Determining the Absolute Configuration of Marine Natural Products


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Overview

The pharmaceutical industry’s increased interest in linear, cyclic, and engineered peptides, revolve around their ability to modulate and engage therapeutic targets. Peptide designs’ rise in significance places greater emphasis on the need for robust methodology in determining absolute configuration of natural and unnatural amino acid chirality without the presence of readily available reference standards. Our laboratory bridges this gap by providing a working model for α-amino acids that utilizes a unique chiral derivatizing agent, an aryltrifluoromethylcarbinol (Pirkle’s alcohol), to discern the presence of readily available reference standards. Our laboratory bridges this gap by employing density functional theory (DFT) calculations in tandem with iterative Boltzmann populations, singular value decomposition (SVD), and the “One Shot” residual chemical shift anisotropy (RCSA) approach to further strengthen the methodology.

Working Model

Our Universal Method vs. Traditional Methods

<table>
<thead>
<tr>
<th>Methodologies</th>
<th>α-chiral proteinogenic amino acid</th>
<th>α-chiral non-proteinogenic amino acids</th>
<th>δ- (α-hydroxy) &amp; tertiary amino acid chirality</th>
<th>Requires authentic reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marfey’s Method</td>
<td>✓</td>
<td>□</td>
<td>□</td>
<td>✓</td>
</tr>
<tr>
<td>Mosher Ester Analysis</td>
<td>□</td>
<td>✓</td>
<td>□</td>
<td>✓</td>
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<tr>
<td>Proposed Method</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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</tbody>
</table>

The central premise of this approach focuses on a syn-periplanar relationship between the methine proton of Pirkle’s alcohol with both the NH proton and carboxyl ester — locking the compound in a predictable conformation. This predictable conformation of the amino acid derivative produces unique shielding environments from the anthracene ring for both R- and S-Pirkle’s alcohol.

Motobamide, produced by a marine bacteria, moderately inhibited the growth of bloodstream forms of Trypanosoma brucei. Current antitrypanosomal drugs have aided as a therapeutic but fail to account for their severe side effects.

Broader Impact

African sleeping sickness is caused by protozoa Trypanosoma brucei, which are transmitted from the sub-Saharan tse-tse fly. Current antitrypanosomal drugs have aided as a therapeutic but fail to account for their severe side effects.

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References