SHORT COMMUNICATION

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

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(Received 12 February, revised 20 March, accepted 25 March 2019)

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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https://doi.org/10.2298/JSC190212026B

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theses of this intriguing molecule have been published so far, two racemic and two enantioselective syntheses.\textsuperscript{11–14}

\textbf{Fig. 1.} Structures of alstoscholarisine A\textemdash{}E (1\textemdash{}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.\textsuperscript{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.

\textbf{Scheme 1.} Structure of lactone 8 and novel C-19 analogues of alstoscholarisine A 6 and 7.

\section*{General methods}

All chromatographic separations were performed on silica gel, 10\textemdash{}18 mesh, 60 Å (dry flash) and Silica 60 (0.063\textendash{}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\textendash{}72 °C. NMR spectra were recorded with a Bruker Avance III 500 (\textsuperscript{1}H-NMR at 500 MHz, \textsuperscript{13}C-NMR at 125 MHz). Chemical shifts are expressed in ppm (\(\delta\)) using tetramethylsilane as the internal standard, coupling constants (\(J\)) are in Hz. IR spectra were recorded with a Nicolet 6700 FT
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 MgSO₄. The solvent was removed on a rotovap and the residue was purified by column chromatography (CH₂Cl₂/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 MgSO₄. 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 trimethylsilyle trifluoro-methanesulfonate (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 MgSO₄ and evaporated to dryness. The crude product was purified by column chromatography (CH₂Cl₂/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 trimethylsilyle trifluoro-methanesulfonate (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 MgSO₄ and evaporated to dryness. The crude product was purified by column chromatography (CH₂Cl₂/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 9¹¹ and N-Allo 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 14¹⁶ 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-
ture of C-16 epimers 15a and b was obtained in almost equimolar ratio (for the NOESY spectrum and correlations, see the literature data\textsuperscript{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, \textit{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 \textit{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.](image)

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
the described conditions, the obtained aldehyde underwent equimerization 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 Et3SiH 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-
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.

Acknowledgements. Support of the Ministry of Education, Science and Technological Development of the Republic of Serbia is acknowledged (Project No. 172027). Work of F. B. is additionally supported by the fellowship “Start up for science, Serbia” 2016 (Company Philip Morris).

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