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 sulfamate 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.