Alkaloid Synthesis

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Total Synthesis of (±)-Alstoscholarisine A

Filip Bihelovic and Zorana Ferjancic**

Abstract: *The first total synthesis of the neuroactive indole alkaloid (±)-alstoscholarisine A is reported. The key step of the concise synthesis is an efficient domino sequence that was used to assemble the 2,8-diazabicyclo[3.3.1]nonane core through the formation of two C–N bonds and one C–C bond in a single step.*

Over last two decades, a new and important interdisciplinary research area has emerged with the aim of manipulating stem cells by using small molecules.[1] In addition to enormous interest in embryonic stem cells, increasing attention has also been paid to adult neural stem cells and their possible use in regenerative medicine. Humans, like other mammals, have reservoirs of neural stem cells (NSCs),[2] which exhibit self-renewal and can produce three major classes of central nervous system cells, namely, neurons, astrocytes, and oligodendrocytes.[3] In recent years, scientific studies have been conducted with the aim of identifying small molecules, either synthetic or from nature, that could promote NSC proliferation and differentiation.[4] Such molecules could provide insight into the mechanism of regulation of the self-renewal of NSCs and could potentially have important therapeutic applications.

In 2014, five pentacyclic monoterpenoid indole alkaloids with unprecedented structures, named alstoscholarisines A–E (**1**–**5**), were isolated from the leaves of *Alstonia scholaris* (Figure 1).[5] Among them, alstoscholarisine A (**1**) exhibits the most significant ability to promote adult NSC proliferation and differentiation, as well as to enhance NSC sphere formation, at low concentrations (0.1 $\mu g\,mL^{-1}$). Its biological activity, coupled with its unique and intricate molecular architecture, with 6/5/6/6/6-fused bridge rings and five contiguous chiral centers, makes alstoscholarisine A an attractive and challenging synthetic target.

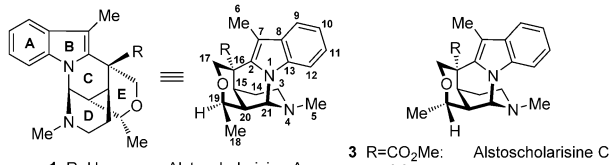

Figure 1. Structures of alstoscholarisines A–E (**1**–**5**).

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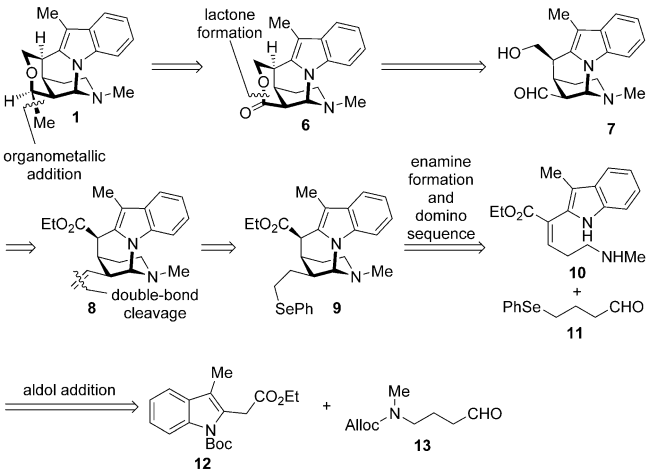
Accordingly, we set out to develop a concise synthesis of the most active member of the alstoscholarisine family, alstoscholarisine A (**1**), which would be flexible enough to allow the synthesis of different analogues for structure–activity relationship (SAR) studies. Given the structural complexity of the target molecule, we were focused on bond disconnection strategies that would lead to a rapid simplification of the pentacyclic core. Therefore, we based our approach on the application of domino reactions for a rapid increase in molecular complexity.

Our retrosynthetic analysis of (±)-alstoscholarisine A (**1**) is shown in Scheme 1. It commences with disconnection of the tetrahydropyrane E-ring, which was planned to be formed through the formal lactonization of alcohol **7**, followed by organometallic addition and diastereoselective reduction of the resulting hemiketal. The precursor **7** would be obtained by

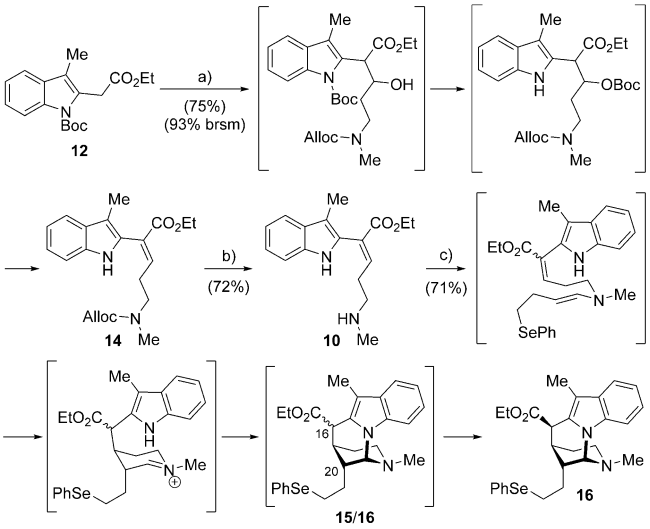


Scheme 1. Retrosynthetic analysis of (±)-alstoscholarisine A (**1**).

a double-bond cleavage and ester-group reduction of alkene **8**, which could be obtained from selenide **9** through an oxidation/elimination sequence. We recognized that the key intermediate **9** possesses a bicyclic skeleton (rings C and D), as well as functional groups suitably positioned to be synthesized in a single domino sequence from a far less complex acyclic amine **10** and selenoaldehyde **11**. In this domino sequence, closure of the 2,8-diazabicyclo-[3.3.1]nonane ring would be triggered by initial formation of an enamine between amine **10** and aldehyde **11**, followed by 6-*exo*-trig cyclization and final intramolecular *N*,*N*-acetal formation. The requisite amino compound **10** could be further simplified to the skatole derivative **12** and aminoaldehyde **13**.

Initial efforts in the synthesis of (±)-alstoscholarisine A (**1**) were oriented toward the preparation of the key

intermediate—the tetracyclic aminal **9**. In the first step, the enolate of ester **12** was allowed to react with *N*-Alloc-protected aldehyde **13** (Scheme 2).[6] After formation of the C–C bond, upon treatment with NaH, a spontaneous migration of the Boc group occurred (from nitrogen to oxygen),

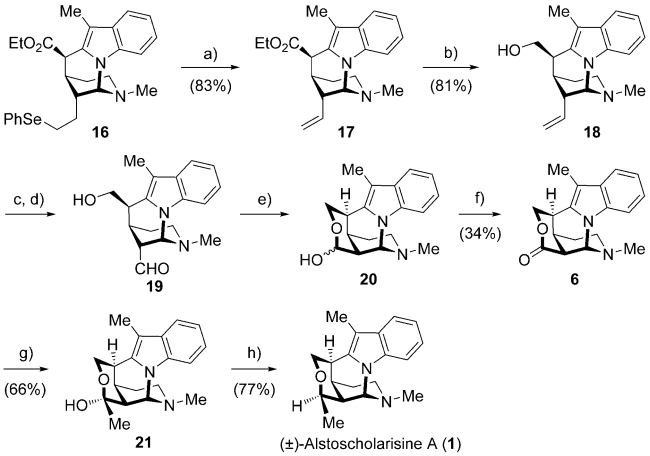


Scheme 2. Synthesis of the tetracyclic core through a domino sequence. Reagents and conditions: a) LDA, THF, −78 °C; then **13**, −40 °C; then NaH, 60 °C (75%; 93% brsm); b) $Pd(OAc)_2$, Ph_3P, morpholine, THF (72%); c) **11**, MeCN, 4 Å molecular sieves, 78 °C; then DBU, 70 °C (71%). brsm = based on recovered starting material, LDA = lithium *N*,*N*′-diisopropylamide, THF = tetrahydrofuran, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

followed by in situ β-elimination of the obtained transient Boc-protected alcohol.[7] Interestingly, the unsaturated product **14** was isolated in high yield as a virtually pure *E* isomer, with only traces of the corresponding *Z* isomer. Palladium-catalyzed deprotection[8] of allyl carbamate **14** furnished free amine **10**, thereby setting the stage for the key domino step. In the initial attempt to trigger the cascade, amine **10** was allowed to react with ethyl propiolate; however, we were able to spectroscopically detect only the enamine, formed in the Michael addition of amine **10** to the triple bond.[9] This enamine proved not to be reactive enough to undergo further cyclization, presumably because of the low nucleophilicity of the stabilized enamine. If this hypothesis is correct, the enhanced reactivity of unstabilized enamines, which originate from the corresponding aliphatic aldehydes, should allow the desired cyclization.[10]

From a synthetic standpoint, 4-(phenylselanyl)butanal (**11**) was chosen as a stable synthetic equivalent of a labile 3-butenal.[11] To our delight, when amine **10** was heated with aldehyde **11** in acetonitrile in presence of molecular sieves, smooth conversion took place and the tetracyclic products **15** and **16** were obtained in almost equimolar amounts. Subsequent analysis of the NOESY spectra of the resulting products showed that C-16 epimers were obtained.[12] Furthermore, we found that the selenium-containing side chain adopts an axial orientation (C-20) in both isomers (**15** and **16**). Although the stereochemical outcome of this cascade could not have been predicted,[13] we assumed that the configuration of both C-16 and C-20 could be corrected in the course of the synthesis through isomerization of the carboethoxy group. Indeed, the ratio of C-16 epimers was significantly improved (up to 5:1), by ester isomerization under thermodynamic conditions (DBU in ethanol), and the tetracyclic diastereomer **16** was isolated in 71% overall yield.

Having established reliable and expedient access to the key intermediate **16**, we next focused on formation of the tetrahydropyran E-ring (Scheme 3). Oxidation of selenide **16**



Scheme 3. E-ring formation and completion of the synthesis of (±)-alstoscholarisine A (**1**). Reagents and conditions: a) *m*CPBA, $CHCl_3$, −20 °C; then Me_2S, DIPA, 65 °C (83%); b) Dibal-H, CH_2Cl_2 (81%); c) OsO_4, NMO, THF/H_2O; d) $Pb(OAc)_4$, EtOAc; e) DBU, $CHCl_3$; f) DMP, $CHCl_3$ (34% over 4 steps); g) MeLi, THF, −78 °C (66%); h) Et_3SiH, TMSOTf, CH_2Cl_2, −78 °C (77%). *m*CPBA = *m*-chloroperbenzoic acid, DIPA = *N*,*N*-diisopropylamine, Dibal-H = diisobutylaluminum hydride, NMO = *N*-methylmorpholine-*N*-oxide, THF = tetrahydrofuran, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMP = Dess–Martin periodinane; TMSOTf = trimethylsilyl trifluoromethanesulfonate.

with *m*CPBA and subsequent selenoxide elimination furnished alkene **17**.[14] The ester group in **17** was reduced to primary alcohol **18**, which was used as a substrate for double-bond cleavage. Ozonolysis of alkene **18**, as well as its Lemieux–Johnson oxidation, led to complete decomposition of the starting material, probably due to incompatibility of desired aldehyde **19** with the oxidizing agents employed. The synthesis of aldehyde **19** was eventually achieved in a two-step procedure involving alkene dihydroxylation under Upjohn conditions, followed by glycol cleavage with lead tetraacetate. The configuration of the aldehyde-group-bearing carbon atom (C-20) in aldehyde **19** had to be inverted in order to form the fifth ring. According to preliminary experimentation,[15] axial aldehyde **19** appeared to be the thermodynamically more stable diastereomer, but it was prone to decomposition under basic conditions, probably as a result of β-elimination. However, in the presence of DBU at room temperature, the isomerization took place and the less stable equatorial diastereomer was immediately trapped as a mixture of stable hemiacetals (**20**). This mixture was then

oxidized with DMP[16] in a one-pot procedure to yield lactone **6**. The completion of the synthesis was originally anticipated to be achieved by Tebbe olefination[17] and subsequent stereoselective hydrogenation of the resulting enol ether from a less hindered, convex face of the molecule. However, application of the Tebbe reagent led to total decomposition of lactone **6**, and the end-game strategy had to be changed to a two-step procedure. In the first step, addition of methyllithium to lactone **6** gave the stable hemiketal **21**.[18] Treatment of **21** with TMSOTf then resulted in the formation of an intermediate oxonium ion, which was diastereoselectively reduced in situ with triethylsilane[19] from the convex face to yield (±)-alstoscholarisine A (**1**). The spectroscopic data for our synthetic sample were consistent in all respects with those reported for the natural product.[5]

To summarize, we have developed the first total synthesis of (±)-alstoscholarisine A, which proceeds in only 13 steps. The key step of the synthesis is an efficient domino sequence, which is used to assemble the bridged tetracyclic core, leading to the formation of three covalent bonds in one step: two C-N bonds and one C–C bond. Closure of the fifth ring relies on chemistry that could be easily modified to allow the synthesis of alstoscholarisine analogues for quantitative structure–activity relationship (QSAR) studies. These studies are currently underway in our laboratories.

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Angew. Chem. **2016**, *128*, 2615–2618

[1] For selected reviews, see: a) C. A. Lyssiotis, L. L. Lairson, A. E. Boitano, H. Wurdak, S. Zhu, P. G. Schultz, *Angew. Chem. Int. Ed.* **2011**, *50*, 200–242; *Angew. Chem.* **2011**, *123*, 210–256; b) J. A. Efe, S. Ding, *Philos. Trans. R. Soc. London Ser. B* **2011**, *366*, 2208–2221.

[2] a) C. G. Gross, *Nat. Rev. Neurosci.* **2000**, *1*, 67–72; b) A. Alvarez-Buylla, D. A. Lim, *Neuron* **2004**, *41*, 683–686; c) G. L. Ming, H. Song, *Neuron* **2011**, *70*, 687–702.

[3] B. A. Reynolds, S. Weiss, *Dev. Biol.* **1996**, *175*, 1–13.

[4] For selected papers, see: a) Y. Zhang, W. Li, T. Laurent, S. Ding, *J. Cell Sci.* **2012**, *125*, 5609–5620; b) J. W. Schneider, Z. Gao, S. Li, M. Farooqi, T. S. Tang, I. Bezprozvanny, D. E. Frantz, J. Hsieh, *Nat. Chem. Biol.* **2008**, *4*, 408–410; c) A. A. Pieper, S. Xie, E. Capota, S. J. Estill, J. Zhong, J. M. Long, G. L. Becker, P. Huntington, S. E. Goldman, C. H. Shen, M. Capota, J. K. Britt, T. Kotti, K. Ure, D. J. Brat, N. S. Williams, K. S. MacMillan, J. Naidoo, L. Melito, J. Hsieh, J. D. Brabander, J. M. Ready, S. L. McKnight, *Cell* **2010**, *142*, 39–51; d) Y. M. Yang, S. K. Gupta, K. J. Kim, B. E. Powers, A. Cerqueira, B. J. Wainger, H. D. Ngo, K. A. Rosowski, P. A. Schein, C. A. Ackeifi, A. C. Arvanites, L. S. Davidow, C. J. Woolf, L. L. Rubin, *Cell Stem Cell* **2013**, *12*, 713–726; e) M. Warashina, K. H. Min, T. Kuwabara, A. Huynh, F. H. Gage, P. G. Schultz, S. Ding, *Angew. Chem. Int. Ed.* **2006**, *45*, 591–593; *Angew. Chem.* **2006**, *118*, 605–607; f) H. Wurdak, S. Zhu, K. H. Min, L. Aimone, L. L. Lairson, J. Watson, G. Chopiuk, J. Demas, B. Charette, R. Halder, E. Weerapana, B. F. Cravatt, H. T. Cline, E. C. Peters, J. Zhang, J. R. Walker, C. Wu, J. Chang, T. Tuntland, C. Y. Cho, P. G. Schultz, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 16542–16547.

[5] a) X.-W. Yang, C.-P. Yang, L.-P. Jiang, X.-J. Qin, Y.-P. Liu, Q. S. Shen, Y.-B. Chen, X.-D. Luo, *Org. Lett.* **2014**, *16*, 5808–5811; b) R. A. Hill, A. Sutherland, *Nat. Prod. Rev.* **2015**, *32*, 111–115; c) Recently, two new biologically inactive alstoscholarisines (E and F) were isolated: X.-W. Yang, C.-W. Song, Y. Zhang, A. Khan, L.-P. Jiang, Y.-B. Chen, Y.-P. Liu, X.-D. Luo, *Tetrahedron Lett.* **2015**, *56*, 6715–6718.

[6] A proper choice of the amino protecting group proved to be crucial for the rest of the synthesis. While the Boc-protected amine gave a complex mixture of products, the Cbz-protected amine led to the desired unsaturated product. However, the Cbz group could not be selectively cleaved in presence of the double bond under various conditions; in all cases, the reduction of the double bond was faster. In another strategy, we used 3-azidopropanal as a reaction partner, but complete decomposition occurred during attempts to perform the requisite β-elimination.

[7] a) J. E. Macor, K. Ryan, M. E. Newman, *J. Org. Chem.* **1989**, *54*, 4785–4795; b) J. E. Macor, M. E. Newman, K. Ryan, *Tetrahedron Lett.* **1989**, *30*, 2509–2512; c) J. C. Badenock, J. A. Jordan, G. W. Gribble, *Tetrahedron Lett.* **2013**, *54*, 2759–2762.

[8] H. Lee, M. Suzuki, J. Cui, S. A. Kozmin, *J. Org. Chem.* **2010**, *75*, 1756–1759.

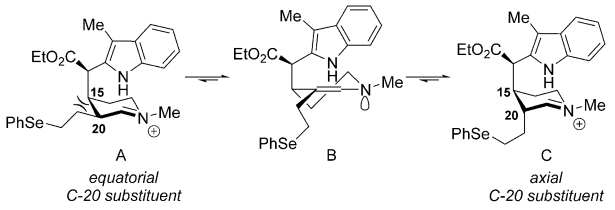
[9] P. Magnus, M. Giles, *Tetrahedron Lett.* **1993**, *34*, 6355–6358.

[10] S. Blechert, R. Knier, H. Schroers, T. Wirth, *Synthesis* **1995**, 592–604.

[11] J. Becker, L. Butt, V. von Kiedrowski, E. Mischler, F. Quentin, M. Hiersemann, *J. Org. Chem.* **2014**, *79*, 3040–3051.

[12] See the Supporting Information for an explanation of NOE correlations and copies of the NOESY spectra.

[13] The observed stereochemical outcome could be explained by an iminium salts (A and C)⇌enamine (B) equilibrium, where the intermediate with an axially oriented substituent on C-20 is thermodynamically more stable than the one with equatorial orientation, owing to the absence of *gauche* interactions between substituents on C-15 and C-20. Related examples: P. Forns, A. Diez, M. Rubiralta, *Tetrahedron* **1996**, *52*, 3563–3574.



[14] A. W. J. Logan, S. J. Sprague, R. W. Foster, L. B. Marx, V. Garzya, M. S. Hallside, A. L. Thompson, J. W. Burton, *Org. Lett.* **2014**, *16*, 4078–4081.

[15] When the vinyl group in ester **17** is cleaved under the described conditions, the obtained aldehyde undergoes epimerization in presence of DBU. However, the equilibrated mixture contains only 10–15% of the desired equatorial isomer, as judged by ^{1}H NMR. Additionally, rapid decomposition of both isomers takes place.

[16] D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277–7278.

[17] a) S. Pine in *Organic Reactions*, *Vol. 43* (Eds.: L. A. Paquette), Wiley, New York, **1993**, pp. 1 – 92; b) R. C. Hartley, J. Li, C. A. Main, G. J. McKiernan, *Tetrahedron* **2007**, *63*, 4825 – 4864.
[18] a) R. Bihovsky, C. Selick, I. Giusti, *J. Org. Chem.* **1988**, *53*, 4026 – 4031; b) F.-D. Boyer, C. Descoins, P.-H. Ducrot, *Eur. J. Org. Chem.* **2003**, 1184 – 1190.
[19] a) M. D. Lewis, J. K. Cha, Y. Kishi, *J. Am. Chem. Soc.* **1982**, *104*, 4976 – 4978; b) Y. Wang, S. A. Babirad, Y. Kishi, *J. Org. Chem.* **1992**, *57*, 468 – 481; c) M. Terauchi, H. Abe, A. Matsuda, S. Shuto, *Org. Lett.* **2004**, *6*, 3751 – 3754.

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