

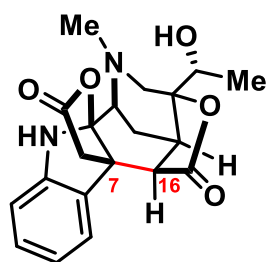
## Total Synthesis of Alstolactines A-C

Beltran Raphaël

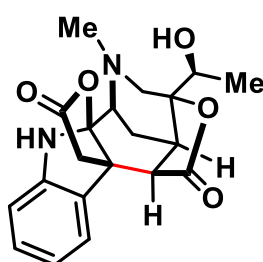
Laboratory of Synthesis and Natural Products – Jieping Zhu Group, EPFL, Lausanne  
[raphael.beltran@epfl.ch](mailto:raphael.beltran@epfl.ch)

Alstolactines A-C were isolated and characterized by Liu, Luo and co-workers in 2014 from the long-term stored leaves of *Alstonia scholaris*.<sup>[1]</sup> This plant is known in traditional Chinese medicine for its potent antitussive, anti-asthmatic and anti-inflammatory activities among others.

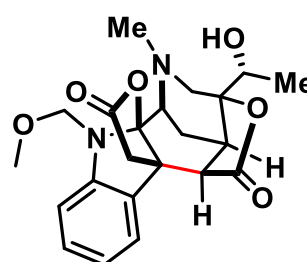
Alstolactines A-C belong to the akuammiline family that has been widely studied for decades. The characteristic structural feature of this class of monoterpene indole alkaloids is the presence of a C7-C16 bond that creates a rigid and cage-like framework.<sup>[2]</sup> This sophisticated hexacyclic cage scaffold is composed of an indoline, an aza-bridged bicyclic system having both six-membered rings in a boat conformation, two  $\gamma$ -lactones and a secondary alcohol. Due to their elegant polycyclic molecular architectures, the akuammiline family is of primary interest in our group.<sup>[3]</sup>



Alstolactine A



Alstolactine B



Alstolactine C

Herein, the 22 step synthesis of alstolactines A and B from commercially available starting materials will be presented. Our approach features: a) creation of a quaternary stereocenter C7 at an early stage; b) rapid build-up of the first  $\gamma$ -lactone; c) diastereoselective azidolactonization; d)  $[\text{Ni}(\text{cod})_2]$ -mediated intramolecular cyclization to construct the [3.3.1] bicycle and e) formation of the last  $\gamma$ -lactone *via* epoxide opening.

- [1] Yang, X. W.; Qin, X. J.; Zhao, Y. L.; Lunga, P. K.; Li, X. N.; Jiang, S. Z.; Cheng, G. G.; Liu, Y. P.; Luo, X. D. *Tetrahedron lett.* **2014**, *55*, 4593-4596.
- [2] Eckermann, R.; Gaich, T. *Synthesis* **2013**, *45*, 2813-2823.
- [3] a) Ren, W.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 1818-1821. b) Ren, W.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 3500-3503.