Stereoselective Synthesis of New Simplified Digitalis-Like Compounds from (+)-(3aS,7aS)-3a-Hydroxy-7a-Methylperhydroindan-1,5-Dione¹

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**INTRODUCTION**

Cardiac glycosides of *Digitalis* species are well known heart-stimulating drugs, clinically used for treatment of congestive heart failure.² In the steroidal moiety of the aglycons (cardenolides) the C/D cis ring junction, the 14β-OH and the 17β-butenolide could be recognized as three peculiar features for a potent pharmacological action, while the A/B ring junction can vary from cis (e.g. *digitoxigenin*) to trans (e.g. *uzarigenin*) (Fig. 1) without a dramatic loss of activity. As a part of our work aimed at searching new digitalis-like compounds with an improved pharmacological profile, we synthesized compound 9 (Fig. 1) in which the C/D part of the molecule was maintained while the A/B part was simplified in a 5β-cyclohexyl substituent.

![Figure 1](image.png)

**CHEMISTRY**

In Scheme 1 the synthetic approach for the synthesis of 9, starting from the known (+)-(3aS,7aS)-3a-hydroxy-7a-methylperhydroindan-1,5-dione 1³ is reported.
Scheme 1. Reagents and condition: (a) CeCl$_3$, PhLi, THF, -78$^\circ$C; (b) Raney-Ni, EtOH, reflux; (c) H$_2$, Rh/Al$_2$O$_3$, 48 psi, MeOH; (d) (i) NH$_2$NH$_2$, TEA, EtOH, reflux; (ii) I$_2$, TEA, THF; (iii) NH$_2$NH$_2$, O$_2$, AcOH, EtOH (96 deg.), reflux; (e) (i) Maleic anhydride, TTMSS, AIBN, PhCH$_3$, 90deg.C; (ii) DBU, Et$_2$O then NaH$_2$PO$_4$/HCl 3N (pH 3.5), Et$_2$O; (f) NaBH$_4$, MeOH, THF, reflux then HCl, pH 1.4; (g) (i) LDA, THF, -20deg.C/0deg.C then, PhSeCl-78deg.C/rt; (ii) H$_2$O$_2$, AcOH, THF.

The first problem was to find a reagent and/or reaction conditions permitting a regio- and stereoselective nucleophilic attack of the 5-keto function.

A reaction with an organometallic reagent could do the trick, owing to the higher reactivity of 5- vs. 1-keto group and the easier approach from the b-face compared to the more hindered a-face (Fig. 1).

Disappointingly the reaction with PhLi gave an almost 1:1 mixture of 5a and 5b-phenyl derivatives in only 40% yield, probably due to enolization of the ketone.

To overcome the problem we repeated the arylation on the CeCl$_3$/C=O complex$^4$: this time the yield was 73% and the ratio between the 5b-phenyl 2 and the corresponding 5a-phenyl was 4.6:1 (Scheme 2).

The two diastereoisomers were easily separated by flash chromatography and the benzylic 5a-hydroxy group of 2 was eliminated by hydrogenolysis with Raney-Nickel with complete retention of configuration.

The desired cyclohexyl derivative 4 was obtained by hydrogenation with Rh/Al$_2$O$_3$ as a catalyst.
At this point, a β-substituent in position 1 had to be introduced.

First we transformed, with a known, stereospecific reaction sequence, the 1-keto derivative 4 into the 1α-iodo compound 5; then applied a stereospecific free-radical reaction with maleic anhydride, recently published by us, to obtain the advanced precursor 7 of the 1β-butenolide target compound, probably through the anhydride 6. Chemoselective reduction of the ester function of 7 led to the butanolide derivative 8 which was transformed into the final compound 9 in 7% overall yield.

CONCLUSIONS

The simplified cardenolide 9, with a perhydroindene skeleton, was obtained from the known, enantiopure compound 1 with a simple and versatile reaction sequence. The key steps were the introduction of a cyclohexyl substituent at 5b-position and of the butenolide moiety at 1b-position. The transformations were achieved through few stereo- and regioselective reactions. The free-radical introduction of an advanced precursor of the butenolide ring, performed by us on a 14b-androstane derivative, could thus be successfully exported to a more flexible nucleus.

REFERENCES and NOTES


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