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Development of a New Family of Chiral Auxiliaries

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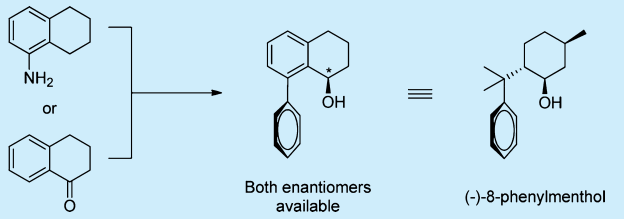
Supporting Information

ABSTRACT: A new family of chiral auxiliaries designed on a conformationally restricted version of (−)-8-phenylmenthol has been developed. Both enantiomers are available from an inexpensive synthesis conducted on multigram scale. A first application has showed comparable diastereoselectivity between the novel auxiliary and (−)-8-phenylmenthol.



Utilization of chiral auxiliaries is one of the main strategies for the synthesis of enantiopure compounds.[1] Transformations tend to be versatile, proceed with a predictable sense of asymmetric induction, and lead to products in enantiomerically enriched form. A successful and popular example is the (−)-8-phenylmenthol auxiliary. It was first introduced by Corey for the realization of highly asymmetric Lewis acid catalyzed Diels−Alder reactions.[2] Since then, it has been used to afford good diastereoselectivity in numerous organic transformations.[3] However, (−)-8-phenylmenthol is expensive, its synthesis is not straightforward, and it is also not very modular since each modification on the substituent requires a separate set of reactions starting from (*R*)-(+)-pulegone.[4] Furthermore, access to its enantiomer, (+)-8-phenylmenthol, is problematic since (*S*)-(−)-pulegone is not accessible from the "chiral pool".[5,6]

Herein, we are introducing a new family of chiral auxiliaries synthesized in both enantiomeric form on multigram scale and from cheap starting materials. Our design (Figure 1) is based on a conformationally restricted version of (−)-8-phenylmenthol using 1-tetralone as the platform. Auxiliary **1** shares most of his backbone with (−)-8-phenylmenthol, but the phenyl substituent is generally perpendicular to the tetralol ring system.

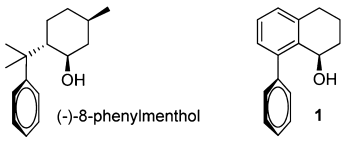
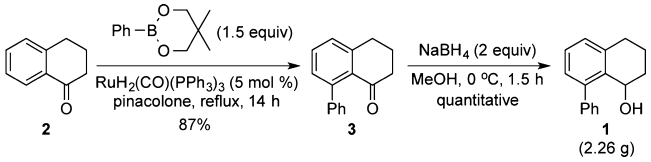


Figure 1. Design of chiral auxiliary based on a restricted conformation of (−)-8-phenylmenthol.

Strategically, to have access to both enantiomers, we decided to resolve the racemic auxiliary instead of using asymmetric synthesis. Racemic alcohol **1** was synthesized via two different pathways. The first one is a two steps synthesis from 1-tetralone (Scheme 1). Following a known procedure,[7] the reaction between tetralone **2** and phenylboronic acid neopentylglycol ester using a ruthenium catalysis in pinacolone at reflux afforded 8-phenyltetralone **3** in 87% yield. Reduction using sodium borohydride in methanol at 0 °C gave 2.26 g of the desired 8-phenyltetralol **1** in a quantitative yield.

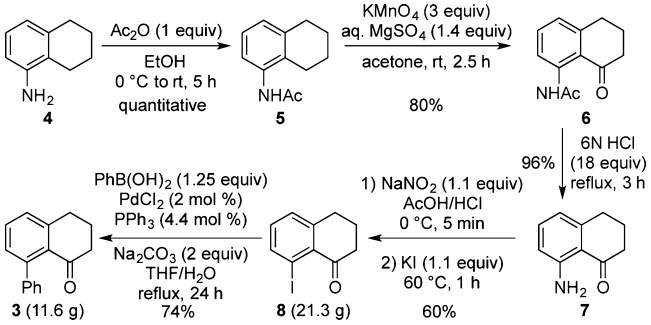
Scheme 1. Synthesis of Racemic Auxiliary from Tetralone



However, the first step of the above sequence using the ruthenium complex, the boronic ester, and an unusual solvent is too expensive for large-scale work. For this reason, we decided to find an alternative for the preparation of **3** (Scheme 2). Following the literature,[8] we obtained 21.3 g of the 8-iodo-1-tetralone **8** in 46% yield over 4 steps, starting from commercially available 5,6,7,8-tetrahydro-1-naphthylamine **4**.

The four steps are simple and only require one purification by column chromatography at the end of the process: (i) acetylation, to **5**, (ii) oxidation **6**, (iii) deprotection to **7**, and (iv) Sandmeyer reaction to **8**. Compound **8** was thus obtained from 25 g of amine **4** in 46% overall yield. Subsequent Suzuki

Scheme 2. Alternative Synthesis for 8-Phenyltetralone 3



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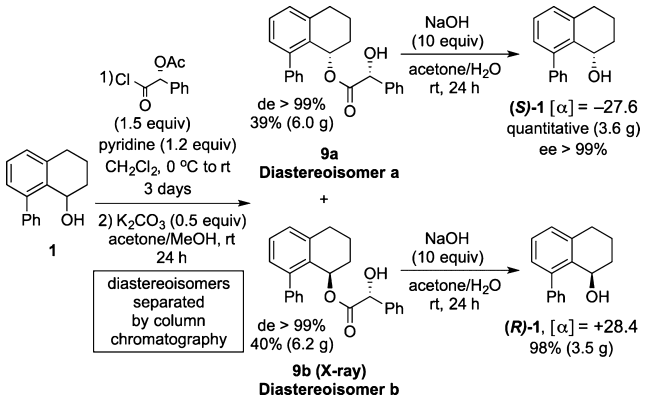
coupling between **8** and phenylboronic acid afforded 11.6 g of the desired 8-phenyltetralone **3** in 74% yield.

The resolution of racemic alcohol **1** was achieved by formation of a mandelate ester followed by the chromatographic separation of both diastereoisomers. This approach has already been used successfully with various alcohol.[9] Esterification of **1** with enantiopure (*R*)-*O*-acetylmandelic acid chloride[10] and pyridine in dichloromethane at 0 °C, followed by deacetylation using K_2CO_3 in an acetone/MeOH mixture at room temperature afforded a mixture of both diastereoisomers **9** in 79% yield (Scheme 3). At this point, the two

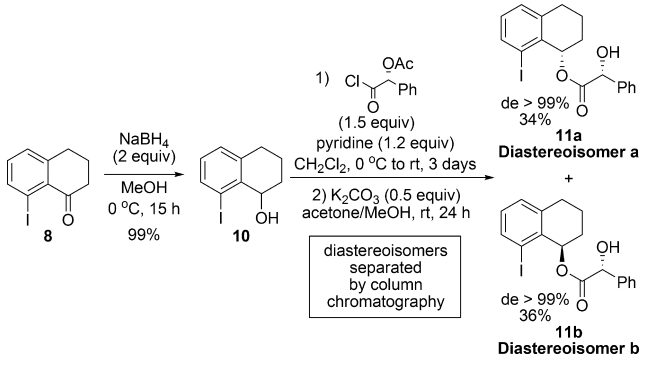
Scheme 3. Resolution of the Chiral Auxiliary



diastereoisomers **9** were separated by column chromatography on silica gel, to afford 6 g of each diastereoisomerically pure compound as a crystalline white solid **9a** and **9b**. The configuration was determined by single X-ray crystallography of **9b**. Hydrolysis of both diastereoisomers by sodium hydroxide in acetone/water at room temperature afforded 3.5 g each of enantiopure auxiliaries **1** in a quantitative yield. A control experiment to establish the integrity of the alcohol stereocenter was conducted. Esterification of enantiopure alcohol (*S*)-**1** by (*R*)-*O*-acetylmandelic acid chloride gave a single diastereoisomer showing that no racemization occurred.

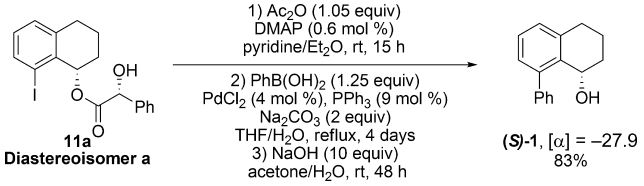
Because a good auxiliary should be modular, the possibility to have a common enantiopure intermediate before functionalization was also investigated. 8-Iodo-1,2,3,4-tetrahydro-naphtalen-1-ol **10** appeared to be an excellent candidate for this purpose. Compound **10** was easily synthesized by reduction of ketone **8**. Fortunately, the same strategy used for the resolution of the chiral alcohol **1** (Scheme 3) was also successful with iodo-alcohol **10** (Scheme 4).

Scheme 4. Resolution of the Key Iodide Intermediate 10



Reduction of 8-iodo-1-tetralone **8** with sodium borohydride in methanol at 0 °C for 15 h afforded the iodo-tetralol **10** in 99% yield. Then esterification using (*R*)-*O*-acetylmandelic acid chloride followed by deacetylation and column chromatography gave both diastereoisomers **11a** and **11b** in a 35% yield each in diastereopure form. At this stage, substitution on the aromatic ring (bulky or substituted aromatic or heteroaromatic) could be accomplished. This was illustrated for the synthesis of auxiliary **1**. Acetylation of diastereoisomer **11a** followed by Suzuki coupling using phenylboronic acid and $PdCl_2/PPh_3$, then hydrolysis afforded the chiral auxiliary (*S*)-**1** in 83% yield (Scheme 5).

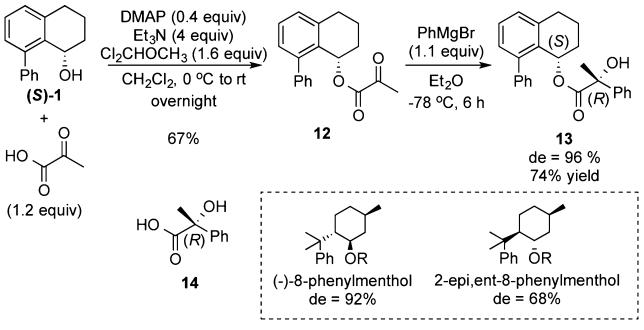
Scheme 5. Synthesis of 1 via the Iodo Key Intermediate 6



The absolute configuration was determined by comparison of the sign of the specific rotation of **1** thereby allowing the configurations of both diastereoisomers of **11** to be established.

To validate the concept of our new chiral auxiliary, we decided to compare the induction of diastereoselectivity between the novel chiral auxiliary and (−)-8-phenylmenthol through a known reaction: addition of a Grignard on a pyruvate ester.[11] Enantiopure chiral alcohol (*S*)-**1** was converted to the corresponding pyruvate **12** in 67% yield, by reaction with pyruvic acid, 4-dimethylaminopyridine, triethylamine, and dichloromethyl methyl ether in dichloromethane (Scheme 6).

Scheme 6. Addition of Phenylmagnesium Bromide to Pyruvate 12



Addition of phenylmagnesium bromide in ether at -78 °C in diethyl ether for 6 h led to a high level of induction. Compound **13** was obtained with a diastereoisomeric excess of 96% in 74% yield. For comparison, (−)-8-phenylmenthol results in 92% de.[11a] Interestingly, 2-epi,ent-8-phenylmenthol, generally used to induce the opposite sense of chirality, led only to 68% de.[11b]

The absolute configuration of ester **13** was determined by hydrolysis using sodium hydroxide in acetone/water at reflux overnight, and comparison of the sign of the specific rotation of the resulting acid **14** gives $[\alpha] = -36.3$ (c 0.8, $CHCl_3$) [lit.[12] $[\alpha] = -36.8$ (c 0.4, EtOH) for ee >95%].

The stereochemistry of this addition reaction can be rationalized by the addition of the nucleophile to the sterically

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accessible *re* face of **12** with a syn-orientation of the carbonyl group (Figure 2).[13]

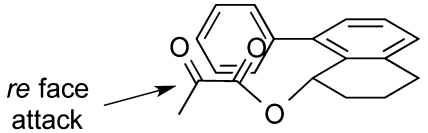

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Figure 2. Rationalization of the stereochemistry.

In conclusion, we have introduced a new chiral auxiliary platform. Both enantiomers of **1** are available on a multigram scale relatively inexpensively from commercial starting materials and through simple reactions. The resolution of key intermediate **10** allows the facile and divergent functionalization on a diastereopure compound at the end of the synthesis. The first application showed that auxiliary **1** displayed a level of diastereocontrol slightly superior to that of (−)-8-phenylmenthol. The modular elaboration of the iodide intermediate with various substituents and extension of the platform will be investigated in future work. Efforts to simplify the resolution procedure will also be made.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, compound characterization data, and HPLC chromatograms. Crystallographic data have been deposited to the Cambridge Crystallographic Data Centre as a CIF file with file number CCDC 1040079 and is also included in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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