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Short communication

SHORT COMMUNICATION

Synthesis of two novel C-19 analogues of (±)-alstoscholarisine A

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Abstract: Two new analogues of alstoscholarisine A, containing a phenyl or butyl substituent at the C-19 position, have been prepared in racemic form from the known skatole derivative. The syntheses of these compounds were accomplished in 13 steps, with a late-stage formation of the C-19 stereocenter. These derivatives are expected to have significantly changed biological activity, compared to alstoscholarisine A – a potent neuroactive natural product.

Keywords: alkaloids; neuronal stem cells; *Alstonia scholaris*.

INTRODUCTION

Over last decades, as medicine made substantial progress towards a better understanding of neurological disorders, neuroactive substances have emerged as a very interesting and challenging area of research for chemists. Among these substances, especially enthralling targets are those that could modulate the proliferation and differentiation of neuronal stem cells (NSC).[1–5] The use of small molecules to affect NSC and prevent a loss of neuronal activity is very attractive and promising from a therapeutic point of view; during the last few years, several such compounds were identified.[6–10]

Recently, five monoterpenoid indole alkaloids, alstoscholarisine A–E (**1**–**5**), were isolated from the leaves of *Alstonia scholaris* (Fig. 1).[10] Although all these compounds show noteworthy ability to enhance adult NSC proliferation, the most potent one, alstoscholarisine A (**1**), has attracted significant attention among synthetic organic chemists. This interest was provoked partially by its exciting bioactivity, but also by its complex molecular structure, with 6/5/6/6/6-fused bridge rings and five contiguous chiral centers. As a result, very elegant syn-

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theses of this intriguing molecule have been published so far, two racemic and two enantioselective syntheses.[11–14]

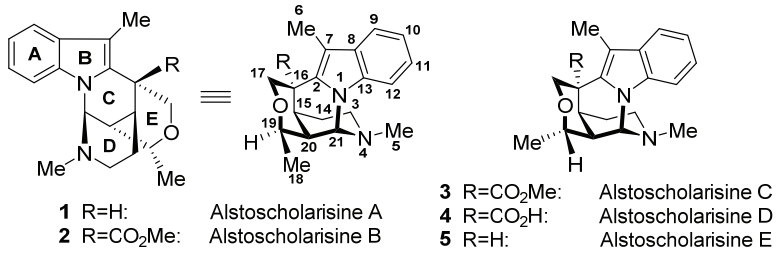
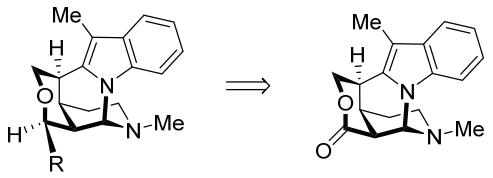


Fig. 1. Structures of alstoscholarisine A–E (**1**–**5**).

However, neither of these synthetic efforts was oriented toward the synthesis of alstoscholarisine A analogues. The fact that the only structural difference between alstoscholarisine A (**1**) and alstoscholarisine E (**5**) (which exhibits slightly lower activity) is the absolute configuration of the carbon C-19, indicates that a substituent at C-19 might be important for the bioactivity.

We have published a racemic synthesis of alstoscholarisine A (**1**) in 2016, in which the stereocenter at C-19 was formed in the last steps of the synthesis.[11] Therefore, it was decided to modify these last steps and to synthesize compounds **6** and **7**, two new C-19 analogues of alstoscholarisine A (Scheme 1), in order to test whether a nonpolar, longer alkyl or an aryl substituent could alter the bioactivity. These two analogs could be accessible from the common lactonic intermediate **8** by the addition of the corresponding alkyl- or aryl-lithium reagent, followed by a subsequent stereoselective reduction of the intermediary hemiketal.



Scheme 1. Structure of lactone **8** and novel C-19 analogues of alstoscholarisine A **6** and **7**.

EXPERIMENTAL

General methods

All chromatographic separations were performed on silica gel, 10–18 mesh, 60 Å (dry flash) and Silica 60 (0.063–0.200 mm), Merck. Standard techniques were used for the purification of the reagents and solvents. Petroleum ether refers to the fraction boiling at 70–72 °C. NMR spectra were recorded with a Bruker Avance III 500 (^{1}H-NMR at 500 MHz, ^{13}C-NMR at 125 MHz). Chemical shifts are expressed in ppm (δ) using tetramethylsilane as the internal standard, coupling constants (J) are in Hz. IR spectra were recorded with a Nicolet 6700 FT

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instrument and expressed in cm^{-1}. Mass spectra were obtained with an Agilent Technologies 6210 TOF LC–MS instrument (LC: series 1200).

*Compound **21***. PhLi (1.9 M in dibutyl ether; 60 μL; 0.114 mmol; 3.4 eq) was added to a cold (–78 °C) solution of lactone **8** (10 mg; 0.033 mmol) in dry tetrahydrofuran (1.5 mL), under argon. After stirring for 15 min, the reaction mixture was diluted with ether, washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed on a rotovap and the residue was purified by column chromatography (CH_2Cl_2/MeOH=95:5), to afford 8.0 mg (63 %) of the hemiketal **21**, as a colorless film.

*Compound **22***. *n*-BuLi (1.6 M in hexanes; 60 μL; 0.094 mmol; 3 eq) was added to a cold (–78 °C) solution of lactone **8** (9.3 mg; 0.031 mmol) in dry tetrahydrofuran (1.5 mL), under argon. After stirring for 15 min, the reaction mixture was diluted with ether, washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed on a rotovap and the residue was purified by column chromatography (EtOAc/MeOH = 95:5), to afford 5.4 mg (49 %) of the hemiketal **22**, as a colorless film.

*Compound **6***. Triethylsilane (12 μL; 0.070 mmol; 3.5 eq) and trimethylsilyl trifluoromethanesulfonate (9 μL; 0.050 mmol; 2.5 eq) were added to a cold (–78 °C) solution of hemiketal **21** (7.2 mg; 0.020 mmol) in dry dichloromethane (1.4 mL), under argon. The mixture was stirred at –78 °C for 45 min before the reaction was quenched by the addition of 3 drops of triethylamine. The reaction mixture was diluted with ether, washed with saturated sodium bicarbonate and brine, dried over anhydrous $MgSO_4$ and evaporated to dryness. The crude product was purified by column chromatography (CH_2Cl_2/MeOH = 95:5), to afford 5.6 mg (66 %) of compound **6**, as a colorless film.

Compound 7. Triethylsilane (14 μL; 0.084 mmol; 3.5 eq) and trimethylsilyl trifluoromethanesulfonate (11 μL; 0.060 mmol; 2.5 eq) were added to a cold (–78 °C) solution of hemiketal **22** (8.9 mg; 0.023 mmol) in dry dichloromethane (0.7 mL) under argon. The mixture was stirred at –78 °C for 45 min before the reaction was quenched by the addition of 3 drops of triethylamine. The reaction mixture was diluted with ether, washed with saturated sodium bicarbonate and brine, dried over anhydrous $MgSO_4$ and evaporated to dryness. The crude product was purified by column chromatography (CH_2Cl_2/MeOH = 95:5), to afford 4.7 mg (68 %) of compound **7** as a colorless film.

The characterization data for the synthesized compounds are given in the Supplementary material to this paper.

RESULTS AND DISCUSSION

The synthesis of analogues **6** and **7** commenced with the aldol reaction of skatole derivative **9**[11] and *N*-Alloc protected aldehyde **10**,[15] which was partially followed by the spontaneous migration of the Boc-group from nitrogen to the newly formed hydroxyl group (Scheme 2). Treatment of the reaction mixture with NaH ensured complete migration and subsequent *in situ β*-elimination of intermediate **11**, to afford stereoselectively (*E*)-**12**. Palladium-catalyzed removal of the Alloc-protecting group delivered free amine **13**, the intermediate for the key domino reaction that allowed the C and D rings of the target molecule to be constructed in one-step. Treatment of amine **13** with aldehyde **14**[16] triggered the sequence, followed by 6-*exo*-*trig* cyclization of the intermediary enamine and final intramolecular *N*,*N*-acetalization. Low diastereoselectivity was observed in the formation of the tetracyclic core and NOESY experiment showed that a mix-

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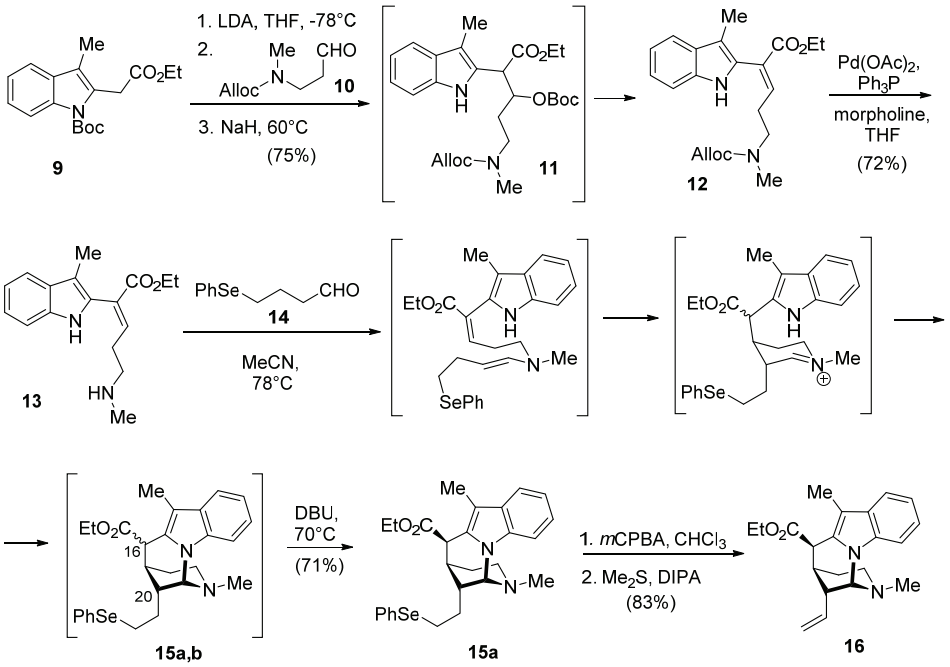
ture of C-16 epimers **15a** and **b** was obtained in almost equimolar ratio (for the NOESY spectrum and correlations, see the literature data[11]). For this reason, we wished to improve further the yield of the desired isomer **15a**. Simple treatment of the crude mixture of diastereoisomers **15a, b** with DBU resulted in ester isomerization and the thermodynamically more stable tetracycle **15a** was isolated in 71 % yield. Furthermore, the above-mentioned NOESY experiment also revealed the incorrect, *i.e.*, axial, position of the selenium-containing substituent. Therefore, epimerization of the C-20 stereocenter prior the construction of tetrahydropyrane E-ring was necessary. Compound **15a** was oxidized with *m*CPBA and thus the obtained selenoxide was treated with DIPA to afford alkene **16** in good yield.



Scheme 2. Synthesis of tetracyclic intermediate **16**.

Reduction of ester group with DIBAL, followed by dihydroxylation of the double bond in **16** cleanly furnished triol **18** in almost quantitative yield, as an inseparable mixture of isomers (Scheme 3). Glycol cleavage in **18** was affected by treatment with lead tetraacetate to afford aldehyde **19**, a substrate suitable for the C-20 epimerization. It is worth mentioning that aldehyde **19** was prone to decomposition, so it was subjected to isomerization directly, without purification. Initial experiments showed that axial position of the aldehyde group in **19** is thermodynamically favored: when the vinyl group in ester **16** was cleaved under

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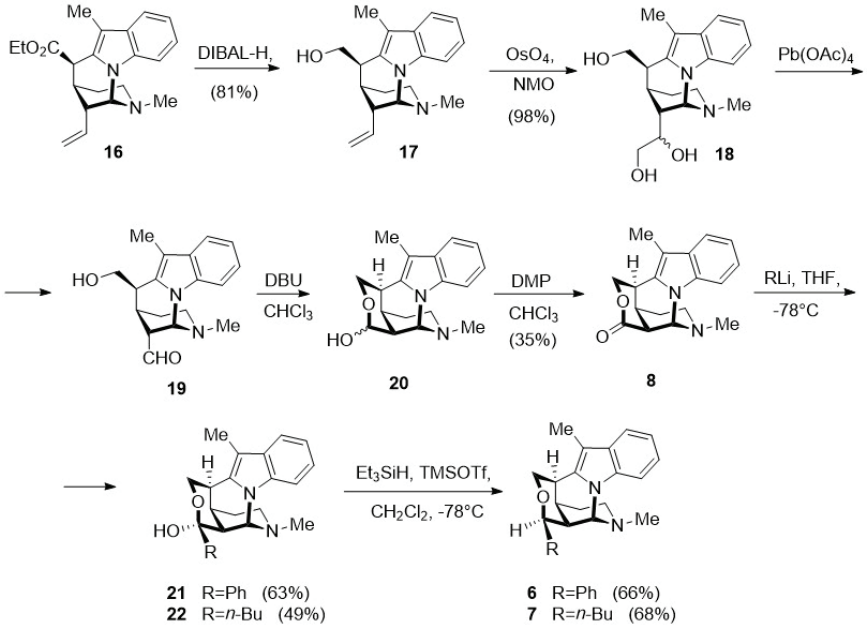
the described conditions, the obtained aldehyde underwent epimerization in the presence of DBU. However, the equilibrated mixture contained only 10–15 % of the desired equatorial isomer, thus indicating that the axial isomer is the thermodynamically more stable one. The hypothesis was that the less stable equatorial isomer could be trapped instantly after epimerization by an intramolecular attack of the hydroxyl group to give the hemiacetal. Indeed, upon exposure to DBU in chloroform, axial aldehyde **19** was converted to a mixture of isomeric hemiacetals **20**, which were immediately oxidized with DMP in a one-pot protocol to yield lactone **8**. Finally, lactone **8** was treated with phenyllithium or *n*-butyllithium, to afford the corresponding hemiketals **21** or **22**, respectively. Addition of organolithium reagent to **8** was completely stereoselective, from the less crowded, convex face of the molecule. These hemiketals **21** and **22** were treated with TMSOTf and thus the formed oxonium ions were stereoselectively reduced with Et_3SiH from the less hindered face to yield the alstoscholarisine A analogues **6** and **7** in good yield.



Scheme 3. E-ring formation and completion of the synthesis of **6** and **7**.

CONCLUSIONS

To summarize, the first syntheses of the C-19 alstoscholarisine A analogues **6** and **7** have been presented. These compounds were prepared in 13 steps, including a late-stage incorporation of the C-19 substituent. As analogues **6** and **7** were obtained in racemic forms, development of a HPLC method for the separ-

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ation of these enantiomers and subsequent evaluation of the biological activity of thus obtained optically pure compounds are currently underway.

SUPPLEMENTARY MATERIAL

Analytical and spectral data are available electronically at the pages of journal website: http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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ИЗВОД

СИНТЕЗА ДВА НОВА С-19 АНАЛОГА (±)-АЛСТОСХОЛАРИЗИНА А

ФИЛИП БИХЕЛОВИЋ, ЗОРАНА ФЕРЈАНЧИЋ и ЗЛАТКО ЈОНЧЕВ

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Два нова аналога алстосхоларизина А, који садрже фенил- или бутил-супституент у положају 19, синтетисана су у рацемском облику из познатог деривата скатола. Синтеза ових једињења остварена је у 13 корака, при чему се стереоцентар у положају 19 формира у последњим корацима синтезе. Очекује се да ће биолошке активности ових једињења бити различите од биолошке активности алстосхоларизина А – неуроактивног природног производа.

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