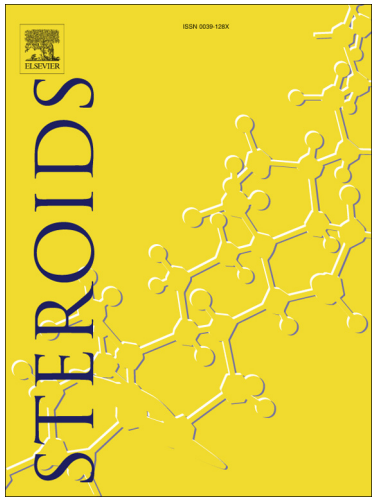

Some observations on solasodine reactivity

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Some observations on solasodine reactivity

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Highlights

- The oxidation of *N*,*O*-diacetylsolasodine with $NaNO_2/BF_3.Et_2O$ or *t*-BuONO/$BF_3.Et_2O$ results in partial degradation of the side chain affording (20*S*)-3β-acetoxypregn-5-ene-20,16β-carbolactone (vespertilin acetate).
- The reaction of *N*,*O*-diacetylsolasodine with TMSOTf leads to the corresponding pseudosapogenin.
- If no aqueous work-up is applied, crude pseudosapogenin readily undergoes autoxidation with concomitant elimination of a five-carbon atom fragment to pregna-5,16-dien-3β-ol-20-one acetate, which is an important intermediate in the synthesis of steroid hormones.

Abstract – This article presents new transformations of solasodine – a representative steroid alkaloid sapogenin from the *Solanum* family. Oxidation of *N*,*O*-diacetylated solasodine with either $NaNO_2/BF_3{\cdot}Et_2O$ or *t*-BuONO/$BF_3{\cdot}Et_2O$ resulted in partial degradation of the side chain to (20*S*)-3β-acetoxypregn-5-ene-20,16β-carbolactone (vespertilin acetate). The same starting compound when treated with TMSOTf afforded the corresponding pseudosapogenin after aqueous work-up. However, when the crude reaction mixture was directly subjected to purification on a silica gel column, efficient autoxidation to pregna-5,16-dien-3β-ol-20-one acetate was observed. One-step synthesis of this important drug intermediate from spirosolan alkaloids may be potentially exploited for large-scale production of steroid hormones.

Keywords: alkaloids, autoxidation, sapogenins, solasodine, steroids

1. Introduction

Steroidal alkaloid glycosides (SAGs) are natural products showing diverse biological activity [1,2]. The largest source of SAGs is the *Solanaceae* family, which includes economically important genera such as the potato, tomato, eggplant, and capsicum. Upon hydrolysis, steroidal alkaloid glycosides yield sugars and steroidal alkaloid sapogenins (SASs). Solanum alkaloids are in fact the nitrogen-analogs of steroidal sapogenins (Figure 1).

Figure 1 insert here

SASs containing oxa-aza spiro (spirosolan) structures may have either an *R* or *S* configuration at the spiro carbon atom (C-22), which is very rare for their oxygen counterparts. The C27 methyl group in spirosolans is always in equatorial position, whereas spirostanes show various orientation of this methyl group. The 21-methyl group is α-oriented (20*S*) in both spirostanes and spirosolans.

The chemistry of steroidal sapogenins has been extensively explored since the 1950s [3,4]. In contrast, knowledge regarding the chemistry of SASs is rather limited [5,6]. In this paper we present the results of a study on selected reactions of the representative steroid alkaloid sapogenin – solasodine.

2. Methods and materials

2.1. Chemistry

2.1.1. General methods

Reagent-grade chemicals were purchased and used as received. Methylene chloride was freshly distilled. Flash column chromatography and dry flash chromatography were performed with silica gel, pore size 40A (70-230 mesh), unless otherwise stated. All reactions were monitored by TLC on silica gel plates 60 F_{254}. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra for all compounds were recorded at ambient temperature and were referenced to TMS

(0.0 ppm) and $CDCl_3$ (77.0 ppm), respectively, unless otherwise noted. NMR resonance multiplicities were reported using the following abbreviations: b = broad, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet; coupling constants *J* were reported in Hz. IR spectra were obtained in a $CHCl_3$ solution with an FT-IR spectrometer, and data are reported in cm^{-1}. Melting points were determined by a Kofler bench (Boetius type) apparatus and are uncorrected.

Acetylation of solasodine acetate: Solasodine acetate (750 mg; 1.6 mmol) was dissolved in pyridine (25 ml) and acetic anhydride (5 ml) was added. The reaction mixture was stirred in room temperature overnight. The reaction mixture was poured into aqueous HCl and extracted with dichloromethane. The combined organic extracts were washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. Silica gel column chromatography with ethyl acetate/hexane 18:82 elution afforded *N,O*-diacetylosolasodine in 80% yield (**1**, 655 mg). Compound **1** proved identical in all respects with the same compound described in the literature [7]. M.p. (DCM/hexane) 161-163°C (lit. [7] 162-164°C); ^{1}H NMR: δ 5.31 (m, 1H), 4.54 (m, 1H), 4. 13 (q, *J* = 7.1 Hz, 1H), 3.95 (bd, *J* = 11.5 Hz, 1H), 3.05 (m, 1H), 2.80 (dd, *J* = 13.0, 6.6 Hz, 1H), 2.14 (s, 3H), 1.98 (s, 3H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.98 (s, 3H), 0.88 (d, *J* = 6.5 Hz, 3H), 0.86 (s, 3H); ^{13}C NMR: δ 170.7 (C), 170.3 (C), 139.6 (C), 122.1 (CH), 101.0 (C), 78.6 (CH), 73.6 (CH), 61.9 (CH), 55.6 (CH), 49.9 (CH), 48.9 (CH_2), 40.8 (C), 39.9 (CH_2), 38.0 (CH), 37.9 (CH_2), 36.8 (CH_2), 36.6 (C), 31.9 (CH_2 x 2), 30.9 (CH), 27.8 (CH), 27.6 (CH_2), 25.1 (CH_3), 24.1 (CH_2), 23.8 (CH_2), 21.2 (CH_3), 20.7 (CH_2), 19.1 (CH_3), 18.4 (CH_3), 16.2 (CH_3), 16.0 (CH_3).

Oxidation of 1 with $NaNO_2$/BF_3Et_2O: *N,O*-Diacetylsolasodine **1** (75 mg; 0.14 mmol) was dissolved in glacial AcOH (10 ml). Then $BF_3.Et_2O$ (0.005 ml; 6 equiv) was added. Sodium nitrite (30 mg; 3 equiv) was added portion-wise for 30 min. The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into water and pH

was adjusted to 8-9 by adding $NaHCO_3$. The product was extracted with dichloromethane. The combined organic layers were washed with saturated aqueous NaCl solution, dried over Na_2SO_4 and evaporated *in vacuo*. Silica gel column chromatography with ethyl acetate/hexane 15:85 elution afforded (20*S*)-3β-acetoxypregn-5-ene-20,16β-carbolactone in 80% yield (**2**, 46 mg). Compound **2** proved identical in all respects with the same compound described in the literature [8]. M.p. (DCM/hexane) 216-220°C (lit. [8] 210-212°C; [9] 216-220°C); ^{1}H NMR: δ 5.38 (m, 1H), 4.96 (m, 1H), 4.61 (m, 1H), 2.60 (q, *J* = 7.6 Hz, 1H), 2.04 (s, 3H), 1.33 (d, *J* = 7.6 Hz, 3H), 1.05 (s, 3H), 0.78 (s, 3H); ^{13}C NMR: δ 181.3 (C), 170.5 (C), 139.8 (C), 121.9 (CH), 82.7 (CH), 73.7 (CH), 58.9 (CH), 54.7 (CH), 49.9 (CH), 41.4 (C), 38.1 (CH_2), 38.0 (CH_2), 36.9 (CH_2), 36.6 (C), 36.0 (CH), 33.1 (CH_2), 31.8 (CH_2), 31.2 (CH), 27.7 (CH_2), 21.4 (CH_3), 20.3 (CH_2), 19.3 (CH_3), 18.0 (CH_3), 13.7 (CH_3).

Oxidation of 1 with *t*-BuONO/BF_3Et_2O: *N*,*O*-Diacetylsolasodine **1** (250 mg; 0.5 mmol) was dissolved in glacial AcOH (10 ml). Then $BF_3.Et_2O$ (0.03 ml; 0.5 equiv) was added followed by *tert*-butyl nitrite (0.3 ml; 5 equiv). The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was poured into water and pH was adjusted to 8-9 by adding $NaHCO_3$. The product was extracted with dichloromethane. The combined organic extracts were washed with saturated aqueous NaCl solution, dried over Na_2SO_4 and evaporated *in vacuo*. Silica gel column chromatography with ethyl acetate/hexane 15:85 elution afforded (20*S*)-3β-acetoxypregn-5-ene-20,16β-carbolactone in 90% yield (**2**, 175 mg). Compound **2** proved identical in all respects with the same compound described in the literature.

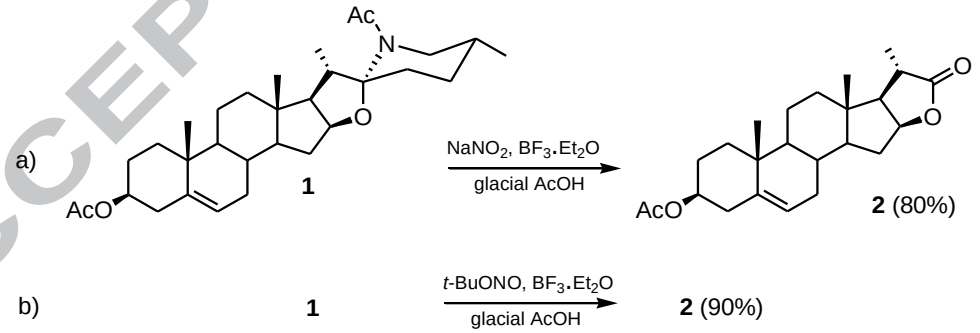
Reaction of 1 with TMSOTf without aqueous work-up: *N*,*O*-Diacetylsolasodine **1** (50 mg, 0.1 mmol) was dissolved in dry dichloromethane (15 ml). TMSOTf (1 equiv, 0.018 ml) was then added to the solution. The solution was placed on a silica gel column after a period of 10 min. The reaction mixture remained on the column for 72 h. Then pregna-5,16-

dien-3β-ol-20-one acetate (21 mg, 60%) was eluted with an ethyl acetate/hexane 35:65 mixture. Compound **3** proved identical in all respects with the same compound described in the literature [10]. M.p. (DCM/hexane) 169-172°C (lit. [10] 172-174°C); ^{1}H NMR: δ 6.72 (m, 1H), 5.35 (d, *J* = 5.0 Hz, 1H), 4.62 (m, 1H), 2.27 (s, 3H), 2.04 (s, 3H), 1.07 (s, 3H), 0.93 (s, 3H); ^{13}C NMR: δ 196.8 (C), 170.5 (C), 155.4 (C), 144.4 (CH), 140.3 (C), 121.9 (CH), 73.8 (CH), 56.3 (CH), 50.4 (CH), 46.1 (C), 38.1 (CH_2), 36.8 (CH_2), 36.7 (C), 34.6 (CH_2), 32.2 (CH_2), 31.5 (CH_2), 30.1 (CH), 27.7 (CH_2), 27.1 (CH_3), 21.4 (CH_3), 20.6 (CH_2), 19.2 (CH_3), 15.7 (CH_3).

Reaction of 1 with TMSOTf followed by aqueous work-up: *N*,*O*-Diacetylsolasodine **1** (40 mg, 0.1 mmol) was dissolved in dry dichloromethane (15 ml). TMSOTf (0.044 ml, 2 equiv) was then added to the solution. After 24 h the reaction mixture was poured into water and extracted with dichloromethane. The combined organic extracts were washed with saturated aqueous NaCl solution, dried over Na_2SO_4 and evaporated *in vacuo*. Silica gel chromatography with ethyl acetate/hexane 7:3 elution afforded *N*-acetylopseudosolasodine acetate (23 mg, 60%). Compound **4** proved identical in all respects with the same compound described in the literature [7]. M.p. (DCM/hexane) 134-137°C (lit. [11] 134-136°C); ^{1}H NMR: δ 5.58 (bs, 1H), 5.38 (d, *J* = 4.6 Hz, 1H), 4.75 (m, 1H), 4.62 (m, 1H), 3.714 (m, 1H), 2.27 (s, 3H), 2.04 (s, 3H), 1.98 (s, 3H), 1.04 (s, 3H), 0.92 (d, *J* = 6.6 Hz, 1H), 0.69 (s, 3H); ^{13}C NMR: δ 170.5 (C), 170.0 (C), 151.3 (C), 139.7 (C), 122.3 (CH), 104.0 (C), 84.3 (CH), 73.8 (CH), 64.1 (CH), 54.9 (CH), 49.9 (CH), 45.3 (CH_2), 43.2 (C), 39.4 (CH_2), 38.1 (CH_2), 36.9 (CH_2), 36.7 (C), 34.1 (CH_2), 32.7 (CH), 32.1 (CH_2), 31.7 (CH_2), 31.2 (CH), 27.7 (CH_2), 23.4 (CH_3), 23.1 (CH_2), 21.4 (CH_3), 20.9 (CH_2), 19.3 (CH_2), 17.6 (CH_3), 13.9 (CH_3), 11.6 (CH_3).

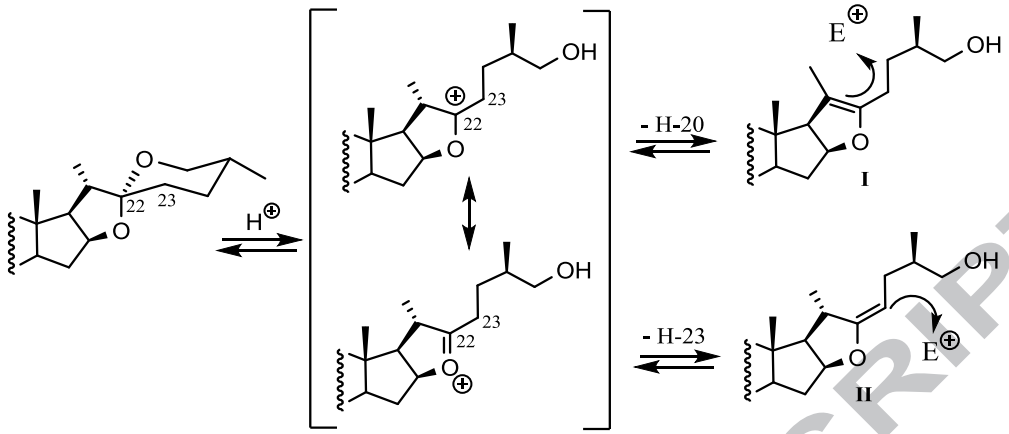
3. Results and discussion

There are many examples of interesting reactions of 23-oxo functionalized steroidal sapogenins in the literature [3,12]. The first aim of this project was to elaborate a convenient route to 23-oxo-solasodine acetate in order to study processes similar to those of 23-oxo-spirostanes. Since direct functionalization of solasodine at C23 failed, the amino group was protected by acetylation with Ac_2O/Py. Then derivative **1** was subjected to oxidation with $NaNO_2/BF_3.Et_2O$ according to the procedure first described by Barton [13] and improved by Iglesias-Arteaga [14] (Scheme 1a). The structure of the obtained product (20*S*)-3β-acetoxypregn-5-ene-20,16β-carbolactone (**2**) (vespertilin acetate) was elucidated from its ^1H NMR, in which the characteristic F ring signals of 26-methylene protons and the 27-methyl group disappeared. Vespertilin is a naturally occurring lactone with a proven biological activity, including antipyretic, anticarcinogenic, and plant growth promotion [8,15]. Because the above reaction did not give the desired result, other conditions as introduced by Fuchs *et al.* were applied [16]. The method employs *t*-butyl nitrite instead of sodium nitrite. In this case, lactone **2** was also the only product (Scheme 1b).



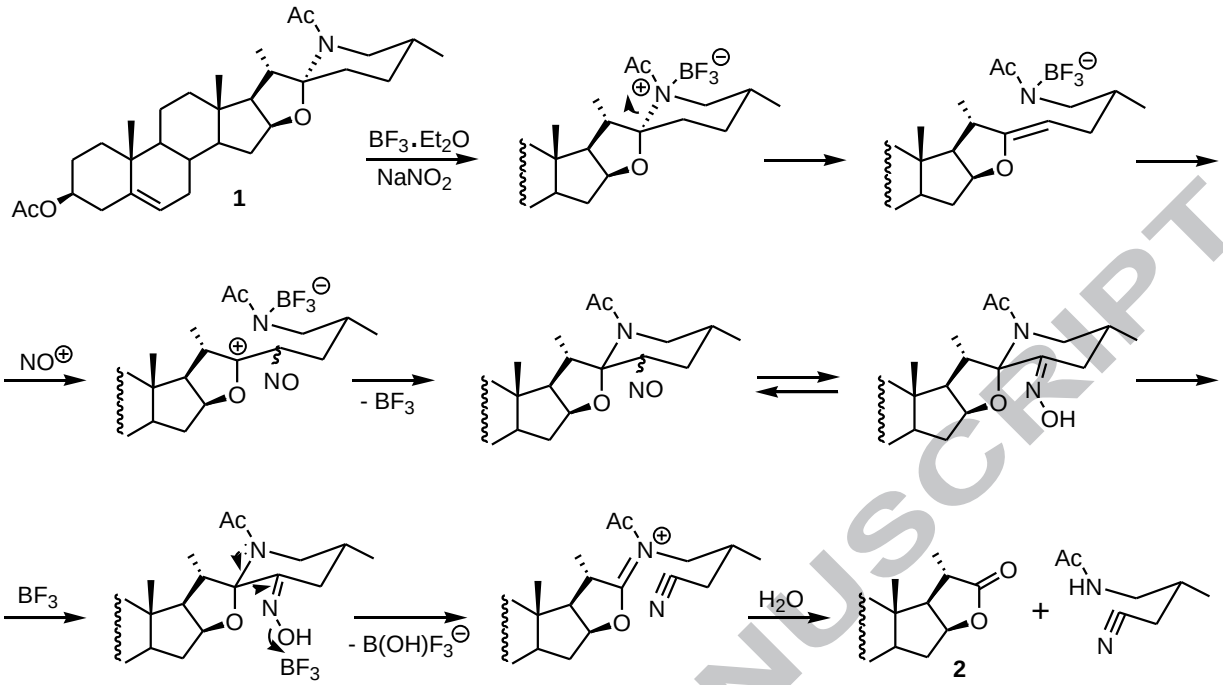
Scheme 1. Oxidation of *N*,*O*-diacetylsolasodine **1**.

In the case of oxidation of spirostanes at C23, the reaction proceeds via intermediate enol-ether **II** [13], which is attacked by the oxidizing agent followed by F ring reclosure in the next step (Scheme 2).



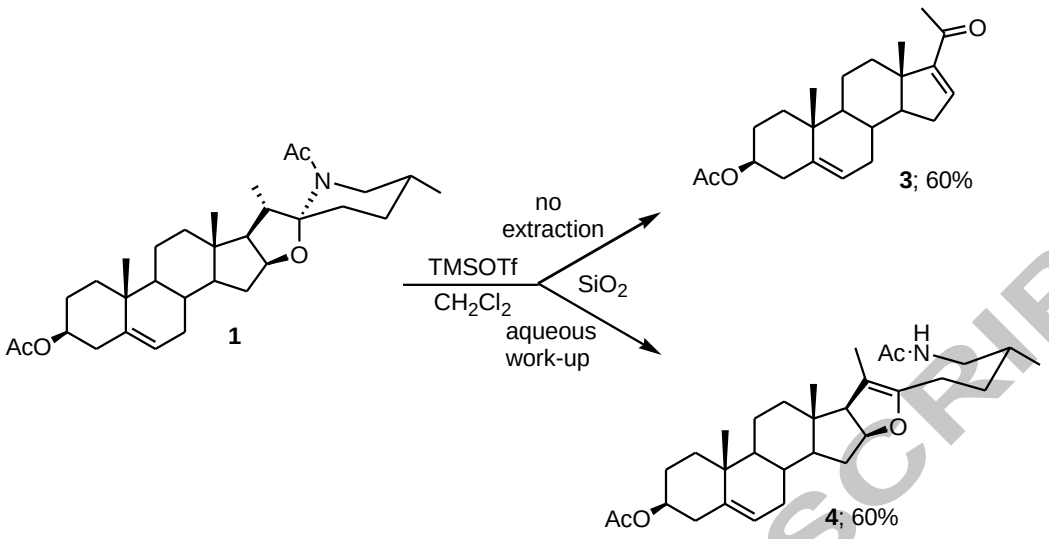
Scheme 2. Formation of enol-ether intermediates **I** and **II** in the presence of acid.

Oxidation of *N*-acetylated solasodine **1** probably follows the same reaction mechanism. In this case, the nitrosonium ion is an electrophile that attacks the pseudosapogenin formed from solasodine diacetate **1**. The initial 23-nitroso product equilibrates to the more stable 23-hydroxyimino tautomer. It has already been proven that the 23-oxime readily undergoes Beckmann fragmentation under the reaction conditions ($BF_3 \cdot Et_2O$, AcOH) [17]. The reaction leads to 20,16β-carbolactone **2** via the loss of a five-carbon atom nitrile fragment. The presumable mechanism of oxidation with $NaNO_2/BF_3 \cdot Et_2O$ is presented in Scheme 3.



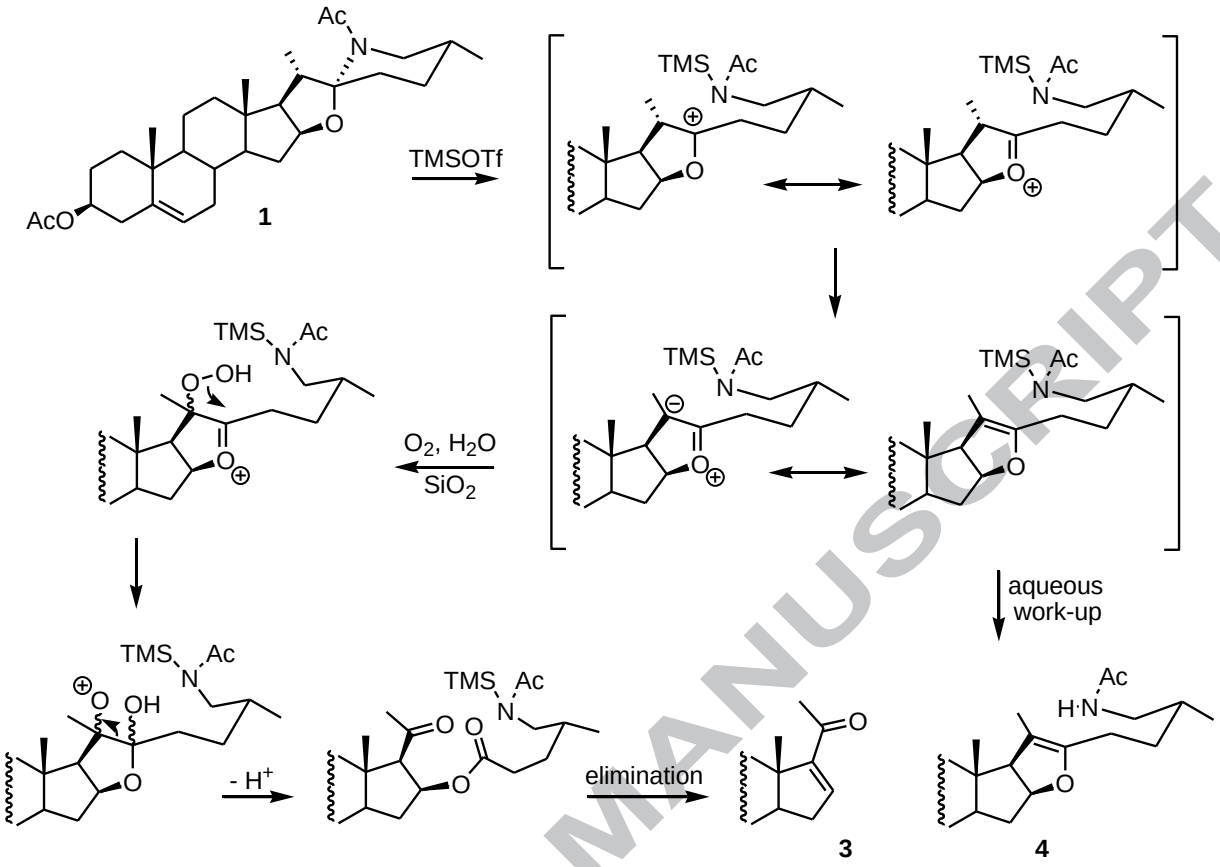
Scheme 3. Tentative mechanism of oxidation of solasodine *N*,*O*-diacetate **1**.

Previous studies on steroidal spirostanes have shown that strongly acidic reagents, e.g. trimethylsilyl trifluoromethanesulfonate (TMSOTf), cause isomerization of sapogenins at C25 [18]. *N*,*O*-Diacetylsolasodine **1** was subjected to TMSOTf in dichloromethane in order to check if such isomerization also takes place in spirosolans. However, the reaction took a rather unexpected course, i.e. when the crude reaction product was subjected to silica gel purification without prior extraction, 16-dehydroprogesterone acetate **3** was obtained in 60% yield (Scheme 4). In contrast, when the reaction mixture was poured into water, extracted, and then further purified on a silica gel column, the isolated product was pseudosolasodine **4** (60%).



Scheme 4. Reaction of *N*,*O*-diacetylsolasodine with TMSOTf.

The process of degradation of sapogenins is well known as the Marker degradation and is used for sex hormone production [19]. In this classical methodology, Ac_2O in the presence of $AlCl_3$ is used to obtain pseudosapogenin, followed by oxidation with CrO_3 and elimination [20]. In our experiment, a similar degradation of rings E and F was observed without using a strong oxidizing agent under mild conditions. It is worth noticing that an important drug intermediate, 16-dehydroprogesterone acetate **3**, was obtained in an efficient autoxidation process from a common spirosolan alkaloid in a single step. The likely mechanism of this process, similar to the Marker degradation, is depicted in Scheme 5. Such an autoxidation process is unique and was not previously observed for other pseudosapogenins. The mechanism assumes an electrophilic attack of dioxygen to the intermediate enol-ether at C20, followed by further transformations of 20-hydroperoxide leading to cleavage of the C20-C22 bond. However, an alternative mechanism of the reaction may be considered involving [2+2] cycloaddition of dioxygen to the double bond C20-C22 of the enol-ether. The dioxetane intermediate may also evolve to 20-ketone by cleavage of the C20-C22 and O-O bonds. This pathway is, however, less likely since the cycloaddition requires singlet oxygen [21].



Scheme 5. Plausible mechanism of degradation of *N*,*O*-diacetylsolasodine **1**.

Interestingly, the formation of degradation products was not observed in the reaction of free solasodine with TMSOTf in dichloromethane. The only product isolated after evaporation of the solvent was the salt solasodinium triflate. The protonation caused significant changes in the ^{1}H NMR spectrum. Signals of 26-H,H are more separated from one another than in solasodine, in which the signals appear as a triplet at 2.61 ppm (axial H pro-*R*, J = 10.6 Hz) and a doublet of doublets at 2.67 ppm (equatorial H pro-*S*, J = 11.1, 4.2 Hz), while for protonated solasodine these two signals showed up at 2.83 ppm (equatorial H pro-*S*, triplet, J = 12.2 Hz) and 3.12 ppm (axial H pro-*R*, doublet of doublets, J = 11.5, 2.6 Hz, 1H) [Figure 2]. Also, the 21-methyl group protons were shifted downfield upon protonation from 0.85 ppm (d, J = 6.3 Hz) in solasodine to 1.20 ppm (d, J = 7.3 Hz) in its salt.

Figure 2. insert here

4. Conclusion

This study presents new reactions of a spirosolan derivative. The oxidation of *N*,*O*-diacetylsolasodine **1** with $NaNO_2/BF_3{\cdot}Et_2O$ afforded (20*S*)-3β-acetoxypregn-5-ene-20,16β-carbolactone (**2**, vespertilin acetate). The same compound **1** when treated with TMSOTf/DCM afforded the corresponding pseudosapogenin **4** or 16-dehydroprogesterone acetate **3** depending on the work-up conditions. The latter compound, which is an important intermediate for the steroid hormone industry, was presumably formed by unprecedented autoxidation of the reaction mixture.

Acknowledgements

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Figure legends:

Figure 1. Structures of steroid alkaloid sapogenins and spirostanes.

Figure 2. Comparison of spectra of a) solasodine and b) protonated solasodine.

Figure 1

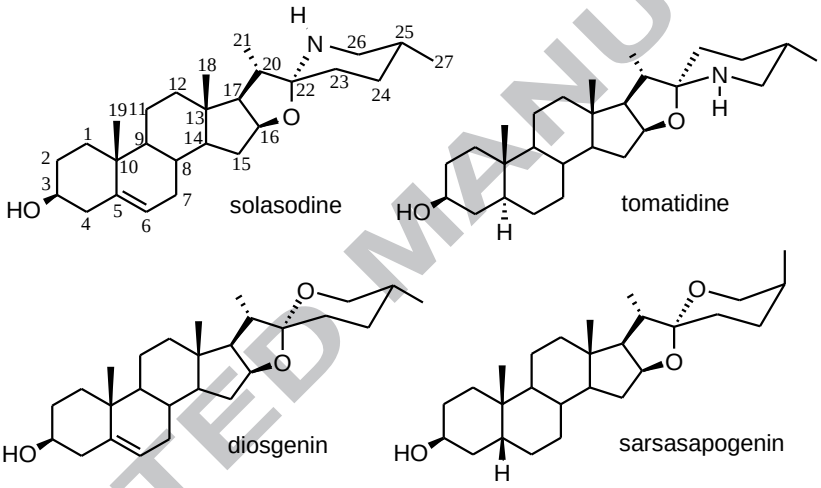
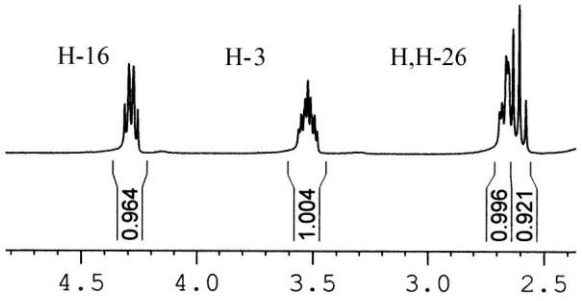
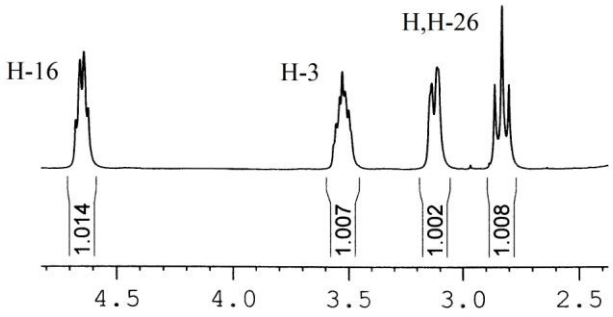


Figure 2

a) solasodine



b) protonated solasodine



Highlights

- The oxidation of *N*,*O*-diacetylsolasodine with $NaNO_2/BF_3.Et_2O$ or *t*-BuONO/$BF_3.Et_2O$ results in partial degradation of the side chain affording (20*S*)-3β-acetoxypregn-5-ene-20,16β-carbolactone (vespertilin acetate).
- The reaction of *N*,*O*-diacetylsolasodine with TMSOTf leads to the corresponding pseudosapogenin.
- If no aqueous work-up is applied, crude pseudosapogenin readily undergoes autoxidation with concomitant elimination of a five-carbon atom fragment to pregna-5,16-dien-3β-ol-20-one acetate, which is an important intermediate in the synthesis of steroid hormones.