

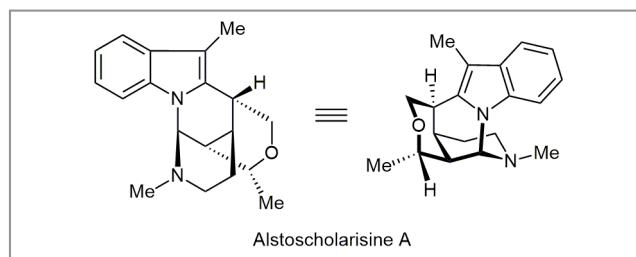
Total Synthesis of (±)-Alstoscholarisine A

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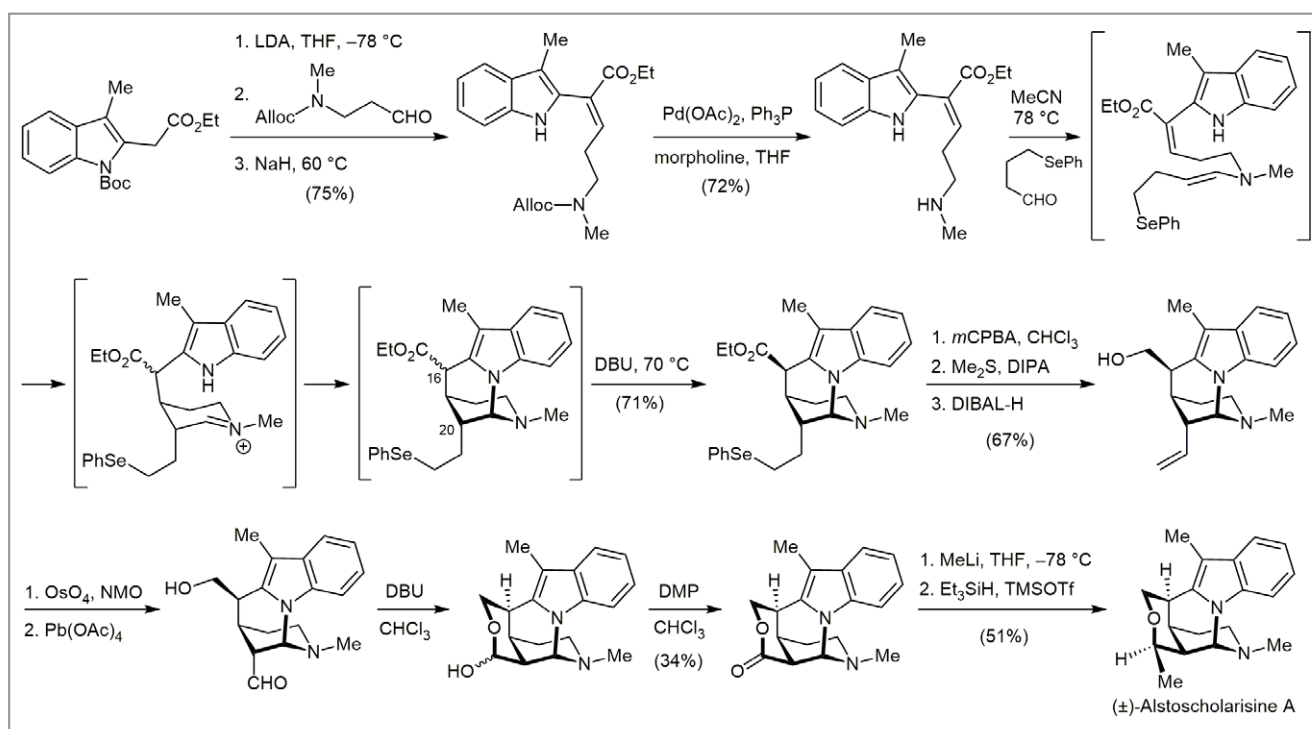
Alzheimer's, Parkinson's and Huntington's disorders, as well as amyotrophic lateral sclerosis, are the most common examples of currently incurable neurodegenerative diseases, characterized by a progressive loss of neuronal function. It has been estimated that Alzheimer's disease alone affects more than 44 million people globally, and this number is rapidly growing. In recent years, it has been realized that small molecules could promote adult neuronal stem cell (NSC) proliferation and differentiation, which could have important therapeutic applications for addressing unmet medical needs such as neurodegeneration.

In 2014, five indole alkaloids were isolated from *Alstonia scholaris*, and alstoscholarisine A was shown to significantly promote adult NSC proliferation and differentiation (see the original paper for references).

Synthetic chemists Professor Filip Bihelovic and Professor Zorana Ferjancic at the University of Belgrade (Serbia) were also impressed by the unique molecular structure of alstoscholarisine A and therefore started a synthetic project aimed at developing a concise yet flexible synthesis, which would also allow the researchers to synthesize its analogues



for SAR studies. Professor Bihelovic said: "We kept in mind a statement by Professor Mulzer, who said: "In fact, the total synthesis of complex natural products has often resulted in unacceptably long and low-yielding unpractical sequences" (*Nat. Prod. Rep.* **2014**, *31*, 595–603)." Consequently, in order to achieve a short synthesis, the researchers considered domino reactions, where the molecular complexity could dramatically increase in a single step. After developing their initial synthetic plan, they commenced their synthesis from skatole. "However, it was an unpleasant surprise when we realized that we didn't have this particular substance in our collection and that it would take more than a month to get it delivered to Serbia,"



remarked Professor Bihelovic. "So we made it and everything was ready for a real beginning."

Although the pair thought that synthesis of the amine for the key domino reaction would be a trivial task, it took a considerable amount of time to get these first steps to work. "The major difficulty was to properly select the aldehyde component for the aldol condensation," explained Professor Bihelovic. Interestingly, *N*-Boc-, *N*-Cbz- and *N*-Alloc-protected 3-aminopropanal all gave different products under the same reaction conditions. "Only *N*-Alloc-protected aldehyde reacted in a feasible way, reminding us again what we usually take for granted when planning synthesis: much more attention should be paid to a proper choice of a protecting group," said Professor Bihelovic.

To their delight, the key cyclization step was amazingly smooth and high-yielding, requiring no catalyst at all. Out of four theoretical stereoisomers, the authors of this study obtained only two, and none had a properly oriented substituent on C-20 at the newly formed bicyclic core. "Aside from elements of bad luck, this wasn't so surprising or disappointing, as we already recognized this possibility during our retrosynthetic analysis," remarked Professor Bihelovic. The first epimerizable stereocenter (C-16) was easily rectified in situ, through a DBU-catalyzed thermodynamic isomerization. A correction of the second stereocenter was more challenging, and they isomerized it also under basic conditions, but it was necessary to intramolecularly trap the thermodynamically less stable aldehyde in form of a hemiacetal, thus completely shifting the equilibrium. "The rest of the synthesis was straightforward and we were very excited to see that the NMR spectrum of the synthetic material matched the reported spectrum of the natural product," said Professor Bihelovic.

"We believe the problems emphasized by Professor Mulzer could be avoided by applying efficient domino reactions, as we hopefully demonstrated in our total synthesis of alstoscholarisine A," said Professor Bihelovic, who concluded: "Additionally, our work could provide a solid basis for easy preparation of new alstoscholarisine A analogues, which would represent a valuable contribution to SAR studies and hopefully help in understanding mechanisms of regulation of adult neural stem cells."

Matthew Ferjancic

About the authors



Prof. F. Bihelovic

Filip Bihelovic was born and raised in Belgrade (Serbia). After earning his BSc degree in chemistry (2005) from the University of Belgrade (Serbia), he joined the laboratory of Professor Radomir N. Saicic for PhD studies. Upon completion of his PhD in 2011, he joined Professor Dirk Trauner at Ludwig-Maximilians-Universität München (Germany) for postdoctoral studies. In 2014, he was promoted to Assistant Professor at the University of Belgrade. His main research interests lie in the area of natural products total synthesis.



Prof. Z. Ferjancic

Zorana Ferjancic was born in Belgrade (Serbia). She obtained her BSc (1996), and MSc (2000) from the University of Belgrade (Serbia). She received her PhD degree from the same institution in 2006 under the supervision of Professor Radomir N. Saicic. During 2007, she carried out postdoctoral research at the Ecole Polytechnique (Palaiseau, France) in Professor Samir Zard's group. In 2008, she was appointed Assistant Professor at the University of Belgrade and then promoted to the position of Associate Professor in 2014. Her main research interest is the synthesis of natural products and biologically active molecules.