



Pergamon

Tetrahedron Letters 41 (2000) 3751–3754

TETRAHEDRON  
LETTERS

## Some reactions of $16\alpha,17\alpha$ -oxido-steroids: a study related to the synthesis of the potent anti-tumor Saponin OSW-1 aglycone

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Received 21 February 2000; accepted 21 March 2000

### Abstract

Five  $16\alpha,17\alpha$ -oxido-steroids were subjected to acids, bases and lithium hydroperoxide. Acids caused Wagner–Meerwein-type rearrangement irrespective of the side-chain structure. The  $16\alpha,17\alpha$ -epoxides proved resistant to bases unless a C(22)=O group was present; in the case of 22-esters or 22-ketones the oxirane rings were cleaved with base and the corresponding allylic alcohols were formed. The reactions of  $16\alpha,17\alpha$ -oxido-22-carbonyl compounds with lithium hydroperoxide resulted in the epoxide cleavage to the desired  $16\beta,17\alpha$ -diols which underwent further transformations. © 2000 Elsevier Science Ltd. All rights reserved.

*Keywords:* steroids; saponin; lithium compounds; epoxides.

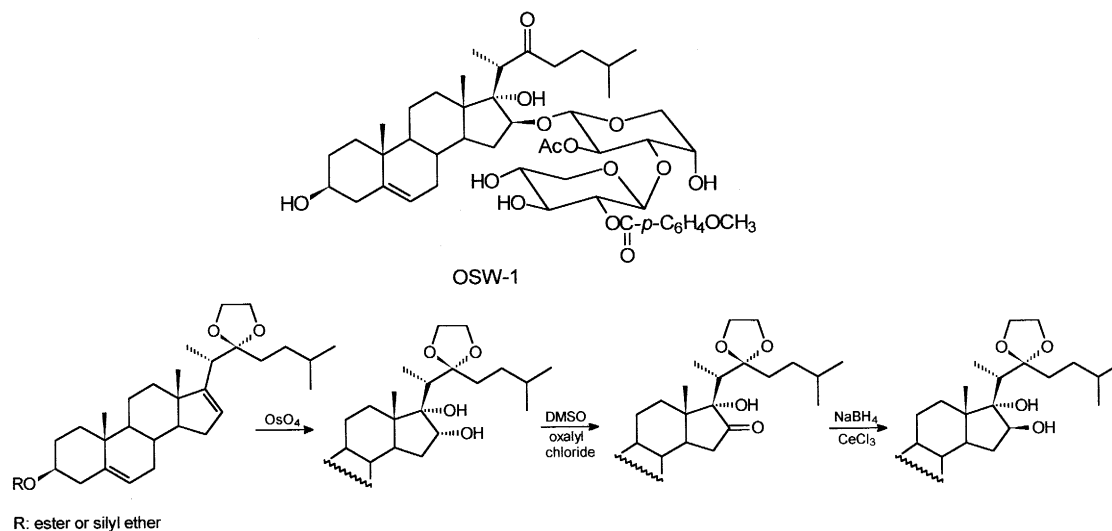
A family of cholestane glycosides with potent cytostatic activity was isolated from *Ornithogalum saundersiae* bulbs a few years ago by Sashida and co-workers.<sup>1,2</sup> The first report on the synthesis of the aglycone of the major component from the extraction (OSW-1) by Fuchs and Guo<sup>3</sup> was recently followed by the paper of Chinese chemists on the full synthesis of the saponin OSW-1 (Scheme 1).<sup>4</sup> A similar synthetic strategy for the aglycone part of the molecule was applied by both research groups. The *trans*-diol functionality in ring D was achieved by regio- and stereoselective osmylation, followed by inversion of configuration at C-16 using an oxidation–reduction procedure.<sup>3–5</sup> This expensive and indirect approach was applied to avoid problems associated with  $16\alpha,17\alpha$ -epoxide cleavage. In principle, base-catalyzed hydrolysis of the epoxide was expected to afford the  $16\beta,17\alpha$ -diol and this would be the best way to this system. However, it was reported that the oxirane ring of  $16\alpha,17\alpha$ -epoxides is resistant to alkaline cleavage, while acid-catalyzed cleavage results in “total decomposition of the starting steroid”.<sup>3</sup>

In spite of these unpromising results we decided to examine the reactions of some  $16\alpha,17\alpha$ -oxido-steroids in detail. The structures of  $16\alpha,17\alpha$ -epoxides chosen for our studies are given in Scheme 2.

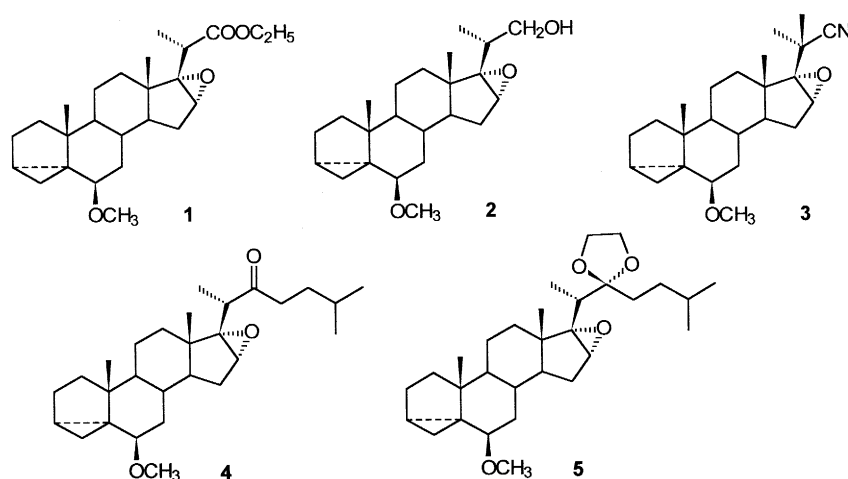
Each of these compounds was treated with sodium ethoxide in ethanol at room temperature; compounds **2**, **3** and **5** proved resistant to these conditions. Contrary to this, the reactions of **1** and **4** were pretty fast and led to the cleavage of the oxirane ring with the formation of the corresponding allylic alcohols.<sup>6</sup> The reaction mechanism is shown in Scheme 3.

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Scheme 1.

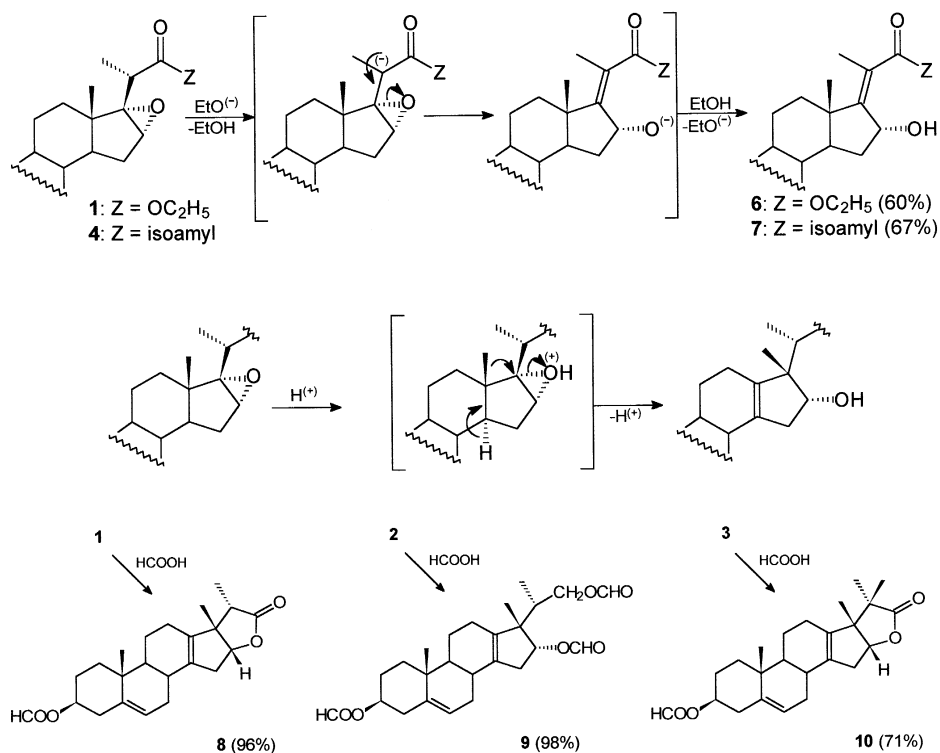


Scheme 2.

The compounds **1**, **2** and **3** were also subjected to acidic conditions. The reactions with 70% formic acid resulted in a Wagner–Meerwein-type rearrangement. Protonation of the epoxide oxygen atom was followed by C(17 $\alpha$ )–O bond cleavage, angular methyl group migration from the 13 $\beta$ - to the 17 $\beta$ -position, and abstraction of a 14 $\alpha$ -proton (see Scheme 3). In the case of compounds **1** and **3** subsequent lactonization took place.

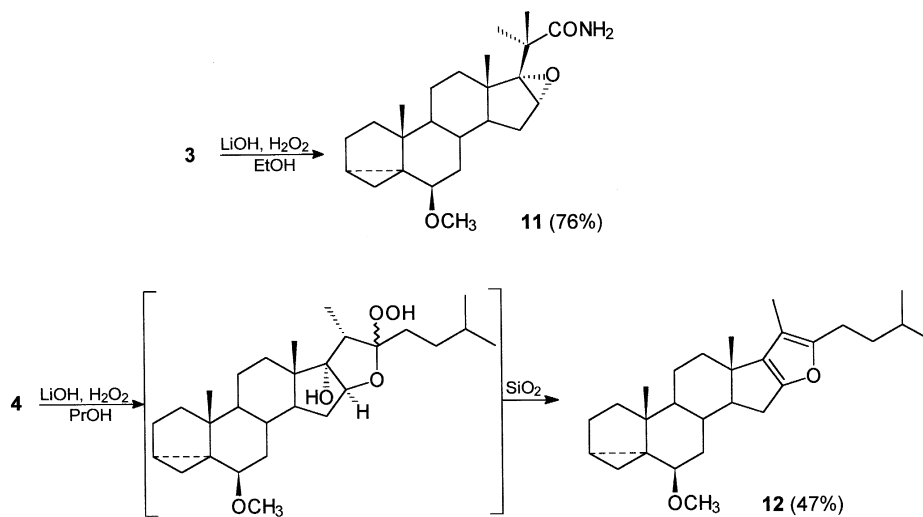
The rearrangement products were also obtained upon treatment of compounds **1**, **2** and **3** with periodic acid or silica gel impregnated with sulfuric acid. A similar rearrangement of 16 $\alpha$ ,17 $\alpha$ -epoxides under the acid conditions in the cholestane series was observed previously.<sup>7</sup>

Attempts to cleave the oxirane ring in compounds **1**–**5** with nucleophiles such as iodide, phenylsulfide or triflate were unsuccessful. However, the reaction with LiOH/H<sub>2</sub>O<sub>2</sub> led to the desired epoxide cleavage product in the case of compound **1**. There was no reaction of **2** or **5** with lithium hydroperoxide, whereas nitrile **3** was only partially hydrolyzed to amide **11** under these conditions (Scheme 4). The cleavage of the oxirane ring in compound **4** was complicated by consecutive reactions leading to the formation of a furan derivative **12**. The reaction of epoxy-ester **1** with this reagent slowly but steadily afforded dihydroxy-acid **13** (Scheme 5). Monitoring of the reaction by TLC proved that cleavage of epoxide was preceded by ester



Scheme 3.

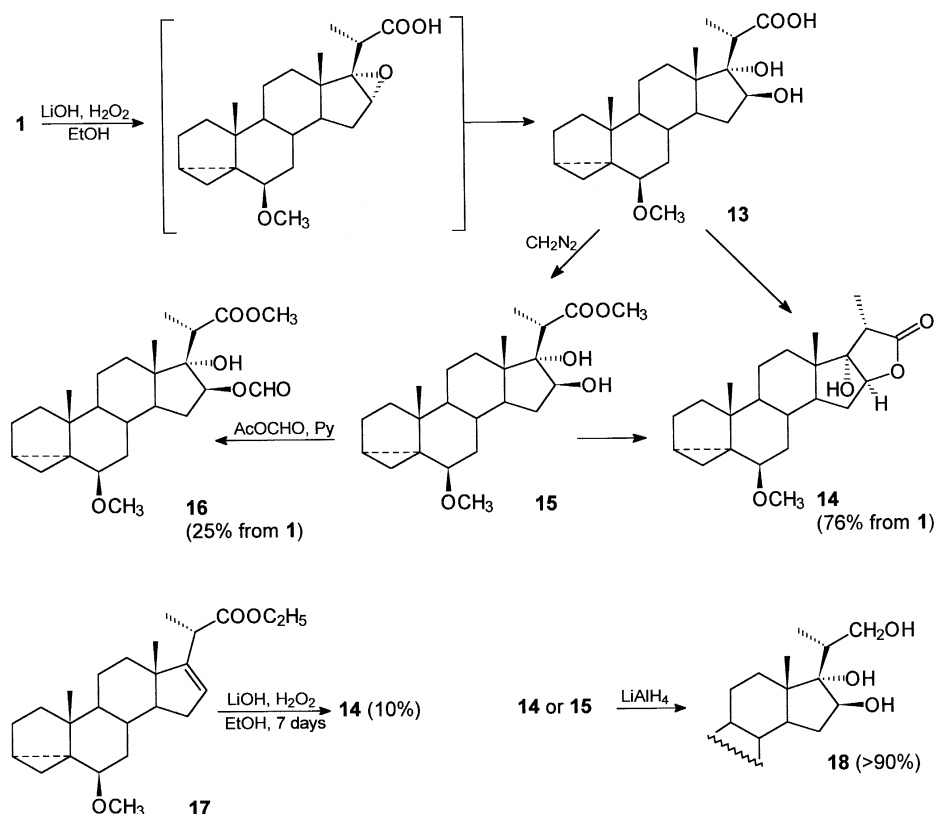
hydrolysis. Dihydroxy-acid **13** was isolated by column chromatography but it appeared to be stable only in solution. Evaporation of the chromatographic fractions resulted in the spontaneous lactonization to **14**.



Scheme 4.

Hydroxy-lactone **14** was also obtained from olefin **17** upon reaction with lithium hydroperoxide. It is most likely that intramolecular epoxidation of the double bond by intermediate steroidal peracid took place during the reaction. However, the yield of **14** from olefin **17** was much lower than from the 16 $\alpha$ ,17 $\alpha$ -epoxide **1**.

In order to protect against lactonization a solution of dihydroxy-acid **13** was treated with diazomethane.



Scheme 5.

However, dihydroxy-ester **15** still showed some tendency to cyclization by intramolecular transesterification. Compound **15** proved to be stable enough for derivatization (e.g. its 16-formate **16** was prepared). Both hydroxy-lactone **14** and dihydroxy-ester **15** afforded the same triol **18** upon LAH reduction in almost quantitative yield.

## Acknowledgements

We thank Professor Samir Zard from the Institut de Chimie des Substances Naturelles, CNRS, Gif sur Yvette, France for fruitful discussions. Financial support from the State Committee for Scientific Research, Poland (Grant No. 3 T09A 054 17) is gratefully acknowledged.

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