Summary

Introduction

The aim of this thesis was to explore different areas of organic chemistry in which the stereocontrol in the design of chemical processes and/or molecular assemblies is necessary. Therefore, the stereoselectivity in asymmetric organometallic syntheses, in total synthesis of bioactive natural products and in the formation of chiral arrangements due to intramolecular hydrogen bonding networks have been investigated.

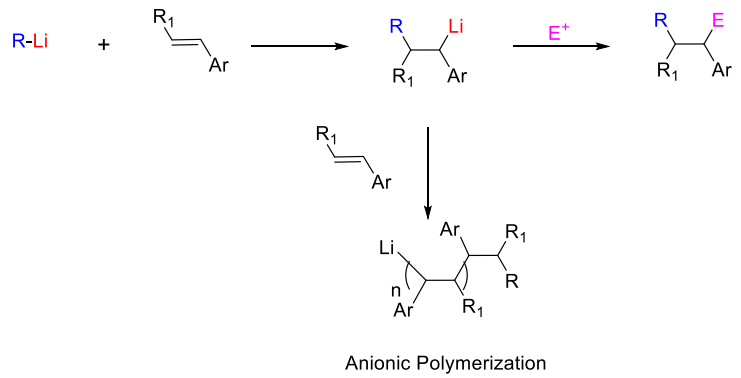
In particular, three different projects were faced in this thesis. The methodological study of carbolithiation reaction of 1-aryl-1-alkenyl *N,N'*-diethylcarbamates, also in enantioselective manner, the asymmetric synthesis of natural products with phytotoxic activity and, finally, the synthesis and the NMR analysis of cyclic triureas showing cyclochirality by virtue of cyclic hydrogen-bonding array only.

Regio- and Stereoselective Carbolithiations of 1-Aryl-1-Alkenyl N,N'-Diethylcarbamates

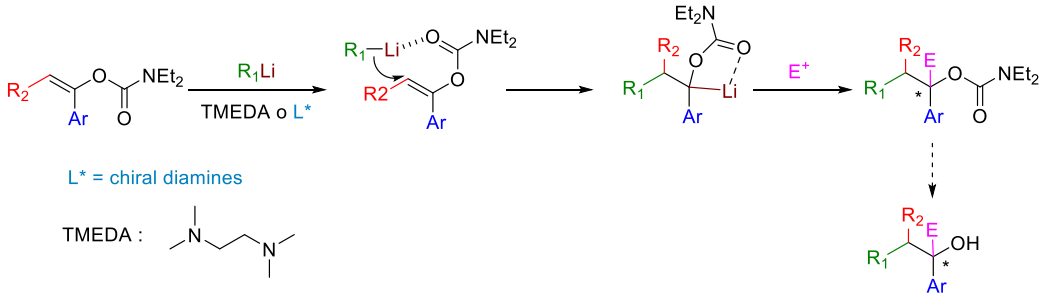
Carbolithiation of styrenyl olefins represent an attractive synthetic methodology, offering pathways for the preparation of highly functionalised aromatic compounds. This transformation generates a benzyllithium species, which, through a tandem carbolithiation-trapping reaction, can be reacted with electrophiles, allowing the efficient regioselective formation of two new bonds and of one or two new stereocentres. A potential limitation to the application of carbolithiation as a synthetic method derives from the difficulty of tempering the reactivity of the organolithium intermediate towards the unsaturated substrate. In fact, the lithiated intermediate can react with a second molecule of the olefin substrate, triggering an unwanted anionic polymerisation process (Scheme 1). For synthetically useful carbolithiation reactions, a special stabilisation of the benzyl lithium intermediate is required. Such a stabilisation can be obtained by either intra- or intermolecular organolithium coordination, which occurs in the presence of chelating

groups proximal to the reacting alkene and/or by means of bidentate ligands such as diamines.

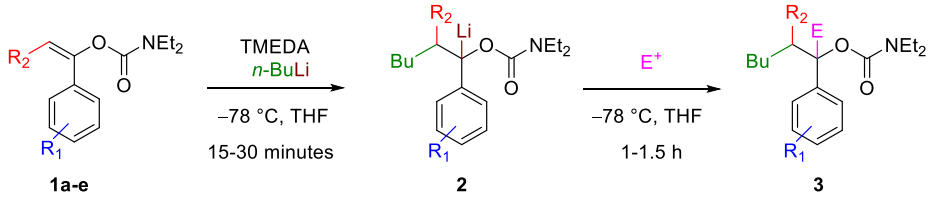
In this project, a methodological study on the tandem one-pot carbolithiation-electrophile trapping process of 1-aryl-1-alkenyl *N*,*N*'-diethylcarbamates, taken as model substrates, was studied, also investigating the influence of substituents on the aromatic ring of starting materials subjected to the carbolithiation. This transformation allows synthesising trisubstituted benzyl carbamates, which are direct precursors of tertiary benzylic alcohols, common structural subunits in naturally occurring bioactive compounds (Scheme 2). The presence of the carbamoyl coordinating group on the double bond of 1-aryl-1-alkenyl *N*,*N'*-diethylcarbamates is essential to prevent polymerisation and promote the carbolithiation reaction, through precoordination of the lithium reagent with the heteroatom. The tandem carbolithiation-trapping reaction with electrophiles was performed adding *n*-BuLi (1.1 eq.) to a solution of 1-aryl-1-alkenyl *N*,*N'*-diethylcarbamate and TMEDA at –78 °C in dry and inert atmosphere. After the addition of the alkyllithium to the double bond, an excess of electrophiles (3.0 eq.) was added affording the trisubstituted benzyl carbamates (Scheme 3). The trisubstituted benzyl carbamates synthesised using different electrophiles are reported in Figure 1.



Scheme 1. Carbolithiation reaction.



Scheme 2. Carbolithiation-trapping process of 1-aryl-1-alkenyl *N*,*N'*-diethylcarbamates.



Scheme 3. Tandem carbolithiation-trapping reaction with electrophiles.

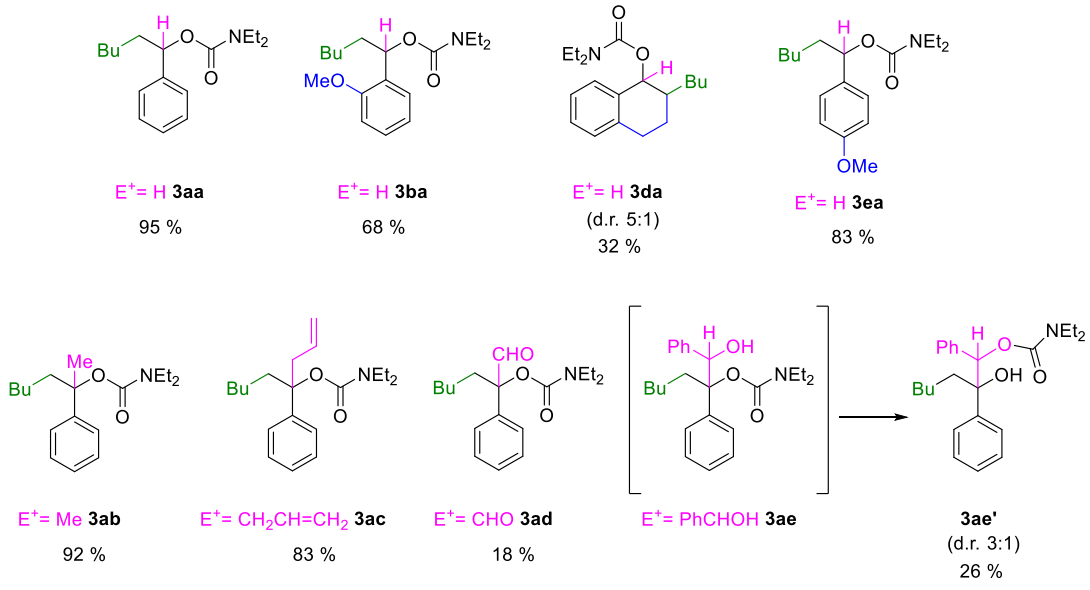
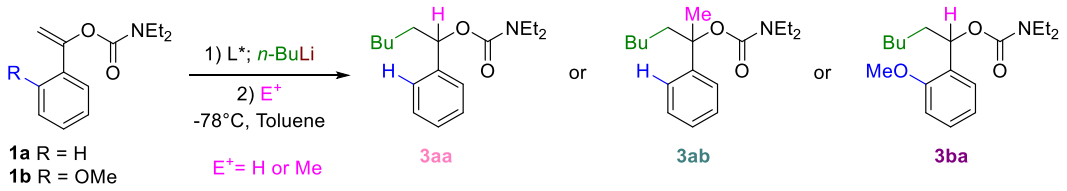


Figure 1. Trisubstituted benzyl carbamates synthesised.

An enantioselective version of this transformation was also investigated, employing chiral ligands with the aim to provide asymmetric induction, thus obtaining enantioenriched tertiary benzyl carbamates (Scheme 4). The chiral diamines used were (+)-sparteine (**L1**), 2,2-Bis((4*S*)-(–)-4-isopropyloxazoline)propane (**L2**), 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (**L3**) and (*S*,*S*)-2,2-bis(4-phenyl-2-oxazolin-2-yl)propane (**L4**) (Figure 2). In particular, this class of BOX ligands have never been used in this kind of reactions before. In the enantioselective version, the reaction was carried out adding the substrate (**1a-b**) (1.0eq.) to a solution of *n*-BuLi (1.1 eq.) and the chiral ligand (1.1 eq.) at –78 °C in dry and inert atmosphere. After the carbolithiation step, the electrophile reagent (3.0 eq.) was added and the reaction mixture was stirred for ca. 1 h, affording the desired product. The best results were obtained using **L2** in dry toluene, providing 22% e.e. using both MeOH and MeI as electrophiles and starting from substrate **64a**.



Scheme 4. Enantioselective carbolithiation-trapping process.

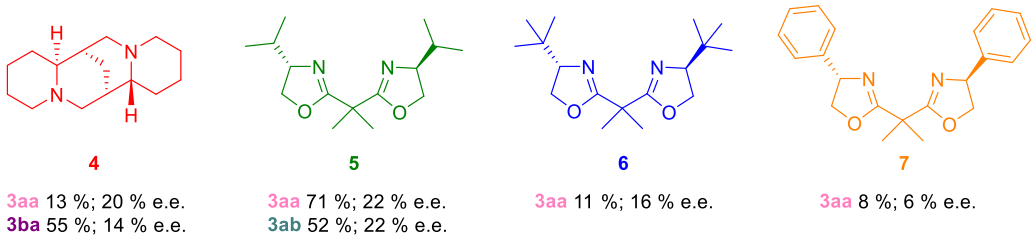


Figure 2. . Chiral diamines employed as ligands in the enantioselective carbolithiation.

Asymmetric Synthesis of the Fungal Phytotoxins Colletochlorin A and Radicinin

Fungi constitute an essentially endless source of bioactive metabolites, often showing phytotoxic activity. One of the most appealing application of fungal phytotoxins lies in the development of bioherbicides, which show lower or nil toxicity, and thus a lower environmental and ecological impact, than the traditional synthetic pesticides. In particular, in this thesis we dealt with the fungal metabolite colletochlorin A (**1b** in Figure 3), which was found to display phytotoxic activity against the *Ambrosia artemisiifolia* weed and the phytotoxin radicinin (**2a** in Figure 4) active against the *Cenchrus ciliaris* weed. Due to their strong activity and selectivity they are promising candidates as natural herbicides for the control of these invasive plants. In order to assay the biological properties and in particular, to develop target-specific bioherbicides for invasive plants, it is necessary to have amounts of the compounds much larger than those obtainable from natural sources. For this reason, the development of an efficient total synthesis of these natural products has appeared mandatory. Therefore, a new stereoselective synthesis of both enantiomers of colletorin A (**1a**) and colletochlorin A (**1b**), as well as of their brominated (**1c**) and fluorinated (**1d**) analogues, in optically active form (Figure 2.4), was designed, with the aim to investigate the effect of both absolute stereochemistry and halogen nature on the biological properties of this class of phytotoxins. Moreover, an efficient synthetic strategy in order to prepare (±)-radicinin (**2a**) and its immediate biosynthetic precursor, (±)-3-deoxyradicinin (**2b**), (Figure 2.5) was ideated.

The retrosynthetic approach to prepare colletochlorin A (**1a**) and its analogues is based on the disconnection of the structure of **1a-d** into an aromatic precursor and an optically active side chain, which can be combined by a cross-coupling reaction (Scheme 5).

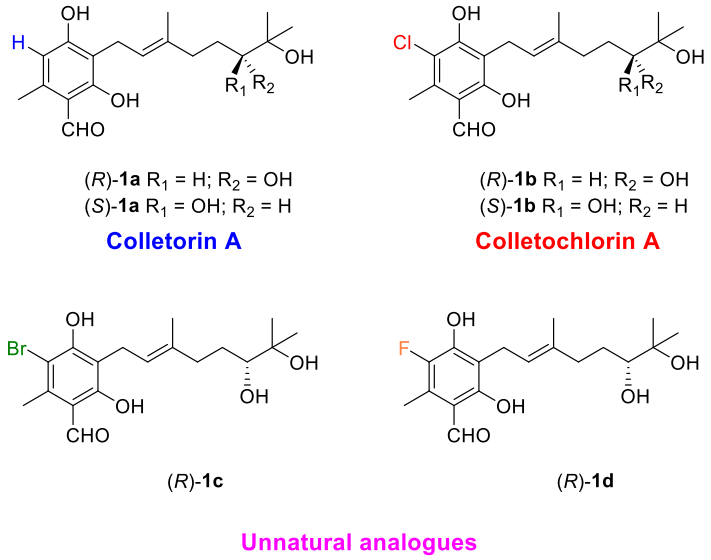


Figure 3. Structure of both enantiomers of colletorin A (**1a**) and colletochlorin A (**1b**) and the unnatural halogenated analogues (**1c** and **1d**), prepared in optically active form.

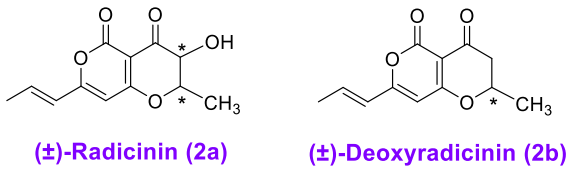
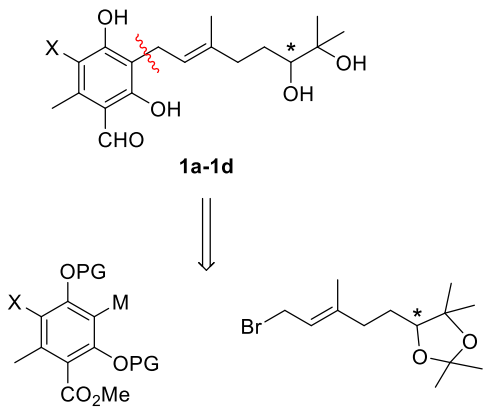
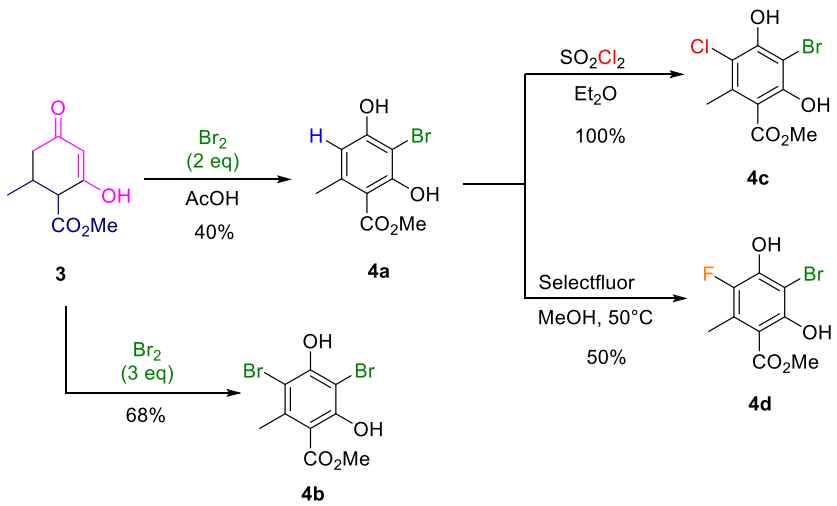


Figure 4. Stuctures of (±)-radicinin (**2a**) and (±)-3-deoxyradicinin (**2b**).

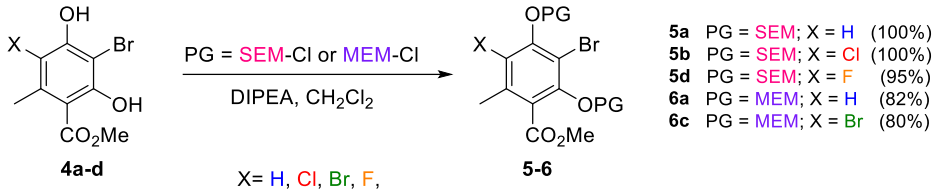


Scheme 5. Retrosynthetic approach.

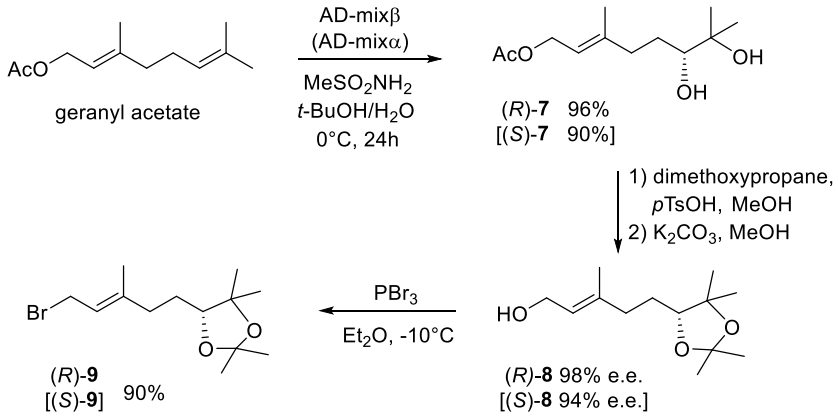
At first, the functionalized aromatic moieties where prepared, thus **3** was brominated and aromatized with either 2 or 3 equivalents of bromine to give **4a** and **4b**. Compound **4a** was chlorinated to give **4c** or fluorinated to give **4d** (Scheme 6). Then, the phenolic groups were protected as either SEM- or MEM-ethers (Scheme 7). Both enantiomers of the side chain were synthesized in high yield, high stereoselectivity and full regioselectivity by Sharpless asymmetric dihydroxylation starting from geranyl acetate. Diols **7** were protected as ketals and the ester groups were hydrolyzed to give alcohols **8**, which were transformed into bromides **9** (Scheme 8). In the coupling reaction, benzoates **5-6** were transformed into the corresponding mixed Gilman cuprates, which were treated with bromides **9** to provide the desired coupling products (Scheme 9). The ester moiety was then transformed into the aldehyde (Scheme 10) and the deprotection of the hydroxilic groups was performed with TBAF and sulfuric acid when the protecting group was SEM and with HCl when the protecting group was MEM (Scheme 11). In this way all the desired compounds **1a-d** were obtained in moderate to good yields. Finally, the synthesized compounds were subjected to bioactivity assays. In particular, their phytotoxicity and insecticidal activity were evaluated. In both cases, the natural enantiomer of colletochlorin A, (*R*)-**1b**, exhibited the strongest activity.



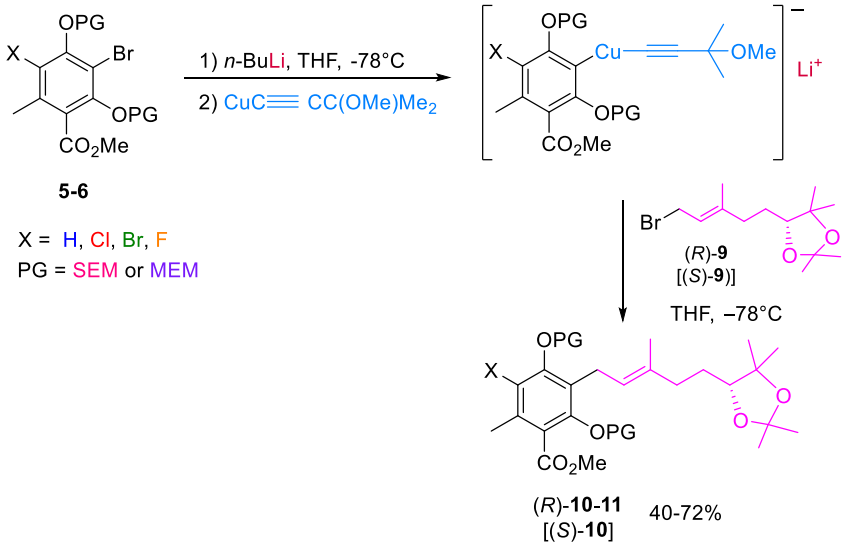
Scheme 6. Preparation of functionalised aromatic moieties **4a-d**.



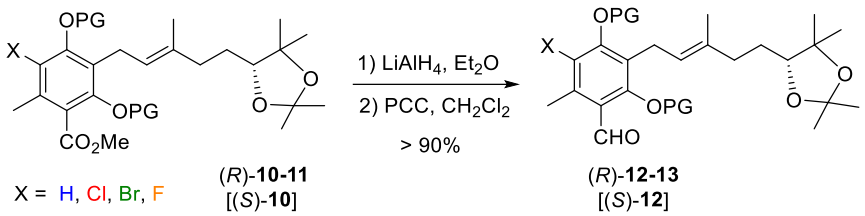
Scheme 7. Protection reaction of the phenolic moieties.



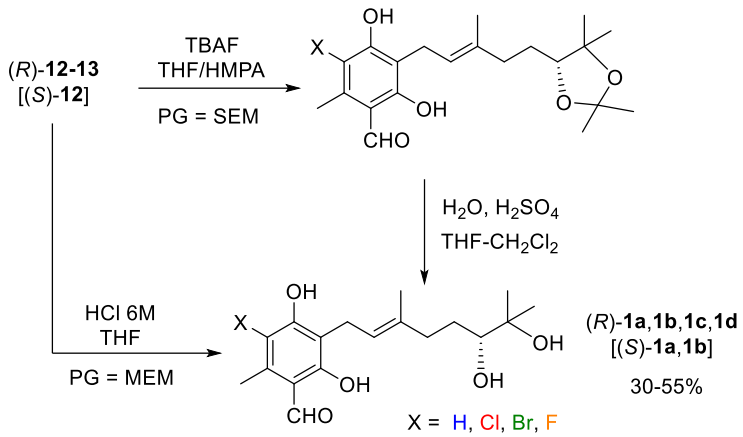
Scheme 8. Asymmetric synthesis of the side chain.



Scheme 9. Cross-coupling reaction.

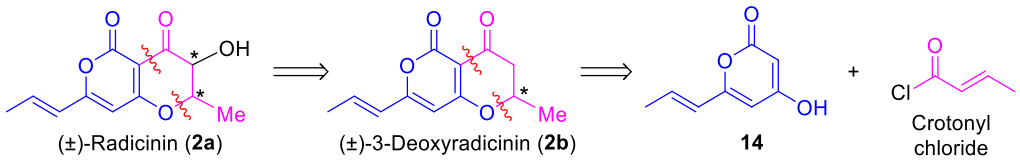


Scheme 10. Conversion of the ester group into aldehyde.



Scheme 11. Final steps of total synthesis.

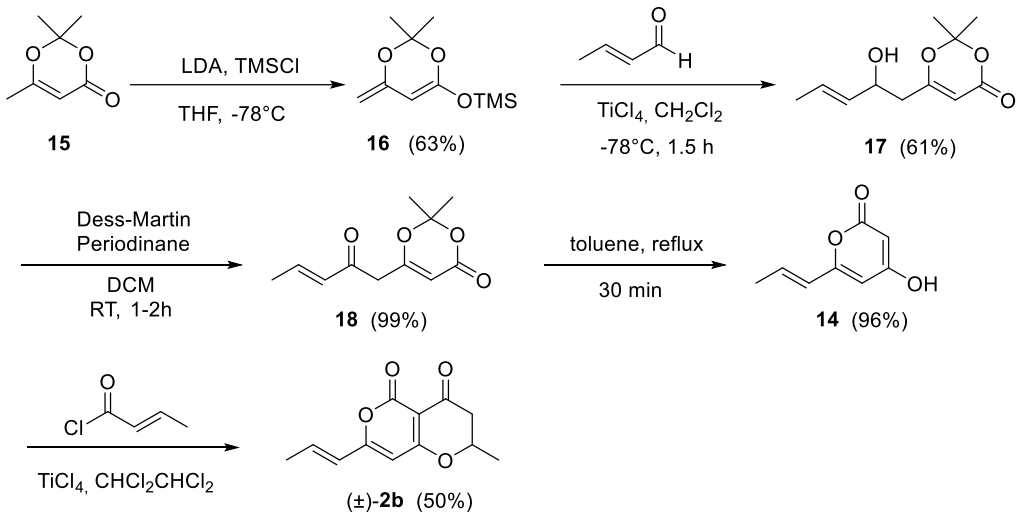
The synthetic approach proposed to prepare (±)-radicinin (**2a**) and its biosynthetic precursor, (±)-deoxyradicinin (**2b**), was based on the disconnection of their structure into pyranone **14** and crotonyl chloride (Scheme 12).



Scheme 12. Retrosynthetic analysis.

Accordingly, **15** was enolized with LDA at –78 °C in dry THF and trapped with TMSCl, providing the silyl dienolether **16** in 63 % yield. Then **16** was reacted with crotonaldehyde through Mukaiyama aldol condensation reaction in the presence of $TiCl_4$ in DCM at –78 °C, affording the alcohol **17** in 61 % yield. Oxidation of **17** gave rise to the corresponding

ketone **18** in quantitative yield. The latter compound spontaneously eliminated acetone and cyclised upon heating in toluene, providing the hydroxy-pyrone **14** in 96 % yield. Finally, acylation of **14** with crotonyl chloride, followed by in situ intramolecular Michael addition of the hydroxy moiety, provided the desired deoxyradicinin ((±)-**2b**) in 50 % yield (overall yield 18 %) (Scheme 13). Attempts to prepare (±)-radicinin (**2a**) were unfortunately inconclusive.



Scheme 13. Synthesis of (±)-3-deoxyradicinin (**2b**).

Finally, compound (±)-**2b** was subjected to phytotoxic activity assays on buffelgrass (*C. ciliaris*) and its activity was evaluated in comparison with that shown by the natural metabolite radicinin (**2a**). It was found that the activity of compound (±)-**2b** is comparable to that of the natural optically active radicinin (**2a**) (Figure 3), much more difficult to obtain both from fungal cultures and total synthesis, thus allowing to envisage its large scale use as selective bioherbicide in place of radicinin itself.

Cyclochirality Emerging from Hydrogen-Bonding Networks in Cyclic Oligoureas

Finally, the emergence of cyclochirality in molecular assemblies was investigated. Cyclochirality was classically defined as an isomerism arising when cyclic arrangements of stereocenters are associated with ring systems. Herein, such intriguing property was evaluated by the construction of a novel conformational motif obtained by synthesising cyclic oligoureas based on TACN structure (Figure 5). It is noteworthy to highlight that in these kind of molecules, the cyclochirality emerges only by virtue of the presence of cyclic intramolecular hydrogen-bonding network, whose establishment was detected by means of NMR experiments. This new class of compounds could be utilised in the future as organocatalysts in asymmetric synthesis or as enantiospecific host molecules, opening a new field of organic chemistry.

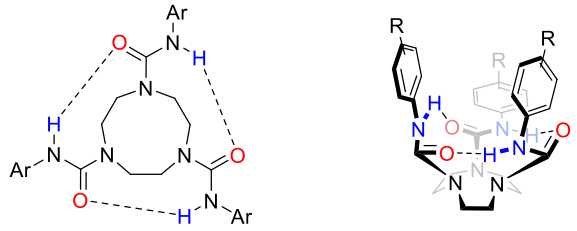


Figure 5. Cyclochiral triureas based on TACN structure.

If the molecules are cyclochiral the methylene protons on the ethylene bridges of the amine skeleton (TACN cycle) become diastereotopic, experiencing distinct chemical environments, thus displaying different chemical shift in the ^{1}H-NMR spectrum. Therefore, the cyclic hydrogen-bonding network, as well as the cyclochirality, can be detected and analysed using NMR spectroscopy. Moreover, the use of VT-NMR techniques make it possible to conduct kinetic studies on the enantiomerisation process of cyclochiral structures. In fact, their atoms are in dynamic exchange by virtue of the interconversion of the two enantiomers when the rate of exchange is comparable to the NMR timescale. When undergoing slow exchange, the NMR spectra of the triureas based on TACN structure (Figure 5) display four distinct signals for each of the methylene protons on the triamine ring. Indeed, such protons are in different environments depending on the orientation of the hydrogen-bonding array, if it is clockwise or anti-clockwise, that is if one enantiomer or its antipode. It can be supposed that the mechanism of racemisation

occurs *via* bowl-to-bowl inversion of the ring or *via* the reversal of the directionality of the hydrogen-bonding network, resulting by the 180° rotation of the side-chains. Any of these mechanisms could result in the formation of the opposite enantiomer. Hence, in one enantiomer H_1 will be proximate to the ureido proton of one side-chain, whilst H_2 will be proximate to the carbonyl of the adjacent side-chain, vice versa will occur in the other enantiomer (Figure 6). Thus, cyclochirality will be able to be detected by the presence of four distinct proton peaks at low temperature, which broaden and coalesce into a singlet at high temperature.

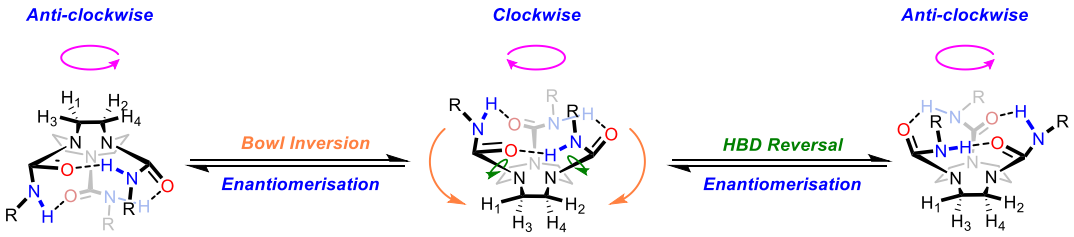
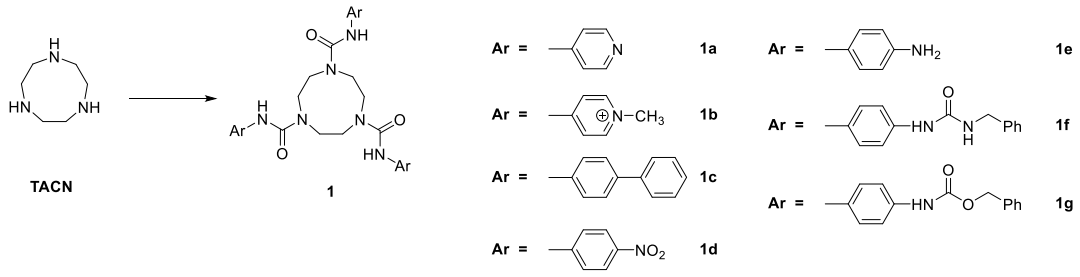


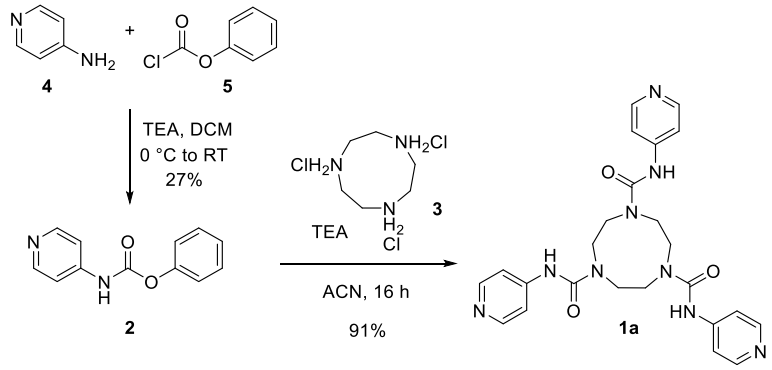
Figure 6. Suggested mechanisms of racemisation for cyclic oligoureas based on TACN structure.

This project was aimed at the preparation of cyclochiral triureas, possessing a sufficiently strong hydrogen-bonding array to prevent racemisation at room temperature, and thus making the two enantiomers separable and useful for the aforementioned functions. To this end the electronic influence of the aromatic group on the robustness of the hydrogen-bonding array, thus on the cyclochirality, was evaluated varying the substituent on the arene. Accordingly, several cyclic triureas differently *para*-substituted on the phenyl ring were to be synthesised (Scheme 3.1). Then the obtained compounds were analysed through NMR spectroscopy, in particular using VT-NMR in order to determine the energy barrier in the process of interconversion between the enantiomers.



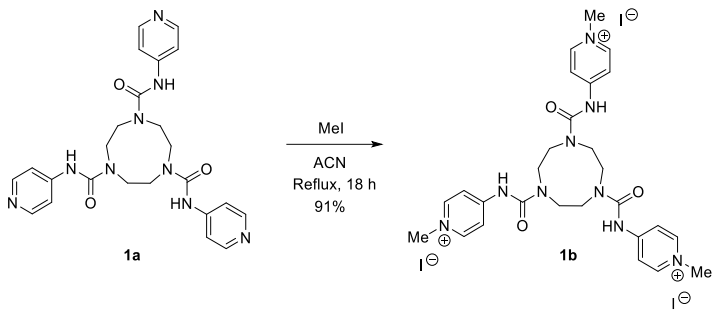
Scheme 14. Cyclic triureas differently *para*-substituted on the phenyl ring.

Unfortunately, only the syntheses of compounds **1a**, **1b** and **1g** were successful. In particular, **1a** was prepared in 91% yield by reaction of 1,4,7-triazacyclononane trihydrochloride (TACN·3HCl) (**3**) with an excess (4.5 eq.) of carbamate **2** in anhydrous ACN and in the presence of TEA at RT. In turn, compound **2** was obtained in 27% yield by reacting 4-aminopyridine (**4**) with phenyl chloroformate (**5**) at RT in the presence of TEA, added at 0 °C, in dry DCM (Scheme 15).



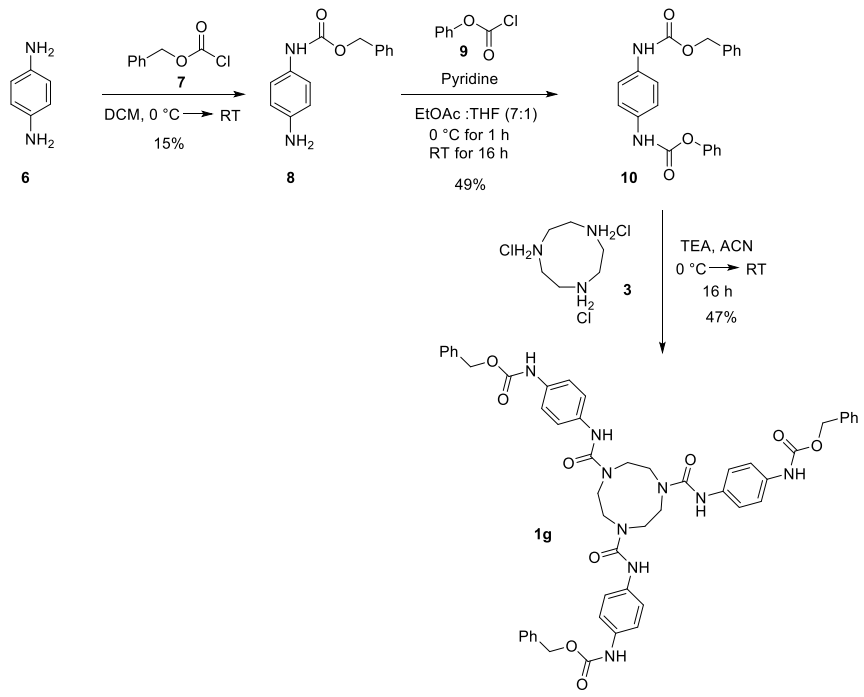
Scheme 15. Synthesis of compound **1a**.

Subsequently, compound **1b** was obtained in 91% yield by treating **1a** with MeI in dry ACN at reflux for 18 h (Scheme 16).



Scheme 16. Synthesis of compound **1b**.

Finally, compound **1g** was prepared as shown in Scheme 17. The reaction of 1,4-diamino benzene (**6**) in anhydrous DCM with benzyl chloroformate (**7**), added at 0 °C, gave rise to mono-Cbz protected amine **8** in 15% yield. Then **8** was reacted with a slight excess of phenyl chloroformate (**9**) in the presence of pyridine and in a mixture of THF and EtOAc (1:7). This reaction was performed at 0 °C for 1 h and then at RT for 16 h and afforded the desired product (**10**) as a white solid in 49% yield. Subsequently an excess of **10** was reacted with 1,4,7-triazacyclononane trihydrochloride (**3**) in the presence of TEA in anhydrous ACN, leading to the preparation of the triurea **1g** obtained in 47% yield as determined by the crude NMR. Compounds **1a** and **1g** were found to display cyclochirality by ^{1}H-NMR analysis at room temperature. Moreover, line shape analysis of VT- NMR spectra and subsequent Eyring plot allowed determining the racemisation barrier for compound **1a**, which was found to be 65.0 kJ·mol^{-1}. Unfortunately, this energy value was still too low to allow the separation between the enantiomers, which occurs if $\Delta G^{\ddagger} \geq$ 96-100 kJ·mol^{-1}.



Scheme 17. Synthesis of compound **1g**.

Conclusions

In this thesis, the stereocontrol in different asymmetric process was explored. In the first project, tandem carbolithiation reaction of 1-aryl-1-alkenyl *N*,*N'*-diethylcarbamates followed by subsequent trapping with electrophiles was investigated. In particular, the use of different electrophiles has been studied and the reaction conditions have been optimised. This procedure provided a method for construction of trisubstituted benzyl carbamates, direct precursors of tertiary benzyl alcohols, in a single pot, creating a chiral quaternary carbon α to oxigen. The carbolitiation-trapping reaction was also performed in an enantioselective manner using chiral diamines. In the second project, the first asymmetric and versatile synthesis of the natural products colletochlorin A and colletorin A and their unnatural halogenated analogues was reported, by a highly enantioselective method. In addition, a novel and versatile synthetic strategy for the preparation of (±)-deoxyradicinin,

the biosynthetic precursor of the phytotoxin radicinin, was developed. In the third project, new cyclochiral triureas based on the TACN structure have been synthesised. This unusual type of chirality is revealed in these structures by using NMR spectroscopy, even if the barrier to racemisation found is still too low to allow the enantiomeric separation of the cyclochiral oligoureas prepared.