

PHOTOCHEMICAL AND TITANIUM-MEDIATED METHODS FOR SYNTHESIS OF MOLECULAR SCAFFOLDS

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Abstract

Screening small molecule libraries is a powerful method for identifying biologically active substances. Current compound libraries are typically comprised of a large number of structurally similar compounds designed around bioactive core structures of known molecules. While the number of tested compounds are increasing, there has been a decline in drug-discovery success due to only a small region of chemical space being represented in these compound libraries. In addition, newly discovered biological targets tend not to be modulated by currently known natural products and molecular scaffolds. Diversity-oriented synthesis (DOS) aims to construct structurally novel and diverse products in a highly efficient manner to generate small-molecule libraries with a high degree of structural diversity and function. There is a need for new organic methodologies to access these atypical molecular scaffolds.

The work presented here utilizes photochemical and titanium-mediated methodologies to access novel molecular scaffolds in two distinct directions: 1) by utilizing [2+2] photocycloaddition of pyridone-enynes to access functionalized cyclobutanoids capable of further modification and 2) by developing a novel Bredt's rule-arrest Kulinkovich-de Meijere reaction to produce alkaloid building blocks with useful functionality.

2-Pyridones are known to undergo photo-initiated [2+2] and [4+4] cycloadditions with themselves and other conjugated π -systems. These transformations provide rapid access to highly functionalized cyclobutanoid and cyclooctanoid derivatives capable of further manipulation to access both known and novel chemical space. Utilizing [2+2] photocycloaddition of pyridones conjugated with enyne partners we prepared polycyclic cyclobutanoids with excellent regio- and stereoselectivity. Further, these products were functionalized to give complex tetracyclic molecular scaffolds.

Our approach to the 5-8-5 framework of the fusicoccane family features a key intramolecular [4+4] photocycloaddition of tethered pyridones. Intelligent design of the tether and proper choice of solvent affords rapid assembly of the polycyclic framework and sets the relative stereochemistry of five stereogenic centers. The strategy for construction of cyclooctanoid natural products is part of a long standing program to utilize the powerful photochemical properties of 2-pyridone.

We have developed a novel approach for rapid access of a structurally diverse array of amino-ketone scaffolds employing a Kulinkovich-de Meijere reaction of inexpensive lactam-olefin building blocks. The formation of cyclopropylamines from alkenes and amides, the Kulinkovich-de Meijere reaction, involves two carbon-carbon bond-forming steps. Strategic use of a tricyclic intermediate can arrest the process if the second step requires formation of a bridgehead double bond. This intramolecular transformation results in formation of carbocyclic amino ketone building blocks. We have further demonstrated access to novel three-dimensional chemical space from these building blocks to produce a spectrum of fused bicyclic scaffolds in a divergent yet predictable manner. These products allow access to complex molecular space that can serve as a platform for medicinal and biochemical investigations.