

Synthesis of D-Homo Analogs of Neurosteroids

P. Di Chenna, A. A. Ghini and G. Burton

Departamento de Química Orgánica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Pabellón 2, Ciudad Universitaria, (1428) Buenos Aires, Argentina

E-mail: burton@qo.fcen.uba.ar

Abstract: 17(13→18)-Abeo and D-homo analogs of the natural neurosteroid 3 α -hydroxy-5 α H-pregnan-20-one were prepared by anionic or radical (mercury (II) hydride mediated) rearrangements of steroidal cyclopropylketones respectively.

Introduction

Certain steroids show an inhibitory effect on the central nervous system by a fast non-genomic action on the γ -aminobutyric acid receptor (GABA-A), similar to that produced by benzodiazepines [1]. Structure-activity relationship studies for this interaction, indicate that the requirements for activity are a reduced pregnane or androstane skeleton (A/B *cis* or *trans*), a 3 α -hydroxyl and a carbonyl at C-20 (or C-17 in androstanes). Several of these compounds have shown anticonvulsant properties (potential antiepileptics) [2]. Conformational studies are very limited and cannot be used to assess the influence of steroid conformation on activity. Our group has developed several efficient procedures for the preparation of steroid hormone analogs, based on radical or anionic expansion of fused cyclopropylketones [3,4]. We have now adapted these procedures for the preparation of 17(13→18)-*abeo* and D-homo analogs of natural neurosteroids, with enhanced flexibility in the C/D ring junction.

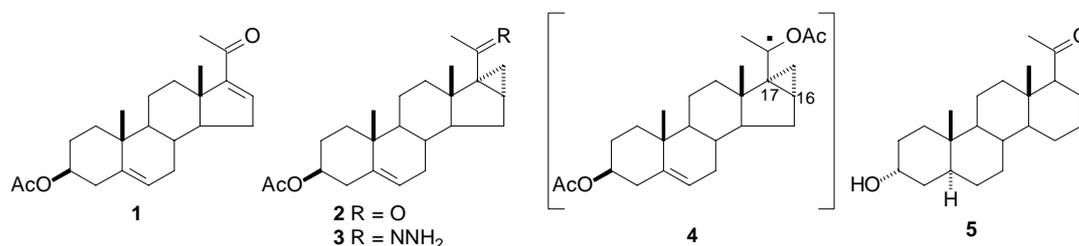
Experimental

16-Dehydropregnenolone acetate (**1**) and 11 α -hydroxyprogesterone were used as starting materials. Products were purified by flash chromatography on silicagel and fully characterized by ^1H and ^{13}C NMR (1D and 2D) and MS.

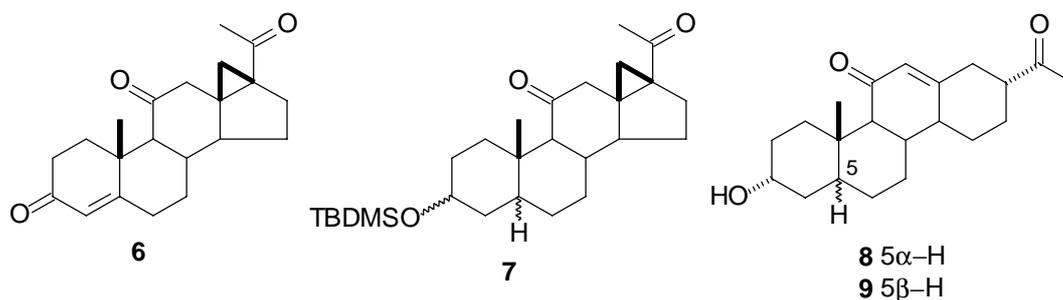
Results And Discussion

Radical rearrangement: Cyclopropylketone **2** obtained by reaction of 16-dehydropregnenolone (**1**) with dimethylsulfoxide methylide, was converted into hidrazone **3** ($\text{N}_2\text{H}_4/\text{BaO}$); reaction of **3** with $\text{HgO}/\text{Hg}(\text{AcO})_2$ followed by treatment with NaBH_4 produced the alkoxy-carbinyl radical **4** which rearranges with cleavage of the 16,17 bond to give the 6 membered D ring. Hydrolysis of the acetate at C-

3, reduction of the 5,6 double bond ($H_2/Pd-C$) and Mitsunobu inversion at C-3 rendered D-homo analog **5**. This compound presents a closer similarity with the natural steroids than the 17(13→18)-abeoanalogs (see below), as the side chain is not displaced and the angular methyl at C-13 is preserved.



Anionic rearrangement: The 5α -H (**8**) and 5β -H (**9**) analogs of 3 α -hydroxy-17(13→18)-abeopregn-12-ene-11,20-dione were prepared by anionic rearrangement of the enolate from the mixture of cyclopropyldiketones (**7**) (NaOH/MeOH) [3]. Other key steps were the chemoselective reduction of the conjugated system in ring A of **6** (Ni/Al, MeOH/HONa) to give the isomer mixture at C-5 and C-3 and the selective deprotection of the TBDMS group from the equatorial hydroxyls at C-3 in the presence of the axial isomers for both series of analogs.



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References and Notes

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3. Ferrara, A.; Burton, G. *Tetrahedron Lett.* **1996**, *37*, 929 and references cited therein
5. Ferrara, A.; Doctoral Thesis, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, 1997.