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STEREOCHEMICAL CONTROL OF PERHYDROINDANES FOR THE SYNTHESIS OF CARDENOLIDE ANALOGS

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Abstract.- The control of the stereochemistry at C-1 of *cis*-perhydroindane compounds, required for the synthesis of cardenolide analogs, has been achieved by epimerization of the dithiane derivative at C-5. Molecular modeling of this kind of compounds predicted the higher stability of the C-1-β-epimer in this and other derivatives, instead of the usually more stable C-1-α-epimer in the natural cardenolides and other calculated compounds.

The synthesis and transformation of (C,D)-*cis*-steroids, as is the case of positive inotropic cardenolides, is complicated by the epimerization at C-17. In fact, the presence of a carbonyl function at C-20 promotes the interconversion of both epimers at this position by the effect of basic conditions, to produce mixtures with the more stable α-epimer as the major product from the β-epimer. Aldehydes or ketones at C-20 produce these *non* -natural α-epimers, thus representing an added difficulty in their transformation and in the synthesis of new analogs with the natural stereochemistry at C-17. Examples of this undesirable transformation [1] are depicted in figure 1.

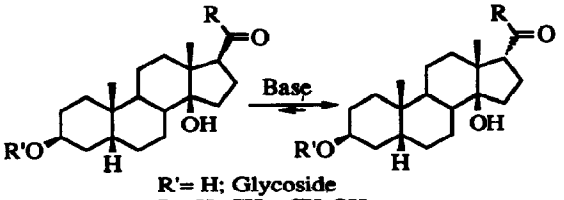
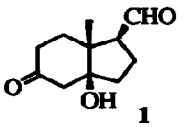


Figure 1.- Preferred epimerization of cardiac glycoside derivatives to the more stable C-17-α-isomers

During our research devoted to the synthesis of simple analogs of cardiac glycosides, we planned the synthesis of the perhydroindane-1-carboxaldehyde 1, as the key intermediate for the preparation of more elaborated derivatives. Starting with the easily accessible (and commercially available) Hajos-Parrish ketone 2[2] it is possible to elaborate compound 1 in a high enantiomeric excess, but the synthesis has two difficulties associated with the basic *cis*-skeleton. Firstly, the low reactivity of the cyclopentanone carbonyl, due to the increase of spatial hindrance during the transformation of this function. Secondly, the preferred reactivity by the more accessible



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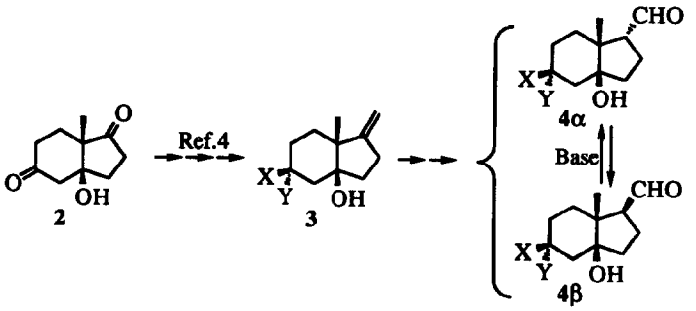
β-face of C-1 (equivalent in (C,D)-*cis*-steroids to the C-17 position) of these derivatives, thus yielding the undesired α-epimers as predominant reaction products. The first problem has been successfully overcome by the use of the Conia[3] modification of the Wittig olefination, which has allowed us to obtain methylene derivatives **3** from 1-perhydroindanones, with >80% yields[4].

We now present an easy solution to the stereochemical difficulty associated with the substitution at C-1 in these compounds, based on the favorable epimerization to the desired β-epimer in an appropriate derivative. In order to find a derivative with favorable equilibration to the β-epimer, we conclude that the functionality (X,Y) present in the cyclohexanic ring could play a crucial role in the stereochemical results, because of the



conformational freedom associated with the *cis*-junction of perhydroindanes type **1-4**. So, we accomplished molecular modeling studies[5] of some derivatives type **4**, to know the relative stabilities associated with both epimers, **4**(α) and **4**(β). Changes in the hybridization and X,Y substituents at C-5 were analyzed to obtain a better knowledge of their influence. The studied compounds were the C-5(sp^2) ketone **1** (**4**; X,Y=O) and C-5(sp^3) derivatives: hydrogenated compound (**4a**; X,Y=H), alcohols (**4b**; X=OH, Y=H. **4c**; X=H, Y=OH), dioxolane (**4d**; X,Y=$O(CH_2)_2$-O) dioxane (**4e**; X,Y=$O(CH_2)_3$-O) and dithiane protected (**4f**; X,Y=$S(CH_2)_3$-S). The results obtained from these calculations are presented in Table 1. To compare these results with the model steroids a similar calculation was performed with the aldehyde (Fig. 1; R=R'=H). In accordance with the described preference for the C-17-α-epimer, a ΔΔH=+0.19 Kcal/mol favoring this epimer was obtained. In the hydrogenated **4a**, the difference was similar , also favoring the C-1-α-epimer. Among the other perhydroindanes **4b-4f** derivatives, some of them have a difference of stability between both epimers opposite to that calculated for **1**, **4a** and the steroid, being the higher difference in the case of dithianes **4f**.

Compound	**1** X,Y=O	**4a** X=Y=H	**4b** X=OH, Y=H	**4c** X=H, Y=OH	**4d** X,Y= $O(CH_2)_2O$	**4e** X,Y= $O(CH_2)_3O$	**4f** X,Y= $S(CH_2)_3S$	Steroid
ΔH(β)-ΔH(α)	-0.02	+0.12	-1.64	+1.39	-1.09	-0.85	-2.98	+0.19

Table 1. Difference of heats of formation between α and β epimers of compounds type **4**.

The ΔΔH=-2.98 Kcal/mol obtained clearly indicate that **4f**(β) would be the major component of the equilibration mixture, with a very low amount of the other epimer **4f**(α). The higher stability of the **4f**-β-isomer is accompanied by a conformational change of the whole indane skeleton in comparison with the **4f**-α-isomer and the C-D rings of calculated steroids. As it can be seen in figure 2, the preferred conformation of 17α and

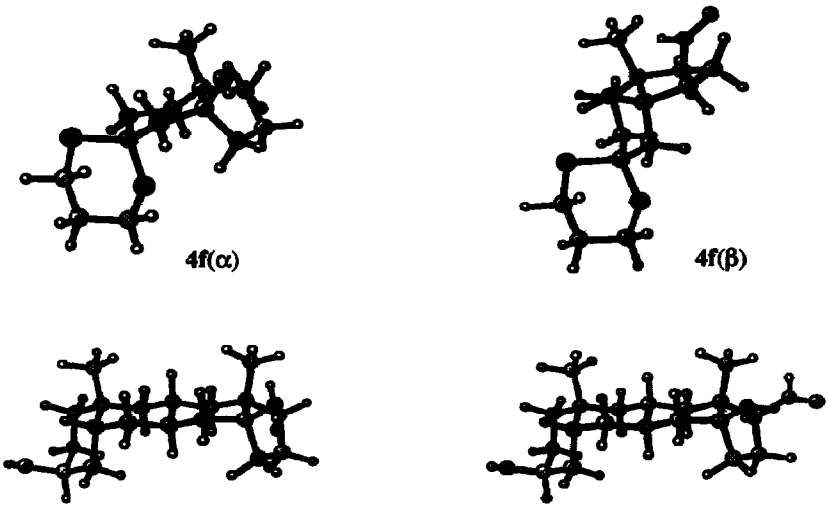
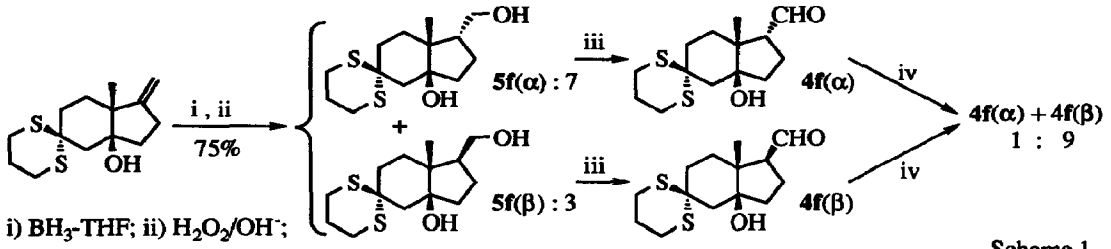


Figure 2. - Preferred conformations of dithianes **4f** and 17-CHO steroids.

17β-steroids (R=CHO) and **4f**(α) have the methyl group in axial disposition, while the preferred conformation of **4f**(β) has the methyl group in equatorial disposition.

The syntheses of both 1-epimers of **4f** were accomplished from dithiane **3f**,[6] as depicted in scheme 1. The hydroboration-oxidation of **3f** produced, as result of the favored attack by the less hindered β-face, a 7:3 mixture of **5f**(α) and **5f**(β)[7]. PCC oxidation of each compound produced the expected aldehydes **4f**(α) and **4f**(β).[8]



Scheme 1

When pure **4f**(α), pure **4f**(β) or the 7:3 mixture **4f**(α)+**4f**(β) (directly obtained by oxidation of the crude **5f**(α)+**5f**(β) mixture) were equilibrated in KOH/MeOH, the same 1:9 mixture of **4f**(α) and **4f**(β) was obtained. Chromatographic purification allowed us to obtain **4f**(β) in >50% from dithiane **3f**.

In this way, pure C-1-β-isomers of indane derivatives, useful for the synthesis of cardenolide like compounds, can be obtained in high yield from the Hajos-Parrish ketone. The effect produced by long distance substituents on the relative stability of both epimers at C-1 is a very convenient method for this purpose.

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5. Calculations were performed on a Silicon Graphics Indigo computer. Compounds were built using Macromodel v.4 and energy minimized with the MM2 force field. Conformational analysis of each compound was performed by using a Monte Carlo systematic search. Full geometry optimization of the lowest-energy conformations of every compound was performed using Stewart's PM3 Hamiltonian in MOPAC 6.0.

6. **3f**: Mp= 92-4°C, $[\alpha]_D$=+5.2°(c=0.96%$CHCl_3$). ^1H NMR: 0.98(3H,s), 1.5-3.3(16H,m), 4.79(1H,t,J=2Hz), 4.86(1H,t,J=2Hz). ^{13}C NMR: 25.1(C8), 25.6(C4-dith), 26.3(C3-dith), 26.4(C5-dith), 26.5(C6), 26.5(C2), 34.5(C3), 34.5(C7), 43.5(C4), 47.7(C7a), 49.0(C5), 80.5(C3a), 105.5(C9), 155.0(C1). MS: *m/z* 270 (M^+,57%). Anal: Calc for $C_{14}H_{22}OS_2$: C, 62.18; H, 8.20. Found C, 62.03; H, 8.25.

7. Sulfoxide derivatives were also detected as more polar products in some of the hydroboratio-oxidation experiments.

8. **4f**(α): $[\alpha]_D$=-4.1°(c=1.11%$CHCl_3$). ^1H NMR: 1.27(3H,s), 1.3-3.0(18H,m), 9.83(1H,d,J=2.0Hz). ^{13}C NMR: 19.9(C8), 19.4(C2), 25.6(C4-dith), 26.4(C3-dith), 26.7(C5-dith), 27.6(C6), 33.2(C3), 37.0(C7), 44.0(C4), 48.7(C7a), 48.7(C5), 60.6(C1), 82.1(C3a), 204.8(C9). MS: *m/z* 286 (M^+,100%). **4f**(β): $[\alpha]_D$=+91.8°(c=0.57%$CHCl_3$). ^1H NMR: 0.96(3H,s), 1.5-3.3(18H,m), 9.70(1H,d,J=2.3Hz). ^{13}C NMR: 18.0(C2), 18.4(C8), 25.4(C4-dith), 26.4(C3-dith), 26.4(C5-dith), 27.7(C6), 33.8(C3), 36.5(C7), 43.2(C4), 46.6(C7a), 48.3(C5), 53.4(C1), 80.8(C3a), 203.6(C9). MS: *m/z* 286 (M^+,100%).

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