Pergamon

Tetrahedron Letters 42 (2001) 5989–5991

TETRAHEDRON LETTERS

Novel transformation of 23-bromosapogenins. Synthesis of (22*S*,23*R*)-22-hydroxy-23,26-epoxyfurostanes

Jacek W. Morzycki* and Izabella Jastrzębska

Institute of Chemistry, University of Bialystok†, *al. Pilsudskiego 11/4, 15-443 Bialystok, Poland*

Received 24 April 2001; revised 19 June 2001; accepted 28 June 2001

Abstract—(22*S*,23*S*)-23-Bromosapogenins undergo rearrangement to the (22*S*,23*R*)-22-hydroxy-23,26-epoxyfurostanes during alkaline hydrolysis. An efficient degradation procedure of sarsapogenin via the corresponding bisfuran to the C_{22} lactone is described. © 2001 Elsevier Science Ltd. All rights reserved.

The sapogenins are aglycones of saponins, a group of glycosides widely distributed in plants. The most common sapogenins are spirostanols with the normal-type spiroacetal form (22*R*). With regard to the configuration at C-25, there are two types: an α-oriented methyl group (25*R* as in hecogenin acetate **1**) and a β-oriented methyl group (25*S* as in sarsasapogenin acetate **8**). The sapogenins are important for their use as the starting materials for the preparation of various steroidal drugs (natural and artificial).[1]

It is well known that sapogenins can be selectively brominated at C-23. The study of the bromination of the sapogenins has a history full of contradictions that would be tedious to detail.[2] Our observations confirm the reports that 25*R*-sapogenins form two isomeric 23-bromo derivatives **2** and **3** (no bromination product at C-11 was detected). Bromination of the 25*S*-sapogenins yields only a single 23-bromo product **9** due to steric hindrance from the axial methyl group at C-25. All three bromo derivatives (23*S*,25*R*; 23*R*,25*R* and 23*S*,25*S*) were subjected to weak alkaline hydrolysis (NH_3 or K_2CO_3, H_2O, *n*-BuOH, reflux several days). Compound **3** with an axial bromine atom did not react under these conditions (Scheme 1). The other compounds (**2** and **9**) yielded bisfuran products with a tertiary hydroxy group (as proved by failure of acetylation attempts). Mass spectra showed a very characteristic pattern of molecular ion fragmentation involving loss of water or methyltetrahydrofuran $(M-C_5H_{10}O)^{+\bullet}$.[3]

^1H and ^{13}C NMR spectra confirmed the hemiacetal structure of the products (**4** and **10**, respectively). Analysis of NOE effects in their ^1H NMR spectra suggests the 23*R* configuration in these compounds. This suggestion was later unequivocally confirmed by X-ray analysis of compound **10** (R = Ac). A general view of the molecule is shown in Fig. 1.

A concerted mechanism is suggested for bisfuran formation (Scheme 2) consisting of simultaneous departure of bromide and shift of an oxygen atom from C-20 to C-22, followed by addition of water to the stabilized carbocation **A**. Non-bonded electrons of the 'pyranose' oxygen atom may, however, assist the departure of the bromine atom of compounds **2** and **9**. The oxonium ion thus formed (**B**) could be preferentially attacked by hydroxide anion at the spiro carbon atom (C-22) bearing some positive charge. The oxonium ion **B** may also be attacked at the secondary position (C-26) to afford epoxy alcohol **C** that could be transformed further to the final product.

There are different stereochemical consequences of these mechanisms. The two former mechanisms (via **A** or **B**) imply inversion of configuration at C-23, whereas the latter (via **C**) retention, as a result of double inversion.

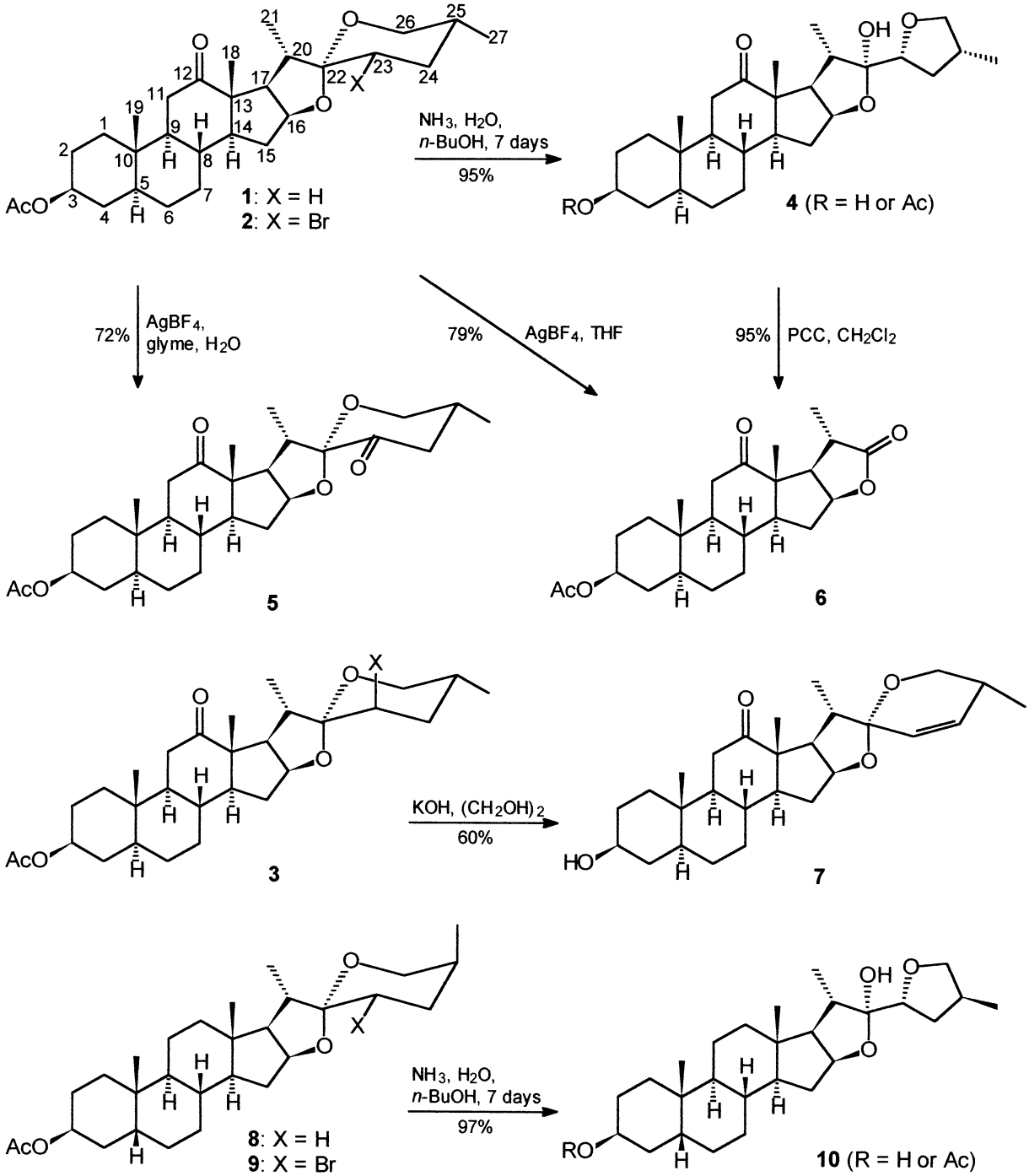
The rearrangement described above is novel in the chemistry of spirostanes. Investigation of various conditions showed that it can also be induced by silver tetrafluoroborate. In this case, however, ketone **5**[4] and/or lactone **6**[5] accompany the rearrangement product **4**. Products **4** and **5** dominate when water is present in the reaction mixture, whereas lactone **6** prevails under anhydrous conditions.

Keywords: steroids; sapogenins; furostanes; rearrangements.

* Corresponding author. Fax: (048 85) 745 75 81; e-mail: morzycki@noc.uwb.edu.pl

† Formerly: University of Warsaw, Bialystok Branch.

PII: S0040-4039(01)01165-0



Scheme 1.

It was proved that the product **4** of the rearrangement easily undergoes oxidation to the lactone **6**, e.g. with pyridinium chlorochromate. The three step degradation procedure of sarsasapogenin acetate **8** to the lactone analogous to **6**, involving bromination, rearrangement and oxidation, is very efficient (overall yield ~90%) and may be of practical significance. The lactones, such as **6**, can be used for the synthesis of numerous steroids bearing the oxygen functional groups at C-16 and C-22.[6]

In the case of the axial bromide **3** no rearrangement was observed even at elevated temperature. There is no evidence for 'furanose' oxygen atom participation (**D**) in the hydrolysis of compound **3**. The sole reaction product of bromide **3** with KOH in refluxing ethylene glycol was olefin **7**.[7]

The bisfuran structures described herein have not been found in the plant kingdom to date.

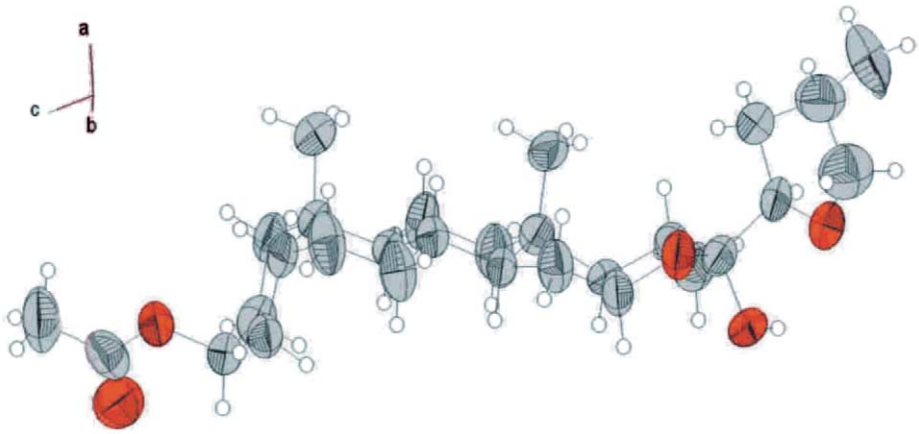
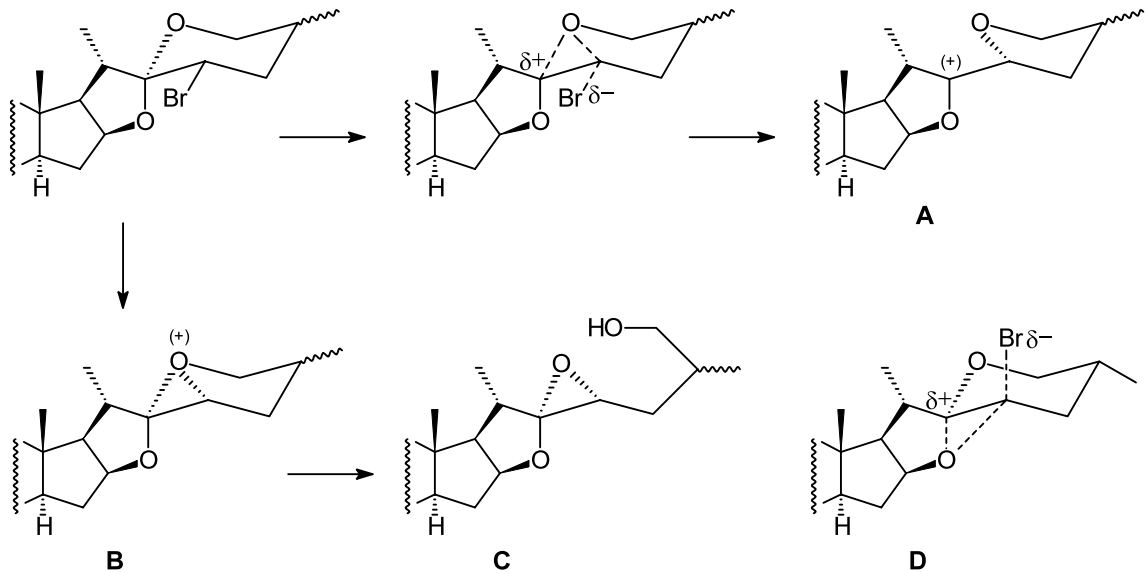


Figure 1. An ORTEP view of the molecule **10**.



Scheme 2.

Acknowledgements

The work was financially supported by the Polish Ministry of Education within the project BST-124. X-Ray analysis was performed by Dr. R. Anulewicz-Ostrowska from the University of Warsaw. I.J. thanks the University of Warsaw for the fellowship.

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3. Compound **4** (R = Ac), EI–MS, *m*/*z* (%): 470 (100), 403 (14). Compound **10** (R = Ac), EI–MS, *m*/*z* (%): 456 (9), 389 (35), 329 (100), 255 (87). The fragmentation pattern is very similar to that of spirostane sapogenins with an electronegative substituent at C-23: (a) González, A. G.; Freire, R.; García-Estrada, M. G.; Salazar, J. A.; Suárez, E. *Tetrahedron* **1972**, *28*, 1289–1297; (b) Faul, W. H.; Djerassi, C. *Org. Mass. Spectrom*. **1970**, *3*, 1187–1213.
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