

First Synthesis of (20S) 3 β ,16 β -Dihydroxy-5-pregnen-20,16-carbolactone (Diosgeninlactone)

Andrea C. Bruttomesso and Eduardo G. Gros

Departamento. de Química. Orgánica, UMYMFOR. Facultad de Ciencias Exactas y Naturales, UBA.
Pabellón II, 3° P. Ciudad Universitaria. (1428). Buenos Aires, Argentina
E-mail: aachiocc@quimor.qo.fcen.uba.ar

Abstract: Diosgeninlactone (**1**), a natural product from *Solanum vespertilio*, was stereo-selectively synthesized in high yield from 3 β -hydroxy-5-androstene.

Introduction

Our development of synthetic approaches to *cis*-20,16- γ -carbolactones originated during the course of studies on the catabolic pathway by which tomato plants degrade steroidal alkaloids into 3 β -hydroxy-5 α -pregn-16-en-20-one.

The isolation of some related compounds, such as (23R)-23-acetoxytomatidine and (23S)-23-acetoxysoladulcidine from *Lycopersicum esculentum*, suggested a probable mechanism for the degradation of nitrogen containing rings [1].

In addition, products containing the 20,16-*cis*- γ -lactone moiety have been isolated from different vegetable sources, and postulated to be metabolic products of the corresponding sapogenins. At the moment none of them have been synthesized. In 1971 Diosgeninlactone (**1**) was isolated from the ethanolic extract of the fruits of *Solanum vespertilio* [2].

In view of the highly efficient protocol developed by us, in the synthesis of tigogeninlactone [3,4] we decided to explore this synthetic strategy to obtain **1**.

Experimental

Wittig reaction on 3 β -(dimethyl-*t*-butylsilyloxy)-5-androsten-17-one yielded the *Z*-olefin stereo-selectively with the introduction of a two-carbon lateral side chain at C-17.

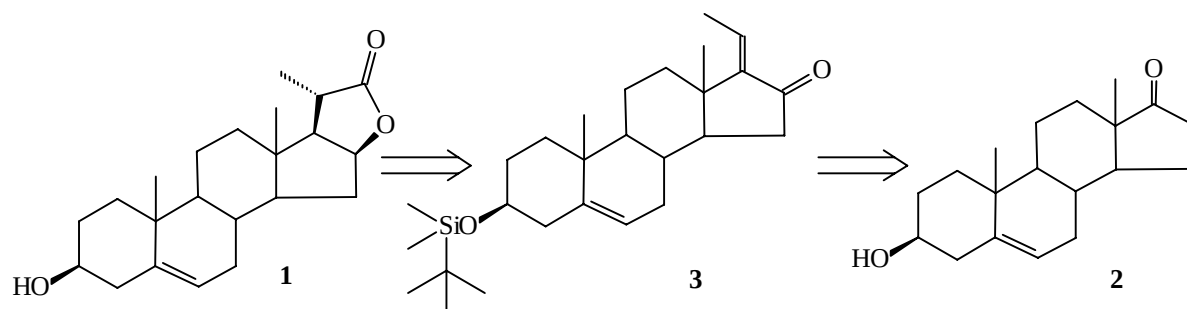
Allylic hydroxylation on C-16 with *t*-butylhydroperoxide in the presence of catalytic amounts of selenium dioxide introduced the hydroxy group from the α -face of the steroid nucleus.

Swern oxidation produced the conjugated ketone **3** in very good yield.

Michael addition of sodium cyanide in a THF/EtOH/H₂O mixture introduced the third carbon atom in the side chain. The addition from the α -face afforded only the 17 β -(20S) nitrile isomer.

Stereoselective reduction of the ketonitrile with lithium tri-*t*-butoxy aluminohydride produced the 16 β -hydroxy-derivative. As expected, the bulky hydride approaches the carbonyl group from the less-hindered α -face, producing in excellent yield and selectivity the needed β -orientation for the hydroxy group on C-16.

Alkaline hydrolysis of the hydroxy-nitrile followed by an acidic work-up produced lactone **1**, as lactonization and deprotection of the 3 β -OTBDMS group took place during acidic work-up.



Results and Conclusions

Many strategies have been explored for the construction of the β -fused γ -lactonic ring E. The attachment of a 2-carbon side chain on C-17 previously to the allylic oxidation of C-16 was the key step in the synthesis.

Early studies involving the connection of a 3-carbon side chain on C-17 of a 17-oxo-16 β -acetoxyandrostane led to the epimeric α -oriented γ -lactone [3,4].

In conclusion, a highly efficient stereoselective protocol has been developed for the β -oriented 20,16-*cis*- γ -carbrolactones. Thus, Diosgeninlactone (**1**) were stereoselectively synthesized in high yield from 3 β -hydroxy-5-androsten-17-one (**2**).

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References and Notes

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