# Preparation and Synthetic Use of Enantiopure Naphthalene Dihydrodiols

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**Abstract:** Asymmetric diols can be used in organic synthesis as chiral synthons or auxiliaries. These two uses show different scopes. In the first case the compound substructure must be present in the final product and, consequently, the possibilities are limited by the number of the possible targets. In the second case the number of variables is greater and the combinations are virtually infinite. In this respect, the use of enantiopure diols has found large coverage, also favored by the availability of enzymatically prepared substrates. In this review we will focus on the use of a special subclass of diols, those derived from naphthalene precursors. An account of both uses will be presented, taking special care of the potential future developments. In addition, a brief account on the preparation methodology of enantiopure 1,2-dihydro-1,2-dihydroxy naphthalenes will be presented.

**Keywords**: 1,2-Dihydro-1,2-dihydroxy naphthalenes, enantioselective preparation, stereoselective preparation, chiral auxiliaries, chiral synthons, enzymatic methods, chemical methods, dioxygenases, monooxygenases.

## 1. INTRODUCTION

In recent years the importance of enantiomerically pure compounds has grown following the evolution of both regulation rules and new material needs. The specific behavior of chiral compounds with respect to interactions with the environment is so decisive that we cannot neglect it; for example, many drugs are active in only one enantiomeric form, and sometimes the presence of the wrong enantiomer has negative effects [1, 2]. As a consequence, the need for new efficient enantioselective preparations has mounted.

Fundamentally, there are two ways to prepare non racemic *chiral* compounds: the first is to synthesize them using enantiopure *chiral* building blocks; the second is to use enantioselective synthetic reactions. In both cases, reactants that already contain the property of being *chiral* are needed. This goal is always reached using natural sources that can provide a number of chiral compounds; these last can be used at different levels to induce chirality into the desired product. In this sense, natural sources supply: chiral auxiliaries to be used in racemate separations; chiral auxiliaries to be used in enantioselective syntheses; chiral synthons to be directly used as synthetic building blocks. In the past, most of the natural compounds derived from natural sources by extraction procedures, but, using enzymatic preparations, it is now possible to prepare many useful compounds in good amounts [3-5]. Microbes represent one of the most fruitful sources of active enzymes, because their enzymatic reserve is rich and easy to use [6]. In the field of oxidations the microbial oxygenases are quite unique and they have been often used in the bioconversion of low cost material into valuable non racemic chiral derivatives [7].

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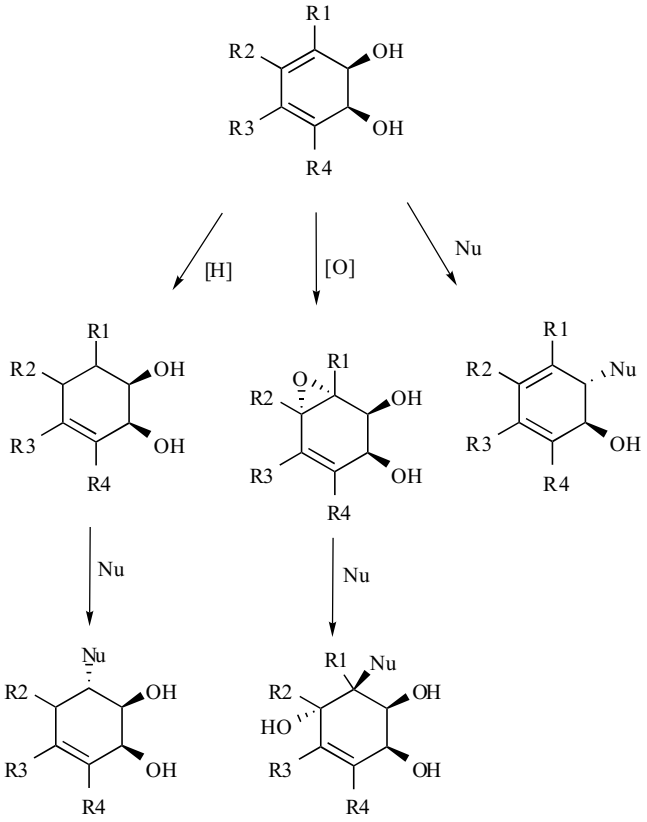
Enantiopure diols are special members of the family of chiral compounds; they can be used both as synthons and auxiliaries. They can be easily transformed into other more interesting compounds, while preserving the non racemic attribute. A recent review by Hudlicky *et al.* [8] has focused on the use of diols mainly derived from monocyclic arenes and obtained by enzymatic dihydroxylation. The authors point to the versatility of this way to prepare many new




**Scheme 1.** Products from modification of benzene diols.

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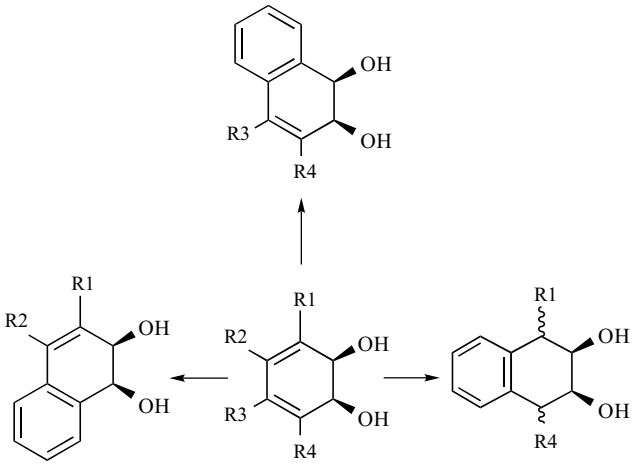
interesting compounds. In fact the 1,2-dihydro-1,2-dihydroxy benzenes can be easily transformed exploiting the functional groups still present on the molecule after the bio-oxidation: i.e. the diene substructure, the diol group, the ring substituent(s) (Scheme **1**).

In the paper by Hudlicky *et al.* [8], the cases where two R groups are part of a ring are not explicitly analyzed; however, in recent literature bicyclic and polycyclic compounds are successfully used in chiral chemistry. The presence of a second ring can be important because the geometry of the molecule is affected, giving rise to better selection of the enantiospace; in addition, it changes the compound interactions with the reaction environment, e.g. it gives a better solubility in apolar solvents.

In this group of compounds naphthalene derivatives have a special role, mainly because they can be prepared using chemoenzymatic procedures and, consequently, are easily available [9-13]. The main difference between benzene and naphthalene derivatives is the presence of the aromatic ring at the end of the enzymatic reaction (Scheme **2**).

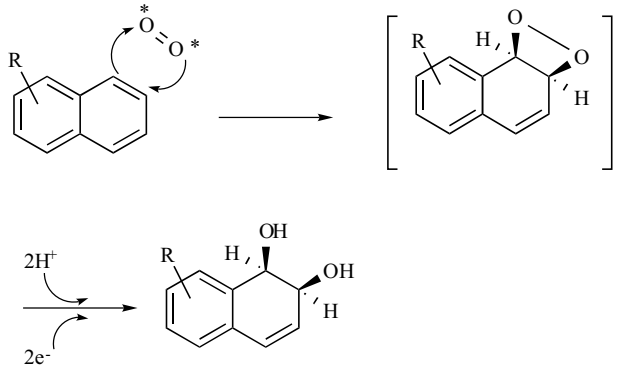



**Scheme 2.** Products from naphthalene diols. At least two ring substituents are part of the remaining aromatic ring.

This fact can decrease the power of the compounds if used as synthons, but it can increase their versatility if used as auxiliaries. In addition, the remaining aromatic ring confers greater rigidity to the molecule improving the stereoselectivity of both its following transformations and of its chiral directing power.

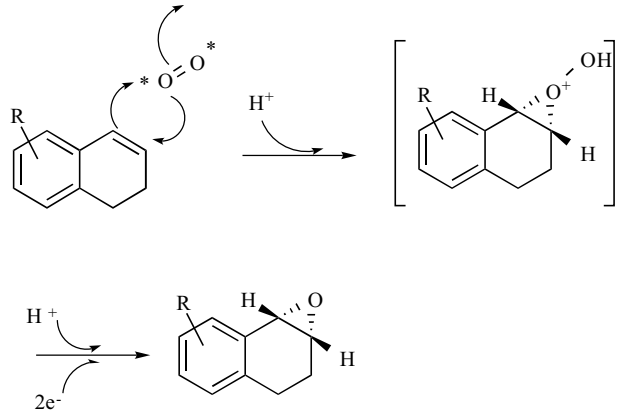
## 2. BIOCHEMICAL SYNTHESIS

As mentioned above the most powerful way to prepare enantiopure 1,2-dihydro-1,2-dihydroxy naphthalenes is offered by the enzymatic preparations. These are usually highly selective, environmentally compatible, and cost effective. One disadvantage of the enzymatic preparation is that only one enantiomer can be usually obtained; however, this disadvantage is less and less important, because, on the one hand, enzymes with new selectivity are discovered, and, on the other hand, the enantiopure compounds can be often transformed into their stereoisomers. We can imagine many enzymatic ways to produce these compounds; but the three most direct approaches are, undoubtedly, double bond dioxygenation, double bond monooxygenation and α-hydroxy ketone racemate resolution. The first activity transforms naphthalenes into the corresponding 1,2-dihydro-1,2-dihydroxy derivatives as shown in Scheme (**3**).




**Scheme 3.** Naphthalene dioxygenation mechanism.

The second activity transforms 1,2-dihydro naphthalenes into the corresponding epoxydes that must be then converted into the 1,2,3,4-tetrahydro-1,2-dihydroxy naphthalenes, as shown in Scheme (**4**).



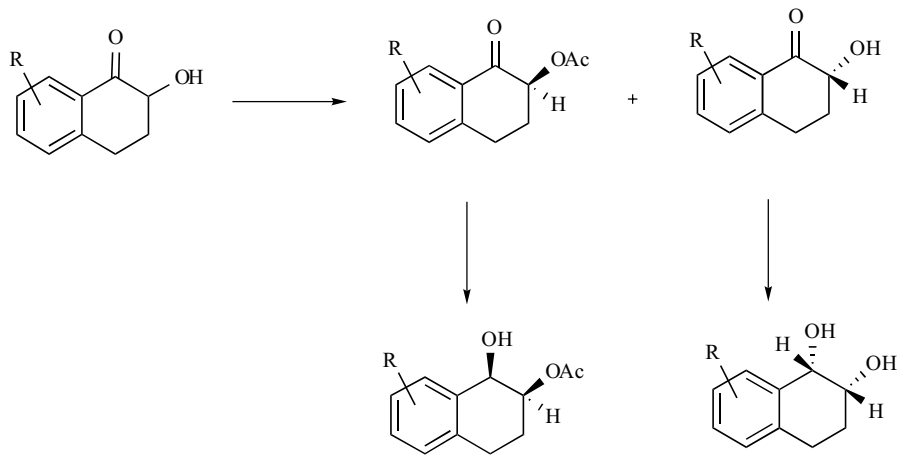

**Scheme 4.** Naphthalene monooxygenation mechanism.

The third activity separates racemic α-hydroxy ketones into the corresponding enantiopure derivatives, which are then reduced to 1,2,3,4-tetrahydro-1,2-dihydroxy naphthalenes following the route shown in Scheme (**5**).

There is an evident difference between the three routes: the first two routes directly produce only one enantiomer, the third one is a racemate resolution and, in principle, can give both enantiomers but only in a 50 % yield, each; however, it is easy to understand that the unwanted substrate can be promptly recycled.

### a. Dioxygenases

Bacterial aromatic ring dioxygenases are multicomponent enzyme systems capable of catalyzing the initial incorporation of molecular oxygen and of two hydrogen atoms into the aromatic substrate to produce the cis-diene diol [14-17]. They are non-heme iron proteins, where the catalytic site is a single iron atom positioned in a flat lipophilic enzymatic cavity. They have been isolated from many microorganisms, but those belonging to the *Pseudomonas* species have been mostly studied. The genes codifying for the protein have been located, sequenced and




**Scheme 5.** Racemate separation by hydrolases and successive carbonyl reduction.

cloned in appropriate plasmids that have been successively inserted into host bacteria producing some recombinant strains; these have been extensively used as biocatalysts [9-13]. The use of whole cell biocatalysts is preferred to that of isolated enzymes, because the dioxygenases are difficult to isolate and purify, and they require the presence of a cofactor (NAD(P)H) that must be regenerated [18]. Using whole cells the main problem is shifted from the biocatalyst to the reaction environment. In fact, microorganisms require a water medium while the substrates and the products are usually scarcely soluble in water. Consequently, in order to increase the conversion productivity much work has been spent in the optimization of the reaction conditions [19-25]. The first considered aspect concerns the substrate delivery; as mentioned, naphthalenes are scarcely soluble in water, thus they tend to aggregate within the medium and to become less and less available to the cell. One solution is represented by the use of an organic solvent that can dissolve large substrate amounts. Obviously, the solvent must have some definite characteristics, it should: dissolve the substrate, be unmixable with the water phase, be non toxic to the microbe, have a high boiling point, be safe and, possibly, cheap. The second environment requisite concerns the stability of the biocatalyst. In fact, besides increasing the *per hour* productivity it is important to be able to carry the transformation on as long as possible. This goal has been pursued both developing new biocatalysts and stabilizing the existing ones, e.g. by immobilization.

In 1999 Quintana and Dalton [9] reported the use of immobilized bacterial strains in the production of diols. This paper opened the way to a really competitive biocatalytic approach to the production of enantiopure diol derivatives. In the paper a procedure for continuously producing the diols from the corresponding arenes is described. The procedure is based on the following points:

- Immobilization of cells. The procedure uses barium alginate beads with a cell load of 6-13 * $10^9$ cells per g. of bead.
- Preparation of large-scale biotransformation. 15 g of beads are packed in a column; a constant flow of medium containing nutrients and substrates then passes through the column.

The production of diols ranges from 0.56 to 6.1 moles * $g^{-1}$ DCW (Dry Cell Weight) in 30 – 90 h. This demonstrates that some productions have been scaled to very good levels and are now competitive with chemical syntheses. There are still chances of improvements, e.g. increasing the production in batch modes. In fact, a suitable goal from a chemist viewpoint is the possibility of performing the reaction in the style chemists like more: mixing reactants (i.e. substrate, biocatalyst, solvent), letting the reaction going for some time (minutes, hours), working the reaction up at the end of the transformation. This can be reproduced by biotransformations if: the biocatalyst is stable and easy to handle; the substrate/product concentration is feasible (0.1-1 M); the work up is easy. This goal has been reached by enzymatic reactions (e.g. racemate resolutions) [26]; however, whole cells reactions still need some improvements. There are some recent developments: cell immobilization to stabilize the biocatalyst; biphasic reactions to improve substrate delivery; surfactant use to increase substrate bio-availability [27-29]. Finally, the reaction work up is usually easy and cost-effective.

But, we must consider that biotransformations possess a quite unique attribute: the products are usually enantiopure 1,2-dihydro-1,2-dihydroxy naphthalenes with *cis* relative stereochemistry and 1R,2S absolute stereochemistry. Often, the regiochemistry is also very high, even if there are cases where more than a single regioisomer forms. In Table 1 the general synopsis of the obtained compounds is reported. In addition, some polycyclic aromatic compounds are transformed.

### b. Monooxygenases

An alternative that can be efficiently used to prepare 1,2-diols is represented by the production of epoxydes followed by their hydrolysis. Presently, there are several enzymes that can introduce an oxygen atom onto a double bond [3, 30-36]. The obtained products are usually enantiopure and the biotransformation yield is comparable to that obtained by dioxygenase enzymes. In particular, Panke *et al.* [31] have recently scaled the reaction up to pilot-scale production in the order of 3 mol*$L^{-1}$. The bioconversion is performed in a 42 L bioreactor using a biphasic system implemented as follows:

**Table 1. Synopsis of Naphthalene Diols Obtained by Dioxygenases[a]**

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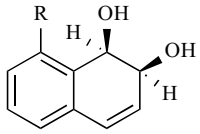
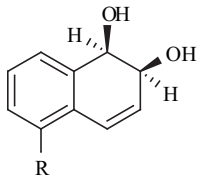
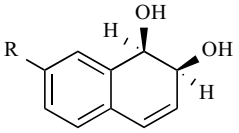
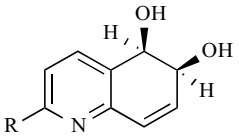
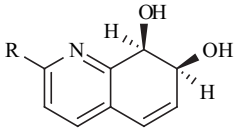
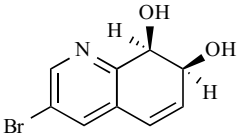
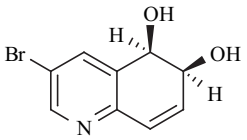
|  | H, $CH_3$, $C_2H_5$<br>$OCH_3$<br>F, Cl, Br<br>$COOCH_3$<br>$NO_2$ |  | H<br>$OCH_3$<br>F, Cl, Br<br>$COOCH_3$<br>$NO_2$ |
|  | H<br>$CH_3$, $C_2H_5$<br>$OCH_3$<br>Cl, Br<br>$COOCH_3$<br>$NO_2$ | | |
|  | H<br>Cl<br>$OCH_3$ |  | H<br>Cl<br>$OCH_3$ |
|  | |  | |

[a] The reported compounds were prepared by various groups. Literature references can be found in [8] and [12].

- Organic phase: bis(2-ethylhexyl) phthalate, 14.8 L
- Water phase: 14.8 L
- Recombinant microorganism: *Escherichia coli* JM101(pSPZ10), containing the monooxygenase from *Pseudomonas* strain VLB120, in growing conditions

These data refer to the production of styrene epoxide, but they can be easily adapted to the production of the 1,2-oxa-1,2,3,4-tetrahydronaphthalene [37].

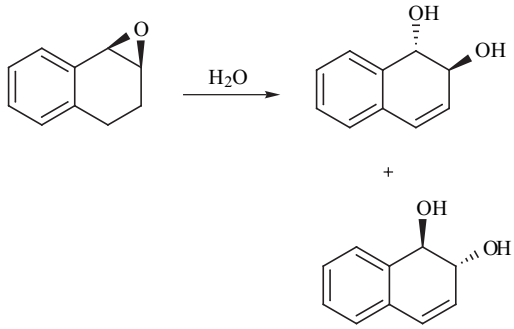
## 3. CHEMICAL SYNTHESIS

The alternative to enzymatic approaches to the synthesis of diols is the use of enantioselective chemical preparations. The theory and the application of chemical enantioselective synthesis have remarkably developed in recent years. Now, the possibility of realizing preparations with more than 90% e.e. is common practice and many methods appear every day.

In the case of 1,2-diols we can distinguish between stereoselective (i.e. syn relative stereochemistry) and enantioselective (i.e. with absolute stereochemistry) syntheses. The former can be still useful in the perspective of a successive racemate resolution in order to obtain both enantiomeric forms; the latter is the desired approach to a single enantiomer.

### a. Stereoselective Synthesis

The most significant transition metal catalyzed oxidation of organic substrates is the osmium catalyzed dihydroxylation of olefins that gives rise to stereospecific cis-selective oxidation of olefins to vicinal diols. This reaction has been known since 1912 [38, 39] when the metal was used in stoichiometric amount; on the contrary, nowadays it is commonly used in catalytic amount in combination with other oxidants that can *in situ* regenerate the reactant [40, 41]. A recent report shows the use of an osmium and NMO (N-methyl morpholine oxide) catalyzed dihydroxylation, in which NMM (N-methyl morpholine) is oxidized to NMO by *m*-CPBA (meta-chloroperbenzoic acid), NMO then regenerates the osmium catalyst. This procedure allows for the preparation of the 1,2,3,4-tetrahydro-1,2(cis)-dihydroxy naphthalene in 90% yield [42].



**Scheme 6.** Racemate production from enantiopure precursor by not-regioselective reaction.

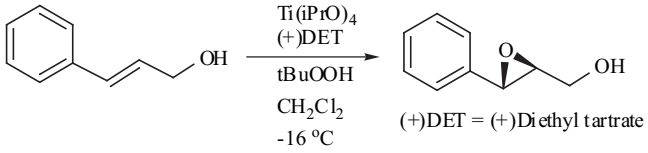
The second possibility to prepare stereospecific diols is *via* epoxide formation and subsequent hydrolysis to arrive to trans diols. This preparation is more versatile than its *osmium* counter part because it is possible to synthesize many derivatives from the epoxyde. Trans opening of the

three-member ring is highly stereospecific, whereas the regioselectivity can vary. This point requires attention in order to produce only one compound; even in the diol case where the two vicinal groups are equal a low regioselectivity could destroy the absolute stereochemistry of the enantiopure epoxide (see Scheme **6**). Nevertheless, this preparation has been systematically studied and optimized and it is highly effective.

### b. Enantioselective Syntheses

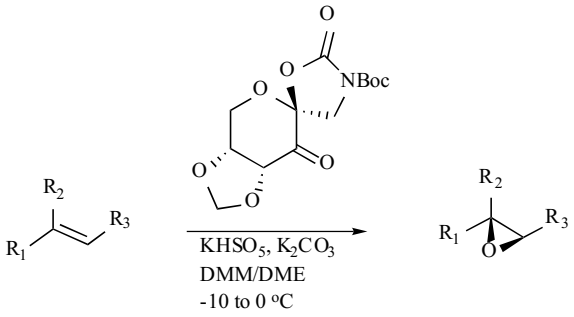
Some of the previous reactions have been modified to preferentially produce one enantiomeric form of the target compound. In particular, Sharpless and collaborators have elaborated methods for the preparation of both 1,2 diols and epoxydes.

Epoxydes of certain ethylenic compounds can be prepared in high e.e. by using hydroperoxide reactants and asymmetric Ti catalysis. The most famous example concerns the oxygenation of allylic alcohols (Scheme **7**) [43].




**Scheme 7.** Enantioselective epoxidation of allyl alcohols.

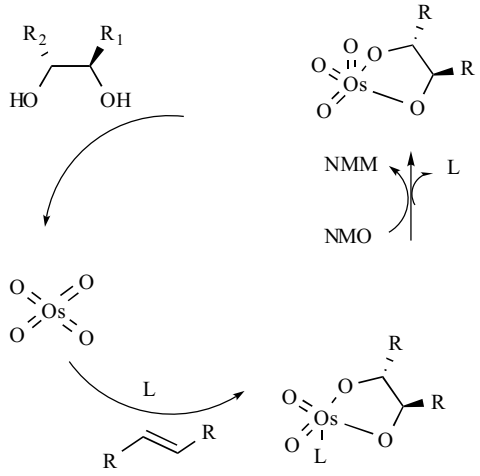
Recently, many more asymmetric epoxide preparations appeared in the literature [44-52]. Most of these methods make use of metal mediated chiral catalysis (Mn, Ni, Ru); they are quite effective in many cases, but 1,2-dihydronaphthalene usually shows limited selectivity. On the contrary, the use of fructose derivatives [43, 46] allows for a good chemical and stereochemical yield, giving the desired epoxide in 88% yield and 84% e.e. [43] (Scheme **8**)




**Scheme 8.** Enantioselective epoxidation of carbon-carbon double bonds.

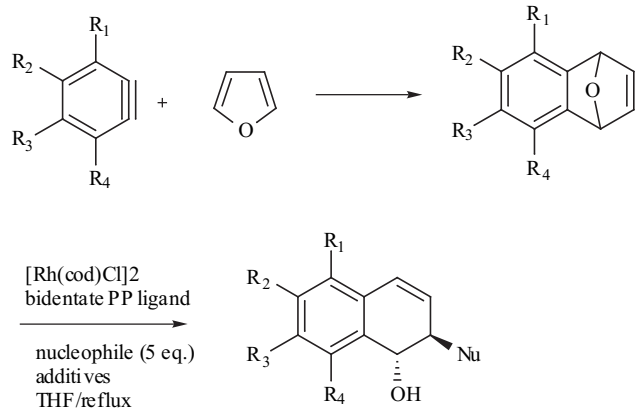
Dihydroxylation of olefins demonstrates much more flexible and efficient. The use of osmium containing asymmetric catalysts gives access to a great number of diols at high e.e. The model reaction (sketched in Scheme (**9**)) makes use of an asymmetric complex of $OsO_4$ to perform the well known oxidation of olefins. The reaction has been developed in recent years and it is now a catalytic process that uses cheap oxidants and that is highly efficient.

NMO, i.e. N-methyl Morpholine N-Oxide, is used to recycle $OsO_4$ that is the real dioxygenation catalyst. Recently, a further improvement uses $H_2O_2$ or ROOH as recycling agents of NMM (N-methyl Morpholine) to minimize secondary reactions generated by excess of NMO. L is the chiral ligand that induces the chirality on the product; much work has been performed in order to select the best ligand and the results are encouraging (e.e. up to 97%) [53-57]. Unfortunately, cyclic olefins do not give high e.e. and, in particular, 1,2,3,4-tetrahydro-1,2-dihydroxy naphthalene has been obtained with a maximum of 29% e.e.




**Scheme 9.** Enantioselective dihydroxylation of C-C double bonds.

Recently a different way to obtain non racemic chiral diols (or similar derivatives) has been reported [58, 59]. It consists in the opening of oxabenzonorbornadienes using nucleophiles in the presence of rhodium complexes (e.g. a chiral ferrocene phosphine complex). Reactants are obtained by 4+2 cycloaddition of benzyne intermediates with furane. The reaction, reported in Scheme (**10**), produces trans diols in good to excellent yield and e.e. (up to 99%).

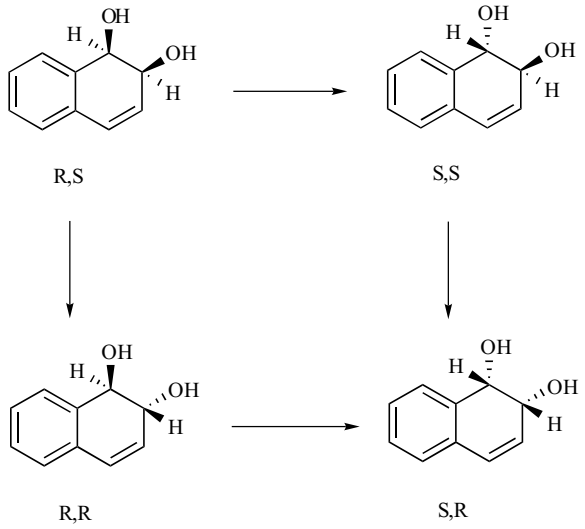



**Scheme 10.** Enantioselective preparation of naphthalene derivatives *via* dihydrofurane ring opening.

## 4. 1,2–DIHYDRO-1,2-DIHYDROXY NAPHTHALENES USES

Enantiopure 1,2 –dihydro-1,2-dihydroxy naphthalenes represent a rich source of chiral compounds that can be of interest both as components of the chiral pool (e.g. drugs, organic advanced materials) and as inducers of chirality (e.g. in enantioselective syntheses; in racemate resolutions). The presence of two hydroxyl groups opens the way to a number of functional group interchanges; in fact, even if the OH

group is considered a bad leaving group, it can be easily transformed into more efficient leaving groups by derivatization. Many of the esters originated from it can be substituted introducing halides, nitrogen atoms, alkyl chains, etc. However, it is clear that the presence of two quasi identical groups complicates their handling. This problem is partially solved in the case of naphthalene derivatives; in fact, here one OH is benzylic and reacts faster than the other, particularly if the hydroxylated ring is reduced in positions 3 and 4. This way, it is possible to access all four the enantiomeric forms of each diol. In addition, at each stage we can exchange a hydroxyl group with a different function (Scheme **11**).

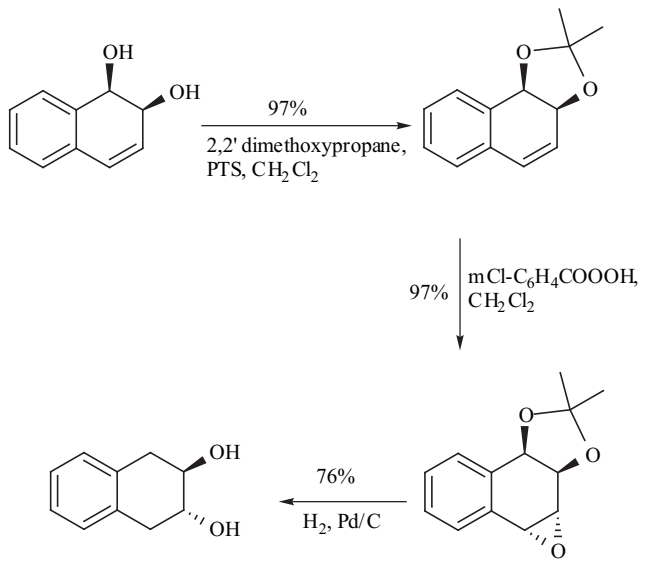



**Scheme 11.** Full enantiospace availability through stereoselective compound correlation.

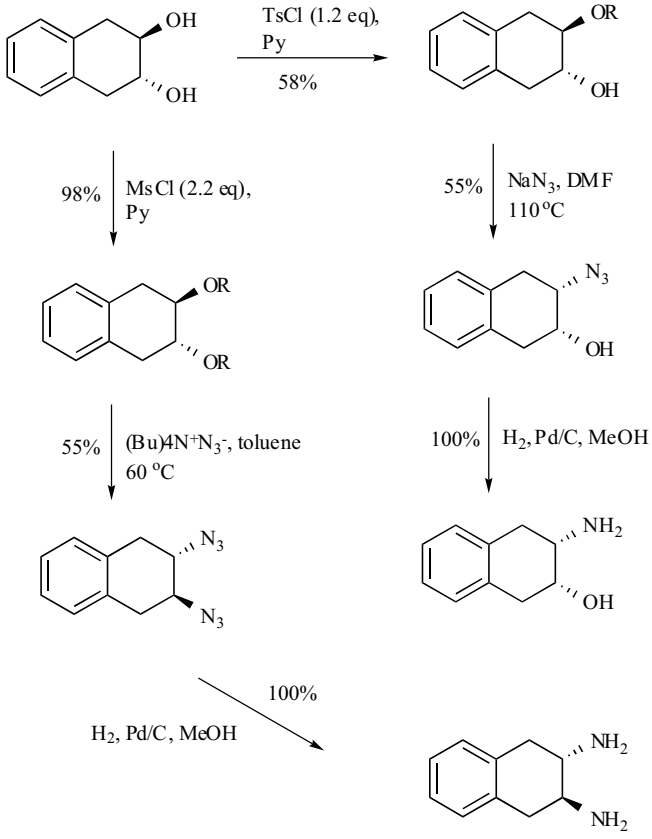
The double bond in position 3,4 is another source of modifications. The simplest is its reduction, but we can easily imagine its oxidation to an epoxide, or to a vicinal diol, a halohydroxy derivative, etc.

### a. Auxiliaries

The first example of transformation of enantiopure 1,2-dihydro-1,2-dihydroxy naphthalenes into a different chiral derivative was published by Orsini *et al.* in 1996 [60]. These authors reported the three step modifications of the (1R,2S)-dihydro-1,2-dihydroxynaphthalene obtained from enzymatic source into the (2R,3R)-dihydroxy-1,2,3,4-tetrahydro derivative in 72% total yield (Scheme **12**). The obtained compound has C2 symmetry and can be used in all the reactions that are known to prefer this particular geometry. Successively, the same group reported the preparation of new compounds by modification of the 2,3-diol; specifically, they prepared the (2S)-amino-(3R)-hydroxy and the (2S,3S)-diamino derivatives, the first in three steps and overall 32% yield, the second in three steps and overall 54% yield [61]. Here, only the diamino compound has the C2 symmetry, but with inverted stereochemistry; whilst the amino alcohol has changed both the absolute and the relative stereochemistry (Scheme **13**). The different coordinating power of the nitrogen containing compounds should permit different uses of this class of auxiliaries.

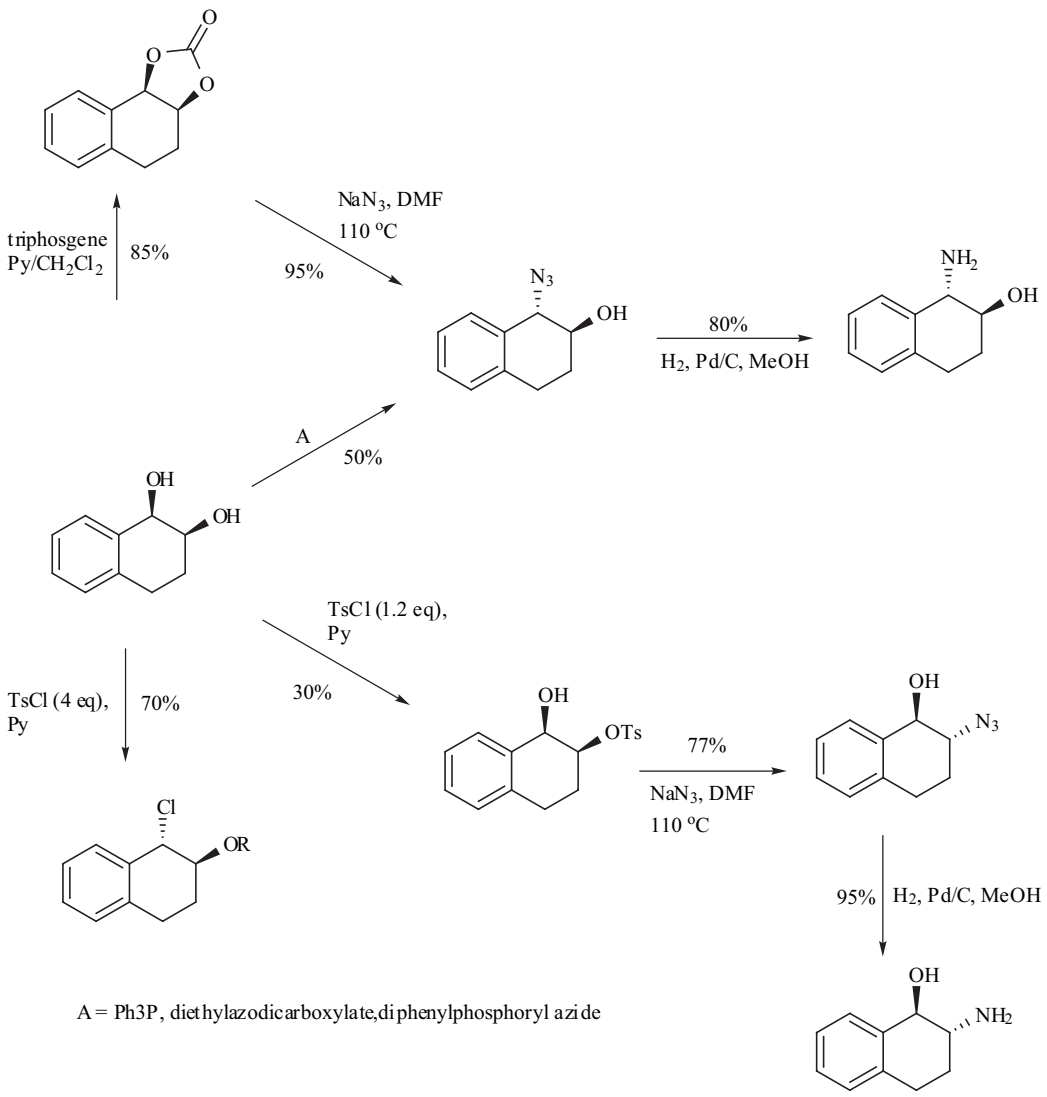



**Scheme 12.** Preparation of enantiopure derivative possessing C2 symmetry.



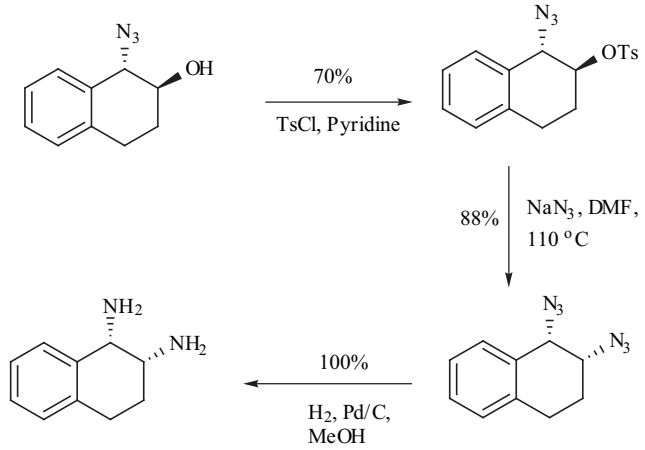

**Scheme 13.** Preparation of further enantiopure 2,3-substituted derivatives.

Finally, starting again from the enantiopure 1,2-dihydro-1,2-dihydroxy naphthalene, Orsini *et al.* [51] prepared a group of 1,2-substituted derivatives with different heteroatomic substituents in different positions and with different stereochemistries. The (1R,2S)-dihydro-1,2-dihydroxy naphthalene has been transformed into the (1S)-amino-(2S)-hydroxy derivative (three steps, 65% overall yield), the (1R)-amino-(2S)-hydroxy derivative (one step, 90% yield), the (1R)-hydroxy-(2R)-amino derivative (three




**Scheme 14.** Preparation of enantiopure 1,2-substituted derivatives.

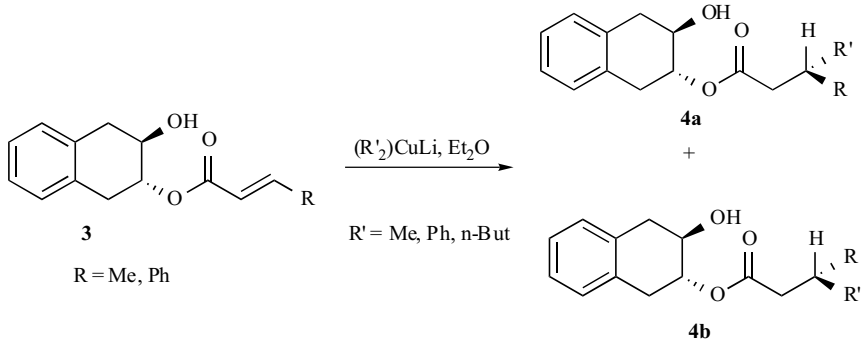
steps, 22% overall yield), and the (1S,2R)-diamino derivative (five steps, 50% overall yield) (Schemes **14**, **15**).




**Scheme 15.** Preparation of enantiopure 1,2-diammino derivative.

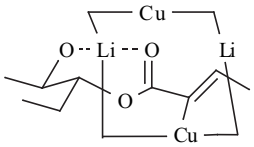
This is the only group that made a general research on the potentially accessible compounds that can be obtained from a single precursor, thus demonstrating that it is possible to prepare a number of new molecules conserving and/or transferring the stereochemistry of one common precursor that can be obtained in enantiomerically pure form. All the other examples concern the preparation and use of one specific auxiliary. The examples of use of 1,2-dihydro-1,2-dihydroxy naphthalene derivatives as chiral auxiliaries are not many, but their number is recently growing.

The first example is the use of the (2R,3R)- dihydroxy-1,2,3,4-tetrahydro naphthalene in two enantioselective reactions: the conjugate addition of alkylcuprates to α,β-unsaturated esters and the alkylation of β-ketoesters [62]. Conjugate addition of alkyl cuprates to α,β-unsaturated esters was performed on both monocrotonate and monocinnamate derivatives of the C2 chiral auxiliary; methyl, phenyl, and n-butyl halides were used as alkylating groups. The yields were between 50% and 90% and the enantioselectivity was always very good, between 80/20 and 94/6, depending on the reactants. The best results were obtained with R = Me and R' = Ph, or n-Butyl (Scheme **16**). The absolute stereochemistry of the major stereoisomer is always the same, pointing to a common intermediate. The




**Scheme 16.** C2-Symmetry auxiliary used in Michael addition to α, β-unsaturated esters.

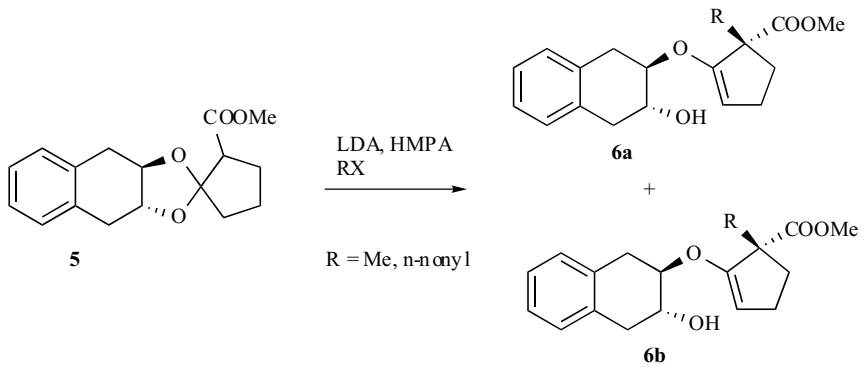
differences in selectivity have been explained through the hypothetic formation of a dimeric intermediate that gives only one stereoisomer, while its enantiomer derives from a more reactive and unselective monomeric intermediate (Scheme **17**).



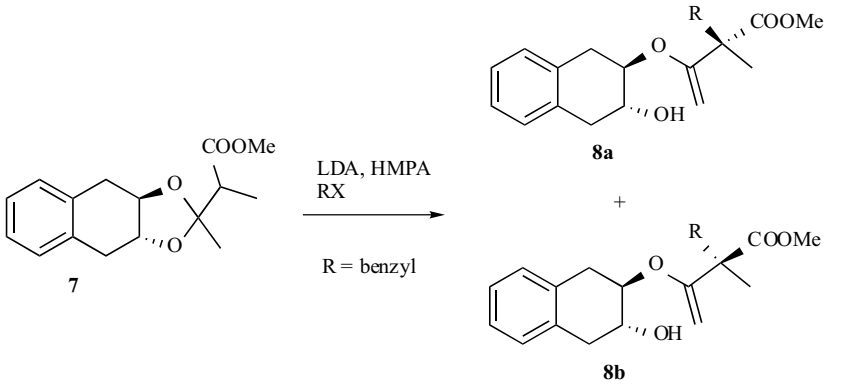

**Scheme 17.** Hypothetical intermediate in asymmetric Michael reaction.

Alkylation of β-ketoesters was performed on both cyclic (Scheme **18**) and acyclic (Scheme **19**) compounds using unhindered alkylating groups. The chiral auxiliary was used to form cyclic ketals that during the reaction open up giving enol ether as final products. Here, the chemical yields were between 65% and 75% and the enantioselectivity in the range 96/4 – 98/2. Again, selectivity is very high and the absolute stereochemistry is always the same. The proximity of the reaction center to the chiral centers is the most probable reason of the success of the reaction and there is no need of invoking a special coordinated intermediate, even if the enolate formed in the first step of the reaction is evidently interacting with the free alcoholic group, thus fixing a preferred conformation for the subsequent alkyl attack.

In 1997, Bellucci *et al.* [63] reported the chemical synthesis and the use of (1S)-amino-(2R)-hydroxy-1,2,3,4-tetrahydronaphthalene together with its N,N-dibutyl derivative. Their synthesis starts from 1,2-dihydronaphthalene and in five steps plus two steps for the enantiomer separation arrives at the enantiopure amino

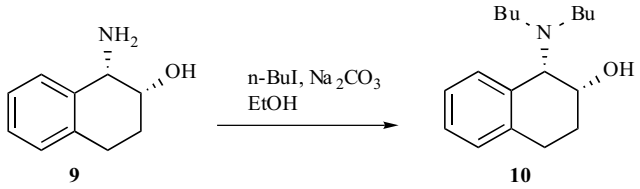



**Scheme 18.** C2-Symmetry auxiliary used in alkylation of cyclic β-keto esters.



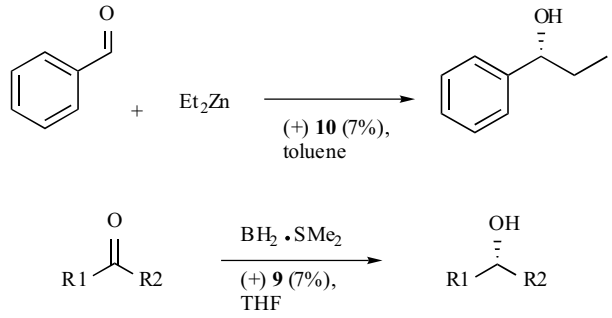

**Scheme 19.** C2-Symmetry auxiliary used in alkylation of acyclic β-keto esters.

alcohol that is then easily transformed into the N,N-dialkyl compound (Scheme **20**).

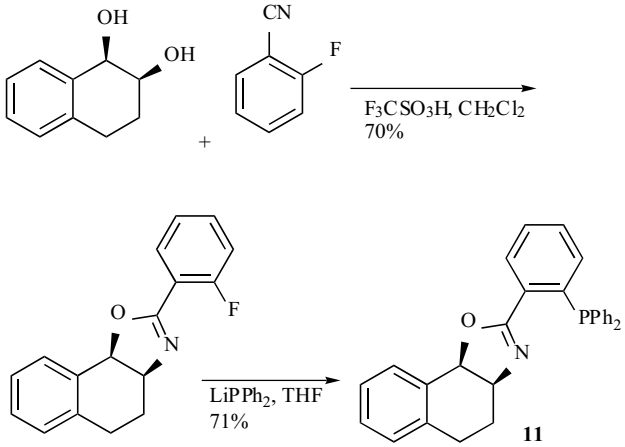



**Scheme 20.** Dibutylation of amino alcohol derivative to prepare the auxiliary used in Scheme 21.

Compound (**10**) is used as chiral auxiliary in the reaction between benzaldehyde and diethyl zinc; the yield is good (80-90%), however, the e.e. is unsatisfactory (~40%). On the contrary, the use of compound (**9**) as chiral auxiliary in the borane reduction of ketones to obtain secondary alcohols gives much better results (chemical yields > 90%, e.e. > 84%) (Scheme **21**). This outcome has been rationalized by the authors that suggest a different intermediate in the two reactions in agreement with previous hypothetical mechanisms [64-67]. In addition, in these reactions the chiral auxiliary is used in catalytic amount, a point that can partially justify the differences in enantioselectivity.

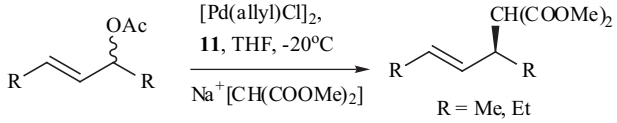



**Scheme 21.** Asymmetric alkylation and reduction of carbonyls using compound (**9**) and (**10**) as catalysts.



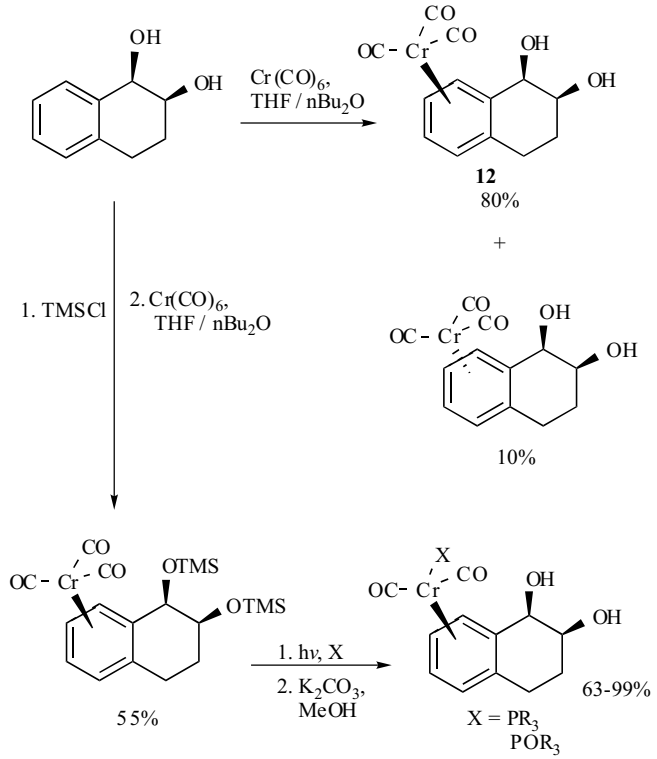

**Scheme 22.** Preparation of auxiliary (**11**) from 1,2,3,4-tetrahydro-1,2-dihydroxy naphthalene.

In 1998, Wiese and Helmchen [68] proposed the use of some chiral phosphines to enhance the enantioselectivity of the Pd-catalyzed allylic alkylation reaction. Among the proposed phosphines there is compound (**11**) that is derived from (1R,2S)-dihydroxy-1,2,3,4-tetrahydro naphthalene following the preparation reported in Scheme (**22**). Compound (**11**) is used in the reaction reported in Scheme (**23**). Chemical yields were good (>95%), and the e.e. (85%) was the best obtained with these class of phosphines in this reaction.



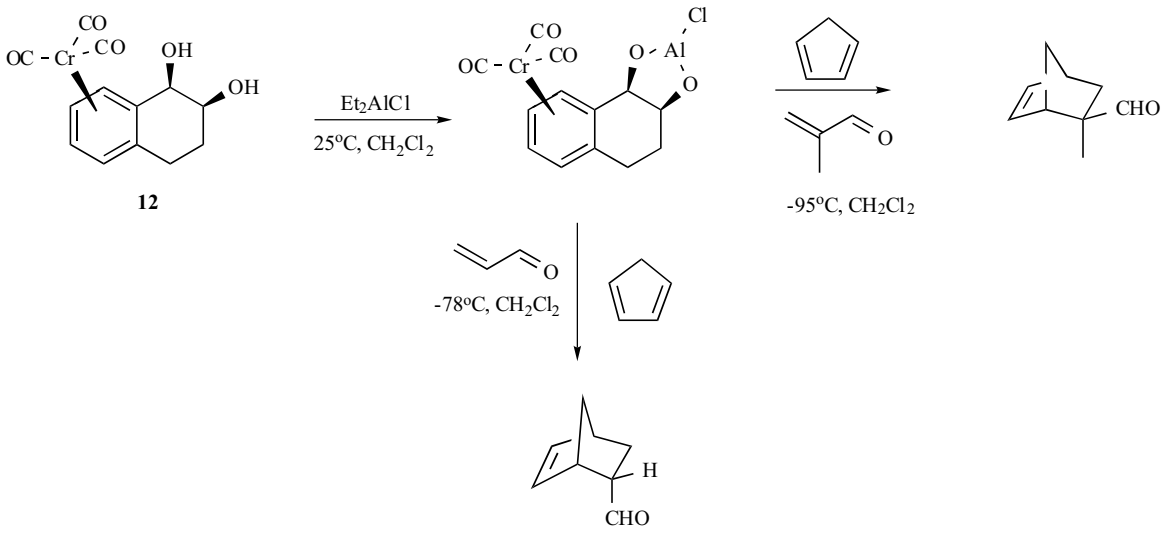

**Scheme 23.** Use of compound (**11**) in asymmetric allylic Pd-mediated substitutions.

Jones *et al.* [69, 70] developed a class of chromium containing compounds that can be used as Lewis catalysts in Diels Alder reactions. The most efficient of these compounds is compound (**12**) that is prepared from commercially available 1,2-dihydroxy-1,2,3,4-tetrahydro naphthalene, through the reaction (Scheme **24**) reported.

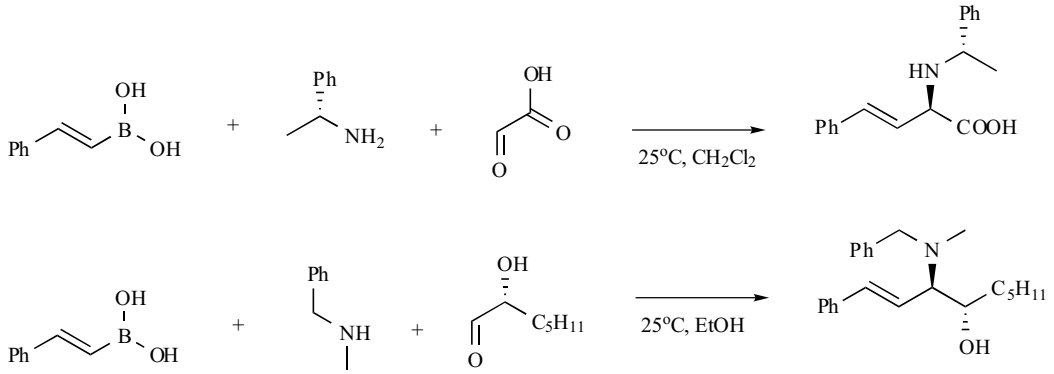



**Scheme 24.** Preparation of chromium asymmetric auxiliary.

All these compounds were used as Lewis chiral catalysts in the Diels Alder addition of cyclo pentadiene to acrolein or 2-methacrolein. Using compound (**12**) it is possible to produce 80% of the adduct in 98:2 exo:endo ratio and in >95% e.e. in the case of methacrolein, while acrolein gives a good chemical yield, but the endo:exo ratio is 85:15 and the e.e. is 85% (Scheme **25**). This is a remarkable result that could be obtained by mixing the power of the chiral diol with the hindering enhancement given by the chromium complex. It is also worthwhile to note the differences in both endo:exo preference and stereoselectivity shown by the two aldehydes. The authors make the hypothesis that the steric hindrance given by the methyl group gives rise to a different coordinative complex, that in one case favors the endo adduct and in the other the exo adduct. This last can be approached more favorably from one enantio face, the other face being buried under the chromium complex.




**Scheme 25.** Use of asymmetric chromium derivative in enantioselective Diels Alder reactions.




**Scheme 26.** Stereoselective Petasis reaction.

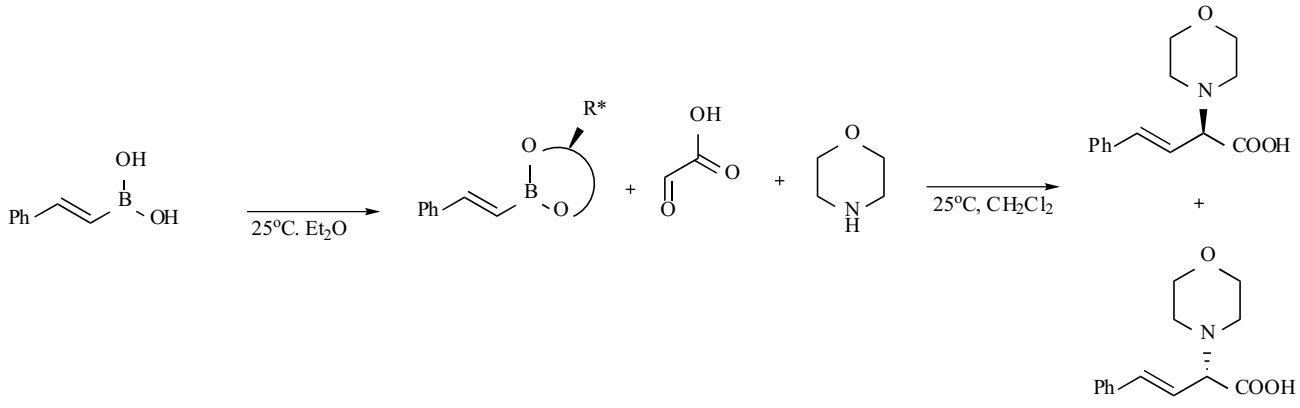
A last example of usage of 1,2-dihydroxy-1,2,3,4-tetrahydro naphthalene as chiral auxiliary is its participation to the modified Petasis condensation [71-73] (Scheme **26**).

This reaction is known to give high diastereoselectivity (66% and 99%, respectively), but there are few examples of its application to give an enantioselective reaction. Koolmeister *et al.* [74] reported the first example of this version of Petasis reaction employing different chiral auxiliaries and following the modified Scheme (**27**) sketched below.

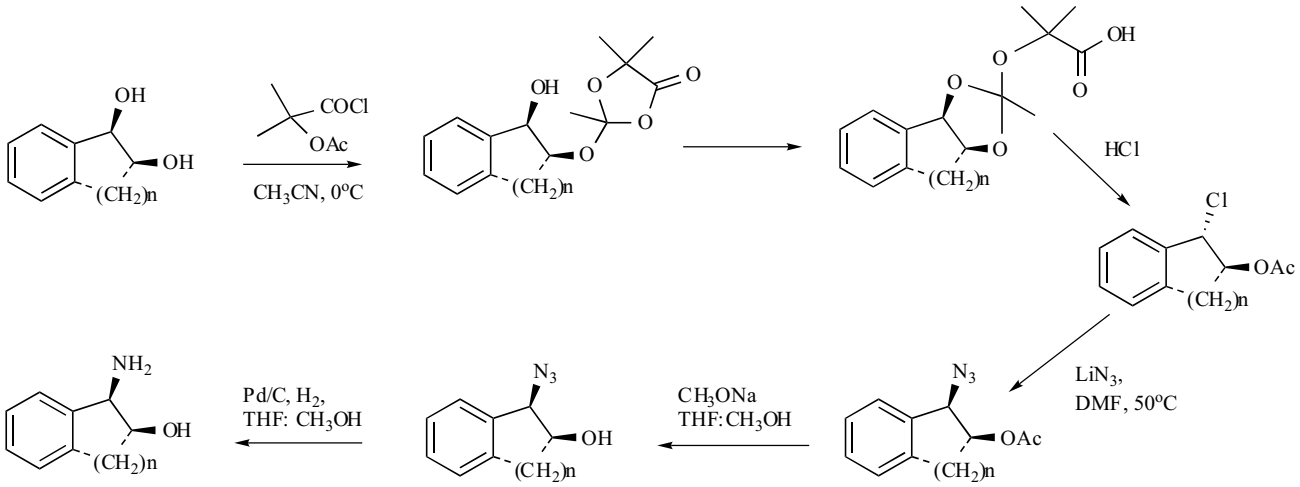
Among the used chiral diols there was 1,2-dihydroxy-1,2,3,4-tetrahydro naphthalene; unfortunately, the e.e. is not very satisfactory (up to 11%).

### b. Synthons

The other common use of chiral compounds is their introduction into a complex molecule as important substructures (commonly called synthons). The straightforward way to effectively locate the part of a structure that can be derived from an available precursor is




**Scheme 27.** Enantioselective Petasis reaction using 1,2,3,4-tetrahydro-1,2-dihydroxy naphthalene derived intermediate.



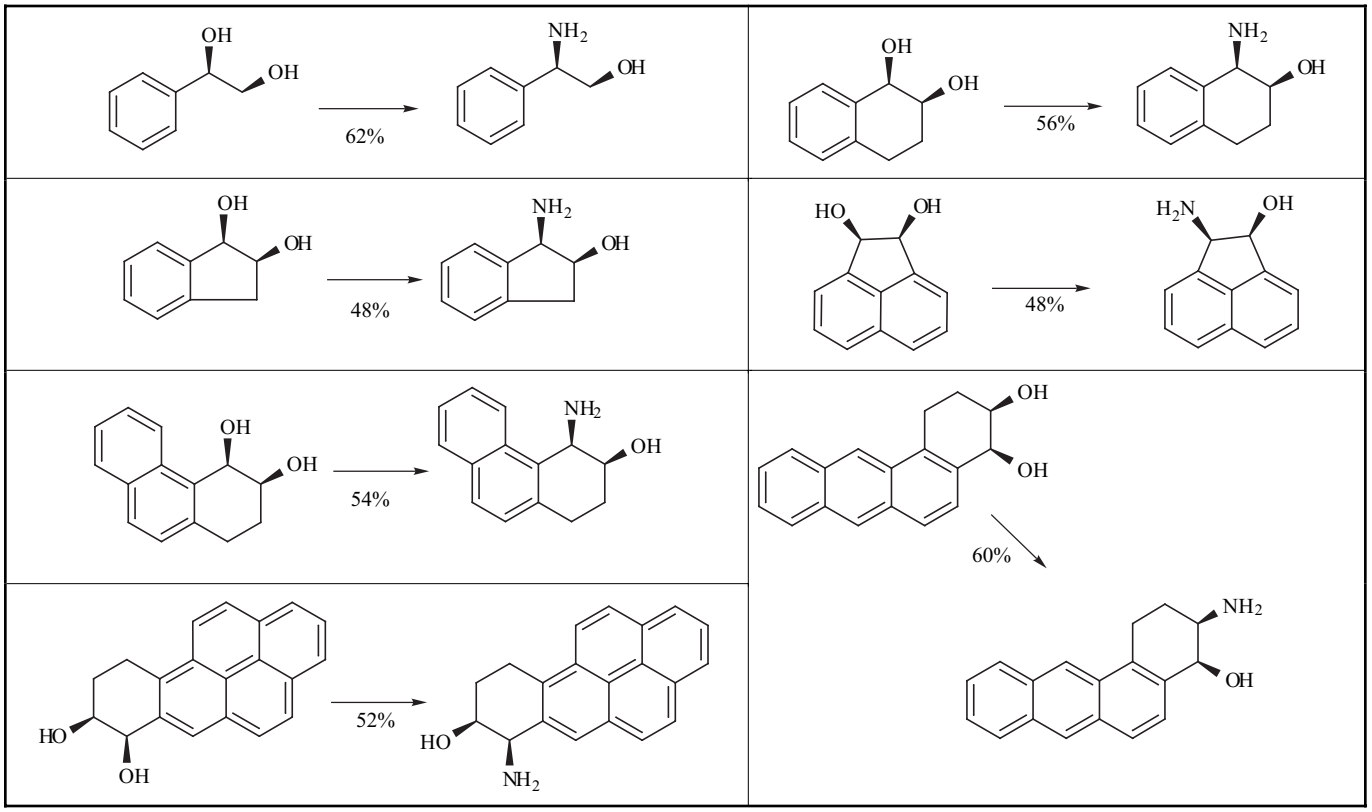

**Scheme 28.** Preparation of enantiopure aminoalcohols.

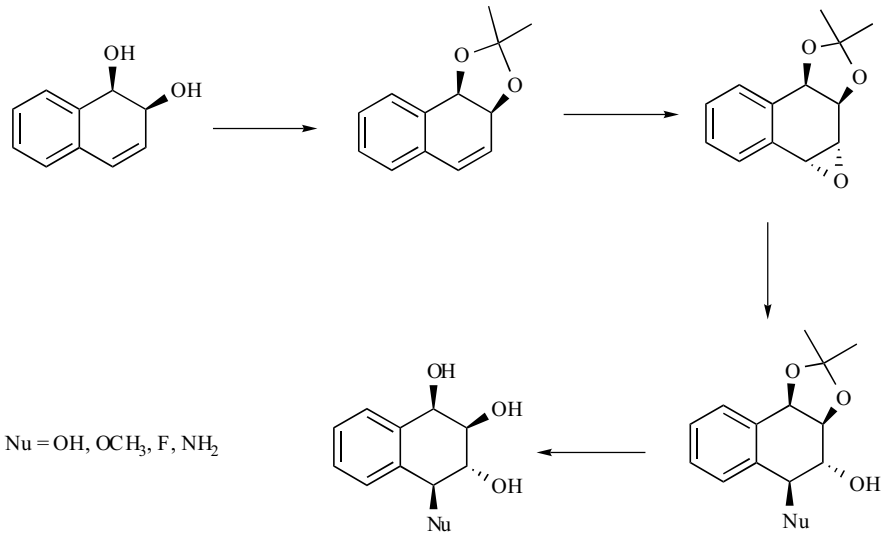
one of the most common and exciting challenges that synthesis planning deals with. The optimization of the choice of suitable synthons depends on the chemist ability to develop a synthesis plan, but also on the availability of the precursors. Consequently, it is common practice to prepare pools of molecules that share some recurring features, and are thus part of a collective synthetic space (e.g. aromatic compounds, amino acids); probably, the most cited of these pools is the chiral pool. It is composed by natural compounds, synthetic commercial compounds, bio prepared compounds, and all their synthetic neighbours. In the case of 1,2-dihydro-1,2-dihydroxy naphthalenes we have few examples of their insertion in diverse structures. Nevertheless, due to the growing production of new derivatives we can expect more examples in the future, with the development of new chiral auxiliaries, as reported in the preceding section.

The first example of synthetic use of diols derived from polycyclic arenes is by Lakshman and Zajc in 1996 [75]. They reported the synthesis of seven amino alcohols derived from the corresponding dihydroxy compounds following the synthetic Scheme (**28**).

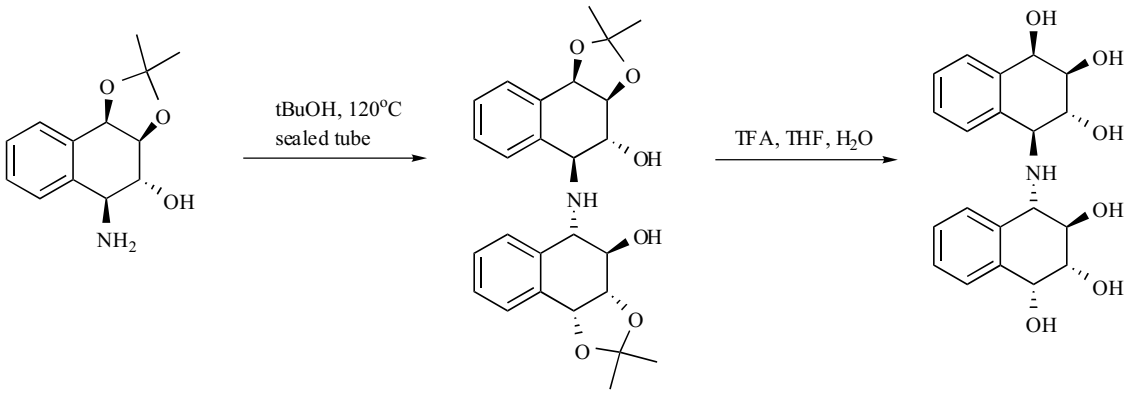
All the precursors were obtained by asymmetric dihydroxylation procedures and they are representative of a large variety of cyclic compounds (Table 2). These syntheses

**Table 2. 1,2-Amino Alcohols Obtained Following the Reaction Scheme (28)**






**Scheme 29.** Preparation of conduritol analogues.

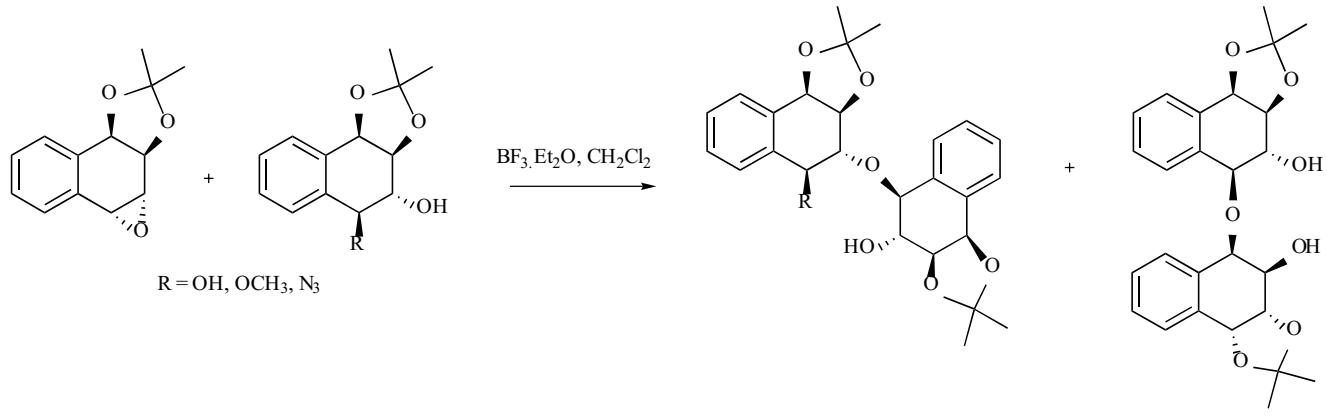



**Scheme 30.** Preparation of a conduritol analogue dimer.

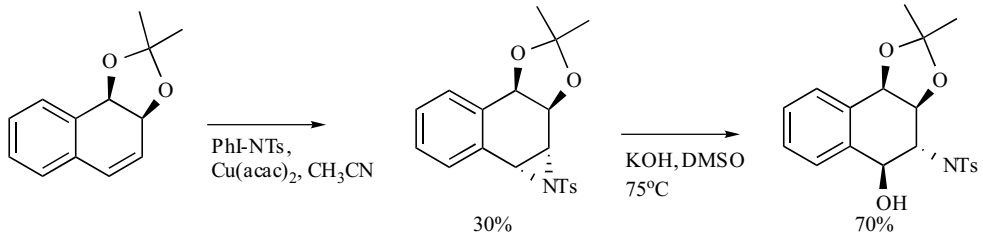
are a remarkable example of the preparation of a group of similar compounds that should become the source of a comparative study.

In 1997, Lallemand *et al.* [76] reported the preparation of some conduritol analogs all deriving from the enantiopure 1,2-dihydro-1,2-dihydroxy naphthalene. The synthetic scheme is sketched below and shows the first example of the use of the preexisting chirality of these compounds to produce complex asymmetric compounds. Here, the common precursor is a commercial compound obtained by enzymatic preparation (Scheme **29**). In the same paper the synthesis of a dimer derivative of one of the previous compounds is reported, producing a highly complex chiral structure (Scheme **30**).

In a following 1998 paper [77], the same authors extended their synthetic effort to more dimeric compounds (Scheme **31**). In addition, some more compounds were obtained modifying in part the previous route, as reported in Scheme (**32**).



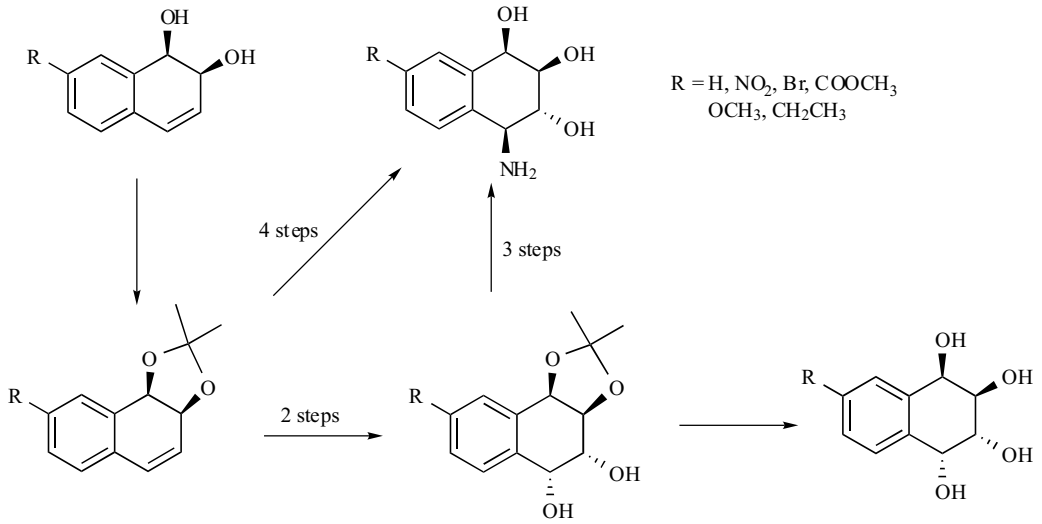

**Scheme 31.** Preparation of another conduritol analogue dimer.



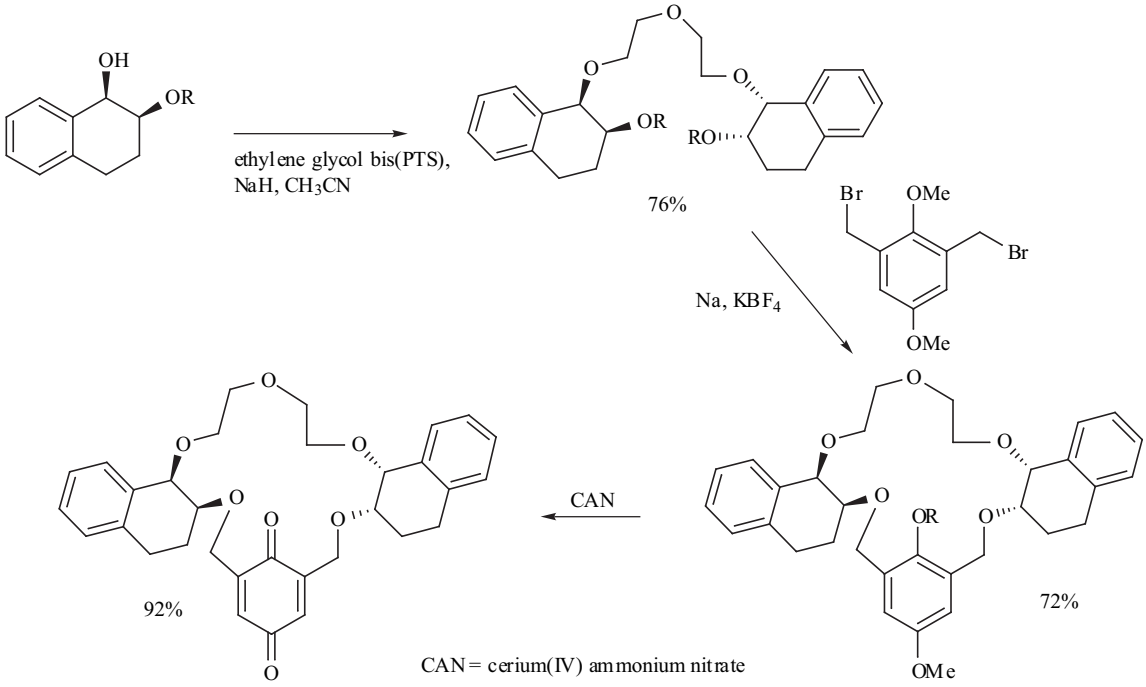

**Scheme 32.** Preparation of other conduritol analogues.

The aziridine intermediate can be also opened by diverse nucleophiles extending the scope of the preparation. This group of compounds was tested as glycosidases inhibitor, showing good results for some compounds and poor results for others. The performance of the class can be more understandable having available all these structural variations.

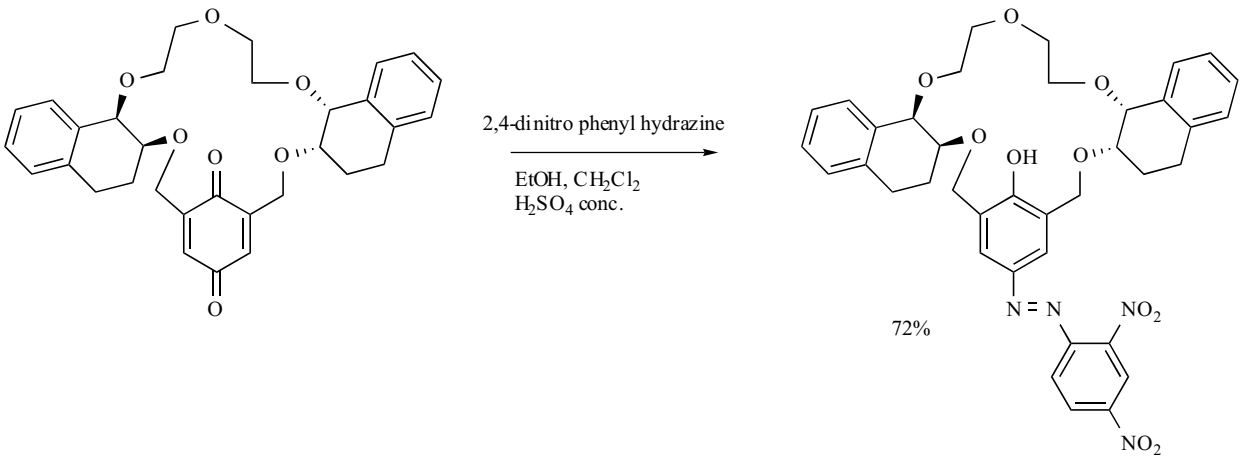
Also in this line of products we can cite the preparation of several conduritol analogs by the group of Orsini *et al.* [78]. They used the 1,2-dihydro-1,2-dihydroxy derivatives obtained by bioconversion of substituted naphthalenes to prepare many derivatives that can be presumably used to test the requirements for glycosidases inhibition (Scheme **33**).




**Scheme 33.** Preparation of conduritol analogues substituted on the aromatic ring.




**Scheme 34.** Preparation of crown ethers containing enantiopure 1,2,3,4-tetrahydro-1,2-dihydroxy naphthalene.



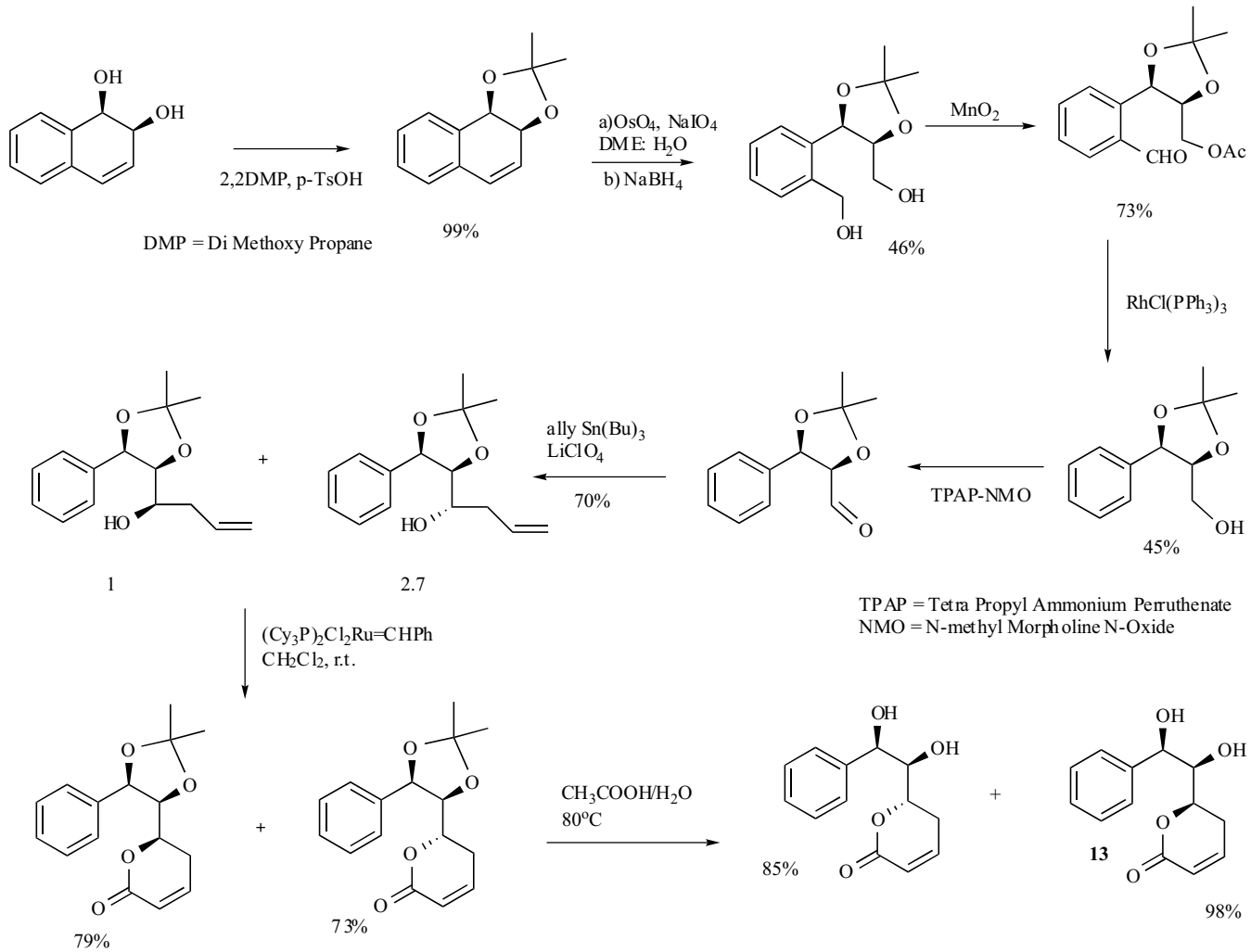

**Scheme 35.** Preparation of a different crown ether containing enantiopure 1,2,3,4-tetrahydro-1,2-dihydroxy naphthalene.

A quite different use is reported by Naemura *et al.* [30]. In this paper the authors' aim was to prepare some chiral crown ethers; the general plan is shown in Scheme (**34**).

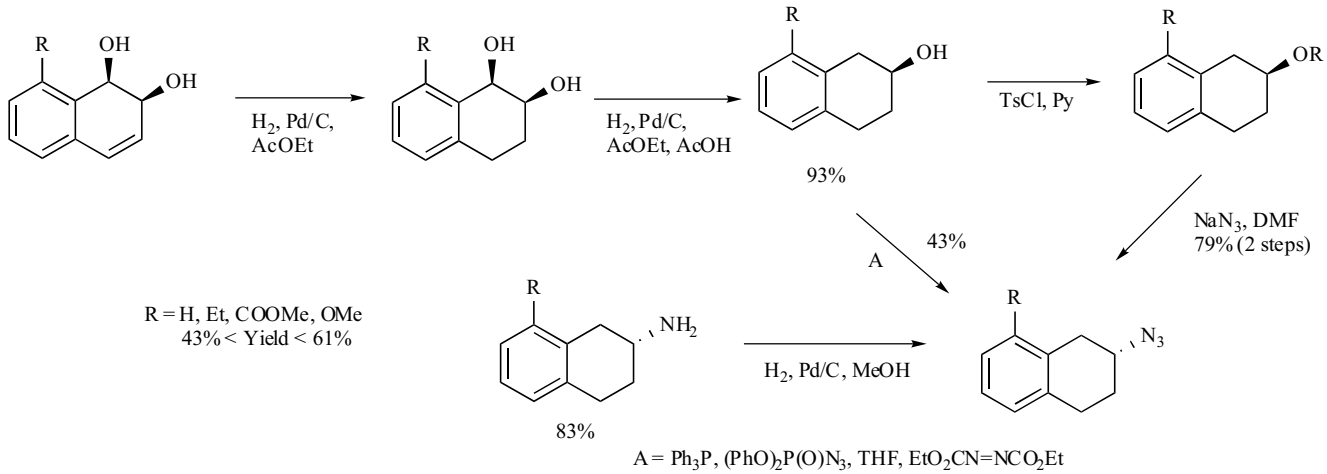
Here, the preparation of the starting enantiopure diol derivative was based on the deracemization procedure that uses α–hydroxy ketones as precursors. The crown ether was then further modified as shown in Scheme (**35**).

This compound was used to coordinate several chiral amines in order to control the stability of the formed complexes; the final aim was to develop the theory of host-guest recognition that this compound class shows.

Recently, Banwell *et al.* [79] reported the use of 1,2-dihydro-1,2-dihydroxy naphthalene in the synthesis of enantiopure gonodiol (**13**). This last is a natural product that




**Scheme 36.** Preparation of enantiopure gonodiol.




**Scheme 37.** Preparation of enantiopure 2-amino tetralines.

has interesting properties. The synthetic scheme is reported below (Scheme **36**).

In this example, the asymmetric induction contributed by the existing chiral diol is not sufficient to produce only the desired stereoisomer; nevertheless, two on three stereocenters are supplied by the synthon in line with this type of utilization of the chiral pool.

The last example that we are going to present concerns the preparation of enantiopure 2-aminotetralines [80]. The 8-substituted 2-aminotetralines possess interesting biological activity and are directly correlated to the corresponding diols that can be obtained by bioconversion. The transformation scheme is straightforward and the yields quite good (Scheme **37**).

In summary, we have seen the use of 1,2-dihydro-1,2-dihydroxy naphthalenes as chiral synthetic precursors of several interesting asymmetric compounds. More examples can be easily imagined and the present possibility of increasing the chiral pool makes this approach very effective.

## 5. CONCLUSION

In this review we analyzed the present state of the preparation and use of enantiopure 1,2-dihydro-1,2-dihydroxy naphthalene derivatives. The numbers of examples are a significant evidence of the importance that the availability of different enantiopure compounds belonging to the same class can have. The competition between the enzymatic and the chemical preparation is stimulating and we expect to see more and more new compounds. The diol use in asymmetric synthesis is also a growing application field. Our impression is that this area will get the most benefit from this class. Impressive examples of preparation of new derivatives together with the already outstanding examples of their potency are a positive indication. The situation of the use as synthons is partially different. In this case, the examples are relatively limited; but this is quite common because the synthesis of new compounds is often a complicated task and, in addition, it must be stimulated by some sounding reasons. Nevertheless, the possibility of preparing many enantiopure starting structures could increase the interest of the chemists.

## ACKNOWLEDGEMENT

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