**Glyco- and Peptidomimetics from Three-Component Joullié–Ugi Coupling Show Selective Antiviral Activity**

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The hydroxylated pyrrolidine scaffold provides valuable sources not only of glycomimetics but also of hydroxyproline derivatives.

With the aim of creating biodivergently targeted libraries, we have exemplified a multicomponent reaction (MCR) giving novel bisamide pyrrolidines accessed through a chlorination–elimination strategy. Previous studies have shown such imines to be efficient scaffolds for reaction with organometallic reagents. We demonstrate here that they are also highly effective components in MCRs that may be applied to library construction.

The mechanism proceeds via intermediates that are common to the Ugi reaction, a widely used reaction in library construction. However, the use of cyclic imine components in MCRs is rare: in 1989 Joullié demonstrated the role of a single cyanophenoxy dihydropyrrole. It is all the more surprising that such a "Joullié" process has not been applied to hydroxylated cyclic scaffolds as this would yield a ready route to compounds that could be considered as either azasugars or dihydroxyprolyl peptides. The motif thus formed would therefore potentially be effective in both carbohydrate processing (e.g., glycosidase) and/or peptide-processing (e.g., prolyl peptidase) inhibitors.

Several important synthoses of dihydroxyproline modules have been reported; many highlight the difficulty, length, relatively low yields, and long reaction times of prolyl amide coupling. Improved access to coupled scaffolds is desirable. We hereby report that they are also highly effective components in MCRs exemplified a multicomponent reaction (MCR) giving novel bisamide scaffolds for reaction with organometallic reagents. We demonstrate here that they are also highly effective components in MCRs that may be applied to library construction.

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Figure 1. Identified inhibitors of glucosylceramide synthase, bovine viral diarrhea virus, and anti-E2 Western assay of 9ia-treated BDV.

In conclusion, a rarely constructed azasugar/dihydroxy prolyl condensate emerged. IC\textsubscript{50} values of 25 and 117 \mu M, respectively (Figure 1). 

Typically no higher than ~70\% and up to 10 days. See ref 9.

Albeit modest in comparison to other compound libraries, this is a promising lead for azasugar development.


Supporting Information Available: Experimental procedures and characterization data for all library members and for biological testing. This material is available free of charge via the Internet at http://pubs.acs.org.

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