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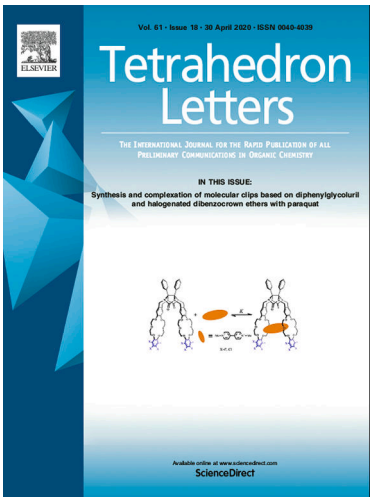

endo-1-Phenylborneol as a Novel, Alternative Chiral Auxiliary for the Aza-Diels-Alder Reaction

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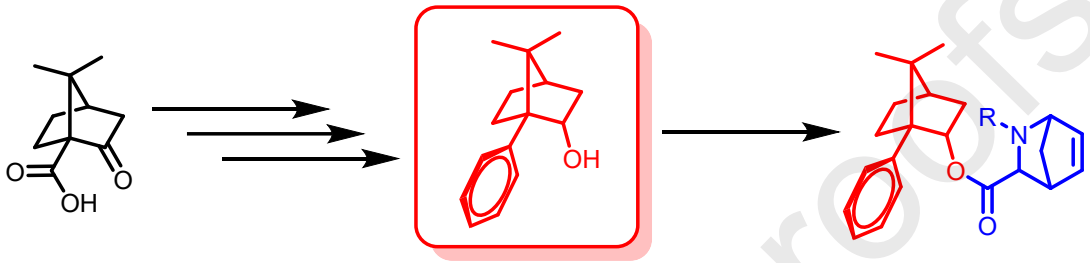

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ABSTRACT

We report the synthesis and preliminary evaluation of (*1S,2S,4R*)-7,7-dimethyl-1-phenylbicyclo[2.2.1]heptan-2-ol **1a**, which was obtained in 3 steps from inexpensive starting materials, as a chiral auxiliary. The potential for asymmetric induction was investigated by carrying out aza-Diels-Alder reactions with cyclopentadiene and imine derivatives of **1a** from (*R*)-(+)-1-phenylethylamine, (*S*)-(-)-1-phenylethylamine and benzylamine. The results showed marked *exo* selectivity and good diastereoisomeric excess when **1a** was combined with (*R*)-(+)-1-phenylethylamine. These results are comparable with those reported using (-)-8-phenylmenthol, suggesting that **1a** can represent an economically viable alternative to current chiral auxiliaries.

1. Introduction

Hetero Diels-Alder (DA) reactions are an important synthetic tool for the synthesis of heterocycles and natural products.[1] Crucially, imino DA reactions can provide rapid access to functionalized heterocyclic rings with controlled stereochemistry; imines can be easily obtained from the corresponding aldehydes and ketones, and are typically the dienophile in DA reactions.[2] The use of chiral auxiliaries is one of the main strategies to exert asymmetric induction in a reaction. Among the most common chiral auxiliaries, Corey's (−)-8-phenylmenthol[3] has been applied to imino cycloadditions such as the synthesis of 3-functionalized 2-azabicyclo[2.2.1]hept-5-enes as intermediates for a range of compounds including amidomycin and carbovir,[4] generally with moderate yields and diastereoisomeric ratios.[2]

Although (−)-8-phenylmenthol has proven to be a very versatile chiral auxiliary, having been applied in various organic transformations with good results,[5–7] it is expensive and requires a 4-step synthesis and a crystallization step in order to be obtained in a distereoisomeric pure form starting from enantioenriched (*R*)-(+)-pulegone.[8] Furthermore, it is worth noting that there is an over 100-fold difference in price between the two enantiomers of pulegone as precursors for chiral auxiliaries, which makes (+)-8-phenylmenthol much more expensive compared to its enantiomer and almost inaccessible in practice. Some efficient alternatives to (−)-8-phenylmenthol, such as (+)- and (-)-*trans*-2-(α-cumyl)cyclohexanol share the same scaffold and require an enzymatic resolution to be obtained.[9,10]

There is thus scope for the identification of novel chiral auxiliaries, which are readily accessible from the chiral pool, possibly available as both enantiomers. Herein we introduce chiral alcohol **1a**, derived from the under explored benzo-camphor scaffold **1**, as an easy to obtain, versatile chiral scaffold for applications as a chiral auxiliary. To the best of our knowledge, **1** has been reported only once as tool compound for chiroptical studies and the present contribution describes its first application in synthesis.[11]

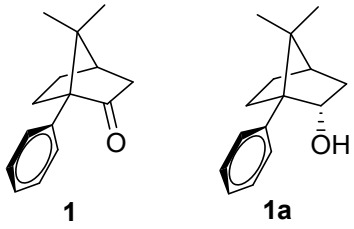


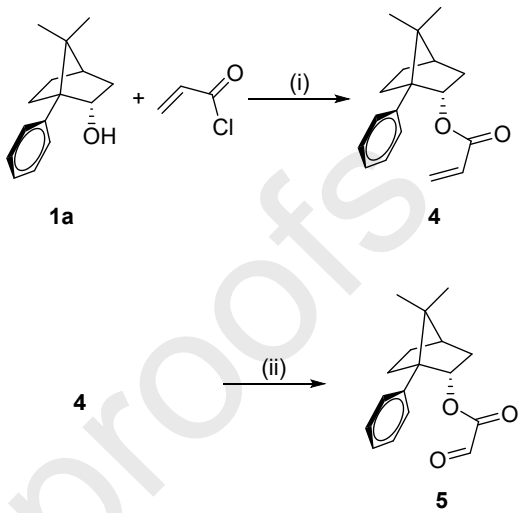
Figure 1. Structures of benzocamphor **1** and the proposed chiral auxiliary alcohol **1a.**

According to our rationale, **1a** should be able to exert strong asymmetric induction on a substrate bound to the hydroxyl moiety through the steric hindrance of the rigid camphor backbone, while the presence of a neighboring phenyl group should provide stabilizing π–π interactions between the aromatic ring and the dienophile in hetero DA reactions.[12] Notably, these features are similar to those of (−)-8-phenylmenthol, whose asymmetric induction properties have been explained based on both steric and electronic effects.[13]

2.

The synthetic route to **1a** started from chetopinic acid **2**, a derivative of (*R*)-camphor. Unlike the starting material for (−)-8-phenylmenthol, (*S*)-camphor, while more expensive than (*R*)-camphor, is still readily available and affordable; therefore the enantiomer of (*R*)-**1a** should be comparatively easier and less expensive to obtain with respect to (+)-8-phenylmenthol.

Benzocamphor **1** was previously obtained *via* the decarboxylation of chetopinic acid in benzene promoted by $Pb(OAc)_4$.[11,14] In our hands this methodology was poorly reproducible and plagued by the low solubility and ease of degradation of $Pb(OAc)_4$ in the reaction medium. Furthermore, the use of $Pb(OAc)_4$ should be discouraged due to its toxicity and environmental impact. We thus sought an alternative methodology to access the benzocamphor scaffold **1**.

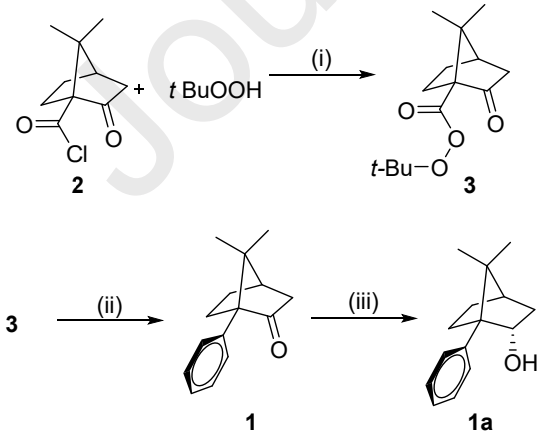


Most tertiary radicals have a tendency to disproportionate rather than react as nucleophiles.[15] In contrast, bridgehead radicals have nucleophilic character due to the rigidity of the fused polycyclic system which disfavours disproportionation.[16] Phenyl derivatives on the bridgehead position of adamantane and 1-apocamphane have been obtained from decomposition to radicals of the corresponding *tert*-butyl peresters in benzene.[16] We applied the same methodology to the camphor scaffold starting from ketopinyl chloride **2**, which can be obtained in quantitative yield from inexpensive ketopinic acid.[17] Acyl chloride **2** afforded perester **3** in 90% yield upon treatment with *tert*-butyl hydroperoxide under standard conditions. Perester **3** then underwent thermal decomposition in benzene giving the benzo-camphor **1** in 37% yield (Scheme1).

Due to the steric hindrance exerted by the apical methyl groups, the approach of hydride agents such as $LiAlH_4$ to the camphor carbonyl group occurs specifically on the (*Si*) face, leading to the *exo* alcohol.[18] We thus obtained **1a** by reduction with sodium in the presence of *tert*-butyl alcohol as a proton source, which favoured the formation of the more stable *endo* anion intermediate and thus of **1a** upon quenching with water.[19] The stereochemistry of the reduction product was confirmed by the NOE interaction between the apical methyl group and the hydrogen atom on the alcoholic carbon.

Scheme 1. Synthesis of glyoxylate **5**. (i) DMAP, Et_3N, CH_2Cl_2, 25 °C, 92%; (ii) OsO_4, $NaIO_4$, dioxane/water, RT, 2 h, 77%.

3. Evaluation of 1a as a chiral auxiliary



In order to evaluate the potential for asymmetric induction using **1a**, we carried out aza-Diels-Alders reactions with cyclopentadiene on its imine derivatives; the resulting 2-azabicyclo[2.2.1]heptenes are used as precursors of a range of compounds of chemical,

biol -8-phenylmenthol as a chiral auxiliary. (-)-8-Phenylmenthol was developed by Corey in 1975 and is one of the most commonly used and effective chiral auxiliaries for various chemical trasformations,[5–7] such as asymmetric Diels-Alder reactions,[5,21,22] nucleophilic alkylation[23] and dihydroxylation.[24]

To this aim, we first synthesized glyoxylate derivative **5** in good yield starting from **1a**. Compound **1a** was reacted with acryloyl chloride under standard conditions, and the resulting acrylate **4** underwent oxidative cleavage by Lemieux–Johnson oxidation (Scheme 2).

We then formed 3 different iminium salts derivatives of glyoxylate **5** by reaction with (*R*)-(+)-1-phenylethylamine, (*S*)-(-)-1-phenylethylamine and benzylamine, which then underwent cycloadditions with cyclopentadiene in CH_2Cl_2 using $BF_3{\cdot}Et_3O$ as a Lewis acid according to an established procedure (Scheme 3).[21] The diastereomeric ratio was assessed by integration of the crude reaction mixture and isolation of the diastereomeric products by column chromatography. The assignment of the absolute configuration of the latters was achieved by conversion of the isolated products into known compounds, according to well established methodologies, and comparing the spectra and optical rotations of the derivatives as detailed in the Supplementary Information.[25,26] The diastereoisomeric distribution of the reaction outcomes was compared with those obtained using (-)-8-phenylmenthol as a benchmark chiral auxiliary,[21,4] as reported in Table 1.

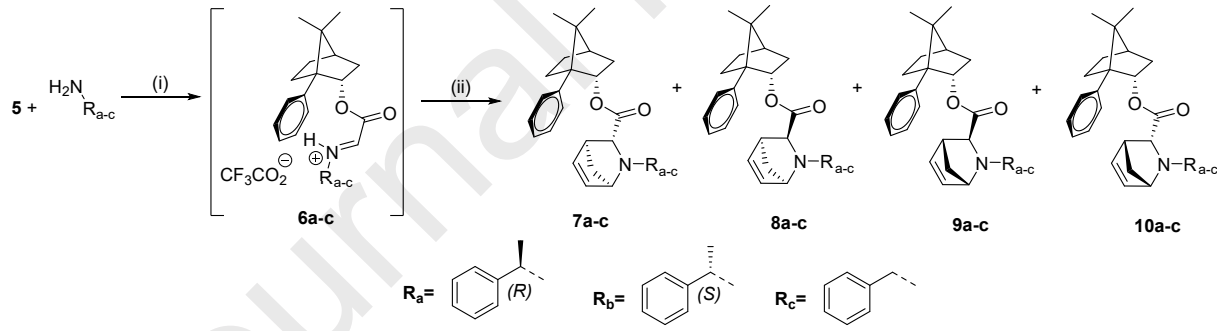
Gratifyingly, the use of (*R*)-(+)-1-phenylethylamine (Table 1, Entry 1) as a secondary chiral auxiliary afforded compound **9a** (*exo*-(1*S*,4*R*) in 60% isolated yield; we were also able to isolate compounds *exo*-(1*R*,4*S*) **7a** and *endo*-(1*R*,4*S*) **8a** in 4% and 8% yield, respectively. These results are comparable with those reported for (-)-8-phenylmenthol and is most likely due to a cooperative effect between the (*R*)-(+)-1-phenylethylamine and the chiral auxiliary (+)-**4** (matching effect), as previously observed for (-)-8-phenylmenthol.[21]

Interestingly, the same reaction carried out using (*S*)-(-)-1-phenylethylamine (Table 1, Entry 2) did not reach completion and led to

Scheme 2. Synthesis of **1a**. Reagents and conditions: (i) DMAP (cat), Py, 0 °C, 18 h, 89%; (ii) Benzene, 150 °C, 2 h, 37%; (iii) Na, THF, 0 °C, 2 h, 32%.

much lower overall yields, affording *exo-(1R,4S)* compound **9b** in 11% isolated yield along with *endo*-(1*R*,4*S*) **10b** and *exo-(1S,4R)* **7b** in 9% and 5% yield, respectively. Again, the diastereomeric ratio of this reaction closely resembles the one obtained with (-)-8-phenylmenthol, albeit with lower isolated yields.

Finally, when benzyl phenylethylamine was employed to form the imino derivative, literature data reports uniquely the isolation of the *exo-(1S,4R)* isomer and no *endo* isomer formed. [4] We were able to isolate both *exo-(1R,4S)* **7c** and *exo-(1S,4R)* **9c** in 6% and 23% yield, respectively (Table 1, Entry 3).



Scheme 3. Synthesis of imino derivatives of **5** and their aza-Diels Alder reactions with cyclopentadiene. (i) CH_2Cl_2, 4Å MS, CF_3COOH, 0 to -78 °C, 1 h; (ii) BF_3Et_2O, cyclopentadiene, -78 °C, 5 h.

AUX=	*exo*-(1*R*,4*S*)	*endo*-(1*R*,4*S*)	*exo*-(1*S*,4*R*)	*endo*-(1*S*,4*R*)

R= (R)

	4%	8%	60% (79%[21])	ND
Entry 2 R= (S)	**7b** 5% (35%[21])	**8b** (15%[21])	**9b** 11% (25%[21])	**10b** 9%
Entry 3 R=	**7c** 6%	**8c** ND	**9c** 23% (57%[4])	**10c** ND

Table 1. Diasteromeric distribution of the aza-Diels Alder reaction between cyclopentadiene and imino derivatives of chiral auxiliary **1a**. In parenthesis are the values observed in the case of (-)-8-phenylmenthol as a chiral auxiliary.

As previously observed, in all cases the cycloaddition reactions were characterized by marked *exo* selectivity;[22,27] this result has been explained by assuming that the dienophile iminium ion adopts an *E* configuration, and that the 1-phenylethyl group exerts a larger steric hindrance with respect to the ester group in proximity of the C=N bond.[4,21] On the basis of what is known in the literature for (-)-8-phenylmenthol, the mechanism of action of **1a** in these aza-Diels-Alder reactions can be rationalised assuming that the dienophile is held in place by π-π interactions with the phenyl ring of the chiral auxiliary. In the case of the (*R*)-(+)-1-phenylethylamine derivative, the phenyl group points away from the benzene ring of **1a** and the approach of the diene from the *Si* face leading to compound **9a** is favoured (Fig. 2A)**.** Conversely, the phenyl group of the (*S*)-(-)-1-phenylethylamine derivative needs to move close to the benzene ring of **4**, causing a steric clash that destabilizes this approach and thus leads to a reduced diastereoselectivity (Fig. 2B).

In conclusion, we demonstrated that enantiopure alcohol **1a** can be synthesised in three steps from inexpensive starting materials avoiding the use of toxic $Pb(OAc)_4$. The evaluation of **1a** as a chiral auxiliary in aza-Diels Alder reactions showed that it induces diastereomeric excesses comparable to (-)-8-phenylmenthol, thus representing a viable alternative to current chiral auxiliaries.

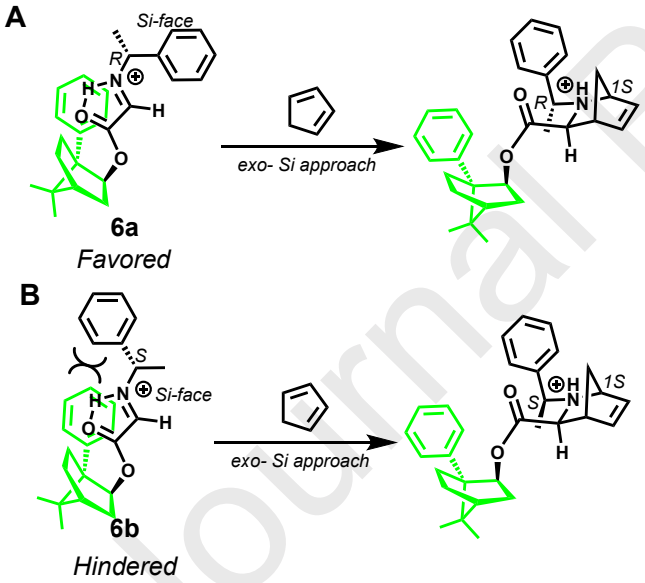


Figure 2. Model for the approach of cyclopentadiene to iminoacetals bearing a secondary chiral auxiliary: the configuration allowing the *exo-Si* approach of the diene is favored for adduct **6a** with (*R*)-(+)-1-phenylethylamine (A) and destabilized for adduct **6b** with (*S*)-(+)-1-phenylethylamine (B).

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Supplementary Material

The following are the Supplementary data to this article:.

Click here to remove instruction text...

- *endo*-1-Phenylborneol **1a** bears the under-explored benzocamphor scaffold
- **1a** was obtained from economic starting materials avoiding the use of toxic reagents
- **1a** was evaluated as a chiral auxiliary in asymmetric aza-Diels Alder reactions
- **1a** induces diastereomeric excesses comparable to (-)-8-phenylmenthol