Journal of the Asiatic Society of Mumbai
ISSN: 0972-0766

UGC Care Group 1 Journal

"EFFICIENT DEHYDRATIVE ANNULATION METHOD FOR THE SYNTHESIS OF (6 R,8A S) OCTAHYDROINDOLIZIN-6-OL: A STUDY IN DIASTEREOSELECTIVE CHEMISTRY"

Jammula, Subbarao[a,]
[a] Custom Pharmaceutical Services, Dr. Reddys Laboratories Limited, Miyapur, Hyderabad, India

[b]Anna,
[b] Department of Chemistry, Koneru Lakshmaiah University (KLU), Vaddeswaram, Guntur District, Andhra Pradesh, India

Venkateswara Rao[b]; Khobare,
[b] Department of Chemistry, Koneru Lakshmaiah University (KLU), Vaddeswaram, Guntur District, Andhra Pradesh, India

Sandip R.[a]; Kumar,
[a] Custom Pharmaceutical Services, Dr. Reddys Laboratories Limited, Miyapur, Hyderabad, India

U. K. Syam[a];Prasad,
[a] Custom Pharmaceutical Services, Dr. Reddys Laboratories Limited, Miyapur, Hyderabad, India

Bagineni[c]; Pal, Manojit[c]
[c] Dr. Reddys Institute of Life Sciences, University of Hyderabad Campus, Gachibowli, Hyderabad, 500046, India

Abstract
A dehydrative annulation strategy, incorporating an intramolecular ring closure within Mitsunobu-Type reaction conditions, has been successfully employed for the synthesis of the octahydroindolizine framework. Remarkably, this approach, previously deemed unsuccessful for a similar system, enabled the diastereoselective synthesis of (6R,8aS)-octahydroindolizin-6-ol, serving as a precursor to (-)-8a-epidesacetoxyslaframine. Initiated from commercially available chiral (S)-epichlorohydrin, this synthesis proceeds through a piperidine intermediate, specifically (3R,6S)-6-(3-hydroxypropyl)piperidin-3-ol. This methodology demonstrates the potential to provide a diverse collection of optically pure small molecules with significant pharmacological relevance, all rooted in the indolizine framework. This innovative strategy opens new avenues for the efficient synthesis of pharmacologically valuable compounds. The abstract summarizes the key findings and significance of the research, highlighting the successful dehydrative annulation strategy for constructing the octahydroindolizine framework and its potential to generate optically pure small molecules of pharmacological importance.

Keywords: octahydroindolizine, (S)-epichlorohydrin, Mitsunobu reaction, diastereoselectivity

Introduction

The development of synthetic methods for constructing optically pure heterocycles with biological significance is a major focus in the fields of organic and medicinal chemistry. These methods enable the rapid synthesis of natural and unnatural analogs, which are crucial for various studies, including investigations into pharmacological activities.

The octahydroindolizine framework, also known as 1-azabicyclo[4.3.0]nonane, is a common structural motif found in a wide range of alkaloids. These alkaloids have diverse properties and applications, from coniceine isolated from amphibian skin secretions to slaframine, a mycotoxin inducing salivation in animals. Other examples include castanospermine, a potent glycosidase inhibitor, and various alkaloids found in poisonous frogs, like pumiliotoxin B1. Consequently, the construction of the octahydroindolizine ring in a stereoselective manner has garnered significant attention in the scientific community.

The specific focus of this research was on the synthesis of (6-R)-octahydroindolizin-6-ol (referred to as compound A), which serves as a precursor for (-)-8a-epidesacetoxyslaframine. Compound A not only paves the way for the synthesis of various indolizine-based small molecules but also holds immense potential for the preparation of (-)-8a-epidesacetoxyslaframine and related compounds.

The research team aimed to develop a new approach for constructing the octahydroindolizine framework of compound A, starting from enantiomerically pure (S)-epichlorohydrin. To achieve this, they employed a dehydrative annulation strategy as a key step. It's noteworthy that previous syntheses of (±)-A relied on an intramolecular nitrone cycloaddition strategy, which utilized 2-pyrrolecarbaldehyde as the starting material, followed by hydrogenation. However, a significant challenge with this approach was the formation of a mixture of isomeric cycloadducts during the nitrone cycloaddition step, which posed practical concerns. Moreover, this method did not yield optically pure compound A.

Interestingly, the dehydrative annulation strategy, akin to the Mitsunobu-like protocol, had previously been unsuccessful when applied to a similar system by Casiraghi et al. This discrepancy underscores the novelty and significance of the current research, which successfully harnessed the dehydrative annulation strategy to achieve the desired stereoselective synthesis of compound A.

This innovative approach not only provides a valuable method for accessing optically pure octahydroindolizine derivatives but also has broader implications in the efficient synthesis of pharmacologically important compounds based on the indolizine framework.

Design / method:

The research design and methodology in this study aimed to achieve the diastereoselective synthesis of (6-R)-octahydroindolizin-6-ol, a precursor for (-)-8a-epidesacetoxyslaframine. The strategy involved a dehydrative annulation approach, which was employed as a key step. Here's a brief overview of the design and methodology:

1. Starting Material Selection: The research began with the selection of enantiomerically pure (S)-epichlorohydrin as the starting material.

2. Dehydrative Annulation Strategy: The central approach was the application of a dehydrative annulation strategy. This strategy involved an intramolecular ring closure within Mitsunobu-Type reaction conditions. This was a critical step in achieving the desired octahydroindolizine framework.
3. omparative Analysis**: The study also considered and compared the dehydrative annulation approach with a previous synthesis method that relied on intramolecular nitrone cycloaddition. The previous method had challenges related to isomeric cycloadduct formation and the absence of optical purity.
4. **Success in Overcoming Previous Limitations**: The research emphasized the successful application of the dehydrative annulation strategy in contrast to its prior lack of success in a similar system. This demonstrated the novelty and effectiveness of the new approach.

By employing this innovative strategy and methodology, the study aimed to provide a practical and efficient route to optically pure (6-R)-octahydroindolizin-6-ol, with implications for the synthesis of diverse indolizine-based compounds, including pharmacologically relevant molecules.

Result and discussion : In the pursuit of synthesizing (6-R)-octahydroindolizin-6-ol (compound A), a comprehensive strategy was devised and executed. The synthesis was initiated from a chiral precursor, (3R,6S)-6-(3-hydroxypropyl)piperidin-3-ol (compound B), obtained through a series of well-planned steps.

The synthetic route began with a retro-synthetic analysis, envisioning the formation of compound A through an intramolecular displacement of the activated primary hydroxy group by the piperidine nitrogen in compound B. The alcohol B was designed to be derived from a chiral γ-hydroxy-ketone (compound C), involving de-benzylation and a stereocontrolled reductive amination process, akin to a previously established strategy.Based on this retro-synthetic plan, the researchers proceeded to synthesize compound A, starting with the precursor, the piperidine intermediate (B). The synthesis of amide 6, a crucial intermediate, had been reported earlier and was prepared using a known method. The reaction of (S)-epichlorohydrin and dibenzylamine produced (S)-N,N-dibenzyl-1-(oxiran-2-yl)methanamine, which, via a series of reactions, yielded the desired amide 6.

To achieve the synthesis of compound B, a one-pot three-step cascade reaction was performed on compound 7. This cascade involved debenzylation, intramolecular cyclization, and the subsequent reduction of the in-situ formed imine bond. A diastereomeric mixture of the piperidine derivative B was obtained, containing the major isomer (3R,6S)-6-(3-hydroxypropyl) piperidin-3-ol (B-1) and the minor isomer (3R,6R)-6-(3-hydroxypropyl) piperidin-3-ol (B-2) in a specific ratio. HCl salt formation and purification were carried out to obtain the HCl salt of the major isomer (B-1). Notably, the observed diastereo selectivity in this step was attributed to the steric influence of the hydroxypropyl chain.

Following the successful preparation of (3R,6S)-6-(3-hydroxypropyl) piperidin-3-ol (B-1) as a precursor to compound A, the researchers then proceeded to construct the final bicyclic skeleton of A. A Mitsunobu-like protocol was employed in the presence of PPh3 and DEAD. This protocol

enabled the intramolecular dehydrative annulation of B-1, resulting in the target product (6R, 8aS)-octahydroindolizin-6-ol (A) in a satisfactory yield of 72%.

In summary, the synthesis of compound A involved a meticulously designed route, commencing with the strategic preparation of the precursor B and culminating in the successful formation of the octahydroindolizine framework of A through a dehydrative annulation approach.

Acknowledgements
We extend our sincere appreciation to all those who played a vital role in the successful execution of this research endeavor.

First and foremost, we would like to express our gratitude to [Name of Funding Organization], whose financial support was instrumental in carrying out this study. Their commitment to advancing scientific research is deeply acknowledged.

We would like to acknowledge the expertise and dedication of the research teams who contributed to the synthesis of key intermediates and the final target compound. Their efforts were indispensable to the project's success.

Our thanks go to [Name of Academic Institution or Research Center] for providing the necessary infrastructure and facilities for conducting various experiments and analyses. The research environment at our institution significantly facilitated the project.

We are grateful to the authors of previous work that inspired and guided our synthetic strategies, especially the insights gained from their innovative approaches.

We also want to express our appreciation to the reviewers and editors who provided valuable feedback and suggestions, contributing to the refinement of our research.

Lastly, we acknowledge the contributions of our colleagues, mentors, and family members who offered their unwavering support and encouragement throughout the research process.

This study was made possible by the collaborative efforts and support of the aforementioned individuals and organizations. We are deeply thankful for their contributions to our scientific endeavors.

Reference:

[1] Michael, J. P. Nat. Prod. Rep. 2005, 22, 603-626.
[2] Michael, J. P. Nat. Prod. Rep. 1999, 16, 675-696.
[3] Franklin, A. S.; Overman, L. E. Chem. Rev. 1996, 96, 505-522.
[4] Groaning, M. D.; Meyers, A. I. Chem. Commun. 2000, 1027-1028.
[5] Arai, Y.; Kontani, T.; Koizumi, T., Chem. Lett., 1991, 2135-2138.
[6] Nukui, S.; Sodeoka, M.; Shibasaki, M., Tetrahedron Lett. 1993, 34, 4965-4968.
[7] Davies, S. B.; McKervey, M. A. Tetrahedron Lett., 1999, 40, 1229-1232

[8] Sanchez-Sancho, F.; Herradon, B.; Tetrahedron Asymm. 1998,
[9] 9, 1951-1965.
[10] Takahata, H.; Kubota, M.; Takahashi, S.; Momose, T. Tetrahedron Asymm. 1996, 7, 3047-3054.
[11] [Casiraghi, G.; Rassu, G.; Spanu, P.; Pinna, L.; Ulgheri; F. J. Org. Chem. 1993, 58, 3397-3400.
[12] Arnone, A.; Broggini, G.; Passarella, D.; Terraneo, A.; Zecchi, G. J. Org. Chem. 1998, 63, 9279-9284.
[13] [Kodimuthali, A.; Prasunamba, P. L.; Pal, M. Beilstein J. Org. Chem. 2010, 6, No. 71, doi:10.3762/bjoc.6.71
[14] Khobare, S. R.; Gajare, V. S.; Jammula, S.; Kumar, U. K. S.; Murthy, Y. L. N. Tetrahedron Lett. 2013, 54, 2909-2913.
[15] Hiromi, U.; Ryo, K.; Yuuki, A.; Miki, H.; Yu, K. Org. Lett. 2011, 23, 6268-6271.
Michael, W.; Ronald, B.; Nobuyoshi, Y.; George, M.; Ulf-H, D.; Edward, G. Tetrahedron Lett. 1995, 36, 5461-5466.
[16] For cis isomer, see: Bates, R. W.; Sivarajan, K.; Straub, B. F. J. Org. Chem. 2011, 76, 6844-6848.
[17] For trans isomer, see: Lovick, H. M.; Mich