Synthesis of a chiral auxiliary derivative of carvone and its use for the dynamic kinetic resolution of ibuprofen

Marcela Amongero and Teodoro S. Kaufman*

Instituto de Química Orgánica de Síntesis (IQUIOS, CONICET-UNR); Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, Suipacha 531, S2002LRK Rosario, Argentina. E-mail: tkaufman@fbioyf.unr.edu.ar

Introduction
Ibuprofen is a non-steroidal anti-inflammatory drug (NSAI) from the family of the arylpropionic acids (Lombardino, 1985). Despite ibuprofen continues to be marketed as racemate, it has been demonstrated that only the (S)-enantiomer is responsible for the desired therapeutic effects (Adams et al., 1976). (R)-Enantiomer shows some risk of toxicity due to be stored into adipose tissue as glyceryl ester, whose long-term effects are currently unknown (Williams et al., 1986). So far there have been numerous attempts aimed to prepare ibuprofen as an optically pure form, including the resolution of diastereoisomeric salts, the resolution by biocconversion, and asymmetric synthesis using chiral auxiliaries as well as chiral catalysts (Harrison et al., 1970; Larsen et al., 1989; Senanayake et al., 1992). In this paper our findings referred to the synthesis of the chiral auxiliary (−)-1 derived from S-(−)-carvone, and the preliminary results of its use as agent for kinetic dynamic resolution of ibuprofen [(±)-2] (Fig. 1) are reported.

Methodology
Chemical reactions were carried out under positive argon pressure; monitoring them by thin layer chromatography. The spots were visualized under UV light (254 nm) and revealed with p-anisaldehyde/H$_2$SO$_4$/EtOH. The separation and purification of the reaction products were performed by column chromatography using gradient elution techniques. IR spectra were acquired in a Shimadzu FT-IR model Prestige 21 spectrophotometer, while $^1$H- and $^{13}$C-NMR spectra were acquired in a Bruker spectrometer AC200-E (operating at 200.13 and 50.33 MHz, respectively).

Results
As shown in Fig. 2, to obtain the conjugate addition product, the reaction of S-carvone (3) with phenylmagnesium bromide (1.2 equiv.) was carried out in the presence of copper (I) iodide and TMSCI (1 equiv.), the latter reagent being required to produce an adequate carbon

![Figure 1. Chemical structures of the chiral auxiliary (−)-1 derived from S-(−)-carvone, and ibuprofen [(±)-2].](image-url)
The resulting silicon enol ether (4) was purified and further deprotected with TBAF in Et₂O, giving rise to ketone 5. Final carbonyl reduction of 5 was more efficiently performed with K-Selectride in THF at low temperature to give a mixture of alcohols, from which (-)-1 was isolated as the major product.

![Diagram](Figure 2. Preparation of (-)-1 chiral auxiliary. Reagents and conditions: (a) PhMgBr, Cu₂I₂, TMSCl, THF, 0 °C (quantit.) (b) TBAF, Et₂O, TA (quantit.) (c) K-Selectride, THF, -70 °C (80%). The ability of (-)-1 chiral auxiliary to carry out the dynamic kinetic resolution of ibuprofen was studied, developing the esterification of (+)-2 acid with (-)-1 chiral auxiliary under various conditions. Results are shown in Table 1.

**Table 1. Dynamic kinetic resolution of ibuprofen [(±)-2] by esterification with (-)-1.**

<table>
<thead>
<tr>
<th>No</th>
<th>Solvent</th>
<th>DCC/DMAP (equiv)</th>
<th>Comp. 2 (equiv)</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Diaster. Rel.</th>
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<tbody>
<tr>
<td>1</td>
<td>CHCl₃</td>
<td>4/1</td>
<td>5</td>
<td>-40 → TA</td>
<td>24</td>
<td>39 (100)</td>
<td>15:85</td>
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<tr>
<td>2</td>
<td>CHCl₃</td>
<td>4/1</td>
<td>5</td>
<td>0 → TA</td>
<td>24</td>
<td>76 (91)</td>
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<tr>
<td>3</td>
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<td>2.5/1</td>
<td>1</td>
<td>-40 → -20</td>
<td>48</td>
<td>100</td>
<td>28:72</td>
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<tr>
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<td>CHCl₃,e</td>
<td>2.5/1</td>
<td>1</td>
<td>0</td>
<td>48</td>
<td>84</td>
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<tr>
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<td>1</td>
<td>0</td>
<td>48</td>
<td>83</td>
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<tr>
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<td>TA</td>
<td>24</td>
<td>62 (100)</td>
<td>38:62</td>
</tr>
<tr>
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<td>1/1</td>
<td>1</td>
<td>40</td>
<td>24</td>
<td>64 (100)</td>
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<tr>
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<td>3</td>
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</tr>
<tr>
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<td>1</td>
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<td>69 (100)</td>
<td>34:66</td>
</tr>
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<td>-40 → -20</td>
<td>48</td>
<td>64</td>
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<td>55 (97)</td>
<td>24:76</td>
</tr>
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</table>

a Except for column 3, DCC was added in the last step.
b Yield between brackets is taking into account the recovery of the starting material.
c Alcohol was added at the end of the reaction.
d A pre-incubation with 200 mg of activated 4Å molecular sieves was carried out.
e Two equivalents of Et₃N were added to the reaction mixture.
f (-)-Menthol was used as chiral auxiliary.

Variables that were taken into account for esterification included: solvent, temperature, number of equivalents of ibuprofen, added amount of DCC, and reaction time. Once isolated
the products, diastereoisomeric relationships were determined by $^1$H-NMR analysis, using the areas of Me-2 and H-3 signals.

In general, it was realized that diastereoselectivity was not influenced to a large extent by the solvent used, CHCl$_3$ yielding the best results. However, temperature affected diastereoselectivity (entries 1 and 8 vs. entries 4 and 9). The presence of molecular sieves in CHCl$_3$ as well as in toluene resulted in an improvement of the overall reaction yield in detriment of diastereoselectivity. The addition of Et$_3$N caused no improvement of selectivity, while overall yield was equivalent to that observed with molecular sieves. The performance of chiral auxiliary was better than that of (-)-menthol (entries 1 and 2 vs. entry 12).

Data showed that the best diastereoisomeric relationship was obtained under the conditions of entry 1, although product yield was not optimal. A slight change of conditions (entry 2) improved product yield, with a slight detriment of the diastereoisomeric relationship.

The best diastereoisomeric relationship of this series is similar to that recently reported by Amoroso group for the dynamic kinetic resolution of (+)-2 with the pyrrolidinamide of the S-lactic acid (Ammazzalorso et al., 2002).

Conclusions:
A preliminary methodological study was performed on the use of the chiral auxiliary (-)-1 derived from S-carvone (3) for the dynamic kinetic resolution of (+)-ibuprofen ([+]-2).

Upon analyzing a variety of conditions, it was shown that at low temperatures CHCl$_3$ was the best solvent, and that yield improvement afforded in the presence of molecular sieves was detrimental for selectivity.

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References