Development of Reactions Constructing Novel Three-Dimensional Skeletons for Exploring New Chemical Space and Protein-Protein Interaction (PPI) Inhibitory Activity

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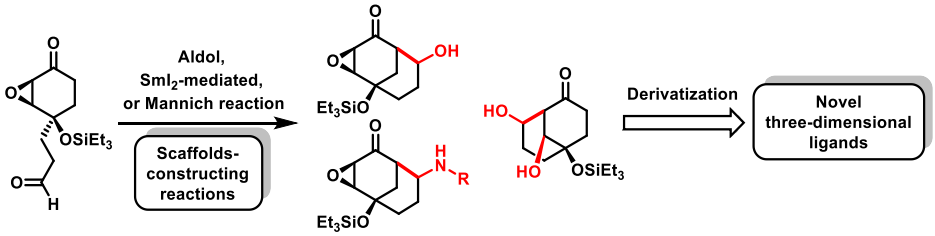
Recently, protein-protein interactions (PPIs) have been investigated for their potential to discover more specific drugs.[1,2] Currently, most approved drugs have a stick-like or planar structure. To target PPIs, three-dimensional ligands are necessary for the mimicry of the secondary structures of interacting peptides. However, due to their structural nature mentioned above, conventional drugs are not suitable for PPI inhibition. Nevertheless, recent progress in sp^2-sp^2 coupling reactions has further increased the proportion of sp^2 carbons in drug candidates.[3] Moreover, there are few reactions that can be used to construct a three-dimensional structure. Advantages of three-dimensional small molecules include that, generally, such molecules have higher specificity in protein binding.[4,5] Also, it is reported that the fraction of sp^3 carbons in the drug candidates correlates with the stages successfully passed in clinical trials.[6] We envisioned to design reactions yielding new three-dimensional molecules.

We previously reported bicyclo[3.3.1]nonanes as hypoxia-inducible factor inhibitors.[7] To obtain compounds with a similar carbon skeleton more concisely, we designed ketoepoxides substrates having an aldehyde group and tried to construct diverse three-dimensional skeletons with different functionalities through an aldol reaction, SmI_2-mediated reductive cyclization or Mannich reaction. We envisioned that it is possible to access diverse products by introducing sidechains to the scaffolds. Herein, we report the results of key cyclization reactions, derivatizations and the evaluation of three-dimensionality.



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