Advances in the stereoselective synthesis of antifungal agents and aromatase inhibitors.

Inaugural-Dissertation
zur Erlangung des Grades eines Doktors der Naturwissenschaften
angefertigt im Fachbereich 9, Naturwissenschaften II
der Bergischen Universität - GH – Wuppertal
(D-468)

von
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1999

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ACKNOWLEDGMENT:

I would like to thank Prof. M. Botta for help, guidance and support throught this research. I would also like to thank Prof.Dr. M. Schneider for helpful suggestions, advices and guidance expecially during my permanence in Wuppertal and for the excellent job at proofreading this manuscript. Without encouragement and support of both professors this work would not be completed. I am also indebted with Prof. Dr. H.-J. Altenbach for the hospitality in his laboratory in Wuppertal. Finally I would like to thank Menarini Ricerche Sud for the finacial support and the opportunity to work in the area of anticancer drugs.

A Valentina e ai miei genitori

NON SEGUIRE UN SENTIERO BATTUTO DA TUTTI PER IL TUO CAMMINO.
VA' DOVE NON C'E' SENTIERO E LASCIA UNA TRACCIA.

Summary:

Numerous drugs are chiral, generally only one enantiomer is therapeutically active while the other antipode is completely inactive or shows often undesired and/or toxic side effects. For this reason, all new chiral drugs are now formulated in enantiopure form. Non-steroidal anticancer and antifungal drugs contain the same chemical structure e.g. Bifonazole **6a** and non-steroidal aromatase inhibitors such as the Menarini anticancer drug **18.** They are characterized by the presence of single chiral centre in benzhydrilic position. The present work was aimed at new procedures for the synthesis of both Bifonazole **6a** and the Menarini aromatase inhibitors **18** in enantiomeric pure form.

In order to prepare enantiopure synthons and final products several synthetic methods were developed.

A chiral lithium aluminiumhydride complex with (*R*)-(-)-2-isoindolinyl-butan-1-ol **(*R*)-(-)-24** as auxiliary was used for the asymmetric reduction of ketones **25a-d** and **26a,c** in order to obtain the corresponding enantiopure alcohols.

Racemic and enantiopure alcohols **27a-c,g,m** and **31a-1** were used as starting materials in multi-step syntheses for the corresponding *N*-imidazole derivatives in racemic and enantiopure forms. Involved are three reaction steps: (a) Mitsunobu reaction with 4,5-dicyano imidazole to obtain the *N*-4,5-dicyanoimidazole derivatives **33a-m**; (b) hydrolyses of the *N*-imidazole-4,5-dicarbonitrile derivatives **33a-m** to the corresponding diacids **34a-m**, (c) thermic decarboxylation of the diacids **34a-m** to the final *N*-imidazole derivatives **35a-d.**

This synthetic procedure was exceptionally well suited for the production of enantiopure *N*-alkyl imidazole derivatives **34a,b**, instead gave high chemical yield but complete racemic products with benzylic alcohols **31d** and benzhydroles **27a-c.**

Using a modified Marckwald procedure starting from chiral amines **(*S*)-(+)-44** and **(*S*)-(+)-51** it was possible to synthesize the imidazole ring and to obtain the corresponding enantiopure (*S*)-(+)-1-(2-octyl) imidazole **(*S*)-(+)-35a** and (*S*)-(+)-1-phenyl-1-ethyl imidazole **(*S*)-(+)-54. (*S*)-(+)-35a** presented an identical specific rotation as the corresponding compound obtained from the three step synthesis discussed above and proved the inversion of the configuration during the Mitsunobu reaction.

In order to obtain the enantiopure aryl-2-benzo[b]furan methanols **27** a new synthetic method was considered instead of the asymmetric reduction of the corresponding ketones that lead to poor results. The use of the lipase SAMII allowed the synthesis of enantiopure 1-aryl-2-propyn-1-ols **(*R*)-(-)-58a-c,e,h-l** in high enantiomeric excesses and good chemical yields *via* hydrolysis of corresponding racemic acetates **60a-c** and chloroacetates **61a-l** (Scheme 7.4).

The racemic and enantiopure 1-aryl-2-propyn-1-ols **58 a-l** were cyclized with 2-iodophenol to the corresponding aryl-2-benzo[b]furan carbinols **27g-h** and **63a-d** and with 2-*N*-Mesyl iodoaniline to aryl-2-(*N*-mesyl)indol carbinols **64a-g** using Pd(0) as catalyst. Both products were obtained in high e.e. and chemical yield. These constitute the first applications of Pd catalyses with enantiopure arylpropynols.

The reaction conditions were optimized in order to maximize chemical yields and enantiomeric excesses. Finally an hypothesis for the mechanism of cyclization was formulated. The first step is the Pd^0 catalyzed addition of the acetylenic compound to the 2-iodophenol leading to **62**; the second step is the CuI catalyzed cyclization to benzo[b]furane derivatives **27** or to *N*-Ms-indol derivatives **64**.

In conclusion the present work led to advances in the stereoselective synthesis of antifungal agents such as bifonazole **6a** and the aromatase inhibitors **18**; in fact the application of the described methodology to an enantiopure amine may probably lead to the target molecule in enantiopure form.

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1.Introduction

1.1. Chiral Drugs

A large fraction of the many thousand drugs on the market are chiral compounds (Fig1.)[1]. Due to economic factors, but also for traditional reasons, many of them are marketed as racemates. Depending on the number of asymmetric centres, they can exist as two or more enantiomers (2^n, where n is the numbers of chiral centres). For long time it was assumed that their manufacture in enantiomerically pure form was too expensive and difficult to perform due to the lack of synthetic methods for their preparation.

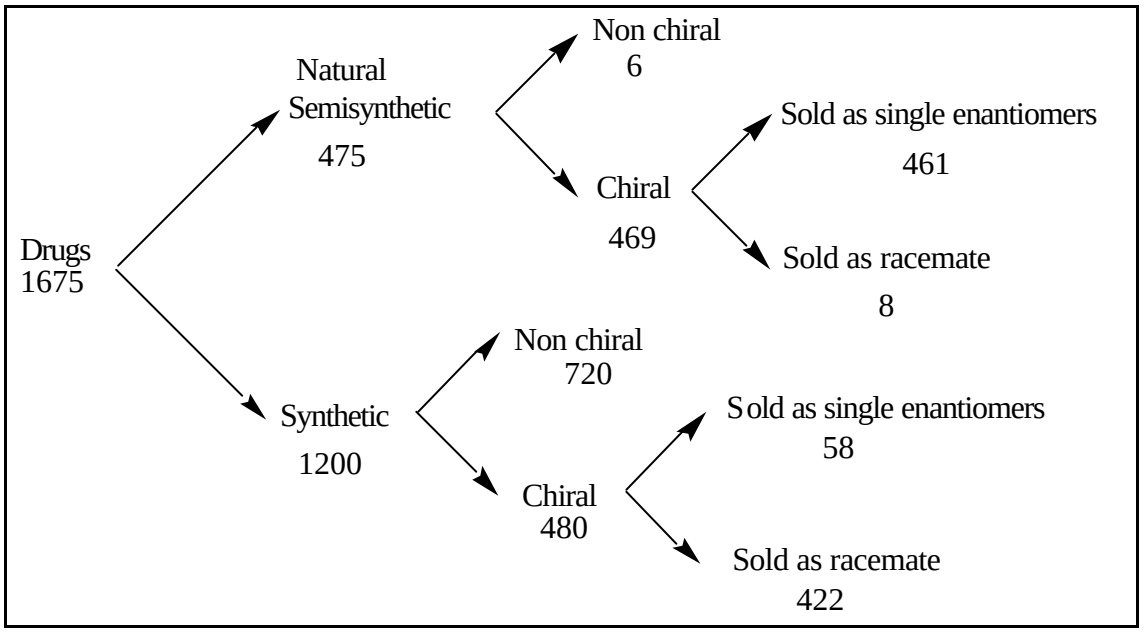

Figure 1.1: Chiral drugs: applications as single enantiomers or as racemic mixtures.

Stereoselective syntheses and techniques for the separation of diastereoisomers are now available and have reached economic feasibility, thus the situation is changing rapidly. Similar arguments are valid for the use and synthesis of agrochemicals (Fig 1.2.).

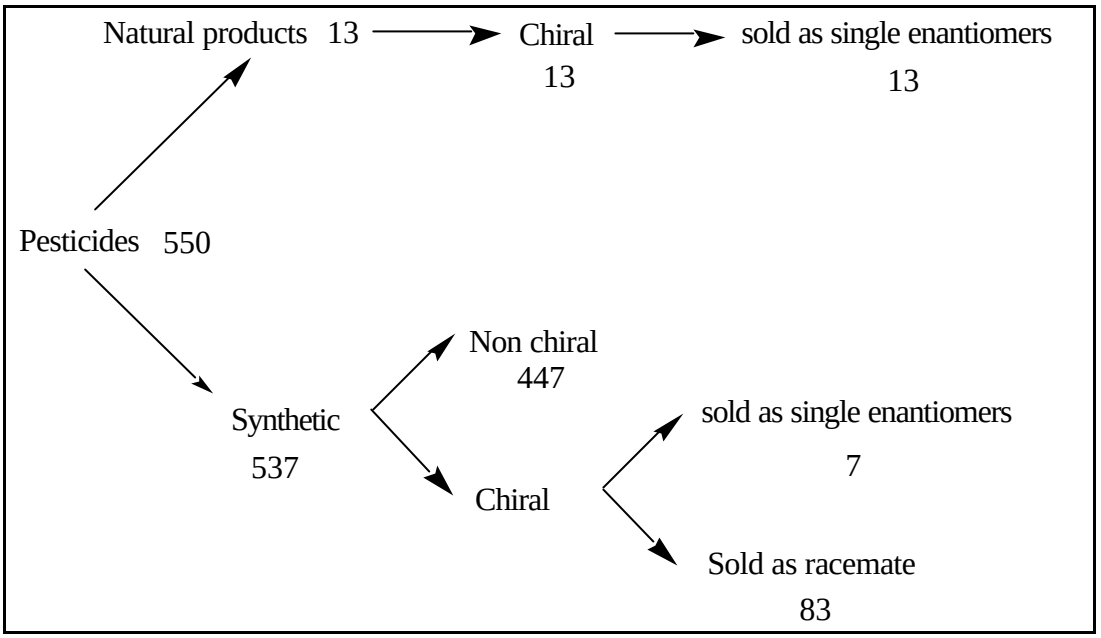

Figure 1.2: Chiral pesticides and their application as single enantiomers or as racemic mixtures.

All life processes are characterized by a high level of dynamic organization requiring an intricate regulatory network for inter- and intracellular communication and for communication between living systems and their environment. Conveyance of information is largely controlled by messenger molecules that selectively interact with particular sites of enzymes, receptors, carrier molecules, etc., which are essential components constituting the basis of life. Drugs, pesticides and pheromones can be regarded as exogeneous messengers. They are designed for particular functions and are "released" under particular conditions . Like endogenous messengers, they usually act on specific sites such as receptors or enzymes. Endogenous and exogeneous messengers can be subject to activation and/or inactivation by metabolic conversion. Examples are prodrugs, prehormones and propesticides.

The selectivity - the discriminatory capacity of the specific sites for messenger molecules and substrates - is based upon complementary chemistry. This can be visualized as the key and lock principle, not as a static but as a dynamic process of mutual adaptation, an "embracement" between substrate and enzyme, or messenger molecule and receptor. The complementary principle concerns the distribution of charge at the interface of interacting molecules and the spatial structure of the interactions. Stereoselectivity of biological systems and stereospecificity in the action of chiral bioactive xenobiotics is a "natural" matter.

The concept of stereochemistry and stereoselectivity in biological processes dates back to Pasteur and van't Hoff-Le Bel, about 100 years ago. The four valences of carbon imply that, if four different groups are attached to one carbon atom, the spatial arrangement results in a centre of asymmetry and thus the occurrence of stereoisomers, such as enantiomers having a mirror image relationship. Based on the concept of a three point interaction, the eutomer[3,4] may bind to its site of action α, β, γ, *via* three groups, A, B, and C. The antipode, frequently called the distomer, in contrast can only fit with two groups (e.g. A B with α and β), with group C being in the wrong position ω, (Fig. 1.3).

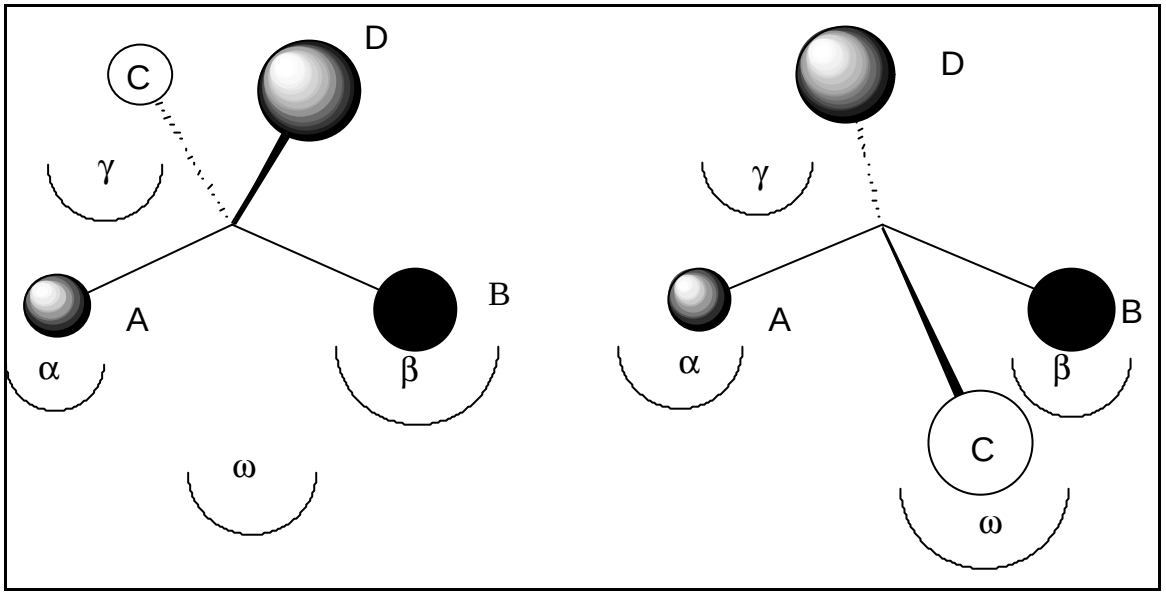

Figure 1.3: Three-point interaction of enantiomers with a receptor (schematic).

The distomer therefore will have a low affinity. It may be totally devoid of action or only "inactive" regarding the desired activity. It can however act in another sense e.g. in causing undesired side reactions or even antagonize the active isomer. In general, it is possible to assume that the two enantiomers of a particular compound can have a) equal pharmacological activity, b) one may be inactive, or c) one may be toxic, or d) the two might have unequal degrees of various kinds of activities.

In the past, medicinal chemists had been content to develop mostly racemic forms of chiral drugs, under the assumption that both enantiomers were equally active or one enantiomer was inactive and innocuos. The extra steps and expensive chemicals needed to synthesize enantiomers meant much higher production cost. However, a number of

trends have developed an irresistable wave of prospects for new chiral drugs to be developed as single enantiomers. There is also a strong movement towards so-called "racemic switches"- single enantiomers derived from older chiral drugs originally marketed as racemates.

The development of chiral drugs as single enantiomers received a big boost from the American Food and Drug Administration (FDA) communication in the summer of 1992 due its its long - awaited guidelines for the marketing of these drugs. The issue to be decided was whether drug companies may market such compounds as racemic mixtures or whether they must develop them as single enantiomers. FDA's position is that drug companies have the choice of whether to develop chiral drugs as racemates or as single enantiomers. But the interpretation of guidelines will rest with individual FDA reviewers considering particular cases. And under the guidelines, drug companies will have to furnish rigorous justification for FDA approval of racemates. So, in order to avoid unpleasant surprises, most drug companies have decided to develop only single enantiomers. Several have also issued instructions to their research departments to avoid, whenever possible, chiral molecules.

This evolving regulatory climate in the development of chiral drugs presents many opportunities to drugs firms and their suppliers. The main beneficiary will be the chemist, because the resolution of racemates, asymmetric synthesis, and the determination of enantiomeric purities are chemical activities.

Many chemists are seeing an advantage in "racemic switches", the redevelopments of drugs, already approved as racemate, as pure enantiomers. Patents of many racemic drugs are expiring or running out, and drug companies, in order to defend themselves against competition from generic drug producers can patent pure enantiomers of the racemic drug.

In this case fewer biological tests are needed for an enantiomer to be approved.

In fact, many older racemic drugs are being switched by third party firms under the very noses of the original discoverers and/or principal marketers. One attraction for these third party entrepreneurs in discovering unexpected and thus patentable properties of enantiomers; or patenting the most economical production process. One of these racemic

switches is in the area of analgesics. Thus Menarini (Italy) has collaborated with the British Company Chiros, (Cambridge, England) to develop (*S*)-(+)-Ketoprofene **1** (Fig 1.4). Discovered by Rhone-Poulenc it was sold in the U.S. as racemate under the name Orudis, while the enantiomer has been registered by Menarini in Spain. The (*S*)-(+) enantiomer is an analgesic/anti-inflammatory drug whereas the (*R*)-(-) isomer shows activity against bone loss in periodontal disease[5].

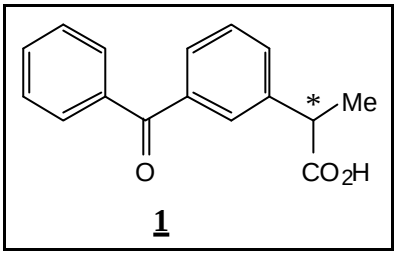

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Figure 1.4: (±) Ketoprofene **1** (±) 2-(3-benzoylphenyl) propionic acid

The discovery of two different pharmacological effects for opposite enantiomers is a common driving force for a racemic switch.

Nebivolol, producted by Janssen Pharmaceuticals, is an example for different pharmacological actions in two enantiomers. It had been developed as a β-blocker for hypertension. But, whereas (+)-Nebivolol is a β-blocker, the (-) enantiomer is a vasodilating agent. Thus, by alleviating hypertension by two different mechanisms of action, the racemate may be considered superior to either enantiomer[5].

There is also a hypothetical case of a chiral drug that is degraded by metabolic reactions at a site distant from the asymmetrically substituted carbon atom. This way both enantiomers would be inactivated at the same rate. Therefore, an inactive enantiomer may serve as a sacrifical substrate for degradation of the enzyme, thus prolonging the residence time of the active enantiomer in the body. To achieve the same therapeutic benefit, the patient would have to take the same dose of expensive enantiomers as of the cheaper racemate.

Clearly, all industrial observers believe that if the potency of an active and inactive enantiomer is such that the dose can be cut in half, the patient will benefit.

Candidates for racemic switches are also antifungal agents, non steroidal inhibitors of aromatase (anticancer), cardiovascular drugs, non steroidal anti inflammatory drugs (NSAIDs), central nervous system

agents, antihystaminica, and prescription drugs being considered for eventual over the counter sale (OTC's).

This thesis will focus on the synthesis of antifungal agents and non steroidal inhibitors of aromatase.These two classes of drugs share general chemical structures and mechanisms of action. In fact both inhibit two different cytochrome P-450 dependent enzymes having a protoporphyrin heme as catalytic site. They present (Fig. 1.5) an heterocyclic moiety such as an imidazole or triazole in a benzylic or benzhydrilic position. Furthermore the asymmetric centre is the benzhydrilic or benzylic carbon wich is the core of the molecules connecting all other parts of the molecule.

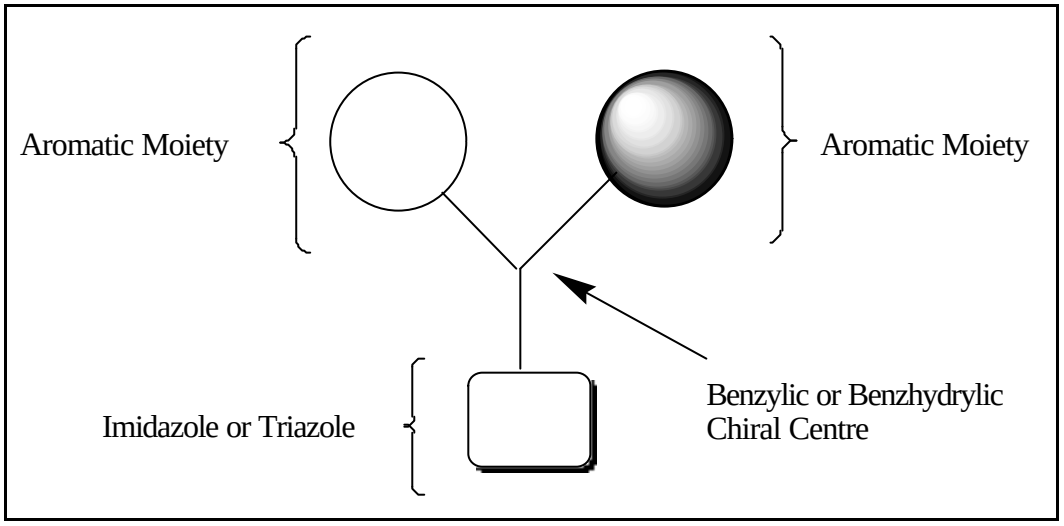


Figure 1.5: General structure of antifungal agents and non steroidal aromatase inhibitors.

Even though these classes of drugs have very simple structures, they have never been synthesized in enantiopure form.

1.2. Enzymes containing the Cofactor Cytochrome P-450.

Cytochrome P-450 dependent enzymes constitute a family of enzymes which catalyze the oxidation of a large range of biological substrates. The P-450 dependent enzymes are divided into 10 groups and 18 subgroups based on sequence alignment with groups sharing greater than 30% sequence homology and subgroups with homology greater than 46%[6,8]. The enzymes bind dioxygen and through a stepwise cleavage of the O_2 double bond incorporate one oxygen atom into non activated C-H

-bonds[9]. It is now widely accepted that some enzymes of the P450 subgroup (notably aromatase and lanosterol 14-α–demethylase) in extension to their role in hydroxylation and related oxygen insertion reactions can catalyze a sequence of reactions leading to C-C bond cleavage[8,9]. Cytochrome P-450-dependent lanosterol 14-α–demethylase (P-450 DM) catalyzes the first step of the biochemically important conversion of lanosterol to cholesterol by removal of the 14-α–methyl group of lanosterol to give the $\Delta^{14\text{-}15}$ desatured sterol[10], or ergosterol. Both cholesterol and ergosterol are essential constituents of the cell membranes in mammals and fungi, respectively.

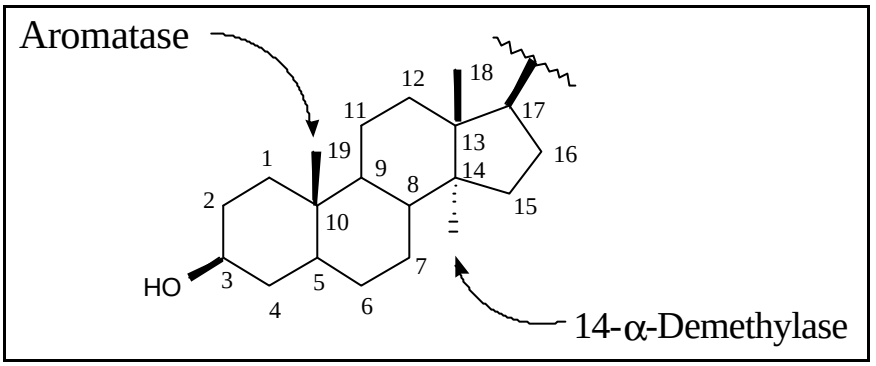


Figure 1.6: Site of action by Aromatase and 14-α-Demethylase

The aromatase Cytochrome P-450 is involved in the specific recognition and binding of C-19 steroid substrates and catalyzes the multistep oxidative reaction sequence leading to aromatization of the A ring of the steroid [72]. In figure 1.6 the reaction sites of the Aromatase Cytochrome P-450 and the Lanosterol 14-α–demethylase (P-450 DM) are shown.

1.2.1. Inhibitory Activity of Antifungal Agents on 14-a-Demethylase.

Ergosterol **2** is the main structural component of fungal cell membranes (Fig.1.7).

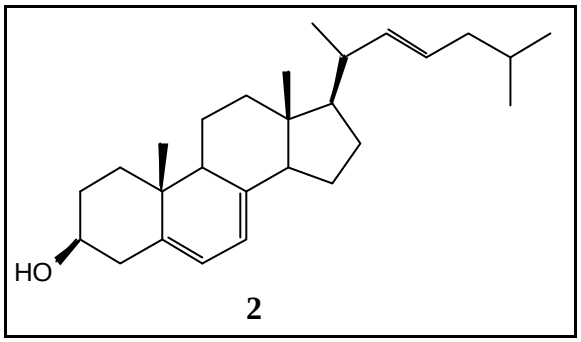


Figure 1.7: Ergosterol **2**

Diminuition of ergosterol **2** is believed to be the primary mechanism by which many fungicides inhibit fungal growth.

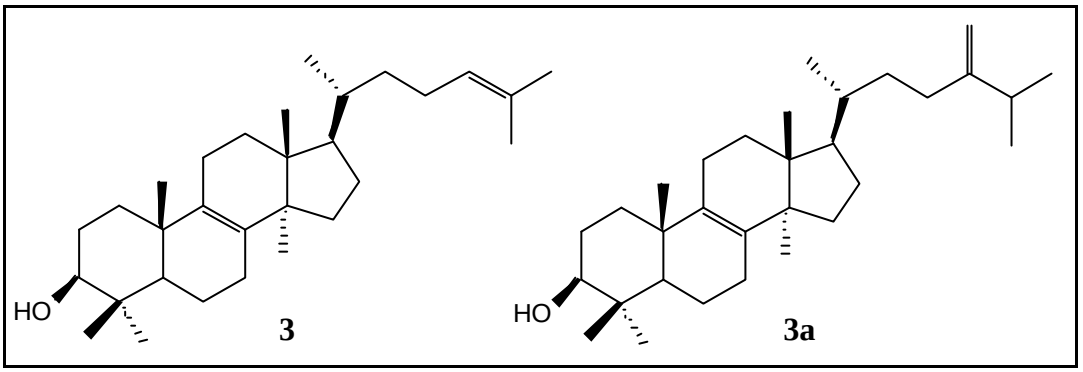
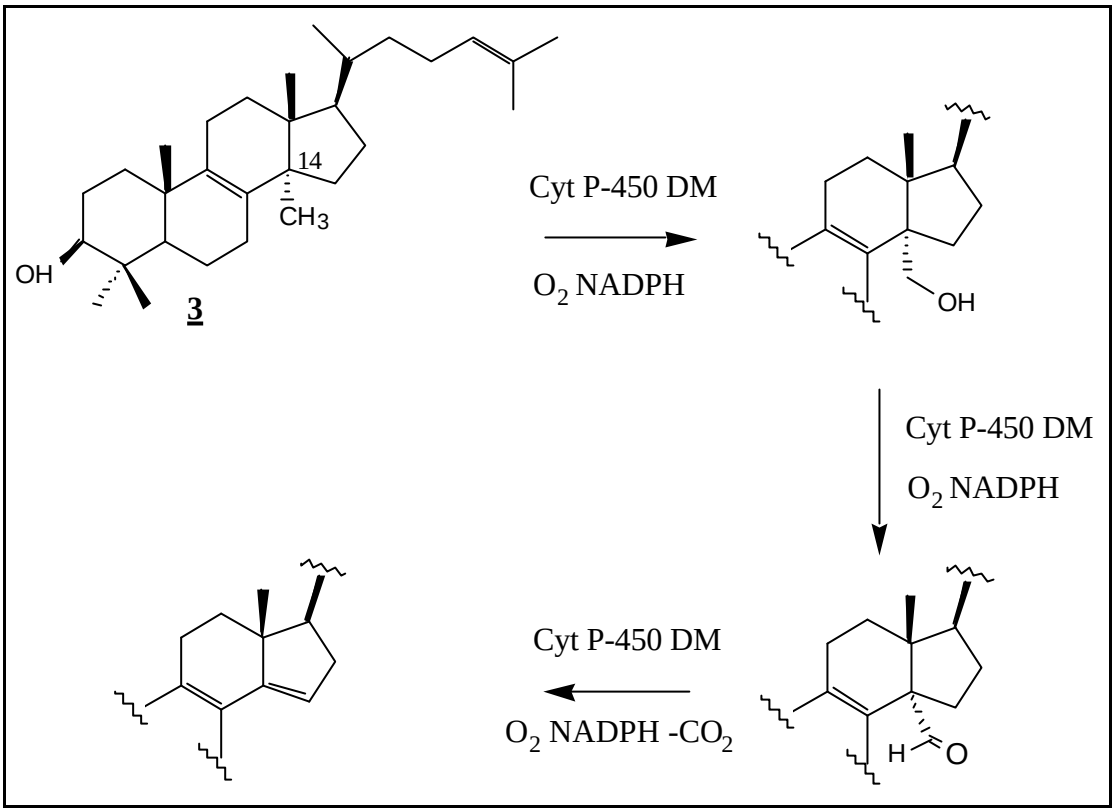


Figure 1.8: Lanosterol **3** and 24-methylenedihydrolanosterol **3a**.

An early precursor in the synthesis of ergosterol **2** is mevalonic acid which is condensed *via* several steps into squalene. The cyclization of squalene oxide leads to lanosterol **3** and 24-methylene-dihydrolanosterol[11,12] **3a** (Fig. 1.8). **3a** accumulates in drug treated cells because of the inability of these cells to remove the C-14 methyl group. In contrast, demethylation would lead to 4,4-dimethylfecosterol, the next sterol along the biosynthetic pathway leading to ergosterol.

The specific action of fungicides in preventing demethylation at C-14 is controlled by a Cytochrome P-450 enzyme involved in the demethylation process. It is believed to involve the association of a heterocyclic nitrogen atom with the protoheme of Cytochrome P-450[13,17]. The demethylation at C-14 of the sterol nucleus involves three reaction steps, shown in Scheme 1.1.



Scheme 1.1: Demethylation of Lanosterol **3** by 14-α-Demethylase

Inibitors prevent the first step of the reaction[14].The inhibition of C-14 demethylation is thought to be due to the binding of a heterocyclic nitrogen atom in an azole to the protoheme iron atom which in turn would prevent the activation of oxygen that would normally take part in the reaction. The non heterocyclic portion in the antifungal agents binds to the lipophilic sites of Cytochrome P-450[15].

Under normal conditions, azole (*N*-substituted imidazole and triazole) antifungal antibiotics cure mycoses by inhibiting the fungal P-450 DM at concentrations which are not expected to affect the corresponding host enzyme[16]. The accumulation of 14-α–methylated sterols in azole-treated fungal cells affects the membrane structure and their function, resulting in the inhibition of fungal growth [16, 18].

Differential inhibition of this cytochrome P-450 enzyme between pathogenic fungi and humans is the basis for the clinically important activity of azole antifungal agents. The analogous differential inhibition of the enzyme between fungi and plants is also responsible for the utility of azole derivatives as agricultural antifungal agents[16]. The specificity of the inhibitors is determined by the differential complementarity between the

structure of the agent and the active sites of the fungal and host enzymes[19]. One of the reasons to continue the search for better antifungal agents is to increase their specificity towards fungal enzymes. This is an important goal especially under pathological circumstances, where the immune system is compromised to a great extent (AIDS pathology, major surgery intervention follow by an infection) and the side effects (inhibition of the host P-450 DM) due to overdosage of the azole compounds may eventually cause the death of the patient[20, 21].

1.2.2 Antifungal Agents on the market.

Since the advent of the antifungal imidazoles in 1969 several of these compounds have been successfully developed and marketed. Many of these compounds are limited in their use due to their intrinsic toxicity and scarse solubility. Nevertheless, they positively contribute in the area of antifungal chemotherapy. A brief survey of some more widely used antifungal imidazoles is given below. All antifungal agents can be classified into three major classes: Ketoconazole **4a** and its analogues **4b-c** (Fig. 1.9), Miconazole **5a** and its analogues **5b-d** (Fig. 1.11) and Bifonazole **6a** and its analogues **6b-d** (Fig. 1.12).

In the Ketoconazole series **4a-c** (Fig. 1.9) the azole moiety is not directely connected to the chiral centre. The second class is represented by the Miconazole series **5a-d** (Fig. 1.11) having the imidazole or triazole ring in a homobenzylic position, while the chiral atom is in the benzylic position. The last group is exemplified by Bifonazole **6a** and its analogues **6b-d** (Fig. 1.12). Here the imidazole moiety is in benzhydrylic position which also constitutes the chiral centre.

1.2.2.1 Ketoconazole and its analogues 4a-c.

The structures of Ketoconazole **4a** and its analogues **4b-c** are shown in Fig. 1.9.

At present the best drug in the imidazole class of antifungal agents is Ketoconazole[22,24]**4a**. It was synthesized and developed by Janssen Pharmaceuticals in 1977; Ketoconazole (*cis*-1-acetyl-4-[[2-(2,4-dichloro-phenyl)-2 (1H-imidazol-1-ylmethyl) -1,3-dioxolan-4-yl] methoxy] phenyl]

piperazine) is also the most extensively documented antifungal imidazole[25,26].

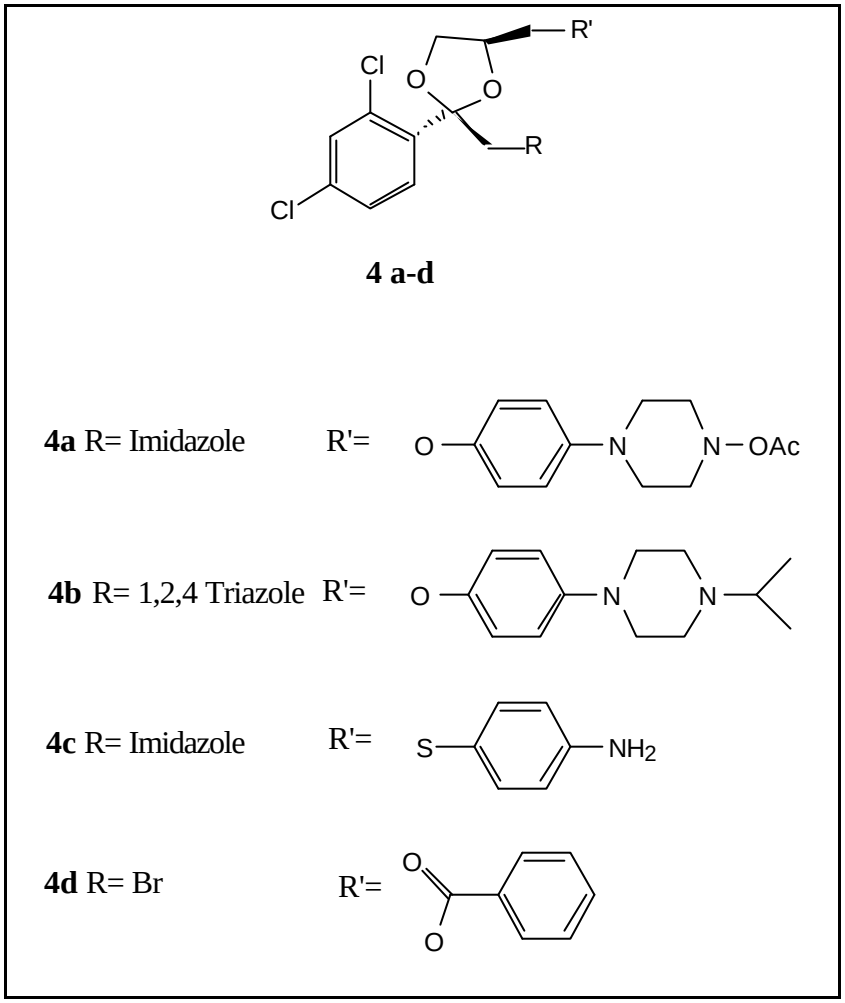


Figure 1.9: Structures of Ketoconazole **4a** and its analogues **4b-c**, and together with the key intermediate for the enantioselective synthesis **4d**.

Ketoconazole **4a** has been shown to have *in vitro* activity against a broad spectrum of fungi including the three genera of dermatophytes, yeasts, dymorphic fungi and a variety of others. *In vivo* studies with several animal species demonstrated a broad spectrum of activities against superficial as well as systemic fungal infections.

The United States Food and Drug Administration approved **4a** in 1981 for the treatment of candidias, chronic mucocutaneous candidias, oral candidias, candiduria, coccidiomycosis, histoplasmosis, chromomycosis and paracoccidiomycosis[27-29]. One of the salient characteristics of

Ketoconazole **4a** is that it was the first orally active antifungal agent of the imidazole class after clotrimazole.

Ketonazole **4a**, as compared with amphotericin B and miconazole, is well tolerated although certain problems in its use in therapy are reported in the literature (nausea, vomiting or anorexia, abdominal complaints)[30]. Gynecomastia has been reported to occur in 3-8% of patients receiving ketoconazole and this may result in a direct effect of the drug on the breast tissue[31]. Another adverse reaction associated with ketoconazole is hepatic toxicity. **4a** has also been shown to have a similar inhibitory effect on the enzyme responsible for the conversion of lanosterol to cholesterol in mammals and has been demonstrated to lower cholesterol levels in humans[32,33]. In addition, it inhibits a number of other cytochrome P450 enzymes involved in steroidal biosynthesis and drug metabolism. It has also been shown to block adrenal steroidogenesis by inhibition of the corticoid 11-β–hydroxylase[34]. For these properties it has been utilized to treat prostate cancer and Cushing's syndrome[35].

Ketoconazole **4a** is marketed as racemic mixture of the *cis*-(2*S*,4*R*) and (2*R*,4*S*) enantiomers as illustrated in figure 1.9.

It is one of the few antifungal agents which has also been synthesized in enantiopure form. Starting from optically pure (*R*)- and (*S*)-solketal tosylate **4e** (figure 1.10), by transketalization with apropiate ketones, both enantiomers of **4a** and also the corresponding *trans* derivatives were prepared[36].

The same chiral building block has been used to synthesize selective inhibitors of the mammalian 14-α-demethylase in order to reduce the cholesterol levels in the humans[37].

The latest stereoselective synthesis of both enantiomers of Ketoconazole **4a** has been reported in 1995. Starting from commercially available (*R*)- or (*S*)-epichlorohydrine[38] **4f** (Fig. 1.10), **(+)**-or **(-)-4a** Ketoconazole was obtained in nine steps[38].

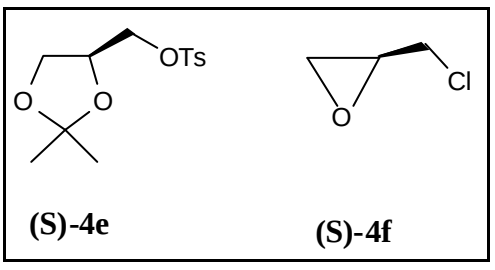


Figure 1.10: (*S*)-solketal tosylate **4e** and (*S*)-epichlorohydrine **4f**.

The four stereoisomers of Ketoconazole **4a** were evaluated for their effectiveness as inhibitors of the cytochrome P450 involved in:

(a) cholesterol biosynthesis and degradation (lanosterol 14-α–demethylase and cholesterol 7-α–hydroxylase); (b) steroid hormone biosynthesis (cholesterol side chain cleavage, progesterone 17α,20-lyase, deoxycorticosterone 11-β hydroxylase and aromatase) and (c) xenobiotic transformation (lauric acid hydroxylation and progesterone 2α –, 6 β –, 15 α –, 16 α –, 21 hydroxylation)[36].

It was shown that the *cis*-isomers are more potent inhibitors of mammalian lanosterol 14-α–demethylase than the diastereomeric *trans*-isomers. The *cis*-(2*S*,4*R*) isomer is three times more active than its antipode[36].

The most important analogues of Ketoconazole **4a** are Terconazole **4b**, *cis*- 1,4,2- (2,4-dichlorophenyl) -2- (1-ylmethyl) -1,3 -dioxolan - 4-ylmetoxyphenyl -4- (methylethyl) piperazine, a triazole ketal synthesized by Janssen Pharmaceuticals.[39]

In this case the heterocyclic moiety is a 1,2,4 triazole instead of the imidazole, and contains a *t*-butyl group instead of an acetate group in position 4 of the piperazine.

In 1995, Menarini reported the first stereoselective synthesis of (+)-or (-)-Terconazole **4b**.

The synthesis of both enantiomers of Terconazole employed as starting material (2*R*,4*R*)-(+)-and (2*S*,4*S*)-(-)-bromobenzoate **4d** (Fig. 1.9) which have been also used as advanced chiral intermediates for the synthesis of both enantiomers of ketoconazole[40]. Another synthesis of the analogues of Ketoconazole **4c** has been reported in 1994[41].

Terconazole **4b** has also been shown to be highly effective *in vivo* for the topical treatment of various experimental models of dermatomycosis and candidiasis. It also shows some oral activity against experimentally induced superficial mycoses [42].

1.2.2.2 Miconazole and its analogues 5a-d.

Miconazole **5a** and its analogues **5b-d** are shown in Fig 1.11.

Miconazole 1 - [2,4 - dichloro -β- (2,4-dichloro-benzyloxy) phenyl] imidazole nitrate **5a** is a phenylethyl imidazole derivative synthesized by Janssen Pharmaceuticals in 1969 [43].

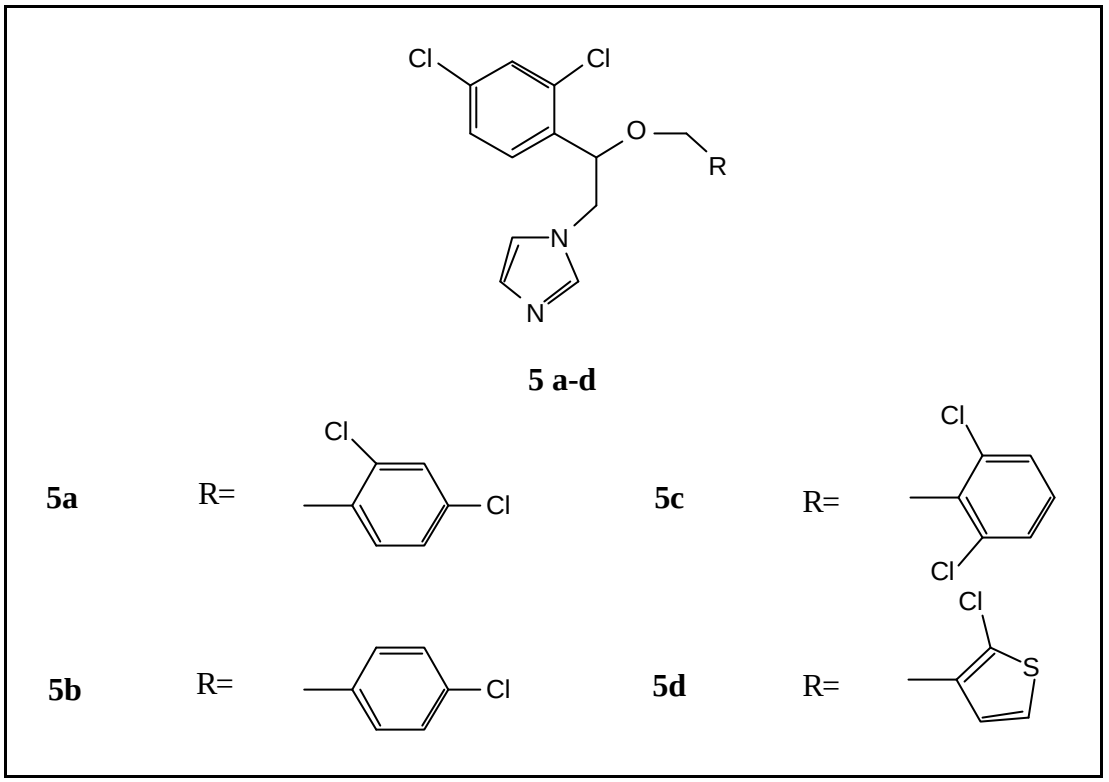


Figure 1.11: Miconazole **5a**, Econazole **5b**, Isoconazole **5c** , Tioconazole **5d** .

No informations are available in the literature regarding the stereoselective synthesis of **5a** and its analogues **5c-d**. Miconazole **5a** has been shown to have a broad spectrum of antifungal activities [44].

Dermatophytes, pathogenic yeasts, dimorphic fungi, *Aspergillus species* and several mycetoma-causing agents have been shown to be susceptible to clinically obtainable concentrations of this compound [45]. Clinically, Miconazole **5a** can be administered either intraveneously or topically. It requires solubilization in polyethoxylated castor oil for intravenous administration, but this vehicle has been suggested to be responsible for many side effects within this therapy [46]. The role of this imidazole derivative in the therapy of fungal diseases remains uncertain, it has never been properly defined. Some authors [47] have reported the oral use of miconazole in the prophylaxis in neutropenic cancer. Topical applications to treat dermatophytes appears to be moderately successful. Fortunately, no side effects resulted from topical treatments[48].

Econazole 1-[2-(2,4-dichlorophenyl)-2-(4-chloro benzyloxy) ethyl] imidazole **5b**, an analogue of **5a** was also synthesized by Janssen Pharmaceuticals [49]. In the literature there are no informations regarding its stereoselective synthesis, but it has been also reported that one of the

single enantiomers and the racemic mixture virtually showed the same antifungal activity [50].

The antimicrobial activity of Econazole **5b** has been shown to be similar to that of **5a** against dermatophytes, pathogenic yeasts, dimorphic and filamentous as well as gram positive bacteria [51,52].

Isoconazole **5c**, 1- [2, 4- dichloro -β- (2, 6 - dichloro benzyloxy) phenylethyl] imidazole nitrate, is an antifugal imidazole structurally related to both Miconazole **5a** and Econazole **5b**, produced by Janssen Pharmaceuticals.

No informations are available on the enantioselective synthesis or chemical resolution of this compound, neither the antimicotic activity of a single enantiomer.

Isoconazole **5c** has been demonstrated to have a broad activity spectrum *in vitro* against dermatophytes, pathogenic yeasts, pathogenic filamentous fungi , gram positive bacteria and tricomonas [53]. It is very effective in the treatment of experimentally induced infections following topical application. In fact, this compound has been developed and marketed for the topical treatment of vaginal candidiasis [53].

Tioconazole, 1-[2-[(2-chloro-3-thienyl) methoxy]-2-(2,4dichloro phenylethyl]-1H-imidazole **5d** is a substituted imidazole derivate sythesized by Pfizer. **5d** has been shown to be 4 fold more active than **5a** against *Candida sp*. while it is comparable to **5a** in its inhibitory activity against *Aspergillus sp*.[54] . The main use of this drug is as a topical agent for the treatment of skin mycose, vaginal candidiasis and tricomoniasis [54].

1.2.2.3. Bifonazole and its analogs 6a-d.

Bifonazole **6a** and its analogues **6b-d** are shown in figure 1.12. Bifonazole, 1-[(4-biphenyl)phenylmethyl]-1H-imidazole **6a**, is an imidazole derivative synthesized by the Bayer AG in racemic form[55]. Up to now there are no reports regarding its stereoselective synthesis.There are also no pharmacological informations available regarding the activities of the single enantiomers.

Bifonazole has been shown to have a broad spectrum of antifungal activity *in vitro* against many pathogenic yeasts, dimorfic pathogens, dermatophytes and pathogenic filamentouses fungi[56].

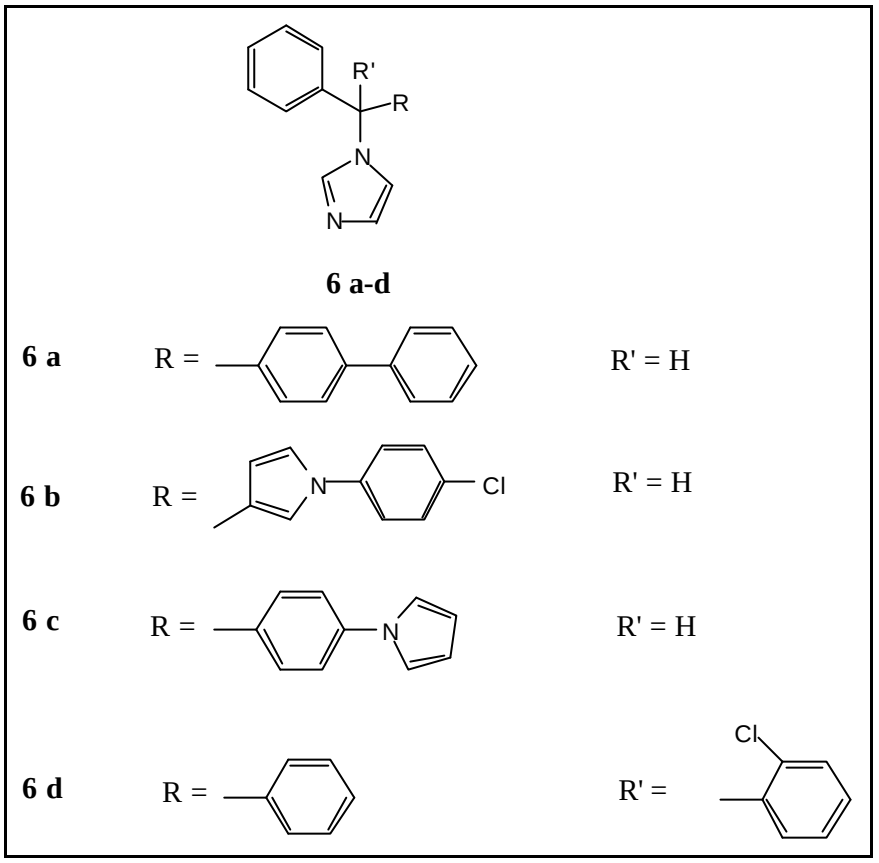


Figure 1.12: Bifonazole **6a** and its analogues **6 b-d**.

Generally, Bifonazole **6a** was found to be comparable to Clotrimazole **6d** in its *in vitro* antifungal activity, although quantitatively Bifonazole **6a** was somewhat less potent than Clotrimazole **6d**. Experimental studies *in vivo* have demonstrated that it is effective in treating dermatophitic infections, this effectivity being attributed to the therapeutically achievable fungicidal effect on dermatophites and to the long residence time of the compound on the skin. Pharmacokinetic studies have demonstrated that this drug is not mutagenic[57] and well tolerated. The efficacy of Bifonazole as a topical antifungal agents has been shown by several clinical studies and it is equal or superior to the comparable antifungal imidazoles tested. It has fewer side effects and has the distinct advantage of a single daily dose treatment[58].

Analogues of bifonazole are **6b** and **6c** in which the biphenyl moiety was modified. **6c** has been shown to be comparable in its activity to bifonazole against *Candida albicans* and *Candida sp*.[59], while **6b** has a higher activity than bifonazole in the treatment of these same diseases [60].

Clotrimazole, 1-(O-chloro-α,α–diphenylbenzyl) imidazole **6d**, is a tritylimidazole in which the benzene ring carries a chlorine substituent. It

was synthesized by the Bayer AG in 1972 [61]. It has been shown to have a broad spectrum of antimicrobial activity against dermatophytes, pathogenic yeasts, filamentous and dimorphic fungi, as well as against some gram-positive bacteria. Studies have shown that **6d** required only a very short contact time in order to achieve maximum inhibitory activity[62] It substantially inhibits the uptake and intracellular pooling of leucine, lysine and other aminoacids in the absence of glucose [63].

Clotrimazole **6d** was shown to be orally active in early *in vivo* studies but problems with toxicity and side effects directed the development towards topic applications. The efficacy in the treatment of experimental fungal infections decreases as a function of time[64]. A progressive decline in serum concentrations of the drug after administration over several days has not been observed. This means a high metabolic stability and a long half life. Other problems following oral administration [65] are unacceptable high incidences of gastrointestinal disturbances, as well as hepatic and adrenal changes.

Clotrimazole **6d** has been proven to be effective and safe in the topical treatment of a variety of fungal infections. It is as effective as hystatin in the treatment of superficial *Candida* infections. Clotrimazole **6d** has been shown to be also active in the treatment of oral Candidiasis.

1.3. Inhibitory activity of anticancer drugs on Aromatase.

The biosynthesis of steroids occurs in the gonads where sexual steroids are produced and in adrenals where glucocorticoids and mineralcorticoids are synthesized. However, extra glandular production of some steroids also takes place in peripheral tissues. For example, aromatase, which converts androgens into estrogens has been identified in a wide variety of tissues.

A number of clinical situations are documented in which steroid hormones, either in normal amounts or when produced in excess play a role in the pathogenesis of diseases. Thus, inhibiton of the steroid-producing enzymes is a valuable means of treating these conditions. Until recently, however, there were relatively few inhibitors available that were specific for any one steroidogenic enzyme. Most of these compounds inhibit steroid hydroxylation and interact with the Cytochrome P-450 component of the enzymes.

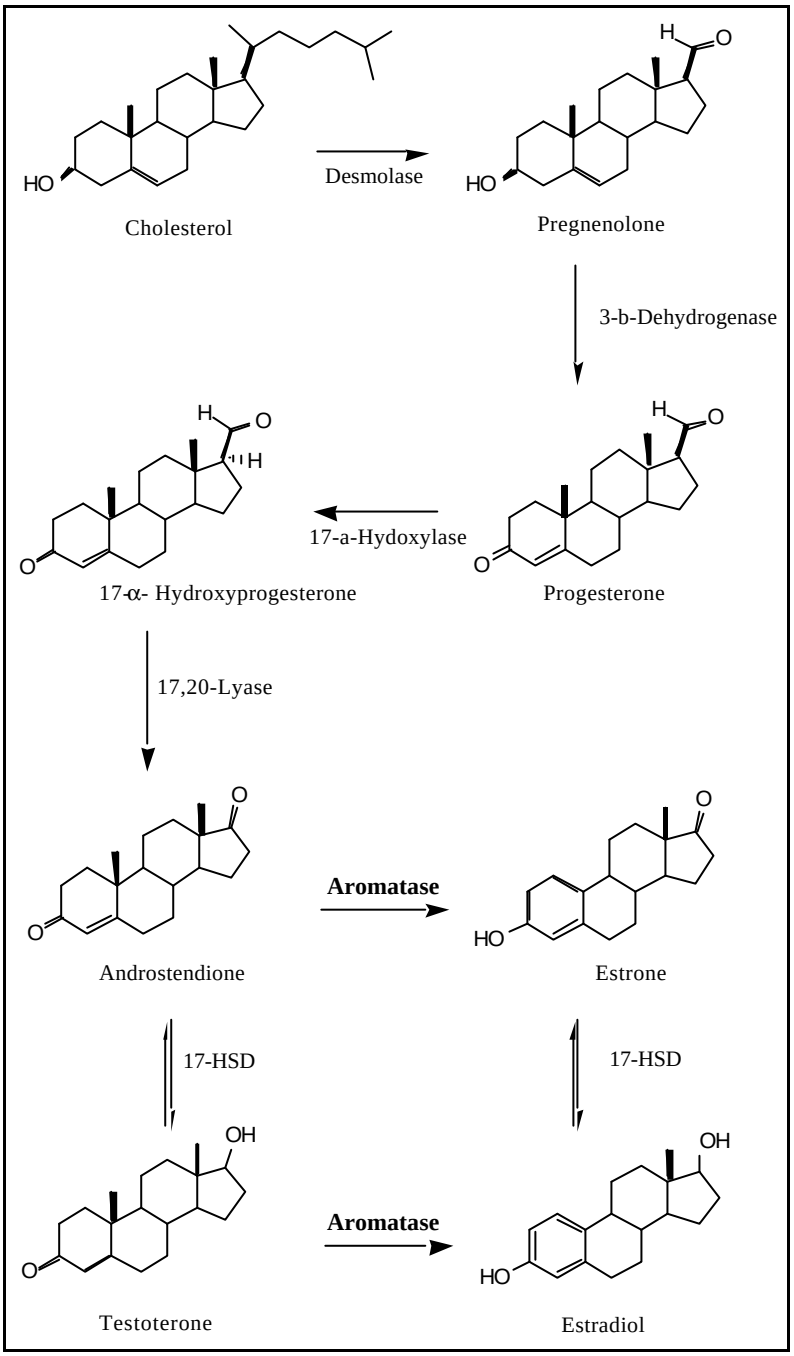
In the last few years, several compounds have been identified that selectively inhibit aromatase. Since estrogens are important in a variety of physiological processes and diseases such as gynaecomastia, precocious puberty, and endometrial and breast cancer - the leading cause of death among women[66] with approximately 40000 deaths per years in the U.S.A. alone[67] , selective inhibitors of aromatase are proving useful for both investigational and therapeutic purposes [68].

Basic and clinical data suggest that human breast cancers can be divided into hormone-dependent and hormone-independent subtypes, the former accounting for one-third of the over 100,000 new cases diagnosed in the USA each year, and even being more prevalent in postmenopausal women [69]. It was envisaged that an effective inhibition in the biosynthesis of estrogens may be useful for controlling the amount of circulating estrogens and, consequently, of estrogen-dependent disorders [70,71].

1.3.1. The Enzyme Complex Aromatase.

The aromatization of C19-steroids (androgens) on the way to C18-steroids (estrogens) constitutes the last and most important step in the biosynthetic pathway from cholesterol to estrogens (Scheme 1.2). This is performed by the enzyme complex aromatase (estrogen synthetase), consisting of a flavoprotein NADPH dependent-cytochrome P-450 reductase that transfers electrons from NADPH (nicotinamide adenine dinucleotide) to the terminal enzyme, and a specific form of the cytochrome P-450 enzyme system, known as aromatase cytochrome P-450, which is the protein involved in the specific recognition and binding of C-19 steroid substrates.

It catalyzes the multistep oxidative reaction sequence leading to aromatization of the ring A of the steroid [72]. Aromatase, along with other steroidogenic enzymes such as the cholesterol side-chain cleavage enzyme (desmolase), 21-hydroxylase, 11β-hydroxylase, 18-hydroxylase, 17α-hydroxylase, and 17,20-lyase, form part of the subgroup of cytochrome P-450 enzymes.



Scheme 1.2: Biosynthesis of androgens and estrogen.

These enzymes are characterized by a heme-iron group, which activates molecular oxygen. A review addressing the mechanicistic aspect of oxidative reactions catalysed by the P-450 enzymes with particular relevance to steroidogenesis has been reported[73].

Selective inhibition of this ultimate step in estrogen biosynthesis by specific inactivators of aromatase may soon become a useful therapeutic

tool for controlling pathological conditions associated with endogenous estrogens, such as breast and endometrial cancer [74-84], and benign prostatic hyperplasia [85-87]and this by reducing their levels without affecting production of other physiological steroids.

Aromatase, therefore, has important functions in female development and reproduction. In humans, it is produced in the ovaries and here first in the theca cells and then in much greater abundance in the granulosa cells of the developing follicle [88]. During pregnancy, the enzyme is produced in the syncytiotrophoblast of the placenta. In the male, aromatase is present in the Leydig cells of the adult testes [89]. Estradiol produced by the testes is thought to be involved in regulating androgen biosynthesis and the proliferation of the Sertoli and Leydig cells. In early development, local production of estrogen in the brain has been shown to be essential for sexual differentiation of the male phenotype. Central aromatization is necessary for the manifestations of many kinds of sex behavior, neuroendocrine and developmental responses of several species.

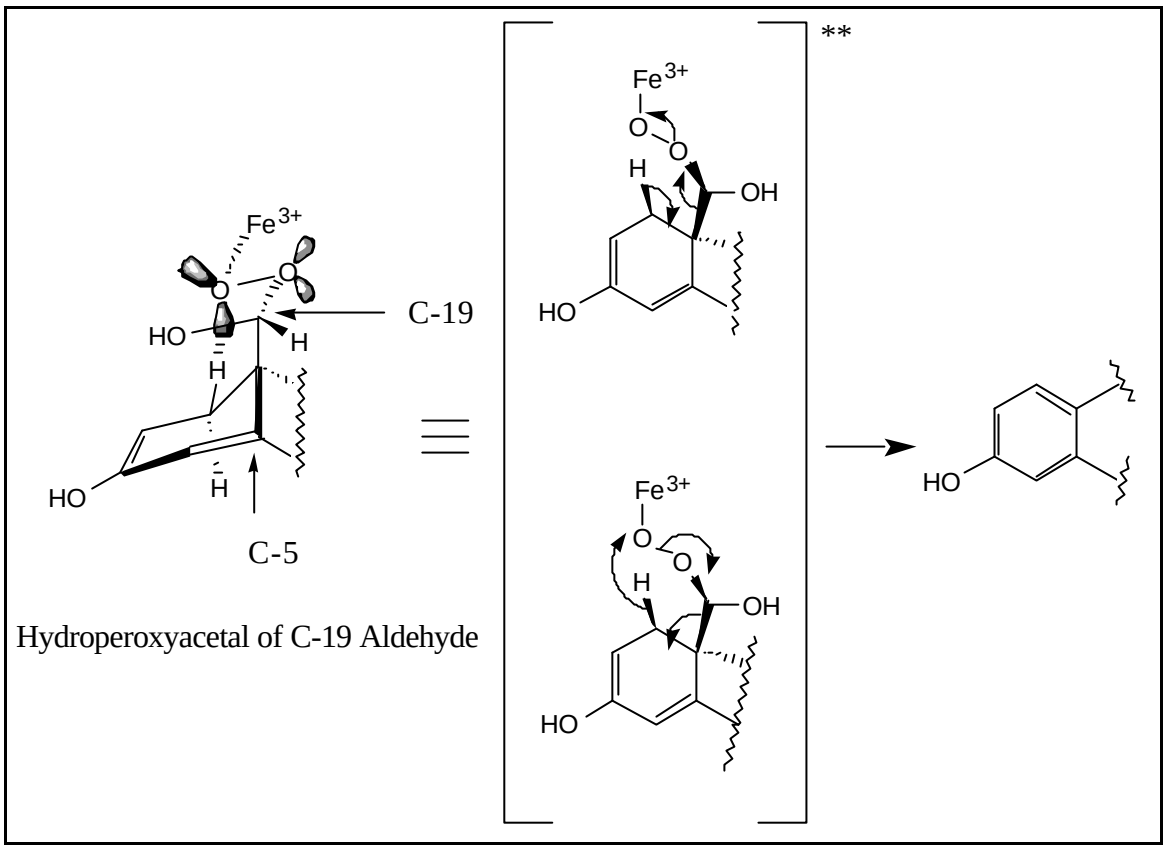
In addition, aromatase is formed in a number of other tissues throughout the body. The most important sites of non-gonadal estrogens are muscle and adipose tissue [90], where production increases with age in both sexes. Peripheral aromatization is the main source of estrogens in post-menopausal women [91].

1.3.2. Enzyme properties.

Aromatization of androgens to estrogen occurs *via* a series of reactions. The enzyme aromatase catalyzes the formation of aromatic C18 estrogenic steroids (estradiol and estrone) from C19 androgen precursors (testosterone and androstenedione), containing the 3-keto-D4 grouping in ring A of the steroid nucleus.

The process (Scheme 1.3) involves three enzymatic hydroxylation [92-96] which are promoted by the ability of the prosthetic group (heme iron porphyrin complex) of the aromatase to activate dioxygen for insertion into nonactivated C-H bonds. The first two occur at the C-19 methyl group, followed by the attack at C-4 by an enzyme nucleophilic group. *Endo* shift of the C-4 - C-5 double bond and of the peroxy link to the heme of the cytochrome and elimination of the C-19 methyl group as

formic acid results in the formation of the enzyme-bound intermediate[93] (scheme 1.3).



Scheme 1.3: Proposed mechanism for the aromatisation of the C-19 Aldehyde intermediate *via* hydroperoxyacetal.

This intermediate collapses to an aromatized product *via* elimination of the 1β-H and enolisation of the resulting keto-diene moiety which releases the estrogen and simultaneously regenerates the unchanged and active free enzyme[95,96].

Whether the third hydroxylation occurs at C-19, C-1 or at C-2 of ring A (as previously hypothesized) [97-100], is still unclear and the stereochemical outcome of the elimination of the 1- and 2- hydrogens are still matters for debate. Recent communications, however, confirm the intermediacy of the C-19 aldehyde , which is then attacked by the (heme-iron)-bound hydroperoxy group to give a hydroperoxy acetal, which collapses to generate the aromatized product and formic acid *via* the concerted loss of the 1β-H and the cleavage of the C-10 -C-19 bond, followed by the enzyme assisted loss of the 2β-hydrogen [101-107]. Regardless which mechanism will eventually emerge as the one best

describing the aromatization of androgens, any hypothesis which provides the basis for designing compounds which selectively inactivate this process will have served its purpose [93].

1.4. Steroidal and irreversible inhibitors [108].

Compounds that interfere with the aromatase enzyme activity may be classified as reversible or irreversible inhibitors. An attractive approach to the irreversible inactivation of aromatase is the use of steroidal compounds possessing latent reactive functionalities which are unmasked at the enzyme's active site.

The first selective aromatase inhibitors reported were C-19 steroids[109]. These compounds were substrates analogues and exihibited typical properties of competitive inhibitors. They included 1,4,6-androstatriene-3,17-dione **7** [109], 4-hydroxyandrostene-3-17-dione (4-OHA) **8** [110] and 4-acetoxyandrostenedione **9** [111] (Fig. 1.13)

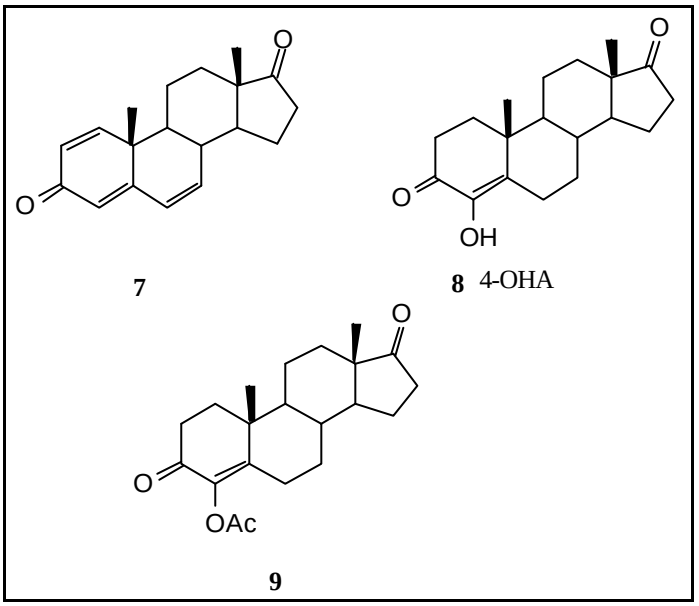
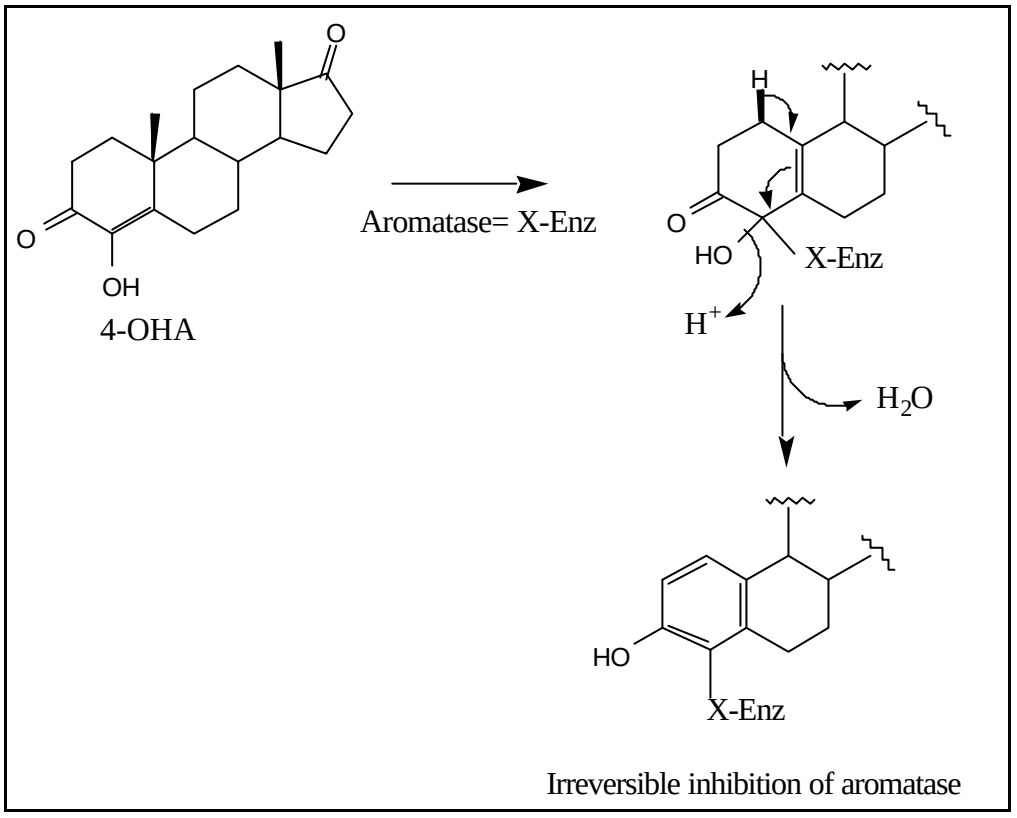


Figure 1.13: Irreversible inhibitors of Aromatase.

Interestingly, some of these inhibitors have been found to cause inactivation of the enzyme[112] and appear to be functioning as mechanism-based inhibitors. While not intrinsically reactive, inhibitors of this type are thought to compete rapidly with the natural substrate and subsequentely interact with the active site of the enzyme. They bind either very tightly or irreversibly to the enzyme and are thus causing its

inactivation.[113]. Because of their binding to the active site, these inhibitors should be quite specific and should also have lost effects *in vivo* as a result of inactivating the enzyme. Thus, the continued presence of the drug to maintain inhibition is not necessary and the chance of toxic side effects, therefore, will be reduced. The inactivation of Aromatase by 4-OHA **8** can be envisaged to result from the redirection of the elimination reaction by the enzyme-bound intermediate as shown in scheme 1.4 with the hydroxy group in position 4 (the latent alkylating group), followed by rapid protonation and loss of water, instead of the normally departing enzyme nucleophile. Enolisation then occurs to aromatize the steroid ring A and inactivation results due to the inability of the enzyme to release the steroid product (scheme 1.4).



Scheme 1.4: mechanism of irreversible inhibition of aromatase by 4- OHA **8.**

Inactivation of aromatase by the potent inhibitor **8** was demonstrated following preincubation of the compound for various lengths of time with microsomes from human placenta or rat ovaries in the presence of NADPH. After removal of the compound, a time dependent loss of enzyme activity was observed, which followed pseudo-first order

kinetics[112]. This inactivation of the enzyme can be prevented, if high concentrations of the substrate are present during the reaction. Thus, binding of [6,7^{3}H] 4-OHA **8** to aromatase purified from human placenta can be prevented by preincubating the enzyme with androstenedione. This finding also suggests that the inhibitor interacts with the enzyme at the same site as the substrate and at its active site.

Other steroidal aromatase inhibitors have been shown to cause inactivation. 7α-substituted androstenedione derivatives have been studied, several of which cause inactivation of aromatase [114, 115]. The covalent nature of the binding of 7α-(4'amino)phenyltio-1,4 androstadienedione (7α-APTADD) **10** (Fig. 1.14) to aromatase was demonstrated by several methods.

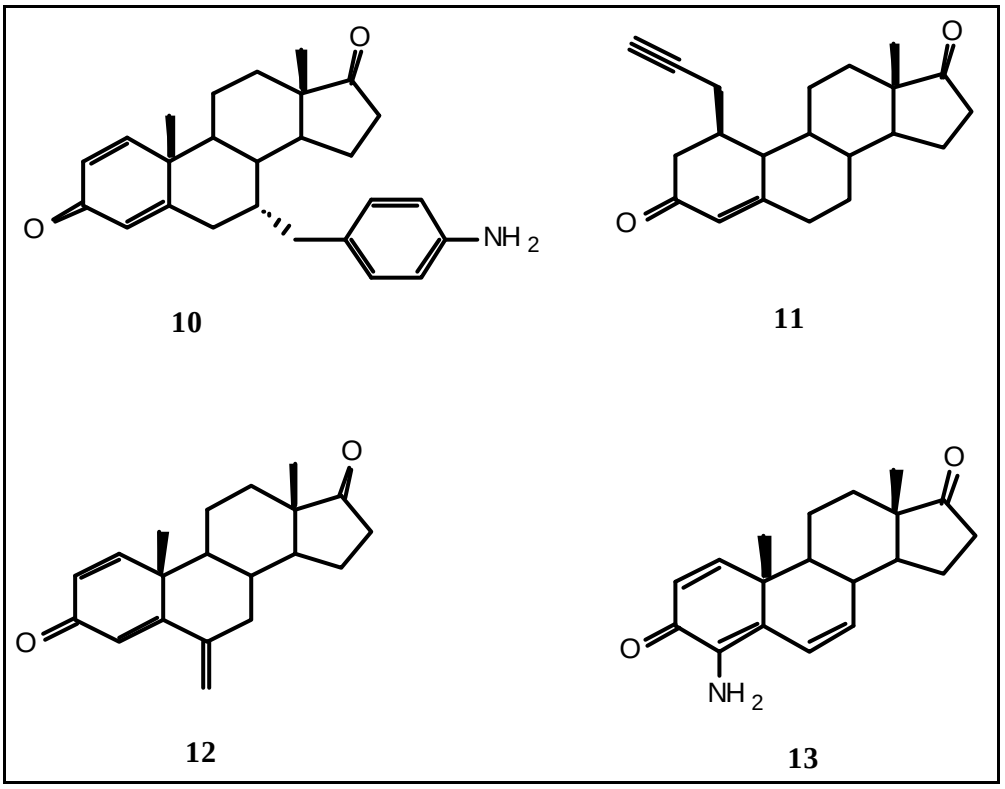


Figure 1.14: Latest generation of irreversible inhibitors of Aromatase

Among several C19 acetylenic analogs of androstenedione designed as mechanism-based or enzyme-activated inhibitors, the 10-(2-propynyl)estr-4-ene-3,17-dione (MDL 18962) **11** has been reported being the most potent aromatase inhibitor [116] (Fig. 1.14). **11** has significant and long lasting biochemical and pharmacological activity *in vivo*.

Two newer compounds which demonstrated biological activity are 6-methylen-androsta-1,4-diene-3,17-dione (FCE 24304) **12** or Examestane[117] and 4-aminoandrosta-1,4,6-triene-3,17-dione (FCE 24928) **13** [118] (Fig. 1.14) which cause inactivation of aromatase.

13, named Minamestane, is an orally active, irreversible aromatase inhibitor without any intrinsic androgenic activity[119]. The *in vivo* and *in vitro* activity of **13** has been compared to that of FCE 24304 **12** (exemestane) and 4-OHA **8** (formestane). No effect was observed on the 5α-reductase and cholesterol side chain cleavage activity and the compound showed no significant affinity for androgen and estrogen receptors.

1.5. Non-steroidal and reversible inhibitors.

The number of structurally distinct non-steroidal Aromatase inhibitors is rapidly growing, and the biggest class still are the azole containing analogues. The diversity of active structures contaning the azole moiety continues to expand, thanks to the ingenuity of chemists and the tolerance of the target enzyme for alternate substrates.

Aromatase is inhibited by non-steroidal compounds such as aminoglutethimide 3-(4-aminophenyl)-3-ethylpiperidine-2,6-dione **14a** (AG) and its analogues **14b-d** (Fig. 1.15).

This compound was first introduced as an anticonvulsant but its use was restricted when it was realized that the drug causes adrenal insufficiency. Aminoglutethimide **14a** was the first aromatase inhibitor used in the treatment of metastatic breast cancer[120] in post menopausal women but it is far from being an optimal drug[121-123].**14a** has a chiral center at C(3) of the glutarimide ring. The *R*-and *S*- enantiomers have very different activities toward aromatase inhibition, the *R*-isomer being 36 fold more active[124-125].

AG **14a** is also an inhibitor of another P-450 enzyme, responsible for the cholesterol side chain cleavage (desmolase)[126] and thus the conversion of cholesterol into pregnenolone. Its inhibition thus reduces the level of corticosteroid production. Patients treated with AG **14a** must therefore receive hydrocortisone replacement therapy in order to counteract this effect. AG **14a** shows effects to the central nervous system

(NCS) producing drowsiness and ataxia. To overcome these side effects, many others analogues have been synthesized as shown in figure 1.15.

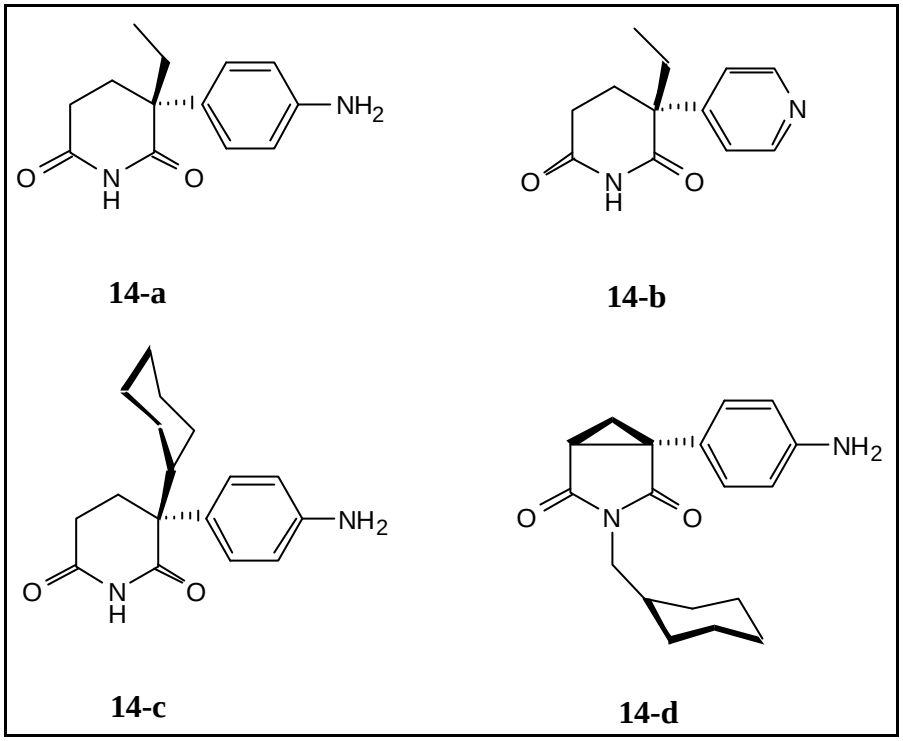


Figure 1.15: Aminoglutethimide **14a** and its analogues **14 b-d**.

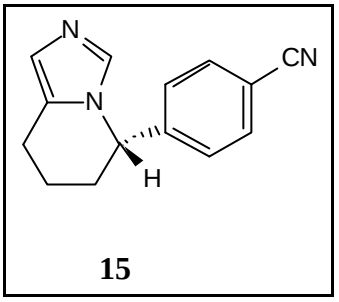
The 4-pyridyl analogue (*R*)-3-ethyl-(4-pyridyl)-piperidine-2-6-dione **14b** has been developed as a selective inhibitor of aromatase [127]. It does not inhibit desmolase and does not produce the CNS side effect of AG **14a** [128]. It is now in the last step of clinical trials in the U.K.

Recently other analogues of AG **14a** possessing an improved selectivity profile and enhanced potency e.g. (*S*)-(+)-3-(4-aminophenyl)-3-cycloexyl-piperidine-2,6 dione **14c** [129] and (1*R*,5*S*)-(+)-1-(4 aminophenyl)-3-cycloexylmethyl-3-azabicyclo-[3;1;0]-hexane-2,4-dione **14d**[130] appeared in the literature as possible back-up for AG **14a**.

1.5.1. Fadrozole 15.

Fadrozole hydrocloride **15** [4-(5,6,7,8-tetrahydroimidazo[1,5-a] pyridin-5-yl) benzonitrile] monohydrocloride **15**, is a drug developed by Ciba Geigy (Fig. 1.16).

15 is an advanced representative of the new class of azoheterocyclic inhibitors of aromatase currently under clinical evaluation[131].



15

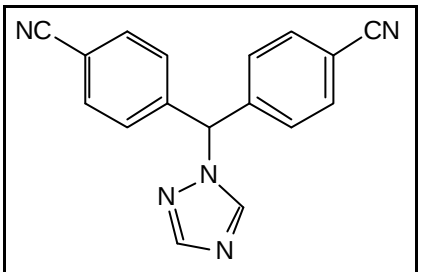
Figure 1.16: (*S*)-(-) Fadrozole **15**.

The pharmacological evaluation of Fadrozole hydrocloride **15** proves this drug to be a very potent inhibitor which effectively inhibits aromatase *in vivo* with an ED_{50} = 0.03 mg/kg[132] leading to a significant reduction of estrogen levels. The excellent selectivity for aromatase over desmolase supports the working hypothesis that the strong binding to iron is responsible for the higher potency of the imidazoles and that the complementarity of the inhibitor with the steroid binding site - while enhancing this potency- more importantly provides selectivity for aromatase over desmolase and other cytochrome P-450 enzymes[133].

Fadrozole **15** has a chiral centre in the benzylic position; the two enantiomers have been separated by chiral HPLC and the absolute configuration has been assigned by X-ray analysis of its corresponding salt with D-(-)-tartaric acid[134]. The *S* - configuration was assigned to the (-)-enantiomer that was shown to be responsible for the high aromatase inhibitory activity of fadrozole [134].

The cyano function in the para position of the phenyl ring it is an essential structural requirement for the high inhibitory activity in fadrozole and its analogues [133]. In fact it seems possible that this polar group might mimic one of the carbonyl functions of the steroidal inhibitors, either that of the A or that of the D ring [134].

Ciba Geigy further developed the 1,2,4 - triazole derivatives CGS 20267 **16**[135], the most potent aromatase inhibitor *in vivo* reported by the end of 1993 (Fig. 1.17).



16

Figure 1.17: CGS 20267 **16**

It is important to note that, in this case the heterocyclic moiety is directly linked to benzhydrilic position.

1.5.2. Vorazole 17.

Vorazole, 6-[(4-chlorophenil)(1H-1,2,4-triazole-1-yl)]-1-methyl-1H-benzotriazole] **17** has been recently developed[136] as a non steroidal aromatase inhibitor, (Fig. 1.18).

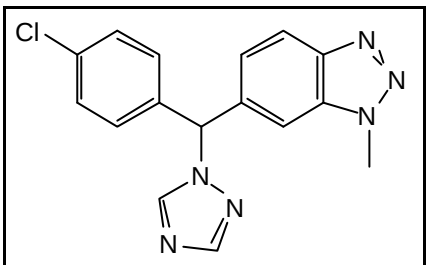


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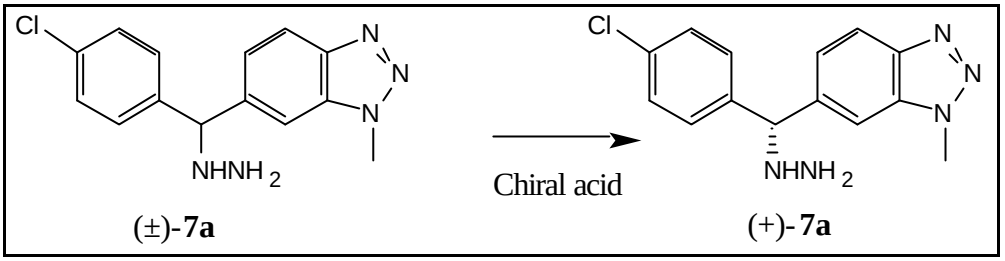
Figure 1.18: Vorazole **17**.

In vitro and *in vivo* studies with animal models demonstrated high potency and specificity and thus its potential clinical usefulness in humans. It has also been demonstrated that almost all aromatase activity resides in the dextroenantiomer (R83842). The (+)-and (-)-enantiomers were separated by chiral semipreparative HPLC column. Studies both in animals and humans showed an almost complete inhibition of *in vivo* human aromatase activity[138].

In May 1994, Janssen Pharmaceuticals patented the synthesis of both enantiomers[139]. The procedure is based on the classical resolution of **17a**[139] (±)-6- [(4-chlorophenyl- hydrazinomethyl) -1-methyl- 1,4-benzotriazole] using a chiral acid (Scheme 1.5) and subsequent

transformation of the appropriate, enantiomerically pure hydrazine intermediate into (+)-Vorazole **17** [139].



Scheme 1.5: resolution of (±)-6-[(4-chlorophenyl-hydrazinomethyl)-1-methyl-1,4-benzotriazole] **17a** using a chiral acid.

1.5.3. Derivatives of 1[(benzo(b)furan-2-yl)-arylmethyl] imidazole 18.

Substituted 1[(benzo(b)furan-2-yl)-phenylmethyl]imidazoles have been demonstrated to be new potent, selective inhibitors of female rat aromatase *in vitro* and *in vivo* by Menarini, Florence[140]. The general structure of **18** is shown in figure 1.16.

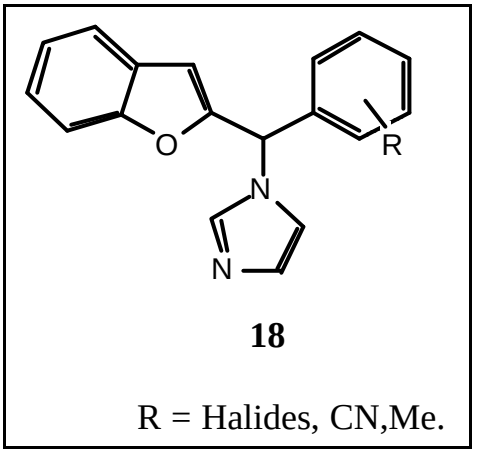


Figure 1.16: General structures of Menarini Aromatase inhibitors **18.**

These compounds with an IC_{50} <10 nM show very similar potency as the best existing non-steroidal reversible aromatase inhibitors, such as fadrozole, vorazole and CGS 20267. Furthermore **18** was shown to be about 3 orders of magnitude more potent that AG **14a**.

In table 1 some of this compounds with their relative activity[140] are reported.

In vivo tests of compounds **18a-g** proved to reduce the estradiol level from 98% to 82% and also to have higher activities than AG **14a**.

Compound	R	IC_{50}(nM)	Relative Potency
18a	4-CN	3	2436
18b	4-Cl	7.7	949
18c	4-F	7.3	1001
18e	2-Me	7.9	925
18d	4-Me	8.8	831
18e	2-Cl	19.5	375
18f	4-Ph	242	30.2
14a	AG	7310	1

Table 1.1: relative potencies of compounds **18a-g** in comparison with the AG **14a**.

The 4-fluoro derivatives **18c** have been separated by analytical chiral HPLC into the two enantiomers and their activity has been tested: the (+)-enantiomer was 15 fold more active than the (-)-enantiomer[141a], and the 4-cloro derivative **18b** has been separated in single enantiomers by fractional crystallization of their dibenzoyltartrate salt, and also for this molecule the (+)-enantiomer was 15 fold more active than the (-)-enantiomer[141b].

Molecular Modelling using the approches of Furet et al.[142] for the study of the binding of fadrozole to Aromatase provided a satisfactory explanation for these observations[141].

1.6. Aim of this thesis.

Aim of the thesis was the synthesis of enantiopure benzhydryl azoles. This target was chosen both for its industrial importance where products of this kind are under development as racemates, and because it is considered a chemistry field not yet explored in depth. In order to achieve this goal three different strategies were chosen (Fig. 1.17):

1) Synthesis and separation of diasteroisomers.
2) Enantioselective synthesis
3) Crystallization of diasteroisomeric salts.

Enantioselective syntheses and the separation of diasteroisomers were investigated in greater detail as compared to the crystallization of diasteroisomeric salts.

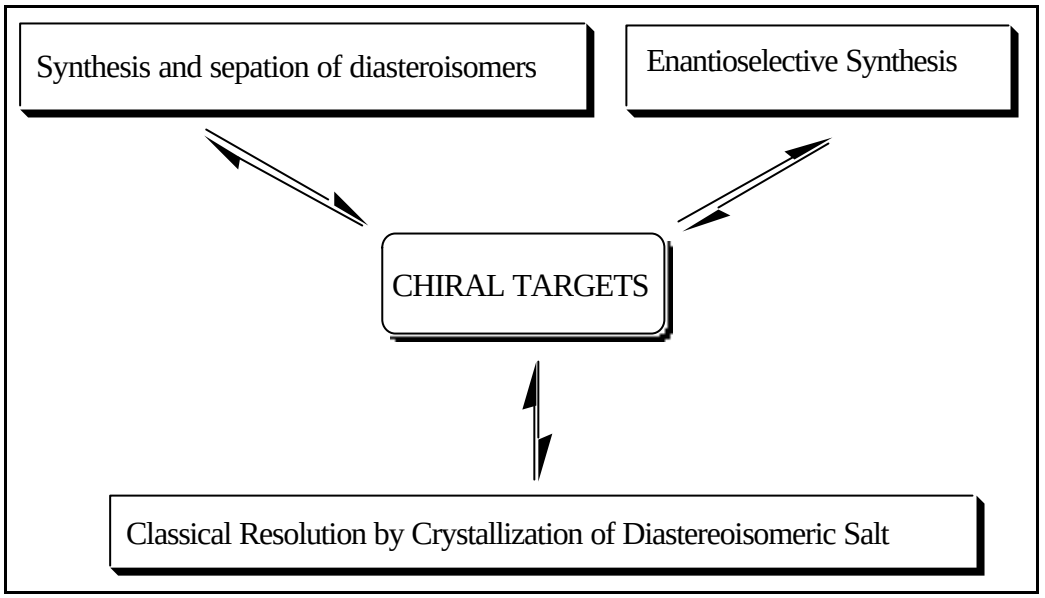
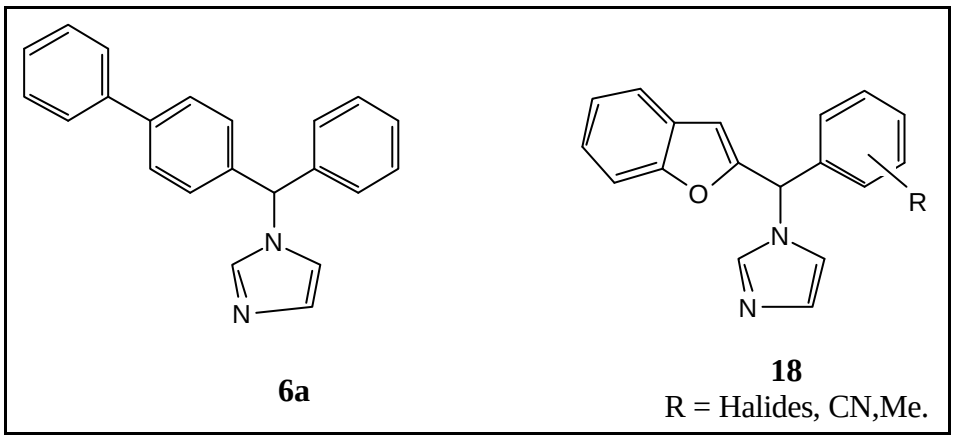


Figure 1.17: Synthetic approaches to enantiopure compounds.

The described work was focused on two different classes of drugs: (a) bifonazole **6a** and its analogues (antifungal agents) and (b) the Menarini anticancer drug **18** (aromatase inhibitor) (Fig 1.18).



6a

18
R = Halides, CN,Me.

Figure 1.18: Bifonazole **6a** and Menarini anticancer drugs **18**.

Neither enantioselective syntheses nor general methods to obtain these classes of compounds in enantiopure form are reported in literature; with the exception of a patent for Vorazole **17a**[139].

These apparently similar two classes of compounds showed a completely different chemical behavior during our investigation as will become clear in the following chapters. Structurally quite simple, these compounds contain only one chiral centre in form of a tertiary carbon bound to three different aromatic substituents. The system is prone to form very stable carbocations[143] under acidic conditions, furthermore the molecules do not posses any site of functionalization which would allow the formation of separable diasteroisomers. The following paragraphs will show the consequences of these features on the employed general strategies.

1.6.1. Approaches based on diasteroisomers.

This approach consists in the synthesis of molecules having a "removable anchor" group, such as a carboxylic acid, amine or alcohol, that could be bound to another molecule with defined chirality in order to form a pair of diasteroisomers. The different physico-chemical properties of the diasteroisomers can be used to separate them by chromatography or by crystallization. After the separation it is necessary to remove the anchor group and to generate the molecule with the defined chiral centre under such mild conditions as to avoid any possible racemization of the single isomer obtained from the separation. The last step is the removal of the anchor from the molecule to generate the free enantiomer of the drug. Again it is necessary to find the mildest conditions in order to avoid racemizations of the final compouds (Fig. 1.20).

Our target molecules are unfunctionalized and we have designed two different functional groups to be introduced as anchors, either on the aromatic moieties or on the imidazole ring (Fig. 1.19).

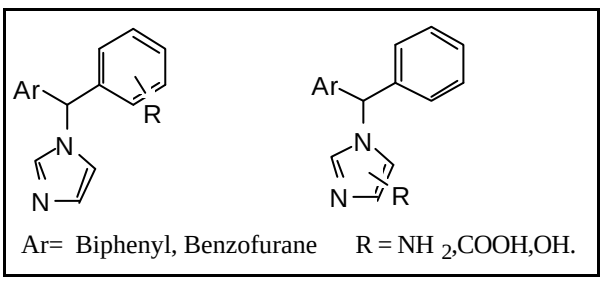


Figure 1.19: Possible positions of anchor groups.

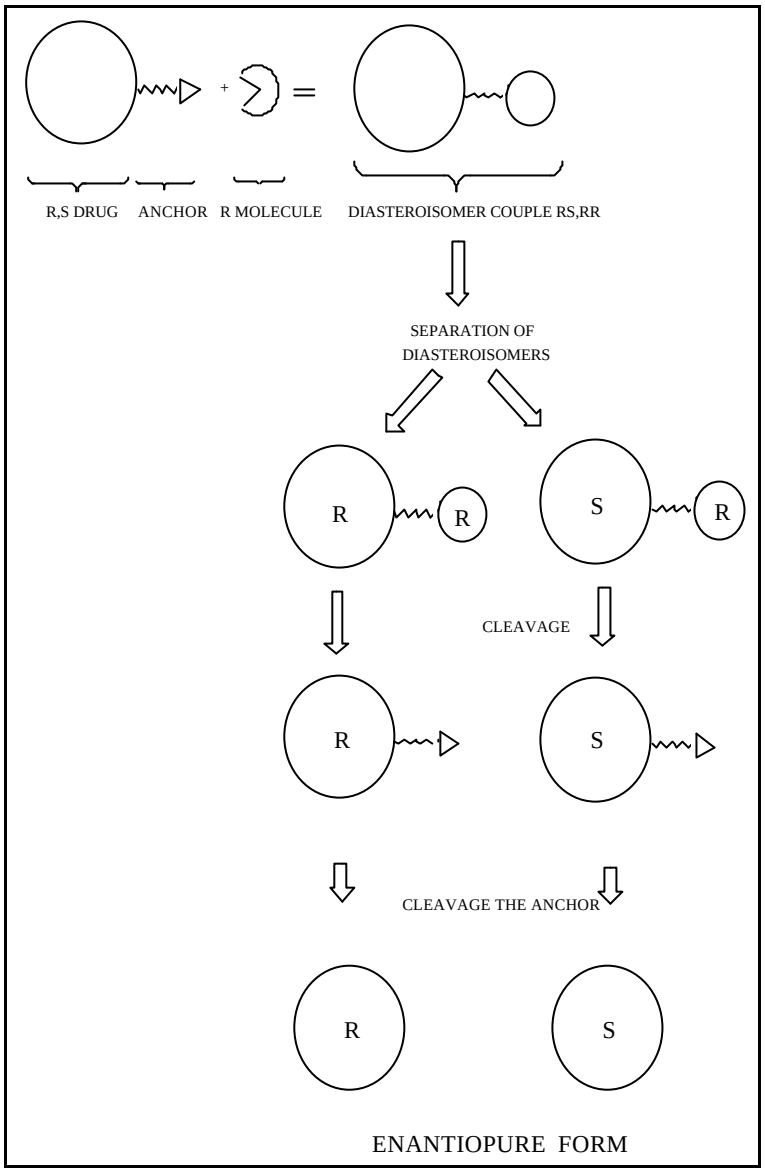
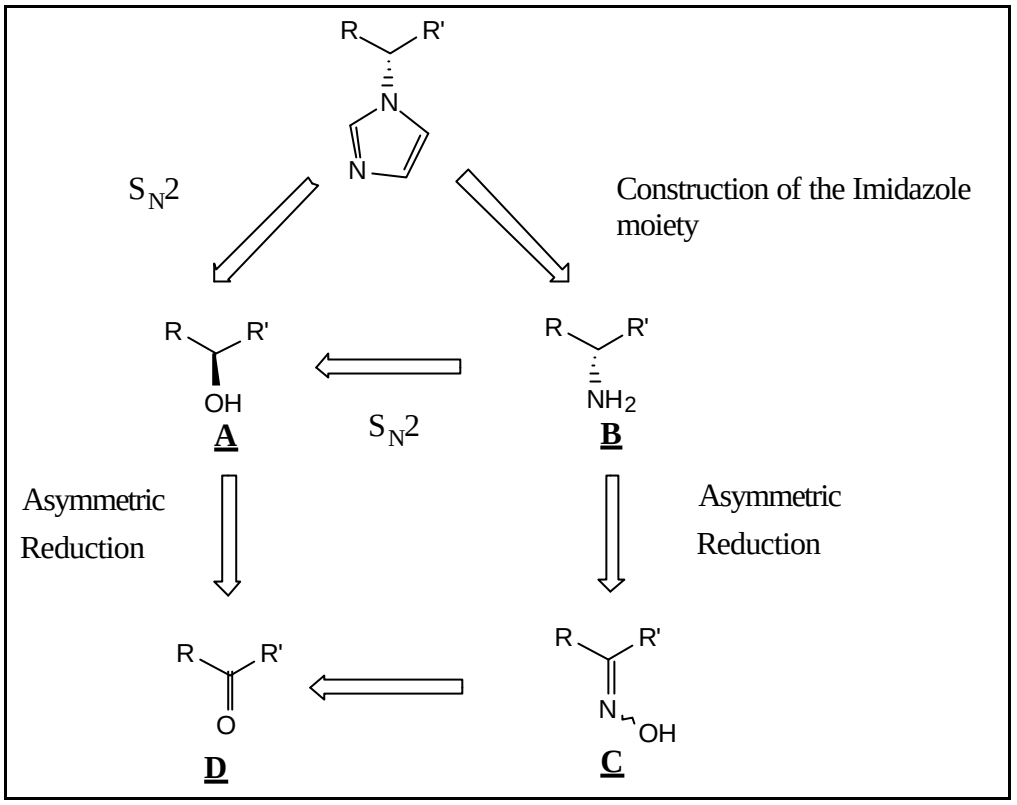


Figure 1.20: Generic procedure used for the production of single enantiomers from a racemic mixture *via* the separation of diasteroisomers.

1.6.2. Approaches towards Enantioselective Synthesis.

Retrosynthetic analysis (Scheme 1.6) of the target molecules based on the easiest synthetic and general pathways results in two possible key intermediates:

1) Enantiopure Alcohol **A**.
2) Enantiopure Amine **B**.



Scheme 1.6: Retrosynthetic analysis

The enantiomerically pure targets could be synthesized using two possible enantiopure precursors such as the alcohol **A** or the amine **B**. Starting from the enantiomerically pure alcohol **A** a clean S_N2 reaction with imidazole would lead to the final product. Enantiomerically pure amine **B** could be synthesized from the enantiomerically pure alcohol **A** by an S_N2 reaction of the appropiate synthons or by asymmetric reduction of the prochiral oxime **C**. Amine **B** is a key intermediate since the imidazole can be synthesized directely from it. The real general precursor for all of the above strategies however is the achiral ketone **D** which by asymmetric reduction would lead to the enantiomerically pure alcohol **A**.

1.6.3. Resolution of Diasteroisomeric Salts by Crystallization .

This is the oldest method to produce enantiopure compounds. It is also the most useful procedure used in industry to produce enantiopure chemicals. A classical example is the resolution of amines with enantiopure tartaric acid, the industrial methodology to produce enantiopure amines. The method is apparently easy: the racemic amine is

solubilized in hot ethanol or an other appropriate solvent in presence of the resolving agent (chiral acid). The diasteroisomeric salts are formed, and if the choice of solvent and resolving agent is correct, only one diasteroisomeric salt will precipitate. After separation of the diasteroisomeric salt by filtration, followed by decomposition with aqueous base, the free enantiomer is usually extracted in organic solvents. This procedure, only apparently easy, is often called "art" because the best solvent and resolving agent can not be predicted *a priori*.

2. Theoretical Discussion of Techniques.

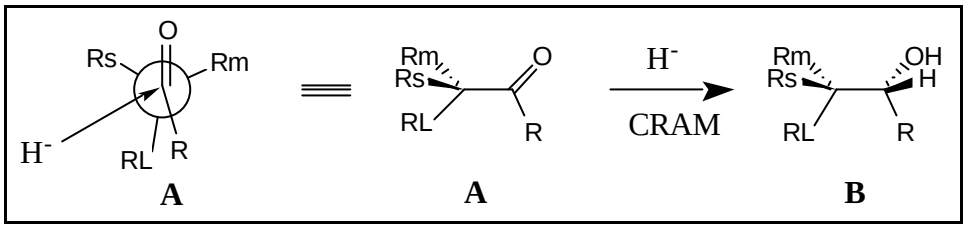
2.1 Synthesis of enantiopure alcohols by asymmetric reduction of prochiral ketones

2.1.1.Introduction

The reduction of carbonyl groups in aldehydes and ketones to the corresponding alcohols is ubiquitous in organic synthesis. Since the first report of such a reduction by diborane more than half a century ago, metal hydride reagents have became of major importance as reagents of choice for these synthetic transformations. The opportunities for variations in the metal, ligands, counterions and reaction conditions have helped to overcome most problems encountered regarding the stereo-, regio-or chemo-selectivity in these reactions.

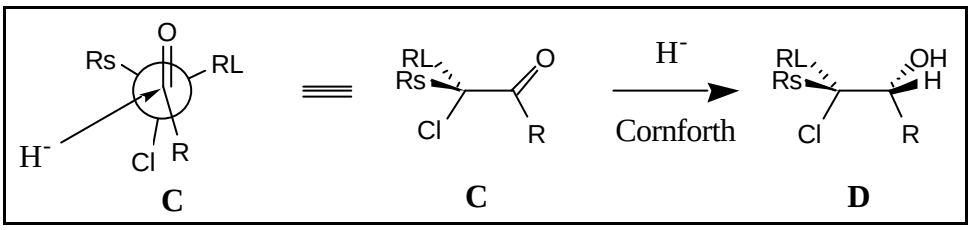
2.1.2. Stereoselectivity.

The origin and magnitude of stereoselectivity observed in the reduction of chiral carbonyl compounds has long been an area of intense theoretical and practical studies. Efforts have concentrated largely on the 1,2-asymmetric induction that occurs in the hydride addition to a carbonyl group flanked by an asymmetric centre. Cram's rule was formulated to rationalize the results of nucleophilic addition to aldehydes and ketones contaning non polar groups[1]. The most stable conformation **A** (Scheme 2.1) was assumed to arise by minimization of the interaction between the largest group R_L and the carbonyl group which was coordinated to the approaching reagent. Addition then occured preferentially from the side of the smallest substituent R_S rather than the larger medium sized group R_M. The outcome of the reduction of ketone **A** to alcohol **B** following Cram's rule is illustrated in Scheme 2.1. This rule enabled a large body of experimental results to be correlated, however its theoretical base was subsequentely shown to be flawed.



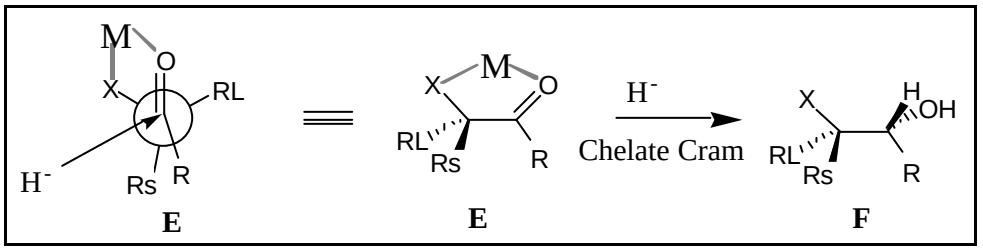
Scheme 2.1: Reduction of ketones: Cram's rule.

The results in the reduction of α-halo-ketones or aldehydes were anomalous and led to Cornforth's dipolar model **C** (Scheme 2.2), in which the dipoles of the carbonyl group and the carbon-halogen bond were in an antiperiplanar arrangement. Reduction then proceeded from the less hindered side of the ketone **C** leading to alcohol **D**[2] (Scheme 2.2).



Scheme 2.2: Reduction of ketones: Cornforth model.

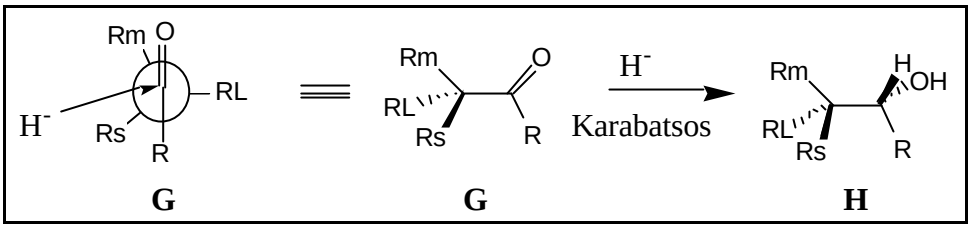
The possibility of chelation in case the α-substituent X was an hydroxy, alkoxy or amino group was covered by Cram's cyclic or chelate model **E** [3](Scheme 2.3). The chelating group X and the carbonyl group were eclipsed and coordinated to the metal M. The reduction occurs again from the less hindered side. This model has been widely used to rationalize the diasteroselectivity in reduction of ketones **E** when chelation is important, depending on the nature of the substituent X and the metal ion M (Scheme 2.3).



Scheme 2.3: Reduction of ketones: Cram's chelate model.

Informations regarding the ground state conformation of carbonyl compounds demonstrated that the conformation in which one bond is

eclipsing the carbonyl group is energetically favored. This led Karabatsos to propose an alternative model[4]. Calculation suggested that the most favored conformation **G** (Scheme 2.4) would have the medium size group R_M of the ketone **G** eclipsing the carbonyl group, and addition of the hydride would occur from the side of the less bulky substituent R_S to give the alcohol **H** (Scheme 2.4).



Scheme 2.4: Reduction of ketones: Karabatsos model.

A comparison of the other possible transition state with this conformation allowed the magnitude of diasteroselectivity to be correlated with the experimental results.

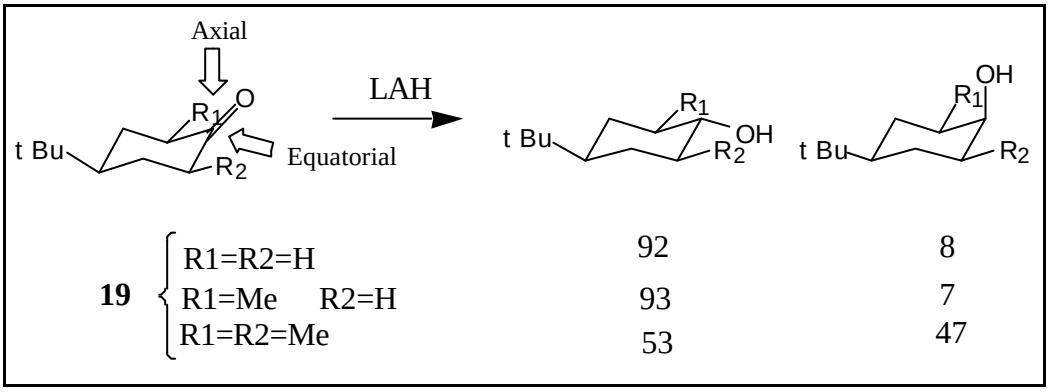
The most influential contribution towards the interpretation of 1,2 asymmetric inductions in carbonyl group reductions was that of Felkin[5]. Attention was directed for the first time to the structure of the transition state, which was assumed to be very similar to that of the substrate. Torsional strain caused by interactions between the partially formed hydride-carbonyl bond and the full bonds at the adjacent centre was assumed to cause attack perpendicular to the carbonyl group plane and staggered to the largest or more electronegative group R_L. The angle of approach was later revised by the Burgi-Dunitz trajectory [6a-c], derived from crystallographic studies. It placed the incoming hydride much closer to the substituent R_S. This interaction was decisive for the selection of this transition state over the alternative one, in which the position of the small R_S and the medium R_M would be exchanged.

Importantly and in agreement with the Felkin model, if two alkyl substitutions are present, the more stable conformation has the larger group perpendicular to the carbonyl group and points the remaining alkyl group away from the incoming nucleophile.

2.1.2.1. Cyclic Carbonyl Compounds.

The stereochemistry and the mechanism of reduction in cyclic ketones by metal hydride reagents provided an unique opportunity for the comparison of experimental results with theoretical expectations. The models proposed by Cram, Cornforth and Karabatsos described above were inadequate for explanations of the stereochemical results. The effect of steric influences, torsional and electronic factors in the reduction, its stereochemical outcome and position of the transition state have also been intensely reviewed.

Felkin identified torsional effects in the cyclohexanone **19** whose reduction accounted for the observed stereoselectivity. Minimization of this torsional effect in the absence of steric hindrance led to the predominance of axial attack (Scheme 2.5)[7].



Scheme 2.5: Reduction of cyclohexanones **19**.

The eclipsing interactions between the incoming nucleophile and the bond α to the carbonyl group are more important, for any given trajectory, for an equatorial direction of attack.

The differences are clearly illustrated in the Newman projection of cyclohexanone **19** (Figure 2.1).

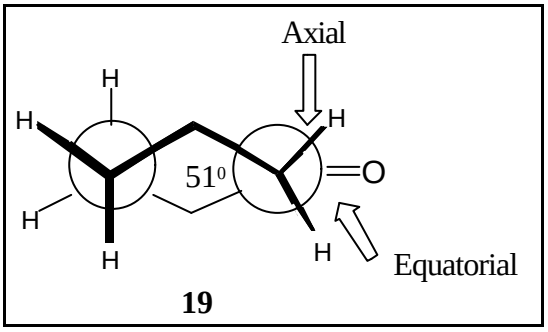


Figure 2.1: Newman projection of cyclohexanone **19**.

The dramatically enhanced axial selectivity demonstrated in the reduction of cyclohexenone as compared to cyclohexanone was explained by the different internal dihedral angle which is reduced from 51^0 in cyclohexanone **19** to 22^0 in cyclohexenone **20**. This in turn produced a dramatic change in torsional interaction regarding both the axial or equatorial attack, as clear from the Newman projection **20** (Fig. 2.2).

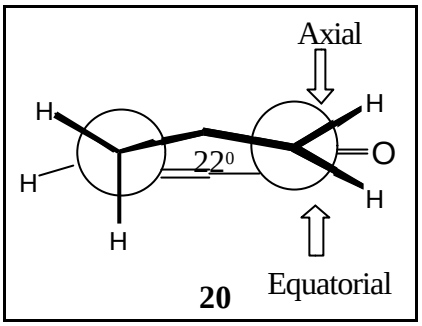


Figure 2.2: Newman projection of cyclohexenone **20**.

This conformation explained also the absence of stereoselectivity in the reduction of conjugated cyclohexenones.

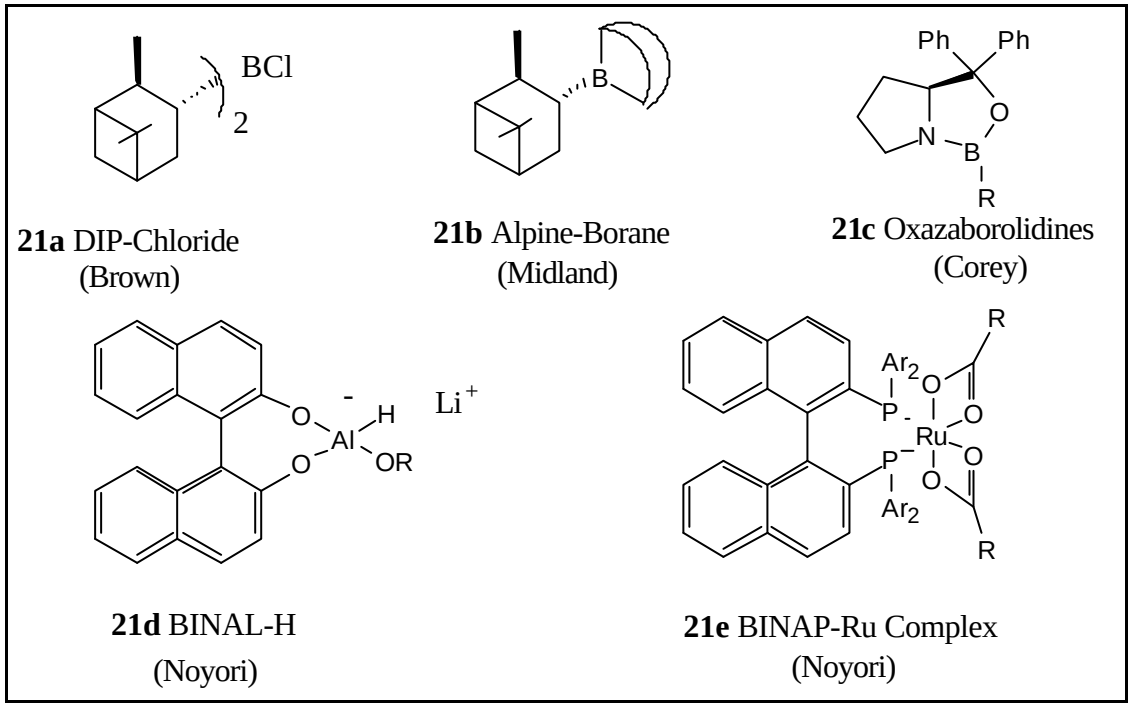
2.1.3. Chiral Reducing Agents.

The reduction of prochiral ketones to optically active alcohols is one of the most useful asymmetric reactions.The alcohols produced by such a process may serve as chiral building blocks at the beginning of a synthesis, or they may serve as the desired end products. In either case, the proper selection of the asymmetric reducing reagent is critical, and several factors may influence the choice of reagent. In choosing an asymmetric reducing agent, one often seeks to mimic the action of enzymes.Thus one would like to use reagents that are catalytic, selective, yield products with high enantiomeric purity and behave predictably with other functional groups. In addition to the selectivities often associated with enzymes, it is also desirable to employ reagents that are effective on a wide range of substrates and allow the convenient isolation of the products which should be available in both enantiomeric forms. Clearly no single reagent can be expected to have all these desirable properties. Thus much efforts have been focused towards developing reagents that provide useful compromises.

An asymmetric reducing agent need not be catalytic if it is inexpensive and can be easily obtained. The cost factor may be further reduced if the chiral ligand can be recycled. Chiral modifications of metal hydride reagents with a wide variety of chiral auxiliaries for the asymmetric reduction of carbonyl compounds have been studied intensively during the last three decades. However, asymmetric reducing agents developed in the early stage of this programme commonly provided only low optical induction in the asymmetric reduction of prochiral ketones[8a-c]. A wide variety of asymmetric reducing agents has now become available for such application. Unfortunally, no one particular reagent is effective for all the different classes of ketones.

Presently there are more than twenty promising reagents[9], however only during the last decade some of these have found a wide application.

At the moment, only five of them are extensively used in asymmetric reduction: (Figure 2.3):**21a** diisopinocamphenyl-chloroborane, IPC_2BCl, (DIP-Chloride^{TM}); **21b** B-isopinocampheyl -9- borabicyclo - [3.3.1] nonane, (Alpine-Borane^{TM}); **21c** oxazaborolidines; **21d** aluminium complexes derived from optically active 1,1- Binaphthyl-2,2'-diol, such as BINAL-H; and **21e** BINAP-Ru complexes.



21a DIP-Chloride (Brown)

21b Alpine-Borane (Midland)

21c Oxazaborolidines (Corey)

21d BINAL-H (Noyori)

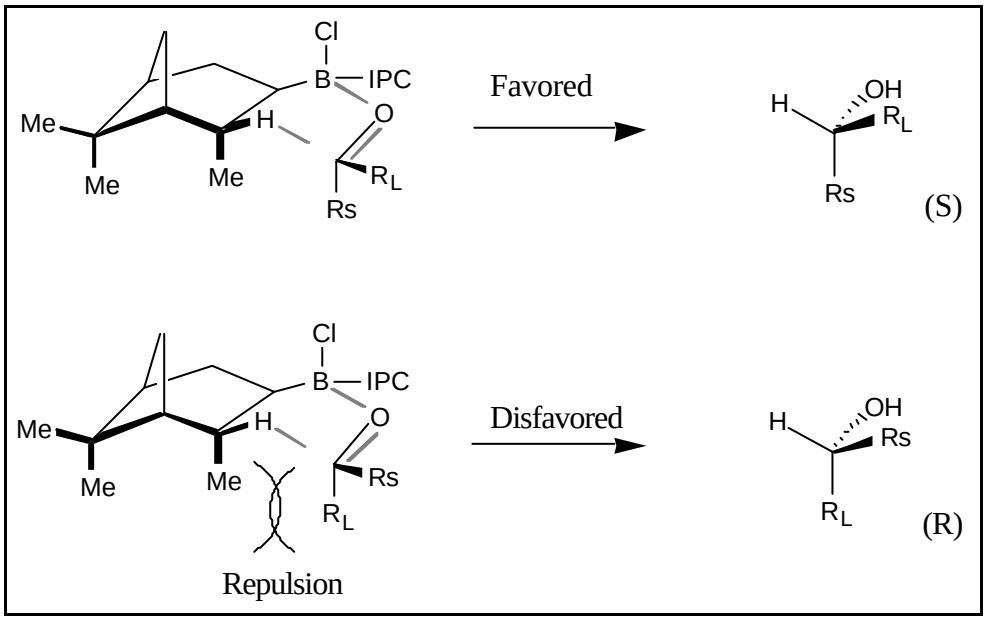
21e BINAP-Ru Complex (Noyori)

Figure 2.3: Chiral Complex **21a-e** for the asymmetric reduction of prochiral ketones.

Brown's DIP-Chloride **21a**, Midland's Alpine-Borane **21b** and Noyori's Binal-H **21d** are used in stoichiometric quantities whereas Corey's Oxazoloboridines **21c** and Noyori's Binap-Ru complexes **21e** are used catalytically.

2.1.3.1. Mechanism of Asymmetric Reduction of Prochiral Ketones.

It is interesting to point out that every chiral reducing agent forms a different chiral complex or transition state with the corresponding prochiral ketones. The proposed mechanism for the reduction of prochiral ketones with **21a** (DIP-chloride) and **21b** (Alpine-borane) is similar[10]. Midland proposed that the reduction proceeds *via* a bimolecular, six membered cyclic, boat like transition state in which the tertiary β-hydrogen (in *syn*-planar B-C-C-H conformation) eclipsed with the boron atom, is transferred to the carbonyl carbon. In the transition state, the smaller alkyl group R_S is in the axial position and *syn*-facial with the methyl group of pinene, while the bulky alkyl group R_L prefers an equatorial position far away from the pinanyl methyl group (Scheme 2.6).



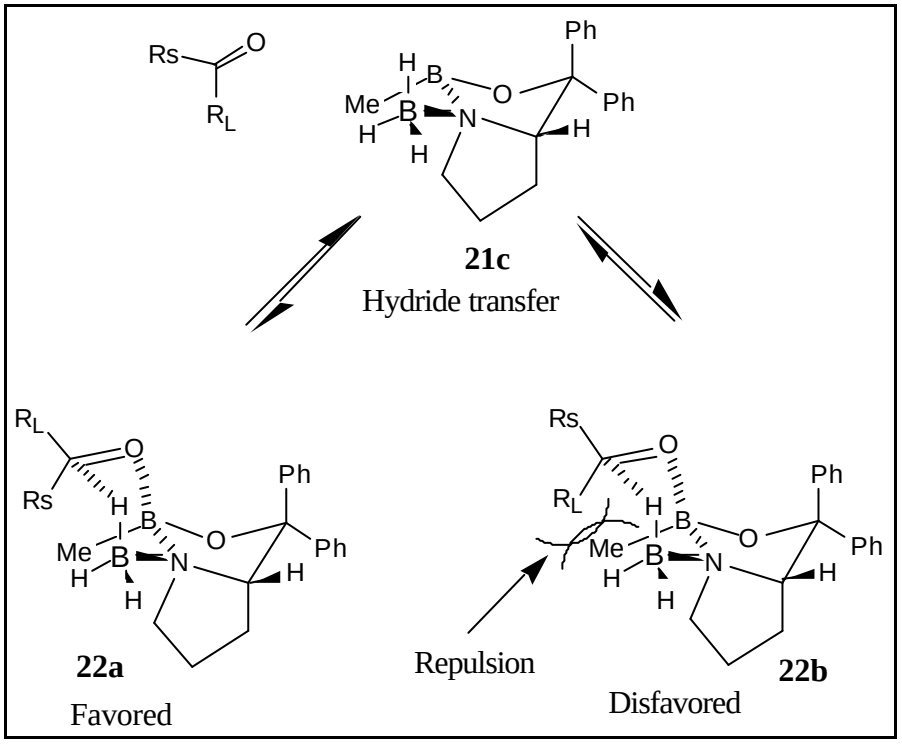
Scheme 2.6: Mechanism and transition state for the chiral reduction of ketones with DIP chloride **21a**

This approach clearly explains the formation of the *S*-isomer from the (-) - DIP chloride **21a** and the *R*-isomer from the (+) - DIP chloride **21a** unless the steric bulk of the carbonyl moiety is changed, as in the case of *t*-butyl phenyl ketone or in the case of acyl silanes.

A different mechanism has been proposed for Corey's oxazaborolidines[11]**21c.** It constitutes an alternate chair transition state assembly to explain the origin of the observed enantioselectivity in oxazaborolidine catalyzed reductions of prochiral ketones.

According to this model (Scheme 2.7), the 1,3 diaxial interaction between the R_L and R_S substituents of the ketones and the oxazaborolidone methyl group differentiates between the two diasteroisomeric transition states **22a** and **22b**, leading to the major *R*-product and the *S*-enantiomers as minor products[12].

Corey's oxazaborolidines can be used in catalytic amounts (5% molar with respect to the ketone); the source of hydride is BMS or BH_3 -THF in an equimolar ratio with the ketone. A complete investigation of the reaction conditions has been reported by the Merck Sharp and Dohme department of process research[12].



Scheme 2.7: Mechanism and transition state for the chiral reduction of ketones with Oxazaborolidine **21c**.

Chiral phosphine complexes of late transition metals in a low oxidation state catalyze enantioselective reductions in a homogeneous phase. Noyori developed an interesting approach for the enantioselective reduction of prochiral α-substituted ketones employing an enantiopure Ru (II) complex with 2,2'-Bis-(diaryl phosphino) 1,1'Binaphtyl (BINAP) **21e/d**.

These organometallic catalysts are endowed with functionality and axial chirality and allow a differentiation between diasteroisomeric transition states differing in energy of only 10 KJ/mol. Such molecular catalysts are not only able to accelerate the reaction rate, but also to control the stereochemical outcome of the reaction in an absolute sense.

BINAP **21e**, a fully arylated, C2 symmetrical chiral diphosphine, is one of the most effective chiral ligands that have been designed[13] (Fig. 2.4).

BINAP ligands can accommodate a wide variety of transition metals to form conformationally unambiguos seven membered chelate rings containing only sp^2 carbons.

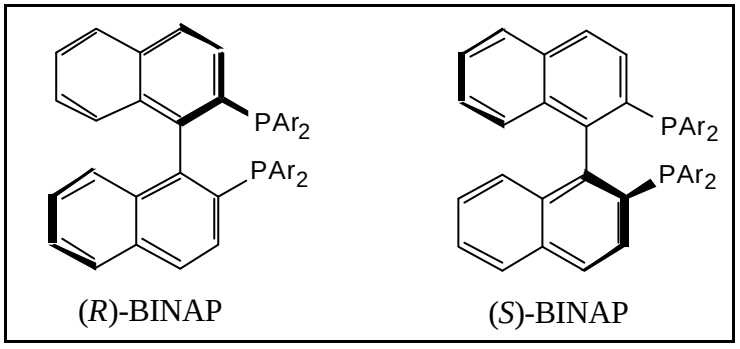


Figure 2.4: *R*- and *S*-BINAP **21e**.

The single crystal X-Ray analysis of certain square planar or octahedral BINAP complexes indicates that the seven membered rings have a higly skewed configuration that provides a distinct chiral microenviroment in which the phosphophenyl groups are oriented into axial and equatorial directions[14] (Fig. 2.5).

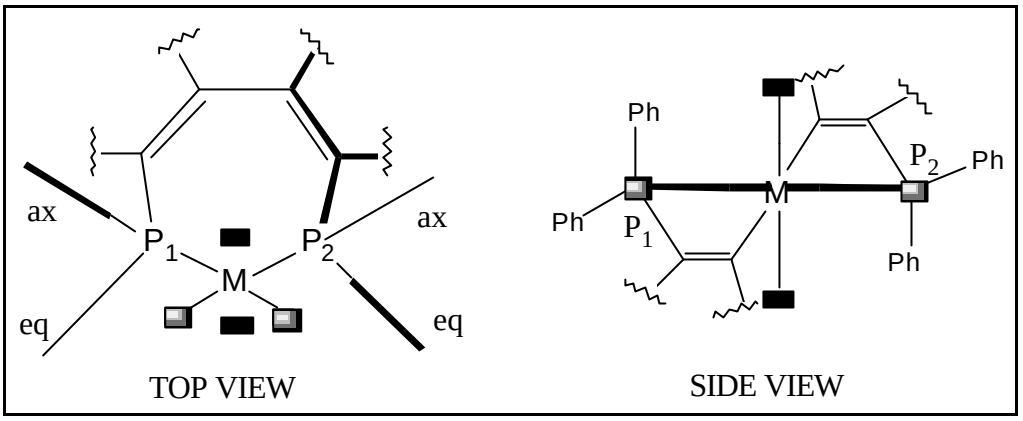


Figure 2.5: Orientation of posphophenyl groups in BINAP

Thus, spatial characteristics exert a significant influence on the substrate coordination sites allowing for exceptional efficiency in BINAP catalysis.

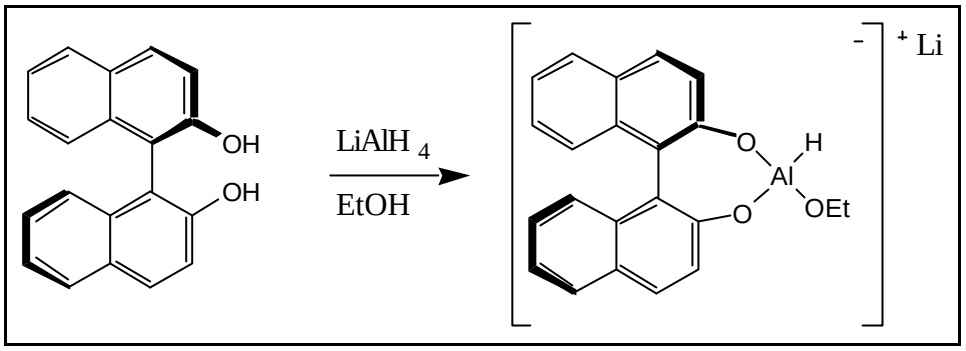
A wide variety of functionalized ketones can be converted into their respective optically pure alcohols *via* homogeneous hydrogenation in the presence of halogen-containing Ru-BINAP catalysts in alcoholic media. The reaction proceeds in a higly enantioselective and predictable fashion. A general mechanism which describes this selective process involves initial coordination of the carbonyl oxygen and the α or β adjacent heteroatom (such as nitrogen, oxygen or halogen) to create a five to seven membered metal chelated ring complex prior to hydrogen transfer.

In the BINAP-Ru catalyzed reaction, diverse polar functionalities facilitate the hydrogenation of the neighboring carbonyl group and allow the efficient enantioface differentation. The halogen containing complexes of type RuX_2-BINAP, the dimeric triethylamine complex or dicarboxylate complex, Ru(OCOR)2-Binap, may be used as catalyst, depending on the ketonic substrates. Methanol or ethanol are the solvents of choice.

The reaction with a substrate:catalyst molar ratio of 2200:230 proceeds with a reasonable rate at room temperature using an initial hydrogen pressure of 40-100 atm.

Noyori, in 1979, reported also the use of optically pure 2,2' dihydroxy-1,1'- binaphthyl as $LiAlH_4$ chelating agent. The 1,1' Binaphthol itself has an axial asymmetry and possesses an extremely high ability of chiral recognition[15].

BINAL-H **21e** is prepared by modification of $LiAlH_4$ with (*R*)- or (*S*)-binaphthol and one equivalent of ethanol (Scheme 2.8).



Scheme 2.8: Formation of BINAL-H **21e**.

Complex hydride reagents of the type $LiAlH_n(OR)_{4-n}$ are known to exist in a complicated equilibrium with a variety of disproportionated and aggregated species[16]. However, the stereochemical outcome arising from the rigid, unique chiral conformation of this reagent is most economically rationalized by the mechanism involving a six membered, chelating transition state[17]. For example, in the transition state of the reaction of acetophenone and (*R*)-BINAL-H containing an ordinary R' group, the R'O oxygen acts as bridging atom because of its highest basicity among the three oxygens bound to Al. Therefore the chair conformation with axial-methyl and equatorial-phenyl groups **23a** is favoured over the diastereomeric transition state **23b** in accordance with the observed enantioselectivity[16] (Fig.2.6).

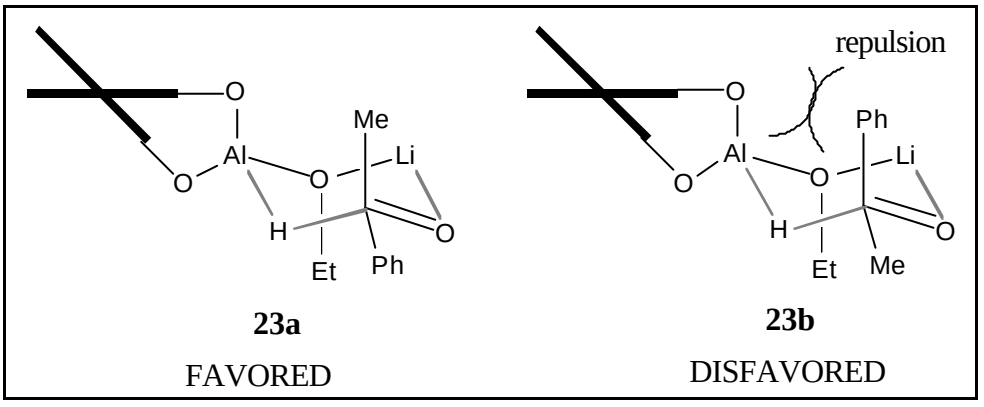


Figure 2.6: BINAL-H transition state **23a/b** in the acetophenon reduction.

The BINAL-H is one of the best chiral $LiAlH_4$ complex reported; many other examples are reported in the literature such as: LAH-Darvon-Alc (Alc=2*S*,3*R*-(+)-4dimethylamino-3-methyl-1,2-diphenyl-2-butanol)[18a-d] , LAH-MEP-ArOH (MEP = *N*-Methyl ephedrine; ArOH = 3,5-dimethylphenol)[19a-b], LAH-diamine[diamine(*S*)-2-(2,6xylidimethyl)-

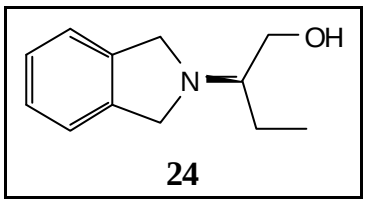
pyrrolidine][20], LAH-aminobutanol [(*S*)-4-anilino-3-(methyl amino) -1 butanol[21], LAH-DBP-EtOH[DBP=(*S*)-(-)10,10'dihydroxy,9,9'biphenylanthranyl][22], LAH-MEP-NEA (MEP=*N*-Methylephedrine,NE A*N*-ethylaniline)[23], LAH-MEP-EAP (MEP = *N*-Methyl ephedrine, EAP = 2-ethylamino aniline[24].

All the classes of chiral reducing agents shown above are used for the reduction of a wide variety of different classes of prochiral ketones. Unfortunally, however, none of them has never been used for the reduction of prochiral benzophenones or diaryl ketones.

In these ketones, both moieties linked to the carbonyl group have roughly the same size. Therefore, the chiral reducing agent fails to discriminate between the two faces.

To the best of our knowledge, only a small number of methods are reported in literature for the synthesis of enantiopure benzhydroles or diaryl methanoles. In particular: (a) asymmetric reduction by *Rodoporidinium toruloides*[25], (b) resolution of diasteroisomeric acetyl mandelate esters[26], (c) nucleophilic addition of aryl groups to aromatic aldehydes by organotitanium chelating agents [27]. A much more interesting approach has been reported by E. Brown in 1991[28]describing the use of the very interesting LAH complexing agent, (*R*)-(-)- (2)- (isoindoliny) butan-1-ol **24** (Fig.2.7) which will be described later.

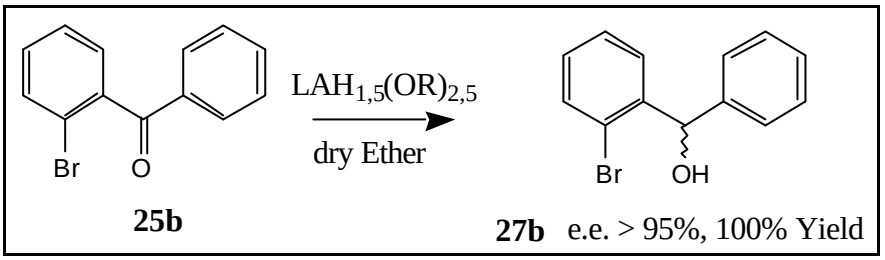
The major advantages of this chiral complexing agent are that the chiral amino alcohol is very cheap and available in both enantiopure forms.



24

Figure 2.7: (*R*)-(-)-2-(2-isoindolynil) butan-1-ol **24,** Brown's chiral amino alcohol for the asymmetric reduction of benzophenones.

An ortho-substituent in one of the aromatic rings seems to be essential for a good stereoselection in the asymmetric reduction of prochiral benzophenones with this chiral LAH complex. The ortho bromobenzophenone **25b** was reduced to the ortho-bromobenzhydrol **27b** with an enantiomeric excess > 95% e.e.and a chemical yield of 100% (Scheme 2.8).



25b **27b** e.e. > 95%, 100% Yield

Scheme 2.8: Chiral reduction of ortho bromobenzophenones **25b** by the Brown procedure.

The best molar ratio between LAH and the chiral ligand **24** is 1 to 2.5; no mechanistic hypothesis regarding the absolute stereochemistry of the alcohol has yet been reported by Brown.

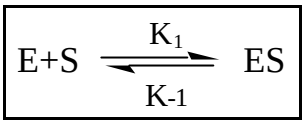
2.2 Synthesis of enantiopure alcohols by enzymatic resolution

2.2.1. Introduction

Enzymes are proteins, which catalyze numerous biological transformation *in vivo* . They are constructed from twenty natural amino acids. The relationship between the amino acid sequence and its catalytic activity is still impossible to predict. It is clear that enzymes represent a valuable class of catalysts for organic transformations and numerous organic reactions can be catalyzed in their presence. For organic synthesis it has to be decided whether an enzymatic approach towards the solution of a particular synthetic problem is more practical than a non-biological approach. In many instances enzymatic transformations represent only one alternative or improvement as compared to an existing chemical methodology. In some cases, however, enzymatic processes are more cost-effective than non biological methods and thus have clear advantages. Several large scale enzymatic processes used in industry (resolution of amino acids with acylase, transformation of pig insuline to human insulin catalyzed by trypsin, preparation of penicillin analogues with penicillin acylase, synthesis of optically pure fine chemicals etc) have demonstrated that enzymatic catalysts can be the best route to fine chemicals.

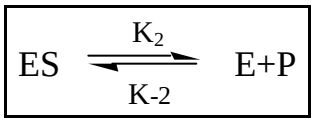
2.2.2. Enzyme kinetics.

Enzymatic reactions are as a whole multistage processes. The substrate S initially binds non-covalently to the enzyme E at a special site called the active site. The reversible complex of substrate S and enzyme E is called the Michaelis-Menten complex. It provides the proper combination of reactant and catalytic groups in the active site of the enzyme (equation 1):



Equation 1

In the active site, after the formation of the Michaelis-Menten complex, the chemical reaction step takes place and the enzyme substrate complex breaks down in a slower second step to yield the free enzyme E and the reaction product P (equation 2):



Equation 2

In this model, the second reaction is slower and therefore is rate limiting for the overall reaction. From this it follows that the overall rate of enzyme-catalyzed reactions must be proportional to the concentration of the ES complex. At any given instant in an enzyme catalyzed reaction, the enzyme exists in two forms, the free or uncombined form E and the combined form, the ES complex. At low [S], most of the enzyme will be in the uncombined form E. Under these conditions the rate will be proportional to [S] because the equilibrium of equation 1 will be shifted towards the formation of more ES as [S] is increased. The maximum initial rate of the catalyzed reaction (V_{MAX}) is observed when virtually all of the enzyme is present as ES complex and the concentration of E is extremely small. Under those conditions, the enzyme is "saturated" with its substrate, Further increases in [S] will not cause any increase in rate. After the ES complex breaks down to give the product P, the enzyme is free to catalyze the transformation of another substrate molecule. The

saturation effect is a distinct characteristic of enzyme catalyzed reactions and is responsible for the plateau observed in figure 2.8.

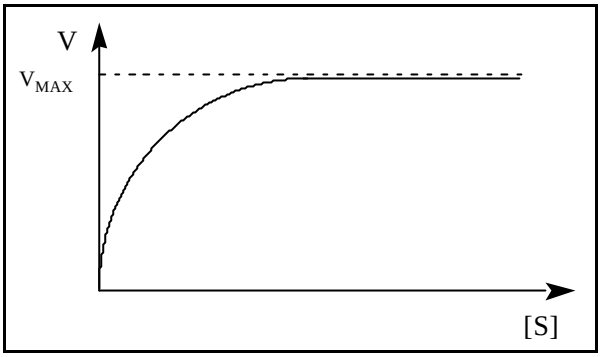


Figure 2.8: Reaction rate as a function of substrate concentration

When the enzyme is treated with a large excess of substrate, there is a phase called "pre-steady state". During this short period of time the concentration of the ES complex builds up, but the pre-steady state is usual too short to be easily observed. The reaction quickly achieves a steady state in which [ES] (and the concentration of any others intermediates) remains approximately constant over time. The measured V generally reflects the steady state even though V_0 is limited to the early part during the course of the reaction. To study quantitatively the relationship between substrate concentration and enzymatic reaction rate, it is necessary to make the following assumptions:

1) The breakdown process of ES is considered to be almost irreversible ($K_2 >> K_{-2}$) and during the early part of the reaction the concentration of the product [P] is negligible and thus the simplifying assumption can be made that K_{-2} is very small. The overall reaction thus is reduced to equation 3:

$$E + S \underset{K_{-1}}{\overset{K_1}{\rightleftharpoons}} ES \underset{K_{-2}}{\overset{K_2}{\rightleftharpoons}} E + P$$

Equation 3

From this assumption the rate of product formation is (equation 4):

$$v = K_2 [ES]$$

Equation 4

As [ES] in equation 4 can not be a measured experimentally, $[E]_0$ is introduced representing the total enzyme concentration (bound and free enzyme); [S] is considered costant because the amount of substrate bound to the enzyme at any given time is negligible as compared to the total concentration of S.

The steady state assumption proposes that the rates of formation and breakdown of ES are equal (equation 5):

$$K_1 [E] [S] = K_2[ES] + K_1 [ES]$$

Equation 5

Where $[E]= [E]_0-[ES]$.

Equation 5 is resolved leading to an expression for [ES] (equation 6):

$$[ES] = \frac{[E]_0 [S]}{\frac{K_2 + K_{-1}}{K_1} + [S]}$$

Equation 6

The value K_2+K_{-1}/K_1 is the Michaelis-Menten constant Km, and equation 6 becomes equation 7:

$$[ES] = \frac{[E]_0 [S]}{Km + [S]}$$

Equation 7

Now it is possible to change the [ES] in eq. 4 with the expression in the eq.7 leading to equation 8:

$$v = \frac{K_2 [E]_0 [S]}{Km + [S]}$$

Equation 8

This equation can be further simplified because the maximum velocity will occur when the enzyme is saturated and $[ES]=[E]_0$. V_{MAX} can then be defined as $K_2[E]_0$. Substitution into eq.8 leads to the Michaelis-Menten equation 9:

$$v = \frac{V_{MAX}[S]}{Km + [S]}$$

Equation 9: Michaelis-Menten equation

The Michaelis-Menten equation 9 expresses the rate equation for the enzyme catalyzed transformed of one single substrate.

2.2.3 Specificity

Selectivity constitutes the major synthetic value of enzyme catalysts. Because enzymes are large chiral molecules with a unique structure at the active site, they can be highly selective for certain types of substrate structures and reactions. Useful types of enzyme catalyzed reactions include the chemoselective reaction of defined functional groups in a given molecule. The reactions are:

Regioselective

Enantioselective with racemic substrates

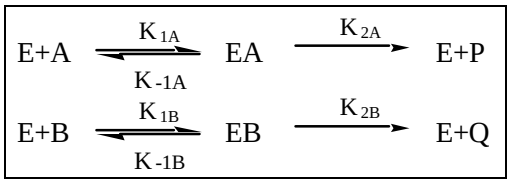
Enantioselective with prochiral substrates

Diasteroselective

All such selective reactions occur because during the reaction the prochiral or chiral reactants form diasteromeric enzyme transition state complexes that differ in transition state energy (G#).

2.2.3.1. Kinetic resolution of a racemate

In the kinetic resolution of a racemate the two enantiomeric substrates are competing for the same active site of the enzyme E. If A and B are two enantiomers, the reaction scheme is as follows (Scheme 2.9):



Scheme 2.9:

In figure 2.9 the transformation for two enantiomers is represented. They obviously have different transition state (G#) energies. If the difference in ΔG # is high, the enantioselection will be high.

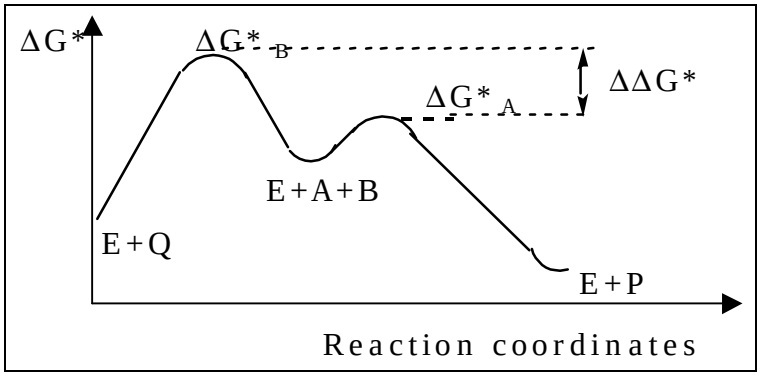


Figure 2.9: Reaction profile for the kinetic resolution of enantiomers.

The steady state or Michaelis Menten equation can be used to describe each reaction rate (equation 10 and 11):

$$v_A = \left(\frac{K_{CAT}}{Km}\right)_A [E]\,[A] \qquad \text{eq.10}$$

$$v_B = \left(\frac{K_{CAT}}{Km}\right)_B [E]\,[B] \qquad \text{eq.11}$$

Equation 10 and 11: reaction rates for two enantiomers.

The ratio of eq. 10 and eq.11 is therefore (equation 12):

$$\frac{v_A}{v_B} = \frac{\left(\frac{K_{CAT}}{Km}\right)_A [A]}{\left(\frac{K_{CAT}}{Km}\right)_B [B]}$$

Equation 12: ratio of reaction rates.

This analysis shows that the ratio of specifity constants $(K_{CAT}/Km)_A/(K_{CAT}/Km)_B$ determines the enantioselectivity of the reaction. These specificity constants are related to free energy terms expressed by $G^0 = -RT \ln K$.

The enantioselectivity of the reaction is related to the difference in energy of the diastereomeric transition states (see Fig.2.9) by equation 13:

$$\Delta\Delta G^* = (\Delta G_A^* - \Delta G_B^*) = -RT \ln [(Kcat/Km)_A / (Kcat/Km)_B]$$

Equation 13

In an enzyme-catalyzed kinetic resolution which proceeds irreversibly, the ratio of specificity constants also known as enantioselectivity value E can be further related to the extent of conversion C and the enantiomeric excess e.e. as shown[30] in equation 14. The parameter E is commonly used in characterizing the enantioselectivity of an enzyme catalyzed resolution.

$$E = \frac{\ln [(1 - C)(1 - ee_A)]}{\ln [(1 - C)(1 + ee_A)]} = \frac{\ln [1 - C(1 + ee_P)]}{\ln [1 - C(1 - ee_P)]}$$

Equation 14: Expression of E value.

The conversion C is expressed as $C = 1 - A+B / A_0+B_0$ and the enantiomeric excess $ee_P = P-Q / P+Q$; the concentrations are in Mol%.

Experimentally, equation 14 can be used to determine one of the three parameters if two are known from experiments. If the E value is known the equation can be used to predict the ee of the product or the remaining substrate at a defined degree of conversion.

In a graphic representation the enantiomeric excess (ee%) of product and substrate is shown as a function of the conversion C (%) for a given E value. In a normal experiment it is possible to follow both enantiomeric purities and to calculate with the equation 14 the E value. Generally, in order, to have a perfect kinetic resolution which can give enantiopure products and starting material at 50% conversion, the E value must be higher than 100. In cases of lower E values, only one enantiomer (always the remaining one) can be obtained enantiomerically pure.

2.2.4 Lipases.

Most lipases are classified as serine proteases which catalyze the hydrolysis of lipids to fatty acids and glycerol[31]. Unlike esterases, which show a normal Michaelis Menten behaviour, lipases display only little activity in aqueous solutions in presence of soluble substrates. A sharp increase in activity is observed when the substrate concentration is increased beyond its critical micellar concentration[32a-c]. The increased lipase activity at the lipid-water interface led to the suggestion that soluble lipases might undergo a conformational change -interfacial activation- at the oil water interface[33]. This conformational change at the interface is supported by the X-Ray structures of human[34a,b] and *Mucor miehei*[35a-c] lipases, phospholipase A_2[36a-b] and their complexes with inhibitors where the shift of a loop called "lid" over the active site is clearly shown.

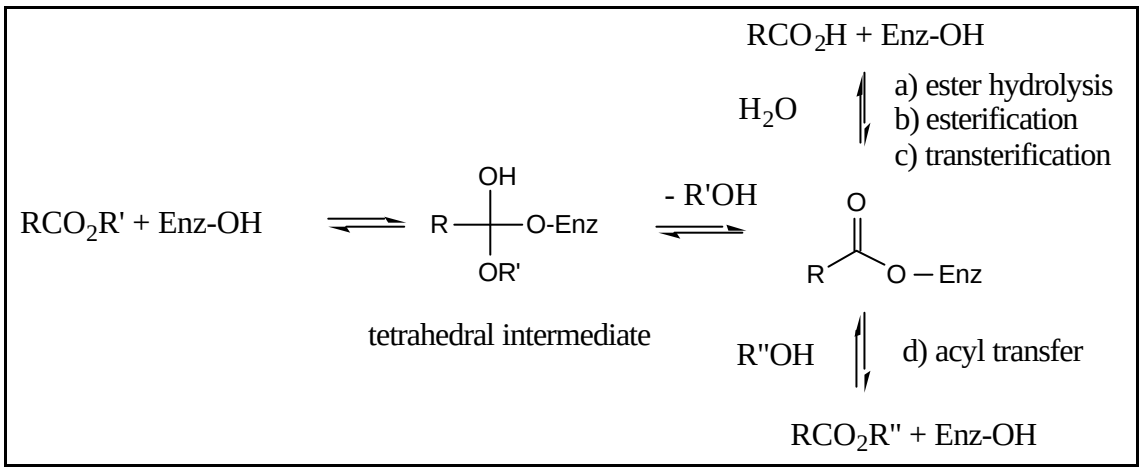


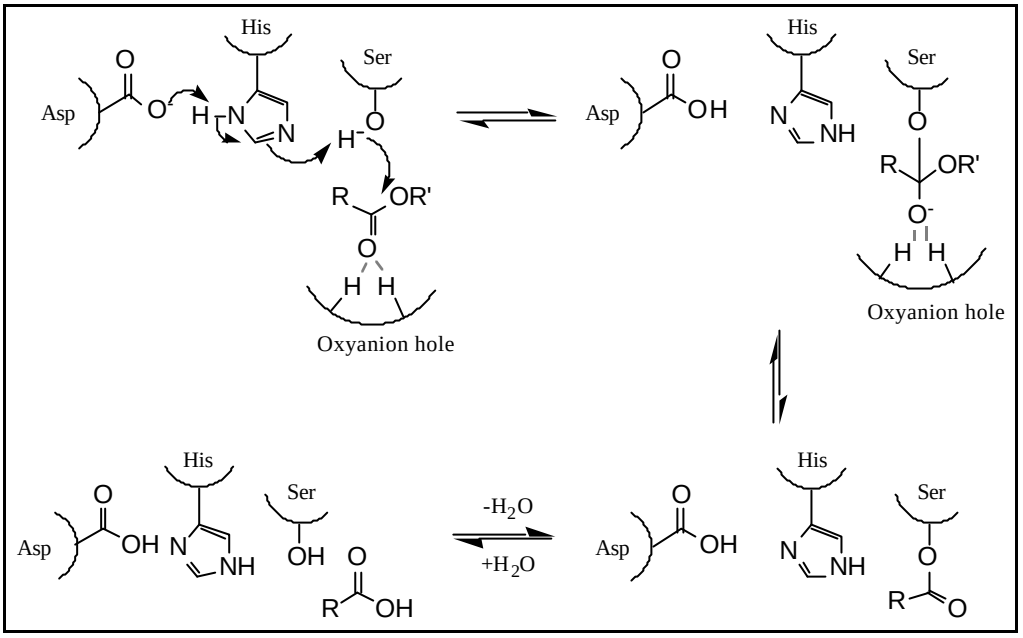
Figure 2.10: The four reactions catalyzed by ester hydrolases

Generally lipases catalyze four different reactions involving carboxylic esters (figure 2.10):

a) Ester hydrolysis
b) Esterification
c) Transesterification
d) Acyl transfer

Although not in all cases proven beyond doubt, it is generally accepted that the catalytic mechanisms are similar to those of serine proteases which have been studied in great detail.

The generally accepted mechanism of serine dependent lipase is shown simplified in scheme 2.10:



Scheme 2.10: hydrolysis mechanism of serine lipases.

The reaction proceeds *via* nucleophilic attack on the carbonyl group of the substrate ester RCO_2R' by the activated primary hydroxy group of the serine in the active site. The tetrahedral intermediate is stabilized by formation of hydrogen bonds between the negative charge on the ester oxygen and the amino acids of the oxyanion hole present in the protein backbone as shown in scheme 2.10.

There are several examples of X-Ray crystal data which support this hypothesis [37].

The tetrahedral intermediate is then stabilized by elimination of R'OH leading to an activated ester termed acyl-enzyme. This is the central intermediate in all four esterase-catalyzed reactions.

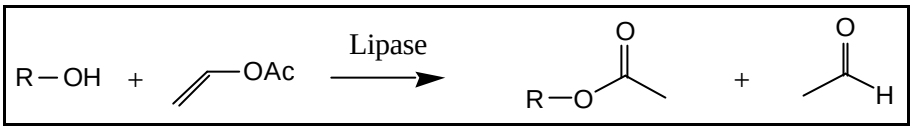
In aqueous media the acyl group of the acyl enzyme is transferred to the nuclephilic H_2O, present in large excess; the equilibrium is shifted towards the hydrolysis product.

In non aqueous systems the reverse reaction is possible and ester synthesis occurs (reaction b and c figure 2.10). Esterifications *via* enzymatic acyl transfer (reaction d figure 2.10) are particularly attractive for synthesis because no water is involved. If the acyl doner, which often serves also as solvent, is used in excess the acyl group from the acyl-

enzyme intermediate can be transferred also to other nucleophiles such as R"OH leading to new esters $RCO_2R"$. The success of such acyl transfer reactions largely depends on the nucleophilicity of the acceptor alcohol R"OH. Upon inspection of reaction d (figure 2.10) it is evident that the desired transfer can be achieved only if the initially eliminated alcohol R'OH is less nucleophilic than R"OH.

This enzymatic process, however is reversible and often requires long reaction times and a large excess of ester as acyl doner to form the acyl-enzyme in order to achieve a reasonable degree of conversion[38ac].

The application of vinyl or isopropenyl esters as acylating agents for lipase catalyzed esterifications [39ac] offers an effective solution of this problem because the end side product of the esterification is immediately converted irreversibly into acetaldehyde or acetone, respectively. (scheme 2.11):



Scheme 2.11: Esterification of alcohol by lipase with vinyl acetate

The only nucleophile present in solution is the alcohol that will be esterified.

The enantioselectivity E of lipase catalyzed reactions in aqueous solution, water organic solvent mixtures, and anhydrous organic solvent follows the classical competitive equation 14 [30,39].

2.2.4.1 Active site model for interpreting and predicting the specificity of lipases.

The previous absence of a complete set for X Ray data of lipases has led to the development of simple models for interpreting and predicting the specifity of enzymatic kinetic resolutions. On the basis of substituent sizes at the stereocenter, rules, allowing a prediction which enantiomer of a secondary alcohol is favoured in a kinetic enzymatic resolution have been developed by analysis of the data reported in the literature and were confirmed by subsequent experiments. This strategy has been applied to

three different enzymes[40] (*cholesterol esterase* CE, *Pseudomonas cepacia* PCL, *Candida rugosa* CRL).

A more detailed model has been developed for *Pig Liver Esterase* (PLE) based on cubic space descriptors that form the active site[41]. For this model, approximately 100 methyl esters with representative structures were identified and the results of their PLE catalyzed hydrolyses on a preparative scale were analyzed collectively. This has led to a model consisting of five binding loci, where the serine region is considered as a sphere with a diameter of 1 Å. The binding regions controlling specificity are represented by two hydrophobic and two more polar pockets. The two hydrophobic sites, which interact with the aliphatic or aromatic hydrocarbon portions of substrate, have a volume of approximately 33 $Å^3$, and 5,5 $Å^3$ respectively. Polar groups, such as hydroxy, amino, carbonyl, nitro funtions etc, are excluded from this area. The hydrophobic pockets can, however, accommodate less polar groups such as ether or ketal groups, if necessary.

The remaining two sites accept groups that are more polar or hydrophilic. They are located at the front and back of the active site.

A model accounting for enantioselective esterifications[42] catalyzed by *Pseudomonas species* has been also developed. Also in this case, from the literature data, a working hypothesis has been developed assuming that the alcohol is resolved most efficiently if it has one small and one relatively large group, the latter slightly removed from the asymmetric center (Fig. 2.11) carrying the hydroxy group.

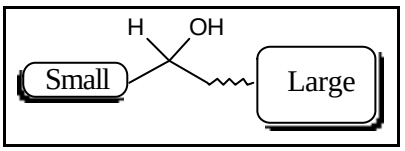


Figure 2.11:Simple model for predicting the resolution of secondary alcohols *via* acylation

This study has led to the development of a model for the lipase *Pseudomonas AK* which seems to be effective for the resolution of molecules with near planar structure. It is not suitable for the resolution of substrates carrying relatively bulky moieties close to the hydroxymethine center, or which are unable to adopt low energy planar conformations around the hydroxy group. The active site is envisaged as a near planar pocket with a hydrophilic canopy for the alcohol functionality

projecting above the plane. The depth of this active site area is sufficient to accomodate at least the terminal methylene group of an allene (>1.8Å). The model is described in figure 2.12:

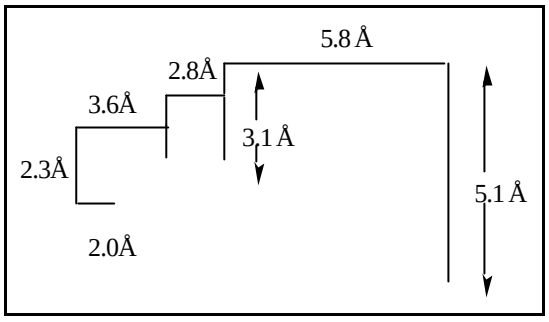


Figure 2.12: Two dimensional representation of the enzyme active site of *Pseudomonas* AK.

Many other well defined substrate structure/enzyme activity relationships are emerging. For instance, numerous resolutions of α-aryl alcohols mediated by SAM II lipase have been reported, allowing to establish that this is a good enzyme preparation for resolution of these substrates, and that the *R*-enantiomer of the alcohol is acylated preferentially in most cases[43-47].

The SAM II lipase shows more than 75% homology with the lipase from *Pseudomonas cepacia*, but no X-Ray structure is available at present in the Cambridge Brookaven Structures Database or has been published. Hence only qualitative models have been reported[48] essentially consistent with that shown in figure 2.11.

2.2.5. Enzymatic kinetic resolution of propargyl alcohols.

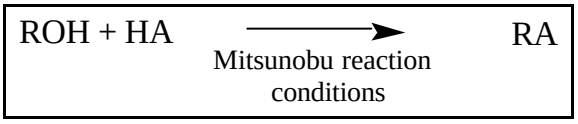
Several enzymes (lipases) are able to resolve racemic mixtures of propargyl alcohols (esters) into the pure enantiomers by a) esterification or b) hydrolysis.

Thus, the highly enantioselective esterification of secondary propargyl alcohols by *Pseudomonas sp*. has been reported in great detail[42,49]. The substrates used in these studies are characterized by the presence of two substituents of largely different bulkiness, but in no case an aromatic ring is attached directly to the hydroxymethine group.

Another example is the resolution of tertiary propargylic alcohols in presence of *Candida cylindracea*[50] where, however, only low enantiomeric purities where obtained.

2.3 Mitsunobu reaction: mechanisms and applications.

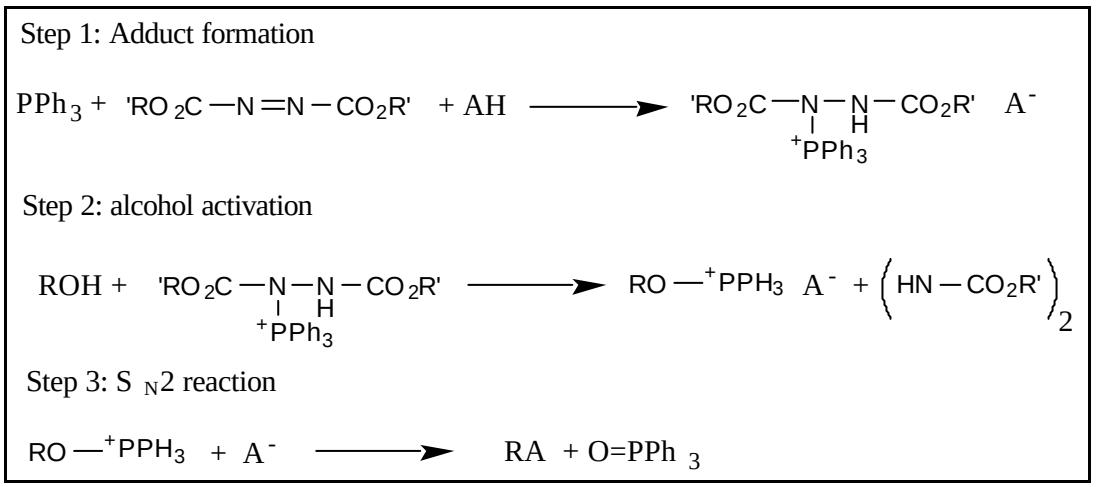
The Mitsunobu reaction, pioneered by Mitsunobu and coworkers in 1967[51], has proven useful in a wide variety of synthetic applications involving alcohols. From the first applications the Mitsunobu reaction has evolved into one of the primary synthetic tools for inverting alcohol stereochemistry as evinced by over 1100 citations of Mitsunobu's 1981 review on the subject[52]. Furthermore, it is a very versatile method for the condensation of alcohols ROH and various nucleophiles (or acids) HA leading to the product RA (Scheme 2.11.).



Scheme 2.11: Mitsunobu reaction.

2.3.1. Reaction Mechanism.

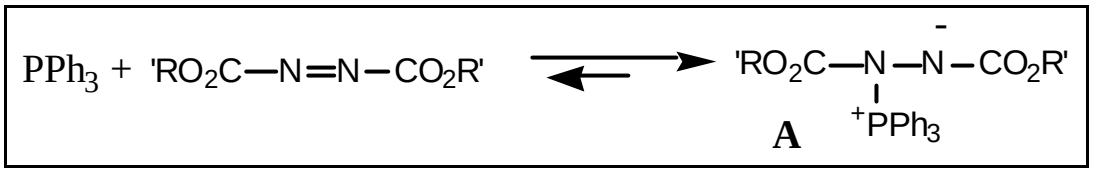
A search of the literature indicated that the mechanism of this reaction has been the subject of only few investigations [53a-d]. The Mitsunobu reaction takes place in three steps as outlined in scheme 2.12.



Scheme 2.12: mechanism of the Mitsunobu reaction.

2.3.1.1. Step 1: Adduct Formation.

The general procedure for the Mitsunobu reaction encompasses the addition of dialkyl diazodicarboxylate to a solution of a carboxylic acid, an alcohol and triphenylphosphine, the usual solvents being dichloromethane or tetrahydrofuran. In these media, formation of the betaine adduct **A** (Scheme 2.13) from dialkyl diazodicarboxylate and triphenylphosphine occurs within seconds at -20 °C, as evidenced by bleaching of DEAD upon addition.

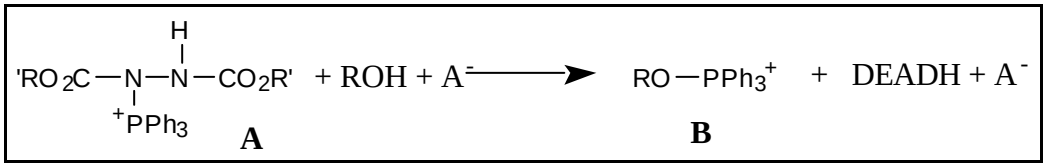


Scheme 2.13: Betaine adduct formation.

The formation of the betaine originally has been proposed by Morrison[54] and was later substantiated by Bunn and Huisgen[55]. It has been generally assumed that the betaine is formed by a Michael type nucleophilic attack of the phosphine on the nitrogen, the reaction has been shown to be irreversible[56]. In the absence of solvent, a deep red solution is produced in an exotermic reaction, this color was first noted by Mitsunobu[57] who suggested that radical or radical ions might be present and this suggestion was subsequently confirmed by Jenkins through EPR studies[58].

2.3.1.2. Step 2: Alcohol Activation.

The second step of the Mitsunobu reaction entails transfer of the PPh_3^+ group from the DEAD-PPh_3 adduct **A** (Scheme 2.14) to the alcohol.



Scheme 2.14: formation of the oxyphosphonium intermediate **B**.

Three different factors control the rate of this transfer:

A) The basicity of the counterion (A^-)generated in the formation of the DEAD-PPh_3 adduct **A.**

B) The extent of hydrogen bonding to this counterion

C) Substituent effects in the phospine

Before discussing these effects, first a note regarding the structure of the oxyphosphonium intermediate. Mitsunobu originally hypothesized a phosphonium salt as an intermediate akin to structure **B** (Fig. 2.15.), where the phosphorus has a positive charge and tetrahedral geometry. However, several recent papers have presented evidence for a neutral phosphorane structure **C** (Fig. 2.15.) that contains two molecules of alcohol per molecule of phosphine[53c-d].

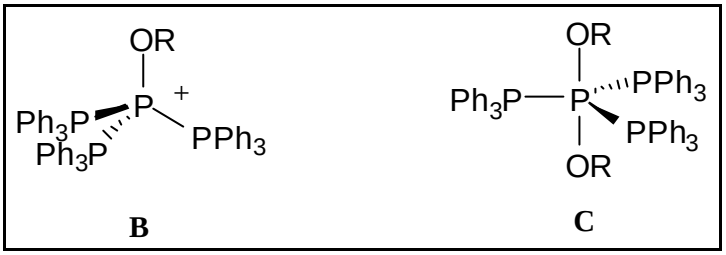


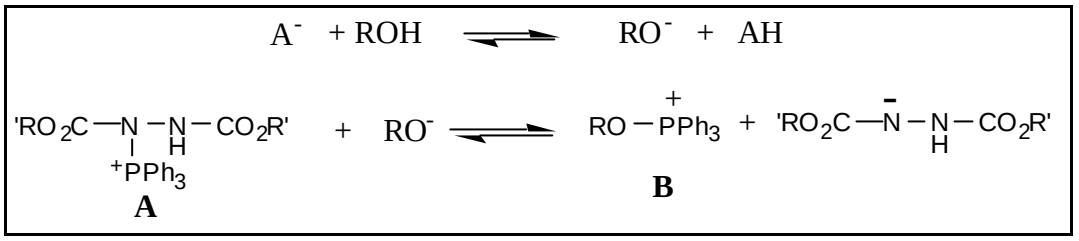
Figure 2.15.: Oxyphosphonium structures.

Generally, a neutral phosphorane is formed in the absence of acidic compounds. The adduct **B** is stable at -20° C but it rapidly decomposes at room temperature. Therefore, formation of the oxyphosphonium intermediate in the presence of the acid component is the best way to prevent undesirable side-reactions.

2.3.1.2.1. Effect of the basicity of the counterion.

The rate of transfer of the PPh_3^+ group from the DEAD-PPh_3 adduct **A** to the alcohol (Scheme 2.14) is highly dependent on the basicity of the counterion generated in forming the DEAD-PPh_3 adduct **A** as well as on the extent of hydrogen bonding to this counterion. These effects have been studied by Hughes[53d] in connection with the substitution of hydroxy groups in the side chain of β-lactames.

Generally, this consideration indicates the role of the counterion as a base for alcohol deprotonation, which in turn must occur before PPh_3^+ transfer takes place (Scheme 2.16.).



Scheme 2.16: oxyphosphonium intermediate **B**.

Hughes[10] studies confirmed this hypothesis. In fact he observed that, when the DEAD-PPh_3 adduct **A** is prepared in presence of *p*-TsOH, formation of the oxyphosphonium intermediate **B** does not occur due to the weak basicity of *p*-TsO^- which cannot appreciably deprotonate the alcohol. However addition of a stronger base to the same reaction, such as triethylamine (TEA), does catalyze the formation of the oxyphosphonium intermediate **B**. This demonstrated that the oxyphosphonium intermediate **B** is formed at a rate wich is dependent on the AH/A^- ratio and on the basicity of A^-.

In summary, the reactivity of A^- as a base and as a nucleophile in the first two steps of Mitsunobu reaction must be carefully controlled in solution. This means that if A^- is a strong base and a poor nucleophile the oxyphosphonium **B** adduct forms, while in the opposite situation, when A^- is a poor base but a strong nucleophile, it competes with DEAD-PPh_3 adduct **B** in reaction with the alcohol.

However, the reaction has a serious limitation regarding the acidity of HA, which must have a pKa <11 in order for the reaction to proceed satisfactorily. If HA has pKa >11, the chemical yield of RA is lowered considerably and with HA having pKa > 13 the reaction does not occur at all. It is also possible to carry out the Mitsunobu reaction with acids having pKa >11 if the normal redox system is changed from DEAD/PPh_3 or DIAD/PPh_3 (diisopropyldiazodicabrboxylate) to ADDP [(1-1' azodicarbonyl) dipiperidine] in association with tributyl phosphine[60], because in this system:

A) The phosphine shows increased nucleophilicity in the formation betaine **A**;

B) The positive charge is localized on P thus facilitating the nuclephilic attack of RO^-

C) The negative charge is localized at the azo nitrogen thus increasing its basicity in the betaine **A**.

2.3.1.2.2. Effect of Substitution in the Triarylphosphine moiety on the Rate of Alcohol Activation.

Hughes studied the effect of substitution in the triarylphosphine on the rate of alcohol activation and found, as expected, that electron withdrawing groups, such as chlorine in positions 2 or 4 increase the electrophilicity of phosphorus. In table 2.1 the relative rates of formation of the oxyphosphonium intermediate **A** at 0 °C with substituted triarylphosphines in CH_2Cl_2 solution are summarized.

Substituent	Relative Rate
m - Cl	6200
p - Cl	3600
H	780
m - Me	300
p - Meo	1

Table 2.1 :Effect of substituents on the rate of formation of the oxyphosphonium intermediate **A.**

The strongly desactivating effect of the 4-MeO group suggests that a significant dπ-pπ overlap may occur between the aryl ring and phosphorus as shown in figure 2.13.

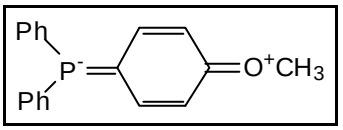


Figure 2.13: dπ-pπ overlap

2.3.1.2.3. The SN2 Reaction.

The final step of the Mitsunobu reaction is the SN2 reaction of the anion A^- with the oxyphosphonium intermediate **B**. Generally the reaction proceeds with complete stereochemical inversion. However, for particular substrates, this general rule is not respected, indicating that an SN1 component becomes relevant. Another side- and competitive reaction is the E1 elimination that in some cases can become the major reaction.

There are various effects which can influence the rate of S_N2 substitution. One of them is the effect of the carboxylate basicity when the nucleophile is an acid. In contrast to the alcohol activation step, there is only a slight dependence of S_N2 rates on the carboxylate basicity. This indicates that the S_N2 transition state has to some extent S_N1 character, with a small incidence of bond formation and a large incidence of bond breaking. This is not unexpected, since carboxylates are weak nucleophiles, while triphenyl phosphine oxide is an excellent leaving group due to the formation of the strong P=O bond.

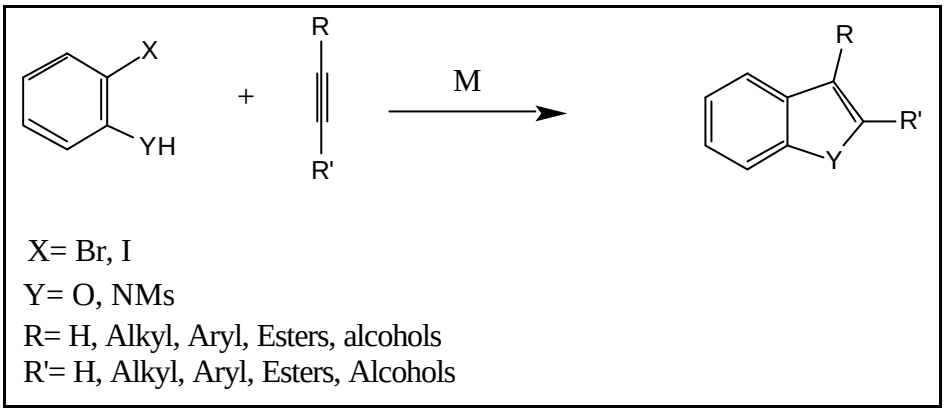
The influence of acidity on the S_N2 reaction has been also studied for aryl substituted acids[61] and it has been demonstrated that less acidic (more basic) carboxylate species dictate a slow S_N2 reaction. However, with more acidic (less basic) species, the rates of alcohol activation and S_N2 displacement (step 2 and 3 respectively) became comparable.

In summary the Mitsunobu reaction is dramatically influenced by the acid component. It appears that there is a relationship between the dissociation constant of the acid and the overall efficiency of the reaction, whereby more acidic species generally provide a higher yield of inverted product.

It is also apparent that synthetically useful yields are dependent on a variety of electron withdrawing substituents on the aryl carboxylic acid.

2.4 Synthesis of heterocycles by transition metal catalysis.

Organotransition metal chemistry is rapidly becoming an important tool for organic synthesis and during the past three decades enormous advances have taken place in our understanding of the structure and reactivity of organotransition metal compounds. These insights have opened the way for applications of these compounds to ever burgeoning, fields of organic synthesis, both as stoichiometric reagents and as catalysts. We were interested in the synthesis of chiral 2-substituted benzo[b]furanes and 2-substituted indoles from alkynes and aryl halides mediated by transition metals(scheme 2.17).



Scheme 2.17: Annulation of triple bonds mediated by transition metals.

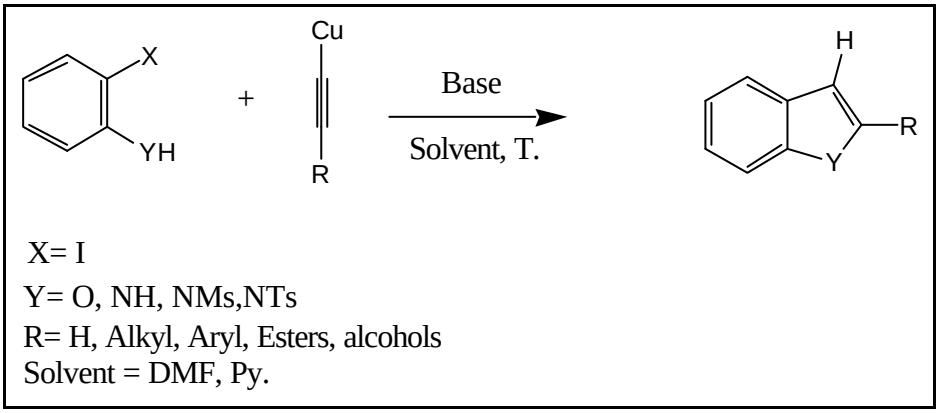
Three differents methods are reported in the literature for the synthesis of these compounds mediated by transition metals:

1) Castro's procedure.
2) Cacchi's procedure.
3) Larock's procedure.

For the first methodology copper(I) was used, for the second and the third Pd catalysts were employed; all of them were applied to racemic or achiral compounds.

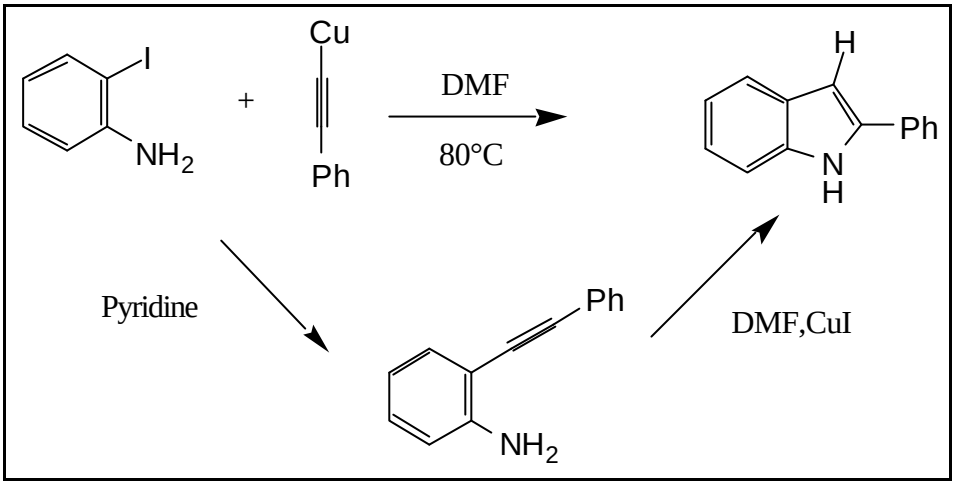
2.4.1 Annulation of triple bonds by Castro's procedure.

Castro and coworkers[62a-d.] were the first to discover and study the substitution of *o*-halophenols and 2-haloanilines with copper(I) acetylide followed by cyclization to the 2-substituted benzo[b]furanes and 2-substituted indoles in the presence of a base (scheme 2.18).



Scheme 2.18: Castro's procedure for the synthesis of benzofuranes and indoles.

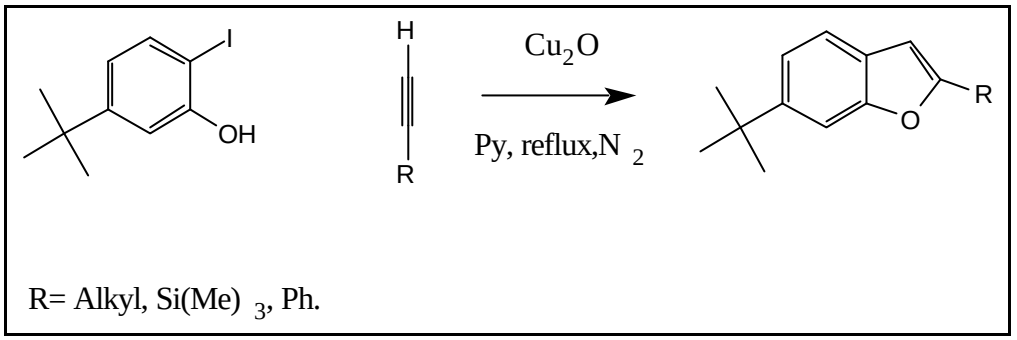
The reactions were found to be strongly dependent on the solvent, in particular on its ability to afford a homogeneous reaction medium. This aspect is very important for the synthesis of 2-substituted indoles. When the reaction was carried out in a homogeneous medium (pyridine as solvent) the ortho amine tolane was obtained (no cyclization to indole occurred), while in heterogeneous medium (DMF as solvent) 2-substituted indoles were synthesized [62b,d] (scheme 2.19).



Scheme 2.19: Influence of the solvent in Castro's procedure.

The Castro procedure has found very good applications in the syntheses of novel adenosine A1 receptor ligands[63].

A limit of this procedure was the fact that the copper(I) acetylides had to be prepared separately and isolated. Also some of them are known to be shock sensitive and explosive. Furthermore, many functionalized copper(I) acetylides cannot be synthesized and isolated in the usual manner, because they are soluble in, or reactive towards, the reaction mixture used for their preparation. To circumvent these problems a modification of Castro's procedure was reported in 1989 by Owen[64], where the copper (I) acetylide was generated *in situ* from the acetylenic compounds and Cu_2O in presence of base, followed by coupling and cyclization to 2-substituted benzo[b] furanes (scheme 2.20).

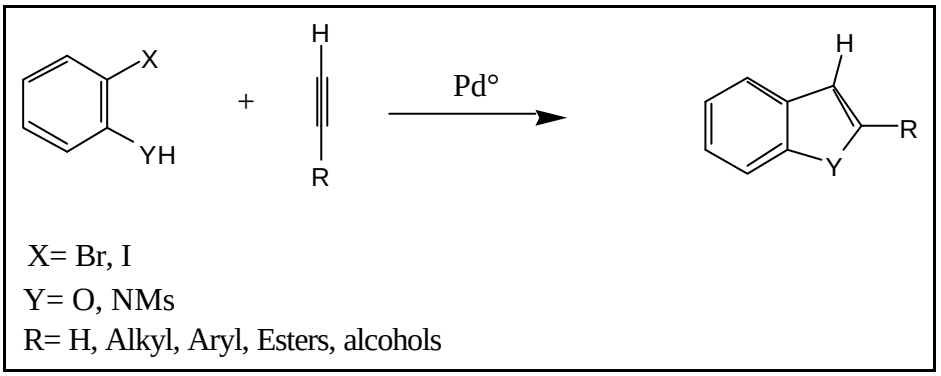


Scheme 2.20: Modification of Castro's procedure by Owen

In all these methods the copper(I) was used in equimolar amounts or in excess depending on the substrate.

2.4.2 General procedure for the synthesis of 2-substituted benzo[b]furanes and 2-substituted indoles *via* Palladium catalyzed heteroannulation of triple bonds.

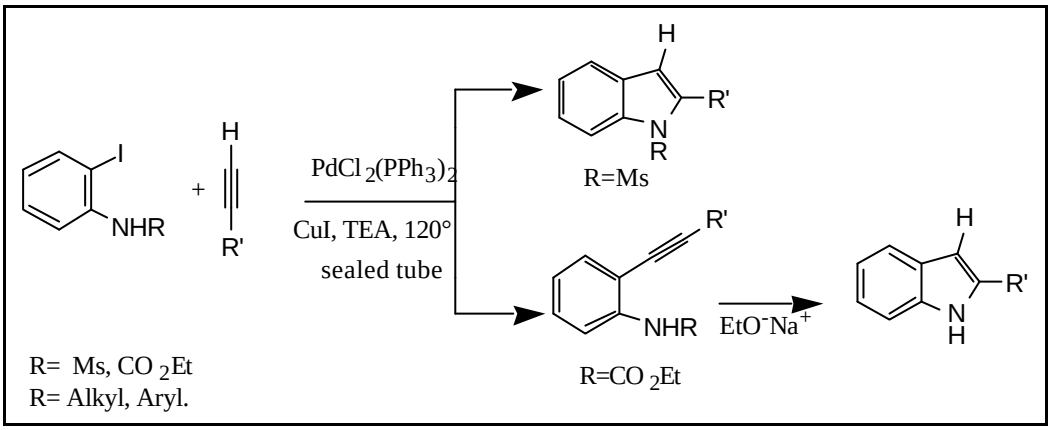
Simultaneously, Cacchi and Yamanaka developed a procedure for the synthesis of 2-substituted benzo[b]furanes and 2-substituted indoles, respectively, by Palladium catalyzed heteroannulation of alkynes (scheme 2.21).



Scheme 2.21: Cacchi and Yamanaka procedure for the synthesis of 2-substituted benzo[b]furanes and 2-substituted indoles

2.4.2.1 Yamanaka's procedure for the synthesis of 2-substituted indoles *via* a Palladium catalyst.

Yamanaka and coworkers have studied[65a-c] an approach to the synthesis of 2-substituted indoles in presence of a Copper-Palladium catalyst. Essentially, this procedure allowed the use of copper (I) in catalytic amounts and did not require prior preparation and isolation of copper(I) acetylide. Palladium then catalyzed the coupling between the aryl iodide and the copper (I) acetylide. Conditions to achieve only the coupling reaction or both coupling and cyclization have been studied in depth showing the important role of the R group on the aniline (scheme 2.22).

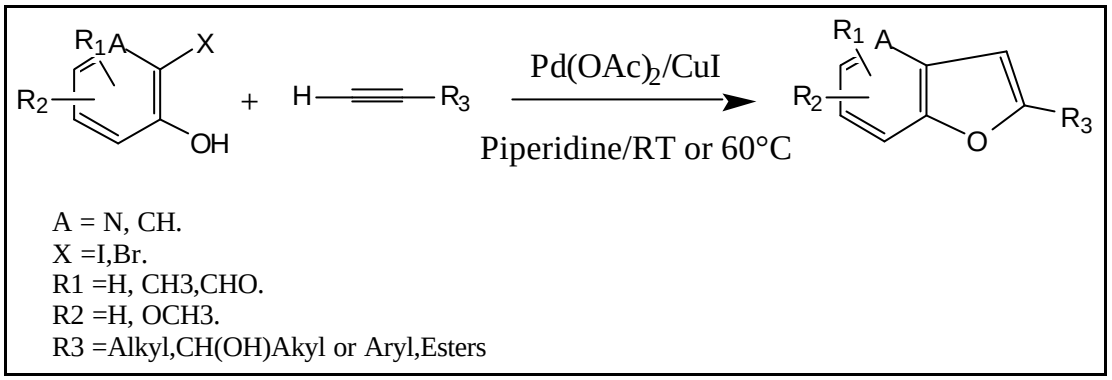


Scheme 2.22.: Influence of activating groups in the Yamanaka cyclization.

In particular, when R is a mesyl group, 2-substituted indoles can be directly obtained, while with less electron withdrawing R groups, such as CO_2Et the reaction affords the intermediate, uncyclized coupling product. This, in turn, can be transformed into the heteroannulated compound by the action of a base.

2.4.2.2. Cacchi's procedure for the synthesis of 2-substituted benzo[b]furanes using Palladium catalyst.

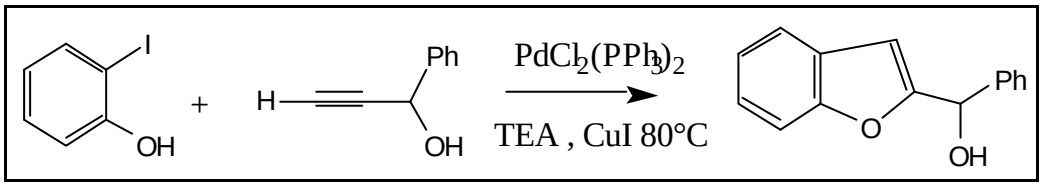
Cacchi and coworkers[66] reported a procedure for the synthesis of 2-substituted benzo[b]furanes from 1-alkynes using a Copper-Palladium catalyst. The reaction of 2-hydroxyaryl or 2-hydroxyheteroaryl halides with several 1-alkynes in the presence of a base, bistriphenylphosphine Pd (II) diacetate and Copper (I) iodide in DMF at RT or 60° C leads to 2-substituted benzo[b]furanes in usually good yields (scheme 2.23).



Scheme 2.23: Synthesis of benzofuranes according to Cacchi's procedure.

A short communication published in 1992 from Kundu N.G.[67a,b] represented our most important reference. This paper described the synthesis of 2-benzo[b]furanyl carbinol by coupling and cyclization of 1-phenyl 2-propyn-1-ol with *o*-iodophenol(scheme 2.24).

The molar ratio between propargylic alcohol and 2-iodophenol was 2:1 and the yield was calculated on the basis of the conversion of *o*-iodophenol as 66%. It is important to emphasize that all of the above described procedures were reported with achiral or racemic acetylenic compounds while our investigation is related to the possibility of applying these methodologies to chiral alkynes.



Scheme 2.24: Kundu's procedure for the synthesis of arylbenzofuranylmethanols.

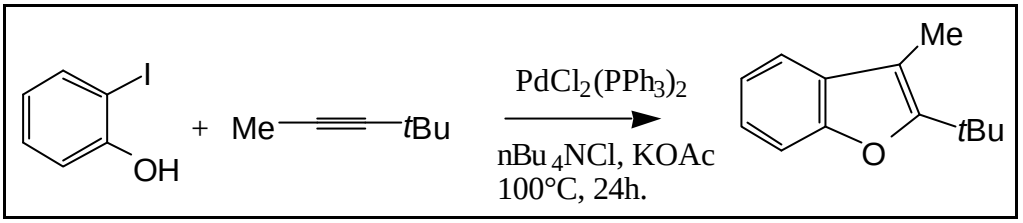
To our knowledge, these are the best conditions reported to date for the synthesis of 2-substituted benzo[b]furanes.

2.4.2.3 Larock's procedure for the annulation of internal alkynes to various heterocycles.

Larock R.C.[68] and coworkers in 1995 reported a very good procedure to synthesize aromatic heterocycles *via* Palladium catalyzed annulation of internal alkynes. Syntheses of various heterocycles, including 1,2-dihydroquinolines, benzofuranes, benzopyranes and isocumarines are reported in this article. Generally, 5% molar $Pd(OAc)_2$,

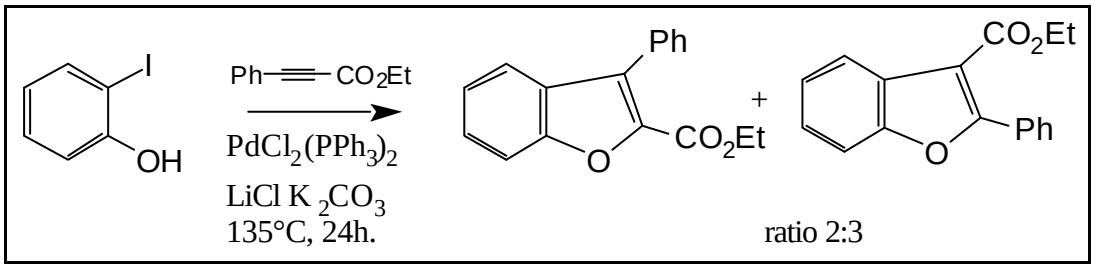
sodium or potassium carbonate as base, lithium chloride or nBu_4NCl as chloride source are employed in DMF as solvent with 5% molar triphenylphosphine sometimes added to the reaction mixture.

Temperatures ranging from 80° C to 140° C were necessary to effect the annulation within a reasonable time. The regiochemistry followed the general trend with the aryl group being added to the less hindered end of the alkyne and the Palladium catalyst to the more hindered one (scheme 2.25).



Scheme 2.25: Regioselectivity in the palladium catalyzed cyclization of asymmetrically substituted alkynes.

The heteroannulation using *o*-iodophenol has been found to be more difficult than the analoguous reaction using *o*-iodoaniline. Generally, higher temperatures were required for the cyclization of *o*-iodophenol, thus reducing the regioselectivity of the process. For example, the annulation of ethylphenylpropynate afforded a 2:3 mixture of regioisomers (scheme 2.26).



Scheme 2.26: Anullation of ethylphenylpropynate

3. Synthesis of Substrates.

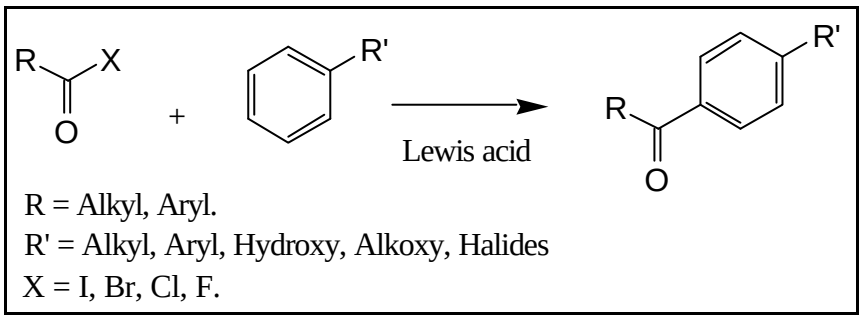
3.1. Synthesis of Ketones.

Ketones are the starting materials for antifungal agents like bifonazole and also for antitumor agents such as **18** (Menarini's compounds).

3.1.1. Synthesis of Ketones 25a-f by Friedel-Crafts Acylation- Starting Materials for further studies on Bifonazole.

Benzophenones are ideal precursors for bifonazole and its analogues. Unfortunately they are not commercially available, with the exception of benzophenone itself.

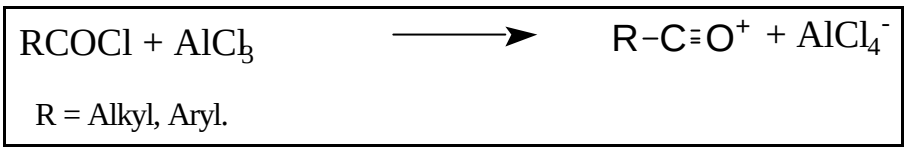
Friedel-Crafts acylation[1,2] is the most important method for the preparation of aryl ketones.The reagents usually employed are acyl halides, carboxylic acids, anhydrides, or ketenes[3]. The general scheme of the reaction is shown in scheme 3.1.



Scheme 3.1: Friedel-Crafts acylation, general scheme.

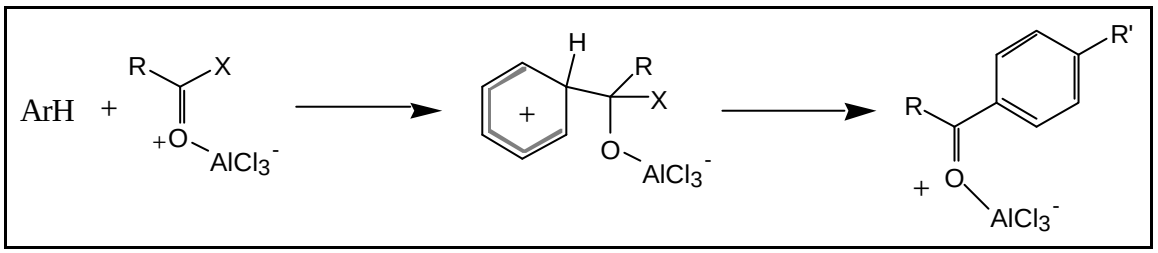
R may constitute either an aryl or an alkyl group. Since the RCO group is deactivating, the reaction stops cleanly after one group is introduced. All four acyl halides can be used, although chlorides are the most commonly employed, the order of reactivity is usually I>Br>Cl>F[4]. Catalysts are Lewis acids such as $AlBr_3$, $AlCl_3$, $GaCl_3$, $FeCl_3$, $SnCl_4$, BCl_3. For the acylation a little more than 1 mole of catalyst is required per mole of reagent, because the first mole is coordinated to the oxygen of the reagent[5,6].

The reaction is quite successful for many types of substrates, including compounds containing ortho and para directing groups such as alkyl, aryl, hydroxy, alkoxy, halogen and acetamido groups. They are easily acylated and lead mainly or exclusively to the para acetylated products, because of the relatively large size of the acetyl group. Friedel-Crafts acylation is usually prevented by meta directing groups. The mechanism of this reaction is not completely understood, but at least two mechanisms could operate, depending on conditions[7]. In most cases the attacking species is the acyl cation, either in its free form or as ion pair[8] (scheme 3.2):



Scheme 3.2: Formation of acyl cation.

If R is a tertiary group, RCO^+ may loose CO to give R^+, so that the corresponding alkylarene ArR is often a side product or, sometimes, also the main product. In the other mechanism an acyl cation may not be involved, in this case the 1:1 complex can attack directly[9,10] (scheme 3.3).

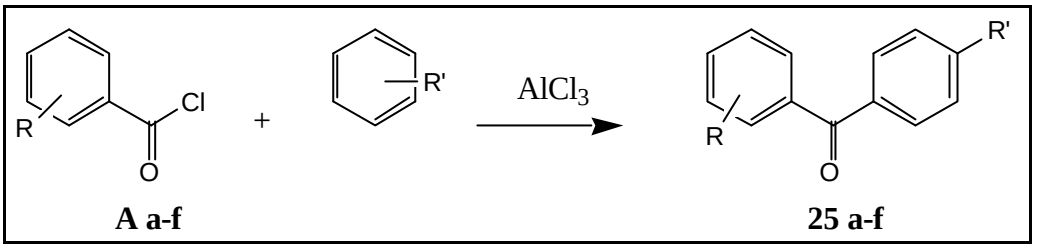


Scheme 3.3: Direct acylation of complex.

A free-ion attack is more likely for sterically hindered groups R[11].

The CH_3CO^+ has been detected (by IR spectroscopy) in the liquid complex between acetyl chloride and aluminium chloride, dissolved in a polar solvent such as nitrobenzene. In non polar solvents such as chloroform, only the complex without the free ion is present[12]. In any case, 1 mole of the catalyst certainly remains complexed to the product at the end of the reaction.

Prochiral Ketones **25a-f** were prepared *via* Friedel-Crafts reaction as shown in scheme 3.4..



A a-f **25 a-f**

Scheme 3.4: Synthesis of prochiral ketones **25 a-f** by Friedel-Crafts acylation.

Only commercially available aroylchlorides were considered as starting materials, the choice was based on the possible synthetic approaches describe in chapter 1.6.

Six different, substituted benzoyl chlorides **Aa-f** were chosen to acylate biphenyl and benzene (time, yields and reaction conditions are summarized in table 3.1).

Product	R	R'	T [°C]	Time h	Yield %
25a	H	Ph	0-reflux	28	97
25b	2-Br	H	0-reflux	16	96
25c	2-Br	Ph	0-reflux	18	98
25d	2-F	Ph	0-reflux	18	97
25e	4-NO_2	Ph	0-50	16	90
25f	3-NO_2	Ph	0-50	12	90

Table 3.1: Prochiral ketones **25a-f by** Friedel Craft acylation.

Aroyl chlorides **A a-f** were reacted in 1,2 dichloroethane (in benzene for **25b**) in presence of $AlCl_3$ as Lewis acid with biphenyl. Compounds **25a-f** represent suitable intermediates for the preparation of the targets *via* the strategies described in chapter 2, such as:

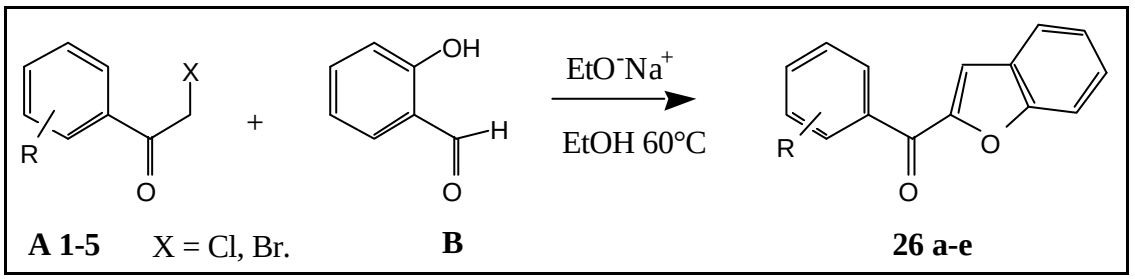
1) 4-Phenyl benzophenone **25a** would be the precursor of bifonazole;
2) **25e-f** bearing nitro groups in positions 3- and 4- of the aromatic ring could be transformed to the corresponding amines which could be coupled with an enantiopure acid to form a separable mixture of diasteroisomers;
3) **25b-d** with halogens in the 2-position of the phenyl ring were used for the asymmetric reduction to chiral benzhydroles using Brown's method[25,26]. 2-Bromo benzophenone **25b** was synthesized with the purpose of validating this method[25,26] reported in

literature as the best substrate for this kind of asymmetric reduction. 2-Bromo-4'-phenyl benzophenone **25c** can be considered as precursor of bifonazole. The ortho substituent is required for good enantioselectivity during the Brown asymmetric reduction, while the para phenyl group is required for the bifonazole structure. The para phenyl group on the aromatic moiety of the molecule does not interfere with the process of chiral recognition by the chiral LAH complex.

The Friedel-Craft's acylation of the biphenyl moiety with all aroyl chlorides **Aa-f** proceded with high regioselectivity, biphenyl was only monoacylated in the para position with respect to the second aromatic ring. Reactions were followed by both GC-MS and ^{1}H-NMR after work up without any purification.The chemical yields were always very high.

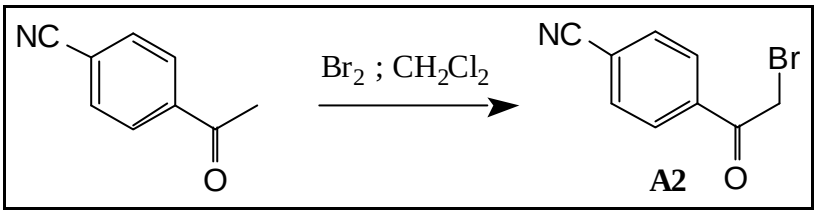
3.2. Synthesis of Aryl-2-Benzo-[b]-Furanones 26 a-e: Prochiral Ketones for the Menarini Anticancer Drugs 18 *via* the Rap Stormer procedure.

The synthesis of Aryl-2-benzo-[b]-furan ketones **26a-e** was achieved *via* the Rap Stormer procedure. For this the ω-bromo-acetophenones **A 1-5** were condensed with salicyl aldehyde **B** under basic conditions (scheme 3.5) leading to the ketones **26a-e**.



Scheme 3.5: Synthesis of Aryl-Benzo[b]furan Ketones **26 a-e.**

The required ω-Bromo-acetophenones **A1,3-5** were commercially available, while **A2** was prepared from the corresponding 4-cyanoacetophenone by bromination with molecular bromine in chloroform at room temperature in high (88%) yield (Scheme3.6).



Scheme 3.6: Bromination of 4-Cyano acetophenone .

The crude reaction product was used directly without any further purification in the following Rap-Stormer synthesis leading to the corresponding 4-cyano-2-benzo[b]furanone **26b**.

In table 3.2 the different ω-bromoacetophenones used as substrates for the condensation to aryl-benzo[b]furan ketones **26a-e** are listed, together with reaction times and obtained chemical yields.

Substrate	X	R	Time h	Product Yield (%)
A1	Br	H	12	**26a** (56)
A2	Br	4-CN	16	**26b** (66)
A3	Cl	2,4-Cl	16	**26c** (88)
A4	Br	4-F	14	**26d** (68)
A5	Br	4-Cl	15	**26e** (72)

Table 3.2: Synthesis of aryl-benzo[b]furan ketones **26a-e** by the Rap Storner procedure.

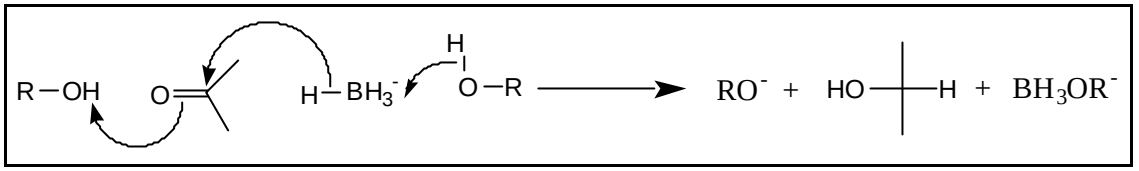
The chemical yields are moderate. In the case of ω-bromo-4-cyanoacetophenone **A2** the chemical yield was calculated based on the corresponding 4-cyano acetophenone.

All compounds **26a-e** are precursors for the most active Menarini Aromatase inhibitors (see table 1.1, chapter 1 for the activities of the corresponding compounds). It is interesting to point out that in the literature no examples for their asymmetric reduction are reported.

3.3. Reduction of Prochiral Ketones 25a-f and 26a-e to Racemic Alcohols (±) 27a-m using $NaBH_4$.

$NaBH_4$ is one of the most useful reducing agents for ketones. It is easy to handle, generally reacts under mild conditions, does not require

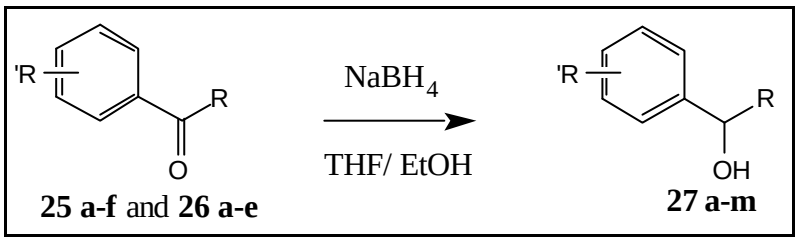
dry solvents and, is cheap. The general mechanism of the reduction is shown in scheme 2.7[14]:



Scheme 2.7: General mechanism of ketone reduction by $NaBH_4$

The Na^+ seems not to participate in the transition state (as does Li^+ in $LiAlH_4$ reductions[15]) but kinetic evidences showed that an OR group of the solvent seems to be involved in the reaction and remains attached to the boron [16].

Both classes of prochiral ketones **25a-f** and **26a-e** were reduced to racemic alcohols **27a-m** with $NaBH_4$. A 1:1 mixture of ethanol and THF was used as solvent to achieve a perfect solubilization of the ketones at low temperature (scheme 3.8.):



Scheme 3.8: Synthesis of racemic aryl-phenyl methanols **(±)27a-f** and aryl-2-benzo[b]furan methanols **(±)27g-m**.

High yields were obtained and no side products were detected neither during the reactions nor after the work up. Products, experimental conditions and chemical yields are reported in table 3.3.

(±)-27a-m were used as reference materials for the determination of the enantiomeric excess in the enantiomerically enriched products. Furthermore they were used as starting materials in all the new synthetic routes in order to prove the feasibility of the strategy. Finally also for the synthesis of separable diasteroisomers.

Product	R	R'	T °C	Yield %
(±)-27a	Biphenyl	H	0	95
(±)-27b	Ph	2Br	0	94
(±)-27c	Biphenyl	2-Br	0	95
(±)-27d	Biphenyl	2-F	0	94
(±)-27e	Biphenyl	4-NO_2	-15-0	98
(±)-27f	Biphenyl	3-NO_2	-15-0	95
(±)-27g	2Benzo[b]furan	H	0	93
(±)-27h	2Benzo[b]furan	4-CN	-15-0	97
(±)-27i	2Benzo[b]furan	2,4-Cl	0	93
(±)-27l	2Benzo[b]furan	4-F	0	94
(±)-27m	2Benzo[b]furan	4-Cl	0	95

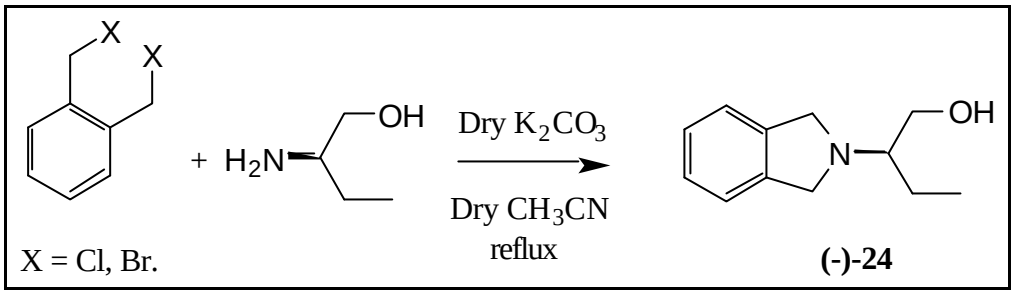
Table 3.3: Reduction of prochiral ketones **25a-f** and **26a-e** to racemic alcohols **(±)-27a-m** by $NaBH_4$.

3.4. Asymmetric Reduction of Prochiral Ketons.

The most widely used chiral agents for the reduction of prochiral ketones to enantiopure alcohols were reported in chapter 2. It was also emphasized that the procedure[25,26] described by E. Brown should be considered the only promising method for our purpose, since all other methods work only very well for ketones having two different substituents either in size (very large-very small) or in structure (aliphatic-aromatic).

3.4.1 Synthesis of (*R*)-(-)-2-(2-isoindolinyl) butan-1-ol (-)-24. An optically active ligand for the asymmetric reduction of prochiral benzophenones.

Brown and coworkers did not report the experimental procedure for the preparation of the (*R*)-(-)-2-(2-iso indolinyl) butan-1-ol **(-)-24.** The synthesis was achieved by alkylation of 1,2-dichloroxylene or 1,2-dibromoxylene with *R*-(-) -2-aminobutan-1-ol in presence of dry K_2CO_3 as base (scheme 3.9).



Scheme 3.9: Synthesis of (*R*)-(-)-2-(2-isoindolinyl)butan-1-ol **(-)-24**.

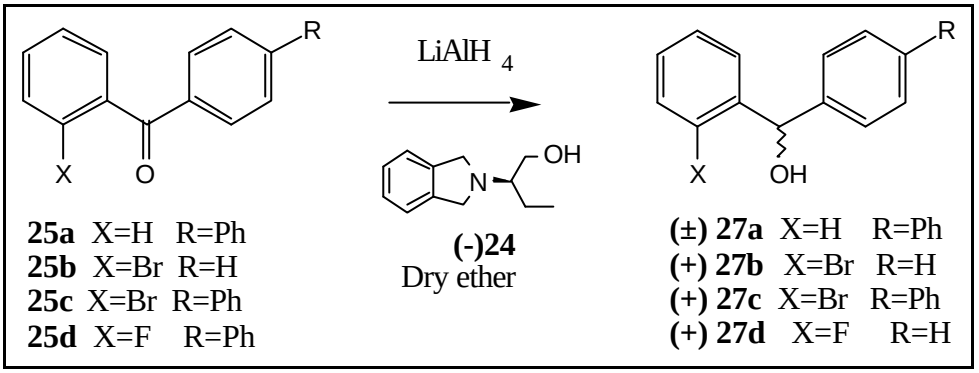
Both substrates were used in small scale syntheses (one gram) but 1,2-dichloroxylene was chosen also for the scale up (150 grams) because it is more safe in comparison with 1,2-dibromoxylene which has very irritating properties. The synthesis of (*R*)-(-)-2-(2-iso indolinyl) butan-1-ol **(-)-24** was performed at different temperatures and in different solvents such as acetone and acetonitrile. Reactions in acetone were always incomplete even under reflux for more than 24 hours. Acetonitrile was found to be the superior solvent for the reaction but only under refluxing conditions. In fact all experiments carried out at lower temperatures led to mixtures of products, mainly the *N*-monoalkylated-2-amino-1-butanol (uncyclized product) in mixture with the desired product **(-)-24**. Generally high dilution conditions were required in order to favour the intramolecular cyclization instead of intermolecular alkylation. Dry potassium carbonate was used as base in all cases. Purification was achieved *via* repeated high vacuum distillation of the crude solid reaction product.

3.4.2 Asymmetric reduction of prochiral benzophenones 25 a-d by a complex between (*R*)-(-)-2-(2-isoindolinyl)-butan-1-ol (-)-24 and $LiAlH_4$.

The first experiment was performed with 2-bromobenzophenone **25b** (scheme 3.10). This substrate was described by Brown in its papers[25,26] and was shown to be the best substrate for this kind of asymmetric reduction. The experiment was done in order to validate the reproducibility of the method.

The reaction was carried out under the reported experimental conditions: a diethyl ether solution of LAH was added to a solution of 2.5 equivalents of (*R*)-(-)-2-(2-isoindolinyl)-butan-1-ol **(-)-24** in dry diethyl

ether at 0°C, under an inert atmosphere in order to form a complex with the gross formula of $LiAl(OR^*)_{2,5}H_{1,5}$; After 45 min. the reaction mixture was cooled to -15°C and a solution of 2-bromobenzophenone **25b** in dry diethyl ether was added dropwise. The asymmetric reduction led to the ortho-(+)-Bromobenzhydrole **(+)-27b** (scheme 3.10). After quenching and work up the optically rotation was compared with the value reported in the literature and an identical rotation was found ($[\alpha]_D$= +46.6; c=1.3 in acetone), corresponding to an enantiomeric excess of higher than 95 %e.e. (table 3.4.). The reaction was then repeated with the prochiral benzophenones **25a-d** (scheme 3.10).



Scheme 3.10: Synthesis of chiral benzhydroles **(+)-27b-d** and racemic **(±)-27a**

Some modifications of the original procedure were introduced. Especially regarding the reaction work up a procedure was chosen which allowed the recyclisation of the chiral auxiliary and the improved recovery of the pure product. The optimal molar ratio of 2.5 equivalents of (*R*)-(-)-2-(2-isoindolinyl)-butan-1-ol **(-)-24** for one mole of LAH which corresponds to the gross formula $LiAl(OR^*)_{2,5}H_{1,5}$ was not changed. It was assumed to be the optimal condition also for the prochiral benzophenones **25a-d**. The chiral reducing complex reagent led to very good enantiomeric excesses only with ortho substituted benzophenones, while meta substituted benzophenones gave markedly lower enantiomeric excesses.

The reason for this remains unclear. Obviously an *o*-substituent on the phenyl ring must be present in order to achieve good enantioselection. Speculations can be based on the results reported by Brown. Due to the chemical nature of the substituents it seems reasonable to exclude that electronic effects are involved in the recognition process between the chiral LAH complex and the ketone. Probably the steric effects of the

substituents are the most important factors governing the enantioselection of the reduction. It is in fact possible that, due to the presence of the ortho substituent, the prochiral benzophenone presents the two aromatic moieties in different planes. The ketone can be almost coplanar with the unsubstituted aromatic ring to form a flat moiety while the aromatic ring bearing the ortho substituent is out of the plane (Fig 3.1).

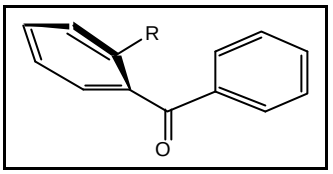


Fig.3.1: Conformation of ortho substituted benzophenones.

2-Bromo-(4'phenyl) benzophenone **25c**, reduced under identical experimental conditions as used for 2-bromobenzophenone **25b** gave (+)-2-bromo-4'phenyl-benzhydrol **(+)-27c** with an enantiomeric excess of higher than 95% e.e. (scheme 3.10; table 3.4) and with 98% of chemical yield. It is interesting to note that in this substrate two substituents are present on the two aromatic rings. The presence of a phenyl ring in the para position did not lead to any loss of stereoselectivity in the chiral reduction probably because this did not change the overall geometry of the prochiral ketone. The enantiomeric excess was determinated by examining the carbinolic proton in the ^{1}H-NMR spectrum (200 MHz) in the presence of the chiral shift reagent tris [3-(heptafluoropropylhydroxy methylen)] camphorato europium 3 [Eu(hfc)$_3$], and also confirmed by chiral HPLC (Chiracel OD).

The procedure was repeated for 4'-phenyl benzophenone **25a** and led to the racemic 4'-phenyl benzhydrole **(±)-27a** in 98% of chemical yield (scheme 3.10; table 3.4). 2-Fluoro-4'-phenyl benzophenone **25d** was reduced to (+) 2-fluoro 4'-phenyl benzhydrole **(+)-27d** with 80% enantiomeric excess and 98% of chemical yield (scheme 3.10; table 3.4). The loss of enantiomeric excess could be attributed to the reduced steric hindrance of the fluorine atom in comparison to the bromine. The enantiomeric excess was determined by chiral HPLC (Chiracel OD), while all attempts to examine the carbinolic proton in the ^{1}H-NMR spectrum recorded in presence of the above chiral shift reagent failed.

Product	X	R	Yield %	e.e. %	$[\alpha_D]$
(±)-27a	H	Ph	95	0	0
(+)-27b	Br	H	97	>95	+ 46.6
(+)-27c	Br	Ph	98	>93	+ 65.6
(+)-27d	F	H	98	80	+ 57.5

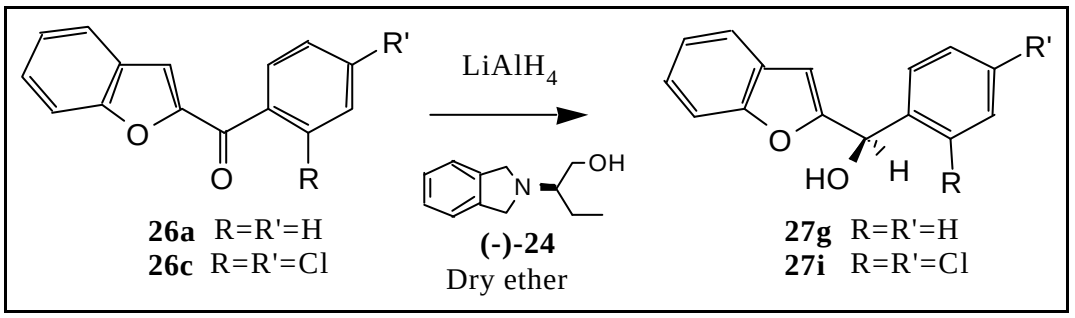
Table 3.4.: Enantioselective reduction of prochiral ketones **25a-d**.

Enantioselective reduction of **25a** with DIP-chloride was also tried in order to obtain directly the enantiopure benzhydrol **27a**. However this reduction only led to the racemic alcohol **(±)-27a**.

3.4.3. Synthesis of enantiomerically enriched 2[benzo(b)furan] phenones by asymmetric reduction.

To the best of our knowledge no examples for the asymmetric reduction of 2 [benzo(b)furan] phenones are reported in literature, and no synthetic strategies for the preparation of the 2-[benzo(b)furan]-aryl methanols in enantiopure form are known.

Asymmetric reductions of these types of prochiral ketones were investigated using the above chiral complexes as reducing reagents. It was expected that the difference between the two aromatic systems would be recognized by the chiral reducing reagent (scheme 3.11), in the hope that the benzo(b)furane oxygen could be coordinated by the aluminium of the reducing agent.



Scheme 3.11 : Asymmetric reduction of prochiral ketones **26a** and **26c.**

This hypothetical coordination should give a stereofacial discrimination in the ketone **26a.** Another hypothesis is that the repulsion between the oxygen of the ketone and the oxygen of the benzofuran

induces a rotation of the bond between these two moieties and the system becomes not as coplanar as in the case of the ortho substituted benzophenones decribed in the previous paragraphs.(*R*)-(-)-2 (2 isoindolinyl) butan-1-ol **(-)-24** was again used as chiral complexing agent of $LiAlH_4$. For this class of prochiral ketones no previous informations regarding the use of this ligand were available. Many experiments were carried out using different molar ratios of the chiral auxiliary and $LiAlH_4$. (1:1; 2:1; 2,5:1; 3:1 molar ratio). While all chemical yields were very high, all reductions led only to racemic alcohols **(±)-27g** (Table 3.5.). Clearly, our hypothesis regarding the coordination of aluminium by the benzofuran oxygen or the possibility of recognition of the two different conformations of the ketone were incorrect.

2-Benzo[b]furan-2',4'dichlorophenone **26c**, in contrast, contains an ortho substituent which seems to be essential for this kind of asymmetric reduction. Again four different reactions were carried out using different molar ratios between chiral auxiliary and $LiAlH_4$ (1:1; 2:1; 2,5:1,0; 3:1) (Table 3.5.). The reduction of **26c,** using a ratio of chiral auxiliary to $LiAlH_4$ = 2.5:1 led indeed to higher enantiomeric excess (66% e.e.) with 96% chemical yield.

Substrate	R;R'	$(RO)_nAlH_{4-n}$	Product	ee %	$\alpha_{D(CHCl_3)}$	C
26a	H,H	n = 1	**(±)-27g**	0	0	1,55
26a	H,H	n = 2	**(±)-27g**	0	0	1,45
26a	H,H	n = 2,5	**(±)-27g**	0	0	1,49
26a	H,H	n = 3	**(±)-27g**	0	0	1,56
26c	Cl,Cl	n = 1	**(±)-27i**	30<	+ 11,01	1,70
26c	Cl,Cl	n = 2	**(±)-27i**	54	+ 18,03	1,31
26c	Cl,Cl	n = 2,5	**(±)-27i**	66	+ 18,98	1.42
26c	Cl,Cl	n = 3	**(±)-27i**	51	+ 18,01	1,36

Table 3.5: Study of the asymmetric reduction of the prochiral ketones **26a** and **26c**.

The different behaviour of the ortho substituted benzophenones **27e,d** as compared to 2-benzo[b]furan-2',4'dichlorophenone (**26c**) is difficult to rationalize, especially considering the fact that the phenyl-2-benzo[b]furan-ketone (**26a**) gave the racemic alcohol **27g** under identical conditions. It could be considered that for some reason, the chlorine by electronic repulsion interacts with the oxygen of the benzofuran moiety

leading to a distortion of the active conformation. Since the reduction of ketones proved to be unsuccessful, this class of enantiopure alcohols was obtained by a different procedure described in the next paragraphs.

The enantiomeric excess of the above compounds was determinated by ^{1}H-NMR with the corresponding esters formed with (*S*)-(-)-1-camphanic chloride. The method of analysis will be described in detail in the next paragraph. Analysis by chiral HPLC (Chiracel OD) of the free alcohols led to identical results. It is interesting to note that all first attempts to determine the enantiomeric excess were, as in the case of the chiral benzhydoles, done by NMR and using shift reagents. Unfortunately none of the many tried reagents was able to resolve completely the signals in the spectrum. For this reason it was necessary to synthesize the corresponding camphanic ester.

3.4.3.1. Determination of the enantiomeric excess in (+)-27i by ^{1}H-NMR.

The enantiomeric excess of **(+)-27i** was determined by ^{1}H-NMR after esterification of **(+)-27i** with (*S*)-(-)-1-camphanic chloride. The principle is based on the known property of diasteroisomers to produce different NMR spectra, next to different physical properties. Calculation of the relative diasteroisomeric ratios in the ^{1}H-NMR was done with the crude product mixture in order to avoid a possible loss of a single diasteroisomer or partial racemization during sample processing.

The crude ^{1}H-NMR spectrum of the reaction products of **(±)-27i** and (*S*)-(-)-1-Camphanic chloride showed only one perfectly resolved signal, allowing integration: the β proton in the furane ring of the benzo[b]furane moiety.

The ^{1}H-NMR of the free alcohol **(±)-27i** showed the β-proton of the furan ring at 6.46 ppm and the carbinol proton at 6.28 ppm, the latter being frequently a doublet because of the coupling between this proton and the alcoholic proton at 2,76 ppm (Fig. 3.2). Generally, if water was present in the sample, due to the low exchange rate between water and the alcoholic proton, this resulting signal was broad and the carbinolic proton appeared as a singlet (the coupling constant is very small and it is not detectable); the same effect was found at high concentrations of the NMR sample. In the absence of these two effects the doublet signals appeared

very sharp and it was possible to calculate the coupling constant, which was found to be 3.16 Hz.

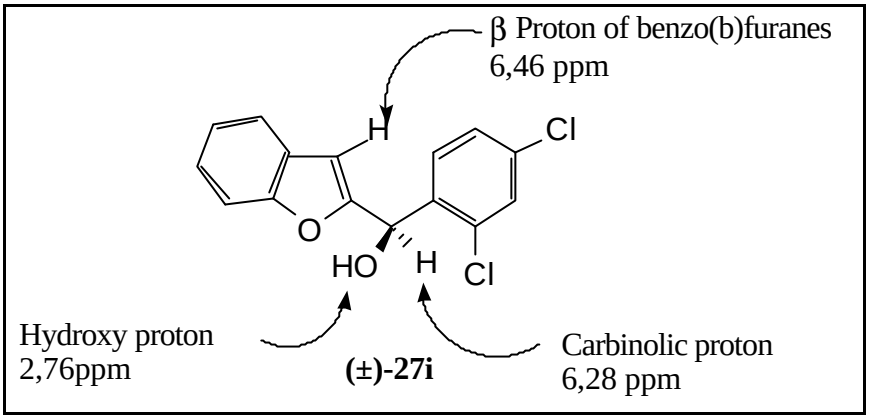


Figure 3.2: Chemical shifts of the protons involved in the determination of the enantiomeric excess.

When the alcohol **(±)-27i** was acylated with (*S*)-(-)-1-Camphanic chloride, the carbinolic proton was shifted by more than 1 ppm into the aromatic region where it could not be detected as a single signal. On the contrary, the β proton of the furane ring in the benzo(b)furane moiety remained at is normal position, and was split in to two well separated singlets (each one belonging to a single diasteroisomer).

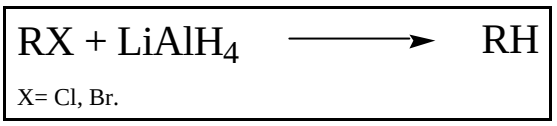
The first experiment was done with racemic **(±)-27i.** The signal of the two diasteroisomers at 6.62 and 6.58 ppm showed the typical 1:1 ratio of a racemic mixture. The experiment was repeated for each asymmetric reduction and the enantiomeric excess produced was calculated in all cases from the relative ratio of the β proton of the furane ring and the benzo(b)furane moiety. The experiment was developed into a routine procedure, and the acylation was directly performed in deuterated chloroform in presence of triethyl amine as base. This was possible since the region of the spectrum needed for the determination of the e.e. was not obscured by any other signal resulting from the base, salt or small excess of the camphanic chloride.

All attempts to separate the diasteroisomers by normal or reverse phase TLC failed. An enrichment of one diasteroisomer was achieved by preparative silica TLC, in collecting the product from the higher part of the spot. The resulting enantiomeric excess was 82% e.e.

3.5 Dehalogenation of alcohols containing halogenated aryl groups.

In order to obtain the benzhydroles and phenyl-2-benzo[b]furan methanole without substituents, the aryl dehalogenation of **(±)-27c** , **(+)-27c** and **(±)-27i** was studied.

Dehydrohalogenations or dehalogenations are a kind of reduction that can be accomplished using a large variety of reducing reagents[27]. The most common one is lithium aluminum hydride (scheme 3.12).



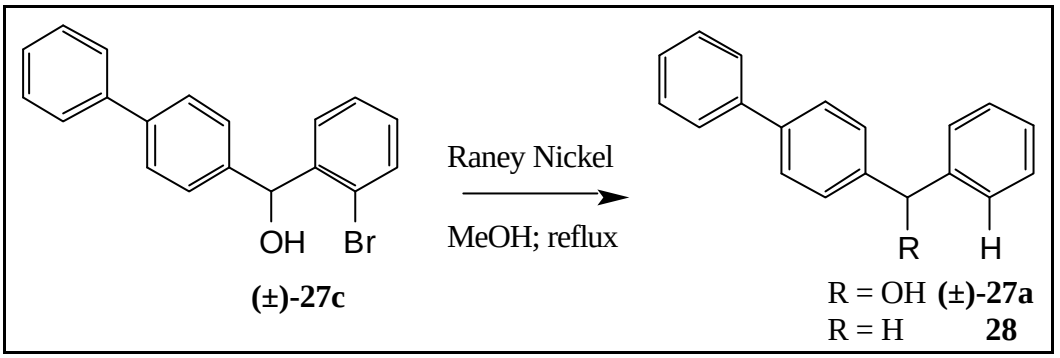
Scheme 3.12: Dehydrohalogenation by $LiAlH_4$.

This reagent reduces almost all types of alkyl[28] and aryl[29,30] halides. Removal of halogen from aromatic rings can also be accomplished by various other reducing reagents, such as n-Bu_3SnH[31], Ph_3SnH[32], metallic Zn in acid or base[33], catalytic hydrogenolysis[34], $NaBH_4$ and a catalyst[35], Nickel-Raney in alkaline solution[36]. Not all of these reagents operate by electrophilic substitution mechanisms, some are involved in nuclephilic substitution and others in free radical processes.

3.5.1 Aryldehalogenation of (±)-27c, (+)-27c and (±)-27i.

Various reagents and experimental conditions were used for the aryl dehalogenation of **(±)-27c** and **(+)-27c.** Originally all the different procedures were carried out on the racemic material in order to obtain informations regarding the chemical behavior during these transformations.

Raney Nickel in methanol (scheme 3.13) was found to be unselective. A mixture of the desired product and the dehydroxylated side product **28** was found in the reaction mixture after a few hours. Both temperature and reaction times were changed but no selective reaction conditions were found.

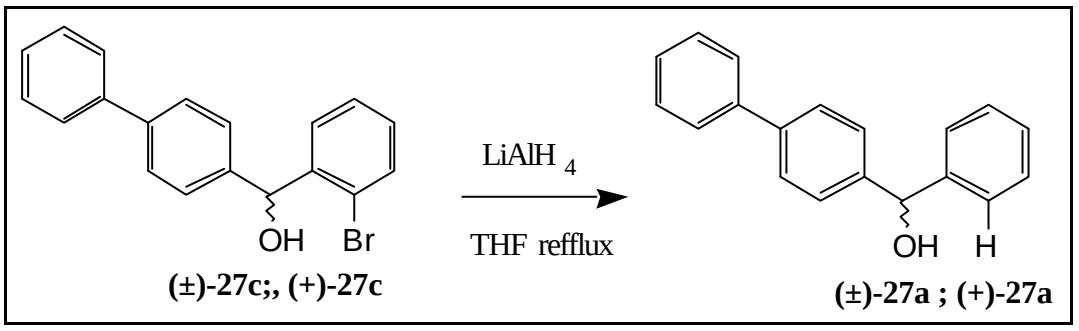


Scheme 3.13: Dehydrohalogenation of **(±)-27c** by Raney Nickel.

At room temperature the reaction did not occur at all and under reflux the ratio between the two products **(±)-27a** and **28** was 1:1. If the reaction was carried out for extended times mainly **28** was recovered. Identical reactions carried out with the benzofurane derivative **(±)-27i** gave a complex mixture of unknown products. However, from the crude NMR it was clear that the benzofurane ring was distroyed.

A second attempt was made with *n*-tributyltinhydride in dry THF,while AIBN was used to initiate the radical process. After twenty four hours under reflux only the starting material was detected by TLC.

Dehydrohalogenation of **(±)-27c** by $LiAlH_4$ was found to be exceptionally selective, and the side product **28** was not detected.

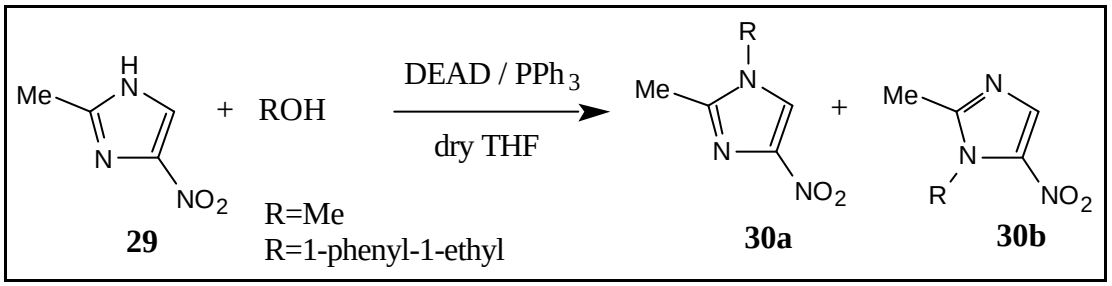


Scheme 3.14: Dehydrohalogenation of **(±)-27c** and **(+)-27c** by $LiAlH_4$.

The reaction was also performed with enantiopure **(+)-27c** (e.e.>93%) and enantiopure **(+)-27a** (>93%e.e.) was obtained. Thus, no racemization occured during the reaction. The e.e. was determinated by chiral HPLC (Chiracel OD). Under completely identical reaction conditions using **(±)-27i** no desired product was detected by TLC. Only unreacted starting material and a series of side products were found.

4. Stereospecific Synthesis of 1-Alkylimidazole Derivatives *via* Mitsunobu Reaction.

The Mitsunobu reaction was considered to be a good method for the synthesis of 1-alkyl imidazoles.To the best of our knowledge the only information (no experimental details were reported) in this regard involved the reaction of both imidazole and 2-methyl-4,(5)- nitroimidazole **29** with either methanol or 1-phenyl-1-ethanol. Imidazole itself is unreactive under the normal reaction conditions probably because of its pKa (higher than 11). The nitroimidazol derivative reacts as expected to give a mixture of *N*-alkyl-2-methyl-4-nitroimidazole **30a** and the corresponding 5-nitro isomer **30b** (Scheme 4.1):



Scheme 4.1: Mitsunobu reaction with 2-methyl-4,(5)- nitroimidazole **29.**

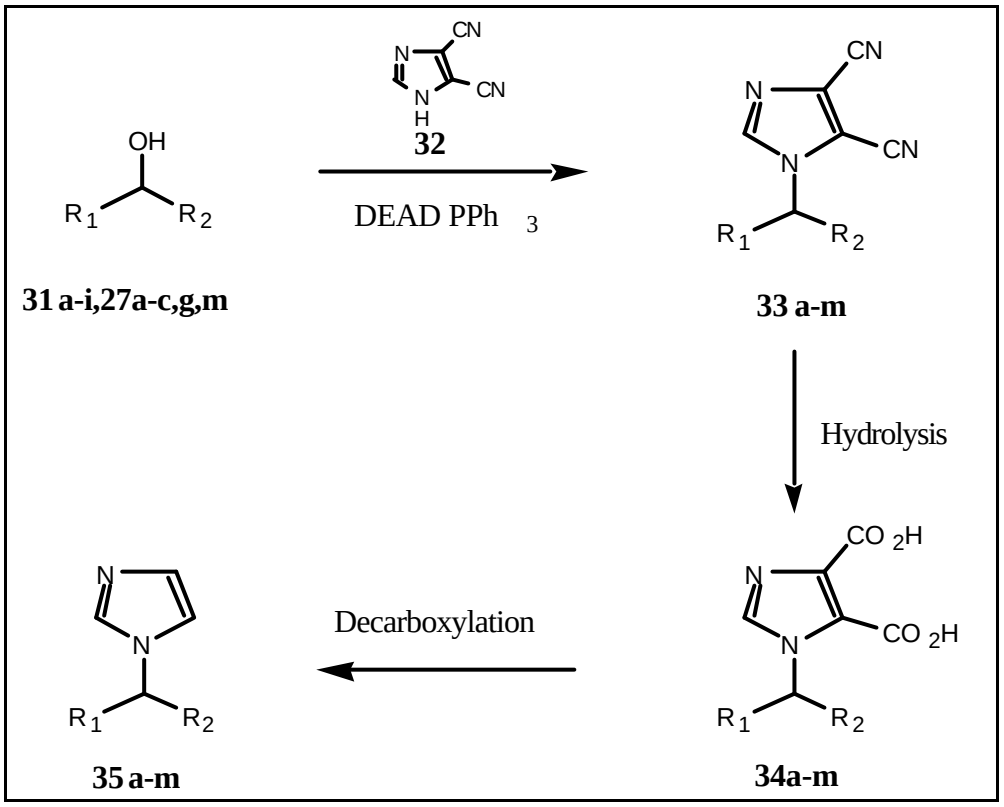
4.1. Alkylation of Imidazole derivatives *via* Mitsunobu reaction.

In order to perform the alkylation with alcohols **31a-f** and **27a-c,g,m** *via* Mitsunobu reaction, commercially available 4,5-dicyano imidazole **32** was chosen as substrate.

This choice has a number of advantages. First, the presence of the two cyano groups decreases the pKa of the imidazole ring to well below 11. This means that the 4,5 dicyano imidazole **32** is a suitable substrate for the alkylation *via* Mitsounobu reaction. Second, **32** has a C-2 symmetry, consequently the two nitrogens of the imidazole moiety are identical and the *N*-alkylation leads to a single product. Thirdly, it is commercially available and cheap. Fourth, the cyano groups can be removed from the final product in two steps: by hydrolysis followed by decarboxylation.

Twenty racemic and enantiopure alcohols were used to study the Mitsunobu reaction with 4,5 dicyanoimidazole **32**. Alkylated products

33a-m were hydrolysed to the dicarboxylic acid derivatives **34a-m** with NaOH and finally **34a-m** were converted *via* a decarboxylation step into the final imidazole products **35a-m** (Scheme 4.2).



Scheme 4.2: Synthetic pathway, Mitsunobu reaction-Hydrolysis-Decarboxylation.

The racemic and enantiopure alcohols **31a-f** and **27a-c,g,m** were used as alkylating agents in order to establish the stereochemical outcome of the Mitsunobu reaction with 4,5 dicyanoimidazole **32**. Alcohols **31 a-f** are commercially available both in racemic and enantiopure form. Alcohols **27a-c,g,m** (entries 11-19 tab 4.1) were synthesized as reported in chapter 3. Results are summarized in Tab. 4.1.

31a-f and **27a-c,e,g,m** were chosen in order to obtain a complete picture of the potential and limits of this methodology; the substrates are primary, secondary, aliphatic, homobenzylic, benzylic, and benzyhydrilic alcohols. Tertiary alcohols such as *t*-butanol are unreactive. The results were very interesting indeed because it was now possible to understand the real limits of the methodology. Special attention was dedicated to the stereochemical control rather than the chemical yield.

Entry	Substrate	Config. (ee%)	R_1	R_2	Product (Yield%)	Config. Pro (% ee)
1	**31a**	-	H	H	**33a** (45)	-
2	**31b**	-	H	nC_7H_{15}	**33b** (98)	-
3	**(±)-31c**	-	Me	nC_6H_{13}	(±)-**33c**(70)	-
4	**(-)-31c**	***R*** (99)	Me	nC_6H_{13}	(+)-**33c**(65)	***S*** (97)
5	**(+)-31c**	***S*** (99)	Me	nC_6H_{13}	(-)-**33c**(67)	***R*** (97)
6	**(±)-31d**	-	Me	Bn	(±)**33d**(40)	-
7	**(-)-31d**	***R*** (99)	Me	Bn	(+)**33d**(39)	***S*** (98)
8	**(±)-31e**	-	Et	Ph	(±)-**33e**(55)	-
9	**(+)-31e**	***R*** (99)	Et	Ph	(-)**33e**(55)	***S*** (41)
10	**31 f**	-	Ph	Ph	**33f** (94)	-
11	**(±)-27a**	-	Ph	$4PhC_6H_4$	(±)-**33g**(96)	-
12	**(+)-27a**	**nd**(>95)	Ph	$4PhC_6H_4$	(±)-**33g**(96)	***R,S*** (0)
13	**(±)-27b**	-	Ph	$2BrC_6H_4$	(±)-**33h**(81)	-
14	**(+)-27b**	**nd**(>95)	Ph	$2BrC_6H_4$	(±)-**33h**(96)	***R,S*** (0)
15	**(±)-27c**	-	$2BrC_6H_4$	$4PhC_6H_4$	(±)-**33i**(82)	-
16	**(+)-27c**	**nd**(>95)	$2BrC_6H_4$	$4PhC_6H_4$	(±)-**33i**86)	***R,S*** (0)
17	**(±)-27g**	-	2Benzo[b] furane	Ph	(±)-**33l**(10)	-
18	**(±)-27m**	-	2Benzo[b] furane	$2,4C_6H_3$	(±)**33m**(5)	-
19	**(+)-27m**	**nd**>60	2Benzo[b] furane	$2,4C_6H_3$	(±)**33m**(5)	***R,S*** (0)

Table 4.1: Mitsunobu reaction of alcohols **31a-f** and **27a-c,e,g,m** with 4,5-dicyanoimidazole.

The experimental results led to the following, very important informations:

1) The reaction did not occur when a tertiary alcohol (e.g. *t*-butanol) was used as substrate, even if an excess of reagent was used.

2) When the diaryl methanoles (entries 10-16) were used as substrates longer reaction times and an excess of reagents (4:1 molar ratio reagents/substrate) were required in order to achieve complete conversion. When in this class of compounds one aromatic ring was substituted with 2-

benzo[b]furane (entries 17-19 Tab 4.1), the reaction led to very low conversions (5/10%). The starting material was always recovered also when the reaction time was very long (>24 hours) and a large excess of reagents was used (molar ratio reagents / substrate 5/1).

3) The reaction showed pure S_N2 mechanism with secondary aliphatic alcohols. Enantiomerically pure aliphatic alcohols **(-)-(*R*)-31c**, **(+)-(*S*)-31c**, **(-)-(*R*)-31d** (entries 4,5 and 7 Table 4.1) gave the corresponding 1-alkyl-4,5-dicyano imidazoles **(+)-(*S*)-33c,(-)-(*R*)-33c** and **(+)-(*S*)-33d** as single enantiomers (97/98% e.e.) with medium to good chemical yields. The molar ratio between substrate and reagents was always 1:1. In these cases the reaction conditions were not further optimized towards higher chemical yields.

4) The reaction had a mixed S_N2-S_N1 mechanism with the benzylic secondary alcohol **(+)-(*R*)-31e** (entry 9 tab 4.1). The resulting product **(-)-(*S*)-33e** showed an enantiomeric excess of 41% e.e.. Thus more than 50% of the enantiomeric excess of the corresponding starting material was lost. In order to establish whether the racemization process occured due to reaction conditions or due to the inherent "mixed" mechanism three different experiments were perfomed:

A) Reverse addition of reagents:

In this experiment the betaine complex between DEAD and triphenyl phosphine was preformed at -20°C in dry THF in absence of alcohol and 4,5-dicyanoimidazole. Then the last two reagents in dry THF were added to the reaction mixture. After 20 hours, the temperature was raised to room temperature for 8 hours. Following this procedure the enantiomeric excess of the product was not increased.

B) Shorter reaction time:

The reaction was carried out for a short time (10') and immediately interrupted. The resulting chemical yield was lower than in the normal experiment, however the enantiomeric excess was identical.

C) Lower temperature:

An experiment as described under B was carried out at a lower temperature. At -25°C the reaction did not occur, at -15°C the chemical yield was decreased to 4%. The enantiomeric excess was identical to those obtained in the other experiments.

The results of these three experiments are summarized in Table 4.2. The substrate was always **(+)-(*R*)-31e**, the molar ratio substrate / reagent

was 1:1, TLC analysis showed an almost complete comsumption of the starting material. However it was impossible to obtain higher chemical yields than 55% after purification by flash chromatography. An unknown side product was detected by NMR analysis, inseparable from the reduced DEAD:

Entry	R_1	R_2	Config. (ee%)	T (°C)	Product yield %	Config. prod. (ee%)
A	Et	Ph	***R*** (99)	25	(-)-**33e**(55)	***S*** (41)
B	Et	Ph	***R*** (99)	25	(-)-**33e**(32)	***S*** (43)
C	Et	Ph	***R*** (99)	-15	(-)-**33e** (4)	***S*** (45)

Table 4.2: Reaction mechanism for **(+)-(R)-31e.**

5) Diaryl methanoles **(+)-27a**, **(+)-27b**, **(+)-27c** (entries 12, 14, 16, Tab. 4.1) and the 2-benzo[b]furane-2,4 dichlorophenyl methanol **(+)-27m** (entry 19 tab 4.1) led to racemic products because of a completely S_N1 reaction mechanism. These reactions were performed using both an equimolar or excess ratio (4:1) of reagents and substrate. Under the latter conditions a quantitative yield of the corresponding alkylate 4,5 dicyanoimidazole derivative with diaryl methanoles **(+)-3a**, **(+)-3g**, **(+)-3e** was obtained.

The use of different phosphines such as *n*-tributyl phosphine or p-methoxytriphenyl phosphine did not show any advantages as compared to the more common triphenyl phosphine. Identical results were obtained in using either diisopropyldiazodicarboxylate DIAD or ADDP [(1,1'-azodicarbonyl) dipepiridine)] instead of DEAD.

On the basis of these results it was clear that the Mitsunobu reaction was not a preferred methodology to obtain our target compounds in enantiopure form. Nevertheless it can be considered an alternative synthesis of the final products in racemic form.

4.1.1 *N*-Alkyl-4,5-dicyanoimidazoles 33c-e,g-i,m: determination of enatiomeric excess.

The determination of the enantiomeric excess in the Mitsunobu reaction products **33c-e,g-i,m** was one of the major problems in the synthetic efforts. These products do not contain functional groups such as

hydroxy or amine groups, that would allow the synthesis of Mosher or mandelate esters, amides or generally diasteroisomers which are easily analyzed by HPLC, GC or ^{1}H-NMR. All attempts using chiral HPLC were unsuccessful.

The only method that gave reasonable results was the analysis by ^{1}H-NMR in presence of the chiral shift reagent[2] Eu(hfc)$_3$ { europium(III) tris[3-((heptafluoropropyl)hydroxymethylene)-(+) champhorato}.

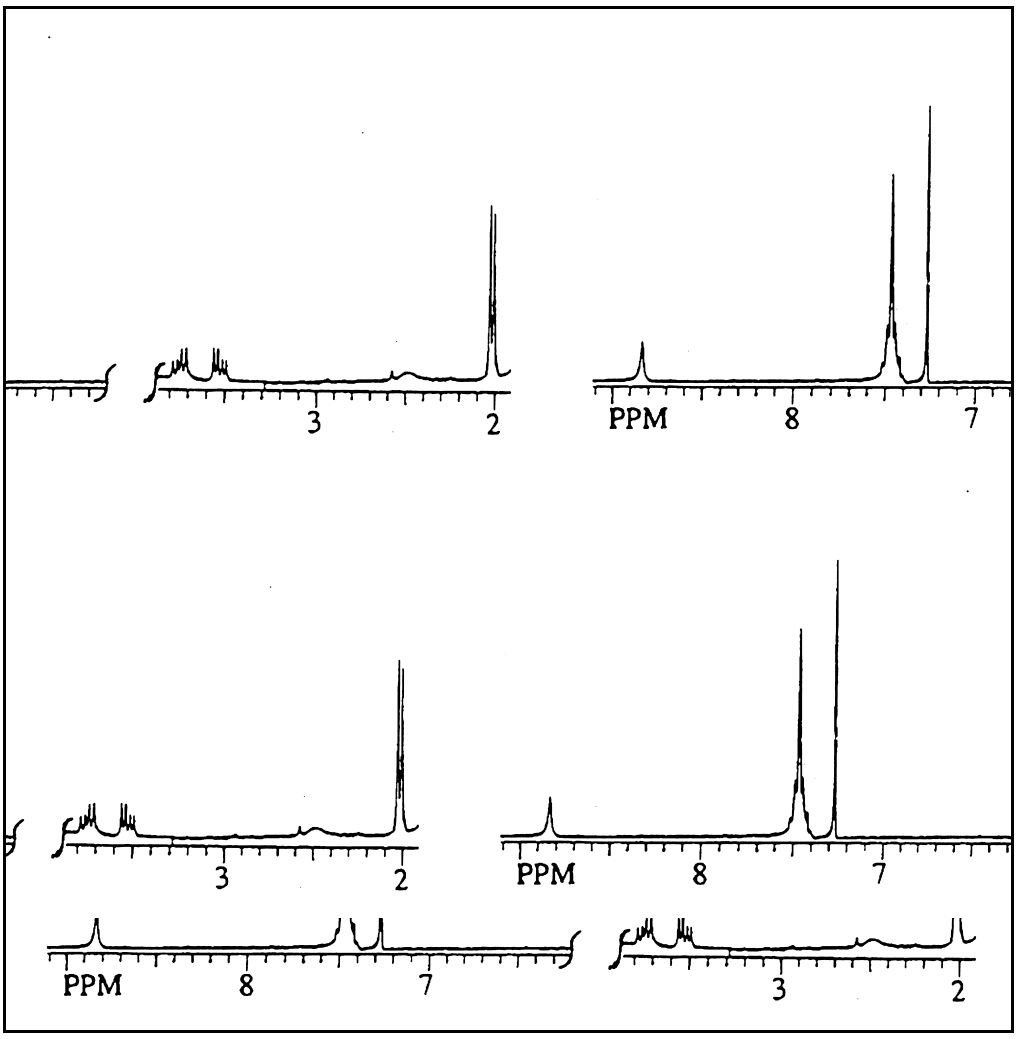


Figure 4.1.:^{1}H-NMR spectrum of **(±)-33d** (above) and **(+)-(*S*)-33d** (below) in presence of chiral shift reagent.

A $CDCl_3$ solution of Eu(hfc)$_3$ of known concentration was prepared and added to the NMR tube containing the sample in $CDCl_3$ solution. Various amounts of shift regent were added until the splitting of the desired signals were observed. The best results were obtained with a molar ratio of the sample and the chiral shift reagent of 1:1.2 to 1.6.

The first measurements were carried out with the racemic product in order to obtain a reference spectrum. The experiment was then repeated with the chiral product. Two points are of importance to note with this method. First, the sample purity must be high in order to avoid the presence of signals that could be coincident with those of the sample. Second, the signal to be integrated must be completely resolved and as sharp as possible, in order to allow a perfect integration. It would be best to have more than one signal for integration and take an average of all values.

The measurements were performed for all racemic and chiral products reported in table 4.1. In some cases it was not possible to detect any signal resulting from the minor enantiomer, in these cases the enantiomeric excess was assigned to be 98% e.e. In figure 4.1 the ^{1}H NMR spectra (300 MHz) of **(±)-33d** and **(+)-(*S*)-33d** in presence of the chiral shift reagent Eu(hfc)$_3$ are shown the selected signals corresponding to the proton of the imidazole (10.28 and 10.70 ppm), the aromatic groups (7.40-7.55 and 7.65-7.80 ppm), chloroform (7.23 ppm), methylen (3.75-3.95 and 4.0-4.15 ppm) and methyl moieties (2.25-2.35 ppm) respectively; the spectrum above is racemic **(±)33d** and the one below from the enantiopure (ee 98%) **(+)-(*S*)-33d**. The Imidazole proton betweeen 10 and 11 ppm were used for the integration.

4.2. Hydrolysis and Decarboxylation of *N*-Alkyl-4,5-dicyanoimidazoles 33c-g.

As reported in scheme 4.2. of the synthetic pathway the alkylation of the 4,5-dicyanoimidazole *via* Mitsunobu reaction is followed by two additional synthetic steps: hydrolysis and decarboxylation. The cyano group is transformed into a carboxylic acid by hydrolysis with 10N NaOH in ethanol under reflux. These harsh conditions were needed for complete conversion. Less concentrated NaOH solution resulted in only partial hydrolysis to the corresponding amide.

The *N*-Alkyl-4,5-dicyanoimidazoles **33c-g** were treated with 10N NaOH in ethanol under reflux for 16-24 h. After acidification with 3N HCl the *N*-Alkyl-4,5-imidazoledicarboxylic acids **34a-e** precipitated out, (entries 1-4,7-8 Table 4.3) and were recovered by filtration. Only for the isolation of **(±)-33e** and **(-)-(*S*)-33e** (entries 5,6 Table 4.3) extraction of

the products with ethyl acetate was necessary since after acidification no precipitation of the products occured. In all cases the chemical yields were high.

In table 4.3 the structures and chemical yields of the products of the hydrolysis are reported.

Entry	Substrate	R_1	R_2	Produc (Yield t%)
1	**(±)-33c**	Me	nC_6H_{13}	**(±)-34a**(77)
2	**(+)-(*S*)-33c**	Me	nC_6H_{13}	**(+)-(*S*)-34a**(65)
3	**(±)-33d**	Me	Bn	**(±)-34b** (79)
4	**(+)-(*S*)-33d**	Me	Bn	**(+)-(*S*)-34b**(76)
5	**(±)-33e**	Et	Ph	**(±)-34c** (73)
6	**(-)-(*S*)-33e**	Et	Ph	**(-)-(*S*)-34c**(73)
7	**33f**	Ph	Ph	**34d** (97)
8	**(±)-33g**	Ph	$4PhC_6H_4$	**(±)-34e** (85)

Table 4.3: Hydrolysis of the *N*-Alkyl-4,5-dicyanoimidazoles **33c-g**.

At this stage the enantiomeric excess of the diacids was not measured because of their low solubility in $CDCl_3$ (the normal solvent used with the shift reagents). Attempts with other solvents like pyridine-d_6 and DMSO-d_6 were unsuccessful. After the addition of the chiral shift reagent precipitations always occured and it was not possible to perform the ^{1}H-NMR experiment. Thus the synthesis was carried on to the desired final imidazole derivatives.

Some of the diacids **34a-e** were used to synthesize separable diasteroisomers by reacting them with enantiopure amines or alcohols as described in paragraph 4.5.

4.2.1. Decarboxylation of *N*-Alkyl-4,5-imidazol dicarboxylic acids 34a-e.

Three different methods were tried for the decarboxylation of the *N*-Alkyl-4,5-imidazoldicarboxylic acids **34a-e**. The first method involved chinoline and copper powder at 120 °C. Almost all of the unreacted starting material was recovered from the reaction mixture. The second method used copper carbonate in DMF under reflux. This reaction did not give any desired product, only decomposition products and starting

material. The third method was purely thermal and was carried out in diphenyl ether at reflux in an inert atmosphere. The desired product was obtained in only 10 minutes and purification was carried out by silica gel filtration with two different solvents: *n*-hexane to remove the the diphenyl ether and ethyl acetate to recover the product.

The chemical yields were moderate to very high. For these compounds it was again possible to calculate the enantiomeric excess using 300 MHz ^{1}H-NMR analysis in presence of the chiral shift reagent Eu(hfc)$_3$ { europium(III) tris[3-((heptafluoropropyl) hydroxymethylene)-(+) champhorato} for **(+)-(*S*)-35a** and europium(III) {tris(d,d-dicampholylmethanate)} for **(+)-(*S*)-35b** and **(±)-35c**.

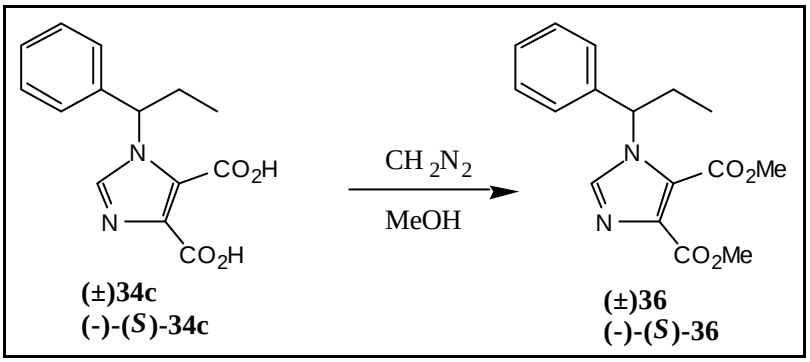
In table 4.4 the chemical yields, the enantiomeric excess and the absolute configurations of the obtained products are reported.

Entry	Substrate	R_1	R_2	Product (yield %)	Con. (% e.e.)
1	**(±)-34a**	Me	nC_6H_{13}	**(±)-35a (81)**	-
2	**(+)-(*S*)-34a**	Me	nC_6H_{13}	**(+)-35a (77)**	***S*** (97)
3	**(±)-34b**	Me	Bn	**(±)-35b (55)**	-
4	**(+)-(*S*)-34b**	Me	Bn	**(+)-35b (53)**	***S*** (98)
5	**(±)-34c**	Et	Ph	**(±)-35c (33)**	-
6	**(-)-(*S*)-34c**	Et	Ph	**(±)-35c (38)**	***R,S*** (0)
7	**34d**	Ph	Ph	**35d (90)**	-
8	**(±)-34e**	Ph	$4PhC_6H_4$	**(±)-6a (98)**	-

Table 4.4: Decarboxylation products of *N*-Alkyl-4,5-imidazoldicarboxylic acid **34a-e**.

300 MHz ^{1}H-NMR analysis in presence of chiral shift reagents revealed an enantiomeric excess higher than 97% e.e. for **(+)-(*S*)-35a** and **(+)-(*S*)-35b**. Therefore no racemization occurs during the final steps. Only in the hydrolysis and the decarboxylation of **(-)-(*S*)-33e** the product **(±)-35c** was produced in racemic form.

In order to establish where racemization took place in the hydrolysis and decarboxylation sequence, the intermediate diacid **(±)-34c** and **(-)-(*S*)-34c** were methylated by an excess of diazomethane to obtain the dimethyl esters **(±)-36** and **(-)-(*S*)-36** (Scheme 4.3).



Scheme 4.3: Esterification of **(±)-34c** and **(-)-(*S*)-34c**.

Since the dimethyl ester **(-)-(*S*)-36** showed an e.e. of only 40 % e.e. it was concluded that the intermediate diacid **(-)-(*S*)-34c** racemized during the decarboxylation process. The dimethyl esters **(±)-36** and **(-)-(*S*)-36** were analyzed again by ^{1}H-NMR in presence of shift reagents in order to determine the enantiomeric excess.

4.3. Mitsunobu reaction with 4-(5)-ethyl imidazole carboxylate 37.

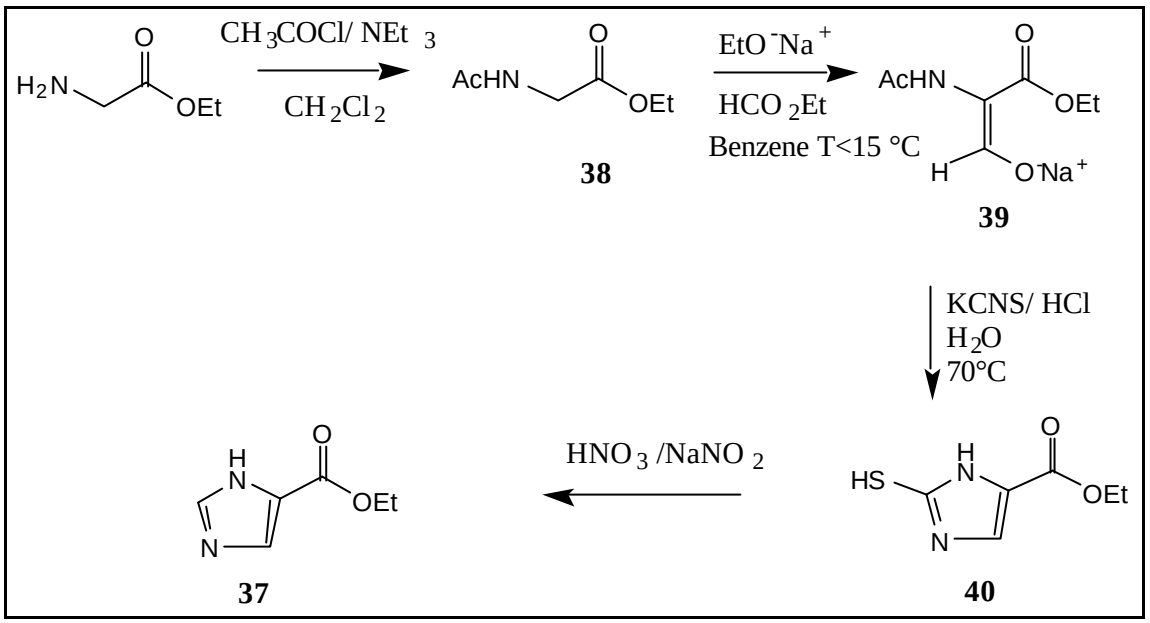
With the aim of avoiding the drastic conditions required in the hydrolysis and decarboxylation sequence of 4,5-dicyanoimidazole derivatives the use of another substituted imidazole was investigated.

4.3.1. Synthesis of 4-(5)-ethyl imidazole carboxylate 37.

The synthesis of 4-(5) - ethyl imidazole carboxylate **37** was reported at the end of the last century[3] without any experimental conditions or physical constants.

The synthesis involved the acetylation of ethyl glycine ester using acetyl chloride in presence of triethyl amine leading in quantitave yield to the acetyl glycine ethyl ester **38**. α–alkylation of **38** with ethyl formiate in dry benzene and sodium ethoxide as base led to the intermediate **39** which was not purified or characterized. The reaction mixture appeared as a white solid after 24h at 0°C. The crude product was dissolved in water and acidified with hydrochloric acid and cyclized to 2-mercapto-4(5)-ethyl imidazolecarboxylate **40** using KCNS. Finally **40** was desulfurated by

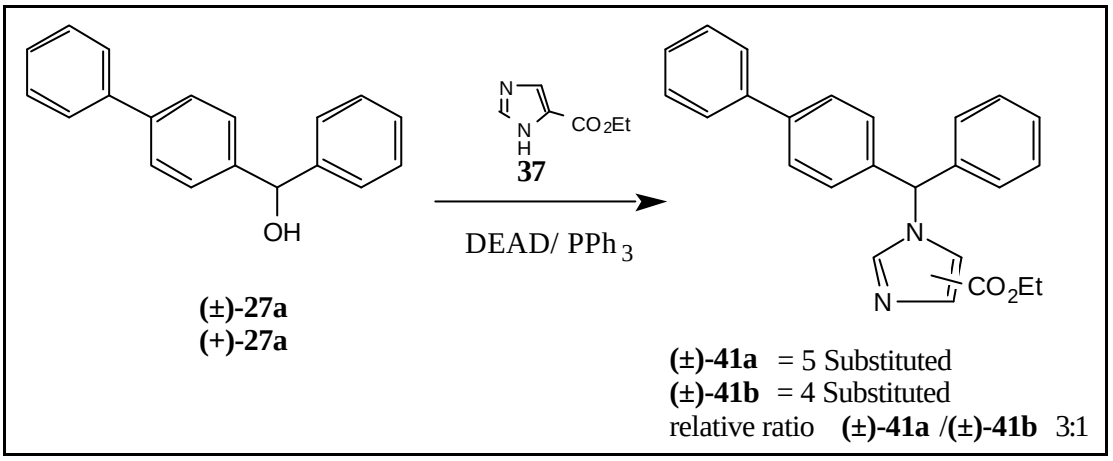
HNO_3 and $NaNO_2$ at 0°C leading the 4(5) ethyl imidazole carboxylate **37** (Scheme 4.4).



Scheme 4.4: Synthesis of 4(5)-ethyl imidazol carboxylate **37**.

4.3.2. Mitsunobu Reaction with 4(5)-ethyl-imidazole carboxylate 37.

The Mitsunobu reaction with 4(5)-ethylimidazole carboxylate **37** was carried out under the normal conditions reported in paragraph 4.2. The alcohols **(±)-27a, (±)-27c** and **(+)-27c** were chosen as substrates because they are the natural precursors of bifonazole. Since the imidazole derivative **37** was unsymmetrical the reaction led to a 3:1 mixture of the regioisomers **(±)-41a** and **(±)-41b** wich were separated by flash chromatography. When the reaction was performed with the enantiopure benzhydrole **(+)-27a**, the resulting products **(±)-41a,b** were, also in this case, racemic (scheme 4.5.). The relative ratio of the regioisomers was 3:1.



Scheme 4.5: Mitsunobu reaction with 4(5) ethyl imidazole carboxylate **37**.

The structural assignment of the two regioisomers **(±)-41a,b** was achieved by monodimensional ^{1}H and ^{13}C-NMR and two dimensional one bond ^{1}H-^{13}C correlation spectra. From these experiments it was possible to assign the benzhydryl and the imidazole methynes, while long range ^{1}H-^{13}C-correlation spectra were used to assign the position of the carboethoxy group on the imidazole ring (Fig. 4.2).

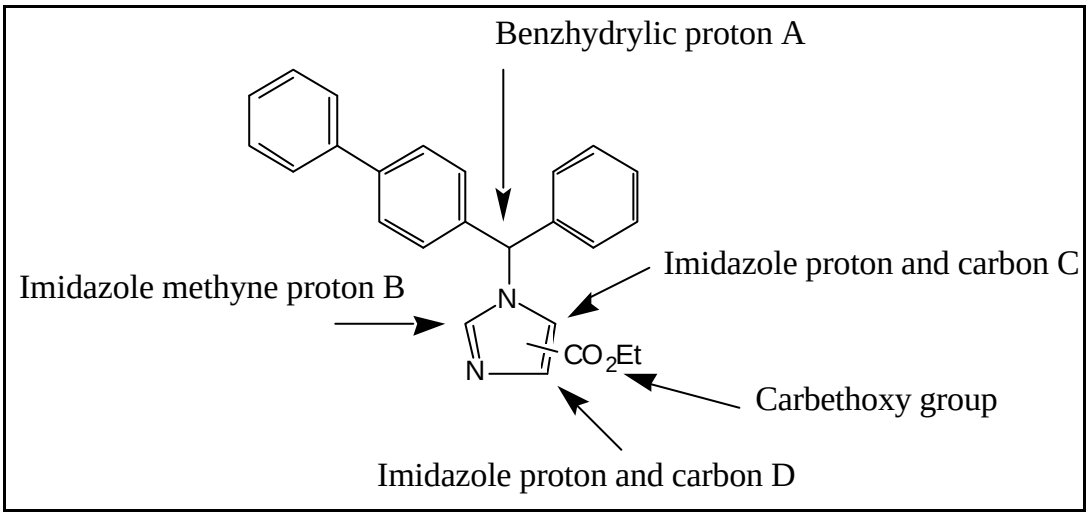


Figure 4.2: representative protons and carbons of **41a,b** for the assignment of regiochemistry.

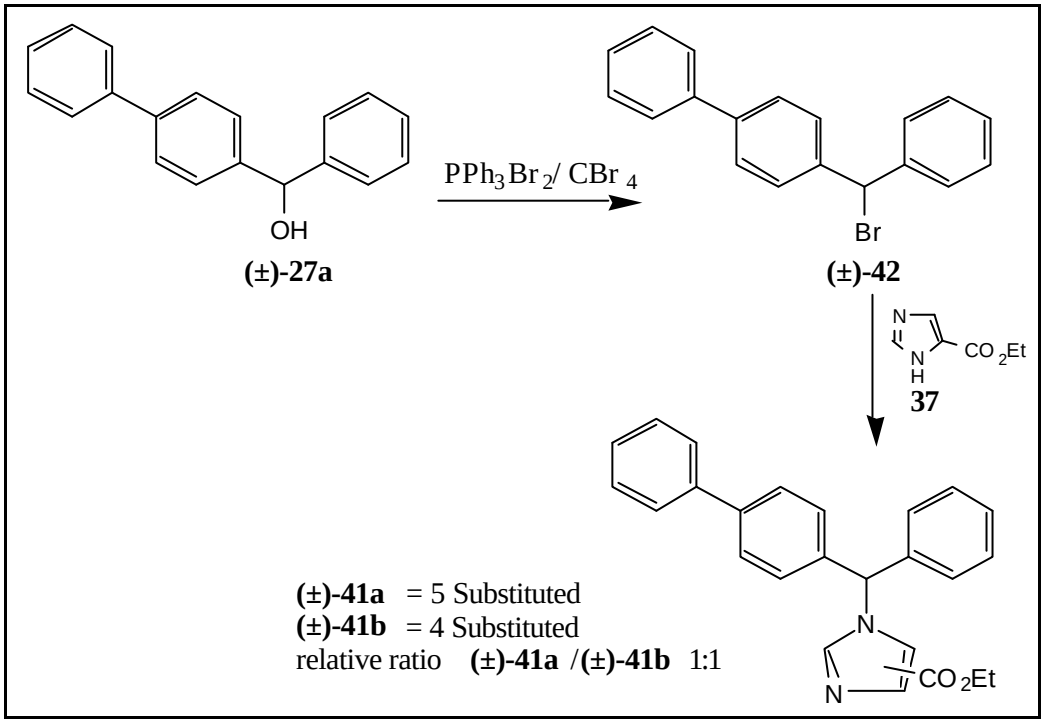
In the case of **(±)-41a** the benzhydrylic proton (proton A fig.4.2) showed a long range correlation only with one of the imidazole methynes (position B and C fig.4.2). For **(±)-41b** the correlation was found with both the methynes of the imidazole ring (position B or C fig.4.2). These results

indicated that the carbethoxy group was at position 5 in **(±)-41a** and at position 4 in **(±)-41b**. The diagnostic resonances are listed in table 4.5.

Position	**(±)-41a dH**	**(±)-41a dC**	**(±)-41b dH**	**(±)-41b dC**
A	7.57	63.5	6.6	65.3
B	7,85	138.0	7.5	138.0
C	7,40	141.7	-	-
D	-	-	7.55	125.7

Table 4.5: chemical shifts (ppm) of the diagonstic protons and carbons in **(±)-41a,b.**

(±)-41a,b were also synthesized using another strategy. For this the alcohol **(±)-27a** was converted into the corresponding bromo derivative **(±)-42** using bromo triphenylphosphine in carbon tetrabromide which, without isolation was treated with **37**. An equimolar mixture of the two regioisomers was obtained in 32 % overall yield (scheme 4.5)



Scheme 4.5 : Alternative synthesis of **(±)-41a,b**.

The different ratio of the two regioisomers obtained in the Mitsunobu reaction can be explained by the different basicity (pKa) of the two nitrogens in 4(5)-ethyl imidazol carboxylate **37**.

As already outlined above (chapter 3, paragraph 3.1.2.1) one of the most important requirement for the Mitsunobu reaction is the pKa value. In this case, the two nitrogens have a different pKa, the one next to the carboxy ethyl group is more acidic (more reactive in the Mitsunobu reaction conditions) because of the electron withdrawing effect of the COOEt group. Probably this effect is stronger than the resonance effect on the nitrogen.

In the bromine substitution (scheme4.5) the pKa is not as important an parameter as the nucleophilicity of the two nitrogens. In the light of the previous considerations the expected experimental results could be opposite to those resulting from the Mitsunobu reaction.

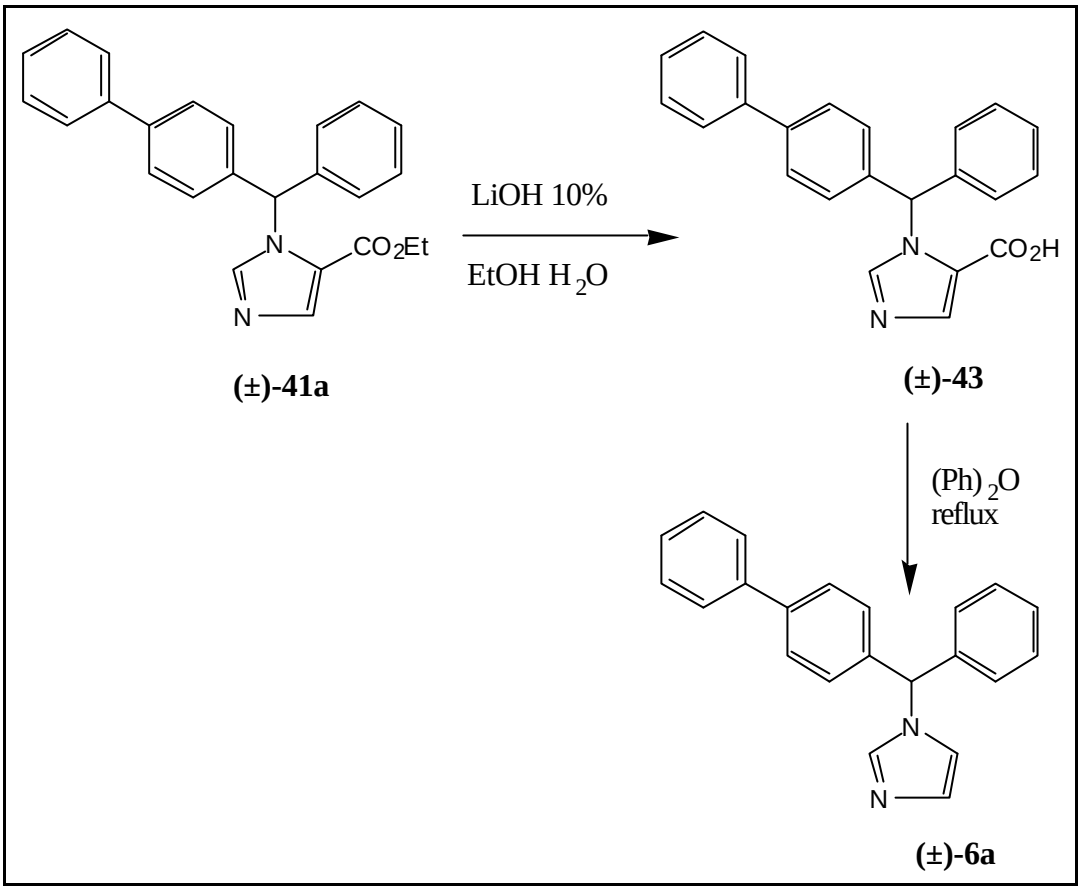
In fact, the nitrogen in the α position of the ester is less nucleophilic than the other, but the experimental results clearly indicate that regioselection did not occur during displacement of the bromine. It is also interesting to note that the reaction is apparently not affected by steric influences on the imidazole ring.

4.3.3. Synthesis of Bifonazole (±)-6a from (±)-41a.

(±)-41a was hydrolyzed to the corresponding acid **(±)-43** in high yield with 10% LiOH in a mixture of ethanol / water 1:1 at 0°C for two hours (scheme 4.6). The reaction conditions were very mild in comparison to the previously reported one for the hydrolysis of dicyano imidazoles derivatives **33c-g.**

Unfortunately, all attempts to decarboxylate **(±)-43** under mild conditions were unsuccessful. The only reaction producing the desired product **(±)-6a** was again the thermal decarboxylation by heating the acid **(±)-43** under reflux in diphenyl ether (scheme 4.6).

In conclusion, the monosubstituted imidazole 4(5)-ethyl imidazol carboxylate **37** can be used in the Mitsunobu reaction but a mixture of regioisomers was obtained. The reaction led to a racemic product when the enantiopure benzhydrylic alcohol **(+)-27a** was used as starting material. While the reaction conditions for hydrolysis of the ester groups are milder than those used for the dicyanoimidazole, unfortunately no mild conditions were found for the decarboxylation step. Thus, this new strategy did not have any advantages over the previously reported method using 4,5-dicyano imidazole.



Scheme 4.6: Hydrolysis and decarboxylation of *N*-alkyl ethyl imidazole carboxylate **(±)-41a**.

The acid **(±)-43a** however offered an opportunity to synthesize separable diasteroisomers as described in paragraph 4.5.

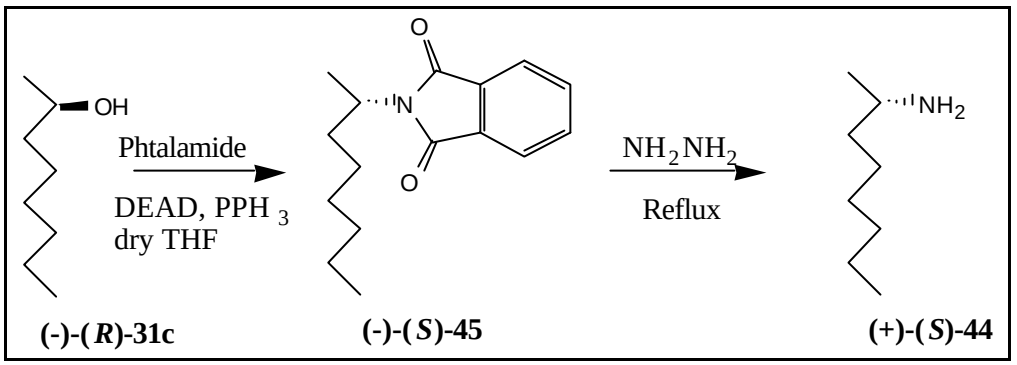
4.4. Stereochemical Assignment of the Mitsunobu Reaction with Imidazole Derivatives.

The stereochemical assignment of the Mitsunobu reaction was another point elucidated in the present work. In the literature there are no data available on these enantiopure compounds. It was the goal to find an alternative synthetic pathway for enantiopure *N*-1-alkylimidazoles and to compare their specific rotation with the products obtained from the Mitsunobu reaction, followed by hydrolysis and decarboxylation as described in the above paragraphs and to assign the correct stereochemistry.

In the literature several polysubstituted imidazoles were obtained starting from an amine by construction of the imidazole ring[4].

(+)-(*S*)-2-octylimidazole **(+)-(*S*)-35a** was chosen as target compound for the alternative synthetic pathway and (+)-(*S*)-2-octyl amine **(+)-(*S*)-44** (not commercially available) as starting material.

The synthesis of (+)-(*S*)-2-octyl amine **(+)-(*S*)-44** is shown in scheme 4.7. For this the commercially available (-)-(*R*)-2-octanol **(-)-(*R*)-11c** was converted by Mitsunobu reaction into the (-)-(*S*)-2-octyl phtalimmide derivative **(-)-(*S*)-45** which by treatment with hydrazine was converted into the desired (+)-(*S*)-2-octylamine **(+)-(*S*)-44**. Using **(+)-(*S*)-44** the first synthesis was performed with racemic **(±)-31c** in order to check the strategy and also to obtain reference compounds.

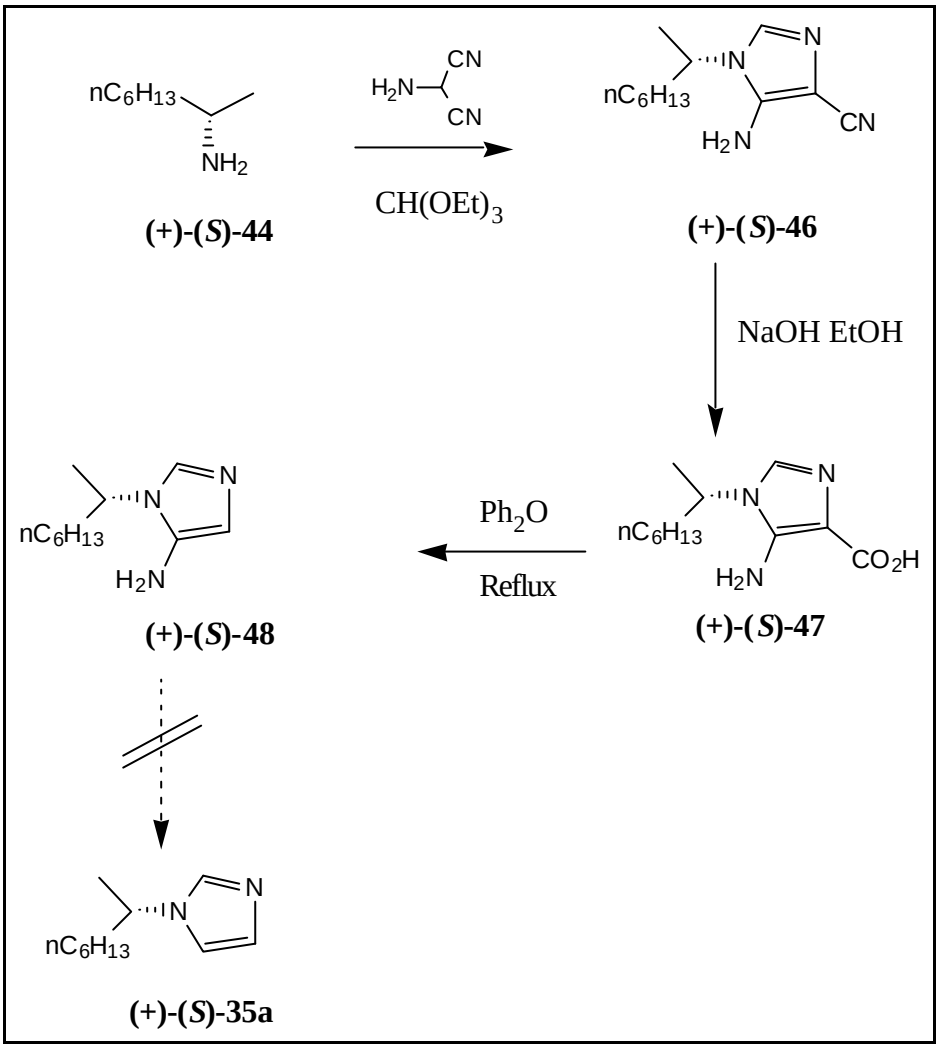


Scheme 4.7: Synthesis of **(+)-(*S*)-44.**

The thus produced **(+)-(*S*)-44** had identical physical constants in comparison with the data reported in the literature[1].

Racemic 2-octylamine **(±)-44** treated with aminomalonitrile and triethyl orthoformiate in acetonitrile was leading the *N*-1-(2-octyl)-4-cyano-5-aminoimidazole **(±)-46**[5] in good yield. Using the same procedure identical results were obtained with enantiopure (+)-(*S)*-2-octyl amine **(+)-(*S*)-44** leading to (+)-(*S*)-*N*-1-(2-octyl)-4-cyano-5-aminoimidazole **(+)-(*S*)-46** in enantiopure form in 52% yield and 98% e.e (scheme 4.8).

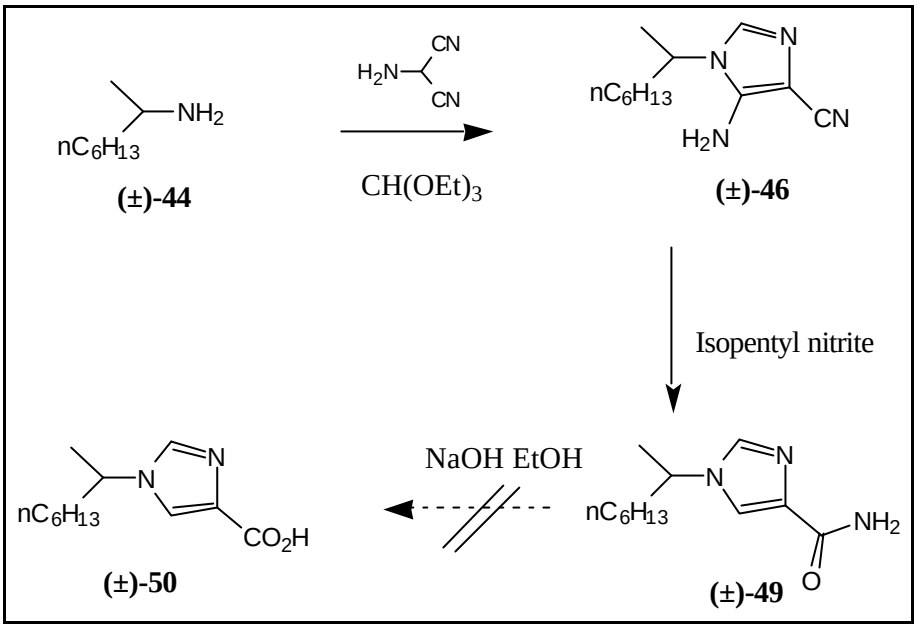
The alkaline hydrolysis of the 5-amino-4-cyano-*N*-1-imidazole derivatives **(±)-46** and **(+)-(*S*)-46** led to the amino acids **(±)-47** and **(-)-(*S*)-47,** respectively**.** The hydrolysis conditions were identical to those used for the hydrolysis of the dicyanoimidazole derivative **(±)-33a** and **(-)-(*R*)-33a**, and no racemization did occur during this step. Compounds **(±)-47** and **(-)-(*S*)-47** were decarboxylated to the *N*-1-(2-octyl)-5-amino imidazole **(±)-48** and **(+)-(*S*)-48.** Also in this case thermal decarboxylation was used since during this step on the compounds **(±)-34a** and **(+)-(*S*)-34a** no racemization occurred.



Scheme 4.8: First attempt to assign the stereochemistry of the Mitsunobu-hydrolysis-decarboxylation reaction (in the scheme represented only by the chiral compounds).

Unfortunately the final deaminations of **(±)-48** and **(+)-(*S*)-48** by $NaNO_2$-HCl or isopentyl nitrite were unsuccessful. Therefore using this synthetic pathway it was not possible to obtain (+)-(*S*)-2-octylimidazole **(+)-(*S*)-35a**.

Another attempt, based on the same synthetic pathway was tried using the intermediate *N*-1-(2-octyl)-4-cyano-5-aminoimidazole **(±)-46.** Unexpectedly the deamination with isopentyl nitrite led to *N*-1-(2-octyl)-4-carboxy amide imidazole **(±)-49** in 45 % yield (scheme 4.9).

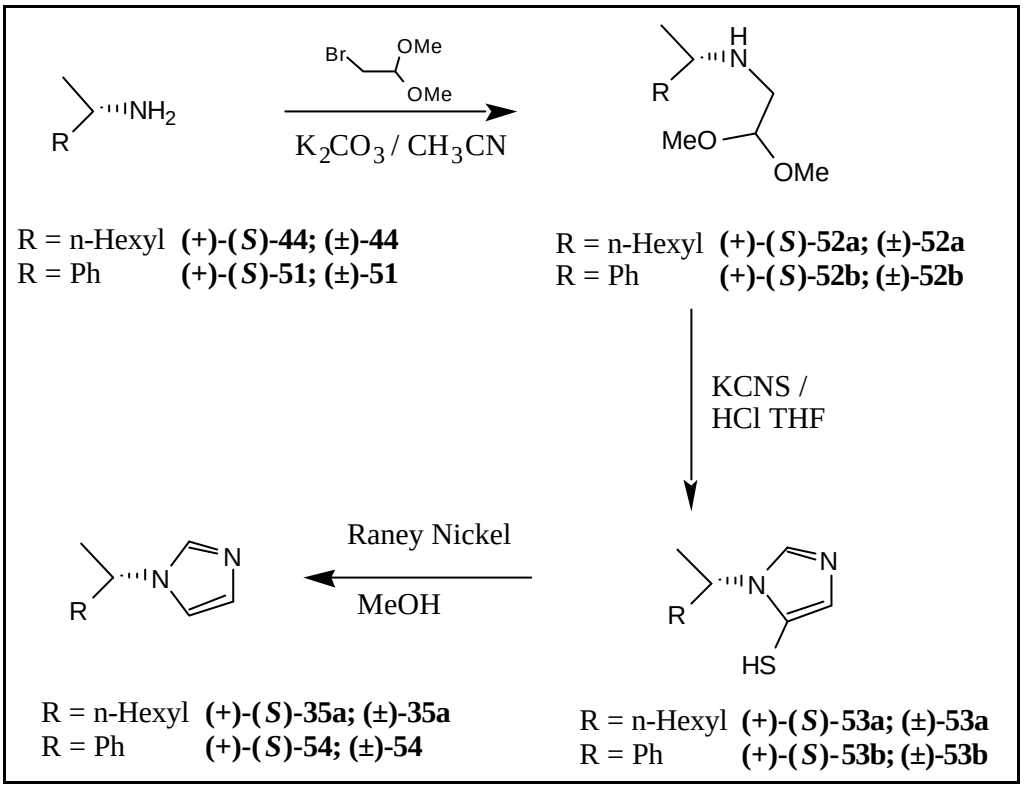


Scheme 4.9: Second attempt to assign the stereochemistry of the Mitsunobu-hydrolysis-decarboxylation reaction. This was done only with the racemic compounds.

Unfortunately all attempts to hydrolize the amide **(±)-49** to the corresponding acid **(±)-50** failed and it was thus impossible to obtain the final target compound using this synthetic pathway.

Next, the strategy was changed in favour of a Markwald procedure[3]. For this, the racemic and enantiopure 2-octyl amines **(±)-44** and **(+)-(*S*)-44**, 1-phenyl-1-ethylamine **(±)-51** and **(+)-(*S*)-51** (commercially available) were alkylated with bromoacetaldehyde dimethylacetal in order to provide the monoalkylated products **52a** (62% yield) and **52b** (70 % yield) in racemic and enantiopure form. These compounds were cyclized to racemic and enantiopure *N*-1-alkyl-5-mercapto imidazoles **53a** and **53b** respectively using KCNS in a aqueous HCl/THF solution. In both cases the yield was 84%. The final desulfuration was performed with Raney-Ni and afforded compounds 2-octylimidazole **35a** and 1-phenylethyl-1-imidazole **54** in racemic and enantiopure form with an enantiomeric excess of higher than 98% e.e. In scheme 4.8 all reaction sequences are shown.

(+)-(*S*)-35a thus obtained proved to be identical in all respects, including specific rotation with **(+)-(*S*)-35c** derived from (-)-(*R)*-2-octanol **(-)-(*R*)-31c** *via* the Mitsunobu-hydrolysis-decarboxylation sequence.



Scheme 4.8: Synthesis of racemic and enantiopure *N*-Alkyl imidazoles **35** and **54***via* the Markwald procedure.

It can therefore be implicated that, as expected, the Mitsunobu condensation proceeded with complete inversion of configuration of the starting alcohols.

It should be pointed out that this is the first application of the Markwald procedure to chiral amines. Furthermore this procedure gave excellent results with the chiral benzylamine **(+)-(*S*)-51** and thus resolved all problems with racemization of the benzylic alcohol during the Mitsunobu-hydrolysis-decarboxylation sequence. Obtained was enantiopure (+)-(*S*)-1-phenyl-1-ethyl imidazole **(+)-(*S*)-54**.

The enantiomeric excess of the final product **(+)-(*S*)-35a**, **(±)-56** and the chiral **(+)-(*S*)-56** was determinated for all compounds by ^{1}H-NMR in presence of chiral shift reagents as described in paragraph 4.1.1.

4.5 Conversion of chiral alcohols to chiral amines.

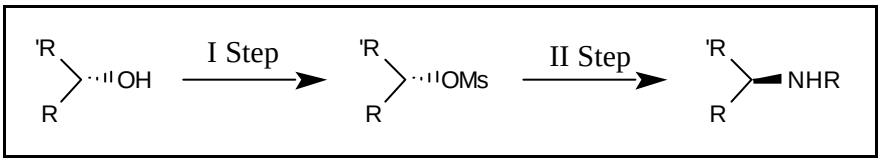
The success achieved in the conversion of the enantiopure benzylic amine **(+)-(*S*)-51** into enantiopure benzylic imidazole **(+)-(*S*)-56** led us to consider the alternative synthetic pathway described in chapter 1.6.2. The

key step is the conversion of the enantiopure benzhydrilic alcohol to enantiopure benzhydrilic amine and *via* the Markwald procedure to synthesize the imidazole.

Different methodologies were investigated in order to convert the enantiopure benzhydrylic alcohol into enantiopure benzhydrilic amine, since, unfortuntaly no reports for these substrates can be found in the literature.

4.5.1. Conversion of chiral alcohols to chiral amines in three steps.

In general the synthesis of an amine from an alcohol proceeds *via* three synthetic steps: (a) activation of the alcohol function by synthesis of e.g. a tosylate, mesylate, triflate or conversion into halides; (b) displacement of these leaving groups with sodium azide, phtalamide and (c) conversion of the resulting function to the primary amine. All attempts to convert the 1-phenyl-1-biphenyl methanol **(±)-27a** and 1-(2-bromophenyl)-1-biphenyl methanol **(±)-27c** into mesylates, tosylates or triflates failed.



Scheme 4. : general synthetic pathway to amines.

The reactions were carried out under different experimental conditions by varying temperature, solvent and reaction time and also with different reagents, such as MsCl, TsCl and bases such as pyridine or triethylamine. In no case a product was isolated. The reasons for this are not well understood. Experiments performed in the NMR-tube indicated that the products were formed but after a few hours they were degraded to unknown products. The product showed to be very sensitive to water and after addition of a drop water the starting material was reformed immediately. After this observation it was tried to displace the mesylate in a one-pot reaction with NaN_3. But also in this case no product was detected. Due to these unsuccessful experiments the attention was turned to other strategies where the alcohols could be converted directly to azides or suitable precursors.

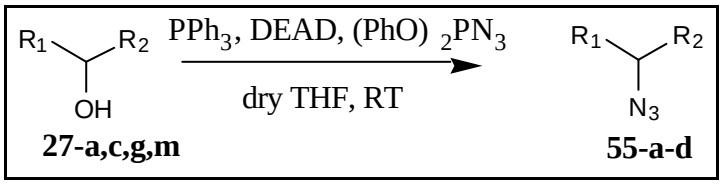
4.5.2. Direct conversion of chiral alchols to chiral amines *via* chiral azides.

The literature provided a number of methods for the conversion of chiral, electron-rich benzylic alcohols into the corresponding azides thereby maintaining optical activity. The use of the Mitsunobu displacement[6] with an azide nucleophile appeared to have the best precedence. It was also the first example in which an amine equivalent was introduced under Mitsunobu conditions using phtalamide as nucleophile[1]. Such reactions with C-N bond formations were extensively reviewed by Hughes[7].

Azide was first introduced under Mitsunobu conditions using hydrazoic acid as azide source[8] and this method was recently extended to chiral α-arylethyl amines[9]. Alternatives to hydrazoic acid include diphenyl phosphorazidate (DPPA)[10] and zinc azide/bis pyridine complex[11]. More recently Merck researchers reported in a paper[12] and expecially in a patent[13] a practical alternative to the Mitsunobu conditions with diphenyl phosphorylazide (DPPA) and DBU (diazabicycloundecene). Several of these methods were investigated with the racemic and chiral benzhydroles and also 2-benzo[b]furane-aryl-methanoles.

4.5.2.1 Mitsunobu reaction with diphenyl phosphorylazide (DPPA) as an organic azide source[10].

This method was applied to racemic and chiral substrates **(±)-27a**,**(±)-27c**, **(+)-27c**, **(±)-27g**, **(±)-27m**, **(+)-27m** (scheme 4.12)



27-a,c,g,m **55-a-d**

Scheme 4.12: Synthesis of azides **55a-d** using DPPA.

The procedure described by Base[10] was modified because under their conditions the chemical yield was very low. The modification consisted in the sequential addition of alcohol and triphenylphosphine to a dry THF solution of diethyldiazodicarboxylate and DPPA at 0° C, similar to a

reverse addition in the Mitsunobu reaction. The results using this procedure are shown in table 4.6.

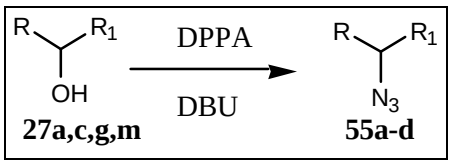
entry	substrate	R_1	R_2	product	yield%	[α]
1	**(±)-27a**	Ph	4Ph C_6H_4	**(±)-55a**	53.8	0
2	**(±)-27c**	2 BrPh	4Ph C_6H_4	**(±)-55b**	57.5	0
3	**(+)-27c**	2 BrPh	4Ph C_6H_4	**(±)-55b**	68.5	0
4	**(±)-27g**	2 benzo[b]furane	Ph	**(±)-55c**	15.0	0
5	**(±)-27m**	2 benzo[b]furane	2,4 C_6H_3	**(±)-55d**	13.3	0
6	**(+)-27m**	2 benzo[b]furane	2,4 C_6H_3	**(+)-55d**	10.8	0

Table 4.6: Synthesis of azide **55a-d** *via* Mitsunobu reaction with DPPA.

All reactions were carried out in dry THF overnight with an excess of reagents. In the case of compounds **27g-m** (entries 4-6, table 4.6) large amounts of starting material were always recovered. With benzhydroles **27a-c** (entries 1-3, table 4.6) products were obtained, however, due to partial decomposition during chromatography yields were low. The benzhydroles (entries 1-3, table 4.6) led to better results regarding chemical yields than the benzo[b]furan aryl methanols (entries 4-6). The results are in good agreement with those obtained in the Mitsunobu reaction with 4,5 dicyanoimidazole using the same substrates. None of the products showed a specific rotation neither at the sodium line nor at all Hg lines. This led to the conclusion that all compounds were racemic. All attempts to measure the enantiomeric excess directly by chiral HPLC or by NMR in the presence of shift reagents failed.

4.5.2.2. Direct conversion of alcohols to azides using diphenylphosphoroazidate and DBU.

These reactions were carried out by dissolving the alcohols and DPPA in dry toluene to a final alcohol concentration of about c.a. 0.5-1.0 M. To the reaction mixture a slight excess of DBU was added (Scheme 4.13). The procedure was applied to the alcohols reported in table 4.7.

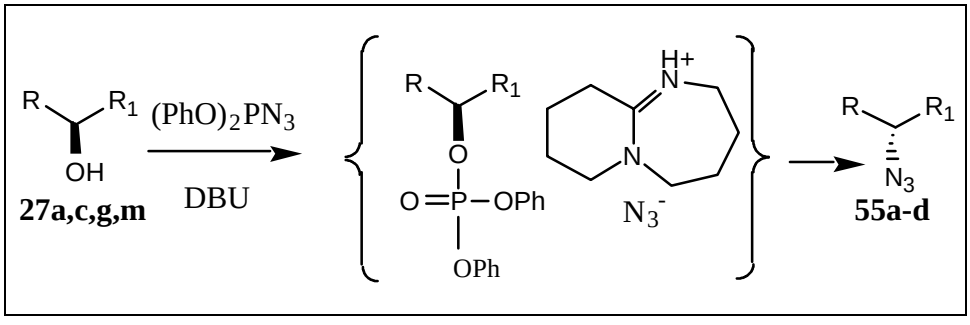


Scheme 4.13: Synthesis of azides **55a-d** by DPPA-DBU.

entry	substrate	R1	R2	product	yield%	[α]
1	**(±)-27a**	Ph	4 PhC_6H_4	**(±)-55a**	0	0
2	**(±)-27c**	2 BrPh	4 PhC_6H_4	**(±)-55b**	5.8	0
3	**(+)-27c**	2 BrPh	4 PhC_6H_4	**(±)-55b**	5.2	0
4	**(±)-27g**	2benzo[b]furane	Ph	**(±)-55c**	54.3	0
5	**(±)-27m**	2benzo[b]furane	2,4ClC_6H_3	**(±)-55d**	67.2	0
6	**(+)-27m**	2benzo[b]furane	2,4ClC_6H_3	**(+)-55d**	69.8	+0.5

Table 4.7: Synthesis of azides **55a-d** by DPPA-DBU.

The results were quite opposite to those obtained by the Mitsunobu reaction described in chapter 4.2.2.1. In fact, the benzo[b]furanes (entries 4-6) reacted better than the benzhydroles (entries 1-3) without any apparent reason. The reaction takes place in two discrete steps, the first one being the phosphate formation, followed by azide displacement (Scheme 4.14).



Scheme 4.14: reaction mechanism for azide synthesis by DPPA-DBU.

The mechanism was proposed by Thompson[13] The reaction has considerable advantages as compared to the Mitsunobu reaction with DPPA. The only by-product of the reaction is the DBU salt of diphenylphosphate. This salt is water soluble and can be removed during aqueous work up. The other two contaminants were: (a) excess of DBU which was eliminated by acidic work up and (b) a slight excess of DPPA

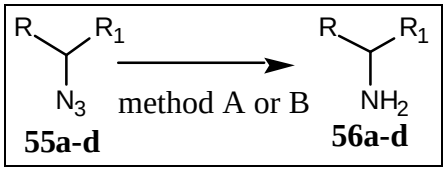
which was eliminated easily by chromatography. Unfortunately, however, also in this case the reaction proceeded without any stereocontrol. All products, with the exception of **(+)-55d**, showed no specific rotation at the Na and Hg wavelenght. As in the case of the Mitsunobu reaction with DPPA measurement of the e.e. of the products was not possible. The last attempt to synthetize the chiral azide from the chiral alcohols was perfomed with zinc azide/bis pyridine complexes. Identical conditions as reported in the literature were used, but no conversion of the starting material was observed.

4.5.3. Reduction of the azides 55a-d to the amines.

From the literature several methods for the reduction of azides to primary amines are known. Two methods (Scheme 4.15) were tried on our compounds:

A) Reduction by Ph_3P/H_2O in THF

B) Reduction by $SnCl_2$/MeOH



Scheme 4.15: Reduction of azides **(±)-55a-d** to amines**(±)-56a-d**.

In table 4.8 the results of both methods used for the reduction of the azides **55a-d** are reported.

entry	substrate	R_1	R_2	product	yield % A	yield %B
1	**(±)-55a**	Ph	$4PhC_6H_4$	**(±)-56a**	50	83
2	**(±)-55b**	2BrPh	$4PhC_6H_4$	**(±)-56b**	55	80
3	**(±)-55c**	2benzo[b]furan	Ph	**(±)-56c**	68	87
4	**(±)-55d**	2benzo[b]furan	Ph	**(±)-56d**	38	85
5	**(+)-55d**	2benzo[b]furan	2,4 Cl_2Ph	**(+)-56d**	42	84

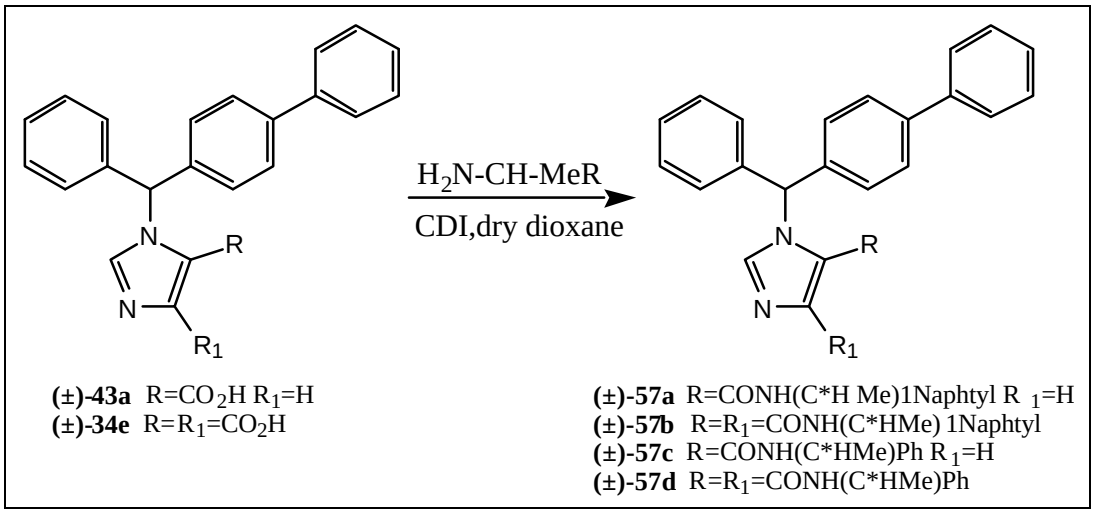
Tab 4.8: reduction of azides **(±)-55a-d** to amines **(±)-56a-d**.

The best results in terms of chemical yields were obtained with $SnCl_2$/MeOH. The reactions were carried out with both the racemic and

enantiopure azides. It was possible to determinate the enantiomeric excess of the amines by chiral HPLC. As expected, all amines were racemic except for **(+)-56d** which showed an e.e. of 20%. Thus, more than 50% of enantiomeric excess was lost during the conversion of the alcohol **(+)-27m** to the amine **(+)-56d**. Again it was clear that these methods are not suitable to obtain the target molecule in enantiopure form.

4.6 Synthesis of separable pairs of diastereoisomers from (±)-34e and (±)-43a.

4,5-imidazoledicarboxylate derivative **(±)-34e** and 5-imidazolecarboxylate derivative **(±)-43a** were obtained as intermediates in the "Mitsunobu-hydrolysis-decarboxylation" procedure. They were considered as an exceptional opportunity to generate pairs of separable diastereoisomers. The first attempt involved the synthesis of chiral amides. For this (+)-(*R*)-1 Naphtyl-1-ethyl amine and (+)-(*R*)-1-Phenyl-1-ethyl amine were used , carbonyldiimidazole (CDI) was the coupling reagent and dry dioxane was the solvent (Scheme 4.16).



Scheme 4.16: Synthesis of separable diasteroisomeric amides.

Chemical yields were very high (>95%), and no racemization occurred during the reactions. More than one hundred TLC eluation systems were tried to separate the diastereoisomers. Finally with CH_2Cl_2:MeOH:AcOH 98:1:1 it was possible to separate the diastereoisomers **(±)-57b** and **(±)-57d** while it proved impossible to

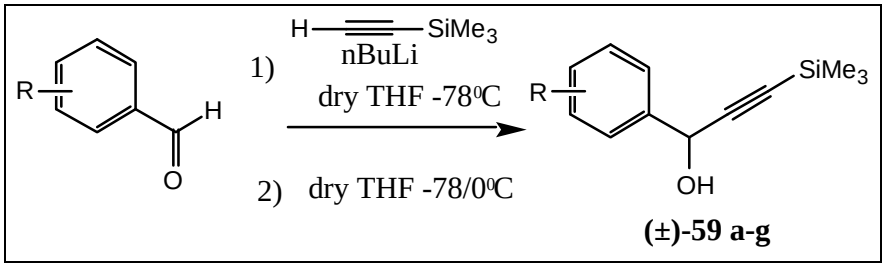
separate **(±)-57a** and **(±)-57c**. Compounds **(±)-57b** and **(±)-57d** are sterically very hindered and one hypothesis was that two conformers were separated instead of the two diastereoisomers. However ^{1}H-NMR spectra recorded in DMSO at high temperature did not show any interconversion between the two separated species **(+)-57b** and **(-)-57b** and **(+)-57d** and **(-)-57d** were really pairs of diastereoisomers. Several attempts were made to cleave the amide bond of the single diastereoisomers in order to recover the single enantiomers **(+)34e** or **(-)-34e.** All attempts were unsuccessful, and sometimes, due to the drastic conditions, the benzhydrylic proton was racemized. The strategy was abandoned because in the meantime the racemization of the benzyl product **(-)-(*S*)-33e** was observed during the decarboxylation step in the "Mitsunobu-hydrolysis-decarboxylation" methodology. It was not possible to overcome this problem.

5. Synthesis of Aryl propargylic alcohols of high enantiomeric purity *via* Lipase catalysed resolution.

The aim of this part of the thesis was the synthesis of aryl propargylic alcohols in enantiopure form, useful building blocks for the synthesis of aryl 2benzo[b]furane methanoles **27** and the Menarini imidazole derivative **18** in enantiopure form.

5.1 Synthesis of racemic 1-Aryl 2-propyne-2-ols (±)-58.

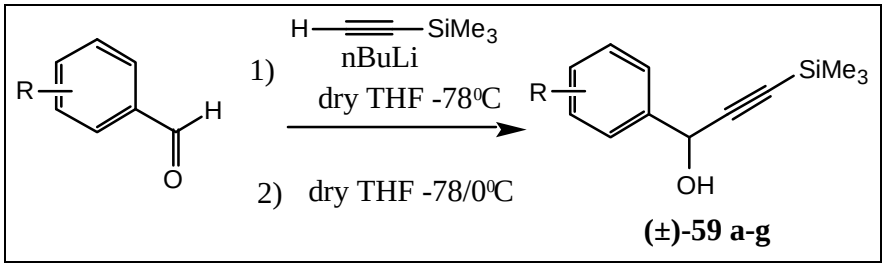
Several methods are described in the literature[1a,b,c] for the synthesis of racemic ethynyl carbinoles. The most useful procedure is the addition of various nucleophilic reagents to aldehydes or ketones, monolithium acetylide being one example. Several methods for the preparation of this reagent[2a,b] are reported in literature. One of the procedures involves the addition of *n*-butyl lithium to acetylen in dry THF at -78°C followed by the addition of aldehydes or ketones[3a,b]. The reported yields of ethynyl carbinoles are high, but the experimental procedure is very complex. Furthermore, the use of acetylene bottles in chemistry departments is regulated by very restricted laws. Lithium acetylide is commercially available as 0,1 N THF solution, and this was used as nucleophile for the addition to the benzaldehyde. In the second procedure, ethylenediamine was used to stabilize the acetylide[3b]. Both experiments gave very poor results, only 45% and 42% yield of 1-Phenyl-2-propyn-1-ol **(±)-58a**, respectively were obtained (Scheme 5.1).



Scheme 5.1:Synthesis of 1 Phenyl-2-propyn-1-ol **(±)-58a.**

The biggest problem encountered with lithium acetylide is its disproportionation to form dilithium acetylide and acetylene[3b]. In order

to avoid this side reaction trimethyl silyl acetylene (TMSA) was used to generate the stable nucleophile lithium trimethyl silyl acetylide. For this TMSA in dry THF was cooled to -75°C and *n*-butyllithium was added dropwise, leading to lithium trimethyl silyl acetylide. The reaction mixture was then cannulated dropwise into a solution of the aryl aldehyde in dry THF at -78°C to form the desired 1-aryl-2-propyn-3-trimethylsilyl -1-ols **(±)-59a-g** (Scheme 5.2).



Scheme 5.2: Synthesis of 1-aryl-2-propyn-3-trimethylsilyl -1-ols **(±)-59a-g.**

These reactions gave very good chemical yields with seven aryl aldehydes as reported in table 5.1.

Entry	R aldehyde	T °C	Product	Yield %
1	H	-15	**(±)-59a**	98.5
2	4Me	-78 / 0	**(±)-59b**	97.0
3	4F	-78 / 0	**(±)-59c**	98.0
4	4Cl	-78 / -15	**(±)-59d**	96.0
5	4CN	-78	**(±)-59e**	87.0
6	4NO2	-78	**(±)-59f**	49.0
7	3,4 OMe	-15	**(±)-59g**	96.0

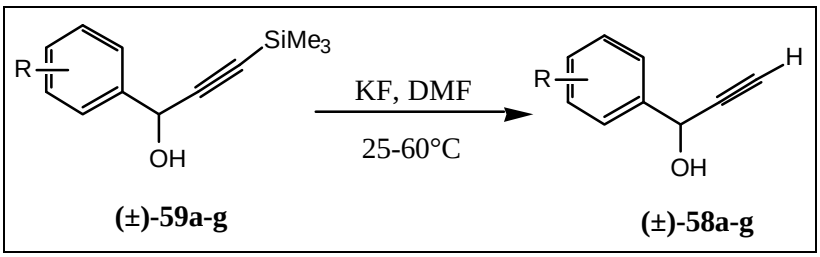
Table 5.1: Reaction conditions and chemical yields for the synthesis of **(±)-59a-f**.

It is interesting that for the first four compounds **(±)-59a-e** (entries 1-4) the reactions were so clean that purifications were unnecessary. For compounds **(±)-59e-f**, (entries 5,6), it was necessary to keep the temperature very low (-78°C). Raising the temperature to -15°C caused complete degradation of both the starting material and the product. It was impossible to recover the materials. Under these conditions, the cyano group does not react with the lithium reagent. This procedure led to the desired ethynyl carbinoles in very good yield with the exception of the

product resulting from 4-nitrobenzol aldehyde which led to **(±)-59f** in only 49 % yield.

5.1.1.Desilylation of Aryl trimethylsilyl propargylic alcohols 59a-d.

1-Aryl-2-propyn-3-trimethylsilyl-1-ols **(±)-59a-d** constitute formally protected acetylenes. Various desilylation methods were tried in order to obtain the acetylenic products **(±)-58a-g**. No reaction occurred when **(±)-59a** was treated with 1 N HCl in THF at different temperatures. Better results were obtained when the alcohols **(±)-59a-g** were treated with KF in DMF (scheme 5.3). The results are reported in table 5.2.



Scheme 5.3: desilylation of **(±)-59a-g** by KF in DMF.

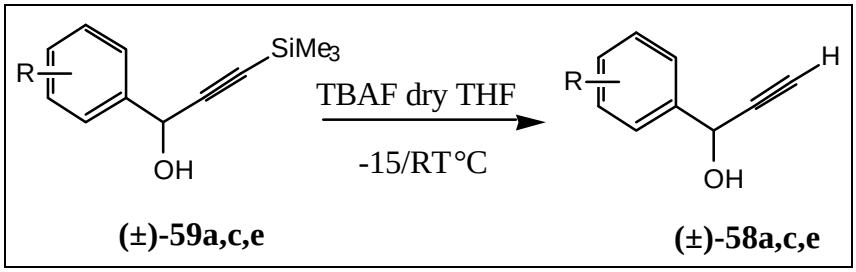
Entry	R	T °C	Product	Yield %
1	4H	60	**(±) - 58a**	87.1
2	4Me	60	**(±) - 58b**	47.5
3	4F	60	**(±) - 58c**	96.9
4	4Cl	60	**(±) - 58d**	93.2
5	4CN	RT-60	**(±) - 58e**	0
6	4NO2	RT-60	**(±) - 58f**	0
7	3,4 OMe	RT-60	**(±) - 58g**	0

Table 5.2: Reaction conditions and chemical yields for the desilylation of **(±)-59a-g** using KF in DMF.

The reaction worked, however, well only for three substrates: **(±)-59a,c,d** (entries 1,3,4), compounds with an unsubstituted aryl moiety or with one halogen in the para position.The presence of a methyl group on the aromatic moiety **(±)-59b** decreased the yield to 47.5% (entry 2).

Complete degradation of the substrates occurred with compounds **(±)-59e-g** carrying nitro, cyano or methoxy groups in the para position (entries 5-7). The reaction did not work at room temperature, at close to 50°C the reaction took place for compounds **(±)-59a-d** while for **(±)-59e-g** the reaction mixtures became dark and it was impossible to detect any products.

Also milder conditions than KF in DMF at 60°C were tried for the desilylation, and TBAF in dry THF was used as an alternative (scheme 5.4).



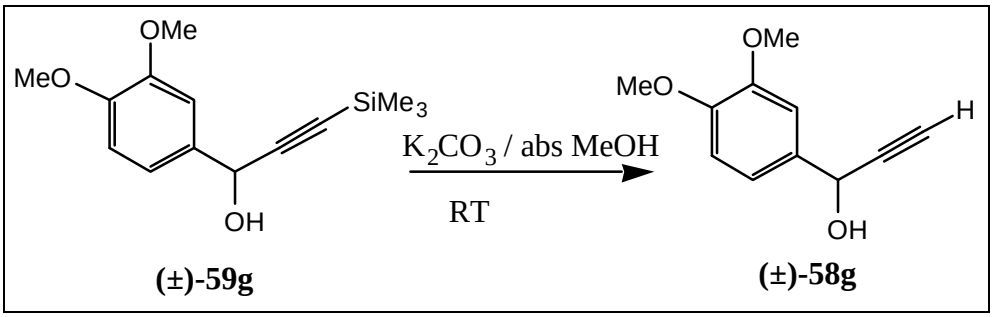
Scheme 5.4: Desilylation of **(±)-59a,c,e** by TBAF.

This procedure was applied only to three substrates **(±)-59a,c,e**. Again **(±)-59a** and **(±)-59c** gave the best results, while **(±)-59e** was degraded during the reaction. The results for this reaction are reported in table 5.3.

Entry	R	T C°	Product	Yield
1	4H	-15/RT	**(±)-58a**	94.8
2	4F	-15/RT	**(±)-58c**	96.9
3	4CN	-15/RT	**(±)-58e**	0

Table 5.3: Reaction conditions and chemical yields for the desilylation of **(±)-59a,c,e** using TBAF in THF.

A last attempt of desilylation was carried out under basic conditions. A saturated solution of K_2CO_3 in absolute MeOH was used and the reaction was tried on **(±)-59g** (one of the arylpropynoles which decomposed in presence of the KF). The reaction was very slow and gave a complex mixture of products. In fact, in order to achieve a complete consumption of the starting material, five days were required and only 43% of the desired product **(±)-58g** was recovered after purification. (Scheme 5.5).



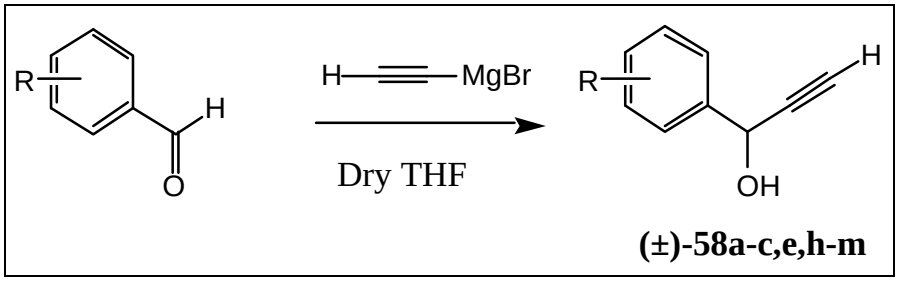
(±)-59g **(±)-58g**

Scheme 5.5: Desilylation of **(±)-59g** under basic condition.

Unfortunately it was not possible to find one generally applicable procedure for the desilylation of all aryl propynoles **(±)-59a-g**.

5.2 Synthesis of Aryl propynols (±)-58 by addition of Grignard reagents to aromatic aldehydes.

Grignard reagents were also considered as nucleophiles for the addition to aryl aldehydes. For this a 1 M solution of magnesiumethynyl bromide or chloride in dry THF (purchased from Aldrich) was added to aryl aldehydes (Scheme 5.7).



(±)-58a-c,e,h-m

Scheme 5.7: Synthesis of aryl-propynols **(±)-58a-c,e,h-m** by addition of Grignard reagent to aryl aldehydes.

Usually the aldehydes were dissolved in dry THF, the resulting solution was cooled to low temperatures (in some cases 0°C was sufficient) in order to have a very clean and fast reaction. In table 5.4 the results and reaction conditions are reported.

The use of this Grignard reagent also allowed the synthesis of 1[4cyanobenzyl]2-propyn-1-ole **(±)-58e** (entry 4). This product could not be obtained with all the other methods reported in the previous paragraphs. This arylpropynole was thus obtained in a single step.

Entry	R	T °C	Product	Yield
1	4H	0	**(±)-58a**	99
2	4Me	-15	**(±)-58b**	98
3	4F	0	**(±)-58c**	89
4	4CN	-78	**(±)-58e**	90
5	3Me	0	**(±)-58h**	91
6	3F	0	**(±)-58i**	78
7	2Me	0	**(±)-58l**	98
8	2,4Cl	0	**(±)-58m**	98

Table 5.4: Reaction conditions and chemical yields for the synthisis of aryl-propynols **(±)-58a-c,e,h-m.**

The chemical yields were very high, the reaction conditions mild and all products could be purified by easy filtration over silica gel. In order to obtain a colorless liquid it was necessary to distill the crude products under high vacuum. The cyano group present in 4-cyano benzaldehyde proved to be unreactive with the Grignard reagent also in presence of a slight excess.

5.3 Enzymatic resolution of 2-substituted-2-propynyl-1-oles (±)-58.

In the literature several methods for the enzymatic resolution of acetylenic alcohols by hydrolysis or esterification are reported. O'Hagan[8] has reported a very good study of the resolution of tertiary acetylene acetate esters in presence of a lipase from *Candida cylindracea*. However, the enantiomeric excesses usually are very low. Much more efficient is the esterification of secondary acetylenic alcohols in presence of *Pseudomonas* (A.K.) in hexane with vinyl acetate[9]. In these cases e.e.'s higher than 95% were reported both for the alcohol and the acetate. E values are higher than 200. Unfortunately, the paper describes only one kinetic resolution of a secondary propynyl alcohol with an internal triple bond. Only one example describes a terminal triple bond and this was the worst substrate, leading to only very low enantiomeric excess. In the master thesis of Claudia Waldinger[6] preliminary results were reported concerning the enzymatic resolution of four different terminal aryl propynoles by hydrolysis or esterification in presence of a lipase from *Pseudomonas*

fluorescens (SAM II). The hydrolysis of the acetates gave better results than the esterification. Only in the case of 1-Phenyl-1-propyn1-ol, the E value was higher than 100 and a perfect resolution of the two enantiomers was achieved. In presence of a methoxy group on the phenyl ring the stereoselectivity decreased dramatically, in fact E values of 1.05 for the *ortho* methoxy, 5.7 for the *meta* - and 2.2 for the *para* - methoxy-compounds were found. These preliminary results opened the possibility of obtaining aryl propynoles in enantiopure form by enzymatic resolution.

5.3.1 Kinetic resolution of aryl propynoles (±)-58: screening for useful enzymes.

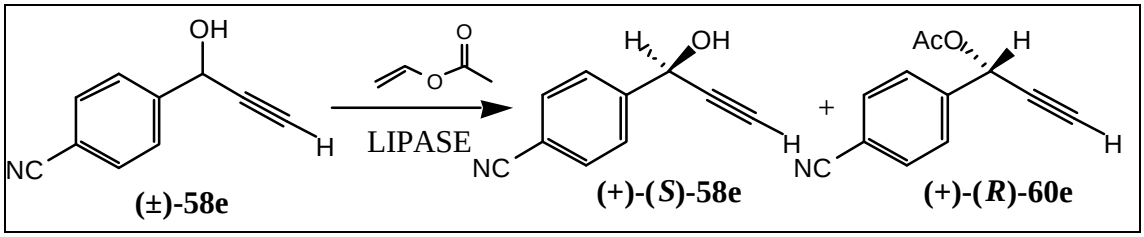
Lipases are known to catalyse both the enantioselective esterification of racemic alcohols and/or the hydrolysis of their corresponding esters. In order to identify the most desirable mode of transformation and the best suited enzyme for the aryl propynoles, a series of screening experiments were carried out. Ten different lipases were used in these experiments.

5.3.1.1 Enzymatic esterification of racemic aryl propargylic alcohols(±)-58: screening experiments.

Transesterification of aryl propynoles in presence of ten lipases [from Hog Pankreas, Porcine Pankreas, *Aspergillus Niger*, *Mucor javanicus*, *Candida cylindracea*, *Candida lipolytica*, *Penicillium roquefortii*, *Mucor miehei* (Lipozyme), SAMI and SAMII] were carried out under the conditions of irreversible acyl transfer. They revealed that only two lipases, those derived from *Pseudomonas species* (SAMI and SAMII) were able to catalyze these reactions, albeit with rather low enantioselectivities and in preparatively unsatisfactory reaction times. (Scheme 5.6 and table 5.5). The substrate chosen for the screening experiments was **(±)-58e** because: (a) it contains a para-substituent on the aromatic ring and (b) it is the most important precursor for the Menarini aromatase inhibitors.

Enzymatic esterifications were carried out in MTBE as solvent. The relative ratio between substrate **(±)-58e** : enzyme : vinyl acetate was

2:1:3 in weight. All ten reactions were carried out simultaneously at room temperature.



Scheme 5.6: Screening of lipases for the esterification of 1(4cyanophenyl)-2-propyn-1-ol **(±)-58e.**

The reactions were monitored by GC every twentyfour hours, for a total of seven days. Only two enzymes were able to catalyze the esterification of **(±)-58e.** In table 5.5 the results obtained after 48 and 96 h are reported.

Lipase	Acetate48h	Acetate 96h	Alcohol 48h	Alcohol 96h
Hog Pancreas	-	-	+	+
PPL	-	-	+	+
Aspergillus Niger	-	-	+	+
Mucor Javanicus	-	-	+	+
Candida Cylindracea	-	-	+	+
Candida Lipolytica	-	-	+	+
Penicillium Roqueforti	-	-	+	+
Mucor Mihei	-	-	+	+
SAM I	+	+	+	+
SAM II	+	+	+	+

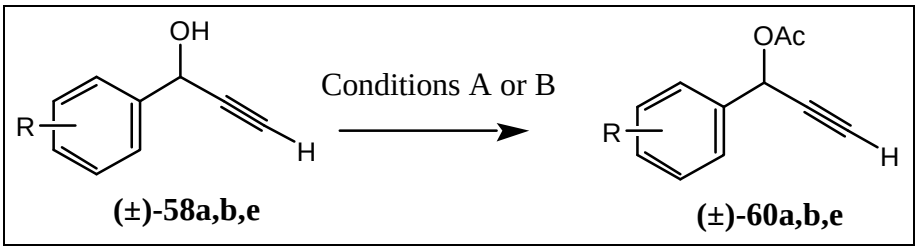
Table 5.5: Enzymatic screening of lipases for the esterification of **(±)-58e**.

All reaction rates were very slow. In fact, after six days SAM I showed 23% of conversion and very poor enantiomeric excess for the alcohol **(±)-58e**, while SAMII showed a conversion of 40%. In this case, the enantiomeric excess of the alcohol **(+)-(*S*)-58e** was 37.6% ee and for the product **(+)-(*R*)-60e** 56.5% ee was observed, corresponding to E>5. All

other batches were checked after 6 days and only PPL showed a low 4% conversion. In table 5.5 the qualitative results are reported, + and - means presence of the material (alcohol or acetate) detected by GC analysis of the crude reaction mixture.

5.3.2 Synthesis of racemic aryl propynyl acetate (±)-60.

In order to study the enzymatic hydrolysis three different arylpropynols were acetylated. Two different conditions were used as described in scheme 5.8 (condition A: Py, acetic anhydride, RT; condition B: AcCl, TEA, CH_2Cl_2 or THF). Scheme 5.7



Scheme 5.7: Acetylation of aryl propynols **(±)-58a,b,e**.

Reaction conditions (A or B), substrates, products and chemical yields are reported in table 5.6.

Entry	Substrate	R	Reac. Con.	Time h	Product	Yield
1	**(±)-58a**	H	A	12.0	**(±)-60a**	95.5
2	**(±)-58a**	H	B	1.0	**(±)-60a**	98.3
3	**(±)-58b**	4Me	B	1.0	**(±)-60b**	97.6
4	**(±)-58e**	4CN	B	1.0	**(±)-60e**	98.0

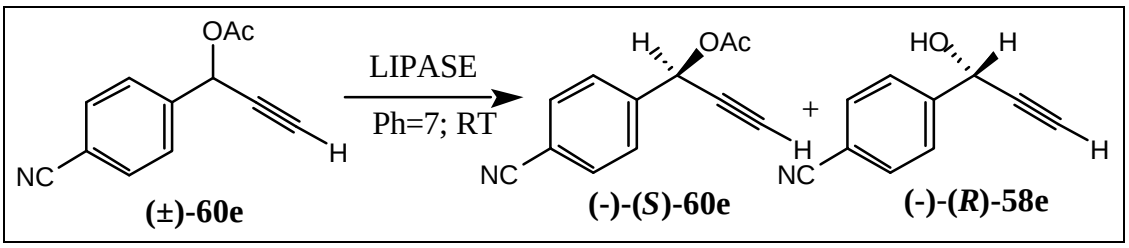
Table 5.6: Acetylation of **(±)-56a,b,e**.

Reactions carried out using method B are much faster than those with method A. Furthermore the work up using method B is very easy.

5.3.2.1 Enzymatic hydrolysis of 1-(4-Cyanophenyl)-2-Propyn-1-Acetate (±)-60e: screening experiments.

The identical set of enzymes used for the esterifications were used also for the screening of the hydrolysis reaction (scheme 5.8). The

reaction conditions were: room temperature, phosphate buffer pH=7.0 and stirring; the ratio between ester and enzyme was 1:1. The substrate was always **(±)-60e** (Scheme 5.8).



Scheme 5.8: lipase screening for the hydrolysis of 1-(4cyanophenyl)-2-propyn1acetate **(±)-60e**

All reactions were monitored by GC after 24 and 48 hours as in the case of esterification. Unexpectedly, a completely different behaviour was found for this reaction in comparison with the corresponding esterification. The qualitative results are reported in table 5.7.

Lipase	Acetate24h	Acetate 48h	Alcohol 24h	Alcohol 48h
Hog Pancreas	+	+	+	+
PPL	+	+	+	+
Aspergillus Niger	-	-	+	+
Mucor Javanicus	+	+	-	-
Candida Cylindracea	-	-	+	+
Candida Lipolytica	+	+	-	-
Penicillium Roqueforti	-	-	+	+
Mucor Mihei	-	-	+	+
SAM I	+	+	+	+
SAM II	+	+	+	+

Table 5.7: Enzymatic screening of lipases for the hydrolyses of **(±)-60e**.

Only two lipases (*Mucor javanicus* and *Candida lipolytica*) were unable to catalyze the hydrolysis and no product was detected by GC after 48 h; three of the enzymes (*Aspergillus niger*, *Candida cylindracea*, *Mucor miehei)* were too "efficient"; after 20 hours all the ester was

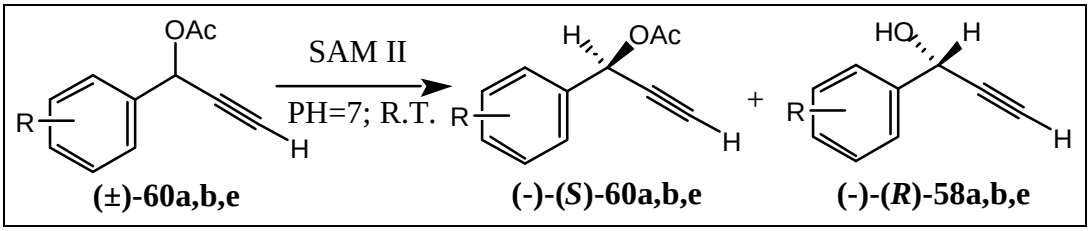
converted into alcohol and consequently there was no enantioselectivity observed. Three other lipases (Hog pancreas, Porcine Pankreas, *Penicillium roquefortii*) showed poor conversion, and after 48 h both acetate and alcohol were present in the reaction mixture in a 95:5 ratio. SAMI and SAMII were the only promising lipases. After 48 h more than fifty percent of the ester **(±)-60e** was converted into the alcohol **(-)-(*R*)-58e.**

The selectivity was not very high. With SAM II after 52 h the conversion was 67.8%. The e.e. of the acetate **(-)-(*S*)-60e** was 86.6 % e.e. and the e.e. of the alcohol **(-)-(*R*)-58e** was 41.2% corresponding to an E value of 6.

This result appeared to be really promising considering that in the previous study the presence of para methoxy led to an E value <1. Therefore, further investigation were carried out only with the lipase of *Pseudomonas fluorescens* SAMII.

5.3.3 Enzymatic hydrolysis of racemic Aryl-2-propyn-1-acetates (±)-60a,b,e in presence of the lipase from *Pseudomonas fluorescens* (SAMII): effect of the cosolvent.

In order to obtain more informations regarding the behaviour of SAMII towards the hydrolysis of this class of acetates, compounds **(±)-60a,b** and **(±)-60e** were including in the screening programme. **(±)-60a** was used as a standard because it had already been studied by Claudia Waldinger in her master thesis. Experiments were carried out at RT using 10% in weight of SAMII in respect of the substrate. Phosphate buffer pH=7 was used as solvent and 1.0 N NaOH as titrating reagent (Scheme 5.9). Results are shown in table 5.8; scheme 5.9.

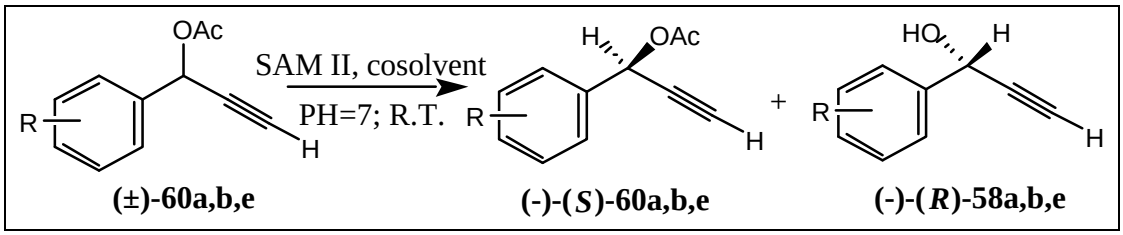


Scheme5.9: Enzymatic hydrolyses of arylpropargylic acetates **(±)-60a,b,e**.

Entry	Substrate	R	Time h	C%	Product	Yield	e.e.	E
1	**(±)-60a**	H	4.5	47.3	**(-)-(*S*)-60a**	45.2	87.0	100
2		H			**(-)-(*R*)-58a**	30.5	97.0	
3	**(±)-60b**	4Me	144	60.7	**(-)-(*S*)-60b**	57.3	99.5	35
4		4Me			**(-)-(*R*)-58b**	33.8	64.8	
5	**(±)-60e**	4CN	52	67.8	**(-)-(*S*)-60e**	60.1	86.6	6
6		4CN			**(-)-(*R*)-58e**	31.0	41.2	

Table 5.8: Enzymatic hydrolyses of arylpropargylic acetates **(±)-60a,b,e**.

As reported in table 5.8, SAMII worked perfectly with the acetate **(±)-60a** which does not contain any substituent on the aromatic moiety, the corresponding E value was >100. For the two others esters having a para- substituent (Me for **(±)-60b** and CN for **(±)-60e**) the selectivity was much lower (**(±)-60b** E=35, and (**±)-60e** E=6). In these experiments (2 mmoles of esters and 10% in weight of lipase Sam II) the solubility of the substrates became a problem. **(±)-60e** was insoluble in the phosphate buffer and appeared as a solid suspension in the reaction mixture. The inhomogeneity of the reaction mixture led to unreproducible results for the three sets of experiments. It is well known that the optimal reaction conditions for lipase catalysed reactions are those in which the substrates are oil emulsions in buffer since the reaction occurs at the interface between the two phases. For this reason it was tried to keep **(±)-60e** as an oil in the reaction mixture, however already after few minutes under stirring in the buffer it became solid. The inhomogeneity of the reaction mixture could be one reason for the low selectivity of the lipase during the hydrolysis. Therefore, the use of a cosolvent was considered as a possible solution for this problem (Scheme 5.10).



Scheme 5.10: Effect of solvent on the enzymatic hydrolyses of **(±)-60a,b,e.**

Three different solvents were considered: MTBE, THF and acetone. THF was found to be the worst solvent; it was impossible to follow the reaction by GC. Solvents were used in different concentrations as reported in table 5.9. For clarity and direct comparison the results obtained without cosolvent are incorporated in the same table.

Entry	Substrate	R	Cosolvent	Product	C%	Time h	e.e	E
1	**(±)-60b**	4Me	-	**(*S*)-60b**	60.7	144	>99.5	35
2		4Me	-	**(*R*)-58b**			64.8	
3	**(±)-60b**	4Me	MTBE 10%	**(*S*)-60b**	38.1	47	47.3	12
4		4Me		**(*R*)-58b**			77.0	
5	**(±)-60b**	4Me	MTBE 25%	**(*S*)-60b**	41.2	40	38.4	5
6		4Me		**(*R*)-58b**			54.7	
7	**(±)-60b**	4Me	Acetone5%	**(*S*)-60b**	48.2	76	79.5	31
8		4Me		**(*R*)-58b**			85.4	
9	**(±)-60e**	4CN	-	**(*S*)-60e**	61.8	52	86.6	6
10		4CN		**(*R*)-58e**			41.2	
11	**(±)-60e**	4CN	MTBE 10%	**(*S*)-60e**	67.7	36	86.6	6
12		4CN		**(*R*)-58e**			41.2	
13	**(±)-60e**	4CN	MTBE 30%	**(*S*)-60e**	66.0	36	86.8	7
14		4CN		**(*R*)-58e**			44.7	

Table 5.9: Effect of cosolvent in the enzymatic hydrolyses of **(±)-60e**.

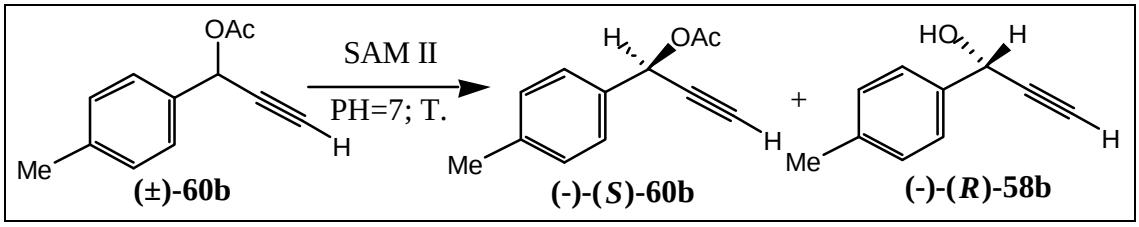
All obtained results were really unsatisfactory. The addition of MTBE as a cosolvent dramatically decreased the enantioselectivity of the enzymatic process for **(±)-60b**. 10% of MTBE gave E = 12 and 25% of MTBE gave E value = 5 (entries 3-5; table 5.9). Acetone (entry 7; table 5.9) was found to be a much better cosolvent because it did not decrease the enantioselectivity of the process as compared with the experiment using no cosolvent (entry1; table5.9).

Its presence did in no way improve the process. The addition of MTBE with 10% and 30% to the reaction mixture containing **(±)-60e** (entries 11,13; table5.9) did not lead to any change of the selectivity as compared with the experiment without cosolvent (entry 9; table 5.9). It led to a homogeneous trend of the reaction and the enzymatic process was much more continuous. The hypothesis that the solid state of **(±)-60b,e** was responsible for the low selectivity was not supported by these

experiments. But it was interesting to find that the addition of MTBE as cosolvent was a good method to obtain reproducible and homogeneous results.

5.3.4 Enzymatic hydrolysis of (±)-60b in presence of SAMII: effect of the temperature.

The last parameter studied was the temperature; here only one substrate **(±)-60b** was used in the experiments (Scheme 5-11.)



Scheme 5.11: Effect of the temperaure on the enzymatic hydrolyses of **(±)-60b.**

Entry	Substrate	T °C	Time h	Product	C %	e.e. %	E
1	**(±)60b**	RT	144	**(*S*)-60b**	60.7	100	35
2		RT		**(*R*)-58b**		64.8	
3	**(±)60b**	35	134	**(*S*)-60b**	50.4	80.8	22
4		35		**(*R*)-58b**		79.7	
5	**(±)60b**	55	32	**(*S*)-60b**	58.1	89.7	14
6		55		**(*R*)-58b**		64.8	
7	**(±)60b**	58	19	**(*S*)-60b**	51.5	47.3	12
8		58		**(*R*)-58b**		77.0	

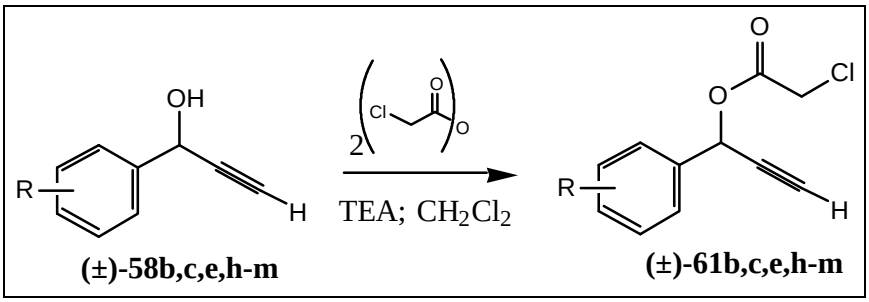
Table5.10: Effect of the temperature on the enzymatic hydrolyses of **(±)-60b.**

Three experiments were carried out at 35°C, 55°C, 58°C. The results were compared with those obtained at room temperature, as shown in Tab.5.10.

The increased temperature reduced the reaction time but simultaneously also reduced the E value. Also in this case no improvement over the original results was achieved, but it is important to note that at 35°C **(±)-60b** was an oil in the reaction mixture.

5.4 Synthesis of the racemic chloroacetate derivatives (±)-61.

The chloroacetate derivatives **(±)-61** of the Aryl propynols **(±)-58** were synthesized in order to increase the rate of the hydrolysis. Reactions were carried out in dichloromethane in presence of chloracetic anhydride as acylating agent and triethylamine as base (Scheme 5.12).



Scheme 5.12: Synthesis of chloroacetates **(±)-61b,c,e,h-m.**

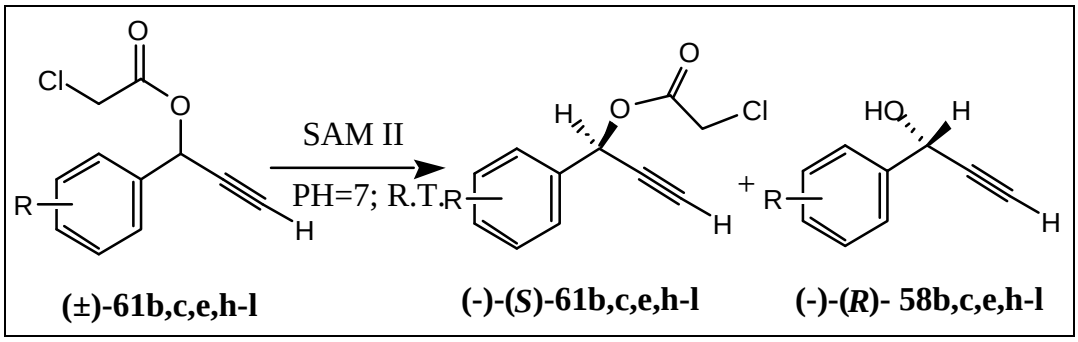
In table 5.11 the results of the acetylation are shown . The obtained yields are very high.

Entry	Substrate	R	Product	Yield
1	**(±)-58b**	4Me	**(±)-61b**	92.8
2	**(±)-58c**	4F	**(±)-61c**	94.8
3	**(±)-58e**	4CN	**(±)-61e**	99.8
4	**(±)-58h**	3Me	**(±)-61h**	99.5
5	**(±)-58i**	3F	**(±)-61i**	98.4
6	**(±)-58l**	2Me	**(±)-61l**	93.0
7	**(±)-58m**	2,4Cl	**(±)-61m**	96.8

Table 5.11: Synthesis of chloroacetates **(±)-61b,c,e,h-m.**

5.5 Enzymatic hydrolyses of the chloroacetyl esters (±)-61.

Six chloroacetyl esters **(±)-61** were hydrolyzed in presence of SAMII in phosphate buffer pH=7 at room temperature, 1.0 N NaOH was used as titrating reagent. These are the most extended sets of experiments carried out with this class of aryl propyl esters (scheme 5.13).



Scheme 5.13: Hydrolysis of Chloroacetates **(±)-61b,c,e,h-l** by lipase SAM II.

The observed reaction rates were much faster as compared to the corresponding hydrolyses of the acetates. In some cases also the selectivity was increased. All chloroacetate esters **(±)-61** were oils in the reaction mixture. This led to homogeneous reactions and all problems previously encountered with the acetate **(±)-60e** were overcome. Table 5.12 shows the results.

Entry	Substrate	R	C %	Time h	Product	e.e%	Yield	E
1	**(±)-61b**	4Me	56.4	10	**(-)-(*S*)-61b**	97.8	40.69	36
2					**(-)-(*R*)-58b**	75.7	51.0	
3	**(±)-61c**	4F	53.8	11	**(-)-(*S*)-61c**	96.8	44.9	45
4					**(-)-(*R*)-58c**	83.2	53.1	
5	**(±)-61e**	4CN	53.0	5.5	**(-)-(*S*)-61e**	96.6	44.5	50
6					**(-)-(*R*)-58e**	85.5	49.5	
7	**(±)-61h**	3Me	51.8	4.5	**(-)-(*S*)-61h**	99.2	43.5	>140
8					**(-)-(*R*)-58h**	92.1	46.1	
9	**(±)-61i**	3F	52.1	2.8	**(-)-(*S*)-61i**	99.4	46.2	127
10					**(-)-(*R*)-58i**	91.5	46.3	
11	**(±)-61l**	2Me	53.9	22.0	**(-)-(*S*)-61l**	94.0	45.1	39
12					**(-)-(*R*)-58l**	80.4	46.9	

Table 5.12: Enzymatic resolution of Chloroacetates **(±)-61b,c,e,h-l** by lipase SAM II

From the comparison of the results obtained in this work and taking in account the preliminary results from the master thesis of Claudia Waldinger, it is possible to draw some general conclusions:

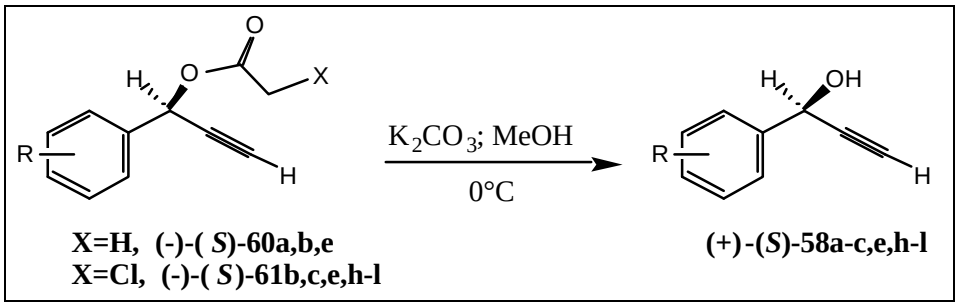
1) the esterification of aryl propynoles by SAMII cannot be considered a good process because of the lack of enantioselectivity and the incredibly low rate;

2) the hydrolysis of aryl propynol acetates and chloroacetates in presence of SAMII can be considered a method to obtain Aryl propargylic alcohols of high enantiomeric purity. The use of chloroacetate esters is recommended due to the higher reaction rates as compared to the acetates. In the case of **(±)-61e** a higher selectivity (E=50) was also achieved in comparison to the corresponding acetate **(±)-60e** (E=6);

3) it is possible to obtain a SAR (Structure Activity Relationship) for this class of compounds even if the observed selectivities expressed as E values were proven to be strongly dependent on the substitution pattern of the benzene moiety, both regarding the type of substituents and their position on the aromatic ring. The best position for a substitution of the aromatic ring is the meta position. Higher E values were observed in all compounds having a meta substituent. No significant differences between ortho and para position and the E values were detectable. At present the variety of the substituents is still too small in order to obtain a complete overview of the stereoelectronic effects. Apparently electrondonors such as OMe (C.Waldinger's results) decrease dramatically the enantioselectivity, while electronwithdrawing groups increase the enantioselectivity (F and CN). Also a small aliphatic group can increase the enantioselectivity.

5.6 Hydrolysis of enantiopure Acetates (-)-(*S*)-60a,b,e and chloroacetates (-)-(*S*)-61b,c,e,h-l resulting from the enzymatic hydrolysis in presence of the lipase SAMII.

Acetates **(-)-(*S*)-60a,b,e** and chloroacetates **(-)-(*S*)-61b,c,e,h-l** resulting from the enzymatic hydrolysis with lipase SAMII had a higher enantiomeric excess as compared to the corresponding alcohols because of the extended conversion rates. It was required to use very mild conditions for the chemical hydrolysis. A saturated solution of potassium carbonate in methanol at 0°C for 30 min was found to provide the best conditions (Scheme 5.14).



Scheme 5.14: Hydrolysis of enantiomeric acetates or chloroacetates **(-)-(*S*)-60** and **(-)-(*S*)-61**

The reaction proceeds smoothly in almost quantitative yield and without racemization of the chiral centre; the enantiomeric excess of the products is identical with that of the starting materials. Purity and enantiomeric excess were determined by chiral GC. In table 5.13. the results of the reaction are summarized.

Entry	Substrate	X	R	Product	e.e %	Yield
1	**(-)-(*S*)-60a**	H	H	**(+)-(*S*)-58a**	87.0	94.1
2	**(-)-(*S*)-60b**	H	4Me	**(+)-(*S*)-58b**	65.0	93.5
3	**(-)-(*S*)-61b**	Cl	4Me	**(+)-(*S*)-58b**	97.7	98.9
4	**(-)-(*S*)-61c**	Cl	4F	**(+)-(*S*)-58c**	98.8	98.9
5	**(-)-(*S*)-61e**	Cl	4CN	**(+)-(*S*)-58e**	95.9	97.9
6	**(-)-(*S*)-60e**	H	4CN	**(+)-(*S*)-58e**	86.6	95.8
7	**(-)-(*S*)-61h**	Cl	3Me	**(+)-(*S*)-58h**	99.2	99.6
8	**(-)-(*S*)-61i**	Cl	3F	**(+)-(*S*)-58i**	98.8	98.7
9	**(-)-(*S*)-61l**	Cl	2Me	**(+)-(*S*)-58l**	94.0	98.5

Table 5.13: Hydrolyses of acetates **(-)-(*S*)-60** and chloroacetates **(-)-(*S*)-61**.

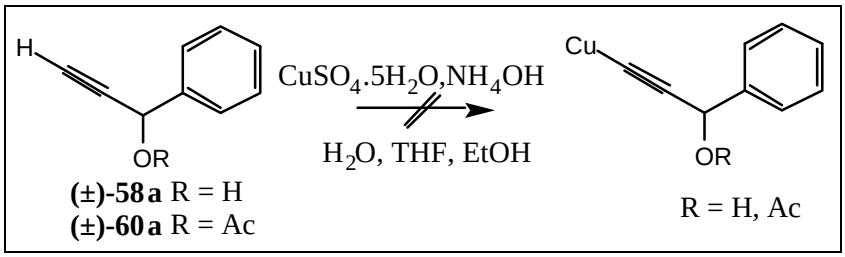
The low enantiomeric excess for some compounds (entries 1,2,6) was due to the low enantiomeric excess of the starting material.

6 Synthesis of Aryl-2-Benzo[b]Furanyl and Aryl-2-Indonyl Carbinols 27 and 64-a-g of High Enantiomeric Purity *via* Palladium-Catalyzed Heteroannulation of Racemic and Enantiopure 1-Aryl-1-Propargylic Alcohols 58.

The synthetic methods reported in chapter 2.4 were applied to synthesize the Aryl-2-Benzo[b]Furanyl and Aryl-2-Indonyl carbinols **27** and **64-a-g** in racemic and enantiopure forms. The synthetic procedures already known in literature were modified, or in some cases completely changed from the original protocol in order to obtain products in high chemical yield. This work, to the best of our knowledge, is the first application of palladium catalysed heteroannulation of enantiopure 1-Aryl-2-Propyl-1-ol alcohols **58** to obtain enantiopure aryl-2-benzo[b]furanyl **27** and aryl-2-indolinyl carbinols **64-a-g**.

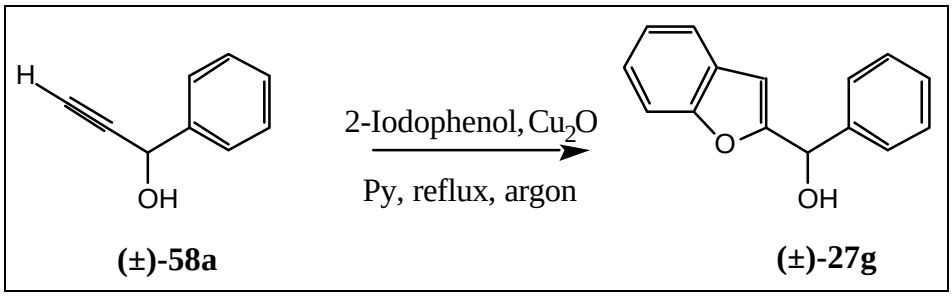
6.1 Application of Castro's procedure for the cyclization of racemic or enantiopure 1-phenyl-2-propyn-1-ol 58a with 2-iodophenol.

Castro's procedure uses a preformed copper (I) acetylide as alkylating reagent of 2-iodophenol. The synthesis of this reagent is performed using $CuSO_4 \cdot 5H_2O$ and NH_4OH in a mixture of ethanol, THF and water in presence of the acetylenic compound. This experimental procedure failed when applied to 1-phenyl-2-propyn-1-ol **(±)-58a:** it was impossible to isolate the product from the reaction mixture by crystallization because of its high solubility in the reaction mixture. In order to decrease the solubility of the Copper (I) acetylide of 1-phenyl-2-propyn-1-ol **(±)-58a** 1-phenyl-2-propyn-1-acetate **(±)-60a** was used under identical reaction conditions as described above. Unfortunately, also in this case it was impossible to recover the product by crystallization (Scheme 6.1). For these reasons Castro's procedure was not further applied and it was necessary to use the modified procedure of Owen[1].



Scheme 6.1: Attempts to form the copper (I) acetylide using Castro's procedure.

The experimental conditions allowed the synthesis of copper (I) acetylide in presence of 2-iodophenol *in situ*. The reaction was carried out in dry pyridine as solvent under reflux in an Argon atmosphere, the copper source was Cu_2O, and the molar ratio between Cu_2O/2-iodophenol/1-phenyl-2-propyn-1-ol **(±)-58a** was 0.7:1:1 (Scheme 6.2).

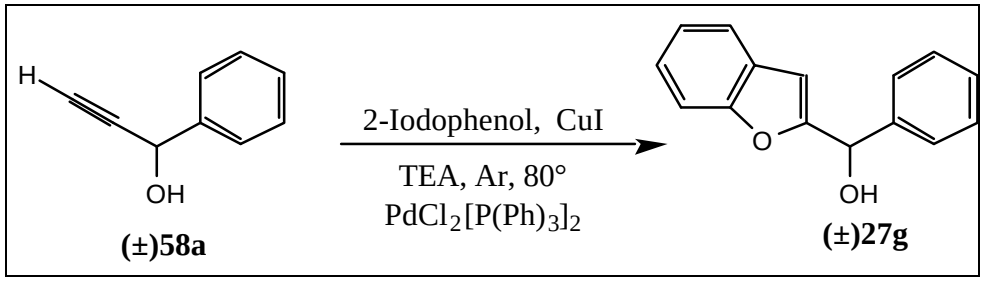


Scheme 6.2: Synthesis of Aryl-2-Benzo[b]Furanyl carbinol **(±)-27g** using Owen's procedure.

Aryl-2-Benzo[b]Furanyl carbinol **(±)-27g** was obtained only with a low chemical yield of ca. 10%. Identical reaction conditions were applied to the enantiopure (-)-(*R*)-1-phenyl-2-propyn-1-ol **(-)-(*R*)-58a**. The harsh experimental conditions and the long reaction time (18h) led to partial racemization of both the unreacted starting material and the product. The reaction was followed by chiral HPLC and it was clear that the amount of racemization was proportional to the reaction time. Futhermore, the product was much more prone to racemization than the starting material. Both attempts demonstrated that Castro's procedure and its modification are not useful for the synthesis of enantiopure aryl-2-benzo[b]furanyl carbinoles **27**.

6.2 Application of Kundu's procedure to cyclize racemic (±)-58a and enantiopure 1-phenyl-2-propyn-1-ol (-)-(*R*)-58a with 2-iodophenol in presence of a Pd catalyst.

1-Phenyl-2-propyl-1-ol **(±)-58a** was one of the substrates that Kundu[2] has used in his paper. The experimental conditions were: 1-phenyl-2-propyn-1-ol **(±)-58a**, o-iodophenol, $PdCl_2[P(Ph)_3]_2$, CuI, TEA in the ratio of 2:1:0.035:0.13:2 at 80°C for 24 h: the chemical yield of phenylbenzo[b]furane carbinol **(±)-27g** was calculated to be 66% based on 2-iodophenol (Scheme 6.3).



Scheme 6.3: Synthesis of phenylbenzo[b]furanecarbinol **(±)-27g** using Kundu's procedure.

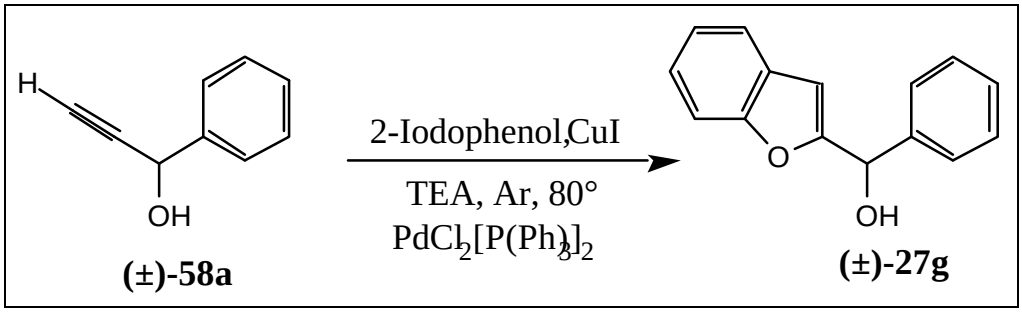
Unfortunately, the procedure proved to be not completely reproducible and the best result obtained in our hands was 50% chemical yield based on 2-iodophenol corresponding to 25% yield starting from the propargylic alcohol. The method was therefore unacceptable because of the low chemical yield and expecially since an excess of arylpropargylic alcohols **58** was required**.** These are not commercially available neither in racemic nor enantiopure forms, and are therefore synthetically most demanding as described in chapter 5. Nevertheless the reaction was carried out also with the chiral substrate **(-)-(*R*)-58a** in order to study the stereochemical outcome. Indeed no racemization occurred when chiral 1-phenyl-2-propyn-1-ole **(-)-(*R*)-58a** was used as a substrate. This discovery was considered a real breakthrough for the synthesis of enantiopure aryl benzofurane carbinoles. Therefore, considerable time was dedicated to the modification of the reaction conditions in order to achieve our requirements. Several parameters were changed:

1) the base
2) the ratio of reactants
3) the temperature
4) the molar percentage of the Pd catalyst and CuI

It was the strategy for the optimization of Kundu's procedure to change only one parameter at a time and mantaining all other parameters constant.

6.2.1 Heteroannullation of Phenyl-2-propyn-1-ol (±)-58a: variation of bases.

Four different bases were tested in order to improve the chemical yield of the product . Only one arylpropynol was used in the study, racemic 1-aryl-2-propyn-1-ol **(±)-58a** (scheme 6.4).



Scheme: 6.4: Effects of different bases on the heteroannulation process of aryl propynol **(±)-58a** mediated by Pd catalyst.

The molar ratio between the reagents was kept as documented in the original paper 2.0 : 1.0 : 0.035 : 0.13 : 2.0 corresponding to arylpropynols : iodophenole : $PdCl_2[P(Ph)_3]_2$: CuI. The results are shown in table 6.1.

Entry	Substrate	Base	n.Eq.	T°C	Product	Yield
1	**(±)-58a**	TEA	2	80	**(±)-27g**	55
2	**(±)-58a**	Py	2	80	**(±)-27g**	35
3	**(±)-58a**	Py	4	80	**(±)-27g**	40
4	**(±)-58a**	TBuA	2	80	**(±)-27g**	60
5	**(±)-58a**	TBuA	4	80	**(±)-27g**	63
6	**(±)-58a**	TMG	2	80	**(±)-27g**	83
7	**(±)-58a**	TMG	3	80	**(±)-27g**	91
8	**(±)-58a**	TMG	4	80	**(±)-27g**	92

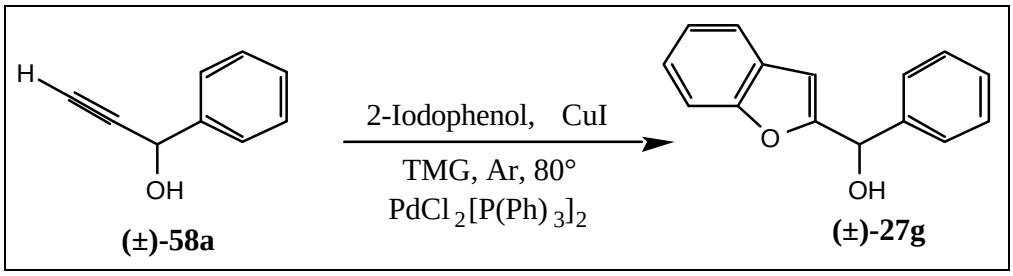
Table 6.1: effect of the bases and no. of equivalents in the synthesis of **(±)-27g.**

The temperature was always mainteined at 80°C and the solvent used was DMF. Chemical yields were calculated based on 2-iodophenol after purification by flash chromatography. Pyridine (Py) was the worst base in terms of chemical yield, difficulties in work up and purification (entries 2,3; Table 6.1). Triethylamine (TEA) gave a low chemical yield (entry1;

Table 6.1), tributylamine (TBuA) was somewhat better (entries 4,5; Table 6.1). Clearly the best base was tetramethyl guanidine (TMG) which increased the chemical yield by more than 35% in comparison to TEA which was the base used in Kundu's paper. The result was considered very satisfactory since almost all of the 2-iodophenole was converted to the corresponding aryl-benzo [b] furanyl carbinol **(±)-27g.**

6.2.2 Optimization of molar ratio between Phenyl-2-propyn-1-ol (±)-58a and 2-iodophenol.

Further optimization was achieved by decreasing the molar ratio of 1-phenyl-2-propyn-1-ole **(±)-58a** and iodophenol from 2:1 to 1:1 with additional ratios of 1.5:1 and 1.1:1. (Scheme 6.5).



Scheme: 6.3: Effects of different ratios between 2-iodophenol and aryl propynol **(±)-58a** on the heteroannulation process mediated by Pd catalyst.

Three equivalents of TMG were used in all of the experiments; Pd catalyst and CuI were also maintained at the original ratio of 0.035 and 0.13 per cent. The results are shown in table 6-2.

With great surprise and enthusiasm it was discovered that excess of 1-phenyl-2-propyn-1-ol **(±)-58a** was indeed not necessary. Almost quantitative yields were obtained with all molar ratios.

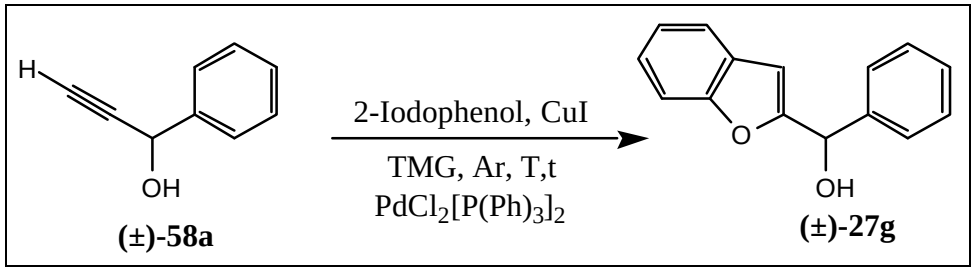
Entry	Substrate	molar ratio	Product	Yield
1	**(±)-58a**	2.0:1.0	**(±)-27g**	95.0
2	**(±)-58a**	1.5:1.0	**(±)-27g**	94.6
3	**(±)-58a**	1.1:1.0	**(±)-27g**	93.4
4	**(±)-58a**	1.0:1.0	**(±)-27g**	90.0

Table 6.2: Optimization of the molar ratio between propynol **(±)-58a** and 2-iodophenol.

This discovery allowed the use of the enantiopure aryl propynols **(+)-(*S*)-58** and **(-)-(*R*)-58** obtained from the enzymatic resolution (chapter 5) in an equimolar ratio with 2-iodophenol.

6.2.3: Optimization of temperature and time.

Temperature and time were optimized together. Four experiments were carried out at different temperatures, the lower temperatures corresponding to longer reaction times (Scheme 6.6).The molecular ratios of the reagents were maintained constant at the optimal value (Paragraphs 6.2.2 and 6.2.1).



Scheme 6.6: Effect of temperature and reaction time on the Pd catalyzed heteroannulation of **(±)-58a**

In table 6.3 the experimental conditions and the results of this study are reported.

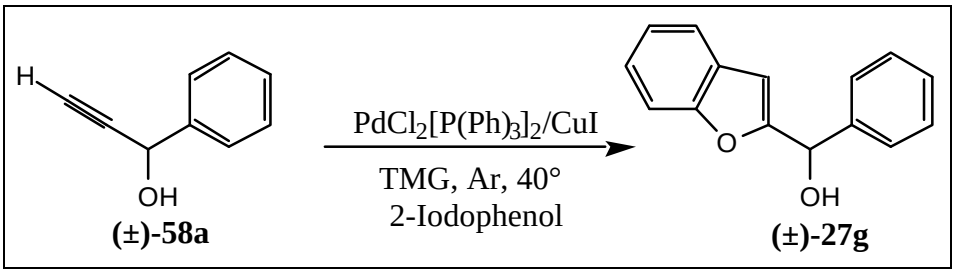
The best compromise between temperature and time was found to be 40°C (entry 3;Table 6.3), corresponding to a reaction time shorter than four hours. Furthermore the crude reaction product was cleaner than that obtained at higher temperature. No reaction occurred at room temperature (entry 4; Table 6.3).

Entry	Substrate	T°C	Time h	Product	yield
1	**(±)-58a**	80	0.5	**(±)-27g**	90.0
2	**(±)-58a**	60	2<	**(±)-27g**	89.4
3	**(±)-58a**	40	4<	**(±)-27g**	90.0
4	**(±)-58a**	25	24	**(±)-27g**	-

Table 6.3: Studies of temperature and reaction time on the Pd catalyzed heteroannulation of **(±)-58a**.

6.2.4. Optimization of catalyst (Pd) amount and CuI.

The last attempt of optimization was aimed at the reduction of the amount of Pd catalyst and copper iodide. Five experiments were carried out to find the best molar ratio (Table 6.4; scheme 6.7).



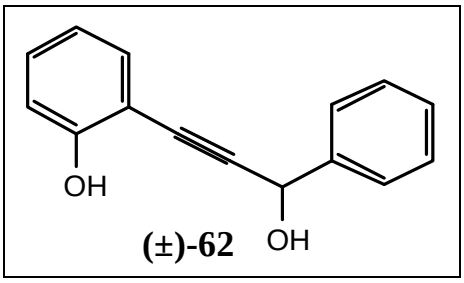
Scheme 6.7: Optimization of Pd catalyst/ CuI ratio.

In the first experiment the ratio reported in the original publication was used where Pd catalyst and CuI were present in 0.035 and 0.13 Mol% in respect to the 2-iodophenole. The chemical yield was very high (table 6.4; entry 1). In the second experiment the amount of CuI was reduced in order to have an equimolar ratio betweeen Pd catalyst and CuI (entry 2, Table 6.7).

Entry	Substrate	Molar ratio Pd/CuI	Time h	Product	Yield
1	**(±)-58a**	0.035:0.13	4<	**(±)-27g**	90.0
2	**(±)-58a**	0.035:0.035	4<	**(±)-27g**	90.0
3	**(±)-58a**	0.025:0.025	4<	**(±)-27g**	90.0
4	**(±)-58a**	0.010:0.025	40	**(±)-27g**	40.3

Table 6.4: Optimization of catalyst (Pd) amount and CuI.

Again the chemical yield was identical to the previous experiment and proved that an excess of CuI is unnecessary.In the third experiment the amounts of Pd and CuI were reduced to 2.5 Mol% (entry 3, table 6.4). Again an identical result was obtained. In the last experiment only 1% of Pd catalyst and CuI were used (entry 4, Table 6.4), leading to **(±)-27g** in 40% yield. The observation that both 2-iodophenol and the starting material **(±)-58a** were completely consumed during the reaction led to the discovery of a very polar side product which, after isolation and characterization, was identified to be the uncyclized product **(±)-62**.



(±)-62

Figure 6.1 : Side product **(±)-62**.

From these result it can be concluded that under these reaction conditions the coupling process is complete while the cyclization was incomplete. For this reason **(±)-62** is recovered as an intermediate of the reaction. **(±)-62** was a very important intermediate for the understanding of the catalytic Pd cycle.

In summary, the optimal reaction conditions after all optimizations were: molecular ratios 1 : 1 : 0.025 : 0.025 : 3 between 2-iodophenol, 1-phenyl-2-propyn-1-ol **(±)-58a**, $PdCl_2[P(Ph)_3]_2$, CuI, TMG. The reaction was carried out in DMF at 40°C and Ar was bubbled through the reaction mixture at all times.

Also the sequence of addition of the reagents was found to be important. In fact the reaction can be devided into three steps:

1) The mixture of DMF and TMG was heated to 40° and an Argon stream led to the solution for 15' before the addition of the other reagents. The argon stream was maintained during the whole reaction. This was necessary in order to exclude oxygen from the reaction mixture and thus to avoid the crosscoupling of the Copper (I) acetylide.

2) 2-Iodophenol, CuI, $PdCl_2[P(Ph_3)]_2$, was added in one portion. The mixture was stirred for 15' before the additon of **(+)-58a**.

3) Addition of 1-Phenyl-2-propyn-1-ol **(±)-58a**. The solution changed colour from pale yellow to red brown.

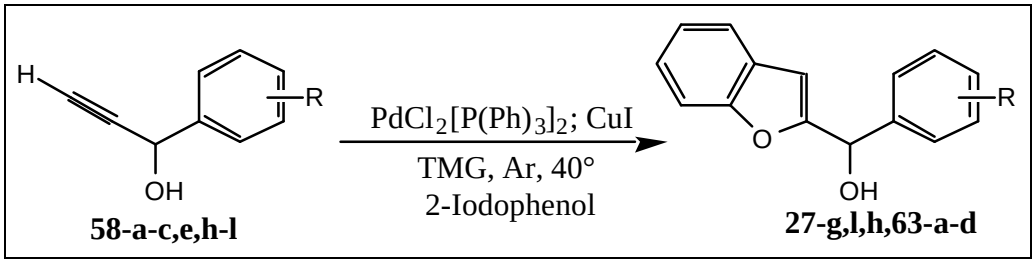
In the same manner, the enantiopure (-)-(*R*)-1-phenyl-2-propyn-1-ol **(-)-(*R*)-58a** was cyclized to (-)-(*S*)-phenyl benzo[b]furanil carbinol **(-)-(*S*)-27g** in 91% of chemical yield and with 97.5% enantiomeric excess.

Reactions were scaled up to 2.5 g. both with the racemic and enantiopure propargylic alcohols. Identical chemical yields and enantiomeric excess were found.

The results of this study were so encouraging that the procedure was applied to all racemic and enantiopure arylpropynols **58**.

6.3 Cyclization of racemic and enantiopure 1-Aryl-2-propyn-1-ols 58-a-c,e,h-l to Aryl-benzo[b]furane methanols 27-g,l,h and 63-a-d.

The optimal reaction conditions described in paragraph 6.2.3 were applied to racemic and enantiopure 1-Aryl-2-propyn-1-ols **58-a-c,e,h-l** in order to explore the application of this reaction for the synthesis of enantiopure Aryl-benzo[b]furane methanols **27-g,l,h** and **63-a-d**. The reaction was always applied first to the racemic compound and then to the enantiopure substrate (scheme 6.8).



Scheme 6.8: Cyclization of racemic and enantiopure 1-Aryl-2-propyn-1-ols **58-a-c,e,h-l** to Aryl-benzo[b]furane methanols **27 g,l,h** and **63a-d**.

The results were very satisfactory indeed as reported in table 6.5. Yields were calculated following flash chromatography. This purification can be considered a mere filtration through silica since after work up the products were always quite pure as judged by NMR and TLC. They were, however, still colored yellow/brown. The enantiomeric excess was determined by chiral HPLC of the crude materials (after the reaction work up) prior to purification. It is interesting to note that the e.e. did not change from the chiral starting material to the product before and after purification.

This method gave very reproducible results both in terms of chemical yields and enantiomeric excess. From the results shown in table 6.5 it is clear that different substituents on the aromatic ring did not lead to any modification of the results.

They were also not influenced by the position of the substituent on the aromatic ring (see entries 3,4,8,9,12,13; table 5.6) nor by stereoelectronic effects (see entries 1,2,3,4,5,6; table 5.6).

Entry	Substrate	R	Time h	Product	Yield	e.e.%
1	**(±)-58a**	H	4.0	**(±)-27g**	91.0	-
2	**(-)-(*R*)-58a**	H	4.0	**(+)-(*S*)-27g**	90.0	97.5
3	**(±)-58b**	4Me	4.0	**(±)-63a**	89.5	-
4	**(+)-(*S*)-58b**	4Me	4.0	**(-)-(*R*)-63a**	89.9	99.0
5	**(±)-58c**	4F	2.5	**(±)27l**	78.0	-
6	**(+)-(*S*)-58c**	4F	2.5	**(-)-(*R*)-27l**	79.7	97.7
7	**(±)-58e**	4CN	8.0	**(±)-27h**	0.0	-
8	**(±)-58h**	3Me	3.0	**(±)-63b**	92.0	-
9	**(+)-(*S*)-58h**	3Me	3.0	**(-)-(*R*)-63b**	93.0	98.1
10	**(±)-58i**	3F	5.0	**(±)-63c**	85.0	-
11	**(+)-(*S*)-58i**	3F	5.0	**(-)-(*R*)-63c**	82.8	98.5
12	**(±)-58l**	2Me	8.0	**(±)-63d**	89.5	-
13	**(+)-(*S*)-58l**	2Me	8.0	**(-)-(*R*)-63d**	82.8	93.3

Table 6.5: Times, yields and e.e. of Aryl-benzo[b]furane methanols **27-g,l,h** and **63a-d**.obtained by heteroannulation of 1-Aryl-2-propyn-1-ols **58-a-c,e,h-l**.

Unfortunately, there was one exception (entry 7; Table 6.5). All attempts to cyclize racemic 1-[4cyanophenyl]-2-propyn-1-ole **(±)-58e** to the corresponding benzo[b]furane, the most active Menarini anticancer drug, failed. The reaction gave a large number of products among which the desired product was not detectable.

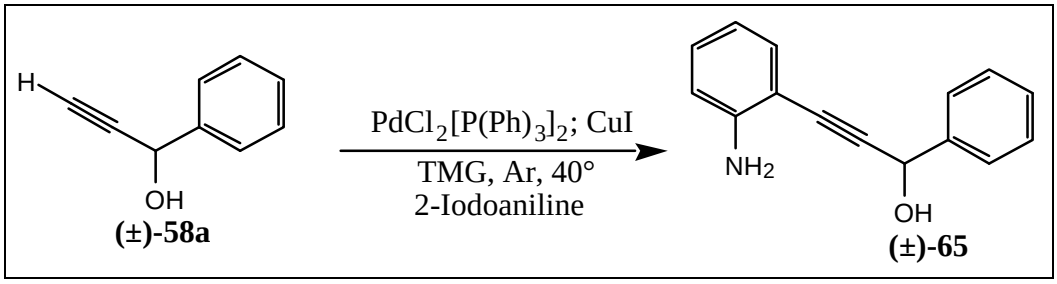
The present work, to our knowledge, is the first application of palladium catalysis for the synthesis of enantiopure aryl-benzo[b]furane methanols **27-g,l,h** and **63-a-d**, derived from enantiopure arylpropynols. Attempts to synthesize the same products by asymmetric reduction of the corresponding prochiral ketones failed (chapter 2), and up to now no chemical chiral synthesis or enzymatic resolution of the racemic alcohols is reported.

6.4 Cyclization of racemic and enantiopure 1-aryl-2-propyn-1-ols 58-a-c,e,h-l to racemic and enantiopure aryl-2-(*N*-mesyl)indolyl methanols 64-a-g.

An obvious expansion of the procedure for the synthesis of enantiopure arylbenzo[b]furan methanols **27-g,l,h** and **63-a-d** described

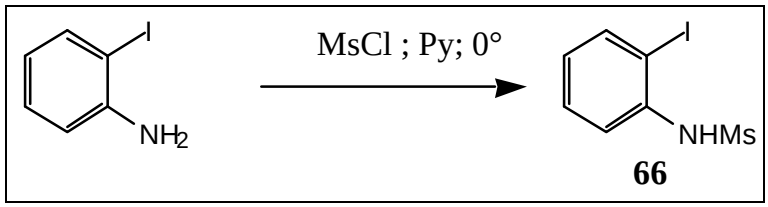
in the previous paragraph was the application of the methodology to the synthesis of aryl-2-indolyl methanols **64-a-g**. Palladium catalysis is well known for the synthesis of indols as described in chapter 2, and benzo[b]furanes and indoles are structurally related. In order to obtain the indoles it was formally sufficient to use the ortho iodoaniline instead of ortho iodophenole.

However ortho iodoaniline under the reaction conditions used for the synthesis of benzofuranes did not lead to the indole. The uncyclized product **(±)-65** was found to be the only reaction product (scheme 6.9). This result was expected because it is described in literature that the free amino group of the iodoaniline must have a strong electronwithdrawing protection group in order to cyclize to indoles.



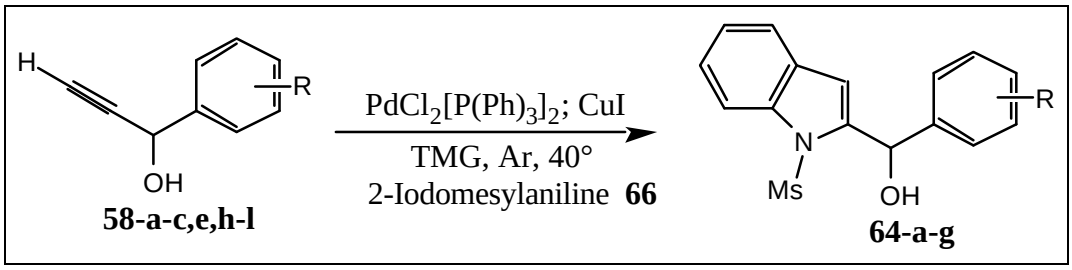
Scheme 6.9: Attempt for the direct cyclization of aryl propargylic alcohol **(±)-58a** to aryl-2-indolylcarbinole.

Thus 2-iodoaniline was first mesylated using mesyl chloride and pyridine (Scheme 6.10). A stoichiometric amount of mesyl chloride was used because an excess led to the dimesylated product.



Scheme 6.10: Mesylation of 2-iodoaniline.

With this material identical reaction conditions were used for the production of the indols **64-a-g** as for the synthesis of benzofuranes **27** and **63** (Scheme 6.11).



Scheme 6.11: Cyclization of racemic and enantiopure arylpropynols **58a-c,e,h-l** to racemic and enantiopure aryl-2-(*N*-mesyl)indolyl methanols **64a-g.**

Entry	Substrate	R	Time h	Product	Yield	e.e %
1	**(±)-58a**	H	1.0	**(±)-64a**	87.4	-
2	**(-)-(*R*)-58a**	H	1.0	**(+)-(*S*)-64a**	87.0	99.1
3	**(±)-58b**	4Me	4.0	**(±)-64b**	83.3	-
4	**(+)-(*S*)-58b**	4Me	4.0	**(-)-(*R*)-64b**	84.3	95.97
5	**(±)-58c**	4F	1.5	**(±)-64c**	79.3	-
6	**(+)-(*S*)-58c**	4F	1.5	**(-)-(*R*)-64c**	78.0	98.1
7	**(±)-58e**	4CN	8.0	**(±)-64d**	0	-
8	**(±)-58h**	3Me	3.5	**(±)-64e**	93.0	-
9	**(+)-(*S*)-58h**	3Me	3.5	**(-)-(*R*)-64e**	93.2	99.1
10	**(±)-58i**	3F	3.0	**(±)-64f**	91.1	-
11	**(+)-(*S*)-58i**	3F	3.0	**(-)-(*R*)-64f**	92.0	99.55
12	**(±)-58l**	2Me	5.0	**(±)-64g**	83.4	-
13	**(+)-(*S*)-58l**	2Me	5.0	**(-)-(*R*)-64g**	85.0	93.2

Table 6.7: Times, yields and e.e.of aryl-2-(*N*-mesyl)indolyl methanols **64a-g** obtained by heteroannulation of 1-Aryl-2-propyn-1-ols **58-a-c,e,h-l**.

Also in this case the results were very satisfactory as shown in table 6.7.

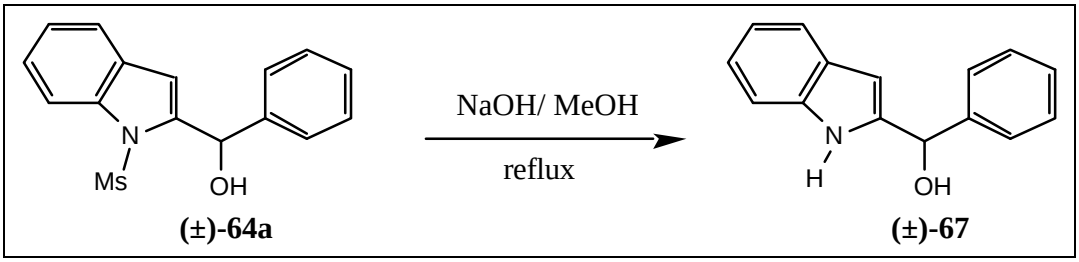
The reaction times were shorter than those with the corresponding benzofurans **27** and **63**. Both chemical yields and enantiomeric excess are very high. No racemization occurred during the process of heteroannulation. Also in this case the 1(4-cyanophenyl)-2-propyn-1ol **(±)-58e** did not cyclize to the corresponding indol. All starting material was decomposed during the reaction.

As in the case of benzofuranes this is the first application of palladium catalysis to the synthesis of enatiopure aryl-2-indolyl carbinols **64-a-g**. These compounds are not obtainable by asymmetric reduction of the

corresponding prochiral ketones or by enzymatic resolution of the racemic alcohols.

6.4.1 Deprotection of Phenyl-2-(*N*-mesyl)Indonyl methanole (±)-64a.

In order to obtain the free amino compounds from the Aryl-2-(*N*-mesyl)-Indolyl carbinols **64-a-g** it was necessary to remove the mesyl group from the nitrogen. Due to the high stability of this protecting group drastic basic reaction conditions were required. The first attempt using K_2CO_3/methanol under reflux was unsuccessful; after eighteen hours no conversion of the starting material was observed. With NaOH in methanol under reflux, after twentyfour hours all starting material was converted to the product aryl-2-indolyl carbinole **(±)67** in 85% yield (Scheme 6.13).



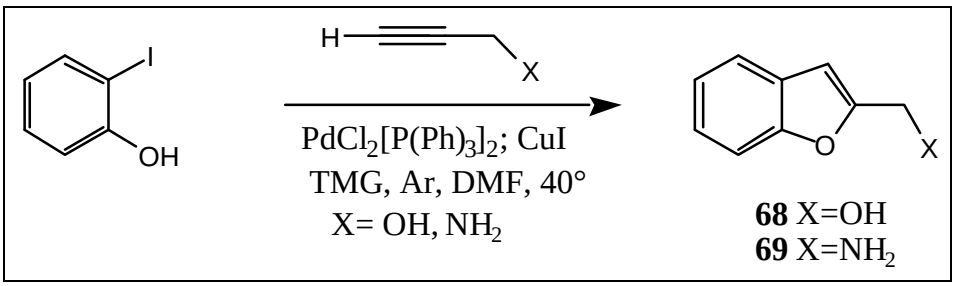
(±)-64a **(±)-67**

Schem 6.13: Deprotection of phenyl-2-(*N*-mesyl)-indolyl methanol **(±)-64a.**

6.5. Cyclization of propargyl alcohol and propargyl amine to Benzo[b]furane-2-methanole 68 and Benzo[b]furane-2-methyl amine 69.

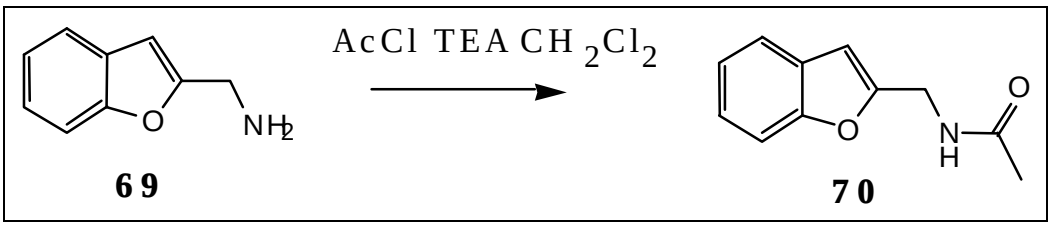
2-iodophenol was used as a substrate for the cyclization with propargylic alcohol and propargylic amine to the corresponding benzofurane derivatives. Identical reaction conditions were used as for the synthesis of aryl-benzo[b]furane carbinols **27** and **63** (see paragraph 6.2.3). In the literature it is reported that the use of these unprotected propargylic derivatives gives poor results and the cyclization process is quite inefficient. With the optimized procedure developed for the aryl-benzo[b]carbinols **27** and **63** the coupling and cyclization of the propargylic alcohol and amine proved to be in fact quite efficient and

afforded the benzo[b]furane-2-methanole **68** and benzo[b]furane-2-methylamine **69** in 97 and 86 % yield, respectively (Scheme 6.14).



Scheme 6.14: Cyclization of unprotected propargylic alcohol and amine to benzo[b]furane derivatives **68** and **69.**

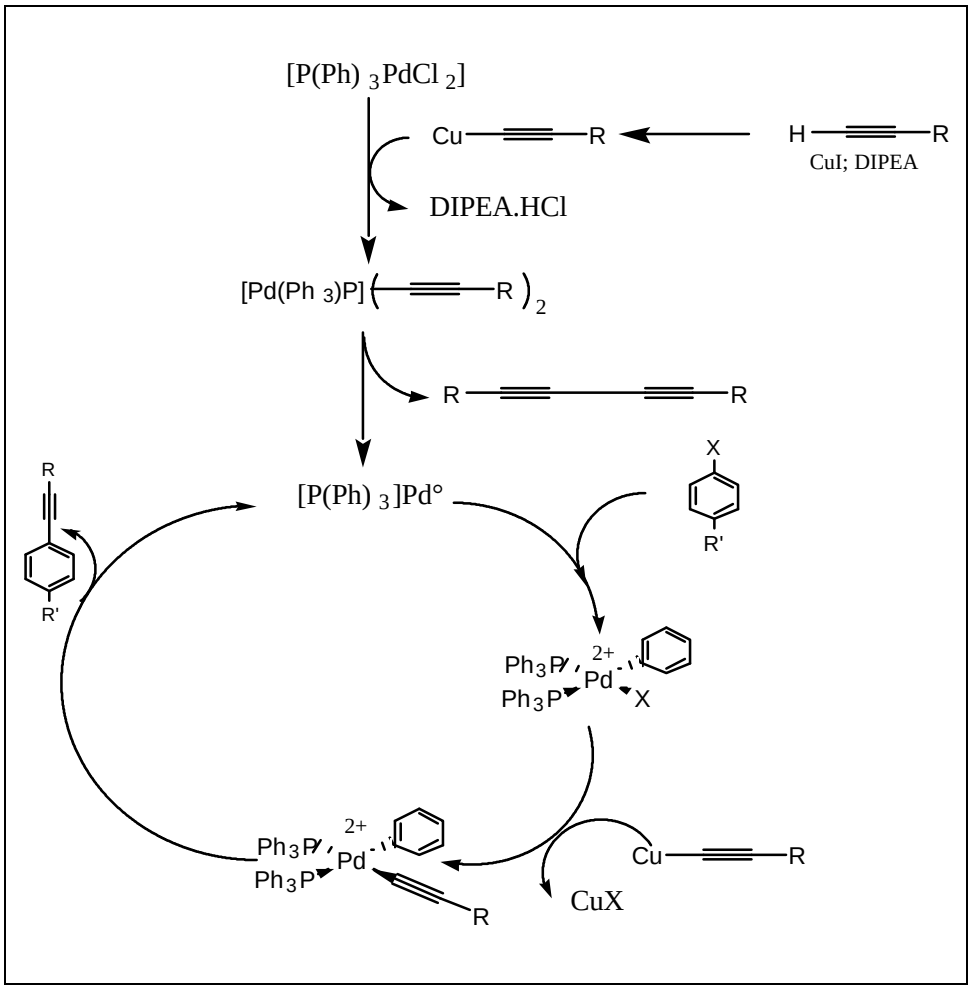
For a full characterization **69** was acetylated in dichloromethane in presence of acetyl chloride and triethylamine in 95 % yield to obtain **70** (Scheme 6.15).



Scheme: 6.15: Acetylation of **69.**

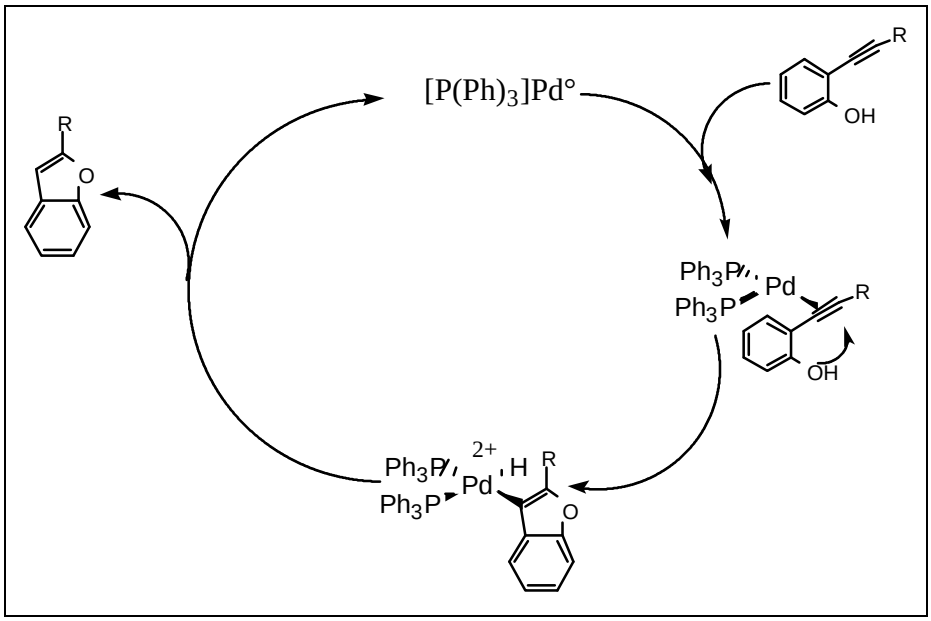
6.6. Studies of the Pd catalyzed reaction mechanism.

Several mechanisms were proposed in the literature for the coupling and cyclization of alkynes under palladium catalysis. The mechanism of coupling between alkynes and aryliodide is well established. On the contrary, for the cyclizations of alkynes to benzofuranes or indoles several hypotheses are existing. One of the most complete descriptions of the coupling reaction was reported by J.Burton[3] and coworkers in 1993 (Scheme 6.16).



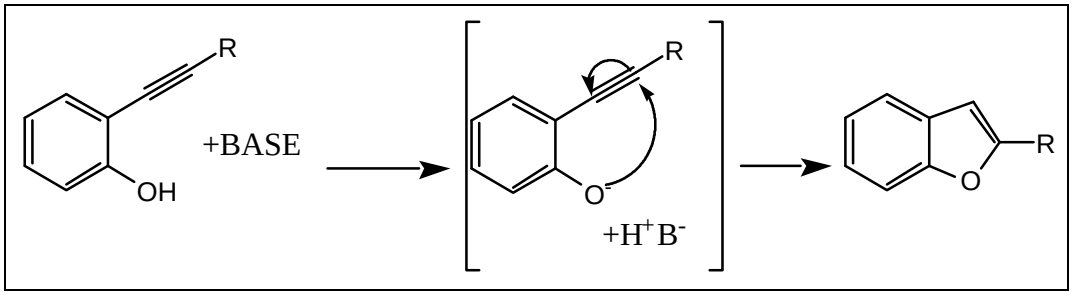
Scheme 6.16: Crosscoupling mediated by Pd^0.

The coupling reaction appears to involve Pd° catalysis, the species being generated by reduction of palladium II in the organopalladium halide by attack of the copper acetylide anion. The thus formed bis (triphenylphophine)dialkynyl palladium undergoes reductive elimination of disubstituted acetylene to form bis(triphenylphosphine) Palladium(0). The thus resulting Palladium(0) species enters the catalytic cycle (scheme 6.16) by oxidative addition of para substituted aryliodide, followed by alkylation to generate again a palladium II species. Finally, reductive elimination leads to a coupling product and the palladium(0) catalyst is regenerated. This mechanism is the most accepted one for the coupling between the aryliodide and acetylenic compounds. It seems reliable also for the coupling between arylpropynols **58** and 2-iodophenol. The second step of the synthesis of benzofurans or indols might involve more than one mechanism. In fact, in the literature[4] it is reported that Pd° can catalyze the annulation step (Scheme 6.17).



Scheme 6.17: Pd° catalysis in the heteroannulation step.

An easier explanation could involve a simple base catalyzed 5-endotrig cyclization favoured by the Baldwin rules (scheme 6.18).



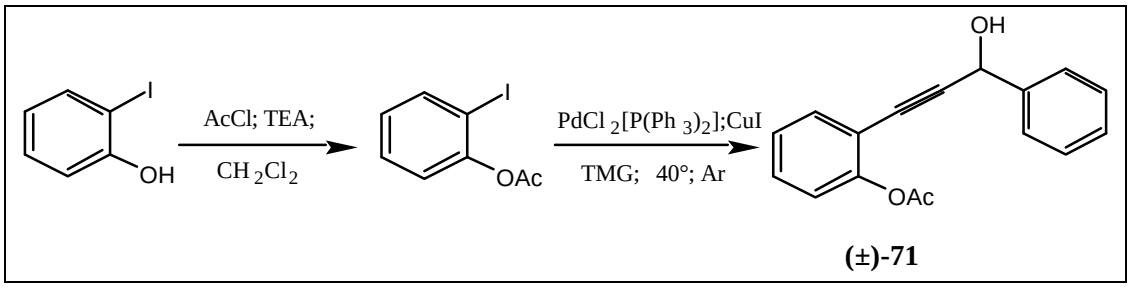
Scheme 6.18: base catalyzed cyclization to benzofuran.

The first hypothesis involving the coordination of the triple bond from Pd° would implicate a double palladium catalytic cycle, whereas the second hypothesis implicates a single Pd° catalytic cycle and a basic cyclization to the final product. In order to shine more light on the mechanism in the next paragraphs studies to elucidate further the mechanism are described.

6.6.1. Cyclization studies.

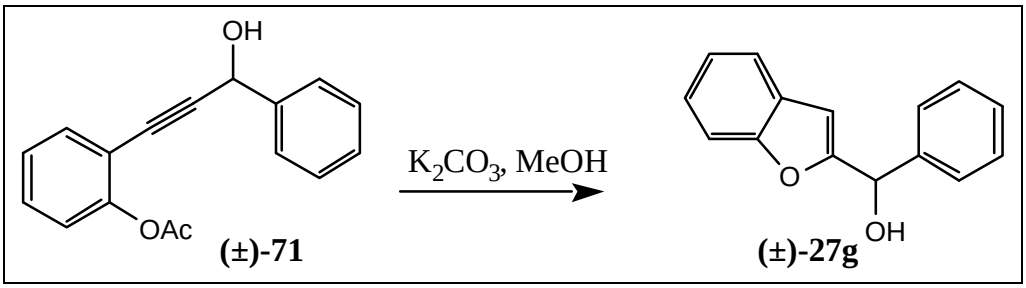
For this 2-iodophenol was first acetylated with acetyl chloride in dichloromethane and then coupled under palladium catalysis with racemic

1-phenyl-2-propyn-1-ol **(±)-58a** to form the compound **(±)-71**(Scheme 6.19)



Schem 6.19: Synthesis of **(±)-71.**

In an attempt to deprotect the acetyl group in **(±)-71** using a saturated solution of K_2CO_3 in absolute methanol at 0°C led to the racemic aryl-benzo[b]furan carbinol **(±)-27g** (Scheme 6.20).

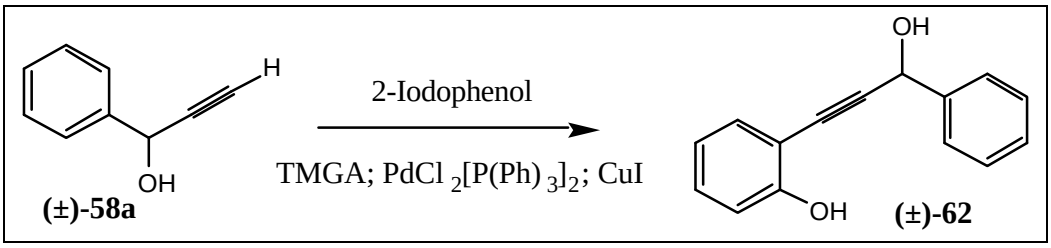


Scheme 6.20: synthesis of **(±)-27g** by 5-endotrig base catalized cyclization.

The formation of **(±)-27g** under these reaction condition proved that the 5-endo trig cyclization can occur in these substrates.

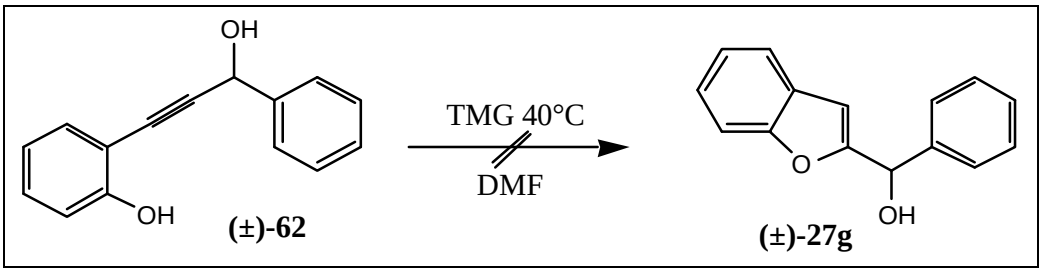
The unprotected analogue of **(±)-71**, e.i.**(±)-62** had already been obtained in 60 % yield as side product of the Pd catalyzed cyclization when only 1% of catalyst was used (entry 4, Table 6.4). In order to improve the chemical yield it was enough to use only one equivalent of base. This way **(±)-62** was obtained in 89.5% chemical yield (scheme 6.21).

(±)-62 can be considered a key intermediate for studying the mechanism involved in the second part of the reaction, e.i. for the synthesis of benzofuranes or indoles.



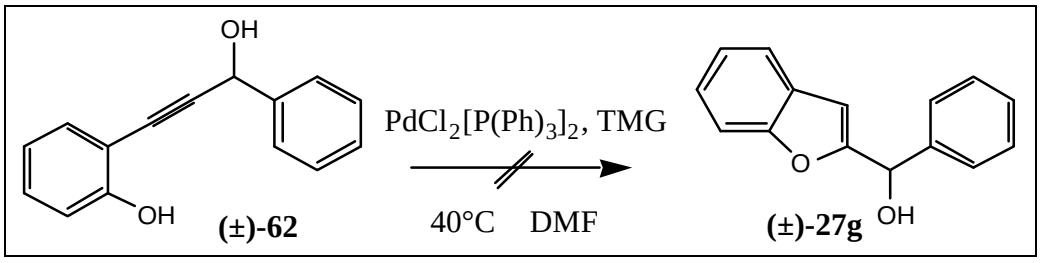
Scheme 6.21: Synthesis of **(±)-62** by Pd catalyses.

The first experiment was carried out to show that the base indeed catalyzes a 5-endotrig cyclization under the reaction conditions used for the synthesis of benzofuranes or indols. Two equivalents of tetramethyl guanidine were added to a solution of **(±)-62** in DMF at 40°C to try the 5-endotrig cyclization leading to the benzofuran **(±)-27.** Surprisingly the cyclization did not occur at all (Scheme 6.22). This result clearly excluded the use of a simple base 5-endotrig catalyzed cyclization which was observed with **(±)-71** using K_2CO_3/MeOH (Scheme 6.20).



Scheme 6.22: Attempt to cyclize **(±)-62** with TMG.

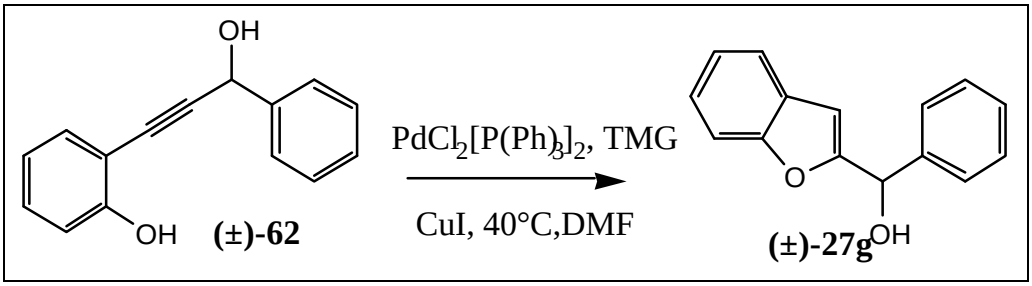
A second attempt of cyclization was carried out by adding $PdCl_2[P(Ph)_3]_2$ and TMG to a solution of **(±)-62** in DMF at 40° (Scheme 6.23).



Scheme 6.23: Attempt to cyclize **(±)-62** with $PdCl_2[P(Ph)_3]_2$ and TMG.

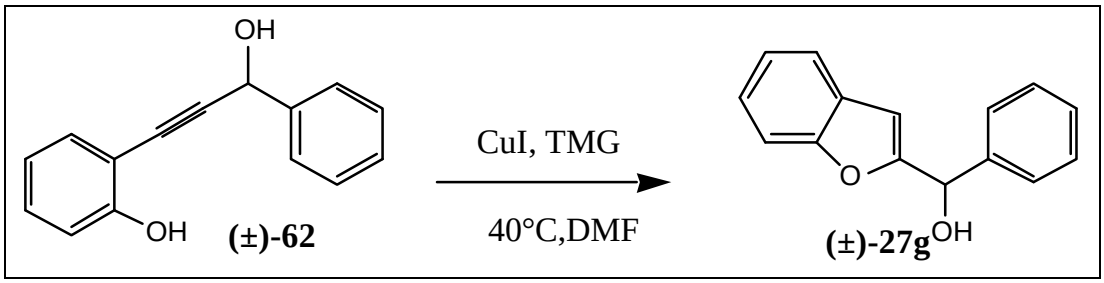
Again no cyclization occured after four hours of reaction time. This result proved that the palladium is involved only in the crosscoupling step

between aryliodide and copper acetylide and not in the final cyclization step. A third attempt was made by using the normal cyclization conditions for the synthesis of benzofurans **(±)-27g** using palladium catalysis. **(±)-62** as expected cyclized in less than three hours to the benzofuranes **(±)-27g** in 89% yield (Scheme 6.24)



Scheme 6.24: Cyclization of **(±)-62** under the optimized conditions for the synthesis of aryl benzofuran carbinols.

A final attempt was made by adding CuI and TMG to a solution of **(±)-62** in DMF at 40°C under argon. Here in less than one hour **(±)-62** was converted completely to the benzofurane (**±)-27g**. The result proved again that cyclization takes place only in presence of CuI in basic media.



Scheme 6.25: Cyclization of **(±)-62** to aryl benzofuran carbinol **(±)-27g** by copper-iodide.

The process is clearly copper mediated as hypothesized in Castro's publications (Scheme 6.25).

The four different experiments decribed above clearly indicate that the palladium catalyst is involved only in the crosscoupling between aryl iodide and the acetylenic compound to form compounds such as **(±)-62** but not in the final cyclization step to benzo[b]furane. The heteroannulation is not working by simple organic base catalysis as proven in the first experiment where tetramethyl guanidine was used as base to cyclize **(±)-62.** In reality it is mediated by the copper iodide in

presence of base as decribed in the last experiment and as tentatively described in figure 6.2.

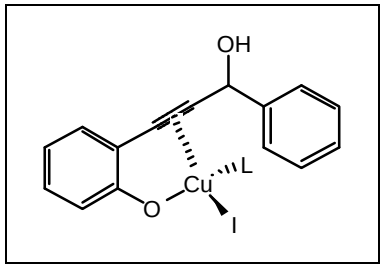
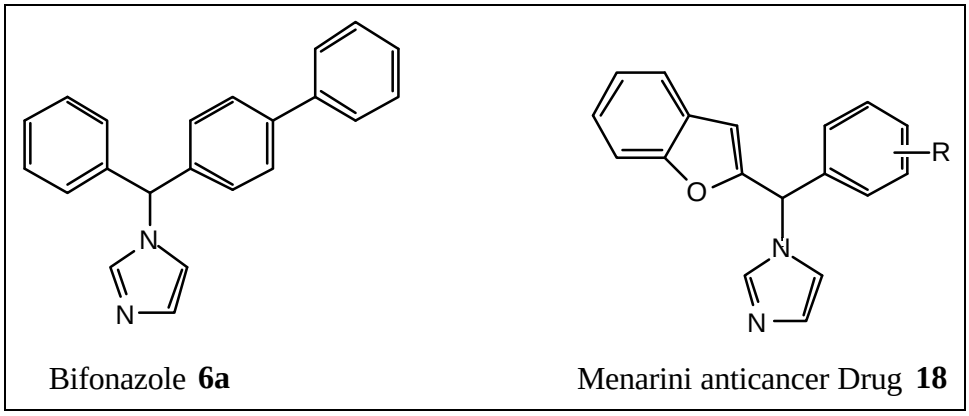


Figure 6.2: possible Copper coordination.

7 Summary:

Numerous drugs are chiral, generally only one enantiomer is therapeutically active while the other antipode is completely inactive or shows often undesired and/or toxic side effects. For this reason, all new chiral drugs are now formulated in enantiopure form, and consequently the synthesis of enantiomerically pure compounds is becoming one of the most important areas in the organic chemistry.

Non-steroidal anticancer and antifungal drugs are particularly interesting as therapeutic agents. Several classes of these two different families of drugs contain the same chemical structure e.g. Bifonazole **6a** and non-steroidal aromatase inhibitors such as the Menarini anticancer drug **18** (Fig.7.1).



Bifonazole **6a** Menarini anticancer Drug **18**

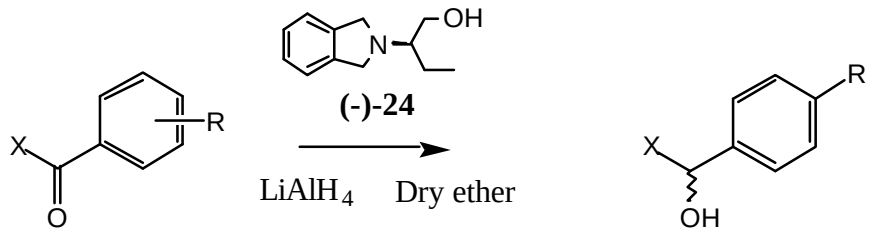
Fig 7.1: Bifonazole **6a** and the Menarini anticancer drug **18.**

They are characterized by the presence of an *N*-imidazole group in a benzhydrilic position. The carbon atom link to the three aromatic moieties is the only chiral centre of the molecule. The present work was aimed at new procedures for the synthesis of both Bifonazole **6a** and the Menarini aromatase inhibitors **18** in enantiomeric form as well as structural analogues.

In order to prepare enantiopure synthons and final products several synthetic methods were developed.

A special attention was dedicated to the synthesis of enantiopure benzhydrols **27a-f** and aryl-2-benzo[b]furancarbinols **27g-i** and **63a-d**.

A chiral lithium aluminiumhydride complex with (*R*)-(-)-2-isoindolinyl-butan-1-ol **(*R*)-(-)-24** as auxiliary was used for the asymmetric reduction of ketones **25a-d** and **26a,c** in order to obtain the corresponding enantiopure alcohols. Using this method with the benzophenones **25b-d** high enantiomeric excesses and chemical yields were obtained, whereas in the case of the aryl-2-benzo[b]furan ketones **25a,c** only low enantiomeric excesses yet high chemical yields were achieved (Scheme 7.1).



25a	X=Ph	R=4-Ph	**(±)-27a**	X=H	R=4-Ph
25b	X=2-BrPh	R=H	**(+)-27b**	X=Br	R=H
25c	X=2-BrPh	R=4-Ph	**(+)-27c**	X=2-BrPh	R=4-Ph
25d	X=2F-Ph	R=4-Ph	**(+)-27d**	X=2-FPh	R=H
26a	X=2-Benzo[b]furan	R=H	**(±)-27g**	X=2-Benzo[b]furan	R=H
26c	X=2-Benzo[b]furan	R=2,4Cl	**(+)-27i**	X=2-Benzo[b]furan	R=2,4Cl

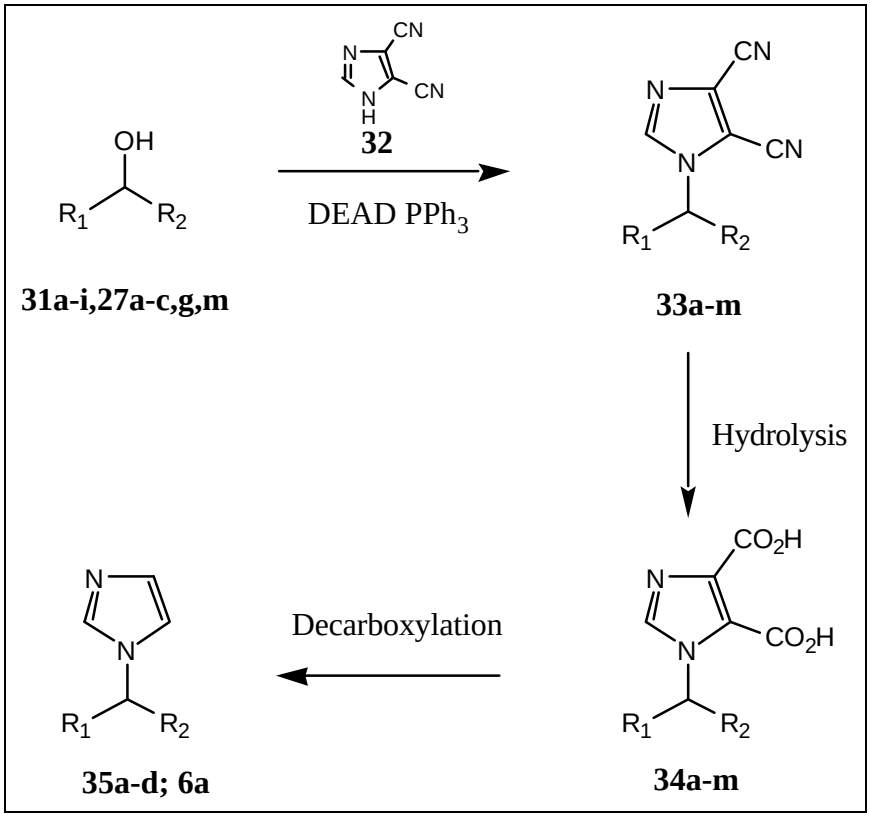
Scheme 7.1: Synthesis of enantiopure alcohols **(+)-27b-d,i** by reduction with chiral lithium aluminium complex

Racemic and enantiopure alcohols **27a-c,g,m** and **31a-1** were used as starting materials in multi-step syntheses for the corresponding *N*-imidazole derivatives in racemic and enantiopure forms. Involved are three reaction steps (Scheme 7.2): (a) Mitsunobu reaction with 4,5-dicyano imidazole to obtain the *N*-4,5-dicyanoimidazole derivatives **33a-m**; (b) hydrolyses of the *N*-imidazole-4,5-dicarbonitrile derivatives **33a-m** to the corresponding diacids **34a-m**, (c) thermic decarboxylation of the diacids **34a-m** to the final *N*-imidazole derivatives **35a-d.**

This synthetic procedure was exceptionally well suited for the production of enantiopure *N*-alkyl imidazole derivatives **34a,b**. Complete inversion of the stereochemistry of the starting alcohol was observed during the Mitsunobu reaction, high enantiomeric excesses were achieved with generally moderate chemical yields.

Benzhydrilic alcohols **31d** showed partial racemization during the synthesis of 1-(1-Phenyl-1-propyl)-imidazole-4,5-dicarbonitrile **33e** in

the Mitsunobu reaction. No evidence for further racemization was found during the hydrolysis to the 1-(1-Phenyl-1-propyl) imidazole-4,5-dicarboxylic acid **34c**, but a complete racemization was observed in the thermic decarboxylation to the final (1-phenyl-1-propyl) imidazole **35c.**

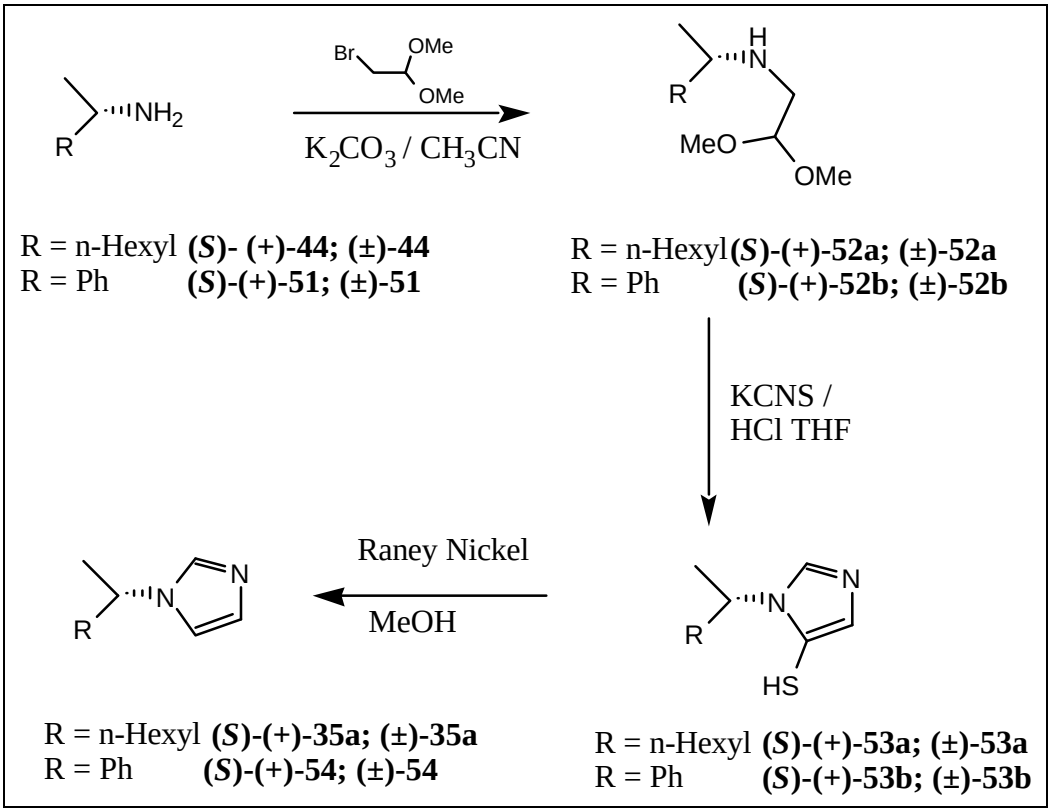


Scheme 7.2: Mitsunobu-Hydrolyses-Decarboxylation for the synthesis of enantiomeric and racemic *N*-Alkyl imidazole derivatives.

The application of the Mitsunobu reaction to the enantiopure benzhydroles **27a-c** led to a completely racemic *N*-4,5-dicyano imidazole derivatives **33g-i** in high chemical yields. The syntheses proceeded through the next two steps with high chemical yields to produce the imidazole derivative **35d** and bifonazole **6a** in racemic form. All synthetic pathways were completely unsatisfactory in the case of the aryl-2-benzo[b]furan methanols **27g,m**. An identical procedure was applied to 4(5)-ethylimidazole carboxylate **37** in order to avoid the drastic conditions during the hydrolyses of the cyano groups of the 4,5-dicyanoimidazole derivatives **33a-m**. Overall no advantages in using this substrate were found.

To demonstrate the complete inversion of the stereocenter during the Mitsunobu reaction, several alternative synthetic methods of *N*-imidazole

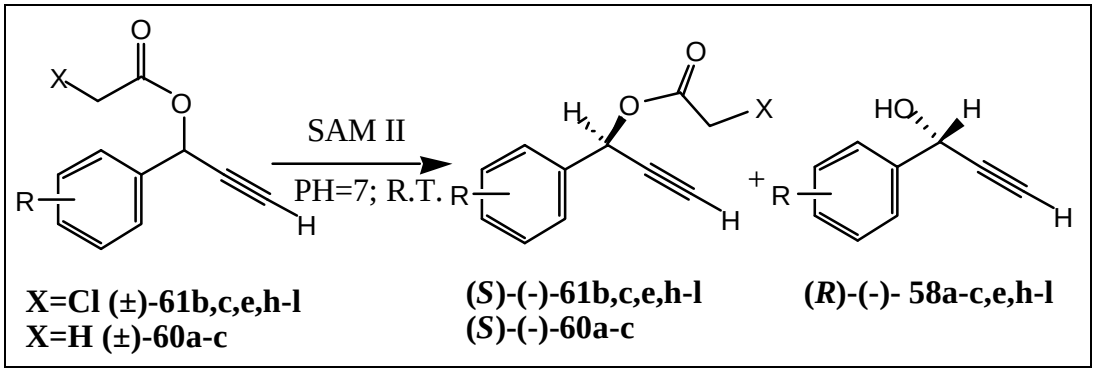
derivatives were tried. Using a modified Marckwald procedure starting from chiral amines **(*S*)-(+)-44** and **(*S*)-(+)-51** it was possible to synthesize the imidazole ring and to obtain the corresponding enantiopure (*S*)-(+)-1-(2-octyl) imidazole **(*S*)-(+)-35a** and (*S*)-(+)-1-phenyl-1-ethyl imidazole **(*S*)-(+)-54** (Scheme 7.3)**. (*S*)-(+)-35a** presented an identical specific rotation as the corresponding compound obtained from the three step synthesis discussed above.



Scheme 7.3: Synthesis of the enantiomeric *N*-alkylimidazole **(*S*)-(+)-35a** and **(*S*)-(+)-54**

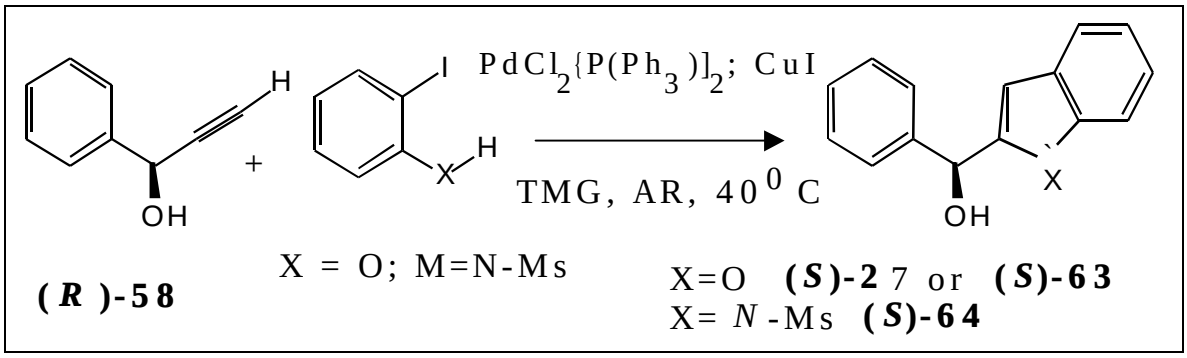
This clearly demonstrated that complete inversion of the stereochemistry occurred in the Mitsunobu reaction. Futhermore the modified Marckwald procedure is a good method for the synthesis of enantiopure benzyl imidazol derivatives. A natural extention was the application of this methodology to enantiopure benzhydrilic amines. Syntheses of chiral benzhydrilic amines **56a,b** and aryl-2-benzo[b]furan methylamines **56c,d** were performed starting from the corresponding chiral alcohols; unfortunally no good results were achieved with this approach.

In order to obtain the enantiopure aryl-2-benzo[b]furan methanols **27** a new synthetic method was considered instead of the asymmetric reduction of the corresponding ketones. The use of the lipase SAMII allowed the synthesis of enantiopure 1-aryl-2-propyn-1-ols **(*R*)-(-)-58a-c,e,h-l** in high enantiomeric excesses and good chemical yields *via* hydrolysis of corresponding racemic acetates **60a-c** and chloroacetates **61a-l** (Scheme 7.4).



Scheme 7.4: Enzymatic hydrolyses of acetates and chloroacetates

The racemic and enantiopure 1-aryl-2-propyn-1-ols **58 a-l** were cyclized with 2-iodophenol to the corresponding aryl-2-benzo[b]furan carbinols **27g-h** and **63a-d** and with 2-*N*-Mesyl iodoaniline to aryl-2-(*N*-mesyl)indol carbinols **64a-g** using Pd(0) as catalyst (Scheme 7.5). Both products were obtained in high e.e. and chemical yield. These constitute the first applications of Pd catalyses with enantiopure arylpropynols.



Scheme 7.5:Cyclization of racemic and enantiomeric 1-aryl-2-propyn-1-ols to aryl-benzo[b]furancarbinols **27** and **63**or Aryl-*N*-Ms indolylcarbinols **64**

The reaction conditions were optimized in order to maximize chemical yields and enantiomeric excesses. The reaction was also applied to propargylic amines to synthesize the 2-benzo[b]furanemethylamines **69**.

Finally an hypothesis for the mechanism of cyclization was formulated. The first step is the Pd^0 catalyzed addition of the acetylenic compound to the 2-iodophenol leading to **62**; the second step is the CuI catalyzed cyclization to benzo[b]furane derivatives **27** or to *N*-Ms-indol derivatives **64**.

In conclusion the present work led to advances in the stereoselective synthesis of antifungal agents such as bifonazole **6a** and the aromatase inhibitors **18**; in fact the application of the described methodology to an enantiopure amine may probably lead to the target molecule in enantiopure form.

8. Synthetic Procedures and Analytical Data

General Methods. Melting points were taken on a Gallenkamp apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. IR spectra ($CHCl_3$ solutions unless otherwise stated) were recorded on a Perkin-Elmer 398 spectrophotometer. NMR spectra were run on Bruker AC 200 (200 MHz), Bruker AV 250 (250 MHz) or Varian XL 300 (300 MHz) spectrometers. ^1H NMR chemical shifts are reported relative to $CDCl_3$ at _ 7.24 ppm and tetramethylsilane at 0.00 ppm. EI low-resolution mass spectra were recorded on a Kratos MS 80 spectrometer with an electron beam of 70 eV. Elemental analyses (C, H, N) were performed in house on a Perkin-Elmer 240C Analyzer.

Anhydrous DMF was purchased from Aldrich Chemical Co. THF was distilled from potassium benzophenone ketyl. CH_3CN was distilled from P_2O_5. Reagents were from commercial suppliers and used without further purification. Extracts were dried over Na_2SO_4 and evaporated under reduced pressure using a rotary evaporator. Merck silica gel 60 was used for chromatography (70-230 mesh) and flash chromatography (230-400 mesh) columns. The plates used for analytical and preparative TLC were Merck silica gel 60 F_{254} (0.2 mm and 2 mm thickness, respectively). Yields of the reactions refer to the purified products and are not optimized.

8.1 Synthesis of prochiral benzophenones 25-a-f:

8.1.1 General synthetic procedure:

Benzoyl chloride (20 mmoles) was added dropwise within 20 min. to a suspension of $AlCl_3$ (28 mmoles) in dry 1,2-dichloroethane cooled to 0°C with an ice bath. A solution of biphenyl (20 mmoles) in dry 1,2-dichloroethane was added to the reaction mixture 10 min. after the first addition. The reaction mixture was heated to reflux for 28 hours, then cooled to R.T. and poured into a 6N HCl solution. The mixture was stirred for 15 min. The organic phase was separated, the water phase was washed with (2 x 100 ml) $CHCl_3$, the organic phases were collected and

were washed with a saturated solution of NaCl until neutral pH and finally dried over anhydrous Na_2SO_4. The organic phase was evaporated on the rotavapor and the resulting crude product was triturated with petroleum ether. 19.4 mmoles of **25a** (97% yield) were recovered as white solid.

Identical procedures were used for compounds **25a-f**. Only for **25b** benzene was used as solvent instead of 1,2-dichloroethane. See table 3.1, chapter 3 for chemical yields, temperatures and reaction times.

8.2 Synthesis of Aryl-2-benzo[b]furanones 26a-e by the Rapp Stormer procedure:

8.2.1 General procedure:

Salicyl aldehyde (469 mmoles, 50 ml) was added to an ethanolic solution of NaOH (469 mmoles in 400 ml of abs. EtOH). Some solid was formed during the addition. The reaction mixture was warmed to 50°C, and 2,4-trichloroacetophenone in 300 ml of abs. EtOH was added dropwise during 30 min. The mixture was refluxed for 24h, than was cooled to R.T. and a white solid precipitated. It was filtered off on a gooch funnel and washed with water and abs. EtOH. Finally it was kept under high vacuum overnight. 118 gr of a white product **26c** were recovered (88% yield).

Identical procedures were used to obtain **26a-e**, see chapter 3, table 3.2 for chemical yields and reaction times.

8.3 Synthesis of racemic alcohols (±)-27a-m by $NaBH_4$ reduction:

8.3.1 General procedure:

The prochiral ketone **25c** (14.8 mmoles) was dissolved in a 1:1 mixture of THF and EtOH. $NaBH_4$ (44,5 mmoles) was added to the

mixture as solid in small portions. The reaction was completed after the last addition. The mixture was diluted with water, and the product was extracted with $CHCl_3$, the organic phase was washed with (50ml) 1N HCl, saturated $NaHCO_3$, saturated NaCl and the organic phase finally dried using anhydrous Na_2SO_4. The organic phase was evaporated on a rotavapor, the resulting crude solid was triturated with *n*-hexane. The alcohol **(±)-27c** (14.6 mmoles, 95% yield) was recovered as white solid.

Identical procedures were used for the syntheses of **27a-m;** see table 3.3, chapter 3 for chemical yields and reaction temperatures.

8.4 Synthesis of (*R*)-(-)-2-(isoindonylinyl)-butane-1-ol (*R*)-(-)-24

R-2-amino-1-butanole (0.84 mole; 79,64 ml) and 1,2-dichloroxylene (0.84 mole; 465.1 g) were added to a suspension of K_2CO_3 (3.36 mol) in 1 L of acetonitrile. The mixture was stirred using a mechanical stirrer under reflux for 24h. The mixture was cooled to room temperature and the K_2CO_3 was filtered off. The solvent was evaporated and the resulting crude oil was dissolved in EtOAc (750 ml). The organic solution was washed with saturated $NaHCO_3$ (2 x 200 ml), then the product was extracted with 2N HCl solution (400 ml). 3N NaOH solution was added to the acid solution until pH 12 was reached. The product was extracted with EtOAc (800 ml) and after solvent evaporation the crude product was purified by two high vacuum distillations. 134 g (84% yield) of product **(*R*)-(-)-24** were recovered.

8.5 Synthesis of chiral alcohols 27a-d,g,i by asymmetric reduction:

8.5.1. General synthetic procedure:

To a 1 M solution of $LiAlH_4$ in Et_2O (30 ml, 30 mmol) a solution of (*R*)-(-)-2-(2-isoindolinyl)butan-1-ol **(*R*)-(-)-24** (14.32 g, 75 mmol) in 200 ml of Et_2O was added dropwise over 3 h at room temperature. After

45 min, the mixture was cooled to -15 °C and a solution of 2-bromo-4'-phenylbenzophenone **25c** (8.43 g, 25 mmol) in 30 ml of Et_2O was slowly added during 2 h under stirring. After a further 15 min, the reaction mixture was quenched with 1 N NaOH (20 ml). The organic phase was successively washed with 1 N HCl (2 x 100 ml) and 1 N NaOH (2 x 100 ml), then with water to neutral pH. Concentration of the dried extracts afforded a crude oil, which was purified by flash chromatography ($CHCl_3$/hexane 8:2) to give the title compound.

Identical synthetic procedures were used to reduce ketones **25a-d** and **26a,c**. See chapter 3, table 3.4 for chemical yields and optical purities (% e.e.) for **25a-d** and chapter 3, table 3.5 for **26a,c**.

8.6 Dehalogenation of (±)-27c, (+)-27c and (±)-27i:

8.6.1 Dehalogenation with Raney Nickel: general procedure.

Excess Ra-Ni (50% slurry in water) was added to a solution of alcohol **27** (2.0 mmol) in 10 ml of MeOH. The mixture was heated to reflux for 30 min. After cooling the reaction mixture was filtered through celite and the filtrate was diluted with $CHCl_3$, washed with brine and dried. Evaporation of the solvent afforded a residue which was purified by column chromatography .

4-phenyl benzhydrole **(±)-27a** was recovered in 35% yield and **28** n 35%yield.

(±)-27i decomposed under identical reaction conditions.

8.6.2 Dehalogenation with $LiAlH_4$: general procedure.

$LiAlH_4$ (1M THF solution, 2 mmol) was added to a solution of **(±)-27c** (1 mmol) in dry THF. The reaction mixture was refluxed for 6 h, then cooled to RT and the 1N HCl solution was added to quench the reaction. The product was extracted with $CHCl_3$ (2x50 ml), the organic phase was dried over anhydrous Na_2SO_4. The crude product was purified by flash chromatography. 4-Phenyl benzhydrole **(±)-27a** was recovered in 89% yield. Identical reactions were carried out with the enantiopure **(+)-27c** leading to enantiopure **(+)-27a** in 85 % yield.

(±)-27i was almost unreactive under identical reaction conditions.

8.7 Mitsunobu Reaction with 4,5-dicyanoimidazole.

8.7.1 General synthetic method a:

Diethylazodicarboxylate (DEAD) (1 ml, 6.0 mmol) was added dropwise to a cooled (0 °C) solution of alcohol **27** or **31** (6.0 mmol), Ph_3P (1.57 g, 6.0 mmol) and 4,5-dicyanoimidazole DCI (0.71 g, 6.0 mmol) in 60 ml of dry THF. The mixture was stirred for 0.5 h at room temperature. Then the solvent was removed and the residue treated with a 1:1 mixture of hexane/Et_2O. The solution was filtered, and the precipitate was washed with hexane. Evaporation of the combined filtrates afforded a crude product **33** which was purified as described below.

8.7.2 General synthetic method b:

The reaction was carried out by adding 1 equivalent of all the reagents to alcohol **27** or **31** at 45 min intervals. After four additions of reagents, the reaction mixture was allowed to stir at room temperature for 24 h and was then treated as above.

For yields, absolute configurations and optical purities (% ee) see Table 4.1 chapter 4.

8.8 Synthesis of the diacids 34.

8.8.1 General Procedure for the Hydrolysis of dicyanoimidazol derivatives 33 to the Diacids 34.

A solution of **33** (10 mmol) in 30 ml of EtOH was refluxed for 24 h in the presence of 10 M NaOH (30 ml, 0.30 mol). The hot solution was poured into 150 ml of cold water, filtered, and brought to pH 2 with 37% HCl. After cooling, the precipitate was filtered, washed with EtOH, then with Et_2O, and dried. For yields, absolute configuration and optical purities (% ee) of the products, see Table 4.3; chapter 4.

8.9 Decarboxylation of the diacids 34 to 1-Alkylimidazoles 35 and Bifonazole 6a.

8.9.1 Decarboxylation: general procedure.

A solution of **34** (10 mmol) in 20 ml of diphenyl ether was heated at reflux for 0.5 h and, after cooling, applied to a silica gel column. Elution with Et_2O eliminated the excess diphenyl ether and further elution with AcOEt led to the products, which were further purified by preparative TLC (AcOEt for **35a** and **35b**, $CHCl_3$/MeOH 98:2 for **35c**) or recrystallization (for **35d** and **6a**). For yields, absolute configurations and optical purities (% ee) of the products, see Table 4.4, chapter 4.

8.10 Synthesis of 4-(5)-ethyl imidazole carboxylate 37:

8.10.1 Synthesis of acetylglycine ethyl ester 38:

To a suspension of acetyl glycine hydrochloride(100 mmol) in dichloromethane (400 ml) at 0° C triethylamine (TEA; 220 mmol) and acetyl chloride (100 mmol) were added. After two hours the reaction mixture was diluted with dichloromethane and water, the organic phase was separated and washed with 1 N HCl solution, saturated NaCl solution, and then dried over anhydrous Na_2SO_4. The solid **38** was recovered after evaporation (98 mmol, 98 % yield).

8.10.2 Synthesis of ethyl 4(5)-(2-thiol)-imidazole carboxylate 40:

Sodium methoxide (95 mmol) was added to a solution of acetyl glycine ethyl ester **38** (86 mmol) in benzene at 0°C in 10 small solid portions. Ethyl formiate (258 mmol) was then added dropwise. The reaction was carried out for 24 h at 0°C. An orange solid precipitated in the reaction mixture and cold water (55ml) was added to the mixture which then became clear. The benzene solution was separated from the

aqueous phase which was cooled again to 0°C and then acidified with 12N HCl (15.6 ml). KCNS (99 mmol) were added, the mixture was heated to 70°C for two hours and was then left to stand in the refrigerator for 48 h. A precipitate was formed during this time , which was filtered off and washed with cold water, and then dried under high vacuum over P_2O_5 overnight. 55 mmol of **40** were recovered (68 % overall yield).

8.10.3 Synthesis of ethyl 4(5)-imidazole carboxylate 37:

1.65 ml of conc. HNO_3 were diluted with 4.75 ml of water and the resulting solution was cooled to 0°C. $NaNO_2$ (100mg) was added after 10 min.in a single portion and 4(5)-(2-thiol)-imidazole carboxylate **40** 1.5 g (8.7 mmol) was added in small solid portions. During the last addition the temperature must be kept below 25 °C. After 30 min solid Na_2CO_3 was added to the reaction mixture to neutralize the pH. The product was extracted in $CHCl_3$ (200 ml), the organic phase was washed with saturated NaCl solution (2x 150 ml) and then dried over anhydrous Na_2SO_4. 840 mg of product **37** were recovered (69% yield).

8.11 Synthesis of ethyl 1-[-(4-Biphenylyl)benzyl]imidazole-5-carboxylate 41a and ethyl 1-[-(4-biphenylyl)benzyl] imidazole-4-carboxylate 41b.

8.11.1 Synthesis 1:

Prepared by Mitsunobu coupling of alcohol **27a** and ethyl 4(5)-imidazole carboxylate **37** as the acidic reagent, following the same procedure (synthetic method 7.7.2 b) as described for the synthesis of **(±)-33g**. After preliminary purification by flash chromatography (n-hexane/AcOEt 3:1), the isomeric mixture was separated by another chromatography using the same eluent affording the less polar compound (*Rf* 0.66), which was assigned to have the structure **(±)-41a**. The second eluted isomer **(±)-41b** (*Rf* 0.22) was further purified by flash chromatography using gradient elution with n-hexane/AcOEt 3:1 to 1:1.

8.11.2 Synthesis 2:

Alcohol **27a** (0.2 mmol) was dissolved in 5 ml of acetonitrile, the solution was cooled to 0°C and bromo triphenyl phosphine (1.4 mmol) was added to the solution. The reaction was stirred for three hours. TLC showed that all of the starting material was consumed and was converted into **42**. Diisopropylethyl amine DIPEA and ethyl 4(5)-imidazole carboxylate **37** were added and the temperature was allowed to rise to RT. Stirring was continued over night, the solvent was evaporated, the crude oil dissolved in $CHCl_3$ and washed consecutively with 1 N HCl, saturated solution of $NaHCO_3$ and saturated NaCl solution. The crude product was purified by flash chromatography (*n*-hexane:EtOAc 1:1). Products **(±)-41a** and **(±)-41b** were recovered in a 1 to 1 ratio with 32.5 % overall yield.

8.12 Synthesis of 1-[a-(4-Biphenylyl)benzyl]imidazole-5-carboxylic Acid (±)-43.

10% aqueous LiOH (1 ml, 4.2 mmol) was added to a solution of **41a** (0.110 g, 0.29 mmol) in 4 ml of EtOH. After being stirred for 2 h, the reaction mixture was cooled to 0 °C and acidified by addition of 1 N HCl. The white precipitate was stirred at 0 °C for another 30 min, and then filtered to give pure **(±)-43** (0.098 g, 96%) as white crystals.

8.13 Synthesis of 5-amino-1-(2-octyl)imidazole-4-carbonitrile (±)-46:

Dry NH_3 was bubbled for 30 min through a stirred suspension of aminomalonitrile *p*-toluensulfonate (3.9 g, 15.5 mmol) in dry CH_3CN (200 ml). After the separated solid was filtered off, the solution was concentrated to 100 ml and then added to triethyl orthoformiate (2.6 ml, 15.5 mmol). The solution was heated under reflux for 15 min. To the cooled mixture 2-octylamine (**44**) (2.6 ml, 15.5 mmol) was added and the solution stirred at room temperature overnight. The solvent was evaporated and the residue was purified by flash chromatography (AcOEt/*n*-hexane 3:2) to give a yellow semisolid product, that after trituration with Et_2O/hexane afforded 5-amino-1-(2-octyl)imidazole-4-carbonitrile (**46**) (1.8 g, 53%) as a white crystalline compound.

8.14 Synthesis of 5-amino-1-(2-octyl)imidazole-4-carboxylic acid (±)-47:

A mixture of 5-amino-1-(2-octyl)imidazole-4-carbonitrile **46** (0.30 g, 1.36 mmol), EtOH (3 ml) and aqueous 10 N NaOH (3 ml) was heated under reflux for 24 h. The solution was cooled to room temperature, diluted with water (2 ml) and neutralized by slow addition of 2 N HCl. After 2 h in a cool place, the precipitate was filtered off and washed with water to give 5-amino-1-(2-octyl)imidazole-4-carboxylic acid (**47**) (0.32 g, 115%) as a chromatographically pure (5% AcOH in AcOEt, *Rf* 0.58), white crystalline solid with no defined melting point, containing some crystal water.

8.15 Synthesis of 5-amino-1-(2-octyl)imidazole 48

The 5-amino-1-(2-octyl)imidazole-4-carboxylic acid **47** was decarboxylated following the same procedure 7.9 as described for acids **34** affording 5-amino-1-(2-octyl)imidazole **48** in 15% yield.

8.16 Synthesis of 1-(2-Octyl)imidazole-4-carboxamide 49:

A solution of 5-amino-1-(2-octyl)imidazole-4-carbonitrile **46** (0.33 g, 1.5 mmol) in 10 ml of THF was added during 1 h to a refluxing solution of isoamyl nitrite (0.63 ml, 4.5 mmol) in 5 ml of THF. After being heated under reflux for 1 h, the reaction mixture was cooled, concentrated and purified by flash chromatography (2.5% Et_3N in AcOEt, *Rf* 0.45) to provide **49** (0.19 g, 45%) as a white amorphous powder with no defined melting point.

8.17 General procedure for the synthesis of *N*-[2,2-(Dimethoxy)ethyl]amines 52a and 52b.

To a solution of (*S*)-(+)-2-octylamine **(+)-44** and (*S*)-(-)-_-methylbenzylamine **(-)-51** (4.0 mmol) in 30 ml of CH_3CN were added anhydrous K_2CO_3 (0.83 g, 6.0 mmol) and bromoacetaldehyde dimethyl acetal (0.68 g, 4.0 mmol). The reaction mixture was heated under reflux

for 48 h. After cooling, the inorganic salts were removed by filtration and the solution was evaporated under reduced pressure. The residue was purified by column chromatography (AcOEt) to give **52a** and **52b** as yellow oils which were used without further purification.

8.18 General procedure for the synthesis of 53a and 53b:

To a solution of **52a** or **52b** (2.0 mmol) in 50 ml of THF were added 3 N HCl (0.8 ml, 2.4 mmol) and KSCN (0.23 g, 2.4 mmol). After stirring at 70 °C for 8 h, the cooled solution was made basic by addition of 1 N NaOH and extracted with CH_2Cl_2. The organic layer was washed with brine, then dried and evaporated. The residue was purified by column chromatography (AcOEt) to give pure **53a** and **53b** both in 84% yield.

8.19 General procedure for the hydrogenolysis of 53a and 53b.

Ra-Ni (50% slurry in water; 500 mg) was added to a solution of **53a** or **53b** (2.0 mmol) in 10 ml of MeOH. The flask was immersed in an oil bath preheated to 100 °C and after 5 min cooled to room temperature. The reaction mixture was filtered through celite and the filtrate was diluted with $CHCl_3$, washed with brine and dried. Evaporation of the solvent afforded a residue which was purified by column chromatography (5% MeOH in AcOEt) to give (*S)*-(+)-**35a** (85% yield) [identical in all the respects to that obtained by decarboxylation of (*S)*-(+)-**34a**)] and (*S*)-(+)-**54** (quantitative yield).

8.20 Synthesis of Azides 55 a-d:

8.20.1 General azide synthesis by diphenylphosphorylazide DPPA under Mitsunobu conditions:

To a solution of alcohol **27** (1 mmol), triphenyl phosphine (1 mmol) and diethyldiazodicarboxylate (1 mmol) in dry THF, a solution of diphenylphosphorylazide (1 mmol) was added over a period of 15 min

and the stirring was continued for about 24 h. The solvent was removed by evaporation on a rotavapor, the crude oil dissolved in CH_2Cl_2, filtered through a Florosil pad and then purified by flash chromatography (CH_2Cl_2) on silica gel.

See chapter 4 and table 4.6 for chemical yields and enantiomeric eccesses.

8.20.2 General azide synthesis by diazabicycloundecene (DBU) and diphenylphosphorylazide (DPPA):

Alcohol **27** (1 mmol) and DPPA (1.2 mmol) were dissolved in dry toluene so that the final concentration of the alcohol was ca. 0.5-1 M. To the mixture was added a slight excess of DBU (1.1-1.5 mmol). The reaction mixture was stirred 12-24 h at RT, was then diluted with toluene and washed consecutively with 1 N HCl, saturated NaCl solution and dried over anhydrous Na_2SO_4. After solvent evaporation the crude oil was purified by flash chromatography (CH_2Cl_2) on silica gel .

See chapter 4, table 4.7 for chemical yields and enantiomeric purities.

8.21 General procedures for the synthesis of amines 56a-d:

8.21.1 Reduction of azides 55 by Ph_3P/H_2O:

To a solution of azide **55** (1 mmol) in THF/water 10:1 a solution of Ph_3P in THF was added. The mixture was stirred for 3 h. The solvent was evaporated and the crude oil was purified by flash chromatography over silica gel.

See chapter 4, table 4.8, method A for the chemical yields.

8.21.2 Reduction of Azides 55 by $SnCl_2$:

To a stirred suspension of stannous chloride (2mmol) in methanol, a solution of azide **55** (1mmol) in methanol was added dropwise. The reaction was exothermic and N_2 gas evolved. The mixture was stirred at

room temperature for two hours. Methanol was evaporated , the resulting oil was dissolved in ethylacetate and washed with 0.5 N NaOH solution. The organic phase was washed with saturated solution NaCl and dried over anhydrous Na_2SO_4. The crude oil was purified by flash chromatography on silica gel.

See chapter 4, table 4.8 for the chemical yields.

8.22 Synthesis of diamides 57: general procedure

Diacid **(±)-34e** (1.25 mmol) was dissolved in dry dioxane (20ml) containing carbonyl diimidazole (CDI; 2.89 mmol) and chiral amine (2.55 mmol). The mixture was refluxed for 8 h and after cooling, the solvent was evaporated. The crude reaction mixture was dissolved in $CHCl_3$, and the solution washed consecutively with 1N HCl, saturated $NaHCO_3$ solution and saturated solution of NaCl. The crude product was purified by preparative TLC (eluent CH_2Cl_2-MeOH- AcOH 98:1:1). The two diasteroisomers were completely separated in 1:1 ratio. Overall yield was 90%.

8.23 Synthesis of Aryl propynoles

8.23.1 Synthesis of 1-phenyl-2-propyn-1-ol (±)-58a by addition of lithium acetylide to benzaldeyde:

Benzaldehyde (3.5 mmol) was dissolved in 10 ml of dry THF, the solution was cooled to -78°C, and a 1N solution of lithium acetylide in THF (3.7 mmol) was added dropwised over 30 min. After the addition the temperature was raised to 0°C. The mixture was quenched with a saturated solution of NH_4Cl and was diluted with CH_2Cl_2 and water. The organic phase was separated and washed with a saturated solution of NaCl, and then dried over anhydrous Na_2SO_4. The product was purified by flash chromatography on silica gel. The 1-phenyl-2-propyn-1-ol **(±)-58a** was recovered as colorless oil in 45 %yield.

Following the same procedure but with the addition of ethylen diamine to the benzaldehyde solution the yield of **(±)-58a** was 42%.

8.23.2 Synthesis of 1-aryl-(2-propyn-3-trimethylsilyl)-1-ols 59a-g: general procedure.

To a solution of trimethylsilyl acetylene (10 mmol) in dry THF at -78°C *n*-butyl lithium (10.5 mmol) was added dropwise over 15 min. This mixture was transferred *via* a needle to a solution of arylaldehyde in dry THF at -78°C. The mixture was stirred without further cooling and the temperature was allowed to raise to 0°C. The reaction was quenched with a saturated solution of NH_4Cl and diluted with CH_2Cl_2 and water. The organic phase was separated and washed consecutively with saturated NaCl solution and dried over anhydrous Na_2SO_4. The product was purified by flash chromatography on silica gel.

See chapter 5, table 5-1 for products **(±)-59a-g** and chemical yields.

8.23.3 Desilylation of 1-aryl-(2-propyn-3-trimethylsilyl)-1-ols 59a-g:

8.23.3.1 Desilylation using KF:

The (±)-1-aryl-(2-propyn-3-trimethylsilyl)-1-ol **(±)-59**(10 mmol) was dissolved in 3 ml of DMF, KF (11 mmol) was added, and the mixture was heated to 60°C for 3 h. It was then cooled to rt and diluted with CH_2Cl_2 and 1N HCl. The organic phase was separated and washed consecutively with 1N HCl, water and saturated NaCl solution. It was finally dried over anhydrous Na_2SO_4. The crude oil was purified by flash chromatography on a silica gel column.

See Table 5-2, chapter 5 for products **(±)-58a-g** and chemical yields.

8.23.3.2 Desilylation using TBAF in dry THF:

1-aryl-(2-propyn-3-trimethylsilyl)-1-ol (59) (10 mmol) was dissolved in 5 ml of dry THF, the solution was cooled to -20°C and a 1 N solution of TBAF in dry THF (11 mmol) was added. The cooling bath was removed after 1 h and the reaction mixture was stirred at room temperature for 4 h. The solvent was evaporated, the crude oil dissolved

in CH_2Cl_2 and washed several times with water, then with a saturated solution of NaCl, and finally dried over anhydrous Na_2SO_4. The crude oil was purified by flash chromatography on silica gel.

See Table 5.3 chapter 5 for products **(±)-58** and chemical yields.

7.23.3.3 Desilylation using K_2CO_3 in MeOH:

1-(3,4 dimethoxyphenyl)-(2-propyne-3-trimethylsilyl)-1-ol **(±)-59g** (10 mmol) was dissolved in 25 ml of saturated K_2CO_3 solution in MeOH. The mixture was stirred for five days at room temperature. The solvent was evaporated and the crude product was dissolved in EtOAc. The solution was washed with water, 1 N HCl and saturated NaCl solution. The crude oil was purified by flash chromatography on silica gel. 1-(3,4 dimethoyphenyl)-2-propyne-1-ol **(±)-58g** was recovered in 43 % yield as oil.

8.23.4 Synthesis of (±)-58a by addition of magnesium methynyl halide to benzaldehyde:

The aromatic aldehyde (15 mmol) was dissolved in dry (100ml) THF, and the solution was cooled to low temperature. A THF solution of magnesium methynyl halide (16 mmol) was added dropwise to the solution within 30 min. The reaction mixture was stirred 1 h and then quenched with 1 N HCl solution. The product was extracted with ethyl acetate, and the organic phase washed with saturated NaCl solution. The crude oil was purified by flash chromatography on silica gel, or by distillation under high vacuum. In both cases further purifications were not necessary.

See Table 5.4, chapter 5 for product **(±)-58**, chemical yield and temperature.

8.24 Screening of lipases for the esterification of arylpropynols.

8.24.1 General screening procedure:

In 10 ml of MTBE 100 mg of 1-(4-cyanophenyl)-2-propyn-1ol **(±)-58e** were suspended, 50 mg of lipase and 150 mg of vinylacetate were added. The reaction mixtures were stirred at room temperature for 7 days, and monitored every 24h by chiral GC. The analysis was quantitative and allowed the determination of the conversion and the enantiomeric excess of both product and starting material. Using this method ten different lipases were tested, see chapter 5, table 5.5 for qualitative results and enzymes tested. Only the lipases SAM I and SAMII were considered for futher applications.

8.25 Synthesis of 1-aryl-2-propyn-1-ol acetate :

8.25.1 General method a:

To a solution of 1-phenyl-2-propyn-1ol **(±)-58a** (10 mmol) and pyridine (10 ml) at 0°C, acetanhydride (10 mmol) was added dropwise over 30 min. Reactions were carried out under stirring at rt for 12 h. The reaction mixture was poured into 1 N HCl solution and the product extracted with ethyl acetate. The organic phase was washed with 1 N HCl solution and saturated NaCl solution and finally dried over anhydrous Na_2SO_4. The crude oil was purified by flash chromatography on silica gel. 1-phenyl-2-propyn-1ol acetate **(±)-60a** was recovered in 95.5 % yield.

See chapter 5, table 5.6 for substrates, products and chemical yields.

8.25.2 General method b:

To a solution of aryl propynol **(±)-58** (10 mmol) and triethylamine (11 mmol) in dichloromethane (40 ml) at 0°C, acetyl chloride (10.5 mmol) was added dropwise over 30 min. The reaction mixture was stirred for 1 h at room temperature, it was then diluted with CH_2Cl_2 and washed consecutively with 1 N HCl solution, saturated NaCl solution and then dried over anhydrous Na_2SO_4. The crude product was so clean that further purification was unnecessary.

See chapter 5, table 5.6 for substrates, products and chemical yields.

8.26 Screening of lipases and reaction conditions for the hydrolysis of arylpropynol acetates (±)-60.

8.26.1 General procedure for the screening of lipases:

In 10 ml of 0.1 N phosphate buffer pH=7.0, 100 mg of 1-(4-cyanophenyl)-2-propyn-1ol **(±)-60e** and 100 mg of lipase were suspended. The reaction mixture was stirred at room temperature for 7 days and the reaction progress was monitored every 24h by chiral GC. The analysis was quantitative and allowed to determine the conversion and the enantiomeric excess of both product and starting material. Under identical reaction conditions ten different lipases were tested, see chapter 5, table 5.8 for qualitative results and screened enzymes. Only the lipases SAM I and SAMII were considered for further applications.

8.26.2 Cosolvent effect on the hydrolysis of arylpropynols acetates (±)-60 by SAMII lipase:

In 10 ml of 0.1 N phosphate buffer pH=7.0 100 mg of 1-aryl-2-propyn-1-ol acetate **(±)-60**, and 10 mg of crude lipase SAMII were suspended. 0.1N NaOH was used as titrating reagent. The cosolvent of choice was added as last component of the mixture. The reaction mixtures were stirred at room temperature and reaction progress was monitored by chiral GC. The analysis was quantitative and allowed the determination of the conversion and the enantiomeric excess of both product and starting material from the single chromatogram.

See chapter 5, table 5.8 for substrates and products, chemical yields, conversions, E values and % of cosolvent used.

8.26.3 Temperature effect on the hydrolysis of arylpropynol acetates (±)-60 in presence of SAMII lipase:

In 10 ml of 0.1 N phosphate buffer pH=7.0 100 mg of 1-aryl-2-propyn-1-ol acetate **(±)-60** and 10 mg of crude lipase SAMII were suspended. 0.1N NaOH was used as titrating reagent. The reaction was

carried out in a thermostated reactor. The reaction mixtures were stirred at the desired temperature and monitored by chiral GC. The analysis was quantitative and allowed the determination of conversion and the enantiomeric excess of both product and starting material from the single chromatogram.

See chapter 5, table 5.10 for substrates and products, chemical yields, conversions and E-values and temperatures.

8.27 Synthesis of 1-aryl-2-propyn-1-ol chloroacetate (±)-61:

To a solution of aryl propynol (±)58 (10 mmol) and triethylamine (11 mmol) in dichloromethane (40 ml) at 0°C, chloroacetic anhydride (10.5 mmol) was added dropwise over 30 min. The mixture was stirred for 1 h at room temperature, then diluted with CH_2Cl_2 and washed consecutively with 1 N HCl solution, saturated NaCl solution and finally dried over anhydrous Na_2SO_4. The crude product was so clean that another purification was unnecessary.

See chapter 5, table 5.11 for substrates, products and chemical yields.

8.28 Enzymatic resolution of chloroacetates (±)-61 b-c,e,h-l:

8.28.1 General procedure:

Chloroacetate **(±)-61** (10 mmol)was suspended in 0.1 N phosphate buffer (10 ml, pH=7.0) and the mixture was stirred 10 min.on the autotitrator in order to test for non-catalyzed hydrolysis. Then the crude lipase preparation of *Pseudomonas species* (SAMII) was added (10% by weight of the ester). The reaction mixture was stirred at room temperature, while the pH of the reaction was kept at pH 7.0 by continuous addition of 1 N NaOH from an autoburette. The reaction progress was monitored by chiral GC allowing simultaneous determination of conversion and enantiomeric purities of both educt and product. After the desired or required conversion was achieved the reaction mixture was diluted with water and diethyl ether and the resulting phases were separated. The organic phase was washed with water and saturated NaCl solution and finally was dried over anhydrous

Na_2SO_4. After removal of the solvent the resulting products were separated and purified by flash chromatography on silica gel. The enantiomeric purities of the products were determinated by chiral GC. The enantiomeric excess of both the purified alcohol and the chloroacetate were identical to those obtained directly from the reaction mixture.

In no case indications for a racemization during the work up or purification were found.

See chapter 5, table 5.12 for products, starting materials, reaction times, E-values, % e.e. and chemical yields.

8.29 Hydrolysis of enantiopure acetate (*S*)-60 and chloroacetate (*S*)-61:

In 10 ml of satured K_2CO_3 the acetate **(*S*)-60** or the chloroacetate **(*S*)-61** (2 mmol) were dissolved at 0°C. The raction mixture was stirred for 30 min until the complete consumption of the starting material was observed on TLC.The mixture was diluted with ethylacetate and water, the organic phase was separated and washed with saturated NaCl and dried over anhydrous Na_2SO_4 to afford the clean product (*S*)-(+)-58 which was recovered in high yield.

See chapter 5, table 5.13 for substrates, products, % e.e and chemical yields.

8.30 Synthesis of Aryl-2-benzo[b]furanyl carbinoles 27g,l and 63a-d in racemic and enantiopure form *via* palladium-catalyzed heteroannulation (general procedure).

Argon was bubbled into a solution of tetramethylguanidine (TMG, 376 µl, 3 mmol) in 2.5 ml of DMF for 15 min at 40°C before the addition of 2-iodophenol (220.01 mg, 1 mmol), bis-triphenylphosphine palladium (II) dichloride (17.5 mg, 0.025 mmol), CuI (4.5mg, 0.025 mmol) and 1-Phenyl-2-propyn-1-ol **(±)-39a** (123.9 µl, 1mmol). The mixture was stirred under argon at 40°C for four hours, whereby the color changed from pale yellow to red/brown. After cooling, the reaction mixture was diluted with 1N HCl (100ml) solution and ethyl acetate (200ml). The organic layer was separated and washed with water, saturated NaCl

solution and finally dried over anhydrous Na_2SO_4. After solvent evaporation the crude oil was purified by flash chromatography on silica gel to afford **(±)-27g** in 91% chemical yield.

The experimental procedure described above was applied also to the racemic and enantiopure aryl propynols **58a-c,e,h-l**. See chapter 6, table 6.5.for reaction times, chemical yields and enantiomeric purities.

8.31 Synthesis of aryl benzo[b]furan carbinol by base catalyzed 5-endotrig cyclization

8.31.1 Synthesis of phenyl-2benzo[b]furanyl carbinol (±)-27g by base catalyzed 5-endotrig cyclization:

(2'-Hydroxyphenyl)-2-propyne-1-phenyl-1-ol **(±)-62** (224 mg, 1 mmol) was dissolved in 2 ml of saturated K_2CO_3 solution in methanol. After two hours the reaction was completed. Methanol was evaporated and the crude product dissolved in ethylacetate. The solution was washed with water and saturated solution of sodium chloride and finally dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was filtered through a silica gel pad to afford phenyl-2benzo[b]furanyl carbinol **(±)-27g** in 92% yield. All spectroscopic data were identical with those obtained *via* other routes.

8.31.2 Cyclization of 1-phenyl-3-(2'acetoxyphenyl)-2-propyn-1-ol (±)71 to phenyl-2benzo[b]furanyl carbinol (±)-2 by basic catalyzed 5-endotrig cyclization.

1-phenyl-3-(2'-acetoxyphenyl)-2-propyn-1-ol **(±)-71** (265 mg, 1mmol) was dissolved in 5 ml of a saturated solution of K_2CO_3 in methanol at 0°C. After one hour the TLC showed complete consumption of the starting material. The methanol was evaporated, and the resulting oil dissolved in ethylacetate and water. The organic phase was separated and washed with saturated NaCl solution, and was finally dried over anhydrous Na_2SO_4. After evaporation of the solvent **(±)-27g** was obtained in 95.0% chemical yield.

NMR and MS analysis were identical to that of **(±)-27g** synthesized by Pd mediated cyclization.

8.32 Synthesis of racemic 1-phenyl-3-(2'aminophenyl)-2-propyn-1-ol (±)-65.

Argon was bubbled trough a solution of tetramethylguanidine (TMG, 2.02 ml, 16 mmol) in 2.5 ml of DMF for 15 min at 40°C before the addition of 2-iodoaniline (883.4 mg, 4 mmol), bis-triphenylphosphine palladium (II) dichloride (141 mg, 0.05 mmol), CuI (38mg, 0.050 mmol) and 1-Phenyl-2-propyn-1-ol **(±)-27g** (500 μl, 4 mmol). The mixture was stirred under argon at 40°C for four hours, whereby color changed from pale yellow to red/brown. After cooling, the reaction mixture was diluted with ethyl acetate and was then washed consecutively with water, saturated NaCl solution and finally dried over anhydrous Na_2SO_4. After evaporation of the solvent the crude oil was purified by flash chromatography on silica gel to afford **(±)-65** in 48.8% chemical yield.

8.33 Synthesis of *N*-Mesyl-2-iodoaniline 46.

To a solution of methanesulfonyl chloride (371.1 μl, 4.79 mmol) in 5 ml of pyridine 2-iodoaniline (1.0 g, 4.56 mmol) was added at 0°C.The reaction was carried out at room temperature for four hours after which the TLC showed complete consumption of the starting material. The reaction mixture was poured into 300ml of ice and the product precipitated out. The solid was separated by filtration and washed with water, then dried in a desiccator under vacuum over P_2O_5. 1.31 g of *N*-Mesyl-2-iodoaniline **46** were obtained corresponding to 95% chemical yield. The reaction was scaled up to 69 mmoles with identical results.

8.34 Synthesis of Aryl 2-(*N*-mesyl)-indolyl carbinols 64a-g in racemic and enantiopure form *via* palladium-catalyzed heteroannulation of arylpropagylic alcohols 58 (general procedure).

Argon was bubbled into a solution of tetramethylguanidine (TMG, 376 l, 3 mmol) in 2.5 ml of DMF for 15 min at 40°C before the

addition of *N*-Mesyl-2-iodoaniline **46** (297.11 mg, 1 mmol), bis-triphenylphosphine palladium (II) dichloride (17.5 mg, 0.025 mmol), CuI (4.5mg, 0.025 mmol) and 1-phenyl-2-propyn-1-ol **58a** (123.9 µl, 1mmol). The mixture was stirred under Argon at 40°C for 4 whereby the color changed from pale yellow to red/brown. After cooling, the reaction mixture was diluted with 1N HCl solution and ethyl acetate. The organic layer was separated and washed consecutively with water and saturated NaCl solution and was finally dried over anhydrous Na_2SO_4. After evaporation of the solvent the crude resulting oil was purified by flash chromatography on silica gel to afford **(±)-64a** in 87% chemical yield.

The same experimental procedure was applied to all of the racemic and enantiopure aryl propynols **58a-c,e,h-l**. See chapter 6, table 6.7 for reaction times, chemical yields and enantiomeric excesses.

8.35 Synthesis of (2'-Hydroxyphenyl)-2-propyn-1-phenyl-1-ol (±)-62.

(±)-62 can be obtained as side product in the synthesis of 1-phenyl-2-benzo[b]furane carbinol **(±)-27g** using 1% of palladium catalyst and CuI (see Chapter 6.2.4.) or by using one equivalent of base (TMG, Chapter 6.3.1) The second procedure is described below.

Argon was bubbled thruogh a solution of tetramethylguanidine (TMG, 125 µl, 1 mmol) in 2.5 ml of DMF for 15 min at 40°C before the addition of 2-iodophenol (220.01 mg, 1 mmol), bis-triphenylphosphine palladium (II) dichloride (7.5 mg, 0.010 mmol), CuI (1.8 mg, 0.010 mmol) and 1-Phenyl-2-propyn-1-ol **(±)-58a** (123.9 µl, 1mmol). The mixture was stirred under argon at 40°C for 4 h, whereby the color changed from pale yellow to red/brown. After cooling, the reaction mixture was diluted with 1N HCl solution and ethyl acetate. The organic layer was separated and washed with water, saturated NaCl solution and was finally dried over anhydrous Na_2SO_4. After evaporation of the solvent the resulting crude oil was purified by flash chromatography on silica gel to afford **(±)-62** in 90% chemical yield.

8.36 Synthesis of racemic 1-Phenyl-3-(2'acetoxyphenyl)-2-propyn-1-ole (±)-71.

Argon was bubbled thrugh a solution of tetramethylguanidine (TMG, 2263.3 µl, 2.1 mmol) in 2.0 ml of DMF for 15 min at 40°C before the addition of 2-acetyliodophenol (500 mg, 1.91 mmol), bis-triphenylphosphine palladium (II) dichloride (66.7 mg, 0.09 mmol), CuI (18.1 mg, 0.09 mmol) and 1-Phenyl-2-propyn-1-ol **58a** (1260.1 µl, 2.1 mmol). The mixture was stirred under argon at 40°C for 4 h, whereby color changed from pale yellow to red/brown. After cooling, the reaction mixture was diluted with ethyl acetate. The organic layer was washed with water and saturated NaCl solution and was finally dried over anhydrous Na_2SO_4. After evaporation of the solvent the resulting crude oil was purified by flash chromatography on silica gel to afford **(±)-71** in 78.9% chemical yield.

8.37 Analytical data:

4-Phenylbenzophenone 25a:
Synthetic procedure 7.1.1
^{1}H-NMR (300 MHz; $CDCl_3$) δ = 7.70-7.31 (m,14H)
IR ($CHCl_3$): ν ($cm^{-1)}$ = 3030, 1690, 1610, 1290.
GC-MS = 258 (M^+ 70%).
M.P. =110-112°C.
4'-Phenyl-2-bromobenzophenone 25c:
Synthetic procedure 7.1.1
^{1}H-NMR (300 MHz; $CDCl_3$) δ = 7.88 (d 2H,8.7 Hz), 7.70-7.59 (m 5H), 7.52-7.31 (m 6H).
IR ($CHCl_3$): ν (cm^{-1}) = 1675, 1625, 1300.
GC-MS = 338 (M^+ 72%), 181 (100%).
M.P. = 97-98 °C.
4'-Phenyl-2-fluorobenzophenone 25d:
Synthetic procedure 7.1.1
^{1}H-NMR (300 MHz; $CDCl_3$) δ = 7.95 (d 2H,8.5 Hz), 7.75-7.35 (m8H), 7.30-7.10 (m 3H).
^{13}C-NMR ($CDCl_3$) δ = 192.92, 162.51, 157.50, 146.12, 139.83, 136.04, 133.03, 132.87, 130.70, 130.65, 130.40, 128.93, 127.29, 127.11, 127.01, 124.32, 124.25, 116.46, 116.03.

IR ($CHCl_3$): ν (cm^{-1}) = 1680, 1600, 1295.

GC-MS = 278 (M^+ 100%).

M.P. = 101-102 °C.

4'-Phenyl-4-nitrobenzophenone 25e:

Synthetic procedure 7.1.1

^{1}H-NMR (300 MHz; $CDCl_3$) δ = 8.35 (d 2H,8.9Hz), 8.10-7.85 (m 3H), 7.80-7.55 (m 4H), 7.50-7.30 (m 3H).

IR ($CHCl_3$): ν (cm^{-1})= 1660.

GC-MS = 304 (M^+ 100%).

M.P. = 135-136 °C.

4'-Phenyl-3-nitrobenzophenone 25f:

Synthetic procedure 7.1.1

^{1}H-NMR (300 MHz; $CDCl_3$) δ = 8.65 (s 1H), 8.46 (d 1H, 7.70 Hz), 8.18 (d 1H, 6.10 Hz), 7.81 (d 2H, 7.7 Hz), 7.73-7.62 (m 5H), 7.49-7.35 (m 3H).

IR ($CHCl_3$): ν (cm^{-1}= 1675.

GC-MS = 304 (M^+ 100%).

M.P. = 154-155 °C.

Phenyl-2-benzo[b]furanone 26a:

Synthetic procedure 7.2.1.

^{1}H-NMR (300 MHz; $CDCl_3$) δ = 8.07-8.02 (m 1H), 7.75-7.46 (m 8H), 7.46-7.25 (m 1H).

IR ($CHCl_3$): ν (cm^{-1}= 1675,1605,1550.

GC-MS = 222 M^+ (100%).

M.P.= 105-106 °C.

4'-Cyanophenyl-2-benzo[b]furanone 26b:

Synthetic procedure 7.2.1.

^{1}H-NMR (300 MHz; $CDCl_3$) δ =8.16 (d 2H, 9.0Hz), 7.84 (d2H, 9.0 Hz), 7.71 (d 1H,7.8Hz), 7.62-7.41 (m3H), 7.30 (d 1H 7.8Hz).

IR ($CHCl_3$): ν cm^{-1}= 2220,1680,1610,1550.

GC-MS = 247 M^+ (100%).

M.P.= 205-206 °C.

2',4'-Dichlorophenyl-2-benzo[b]furanone 26c:

Synthetic procedure 7.2.1.

^{1}H-NMR (300 MHz; $CDCl_3$) δ = 7.70 (d1H, 8.1 Hz), 7.59-7.51 (m3H), 7.47 (s1H), 7.40 (m 3H).

IR ($CHCl_3$): ν cm^{-1}= 1675,1600,1560.
GC-MS = 291 M^+ (100%)
M.P.= 96-97 °C.

4'-Fluorophenyl-2-benzo[b]furanone 26d:
Synthetic procedure 7.2.1.
^{1}H-NMR (300 MHz; $CDCl_3$) δ =7.99-7.92 (m 2H), 7.56 (d 1H 8.5Hz) 7.50 (m3H), 7.20-7.00 (m 3H).
IR ($CHCl_3$): ν cm^{-1}= 1685,1600,1550.
GC-MS = 240 M^+ (100%)
M.P.= 145-147°C.

4'-Chlorophenyl-2-benzo[b]furanone 26e:
Synthetic procedure 7.2.1.
^{1}H-NMR (300 MHz; $CDCl_3$) δ =8.03 (d 2H, 9.2 Hz), 7.75-7.61 (m 2H), 7.55-7.38 (m4H), 7.37-7.30 (m 1H).
IR ($CHCl_3$): ν cm^{-1}= 1680,1595,1540.
GC-MS = 256 M^+ (100%)
M.P.= 152-153°C.

(±)-4-Phenyl benzhydrol (±)-27a:
Synthetic procedure 7.3.1.or 7.6.1 or 7.6.2.
^{1}H-NMR (300 MHz; $CDCl_3$) δ =7.64 (m;3H), 7.50 (m, 9H), 7.32 (m,2H), 5.85 (s,1H), 2.45 (s,1H).
IR ($CHCl_3$): ν cm^{-1}= 3380, 1605, 1295.
GC-MS = 260 M^+ (58%), 243 M-OH (100%).
M.P. = 115-117°C.

(±)-2-Bromobenzhydrol (±)-27b:
Synthetic procedure 7.3.1.
^{1}H-NMR (200 MHz; $CDCl_3$) δ =7.59 (1H), 7.53 (1H), 7.40 (2H),7.33 (3H), 7.27 (1H), 7.15 (1H), 6.19 (1H, d 3.7 Hz), 2.41 (1H,d 3.7 Hz).
IR ($CHCl_3$): ν cm^{-1}= 3375, 1580, 1325.
GC-MS: 262 M^+(76%), 246 M-OH (100%)
M.P = 58-59 °C.

(+)-2-Bromo-benzhydrol (+)-27b:
Synthetic procedure 7.5.1
$[\alpha]^{20}_D$ +46.6 (*c* 1.30, acetone). e.e. >95 %.
Absolute stereochemistry not determinated.

Physical and spectral data were identical with those described above for the racemate **(±)-27b.**

(±)-2-Bromo-4'-phenyl benzhydrol (±)-27c:

Synthetic procedure 7.3.1.

^{1}H-NMR (200 MHz; $CDCl_3$) δ =7.48 (m,13 H), 6.24 (s, 1H), 2.44 (s, 1 H).

IR ($CHCl_3$): ν cm^{-1}= 3365,1530,1350.

GC-MS: 339 M^+ (68%), 322 M-OH (100%).

M.P. = 101-103 °C.

Anal. Calcd for $C_{19}H_{15}BrO$: C, 67.27; H, 4.46. Found: C, 67.35; H, 4.40.

(+)-2-Bromo-4'-phenylbenzhydrol (+)-27c.

Synthetic procedure 7.5.1

$[\alpha]^{20}_D$ +65.4 (*c* 2.60, $CHCl_3$).

e.e.>95 % HPLC: chiracel OD n-hexane/EtOH 90:20; 1 ml/min. rt= 9.92 min **(+)-27c;** 13.44 min **(-)-27c.**

Absolute stereochemistry not determinated.

Physical and spectral data were identical with those described above for the racemate **(±)-27c.**

(±)-2-Fluoro-4'-phenyl benzhydrol (±)-27d:

Synthetic procedure 7.3.1.

^{1}H-NMR (200 MHz; $CDCl_3$) δ = 7.85 (d 2H,8.5 Hz), 7.75-7.45 (m 8H), 7.35-7.10 (m 3H), 6.35 (s 1H), 2.48 (s 1H).

MP=oil

(+)-2-Fluoro-4'-phenylbenzhydrol (+)-27d:

Synthetic procedure 7.5.1

$[\alpha]^{20}_D$ +58.4 (*c* 2.35, $CHCl_3$).

e.e.>95 % HPLC: chiracel OD n-hexane/EtOH 90:20; 1 ml/min. rt= 8.52**(+)-27d**; 12.44 **(-)-27d**.

Absolute stereochemistry not determinated.

Physical and spectral data were identical with those described above for the racemate **(±)-27d.**

(±)-4-Nitro-4'-phenyl benzhydrole (±)-27e:

Synthetic procedure 7.3.1.

^{1}H-NMR (200 MHz; $CDCl_3$) δ= 7.85 (d, 2H, 9.1Hz), 7.50 (m, 11 H), 5.95 (s1H), 2.60 (s, 1H).

IR ($CHCl_3$): ν cm^{-1}= 3375, 1515, 1340.

GC-MS: 305 M^+ (68%), 288 M-0H (100%).
M.P. = 165-166 °C.

(±)-3-Nitro-4'-phenyl benzhydrol (±)-27f:

Synthetic procedure 7.3.1.
^{1}H-NMR (200 MHz; $CDCl_3$) δ =8.32 (s, 1H), 8.07 (d 1H, 9.1Hz), 7.73 (d 1H, 7.6Hz), 7.42 (m, 10H), 5.95 (s 1H), 2.34 (s 1H).
IR ($CHCl_3$): ν cm^{-1}= 3380,1525,1335.
GC-MS: 305 M^+ (78%), 288 M-OH (100%).
M.P. = 143-144 °C.

(±)-Phenyl-2-benzo[b]furanyl carbinol (±)-27g:

Synthetic procedure 7.3.1. or 7.30
^{1}H-NMR (200 MHz, $CDCl_3$) δ = 2.70 (d,1H), 5.92 (d,1H), 6.51(s,1H), 7.55-7.16 (m, 9H);
^{13}C-NMR ($CDCl_3$) δ = 70.514, 103.912, 111.241, 121.057, 122.735, 124.191, 126.727, 127.969, 128.220, 128.477, 140.237, 155.010; 158.484;
^{13}C-J MOD-NMR ($CDCl_3$) δ =(+)70.514, (+)103.912, (+)111.241, (+)121.057, (+)122.735, (+)124.191, (+)126.727, (-)127.969, (+)128.220, (+)128.477, (-)140.237, (-)155.010; (-)158.484;
GC-MS = M^+ 224 (100%), M^+-OH 207.
IR ($CHCl_3$): ν cm^{-1}= 3390,1640,1600.
M.P. = 53-54 °C.

(*S*)-(+)-Phenyl-2benzo[b]furanyl carbinol (*S*)-(+)-27g:

Synthetic method 7.30:
$[\alpha]^{20}_D$ +16.94, (c 1.18 $CHCl_3$)97.53% ee (Chiracel OD n-hexane/isopropanol) **(*S*)-(+)-2a** rt=10.00 min., **(*R*)-(-)-2a** rt=11.62 min.
Physical and spectral data were identical to those described above for the racemate **(±)-27g.**

(±)-4'-Cyanophenyl-2-benzo[b]furanyl carbinol (±)-27h:

Synthetic procedure 7.3.1.
^{1}H-NMR (200 MHz, $CDCl_3$) δ = 7.69-7.59 (m 4H), 7.54-7.41 (m 2H), 7.28-7.18 (m 2H), 6.55 (s 1H), 6.00 (d 1H, 4.3 Hz), 2.71 (d 1H, 4.3 Hz).
IR ($CHCl_3$): ν cm^{-1}= 3385,1620,1590.
GC-MS = M^+ 249 (73%), M^+-OH 232 (100%).
M.P. = 115-116 °C

(±)-2',4'-Dichlorophenyl-2-benzo[b]furanyl carbinol (±)-27i:

Synthetic procedure 7.3.1.

^{1}H-NMR (200 MHz, $CDCl_3$) δ = 7.64 (d 1H,8.6 Hz), 7.51-7.16 (m 5H), 6.46 (s 1H), 6.28 (d 1H, 3.16 Hz), 2.76 (d 1H, 3.16 Hz).

IR ($CHCl_3$): ν cm^{-1}= 3380,1630,1590.

GC-MS = M^+ 293 (87%), M^+-OH 276 (100%).

M.P. = 85-86 °C.

(+)-2',4'-Dichlorophenyl-2-benzo[b]furanyl carbinol (+)-27i:

Synthetic procedure 7.5.1

$[\alpha]^{20}_D$ +38.5(*c* 2.98, $CHCl_3$).

e.e. = 66 % HPLC: Chiracel OD n-hexane/propanole 99-1; 1 ml/min. rt= 61.52 min **(+)-27i;** 53.46 min **(-)-27i**

^{1}H-NMR (200 MHz, $CDCl_3$) of the crude of **(+)-27i** camphanic ester (significant signals) δ= 6.62 (s) **(+)-27i**, 6.58 (s) **(-)-27i** relative ratio 7.99 / 1.72; e.e. 66%.

Unknown absolute stereochemistry.

Physical and spectral data were identical to those described above for the racemate **(±)-27i.**

(±)-4'-Fluorophenyl-2benzo[b]furanyl carbinol (±)-27 l:

Synthetic procedure 7.3.1. or 7.30

^{1}H NMR (200 MHz, $CDCl_3$) δ = 3.97 (s,1H), 5.85 (s,1H), 6.48 (s,1H), 7.05 (t,10 Hz,2H), 7.55-7.21 (m, 6H).

^{13}C NMR ($CDCl_3$) δ= 69.764, 103.937, 111.206, 115.070, 115.499, 121.101, 122.833, 124.331, 127.847, 128.453 d, 136.003 d, 154.975, 158.177, 160.042, 164.942.

^{13}C J MOD NMR ($CDCl_3$) δ= (+)69.764, (+)103.937, (+)111.206, (+)115.070, (+)115.499, (+)121.101, (+)122.833, (+)124.331, (-)127.847, (-)128.453 d, (-)136.003 d, (-)154.975, (-)158.177, (-)160.042, (-)164.942.

IR ($CHCl_3$): ν cm^{-1}= 3370,1660,1600.

GC-MS M^+ 242(100%), M^+ -OH 225 (86%).

M.P.=58-59°C

(*R*)-(-)-4'-Fluorophenyl-2benzo[b]furanyl carbinol (*R*)-(-)-27 l:

Synthetic method 7.31.

$[\alpha]^{20}_D$ -5.7 (*c* 1.75, $CHCl_3$), enantiomeric excess 97.66% (Chiracel OD n-hexane/isopropanole), rt= **(*S*)-(+)-27 l** 72.90 min., **(*R*)-(-)-27 l** 76.29 min.

Physical and spectral data were identical to those described above for the racemate **(±) 27 l.**

(±)-4'-Chlorophenyl-2-benzo[b]furanyl carbinol (±)-27-m:

Synthetic procedure 7.3.1.

^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.53-7.15 (m 8H), 6.51 (s 1H), 5.91 (d1H, 4.4Hz), 2.53 (d 1H, 4.4 Hz).

IR ($CHCl_3$): ν cm^{-1}= 3385,1655,1620.

GC-MS M^+ 258(90%), M^+ -OH 241 (100%).

M.P.=77-79°C.

(*R*)-(-)-2-(Isoindonylinyl) butan-1-ol (*R*)-(-)24:

Synthetic procedure 7.4.

^{1}H-NMR (200 MHz, $CDCl_3$) δ =7.20 (s 5H), 4.04 (s 4H), 3.76 (d 1H, *J* = 4.1Hz), 3.71 (d 1H, *J* = 4.1Hz), 2.78 (s1H), 170-1.49 (m 2H) 0.97 (t 3H, *J*= 7.7 Hz).

M.P.= 59-60 °C.

$[\alpha]^{20}_D$ -20.01 (*c* 1.5, $CHCl_3$).

1-Methylimidazole-4,5-dicarbonitrile 33a

Synthetic method 7.7.1

Purified by chromatography (AcOEt) and then recrystallized from CH_2Cl_2/hexane.

^{1}H-NMR (200 MHz, $CDCl_3$) δ = 3.85 (s, 3H), 7.70 (s, 1H).

IR ($CHCl_3$): ν cm^{-1}= 2260

M.P.= 96-98 °C.

Elementary Analysis. calcd. for $C_6H_4N_4$: C, 54.54; H, 3.05; N, 42.41. Found: C, 54.70; H, 3.00; N, 42.30.

1-(*n*-Octyl)imidazole-4,5-dicarbonitrile 33b

Synthetic method 7.7.1.

Purified by flash chromatography (AcOEt).

^{1}H-NMR (200 MHz, $CDCl_3$) δ = 1.27 (t, *J* = 5 Hz, 3H), 1.66 (m, 10H), 1.93 (q, *J* = 5 Hz, 2H), 4.18 (t, *J* = 6 Hz, 2H), 7.69 (s, 1H).

IR ($CHCl_3$): ν cm^{-1}= 2250 cm^{-1};

M.P. = Colorless oil.

Elementary Analysis. calcd.for $C_{13}H_{18}N_4$: C, 67.79; H, 7.88; N, 24.33. Found: C, 68.08; H, 7.73; N, 24.19.

(*R*,*S*)-(±)-1-(2-Octyl)imidazole-4,5-dicarbonitrile (±)-33c

Synthetic method 7.7.1.

Purified by preparative TLC (hexanes/AcOEt 3:1).

^{1}H-NMR (200 MHz, $CDCl_3$) δ = 0.88 (t, *J* = 5.7 Hz, 3H), 1.28 (m, 8H), 1.65 (d, *J* = 5.7 Hz, 3H), 1.93 (m, 2H), 4.43 (sextet, *J* = 5.7 Hz, 1H), 7.75 (s, 1H).

IR ($CHCl_3$): ν cm^{-1}= 2240 cm^{-1}.

M.P.= Colorless oil.

Elementary Analysis. calcd. for $C_{13}H_{18}N_4$: C, 67.79; H, 7.88; N, 24.33. Found: C, 67.92; H, 7.93, N, 24.15.

(*S*)-(+)-1-(2-Octyl)imidazole-4,5-dicarbonitrile (*S*)-(+)-33c

Synthetic method 7.7.1**:**

$[\alpha]^0_{546}$ +1.1 (*c* 2.91, $CHCl_3$).

Physical and spectral data were identical with those described above for the racemate **(±)-33c**.

(*R*)-(-)-1-(2-Octyl) imidazole-4,5-dicarbonitrile (*R*)-(-)-33c

Synthetic method 7.7.1

$[\alpha]^{20}_{546}$ -1.0 (*c* 2.18, $CHCl_3$).

Physical and spectral data were identical with those described above for the racemate **(±)-33c**.

(*R*,*S*)-(±)-1-(1-Phenyl-2-propyl)imidazole-4,5-dicarbonitrile (±)-33d

Synthetic method 7.7.1.

Purified by flash chromatography (n-hexane/AcOEt 3:1). An analytical sample was prepared by recrystallization from benzene/cyclohexane.

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 1.48 (d, *J* = 4.3 Hz, 3H), 2.86 (dd, *J* = 14.1, 4.3 Hz, 2H), 2.93 (dd, *J* = 14.1, 4.3 Hz, 2H), 4.38 (sextet, *J* = 4.3 Hz, 1H), 6.83 (m, 2H), 7.05 (m, 3H), 7.26 (s, 1H).

IR ($CHCl_3$): ν cm^{-1}=2240 cm^{-1};

M.P.= 138-140 °C.

Elementary Analysis. calcd. for $C_{14}H_{12}N_4$: C, 71.17; H, 5.12; N, 23.71. Found: C, 71.33; H, 5.01; N, 23.57.

(*S*)-(+)-1-(1-Phenyl-2-propyl)imidazole-4,5-dicarbonitrile (*S*)-(+)-33d

Synthetic method 7.7.1

$[\alpha]^{20}_D$ +58.8 (*c* 0.85, $CHCl_3$).

Physical and spectral data were identical with those described above for the racemate **(±)-33d**.

(*R*,*S*)-(±)-1-(1-Phenyl-1-propyl)imidazole-4,5-dicarbonitrile (±)-33e

Synthetic method 7.7.1

Purified by flash chromatography (n-hexane/AcOEt 2:1). An analytical sample was obtained by preparative TLC.

^{1}H NMR (200 MHz, $CDCl_3$) δ= 1.05 (t, *J* = 7.4 Hz, 3H), 2.38 (quintet, *J* = 7.4 Hz, 2H), 5.23 (t, *J* = 7.4 Hz, 1H), 7.28 (m, 2H), 7.38 (m, 3H), 7.88 (s, 1H).

IR ($CHCl_3$): ν cm^{-1}= 2250 cm^{-1};

M.P.= Colorless oil.

Elementary Analysis. calcd. for $C_{14}H_{12}N_4$: C, 71.17; H, 5.12; N, 23.71. Found: C, 71.38; H, 5.20; N, 23.42.

(*S*)-(-)-1-(1-Phenyl-1-propyl)imidazole-4,5-dicarbonitrile (*S*)-(-)-33e

Synthetic method 7.7.1

$[\alpha]^{20}_D$ -44.3 (*c* 2.82, $CHCl_3$).

Physical and spectral data were identical with those described above for the racemate **(±)-33e**.

1-(_-Phenylbenzyl)imidazole-4,5-dicarbonitrile 33f

Synthetic method 7.7.2

Purified by flash chromatography (n-hexane/AcOEt 2:1) followed by recrystallization from Et_2O.

^{1}H NMR (200 MHz, $CDCl_3$) δ = 6.70 (s, 1H), 7.13 (m, 4H), 7.43 (m, 7H).

IR ($CHCl_3$): ν cm^{-1}= 2240 cm^{-1}

M.P.= mp 137-138 °C.

Elementary Analysis. calcd. for $C_{18}H_{12}N_4$: C, 76.04; H, 4.25; N, 19.71. Found: C, 76.24; H, 4.18; N, 19.58.

(±)-1-[_-(4-Biphenyl)benzyl]imidazole-4,5-dicarbonitrile (±)-33g

Synthetic method 7.7.2.

Purified by flash chromatography (n-hexane/AcOEt 5:1 to 3:1). An analytical sample was prepared by recrystallization from Et_2O.

^{1}H-NMR (200 MHz, $CDCl_3$) δ = 6.74 (s, 1H), 7.45 (m, 4H), 7.6 (m, 11H).
IR ($CHCl_3$): ν cm^{-1}= 2225 cm^{-1}.
M.P.= 58-59 °C.
Elementary Analysis. calcd. for $C_{24}H_{16}N_4$: C, 79.98; H, 4.47; N, 15.54. Found: C, 80.12; H, 4.39; N, 15.49.

(*R,S*)-(±)-1-[_-(2-Bromophenyl)benzyl]imidazole-4,5-dicarbonitrile (±)-33h

Synthetic method 7.7.2
Purified by flash chromatography (n-hexane/AcOEt 2:1) followed by recrystallization from methanol.
^{1}H-NMR (200 MHz, $CDCl_3$) δ = 6.82 (dd, *J* = 5.7, 2.0 Hz, 1H), 7.05 (s, 1H), 7.10 (m, 2H), 7.38 (m, 3H), 7.45 (m, 3H), 7.70 (dd, *J* = 5.7, 2.0 Hz, 1H).
IR ($CHCl_3$): ν cm^{-1}= 2240 cm^{-1}
M.P.= 176-177 °C.
Elementary Analysis. calcd. for $C_{18}H_{11}BrN_4$: C, 59.52; H, 3.05; N, 15.43. Found: C, 59.43; H, 3.12; N, 15.58.

(*R,S)*-(±)-1-[_-(2-Bromophenyl)-4-phenylbenzyl]imidazole-4,5-dicarbonitrile (±)-33i

Synthetic method 7.7.2.
Purified by flash chromatography (n-hexane/AcOEt 3:1) followed by recrystallization from MeOH.
^{1}H=NMR (200 MHz, $CDCl_3$) δ = 6.89 (dd, *J* = 6.0, 1.8 Hz, 1H), 7.06 (s, 1H), 7.14 (d, *J* = 7.0 Hz, 2H), 7.41 (m, 6H), 7.65 (m, 5H).
IR ($CHCl_3$): ν cm^{-1}= 2230 cm^{-1}
M.P.= 169-171 °C.
Elementary Analysis. calcd. for $C_{24}H_{15}BrN_4$: C, 65.62; H, 3.44; N, 12.75. Found: C, 65.80; H, 3.33; N, 12.91.

(*R,S*)-(±)-1-{_-[2-Benzo(b)furan]-4-phenylbenzyl} imidazole-4,5-dicarbonitrile (±)-33 l

Synthetic method 7.7.2.
Purified by flash chromatography (n-hexane/AcOEt 2:1) ^{1}H-NMR (200 MHz, $CDCl_3$) δ = 6.68 (s 1H), 6.77 (s1H), 7.47-7.21 (m 8H), 7.55 (1H d, *J* =6.1Hz), 7.68 (s1H).
IR ($CHCl_3$): ν cm^{-1}= 2220 cm^{-1}

(*R,S*)-(±)-1-(2-Octyl)imidazole-4,5-dicarboxylic acid (±)-34a.

Synthetic method 7.8.1

Recrystallized from EtOH.

^{1}H NMR (200 MHz, $CDCl_3$) δ = 0.86 (t, *J* = 6.0 Hz, 3H), 1.28 (m, 8H), 1.70 (d, *J* = 6.0 Hz, 3H), 1.90 (m, 2H), 5.93 (m, 1H), 8.68 (s, 1H).

IR ($CHCl_3$): ν cm^{-1}= 1735 cm^{-1}

M.P. = 188-190 °C.

Elementary Analysis. calcd. for $C_{13}H_{20}N_20_4$: C, 58.19; H, 7.51; N, 10.44. Found: C, 58.31; H, 7.58; N, 10.29.

(*S*)-(+)-1-(2-Octyl)imidazole-4,5-dicarboxylic acid (*S*)-(+)-34a.

Synthetic method 7.8.1

$[\alpha]^{20}_D$ +20.0 (*c* 0.95, $CHCl_3$).

Physical and spectral data were identical with those described above for the racemate **(±)-34a**.

(*R,S*)-(±)-1-(1-Phenyl-2-propyl)imidazole-4,5-dicarboxylic acid (±)-34b.

Synthetic method 7.8.1

Recrystallized from EtOH,

^{1}H NMR (200 MHz, DMSO-d_6) δ= 1.51 (d, *J* = 6.9 Hz, 3H), 3.10 (dd, *J* = 13.1, 6.7 Hz, 1H), 3.25 (dd, *J* = 13.1, 6.7 Hz, 1H), 6.07 (sextet, *J* = 6.9 Hz, 1H), 7.23 (m, 5H), 9.36 (s, 1H).

IR (nujol mull) ν cm^{-1}=1735

M.P.= 210-212 °C.

Elementary Analysis. calcd. for $C_{14}H_{14}N_20_4$: C, 61.30; H, 5.14; N, 10.22. Found: C, 61.44; H, 5.27; N, 9.98.

(*S*)-(+)-1-(1-Phenyl-2-propyl)imidazole-4,5-dicarboxylic acid (*S*)-(+)-34b.

Synthetic method 7.8.1

$[\alpha]^{20}_D$ +2.0 (*c* 1.40, C_6H_5N).

Physical and spectral data were identical with those described above for the racemate **(±)-34b**.

(*R,S*)-(±)-1-(1-Phenyl-1-propyl)imidazole-4,5-dicarboxylic acid (±)-34c.

Synthetic method 7.8.1

Recrystallized from EtOH/H_2O (7:3),
^{1}H-NMR (200 MHz, $CDCl_3$) δ =0.98 (t, *J* = 6.8 Hz, 3H), 2.34 (quintet, *J* = 6.8 Hz, 2H), 6.83 (t, *J* = 6.8 Hz, 1H), 7.42 (s, 5H), 8.65 (s, 1H).
IR (nujol mull) ν cm^{-1}=1730;
M.P.= 180-182 °C.
Elementary Analysis. calcd. for $C_{14}H_{14}N_20_4$: C, 61.30; H, 5.14; N, 10.22. Found: C, 61.51; H, 5.00; N, 10.06.

(*S*)-(-)-1-(1-Phenyl-1-propyl)imidazole-4,5-dicarboxylic acid (*S*)-(-)-34c.

Synthetic method 7.8.1
$[\alpha]^{25}_{365}$ -72.8 (*c* 2.80, DMF).
Physical and spectral data were identical to those described above for the racemate **(±)-34c**.

1-(_-Phenylbenzyl)imidazole-4,5-dicarboxylic acid 34d.

Synthetic method 7.8.1
Recrystallized from EtOH.
^{1}H-NMR (200 MHz, DMSO-d_6) =7.15 (m, 4H), 7.46 (m, 6H), 8.10 (s, 1H), 8.56 (s, 1H).
IR (nujol mull) ν cm^{-1}=1730 ;
M.P. = 202-204 °C.
Elementary Analysis. calcd. for $C_{18}H_{14}N_20_4$: C, 67.07; H, 4.38; N, 8.69. Found: C, 67.30; H, 4.49; N, 8.50.

(*R,S*)-(±)-1-[_-(4-Biphenylyl)benzyl]imidazole-4,5-dicarboxylic acid (±)-34e.

Synthetic method 7.8.1
Recrystallized from EtOH (70%)/DMF (98:2),
^{1}H-NMR (200 MHz, DMF-d_7) δ = 7.45 (m, 10H), 7.85 (m, 4H), 8.41 (s, 1H), 8.95 (s, 1H).
mp 211-213 °C. IR (nujol mull) 1740 cm^{-1};
Elementary Analysis. calcd. for $C_{24}H_{18}N_20_4$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.61; H, 4.38; N, 6.88.

(*R,S*)-(±)-1-(2-Octyl)imidazole (±)-35a.

Synthetic procedure 7.9.1. or 7.19.
^{1}H-NMR (200 MHz, $CDCl_3$) δ = 0.76 (t, *J* = 7.0 Hz, 3H), 1.19 (br s, 8H), 1.41 (d, *J* = 7.0 Hz, 3H), 1.65 (q, *J* = 7.0 Hz, 2H), 4.04 (sextet, *J* = 7.0 Hz, 1H), 6.82 (s, 1H), 6.97 (s, 1H), 7.38 (s, 1H).

M.P. = oil.

Elementary Analysis. calcd. for $C_{11}H_{20}N_2$: C, 73.28; H, 11.18; N, 15.54. Found: C, 73.48; H, 11.26; N, 15.26.

(*S*)-(+)-1-(2-Octyl)imidazole (*S*)-(+)-35a.

Synthetic procedure 7.9.1. or 7.19

$[\alpha]^{20}_D$ +16.0 (*c* 1.1, $CHCl_3$).

Physical and spectral data were identical with those described above for the racemate **(±)-35a**.

(±)-1-(1-Phenyl-2-propyl)imidazole (±)-35b.

Synthetic procedure 7.9.1.

^{1}H-NMR (200 MHz, $CDCl_3$) δ = 1.45 (d, *J* = 7.0 Hz, 3H), 2.92 (d, *J* = 7.0 Hz, 2H), 4.30 (sextet, *J* = 7.0 Hz, 1H), 6.93 (m, 4H), 7.17 (m, 4H).

M.P. = oil.

Elementary Analysis. calcd for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.51; H, 7.67; N, 14.82.

(*S*)-(+)-1-(1-Phenyl-2-propyl)imidazole (*S*)-(+)-35b.

Synthetic procedure 7.9.1.

[ ]$^{20}_D$ +93.3 (*c* 0.75, $CHCl_3$).

Physical and spectral data were identical to those described above for the racemate **(±)-35b**.

(*R,S*)-(±)-1-(1-Phenyl-1-propyl)imidazole (±)-35c.

Synthetic procedure 7.9.1.

^{1}H-NMR (200 MHz, $CDCl_3$) δ =0.94 (t, *J* = 7.0 Hz, 3H), 2.23 (m, 2H), 5.00 (t, *J* = 7.0 Hz, 1H), 6.94 (s, 1H), 7.07 (s, 1H), 7.16 (m, 2H), 7.36 (m, 3H), 7.59 (s, 1H).

M.P.= oil.

Elementary Analysis. calcd. for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.48; H, 7.49; N, 15.03.

Starting from **(*S*)-(-)-34c** the racemic compound **(±)-35c** was obtained.

(±)-1-(_-Phenylbenzyl)imidazole (±)-35d.

Synthetic procedure 7.9.1.

^{1}H-NMR (200 MHz, $CDCl_3$) δ = 6.55 (s, 1H), 6.85 (s, 1H), 7.08 (m, 5H), 7.36 (m, 7H).

M.P. = 88-89 °C (CH_3CN).

Elementary Analysis. calcd. for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96. Found: C, 81.89; H, 5.95; N, 12.16.

(*R,S*)-(±)-1-[_-(4-Biphenylyl)benzyl]imidazole [Bifonazole (±)-6a].

Synthetic procedure 7.9.1.

^{1}H-NMR (200 MHz, $CDCl_3$) δ = 6.58 (s, 1H), 6.88 (s, 1H), 7.13 (m, 10H), 7.42 (m, 6H). Anal. Calcd for $C_{22}H_{18}N_2$: C, 85.13; H, 5.84; N, 9.03. Found: C, 85.21; H, 5.80; N, 8.99.

M.P. = 145-147 °C (EtOH) (lit.142 °C, from CH_3CN).

Following the same procedure **(±)-6a** was also obtained in 94% yield by decarboxylation of **(±)-43**.

Ethyl 4(5)-imidazol carboxylate 37:

Synthetic procedure 7.10.3

^{1}H-NMR (200 MHz, $CDCl_3$) δ = 1.36 (3H, t J=7.13Hz), 4.38 (2H, q J=7.13 Hz), 7.77 (s1H) 7.82 (s1H), 8.03 (s 1H).

Acetylglycine ethyl ester 38:

Synthetic procedure 7.10.1

^{1}H-NMR (200 MHz, $CDCl_3$) δ = 1.28 (3H, Tr *J* =7.1 Hz), 2.04 (s, 3H), 4.05 (d 2H J=5.4 Hz), 4.21 (q 2H, J=7.4 Hz).

4(5)-(2-Thiol)-imidazol carboxylate 40:

Synthetic procedure 7.10.2

^{1}H-NMR (200 MHz, DMSO) δ = 1.29 (3H, t J= 7.06 Hz), 4.24 (2H, q J= 7.06 Hz) 7.64 (s1H), 12.50 (s 1H), 12,76 (s1H).

(±)-Ethyl-1-[_-(4-biphenylyl)benzyl]imidazole-5-carboxylate (±)-41a:

Synthetic method 7.11.1 50% yield; Synthetic method 7.11.2 16%yield

^{1}H-NMR (200 MHz, $CDCl_3$) δ =1.27 (t, *J* = 7.1 Hz, 3H), 4.29 (q, *J* = 7.1 Hz, 2H), 7.13 (m, 4H), 7.36 (m, 7H), 7.58 (m, 5H), 7.85 (s, 1H).

M.P. = 136-137 °C (EtOH).

Elementary Analysis. calcd. for $C_{25}H_{22}N_2O_2$: C, 78.51; H, 5.80; N, 7.33. Found: C, 78.70; H, 5.75; N, 7.24.

(±)-Ethyl-1-[_-(4-biphenylyl)benzyl]imidazole-4-carboxylate (±)-41b :

Synthetic method 7.11.1 16% yield; Synthetic method 7.11.2 16%yield

^{1}H-NMR (200 MHz, $CDCl_3$) δ =1.36 (t, *J* = 6.9 Hz, 3H), 4.34 (q, *J* = 6.9 Hz, 2H), 6.58 (s, 1H), 7.16 (m, 4H), 7.54 (m, 12H).

M.P.= 149-151 °C (EtOH).

Elementary Analysis. calcd. for $C_{25}H_{22}N_2O_2$: C, 78.51; H, 5.80; N, 7.33. Found: C, 78.73; H, 5.84; N, 7.19.

(±)-1-[_-(4-Biphenylyl)benzyl]imidazole-5-carboxylic acid (±)-43.

Synthetic method 7.12

^{1}H-NMR (200 MHz, DMSO-d_6) δ =7.41 (m, 4H), 7.62 (m, 6H), 7.69 (m, 7H). Anal. Calcd for $C_{23}H_{18}N_2O_2$: C, 77.95; H, 5.12; N, 7.91. Found: C, 78.12; H, 5.19; N, 7.83.

IR (nujol mull) ν cm^{-1}=1740;

M.P.= 163-166 °C (EtOH/H_2O).

(±)-5-Amino-1-(2-octyl)imidazole-4-carbonitrile (±)-46

Synthetic method 7.13.

^{1}H-NMR (200 MHz, $CDCl_3$) δ =0.87 (t, *J* = 6.5 Hz, 3H), 1.26 (br s, 8H), 1.46 (d, *J* = 6.7 Hz, 3H), 1.75 (m, 2H), 3.96 (m, 1H), 7.13 (s, 1H).

IR 3360, 2240 cm^{-1};

M.P.=110 °C (cyclohexane).

Elementary Analysis. calcd. for $C_{12}H_{20}N_4$: C, 65.41; H, 9.15; N, 25.44. Found: C, 65.67; H, 9.08; N, 25.25.

(±)-5-Amino-1-(2-octyl)imidazole-4-carboxylic acid (±)-47

Synthetic method 7.14

^{1}H-NMR (200 MHz, DMSO-d_6 + D_2O) δ =0.84 (t, *J* = 7.3 Hz, 3H), 1.25 (br s, 8H), 1.37 (d, *J* = 7.4 Hz, 3H), 1.73 (m, 2H), 4.11 (m, 1H), 7.18 (s, 1H).

IR (nujol mull) ν cm^{-1}=3350, 1735;

47 was not further purified and was directly used in the next step.

(±)-5-Amino-1-(2-octyl)imidazole (±)-48

Synthetic method 7.15

^{1}H=NMR (200 MHz, $CDCl_3$ + D_2O) δ = 0.88 (t, *J* = 6.8 Hz, 3H), 1.30 (br s, 8H), 1.48 (d, *J* = 7.0 Hz, 3H), 1.75 (m, 2H), 4.04 (m, *J* = 7.2 Hz, 1H), 4.75 (s, 1H), 7.21 (s, 1H).

IR ($CHCl_3$) ν cm^{-1} = 3350;

M.P.= Colorless oil.

Elementary Analysis. calcd. for $C_{11}H_{21}N_3$: C, 67.64; H, 10.84; N, 21.52. Found: C, 67.80; H, 10.72; N, 21.35.

(±)-1-(2-Octyl)imidazole-4-carboxamide (±)-49

Synthetic method 7.16.

^{1}H-NMR (200 MHz, $CDCl_3$ + D_2O) δ =0.86 (t, *J* = 6.7 Hz, 3H), 1.32 (m, 8H), 1.49 (d, *J* = 6.8 Hz, 3H), 1.75 (m, 2H), 4.17 (m, 1H), 7.59 (s, 1H), 7.67 (s, 1H).

IR ($CHCl_3$) ν cm^{-1} = 3540, 3420, 1670;

Elementary Analysis. calcd. for $C_{12}H_{21}N_3O$: C, 64.51; H, 9.51; N, 18.81. Found: C, 64.84; H, 9.30; N, 18.48.

(±)-*N*-[2,2-(Dimethoxy)ethyl]-2-octylamine (±)-52a:

Synthetic method 7.17, 62% yield.

^{1}H-NMR (200 MHz, $CDCl_3$) δ =0.88 (t, *J* = 6.3 Hz, 3H), 1.04 (d, *J* = 6.2 Hz, 3H), 1.27 (m, 8H), 2.05 (s, 1H), 2.72 (m, 4H), 3.85 (s, 6H), 4.65 (t, *J* = 6.2 Hz, 1H).

IR ($CHCl_3$) ν cm^{-1} = 3340;

(*S*)-*N*-[2,2-(Dimethoxy)ethyl]-2-octylamine (*S*)-52a:

Synthetic method 7.17, 65% yield

No specific rotation could be measured at different wavelengths.

Physical and spectral data were identical to those described above for the racemate **(±)-52a.**

(±)-*N*-[2,2-(Dimethoxy)ethyl]-1-phenyl-1-ethylamine(±)-52b:

Synthetic method 7.17, 70% yield.

^{1}H-NMR (200 MHz, $CDCl_3$) δ =1.37 (d, *J* = 6.5 Hz, 3H), 1.65 (s, 1H, exchangeable with D_2O), 2.55 (dd, *J* = 12.1, 6.3 Hz, 1H), 2.65 (dd, *J* = 12.1, 6.3 Hz, 1H), 3.29 (s, 3H), 3.34 (s, 3H), 3.76 (q, *J* = 6.5 Hz, 1H), 4.45 (t, *J* = 6.5 Hz, 1H), 7.35 (m, 5H).

IR ($CHCl_3$) ν cm^{-1} = 3345;

***(S)N*-[2,2-(Dimethoxy)ethyl]-1-phenyl-1-ethylamine (*S*)-(-)-52b:**

Synthetic method 7.17

$[\alpha]^{20}_D$ -31.0 (*c* 2.09, $CHCl_3$).

Physical and spectral data were identical to those described above for the racemate **(±)-52b**

(±)-*N*-1-(2-Octyl)-2-thiol-imidazole (±)-53a:

Synthetic method 7.18,84% yield;

^{1}H NMR (200 MHz, $CDCl_3$) δ= 0.82 (t, *J* = 7.0 Hz, 3H), 1.25 (m, 8H), 1.33 (d, *J* = 7.0 Hz, 3H), 1.70 (m, 2H), 4.92 (m, *J* = 7.0 Hz, 1H), 6.69 (s, 1H), 6.75 (s, 1H), 11.40 (br s, 1H, exchangeable with D_2O).

IR ($CHCl_3$) ν cm^{-1} = 2580;

M.P.= 84-85 °C (Et_2O).

Elementary Analysis. calcd. for $C_{11}H_{20}N_2S$: C, 62.21; H, 9.49; N, 13.19. Found: C, 62.41; H, 9.53; N, 13.25.

(*S*)-(-)-*N*-1-(2-Octyl)-2-thiol-imidazole (*S*)-(-)-53a:

Synthetic method 7.18

$[\alpha]^{20}_D$ -35.6 (*c* 0.45, $CHCl_3$).

Physical and spectral data were identical to those described above for the racemate **(±)-53a**.

(±)-*N*-1-(1-Phenylethyl)-2-thiol-imidazole-(±)-53b:

Synthetic method 7.18, 84% yield;

^{1}H-NMR (200 MHz, $CDCl_3$) δ =1.74 (d, *J* = 7.4 Hz, 3H), 6.20 (q, *J* = 7.4 Hz, 1H), 6.58 (s, 1H), 6.70 (s, 1H), 7.32 (m, 5H), 11.93 (br s, 1H, exchangeable with D_2O).

IR ($CHCl_3$) ν cm^{-1} = 2585;

M.P.=124-127 °C (Et_2O).

Elementary Analysis. calcd.for $C_{11}H_{12}N_2S$: C, 64.66; H, 5.92; N, 13.72. Found: C, 64.52; H, 5.88; N, 13.80.

(*S*)-(-)-*N*-1-(1-Phenylethyl)-2-thiol-imidazole (*S*)-(-)-53b:

Synthetic method 7.18

$[\alpha]^{20}_D$ -239.2 (*c* 4.10, $CHCl_3$).

Physical and spectral data were identical to those described above for the racemate **(±)-53b**

(±)-*N*-1-Phenyl-1-ethyl imidazole (±)-54:

Synthetic method 7.19

^{1}H-NMR (200 MHz, $CDCl_3$) δ =1.87 (d, *J* = 8.0 Hz, 3H), 5.34 (q, *J* = 8.0 Hz, 1H), 6.90 (s, 1H), 7.08 (s, 1H), 7.14 (m, 2H), 7.30 (m, 3H), 7.58 (s, 1H).

M.P. =yellow oil.

Anal. Calcd for $C_{11}H_{12}N_2$: C, 76.71; H, 7.03; N, 16.27. Found: C, 76.86; H, 7.10; N, 16.04.

(*S*)-(+)-1-Phenyl-1-ethyl imidazole (*S*)-(+)-54:

Synthetic method 7.19

$[\alpha]^{20}_D$ +5.20 (*c* 3.84, $CHCl_3$). e.e. > 98%.

Physical and spectral data were identical to those described above for the racemate **(±)-54.**

(±)-55a:

Synthetic method 7.20.1

^{1}H-NMR (200 MHz, $CDCl_3$) δ = 4.95 (s 1H), 7.14-7.27 (m 14H).

IR ($CHCl_3$) ν cm^{-1} = 2120;

MP: Oil

(±)-55b:

Synthetic method 7.20.1 or 7.20.2

^{1}H-NMR (200 MHz, $CDCl_3$) δ = 6.1 (s1H),7.13-7.29 (m3H), 7.31-7.59 (m10H).

IR ($CHCl_3$): ν cm = 2105 cm^{-1};

MP: Oil

(±)-55c:

Synthetic method 7.20.1 or 7.20.2

^{1}H-NMR (200 MHz, $CDCl_3$) δ = 5.34 (s1H), 6.25 (s1H), 7.23-7.30 (m 3H), 7.41-7.60 (m 6H).

IR ($CHCl_3$) ν cm^{-1} = 2105;

MP: Oil

(±)-55d:

Synthetic method 7.20.1 or 7.20.2

^{1}H-NMR (200 MHz, $CDCl_3$) δ = 6.22 (s 1H), 6.58 (s 1H), 7.17- 7.39 (m 3H), 7.43-7.54 (m 4H).

IR ($CHCl_3$) ν cm^{-1} = 2125;

MP: Oil

(+)-55d:

Synthetic method 7.20.2

$[\alpha]^{20}_D$ = +0.5 (*c* 4, $CHCl_3$). e.e. ND

Physical and spectral data were identical to those described above for the racemate **(±)-55d.**

(±)-56a

Synthetic method 7.21.1 or 7.21.2

^{1}H-NMR (200 MHz, $CDCl_3$) δ = 1.98 (s 2H), 5.38 (s 1H), 7.28-7.55 (m14H).

IR ($CHCl_3$) ν cm^{-1} = 420,3020,1620, 1600;
MP: Oil
(±)-56b:
Synthetic method 7.21.1 or 7.21.2
^{1}H-NMR (200 MHz, $CDCl_3$) δ = 2.55 (s 2H), 5.22 (s 1H), 7.33-7.65 (m13H).
IR ($CHCl_3$) ν cm^{-1} = 3080,3020,1610, 1590;
MP: Oil
(±)-56c:
Synthetic method 7.21.1 or 7.21.2
^{1}H-NMR (200 MHz, $CDCl_3$) δ = 2.28 (s 2H), 5.21 (s1H), 6.45 (s1H), 7.10-7.21 (m 3H), 7.27-7.47 (m 6H).
IR ($CHCl_3$) ν cm^{-1} = 3420,3120,1620, 1600;
MP: Oil.
(±)-56d:
Synthetic method 7.21.1 or 7.21.2
^{1}H-NMR (200 MHz, $CDCl_3$) δ = 1.91 (s 2H), 5.69 (s 1H), 6.55 (s 1H), 7.15-7.7.27 (m 3H), 7.39-7.52 (m 4H).
IR ($CHCl_3$) ν cm^{-1} = 3390,3120,1620, 1600;
MP: Oil.
(+)-56d:
Synthetic method 7.21.1 or 7.21.2
$[\alpha]^{20}_D$ = not measurable 20%e.e. by chiral HPLC(Chiracel OD).
Physical and spectral data were identical with those described above for the racemate **(±)-56d.**
(±)-57a as mixture of diasteroisomers:
Synthetic method 7.22.
^{1}H-NMR (300 MHz, $CDCl_3$) δ = 1.63 (d 3H *J* =6.7 Hz), 5.94 (m 1H), 6.25 (s 1H), 7.06-7.28 (m 4H), 7.33-7.59 (m19H), 7.68-7.91 (m 4H).
57b:
Synthetic method 7.22.
^{1}H-NMR (300 MHz, $CDCl_3$) δ = 1.75 (d 3H *J* =7.0 Hz), 1.85 (d3H *J* =7.0 Hz), 6.05 (q *J* =7.0 Hz, dq *J* =6.17 Hz and *J* =8.8 Hz) 7.05-804 m, 8.13 (d 1H, *J* =8.8 Hz), 11.95 (d 1H, *J* =7.0 Hz).
FAB MS= 705 M^+.
HPLC: Lichrocart 250X4, Lichrospher n-hexane/EtAc gradient rt 16.40 min

57c:
Synthetic method 7.22.
^{1}H-NMR (300 MHz, $CDCl_3$) δ = 1.75 (d 3H *J* =7.0 Hz), 1.85 (d3H *J* =7.0 Hz), 6.05 (q *J* =7.0 Hz, dq *J* =6.17 Hz and *J* =8.8 Hz) 7.05-804 m, 8.05 (d 1H, *J* =8.8 Hz), 11.88 (d 1H, *J* =7.0 Hz).
FAB MS= 705 M^+.
HPLC: Lichrocart 250X4, Lichrospher n-hexane/EtAc gradient rt 17.66 min
(±)-57d mixture of diasteroisomers:
Synthetic method 7.22.
^{1}H-NMR (200 MHz, $CDCl_3$) δ = 1.52 (d 3H *J* =7.10 Hz), 1.62 (d 3H *J* =7.10 Hz), 5.13 (m 1H), 5.32 (m m1H), 7.03-7.58 (m 24H), 8.01 (d 1H J=8.5 Hz) 8.27 (s 1H) 11.62 (m2H).
FAB MS= 604 M^+.
(±)-1-Phenyl-2-propyn-1-ol (±)-58a:
Synthetic methods 7.23.1, 7.23.3.1, 7.23.3.2, 7.23.4. The compound is commercially available.
^{1}H-NMR (200 MHz, $CDCl_3$) δ = 2.28 (d 1H, 6.23 Hz), 2.69 (d 1H, J = 2.17 Hz), 5.48 (dd 1H, J=2.17 Hz; J=6.21 Hz), 7.59-7.32 (m3H).
^{13}C NMR ($CDCl_3$) ν = 64.05, 74.65, 83.36, 126.43, 128.27, 128.42, 139.81.
IR ($CHCl_3$) ν cm^{-1} = 3510, 3320, 3080, 2840, 2120.
MP =oil.
(±)-1-(4-Methylphenyl)-2-propyn-1-ol (±)-58b:
Synthetic method 7.23.3.1 or 7.23.4.
^{1}H-NMR (200 MHz, $CDCl_3$) δ = 2.19 (d 1H, J =4.12 Hz), 2.40 (s 3H), 2.69 (d 1H, J = 2.2 Hz), 5.48 (d 1H, J = 4.12 Hz), 7.24 (d 2H, J= 8.12 Hz), 7.48 (d 2H, J= 8.12 Hz).
^{13}C NMR ($CDCl_3$) δ = 21.29, 64.49, 74.72, 83.85, 126.71, 129.51, 137.42, 138.59.
IR ($CHCl_3$) ν cm^{-1} = 3540, 3380, 3280, 2120, 1610, 1510.
MP = oil.
(*R*)-(-)-1-(4-Methylphenyl)-2-propyn-1-ol (*R*)-(-)-58b:
Synthetic methods 7.28.1, 7.28.2
$[\alpha]^{20}_D$ -27.9 (*c* 3.05, $CHCl_3$). 75.7% ee.
Physical and spectral data were identical to those described above for the racemate **(±)58b.**

(±)-1-(4-Fluorophenyl)-2-propyn-1-ol (±)-58c:
Synthetic methods 7.23.3.1, 7.23.3.2, 7.23.4.
^{1}H-NMR (200 MHz, $CDCl_3$) δ = 2.71 (d 1H, J= 2.9 Hz), 2.73 (s1H), 5.47 (d1H, J =2.90 Hz), 7.12-7.07 (m 2H), 7.57-7.53 (m 2H).
^{13}C NMR ($CDCl_3$) = 63.85, 75.25, 83.53, 115.79, 116.23, 128.69, 136.9, 161.71, 164.166.
IR ($CHCl_3$) ν cm^{-1} = 3400, 3390, 3280, 2120, 1610, 1520.
GC-MS = M+ 149 (45%) 133.7 (73%), 101.8 (100%)
MP = oil.
(*R*)-(-)-1-(4-Fluorophenyl)-2-propyn-1-ol (*R*)-(-)-58c:
Synthetic method 7.28.2
$[\alpha]^{20}_D$ -28.3 (*c* 2.11, $CHCl_3$). 83.2% ee.
Physical and spectral data were identical to those described above for the racemate **(±)-58c.**
(±)-1-(4-Chlorophenyl)-2-propyn-1-ol (±)-58d:
Synthetic method 7.23.3.1
^{1}H-NMR (200 MHz, $CDCl_3$) δ = 2.20 (s1H), 2.65 (d 1H, J = 1.91 Hz), 5.44 (d 1H, J = 1.91 Hz), 7.28 (d 2H, J = 8.51 Hz), 7.38 (d 2H, J= 8.51 Hz).
^{13}C NMR ($CDCl_3$) ν = 63.77, 75.13, 83.41, 128.16, 128.91, 134.47, 138.83.
MP = oil.
(±)-1-(4-Cyanophenyl)-2-propyn-1-ol (±)-58e:
Synthetic method 7.23.4
^{1}H-NMR (200 MHz, $CDCl_3$) δ = 2.72, (d 1H, J=6.10 Hz), 2.74 (d 1H, J=2.10 Hz), 5.56 (dd 1 H, J=2.10 Hz, J = 6.10 Hz), 7.71 (s 4H).
^{13}C NMR ($CDCl_3$) δ = 63.10, 75.47, 82.39, 111,68, 118.43, 127.07, 132.23, 145.12.
GC-MS = 157 M+ (100%).
IR ($CHCl_3$) ν cm^{-1} = 3445,3300, 2235, 1660, 1408.
MP= 79.5-80.5.
(*R*)-(-)-1-(4-Cyanophenyl)-2-propyn-1-ol (*R*)-(-)-58e:
Synthetic methods 7.28.1,7.28.2
$[\alpha]^{20}_D$ -20.8 (*c* 0.60, $CHCl_3$). 85.5% ee .
Physical and spectral data were identical to those described above for the racemate **(±)-58e.**
(±)-1-(3,4-Dimethoxyphenyl)-2-propyn-1-ol (±)-58g:

Synthetic method 7.23.3.3.

^{1}H-NMR (200 MHz, $CDCl_3$) δ =2.52 (d 1H, J=5.7 Hz), 2.69 (d 1H, J=2.1 Hz), 3.89 (s 3H), 3.91 (s 3H), 5,42 (dd 1H, J=2.1Hz, J=5.7 Hz), 6.87 (d 1H, J=8.7 Hz), 7.09 (d 1H, J=8.7 Hz), 7.11 (s 1H).

^{13}C NMR ($CDCl_3$) δ = 56,12, 64.35, 74.78, 83.90, 110. 12, 111.24, 119.22, 128.95, 131.01, 133.02, 149.33.

MP= oil.

(±)-1-(3-Methylphenyl)-2-propyn-1-ol (±)-58h:

Synthetic method 7.23.4.

^{1}H-NMR (200 MHz, $CDCl_3$) δ =2.33 (d 1H, J= 6.1 Hz), 2.42 (s 3H), 2.70 (d 1H, J= 2.21 Hz), 5.46 (dd 1H, J= 6.1 Hz,J= 2.21 Hz), 7.20 (d 1H, J= 8.1 Hz), 7.32 (t 1H, J=8.1Hz), 7.39 (d 1H, J=8.1 Hz), 7.41 (s 1H).

^{13}C NMR ($CDCl_3$) δ = 21.54, 64.63, 74.87, 83.83, 123.816, 127.42, 128.76, 129.48, 138.61, 140.19.

IR ($CHCl_3$) ν cm^{-1} = 3380, 3280, 2120, 1620, 1480.

GC-MS= 146 M+ (56%), 131 (100%).

MP= oil.

(*R*)-(-)-1-(3-Methylphenyl)-2-propyn-1-ol (*R*)-(-)-58h:

Synthetic method 7.28.2

$[\alpha]^{20}_{D}$ -27.5 (*c* 0.65, $CHCl_3$). 92.1% ee .

Physical and spectral data were identical to those described above for the racemate **(±)-58h.**

(±)-1-(3-Fluorophenyl)-2-propyn-1-ol (±)-58i:

Synthetic method 7.23.4

^{1}H-NMR (200 MHz, $CDCl_3$) δ =2.45 (d 1H, J=6.10 Hz), 2.72 (d 1H, J= 2.10 Hz), 5.50 (dd 1H, J= 2.1Hz, J= 6.10 Hz) 7.09-7.04 (m 1H) 7.42-7.30 (m 3H).

^{13}C NMR ($CDCl_3$) δ = 63.89, 75.32, 83.14, 113.91, 115.65, 230.37, 142.66, 161.85, 164.29.

IR ($CHCl_3$) ν cm^{-1} = 3340, 3300, 2120, 1640, 1590.

GC-MS= 150 M^+ (100%), 133 (70%).

MP= oil.

(*R*)-(-)1-(3-Fluorophenyl)-2-propyn-1-ol (*R*)-(-)-58i:

Synthetic method 7.28.2

$[\alpha]^{20}_{D}$ -21.1 (*c* 1.44, $CHCl_3$). 91.5% ee .

Physical and spectral data were identical to those described above for the racemate **(±)-58i.**

(±)-1-(2-Methylphenyl)-2-propyn-1-ol (±)-58 l:

Synthetic method 7.23.4

^{1}H-NMR (200 MHz, $CDCl_3$) δ =2.38 (d 1H, J=51 Hz) 2.49 (s 3H), 2.68 (d 1H, J=2.1 Hz), 5.65 (dd 1H, J=2.1 Hz, J= 5.03 Hz), 7.24-7.22 (m 1H), 7.31-7.27 (m 2 H), 7.72-7.70 (m 1H).

^{13}C NMR ($CDCl_3$) ν = 19.04, 62.39, 74.84, 83.52, 126.42, 126.57, 128.72, 130.95, 136.07, 138.042.

GC-MS= 145 M^+ (18%), 121 (100%).

MP= 30.6-32.0.

(*R*)-(-)-1-(2-Methylphenyl)-2-propyn-1-ol (*R*)-(-)-58 l:

Synthetic method 7.28.2

$[\alpha]^{20}_D$ -18.1 (*c* 0.65, $CHCl_3$). 80.4% ee .

Physical and spectral data were identical to those described above for the racemate **(±)58 l.**

(±)-1-(2,4 Dichlorophenyl)-2-propyn-1-ol (±)-58 m:

Synthetic method 7.23.4

^{1}H-NMR (200 MHz, $CDCl_3$) δ =22.68 (d 1H, J=5.43 Hz), 2.71 (d 1H, J=2.04 Hz), 5.79 (dd 1H, J=5.43 Hz,J=2.04 Hz), 7.33 (d 1H, J=8.35 Hz), 7.43 (s 1H), 7.73 (d 1H J=8.35 Hz).

^{13}C NMR ($CDCl_3$) δ = 61.29, 75.29, 82.18, 127.73, 129.31, 129.68, 133.56, 135.18, 136.22.

MP=oil.

(±)-1-Phenyl-2-propyn-3-trimethylsilyl-1-ol (±)-59a:

Synthetic method 7.23.2

^{1}H-NMR (200 MHz, $CDCl_3$) δ = 0.00 (s 9H), 2.40 (s1H), 5.65 (s1H), 7.67-7.23 (m5H).

IR ($CHCl_3$) ν cm^{-1} = 3620, 3450,3020,2090.

MP = oil.

(±)-1-(4-Methylphenyl)-2-propyn-3-trimethylsilyl-1-ol (±)-59b:

Synthetic method 7.23.2

^{1}H-NMR (200 MHz, $CDCl_3$) δ = 0.00 (s 9H), 2.12 (s 1H), 2.34 (s 3H), 5.39 (s 1H), 7.16 (d 2H, J =8.02 Hz), 7.41 (d 2H, J = 8.02 Hz).

IR ($CHCl_3$) ν cm^{-1} = 3600, 3470,3020,2100.

MP = oil

(±)-1-(4-Fluorophenyl)-2-propyn-3-trimethylsilyl-1-ol (±)-59c:

Synthetic method 7.23.2

^{1}H-NMR (200 MHz, $CDCl_3$) δ = 0.00 (s 9H), 2.16 (d 1H, J = 5.1 Hz), 5.42 (d 1H, J = 5.1 Hz), 7.06 (t 2H, 9.1 Hz), 7.51 (dd 2H, J= 6.1 Hz, 9.1 Hz).

IR ($CHCl_3$) ν cm^{-1} = 3580, 3460,3010,2080.

MP = oil

(±)-1-(4-Chlorophenyl)-2-propyn-3-trimethylsilyl-1-ol (±)-59d:

Synthetic method 7.23.2

^{1}H-NMR (200 MHz, $CDCl_3$) δ = 0.00 (s 9H), 2.01 (s 1H), 5.40 (s 1H). 7.30 (d 2H, J = 8.24 Hz), 7.46 (d 2H, J = 8.24 Hz).

IR ($CHCl_3$) ν cm^{-1} = 3580, 3460,3010,2080.

MP = oil

(±)-1-(4-Cyanophenyl) – 2 – propyn – 3 – trimethylsilyl – 1 - ol (±)-59e:

Synthetic method 7.23.2

^{1}H-NMR (200 MHz, $CDCl_3$) δ = 0.00 (s 9H), 2.31 (s 1H), 5.50 (s 1H), 7.66 (m 4H).

IR ($CHCl_3$) ν cm^{-1} = 3544, 3425, 2960, 2232, 2173, 1608.

MP = oil

(±)-1-(4-Nitrophenyl)-2-propyn-3-trimethylsilyl-1-ol (±)-59f:

Synthetic method 7.23.2

^{1}H-NMR (200 MHz, $CDCl_3$) δ = 0.00 (s 9H), 2.27 (s 1H), 5.54 (s1H), 7.71 (d 2H, J= 8.73 Hz), 8,22 (d 2H, J= 8.73 Hz).

MP = oil.

(±)-1-(3,4-Dimethoxyphenyl)-2-propyn-3-trimethylsilyl-1-ol (±)-59g:

Synthetic method 7.23.2

^{1}H-NMR (200 MHz, $CDCl_3$) δ = 0.00 (s 9H), 2.20 (d 1H, J = 4.42 Hz), 3.92 (s 3H), 3.96 (s 3H), 5,44 (d 1H, J = 4.42 Hz), 6.90 (d 1H, J = 8.17 Hz) 7.11 (d 1H, J = 8.17 Hz), 7.15 (s 1H).

^{13}C NMR ($CDCl_3$) δ = 0.000, 55.98, 56.14, 91.67, 105.312, 110.29, 111,22, 119,36, 133.25, 145.68, 149.37.

MP= oil.

(±)-1-(Phenyl)-2-propyn-1-ol acetate (±)-60a:
Synthetic method 7.26.1 or 7.26.2.
^{1}H-NMR (200 MHz, $CDCl_3$) δ =2.13 (s 3H), 2.67 (d 1H, J=2.29 Hz), 6.43 (d 1H, J =2.29 Hz) 7.57-7.34 (m5H).
13C NMR (CDCl3) δ = 20.74, 65.04, 75.04, 80.04, 127.46, 128.47, 128.85, 136.25, 169.39.
IR (CHCl3) ν cm-1 = 3320, 3080, 2120, 1760.
GC-MS 174 M+ (100%)
(±)-1-(4-Methylphenyl)-2-propyn-1-ol acetate (±)-60b:
Synthetic method 7.26.2
1H-NMR (200 MHz, CDCl3) δ = 2.14 (s 3H), 2.41 (s3H), 2.67 D 1H, J=2.9 HZ), 6.46 (d 1H J=2.19 Hz), 7.23 (d 2H, J=8.2 Hz), 7.46 (d 2H, J=8.2 Hz).
13C NMR (CDCl3) δ = 21.34, 31.01, 65.36, 75.27, 80.61, 127.83, 129,52, 133.79, 139.22, 169.84.
(±)-1-(4-Cyanolphenyl)-2-propyn-1-ol acetate (±)-60c:
Synthetic method 7.26.2
1H-NMR (200 MHz, CDCl3) δ =2.17 (s 3H), 2.73 (d 1H, J=2.28 Hz), 6.51 (d 1H, J=2.28 Hz), 7.68 (d 2H J=8.40 Hz), 7.73 (d 2H J=8.40 Hz).
^{13}C NMR ($CDCl_3$) δ = 31.01, 65.01, 76.84, 78.30, 111.62, 118.25, 128.51, 132.79, 140.54, 169.73.
(±)-1-(4Methylphenyl)-2-propyn-1-chloroacetate (±)-61b:
Synthetic method 7.27.
^{1}H-NMR (200 MHz, $CDCl_3$) δ = 2.47 (s 3H), 2.74 (s1H), 4.12 (dd 2H, J=4.9 Hz, J=7.2 Hz), 6.52 (s 1H), 7.26 (d2H, J= 8.1 Hz), 7.49 (d2H, J= 8.1 Hz).
^{13}C NMR ($CDCl_3$) δ = 21.38, 40.95, 67.29, 76.58, 79.88, 128.01, 129.64, 132.88, 139.73, 166.31.
IR (film) cm^{-1} = 3090, 2120, 1780, 1760, 1520.
GC-MS = 218 M^+ (18%), 128 (100%).
MP= oil
(*S*)-(-)-1-(4-Methylphenyl)-2-propyn-1-chloroacetate (*S*)-(-)-61b:
Synthetic method 7.28.2
$[\alpha]^{20}_D$ - 23.3 (*c* 1.12, $CHCl_3$). 97.8% ee .
Physical and spectral data were identical to those described below for

the racemate **(±)-61 b.**

(±)-1-(4-Fluorophenyl)-2-propyn-1-chloroacetate (±)-61c:

Synthetic method 7.27.

^{1}H-NMR (200 MHz, $CDCl_3$) δ = 2.77 (d 1H, J= 2.25 Hz), 4.11 (dd 2H, J=5.1Hz, J=10.8 Hz), 6.51 (d 1H, 2.25 Hz), 7.11 (t 2H, J=6.66 Hz), 7.57 (m 2H).

^{13}C NMR ($CDCl_3$) δ = 38.94, 66.63, 76.80, 79.28, 116.06, 130.12, 131.76, 145.65, 162.19, 164.67, 166.25.

IR (film): ν cm^{-1}= 3290, 2980, 2120, 1780-1740,1610.

MP= oil.

(*S*)-(-)-1-(4-Fluorophenyl)-2-propyn-1-chloroacetate (*S*)-(-)-61c:

Synthetic method 7.28.2

$[\alpha]^{20}_{D}$ - 11.8 (*c* 1.01, $CHCl_3$). 96.8% ee .

Physical and spectral data were identical to those described below for the racemate **(±)-61c.**

(±)-1-(4-Cyanophenyl)-2-propyn-1-chloroacetate (±)-61e:

Synthetic method 7.27.

^{1}H-NMR (200 MHz, $CDCl_3$) δ = 2.80 (d 1H, J=2.34 Hz), 4.14 (m 2H), 6.56 (d 1H, J=2.34 Hz), 7.70 (d 2H, J=8.11 Hz), 7.75 (d 2H, 8.51 Hz).

^{13}C NMR ($CDCl_3$) δ = 40.65, 66.25, 76.84, 78.30, 113.62, 118.23, 128.51, 132.80, 140.58, 166.10.

IR (CHCl3): ν cm^{-1} = 3290, 2220, 2120, 1740,1620, 1510.

MP= 61-62 °C.

(*S*)-(-)-1-(4-Cyanophenyl)-2-propyn-1-chloroacetate (*S*)-(-)-61e:

Synthetic method 7.28.2

$[\alpha]^{20}_{D}$ - 31.3 (*c* 0.98, $CHCl_3$). 96.6% ee .

Physical and spectral data were identical to those described below for the racemate **(±)-61e.**

(±)-1-(3-Methylphenyl)-2-propyn-1-chloroacetate (±)-61h:

Synthetic method 7.27.

^{1}H-NMR (200 MHz, $CDCl_3$) δ = 2.42 (s 3H), 2.74 (d 1H, J=2.15 Hz), 4.13 (dd 2H, J= 6.6Hz; J=15.10 Hz), 6.52 (d 1H, J=2.15 Hz), 7.24 (d 1H J=7.6 Hz), 7.39 (m 3H).

^{13}C NMR ($CDCl_3$) δ = 21.94, 40.94, 67.40, 76.41, 79.58, 125.05,

128.61, 128.87, 130.39, 135.66, 138.81, 166.28.
IR (film): __cm^{-1}= 3290, 2135, 1785,1740,1610.
GC-MS = 222 M^+ (18%), 128 (100%).
MP= oil

(*S*)-(-)1-(3-Methylphenyl)-2-propyn-1-chloroacetate (*S*)-(-)-61h:

Synthetic method 7.28.2
$[\alpha]^{20}_D$ - 13.9 (*c* 0.84, $CHCl_3$). 99.2% ee .
Physical and spectral data were identical to those described below for the racemate **(±)-61 h.**

(±)-1-(3-Fluorophenyl)-2-propyn-1-chloroacetate (±)-61i:

Synthetic method 7.27.
^{1}H-NMR (200 MHz, $CDCl_3$) δ = 2.77 (d 1H, J=2.22 Hz), 4.15 (m 2H), 6.53 (d 1H; 2.22 Hz), 7.13 (m 1H), 7.36 (m 3H).
^{13}C NMR ($CDCl_3$) = 40.79, 66.48, 78.89, 115.11, 116.72, 123.56, 130.61, 161.73, 164.19, 166.19.
IR (film): ν cm^{-1}= 2980, 2135, 1745,1590.
MP= oil.

(*S*)-(-)1-(3-Fluorophenyl)-2-propyn-1-chloroacetate (*S*)-(-)-61 i:

Synthetic method 7.28.2
$[\alpha]^{20}_D$ - 5.3 (*c* 1.33, $CHCl_3$). 99.4% ee .
Physical and spectral data were identical to those described below for the racemate **(±)-61 i.**

1-(2-Methylphenyl)-2-propyn-1-chloroacetate (±)-61 l:

Synthetic method 7.27.
^{1}H-NMR (200 MHz, $CDCl_3$) δ = 2.48 (s 3H), 2.73 (d 1H, J=2.2Hz), 4.15 (m2H), 6.67 (d 1H, J=2.2Hz), 7.36-7.24 (m 3H), 7.66 (d 1H, J=7.82).
^{13}C NMR ($CDCl_3$) δ = 19.85, 40.84, 65.44, 76.44, 79.37, 126.57, 128.25, 129.61, 131.11, 133.87, 166.21.
IR (film): ν cm^{-1}= 3290, 2120, 1770,1730.
MP= oil.

(*S*)-(+)1-(2-Methylphenyl)-2-propyn-1-chloroacetate (*S*)-(+)-61 l:

Synthetic method 7.28.2
$[\alpha]^{20}_D$ + 16.2 (*c* 1.25, $CHCl_3$). 94.0% ee .

Physical and spectral data were identical to those described below for the racemate **(±)-61 b.**

1-(2,4-Dichlorophenyl)-2-propyn-1-chloroacetate (±)-61m:

Synthetic method 7.27.

^{1}H-NMR (200 MHz, $CDCl_3$) δ = 2.77 (d 1H, J=2.21 Hz), 4.14 (m 2H), 6.78 (d 1H, J=2.21 Hz), 7.36 (d 2H, J=8.51 Hz), 7.46 (s 1H), 7.77 (d 1H, J=8.51 Hz).

MP= oil.

(2'-HydroxyPhenyl)-2-propyn-1-phenyl-1-ol (±)-62.

Synthetic method 7.35

^{1}H NMR ($CDCl_3$) δ =2.90 (s, 1H), 5.65 (s, 1H), 6.85 (m,3H), 7.32 (m,4H), 7.68 (m, 2H).

^{13}C NMR ($CDCl_3$) δ= 65.165, 81.590, 98.845, 108.809, 115.346, 120.174, 126.708, 128.568, 128.722, 130.589, 131.951, 140.068, 157.028.

^{13}C J MOD NMR ($CDCl_3$) δ= (+)65.165, (-)81.590, (-)98.845, (-) 108.809, (+)115.346, (+)120.174, (+)126.708, (+)128.568, (+)128.722, (+)130.589, 131.951, (-) 140.068, (-)157.028.

GC-MS M^+ 224(100%), M^+ -OH 207 (80%).

M.P.: oil.

(±)-(4'-Methylphenyl)-2-benzo[b]furanyl carbinol (±)-63a:

Synthetic method 7.30

^{1}H NMR ($CDCl_3$) δ= 2.35 (s,3H), 2.44 (d, 2H, 4.5Hz), 5.90 (d, 2H, 4.5Hz), 6.52 (s,1H), 7.27-7.14 (m 5H), 7.51-7.34 (m 3H);

^{13}C NMR ($CDCl_3$) δ= 21.076, 70.388, 103.729, 111.224, 121.002, 122.673, 124.078, 126.706, 128.032, 129.150, 137.392, 137.957, 155.003, 158.743;

^{13}C J MOD NMR ($CDCl_3$) δ= (+)21.076, (+)70.388, (+)103.729, (+)111.224, (+)121.002, (+)122.673, (+)124.078, (+)126.706, (-) 128.032, (+)129.150, (-)137.392, (-)137.957, (-)155.003, 1(-) 58.743;

GC-MS M^+ 238 (100%); M^+-OH 221.

(*R*)-(-)-4'-Methylphenyl- 2 benzo[b]furanyl carbinol (*R*)-(-)-63a:

Synthetic method 7.30

$[\alpha]^{20}_D$ -8.05, (*c* 1.6 $CHCl_3$); 99.0% ee (Chiracel OD n-hexane/isopropanole), rt **(*S*)-(+)-2b** 55.28 min., **(*R*)-(-)-2b** 59.44

min.

Physical and spectral data were identical to those described above for the racemate (±)-63a.

(±)-(3'-Methylphenyl)-2 benzo[b]furanyl carbinol (±)-63b:

Synthetic method 7.30.

1H NMR (CDCl3) δ= 2.39 (s,3H), 2.53 (d, 4.3 Hz, 1H), 5.93 (d, 4.3 Hz, 1H), 6.57 (s, 1H), 7.32-7.18 (m,6H), 7.72-7.45 (m,2H).

13C NMR ($^{CDCl}3$) δ= 21.294, 70.509, 103.744, 111,$_{21}$9, 121.000, 122.664, 123.816, 124.075, 127.358, 128.003, 128.356, 128.957, 138.136, 140.211, 154.980, 158.653.

13C J MOD NMR (CDCl3) δ= (+)21.294, (+)70.509, (+)103.744, (+)111,219, (+)121.000, (+)122.664, (+)123.816, (+)124.075, (+)127.358, (-) 128.003, (+)128.356, (+)128.957, (-)138.136, (-)140.211, (-)154.980, (-) 158.653.

GC-MS M^+ 238(100%), M^+ -OH 221.

M.P: oil

(*R*)-(-)-(3'-Methylphenyl)-2benzo[b]furanyl carbinol (*R*)-(-)-63b:

Synthetic method 7.30.

$[\alpha]^{20}_D$ -3.55, (*c* 2.81 $CHCl_3$), 98.11% ee (Chiracel OD n-hexane/isopropanole), (S)-(+)-2d rt= 15.38 min., (R)-(-)-2d rt = 17.86 min.

Physical and spectral data were identical to those described above for the racemate (±)-63b.

(±)-3'-Fluorophenyl-2 benzo[b]furanyl carbinol (±)-63c:

Synthetic method 7.30.

1H NMR (CDCl3) δ= 2.55 (d,4.2Hz,1H), 5.94 (d,4.2Hz,1H) 6.54 (s,1H), 7.37-6.98 (m,4H), 7.53-7.40 (m, 3H).

13C NMR (CDCl3) δ= 69.745d, 104.097, 111.233, 113.435, 113878, 114.794, 115,215, 121.144, 122.236d, 124.390, 127.802, 130.014d, 142.757d, 154.979, 157.728, 160.334, 165.226.

13C J MOD (CDCl3) NMR (+)69.745d, (+)104.097, (+)111.233, (+)113.435, (+)113878, (+)114.794, (+)115,215, (+)121.144, (+)122.236d, (+)124.390, (-)127.802, (+)130.014d, (-)142.757d, (-) 154.979, (-)157.728, (-)160.334, (-)165.226.

GC-MS M+ 242(100%), M+ -OH 225.

M.P: oil

(R)-(+)-3'-Fluorophenyl-2 benzo[b]furanyl carbinol (R)-(+)-63c:

Synthetic method 7.30.

[20D +6.23, (c 2.41 CHCl3) 98.50% ee (Chiracel OD n-hexane/isopropanole), **(S)-(-)-2e** rt=73.36 min., **(R)-(+)-2e** rt=83.54 min.

Physical and spectral data were identical to those described above for the racemate **(±) 63c**.

(±)-2'-Methylphenyl-2benzo[b]furanyl carbinole (±)-63d:

Synthetic method 7.30.

1H NMR (CDCl3) δ= 2.02 (s,1H), 2.48 (d,4.2Hz, 1H), 6.13 (d,4.2Hz, 1H), 6.40 (s,1H), 7.27-7.15 (m, 5H), 7.57-7.42 (m,3H).

^{13}C NMR ($CDCl_3$) δ= 18.933, 67.475, 104.130, 111.253, 121.037, 122.718, 124.184, 126.219, 126.380, 128.083, 130.445, 135.512, 138.288, 155.036, 158.217.

^{13}C J MOD NMR ($CDCl_3$) δ= (+)18.933, (+)67.475, (+)104.130, (+)111.253, (+)121.037, (+)122.718, (+)124.184, (+)126.219, (+)126.380, (-) 128.013, (+)128.083, (+)130.445, (-)135.512, (-)138.288, (-)155.036, (-) 158.217.

GC-MS M^+ 238(100%), M^+ -OH 221.

M.P: oil

(*R*)-(-)-2'-Methylphenyl-2-benzo[b]furanyl carbinol (*R*)- (-) 63d:

Synthetic method 7.30.

$[\alpha]^{20}_D$ -32.53, (*c* 1.076 $CHCl_3$) 93.26% ee (Chiracel OD n-hexane/isopropanole), **(*S*)-(+)-2f** rt=30.56 min., **(*R*)-(-)-2f** rt=33.92 min.

Physical and spectral data were identical to those described above for the racemate **(±) 63d.**

(±)-Phenyl-2-(*N*-mesyl)indolyl carbinol (±)-64a:

Synthetic method 7.33:

^{1}H NMR ($CDCl_3$) δ= 3.02 (s,3H), 3.24 (d, 5.7 Hz,1H), 6.27 (s,1H), 6.37 (d,5.7Hz,1H), 7.51-7.24 (m,8H), 7.98 (7.56Hz,1H).

^{13}C NMR ($CDCl_3$) δ= 40.772, 69.230, 111.256, 113.9912, 121.348, 123.677, 125.083, 127.122, 128.097, 128.351, 128.568, 137.134, 140.767, 143.037.

^{13}C J MOD NMR ($CDCl_3$) δ= (+)40.772, (+)69.230, (+)111.256, (+)113.912, (+)121.348, (+)123.677, (+)125.083, (+)127.122, (+)128.097, (+)128.351,(-)128.568, (-)137.134, (-)140.767, (-)143.037.

GC-MS M^+ 301(75%), M^+ -OH 284 (30%), M^+ -Ms 221 (100%)

M.P: 131.7-131.9 (DCM-Petroleum ether)

(*S*)-(+)-Phenyl-2-(N-mesyl)indolyl carbinol (*S*)-(+)-64a:

Synthetic method 7.33

$[\alpha]^{20}_D$ +22.3, (*c* 2.02 $CHCl_3$) 96.74% ee (Chiracel OD n-hexane/isopropanole), **(*R*)-(-)-64a** rt=12.69 min., **(S)-(+)-64a** rt=15.13 min.

(±)-4'-Methylphenyl-2-(N-mesyl)indolyl carbinol (±)-64b:

Synthetic method 7.33

^{1}H NMR ($CDCl_3$) δ= 2.37 (s,3H), 3.01 (s,3H), 3.15 (d,5.4 Hz, 1H), 6.29 (s,1H), 6.33 (d,5.4 Hz, 1H), 7.40-7.17 (m,5H), 7.45 (d,8.49 Hz, 1H), 7.98 (d,8.64 Hz, 1H).

^{13}C NMR ($CDCl_3$) 21.106, 40.735, 69.040, 110.950, 113,859, 121.257, 123.576, 124.924, 127.036, 128.553, 128.982, 137.095, 137.786, 137.904, 143.205.

^{13}C J MOD NMR ($CDCl_3$) δ= (+)21.106, (+)40.735, (+)69.040, (+)110.950, (+)113,859, (+)121.257, (+)123.576, (+)124.924, (+)127.036, (-)128.553, (+)128.982, (-)137.095, (-)137.786, (-)137.904, (-)143.205.

GC-MS M^+ 315(56.5%), M^+ -OH 298 (20%), M^+ -Ms 235 (100%)

M.P: 131.0-131.6 (DCM-Petroleum ether).

(*R*)-(-)-4'Methylphenyl-2-(N-mesyl)indolyl carbinol (*R*)-(-)-64b:

Synthetic method 7.33

95.97% ee (Chiracel OD n-hexane/isopropanole), **(*R*)-(-)-64b** rt=12.64 min., **(*S*)-(+)-64b** rt=16.08 min.

(±)-4'-Fluorophenyl-2-(N-mesyl)indolyl carbinol (±)-64c:

Synthetic method 7.33.

^{1}H NMR ($CDCl_3$) δ= 2.98 (s,3H), 3.30 (d,5.38 Hz, 1H), 6.29 (s,1H), 6.34 (d,5.38 Hz, 1H), 7.05 (m,2H), 7.55-7.21 (m,6H).

GC-MS M^+ 319(63%), M^+ -OH 302 (12%), M^+ -Ms 239 (100%)

M.P: oil.

(*R*)-(-)-4'-Fluorophenyl-2-(N-mesyl)indolyl carbinol (*R*)-(-) -64c:

Synthetic method 7.33

98.20% ee (Chiracel OD n-hexane/isopropanole), **(*R*)-(-)-64c** rt=33.14 min., **(*S*)-(+)-64c** rt=39.78 min.

(3-Methylphenyl)-2-(N-mesyl)indolyl carbinol (±)-64e:

Synthetic method 7.33.

^{1}H NMR ($CDCl_3$) δ= 2.36 (s,3H), 3.03 (s,3H), 3.17 (d,5.5Hz,1H), 6.27 (s,1H), 6.34 (d,5.5Hz,1H),7.35-7.14 (m,6H), 7.46 (d,8.1Hz,1H), 7.98 (d, 8.0Hz,1H).

^{13}C NMR ($CDCl_3$) δ= 21.386, 40.770, 69.211, 111.236, 113.897, 121.313, 123.639, 124.165, 125.024, 127.719, 128.218, 128.582, 128.823, 137.115, 138.049, 140.752, 143.102.

^{13}C J MOD NMR ($CDCl_3$) δ = 21.386, ___40.770, ___69.211, ___111.236, ___113.897, ___121.313, ___123.639, ___124.165, ___125.024, ___127.719, ___128.218, ___128.582, ___128.823, ____137.115, ___138.049, ___140.752, ___143.102.

GC-MS M^+ 315(56.34%), M^+ -OH 298 (12%), M^+ -Ms 235 (100%)

M.P: 119.4-120.4 (DCM-Petroleum ether).

(*R*)-(-)-(3'-Methylphenyl)-2-(N-mesyl)indolylcarbinol (*R*)-(-)-64e:

Synthetic method 7.34.

$[\alpha]^{20}_{D}$ -16.7, (*c* 1.45 $CHCl_3$) 99.12% ee (Chiracel OD n-hexane/isopropanole), **(*R*)-(-)-64e** rt=10.76 min., **(*S*)-(+)-64e** rt=13.16 min.

(±)-3'-Fluorophenyl-2-(*N*-mesyl)indolyl carbinol (±)-64f:

Synthetic method 7.34

^{1}H NMR ($CDCl_3$) δ = 2.98 (s,3H), 3.32 (d,5.38Hz, 1H), 6.21 (s,1H), 6.34 (d,5.38Hz, 1H), 7.53-6.98 (m,7H), 7.98 (d, 8.5 Hz,1H).

GC-MS M^+ 319(46.34%), M^+ -Ms 239 (100%)

M.P: 109.4-110.6 (DCM-Petroleum ether).

(*R*)-(-)-3'-Fluorophenyl-2-(N-mesyl)indolyl carbinol (*R*)-(-)-64f:

Synthetic method 7.34

$[\alpha]$ $^{20}_{D}$-22.46, (*c* 1.50 $CHCl_3$) 99.55% ee (Chiracel OD n-hexane/isopropanole), **(*R*)-(-)-64f** rt=12.50 min., **(*S*)-(+)-64f** rt=16.00 min.

(±)-2'-Methylphenyl-2-(N-mesyl)indolyl carbinol (±)-64g:
Synthetic method 7.34.
^{1}H NMR ($CDCl_3$) δ = 2.24(s,3H), 3.18 (s,3H), 6.58 (d, 5.3 Hz,1H), 7.47-7.18 (m,6H), 7.63 (m,1H) 8.03 (d, 8.8 Hz).
^{13}C NMR ($CDCl_3$) δ= 18.903, 40.898, 65.742, 110.980, 113.933, 121.342, 123.651, 125.087, 126.065, 126.200, 127.921, 128.582, 130.308, 135.395, 137.192, 139.229, 142.456.
^{13}C J MOD NMR ($CDCl_3$) δ= (+)18.903, (+)40.898, (+)65.742, (+)110.980, (+)113.933, (+)121.342, (+)123.651, (+)125.087, (+)126.065, (+)126.200, (+)127.921, (-) 128.582, (+)130.308, (-) 135.395, (-)137.192, (-)139.229, (-)142.456.
GC-MS M^+ 315(32.34%),, M^+ -Ms 235 (100%)
M.P: 142.4-144.4 (DCM-Petroleum ether).
(*R*)-(-)-2'-Methylphenyl-2-(N-mesyl)indolyl carbinol (*R*)-(-)-64g:
Synthetic method 7.34.
93.21% ee (Chiracel OD n-hexane/isopropanole), **(*R*)-(-)-64g** rt=54.69 min., **(*S*)-(+)-64g** rt=63.38 min.
(±)-1-Phenyl-3-(2'aminophenyl)-2-propyn-1-ol (±)-65:
Synthetic method 7.32
^{1}H NMR ($CDCl_3$) δ= 5.74 (s,1H), 6.66 (m,2h), 7.13 (t, 7.8Hz, 1H), 7.45-7.26 (m, 4H), 7.65 (d, 7.8 Hz, 2H).
^{13}C NMR ($CDCl_3$) δ= 64.733, 83.047, 94.450, 107.241, 114.539, 117.850, 126.548, 128.080, 128.449, 129.738, 132.068, 140.733, 147.835.
^{13}C J MOD NMR ($CDCl_3$) δ= (+)64.733, (-)83.047, (-)94.450, (-) 107.241, (+)114.539, (+)117.850, (+)126.548, (+)128.080, (+)128.449, (+)129.738, (+)132.068, (-)140.733, (-)147.835.
M.P: oil.
***N*-Mesyl-2-iodoaniline 66**:
Synthetic method 7.33:
^{1}H NMR ($CDCl_3$) δ= 2.98 (s, 3H), 6.61 (s,1H), 6.91 (t, 7.9 Hz, 1H), 7.36 (t, 7.9 Hz, 1H), 7.63 (d, 7.9 Hz, 1H), 7.81 (d, 7.9 Hz, 1H).
GC-MS M^+ 297(100%), M^+ -Ms 218(75%).
(±)-1-Phenyl-3-(2'acetoxyphenyl)-2-propyn-1-ol (±)-71.
Synthetic method 7.36

^{1}H NMR ($CDCl_3$) δ = 2.13 (s,3H), 2.53 (s,3H), 5.65 (s,1H), 7.45-6.90 (m,9H).

^{13}C NMR ($CDCl_3$) δ= 20.551, 64.772, 81.287, 94.138, 116.661, 122.169, 125.860, 126.612, 128.281, 1288.556, 129.734, 133.045, 140.617, 151.727, 169.177.

^{13}C J MOD NMR ($CDCl_3$) δ= (+)20.551, (+)64.772, (-)81.287, (-) 94.138, (-)116.661, (+)122.169, (+)125.860, (+)126.612, (+)128.281, (+)1288.556, (+)129.734, (+)133.045, (-)140.617, (-)151.727, (-) 169.177.

GC-MS M^+ 266(100%), M^+ -OH 249 (39%), M^+ -Ac 223 .

IR(film) ν cm^{-1}= 3500, 2900, 1760.

M.P. :oil

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