

Short Note

(1*R*,4*S*,5*S*)-5-((3-Hydroxypropyl)amino)-4-((1-methyl-1*H*-tetrazol-5-yl)thio)cyclopent-2-en-1-ol

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Abstract: Using environmentally friendly conditions, the nucleophilic ring-opening reaction of 6-azabicyclo[3.1.0]hex-3-en-2-ol with 1-methyl-1*H*-tetrazole-5-thiol provided a novel thiol-incorporated aminocyclopentitol, (1*R*,4*S*,5*S*)-5-((3-hydroxypropyl)amino)-4-((1-methyl-1*H*-tetrazol-5-yl)thio)cyclopent-2-en-1-ol, in excellent yield (95%). The newly synthesized compound was analyzed and characterized via ¹H, ¹³C-NMR, HSQC, and mass spectral data.

Keywords: aminocyclopentitol; bicyclic aziridine; water chemistry; nucleophilic substitution

1. Introduction

Aziridines are recurrent motifs in anticancer compounds (Figure 1A) and are useful building blocks in organic synthesis, largely due to their ring strain [1].



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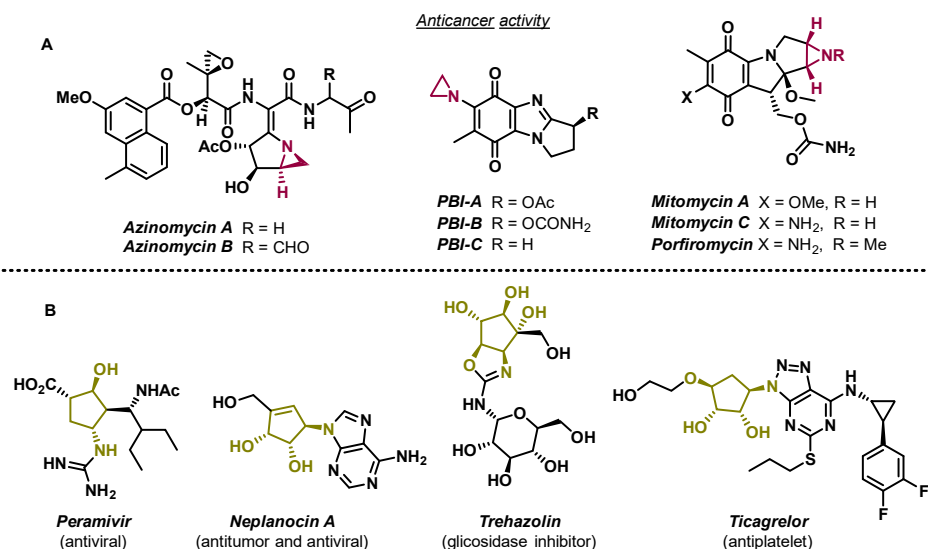
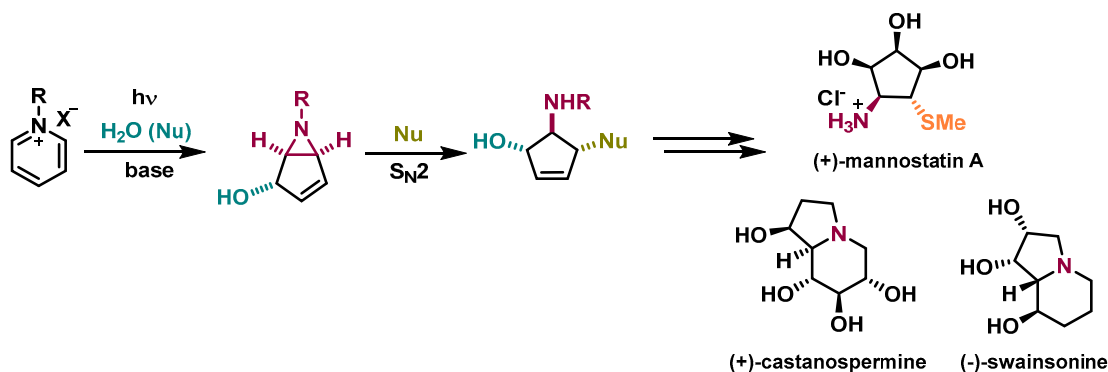


Figure 1. Examples of chemical structures of bioactive compounds containing aziridines (A) and important biological compounds containing the aminocyclopentitol scaffold (B) [2–4].

In 1972, Kaplan and co-workers implemented an innovative methodology to prepare 6-azabicyclo[3.1.0]hex-3-en-2-ol (bicyclic vinyl aziridines) via the photochemical conversion of pyridinium salts (Scheme 1) [5]. Bicyclic vinyl aziridines are useful intermediates to access aminocyclopentitols, a family of natural compounds known for being glycosidase inhibitors (Figure 1B) [6,7]. The synthetic methodology to prepare aminocyclopentitols involves the synthesis of bicyclic vinyl aziridines, followed by a ring-opening reaction to originate an aminocyclopentene, which after further functionalization originate the

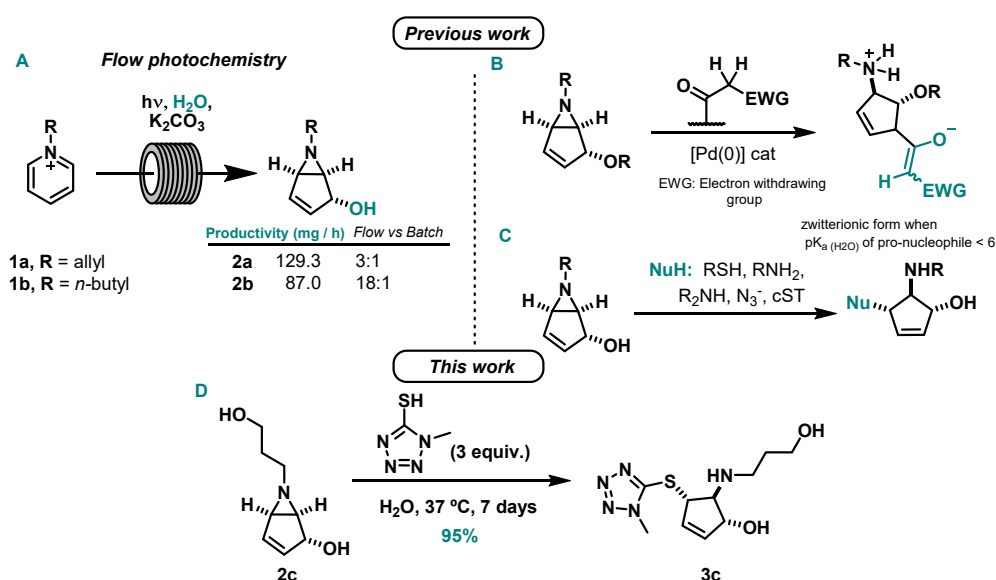
desired aminocyclopentitol. This methodology was developed by Mariano [8] and applied to the synthesis of several aminocyclopentitols, such as (+)-mannostatin A [9], (+)-castanospermine [10], and (-)-swainsonine [11] (Scheme 1).



Scheme 1. Synthetic methodology to prepare aminocyclopentitols by taking advantage of bicyclic vinyl aziridines prepared via photoreactions of pyridinium salts [9–11].

Mannostatin A is a natural product, first isolated from a soil microorganism *Streptover-ticillus*, and is among the most potent inhibitors of class II α -mannosidase. The chemical structure of Mannostatin A contains a thiol functionality, responsible for the high affinity to the enzyme's binding site [12]. Inhibitors of glycosidases are leading the drug discovery across cancer, and viral and bacterial infections. Mannostatin A and its analogs [13] have been used to study the inhibition of glycosidases to orientate the development of drug candidates [6,7].

Our group studied the photochemical reactions of pyridinium salts to bicyclic vinyl aziridines under continuous-flow [14,15]. The implementation of flow enabled the synthesis of bicyclic vinyl aziridines with larger productivity when compared to reported batch methods [16] and also the achievement of a gram scale production [15] (Scheme 2A).

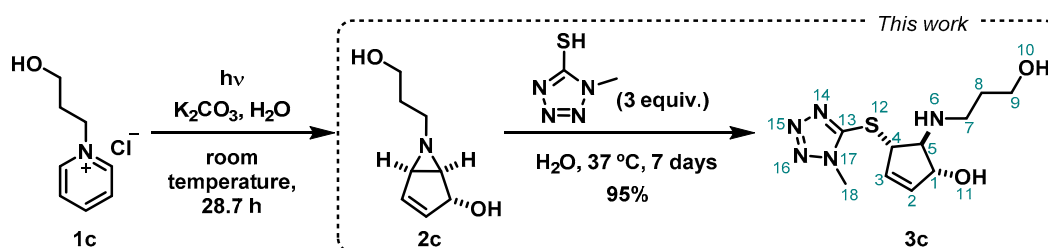


Scheme 2. (A) Flow photocyclization of pyridinium salts [14,15], improvements over batch methodology [16,17]; previous work on (B) palladium-catalyzed allylic substitutions on bicyclic vinyl aziridines using carbon-based nucleophiles [18] and (C) nucleophilic ring-opening reactions of bicyclic vinyl aziridines with thiol and nitrogen nucleophiles [17]; (D) this work: nucleophilic ring-opening reaction of bicyclic vinyl aziridine ring (2c) by 1-methyl-1H-tetrazole-5-thiol to produce 3c.

We also studied several bicyclic vinyl aziridines transformations. In collaboration with G. Poli, we reported a palladium-catalyzed allylic substitutions using C-nucleophiles [18] (Scheme 2B). Additionally, we accomplished several ring-opening reactions using sulfur and nitrogen-based nucleophiles in an aqueous medium, including a bioconjugation with the peptide hormone salmon calcitonin (sCT) [17] (Scheme 2C). Within the reactions performed, the best yields were achieved for thiol-nucleophiles. In line with this work, we herein present the ring-opening reaction of 6-(3-hydroxypropyl)-6-azabicyclo[3.1.0]hex-3-en-2-ol by a thiol-based nucleophile, 1-methyl-1*H*-tetrazole-5-thiol (Scheme 2D).

2. Results and Discussion

The starting material, 1-(3-hydroxypropyl)pyridin-1-ium chloride (**1c**), was prepared from pyridine and 3-chloropropanol following our reported method. 6-(3-hydroxypropyl)-6-azabicyclo[3.1.0]hex-3-en-2-ol (**2c**) was obtained by photohydration of the pyridinium salt **1c** (Scheme 3), also taking advantage of our previous reported synthetic methodology [18]. In this work, the bicyclic vinyl aziridine **2c** was subjected to thiol-nucleophilic attack by 1-methyl-1*H*-tetrazole-5-thiol, applying our reported optimized conditions [17]. An excess of the nucleophile (3 equivalents) was used under mild reaction conditions (37 °C, in water), and we obtained the product **3c** as a brown oil, in excellent yield (95%) after purification by silica gel chromatography (Scheme 3). The ring-opening reaction occurs via the S_N2 pathway in a regio- and stereospecific manner, and the nucleophile attacks in the less sterically hindered carbon of the aziridine moiety, as previously reported by Mariano [19] and Burger [20], and more recently also by us [17].



Scheme 3. Synthetic pathway from photocyclization of 1-(3-hydroxypropyl)pyridin-1-ium chloride (**1c**) [18], followed by a nucleophilic attack to the bicyclic vinyl aziridine ring (**2c**) by 1-methyl-1*H*-tetrazole-5-thiol to produce **3c**.

The product **3c** was characterized by ¹H-NMR, ¹³C-NMR, HSQC, and HRMS. By analyzing the ¹H-NMR spectrum (Figure S1), we can observe characteristic peaks from product **3c**: a singlet at 3.96 ppm, corresponding to the methyl group linked to the tetrazole ring (H-18), and multiplets corresponding to the geminal protons of the thioether at 4.30–4.29 ppm (H-4), the alcohol at 4.59–4.58 ppm (H-1), and the amine at 3.29–3.26 ppm (H-5). The signals for the hydroxypropyl chain can be observed as a quartet (*J* = 6.9 Hz, 2.77 ppm), a multiplet (1.76–1.67 ppm), and a triplet (*J* = 6.4 Hz, 3.60 ppm), corresponding to the protons vicinal to the amine (H-7), to the middle-chain methylene (H-8), and to the protons geminal to the hydroxyl group (H-9), respectively. Additionally, the ¹³C-NMR (Figure S2) shows the characteristic peaks from the tetrazole ring: a quaternary carbon at 153.32 ppm (C-13), which does not correlate with a proton signal in the HSQC (Figure S3), and the carbon from the methyl group at 33.87 ppm (C-18).

The product **3c** can be further functionalized, since it has a primary and a secondary hydroxyl group. Moreover, **3c** has a tetrazole ring which could lead to potential biological activity, since the tetrazole moiety can be found in different approved [21] and candidate drugs [22,23]. Accomplishing the synthesis of **3c** contributed to expanding our previous aminocyclopentitols library [17].

3. Materials and Methods

All chemicals, reagents, and solvents were of analytical grade, purchased from commercial sources, namely, Merck (Algés, Portugal) and Alfa Aesar (Kandel, Germany) and were used without further purification. NMR spectra were obtained on a Bruker Fourier 300 spectrometer (Bruker BioSpin AG, Fallanden, Switzerland) using TopSpin® software (Bruker BioSpin GmbH, Rheinstetten, Germany). NMR experiments were performed in D₂O at room temperature. Chemical shifts are given in parts per million (ppm); the terms m, s, d, t, and q represent multiplet, singlet, doublet, triplet, and quartet, respectively; and the coupling constants (*J*) are given in Hertz (Hz). High-resolution mass spectroscopy (HRMS) was performed in a LTQ Orbitrap XL mass spectrometer, Thermo Fischer Scientific, Bremen, Germany.

1-(3-Hydroxypropyl)pyridin-1-ium chloride (**1c**) and (1*R*,2*R*,5*R*)-6-(3-hydroxypropyl)-6-azabicyclo[3.1.0]hex-3-en-2-ol (**2c**) were prepared as previously described by us [18].

(1*R*,4*S*,5*S*)-5-((3-hydroxypropyl)amino)-4-((1-methyl-1*H*-tetrazol-5-yl)thio)cyclopent-2-en-1-ol **3c**: To a solution of (1*R*,2*R*,5*R*)-6-(3-hydroxypropyl)-6-azabicyclo[3.1.0]hex-3-en-2-ol **2c** (29.6 mg; 0.19 mmol) in distilled water (1 mL), 1-methyl-1*H*-tetrazole-5-thiol (60.1 mg; 0.57 mmol, 3 equiv.) was added. The reaction mixture was stirred at 37 °C and followed by TLC (eluent: dichloromethane/methanol, 9:1) until the complete disappearance of the starting material, observed after 7 days. The crude reaction was concentrated under reduced pressure and purified by silica gel chromatography eluting with dichloromethane, methanol, and triethylamine (9:1:0.1) to afford the ring-opening product **3c** as a brown oil in 95% yield (49.23 mg).

¹H-NMR (300 MHz, D₂O) δ 5.95–5.90 (m, 2H, H-2 and H-3), 4.59–4.58 (m, 1H, H-1), 4.30–4.29 (m, 1H, H-4), 3.96 (s, 3H, H-18), 3.60 (t, *J* = 6.4 Hz, 2H, H-9), 3.29–3.26 (m, 1H, H-5), 2.77 (q, *J* = 6.9 Hz, 2H, H-7), 1.76–1.67 (m, 2H, H-8).

¹³C-NMR (100 MHz, D₂O) δ 153.32 (C-13), 135.02 (C-3), 131.91 (C-2), 80.01 (C-1), 72.44 (C-5), 59.60 (C-9), 55.55 (C-4), 44.05 (C-7), 33.87 (C-18), 30.67 (C-8).

HRMS *m/z* calc. for C₁₀H₁₇N₅O₂S [M + H]⁺ 272.11757, obtained 272.11740.

4. Conclusions

We obtained (1*R*,4*S*,5*S*)-5-((3-hydroxypropyl)amino)-4-((1-methyl-1*H*-tetrazol-5-yl)thio)cyclopent-2-en-1-ol (**3c**) through bicyclic vinyl aziridine ring-opening reaction, with 1-methyl-1*H*-tetrazole-5-thiol. The reaction was executed under mild (37 °C) and sustainable (water as reaction medium) conditions. The compound **3c** was characterized using ¹H NMR, ¹³C NMR, HSQC, and HRMS.

Supplementary Materials: The following are available online, Figure S1: ¹H NMR spectrum; Figure S2: ¹³C-NMR spectrum; Figure S3: HSQC spectrum; Figure S4: HRMS.

Author Contributions: Conceptualization and supervision, F.S. and C.A.M.A.; investigation, M.A.G.F.; data curation and formal analysis, M.A.G.F. and F.S.; writing, M.A.G.F., F.S. and C.A.M.A. All authors have read and agreed to the published version of the manuscript.

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