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Stereospecific Synthesis of Substituted Sulfamidates as Privileged Morpholine Building Blocks
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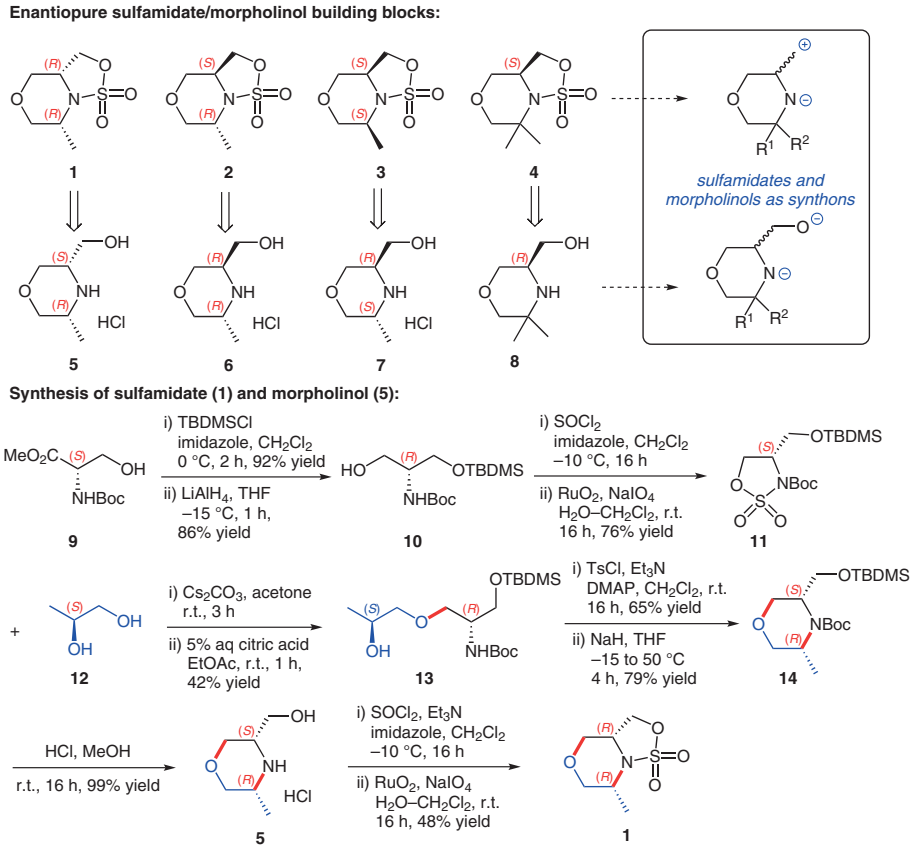
Synthesis of Versatile Enantiopure Morpholine Fragments from Chiral-Pool Starting Materials



Significance: The favorable physicochemical properties of morpholines make them attractive motifs for incorporation into bioactive molecules, often as bioisosteric replacements for piperidines; this is a common strategy owing, not only to the lower basicity of the nitrogen, but also because the CYP-mediated degradation of the morpholine ring often leads to nontoxic metabolites. The current report describes methods for synthesizing enantiopure functionalized morpholine fragments, with the 3-hydroxymethylmorpholines **5–8** featuring two nucleophilic groups, whereas the corresponding sulfamidates **1–4** can be viewed as aziridine equivalents and used in annulation reactions for the introduction of morpholine moieties.

Comment: The integral stereochemistry of the desired building blocks is imparted through appropriate selection of readily available enantiopure starting materials specifically derived from Boc-protected serine (e.g., **9**) or 1,2-propanediol (e.g., **12**). Optimization studies involving the selection of a suitable base–solvent combination were carried out for the critical ring opening of the cyclic sulfamidate **11** with diol **12**; aqueous citric acid was used to cleave the resulting sulfamate intermediate. Sulfamidates **1–3** were synthesized in ~10% yield over seven steps (three chromatographic purifications) whereas the dimethyl-substituted derivative **4** was obtained in a similar yield, also in seven steps, but with four chromatographic purifications; a double-Grignard addition to a readily available lactam served as the key step in this synthesis.

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Category
Synthesis of Heterocycles

Key words
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cyclic sulfamidates
chiral pool
building blocks
bioisosterism
asymmetric synthesis

Synfact of the Month