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Dynamic resolution of α-substituted dihydrocinnamic aldehydes. A new asymmetric synthesis of pharmaceutically important amine building blocks.

Experimental Master Thesis

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Abstract

Crystallization-induced diastereoisomer transformation (CIDT) was successfully employed in the enantioselective synthesis of 2-alkyl-3-aryl-propan-1-amines. These products are seen as potentially useful building blocks in the field of asymmetric organic chemistry, notably for pharmaceutically relevant compounds. The procedure was based on a recently reported protocol for deracemization of dihydrocinnamic aldehydes in which enantiomerically enriched 1-(amino(phenyl)methyl)naphthalen-2-ol (Betti base) is employed as a resolving agent. Additionally, fenpropimorph, a biologically active substance which contains the 2-alkyl-3-aryl-propan-1-amine moiety was synthetized, as an attempt to assess the usefulness of the enantiomerically enriched amines.

Summary

1 Introduction

1.1 Chirality and its relevance to biological systems

Chirality is a spatial concept with a wide range of implications in science. By definition, an object is said is to be chiral when it cannot be superimposed onto its mirror image. Analogously, in chemistry, mirror image molecules that cannot be reciprocally superimposed by translation and rotation symmetry operations are chiral. These pairs of mirror image molecules are called enantiomers and constitute one of the main concerns in the field of stereochemistry.

The capacity of enantiomers to rotate plane-polarized light was known even before their relation was comprehended. Some substances crystallize as enantiomerically pure crystals. In such cases, the chirality might be perceivable macroscopically and the mirror image crystals sorted by hand. This is what Louis Pasteur did in a series of experiments that greatly contributed to the debate on molecular asymmetry and early development of stereochemistry. By noticing the handedness and laboriously sorting the crystals of tartrate salts which deposited in the bottom of wine casks during fermentation, Pasteur prepared separate solutions of enantiomorphic crystals and verified their property of rotating plane-polarized light with the same intensity, but in opposite directions.[1] Nearly contemporary debates on the geometry of carbon compounds would then ultimately lead to the acknowledgment of sp^3 carbons bound to four different atoms or groups of atoms, or asymmetric carbons, as the main source of chirality in organic chemistry.

Enantiomers present identical physical and chemical behavior, unless they are subjected to an interaction with another chiral medium. Biological systems are essentially chiral environments. Amino acids and saccharides, for instance, are most predominantly found in one of its enantiomeric forms in nature. Therefore, the interaction of chiral molecule with a given organism may greatly differ from that of its enantiomer pair. For that reason, the control over the stereochemistry of biologically active compounds if of particular importance. The distinct interactions of enantiomers *in vivo* may be perceived, for instance, in flavor, odor, toxicity and drug effectiveness. Perhaps the most well-known example of distinct biological activity between a pair of enantiomers is that of thalidomide, a

sedative and antiemetic drug. Among other uses, thalidomide was widely prescribed to pregnant women to prevent morning sickness in the late 1950's. Until its side effects became known and it was finally withdrawn from the market, thousands of children were born with birth defects due to its use. The teratogenicity of thalidomide has been attributed to its (*S*)-enantiomer.

Citalopram a *selective serotonin-reuptake inhibitor* antidepressant, is marketed in both its racemic form and as the (*S*)-enantiomer (escitalopram), to which the therapeutic activity is mainly attributed. The (*R*)-enantiomer is not known for any specific side effects, but even in such cases both technical and pharmacological aspects may justify the development of enantiomerically pure formulations. First, the use of racemic mixture in which only one of its enantiomers is active represents a considerable waste of raw material. And second, pharmaceuticals are subjected to long term post-marketing research, which occasionally unveils previously unknown side effects and may ultimately lead to the withdrawal of a drug from the market.

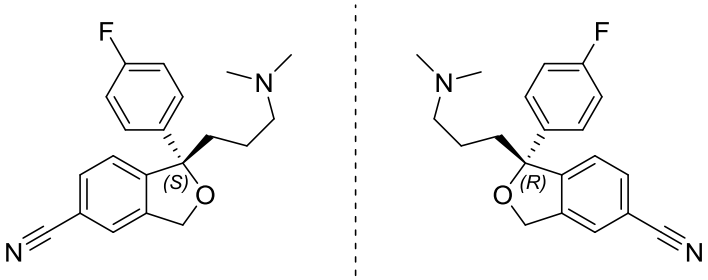


Figure 1. Citalopram enantiomers

1.2 Separation of enantiomers

Obtaining enantiomerically pure compounds from achiral or racemic precursors can be technically challenging and/or economically impracticable. This is currently one of the most important fields of research in organic chemistry and it has shown great advance in the past couple of decades. The methods through which it can be accomplished can be primarily divided into resolutions methods and stereoselective syntheses. Sometimes the underlying concepts overlap into hybrid processes.[2]

1.2.1 Resolution methods

A resolution consists of separating a mixture of enantiomers into its constituents and it can be further divided into several methods. *Total spontaneous resolution* consists on the separation of enantiomers with no conversion into diastereoisomeric states. It is conceptually simple, but of limited practical application. Very specific criteria must be met, including intrinsic properties and experimental conditions. Some enantiomers crystallize as conglomerates, mechanical mixtures of enantiomerically pure crystals. This phenomenon can be pronounced to the point that enantiomorphic crystals are macroscopically sortable. More often, however, satisfactory separation is not so easily achieved. In such cases, preferential crystallization may be induced, for instance, by seeding a saturated solution of a racemate with one of its enantiomers. A conglomerate like crystallization, however, is equally necessary.[2]

Nevertheless, enantiomers are most often resolved through their conversion into diastereoisomers via reaction with a chiral substance.[2] Stereoisomers are molecules that present the same molecular formula and connectivity between atoms, but a different three-dimensional arrangement. Among them, those which are not superimposable mirror images are defined as diastereoisomers. For instance, a molecule with two asymmetric carbons as the only stereogenic elements and no plane of symmetry presents four stereoisomers (Figure 2). In this case, each pair of molecules will present particular relationship. If both asymmetric centers are inverted, the molecules will be mirror images and thus enantiomers. On the other hand, if only one of the chiral centers is inverted, their relation will be diastereoisomeric.

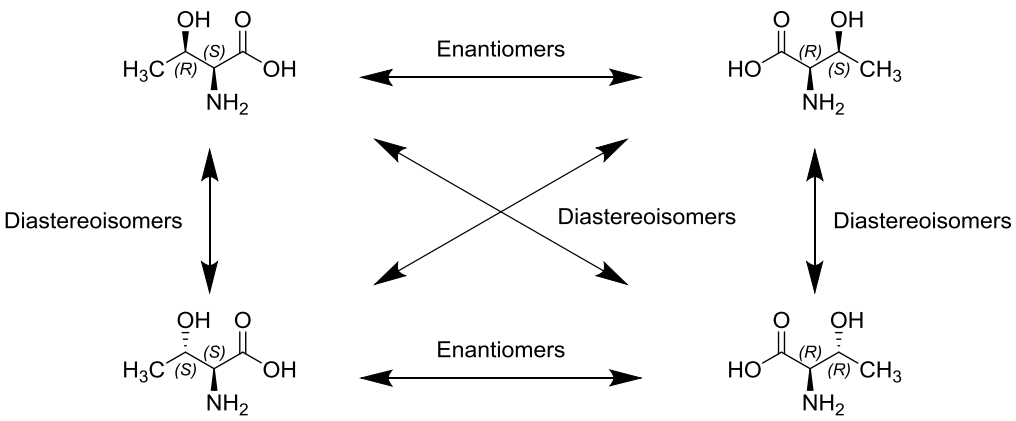


Figure 2. Stereoisomers of the amino acid threonine and their isomeric relationship.

Even though diastereoisomers may present similar physical and chemical properties, they are for all purposes different molecules. That is precisely the reason why the conversion of a pair of enantiomers into diastereoisomers renders them more easily separable. The reaction between a racemic mixture of and an enantiomerically pure substance, for example, generates two or more diastereoisomers. This substance is called resolving agent and its choice should be based, among other factors, on the possibility of recovery of the initial product. The separation between diastereoisomers can rely, in principle, in various physical or chemical properties. The majority of resolutions mediated by diastereoisomers, however, are based on solubility differences.[2]

Enantiomers can be alternatively separated by kinetic resolution. In this case, the reaction rates between a pair of enantiomers and a chiral reactant must be significantly different. The desired product is more commonly the one with the lower reaction rate, being directly recovered in its enantiomerically enriched form. Nonetheless, it is sometimes possible to recover its enantiomeric pair from the reaction product, which is a factor that should be considered if both are potentially useful.

Chromatographic separation through high performance liquid chromatography (HPLC) or gas chromatography (GC) can also be employed. The control over several chromatographic parameters makes it a versatile technique. However, the scaling-up costs for preparative purposes, especially due to the need for chiral stationary phases, is one of the main disadvantages of this technique.

1.2.2 Stereoselective synthesis

Synthetic routes which produce exclusively or predominantly one among related stereoisomers fit the concept of stereoselective synthesis. When an enantiomerically enriched product is desired, a chiral element must be present at some stage of the process. The first approach is to use enantiomerically enriched substances as reactants or building blocks for more complex ones. The asymmetric elements are either conserved or inverted and avoiding racemization throughout the synthetic pathway should be a major concern. The chiral reactants can be naturally available or obtained from previously resolved racemic mixtures.

The second approach is asymmetric catalysis. The relation between two transition states involving a pair of enantiomers and a chiral catalyst are essentially diastereoisomeric. Therefore, they present different energies, which ideally allows kinetic control over the reactions (Figure 3).

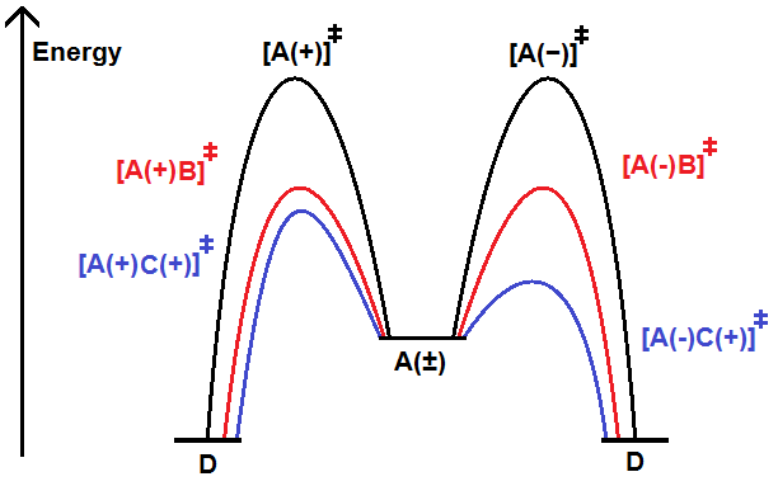


Figure 3. General vs. asymmetric catalysis.
A: reactant as racemic mixture; B: non-chiral catalyst; C: enantiopure chiral catalyst; D: reaction product

As in general catalysis, substoichiometric quantities of the catalyst are used. The nature of the catalyst may vary and the methods can be further divided into organocatalysis, biocatalysis and organometallic catalysis. The first employs small chiral organic molecules, either natural or synthetic. Asymmetric biocatalysis, in its turn, relies on the ability of biomolecules, notably enzymes, which are chiral catalysts *par excellence*, to induce stereoselective synthesis. The latter method employs chiral organometallic complexes as asymmetric catalysts.

1.2.3 Dynamic resolutions and *Crystallization Induced Diastereoisomer Transformation* (CIDT)

Classical resolutions are not asymmetric methods. In other words, they are limited to a 50% yield of a given enantiomer. Dynamic resolutions, on the other hand, allow the conversion of both enantiomers from a racemate into a single stereoisomer. These processes rely on the interconversion between optically labile molecules, either the enantiomers themselves or diastereoisomeric intermediate, and on a concomitant equilibrium displacement factor.

Crystallization-induced enantiomer transformation (CIET) is the dynamic variation of *total spontaneous resolution*. Therefore, the same constraints apply. The compound must crystallize as a conglomerate and very specific experimental conditions might be necessary. Enantiopure seeds, for instance, can be used to induce preferential crystallization and the concomitant interconversion of one enantiomer into its mirror-image in solution allows the resolution yield to surpass 50%. Nevertheless, CIET is of limited practical application, since approximately 90% of all chiral systems crystallize as racemic compounds.[3]

Crystallization-induced diastereoisomer transformation (CIDT), in its turn, is analogous to classic resolutions which rely on solubility differences of diastereoisomeric intermediates. An optically pure resolving agent is used to generate diastereoisomers from a racemic mixture. Being a dynamic resolution, however, the epimerization of the diastereoisomers allow their interconversion in solution. As the less soluble diastereoisomer precipitates, the soluble fraction of the more soluble one is continuously converted into its epimer.[4] This is the driving force that ultimately leads to a progressive diastereoisomeric enrichment of the precipitate (Figure 4).[2] The last step is the recovery of the desired enantiomer from its diastereoisomer derivative.

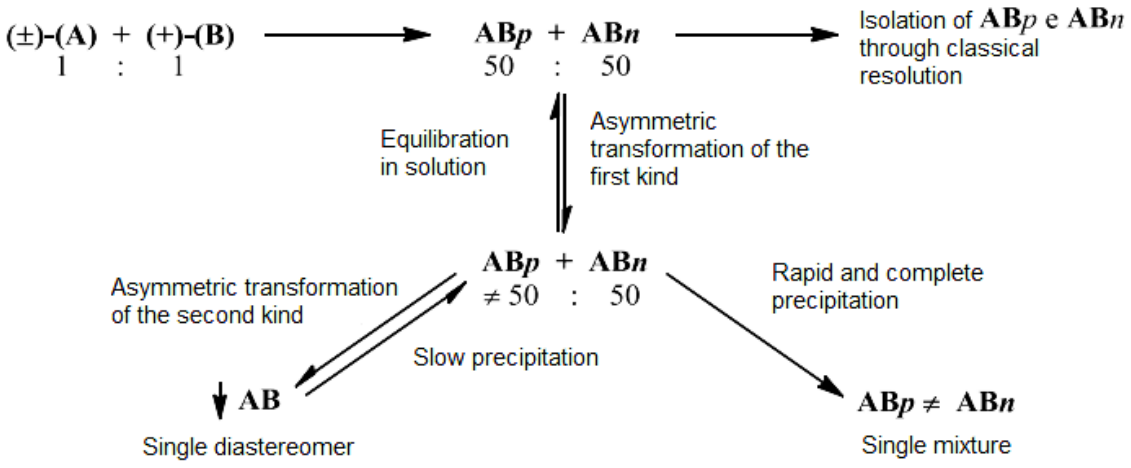


Figure 4. Asymmetric resolution; A: racemate; B: resolving agent

There are three main criteria that should be considered in the development of a CIDT method: establishing conditions that enable epimerization; finding a suitable resolving agent that is effective and stable under the epimerization

conditions; isolating and handling the product under conditions that prevent degradation.[5] The equilibration mechanisms include rotation around hindered bonds or formation and cleavage of activated bonds. It is worth noting, however, that many discoveries of CIDT processes remain fortuitous.[3]

Thorough reviews on CIDT and mechanisms of epimerization have been conducted.[3,5] Early examples often include the use of alkaloids as resolving agents. For instance, racemic indanone was successfully resolved into its (+)-enantiomer with brucine in 93% yield (Figure 5). In this case, the keto/enol interconversion is the underlying mechanism that leads to epimerization. There are many other examples in which the relative acidity of a carbon-hydrogen bond plays a role in CIDT.[3]

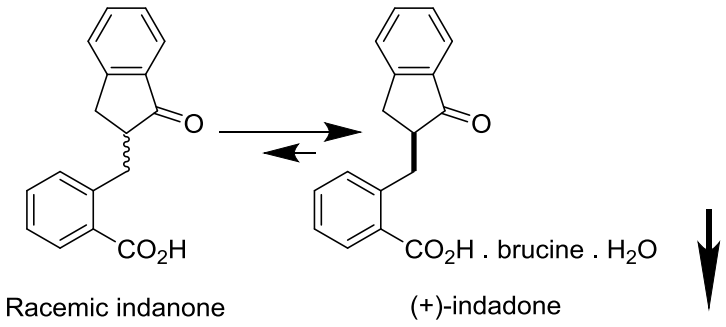


Figure 5. CIDT of indanone

1.3 The Betti base

The Betti base is an aminobenzylnaphthol, product of the a three-component condensation: β-naphthol, aryl aldehydes and ammonia. It is named after Mario Betti (1875-1942), who was responsible for its synthesis and early investigation of its properties, including as a resolving agent in asymmetric chemistry.[4,6]

The field of research concerning the use of the Betti base and its derivatives has been intensified in the last decade. Several applications have been reported, including, for instance, stereoselective reaction of organometallic reagents, preparation of *B*-chiral boronate complexes, separation of enantiomers and as an organocatalyst.[6] The straight forward synthesis and resolution of the Betti base along with its high reactivity makes it an interesting compound in the field of asymmetric organic chemistry.[7]

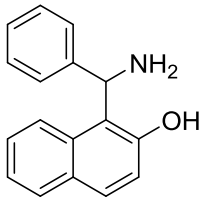
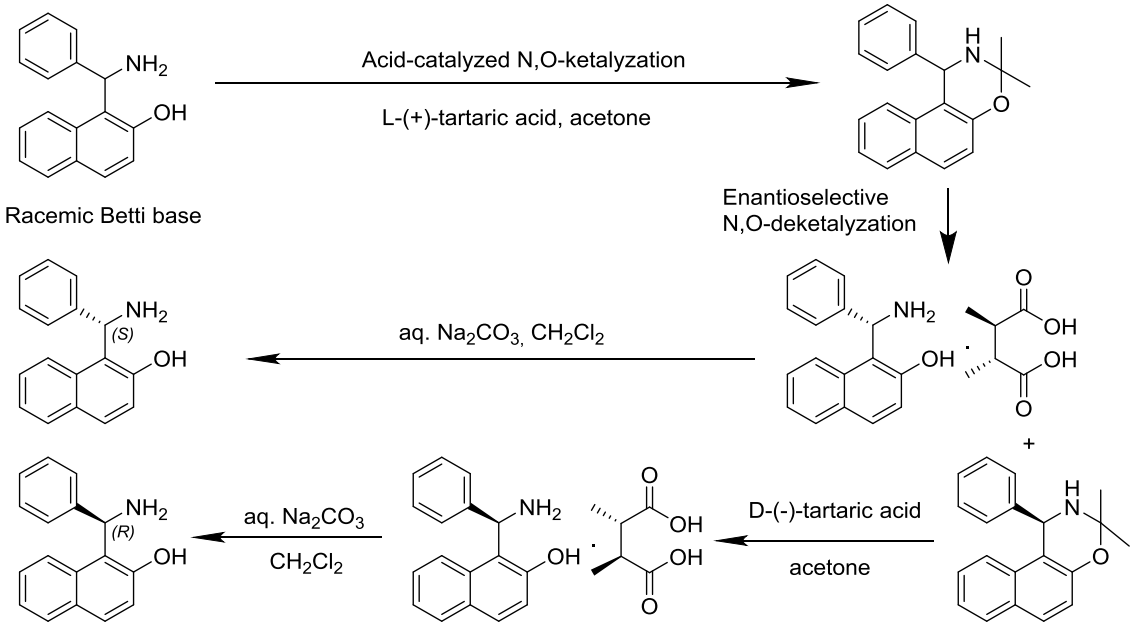


Figure 6. Betti base

Tartaric acid is often used to resolve the Betti base into its enantiomers. In a successful attempt to further improve the chemical and optical yield of the procedures which had been reported, Hu and co-workers established an efficient resolution of racemic Betti base, which relies on enantioselective *N*,*O*-deketalization of the racemic ketal in acetone solution.[7]

L-(+)-tartaric acid initially promotes an acid-catalyzed *N*,*O*-ketalization of the Betti base, leading to the formation of the racemic ketal. Then, as a chiral acidic reagent, it selectively leads to the *N*,*O*-deketalization of the (*S*)-Betti base enantiomer. Subsequently, the L-(+)-tartaric acid selectively captures the (*S*)-Betti base, precipitating it in its salt form. [7]

The (*R*)-Betti base, in its turn, is recovered from the filtrate as a *N*,*O*-ketal. Analogously, the use of D-(-)-tartaric acid allows the (*R*)-Betti base tartrate salt to be obtained from the ketal. Finally, both enantiomers may be obtained in high yield and enantiomeric excess from their respective tartrate salts, through neutralization and extraction.[7]



Scheme 1. Hu's kinetic resolution of the Betti base

1.4 Importance of amines in asymmetric organic chemistry

Amines are widely employed in the previously described methods for resolution of racemic mixtures or synthesis of enantiomerically enriched compounds. A well-known enantioselective synthesis by List and co-workers employing the amino acid proline as a chiral catalyst is an example of asymmetric aldol reaction.[8] Aminocatalysis is a whole field of study devoted to the application of amines as catalysts and to the investigation of the underlying mechanisms. Additionally, amines are often employed as resolving agents for acidic compounds, like in the previously mentioned example of indanone.[3]

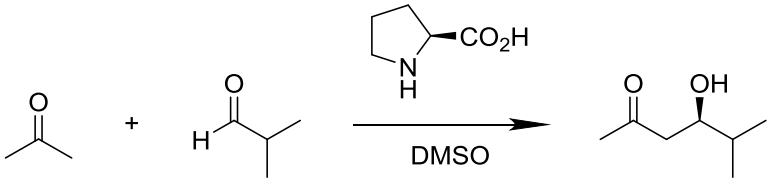


Figure 7. Asymmetric aldol reaction.

Enantiomerically enriched amines are equally useful in asymmetric synthesis as building blocks for more complex molecules. Souers and co-workers studied the affinity between 2-amino-8-alcoxy quinolines and melanine-concentrating hormone (MCH) receptors, envisaging their application as MCH antagonists. By synthetizing several structural analogs from three moieties and assessing their affinity to the MCH receptor, a pair of enantiomers was shown to have a 20-fold difference in binding.[9]

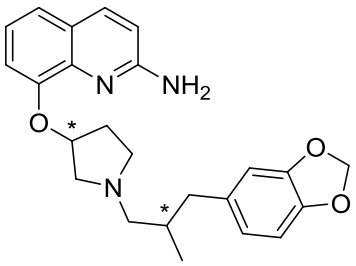


Figure 8. MCHr1 antagonist

2 Research Project

2.1 Acid promoted CIDT deracemization of dihydrocinnamic aldehydes

The research group in which the present work was developed has recently established a procedure for the deracemization of α-alkylated, α-epimerizable aldehydes of industrial interest, notably in perfumery, using 1-(aminobenzyl)-2-naphthol (Betti base) as a resolving agent.[4] This project was preceded by the work of Košmrlj and Weigel, who demonstrated that that (±)-2-ethylhexanal can be successfully converted into (*R*)-2-ethylhexanal (94% yield, er = 99 : 1) by CIDT with diastereoisomeric imines obtained with *trans*-(1*R*,2*R*)-6-nitro-1-aminoindan-2-ol.[10]

The condensation between the Betti base and aldehydes leads to the formation of 1,3-naphthoxazines which are subjected to an imine/enamine equilibrium. When a racemic α-alkylated aldehyde and a single Betti base enantiomer react, the resulting oxazine presents three stereogenic centers, one of which is defined.[4] Fülöp and co-workers studied the tautomeric equilibrium of the condensation products between Betti base derivatives and aromatic aldehydes. Through NOESY spectra, it was unequivocally shown that the *trans*-disposed configuration of the 2,6-diaryl substituents in the perhydro-1,3-oxazine ring is favored.[11]

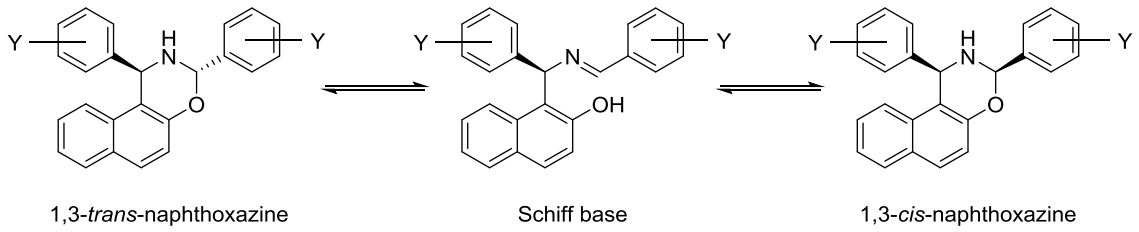


Figure 9. Tautomeric equilibrium of 2,6-diaryl-perhydro-1,3-oxazines

For this reason, two out of the three stereogenic centers of the condensation product between α-alkylated aldehydes and a single Betti base enantiomer may be considered as defined, for practical purposes. Therefore, the resulting equilibrium can be represented by two epimeric naphthoxazines, their corresponding imines and a common enamine intermediate (Figure 10).

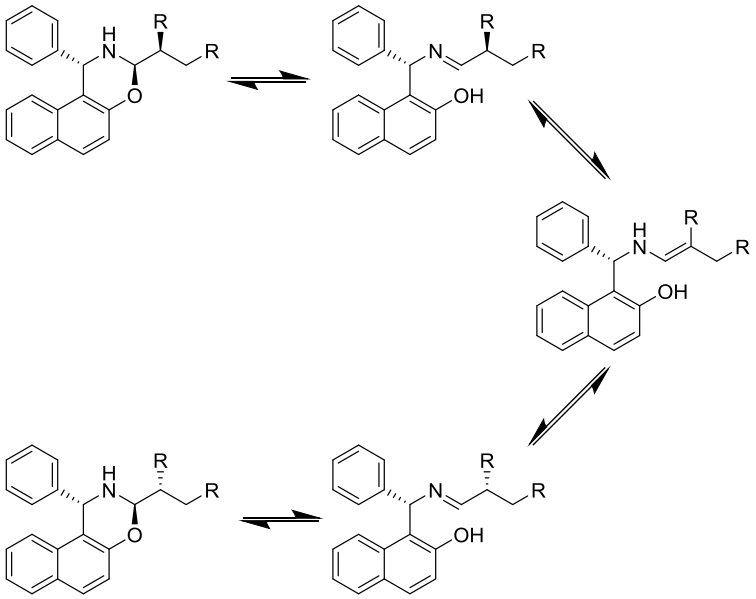


Figure 10. Imine/enamine equilibrium of naphthoxazines derived from Betti base and α-alkylated aldehydes

By applying experimental conditions which simultaneously allowed the interconversion of diastereoisomers and the preferential precipitation of one of them, and by using the Betti base as a resolving agent, racemic mixtures of five different dihydrocinnamic aldehydes were successfully resolved into their enantiomers. The procedure was so efficient that even when an indepently prepared diastereoisomerically enriched sample of the more soluble naphthoxazine (dr = 97.8 : 2.2) was employed, the less soluble naphthoxazine could be isolated by filtration in 95% yield and dr = 93 : 7, after 32 hours.[4]

The reactions were initially carried out with racemic aldehydes in methanol, leading to the precipitation of nearly quantitative 1:1 mixtures of the resulting diastereoisomers. The suspension of the mixtures in refluxing methanol did not have any impact on the diastereoisomeric ratio. Nevertheless, when the mixtures were suspended in 2.5% acetic acid in methanol and heated to 65ºC, a progressive enrichment of the less soluble diastereoisomer was observed (Figure 11). Through acid promoted CIDT, diastereoisomeric ratios of up to 97:3 were reached and the products were isolated by simple filtration. Finally, the enriched enantiomers and the resolving agent were recovered through the hydrolysis of naphthoxazinic derivatives. Final enantiomeric ratios of up to 96:4 were obtained.[4]

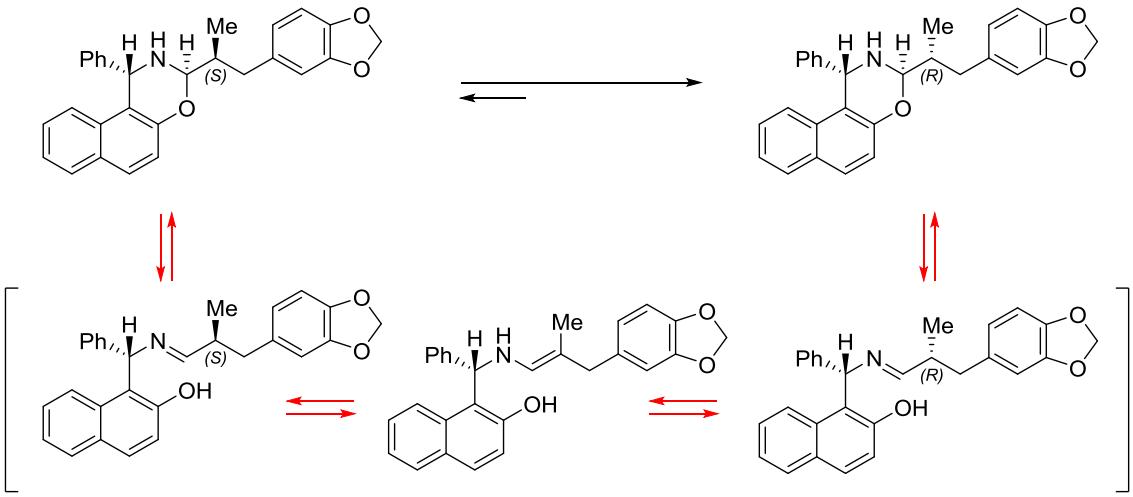


Figure 11. Acid promoted CIDT of Helional® with (*S*)-Betti base

2.2 Amine building blocks

Based on the protocol for deracemization of dihydrocinnamic aldehydes[4] and by analyzing other potentially useful molecules that could be obtained from the diastereisomerically enriched naphthoxazines, an alternative synthetic pathway was contemplated.

A structural search (SciFinder®) of a 2-alkyl-3-aryl-propan-1-amine moiety (Figure 12) was carried out and returned over 6000 substances. Over 2000 were related to biological applications, among which anti-tumoral, anti-infective and central nervous system related studies stood out. Envisaging the application of amines as possibly useful building blocks for biologically active compounds and considering the possibility of control over the stereochemistry of the 2-alkyl position, a synthetic route for enantiomerically enriched 2-alkyl-3-aryl-propan-1-amines was proposed (Scheme 2).

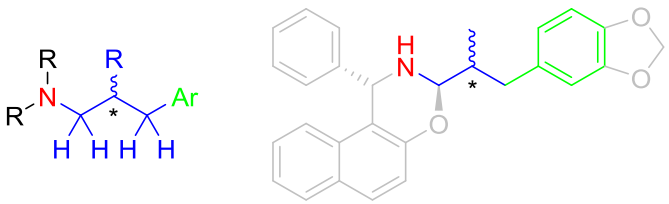
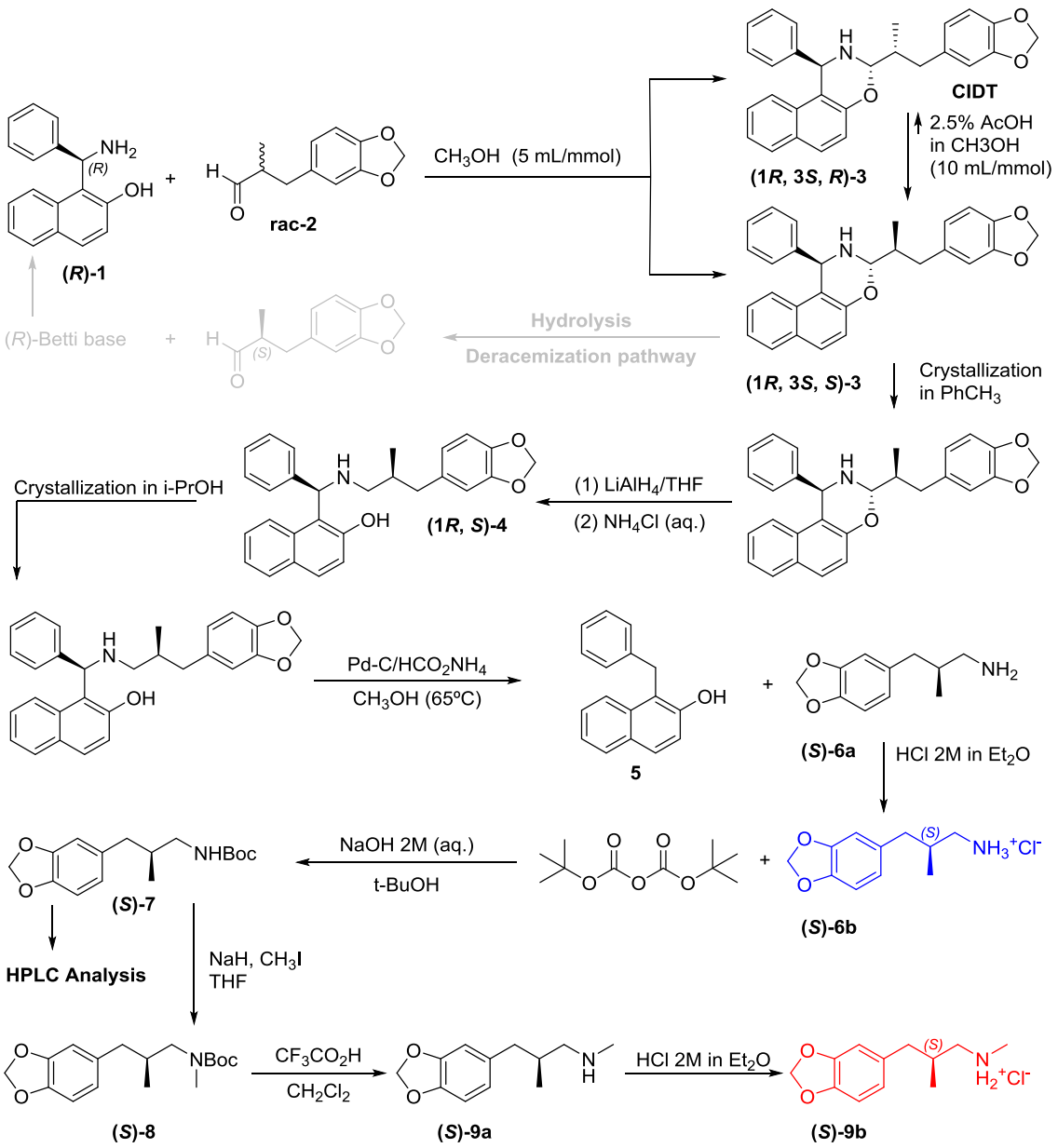


Figure 12. Structural search moiety

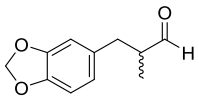
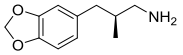
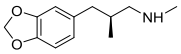
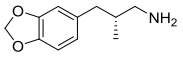
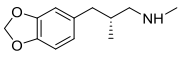
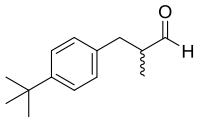
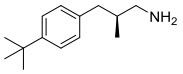
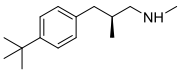
The procedure was equally based on *crystallization-induced diastereoisomeric transformation* of *trans* 2,6-disubstituted 1,3-naphthoxazines **3**. Nevertheless, by modifying the subsequent reactions to the CIDT, 2-methyl-3-arylpropan-1-amines ((*S*)-**6**, (*R*)-**6,** (*S*)-**25**) and their *N*-methyl derivatives ((*S*)-**9**, (*R*)-**9**, (*S*)-**28a**) were obtained, rather than the dihydrocinnamic aldehydes (Table 1).



Scheme 2. Synthetic pathway with Helional® and (*R*)-Betti base.

The Betti base, which was employed as a resolving agent in the previously described procedure[4], was equally necessary for deracemization. However, it was essentially used as a reactant, considering that its nitrogen atom was retained in the structure of the final product.

Table 1. Dihydrocinnamic aldehydes and corresponding final products

Betti base enantiomer	Dihydrocinnamic aldehyde	2-alkyl-3-aryl-propan-1-amines	*N*-methyl derivatives
(***R***)			
		(*S*)-**6a**	(*S*)-**9a**
(***S***)	*rac*-**2**		
		(*R*)-**6a**	(*R*)-**9a**
(***S***)			
	rac-**22**	(*S*)-**25a**	(*S*)-**28a**

Crystallization allowed further increase of the diastereoisomeric ratio after the CIDT. The fact that the naphthoxazinic diastereoisomers present significantly different solubilities in methanol[4] was an indication that they could present similar behavior in different solvents. Therefore, crystallization assays were carried out and a suitable solvent was selected for each diastereoisomeric mixture (**3** and **23**).

The amines were obtained from two consecutive hydrogenolysis of the diastereoisomerically enriched naphthoxazines (**3** and **23**). Fülop and coworkers have synthetized several Betti base derivates and explored their potentiality as chiral ligands in asymmetric chemistry.[12,13] In some synthetic routes, the authors reported the use of hydrides, either $NaBH_4$ and $LiAlH_4$, in the reduction of the oxazinic *C-O* bond. Therefore, $LiAlH_4$ was employed on the first hydrogenolysis step. The diastereoisomeric ratio of the resulting products (**4** and **24**) was likewise increased by crystallization.

Catalytic hydrogen transfer (CHT) was then used to reduce the *C-N* bond and consequently release the enantiomerically enriched amines (**6, 25**) and 1-benzylnaphthalen-2-ol **5** as a byproduct. This step, in its turn, transcends the context in which the Betti base is generally reported, despite the number of applications to which it has been associated.

The core moiety of the Betti base (aminobenzylnaphtol) is most often preserved throughout the synthetic routes discussed in related studies. When used as a chiral catalyst or resolving agent, for instance, it should in theory be recoverable. And when used as a reactant in asymmetric synthesis, the desired products are usually derivatives of the prototypical Betti base with applications in various fields. No references were found in which the *N*-*C* bond of a Betti base derivative was reduced to yield enantiomerically enriched compounds.

The hydrogenolysis of *N*-*C* bond is often employed in deprotection *N*-benzyl protected amines. Ammonium formate was used as hydrogen donor and 10% palladium on carbon as catalyst.[14] The reaction products were converted into hydrochloride salts to be recoverable by filtration and rendered more stable for storage.

The reduction of both the *C*-*O* and *C*-*N* oxazinic bonds within a single step was not attempted, since the initial hydrogenolysis with $LiAlH_4$ yields diastereoisomeric mixtures which could be enriched by crystallization.

Through the reaction with Di-tert-butyl dicarbonate, a fraction of the product was *N*-protected. This procedure served two purposes. The first was to allow the determination of the enantiomeric ratio of the *N*-Boc derivatives **7** through chiral HPLC. The amine itself presented technical constraints which hampered its direct chromatographic analysis.

The second was to allow monomethylation of the amines with methyl iodine. If an unprotected amine was used, dimethylation was most likely to occur. After alkylation, deprotection of the amine was carried out with trifluoroacetic acid, yielding the monomethylated amines **9a** and (*S*)-**25a**, which were likewise converted into hydrochloride salts.

Parallel syntheses with non-enriched mixtures of the epimeric naphthoxazines were conducted in order to allow the determination of suitable chromatographic parameters. This was accomplished simply by skipping the CIDT stage.

2.3 Synthetic application to real world target

As an attempt to assess the usefulness of the amines as building blocks, the (***S***)-enantiomer of (2*S*,6*R*)-4-((*******)-3-(4-(tert-butyl)phenyl)-2-methylpropyl)-2,6-dimethylmorpholine (fenpropimorph, **cis-(S)-21**) and its related diastereoisomer (2*R*,6*R*)-4-((***S***)-3-(4-(tert-butyl)phenyl)-2-methylpropyl)-2,6-dimethylmorpholine **trans-(*S*)-21** were synthetized (Scheme 3).

Fenpropimorph is a morpholine fungicide whose biological activity is attributed to the inhibition of ergosterol synthesis. It is the active ingredient of agricultural formulations for the control of disease in banana and cereal crops and it is extensively used worldwide.[15] It does not present any current pharmacological use. Nevertheless, the mechanism through which it operates is pharmacologically related to that of azole antifungals, which are widely employed as sterol biosynthesis inhibitors in the treatment of fungal infections. More importantly, fenpropimorph is structurally related to amorolfine **30**, the active substance in nail lacquer formulations used in the treatment of mild fungal infections.

Fenpropimorph, **cis-21** Amorolfine, **30**

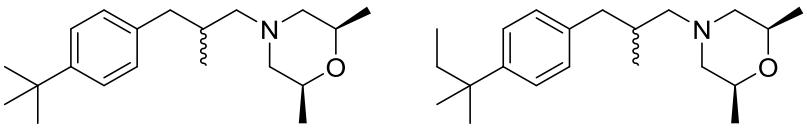
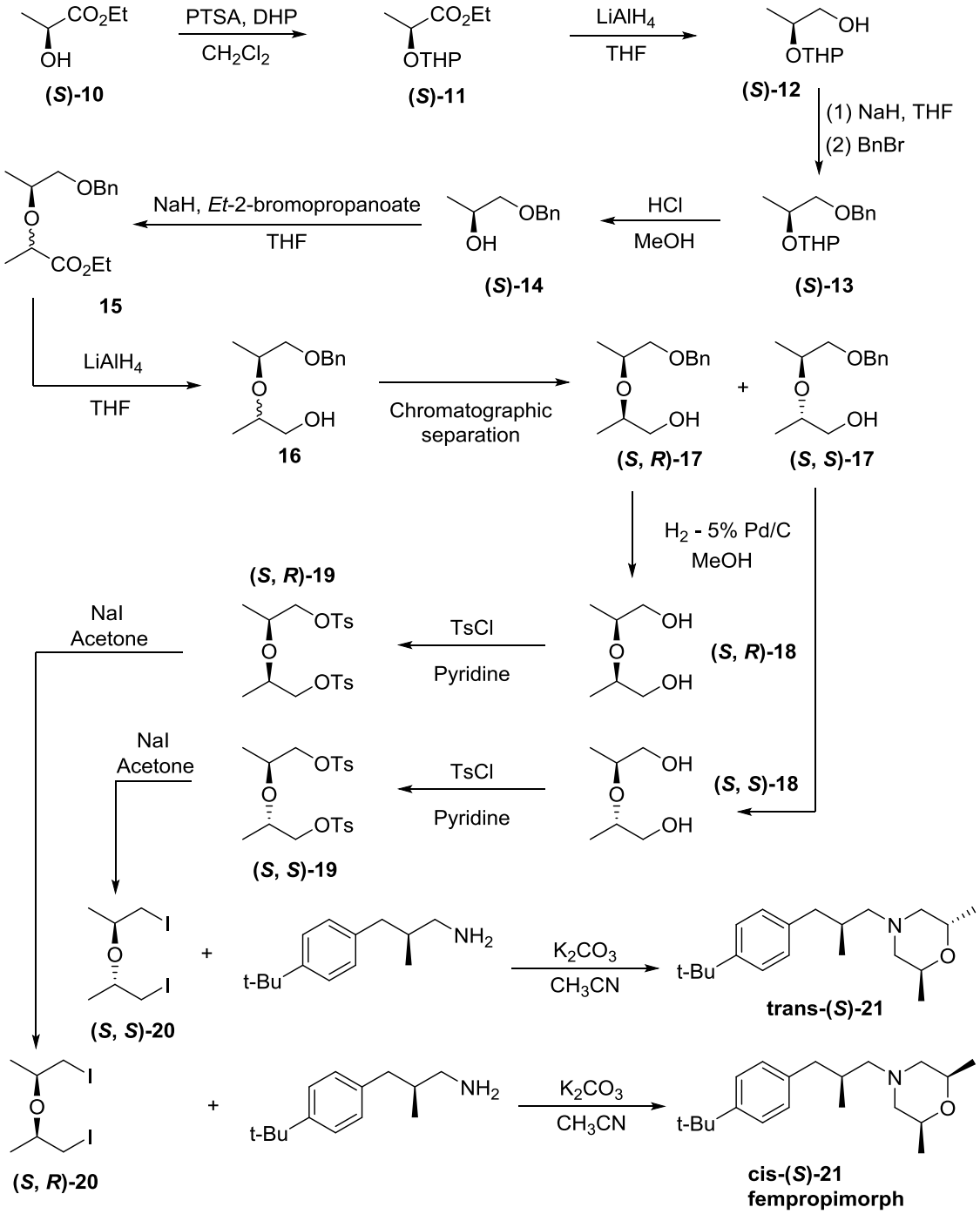


Figure 13. Morpholine fungicides

Even though the cis-(*S*)-enantiomer is known to present a higher biological acitivity, fenpropimorph is still marketed as a racemic mixture of the cis isomer.[15] Nevertheless, enantioselective synthetic routes have been reported, either employing biocatalysis[16] or asymmetric induction[17].

Considering the structure of the 2-alkyl-3-aryl-propan-1-amines, an alternative synthetic route for fenpropimorph was envisaged (Scheme 3). After protecting the hydroxyl group of lactic acid **(*S*)-10** with dihydropyran, the carboxylic acid group was reduced. The resulting hydroxyl group was protected with benzyl chloride, followed by hydrolysis of the tetrahydropyranyl ether. Through nucleophilic substitution of racemic ethyl 2-bromopropanoate, a mixture of two diastereoisomers were formed **15**.[18,19] The ester group was then reduced and

the resulting products **16** were separated by chromatography. The benzyl ethers **17** were then deprotected through hydrogenolysis, followed by ditozylation. Finally, the diol leaving group was converted to iodide prior to the cyclization step.

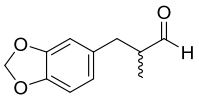
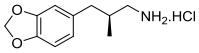
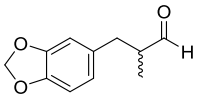
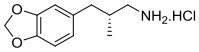
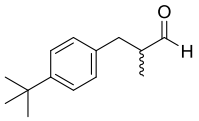
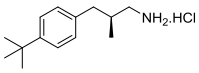


Scheme 3. Morpholine derivatives synthetic pathway.

3 Results and discussion

3.1 Amine building blocks

Table 2. Enantiomerically enriched amine building blocks

Racemic aldehyde	Betti base	CIDT overall yield[a]; dr	1st hydrogenolysis overall yield[b], dr	Amine hydrochloride overall yield[c]; er	
 *rac*-**2**	(***R***)	56.3%; 97.6 : 2.4	36.7%; 98.6 : 1.4	 (*S*)-**6b**	**32.8%; 97 : 3**[d]
 *rac*-**2**	(***S***)	64.6%; 97.2 : 2.8	51.7%; 98.4 : 1.6	 (*R*)-**6b**	**44.4% 97.2: 2.8**[d]
 *rac*-**23**	(***S***)	64.8%; 94.4 : 5.6	47.75%; 96.4 : 3.7	 (*S*)-**25b**	**38.3%; 97 : 3**[e]

[a]Up to the first crystallization. [b]Up to the second crystallization. [c]Up to the recovery of the amine hydrochloride. [d] From *N*-Boc derivative of **6**. [e] From *N*-Ts derivative of **28**.

The results show that the enantiomeric ratios of the 2-methyl-3-arylpropan-1-amines indeed reflect the diastereoisomeric enrichment of their respective naphthoxazines. The products were obtained with a very straightforward procedure and in high enantiomeric ratios (er = 97 : 3). The initial two steps yield the naphthoxazine, which is a solid easily collected by filtration. The product of the first hydrogenolysis, in its turn, is simply obtained from the concentration of the filtrate followed by crystallization. Finally, the enantiomerically enriched 2-methyl-3-arylpropan-1-amines are obtained from the second hydrogenolysis and their conversion into hydrochloride salts allows them to be directly separated from the only major byproduct (1-benzylnaphthalen-2-ol) by filtration. In summary, laborious work-up and purification steps are avoided throughout the procedure.

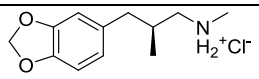
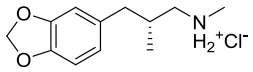
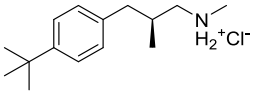
It is worth noting that the synthesis and resolution of the Betti base is inexpensive and equally straightforward. Both its enantiomers can be recovered in high yields from the kinetic resolution with tartaric acid.

The reaction yields up to the recovery of the amine hydrochloride can also be considered as satisfactory. If a classical resolution was employed, for instance, the resolution itself would limit the yield of a given enantiomer to 50%.

Considering the additional synthetic steps, the overall yield would probably be considerably lower. A 44.4% yield was obtained with the (*R*)-**6b** enantiomer. The difference to its enantiomer pair (*S*)-**6b** (32.8%) is merely circumstantial, since the synthetic pathway is reciprocal and chemically equivalent.

The fraction of the product which is lost in the first crystallization step can be recycled. After all, it contains the epimeric naphthoxazines which can ungergo acid promoted CIDT. As previously mentioned, even diastereoisomerically mixtures that initially contain a higher concentration of the more soluble isomer are eventually converted into an enriched mixture of the less soluble one, when provided sufficient time during the acid promoted CIDT.[4] Therefore, the loss generated by this step can be disregarded for practical purposes. The yield for the (*R*)-**6b** isomer, for instance, would reach 55%, surpassing the maximum theoretical threshold of a classical resolution.

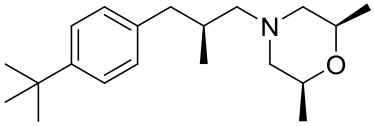
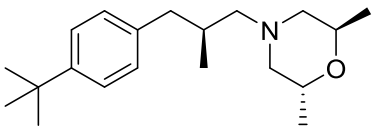
Table 3. Enantiomerically enriched *N*-methyl derivatives

N-methyl hydrochloride derivative	Yield[a]	Overall yield[b]
 (*S*)-**9b**	59.1%	19.3%
 (*R*)-**9b**	78.4%	34.4%
 (*S*)-**28b**	59.8%	22.9%

[a] From (*S*)-**6b**, (*R*)-**6b** and (*S*)-**25b**. [b] From racemic aldehyde

3.2 Synthetic application do real world target

Table 4. Morphiline derivatives

Morpholine derivative	Cyclization yield[a]
 fenpropimorph, **cis-(*S*)-21**	82%
 **trans-(*S*)-21**	90%

[a] Section 5.3.9

The (*S*)-enantiomer of Fenpropimorph, to which its biological fungicide activity is mainly attributed, was successfully synthetized using the 2-alkyl-3-aryl-propan-1-amine (*S*)-**25b** as an enantiomerically enriched building block. The NMR spectrum of the product was consistent with its structure and its molecular weight confirmed by mass spectrometry.

Scaling-up costs were not yet evaluated. However, they should be considered in the future and confronted with the protocol established by Vinković and Šunjić through an asymmetric Mannich reaction (er = 97.6 : 2.4).[17] The same research group had already accomplished enantioselective synthesis through biocatalysis and pointed out its scaling-up limitations.[16,17] The use of the racemic mixture might be satisfactory for agricultural purposes. Nevertheless, if structurally related molecules eventually display therapeutic potential, the control over the stereochemistry might become particularly interesting.

Some stages of the preparation of the 1-iodo-2-((1-iodopropan-2-yl)oxy)propane **20** moieties initially presented some difficulties. The synthesis of ethyl 2-(((*S*)-1-(benzyloxy)propan-2-yl)oxy)propanoate **15** (section 5.3.4) yielded some byproducts which were presumably the result of transesterification. Nevertheless, the addition of absolute ethanol and NaH led to the convergence of the reaction to 2-(((*S*)-1-(benzyloxy)propan-2-yl)oxy)propanoate **15** and ethyl 2-ethoxypropanoate as main co-product, which was compatible with the hypothesis. And secondly, the final cyclization step was initially attempted with the ditosylated diol, but the yields were unsatisfactory. Therefore, the cyclization was preceded by a conversion of the leaving group into iodide.

The stereochemistry of the final products was inferred from that of its two moieties: the enantiomerically enriched amine building block (*S*)-**25a** and the 1-iodo-2-((1-iodopropan-2-yl)oxy)propane **20**. One of the two stereocenters of **20** is defined by the use of enantiomerically pure (*S*)-**10** lactic acid. The stereochemistry of the second stereocenter, in its turn, is not so trivial. (*S*,*R*)-**17** and (*S*,*S*)-**17** are diastereoisomers which are obtained through chromatographic separation of isomeric mixture **16**. After hydrogenolysis of the benzyl protecting group, two diols **18** are obtained, which are likewise diastereoisomers. The (*R*,*S*)-**18**, however, is a meso compound. Therefore, it

was possible to associate the elution profile of **17** to the corresponding diastereoisomer through the lack of optical activity of (*R*,*S*)**-18**.

No discussions concerning the stereochemistry of amorolfine (**30**) or the implications on the biological properties were found. It is plausible to assume that its enantioselective synthesis could be accomplished with the same protocol, simply by using an aldehyde containing a *tert*-pentyl instead of a *tert*-butyl substituent. However, the diastereoisomeric enrichment of the corresponding naphthoxazine should be attempted before any conclusions are drawn.

No references were found concerning the trans-(*S*)-**21** compound. Its NMR and MS spectra were equally compatible with its structure.

4 Conclusion

The synthesis of enantiomerically enriched 2-alkyl-3-aryl-propan-1-amines was successfully accomplished. Given the high enantiomeric ratio achieved, these building blocks are potentially useful in the field of asymmetric organic chemistry, notably for pharmaceutically relevant compounds. A structural search reveled that these moieties, including specifically the ones which were obtained in this project, are present in numerous compounds of biological interest.

As a preliminary attempt to assess the usefulness of the building blocks, fenpropimorph, a biologically active compound which contains the 2-alkyl-3-aryl-propan-1-amine moiety, was synthetized in its enantiomerically enriched and most active form.

This project is an example of how *crystallization-induced diastereoisomer transformation* (CIDT) can be useful in the field of asymmetric organic synthesis as a dynamic resolution method. Additionally, it provides a somewhat new perspective on the use of the Betti base. Even though the deracemization procedure was based on a previously reported resolution of dihydrocinnamic aldehydes, the hydrogenolysis of Betti base derived naphthoxazines as a source of enantiomerically enriched compounds had not yet been reported.

As suggestions for future related projects, the search for biologically active compounds which contain the 2-alkyl-3-aryl-propan-1-amine moiety and in which the control over the stereochemistry of the 2-alkyl position is relevant could provide a starting point. Moreover, the synthesis of enantiomerically enriched amorolfine, a substance with known therapeutic properties, could be attempted, by applying the same protocol to the p-tert-pentyl substituted dihydrocinnamic aldehyde.

5 Experimental procedures

NMR**:** ^{1}H spectra were recorded at 400 and 600 MHz; ^{13}C spectra were recorded at 75 and 100 MHz. Carbon multiplicity was assessed with DEPT. Solvent: $CDCl_3$ (tetramethylsilane 0.03%), except when otherwise specified.

HPLC: *Hewlett Packard 1100*; column and chromatographic parameters are specified in corresponding assays; diode array detector (DAD).

Gas chromatography: *Agilent 6850*, Agilent HP1 column, 100% dimethylpolysiloxane 30 m x 0,32 mm, 0,25 µm; chromatographic parameters are specified in corresponding assays; flame ionization detector (FID).

Mass spectrometry: *Waters Micromass 4000*, ESI-MS, solvent: MeOH, positive ion scan.

Flash chromatography: stationary phase SiO_2: *Kieselgel Merck* (230-400 Mesh, 60 Å, *Sigma-Aldrich*).

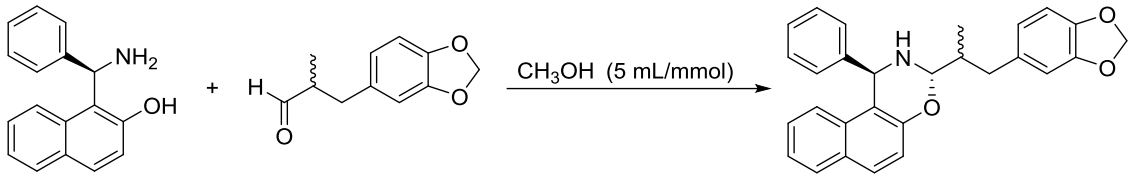
Melting point: *Bibby Stuart Scientific SMP3.*

Specific rotation: *Perkin Elmer 341* polarimeter.

Vacuum distillation: *Büchi GKR-50*.

5.1 Synthesis of 3-(benzo[d][1,3]dioxol-5-yl)-2-methylpropan-1-amine 6a and *N*-methyl derivative 9a.

5.1.1 Synthesis of 3-(1-(benzo[d][1,3]dioxol-5-yl)propan-2-yl)-1-phenyl-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine (1*R*, 3*S*)**-3** and (1*S*, 3*R*)-**3**.[4]

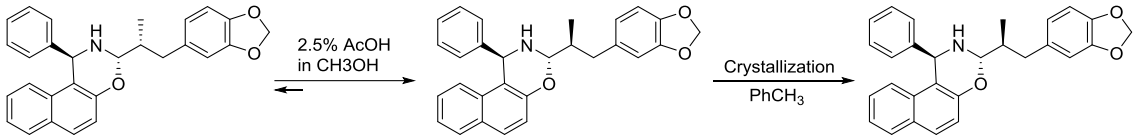


(*R*)-1 rac-2 (1*R*,3*S*)-3

(*R*)-**1** (3.74 g, 15 mmol) was suspended in methanol (75 mL) at room temperature. *rac*-**2** (3.03g, 15.75mmol) was added and the suspension was left under stirring for two hours. (1*R*,3*S*)**-3** was collected by filtration as a white solid, washed with methanol and dried under reduced pressure (6.04 g). Yield: 95%; dr = 50 : 50. NMR spectra were compatible with those reported in literature.[4]

The same protocol was applied in the synthesis of (1*S*,3*R*)**-3.** The (*S*)**-1** Betti base was instead used. Yield: 95%. NMR spectra were compatible with those reported in literature.[4]

5.1.2 CIDT of 3-(1-(benzo[d][1,3]dioxol-5-yl)propan-2-yl)-1-phenyl-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine **3**.



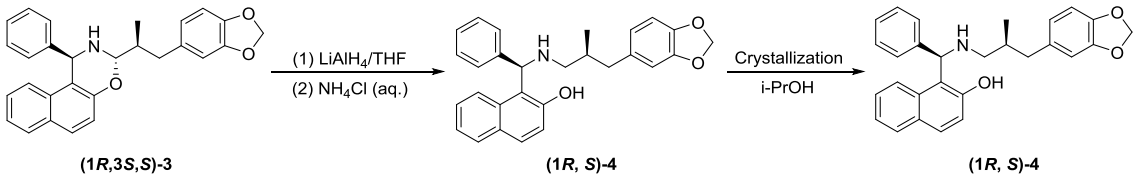
(1*R*, 3*S*, *R*)-3 (1*R*, 3*S*, *S*)-3 (1*R*, 3*S*, *S*)-3

The approximately 1:1 mixture of the (1*R*,3*S*,*R*)**-3** and (1*R*,3*S*,*S*)**-3** isomers (5.94 g, 14 mmol) was suspended in a 2.5% acetic acid solution in methanol (140 mL). After 48 hours under stirring at 60ºC, the solid was collected by filtration, washed with methanol and dried under reduced pressure. Yield: 4.52g, 76%; dr = 95.8 : 4.2.

The solid (4.50g) was crystallized in toluene (10 mL/g). After filtration and drying, (1*R*,3*S*,*S*)**-3** was recovered. Yield: 3.52g, 78%; dr = 97.6 : 2.4. NMR spectra were compatible with those reported in literature.[4]

The same protocol was applied in the CIDT of (1*S*,3*R*)**-3**, which yields the (1*S*,3*R*,*R*)-**3** enriched mixture. Yield: 85%; yield (crystallization): 80%. dr = 97.2 : 2.8. NMR spectra were compatible with those reported in literature.[4]

5.1.3 Synthesis of 1-(((3-(benzo[d][1,3]dioxol-5-yl)-2-methylpropyl)amino)(phenyl)methyl)naphthalen-2-ol (1*R*,*S*)**-4** and (1*S*,*R*)**-4**.



(1*R*,3*S*,*S*)-3 (1*R*, *S*)-4 (1*R*, *S*)-4

(1*R*,3*S*,*S*)-**3** (2.06 g, 4.87 mmol) was dissolved in anhydrous THF (28mL). This solution was added dropwise to a cooled suspension of $LiAlH_4$ (0.23 g, 6.1 mmol) in anhydrous THF (6mL), maintaining the temperature under 20ºC. The suspension was then heated to reflux and the reaction was monitored by TLC. After an hour, the suspension was cooled the reaction slowly quenched with a saturated aqueous NH_4Cl solution (3 mL) and left under stirring for two hours. The suspension was filtered and the solid consecutively washed with CH_2CH_2 and THF. The filtrate fractions were concentrated dried under reduced pressure (2.05 g). Yield = 79.3%.

The solid (2.05 g) was then heated in 60mL of isopropyl alcohol until complete dissolution, left at ambient pressure for several hours and finally cooled with an ice bath. After filtration and drying, (1*R*,*S*)-**4** was recovered. Yield: 1.70g, 82%; mp = 121-122 ºC; dr = 98.6 : 1.4; $[\alpha]_D^{22}$ = -122.2 (c 1.06, $CHCl_3$).

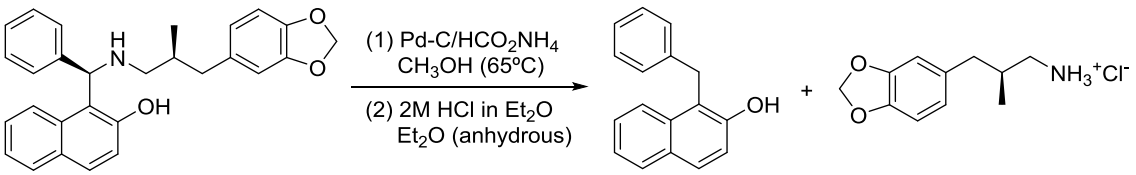
^{1}H NMR 600 MHz (*$CDCl_3$*): δ ppm 13.60 (bs, 1H), 7.77-7.67 (m, 3H), 7.41-7.37 (m, 2H), 7.32 (m, 1H), 7.26 (m, 2H), 7.23-7.19 (m, 2H), 7.15 (d, *J* = 8.8 Hz, 1H), 6.66 (d, *J* = 8.8 Hz, 1H), 6.60 (d, *J* = 1.5 Hz, 1H), 6.54 (dd, *J* = 7.9 and 1.6 Hz, 1H), 5.86 (dd, *J* = 7.9 and 1.4 Hz, 2H), 5.57 (s, 1H), 2.77 (dd, *J* = 11.8 and 5.6 Hz, 1H), 2.64 (m, 1H), 2.50 (dd, *J* = 13.8 and 6.7 Hz, 1H), 2.38 (dd, *J* = 13.8 and 7.6 Hz, 1H), 1.79 (m, 1H), 1.61 (bs, 1H), 0.96 (d, *J* = 6.7 Hz, 3H). **Diagnostic signal** (dr): δ ppm 5.57.

^{13}C NMR 150 MHz (*$CDCl_3$*): δ ppm 156.6, 147.5, 145.8, 141.5, 133.8, 132.6, 129.6, 129.0, 128.8, 128.6, 128.0, 127.6, 126.4, 122.3, 121.8, 121.1, 120.0, 113.3, 109.2, 108.1, 100.7, 64.3, 55.3, 41.5, 33.4, 18.3.

Using the same protocol, the (1*S*,3*R*,*R*)**-3** enriched mixture was used in the synthesis of the corresponding enantiomer (1*S*,*R*)**-4**. Yield (overall): 80%; mp = 122-123 ºC; dr = 98.4 : 1.6; $[\alpha]_D^{19}$ = -101.0 (c 1.2, $CHCl_3$). The NMR estimated

diastereoisomeric ratio was confirmed by chromatography with the *N*-Boc/*O*-Boc derivative of (1*S*, *R*)-**4**, HPLC Chiralcel® AD-H, hexane/*i*-PrOH 95:5, 1 mL/min, 230 nm, tr_{min} = 6.56, tr_{maj} = 7.69.

5.1.4 Synthesis of 3-(benzo[d][1,3]dioxol-5-yl)-2-methylpropan-1-aminium chloride (*S*)-**6b** and (*R*)-**6b**.



(1*R*, *S*)-4 **5** **(*S*)-6b**

(1*R*,*S*)-**4** (2.13 mg, 5.0 mmol) was added to methanol (250 mL) and heated to reflux temperature (65 ºC) until complete dissolution. 10% palladium on carbon (426 mg) and HCO_2NH_4 (1.10 g, 17.5 mmol) were consecutively added to the solution. The suspension was kept at reflux and the reaction was monitored by TLC. After 16 hours, the catalyst was separated by filtration with Celite®. The filtrate was concentrated and the crude product was dissolved in anhydrous Et_2O (8mL).

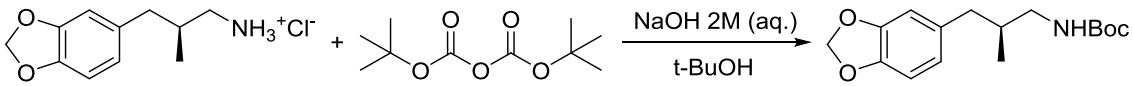
The solution was cooled with an ice bath and HCl 2M in Et_2O was slowly added (5 mL), under nitrogen and stirring. After two hours, the hydrochloride salt was collected by filtration, washed with anhydrous Et_2O and dried under reduced pressure. Yield: 1.03 g, 89.7%; crystallized from *i*-PrOH, mp = 179-181 ºC; $[\alpha]_D^{21}$ = +1.3 (c 1.55, MeOH). In order to recover the byproduct **5**, the filtrate was neutralized with $NaHCO_3$ solution, dried with Na_2SO_4 and concentrated. Its NMR spectrum was compatible with the literature.[20]

^{1}H NMR 600 MHz (*CD_3OD*): δ ppm 6.73 (d, *J* = 7.8 Hz, 1H), 6.71 (s, 1H), 6.65 (d, *J* = 7.8 Hz, 1H), 5.89 (s, 2H), 2.91 (dd, *J* = 12.6 and 5.3 Hz, 1H) , 2.74 (dd, *J* = 12.6 and 8.3 Hz, 1H), 2.65 (dd, *J* = 13.7 and 6.3 Hz, 1H), 2.41 (dd, *J* = 13.7 and 8.3 Hz, 1H), 2.06 (m, 1H), 0.97 (d, J = 6.8 Hz, 3H).

^{13}C NMR 150 MHz (*CD_3OD*): δ ppm 147.8, 146.2, 132.8, 121.8, 108.9, 107.7, 100.8, 44.6, 39.7, 33.7, 15.8.

The same protocol was applied with (1*S*,*R*)-**4** in the synthesis of the corresponding enantiomer (*R*)-**6b**. Yield: 86%, crystallized from *i*-PrOH mp = 180-181 ºC; $[\alpha]_D^{21}$ = -1.1 (c 1.3, MeOH).

5.1.5 Synthesis of tert-butyl (3-(benzo[d][1,3]dioxol-5-yl)-2-methylpropyl)carbamate (*S*)-**7** and (*R*)-**7**.



(***S***)-**6b** (***S***)-**7**

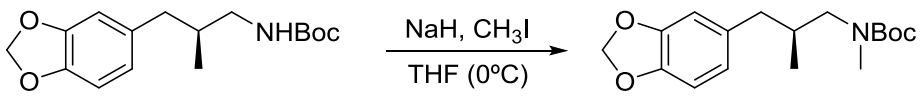
NaOH 2M aq. (1.65 mL, 3.3 mmol) was added dropwise to a suspension of **(*S*)-6b** (344 mg, 1.5 mmol) in *t*-BuOH (1.1 mL). After dissolution, a solution of di-*tert*-butyl dicarbonate (334 mg, 1.53 mmol) in *t*-BuOH (0.5 mL) was added dropwise and under stirring to the previous solution along one hour. The reaction was monitored by TLC. After 6 hours, the aqueous phase was separated with 15 mL of Et_2O in a separating funnel. The organic phase was dried with $NaSO_4$, the product purified by flash chromatography (5-10% EtOAc in petroleum ether) and dried under reduced pressure. Yield: 433 mg, 98.4%; HPLC Phenomenex Lux Amylose-2, hex/*i*-PrOH 90:10, 1 mL/min, 230 nm, tr_{maj} = 10.91 min, tr_{min} = 9.19, er = 97 : 3; $[\alpha]_D^{18}$ = +10.8 (c 1.48, $CHCl_3$).

^{1}H NMR 600 MHz (*CD_3OD*): δ ppm 6.72 (d, *J* = 7.8 Hz, 1H), 6.64 Hz (s, 1H), 6.59 Hz (d, *J* = 7.8 Hz, 1H), 5.91 (s, 2H), 4.56 (bs, 1H), 3.09 (m, 1H), 2.97 (m, 1H), 2.60 (dd, *J* = 13.7 and 5.9 Hz, 1H), 2.30 (dd, *J* = 13.7 and 8.4 Hz, 1H), 2.85 (m, 1H), 1.44 (s, 9H), 0.86 (d, J = 6.8 Hz, 3H).

^{13}C NMR 150 MHz (*CD_3OD*): δ ppm 156.0, 147.5, 145.7, 134.2, 121.8, 109.3, 108.0, 100.7, 79.0, 46.2, 40.6, 35.9, 28.4, 17.3.

The same protocol was applied with (*R*)-**6b** in the synthesis of the corresponding enantiomer (*R*)-**7**. Yield: 93%; HPLC Phenomenex Lux Amylose-2, hexane/*i*-PrOH 90:10, 1 mL/min, 230 nm, tr_{maj} = 9.19 min, tr_{min} = 10.9 min, er = 97.2 : 2.8; $[\alpha]_D^{20}$ = -9.4 (c 0.84, $CHCl_3$).

5.1.6 Synthesis of tert-butyl (*S*)-(3-(benzo[d][1,3]dioxol-5-yl)-2-methylpropyl)(methyl)carbamate **(*S*)-8**.



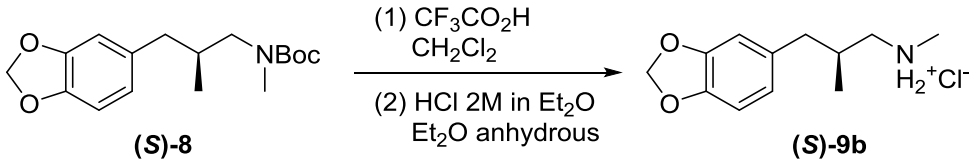
(*S*)-7 **(*S*)-8**

60% NaH in mineral oil (71 mg, 1.78 mmol) was added to a solution of **(*S*)-7** (433 mg, 1.48 mmol) in THF cooled with an ice bath. Methyl iodine was then added (0.14 mL, 2.29 mmol). After three hours under stirring, a TLC (5% EtOAc in petroleum ether) showed no evidence of the product. The reaction was then left at room temperature for another three hours, after which the reaction was apparently complete. Saturated aqueous NH_4Cl was used to quench it. The organic phase was concentrated and the aqueous phase washed with Et_2O, which was used to redissolve the product. This solution was then washed with brine-H_2O 1:1 to neutrality, dried with Na_2SO_4 and concentrated. The product was purified by flash chromatography. Yield: 353 mg, 77%; $[\alpha]_D^{23}$ = +2.7 (c 1.9, $CHCl_3$).

^{1}H NMR 400 MHz (*$CDCl_3$*) temp = 50 ºC: δ ppm 6.71 (d, *J* = 7.8 Hz, 1H), 6.63 (d, *J* = 1.4 Hz, 1H), 6.58 (dd, J = 7.8 and 1.4 Hz, 1H), 5.90 (s, 2H), 3.15 (dd, *J* = 13.7 Hz and 6.8 Hz, 1H), 3.08 (bs, 1H), 2.83 (bs, 3H), 2.58 (dd, *J* = 13.7 and 5.5 Hz, 1H), 2.25 (dd, J = 13.7 and 8.6 Hz, 1H), 2.00 (m, 1H), 1.45 (s, 9H), 0.83 (d, *J* = 6.6 Hz, 3H).

The same protocol was applied with (*R*)-**7** in the synthesis of the corresponding enantiomer (*R*)-**8**. Yield: 98%, $[\alpha]_D^{21}$ = -0.46 (c 3.0, $CHCl_3$).

5.1.7 Synthesis of (*S*)-3-(benzo[d][1,3]dioxol-5-yl)-N,2-dimethylpropan-1-amine hydrochloride **(*S*)-9b**.



(*S*)-8 **(*S*)-9b**

(*S*)-**8** (352 mg, 1.14 mmol) was added to a solution of CF_3CO_2H (1 mL) and CH_2Cl_2 (1 mL), which was left under stirring for one hour and then concentrated. Saturated aqueous $NaHCO_3$ (3 mL) was added to the residue under stirring. A progressive color change was observed, which ceased after two hours. THF (2 mL) was then added. The product was extracted with $CHCl_3$ (3 x 4 mL) and the organic phase washed with brine-H_2O 1:1 (2 x 2 mL), brine (1 mL) and dried with Na_2SO_4.

HCl 2M in Et_2O (1.5 mL) was added to a solution of the product in anhydrous Et_2O (3 mL), which was kept under stirring for one hour. The resulting suspension was filtrated. The solid was washed with anhydrous Et_2O and dried under reduced pressure. Yield: 219 mg, 78.8%; crystallized from CH_3CN mp = 147-149 ºC; $[\alpha]_D^{22}$ = +8.2 (c 1.55, MeOH).

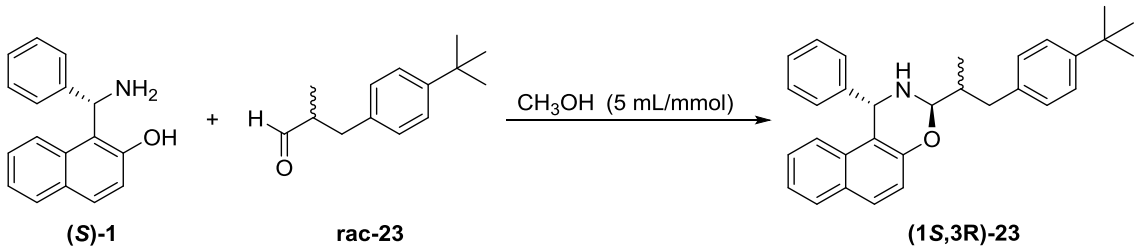
^{1}H NMR 600 MHz (*CD_3CN*): δ ppm 8.97 (bs, 2H), 6.78 (bs, 1H), 6.74 (d, *J* = 7.9 Hz, 1H), 6.67 (d, J = 7.9 Hz, 1H), 5.93 (m, 2H), 2.88-2.79 (m, 1H), 2.79-2.69 (m, 2H), 2.55 (bs, 3H), 2.37 (m, 1H), 2.23 (m, 1H), 0.96 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR 150 MHz (*CD_3CN*): δ ppm 149.1, 147.4, 134.8, 123.6, 110.8, 109.3, 102.5, 55.9, 41.2, 34.6, 34.1, 18.2.

The same protocol was applied with (*S*)-**8** in the synthesis of the corresponding enantiomer (*S*)-**9b**. Yield: 86%; crystallized from CH_3CN mp = 145-148 ºC; $[\alpha]_D^{20}$ = -1.8 (c 1.4, MeOH).

5.2 Synthesis of (*S*)-3-(4-(tert-butyl)phenyl)-2-methylpropan-1-amine (*S*)-25a and *N*-methyl derivative (*S*)-28a.

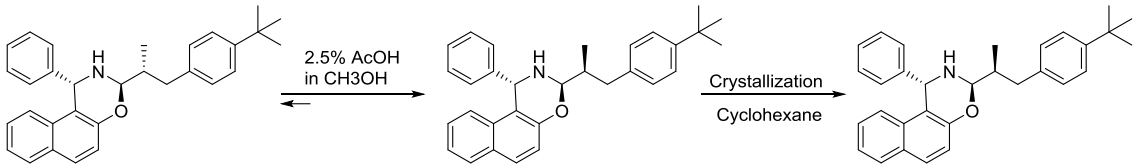
5.2.1 Synthesis of (1*S*,3*R*)-3-(1-(4-(tert-butyl)phenyl)propan-2-yl)-1-phenyl-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine **(1*S*,3*R*)-23**.



(*S*)-1 **rac-23** **(1*S*,3R)-23**

(*S*)-**1** (2.49g, 10 mmol) was suspended in methanol (50 mL) at room temperature. rac-**23** (2.14 g, 10.1 mmol) was added and the suspension was left under stirring for two hours. (1*S*,3*R*)-**23** was collected by filtration as a white solid, washed with methanol and dried under reduced pressure. Yield: 3.9 g, 90%; dr = 50 : 50.[4]

5.2.2 CIDT of (1*S*,3*R*)-**23** followed by crystallization in cyclohexane.

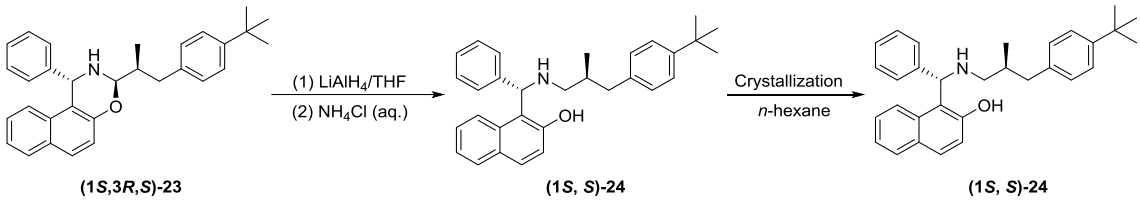


(1***S***, 3***R***, ***R***)-23 (1***S***,3***R***,***S***)-23 (1***S***,3***R***,***S***)-23

The approximately 1:1 mixture of (1*S*,3*R*,S) and (1*S*,3*R*,*R*) isomers (4.35g, 10 mmol) was suspended in a 10% acetic acid solution in methanol (30 mL). After 60 hours under stirring at 60ºC, the solid was collected by filtration, washed with methanol and dried under reduced pressure. Yield: 4.17g, 96%; dr = 90 : 10.[4]

The solid (4.10g) was crystallized in cyclohexane (105 mL). After filtration and drying, **(1*S*,3*R*,*S*)-23** was recovered. Yield: 3.07g, 75%; dr = 94.4 : 5.6.[4]

5.2.3 Synthesis of 1-((*S*)-(((*S*)-3-(4-(tert-butyl)phenyl)-2-methylpropyl)amino)(phenyl)methyl)naphthalen-2-ol **(1*S*,*S*)-24** followed by crystallization in *n*-hexane.



(1*S*,3*R*,*S*)-23 (1*S*, *S*)-24 (1*S*, *S*)-24

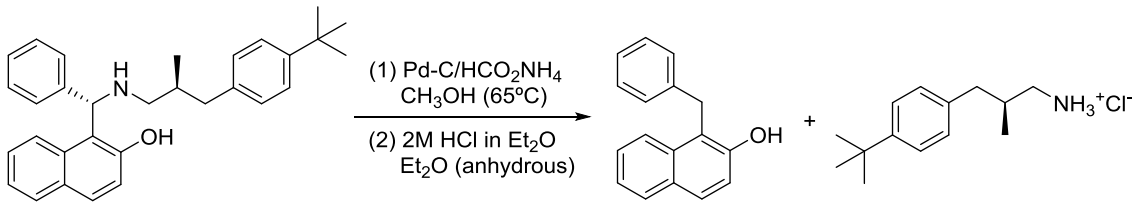
(1*S*,3*R*)-23 (5.05g, 11,59 mmol) was dissolved in anhydrous THF (70 mL). This solution was added dropwise to a cooled suspension of $LiAlH_4$ (0.56 g, 14.8 mmol) in anhydrous THF (10 mL), maintaining the temperature under 20ºC. The suspension was then heated to reflux temperature (66 ºC) and the reaction was monitored by TLC (5% EtOAc in petroleum ether). After three hours, the suspension was cooled with an ice bath. The reaction was slowly quenched with a saturated aqueous NH_4Cl solution (7.5 mL) and left under stirring for two hours. The organic phase was separated and filtered. The remaining solid was consecutively washed with THF (20 mL) and CH_2CH_2 (20 mL). The organic phases were then concentrated. The resulting solid was redissolved in 70 mL of CH_2Cl_2 and consecutively washed with water (2 x 10 mL) and brine (10 mL). The solution was finally dried with Na_2SO_4, concentrated and dried under reduced pressure. Yield = 4.27g, 84%.

The solid (4.27g) was crystallized in *n*-hexane (45 mL). After filtration and drying, **(1*S*,*S*)-24** was recovered. Yield: 3.34g, 78% overall; dr = 96.3 : 3.7.

^{1}H NMR 600 MHz (*$CDCl_3$*): δ ppm 13.60 (bs, 1H), 7.73-7.67 (m, 3H), 7.43 (m, 2H), 7.35-7.19 (m, 7H), 7.16 (d, *J* = 8.7 Hz, 1H), 7.05 (m, 2H), 5.62 (s, 1H), 2.81 (bs, 1H), 2.71 (dd, *J* = 13.8 and 5.8 Hz, 1H), 2.67 (dd, *J* = 11.8 and 6.6 Hz, 1H), 2.39 (dd, *J* = 13.8 and 8.7 Hz, 1H), 2.07 (m, 1H), 1.96 (bs, 1H), 1.28 (s, 9H), 0.91 (d, J = 6.7 Hz, 3H). **Diagnostic signal** (dr): δ ppm 5.62.

^{13}C NMR 150 MHz (*$CDCl_3$*): δ ppm 156.7, 148.8, 141.6, 136.9, 132.6, 129.6, 129.1, 128.8, 128.64, 128.60, 128.1, 127.7, 126.4, 125.2, 122.3, 121.1, 120.1, 113.5, 64.4, 55.2, 40.6, 34.7, 34.7, 31.4, 17.9.

5.2.4 Synthesis of (*S*)-3-(4-(tert-butyl)phenyl)-2-methylpropan-1-amine hydrochloride **(*S*)-25b**.



(1*S*, *S*)-24 **5** **(*S*)-25b**

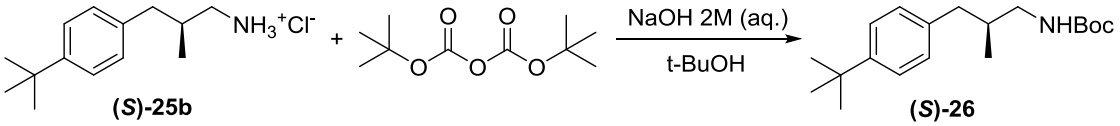
(1*S*,*S*)-24 (1.95 mg, 4.44 mmol) was added to methanol (80 mL) and heated to reflux temperature (65 ºC) until complete dissolution. 10% palladium on carbon (195 mg) and HCO_2NH_4 (1.12 g, 17.8 mmol) were consecutively added to the solution. The suspension was kept at reflux and the reaction was monitored by TLC. After 24 hours, the catalyst was separated by filtration with Celite®. The filtrate was concentrated and the crude product was dissolved in anhydrous CH_2Cl_2. This solution was dried with Na_2SO_4 and concentrated.

The crude product was then redissolved in anhydrous Et_2O (4.4 mL) and the solution was cooled with an ice bath. HCl 2M in Et_2O was slowly added (2.5 mL) under nitrogen and stirring. After 40 minutes, the hydrochloride salt was collected by filtration, washed with anhydrous Et_2O and dried under reduced pressure. Yield: 865 mg, 80.6%; crystallized from *i*-PrOH mp = 162-164 ºC; $[\alpha]_D^{21}$ = +1.6 (c 1.00, MeOH).

^{1}H NMR 600 MHz (*CD_3OD*): δ ppm 7.33 (m, 2H), 7.14 (m, 2H), 2.93 (dd, J = 12.6 and 5.5 Hz, 1H), 2.76 (dd, J = 12.6 and 8.4 Hz, 1H), 2.71 (dd, J = 13.4 and 6.5 Hz, 1H), 2.48 (dd, 13.4 and 8.2 Hz, 1H), 2.11 (m, 1H), 1.30 (s, 9H), 0.99 (d, J = 6.7 Hz, 3H).

^{13}C NMR 150 MHz (*CD_3OD*): δ ppm 151.2, 138.2, 130.7, 127.2, 46.9, 41.8, 36.1, 35.8, 32.7, 18.1.

5.2.5 Synthesis of tert-butyl (*S*)-(3-(4-(tert-butyl)phenyl)-2-methylpropyl)carbamate **(*S*)-26**.



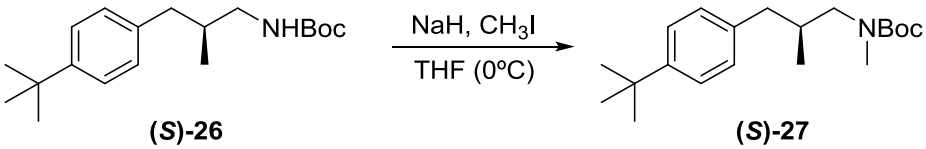
(*S*)-25b **(*S*)-26**

NaOH 2M aq. (2.20 mL, 3.3 mmol) was added dropwise to a suspension of **(S)-25b** (482 mg, 2.0 mmol) in *t*-BuOH (1.1 mL). After dissolution, a solution of di-tert-butyl dicarbonate (445 mg, 2.0 mmol) in *t*-BuOH (0.7 mL) was added dropwise and under stirring to the previous solution along one hour. The reaction was monitored by TLC (5% of (10% NH_4OH aq. in methanol) in CH_2Cl_2; $KMnO_4$ as visualization agent). After 6 hours, the aqueous phase was separated with 20 mL of Et_2O in a separating funnel. The organic phase was dried with $NaSO_4$, the product purified by flash chromatography and dried under reduced pressure. Yield: 515 mg, 84.7%; $[\alpha]_D^{26}$ = +10.1 (c 1.50, $CHCl_3$).

^{1}H NMR 600 MHz (*$CDCl_3$*): δ ppm 7.29 (m, 2H), 7.07 (m, 2H), 4.54 (bs, 1H), 3.10 (m, 1H), 2.99 (m, 1H), 2.64 (dd, *J* = 13.7 and 6.0 Hz, 1H), 2.36 (dd, *J* = 13.7 and 8.2 Hz, 1H), 1.91 (m, 1H), 1.44 (s, 9H), 1.30 (s, 9H), 0.88 (d, J = 6.8 Hz, 3H).

^{13}C NMR 150 MHz (*$CDCl_3$*): δ ppm 156.1, 148.7, 137.2, 128.7, 125.1, 79.0, 46.3, 40.4, 35.7, 34.3, 31.4, 28.4, 17.5.

5.2.6 Synthesis of tert-butyl (*S*)-(3-(4-(tert-butyl)phenyl)-2-methylpropyl)(methyl)carbamate **(*S*)-27**.

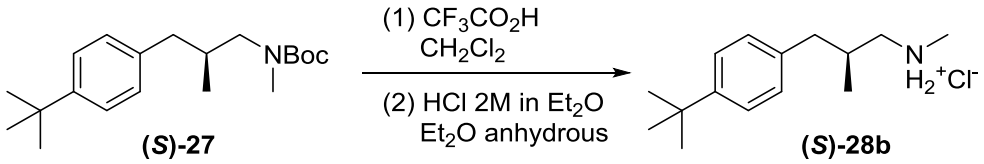


(*S*)-26 **(*S*)-27**

A solution of **(*S*)-26** (504 mg, 1.65 mmol) in anhydrous THF (2 mL) was added to a suspension of 60% NaH in mineral oil (99 mg, 2.48 mmol) in anhydrous THF (0.5 mL) cooled with an ice bath. Methyl iodine was added (0.20 mL, 3.30 mmol) under stirring and the reaction was monitored by tlc (5% EtOAc in petroleum ether). After 6 hours at room temperature, the reaction was apparently complete and saturated aqueous NH_4Cl was used to quench it. The organic phase was concentrated and the aqueous phase washed with Et_2O, which was used to redissolve the product. TLC showed the presence of the product in the aqueous phase, which was washed with CH_2Cl_2. The organic phases were then washed with brine-H_2O 1:1 to neutrality, dried with Na_2SO_4 and concentrated. The product was purified by flash chromatography. Yield: 465 mg, 88.2%; $[\alpha]_D^{24}$ = +2.1 (c 1.06, $CHCl_3$).

^{1}H NMR 600 MHz (*$CDCl_3$*) temp = 50ºC: δ ppm 7.28 (m, 2H), 7.06 (m, 2H), 3.17 (dd, *J* = 13.6 and 6.7 Hz, 1H), 3.08 (bs, 1H), 2.83 (bs, 3H), 2.63 (dd, *J* = 13.4 and 5.1 Hz, 1H), 2.30 (dd, *J* = 13.6 and 8.8 Hz, 1H), 2.06 (m, 1H), 1.44 (s, 9H), 1.30 (s, 9H), 0.84 (d, *J* = 6.7 Hz, 3H).

5.2.7 Synthesis of (*S*)-3-(4-(tert-butyl)phenyl)-N,2-dimethylpropan-1-amine hydrochloride **(*S*)-28b**.



(*S*)-27 **(*S*)-28b**

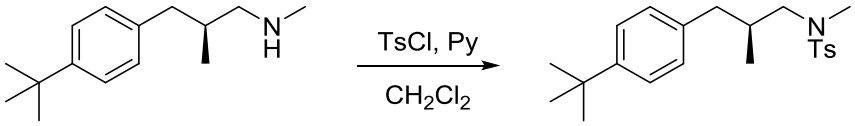
CF_3CO_2H (1 mL) was added to a solution **(*S*)-27** (454 mg, 1.42 mmol) in CH_2Cl_2, which was left under stirring for 30 minutes and then concentrated. Et_2O (4 mL) and saturated aqueous Na_2CO_3 (1 mL) were added to the residue. The organic phase was then separated, washed with brine (1 mL) and concentrated. The product was dried under reduced pressure. Yield: 300 mg, 96.3%.

HCl 2M in Et_2O (1.5 mL) was added to a solution of the product in anhydrous Et_2O (4 mL), which was kept under stirring for 30 minutes. The resulting suspension was filtrated. The solid was washed with anhydrous Et_2O and dried under reduced pressure. Yield: 289 mg, 80.0%; crystallized from *i*-PrOH mp = 219-222 ºC; $[\alpha]_D^{25}$ = +8.1 (c 1.23, CH_3OH).

^{1}H NMR 600 MHz (*CD_3OD*): δ ppm 7.34 (m, 2H), 7.12 (m, 2H), 2.95 (dd, *J* = 12.5 and 5.3 Hz, 1H), 2.84 (dd, 12.5 and 8.7 Hz, 1H), 2.68 (s, 3H), 2.68 (dd, *J* = 13.7 and 6.5 Hz, 1H), 1.48 (dd, 13.7 and 8.2 Hz, 1H), 2.13 (m, 1H), 1.29 (s, 9H), 0.99 (d, 6.7 Hz, 3H).

^{13}C NMR 150 MHz (*CD_3OD*): δ ppm 151.3, 138.0, 130.7, 127.3, 57.0, 41.8, 36.1, 35.1, 35.0, 32.7, 18.2.

5.2.8 Synthesis of ((S)-N-(3-(4-(tert-butyl)phenyl)-2-methylpropyl)-N,4-dimethylbenzenesulfonamide **(*S*)-29**.



(*S*)-28a **(*S*)-29**

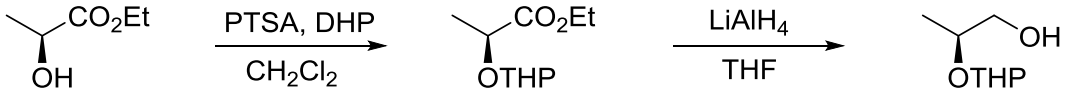
Pyridine (0,03 mL) and TsCl (36 mg, 0.19 mmol) were consecutively added to a solution of (S)-28a (27 mg, 0.124 mmol) in CH_2Cl_2 (0,2 mL), under nitrogen and stirring. After four hours at 0 ºC, the reaction was left at room temperature for another 20 hours. Et_2O (10 mL) was added and the solution was washed with water (3 x 1 mL) and brine (1 mL) and dried with Na_2SO_4. The residue was purified by flash chromatography. Yield: 37.4 mg, 80%; $[\alpha]_D^{26}$ = +20.4 (c 1.67, $CHCl_3$); HPLC Chiralcel® OJ-H, *n*-hexane:*i*-PrOH 85:15, 1 mL/min, λ=220 nm, tr_{min} = 38.58, tr_{maj} = 45.43, er = 97 : 3.

^{1}H NMR 600 MHz (*$CDCl_3$*): δ ppm 7.65 (m, 2H), 7.30 (m, 2H), 7.29 (m, 2H), 7.07 (m, 2H), 2.86 (dd, *J* = 13.0 and 6.9 Hz, 1H), 2.81 (dd, *J* = 13.0 and 7.9 Hz, 1H), 2.75 (dd, *J* = 13.7 and 5.3 Hz, 1H), 2.70 (s, 3H), 2.42 (s, 3H), 2.33 (dd, *J* = 13.7 and 8.9 Hz, 1H), 2.01 (m, 1H), 1.31 (s, 9H), 0.92 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR 150 MHz (*$CDCl_3$*): δ ppm 148.7, 143.1, 137.1, 134.4, 129.6, 128.7, 127.4, 125.1, 56.3, 40.1, 35.3, 34.3, 33.5, 31.4, 21.4, 17.3.

5.3 Synthesis of (2*S*,6*R*)-4-((*S*)-3-(4-(tert-butyl)phenyl)-2-methylpropyl)-2,6-dimethylmorpholine cis-(*S*)-21 and (2*S*,6*S*)-4-((*S*)-3-(4-(tert-butyl)phenyl)-2-methylpropyl)-2,6-dimethylmorpholine trans-(*S*)-21.

5.3.1 Synthesis of (1S)-1-((tetrahydro-2H-pyran-2-yl)oxy)ethan-1-ol *(S)*-**12**.



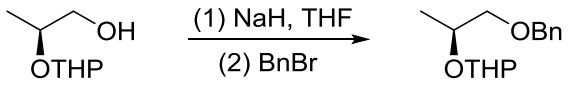
(*S*)-10 **(*S*)-11** **(*S*)-12**

PSTA mohohydrate (2.4 mg) was added to a solution of ethyl (S)-2-hydroxypropanoate 98% (2.06 g, 17 mmol) in CH_2Cl_2 (5 mL). The solution was cooled to 5ºC and DHP 97% (1.41 mL, 15 mmol) was added dropwise. The reaction was maintained for 5ºC for 15 minutes and then left at ambient temperature. It was monitored by TLC (25% EtOAc in hexane) and after five hours the starting material was apparently consumed. The mixture was diluted with Et_2O (5 mL), quenched with saturated aqueous $NaHCO_3$ (5 mL) and kept under vigorous stirring for 30 minutes. The aqueous phase was then separated. The organic phase was consecutively washed with water (2 x 3 mL) and brine (3 mL), dried with Na_2SO_4 and concentrated. Yield (crude product): 3.01 g. The NMR spectra were compatible with those reported in literature.[17]

The crude product (3.00 g) was dissolved in anhydrous THF (80 mL) and added dropwise to a suspension of $LiAlH_4$ in anhydrous THF (20 mL), maintaining the temperature at approximately 30 ºC. The mixture was left at ambient temperature for one hour and then at reflux for two hours. The suspension was filtered and the filtrate concentrated. The residue was dissolved in Et_2O (50 mL), washed with water (2 x 5 mL) and brine (5 mL), and dried with Na_2SO_4. The product was purified with flash chromatography. Yield (1,40 g, 87%, two stereoisomers with 63 : 37 ratio).

^{13}C NMR 100 MHz (*$CDCl_3$*): Major isomer: δ ppm 99.0, 74.8, 66.1, 63.0, 31.0, 25.3, 20.0, 17.6. Minor isomer: δ ppm 99.8, 77.6, 67.1, 64.4, 31.5, 25.0, 20.8, 17.1.

5.3.2 Synthesis of 2-((*S*)-1-(benzyloxy)ethoxy)tetrahydro-2H-pyran **(*S*)-13**.

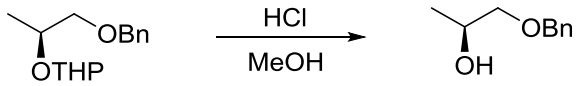


(*S*)-12 **(*S*)-13**

A solution of **(*S*)-12** (5.4 g, 33.7 mmol) in anhydrous THF (60 mL) was added dropwise to a suspension of NaH (1.57 g, 39.3 mmol) in THF (20 mL) cooled with an ice bath. The reaction was left ambient temperature for 30 minutes and once again cooled with an ice bath. Benzyl bromide 98% (1.46 mL, 35 mmol) was added dropwise. The reaction was then left at ambient temperature and monitored by TLC. After 24 hours, the product was purified by flash chromatography. Yield: 6.8 g, 80,7%.

^{13}C NMR 100 MHz (*$CDCl_3$*). Major isomer: δ ppm 138.4, 128.3, 127.6, 127.5, 98.9, 74.3, 73.2, 72.0, 62.7, 31.0, 25.5, 19.9, 18.7. Minor isomer: δ ppm 138.8, 128.3, 127.5, 127.4, 96.2, 74.2, 73.2, 70.5, 62.2, 31.0, 25.5, 19.5, 16.5.

5.3.3 Synthesis of (*S*)-1-(benzyloxy)propan-2-ol **(*S*)-14**.



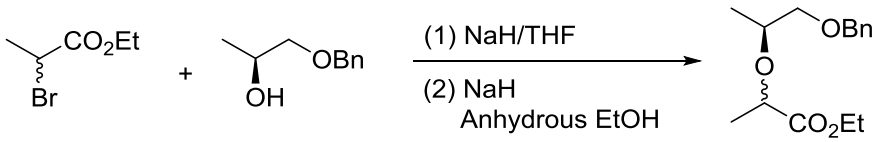
(*S*)-13 **(*S*)-14**

HCl 6M in water (0,30 mL) was added to a solution of **(*S*)-13** (2.25 g) in methanol (40 mL). The reaction was monitored by TLC and after 24 hours it was neutralized with a saturated aqueous solution of $NaHCO_3$. The product was recovered with CH_2Cl_2 with a separating funnel. The organic phase was washed with water and brine and dried with Na_2SO_4. Purified by flash chromatrography and distilled Kugelrohr (105ºC/0.3 mm); yield (1.46 g, 98%); $[\alpha]_D^{23}$ = +15.2 (c 1.59, $CHCl_3$).

^{1}H NMR 400 MHz (*$CDCl_3$*): δ ppm 7.28-7-16 (m, 5H), 4.45 (s, 2H), 3.89 (m, 1H), 3.35 (dd, *J* = 9.5 and 3.3 Hz, 1H), 3.19 (dd, *J* = 9.5 and 7.9 Hz, 1H), 2.67 (bs, 1H), 1.04 (dd, *J* = 6.4 Hz, 3H).

^{13}C NMR 100 MHz (*$CDCl_3$*): δ ppm 137.9, 128.4, 127.8, 127.7, 75.8, 73.3, 66.5, 18.6.

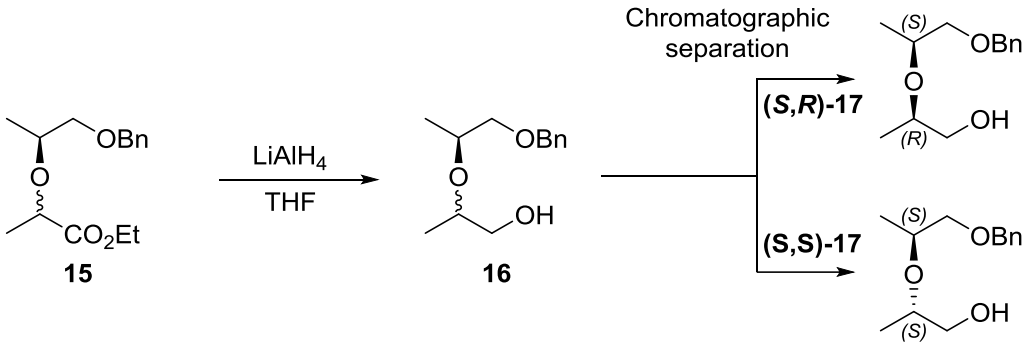
5.3.4 Synthesis of ethyl 2-(((*S*)-1-(benzyloxy)propan-2-yl)oxy)propanoate **15**.



(*S*)-14 **15**

A solution of **(*S*)-14** (665 mg, 4 mmol) in anhydrous THF (1 mL) was added to a cooled suspension of NaH 60% in mineral oil (176 mg, 4.4 mmol) in anhydrous THF (4 mL) under stirring. The mixture was left at room temperature for 30 minutes. A solution of racemic ethyl 2-bromopropanoate (1.58 mL, 12 mmol) in anhydrous THF was then added dropwise, along 45 minutes, maintaining the temperature at approximately 3ºC. The reaction was monitored by GC (initial temp = 60ºC, hold time$_1$ = 2 min; ramp 10ºC/min to 270 ºC, hold time$_2$ = 15 min; carrier gas H_2;) and initial assays revealed the presence transesterification byproducts. For this reason, anhydrous EtOH (0,28 mL) and NaH (170 mg, 4,25 mmol) were added, leading to the convergence of the reaction to ethyl 2-(((*S*)-1-(benzyloxy)propan-2-yl)oxy)propanoate **15** and ethyl 2-ethoxypropanoate as main products. The products were purified by flash chromatography to give two diastereoisomers in a 1:1 ratio, which were not separable by flash chromatography. Yield: 0.628, 59%.

5.3.5 Synthesis of 2-(((S)-1-(benzyloxy)propan-2-yl)oxy)propan-1-ol **16** and chromatographic separation of its diastereoisomers **(*S*, *R*)-17** and **(*S*, *S*)-17**.



15 (3.70 g, 13.9 mmol) was dissolved in anhydrous THF (100 mL). This solution was added dropwise to a cooled suspension of $LiAlH_4$ (0.53 g, 13.9 mmol) in anhydrous THF (20 mL), maintaining the temperature at approximately 20ºC. The suspension was then heated to reflux temperature (66 ºC) and the reaction was monitored by TLC. After two hours, the suspension was cooled with an ice bath. The reaction was slowly quenched with a saturated aqueous NH_4Cl solution and left under stirring for one hour. The organic phase was separated and filtered. The remaining solid was washed with CH_2CH_2 (20 mL) and the organic phase was then concentrated. The resulting solid was redissolved in CH_2Cl_2 and consecutively washed with water and brine. The solution was finally dried with Na_2SO_4 and concentrated. The diastereoisomers were successfully separated by flash chromatography (30% EtOAc in *n*-hexane).

First eluted isomer (*S*,*R*)-**17** (418 mg, 49%).

^{1}H NMR 600 MHz (*$CDCl_3$*): δ ppm 7.36-7.26 (m, 5H), 4.59 (d, J = 12.1 Hz, 1H), 4.53 (d, J = 12.1 Hz, 1H), 3.82 (m, 1H), 3.65 (m, 1H), 3.55 (m, 2H), 3.45-3.38 (m, 3H), 1.11 (d, J = 6.5 Hz, 6H).

^{13}C NMR 150 MHz (*$CDCl_3$*): δ ppm 137.5, 128.4, 127.72, 127.67, 76.6, 74.9, 74.5, 73.3, 67.0, 18.1, 17.9.

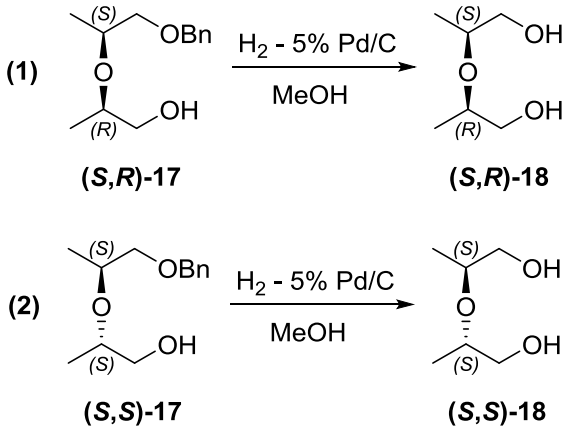
Second eluted isomer (*S*,*S*)-**17** (413 mg, 48.7%); $[\alpha]_D^{25}$ = +39.6 (c 1.14, $CHCl_3$).

^{1}H NMR 600 MHz (*$CDCl_3$*): δ ppm 7.37-7.25 (m, 5H), 4.57 (d, J = 12.1 Hz, 1H) , 4.53 (d, *J* = 12.1 Hz, 1H), 3.80 (m, 1H), 3.71 (m, 1H), 3.54-3.41 (m, 2H), 3.47

(dd, *J* = 10.0 and 6.6 Hz, 1H), 3.38 (dd, 10.0 and 4.5 Hz, 1H), 2.56 (bs, 1H), 1.16 (d, J = 6.3 Hz, 3H), 1.11 (d, J = 6.3 Hz, 3H).

^{13}C NMR 150 MHz (*$CDCl_3$*): δ ppm 138.1, 128.3, 127.5 (two C's), 74.3, 73.9, 73.2, 71.8, 66.2, 17.6, 16.6.

5.3.6 Synthesis of (2*S*,2'*R*)-2,2'-oxybis(propan-1-ol) **(*S*,*R*)-18** and (2*S*,2'*S*)-2,2'-oxybis(propan-1-ol **(*S*,*S*)-18**.



The reactions were carried out in with a shaker hydrogenation apparatus (Parr) and monitored by.

Reaction 1: **(*S*,*R*)-17**: 330 mg, 1.05 mmol; catalyst: 5% Pd/C (50 mg); pressure: 2 bar; solvent: CH_3OH (10 mL); total reaction time: 24 hours. Yield: 130 mg, 92%.

^{1}H NMR 600 MHz (*$CDCl_3$*): δ ppm 4.00 (bs, 2H), 3.66 (m, 2H), 3.60 (dd, *J* = 11.5 and 2.9 Hz, 1H), 3.48 (dd, J = 11.5 and 8.1 Hz, 2H), 1.11 (d, J = 6.4 Hz, 6H).

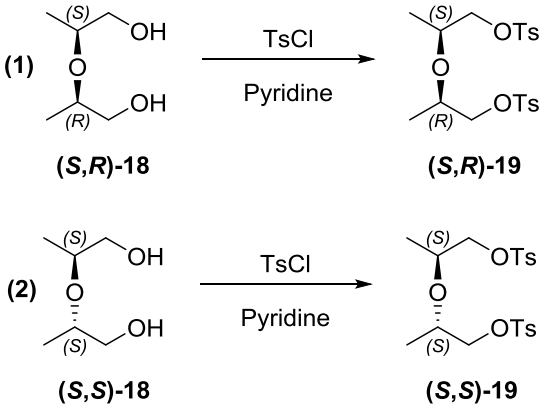
^{13}C NMR 150 MHz (*$CDCl_3$*): δ ppm 76.3, 66.7, 17.8.

Reaction 2: **(*S*,*S*)-17**: 899 mg, 4.0 mmol; catalyst: 5% Pd/C (200 mg); pressure: 2 bar; solvent: CH_3OH (30 mL); total reaction time: 14 hours. Yield: 461 mg, 86%; $[\alpha]_D^{25}$ = +86.8 (c 1.35, $CHCl_3$).

^{1}H NMR 600 MHz (*$CDCl_3$*): δ ppm 3.71 (m, 2H), 3.56 (dd, *J* = 11.5 and 3.2 Hz, 2H), 3.47 (dd, *J* = 11.5 and 7,3 Hz, 2H), 2.86 (bs, 2H), 1.13 (d, *J* = 6.2, 6H).

^{13}C NMR 150 MHz (*$CDCl_3$*): δ ppm 73.0, 66.4, 16.1.

5.3.7 Syntheses of (2*S*,2'*R*)-oxybis(propane-2,1-diyl) bis(4-methylbenzenesulfonate) **(*S*,*R*)-19** and (2*S*,2'*S*)-oxybis(propane-2,1-diyl) bis(4-methylbenzenesulfonate) **(*S*,*S*)-19**.



Reaction 1: TsCl (953 mg, 5 mmol) was added to a solution of **(*S*,*R*)-18** (142 mg, 1.05 mmol) in anhydrous pyridine (2 mL) under stirring and cooled with an ice bath. The reaction was kept at approximately 4ºC for 48 hours. Water/ice (15 mL) was then added and the reaction remained under stirring for 60 minutes. The resulting product was not filterable, so it was extracted with CH_2Cl_2 (4 x 5 mL). HCl 3M aq. (8 mL) was added under vigorous agitation in order to allow the elimination of excess pyridine from the organic phase. The organic phase was consecutively washed with water (3 x 5 mL) and brine (3 mL), dried with $MgSO_4$ and concentrated. The product was purified by flash chromatography (20% EtOAc in petroleum ether). Yield 412 mg, 88.6%.

^{1}H NMR 400 MHz (*$CDCl_3$*): δ ppm 7.78 (m, 4H), 7.35 (m, 4H), 3.81 (dd, J = 10.2 and 4.5 Hz, 2H), 3.87 (dd, J = 10.2 and 6.2 Hz, 2H), 2.71 (m, 2H), 2.45 (s, 6H), 1.06 (d, J = 6.4 Hz, 6H).

^{13}C NMR 100 MHz (*$CDCl_3$*): δ ppm 145.0, 132.8, 129.9, 127.9, 72.6, 72.0, 21.6, 17.5.

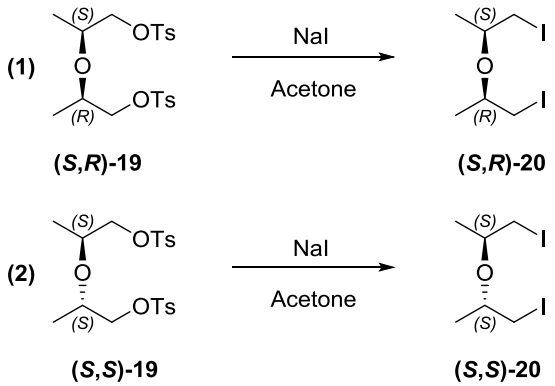
Reaction 2: TsCl (1.89 g, 9.9 mmol) was added to a solution of **(*S*,*S*)-18** (440 mL, 3.3 mmol) in anhydrous pyridine (3.3 mL) under stirring and cooled with an ice bath. The reaction was kept at approximately 4ºC for 48 hours. Water/ice (10 mL) was then added and the reaction remained under stirring for 60 minutes. Differently from the reaction with the (*S*, *R*) diastereoisomer, a solid

was formed. After filtration, the solid was washed with HCl 2M aq. (2 mL), water (2 x 2 mL) and brine (2 mL). The solution was then dried with $MgSO_4$. The product was crystallized in 5 mL of methanol. Yield: 1.25 g, 86%; mp = 78-80 ºC; $[\alpha]_D^{23}$ = +3.8 (c 1.30, $CHCl_3$).

^{1}H NMR 400 MHz (*$CDCl_3$*): δ ppm 7.77 (m, 4H), 7.34 (m, 4H), 3.85 (m, 4H), 7.74 (m, 2H), 2.45 (s, 6H), 1.04 (d, J = 6.3 Hz, 6H).

^{13}C NMR 100 MHz (*$CDCl_3$*): δ ppm 144.9, 132.9, 129.8, 127.9, 73.0, 72.5, 21.6, 17.1.

5.3.8 Syntheses of (*S*)-1-iodo-2-(((*R*)-1-iodopropan-2-yl)oxy)propane **(*S*,*R*)-20** and (*S*)-1-iodo-2-(((*S*)-1-iodopropan-2-yl)oxy)propane **(*S*,*S*)-20**.



Reaction 1: **(*S*,*R*)-19** (206 mg, 0.47 mmol) was added to a saturated solution of NaI (279 mg, 1.86 mmol) in acetone (1 mL), which was then heated to 60ºC. After 18 hours, the suspension was diluted with Et_2O (15 mL). The resulting solution was washed with water (2 x 3 mL) and brine (3 mL) and dried with $MgSO_4$. Yield: 140 mg, 85%.

^{1}H NMR 400 MHz (*$CDCl_3$*): δ ppm 3.58 (m, 4H), 3.28 (dd, J = 10.1 and 5.2 Hz, 2H), 3.16 (dd, J = 10.1 and 6.2, 2H), 1.29 (d, J = 6.1, 6H).

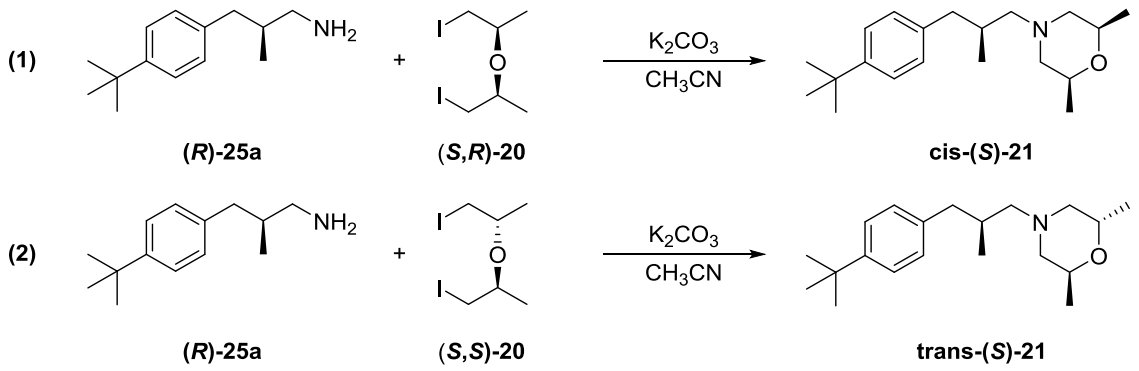
^{13}C NMR 100 MHz (*$CDCl_3$*): δ ppm 73.8, 20.8, 11.2.

Reaction 2: **(*S*,*S*)-19** (1.20 g, 2.84 mmol) was added to a saturated solution of NaI (1.5 g, 10 mmol) in acetone (3.5 mL) under stirring and nitrogen. Heated to 50ºC for 14 hours. The suspension was then cooled diluted with Et_2O (40 mL). The resulting solution was washed with water (2 x 4 mL) and brine (4 mL) and dried on $MgSO_4$. The residue, after solvent evaporation, was purified by flash chromatography. Yield: 855 mg, 85%; $[\alpha]_D^{23}$ = +11.0 (c 2.0, $CHCl_3$).

^{1}H NMR 400 MHz (*$CDCl_3$*): δ ppm 3.57 (m, 2H), 3.21 (dd, J = 10.2 and 5.2 Hz, 2H), 3.16 (dd, J = 10.2 and 5.9 Hz, 2H), 1.32 (d, J = 6.1 Hz, 6H).

^{13}C NMR 100 MHz (*$CDCl_3$*): δ ppm 73.8, 21.1, 11.3.

5.3.9 Syntheses of (2*S*,6*S*)-4-((*S*)-3-(4-(tert-butyl)phenyl)-2-methylpropyl)-2,6-dimethylmorpholine trans-(*S*)-**21** and (2*S*,6*R*)-4-((*S*)-3-(4-(tert-butyl)phenyl)-2-methylpropyl)-2,6-dimethylmorpholine cis-(*S*)-**21**.



Reaction 1: (*S*,*R*)-**20** (140 mg, 0.40 mmol) and K_2CO_3 (107 mg, 0.78 mmol) were consecutively added to a solution of (*R*)-**25a** (75 mg, 0.36 mmol) in anhydrous CH_3CN (1 mL). The reaction was heated to 70 ºC and monitored by TLC. After 20 hours, the reaction was cooled and CH_2Cl_2 (15 mL) was added. The organic phase was washed with water (2 x 2 mL) and brine (2 mL), dried and concentrated. The product was purified by flash chromatography. Yield 90 mg, 82%; $[\alpha]_D^{25}$ = -1.2 (c 1.32, $CHCl_3$).

^{1}H NMR 400 MHz (*$CDCl_3$*): δ ppm 7,28 (m, 2H), 7.08 (m, 2H), 3.67 (m, 2H), 2.76 (dd, J = 13.4 and 4.7 Hz, 1H), 2.70 (m, 1H), 2.66 (m, 1H), 2.28 (dd, J = 13.4 and 8.6 Hz, 1H), 2.18 (dd, J = 12.2 and 7.2 Hz, 1H), 2.09 (dd, J = 12.2 and 7.5 Hz, 1H), 1.79 (m, 1H), 1.69 (m, 1H), 1.66 (m, 1H), 1.31 (s, 9H), 1.150 (d, J = 6.2 Hz, 3H), 1.147 (d, 6.2 Hz, 3H), 0.85 (d, 6.4 Hz, 3H).

^{13}C NMR 100 MHz (*$CDCl_3$*): δ ppm 148.4, 137.9, 128.8, 124.9, 71.71, 71.68, 65.0, 60.1, 59.9, 40.7, 34.3, 32.0, 31.4, 19.2, 18.0.

Mass spectrometry: ESI-MS, MeOH, positive ion scan, $[M+H]^+$ 304 m/z 100%, $[M+Na]^+$ 326 m/z 22%.

Reaction 2: (*S*,*S*)-**20** (179 mg, 0.50 mmol) and K_2CO_3 (138 mg, 1 mmol) were consecutively added to a solution of (*R*)-**25a** (95 mg, 0.46 mmol) in anhydrous CH_3CN (1 mL). The reaction was heated to 70 ºC and monitored by TLC. After 20 hours, the reaction was cooled and CH_2Cl_2 (15 mL) was added. The organic phase was washed with water (2 x 2 mL) and brine (2 mL), dried and

concentrated. The product was purified by flash chromatography. Yield: 126 mg, 90%; $[\alpha]_D^{23}$ = -11.8 (c 1.40, $CHCl_3$).

^{1}H NMR 400 MHz (*$CDCl_3$*): δ ppm 7.28 (m, 2H), 7.08 (m, 2H), 4.00 (m, 2H), 2.75 (dd, J = 13.5 and 4.9 Hz, 1H), 2.42 (m, 2H), 2.32 (dd, J = 13.5 and 8.2 Hz, 1H), 2.15-2.08 (m, 3H), 2.05 (m, 1H), 1.94 (m, 1H), 1.31 (s, 9H), 1.23 (d, J = 6.5 Hz, 6H), 0.86 (d, J = 6.7 Hz, 3H).

^{13}C NMR 600 MHz (*$CDCl_3$*): δ ppm 148.4, 137.9, 128.9, 124.9, 66.8, 65.0, 59.2, 40.7, 34.3, 32.1, 31.4, 18.2, 17.9.

Mass spectrometry: ESI-MS, MeOH, positive ion scan, $[M+H]^+$ 304 m/z 53%, $[M+Na]^+$ 326 m/z 100%.

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