterisation of **I-8** :*

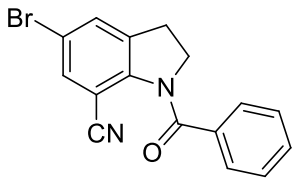


1,2-bis(2-(2,2,2-trifluoroethoxy)phenoxy)ethane

GC-MS: m/z = 410, 219

^{1}H-NMR (300 MHz, $CDCl_3$), δ (ppm) : 6.83-7.18 (8H, m), 4.39 (4H, s), 4.36 (4H, q, J = 8.4 Hz).

*Synthesis of compound **180** :*



1-benzoyl-5-bromoindoline-7-carbonitrile

The crude of **76** (1.015 mol) was dissolved in toluene (920 mL), TEA (154.0 g, 1.53 mol) and benzoyl chloride (207 g, 1.23 mol) were added and stirring was continued for 48 hours at 20°C. An aqueous solution of NaOH 10% was added, toluene was then evaporated over reduced pressure and the mixture was allowed to stir at rt overnight. The suspension was filtered, the solid was washed with toluene and dried at 50°C under vacuum to obtain 1-benzoyl-5-bromoindoline-7-carbonitrile **180** as a white solid, (172 g, 0.52 mol, 51% yield).

m.p. : 212-213 °C.

GC-MS : *m/z* = 326 (M+ -0), 328 (M+ +2).

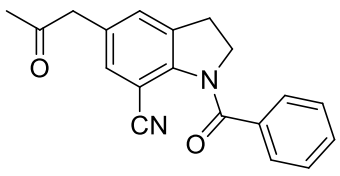
^{1}H-NMR (300 MHz, $CDCl_3$), δ (ppm) : 7.72 (2H, d, J = 7.2 Hz), 7.61 (1H, s), 7.57 - 7.43 (4H, m), 4.18 (2H, t, J = 8.1 Hz), 3.10 (2H, t, J = 8.1 Hz).

^{13}C-NMR (75 MHz, $CDCl_3$), δ (ppm) : 169.4; 143.9; 137.8; 134.2; 133.8; 132.3; 132.2; 128.8 (2C); 128.6 (2C); 116.8; 115.5; 104.9; 53.3; 29.4;

HPLC method **B**: Retention time: 26.6 min.

Elemental analysis: Anal. Calcd for $C_{16}H_{11}BrN_2O$: C, 58.74; H, 3.39; N, 8.56; found: C, 58.14; H, 3.29; N, 8.18.

*Synthesis of compound **181*** :



1-benzoyl-5-(2-oxopropyl)indoline-7-carbonitrile

In a 3 L reactor equipped with mechanical stirrer under nitrogen atmosphere, 1-benzoyl-5-bromoindoline-7-carbonitrile **180** (250 g, 0.764 mol), K_2CO_3 (317.3 g, 2.29 mol), DMSO (715 mL), acetilacetone (229.2 g, 2.29 mol) and H_2O (35 mL) were added. The system was degassed and CuI (14.52 g, 0.076 mol) was added, and stirring was continued for 21 hours at 95°C. The mixture was cooled to rt, CH_2Cl_2 (750 mL), H_2O (1200 mL) and NH_3 al 30% (300 mL) were added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 500 mL). The organic phases were washed with aqueous NH_3 10 %, aqueous NaOH al 10%, aqueous HCl 1 M and brine. The combined organic layers are dried with Na_2SO_4, the solid is filtered off and the filtrate is concentrated until dryness obtaining a brown solid (262 g). The crude was triturated in AcOEt at 70°C. The suspension was filtered, the solid was washed with AcOEt and dried at 50°C under vacuum to obtain 1-benzoyl-5-(2-oxopropyl)indoline-7-carbonitrile **181** as pale yellow solid (105 g, 0.34 mol, 45% yield).

m.p. : 203-204 °C.

GC-MS : m/z = 304 (M+ -0).

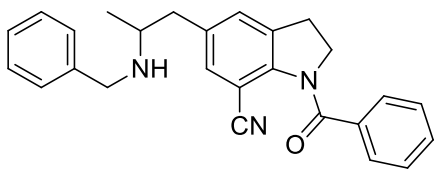
^{1}H-NMR (300 MHz, $CDCl_3$), δ (ppm) : 7.73 (2H, d, J = 6.9 Hz), 7.48 (3H, m), 7.32 (1H, s), 7.28 (1H, s), 4.18 (2H, t, J = 7.8 Hz), 3.70 (2H, s), 3.08 (2H, t, J = 7.8 Hz), 2.21 (3H, s).

^{13}C-NMR (75 MHz, $CDCl_3$), δ (ppm) : 205.0; 169.4; 143.7; 136.2; 134.6; 132.6; 132.0; 131.2; 130.4; 128.8 (2C); 128.6 (2C); 116.7; 103.6; 53.3; 49.5; 29.7; 29.5.

HPLC method **B**: Retention time: 18.9 min.

Elemental analysis: Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20; found: C, 74.24; H, 5.17; N, 8.78.

*Synthesis of compound **185** :*



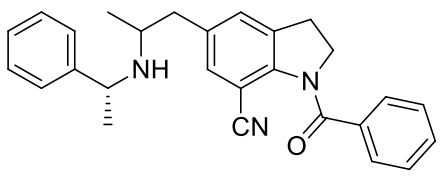
1-benzoyl-5-(2-(benzylamino)propyl)indoline-7-carbonitrile

A suspension of $NaBH_4$ (9.86 g, 0.259 mol) in THF (400 mL) was cooled to 0°C, and acetic acid (47.9 g, 0.798 mol) was added dropwise, stirring was continued for 80 min at 0°C. A solution of benzyl amine (23.43 g, 0.219 mol) in THF (100 mL), acetic acid (13.2 g, 0.219 mol) were added. After 20 minutes a solution of 1-benzoyl-5-(2-oxopropyl)indoline-7-carbonitrile **181** (60.75 g, 0.199 mol) in THF (100 mL) was added. The mixture was stirred for 21 hours at 0°C, the solvent was then removed under reduced pressure and the resulting suspension was treated with H_2O and AcOEt, basified with aqueous NaOH 10%. The phases were separated, the aqueous phase was extracted with AcOEt (3 x 100 mL). The combined organic layers are dried with Na_2SO_4, the solid is filtered off and the filtrate is concentrated until dryness obtaining a crude containing 1-benzoyl-5-(2-((1-phenyletyl)amine)propyl)indoline-7-carbonitrile **185** as brown oil.

^{1}H-NMR (300 MHz, d_6-DMSO), δ (ppm) : 7.74 (2H, d, J = 6.9 Hz), 7.38-7.63 (10H, m), 4.20 (2H, s), 4.13 (2H, t, J = 7.5 Hz), 3.48 (1H, m), 3.08 (2H, t, J = 7.5 Hz), 2.65-2.82 (2H, m), 1.18 (3H, d, J = 6.0 Hz).

HPLC method **C**: Retention time: 13.4 min.

*Synthesis of compound **188** :*



1-benzoyl-5-(2-(((*R*)-1-phenylethyl)amino)propyl)indoline-7-carbonitrile

A suspension of $NaBH_4$ (9.86 g, 0.259 mol) in THF (400 mL) was cooled to 0°C, and acetic acid (47.9 g, 0.798 mol) was added dropwise, stirring was continued for 80 min at 0°C. A solution of (R)-phenyletylamine (26.56 g, 0.219 mol) in THF (100 mL), acetic acid (13.2 g, 0.219 mol) were added. After 20 minutes a solution of 1-benzoyl-5-(2-oxopropyl)indoline-7-carbonitrile **181** (60.75 g, 0.199 mol) in THF (100 mL) was added. The mixture was stirred for 21 hours at 0°C, the solvent was then removed under reduced pressure and the resulting suspension was treated with H_2O and AcOEt, basified with aqueous NaOH 10%. The phases were separated, the aqueous phase was extracted with AcOEt (3 x 100 mL). The combined organic layers are dried with Na_2SO_4, the solid is filtered off and the filtrate is concentrated until dryness obtaining a crude containing 1-benzoyl-5-(2-((1-phenyletyl)amine)propyl)indoline-7-carbonitrile **188** as brown oil, in a 4:1 diastereomeric ratio.

MS (ESI^+) *m/z* = 410.08 (M^+ + H).

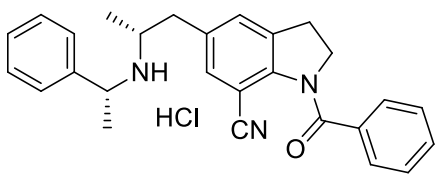
Major diastereoisomer:

^{1}H-NMR (300 MHz, $CDCl_3$), δ (ppm) : 7.73 (2H, d, J = 6.9 Hz), 7.70-7.44 (3H, m), 7.34-7.24 (5H, m), 7.21 (1H, s), 7.14 (1H, s), 4.15 (2H, t, J = 7.5 Hz), 3.94 (1H, q, J

= 6.6 Hz), 3.03 (2H, t, J = 7.5 Hz), 2.85 (1H, dd, J = 12.9, 4.5 Hz), 2.74 (1H, m), 2.47 (1H, dd, J = 12.9, 7.2 Hz), 1.60 (1H, bs), 1.33 (3H, d, J = 6.6 Hz), 0.91 (3H, d, J = 6.0 Hz).

HPLC method **C**: Retention time: 18.3 min.

*Synthesis of compound **192** :*



1-benzoyl-5-((*R*)-2-(((*R*)-1-phenylethyl)amino)propyl)indoline-7-carbonitrile hydrochloride

A suspension of 1-benzoyl-5-(2-((1-phenyletyl)amine)propyl)indoline-7-carbonitrile **188** in iso-propanol (178 g, 0.398 mol) in iso-propanol (500 mL) was heated at 50°C until solution was formed, aqueous HCl 37% was added dropwise until pH 3, the newly formed suspension was stirred for 1hour and then cooled to rt. The suspension was filtered and the solid washed with iso-propanol, the solid was suspended in methanol (625 mL) and H_2O (250 mL). The suspension was refluxed for 1 hour, cooled to 20°C and filtered. The solid was washed with methanol and dried under vacuum at 40°C to obtain 1-benzoyl-5-(2R-((1R-phenyletyl)amine)propyl)indoline-7-carbonitrile hydrochloride **192** as a white solid (106 g; 0,238 mol, 60% yield).

m.p. : 287 °C.

MS (ESI^+) *m/z* = 410.08 (M^+ + H).

$[\alpha]^{34}_D$ + 37.18 (c: 1.155 w/v%, DMSO);

^{1}H-NMR (300 MHz, $CDCl_3$), δ (ppm) : 9.93 (1H, bs), 9.22 (1H, bs) 7.74-7.30 (12H, m), 4.57 (1H, m), 4.10 (2H, t, J = 7.8 Hz), 3.38 (1H, bd), 3.08 (1H, m), 3.03 (2H, t,

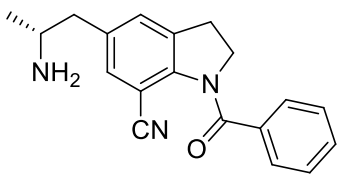
J = 7.8 Hz), 2.65 (1H, dd, J = 12.6, 11.1 Hz), 1.63 (3H, d, J = 6.6 Hz), 1.12 (3H, d, J = 6.3 Hz).

^{13}C-NMR (75 MHz, DMSO-d_6), δ (ppm) : 168.5; 142.9; 137.6; 136.9; 134.5; 133.9; 131.8; 131.3; 130.4; 128.9 (2C); 128.5 (2C); 128.4 (2C); 127.8 (2C); 116.6; 102.0; 54.5; 53.0; 52.3; 36.8; 28.8; 19.6; 15.9;

HPLC method **C**: Retention time: 18.3 min.

Elemental analysis: Anal. Calcd for $C_{27}H_{28}N_3OCl$: C, 78.99; H, 6.87; N, 10.24; found: C, 78.10; H, 6.73; N, 9.83.

*Synthesis of compound **183** :*



(*R*)-5-(2-aminopropyl)-1-benzoylindoline-7-carbonitrile

Pd/C 20% (0,22 g; 0,415 mmol) and amonium formate (16,98 g; 0,269 mol) were added to a suspension of compound **192** (24 g; 0,054 mol) in methanol (480 mL). The mixture was refluxed for 20 hours, then cooled to rt, filtered on celite, concentrated under reduced pressure and basified with aqueous NaOH 10% (600 mL) and extracted with AcOEt (4 x 300 mL). The combined organic layers are dried with Na_2SO_4, the solid is filtered off and the filtrate is concentrated until dryness obtaining (R)-1-benzoyl-5-(2-aminopropyl)indoline-7-carbonitrile (18 g) as brown oil, yield 90% enantiomeric ratio: 97:3.

It could be isolated as a pink powder crystallising it with AcOEt (1 volume, 54% yield).

A sample (0.5 g) was purified by flash chromatography (CH_2Cl_2 : MeOH = 9 : 1) obtaining pure compound **183** as pale yellow oil in 98% yield.

m.p.: racemate 184-185 °C, R-enantiomer 146°C.

MS (ESI^+) *m/z* = 306.13 ($M^+ + H$). $[\alpha]^{30}_D$ – 14.55 (c: 1.090 w/v%, MeOH).

^{1}H-NMR (300 MHz, $CDCl_3$), δ (ppm) : 7.74 (2H, d, J = 6 Hz), 7.48 (3H, m), 7.34 (1H, s), 7.28 (1H, s), 4.18 (2H, t, J = 7.8 Hz), 3.15 (1H, m), 3.08 (2H, t, J = 7.8 Hz),

2.68 (1H, dd, J = 13.5, 5.7 Hz), 2.53 (1H, dd, J = 13.5, 7.5 Hz), 1.12 (3H, d, J = 6,3 Hz).

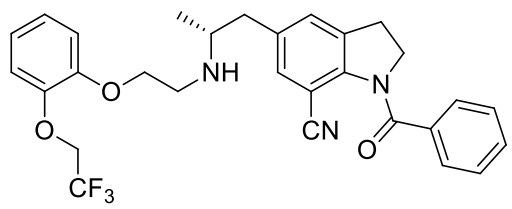
^{13}C-NMR (75 MHz, $CDCl_3$), δ (ppm) : 169.4; 142.8; 137.0; 135.8; 134.6; 132.1; 131.8; 130.1; 128.7 (2C); 128.5 (2C); 116.9;103.3; 53.3; 48.3; 45.6; 29.4; 23.5;

HPLC method **C**: Retention time 11.3 min.

Chiral HPLC method **D**: Retention time$_{(R\text{-enant.})}$: 24.0 min, Retention time$_{(S\text{-enant.})}$: 26.9 min

Elemental analysis: Anal. Calcd for $C_{19}H_{19}N_3O$: C, 74.73; H, 6.27; N, 13.76; found: C, 73.99; H, 6.14; N, 13.21.

*Synthesis of compound **186** :*



(*R*)-1-benzoyl-5-(2-((2-(2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)amino)propyl)indoline-7-carbonitrile

2-(2-(2,2,2-trifluoroetoxy)phenoxy)ethyl metansulfonate, compound **14**, (20.5 g, 0.065 mol), K_2CO_3 (26.9 g, 0.195 mol) and KI (3.2 g, 0.019 mol) were added to a solution of (R)-1-benzoyl-5-(2-aminopropyl)indoline-7-carbonitrile (22.0 g, 0.072 mol) in acetonitrile (220 mL) and refluxed for 14 hours. The mixture was then cooled to rt and H_2O was added, the acetonitrile was removed under reduced pressure and the aqueous phase was extracted with AcOEt (3 x 100 mL), the organic phases were washed with aqueous HCl 1 M, aqueous NaOH 10%, and brine. The combined organic layers are dried with Na_2SO_4, the solid is filtered off and the filtrate is concentrated until dryness obtaining compound **186** (33,0 g) as a red oil.

A sample (0.5 g) was purified by flash chromatography (CH_2Cl_2 : MeOH = 9 : 1) obtaining pure compound **186** as pale yellow oil.

MS (ESI^+) *m/z*: (M^+ + H) 524.63. $[\alpha]^{32}_D$ – 10.19 (c: 1.135 w/v%, MeOH);

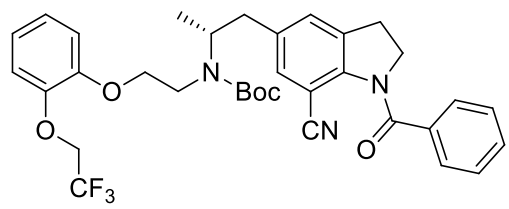
^{1}H-NMR (300 MHz, $CDCl_3$), δ (ppm) : 7.71 (2H, d, J = 6,9 Hz), 7.54-7.38 (3H, m), 7.32 (1H, s), 7.27 (1H, s), 7.06-6.85 (4H, m), 4.34 (2H, q, J=8.1 Hz), 4.16-4.05 (4H, m), 3.11-2.92 (2H, m), 2.77 (1H, dd, J = 13.5, 6.3 Hz), 2.57 (1H, dd, J = 13.5, 6.9 Hz, 2H), 1.66 (1H, bs), 1.06 (3H, d, J = 6.3 Hz).

^{13}C-NMR (75 MHz, $CDCl_3$), δ (ppm) : 169.2; 149.5; 147.3; 142.7; 136.5; 145.7; 134.6; 132.0; 131.7; 128.6 (2C); 128.4 (2C); 124.1; 123.5 (1C, q, J = 277.1 Hz); 121.5; 117.7; 116.9; 114.6; 103.0; 68.7; 67.9 (1C, q, J = 34.5 Hz); 60.2; 54.2; 53.1; 46.0; 42.5; 29.6; 29.2; 20.9; 19.8; 14.1.

HPLC method **C**: Retention time: 9.1 min.

Elemental analysis: Anal. Calcd for $C_{29}H_{28}F_3N_3O_3$: C, 66.53; H, 5.39; N, 8.03; found: C, 65.97; H, 5.25; N, 7.74.

*Synthesis of compound **186** :*



(*R*)-*tert*-butyl (1-(1-benzoyl-7-cyanoindolin-5-yl)propan-2-yl)(2-(2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)carbamate

Compound **14**, (20.5 g, 0.065 mol), K_2CO_3 (26.9 g, 0.195 mol) and KI (3.2 g, 0.019 mol) were added to a solution of compound **183** (22.0 g, 0.072 mol) in acetonitrile (220 mL). The mixture was stirred at 85°C monitoring the reaction by HPLC analysis. After 14 hours the reaction was completed, the mixture was cooled to 25°C and H_2O was added. Acetonitrile was removed under reduced pressure and the aqueous phase was extracted with AcOEt (3 x 100 mL), the organic phases were washed with aqueous HCl 1 M, aqueous NaOH 10%, and brine. The combined organic layers are dried with Na_2SO_4, the solid is filtered off and the filtrate is concentrated until dryness obtaining compound **186** (33.0 g) as a red oil.

A sample (0.5 g) was purified by flash chromatography (toluene : ethyl acetate = 9 : 1) obtaining pure compound **8** as a pale yellow oil in 98% yield.

MS (ESI^+) *m/z*: (M^+ + H) 624.51. $[\alpha]^{32}_D$ – 10.19 (c: 1.135 w/v%, MeOH);

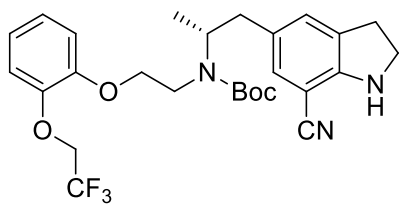
^{1}H-NMR (300 MHz, $CDCl_3$), δ (ppm) : 7.71 (2H, d, J = 6,9 Hz), 7.54-7.38 (3H, m), 7.32 (1H, s), 7.27 (1H, s), 7.06-6.85 (4H, m), 4.34 (2H, q, J=8.1 Hz), 4.16-4.05 (4H, m), 3.11-2.92 (2H, m), 2.77 (1H, dd, J = 13.5, 6.3 Hz), 2.57 (1H, dd, J = 13.5, 6.9 Hz, 2H), 1.66 (1H, bs), 1.06 (3H, d, J = 6.3 Hz).

^{13}C-NMR (75 MHz, $CDCl_3$), δ (ppm) : 169.2; 149.5; 147.3; 142.7; 136.5; 145.7; 134.6; 132.0; 131.7; 128.6 (2C); 128.4 (2C); 124.1; 123.5 (1C, q, J = 277.1 Hz); 121.5; 117.7; 116.9; 114.6; 103.0; 68.7; 67.9 (1C, q, J = 34.5 Hz); 60.2; 54.2; 53.1; 46.0; 42.5; 29.6; 29.2; 20.9; 19.8; 14.1.

HPLC method **B**: Retention time: 42.5 min.

Elemental analysis: Anal. Calcd for $C_{29}H_{28}F_3N_3O_3$: C, 66.53; H, 5.39; N, 8.03; found: C, 65.97; H, 5.25; N, 7.74.

*Synthesis of compound **18** :*



(*R*)-*tert*-butyl (1-(7-cyanoindolin-5-yl)propan-2-yl)(2-(2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)carbamate

Crude compound **186** (40,0 g) was dissolved in methanol (160 mL), and sodium methoxide (3,5 g; 0,065 mol) was added. The mixture was stirred for 6 hours at 40°C, then treated with water (20 mL) and left stirring for 3 hours at 40°C. The mixture was then cooled to rt and H_2O was added, the acetonitrile was removed under reduced pressure and the aqueous phase was extracted with AcOEt (3 x 100 mL). The combined organic layers are dried with Na_2SO_4, the solid is filtered off and the filtrate is concentrated until dryness obtaining compound **18** (37.98 g) as a brown oil.

Compound could be isolated as solid in 26% yield adding water (forming a MeOH/H2O 30% solution) at the end of the reaction and filtering the suspension thus obtained.

A sample (0.5 g) was purified by flash chromatography (toluene : ethyl acetate = 2 : 1) obtaining pure compound **18** as pale yellow oil in 90% yield.

m.p.: racemate 81.34°C, *R*-enantiomer 93.5°C.

(ESI^+) *m/z*: (M^+ + H) 519.90.

$[\alpha]^{30}_{D}$ – 55.74 (c: 0.04 w/v%, MeOH).

^{1}H-NMR ($CDCl_3$, 300 MHz), δ (ppm) : 7.11-6.97 (m, 6H), 4.37 (q, J=8.4 Hz, 2H), 4.19-3.98 (bm, 3H), 3.66 (t, J=8.4 Hz, 2H), 3.53-3.33 (bm, 2H), 3.01 (t, J=8.5 Hz, 2H), 2.81 (m, 1H), 2.57 (dd, J=13.8, 6.6 Hz, 1H), 1.43 (s, 9H), 1.25 (d, J=6.9 Hz, 3H).

Two Boc rotamers carbon signals:

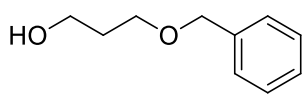
^{13}C-NMR (75 MHz, $CDCl_3$), δ (ppm) : 155.6; 155.1; 153.7; 149.5; 147.5; 147.2; 130.7; 130.0; 129.3; 124.1; 123.6 (1C, q, J = 276.9 Hz); 121.6; 121.2; 117.9; 117.2; 114.3; 113.8; 90.0; 68.0; 67.9 (1C, q, J = 35.0 Hz); 55.2; 54.5; 47.2; 44.1; 40.6; 40.0; 29.8; 29.2; 28.8; 28.5 (3C); 19.1; 18.3.

HPLC method **B**: Retention time: 40.9 min.

HPLC method **C**: Retention time: 18.8 min.

Elemental analysis: Anal. Calcd for $C_{27}H_{32}F_3N_3O_4$: C, 62.42; H, 6.21; N, 8.09; found: C, 61.76; H, 6.06; N, 7.78.

*Synthesis of compound **199** :*



3-(benzyloxy)propan-1-ol

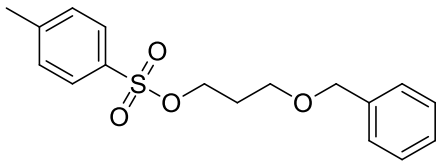
A suspension of sodium hydride 60% (17.5 g; 0.438 mol) in THF (700 mL) was cooled to 15°C, and 1,3-propandiol **198** (120 g; 1.57 mol) was added dropwise over 40 min. Stirring was continued for 60 min at 30°C, benzyl bromide (75 g; 0.438 mol) was then added dropwise over 30 min, and the mixture was left reacting overnight at 20°C. Water (150 mL) was added to the mixture and concentrated under reduced pressure to remove the THF, the aqueous solution was extracted with AcOEt (3 x 200 mL). The combined organic layers are dried with Na_2SO_4, the solid is filtered off and the filtrate is concentrated until dryness obtaining a yellowish oil (120 g), that was purified by fractional distillation under reduced pressure (170°C; 18 mmHg). 3-benziloxypropanol (60 g, 93% GC-MS purity) was obtained as a transparent oil.

GC-MS : *m/z* = 166 (M^+ -0).

^{1}H-NMR (300 MHz, $CDCl_3$), δ(ppm) : 7.33-7.25 (5H, m), 4.52 (2H, s), 3.78 (2H, t, J = 5.7 Hz), 3.66 (2H, d, J = 5.7 Hz), 1.86 (2H, p, J = 5.7 Hz).

^{13}C-NMR (75 MHz, $CDCl_3$), δ (ppm) : 138.1; 128.3 (2C); 127.5 (2C); 73.1; 68.6; 60.9; 32.1.

*Synthesis of compound **98** :*



3-(benzyloxy)propyl 4-methylbenzenesulfonate

TEA (47,4 g; 0,469 mol) and DMAP (4,4 g; 0,036 mol) were added to the solution of 1-benziloxy-3-propanol **199** in toluene (420 mL) and cooled to 5°C. Para-toluensulfonyl chloride (73,9 g; 0,387 mol) was then added portionwise over 40 min, and stirring was continued overnight at 20°C. The mixture was diluted with water (500 mL) the phases were separated and the aqueous phase was extracted with toluene (2 x 100 mL). The combined organic layers are dried with Na_2SO_4, the solid is filtered off and the filtrate is concentrated until dryness obtaining a yellowish oil (120 g) that was crystallised from iso-propanol (120 mL) obtaining 3-benziloxypropyl-1-tosylate **98** (66,7 g; 0,208 mol) as a white solid, yield 47%.

m.p.: 33-34°C (lit[137]. 33°C).

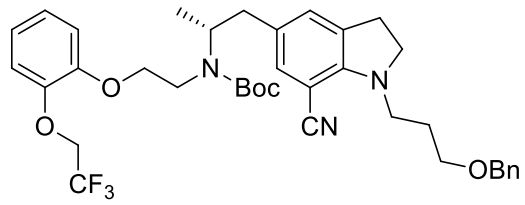
GC-MS : *m/z* = 320 (M^+ -0).

^{1}H-NMR (300 MHz, $CDCl_3$), δ(ppm) : 7.78 (2H, d, J = 8.4 Hz), 7.35-7.22 (7H, m), 4.40 (2H, s), 4.17 (2H, t, J = 6.3 Hz), 3.50 (2H, d, J = 6.3 Hz), 2.42 (3H, s), 1.94 (2H, p, J = 6.3 Hz).

^{13}C-NMR (75 MHz, $CDCl_3$), δ (ppm) : 144.7; 138.1; 133.1; 129.9; 128.4 (2C); 127.9 (2C); 127.6 (2C); 127.5 (2C); 73.1; 67.7; 65.7; 29.4; 21.6.

[137] Butler, C. L.; Renfrew, A. G.; Clapp, M.; *J. Am. Chem. Soc.*, **1938**, *60*, 1472 – 1473.

*Synthesis of compound **68** :*



(*R*)-*tert*-butyl (1-(1-(3-(benzyloxy)propyl)-7-cyanoindolin-5-yl)propan-2-yl)(2-(2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)carbamate

A solution of compound **18** (37.98 g) in DMF(240 mL) was cannulated to a stirred suspension of NaH (2,4 g; 0,097 mol) in DMF (60 mL) and stirring was continued for 60 min at 0°C. 3-benziloxy-propyl-1-tosylate (22,9 g; 0,071 mol) was added portionwise, the mixture was left to stir for 3 hours at rt, cooled to 0°C and quenched with H_2O (20 mL), diluted with H2O (500 mL) and extracted with MTBE (3 x 200 mL). The combined organic layers are dried with Na_2SO_4, the solid is filtered off and the filtrate is concentrated until dryness obtaining tert-butyl ((2R)-1-(1-(3-benziloxypropyl)-7-cianoindolin-5-yl)propan-2-yl)(2-(2-(2,2,2-trifluoroetoxy)fenoxy)ethyl) carbamate **68** (48 g) as an oil.

A sample (0.5 g) was purified by flash chromatography (toluene : ethyl acetate = 2 : 1) obtaining pure compound **68** as pale yellow oil in 85% yield.

MS (ESI^+) *m/z* = 668.20 (M^+ + H), 690.24 (M^+ + Na).

^{1}H-NMR (300 MHz, $CDCl_3$), δ (ppm) : 7.39-7.25 (5H, m), 7.10-6.87 (6H, m), 4.54 (2H, s), 4.38 (2H, q, J=8.3 Hz), 4.25-3.84 (3H, m), 3.76-3.59 (4H, m), 3.58-3.35 (4H, m), 2.90 (2H, t, J=8.6 Hz), 2.86-2.66 (1H, m), 2.55 (1H, dd, J=13.8, 6.6 Hz), 1.99 (2H, p, J=6.5 Hz), 1.45 (9H, s), 1.26 (3H, d, J=6.9 Hz).

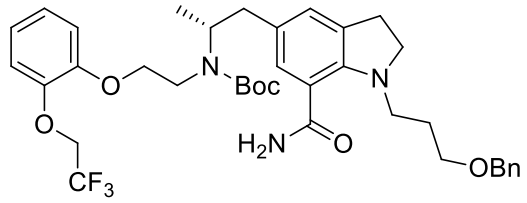
Two Boc rotamers carbon signals:

^{13}C-NMR (75 MHz, $CDCl_3$), δ (ppm) : 155.6; 155.1; 151.8; 149.5; 147.4; 147.2; 138.5; 132.7; 131.4; 129.5; 128.6; 128.4 (2C); 127.8; 127.7 (2C); 127.6; 124.1; 123.6 (1C, q, J = 277.2 Hz); 121.5; 121.1; 119.6; 117.3; 114.3; 113.8; 87.6; 79.9;73.2; 67.6; 67.7 (1C, q, J = 24.7 Hz); 55.0; 54.3; 53.3; 45.3; 43.9; 40.3; 39.8; 28.5 (3C); 28.0; 27.4; 19.1; 18.3.

HPLC method **C**: Retention time 32.4 min.

Elemental analysis: Anal. Calcd for $C_{37}H_{44}F_3N_3O_5$: C, 66.55; H, 6.64; N, 6.29; found: C, 65.88; H, 6.49; N, 6.01.

*Synthesis of compound **69** :*



(*R*)-*tert*-butyl (1-(1-(3-(benzyloxy)propyl)-7-carbamoylindolin-5-yl)propan-2-yl)(2-(2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)carbamate

NaOH (8,2 g; 0,206 mol) and aqueous H_2O_2 50% (28 g; 0,412 mol) were added to a solution of compound **68** (55,0 g, 0.0825 mol) in DMSO (360 mL), and stirred at 25°C monitoring the reaction by HPLC analysis. After 16 hours the reaction was completed, the mixture was diluted with water (700 mL) and extracted with MTBE (3 x 100 mL). The combined organic layers are dried with Na_2SO_4, the solid is filtered off and the filtrate is concentrated until dryness obtaining compound **69** (58,2 g) as a yellow oil.

A sample (0.5 g) was purified by flash chromatography (toluene : ethyl acetate = 1 : 1) obtaining pure compound **69** as pale white oil in 92% yield.

MS (ESI^+) *m/z*: 686.15 (M^+ + H), 708.22 (M^+ + Na).

^{1}H-NMR (300 MHz, $CDCl_3$), δ (ppm) : 7.36-7.27 (5H, m), 7.15-6.82 (6H, m), 5.42 (1H, bs), 4.70 (2H, s), 4.35 (2H, q, J = 8.4 Hz,), 4.14-3.86 (3H, m), 3.50-3.42 (6H, m), 3.13 (2H, t, J = 7.5 Hz), 2.93 (2H, t, J = 8.4 Hz), 2.90-2.75 (1H, m), 2.63 (1H, dd, J = 13.8, 6.6 Hz), 1.86 (2H, p, J = 6.3 Hz), 1.39 (9H, s), 1.23 (3H, d, J = 6.0 Hz).

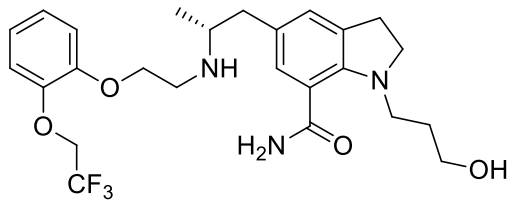
Two Boc rotamers carbon signals:

^{13}C-NMR (75 MHz, $CDCl_3$), δ (ppm) : 171.7; 169.7; 155.5; 154.9; 149.6; 149.3; 147.1; 146.9; 138.2; 134.2; 131.2; 130.9; 130.0; 129.0; 128.3 (2C); 128.2 (2C); 127.9; 127.7; 127.5; 127.4; 123.8; 123.4 (1C, q, J = 277.2 Hz); 121.2; 120.8; 119.2; 119.0; 117.2; 117.1; 114.0; 113.6; 100.8; 79.5; 72.7; 68.0; 67.9 (1C, q, J = 40.2 Hz); 67.7; 67.0; 45.5; 54.1; 53.4; 51.9; 45.5; 43.6; 40.5; 40.0; 28.4 (3C); 19.1; 18.3.

HPLC method **C**: Retention time: 30.0 min.

Elemental analysis: Anal. Calcd for $C_{37}H_{46}F_3N_3O_6$: C, 64.80; H, 6.67; N, 6.13; found: C, 64.14; H, 6.47; N, 5.85.

*Synthesis of compound **1** (**Silodosin**) :*



(*R*)-1-(3-hydroxypropyl)-5-(2-((2-(2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)amino)propyl)indoline-7-carboxamide

In an autoclave, Pd/C 20% (1,0 g; 0,002 mol) and HCl 37% (11,3 g; 0,116 mol) were added to a solution of compound **69** (20 g), and the mixture was degassed. The mixture was stirred under hydrogen pressure for 20 hours at 30°C, filtered over celite and concentrated under reduced pressure. The crude thus obtained was dissolved in water (300 mL),washed with AcOEt, basified with aqueous NaOH al 10% (100 mL) and extracted with AcOEt (3 x 100 mL). The combined organic layers are dried with Na_2SO_4, the solid is filtered off and the filtrate is concentrated until dryness obtaining Silodosin as a yellowish oil (14,5 g) that was cristallised from mixture of AcOEt/hexane 1:1 to give compound **1** (**silodosin**) as white solid (11.1 g; 0,021 mol) yield 74% over 6 synthetic step, calculate on compound **14** mole.

mp: 100-101°C; (lit.[138] 100°C)

MS (ESI^+) *m/z*: 496.20 (M^+ + H).

$[\alpha]^{34}_D$ - 14.19 (c: 1.175 w/v%, MeOH);

[138] Barve, I. J.; Chen, L. H.; Wei, P. C. P.; Hung, J.T.;Sun, C. M.; *tetrahedron*, **2013**, *69*, 2834 – 2843.

^{1}H-NMR ($CDCl_3$, 300 MHz), δ (ppm) : 7.15 (1H, s), 7.06-6.85 (5H, m), 6.63 (1H, bs), 5.83 (1H, bs), 4,29 (2H, q, J = 8.4 Hz), 4.08-4.03 (2H, m), 3.74 (2H, t, J = 5.6 Hz), 3.40 (2H, t, J = 8.4 Hz), 3.18 (2H, t, J = 6.6 Hz), 3.10-2.87 (6H, m), 2.66 (1H, dd, J = 13.5, 6.6 Hz), 2.51 (1H, dd, J = 13.5, 6.9 Hz), 1.79 (2H, p, J = 6.0 Hz), 1.63 (1H, bs), 1.06 (3H, d, J = 6.3 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz), δ (ppm) : 171.5; 149.9; 149.8; 147.5;133.9; 130.4; 128.2; 128.1; 123.6 (1C, q, J = 277.2 Hz); 124.4; 121.6; 118.3; 118.3; 114.9;69.0; 68.2 (q, 1C, J = 34.4 Hz); 59.6; 54.5; 53.6; 50.8; 46.2; 42.7; 31.1; 28.3; 20.0;

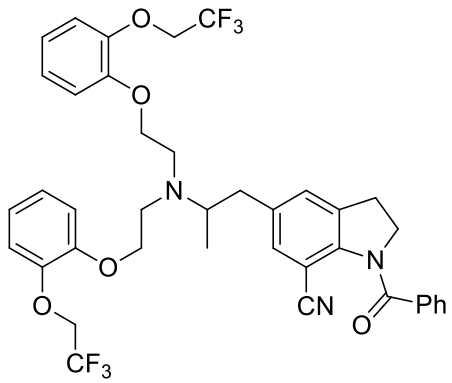
HRMS (ESI) calcd for [M + H, $C_{25}H_{33}F_3N_3O_4$]$^{+}$: 496.2425, Found: 496.2429.

HPLC method **C**: Retention time 11.3 min.

Chiral HPLC method **D**: Retention time$_{(R\text{-enant.})}$: 9.3 min, Retention time$_{(S\text{-enant.})}$: 7.1 min.

Elemental analysis: Anal. Calcd for $C_{25}H_{32}F_3N_3O_4$: C, 60.59; H, 6.51; N, 8.48; found: C, 59.98; H, 6.35; N, 8.11.

*Characterisation of impurity **I-9** :*

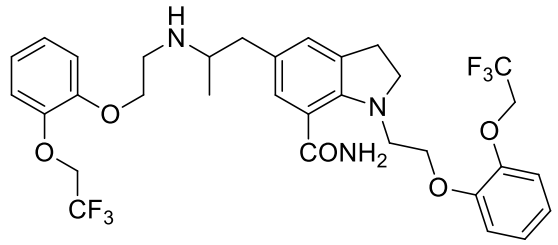


1-benzoyl-5-(2-(bis(2-(2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)amino)propyl)indoline-7-carbonitrile

MS (ESI^+) *m/z*: 742.16 (M^+ + H).

^{1}H-NMR ($CDCl_3$, 300 MHz), δ (ppm) : 7.71 (2H, d, J = 6,9 Hz), 7.54-7.38 (3H, m), 7.15 (1H, s), 7.11 (1H, s), 7.06-6.85 (8H, m), 4.34 (4H, q, J=8.1 Hz), 4.16-4.05 (6H, m), 3.11-2.92 (7H, m), 2.89 (1H, dd, J = 13.5, 6.3 Hz), 2.46 (1H, dd, J = 13.5, 6.9 Hz, 2H), 1.06 (3H, d, J = 6.3 Hz).

*Characterisation of impurity **I-14** :*



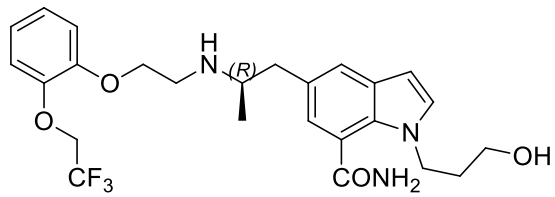
1-(2-(2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)-5-(2-((2-(2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)amino)propyl)indoline-7-carboxamide

MS (ESI^+) *m/z*: = 656.20 (M^+ + H).

^{1}H-NMR ($CDCl_3$, 300 MHz), δ (ppm) : 7.38 (1H, s), 7.21 (1H, br s),7.05 (1H, s), 6.86-7.03 (8H, m), 7.11 (1H, s), 5.60 (1H, br s), 4.43 (H, q, J = 8.1 Hz), 4.31 (H, q, J = 8.4 Hz), 4.17 (2H, t, J = 4.8 Hz), 4.05-4.11 (2H, m), 3.63 (2H, t, J = 8.4 Hz), 3.50 (2H, t, J = 5.1 Hz), 2.91-3.10 (5H, m), 2.72 (1H, dd, J = 13.2, 6.3 Hz), 2.52 (1H, dd, J = 13.2, 7.2 Hz, 2H), 1.06 (3H, d, J = 6.3 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz), δ (ppm) : 169.0, 150.0, 149.9, 149.7, 147.8, 147.5, 135.1, 132.3, 129.3, 128.7, 124.6, 124.1, 123.5 (q, J = 202.2 Hz), 122.9 (q, J = 199.8 Hz), 122.0, 121.7, 119.2, 118.6, 116.2, 115.4, 114.1, 69.1, 68.8 (q, J = 32.5 Hz), 68.4 (q, J = 31.8 Hz), 68.1, 54.5, 53.7, 46.4, 42.8, 30.7, 28.2, 20.0.

*Characteriasation of impurity **I-12** :*

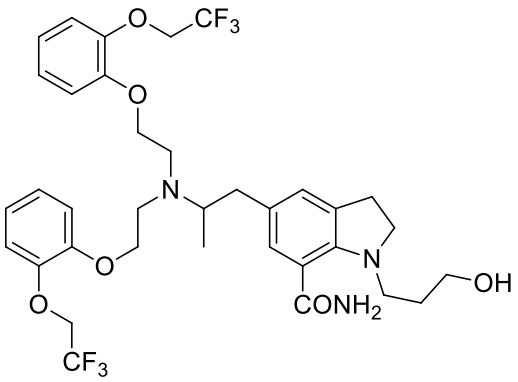


(*R*)-1-(3-hydroxypropyl)-5-(2-((2-(2-(2,2,2-trifluoroethoxy) phenoxy)ethyl)amino)propyl)-1*H*-indole-7-carboxamide

MS (ESI^+) *m/z*: = 494.18 (M^+ + H).

^{1}H-NMR ($CDCl_3$, 300 MHz), δ (ppm) : 7.51 (1H, s), 7.15 (1H, s), 7.11 (1H, d, J = 3.0 Hz), 7.02-6.81 (4H, m), 6.48 (1H, d, J = 3.0 Hz), 6.30 (1H, br s), 6. 14 (1H, br s), 4.36 (4H, app t, J = 6.9 Hz), 4.02-4.21 (4H, m), 3.52 (2H, t, J = 5.4 Hz), 2.92-3.09 (3H, m), 2.81 (1H, dd, J = 13.8, 6.9 Hz), 2.74 (1H, dd, J = 13.8, 6.6 Hz, 2H), 2.34 (2H, br s), 2.00 (2H, p, J = 6.0 Hz), 1.11 (3H, d, J = 6.0 Hz).

*Characterisation of impurity **I-13** :*



5-(2-(bis(2-(2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)amino)propyl)-1-(3-hydroxypropyl)indoline-7-carboxamide

MS (ESI^+) *m/z*: = 714.24 (M^+ + H)

^{1}H-NMR ($CDCl_3$, 300 MHz), δ (ppm) : 7.32 (1H, s), 7.04-6.81 (9H, m), 4.34 (4H, q, J=8.7 Hz), 3.93-4.08 (4H, m), 3.40 (2H, t, J = 8.4 Hz), 3.22 (3H, t, J = 6.3 Hz), 2.94-3.11 (7H, m), 2.87 (2H, t, J = 8.7 Hz), 2.76 (1H, dd, J = 13.2, 5.1 Hz), 2.40 (1H, dd, J = 13.5, 8.1 Hz, 2H), 1.80 (2H, p, J = 5.7 Hz), 1.03 (3H, d, J = 6.3 Hz).