SYNTHESIS OF NOVEL HIGHLY FUNCTIONALIZED CYCLIC β-AMINO ACIDS

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Introduction

Cyclic β-amino acids possessing valuable pharmacological potential have attracted a great interest during last two decades. A number of cyclic amino acids exhibit remarkable antifungal and antiinflammatory activities, such as cispentacin, icofungipen, and oryzoxymicin.\textsuperscript{1,2} The synthetic generation of alkylated cyclic β-amino acids has been slightly examined. The aim of the current project was the design and synthesis of novel trans and cis dialkylated cispentacin derivatives.

Results and Discussion

The concept of the synthetic route was the functionalization of the C-C double bond of diexo-norbornene β-lactam 1 through stereoselective dihydroxylation and oxidative ring cleavage. The resulted key intermediate dialdehyde 4 was then subjected to Wittig reaction, followed by the reduction of the C-C double bond.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Scheme1}
\caption{Scheme 1. Generation of di-trans-dialdehyde 4 starting from β-lactam 1}
\end{figure}

Ring opening reaction of diexo-β-lactam 1, followed by an N-hydroxylation led to diexo-bicyclic N-protected β-amino ester 2. Then, 2 was treated with catalytic amount of OsO\textsubscript{4} in the presence of N-methylmorpholine-N-oxide, affording dihydroxylated derivative 3. Subsequent rapid oxidative C-C bond cleavage by means of NaIO\textsubscript{4} resulted in the di-trans dialdehyde 4, which could be isolated in a stable form. (Scheme 1).

Next, key intermediate 4 was transformed into the corresponding dialkenylated products 5 and 7 via a Wittig reaction. Subsequent catalytic hydrogenation gave access to saturated final products 6 and 8 in moderate yields. (Scheme 2).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Scheme2}
\caption{Scheme 2. Synthesis of dialkenylated products 5 and 7 and saturated final products 6 and 8}
\end{figure}

Ylides for the next two reactions were prepared in situ by stirring the methylenetriphenylphosphonium bromide salts with tBuOK in dry THF. Then, the solution of dialdehyde 4 was added dropwise to the ylides, furnishing the corresponding dialkenylated products 9 and 11 in moderate yields. Similarly to the previous case, Pd-catalyzed hydrogenation gave access to saturated final product 10 and 12. (Scheme 3).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Scheme3}
\caption{Scheme 3. Synthesis of dialkenylated products 9 and 11 and saturated final products 10 and 12}
\end{figure}

Conclusion

In summary, a number of novel di-trans and all-cis 3,5-dialkenylated and dialkylated cispentacin derivatives were successfully synthesized. The monocyclic dialdehydes were prepared via an oxidative C-C bond cleavage of the bicyclic system. Wittig transformation of these key intermediates, followed by a reduction led to 14 novel highly functionalized cispentacin analogues.

References


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